Fred Hutch Cancer Center

Non-Small Cell Lung Cancer - Adjuvant/Locally Advanced, 2024

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UW Medicine

Disclosures

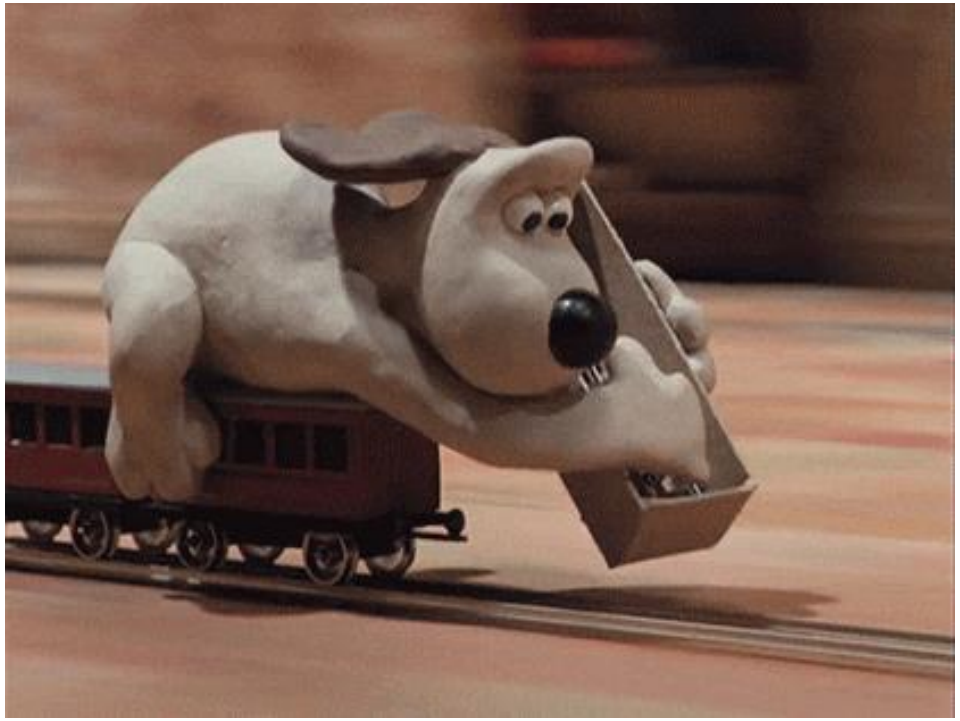
- Honoraria Advisory Boards.
  - Astra Zeneca, Genentech, Mirati Therapeutics, Catalyst Pharmaceuticals, Amgen.

- Research support (inst.)
  - Lilly, Genentech, BeyondSpring Pharmaceuticals, ISA Pharmaceuticals, Merck, Pfizer, ALX Oncology, Astra Zeneca, Daiichi Sankyo, Abbvie, Astellas Pharma, Jounce Therapeutics, A.lpine Immune Sciences

Early-stage lung cancer.

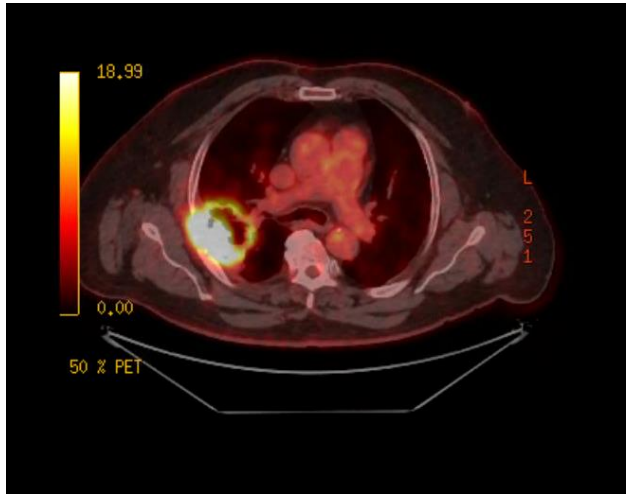
- Between 30-50% of patients present with early-stage disease for which treatment is curative.
- Screening has and will increase this percentage.
- Although treatment goal is curative outcome with surgery alone still suck.
- 40-50% of patients with stage IB, 55-70% of stage II, and a greater percentage of those with stage IIIA NSCLC eventually recur.

Significant changes in the last 2 years.

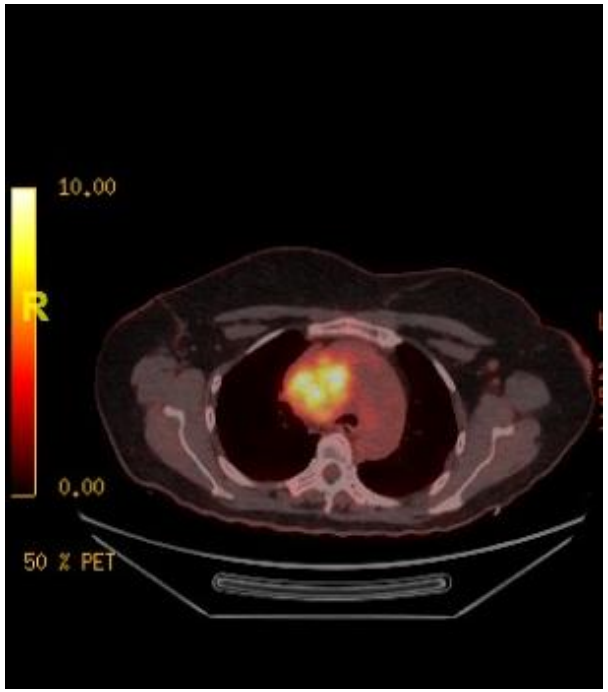


- Treatment of early-stage lung cancer is currently influx. Not sure how the boards will address this moving target.

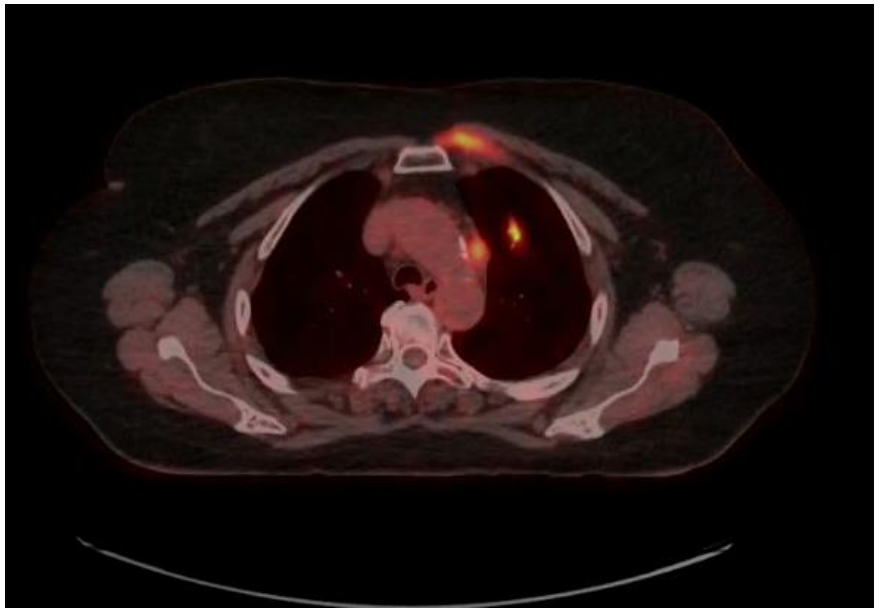
Heterogenous group

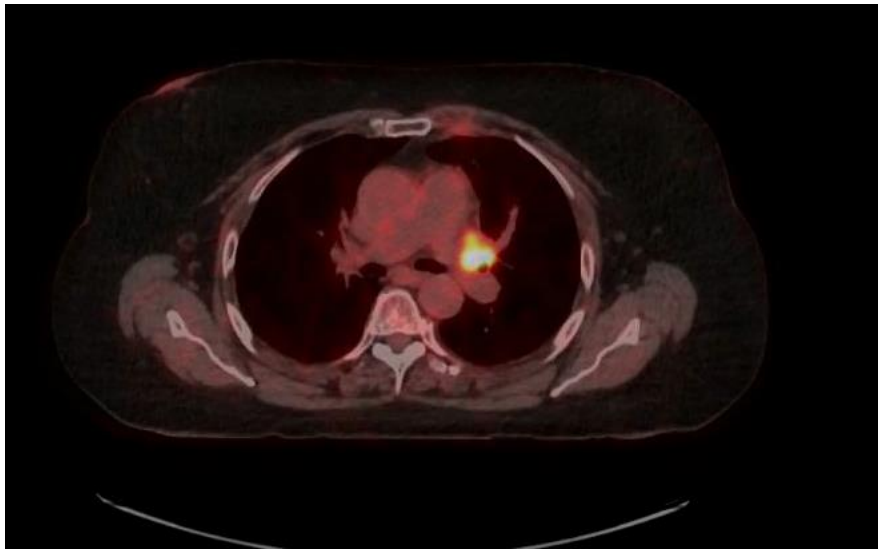


T3, NO, MO Stage IIIA



T1A, N2, MO Stage IIIA





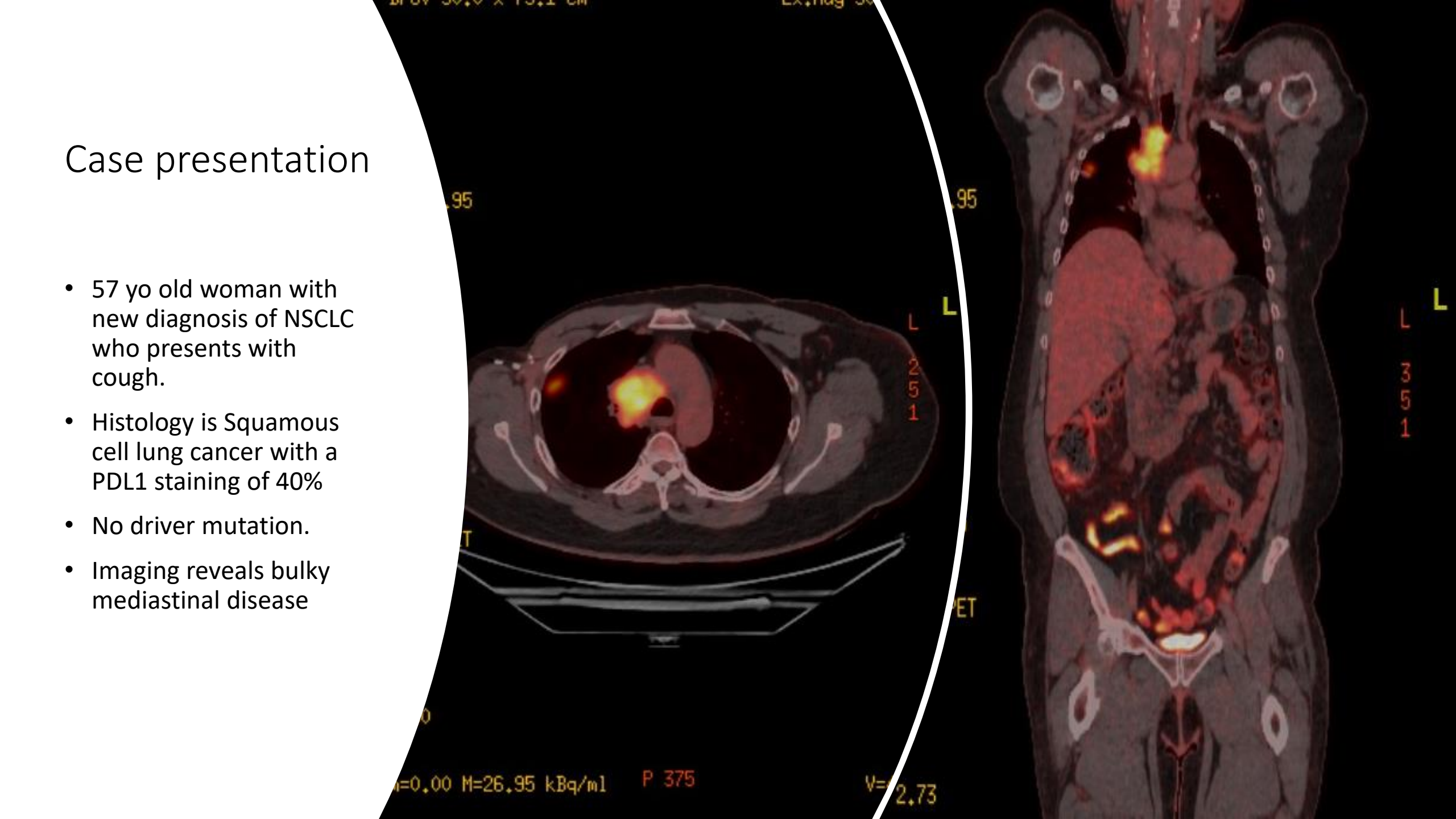
T1A, N2, MO Stage IIIA

Index.

- Chemoradiation.
- Neoadjuvant chemotherapy followed by resection.
- Adjuvant therapy following resection.

Case presentation

- 57 yo old woman with new diagnosis of NSCLC who presents with cough.
- Histology is Squamous cell lung cancer with a PDL1 staining of 40%
- No driver mutation.
- Imaging reveals bulky mediastinal disease

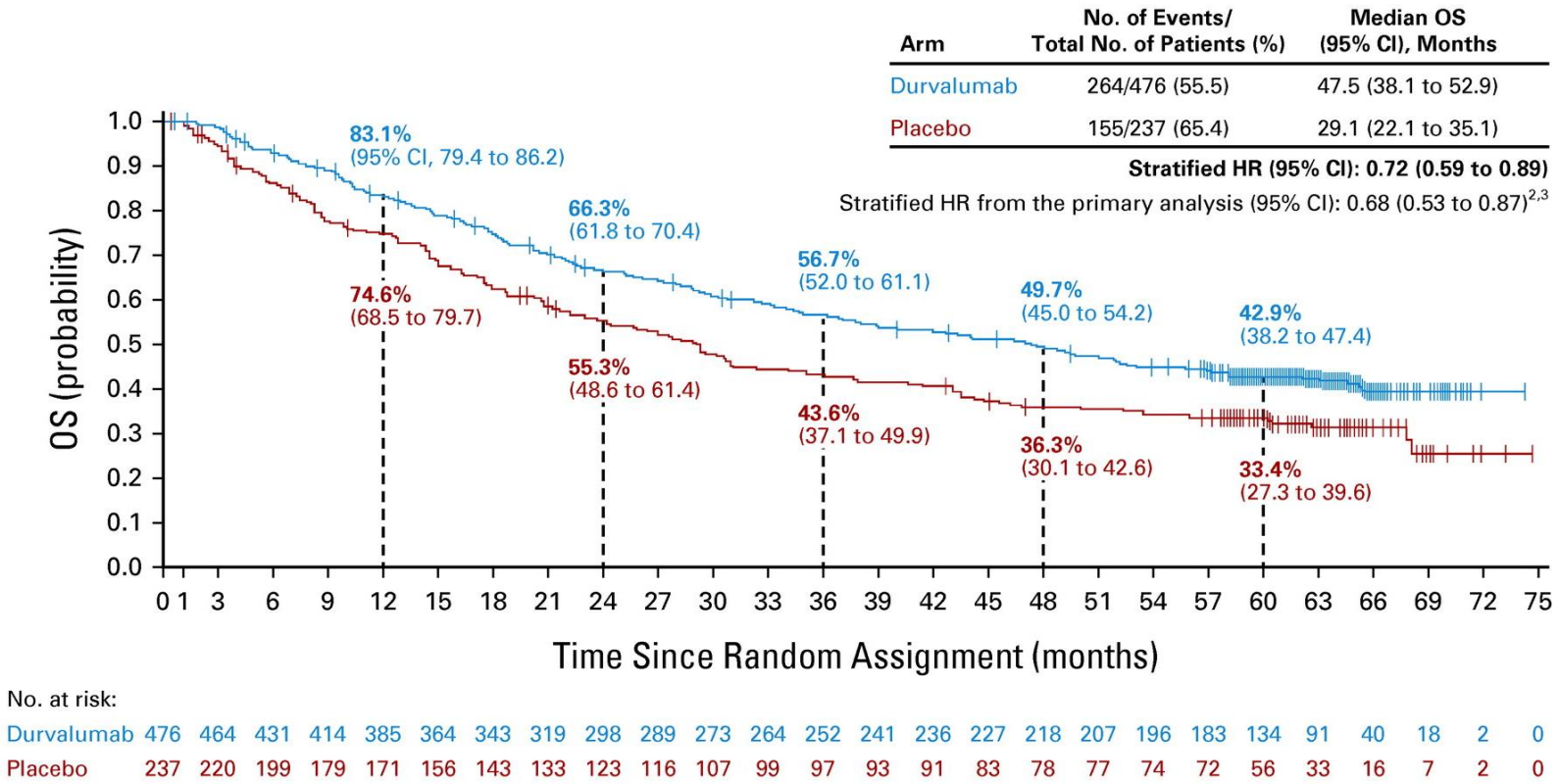


Chemotherapy and radiation

- PACIFIC study was the most important game changer.
- 713 patients were randomized 2:1 to receive durvalumab after the concurrent phase of radiation.
- Chemotherapy partners was dealer's choice but no consolidation treatment was allowed.

Antonia SJ et al. N Engl J Med 2017;377:1919-1929.

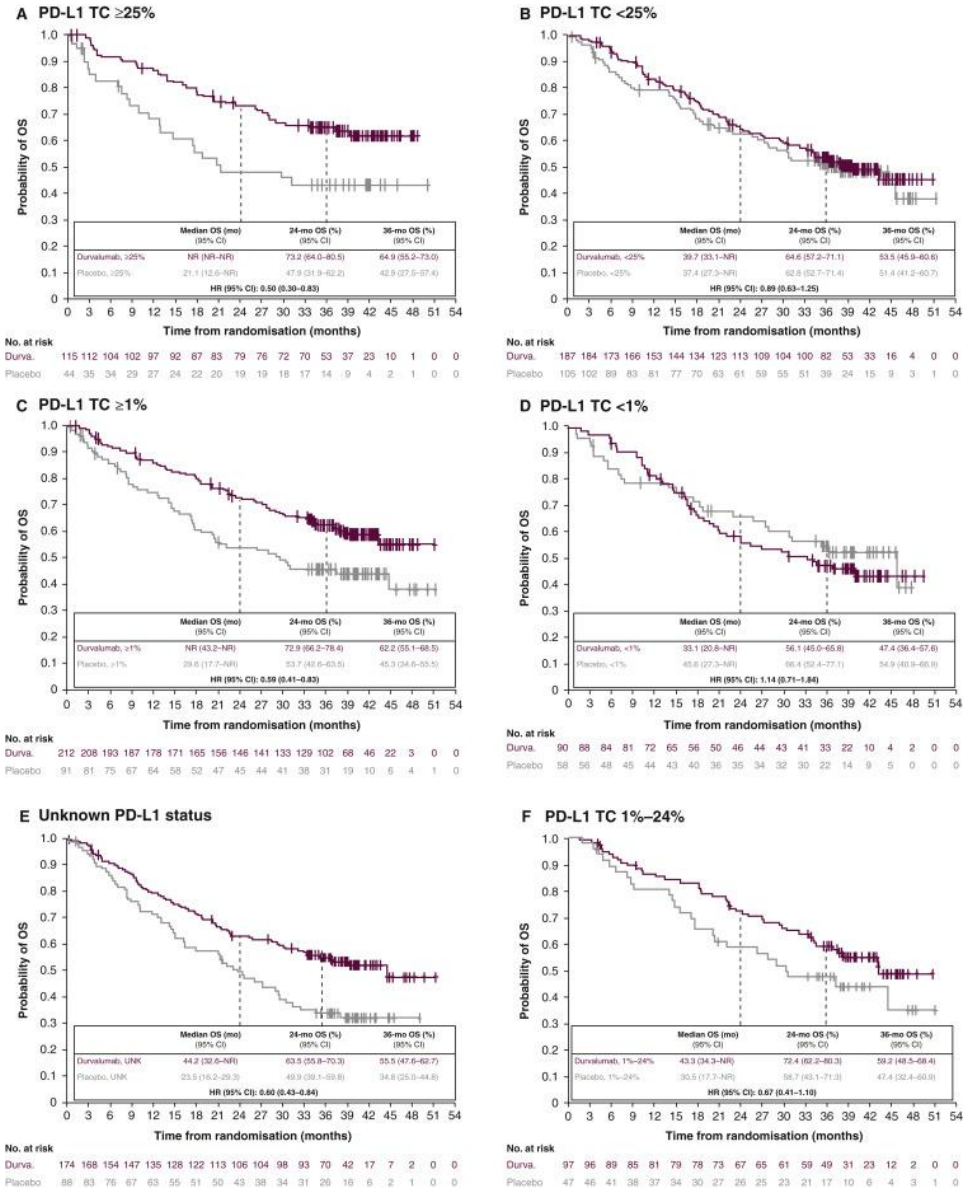
PACIFIC trial



Spigel, JCO. 2022. PMID: 35108059

PDL1 status.

- OS favored durvalumab, versus placebo, across all PD-L1 subgroups but one, patients with TC <1% (HR, 1.36; 95% CI, 0.79–2.34).
- However, this is not a proper endpoint and was done post-hoc.



Paz-Ares. Ann Oncol. 2020

Adverse Events of Any Cause.

Table 3. Adverse Events of Any Cause.

Event	Durvalumab (N=475)		Placebo (N=234)	
	Any Grade*	Grade 3 or 4	Any Grade*	Grade 3 or 4
	number of patients with event (percent)			
Any event	460 (96.8)	142 (29.9)	222 (94.9)	61 (26.1)
Cough	168 (35.4)	2 (0.4)	59 (25.2)	1 (0.4)
Pneumonitis or radiation pneumonitis†	161 (33.9)	16 (3.4)	58 (24.8)	6 (2.6)
Fatigue	113 (23.8)	1 (0.2)	48 (20.5)	3 (1.3)
Dyspnea	106 (22.3)	7 (1.5)	56 (23.9)	6 (2.6)
Diarrhea	87 (18.3)	3 (0.6)	44 (18.8)	3 (1.3)
Pyrexia	70 (14.7)	1 (0.2)	21 (9.0)	0
Decreased appetite	68 (14.3)	1 (0.2)	30 (12.8)	2 (0.9)
Nausea	66 (13.9)	0	31 (13.2)	0
Pneumonia	62 (13.1)	21 (4.4)	18 (7.7)	9 (3.8)
Arthralgia	59 (12.4)	0	26 (11.1)	0
Pruritus	58 (12.2)	0	11 (4.7)	0
Rash	58 (12.2)	1 (0.2)	17 (7.3)	0
Upper respiratory tract infection	58 (12.2)	1 (0.2)	23 (9.8)	0
Constipation	56 (11.8)	1 (0.2)	20 (8.5)	0
Hypothyroidism	55 (11.6)	1 (0.2)	4 (1.7)	0
Headache	52 (10.9)	1 (0.2)	21 (9.0)	2 (0.9)
Asthenia	51 (10.7)	3 (0.6)	31 (13.2)	1 (0.4)
Back pain	50 (10.5)	1 (0.2)	27 (11.5)	1 (0.4)
Musculoskeletal pain	39 (8.2)	3 (0.6)	24 (10.3)	1 (0.4)
Anemia	36 (7.6)	14 (2.9)	25 (10.7)	8 (3.4)

Event†	Durvalumab (N=475)		Placebo (N=234)	
	Any Grade‡	Grade 3 or 4	Any Grade‡	Grade 3 or 4
	number of patients with an event (percent)			
Any event	115 (24.2)	16 (3.4)	19 (8.1)	6 (2.6)
Pneumonitis	51 (10.7)	8 (1.7)	16 (6.8)	6 (2.6)
Hypothyroidism	44 (9.3)	1 (0.2)	3 (1.3)	0
Hyperthyroidism	13 (2.7)	0	0	0
Rash	5 (1.1)	2 (0.4)	1 (0.4)	0
Dermatitis	5 (1.1)	0	0	0

Antonia SJ et al. N Engl J Med 2017;377:1919-1929.

What chemotherapy to use?

- Not defined and not clear consensus.
- Options are
  - Platinum/etoposide. 2 cycles while on treatment (6 days of infusion per cycle).
  - Platinum/pemetrexed. 2 cycles per treatment (1 day of infusion per cycle)
  - Carboplatin/paclitaxel. Weekly treatment while on radiation.
- My personal bias.
  - Decision is made based on the ability to tolerate ”full dose” chemotherapy.

Locally advanced EGFR +ve lung cancer

- For patients with locally advanced NSCLC that standard of care is chemotherapy and radiation followed by durvalumab.
- Very few patient with driver mutations were enrolled in the PACIFIC study.
- Controversy regarding the effectiveness of immunotherapy in patients with EGFR, ALK, ROS, RET.
- Two Phase 3 studies now show no activity in metastatic EGFR.
- Increase incidence of pneumonitis when using TKI if patients have had CPI treatment.
- Primary endpoint was PFS.

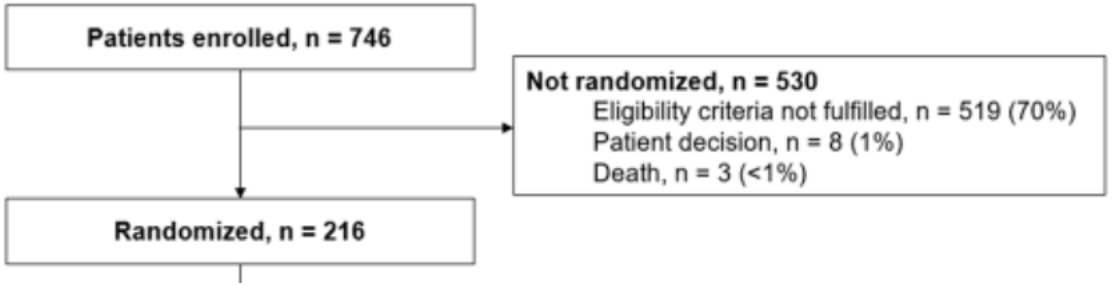
Lu, S. *et al.* Osimertinib after Chemoradiotherapy in Stage III EGFR - Mutated NSCLC. *New England Journal of Medicine* (2024).

LAURA study

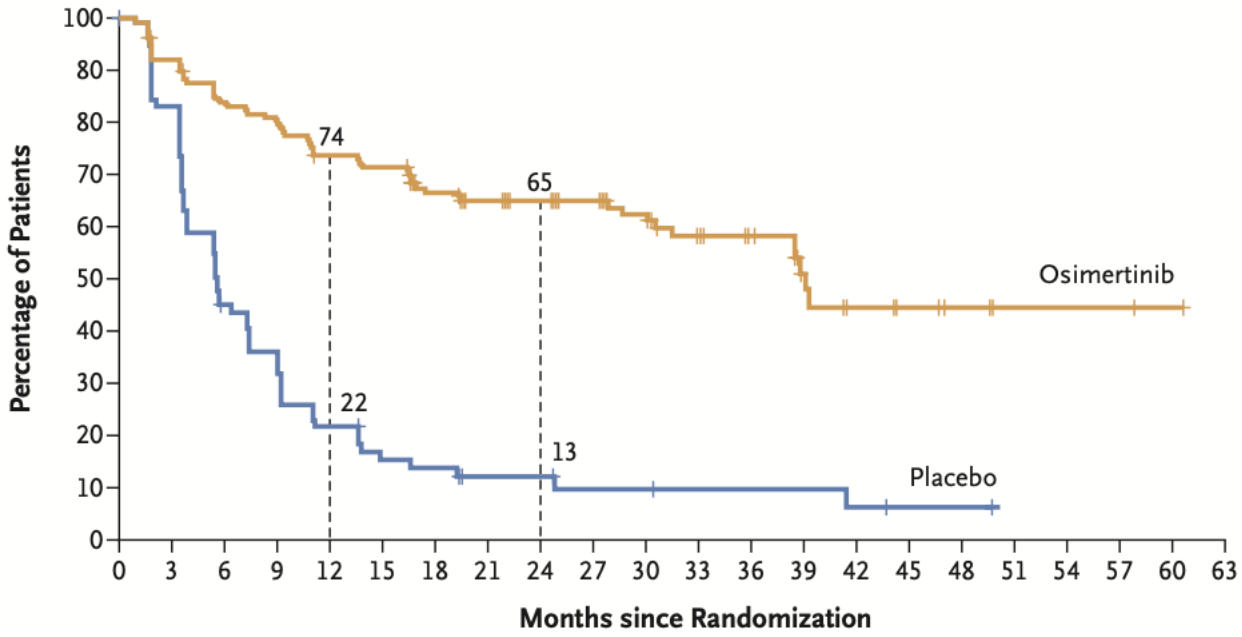
- Randomized phase 3 study where patients with common EGFR mutations and stage III underwent randomization 2:1 to osimertinib or placebo.
- Little details are provided regarding confirmation of stage III disease. Meaning we don’t know % of patients that had mediastinoscopy or PET scan prior to chemorads.
- Chemotherapy was dealer’s choice, it appears that close to half received weekly carboplatin and paclitaxel.

Trial

- A CT chest and abdomen and no evidence of brain mets was required prior to study entry.



Results



No. at Risk

Osimertinib	143	127	114	109	99	96	83	76	69	61	49	37	28	16	9	6	4	2	2	2	1	0
Placebo	73	59	31	25	15	10	9	6	6	4	4	3	3	3	2	1	1	0	0	0	0	0

Median Progression-free Survival (95% CI)

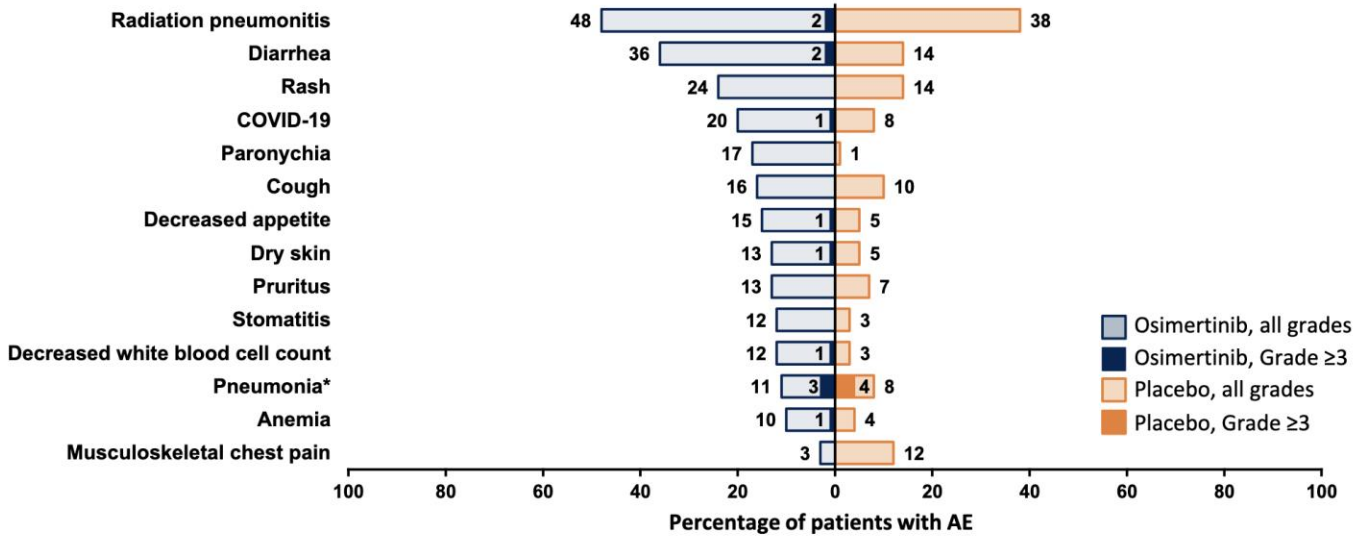
	mo
Osimertinib	39.1 (31.5–NC)
Placebo	5.6 (3.7–7.4)

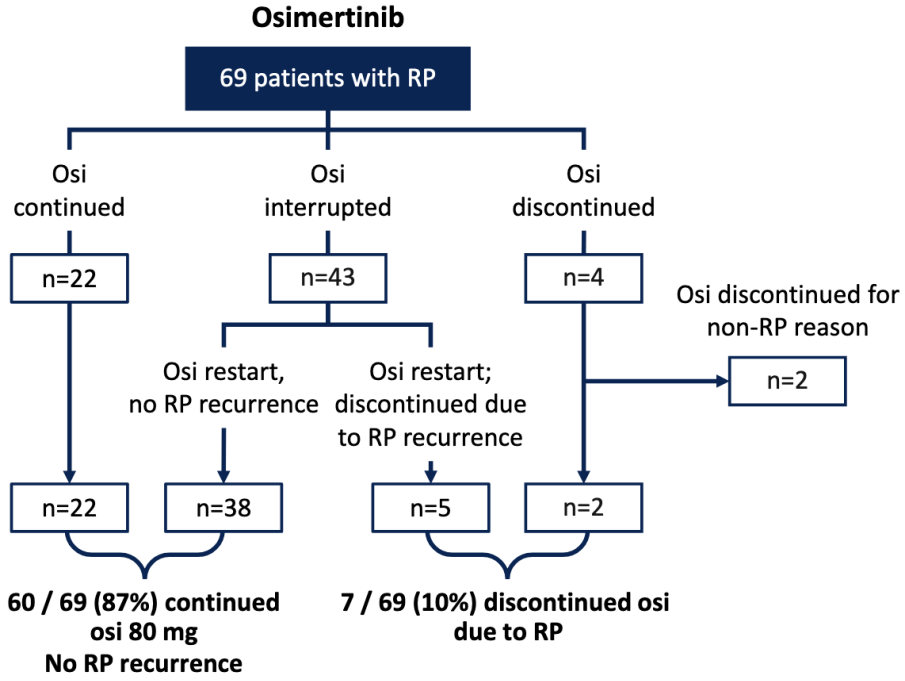
Hazard ratio for disease progression or death, 0.16 (95% CI, 0.10–0.24)
P<0.001

Adverse events

All-causality AEs (≥10%)

- 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

Now what.

- Not a perfect study. But is what we got.
- Endorsed by NCCN and is now SOC.
- But who needs lifelong osimertinib?
- Is therefore stage III treatment palliative?
- How are we going to figure out in whom to stop.
- Is radiation even needed?

Summary for chemotherapy and radiation.

- Chemotherapy radiation followed by durvalumab is the standard treatment for patients that have unresectable disease stage II/III NSCLC that do not have a driver mutation.
- No standard for chemotherapy, choice to be made depending on clinical characteristics.
- Pembrolizumab alone can be used for patients with stage III, but this is a palliative approach.
- Osimertinib should be considered for patients with EGFR+ve disease

Index.

- Chemoradiation.
- Neoadjuvant chemotherapy followed by resection.
- Adjuvant therapy following resection.

Adjuvant treatment of NSCLC

- For patients with stage II and IIIA cisplatin-based adjuvant chemotherapy has been the SOC.
- LACE meta-analysis showed a HR 0.89, 95% CI 0.82-0.96. The effect on survival varied by stage, but a benefit that reached statistical significance was seen for patients with stage II (HR of death 0.83, 95% CI 0.73-0.95) and IIIA disease (HR of death 0.83, 95% CI 0.72-0.94).
- 5-year absolute benefit of 5.4% from chemotherapy.
- Stage IB remains controversial.

Pignon JP, JCO 2008. PMID 18506026

Neoadjuvant vs Adjuvant

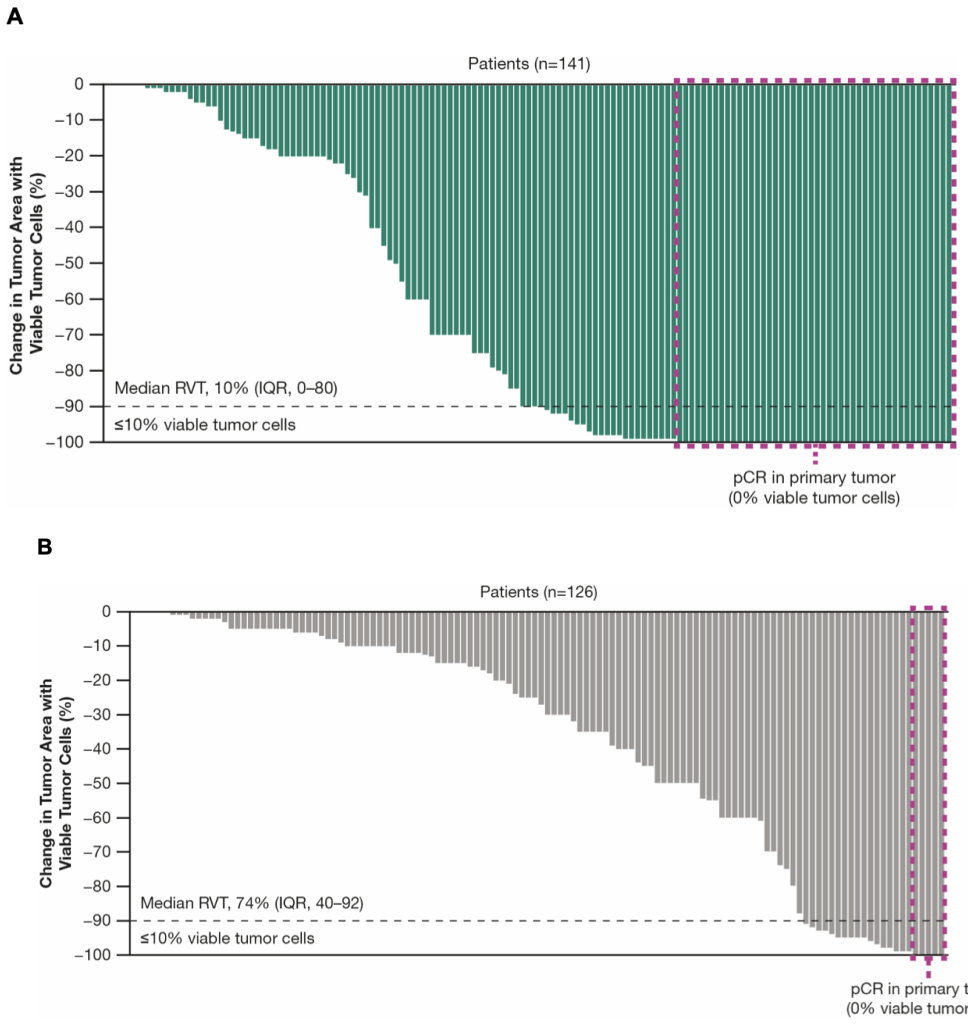
- In meta-analyses, the OS advantage of neoadjuvant and adjuvant therapies appeared comparable.
- Neoadjuvant approach has some advantages.
  - Provides a stress test that defines the biology of the disease.
  - Gets it “out of the way”.
  - Offers prognostic information depending on results.
  - Intact tumor and primary lymphatics allow better T-cell priming.

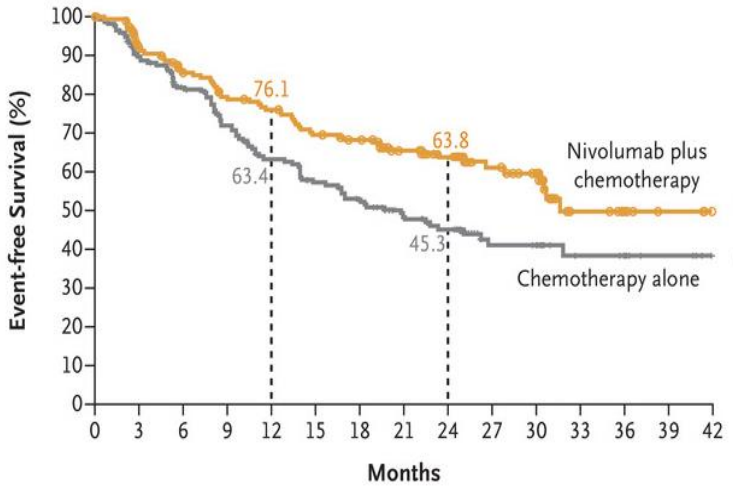
Felip E, JCO 2010. PMID 20516435

Four trials done with immunotherapy

- Checkmate 816
- Checkmate 77T
- Aegean
- Keynote.

Efficacy



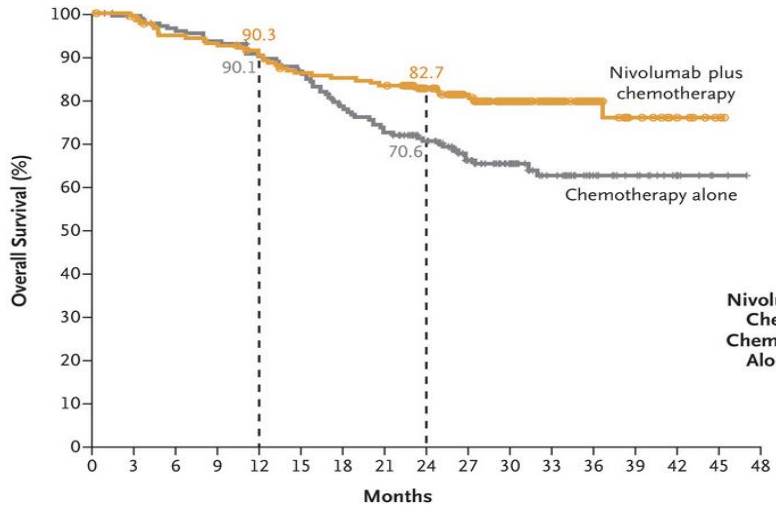


	No. of Patients	Median Event-free Survival (95% CI) mo
Nivolumab plus Chemotherapy	179	31.6 (30.2–NR)
Chemotherapy Alone	179	20.8 (14.0–26.7)

Hazard ratio for disease progression, disease recurrence, or death, 0.63 (97.38% CI, 0.43–0.91)
P=0.005

No. at Risk

Nivolumab plus chemotherapy	179	151	136	124	118	107	102	87	74	41	34	13	6	3	0
Chemotherapy alone	179	144	126	109	94	83	75	61	52	26	24	13	11	4	0



	No. of Patients	Median Overall Survival (95% CI) mo
Nivolumab plus Chemotherapy	179	NR (NR–NR)
Chemotherapy Alone	179	NR (NR–NR)

Hazard ratio for death, 0.57 (99.67% CI, 0.30–1.07)
P=0.008

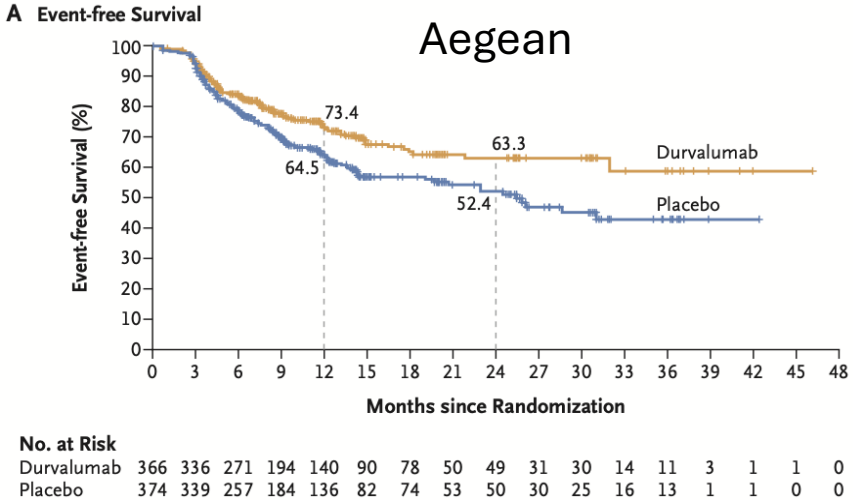
No. at Risk

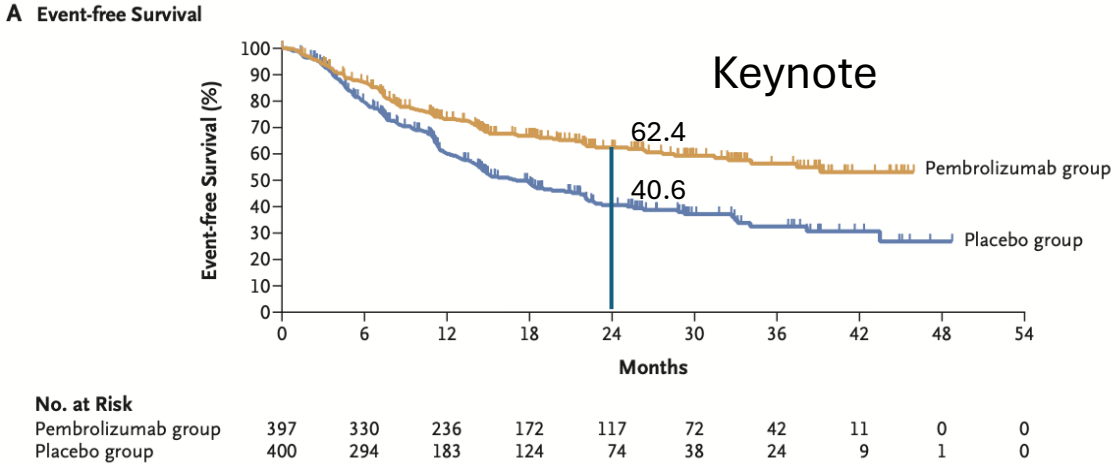
Nivolumab plus chemotherapy	179	176	166	163	156	148	146	143	122	101	72	48	26	16	7	3	0
Chemotherapy alone	179	172	165	161	154	148	133	123	108	80	59	41	24	16	7	2	0

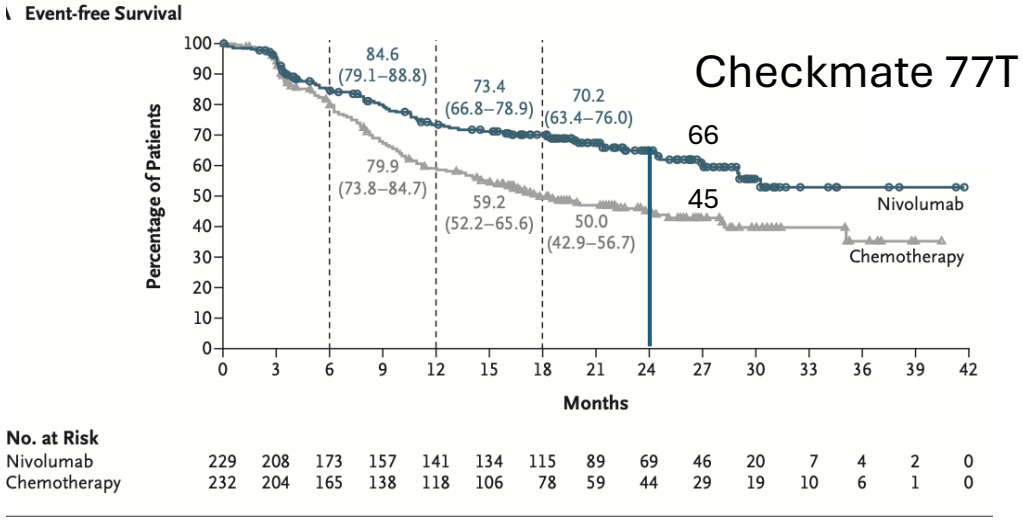
PM Forde et al. N Engl J Med 2022;386:1973-1985.

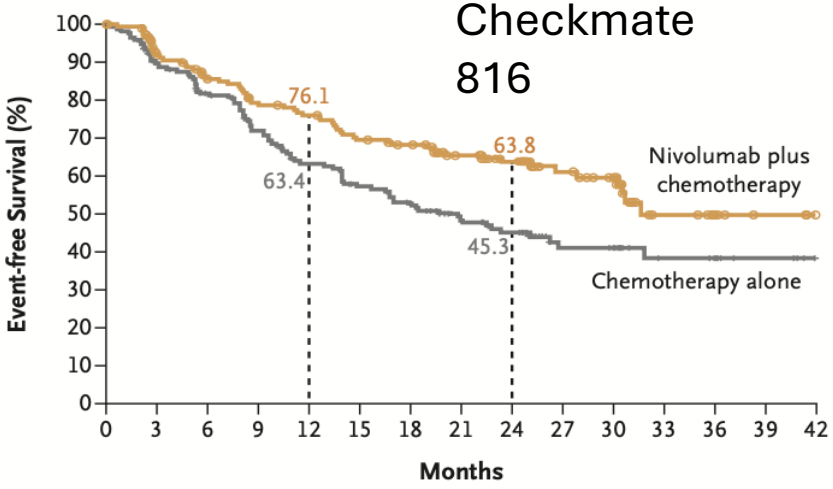
Name	Checkpoint 77T	Keynote 671	Checkmate 816	Aegean
Patient Population	Resectable stage IIA(>4 cm)-IIIa NSCLC	Resectable stage II-IIIB NSCLC	Resectable stage IB (>d4cm)-IIIA NSCLC	Resectable stage IIA-IIIB NSCLC
Treatment	4 cycles of neoadjuvant chemo/nivolumab followed by neoadjuvant nivolumab	4 cycles of neoadjuvant chemo/ pembrolizumab followed by neoadjuvant pembrolizumab	3 cycles of neoadjuvant chemotherapy/ nivolumab and no mandated adjuvant treatment	4 cycles of neoadjuvant chemo/ durvalumab followed by adjuvant durvalumab
Primary Endpoint	EFS	Dual EFS and OS	Dual EFS and pCR	Dual EFS and pCR
Underwent surgery	77.7 vs 76.7%	82.1 vs 73.2%	83.2 vs 75,4%	77.6 vs 76.7%
Received adjuvant treatment	62 vs 65.5%	73.2 vs 66.9%	11.9 vs 22.2%	65.8 vs 63.4%
Pathological Complete Response	25.3 vs 4.7%	18.1 vs 4%	24 vs 2.2%	17.2 vs 4.3%
Major Pathological Response	35.4 vs 12.1%	30.2 vs 11%	36.9%	33.3 vs 12.3%
EFS at 2 years	66 vs 45%*	62.4 vs 40.6%	63 vs 45.3%	63.3 vs 52.4%
HR for EFS	0.58; 97.36%CI, 0.42 to 0.81; P<0.001	0.58; 95% CI, 0.46 to 0.72; P<0.001	0.66; 95% CI, 0.49 to 0.9; P=0.005	0.68 (95% CI 0.53 to 0.88; p=0.004)
Overall Survival	Not reached	NR vs 45.5m	NR vs NR. HR 0.71; 98.36% CI 0.47-1.07	Not reported
Latest reference			ASCO 2024	

No obvious differences in outcomes, so far



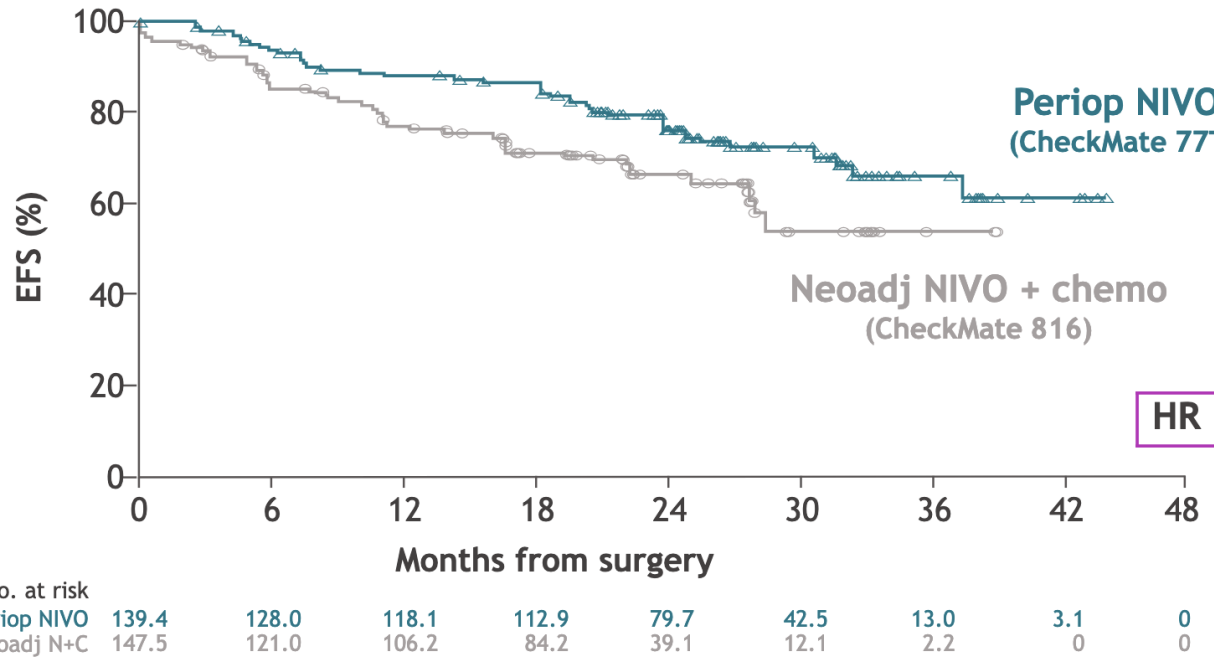






Checkmate 77T vs 816

Landmark EFS (BICR) from definitive surgery

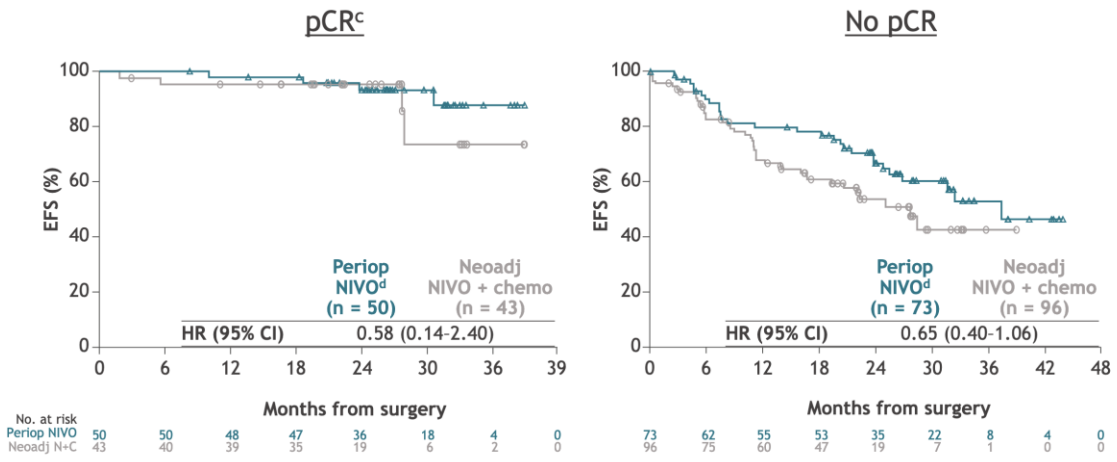


Weighted (ATE)[b]	Periop NIVO[a] (n = 139.4[c])	Neoadj NIVO + chemo (n = 147.5[c])
HR (95% CI)	0.61 (0.39-0.97)	

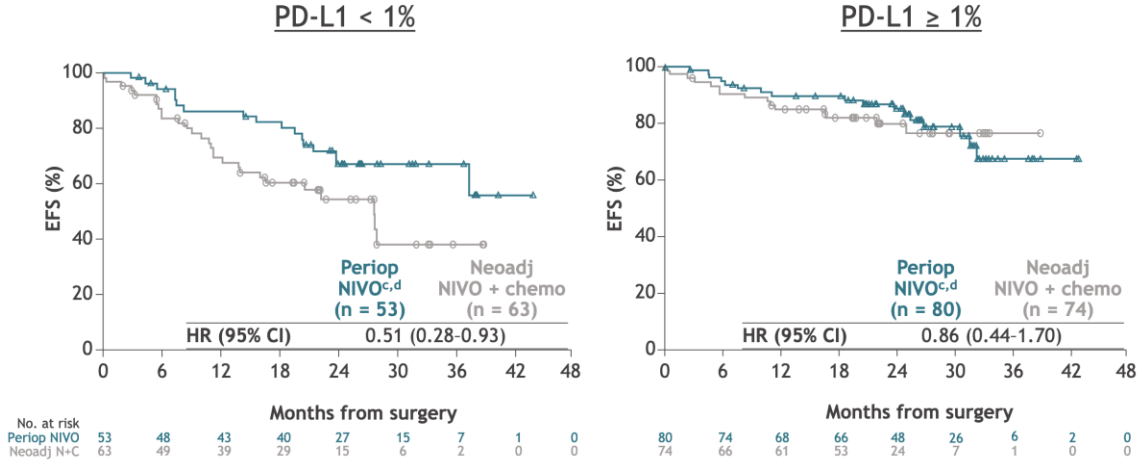
- HR (95% CI): ATT[d] weighted analysis, 0.56 (0.35-0.90); unweighted analysis, 0.59 (0.38-0.92)

Checkmate 77T vs 816

Landmark EFS[a] (analysis population) by pCR status[a,b]



Landmark EFS (analysis population) by tumor PD-L1 expression[a,b]



Safety summary[a]: analysis populations

Patients, n (%)	Perioperative NIVO (n = 139)		Neoadjuvant NIVO + chemo (n = 147)	
	Any grade[b]	Grade 3-4[b]	Any grade[c]	Grade 3-4[c]
All AEs	137 (99)	64 (46)	138 (94)	63 (43)
TRAEs	130 (94)	38 (27)	125 (85)	52 (35)
All AEs leading to discontinuation	29 (21)	10 (7)	16 (11)	8 (5)
TRAEs leading to discontinuation	22 (16)	9 (6)	16 (11)	8 (5)
All SAEs	57 (41)	37 (27)	23 (16)	16 (11)
Treatment-related SAEs	23 (16)	14 (10)	17 (12)	13 (9)
Surgery-related AEs[d]	53 (38)	15 (11)	61 (42)	17 (12)
Treatment-related deaths[e]	0		0	

Conclusions and Practical Matters

- All patients with early-stage disease should be discussed in a multi-D clinic.
- Neoadjuvant therapy with a CPI should be considered for all patients with plan resections. (KEYWORD: **Planned**)
- Patients need a biopsy where molecular markers are analyzed.
- OK to give 1 cycle of neoadjuvant chemo alone while waiting.
- Patients prognosis is still limited. Need to design prospective trials that take into account PCR and CT DNA in decision making.

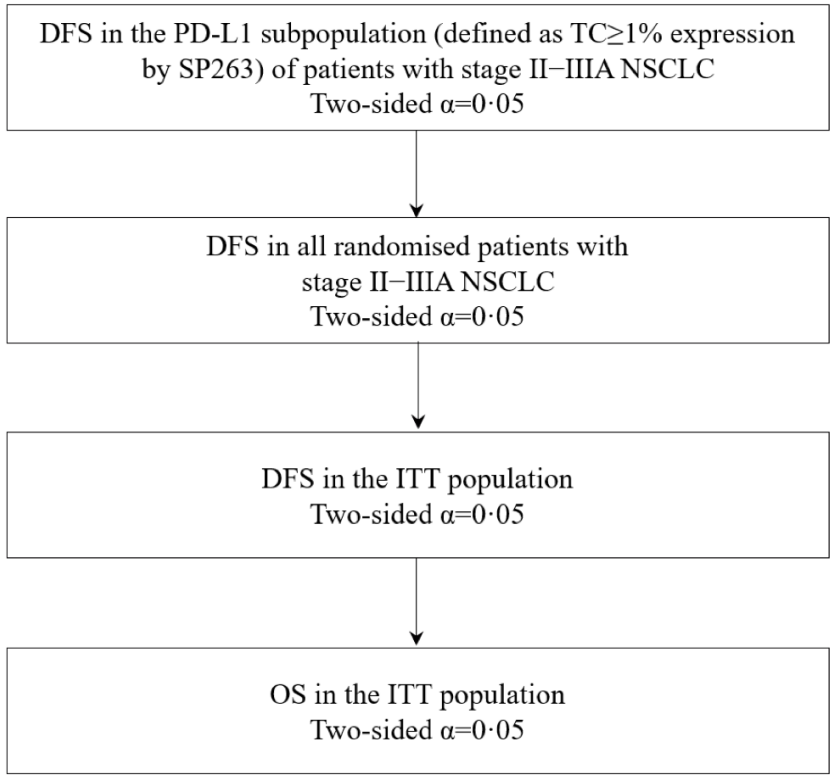
Atezolizumab

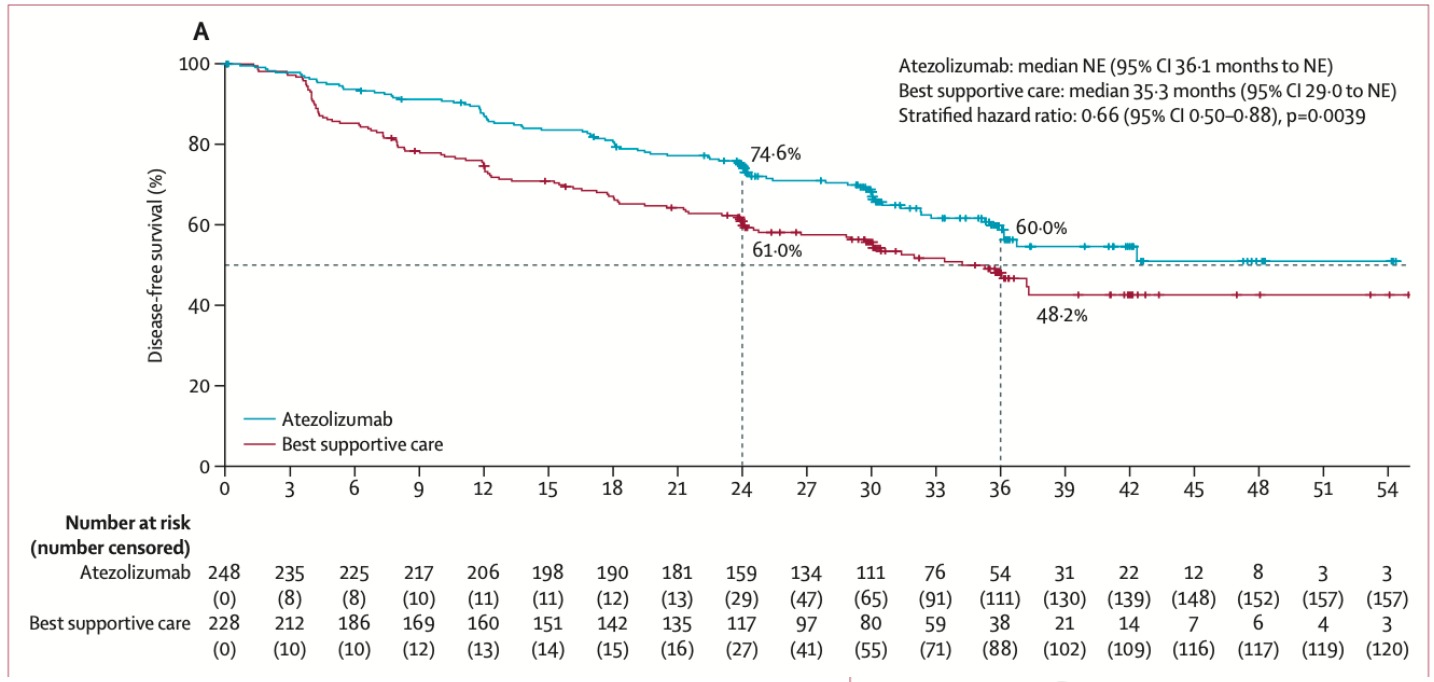
- IMpower010 is a RCT of atezolizumab versus BSC after adjuvant cisplatin-based chemotherapy in patients with completely resected stage IB–IIIA NSCLC.
- Patients enrolled after surgery. Scheduled to receive chemotherapy.
- Key Eligibility criteria
  - Resected stage IB-IIIA.
  - Able to receive cisplatin-based chemotherapy.
  - EGFR and ALK patients could enroll.
  - Surgery done 28-84 days before enrollment.
  - Strict mediastinal staging.
- Chemotherapy was dealers' choice. 86% receive 4 cycles of treatment. 472 (37%) pemetrexed, 406 (32%) vinorelbine, 205 (16%) gemcitabine, and 186 (15%) docetaxel.
- After initial enrollment phase, patients were randomized 1:1. Stratified by sex, histology, stage and PD-L1 expression. Patients underwent reimaging studies with CT and MRI at this point.
- Randomized to BSC vs Atezolizumab, 1200 mg q21 days for 16 cycles or 1 year.

Felip E, Lancet, 2021, 1344-57

Endpoints

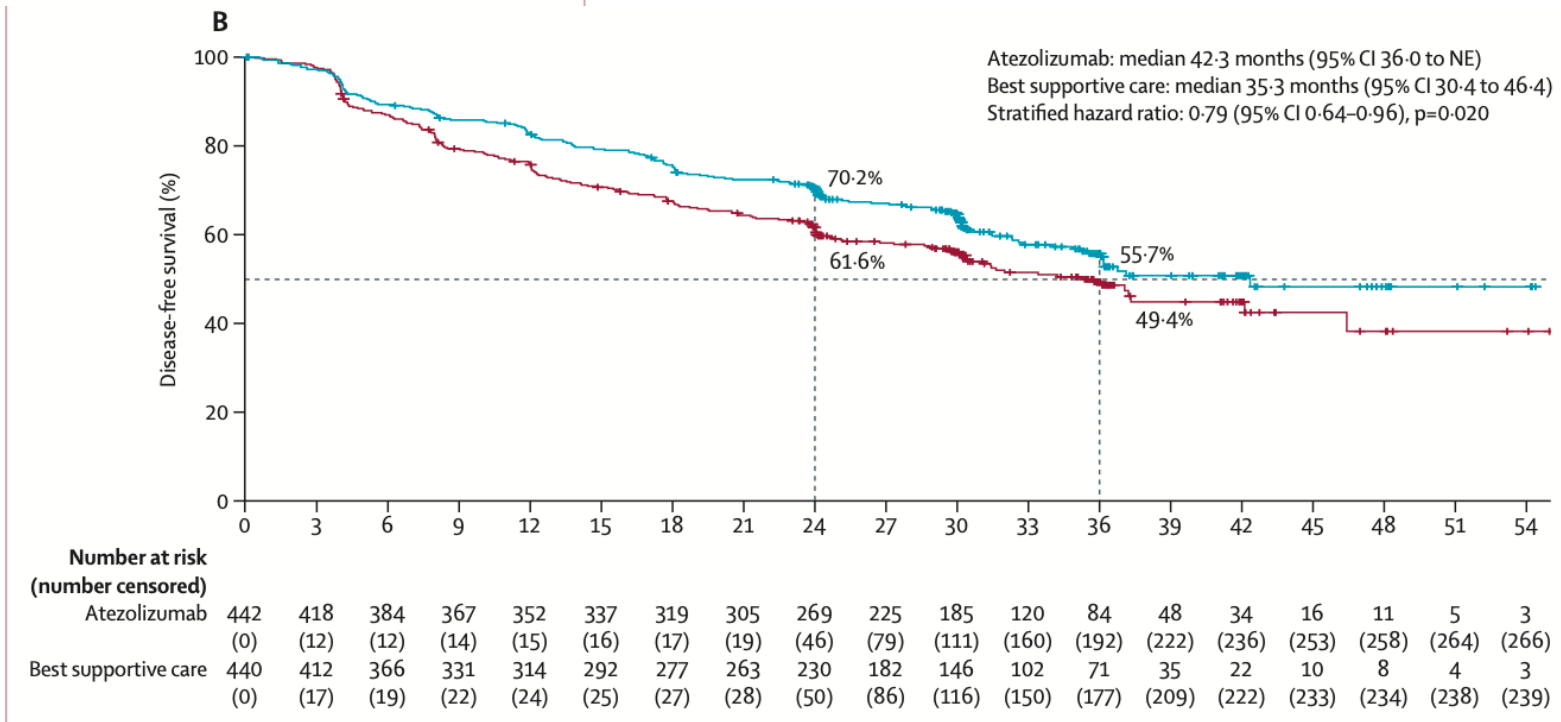
- Primary endpoint DFS. Statistical hierarchical testing.



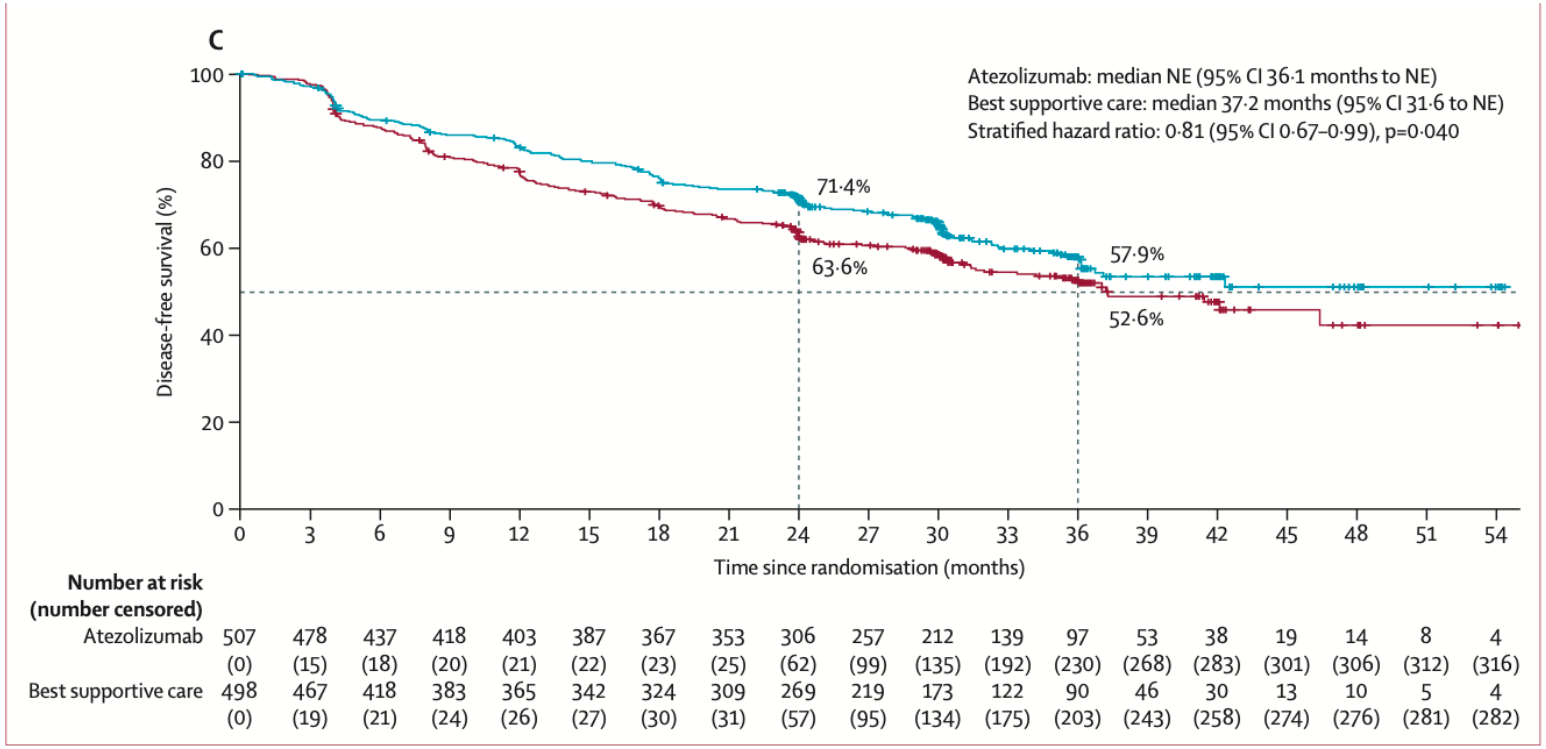


PD-L1 TC ≥1% stage II–IIIA group

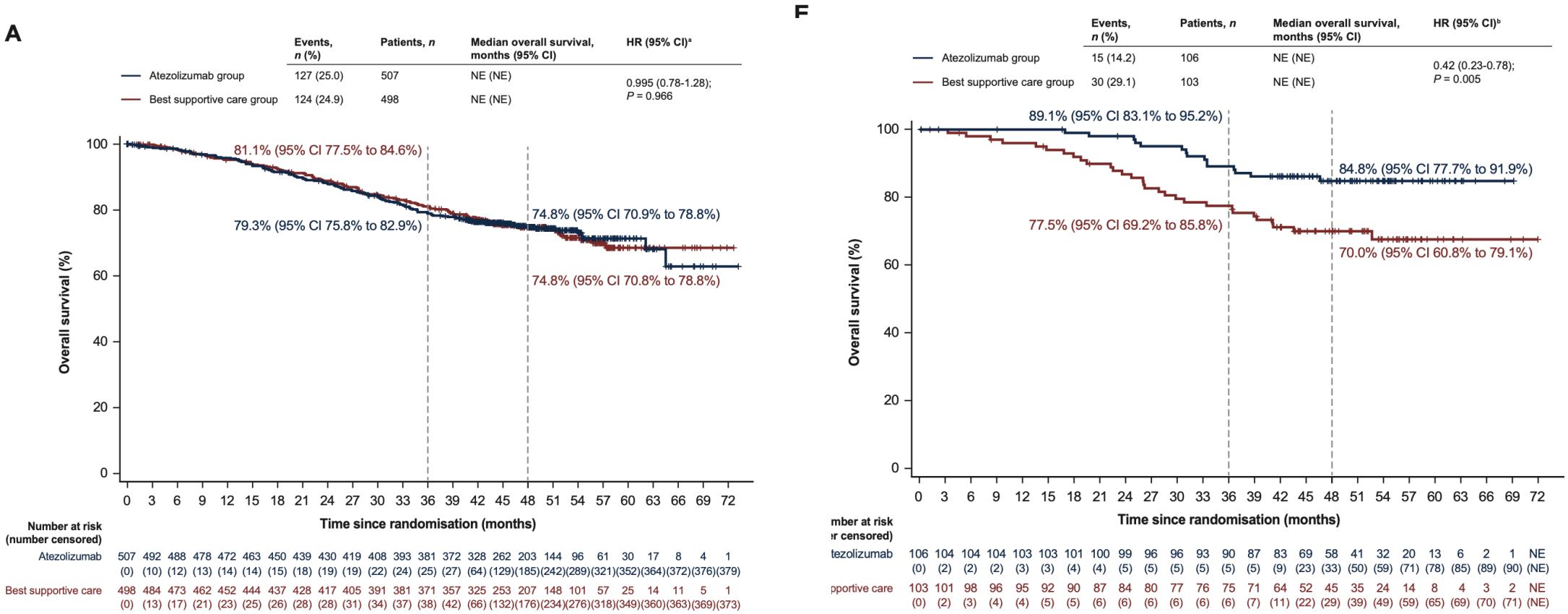
All stage II–IIIA group



Intention-to-treat group (stage IB–IIIA)



Overall survival



Felip, E. *et al.* Overall survival with adjuvant atezolizumab after chemotherapy in resected stage II-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase III trial. *Ann Oncol* **34**, 907–919 (2023). PMID (37467930)

What about immune adverse events

- Immunotherapy side effects don't just go away in a couple of weeks.
- Can be long lasting and life changing. i.e. DM-1, myocarditis
- Can be accompanied by a prolong course of steroids that is its own problem.

	Atezolizumab group (n=495)	Best supportive care group (n=495)
Adverse event		
Any grade	459 (93%)	350 (71%)
Grade 3–4	108 (22%)	57 (12%)
Serious	87 (18%)	42 (8%)
Grade 5	8 (2%)*	3 (1%)†
Led to dose interruption of atezolizumab	142 (29%)	..
Led to atezolizumab discontinuation	90 (18%)	..
Immune-mediated adverse events		
Any grade	256 (52%)	47 (9%)
Grade 3–4	39 (8%)	3 (1%)
Required the use of systemic corticosteroids‡	60 (12%)	4 (1%)
Led to discontinuation	52 (11%)	0

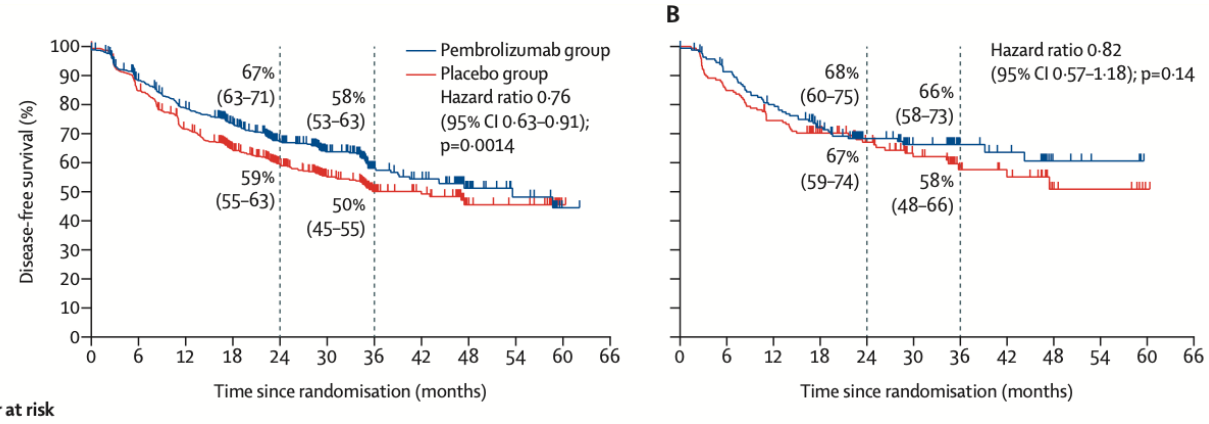
Data are n (%). *Interstitial lung disease, multiple organ dysfunction syndrome, myocarditis, and acute myeloid leukaemia (all four events related to atezolizumab), and pneumothorax, cerebrovascular accident, arrhythmia, and acute cardiac failure. †Pneumonia; pulmonary embolism; and cardiac tamponade and septic shock in the same patient. ‡Atezolizumab-related.

Table 2: **Safety summary in the safety evaluable population**

Pembrolizumab

- KEYNOTE-091 (PEARLS) trial also demonstrated improvement in DFS for patients with stage IB (≥4 cm) to IIIA NSCLC who received up to a year of adjuvant pembrolizumab.
- No association of greater or lesser efficacy in the KEYNOTE-091 trial by PD-L1 expression: The HR for DFS with PD-L1 ≥ 50% was 0.82 (0.57-1.18) versus 0.76 (0.63-0.91) in the overall trial population

O'Brien. Lancet. 2022

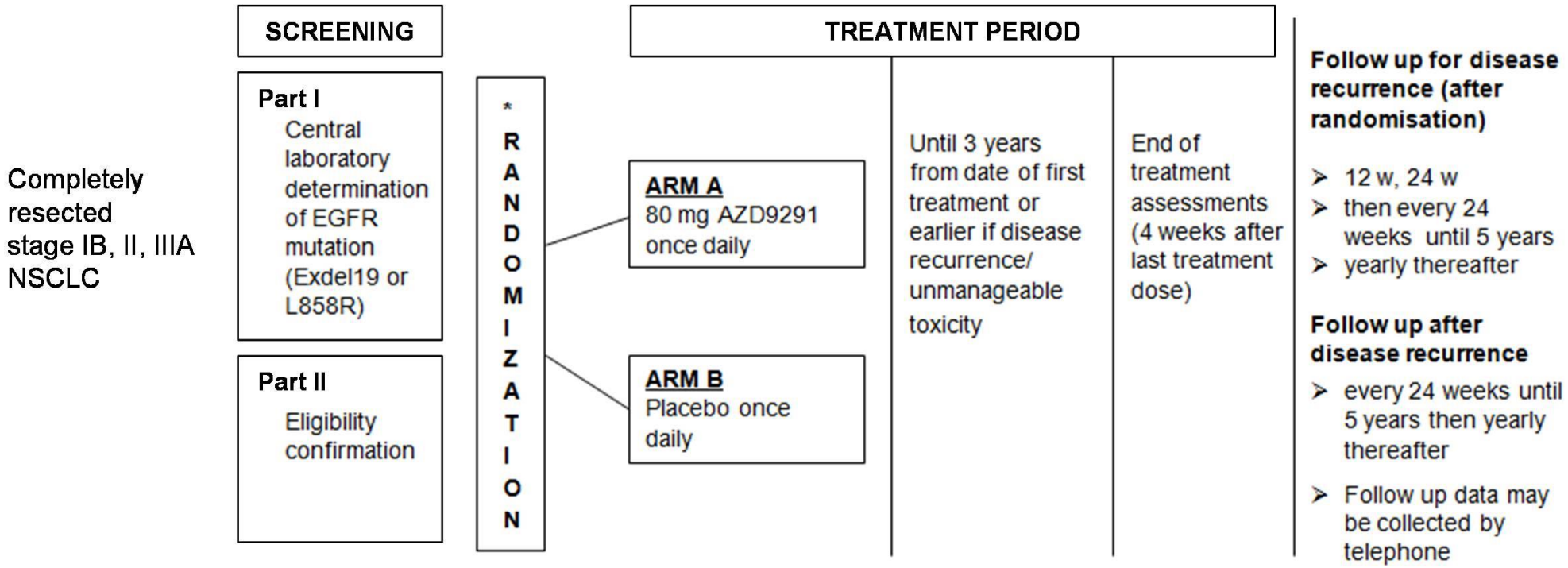


Conclusions Adjuvant CPI.

- Should be discussed in patients who have undergone surgery and adjuvant chemotherapy.
- Unknown if PDL1 plays any role in decision making. Although it makes sense to me and more data is needed.
- Should discuss the need for 1 year of treatment, the considerable financial cost, and the potential for even permanent immune-related adverse events from adjuvant immune checkpoint inhibitors.
- Overall survival data has not matured.

ADAURA

Figure 1 Study Design



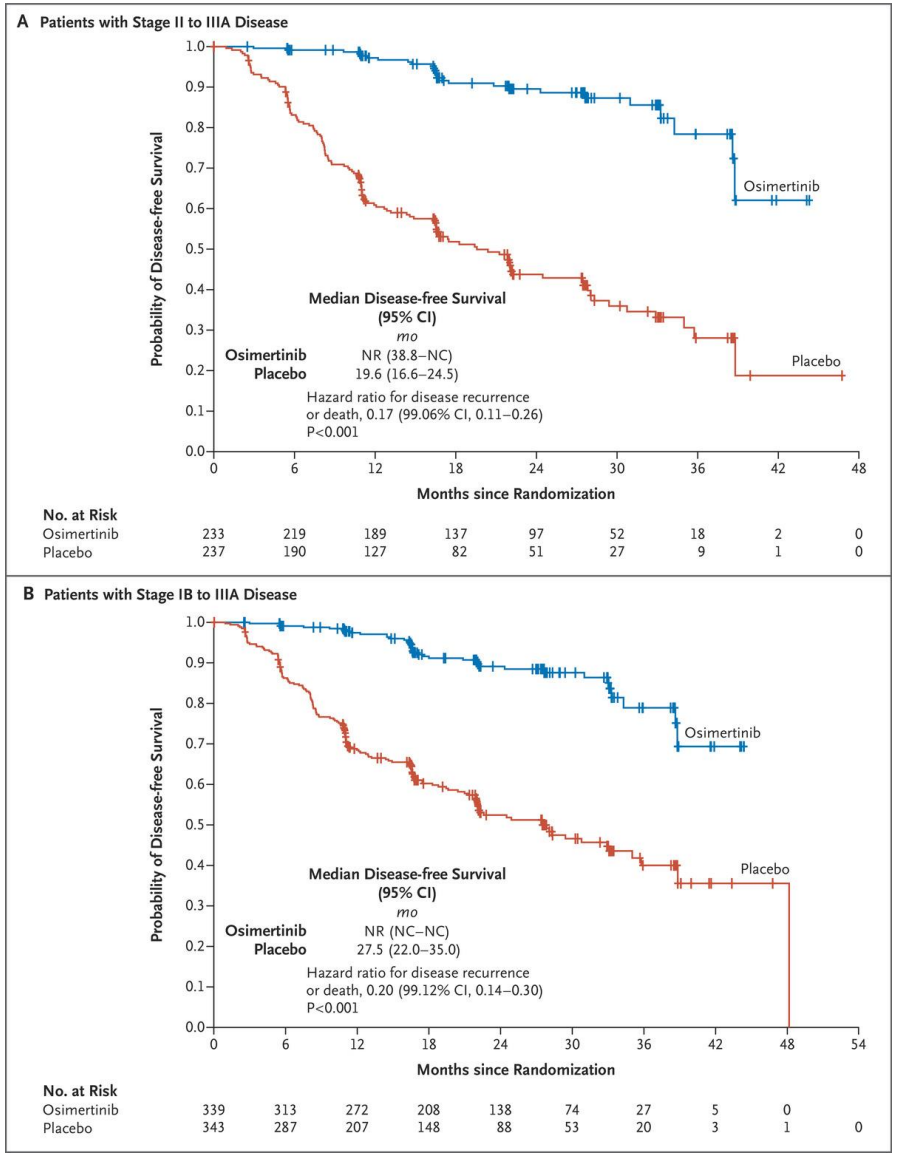
***Stratification:**
– Stage (IB vs. II vs IIIA)
– EGFR mutation (Exdel19 or L858R)
– Race (Asian/non-Asian)

Randomization will be 1:1

Y Wu et al. N Engl J Med 2020;383:1711-1723.

Special populations

- EGFR.
- The independent data monitoring committee recommended that the trial be unblinded in April 2020.

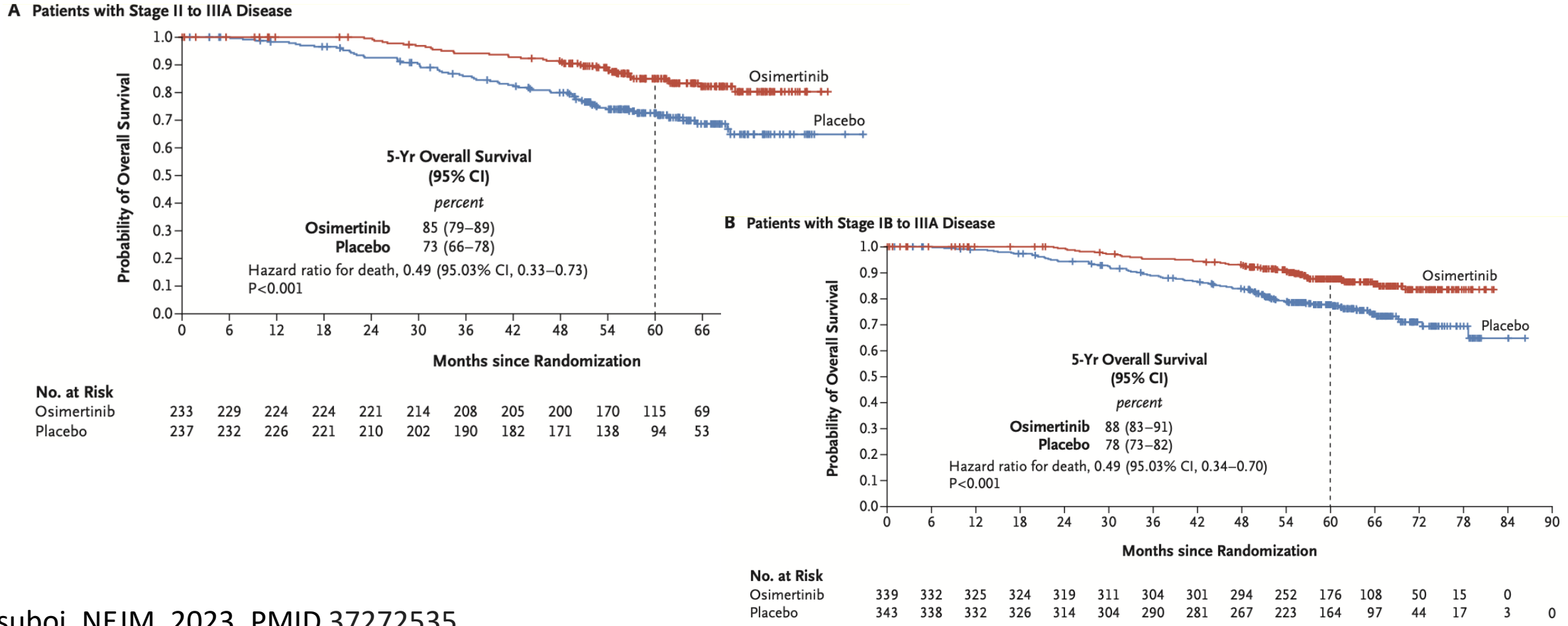


Y Wu et al. N Engl J Med 2020;383:1711-1723.

Table S3. Sites of disease recurrence in the overall population

Number of patients, n (%)	Osimertinib (n=339)	Placebo (n=343)
Total disease recurrence or death events*	37 (11)	159 (46)
Disease recurrence	37 (11)	157 (46)
Local/regional only	23 (7)	61 (18)
Distant only	10 (3)	78 (23)
Local/regional and distant	4 (1)	18 (5)
Death†	0	2 (1)
Total CNS disease recurrence or death events‡	6 (2)	39 (11)
CNS disease recurrence	4 (1)	33 (10)
Death§	2 (1)	6 (2)

Overall survival



Tsuboi. NEJM, 2023. PMID 37272535

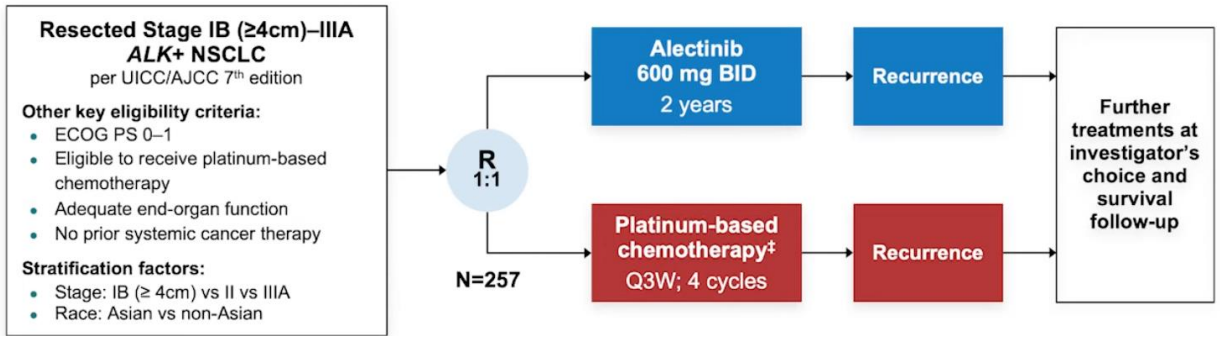
So, now what?

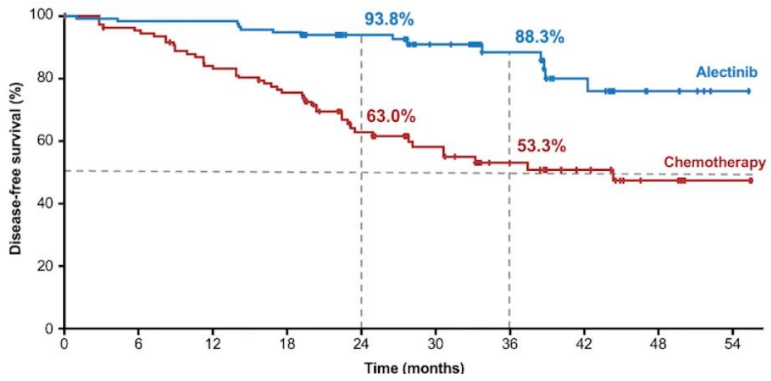
- Approved by the FDA.
- Main criticism is 43% of the patients who got subsequent treatment received osimertinib, with the others getting another EGFR TKI which is known inferior.
- A better trial in a perfect world would have all patients receive Osimertinib at relapse.
- What is the role of chemotherapy?
- Cost for 3 years of therapy is exorbitant.

What about chemotherapy.

- Chemotherapy has a proven benefit in the adjuvant setting.
- Evidence that EGFR NSCLC is less chemoresistant than NSCLC and therefore patients might have a higher benefit from adjuvant treatment.
- The use of adjuvant Osimertinib should not supplant the use of chemotherapy.

ALK+ NSCLC: Adjuvant alectinib (ALINA)





	Alectinib (N=116)	Chemotherapy (N=115)
Patients with event Death Recurrence	14 (12%) 0 14	45 (39%) 1 44
Median DFS, months (95% CI)	Not reached	44.4 (27.8, NE)
DFS HR (95% CI)	**0.24** (0.13, 0.45) p‡<0.0001	

- Ph 3, open-label, randomized, international, (N=257), stage IB (>4cm)-IIIA, resected:
  - Alectinib x 2 years v. platinum chemo x 4 cycles 3-yr DFS 88% (alectinib) v. 53% (chemo). HR 0.24
- 3-yr DFS 88% (alectinib) v. 53% (chemo). HR 0.24
- HR for CNS recurrence/death: 0.22
- OS data is immature
- May 2024: FDA approved alectinib for adjuvant use in resected, ALK+ NSCLC, stage IB (>4cm), II or IIIA.

Slide poached from Sylvia Lee.

Wu, Y. L. *et al*. Alectinib in Resected ALK-Positive Non-Small-Cell Lung Cancer. *N Engl J Med* **390**, 1265–1276 (2024). PMID (38598794)

ALINA: Considerations

- Same concerns as LAURA: OS benefit is not yet known
- Omission of adjuvant chemotherapy:
  - Adjuvant chemo cures 5.4% patients (LACE meta-analysis)
  - Are TKIs curing any patients, or just prolonging disease recurrence?
  - Should alectinib be given after adjuvant chemo?
- ALK+ NSCLC has higher rates of CNS metastases (50%)
  - CNS protection may have bigger impact on QOL
- Duration of alectinib?
- Do we need to consider lorlatinib in adjuvant setting?

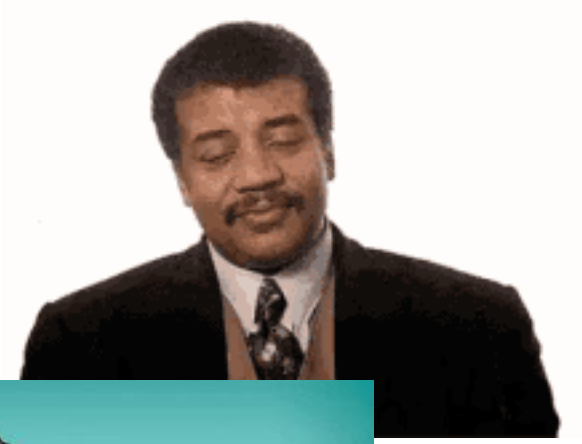
Wu, Y. L. *et al.* Alectinib in Resected ALK-Positive Non-Small-Cell Lung Cancer. *N Engl J Med* **390**, 1265–1276 (2024). PMID (38598794)

Slide poached from Sylvia Lee.

Ongoing questions.

- What about neoadjuvant targeted therapy?
- Is there a role of maintenance immunotherapy after neoadjuvant?
- What about chemo-immunotherapy as adjuvant treatment?
- What is the role of other targeted therapy in other driver mutations?
  - Should we extrapolate ROS-1, BRAF, RET, NTRK, METex14?
- Several clinical trials with immunotherapy are ongoing and more data will be presented.
- **Is there a role for molecular disease monitoring? Key role of Molecular residual disease and circulating DNA in the future but technology is still being developed.**


@LateNightSeth



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