Cytostatika + Immunterapi NSCLC

Ronny Öhman

Lungmedicin

SUS/Lund

Neoadjuvant behandling innan kirurgi

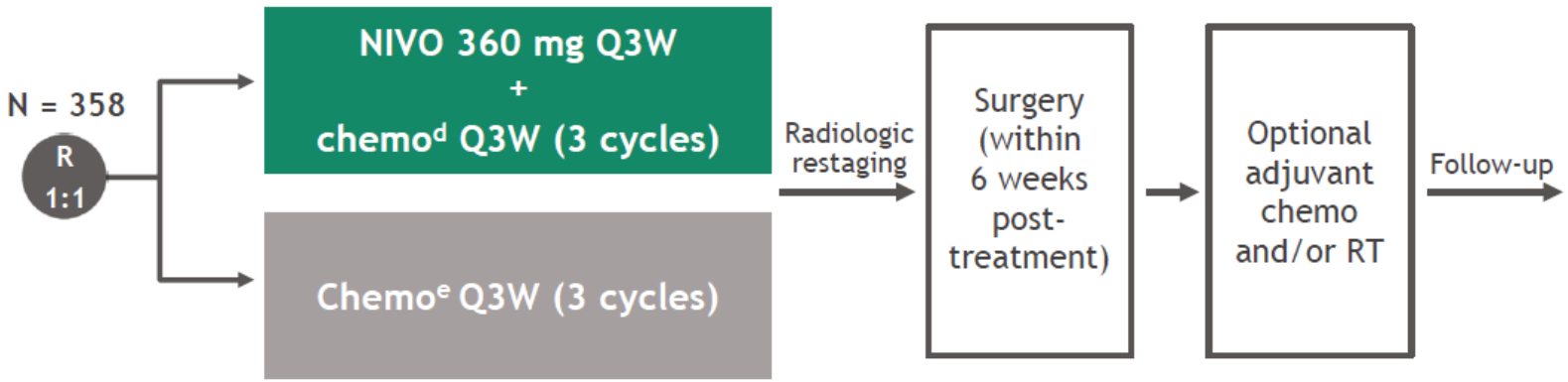
- Cytostatika + Radioterapi Cis-Vin + RT 44 Gy konkommitant stadium IIIA
- Checkmate 816 stadium II - IIIA
- Keynote 671 stadium II - IIIA

CheckMate 816 study design[a]

Key eligibility criteria

- Newly diagnosed, resectable, stage IB (≥ 4 cm)-IIIA NSCLC (per AJCC TNM 7th edition)
- ECOG PS 0-1
- No known sensitizing *EGFR* mutations or *ALK* alterations

Stratified by
stage (IB-II vs IIIA), PD-L1[b] (≥ 1% vs < 1%[c]), and sex



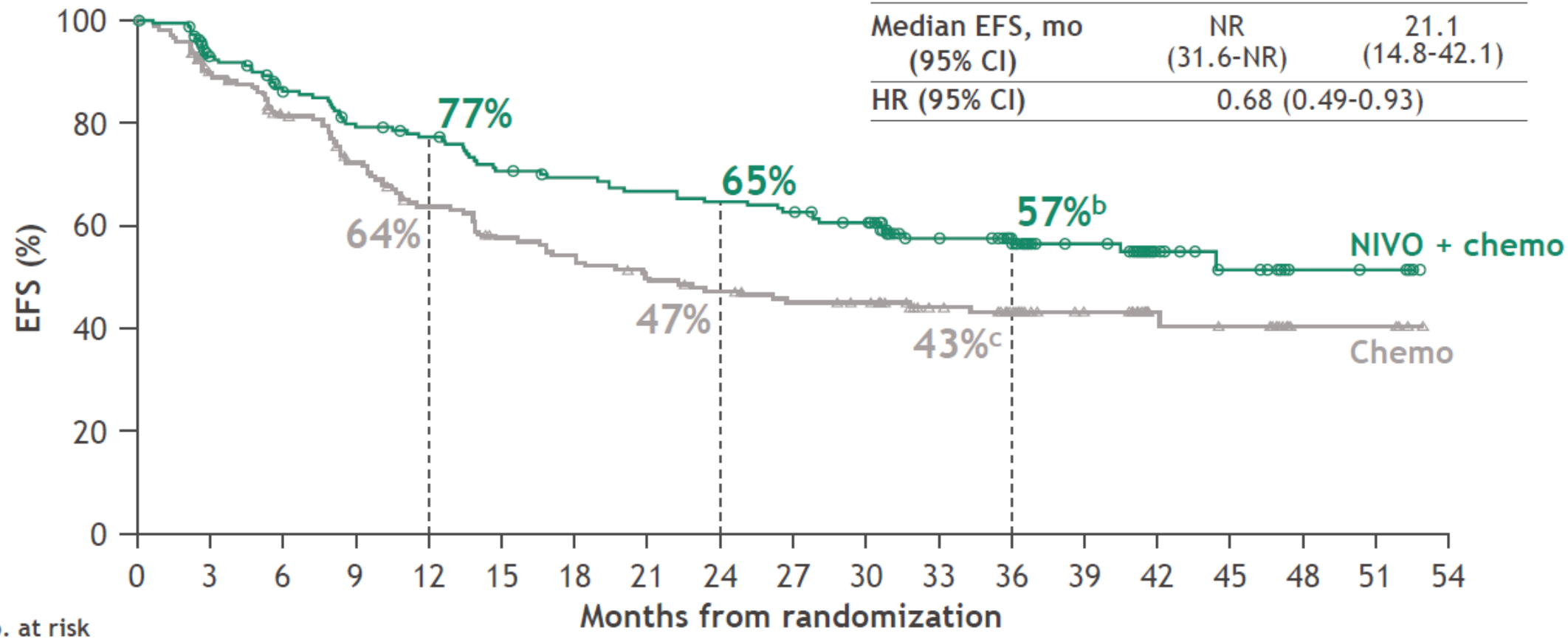
Primary endpoints
- pCR by BIPR
- EFS by BICR

Secondary endpoints
- MPR by BIPR
- OS
- TTDM

Exploratory analyses
- EFS by surgical outcomes
- pCR and EFS by 4-gene inflammatory signature score

EFS with neoadjuvant NIVO + chemo vs chemo: 3-year update[a]

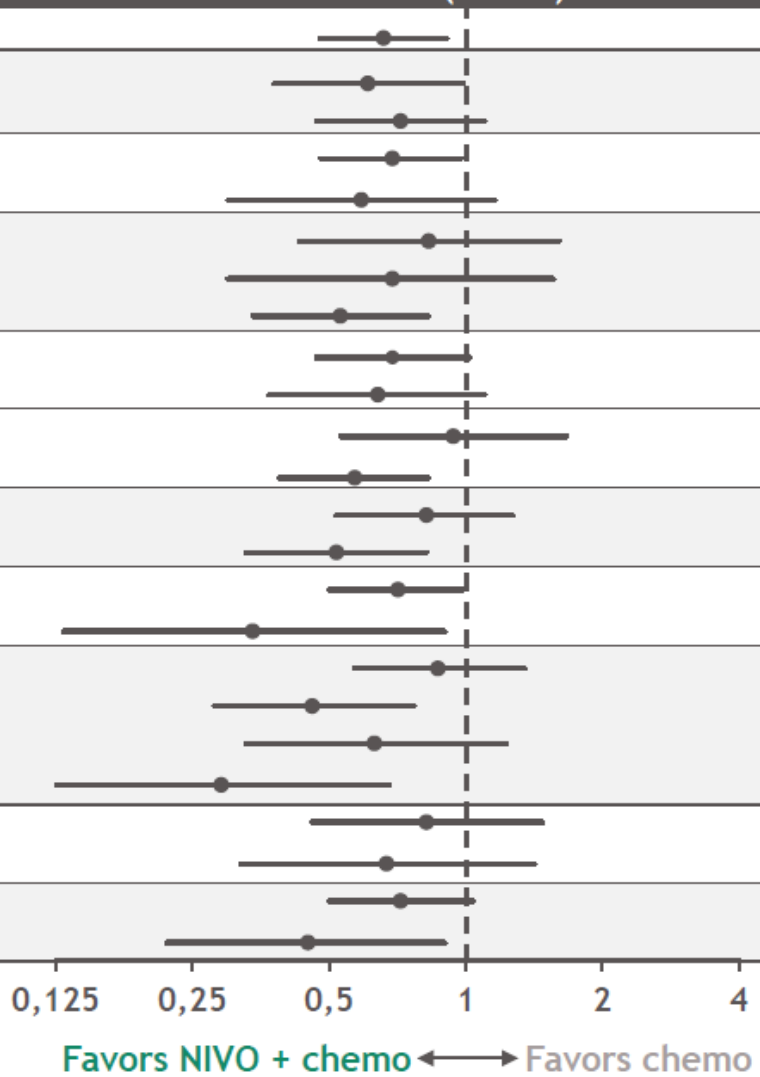
	NIVO + chemo (n = 179)	Chemo (n = 179)
Median EFS, mo (95% CI)	NR (31.6-NR)	21.1 (14.8-42.1)
HR (95% CI)	0.68 (0.49-0.93)	



No. at risk																			
NIVO + chemo	179	152	136	125	119	108	104	100	97	94	88	69	57	38	20	13	6	5	0
Chemo	179	146	128	110	95	84	79	72	67	62	60	48	39	27	15	13	4	4	0

EFS[a] subgroup analysis: 3-year update

	Median EFS, mo		Unstratified HR[a] (95% CI)	Unstratified HR
	NIVO + chemo (n = 179)	Chemo (n = 179)		
Overall (N = 358)	NR	21.0		0.66
< 65 years (n = 176)	NR	22.4		0.61
≥ 65 years (n = 182)	40.4	20.9		0.72
Male (n = 255)	44.4	18.0		0.69
Female (n = 103)	NR	NR		0.59
North America (n = 91)	NR	42.1		0.83
Europe (n = 66)	NR	21.1		0.69
Asia (n = 177)	NR	16.5		0.53
ECOG PS 0 (n = 241)	NR	31.8		0.69
ECOG PS 1 (n = 117)	NR	14.0		0.64
Stage IB-II (n = 126)	NR	NR		0.94
Stage IIIA (n = 229)	NR	16.9		0.57
Squamous (n = 182)	40.4	22.9		0.82
Nonsquamous (n = 176)	NR	20.8		0.52
Current/former smoker (n = 318)	NR	23.3		0.71
Never smoker (n = 39)	44.4	10.4		0.34
PD-L1 < 1% (n = 155)	26.4	20.8		0.87
PD-L1 ≥ 1% (n = 178)	NR	26.7		0.46
PD-L1 1%-49% (n = 98)	NR	31.8		0.63
PD-L1 ≥ 50% (n = 80)	NR	19.7		0.29
TMB < 12.3 mut/Mb (n = 102)	44.4	31.8		0.82
TMB ≥ 12.3 mut/Mb (n = 76)	NR	NR		0.67
Cisplatin (n = 258)	44.4	21.1		0.72
Carboplatin (n = 72)	NR	10.6		0.45

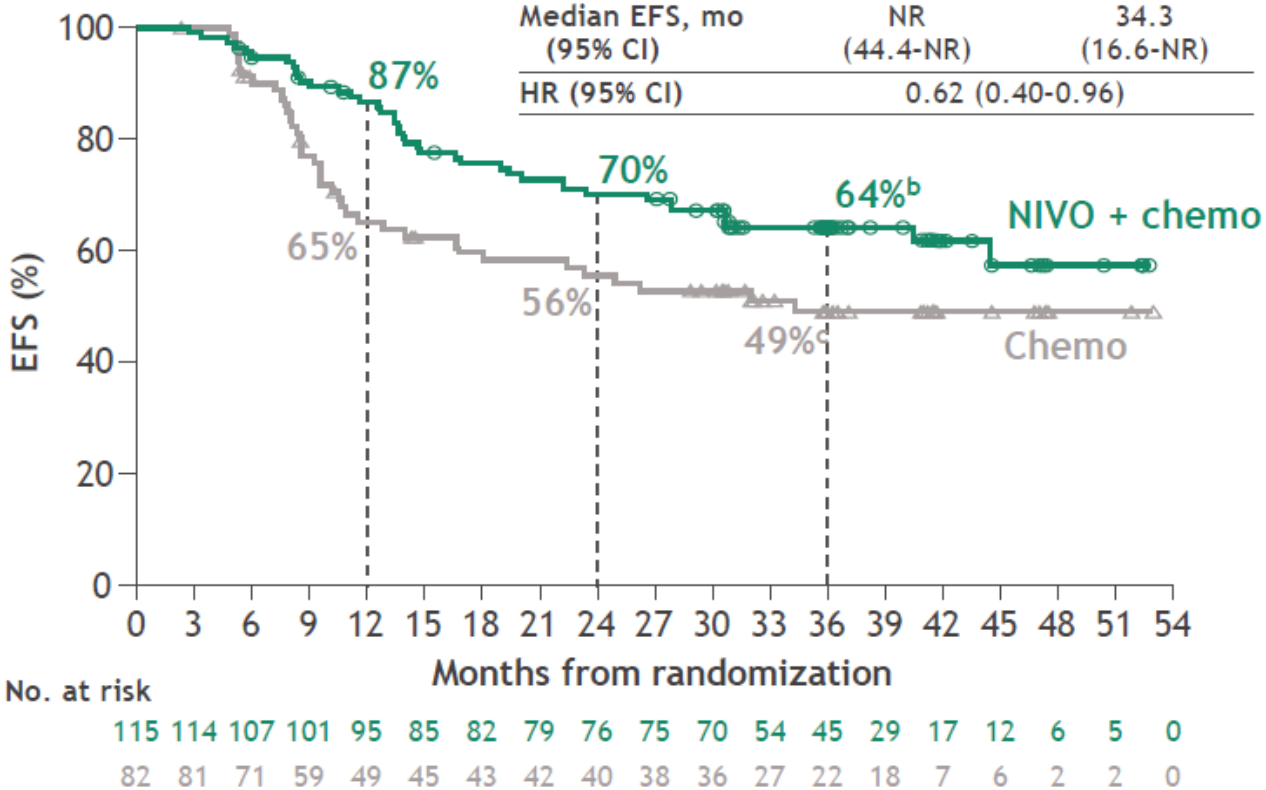


Minimum/median follow-up: 32.9/41.4 months.
[a]Per BICR.

EFS by extent/completeness of resection[a]: 3-year update

Lobectomy

	NIVO + chemo (n = 115)	Chemo (n = 82)
Median EFS, mo (95% CI)	NR (44.4-NR)	34.3 (16.6-NR)
HR (95% CI)	0.62 (0.40-0.96)	

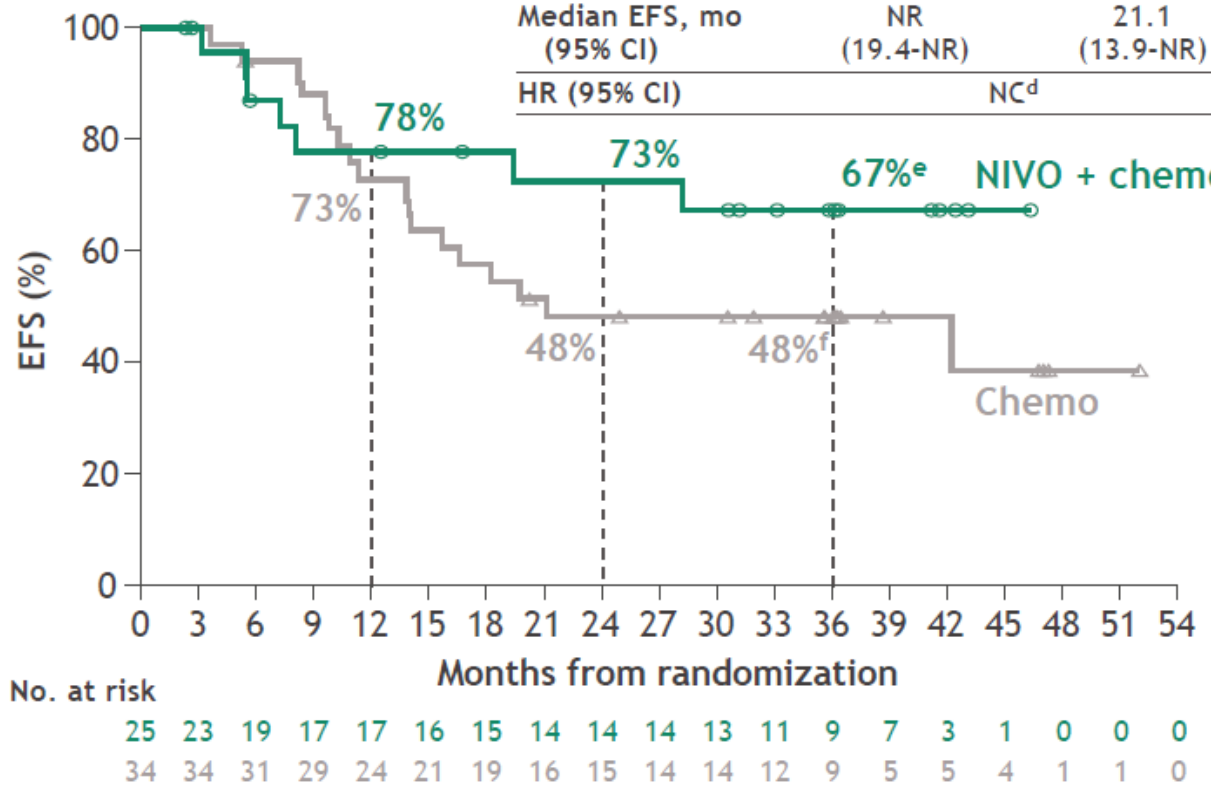


No. at risk

115	114	107	101	95	85	82	79	76	75	70	54	45	29	17	12	6	5	0
82	81	71	59	49	45	43	42	40	38	36	27	22	18	7	6	2	2	0

Pneumonectomy

	NIVO + chemo (n = 25)	Chemo (n = 34)
Median EFS, mo (95% CI)	NR (19.4-NR)	21.1 (13.9-NR)
HR (95% CI)	NC[d]	



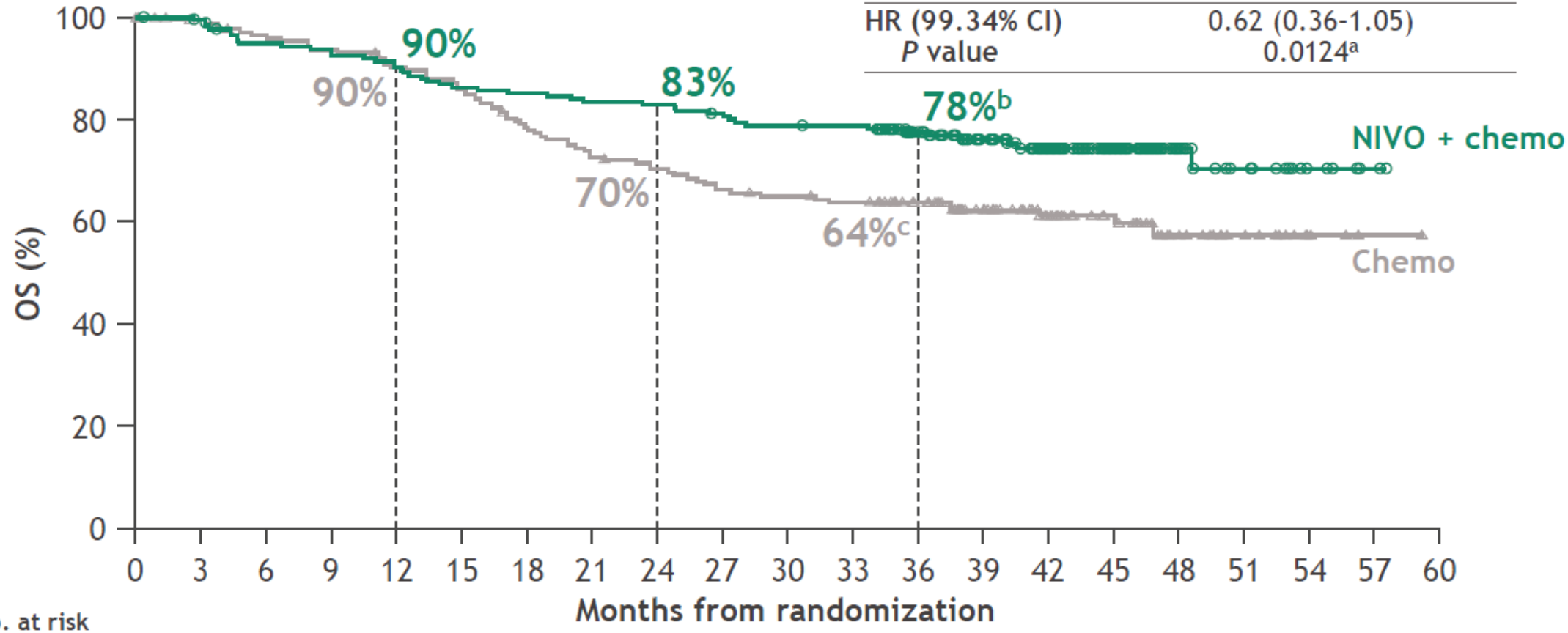
No. at risk

25	23	19	17	17	16	15	14	14	14	13	11	9	7	3	1	0	0	0
34	34	31	29	24	21	19	16	15	14	14	12	9	5	5	4	1	1	0

- In patients with R0 resection,[a] 3-year EFS rates were 64%[g] vs 51%[h] for NIVO + chemo vs chemo, respectively (HR, 0.65; 95% CI, 0.43-0.98)

OS with neoadjuvant NIVO + chemo vs chemo: 3-year update

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median OS, mo (95% CI)	NR (NR-NR)	NR (46.8-NR)
HR (99.34% CI)	0.62 (0.36-1.05)	
P value	0.0124[a]	



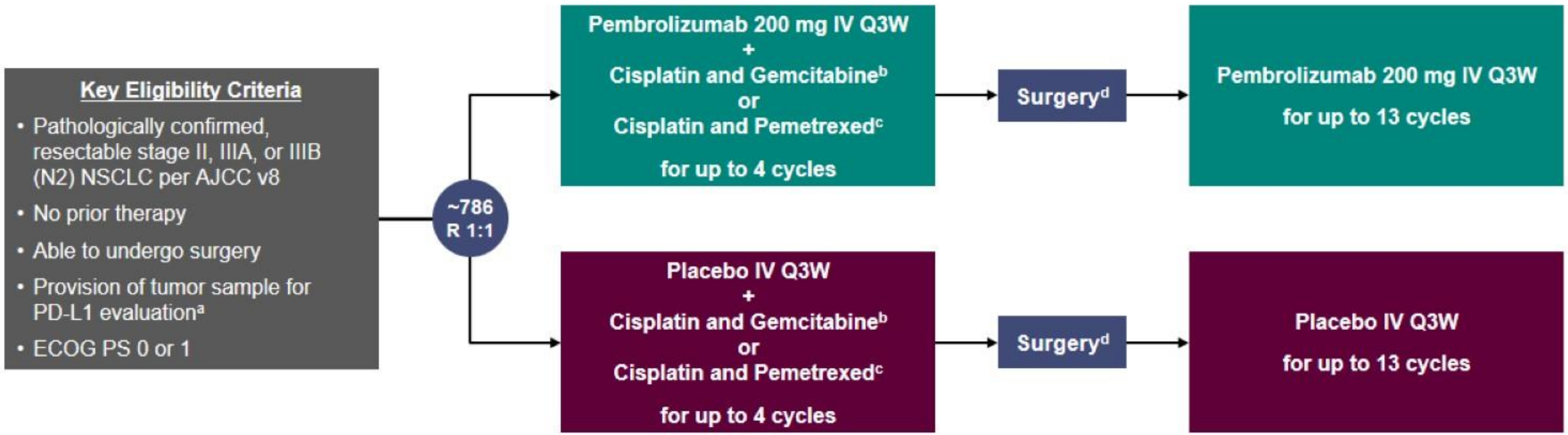
No. at risk

NIVO + chemo	179	176	166	163	158	151	149	146	145	141	137	136	117	95	67	44	23	14	6	2	0
Chemo	179	173	166	162	155	149	134	124	119	112	109	106	95	75	52	38	22	14	4	1	0

Summary

- In this 3-year analysis from CheckMate 816, neoadjuvant NIVO + chemo showed long-term EFS benefit vs chemo in patients with resectable NSCLC
  - Benefit was seen regardless of surgical approach or extent of resection, and in patients with R0 resection
- Fewer patients treated with neoadjuvant NIVO + chemo vs chemo had recurrence overall after surgery, including distant recurrence in the CNS
  - TTDM also continued to favor NIVO + chemo vs chemo
- Exploratory analyses of the 4-gene inflammatory signature suggested that high baseline tumor inflammation may be associated with improved EFS and pCR with neoadjuvant NIVO + chemo
- OS remained immature at this update but continued to show a promising trend favoring neoadjuvant NIVO + chemo
- The safety profile of neoadjuvant NIVO + chemo was consistent with previous reports
- These results from CheckMate 816 further support the use of NIVO + chemo as a standard neoadjuvant treatment for patients with resectable NSCLC

KEYNOTE-671 Study Design
Randomized, Double-Blind, Phase 3 Trial



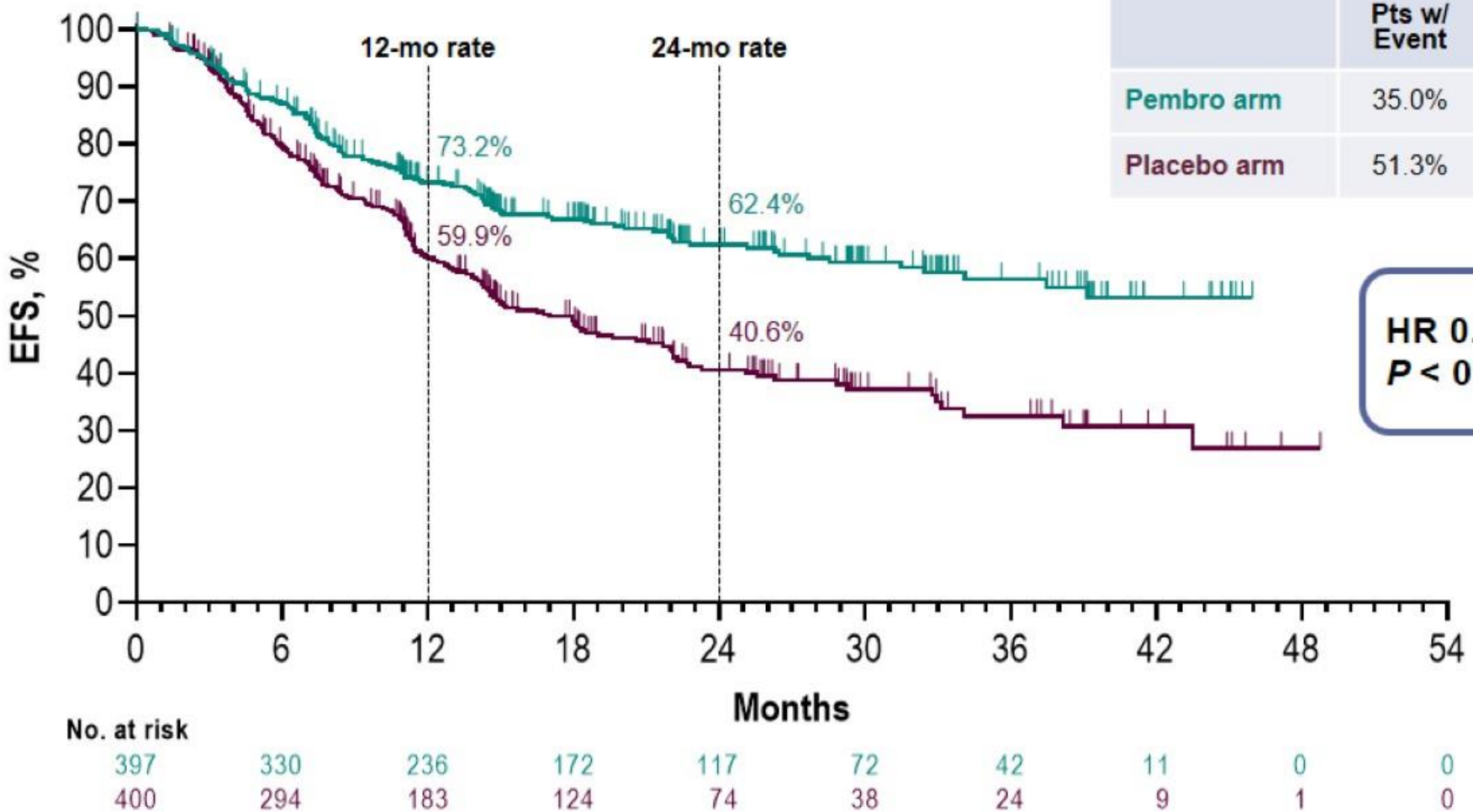
Stratification Factors
- Disease stage (II vs III)
- PD-L1 TPS[a] (<50% vs ≥50%)
- Histology (squamous vs nonsquamous)
- Geographic region (east Asia vs not east Asia)

Dual primary end points: EFS per investigator review and OS

Key secondary end points: mPR and pCR per blinded, independent pathology review, and safety

[a] Assessed at a central laboratory using PD-L1 IHC 22C3 pharmDx. [b] Cisplatin 75 mg/m^2 IV Q3W + gemcitabine 1000 mg/m^2 IV on days 1 and 8 Q3W was permitted for squamous histology only. [c] Cisplatin 75 mg/m^2 IV Q3W + pemetrexed 500 mg/m^2 IV Q3W was permitted for nonsquamous histology only. [d] Radiotherapy was to be administered to participants with microscopic positive margins, gross residual disease, or extracapsular nodal extension following surgery and to participants who did not undergo planned surgery for any reason other than local progression or metastatic disease.
ClinicalTrials.gov identifier: NCT03425643.

Event-Free Survival

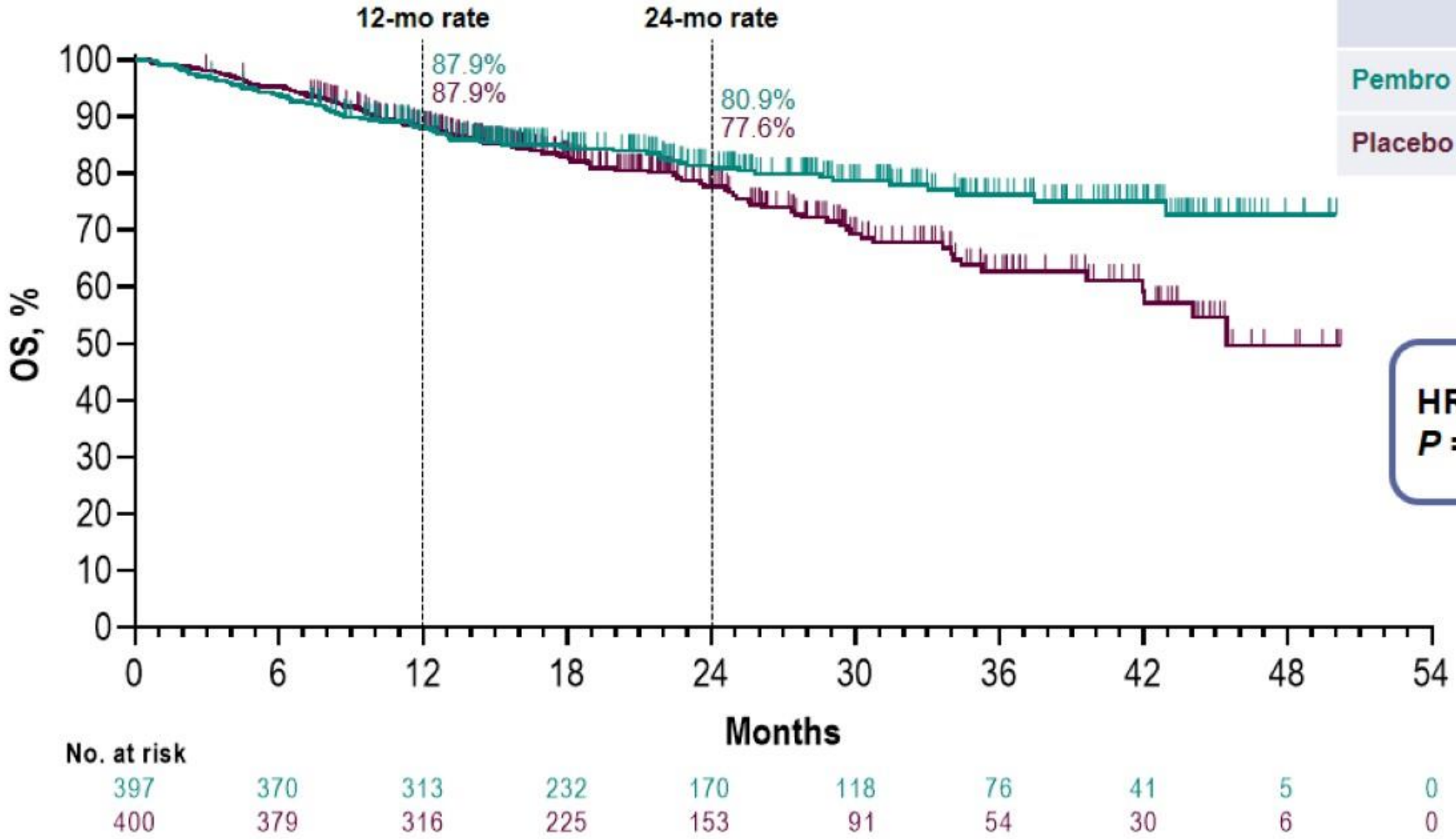


	Pts w/ Event	Median (95% CI), mo
Pembro arm	35.0%	NR (34.1-NR)
Placebo arm	51.3%	17.0 (14.3-22.0)

HR 0.58 (95% CI, 0.46-0.72)
***P* < 0.00001**

EFS defined as time from randomization to first occurrence of local progression precluding planned surgery, unresectable tumor, progression or recurrence per RECIST v1.1 by investigator assessment, or death from any cause. Data cutoff date for IA1: July 29, 2022 (median follow-up, 25.2 mo [range, 7.5-50.6]).

Overall Survival



	Pts w/ Event	Median (95% CI), mo
Pembro arm	19.1%	NR (NR-NR)
Placebo arm	25.3%	45.5 (42.0-NR)

HR 0.73 (95% CI, 0.54-0.99)
***P* = 0.02124[a]**

OS defined as time from randomization to death from any cause. [a] Significance boundary not met at IA1; significance will continue to be tested at future analyses according to the statistical analysis plan.
Data cutoff date for IA1: July 29, 2022 (median follow-up, 25.2 mo [range, 7.5-50.6]).

Summary and Conclusions

- Neoadjuvant pembrolizumab plus chemotherapy followed by surgery and adjuvant pembrolizumab provided statistically significant, clinically meaningful improvement in EFS compared with neoadjuvant chemotherapy and surgery alone
  - Median EFS was not reached in the pembrolizumab arm vs 17.0 months in the placebo arm; 24-month EFS estimates were 62.4% vs 40.6%
  - EFS benefit was generally consistent across all subgroups analyzed
- Pathological response rates were significantly higher in the pembrolizumab arm versus the placebo arm
  - mPR rates were 30.2% vs 11.0%; pCR rates were 18.1% vs 4.0%
- Exploratory analysis showed EFS benefit for perioperative pembrolizumab regardless of whether patients achieved pCR or mPR
- OS benefit of perioperative pembrolizumab was not statistically significant at IA1
  - OS will continue to be tested according to the statistical analysis
- AE profile was as expected based on the known profiles of the individual treatment components

- **Data support perioperative pembrolizumab as a new treatment option for patients with resectable stage II, IIIA, or IIIB (N2) NSCLC**

Post op adjuvant cytostatika

- Ges efter radikal kirurgi för:
  - Stadium 1B (ev om liten resektionsmarginal) relativ indikation
  - Stadium II
  - Stadium IIIA

  Cisplatin +Vinorelbin 3-4 kurer
  Karboplatin + Vinorelbin; om nedsatt AT, njurfunktion, hörselnedsättning.

Post op behandling

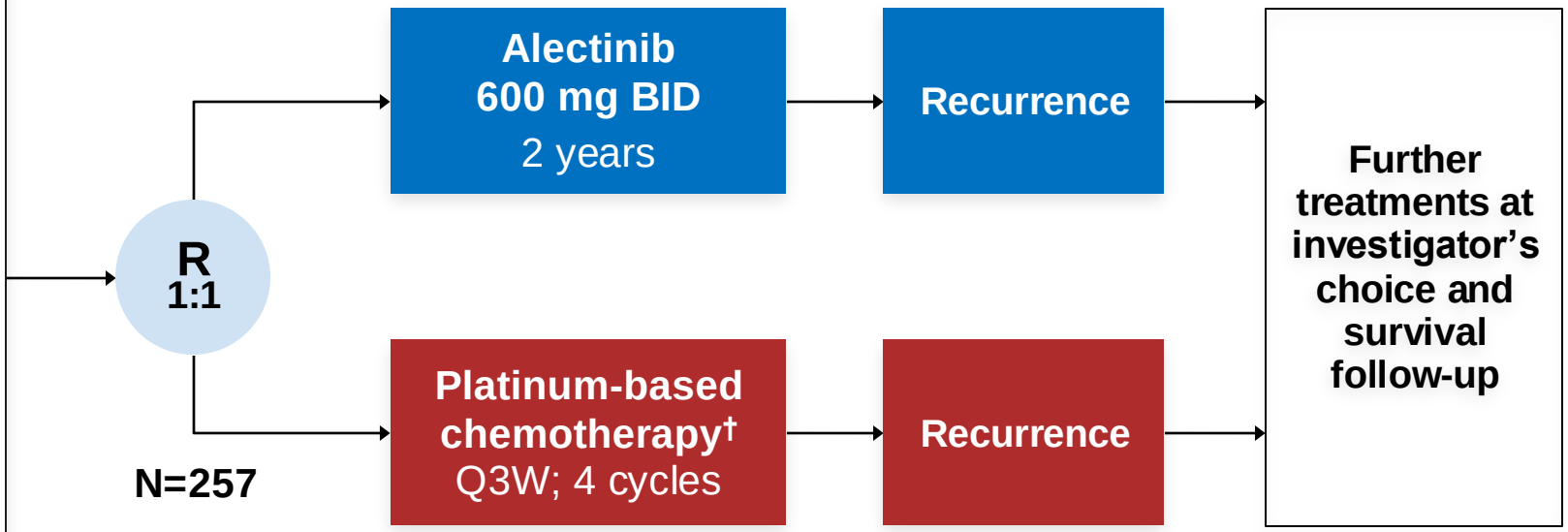
- Efter Adjuvant cyto kan ges;
  - Atezolizumab 1 år om PDL1>50% (Impower 010).
  - Osimertinib 3 år om EGFR mutation exon 19/exon 21(L858R) stadium IB – IIIA (Adaura)
  - Alectinib 2 år om ALK translokation stadium IB – IIIA (Alina)

ALINA study design*

Resected Stage IB (≥4cm)–IIIA *ALK*+ NSCLC
per UICC/AJCC 7th edition

Other key eligibility criteria:
- ECOG PS 0–1
- Eligible to receive platinum-based chemotherapy
- Adequate end-organ function
- No prior systemic cancer therapy

Stratification factors:
- Stage: IB (≥ 4cm) vs II vs IIIA
- Race: Asian vs non-Asian



Primary endpoint
- DFS per investigator,‡ tested hierarchically:
  - Stage II–IIIA → ITT (Stage IB–IIIA)

Other endpoints
- CNS disease-free survival
- OS
- Safety

Disease assessments (including brain MRI)§ were conducted: at baseline, every 12 weeks for year 1–2, every 24 weeks for year 3–5, then annually

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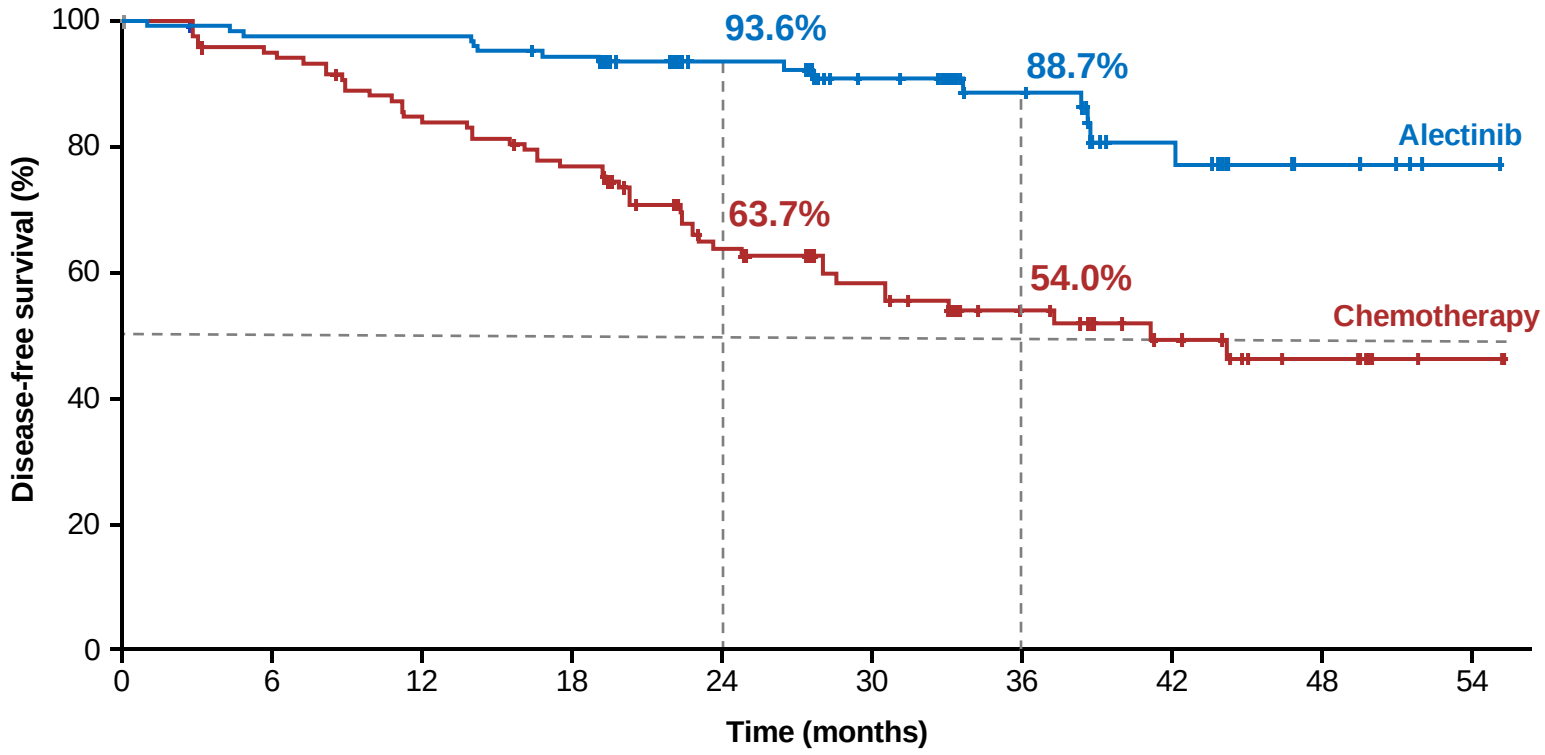
Data cut-off: 26 June 2023; CNS, central nervous system; DFS, disease-free survival; ITT, intention to treat
*Superiority trial; †Cisplatin + pemetrexed, cisplatin + vinorelbine or cisplatin + gemcitabine; cisplatin could be switched to carboplatin in case of intolerability; ‡DFS defined as the time from randomisation to the first documented recurrence of disease or new primary NSCLC as determined by the investigator, or death from any cause, whichever occurs first; §Assessment by CT scan where MRI not available; NCT03456076

Disease-free survival: ITT (stage IB–IIIA)*



No. at risk

Alectinib	130	123	123	118	74	55	39	22	10	3
Chemo	127	112	98	89	55	41	27	18	11	2

	Alectinib (N=130)	Chemotherapy (N=127)
Patients with event Death Recurrence	15 (12%) 0 15	50 (39%) 1 49
Median DFS, months (95% CI)	Not reached	41.3 (28.5, NE)
DFS HR (95% CI)	**0.24** (0.13, 0.43) p†<0.0001	

At the data cutoff date, **OS data were immature** with only 6 (2.3%) OS events reported‡

Median survival follow up: alectinib, 27.8 months; chemotherapy, 28.4 months

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Data cut-off: 26 June 2023; Time from last patient in to data cut off was ~18 months

*Per UICC/AJCC 7th edition; †Stratified log rank; ‡2 events in the alectinib arm, 4 events in the chemo arm; one additional patient in the chemo arm died but was censored due to incomplete date of death recorded. DFS defined as the time from randomisation to the first documented recurrence of disease or new primary NSCLC as determined by the investigator, or death from any cause, whichever occurs first

Stadium III

- Stadium IIIa — Ev trippelbehandling med Kemoradio + operation.
  Neoadjuvant eller adjuvant.

  Checkmate 816

- Stadium IIIb+c — Kemoradioterapi, RT upp mot 60-66 Gy.
  Ev immunterapi Durvalumab därefter (PDL1>1%)
  Pacific-studien.

PACIFIC: Study Design

Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter, International Study[1]

- Unresectable, Stage III NSCLC without progression after definitive platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- If available, archived pre-cCRT tumor tissue for PD-L1 testing*

All-comers population (i.e. irrespective of PD-L1 status)

N=713 randomized

1–42 days post-cCRT

R

2:1 randomization, stratified by age, sex, and smoking history

Durvalumab
10 mg/kg q2w for up to 12 months
N=476

Placebo
10 mg/kg q2w for up to 12 months
N=237

Primary endpoints

- PFS by BICR using RECIST v1.1†
- OS

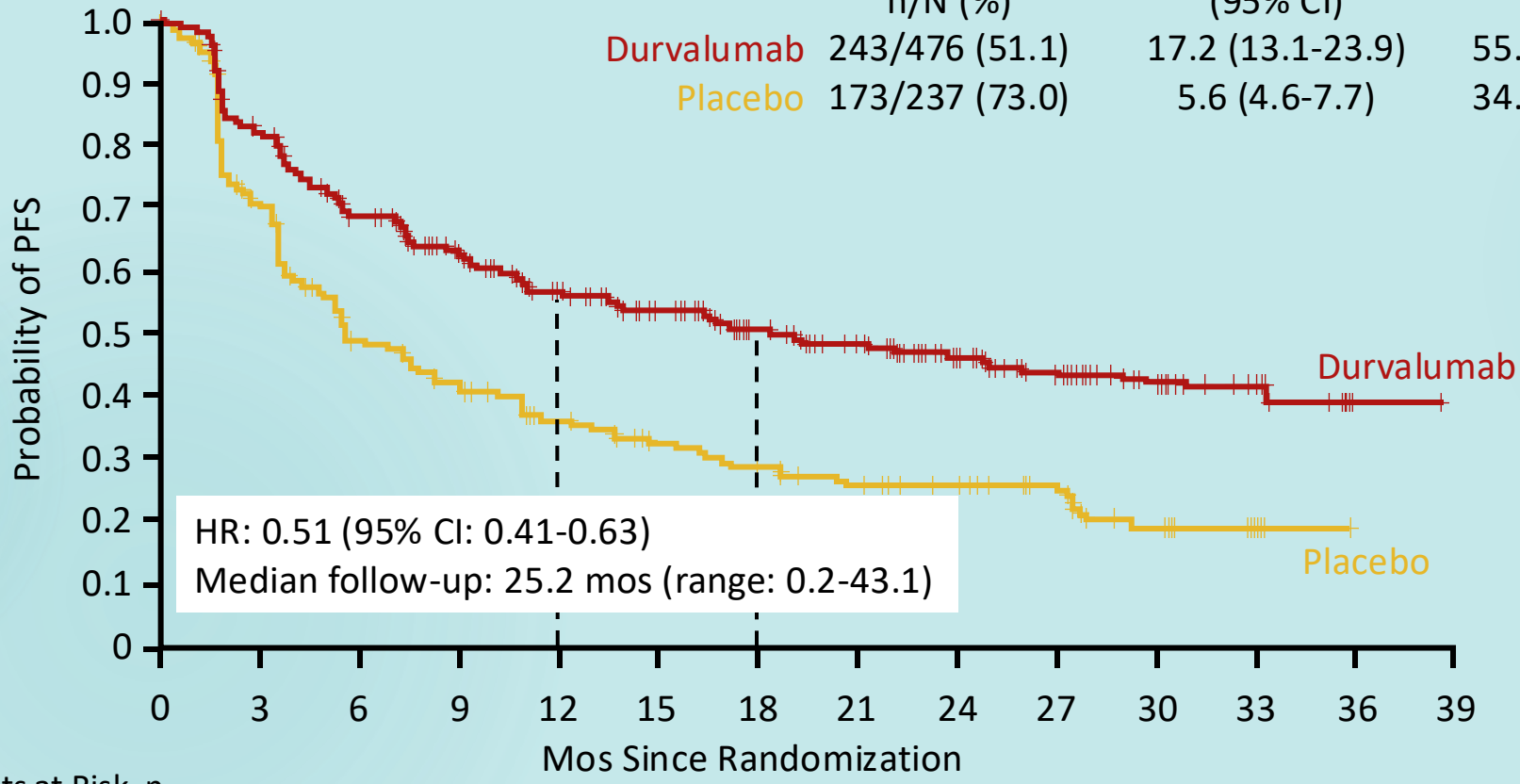
Key secondary endpoints

- ORR, DoR and TTDM by BICR
- PFS2 by investigator
- Safety
- PROs

I Sverige 1% PDL1 eller mer

PACIFIC: Updated PFS by BICR (ITT)

	Events/Patients, n/N (%)	Median PFS, Mos (95% CI)	12-Mo PFS, % (95% CI)	18-Mo PFS, % (95% CI)
Durvalumab	243/476 (51.1)	17.2 (13.1-23.9)	55.7 (50.9-60.2)	49.5 (44.6-54.2)
Placebo	173/237 (73.0)	5.6 (4.6-7.7)	34.4 (28.2-40.7)	26.7 (20.9-32.9)



Patients at Risk, n

Durvalumab	476	377	302	268	213	188	163	143	116	83	43	23	1	0
Placebo	237	163	106	86	67	55	46	39	32	24	10	5	0	0

Antonia SJ, et al. N Engl J Med. 2018;[Epub ahead of print].

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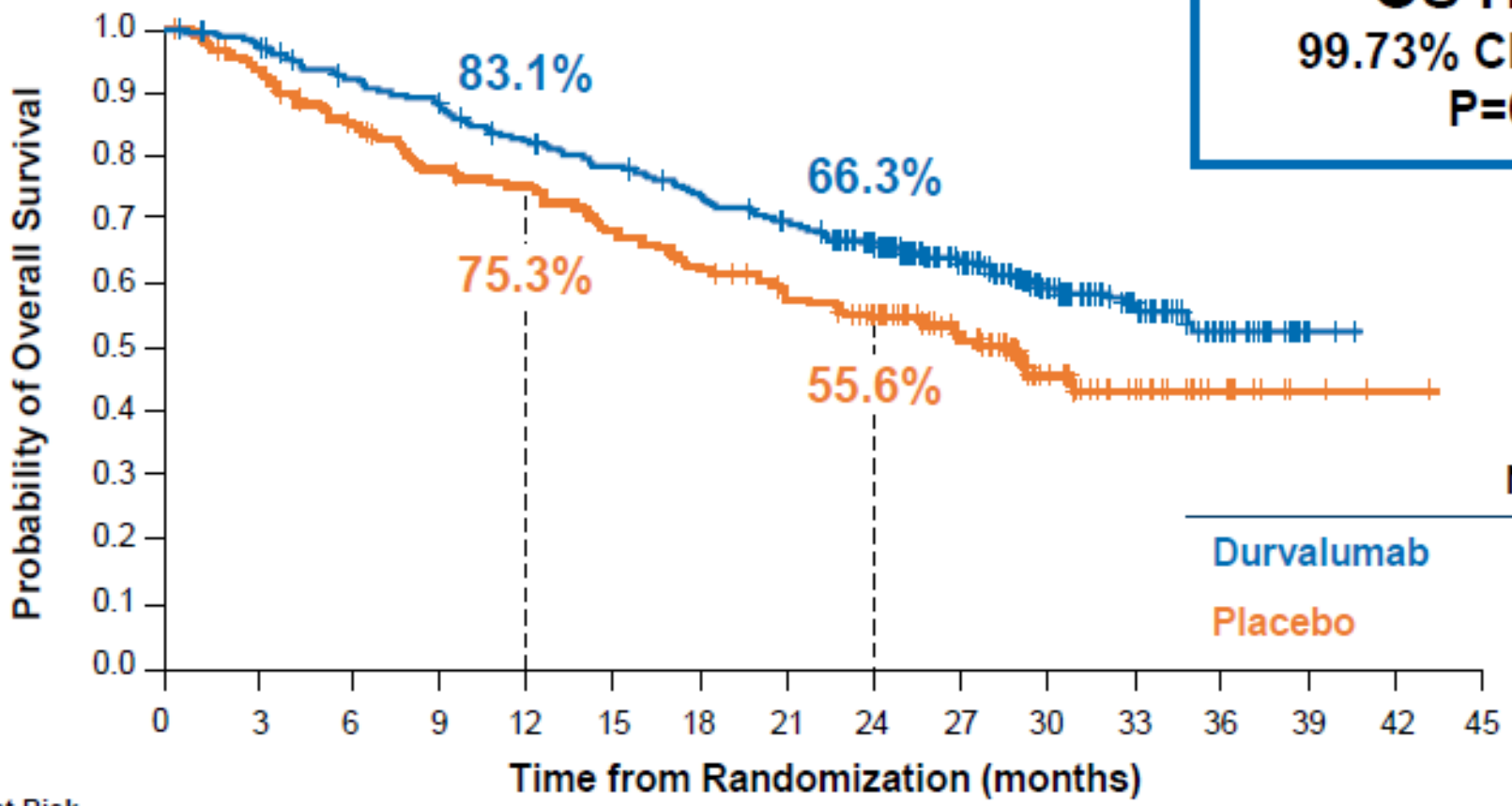
Overall Survival* (ITT)



OS HR = 0.68
99.73% CI, 0.469–0.997†
P=0.00251

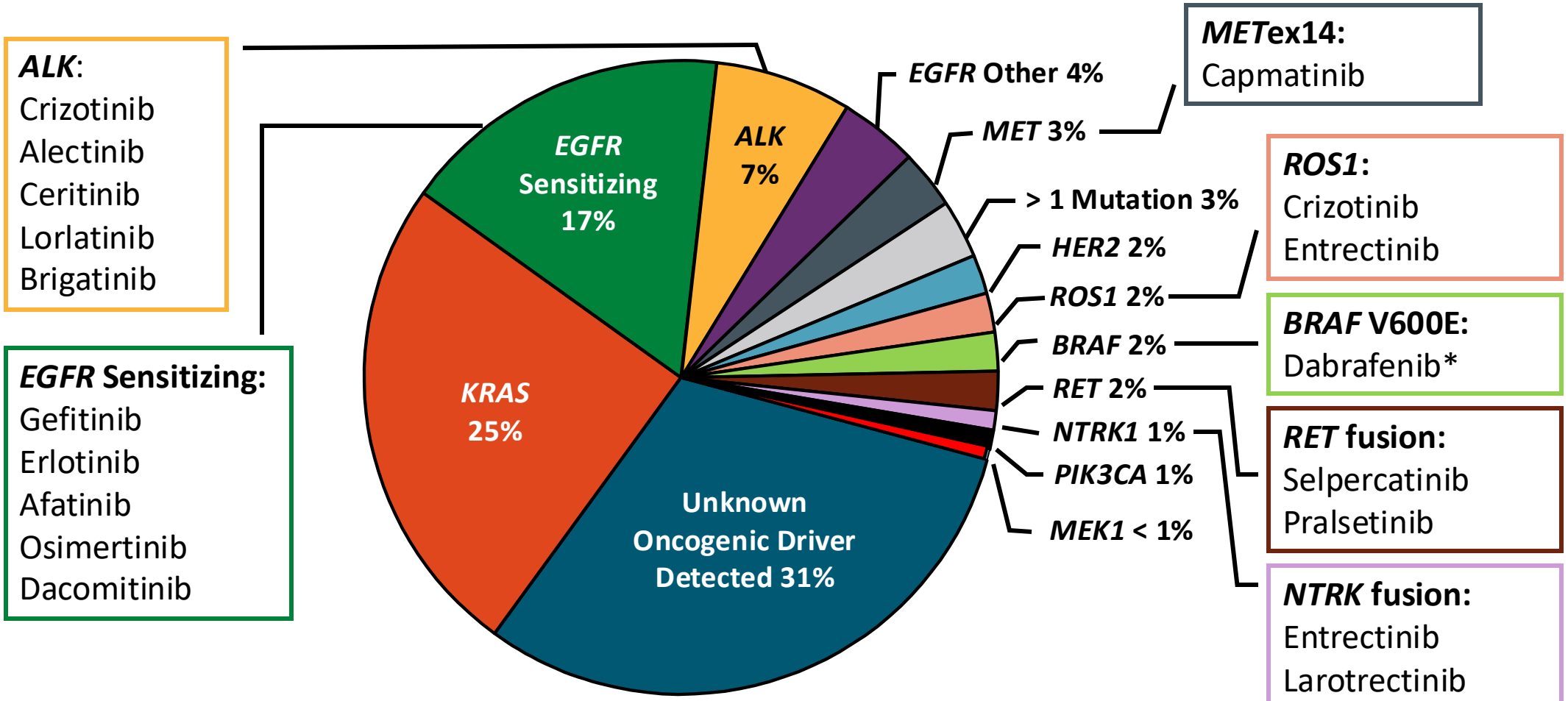
	No. of events / No. of patients (%)	Median OS (95% CI) months
Durvalumab	183/476 (38.4)	NR (34.7–NR)
Placebo	116/237 (48.9)	28.7 (22.9–NR)

No. at Risk																
Durvalumab	476	464	431	415	385	364	343	319	274	210	115	57	23	2	0	0
Placebo	237	220	198	178	170	155	141	130	117	78	42	21	9	3	1	0

WCLC

Durvalumab 47 mån
Placebo 29 mån

~ 35% of Patients With Advanced Nonsq NSCLC Have a Driver Mutation Targetable by an FDA-Approved Agent



*Approved in combination with trametinib (MEK inhibitor) for *BRAF* V600E mutation.

Li. JCO. 2013;31:1039. Tsao. J Thorac Oncol. 2016;11:613.

Slide credit: clinicaloptions.com

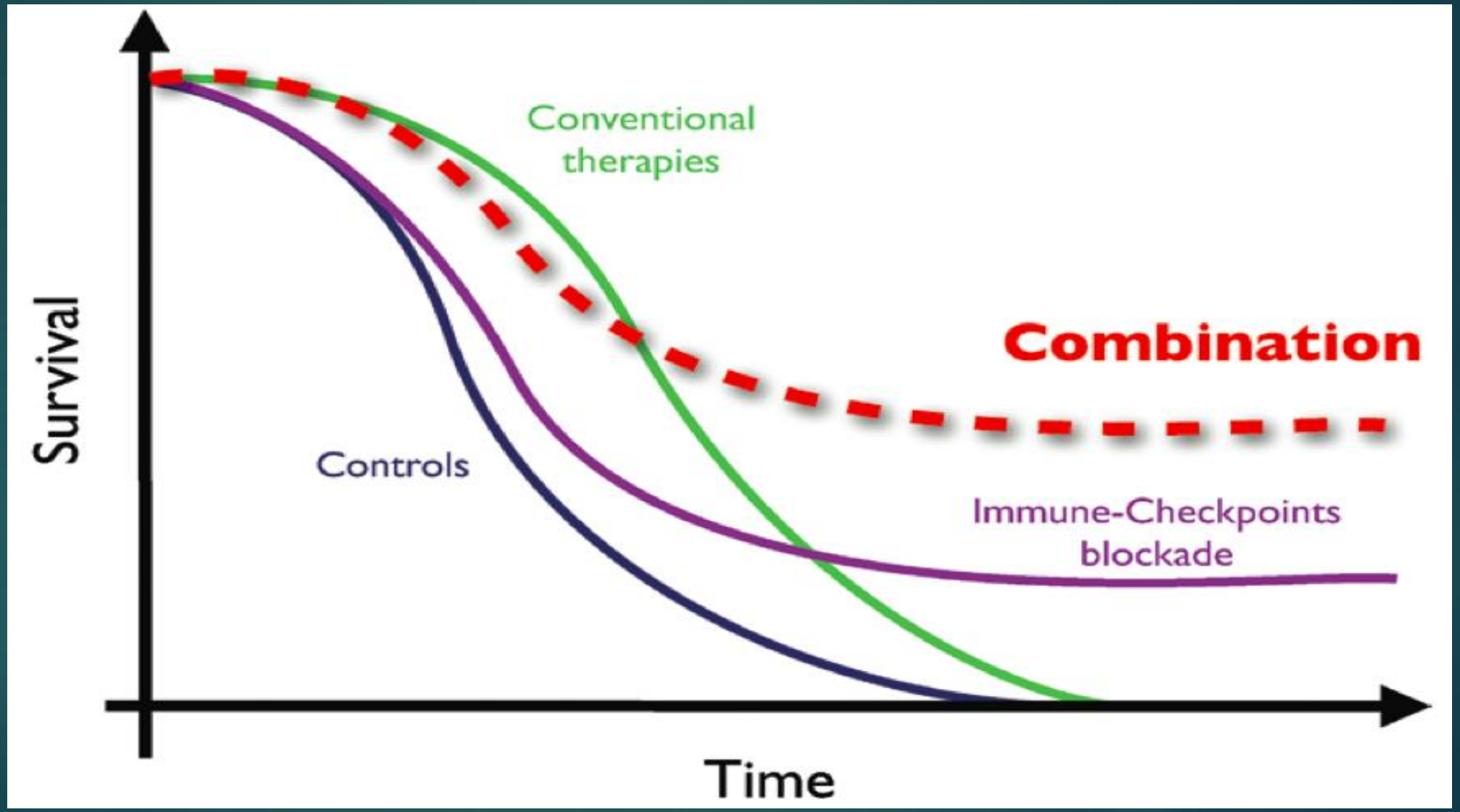
Histologi för val av behandling NSCLC

- Histologi
  - Adenocarcinom 40 - 45%
  - Skivepitel 30 -35%
  - Odifferentierad storcellig cancer 10%

Biomarkörer för val av behandling

- PDL1
  - 22C3 (Pembrolizumab)
  - 28-8 (Nivolumab)
  - SP 263 (Durvalumab)
  - SP 142 (Atezolizumab)
- TMB Tumor mutational burden
- STK-11
- KEAP-1

Immunoterapi



Cytostatika NSCLC

- Cisplatin
- Karboplatin
- Pemetrexed
- Gemcitabin
- Vinorelbin
- Paclitaxel
- Docetaxel
- Nab-Paclitaxel
- Temozolomide

PDL1

- > 50% 20 – 25% Singel immunterapi, komb cyto+immun
- 1-49% 40 – 50% Kombination cyto+immun, bara cyto.
- < 1% 25 – 30% Bara cyto, komb cyto+immun
- Ev dela upp i två grupper; >50% - 74%, >75%

Behandling PDL1>50%

- Pembrolizumab-Keytruda (Keynote 024) 3 eller 6 veckors intervall
  - PFS 8 mån OS 24 mån
- Atezolizumab-Tecentriq (Impower 110) 3 eller 4 veckors intervall
  - PFS 8 mån OS 20 mån
- Cemiplimab-Libtayo (Empower-Lung 1) 3 veckors intervall
  - PFS 8 mån OS 22 mån
- Kombination cyto+immun om avancerad tumör med pat i gott AT.

Behandling PDL1 1-49% Kombination cyto+immun

- Keynote 189 Pembro icke skivepitel
- Keynote 407 Pembro Skivepitel
- Impower 130 Atezo icke skivepitel
- Impower 150 Atezo+ Bev icke skivepitel
- Empower Lung-3 Cemiplimab alla NSCLC (PDL1>1%)
- Checkmate 9LA Nivo+Ipi alla NSCLC

Behandling PDL1 1-49% Kombination cyto+immun

- Keynote 189 PFS 9, OS 22
- Keynote 407 PFS 8, OS 17
- Impower 130 PFS 5,5, OS 18
- Impower 150 PFS 8, OS 19
- Empower Lung-3 PFS 8 , OS 22
- Checkmate 9LA PFS 7, OS 16

Jämförelse olika regimer

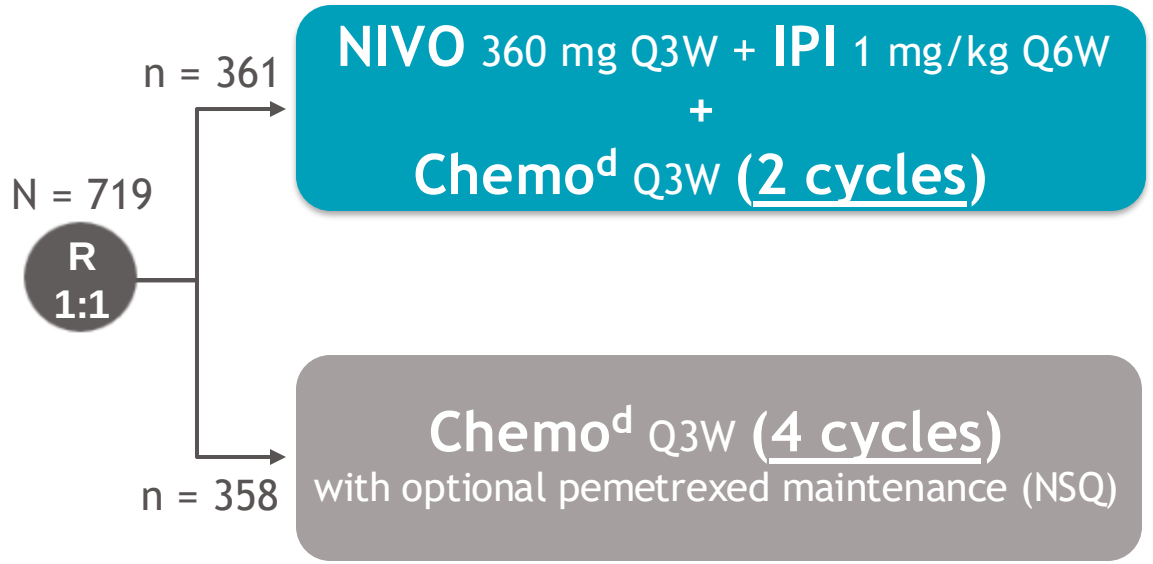
PDL1 <1%	OS
9LA	16.8 (Adeno 69+Skiv 31)
Keynote 189	17.2 (Adeno)
Keynote 407	15.9 (Skiv)

CheckMate 9LA study design[a]

Key Eligibility Criteria

- Stage IV or recurrent NSCLC
- No prior systemic therapy
- No sensitizing *EGFR* mutations or known *ALK* alterations
- ECOG PS 0–1

Stratified by PD-L1[b] (< 1%[c] vs ≥ 1%), sex, and histology (SQ vs NSQ)



Until disease progression, unacceptable toxicity, *or* for 2 years for immunotherapy

Primary endpoint

- OS

Secondary endpoints

- PFS by BICR[e]
- ORR by BICR[e]
- Efficacy by tumor PD-L1 expression

Interim database lock: October 3, 2019; minimum follow-up: 8.1 months for OS and 6.5 months for all other endpoints.
Updated database lock: March 9, 2020; minimum follow-up: 12.7 months for OS and 12.2 months for all other endpoints.

[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.

Cytostatika i studien

- Experimentarm:
- Cisplatin – Pemetrexed Adeno 2 cykler + ev underhåll Pem
- Karboplatin – Pemetrexed Adeno 2 cykler + ev underhåll Pem
- Karboplatin – Paclitaxel Skivepitel 2 cykler

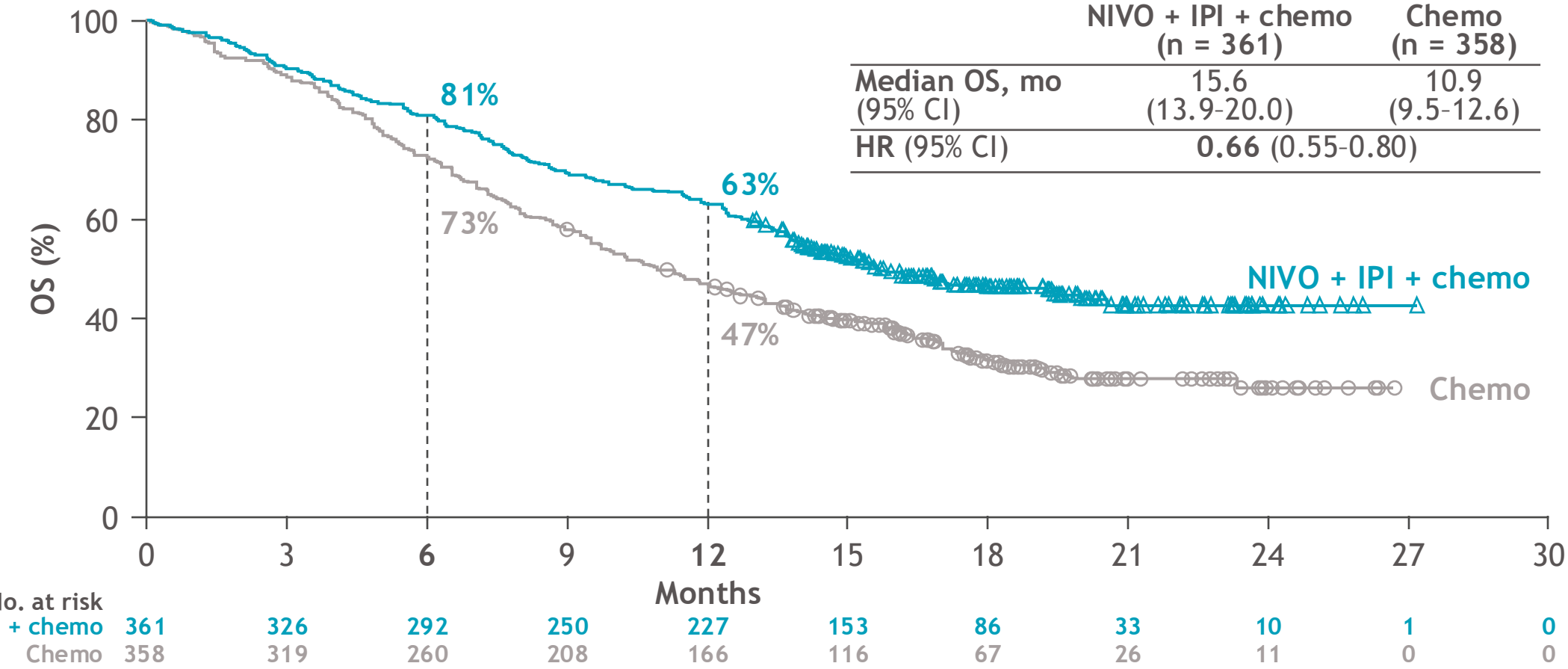
- Kontrollarm:
- Cis-Pem 4 cykler + ev underhåll Pem
- Karbo-Pem 4 cykler + ev underhåll Pem
- Karbo-Pac 4 cykler

Baseline characteristics

	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
Age, median (range), years	65 (35–81)	65 (26–86)
Female, %	30	30
ECOG PS,[a] %		
0	31	31
1	68	68
Smoking status, %		
Never smoker	13	14
Current / former smoker	87	86
Histology, %		
Squamous	31	31
Non-squamous	69	69
Metastases, %		
Bone	27	31
Liver	19	24
CNS	18	16
Tumor PD-L1 expression,[b] %		
< 1%[c]	40	39
≥ 1%[c]	60	61
1–49%[c]	38	32
≥ 50%[c]	22	29

[a]ECOG PS was not reported for 1 patient (0.3%) in each of the NIVO + IPI + chemo and chemo arms; [b]6% and 7% of patients in the NIVO + IPI + chemo and chemo arms, respectively, were unevaluable for PD-L1; [c]Calculated as a percentage of quantifiable patients.

Primary endpoint (updated): Overall survival[a]



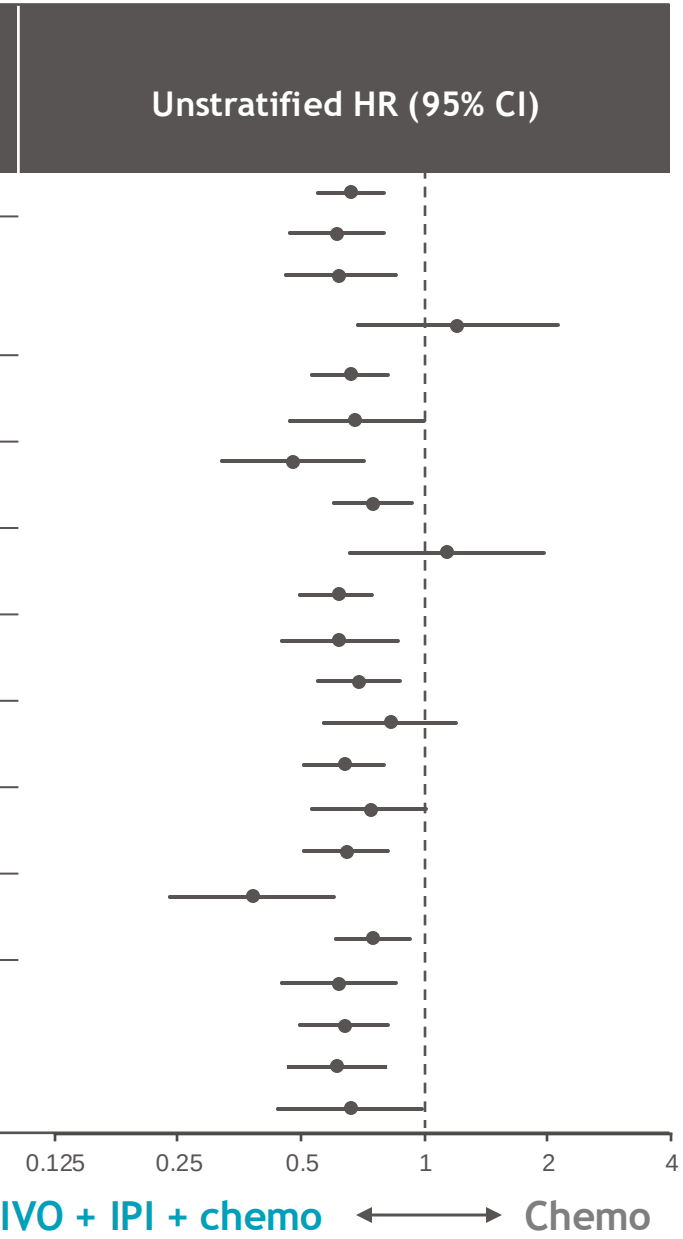
	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
Median OS, mo (95% CI)	15.6 (13.9–20.0)	10.9 (9.5–12.6)
HR (95% CI)	**0.66** (0.55–0.80)	

Minimum follow-up: 12.7 months.

[a]Patients remaining in follow-up were censored on the last date they were known to be alive; 47% of patients in the NIVO + IPI + chemo arm and 32% of patients in the chemo arm were censored. Subsequent systemic therapy was received by 31% of patients in the NIVO + IPI + chemo arm and 40% in the chemo arm; subsequent immunotherapy was received by 5% and 30%, and subsequent chemotherapy by 29% and 22%, respectively. Among patients with BICR-confirmed disease progression on study, subsequent systemic therapy was received by 40% in the NIVO + IPI + chemo arm and 44% in the chemo arm; subsequent immunotherapy was received by 7% and 34%, and subsequent chemotherapy by 38% and 24%, respectively

Overall survival subgroup analysis

Subgroup	Median OS, mo		Unstratified HR
	NIVO + IPI + chemo n = 361	Chemo n = 358	
All randomized (N = 719)	15.6	10.9	0.66[a]
< 65 years (n = 354)	15.6	10.7	0.61
65 to < 75 years (n = 295)	19.4	11.9	0.62
≥ 75 years (n = 70)	8.5	11.5	1.21
Male (n = 504)	14.1	9.8	0.66
Female (n = 215)	19.4	15.8	0.68
ECOG PS 0 (n = 225)	NR	15.4	0.48
ECOG PS 1 (n = 492)	13.6	9.7	0.75
Never smoker (n = 98)	14.1	17.8	1.14
Smoker (n = 621)	15.6	10.4	0.62
Squamous (n = 227)	14.5	9.1	0.62
Non-squamous (n = 492)	17.0	11.9	0.69
Liver metastases (n = 154)	10.2	8.1	0.83
No liver metastases (n = 565)	19.4	12.4	0.64
Bone metastases (n = 207)	11.9	8.3	0.74
No bone metastases (n = 512)	20.5	12.4	0.65
CNS metastases (n = 122)	NR	7.9	0.38
No CNS metastases (n = 597)	15.4	11.8	0.75
PD-L1 < 1% (n = 264)	16.8	9.8	0.62
PD-L1 ≥ 1% (n = 407)	15.8	10.9	0.64
PD-L1 1–49% (n = 233)	15.4	10.4	0.61
PD-L1 ≥ 50% (n = 174)	18.0	12.6	0.66



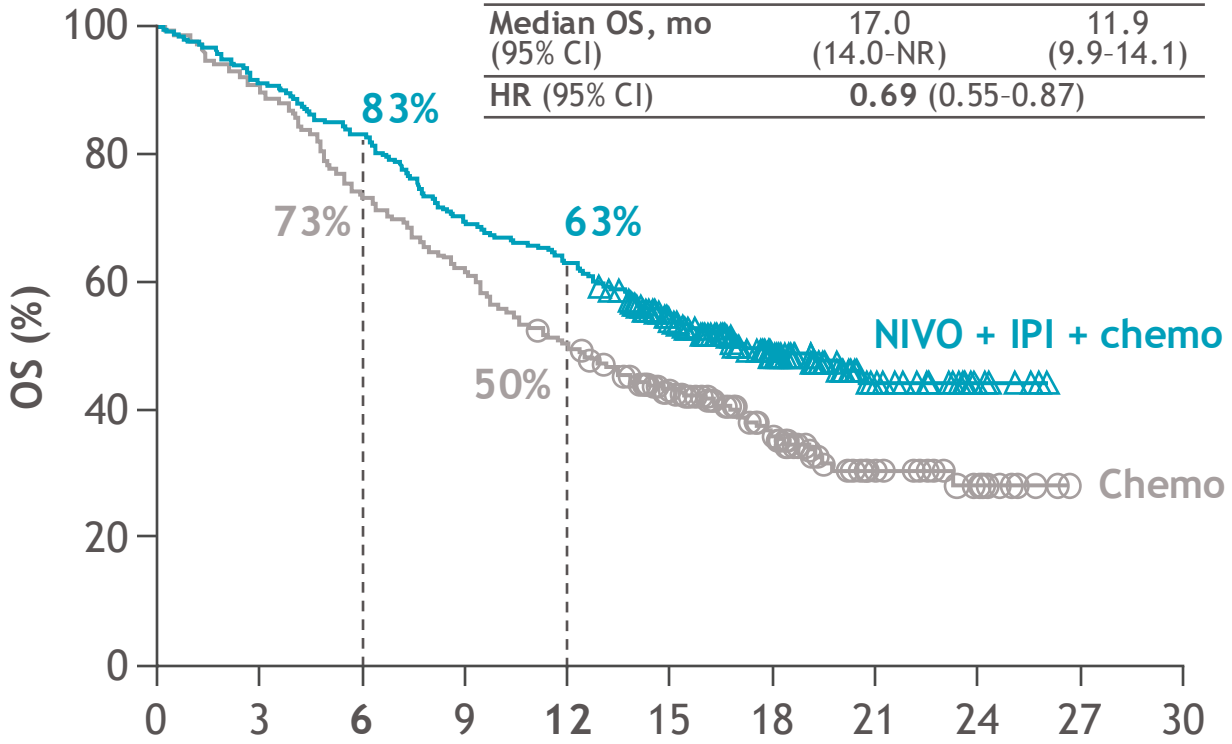
Minimum follow-up: 12.7 months.

[a]Stratified HR; unstratified HR was 0.67 (95% CI, 0.55–0.81).

Overall survival by histology

NSQ NSCLC[a]

	NIVO + IPI + chemo (n = 246)	Chemo (n = 246)
Median OS, mo (95% CI)	17.0 (14.0-NR)	11.9 (9.9-14.1)
HR (95% CI)	**0.69** (0.55-0.87)	

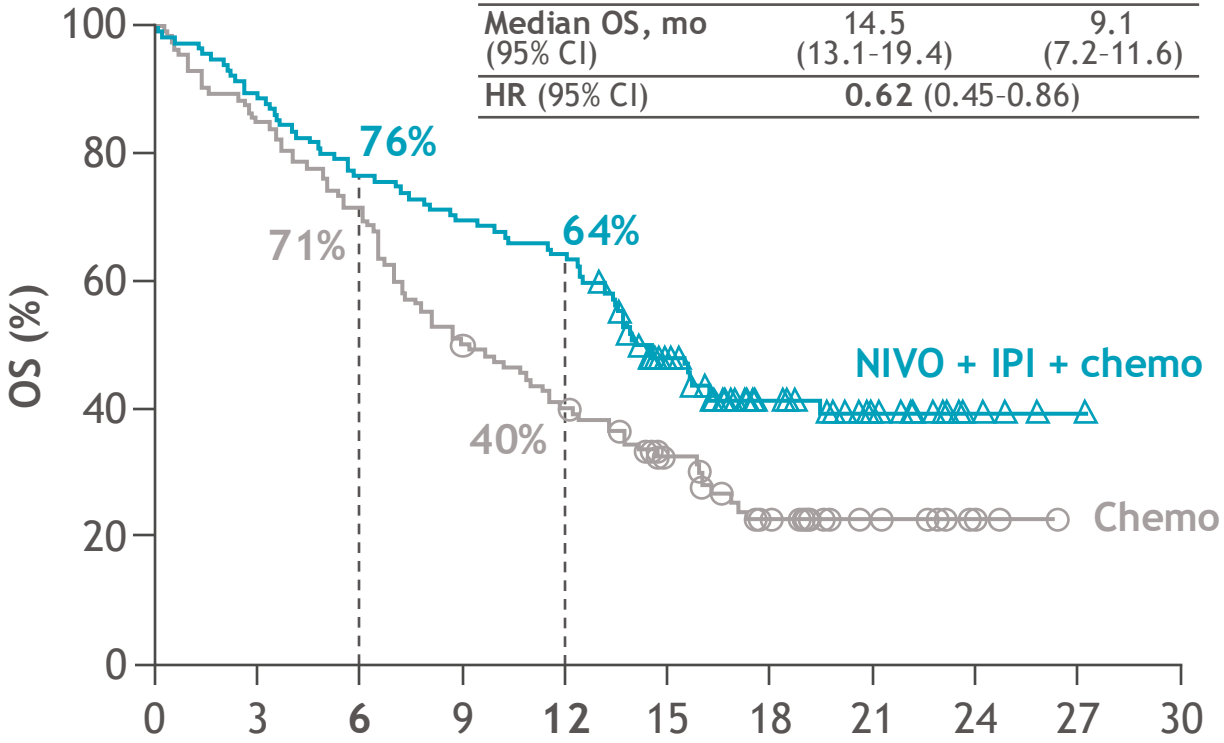


No. at risk

NIVO + IPI + chemo	246	224	204	170	154	107	62	20	6	0	0
Chemo	246	223	180	152	122	87	53	18	9	0	0

SQ NSCLC[b]

	NIVO + IPI + chemo (n = 115)	Chemo (n = 112)
Median OS, mo (95% CI)	14.5 (13.1-19.4)	9.1 (7.2-11.6)
HR (95% CI)	**0.62** (0.45-0.86)	

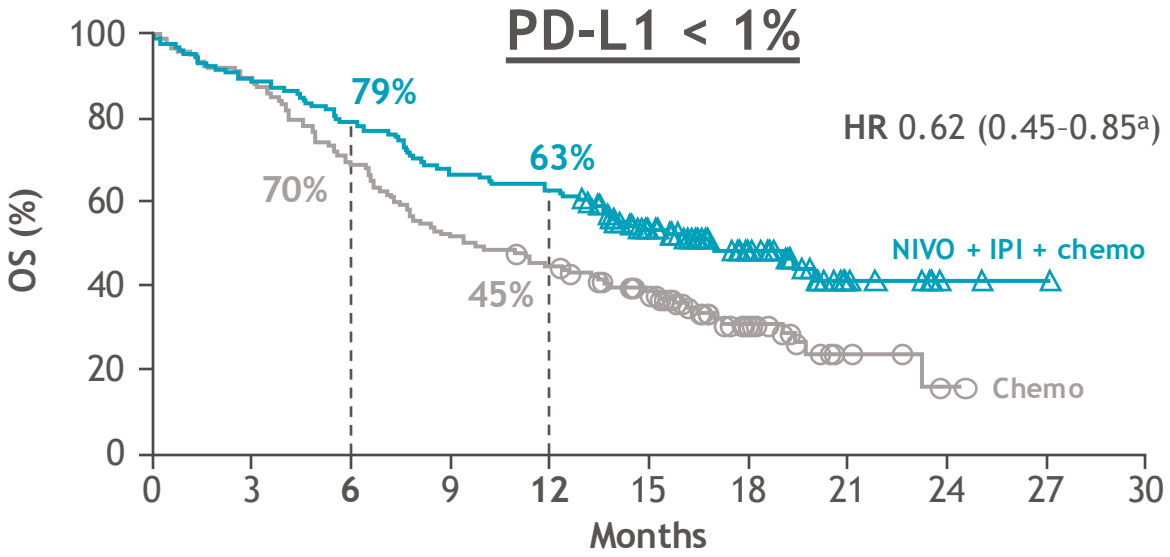


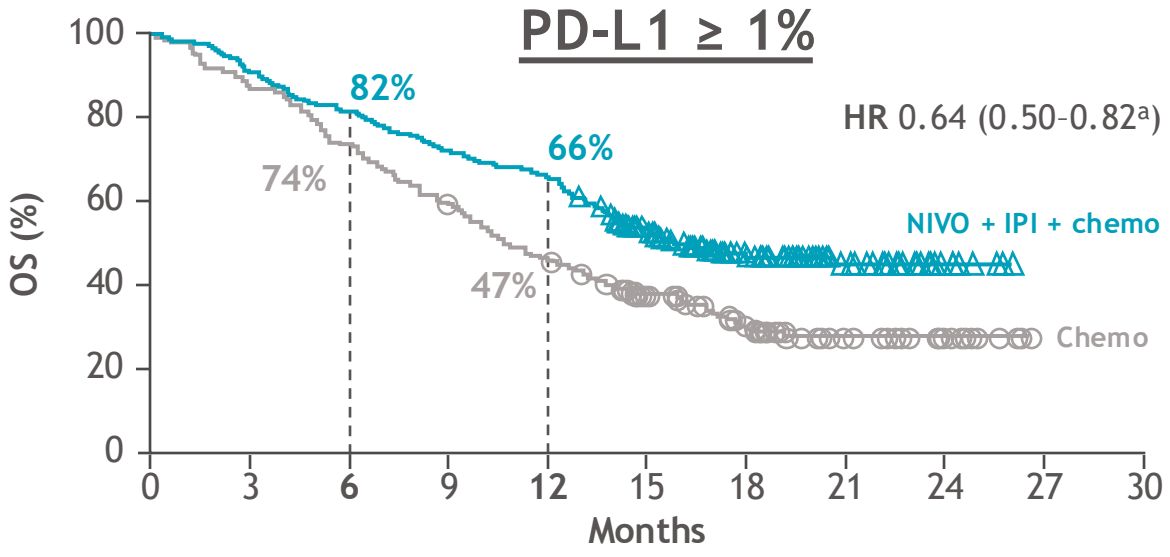
NIVO + IPI + chemo	115	102	88	80	73	46	24	13	4	1	0
Chemo	112	96	80	56	44	29	14	8	2	0	0

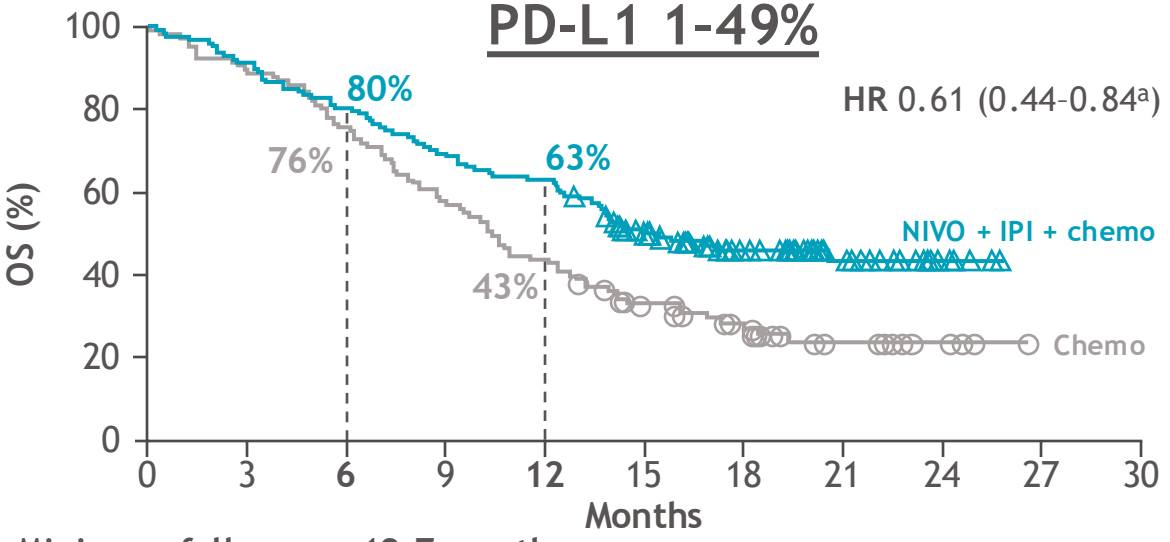
Minimum follow-up: 12.7 months.

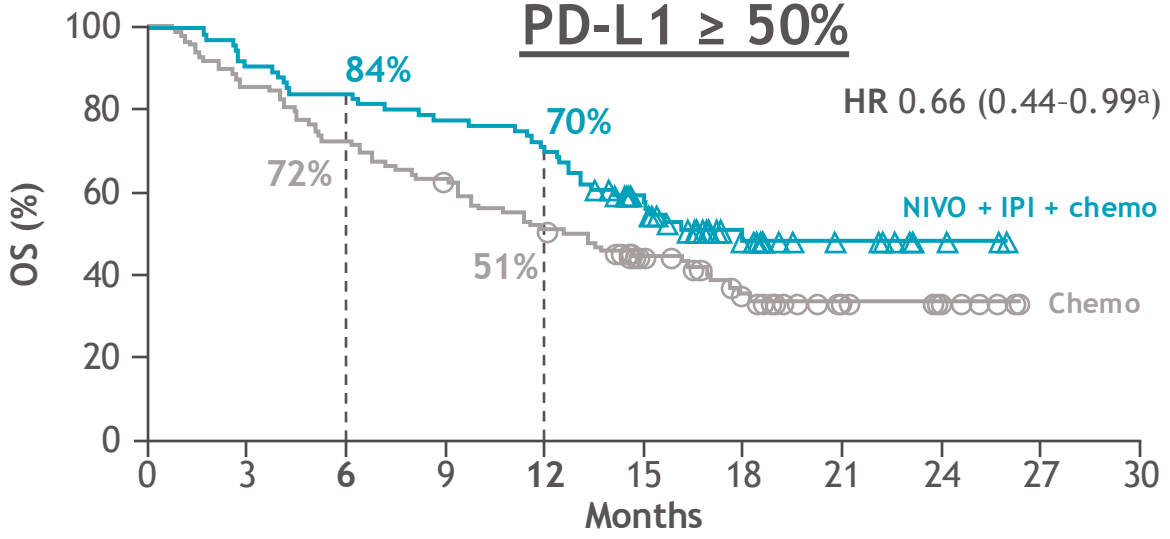
[a]Subsequent systemic therapy was received by 30% of patients in the NIVO + IPI + chemo arm and 39% of patients in the chemo arm; subsequent immunotherapy was received by 6% and 28%, and subsequent chemotherapy by 29% and 22%, respectively; [b]Subsequent systemic therapy was received by 31% of patients in the NIVO + IPI + chemo arm and 44% of patients in the chemo arm; subsequent immunotherapy was received by 4% and 35%, and subsequent chemotherapy by 30% and 24% of patients, respectively

Overall survival by PD-L1 expression level







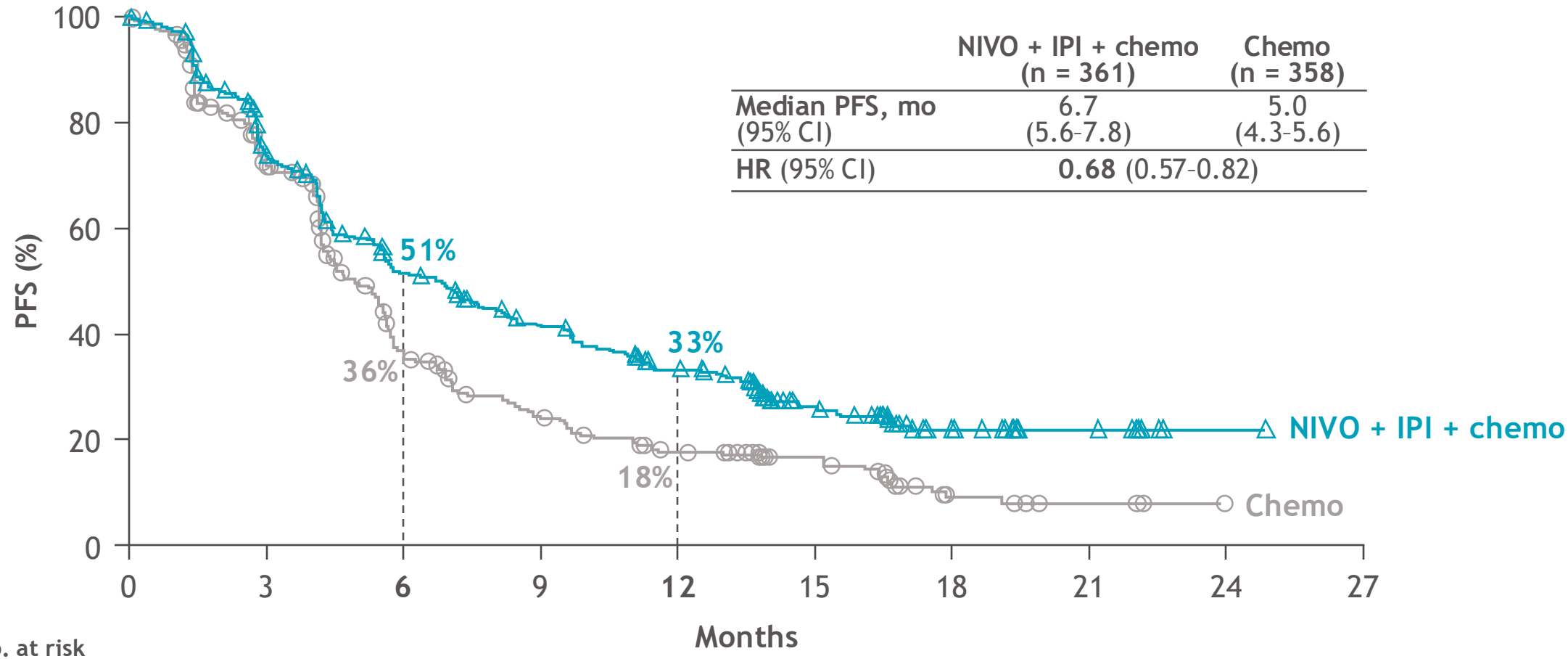


Minimum follow-up: 12.7 months.

[a]95% CI.

Progression-free survival per BICR[a]

	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
Median PFS, mo (95% CI)	6.7 (5.6–7.8)	5.0 (4.3–5.6)
HR (95% CI)	**0.68** (0.57–0.82)	



No. at risk									
NIVO + IPI + chemo	361	252	170	130	94	46	19	8	1	0
Chemo	358	230	103	66	43	29	7	3	0	0

Minimum follow-up: 12.2 months.

[a]Patients who did not progress or die were censored on the date of their last evaluable tumor assessment; those who did not have any study tumor assessments and did not die were censored on their date of randomization; patients without reported progression who went on to receive palliative local therapy or subsequent anti-cancer therapy were censored on the date of their last evaluable tumor assessment prior to starting either therapy.

Safety summary of TRAEs

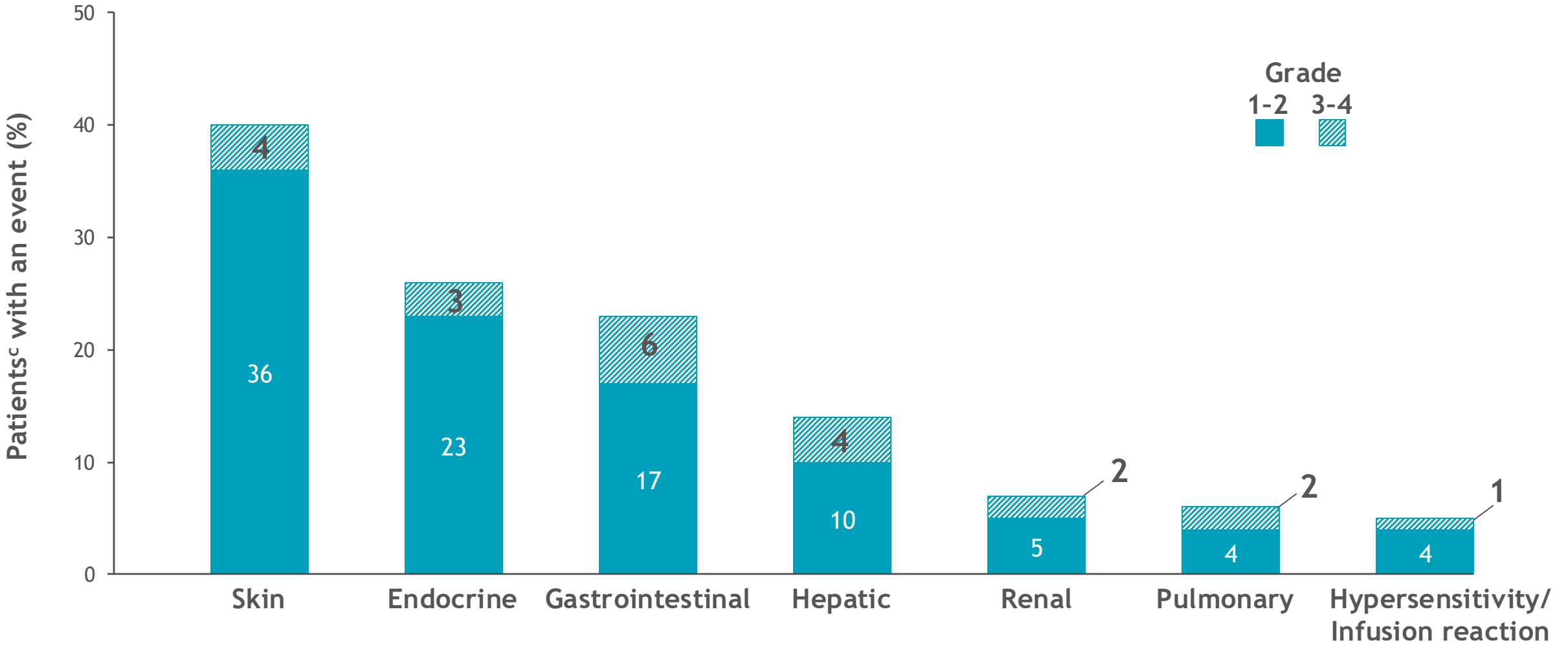
TRAE,[a] %	NIVO + IPI + chemo (n = 358)		Chemo (n = 349)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any TRAE	92	47	88	38
TRAEs leading to discontinuation of any component of the regimen	19	16	7	5
Serious TRAEs	30	25.4	18	15
Treatment-related deaths[b]	2		2	

- Median (range) duration of therapy was 6.1 (0–23.5) months and 2.4 (0–24.0) months for NIVO + IPI + chemo versus chemo, respectively
- Most common any-grade TRAEs (≥ 15%) were nausea, anemia, asthenia and diarrhea

Minimum follow-up: 12.2 months.

[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 = 7; 1 for each event) were due to acute renal failure due to chemotherapy, thrombocytopenia, pneumonitis, hepatic toxicity, hepatitis, diarrhea, sepsis, and acute renal insufficiency; treatment-related deaths in the chemo arm (n = 6; 1 for each event) were due to sepsis, anemia, pancytopenia, respiratory failure, pulmonary sepsis, and febrile neutropenia (1 grade 5 AE was reported [sudden death due to fall] as potentially treatment-related but cause of death was recorded as unknown).

Treatment-related select AEs with NIVO + IPI + chemo[a,b]



[a]Treatment-related select AEs are those with potential immunologic etiology that require frequent monitoring/intervention; [b]Includes events reported between first dose and 30 days after last dose of study drug; [c]The total number of patients treated with NIVO + IPI + chemo was 358.

Summary: NIVO + IPI + chemo in first-line advanced NSCLC

- CheckMate 9LA met its primary endpoint of OS at the pre-planned interim analysis (HR 0.69, *P* = 0.0006)
- Clinically meaningful improvement of all efficacy endpoints was observed and increased with longer follow-up
  - With a minimum follow-up of 12 months, OS benefit was further improved (HR 0.66)
- Magnitude of benefit with NIVO + IPI + 2 cycles of chemo vs chemo was consistent across histologies and all PD-L1 expression levels, including PD-L1 < 1% and 1-49% populations
- No new safety signals were observed for NIVO + IPI + 2 cycles of chemo
- With early separation of OS curves and lower PD rates as BOR, the hypothesis for CheckMate 9LA study design was validated
- CheckMate 9LA demonstrated that NIVO + IPI with a limited course of chemo should be considered as a new first-line treatment option for advanced NSCLC

Phase III KEYNOTE-189: First-line Platinum/Pemetrexed ± Pembrolizumab in Advanced NSCLC

Stratified by PD-L1 TPS (< 1% vs ≥ 1%), cisplatin vs carboplatin, smoking history (never vs former/current)

Patients with untreated stage IV nonsquamous NSCLC; *EGFR, ALK* neg; ECOG PS 0 or 1; any PD-L1 expression; no prior systemic treatment; no systematic brain metastases (N = 616)

2:1

Cisplatin 75 mg/m² or **Carboplatin AUC 5** + **Pemetrexed** 500 mg/m² + **Pembrolizumab** 200 mg Q3W for 4 cycles (n = 410)

→ **Maintenance**: **Pemetrexed** 500 mg/m² Q3W + **Pembrolizumab** 200 mg Q3W for up to a total of 35 cycles

Cisplatin 75 mg/m² or **Carboplatin AUC 5** + **Pemetrexed** 500 mg/m² + **Placebo** (normal saline) Q3W for 4 cycles (n = 206)

→ **Pemetrexed** 500 mg/m² + **Placebo** (normal saline) Q3W for up to a total of 35 cycles

PD ↓

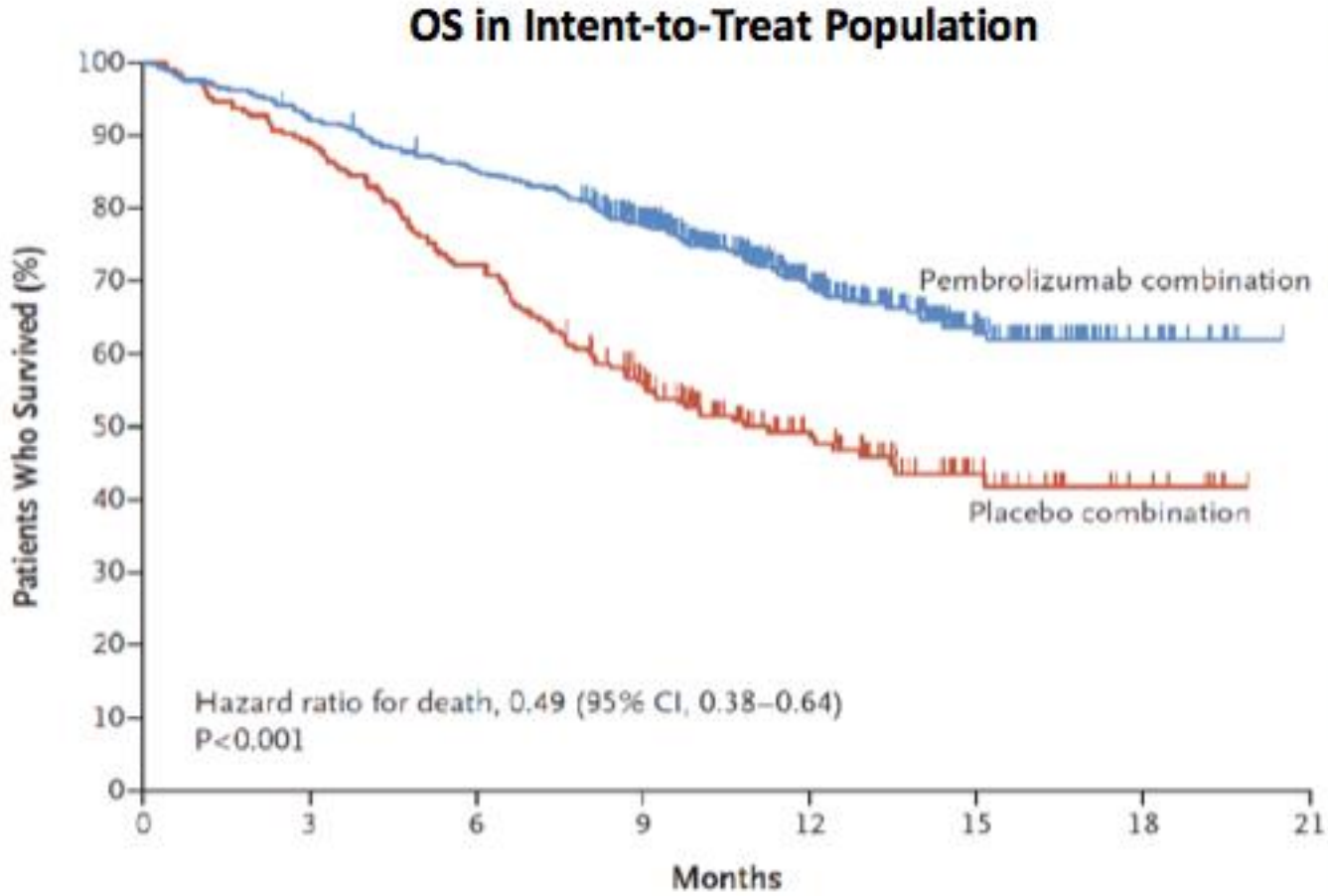
Pembrolizumab 200 mg Q3W for up to a total of 35 cycles

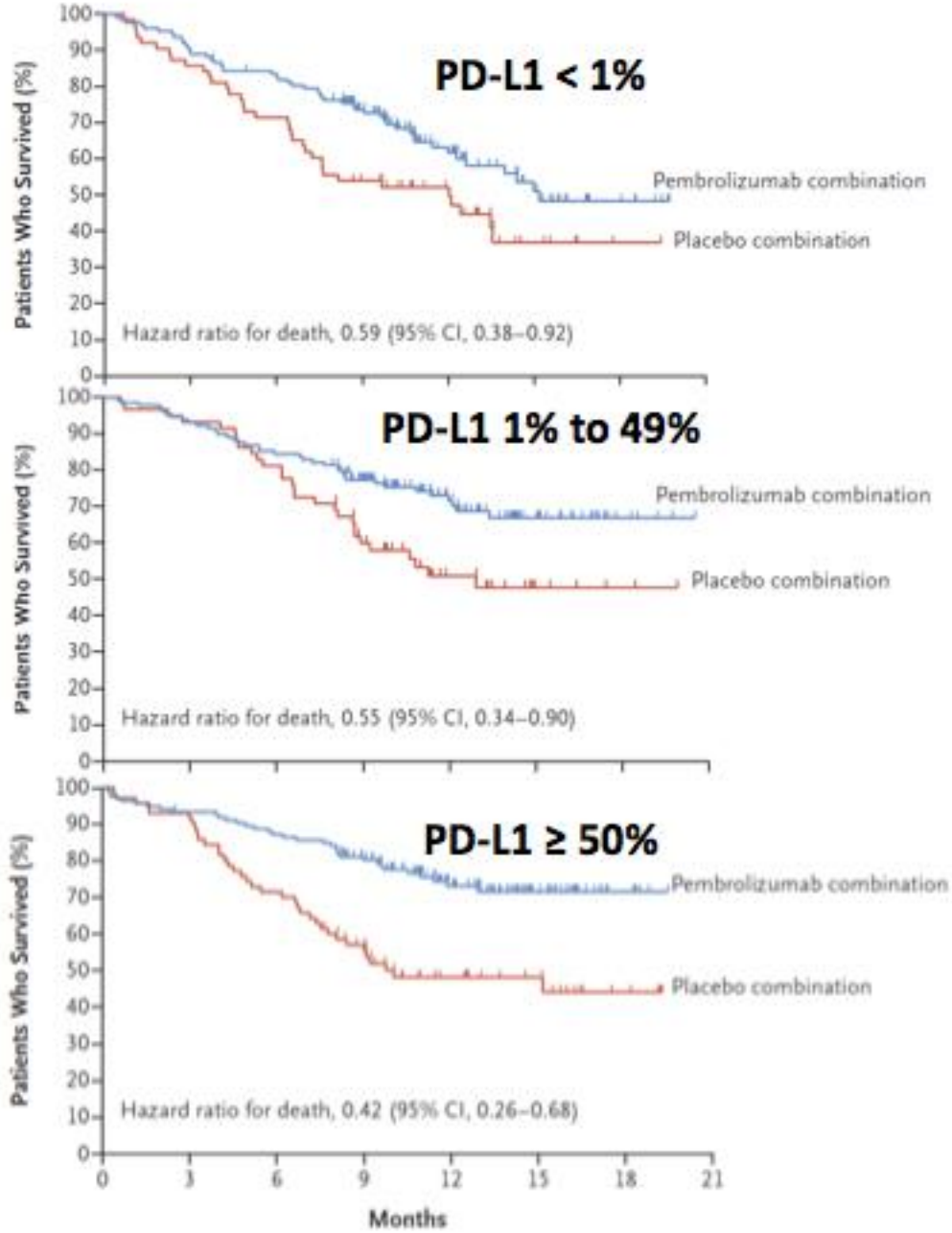
- Primary endpoints: PFS, OS
- Secondary endpoints: ORR, DoR, safety

Gandhi L, et al. N Engl J Med. 2018;[Epub ahead of print].

Slide credit: clinicaloptions.com

KEYNOTE-189: OS

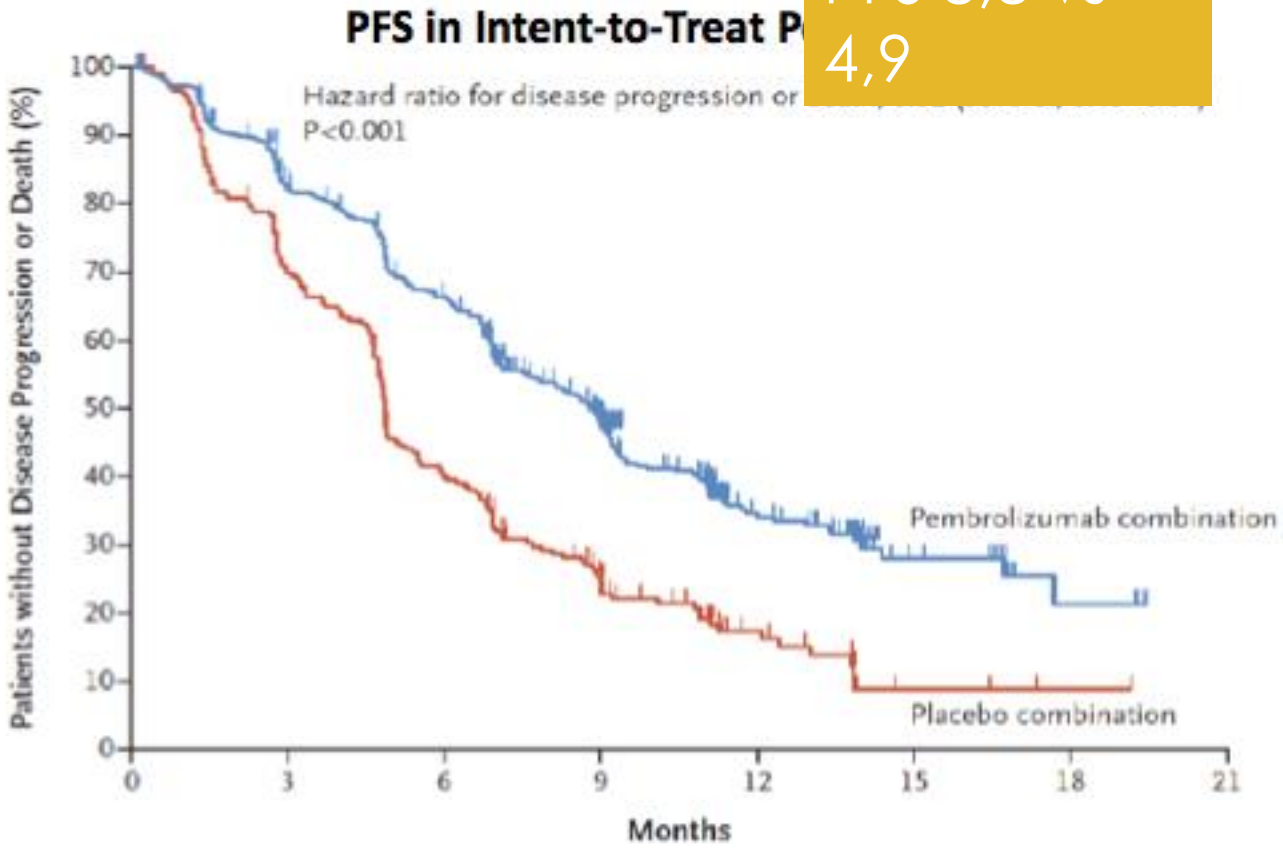


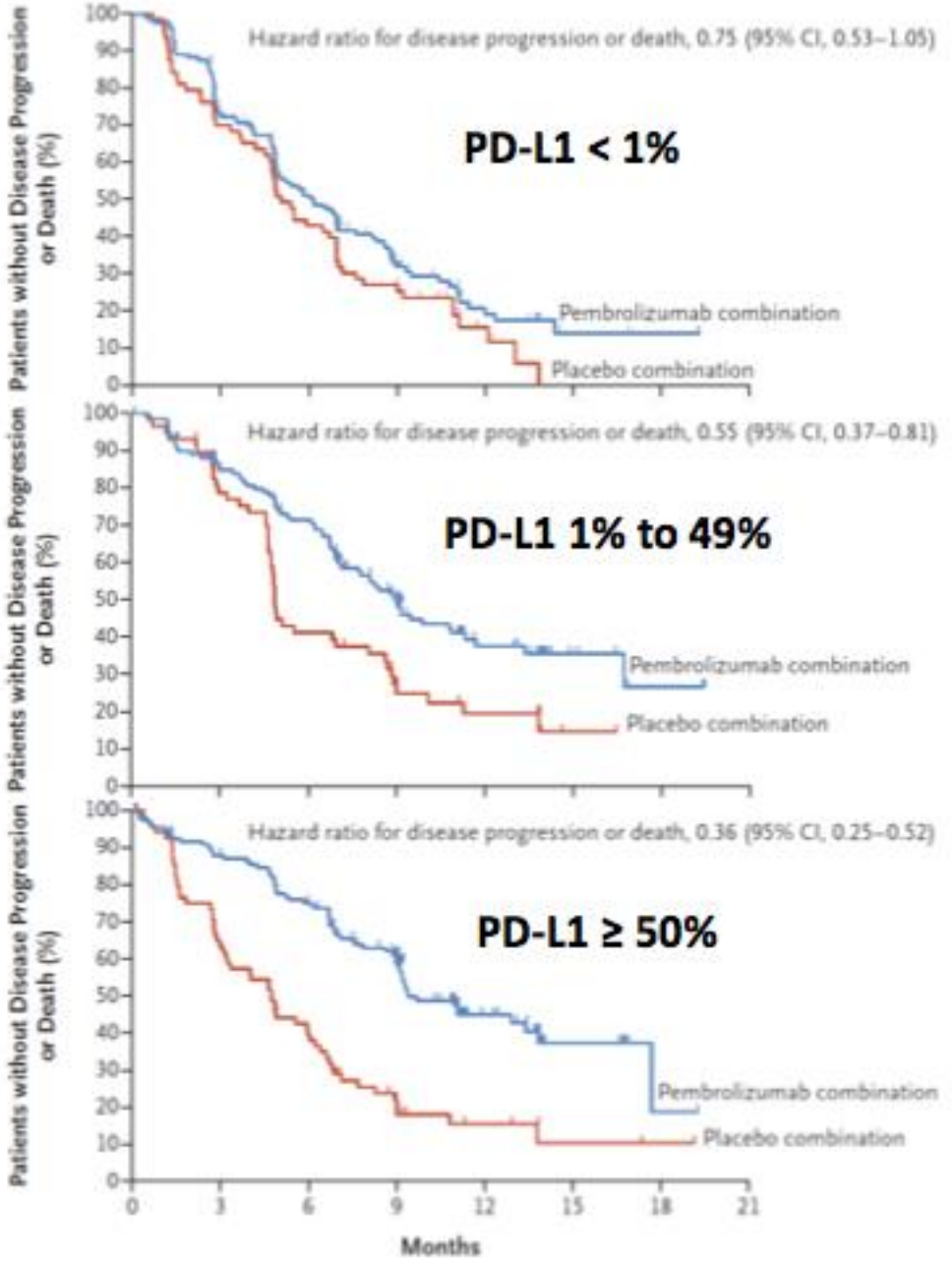


Gandhi L, et al. N Engl J Med. 2018;[Epub ahead of print].

KEYNOTE-189: PFS

PFS 8,8 vs 4,9





Gandhi L, et al. N Engl J Med. 2018;[Epub ahead of print].

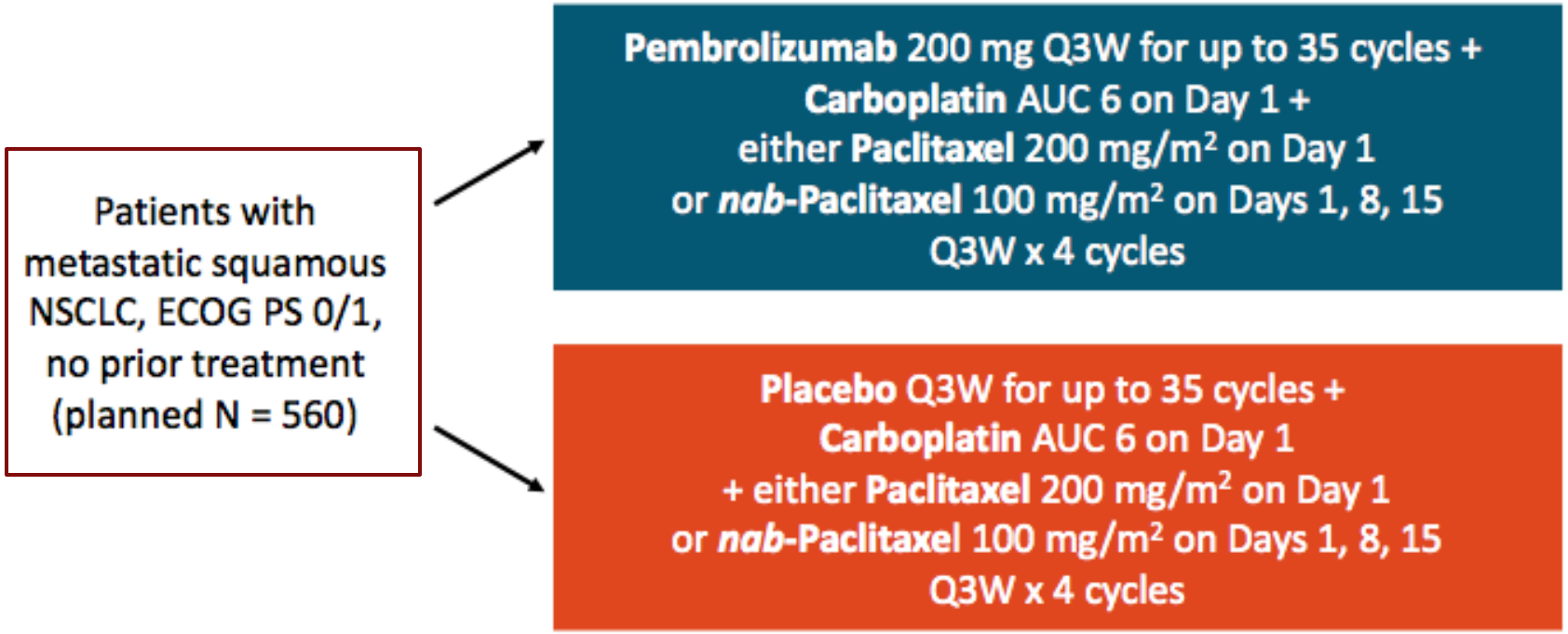
KEYNOTE-189: Adverse Events

Adverse Event, n (%)	Pembrolizumab/Pemetrexed/ Platinum (n = 405)	Placebo/Pembrolizumab/ Platinum (n = 202)
Any cause	404 (99.8)	200 (99.0)
▪ Grade 3-5	202 (67.2)	133 (65.8)
▪ Resulting in death	27 (6.7)	12 (5.9)
▪ Resulting in discontinuation of all treatment	56 (13.8)	16 (7.9)
▪ Resulting in discontinuation of any treatment	112 (27.7)	30 (14.9)
Immune mediated	92 (22.7)	24 (11.9)
▪ Grade 3-5	36 (8.9)	9 (4.5)
▪ Resulting in death	3 (0.7)	0

Gandhi L, et al. N Engl J Med. 2018;[Epub ahead of print].

Slide credit: clinicaloptions.com

Phase III KEYNOTE-407: First-line Chemotherapy ± Pembrolizumab in Metastatic, Squamous NSCLC



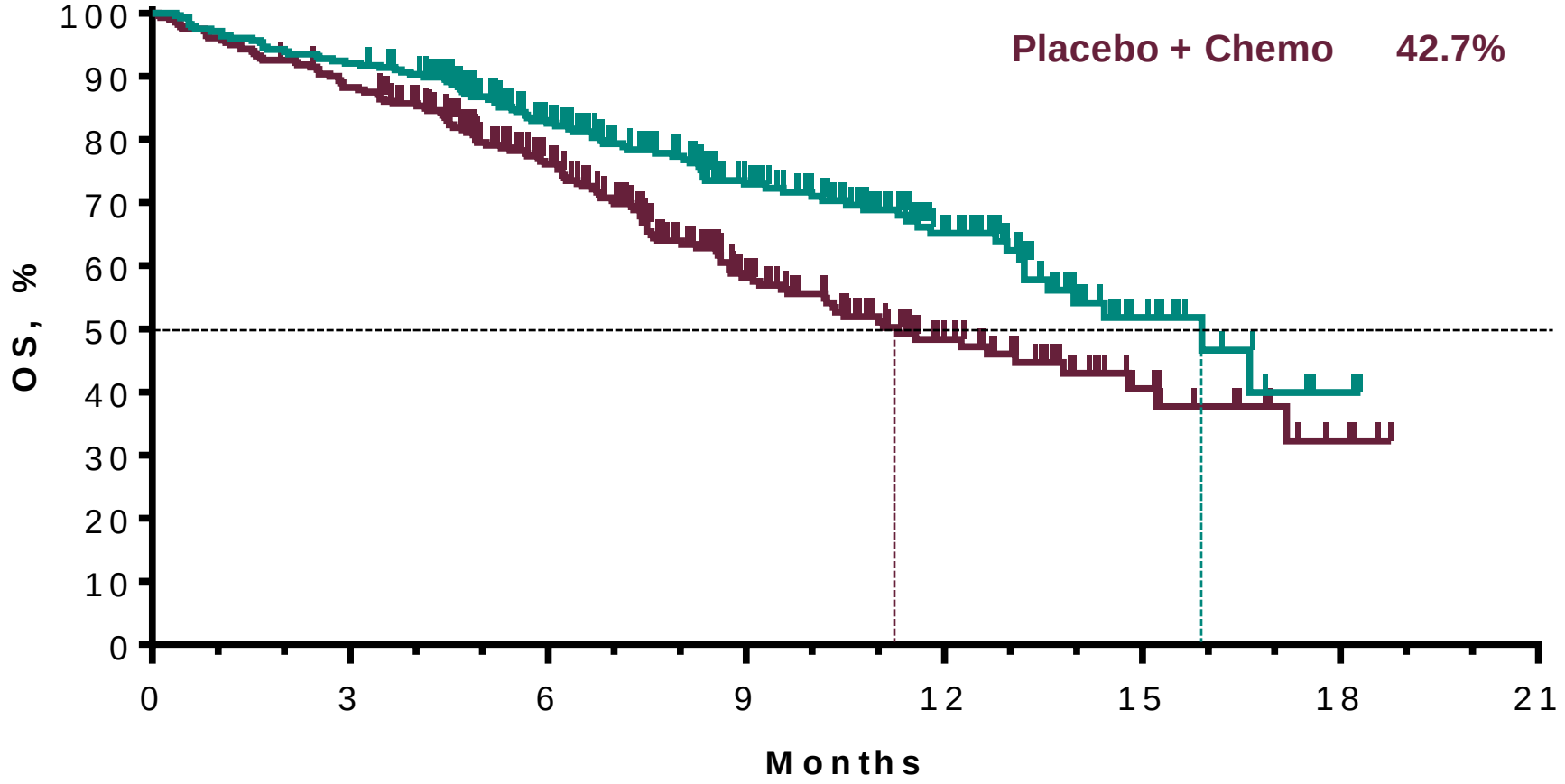
- Primary endpoints: PFS, OS
- Secondary endpoint: ORR

Paz-Ares LG, et al. ASCO 2018. Abstract 105.

Slide credit: clinicaloptions.com

Overall Survival at IA2, ITT

	Events	HR (95% CI)	*P*
Pembro + Chemo	30.6%	0.64 (0.49-0.85)	0.0008
Placebo + Chemo	42.7%		



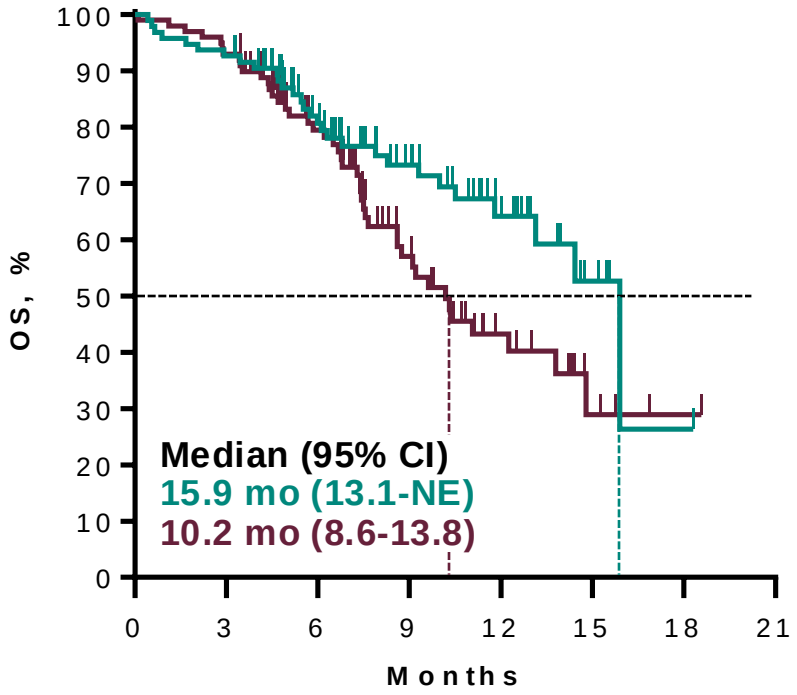
Median (95% CI)
15.9 mo (13.2-NE)
11.3 mo (9.5-14.8)

Data cutoff date: Apr 3, 2018.

Overall Survival at IA2 by PD-L1 TPS

TPS <1%

	Events	HR (95% CI)
Pembro + Chemo	30.5%	0.61 (0.38-0.98)
Placebo + Chemo	44.4%	

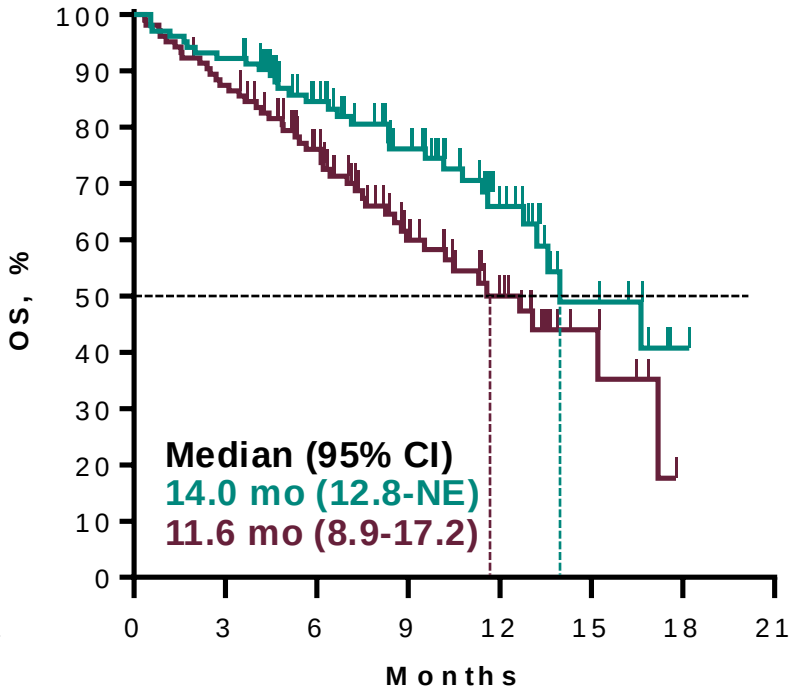


No. at Risk

95	88	62	41	20	5	1	0
99	92	63	32	14	4	1	0

TPS 1-49%

	Events	HR (95% CI)
Pembro + Chemo	30.1%	0.57 (0.36-0.90)
Placebo + Chemo	43.3%	

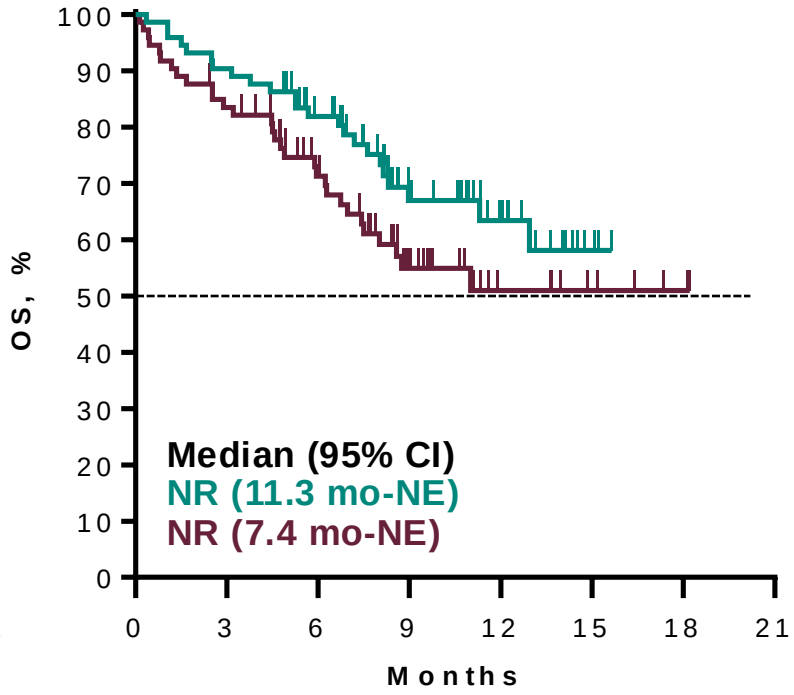


No. at Risk

103	95	68	50	25	9	1	0
104	90	66	37	21	6	0	0

TPS ≥50%

	Events	HR (95% CI)
Pembro + Chemo	31.5%	0.64 (0.37-1.10)
Placebo + Chemo	41.1%	



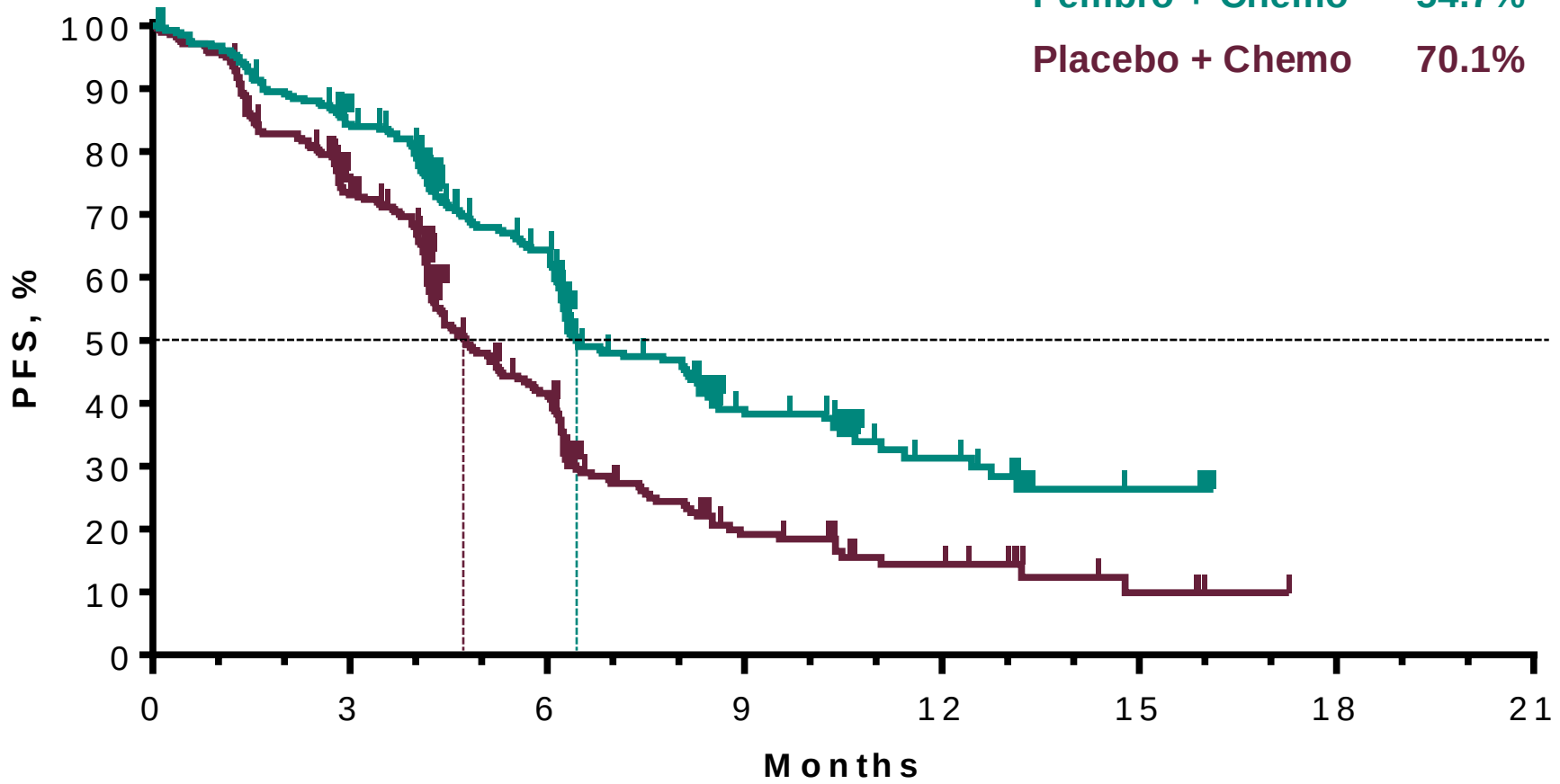
No. at Risk

73	66	53	28	15	3	0	0
73	60	42	21	9	5	2	0

Data cutoff date: Apr 3, 2018.

Progression-Free Survival at IA2, ITT (RECIST v1.1, BICR)

	Events	HR (95% CI)	*P*
Pembro + Chemo	54.7%	0.56 (0.45-0.70)	<0.0001
Placebo + Chemo	70.1%		



Median (95% CI)
6.4 mo (6.2-8.3)
4.8 mo (4.3-5.7)

No. at Risk

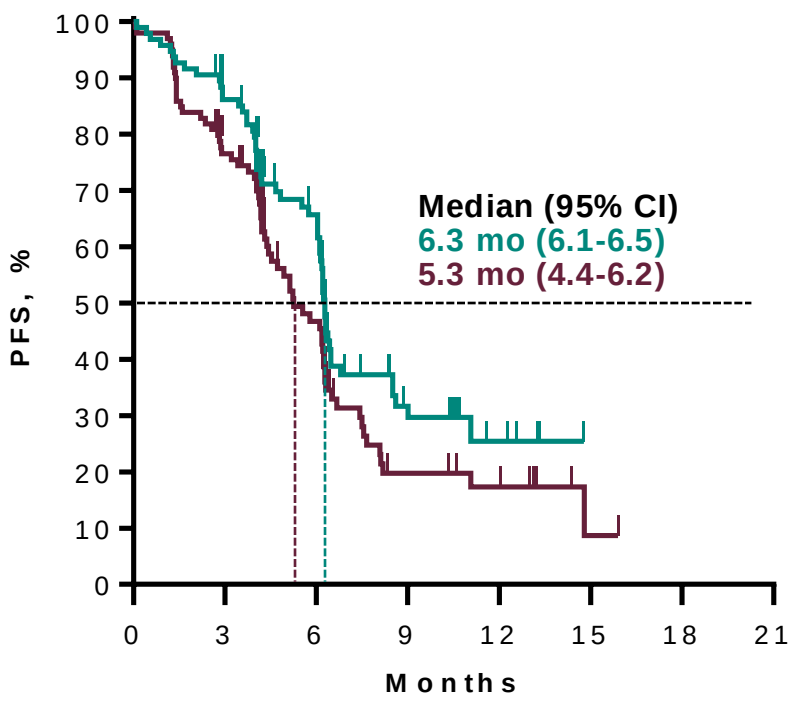
278	223	142	57	23	5	0	0
281	190	90	26	12	4	0	0

BICR, blinded, independent central review. Data cutoff date: Apr 3, 2018.

Progression-Free Survival by PD-L1 TPS (RECIST v1.1, BICR)

TPS <1%

	Events	HR (95% CI)
Pembro + Chemo	57.9%	0.68 (0.47-0.98)
Placebo + Chemo	67.7%	

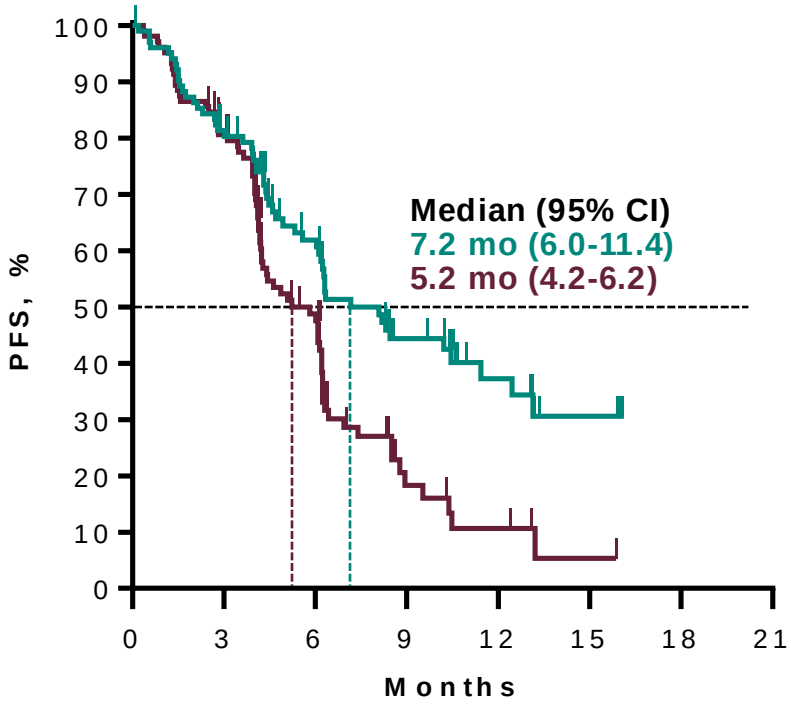


No. at Risk

95	78	48	16	5	0	0	0
99	71	35	11	6	1	0	0

TPS 1-49%

	Events	HR (95% CI)
Pembro + Chemo	52.4%	0.56 (0.39-0.80)
Placebo + Chemo	70.2%	

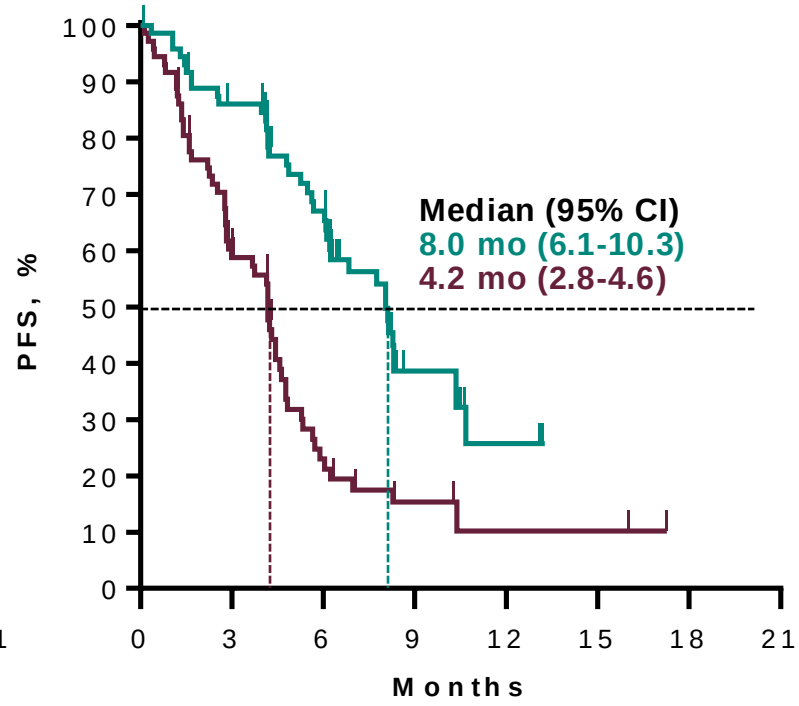


No. at Risk

103	79	49	26	13	5	0	0
104	79	40	8	4	1	0	0

TPS ≥50%

	Events	HR (95% CI)
Pembro + Chemo	53.4%	0.37 (0.24-0.58)
Placebo + Chemo	75.3%	



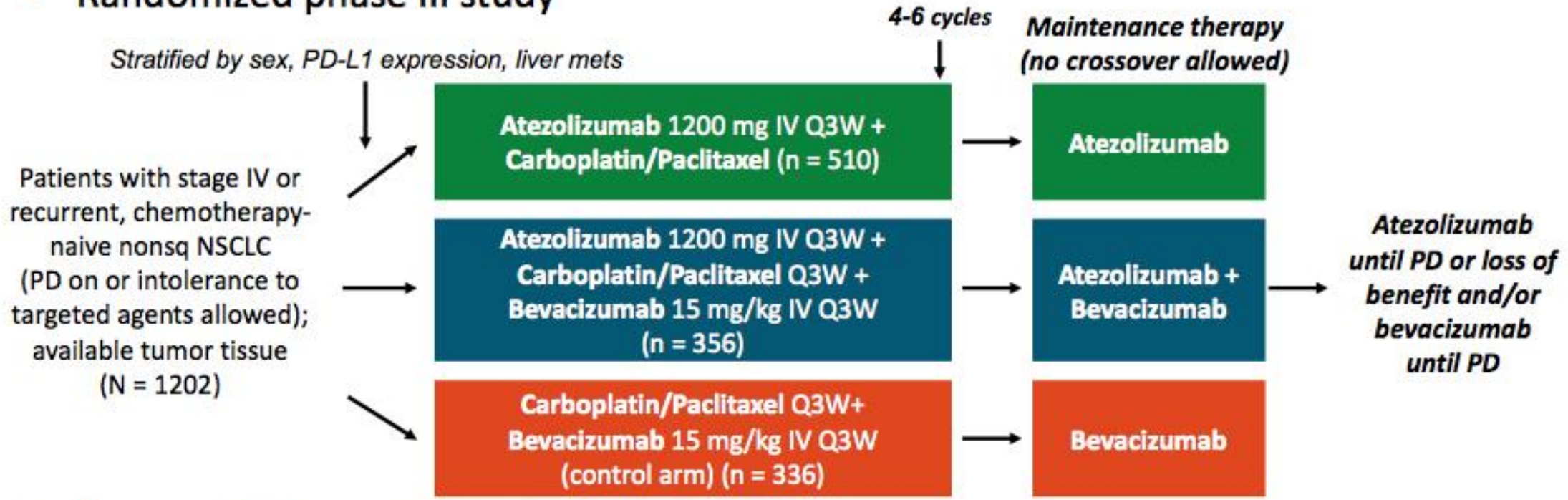
No. at Risk

73	60	41	12	4	0	0	0
73	38	13	5	2	2	0	0

BICR, blinded, independent central review. Data cutoff date: Apr 3, 2018.

IMpower150: Addition of Atezolizumab to Carbo/Pac + Bevacizumab in Advanced NSCLC

- Randomized phase III study



- Primary endpoints: PFS, OS
- Secondary endpoints: PFS (IRF), ORR, OS at Yrs 1 and 2, QoL, safety, PK

Reck M, et al. ESMO I-O Congress 2017. Abstract LBA1_PR.
Kowanetz M, et al. AACR 2018. Abstract CT076.

Slide credit: clinicaloptions.com

EMPOWER-Lung 3 (Part 2) Study Design (NCT03409614)

Background: Cemiplimab (a high-affinity, fully human anti–PD-1) is approved as first-line monotherapy for advanced NSCLC with PD-L1 ≥50% (EMPOWER-Lung 1 Study[1])

Key eligibility criteria
- Treatment-naive advanced NSCLC (non-squamous and squamous histology; Stage IIIb/c†, IV)
- Any PD-L1 expression
- No *EGFR*, *ALK*, or *ROS1* mutations
- ECOG PS 0 or 1
- Treated, clinically stable CNS metastases ‡

Stratification factors
- PD-L1 expression: <1% vs 1–49% vs ≥50%
- Histology: non-squamous vs squamous

Endpoints
- Primary: OS
- Key secondary: PFS and ORR
- Additional secondary: DOR, BOR, safety, and PRO

R 2:1

Arm A
Cemiplimab 350 mg Q3W + investigator's choice platinum-doublet chemo Q3W for 4 cycles§

Arm B
Placebo Q3W + investigator's choice platinum-doublet chemo Q3W for 4 cycles§

PD or 108 weeks

PD or 108 weeks

Follow-up

N=466

Two interim analyses were prespecified per protocol
Second interim analysis (14 June 2021) presented here

†Patient not a candidate for definitive chemoradiation. ‡Patient must have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment). §For patients with non-squamous NSCLC, pemetrexed is mandatory as maintenance therapy for those patients initially assigned to receive a pemetrexed-containing regimen. *ALK*, anaplastic lymphoma kinase gene; BOR, best overall response; chemo, chemotherapy; CNS, central nervous system; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor gene; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PRO, patient-reported outcomes; Q3W, every 3 weeks; R, randomised; *ROS1*, c-ros oncogene 1.

1. Sezer A et al. *Lancet* 2021;397:592–604.

Disposition and Baseline Characteristics

n	Cemiplimab + chemo (n=312)	Placebo + chemo (n=154)
Number of patients treated	312	153
Ongoing treatment	108	15
Discontinued treatment†	204	138
PD	137	100
Death‡	24	10
AE	14	4
Patient decision	13	7
Withdrew consent	8	3
Physician decision	4	1
Lost to follow-up	1	3

n (%), unless otherwise stated		Cemiplimab + chemo (n=312)	Placebo + chemo (n=154)	Total (n=466)
Age	Median (range), years	63.0 (25–82)	63.0 (34–84)	63.0 (25–84)
	≥65 year	128 (41.0)	60 (39.0)	188 (40.3)
Male		268 (85.9)	123 (79.9)	391 (83.9)
Histology	Non-squamous	179 (57.4)	87 (56.5)	266 (57.1)
	Squamous	133 (42.6)	67 (43.5)	200 (42.9)
PD-L1 expression	<1%	95 (30.4)	44 (28.6)	139 (29.8)
	1–49%	114 (36.5)	61 (39.6)	175 (37.6)
	≥50%	103 (33.0)	49 (31.8)	152 (32.6)
ECOG PS	0	51 (16.3)	18 (11.7)	69 (14.8)
	1	259 (83.0)	134 (87.0)	393 (84.3)
Brain metastases		24 (7.7)	7 (4.5)	31 (6.7)
Cancer stage at screening	Metastatic	267 (85.6)	130 (84.4)	397 (85.2)
	Locally advanced	45 (14.4)	24 (15.6)	69 (14.8)
Smoking history	Current smoker	173 (55.4)	75 (48.7)	248 (53.2)
	Past smoker	96 (30.8)	55 (35.7)	151 (32.4)
	Never smoked	43 (13.8)	24 (15.6)	67 (14.4)

†Median duration of exposure (range) was 38.45 (1.4–102.6) weeks for cemiplimab + chemo and 21.30 (0.6–95.0) weeks for placebo + chemo. ‡Only includes deaths that led to discontinuation of treatment; does not reflect overall death count.
AE, adverse event; chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; PD, progressive disease; PD-L1, programmed cell death-ligand 1.

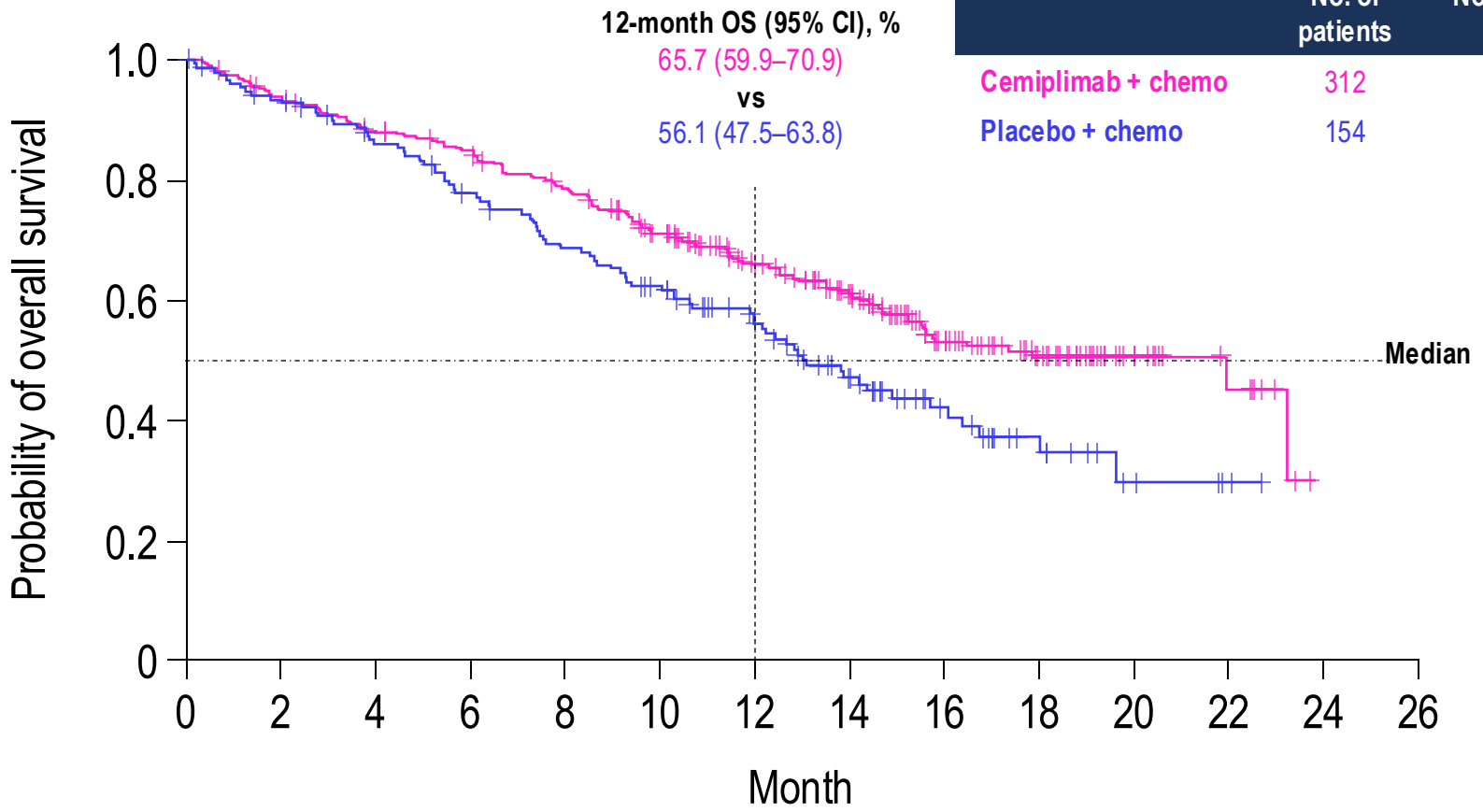
Data cut-off date: 14 June 2021

Overall Survival

Median duration of follow-up (range): 16.4 (8.5–24.0) months

	No. of patients	No. of events, n (%)	OS, median (95% CI), months
Cemiplimab + chemo	312	132 (42.3)	21.9 (15.5–NE)
Placebo + chemo	154	82 (53.2)	13.0 (11.9–16.1)

HR (95% CI) = 0.71 (0.53–0.93); *P*=0.014



No. at risk:

Cemiplimab + chemo	312	289	269	256	233	199	162	131	86	52	18	8	0	0
Placebo + chemo	154	141	126	112	98	85	65	46	26	14	5	2	0	0

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Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; OS, overall survival.

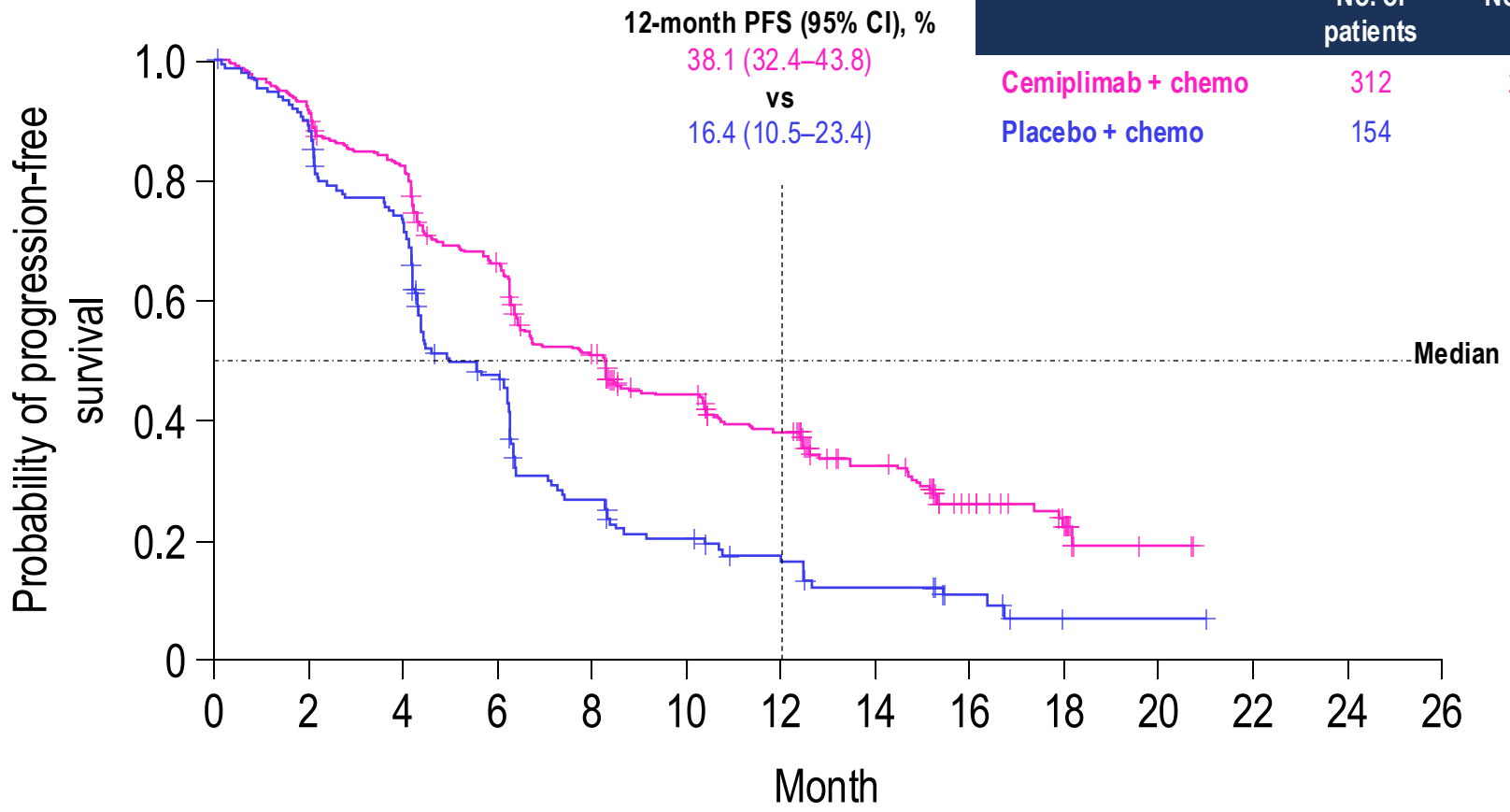
Data cut-off date: 14 June 2021

Progression-Free Survival

Median duration of follow-up (range): 16.4 (8.5–24.0) months

	No. of patients	No. of events, n (%)	PFS, median (95% CI), months
Cemiplimab + chemo	312	204 (65.4)	8.2 (6.4–9.3)
Placebo + chemo	154	122 (79.2)	5.0 (4.3–6.2)

HR (95% CI) = 0.56 (0.44–0.70); *P*<0.0001



No. at risk:

Cemiplimab + chemo	312	280	248	194	145	113	90	57	27	15	2	0	0
Placebo + chemo	154	133	106	64	34	24	16	11	6	1	1	0	0

Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Data cut-off date: 14 June 2021

Conclusions

- In patients with advanced NSCLC, 1L cemiplimab in combination with chemotherapy demonstrated clinically meaningful and statistically significant improvement in OS, PFS, ORR, and DOR versus chemotherapy alone.
  - OS (primary endpoint): median 21.9 vs 13.0 months; HR, 0.71 (95% CI, 0.53–0.93); *P*=0.014
  - PFS: median 8.2 vs 5.0 months; HR, 0.56 (95% CI, 0.44–0.70); *P*<0.0001
  - ORR: odds ratio, 2.68 (95% CI, 1.72–4.19); *P*<0.0001

- Cemiplimab in combination with chemotherapy demonstrated an acceptable benefit-risk profile, favourable PROs, low rates of AEs leading to discontinuation, and a safety profile generally consistent with those known for cemiplimab and for platinum-based chemotherapy.

- Cemiplimab in combination with platinum-doublet chemotherapy is a new 1L treatment option for patients with advanced NSCLC without targetable mutations irrespective of histology and PD-L1 levels.

1L, first-line; AE, adverse event; CI, confidence interval; DOR, duration of response; HR, hazard ratio; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; PRO, patient-reported outcomes; vs, versus.

Viktbaserad dosering av Nivolumab och Pembrolizumab

- Baseras på initiala studier av dessa läkemedel i andra/tredje linjen singelterapi
- Dosering:
- Nivolumab 4.5 mg/kg 3 veckors regim
- Pembrolizumab 2 mg/kg 3 veckors regim

- palliativ/kurativ indikation
- Avrundning till hel och/eller halv ampull

Adenocarcinom Andra linjens behandling

- Om Cyto+Immun i 1:a
  - Docetaxel,
  - Pemetrexed,
  - Vinorelbin,
  - Gemcitabine
  - Nab-Paclitaxel
- Om Cyto i 1:a
  - Immun (om PDL1 1% eller mer)
  - Cyto; (om PDL1<1%) Docetaxel, Vinorelbin, Gemcitabine, Nab-Pac

Skivepitel Andra linjen

- Om Cyto+Immun i 1:a
  - Docetaxel
  - Gemcitabine
  - Vinorelbine
  - Nab-paclitaxel
- Om Cyto i 1:a
  - Immun; Nivo, Atezo
  - Cyto; Docetaxel, Vinorelbin, Nab-paclitaxel

NSCLC Tredje linjen

- Cyto alt Immun som inte givits tidigare

NSCLC Progress CNS metastaser

- Om Radioterapi givits tidigare

- Temozolomide