The Establishment of the NCTN-CCSC: A Decade of Progress

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NCTN Fred Hutch
Translational Science Workshop

Biomarkers – Cancer Development

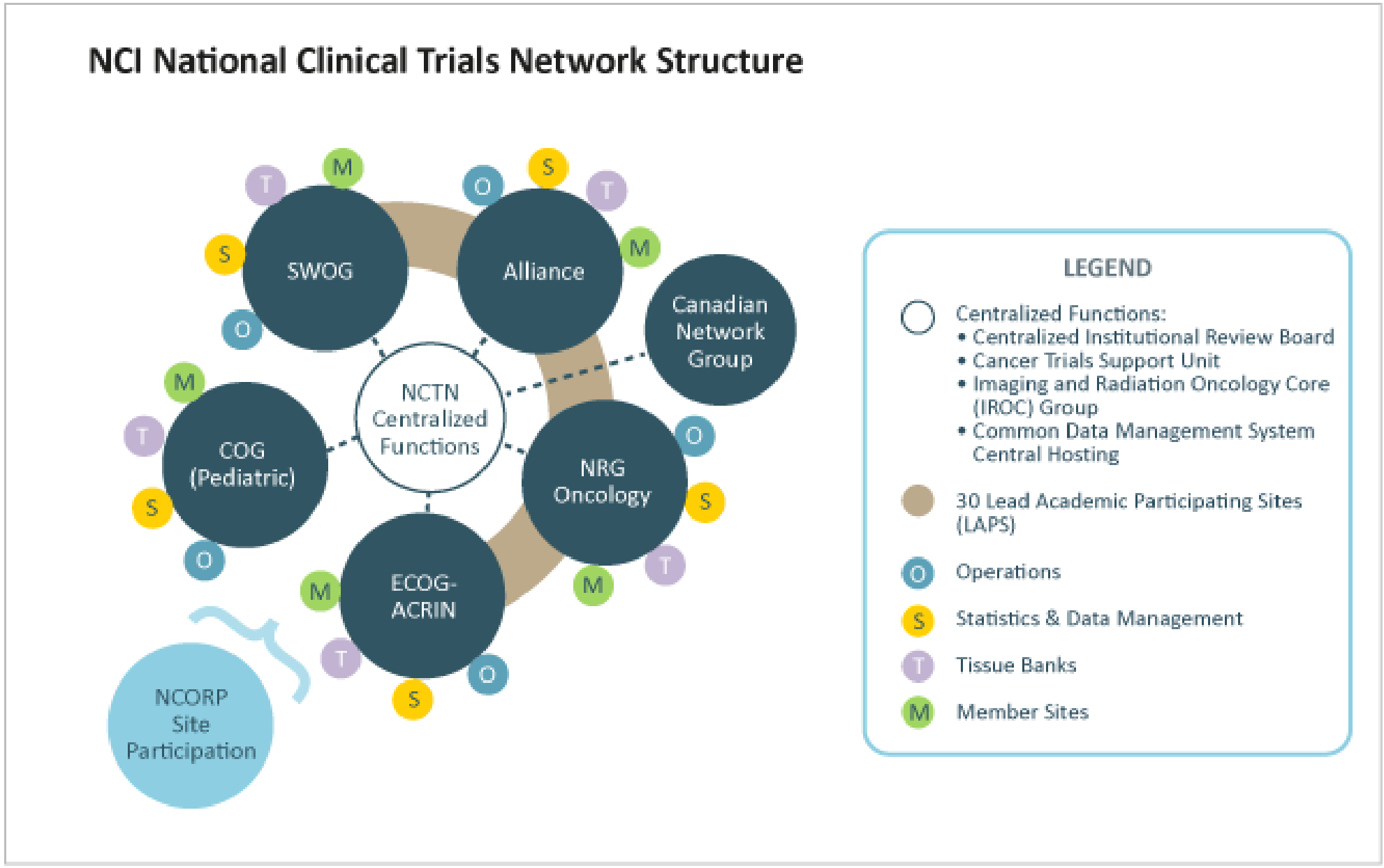
Types of Biomarkers

- Prognostic
- Predictive
- Pharmacodynamic
- Pharmacogenomic

Uses

- Regulatory
- Optimize drug use
- Explore mechanisms of action, toxicity, sensitivity, resistance
- Explore other aspects of biology
- Should be fit for purpose
  - Assay: Sample handling, Analytic methods
  - Context: Drug, Target, Pathway, Disease and setting
  - Goals: Immediate needs versus Long term uses

NCI - National Clinical Trials Network



Implementation of Biomarkers in NCTN Studies

Before 2015

- Biomarkers are incorporated into most studies up front
- Full development of biomarker approach and strategy
- Funding (in many cases) provided at onset of study
- Locked samples into protocol-specific biomarker analyses
- Very little “banking only”
  - Without hypothesis, what was the justification?

After 2015

- Goal of leveraging best science, technology and laboratories
- Prioritized optimal use of NCTN specimens
- Most biomarkers are NOT being defined in the protocol
- NCI allowing banking only protocols to collect and store biospecimens for future work
- Biomarker proposals can be submitted at the end of the study

What Changed?

Establishment of the Core Correlative Sciences Committee (CCSC)

NCTN Core Correlative Sciences Committee

- Established committee of NCTN Network Group Representatives, Bank representatives, advocates, & NCI representatives, with appropriate clinical, statistical, and scientific expertise to provide review & consideration of use of irreplaceable biospecimen resources.
- Biospecimen collections developed from cancer clinical trials conducted by the NCI NCTN are highly annotated with carefully collected clinical data, including outcome data.
- NCTN-CCSC is charged with scientific review & prioritization of proposals requesting use of banked, non-reserved biospecimens collected from NCTN trials for use in correlative science studies.
- NCTN-CCSC prioritization helps ensure optimal use of these irreplaceable clinical trial biospecimens.

NCTN – CCSC Membership

Committee Organization
Alliance translational representative
ECOG-ACRIN translational representative
NCIC CTG translational representative
NRG translational representative
SWOG translational representative
COG translational representative
Extramural statistician from NCTN
Extramural statistician from NCTN
Pathologist from NCTN
Laboratory scientist from NCTN
Group Banking Committee representative
Patient advocate from NCTN
NCI/Biometrics Research Program
NCI/Clinical Investigations Branch
NCI/Cancer Diagnostics Program

*Second committee has been formed to handle increased protocol review

Biomarkers – Cancer Development

Biomarker Definitions

- **Integral** - markers are integral when they are essential for conducting the study as they define eligibility, stratification, disease monitoring or study endpoints. Real-time analyses conducted in a CLIA-certified laboratory.
- **Integrated** - Markers are considered integrated when they test a hypothesis based on preexisting data and is not hypothesis-generating. Integrated markers need to demonstrate reproducible analytic qualities, data reviewed by NCI Biomarker Review Committee. Samples allocated to these biomarkers at protocol development.
- **Exploratory** - not be performed on all subjects in a trial, and collection of these exploratory markers by investigators participating in the trial may be voluntary. Exploratory biomarkers are not specified in protocol upfront, opportunities exist at the conclusion of the study using banked samples.

Biomarkers – Cancer Development

Biomarker Definitions

- **Integral** - Approved During Protocol Development

- **Integrated** - Approved During Protocol Development
  Incorporated as Secondary Objective
  Review by Biomarker Review Committee (BRC)

- **Exploratory** - CCSC Review – After completion of study, secondary use protocols generated

Biomarkers – Cancer Development

Biomarker Definitions

- **Integrated**

Approved During Protocol Development
~~**Incorporated as Secondary Objective**~~
Review by Biomarker Review Committee (BRC)

- Recently, moving to incorporate these as Translational Research Objectives
  - Reverting back to previous approach, not subject to specific FDAAA reporting

Biomarkers – Who Approves?

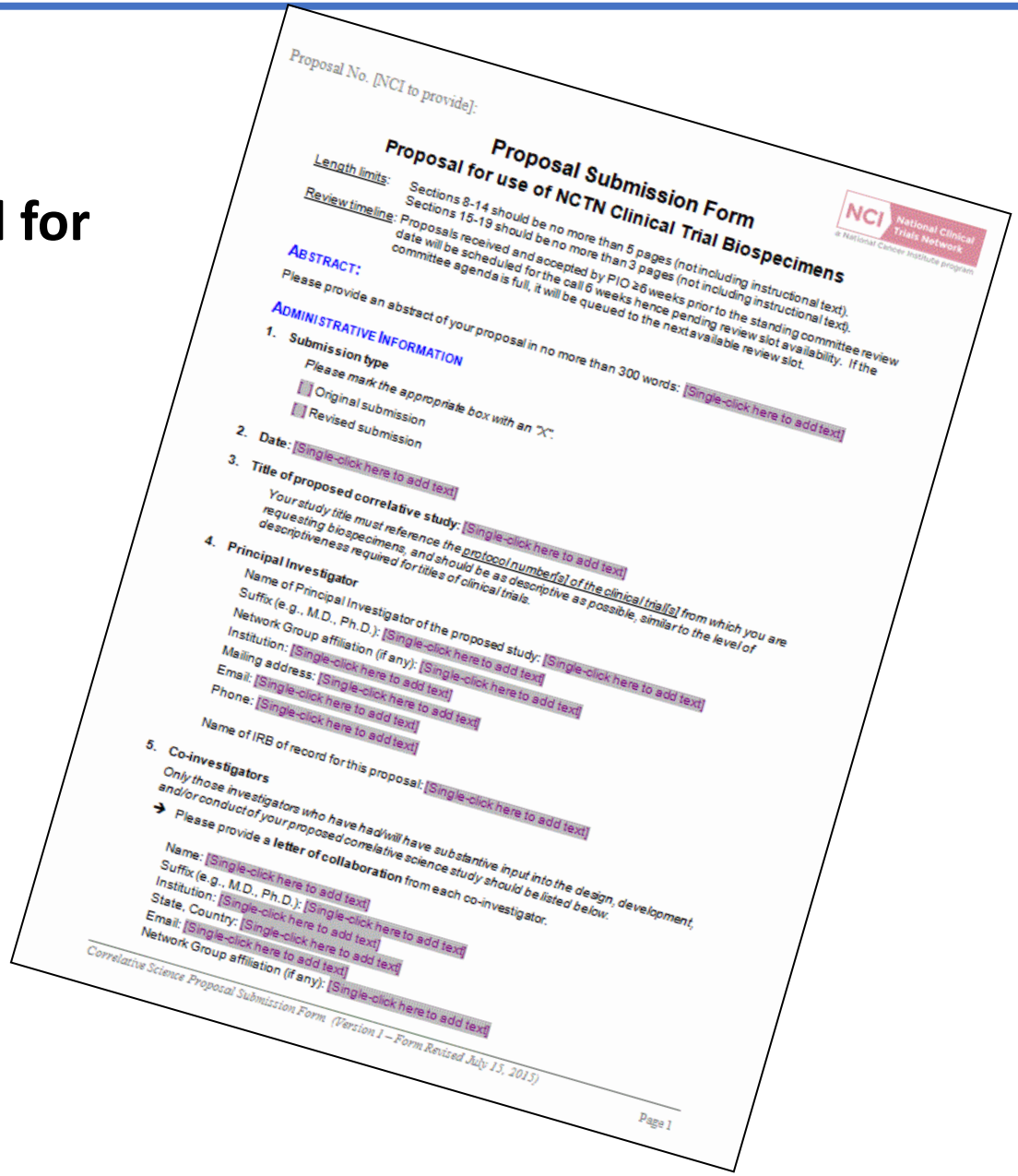
<u>If Integral or Integrated:</u>
Biomarker is in the protocol and approved by CTEP

<u>If Exploratory:</u>
New proposal needs to be developed and submitted to the CCSC for approval

NCTN-CCSC Proposal Submission Form

Proposal content

- **Abstract: Used to assist in reviewer selection and for archiving information about proposals**
- **Objectives and Hypotheses**
- **Background and Significance**
  - **Trial(s) from which samples are being requested**
  - **Preliminary data and study justification**
- **Research Design and Methods**
- **Tissue/Biospecimen type**
- **Data-sharing Plan**
- **Statistical Considerations are KEY**



Proposal No. [NCI to provide]:

Proposal Submission Form
Proposal for use of NCTN Clinical Trial Biospecimens

Length limits: Sections 8-14 should be no more than 5 pages (not including instructional text).
Sections 15-19 should be no more than 3 pages (not including instructional text).
Review timeline: Proposals received and accepted by PIO ≥6 weeks prior to the standing committee review date will be scheduled for the call 6 weeks hence pending review slot availability. If the committee agenda is full, it will be queued to the next available review slot.

ABSTRACT:

Please provide an abstract of your proposal in no more than 300 words: [Single-click here to add text]

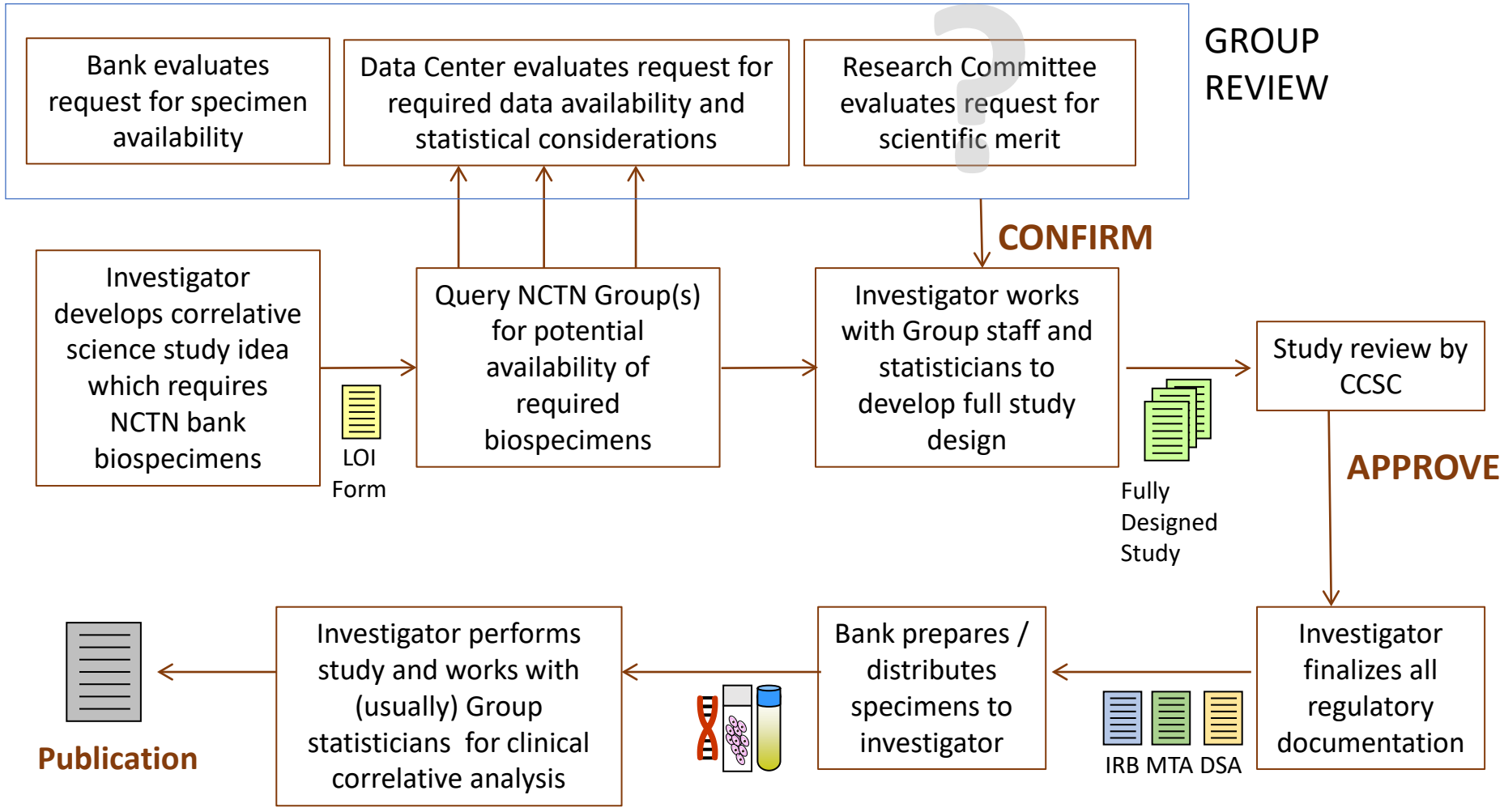
ADMINISTRATIVE INFORMATION

1. **Submission type**
   Please mark the appropriate box with an "X":
   ☐ Original submission
   ☐ Revised submission
2. **Date**: [Single-click here to add text]
3. **Title of proposed correlative study**: [Single-click here to add text]
   Your study title must reference the protocol number[s] of the clinical trial[s] from which you are requesting biospecimens, and should be as descriptive as possible, similar to the level of descriptiveness required for titles of clinical trials.
4. **Principal Investigator**
   Name of Principal Investigator of the proposed study: [Single-click here to add text]
   Suffix (e.g., M.D., Ph.D.): [Single-click here to add text]
   Network Group affiliation (if any): [Single-click here to add text]
   Institution: [Single-click here to add text]
   Mailing address: [Single-click here to add text]
   Email: [Single-click here to add text]
   Phone: [Single-click here to add text]
   Name of IRB of record for this proposal: [Single-click here to add text]
5. **Co-investigators**
   Only those investigators who have had/will have substantive input into the design, development, and/or conduct of your proposed correlative science study should be listed below.
   ➔ Please provide **a letter of collaboration** from each co-investigator.
   Name: [Single-click here to add text]
   Suffix (e.g., M.D., Ph.D.): [Single-click here to add text]
   Institution: [Single-click here to add text]
   State, Country: [Single-click here to add text]
   Email: [Single-click here to add text]
   Network Group affiliation (if any): [Single-click here to add text]

Correlative Science Proposal Submission Form (Version 1 – Form Revised July 15, 2015)

Page 1

NCTN-CCSC Workflow



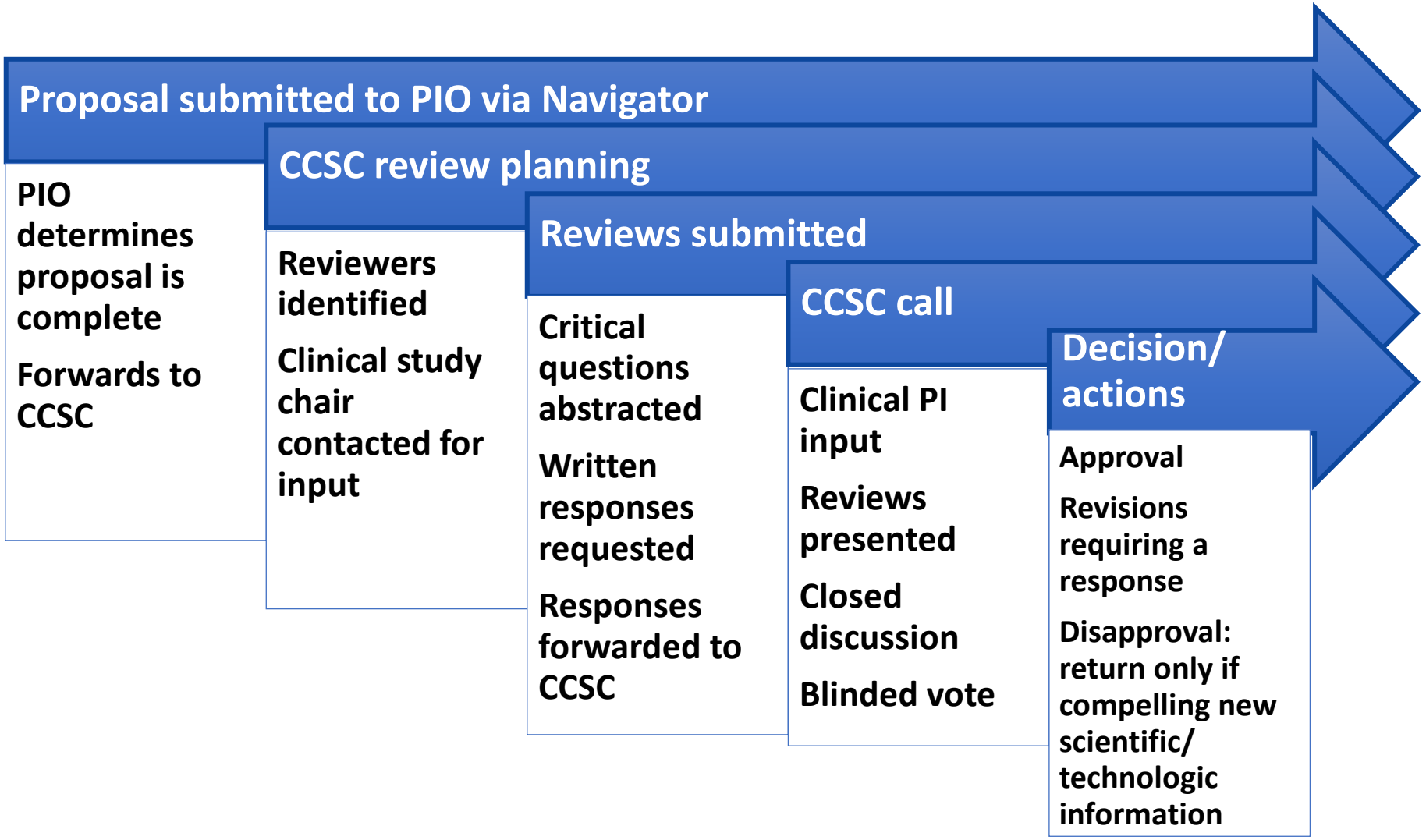
NCTN-CCSC Workflow for Exploratory Biomarkers

New Process Prior to Protocol Development

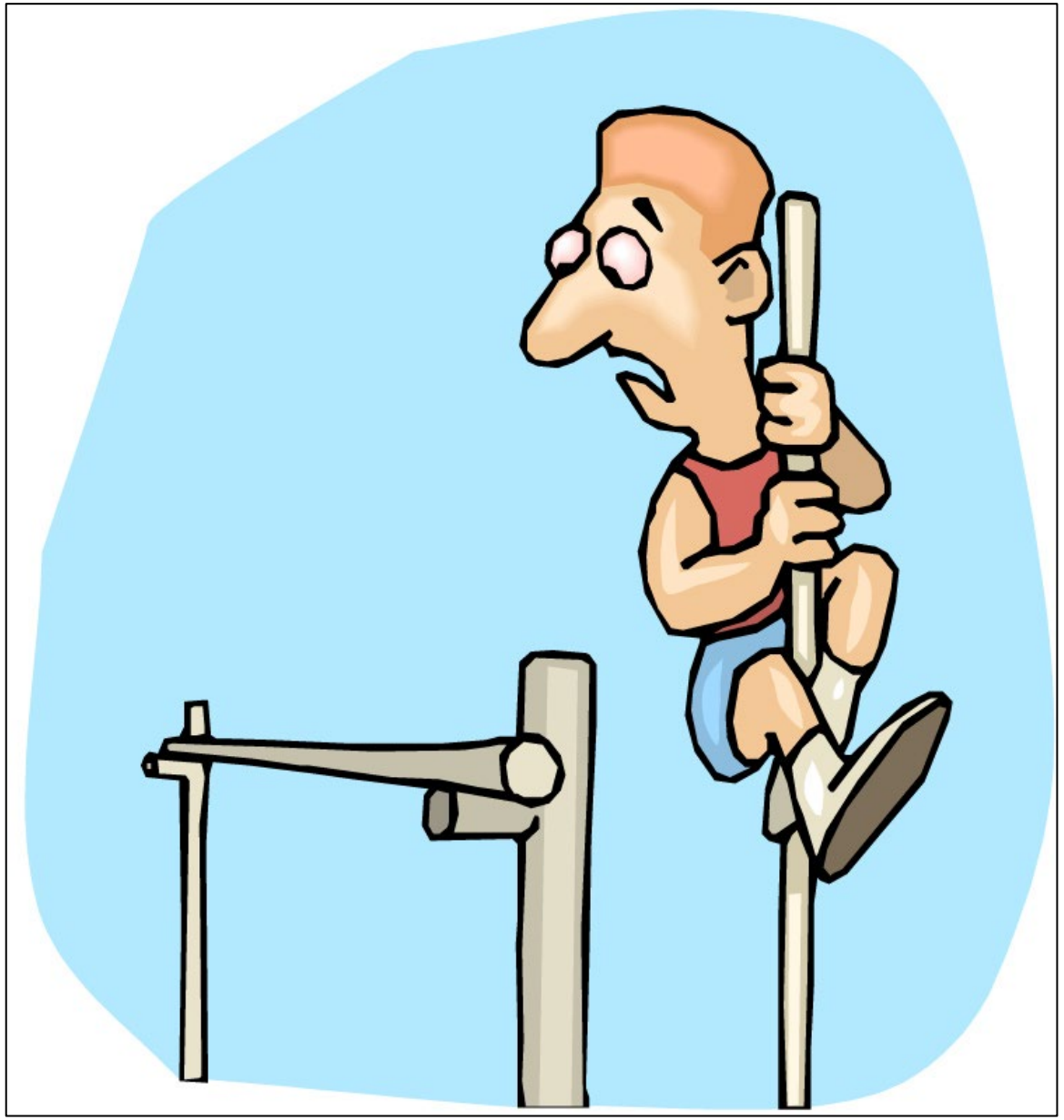
LOI

Feasibility Query (FQ)

- *Use the Navigator website to query biospecimen availability*
- *Fill out a simple LOI form*
- *The Lead Protocol Organization will review LOI to determine the feasibility of request.*
- *Once LOI is reviewed by LPO and determined feasible, you can proceed to protocol development*



Lowering the Bar……



Expanded Evaluation Guidelines

While highest priority is for validation studies, biospecimens MAY be considered available for use for broad exploratory/discovery studies:

- Rare cancer and had a negative result
- Fewer than 50% of the biospecimens remain from the clinical trial
- Phase 3 randomized trial, negative primary endpoint outcome, published >5 years
  - Experimental agent no longer under active investigation in this or a different setting
- The proposal does not consume specimen (such as a slide imaging study) and the specimens used will be returned unaltered to the Bank

Expanded Evaluation Guidelines

Examples of proposed exploratory/discovery studies:

- Purely exploratory analyses aiming to **discover novel biological subgroups** irrespective of clinical outcomes
- **High-throughput screening** of very large numbers of molecular characteristics, individually or in combination, for their association with clinical outcomes or other clinical or pathological phenotypes.
- Studies still need **appropriate statistical plans** to demonstrate:
  - adequacy of the proposed sample size
  - statistical techniques will spurious results (e.g., false discovery control)
  - avoid overfitting of complex models (e.g., model validation)

Words of Wisdom

- Whenever possible, work with someone who understands the parent trial (e.g., statistician, parent trial study chairs/co-chairs, correlative chairs)
  - at least have some conversation to understand the specimens and data sets
- Request the appropriate use of the samples
  - validation proposals for positive studies, exploratory proposals for negative studies
  - propose to use the correct samples needed to successfully execute the work
- Put together a good, yet succinct, proposal
  - adequate background, clear objectives and hypotheses, sufficient assay information, solid statistical section
- Read and follow the directions!

Takeaways

- NCTN-CCSC helps ensure optimal use of these irreplaceable NCI-NCTN clinical trial biospecimens
- There is a wealth of samples at your disposal (as of 1/2025)
  - >275 trials
  - 170,327 unique patients
  - 2,452,107 specimens
- We are committed to distributing these samples to conduct appropriate research with best science
- The committee is available for questions, work with your liaison. We want to help!

Types of Studies Intergroups are Good / Bad For

Good

- Un-addressed clinical scenarios (e.g. 2nd line pancreatic cancer)
- Two established / approved regimens (e.g. FOLFOX Bev vs. FOLFOX Cetuximab in colon cancer)
- Sequencing (neoadjuvant vs. adjuvant in resectable Pancreatic Cancer)

Not so good

- New drug X (often owned and controlled by Pharma)
- Local therapy Y (local practices are hard to standardize)

Advantages/Disadvantages of Participation in NCTN Cooperative Groups

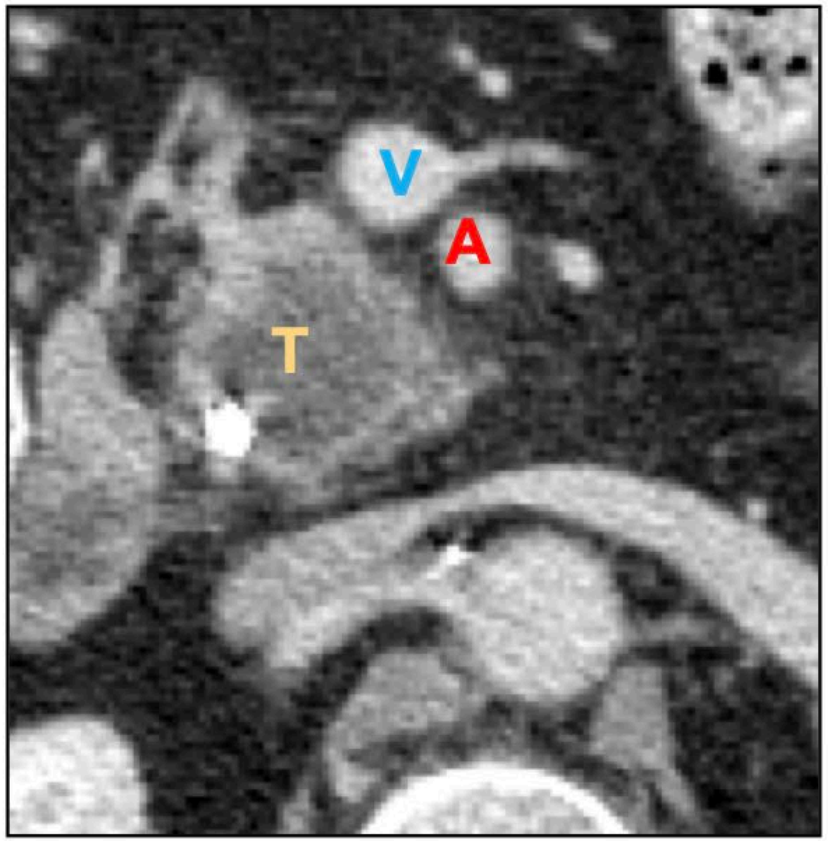
- Publicly funded clinical trials research
- Address tough clinical questions (things often pharma don't want to do)
- Networking opportunities w/ national leaders
- Regarded with high academic prestige

- Trial development may take longer
- Rigorous review by multiple committees
- Concepts often turned down at NCI level (frustrating for early investigators)
- Funding limited mainly to conduct of study (need additional funds for translational work; few monetary reimbursement to PI/institutions)

My ALLIANCE Experience

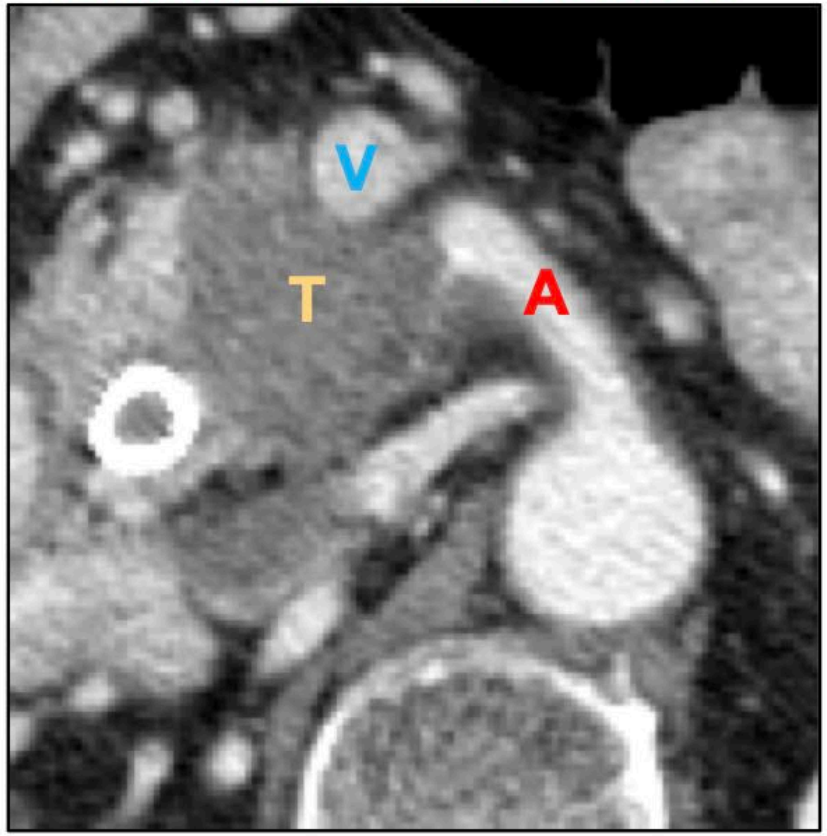
Clinical spectrum of resectability

Resectable



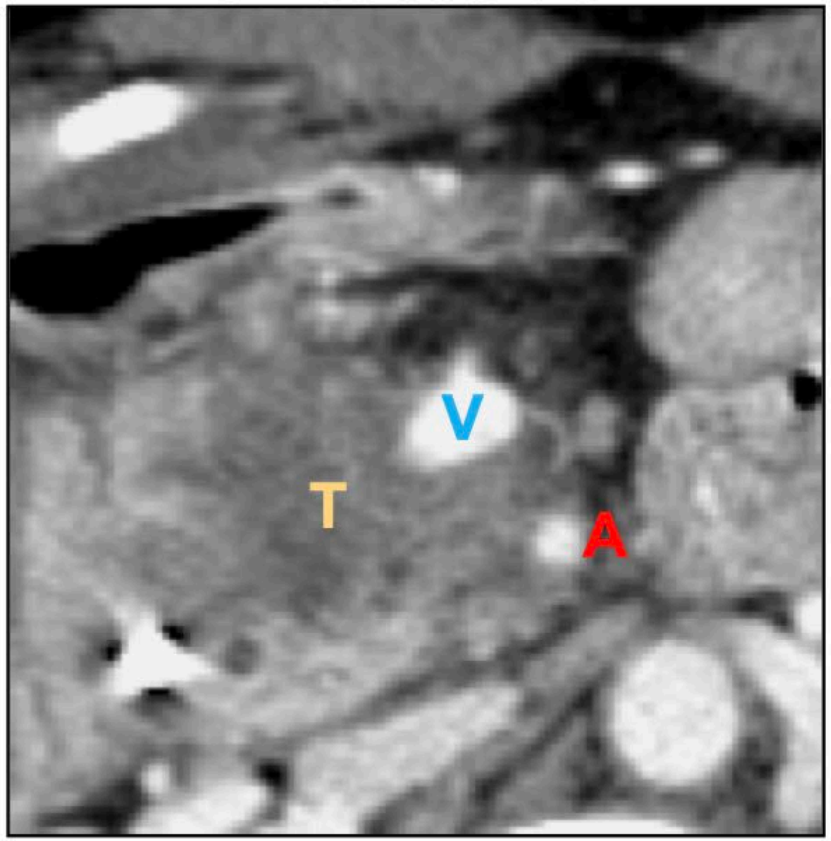
R0 likely
Surgery/adjuvant tx standard

Borderline Resectable



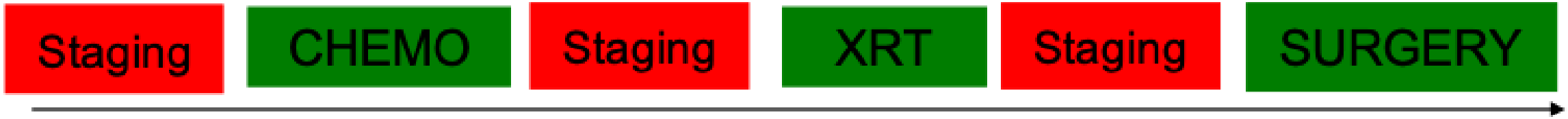
R1 likely
Surgery possible but results suboptimal

Unresectable



R2 likely
Surgery not a technical option

Borderline resectable PDAC: Treatment based on consensus not data



- ***CHEMO:*** *Cytotoxic effect on systemic disease*
- ***XRT:*** *Sterilization of surgical margins (R0)*
- ***Time:*** *Selection of tumor biology and patient physiology for surgery*

Provides an opportunity to impact the natural history of the disease

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

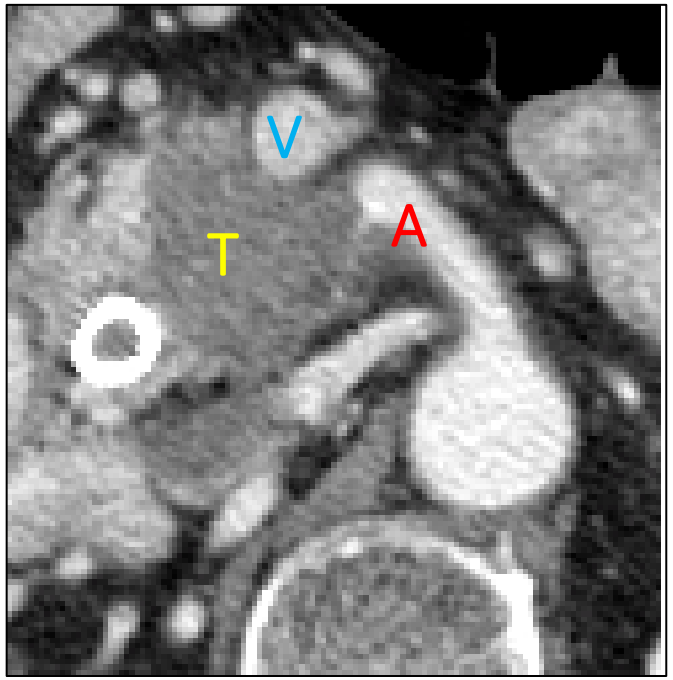
Potentially Curable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline

Alok A. Khorana, Pamela B. Mangu, Jordan Berlin, Anitra Engebretson, Theodore S. Hong, Anirban Maitra, Supriya G. Mohile, Matthew Mumber, Richard Schulick, Marc Shapiro, Susan Urba, Herbert J. Zeh, and Matthew H.G. Katz

Preoperative therapy is recommended for patients with pancreatic cancer … who [have] a radiographic interface between the primary tumor and mesenteric vasculature on cross-sectional imaging that does not meet appropriate criteria for primary resection.

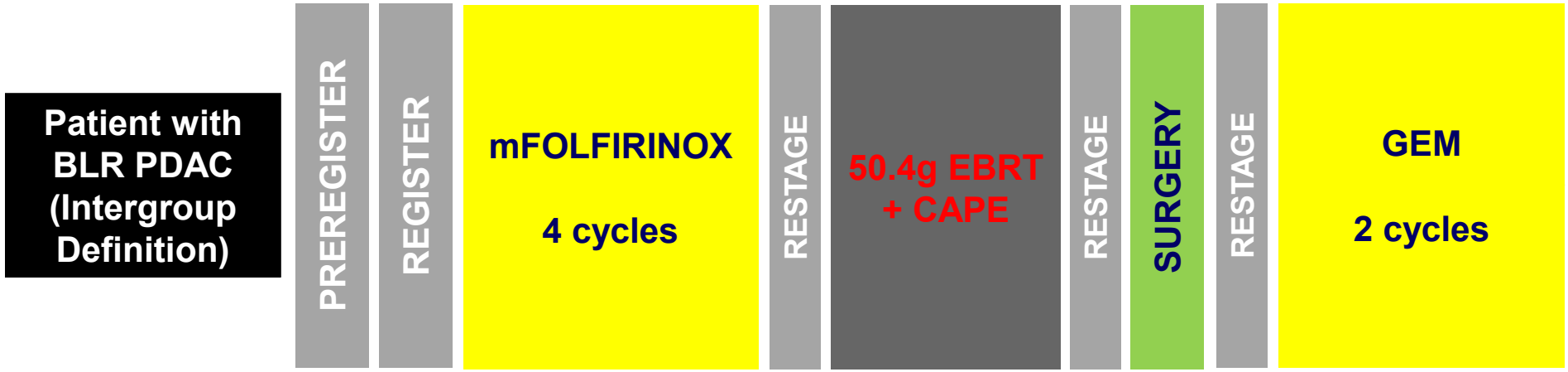
- Preop chemotherapy + RT common, but RT controversial
- Need reference regimen for future studies

Interface with SMV/PV ≧ 180° or SMA < 180°



Khorana, JCO 2016
Katz, JAMA Surgery 2016

Alliance A021101



- 14 high volume pancreatic treatment centers
- Feasibility – QC, accrual, resection rate
- 22 patients initiated therapy: 68% underwent pancreatectomy, mOS 21.7 months, 18-mo OS 55%

Alliance A021501

[1] Oxaliplatin 85 mg/m^2, irinotecan 180 mg/m^2, leucovorin 400 mg/m^2 and infusional 5-fluorouracil 2400 mg/m^2 over 46 h

[2] Stereotactic Body RT, 33-40 Gy in 5 fx or hypofractionated image guided RT, 25 Gy in 5 fx

[3] Segmental pancreatectomy with regional lymphadenectomy +/- vascular resection

[4] Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2 and infusional 5-fluorouracil 2400 mg/m^2 over 46 h

Statistics

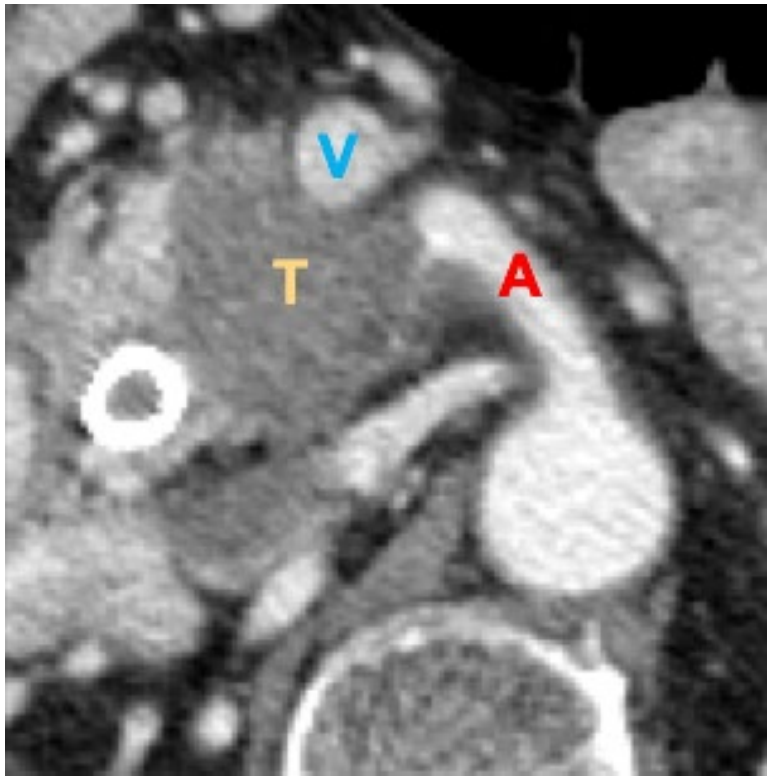
- **Primary Endpoint**
  - Binary 18-month OS rate

  Secondary

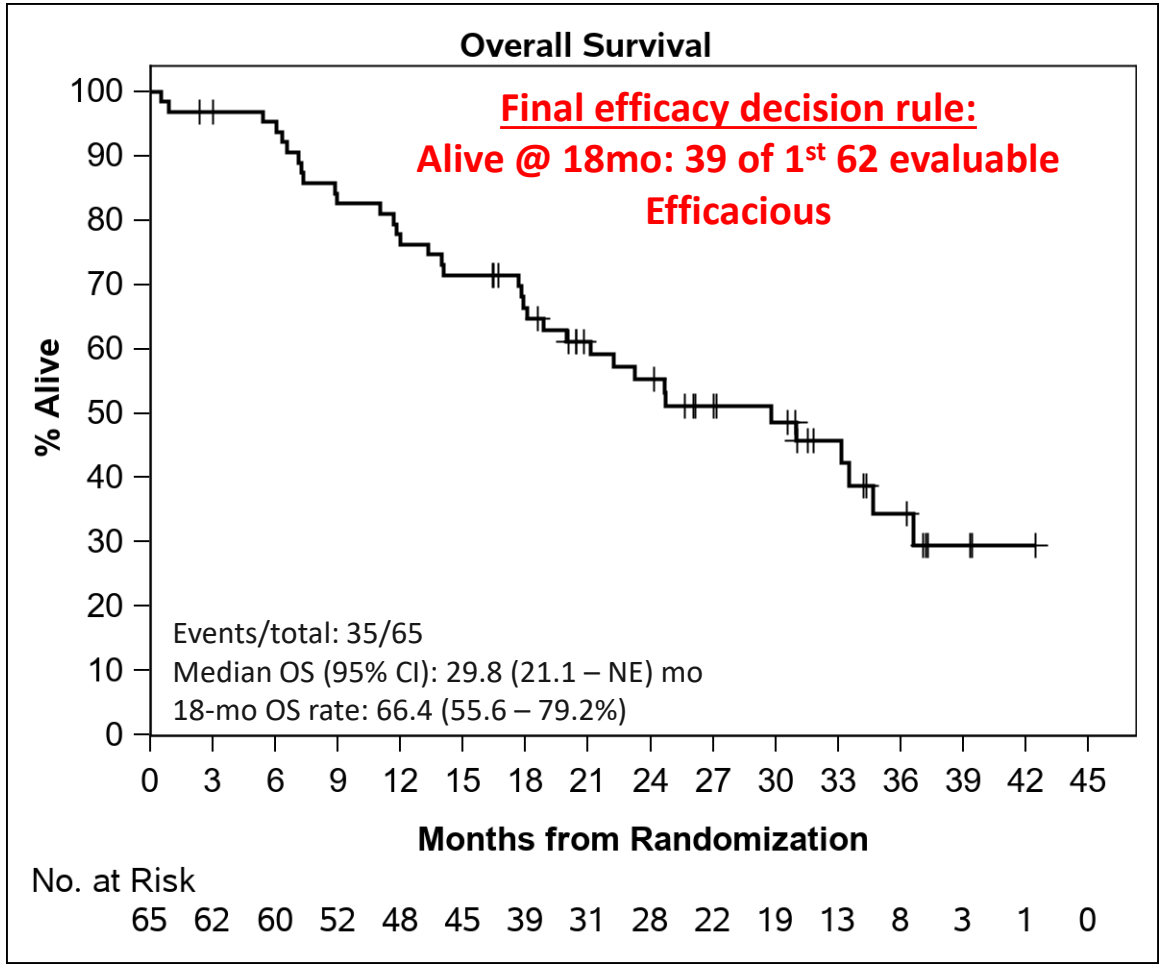
  1. EFS: Time from randomization to first of: progression, R2 resection, recurrence following resection, death
  2. AE rates during preoperative therapy, 90-day perioperative window, adjuvant therapy
  3. R0 resection rate
  4. pCR rate
- **Interim futility analysis**
  - Closure of either arm in which ≦ 11 (37%) of first 30 patients underwent R0 resection
- **Final efficacy analysis**
  - Sample size: 62 patients/arm to detect an improvement in the 18-month OS rate of 13% over historical rate of 50%
  - 82% power at one sided alpha 0.07
  - Either arm which reached full accrual and in which at least 36 patients alive 18 months after randomization declared efficacious
  - If both arms successful: pick the winner

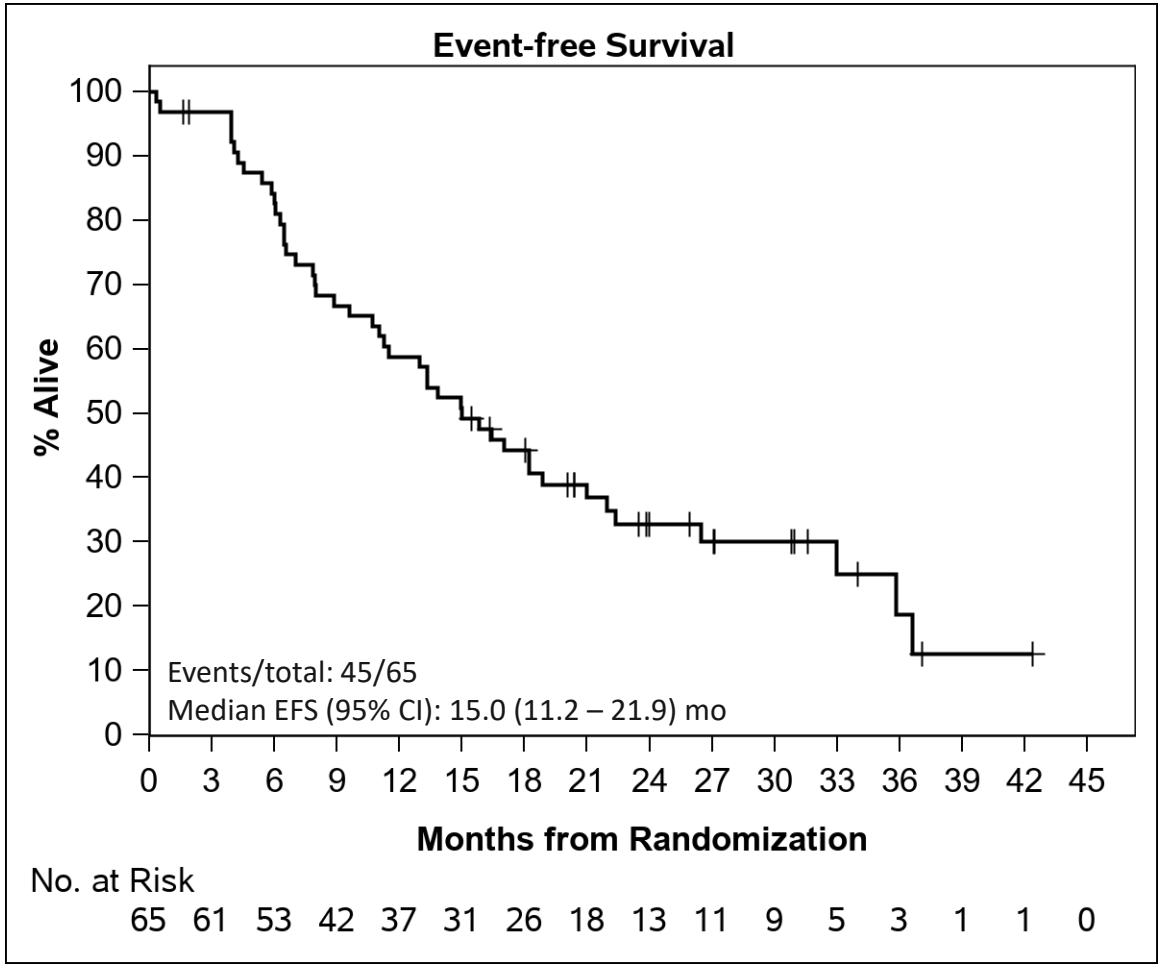
Eligibility

- Biopsy-proven pancreatic adenocarcinoma
- One or more centrally-reviewed radiographic criteria
  - Interface with SMV or PV ≧ 180°
  - Short-segment occlusion of SMV-PV, amenable to reconstruction
  - Interface (of any degree) with HA, amenable to reconstruction
  - Interface with SMA or CA < 180°
- Age ≧ 18, PS 0-1
- Normal physiologic parameters including bilirubin ≦ 2 mg/dL
- M1 to distant nodes or organs; ascites; prior treatment excluded

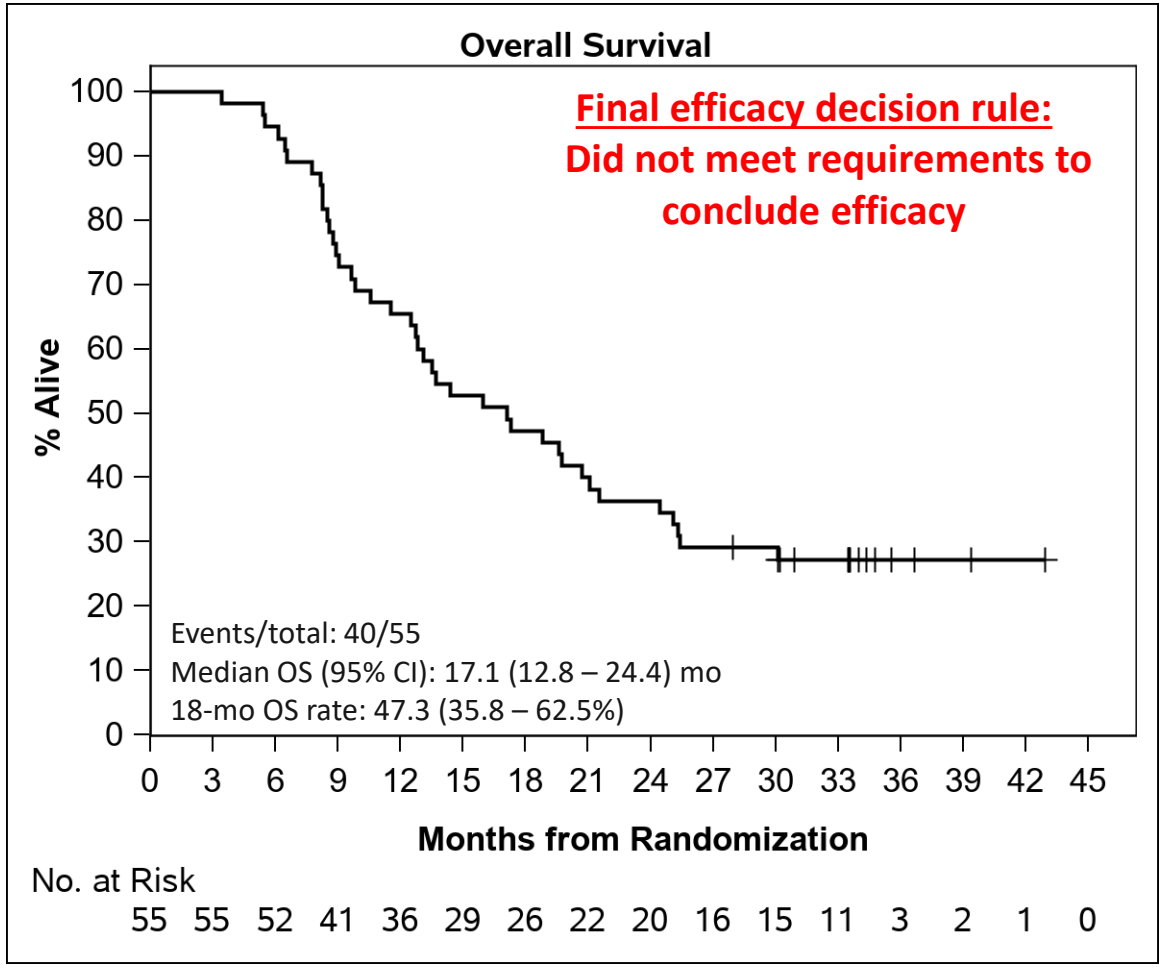


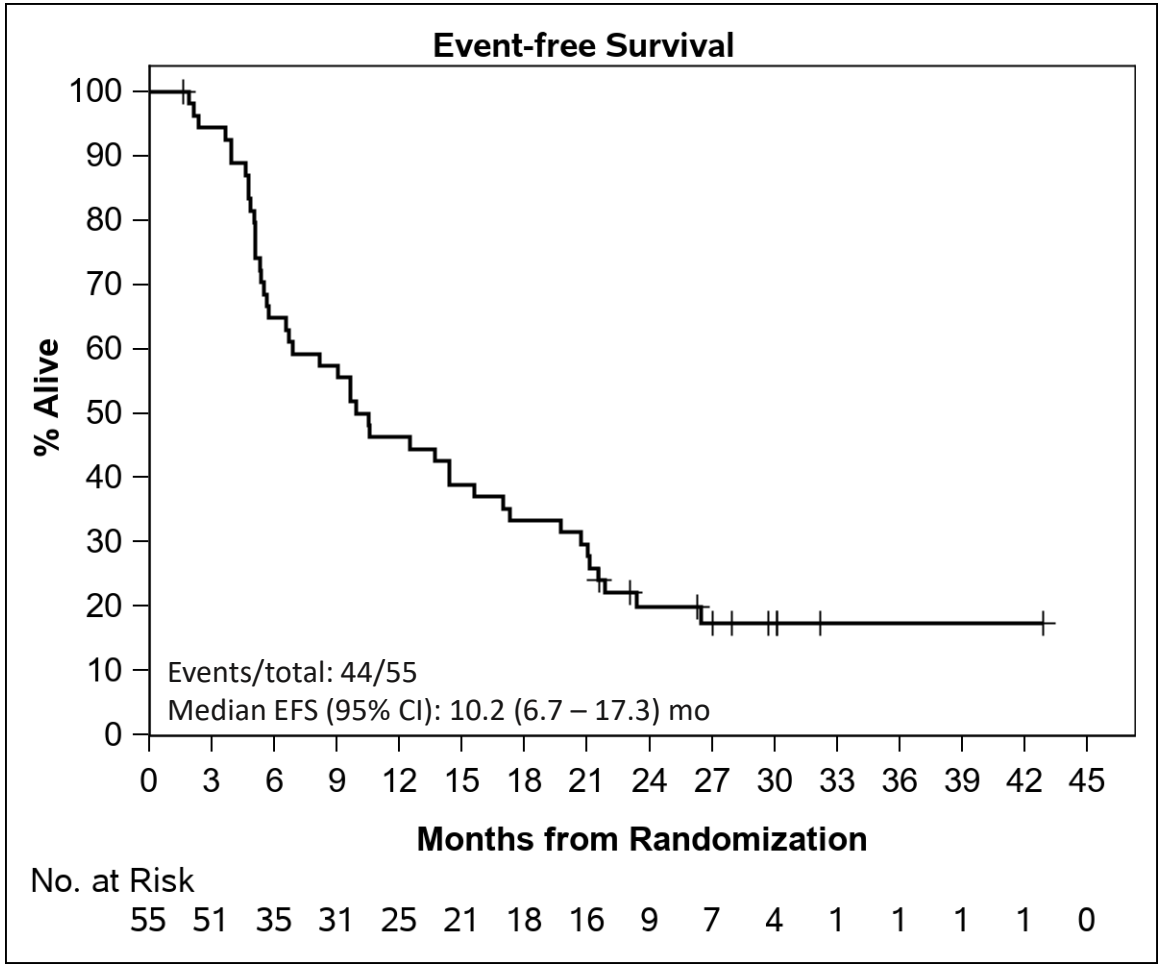
Arm A: mFOLFIRINOX





Arm B: mFOLFIRINOX → RT





Summary

Arm A: mFOLFIRINOX

Efficacious

18-month OS rate (KM) 66.4%

EFS: 15.0 months

Resection rate: 49%

pCR rate: 0%

Preoperative 3+ AE rate: 57%

Arm B: mFOLFIRINOX → RT

Did not meet requirements to conclude efficacy

18-month OS rate (KM) 47.3%

EFS: 10.2 months

Resection rate: 35%

pCR rate: 11%

Preoperative 3+ AE rate: 64%

Conclusion/Takeaway

- Preoperative mFOLFIRINOX was associated with favorable OS relative to historical data in patients with BR PDAC
- mFOLFIRINOX → RT met the predefined ***futility boundary*** for R0 resection at interim analysis
- mFOLFIRINOX represents a reference preoperative regimen for patients with borderline resectable PDAC

Lessons / Take Aways

Pros

- Worked closely with Surgeons and Radiation Oncologists (Katz and Herman)
- Two high profile papers
- Now lead GI Correlatives in ALLIANCE (with Andy Nixon) and SWOG (with Dan Duda)

Cons

- Failed to collect a lot of samples
- Failed to execute most of the correlatives we proposed
- Now lead GI Correlatives in ALLIANCE (with Andy Nixon) and SWOG (with Dan Duda)

Questions?

Eric Collisson – eric@fredhutch.org