XXIV

Simposio de Revisiones en Cáncer

"Tratamiento médico del cáncer en el año 2022"

El valor de la doble inmunoterapia y la supervivencia a largo plazo para el paciente con cáncer

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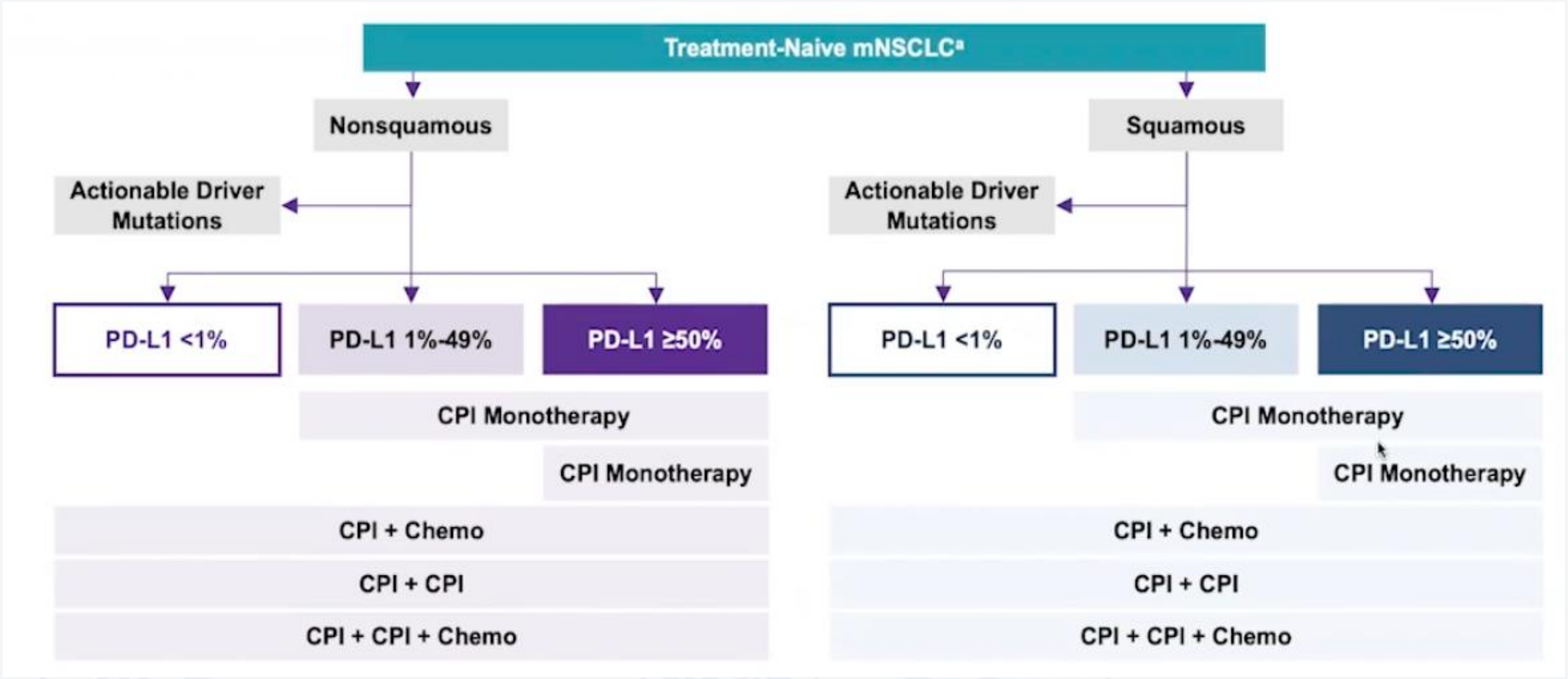
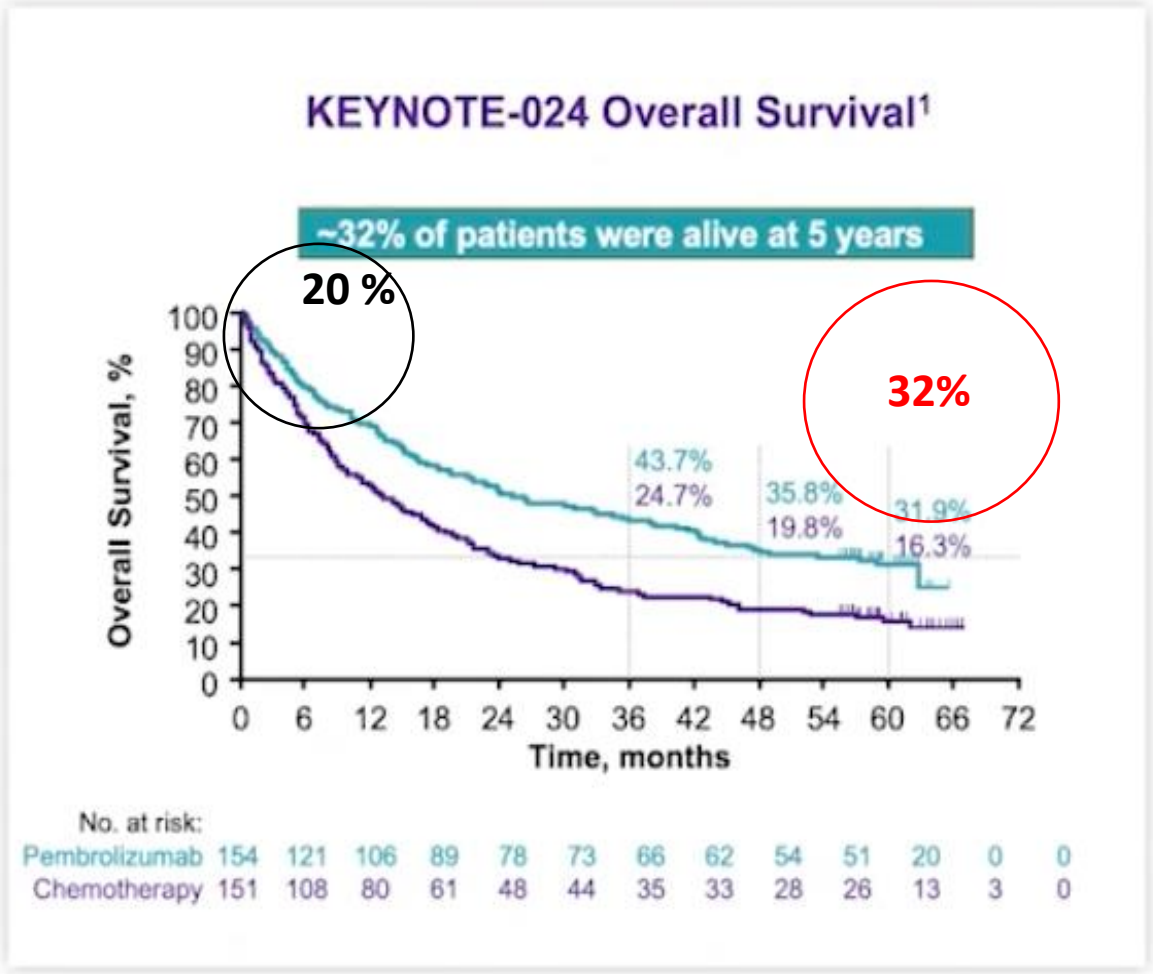
Disclosure

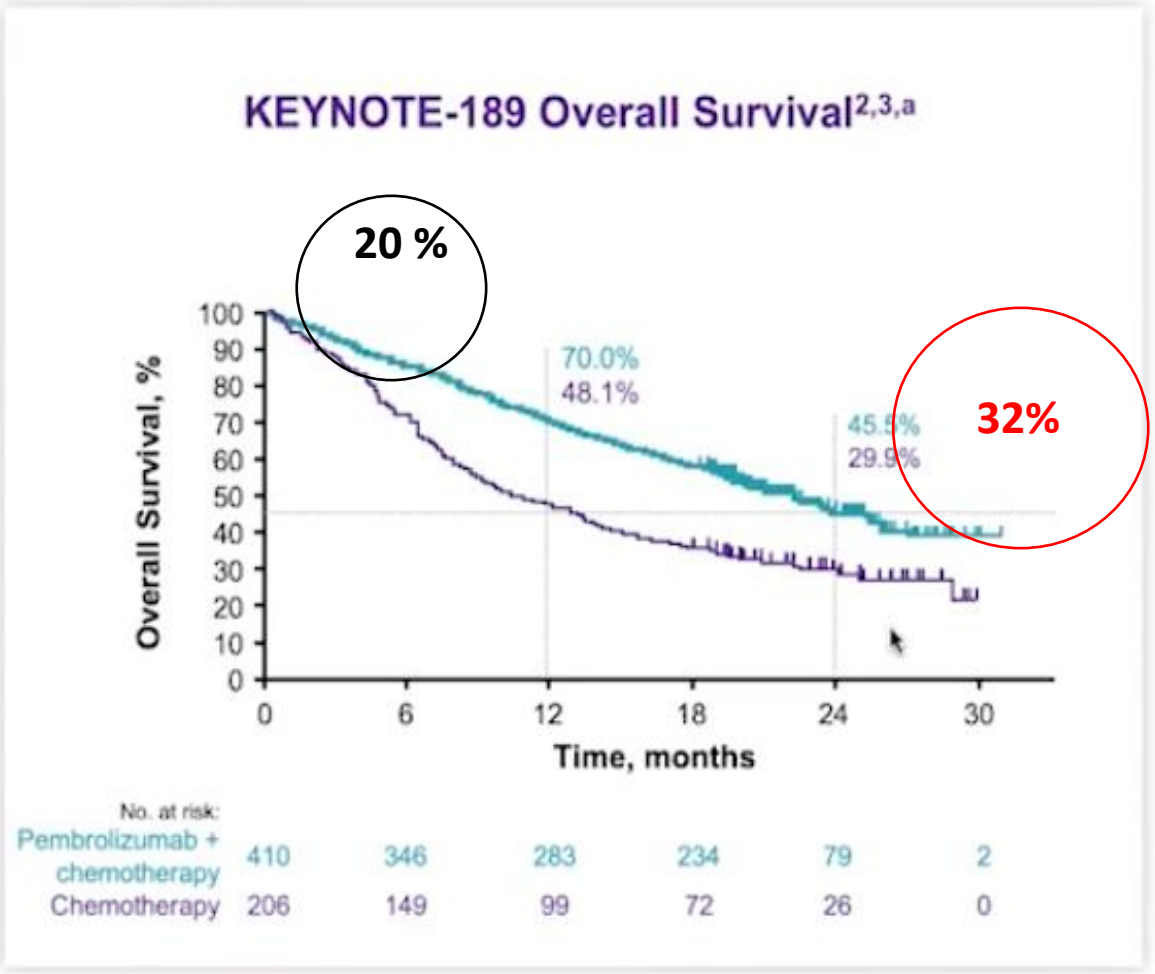
- Educational fees: Astra Zeneca, Boehringer Ingelheim, Bristol Myers Squibb, Merck Sharp and Dohme and Roche.
- Advisory board: Astra Zeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Glaxo-Smithkline, Janssen-Cilag, Lilly, Merck Sharp and Dohme, Novartis, Pfizer, Roche and Takeda.
- Speaker bureau: Roche
- Employment: Hospital Universitario La Paz

Inmunoterapia en mNSCLC



Pembrolizumab en PD-L1 ≥ 50% /Pembro + CT en No escamosos



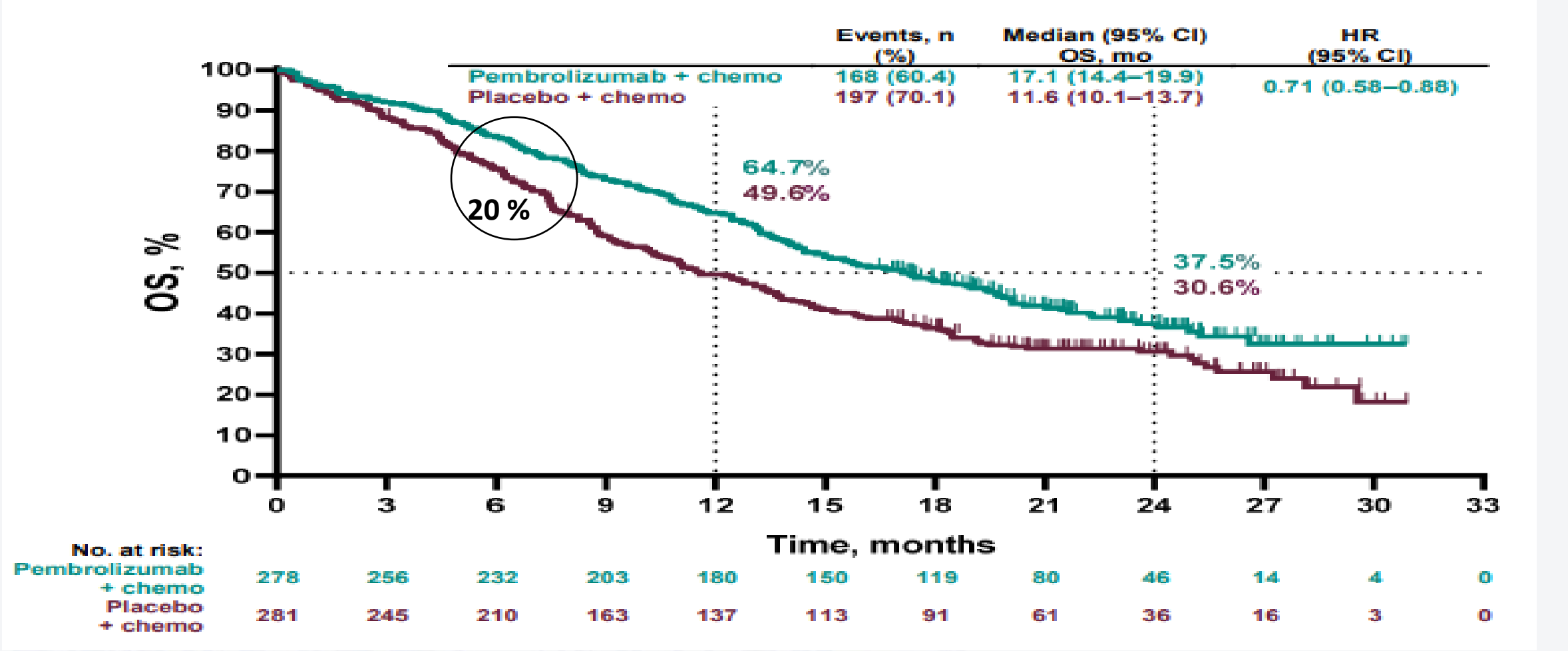


Brahmer et al. ESMO 2020

Rodrguez-Abreu et al. Ann Oncol 2021

Pembro + CT en escamosos

KEYNOTE-407



Paz-Ares L *et al.* N Engl J Med. 2018

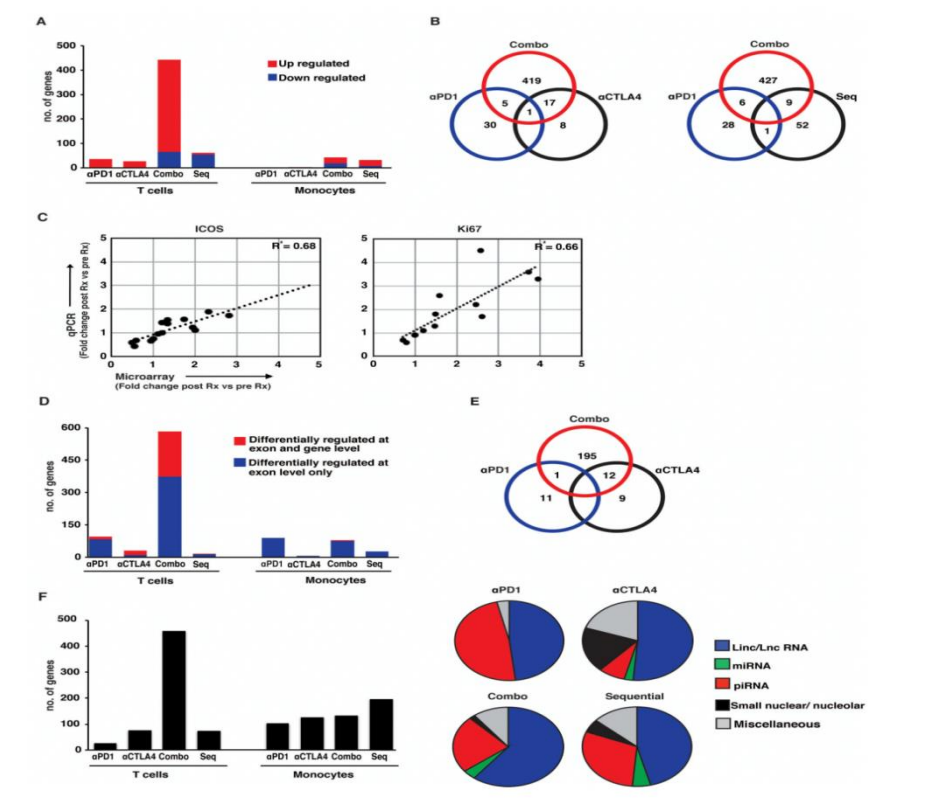
¿Cómo mejorar estos resultados?

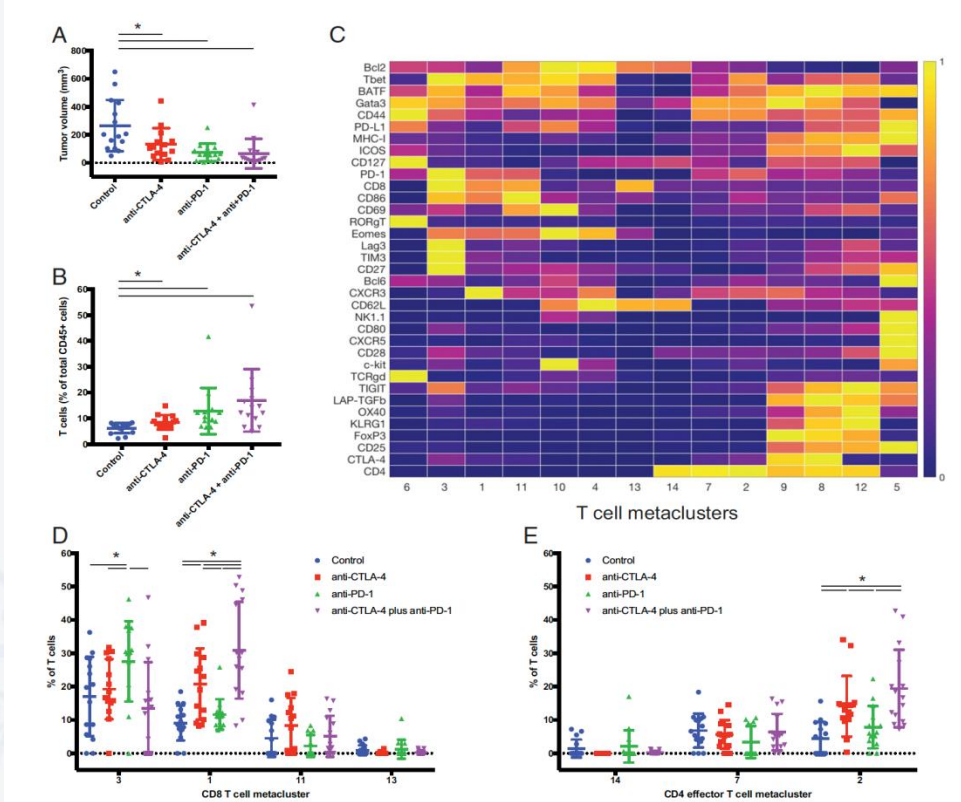
Implementar el beneficio

- Asociando nuevos agentes
- Revirtiendo resistencias
- Rechallenge
- Biomarcadores

Combinando anti-PD-1/anti-CTLA-4

- Racional Biológico



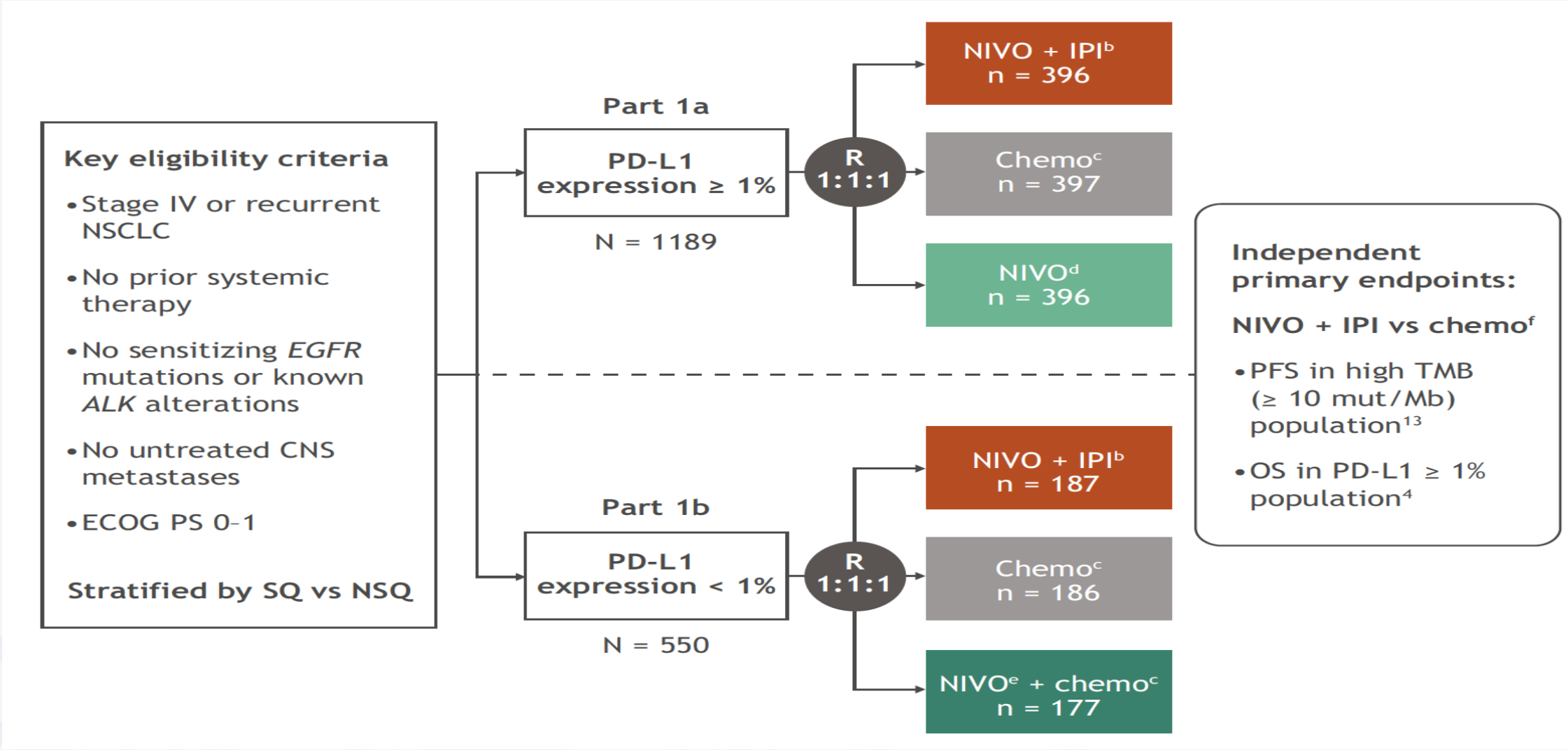


- Racional Clínico

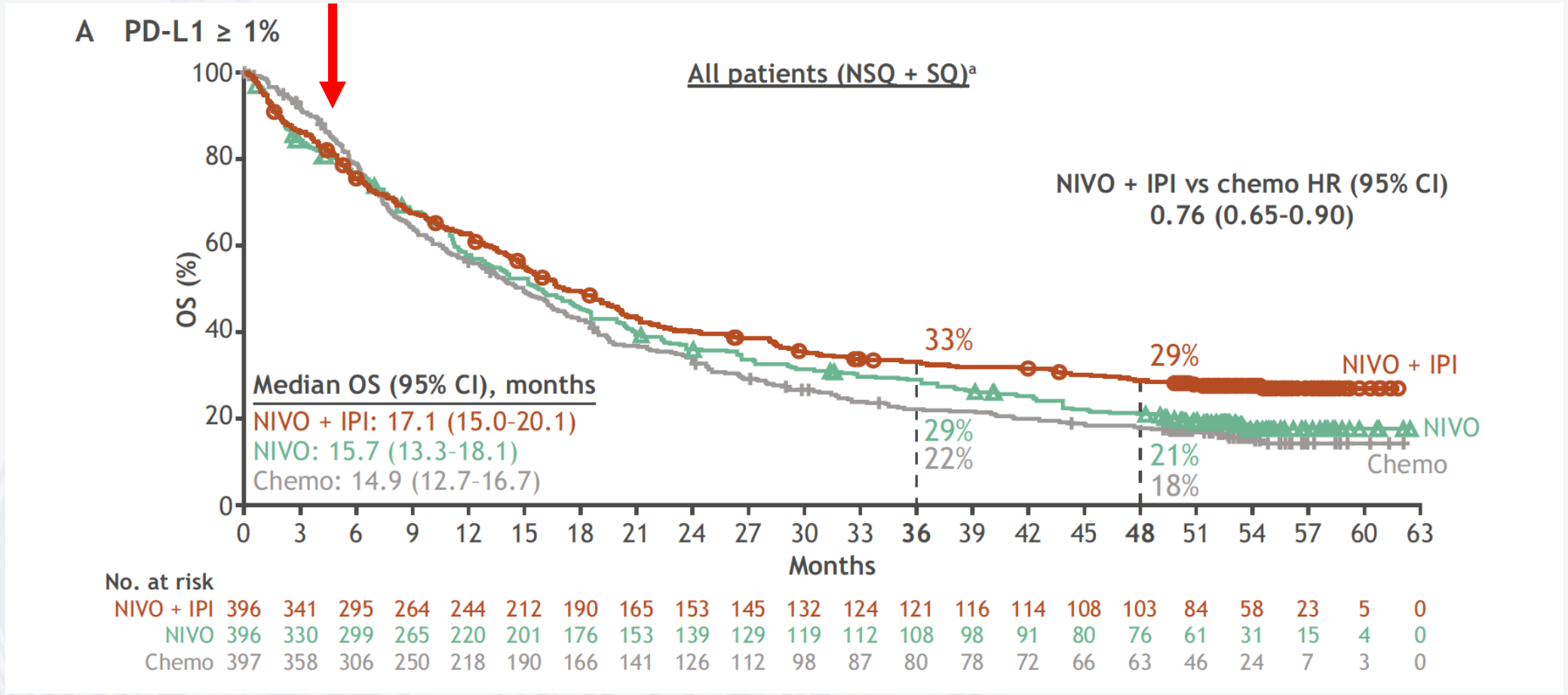
Ensayos en melanoma, carcinoma renal, pulmón, mesotelioma

1. Sharma P, et al. *Nat Rev Immunol* 2020;20:75-76; 2. Wei SC, et al. *Cancer Discov* 2018;8:1069-1086; 3. Das R, et al. *J Immunol* 2015;194:950-959; 4. Ramalingam SS, et al. Oral presentation at the ASCO Annual Meeting; May 29–31, 2020; virtual. Abstract 9500; 5. Larkin J, et al. *N Engl J Med* 2019;381:1535-1546; 6. Motzer RJ, et al. *Lancet Oncol* 2019;20:1370-1385; 7. Baas P, et al. *Lancet* 2021;397:375-386; 8. Paz-Ares L, et al. *Lancet Oncol* 2021;22:198-211; 9. OPDIVO® (nivolumab) [package insert]. Princeton, NJ: Bristol Myers Squibb; April 2021; 10. eCancer.

Checkmate 227

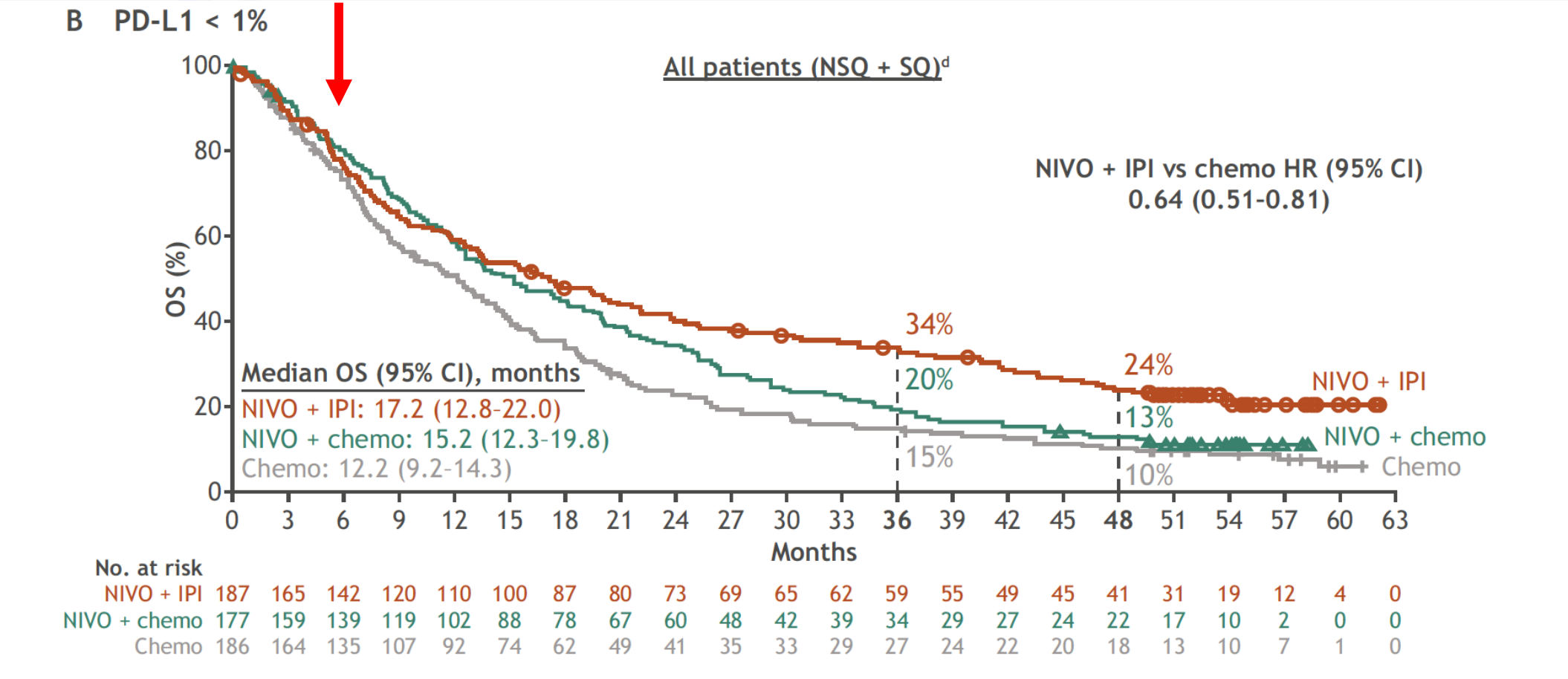


Checkmate 227: Análisis Supervivencia a 4 años PD-L1 ≥ 1%



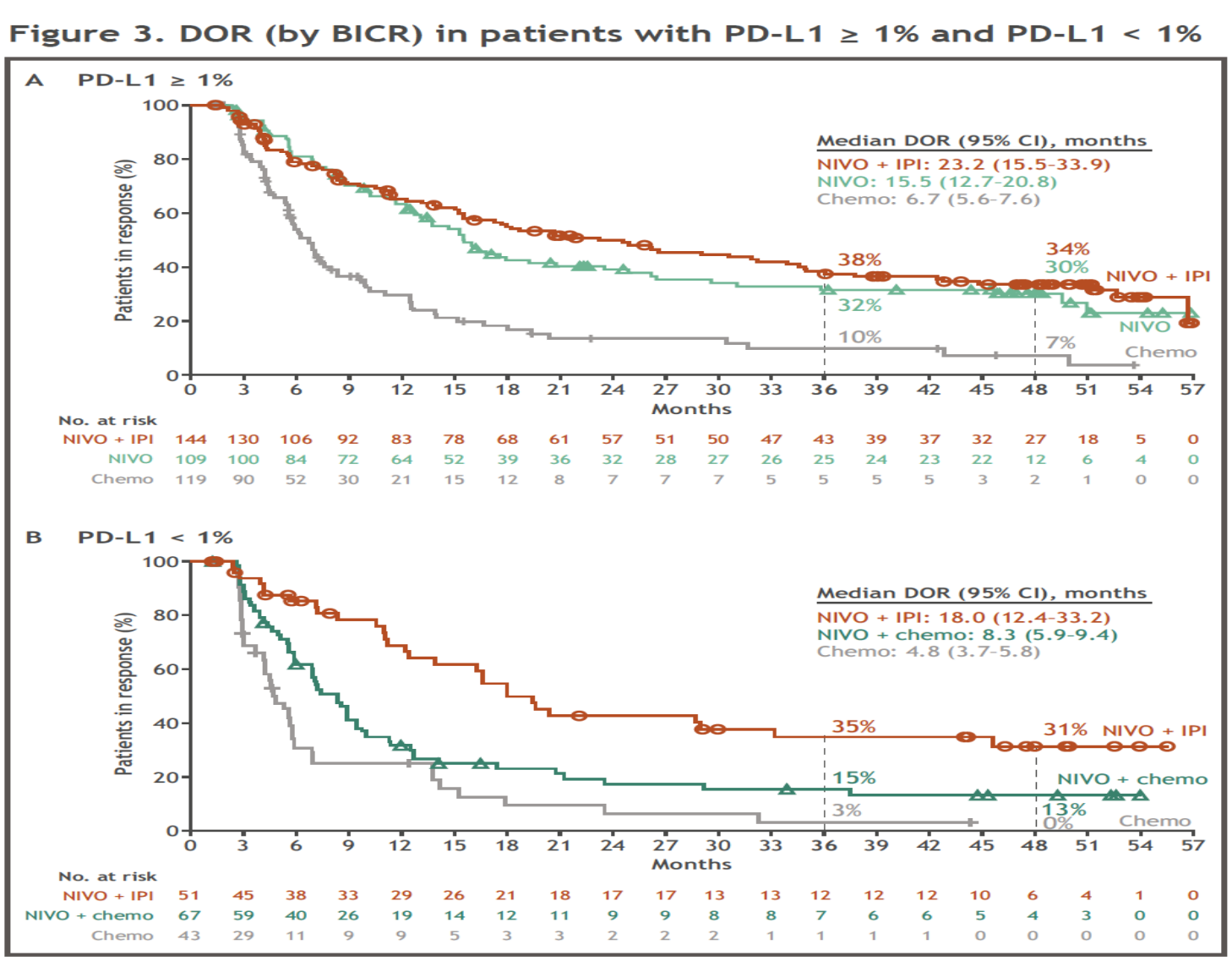
Paz-Ares L et al, ASCO 2021

Checkmate 227: Análisis Supervivencia a 4 años PD-L1 <1%



Paz-Ares L et al, ASCO 2021

Checkmate 227: duración de la respuesta



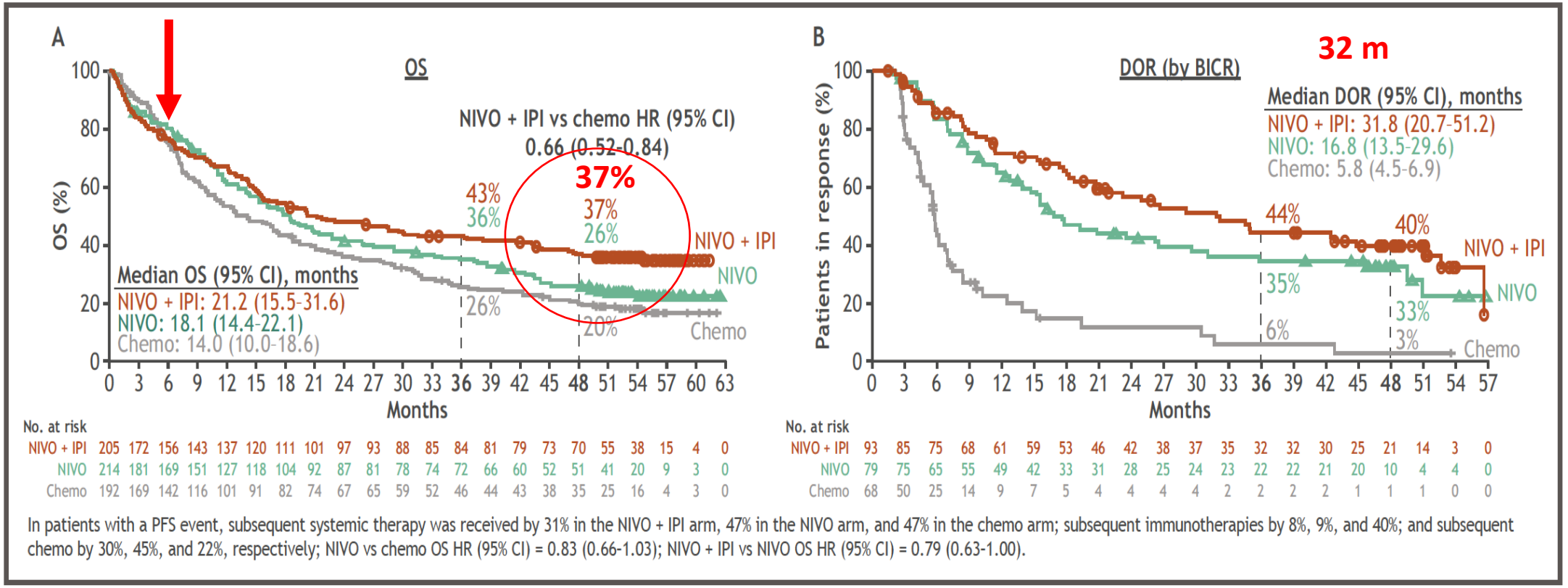
23 meses

18 meses

Paz-Ares L et al, ASCO 2021

Checkmate 227: Análisis Supervivencia a 4 años PD-L1 ≥ 50%

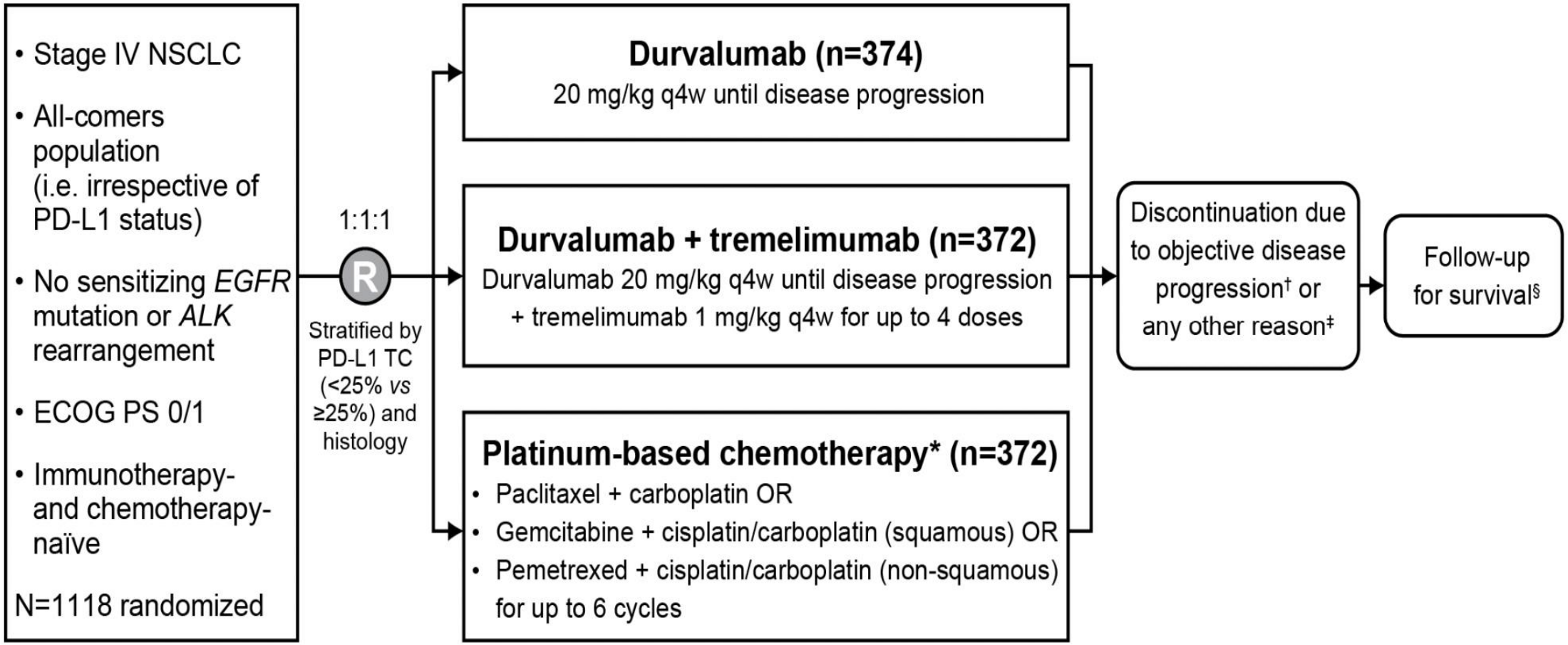
Figure 4. Efficacy in patients with PD-L1 ≥ 50%



In patients with a PFS event, subsequent systemic therapy was received by 31% in the NIVO + IPI arm, 47% in the NIVO arm, and 47% in the chemo arm; subsequent immunotherapies by 8%, 9%, and 40%; and subsequent chemo by 30%, 45%, and 22%, respectively; NIVO vs chemo OS HR (95% CI) = 0.83 (0.66-1.03); NIVO + IPI vs NIVO OS HR (95% CI) = 0.79 (0.63-1.00).

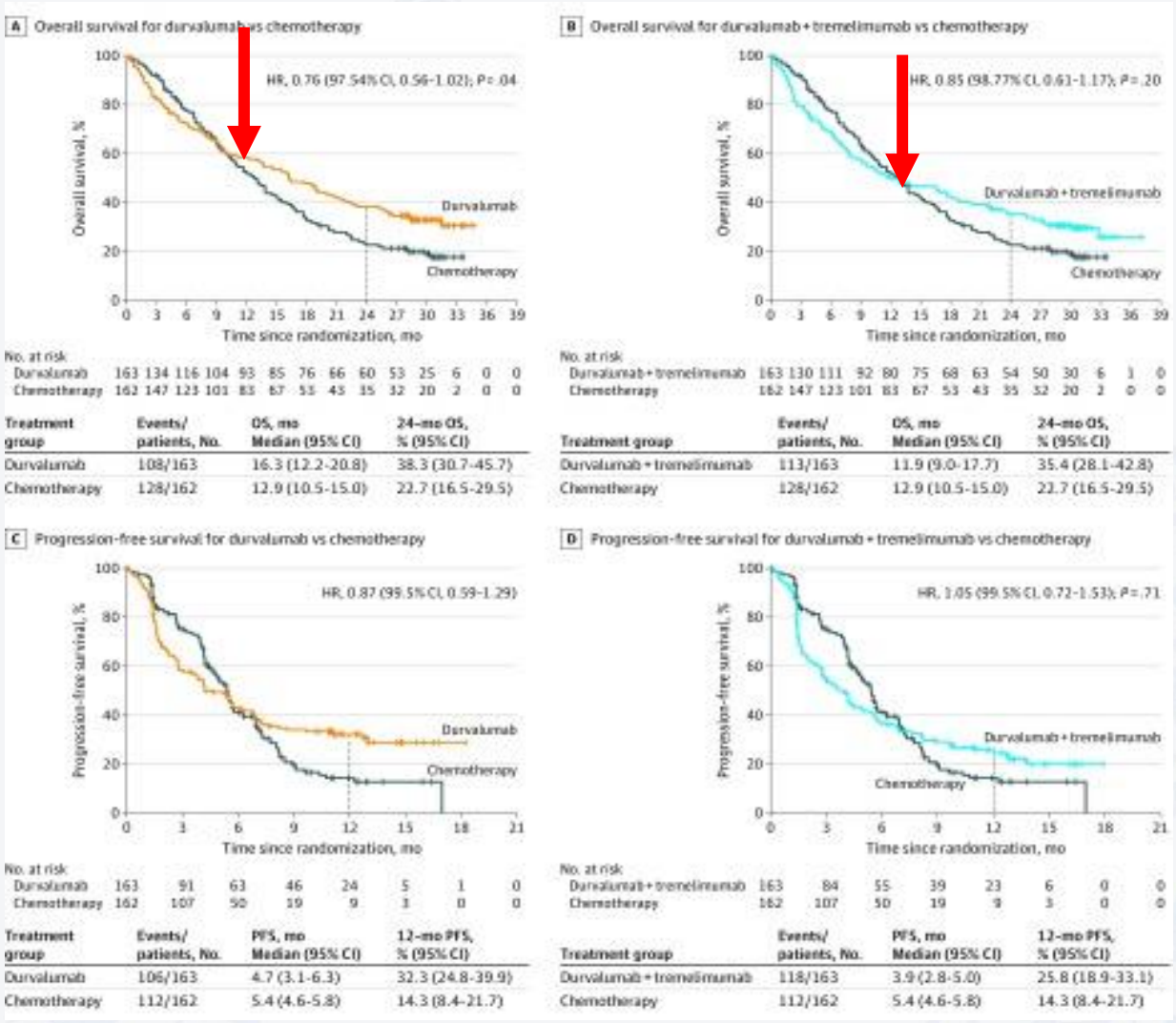
Paz-Ares L et al, ASCO 2021

MYSTIC study



Rizvi NA et al, *JAMA Oncol* 2020

MYSTIC study
PFS and OS

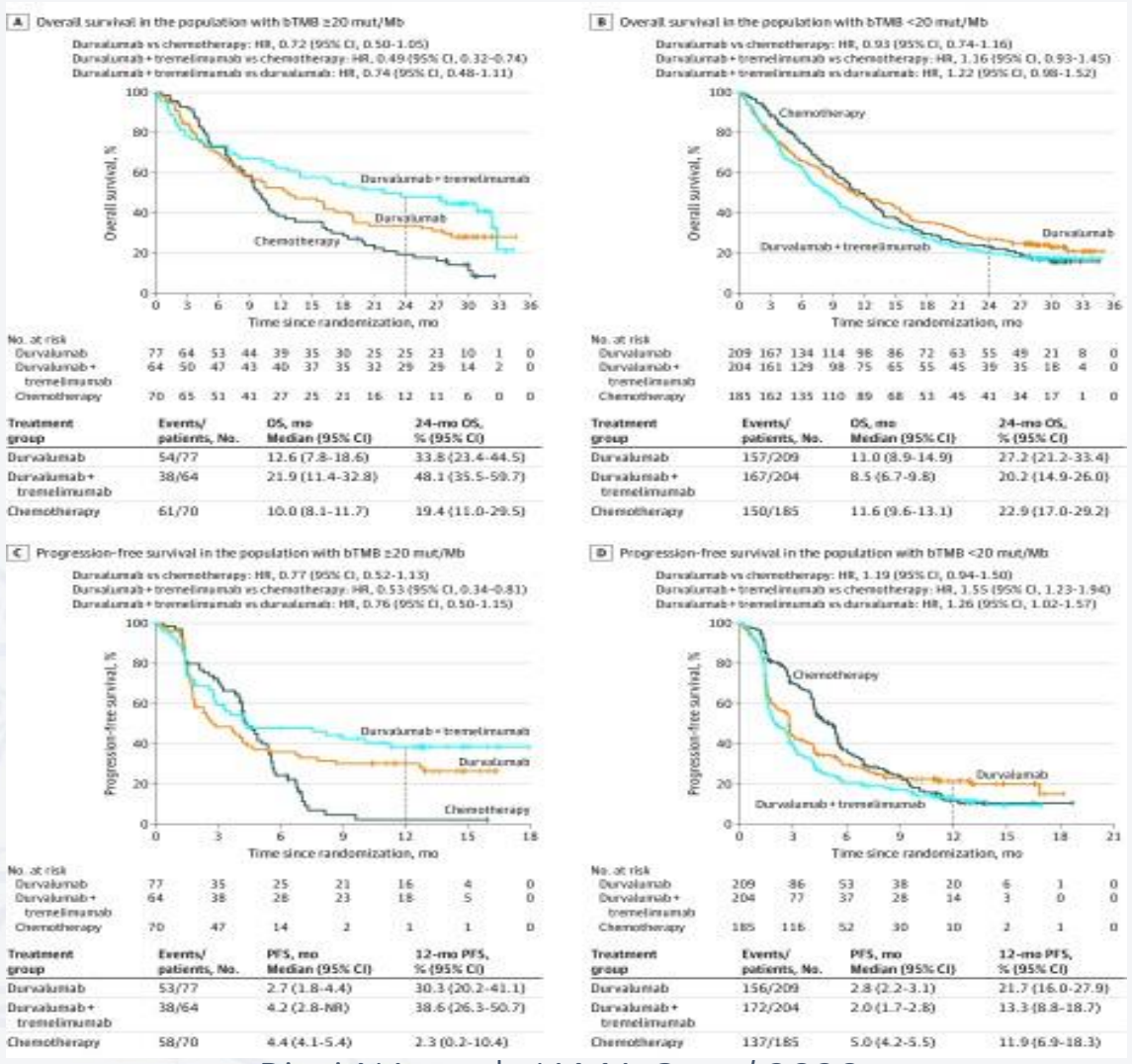


Treatment group	Events/ patients, No.	OS, mo Median (95% CI)	24-mo OS, % (95% CI)
Durvalumab	108/163	16.3 (12.2-20.8)	38.3 (30.7-45.7)
Chemotherapy	128/162	12.9 (10.5-15.0)	22.7 (16.5-29.5)

Treatment group	Events/ patients, No.	OS, mo Median (95% CI)	24-mo OS, % (95% CI)
Durvalumab + tremelimumab	113/163	11.9 (9.0-17.7)	35.4 (28.1-42.8)
Chemotherapy	128/162	12.9 (10.5-15.0)	22.7 (16.5-29.5)

Treatment group	Events/ patients, No.	PFS, mo Median (95% CI)	12-mo PFS, % (95% CI)
Durvalumab	106/163	4.7 (3.1-6.3)	32.3 (24.8-39.9)
Chemotherapy	112/162	5.4 (4.6-5.8)	14.3 (8.4-21.7)

Treatment group	Events/ patients, No.	PFS, mo Median (95% CI)	12-mo PFS, % (95% CI)
Durvalumab + tremelimumab	118/163	3.9 (2.8-5.0)	25.8 (18.9-33.1)
Chemotherapy	112/162	5.4 (4.6-5.8)	14.3 (8.4-21.7)



Treatment group	Events/ patients, No.	OS, mo Median (95% CI)	24-mo OS, % (95% CI)
Durvalumab	54/77	12.6 (7.8-18.6)	33.8 (23.4-44.5)
Durvalumab + tremelimumab	38/64	21.9 (11.4-32.8)	48.1 (35.5-59.7)
Chemotherapy	61/70	10.0 (8.1-11.7)	19.4 (11.0-29.5)

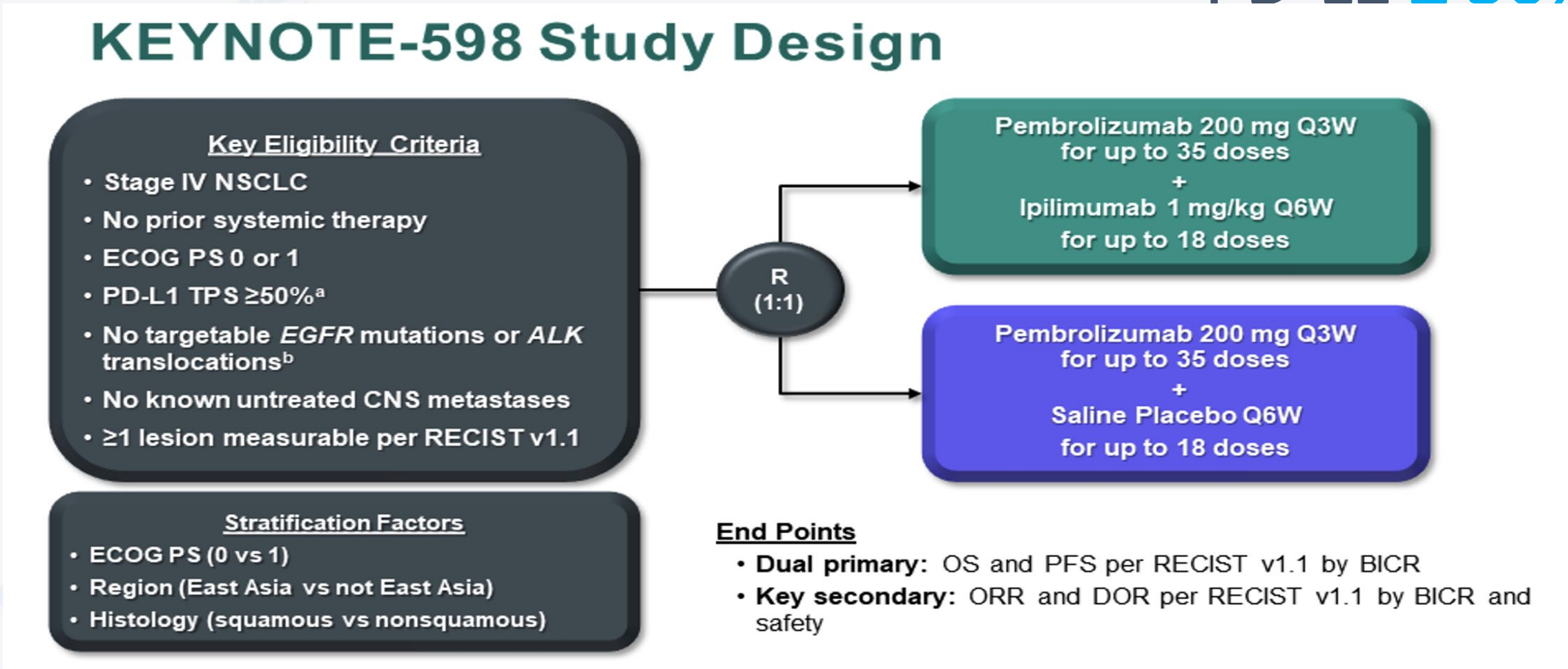
Treatment group	Events/ patients, No.	OS, mo Median (95% CI)	24-mo OS, % (95% CI)
Durvalumab	157/209	11.0 (8.9-14.9)	27.2 (21.2-33.4)
Durvalumab + tremelimumab	167/204	8.5 (6.7-9.8)	20.2 (14.9-26.0)
Chemotherapy	150/185	11.6 (9.6-13.1)	22.9 (17.0-29.2)

Treatment group	Events/ patients, No.	PFS, mo Median (95% CI)	12-mo PFS, % (95% CI)
Durvalumab	53/77	2.7 (1.8-4.4)	30.3 (20.2-41.1)
Durvalumab + tremelimumab	38/64	4.2 (2.8-NR)	38.6 (26.3-50.7)
Chemotherapy	58/70	4.4 (4.1-5.4)	2.3 (0.2-10.4)

Treatment group	Events/ patients, No.	PFS, mo Median (95% CI)	12-mo PFS, % (95% CI)
Durvalumab	156/209	2.8 (2.2-3.1)	21.7 (16.0-27.9)
Durvalumab + tremelimumab	172/204	2.0 (1.7-2.8)	13.3 (8.8-18.7)
Chemotherapy	137/185	5.0 (4.2-5.5)	11.9 (6.9-18.3)

Rizvi NA et al, *JAMA Oncol* 2020

KEYNOTE-598: Pembro + Ipi vs Pembro PD-L1 ≥ 50%

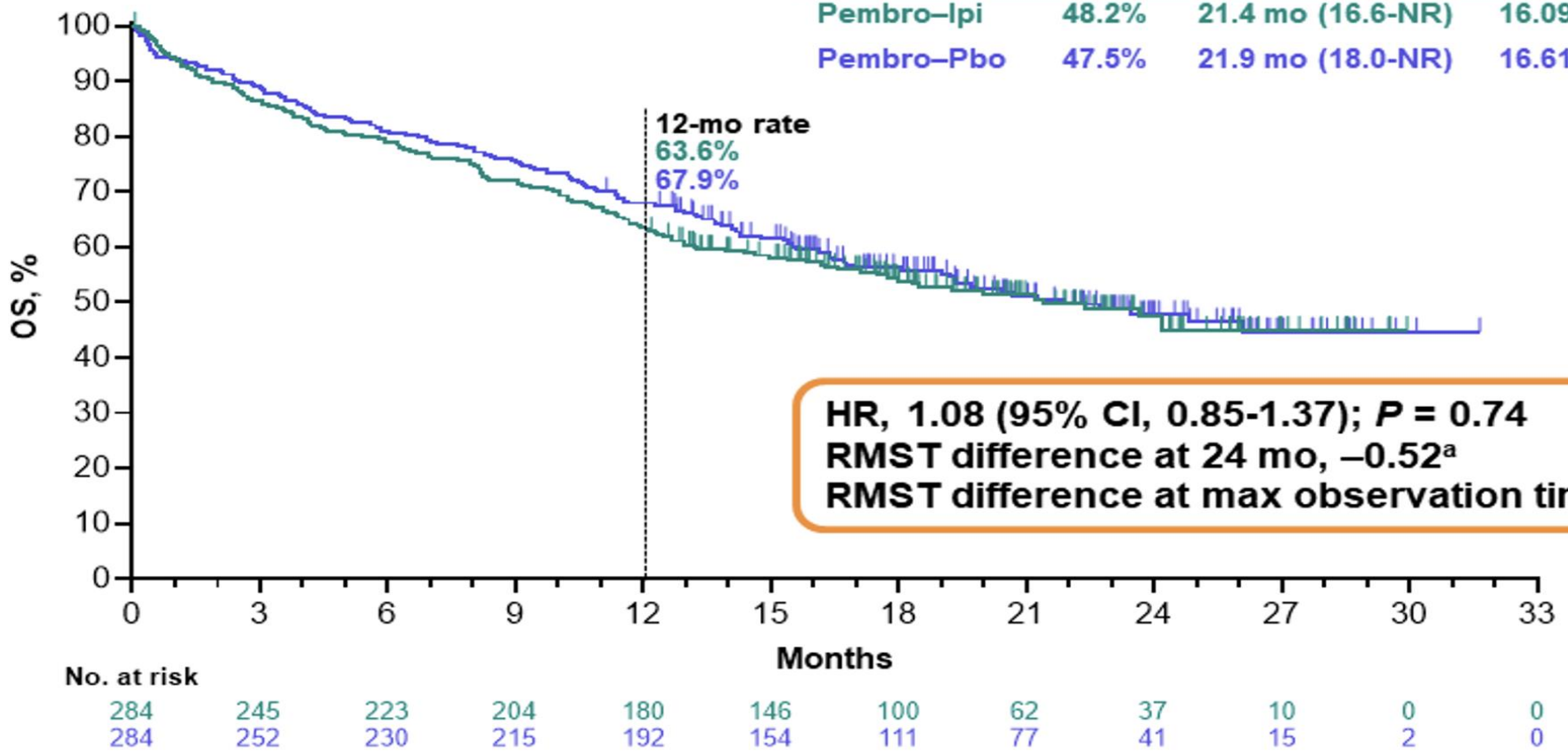


Boyer et al, WCLC 2020

KEYNOTE-598: Pembro + Ipi vs Pembro PD-L1 ≥ 50%

Overall Survival

	Pts w/ Event	Median (95% CI)	RMST at 24 mo	RMST at Max Time
Pembro–Ipi	48.2%	21.4 mo (16.6-NR)	16.09 mo	18.76 mo
Pembro–Pbo	47.5%	21.9 mo (18.0-NR)	16.61 mo	19.32 mo

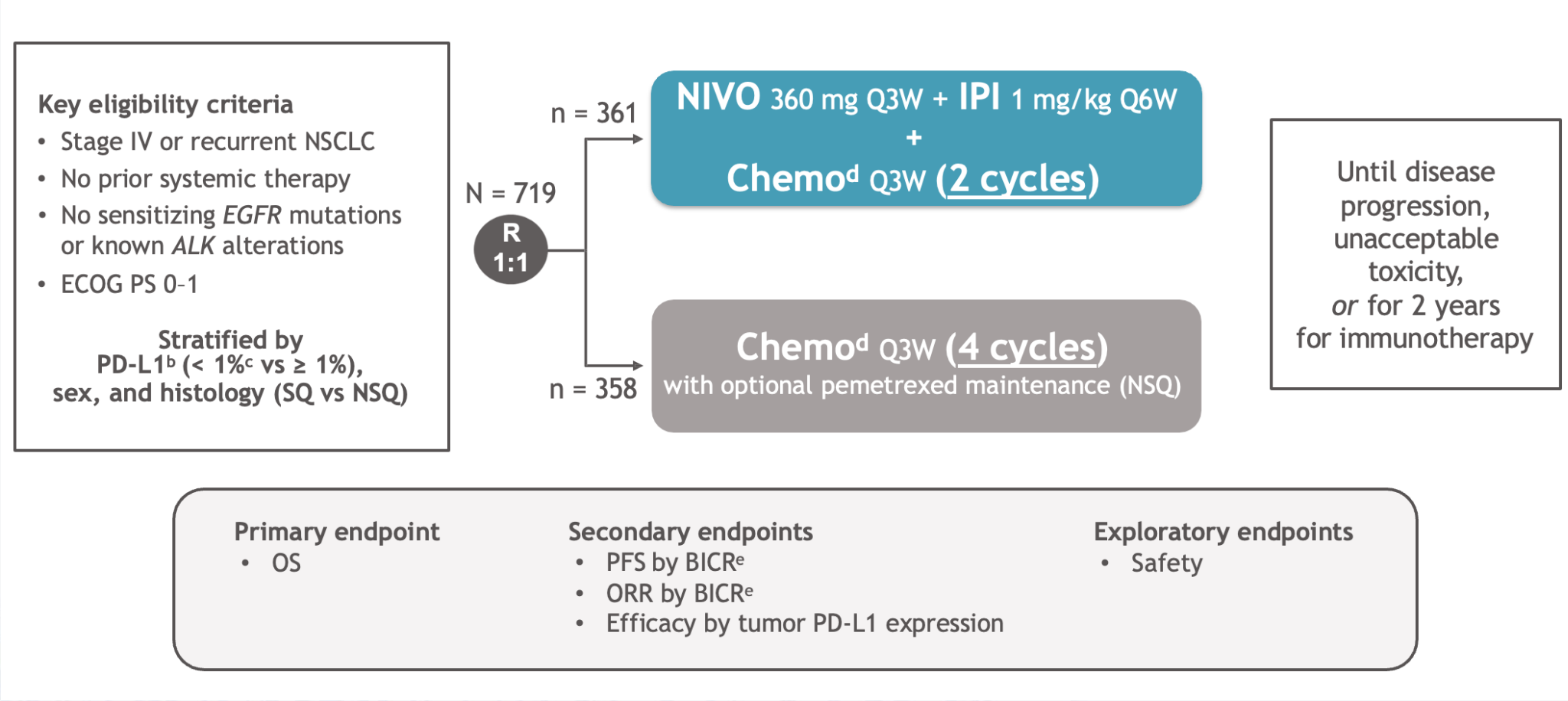


HR, 1.08 (95% CI, 0.85-1.37); *P* = 0.74
RMST difference at 24 mo, –0.52[a]
RMST difference at max observation time, –0.56[a]

[a]Nonbinding futility criteria met.
Data cutoff date: Sep 1, 2020.

Boyer et al, WCLC 2020

CheckMate 9LA study

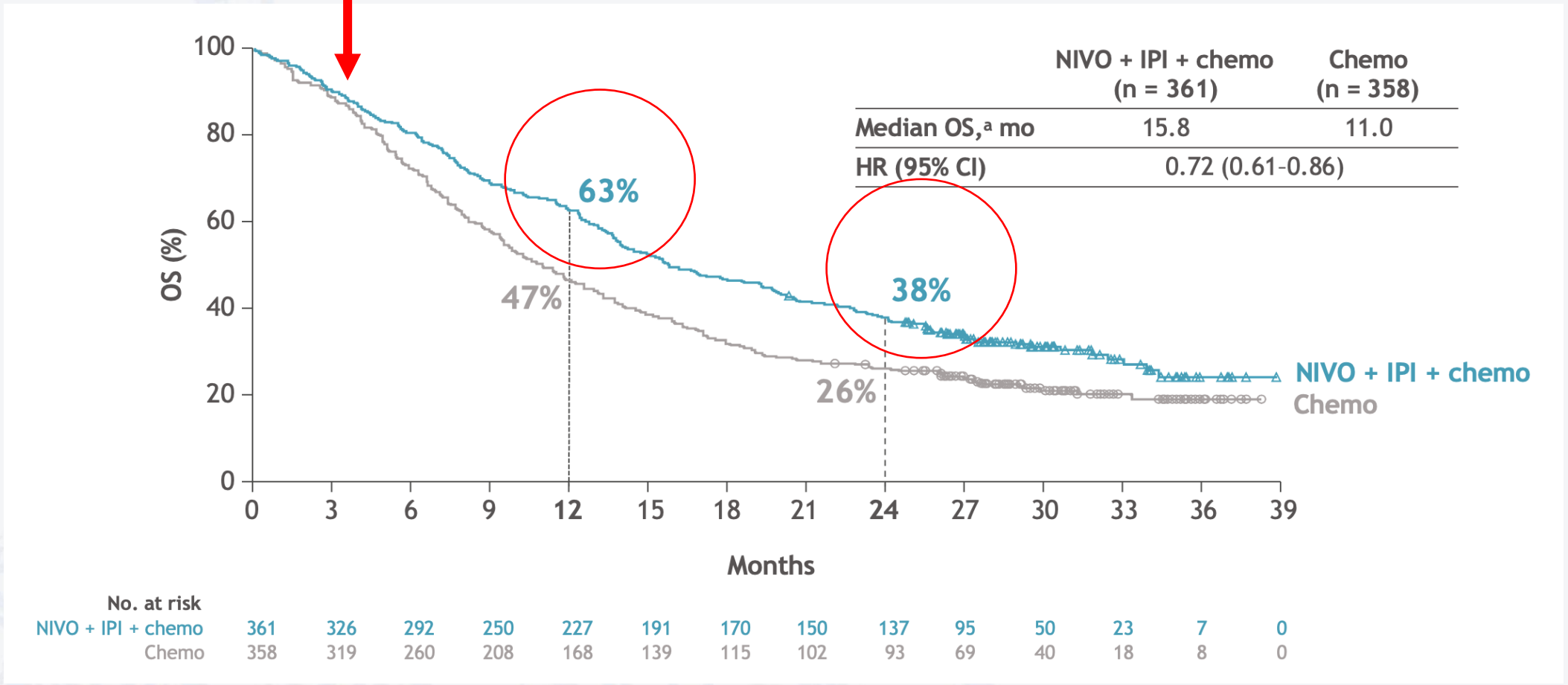


DBL: February 18, 2021; minimum / median follow-up for OS: 24.4 months / 30.7 months.

[a]NCT03215706; [b]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [c]Patients unevaluable for PD-L1 were stratified to PD-L1 < 1% and capped to 10% of all randomized patients; [d]NSQ: pemetrexed + cisplatin or carboplatin; SQ: paclitaxel + carboplatin; [e]Hierarchically statistically tested.

Paz-Ares L, et al. *Lancet Oncol* 2021

CheckMate 9LA study
2-Year update: OS in all randomized patients

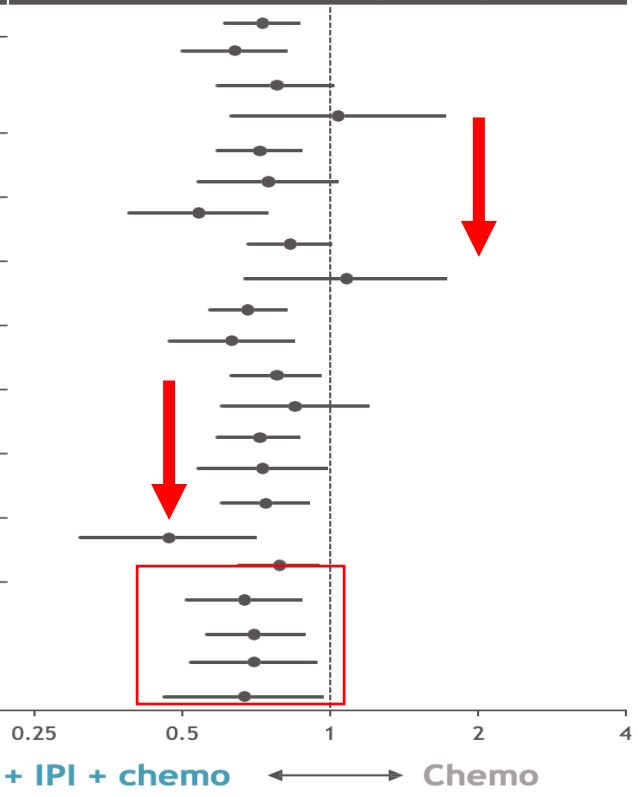


Minimum follow-up: 24.4 months.
[a]95% CI = 13.9-19.7 (NIVO + IPI + chemo) and 9.5-12.7 (chemo).

Reck M et al, ASCO 2021; Paz-Ares L, et al. *Lancet Oncol* 2021

CheckMate 9LA study
2-Year update: OS subgroup analysis

Subgroup	Median OS, mo		Unstratified HR
	NIVO + IPI + chemo n = 361	Chemo n = 358	
All randomized (N = 719)	15.8	11.0	0.73
< 65 years (n = 354)	15.9	10.7	0.64
≥ 65 to < 75 years (n = 295)	19.0	11.9	0.78
≥ 75 years (n = 70)	8.5	11.5	1.04
Male (n = 504)	14.2	9.8	0.72
Female (n = 215)	22.2	15.9	0.75
ECOG PS 0 (n = 225)	27.1	14.1	0.54
ECOG PS 1 (n = 492)	13.6	9.7	0.83
Never smoker (n = 98)	14.1	14.4	1.08
Smoker (n = 621)	16.2	10.4	0.68
SQ (n = 227)	14.5	9.1	0.63
NSQ (n = 492)	17.8	12.0	0.78
Liver metastases (n = 154)	10.2	8.1	0.85
No liver metastases (n = 565)	19.3	12.4	0.72
Bone metastases (n = 207)	11.9	8.3	0.73
No bone metastases (n = 512)	19.7	12.4	0.74
CNS metastases (n = 123)	19.9	7.9	0.47
No CNS metastases (n = 596)	15.6	11.8	0.79
PD-L1 < 1% (n = 264)	17.7	9.8	0.67
PD-L1 ≥ 1% (n = 407)	15.8	10.9	0.70
PD-L1 1-49% (n = 233)	15.2	10.4	0.70
PD-L1 ≥ 50% (n = 174)	18.9	12.9	0.67

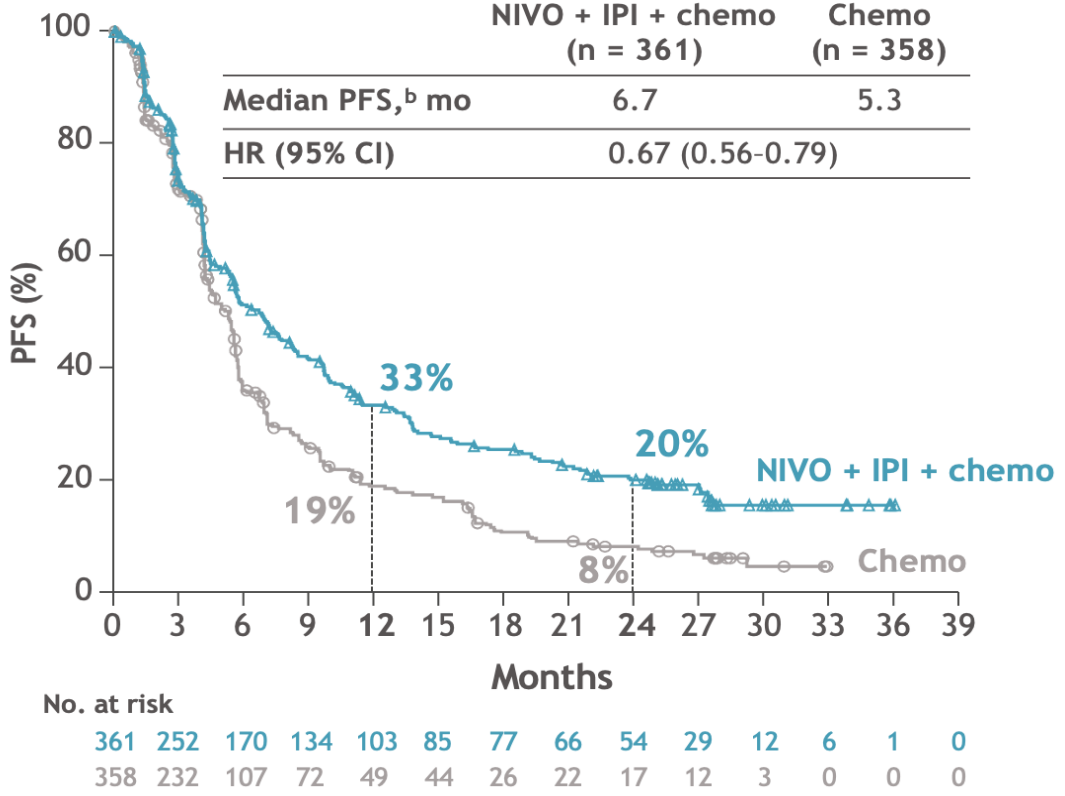


Paz-Ares L, et al. *Lancet Oncol* 2021

CheckMate 9LA study
2-Year update: PFS and DOR

PFS[a]

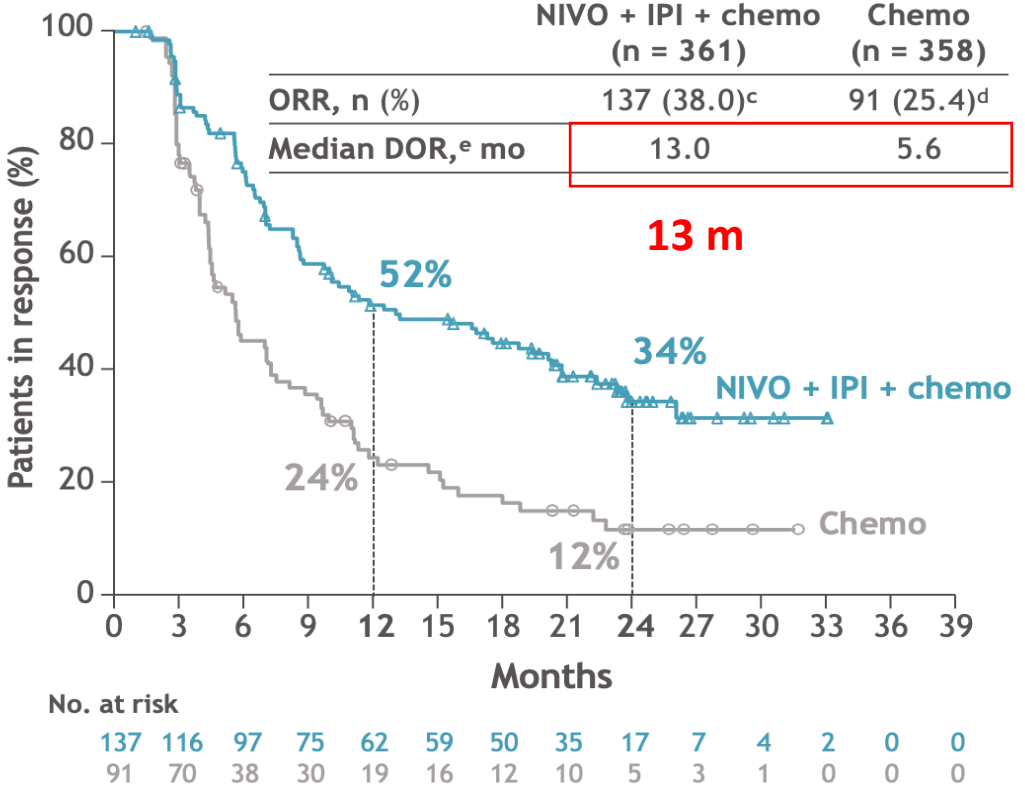
	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
Median PFS,[b] mo	6.7	5.3
HR (95% CI)	0.67 (0.56-0.79)	



DOR[a]

	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
ORR, n (%)	137 (38.0)[c]	91 (25.4)[d]
Median DOR,[e] mo	13.0	5.6

13 m



Minimum follow-up: 23.3 months.

[a]Per BICR; [b]95% CI = 5.6–7.8 (NIVO + IPI + chemo) and 4.4–5.6 (chemo); [c]Includes 3.3% CR and 34.6% PR; 4 patients who had a PR as best response at a previous DBL (12.2 months minimum follow-up for response) improved to CRs; [d]Includes 1.1% CR and 24.3% PR; [e]95% CI = 8.7–20.2 (NIVO + IPI + chemo) and 4.4–7.2 (chemo).

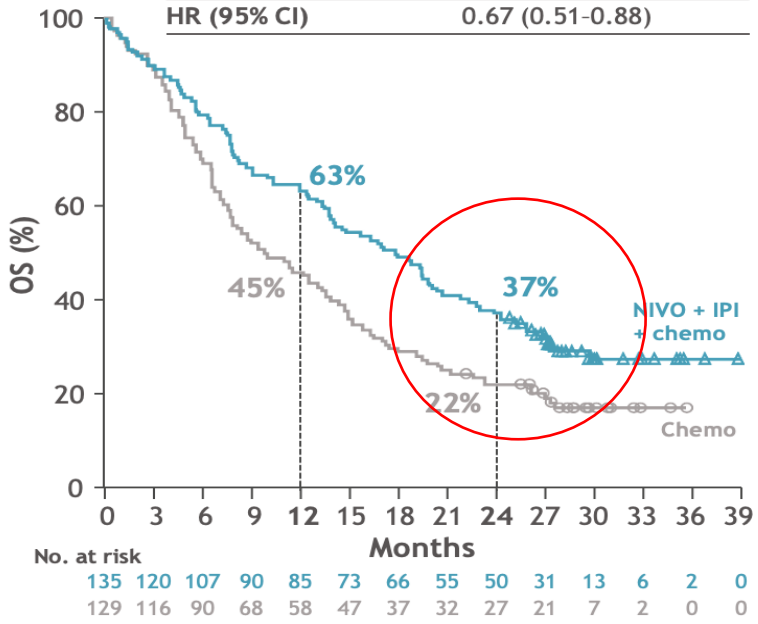
Paz-Ares L, et al. *Lancet Oncol* 2021

CheckMate 9LA study

PD-L1 < 1%: efficacy outcomes

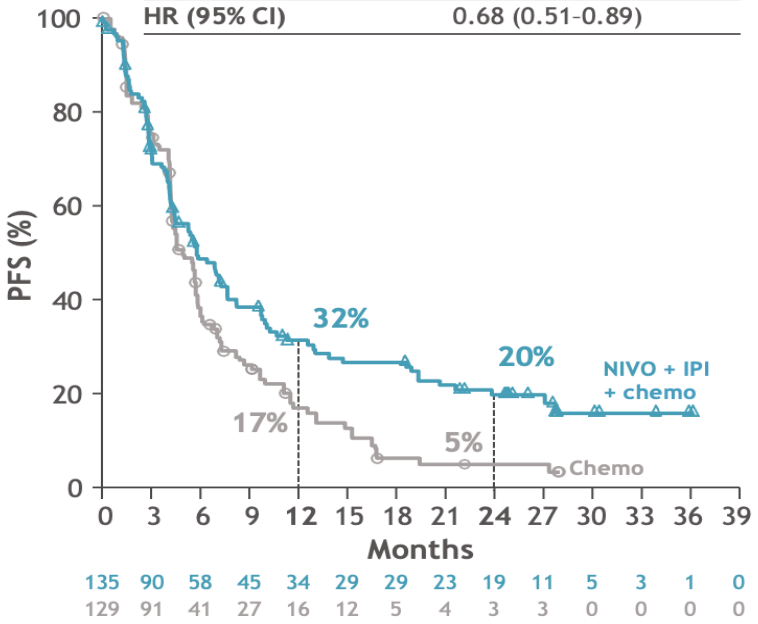
OS

	NIVO + IPI + chemo (n = 135)	Chemo (n = 129)
Median OS,[b] mo	17.7	9.8
HR (95% CI)	0.67 (0.51-0.88)	



PFS[a]

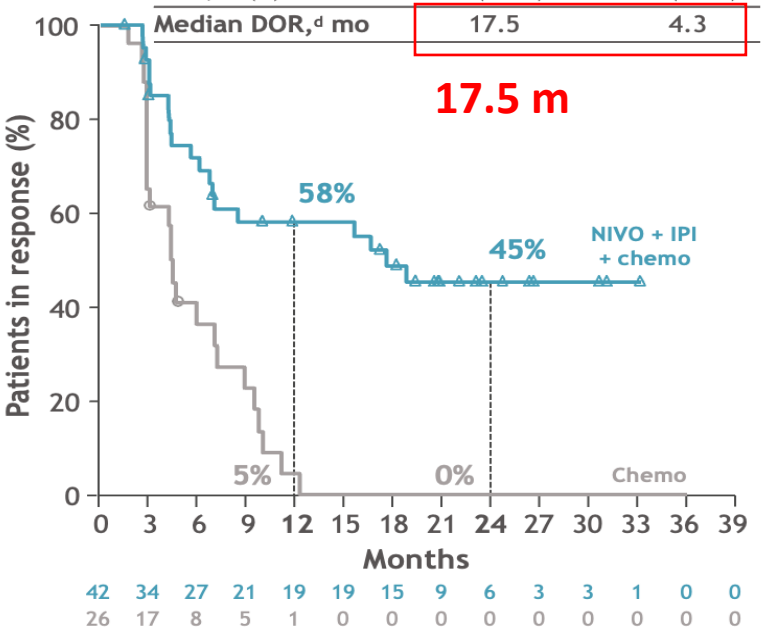
	NIVO + IPI + chemo (n = 135)	Chemo (n = 129)
Median PFS,[c] mo	5.8	4.9
HR (95% CI)	0.68 (0.51-0.89)	



DOR[a]

	NIVO + IPI + chemo (n = 135)	Chemo (n = 129)
ORR, n (%)	42 (31.1)	26 (20.2)
Median DOR,[d] mo	17.5	4.3

17.5 m



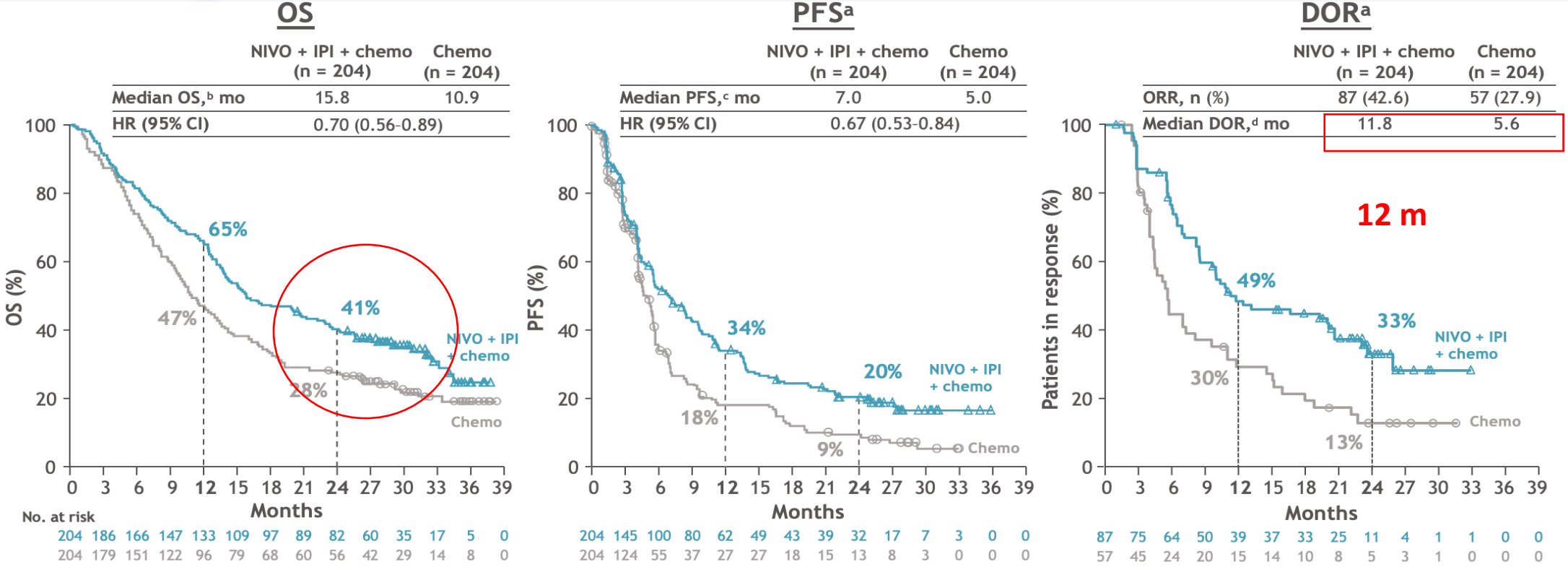
- Exploratory analysis of OS by histology in PD-L1 < 1% (HR; NIVO + IPI + chemo vs chemo): 0.75[e] (NSQ) and 0.48[f] (SQ)
  - 2-year OS rates were 38% vs 26% (NSQ) and 33% vs 11% (SQ)

- Exploratory analysis of OS by histology in PD-L1 < 1% (HR; NIVO + IPI + chemo vs chemo): 0.75[e] (NSQ) and 0.48[f] (SQ)
  - 2-year OS rates were 38% vs 26% (NSQ) and 33% vs 11% (SQ)

[a]Per BICR; [b]95% CI = 13.7–20.3 (NIVO + IPI + chemo) and 7.7–13.5 (chemo); [c]95% CI = 4.4–7.6 (NIVO + IPI + chemo) and 4.2–5.7 (chemo); [d]95% CI = 6.7–NR (NIVO + IPI + chemo) and 2.8–7.1 (chemo); [e]95% CI = 0.54-1.04 (NSQ); [f]95% CI = 0.28-0.81 (SQ).

Paz-Ares L, et al. *Lancet Oncol* 2021

CheckMate 9LA study
PD-L1 ≥ 1%: efficacy outcomes



- Exploratory analysis of OS by histology in PD-L1 ≥ 1% (HR; NIVO + IPI + chemo vs chemo): 0.71[e] (NSQ) and 0.70[f] (SQ)
  - 2-year OS rates were 42% vs 29% (NSQ) and 38% vs 26% (SQ)

- Exploratory analysis of OS by histology in PD-L1 ≥ 1% (HR; NIVO + IPI + chemo vs chemo): 0.71[e] (NSQ) and 0.70[f] (SQ)
  - 2-year OS rates were 42% vs 29% (NSQ) and 38% vs 26% (SQ)

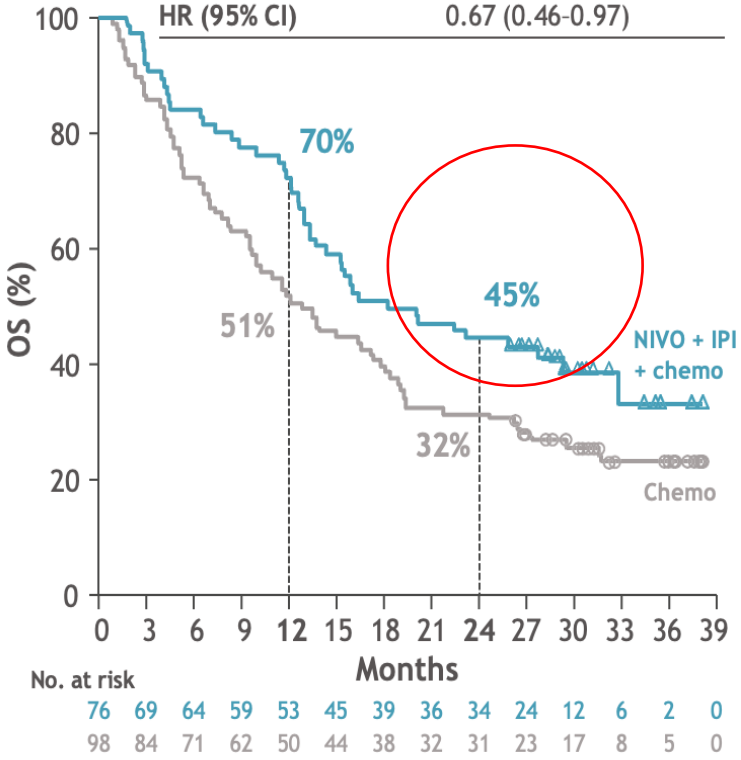
[a]Per BICR; [b]95% CI = 13.8–22.2 (NIVO + IPI + chemo) and 9.5–13.2 (chemo); [c]95% CI = 5.6–8.9 (NIVO + IPI + chemo) and 4.2–5.6 (chemo); [d]95% CI = 8.5–20.7 (NIVO + IPI + chemo) and 4.3–9.6 (chemo); [e]95% CI = 0.53-0.95

Paz-Ares L, et al. *Lancet Oncol* 2021

CheckMate 9LA study
PD-L1 ≥ 50%: efficacy outcomes

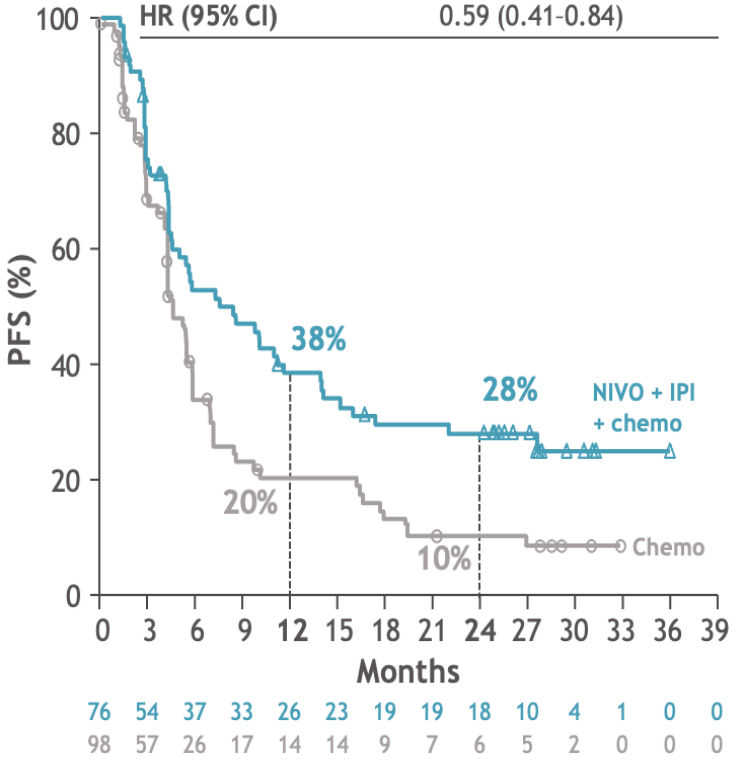
OS

	NIVO + IPI + chemo (n = 76)	Chemo (n = 98)
Median OS,[b] mo	18.9	12.9
HR (95% CI)	0.67 (0.46-0.97)	



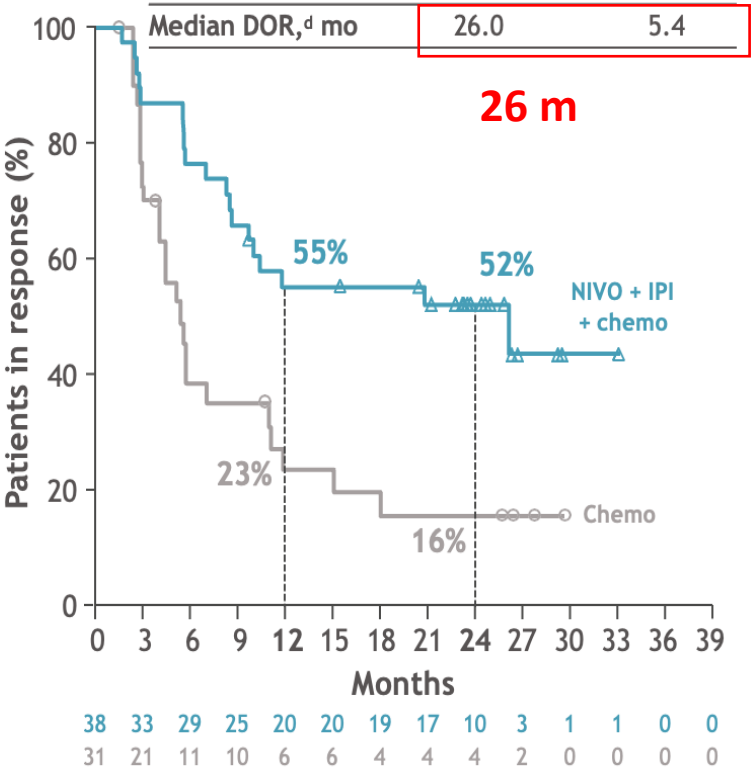
PFS[a]

	NIVO + IPI + chemo (n = 76)	Chemo (n = 98)
Median PFS,[c] mo	7.5	4.5
HR (95% CI)	0.59 (0.41-0.84)	



DOR[a]

	NIVO + IPI + chemo (n = 76)	Chemo (n = 98)
ORR, n (%)	38 (50.0)	31 (31.6)
Median DOR,[d] mo	26.0	5.4



[a]Per BICR; [b]95% CI = 13.1–32.5 (NIVO + IPI + chemo) and 9.4–17.6 for (chemo); [c]95% CI = 4.4–11.5 (NIVO + IPI + chemo) and 4.1–5.6 (chemo); [d]95% CI = 8.6–NR (NIVO + IPI + chemo) and 3.9–10.9 (chemo).

Paz-Ares L, et al. *Lancet Oncol* 2021

CheckMate 9LA study
2-Year update: safety and exposure summary

TRAE,[a] %	NIVO + IPI + chemo (n = 358)		Chemo (n = 349)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any TRAE	92	48	88	38
TRAEs leading to discontinuation of any component of the regimen	22	18	8	5
TRAEs leading to discontinuation of all components of the regimen	17	14	6	3
Serious TRAEs	30	26	18	15
Treatment-related deaths[b]	2		2	

- Median (range) duration of therapy: 6.1 (0–24.4) months with NIVO + IPI + chemo; 2.5 (0–34.5) months with chemo
- In the NIVO + IPI + chemo arm, patients received a median (range) of 9.0 (1–36) doses of NIVO and 4.0 (1–18) doses of IPI; 93% of patients received 2 cycles of chemo
- Incidence of exposure-adjusted TRAEs per 100 patient-years: 714.8 (NIVO + IPI + chemo); 880.0 (chemo)

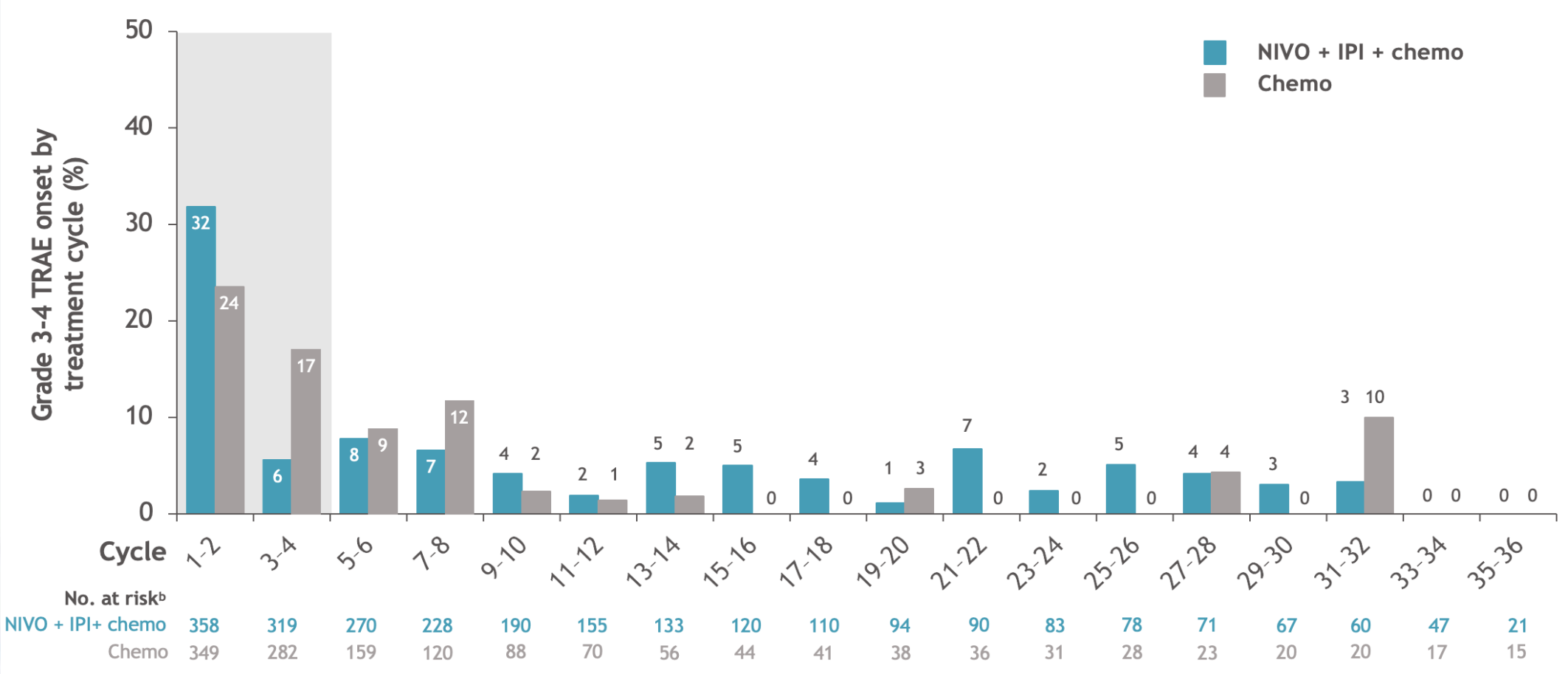
Minimum follow-up: 23.3 months for safety.

[a]Includes events reported between first dose and 30 days after last dose of study drug; [b]Treatment-related deaths in the NIVO + IPI + chemo arm (n = 8): acute renal failure due to chemo only, thrombocytopenia due to chemo only, pneumonitis, hepatic toxicity, hepatitis, sepsis with acute renal insufficiency (n = 1 each); diarrhea (n = 2; one of which was not reported as treatment-related at previous DBLs but updated by the investigator as treatment-related prior to this DBL); treatment-related deaths in the chemo arm (n = 6; 1 for each event): sepsis, anemia, pancytopenia, respiratory failure, pulmonary sepsis, febrile neutropenia (1 grade 5 SAE [sudden death due to fall] was reported as potentially treatment-related but cause of death was recorded as unknown).

Paz-Ares L, et al. *Lancet Oncol* 2021

CheckMate 9LA study

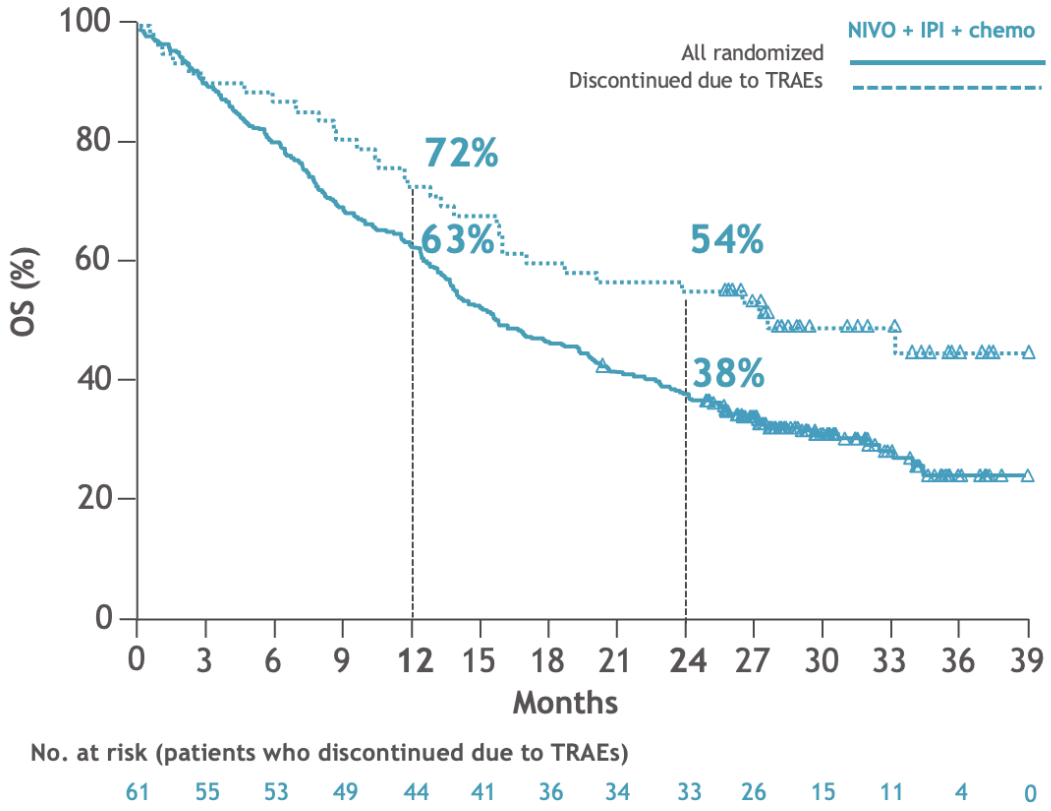
Grade 3-4 TRAE onset by treatment cycle



X-axis shows 2-year maximum duration (~ cycle 35); there were no grade 3–4 TRAEs after cycle 32.
[a]Includes events reported between first dose and 30 days after last dose of study therapy; for both treatment arms, patients were counted once in each cycle interval if they experienced an onset of a grade 3–4 TRAEs in that cycle interval; [b]Patients were considered at risk in a cycle interval if exposed to any study drug during that interval.

Paz-Ares L, et al. *Lancet Oncol* 2021

CheckMate 9LA study
Efficacy in patients who discontinued NIVO + IPI + chemo due to TRAEs[a]



Patients who discontinued all components of NIVO + IPI + chemo due to TRAEs

	NIVO + IPI + chemo (n = 61)
Median OS,[b] mo	27.5
2-year OS rate, %	54
ORR, n (%)	31 (51)
Median DOR after discontinuation,[c] mo	14.5
Ongoing response for ≥ 1 year after discontinuation,[c] %	56

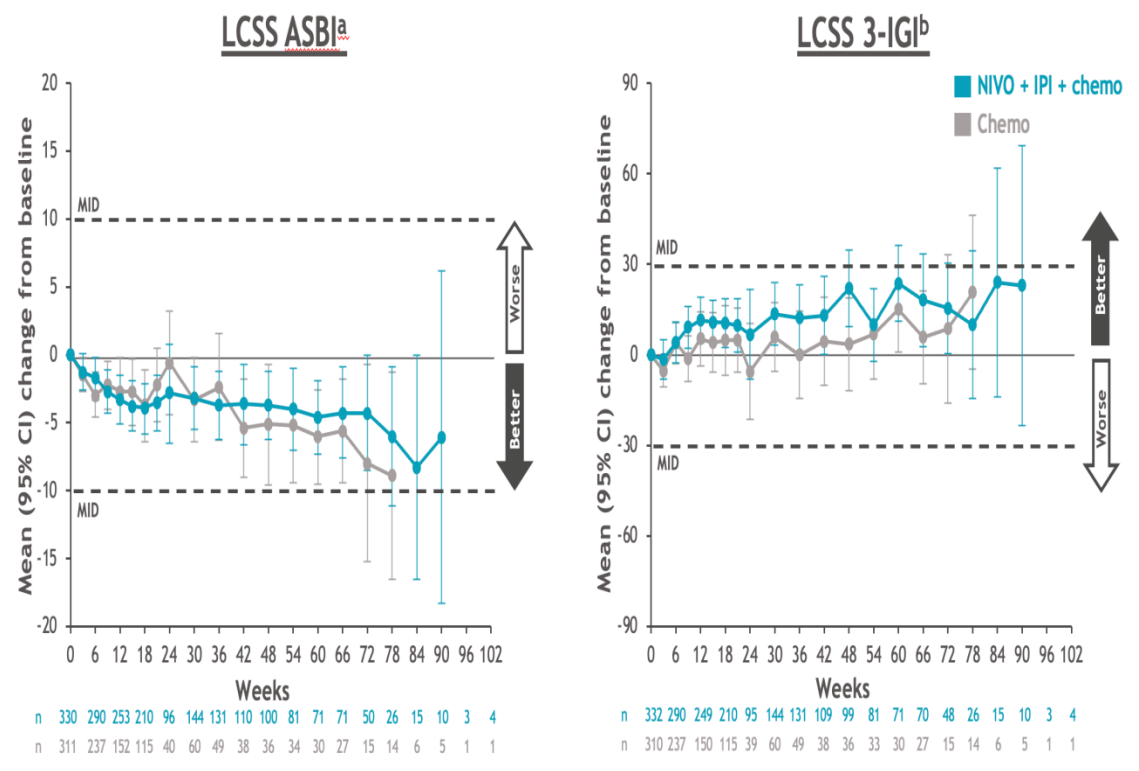
Among patients who discontinued all components of NIVO + IPI + chemo due to TRAEs:
- Median (range) number of doses was 7 (1–33) for NIVO and 3 (1–17) for IPI
- Median (range) duration of treatment was 4.4 (0–23.3) months

[a]Post hoc analysis and includes patients with TRAEs (reported between first dose and 30 days after last dose of study treatment) that were considered leading to discontinuation of all components of study treatment; [b]95% CI = 15.8–NR; [c]2 responders (among patients who discontinued due to TRAEs) in the NIVO + IPI + chemo arm had their responses ended before treatment end date and therefore were excluded from the analysis of duration of response after discontinuation.

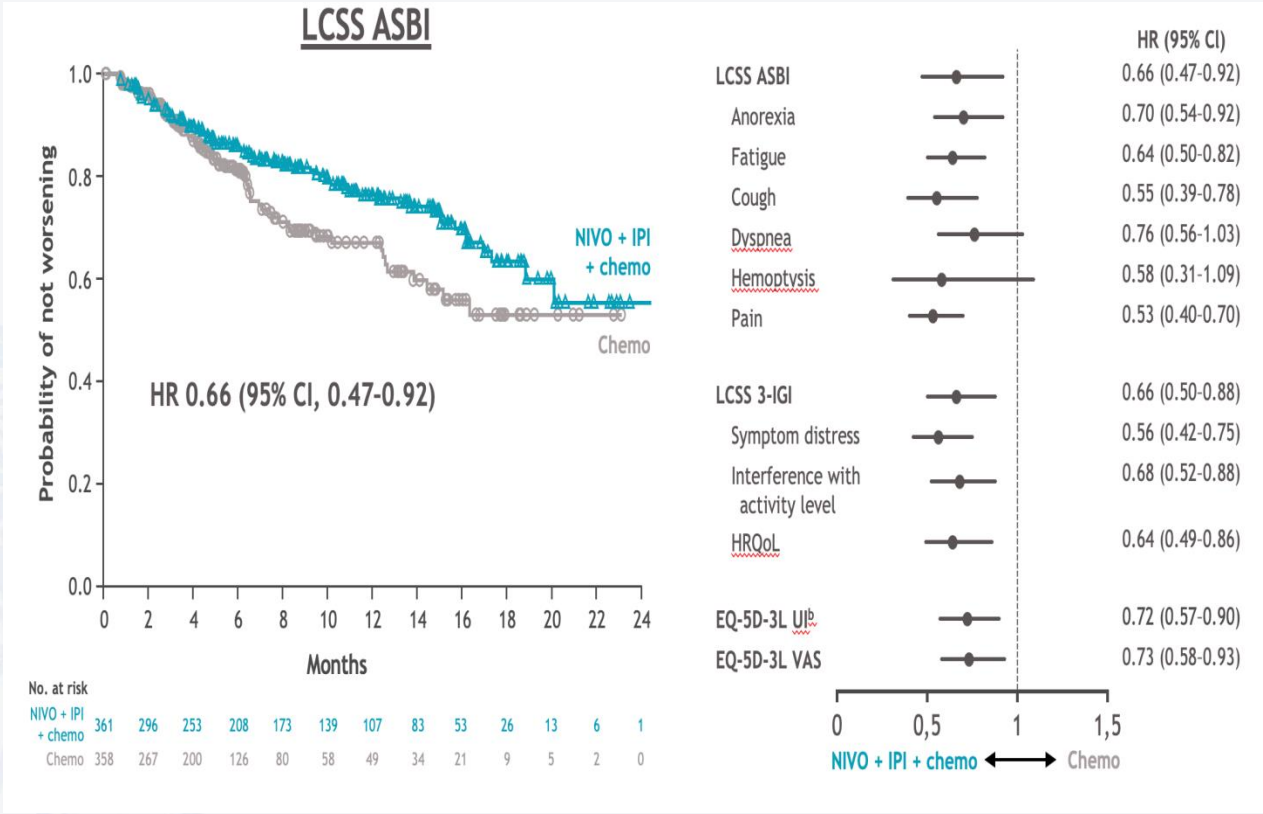
Paz-Ares L, et al. *Lancet Oncol* 2021

CheckMate 9LA study
Calidad de vida

Disease-related symptom burden: Changes from baseline (on treatment)

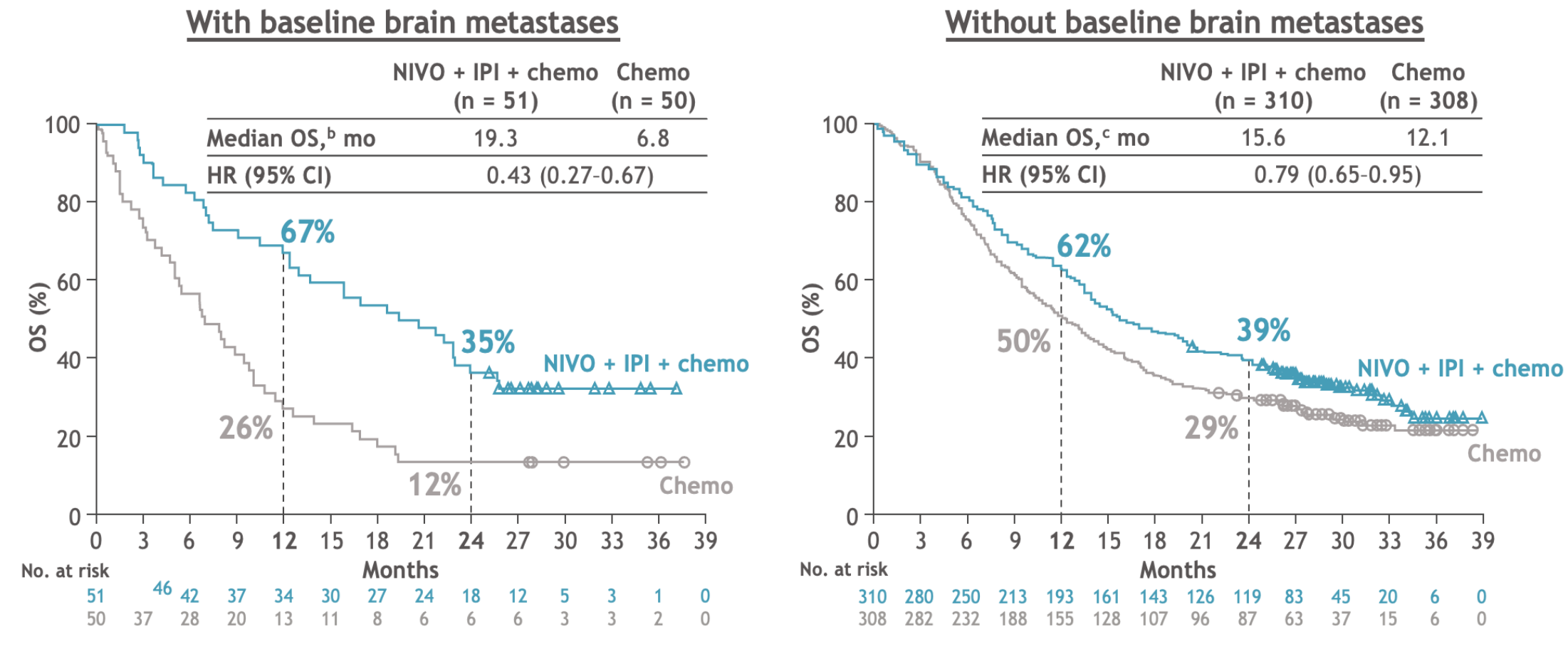


Time to definitive deterioration[a] (on treatment and follow-up)



Reck M et al, ESMO 2020

CheckMate 9LA study
OS: NIVO + IPI + chemo vs chemo
Brain metastases



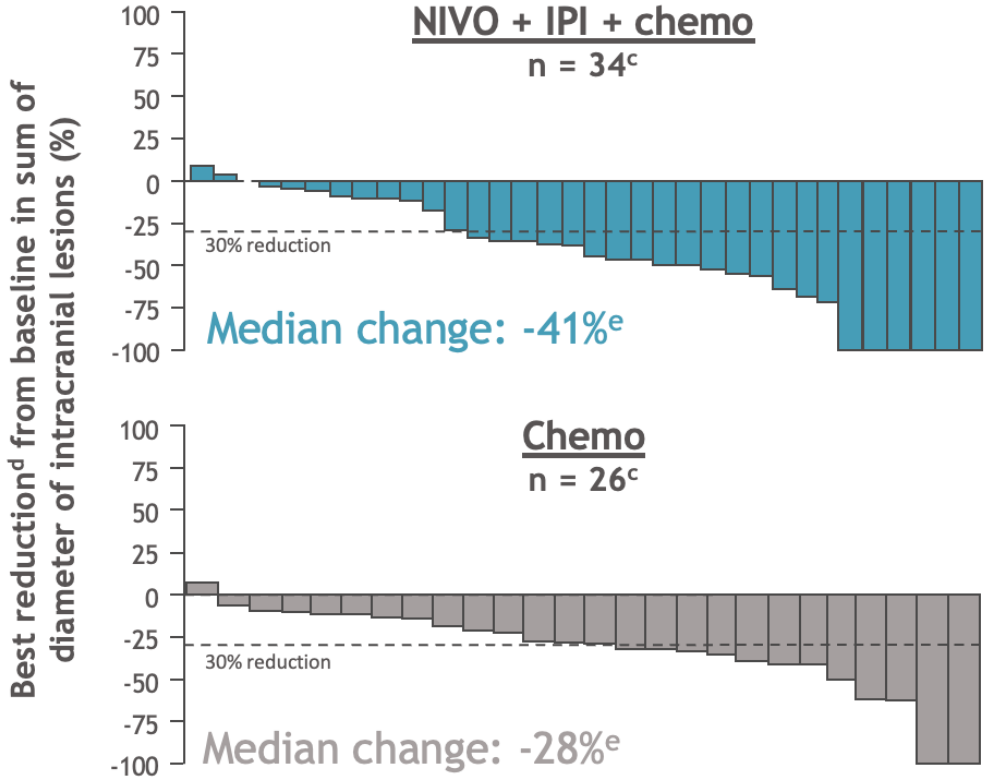
Minimum follow-up: 24.4 months.

[a]Patients with brain metastases at baseline: subsequent radiotherapy was received by 18% (NIVO + IPI + chemo) and 20% (chemo); subsequent systemic therapy by 29% and 34%; subsequent immunotherapy by 4% and 26%; subsequent chemo by 29% and 14%, respectively. Patients without brain metastases at baseline: subsequent radiotherapy was received by 14% (NIVO + IPI + chemo) and 14% (chemo); subsequent systemic therapy by 34% and 47%; subsequent immunotherapy by 8% and 37%; subsequent chemo by 32% and 25%, respectively; [b]95% CI = 12.3-23.9 (NIVO + IPI + chemo) and 4.7-9.7 (chemo); [c]95% CI = 13.8-19.4 (NIVO + IPI + chemo) and 10.2-13.7 (chemo).

Carbone DP et al, WCLC 2021

CheckMate 9LA study
Intracranial response in patients with baseline brain metastases

Intracranial response	NIVO + IPI + chemo (n = 51)	Chemo (n = 50)
ORR, n (%)	20 (39)	10 (20)
BOR,[b] n (%)		
CR	5 (10)	4 (8)
PR	15 (29)	6 (12)
SD	18 (35)	18 (36)
PD	1 (2)	3 (6)
DCR, n (%)	38 (74)	28 (56)
Median time to response, mo (range)	2.8 (1.3-11.4)	2.2 (1.3-5.8)
Median DOR, mo (95% CI)	22.3 (9.7-NR)	18.9 (1.8-NR)



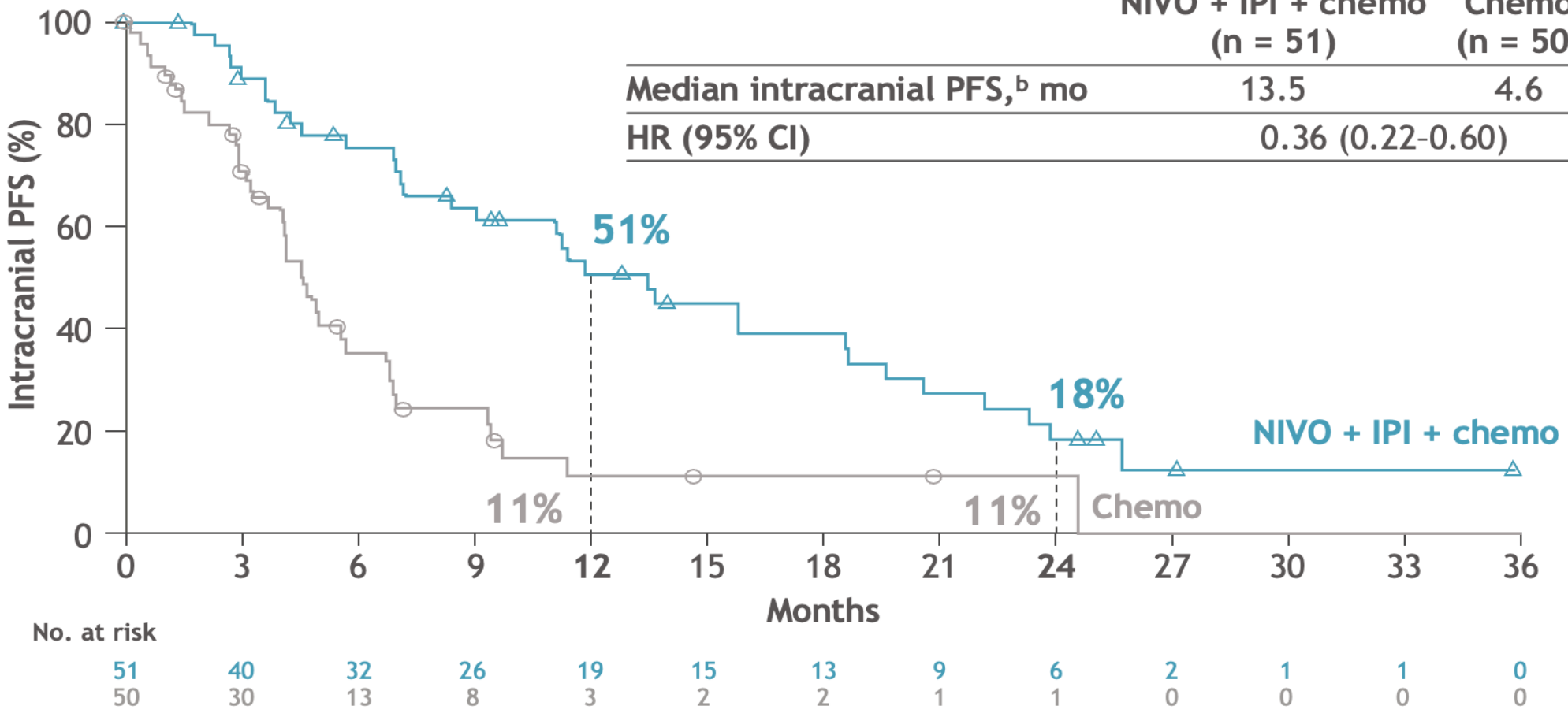
Minimum follow-up: 23.3 months.

[a]Per BICR; [b]Unable to be determined or not reported in 4% and 20% of the NIVO + IPI + chemo arm, and 10% and 28% of the chemo arm, respectively; [c]Patients with measurable intracranial lesion(s) at baseline and at least one on-treatment brain lesion assessment per BICR (modified RECIST v1.1 [adapted for brain metastases]); [d]Best reduction is based on evaluable intracranial target lesions measurements up to progression or start of subsequent anticancer therapy; [e]Range of best reduction from baseline: −100% to 9% (NIVO + IPI + chemo) and −100% to 7% (chemo).

Carbone DP et al, WCLC 2021

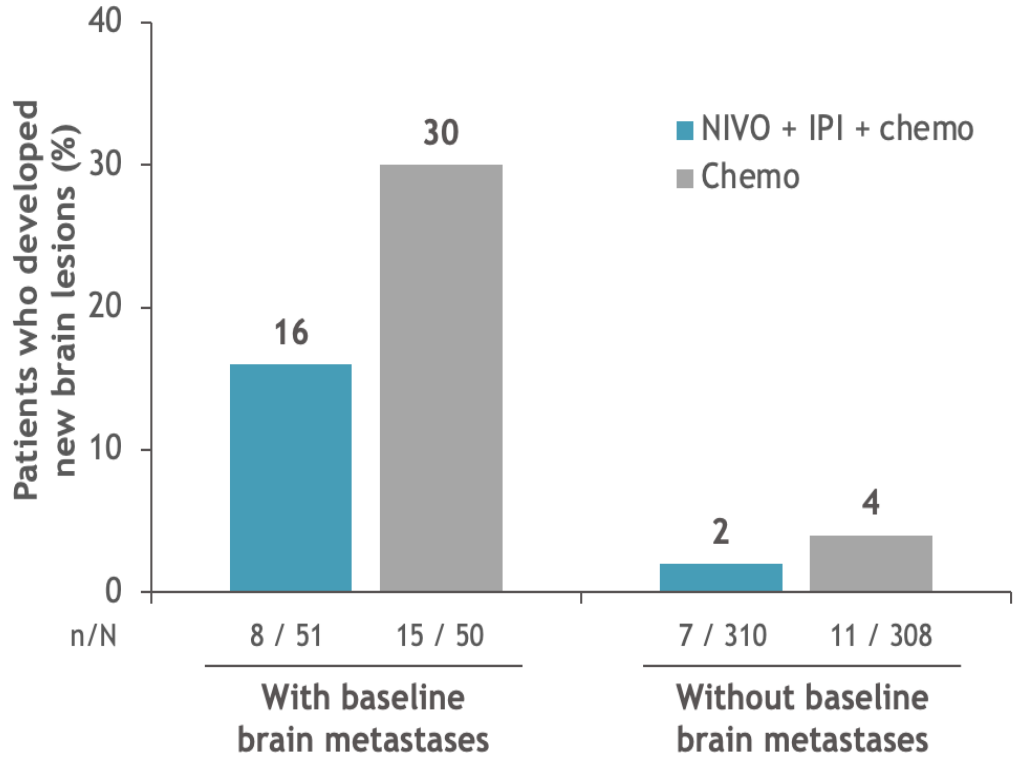
CheckMate 9LA study
Intracranial PFS in patients with baseline brain metastases

	NIVO + IPI + chemo (n = 51)	Chemo (n = 50)
Median intracranial PFS,[b] mo	13.5	4.6
HR (95% CI)	0.36 (0.22-0.60)	



Carbone DP et al, WCLC 2021

CheckMate 9LA study
Development of new brain lesions[a]

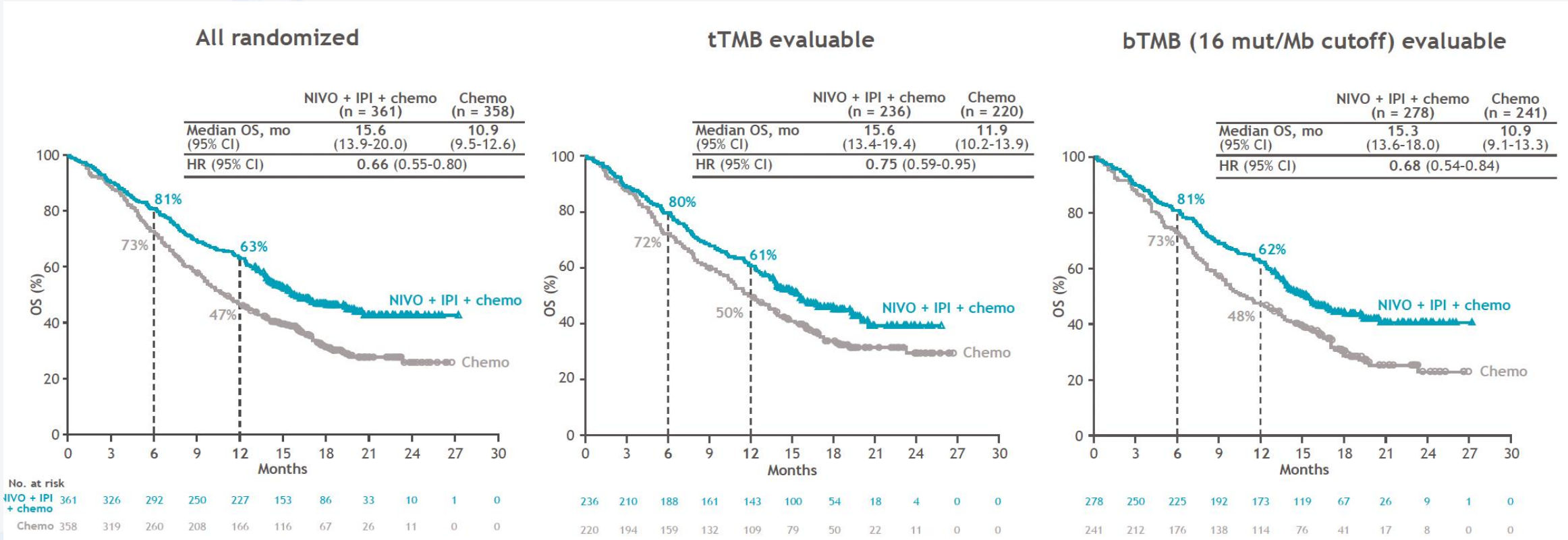


	With baseline brain metastases		Without baseline brain metastases	
	NIVO + IPI + chemo (n = 51)	Chemo (n = 50)	NIVO + IPI + chemo (n = 310)	Chemo (n = 308)
Median time to development of new brain lesions, mo (range)	9.0 (2.3-19.6)	4.6 (1.9-9.5)	6.9 (1.4-18.8)	5.3 (1.2-26.7)
Tumor burden in patients who developed new brain lesions, mm,[b,c] range	13-19	10-38	4-74	6-37

[a]By initial PD; [b]Sum of longest diameter in brain lesions; [c]Number of patients with measurable new brain lesions in NIVO + IPI + chemo vs chemo: 2 vs 5 (with baseline brain metastases); 7 vs 10 (without baseline brain metastases).

Carbone DP et al, WCLC 2021

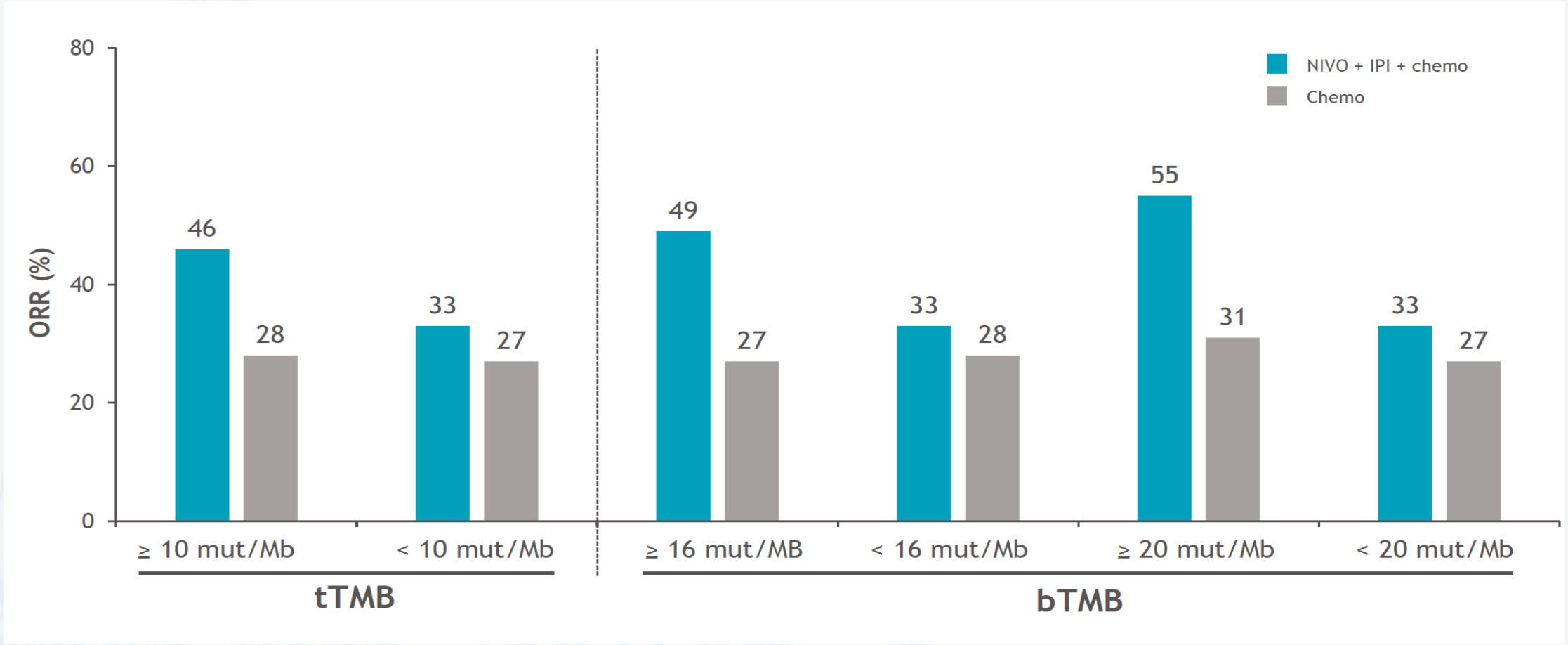
CheckMate 9LA study
Efficacy in all randomized patients and TMB evaluable subgroups



- OS, PFS, and ORR in tTMB evaluable and bTMB evaluable subgroups were generally consistent with those in the all-randomized population

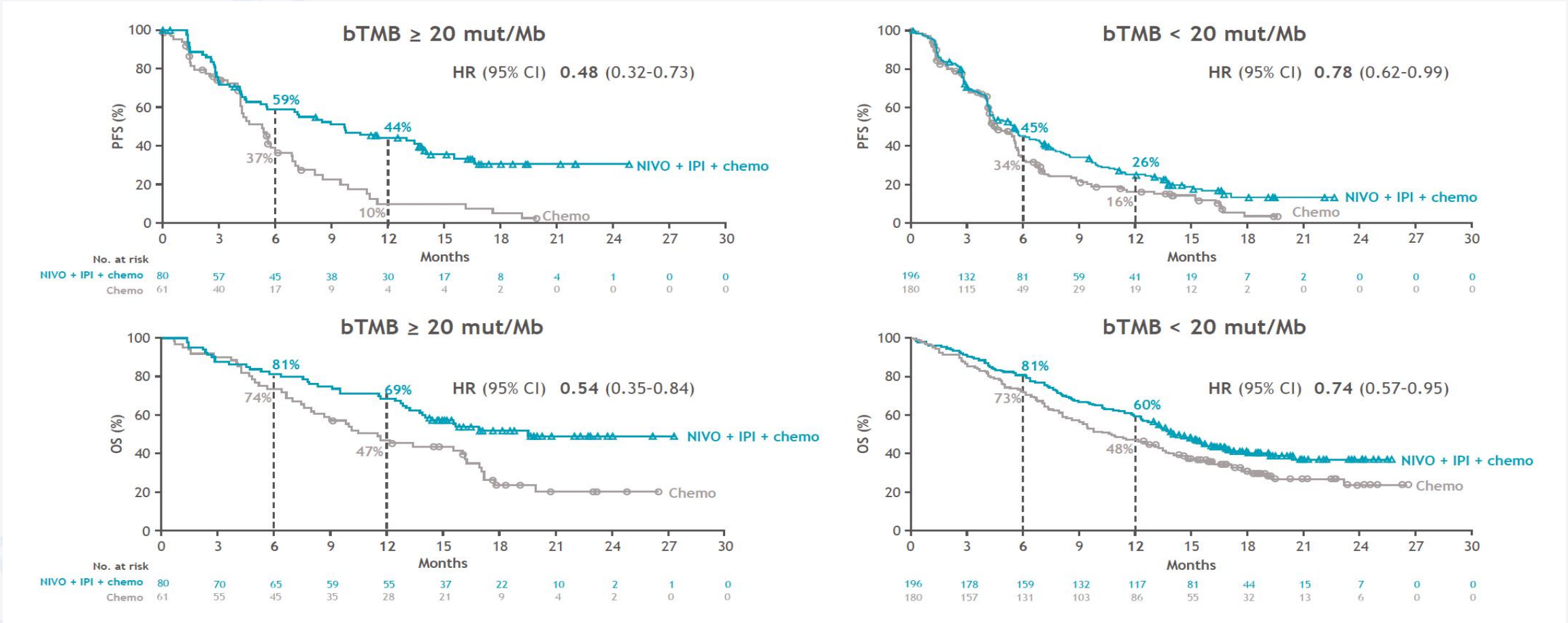
Paz-Ares L et al, ECLC 2021

CheckMate 9LA study
Efficacy in all randomized patients and TMB evaluable subgroups



Paz-Ares L et al, ECLC 2021

CheckMate 9LA study
PFS and OS in bTMB 20 mut/Mb subgroups



Paz-Ares L et al, ECLC 2021

POSEIDON study

POSEIDON Study Design

Phase 3, global, randomized, open-label, multicenter study

- Stage IV NSCLC
- No *EGFR* or *ALK* alterations
- ECOG PS 0 or 1
- Treatment-naïve for metastatic disease

N=1013 (randomized)

R 1:1:1

Stratified by:
- PD-L1 expression (TC ≥50% vs <50%)
- Disease stage (IVA vs IVB)
- Histology

Durvalumab 1500 mg + CT* q3w (4 cycles) → **Durvalumab 1500 mg q4w + pemetrexed† until PD**

Durvalumab 1500 mg + tremelimumab 75 mg + CT* q3w (4 cycles) → **Durvalumab 1500 mg q4w + tremelimumab 75 mg (week 16 only)‡ + pemetrexed† until PD**

Platinum-based CT* q3w (up to 6 cycles) → **Pemetrexed† until PD**

Primary endpoints
- PFS by BICR (D+CT vs CT)
- OS (D+CT vs CT)

Key secondary endpoints
- PFS by BICR (D+T+CT vs CT)
- OS (D+T+CT vs CT)
- OS in patients with bTMB ≥20 mut/Mb (D+T+CT vs CT)

Additional secondary endpoints
- ORR, DoR, and BOR by BICR
- PFS at 12 months
- HRQoL
- Safety and tolerability

*CT options: gemcitabine + carboplatin/cisplatin (squamous), pemetrexed + carboplatin/cisplatin (non-squamous), or nab-paclitaxel + carboplatin (either histology);
†Patients with non-squamous histology who initially received pemetrexed during first-line treatment only (if eligible); ‡Patients received an additional dose of tremelimumab post CT (5th dose)

Johnson ML et al, WCLC 2021

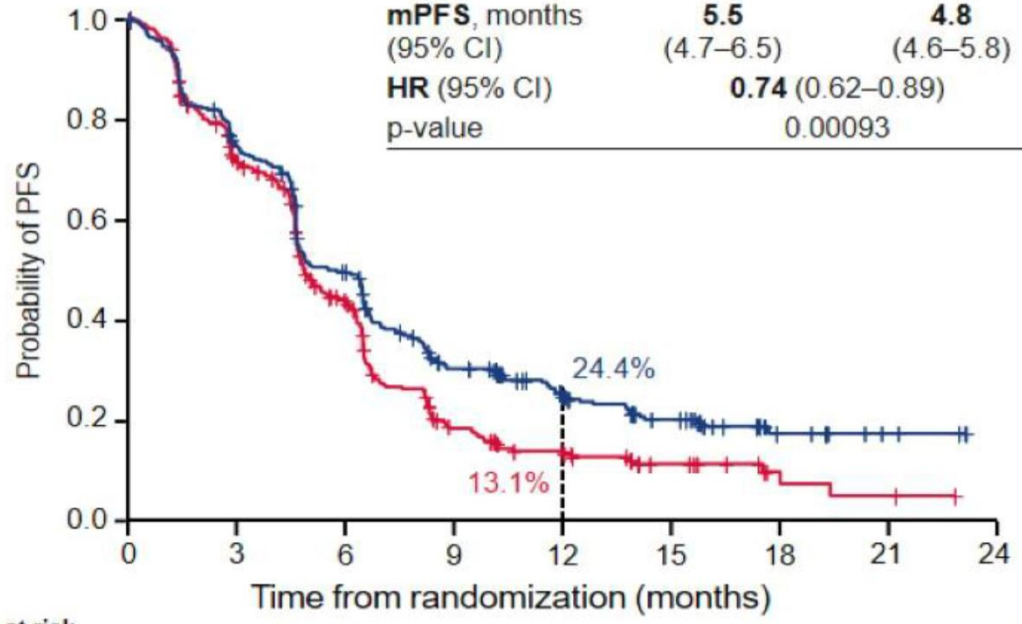
POSEIDON study

1º O: Durva + CT VS CT: PFS and OS

Durvalumab + CT vs CT: PFS and OS

PFS

	D+CT	CT
Events, n/N (%)	253/338 (74.9)	258/337 (76.6)
mPFS, months (95% CI)	**5.5** (4.7–6.5)	**4.8** (4.6–5.8)
HR (95% CI)	**0.74** (0.62–0.89)	
p-value	0.00093	



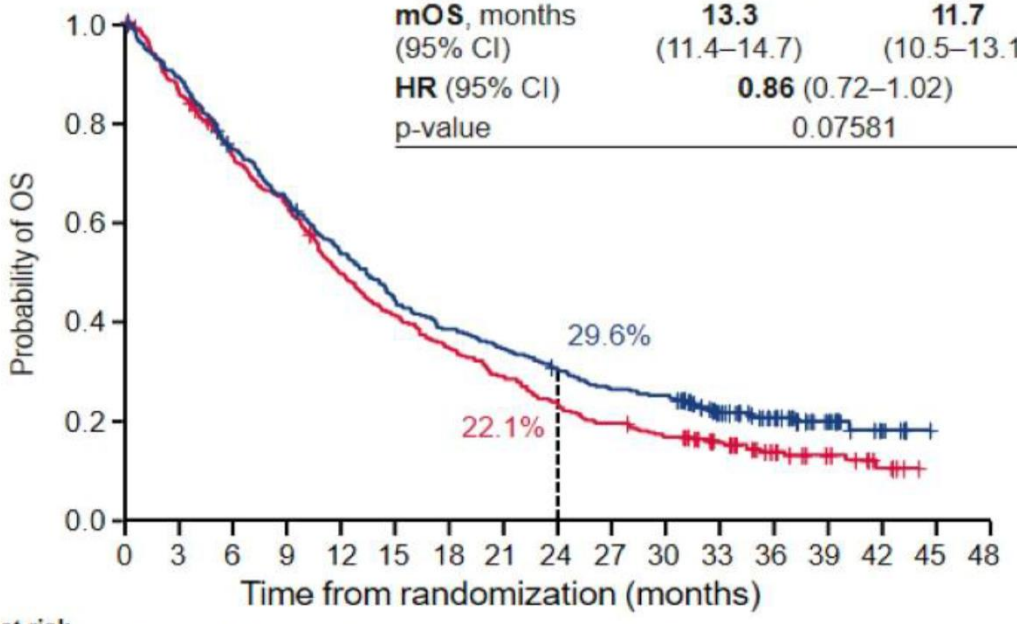
No. at risk

D+CT	338	246	158	88	53	35	11	4	0
CT	337	219	121	43	23	12	3	2	0

- Median follow-up in censored patients at DCO: 10.3 months (range 0–23.1)

OS

	D+CT	CT
Events, n/N (%)	264/338 (78.1)	285/337 (84.6)
mOS, months (95% CI)	**13.3** (11.4–14.7)	**11.7** (10.5–13.1)
HR (95% CI)	**0.86** (0.72–1.02)	
p-value	0.07581	



No. at risk

D+CT	338	296	247	212	176	142	126	112	97	85	81	51	33	15	5	0	0
CT	337	284	236	204	160	132	111	91	72	62	52	38	21	13	6	0	0

- Median follow-up in censored patients at DCO: 34.9 months (range 0–44.5)

Johnson ML et al, WCLC 2021

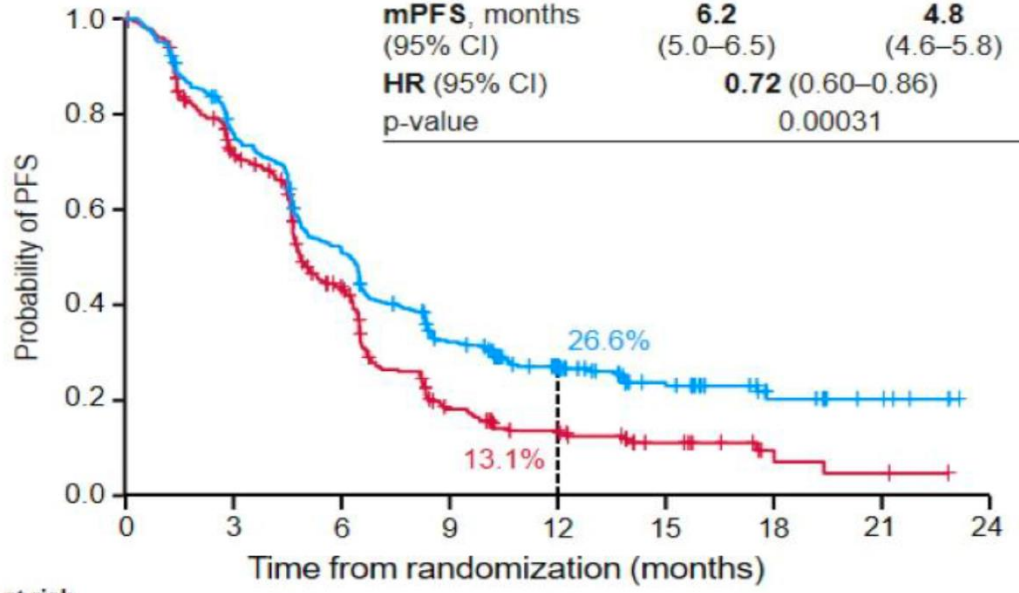
POSEIDON study

2ª: Durva + Trem+ CT VS CT: PFS and OS

Durvalumab + Tremelimumab + CT vs CT: PFS and OS

PFS

	D+T+CT	CT
Events, n/N (%)	238/338 (70.4)	258/337 (76.6)
mPFS, months (95% CI)	**6.2** (5.0–6.5)	**4.8** (4.6–5.8)
HR (95% CI)	**0.72** (0.60–0.86)	
p-value	0.00031	



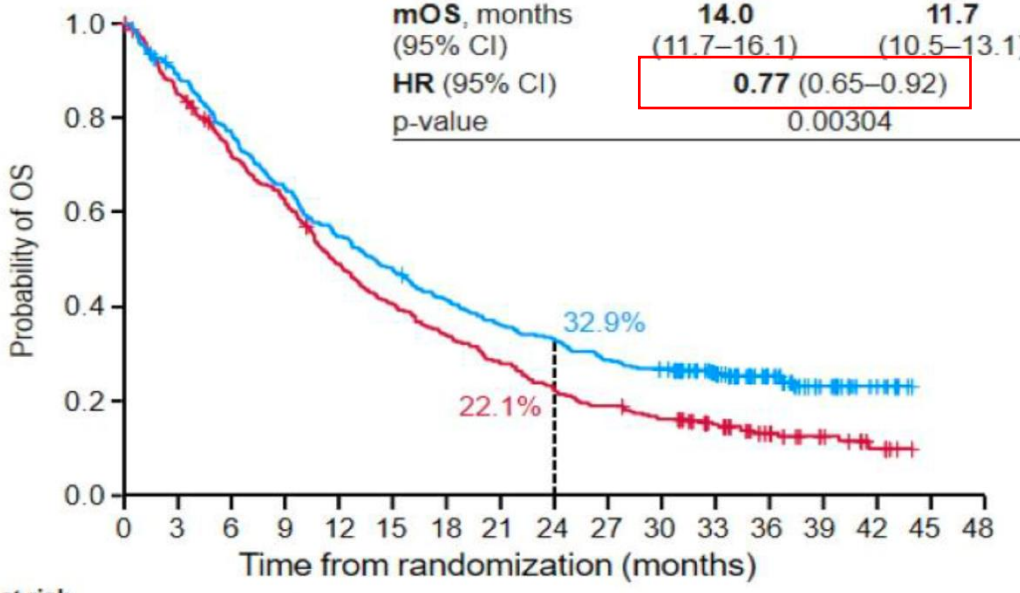
No. at risk

D+T+CT	338	243	161	94	56	32	13	5	0
CT	337	219	121	43	23	12	3	2	0

- Median follow-up in censored patients at DCO: 10.3 months (range 0–23.1)

OS

	D+T+CT	CT
Events, n/N (%)	251/338 (74.3)	285/337 (84.6)
mOS, months (95% CI)	**14.0** (11.7–16.1)	**11.7** (10.5–13.1)
HR (95% CI)	**0.77** (0.65–0.92)	
p-value	0.00304	



No. at risk

D+T+CT	338	298	256	217	183	159	137	120	109	95	88	64	41	20	9	0	0
CT	337	284	236	204	160	132	111	91	72	62	52	38	21	13	6	0	0

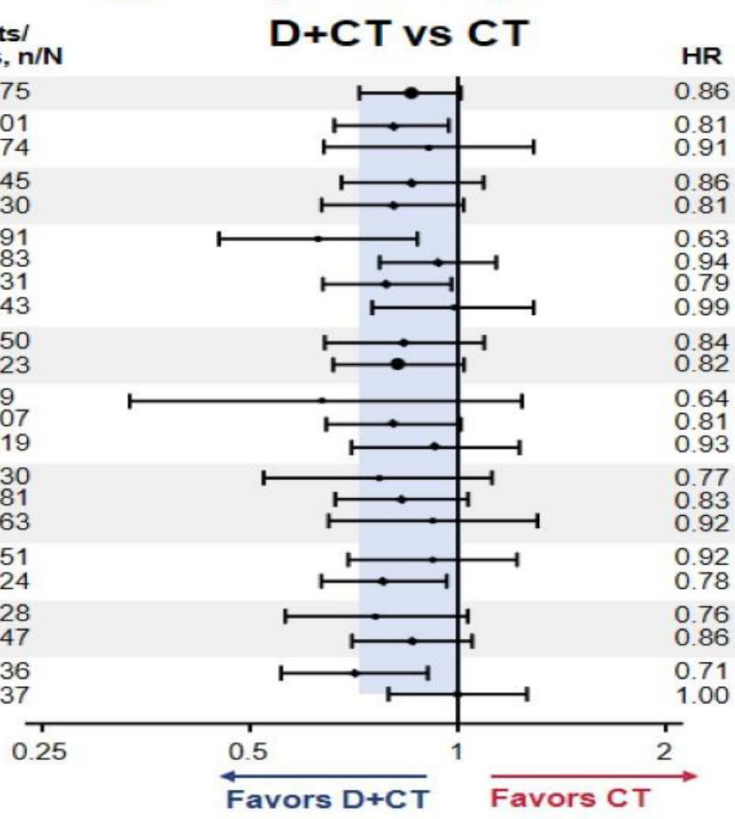
- Median follow-up in censored patients at DCO: 34.9 months (range 0–44.5)

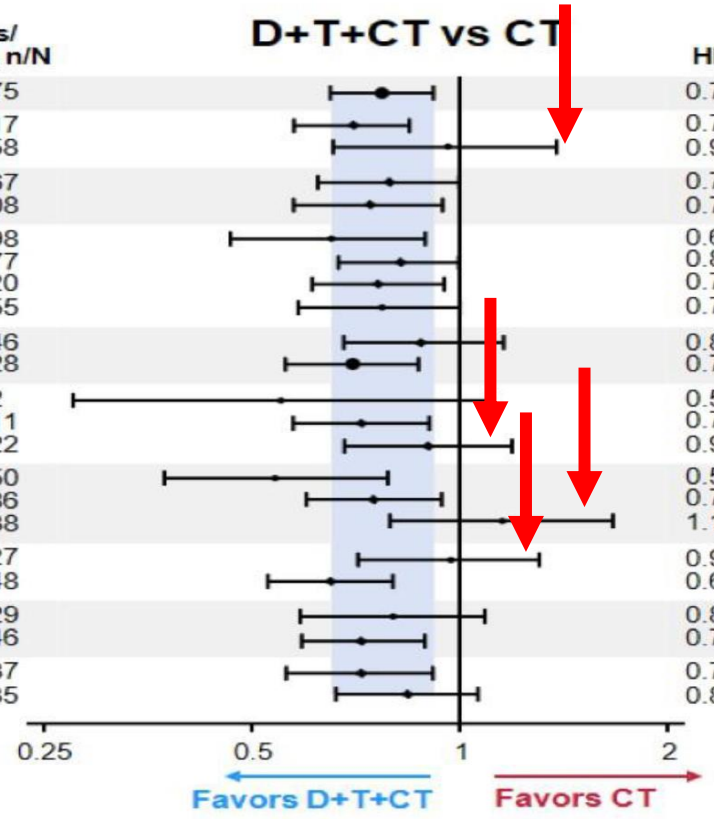
Johnson ML et al, WCLC 2021

POSEIDON study
Subgroup analysis

Overall Survival: Subgroup Analysis

		D+CT vs CT Events/ patients, n/N	HR	D+T+CT vs CT Events/ patients, n/N	HR
All patients		549/675	0.86	536/675	0.77
Sex	Male	423/501	0.81	422/517	0.70
	Female	126/174	0.91	114/158	0.96
Age	<65 years	273/345	0.86	280/367	0.79
	≥65 years	276/330	0.81	256/308	0.74
Tumor PD-L1 expression	TC ≥50%	144/191	0.63	149/198	0.65
	TC <50%	405/483	0.94	387/477	0.82
	TC ≥1%	335/431	0.79	321/420	0.76
	TC <1%	214/243	0.99	215/255	0.77
Histology	Squamous	220/250	0.84	217/246	0.88
	Non-squamous	327/423	0.82	318/428	0.70
Planned CT	Nab-paclitaxel doublet	40/49	0.64	33/42	0.55
	Pemetrexed doublet	311/407	0.81	304/411	0.72
	Gemcitabine doublet	198/219	0.93	199/222	0.90
Smoking history	Current	107/130	0.77	115/150	0.54
	Former	314/381	0.83	306/386	0.75
	Never	127/163	0.92	114/138	1.15
Race	Asian	195/251	0.92	175/227	0.97
	Non-Asian	354/424	0.78	361/448	0.65
ECOG PS	0	168/228	0.76	166/229	0.80
	1	381/447	0.86	370/446	0.72
AJCC disease stage	IVA	259/336	0.71	259/337	0.72
	IVB	288/337	1.00	276/335	0.84



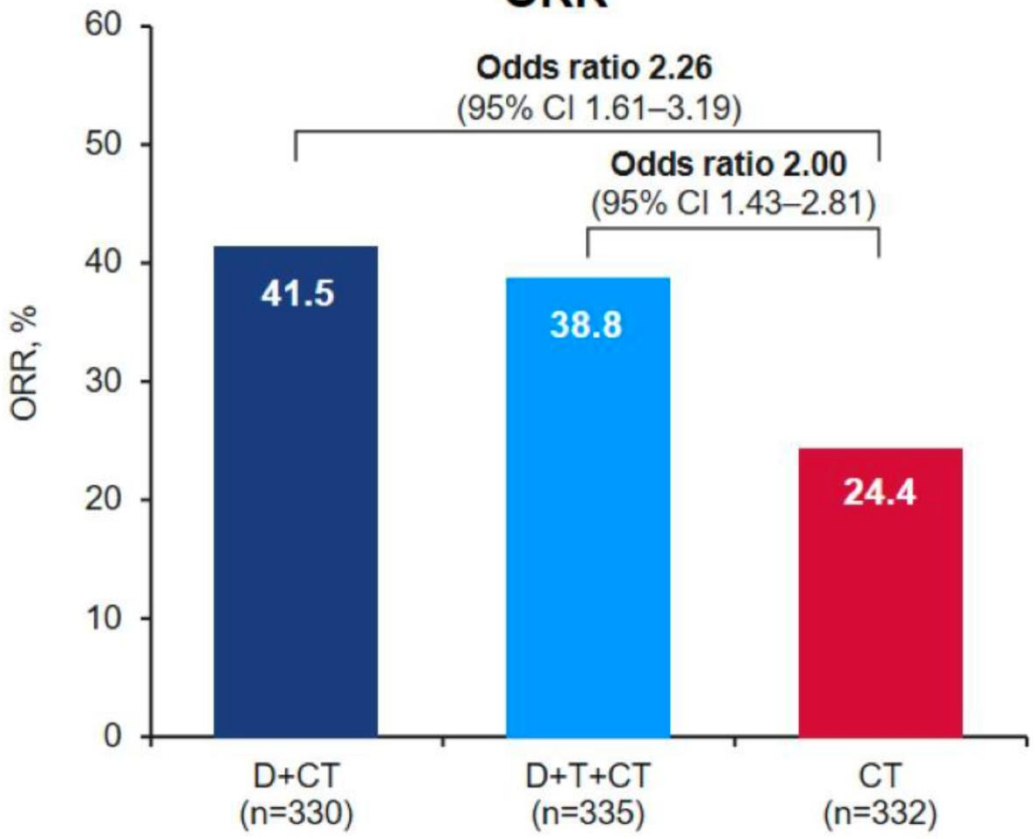


Johnson ML et al, WCLC 2021

POSEIDON study
Objective Response Rate

Confirmed Objective Response Rate and Duration of Response

ORR*



Duration of Response

	D+CT	D+T+CT	CT
Responders*, n	137	130	81
Median DoR, months (95% CI)	**7.0** (5.7–9.9)	**9.5** (7.2–NE)	**5.1** (4.4–6.0)
Remaining in response at 12 months, %	**38.9**	**49.7**	**21.4**

Johnson ML et al, WCLC 2021

POSEIDON study
Outcomes by Histology

Outcomes in Patients with Non-Squamous Histology

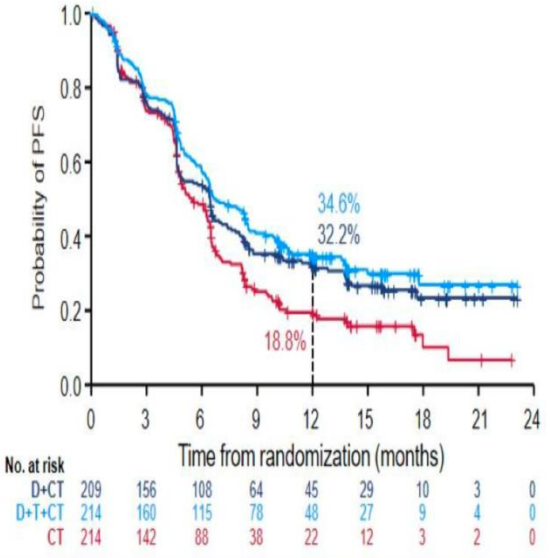
95.5% of patients with non-squamous histology receiving CT had pemetrexed + platinum

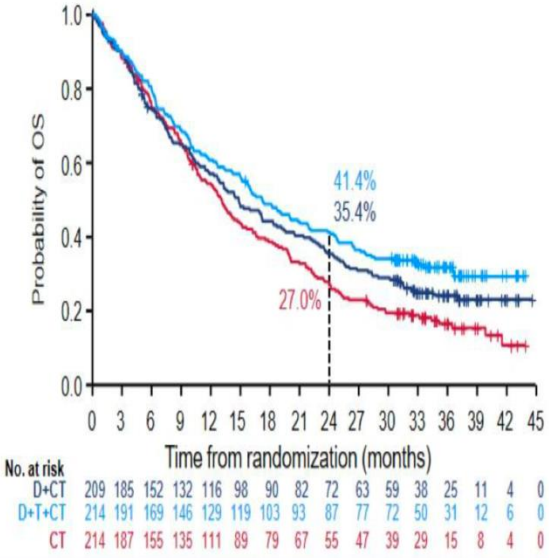
PFS and ORR

	D+CT	D+T+CT	CT
Events, n/N (%)	144/209 (68.9)	136/214 (63.6)	154/214 (72.0)
mPFS, months (95% CI)	**6.4** (4.7–7.4)	**6.8** (6.1–8.5)	**5.5** (4.8–6.4)
HR* (95% CI)	**0.77** (0.61–0.96)	**0.66** (0.52–0.84)	–
Confirmed ORR†, % (n/N)	**44.3** (90/203)	**45.5** (96/211)	**23.7** (50/211)
mDoR†, months (95% CI)	**10.6** (6.6–NE)	**16.4** (9.3–NE)	**6.0** (4.4–8.7)

OS

	D+CT	D+T+CT	CT
Events, n/N (%)	154/209 (73.7)	145/214 (67.8)	173/214 (80.8)
mOS, months (95% CI)	**14.8** (11.8–18.3)	**17.2** (14.9–21.8)	**13.1** (10.6–15.1)
HR* (95% CI)	**0.82** (0.66–1.03)	**0.70** (0.56–0.87)	–





Outcomes in Patients with Squamous Histology

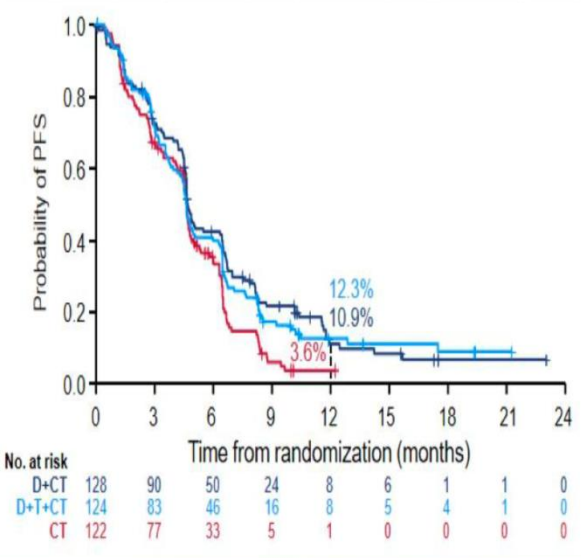
88.3% of patients with squamous histology receiving CT had gemcitabine + platinum

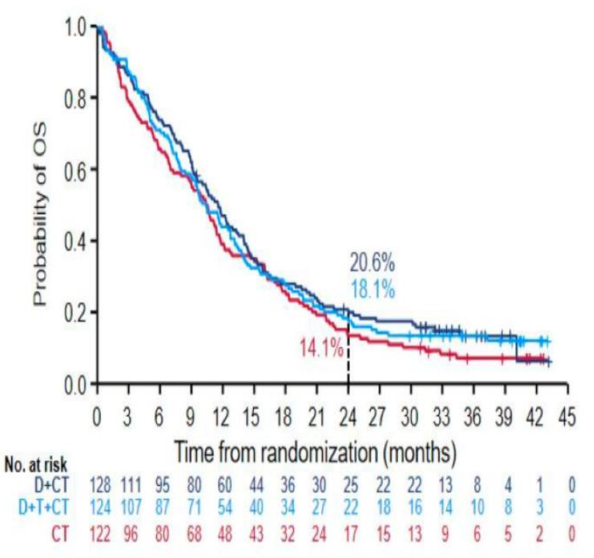
PFS and ORR

	D+CT	D+T+CT	CT
Events, n/N (%)	108/128 (84.4)	102/124 (82.3)	104/122 (85.2)
mPFS, months (95% CI)	**4.7** (4.6–6.3)	**4.6** (3.9–5.1)	**4.6** (4.2–4.8)
HR* (95% CI)	**0.68** (0.52–0.90)	**0.77** (0.58–1.01)	–
Confirmed ORR†, % (n/N)	**37.3** (47/126)	**27.4** (34/124)	**25.6** (31/121)
mDoR†, months (95% CI)	**5.5** (4.9–6.7)	**5.6** (4.3–7.2)	**4.8** (3.7–5.2)

OS

	D+CT	D+T+CT	CT
Events, n/N (%)	109/128 (85.2)	106/124 (85.5)	111/122 (91.0)
mOS, months (95% CI)	**11.5** (9.4–14.0)	**10.4** (8.4–12.7)	**10.5** (8.0–11.7)
HR* (95% CI)	**0.84** (0.64–1.10)	**0.88** (0.68–1.16)	–





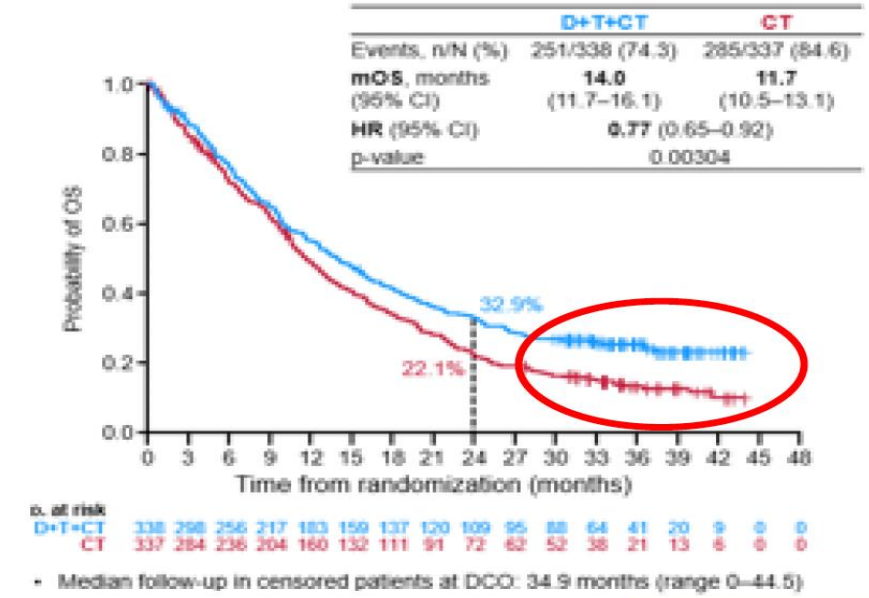
Johnson ML et al, WCLC 2021

POSEIDON vs CHECKMATE 9LA

Key Results – Similar Across Trials

POSEIDON

OS

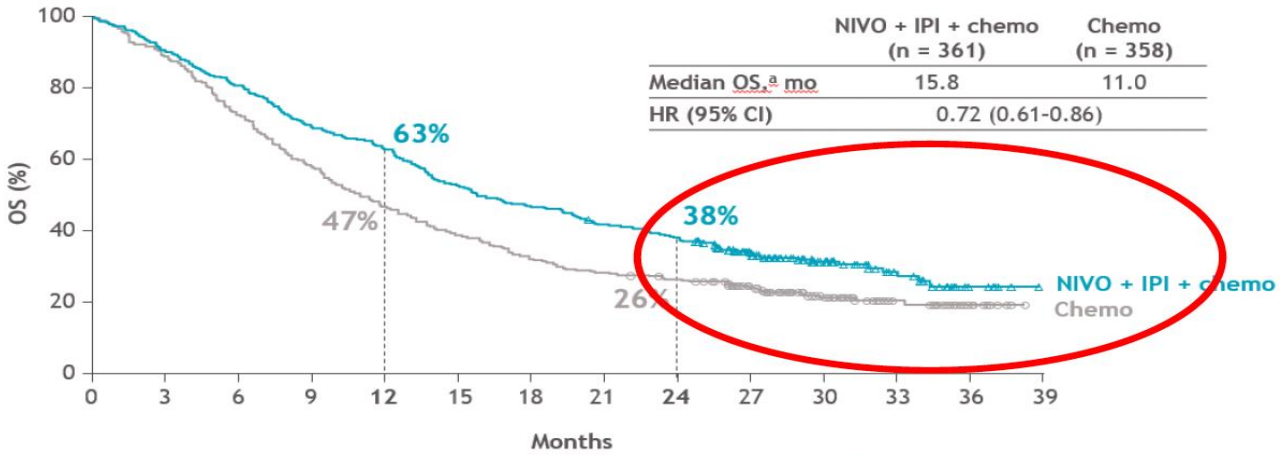


- Median follow-up in censored patients at DCO: 34.9 months (range 0–44.5)

	D+T+CT	CT
Events, n/N (%)	238/338 (70.4)	258/337 (76.6)
mPFS, months (95% CI)	**6.2** (5.0–6.5)	**4.8** (4.6–5.8)
HR (95% CI)	**0.72** (0.60–0.86)	
p-value	0.00031	

	D+T+CT	CT
ORR (%)	38.8	24.4
Median DOR, mo	9.5	5.1

CheckMate 9LA



	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
Median OS,[a] mo	15.8	11.0
HR (95% CI)	0.72 (0.61-0.86)	

	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
Median PFS,[b] mo	6.7	5.3
HR (95% CI)	0.67 (0.56-0.79)	

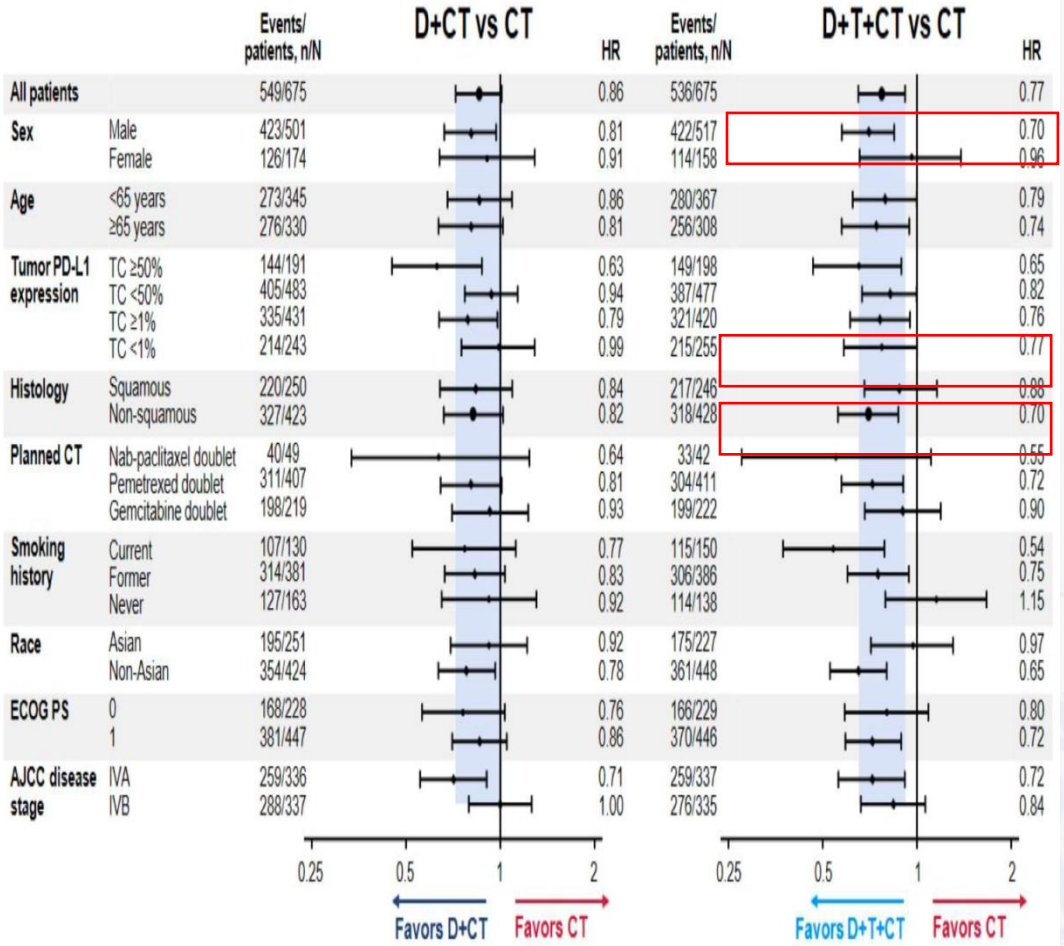
	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
ORR, n (%)	137 (38.0)[c]	91 (25.4)[d]
Median DOR,[e] mo	13.0	5.6

Johnson M et al WCLC 2021, Reck M et al ASCO 2021

Brahmer J, WCLC 2021

POSEIDON vs CHECKMATE 9LA

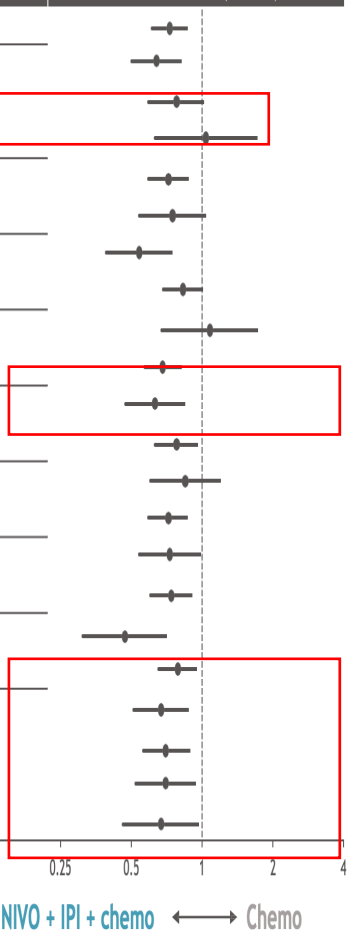
Overall Survival: Subgroup Analysis



Johnson ML et al, WCLC 2021

Sexo
Edad
Nunca fumador
Escamoso
PD-L1

Subgroup	Median OS, mo: NIVO + IPI + chemo n = 361	Median OS, mo: Chemo n = 358	Unstratified HR
All randomized (N = 719)	15.8	11.0	0.73
< 65 years (n = 354)	15.9	10.7	0.64
≥ 65 to < 75 years (n = 295)	19.0	11.9	0.78
≥ 75 years (n = 70)	8.5	11.5	1.04
Male (n = 504)	14.2	9.8	0.72
Female (n = 215)	22.2	15.9	0.75
ECOG PS 0 (n = 225)	27.1	14.1	0.54
ECOG PS 1 (n = 492)	13.6	9.7	0.83
Never smoker (n = 98)	14.1	14.4	1.08
Smoker (n = 621)	16.2	10.4	0.68
SQ (n = 227)	14.5	9.1	0.63
NSQ (n = 492)	17.8	12.0	0.78
Liver metastases (n = 154)	10.2	8.1	0.85
No liver metastases (n = 565)	19.3	12.4	0.72
Bone metastases (n = 207)	11.9	8.3	0.73
No bone metastases (n = 512)	19.7	12.4	0.74
CNS metastases (n = 123)	19.9	7.9	0.47
No CNS metastases (n = 596)	15.6	11.8	0.79
PD-L1 < 1% (n = 264)	17.7	9.8	0.67
PD-L1 ≥ 1% (n = 407)	15.8	10.9	0.70
PD-L1 1-49% (n = 233)	15.2	10.4	0.70
PD-L1 ≥ 50% (n = 174)	18.9	12.9	0.67



Paz-Ares L, et al. *Lancet Oncol* 2021

COMPARATIVA ENTRE ESTUDIOS

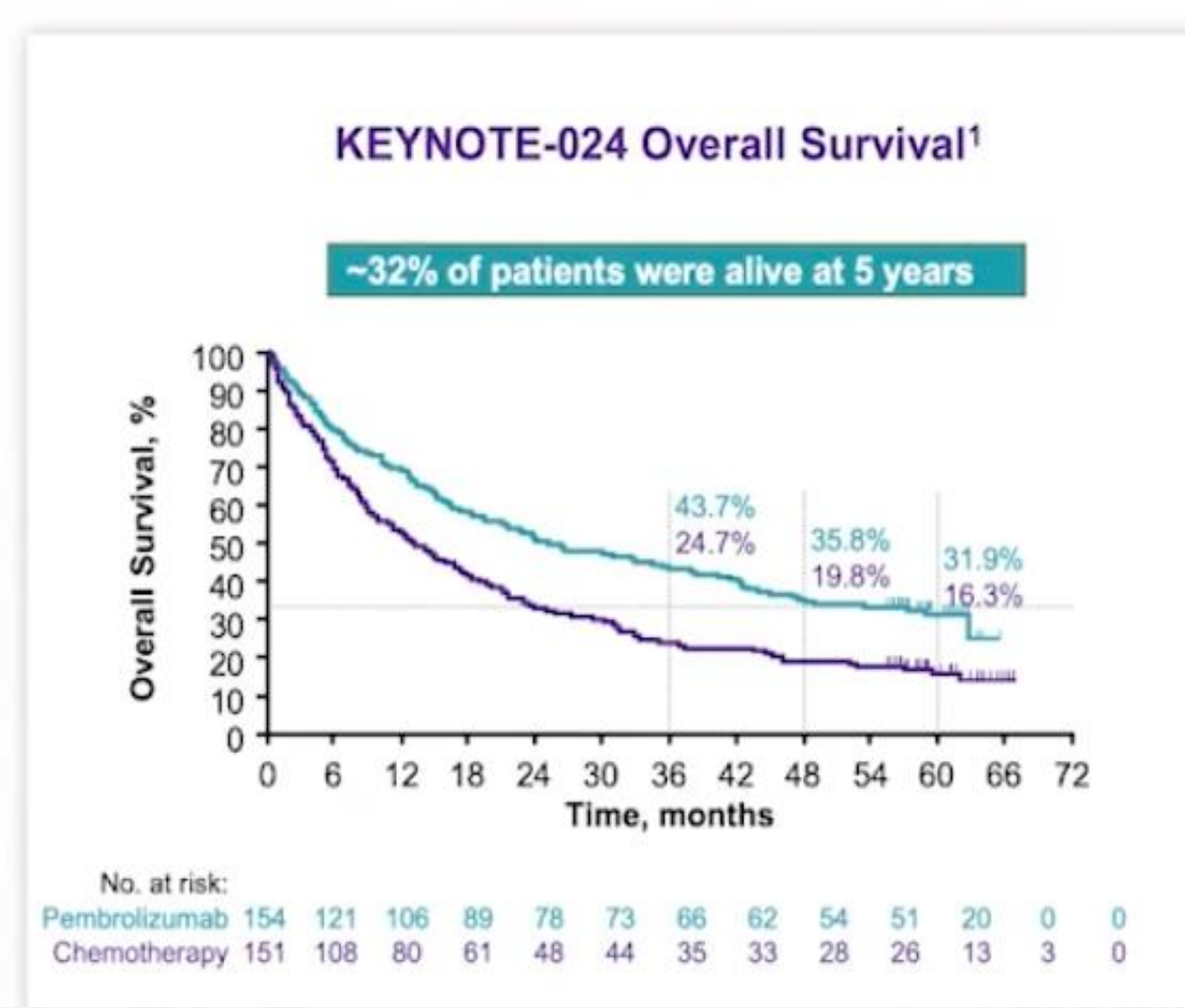
PD-L1 "High" Disease Across Histologies

	Pembro KN 024	Atezo IMpower 110	Cemiplimab EMpower	Ipi/Nivo CM-227	Ipi/Nivo/ Chemo CM9LA	Durva/Tremi/ Chemo Poseidon
OS median (mo)	26.3 (HR-0.62)	20.2 (HR-0.59)	22.1 (HR-0.68) or NR (HR-0.57)	21.2 (HR-0.66)	18.9 (HR-0.67)	NR (HR-0.65)
PFS median (mo)	7.7 (HR-0.5)	8.1 (HR-0.63)	6.2 or 8.2 in confirmed PD-L1 (HR-0.54)	6.7 (HR-0.60)	7.5 (HR-0.59)	NR
ORR	46%	38.3%	36.5% or 39.2%	45.4%	50%	NR
Median DOR (mo)	29.1		21	31.8	26	NR

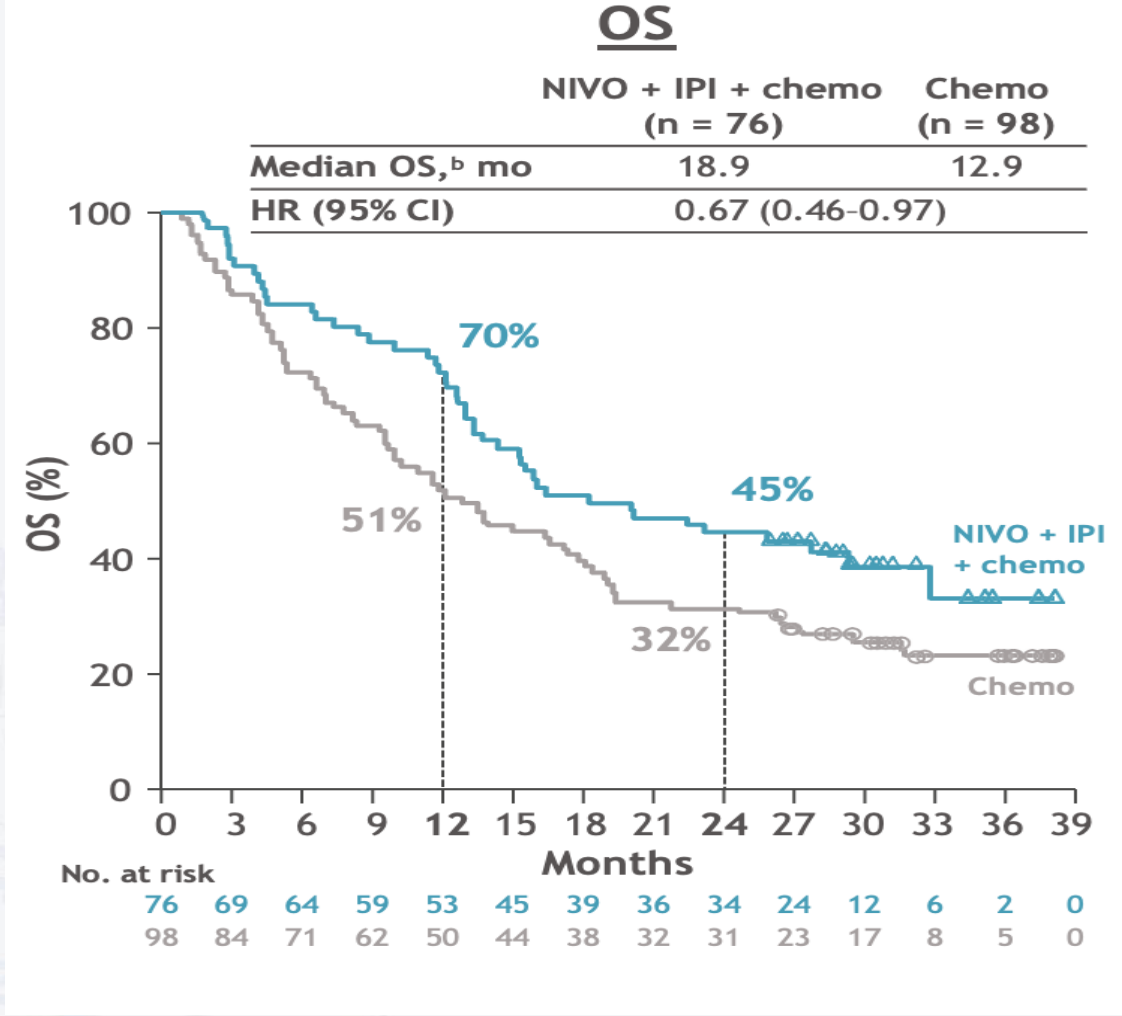
Reck M et al JCO 2021, Herbst R et al NEJM 2020, Sezer A Ann Oncol 2020 LBA52, Paz-Ares L et al ASCO 2021 #9016, Reck M et al ASCO 2021 #9000, Johnson M et al WCLC 2021

Brahmer J, WCLC 2021

KEYNOTE 024 vs CHECKMATE 9LA
PD-L1 ≥ 50%:



Brahmer J, et al. *ESMO* 2020



Paz-Ares L, et al. *Lancet Oncol* 2021

COMPARATIVA ENTRE ESTUDIOS

PD-L1 Negative Disease

All Histologies	CM227	CM9LA	Poseidon
OS (mo) median	17.2 (HR-0.64)	17.7 (HR-0.67)	NR (HR-0.77)
PFS (mo) median	5.1 (HR-0.74)	5.8 (HR-0.68)	NR
ORR	27.3%	31.1%	NR
DOR (mo) median	18	17.5	NR

Squamous	CM227	CM9LA	KN407
OS (mo) median	15.9 (HR-0.53)	(HR-0.48)	15.0 (HR-0.78) NS

Adeno	CM227	CM9LA	KN189
OS (mo) median	17.5 (HR-0.69)	(HR-0.75) NS	17.2 (HR-0.52)

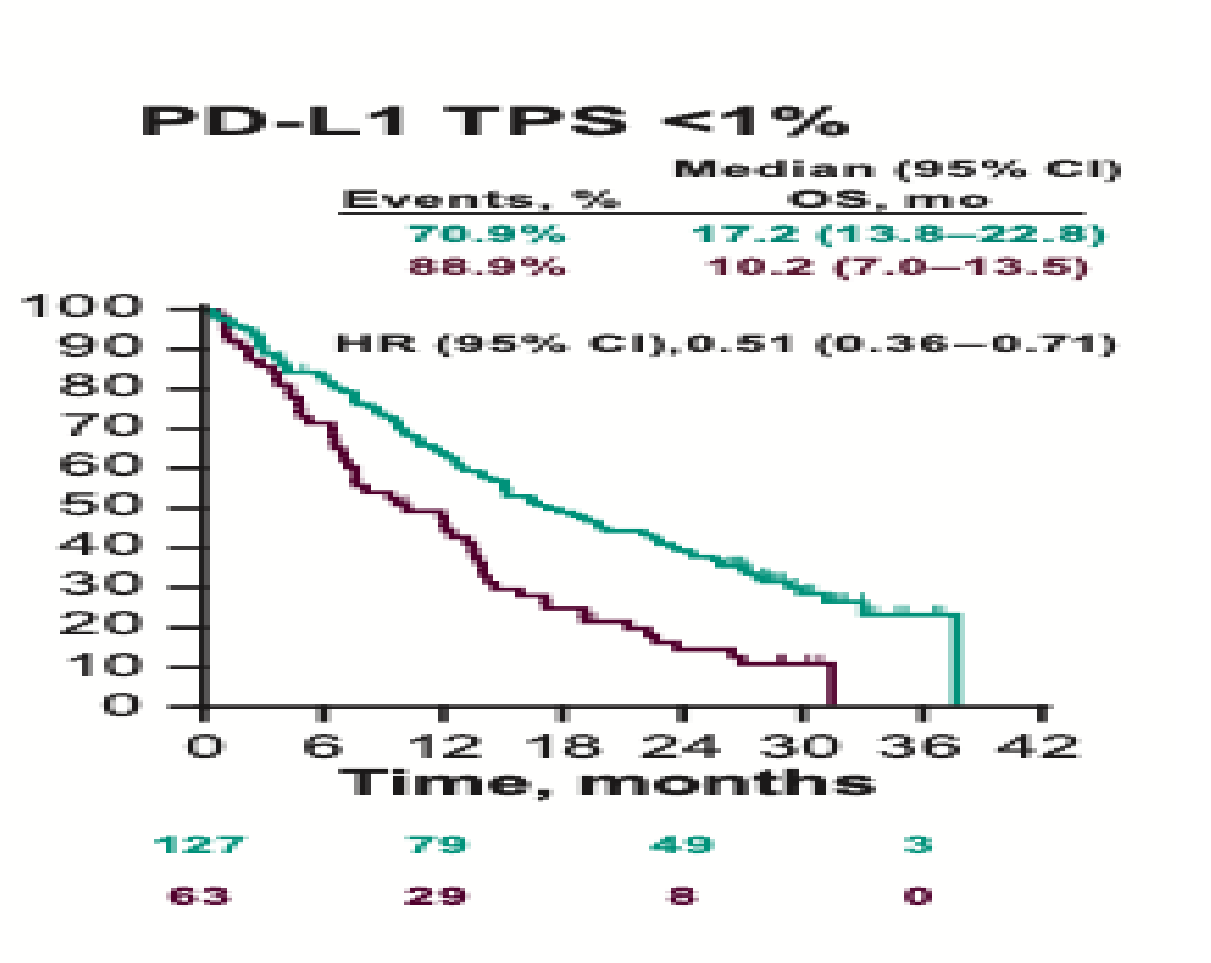
Poseidon was not analyzed by histology and PD-L1 Status

Paz-Ares L et al ASCO 2021 9016, Reck M et al ASCO 2021 9000, Robinson A et al ELCC 2021, Gray J et al ASCO 2020, Johnson M et al WCLC2021

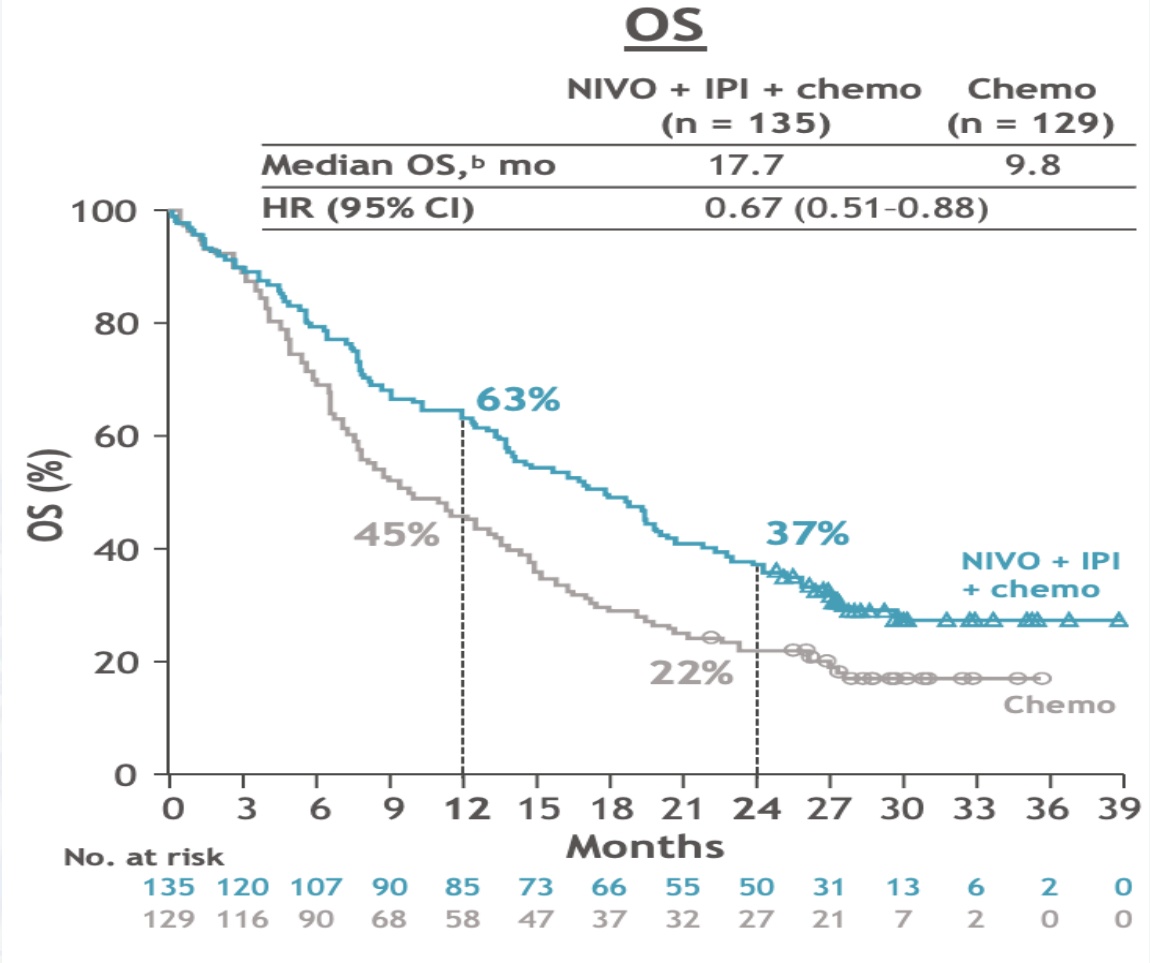
Brahmer J, WCLC 2021

KEYNOTE 189 vs CHECKMATE 9LA

PD-L1 < 1% / no escamosos



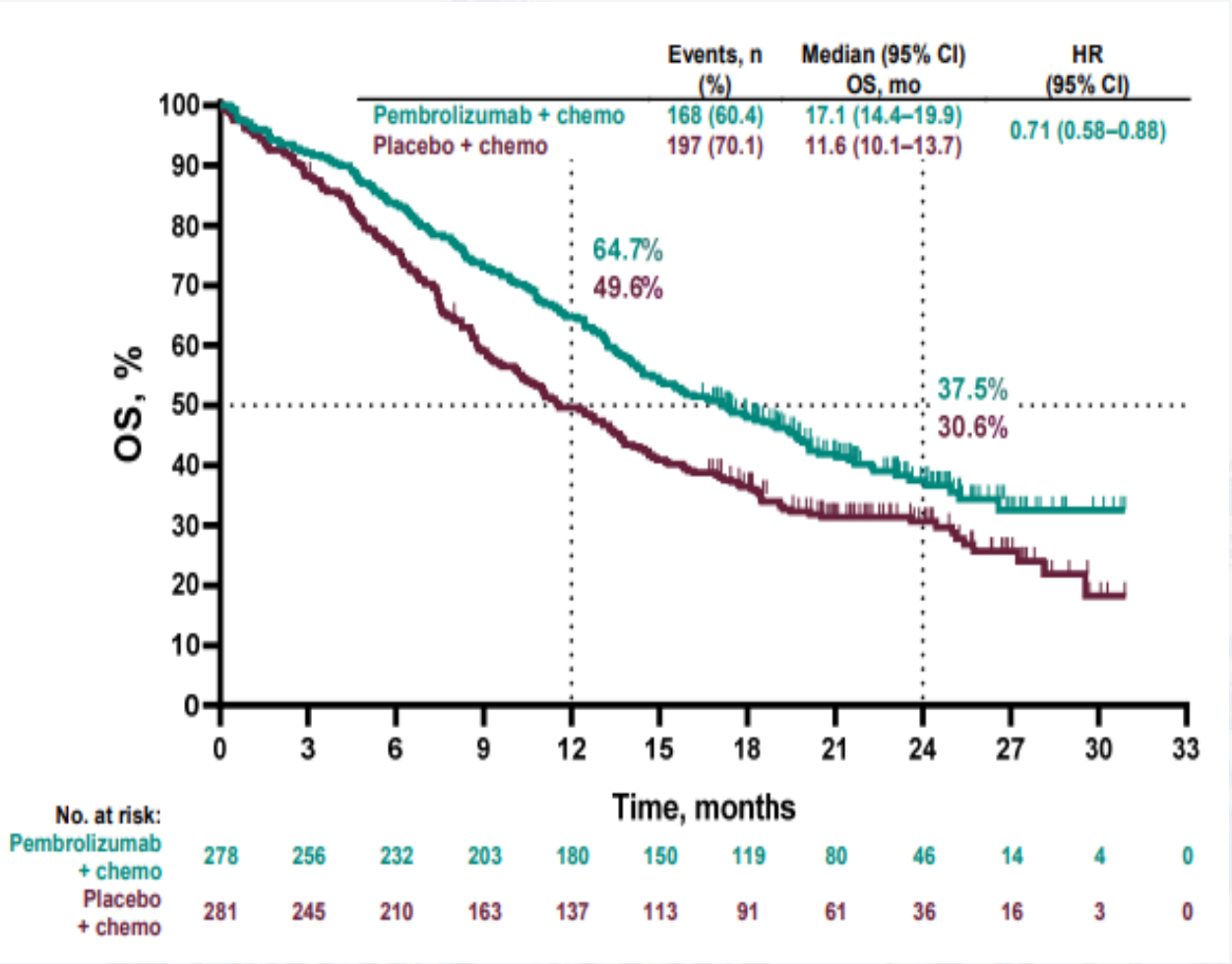
Rodríguez-Abreu D et al, ASCO 2020



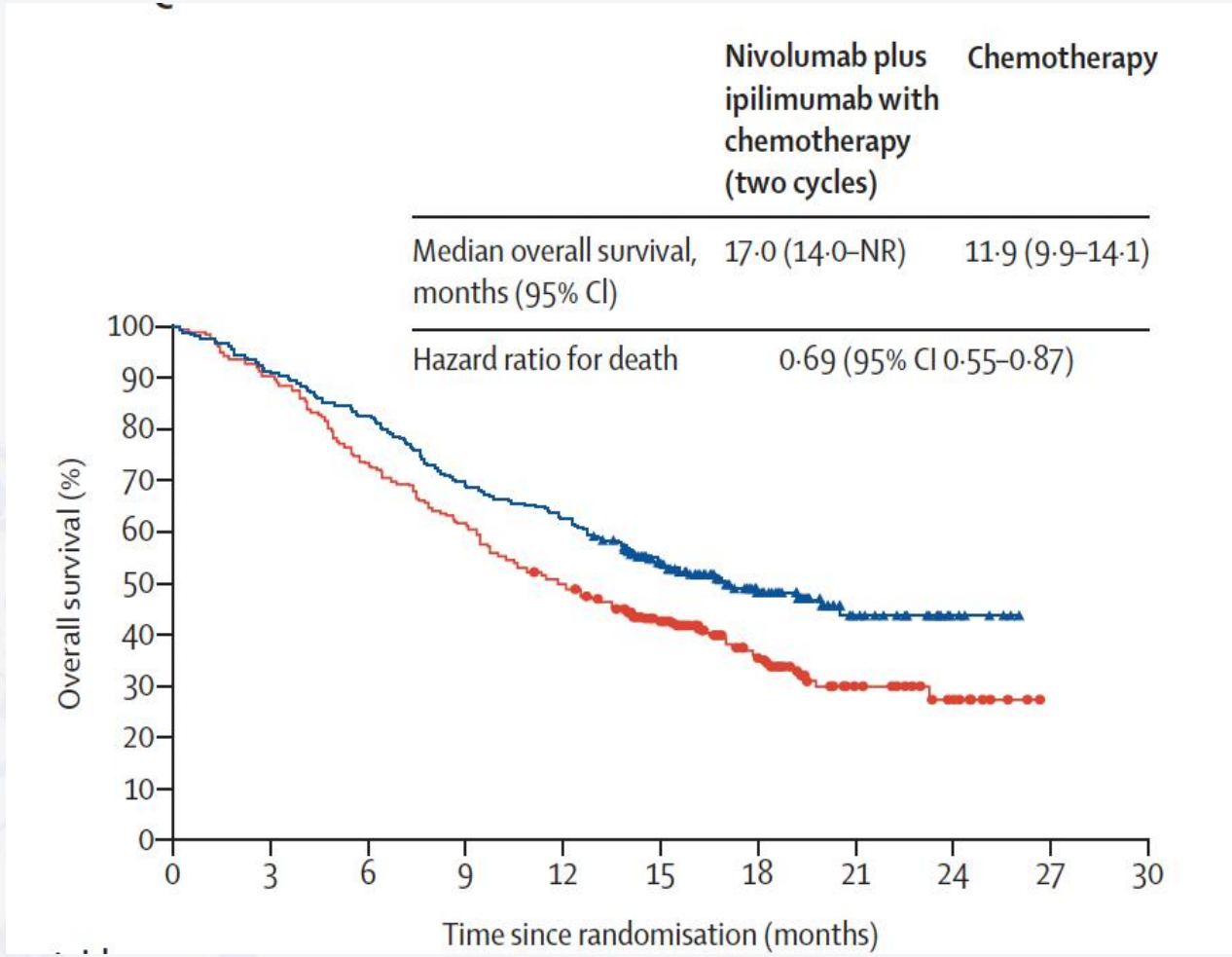
Paz-Ares L, et al. *Lancet Oncol* 2021

KEYNOTE 407 vs CHECKMATE 9LA

Escamosos



Paz-Ares L *et al.* N Engl J Med. 2018



Paz-Ares L, et al. *Lancet Oncol* 2021

Conclusiones

- Doble Imunoterapia + Quimioterapia

  CHECKMATE 9LA / POSEIDON

- Eficacia en todos los grupos de pacientes

  CHECKMATE 9LA

  - reduce la quimioterapia
  - beneficio en PD-L1 > 1% / PD-L1 < 1%
  - eficaz en ambas histologías
  - duración de la respuesta prolongada
  - eficaz en población con mets SNC
  - toxicidad incrementada pero controlada
  - Incrementa la supervivencia a largo plazo

Cuestiones pendientes

- Doble Inmunoterapia + Quimioterapia
  - selección del paciente adecuado
    - carga tumoral? Afectación en SNC? PD-L1 <1%
    - quimio reducida
  - incremento de toxicidad aceptable?
  - ausencia de un biomarcador adecuado
  - hay diferencias entre los CTTLA-4?
  - seguimiento mayor

NUEVA OPCIÓN DE TRATAMIENTO EN CÁNCER DE PULMÓN AVANZADO

XXIV SIMPOSIO DE REVISIONES EN CÁNCER

"Tratamiento médico del cáncer en el año 2022"

Gracias

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ARÁN