Stage IIIA-B-C NSCLC: Does The PACIFIC Data Fit All Comers?

Jorge E. Gomez, MD

Center for Thoracic Oncology

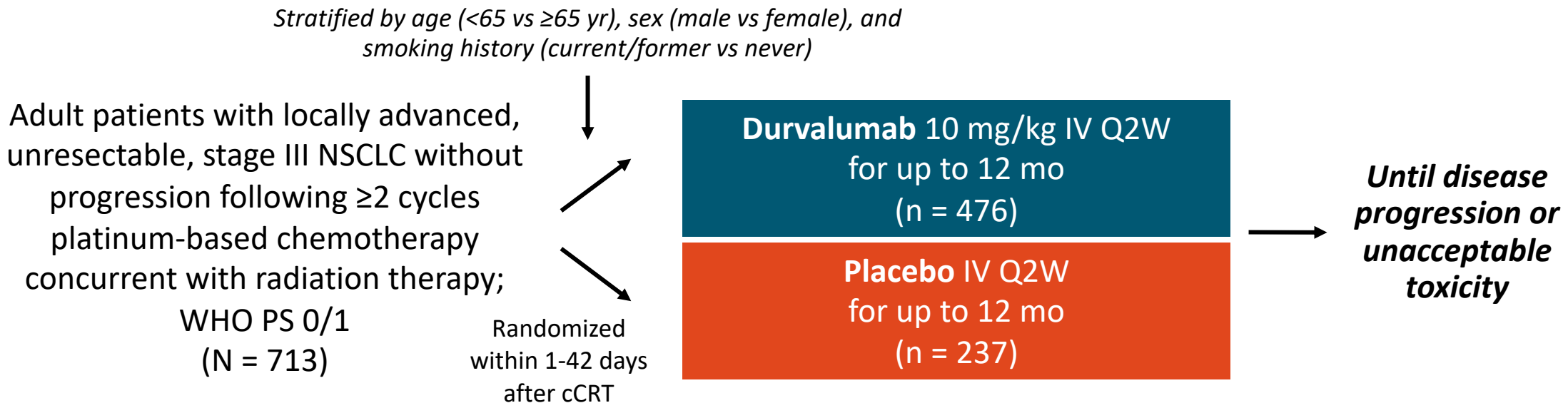
Tisch Cancer Institute

Icahn School of Medicine at Mount Sinai

Mount Sinai

PACIFIC 5-Yr Update: Study Design

- Randomized, double-blind, placebo-controlled phase III trial



Patients enrolled regardless of PD-L1 status. If available, pre-cCRT tumor tissue archived for PD-L1 testing.

- Primary endpoints: PFS by BICR per RECIST v1.1, OS
- Secondary endpoints: ORR, DoR, TTDM, safety, PROs

Spigel. ASCO 2021. Abstr 8511.

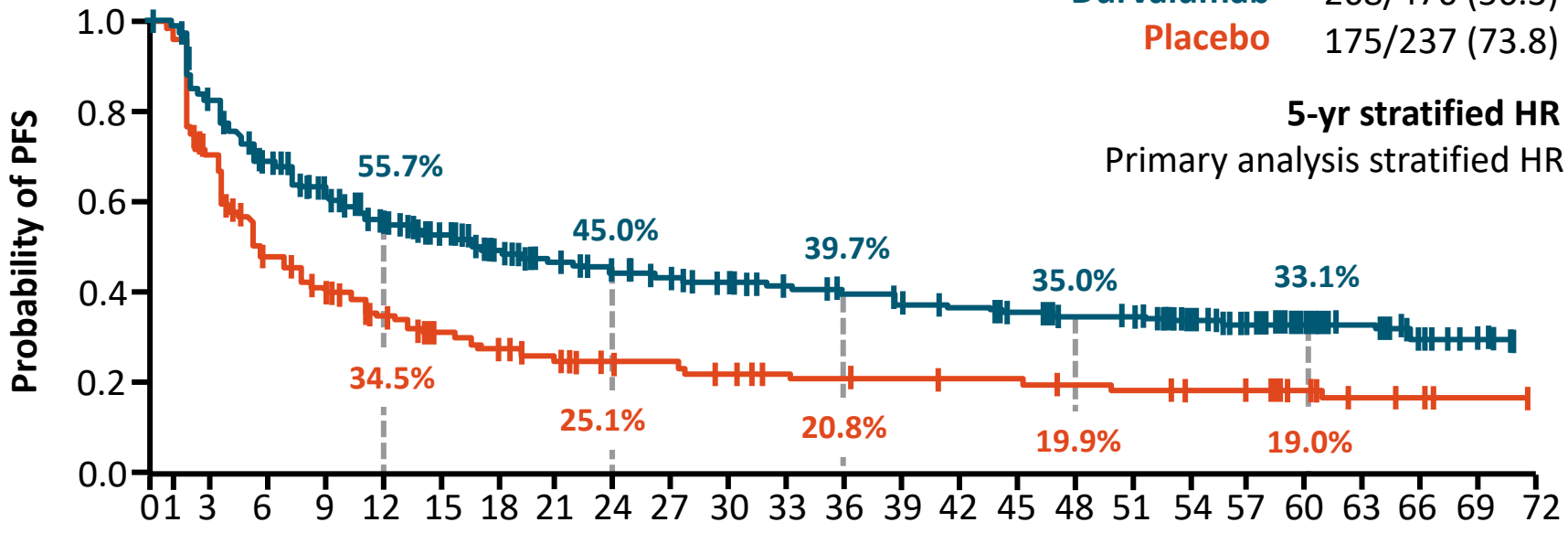
Slide credit: clinicaloptions.com

PACIFIC 5-Yr Update: PFS (ITT)

	Events/Patients, n/N (%)	Median PFS, Mo (95% CI)
Durvalumab	268/476 (56.3)	16.9 (13.0-23.9)
Placebo	175/237 (73.8)	5.6 (4.8-7.7)

5-yr stratified HR (95% CI): 0.55 (0.45-0.68)

Primary analysis stratified HR (95% CI): 0.52 (0.42-0.65)



Patients at Risk, n																									
Durvalumab	476	377	301	267	215	190	165	147	137	128	119	110	103	97	92	85	81	78	67	57	34	22	11	5	0
Placebo	237	164	105	87	68	56	48	41	37	36	30	27	26	25	24	24	22	21	19	19	14	6	4	1	0

- 72 additional PFS events reported since time of primary analysis (data cutoff: February 13, 2017); updated results, including across patient subgroups, consistent with those from primary analysis

Spigel. ASCO 2021. Abstr 8511.

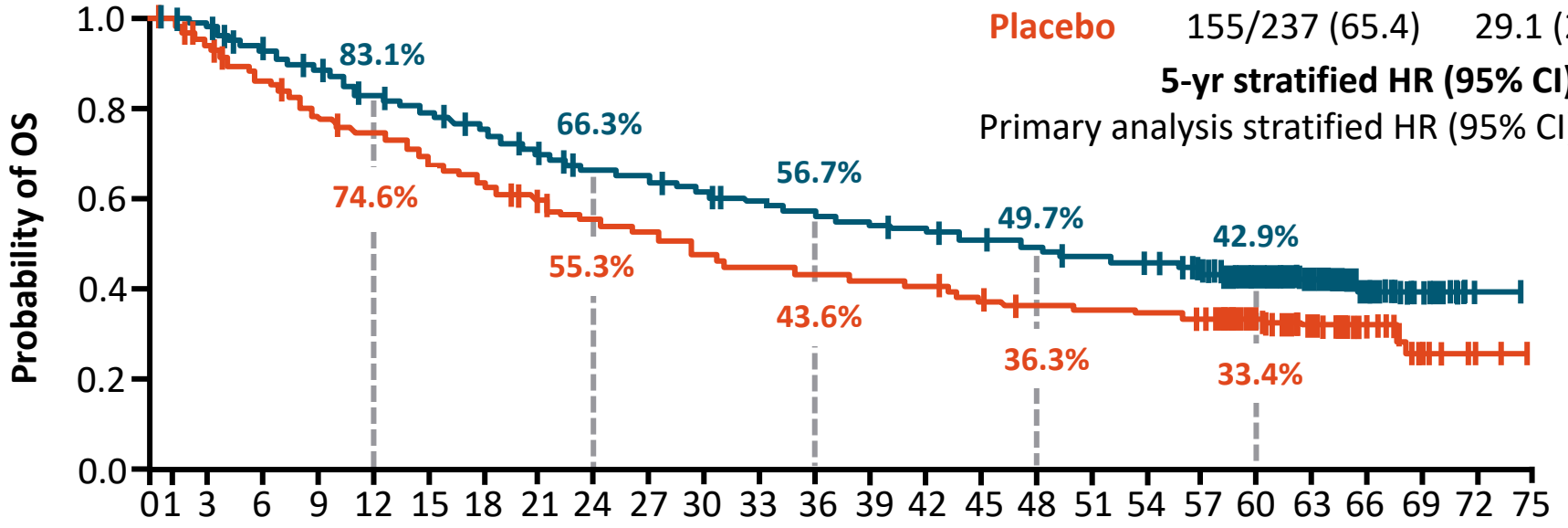
Slide credit: clinicaloptions.com

PACIFIC 5-Yr Update: OS (ITT)

	Events/Patients, n/N (%)	Median OS, Mo (95% CI)
Durvalumab	264/476 (55.5)	47.5 (38.1-52.9)
Placebo	155/237 (65.4)	29.1 (22.1-35.1)

5-yr stratified HR (95% CI): 0.72 (0.59-0.89)

Primary analysis stratified HR (95% CI): 0.68 (0.53-0.87)



Patients at Risk, n

Durvalumab	476	464	431	414	385	364	343	319	298	289	273	264	252	241	236	227	218	207	196	183	134	91	40	18	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	78	77	74	72	56	33	16	7	2	0

- 120 additional OS events reported since time of primary analysis (data cutoff: March 22, 2018); updated results, including across patient subgroups, consistent with those from primary analysis

Spigel. ASCO 2021. Abstr 8511.

Slide credit: clinicaloptions.com

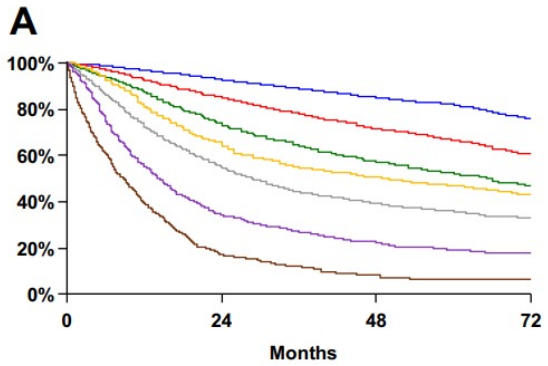
Are all stage III lung cancers equal?

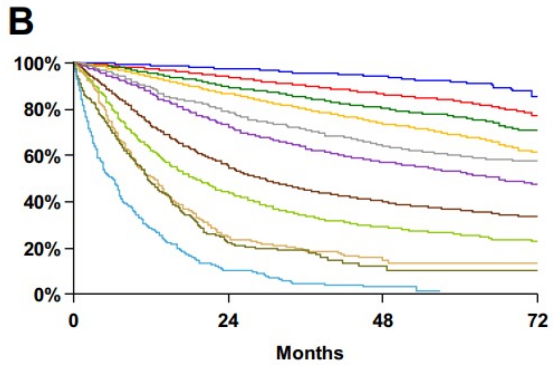
- Stage IIIA vs IIIB vs IIIC (resectable versus unresectable)
- PD-L1 <1, 1-24, <25
- Oncogene driven cancers
- Patients who are ineligible for concurrent chemotherapy and radiation
- Will not address possible OS differences in Age/Race/Sex/Histology

T/M	Label	N0	N1	N2	N3
T1	T1a *≤1*	IA1	IIB	IIIA	IIIB
	T1b *>1-2*	IA2	IIB	IIIA	IIIB
	T1c *>2-3*	IA3	IIB	IIIA	IIIB
T2	T2a *Cent, Yisc Pl*	IB	IIB	IIIA	IIIB
	T2a *>3-4*	IB	IIB	IIIA	IIIB
	T2b *>4-5*	IIA	IIB	IIIA	IIIB
T3	T3 *>5-7*	IIB	IIIA	IIIB	IIIC
	T3 *Inv*	IIB	IIIA	IIIB	IIIC
	T3 *Satell*	IIB	IIIA	IIIB	IIIC
T4	T4 *>7*	IIIA	IIIA	IIIB	IIIC
	T4 *Inv*	IIIA	IIIA	IIIB	IIIC
	T4 *Ipsi Nod*	IIIA	IIIA	IIIB	IIIC
M1	M1a *Contr Nod*	IVA	IVA	IVA	IVA
	M1a *Pl Dissem*	IVA	IVA	IVA	IVA
	M1b *Single*	IVA	IVA	IVA	IVA
	M1c *Multi*	IVB	IVB	IVB	IVB

AJCC 8th Edition Lung Cancer Staging

Are all stage III lung cancers equal?





7th Ed.	Events / N	MST	24 Month	60 Month
IA	1119 / 6303	NR	93%	82%
IB	768 / 2492	NR	85%	66%
IIA	424 / 1008	66.0	74%	52%
IIB	382 / 824	49.0	64%	47%
IIIA	2139 / 3344	29.0	55%	36%
IIIB	2101 / 2624	14.1	34%	19%
IV	664 / 882	8.8	17%	6%

Proposed	Events / N	MST	24 Month	60 Month
IA1	68 / 781	NR	97%	92%
IA2	505 / 3105	NR	94%	83%
IA3	546 / 2417	NR	90%	77%
IB	560 / 1928	NR	87%	68%
IIA	215 / 585	NR	79%	60%
IIB	605 / 1453	66.0	72%	53%
IIIA	2052 / 3200	29.3	55%	36%
IIIB	1551 / 2140	19.0	44%	26%
IIIC	831 / 986	12.6	24%	13%
IVA	336 / 484	11.5	23%	10%
IVB	328 / 398	6.0	10%	0%

Overall survival by clinical stage according to the seventh edition (A) and the proposed eighth edition (B) groupings using the entire database available for the eighth edition

Goldstraw et al, JTO 2016

Practical Differences

Resectable

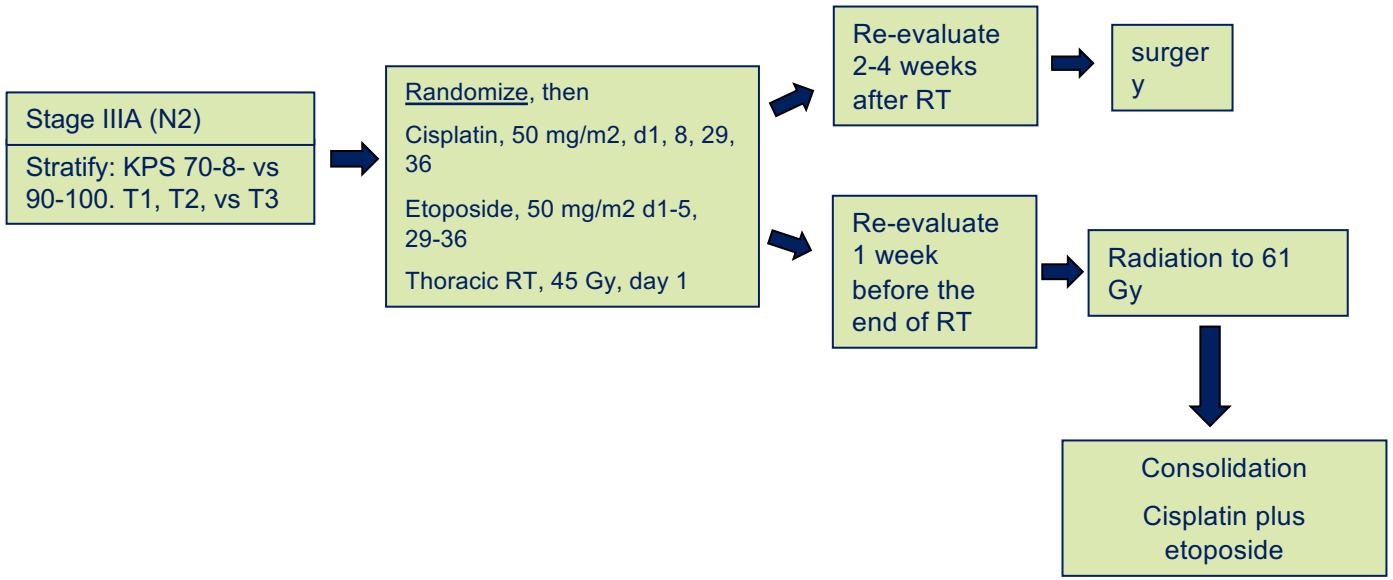
- Stage IIIA
  - T3 N1
  - T4
  - T4 N1
  - T1-2 N2
  - T3 N2? (IIIB)

Unresectable

- Stage IIIA
- Stage IIIB
- Stage IIIC

Pacific: Stage IIIA

Lung Intergroup 0139



- Patients with Stage IIIA N2
- "Unresectable"
- 396 patients eligible

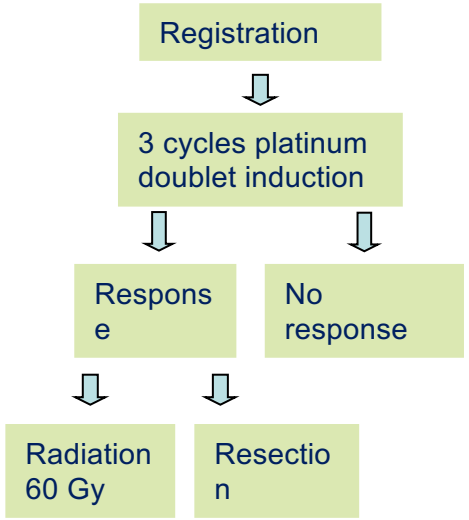
Endpoint	CT+RT+S	CT+RT
PFS		p=0.017
Median	12.8 months	10.5 months
5 yr	22.4%	11.1%
OS		p=0.24
Median	23.6 months	22.2 months
5 yr	27.2%	20.3%

Albain, Lancet 2009

EORTC 08941

- Clinical IIIA-N2
- NSCLC, “unresectable”
- Pathologically confirmed
- 332 patients randomized(247 off study)
- Chemo response rate 62%(4% CR)

	Radiotherapy N=165	Surgery N=167
Median OS (mo)	**17.5**	**16.4**
5 y OS (%)	**14**	**15.7**



van Meerbeeck, ASCO 2005

Prognostic Significance of downstaging

0139

T/N subset	MS (mo)	5 yr OS (%)
T any N0	34	41%
T any, N1-3	26	24%

08941

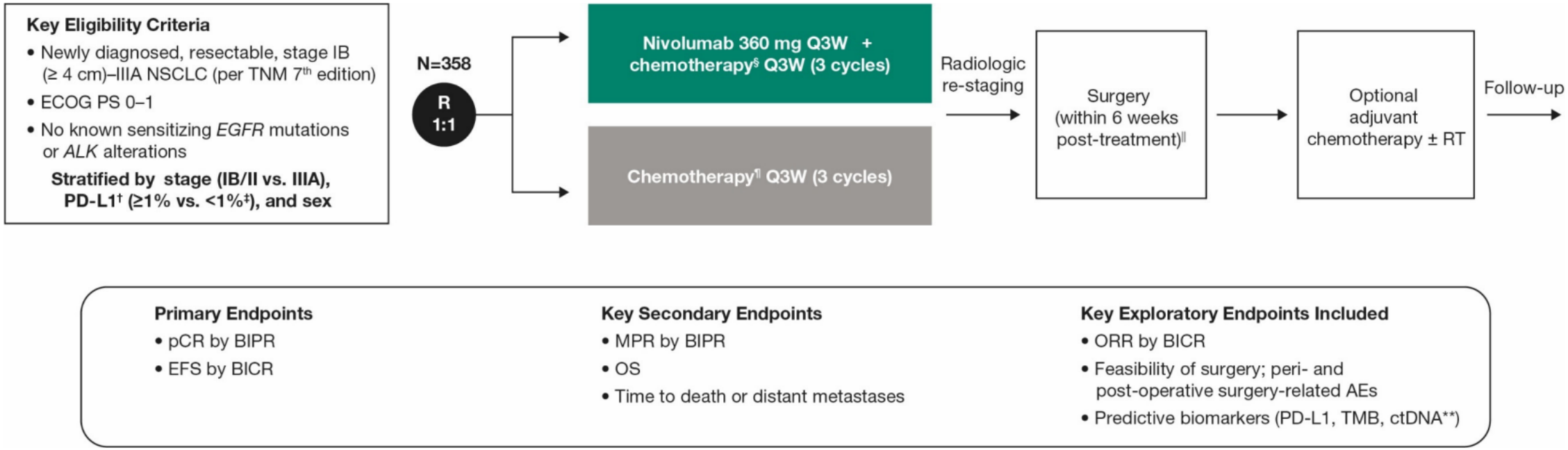
154 surgery patients	N	Median OS(m)	5y OS(%)	p
N0/N1	64	22.7	29	.0009
N2	86	14.9	7	

Albain, Lancet 2009

van Meerbeeck, ASCO 2005

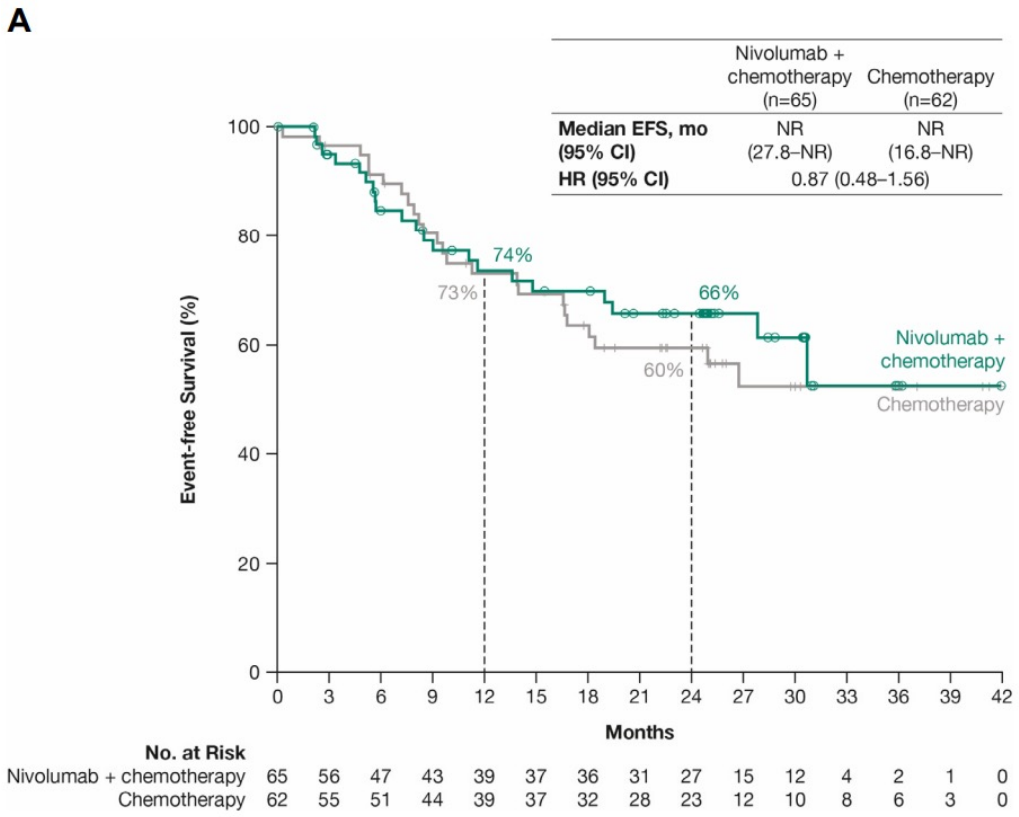
Checkmate 816: study design

- Forde, NEJM 2022

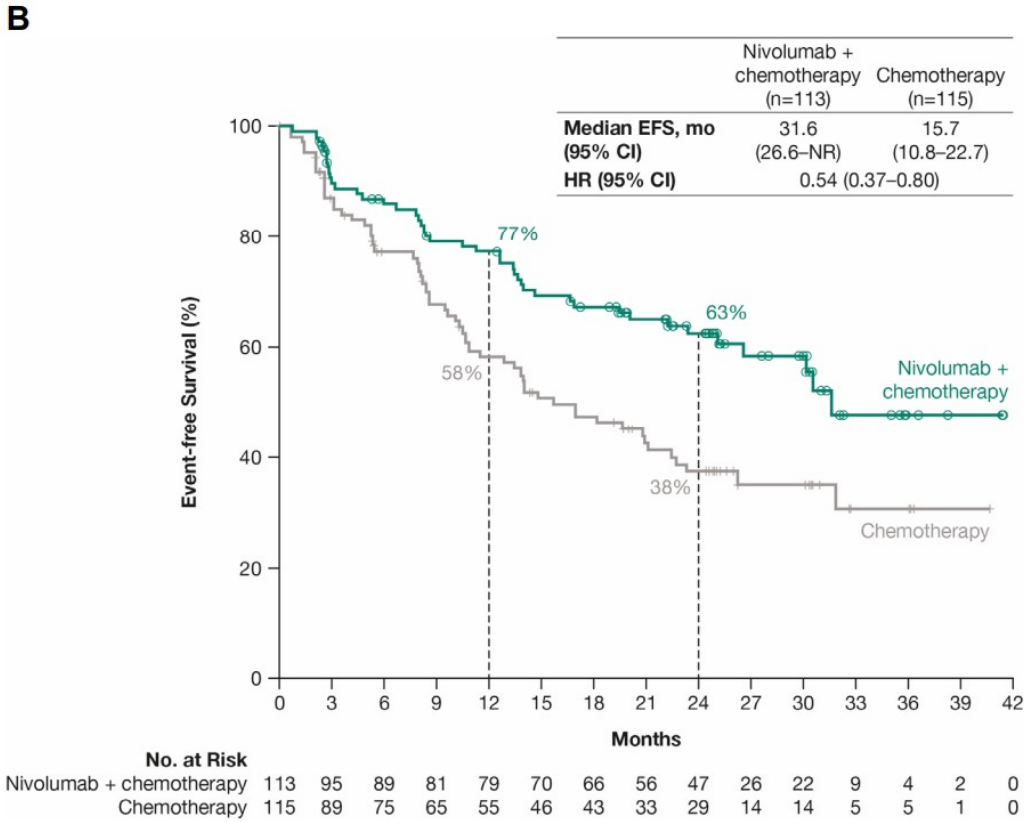


Checkmate 816: event free survival

Stage IB-II

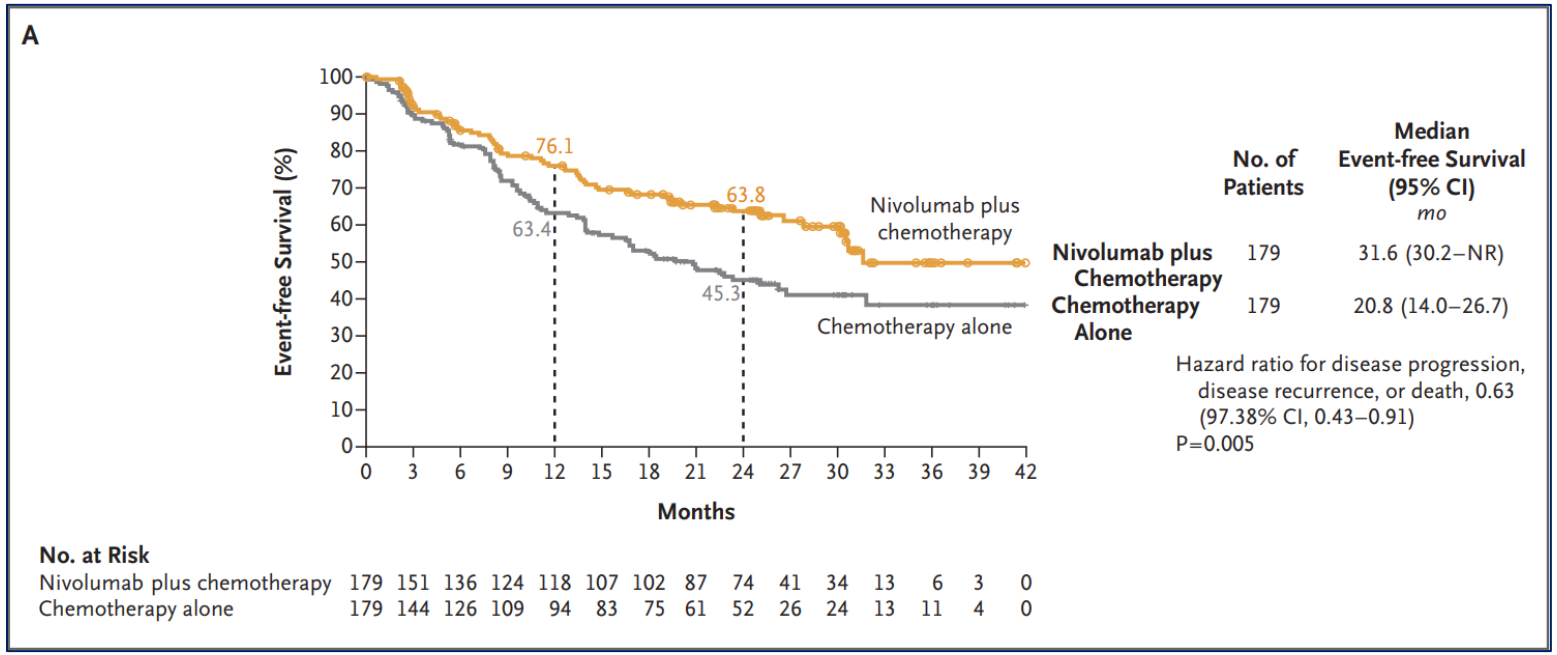


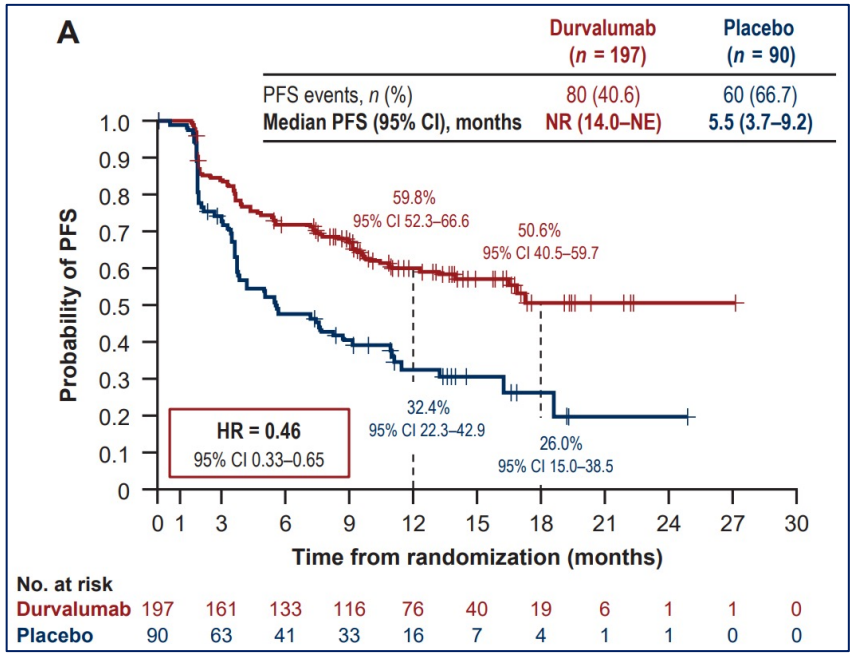
Stage IIIA



Forde, NEJM 2022

Checkmate 816 vs Pacific EFS/PFS for Stage IIIA

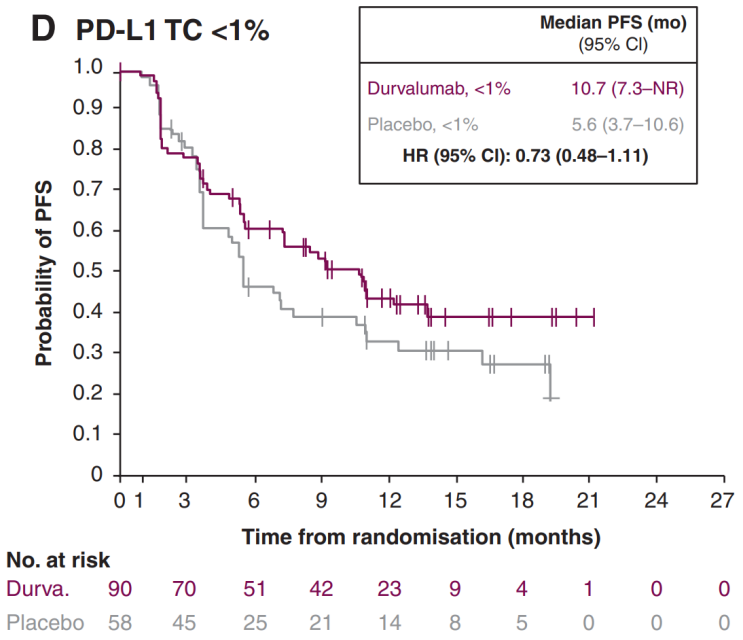


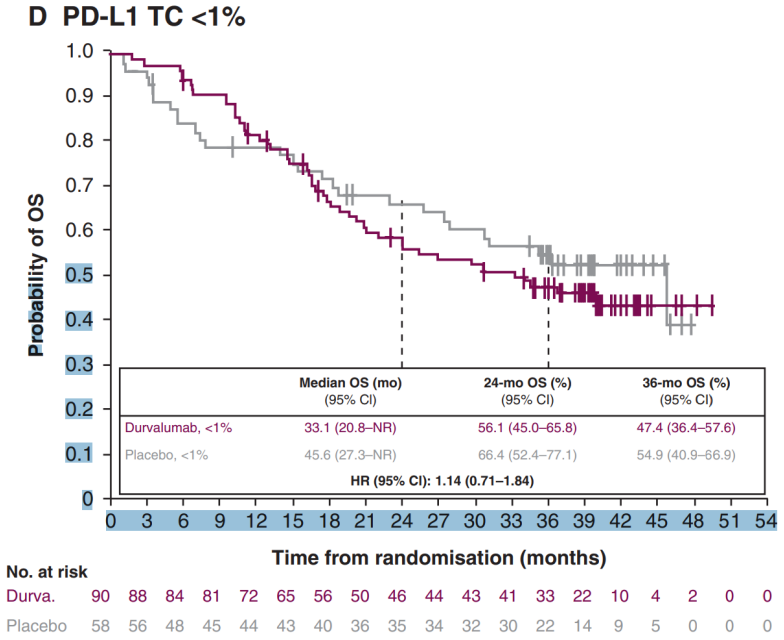


Forde, NEJM 2022 Senan, ESMO OPEN 2022

Pacific: PD-L1 Expression

Pacific: PD-L1 Expression





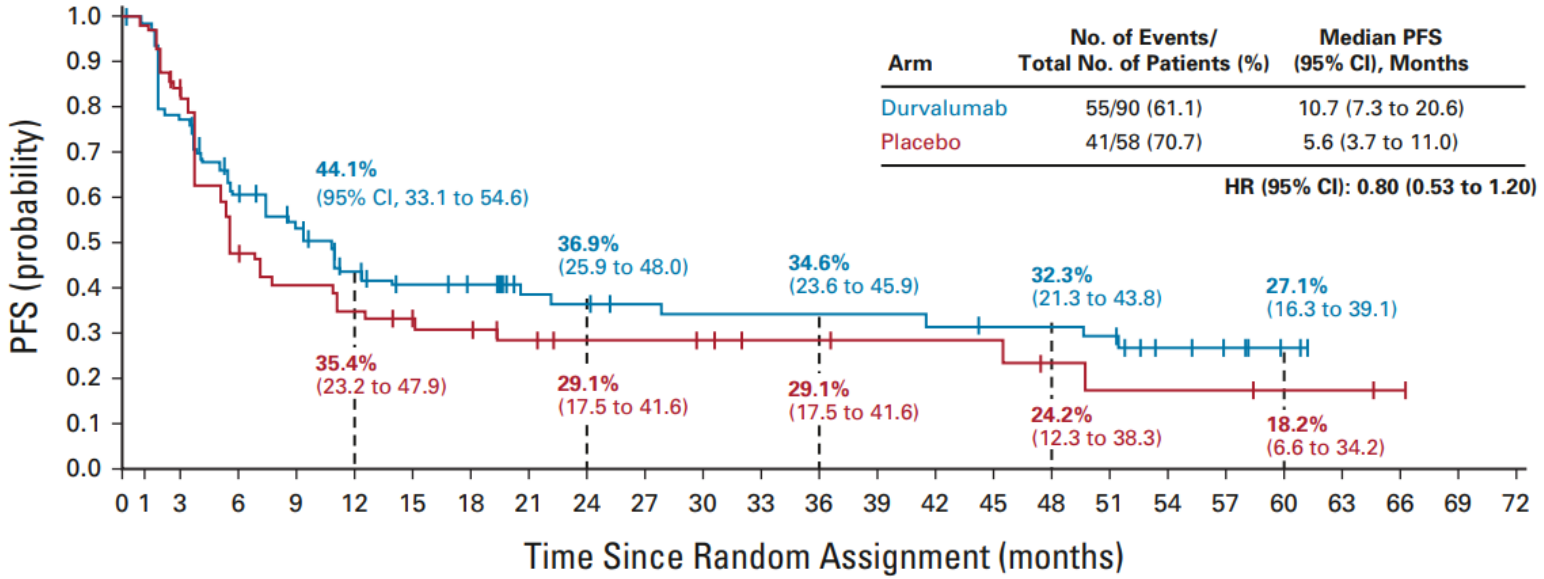
Supplementary Table S5. Time to death or distant metastasis by tumour PD-L1 expression status (BICR; ITT population)

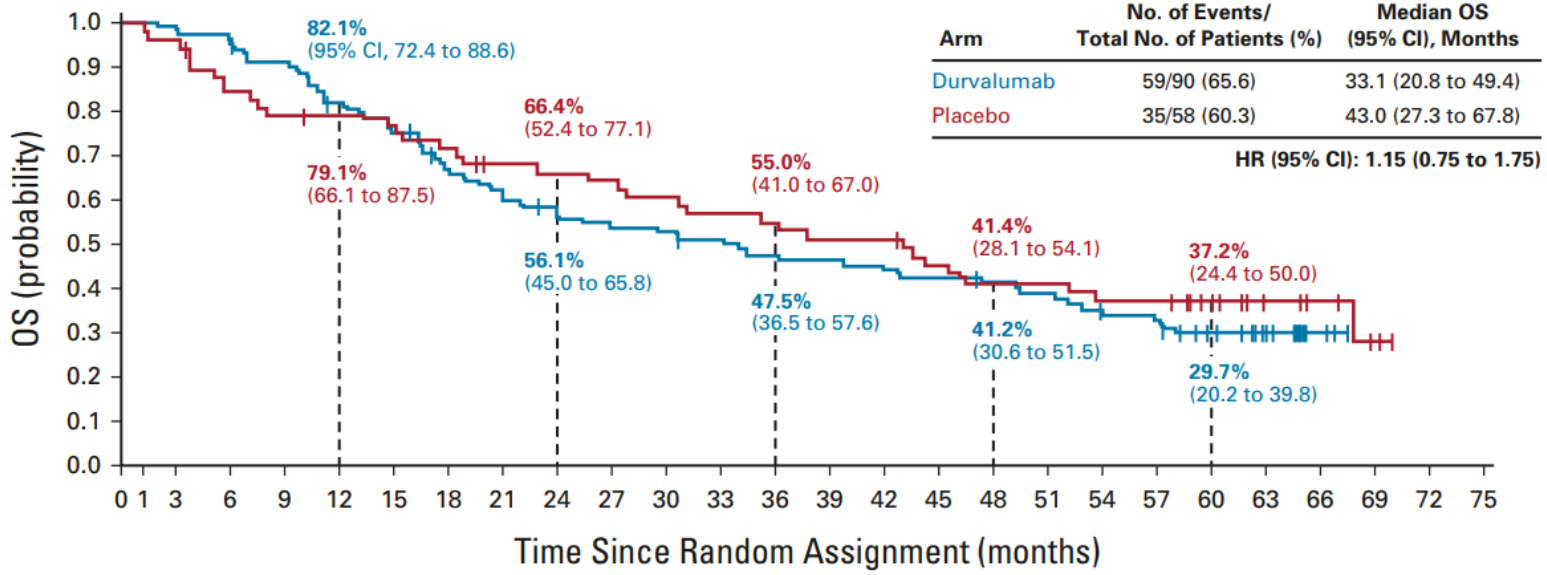
	PD-L1 TC <1%		PD-L1 TC ≥1%		PD-L1 TC <25%		PD-L1 TC ≥25%		PD-L1 TC unknown	
	Durvalumab (N=90)	Placebo (N=58)	Durvalumab (N=212)	Placebo (N=91)	Durvalumab (N=187)	Placebo (N=105)	Durvalumab (N=115)	Placebo (N=44)	Durvalumab (N=174)	Placebo (N=88)
Median (95% CI), months†	14.6 (12.3–NR)	NR (10.6–NR)	23.2 (23.2–NR)	14.8 (9.2–18.6)	NR (NR–NR)	17.7 (14.0–NR)	23.2 (23.2–NR)	12.6 (4.4–20.6)	NR (15.7–NR)	13.0 (8.3–25.9)
HR (95% CI)	0.93 (0.52–1.67)		0.40 (0.26–0.60)		0.65 (0.43–1.00)		0.34 (0.20–0.59)		0.61 (0.40–0.92)	

Antonia, NEJM 2018

Paz-Ares, Annals of Oncology 2020

Pacific 5 Year PFS and OS in PD-L1 <1





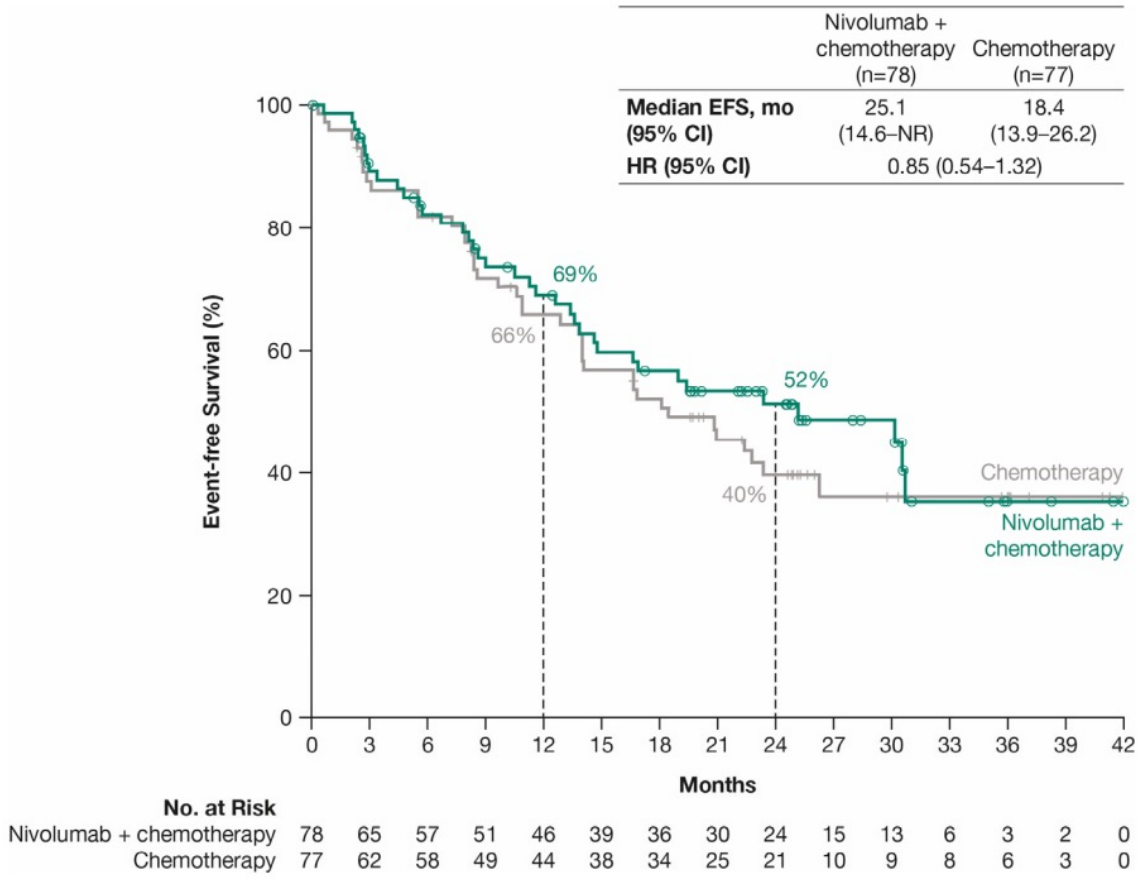
Spigel, JCO 2022

Pacific PD-L1 Limitations

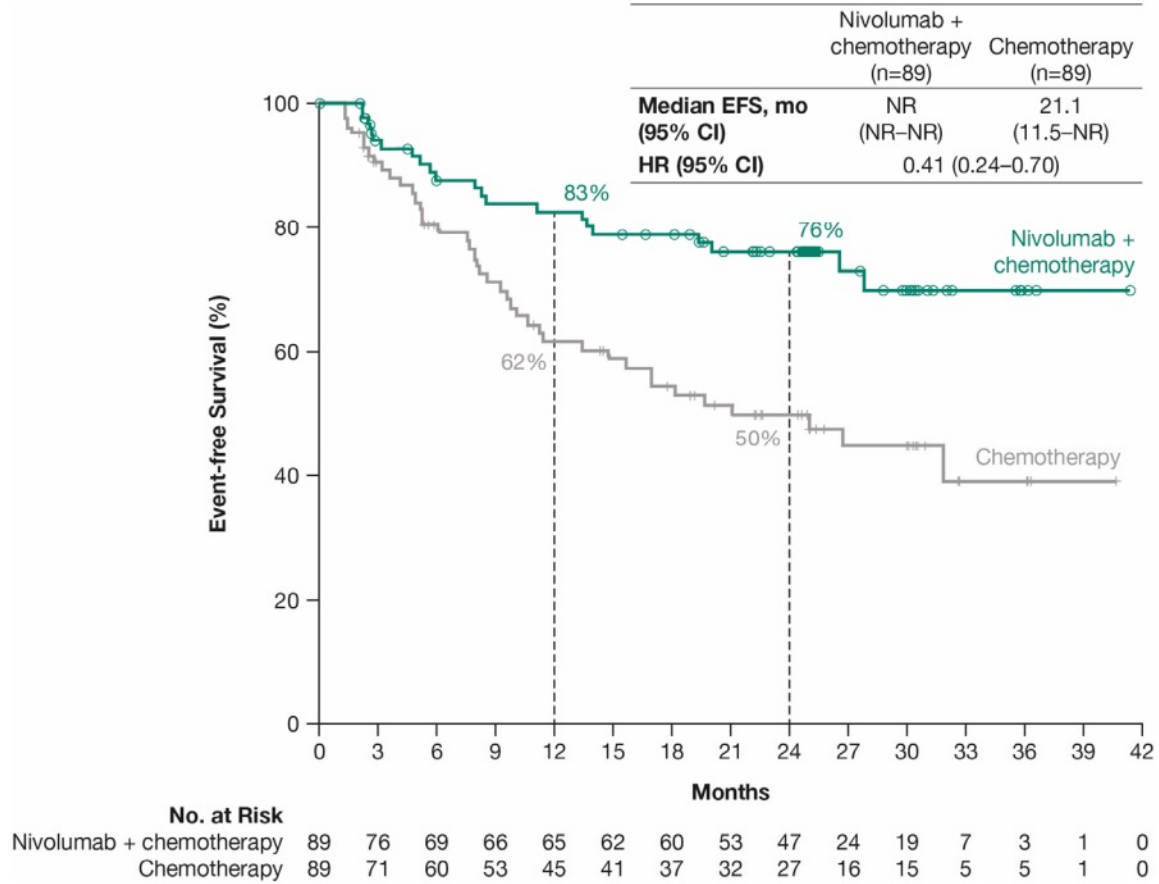
- These include the use of tumor samples collected before CRT to determine PD-L1 expression
- PD-L1–assessable samples were not available for 37% of randomly assigned patients
- Relatively small number of patients with PD-L1 TC expression < 1% (n = 148).
- The placebo arm appeared to overperform with respect to OS among patients with PD-L1 TC expression < 1% compared with the full PACIFIC ITT population which may have been driven by imbalances in potentially prognostic baseline factors.

Event Free Survival: PD-L1 level

PDL-1 < 1

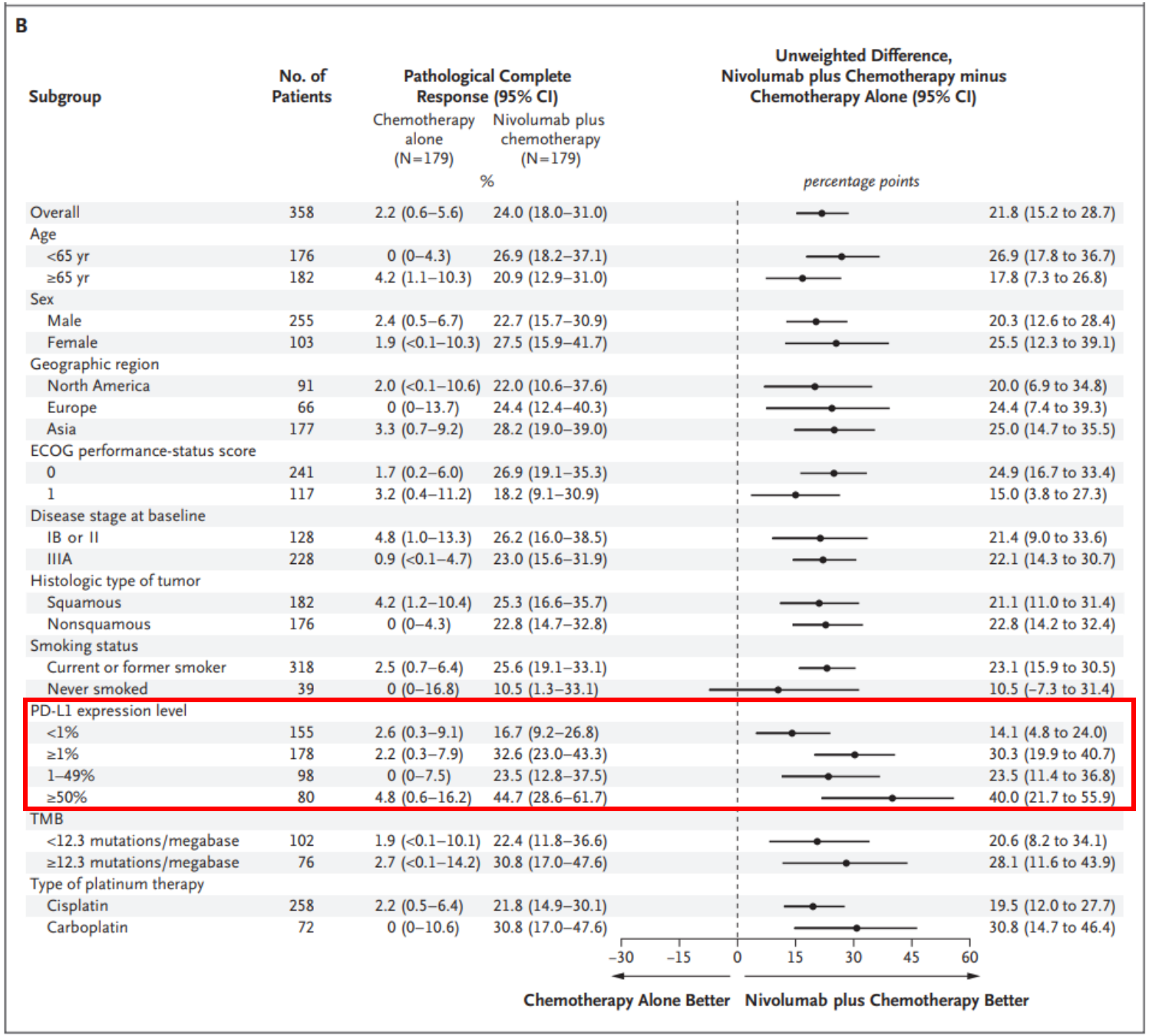


PDL-1 ≥ 1



Forde, NEJM 2022

Checkmate 816: pathological complete response

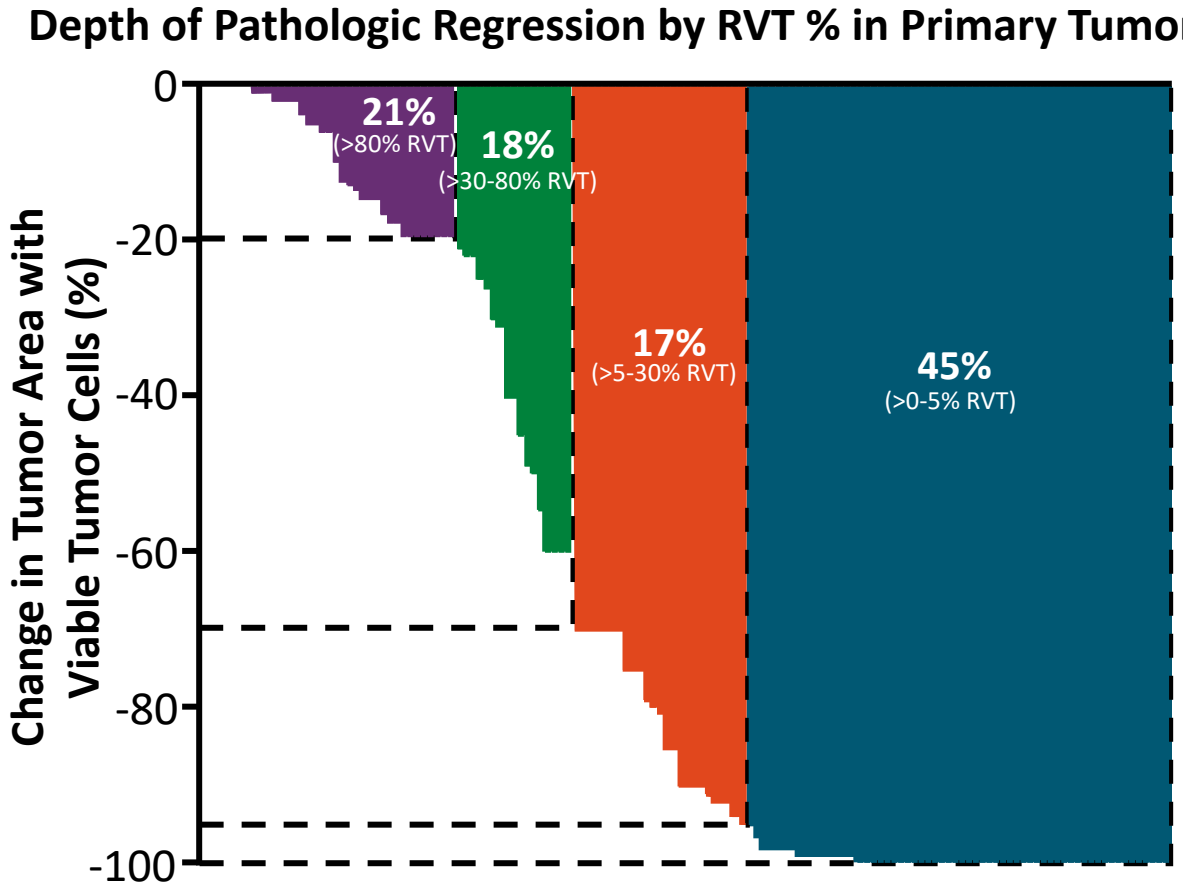


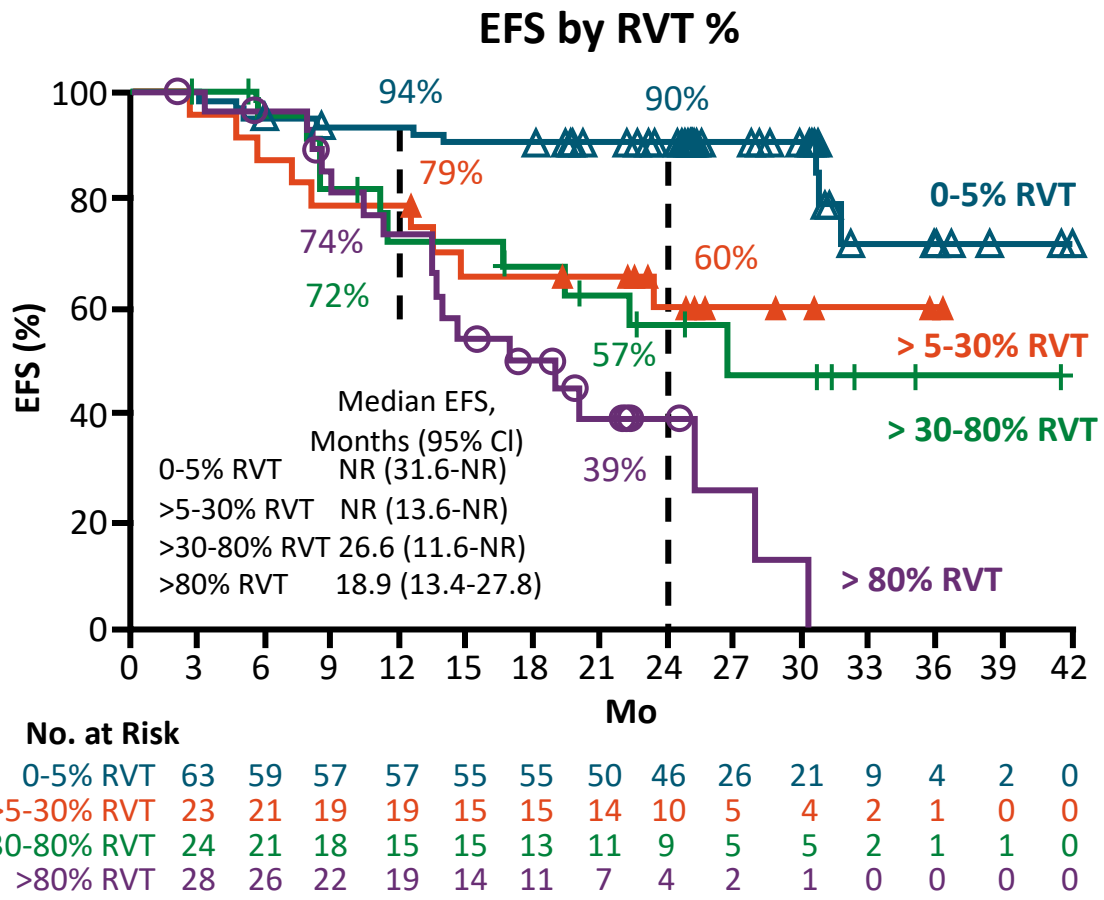
B

Subgroup	No. of Patients	Pathological Complete Response (95% CI)		Unweighted Difference, Nivolumab plus Chemotherapy minus Chemotherapy Alone (95% CI)
		Chemotherapy alone (N=179)	Nivolumab plus chemotherapy (N=179)	
		%		*percentage points*
Overall	358	2.2 (0.6–5.6)	24.0 (18.0–31.0)	21.8 (15.2 to 28.7)
Age				
<65 yr	176	0 (0–4.3)	26.9 (18.2–37.1)	26.9 (17.8 to 36.7)
≥65 yr	182	4.2 (1.1–10.3)	20.9 (12.9–31.0)	17.8 (7.3 to 26.8)
Sex				
Male	255	2.4 (0.5–6.7)	22.7 (15.7–30.9)	20.3 (12.6 to 28.4)
Female	103	1.9 (<0.1–10.3)	27.5 (15.9–41.7)	25.5 (12.3 to 39.1)
Geographic region				
North America	91	2.0 (<0.1–10.6)	22.0 (10.6–37.6)	20.0 (6.9 to 34.8)
Europe	66	0 (0–13.7)	24.4 (12.4–40.3)	24.4 (7.4 to 39.3)
Asia	177	3.3 (0.7–9.2)	28.2 (19.0–39.0)	25.0 (14.7 to 35.5)
ECOG performance-status score				
0	241	1.7 (0.2–6.0)	26.9 (19.1–35.3)	24.9 (16.7 to 33.4)
1	117	3.2 (0.4–11.2)	18.2 (9.1–30.9)	15.0 (3.8 to 27.3)
Disease stage at baseline				
IB or II	128	4.8 (1.0–13.3)	26.2 (16.0–38.5)	21.4 (9.0 to 33.6)
IIIA	228	0.9 (<0.1–4.7)	23.0 (15.6–31.9)	22.1 (14.3 to 30.7)
Histologic type of tumor				
Squamous	182	4.2 (1.2–10.4)	25.3 (16.6–35.7)	21.1 (11.0 to 31.4)
Nonsquamous	176	0 (0–4.3)	22.8 (14.7–32.8)	22.8 (14.2 to 32.4)
Smoking status				
Current or former smoker	318	2.5 (0.7–6.4)	25.6 (19.1–33.1)	23.1 (15.9 to 30.5)
Never smoked	39	0 (0–16.8)	10.5 (1.3–33.1)	10.5 (–7.3 to 31.4)
PD-L1 expression level				
<1%	155	2.6 (0.3–9.1)	16.7 (9.2–26.8)	14.1 (4.8 to 24.0)
≥1%	178	2.2 (0.3–7.9)	32.6 (23.0–43.3)	30.3 (19.9 to 40.7)
1–49%	98	0 (0–7.5)	23.5 (12.8–37.5)	23.5 (11.4 to 36.8)
≥50%	80	4.8 (0.6–16.2)	44.7 (28.6–61.7)	40.0 (21.7 to 55.9)
TMB				
<12.3 mutations/megabase	102	1.9 (<0.1–10.1)	22.4 (11.8–36.6)	20.6 (8.2 to 34.1)
≥12.3 mutations/megabase	76	2.7 (<0.1–14.2)	30.8 (17.0–47.6)	28.1 (11.6 to 43.9)
Type of platinum therapy				
Cisplatin	258	2.2 (0.5–6.4)	21.8 (14.9–30.1)	19.5 (12.0 to 27.7)
Carboplatin	72	0 (0–10.6)	30.8 (17.0–47.6)	30.8 (14.7 to 46.4)

Forde, NEJM 2022

CheckMate 816 Pathologic Response and Survival: EFS by Depth of Pathologic Regression: Nivo + CT





- Based on ROC curve analysis, depth of pathologic regression (measured by RVT %) as a continuous variable in primary tumor appeared to be predictive of 2-yr EFS for nivolumab + CT but not for CT

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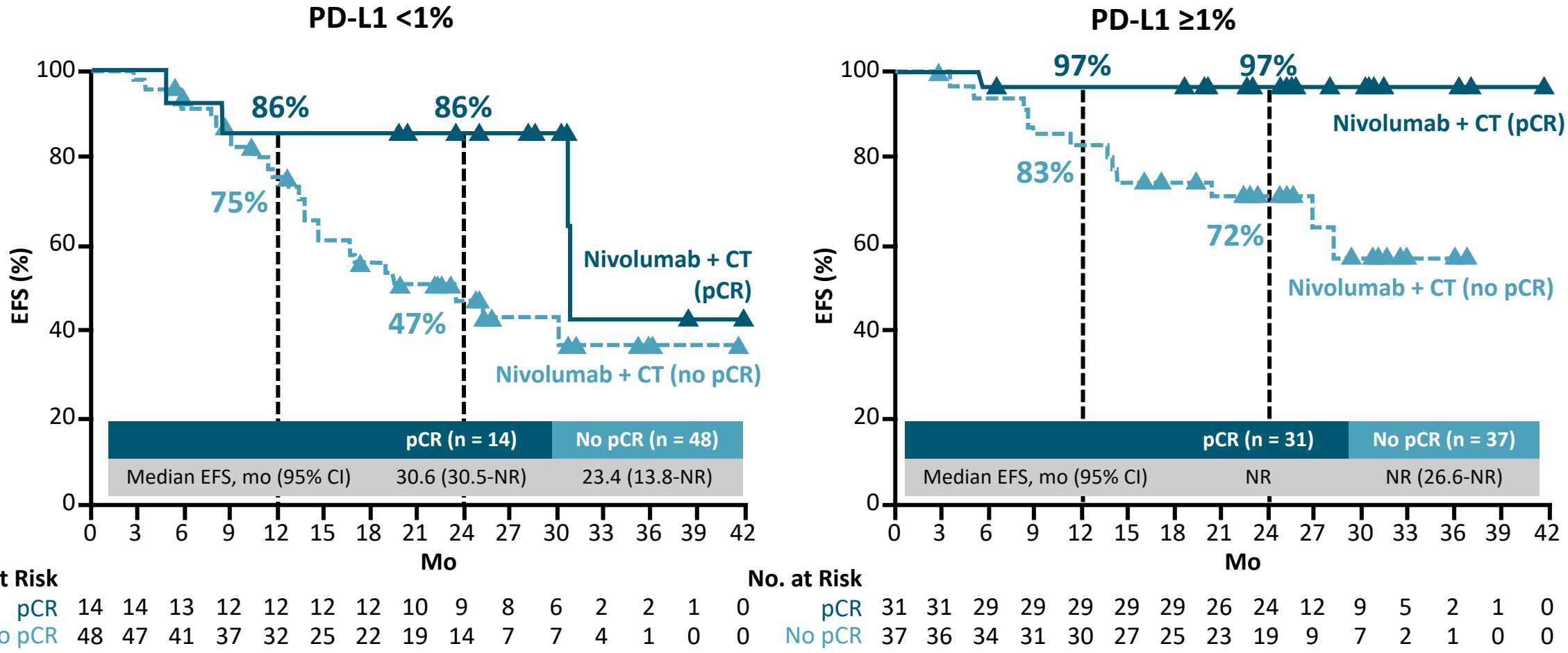
CheckMate 816 Pathologic Response and Survival: EFS by pCR Status* and PD-L1 Level (Nivo + CT)



*Primary tumor pCR status

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Pacific: Oncogene Driven Cancers

Oncogene Driven Cancers: What we think we know

- Significant evidence of lack of efficacy of checkpoint inhibitors as single agent therapy in patients with EGFR and ALK mutations.
- Small studies showing potential efficacy of combinations.
- Evidence of increased toxicity when combining checkpoint inhibitors and TKI.
- Checkpoint inhibitors may have some efficacy in other mutations.

Pacific: Oncogene Driven Cancers

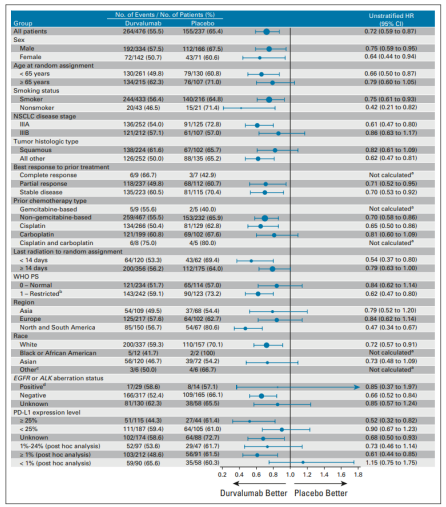
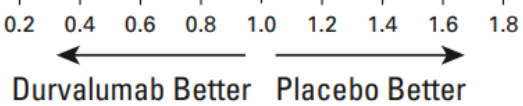


FIG 3. Updated OS by prespecified and exploratory, post hoc subgroups. *HRs and 95% CIs were not calculated if the subgroup had < 20 events. †Three patients with missing WHO PS were included in the PS 1 subgroup. ‡The other race category includes American Indian or Alaskan Native (n = 9), Native Hawaiian or Other Pacific Islander (n = 2), and Other (n = 1). §The subgroup includes 35 patients with tumors harboring *EGFR* mutations and, on the basis of local testing, eight patients with tumors harboring *ALK* alterations. ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non–small-cell lung cancer; OS, overall survival; PD-L1, programmed cell death-ligand 1; PS, performance status.

EGFR or *ALK* aberration status			
Positive[d]	17/29 (58.6)	8/14 (57.1)	0.85 (0.37 to 1.97)
Negative	166/317 (52.4)	109/165 (66.1)	0.66 (0.52 to 0.84)
Unknown	81/130 (62.3)	38/58 (65.5)	0.85 (0.57 to 1.24)
PD-L1 expression level			
≥ 25%	51/115 (44.3)	27/44 (61.4)	0.52 (0.32 to 0.82)
< 25%	111/187 (59.4)	64/105 (61.0)	0.90 (0.67 to 1.23)
Unknown	102/174 (58.6)	64/88 (72.7)	0.68 (0.50 to 0.93)
1%-24% (post hoc analysis)	52/97 (53.6)	29/47 (61.7)	0.73 (0.46 to 1.14)
≥ 1% (post hoc analysis)	103/212 (48.6)	56/91 (61.5)	0.61 (0.44 to 0.85)
< 1% (post hoc analysis)	59/90 (65.6)	35/58 (60.3)	1.15 (0.75 to 1.75)



OS by prespecified and exploratory, post hoc subgroups

Spigel, JCO 2022

Patients Ineligible for CH/RT

Single agent pembrolizumab

NCT03706690: A Study of Durvalumab as Consolidation Therapy in Non-Small Cell Lung Cancer Patients (PACIFIC-5)

NCT03693300: A Study to Determine Safety of Durvalumab After Sequential Chemo Radiation in Patients With Unresectable Stage III Non-Small Cell Lung Cancer

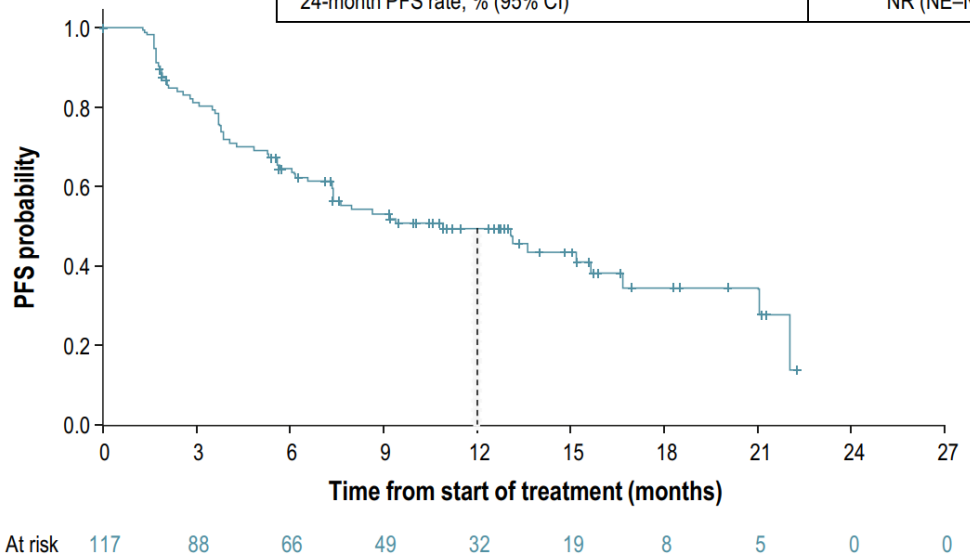
Durvalumab After Sequential Chemoradiotherapy in Stage III, Unresectable NSCLC: The Phase 2 PACIFIC-6 Trial

Arm	No. of Events/ Total No. of Patients (%)	Median PFS (95% CI), Months
Durvalumab	268/476 (56.3)	16.9 (13.0 to 23.9)
Placebo	175/237 (73.8)	5.6 (4.8 to 7.7)

Stratified HR (95% CI): 0.55 (0.45 to 0.68)

A

	All patients (N = 117)
Total progression events, n (%)	61 (52.1)
Median PFS, months (95% CI)	10.9 (7.3–15.6)
12-month PFS rate, % (95% CI)	49.6 (39.5–58.9)
24-month PFS rate, % (95% CI)	NR (NE–NE)

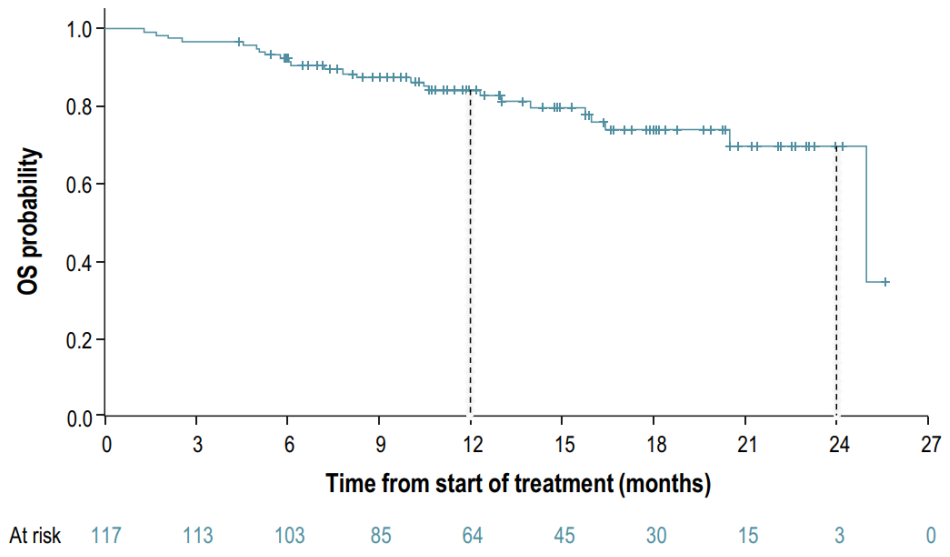


Arm	No. of Events/ Total No. of Patients (%)	Median OS (95% CI), Months
Durvalumab	264/476 (55.5)	47.5 (38.1 to 52.9)
Placebo	155/237 (65.4)	29.1 (22.1 to 35.1)

Stratified HR (95% CI): 0.72 (0.59 to 0.89)

B

	All patients (N = 117)
Deaths, n (%)	25 (21.4)
Median OS, months (95% CI)	25.0 (25.0–NE)
12-month OS rate, % (95% CI)	84.1 (75.6–89.9)
24-month OS rate, % (95% CI)	69.8 (55.8–80.2)



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Personal Conclusions

- The Pacific regimen is currently the ideal treatment choice for most patients with unresectable Stage III NSLCL.
- Patients with resectable stage III NSCLC should consider neoadjuvant therapy, especially patients with negative PDL-1
- I have long discussions explaining clinical trial data with patients whose tumors have EGFR or ALK aberrations.
- More data is needed in patients with negative PDL-1