

# Updates in Treatment of Early Stage and Locally Advanced NSCLC

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Cancer Center

Keck Medicine of **USC**

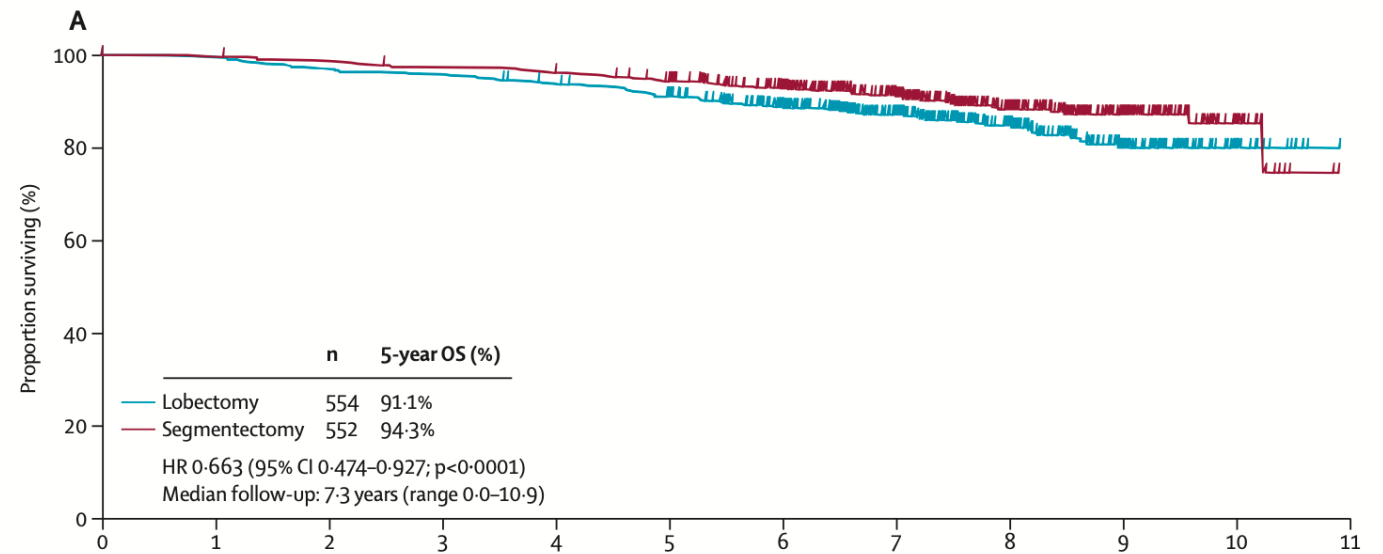
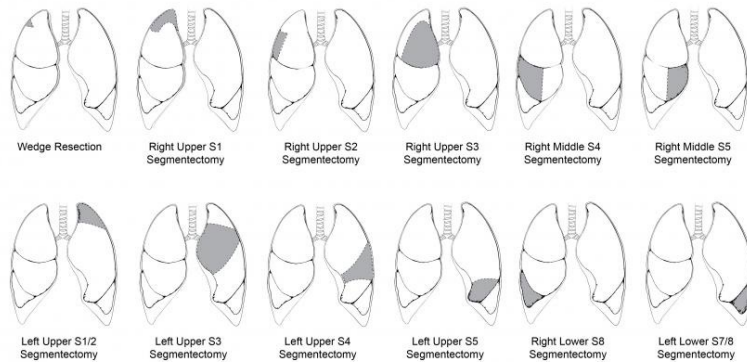
# Outline

- Review new data on local therapy for stage 1 lung cancer
- Updates on adjuvant therapy
- Neoadjuvant and perioperative therapy
- Updates on chemoradiation for locally advanced disease

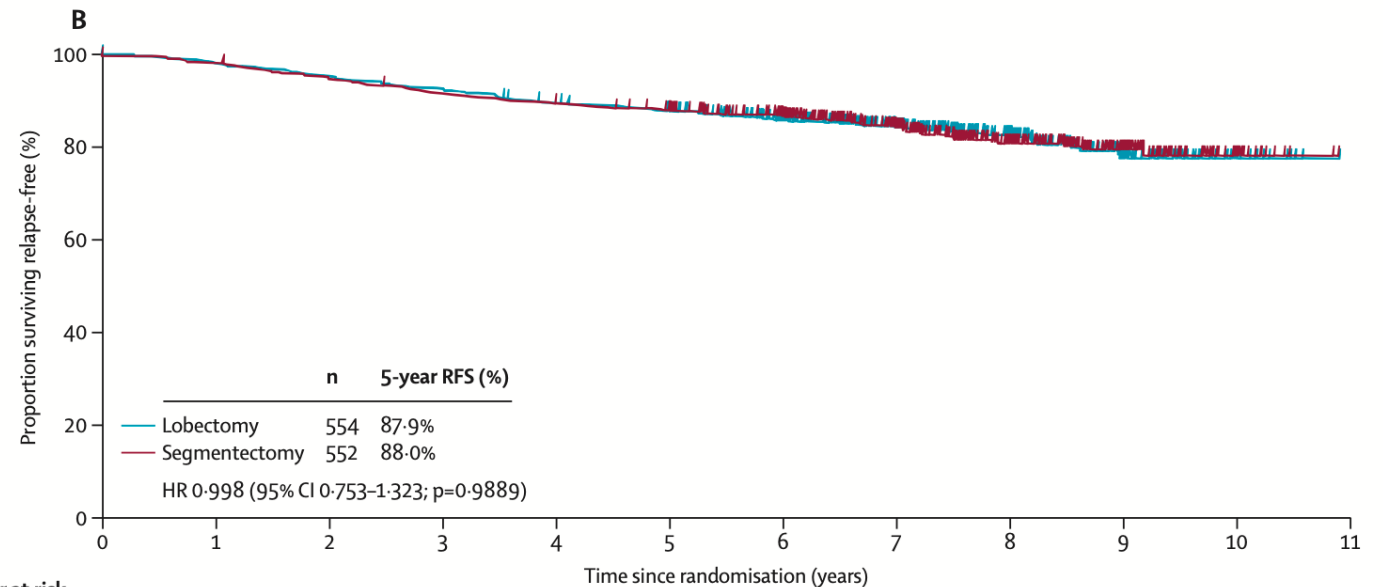
# Stage 1

## Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer (JCOG0802/WJOG4607L)

Saji H, et al. Lancet. 2022 Apr 23;399(10335):1607-1617.



Number at risk (number censored)	0	1	2	3	4	5	6	7	8	9	10	11
Lobectomy	554 (0)	550 (1)	537 (0)	530 (0)	525 (3)	495 (6)	426 (57)	322 (97)	190 (125)	90 (92)	23 (67)	0 (23)
Segmentectomy	552 (0)	549 (1)	543 (1)	534 (1)	528 (0)	512 (6)	457 (47)	332 (118)	202 (122)	104 (96)	25 (78)	0 (24)

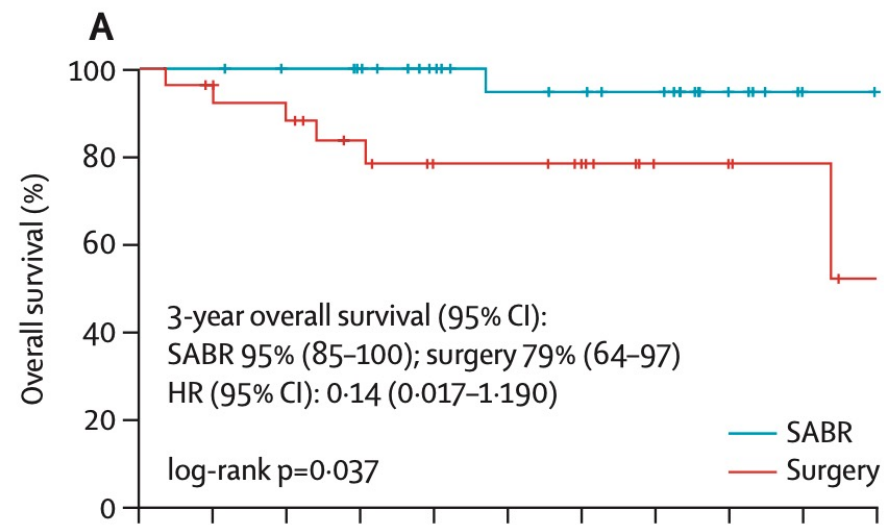


Number at risk (number censored)	0	1	2	3	4	5	6	7	8	9	10	11
Lobectomy	554 (0)	542 (1)	527 (0)	512 (0)	492 (3)	477 (6)	409 (57)	310 (93)	184 (121)	85 (91)	22 (63)	0 (22)
Segmentectomy	552 (0)	541 (1)	521 (1)	503 (1)	491 (0)	477 (6)	426 (45)	304 (112)	181 (112)	89 (90)	21 (67)	0 (21)

# Radiation or surgery?

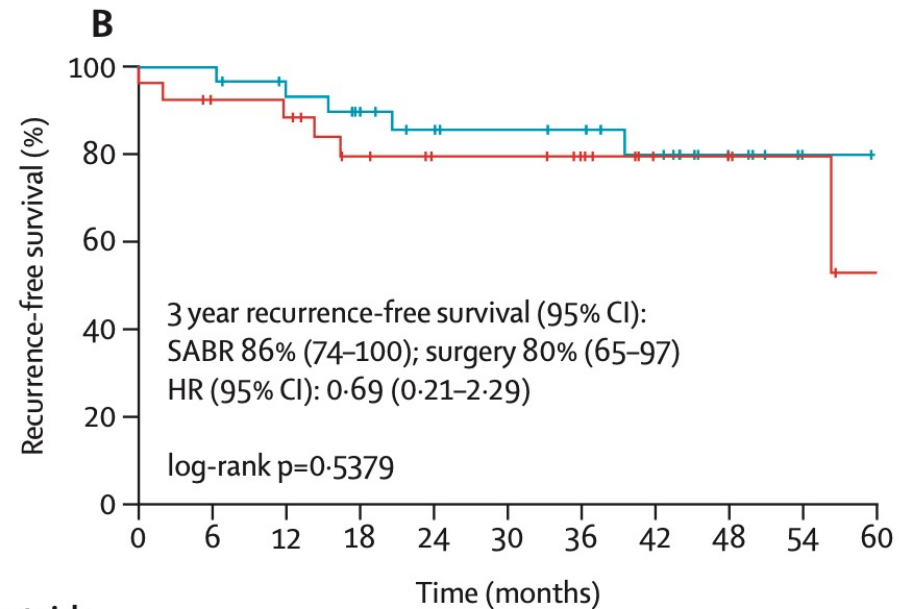
**Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials.**

Chang JY, et al . Lancet Oncol. 2015 Jun;16(6):630-7. PMID: 25981812; PMCID: PMC4489408.



Number at risk

SABR	31	31	29	27	22	18	17	15	7	1	0
Surgery	27	24	22	18	13	13	10	5	4	3	1



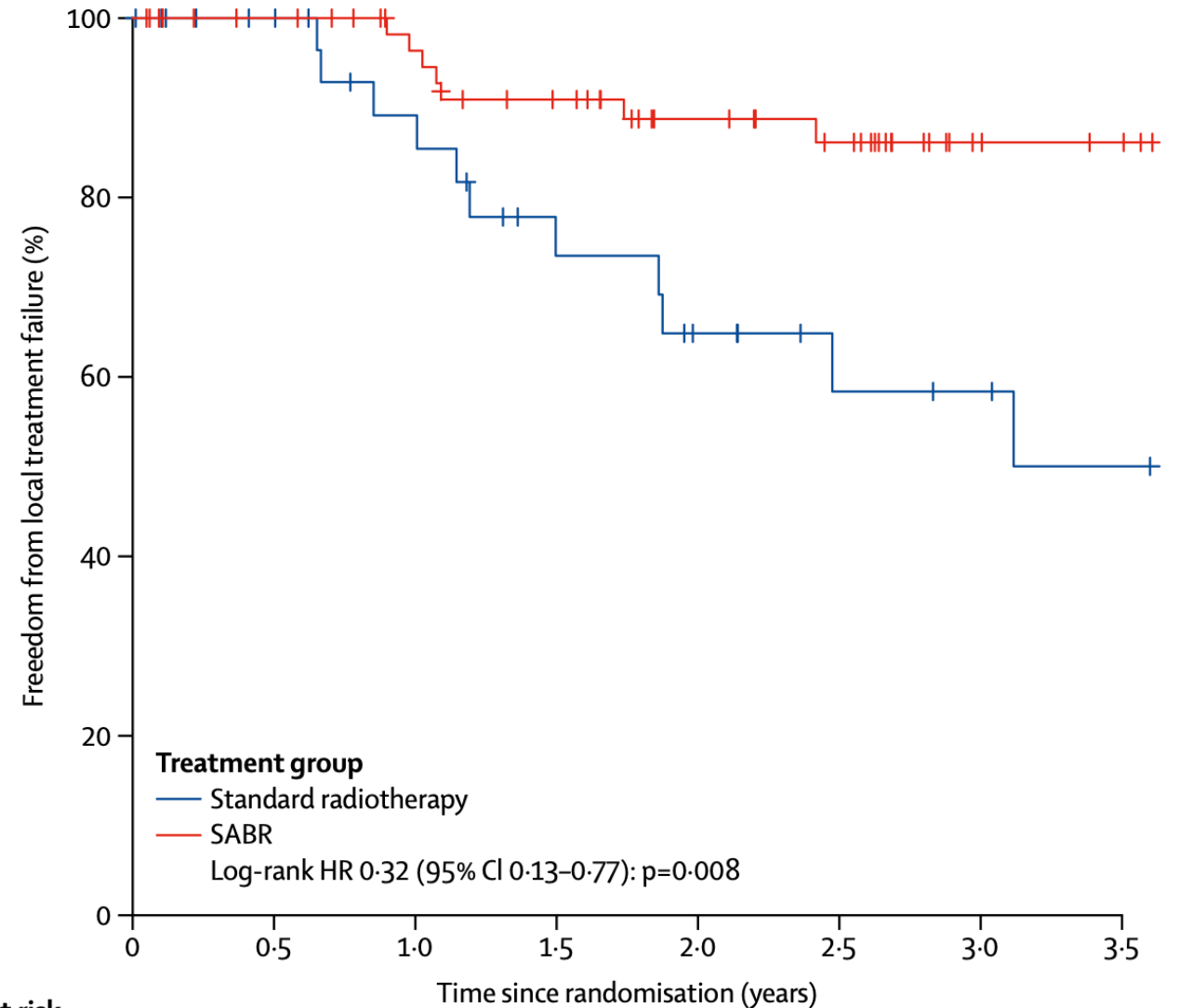
Number at risk

SABR	31	31	28	24	20	18	17	14	7	1	0
Surgery	27	23	22	17	13	13	10	5	4	3	1

# SBRT vs conventional radiation

stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): a phase 3, open-label, randomised controlled trial

Ball D, et al. Lancet Oncol. 2019 Apr;20(4):494-503.

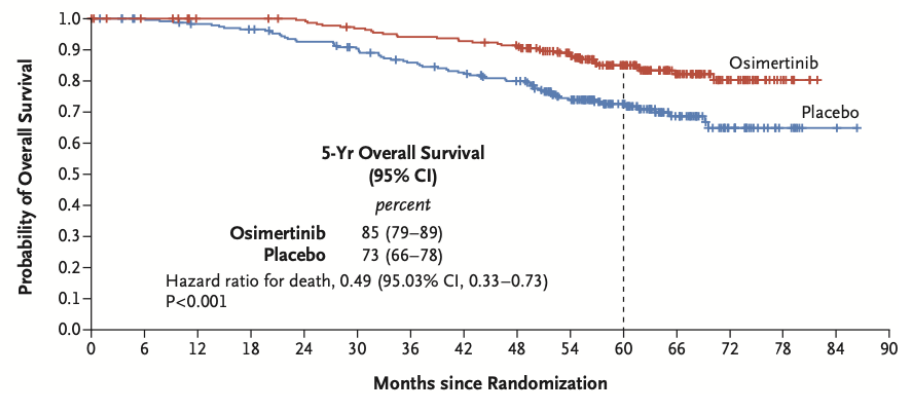


	Number at risk (number censored)							
	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5
Standard radiotherapy	35 (0)	30 (5)	24 (8)	17 (11)	13 (13)	9 (16)	8 (17)	6 (18)
SABR	66 (0)	60 (6)	53 (11)	46 (15)	37 (23)	32 (27)	19 (40)	17 (42)

# Stage Ib-IIIa – Adjuvant therapy EGFR

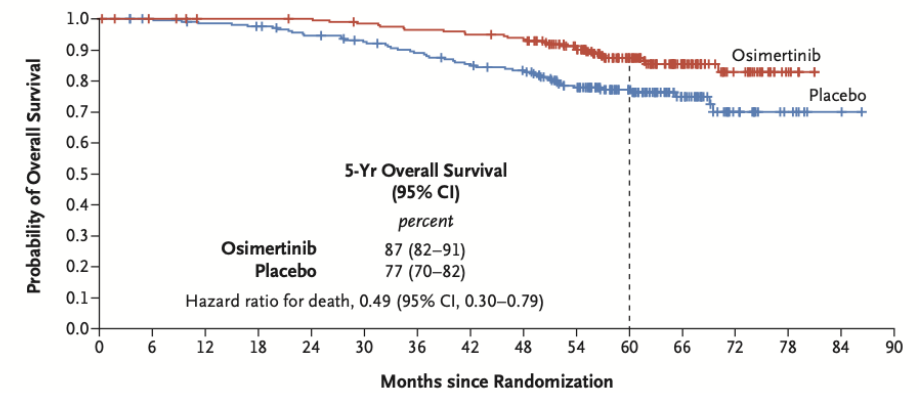
Tsuboi M, et al. N Engl J Med. 2023 Jul 13;389(2):137-147. PMID: 37272535.

**A Patients with Stage II to IIIa Disease**



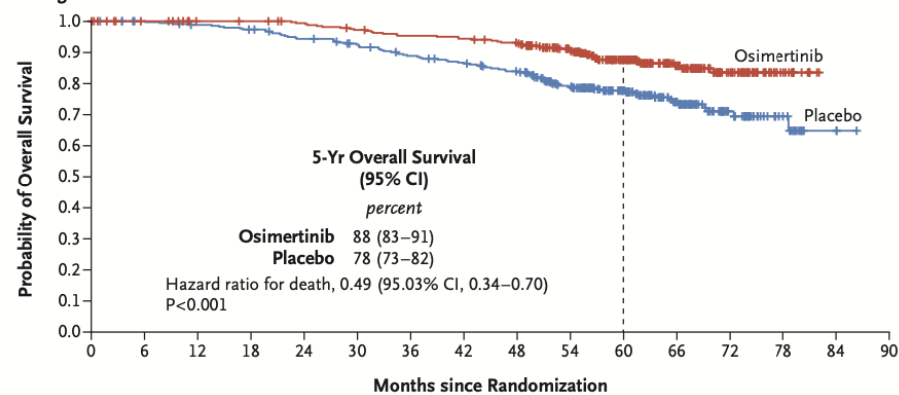
No. at Risk	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90
Osimertinib	233	229	224	224	221	214	208	205	200	170	115	69	33	9	0	0
Placebo	237	232	226	221	210	202	190	182	171	138	94	53	25	8	2	0

**A Patients Who Received Adjuvant Chemotherapy**



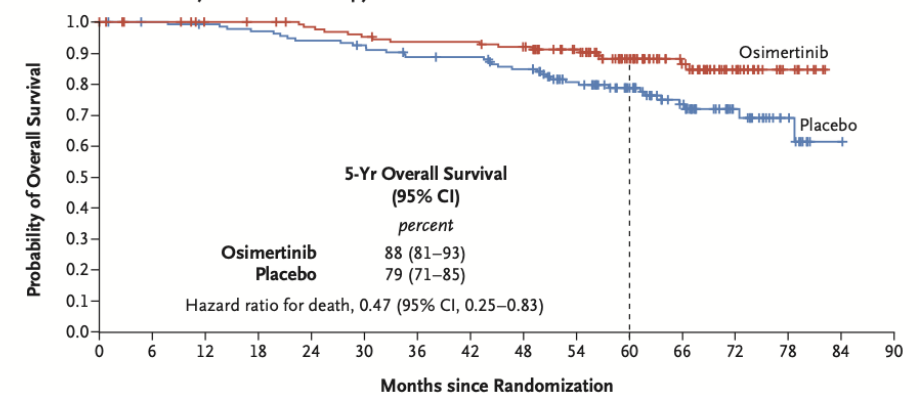
No. at Risk	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90
Osimertinib	203	200	197	197	196	192	188	185	182	155	104	58	25	7	0	0
Placebo	207	204	200	197	189	182	174	166	159	133	92	48	19	7	2	0

**B Patients with Stage Ib to IIIa Disease**



No. at Risk	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90
Osimertinib	339	332	325	324	319	311	304	301	294	252	176	108	50	15	0	0
Placebo	343	338	332	326	314	304	290	281	267	223	164	97	44	17	3	0

**B Patients Who Did Not Receive Adjuvant Chemotherapy**

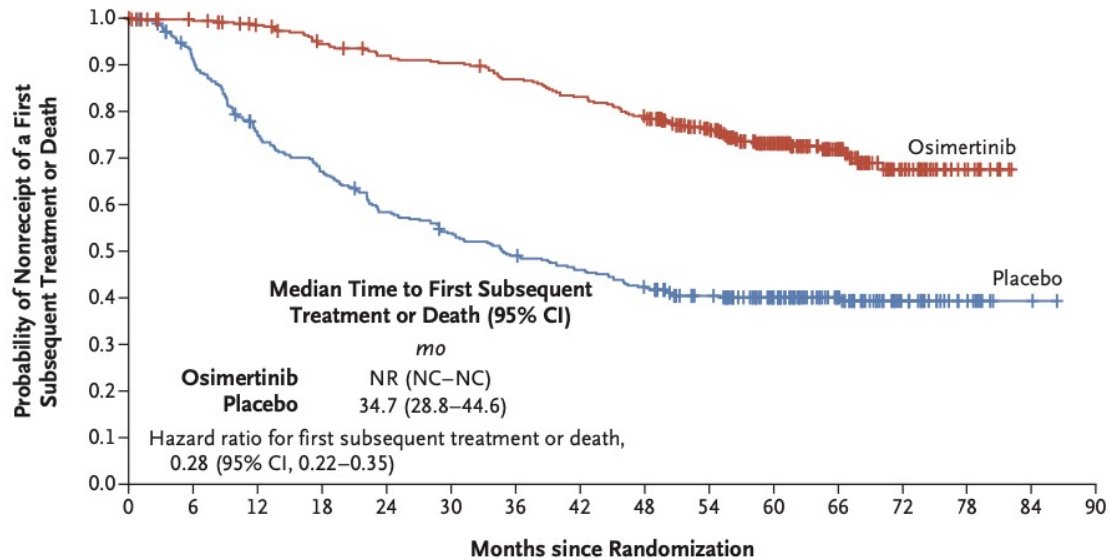


No. at Risk	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90
Osimertinib	136	132	128	127	123	119	116	116	112	97	72	50	25	8	0	0
Placebo	136	134	132	129	125	122	116	115	108	90	72	49	25	10	1	0

# Aduvant Osimertinib in Early Stage

Table S4. Summary of Subsequent Anticancer Treatments\* Received in the Overall Population

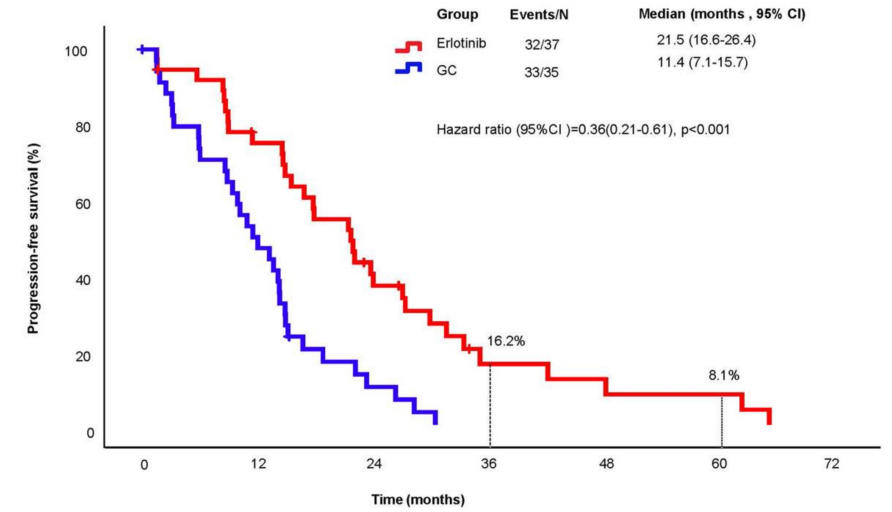
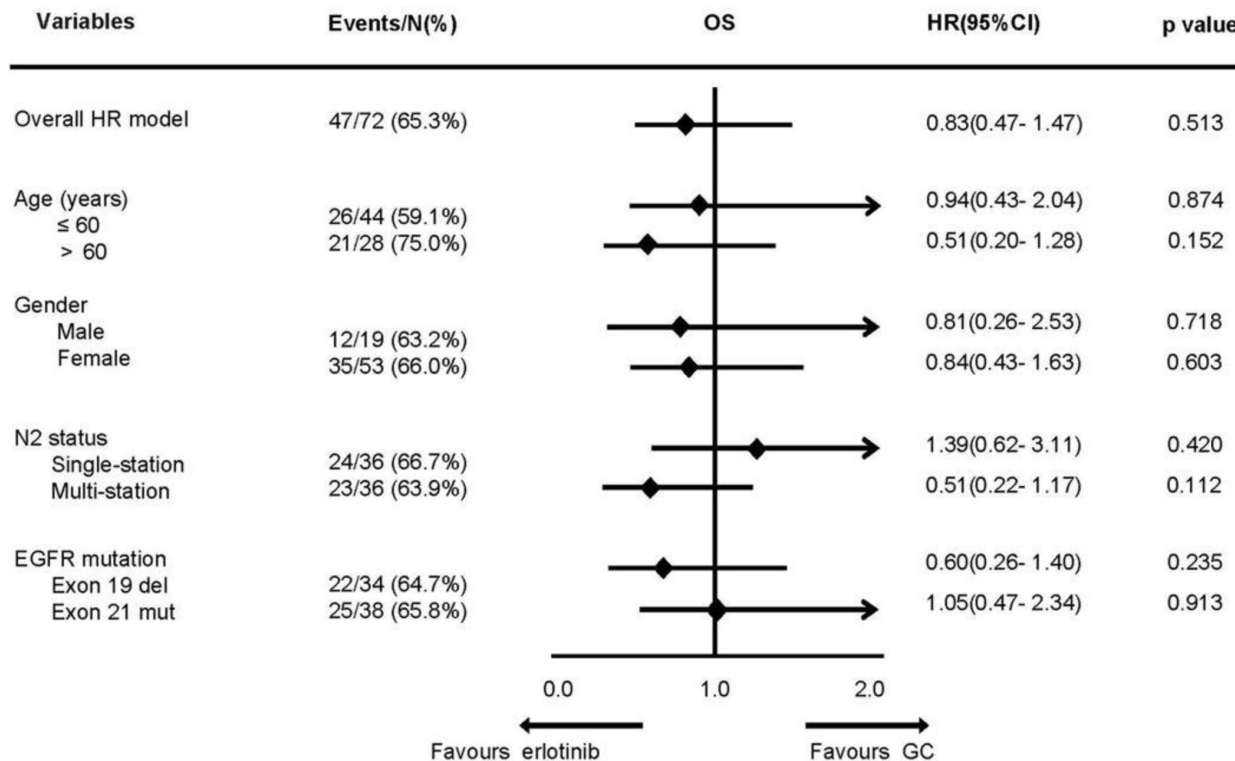
	Osimertinib	Placebo
	<i>number of patients (percent)</i>	
<b>All patients</b>	<b>N = 339</b>	<b>N = 343</b>
Patients who received subsequent anticancer treatment*	n = 76 (22)	n = 184 (54)
EGFR-TKIs <sup>†</sup>	58 (76)	162 (88)
Osimertinib	31 (41)	79 (43)
Gefitinib	13 (17)	55 (30)
Afatinib	7 (9)	30 (16)
Erlotinib	6 (8)	24 (13)
Icotinib	2 (3)	15 (8)



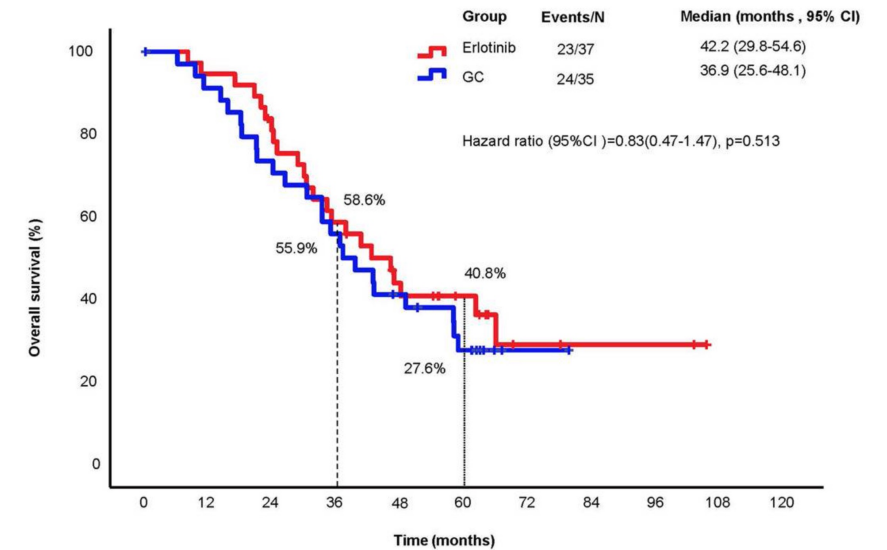
No. at Risk	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90
Osimertinib	339	328	318	302	292	287	275	263	249	208	147	87	37	12	0	
Placebo	343	308	250	224	194	178	162	151	138	118	89	54	27	10	2	0

# Adjuvant Erlotinib vs Chemotherapy

EMERGING-CTONG 1103 randomised phase II trial  
Zhong et al 2023



Number at Risk (number censored)	0	12	24	36	48	60	72
Erlotinib	37(0)	26(2)	12(1)	4(2)	2(0)	2(0)	0(0)
GC	35(0)	16(1)	3(1)	0(0)	0(0)	0(0)	0(0)



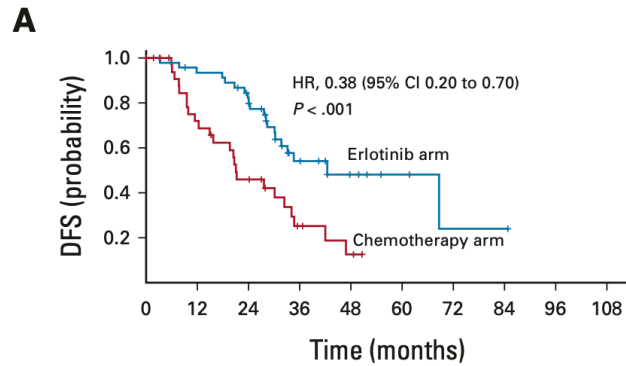
Number at Risk (number censored)	0	12	24	36	48	60	72	84	96	108	120
Erlotinib	37(0)	35(0)	28(1)	21(0)	13(2)	9(4)	3(4)	2(1)	2(0)	0(2)	0(0)
GC	35(0)	31(1)	24(0)	19(0)	13(1)	8(1)	1(7)	0(1)	0(0)	0(0)	0(0)



# Erlotinib vs Cisplatin/Vinorelbine

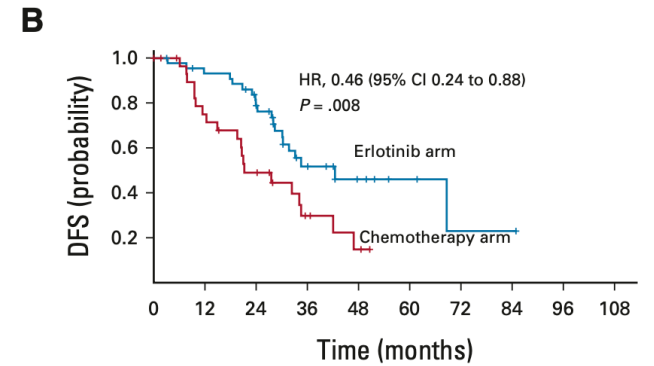
Exploratory Analysis From Randomized, Phase II EVAN Study of Erlotinib Versus Vinorelbine Plus Cisplatin Adjuvant Therapy in Stage IIIA Epidermal Growth Factor Receptor+ Non-Small-Cell Lung Cancer.

Yue D et al. J Clin Oncol. 2022 Dec 1;40(34):3912-3917.



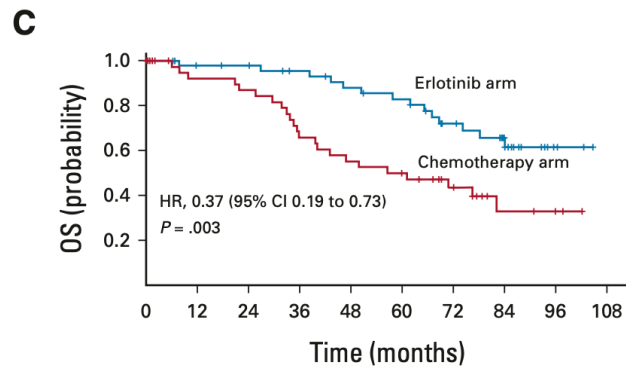
No. at risk:

Erlotinib	51	42	33	15	6	3	1	1	0
Chemotherapy	51	23	14	5	2	0			



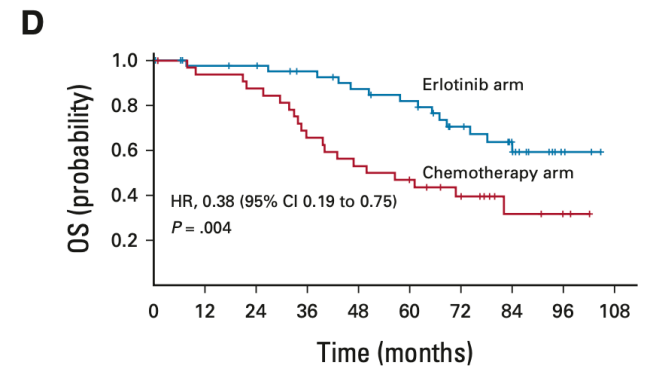
No. at risk:

Erlotinib	46	40	31	14	6	3	1	1	0
Chemotherapy	33	21	13	5	2	0			



No. at risk:

Erlotinib	51	44	43	39	35	32	24	15	3	0
Chemotherapy	51	35	33	25	21	18	12	5	2	0

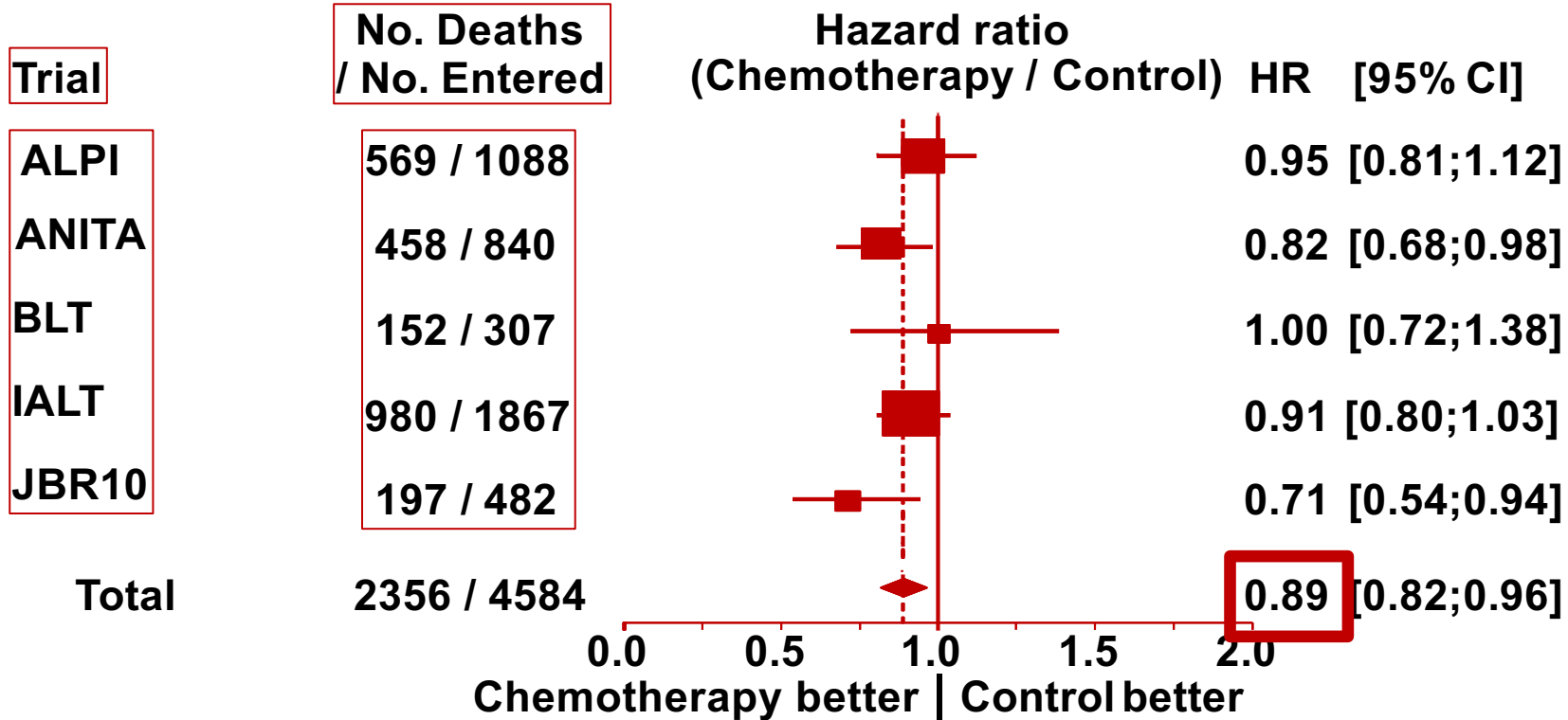


No. at risk:

Erlotinib	46	42	41	37	33	30	22	14	3	0
Chemotherapy	33	30	28	21	17	14	10	4	2	0

# LACE Meta-analysis: Cisplatin-based

Pignon JP et al, J Clin Oncol 2006; 24



Test for heterogeneity:  $p = 0.34$

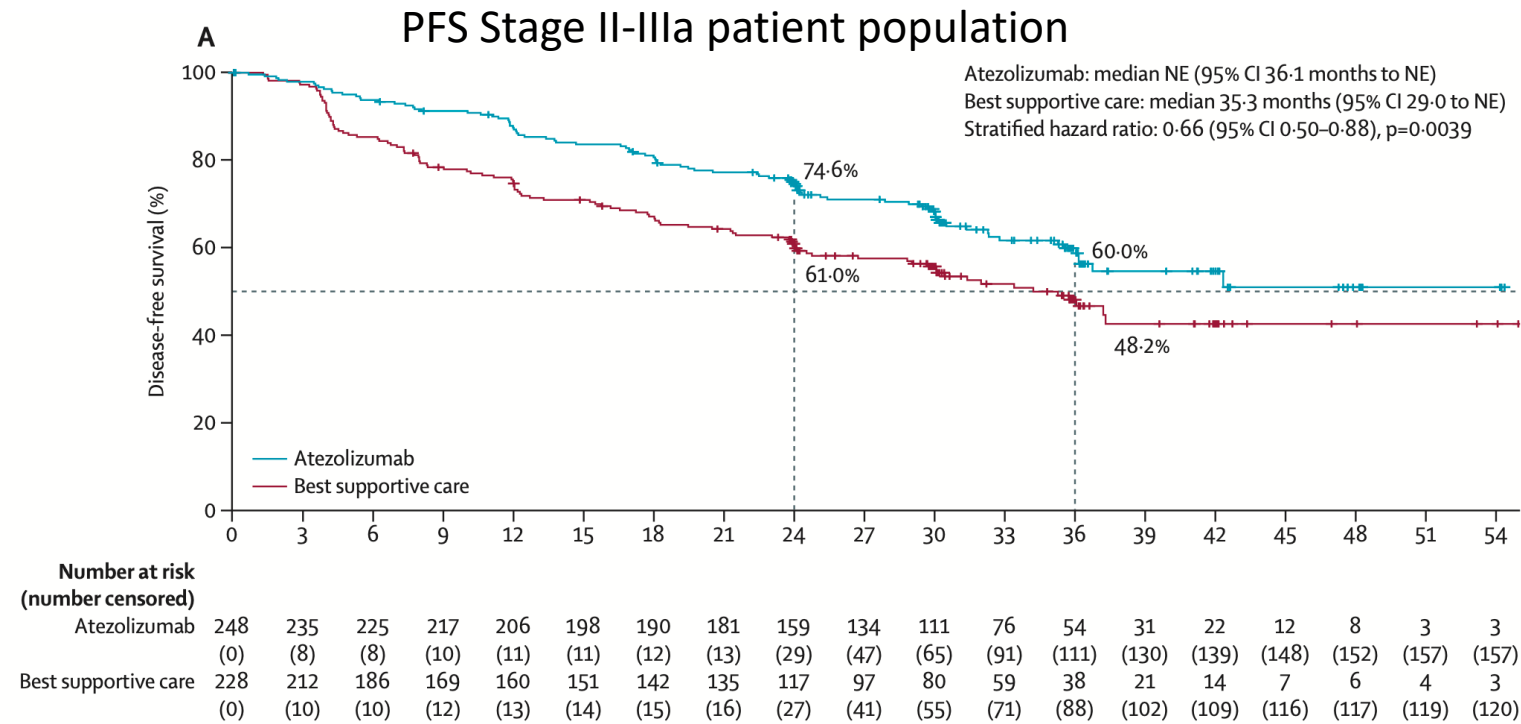
Chemotherapy effect:  $p = 0.004$

ABSOLUTE survival benefit gain is SMALL (~5%)

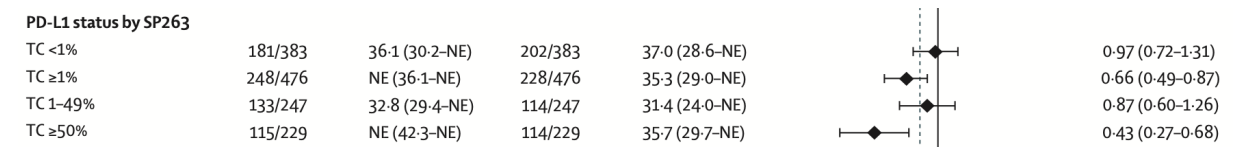
# Adjuvant Atezolizumab

Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIa non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial.

Felip et. Al Lancet. 2021 Oct 9;398(10308):1344-1357.

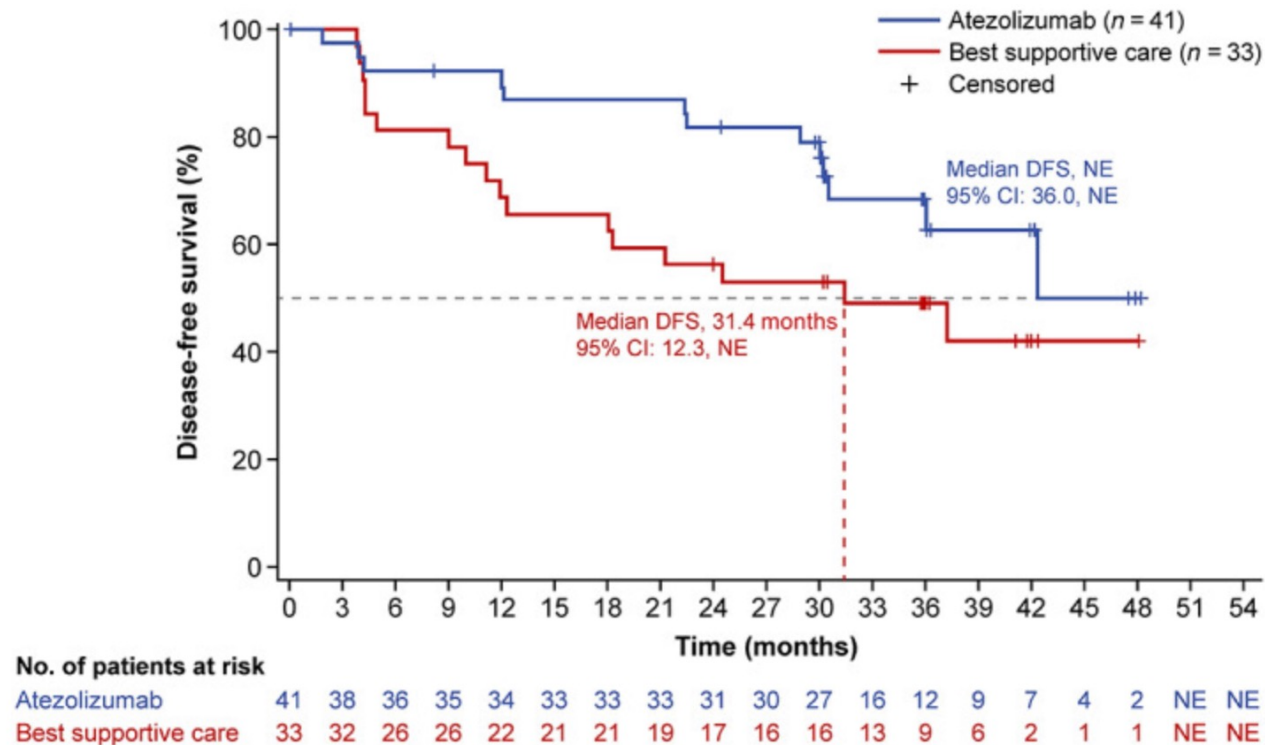


Adverse event	Atezolizumab group (n=495)	Best supportive care group (n=495)
<b>Any grade</b>	459 (93%)	350 (71%)
Grade 3-4	108 (22%)	57 (12%)
<b>Serious</b>	87 (18%)	42 (8%)
Grade 5	8 (2%)*	3 (1%)†
Led to dose interruption of atezolizumab	142 (29%)	..
Led to atezolizumab discontinuation	90 (18%)	..
<b>Immune-mediated adverse events</b>		
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

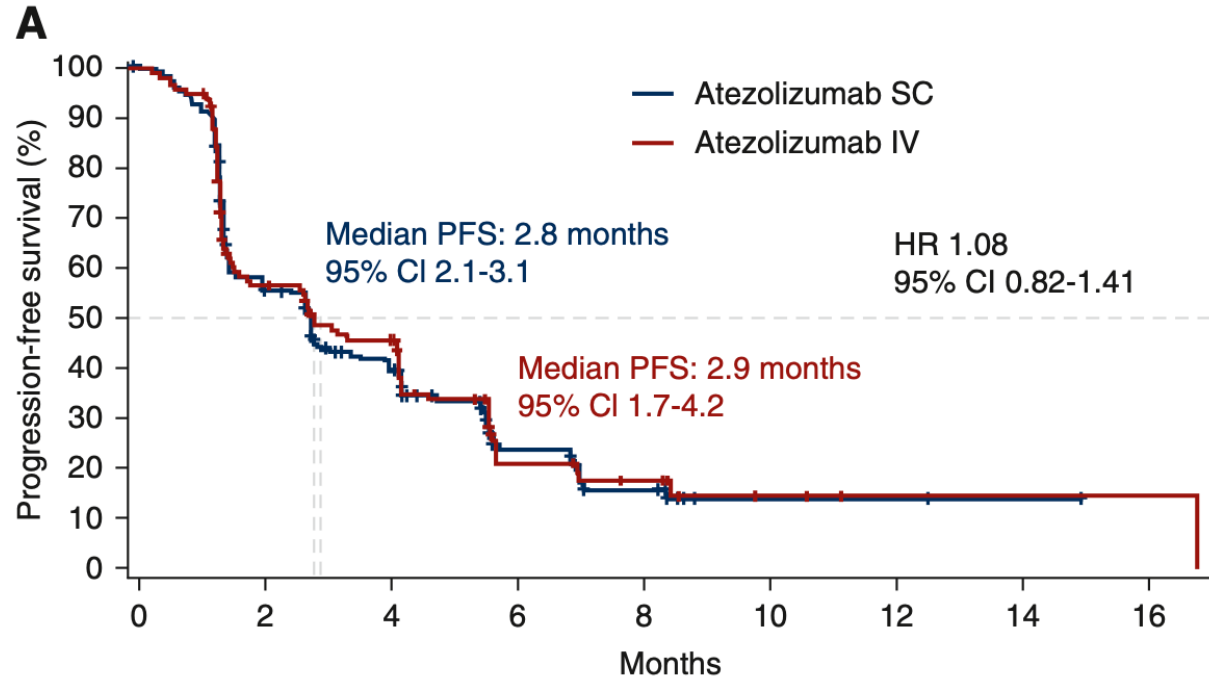


# Does Ethnicity Matter?

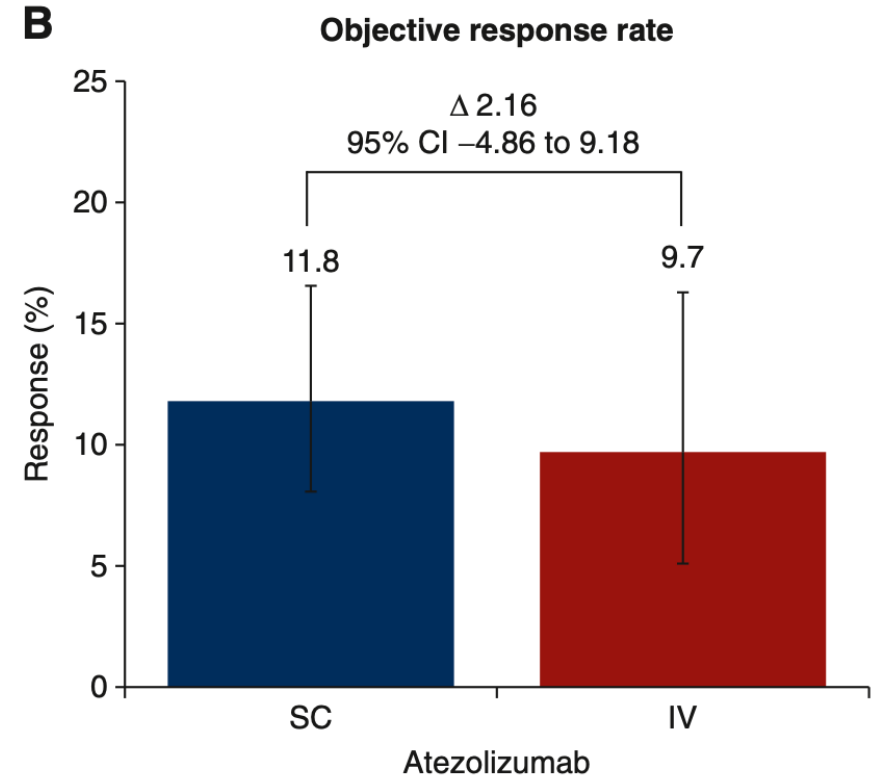
Kenmotsu et al 2022: Analysis of Japanese patients enrolled in IMpower 010 with PD-L1 >1%



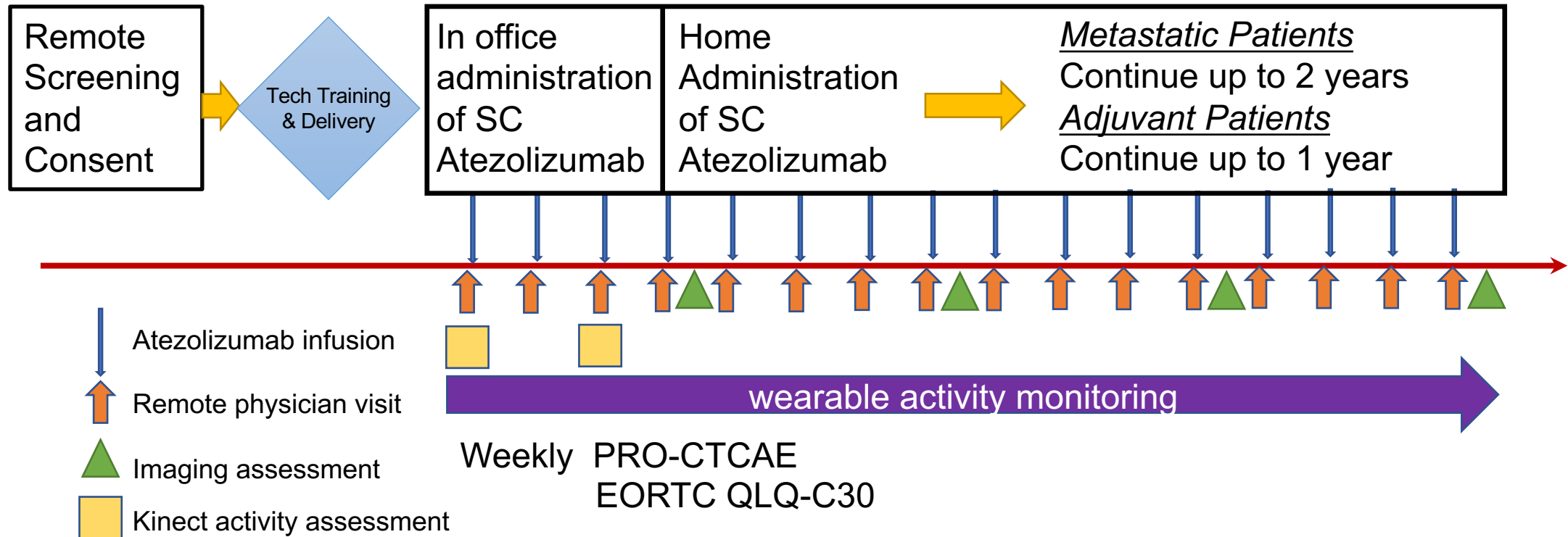
# Coming Soon – Subcutaneous Atezolizumab



	No. at risk								
Atezolizumab SC	247	124	80	28	12	2	2	1	NE
Atezolizumab IV	124	60	45	14	9	3	1	1	1



# Coming Soon – Subcutaneous Atezolizumab



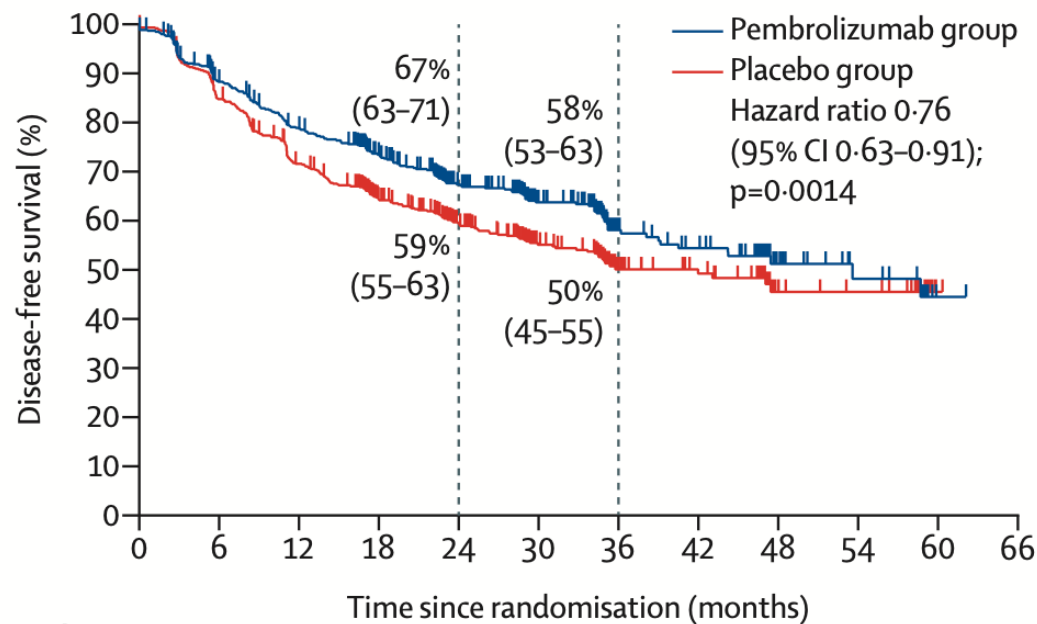
# Adjuvant Pembrolizumab

EORTC-1416-LCG/ETOP 8-15 – PEARLS/KEYNOTE-091 Investigators.  
Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB-IIIa non-small-cell lung cancer

O'Brien M et al Lancet Oncol. 2022 Oct;23(10):1274-1286.

A

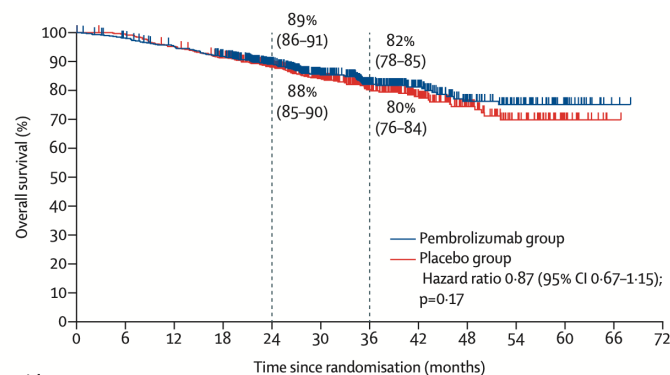
## Progression Free Survival



Number at risk  
(number censored)

Pembrolizumab	590	493	434	358	264	185	82	70	28	16	1	0
	(0)	(30)	(36)	(84)	(150)	(216)	(306)	(313)	(352)	(363)	(377)	(378)
Placebo	587	493	409	326	241	160	72	57	22	18	1	0
	(0)	(5)	(13)	(56)	(118)	(183)	(259)	(273)	(305)	(309)	(326)	(327)

## Overall Survival



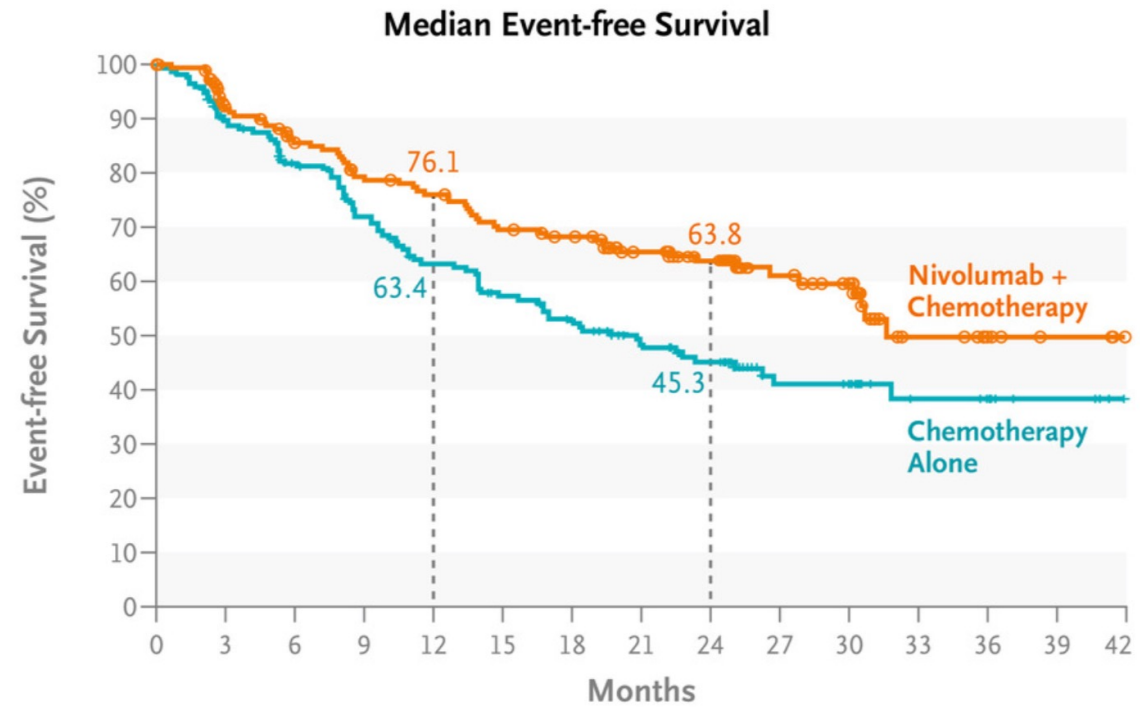
Number at risk (number censored)													
Pembrolizumab	590	572	548	520	419	318	226	143	83	52	23	2	0
	(0)	(7)	(14)	(22)	(109)	(194)	(276)	(357)	(410)	(440)	(469)	(490)	(492)
Placebo	587	582	556	524	420	309	213	135	78	44	16	1	0
	(0)	(2)	(3)	(12)	(99)	(193)	(277)	(350)	(402)	(432)	(460)	(475)	(476)

Histology	Pembrolizumab	Placebo	Hazard Ratio (95% CI)
Non-squamous	146/398	184/363	0.67 (0.54-0.83)
Squamous	66/192	76/224	1.04 (0.75-1.45)
PD-L1 TPS			
<1%	89/233	106/232	0.78 (0.58-1.03)*
1-49%	69/189	91/190	0.67 (0.48-0.92)*
≥50%	54/168	63/165	0.82 (0.57-1.18)*
EGFR mutation			
No	84/218	102/216	0.78 (0.59-1.05)
Yes	18/39	22/34	0.44 (0.23-0.84)

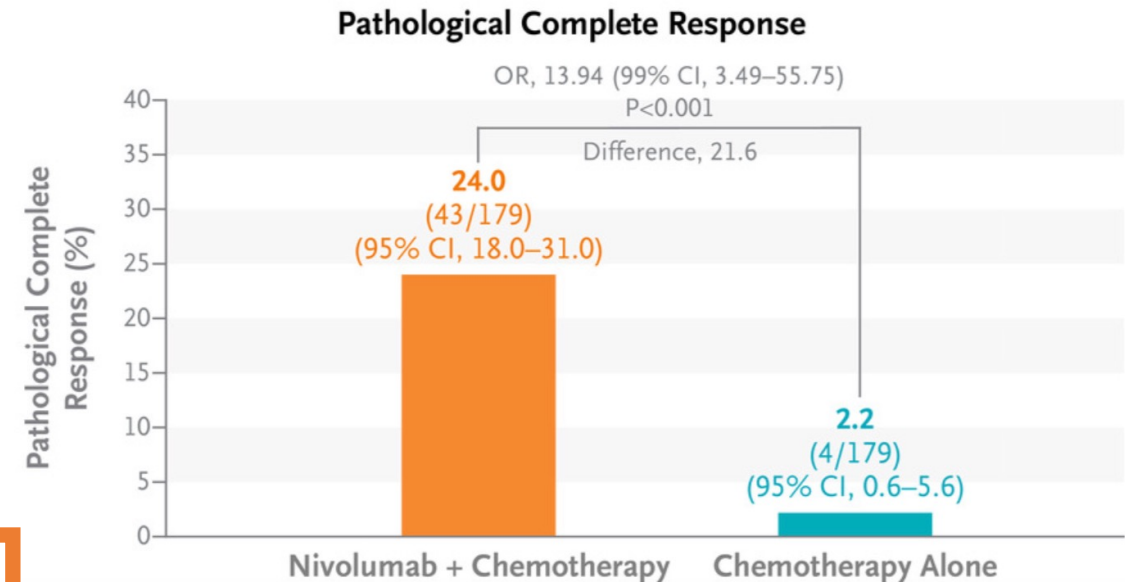
# Checkmate 816 Neoadjuvant Nivolumab

Neoadjuvant Nivolumab plus Chemotherapy  
in Resectable Lung Cancer.

Forde PM et al. N Engl J Med. 2022 May  
26;386(21):1973-1985



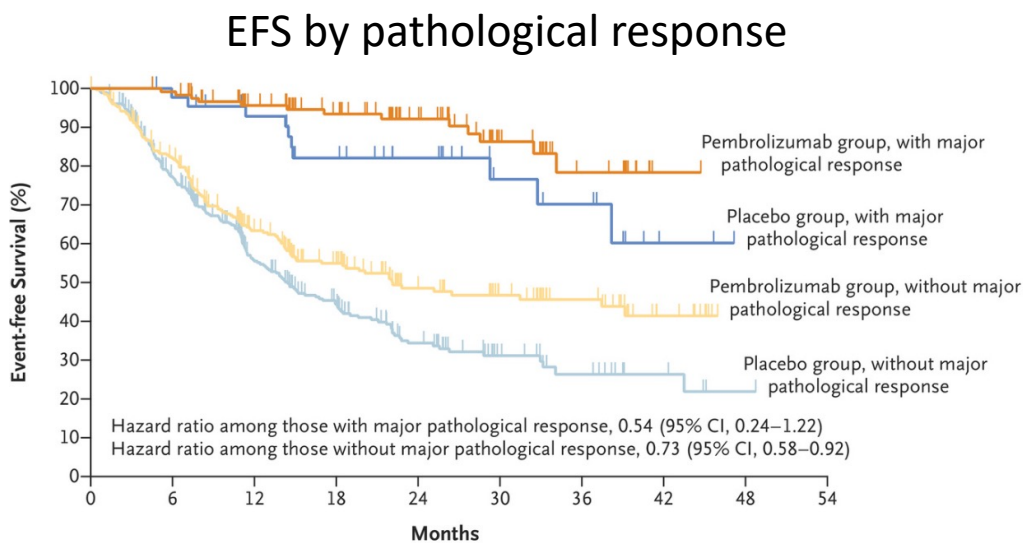
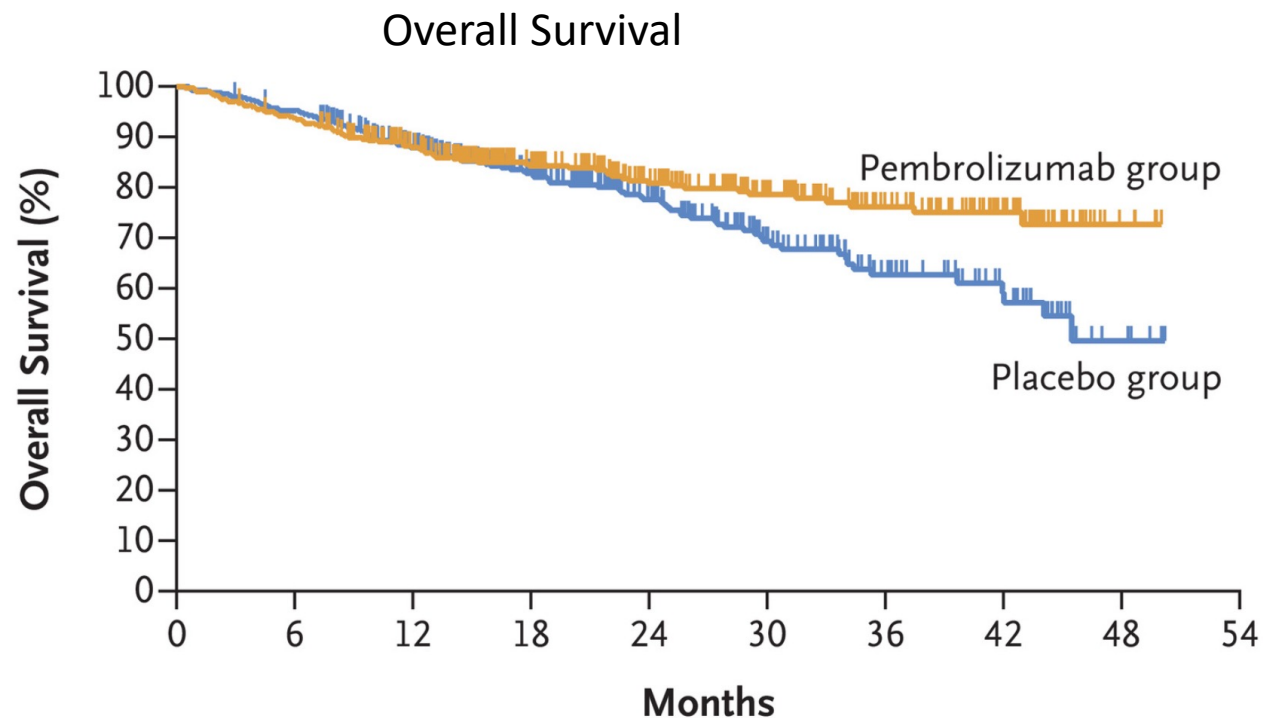
Event	Nivolumab plus Chemotherapy (N=176)		Chemotherapy Alone (N=176)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Adverse events of any cause — no. (%)†				
All	163 (92.6)	72 (40.9)	171 (97.2)	77 (43.8)
Leading to discontinuation of treatment	18 (10.2)	10 (5.7)	20 (11.4)	7 (4.0)
Serious	30 (17.0)	19 (10.8)	24 (13.6)	17 (9.7)
Treatment-related adverse events — no. (%)†				
All	145 (82.4)	59 (33.5)	156 (88.6)	65 (36.9)
Leading to discontinuation of treatment	18 (10.2)	10 (5.7)	17 (9.7)	6 (3.4)
Serious	21 (11.9)	15 (8.5)	18 (10.2)	14 (8.0)
Death‡	0	—	3 (1.7)	—
Surgery-related adverse events — no./total no. (%)§				
	62/149 (41.6)	17/149 (11.4)	63/135 (46.7)	20/135 (14.8)





# Keynote-671 Perioperative Pembrolizumab

Wakelee H et al. N Engl J Med. 2023 Jun 3.



### No. at Risk

group	0	6	12	18	24	30	36	42	48	54
Pembrolizumab	397	370	313	232	170	118	76	41	5	0
Placebo group	400	379	316	225	153	91	54	30	6	0

### PD-L1 TPS (50% cutoff)

<50%	107/265	142/266	0.64 (0.49–0.82)
≥50%	32/132	63/134	0.42 (0.28–0.65)

### PD-L1 TPS (1% cutoff)

<1%	63/138	80/151	0.77 (0.55–1.07)
≥1%	76/259	125/249	0.47 (0.36–0.63)

### PD-L1 TPS

<1%	63/138	80/151	0.77 (0.55–1.07)
1–49%	44/127	62/115	0.51 (0.34–0.75)
≥50%	32/132	63/134	0.42 (0.28–0.65)

### EGFR mutation

No	31/111	64/127	0.48 (0.31–0.74)
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# NeoTorch – Perioperative Torpalimab

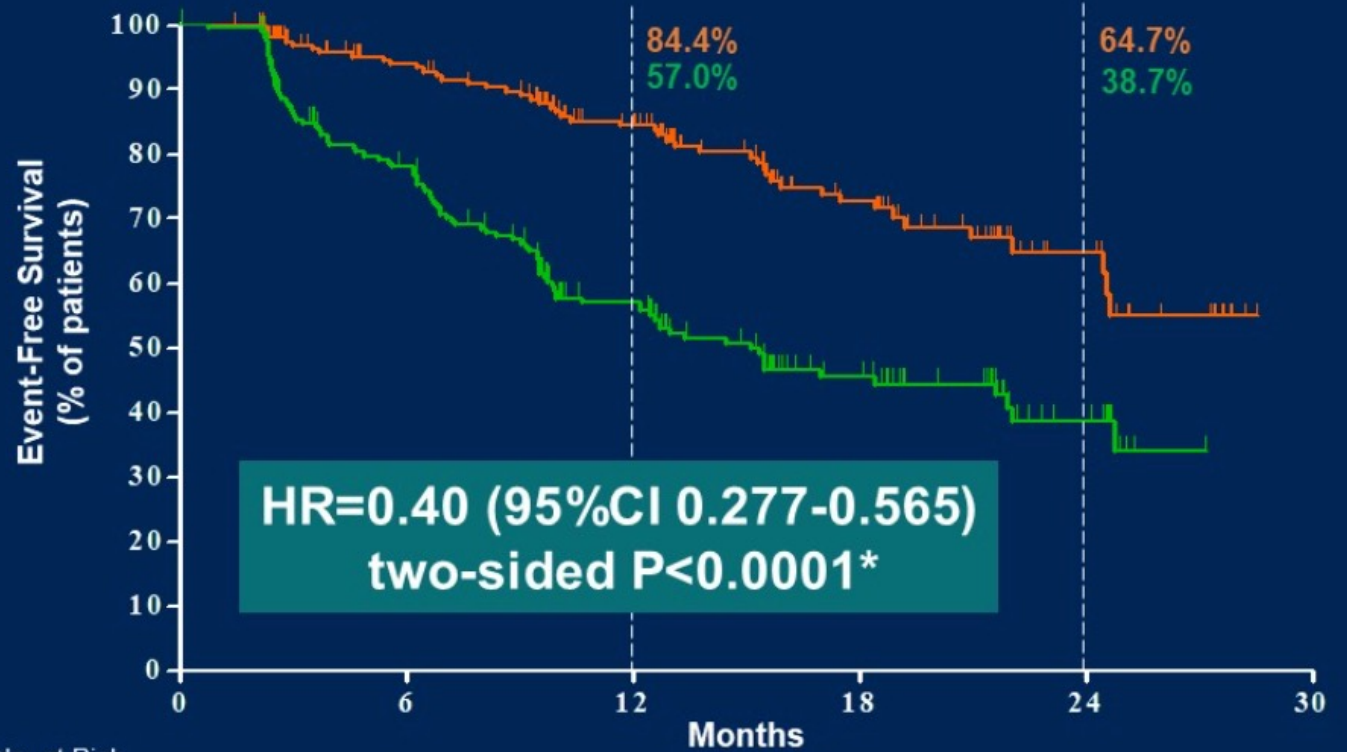
Lu et al ASCO annual meeting 2023

## EFS by investigator

No. of Events/No. of Patients      Median EFS mos. (95% CI)

Toripalimab + chemo      47/202      NE (24.4, NE)  
 Placebo + chemo      97/202      15.1 (10.6, 21.9)

Median follow-up: 18.25 months

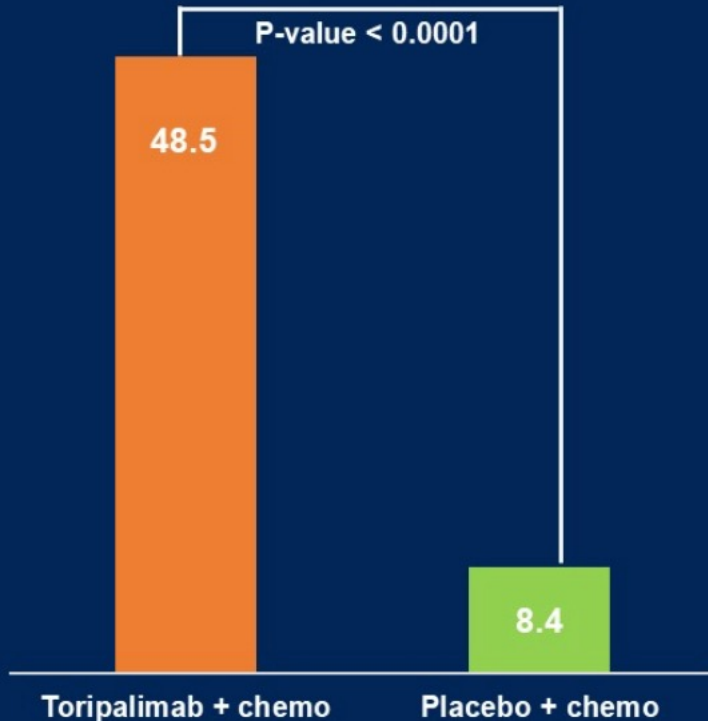


No. at Risk	0	6	12	18	24	30
Toripalimab + chemo	202	156	116	66	23	0
Placebo + chemo	202	139	86	43	15	0

## MPR by BIPR

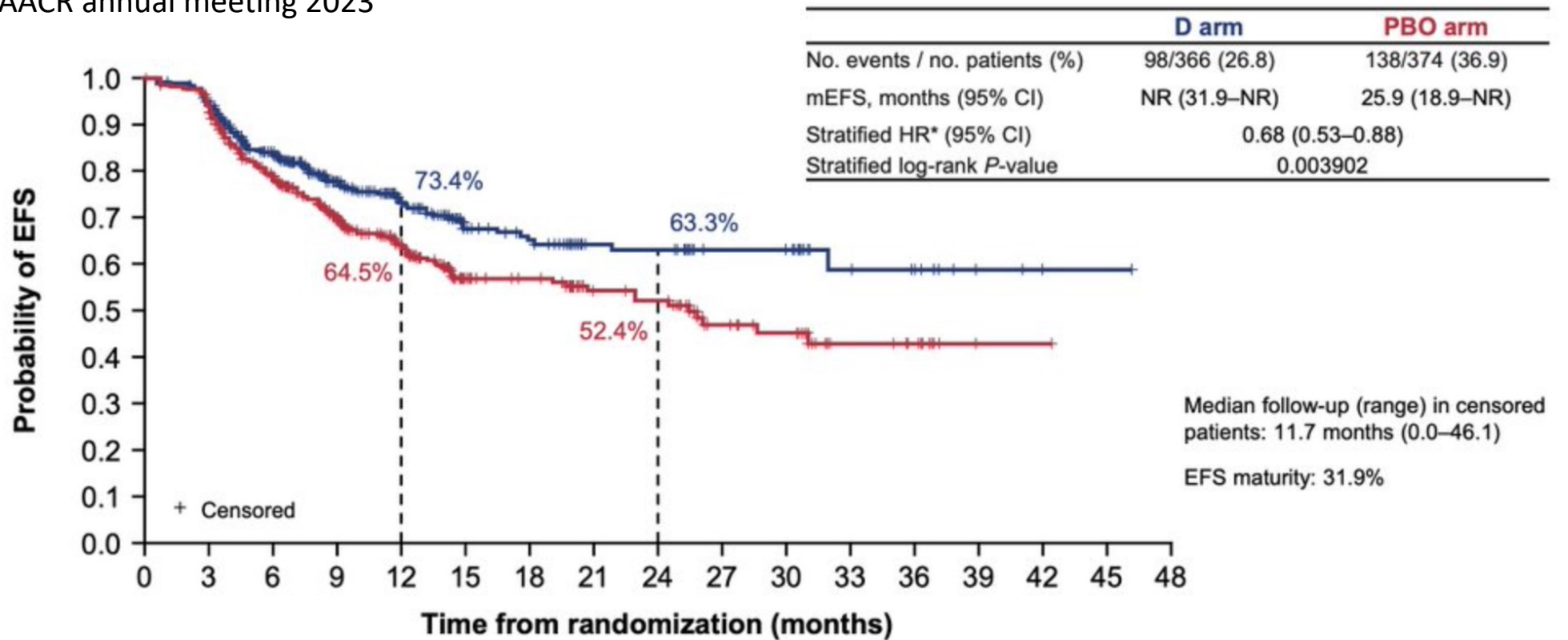
Difference=40.2%  
(95% CI: 32.2-48.1)

P-value < 0.0001



# AEGEAN – Perioperative Durvalumab

Heymach et al. AACR annual meeting 2023

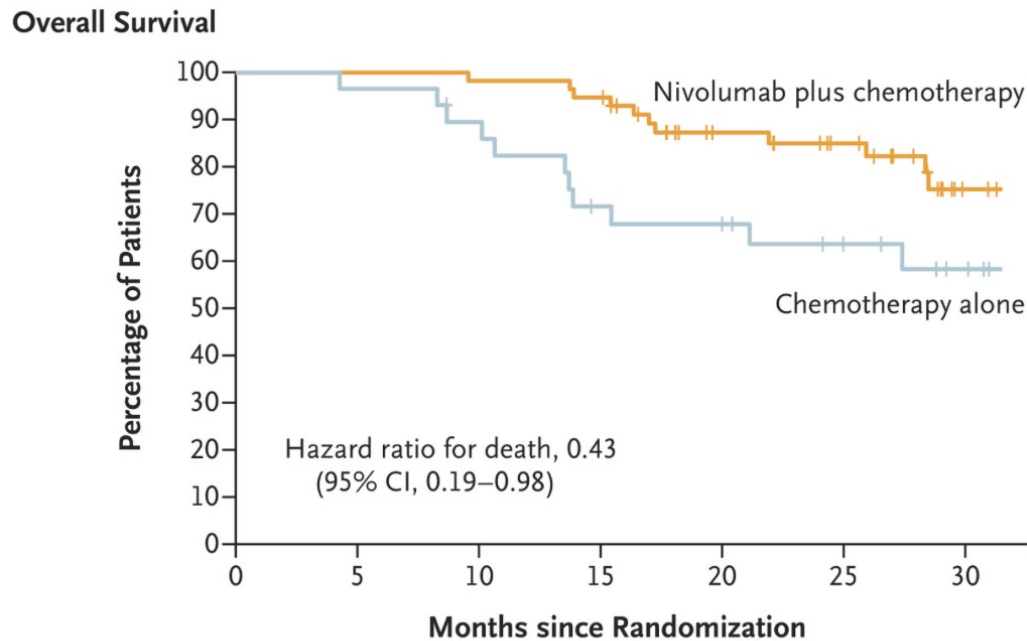


No. at risk:

<b>D arm</b>	366	336	271	194	140	90	78	50	49	31	30	14	11	3	1	1	0
<b>PBO arm</b>	374	339	257	184	136	82	74	53	50	30	25	16	13	1	1	0	0

# Perioperative Nivolumab (6 months) NADIM – Stage IIIA/B

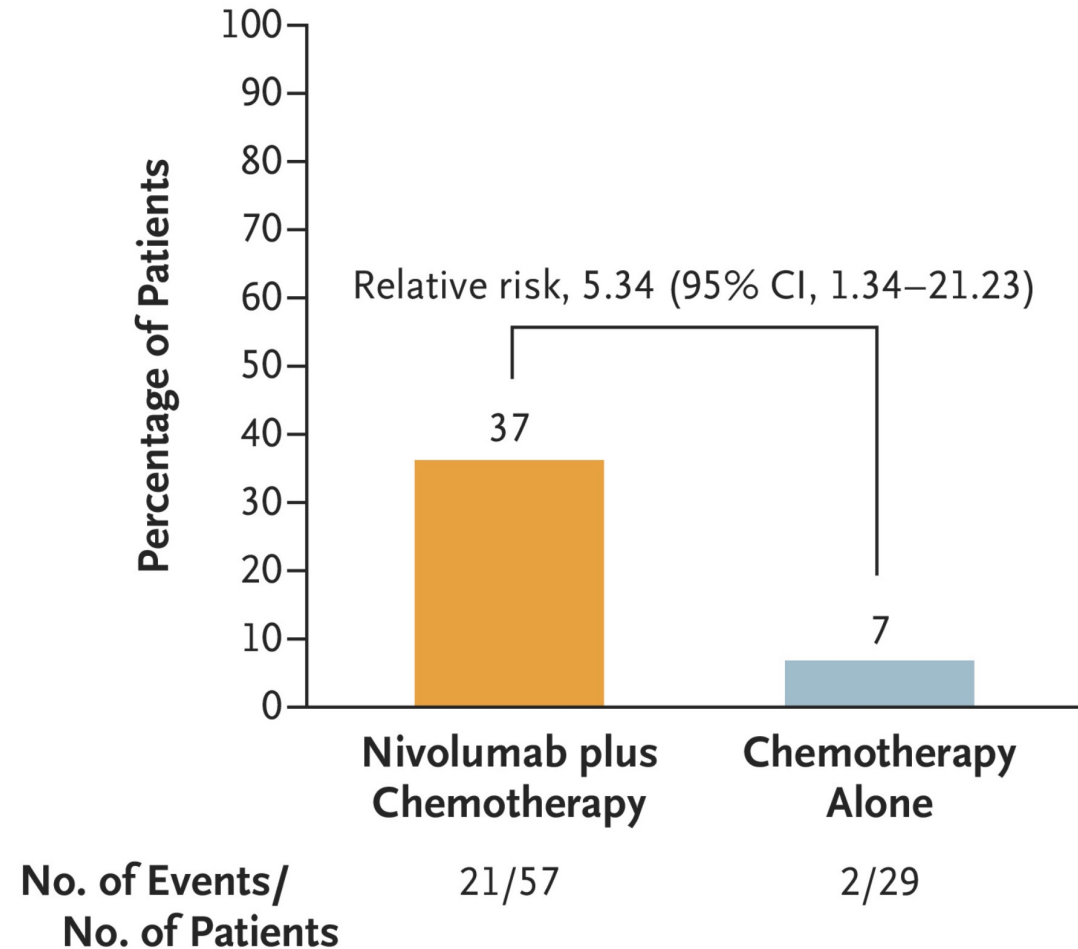
Provencio et al New Engl J Med 2023



### No. at Risk

Nivolumab plus chemotherapy	57	57	56	54	38	32	15
Chemotherapy alone	29	28	25	19	17	13	9

## Pathological Complete response



# NADIM-II Biomarker Analysis

Provencio et al J Clin Oncol 2022

## At Baseline

Feature	Hazard Ratio
ctDNA <1%	0.20
TMB > 10 mut/MB	1.67
PD-L1 > 1%	0.64

## At Surgery

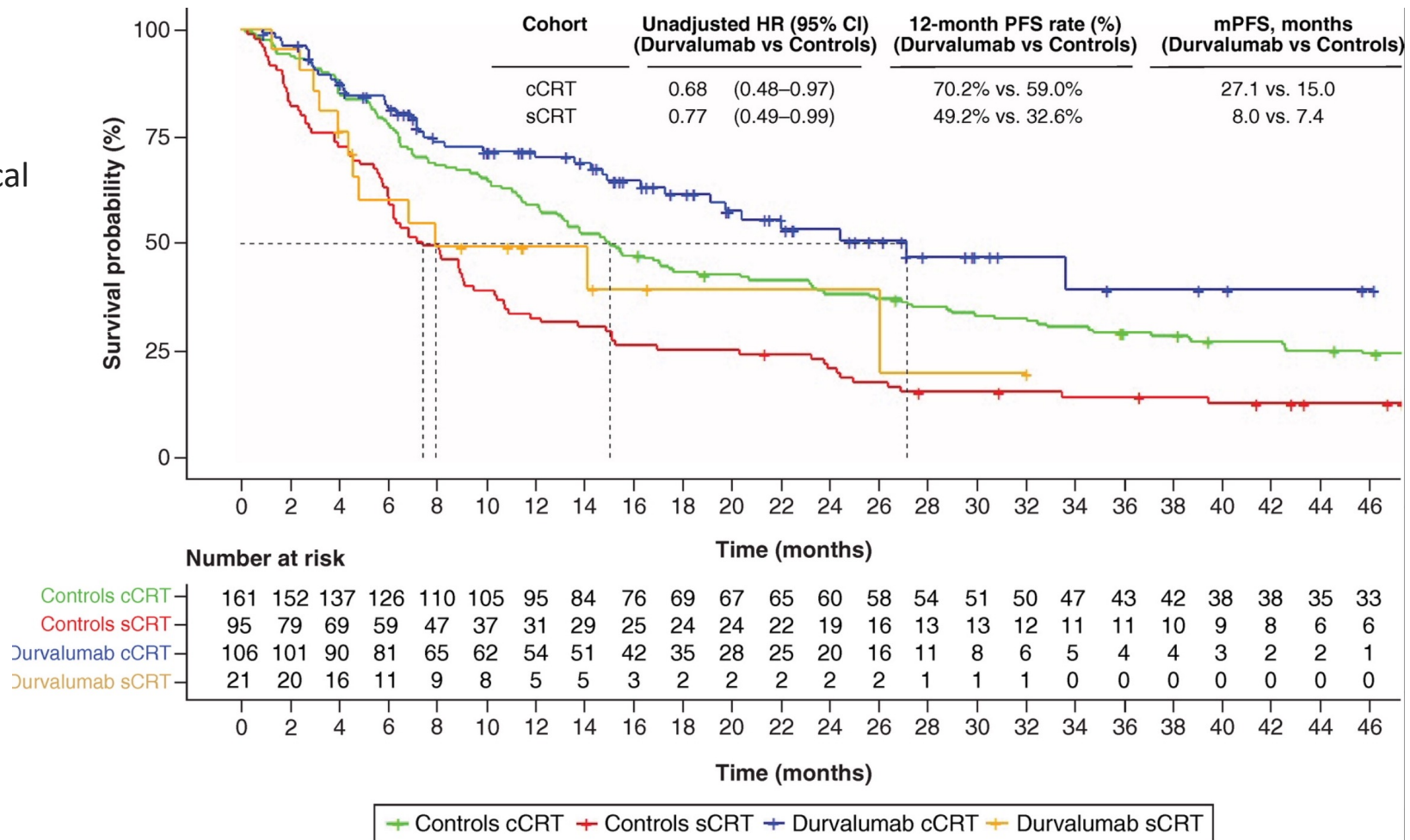
Feature	Hazard Ratio
CR or PR	0.79
Pathological CR	0.38
Undetectable ctDNA	0.26

# Dutch Experience with Pacific Style Treatment Real World Evidence

Durvalumab after chemoradiotherapy in patients with stage III non-small-cell lung cancer: real-world outcomes versus clinical trial results.

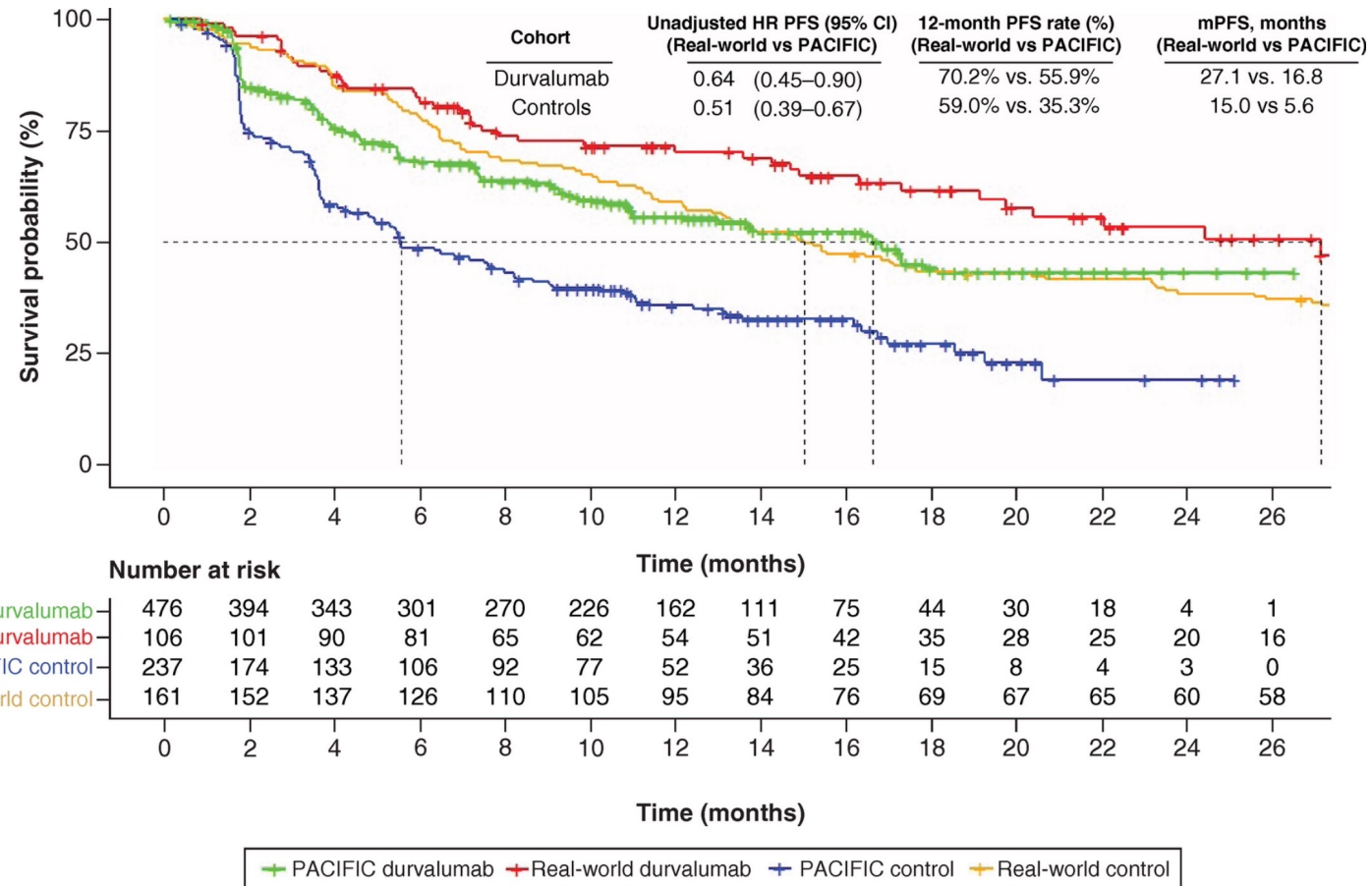
Verschuieren et al. Immunotherapy. 2023 Aug;15(11):839-851.

## Sequential vs Concurrent chemoradiation



# Comparing Real World patients with clinical trial patients

Verschuieren et al. Immunotherapy. 2023 Aug;15(11):839-851



# Conclusions

- For small peripheral lung lesions, segmentectomy is preferred to lobectomy. SBRT is still good too.
- Adjuvant EGFR inhibition is appropriate for resected EGFRm cancer
- Adjuvant, neoadjuvant, and perioperative immunotherapy improves outcomes.
  - How much your patient needs is an open question
  - There is good preclinical rationale for giving immunotherapy with the lymph nodes still in place
- The Pacific trial remains the standard for chemoradiation in stage III disease



Questions?

