# Novel Treatment Strategies for Stage III NSCLC Beyond PACIFIC


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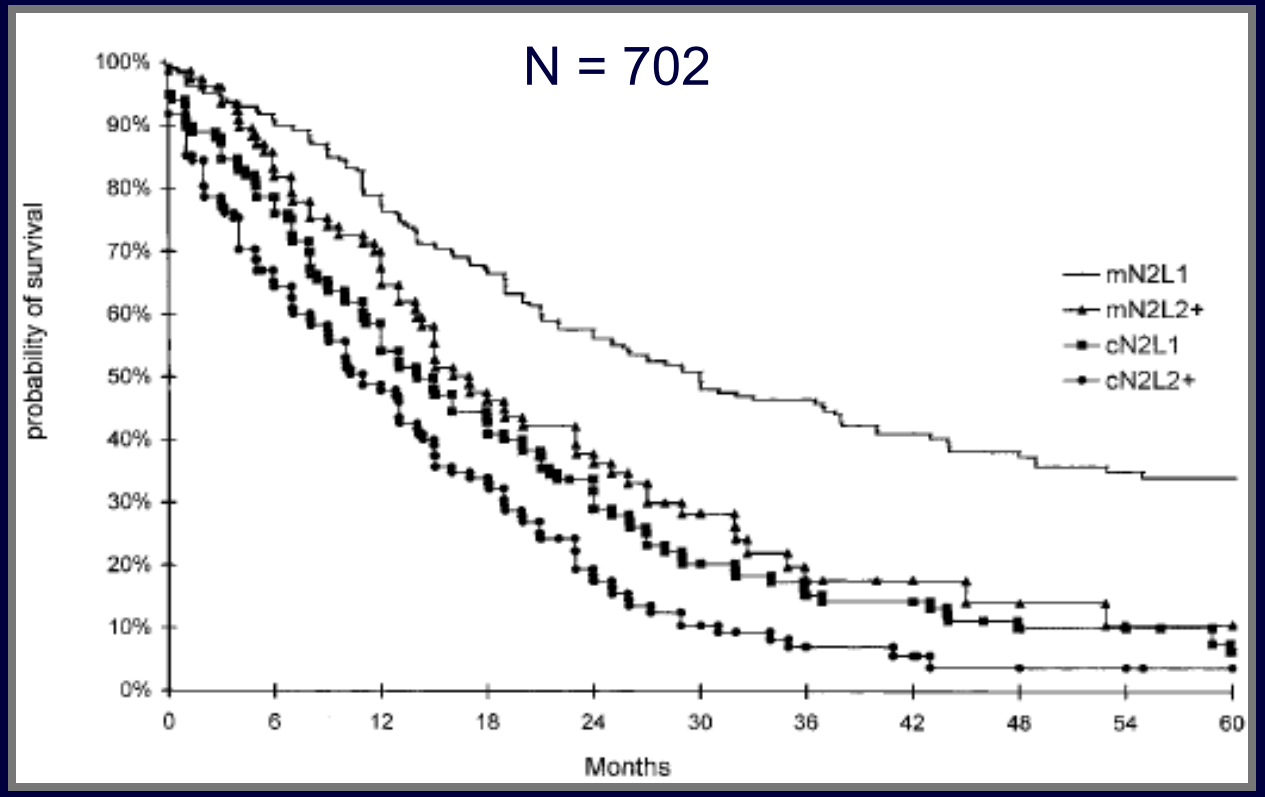
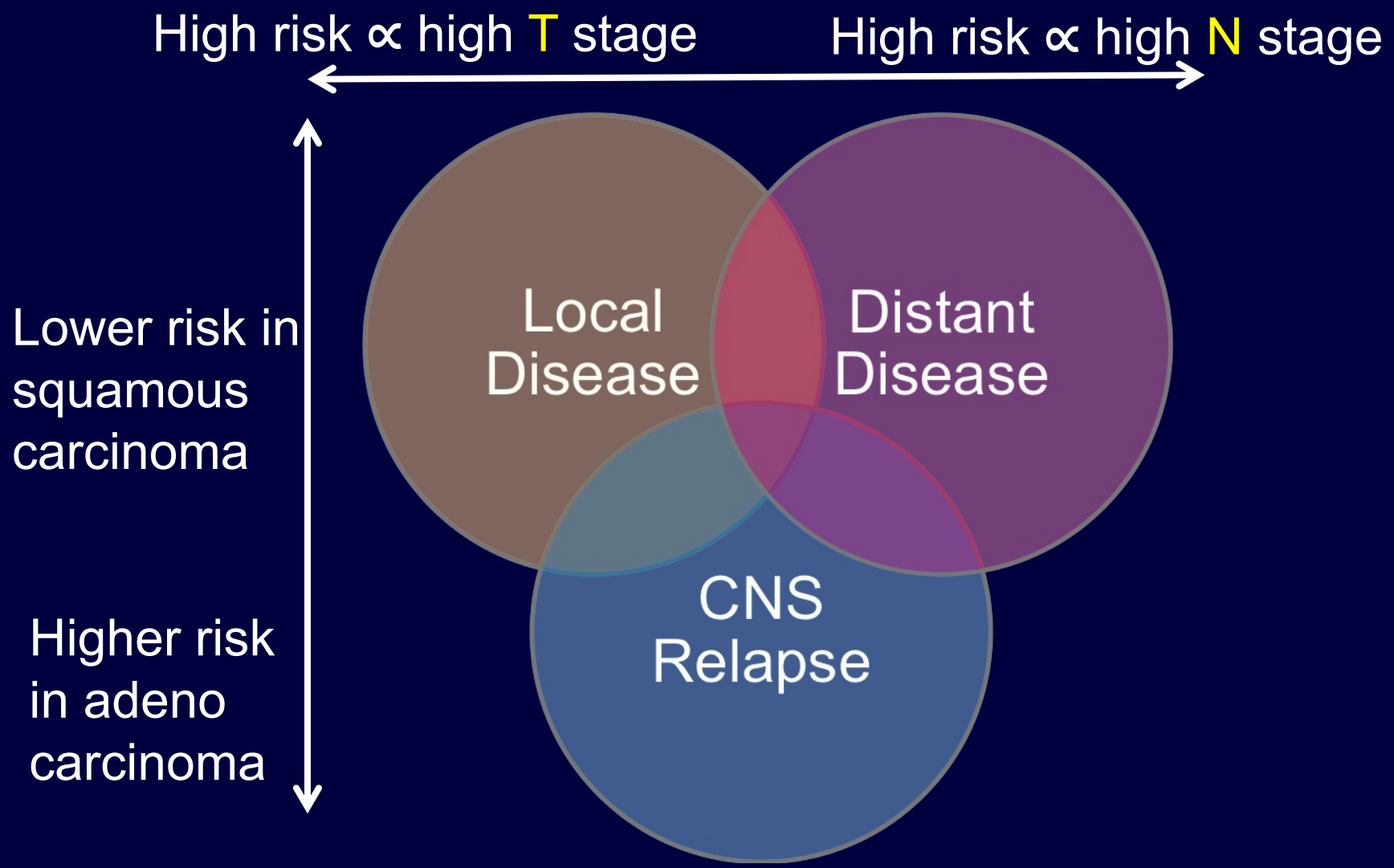
# Heterogeneity within the Stage IIIA N2 LN-Positive Population

Andre, J Clin Oncol 2000

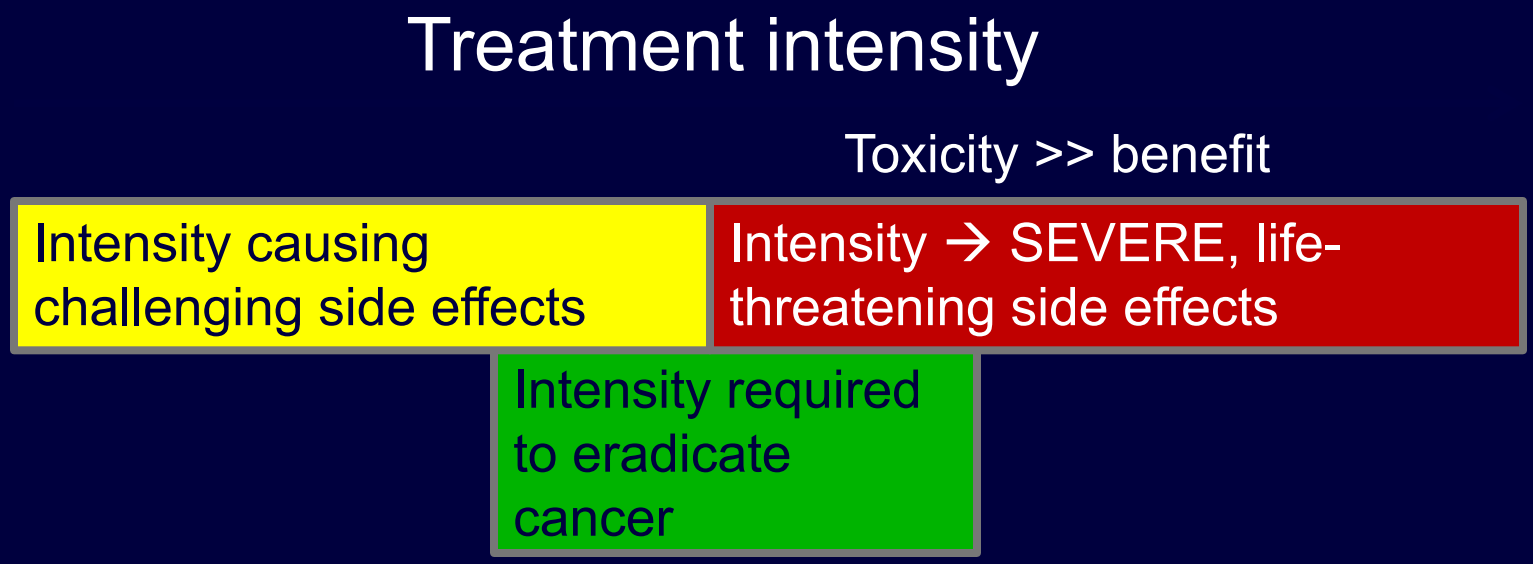



- Huge range of prognosis within stage IIIA N2
- Is optimal treatment really same for microscopic, enlarged, and bulky LNs? Single node and multi-station?

# Spectra of Risk in Locally Advanced NSCLC



# The Challenging Therapeutic Window of Locally Advanced NSCLC




Narrow window of treatment intensity sufficient to eradicate cancer within the range of what is tolerable

Some patients far more able to tolerate than others

# Attempts to Improve on Concurrent Chemoradiation over ~2 Decades

| Escalated Variable | Impact | Reference |
|---|---|---|
| Add consolidation chemo | Higher tox, no better efficacy | Hanna, JCO 2008 |
| Add consolidation gefitinib | Significant detrimental impact on OS (med OS 12 mo lower w/gefitinib vs. placebo) | Kelly, JCO 2008 |
| Substitute newer chemo (cis/pemetrexed w/RT & after) | No improvement in efficacy or tolerability vs. established standards | Senan, JCO 2015 |
| Increase radiation dose to 74 Gy | Significant detrimental effect (med OS 8.4 mo worse w/74 Gy vs. 60 Gy) | Bradley, Lancet Oncol 2015 |
| Add cetuximab to chemo/RT | No efficacy benefit, increased toxicity | Bradley, Lancet Oncol 2015 |

More is worse, not better, if that therapy is

- Ineffective against that cancer
- Less effective than it is toxic to the patient

# PACIFIC: Consolidation Durvalumab After Concurrent CT/RT for Unresectable St 3 NSCLC

Stage III Unresectable NSCLC s/p chemo/RT N = 713

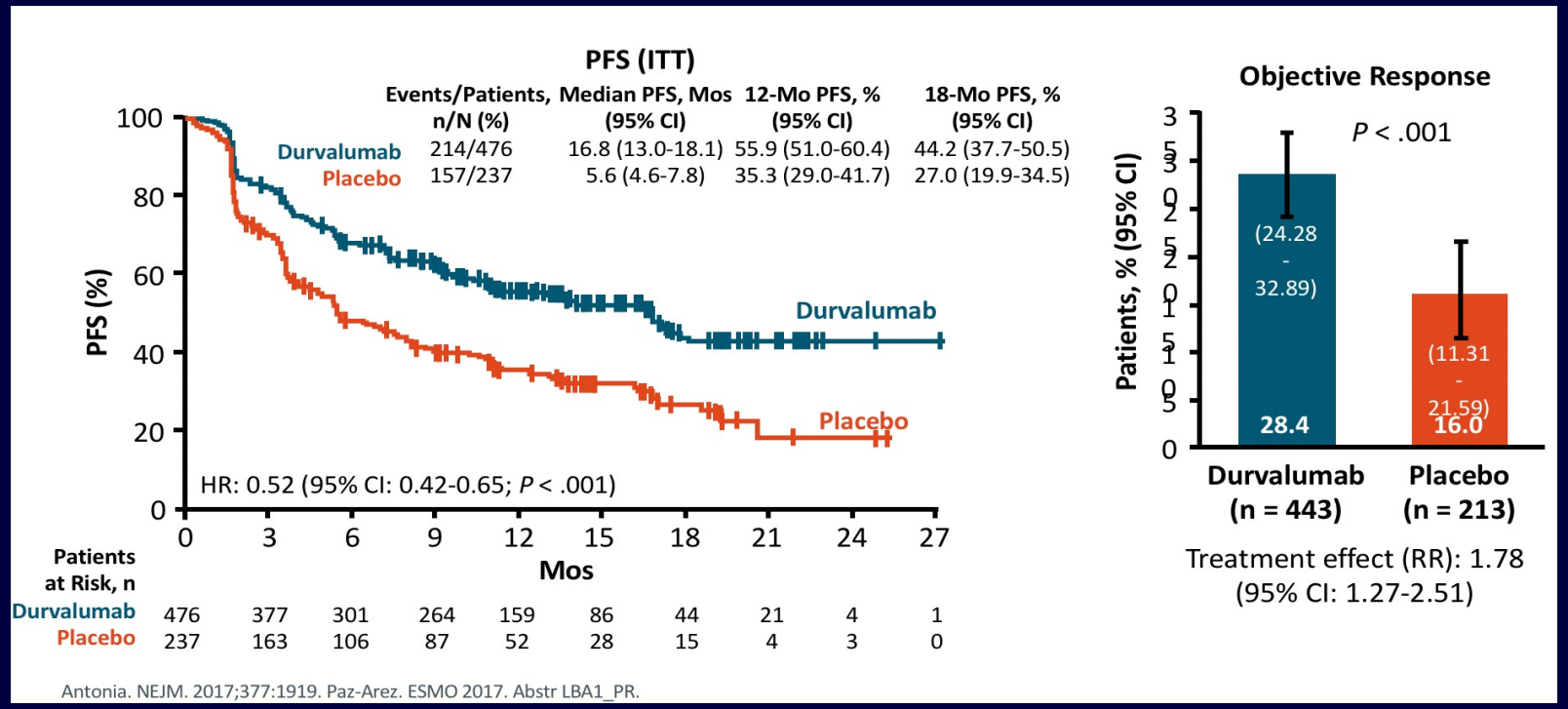
If no PD

RAND

Durvalumab every 2 weeks x 1 year

Placebo every 2 weeks x 1 year

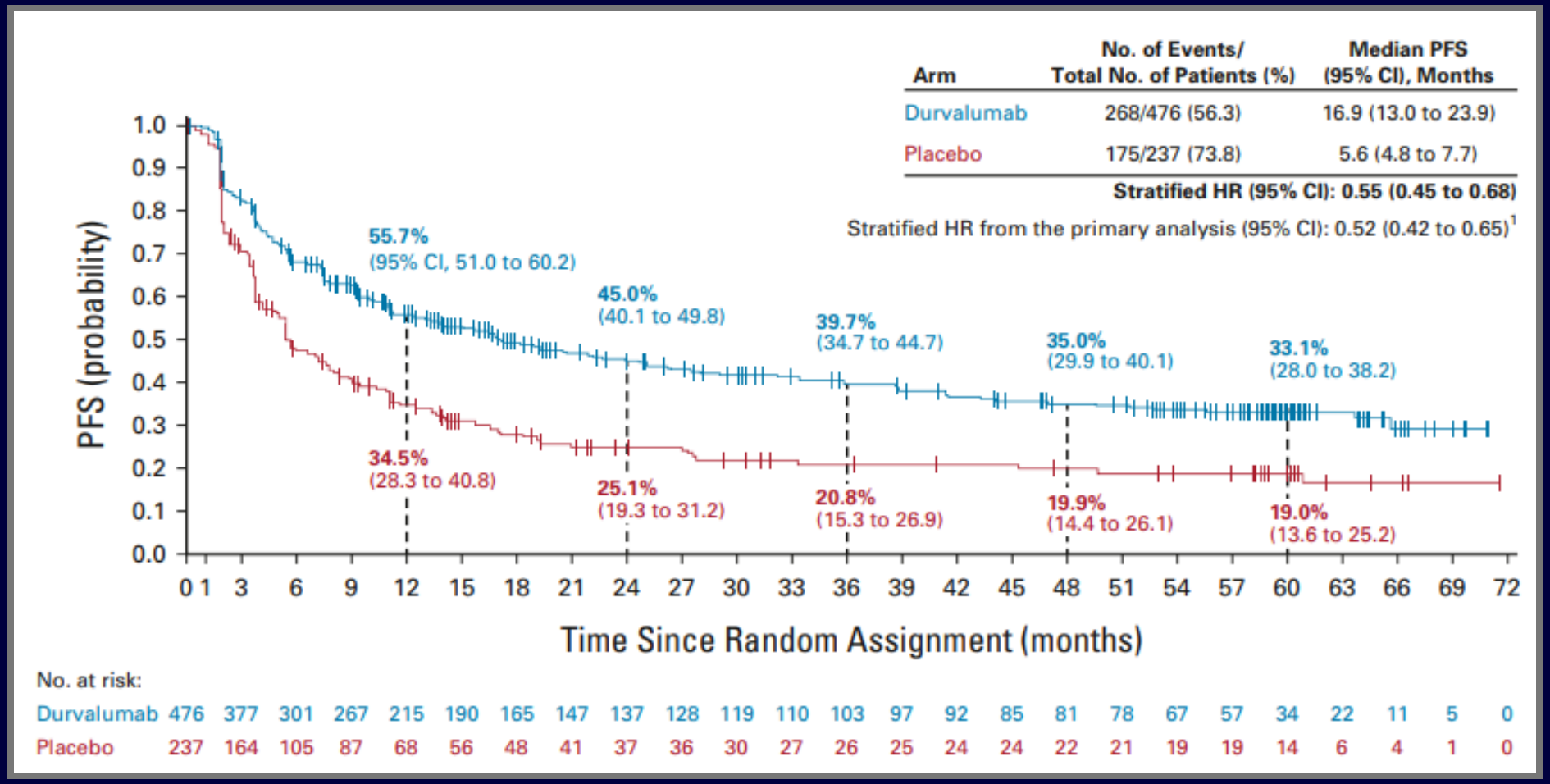
Follow for PD, OS




Antonia. NEJM. 2017;377:1919. Paz-Arez. ESMO 2017. Abstr LBA1_PR.

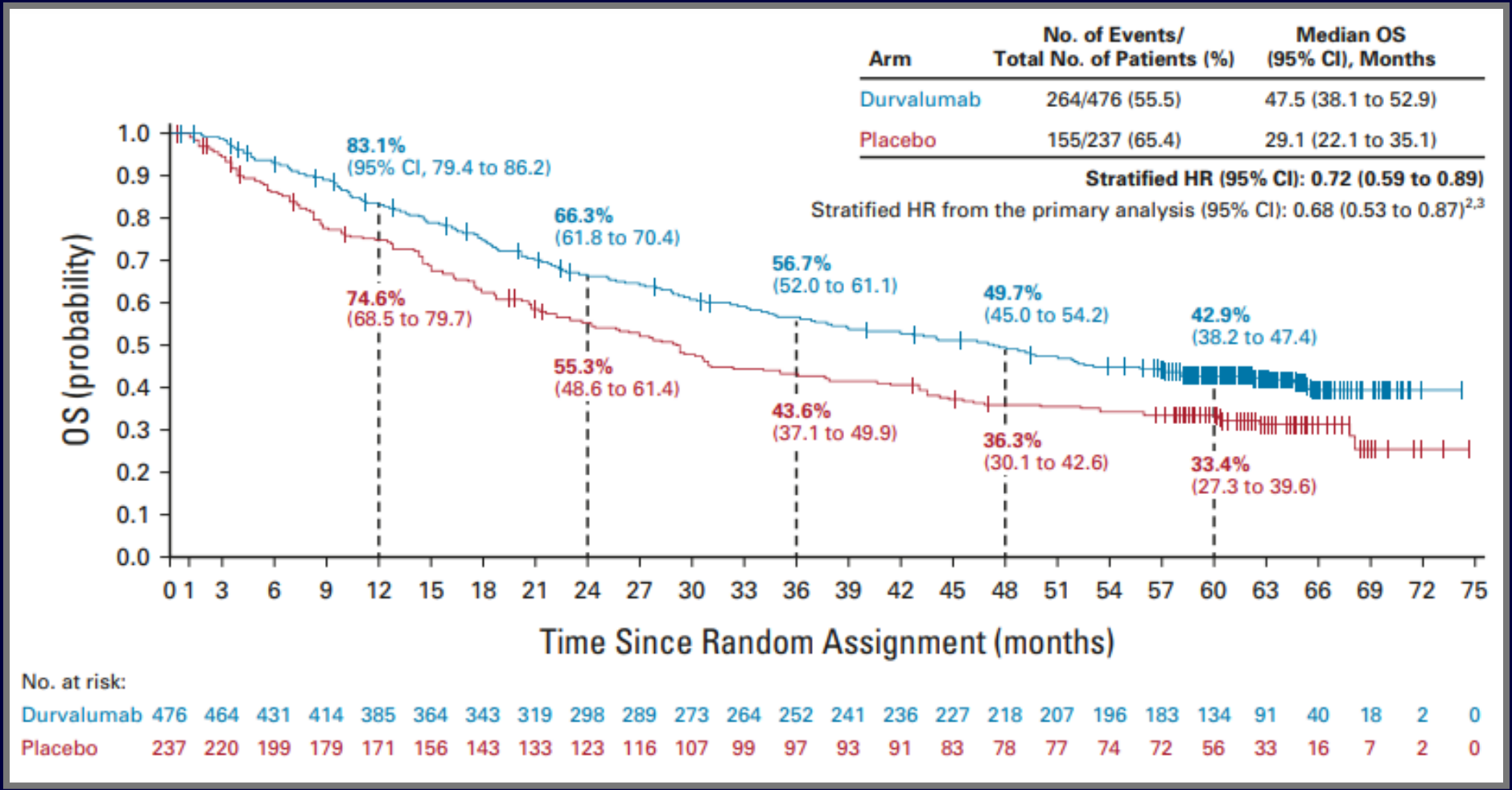
Antonia, NEJM 2017

# PACIFIC: 5-Year PFS Outcomes



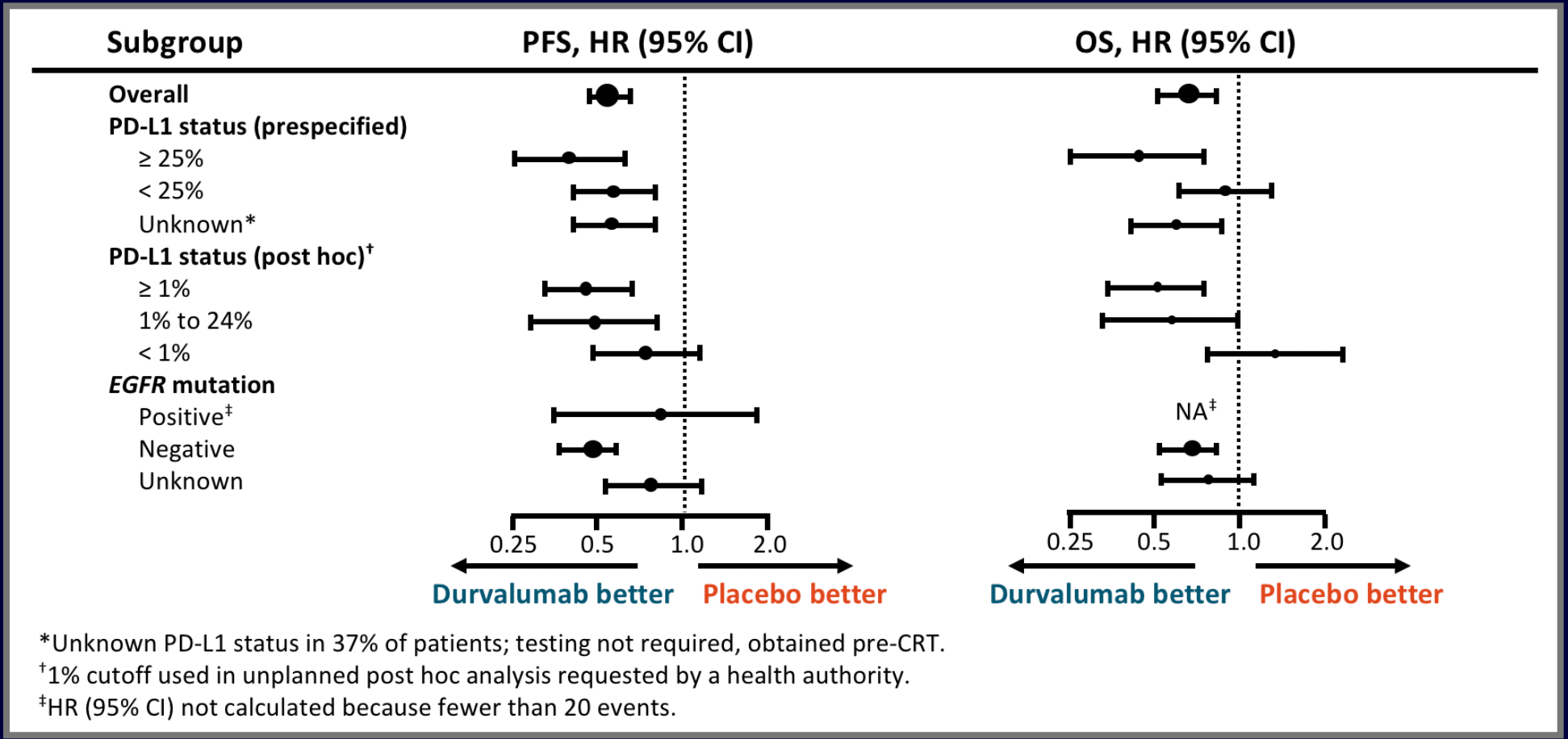

Spigel, J Clin Oncol 2022

# PACIFIC: 5-Year OS Outcomes




Spigel, J Clin Oncol 2022

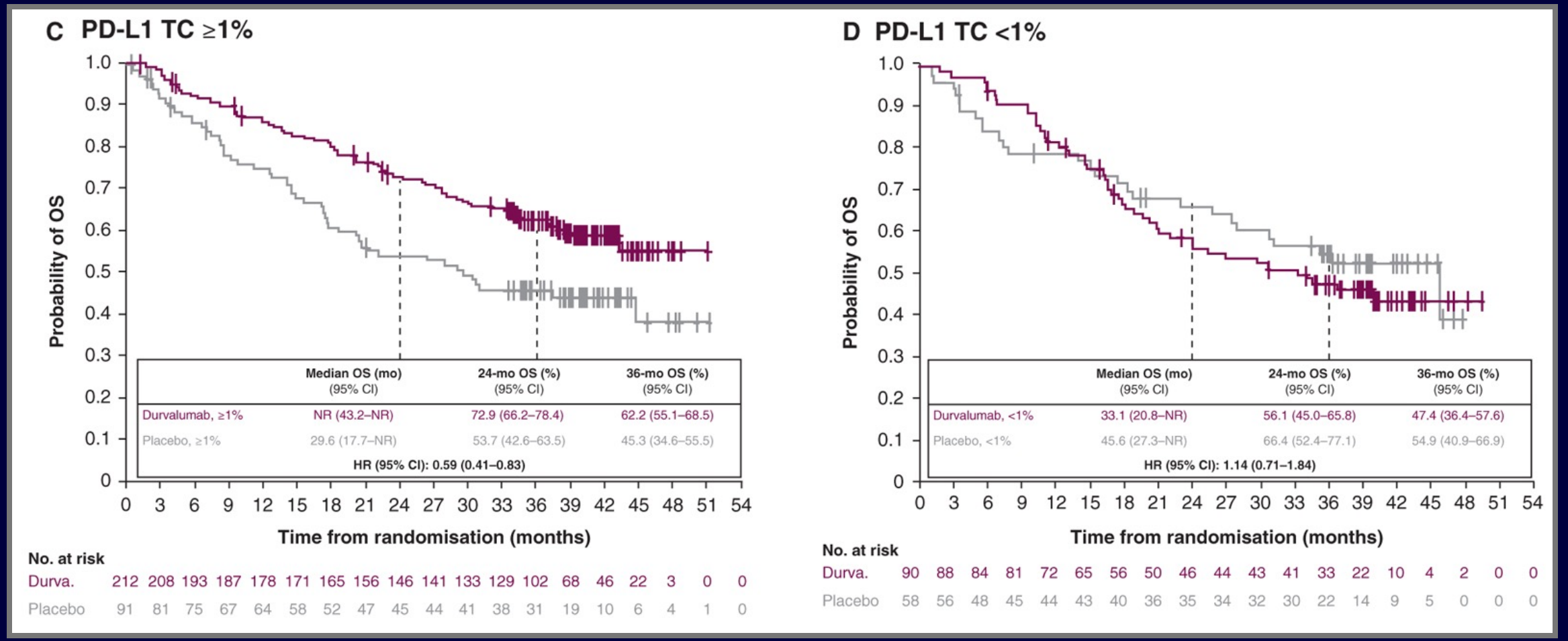
# PACIFIC: Clinical Outcomes in Subgroups




*Unknown PD-L1 status in 37% of patients; testing not required, obtained pre-CRT.
†1% cutoff used in unplanned post hoc analysis requested by a health authority.
‡HR (95% CI) not calculated because fewer than 20 events.

Antonia, NEJM 2018

# PACIFIC: No Benefit in Patients with PD-L1 <1% (Post-Hoc Analysis)

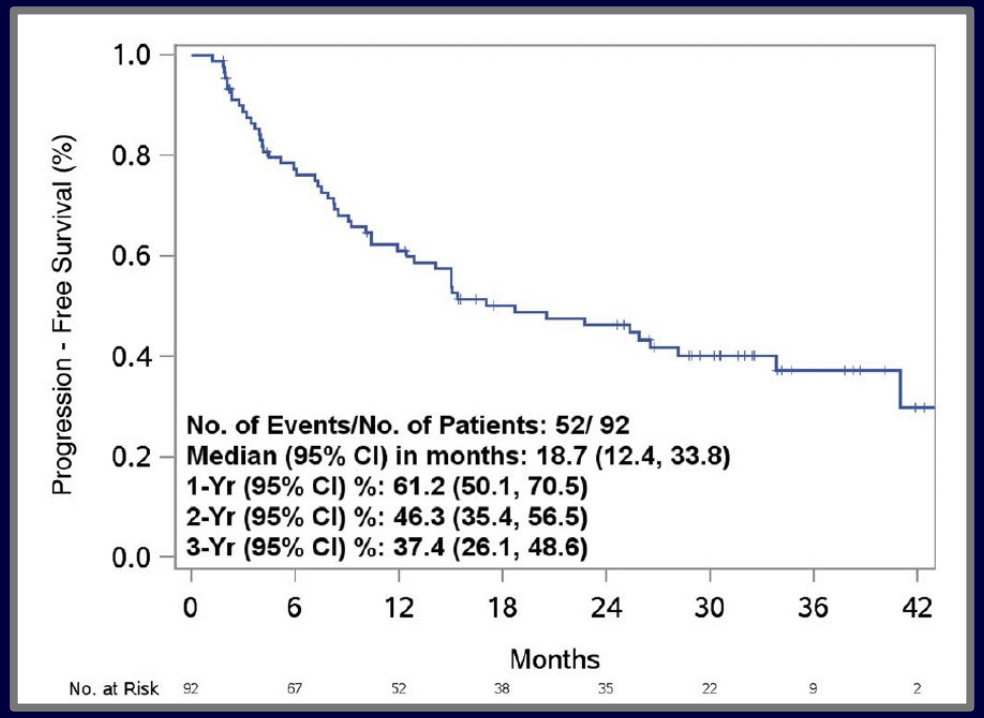



Paz-Ares, Ann Oncol 2020

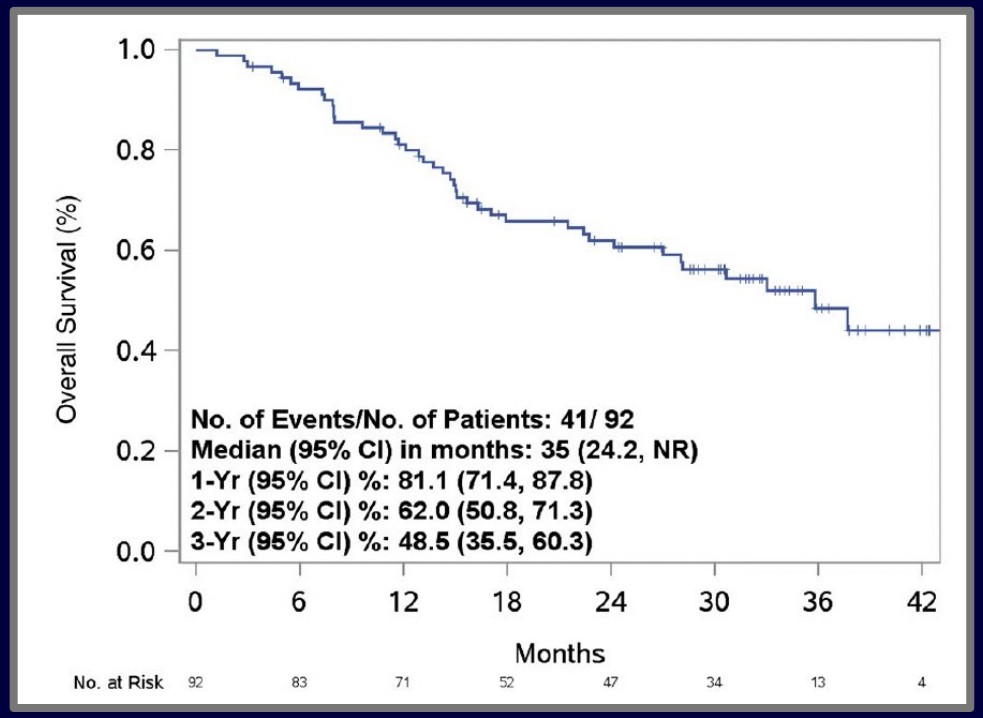
# Substitution of Consolidation Pembro for Durvalumab

- N = 93, single arm trial, chemo/radiation → pembro q3 week x 1 year

Progression-Free Survival



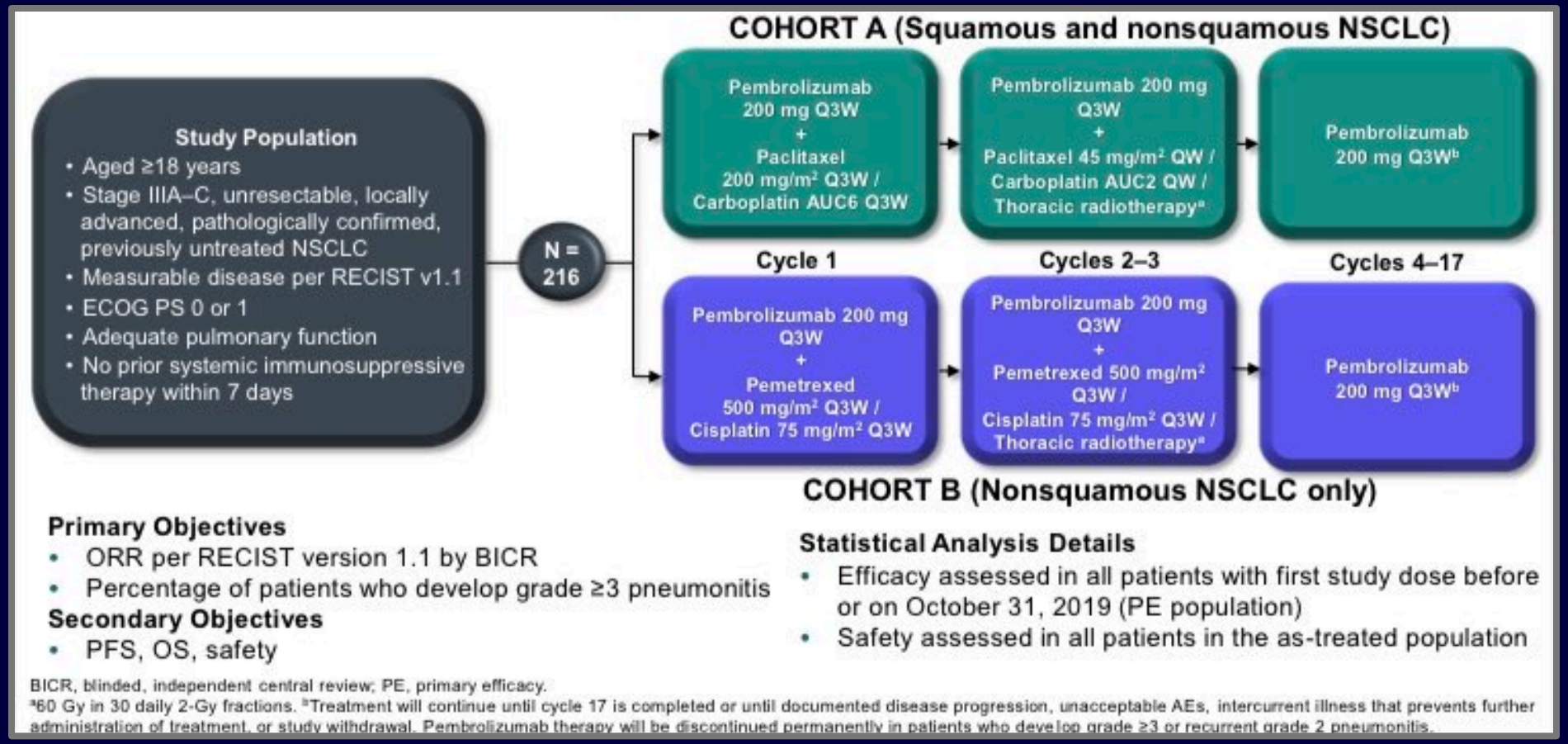

Overall Survival




- These results are not better than phase 3 PACIFIC, FDA-approved standard of care

Durm, Cancer 2020

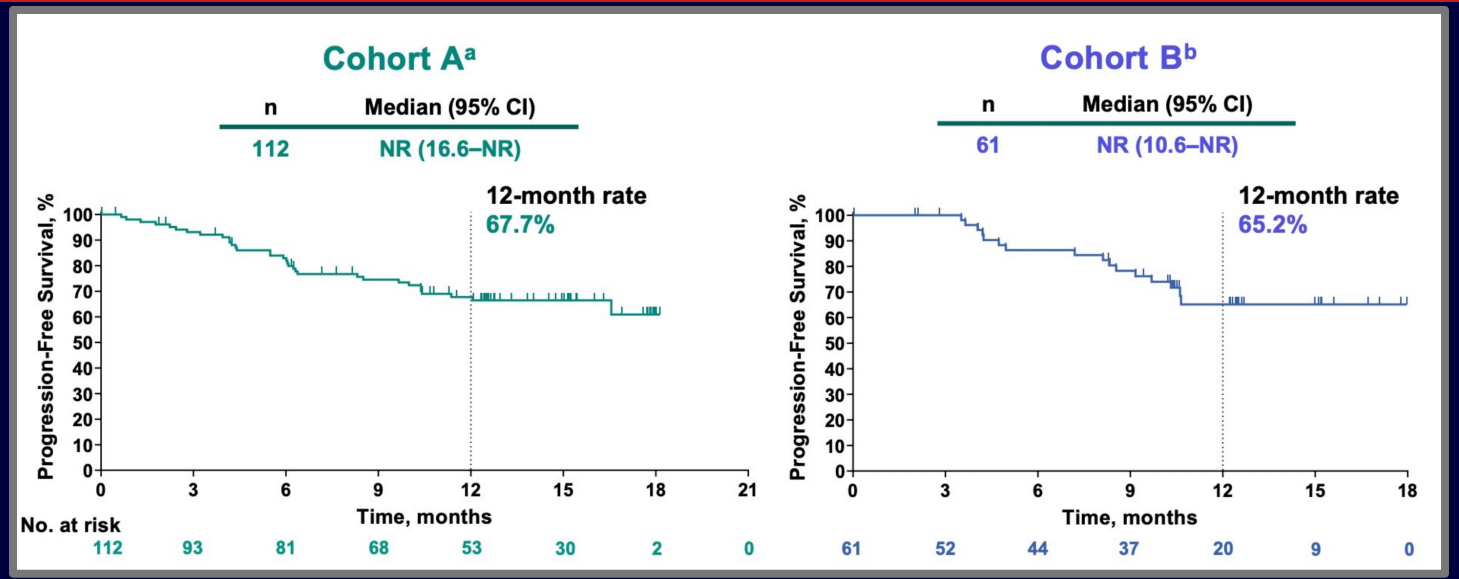
# Introducing Immunotherapy with Chemo/Radiation: KEYNOTE-799



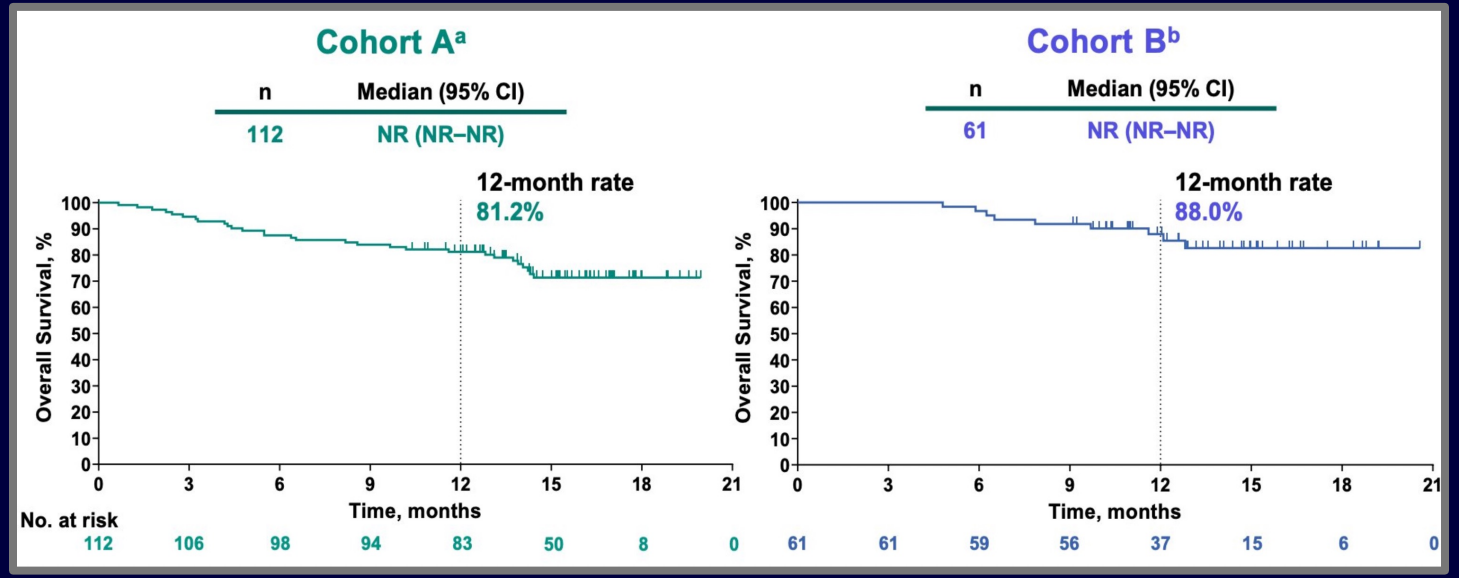

Reck, WCLC 2020
Jabbour, JAMA Oncol 2021

# KEYNOTE-799: Progression-Free and Overall Survival

Progression-Free Survival




Overall Survival




Reck, WCLC 2020
Jabbour, JAMA Oncol 2021

# KEYNOTE-799; Incidence of Grade >3 Pneumonitis/Safety

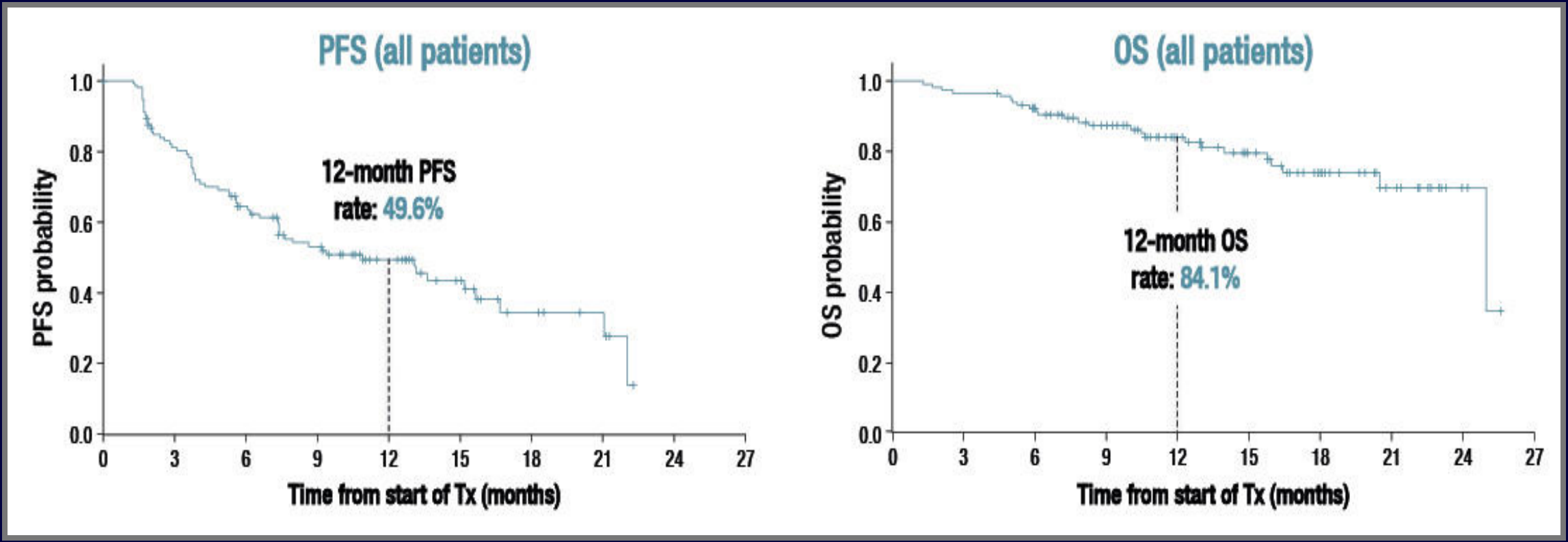
| | Cohort A[a] (n = 112) | Cohort B[b] (n = 101) |
|---|---|---|
| **Grade ≥3 pneumonitis (all cause),[c,d] n (%) [95% CI]** | **9 (8.0) [3.7–14.7]** | **8 (7.9) [3.5–15.0]** |
| Treatment-related AEs, n (%) | 105 (93.8) | 96 (95.0) |
| Grades 3–5 | 72 (64.3) | 47 (46.5) |
| Led to death | 4[c] (3.6) | 1 (1.0) |
| Led to discontinuation of any treatment component | 38 (33.9) | 16 (15.8) |
| Discontinued pembrolizumab | 27 (24.1) | 15 (14.9) |
| Discontinued radiotherapy | 2 (1.8) | 0 |
| Discontinued any chemotherapy | 18 (16.1) | 3 (3.0) |
| Immune-mediated AEs and infusion reactions, n (%) | 59 (52.7) | 36 (35.6) |
| Grades 3–5 | 18 (16.1) | 10 (9.9) |
| Led to death[d] | 4 (3.6) | 1 (1.0) |

[a]Squamous and nonsquamous. [b]Nonsquamous only. [c]Includes immune-mediated AE of "pneumonitis" and the MedDRA preferred term of "radiation pneumonitis". [d]Includes 4 patients (3.6%) with grade 5 pneumonitis in cohort A and 1 patient (1.0%) with grade 5 interstitial lung disease in cohort B. These events were classified as both treatment-related events and under immune-mediated AEs and infusion reactions.
Data cutoff date: July 30, 2020.

Reck, WCLC 2020
Jabbour, JAMA Oncol 2021

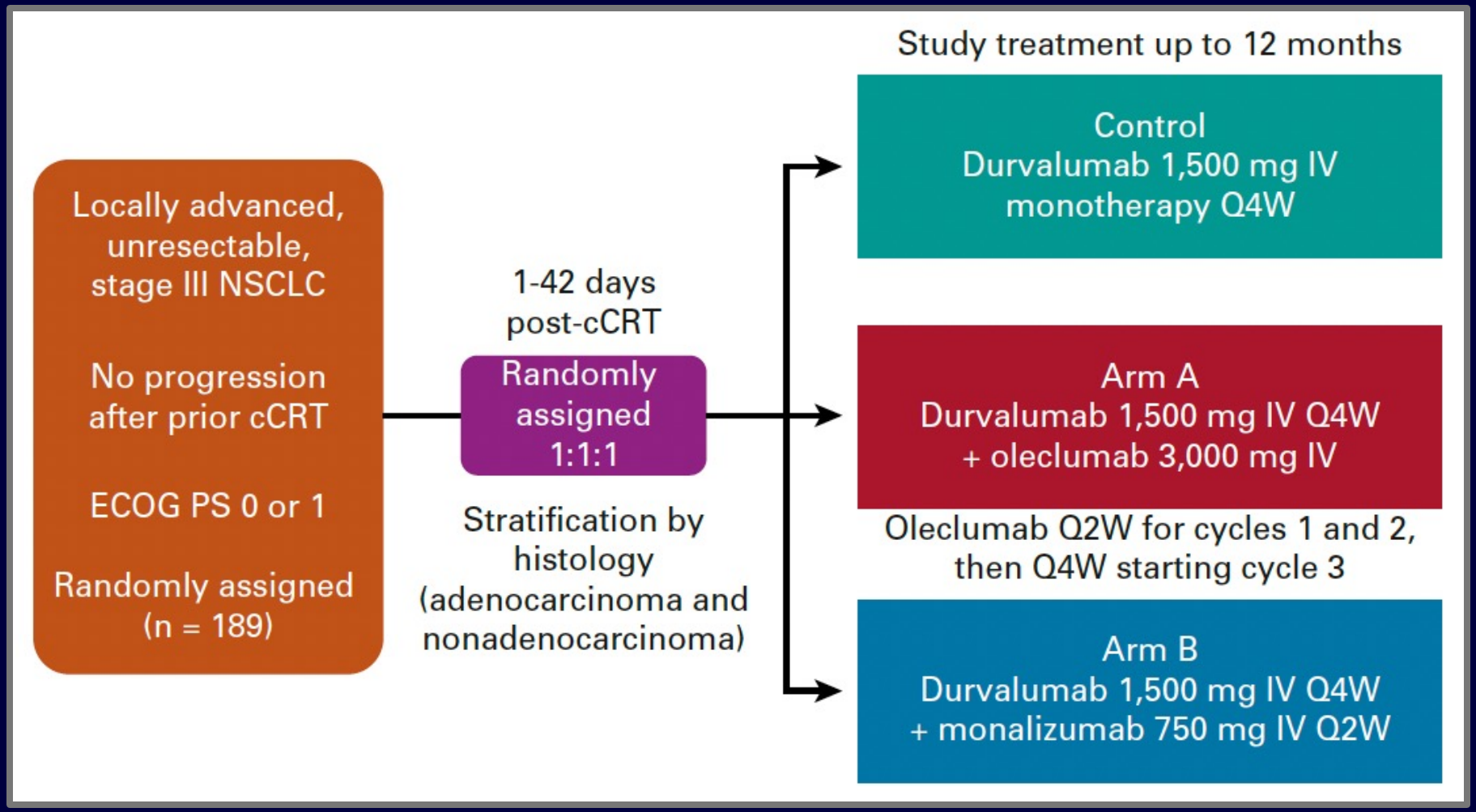
# PACIFIC-6: Durvalumab after Sequential Chemo/Radiation: Efficacy

N = 117, PS 0-2




Garassino, ELCC 2022 A#108

# COAST: Adding to Consolidation Durvalumab



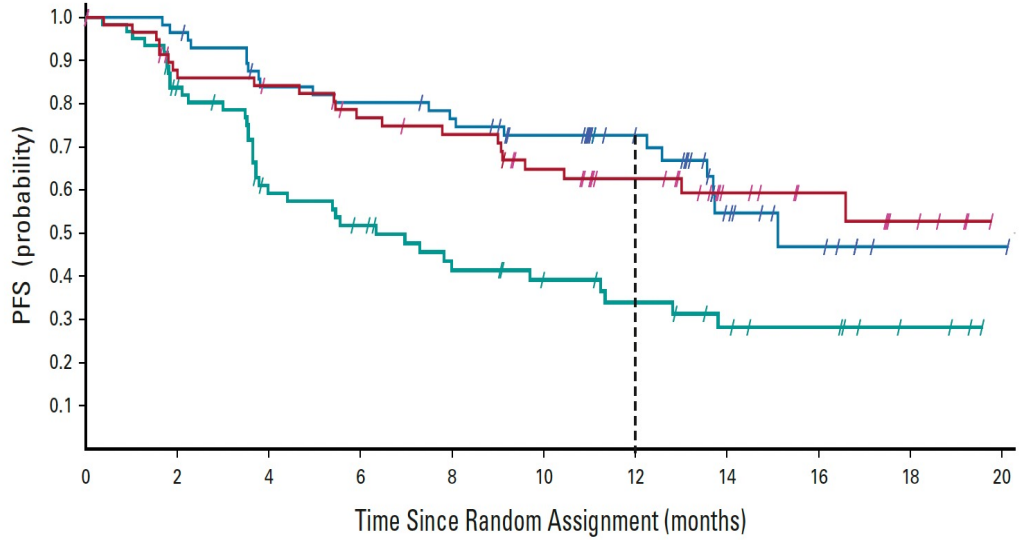

Anti-CD-73 moAb

Anti-NKG2A moAb

Herbst, J Clin Oncol 2022

# COAST: Progression-free Survival of 3 Arms

| Treatment Arm | No. of Events/ Total No. of Patients (%) | Median PFS, Months (95% CI)[a] | 12-Month PFS Rate, % (95% CI) | HR, % (95% CI)[b,c] |
|---|---|---|---|---|
| Durvalumab + monalizumab | 21/62 (33.9) | 15.1 (13.6 to NE) | 72.7 (58.8 to 82.6) | 0.42 (0.24 to 0.72) |
| Durvalumab + oleclumab | 22/60 (36.7) | NR (10.4 to NE) | 62.6 (48.1 to 74.2) | 0.44 (0.26 to 0.75) |
| Durvalumab | 38/67 (56.7) | 6.3 (3.7 to 11.2) | 33.9 (21.2 to 47.1) | – |




No. at risk:

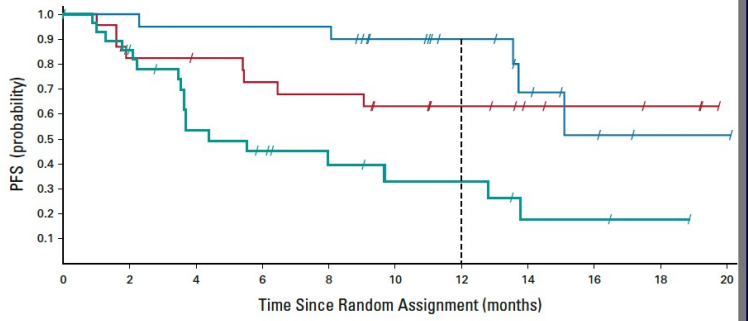
| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Durvalumab + monalizumab | 62 | 55 | 46 | 44 | 41 | 35 | 25 | 11 | 6 | 1 | 1 |
| Durvalumab + oleclumab | 60 | 49 | 46 | 40 | 37 | 30 | 22 | 13 | 9 | 5 | 0 |
| Durvalumab | 67 | 50 | 32 | 27 | 20 | 16 | 13 | 9 | 7 | 3 | 0 |

- Underperformance of control arm vs. PACIFIC

Herbst, J Clin Oncol 2022

**A** PD-L1 TC ≥ 1%

| Treatment Arm | No. of Events/ Total No. of Patients (%) | Median PFS, Months (95% CI)[a] | 12-Month PFS Rate, % (95% CI) | HR, % (95% CI)[b] |
|---|---|---|---|---|
| Durvalumab + monalizumab | 5/20 (25.0) | NR (13.6 to NE) | 90.0 (65.6 to 97.4) | 0.19 (0.07 to 0.54) |
| Durvalumab + oleclumab | 8/23 (34.8) | NR (5.5 to NE) | 63.0 (39.3 to 79.6) | 0.40 (0.17 to 0.94) |
| Durvalumab | 18/30 (60.0) | 4.4 (3.5 to 12.8) | 32.9 (14.4 to 52.9) | — |

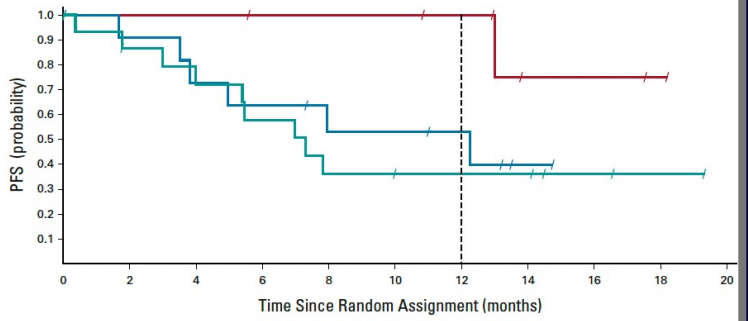



No. at risk:

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Durvalumab + monalizumab | 20 | 20 | 19 | 19 | 19 | 14 | 10 | 6 | 3 | 1 | 1 |
| Durvalumab + oleclumab | 23 | 18 | 17 | 15 | 14 | 11 | 8 | 5 | 4 | 3 | 0 |
| Durvalumab | 30 | 23 | 13 | 10 | 7 | 5 | 5 | 2 | 2 | 1 | 0 |

**B** PD-L1 TC < 1%

| Treatment Arm | No. of Events/ Total No. of Patients (%) | Median PFS, Months (95% CI)[a] | 12-Month PFS Rate, % (95% CI) | HR, % (95% CI)[b] |
|---|---|---|---|---|
| Durvalumab + monalizumab | 6/12 (50.0) | 12.3 (3.5 to NE) | 53.0 (20.9 to 77.3) | 0.87 (0.31 to 2.48) |
| Durvalumab + oleclumab | 1/7 (14.3) | NR (13.0 to NE) | 100.0 (100.0 to 100.0) | NE |
| Durvalumab | 9/16 (56.3) | 7.3 (3.0 to NE) | 36.1 (13.2 to 59.9) | — |




No. at risk:

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Durvalumab + monalizumab | 12 | 10 | 8 | 7 | 5 | 5 | 4 | 1 | 0 | 0 | 0 |
| Durvalumab + oleclumab | 7 | 7 | 7 | 6 | 6 | 6 | 5 | 2 | 2 | 1 | 0 |
| Durvalumab | 16 | 12 | 10 | 8 | 5 | 4 | 4 | 4 | 2 | 1 | 0 |

# Consolidation Nivo vs. Nivo/Ipi After Chemo/Radiation

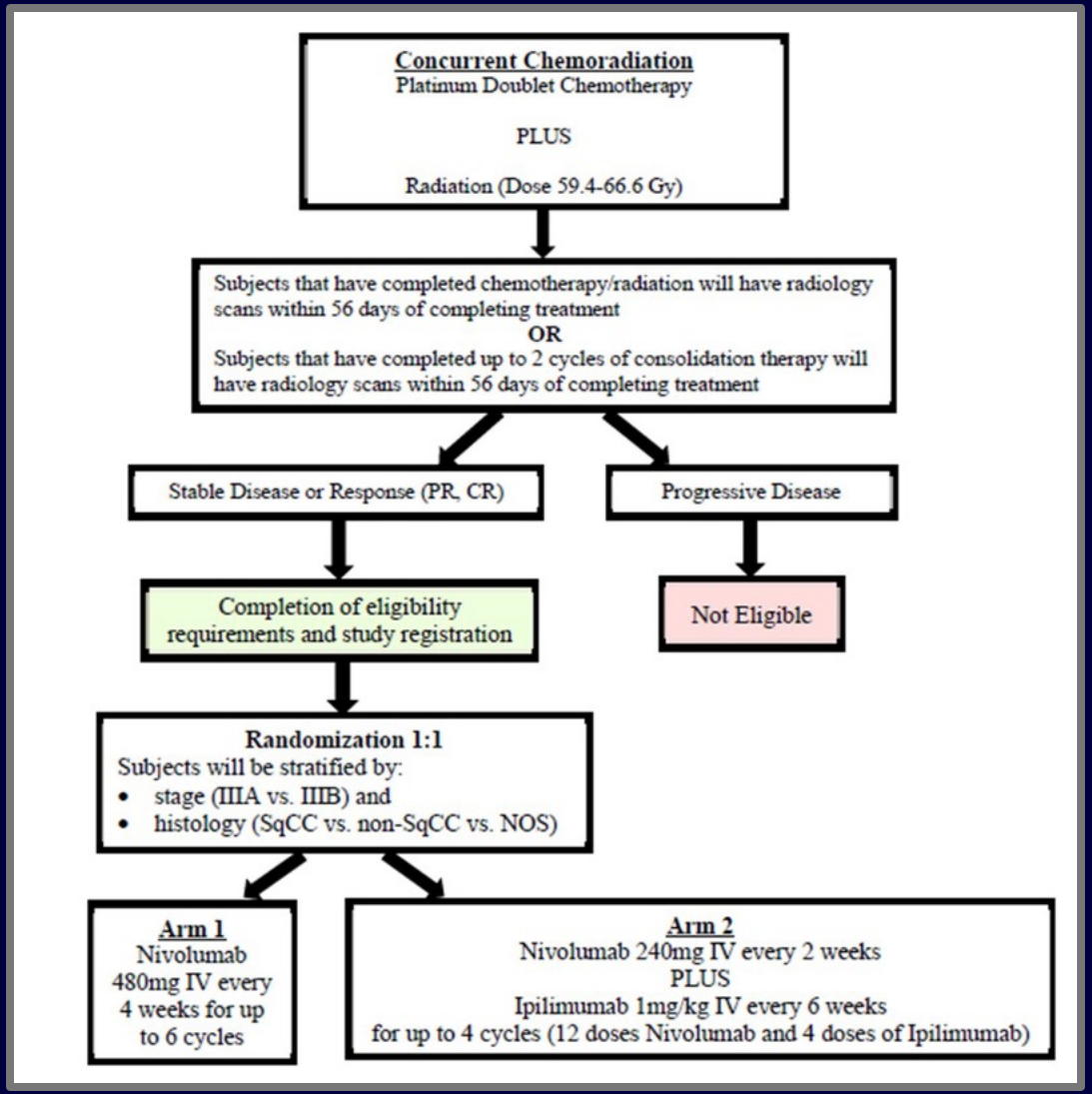
Patients enrolled after completion of cCRT

No progression

N = 105 randomized 1:1

6 months of therapy in each arm

Durm, ASCO 2022, #8509



# Consolidation Nivo or Nivo/Ipi after cCRT: Toxicity

More toxicities with consolidation nivo/ipi

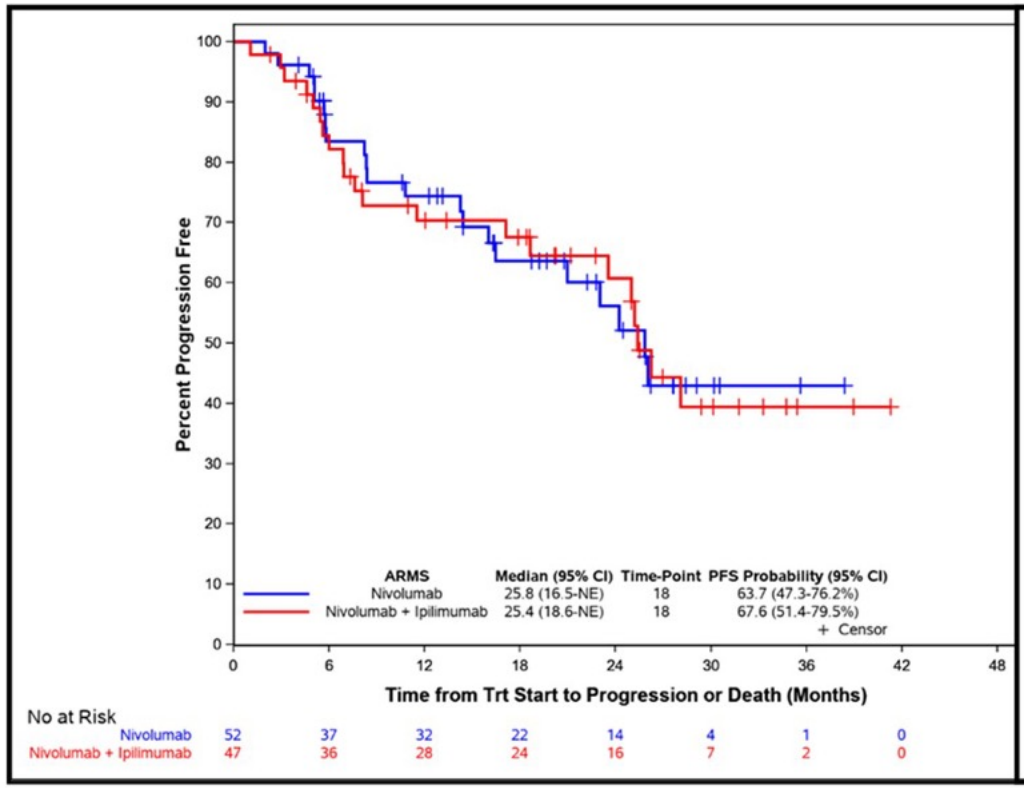
Greater dyspnea, diarrhea, pruritis, arthralgia, nausea, and pneumonitis with nivo/ipi

| | Nivolumab Alone (N=54) | Nivolumab/Ipilimumab (N=51) |
|---|---|---|
| Any Treatment-Related AE (TRAE), n (%) | 39 (72.2) | 41 (80.4) |
| Any Grade ≥3 AE, n (%)* | 21 (38.9) | 27 (52.9) |
| Any Grade ≥3 TRAE, n (%) | 10 (18.5) | 14 (27.5) |
| TRAE Occurring in ≥ 10% Pts, n (%) | | |
| Fatigue | 17 (31.5) | 16 (31.4) |
| Dyspnea | 8 (14.8) | 10 (19.6) |
| Rash | 9 (16.7) | 8 (15.7) |
| Hypothyroidism | 7 (13) | 8 (15.7) |
| Diarrhea | 4 (7.4) | 10 (19.6) |
| Pruritus | 5 (9.3) | 9 (17.7) |
| Arthralgia | 2 (3.7) | 6 (11.8) |
| Nausea | 2 (3.7) | 6 (11.8) |
| Pneumonitis | | |
| Grade ≥2 | 12 (22.2) | 16 (31.4) |
| Grade 3 (no Gr 4/5 pneumonitis) | 5 (9.3) | 9 (17.6) |
| Median time to Gr ≥2 Pneum, mo. (range) | 11.9 (4.1-36.6) | 7.3 (1.3-36.9) |

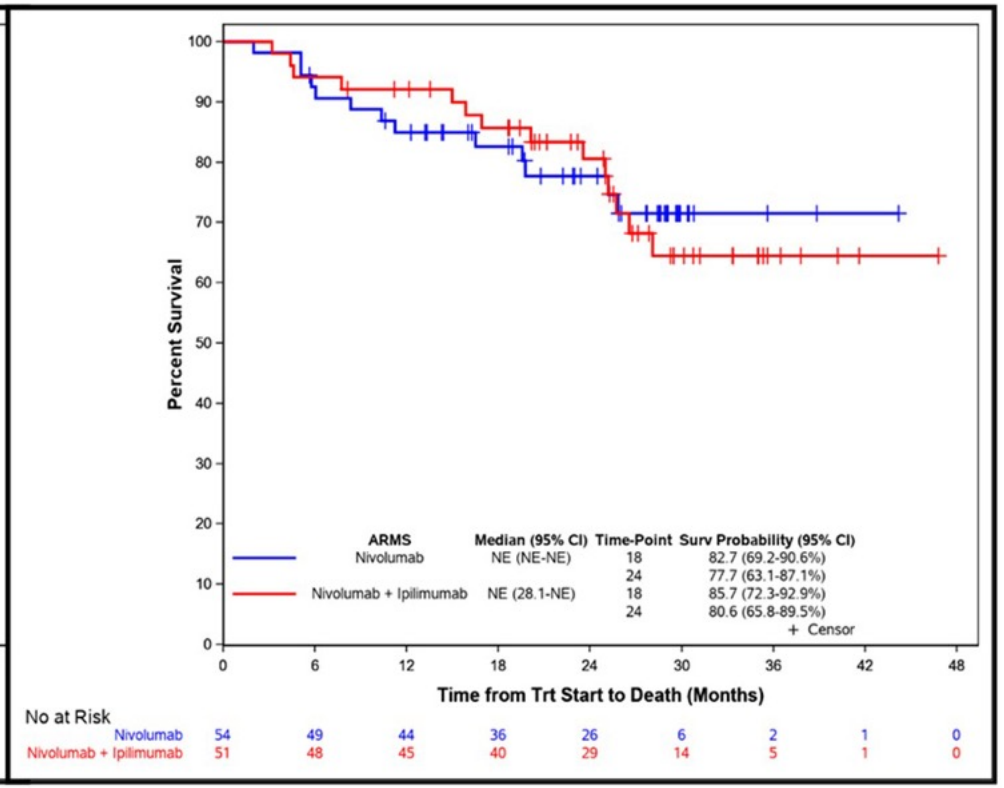
Durm, ASCO 2022, #8509

# Consolidation Nivo vs. Nivo/Ipi After Chemo/Radiation

Progression-Free Survival

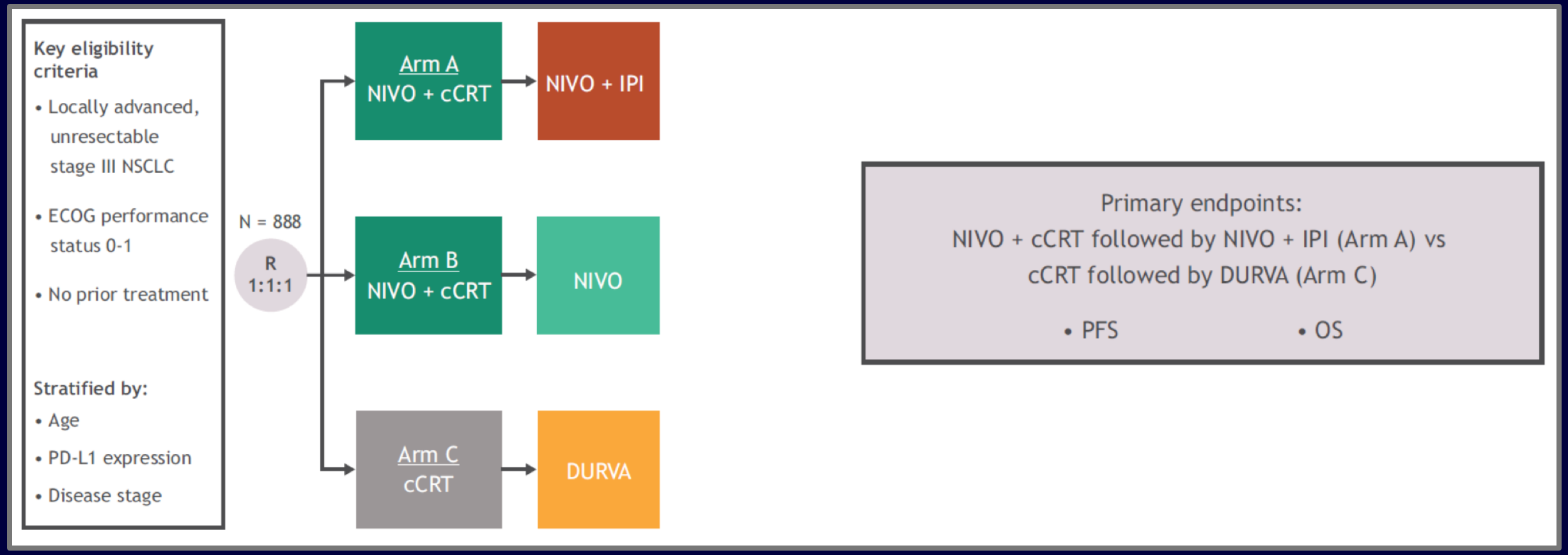



Overall Survival

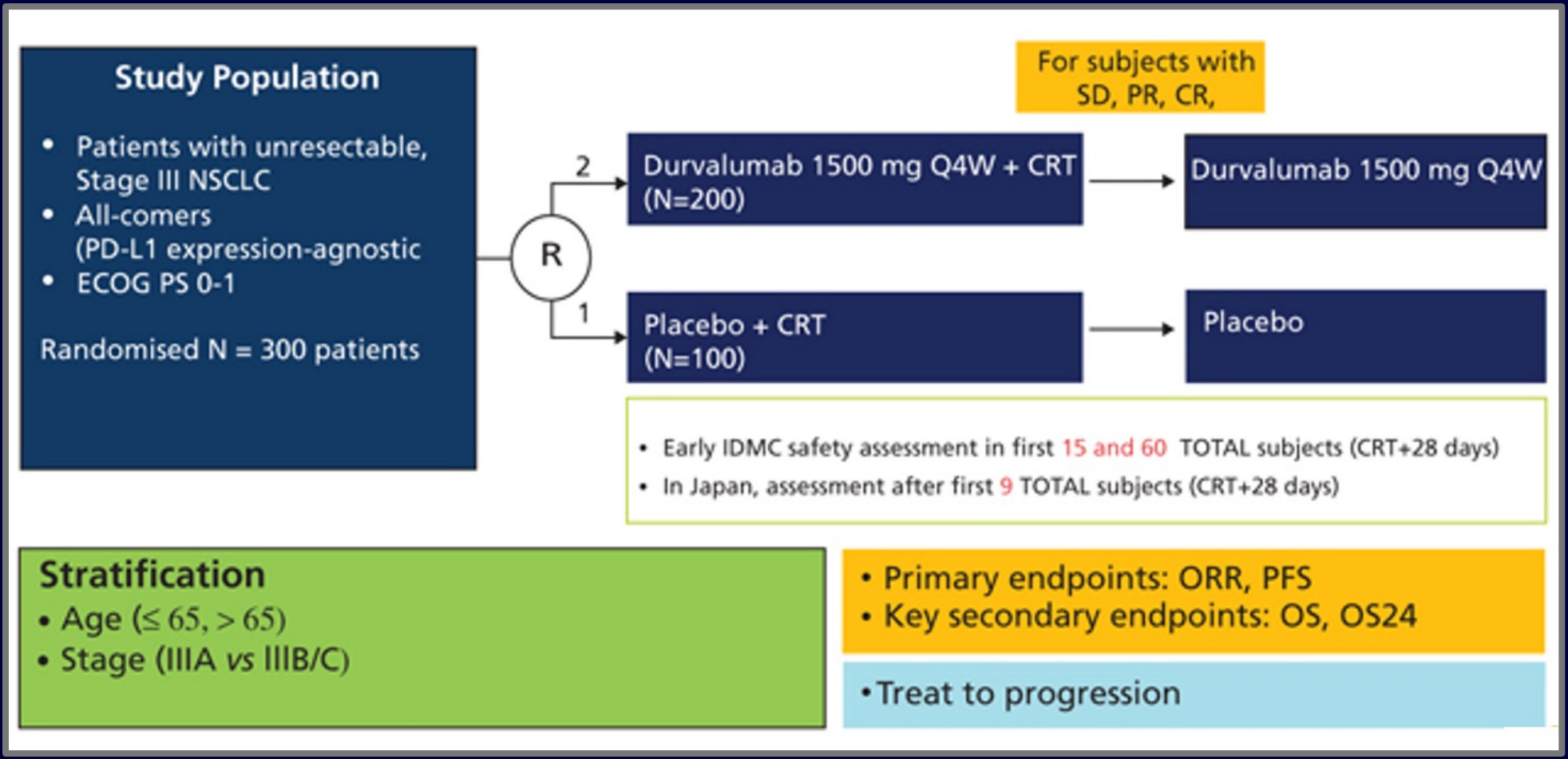



Durm, ASCO 2022, #8509

# CheckMate-73L: Chemo/RT/Nivo → Nivo or Nivo/Ipi vs. PACIFIC



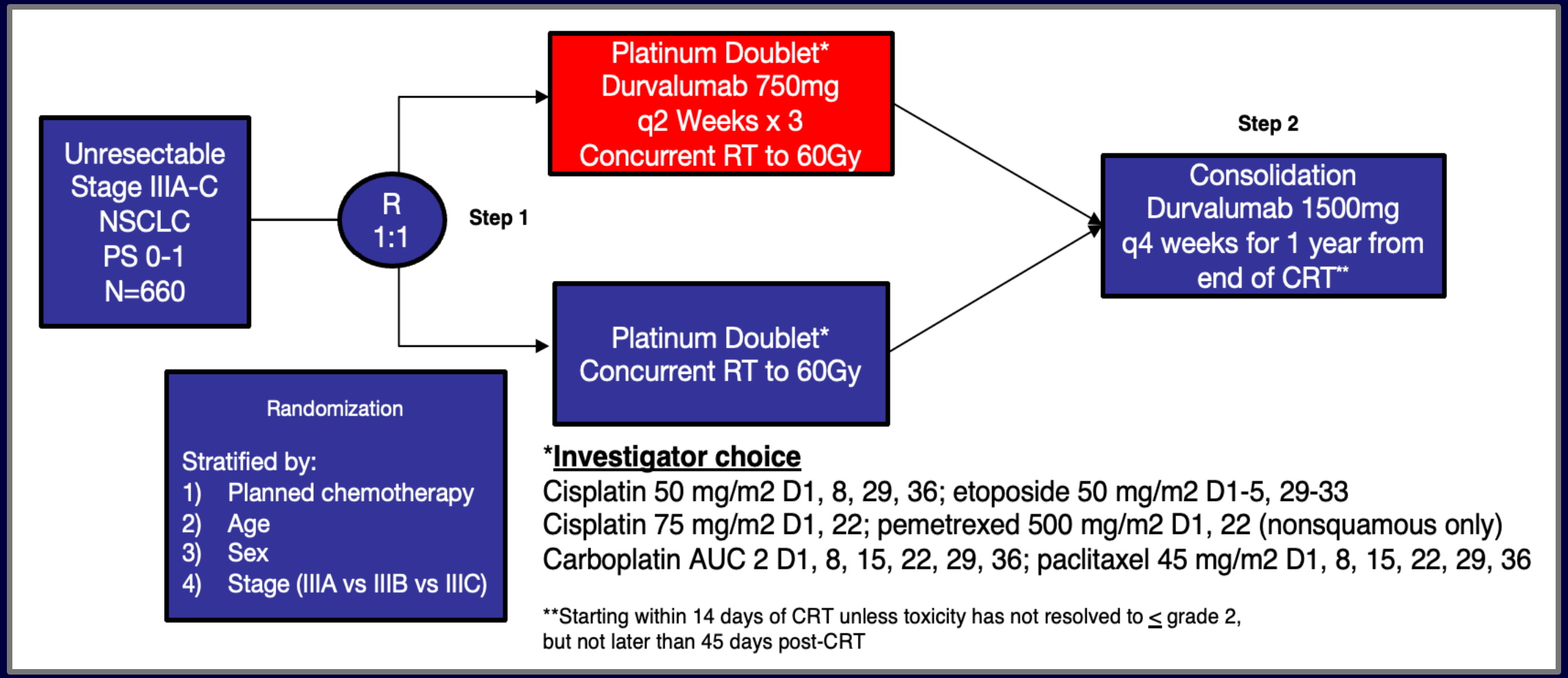
# PACIFIC-2: Study Design




Ex-US

- Enrollment completed; estimated study completion 2023

# EA-5181 (PACIFIC vs. PACIFIC-2)

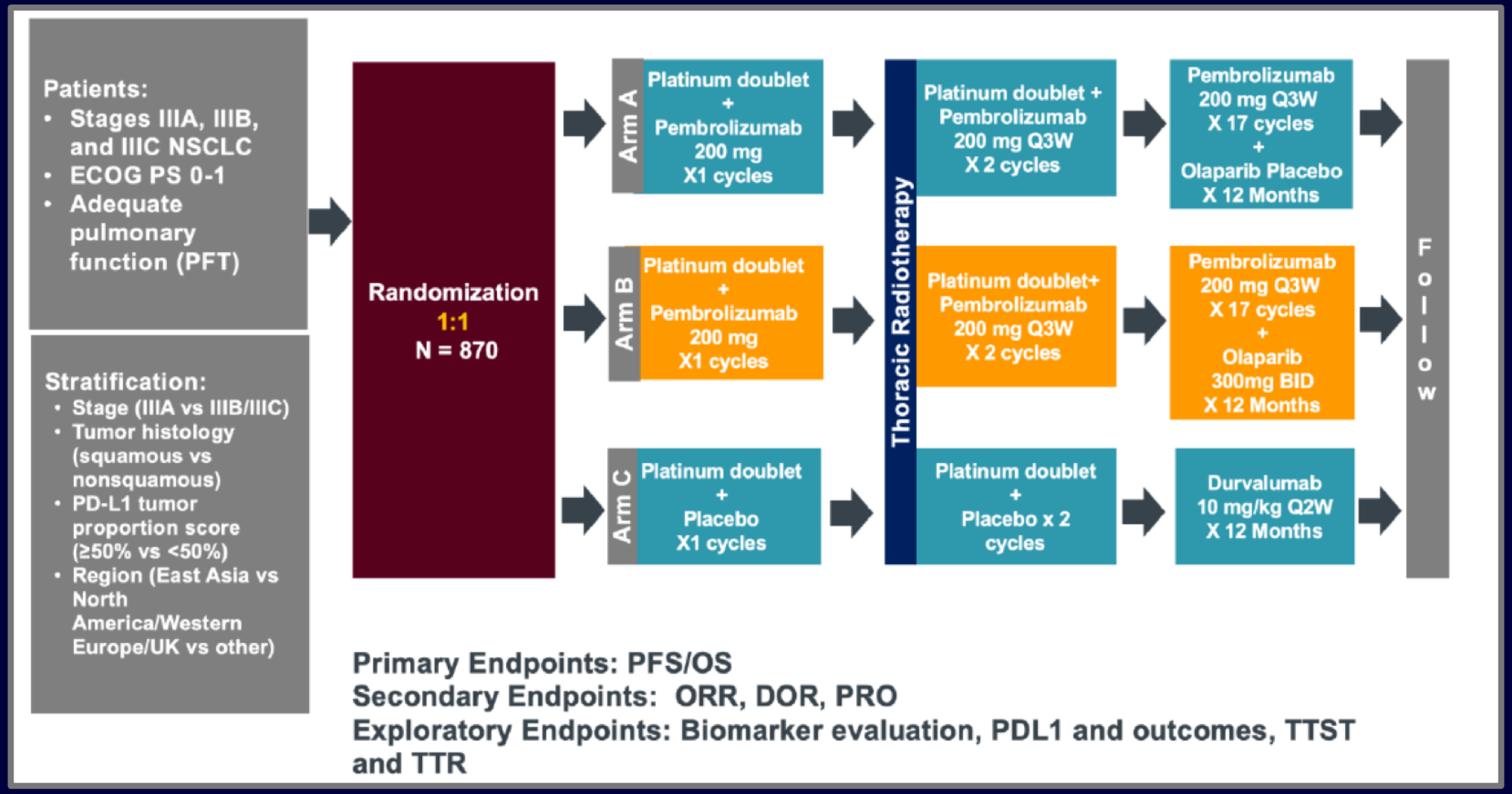



PI: N. Pennell

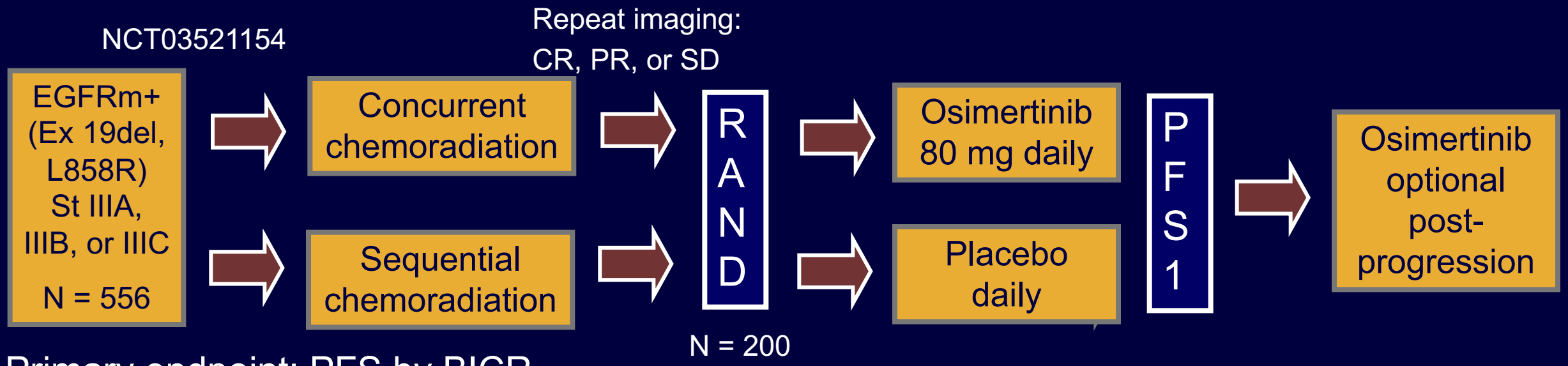
# EA-5181: Endpoints and Exploratory Questions

- Primary Endpoint: Overall survival (OS HR 0.75 compared to SOC arm)
- Secondary:
  - Objective response rate using RECIST 1.1
  - Progression-free survival, Recurrence pattern (distant versus local)
  - Toxicity (safety assessment after first 15 pts on any concurrent regimen)
- Exploratory:
  - Outcomes by PD-L1 level (≥1% and <1%) using SOC PD-L1 testing
  - Follow ctDNA levels pre and post-CRT, during and at end of consolidation
  - Determine the prevalence of clonal hematopoiesis (CHIP) at baseline and after chemoradiation and the association between CHIP and cardiovascular events
- Activated **April 2020**. **~60% enrolled**

# KEYLYNK-12: Integration of Pembrolizumab Before, During, and After Chemo/radiation +/- Olaparib



# LAURA Trial: Chemoradiation for Unresectable Stage III NSCLC, Followed by (Indefinite) Osimertinib or Placebo




Primary endpoint: PFS by BICR

Secondary endpoints: OS, CNS PFS, PFS2, more

- First pt 7/2018, primary data readout in next year

*BUT*

- PFS is an easy win; OS is really the critical variable: can patients do just as well with osimertinib given at relapse
- Some people will have been cured but remain on indefinite osi

# Conclusions for Unresectable Stage III NSCLC

- Marked patient & cancer heterogeneity
- Need to treat at (or beyond) upper limits of tolerability for many
- Consolidation durvalumab after cCRT is current standard of care
  - Debatable for PD-L1 negative, patients with driver mutation-positive NSCLC
- Alternatives (ph 2) have yet to show superiority by moving ICI earlier
- PACIFIC-6 suggests potential utility of consolidation durvalumab after sequential chemo/radiation
- Various trials are evaluating alternative ways to add to PACIFIC (consol) or integrate immunotherapy with chemo/radiation
- Phase 3 trials need to demonstrate superiority vs. PACIFIC regimen
- Anticipate integration of targeted Rx for driver mut'n-positive NSCLC

# Questions?