



Multidisciplinary Approaches to Cancer Symposium

Scalpel or Beam or Both? Treatment Strategies in Locally Advanced Non-Small Cell Lung Stage III Cancer

Arya Amini, MD

Associate Professor, Department of Radiation Oncology
Section Chief, Thoracic and Skin Radiation Oncology
Associate Director of Clinical Research
Medical Student Clerkship Director
City of Hope

Disclosures

- Consultant for AstraZeneca, and Elsevier
- Grant/Research Support from AstraZeneca, Genentech, RefleXion, and Varian

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.



Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.



Roadmap for Today

Stage III NSCLC: overview and workup

The pivotal fork: resectable versus unresectable disease

Resectable disease: perioperative immunotherapy and adjuvant osimertinib

Unresectable disease: PACIFIC, LAURA, and the lessons of PACIFIC-2

Putting it together: a biomarker- and multidisciplinary-driven algorithm



Workup: Stage Accurately Before You Treat

Stage III decisions hinge on nodal accuracy and molecular characterization — complete both before therapy.

Anatomic staging

Contrast-enhanced chest/upper abdomen CT plus whole-body FDG PET/CT in all patients

Contrast-enhanced brain MRI required

Pathologic mediastinal staging: EBUS/EUS first; mediastinoscopy if needle sampling is negative

PET alone cannot establish N2 or N3 — false positives from infection and inflammation

Define nodal burden: single-station vs multistation, discrete vs bulky

Biomarkers and patient fitness

Reflex broad NGS and PD-L1 immunohistochemistry on all stage III tumors — results change treatment choices

Never start neoadjuvant immunotherapy with molecular results pending, especially never-smokers and adenocarcinoma

Pulmonary function and cardiopulmonary testing establish surgical and radiation candidacy

Performance status, weight loss, comorbidity drive trimodality tolerance

Multidisciplinary review: thoracic surgery, radiation and medical oncology, pulmonology, pathology, radiology

Surgery or Radiation? A Decision Map

Resectability turns on nodal burden, local invasion, and the operation required — not stage alone.

Pathologically staged stage III NSCLC at multidisciplinary tumor board



Favors resection

T3–T4 by size or chest wall, N0–N1
Single-station, non-bulky N2
R0 resection achievable by lobectomy
Adequate reserve and performance status

Gray zone — tumor board call

Single-station N2, borderline bulk
Superior sulcus after induction
Sleeve resection at high-volume centers
Comorbidity, preference, surgeon experience

Favors definitive chemoradiation

Bulky or multistation N2
Any N3 nodal involvement
T4 invasion: carina, aorta, heart, esophagus, spine
Pneumonectomy required for clearance
Marginal pulmonary function or performance status

If surgeons disagree on resectability, treat as unresectable — concurrent chemoradiation with consolidation loses nothing.

Before We Argue: A Case

THE CASE

63-year-old woman, never-smoker, ECOG 0

Persistent cough. CT: 6.4 cm left lower lobe mass.

PET/CT: avid primary, single avid level 7 node (1.2 cm) and level 10. No distant disease.

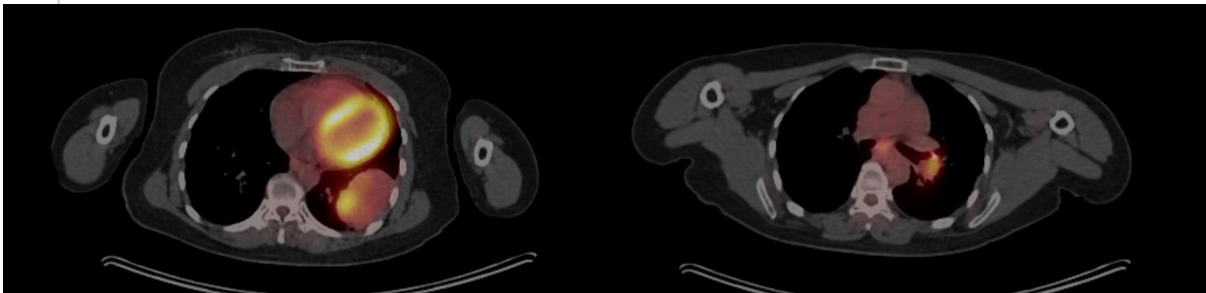
Brain MRI: negative.

EBUS: adenocarcinoma, station 4L, 7, 10.

Stage: T3 N2 M0 — stage IIIB.

FEV1 78% predicted. Lobectomy feasible; surgery calls it resectable.

Molecular: PD-L1 45%. NGS pending.



AUDIENCE POLL: WHAT WOULD YOU DO?

- A. Neoadjuvant chemoimmunotherapy, then lobectomy
- B. Concurrent chemoradiation, then durvalumab
- C. Surgery first, then pathology-guided adjuvant
- D. Wait for NGS before deciding

Scalpel vs Beam: The Head-to-Head Trials

Every head-to-head surgery-vs-radiation trial in N2 disease ended in a tie in the pre-IO era.

INT 0139 (Albain, 2009)

Stage IIIA pN2: chemoradiation plus surgery vs definitive chemoradiation

Progression-free survival

12.8 vs 10.5 months, HR 0.77

Overall survival

23.6 vs 22.2 months — no difference

Treatment-related death

8% surgery vs 2%; 26% after pneumonectomy

The famous subset

Lobectomy better (33.6 vs 21.7 months);
pneumonectomy worse

EORTC 08941 (2007)

N2 responding to induction chemo: surgery vs radiotherapy

Overall survival

16.4 vs 17.5 months — a dead heat

Five-year survival

15.7% vs 14%

Operative mortality

4% overall, 7% after pneumonectomy

The message

Chemotherapy response does not mandate an operation

ESPAUE (Eberhardt, 2015)

Stage IIIA(N2)/selected IIIB after induction chemoradiation: surgery vs radiation boost

Five-year overall survival

44% vs 40% — no difference

Both arms

Excellent outcomes, rigorous selection

Operative mortality

Low in expert hands

The message

In fit, well-selected patients, either modality cures

Three randomized trials, three ties on overall survival — no winner, so selection does the work.

Tale of the Tape

Two corners, one patient — and three randomized trials that refused to name a winner.



TEAM SCALPEL — DAN RAZ, MD

Brings the pathology. Also brings a chest tube.

VS



TEAM BEAM — ARYA AMINI, MD

No operative mortality. Please hold your pneumonitis questions — its med oncs fault.

The Scorecard: Scalpel vs Beam

Five rounds, judged on randomized data — and one on perception.

IN THIS CORNER: THE SCALPEL	THE ROUND	AND IN THIS CORNER: THE BEAM
Pathology tells the truth — pN0 patients lived a median 34.4 months	Nodal clearance Edge: scalpel	Excellent local control, but the nodes stay unconfirmed
INT 0139: 23.6 months, HR 0.87 — no win	Overall survival Round: a draw	EORTC 08941 and ESPATUE matched it
Treatment-related death 8% — a high 26% after pneumonectomy	Cost of winning Edge: beam	Treatment-related death 2% — pneumonitis is the toll (<1% in PACIFIC)
Perioperative immunotherapy: EFS HR 0.58 to 0.68, pCR up four-fold	The modern era Both corners got stronger	PACIFIC five-year survival 42.9%; LAURA 39.1 months PFS
"Chemoradiation is just palliative"	Patient perceptions Edge: neither — correct it	Definitive chemoradiation plus durvalumab is curative-intent therapy
The verdict: a draw. Lobectomy candidates win with the scalpel, pneumonectomy candidates with the beam — and both corners now beat the trials that compared them – we need data in the modern era!		

Selection Bias and the Limits of Cross-Trial Comparison

Comparing numbers that were never comparable.

Why non-randomized surgery series flatter the scalpel

Operable patients are healthier by definition
Immortal time bias: must survive to and through surgery to enter the series
Pathologic versus clinical staging drives stage migration — the Will Rogers phenomenon
Bulky, multistation N2 routed systematically to radiation
Registries cannot capture the tumor board's reasoning
Every randomized comparison erased the advantage

Why PACIFIC and CheckMate 816 cannot be laid side by side

Populations: unresectable stage III versus resectable IB–IIIA
PACIFIC randomized only non-progressors after chemoradiation — a built-in filter
Clocks start differently: post-chemoradiation landmark versus pre-therapy randomization
Different endpoints — progression-free versus event-free survival
Different stage mix, nodal burden, imaging era, control arms
Different population in both

Why ADAURA and LAURA are not a horse race

ADAURA: fully resected, stage IB–IIIA
LAURA: unresectable, stage III
Disease-free survival after R0 and progression-free survival after chemoradiation measure different things
Fixed three-year course versus treatment to progression
Different recurrence patterns, competing risks
Both establish osimertinib in their own setting — neither outranks
Different population and cross-trial OS comparison is not appropriate

Honest comparison is within a trial. Across trials, compare populations — never hazard ratios.

Surgery or Radiation: Pros and Cons

Two curative strategies, each with distinct advantages and a distinct price.

SURGERY-BASED THERAPY

PROS

- Pathology, not imaging — nodal clearance and prognosis confirmed
- Downstaging to pN0 marks a favorable group (median 34.4 months, INT 0139)
- Usable pCR endpoint: 24% with neoadjuvant chemoimmunotherapy
- Perioperative immunotherapy: EFS HR 0.58 to 0.68 — CheckMate 816, AEGEAN, KEYNOTE-671, CheckMate 77T
- Resected tissue enables NGS if needed

CONS

- Treatment-related death 8% in INT 0139; 26% after pneumonectomy
- Permanent lung function loss; morbidity rises with resection extent
- Roughly one in five never reach surgery after induction
- Needs high-volume surgeon, strict selection; bulky or multistation N2 not-recommended
- No randomized survival advantage over chemoradiation
- May lead to over-treatment if upfront borderline resectable becomes unresectable

RADIATION-BASED THERAPY

PROS

- No operative mortality — treatment-related death 2%, INT 0139
- Treats bulky, multistation N2 and N3 surgery cannot clear
- PACIFIC: median OS 47.5 months, 42.9% alive at five years
- LAURA: consolidation osimertinib, 39.1 months PFS in EGFR-mutant disease
- Open to marginal pulmonary reserve or comorbidity

CONS

- Nodal status never confirmed unless you precede with EBUS first
- Pneumonitis, esophagitis; late cardiac and pulmonary dose effects
- In-field local recurrence remains albeit low is still higher than surgery
- Fibrosis makes later salvage surgery difficult or impossible
- Immunotherapy consolidation, not concurrent or neoadjuvant— PACIFIC-2 negative
- Logistically challenging (6 weeks)

Neither column wins outright — it resolves only once you know the nodal burden and the operation required.

Resectable Stage III

Perioperative immunotherapy and targeted therapy

The Perioperative Trials at a Glance

Four practice-shaping phase III trials, differing mainly in post-resection immunotherapy.

CheckMate 816 — neoadjuvant only

Nivolumab plus chemotherapy, three cycles, then surgery; resectable stage IB–IIIA

Pathologic complete response 24% vs 2.2%

Median event-free survival 31.6 vs 20.8 months (HR 0.63)

Overall survival benefit confirmed on longer follow-up

Cleanest evidence for neoadjuvant immunotherapy alone

KEYNOTE-671 and AEGEAN — perioperative

Pembrolizumab or durvalumab plus chemotherapy, before and after surgery; stage II–IIIB

KEYNOTE-671: pathologic complete response 18.1% vs 4.0%; positive overall survival (HR 0.72)

AEGEAN: pathologic complete response 17.2% vs 4.3%; event-free survival HR 0.68

Established the perioperative sandwich as standard

CheckMate 77T and NADIM II

CheckMate 77T: perioperative nivolumab; event-free survival HR 0.58, pathologic complete response 25.3% vs 4.7%

NADIM II (phase II): nivolumab plus chemotherapy; pathologic complete response 37%, better overall survival

Together, reinforce a class effect across agents

No head-to-head data — choose by access, comorbidity, toxicity

ADAURA: Adjuvant Osimertinib in EGFR-Mutant NSCLC

In resected EGFR exon 19del or L858R NSCLC, three years of adjuvant osimertinib gave the largest benefit yet in this setting.

What ADAURA established

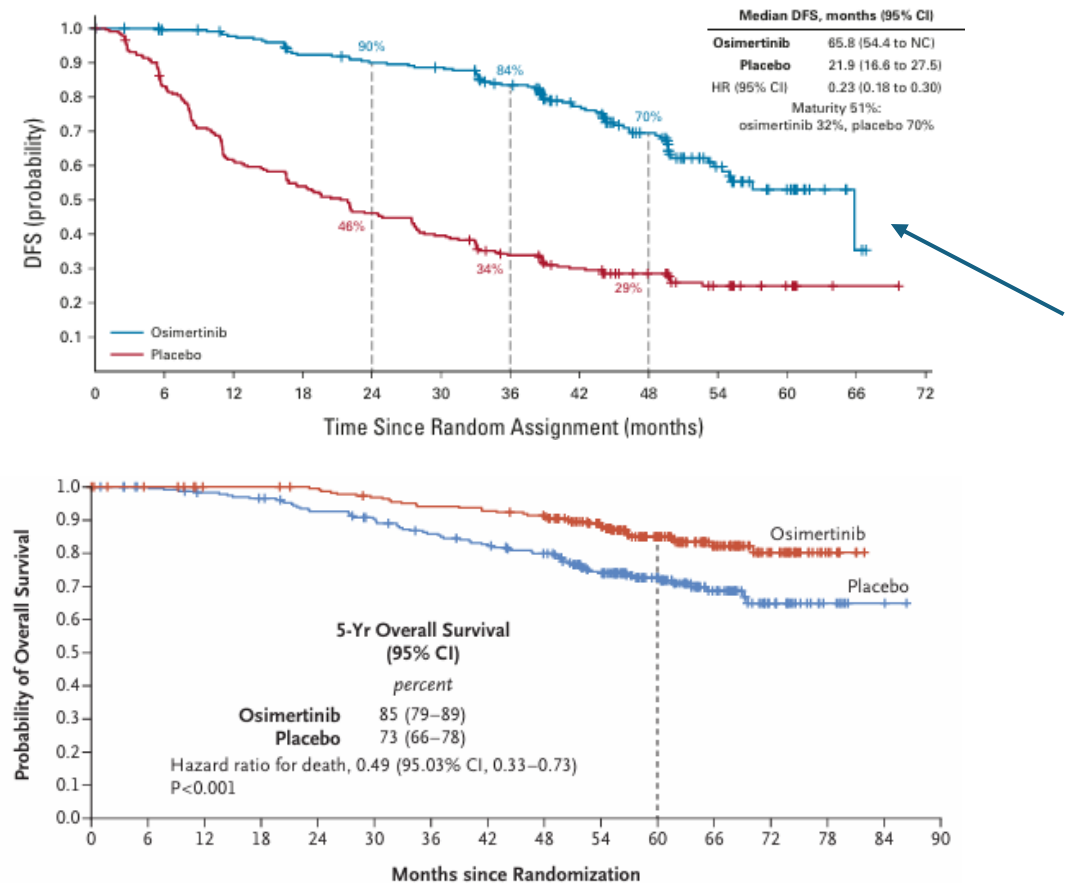
Phase III, resected stage IB–IIIA EGFR-mutant NSCLC: osimertinib 80 mg daily x3 years vs placebo, after optional chemotherapy

DFS in stage II–IIIA: HR 0.17; four-year DFS 70% vs 29%

CNS DFS HR 0.24 — fewer brain relapses, the dominant failure pattern

OS now positive: 5-year OS 85% vs 73% in stage II–IIIA (HR 0.49)

Adjuvant platinum chemotherapy still advised in resected stage II–III before osimertinib



Postoperative Radiation for pN2: What Changed

Two randomized trials moved PORT from routine to case-by-case.

LungART (Le Péchoux, 2022)

501 resected pN2, PORT 54 Gy versus none

Median DFS 30.5 versus 22.8 months, HR 0.86 — NS

Three-year DFS 47.1% versus 43.8%

Three-year OS 66.5% versus 68.5%

Mediastinal relapse halved: 25% versus 46%

Grade 3–4 cardiopulmonary toxicity 11% versus 5%

Verdict: not standard after complete resection

PORT-C (Hui, 2021)

364 resected pIIIA-N2 post-chemo, IMRT 50 Gy versus observation

ITT three-year DFS 40.5% versus 32.7%, HR 0.84 — NS

No OS difference

Locoregional RFS improved

Per-protocol: DFS benefit

Modern IMRT, same result

Verdict: better local control, no survival gain

The retrospective era

Registry and subset data pointing the other way

Large NCDB and SEER analyses, including Amini et al., linked PORT to better OS in pN2

ANITA subset and older meta-analyses agreed

NCDB machine learning: OS benefit with 3+ positive nodes, HR 0.91 — nodal burden and LNR 0.34+ as selection tools

Selection bias, stage migration, incomplete staging inflate benefit

Cardiac harm in the 1998 PORT meta-analysis: obsolete cobalt and 2D

Verdict: hypothesis-generating — lost on randomization

PORT still earns a seat: R1/R2 resection, extracapsular extension, unexpected multistation N2 — IMRT or IMPT, strict heart and lung constraints.

Unresectable Stage III

Definitive chemoradiation and consolidation

PACIFIC: Durvalumab After Chemoradiation

Concurrent chemoradiation plus a year of durvalumab: the backbone of unresectable stage III care.

The trial that set the standard

Phase III, unresectable stage III without progression after chemoradiation: durvalumab up to twelve months vs placebo

Median PFS 16.9 vs 5.6 months (HR 0.55)

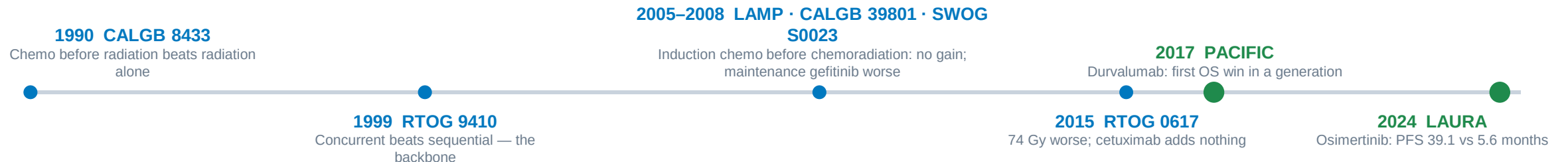
Five-year OS 42.9% vs 33.4%;

Start promptly — within 42 days of radiation; earlier is better

Pneumonitis the key toxicity; careful planning and lung dose constraints

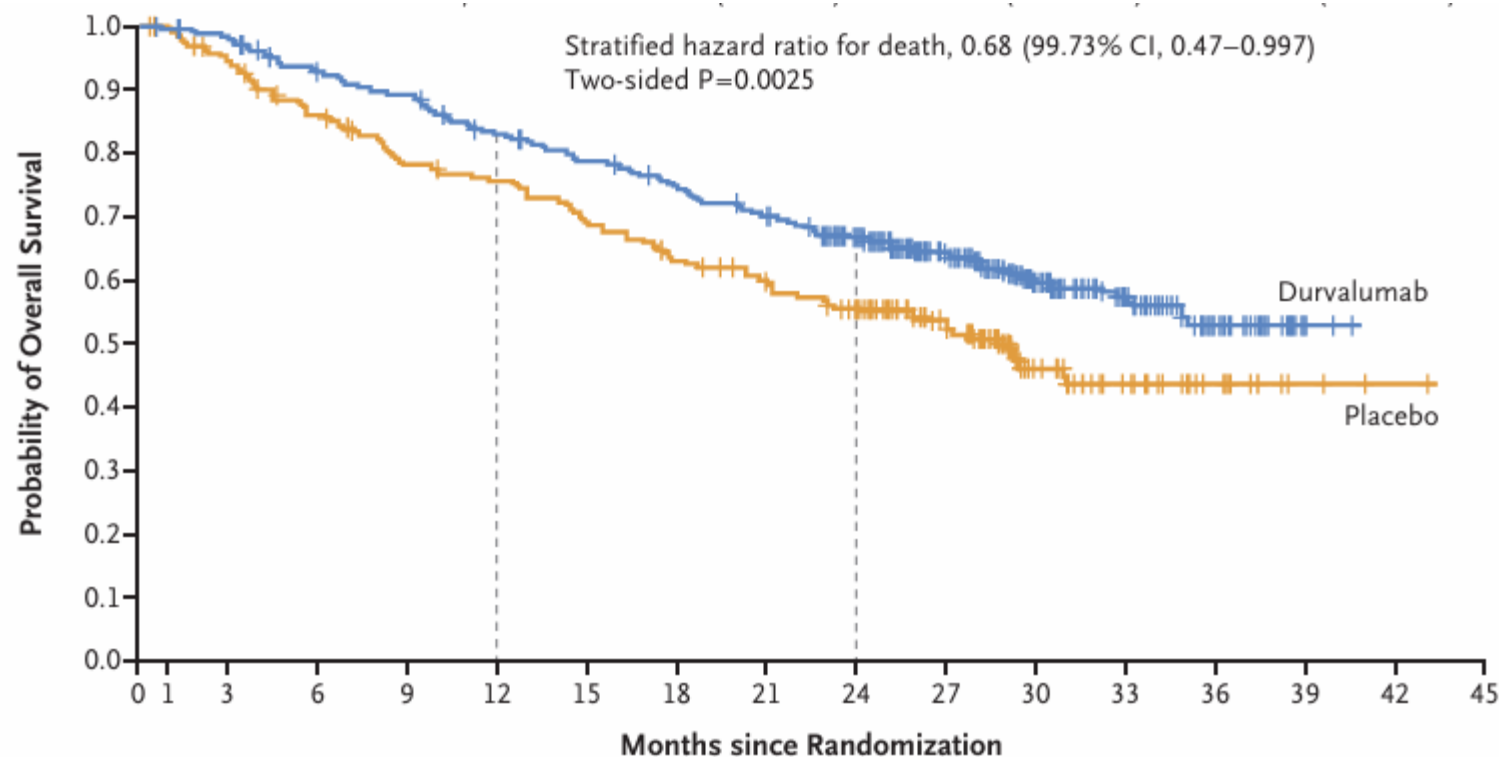
Minimal benefit in EGFR-mutant tumors — motivated the LAURA trial

Thirty years of trials in unresectable stage III — and the two that finally moved the needle!



PACIFIC: Overall Survival

Consolidation durvalumab after concurrent chemoradiation produced a durable survival plateau in unresectable disease.



Median overall survival

47.5 months with durvalumab versus 29.1 with placebo

Five-year overall survival 42.9% versus 33.4%

Progression-free survival 16.9 versus 5.6 months (HR 0.55)

A genuine tail on the curve — a meaningful subset is cured!!!

LAURA: Osimertinib After Chemoradiation

In unresectable stage III EGFR-mutant NSCLC, consolidation osimertinib — not durvalumab — is standard of care.

A practice-changing magnitude of benefit

Phase III: unresectable stage III EGFR exon 19 deletion or L858R, no progression after chemoradiation — osimertinib versus placebo

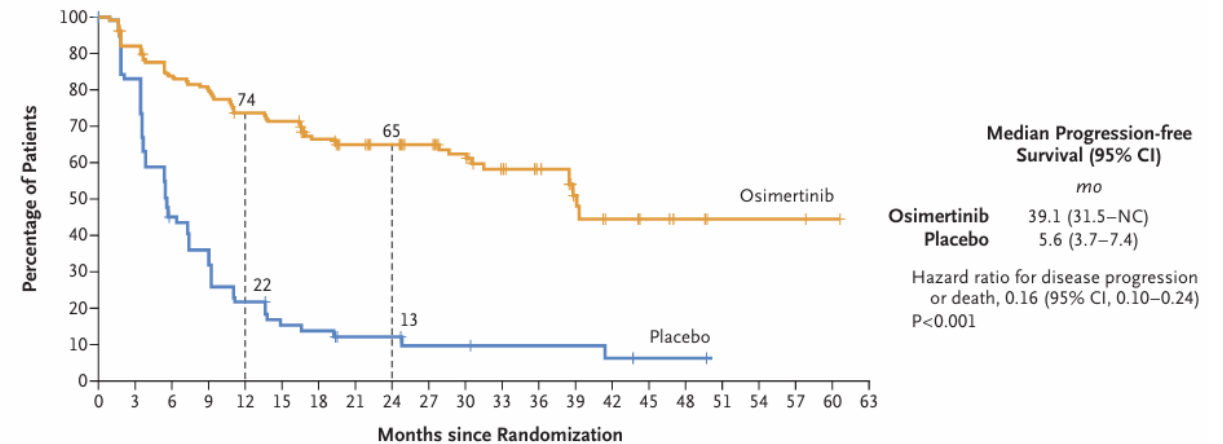
Median PFS 39.1 versus 5.6 months (HR 0.16)

CNS progression sharply reduced — new brain lesions 8% versus 29%

Overall survival immature; interim analysis encouraging

FDA approval September 2024 — EGFR testing now mandatory in unresectable disease

More radiation pneumonitis with osimertinib, mostly low grade — coordinate with radiation oncology



Pneumonitis: the one toxicity with two owners.

PACIFIC-2: Concurrent Durvalumab Did Not Help

Immunotherapy moved earlier — concurrent with chemoradiation, not after — failed to improve outcomes.

A negative trial worth teaching

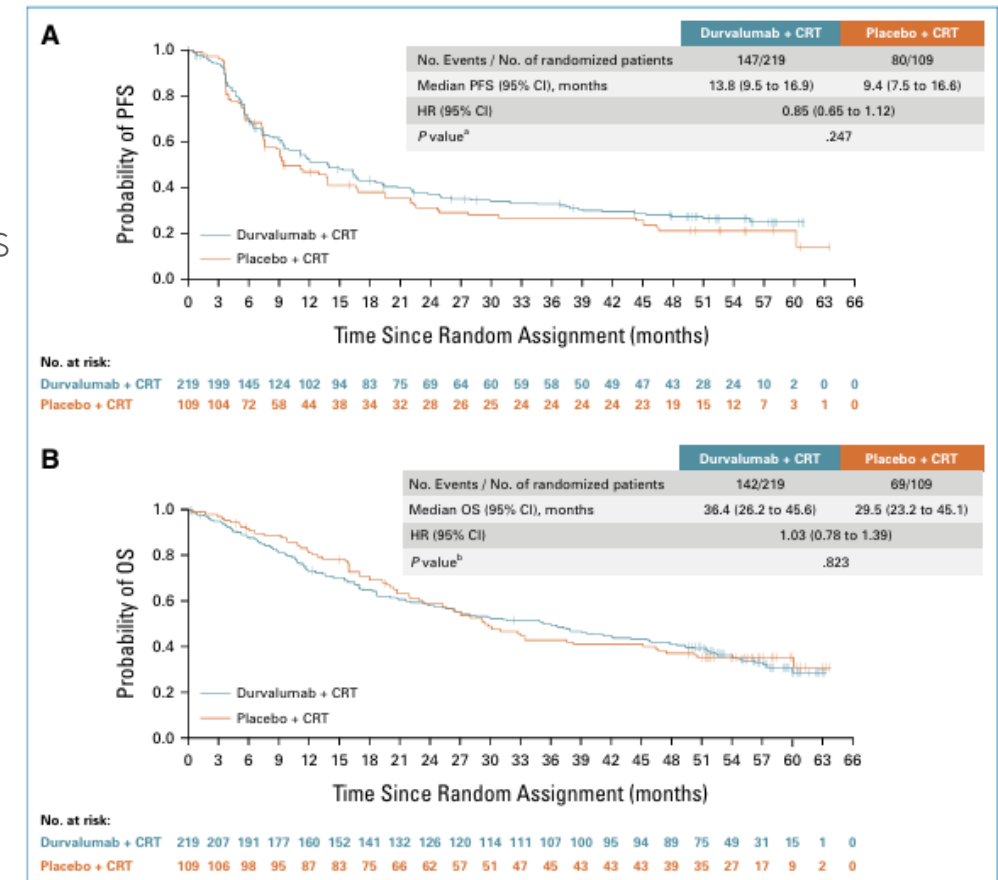
Phase III: durvalumab concurrent with definitive chemoradiation plus consolidation, versus chemoradiation alone

Primary endpoint missed: median PFS 13.8 versus 9.4 months, not significant

Overall survival numerically no better: 36.4 versus 29.5 months

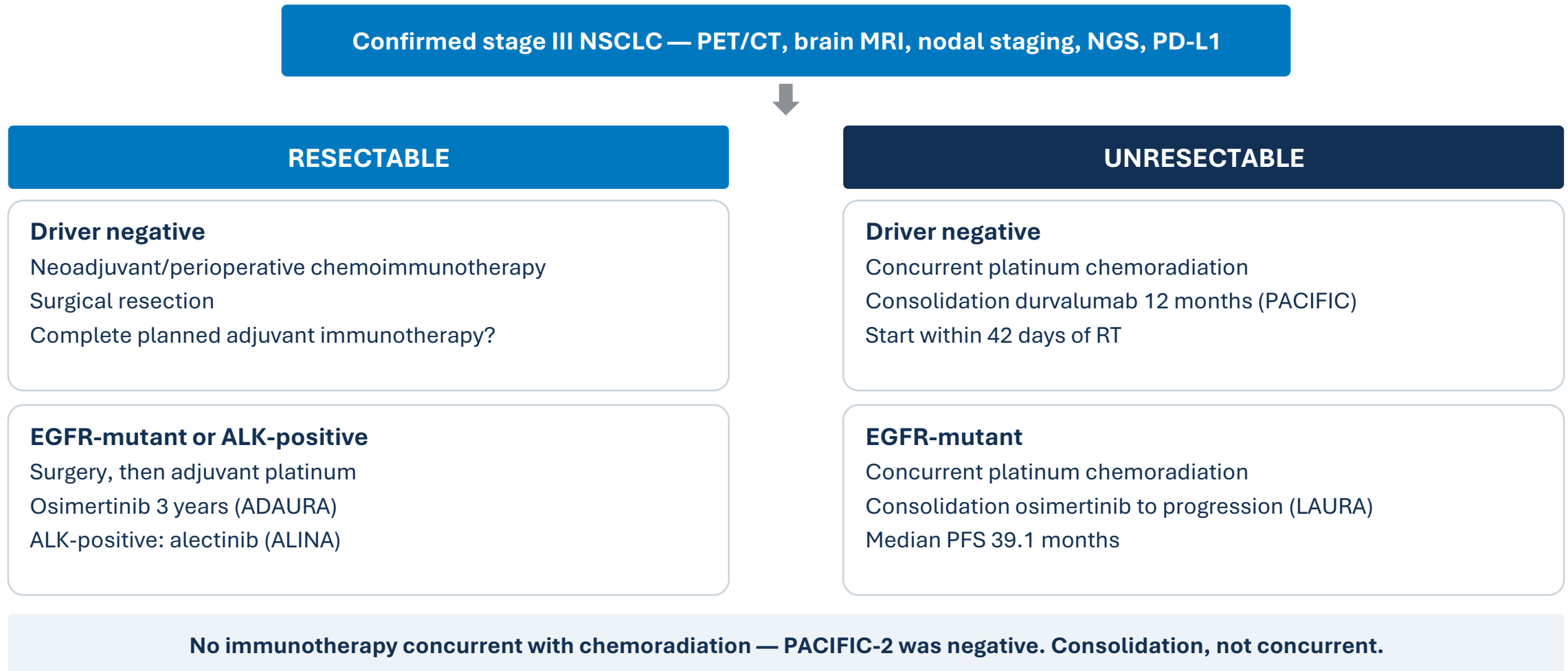
More discontinuations for adverse events; more pneumonitis and radiation toxicity

Sequence matters: give durvalumab as consolidation after chemoradiation, as in PACIFIC



The Stage III Algorithm on One Slide

Two questions drive everything: resectable? Actionable driver mutation?



MDT-BRIDGE: A Bridge Between the Two Pathways

A prospective attempt to make resectability a decision you arrive at, not one you guess at up front.

What the Study Does

Phase II, NCT05925530, ~140 patients, stage IIB–IIIB (N2), EGFR/ALK wild-type

Resectable or borderline-resectable disease enters a single up-front pathway

1–2 cycles of neoadjuvant durvalumab plus platinum chemotherapy for everyone

Multidisciplinary reassessment after induction decides the definitive local therapy

Surgery then adjuvant durvalumab, or definitive chemoradiation then consolidation durvalumab

Both arms of the fork stay on the same immunotherapy backbone

Why It Matters

It treats the resectability question as dynamic rather than fixed at diagnosis

Borderline-resectable patients may be converted to a complete resection

Patients who become unresectable or inoperable are not stranded — they move to chemoradiation and consolidation

Avoids committing a patient to a path before tumor biology has declared itself

Interim analysis reported at ESMO 2025 (LBA65) shows the design is feasible

Response-adapted local therapy is the idea the field has been circling for years

How This Could Change Practice

A possible future model — hypothesis-generating, not yet standard of care

Suggests one answer to today's debate: induction first, then let the tumor board choose

Single-arm phase II — no randomized comparison with either standard pathway

Reassessment criteria still need standardization across centers

Circulating tumor DNA is being explored to help guide the decision point

Watch for mature outcomes before adopting outside a trial

A potential way forward: rather than arguing scalpel versus beam at diagnosis, give everyone chemoimmunotherapy first and let the multidisciplinary team pick the local therapy the tumor has earned — promising, but still investigational.

Back to the Case: The Answer

The NGS report landed after the room voted.

THE NGS RESULT: EGFR EXON 19 DELETION. PD-L1 45% IS NOW A DISTRACTION.

WHAT THE ROOM VOTED

A. Neoadjuvant chemoimmunotherapy, then lobectomy

Crowd favorite — wrong here.

B. Chemoradiation with consolidation durvalumab

Fine if unresectable. This one is resectable.

C. Surgery first, adjuvant guided by pathology

Close — only if you wait for molecular.

D. Wait for NGS before deciding

The quiet, correct answer.

WHY THE DRIVER CHANGES IT

EGFR-mutant tumors respond poorly to immunotherapy; perioperative chemoimmunotherapy trials barely enrolled them.

Immunotherapy first adds toxicity when osimertinib follows.

Single-station, non-bulky N2 with achievable R0 favors resection.

ADAURA applies: 4-year DFS 70% versus 29%, HR 0.17; CNS HR 0.24.

If unresectable, it flips to chemoradiation plus consolidation osimertinib — LAURA, 39.1 months.

WHAT WE DID

Lobectomy with mediastinal nodal dissection

Pathology: ypT3 pN2, R0

Adjuvant platinum chemotherapy, four cycles

Osimertinib three years per ADAURA

Postoperative radiation declined — LungART and PORT-C: no DFS benefit, more cardiopulmonary toxicity

Surveillance with brain imaging, given late recurrence after therapy stops

Never scalpel versus beam — do you know enough to choose? Stage sets the field; the driver calls the play.

Thank You

cityofhope.org
aamini@coh.org
@DrAryaAmini

