Update of immunotherapy in Lung Cancer

何肇基醫師

臺大醫院

Disclosure

- Grants: AstraZeneca (#ISSIRES0105)
- Honorarium for speech or participated in compensated advisory board: Boehringer Ingelheim, Eli Lilly, Roche/Genentech/Chugai, MSD, Pfizer, Novartis, BMS and Ono pharmaceutical.

Potential IO treatment approaches for patients with different PD-L1 expression

			Adenocarcinoma, large cell, NSCLC NOS				Squamous		
Combination Type	**Trial**	**Regimen**	**≥ 50%**	**1-49%**	**< 1%**		**≥ 50%**	**1-49%**	**< 1%**
CIT Mono	IMpower110	Atezolizumab	✓				✓		
	Keynote 024 Keynote 042	Pembrolizumab	✓	○			✓	○	
CIT + CIT	CM-227	Nivo+Ipi	○	○	○		○	○	
CIT + Chemo	IMpower130	Atezo + carbo + nab-pac	✓	✓	✓				
	KN-189	Pembro+carbo/Cis+Pem	✓	✓	✓				
	KN-407	Pembro+Carbo+(Nab)-pac					✓	✓	✓
CIT+ anti-VEGF+ Chemo	IMpower150	Atezo+carbo+pac+beva	✓	✓	✓				
CIT + CIT + Chemo	CM-9LA	Nivo+Ipi+pem+Carbo/cis	✓	✓	✓				
		Nivo+Ipi+pac+carbo					✓	✓	✓

✓ **Recommend** ○ **Useful in certain circumstances**

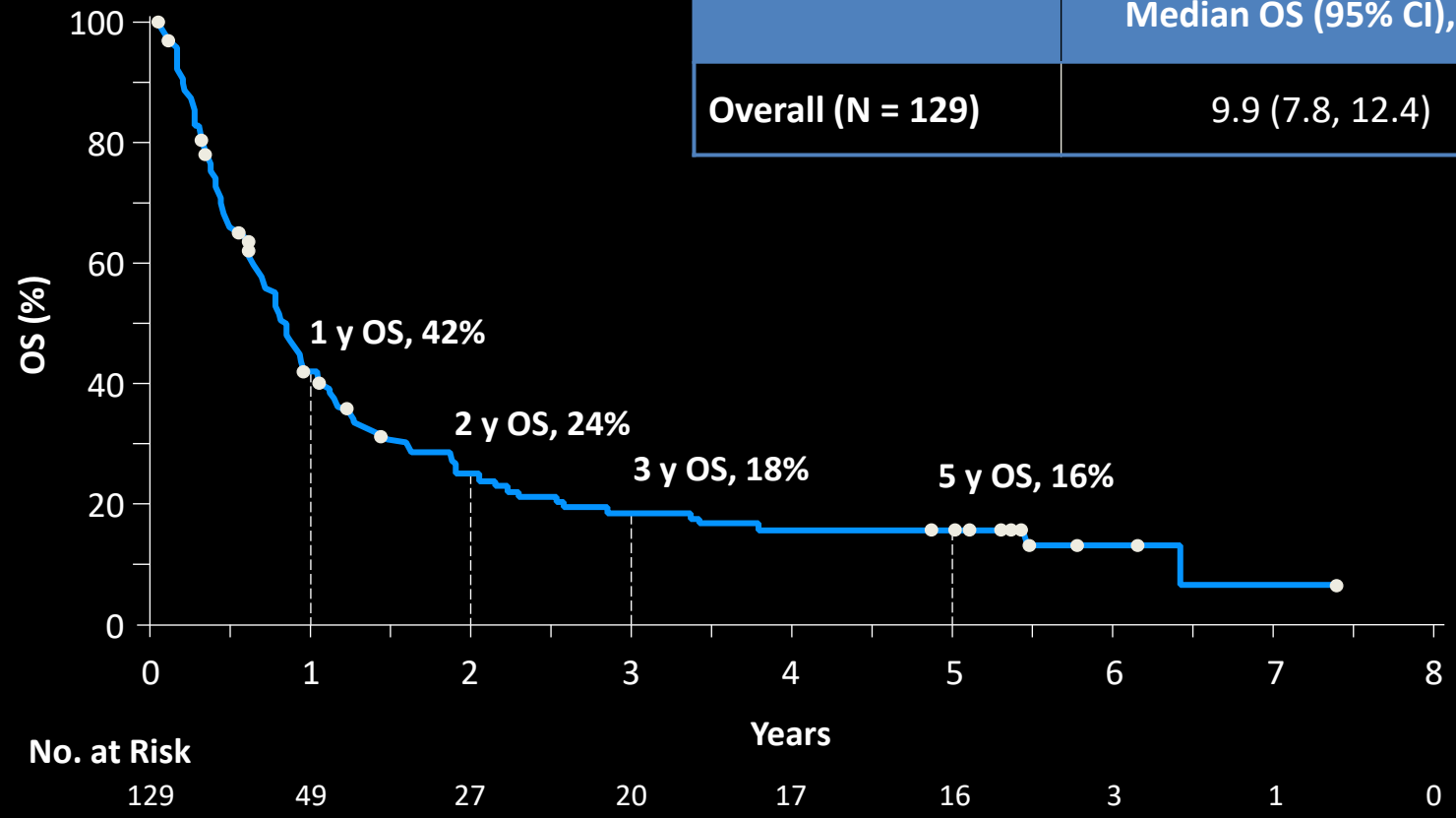
NCCN guideline v1 2021

Clinical Trial Endpoints

- **Overall Survival (OS): Gold standard** in oncology clinical trials esp. in immunotherapy
- **Progression-Free Survival (PFS)**
- **Overall Response Rate (ORR)**
- **Duration of Response (DoR)**: The length of time that a tumor continues to response to a drug without the cancer growing or spreading

Phase 1 Nivolumab in Advanced NSCLC (CA209-003): Long tail (Long DoR)

	Median OS (95% CI), mo
Overall (N = 129)	9.9 (7.8, 12.4)



[a]There were 3 deaths between 3 and 5 years, all due to disease progression; 1 surviving patient was censored for OS prior to 5 years (OS: 58.2+ months)

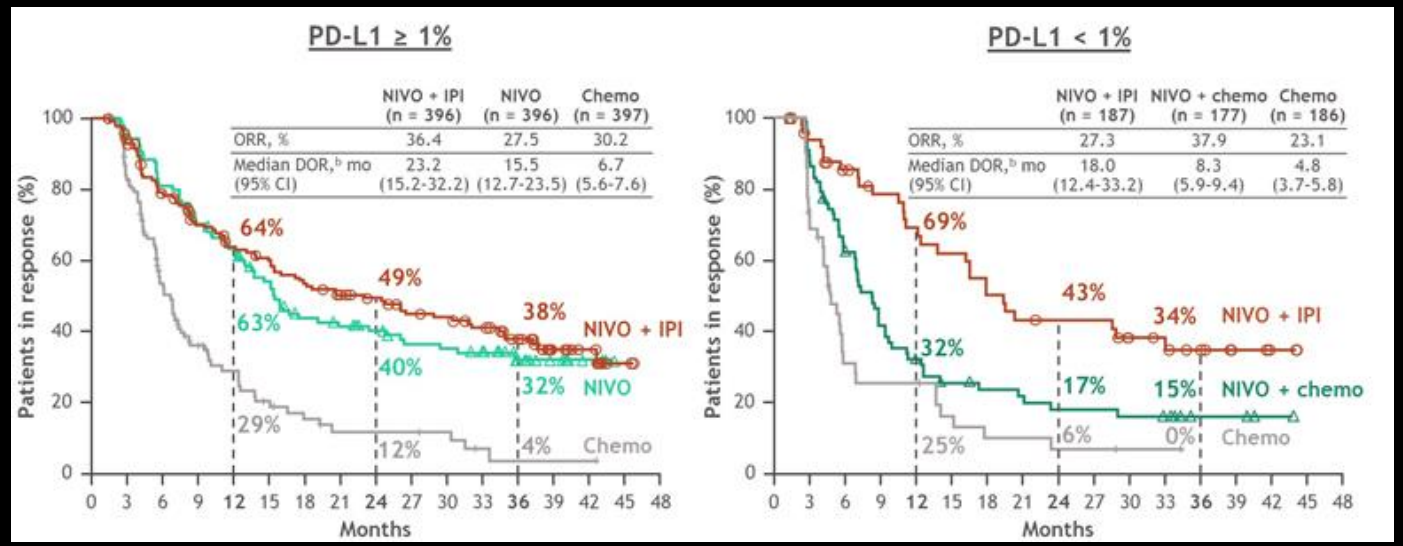
DoR is longer in IO, IO + IO but not in IO + Chemo

Trial	KN-024 Pembro	EMPOWER-Lung 1	KN-189 Carbo/Pem/ Pembro	KN-407 Carbo/Tax/P embro	IMpower150 Carbo/Pacli/ Bev/Atezo	Checkmate 227 part-1 Nivo/Ipi	Checkmate 227 part-1 Nivo/Ipi	Checkmate 9LA Nivo/Ipi/Ch emo
N	305	710	410	278	356	793	373	719
PD-L1	≥ 50%	≥ 50%	Any	Any	Any	≥ 1%	<1%	Any
mDOR	29.1 vs 6.3	21.0 vs 6.0	11.2 vs. 7.8	7.7 vs. 4.8	10.8 vs. 6.5	23.2 vs. 6.2	18.0 vs. 4.8	11.5 vs. 5.6

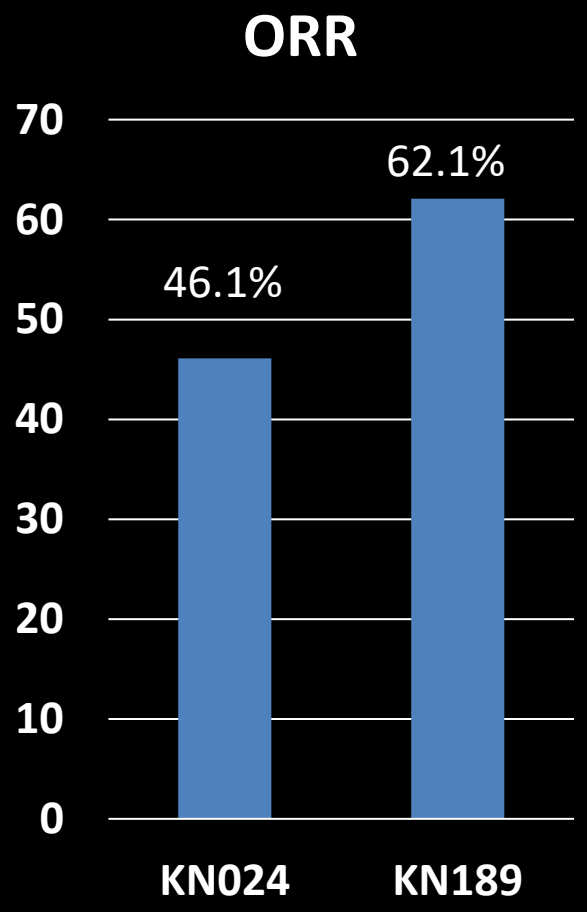
KeyNote 024

	Pembrolizumab N = 154	Chemotherapy N = 151
Objective response, n (%)	71 (46.1)	47 (31.1)
Best objective response, n (%)		
Complete response	7 (4.5)	0
Partial response	64 (41.6)	47 (31.1)
Stable disease	37 (24.0)	60 (39.7)
Progressive disease	35 (22.7)	25 (16.6)
Not evaluable	0	1 (0.7)
No assessment	11 (7.1)	18 (11.9)
Time to response, median (range), M	2.1 (1.4–14.6)	2.1 (1.1–12.2)
DOR, median (range), mo	29.1 (2.2–60.8+)	6.3 (3.1–52.4)

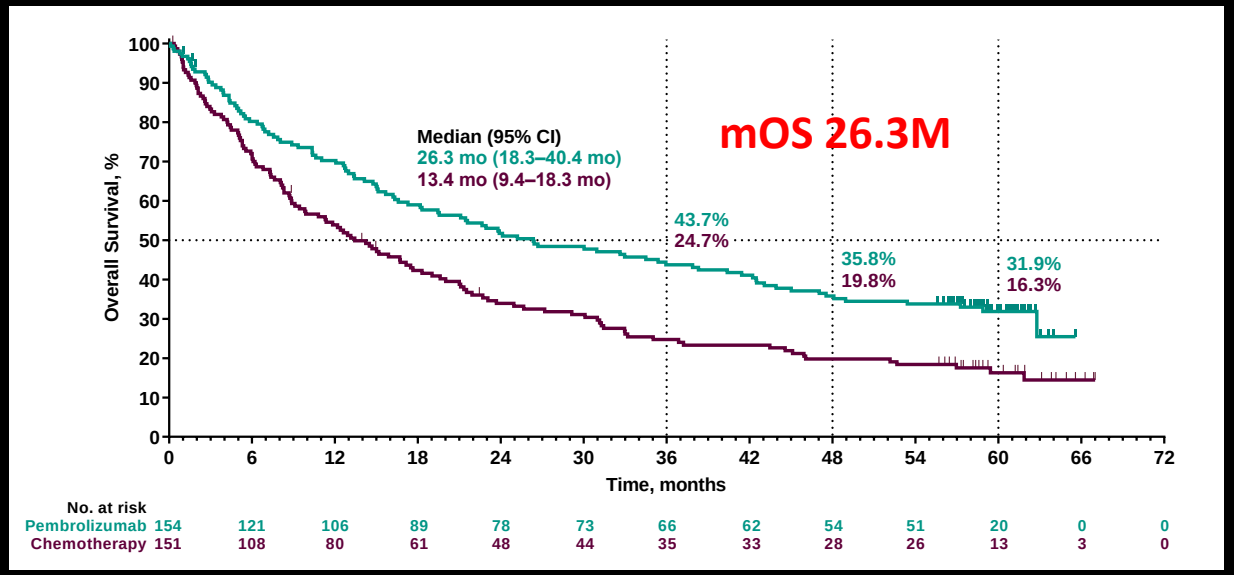
Checkmate 227



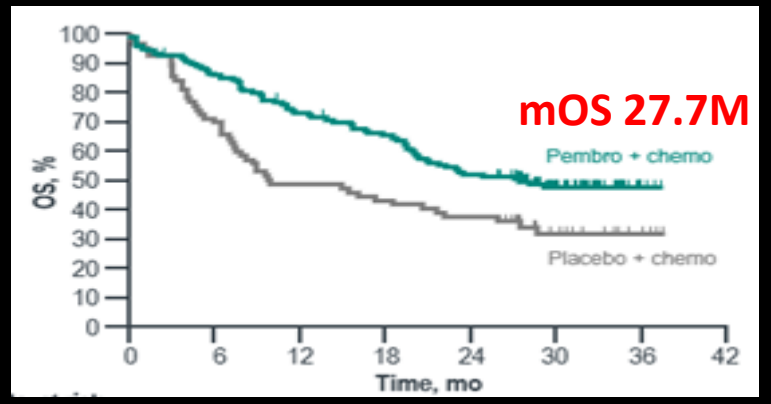
IO vs. IO + Chemo in PD-L1 ≥ 50%: Different ORR but similar OS



KN 024



KN 189



Longer OS:
Contribution by IO DoR?

It is no intention to promote.

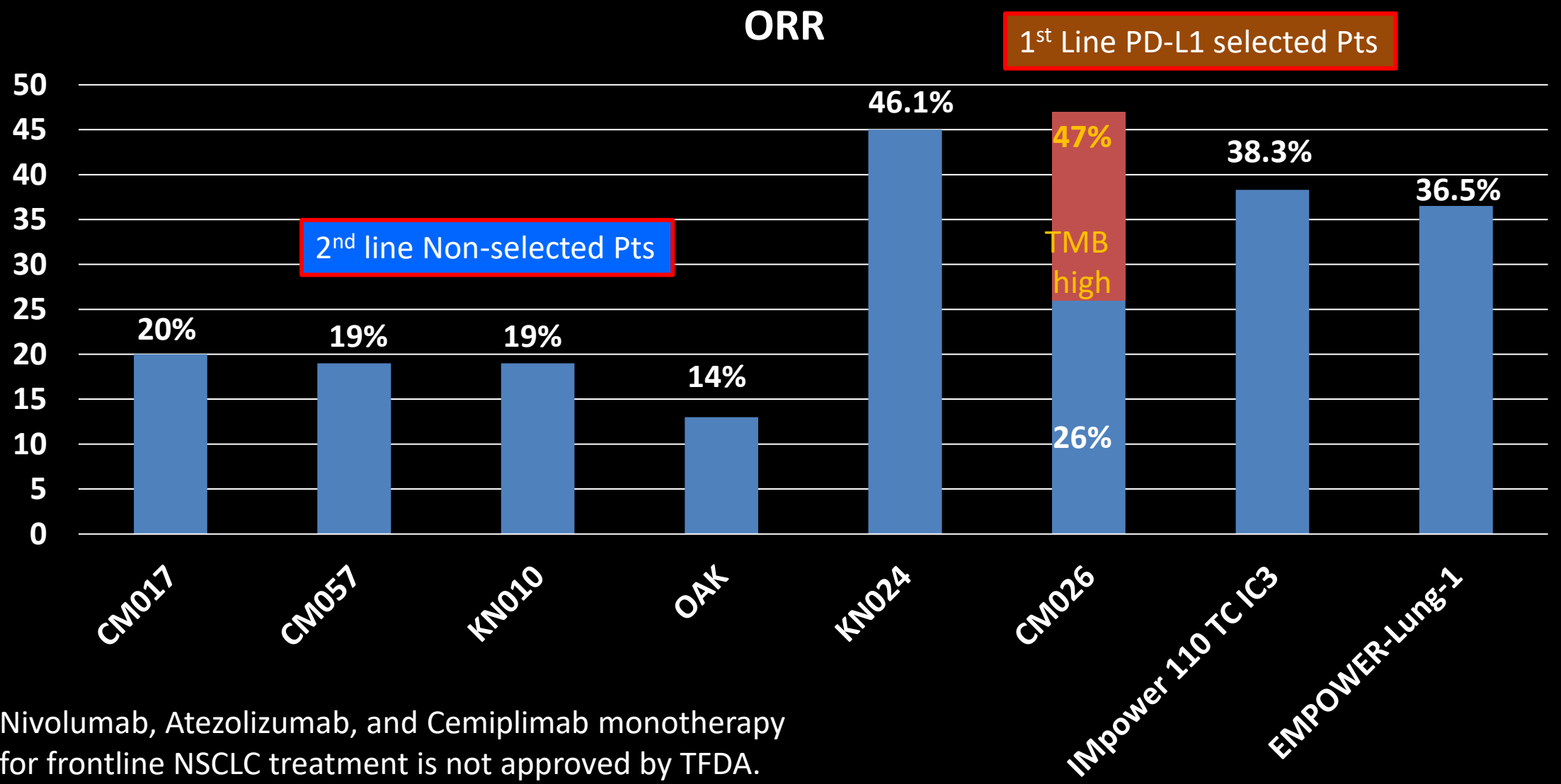
Brahmer, J et al. KN-024 Draft. ESMO 2020
Rodríguez-Abreu KN189 ASCO 2020

In PD-L1 ≥ 50%

IO Plus Chemo = IO followed by Chemo

Additive effect 1 + 1 = 2

ICI monotherapy ORR



Nivolumab, Atezolizumab, and Cemiplimab monotherapy for frontline NSCLC treatment is not approved by TFDA. It is no intention to promote.

IMpower110: a randomised, phase III, multicentre study

Stage IV non-squamous or squamous NSCLC
Chemotherapy naïve
PD-L1 selected*
***EGFR/ALK* negative**
Stratification factors:
- **Sex**
- **ECOG PS**
- **Histology**
- **PD-L1 IHC expression‡**

N=572§

R 1:1

Atezolizumab 1200 mg q3w → **Atezolizumab** 1200 mg q3w → **PD or loss of clinical benefit****

NON-SQUAMOUS: Carboplatin or cisplatin + pemetrexed¶ → **NON-SQUAMOUS: pemetrexed** → **PD‡‡**

SQUAMOUS: Carboplatin or cisplatin + gemcitabine‖ → **SQUAMOUS: Best Supportive Care**

Survival follow-up

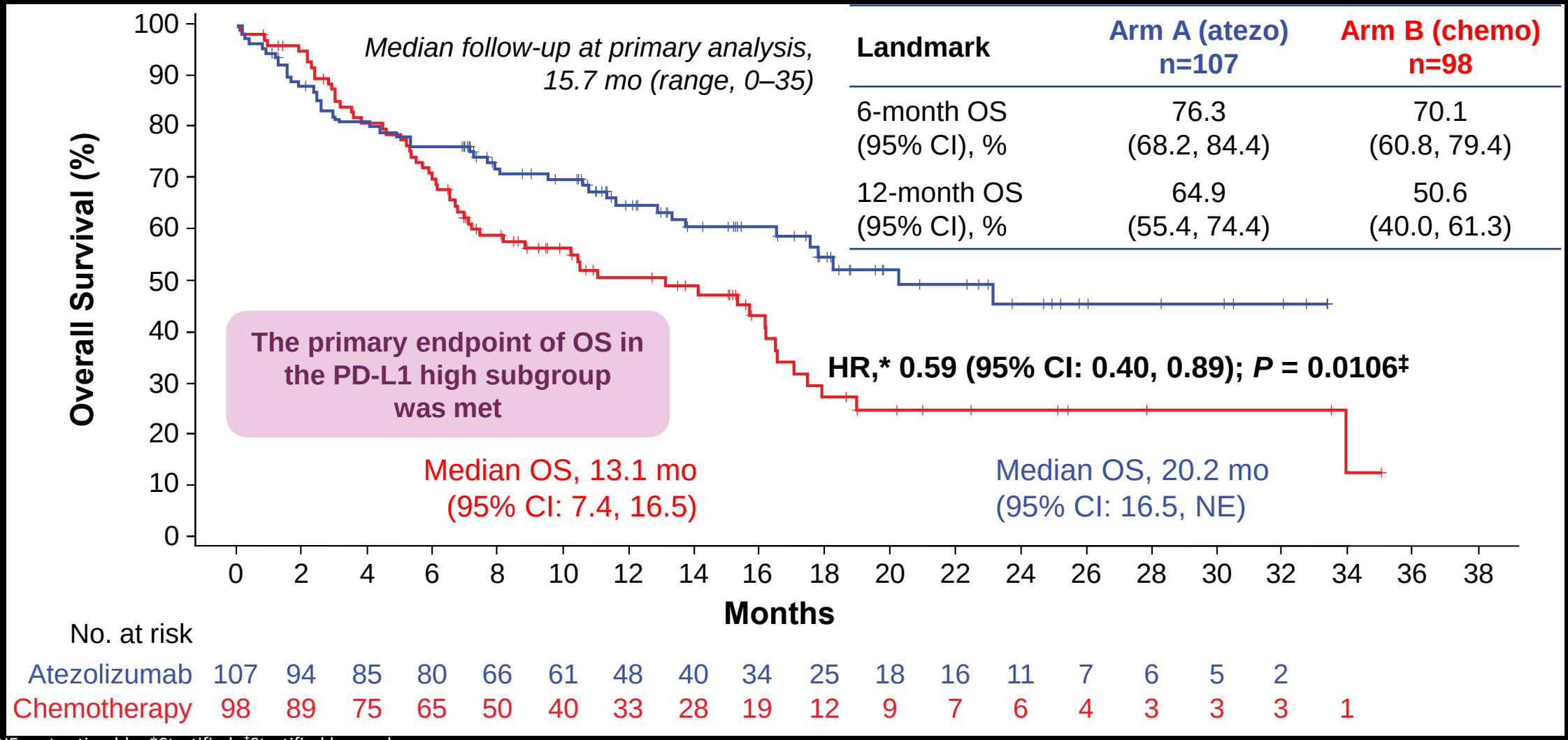
Primary endpoint: OS in WT population (excluding patients with *EGFR*+/*ALK*+ NSCLC)

Key secondary endpoints: investigator-assessed PFS, ORR and DOR (per RECIST version 1.1)

*PD-L1 positive defined as TC1/2/3 or IC1/2/3 (PD-L1 expression ≥1% on TC or IC), with tumour PD-L1 expression determined by IHC assay (VENTANA SP142 IHC assay) performed by a central laboratory; ‡TC1/2/3 and any IC vs TC0 and IC1/2/3; §554 patients in the WT population; ¶Cisplatin 75 mg/m^2 or carboplatin area under the curve (AUC) 6 + pemetrexed 500 mg/m^2 IV q3w; ‖Cisplatin 75 mg/m^2 + gemcitabine 1250 mg/m^2 or carboplatin AUC 5 + gemcitabine 1000 mg/m^2 IV q3w; **Defined as any of the following: signs or symptoms of PD; decline in ECOG PS; progression at critical anatomical sites that cannot be managed by permitted medical interventions; ‡‡By RECIST v1.1

- Spigel, et al. ESMO 2019 (Abs LBA78)

IMpower110: OS in the TC3/IC3 population



Landmark	Arm A (atezo) n=107	Arm B (chemo) n=98
6-month OS (95% CI), %	76.3 (68.2, 84.4)	70.1 (60.8, 79.4)
12-month OS (95% CI), %	64.9 (55.4, 74.4)	50.6 (40.0, 61.3)

NE, not estimable; *Stratified; ‡Stratified log-rank

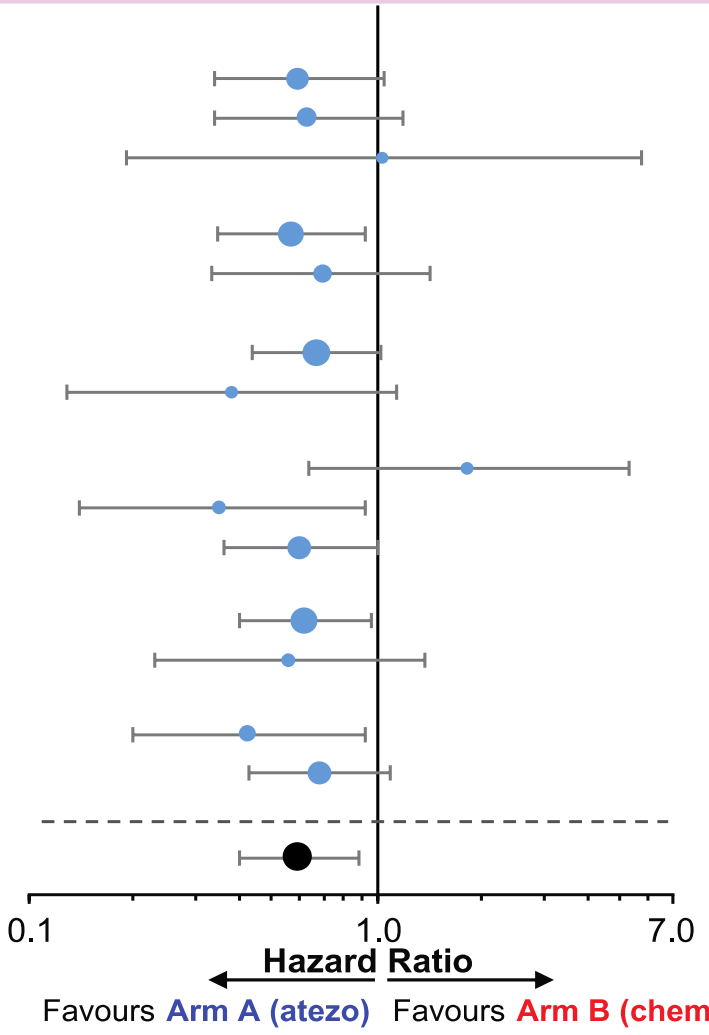
Data cut-off: 10 September 2018

- Spigel, et al. ESMO 2019 (Abs LBA78)

IMpower110: OS in key subgroups (TC3/IC3-WT population)

OS benefit observed in all clinically relevant subgroups

Subgroup*	n (%)	OS HR (95% CI)‡	Median OS, mo	
			Arm A	Arm B
< 65 years	102 (49.8)	0.59 (0.34, 1.04)	NE	13.1
65-74 years	80 (39.0)	0.63 (0.34, 1.19)	17.8	10.4
75-84 years	22 (10.7)	1.04 (0.19, 5.70)	NE	16.2
Male	143 (69.8)	0.57 (0.35, 0.93)	23.1	13.1
Female	62 (30.2)	0.69 (0.34, 1.39)	17.8	14.1
White	169 (82.4)	0.67 (0.44, 1.03)	17.8	13.1
Asian	35 (17.1)	0.38 (0.13, 1.13)	NE	14.1
Never used tobacco	24 (11.7)	1.83 (0.63, 5.31)	8.0	15.9
Current tobacco user	49 (23.9)	0.35 (0.14, 0.88)	NE	10.2
Previous tobacco user	132 (64.4)	0.60 (0.36, 1.00)	23.1	13.1
Non-squamous histology	155 (75.6)	0.62 (0.40, 0.96)	20.2	10.5
Squamous histology	50 (24.4)	0.56 (0.23, 1.37)	NE	15.3
ECOG PS 0	73 (35.6)	0.42 (0.20, 0.92)	NE	15.7
ECOG PS 1	132 (64.4)	0.69 (0.43, 1.10)	16.5	13.1
All TC3 or IC3 WT patients	**205 (100)**	**0.59 (0.40, 0.89)**§	**20.2**	**13.1**

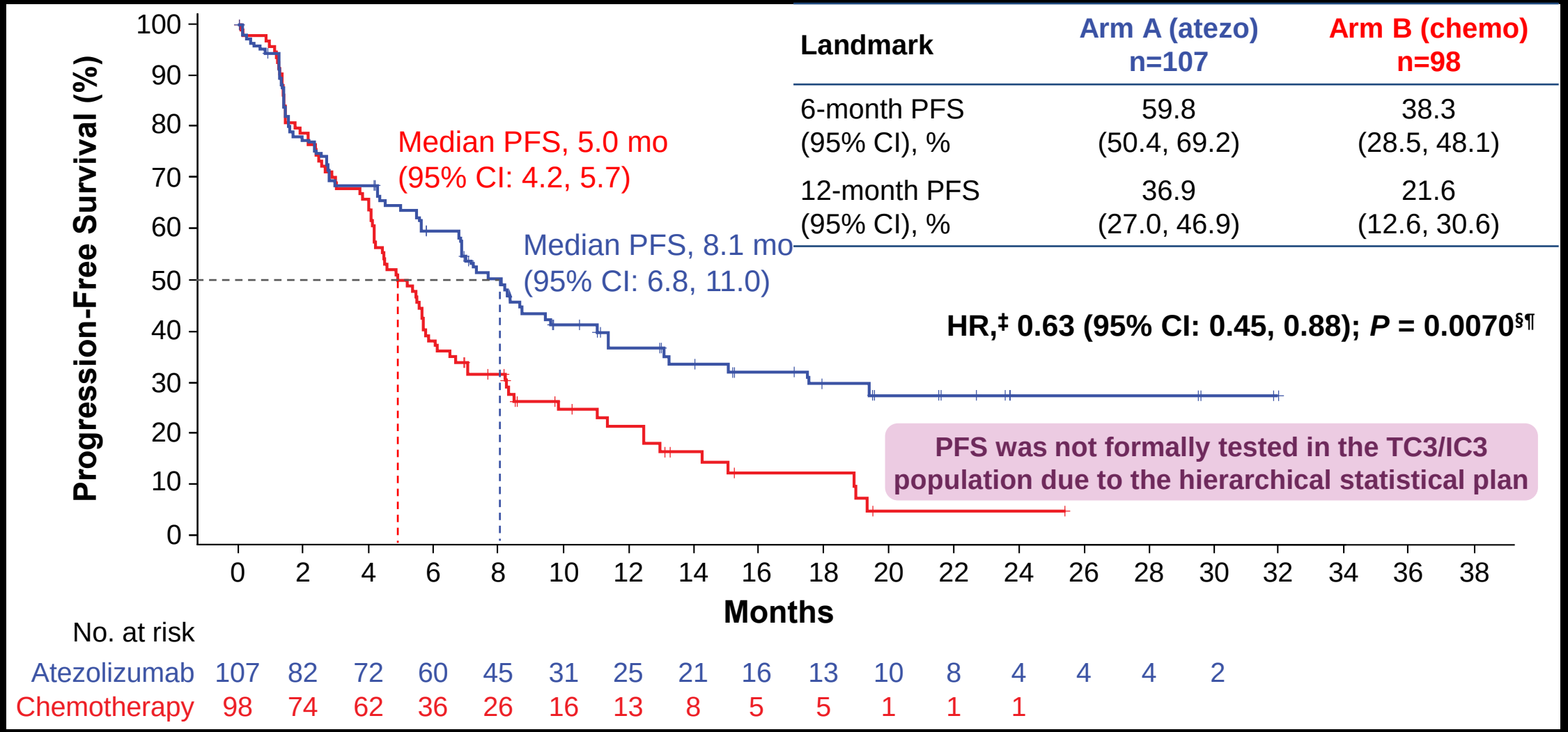


*The 1 patient in the ≥85 years subgroup is not included, and 1 patient's race was unknown;
‡Unstratified; §Stratified

Data cut-off: 10 September 2018

- Spigel, et al. ESMO 2019 (Abs LBA78)

IMpower110: PFS in TC3/IC3 population



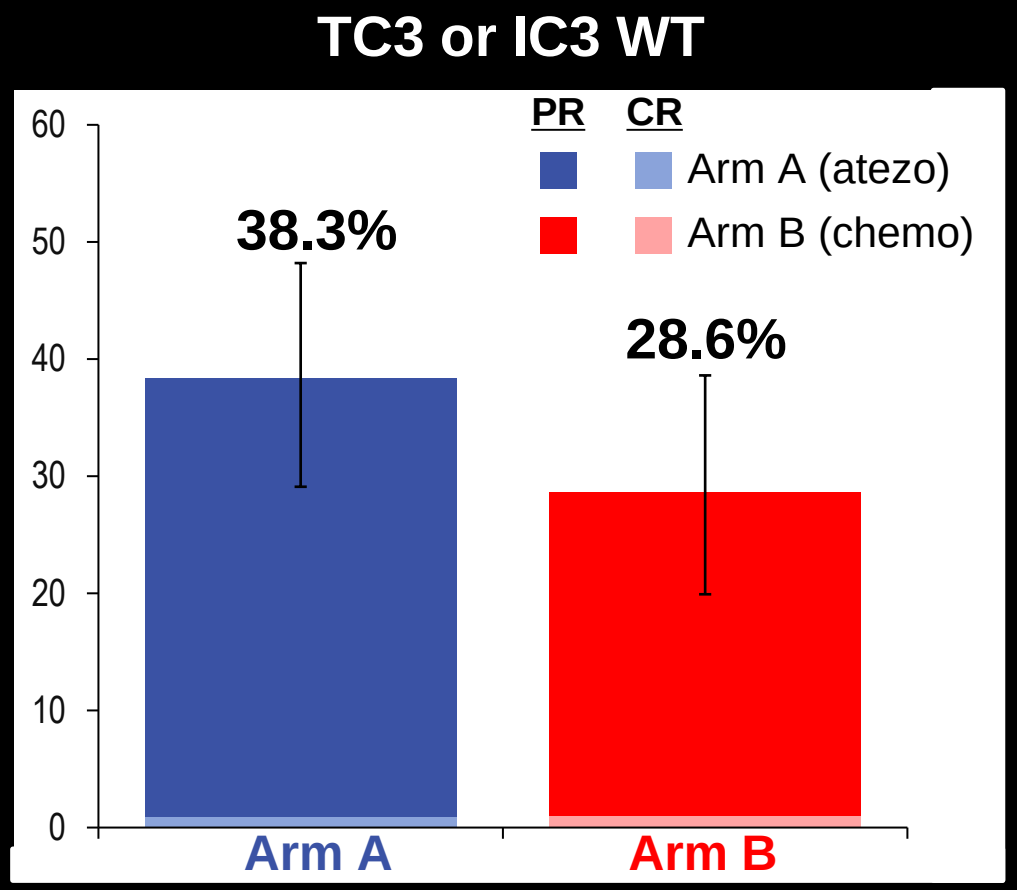
Landmark	Arm A (atezo) n=107	Arm B (chemo) n=98
6-month PFS (95% CI), %	59.8 (50.4, 69.2)	38.3 (28.5, 48.1)
12-month PFS (95% CI), %	36.9 (27.0, 46.9)	21.6 (12.6, 30.6)

*Investigator assessed per RECIST 1.1; ‡Stratified; §Stratified log-rank; ¶For descriptive purposes only

Data cut-off: 10 September 2018

- Spigel, et al. ESMO 2019 (Abs LBA78)

IMpower110: confirmed ORR (TC3 or IC3 population)



+, censored

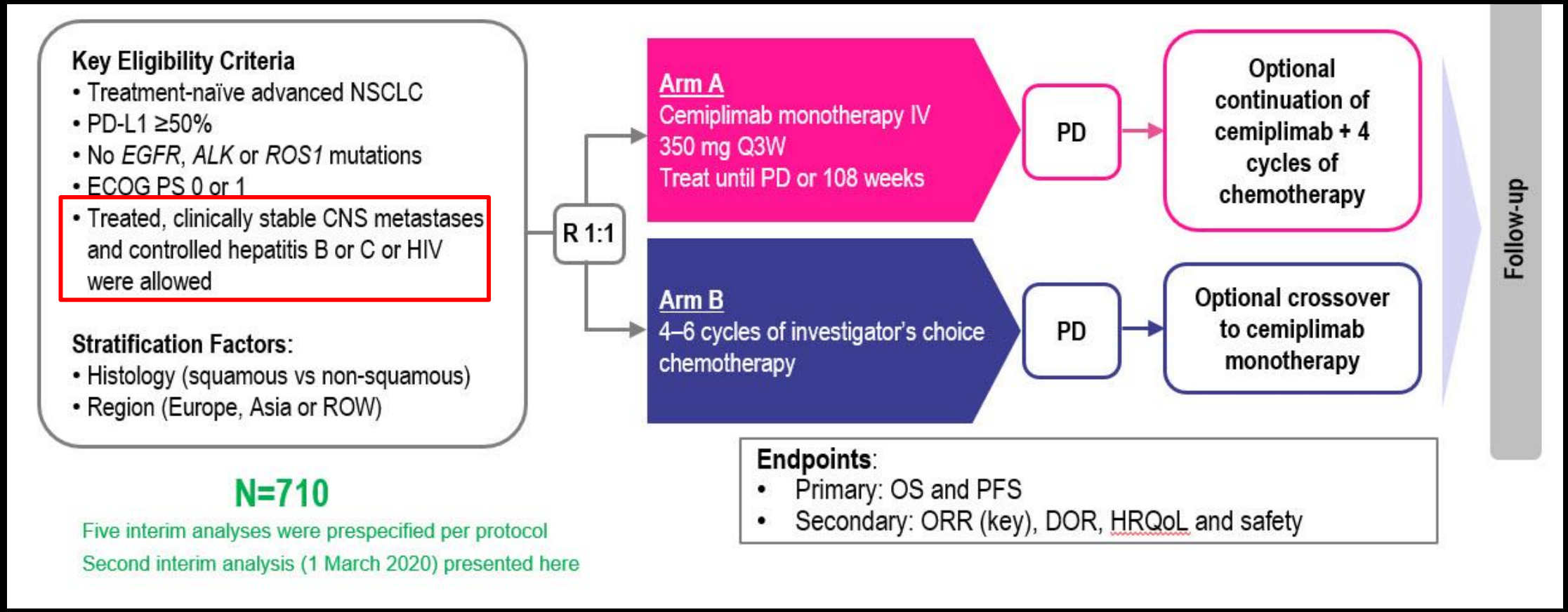
Data cut-off: 10 September 2018

Confirmed ORR was improved with atezolizumab in the TC3/IC3 population

	Arm A (atezo)	Arm B (chemo)
TC2/3 or IC2/3 WT	**n=166**	**n=162**
ORR (95% CI), %	30.7 (23.8, 38.3)	32.1 (25.0, 39.9)
Median DOR (range), mo	NE (1.8+ to 29.3+)	5.8 (2.6 to 23.9+)
TC1/2/3 or IC1/2/3 WT	**n=277**	**n=277**
ORR (95% CI), %	29.2 (24.0, 35.0)	31.8 (26.3, 37.6)
Median DOR (range), mo	NE (1.8+ to 29.3+)	5.7 (2.4 to 23.9+)

- Spigel, et al. ESMO 2019 (Abs LBA78)

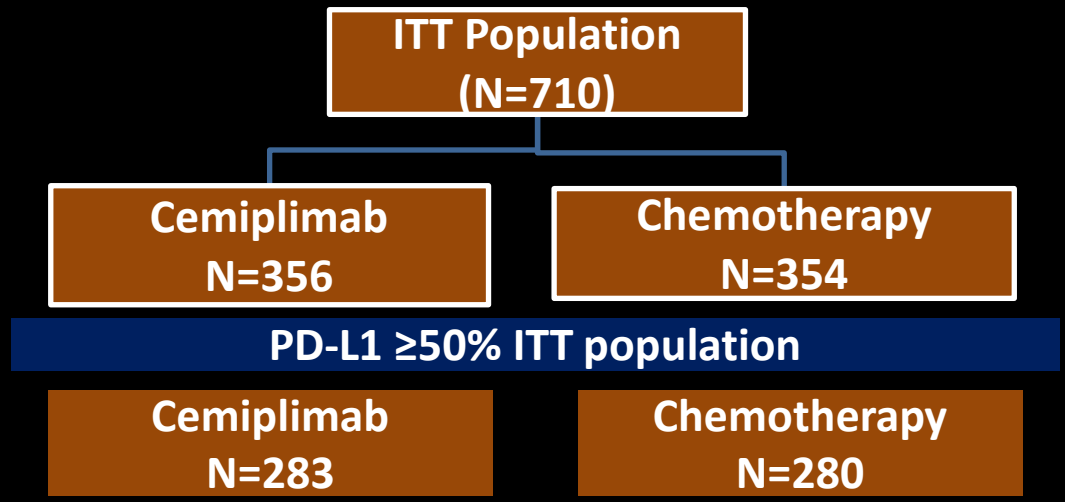
EMPOWER-Lung 1 Study Design



Never smokers (i.e., those who smoked <100 cigarettes in their lifetime) were excluded from the study

Sezer, A et al. EMPOWER-Lung-1. ESMO 2020.

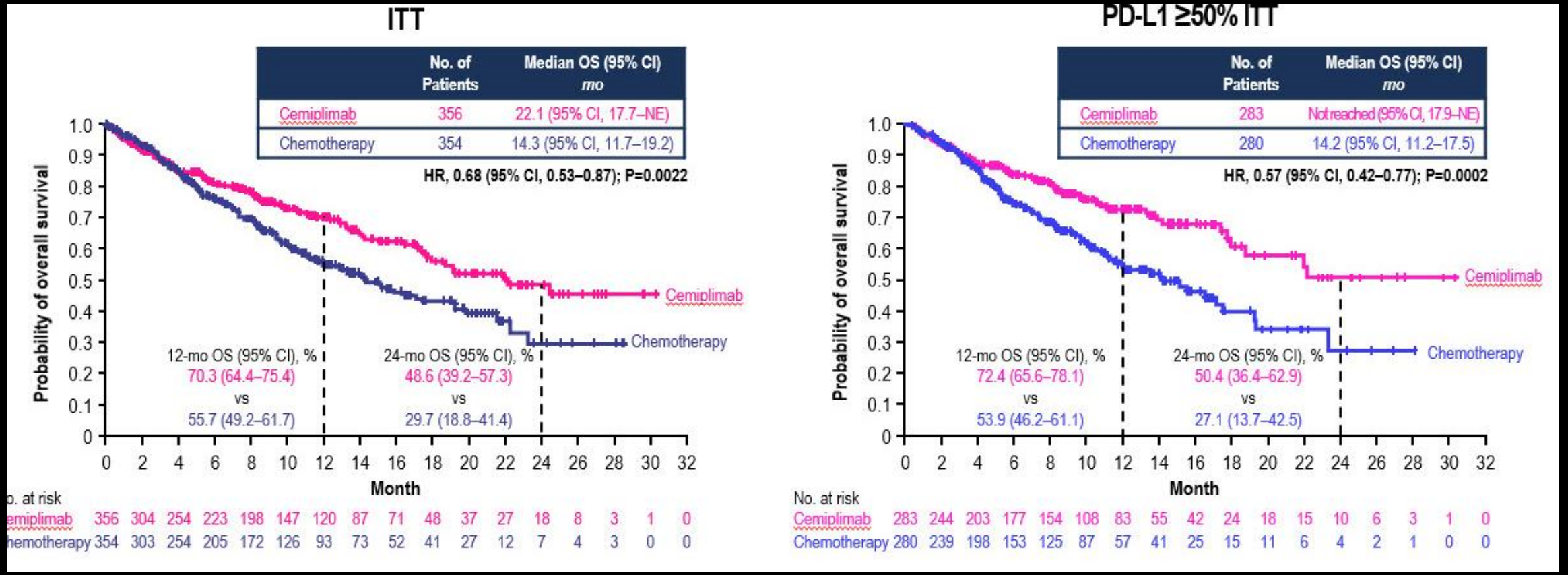
Disposition by PD-L1 Testing Status and Retest



- The initial PD-L1 central testing was not performed according to instructions for use, this led to a modified ITT analysis performed on a subset of 563 patients (79% of the overall ITT) identified as PD-L1 ≥50% by a 22C3 validated test)
- This population comprised patients from:
  - The overall ITT population who were initially tested not according to the instructions for use at entry (n=88; PD-L1 testing pre-August 2018)
  - Those who were re-tested according to instructions for use (n=475; PD-L1 testing post-August 2018)

Sezer, A et al. EMPOWER-Lung-1. ESMO 2020.

Overall Survival



ITT population:
Median follow-up was: 13.1 months (0.1-31.9) for cemiplimab and 13.1 months (0.2-32.4) for chemotherapy

PD-L1 TPS ≥50% population:
Median follow-up was: 10.8 months (0.1-3.9) for cemiplimab and 10.2 months (0.2-29.5) for chemotherapy

Data cut-off date: 1 March 2020

Sezer, A et al. EMPOWER-Lung-1. ESMO 2020.

Objective Response Rate and Duration of Response

	ITT Population		PD-L1 ≥50% ITT	
	Cemiplimab (n=356)	**Chemotherapy (n=354)**	**Cemiplimab (n=283)**	**Chemotherapy (n=280)**
ORR (95% CI)	36.5% (31.5–41.8)	20.6% (16.5–25.2)	39.2% (33.5–45.2)	20.4% (15.8–25.6)
Complete Response	3.1%	0.8%	2.1%	1.1%
Partial Response	33.4%	19.8%	37.1%	19.3%

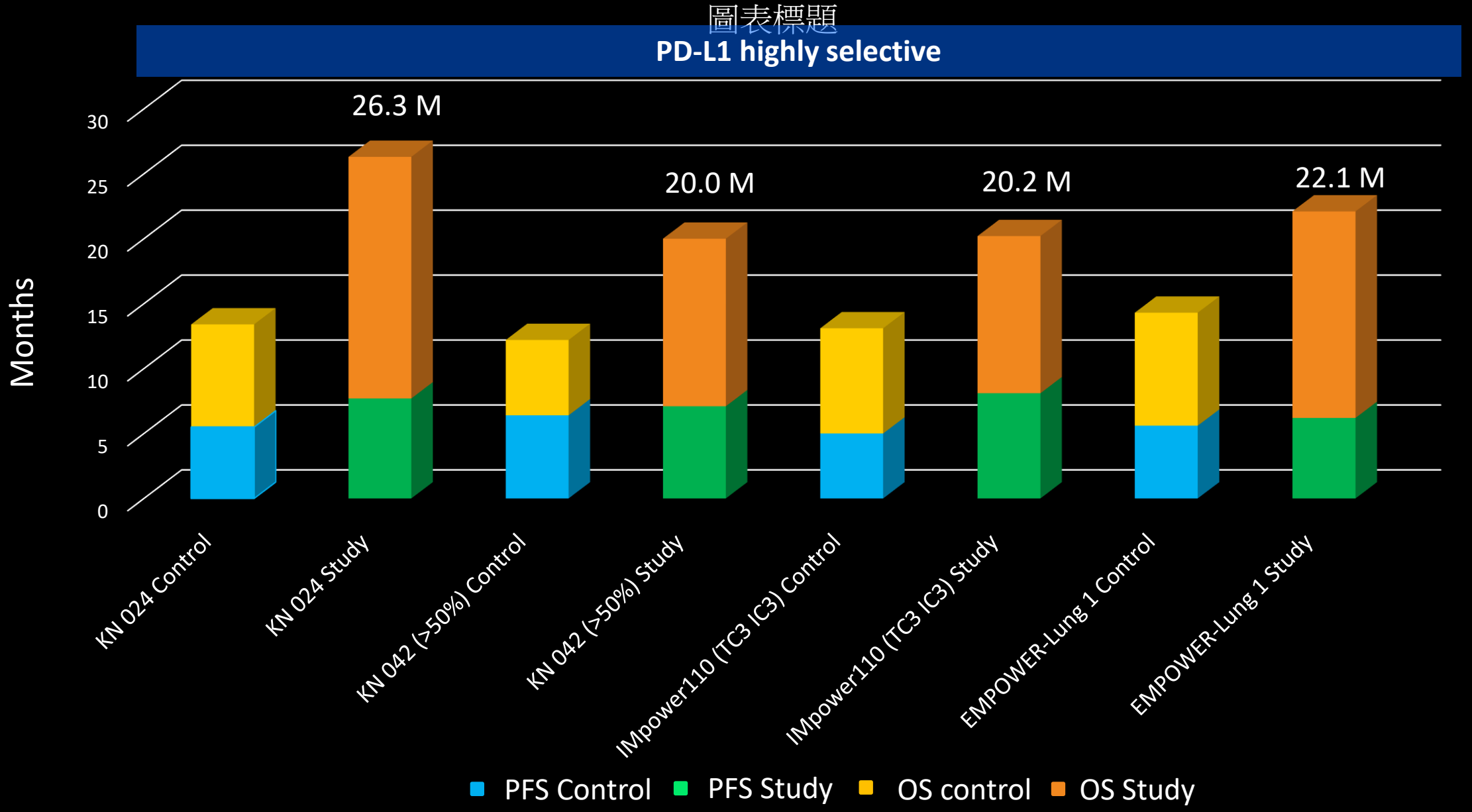
Data cut-off date: 1 March 2020

Median Duration of Response (Cemiplimab vs Chemotherapy):

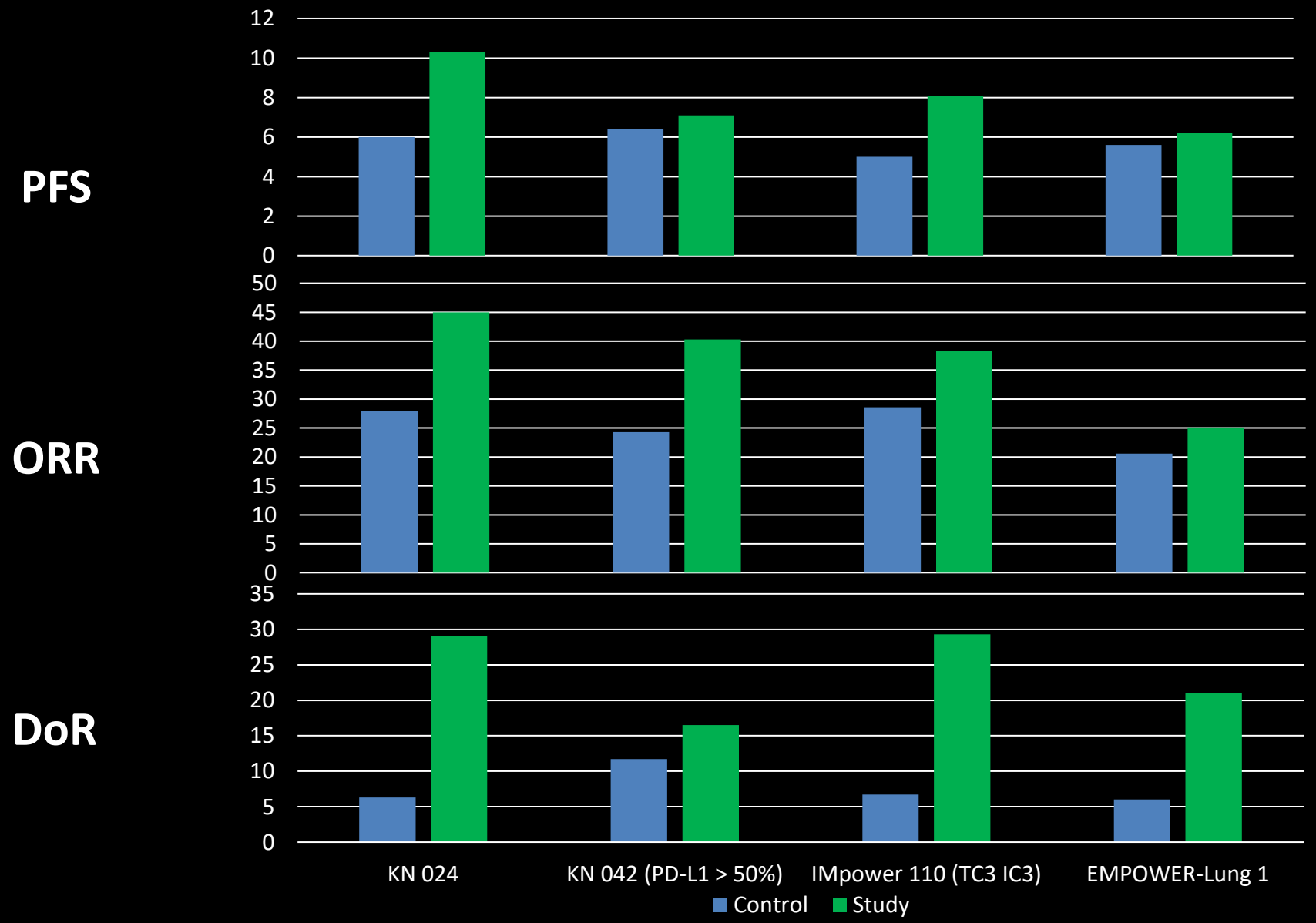
- ITT Population: 21.0 months vs 6.0 months
- PD-L1≥50% ITT Population: 16.7 months vs 6.0 months

Sezer, A et al. EMPOWER-Lung-1. ESMO 2020.

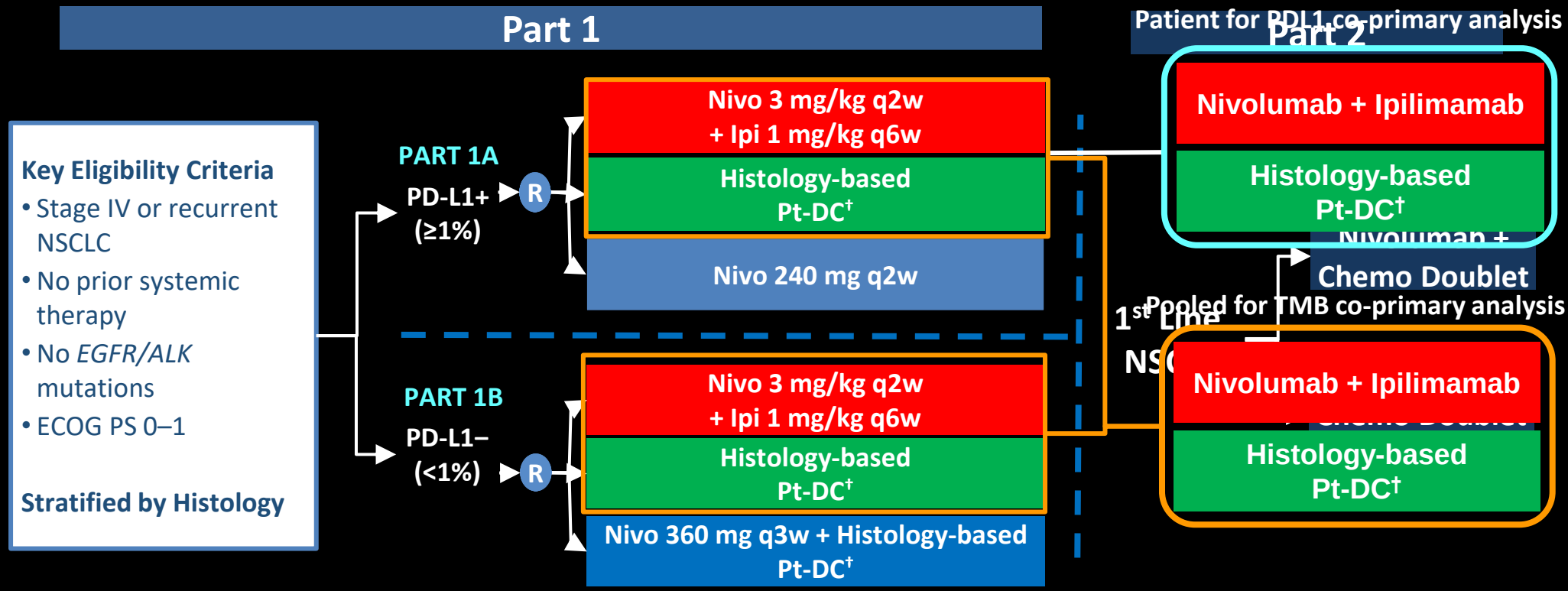
Frontline Treatment OS: IO mono



Frontline Treatment IO mono: PFS, ORR and DoR



CheckMate 227 Study Design: IO + IO in all comer



Independent co-primary endpoints: NIVO + IPI vs chemo

PFS in high TMB (≥10 mut/Mb) population[f]

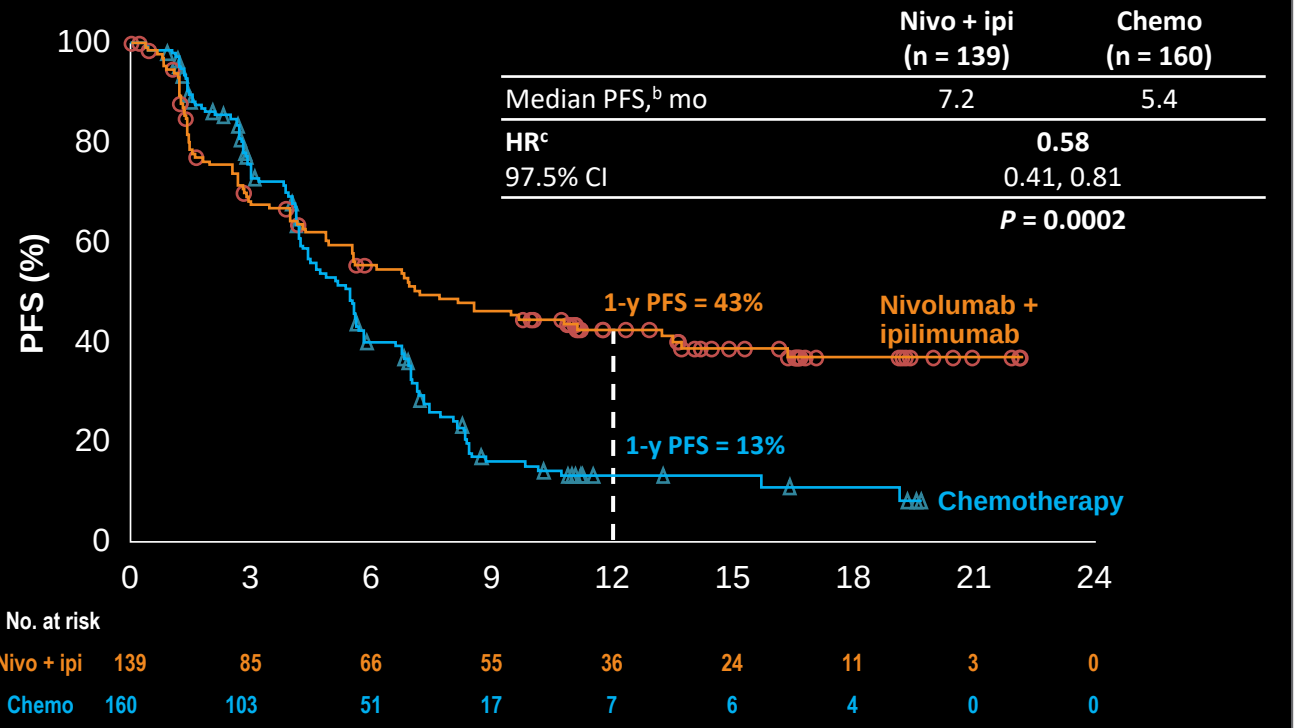
- OS in PD-L1 ≥ 1% population[g]

Secondary endpoints (PD-L1 hierarchy):

- PFS: **NIVO + chemo vs chemo** in PD-L1 < 1%
- OS: **NIVO + chemo vs chemo** in PD-L1 < 1%
- OS: **NIVO vs chemo** in PD-L1 ≥ 50%

Adopted from Clinicaltrial.gov NCT02477826

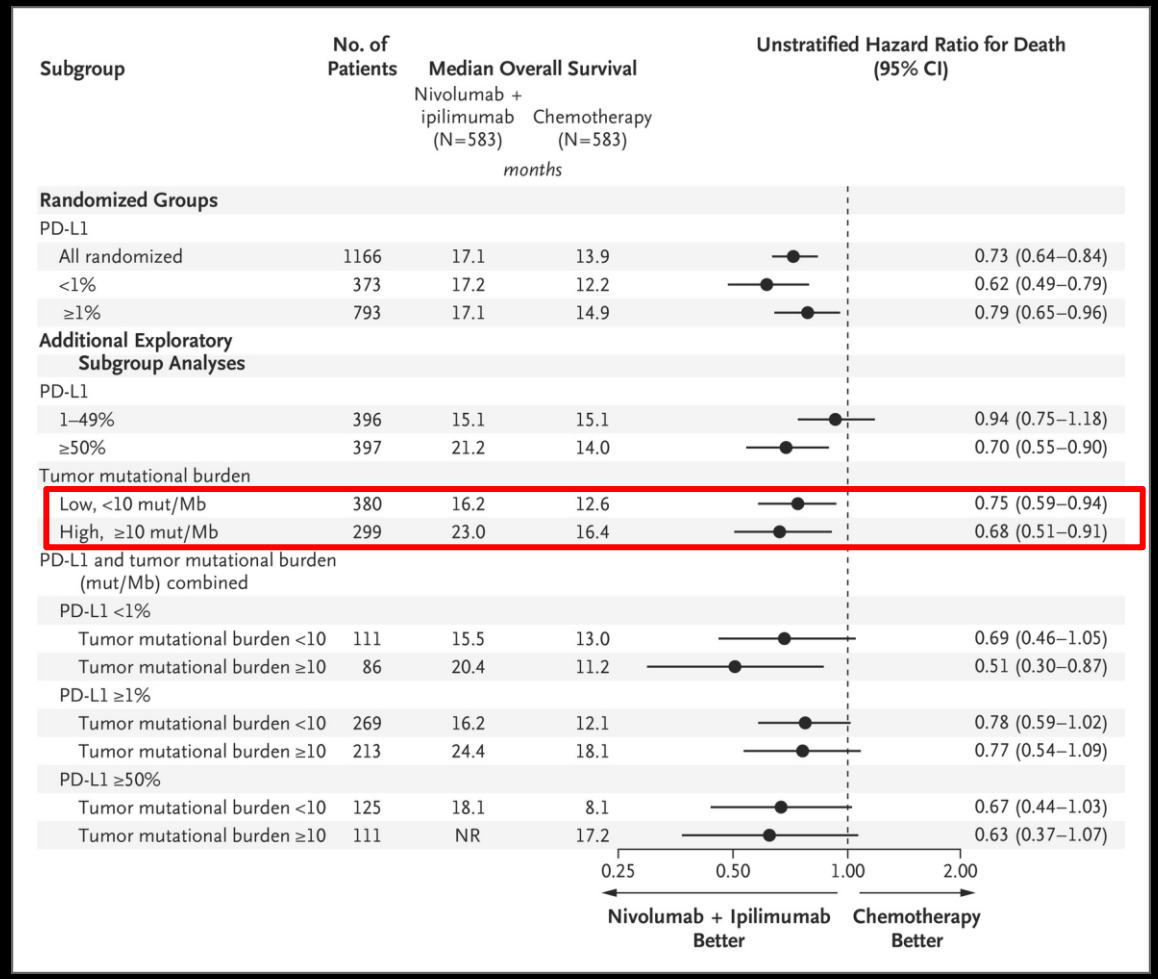
Co-primary Endpoint: PFS With Nivolumab + Ipilimumab vs Chemotherapy in Patients With High TMB (≥10 mut/Mb)[a]



	Nivo + ipi (n = 139)	Chemo (n = 160)
Median PFS,[b] mo	7.2	5.4
HR[c]	**0.58**	
97.5% CI	0.41, 0.81	
	***P* = 0.0002**	

- In patients with TMB <10 mut/Mb treated with nivo + ipi vs chemo, the HR was 1.07 (95% CI: 0.84, 1.35)[d]

[a]Per blinded independent central review (BICR); median (range) of follow-up in the co-primary analysis population was 13.6 mo (0.4, 25.1) for nivo + ipi and 13.2 mo (0.2, 26.0) for chemo; [b]95% CI: nivo + ipi (5.5, 13.2 mo), chemo (4.4, 5.8 mo); [c]95% CI: 0.43, 0.77 mo; [d]The *P*-value for the treatment interaction was 0.0018

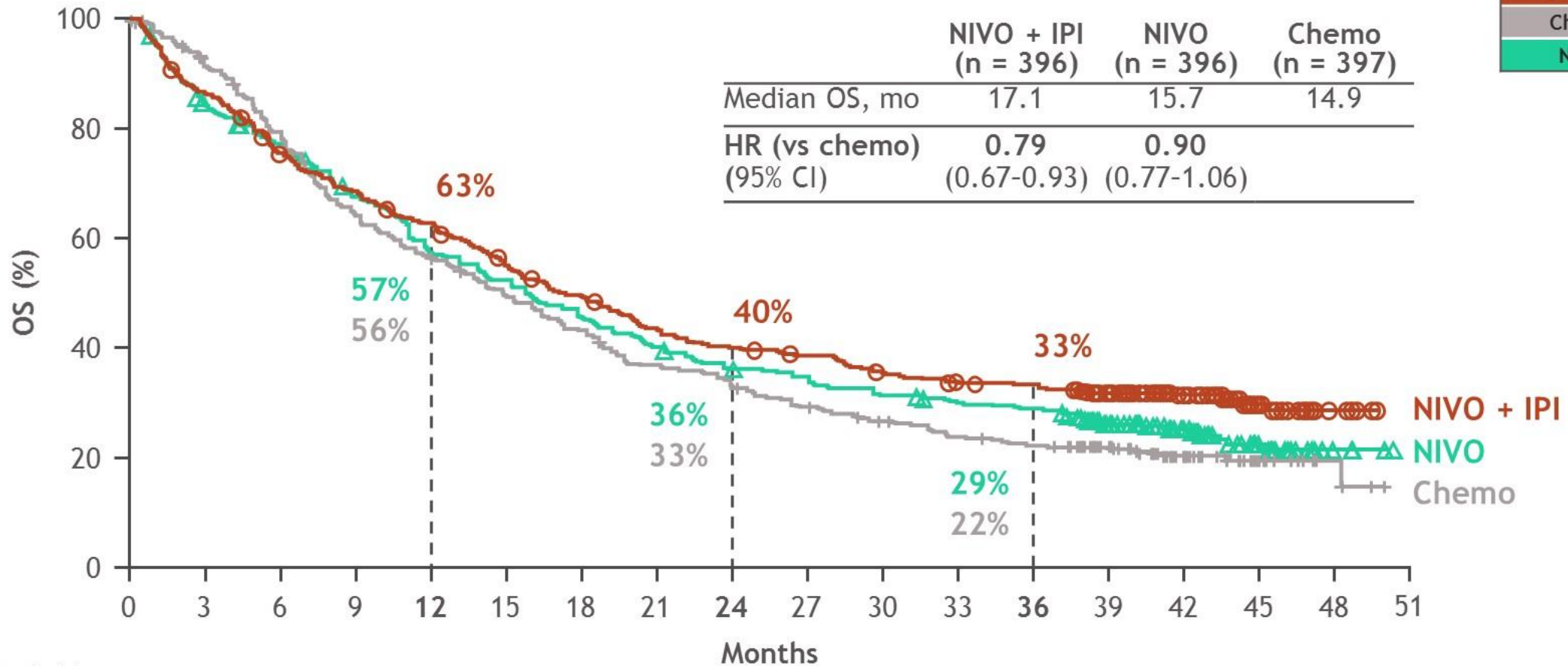


Hellmann MD et al. N Engl J Med 2019; 381:2020-2031

3-year update: OS with NIVO + IPI vs chemo vs NIVO (PD-L1 ≥ 1%)

Part 1a
NIVO + IPI
Chemo
NIVO

	NIVO + IPI (n = 396)	NIVO (n = 396)	Chemo (n = 397)
Median OS, mo	17.1	15.7	14.9
HR (vs chemo) (95% CI)	0.79 (0.67-0.93)	0.90 (0.77-1.06)	



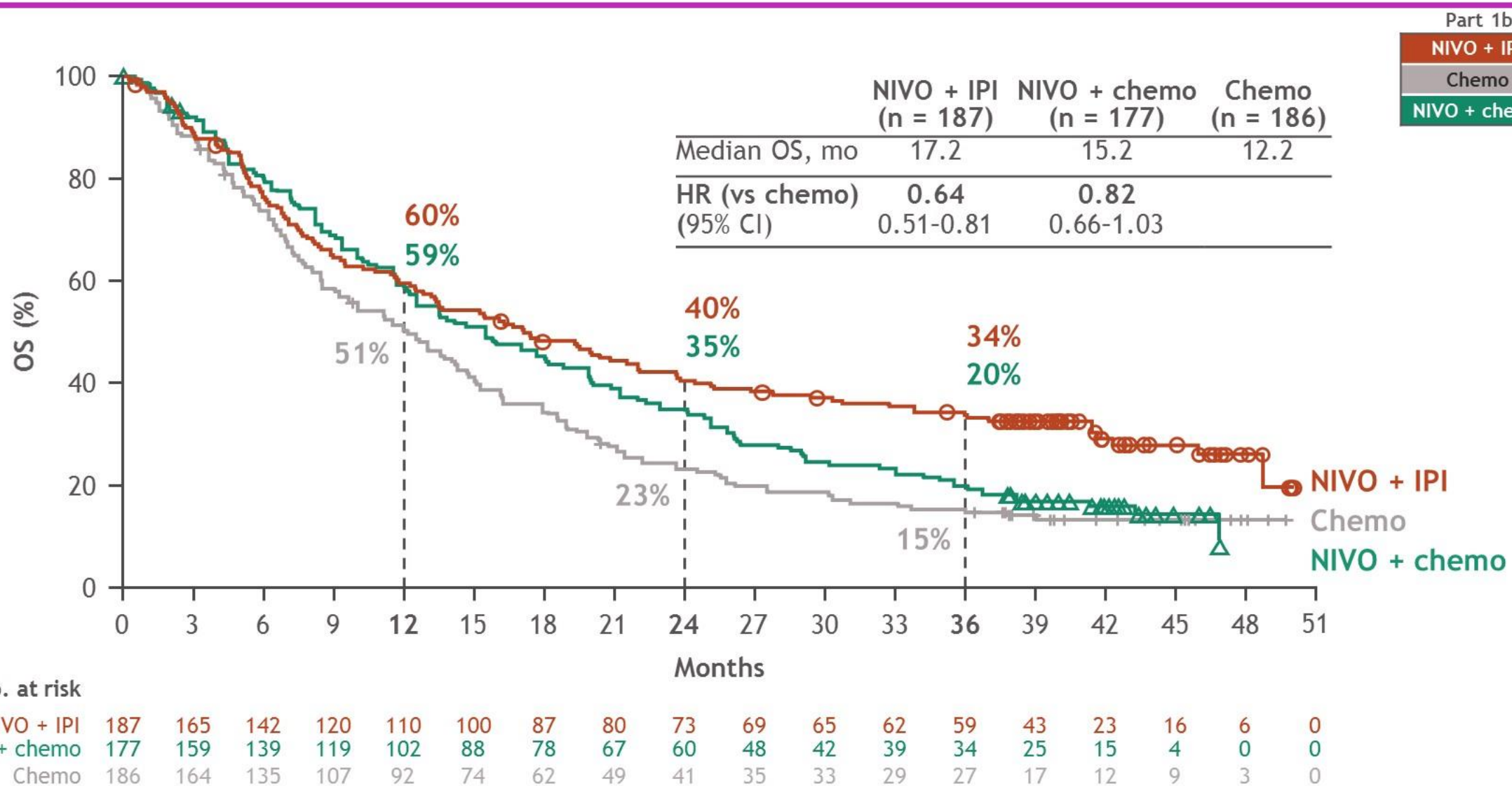
No. at risk

NIVO + IPI	396	341	295	264	244	212	190	165	153	145	132	124	121	97	67	27	5	0
NIVO	396	330	299	265	220	201	176	153	139	129	119	112	108	83	45	21	4	0
Chemo	397	358	306	250	218	190	166	141	126	112	98	87	80	62	32	13	4	0

Database lock: February 28, 2020; minimum follow-up for OS: 37.7 months.

Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W) and NIVO (240 mg Q2W). Among patients who were alive at 3 years, subsequent systemic therapy was received by 35% in the NIVO + IPI arm, 45% in the NIVO arm, and 76% in the chemo arm; subsequent immunotherapies were received by 13%, 21%, and 71%; and subsequent chemotherapy was received by 28%, 33% and 30%, respectively.

3-year update: OS with NIVO + IPI vs Chemo vs NIVO + Chemo (PD-L1 < 1%)



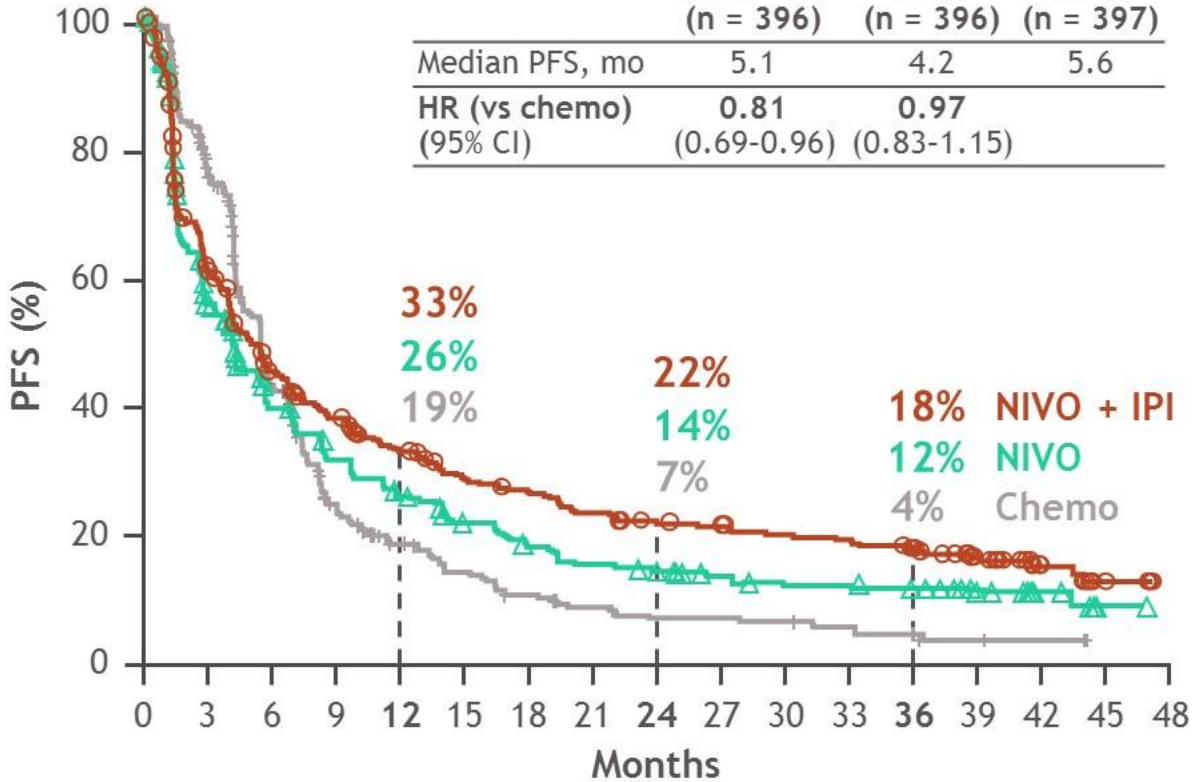
Database lock: February 28, 2020; minimum follow-up for OS: 37.7 months.

Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W), and NIVO (360 mg Q3W) plus chemo. Among patients who were alive at 3 years, subsequent systemic therapy was received by 49% in the NIVO + IPI arm, 38% in the NIVO + chemo arm, and 78% in the chemo arm; subsequent immunotherapies were received by 12%, 12%, and 74%; and subsequent chemotherapy was received by 46%, 35% and 33%, respectively.

3-year update: PFS[a] among patients with PD-L1 ≥ 1% or < 1%

PD-L1 ≥ 1%

	NIVO + IPI (n = 396)	NIVO (n = 396)	Chemo (n = 397)
Median PFS, mo	5.1	4.2	5.6
HR (vs chemo) (95% CI)	**0.81** (0.69-0.96)	**0.97** (0.83-1.15)	

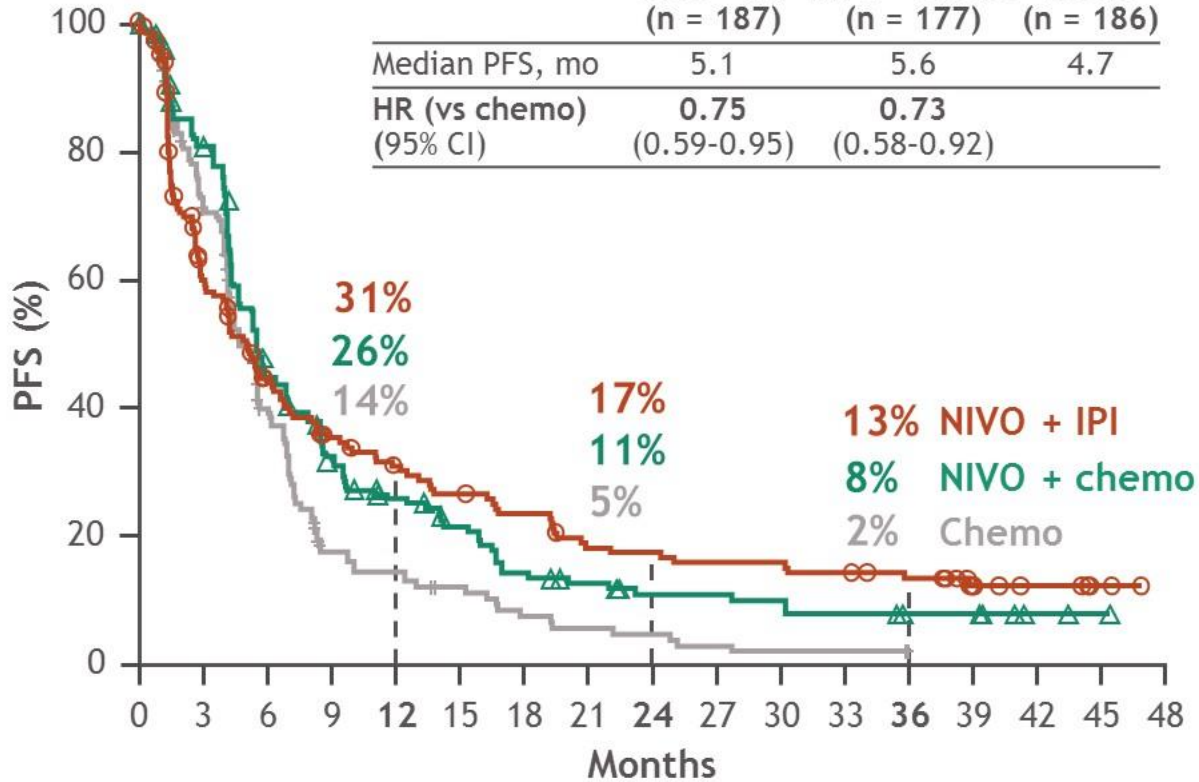


No. at risk

396	221	158	130	108	91	83	73	65	62	56	54	44	31	13	4	0
396	199	136	104	85	68	56	47	42	36	31	31	24	14	6	1	0
397	253	130	63	44	32	23	17	12	12	11	9	7	3	2	0	0

PD-L1 < 1%

	NIVO + IPI (n = 187)	NIVO + chemo (n = 177)	Chemo (n = 186)
Median PFS, mo	5.1	5.6	4.7
HR (vs chemo) (95% CI)	**0.75** (0.59-0.95)	**0.73** (0.58-0.92)	



No. at risk

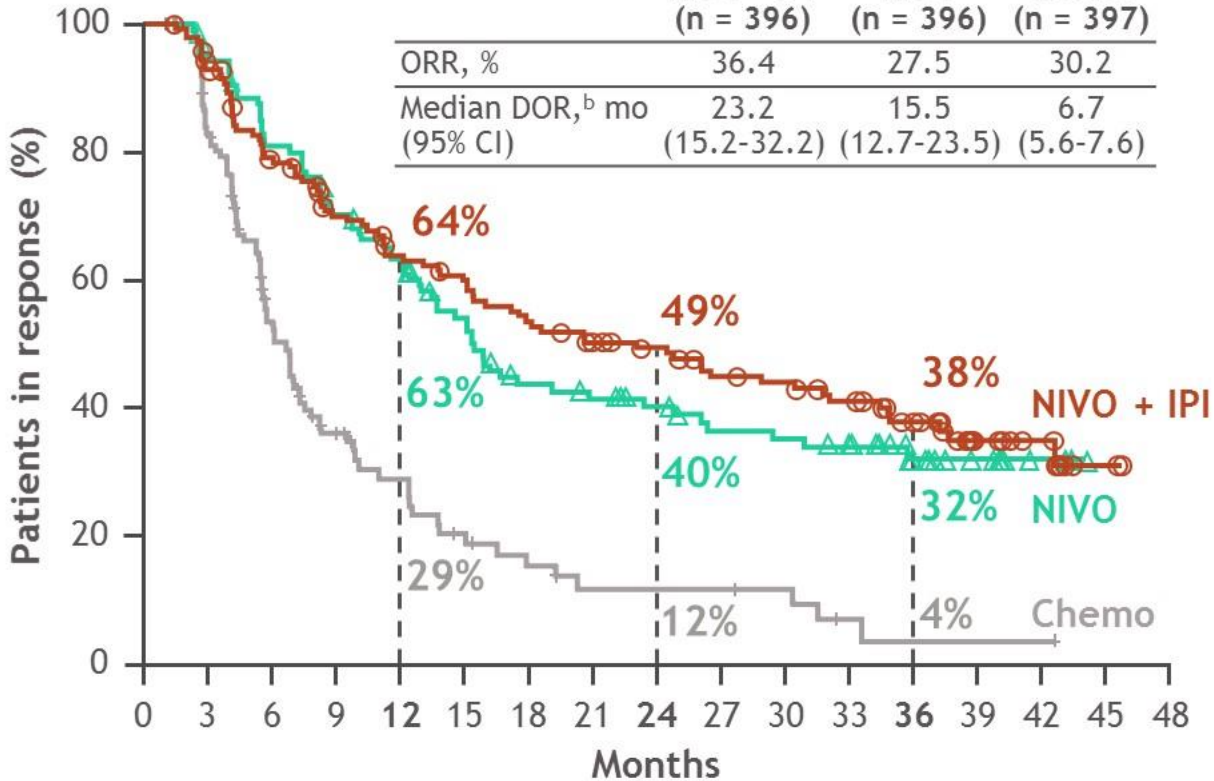
187	95	66	50	42	36	31	23	22	20	20	18	15	8	5	2	0
177	135	73	48	37	29	19	15	11	11	10	8	6	6	2	1	0
186	121	57	22	18	13	8	6	5	3	2	2	1	0	0	0	0

Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W), NIVO (240 mg Q2W), and NIVO (360 mg Q3W) + chemo. [a]PFS was assessed by blinded independent central review.

3-year update: ORR[a] and DOR[a] among patients with PD-L1 ≥ 1% or < 1%

PD-L1 ≥ 1%

	NIVO + IPI (n = 396)	NIVO (n = 396)	Chemo (n = 397)
ORR, %	36.4	27.5	30.2
Median DOR,[b] mo (95% CI)	23.2 (15.2-32.2)	15.5 (12.7-23.5)	6.7 (5.6-7.6)

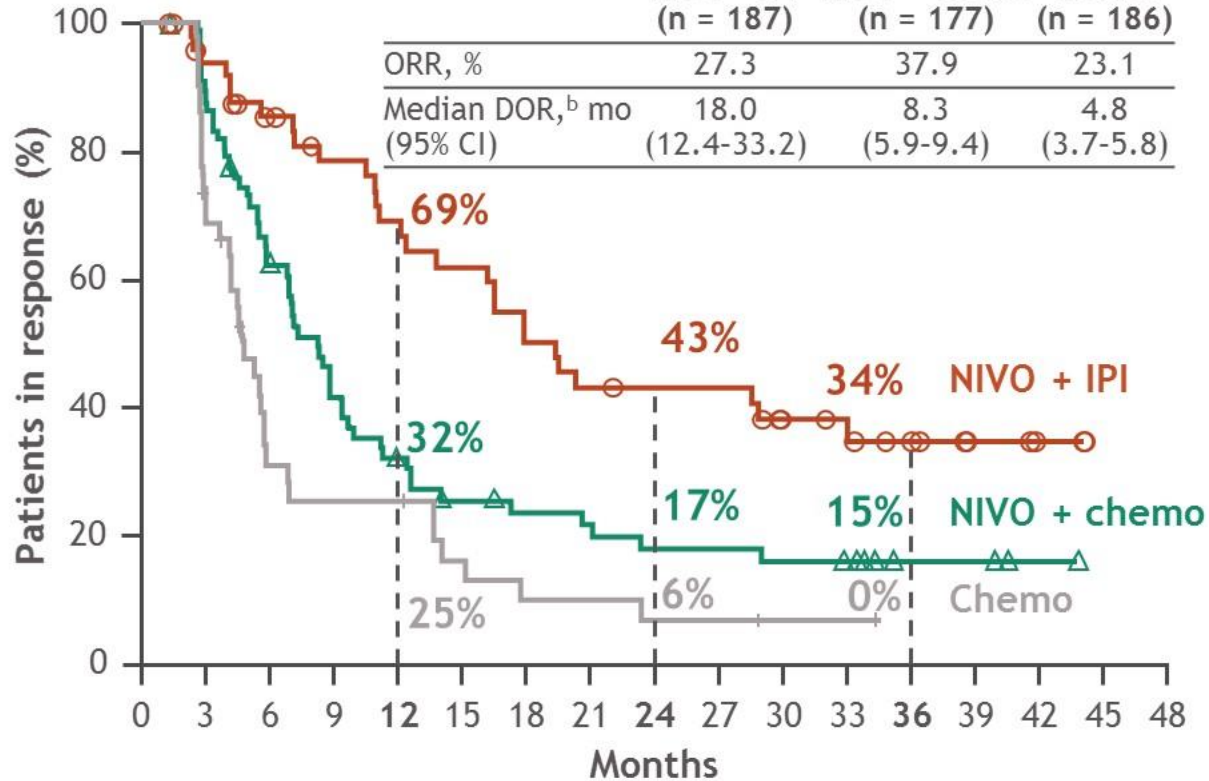


No. at risk

144	130	107	91	81	76	67	60	56	49	47	42	33	17	10	2	0
109	100	84	72	64	52	40	37	33	28	27	25	16	11	3	0	0
120	91	52	29	20	13	10	6	6	6	5	2	1	1	1	0	0

PD-L1 < 1%

	NIVO + IPI (n = 187)	NIVO + chemo (n = 177)	Chemo (n = 186)
ORR, %	27.3	37.9	23.1
Median DOR,[b] mo (95% CI)	18.0 (12.4-33.2)	8.3 (5.9-9.4)	4.8 (3.7-5.8)

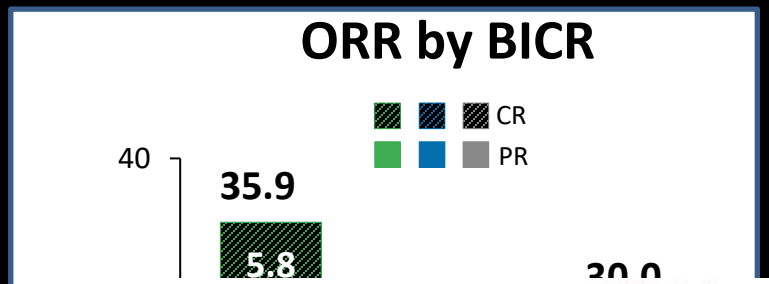


51	45	38	33	29	26	21	18	17	17	12	11	8	4	2	0	0
67	59	40	26	19	14	12	11	9	9	8	7	3	3	1	0	0
43	29	11	9	9	5	3	3	2	2	1	1	0	0	0	0	0

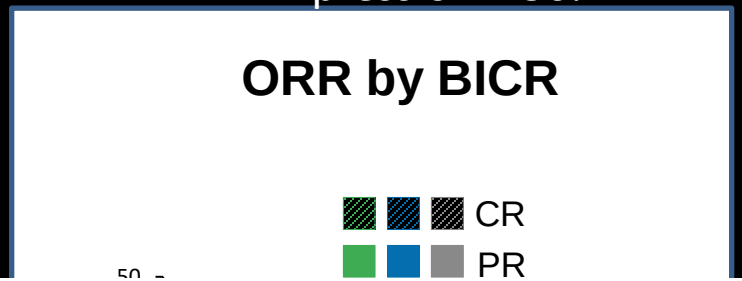
Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W), NIVO (240 mg Q2W), and NIVO (360 mg Q3W) + chemo. [a]ORR and DOR were assessed by blinded independent central review; [b]DOR was reported for responders only in each treatment arm.

IO + IO ORR is good, but not good enough in NSCLC compared with chemotherapy

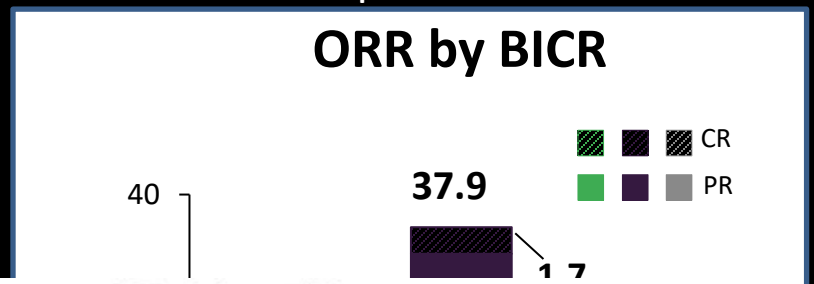
PD-L1 Expression ≥ 1%



PD-L1 Expression ≥ 50%



PD-L1 Expression < 1%



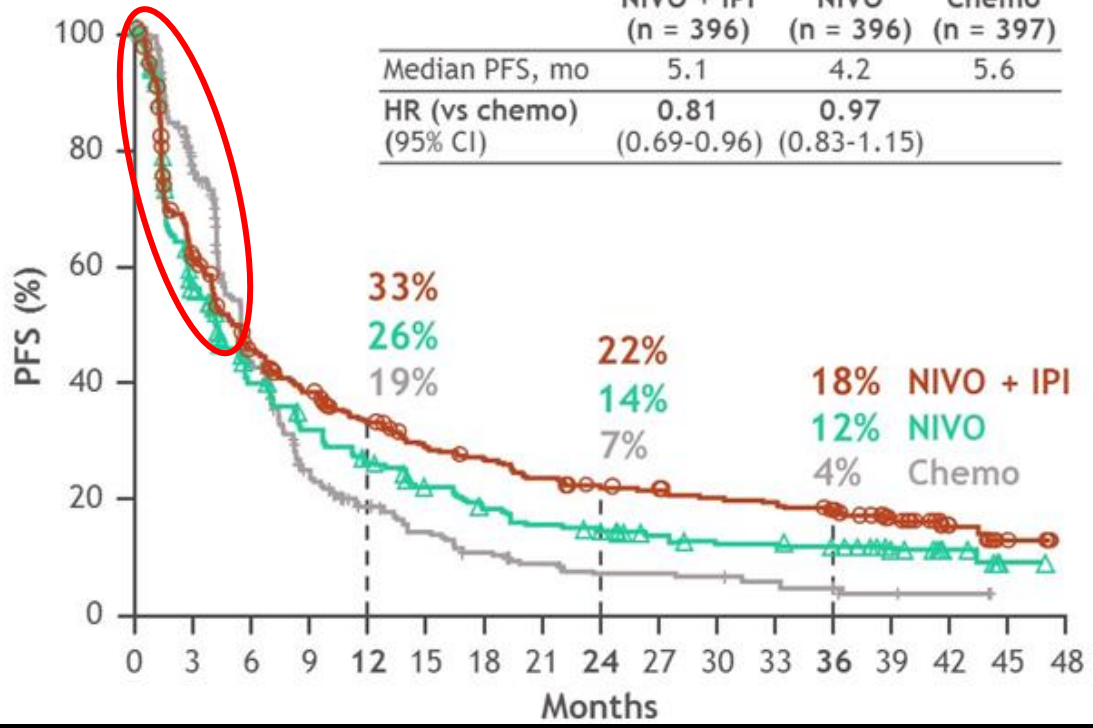
PD-L1 ≥ 1%

PFS

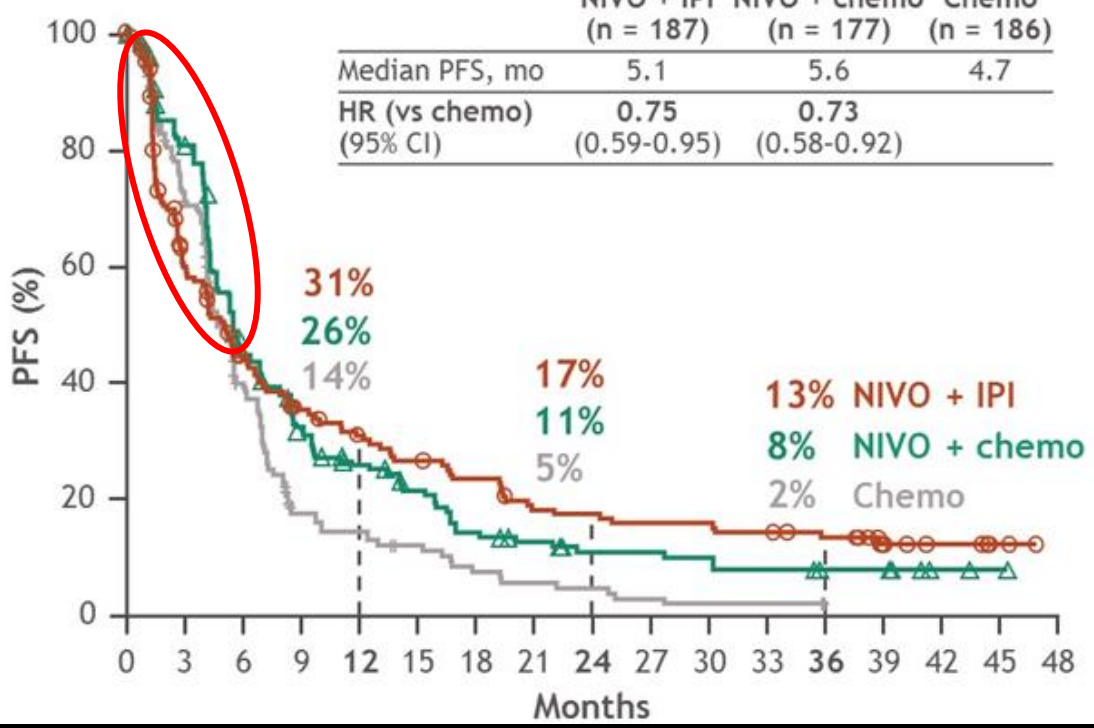
PD-L1 < 1%

ORR (%)

	NIVO + IPI (n = 396)	NIVO (n = 396)	Chemo (n = 397)
Median PFS, mo	5.1	4.2	5.6
HR (vs chemo) (95% CI)	0.81 (0.69-0.96)	0.97 (0.83-1.15)	



	NIVO + IPI (n = 187)	NIVO + chemo (n = 177)	Chemo (n = 186)
Median PFS, mo	5.1	5.6	4.7
HR (vs chemo) (95% CI)	0.75 (0.59-0.95)	0.73 (0.58-0.92)	



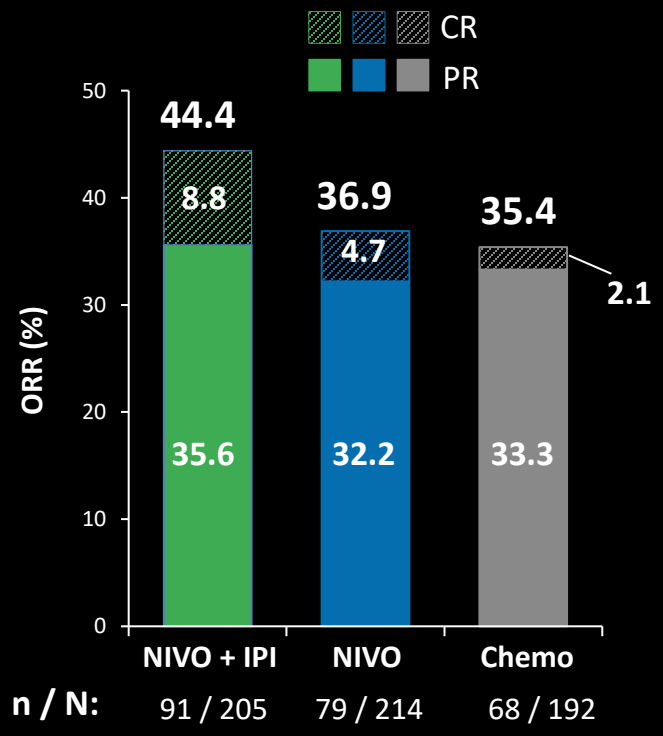
n / N:

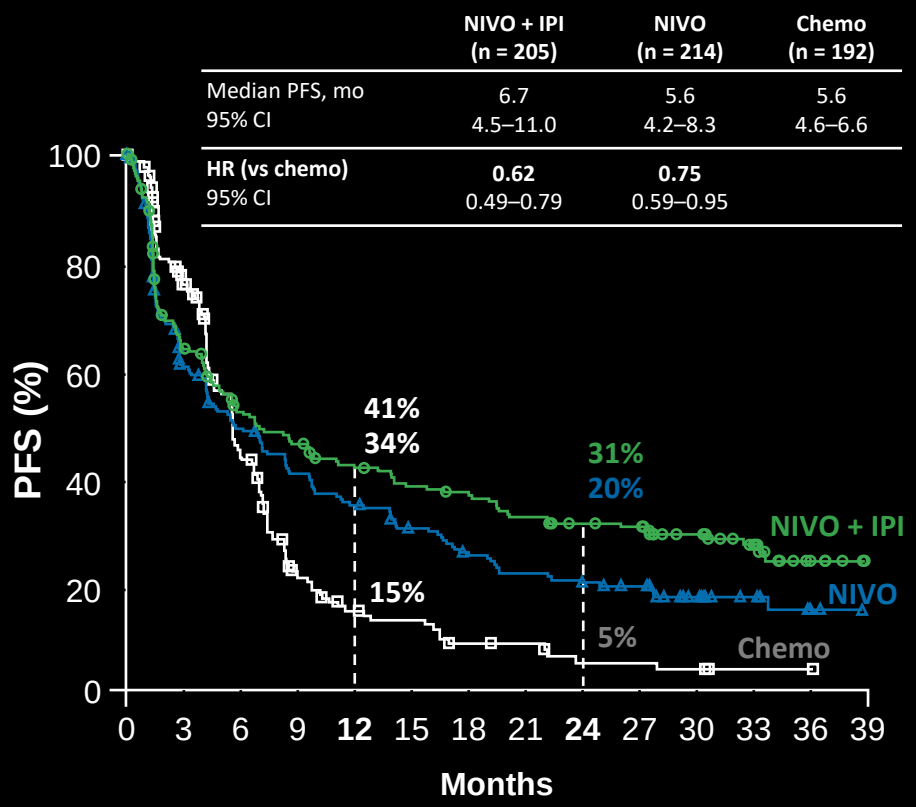
1

Efficacy With NIVO + IPI and NIVO vs Chemo in Patients With Tumor PD-L1 Expression ≥ 50%

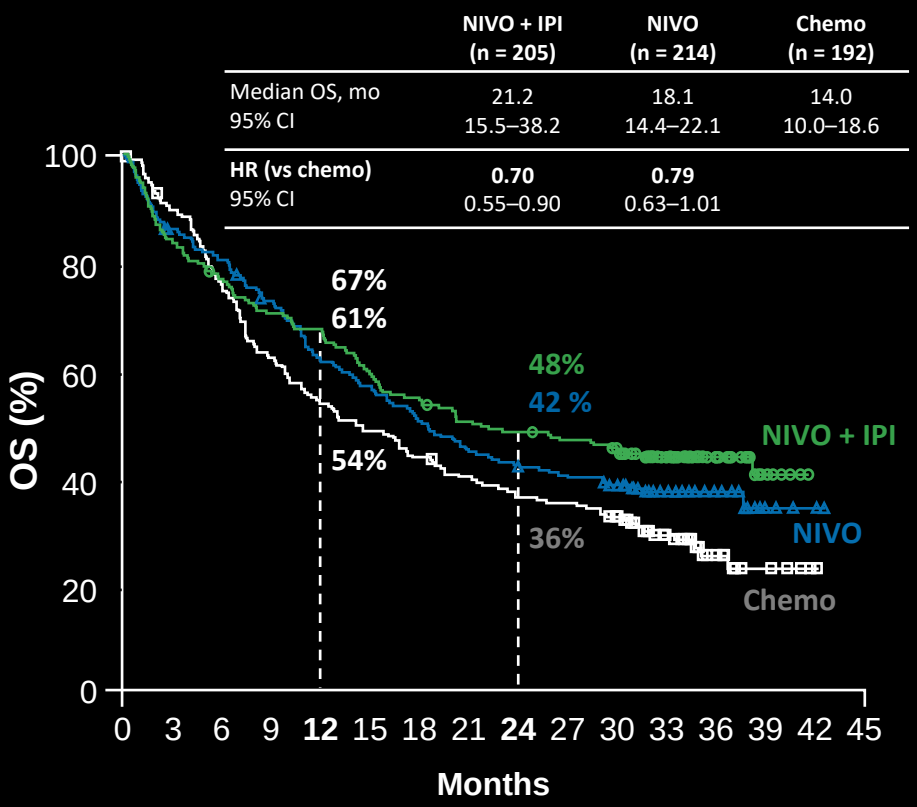
NIVO + IPI
Chemo
NIVO

ORR by BICR





	NIVO + IPI (n = 205)	NIVO (n = 214)	Chemo (n = 192)
Median PFS, mo 95% CI	6.7 4.5–11.0	5.6 4.2–8.3	5.6 4.6–6.6
HR (vs chemo) 95% CI	**0.62** 0.49–0.79	**0.75** 0.59–0.95	

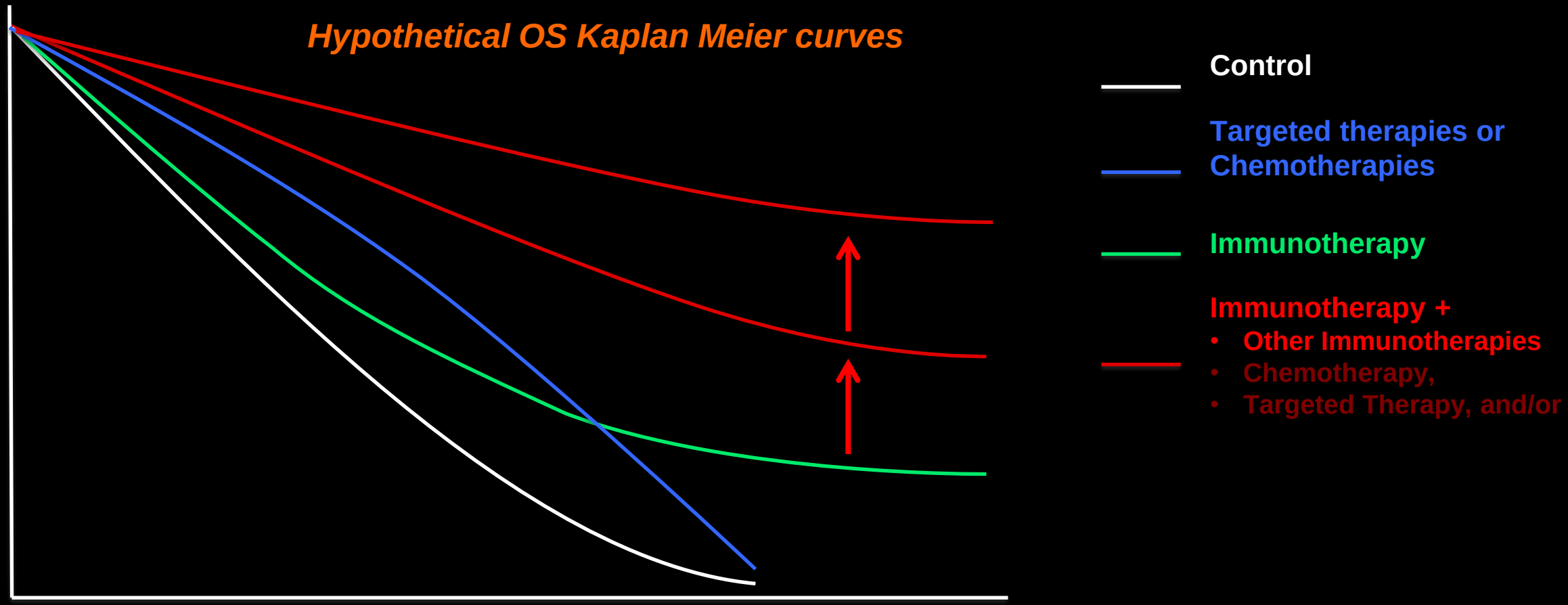


	NIVO + IPI (n = 205)	NIVO (n = 214)	Chemo (n = 192)
Median OS, mo 95% CI	21.2 15.5–38.2	18.1 14.4–22.1	14.0 10.0–18.6
HR (vs chemo) 95% CI	**0.70** 0.55–0.90	**0.79** 0.63–1.01	

- Median DOR with NIVO + IPI, NIVO and chemo was 31.8, 17.5 and 5.8 months, respectively

Dosages were NIVO (3 mg/kg Q2W) plus IPI (1 mg/kg Q6W), and NIVO (360 mg Q3W) plus chemo.

The Goal of Cancer Immunotherapy Combinations is to Enable more Potential Cures



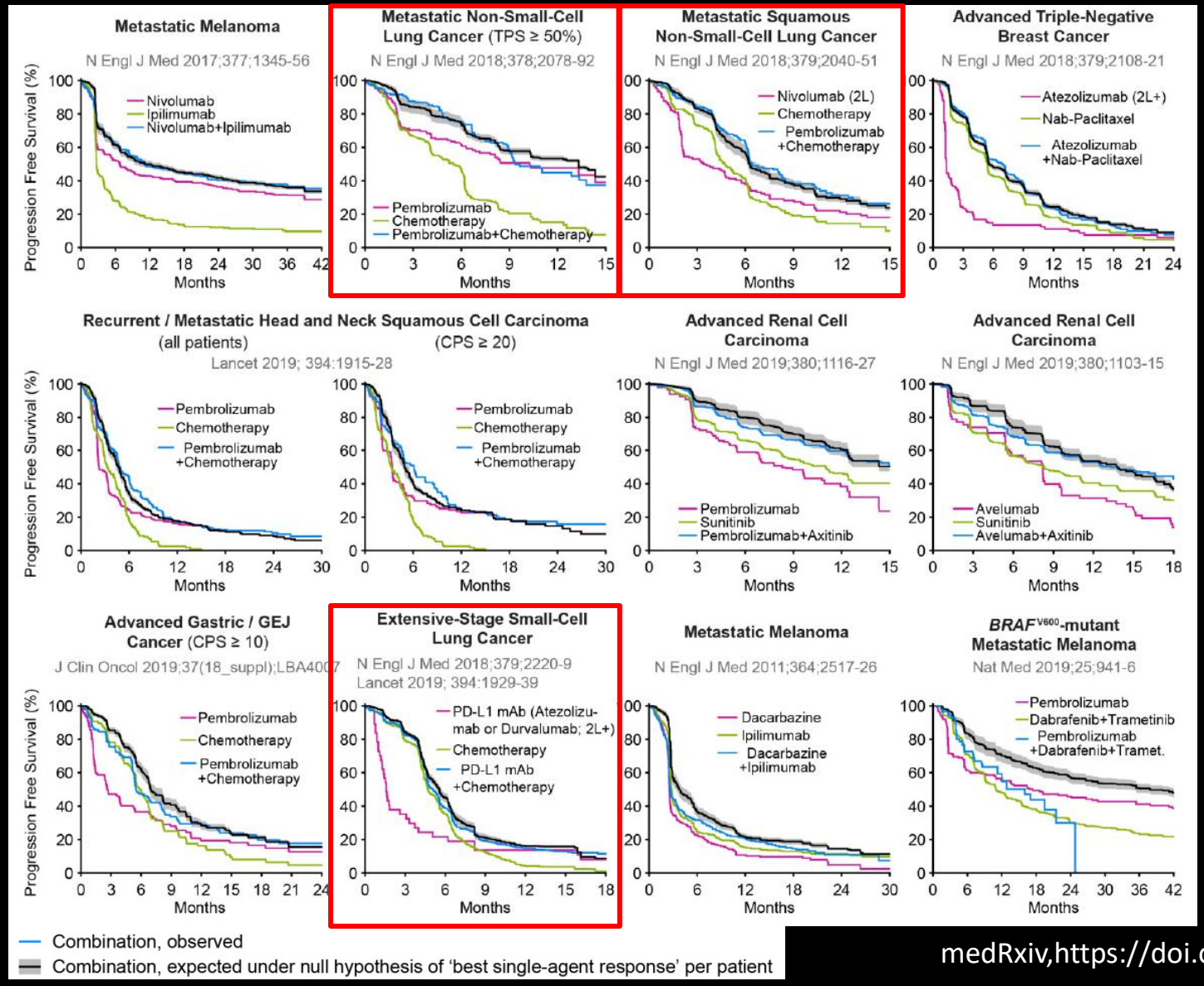
- Agents must be safe in combination
- The additional therapy should not interfere with the immunotherapeutic mechanism of action that is driving the anti-tumor response

Combination Immunotherapy

	$1 + 1 = 1$	IO + Targeted therapy ?
	$1 \leqq 1 + 1 \leqq 2$	IO + IO ? IO + chemotherapy ?
Additive effect	$1 + 1 = 2$	IO + IO? IO + chemotherapy?
Synergistic effect	$1 + 1 \geqq 2$	Personalized IO combination ?

Our dream

IO + Chemo : additive effect by mathematic model



Progression Free Survival for combination therapies as observed in clinical trials and as predicted from independent activity of the therapies comprising the combination.

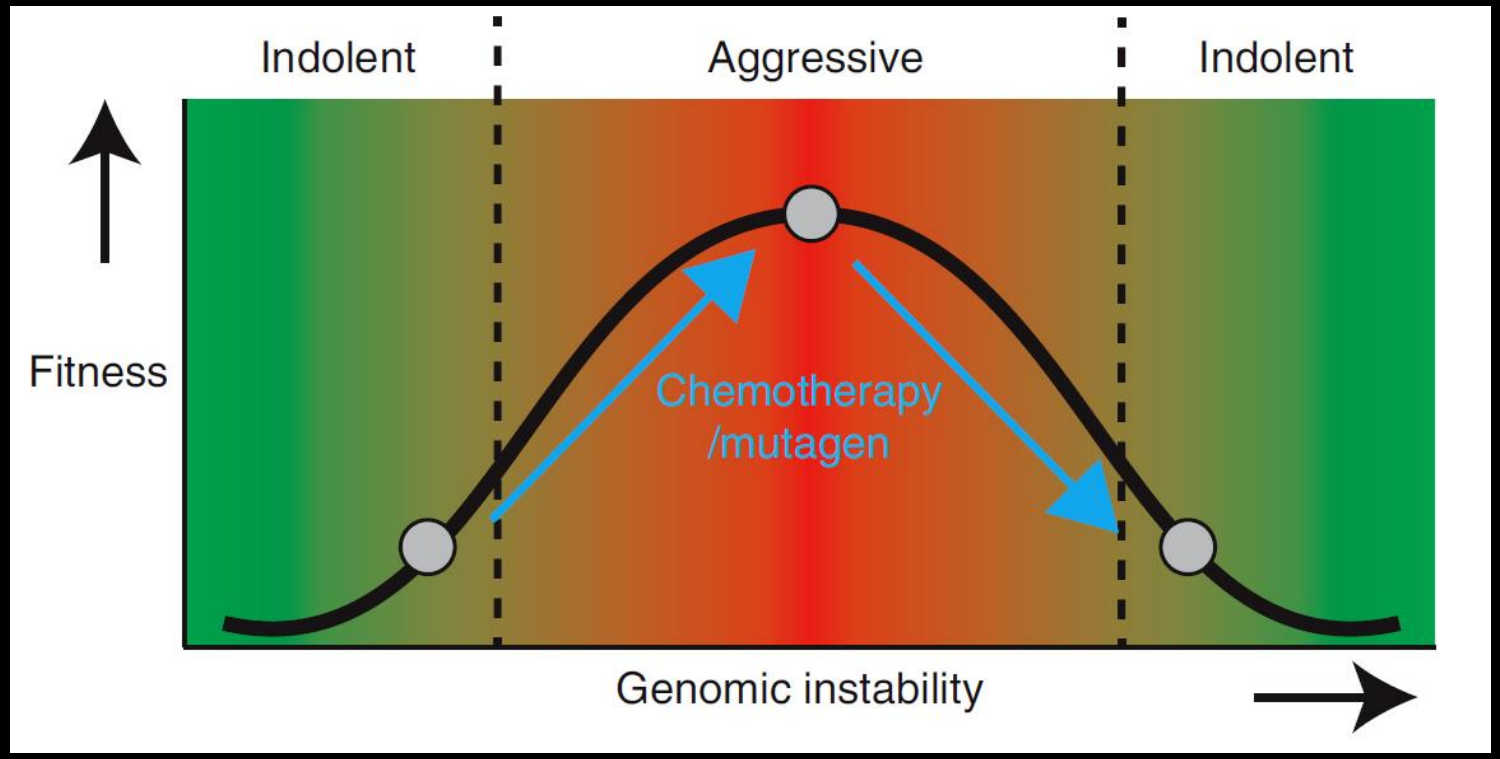
Palmer AC, AACR Part II
medRxiv,https://doi.org/10.1101/2020.01.31.20019604, version JUL 10, 2020

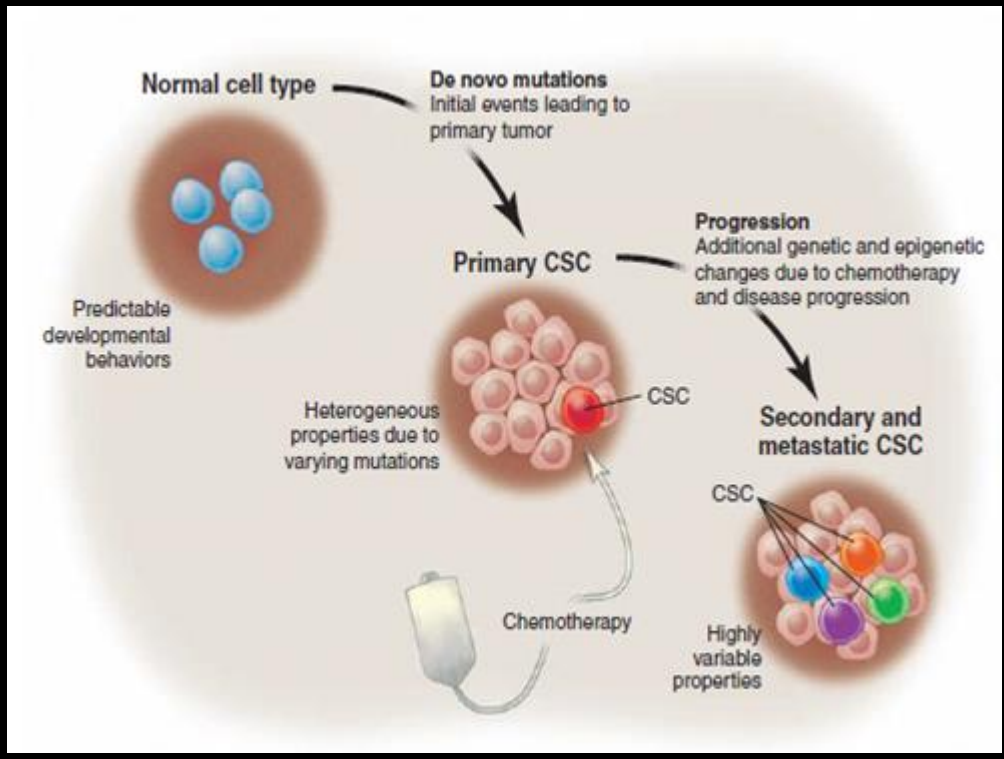
Lack of synergistic effect: what does it mean in clinical practice?

- **If there is no synergistic effect, should we still choose combo?**
  - IO combo “longer median PFS (and OS) ”more patients can survive longer.
  - “Bet hedging” effect
- **Probably YES**, combo is still recommended.
  - Caution: financial toxicity
- **Can we use these drugs in sequence?**
  - If you are confident: the patient can survive and take the subsequent therapy.
  - The efficacy may not be identical if the drug is used in subsequent lines.
- **Unmet needs in clinical practice**
  - Biomarkers? To guide monotherapy or (different types of) combo?
  - If synergistic effect exists: personalized IO combo?

Palmer AC, AACR Part II

Chemotherapy potentially increase the level of genomic instability and create cancer stem cells (CSCs)





CSCs are highly tumorigenic, fundamentally responsible for continued malignant growth, chemoresistance inducer, and initiators of metastasis as well as they have many **immunomodulatory characteristics to create an immune-suppressive microenvironment** for being safe from immune attack

Life Sci. 2020 Jun 25:118005
*Science 2009;*24:1670-1673
Venkatesan S et al. Cold Spring Harb Perspect Med doi: 10.1101/cshperspect.a026617

What is the role of Limited course of chemotherapy in combination immunotherapy?

- Provide rapid disease control, improve ORR, PFS,
- Avoid prolong chemotherapy adverse effects
- Improve immunotherapy effect (We still don’t know the impact of longer duration of chemotherapy on immunotherapy)

2020 ASCO ANNUAL MEETING
UNITE AND CONQUER: ACCELERATING PROGRESS TOGETHER

Nivolumab + ipilimumab + 2 cycles of platinum-doublet chemotherapy vs 4 cycles chemotherapy as first-line treatment for stage IV/recurrent NSCLC: CheckMate 9LA

Martin Reck,[1] Tudor-Eliade Ciuleanu,[2] Manuel Cobo,[3] Michael Schenker,[4] Bogdan Zurawski,[5] Juliana Menezes,[6] Eduardo Richardet,[7] Jaafar Bennouna,[8] Enriqueta Felip,[9] Oscar Juan-Vidal,[10] Aurelia Alexandru,[11] Hiroshi Sakai,[12] Arnaud Scherpereel,[13] Shun Lu,[14] Thomas John,[15] David P. Carbone,[16] Stephanie Meadows-Shropshire,[17] Jinchun Yan,[17] Luis G. Paz-Ares[18]

[1]Department of Thoracic Oncology, Airway Research Center North, German Center for Lung Research, LungClinic, Grosshansdorf, Germany; [2]Institutul Oncologic Prof. Dr. Ion Chiricuta and UMF Iuliu Hatieganu, Cluj-Napoca, Romania; [3]Unidad de Gestión Clínica Intercentros de Oncología Médica, Hospitales Universitarios Regional y Virgen de la Victoria, IBIMA, Málaga, Spain; [4]SF. Nectarie Oncology Center, Craiova, Romania; [5]Ambulatorium Chemioterapii, Bydgoszcz, Poland; [6]Hospital Nossa Senhora Da Conceição, Porto Alegre, Brazil; [7]Instituto Oncológico De Córdoba, Córdoba, Argentina; [8]Thoracic Oncology Unit, University Hospital of Nantes, Nantes, France; [9]Vall d'Hebron University Hospital, Barcelona, Spain; [10]Hospital Universitario La Fe, Valencia, Spain; [11]Institute of Oncology "Prof. Dr. Alexandru Trestioreanu" Bucha, Bucharest, Romania; [12]Saitama Cancer Center, Saitama, Japan; [13]Regional University Hospital Center of Lille, Hospital Calmette, Lille, France; [14]Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai JiaoTong University, Shanghai, China; [15]Austin Hospital, Heidelberg, Australia; [16]The Ohio State University Comprehensive Cancer Center, Columbus, Ohio, USA; [17]Bristol-Myers Squibb, Princeton, NJ, USA; [18]Hospital Universitario 12 de Octubre, CNIO, Universidad Complutense & CiberOnc, Madrid, Spain

Abstract Number 9501

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)

N = 719

R 1:1

n = 361

NIVO 360 mg Q3W + **IPI** 1 mg/kg Q6W
+
Chemo[d] Q3W **(2 cycles)**

n = 358

Chemo[d] Q3W **(4 cycles)**
with optional pemetrexed maintenance (NSQ)

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

Primary endpoint

- OS

Secondary endpoints

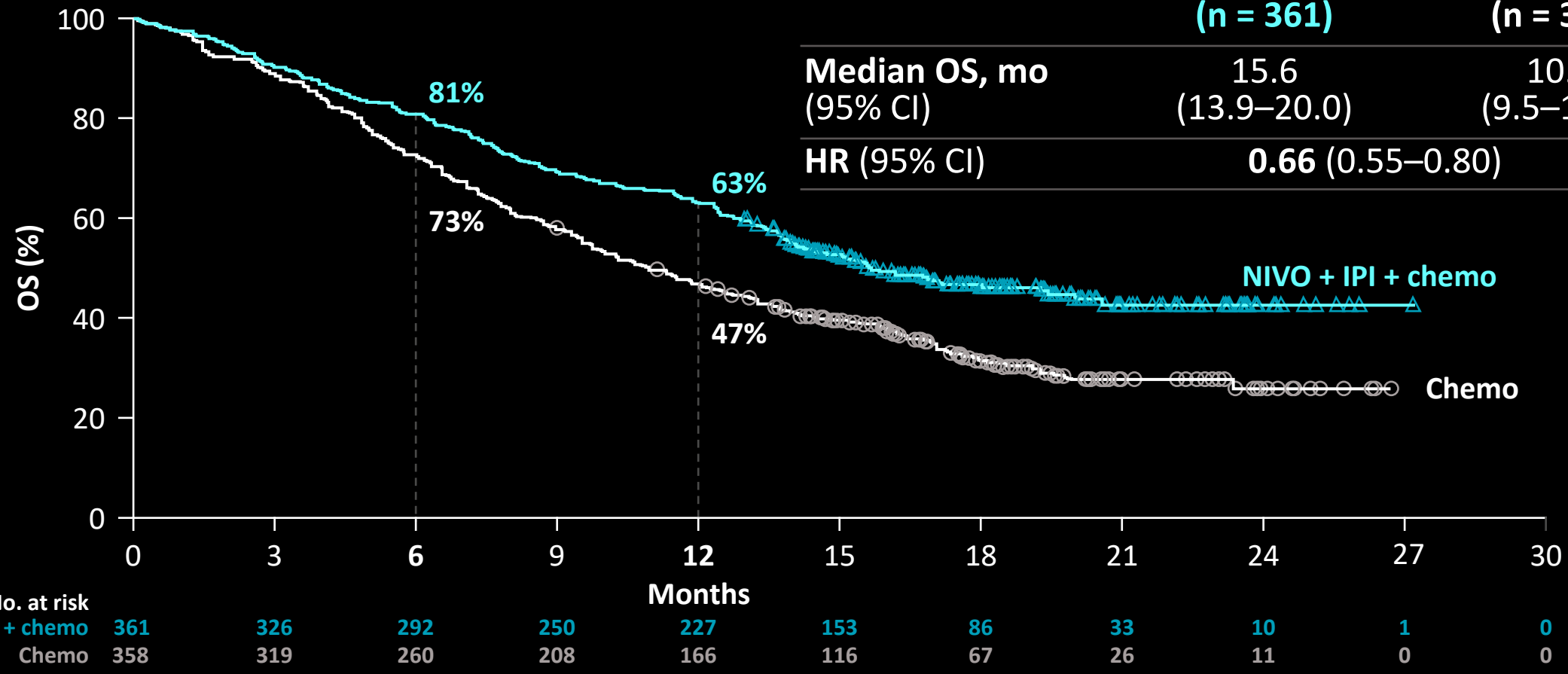
- PFS by BICR[e]
- ORR by BICR[e]
- Efficacy by tumor PD-L1 expression

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.

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)	



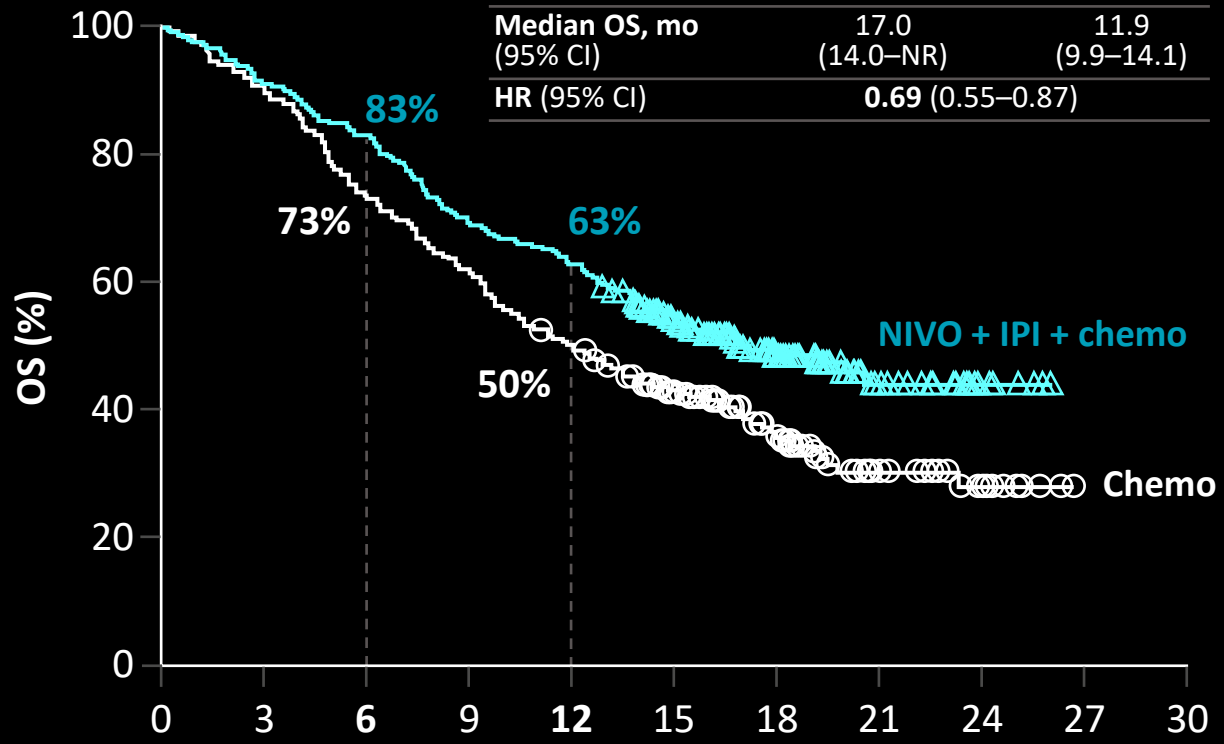
Minimum follow-up: 12.7 months.

[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 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)	

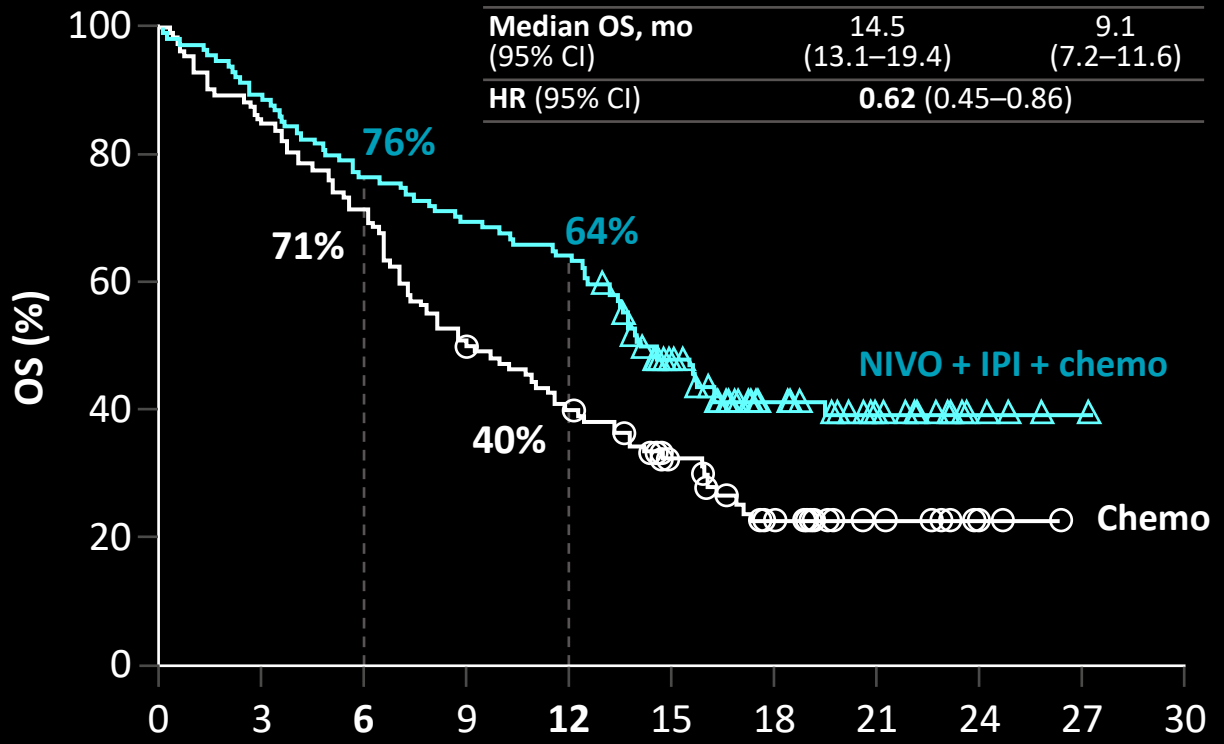


No. at risk

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)	



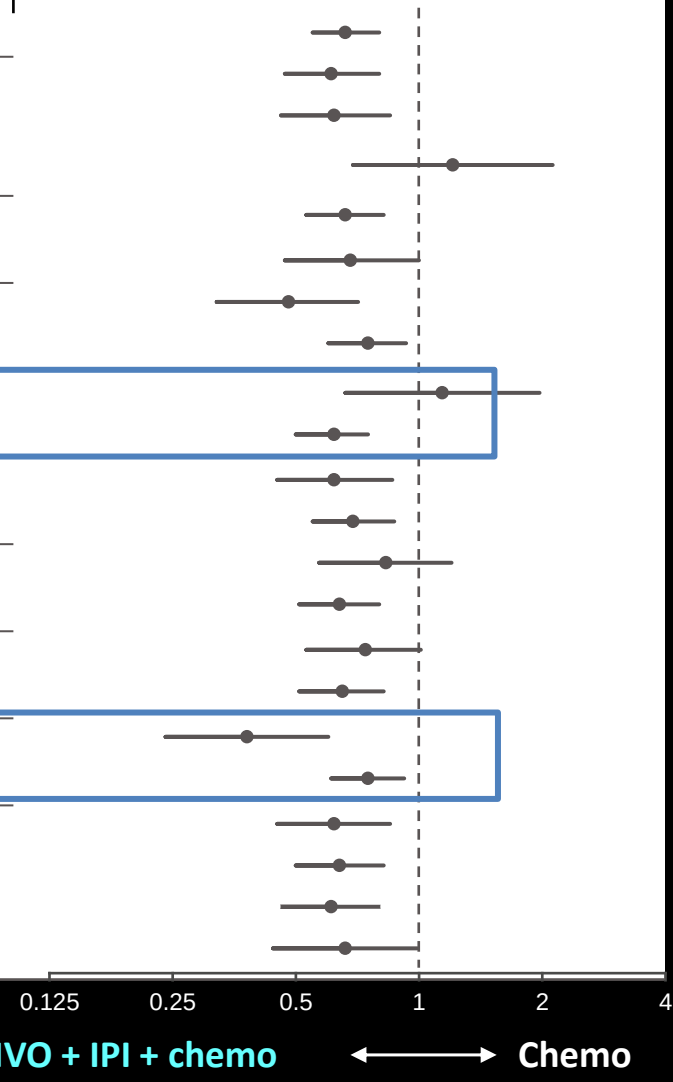
NIVO + IPI + chemo	115	102	88	80	73	46	24	13	4	1	0
Chemo	112	96	80	56	44	29	14	8	2	0	0

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 subgroup analysis

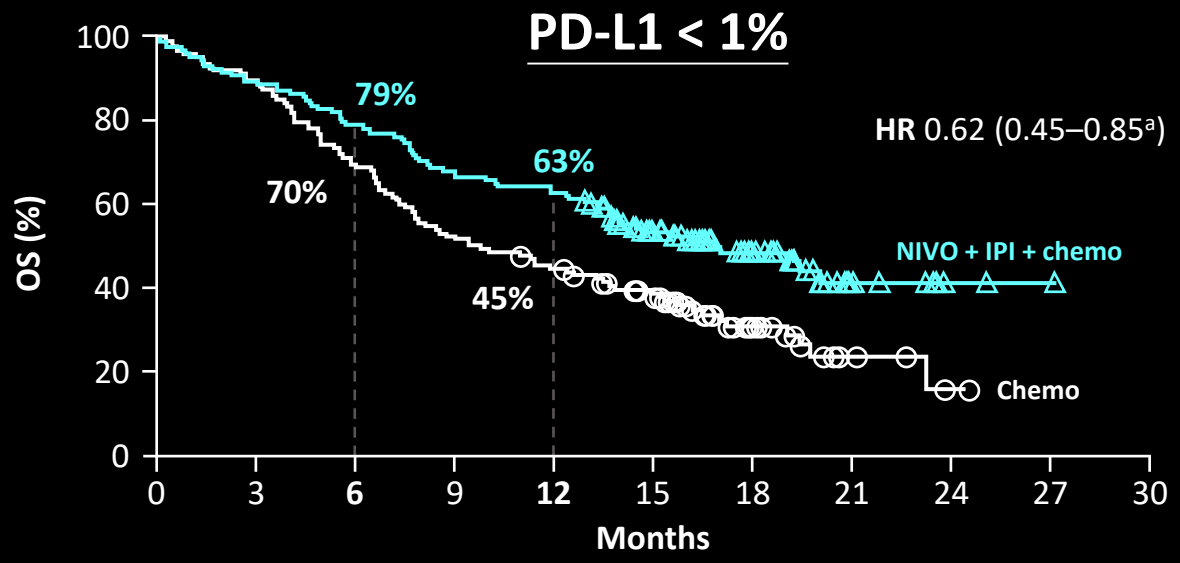
Subgroup	Median OS, mo		Unstratified HR
	NIVO + IPI + chemo n = 361	Chemo n = 358	
All randomized (N = 719)	15.6	10.9	0.66[a]
< 65 years (n = 354)	15.6	10.7	0.61
65 to < 75 years (n = 295)	19.4	11.9	0.62
≥ 75 years (n = 70)	8.5	11.5	1.21
Male (n = 504)	14.1	9.8	0.66
Female (n = 215)	19.4	15.8	0.68
ECOG 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

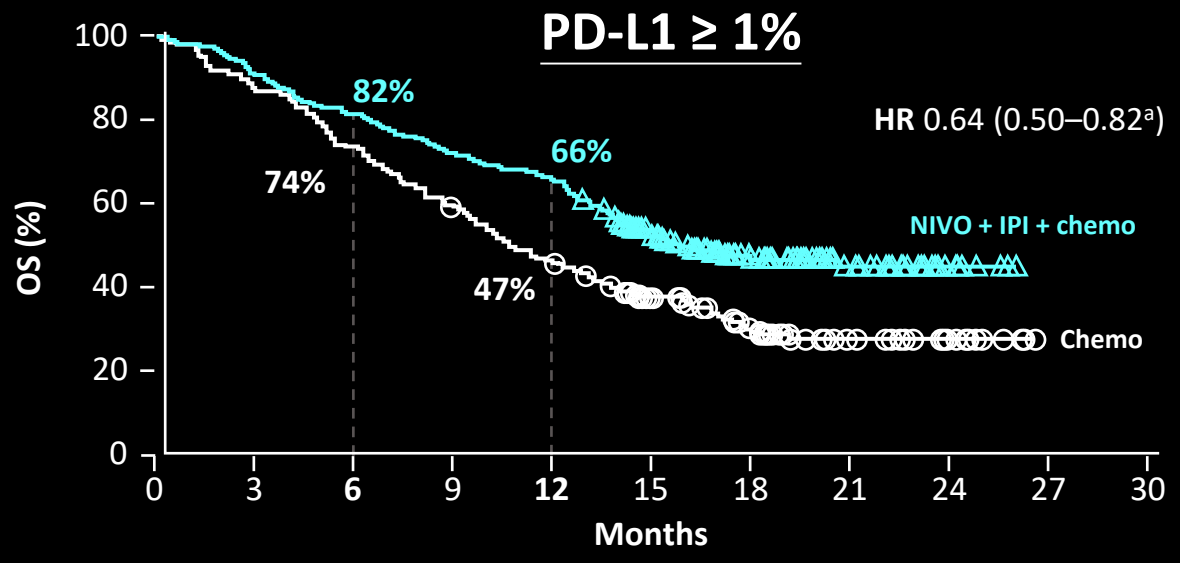


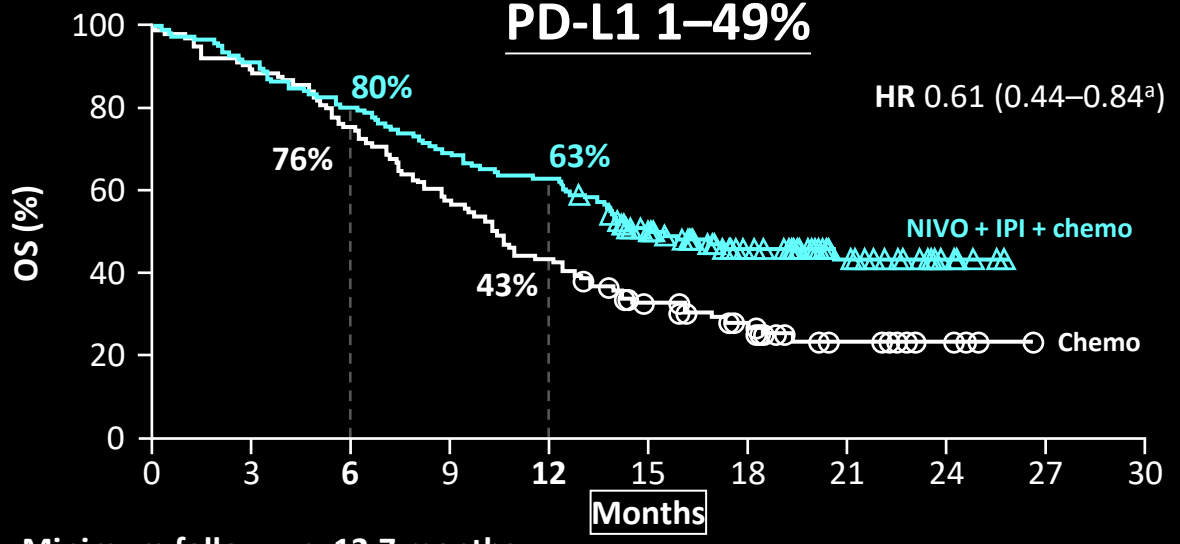
Minimum follow-up: 12.7 months.

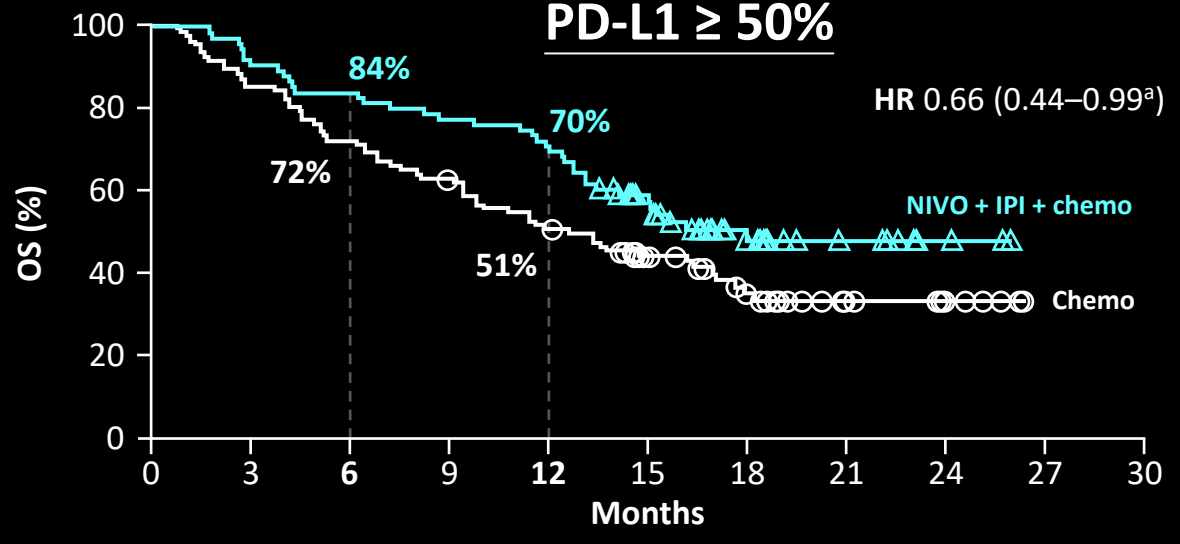
[a]Stratified HR; unstratified HR was 0.67 (95% CI, 0.55–0.81).

Overall survival by PD-L1 expression level





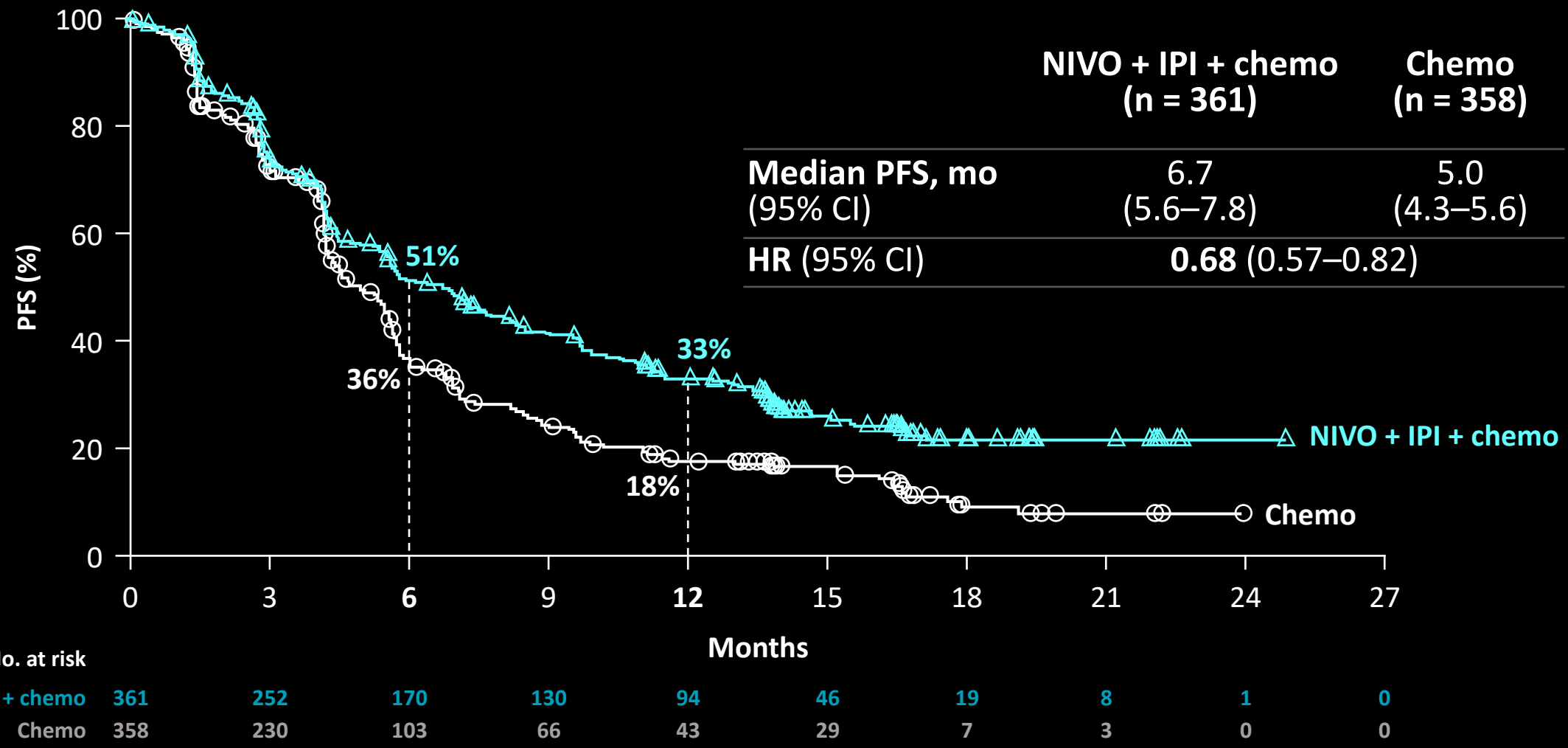




Minimum follow-up: 12.7 months.

[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.

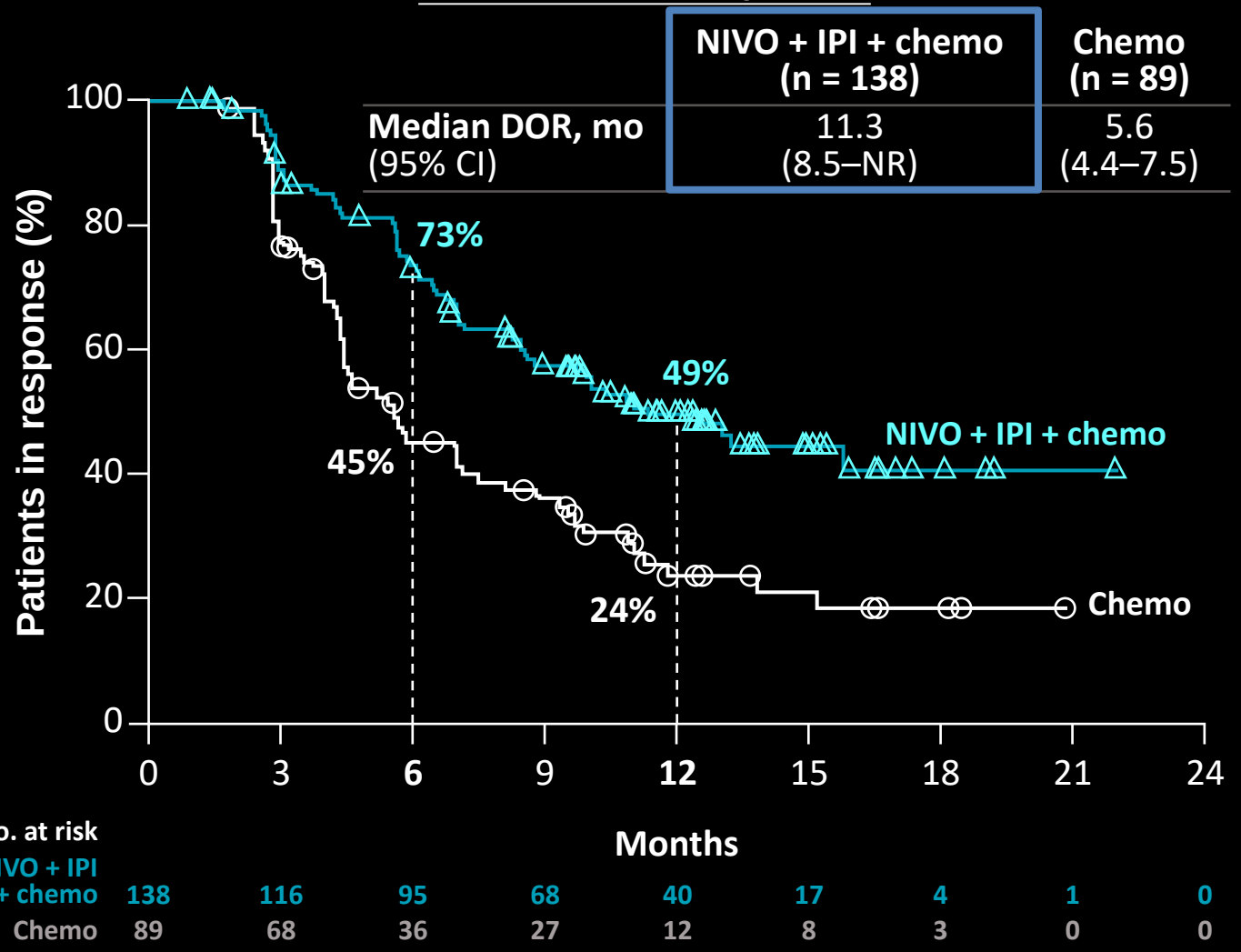
[a]Patients who did not progress or die were censored on the date of their last evaluable tumor assessment; those who did not have any study tumor assessments and did not die were censored on their date of randomization; patients without reported progression who went on to receive palliative local therapy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

ORR per BICR and DoR

Response rates

	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
ORR, n (%)	138 (38)	89 (25)
Odds ratio (95% CI)	1.9 (1.4–2.6)	
BOR, n (%)		
CR	8 (2)	4 (1)
PR	130 (36)	85 (24)
SD	164 (45)	185 (52)
PD	32 (9)	45 (13)
DCR, n (%)	302 (84)	274 (76)

Duration of response



Minimum follow-up: 12.2 months.

Safety summary of TRAEs

Due to differences in study designs and study populations, comparisons with other NSCLC IO studies should not be made.

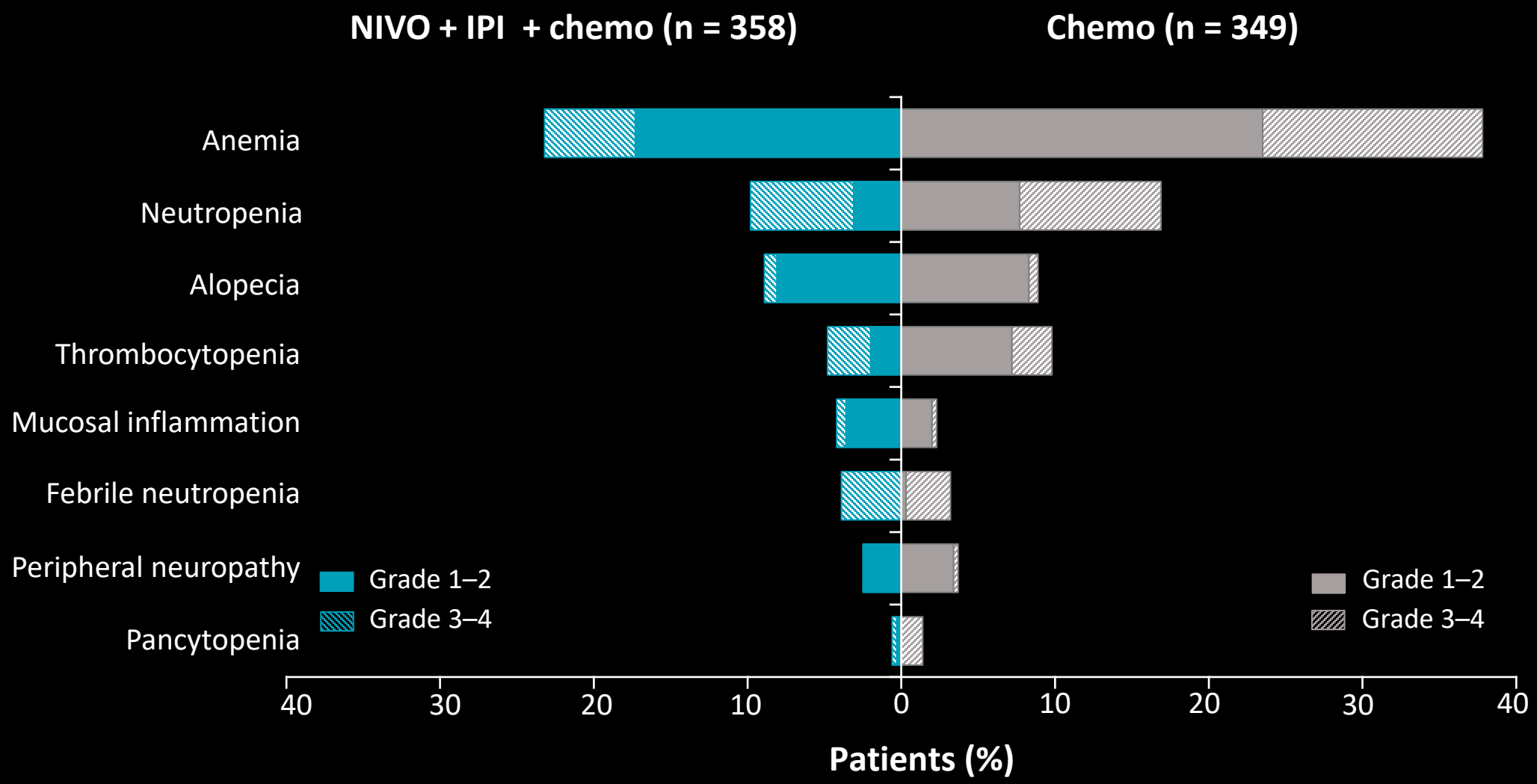
TRAE,[a] %	NIVO + IPI + chemo (n = 358)		Chemo (n = 349)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Any TRAE	92	47	88	38
TRAEs leading to discontinuation of any component of the regimen	19	16	7	5
Serious TRAEs	**30**	**25.4**	**18**	**15**
Treatment-related deaths[b]	2		2	

- 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.

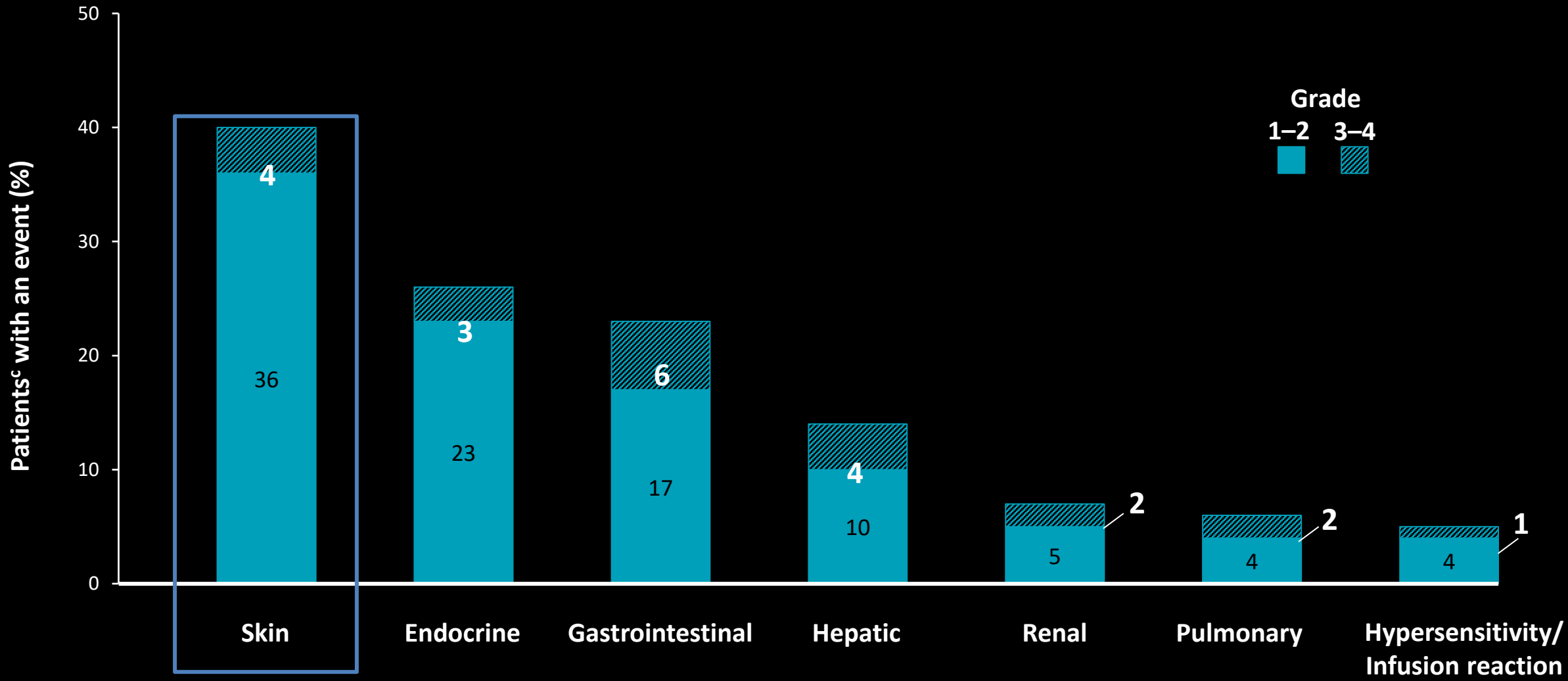
[a]Includes events reported between first dose and 30 days after last dose of study drug; [b]Treatment-related deaths in the NIVO + IPI + chemo arm (n = 7; 1 for each event) were due to acute renal failure due to chemotherapy, thrombocytopenia, pneumonitis, hepatic toxicity, hepatitis, diarrhea, sepsis, 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).

TRAEs typically associated with chemo[a]



[a]Includes events reported between first dose and 30 days after last dose of study drug.

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

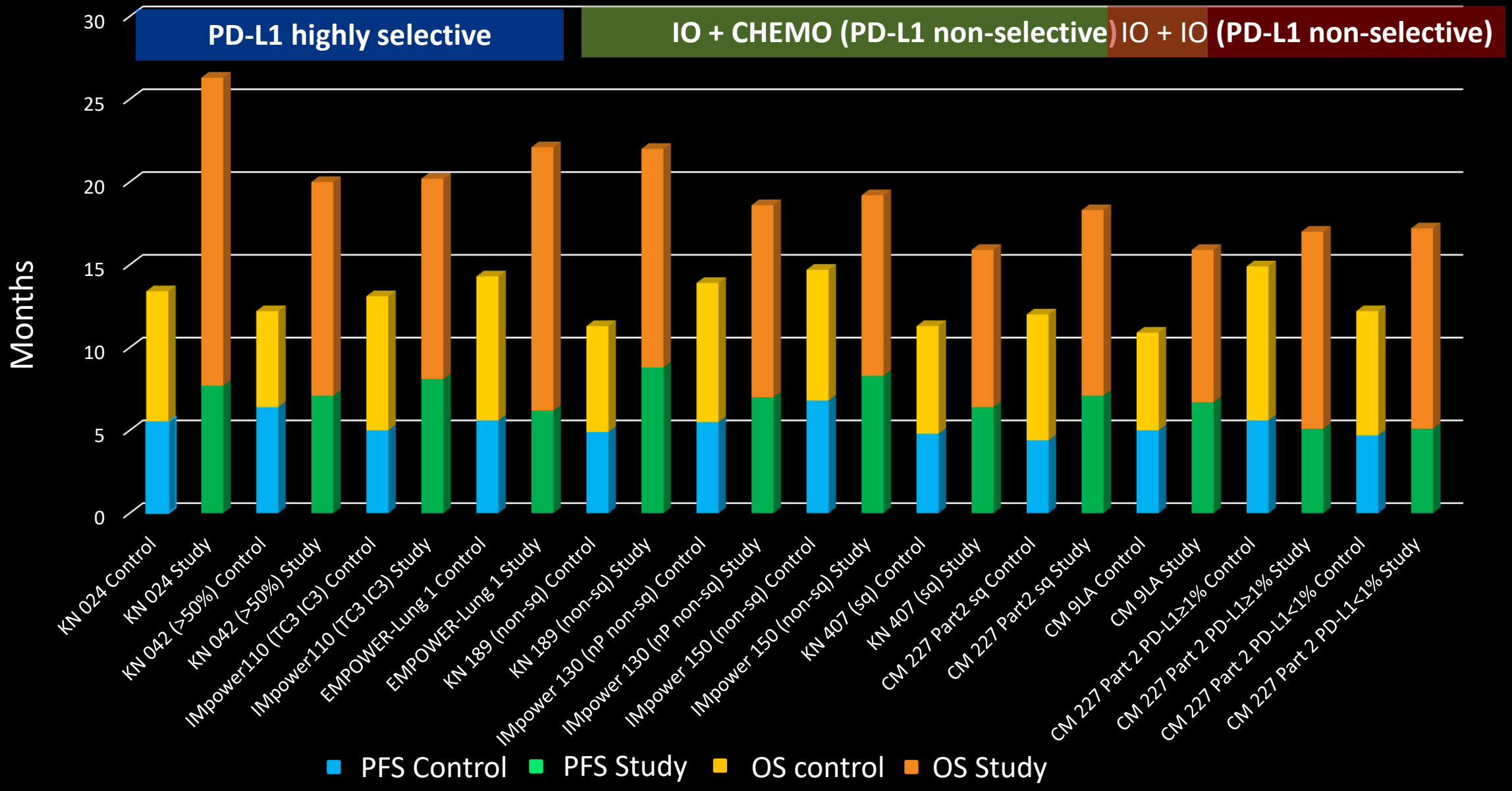


[a]Treatment-related select AEs are those with potential immunologic etiology that require frequent monitoring/intervention; [b]Includes events reported between first dose and 30 days after last dose of study drug; [c]The total number of patients treated with NIVO + IPI + chemo was 358.

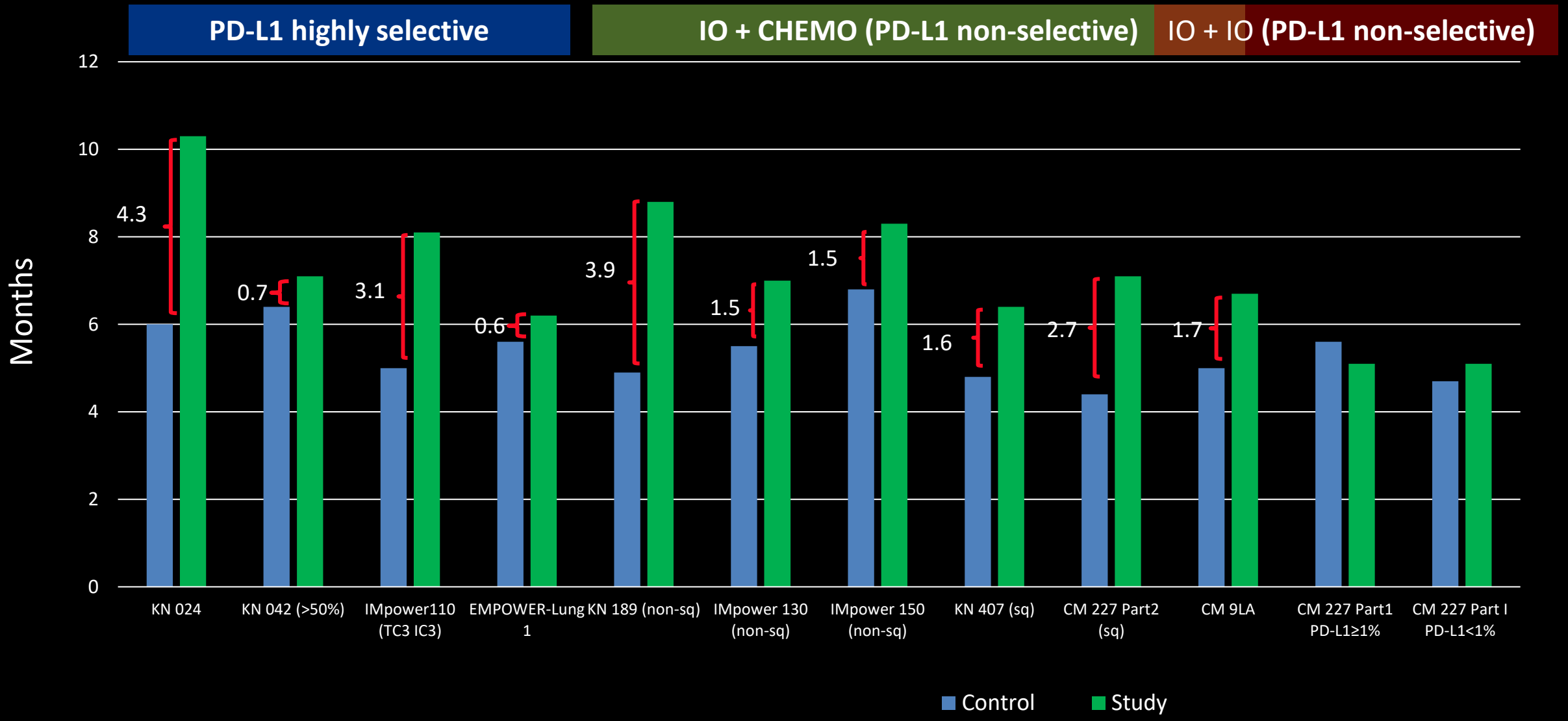
Summary: NIVO + IPI + chemo in first-line advanced NSCLC

- 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

Frontline Treatment OS: IO mono vs. IO + C/T

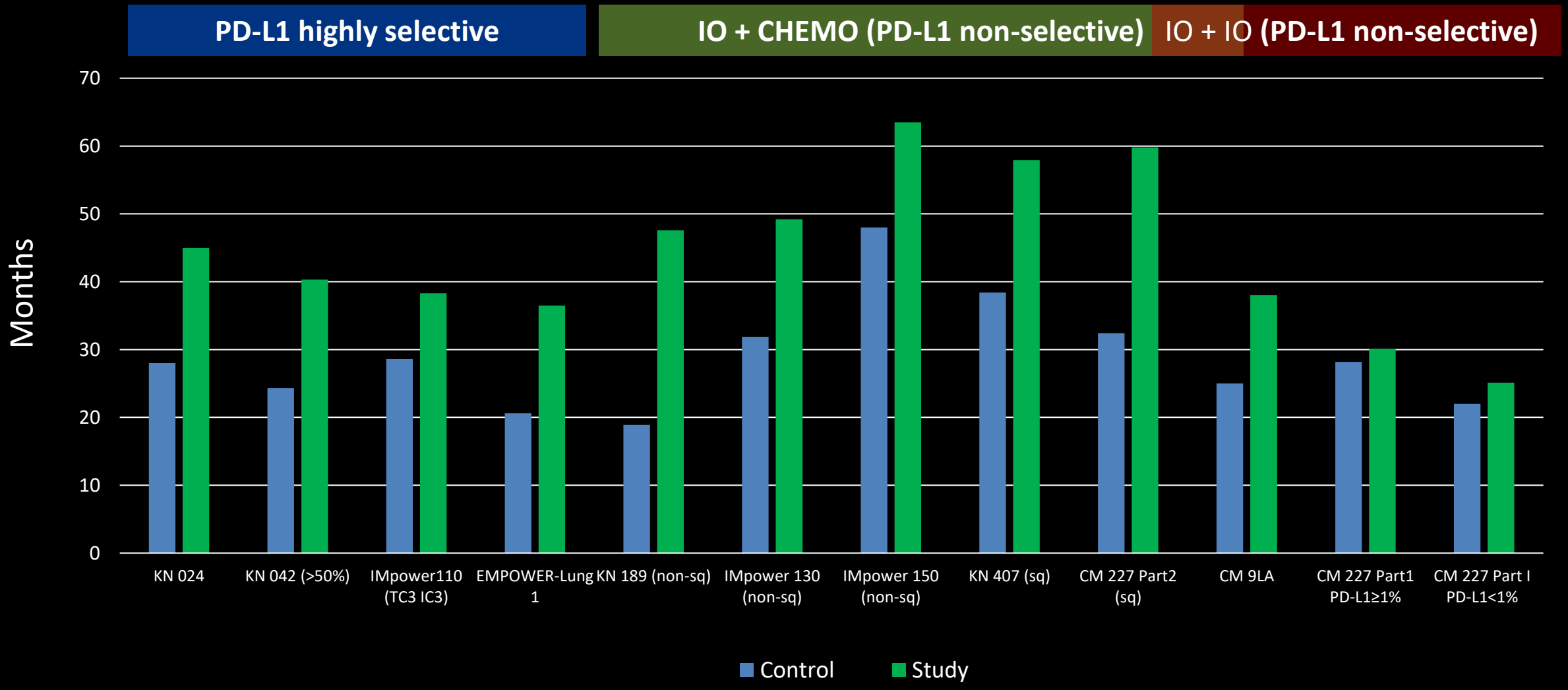


Frontline Treatment PFS: IO mono vs. IO + C/T



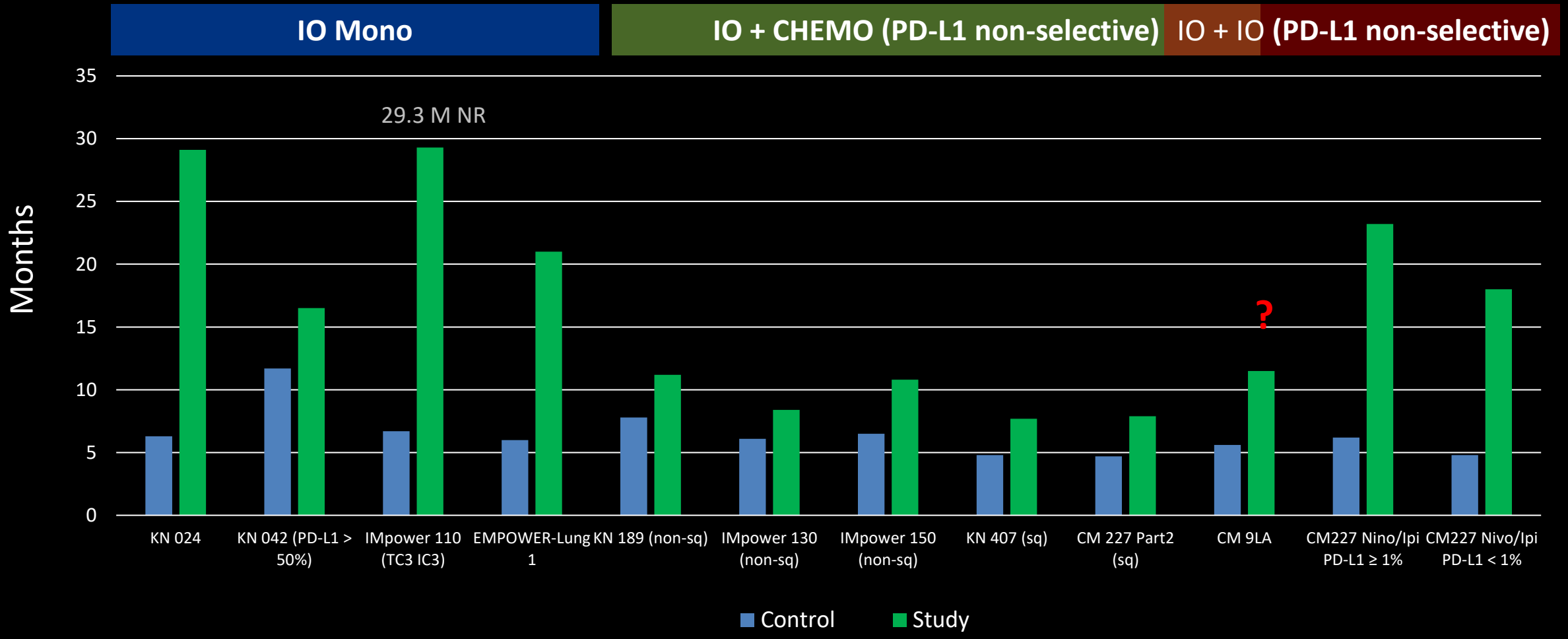
Some trials are not approved by TFDA. It is no intention to promote.

Frontline Treatment ORR: IO mono vs. IO + C/T



Some trials are not approved by TFDA. It is no intention to promote.

Frontline Treatment DoR: IO mono vs. IO + C/T vs. IO + IO



Some trials are not approved by TFDA. It is no intention to promote.

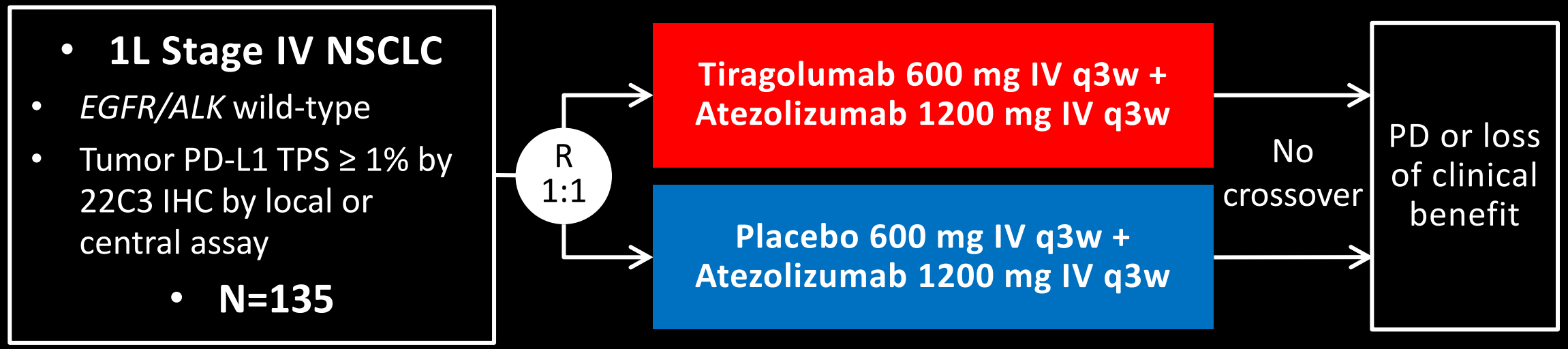
How to Choose in Clinics?

PD-1 (-)	PD-1 ≥1%, <50%	PD-1 ≥50%
Chemo + Pembro	Chemo + Pembro	Pembro
Chemo + Bev + Atezo (NSQ)	Chemo + Bev + Atezo (NSQ)	Atezo
Nivo + Ipi	Nivo + Ipi	Chemo + Pembro
Chemo + Nivo + Ipi	Chemo + Nivo + Ipi	Chemo + Bev + Atezo (NSQ)
	Pembro (in selected patients)	Nivo + Ipi
		Chemo + Nivo + Ipi
IO + IO long DoR, but ORR no change	Chemo increases ORR, but …	**IO mono may be good, but not good enough**

- PS, age, perceived regimen toxicity/ schedule/ patient preference,? Hx of AI,? STK11m/TMB
- Cost

Modified from Scott Gettinger ASCO 2020

CITYSCAPE Study Design



Stratification Factors:

- PD-L1 TPS (1-49% vs ≥ 50%)
- Histology (Non-Squamous vs Squamous)
- Tobacco use (yes vs no)

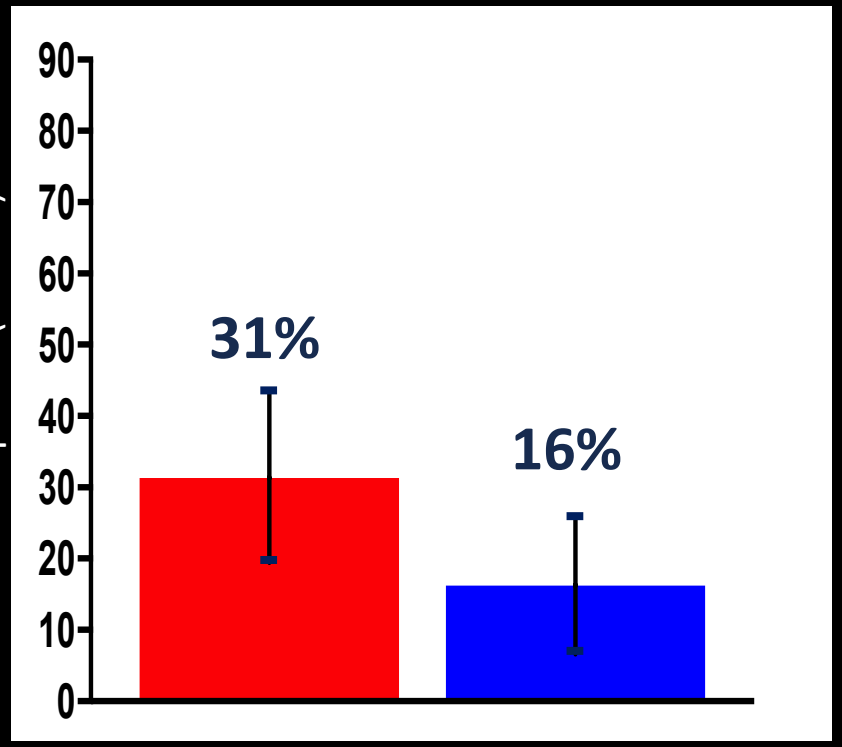
- **Co-Primary Endpoints: ORR** and **PFS**
- **Key Secondary Endpoints: Safety**, DOR, OS, Patient-reported outcomes (PROs)
- **Exploratory Endpoints:** Efficacy analysis by PD-L1 status

DOR = duration of response; IHC = immunohistochemistry; ORR = confirmed overall response rate; OS = overall survival; PD = progressive disease; PFS = progression free survival ; q3w = every 3 weeks; R = randomized; TPS = tumor proportion score

Confirmed Overall Response Rate (ORR) and PFS

ITT: ORR

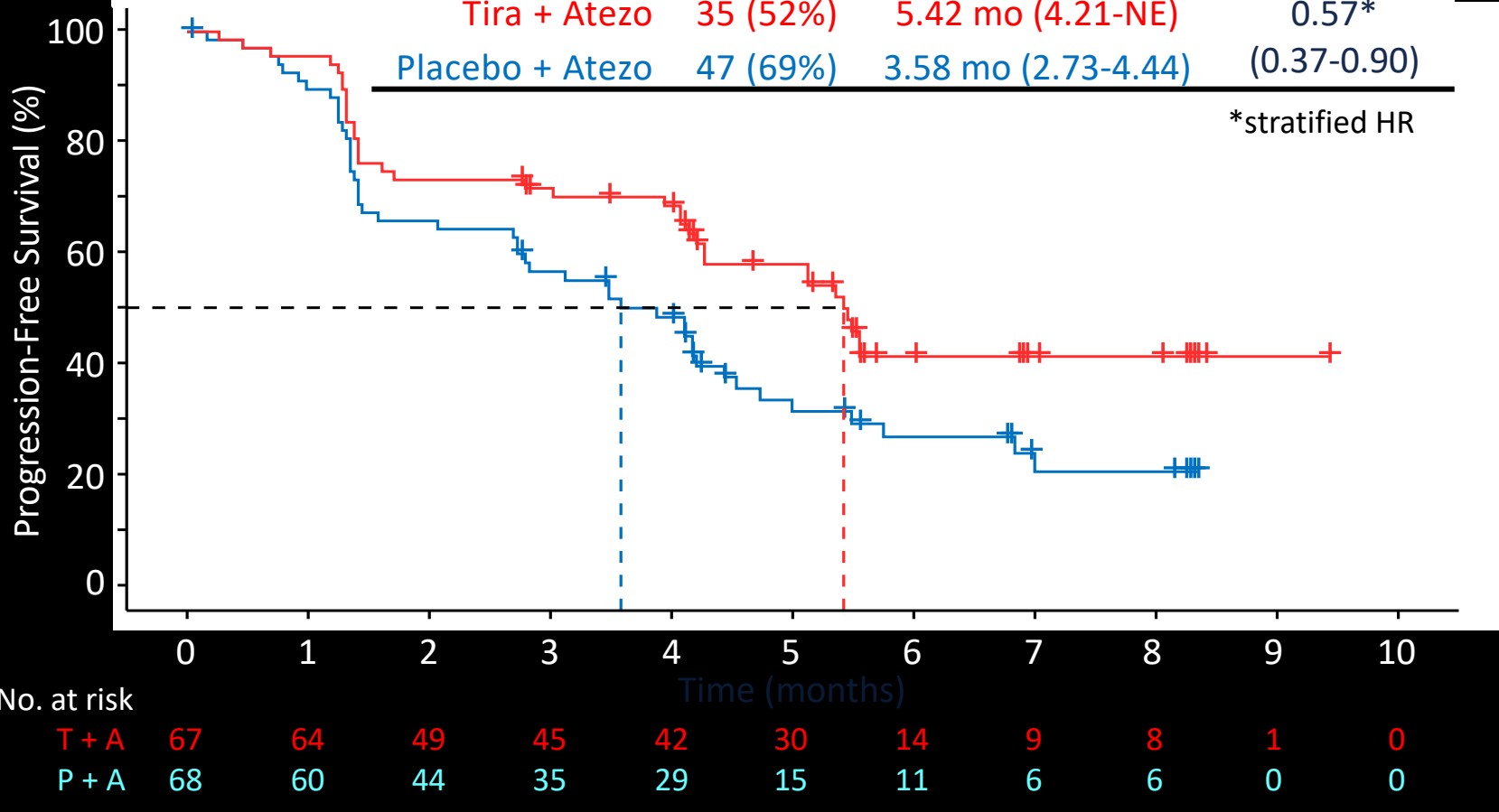
(n=135)



ITT: Investigator-Assessed PFS

	Events	Median (95% CI)	HR (95% CI)
Tira + Atezo	35 (52%)	5.42 mo (4.21-NE)	0.57* (0.37-0.90)
Placebo + Atezo	47 (69%)	3.58 mo (2.73-4.44)	

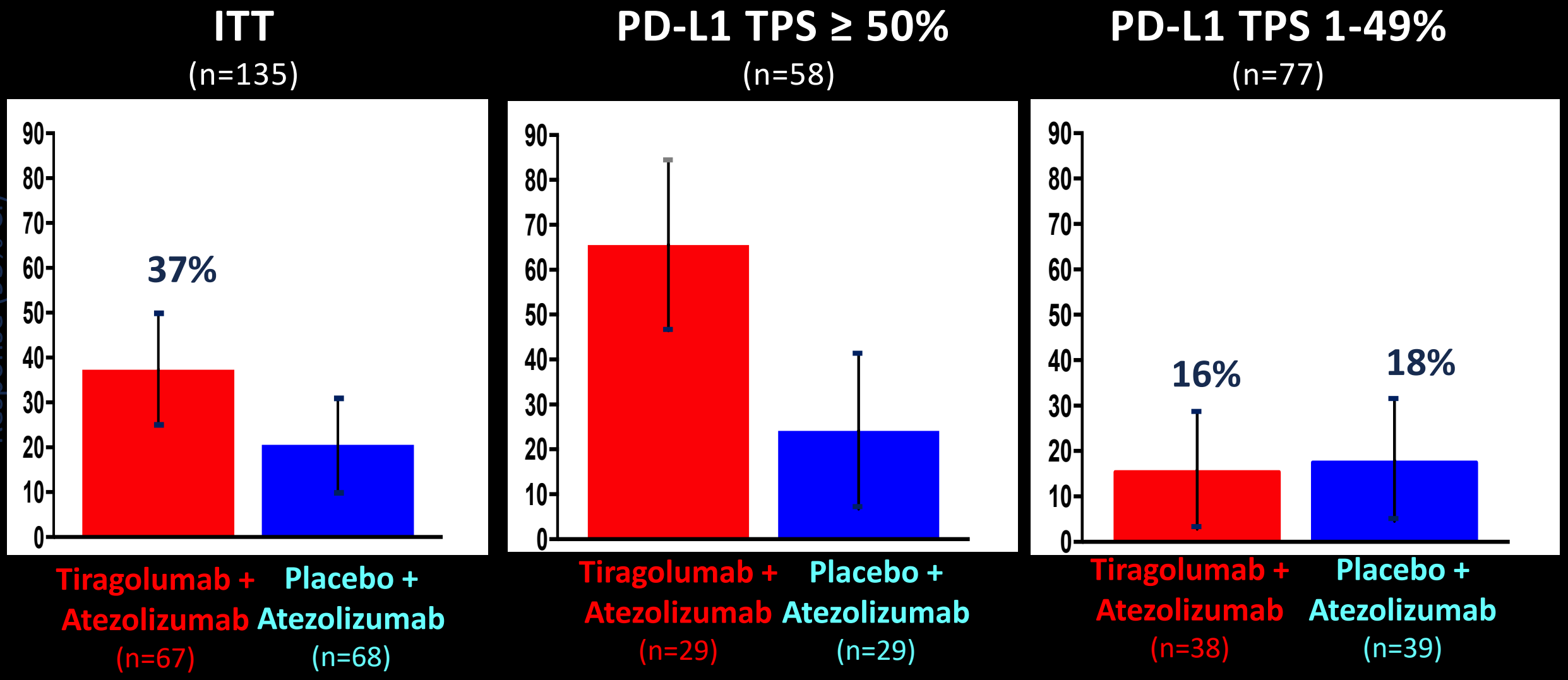
*stratified HR



ITT= intention-to-treat; NE = non-evaluable, P+A = placebo + atezolizumab; T+A = tiragolumab + atezolizumab

Primary analysis data cutoff: 30 June 2019

Updated Confirmed Overall Response Rate (ORR)

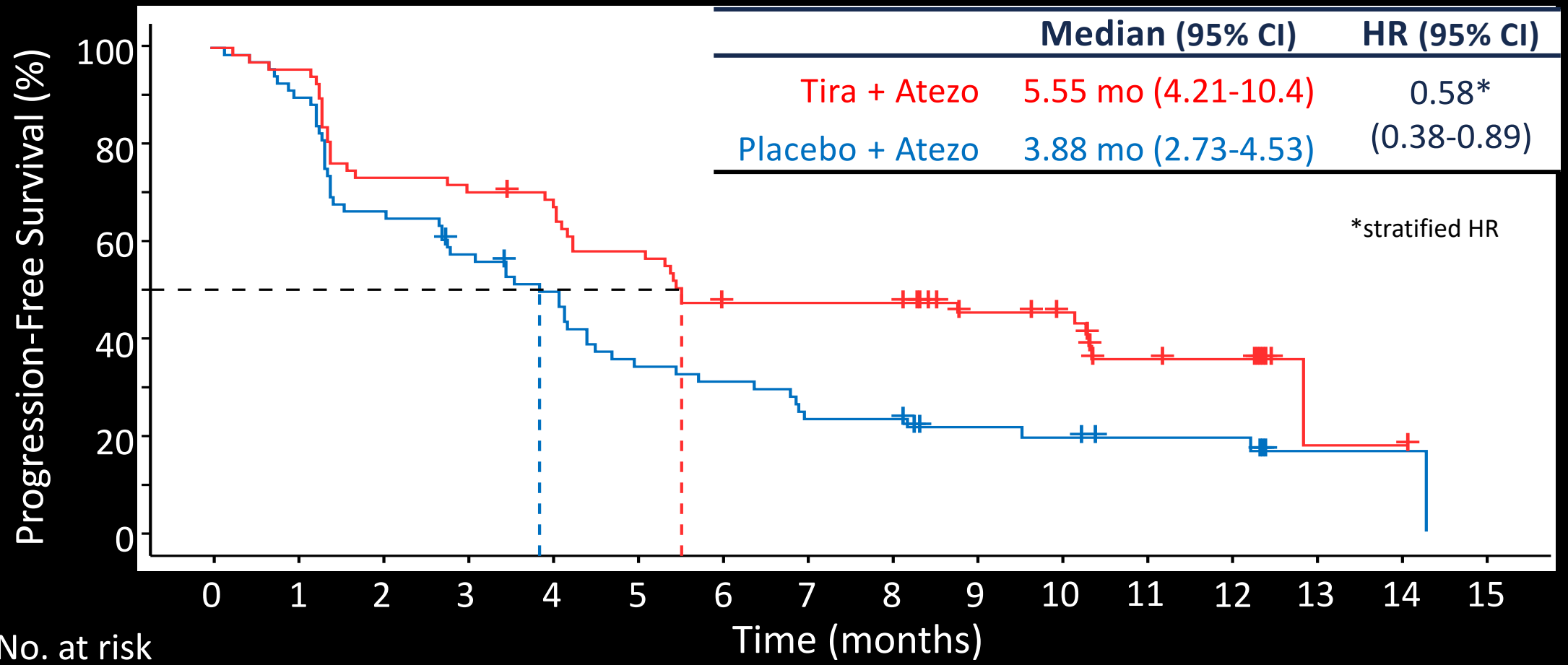


ITT = intention-to-treat; TPS = tumor proportion score

Updated data cutoff: 02 Dec 2019

Melissa Johnson ASCO 2020

Updated Investigator-Assessed PFS: ITT



	Median (95% CI)	HR (95% CI)
Tira + Atezo	5.55 mo (4.21-10.4)	0.58* (0.38-0.89)
Placebo + Atezo	3.88 mo (2.73-4.53)	

No. at risk																Events
T + A	67	64	49	48	45	38	31	30	30	22	20	10	9	1	1	0	41 (61%)
P + A	68	61	45	38	32	22	20	15	15	10	9	7	7	1	1	0	55 (81%)

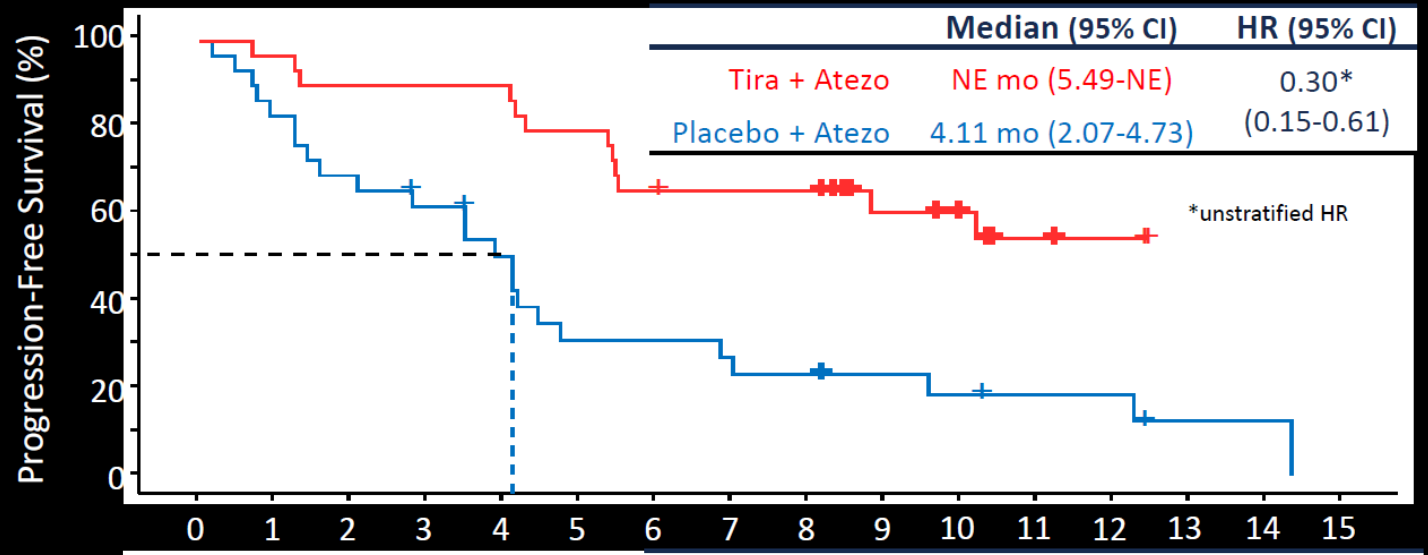
ITT= intention-to-treat; P+A = placebo + atezolizumab; T+A = tiragolumab + atezolizumab

Follow data cutoff: 02 December 2019

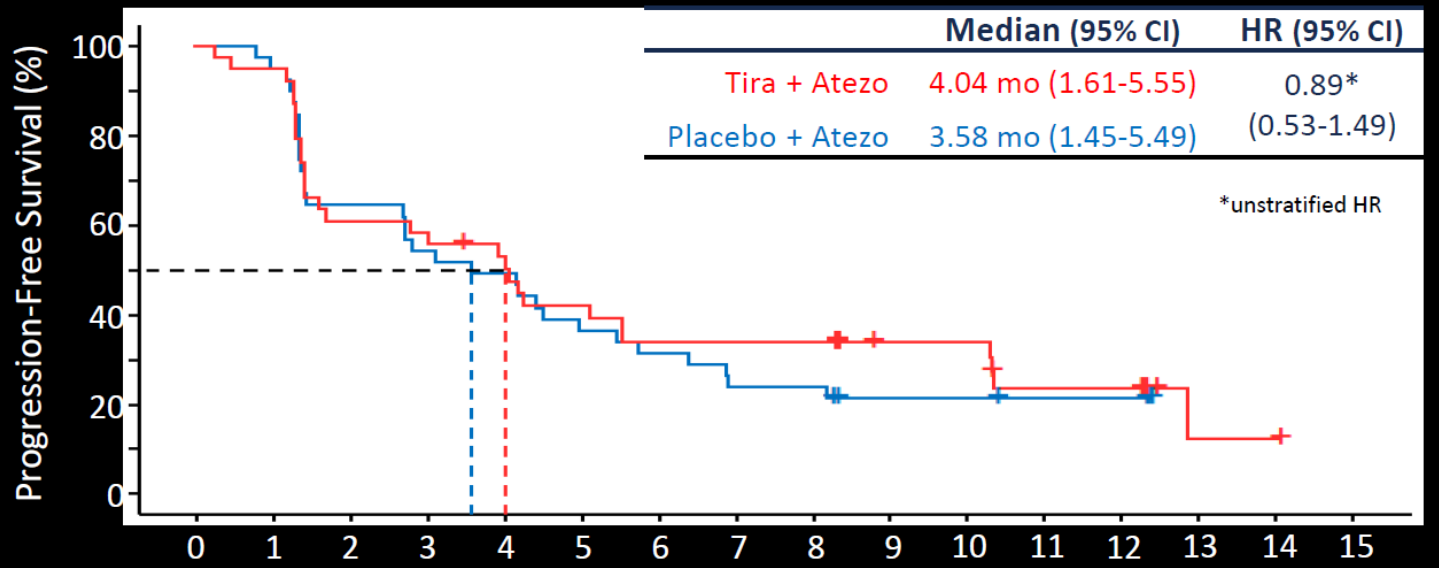
Melissa Johnson ASCO 2020

Investigator-Assessed PFS: PD-L1 TPS ≥ 50% vs. 1-49%

PD-L1 TPS ≥ 50%



PD-L1 TPS 1-49%



Melissa Johnson ASCO 2020

Updated Safety Summary: Exposure and Adverse Events

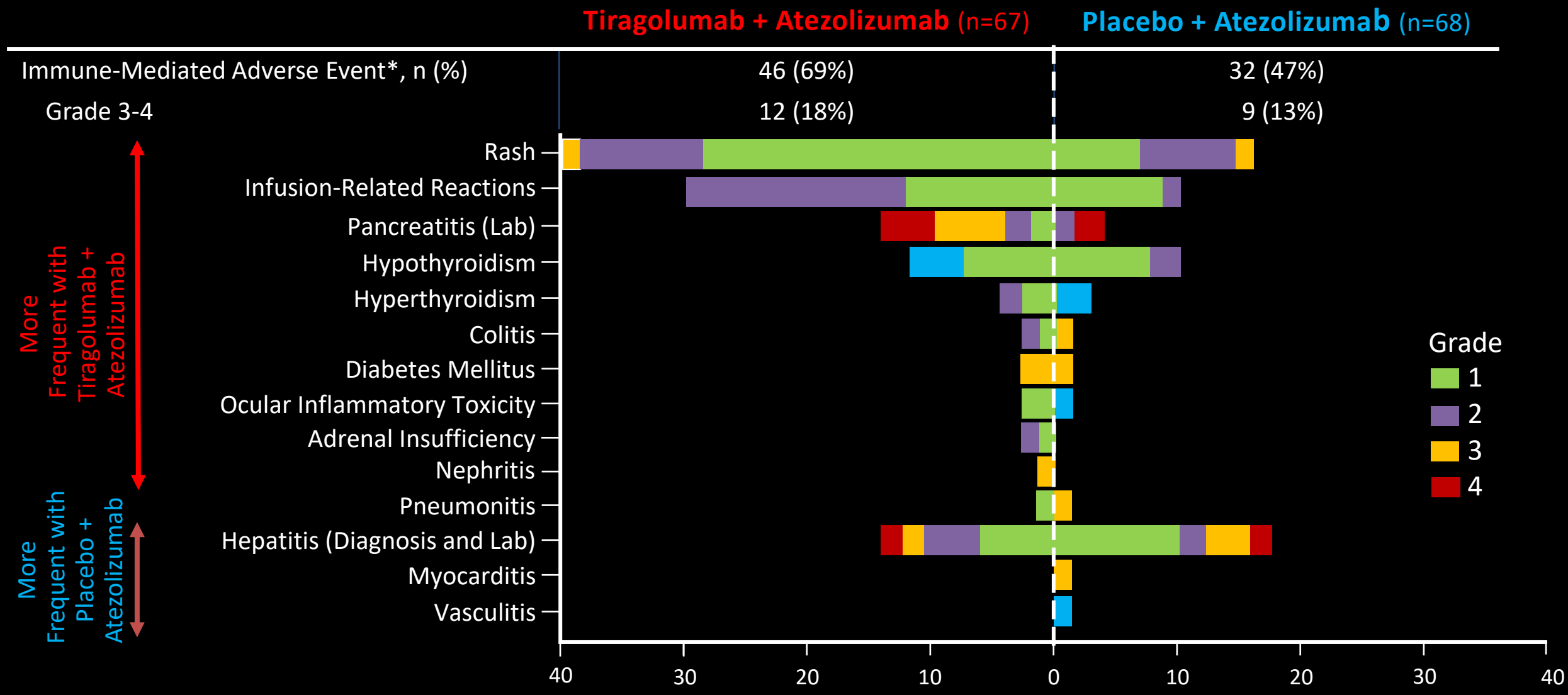
	Tiragolumab + Atezolizumab (n=67)	Placebo + Atezolizumab (n=68)
Median treatment duration, mo. (min-max)	4.99 (0–15.1)	2.81 (0–14.3)
Any-cause AE, n (%)	66 (99%)	65 (96%)
Grade 3-5 AE	32 (48%)	30 (44%)
Grade 5*	3 (5%)	5 (7%)
Serious AE	25 (37%)	24 (35%)
AE leading to dose modification/interruption	27 (40%)	19 (28%)
AE leading to treatment withdrawal	7 (10%)	6 (9%)

Updated data cutoff: 2 Dec 2019

AE = adverse event

* Grade 5 AEs for tiragolumab + atezolizumab: Epstein-Barr virus infection, pyrexia, and pneumonia
Grade 5 AEs for placebo + atezolizumab: cardiorespiratory arrest, cerebrovascular accident, multiple organ dysfunction, pneumonia, and pulmonary embolism

Updated Immune-Mediated Adverse Events



*imAE's captured using Atezo AESI basket strategy to identify possibly immune related PT's

Updated data cutoff: 2 Dec 2019

Melissa Johnson ASCO 2020

Conclusions

- IO along or IO + IO has long DoR, but ORR is lower than IO + Chemo
- If we increase ORR of IO + IO, we might have longer OS
- Our practice is dependent on PD-L1 expression, how about other biomarkers such as TMB, T cell infiltration…
- How to choose IO? We need more information
- Cost, adverse effects are also important in choosing IO therapy

Thanks for Your Attention ！