# Locally Advanced Non-Small Cell Lung Cancer

Arya Amini MD

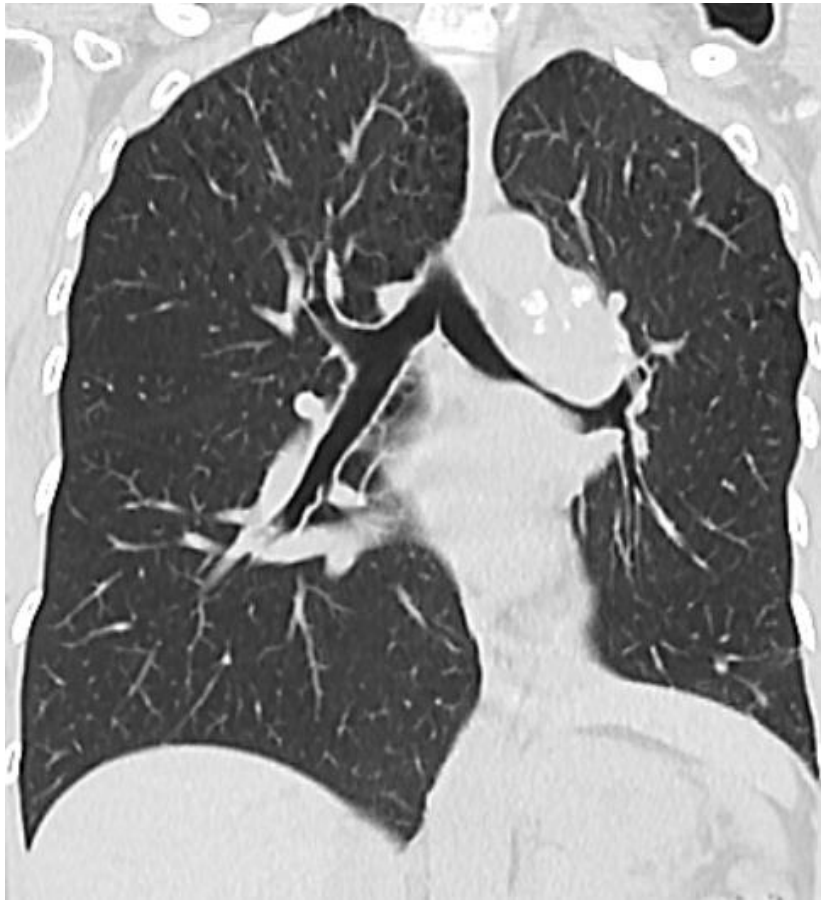
Department of Radiation Oncology

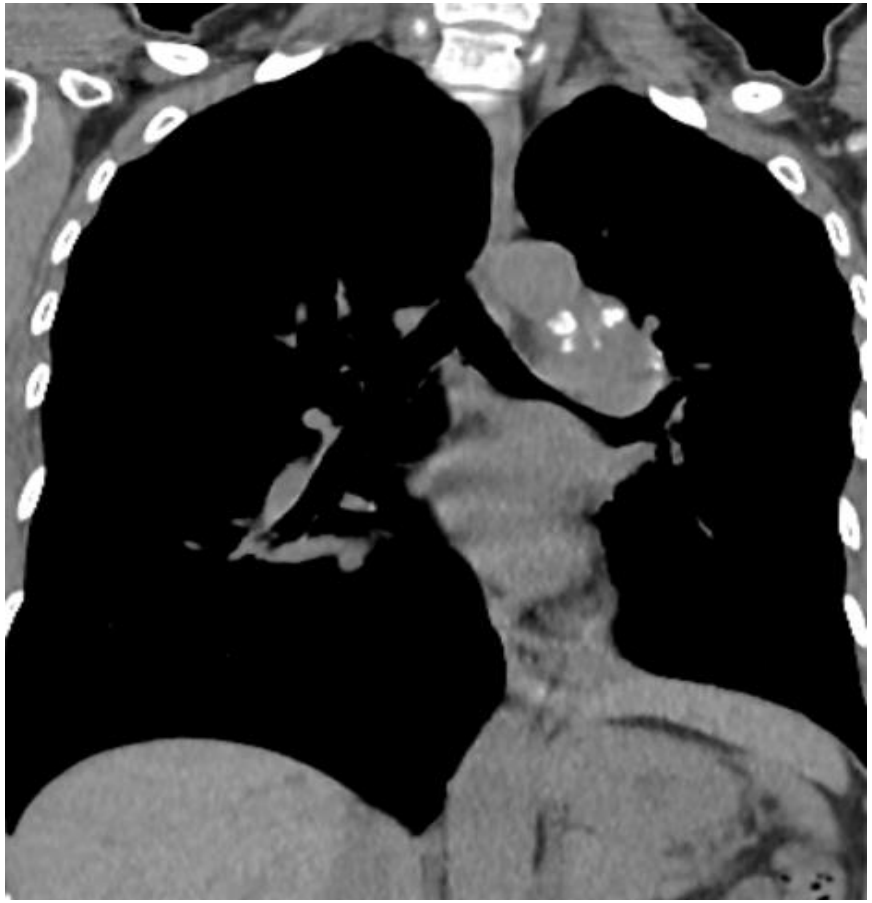
City of Hope

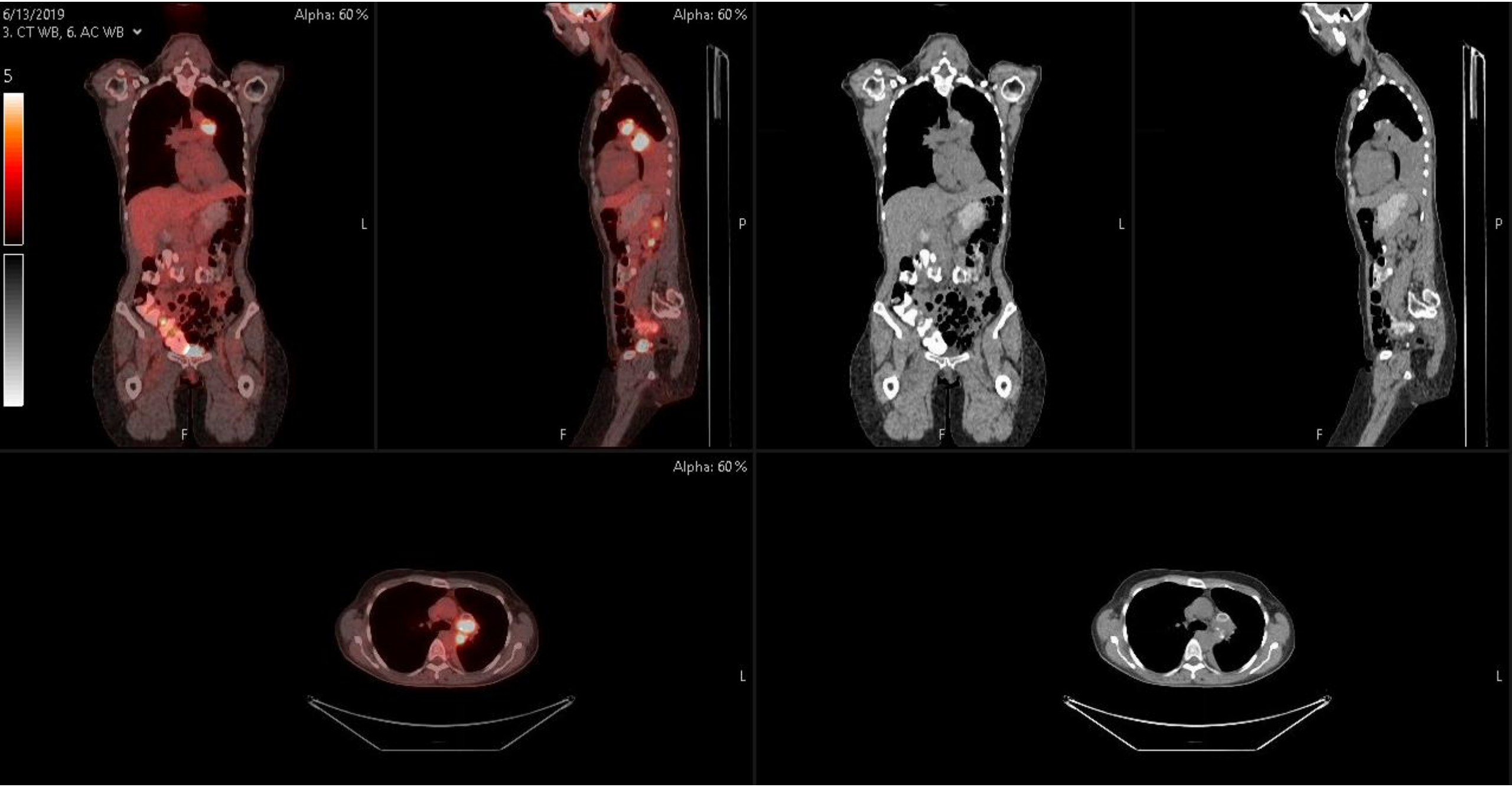
# Case Presentation

- 52-year-old female, 60-pack-year smoking history
- T2a N2 M0 adenocarcinoma of the left lower lobe
- Presented with intermittent shortness of breath which became worse
- Chest x-ray: opacity in the left lung
- June 6, 2019, CT chest: 3.6 × 2.6 cm mass in the left lung with enlarged left hilar and suprahilar nodes
- June 11, 2019, endobronchial ultrasound (EBUS) and bx: squamous cell carcinoma
- June 13, 2019, PET / CT: hypermetabolic left lower lobe mass with uptake in upper paratracheal nodes
- June 28, 2019, MRI brain: negative

# Imaging



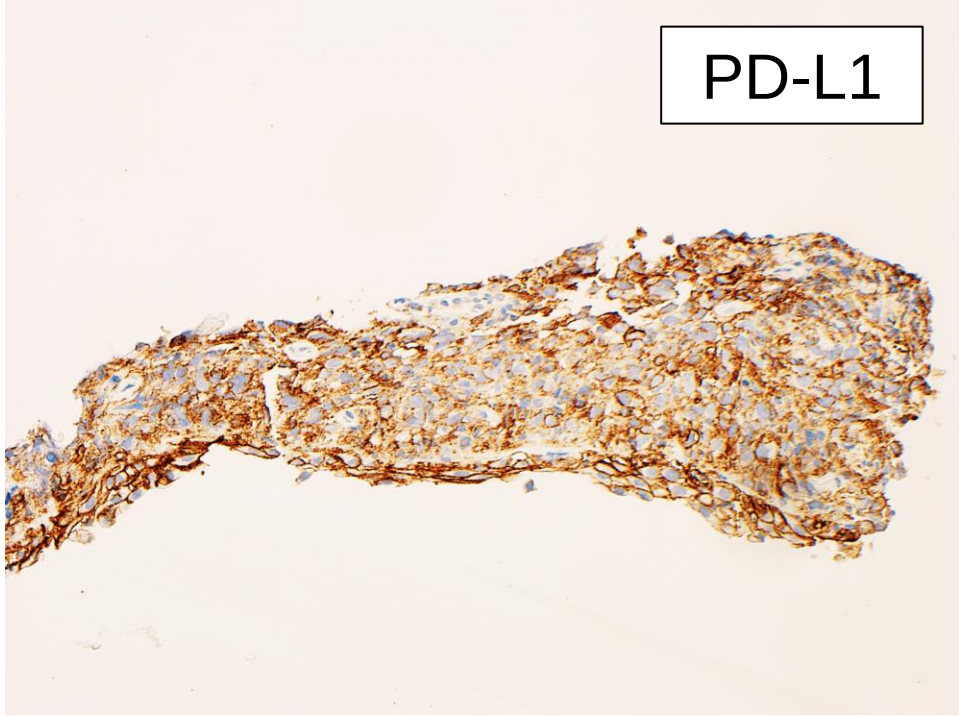


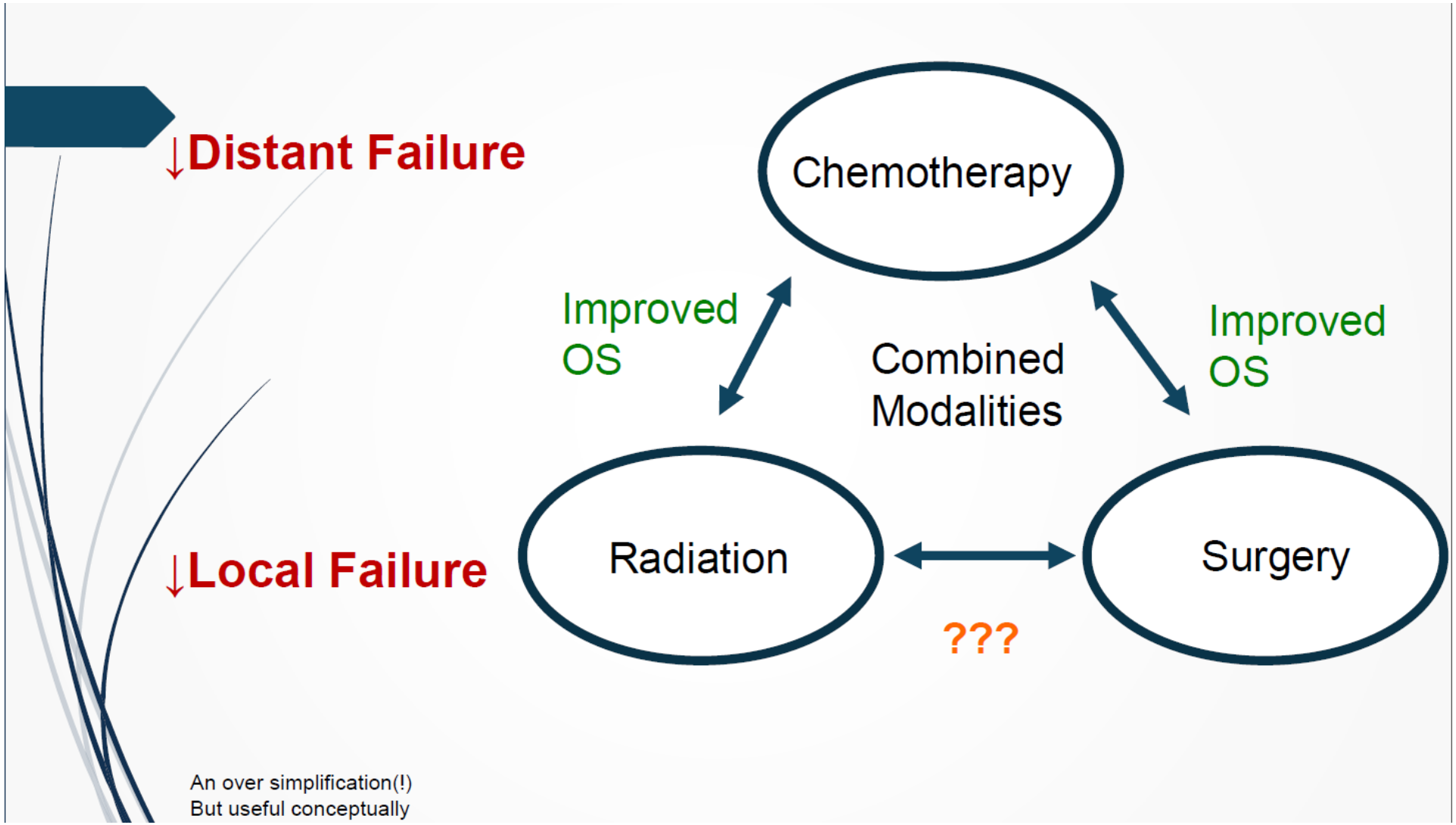

6/13/2019
3. CT WB, 6. AC WB
Alpha: 60 %
5
L
F
Alpha: 60 %
P
F
L
F
P
F
Alpha: 60 %
L
L

# Pathology

Lung, left lower lobe, core biopsy:

- Adenocarcinoma, solid type
- TTF-1 positive, p63 and Napsin A negative




↓Distant Failure
↓Local Failure
Chemotherapy
Improved OS
Combined Modalities
Improved OS
Radiation
Surgery
???
An over simplification(!)
But useful conceptually

# High local recurrence in stage III patients after surgery alone

| Study | No. | Stage | XRT dose | Survival | LRF w/o RT |
|---|---|---|---|---|---|
| **Belgium** (van Houtte et al. 1980) | 202 | I-III | 60 Gy | 43% | 11% |
| **LCSG** (Weisenburger 1986) | 230 | II-III | 50 Gy | 40% | 21% |
| **CAMS** (Feng et al. 2000) | 317 | II-III | 60 Gy | 41% | 33% |
| **Lille** (Lafitte et al., 1996) | 163 | I | 45-60 Gy | 52% | 17% |
| **MRC LU11** (Stephens et al 1996) | 308 | II-III | 40 Gy | 25% | 29% |
| **Austria** (Mayer et al. 1997) | 155 | I-III | 50-56 Gy | 20% | 24% |
| **GETCB** (Dautzenberg et al. 1999) | 720 | I-III | 60 Gy | 43% | 34% |
| **Slovenia** (Debevec et al. 1996) | 74 | III | 30 Gy | 20% | NA |
| **Italy** (Trodella et al. 2002) | 104 | I | 50 Gy | 58% | 22% |

# Treatment for IIIA NSCLC

## Pattern of Relapse Following Resection

| Stage | Nodal Status | % chest | % distant |
|---|---|---|---|
| IA | N0 | 10 | 15 |
| IB | N0 | 10 | 30 |
| II | N1 | 12 | 40 |
| IIIA | N2 | 15 | 60 |

*Feld 1984; Pairolero 1984; Martini 1980; Thomas 1990*

# Trimodality Therapy for Stage IIIA Intergroup 0139, "The Albain Study

429 pts w/ resectable biopsy proven N2
+ IIIA NSCLC randomized to:

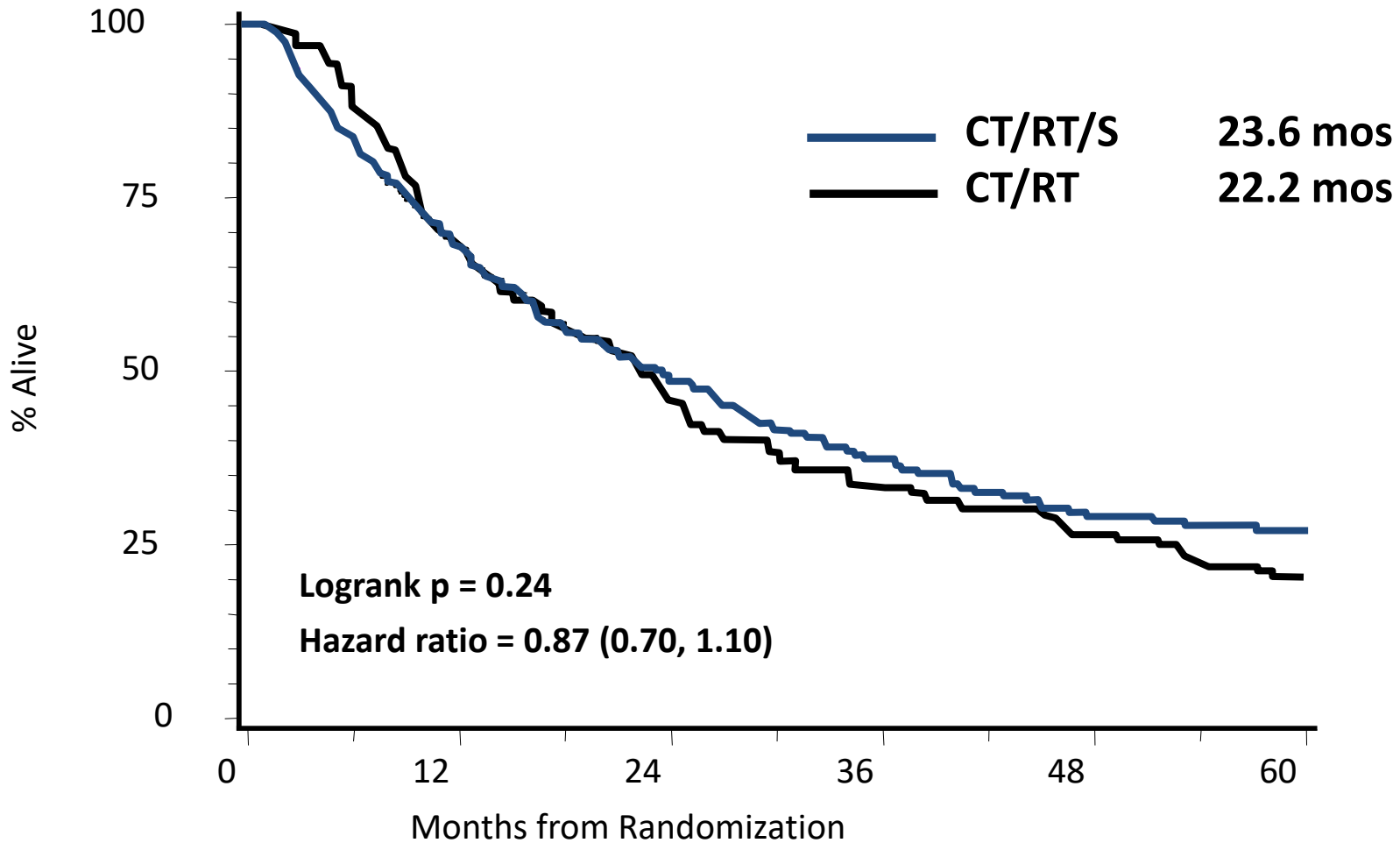
Chemo/XRT 45 Gy + Surgery +
Consolidation chemo

vs.

Chemo/XRT 61 Gy + Consolidation
Chemo

*Albain K. Lancet, 2009.*

# Trimodality Therapy for Stage IIIA Intergroup 0139




*Albain K. Lancet, 2009.*

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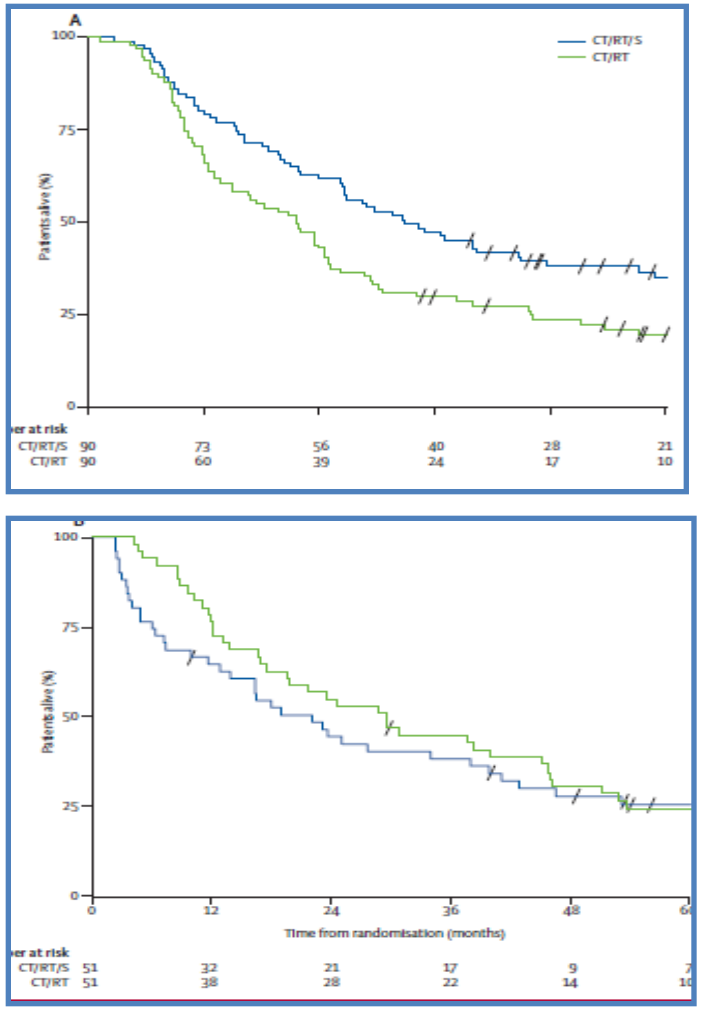
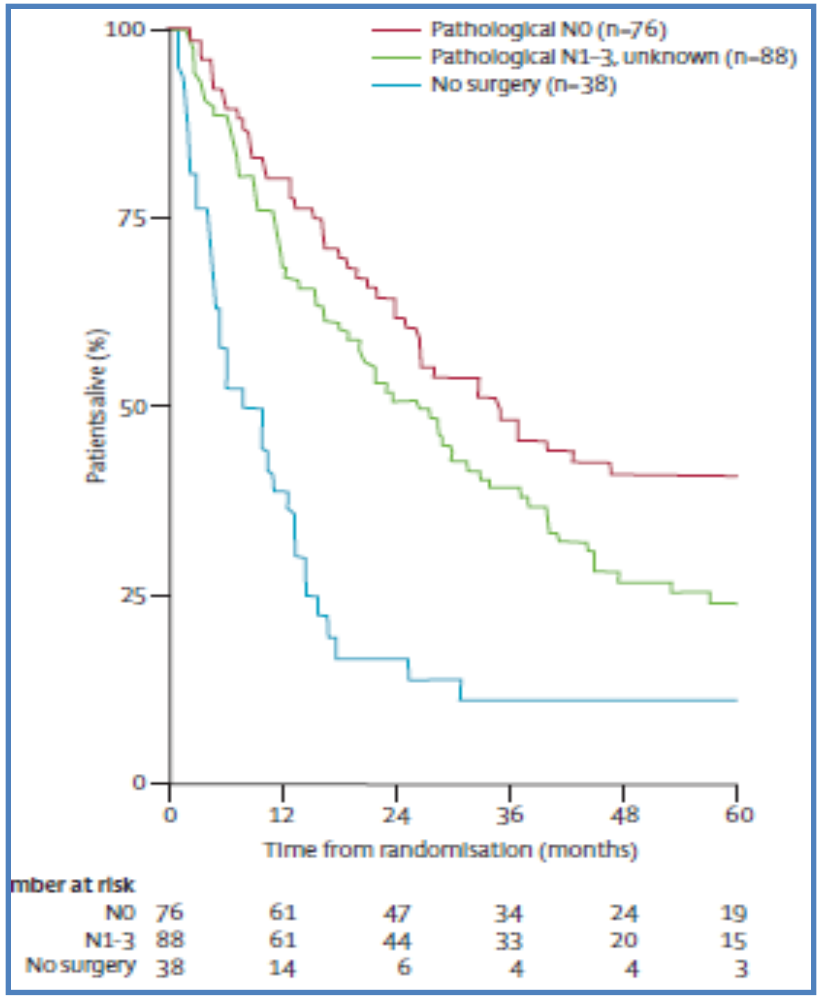



**Lobectomy** – following neoadjuvant chemoradiation is reasonable treatment option, associated with survival >40%

**Pneumonectomy** – following neoadjuvant chemoradiation is associated with increased mortality

*Albain, K. Lancet, 2009*

# Trimodality Therapy for Stage IIIA Intergroup 0139




- Eradication of N2 disease by neoadjuvant therapy correlated strongly with survival following surgery
- 46% of patients were downstaged to N0
- Chemoradiation increased N2 clearance compared to neoadjuvant chemotherapy alone

*Albain, K. Lancet, 2009*

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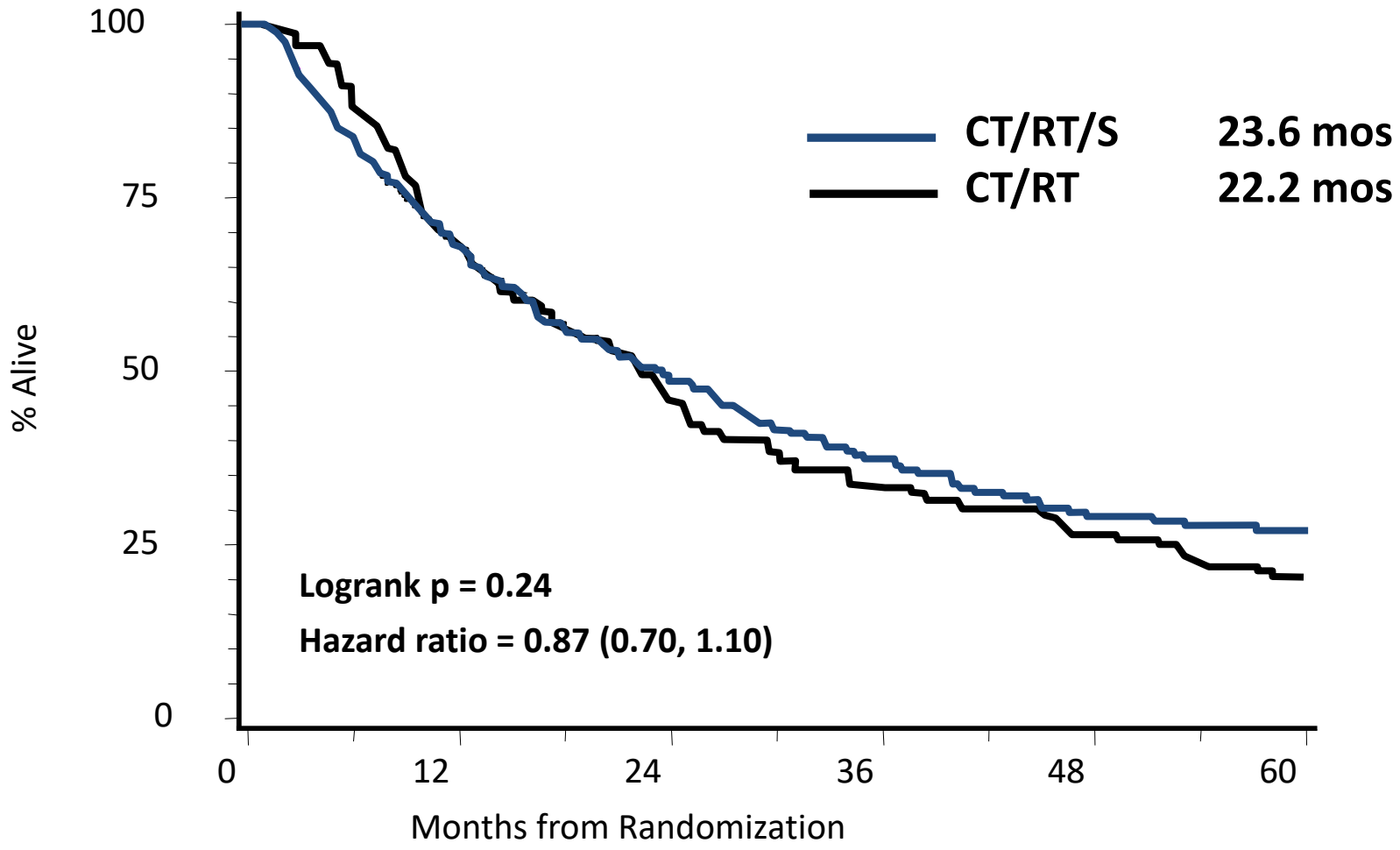


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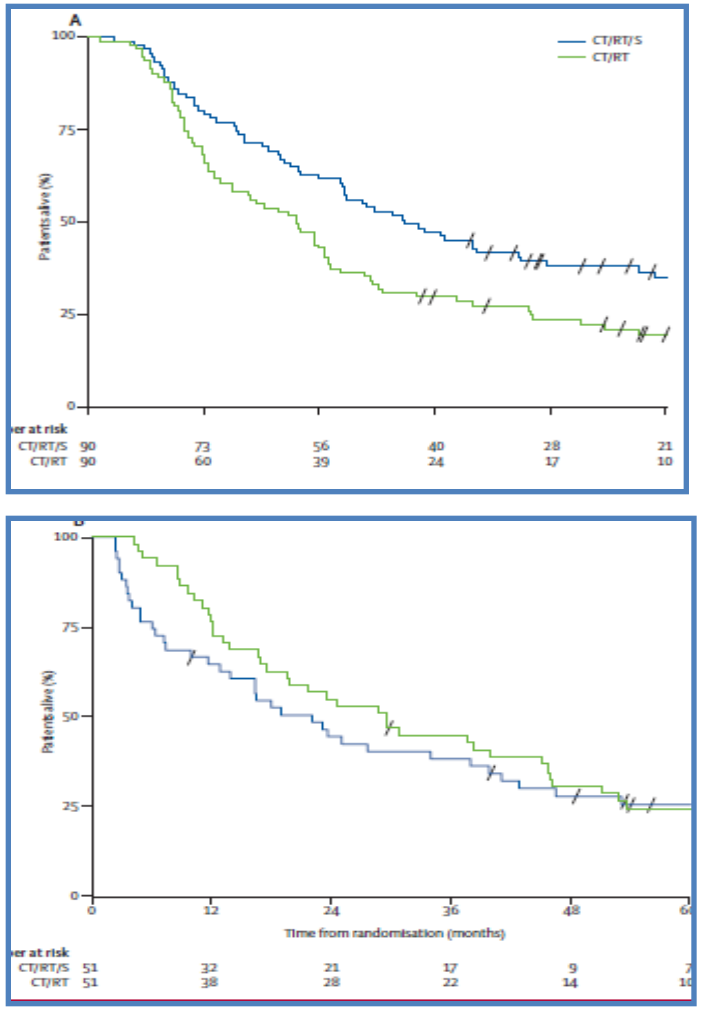


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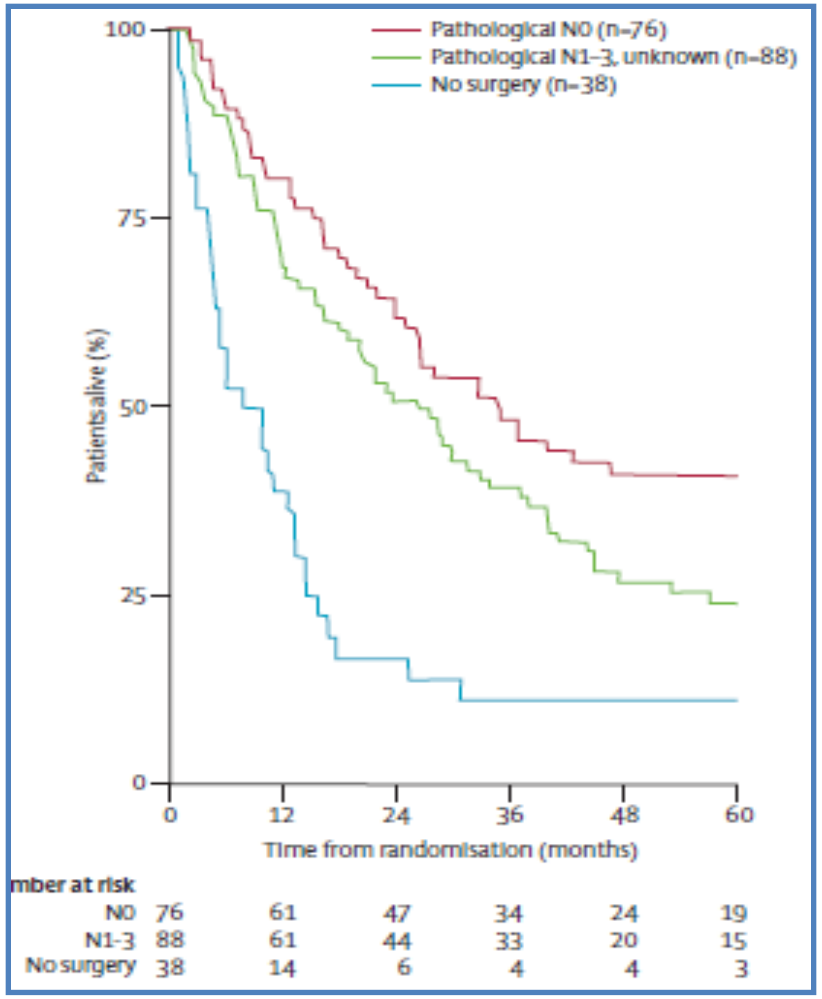


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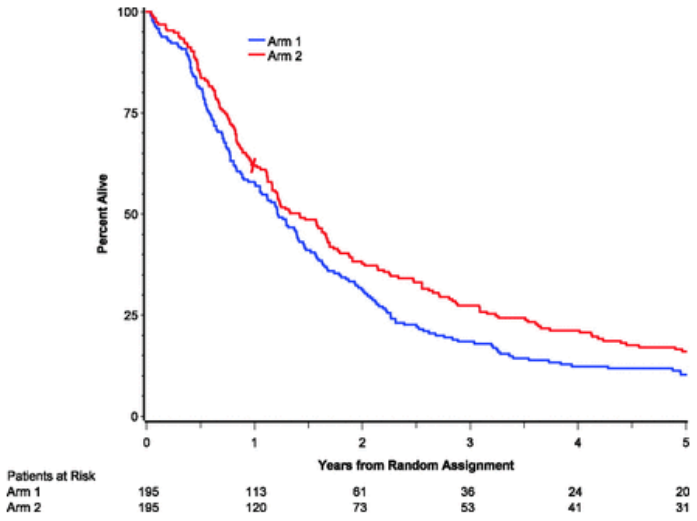
# Summary of Data on Radiation and Chemotherapy

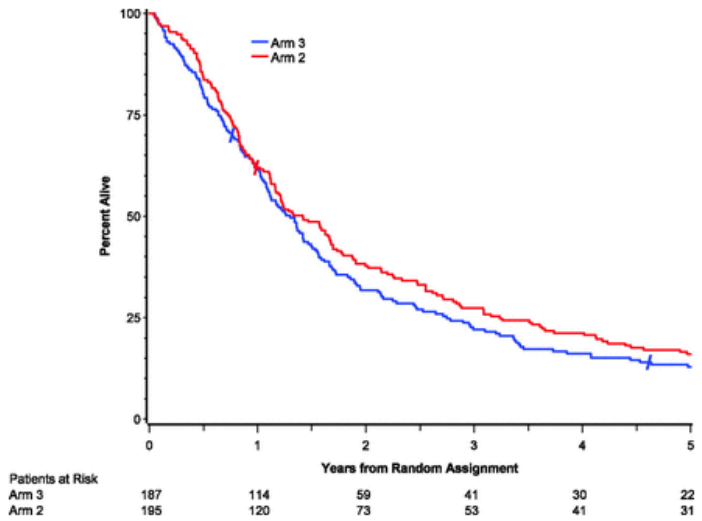
- RT dose
  - RTOG 7301 (highest local control at 60 Gy)
- Sequential CRT vs RT alone
  - CALGB 8433 (7-yr OS higher, 13% vs 6%)
- Concurrent chemotherapy better than sequential
  - RTOG 9410 (5-yr OS higher with concurrent; improved LRC)
  - Meta-analysis
- Concurrent CRT +/- induction chemo
  - LAMP: no difference with induction

Perez et al. Cancer 1980 Jun; 45(11):2744-53.
Dillman et al. J Natl Cancer Inst. 1996 Sep; 88(17):1210-15.
Curran et al. J Natl Cancer Inst. 2011 Oct; 103(19):1452-60.
Auperin et al. JCO 2010 May; 28(13):2181-90.
Belani et al. JCO 2005 Sep; 23(55):5883-91.

# Data for Chemotherapy Combined with Radiation

- RTOG 9410 (Curran et al, JNCI 2011)
  - Unresected stage III lung, randomized to 3 arms
    - 60 Gy RT -> sequential chemo (cis/vinb) (median OS 14.6 mo)
    - 60 Gy RT + concurrent chemo (cis/vinb) (median OS 17 mo)
    - 69.2 Gy Hyperfrac RT + concurrent chemo (cis/etop) (median OS 15.6 Gy)



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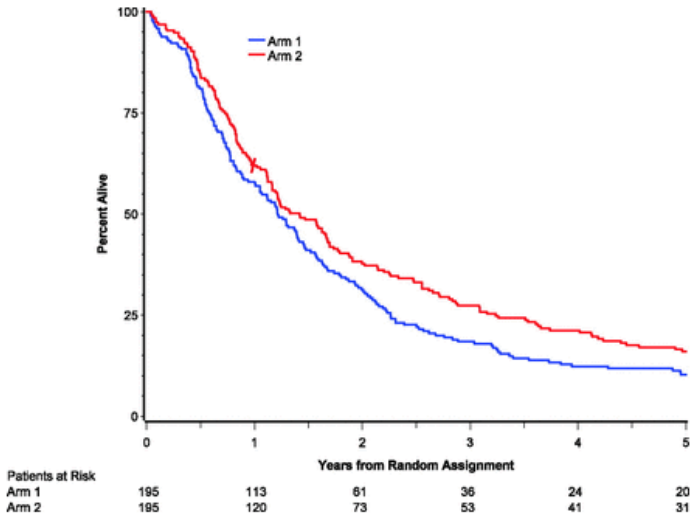
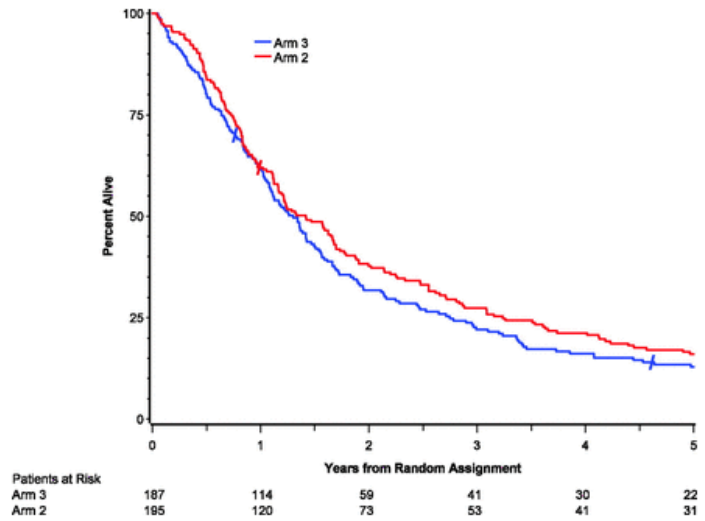


# RTOG 9410

**Table 3.** Patterns of failure*

| Component of first failure | No. (%) Arm 1 (n = 195) | Arm 2 (n = 195) | Arm 3 (n = 187) |
|---|---|---|---|
| Primary tumor | 65 (33) | 56 (29) | 47 (25) |
| Thoracic lymph nodes (infield) | 34 (17) | 24 (12) | 18 (10) |
| Thoracic lymph nodes (out of field) | 4 (2) | 8 (4) | 3 (2) |
| Brain metastases | 24 (12) | 28 (14) | 24 (13) |
| Other metastases | 65 (33) | 64 (33) | 60 (32) |
| Infield only | 59 (30) | 49 (25) | 38 (20) |
| Out of field only | 67 (34) | 73 (37) | 69 (37) |
| Both infield and out of field | 22 (11) | 20 (10) | 16 (9) |

* Arm 1 was the sequential arm. Arm 2 used the same chemotherapy regimen as arm 1 with 60 Gy thoracic radiotherapy beginning on day 1. Arm 3 used cisplatin at 50 mg/m$^2$ on days 1, 8, 29, and 36 with oral etoposide at 50 mg twice daily for 10 weeks on days 1, 2, 5, and 6 with 69.6 Gy delivered as 1.2-Gy twice-daily fractions beginning on day 1

Arm 1: Sequential
Arm 2: Concurrent
Arm 3: HyperFx Conc

Total In-field failures as site of first failure ~30-40% (lower at 30-35% with concurrent chemoRT)

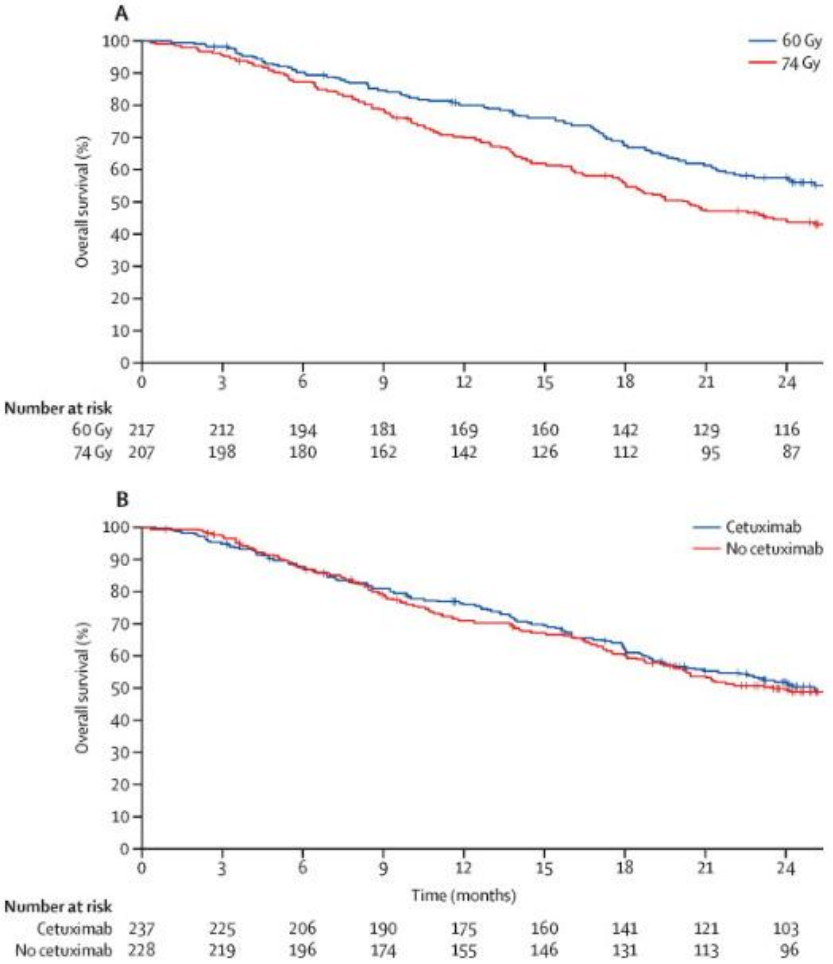
Gr3+ Esophagitis higher with concurrent chemoRT arms (4 vs 22 vs 45%)

No diff in late toxicity

Curran et al. J Natl Cancer Inst. 2011 Oct; 103(19):1452-60.

# RTOG 0617

- Randomized, 2x2 factorial phase 3
- Concurrent carbo (AUC 2)/paclitaxel (45 mg/m2) +/- CTX, 2c consolidation (AUC 6/ 200 mg/m2) +/- CTX
- 60 vs 74 Gy
- Median OS worse for 74 Gy, 20.3 vs 28.7 mo (HR 1.38, p=0.004)
- Median OS no different with CTX




Bradley et al. The Lancet 2015 Jan; 16(2):187-99.

# RTOG 0617

- Not just a negative trial

- We learned
  - Higher dose may not be the answer
  - IMRT should be standard
    - Gr ≥ 3 pneumonitis, decrease heart dose,
  - Lung V20 associated with Gr ≥ 3 pneumonitis; V5 did not
  - Heart V40 -> predicted OS

Curran et al. J Natl Cancer Inst. 2011 Oct; 103(19):1452-60.

# PACIFIC Trial – The current standard of care for Unresectable Stage III NSCLC

- Purpose: evaluate the role of adjuvant durvalumab (anti-PDL1) after chemoradiation in stage III NSCLC

- Enrolled: stage III, unresectable; excluded grade 2+ pneumonitis from CRT or grade 2+ unresolved

- Treatment:
  - Platinum-based chemotherapy (etopiside, vinablastine, vinorelbine & taxane [paclitaxel or docetaxel] or pemetrexed)
  - Concurrent RT (54-66 Gy)
  - Durvalumab 10 mg/kg or placebo q2 weeks for 1 year (2:1 randomization)

Antonia et al. NEJM 2017 Nov; 377:1919-29.

# PACIFIC Trial - Results

- PFS with Durvalumab vs Placebo (p<0.001)
  - Median: 16.8 vs 5.6 mo
  - 12-mo: 55.9% vs 35.3%
  - 18-mo: 44.2% vs 27.0%
- Median time to death or DM
  - 23.2 mo vs 14.6 mo (p<0.001)
- **Analysis of OS was not planned at this interim**

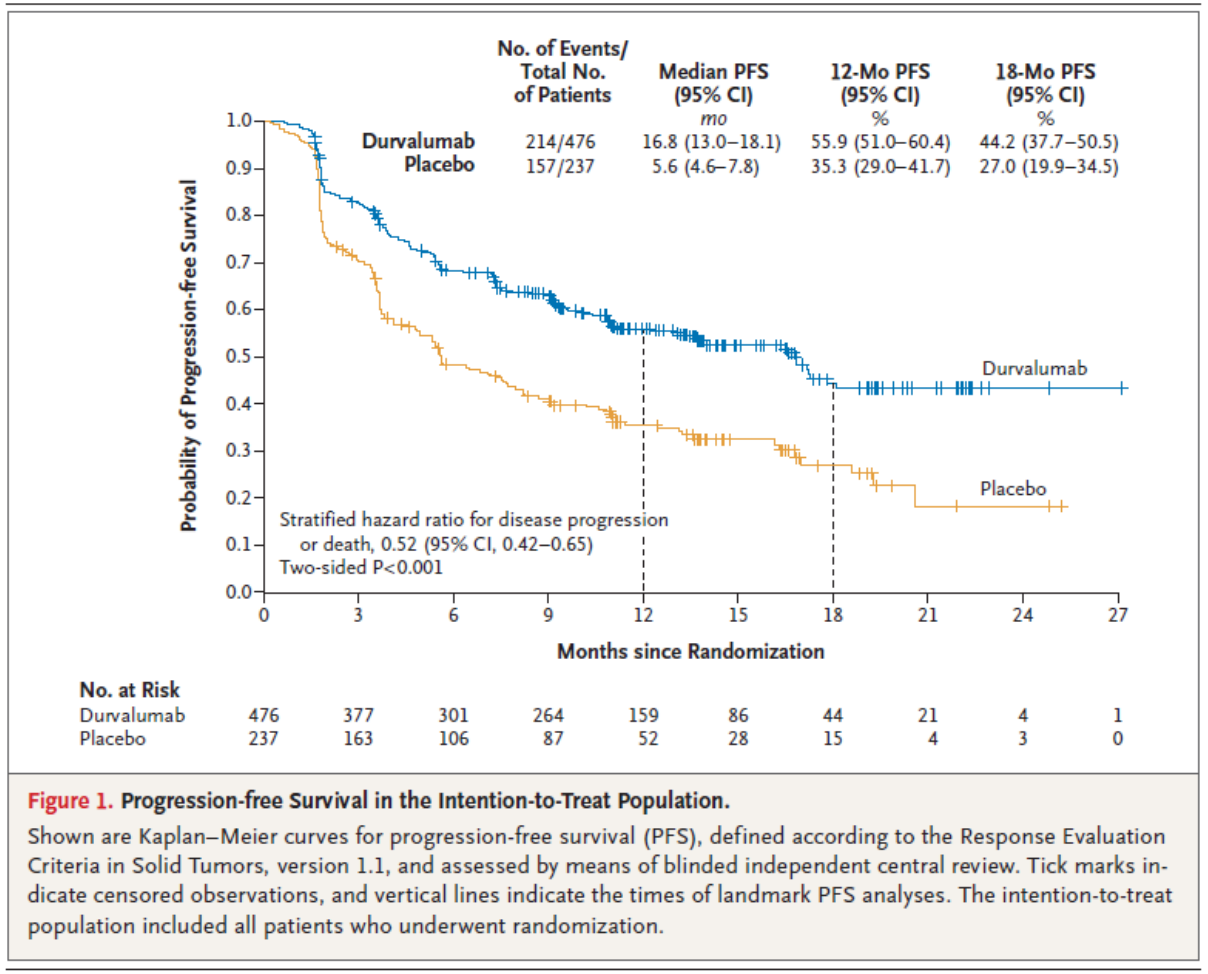
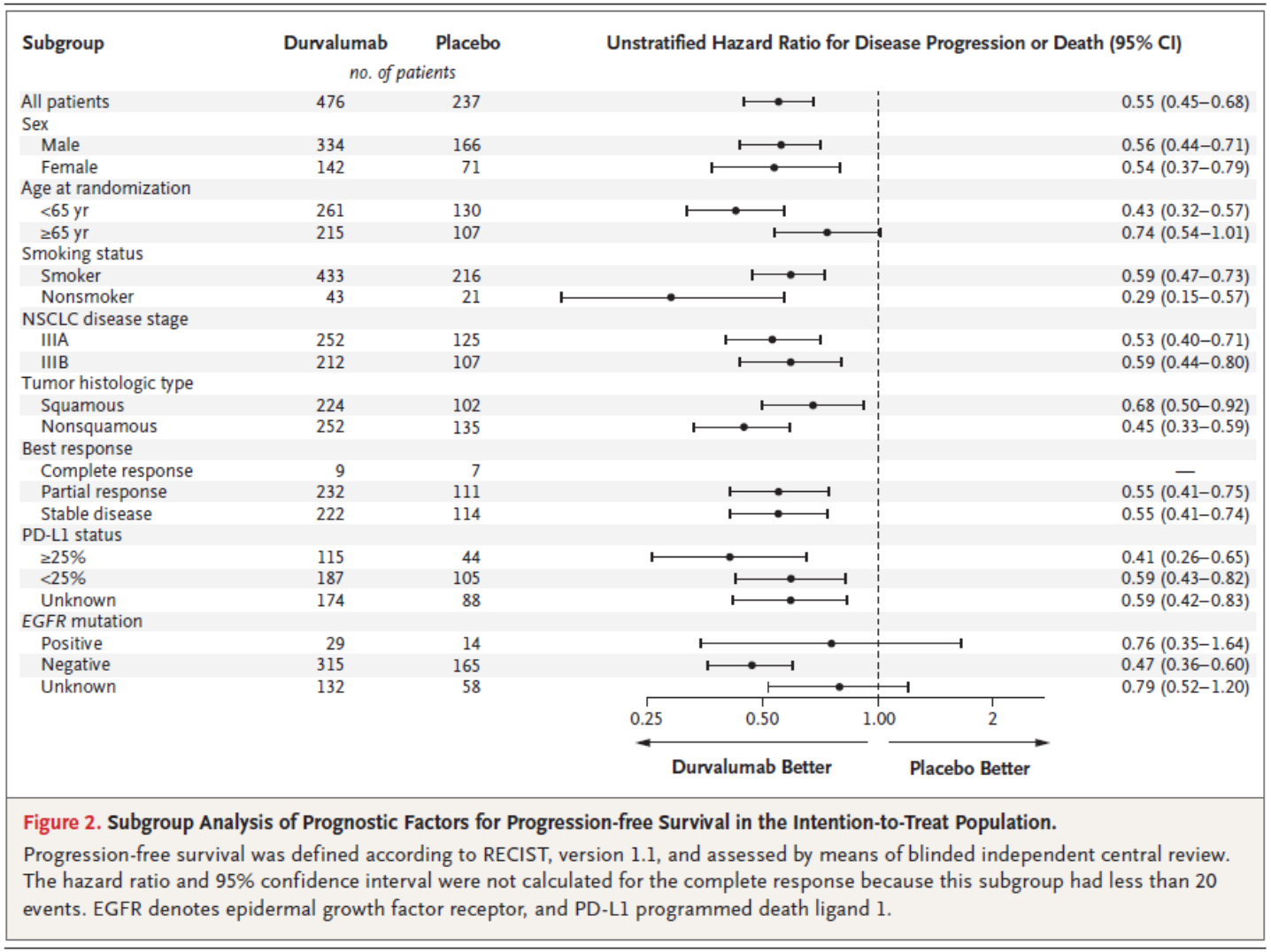



**Figure 1. Progression-free Survival in the Intention-to-Treat Population.**

Shown are Kaplan–Meier curves for progression-free survival (PFS), defined according to the Response Evaluation Criteria in Solid Tumors, version 1.1, and assessed by means of blinded independent central review. Tick marks indicate censored observations, and vertical lines indicate the times of landmark PFS analyses. The intention-to-treat population included all patients who underwent randomization.

# PACIFIC Trial – Results



| Subgroup | Durvalumab | Placebo | Unstratified Hazard Ratio for Disease Progression or Death (95% CI) |
|---|---|---|---|
| | *no. of patients* | | |
| All patients | 476 | 237 | 0.55 (0.45–0.68) |
| Sex | | | |
| Male | 334 | 166 | 0.56 (0.44–0.71) |
| Female | 142 | 71 | 0.54 (0.37–0.79) |
| Age at randomization | | | |
| <65 yr | 261 | 130 | 0.43 (0.32–0.57) |
| ≥65 yr | 215 | 107 | 0.74 (0.54–1.01) |
| Smoking status | | | |
| Smoker | 433 | 216 | 0.59 (0.47–0.73) |
| Nonsmoker | 43 | 21 | 0.29 (0.15–0.57) |
| NSCLC disease stage | | | |
| IIIA | 252 | 125 | 0.53 (0.40–0.71) |
| IIIB | 212 | 107 | 0.59 (0.44–0.80) |
| Tumor histologic type | | | |
| Squamous | 224 | 102 | 0.68 (0.50–0.92) |
| Nonsquamous | 252 | 135 | 0.45 (0.33–0.59) |
| Best response | | | |
| Complete response | 9 | 7 | — |
| Partial response | 232 | 111 | 0.55 (0.41–0.75) |
| Stable disease | 222 | 114 | 0.55 (0.41–0.74) |
| PD-L1 status | | | |
| ≥25% | 115 | 44 | 0.41 (0.26–0.65) |
| <25% | 187 | 105 | 0.59 (0.43–0.82) |
| Unknown | 174 | 88 | 0.59 (0.42–0.83) |
| *EGFR* mutation | | | |
| Positive | 29 | 14 | 0.76 (0.35–1.64) |
| Negative | 315 | 165 | 0.47 (0.36–0.60) |
| Unknown | 132 | 58 | 0.79 (0.52–1.20) |



**Figure 2. Subgroup Analysis of Prognostic Factors for Progression-free Survival in the Intention-to-Treat Population.**

Progression-free survival was defined according to RECIST, version 1.1, and assessed by means of blinded independent central review. The hazard ratio and 95% confidence interval were not calculated for the complete response because this subgroup had less than 20 events. EGFR denotes epidermal growth factor receptor, and PD-L1 programmed death ligand 1.

**Randomization to durvalumab or placebo within 14 days of completion of CRT: 0.39 (95% CI, 0.26-0.58) vs 0.63 (95% CI, 0.49-0.80) when randomized between 14-72 days**

# PACIFIC Trial – Adverse Events

- Grade 3 or 4 toxicity in 29.9% durvalumab and 26.1% placebo
  - Most common pneumonia
- Grade 5 in 4.4% durvalumab and 5.6% placebo
- Most frequent AEs leading to discontinuation of durvalumab and placebo were pneumonitis (6.3% vs 4.3%) and pneumonia (1.1% vs 1.3%)
- Durvalumab related toxicities (any grade): diarrhea (18.3% vs 18.8%), pneumonitis (12.6% vs 7.7%), rash (12.2% vs 7.3%) and pruritis (12.2% vs 7.7%)

# PACIFIC Trial – OS Results

- Updated Results including **OS** (published Dec 2018) comparing durvalumab vs placebo
- 2-yr OS 66.3% vs 55.6%; (HR 0.68, 0.47-0.997; p=0.0025)
- 30.5% vs 26.1% had G3-4 toxicity; 15.4% vs 9.8% discontinued the trial 2/2 toxicity

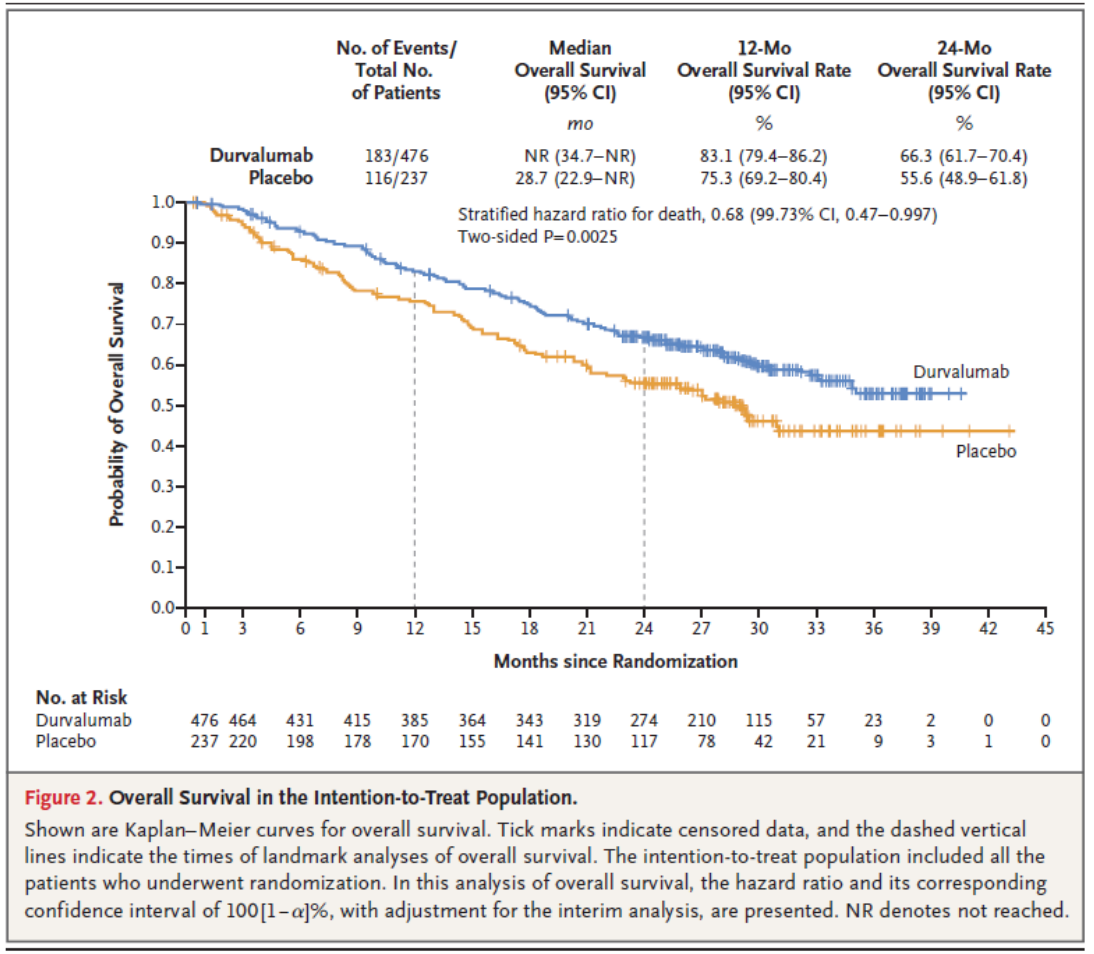



**Figure 2. Overall Survival in the Intention-to-Treat Population.**

Shown are Kaplan–Meier curves for overall survival. Tick marks indicate censored data, and the dashed vertical lines indicate the times of landmark analyses of overall survival. The intention-to-treat population included all the patients who underwent randomization. In this analysis of overall survival, the hazard ratio and its corresponding confidence interval of $100[1-\alpha]\%$, with adjustment for the interim analysis, are presented. NR denotes not reached.

Antonia et al. NEJM 2018 Dec; 379:2342-50.

# PACIFIC Trial – Time to Death or DM

- Time to death longer with durvalumab, 28.3 vs 16.2 mo
- Frequency of newer lesions reduced, 22.5% vs 33.8%
- Reduced new brain metastases, 6.3% vs 11.8%

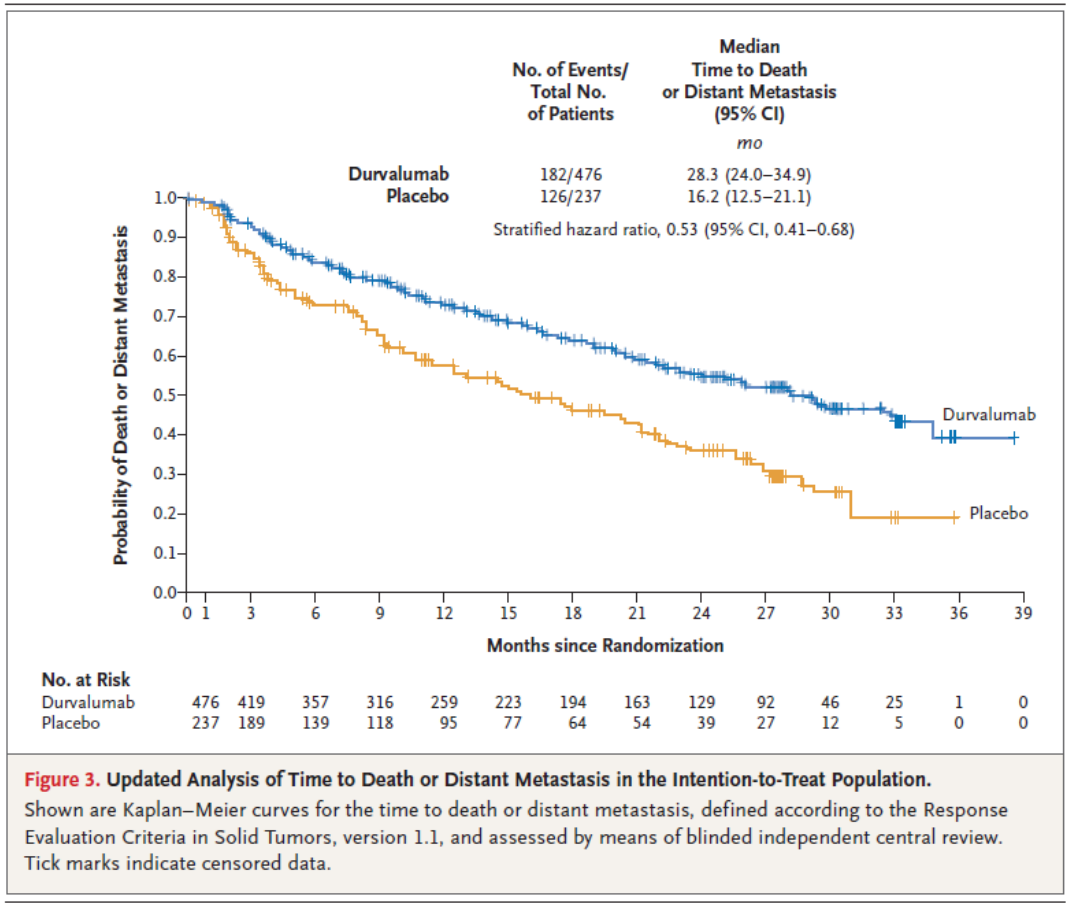
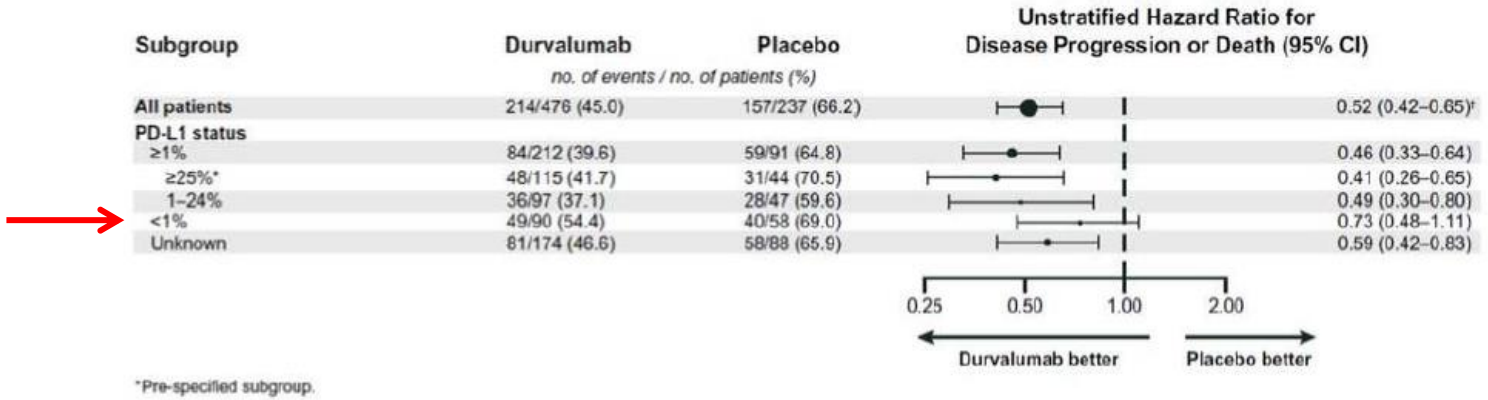



**Figure 3. Updated Analysis of Time to Death or Distant Metastasis in the Intention-to-Treat Population.**
Shown are Kaplan–Meier curves for the time to death or distant metastasis, defined according to the Response Evaluation Criteria in Solid Tumors, version 1.1, and assessed by means of blinded independent central review. Tick marks indicate censored data.

# PACIFIC Trial – Significance of PD-L1

PFS



| Subgroup | Durvalumab | Placebo | Unstratified Hazard Ratio for Disease Progression or Death (95% CI) |
|---|---|---|---|
| | *no. of events / no. of patients (%)* | | |
| **All patients** | 214/476 (45.0) | 157/237 (66.2) | 0.52 (0.42–0.65)† |
| **PD-L1 status** | | | |
| ≥1% | 84/212 (39.6) | 59/91 (64.8) | 0.46 (0.33–0.64) |
| ≥25%* | 48/115 (41.7) | 31/44 (70.5) | 0.41 (0.26–0.65) |
| 1–24% | 36/97 (37.1) | 28/47 (59.6) | 0.49 (0.30–0.80) |
| <1% | 49/90 (54.4) | 40/58 (69.0) | 0.73 (0.48–1.11) |
| Unknown | 81/174 (46.6) | 58/88 (65.9) | 0.59 (0.42–0.83) |

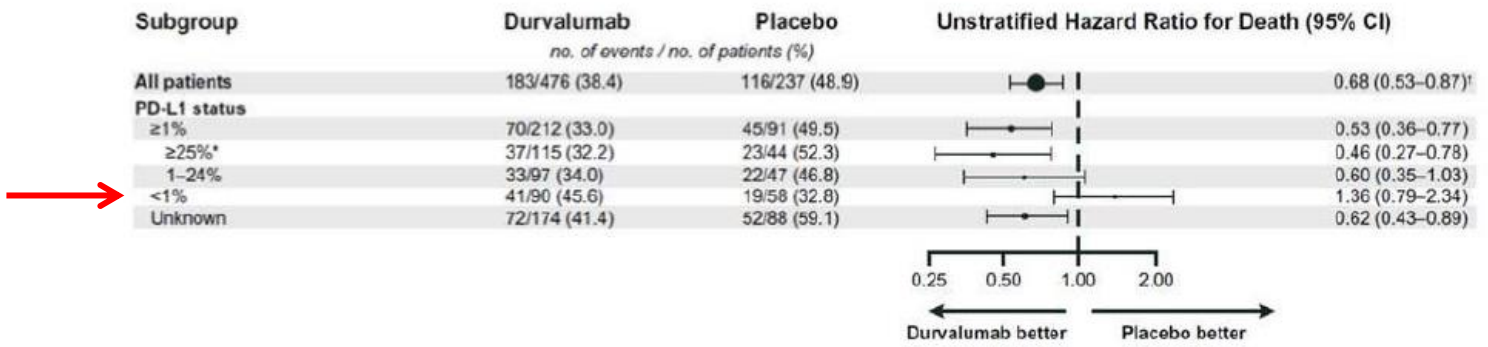


*Pre-specified subgroup.

†The hazard ratio and 95% CI for all patients were calculated using a stratified log-rank test adjusted for age at randomization (<65 vs. ≥65 years), sex (male vs female) and smoking history (smoker vs. non-smoker).

( C )

OS



| Subgroup | Durvalumab | Placebo | Unstratified Hazard Ratio for Death (95% CI) |
|---|---|---|---|
| | *no. of events / no. of patients (%)* | | |
| **All patients** | 183/476 (38.4) | 116/237 (48.9) | 0.68 (0.53–0.87)† |
| **PD-L1 status** | | | |
| ≥1% | 70/212 (33.0) | 45/91 (49.5) | 0.53 (0.36–0.77) |
| ≥25%* | 37/115 (32.2) | 23/44 (52.3) | 0.46 (0.27–0.78) |
| 1–24% | 33/97 (34.0) | 22/47 (46.8) | 0.60 (0.35–1.03) |
| <1% | 41/90 (45.6) | 19/58 (32.8) | 1.36 (0.79–2.34) |
| Unknown | 72/174 (41.4) | 52/88 (59.1) | 0.62 (0.43–0.89) |

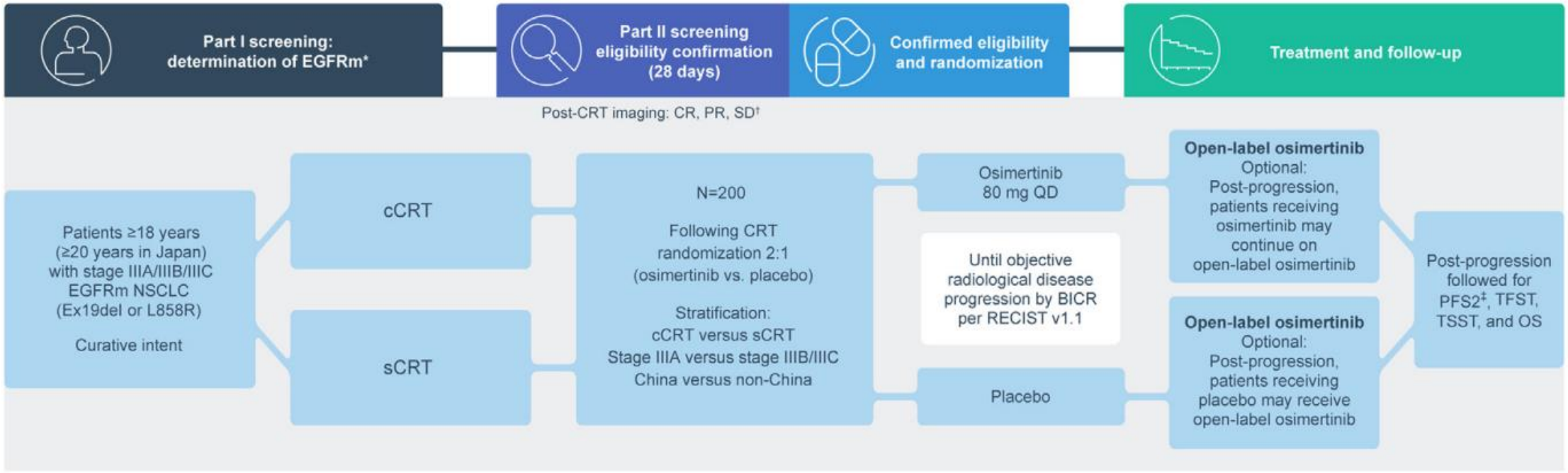


*Pre-specified subgroup.

# Current and Future Points of Discussion

- Role of concurrent ICI with radiation treatment
- Dose of radiation: >60 Gy?, hypofractionation?
- How do we interpret data from ICI -> surgery trials or surgery + TKI when compared to CRT/ICI?
- Duration of ICI? Which ICI?
- ? of maintenance therapy selection after CRT for actionable mutation (EGFR/ALK) patients?

# LAURA Trial


Part I screening: determination of EGFRm*
Part II screening eligibility confirmation (28 days)
Confirmed eligibility and randomization
Treatment and follow-up
Post-CRT imaging: CR, PR, SD†
Patients ≥18 years (≥20 years in Japan) with stage IIIA/IIIB/IIIC EGFRm NSCLC (Ex19del or L858R)
Curative intent
cCRT
sCRT
N=200
Following CRT randomization 2:1 (osimertinib vs. placebo)
Stratification:
cCRT versus sCRT
Stage IIIA versus stage IIIB/IIIC
China versus non-China
Osimertinib 80 mg QD
Until objective radiological disease progression by BICR per RECIST v1.1
Placebo
Open-label osimertinib
Optional:
Post-progression, patients receiving osimertinib may continue on open-label osimertinib
Open-label osimertinib
Optional:
Post-progression, patients receiving placebo may receive open-label osimertinib
Post-progression followed for PFS2‡, TFST, TSST, and OS

# PACIFIC-2

- Phase 3 study of concurrent durvalumab and platinum-based chemoradiotherapy in patients with unresectable, stage III NSCLC
- 300 pts with unresectable stage III NSCLC will be randomized (2:1) to receive either durvalumab (intravenous 1500 mg) every 4 weeks (q4w) + cCRT, or placebo q4w + cCRT
- Primary endpoints are PFS and ORR

# NRG LU-004

| Cohort 1, n=6<br>MEDI4736 (durvalumab)[†] **q4 weeks** x 13 doses<br>+ ACRT 60 Gy in 15 fractions x 3 weeks (weeks 1-3) |
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| Cohort 2, n=6<br>MEDI4736 (durvalumab)[†] **q4 weeks** x 13 doses<br>+ standard RT 60 Gy in 30 fractions x 6 weeks (weeks 1-6) |
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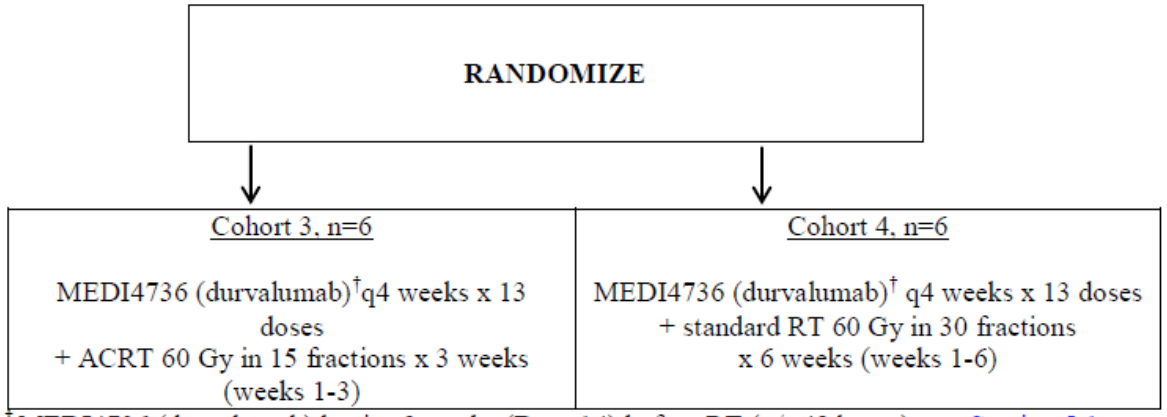
[†] MEDI4736 (durvalumab) begins 2 weeks (Day -14) before RT (+/- 48 hours); see Section 5.1 for dosing details

**EXPANSION COHORTS**

**After completing one of the Initial Safety Schedules of concurrent RT+MEDI4736 (durvalumab):**

- If Cohort 1 only is deemed safe, all patients will be registered to Cohort 3.
- If Cohort 2 only is deemed safe, all patients will be registered to Cohort 4.
- **If both Cohorts 1 and 2 are deemed safe, patients will be randomized to either Cohort 3 or Cohort 4 with 1:1 randomization.**




[†] MEDI4736 (durvalumab) begins 2 weeks (Day -14) before RT (+/- 48 hours); see Section 5.1 for dosing details