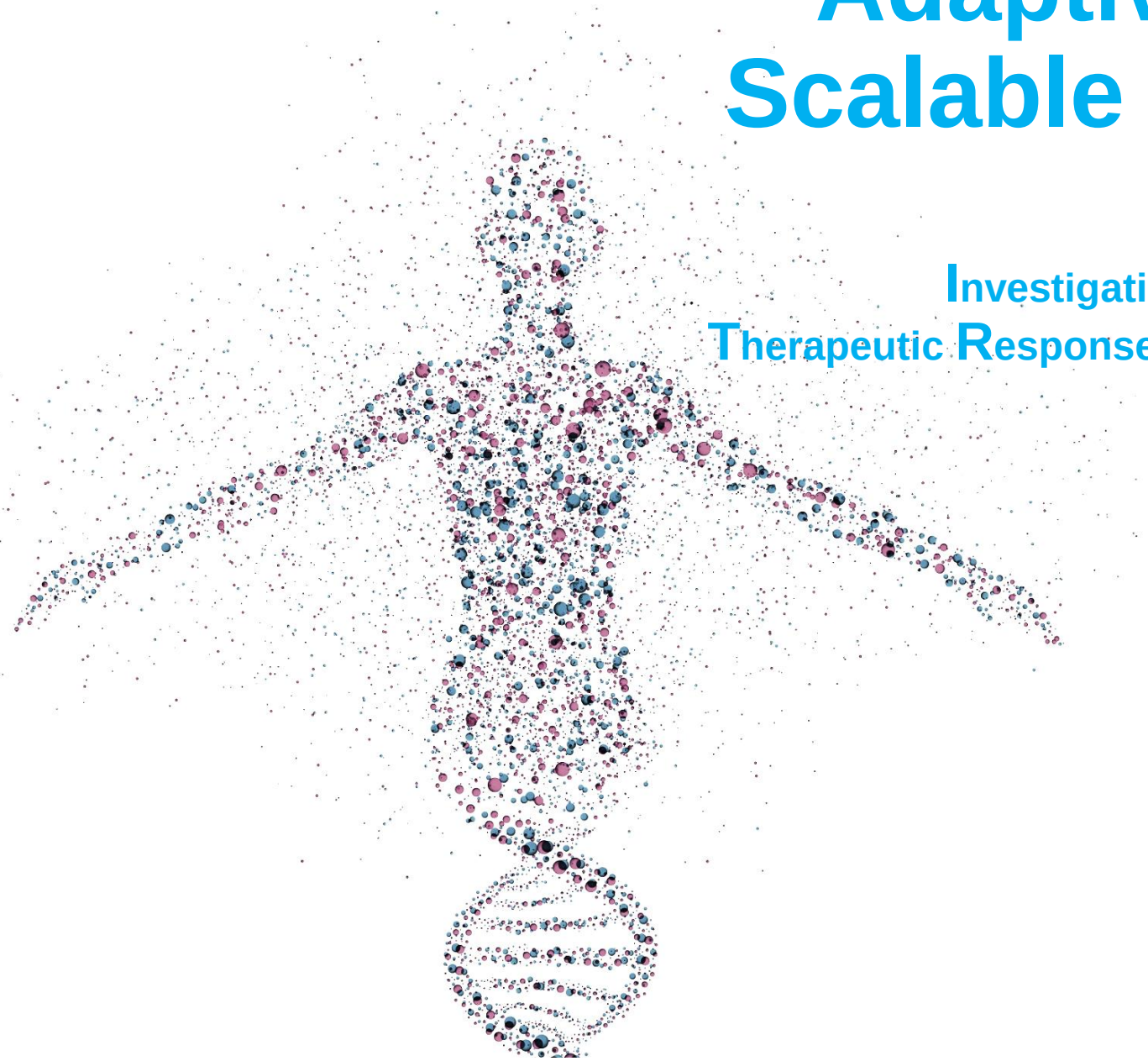


Adaptive Platform Trials: Scalable from Breast Cancer to COVID"

Investigation of Serial studies to Predict Your Therapeutic Response with biomarker Imaging, integration and Adaptive Learning

Laura J Esserman MD MBA

Alfred A. de Lorimier Chair in General Surgery

Professor of Surgery and Radiology

Director, UCSF Carol Franc Buck Breast Care Center

Founder Quantum Leap Healthcare Collaborative

Concepts for Improving the Way We Evaluate New Treatments

- Accelerate Knowledge turns: drive urgency and innovation
- Design trials that incorporating disease heterogeneity
- Metastatic/end stage disease may not be the ideal place for drug development: Move drug development into the earlier stage setting
  - “ethical” dilemma because safety trade offs
  - No chance for cure eliminates concern over lethal harm
- Identify early endpoints that can be captured in the course of care
- Demand- willingness of patients to try a new approach
- Look for big signals (screening phase 2) with seamless confirmation
- Breast cancer was a great place to start

I-SPY 2 VISION

"Make new, better and more personalized treatments, available faster, at a time when patient's need them most"

- Better: Higher Distant Disease Free Survival AND less toxic
- Personalized: Matching patient's biology
- Faster: Use early endpoints; Continuous learning

I-SPY 2 : Saving Lives by Accelerating Learning

- Focus: Women with Stage 2/3 Breast Cancer at High Risk for Early Recurrence
  - Moving treatment earlier when a great response means CURE

- Maximize the ability to learn about response early in course of care
  - Early endpoint: complete pathologic response (pCR) and MRI tumor volume change
  - Net monetary benefit for achieving pCR: $160,000 (ICER -$45,000)

- Create an adaptive platform:
  - ***Efficient:*** One trial, 22 agents over 9 years
  - ***Flexible:*** ***S***tandard treatments have evolved
  - ***Learning System:*** Care and outcomes have improved at all sites
  - ***Collaborative:*** FDA, Advocates, Pharma, Clinicians/Researcher, imagers, IT scientists
  - ***Engine for Discovery:*** biomarker rich, qualifying biomarkers can be validated (RCB, ct DNA etc)

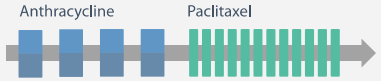
Greater Personalization: Driving toward optimal early endpoints

I-SPY 1

Measure outcomes by subtype

- Standardize imaging, pathology, biomarkers, data collection

GOAL: create collaborative framework



1

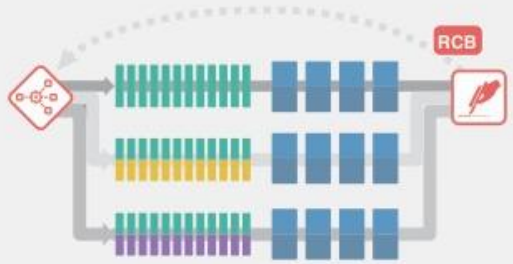
- Absence of tumor after neoadjuvant chemo (pCR) is optimal early endpoint
- for molecularly high risk disease
- Better by subtype

I-SPY 2

Adapt therapy within trial

- pCR regulatory endpoint (accelerated approval)
- Test multiple novel agents adaptively
- Operational efficiencies, platform trial, culture of innovation

GOAL: Increase pCR in each biomarker signature



2

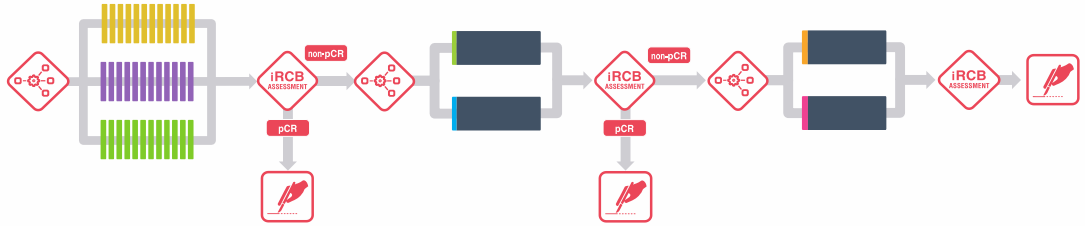
- pCR predicts DRFS HR 0.18 regardless of subtype, therapy
- RCB stratifies outcome
- MRI and biopsy predict pCR
- Many agents identified that improve subtype specific pCR
- Molecular markers better classifiers than receptors

I-SPY 2+

Adapt therapy within patients

- iRCB, Imaging as a regulatory endpoint for poor responders
- SMART approach
- Compare pathways vs receptors to select agents

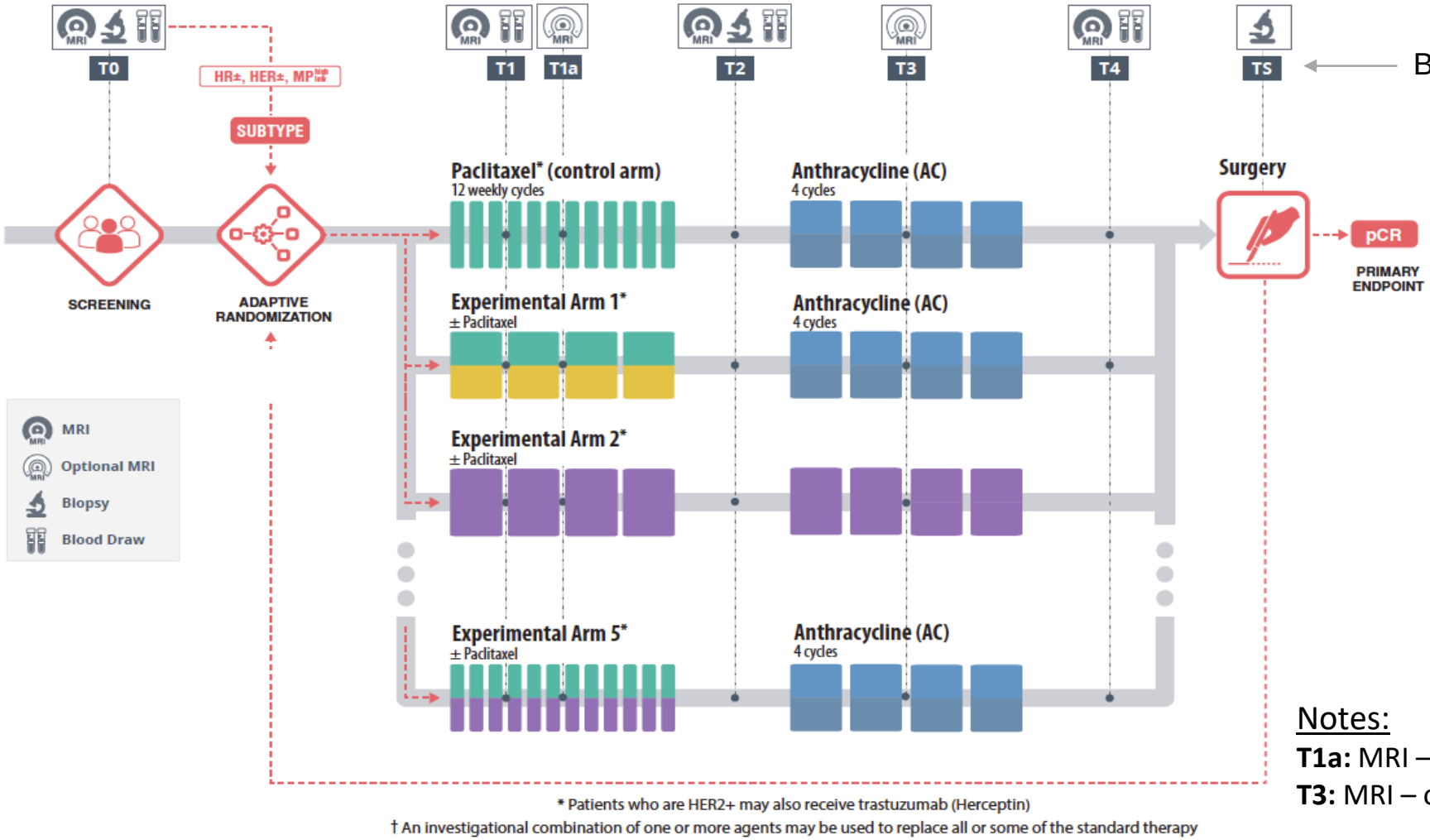
GOAL: Increase chance of pCR for each patient



2+

- Optimize pCR for each patient
- Stop at pCR, continue if not
- Accelerated approve for agents that generate optimal pCR rates
- Confirm DRFS at 3 years ≥92% for full approval

I-SPY 2 TRIAL Current Study Schema

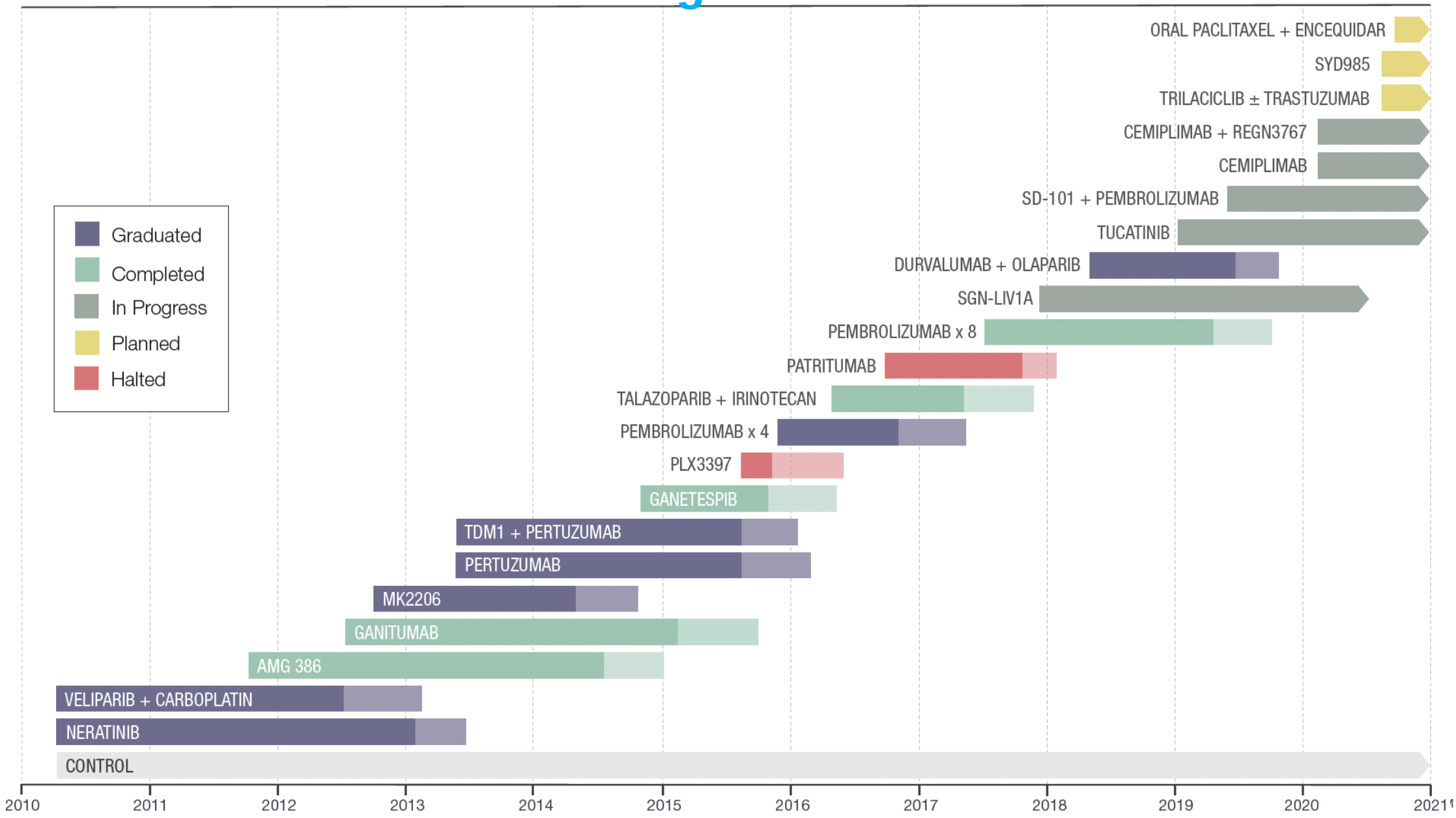


Notes:

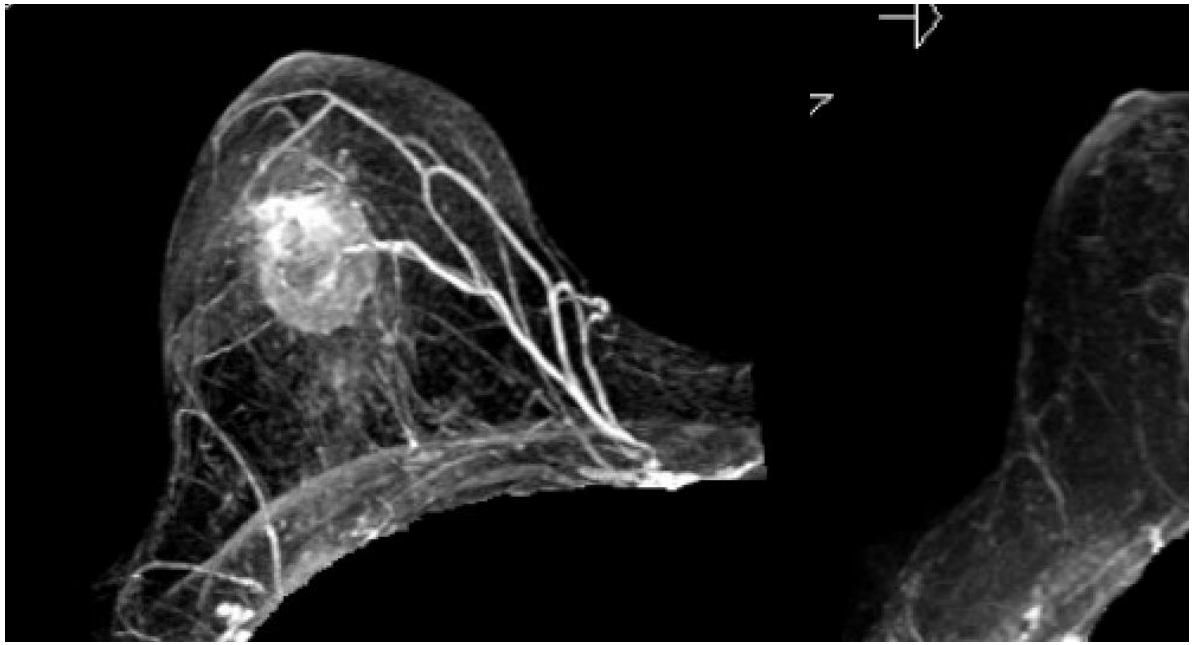
T1a: MRI – optional, physician discretion

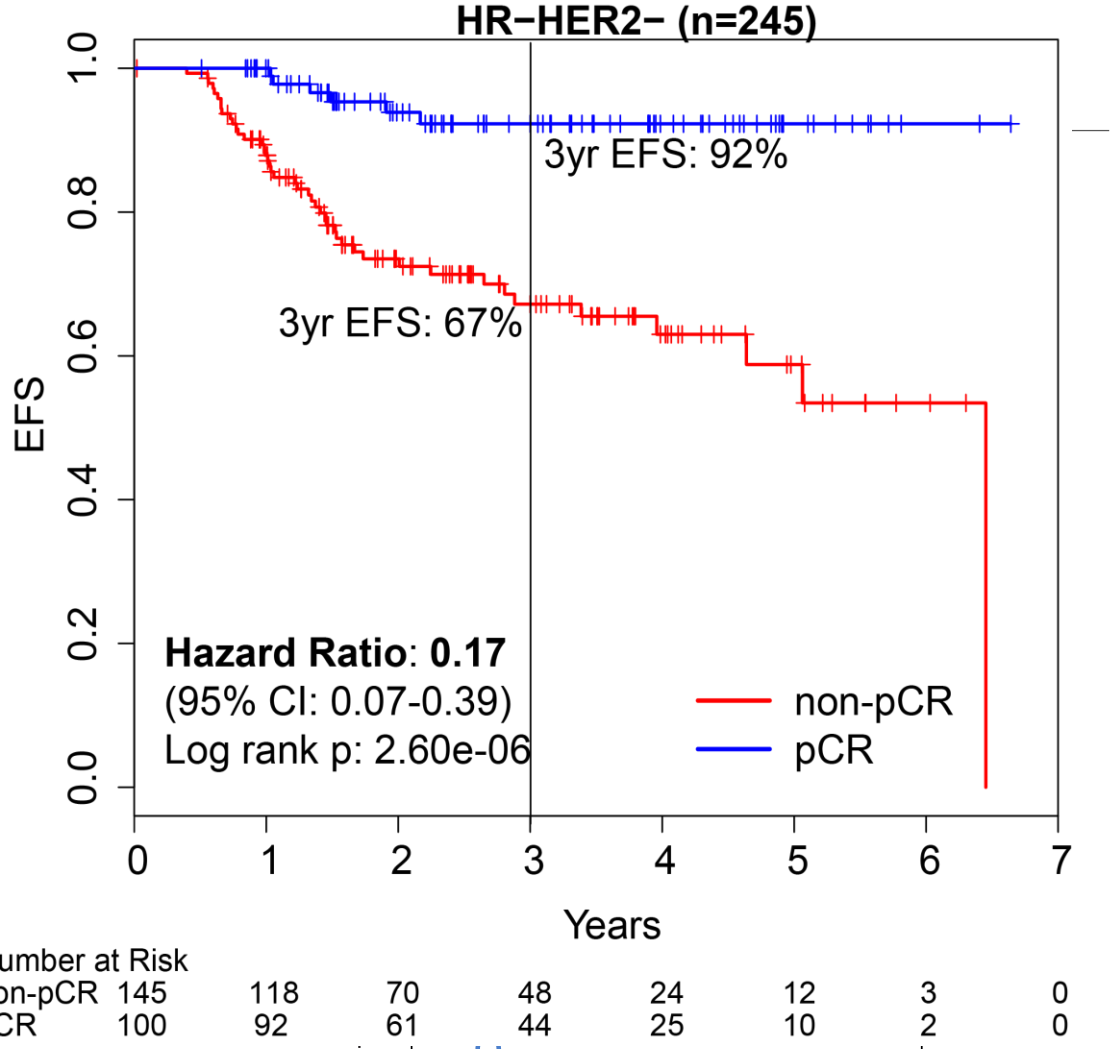
T3: MRI – only for patients with FTV<80%

I-SPY 2 Agent Timeline



I-SPY2: Early endpoint→ Pre
Event Free Survival for Patie





Yee et al 2020

Original Investigation

February 13, 2020

Effect of Pembrolizumab Plus Neoadjuvant Chemotherapy on Pathologic Complete Response in Women With Early-Stage Breast Cancer

An Analysis of the Ongoing Phase 2 Adaptively Randomized I-SPY2 Trial

Rita Nanda, MD[1]; Minetta C. Liu, MD[2]; Christina Yau, PhD[3]; et al

» Author Affiliations | Article Information

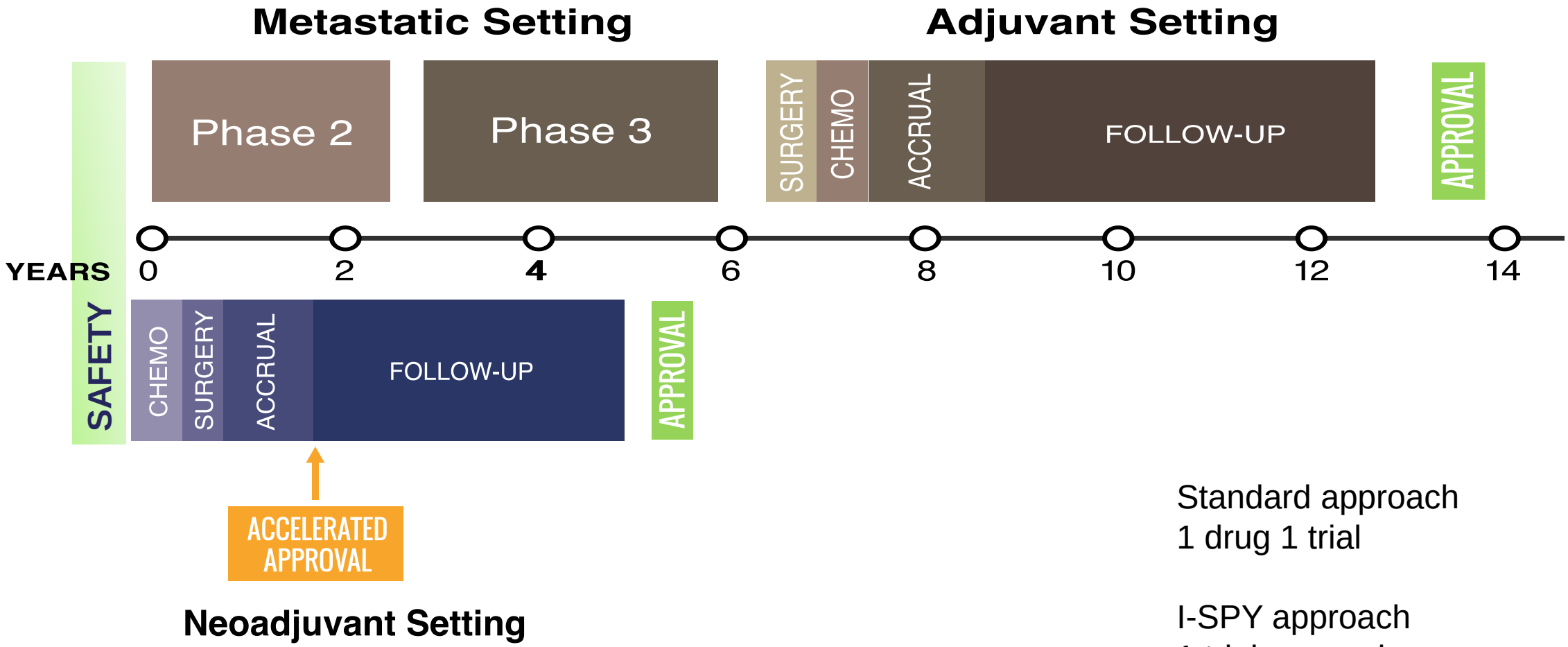
JAMA Oncol. 2020;6(5):676-684. doi:10.1001/jamaoncol.2019.6650

JAMA Oncology | Original Investigation

Correlation of Event-Free and Distant Recurrence–Free Survival With Individual-Level Pathologic Complete Response in Neoadjuvant Treatment of Stages 2 and 3 Breast Cancer

The I-SPY2 Adaptively Randomized Clinical Trial

Save Lives, Save Time, Save Resources



Standard approach
1 drug 1 trial

I-SPY approach
1 trial, many drugs

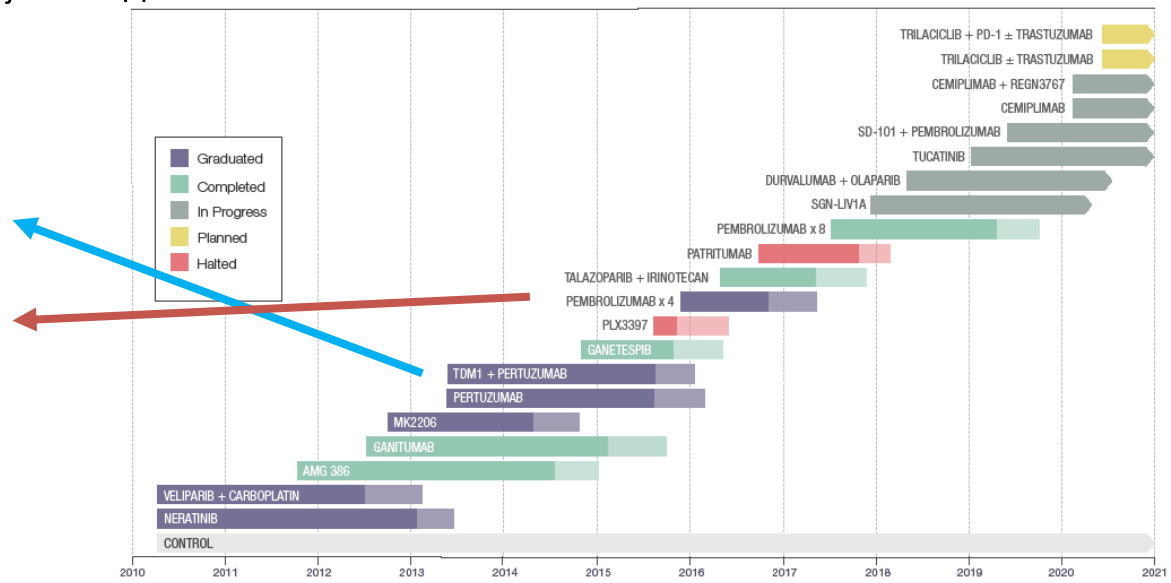
Accelerating Knowledge Turns

Time from first introduction in the metastatic (late stage) setting until an effective new drug is available in the high-risk early stage setting where it can save lives

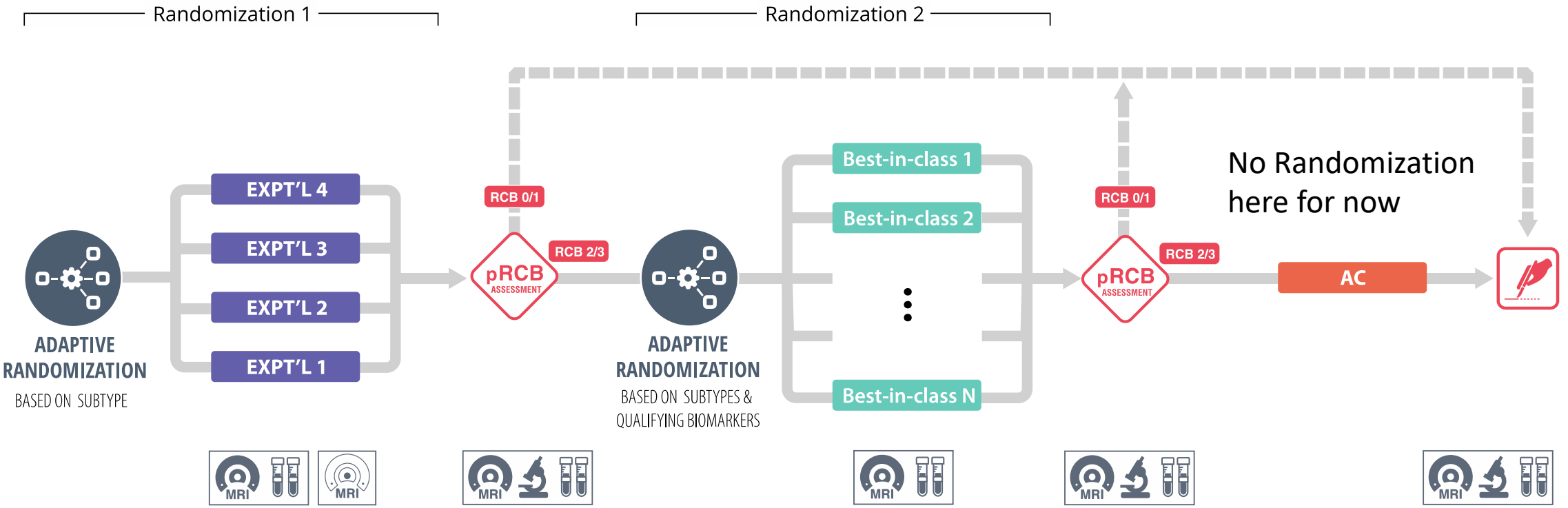
Time (years)	Number of patients	Neoadjuvant Approval
Herceptin: 16 years	>13,000*	No
Perjeta: 9 years (pCR*)	5.447	Yes
Pembroluzimab: 6 years	1,200	Yes
XX: 3 years	300	Yes

*pCR as accelerated endpoint enabled access 4 years ahead of the adjuvant APHINITY results

I SPY AGENT TIMELINE



I SPY 2.2: Getting Less Toxic New Therapies to Patients



A. Untested regimens

B. Subtype specific rescue

C. Eventually we will randomize here as well

Benefits of this approach

- Allows non-chemo regimens to start – there are plenty of exciting drugs in development
  - Why not start in the people who would benefit most?
- Moves toward goal of getting away from standard chemo: taxol and AC
  - We can predict whose tumor has gone away by 12 and 24 weeks, and continuously refine capability
- If first combination doesn't work
  - "rescue" is something patients can feel confident is highly likely to work - SOC option that fits the receptor subtype/biomarker signature for the individual patient's tumor
- Rank sequences (metrics) to favor least toxic, greatest healthcare value
  - Based on when the pCR is achieved, use PROs (Benefit Index: QALYs)
  - Less duration of therapy and avoiding additional blocks, esp AC has higher value
    - E.g. (%pCR Block A)* 100% +(%pCR Block B)* 80% + (%pCR Block C)*60%
- Single trial that integrates regulatory confirmation

I SPY will enable a Sea Change

- Goal: 90% of Patients to pCR without Standard Chemotherapy
- Targeted de-escalation and escalation of therapy based on response
- Improve survival AND decrease toxicity
- Approach in trials should mirror care

I-SPY 2 TRIAL Study Team

Working Group Chairs

PI:	Laura Esserman	**Operations:**	Angie DeMichele
PI:	Don Berry	**Biomarkers:**	Laura van 't Veer
Imaging:	Nola Hylton	**Pathology:**	Fraser Symmans
Agents:	Doug Yee	**Advocates:**	Jane Perlmutter
Safety:	Hope Rugo	**PRO/QOL:**	Michelle Melisko

Site PIs

Columbia:	Kevin Kalinsky	**UAB**:	Andres Forero-Torres
Denver:	Anthony Elias	**UChi**:	Rita Nanda
Gtown:	Claudine Isaacs	**UCSD**:	Anne Wallace
Loyola:	Kathy Albain	**UCSF**:	Jo Chien
Mayo:	Judy Boughey	**UMinn**:	Doug Yee
Moffitt:	Heather Han	**UPenn**:	Amy Clark
OHSU:	Kathleen Kemmer	**USC**:	Julie Lang
Swedish:	Erin Ellis	**Yale**:	Tara Sanft

Sponsor:

Quantum Leap Healthcare Collaborative

Dave Mandelkern, Nancy Lisser, Mike Bankert, Adam Asare, Smita Asare, Julie Sudduth-Klinger, Dan Dornbusch

Project Oversight:

Anna Barker/ASU, Gary Kelloff/NCI, Janet Woodcock/FDA, Richard Pazdur/FDA, Robert Becker/FDA, ShaAvhree Buckman/FDA,CDER, Steve Gutman, David Wholley/FNIH

Program Management Office

Executive Director: Smita Asare
Program Administration: Kat Steeg, Lorena Kanu, Julie LeDuc, Jill Parker, Melanie Hanson
Safety: Sausan Abouharb**,** Linda Doody, Monina Angeles, CCSA
Data Analysis & IT
Christina Yau, Adam Asare, Garry Peterson, Amy Wilson, Tim Fu
Operations Manager:
Ruby Singhrao
I-SPY 2 Biomarkers/Specimens:
Lamorna Brown-Swigart, Gillian Hirst, Denise Wolf, Chip Petricoin, Julie Wulfkuhle
I-SPY Imaging Lab:
Jessica Gibbs, Melanie Regan
Business Development:
Julie Sudduth-Klinger, Dan Dornbusch
Grants:
Jeff Matthews

Thank you to the remarkable patients and families, and all of the investigators, staff, our DSMB and advocates for supporting the trial

Many pharma, biotech, and diagnostic companies

A Personalized Approach for Breast Cancer

Do more for the people with higher risk:

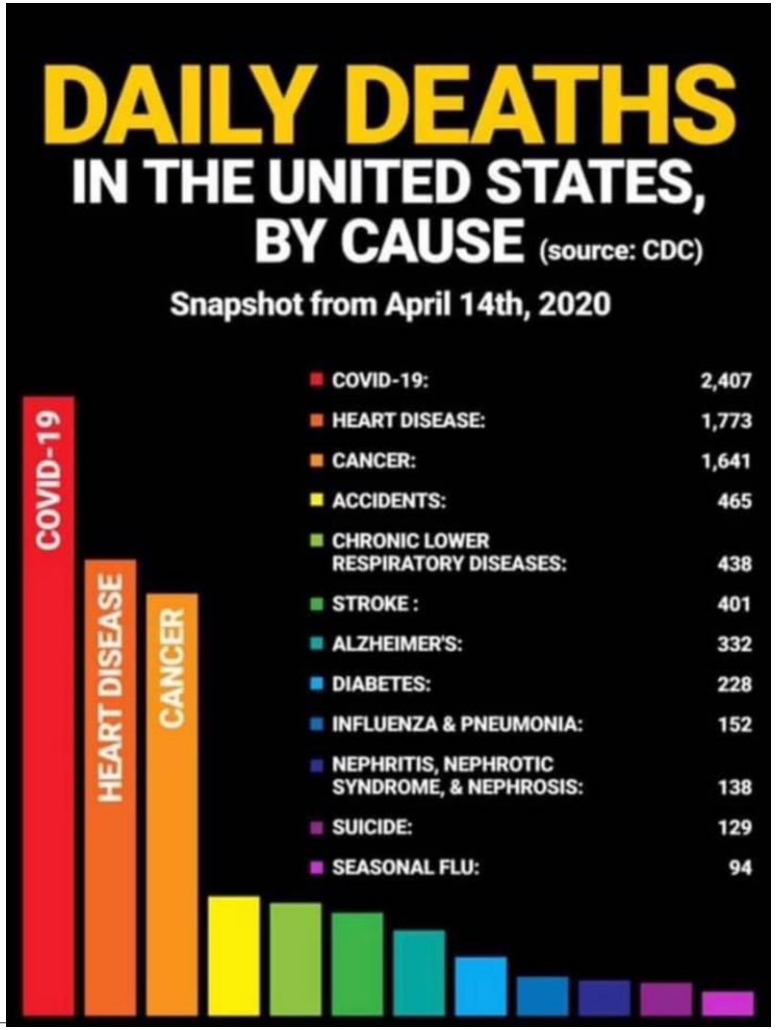
De-escalate when treatments are effective: LESS TOXIC

And escalate when treatments are not effective: SAVE LIVES

This can be accomplished if we have the tools and the framework to know the difference

With COVID, there is an Even Greater Urgency

- The COVID 19 pandemic is a crisis primarily because of the pulmonary toxicity and high associated mortality
  - for a minority of those infected
  - Like cancer, everyone does not have a lethal case
- Solving this problem is critical for SARS-COV2 and other future viruses
- We must prioritize finding high impact treatments to reduce mortality and time on ventilators
  - Independent of vaccine efforts
- The Economy will not recover until we solve this problem
- Every one of us could wind up in the ICU . . .



What is the fastest way forward for those critically ill?

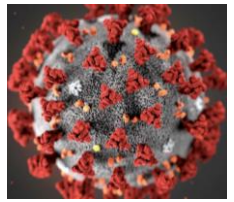
- A pragmatic, real world evidence based adaptive platform trial/learning system
  - Find agents with a **big** impact : ***speed*** time to recovery, drop mortality
  - Find FAST what does not have an impact

- Harness the infrastructure built for the I-SPY 2 TRIAL: Human/Intellectual Capital
  - Best and brightest in ICU medicine, drug development: Cancer and COVID
  - Culture of innovation and collaboration
  - Process efficiencies
  - Partnership with FDA
  - Precompetitive collaboration with industry (pharma/biotech/diagnostics/information technology)

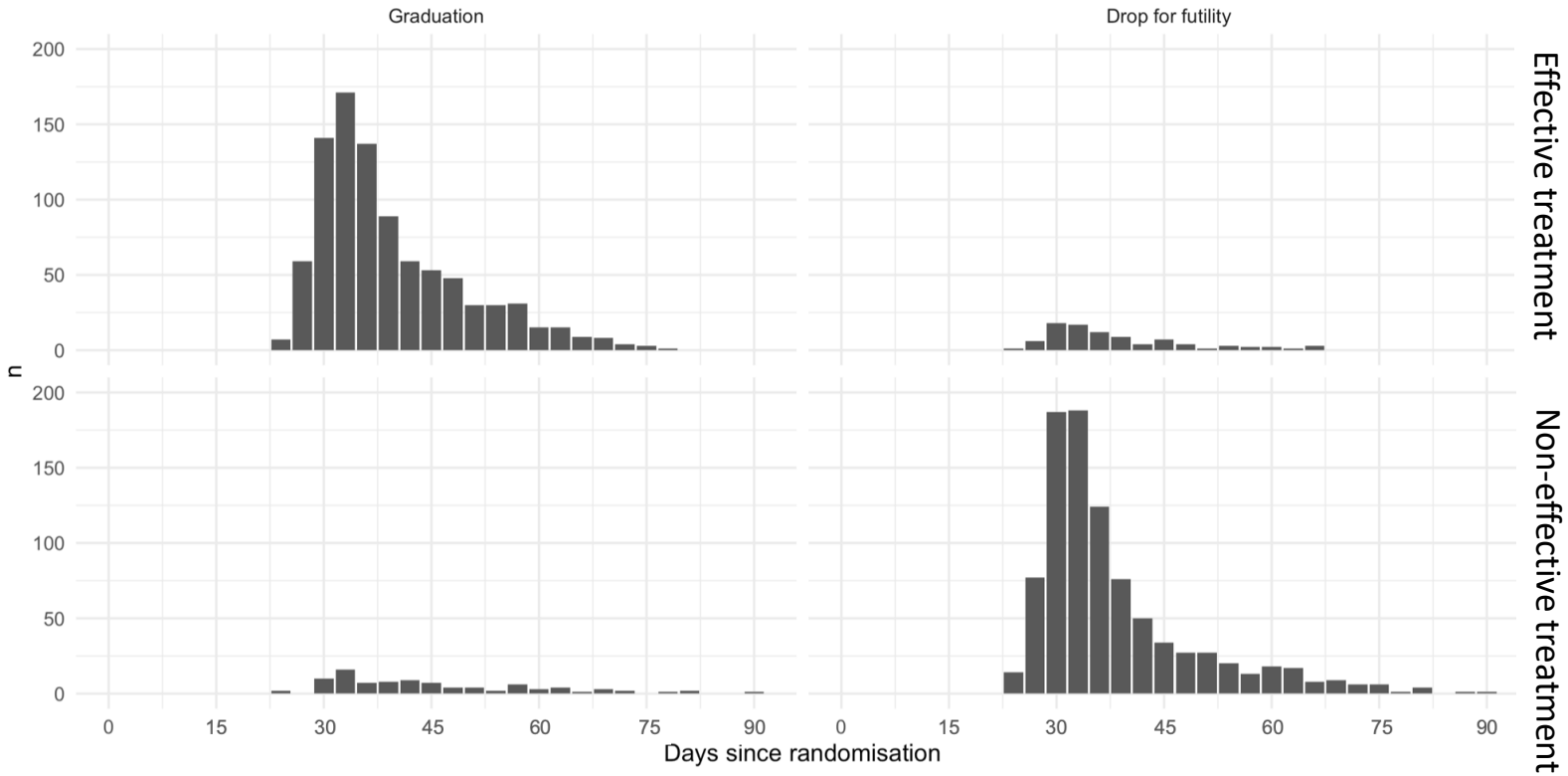
- Engage investigators to build a learning engine that serves patients, *science, learning- *biologic/omics, clinical, management, and regulatory*

The I-SPY COVID TRIAL

Investigation of Serial studies to Predict Your Therapeutic Response with biomarker Integration and Adaptive Learning

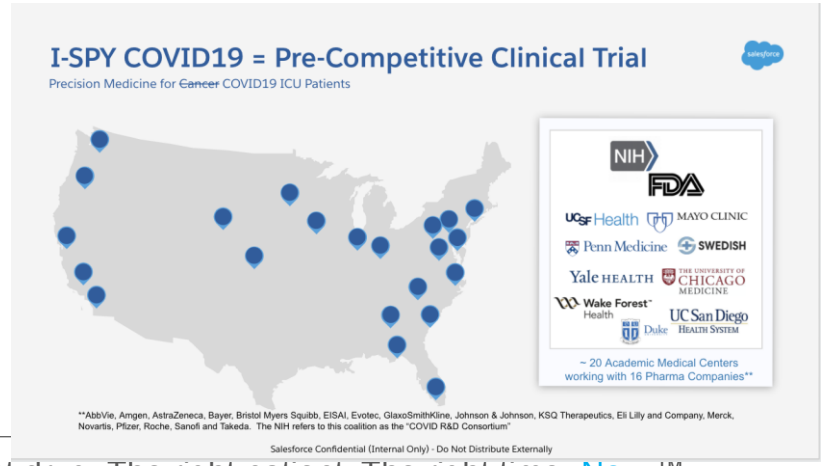


Time to Decision for Graduation or Futility Drop, Accrual = 50 per week



How Does the Trial Work?
Probability distribution for time to decision for effective candidates

This shows that even with 4 agents running simultaneously, a highly effective agent would be recognized and graduate within about 5 weeks. Likewise, most agents would drop for futility in 5 weeks.



In months, not years

Working together, 15-20 sites could test 10 agents in 4 months

FIND 3-4 agents, that dramatically reduce death/time on ventilators

Targeted Immune modulators and antivirals

Working groups

Separate but Aligned

- Operations
- Agents
- Biomarkers: critical opportunity to learn
- Safety
- Stats
- Project Management
- (DMC)

(I SPY 2: Imaging, Pathology)

Shared

- Information Technology
  - clinical and research data. Including Institute for Systems Biology
- IRB
  - Central IRB is Wake Forrest
- Advocates

Strategy for Agent prioritization

1. Scientific validity:

   scientific rationale for efficacy in the setting of pulmonary distress from COVID.

   Endothelial cell repair, immune modulation, complement pathway, anti-virals

2. Ability to scale immediately or within 3-4 months (for global distribution)

   example of remdesivir scarcity is a lesson- and we should prioritize testing of agents that can be deployed now- if none work, obviously we will move to less available agents)

3. Willingness of the manufacturer to partner, be nimble, and ship drug

4. Ease of administration of the drug

Compound Prioritization Process Overview

- A standing committee, the Agents Working Group, of the I-SPY COVID Trial evaluate the safety & potential efficacy of numerous agents – both repurposed and novel drugs.
- No open portal submission but have received significant interest
- 6 sources of compounds:
  - Initial agents were proposed by the COVID R&D Alliance
  - Recently, other large pharma and major biotech companies have submitted compounds for evaluation
  - KOLs, investigators and academia
  - Venture capitalists and investors
  - Disease advocacy organizations but not directly from patients
  - Small biotechs including from Australia and Greece
  - Defense Threat Reduction Agency (DTRA), Department of Defense
  - Operation Warp Speed

COVID R&D was established in mid March to accelerate the development of therapies for COVID-19

Three of first 6 agents have come from this consortium

Context

Industry R&D leaders believe that **everything should be done to tackle the COVID-19 humanitarian challenge**

Principles of consortium

Accelerate new Covid-19 therapies and vaccines and **remain agnostic to consideration for market potential**

Group relinquishes rights to intellectual property or contractual alignment for support it provides to independent companies

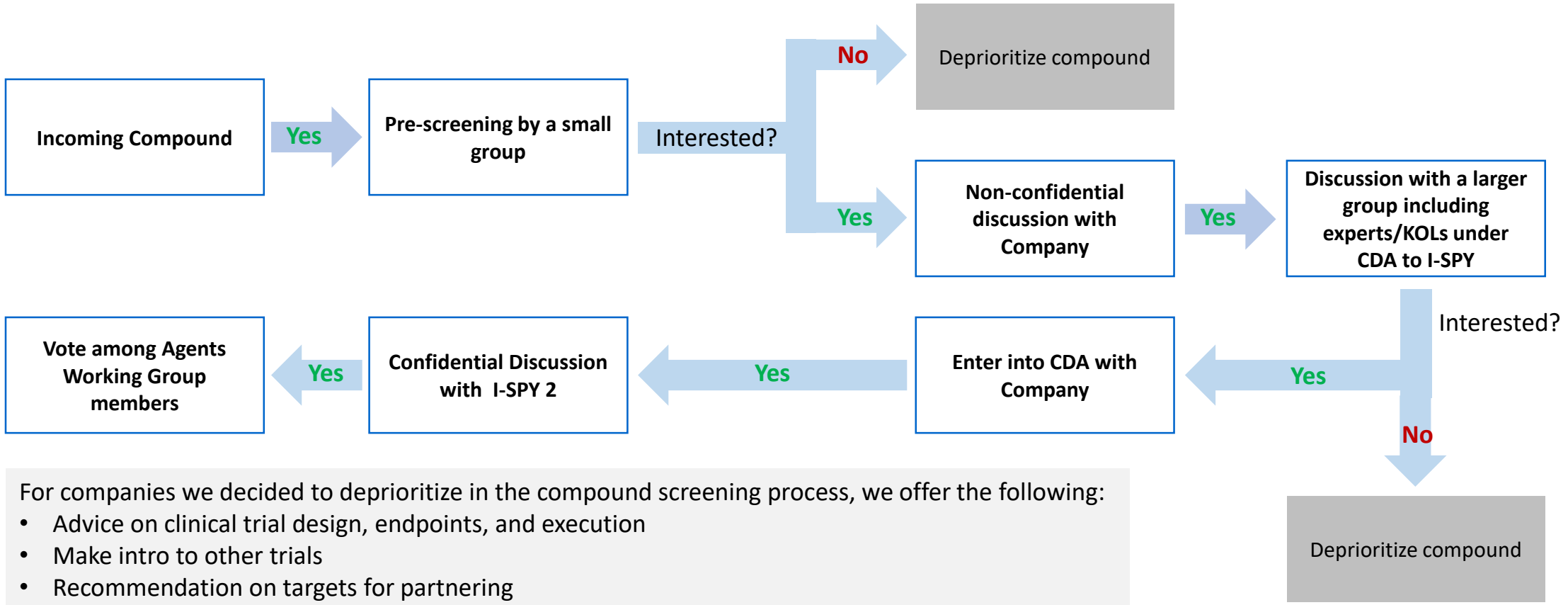
Approach in agile manner with **focus on eliminating all bureaucratic and technical barriers**

Focus on filling gaps not adequately filled by other initiatives and where we are uniquely suited to address

Participants

Takeda, Novartis, Bayer, Alnylam, 5AM Ventures, Amgen, Gilead, evotec, Johnson & Johnson, gsk, Roche, AstraZeneca, BioCentury, Arbutus Biopharma, Versant Ventures, Pfizer, Bristol Myers Squibb, abbvie, Lilly, Allergan, Eisai

Key Steps in Compound Screening



For companies we decided to deprioritize in the compound screening process, we offer the following:

- Advice on clinical trial design, endpoints, and execution
- Make intro to other trials
- Recommendation on targets for partnering
- Recommendation on potential source of capital

I-SPY COVID Agents

- Cenicriviroc, CCR2/5 Inhibitor (Allergan/Abbvie)
- Firazyr (Icatibant), Bradykinin B2 Agonist (Takeda)
- Otezla (Apremilast), PDE4 inhibitor (Amgen)
- Razoprotafib, Tie2 activation (Aerpio Pharmaceuticals)
- Pulmozyme, inhaled DNAse (Roche/Genentech)

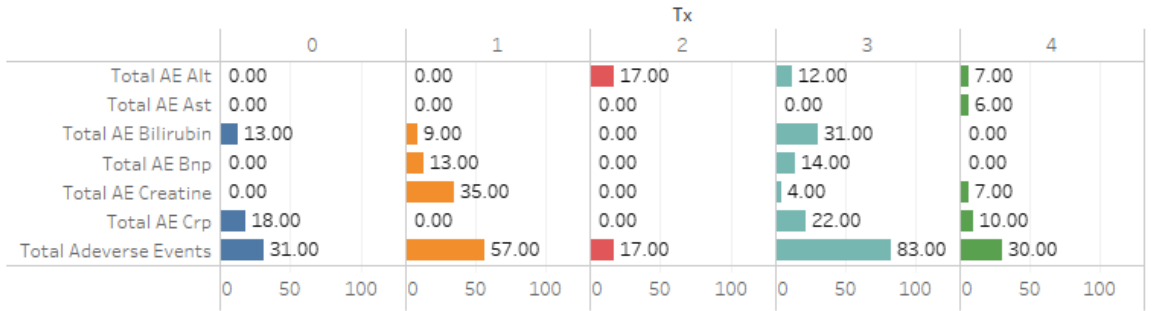
Appendices in preparation for several others

Check List as a standard: Integrates with tools that integrate in HER
CMS could pay for completion of a daily check list

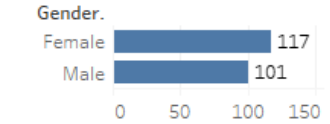
- COVID WHO Scale (FDA standard)
  - If level 6/7 (intubation), standard ventilator settings:
    - paO2/Fio2 OR sp02
    - use of proning
    - Tidal volume
    - Volume control (plateau pressure)
  - If level 7
    - Vasopressors
    - ECMO
    - Dialysis (Kidney Replacement Therapy)
- Major Adverse Event over previous 24 hours
  - MI
  - Pneumothorax
  - PE
  - Stroke
  - Dialysis (if not ventilated)
- Daily
  - Off Study drug (reason)
  - Continue study drug
  - Dose modification. (reason)
  - Dose Hold (reason)
- Labs/ site reference range
  - Creatinine, AST, ALT, Bilirubin, CBC/ Differential, PT, PTT, D-Dimer, CRP, BNP, troponin
  - directly pulled from EMR and
  - programmed with Reference Ranges for automated adverse event grading)
- Short list of concomitant medications
  - Steroids
  - Convalescent plasma
  - Inhaled NO (nitric oxide)
  - Flolan
  - Vasopressors (1-3)
  - Antibiotics (1-3)

Adverse Event Analysis

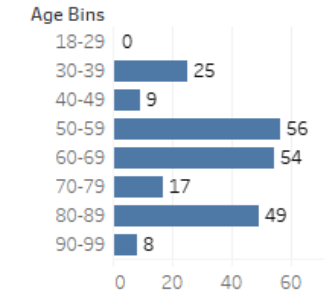
Adverse Event Type



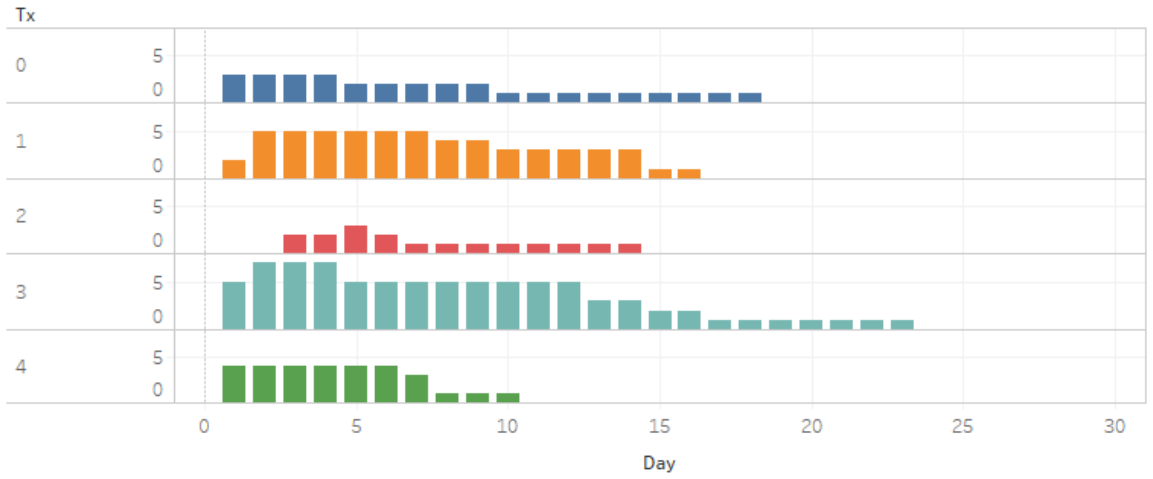
Adverse Events Gender



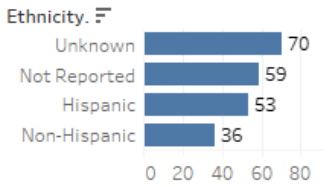
Adverse Events Age



Adverse Events by Day



Adverse Events Ethnicity



THE ONESOURCE SOLUTION

Why do we need better systems?

"There are so many people working so hard and achieving so little"
– Andy Grove

Commentary

July 27, 2005

Efficiency in the Health Care Industries A View From the Outside

Andrew S. Grove, PhD

Author Affiliations Article Information

JAMA. 2005;294(4):490-492. doi:10.1001/jama.294.4.490

The health science/health care industry and the microchip industry are similar in some important ways: both are populated by extremely dedicated and well-trained individuals, both are based on science, and both are striving to put to use the result of this science. But there is a major difference between them, with a wide disparity in the efficiency with which results are developed and then turned into widely

Source Data Capture from EHRs to Improve Quality and Efficiency

2019

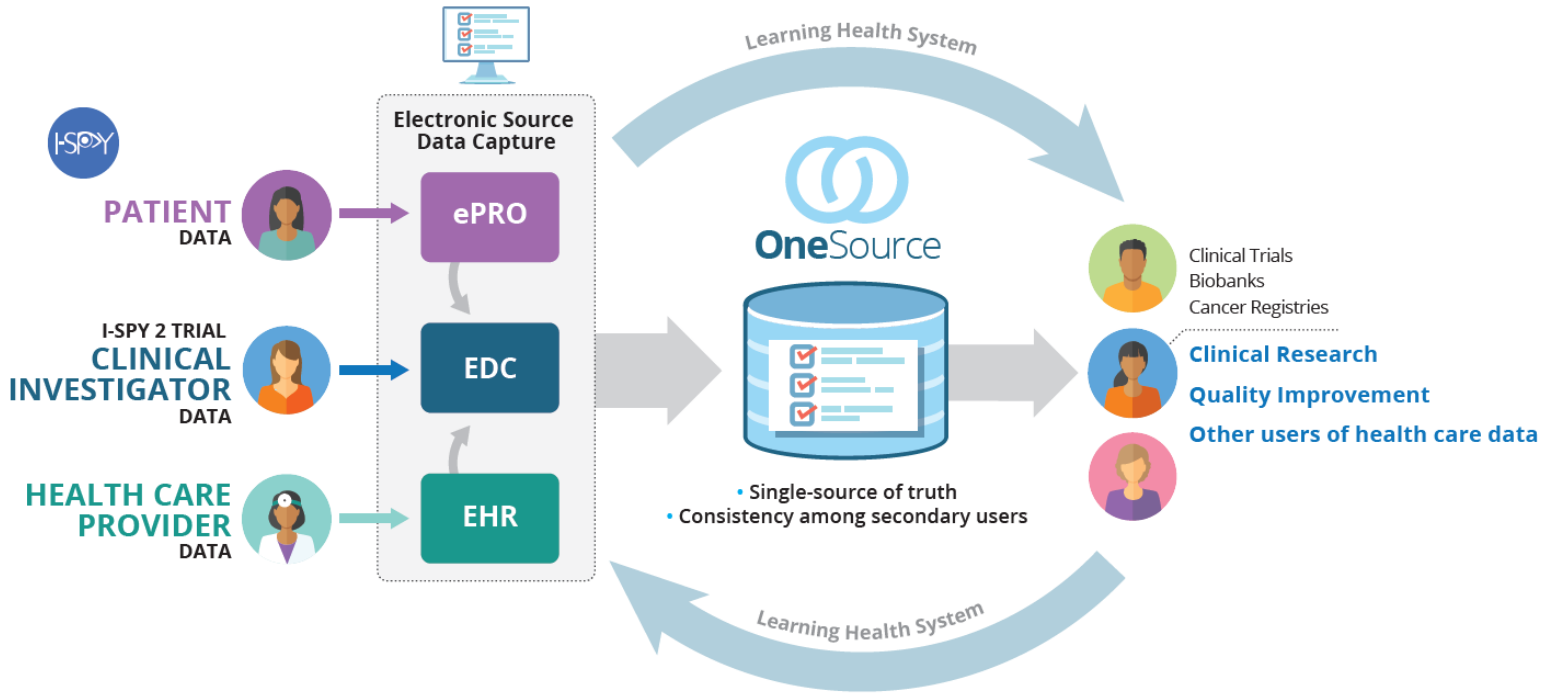
U.S. FOOD & DRUG ADMINISTRATION

Source Data Capture from EHRs: Using Standardized Clinical Research Data

Mitra Rocca[1], Adam Asare[2,3], Laura Esserman[2], Sue Dubman[2], Gideon Gordon[1]

[1]Center for Drug Evaluation and Research, Food and Drug Administration
[2]University of California - San Francisco (UCSF)
[3] Quantum Leap Healthcare Collaborative

This project was funded by the Office of the Secretary Patient-Centered Outcomes Research Trust Fund (PCORTF) under the Intra-Departmental Delegation of Authority Request #075-X-0145-000 with the FDA.



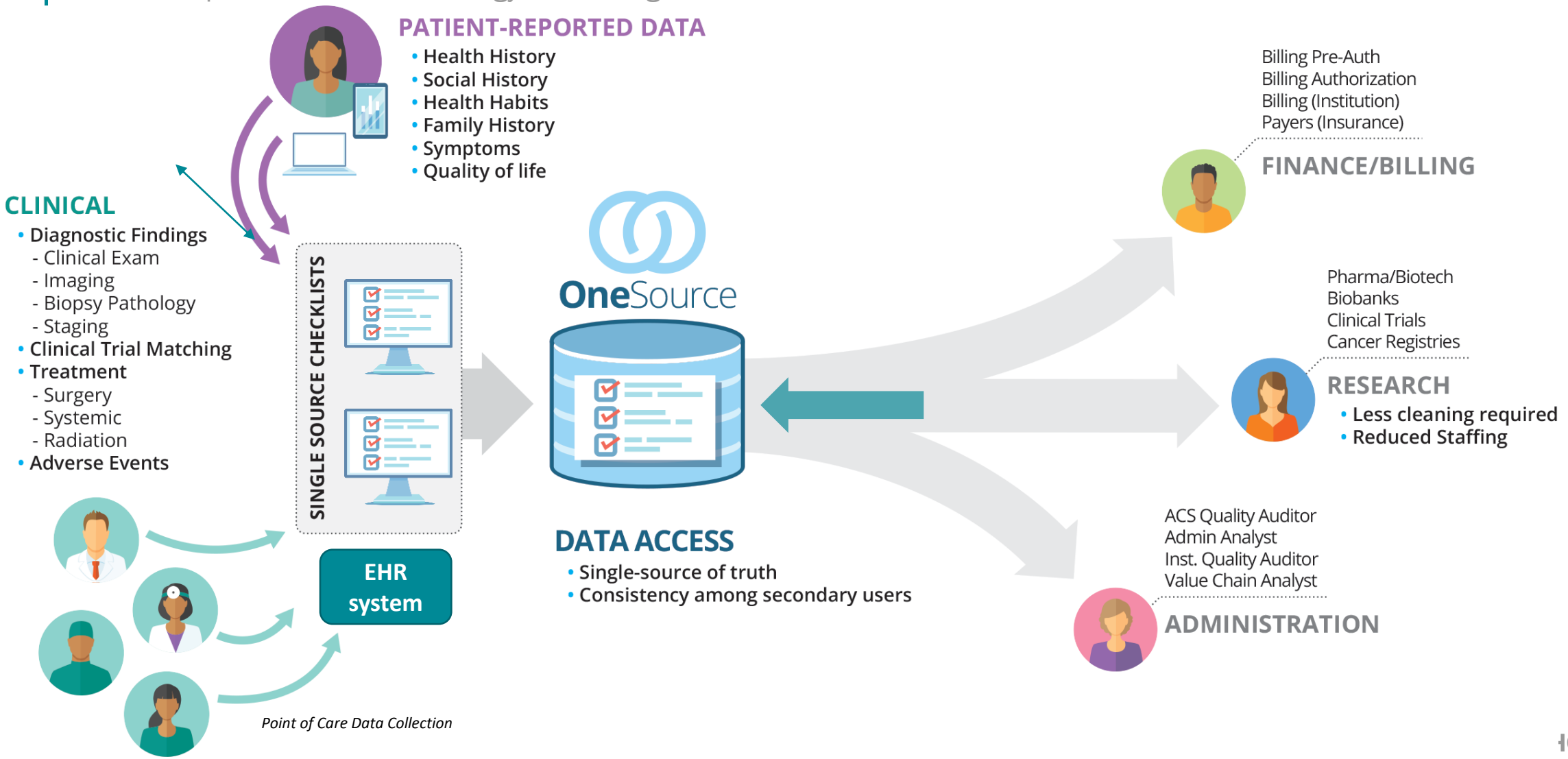
ePRO: Electronic Patient Reported Outcomes
EDC: Electronic Data Capture
EHR : Electronic Health Record

CRFs ask for data that is not in or easy to find in the notes

QL HC Quantum Leap Healthcare Collaborative

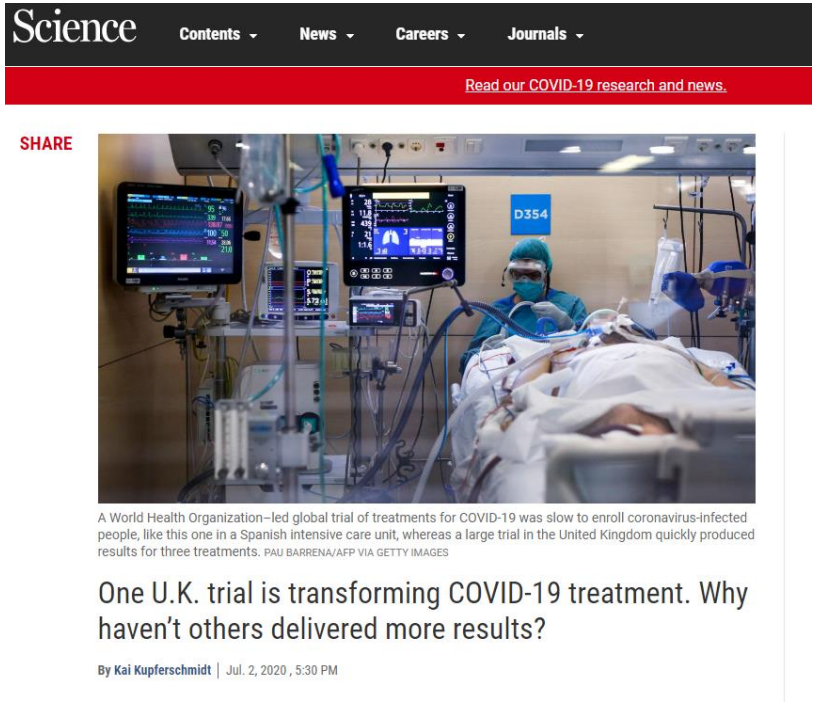
Structured data as “source”

Enable improvements in technology with changes to clinical workflows



Evidence Generation Landscape (Interventional Studies)

- Evidence generation for COVID
  - 1,200 trials initiated
  - Limited results to inform standard of care – positive (remdesivir, dexamethasone) and negative (hydroxychloroquine, lopinavir-ritonavir)
  - Over 99% of the 4.5 million Americans infected unable to participate in trials
- Efforts to address outstanding clinical questions
  - NIH ACTIV Partnership
  - Other networks
  - Practical master protocol trials



See Last Slide for References

Practical Trial Network Goals

What | Expansion of existing COVID-19 practical trial networks to develop meaningful evidence faster, by engaging sites that would otherwise not participate in trials

When | Fall 2020

Duke-Margolis Work on Practical COVID-19 RCTs

- Convening series with Master Protocol investigators, Regulators, Health Systems, and Tech Vendors

- Takeaways—
  - Transparent compound selection
  - Multiple Tx and Adaptable Trials
  - Randomization at scale
  - Streamlined data collection and alignment on endpoints

I-SPY COVID

Opportunity to enable trial participation: 20-30% across US

- Standardize data collection tools (foundation for learning healthcare system with wide dissemination)
  - Check list facilitates/standardizes clinical assessment and management, is also trial data
  - Compensation can be for completion of checklist, checklist automates a note
  - Use of QI overlay system that is nimble accelerates learning across pandemic, serious disease
  - Lab data/lab chain of custody/ reference range standards
- Set up a central coordinator hub, not to monitor, but to facilitate care and trials
  - Central pharmacy function could enable non academic sites to participate
  - Bring GCP compliance capability to smaller facilities
    - Site training, site set up
- Central coordinators (that are part of the hub) work to
  - Consent patients (docusign CFR part 11 compliant/FDA tokens)
  - Making sure orders are in and correct
  - Facilitating lab collections
  - Coordinating with local pharmacies for training
  - Coordinating with central pharmacy to make sure the right drug is delivered (12 hrs?)

Strategy for Agent prioritization

1. Scientific validity:

   scientific rationale for efficacy in the setting of pulmonary distress from COVID. The order we put agents in will depend on the answers below.

2. Ability to scale immediately or within 3-4 months (for global distribution)

   example of remdesivir scarcity is a lesson- and we should prioritize testing of agents that can be deployed now- if none work, obviously we will move to less available agents)

3. Willingness of the manufacturer to partner, be nimble, and ship drug

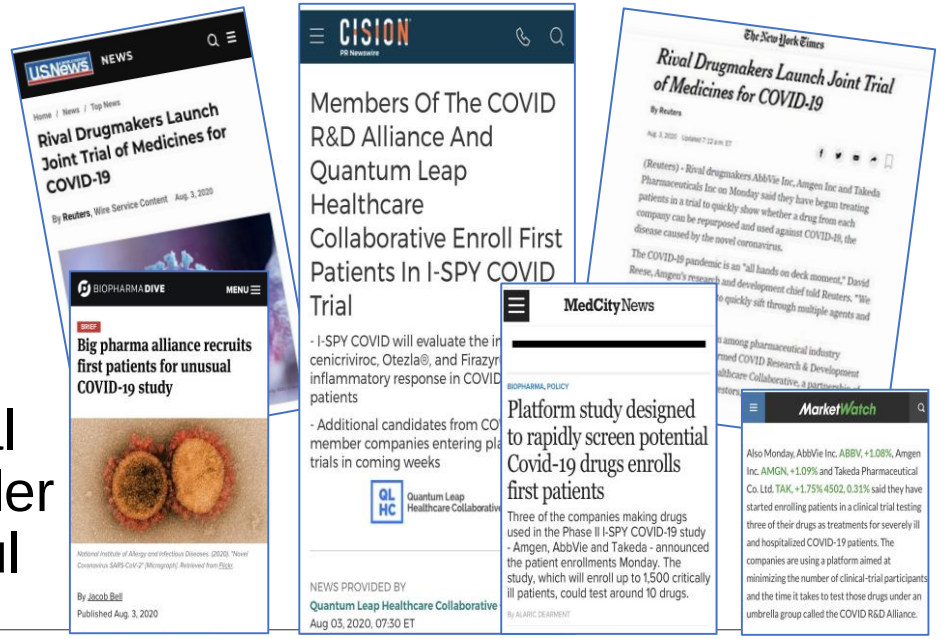
4. Ease of administration of the drug

What do these agents do?

- Immunomodulators- turning down the immune response (opposite of cancer), anti-inflamatory
  - Otezla (apremilast), Icatibant, celebrex
- Repairing the cells that are attacked: Endothelial cell, clotting system
  - Razoprotofib, Pulmozyme, Complement drugs, BTK inhibitors
- Antivirals
  - Neutralizing antibodies
  - Hyperimmune serum: passive immunotherapy from recovered patients

I SPY COVID is OPEN!!!!!

- First site/ first patient in Thursday July 30 2020
- 6 sites with IRB approval – 4 more next week
- 10 patients enrolled, 20+ in observational cohort
- New sites identified
- Many collaborators
  - PIs: Carolyn Calfee, Kathleen Liu
  - Investigators: Nuala Meyer, Derek Russels, Sheetal Gandotra, Michelle Gong, Mark Moss, Jeremy Beitler , Ellen Burnham, Rada Savic, Paul Volberding, Paul Henderson, Michael Matthay, Clark Files, Karl Thomas and many others



Approach to Solving Clinical Problems with Serious Morbidity, Mortality

- Pre-competitive consortium with common purpose
  - FDA, Academics, Community Hospitals, Industry, Advocates, Investigators
- Efficient: Screening many NEW promising agents
- Look for big impact
  - Fail fast
  - Find winners FAST TO SAVE PEOPLES' LIVES!!!!!
- Replication of the process from Breast Cancer to COVID shows scalability
  - Entire trial process replicated in 8 weeks
    - Consortium/ master protocol/ trial specific data checklists with embedded structure and analytics/ agent selection, ratification, trial "arm"/approval/engagement of investigators and clinicians
    - Entire community across many disciplines working with energy, urgency and purpose
  - 6 agents already approved ready to test, many more in the pipeline