Oishi Symposium

Thursday, May 11th, 2023

8 am – 11:00 am

San Francisco, California

SWOG CANCER RESEARCH NETWORK

NCI National Clinical Trials Network
a National Cancer Institute program

NCI Community Oncology Research Program
A program of the National Cancer Institute of the National Institutes of Health

In honor of and with gratefulness for

Noboru Oishi MD

(1928 – 2020)

and

Jeri Oishi, RN

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The SWOG Oncology Research Professionals (ORP) Committee & Sub-Committees

Serving >10,000 ORPs

SWOG ORP Executive Committee
Chair: Connie Szczepanek
Vice-Chair: Dana Little

Nursing Research
Chair: Jamie Myers

ORP Liaison
Co-Chairs:
Sandy Annis
Erin Cebula

Membership
Co-Chairs:
Anthony Hicks
Lisa Stoppenhagen

Education
Co-Chairs:
Deb Bergevin
Joyce Tull

Site Operations
Co-Chairs:
Connie Szczepanek
Liz Edwards
Caitlin Hutchinson

SWOG Cancer Research Network's Mission

- To significantly improve lives through cancer clinical trials and translational research.

ORP Committee Mission

- To support SWOG activities through promotion of integrity and excellence in clinical research through education, guidance, & collaborative contributions.

Acknowledgements

ORP Executive Committee Members	
Sandy Annis	Dana Little
Deb Bergevin	Jamie Myers
Annette Betley ★	Joyce Nancarrow-Tull
Erin Cebula **	Ceil Petrowsky ★
Liz Edwards **	Lisa Stoppenhagen
Anthony Hicks	Connie Szczepanek
Caitlin Hutchinson	

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To get more deeply involved…

…See the SWOG Website:

Member Resources / Membership / Committee Membership

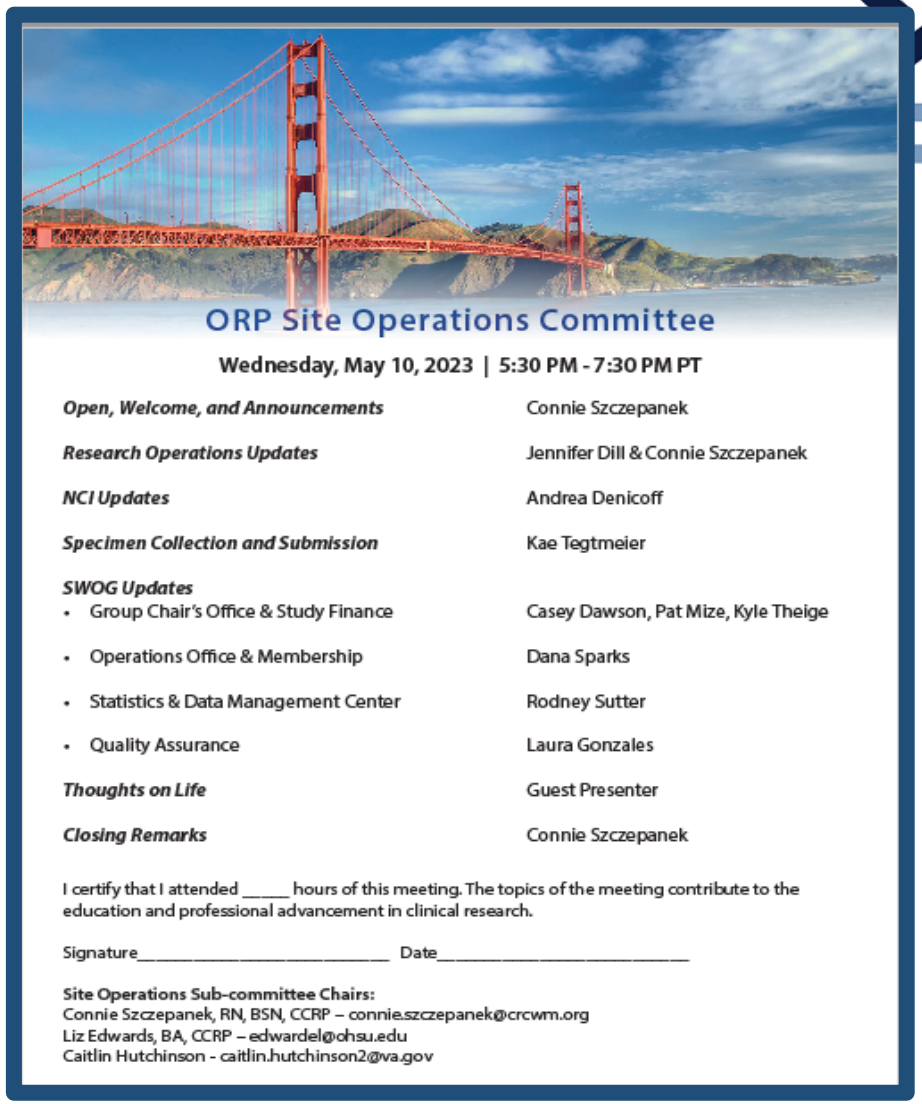
https://www.swog.org/member-resources/membership/committee-membership

Key Involvement Opportunities

- Disease Specific Liaisons
- Liaisons at Large
- Education Team

Although there are no formal CE credits for this meeting, you may print a copy of the agenda to reflect your attendance

(e.g.: for use with SOCRA or ACRP).



ORP Site Operations Committee

Wednesday, May 10, 2023 | 5:30 PM - 7:30 PM PT

Open, Welcome, and Announcements	Connie Szczepanek
Research Operations Updates	Jennifer Dill & Connie Szczepanek
NCI Updates	Andrea Denicoff
Specimen Collection and Submission	Kae Tegtmeier
SWOG Updates	
• Group Chair's Office & Study Finance	Casey Dawson, Pat Mize, Kyle Theige
• Operations Office & Membership	Dana Sparks
• Statistics & Data Management Center	Rodney Sutter
• Quality Assurance	Laura Gonzales
Thoughts on Life	Guest Presenter
Closing Remarks	Connie Szczepanek

I certify that I attended _____ hours of this meeting. The topics of the meeting contribute to the education and professional advancement in clinical research.

Signature_____ Date_____

Site Operations Sub-committee Chairs:
Connie Szczepanek, RN, BSN, CCRP – connie.szczepanek@crcwm.org
Liz Edwards, BA, CCRP – edwardel@ohsu.edu
Caitlin Hutchinson - caitlin.hutchinson2@va.gov

Participants,

This Spring, the ORP Education Committee decided we'd take you on a long journey, to a place "where there wasn't any trouble"(?), "not a place you can get to by a boat or a train", "it's far, far away, behind the moon, beyond the rain..."

.....where happy little bluebirds fly and dreams come true.

The Journey Of A Protocol From Idea Through Published Results

"Finding Our Way on the Yellow Brick Road"

The Journey Begins: Cathy Tangen

Greetings from the SWOG Stat Center Leadership!

The Twister Comes!

Cathy Tangen

Deputy Director

SWOG Statistical Center

Faculty stat: GU, Prevention

Incubating a Trial Idea – The Big Funnel

- Initial presentation – floating the concept
- Right fit for NCTN?
- Prioritizing within a committee, can take a few years to move forward
- Feasibility? SWOG's prior experience?
- Complexity? Community participation?
- Investigator reaches out to stats team for initial pass at design considerations
- Include young investigators as part of the team

Basic Design Considerations

(iterative process with study team)

- Target population: impacts accrual rate, generalizability of results, event rate
- Endpoint: Survival, PFS, response -> impacts event rate, duration of trial, sample size
- Treatment effect: The bigger the hypothesized difference between arms -> the smaller sample size, clinically meaningful difference
- Trial duration: potential relevance

Clinically meaningful vs. Pragmatic

Median OS	Sample size
12 vs 18 mo	200/arm
12 vs. 16 mo	400/arm
12 vs. 15 mo	600/arm

NCI Task Force Review – Site specific

- SWOG is staking its claim to a research area
- NCTN disease-specific expertise to review “rough” concept
- Ensure best science, review for overlap with NCTN and pharma
- Other suggestions (TM, PROs, imaging, etc.)
- Trying to get to “We’re “supportive of submitting to the Steering Committee”
- Back and forth, less formal than SC

Statistical Review (aka PRC)

- Weekly meeting in Seattle
- Standards, consistency, clarity
- Statistical principles for design

  and analysis plans
- Logistical flow of study
- Burden on site and patients
- Shared SWOG knowledge, don’t reinvent the wheel

SWOG Executive Review (aka “Triage”)

- Weekly, Monday mornings
- Leaders from all SWOG offices, GCO, Ops, Stats, E.O.s, Advocates
- Is trial scientifically sound? Acceptability of randomization?
- Good use of SWOG resources?
- Fit in disease committee portfolio?
- Burden on sites and patients

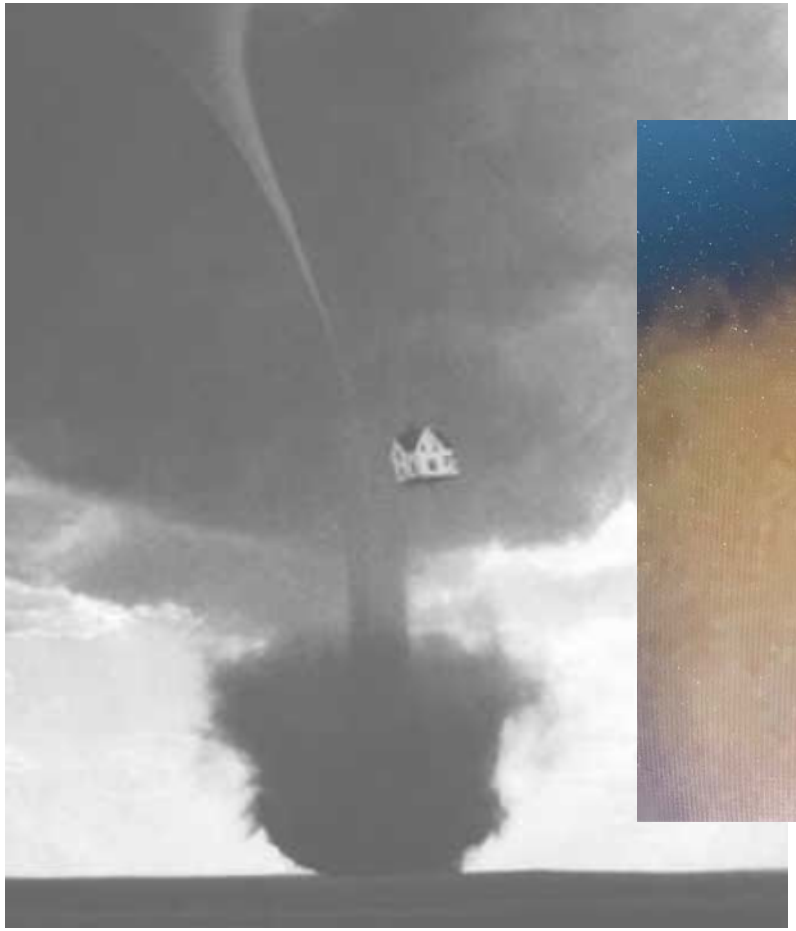
  (e.g., PROs, TM sample collection)
- Extra resources needed? (e.g., FDA registration)
- Rejections are rare, but plenty of review comments

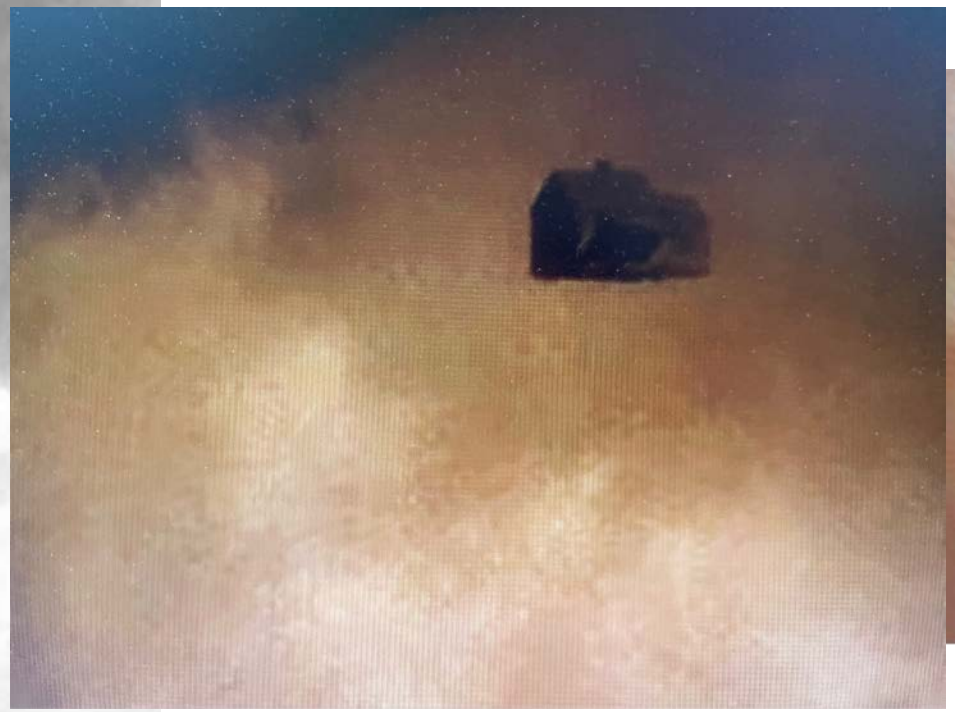
NCI Steering Committee – Clock starts!

- Polished concept submitted, most logistics, funding worked out
- Formal review with national leaders from NCTN and NCI
- Medical, RT, surgical oncologists, TM experts, advocates, biostatisticians
- Open and closed session
- Unusual to get approved on first try (approve vs. revise and resubmit vs. disapproved)
- SWOG rule: Only 3 on the clock at any given time

Concept Approved by Steering Committee

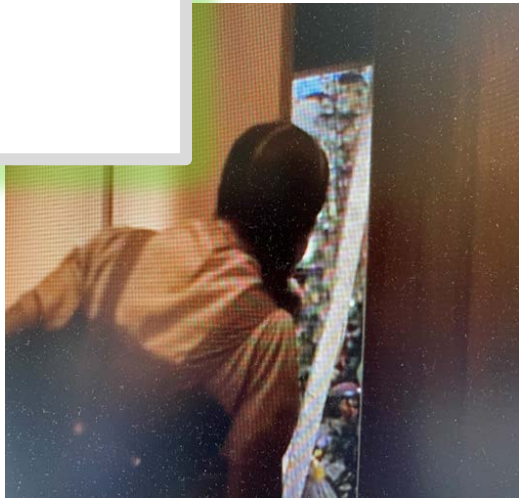
(and Tornado officially hits)





The fun begins at a very fast pace for a lot of people!

From Concept To Protocol: Crystal Miwa



PROFESSOR MARVEL

Crystal Miwa

Protocol Department Manager,

SWOG Operations

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Meeting the Capsule

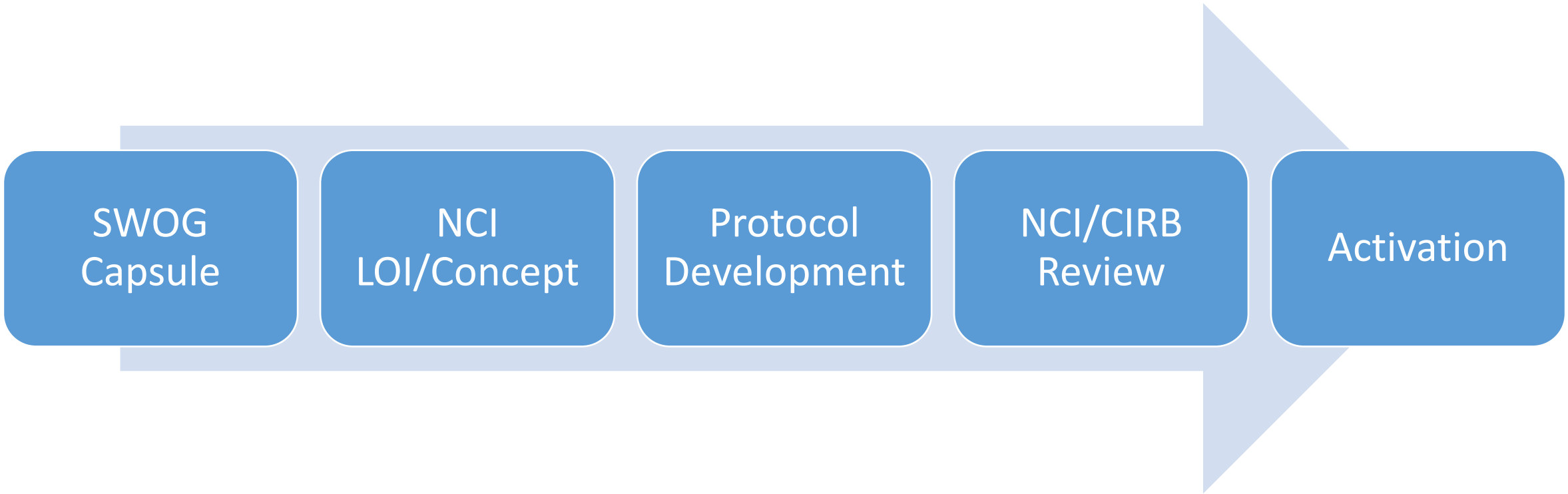
"Let me guess…"

Wizardly Thinking

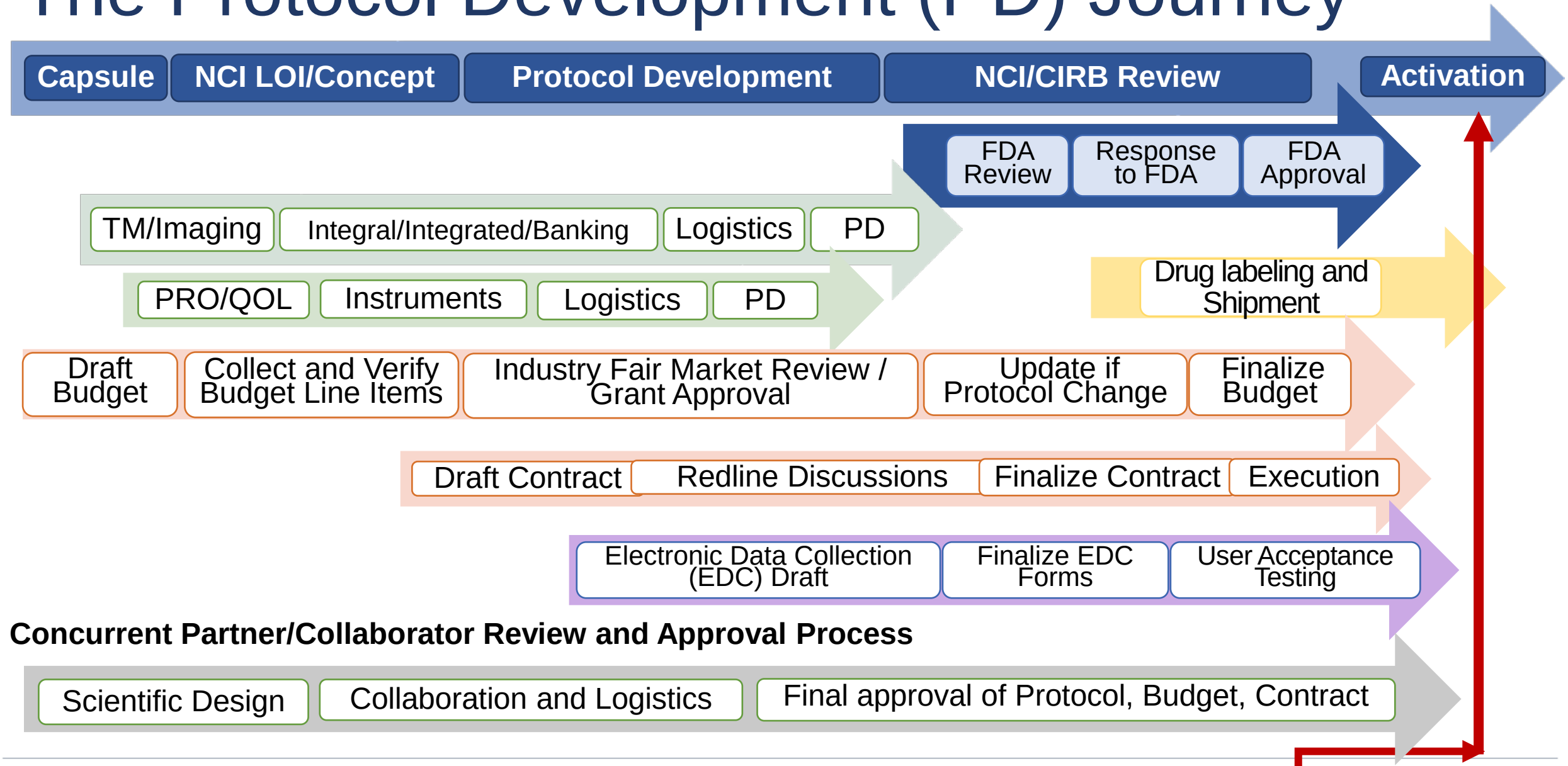
- Study Design
  - Patient Flow
  - Number of registration steps, consents
- Treatment/Non-Treatment
- Correlative Studies
  - Translational Medicine
  - Patient Report Outcomes
  - Imaging

Study Assumptions Worksheet

The Protocol Development Journey



The Protocol Development (PD) Journey

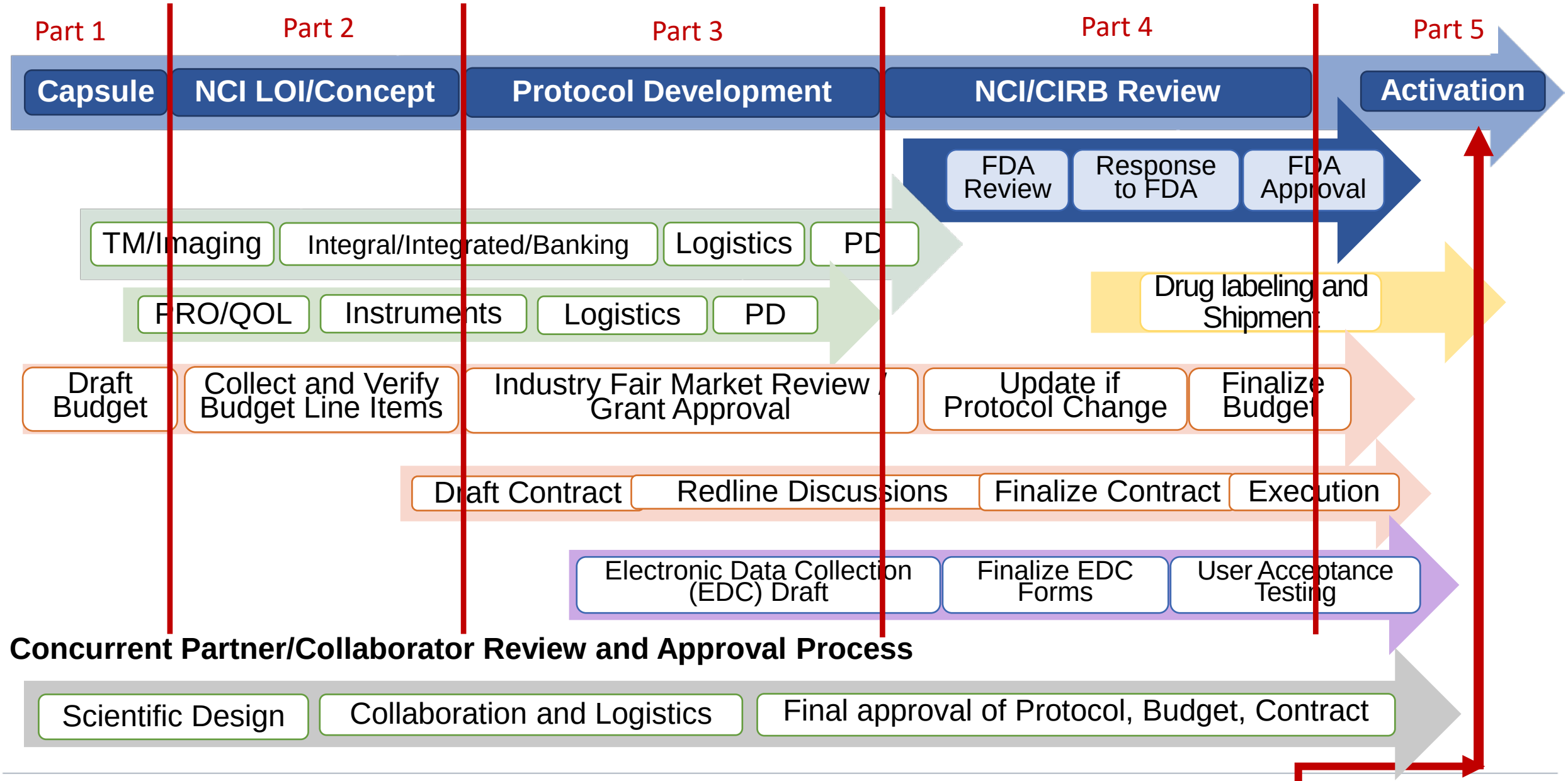


The Protocol Development Journey

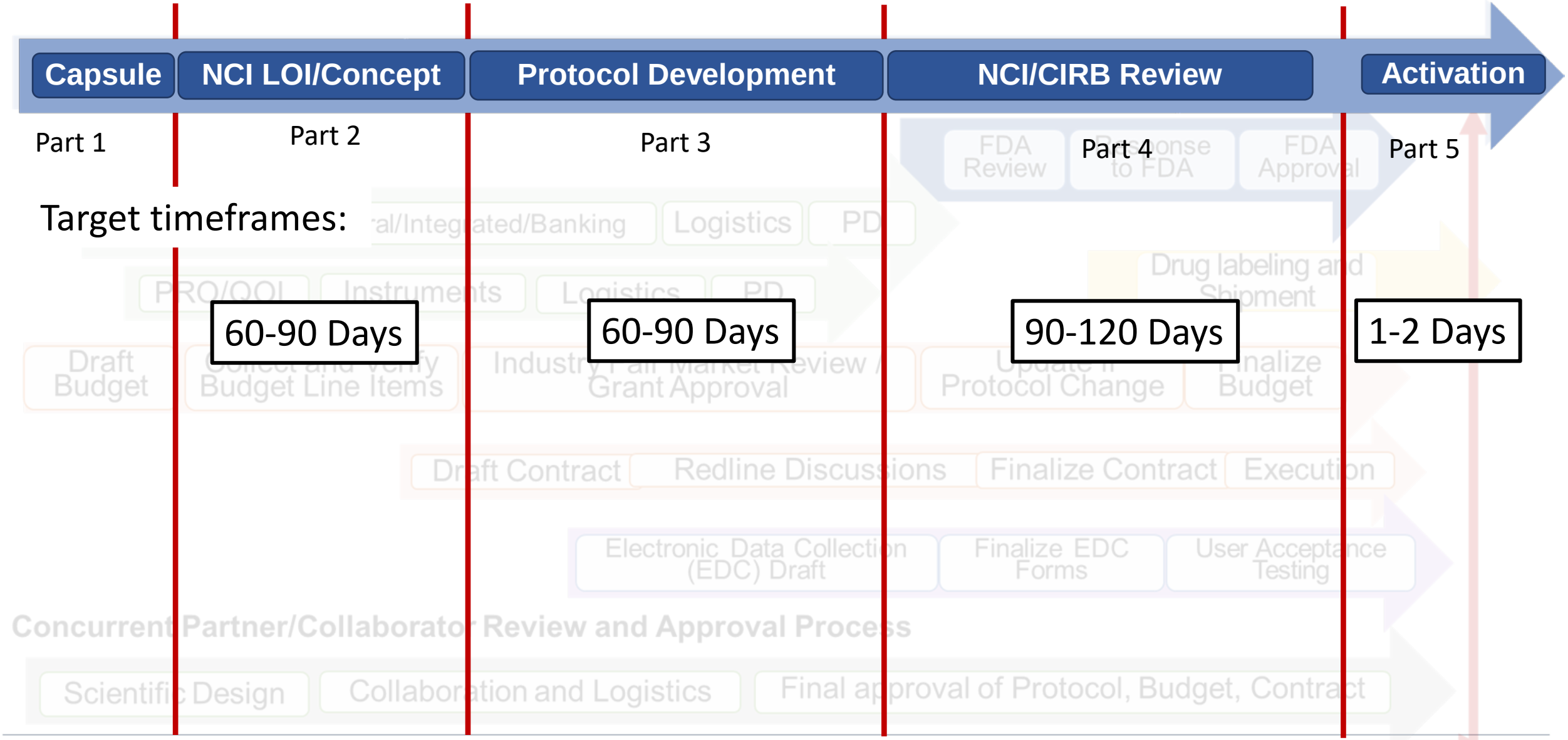
OEWG Timelines

(Operational Efficiency Working Group)

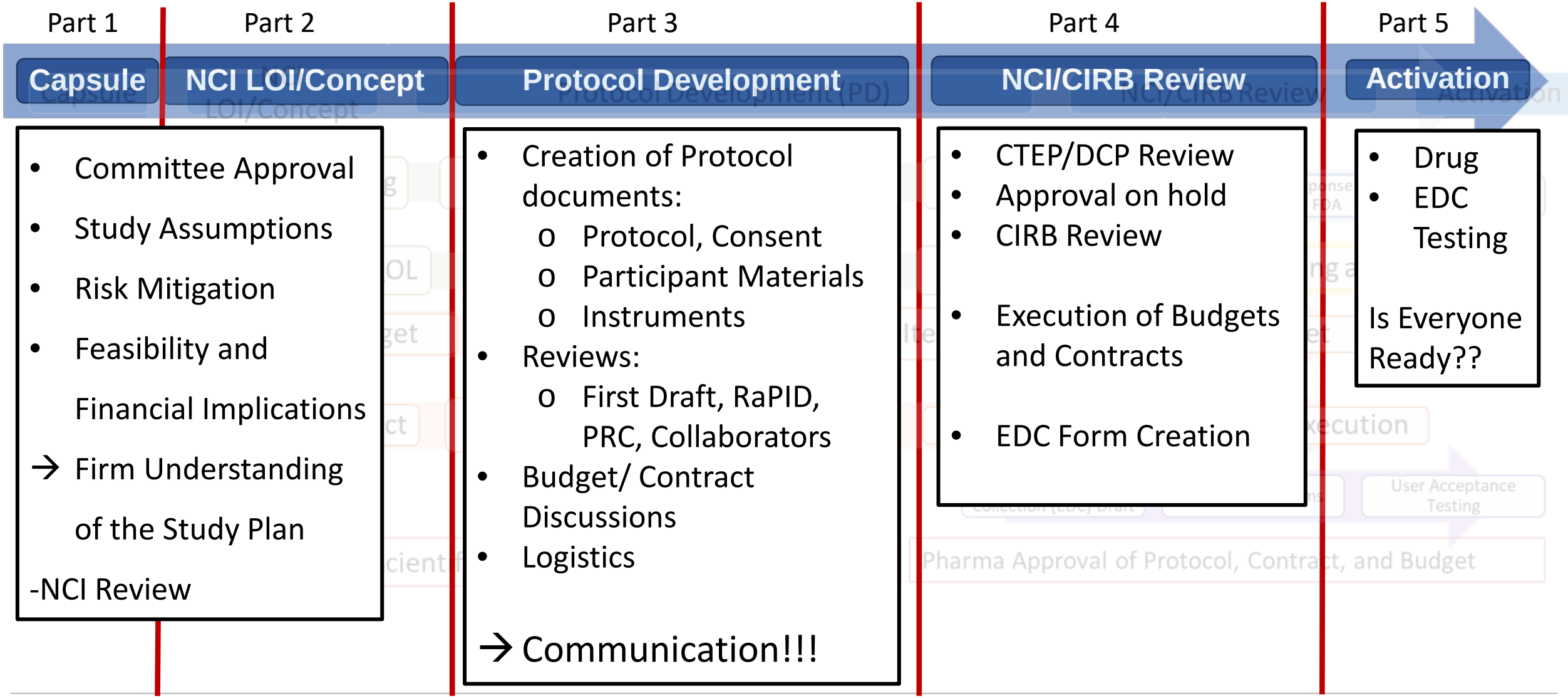
Phase 1 or 2 LOIs:	400 Days
Phase 1/2 or 2 Concepts:	450 Days
SWOG target:	210 days
Phase 3 Concepts:	540 Days
SWOG target:	300 days


Part 1
Part 2
Part 3
Part 4
Part 5
Capsule
NCI LOI/Concept
Protocol Development
NCI/CIRB Review
Activation
FDA Review
Response to FDA
FDA Approval
TM/Imaging
Integral/Integrated/Banking
Logistics
PD
PRO/QOL
Instruments
Logistics
PD
Drug labeling and Shipment
Draft Budget
Collect and Verify Budget Line Items
Industry Fair Market Review / Grant Approval
Update if Protocol Change
Finalize Budget
Draft Contract
Redline Discussions
Finalize Contract
Execution
Electronic Data Collection (EDC) Draft
Finalize EDC Forms
User Acceptance Testing
Concurrent Partner/Collaborator Review and Approval Process
Scientific Design
Collaboration and Logistics
Final approval of Protocol, Budget, Contract
Confirmation of All Regulatory, Financial & Logistical Requirements for Activation

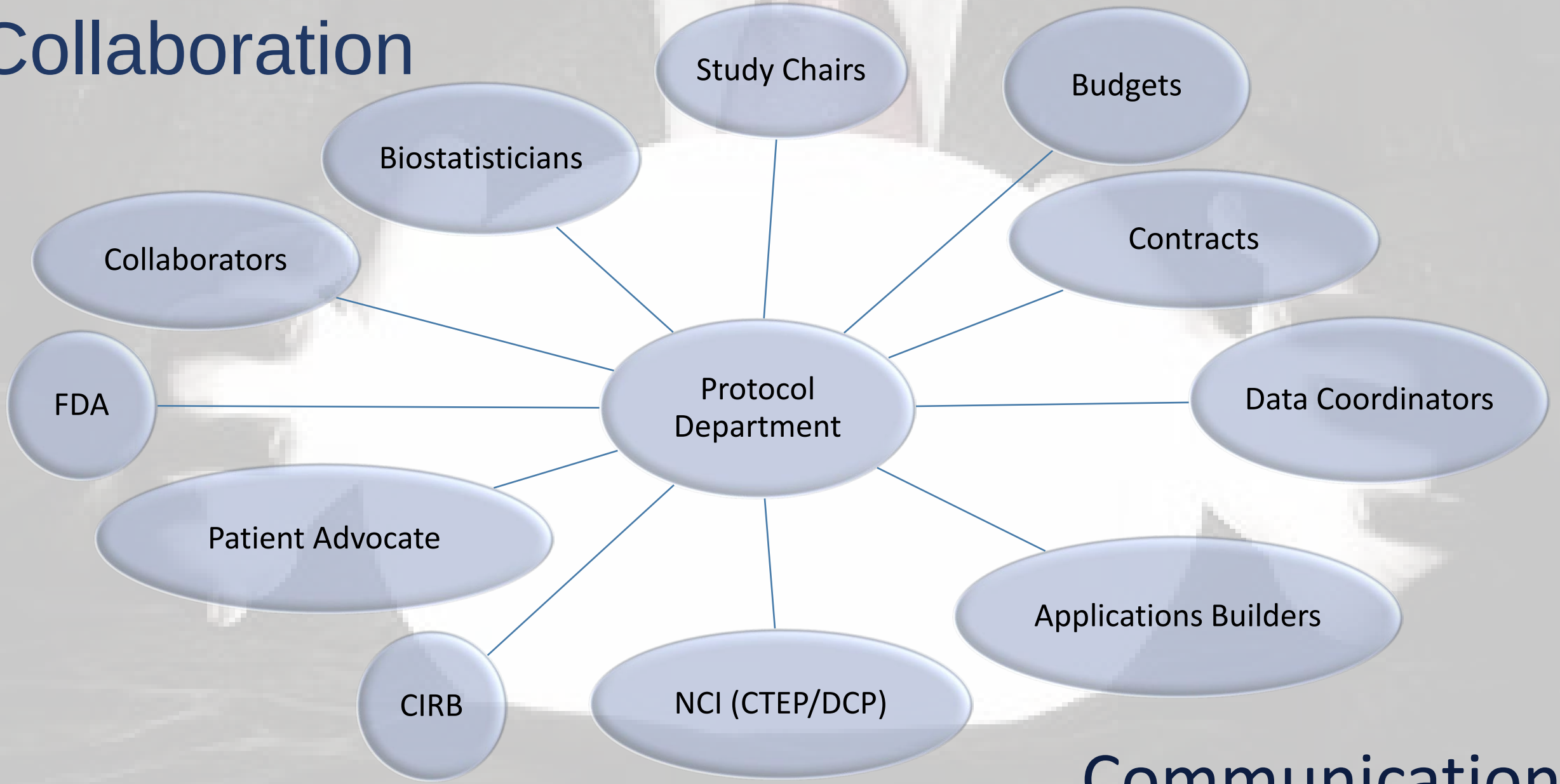
The Protocol Development Journey



The Protocol Development Journey



Collaboration



Communication

We can dive deep into our Crystal Ball……..or

into our basket of

knowledgeable experts

to create a great protocol

product for patients and sites

.....all you have to do, is follow the Yellow Brick Road.....

Our SWOG Oishi Symposium Featured Speaker

David B. Zhen, MD
Assistant Professor, Medical Oncology
Co-director, Neuroendocrine Tumor Program
Fred Hutchinson Cancer Center I University of Washington

Fred Hutch
Cancer Center

Insights and Lessons from Developing an NCTN Study: My Journey with SWOG S2012

David B. Zhen, MD
Assistant Professor, Medical Oncology
Co-director, Neuroendocrine Tumor Program
Fred Hutchinson Cancer Center I University of Washington

May 11, 2023

Outline

- Personal experiences and my journey of developing a trial in the NCTN
- Insights and lessons learned for conducting research in the NCTN

My journey through the NCTN……

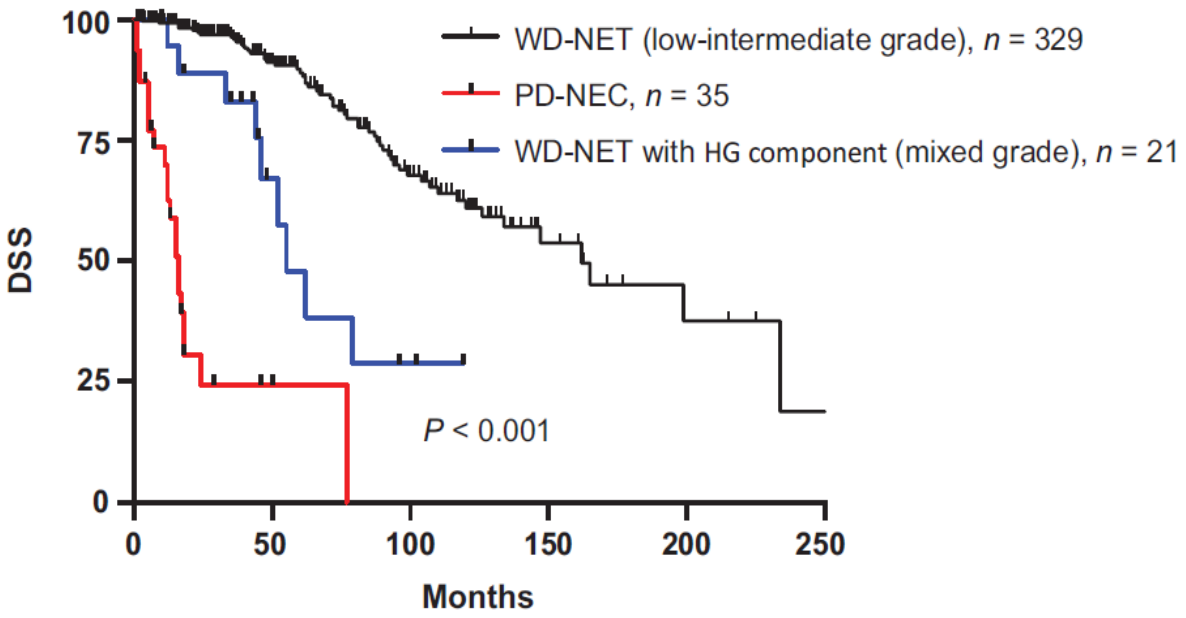
Starting in **2018**

2019 (now 2022) WHO Pathological Classification of GI Neuroendocrine Neoplasms (NEN)

Differentiation	Proliferation Indices	Designation
Well differentiated Neuroendocrine tumor (NET)	Ki-67 <3% Mitotic index <2/HPF	Low grade/ Grade 1
	Ki-67 3 – 20% Mitotic index <2-20/HPF	Intermediate grade/ Grade 2
New category compared to prior WHO classifications →	Ki-67 >20% Mitotic index >20/HPF	High grade/ Grade 3
Poorly Differentiated Neuroendocrine carcinoma (NEC)	Ki-67 >20% Mitotic index >20/HPF	High grade by default Subclassified by histology • Small Cell • Large Cell

Adapted from Rindi G et al. *Mod. Pathol.* 2018; **31**; 1770 – 1786.

Relevance of WHO Pathological Criteria



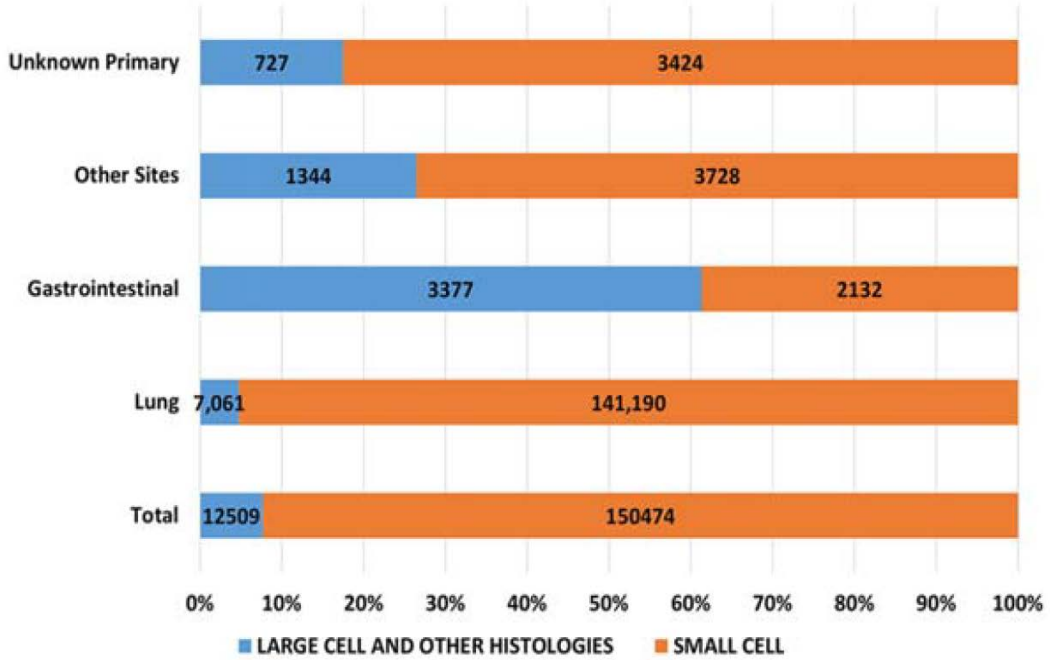
Tang et al. Clin Cancer Res 2015; 22:1011.

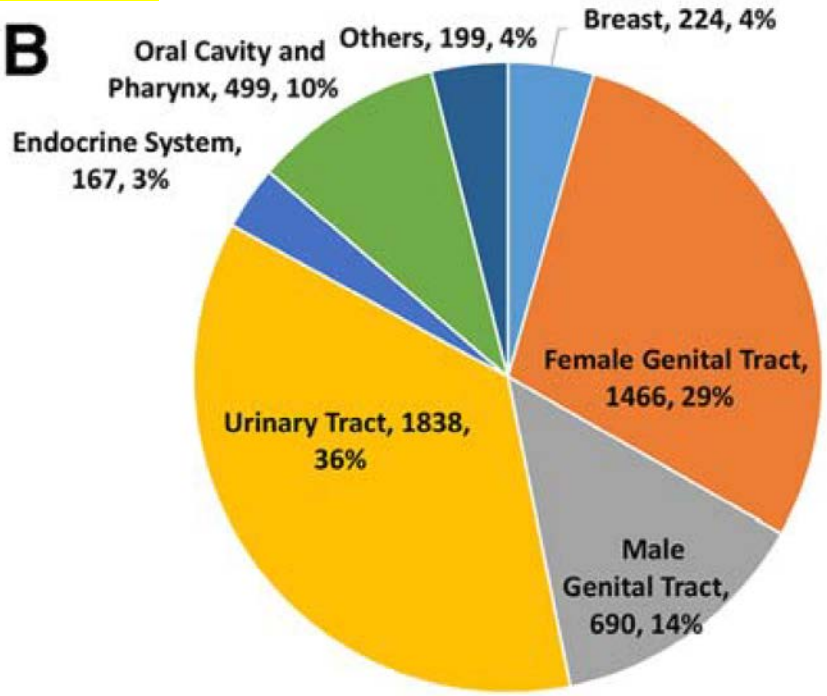
WD: Well differentiated, PD: Poorly differentiated
Gr: Grade; HG: High grade

- Prognosis:
  - WD-Gr1/2 NET: Years (Median ~12 years)
  - PD-NEC: <12 months
  - WD-Gr 3 NET: In between the above
- WD-Gr3 NET mutational profiles more similar to WD-Gr1/2 NET
  - NET: *MEN1, DAXX, ATRX*
  - NEC: *TP53, RB1*
- WD-Gr3 NET less responsive to platinum/etoposide compared to PD-NEC
- Hence differentiating from WD-Gr3 from PD-NEC is important for prognostic and treatment considerations

NEC Prevalence (SEER Database 1973-2012)

Extrapulmonary NEC is a rare disease = 1/100,000





Dasari A et al. Cancer 2018

Current Treatment Paradigm in NEC

- Extrapolated from small cell lung cancer (SCLC) with use of platinum (cisplatin or carboplatin)/etoposide
- Data from retrospective series, except 1 prospective study in GI

Study	N	Histology (%)	Ki-67 Proportion	OS	PFS	RR
NORDIC-NEC[1] (GI)	305	Small Cell: 38% Non-small cell: 49% Unknown: 13%	**≥55%:** 54%	11 mo	4 mo	**Overall:** 31% **Ki-67 ≤ 55%:** 15% **Ki-67 ≥55%:** 42%
FFCD-GTE[2] (GI & unknown primary)	Total: 253 GI-NEC: 189	Small Cell: 39% Large Cell: 61%	**51-80%:** 47% **>80%:** 18%	11.6 mo	6.2 mo	50%
Mackey JR et al.[3] (GU)	Total 180 (106 bladder, 60 prostate, 8 renal, 6 ureter)	42.7% with mixed histology (adeno+ small cell);	Not reported	**Overall:** 10.5 mo Prostate: 7 mo Bladder: 13 mo	?	?
Margolis B et al.[4] (Cervix)	1,896	Not reported	Not reported	~10 mo	?	?
Morizane C et al. (GI, prospective)[5]	170	Small Cell: 48% Large Cell: 52%	Ki-67 ≥50%: 85%	12.5 mo	5.6 mo	54.5%

[1]Sorbye H et al. Ann Oncol 2013 [2]Walter T et al. Eur J Cancer 2017 [3]Mackey J et al. J Urol 1998 [4]Margolis B et al. Gynecol Oncol 2016

Monotherapy PD-1/PD-L1 Studies in SCLC

Study	Agent	N	Phase	Line of Therapy	ORR	SD	PFS (mo)	OS (mo)	Notes
IFCT-1603[a] (Non-comparative study against chemo)	Atezolizumab	43	2	2nd line	2.3%	20.9%	1.4	9.5	No efficacy vs chemo (i.e. negative study)
CheckMate 032[b]	Nivolumab	98	2	≥2nd line (56% w/ 2-3 prior therapies)	10%	22%	1.4	4.4	
CheckMate 331[c] (Randomized against 2nd line chemo)	Nivolumab	569	3	2nd line	14%	?	1.4	7.5	No efficacy vs chemo (i.e. negative study)
KEYNOTE 028[d]	Pembrolizumab	24	1b	≥3rd line	33%	4.2%	1.9	9.7	
KEYNOTE 158[e]	Pembrolizumab	107	2	≥2nd line	18.7%	?	2.0	9.1	

[a]Pujol JL et al. J Thorac Oncol 2019; 14(5): 903-13 [b]Antonia SJ et al. Lancet Oncol 2016; 17:883-95 [c]Reck M et al. ESMO 2018, Abstract LBA5.
[d]Ott PA et al. J Clin Oncol 2017; 35:3823-29 [e]Chung HC et al. ASCO 2018, Abstract 8506

Monotherapy PD-1/PD-L1 Studies in Extrapulmonary NEC

Study	Agent	N	Histologic Characteristics	Phase	Line of Therapy	ORR	SD	PFS (mo)	OS (mo)
Vijayvergia N et al[a]	Pembrolizumab	**21** • 14 GI • 1 kidney • 6 unknown	**Small cell:** Unknown **Ki-67:** 48% ≥ 55%	2	≥2nd	4.7%	14.2%	2.3	3.9
Mulvey C et al[b]	Pembrolizumab (Part A Results)	**14** • 6 GI • 4 GU • 4 Other	**Small Cell:** 79% **Ki-67:** Median 80%	2	≥2nd	7%	14%	1.9	4.8
AVENEC[c]	Avelumab	**29** • 21 GI • 2 ENT • 2 Lung • 4 GU	**19 NEC, 10 NET** **Small Cell:** Unknown **Mean Ki-67:** 73%	2	≥2nd	6.9%	20.7%	3.9	4.7

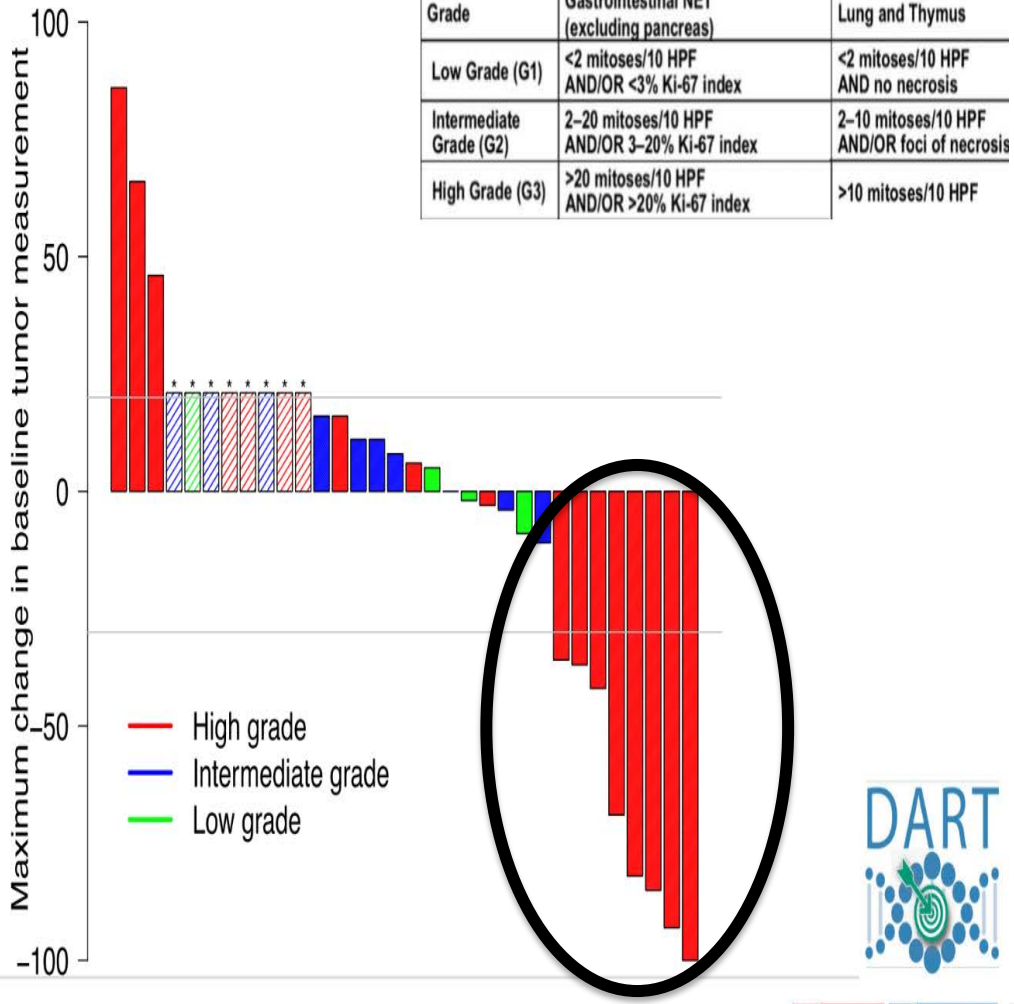
Similar lack of activity with single agent anti PD-1/PDL1 in SCLC and high-grade NEC
RR 5-10%
PFS 1.4-2 months

[a]Vijayvergia N et al. ASCO 2018: Abstract 4104
[b]Mulvey C et al. GI ASCO 2019: Abstract 363
[c]Fottner C et al. ASCO 2019: Abstract 4103

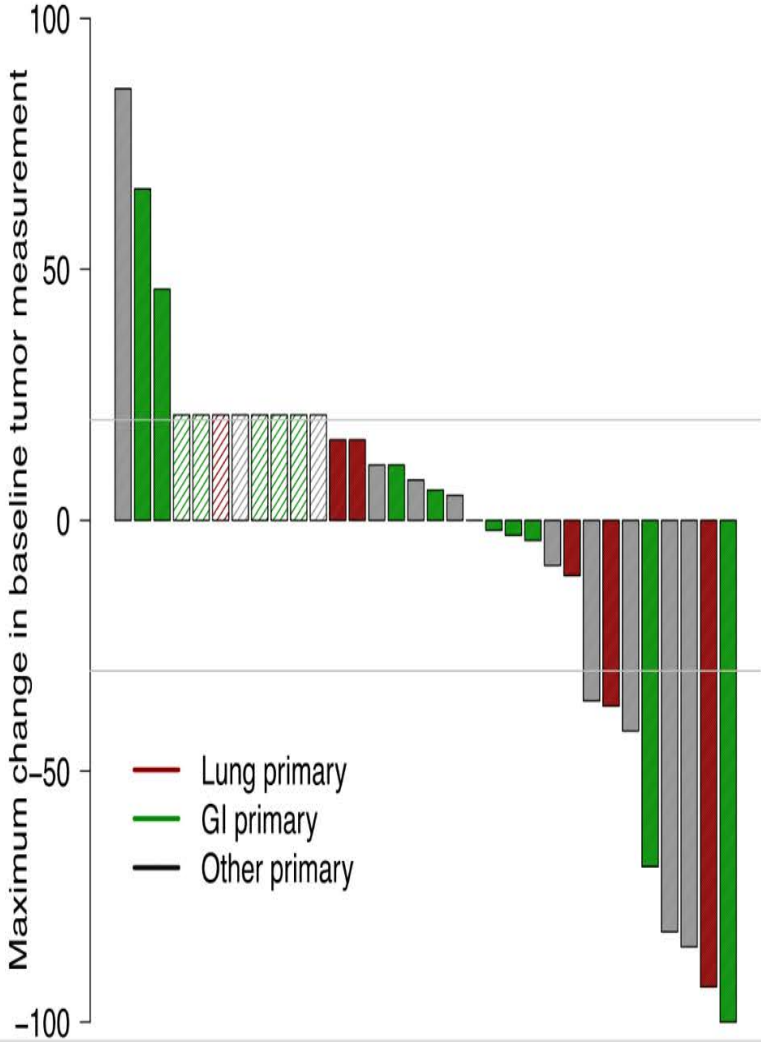
SWOG S1609 (DART Study): Nivolumab (PD-1) + Ipilimumab (CTLA-4) in Rare Cancers: Neuroendocrine Cohort

Response Rate by Tumor Grade of Neuroendocrine Neoplasm

Grade	Gastrointestinal NET (excluding pancreas)	Lung and Thymus
Low Grade (G1)	<2 mitoses/10 HPF AND/OR <3% Ki-67 index	<2 mitoses/10 HPF AND no necrosis
Intermediate Grade (G2)	2–20 mitoses/10 HPF AND/OR 3–20% Ki-67 index	2–10 mitoses/10 HPF AND/OR foci of necrosis
High Grade (G3)	>20 mitoses/10 HPF AND/OR >20% Ki-67 index	>10 mitoses/10 HPF

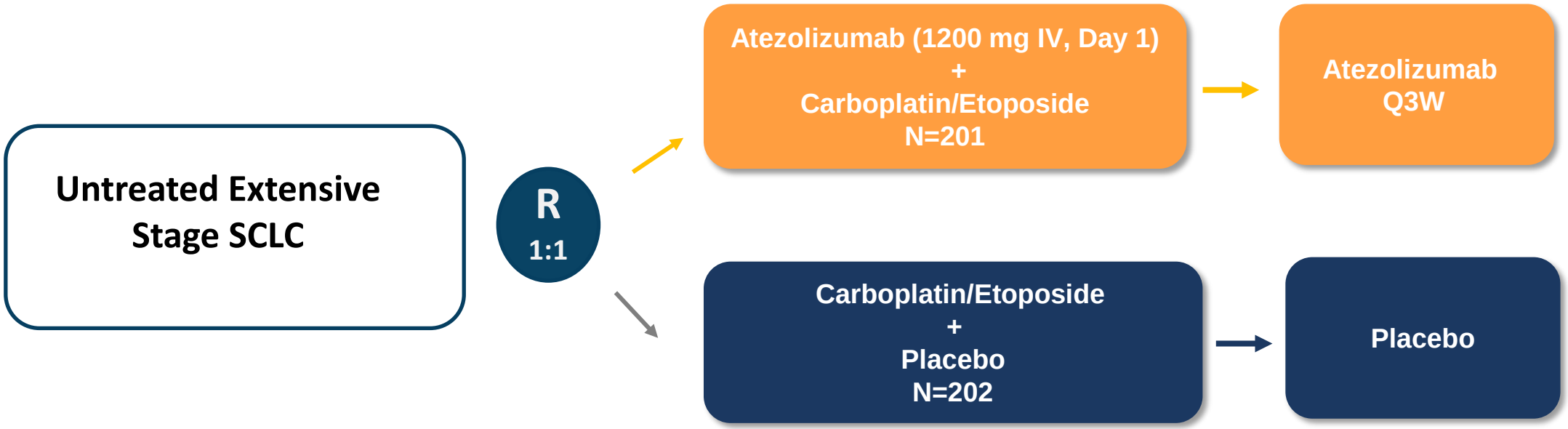


Response Rate by Primary Site of Neuroendocrine Neoplasm



Patel SP, Othus M, Chae YK, et al. Clin Cancer Res 2020; 26: 2290-6

IMpower133: Ph1/3 study of 1L carboplatin/etoposide ± atezolizumab in extensive-stage SCLC

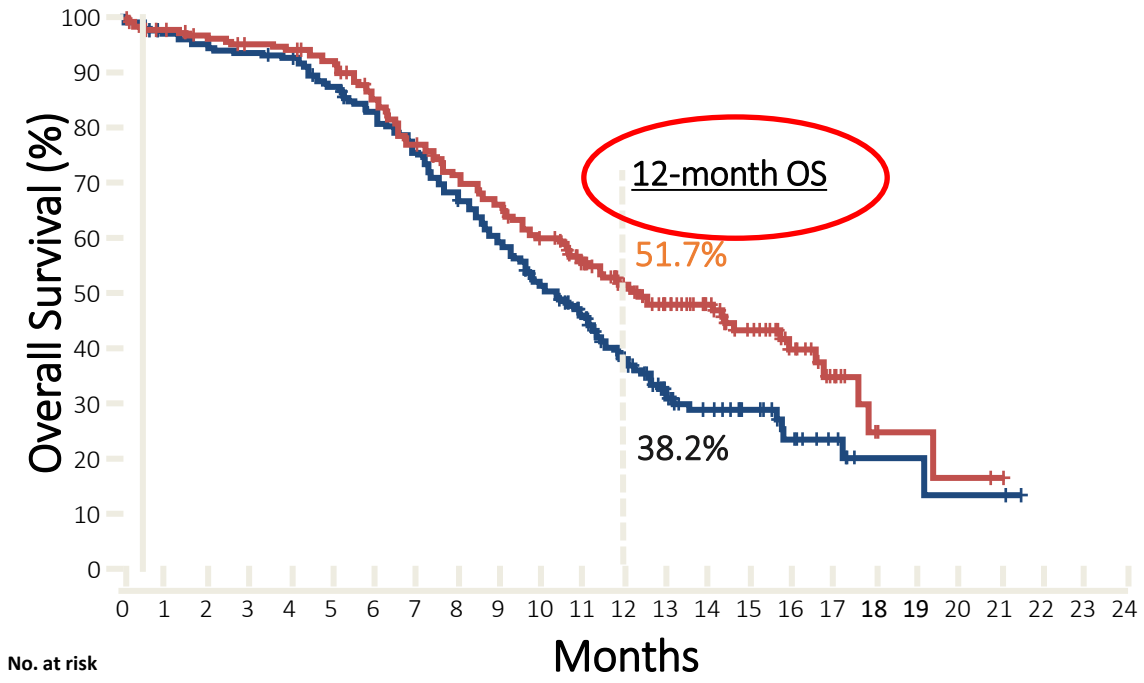


Primary Endpoints: Overall survival (OS) and Progression Free Survival (PFS)

Secondary Endpoints: Objective Response Rate (ORR) and Duration of Response (DOR)

Horn L et al. N Engl J Med 2018

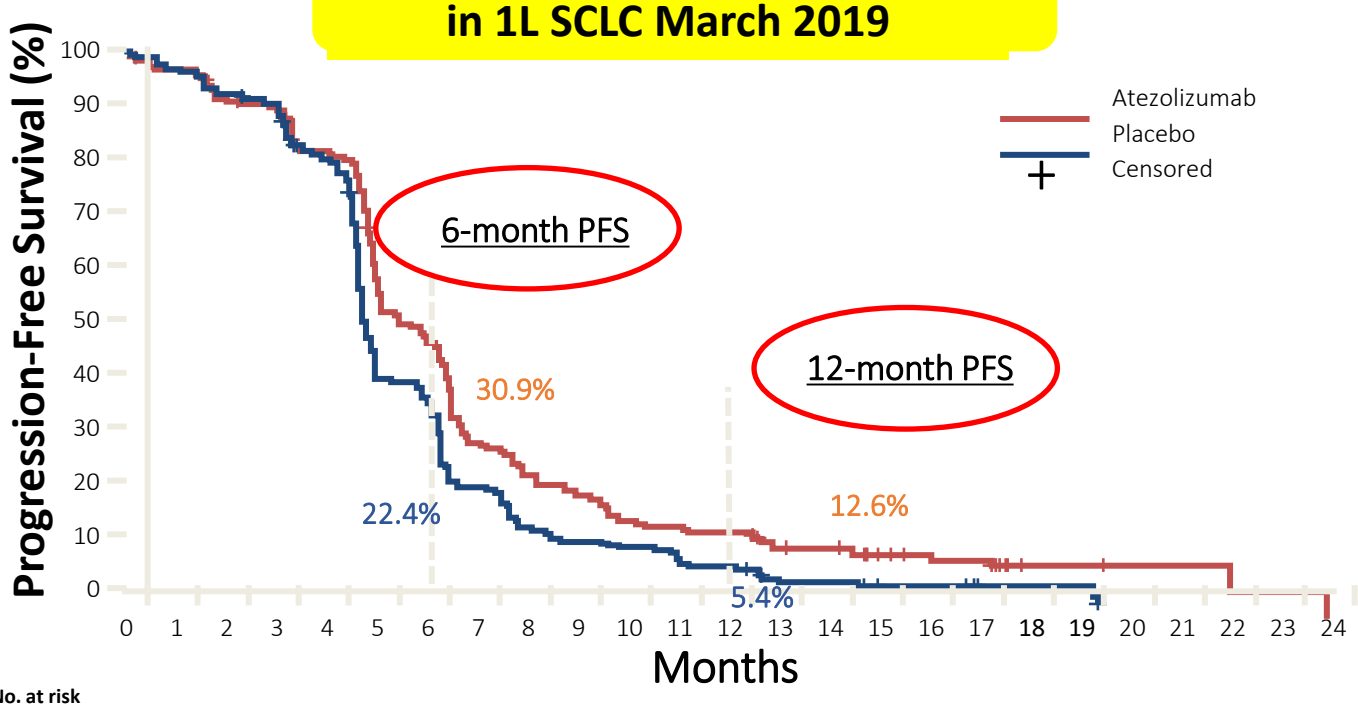
IMpower133: 1L Carboplatin/Etoposide ± Atezolizumab in Extensive-Stage SCLC



No. at risk

Atezolizumab	201	191	187	182	180	174	159	142	130	121	108	92	74	58	46	33	21	11	5	3	2	1	
Placebo	202	194	189	186	183	171	160	146	131	114	96	81	59	36	27	21	13	8	3	3	2	2	

FDA approval of Atezolizumab in 1L SCLC March 2019



No. at risk

Atezolizumab	201	190	178	158	147	98	58	48	41	32	29	26	21	15	12	11	3	3	2	2	1	1	
Placebo	202	193	184	167	147	80	44	30	25	23	16	15	9	9	6	5	3	3					

	Atezolizumab (N=201)	Placebo (N=202)
OS events, n (%)	104 (51.7)	134 (66.3)
Median OS, months (95% CI)	12.3 (10.8, 15.9)	10.3 (9.3, 11.3)
HR (95% CI)	0.70 (0.54, 0.91) *P* = 0.0069	
Median follow-up, months[a]	13.9	

	Atezolizumab (N=201)	Placebo (N=202)
PFS events, n (%)	171 (85.1)	189 (93.6)
Median PFS, months (95% CI)	5.2 (4.4, 5.6)	4.3 (4.2, 4.5)
HR (95% CI)	0.77 (0.62, 0.96) *P* = 0.017	
Median follow-up, months[a]	13.9	

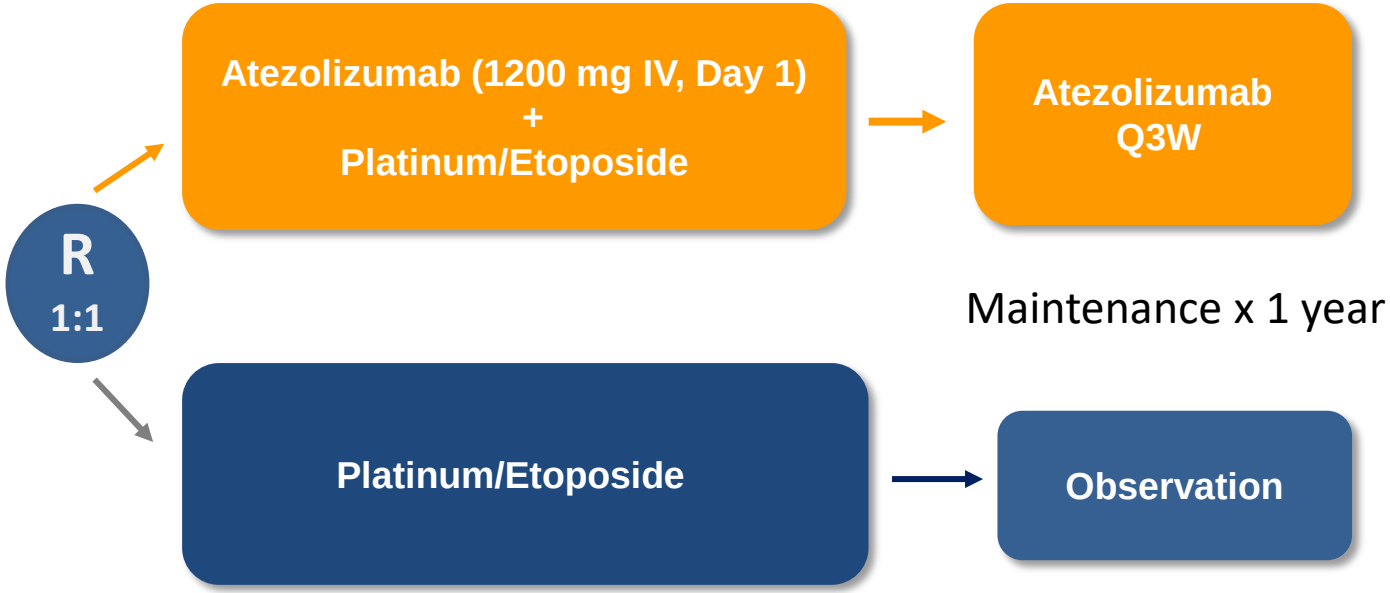
Horn L et al.
New Engl J Med 2018

Original Study Proposal

Phase 2 Randomized Trial

Key Eligibility:

- Metastatic poorly differentiated, grade 3 **GEP NECs (small cell or large cell Ki67>50%)**
- Known or suspected GI origin
- Measurable disease (RECIST v1.1)
- ECOG PS 0-2
- No prior treatment EXCEPT one cycle of platinum/etoposide allowed
- Treated asymptomatic brain metastases eligible



PFS improvement from 4 to 7 months
n=33 patients/arm
2 yrs accrual

Primary Endpoint:

- PFS

Secondary Endpoints

- ORR
- DOR
- OS

Exploratory Biomarkers

- Ki-67
- PD-L1
- TMB

In archival tumor tissue

Initial Feedback from SWOG GI Committee in 2018

- Mixed but overall favorable reviews
- Accrual major concern
  - Although DART study enrolled ~3 pts/month
  - Competing with another ECOG neuroendocrine study (ECOG EA2142: Enrolled WD-Gr3 and large cell; Excluded small cell)
- What is the relevant endpoint (PFS or OS)?
  - PFS would keep pt # low but might not be as meaningful clinically
- Approve to discuss at the NCI Neuroendocrine Task Force

Several Presentations to NCI Neuroendocrine Task Force--2019

- Majority felt clinical question was important
- Agreed OS should be primary endpoint
- Accrual was major concern
  - Need study w/ quick read out but with clinical impact (i.e. design as phase 2/3 study)
  - Avoid any barriers (no central pathology read, allow 1 prior cycle therapy)
  - Despite trying to avoid barriers, final recommendation was to RESTRICT to small cell only AND broaden to all extrapulmonary sites (ie GU/Gyn) to avoid competition with other NCTN neuroendocrine study

- In late 2019, SWOG leadership decided study would be run through Early Therapeutics/Rare Cancers Committee with GI as a secondary committee

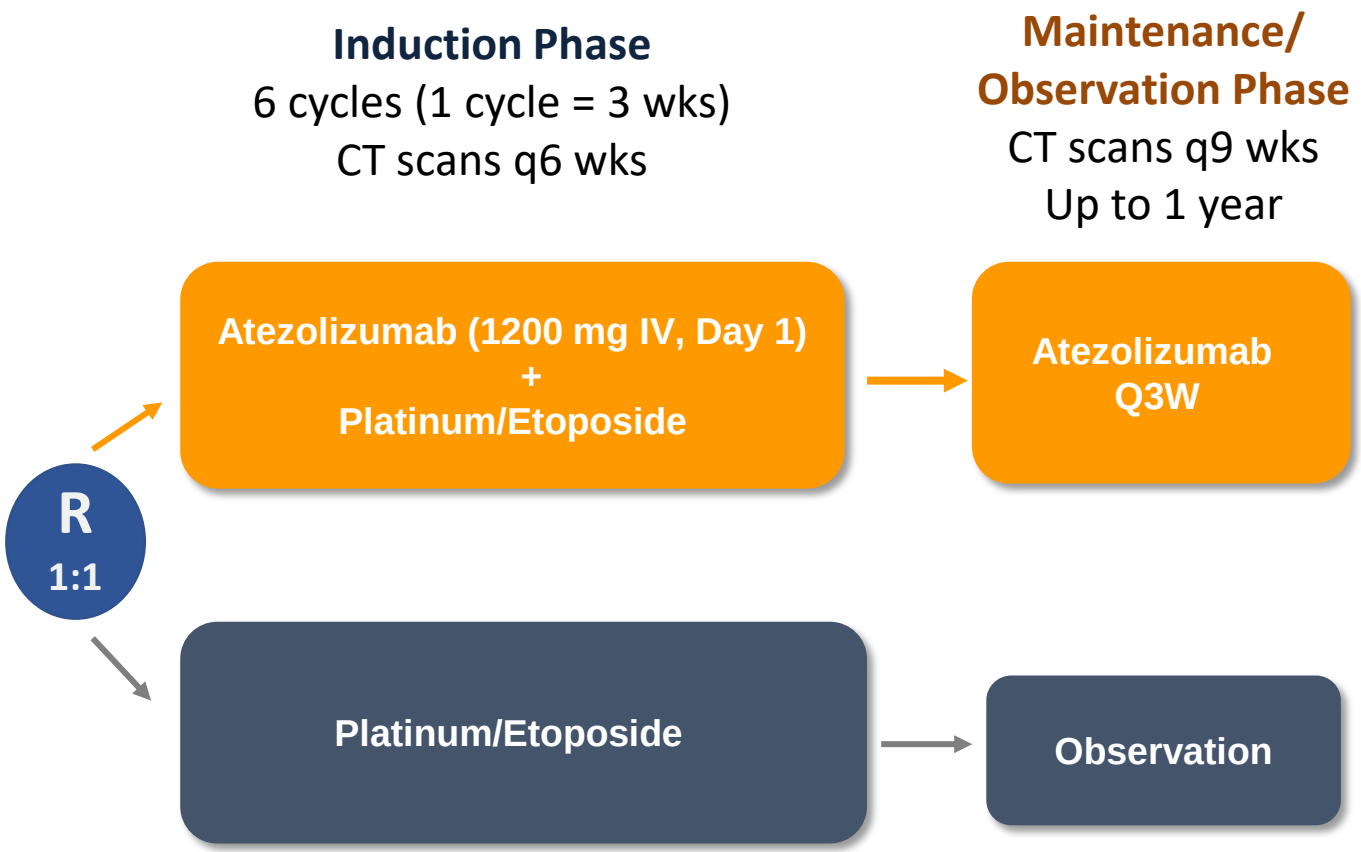
Updated Study Schema

Phase 2 Randomized Trial

N=134 pts

Key Eligibility:

- **Metastatic poorly-differentiated extrapulmonary (i.e. exclude lung) small cell NEC of any origin**
- Measurable disease (RECIST v1.1)
- ECOG PS 0-2
- No prior treatment EXCEPT one cycle of platinum/etoposide allowed
- Treated asymptomatic brain metastases eligible
- Stratification factors:
  - ❑ 1) Received (Y/N) one cycle of therapy prior to randomization
  - ❑ 2) Known pancreatic origin vs other GI origin vs non-GI origin



Primary Endpoint:

- OS

Secondary Endpoints

- PFS
- ORR
- Clinical benefit rate
- Duration of response

Exploratory:

- Banking archival tumor tissue and blood for future research (e.g. Ki-67 index, PD-L1, TMB, cell-free DNA)

Roller coaster ride in 2020-2021

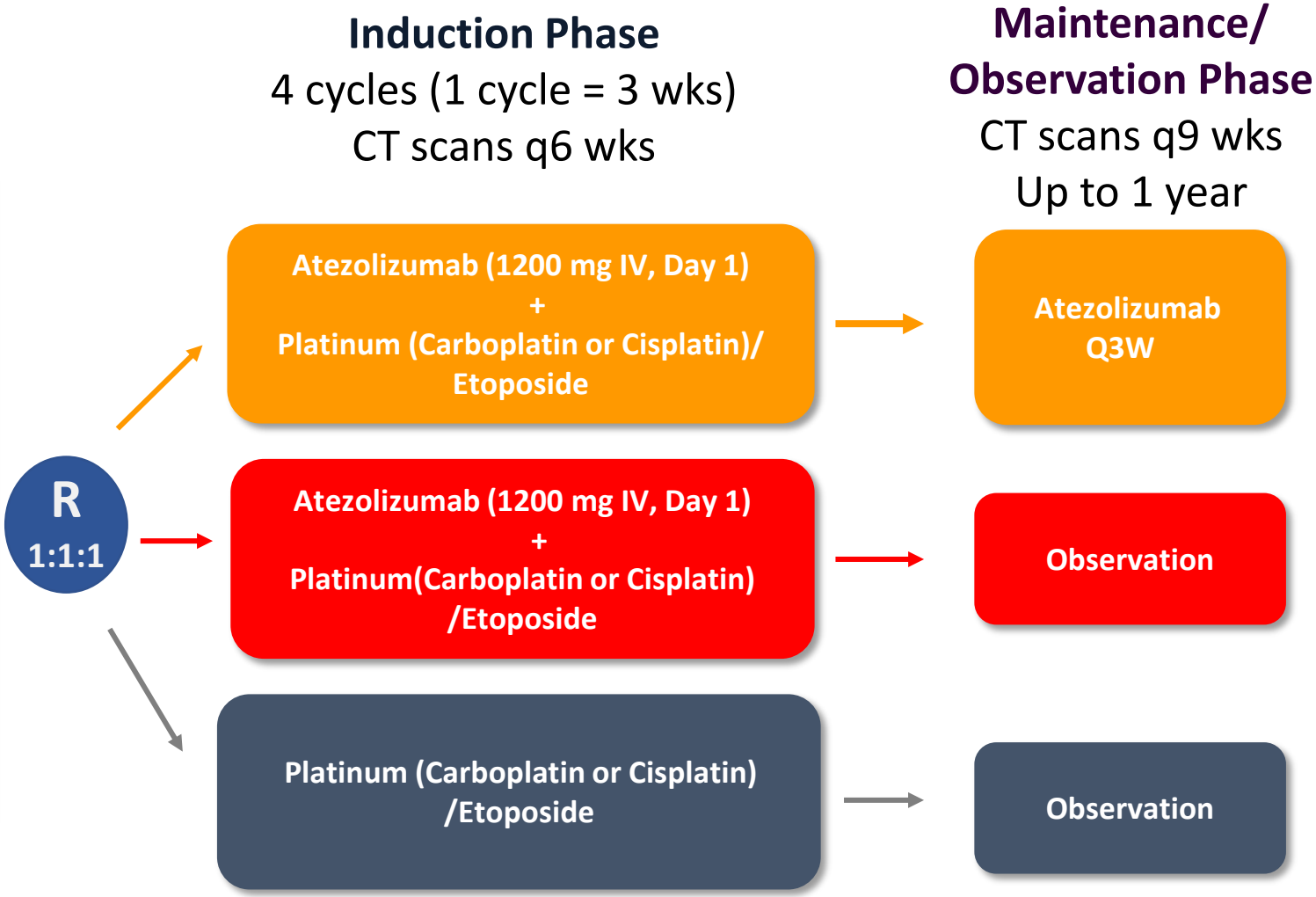
- SWOG leadership approves the study Feb 2020 - S2012 name given!!
- Study undergoes formal review at NCI GI Steering Committee and CTEP
  - All felt clinical question important, but accrual is concern
  - And yet, concern raised about lack of prospective data for the maintenance checkpoint inhibitor
  - Study rejected and needs to be modified to include another treatment arm of chemoimmunotherapy induction and no maintenance therapy (so more patients????)
- Roche/Genentech will not support 3 arm study
- CTEP will not approve 2 arm study
- Study seemed like it was going to fail
- Multiple meetings with CTEP and Genentech
- After much debate for 1 year, ultimately all parties agreed to 3 arm study

SWOG S2012: Randomized Ph 2/3 Trial of First Line Platinum/Etoposide +/- Atezolizumab for Extrapulmonary Small Cell NEC

Activated Dec 2, 2021

Key Eligibility: **N=189**

- Metastatic poorly-differentiated extrapulmonary (i.e. exclude lung) small cell NEC with Ki-67≥55%
- Evaluable, measurable and non-measurable disease
- Zubrod PS 0-2
- No prior treatment EXCEPT one cycle of platinum/etoposide allowed
- Asymptomatic brain metastases eligible
- **Stratification factors:**
  - ❑1) PS 0-1 vs 2
  - ❑2) Known prostate vs GI vs other origin



Primary endpoint: OS (from time of randomization)

Secondary endpoints: OS (from time of maintenance/observation), PFS, ORR, DOR

Translational analyses: Banking tissue and blood for future biomarker analyses

Zhen DB, Chiorean EG, et al. Abstract TPS4179. ASCO 2022 Annual Meeting

Status of SWOG S2012

- As expected, accrual was slow with restriction of small cell histology only (3 pts in 1 year)
- Ultimately the other study closed in 2021, providing opportunity to amend S2012 to allow enrollment of all NEC subtypes (ie small and large cell)
- NCI initially disapproved amendment regarding over GU NEC (wanting de-novo cases and not mixed cases, which is rare and will hinder accrual)
- With support from other members at NCI, SWOG and NCI NET committees, GU investigators, and patient advocates, ultimately CTEP agreed to approve amendment, activated 1/2023
- Amendment has helped accrual (~3-4 per month)!!

Career Development as a Result of My NCTN Trial

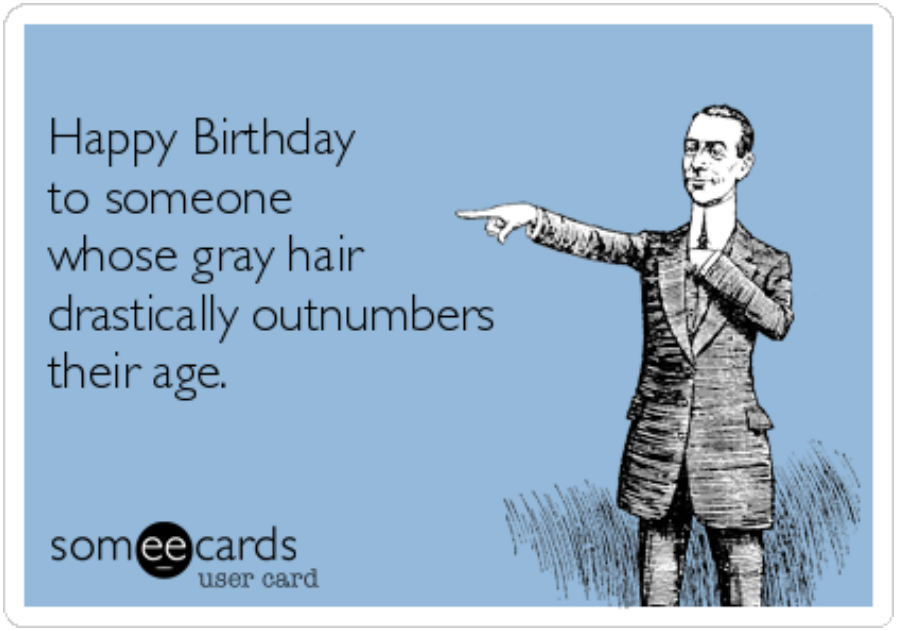
- Invited to be SWOG Champion for 2 other NCTN cooperative group trials
- Elected to be an Early Career Member of the NCI Neuroendocrine Task Force
- Elected to be FHCC representative on NCCN Neuroendocrine and Adrenal Guidelines Panel
- Developed a NET Tumor Board in 2019 and now co-lead our neuroendocrine program
- Providing mentorship to other investigators proposing trials

Lessons Learned for Developing Trials in NCTN Cooperative Groups

- **MENTORSHIP IS KEY!!!!—Need advocate(s)**
- Be prepared (know your stuff, anticipate feedback)
- Be ready to handle critiques (do not take things personally!!!)
- Be patient (it's a very long process)
- Take ownership (respond to requests promptly)
- Be persistent but flexible (have less control over some things)
- Even if your trial doesn't happen, people will recognize your effort and could open other opportunities (help with other studies, serve on committees)

Conclusions

- Would I do it all over again---interestingly, YES! (and I will)
- Grew personally and professionally through this experience
- Gained significant knowledge and skills that have helped me in all my clinical trials research
- Many networking opportunities (even outside of my GI area)
- Even though it's hard, the payoff is getting to be involved in national practice changing research that could affect the lives of many cancer patients



"All you have to do is follow the Yellow Brick Road...."

All you need are friends along the way!

An NCI Perspective:
Andrea Denicoff, RN, MS, ANP
and
Grace Mishkin, PhD. MPH

Key NCI Roles During the Life of an NCTN Protocol

What are all of these NCI acronyms?

- Cancer treatment, imaging, and biomarker clinical trials are supported through NCI's Division of Cancer Treatment and Diagnosis **(DCTD).**
  - In DCTD, the Cancer Therapy Evaluation Program (**CTEP**) supports the National Clinical Trials Network (**NCTN**).
- Cancer prevention, screening, symptom management, and cancer control clinical trials are supported through NCI's Division of Cancer Prevention **(DCP). DCP** also supports Quality of Life (QOL) endpoints in NCTN cancer treatment trials.
  - DCP supports NCI's Community Oncology Research Program (**NCORP**).
- In the NCI Office of the Director, the Coordinating Center for Clinical Trials **(CCCT**) oversees the NCTN Steering Committees **(SCs)** that review NCTN trial concepts.

NCI involvement in early trial development in the NCTN

CTEP works with industry partners to develop and maintain a portfolio of cancer therapy agents that may be used in trials conducted under CTEP IND

CCCT Steering Committees and Task Forces discuss trial ideas, disease portfolios, and occasionally coordinate Clinical Trial Planning Meetings

https://ctep.cancer.gov/industryCollaborations2/agreements_agents.htm

https://www.cancer.gov/about-nci/organization/ccct/steering-committees/nctn

What happens when NCTN trial ideas are submitted to CTEP for review?

Ideas for early-phase trials that plan to enroll fewer than 90-100 participants are submitted as **Letters of Intent (LOIs)** and a decision is made by NCI

Ideas for late-phase and larger trials are submitted as **Concepts** and a decision is made by the Steering Committees

Either way, the LOI or Concept is evaluated by reviewers from across NCI: experts in the disease area, experts who focus on that agent or type of treatment, biostatisticians, and others as needed

If an LOI or Concept is approved, the NCTN Group works on developing the protocol based on the approved trial design

CTEP has deadlines for the time from **initial review of a trial idea** to **trial activation**:

- **LOIs:** 400 days from initial CTEP review to trial activation
- **Early Phase Concepts:** 450 days from initial Steering Committee review to trial activation
- **Phase 2/3 or Phase 3 Concepts:** 540 days from initial Steering Committee review to trial activation

These deadlines, also called OEWG timelines, were developed by the Operational Efficiency Working Group (OEWG), which had the goal of improving trial timelines.

https://ctep.cancer.gov/protocolDevelopment/OEWG.htm

When the NCTN Group submits the protocol and consent documents,

they are closely reviewed by NCI experts and a full review is conducted by CTEP's Protocol Review Committee (PRC)

NCI Reviewers Include:

- Disease Experts
- Agent Experts
- Radiation Oncologists
- Biostatisticians
- Regulatory Specialists
- Pharmacists
- Imaging Experts
- Translational Scientists
- Quality of Life Reviewers from DCP

… and other experts, as needed

CTEP communicates with the lead group and study team throughout protocol revisions until a protocol and consent are finalized. CTEP staff approve the funding sheets based on the final protocol.

If the study is under CTEP IND, then CTEP is the study sponsor and coordinates closely with the FDA for regulatory submissions and the company for drug distribution.

When the protocol and consent have been approved by all NCI reviewers, the study is sent to the NCI CIRB for review and (if required) revisions.

Throughout this, CTEP contractors work with the lead group to set up the study in CTEP systems (including the CTSU and OPEN) and develop support documents like the National Coverage Analysis and **(starting this spring!)** EMR Templates.

Protocol Revisions and Preparation for Activation

Key Activities After Activation: General

Review	Review all proposed amendments
Request	Request amendments if warranted (e.g., changes in agent risks)
Participate	Participate on Group Data Safety Monitoring Boards (DSMBs)
Update	Update systems and funding sheets as needed
Track	Track accrual during first two years using slow accrual tracking rules
Ensure	Ensure compliance with regulations and NIH grant requirements

https://ctep.cancer.gov/protocolDevelopment/cde_data_policies.htm

Key Activities After Activation: CTEP IND Trials

Monitor	Monitor adverse events
Distribute	Distribute IND agent
Coordinate	Coordinate company agreements and requests
Submit	Submit reports to the FDA
Complete	Complete all activities required of an IND sponsor

....and more supportive friends along the way!

SWOG ORP DISEASE LIAISON COMMITTEE

Chairs: Sandy Annis, BA CCRP

and

Erin Cebula, MPH, CCRP

WHAT IS A DISEASE LIAISON?

- Participates in the development of tools to assist research sites with study selection, implementation and compliance.
- Reviews protocols in development and provides feedback from a site perspective, addressing feasibility and concerns regarding potential logistical challenges with implementation.
- Provides site implementation feedback to SWOG Disease Committees after the study is activated.
- Maintains active lines of communication with SWOG Protocol Coordinators and committees
- Mentors and supports development of new liaisons.

CURRENT ORP LIAISON OPENINGS

- Cancer Control and Prevention – Symptom Control/QOL – Need RN
- Early Therapeutics and Rare Cancers – Need a CRA and a RN
- GI – Need RN
- GU – Need RN
- Leukemia – Need RN
- Myeloma – Need RN
- Liaison at Large – CRAs AND RNs!

We're Off to See the Wizard Feasibility

Ashley Tydon, Deputy Director, UC Davis Cancer Care Network

Anthony Hicks, Operations Supervisor, Cancer Research Consortium of West Michigan

Rachel Kitchen, Sr. Regulatory Affairs Coordinator, UC Davis Cancer Care Network

How do you monitor the availability of new trials and assess interest?

Many Choices of Trials

How do you assess interest in new trials?

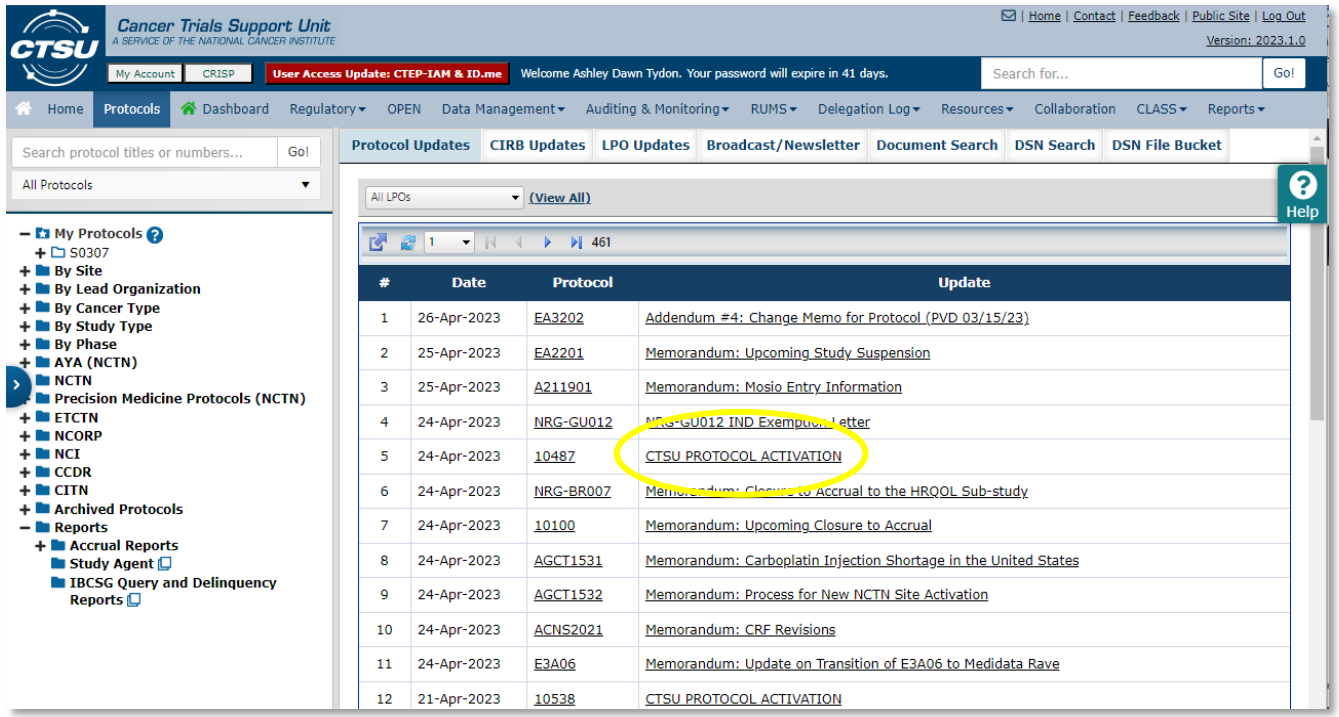
Anthony Hicks

- All activated trials through NCTN (on CTSU and activation emails)
- Interest emails sent to sites and treating investigators of specific disease
- Endorsed trials move on to the next step of feasibility

How do you assess interest in new trials?

Ashley Tydon

- Review activation emails
- Search CTSU website monthly for new trial activations
- Trials that match our patient population are discussed at monthly meetings
- Endorsed trials move on to feasibility and activation process



How do you assess your site(s) potential to accrue to new trials?

How do you assess accrual potential?

Anthony Hicks

- Potential to accrue is important but part of our mission is to provide access to the latest cancer research for anyone in our community

How do you assess accrual potential?

Group Code	Site Group	Total Cases	Class			Sex			Stage					
			Analytic	NonAn	Other	M	F	Other	Stage 0	Stage I	Stage II	Stage III	Stage IV	Unknown
	ALL SITES	359	358	1	0	166	193	0	17	108	46	58	59	37
740	BREAST	95	95	0	0	0	95	0	6	57	15	8	7	2
850	PROSTATE	59	59	0	0	59	0	0	0	25	10	16	7	1
541	RECTUM & RECTOSIGMOID	9	9	0	0	5	4	0	0	2	1	3	2	1
733	OTHER SKIN CA	2	2	0	0	1	1	0	0	0	0	1	1	0
610	LARYNX	3	3	0	0	3	0	0	0	1	0	0	2	0
710	SOFT TISSUE	2	2	0	0	0	2	0	0	0	0	0	0	1
820	CORPUS UTERI	7	7	0	0	0	7	0	0	0	0	1	0	6
692	MYELOMA	5	5	0	0	4	1	0	0	0	0	0	0	0
621	LUNG/BRONCHUS-SMALL CELL	5	5	0	0	1	4	0	0	0	1	1	3	0
860	TESTIS	1	1	0	0	1	0	0	0	1	0	0	0	0
999	UNKNOWN OR ILL-DEFINED	7	7	0	0	5	2	0	0	0	0	0	0	0
530	COLON	15	15	0	0	6	9	0	0	1	3	6	2	3
880	BLADDER	19	19	0	0	14	5	0	10	1	3	3	2	0
930	THYROID	3	3	0	0	0	3	0	0	1	0	0	0	1
891	KIDNEY AND RENAL PELVIS	11	11	0	0	6	5	0	0	6	0	2	3	0
731	MELANOMA OF SKIN	11	11	0	0	10	1	0	1	3	4	2	0	1
400	LIP	1	1	0	0	0	1	0	0	0	0	0	0	1
640	PLEURA	1	1	0	0	1	0	0	0	0	0	1	0	0
570	PANCREAS	9	9	0	0	5	4	0	0	2	2	0	5	0
962	NON-HODGKIN'S LYMPHOMA	20	20	0	0	11	9	0	0	2	3	1	3	11
622	LUNG/BRONCHUS-NON SM CEL	29	29	0	0	12	17	0	0	5	1	4	13	4

How do you assess accrual potential?

Rachel Kitchen

- Site leaders provide estimated accrual goals based upon group discussion, cancer registry, and EMR
- Regulatory Coordinator is responsible for validating the estimate based on similarly sized institutions, registry data, and accrual history on similar/previous trials

What are common barriers or feasibility issues? How do you address them?

What are common feasibility issues?

Anthony Hicks

- No physician interest
- Intense credentialing or study complexities
- Financial or coverage analysis issues
- Protocol issues identified (e.g., protocol or ICF inconsistencies)
- Utilize a weekly feasibility committee to identify and address issues

Clinical Trial Review Guide

Site Study ID: Click or tap here to enter text.	**Protocol ID**: Click or tap here to enter text.	**Version:** Click or tap here to enter text.
Title: Click or tap here to enter text.		

This guide was developed in collaboration with the SWOG ORP Liaison Committee and the SWOG Protocol Coordinators Operations Office. The purpose of the guide is to facilitate a thorough review of a NCI NCTN Group Clinical Trial for the following purposes; determining site feasibility, protocol implementation planning and a study aide for research staff training. Each section is organized to follow the process for learning and planning the implementation of the trial at your site. You may need to update the specific study guide as new amendments are generated.

Suggested documents to include during the clinical trial review: Study protocol. Consent, Funding memorandum, National coverage analysis, Local Coverage Analysis, Data collection forms and other trial related documents as needed.

To ensure accurate and current information, update this form with new protocol amendments as needed and include the specific section or page of the protocol for a quick reference.

This Section may be completed in collaboration with a business administrator.		
Intervention / Therapeutic ☐	**Non-Interventional** ☐	**NCT#:** Click or tap here to enter text.
NCI Anticipated Accrual: Click or tap here to enter text.	**NCTN Group credit assignment(s):** 1 group or split between the following:	
	☐ SWOG ☐ Alliance ☐ NRG ☐ ECOG ☐ CCTG	
Site Reimbursement Considerations:	**Base Award**: Click or tap here to enter text. **Credits**: Click or tap here to enter text. **See attached funding memo for specific reimbursement**	
Participating Site(s): Click or tap here to enter text.		
National CA Available?	☐ Yes ☐ No	**Are there any special billing or contractual considerations?** **Local CA considerations**: Click or tap here to enter text. **Patient billing contact**: Click or tap here to enter text. ** Patient Billing Considerations: Is your local CA consistent with the National CA and do you need any further institutional approvals for non- funded clinical services?*
Is this an FDA Registration Trial?	☐ Yes ☐ No	**What is the monitoring plan?** Click or tap here to enter text.
Are there additional regulatory requirements? *Consider additional resources and /or training to comply with any additional regulatory requirements.*		Click or tap here to enter text.

Clinical Trial Review Guide

Site Study ID: Click or tap here to enter text.	**Protocol ID**: Click or tap here to enter text.	**Version:** Click or tap here to enter text.
Title: Click or tap here to enter text.		

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Secondary:
Click or tap here to enter text.

Additional:
Click or tap here to enter text.

Background
Provide rationale for doing the study. Should include history of toxicities from previous studies to allow some assessment of expected toxicities and severity. This will provide a reference point for development of study parameters, case report forms and eligibility. (For protocol development reviewer: Are the references applicable for the patient population?)

Notes:
Click or tap here to enter text.

Non-Treatment Studies: Schema and/or Plan (*ONLY complete this section for non-therapeutic/cancer control trials*).
Protocol Section: Click here to enter text.
Include the protocol sections/ pages where you found the information for future reference.

Guide Questions	Review	Site Implementation Plan / Considerations
How will patients be identified and screened for this study?	Click or tap here to enter text.	Click or tap here to enter text.
What if any departments need to be involved in conducting the trial?	Click or tap here to enter text.	Click or tap here to enter text.
Are there any supplies or equipment provided for this study?	Click or tap here to enter text.	Click or tap here to enter text.
Required training?	Click or tap here to enter text.	Click or tap here to enter text.

Study Participant Selection (eligibility, staging, stratification) **Protocol Section:** Click here to enter text.
A great quick reference section for information including staging, related references and time frames. What are the histological classifications and staging?

How do you manage your study teams with regards to roster upkeep and Delegation of Tasks Logs (DTLs)? Can you recommend any best practices?

What about rosters and DTLs?

Anthony Hicks

- Dedicated rostering individuals in charge of on-boarding and off-boarding
- Dedicated staff members for DTLs
- Communication is key

What about rosters and DTLs?

Ashley Tydon

- CTSU RUMS updates are a part of our on-boarding and off-boarding checklists
- Rosters are reviewed at least annually for accuracy
- Always designate a back-up and communicate with your team who has roster admin access

What about rosters and DTLs?

Rachel Kitchen

- Central CTEP ID administrator
- Central DTL administrator who can make the updates in real time
- Decentralized approaches seem to cause delayed updates and miscommunication of roles

The Community Perspective: Community Advisory Boards

The Importance of Community

.....as told by
Auntie Em

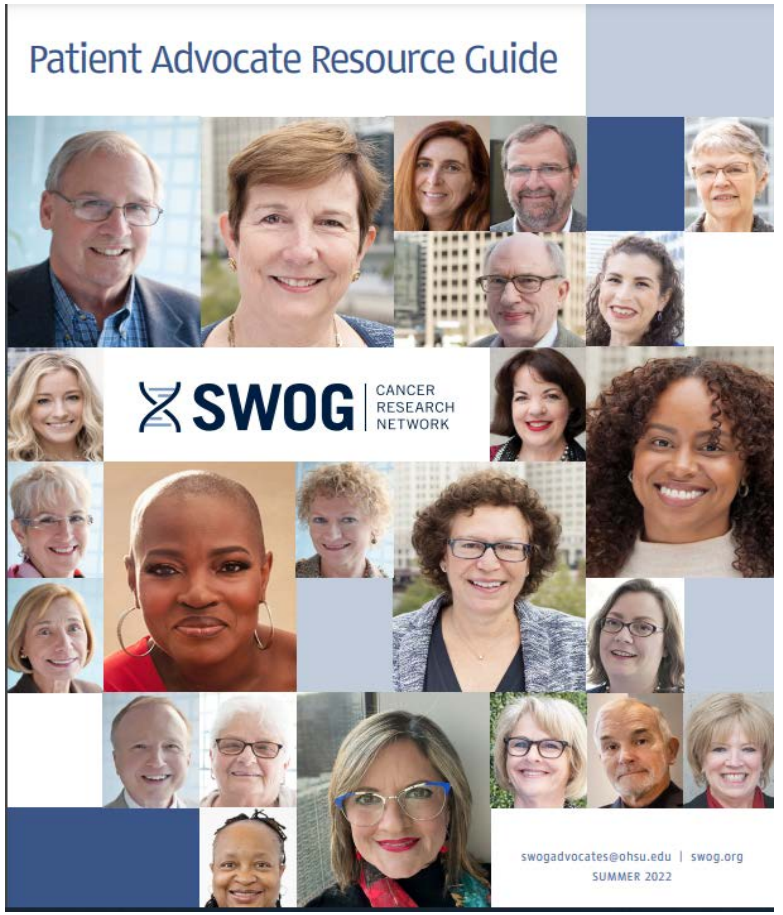
(aka Connie Szczepanek, RN, BSN,
Cancer Consortium of West Michigan, Grand Rapids, MI)

Research advocates can

- Provide a link to the community
- Share important perspectives and experiences
- Increase awareness about clinical trials by talking with patients and the public about clinical trials
- Help reduce the barriers patients face in gaining access to clinical trials
- Talk to patients about their experience participating in a clinical trial
- Provide resources to patients and their families
- Act as an advisor to your program
- Develop/review educational materials about clinical trials
- Serve as the community member of your IRB or Ethics Committee

Engaging Patient and Community Voices

- Nationally
- Across SWOG
- Locally



Engaging Patient and Community Voices… Locally

Think about:

- WHAT your mission and vision are
- WHERE you can make a difference
- Set a course
  - –Map out a strategic plan
  - –Identify a starting point
  - –Make it feasible: i.e.: start small and build on success
- WHO can help

Patient and Community Advisory Boards

- Are composed of patients &/or community members who share an experience related to cancer research
- Convene to contribute the patient and community voice to a program, policy, project, trial, or other business of the research
- Identifies local perspective and may develop ways to address those needs using a community approach
- Non-binding suggestions, advise, and recommendations
- Usually voluntary; often viewed as a way of “giving back” to the community who helped them

How do you form a Community Advisory Board?

- Determine the purpose, structure, and questions you want the CAB to address.
- Enlist the help of staff members, providers, hospital leaders, and other constituents to recommend potential participants.
- Recruit, recruit, recruit! This doesn't end because people move on and off the CAB service depending on their life events.
- Utilize online resources from known sources and network with existing advisory board knowledge experts.
- Work with a core group to develop the mission, vision, and actions the committee will be involved in.

Patient Advisory Board for Clinical Research

established May 2008

Real World Impact in West Michigan

- Getting the word out
- Sharing perspective
  - –Media Opportunities
  - –Articles and Interviews
  - –Cancer Center Walk-Throughs
- Building Tools
  - –Web Site Design
  - –Educational and Study Materials
  - –Survivorship Care Plan—Clinical Trials Summary
  - –Our own local Clinical Trials Video

Real World Impact in West Michigan

- Testing tools and plans
  - –Kick the tires and test drive ideas
  - –Offer ‘brutally honest’ feedback and opinions
- Planning recruitment strategies
- Providing accurate information and personal experience
- Advising Program Leadership
- Renaming our Program
- Inspiring the Research Team!!!!

Trials Of Note for Accrual (AKA Please Enroll!)

SWOG S2302: Pragmatica-Lung: A Prospective Randomized Study of Ramucirumab Plus Pembrolizumab Versus Standard of Care for Participants Previously Treated With Immunotherapy for Stage IV or Recurrent Non-Small Cell Lung Cancer

SWOG S1823: A Prospective Observational Cohort Study to Assess miRNA371 for Outcome Prediction in Patients with Early-Stage Germ Cell Tumors

SWOG S2010: A Randomized Phase III Trial Comparing Active Symptom Monitoring Plus Patient Education Versus Patient Education Alone to Improve Persistence with Endocrine Therapy in Young Women with Stage I-III Breast Cancer (ASPEN)

Lung-MAP: S1800D & S1900E are open to accrual

The following trials will have attended tables at Open Forum for your interactive questions

SWOG S2302: Pragmatica-Lung: A Prospective Randomized Study of Ramucirumab Plus Pembrolizumab Versus Standard of Care for Participants Previously Treated With Immunotherapy for Stage IV or Recurrent Non-Small Cell Lung Cancer

SWOG S1823: A Prospective Observational Cohort Study to Assess miRNA371 for Outcome Prediction in Patients with Early-Stage Germ Cell Tumors

SWOG S1826: A Phase III, Randomized Study of Nivolumab (Opdivo) Plus AVD or Brentuximab Vedotin (Adcetris) Plus AVD in Patients (Age >/= 12 years) with Newly Diagnosed Advanced Stage Classical Hodgkin Lymphoma

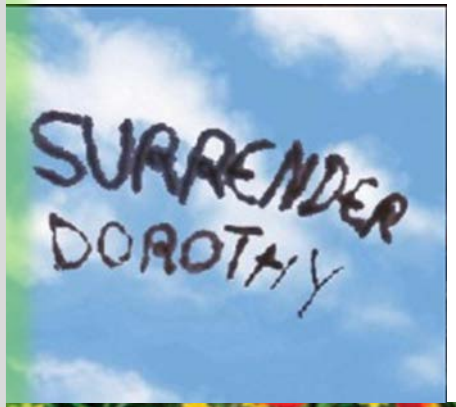
SWOG S1900G: A Randomized Phase II Study of INC280 (Capmatinib) Plus Osimertinib with or Without Ramucirumab in Participants with EGFR-Mutant, MET-Amplified Stage IV or Recurrent Non-Small Cell Lung Cancer (Lung-MAP Sub-Study)

SWOG S1803: Phase III Study of Daratumumab/rHuPH20 (NSC-810307) + Lenalidomide or Lenalidomide as Post-Autologous Stem Cell Transplant Maintenance Therapy in Patients with Multiple Myeloma (MM) Using Minimal Residual Disease to Direct Therapy Duration (DRAMMATIC Study)

"I can see the Emerald City"

Wait...
Poppies,
Poppies

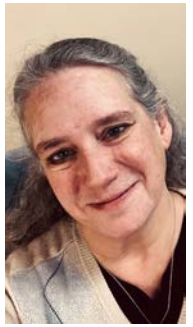
(aka last-minute hitches and glitches)



The Implementation Bridge
-taking a study from feasibility to activation-

Amy Koffarnus

- Research Administrator,
- CROWN Consortium



Jodi Koch

-Team Lead, HSHS St. Vincent Hospital, CROWN Consortium

Nichole Mahaffey

-Assistant Director of PRMS,
UC Davis Comprehensive Cancer Center

Kristen Ford

-Research Manager, Oncology Treatment, Quality Assurance, UC-NCORP

We can do it, but how?

Panelists will discuss:

- How their site was able to standardize processes
- Common hurdles to activation
- Tips and Tricks

When implementing/activating a clinical trial locally, what information from your sites' feasibility assessment is utilized to ensure successful enrollment?

Nichole –

- **Feasibility informs tools developed during activation so all team members can implement the trial.**
- **Work with outside departments to develop 'good to go' signals**
- **Established checkpoints for mandatory processes**

Jodi -

- **Opening Studies on an as needed basis for patients**
- **Look for specific problems/concerns found on the feasibility review**
- **Should we open all our sites**

Kristen -

- **Physician Champions**
- **Ancillary reviews (path, biospecimen coordinator, research pharmacy, IT, etc)**
- **Cancer Data Management**

What tools or standardization processes have you implemented to streamline and improve protocol activation?

Jodi -

We have a worksheet
We develop pill diaries/drug information sheets as needed
Request the Epic beacon build prior/during activation

Kristen -

We use a web-based program called Air Table to track all study start up activities.
Staff can see where the trial currently is in the process and what the next steps will be prior to opening Internal Site Initiation Visit Checklist- multiple areas within clinical research are included

Nichole –

We utilize a CTMS system and have a pending trials team for activation
Research meetings with outside departments to streamline research specific activities.
Created expedited pathways for federal trials

What are some successful tips and tricks or examples of how you overcame an implementation hurdle with a recent SWOG trial?

Kristen-

A thorough feasibility review!
Our launch and review of S2302 was much faster due to the streamlined protocol.
Things moved quicker without many of the ancillary reviews which are usually needed and can be time consuming.

Nichole –

Recent radiology agreement for federal trials with non-standard of care scans

Jodi -

An email blast is sent out to our investigators/any ancillary dept once the study is open
For S2010 we started screening/making a list of patients going through chemo/XRT that might be eligible in the future

Last Step!

- Protocol Training before site activation
- You are now at the emerald city of enrollment!

That's a horse of a different color...come on in!

Site Perspectives:

Quality Assurance, Query Management, IPRs and Keepin' It Compliant

Amanda Dinsdale, MHA,
CCRC, ACRP-PM, CRCP
Director, Montana NCORP

Sheree Oxley RN, MS
Executive Director
Columbus NCORP

Barb Lomasney RN, BSN, OCN
Lead Clinical Research Nurse
Cancer Research Consortium of West Michigan

Communication!

- Regulatory Coordinators send out protocol update emails as received from group
- Bi-monthly emails with website updates
- Website with resources updated bi-monthly

Help Each Other

- If you are in RAVE or DQP and see a query for a fellow workmate, let them know.
- Share lessons learned with each other
- Central shared file with protocol resources

Always be Audit Ready

- Identify protocol deviations in real time
- Helps to track trends and address issues before they are repeated

Prioritize

- Active patients should be prioritized over follow-up
- Designate a day of the week or a set period of time to focus on follow-up

Organization

- Track your patients
- Use your calendars for reminders

- Quality Assurance: Cycle one QA - catch it early
- Query Management: Finding trends
- Educational Moments - Learning from our mistakes
- Protocol Clarifications - Prevent duplicate questions
- Protocol Deviations - Real time CAPAs
- Q.A. Prep for Audits

Follow the Road to Best Practices

Take Courage, Lion

You Have Heart, Tin Man

Scarecrow, You Really Do Have a Brain!

From the Perspective of a Cancer Survivor

A Conversation with
Dana A. Little, MHA, CCRP
and
Glinda, the Good Witch of the North

Somewhere over the Rainbow

Ensuring the Story is Told from Beginning, Middle to the End

Michael LeBlanc

Director, Statistical Center,

Faculty Statistician Lymphoma and iMATCH

End: The primary analysis

Excitement - is there a new effective treatment?

Ways to limit toxicity

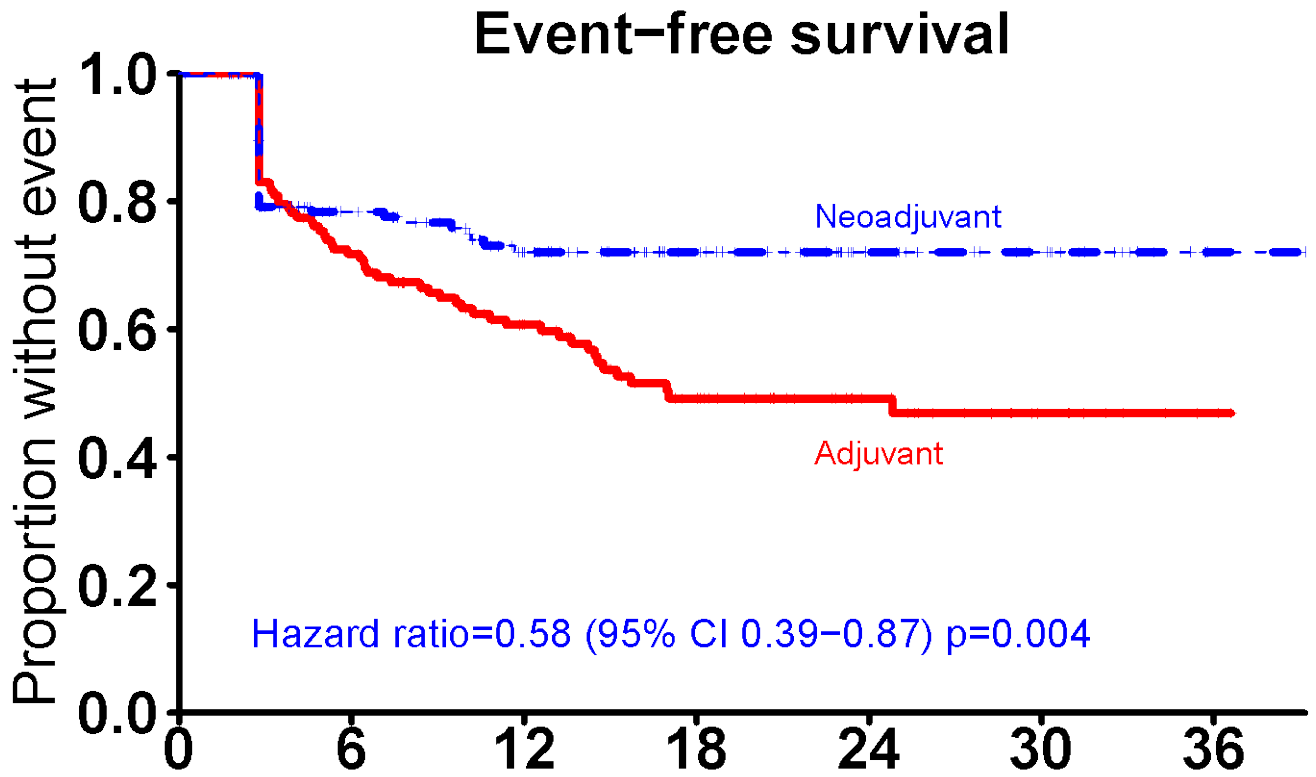
Publication

FDA Registration

Do we just need all the data for the publication?

No. Not just at the end

S1801 A Phase II Randomized Study of Adjuvant versus Neoadjuvant Pembrolizumab for Clinically Detectable Stage III-IV High-risk Melanoma



No. at Risk

159	98	67	40	22	10	2	Adjuvant
154	96	69	46	25	17	1	Neoadjuvant

The Middle: Data Quality is Always Critical

- Accrual monitoring
- Adverse event monitoring
  - CTEP-AERS reporting
  - Monthly reports (AE and dose summaries)
- Data and Safety Monitoring Committee (DSMC)
- Interim Analyses

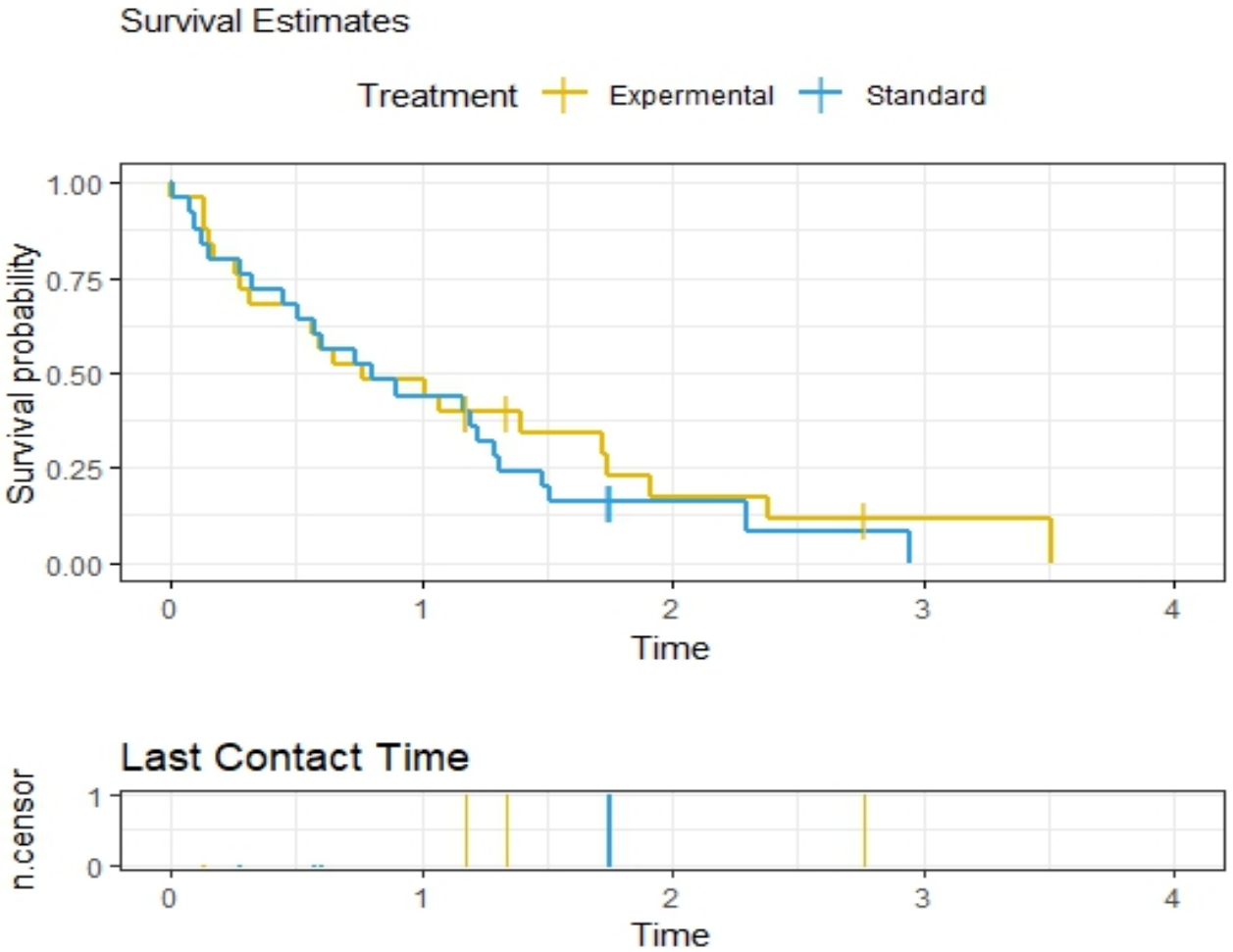
The Middle: Following the protocol

- Avoidance of Deviations protocol treatment and evaluations and timing
- Submission of complete and timely data
- Resolution of ongoing queries

- Data Coordinator Evaluations
- Study Chair Evaluations

Estimated Survival: The value of every patient's data

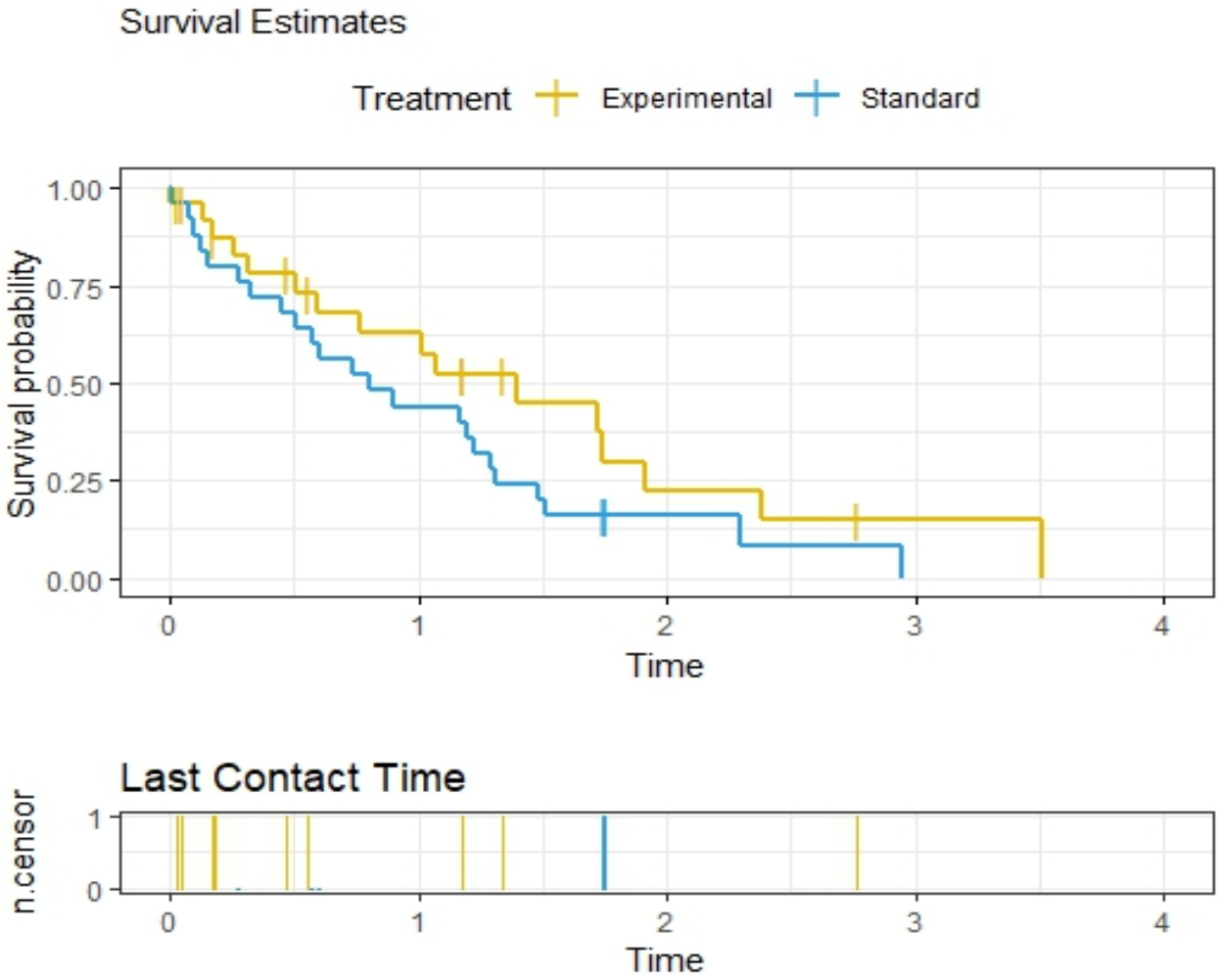
Study design: accrued over 3 years + 1 year of follow-up



Correct conclusion: new treatment does not help survival outcome

Estimated Survival: the value of every patient's data

Some Patients lost to follow-up on one arm



Incorrect conclusion: new treatment helps survival outcome

The Middle: SWOG Data Safety Monitoring Committee

- Evaluation of interim results (endpoints, safety)
- Recommendations on when to stop accrual, when to report early results
- Evaluate data requests from disease committee leadership for planning purposes
- Need high quality current data to make critical recommendations

The Beginning

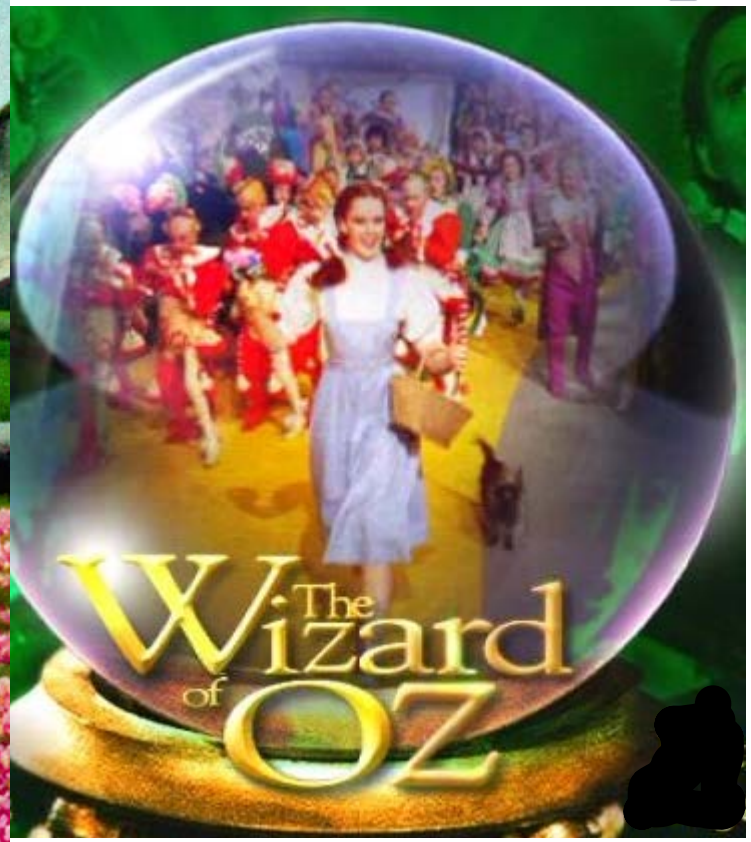
- The Statistical Design
- Everything you saw today before over the Rainbow.

Coming Home

Lessons from the Journey

KEY TAKE-AWAYS

- The journey is long, detailed, and requires persistence. Many people have participated in making it possible; careers and lives are affected.
- "Team-work makes the dream work." It took the foursome working together to beat the wicked witch and help Dorothy find her way home, so take note of that and encourage teamwork.
- There will be obstacles along the way; persevere! Surmounting obstacles is a primary role for research operations support personnel (like you!). You can do it!
- Quality Assurance is key; the Stats Center keeps us on track and focused so the work is complete.
- Find humor and joy in every day. Our participants remind us every day of how precious life is!



Thank you
For
Your Participation
And
Attendance
This Spring!

SWOG CANCER RESEARCH NETWORK

Thank you to The Wizard of Oz for being our inspiration!

NCI National Clinical Trials Network
a National Cancer Institute program

NCI Community Oncology Research Program
A program of the National Cancer Institute of the National Institutes of Health