ALCHEMIST Study updates

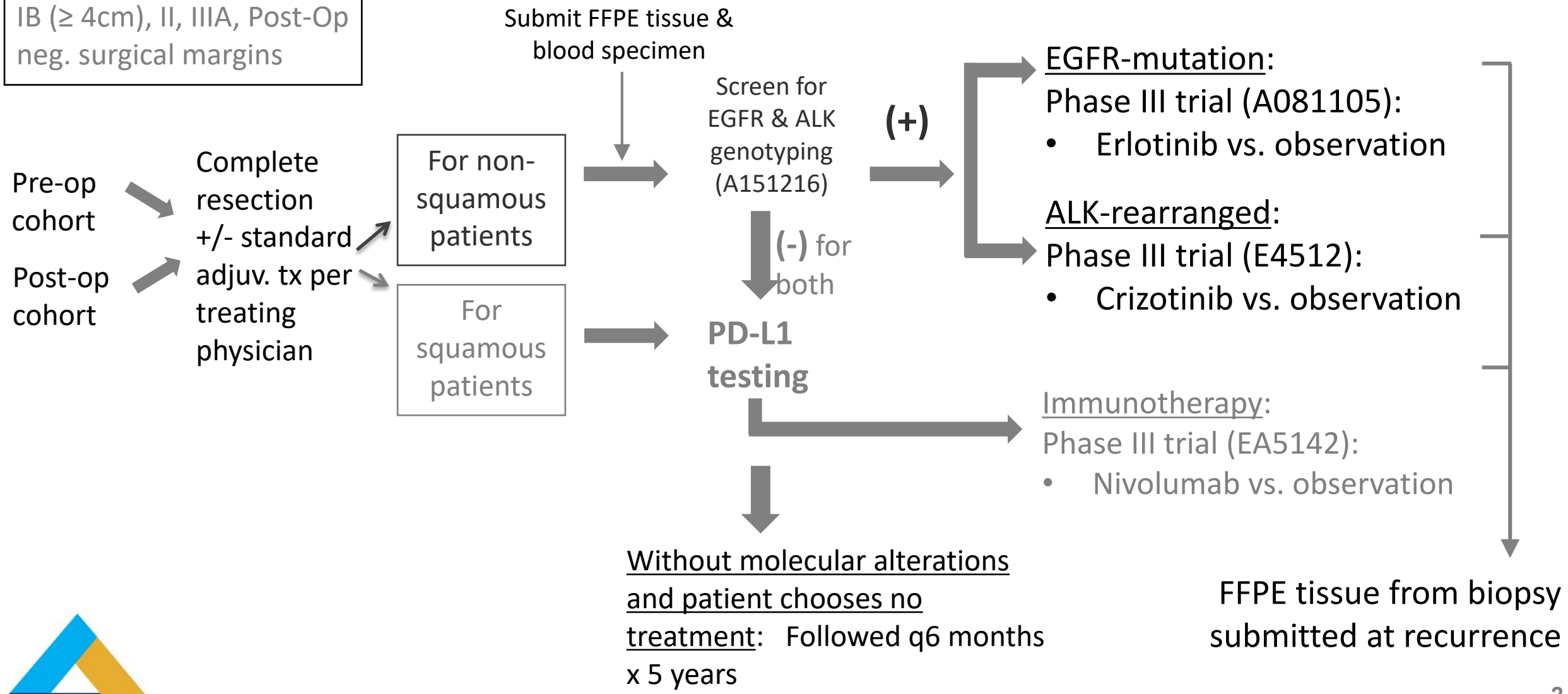
Dennis Wigle

GTSC Trials Day, Bonita Springs FLA

March 10, 2022

ALCHEMIST Schema & Update

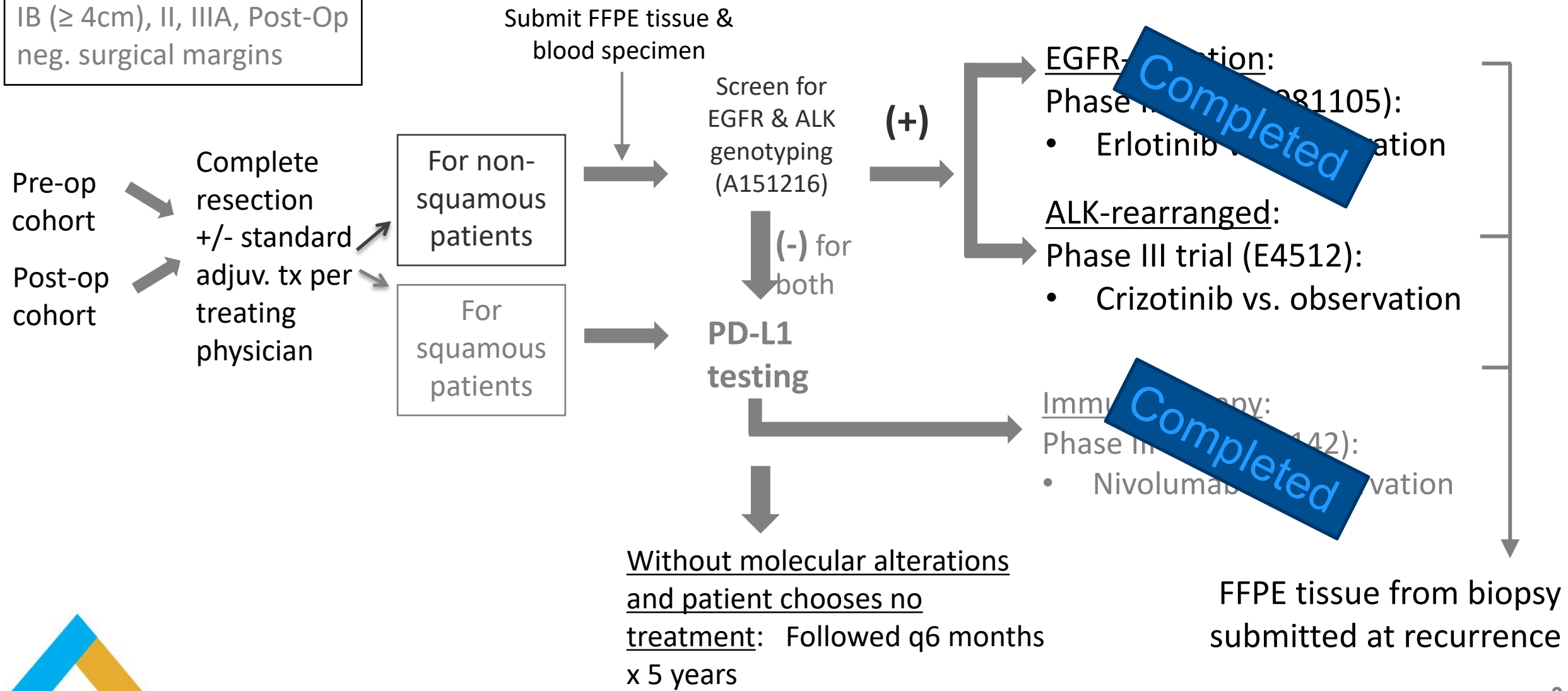
Non-squamous & Squamous NSCLC
Clinical/Pathologic Stage IB (≥ 4cm), II, IIIA, Post-Op neg. surgical margins



ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALCHEMIST Schema & Update

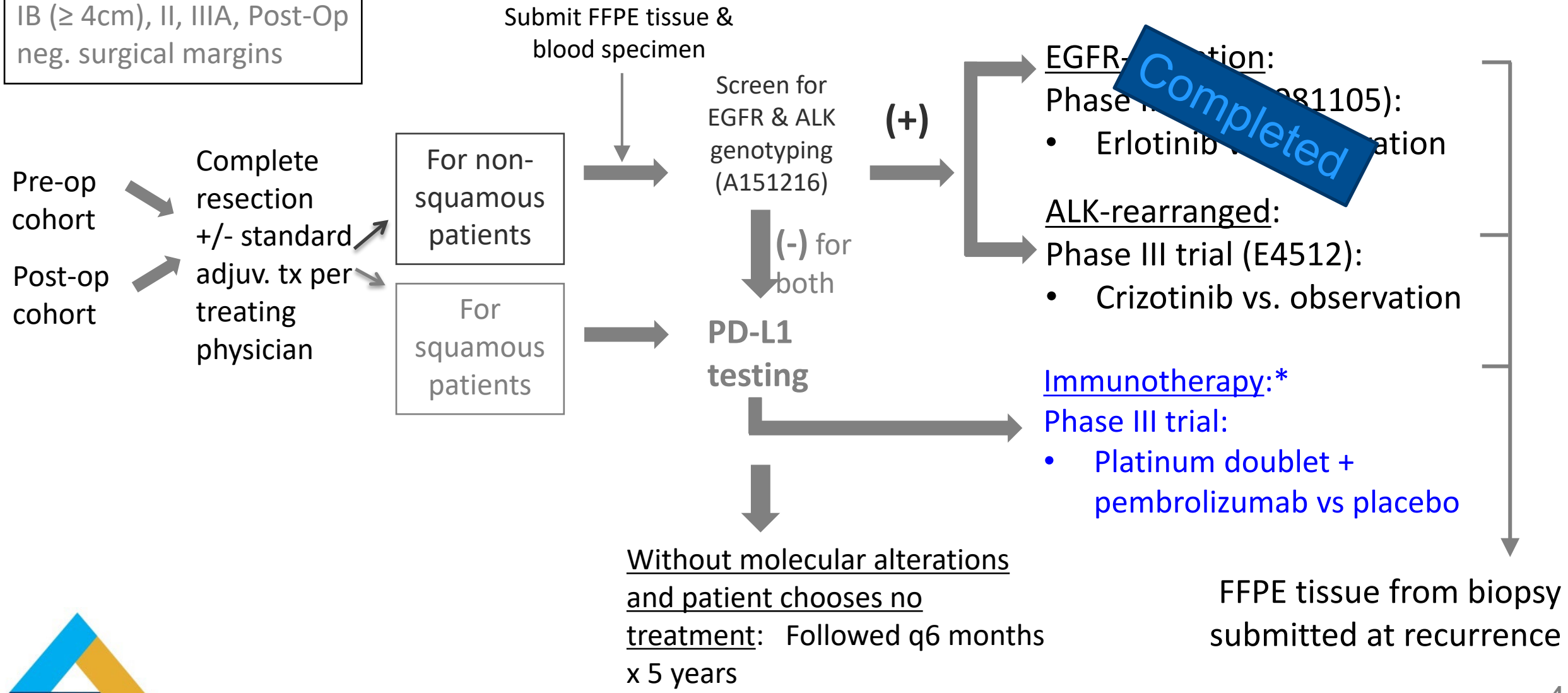
Non-squamous & Squamous NSCLC
Clinical/Pathologic Stage IB (≥ 4cm), II, IIIA, Post-Op neg. surgical margins



ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALCHEMIST Schema & Update

Non-squamous & Squamous NSCLC
Clinical/Pathologic Stage IB (≥ 4cm), II, IIIA, Post-Op neg. surgical margins



ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALCHEMIST Accrual Update
(as of Feb 2022)

Status	N
Total sites open for A151216 (screening trial)	1229
Total pts registered to A151216 (screening trial)	6473
Total pts registered to A081105 (adjuvant erlotinib)	390 closed
Total pts registered to E4512 (adjuvant crizotinib)	133
Total pts registered to EA5142 (adjuvant nivolumab)	935 closed
Total pts registered to EA5142 (adjuvant chemo-pembro)	223

ALCHEMIST trial

Dennis Wigle, Mayo Clinic

Biospecimen Core Resource (update Feb 2022)

- 6,487 patients with various samples at the BCR (tumor, blood, or slide)
- 3,352 cases have shipped to Genomic Characterizations Centers
- 8,607 kits have shipped to sites (2 Streck tubes per kit)
- 12,407 Streck tubes received (for 4495 patients) at the BCR

ALCHEMIST trial

Dennis Wigle, Mayo Clinic

Thanks & enjoy the meeting!

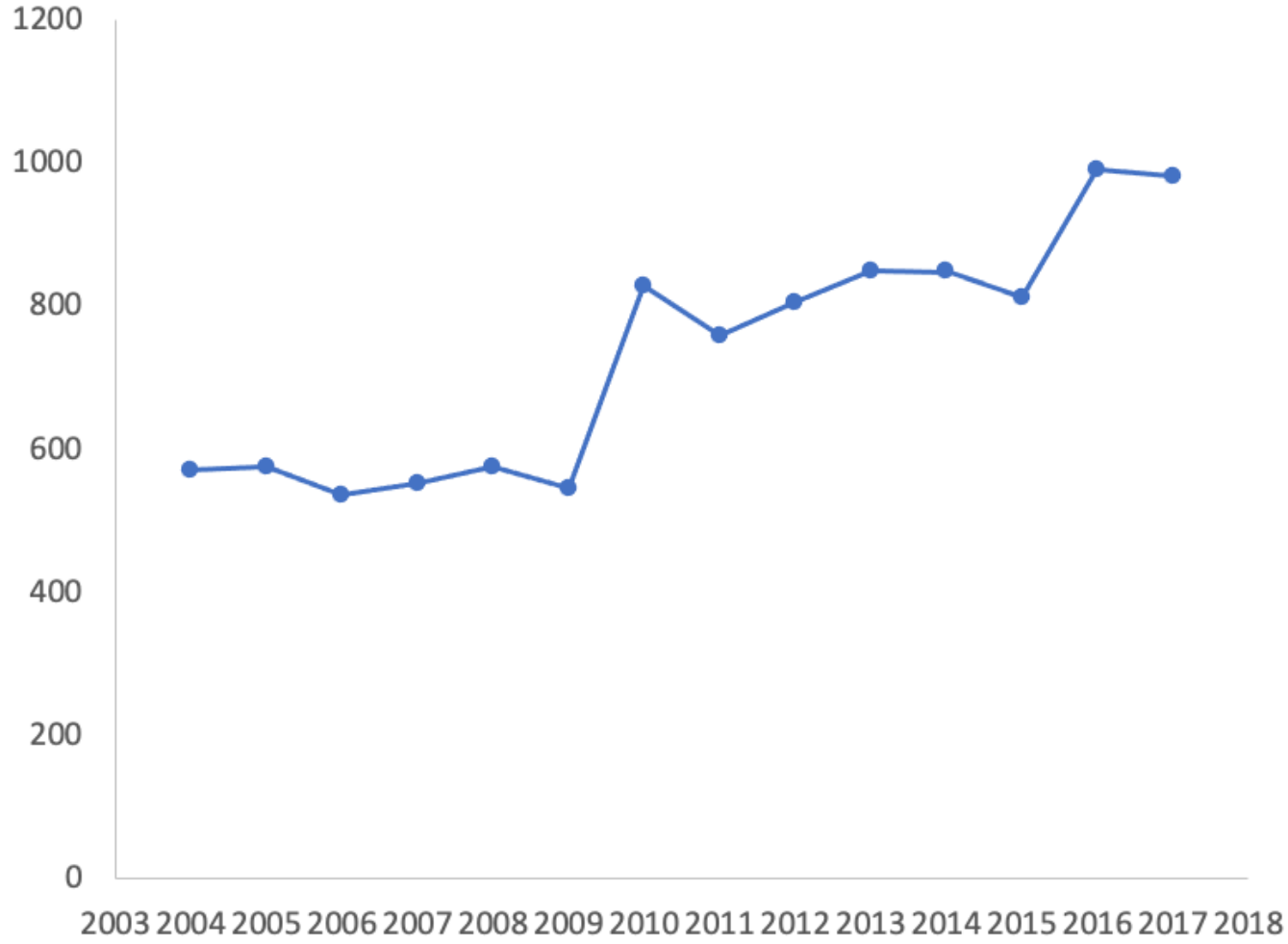
wigle.dennis@mayo.edu

Adjuvant chemotherapy with immunotherapy for patients with completely resected SCLC: Phase II trial

Chi-Fu Jeffrey Yang, MD
Division of Thoracic Surgery
Massachusetts General Hospital
Ginsberg Clinical Trials Day, March 10th, 2021

Alliance for Clinical Trials in Oncology

Number of SCLC Resections from 2003-2018



Current studies on immunotherapy for SCLC

Study	Stage	Centers
CASPIAN[1] : Durvalumab +/- tremelimumab, + platinum–etoposide vs platinum–etoposide	Extensive-Stage	805
IMpower133[2] : Atezolizumab plus Chemotherapy	Extensive-Stage	403
ADRIATIC[3]**:** Durvalumab +/- Tremelimumab After Concurrent Chemoradiotherapy	Limited Stage	600 (approx.)
NRG LU005[4]**:** Atezolizumab plus Chemotherapy	Limited Stage	444

1. Paz Ares et al. *Lancet.* 2019; 394:1929-19392.
2. Horn et al. *NEJM* 2018; 379:2220-2229
3. Senan et al. *Clin Lung Cancer* 2020; 21(2): e84-e88
4. Ross et al. ASCO 2020.

Proposed Phase II Trial

Adjuvant chemotherapy with immunotherapy for patients with completely resected small cell lung cancer

Study Design

Surgery
Patients with
Path T1–T2 N0-1 M0 SCLC

ECOG PS 0-1,
Age > 18 & < 80 years

ENROLL

Adj. chemotherapy * with immunotherapy

Primary endpoint
- 2 year DFS

Secondary endpoints
- 3-year DFS rate, 5-year DFS rate, 5-year OS rate

ECOG PS: Eastern Cooperative Oncology Group Performance Status;
DFS: disease-free survival

* Durvalumab

Endpoints

- **Primary endpoint**
  - 2 year DFS
- **Secondary endpoints**
  - Safety Profile (Grade 3 + AE)
  - Feasibility (rate of drug discontinuation due to adverse events)
  - Median DFS, 2-year overall survival

Sample size requirement is **35** patients.

Goal accrual: **55** patients

Updates

- **Approved by the Alliance Respiratory Committee**
- **Approved by the Alliance Foundation**
- **Finalizing budget**

SCLC Registry/Multi-institutional database

- **Evaluating outcomes of operable SCLC from 2010-2022**
  - specific focus on disease-free survival

- **Welcome all centers to participate!**
  - Shouldn't be too time consuming

Questions/recommendations

Email: cjyang@mgh.harvard.edu

Cell: 814 574 8695

immunotherapy.

However, current studies of immunotherapy are all entirely focused on limited stage or extensive stage disease. These studies have demonstrated exciting findings, showing that the use of immunotherapy improves survival.

We thought it would be important to see if we could get a trial going that looks at immunotherapy in the adjuvant setting for patients with completely resected small cell lung cancer

This is the study schema. All patients with completely resected pathologic T1-T2, N0-1 M0 Small cell lung cancer would be eligible. They would get adjuvant chemotherapy with durvalumab.

The primary endpoint would be 2-year disease free survival.

Secondary endpoints would be traditional endpoints evaluating safety, feasibility.

We're going to try to see if we can enroll 55 patients in the study.

So with regard to updates, we've made good progress so far. It's been approved by the Alliance respiratory committee, and approved by the alliance foundation leadership. Astrazeneca would like to support this study and we're currently finalizing

Statistical Considerations

Assuming the 2-year DFS is 72% for the patients treated with adjuvant chemo and the 2-year DFS is 87% for the patients treated with adjuvant chemo-IO, with 33 evaluable patients, the trial has approximately 87% power to detect a 15% increase in 2-year DFS for the chemo-IO over the chemo using a one-sided binomial exact test with a target significance level of 0.15. The actual significance level achieved by this test is 0.143.

Sample size requirement is **35** patients.

Statistical Considerations on

Adjuvant Chemo I/O for Patients with completely Resected SCLC

5/30/2021

Overview

The primary objective of this single-arm phase II trial is to initially determine the 2-year diseases-free survival rate (2-year DFS). The secondary objectives are to determine treatment-related adverse events, the treatment failure rate and overall survival. Diseases-free survival (DFS) is defined as the time between registration and disease recurrence. Disease recurrence is defined as an occurrence of the following events, whichever come first: disease recurrence as confirmed by biopsy, any new lung cancer (even in the opposite lung) as confirmed by biopsy, and death from any cause. Patients with new primaries at other sites will be followed for disease recurrence for original cancer and the new primaries do not constitute recurrence. Overall survival (OS) is defined as the time between registration and death of all cause. Treatment failure rate is the percentage of the patients who have to discontinue the treatment due to excessive adverse events. Correlative sciences objective is to evaluate the association between MRD positives and poorer DFS and OS.

The following correlative sciences hypothesis cannot be tested due to the fact that there are no concurrent control data on adjuvant chemo: MRD positive patients will gain greater benefit from adjuvant chemo-IO.

Assuming 95% of registered patients meet eligibility criteria and receive at least one cycle of the experimental therapy, we will enroll approximately 35 patients and yield a total of 33 patients with evaluable 2-year DFS status. In other words, all patients will be followed more than 2 years and these patients have no any of the three events that define disease recurrence, a patient has disease recurrence or death within 2 years of follow-up. All patients will be followed for a maximum of 3 years from registration for long term survival endpoints.

Sample Size Determination

This is a single-arm phase II trial to initially determine the 2-year DFS rate of eligible patients who receive adjuvant chemo-IO therapy after surgical resection for the primary tumor. We are interested in detecting a 15% absolute increase in the 2-year DFS of adjuvant chemo-IO from that of the adjuvant chemo. The 2-year DFS for the adjuvant chemo is estimated from Figure 4 in Zhou et al. (2021) with the 2-year DFS rate for N1 patient is 60% and N0 patients is 75%. We expect that N1 patients have a stronger motivation to enroll as compared to N0 patients.

The following table lists the power of rejecting the null hypothesis with 33 evaluable patients when the 2-year DFS of the adjuvant chemo-IO is indeed 15% higher than that of the historical control.

n	**N1 proportion**	**2yDFS** H_0	**2yDFS** H_1	**mDFS** H_0	**mDFS** H_1	**HR**	**alpha**	**Power**
33	0.2	0.72	0.87	4.22	9.95	0.42	0.143	0.8716
33	0.25	0.7125	0.8625	4.09	9.37	0.44	0.123	0.8409
33	0.3	0.705	0.855	3.97	8.85	0.45	0.105	0.8069
33	0.35	0.6975	0.8475	3.85	8.38	0.46	0.089	0.7700
33	0.4	0.69	0.84	3.74	7.95	0.47	0.076	0.7307

- 2yDFS: 2-year DFS rate
- mDFS: median DFS in years
- HR: hazard ratio of chemo-IO over chemo

Design Assumptions

Assuming the 2-year DFS is 72% for the patients treated with adjuvant chemo and the 2-year DFS is 87% for the patients treated with adjuvant chemo-IO, with 33 evaluable patients, the trial has approximately 87% power to detect a 15% increase in 2-year DFS for the chemo-IO over the chemo using a one-sided binomial exact test with a target significance level of 0.15. The actual significance level achieved by this test is 0.143.

Sample size requirement is **35** patients.

Accrual Estimation and Duration of Trial

- How many centers will enroll -- high enthusiasm among thoracic surgeons
- If each center can enroll 2-3 patients, then accrual duration ~24 months?
- Study duration ~ 51-60 months (maximum)

Notes from the talk

- Make it clear about radiation be dealer's choice
- Make it clear what you are going to do for clinical N1 (like upfront clinical N1)
- Resectable --
- People are allowed to be on the PCI study
- If chemotherapy/radiation concurrent?
- what is the drop out rate?
- Won't the limited stage results already help us figure out the adjuvant question (what's the point of doing another adjuvant therapy)
- There will be benefit with the tissue and blood specimens
- How long does the immunotherapy go for? 1 year

Endpoints

- Disease-Free Survival (DFS): the time from surgery to the earliest event defined as
  - Disease recurrence (confirmed by biopsy)
  - Any new lung cancer (even in the opposite lung) confirmed by biopsy
  - Death from any cause at any known point in time

  Patients with new primaries at other sites will be followed for disease recurrence of original cancer (the new primaries do not constitute recurrence).

  Patients that have not had an event reported at the time of analysis will be censored at their date of last adequate disease evaluation defined as: time of chest x-ray or CT.

Interim Monitoring

- Futility analysis will be done at an interval time point based upon discussion with statistician in the development protocol

Correlative Research

Hypothesis:

- (Minimal Residual Disease) MRD positive patients will have a poorer prognosis
- MRD positive patients will gain greater benefit from adjuvant chemo-IO
- MRD positive patients (with a poorer prognosis) could offer an opportunity for an early read-out of the efficacy of this regimen
- Will need more preliminary data before we can prospectively plan for subgroup analysis of MRD

Questions for Group Input/ Notes

- Should pathologically detected N1 disease be included?
- Should PCI be specified?

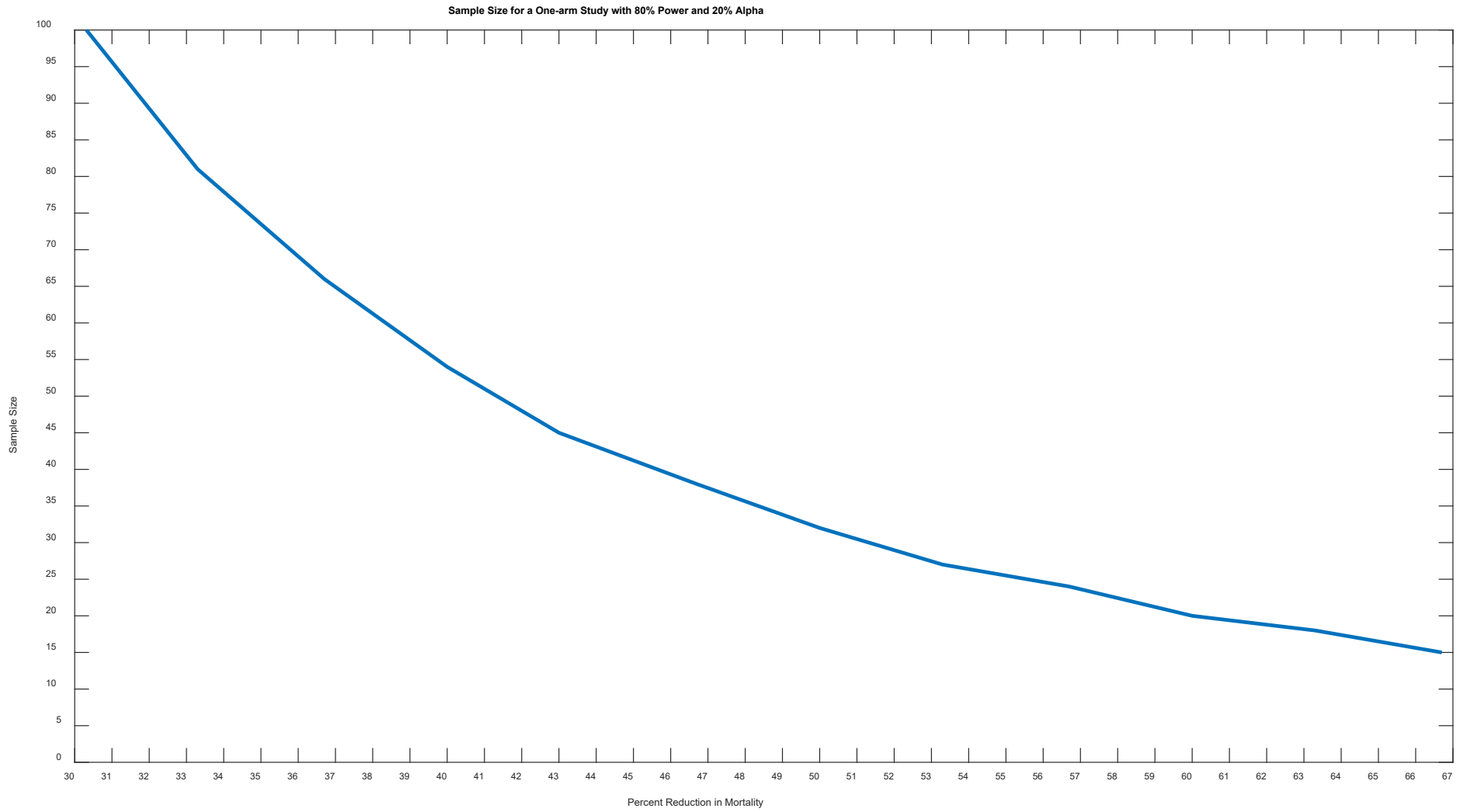
Other Notes

Sample Processing

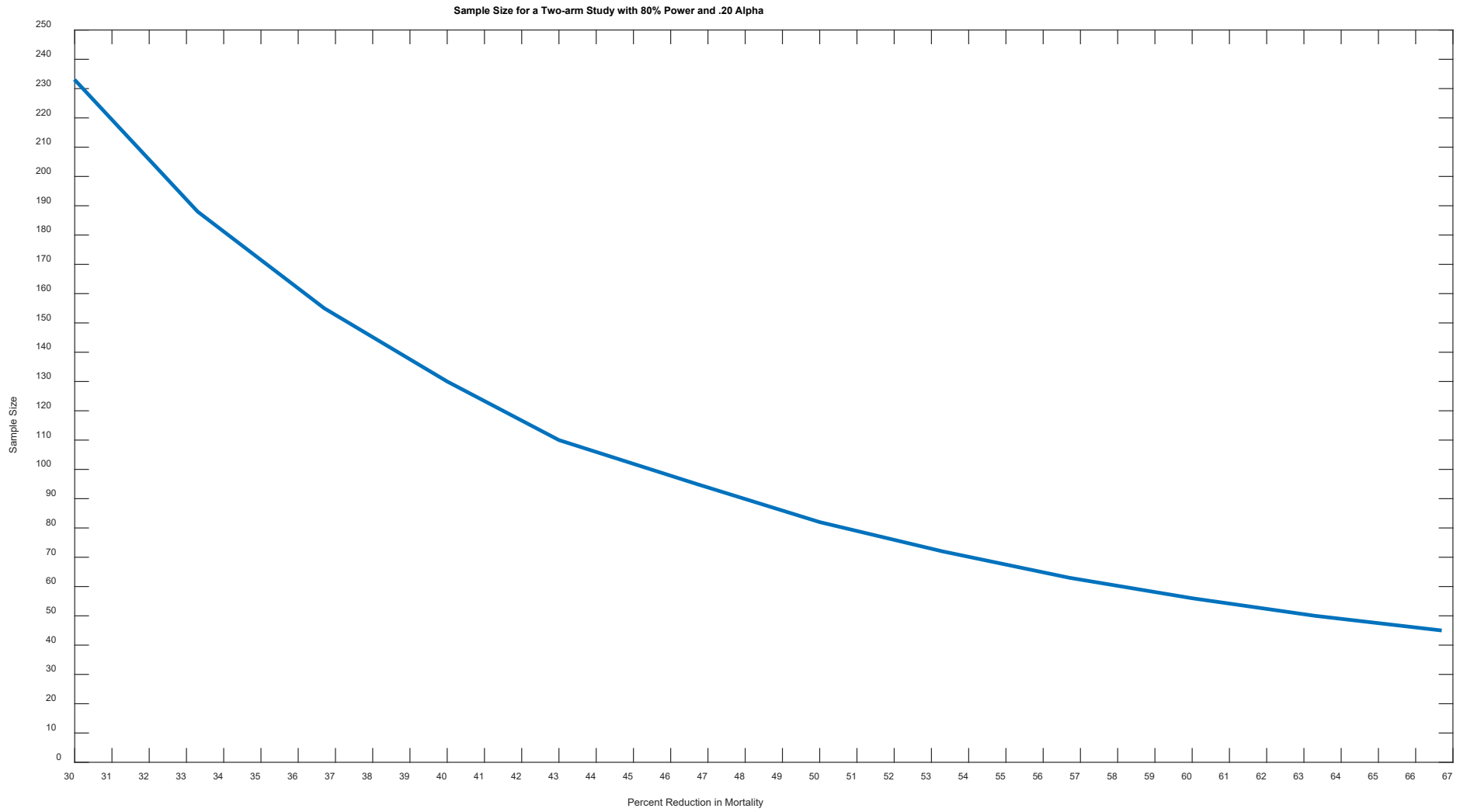
- Cell free DNA testing options on proposed study
  - Bank specimens for future testing
  - Collect and test real time for investigational purposes only
  - Collect and test real time and report to investigator

Sample Processing

- Cell free DNA testing options on proposed study
  - Bank specimens for future testing
    - Allows time to determine assay, may decrease cost
    - Results may take longer to report
  - Collect and test real time for study purposes only
    - Provides results fastest, ready to report with clinical data
    - Potentially risky to perform an interim analysis of a high-risk MRD-positive population before enrollment is complete
  - Collect and test real time, report to investigator
    - Would requires significant utility data
    - Potential for further treatment



*Assuming a baseline 30% risk



*Sample Size is per arm

*Assuming a baseline 30% risk

- *Assuming a 30% baseline risk, 80% power and .20 alpha

Reduction in Risk	2-year DFS (%) of Treatment Arm	One Arm Sample Size	Two Arm Sample Size
16.7	75	354	758
20	76	242	526
23.3	77	175	386
26.7	78	132	295
30	79	102	233
33.3	80	81	188
36.7	81	66	155
40	82	54	130
43	83	45	110
46.7	84	38	95
50	85	32	82
53.3	86	27	72
56.7	87	24	63
60	88	20	56
63.3	89	18	50
66.7	90	15	45

1:1 Ratio of N0:N1 (assuming 2-yr DFS of N0 is 70% and 2-yr DFS of N1 is 50%, power of 80%, alpha of .20)				
Reduction of Risk	2-yr DFS for N0	2-yr DFS for N1	One Arm	Two Arm
30%	79%	65%	56	156
40%	82%	70%	36	88
50%	85%	75%	22	56

3:1 Ratio of N0:N1 (assuming 2-yr DFS of N0 is 70% and 2-yr DFS of N1 is 50%, power of 80%, alpha of .20)				
Reduction of Risk	2-yr DFS for N0	2-yr DFS for N1	One Arm	Two Arm
30%	79%	65%	83	189
40%	82%	70%	44	106
50%	85%	75%	26	68

- For a two-arm study:
  - Based on a power of 80%, alpha of 0.20, and assuming the baseline risk is 30% (meaning 70% 2-year DFS), in order to detect 50% reduction of risk (85% 2-year DFS), the sample size requirement is 82 patients per arm.
  - Alternatively, in order to detect 40% reduction of risk using the same parameters, the sample size requirement is 130 patients per arm.

Design Assumptions

Sample Size Consideration:

- **For a two-arm study assuming a 1:1 ratio of patients with pT1-T2 N0 to pT1-T2 N1 disease:**
- Based on a power of 80%, alpha of 0.20, and assuming the baseline risk is 30% for N0 patients and 50% for N1 patients (meaning 70% DFS for N0 and 50% 2-year DFS for N1), in order to detect 30% reduction of risk (79% 2-year DFS for N0 and 65% 2-year DFS for N1), the sample size requirement is 156 patients in one arm. In order to detect 40% reduction of risk (82% 2-year DFS for N0 and 70% 2-year DFS for N1), using the same parameters, the sample size requirement is 88 patients in one arm. In order to detect 50% reduction of risk (85% 2-year DFS for N0 and 75% 2-year DFS for N1), using the same parameters, the sample size is 56 patients in one arm.
- **For a two-arm study assuming a 3:1 ratio of patients with pT1-T2 N0 to pT1-T2 N1 disease:**
- Based on a power of 80%, alpha of 0.20, and assuming the baseline risk is 30% for N0 patients and 50% for N1 patients (meaning 70% DFS for N0 and 50% 2-year DFS for N1), in order to detect 30% reduction of risk (79% 2-year DFS for N0 and 65% 2-year DFS for N1), the sample size requirement is 189 patients in one arm. In order to detect 40% reduction of risk (82% 2-year DFS for N0 and 70% 2-year DFS for N1), using the same parameters, the sample size requirement is 106 patients in one arm. In order to detect 50% reduction of risk (85% 2-year DFS for N0 and 75% 2-year DFS for N1), using the same parameters, the sample size is 68 patients in one arm.

- The N1 group is more likely to have recurrence and therefore the group that’s most likely to benefit from effective intensified therapy. Within this trial, the goal is not to have definitive data for each subset but rather to collect data for each subset understanding that it is underpowered to draw definitive conclusions but that the data will drive statistical planning for a larger trial pending the feasibility demonstration for this one.

Active studies by Cooperative Group

Alliance Thoracic Group Co-Chairs:

Linda Martin and Dennis Wigle

Disclosures – L Martin

Commercial Interest	**Relationship(s)**
Astra Zeneca	Advisory Board for Aduara Trial dissemination
On Target Laboratories	Steering Committee for ELUCIDATE trial

Alliance Trials

- Champions for Esophageal trial (EA2174 – Dr Khullar to present today)
- ALCHEMIST – Dennis Wigle – updates
- Small Cell Concept – Jeff Yang
- CHIO3 (AFT 46)
- In Development:
  - AFT 51 Intraoperative Molecular Imaging for Metastatic Disease
  - Phase 3 trial for stage 3A/B lung cancer – some ideas but nothing firm yet

Alliance Foundation Trial-46

CHIO3 Trial: CHemotherapy Combined with Immune Checkpoint Inhibitor for Operable Stage 3A/B Non-Small Cell Lung Cancer

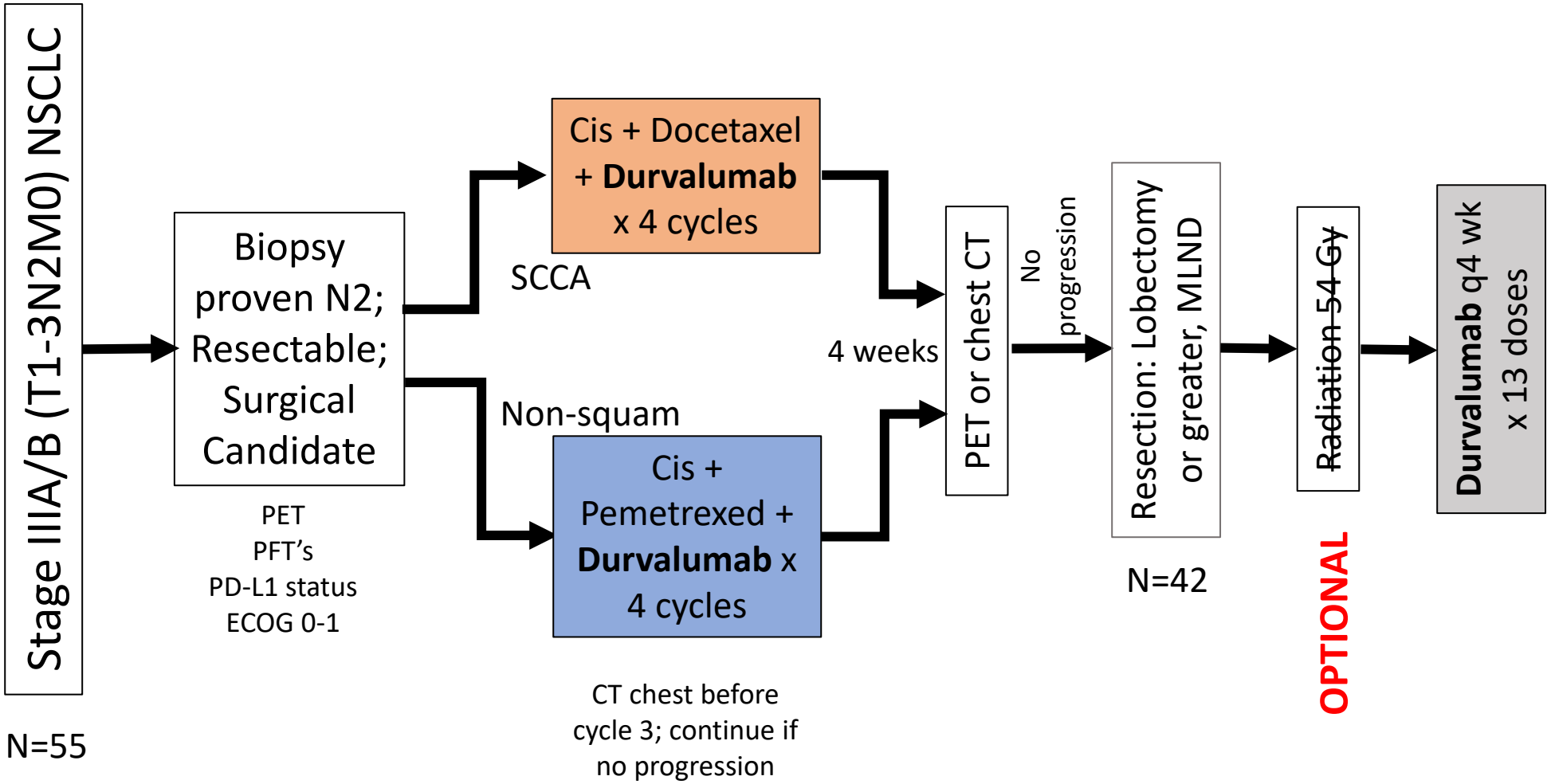
Linda W Martin, MD, MPH - Thoracic Surgery, University of Virginia

Jyoti Patel, MD - Medical Oncology, University of Chicago

James Urbanic, MD - Radiation Oncology, UC San Diego

AFT 46 Phase II Single Arm Trial

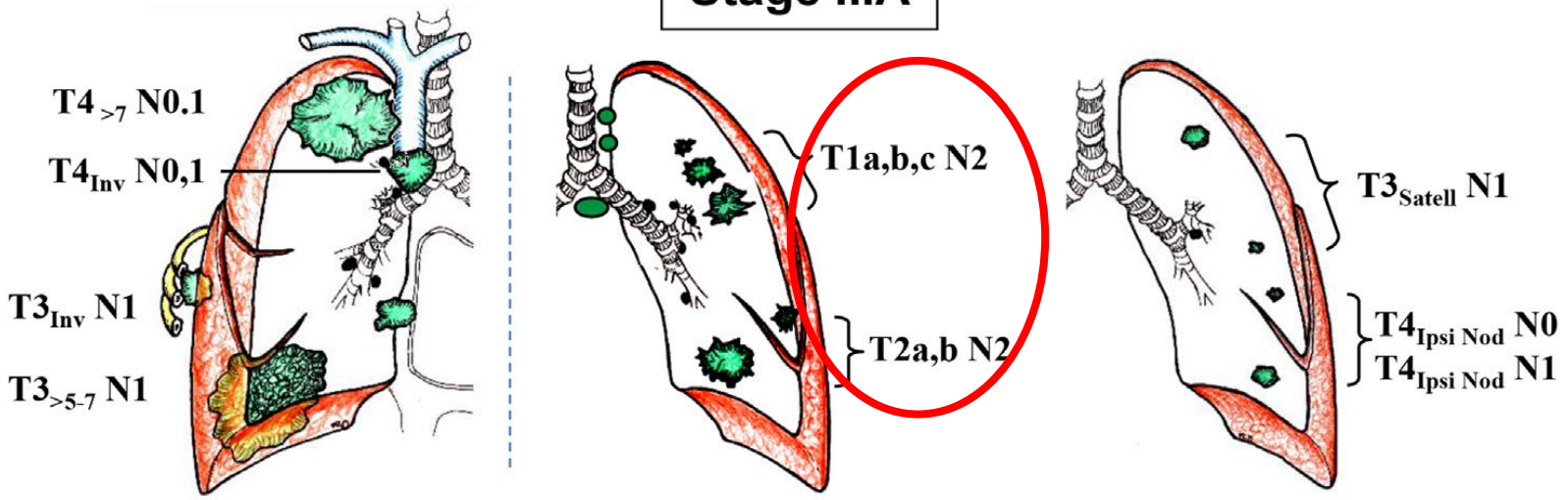
CHIO 3: Chemotherapy Combined with Immune Checkpoint Inhibitor for Operable Stage III NSCLC



Primary Endpoint: N2 nodal clearance (Estimated 50%, historical control 30%)

L Martin, J Patel, J Urbanic

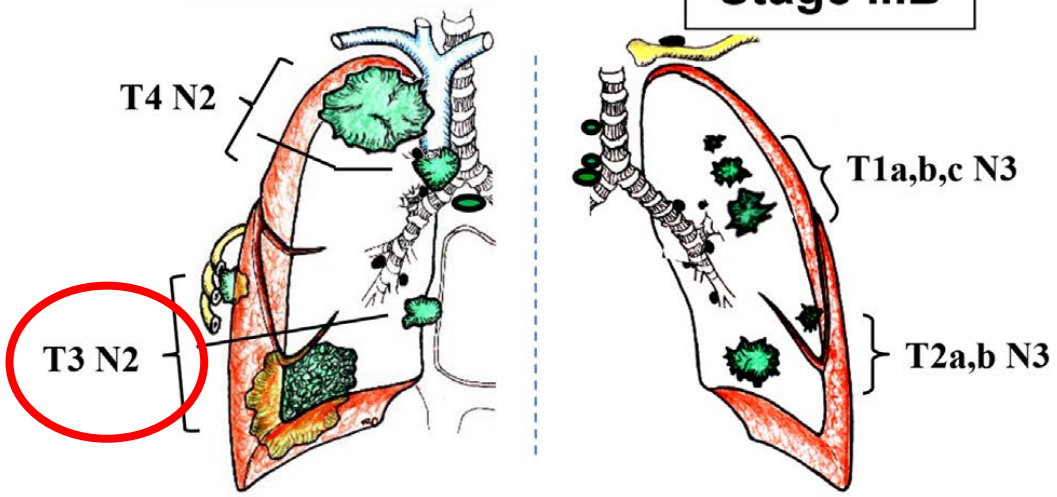
Stage IIIA



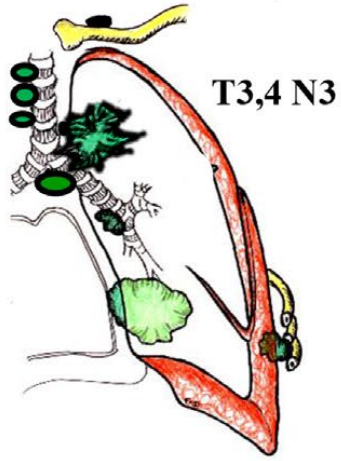
Specific Notes:

- Tumor size defined as largest dimension of the solid (imaging, c-stage) or invasive (p-stage) component
- Direct extension of the primary tumor into an adjacent node counts as nodal involvement
- Extension of a nodal metastasis into a T structure does not count for the T category
- The highest T category is used when there is a discrepancy between T by size or by other factors

Stage IIIB



Stage IIIC



AJCC 8th edition: CHEST 2017; 151(1):193-203

Surgery

- Lobectomy or greater
- Mediastinal Lymph Node Dissection
- Per Operative Standards for Cancer Surgery “rules”

Adjuvant radiation – “PORT” criteria

- OPTIONAL – per treating team

- Positive margins must get it
- Use treatment planning guidelines from Lung ART trial

Endpoints

Primary:

- To increase N2 nodal clearance rate from 30% (with platinum doublet alone as induction therapy) to 50% (with combined platinum doublet with durvalumab) in patients with potentially resectable stage IIIA (N2) NSCLC

Secondary:

- To assess the radiographic response rate of the combination of chemotherapy and durvalumab in patients with potentially resectable stage III (N2) NSCLC

Progress

- LOI submitted April 2017
- Final proposal submitted 7/31/18, revisions reviewed 10/30/18
- Approved by Alliance Foundation and Astra Zeneca Dec 2018
- Alliance Foundation Trial, using the Alliance trial mechanism and resources
- CIRB approval underway Feb 2020
- Covid…. Contracts… Delays…

AFT-46 Newsletter #6 - March 2022

AFT-46, CHIO3 Trial: CHemotherapy Combined with Immune Checkpoint Inhibitor for Operable Stage IIIA/B Non-Small Cell Lung Cancer

Study Chairs: Jyoti Patel, MD; Linda Martin, MD, MPH; James Urbanic, MD

Enrollment Updates

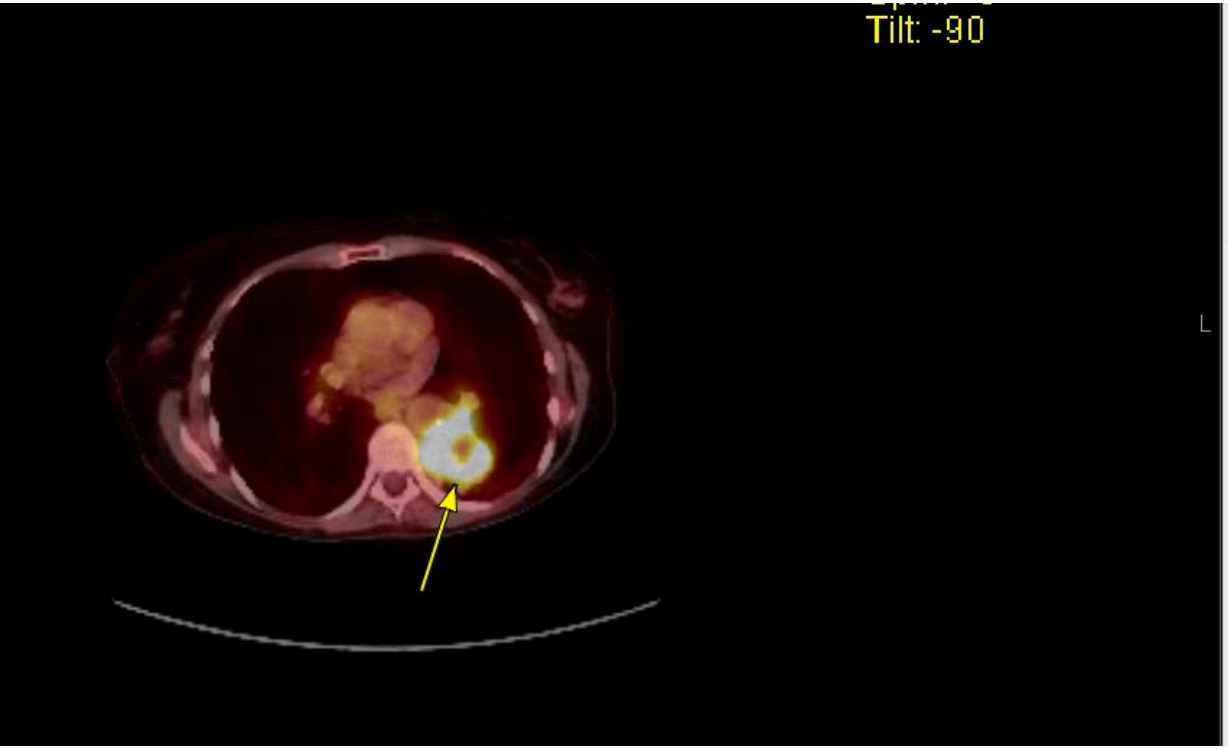
# of sites: 13 open to enrollment (out of 15 sites)
# of patients: 18 enrolled (out of 55 patients)

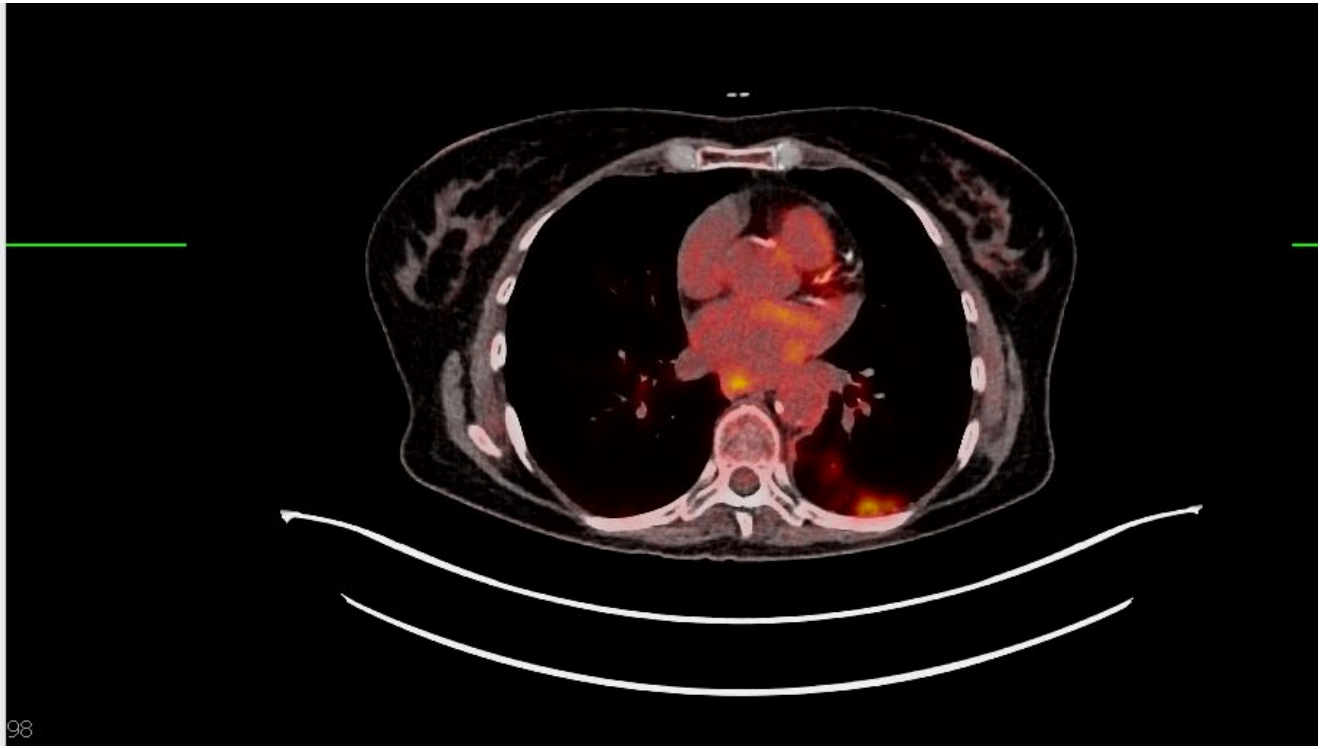
Only need 42 surgical patients

Sites Open or Pending

- MGH
- U of Oklahoma
- MDACC
- Mayo MN
- Brigham/DFCI
- UVA
- Lowell General Hospital/Boston
- U Chicago
- Northwestern
- UCSD
- Roswell Park
- Michigan CCOP
- Ohio State
- Baptist Memorial Hospital Memphis
- SUNY Upstate
- Dartmouth

Patient numero uno

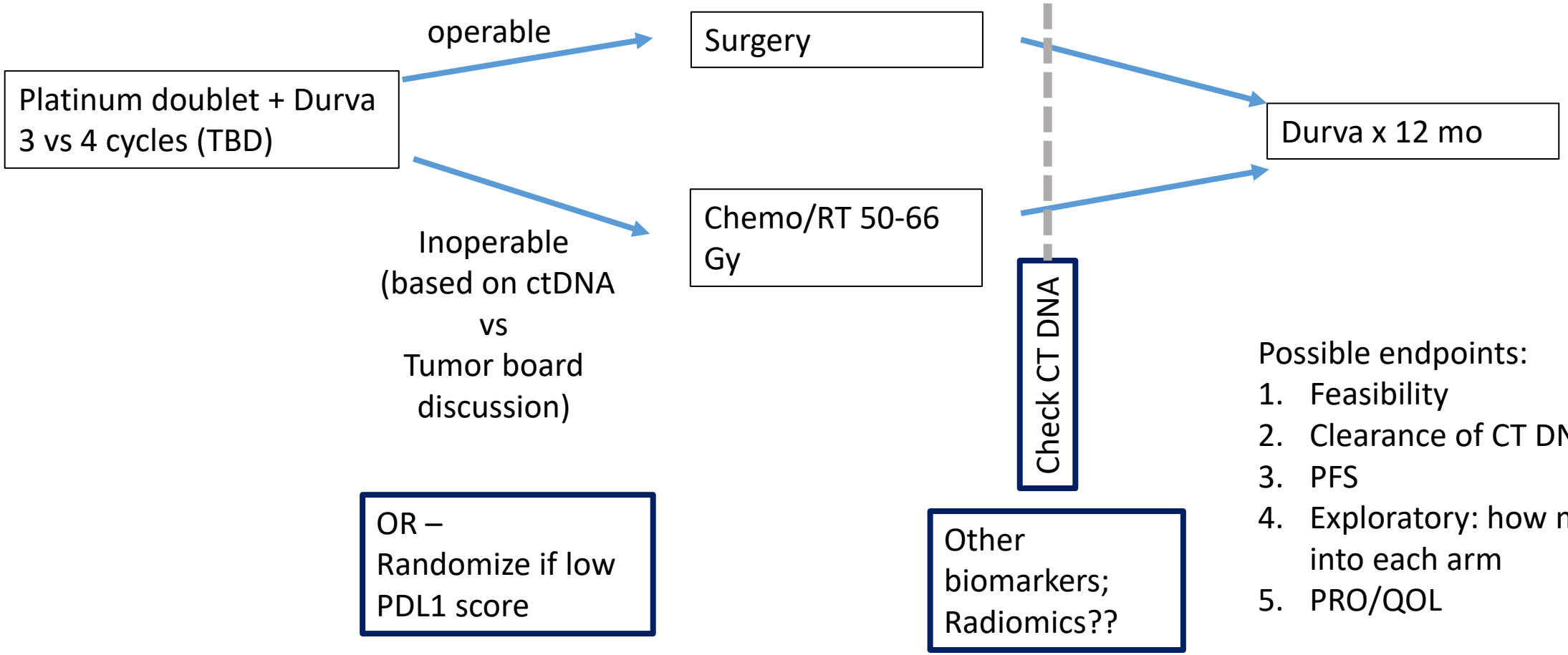




Trials in Development

Operable, or borderline resectable

T1-4 **N2** NSCLC



Possible endpoints:

1. Feasibility
2. Clearance of CT DNA
3. PFS
4. Exploratory: how many go into each arm
5. PRO/QOL

AFT 51

Linda Martin, MD, MPH
and Sunil Singhal, MD

Pulmonary Metastasectomy

SURGEONS GOAL:

COMPLETE DISEASE CLEARANCE

Problem

Identification of all disease

Hypothesis

Near infrared imaging can improve detection of metastases missed by

(a) preoperative CT imaging

(b) intraoperative inspection

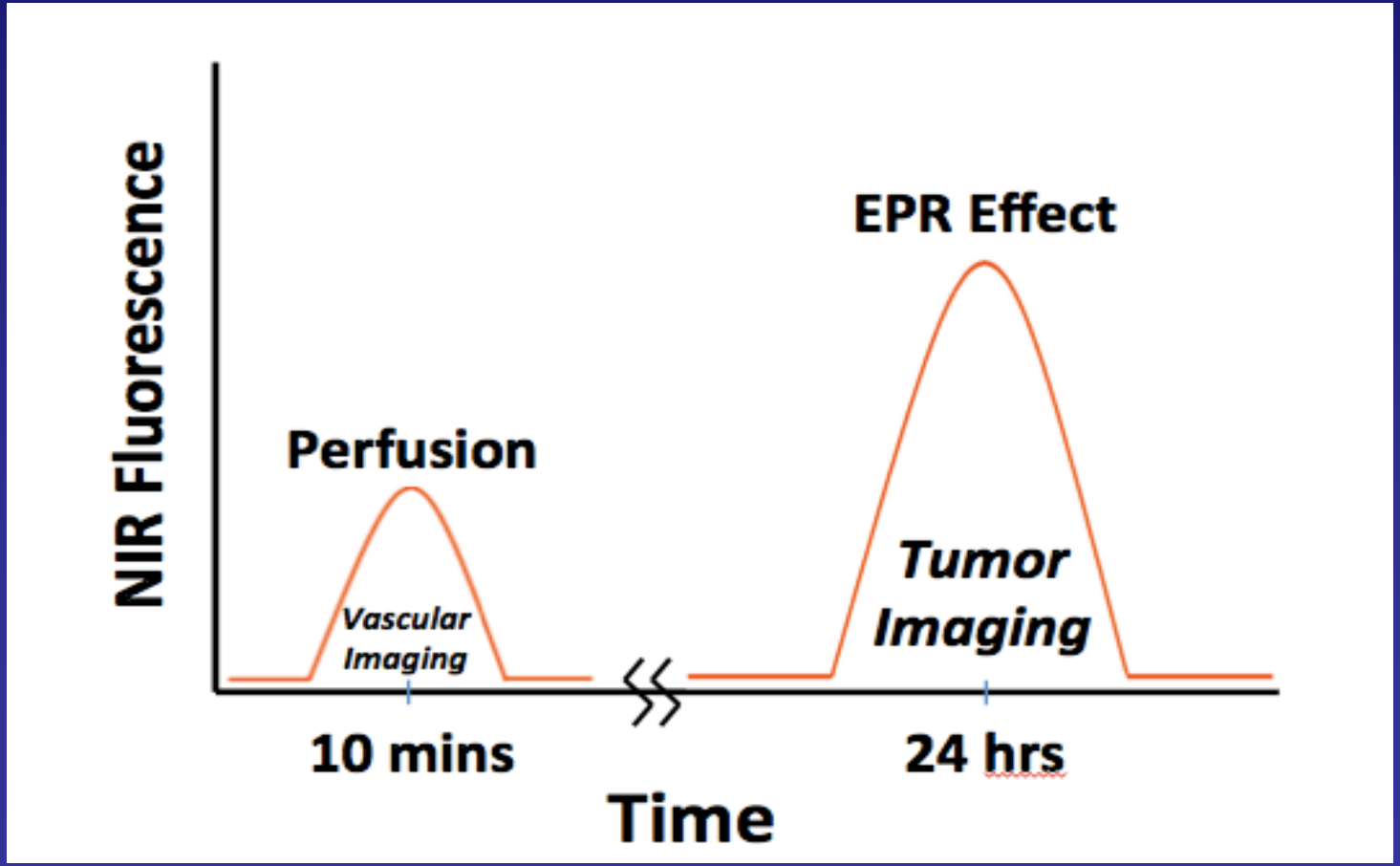
NIR Imaging—TumorGlow®

ICG GIVEN SYSTEMICALLY (NOT INTRATUMORAL)

DIFFERENT DOSE—5 mg/kg

NIR Imaging—TumorGlow®

Imaging 24h later



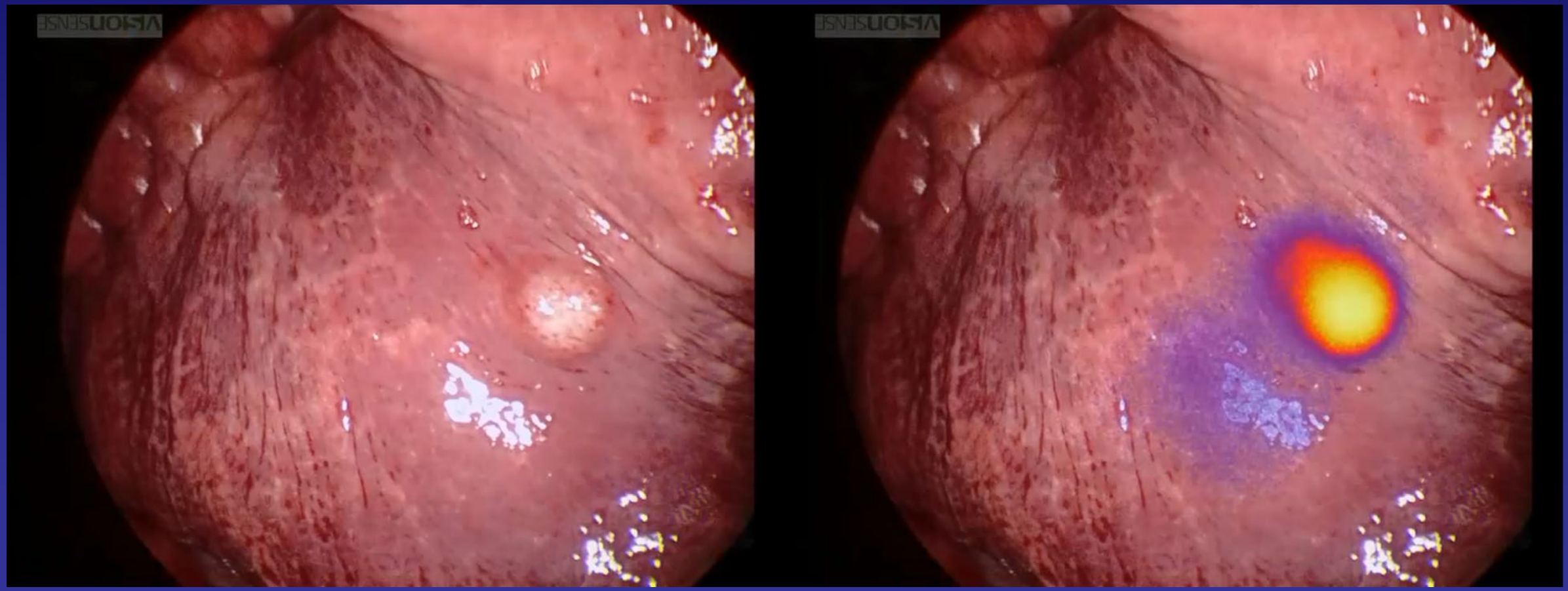
Clinical Trial

Example 1

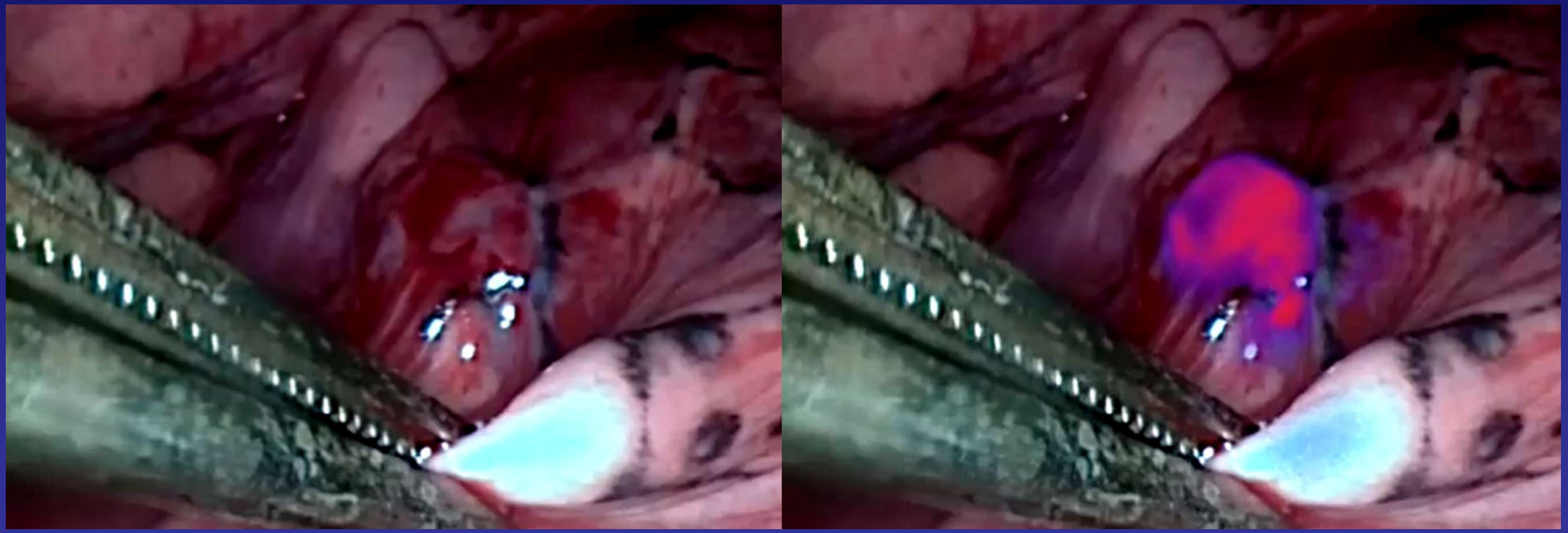
32M, femur osteosarcoma, RLL mets (known)

White Light

NIR Imaging



Additional lesion? (right middle lobe)



Future Directions

WELCOME A MULTI-INSTITUTIONAL CLINICAL TRIAL

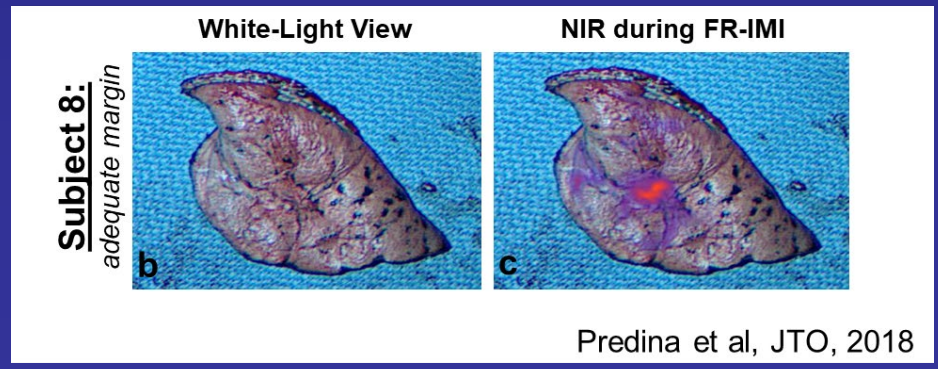
sunil.singhal@uphs.upenn.edu (Sunil Singhal)

lm6yb@virginia.edu (Linda Martin)

- AFT 51 in development
- 120 patients, 10-15 sites

QUESTIONS TO ANSWER:

- Is this reproducible nationwide?
- Are particular histologies better at imaging?
- Ex vivo margin assessment (growing importance)?



Predina et al, JTO, 2018