Radiation in Early-Stage NSCLC

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DISCLOSURES

Commercial Interest	Relationship(s)
EMD Serono	Research Funding
Genentech	Research Funding
Merck	Research Funding
Boston Scientific	Advisory Board

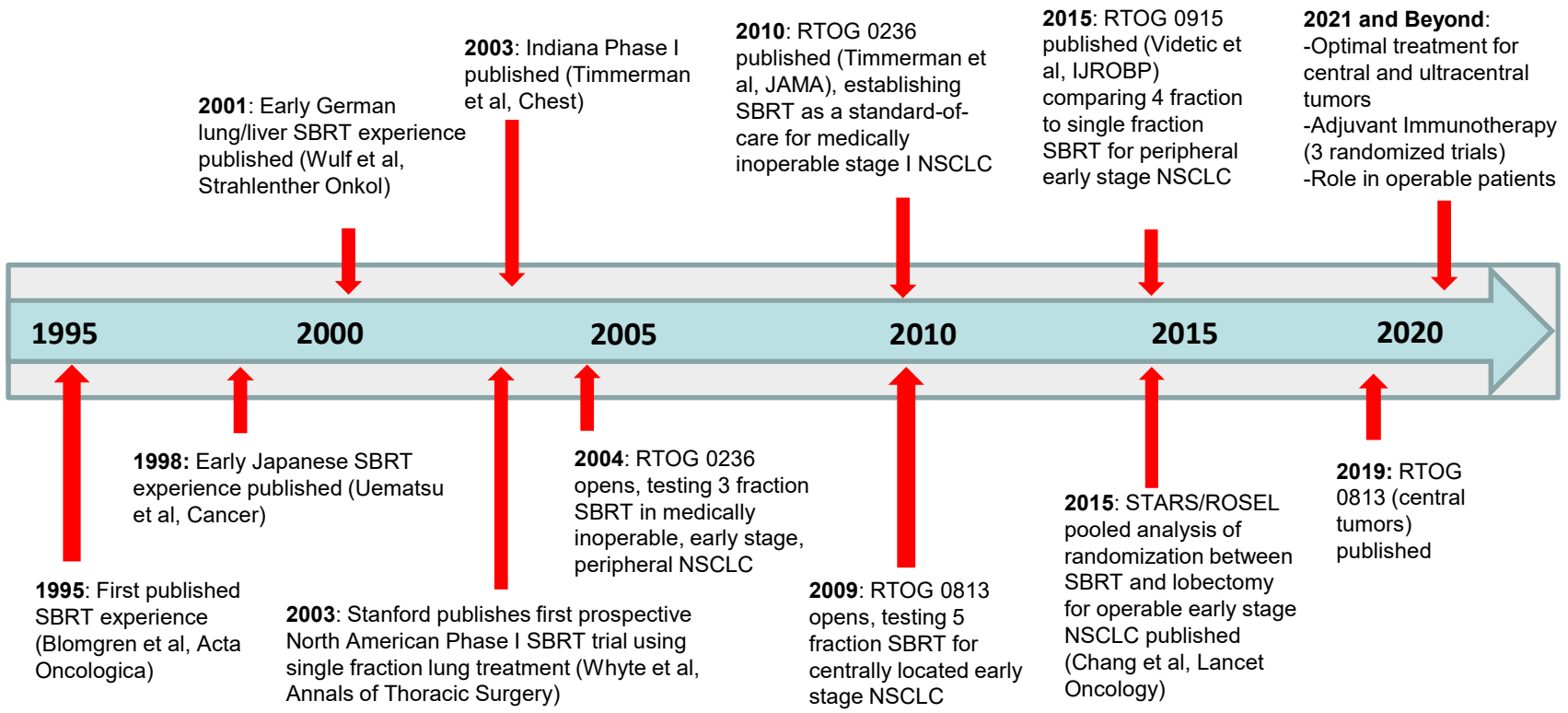
Overview

- Ongoing trials of SBRT in operable NSCLC
- Ongoing and completed trials of SBRT + Immunotherapy in Early-Stage NSCLC
  -Lessons from operable disease (LCMC-3: PS-01-05)
- RT + IO + Surgery in Operable NSCLC (Education Session 06-02)

Current Status of SBRT/SABR for NSCLC

- Standard-of-care for medically inoperable early-stage NSCLC
- High rates of local (in-field) control ~90% at 3 years w/ BED ≥100 Gy_{10}
- Reported toxicity rates following lung SBRT are low
- Regional and distant failure remain problematically high
- Role of systemic therapy remains investigational but is currently the subject of multiple ongoing randomized phase III trials
  - Lessons from the operative setting?
- Ongoing interest in use of SABR for operable patients

Timeline of the Development of SBRT/SABR



Prospective Randomized Trials of SBRT in Operable NSCLC

Trial	Eligibility	Design	Status
STARS	T1-2aN0M0 <4 cm, fit for lobectomy	Randomized Phase III comparing lobectomy to SBRT	Terminated due to poor accrual
ROSEL	T1-2aN0M0 <4 cm, fit for lobectomy	Randomized Phase III comparing lobectomy to SBRT	Terminated due to poor accrual
ACOSOG Z0499	Peripheral NSCLC ≤ 3 cm; "high" surgical risk	Randomized Phase III comparing sublobar resection to SBRT	Terminated due to poor accrual
SABR-TOOTH	T1-2N0M0 ≤ 3 cm, "high-risk", either lobectomy or sub-lobar resection	Randomized Feasibility	Terminated due to poor accrual
JoLT-Ca STABLE-MATES	Peripheral NSCLC ≤ 4 cm; "high" surgical risk	Pre-randomization design; phase III	Actively accruing
VALOR (VA)	T1-2N0M0<5 cm, fit for lobectomy	Randomized Phase III	Actively accruing
RTOG Foundation 3502 (POSTILV)	T1N0M0 ≤ 3 cm, fit for lobectomy	Randomized Phase II	Actively accruing

JOLT-CA STABLEMATES Trial

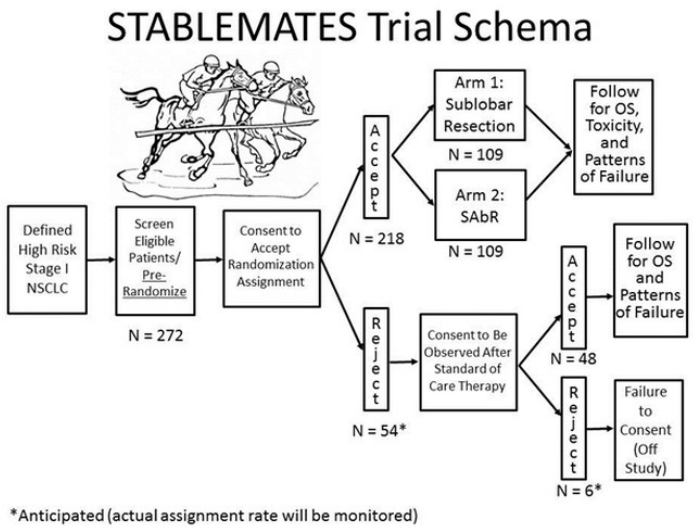
Study Design

Phase III, pre-randomization design

Primary endpoint: Overall Survival

Secondary endpoints:
- Progression-free survival
- Local and regional recurrence
- Distant Recurrence
- Toxicity

Eligibility: **High-risk for surgery** based on one major or 2 minor criteria



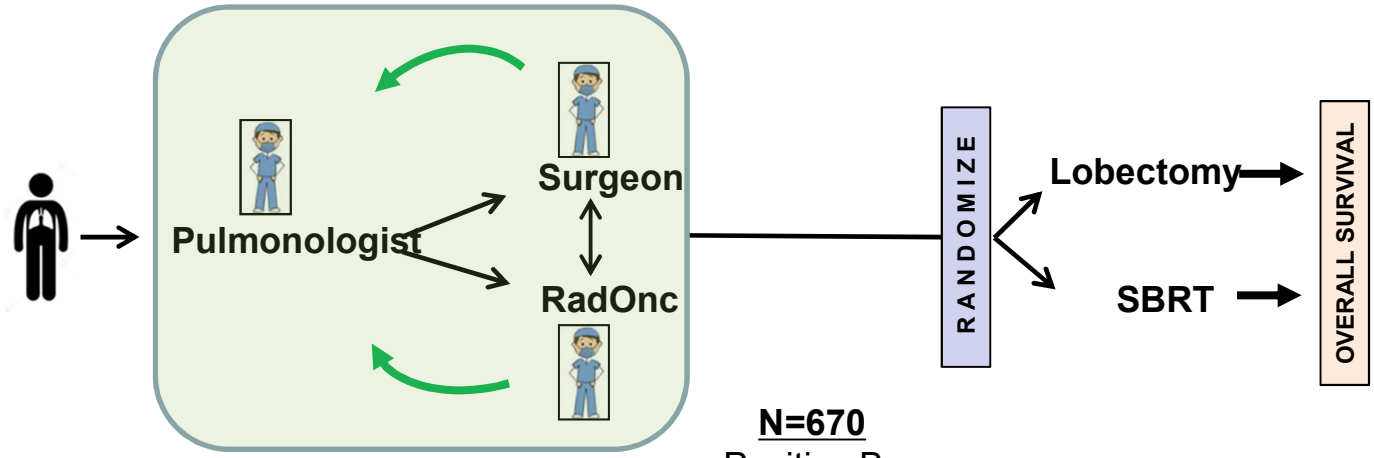
https://www.joltca.org/

PIs: Hiran Fernando MD, Robert Timmerman MD

VALOR Trial

Veterans Affairs Lung Cancer Surgery or Stereotactic Radiotherapy Trial

PIs Drew Moghanaki and David Harpole

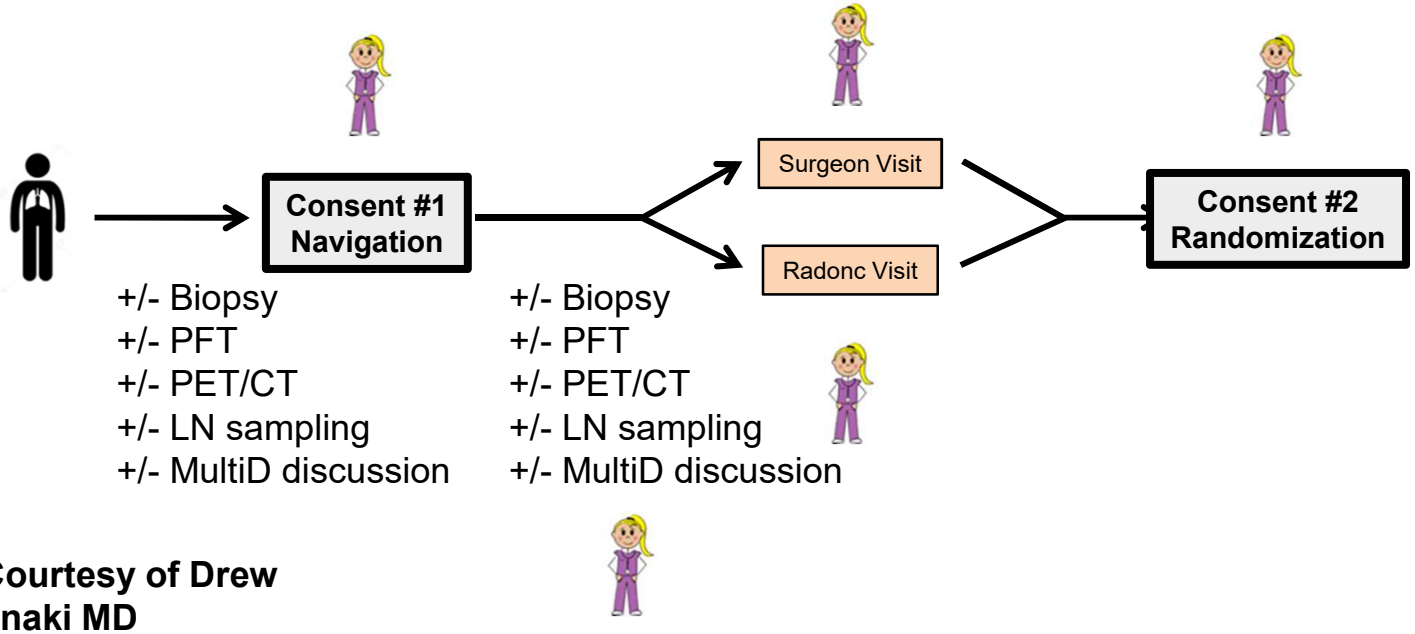


N=670
Positive Bx
Clinical IA v IB
Central v Peripheral

VALOR

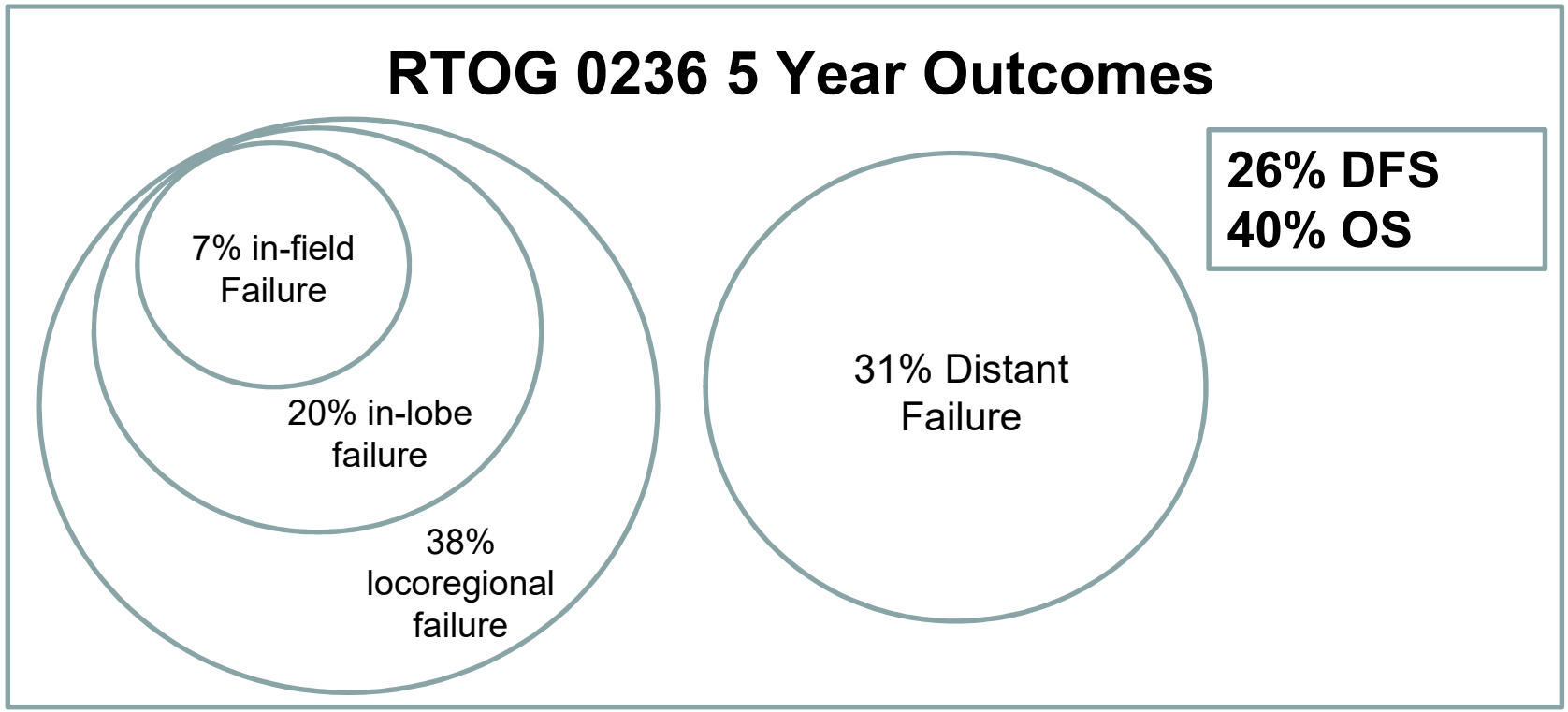
Slide Courtesy of Drew Moghanaki MD MPH

VALOR Navigated Recruitment Pathway



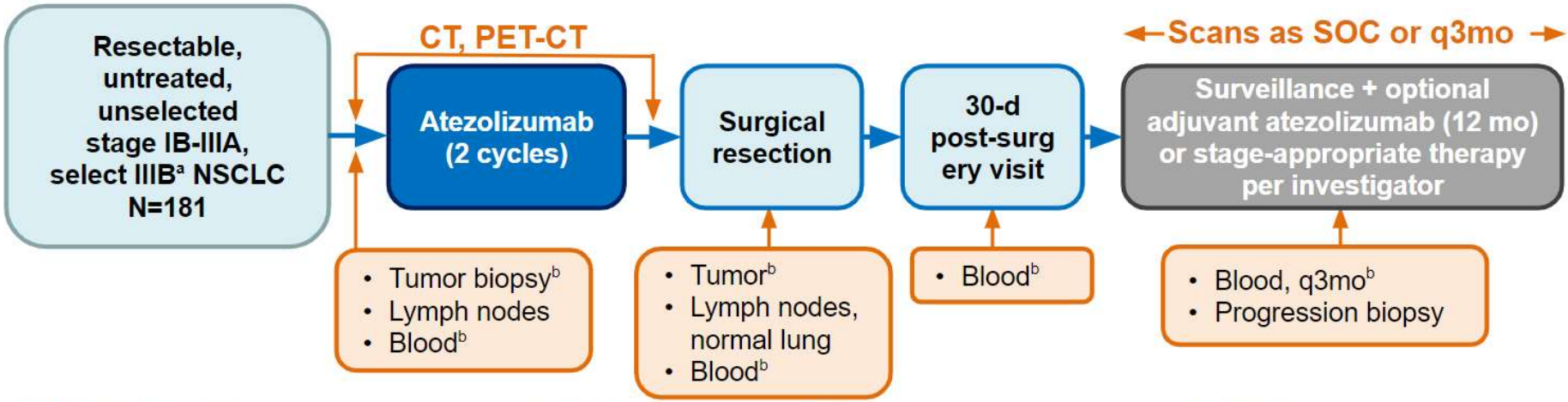
Slide Courtesy of Drew Moghanaki MD

Failure Patterns in Early-Stage NSCLC



Timmerman RD et al. Long-term results of RTOG 0236: A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Medically Inoperable Stage I Non-Small Cell Lung Cancer. ASTRO 2016.

LCMC3: Neoadjuvant Immunotherapy for Operable NSCLC



Primary endpoint:

- Major pathologic response (≤10% viable tumor cells)

Secondary endpoints:

- Pathologic response by PD-L1
- Radiographic response by
  - PD-L1, TMB, neoantigen, gene expression profiling

Exploratory endpoints:

- DFS, OS
- Biomarkers
  - ctDNA, TCRseq, flow cytometry, IF, IHC, NGS

Safety:

- Adverse events

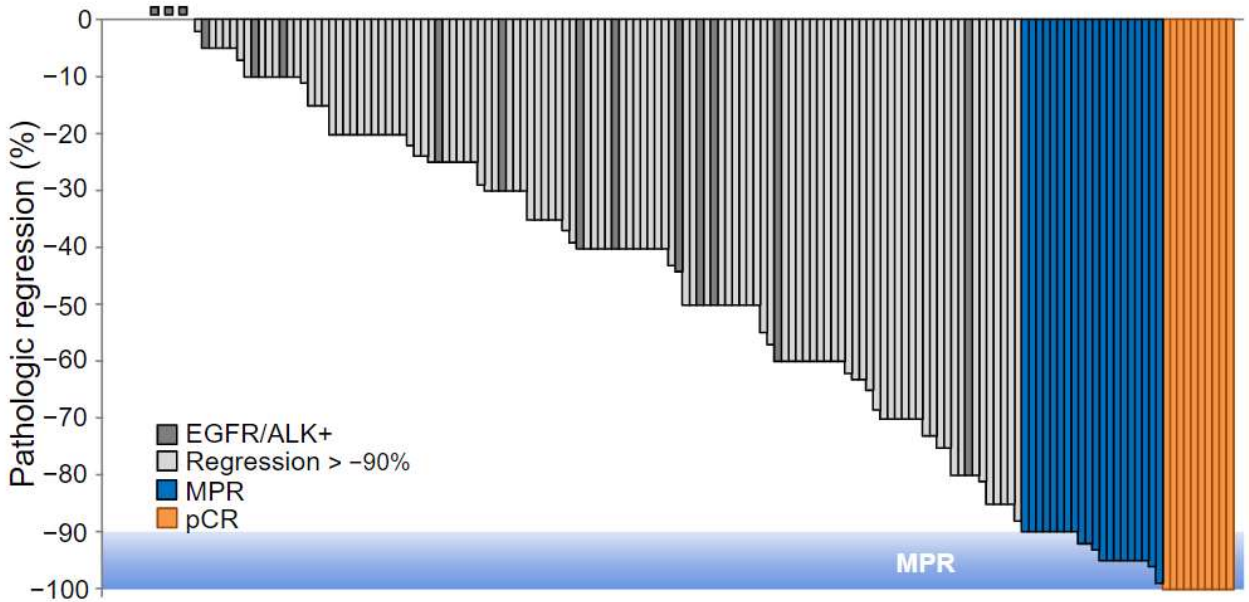
NCT02927301

ctDNA, circulating tumor DNA; DFS, disease-free survival; IF, immunofluorescence; NGS, next-generation sequencing; PET-CT, positron emission tomography–computed tomography; q3mo, every 3 months. SOC, standard of care; TCRseq, T-cell receptor sequencing; TMB, tumor mutational burden.

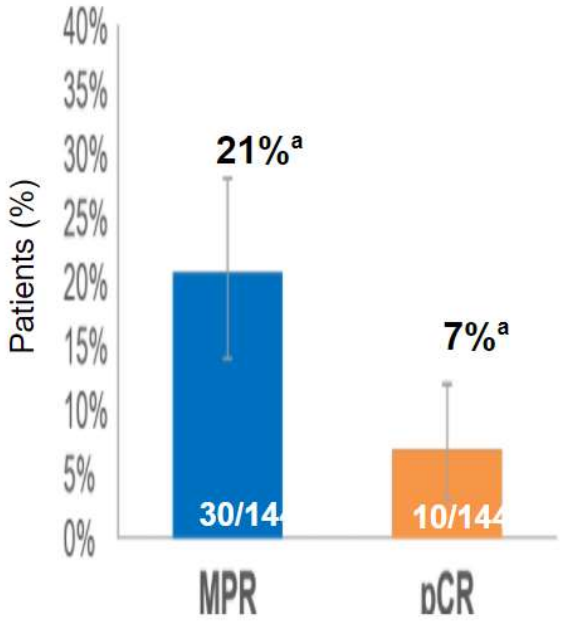
[a] T4 due to mediastinal organ invasion were excluded. [b] Mandatory

Primary endpoint: major pathologic response in surgery population

Pathologic response in surgery population (n=159)



Major pathologic response in primary efficacy population (n=144)

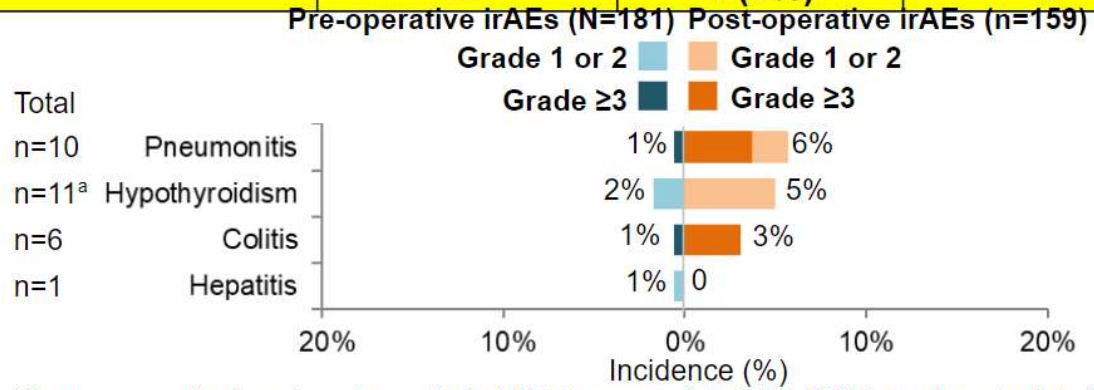


Pathologic regression defined as % viable tumor cells – 100%.
MPR, major pathologic response; pCR, pathologic complete response.
[a] Error bars indicate 95% CI.

Pre- and post-operative treatment-related AEs and immune-related AEs

Pre-operative (N=181) and post-operative AEs (n=159)

Patients with ≥1 AE, n (%)	Pre-operative TRAE N=181	Post-operative TRAE n=159	Pre-operative irAEs N=181	Post-operative irAEs n=159
Grade 1	55 (30%)	13 (8%)	22 (12%)	18 (11%)
Grade 2	36 (20%)	18 (11%)	16 (9%)	12 (8%)
Grade 3	**11 (6%)**	**17 (11%)**	**3 (2%)**	**11 (7%)**
Grade 4	**0**	**3 (2%)**	**0**	**1 (1%)**
Grade 5	**0**	**1 (1%)**	**0**	**1 (1%)**



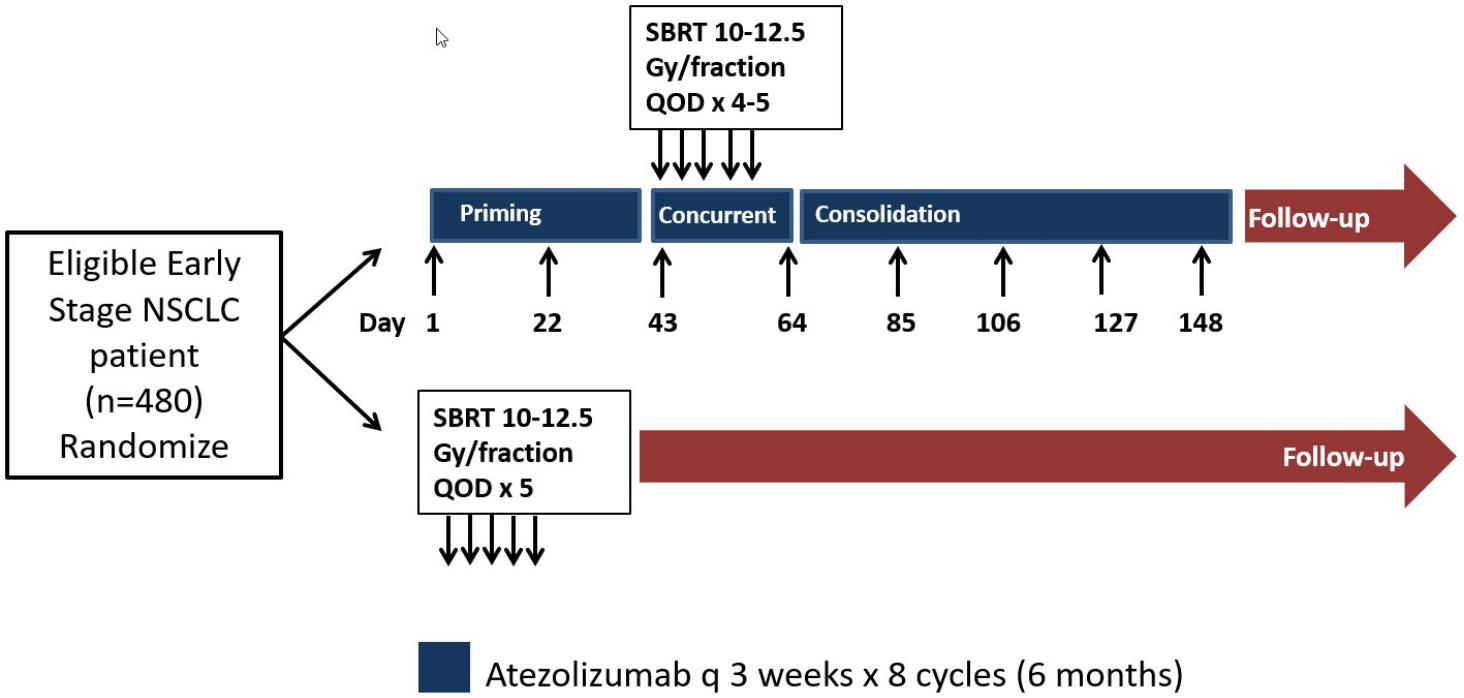
[a] One patient had hypothyroidism preoperatively and postoperatively irAE, immune-related AE; TRAE, treatment-related AE.

Conclusions

- The primary endpoint of MPR was met, with an observed MPR of 21%
  - pCR rate was 7%
- Neoadjuvant atezolizumab monotherapy was well tolerated, with no new safety signals
- Following neoadjuvant atezolizumab, resection was performed:
  - with low perioperative morbidity and mortality
  - usually within the narrow protocol window (88%)
  - within short time frame from completion of atezolizumab
  - with high R0 resection rates (92%)
- This study provides additional clinical evidence for the ongoing placebo-controlled Phase III IMpower030 study of atezolizumab combined with platinum-based chemotherapy[1]

1. NCT03456063.

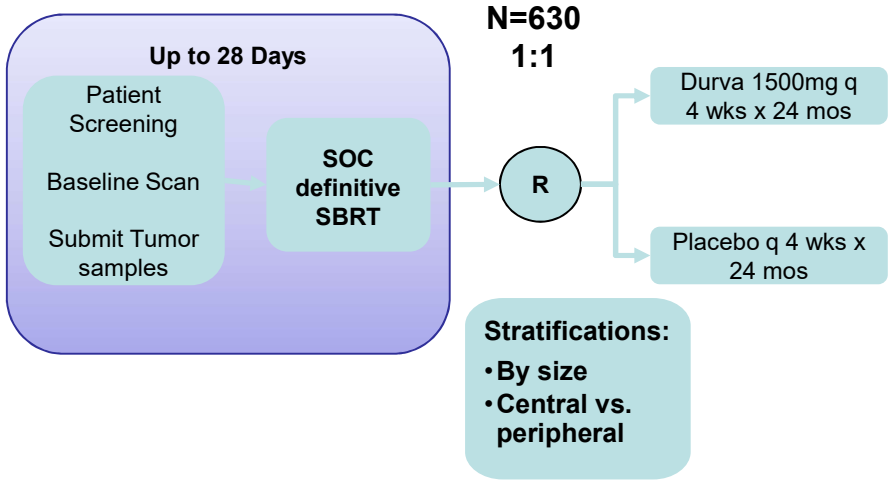
SWOG/NRG 1914: Phase III Randomized Trial



PACIFIC 4 / RTOG 3515

Inclusion Criteria

- **Clinical Stage I/II node negative (T1 – T3 N0)**
- **Medically inoperable or refuse surgery**
- **ECOG PS 0-2**
- **All comers**



Primary Endpoint: PFS

Key Secondary Endpoint: OS

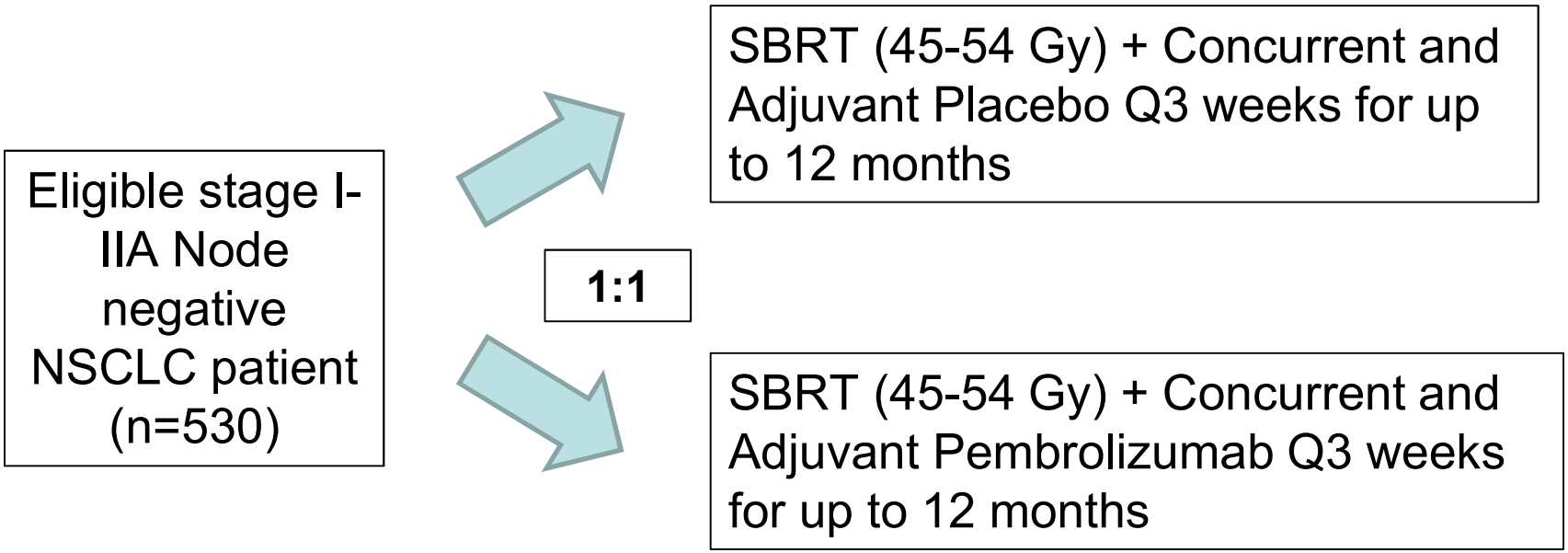
Lung Cancer Mortality

Additional Key points

- NSCLC proven by histology / cytology
- Tissue submission mandated – core preferred but will accept FNA samples for translational analysis
- SOC SBRT taking place during screening. SBRT planning can occur before study enrollment
- Randomization within **7 days of completion of SOC SBRT**

Slide Courtesy of Cliff Robinson MD

KEYNOTE 867



Co-Primary Endpoints: Event-Free Survival and Overall Survival

Radiation and IO for Operable Early Stage NSCLC

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MISSILE-NSCLC

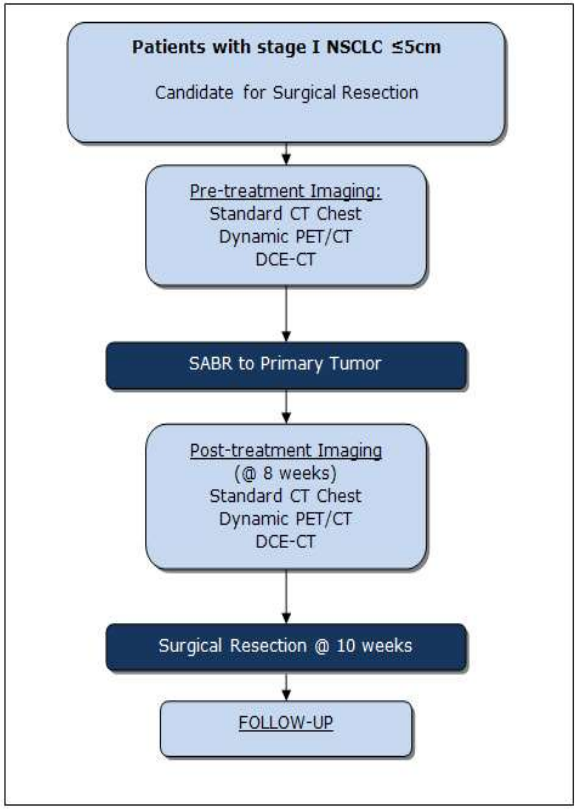
A Phase II Trial Measuring the Integration of Stereotactic Radiotherapy *plus* Surgery in Early NSCLC

Primary Endpoint

To assess the true primary tumor pCR rate after SABR, based on H&E staining

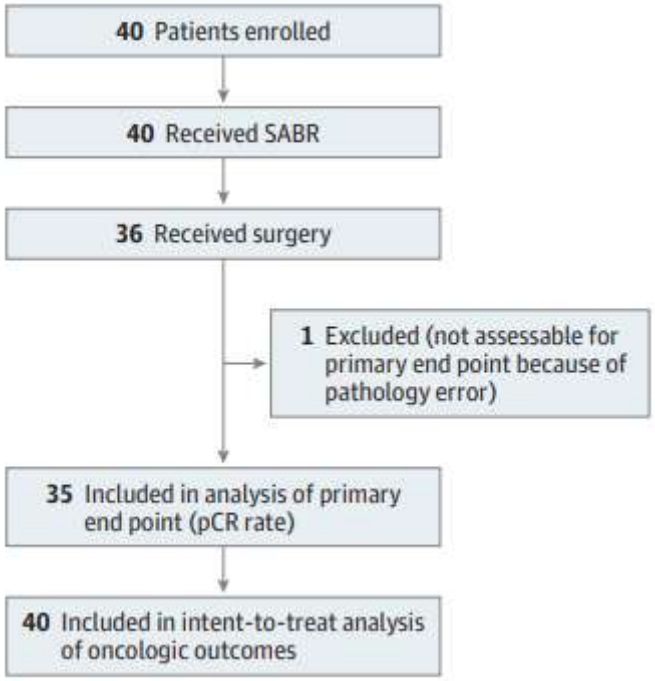
Secondary Endpoints

To assess local recurrence, regional recurrence, distant recurrence, overall survival, quality of life (QOL) and toxicity



Palma DA et al. Measuring the Integration of Stereotactic Ablative Radiotherapy Plus Surgery for Early-Stage Non-Small Cell Lung Cancer: A Phase 2 Clinical Trial. JAMA Oncology May 2019

MISSILE NSCLC



Phase II, single arm trial

Enrolled medically operable, early stage NSCLC patients

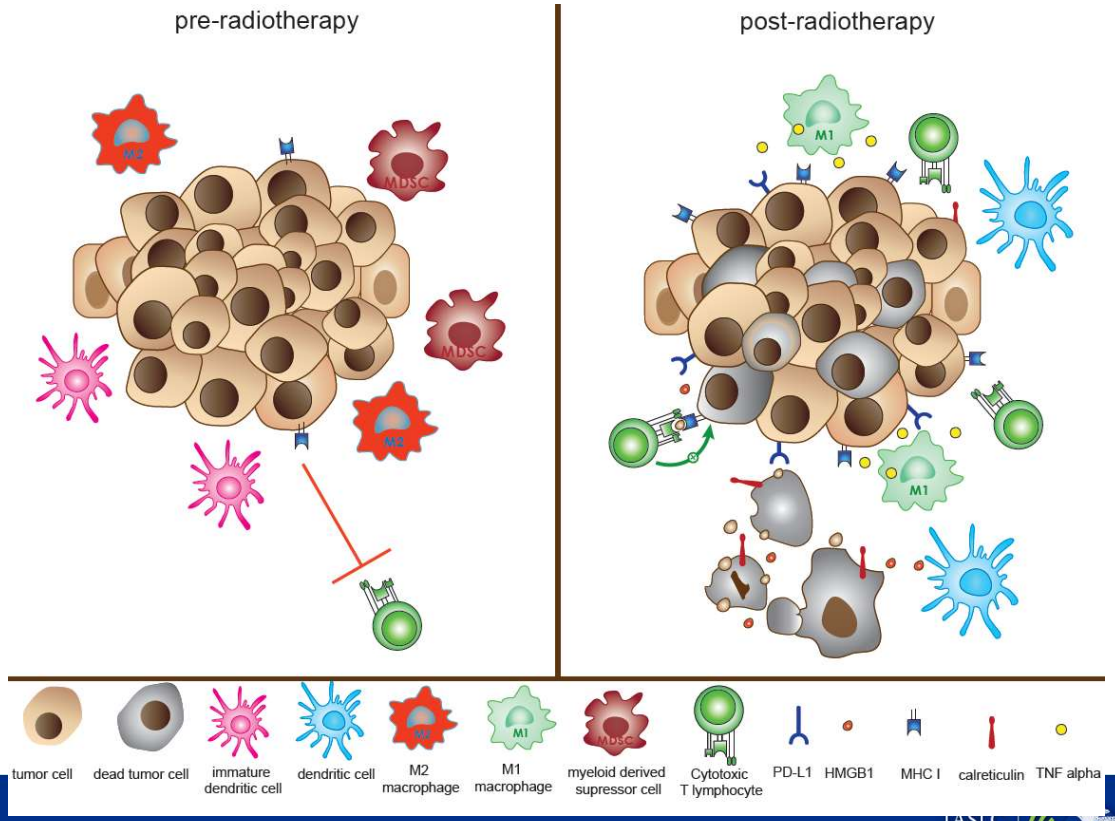
Treated with SABR followed by surgical resection 10 weeks later

pCR rate was 60% (95% CI 4%-91%)

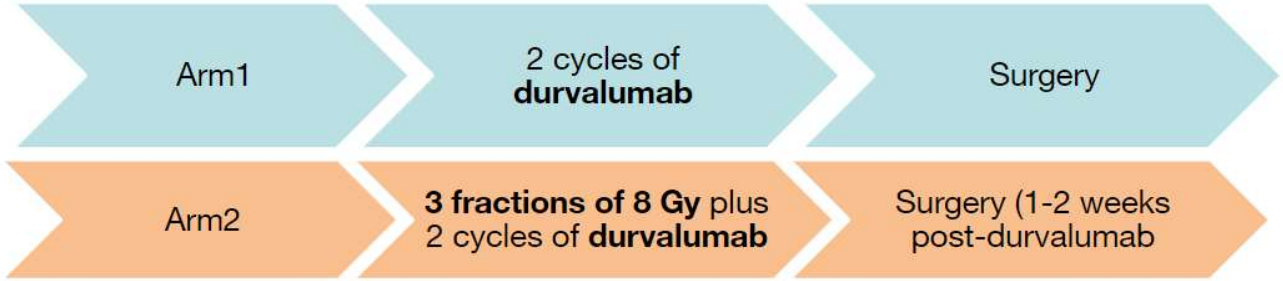
Palma DA et al. Measuring the Integration of Stereotactic Ablative Radiotherapy Plus Surgery for Early-Stage Non-Small Cell Lung Cancer: A Phase 2 Clinical Trial. JAMA Oncology May 2019

What about using radiation + immunotherapy + Surgery?

Rationale for Incorporating Radiation



Neoadjuvant Durvalumab +/- Sub-ablative SABR in Resectable NSCLC (NCT02904954)



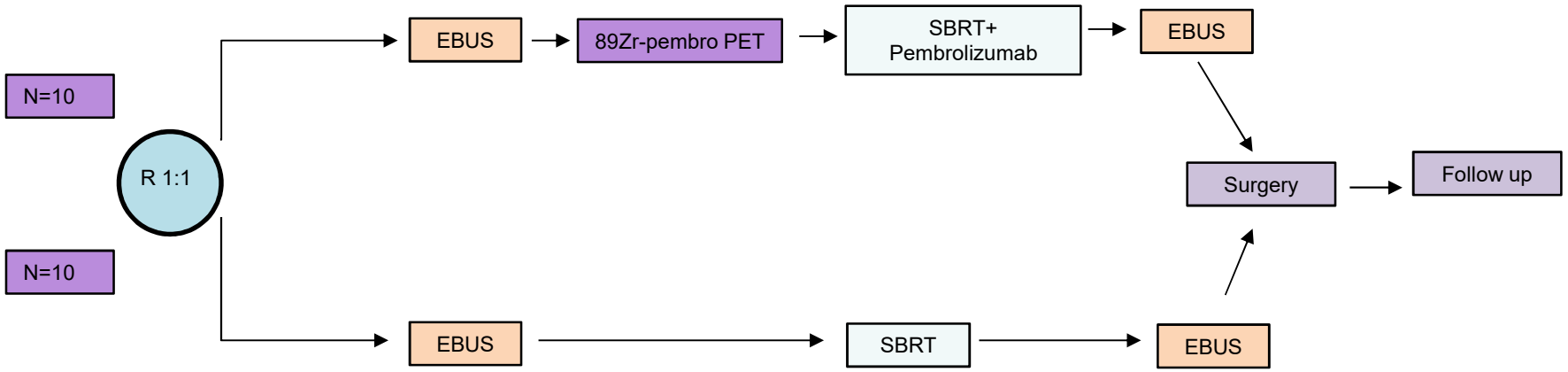
- 34 patients randomized
- 47% of patients in durvalumab + RT had major pathologic response compared to 0% with durvalumab alone

Primary endpoint: DFS for both arms versus historical controls.
Secondary endpoints: safety and efficacy (clinical/pathological response rates)

Tumor immunephenotypes in pre- and post-treatment samples by XCell deconvolution of RNAseq transcriptomic data

Borczuk A, WCLC 2019. Abstract P2.04-92

Pre-Operative SABR +/- pembrolizumab (NCT03446911)



Lobectomy with lymph node dissection

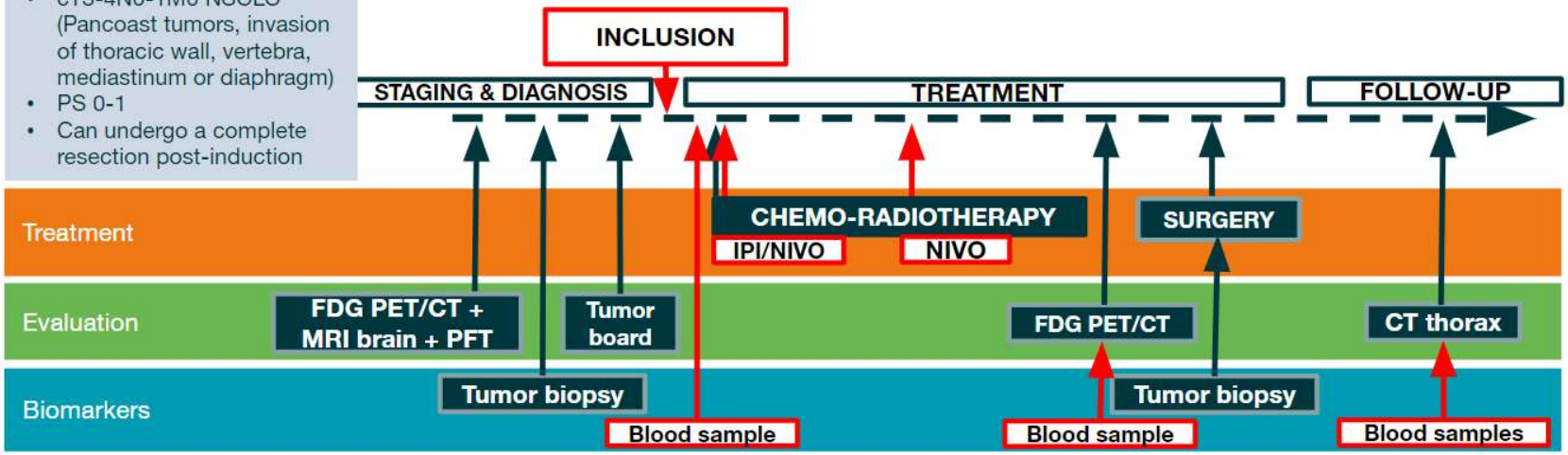
Translational Research:

-Immuno-PET

-Immune effector subsets in tumor, peripheral blood, and TDLNs by mean of FNA pre- and post SBRT and at surgery

INCREASE trial (EudraCT-Number: 2019–003454-83)

Key Inclusion Criteria:
- cT3-4N0-1M0 NSCLC (Pancoast tumors, invasion of thoracic wall, vertebra, mediastinum or diaphragm)
- PS 0-1
- Can undergo a complete resection post-induction



Dickhoff C, BMC Cancer 2020

Takeaway Points

- **Ongoing studies in early-stage NSCLC evaluate SBRT in operable patients**
- **Ongoing studies in early-stage NSCLC evaluate the integration of immunotherapy in both operable and inoperable disease, with promising results from LCMC3**
- **SBRT remains the standard treatment for early stage, medically inoperable NSCLC with excellent in-field control and low toxicity**