SWOG and the National Clinical Trials Network: A Vision for Optimizing Patient Outcomes

Lois O'Grady Lectureship

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Charles D. Blanke, MD, FASCO
Group Chair

DISCLOSURES

NONE

SWOG, the NCTN, and Optimizing Outcomes

- The SWOG Cancer Research Network as a model for the cooperative groups: Background, organization, and functions
- NCI National Clinical Trials Network: Structure and functions
- Conclusions and future directions

Who We Are/What We Do

- Major part of the U.S. publicly-funded cancer research infrastructure
- 1 of 4 adult cooperative oncology research groups in the NCI National Clinical Trials Network (NCTN)
  - SWOG
  - ECOG-ACRIN
  - NRG (NSABP, RTOG, GOG)
  - Alliance (CALGB, ACOSOG, NCCTG)
- We primarily design and conduct multi-institution cancer trials
  - And do data aggregation/analyses, etc.

Our Members

- Network of 1,200+ sites, including:
  - 33 NCI-designated cancer centers
  - 14 NCTN Lead Academic Participating Sites (LAPS)
  - 800+ NCI Community Oncology Research Program (NCORP) sites
  - 27 Specialized Programs of Research Excellence (SPORE)
  - Modestly extensive Canadian collaborations
  - Multiple other member sites and collaborations outside US
- Members included:
  - 6,000+ researchers and clinicians
  - 7,000+ research nurses, clinical research associates, patient advocates and others

SWOG Impact

- 215,000+ patients enrolled
- 1,300+ trials opened
- 15 drugs approved by FDA
  - 2 drugs off market due to safety or efficacy
- 100+ changes to standard of care
- 800,000+ bio-samples banked
- Database holding 62 years of trial information

SWOG Research Committees

NCTN

- Breast
- Rare Cancers
- Gastrointestinal
- Genitourinary
- Leukemia
- Lung
- Lymphoma
- Melanoma
- Myeloma

NCORP

- Cancer Care Delivery
- Palliative/End of Life Care
- Prevention & Epidemiology
- Symptom Control & Quality of Life
- Survivorship

SWOG Research Support Committees

- Patient Advocacy Committee
- Adolescent & Young Adult Committee
- Digital Engagement Committee
- Recruitment & Retention Committee
- Pharmaceutical Sciences Committee

MORE SWOG IMPACT:
*>3.34 million years of life saved, at a cost of $125 per life-year**

*SWOG-only; analysis pending for entire NCTN

Unger JAMA Oncol 2017

NCTN: Background

- 1912 - Congress establishes Public Health Service (PHS)
- 1937 - Congress establishes National Cancer Institute (NCI) within PHS
- 1948 - Congress establishes National Institutes of Health (NIH)
- 1953 - James Holland begins trials in acute leukemia at NCI

Courtesy Dr. Rich Schilsky

NCTN: Background (cont.)

- 1955-6: Senate Appropriations Committee instructs NCI to establish “Cooperative System”
- Three groups established:
  - Acute Leukemia Group A — Joseph Burchenal
    - Became Children’s Cancer Study Group
  - Acute Leukemia Group B — Emil Frei
    - Became CALGB
  - Eastern Solid Tumor Group — Gordon Zubrod
    - Became ECOG-ACRIN

Courtesy Dr. Rich Schilsky

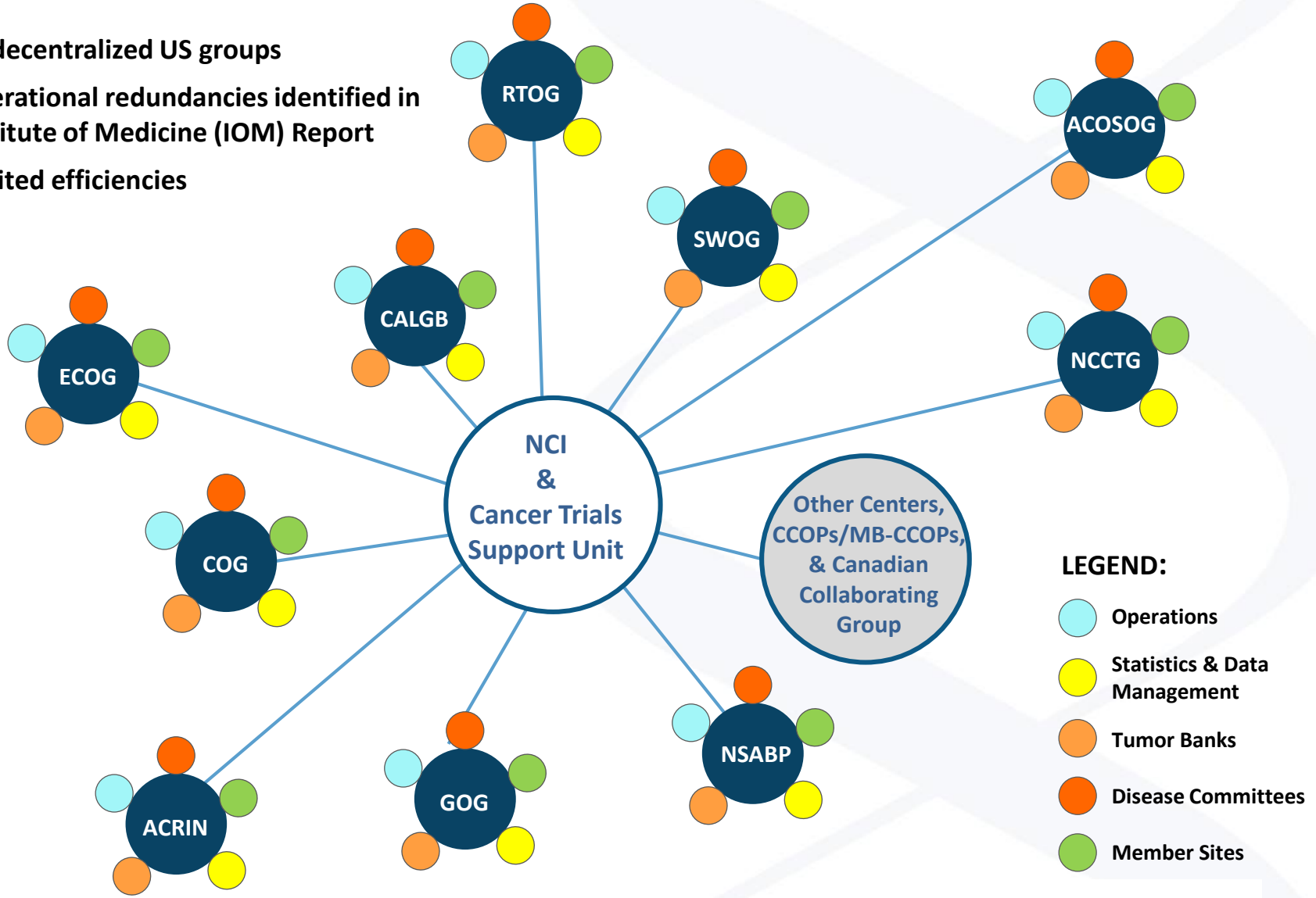
Goals of Therapeutic Clinical Trials: Sponsorship

Pharma	Federal
Drug Registration	Optimize Treatment
Label Extension	Label Extension
Expand Market Share	Create New Knowledge
Create Shareholder Value	Improve Public Health

Adapted Dr. Rich Schilsky

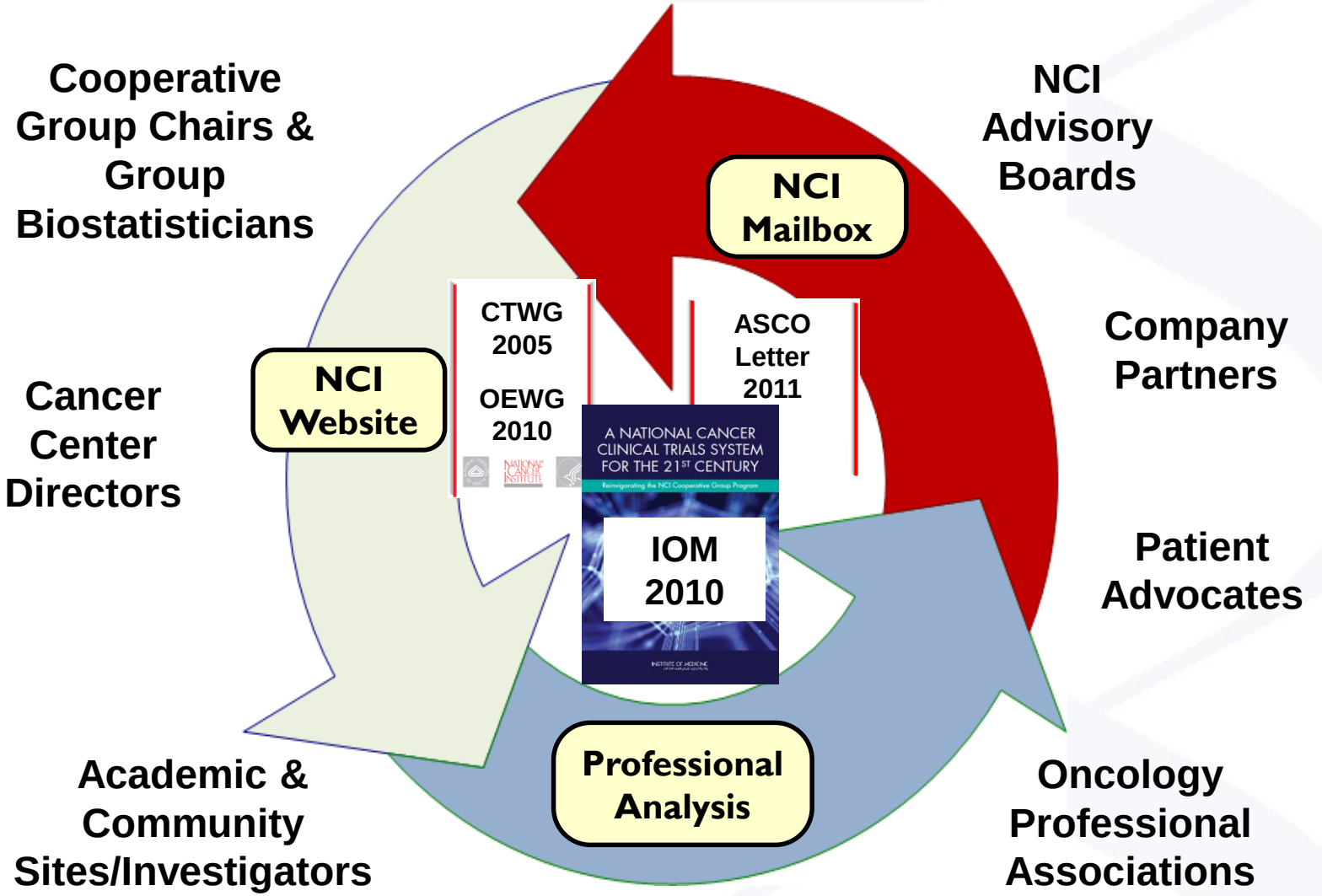
Structure of Clinical Trials Program Prior to NCTN *(Former Cooperative Group Program)*

- 10 decentralized US groups
- Operational redundancies identified in Institute of Medicine (IOM) Report
- Limited efficiencies

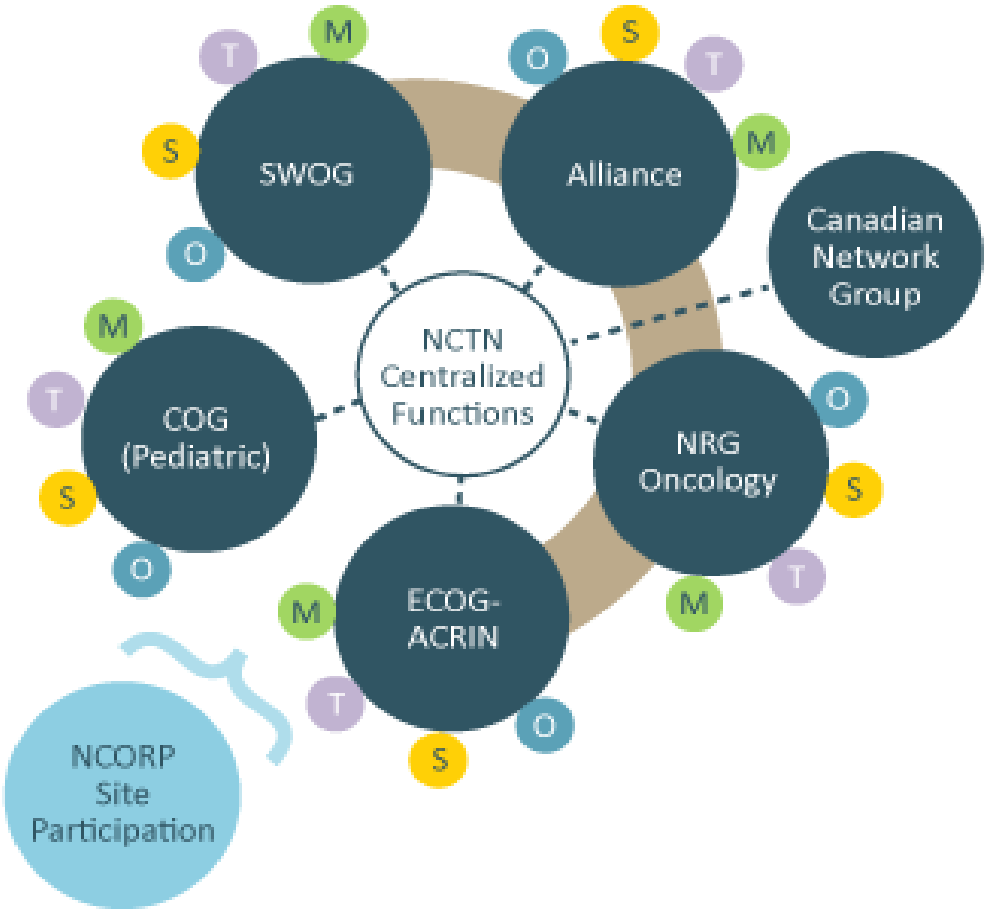


Courtesy Dr. Meg Mooney

Extensive Review & Stakeholder Input on Revising NCI's Late-Phase Clinical Trials System in 2010-2011



NCI National Clinical Trials Network Structure



www.cancer.gov

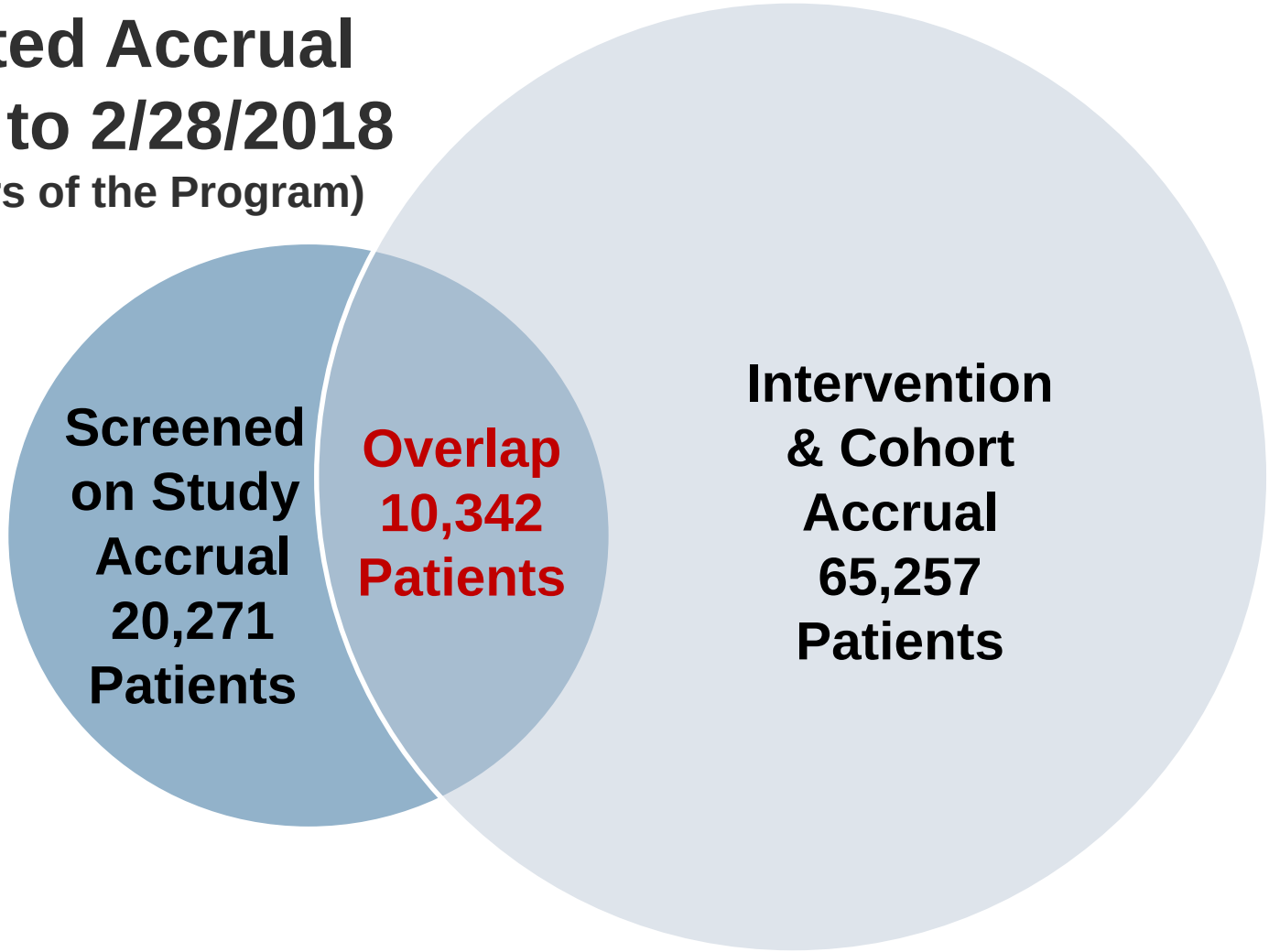
Early Successes for the NCTN

- Opening of large umbrella trials with national catchment areas
- Opening of multi-modality and non-drug trials
- Successful combination therapy trials (including chemorx + immuno)
- New initiatives
  - NCTN and NCORP Data Archives
  - Navigator Biospecimen Access Program

Adapted Meg Mooney

NCTN Program Estimated Accrual 3/1/2014 to 2/28/2018

(First 4 Years of the Program)



Total Enrollments (Screened on Study & Intervention) = 85,528
Total Number of Unique Patients = 75,186

Courtesy Meg Mooney[5]

Why I am Here: How Publicly Funded Research Optimizes Patient Outcomes

- Can study less expensive treatment options
- Can test multi-modality therapies
- Can identify patient and tumor subsets most likely to benefit from interventions
  - Can screen huge numbers, with that as primary objective
- Allows development of therapies for rare diseases
- Study survivorship, palliative and end of life care, and quality of life issues
- Only way to effectively study cancers in children

A Duration Question Could *Only* be Studied Through Cooperative Research

- Background: Chemotherapy following colon cancer surgery increases the cure rate
  - 5FU/oxaliplatin has been SOC since 2004
- Duration of adjuvant therapy decreased from 12 to 6 months in the 90's
- A pilot study from the UK suggested 12 weeks is/are good
- Shorter than 6 months would be better: re side effects
  - Severe neurotoxicity develops at about 4 months

NEJM 1990; J Clin Oncol 2004, 2009; Ann Oncol 2005

International Duration Evaluation of Adjuvant therapy: IDEA

- Prospectively planned pooled analysis of 6 large-scale cooperative studies
- Each randomized post-operative pts with CRC to 3 versus 6 months of therapy
- Study only looked at stage III and FOLFOX/CapOX components
- Non-inferiority study
  - Major goal was seeing if oxali-neurotoxicity was lessened

NEJM 2017

IDEA: Methods

- 90% power to declare NI given upper confidence interval did not exceed 1.12
- Multiple pre-planned analyses (e.g., IV vs. po)
- 12,834 patients were enrolled
- North American cooperative group study C80702
  - Also looked at effect effect of celecoxib

IDEA: Other

- >Grade 2 neurotox dramatically lower 3 vs 6 mo
  - FOLFOX/CapOX 17/14 vs 48/45%

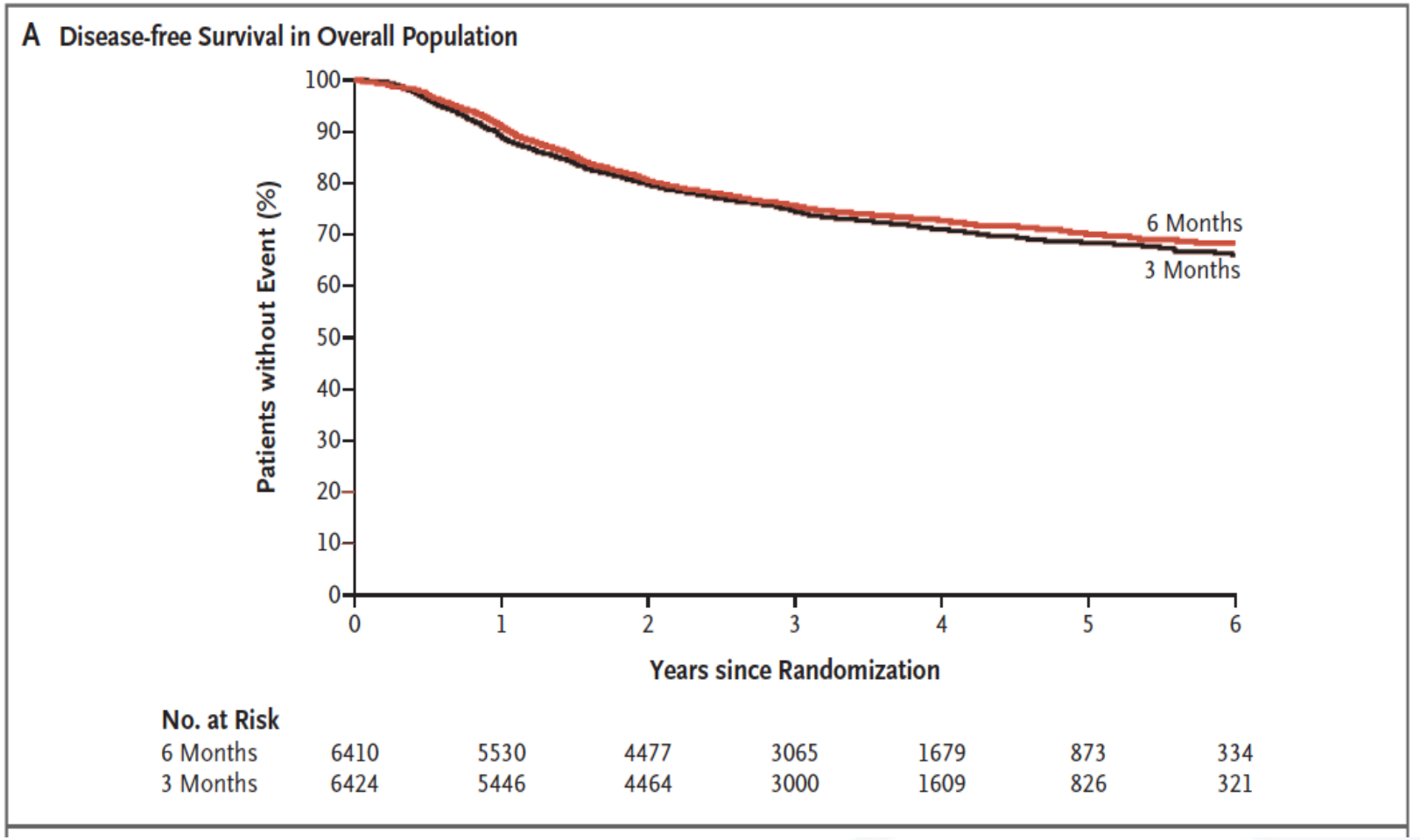
- Also, less diarrhea, GCP, nausea, mucositis, fatigue, HFS

- If non-inferior, better than any new drug ever to come along (in terms of optimizing patient outcomes)

IDEA: Complicated Efficacy Results

- 3-year DFS 3 vs. 6 mo. 74.6% and 75.5%
- HR 1.07 (95% CI 1-1.15)
  - *Not* non-inferior
- For CapOX 0.95 (95% CI 0.85-1.06)
- For low-risk CapOX 0.85 (95% CI 0.71-1.01)

IDEA: Disease-Free Survival



Why was IDEA so Important?

- Largest ever prospective CRC study
- Conducted without commercial support
  - Pharma, in fact, refused to do
- Showed a risk-based approach to adjuvant CRC therapy is warranted
  - Low-risk pts may receive shorter, markedly less toxic therapy, especially if capecitabine is used

Multimodality Cooperative Group Research: Background

- Squamous cn of larynx affects >12,000 pts/yr
- Standard rx was total laryngectomy +/- RT
  - *Not* an optimal patient outcome
- Chemorx effective in advanced H and N cancers
- Small pilots suggested chemorx + RT could cure laryngeal cn
- In 1985, VA Cooperative Studies Group decided to perform definitive study

NEJM 1991

VA Cooperative Laryngeal Study: Methods

- Eligibility: Stage III/IV disease without metastases
- Pts underwent staging and speech assessment
- Received surgery/RT or CDDP/FU + RT
  - Pts not responding to latter went to immediate surgery
- OS and DFS

VA Cooperative Laryngeal Study: Results

- 332 pts followed for 3 years
- 3 and 5 died respectively during treatment
- Surgical and RT complications similar
- Complete responses seen 49% chemorx arm
- *Larynx preserved 64%*

Organ Preservation Occurred without Lowering Cure Rate*

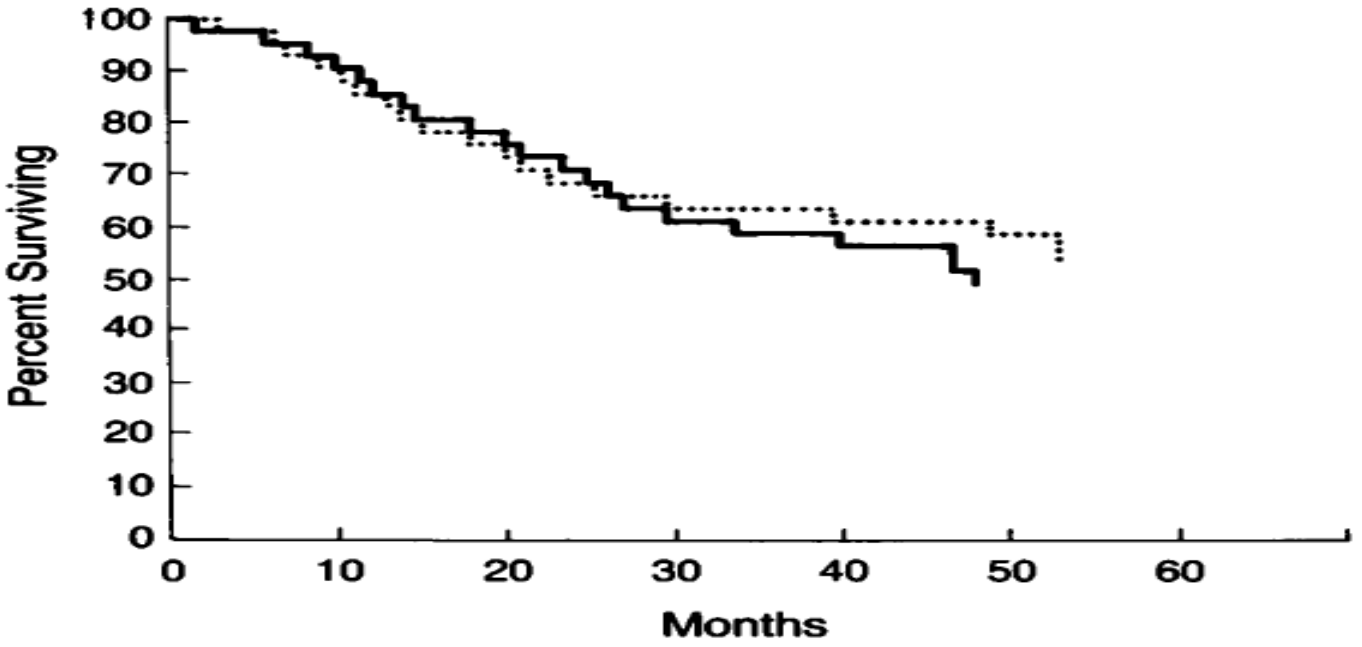


Figure 1. Overall Survival of 332 Patients Randomly Assigned to Induction Chemotherapy and Radiation Therapy (Solid Line) or Conventional Laryngectomy and Postoperative Radiation (Dotted Line).

Survival rates at two years were 68 percent for both groups (P = 0.9846). The median follow-up was 33 months.

- 2-year survival identical at 68%
- Still true at 10 years

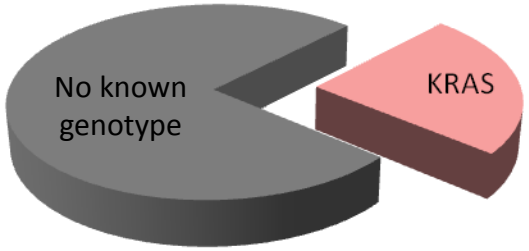
*Pretty optimal

At Least 4 More Cooperative Group Laryngeal Studies Followed

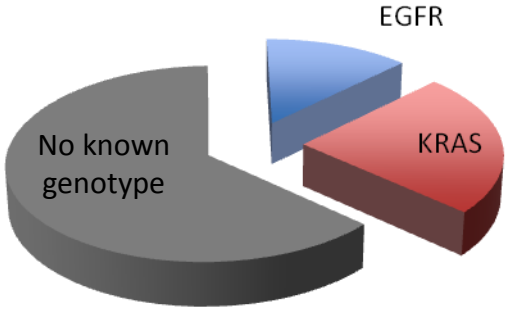
- Tested a variety of schedules and doses
- Looked to further optimize outcome by decreasing toxicity
- Reiterated concept cooperative groups excel at Quality of Life and assessment of late effects

J Clin Oncol 2015

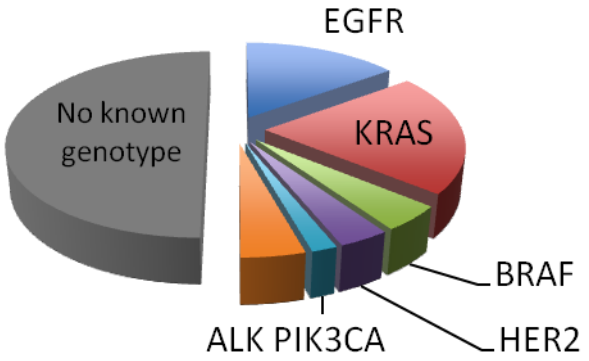
Evolution of Identification of Genomic Alterations in Lung Adenocarcinoma



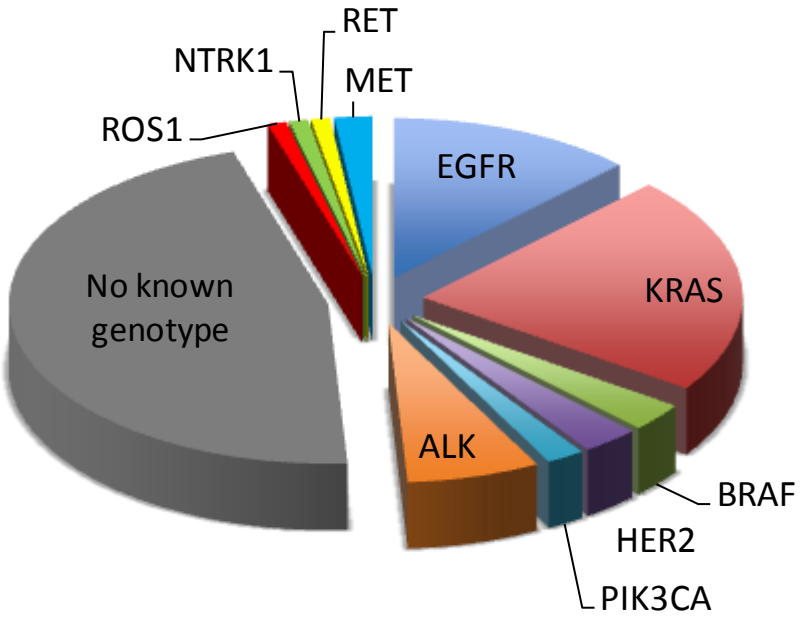
1984 - 2003



2004



2009



2014

Genomic analysis of SQUAMOUS Cell Lung Cancers

Gene	Event Type	Frequency
FGFR1	Amplification	20-25%
FGFR2	Mutation	5%
PIK3CA	Mutation	9%
PTEN	Mutation/Deletion	18%
CCND1	Amplification	8%
CDKN2A	Deletion/Mutation	45%
PDGFRA	Amplification/Mutation	9%
EGFR	Amplification	10%
MCL1	Amplification	10%
BRAF	Mutation	3%
DDR2	Mutation	4%
ERBB2	Amplification	2%

Estimated 63% of lung SCCs had identifiable therapeutic target

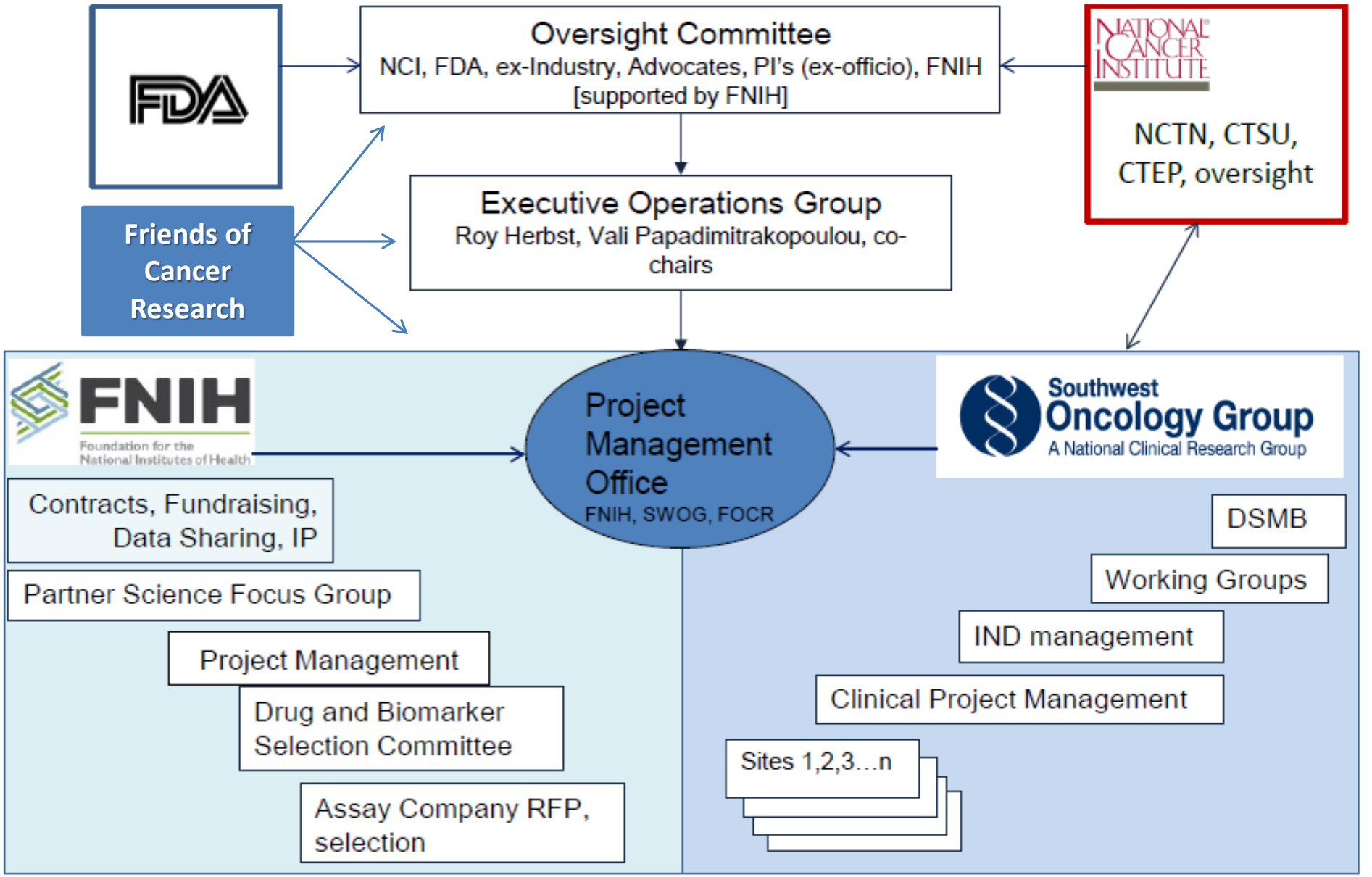
Peter Hammerman et al. WCLC 2011

Rationale for Master Protocol Design

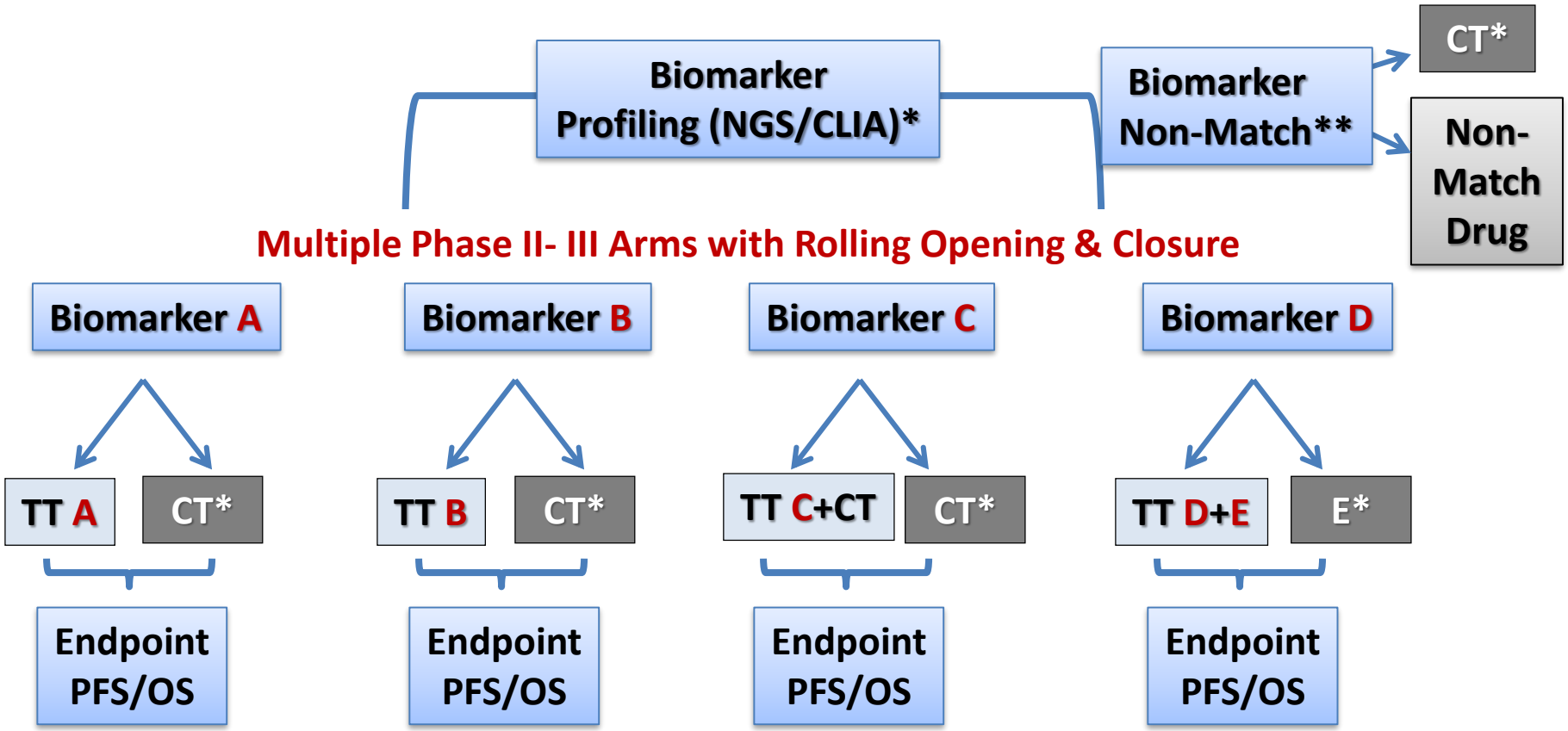
- **Multi-arm Master Protocol**
  - Homogeneous patient populations & consistent eligibility from arm to arm
  - Each arm independent of the others
  - Infrastructure facilitates opening new arms faster
  - Allows rapid drug/biomarker testing for detection of "large effects"
- **Screening** large numbers of patients for multiple targets by a broad-based NGS platform reduces the screen failure rate
- Provides a **sufficient "hit rate"** to engage patients & physicians
- **Bring safe & effective drugs to patients faster**
- Designed to facilitate **FDA approval** of new drugs

Adapted Herbst

Cooperativity, but Public-Private: Lung MAP Governance and $$$



Generic Master Protocol Design

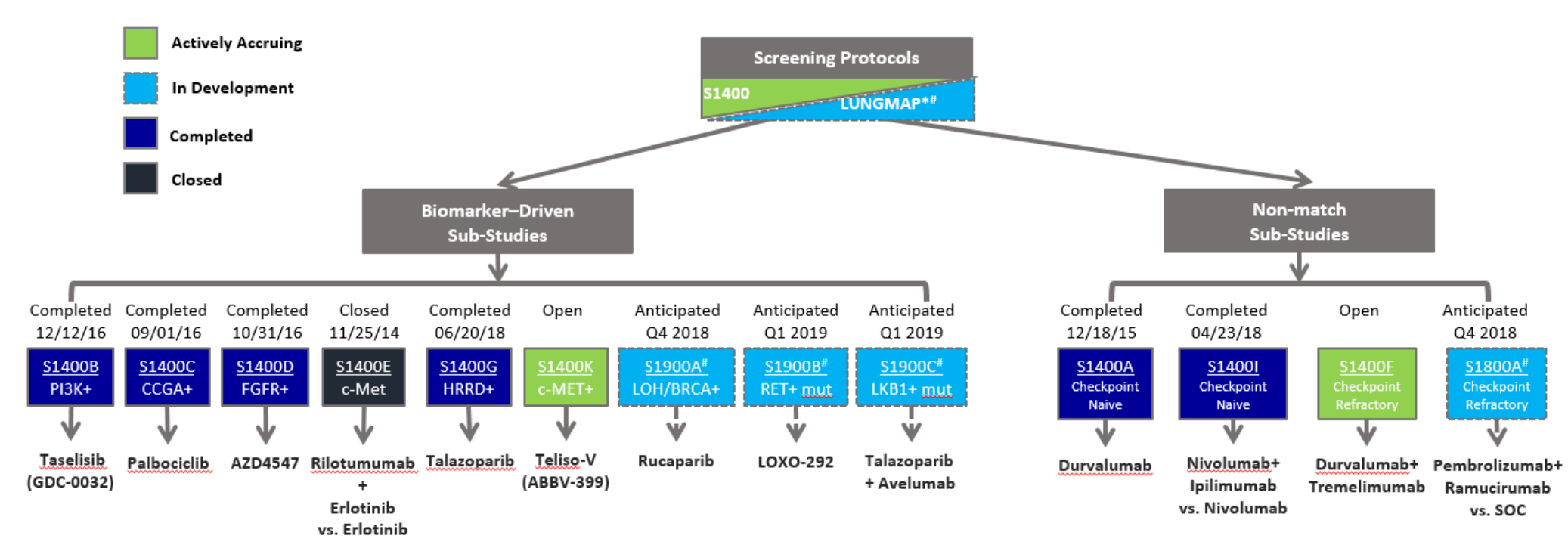


TT=Targeted therapy, CT=chemotherapy, E="standard" biologic therapy

*Derailed by immunotherapy

**Amplified 1000x by immunotherapy

Where Lung-MAP is Going – Current Schema



LUNG-MAP

SWOG

What has Been Achieved so Far

Over the last 4 ½ years:

- 1443 site registration applications have been received by CTSU
  - 654 approved sites, 324 CCOPs approved for enrollment
  - 427 sites that have enrolled patients
- 1769 Total Patient Registrations

  48% SWOG, 22% ALLIANCE, 1% CCTG, 18% ECOG-ACRIN, 11% NRG
  - Screened: 960
  - Pre-screened: 347 (started in April 2015)
- 648 Patient Registrations to a Sub-study
- Opened 9 Treatment Sub-studies
- Completed 7 Sub-studies

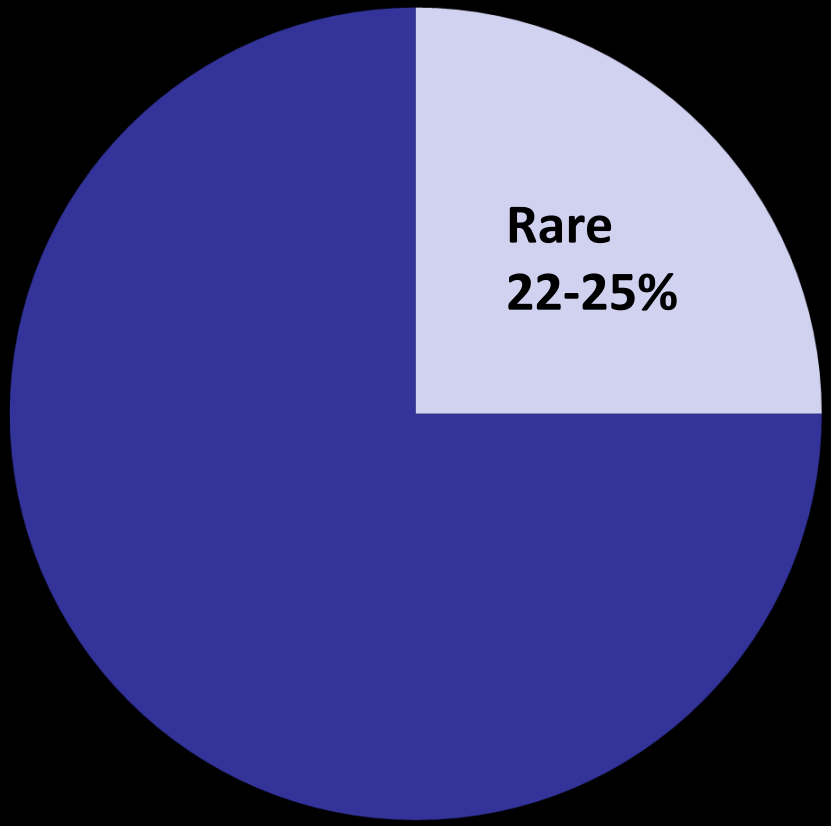
As of Sept 9, 2018

Molecular Analysis for Therapy Choice (NCI MATCH)

Histology-agnostic trial assigning patients to receive an agent/regimen defined to work on one of their identified mutations/ amplifications, based on other work

Adapted NCI

Rare Tumors



Rare cancers:
<6/100,000/year incidence:
RareCare (Europe)

Ultra-rare cancers: <2 cases per 100,000 or prevalence of less than 2000

186 cancer types

- Rare cancers are cumulatively common
- Rare cancers are exceedingly hard to screen for and formally study

Slide series adapted Kurzrock

DART: *D*ual *A*nti-CTLA-4 & Anti-PD-1 Blockade in *R*are *T*umors

Sandip Patel, MD
Assistant Professor
Co-Lead Experimental Therapeutics
UCSD Moores Cancer Center

Young Chae, MD
Assistant Professor
Vice Chair, SWOG Early Therapeutics
and Rare Cancers Committee
Co-Director Developmental Therapeutics
Northwestern University

Razelle Kurzrock, MD
Professor
Chief, Division of Hematology,
Medical Oncology
Chair, SWOG Early Therapeutics
and Rare Cancers Committee
Director, Center for Personalized Cancer Therapy
UCSD Moores Cancer Center

DART Eligibility

- Rare Cancer histologic subtypes (incidence of < 6/100,000 persons/year).
- NCI-MATCH screen or treatment failures, w/o further MATCH options (Amendment 1, 2)
  - Amendment 3: Direct Enrollment into DART
- Histologic subtypes n=37 cohorts; includes chordomas, adenoid cystic carcinoma, CUP, vulvar cancer, metaplastic breast carcinoma, etc.

DART: Dual Anti-CTLA-4 & Anti-PD-1 Blockade in Rare Tumors

Primary study objective:

- To evaluate the overall response rate (ORR) in patients with advanced rare cancers treated with ipilimumab plus nivolumab combination therapy
  - Primary Endpoint: Overall response rate (ORR) as assessed by traditional RECIST v1.1 measurement criteria will be used.

Secondary objectives:

- To evaluate toxicities in each cohort
- To estimate overall survival, progression-free survival, and immune-related ORR, PFS in each cohort
- TM

Treatment and Stats

- Treatment: Nivolumab 240mg IV q2 weeks

  Ipilimumab 1 mg/kg IV q6 weeks

- Must have 1 objective response in first 6 patients to continue
  - Then accrue another 10 patients and if $\geq$ 2 responses total, will do further study

If the true ORR is 5% the probability of stopping accrual after the first stage is 74%; if the true ORR is 30% the probability of stopping accrual after the first stage is 12%.

DART by the Numbers

- Date of activation = January 2017
- Number of patients accrued = 526
- Number of sites = 853
- Number of cohorts permanently closed after stage 1 = 14
- First cohort to complete stage II = neuroendocrine
  - → response rate ~30 percent;
  - → response rate in high grade ~50%

Precision Immuno-oncology in DART: Translational Studies

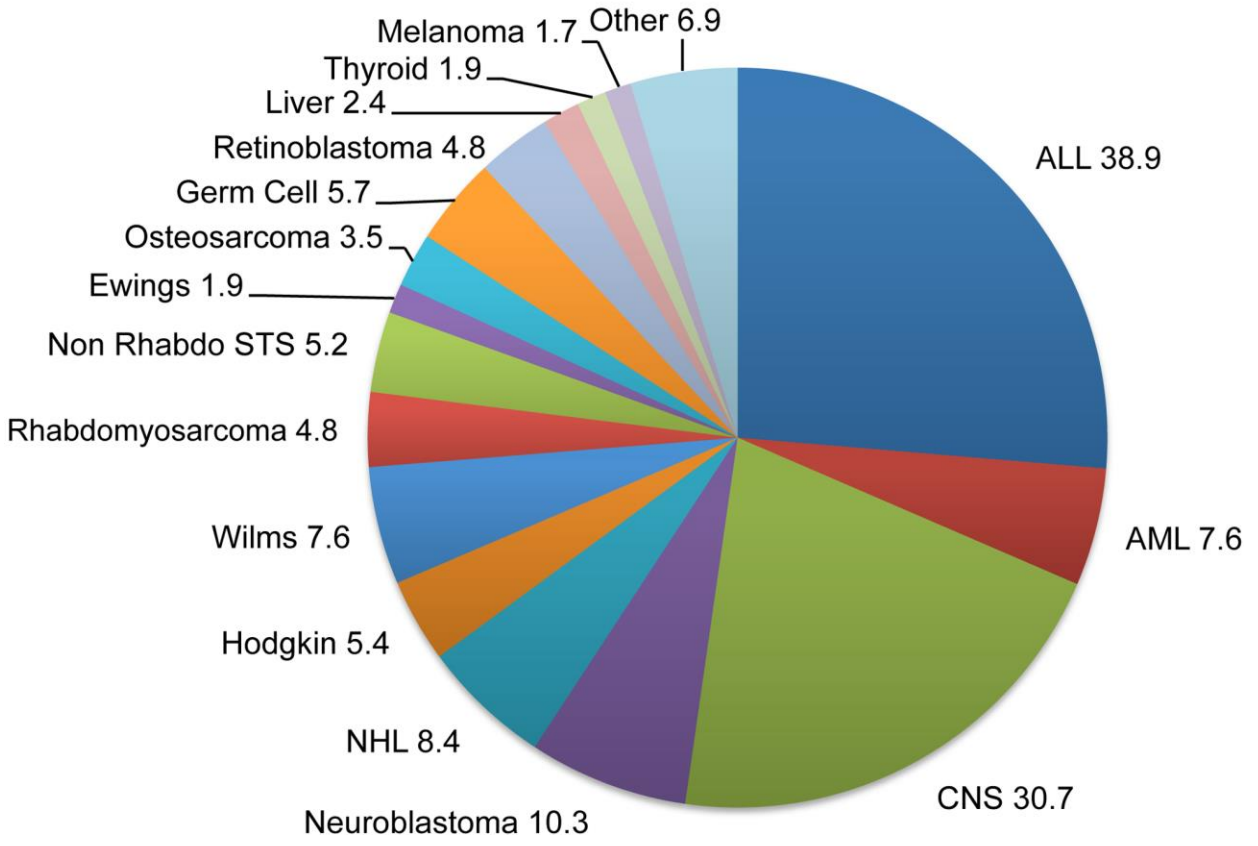
	PD-L1 IHC	Immune biomarkers	Germline DNA sequencing	Proteomic immune signature	cDNA sequencing	Tumor NGS
Performing Lab	**UCSD**	**Jackson Labs (JAX)**	**Counsyl**	**Biodesix**	**Circulogene**	**NCI**
Sample source	Tumor tissue (FFPE) or unstained slide	Blood in collected in Tempus tubes (one 2cc vial for RNA, another 2cc vial for DNA)	Blood collected in the EDTA tube	Blood collected in the EDTA tube	Blood collected in the EDTA tube	Tumor tissue (FFPE) collected as part of NCI-MATCH & DART
Biomarker Target	PD-L1 protein expression by 28-8 IHC analysis	DNA, RNA sequencing (Nanostring) of tumor tissue and blood	Leukocyte DNA sequencing (Illumina)	Serum proteins	Cell free DNA sequencing (Illumina)	Whole exome sequencing and RNAseq
Biomarker output	PD-L1 strata will be grouped <1%, 1-5%, 6-25%, 26-49%, >50%	Immune and Cancer pathway Nanostring (gene expression of 770 genes assaying 24 immune cell types and 500 immune response genes)	Genetic alteration	Predictive signature (good, intermediate, poor group)	Genetic alteration and mutational load	Genetic alteration and mutational load & Transcriptomic Profiling
Statistical Considerations	Binary endpoint by strata	Log-expression	Categorical variable	Categorical variable	Percentile rank of mutational load	Percentile rank of mutational load & Transcriptomic Signature

DART: The “TCGA of rare tumors”

NCTN Population Science Concepts*

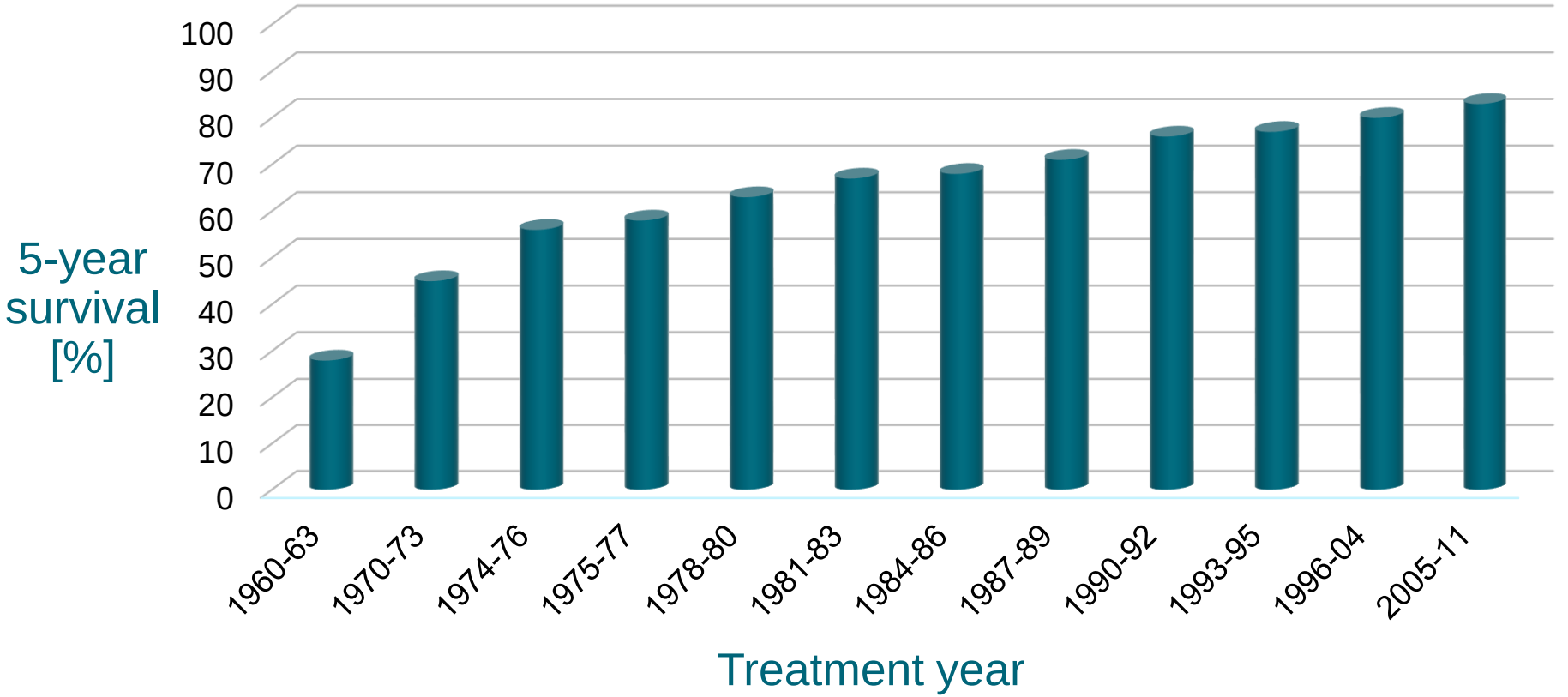
- S1703 Surveillance: Randomized trial using *tumor-marker-directed disease monitoring* in breast cancer
  - Similar study in testis cancer might eliminate CT scanning
- S1904: Cluster-randomized pragmatic trial evaluating chemoprevention uptake, using a *web-based support tool* integrated in the EMR
- SWOG NCORP grant application 2018: financial toxicity, biomarker studies to reduce late effects of treatment, improve patient/caretaker-medical team communication

Childhood Cancers are a Collection of Rare and Ultra-rare Diseases



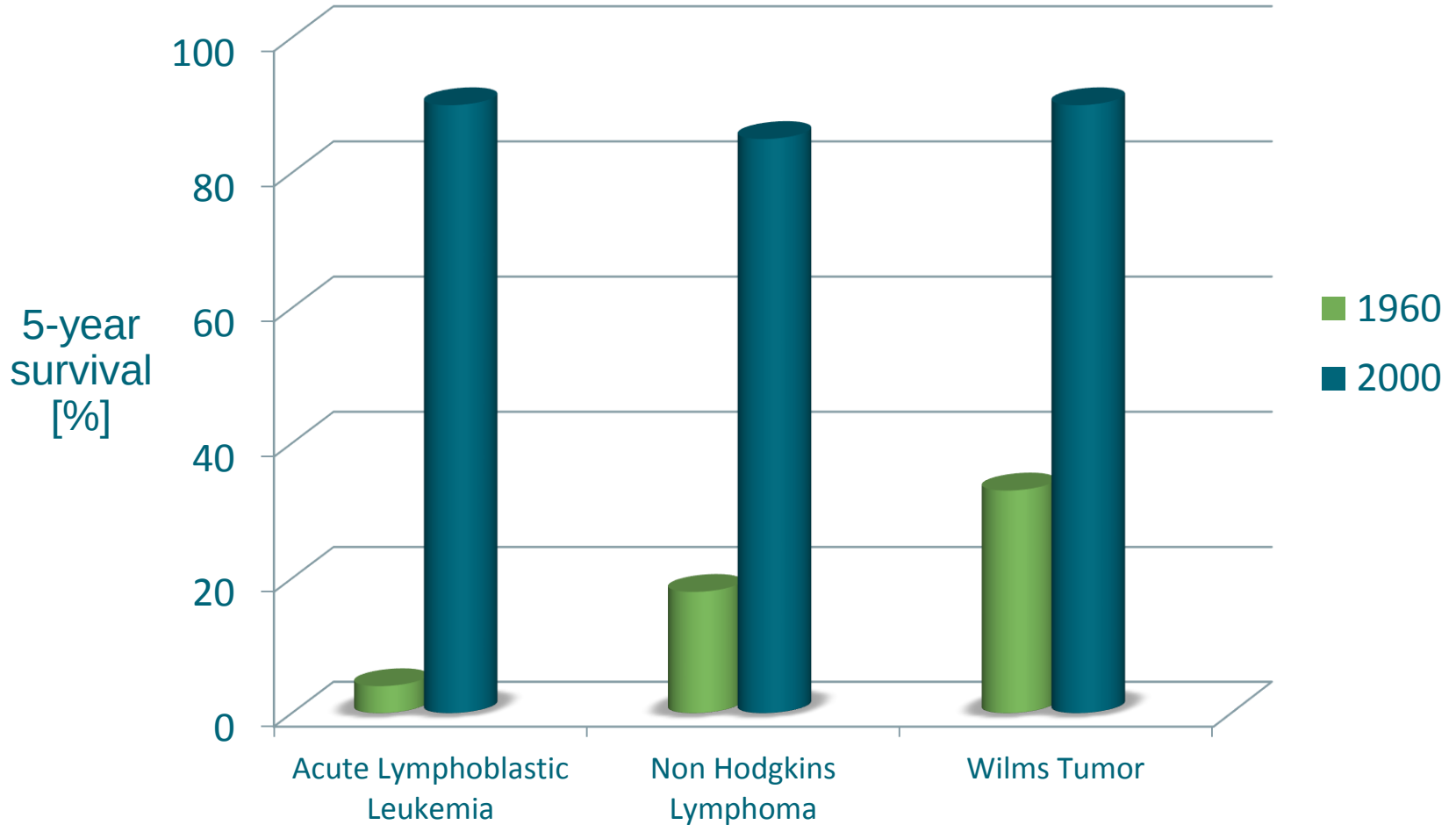
Adapted Peter Adamson

5-Year Survival Rates Have Dramatically Improved*



*90% of children with cancer are seen by COG

The Best Patient Optimization: *Cure*



NCTN: Why Publicly Funded Research is Important (more!)

- Can combine/compare drugs developed by different sponsors: C80405 showed bevacizumab and cetuximab are equivalent in advanced CRC
- Enables addressing of optimal dosing: CALGB 9741 showed dose-dense adjuvant chemorx for breast cancer is ideal
- Publish negative results: 2 cooperative group trials showed adjuvant irinotecan does not work in CRC
- Provide FDA-accepted “gold standard” data for registry studies: Multiple

**But,* results differed by sidedness

How Else Can NCTN Groups Broadly Help Patients? SWOG Latin American Initiative (SLAI)

- Decade-old program that is a major part of grant applications
- Several components:
  - Research: Locally-conducted by SWOG members, with eventual applications to US Hispanic patients subpopulation
  - Education: Yearly biostats and clinical research course in LA
  - Service: Provide expertise in trial design and aim to develop an effective dedicated LA cooperative group network

NCTN Will Help Veterans

- SWOG has been offering infrastructure grants for ~3 years
  - Early, but has increased VA accrual 3X
- Recent launch NCI/VA Interagency Group to Accelerate Trials Enrollment (NAVIGATE)
  - NCI provides infrastructure $$$ for VAs to conduct NCTN trials
  - VA will establish a network to focus on NCTN goals

Veterans will be able to get promising Rx locally

Conclusions

- Network and other cooperative groups do trials no one else can or will do
- This research is remarkably inexpensive
- Cooperative research optimizes patient outcomes