

How it Works April 9, 2013

The Challenge in Breast Cancer

- Breast Cancer is a common and serious disease
 - Over 200,000 new cases of invasive breast cancer each year
 - Over 40,000 women will die each year because of breast cancer
 - Added complication is the heterogeneity of the disease





The Challenge in Breast Cancer



- Screening is prevalent
 - Has increased the fraction of low risk tumors but only minimally decreased the fraction of high risk tumors
 - Denominator of many adjuvant trials includes lower risk tumors







- Many treatments have been successful in improving outcomes
 - But for women with aggressive cancers that do not respond well to current treatments, their prospect for survival is grim

Neoadjuvant Approach Dramatically Accelerates Knowledge Turns

Metastatic Approach \rightarrow 2 to 4 year knowledge turns **Adjuvant Approach** \rightarrow 6 to 9 year knowledge turns



Neoadjuvant Approach → 1 year knowledge turns

Current Model Drug Discovery



One FDA-Approved Drug - Start to Finish

- 10-15 Years
- 1,000 6,000 Volunteers
 - \$1 Billion

CALGB INTERSPORE ACRIN NCICB

CALGB 150012/150007 and ACRIN 6657

Investigation of Serial studies to Predict Your **T**herapeutic **R**esponse with maging And **MoLecular Analysis**



I SPY WITH MY LITTLE EYE A BIO-MARKER BEGINNING WITH X

I-SPY 1 / ACRIN 6657 (Open 2002-2006)



- Tumors \geq 3cm eligible
- Enrolled 237 patients, 221 completed the study

I-SPY 2 TRIAL

Primary Imaging Measurement in I-SPY 1 Longest Diameter, Volume, Signal Enhancement Ratio

Tumor volume based on the Signal Enhancement Ratio (SER)



Rates of pCR Differ Based on Biomarker Profile, I-SPY 1



	HR+	HR-	
HER2+	33%	45%	39%
HER2-	9%	33%	18%
	14%	38%	27%

*Excludes patients who received trastuzumab (n=20)

Response to Therapy is Associated with Better Relapse Free Survival, I-SPY 1



pCR Performs better by Subtype, Simpson's Paradox



Overall Findings from I-SPY 1



- Patients in I-SPY 1 are most at risk of relapse, death
 - 91% of I-SPY patients had poor risk biology (tumors \geq 3cm)
- pCR is highly predictive of outcome
 - Stronger predictor when analyzed by subgroup (Simpson's Paradox)
 - Can be used as trial endpoint for evaluation of novel agents
- MRI Volume change is a non-invasive way to predict pCR
 - Standard developed for MRI volume change

Why I-SPY 2?



Increase the number of agents and targets tested within 1 clinical trial



- Reduce time to conclusive results with neoadjuvant treatment
- Concurrent development of predictive biomarkers for each agent tested
- Reduce number of patients/volunteers required with adaptive randomization





I-SPY 2 TRIAL Design Summary

- Neoadjuvant standard control (taxane-based)
- Balance randomization to investigational agents initially
- Build predictive index for each therapy/biomarker combination
- Adaptively randomize incoming participants
- Evaluate many drugs & combinations
 - Successes graduate to phase 3
 - Underperformers dropped for futility

Summary of Study Plan



* HER2 positive participants also receive Trastuzumab. An investigational agent may be used instead of Trastuzumab.

Learn, Drop, Graduate, and Replace Agents Over Time



* HER2 positive participants also receive Trastuzumab.

I-SPY 2 TRIAL: Protocol & Master IND Structure

- 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-SPY 2 PROTOCOL STRUCTURE

* The Master IND structure allows new investigational agents to be added to the protocol without the 30-day FDA review period.

Two Part Consent Process



Screening Consent

- Allows *Surgeons*, *Oncologist*, or *Radiologists* to consent a patient
 - Consent covers screening phase procedures, overview of treatment phase procedures, and randomization but <u>not</u> specific treatment information
 - Part of Screening is to determine biomarker profile for which treatment patient is eligible for

Treatment Consent

- Details treatment patient is actually randomized to along with re-reviewing treatment phase study procedures
- Treatment Consent is 2 parts: Main treatment consent + Investigational agent supplemental consent
 - Treatment Consent is obtained after randomization, and only for agent(s) patient is randomized to

Two Part Consent Process



Two Part Consent Process



Tools for Discussing Trial to Patients

- Patient Brochure
 - General introduction to I-SPY 2
- Video/DVD
 - General introduction to I-SPY 2
- Website <u>www.ispy2.org</u>
 - Detailed information about I-SPY 2





A Study for Women Newly Diagnosed with Breast Cancer

Will we be able to personalize treatment for breast cancer?

Consider joining a trial that tries to answer that question.

Informatics System for Trial Data

Data collection is real-time, web based

- Trial depends on rapid
 - Eligibility assessment & assignment of therapeutic intervention
 - Outcome data (MRI volume & surgical pathology)
 - Safety data
- Verification of data by DCC

Simultaneous evaluation of treatment efficacy and response by biomarkers

- MRI Volume, pCR, RCB
- ER, PR, HER2, MammaPrint
- Qualification & Exploratory Biomarkers

Researchers have access to data early and in an integrated fashion

Randomization as a web service

• Updated daily based upon previous patient's response data

TRANSCEND Overall Objectives

- Develop an information management platform to support adaptive clinical trials like I-SPY 2
 - Manage trial data across multiple sites with 1 central data coordinating
 - Provide real-time data verification for more efficient analysis of trial data
 - Randomization as an automated web service
 - Combining evaluation of drugs and biomarkers together
 - Biomarker data of various types (microarray, imaging, sequencing, etc..)
 - Scientists need access to data early and in an integrated fashion (one stop shopping)
- Provide a demonstration of caBIG infrastructure in use in a large multi-center trial

TRANSCEND v1.5 – with THE Force

(Trial 2 Health Expedited on SalesForce)



Data Capture and Integration with THE Force:

• Data is captured on CRFs, verified and approved for accuracy by DCC. Data is share with other applications to support the conduct of clinical research, including randomization as a web service

THE Force Functionality – Case Report Forms

		Search				Partner Golden 🔻 Help & Train	ing I SPY
Home Patients +							
				Edit			
Personal Info A	Address	Physicians					
First Nan	ne: Jane			Mi	iddle Name:		
Last Nam	ne: Dias				Suffix:		
Gend	ler: Female				Birthdate:	10/31/1952	
Ag	ge: 60				Institution:	University of California, San Francisco	
Own	er: Partner Gold	en			Subject Id:	05024	
Ran	ce: Asian				Ethnicity:	Not Hispanic or Latino	
Medical Record Numb	er: MRN1234						
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THE Force Functionality – Case Report Forms

• Data elements are coded at point of data entry

Personal Info	Address	Physicians			
First Name:	Jane	Mic	ddle Name:		
Last Name:	Dias		Suffix:		
Gender:	Female		Birthdate:	10/31/1952	
Age:	60		Institution:	University of California, San Francisco	
Owner:	Partner Golden		Subject Id:	05024	
Race:	Asian		Ethnicity:	Not Hispanic or Latino	
Medical Record Number:	MRN1234				
	Cancel				
Menopausal Status	Cancel Comments And Attachments	Complete			1
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TRANSCEND – CRF & Source Documents

- Electronic copy of source documentation with each CRF
- DCC can verify CRF in real-time, approved data is locked

	Previous Next	
Please redact all PHI informati	on from attachments.	
Hide Feed 🖨 Follow		
Post File & Link	Poll	Followers
Select a file from Salesfor	ce Upload a file from your comput	er No followers.
	Error: You must enter a value	
Patient 12345 Clinical History note		
Го	0	Share

THE Force Functionality – Randomization

Randomization Form		Trial: MO-I-SPY 2 TRIAL	
		Save & Close	
Randomization	Complete		
		Next	
CRF	Submitted	Approved	 March 2013
MRI Volume Form	Yes	Yes	Sun Mon Tue Wed Thu Fri Sat
On Study Pathology Form	Yes	Yes	24 25 26 27 28 1 2
On Study Eligibility Form	Yes	Yes	10 11 12 13 14 15 16
MammaPrint Form	Yes	Approval Not Required	17 18 19 20 21 22 23
Patient is eligible to Randomized.		The • produce of the second second • (the second se	24 25 26 27 28 29 30
Treatment patient has been randomiz	ed to: Paclitaxel		31 1 2 3 4 5 6 Today
Did patient sign treatment consent for	m for their randomized treat	ment? • Yes • No - Reason why not:	Date: 3/7/2013 [3/11/2013]
		Decided not to have neoadjuvant of the second se	chemotherapy
		Decided not to be treated with a new provide the second	ovel agent
		Patient found to be ineligible for the	ne study
		Patient found to be ineligible beca	ause they are MammaPrint I ow ER Positive HER2 Negative
		Retient found to be incligible beca	ause inchility to complete MammaPrint Test
		 Patient found to be ineligible beca Ratient found to be ineligible beca 	ause they did not meet other eligibility criteria
		Patient found to be ineligible beca	
		Patient found to be ineligible beca	ause patient could not complete MRI
		Patient found to be ineligible beca	ause patient could not complete core biopsy
		Other	

• Only when completed and approved CRFs are done will patient be randomized. Randomization happens when user selects this Form (< 1 sec)

2TRANSCEND – Deploying June 2013



- Patient Portal in THE Force, including patient study calendaring
- Additional Integration with Applications (e.g. caAers, caCIS data warehouse, PRO-CTCAE, updated versions of caTissue, caIntegrator, caArray