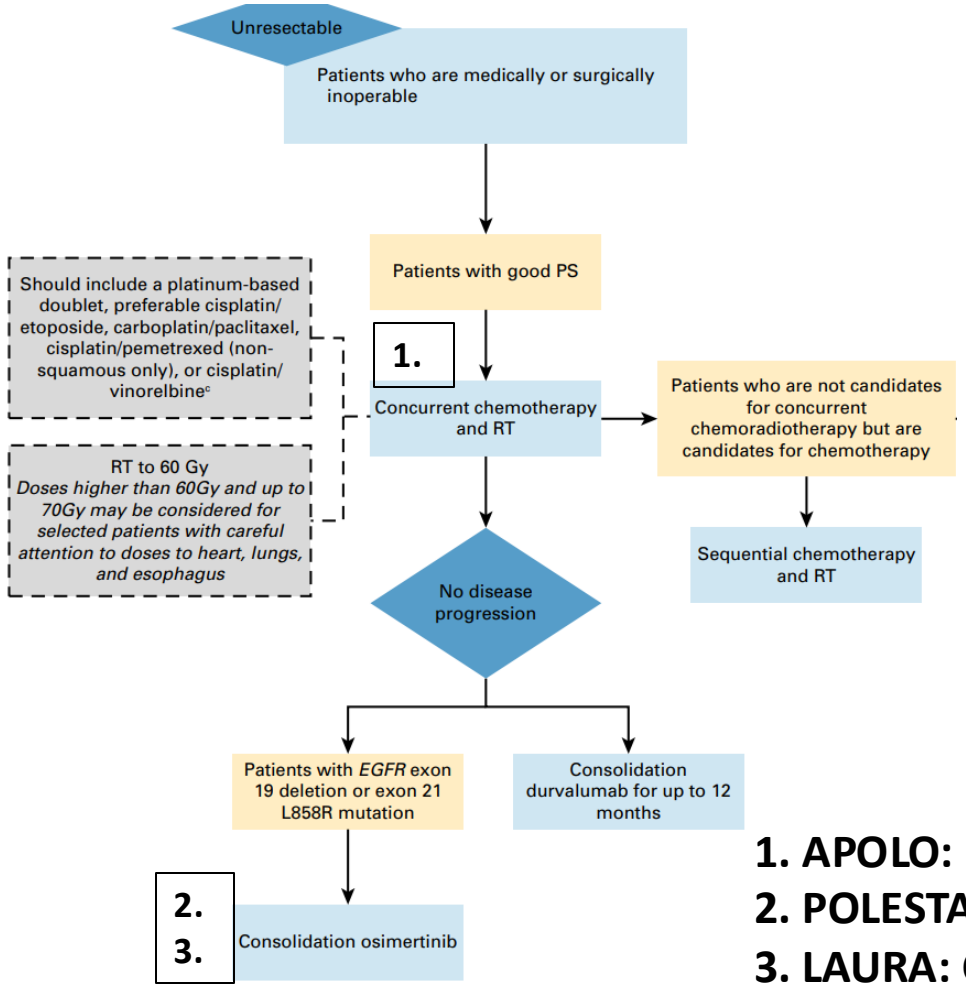
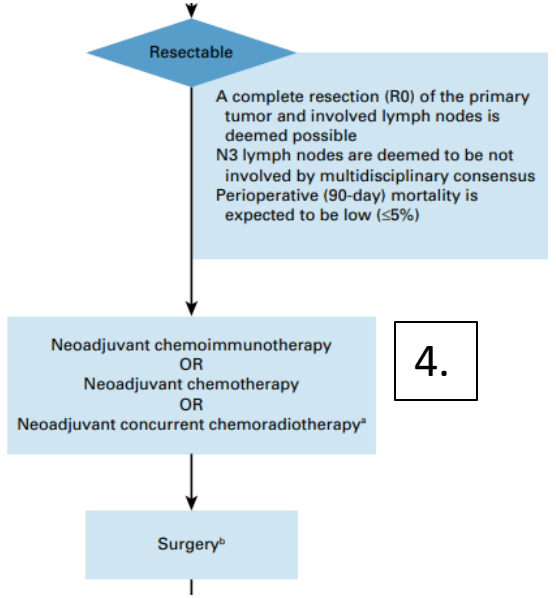
Best of Locally Advanced NSCLC- Radiation Therapy Perspective

Lucas Vitzthum
Clinical Associate Professor
Stanford University

OUTLINE

- Important trials for LA-NSCLC presented at WCLC
  - APOLO: Induction Chemo + Atezo → CRT → Atezo
  - POLESTAR: CRT +/- Adjuvant Aumolertinib
  - LAURA: Safety Data
  - SQUAT: Neoadjuvant CRT + Durva → Surgery → Durva
- Advances in RT discussed at WCLC 2024





1. APOLO: Induction Chemo + Atezo → CRT → Atezo
2. POLESTAR: CRT +/- Adjuvant Aumolertinib
3. LAURA: CRT +/- Adjuvant Osimertinib [SAFETY DATA]
4. SQUAT: Neoadjuvant CRT + Durva → Surgery → Durva

Still Room For Improvement

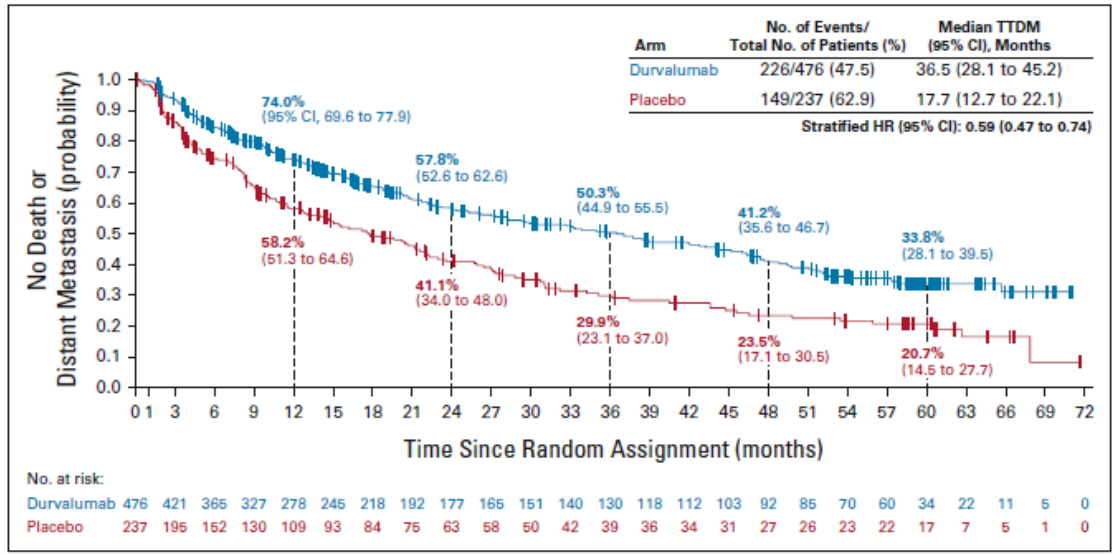
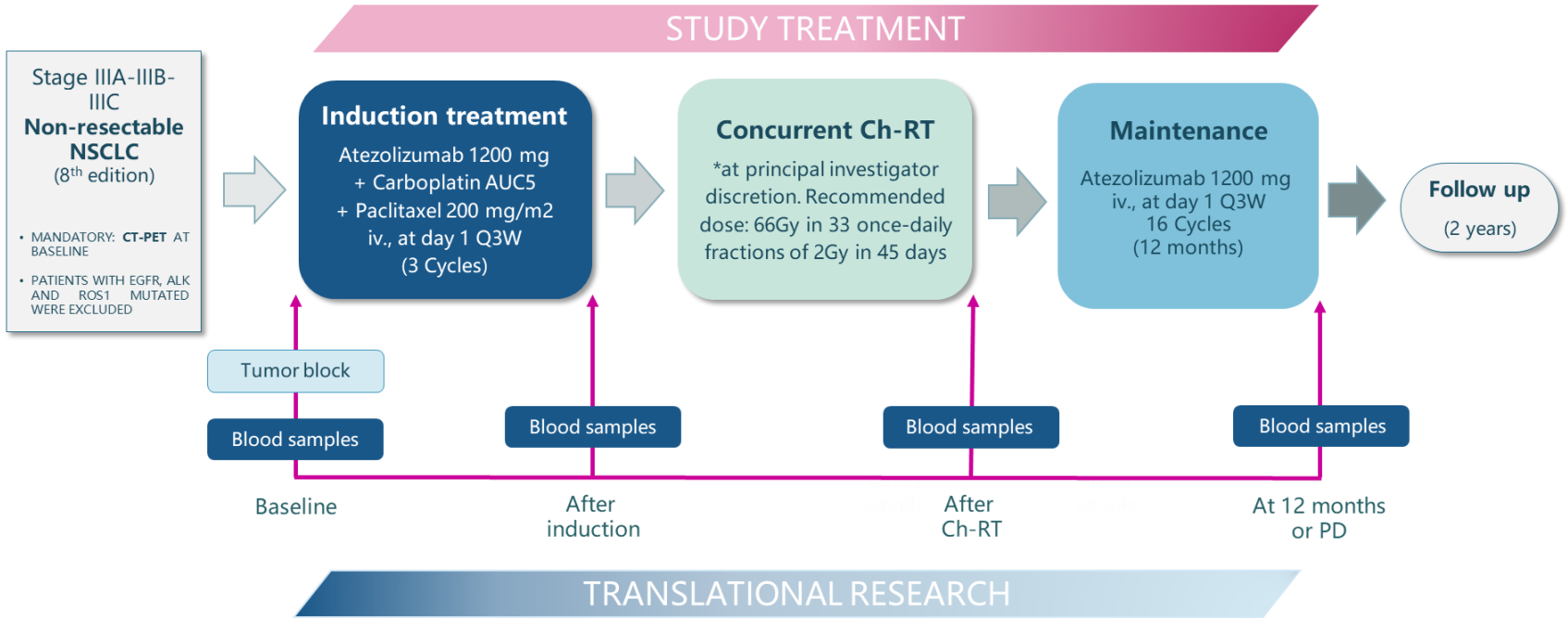


FIG 4. Updated TTDM (blinded independent central review) in the intent-to-treat population. The vertical dashed lines indicate yearly landmarks; the associated numerical values represent the TTDM rates at the landmark. TTDM was defined as time from random assignment until the first date of distant metastasis or death in the absence of distant metastasis. HR, hazard ratio; TTDM, time to death or distant metastasis.

PACIFIC 5-yr Update
Spigel et al. JCO 2022

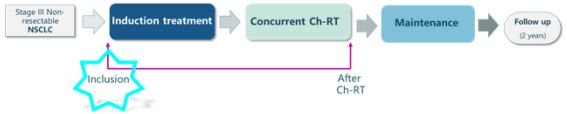
APOLO Study: Induction Chemo + Atezo → CRT → Atezo

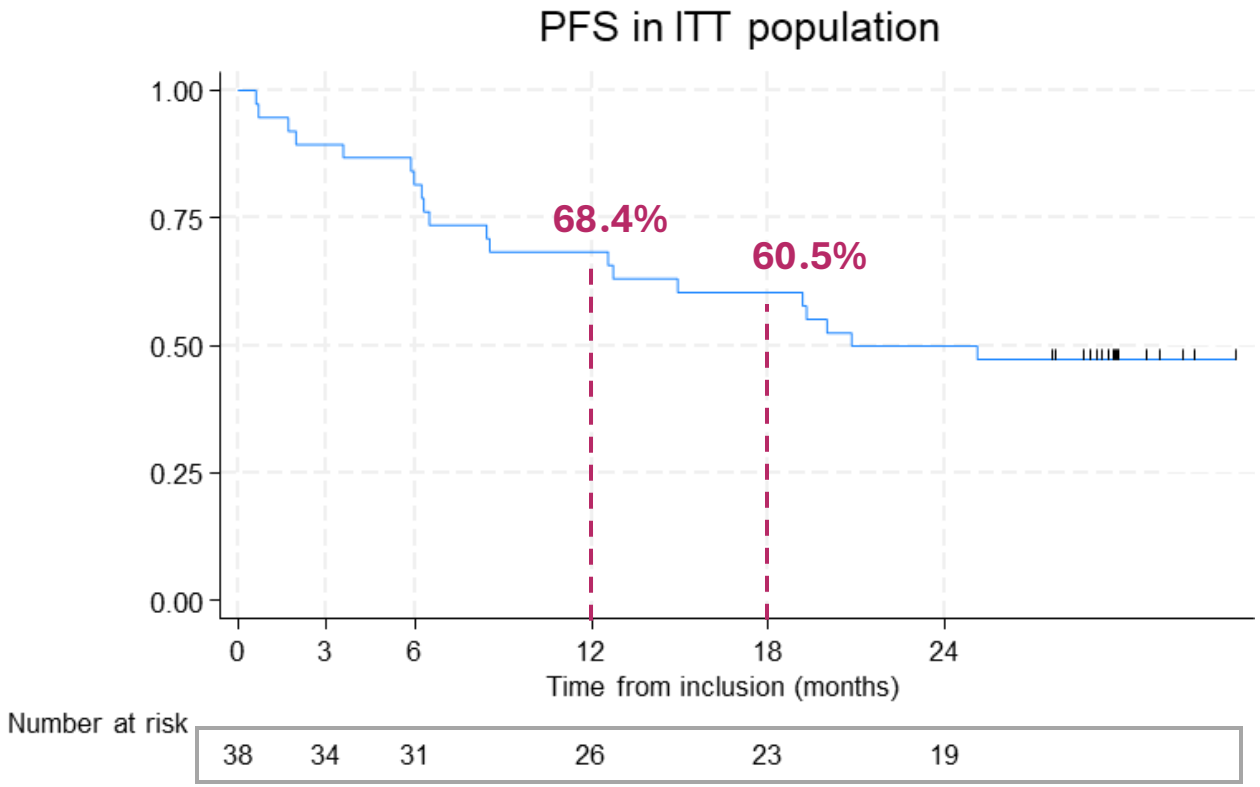


- **Primary Endpoint- 12 mo PFS**

APOLO

PRIMARY ENDPOINT – PFS in ITT population



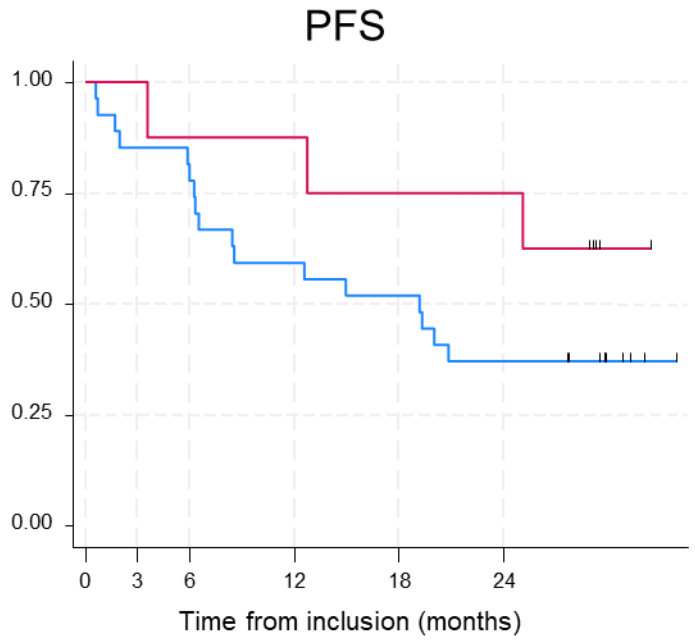


PFS 20.8 (95%CI 12.6; NR) months.

PFS in ITT population was **68.4%** (95%CI: 51.1-80.6%) **at 12 months** and **60.5%** (95%CI: 43.3-74%) **at 18 months.**

Median for follow-up: 29.6 months (95%CI: 28.8-29.8)

PFS, progression free survival; ITT, intention to treat



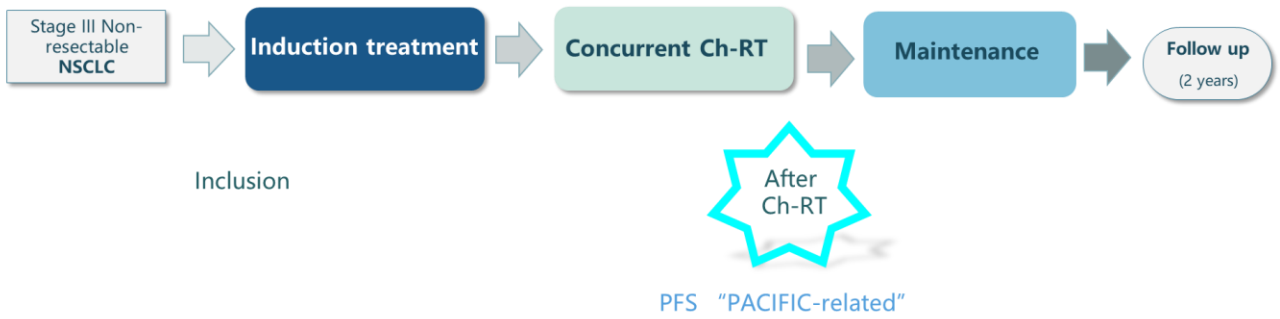
	12 m (95%CI)	24 m (95%CI)
PDL1 Negative or <50%	59.2% (38.6-74.9)	37% (19.6-54.5)
PDL1 ≥50%	87.5% (38.7-98.1)	75% (31.4-93)

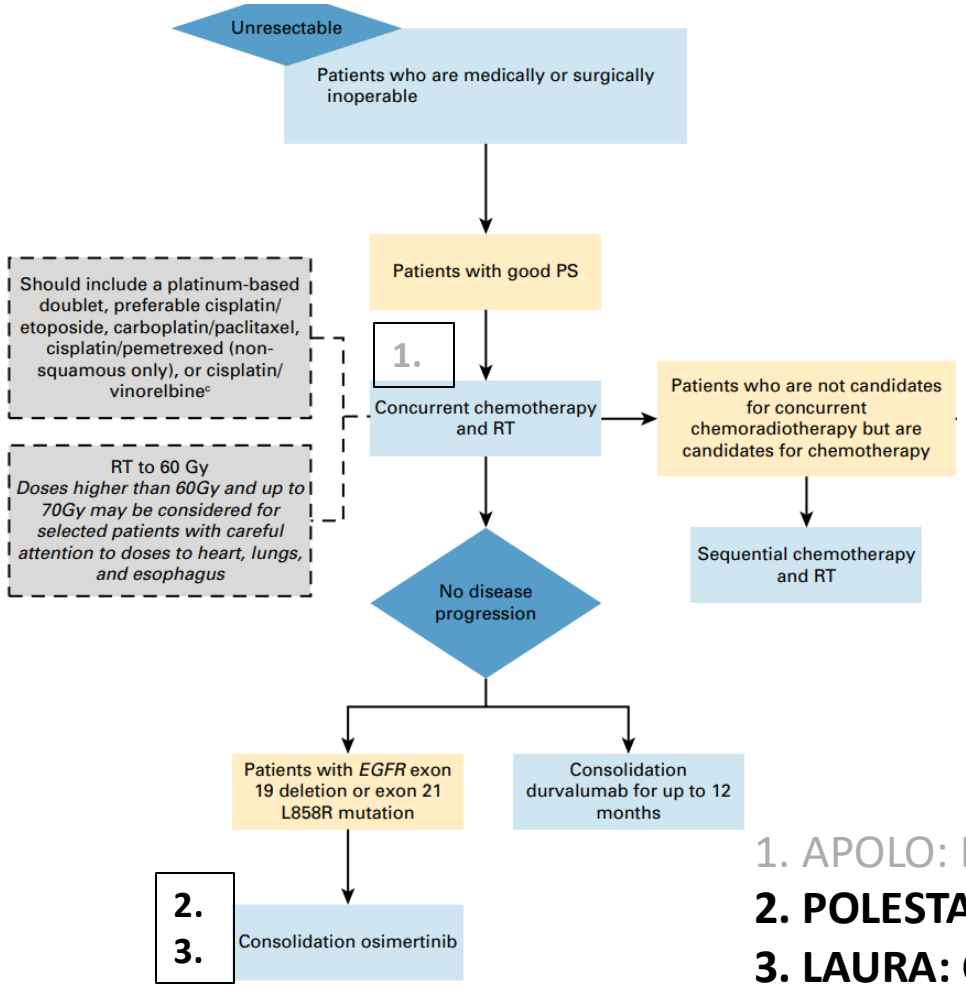
Author Conclusions

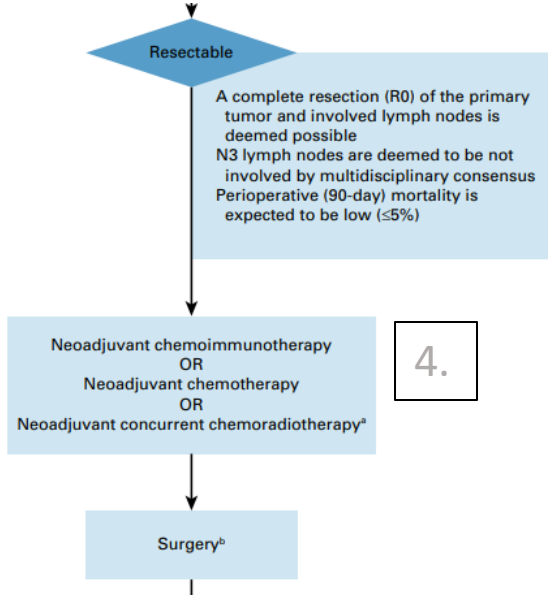
- There are no concerning safety data or treatment-related deaths.
- **ctDNA clearance** after induction treatment showed a **good prediction of PFS and OS**
- *Compared to other trials, APOLO shows a major benefit:*
- *"PACIFIC-related" PFS 12m: 68.9% (95%CI: 48.8-82.4%) vs 55.9% (95%CI: 51.0–60.4) (SJ Antonia et al NEJM 2017)*

My Thoughts

- Interesting approach worthy of further study
  - Would not routinely implement in clinic now
  - Encouraging safety signal for those who switch from neoadj Chemo/IO for surgery to RT
  - Appealing for bulky disease w/ high likelihood to respond
- Comparisons to PACIFIC are limited by immortal time bias
- Prior RCT (CALGB 39801) for +/- induction chemo → CRT
  - Added toxicity (neutropenia) without benefit







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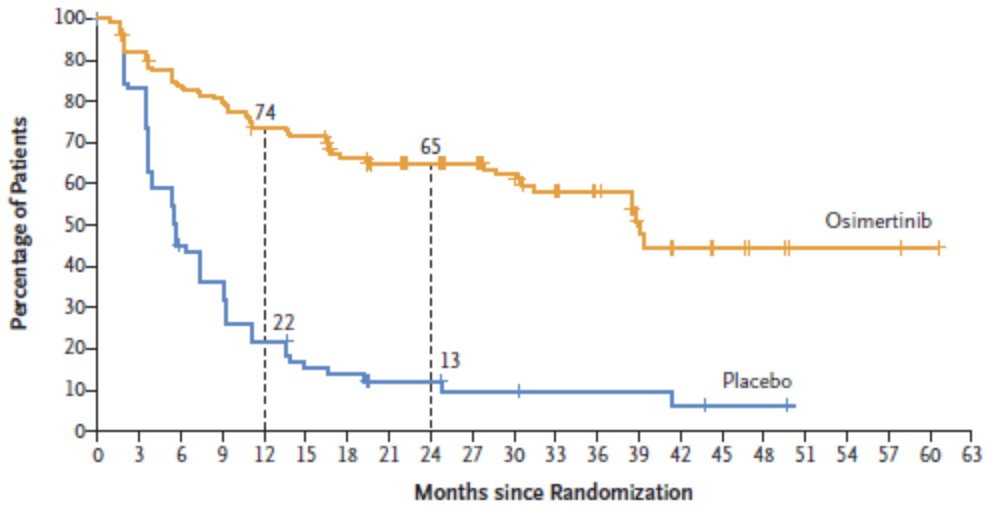


Median Progression-free Survival (95% CI)

	mo
Osimertinib	39.1 (31.5–NC)
Placebo	5.6 (3.7–7.4)

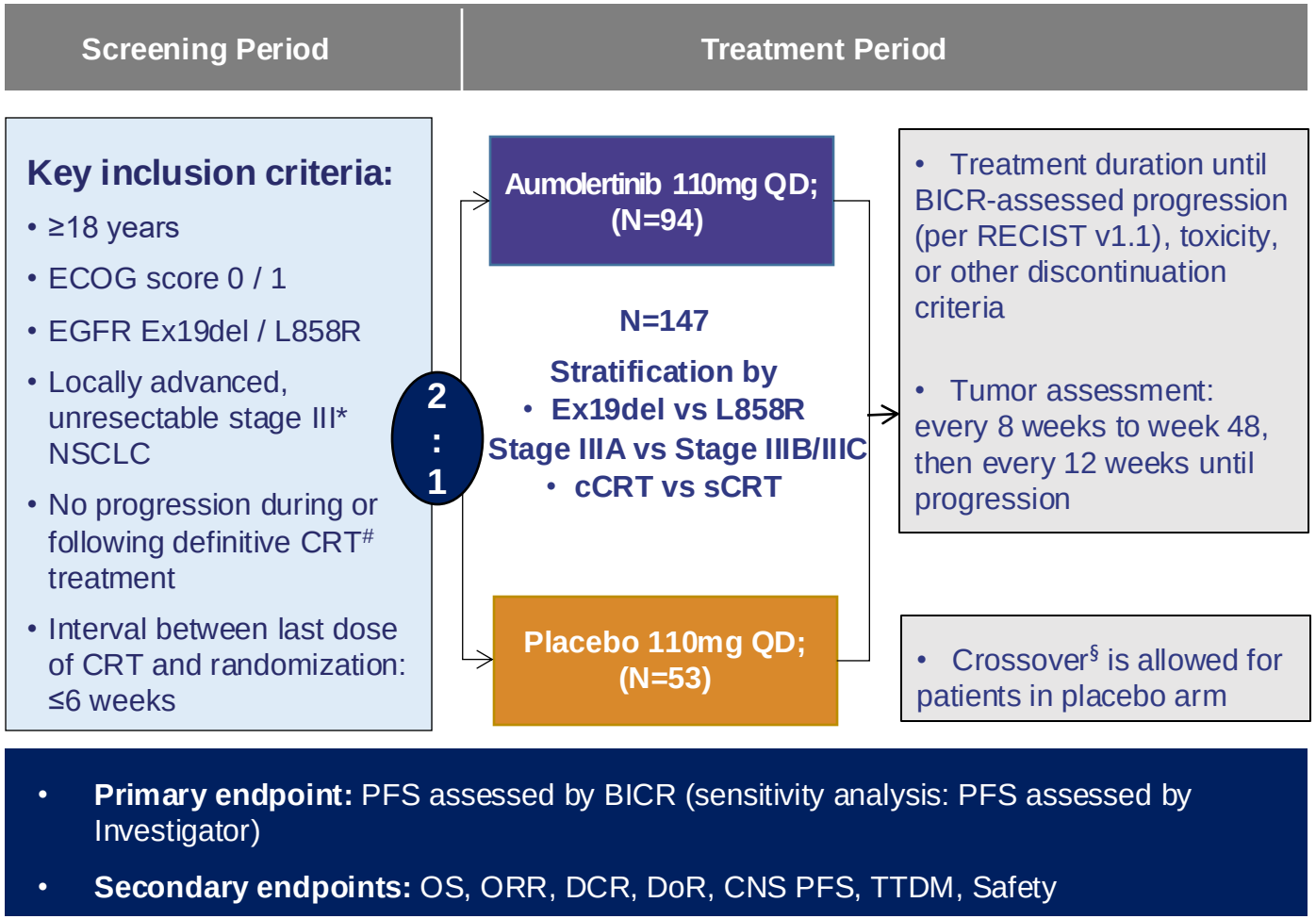
Hazard ratio for disease progression or death, 0.16 (95% CI, 0.10–0.24)
P<0.001

Figure 1. Progression-free Survival According to Blinded Independent Central Review.

The figure shows Kaplan–Meier estimates of the duration of progression-free survival (assessed by blinded independent central review with the use of Response Evaluation Criteria in Solid Tumors, version 1.1). Tick marks indicate censored data, and vertical dashed lines indicate the times of landmark analyses of progression-free survival. The median duration of follow-up for progression-free survival in all patients was 22.0 months (range, <0.1 to 60.6) in the osimertinib group and 5.6 months (range, <0.1 to 49.7) in the placebo group; the median duration of follow-up for progression-free survival in patients whose data were censored was 27.7 months (range, <0.1 to 60.6) in the osimertinib group and 19.5 months (range, <0.1 to 49.7) in the placebo group. CI denotes confidence interval, and NC not calculable.

LAURA : CRT→ Osimertinib vs. Placebo until progression

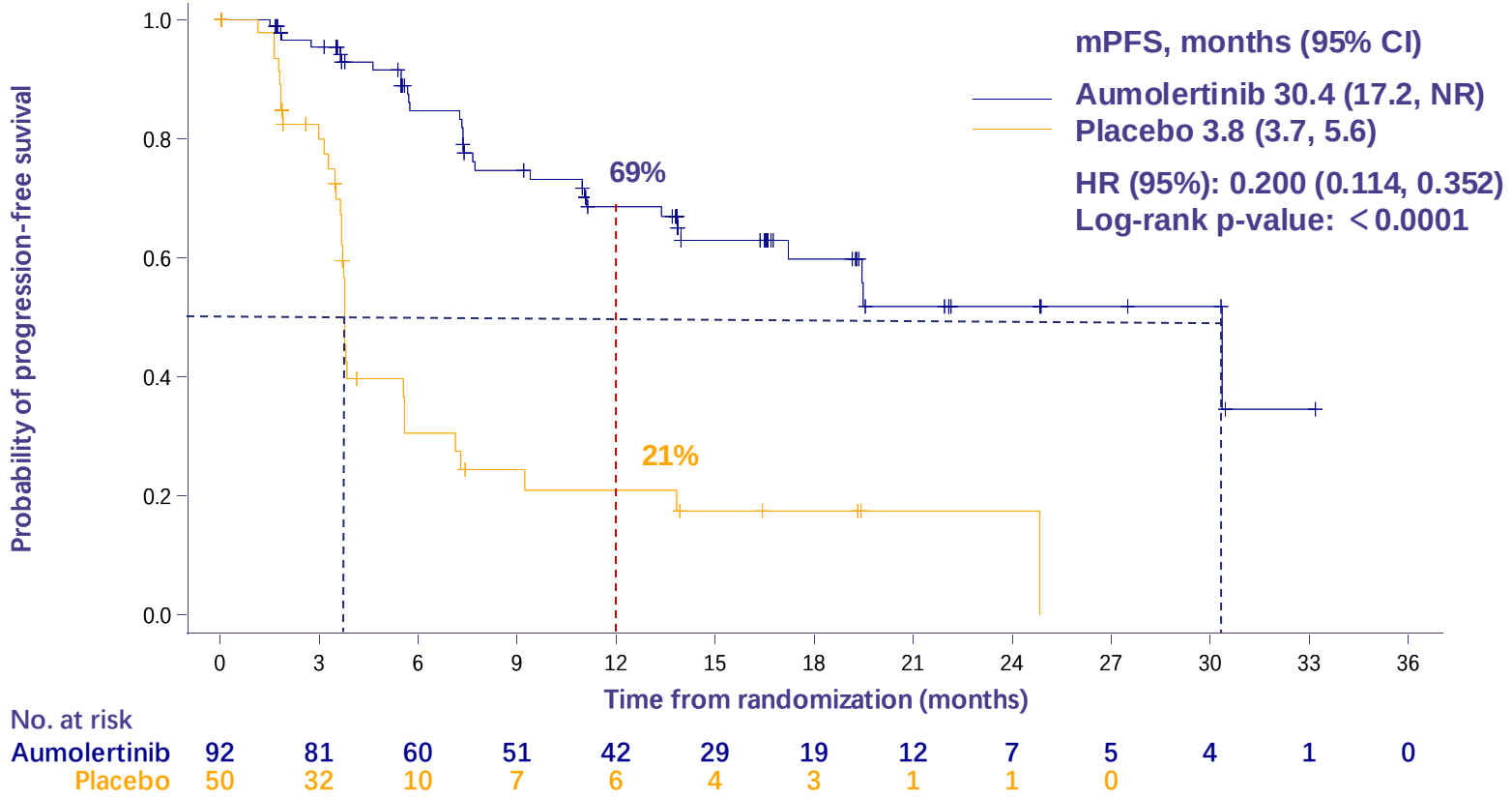
POLESTAR: Adjuvant Aumolertinib



* According to AJCC / UICC staging (8th edition).
# Concurrent or sequential CRT comprising ≥2 cycles of platinum-based chemotherapy (or 5 doses of weekly platinum-based chemotherapy) and a total dose of radiation of 60 Gy±10%.
§ Open-label aumolertinib after progression by the judgement of treating physician.
Abbreviations: cCRT, concurrent chemoradiotherapy; sCRT, sequential chemoradiotherapy; EGFRm, EGFR-mutant; NSCLC, non-small cell lung cancer; PFS, progression free survival; TKI, tyrosine kinase inhibitor; BICR, blinded independent central review; HR, hazard ratio.

PFS by BICR Assessment

- Median follow-up of PFS was 16.36 months (0–33.2) for aumolertinib and 13.93 months (0–24.8) for placebo.
- PFS HR (95% CI) by BICR analyzed with Cox proportional hazards regression was 0.200 (0.114, 0.352).
- PFS HR (95% CI) by BICR analyzed with a log rank test was 0.135 (0.070, 0.258), which is a sensitivity analysis.

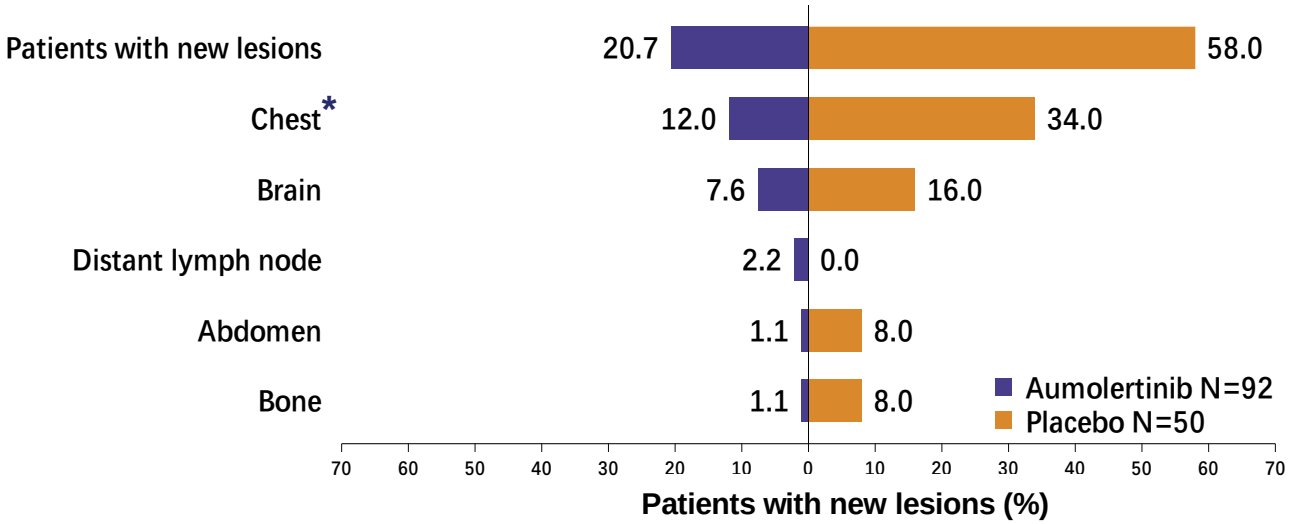


Abbreviations: PFS, progression free survival; BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NR, not reach.

Data cut-off: February 5, 2024.

OS and New lesions by BICR

- Median follow-up of OS was 16.6 months (range 1.5–33.2) for aumolertinib and 14.9 months (range 0.4–31.4) for placebo.
- Median OS (9.8% maturity for aumolertinib and 6.0% maturity for placebo) was not reached in either group.
- Lower incidences of CNS lesions and distant metastases were observed in aumolertinib arm than in the placebo arm.



Endpoint	Aumolertinib (N=92)	Placebo (N=50)	HR, 95% CI) p value
Median CNS PFS#, months (95% CI)	NR (NR, NR)	NR (NR, NR)	0.33 (0.12-0.92) p=0.0270
Median TTDM§, months (95% CI)	NR (NR, NR)	NR (3.84, NR)	0.21 (0.09, 0.49), p<0.0001

CNS PFS: survival without progression of CNS disease.

§ TTDM: time to death or distant metastasis.

* Chest: including lungs and N1~N3 regional lymph node lesions.

Abbreviations: OS, overall survival; CI, confidence interval; NR, not reach; HR, Hazard ratio.

Data cut-off: February 5, 2024.

Author Conclusions

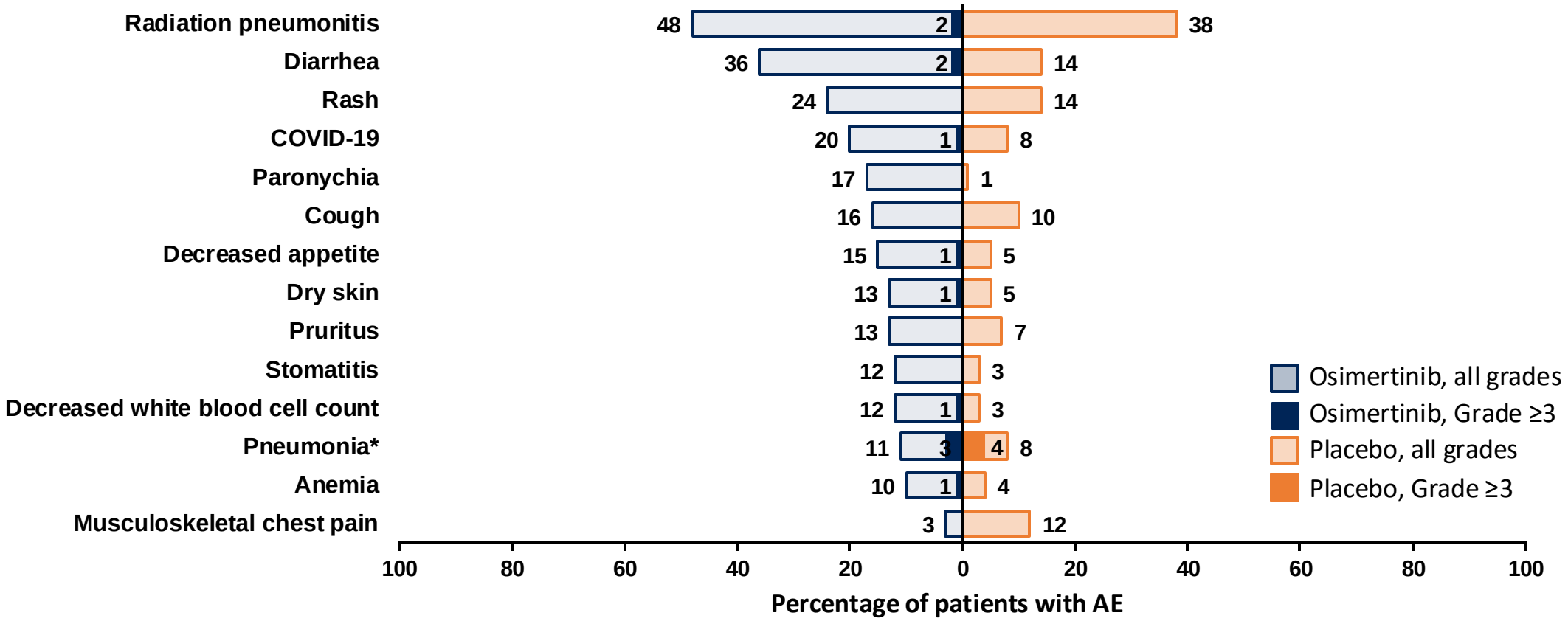
- Adjuvant aumolertinib significantly improves PFS after CRT (median 30.4 mo vs 3.8 mo, $p < 0.001$)
- Overall aumolertinib was well tolerated w/o new safety signal

My thoughts

- Data support LAURA findings
- Crossover was allowed and 85% of placebo got aumolertinib on progression
- Baseline rates of PET and MRI staging?
- Overall aumolertinib was well tolerated w/o new safety signal

LAURA SAFETY DATA

- Most common AEs were as expected for patients who had received prior CRT (radiation pneumonitis) or osimertinib treatment (diarrhea and rash)



Data cut-off: January 5, 2024.

AEs with incidence of ≥10% in either arm shown. Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories. Includes AEs with an onset date on or after the date of first dose and up to and including 28 days following the discontinuation of study treatment and before starting subsequent cancer therapy.

*One Grade 5 AE of pneumonia was reported in a patient in the osimertinib arm.

Lu et al. N Engl J Med 2024;391:585–597.

AE, adverse event; COVID-19, coronavirus disease 2019; CRT, chemoradiotherapy

Toxicity management guidelines for radiation pneumonitis and ILD* in LAURA

Grade 1
Asymptomatic, clinical, or diagnostic observations only, intervention not indicated

→ **No dose modification required**

Grade 2
Symptomatic, medical intervention indicated,† limiting instrumental ADL

→ **Hold study drug until resolution of symptoms‡**

→ **Re-initiation at 80 mg (or at 40 mg as clinically appropriate)**

If symptoms **have not resolved within 4 weeks** after interrupting study treatment

Grade 3
Severe symptoms, limiting self-care ADL; oxygen indicated§

Grade 4
Life-threatening respiratory compromise, urgent intervention indicated, e.g., tracheostomy or intubation

→ **Permanently discontinue study drug**

If Grade ≥2 pneumonitis (symptomatic) **occurs following restarting** study drug

Data cut-off: January 5, 2024.

*Grouped terms; radiation pneumonitis (grouped): preferred terms of radiation pneumonitis and lung radiation fibrosis reported; ILD (grouped): preferred terms of ILD, pneumonitis and pulmonary fibrosis reported; †Patients who were given treatment for asymptomatic changes were not mandated to interrupt study drug and guidance for Grade 1 was followed; ‡Holding study drug was considered as clinically appropriate and during diagnostic work-up for other etiologies; §Patients given oxygen in the absence of symptoms did not require permanent discontinuation of study drug.

ADL, activities of daily living; ILD, interstitial lung disease

Safety analysis: Radiation pneumonitis

- Radiation pneumonitis (grouped term) included PTs of radiation pneumonitis and lung radiation fibrosis
- No Grade 4 or 5 events were reported

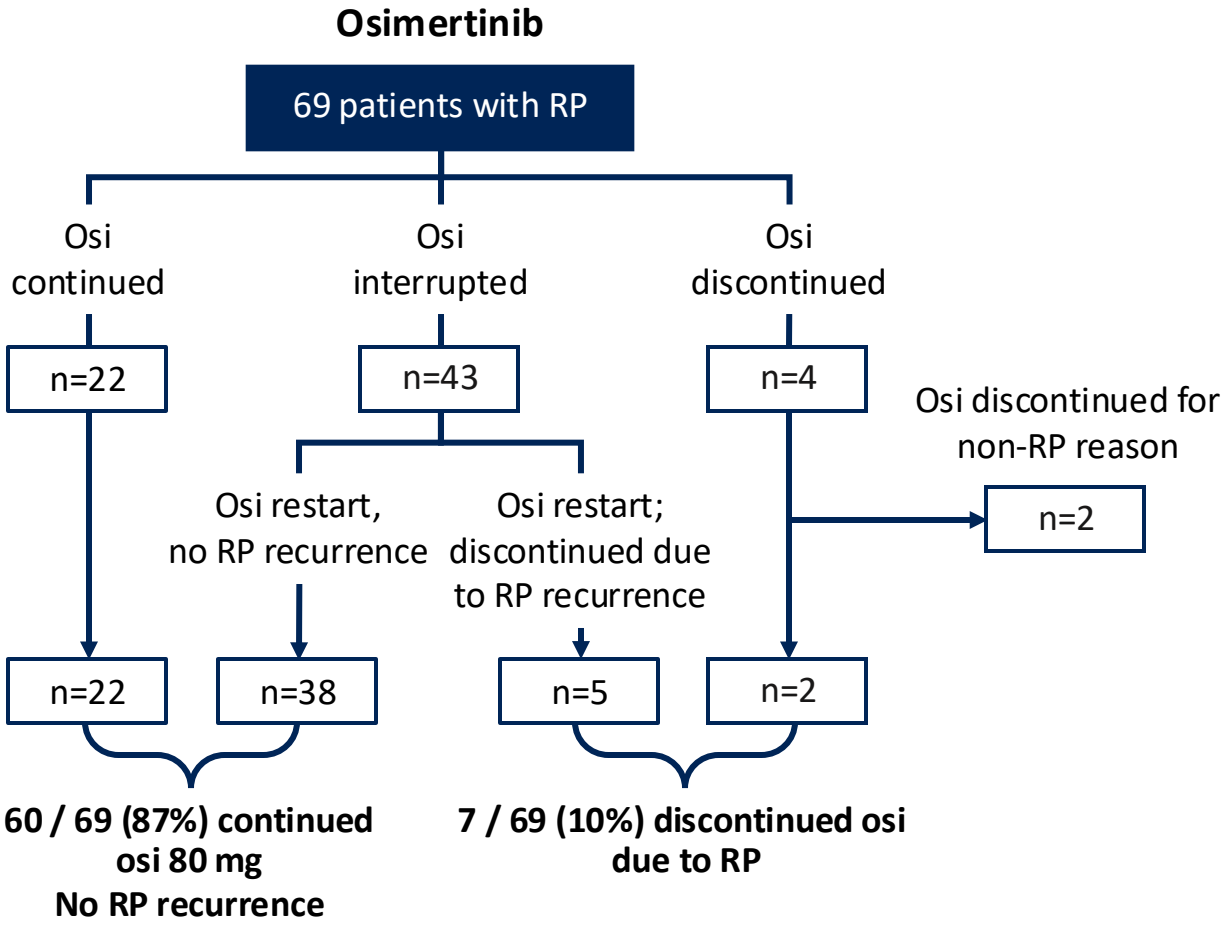
Radiation pneumonitis, n (%)	Osimertinib (n=143)	Placebo (n=73)
Total	**69 (48)**	**28 (38)**
Grade 1	22 (15)	14 (19)
Grade 2	44 (31)	14 (19)
Grade 3	3 (2)	0
CTCAE Grade ≥3	3 (2)	0
SAE	15 (10)	2 (3)
Discontinuations	7 (5)	2 (3)

- Most dose interruptions due to AEs were driven by radiation pneumonitis, in line with toxicity management guidelines
  - Osimertinib, n=46 (32%); placebo, n=10 (14%)
  - No dose reductions due to radiation pneumonitis occurred

Data cut-off: January 5, 2024.
Patients with asymptomatic radiation pneumonitis / pneumonitis post-CRT were eligible for inclusion in LAURA.
Includes AEs with an onset date on or after the date of first dose and up to and including 28 days following the discontinuation of study treatment and before starting subsequent cancer therapy.
*Patients randomized in countries within the Asia region and who also declare themselves as Asian.
AE, adverse event; CRT, chemoradiotherapy; CTCAE, Common Terminology Criteria for Adverse Events; PT, preferred term; SAE, serious AE

Treatment restart following radiation pneumonitis

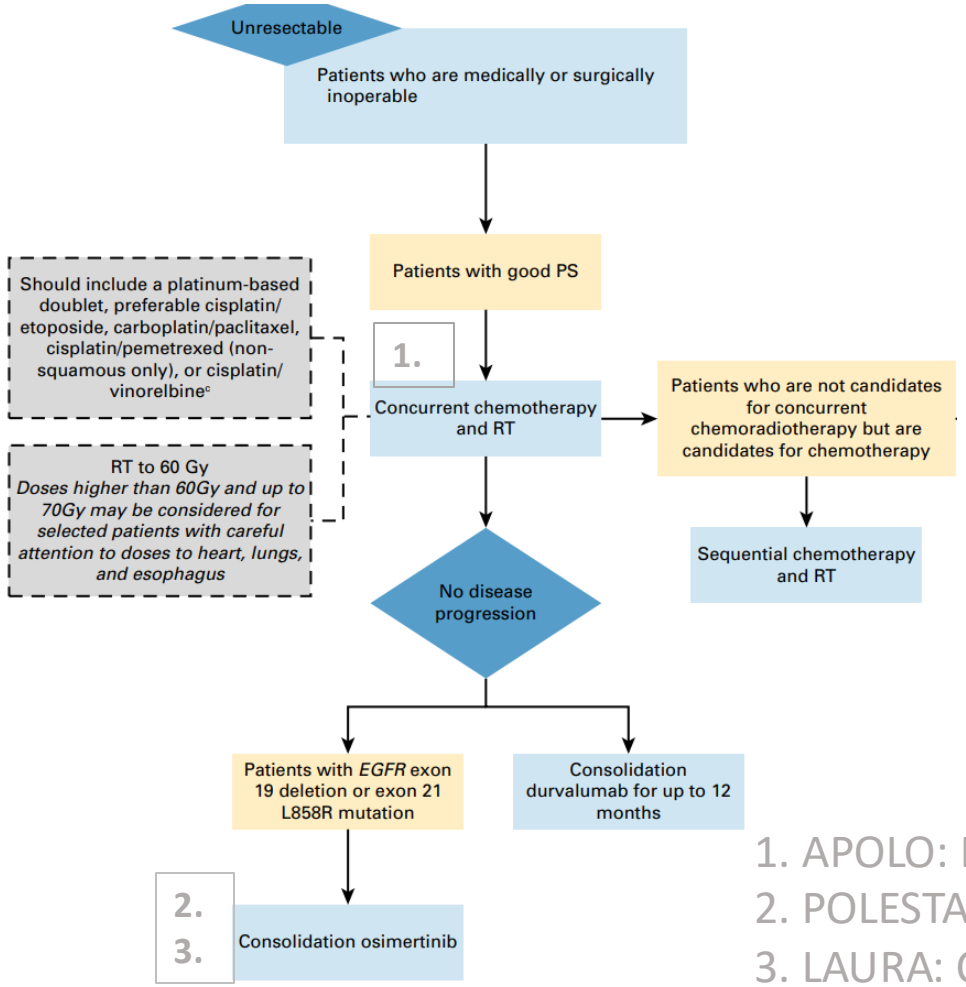
- In the osimertinib arm, the majority of patients (60 / 69; 87%) with radiation pneumonitis continued or restarted osimertinib without recurrence
- Across both arms, the majority of patients who restarted after a dose interruption remained on treatment; few discontinued

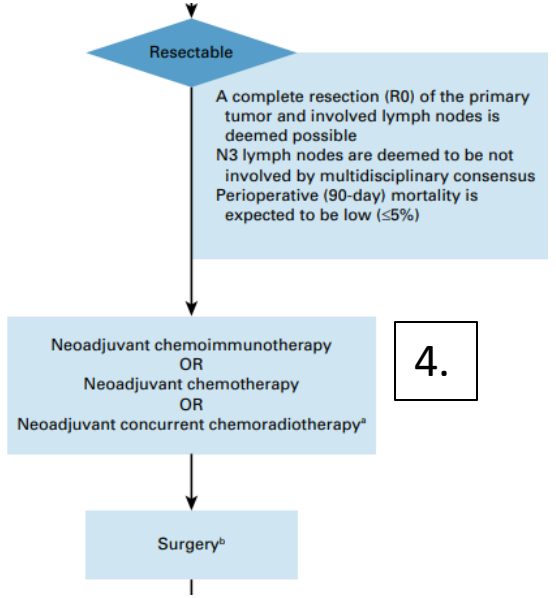


Data cut-off: January 5, 2024.
RP analyzed as a grouped term; preferred terms of RP and lung radiation fibrosis reported.
osi, osimertinib; RP, radiation pneumonitis

Author conclusions

- Safety profile of osimertinib after definitive CRT was consistent with the established profile of osimertinib and CRT;
  no new safety concerns were identified
- Most AEs with osimertinib were **mild or moderate** in severity, and did not lead to treatment discontinuation
- Radiation pneumonitis events were primarily Grade 1 / 2, managed with dose interruptions per the mandated toxicity management guidelines; no Grade 4 / 5 events
- Most patients could continue or restart osimertinib following a radiation pneumonitis event; in both arms there were **low rates of radiation pneumonitis recurrence** after restart of study drug





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Neoadjuvant Concurrent Chemo-immuno-Radiation Therapy Followed by Surgery for Stage III-N2 NSCLC: SQUAT trial (WJOG 12119L)

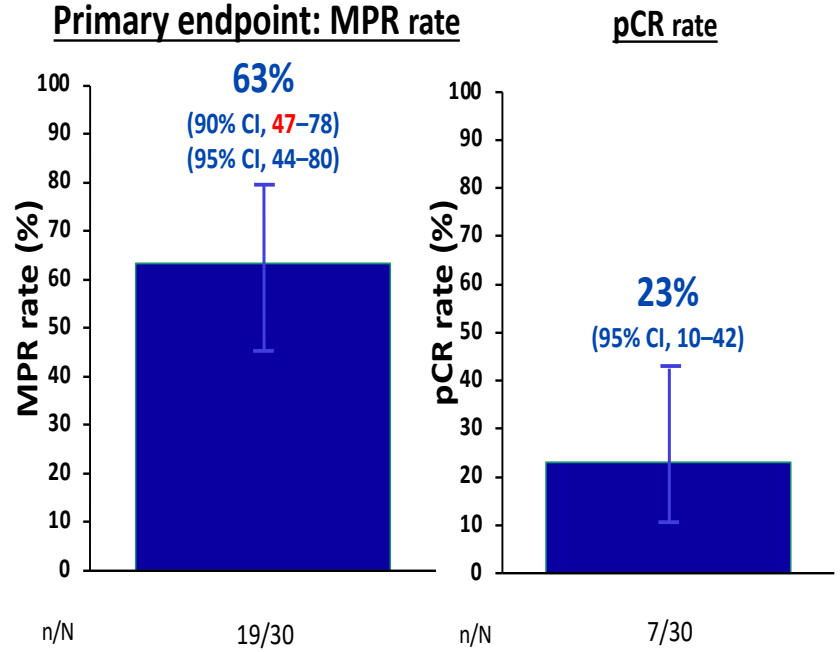
Key eligibility criteria
- Resectable Stage IIIA-B-N2 NSCLC (TNM8th)
- Discrete N2, pathologically confirmed
- ECOG PS 0-1

N=31

Neoadjuvant Chemo-Immuno-Radiation therapy
- PTX (40mg/m^2)+CBDCA (AUC=2) Day 1 8 15 22 29
- IFRT[a] 50Gy (2Gy × 25fr) Day 1–35
- Durvalumab (1500mg) Day 1, 29

Surgery

Adjuvant Immunotherapy
- Durvalumab (1500mg) 12 months



Primary endpoint
- MPR; ≤10% residual viable tumor) according to the central pathologic assessment.

Secondary endpoint
- Progression-free survival (PFS), overall survival (OS), pathologic complete response (pCR), and safety.

[a]IFRT: Involved Field radiation therapy

SQUAT Study

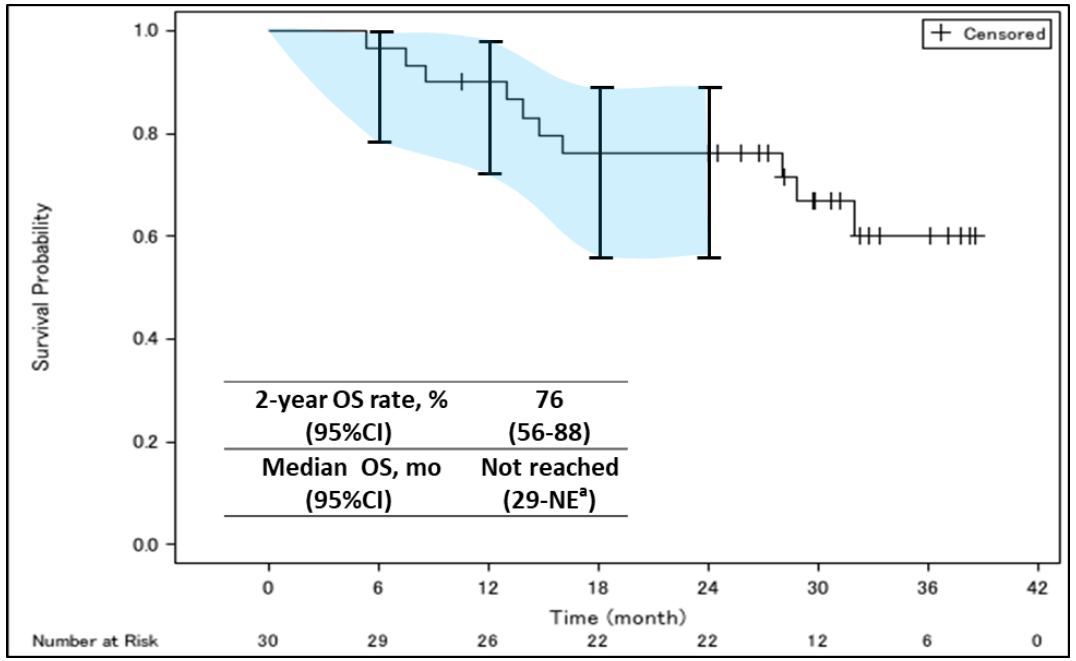
Baseline Factors	
N2 status, n (%)	
Single	25 (83)
Multiple	5 (17)
PD-L1 status, n (%)	
< 1%	10 (33)
1-49%	11 (37)
≥ 50%	9 (30)

Surgery	
Completed neoadjuvant therapy, n (%)	29 (97)
Discontinued neoadjuvant therapy, n (%)	1 (3)
Adverse event	1 (3)[a]
Underwent definitive surgery, n (%)	27 (90)
Cancelled definitive surgery, n (%)	3 (10)
Disease progression	2 (7)
Adverse event	1 (3)

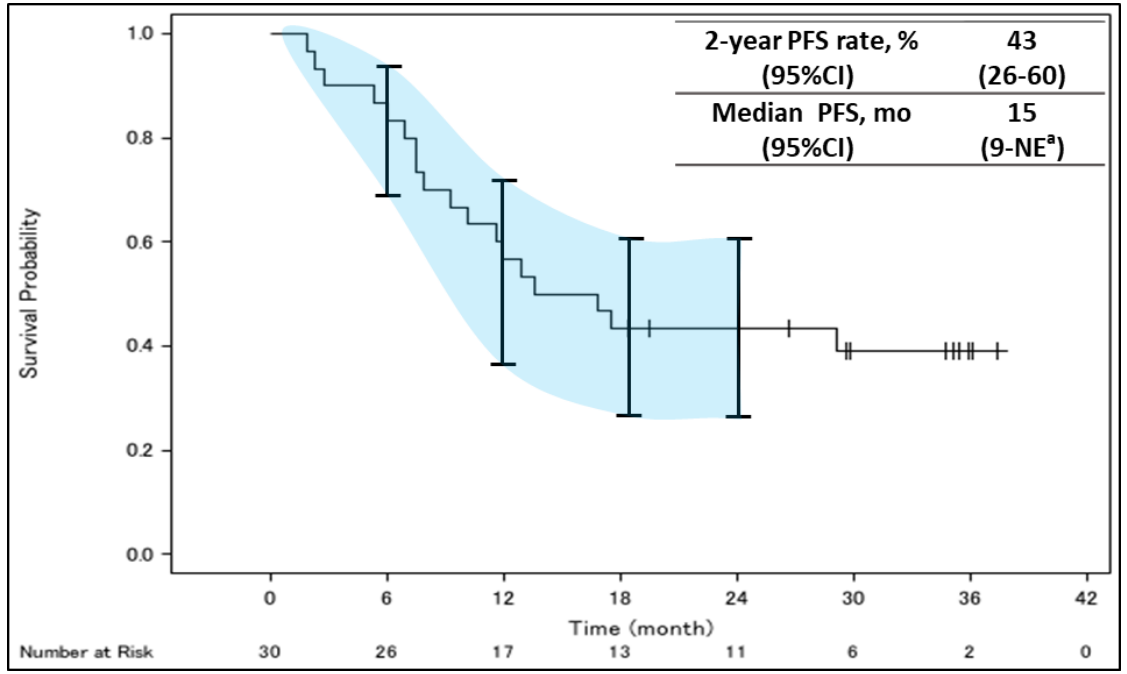
Adjuvant therapy	N=25[d]
Received adjuvant therapy, n (%)	16 (64)
Completed adjuvant therapy (1 year), n (%)	8 (32)

ITT Survival on SQUAT

OS



PFS



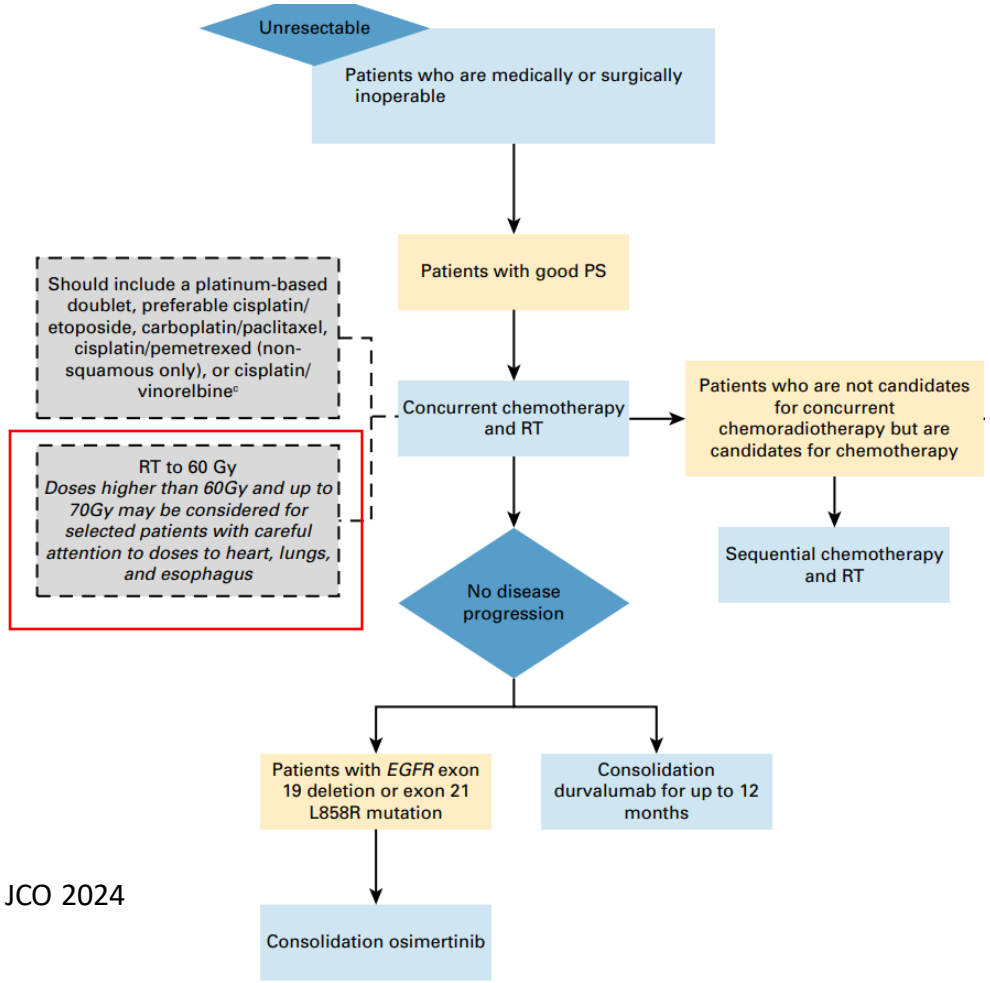
Author Results and Conclusions

- 48% G3+ toxicity, 7% led to DC treatment
- Rates of MPR (63%) compare favorably to previously published chemo/ICI trials w/o RT
- MPR or pCR was associated w/ improved PFS/OS
- *The benefit of adding radiation to neoadjuvant chemo-immunotherapy is questionable, although it warrants longer observation as well as verification by other studies.*

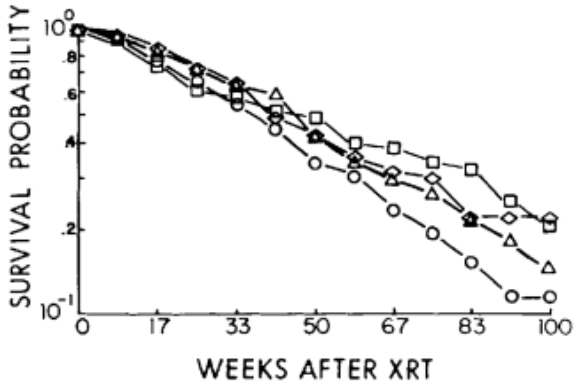
My Thoughts

- Makes sense that RT improves path response
- Agree that there is a burden to show improvement in patient centered endpoint rather than surrogate endpoint
- Our current practice is to plan for one local treatment modality

Advances in Radiation for Stage III NSCLC



Daly et al. JCO 2024



TREATMENT	ALIVE	DEAD	TOTAL	MEDIAN
○ 4000 SPLIT	25	68	93	36.8
△ 4000 CONT	31	66	97	45.5
◇ 5000 CONT	33	58	91	41.0
□ 6000 CONT	28	56	84	47.2

FIG. 4. RTOG-lung 73-01 (Jan. 1979). Survival of patients according to treatment regimen. Difference is not statistically significant.

Perez et al. Cancer 1980

NRG LU008

Phase III Prospective Randomized Trial of Primary Lung Tumor Stereotactic Body Radiation Therapy Followed by Concurrent Mediastinal Chemoradiation for Locally-Advanced Non-Small Cell Lung Cancer

- Replace conventionally fractionated radiotherapy to the primary tumor with SBRT followed by concurrent chemoradiation to the mediastinum

- Hypotheses:
  - Well-tolerated , lower rates of radiation pneumonitis due to increase conformity with SBRT
  - Improve local control that will drive an improvement in progression-free survival and overall survival

Courtesy of Charles Simone

NRG ONCOLOGY™

NRG LU008 Schema
Phase III Randomized Trial

Population: Locally advanced stage II-III (node positive) NSCLC

Patient Screening → **R**

Stratification:
T Stage (T1-T2a vs. T2b or higher)
PD-L1 Status (<1%, 1%-49%, 50-100%)

- **SBRT (primary) BED ≥100 Gy** → **Chemoradiation (mediastinum) 60 Gy/2 Gy per fraction**
- **Chemoradiation (primary + mediastinum) 60 Gy/2 Gy per fraction**

→ **Maintenance Immunotherapy x 12 months**

Primary Endpoint:
OS and PFS

Secondary Endpoints:
- **ORR (RECIST v 1.1)**
- **Local Control**
- **Failure Patterns**
- **PFT Effects**
- **Changes in QOL + PROs**
- **Acute and late toxicities (CTCAEv5)**

SBRT to primary tumor:
- 3 fractions to 54 Gy (BED10 of 151.2 Gy) [peripheral]
- 4 fractions to 50 Gy (BED10 of 112.5 Gy) [peripheral]
- 5 fractions to 50 Gy (BED10 of 100 Gy) [peripheral or central]

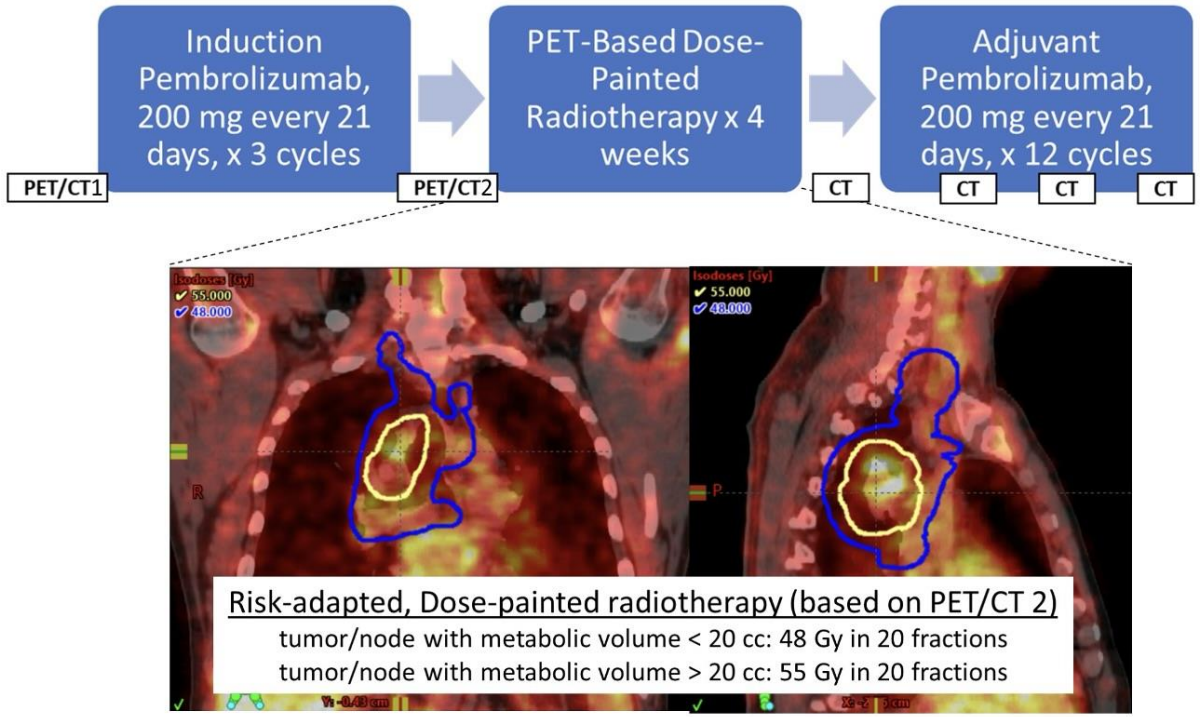
Current Accrual: n=81/474

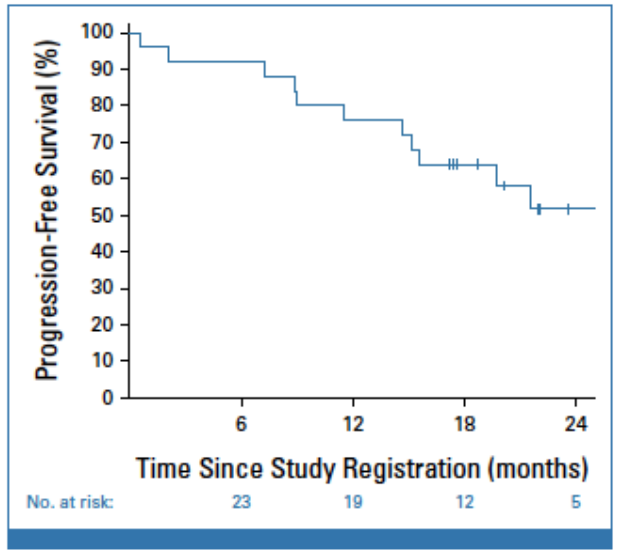
@NRGOnc NRG Oncology PIs: Charles B. Simone II, John Heinzerling

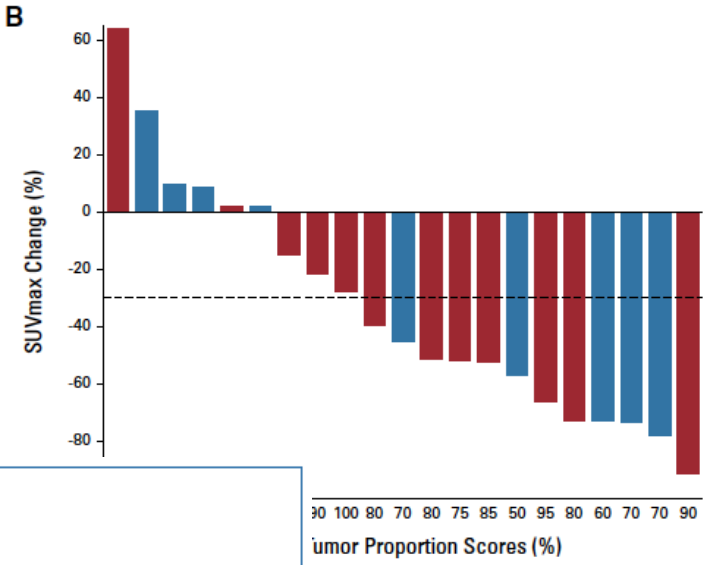
NCI National Clinical Trials Network — a National Cancer Institute program
NCI Community Oncology Research Program — A program of the National Cancer Institute of the National Institutes of Health

SPRINT trial: PD-L1 driven, response-adapted (PET-based), chemo-free study of pembrolizumab plus RT

Study Design:

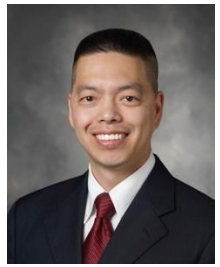






Ohri et al. JCO 2024

Stanford Thoracic Radiation Oncology Service



Bill Loo, MD PhD
Professor

Max Diehn, MD PhD
Professor

Alex Chin, MD
Assistant Professor

Lucas Vitzthum, MD
Associate Professor

Susie Owen, RN BSN
Nurse Coordinator (Loo, Diehn)

Leslie Hernandez-Sanchez, RN BSN
Nurse Coordinator (Vitzthum)

Medical Oncology

Heather Wakelee
Millie Das
Nathaniel Myall
Joel Neal
Kavitha Ramchandran
Mohana Roy

Thoracic Surgery

Joseph Shrager
Leah Backhus
Mark Berry
Natalie Lui
Douglas Liou

Interventional Pulmonology

Arthur Sung
Harmeet Bedi
Meghan Ramsey
Brian Shaller