Innovation in SWOG Treatment Trials: Breast and Lung Cancer

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SWOG 8814 (Breast Intergroup Trial 0100): Adjuvant Chemohormonal Therapy for ER+, LN+ Primary Breast Cancer

Kathy Albain, MD, Principle Investigator
Bill Barlow, PHD, Lead Statistician
Steve Shak, MD, and all Genomic Health R+D scientists
Peter Ravdin, MD, Translational Medicine
Dan Hayes, MD, Translational Medicine
Julie Gralow, MD,SWOG Breast Committee co-Chair
C Kent Osborne, MD, SWOG Breast Committee Chair
Silvana Martino, DO, SWOG Breast Committee Chair
Robert Livingston, MD, SWOG Breast Committee Chair
Gabriel Hortobagyi, MD, SWOG Breast Committee Chair

SWOG 8814: Adjuvant Chemohormonal Therapy

Postmenopausal, Node+, ER+ Breast Cancer

STRATIFY

Nodes 1-3+ vs 4+

PR+(ER+ or ER-) vs PR-(ER+)

Time from surgery ≤ 6 vs >6-12 weeks

↓

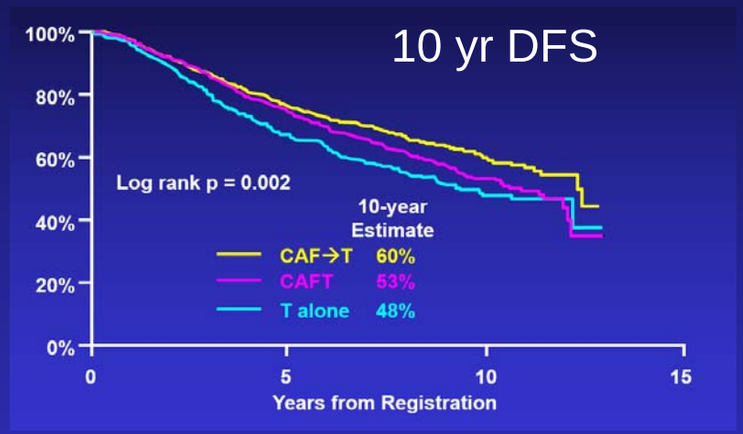
RANDOMIZE (2:3:3) n = 1477

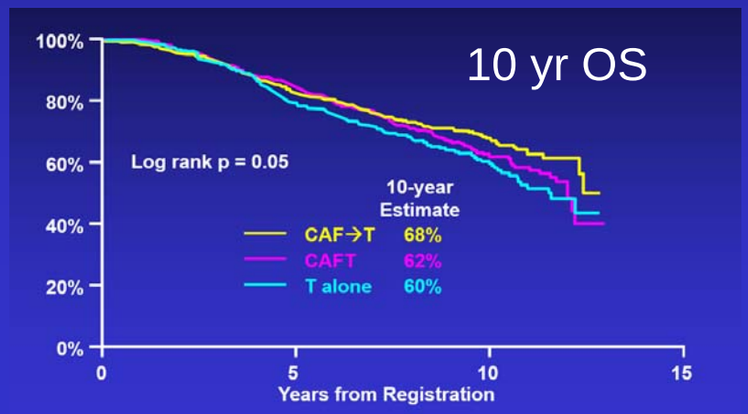
Tamoxifen	CAF, then tamoxifen	CAF,concurrent tamoxifen
(n = 361)	(n = 550)	(n = 566)

SWOG 8814: Adjuvant Chemohormonal Therapy in Node-Positive Breast Cancer

Albain KS et al, Breast Cancer Res Treat 2005

- **1st objective: Tamoxifen +/- CAF**
  - CAF + T (CAFT and CAF-T combined) superior to T alone
  - 12% absolute DFS benefit for CAF+ T over tamoxifen alone
  - **Chemotherapy plus endocrine therapy became standard of care for ER+, LN+ patients**
- **2nd objective: Concurrent (CAFT) vs Sequential (CAF –T)**
  - Adjusted HRs favored CAF-T over CAFT
  - Estimated 16% improvement in DFS and 10% in OS by delaying tamoxifen until the completion of CAF vs concurrent use
  - **Sequential chemo followed by endocrine therapy became standard of care**
- **Toxicities:** More frequent in CAF + T groups than with T-alone
  - Neutropenia, stomatitis, thromboembolism, CHF, leukemia





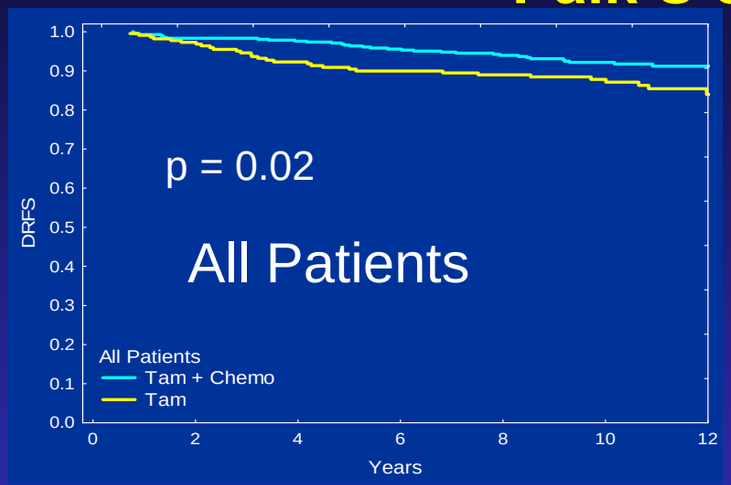
Chemotherapy for Early Stage Breast Cancer

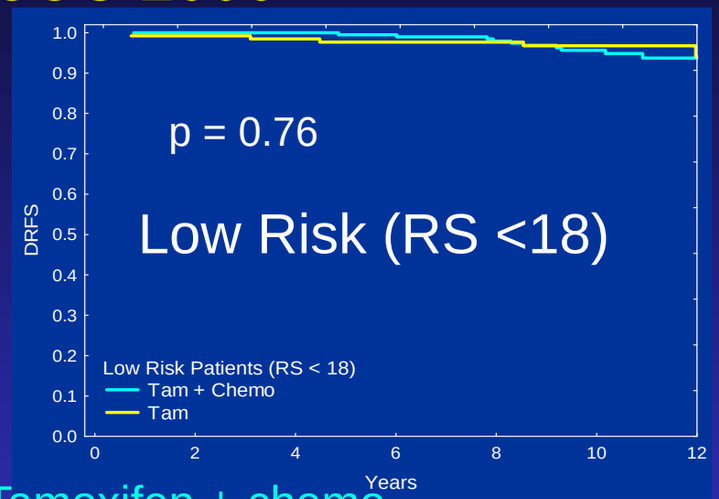
- **THE PAST (2000 NCI Consensus Development Conference on Adjuvant Breast Cancer)**
  - ***Chemotherapy should be offered to the majority of women with early stage breast cancer regardless of size, lymph node, menopausal or hormone receptor status***
- **THE PRESENT AND FUTURE**
  - **Individualizing estimates of recurrence risk and chemotherapy benefit using genomic profiling**
  - **Not all patients/tumors benefit from chemotherapy!**

NSABP B-20: 21-gene Recurrence Score Assay and Distant Disease Free Survival (Node Negative)

High Recurrence Score Group Benefits from Chemotherapy

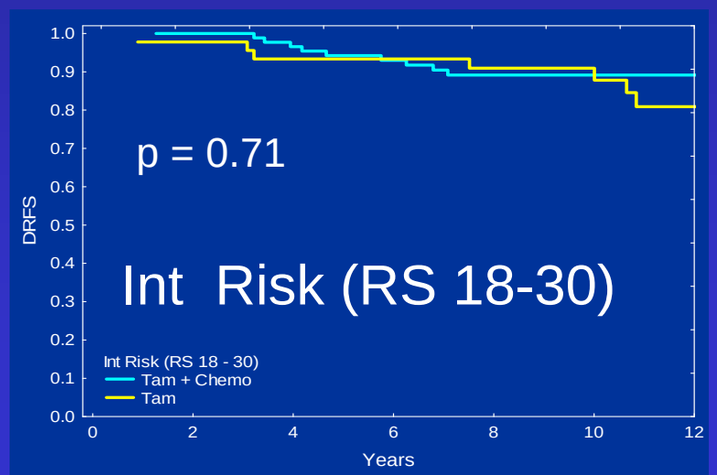
Paik S et al, JCO 2006

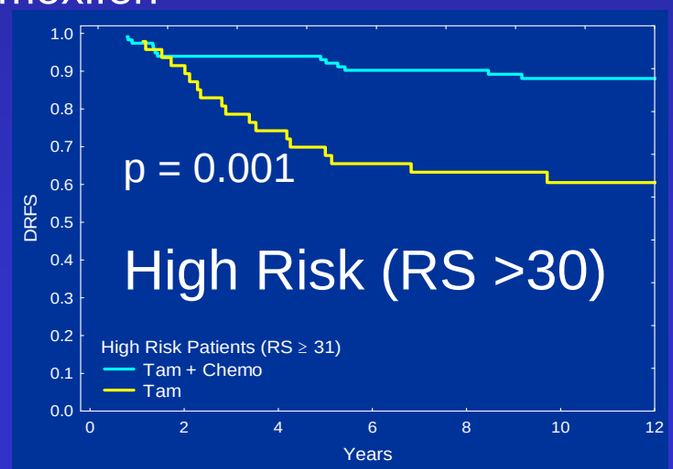




Tamoxifen + chemo

Tamoxifen





PACCT-1/TAILORx: Prospective Validation Trial for 21-Gene Recurrence Score (Node Negative)

PI: J Sparano (SWOG co-PI D Hayes)
Sparano J et al, N Engl J Med 2015

Node Negative, ER+ and/or PR+, HER2-
Size: 1.1 - 5 cm (Int-High grade 0.6 - 1 cm allowed)

Recurrence Score Assay

RS < 11
Hormone Therapy Alone

At 69 mo f/up, distant DFS 99.3%

RS 11-25
Randomize Hormone Rx vs. Chemotherapy + Hormone Rx

RS > 25
Chemotherapy + Hormone Rx

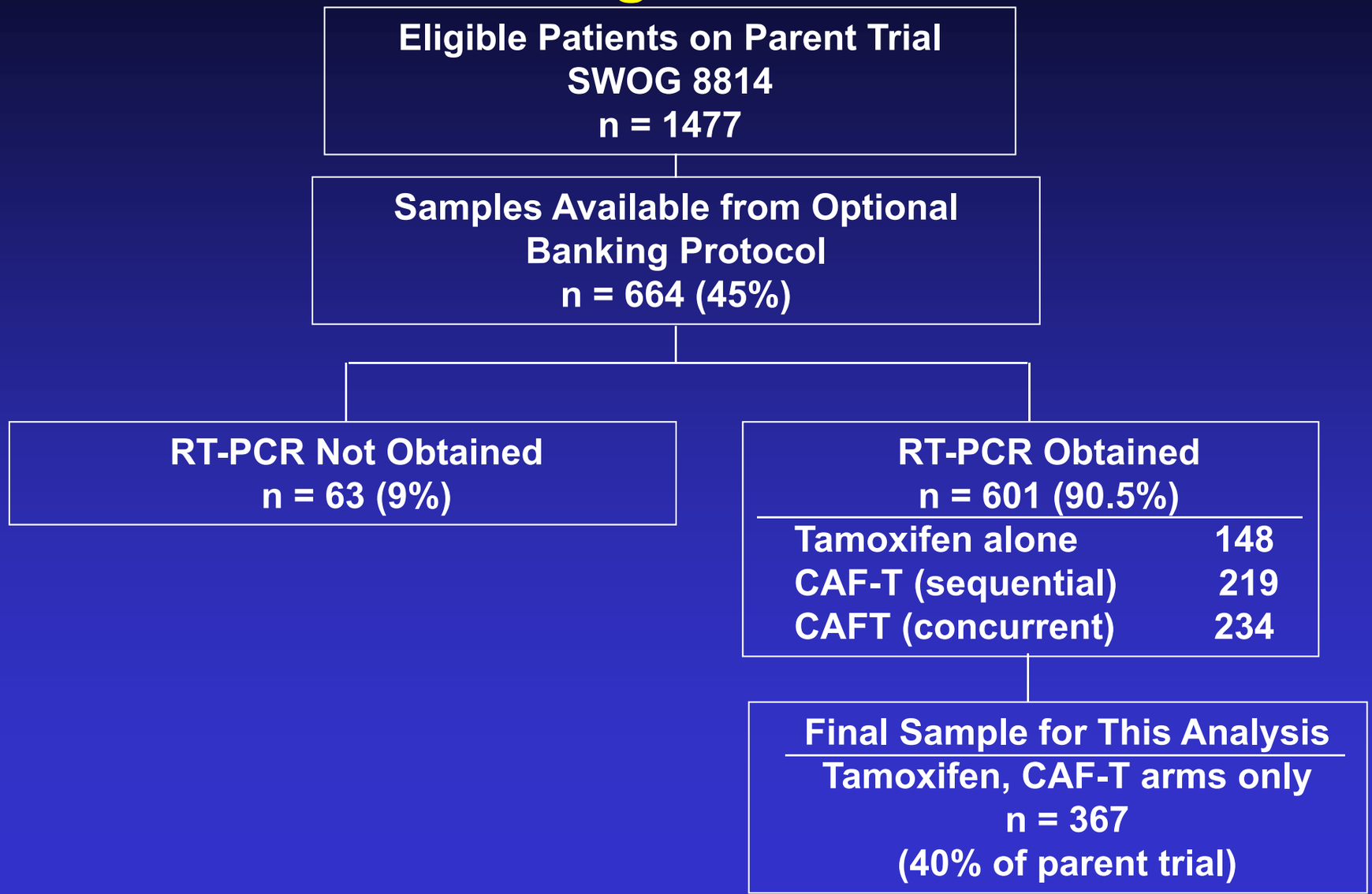
Closed 8/10
Accrual = 10,253

Conclusion from initial S8814 publication: ***It might be possible to identify some subgroups that do not benefit from anthracycline-based chemotherapy despite positive nodes***

Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, ER-positive breast cancer: a retrospective analysis of SWOG 8814

Albain KS et al, Lancet Oncology 11:55-65, 2010

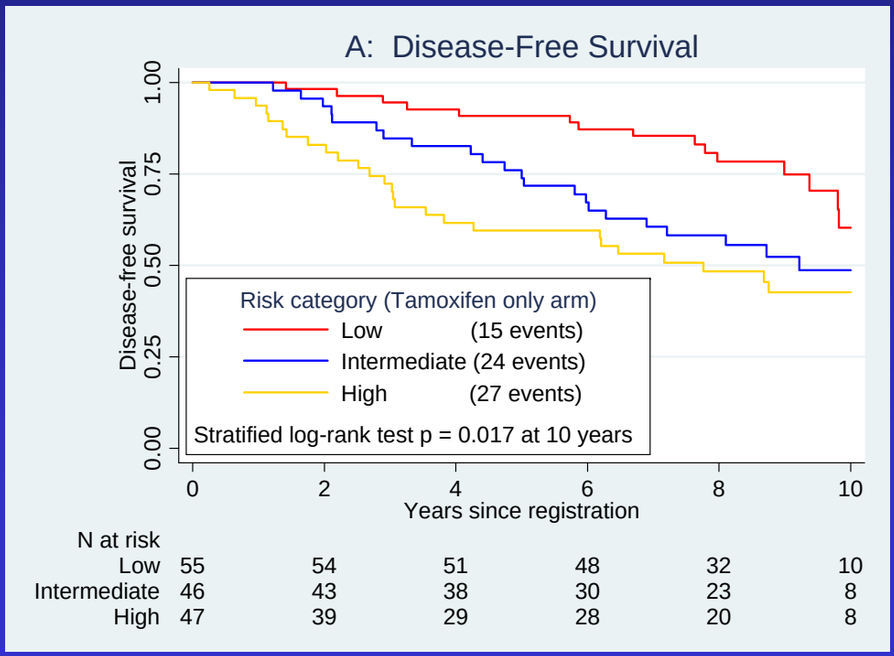
S8814 Tissue Availability from Optional Banking Protocol

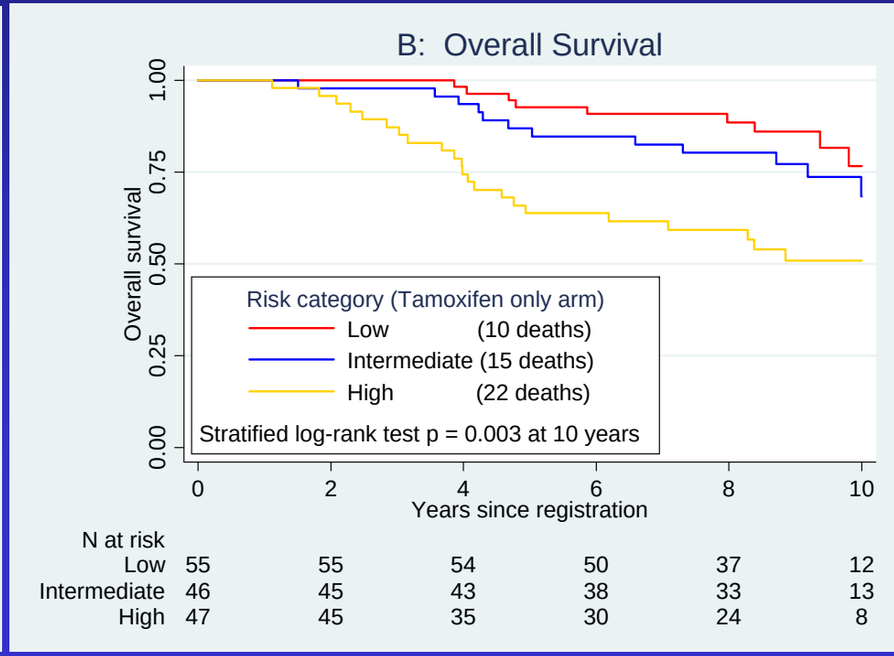


S8814 ER+ LN+ Prognosis by 21 Gene Recurrence Score in Tamoxifen Alone Arm

Albain KS et al, Lancet Oncol 2010

21-gene Recurrence Score Assay provides prognostic information for women with LN+ disease treated only with tamoxifen (similar to LN- data)

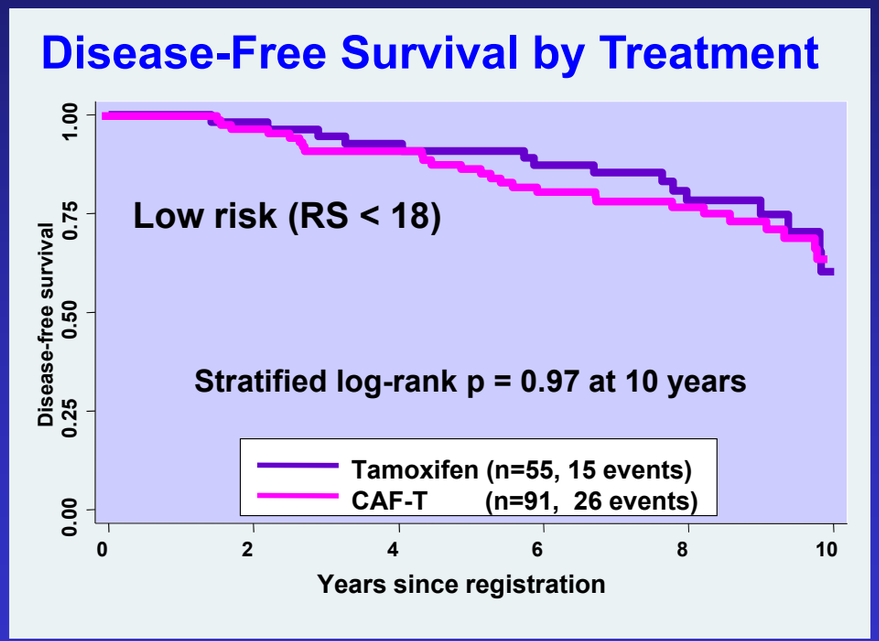


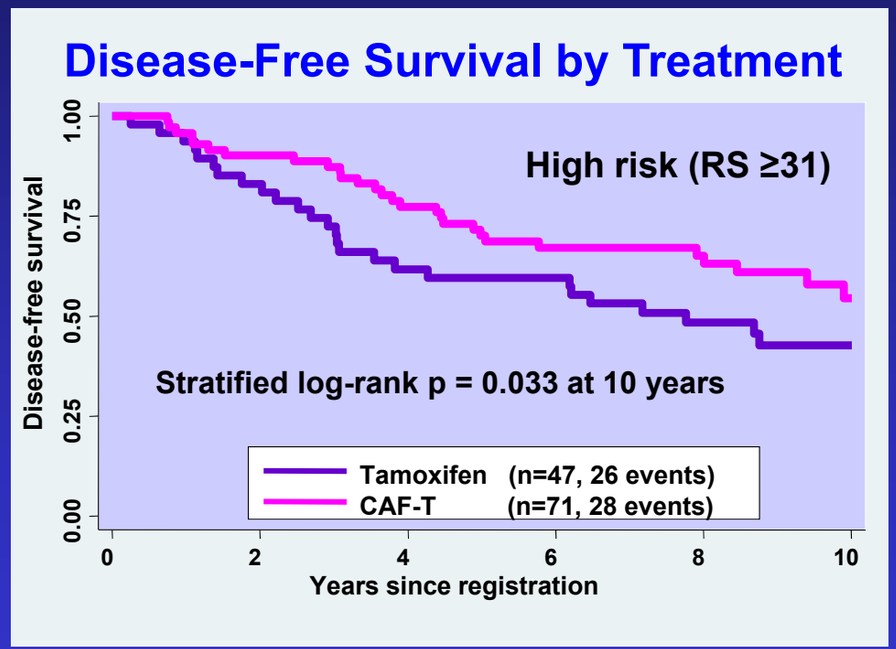


S8814 ER+ LN+ Prognosis by 21 Gene Recurrence Score in Tamoxifen Alone vs CAF-Tamoxifen Arms

Albain KS et al, Lancet Oncol 2010

21-gene Recurrence Score Assay allows prediction of a LN+ group with no benefit from chemotherapy (similar to LN- data)





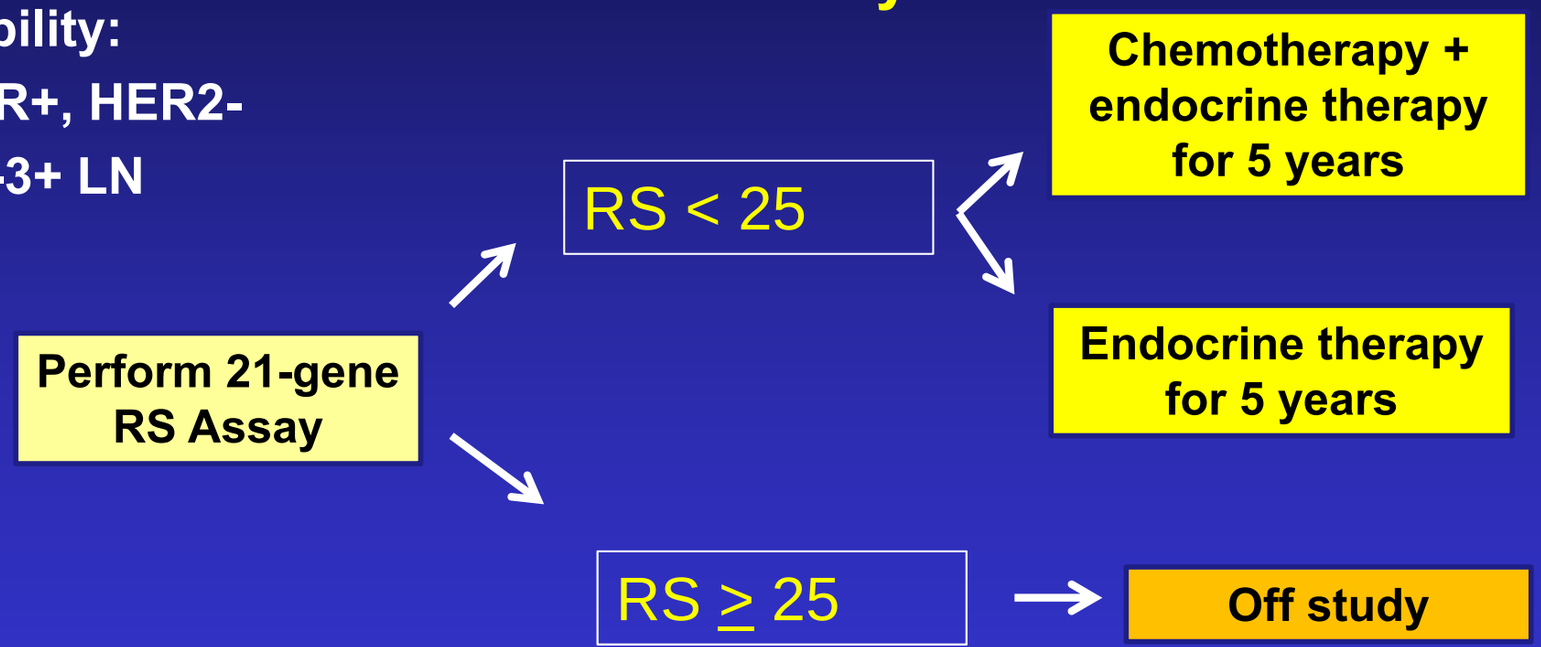
No benefit to CAF over time if low RS; Strong benefit if high RS

Translational work from SWOG 8814 led to

S1007 (RxPONDER) Trial: Prospective Validation for 21-Gene Recurrence Score in Node Positive Breast Cancer

PI: K Kalinsky

- **Eligibility:**
  - **ER+, HER2-**
  - **1-3+ LN**



N=6,000 randomized
Closed in US, remains open within UNICANCER/France

Translational work from SWOG 8814 led in part to
ONGOING SWOG/NRG S1207 Phase III Trial of Adjuvant Endocrine Therapy +/- 1 Year of Everolimus (mTOR inhibitor) in ER+ Breast Cancer

PI: M. Chavez MacGregor, E Mamounas

- **Eligibility:**
  - **ER+/HER2-**
  - **High risk early stage breast cancer**
    - **1-3+ LN and RS≥25 or grade III**
    - **≥4+ LN**
    - **>1+ LN after preop chemo**

Complete chemo and XRT (if indicated)

Everolimus for 1 year + endocrine therapy for 5 years

Placebo for 1 year + endocrine therapy for 5 years

N= 1,900

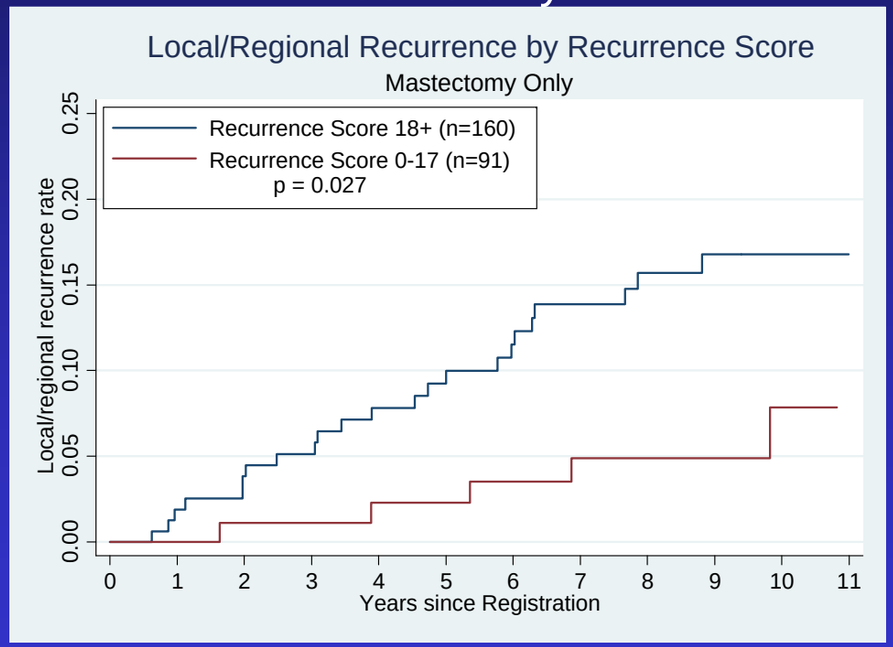
Can combinations of endocrine therapy + targeted agents improve outcomes in high risk, early stage, ER+ breast cancer?

SWOG 8814: 21-gene Recurrence Score and Locoregional Recurrence (LRR) in ER+, Node+ Breast Cancer Post-Mastectomy without Radiation

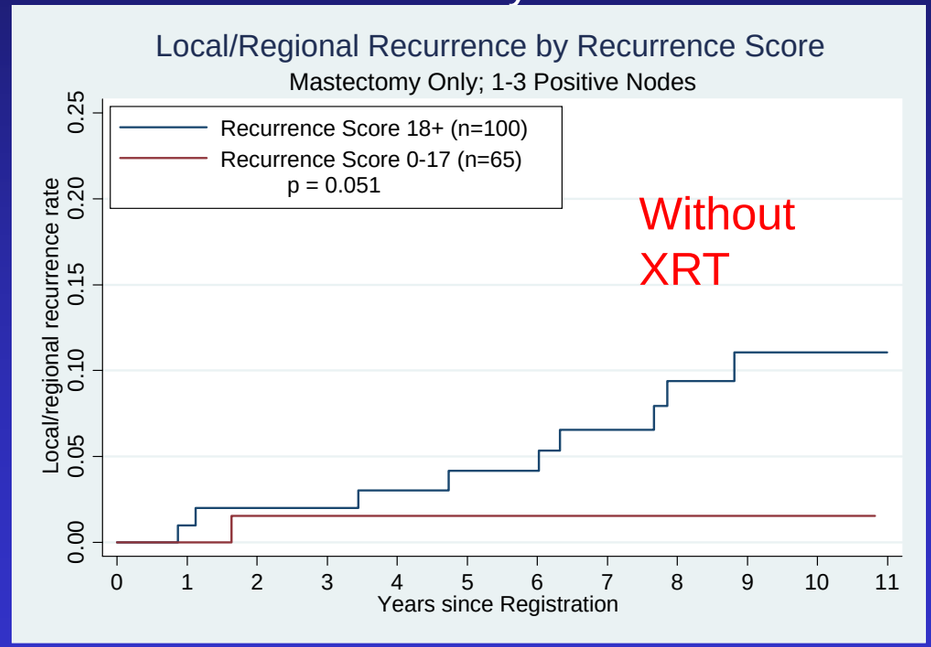
Woodward WA et al, ASTRO 2016, abstract 329

Background: 21-gene RS correlated with LRR in node- pts in NSABP B-14/B-20, node+ in B-28

All Mastectomy



Mastectomy 1-3 LN+



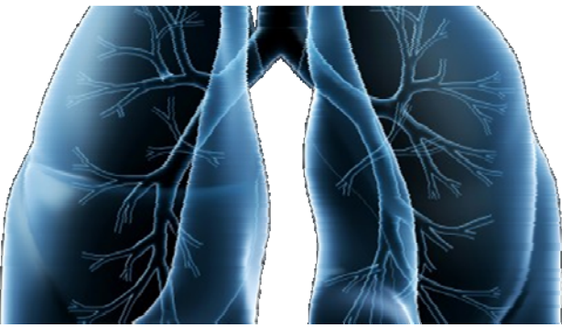
- **Low RS, ER+, 1-3+ LN may avoid XRT after mastectomy with low risk of LRR – to be validated on further study (in planning)**

SWOG 8814: Adjuvant Chemohormonal Therapy in Node-Positive Breast Cancer

- Data from SWOG 8814 trial spanning many decades continues to provide information about adjuvant therapy decision-making in ER+ breast cancer
  - Allows withholding of toxic therapies where little benefit exists
  - Spawned multiple subsequent trials

Lesson learned from SWOG 8814:

The benefit of prospective tissue collection for studies that could not have even been imagined at the time of study start-up!



LUNG-MAP

S1400 Lung Master Protocol

Biomarker-Targeted Second-Line Therapy in Treating Patients With Recurrent Stage IV Squamous Cell Lung Cancer

Vassiliki Papadimitrakopoulou, MD, STUDY ChAIR

Roy Herbst, MD, PhD, Study co-Chair

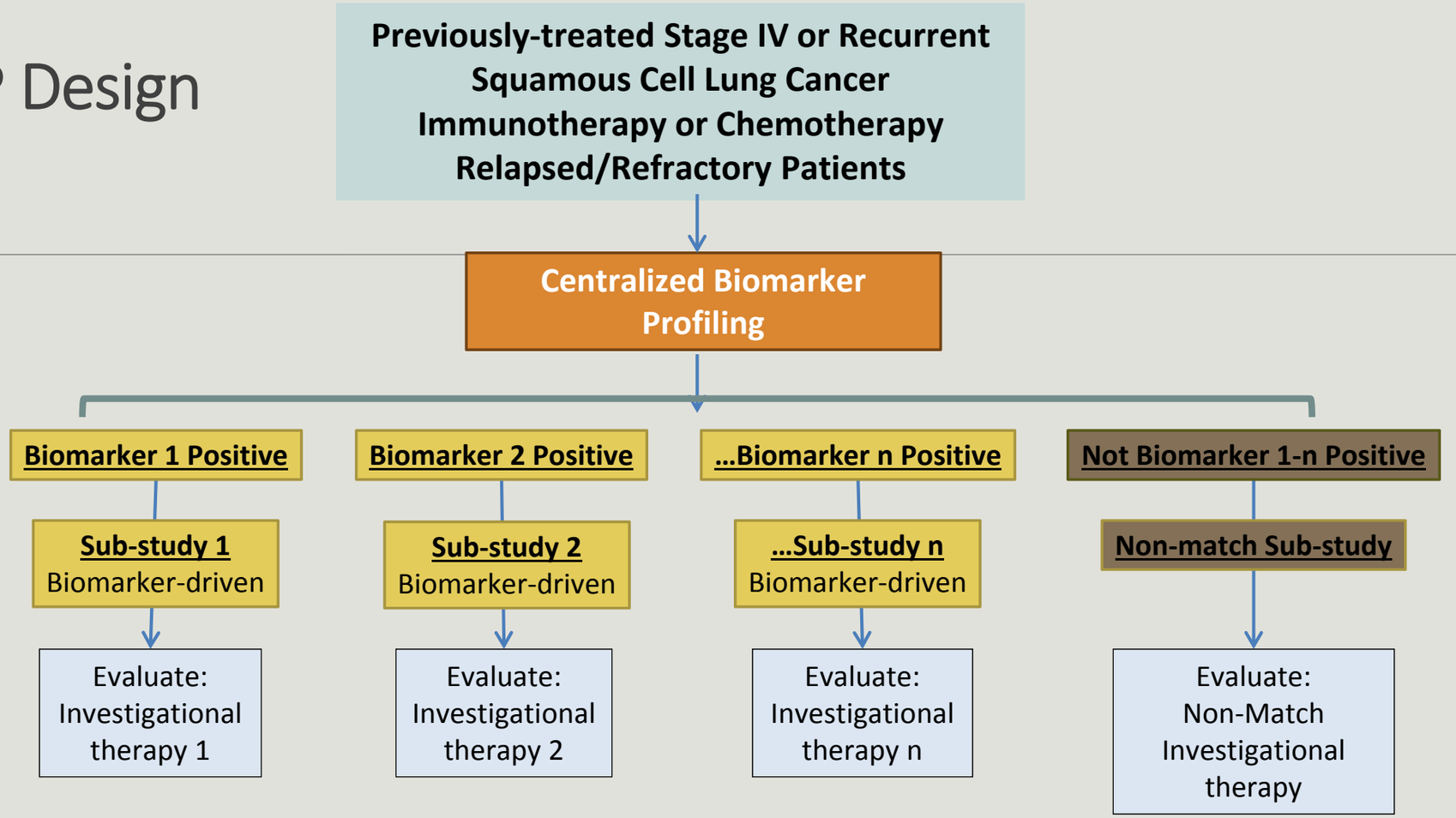
David Gandara, md, Study Co-Chair

Fred Hirsch, MD, PhD, and Phil Mack, PHD, Study co-ChairS, Translational Medicine

Mary Redman, PhD, Study Lead Biostatistician

Karen Kelly, MD – swog lung cancer committee chair

Lung-MAP Design



Biomarker-driven sub-studies may progress to Phase III if study meets endpoint and Phase III is feasible

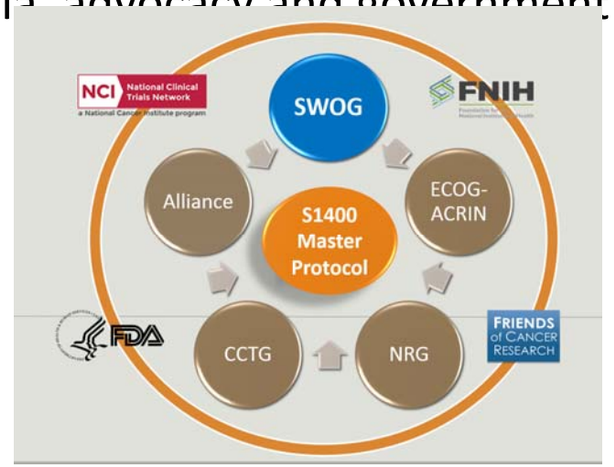
Overall Study Goal:

Quickly identify and test new targeted treatments and immunotherapies for squamous cell lung cancer, and, if effective, move those drugs to FDA approval.

SWOG S1400 LUNG-MAP Trial: Unique Features

1. Collaboration

- Brings together key stakeholders – industry, academia, advocacy and government – to advance precision medicine research and development



2. Addresses 4 primary goals from IOM 2010 report for Cancer Clinical Trials Modernization

- Improve speed & efficiency of trial development & activation
- Incorporate innovative science and trial design
- Improve prioritization, support, and completion of trials
- Incentivize participation of patients and physicians

SWOG S1400 LUNG-MAP Trial: Unique Features

3. **Broad NGS genomic testing improves enrollment efficiency**
   - More efficient than multiple separate single-gene tests for each trial
   - Improves likelihood of receiving a drug targeted to tumor genetic profile
   - Enhances ability to study rare subsets of lung squamous cell carcinoma
4. **Master Protocol design allows new therapies to be added as the trial progresses**
   - Improves operational efficiency
   - Single master protocol amended as needed as drugs enter and exit the trial, rather than developing and launching a separate protocol for each new drug
   - LUNG MAP Drug Selection committee
5. **Designed to facilitate FDA approval of new drugs**
   - Industry and FDA at the table from the beginning
   - If drug meets predetermined efficacy and safety criteria, drug and accompanying diagnostic biomarker eligible for FDA approval
   - Potential to bring safe & effective drugs to patients faster
6. **Non-match arms allow all patients access to some form of investigational therapy**

SWOG S1400 LUNG-MAP Trial: Unique Features

7. Tissue pre-screening to speed up enrollment/treatment at time of progression

- Prescreening can be performed while the patient is still on 1st line therapy for Stage IV disease, before progression

8. Active Site Coordinators Committee

- Represent study site staff at nursing, CRA, data management, and regulatory levels
- Provide feedback to and from study leadership to enhance accrual and improve study management

9. Important Patient Reported Outcomes (PRO) study added to immunotherapy arms

Current Status of Sub-Studies

- **S1400A [Durvalumab/MEDI4736/Anti-B7H1 vs Docetaxel]**
  - Initial non-match study
  - Closed 12/18/2015
- **S1400B [Taselisib/GDC-0032 vs Docetaxel]**
  - PI3K+
  - Closed 12/12/2016
- **S1400C [Palbociclib/CDK 4/6 inhibitor vs Docetaxel]**
  - CCGA+
  - Closed 9/1/2016
- **S1400D [AZD4745/FGFR inhibitor vs Docetaxel]**
  - FGFR+
  - Closed 10/31/16
- **S1400E (Erlotinib vs Erlotinib/Rilotumumab]**
  - HGF/c-MET+
  - Closed 11/25/14

- **S1400F [Durvalumab + Tremilimumab]**
  - Non-match study for checkpoint refractory disease
  - Pending
- **S1400G [Talazoparib – PARP inhibitor]**
  - Patients with alterations in BRCA1/2, ATM, CHEK1, HHRD genes
  - Actively accruing
- **S1400I [Nivolumab vs Nivolumab/Ipilimumab]**
  - Non-match study for checkpoint naïve disease
  - Actively accruing
- **S1400K: [**ABBV-399]
  - c-MET positive patients
  - Submitted to CTEP
- **S1400GEN:** Ancillary Study to Evaluate Patient/Physician Knowledge, Attitudes, Preferences Related to Return of Genomic Results
  - Pilot ongoing

Lung-MAP Biomarker Results

Total Screening/Pre-screening registrations:	N=1191
• Pre-screened prior to PD	410 (34%)
• Screened at PD	781 (66%)
Biomarker testing results:	N=1053
Pi3K+ (S1400B biomarker)	82 (8%)
CCGA+ (S1400C biomarker)	197 (19%)
FGFR+ (S1400D biomarker)	167 (16%)
HRRD+ (S1400G biomarker)	159 (15%)
Multiple Biomarkers	103 (10%)
Others (non-eligible biomarkers):	
EGFR	7 (1%)
ALK	1 (<1%)

As of Mar 15, 2017

Efficacy Outcomes

(presented in lung working group at this meeting)

Important negative findings

Need evaluation of exceptional responders

	Best Objective Response		Response N (%)	PFS Median (95% CI)	OS Median (95% CI)
S1400A (MEDI4736)	1 CR 7 PR 3 UPR	26 SD 30 PD 1 NASS	11 (16%)	2.9 (1.8, 4.1)	11.6 (10.1, 15.4)
S1400B (taselisib)	1 PR	17 SD 6 PD 2 NASS	1 (4%)	2.8 (1.7, 4.0)	5.9 (4.1, 11.5)
S1400C (palbociclib)	2 PR	12 SD 16 PD 1 SYMP DET 1 NASS	2 (6%)	1.8 (1.6, 2.9)	7.2 (4.0, 14.6)
S1400D (AZD4547)	1 PR 1 UPR	13 SD 10 PD 1 SYMP DET 1 NASS	2 (7%)	2.7 (1.4, 4.5)	7.5 (3.6, 9.3)
Combined Docetaxel	2 PR 1 UPR	29 SD 13 PD 5 SYMP DET 6 NASS	3 (5%)	2.7 (1.9, 2.9)	7.7 (6.7, 9.2)

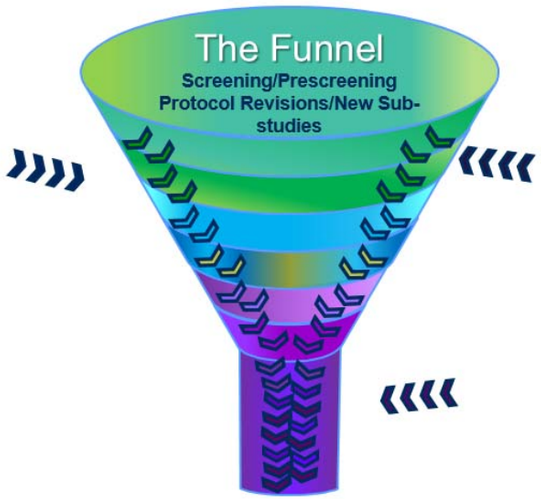
SWOG S1400 LUNG-MAP Trial: Lessons Learned

1. **Unique Private-Public partnership working**
   - 4 primary partners – NCI, FNIH, SWOG, Friends of Cancer Research
   - NCTN sites beyond SWOG are active partners
   - 7 precision medicine and precision medicine companies
   - Multiple advocacy partners
2. **Master Protocols are feasible**
   - Infrastructure facilitates opening new arms quickly
   - Phase II-III design allows rapid drug/biomarker testing for detection of “large effects”
3. **Sites and patients are interested in the study**
   - Screening large numbers of patients for multiple targets by a broad-based NGS platform reduces screen failure rate and provides sufficient “hit rate” to engage patients & physicians
   - 740 sites with IRB approval, 365 sites with at least 1 patient accrued
   - 1238 patients registered, 943 patients notified of sub-study assignment, 456 patients registered to a sub-study

SWOG S1400 LUNG-MAP Trial: Lessons Learned

4. Biopsies and broad screening by NGS is feasible

- Rapid tissue shipment and return of NGS results possible
- Median 1 day for receipt of tissue
- Median 9 days for results reported to SWOG
- > 90% analyzable



5. Trial is able to be flexible and current – keeping up with evolving treatment landscape

- 3 studies closed, questions answered, multiple new arms opened
- Changed to Phase II format, expanding to Phase III with positive results
- When 2 immunotherapy agents approved by FDA in 2015, immunotherapy became a major component of S1400
  - Research added to predict response to immunotherapies and if responses can be enhanced by combinations of immunotherapy + chemo or immunotherapy + targeted agents

SWOG S1400 LUNG-MAP Trial: Lessons Learned

6. **Adequate funding is needed**
   - Sites receive up to $5,869 ($1,079 screening/$4,790 registration) for each patient on trial
   - Reimbursements of $3,000 (CT-guided)/$6,000 (bronchoscopy) for biopsies performed at screening and/or progression after initial response
   - Additional reimbursement for research-based procedures and on-site visits ($1,333) outside regular audit schedule
7. **The future of S1400:**
   - Infrastructure allowing expansion to all lung cancer histologies in immunotherapy refractory disease, to respond to unmet needs
   - Expansion in leadership structure, including across NCTN groups

S1400: A new paradigm for drug development and scientific discovery