IO-IO COMBINATIONS: CTLA4/PD-1 combinations

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Disclosures

Personal financial interests

- Advisory board: AstraZeneca, Janssen, Syndax, Genentech, BMS, Merck, Eli Lilly, Celgene, Amgen
- Grant funding: BMS

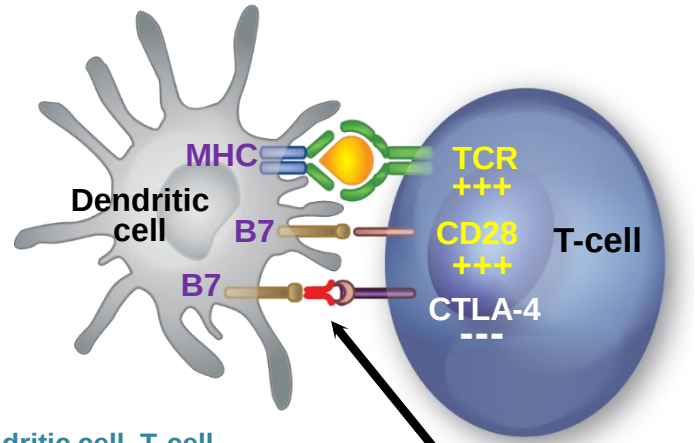
Institutional financial interests

- Clinical trial: Incyte, BMS, MedImmune/AstraZeneca, Janssen, FLXBio

PD-1 and CTLA-4 Mechanisms of Action: Distinct but Complementary

anti-CTLA-4

- **Induces *de novo* anti-tumor T-cell responses[1,2]**
  - Enables adaptation to evolving tumor[2,3]
  - Promotes emergence of memory T cells[4]
  - Causes compensatory increase in tumor PD-L1[2]



Dendritic cell–T-cell interaction in lymph nodes

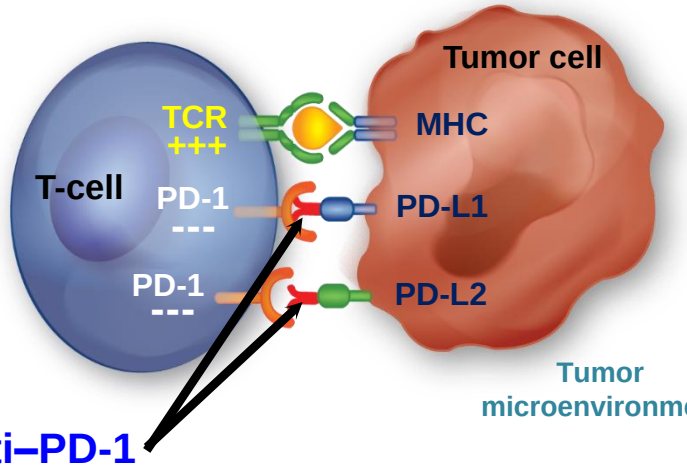
CTLA-4 is expressed on T cells and inhibits T-cell activation[1]

Anti–CTLA-4

anti-PD-1

- **Restores anti-tumor T-cell function[5,6]**
  - Enhances pre-existing T-cell response[5]
  - Increases cytokine production[7]

PD-1 expression on tumor-infiltrating lymphocytes interacting with PD-L1 / PD-L2 is associated with reduced effector function



Tumor microenvironment

Anti–PD-1

Adapted from Peters S et al ESMO 2019

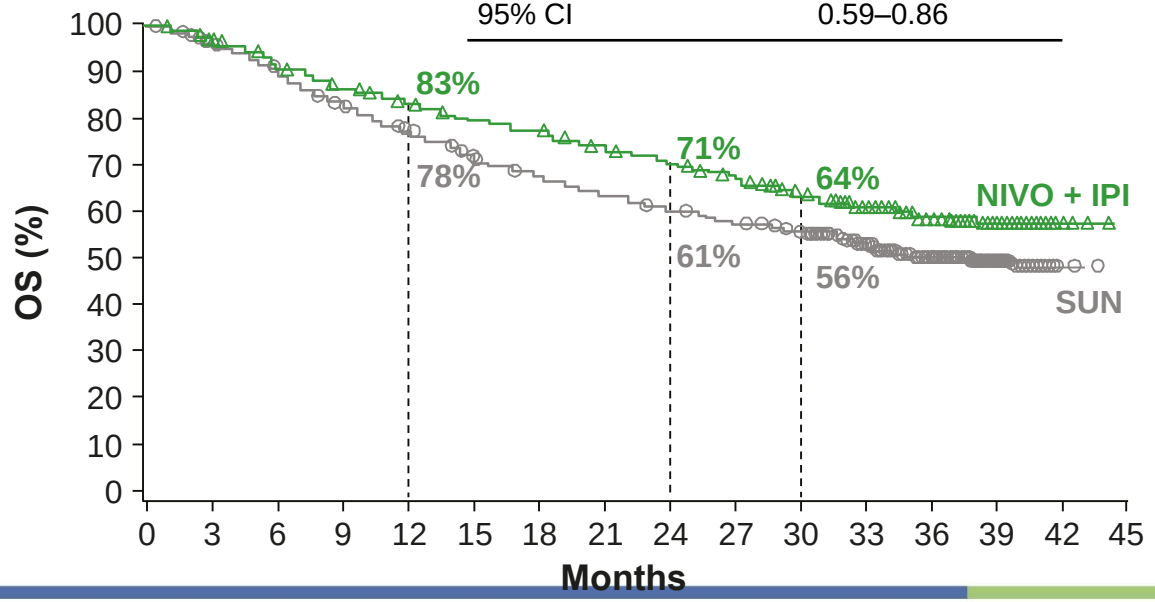
1. Pardoll DM. *Nat Rev Cancer* 2012;12:252–264. 2. Wei SC, et al. *Cancer Discov* 2018;8:1069–1086. 3. Wei SC, et al. *Immunity* 2019;50:1084–1098. 4. Das R, et al. *J Immunol* 2015;194:950–959.
5. Wang C, et al. *Cancer Immunol Res* 2014;2:846–856. 6. Brahmer JR, et al. *J Clin Oncol* 2010;28:3167–3175. 7. Hamanishi J, et al. *Proc Natl Acad Sci U S A* 2007;104:3360–3365.

PD-1 and CTLA-4 Activity in Other Diseases

- Nivolumab + ipilimumab (NIVO + IPI) demonstrated improved survival in phase 3 studies in RCC and melanoma[1,2]

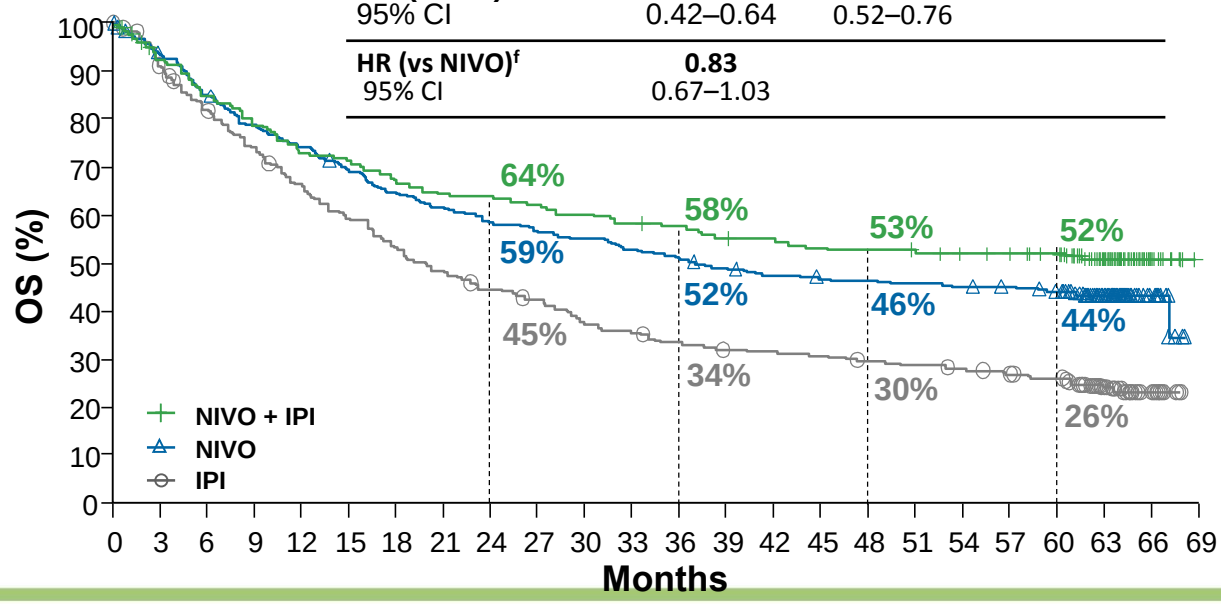
RCC: CheckMate 214 (30-mo update)[1]

	NIVO + IPI[a] (n = 550)	SUN[b] (n = 546)
Median OS, mo	NR	37.9
HR 95% CI	**0.71** 0.59–0.86	



Melanoma: CheckMate 067 (5-y update)[2]

	NIVO + IPI[c] (n = 314)	NIVO[d] (n = 316)	IPI[e] (n = 315)
Median OS, mo	NR	36.9	19.9
HR (vs IPI) 95% CI	**0.52** 0.42–0.64	**0.63** 0.52–0.76	
HR (vs NIVO)[f] 95% CI	**0.83** 0.67–1.03		



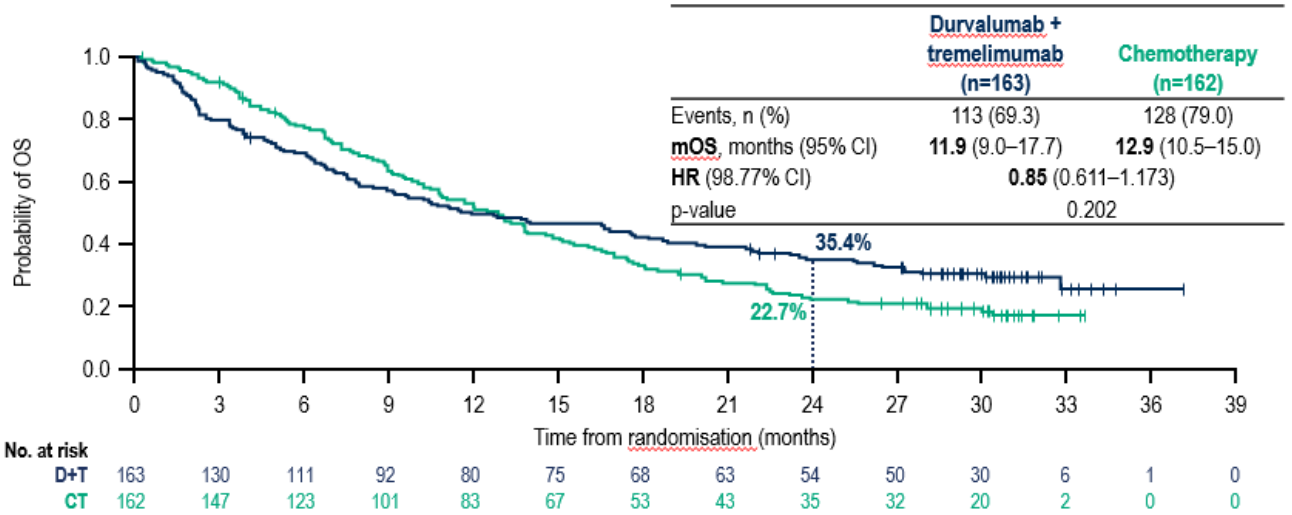
Adapted from Peters S et al ESMO 2019

[a]NIVO (3 mg/kg Q3W) + IPI (1 mg/kg Q3W); [b]Sunitinib 50 mg QD; [c]NIVO (1 mg/kg Q3W) + IPI (3 mg/kg Q3W); [d]NIVO (3 mg/kg Q2W); [e]IPI (3 mg/kg Q3W); [f]Descriptive analysis.

1. Tannir NM, et al. *J Clin Oncol* 2019;37(suppl 7). Abstract 547. 2. Larkin J, et al. Oral presentation at ESMO Sept 27–Oct 1, 2019; Barcelona, Spain. Abstract LBA68.

CTLA-4 and PD-1 Pathway Blockade in NSCLC – Mixed Results

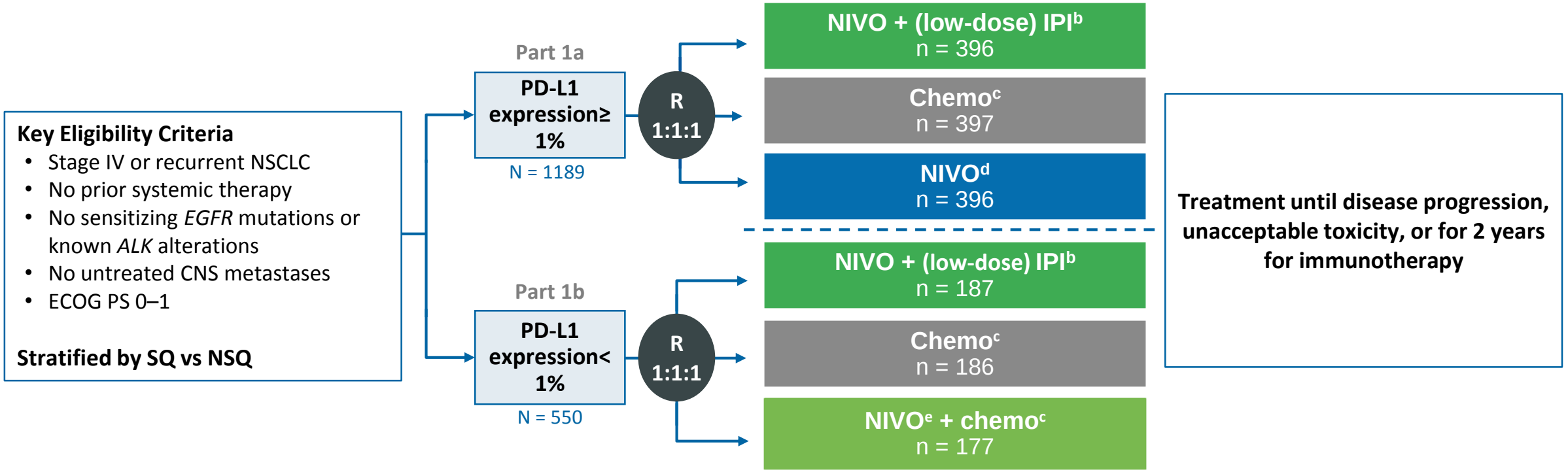
- Durvalumab and Tremelimumab did not show a survival advantage over chemotherapy in the MYSTIC study in PD-L1 positive disease.



- NIVO + IPI showed promising activity in earlier studies where the IPI dose and schedule (1 mg/kg Q6W) were optimized for NSCLC patients; safety profile was manageable[1–3]

1. Hellmann MD, et al. *Lancet Oncol* 2017;18:31–41. 2. Ready N, et al. *J Clin Oncol* 2019;37:992–1000. 3. Paz-Ares L, et al. Poster presentation at IASLC 19th World Conference on Lung Cancer; September 23–26, 2018; Toronto, Canada. Abstract P1.01-79. , Rizvi N et al ESMO-IO 2018

CheckMate 227 Part 1 Study Design

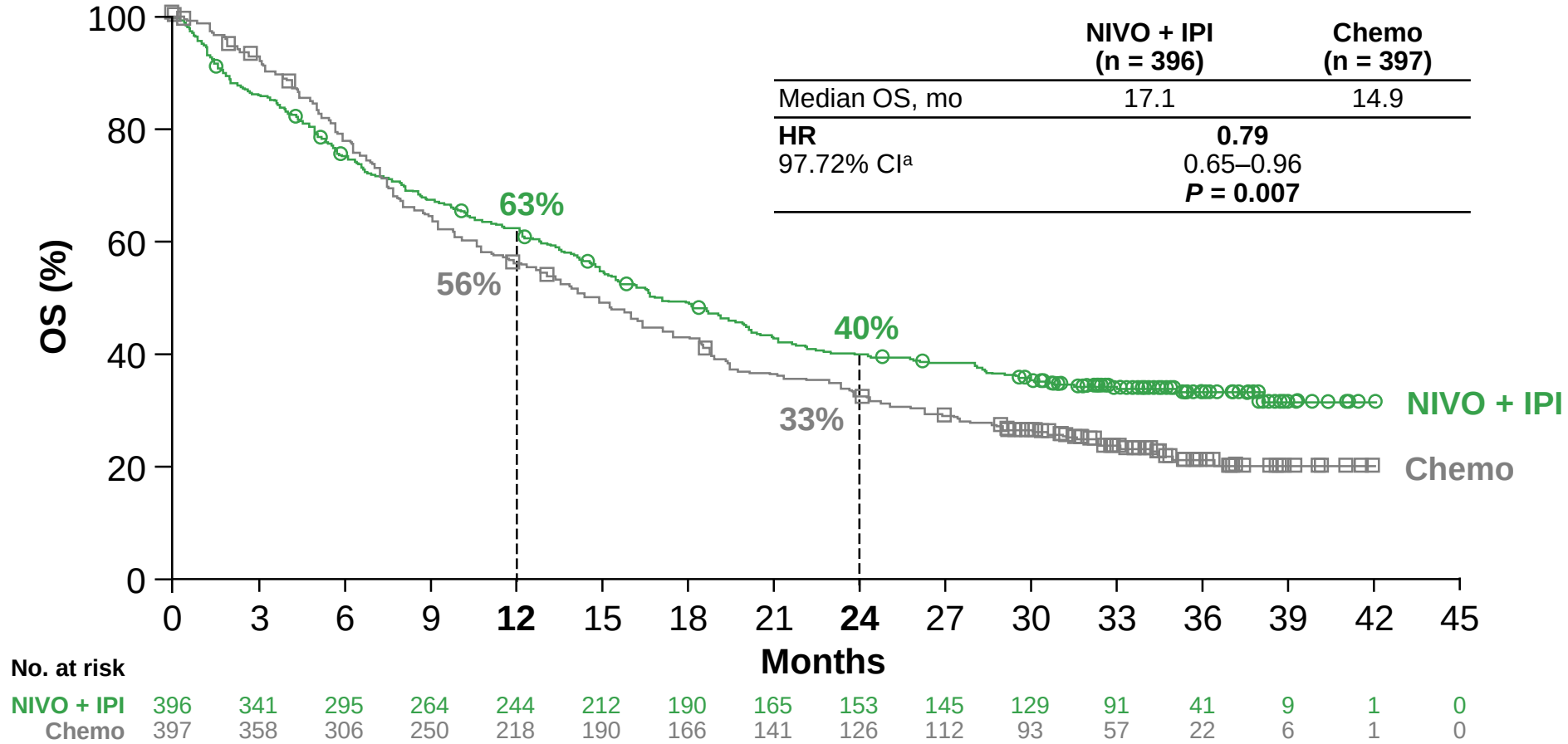


Independent co-primary endpoints: NIVO + IPI vs chemo
- PFS in high TMB (≥10 mut/Mb) population[f]
- OS in PD-L1 ≥ 1% population[g]

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%

Primary Endpoint: OS With NIVO + IPI vs Chemo in Patients With Tumor PD-L1 Expression ≥ 1%

Part 1a
NIVO + IPI
Chemo
NIVO



	NIVO + IPI (n = 396)	Chemo (n = 397)
Median OS, mo	17.1	14.9
HR 97.72% CI[a]	**0.79** 0.65–0.96 ***P* = 0.007**	

Adapted from Peters S et al ESMO 2019

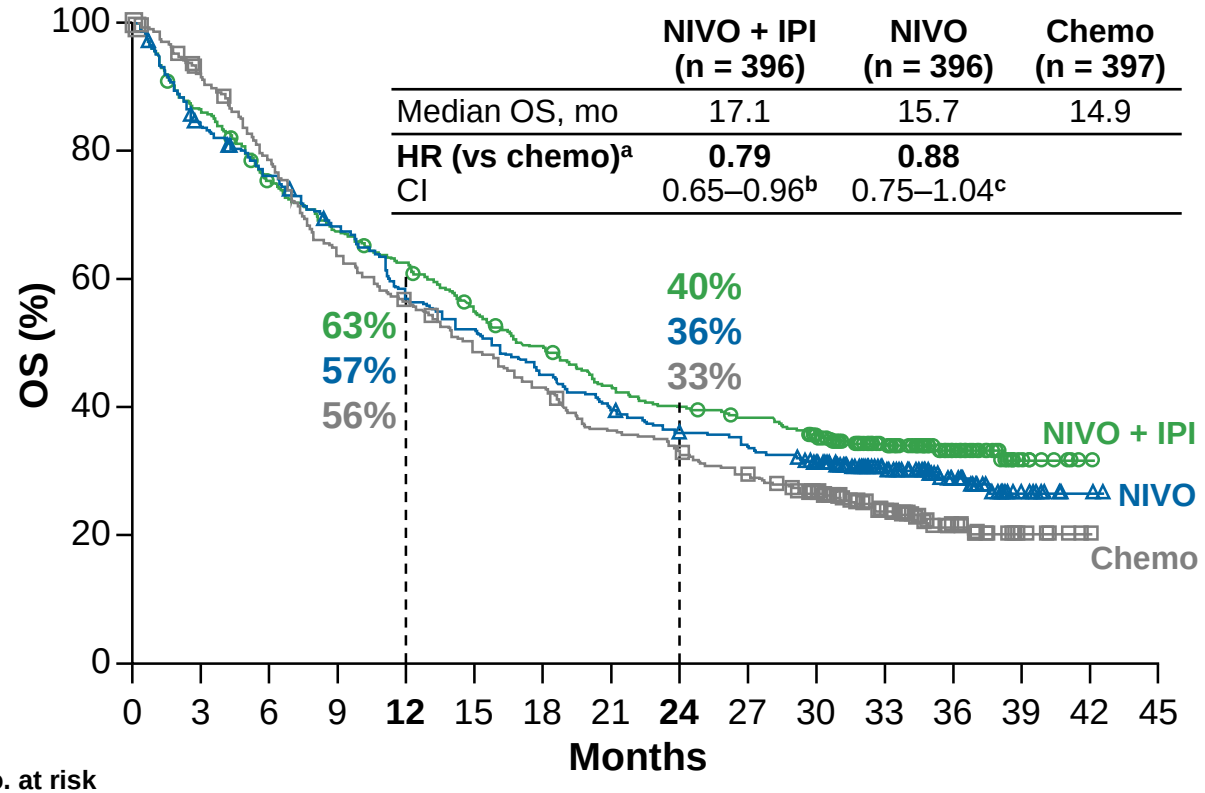
OS and PFS With NIVO + IPI vs NIVO vs Chemo in Patients With Tumor PD-L1 Expression ≥ 1%

Part 1a

NIVO + IPI
Chemo
NIVO

OS

	NIVO + IPI (n = 396)	NIVO (n = 396)	Chemo (n = 397)
Median OS, mo	17.1	15.7	14.9
HR (vs chemo)[a]	**0.79**	**0.88**	
CI	0.65–0.96[b]	0.75–1.04[c]	

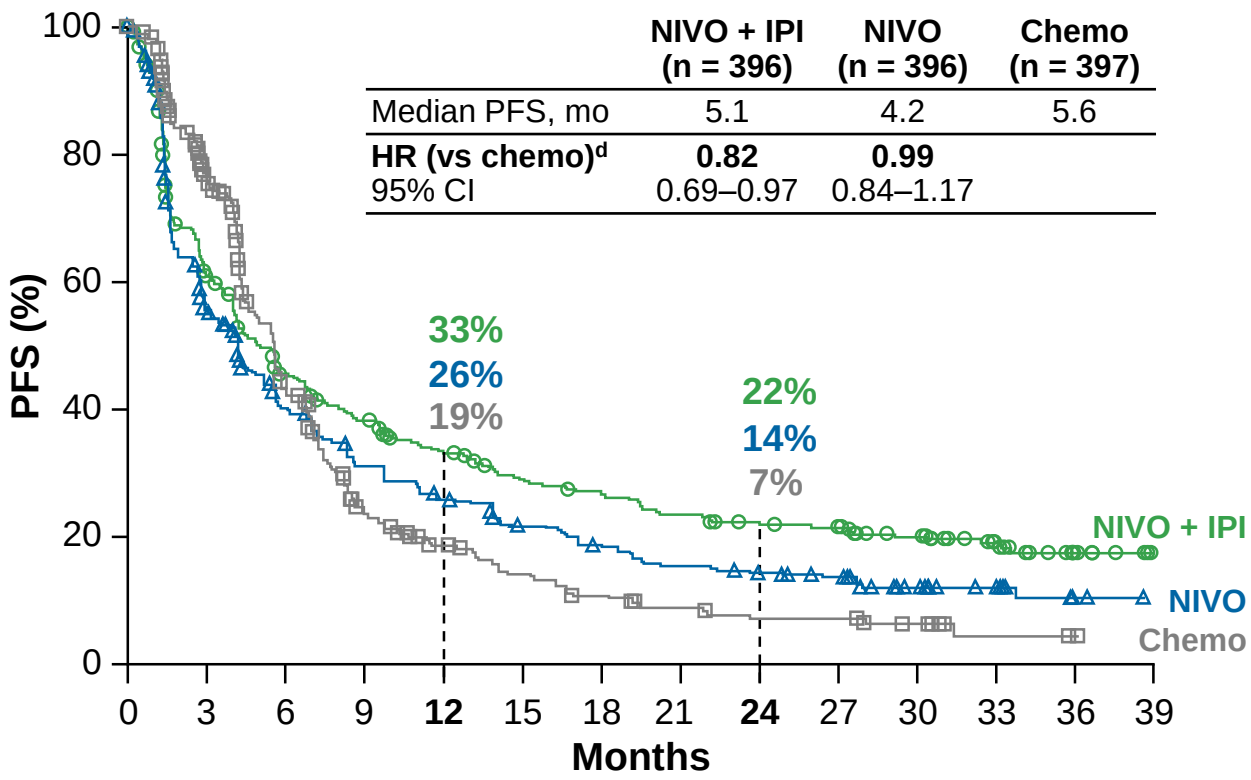


No. at risk

NIVO + IPI	396	341	295	264	244	212	190	165	153	145	129	91	41	9	1	0
NIVO	396	330	299	265	220	201	176	153	139	129	115	70	36	10	2	0
Chemo	397	358	306	250	218	190	166	141	126	112	93	57	22	6	1	0

PFS by BICR

	NIVO + IPI (n = 396)	NIVO (n = 396)	Chemo (n = 397)
Median PFS, mo	5.1	4.2	5.6
HR (vs chemo)[d]	**0.82**	**0.99**	
95% CI	0.69–0.97	0.84–1.17	

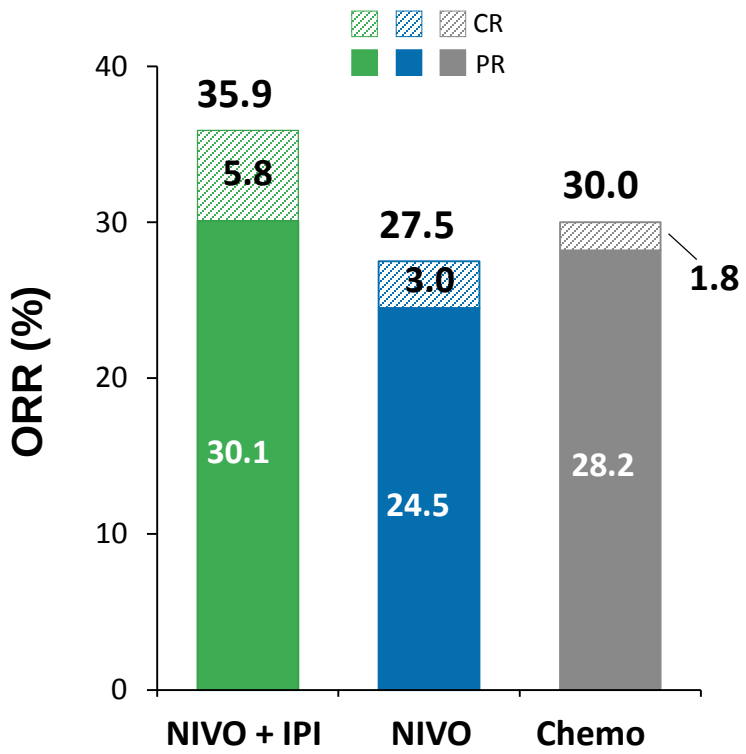


396	221	158	130	108	91	83	73	65	62	47	31	7	0
396	199	136	104	85	68	56	47	42	37	24	15	3	0
397	253	130	63	44	32	23	17	12	12	8	2	1	0

ORR and DOR for NIVO + IPI and NIVO vs Chemo in Patients With Tumor PD-L1 Expression ≥ 1%

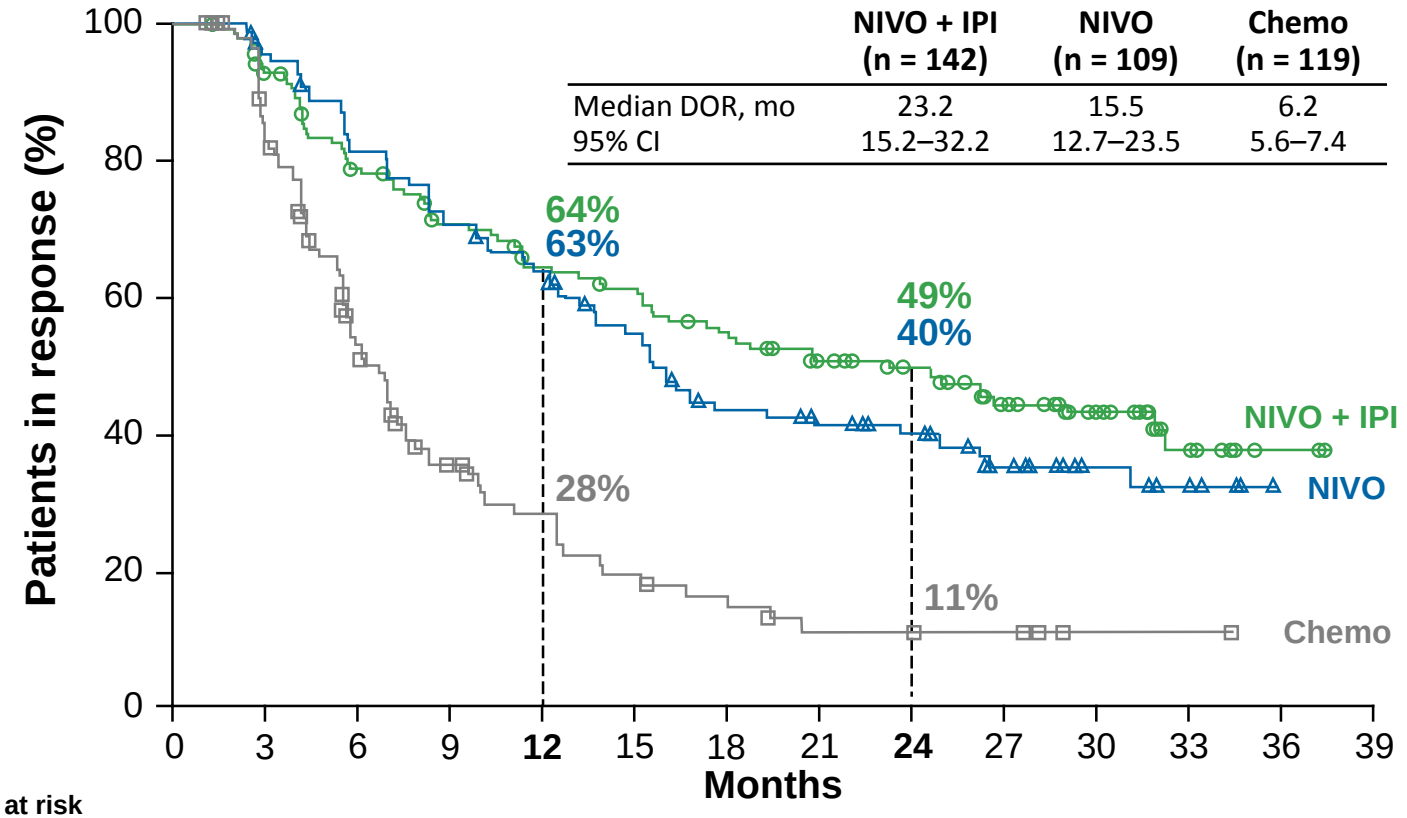
Part 1a
NIVO + IPI
Chemo
NIVO

ORR by BICR



n / N:	142 / 396	109 / 396	119 / 397

DOR by BICR[a]



	NIVO + IPI (n = 142)	NIVO (n = 109)	Chemo (n = 119)
Median DOR, mo	23.2	15.5	6.2
95% CI	15.2–32.2	12.7–23.5	5.6–7.4

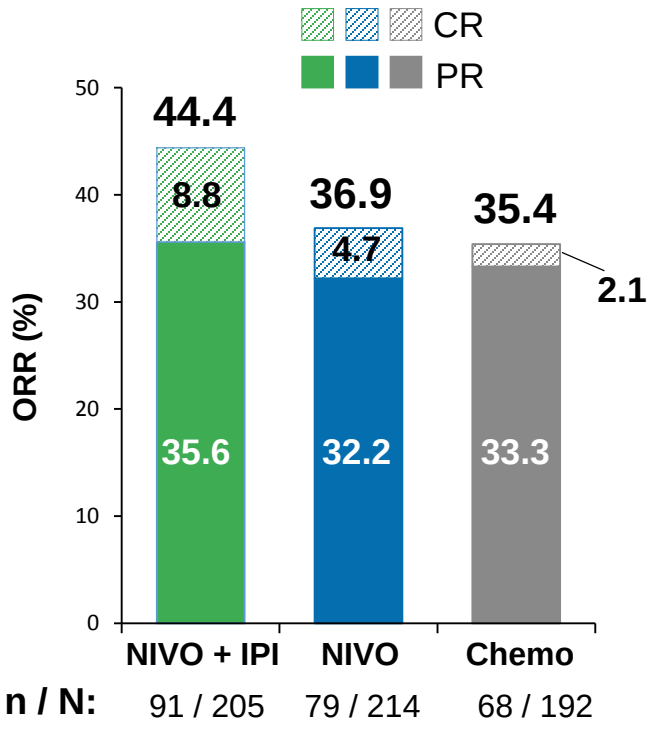
No. at risk

NIVO + IPI	142	128	105	91	81	76	66	58	52	42	28	12	2	0
NIVO	109	100	84	73	65	53	40	36	31	20	12	5	0	0
Chemo	119	90	51	28	19	13	10	6	6	5	1	1	0	0

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

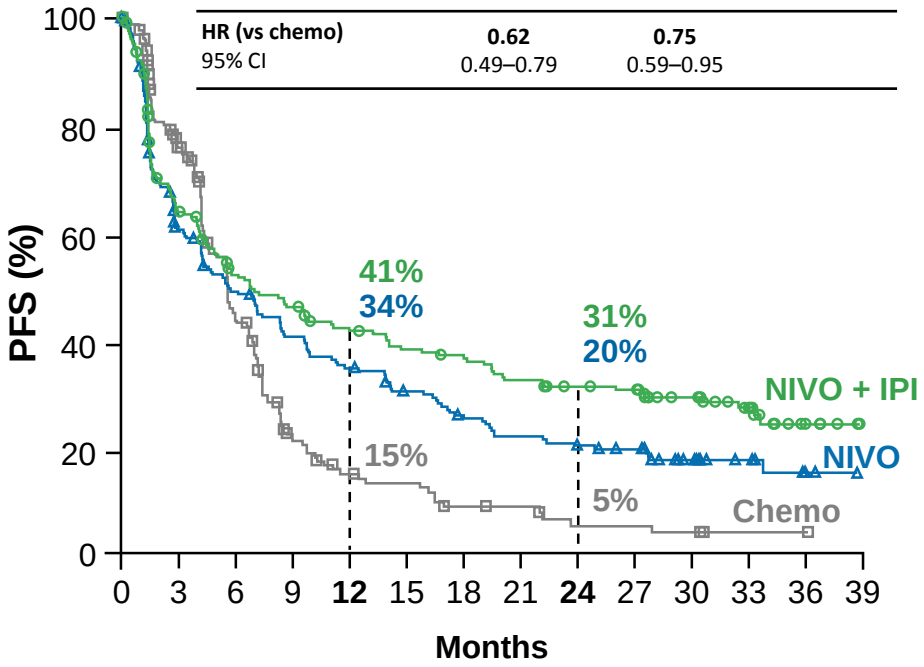
Part 1a
NIVO + IPI
Chemo
NIVO

ORR by BICR



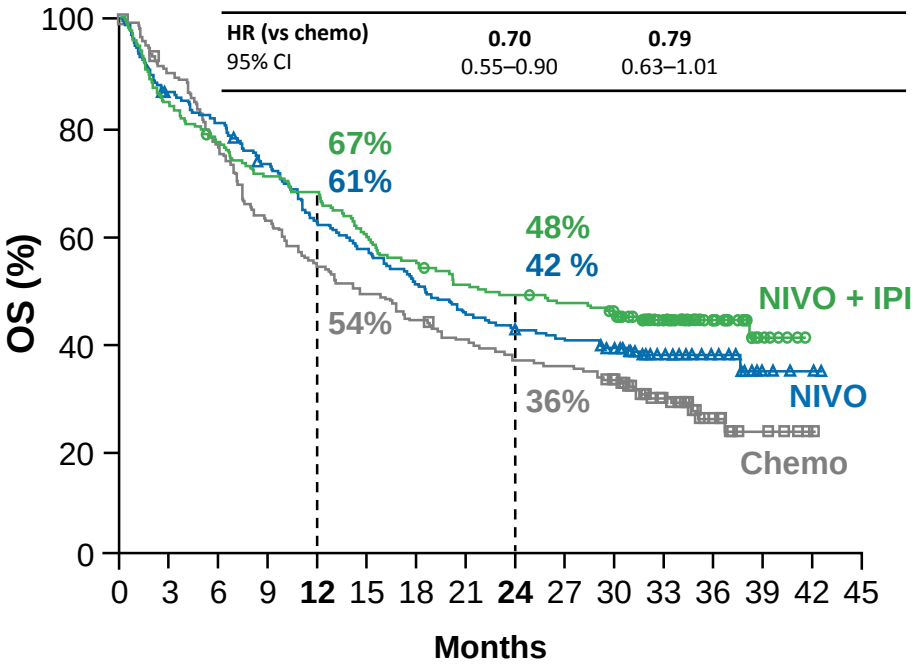
PFS by BICR

	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	



OS

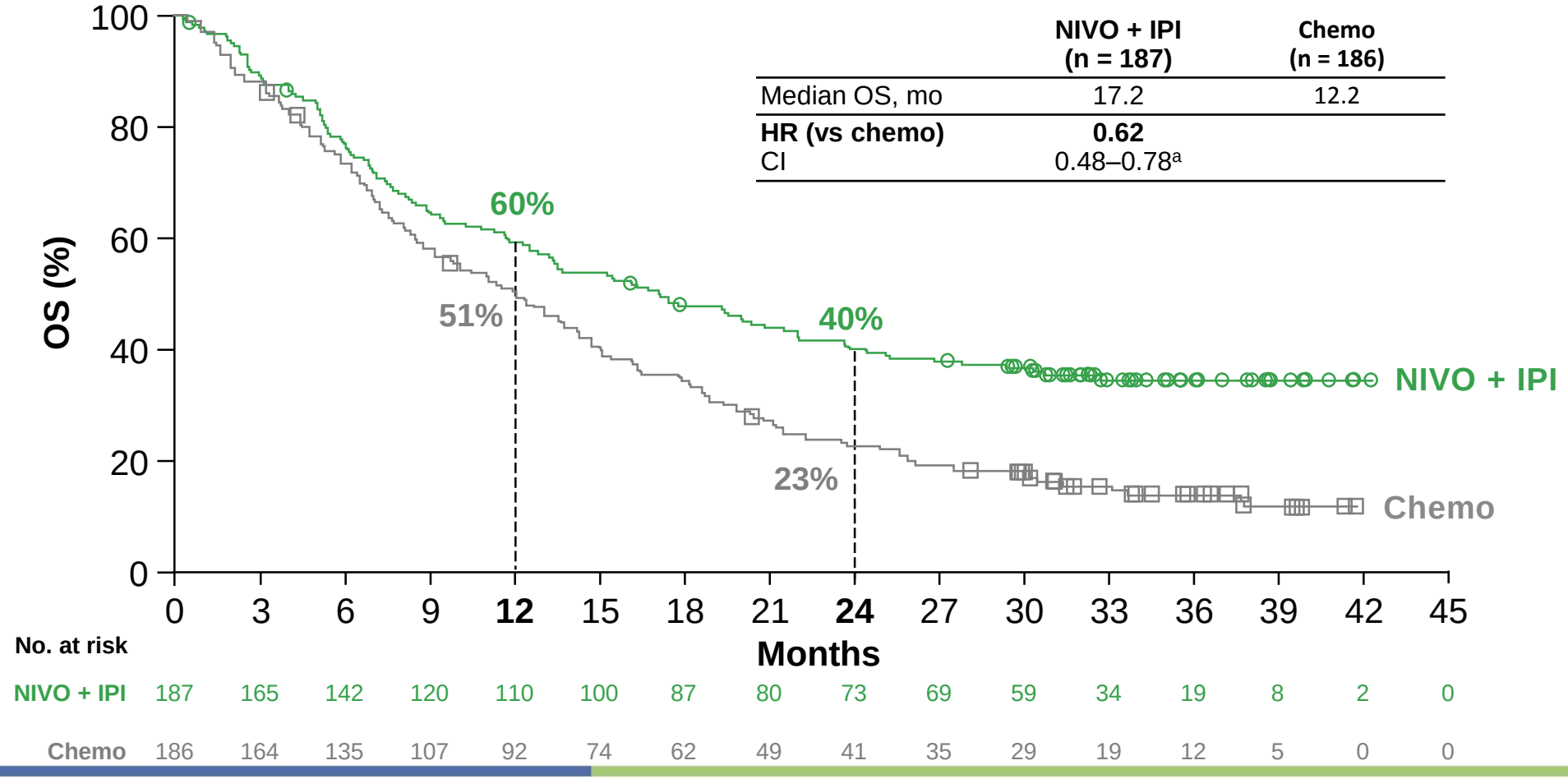
	NIVO + IPI (n = 205)	NIVO (n = 214)	Chemo (n = 192)
Median OS, mo 95% CI	21.2 15.5–38.2	18.1 14.4–22.1	14.0 10.0–18.6
HR (vs chemo) 95% CI	**0.70** 0.55–0.90	**0.79** 0.63–1.01	



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

OS With NIVO + IPI vs Chemo in Patients With Tumor PD-L1 Expression < 1%

Part 1b
NIVO + IPI
Chemo
NIVO + chemo



	NIVO + IPI (n = 187)	Chemo (n = 186)
Median OS, mo	17.2	12.2
HR (vs chemo)	**0.62**	
CI	0.48–0.78[a]	

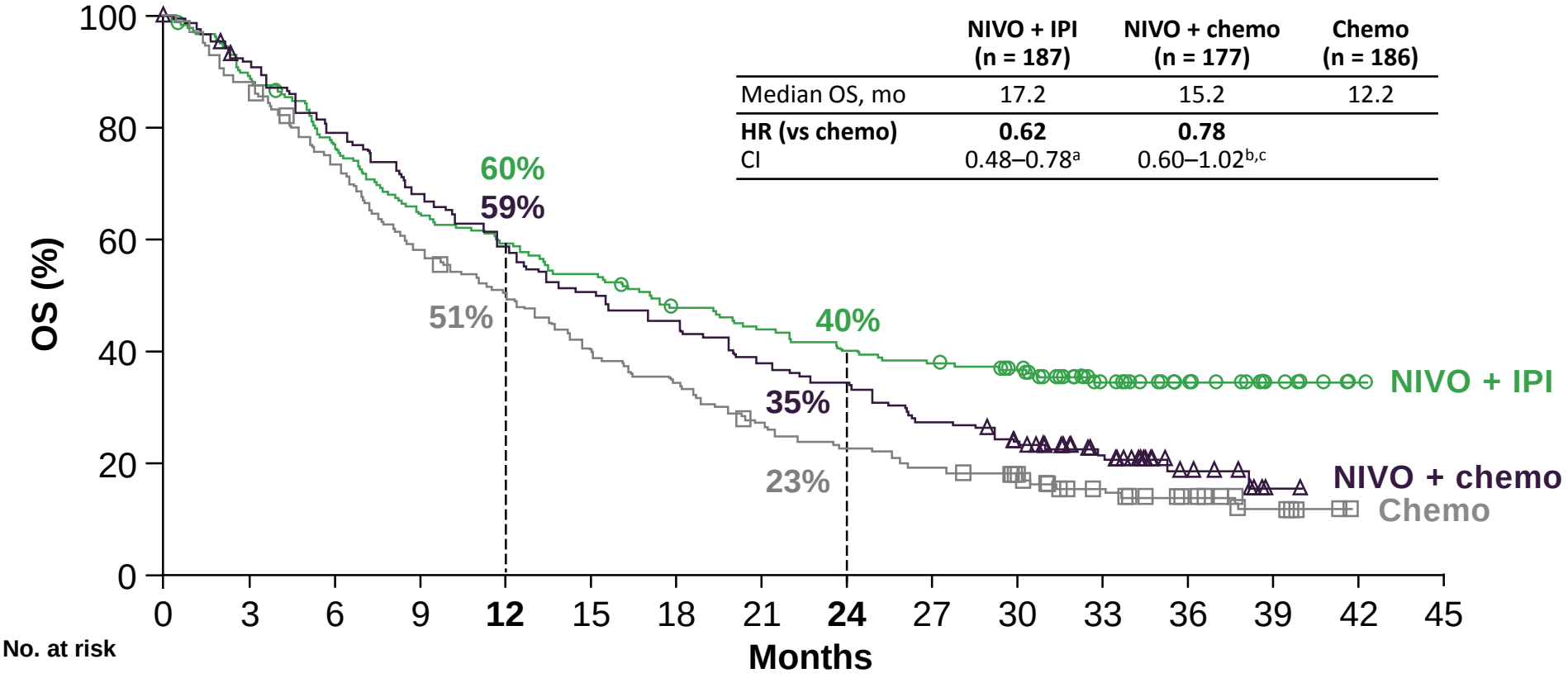
No. at risk																
NIVO + IPI	187	165	142	120	110	100	87	80	73	69	59	34	19	8	2	0
Chemo	186	164	135	107	92	74	62	49	41	35	29	19	12	5	0	0

OS With NIVO + IPI and NIVO + Chemo vs Chemo in Patients With Tumor PD-L1 Expression < 1%

Part 1b

NIVO + IPI
Chemo
NIVO + chemo

	NIVO + IPI (n = 187)	NIVO + chemo (n = 177)	Chemo (n = 186)
Median OS, mo	17.2	15.2	12.2
HR (vs chemo)	**0.62**	**0.78**	
CI	0.48–0.78[a]	0.60–1.02[b,c]	



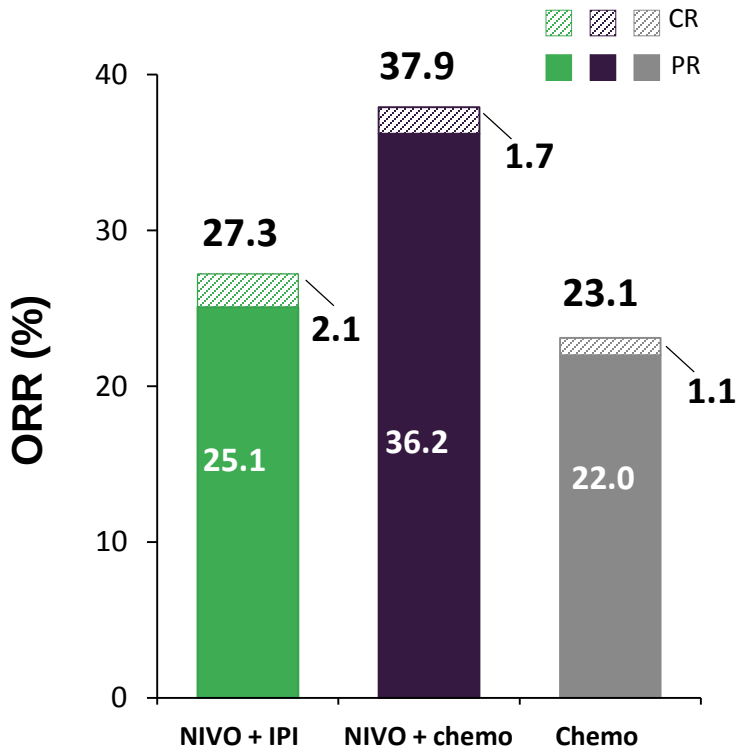
No. at risk

NIVO + IPI	187	165	142	120	110	100	87	80	73	69	59	34	19	8	2	0
NIVO + chemo	177	159	139	119	102	88	78	67	60	48	40	23	9	1	0	0
Chemo	186	164	135	107	92	74	62	49	41	35	29	19	12	5	0	0

ORR and DOR for NIVO + IPI and NIVO + Chemo vs Chemo in Patients With Tumor: PD-L1 Expression < 1%

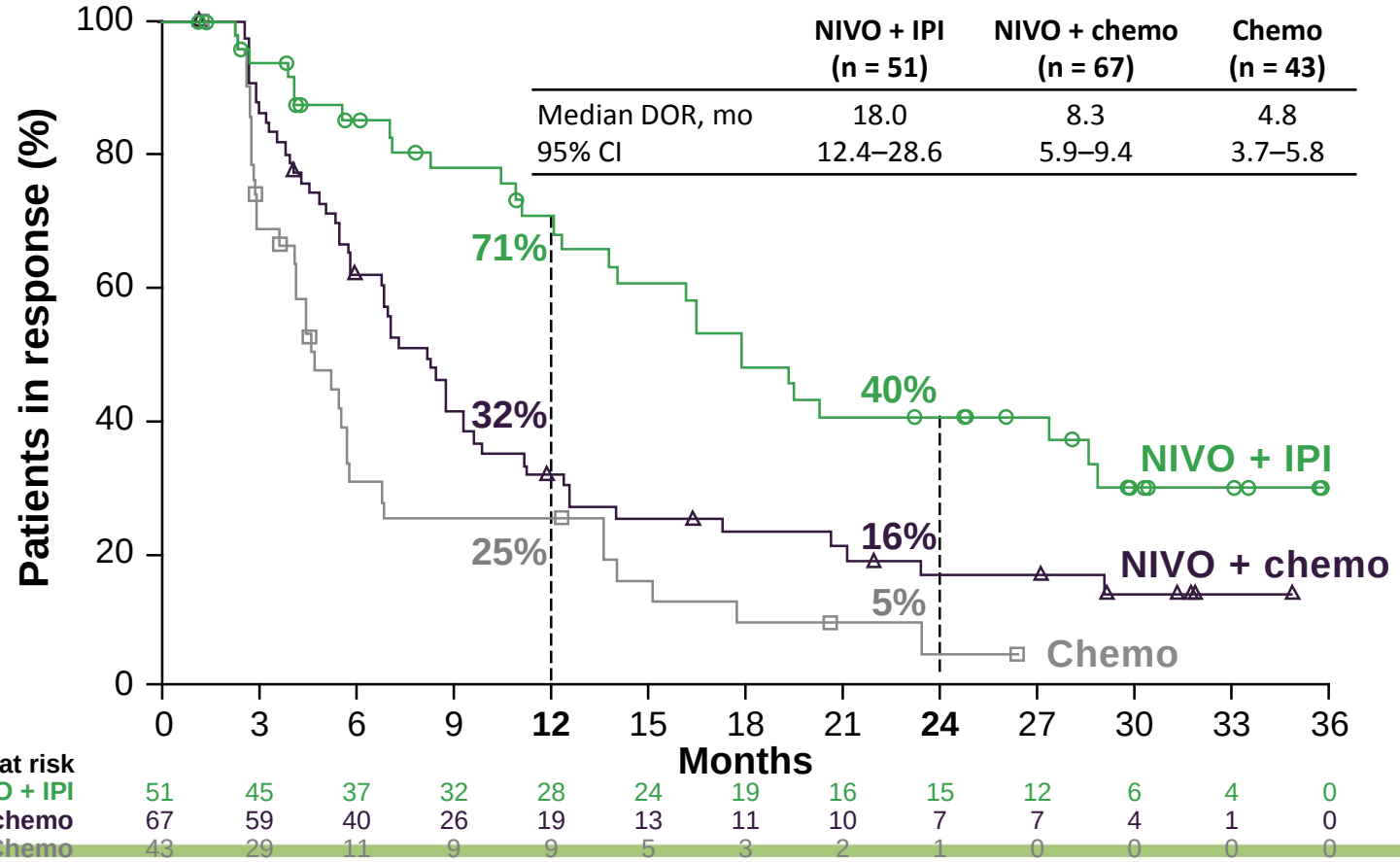
Part 1b
NIVO + IPI
Chemo
NIVO + chemo

ORR by BICR



n / N: 51 / 187 67 / 177 43 / 186

DOR by BICR[a]



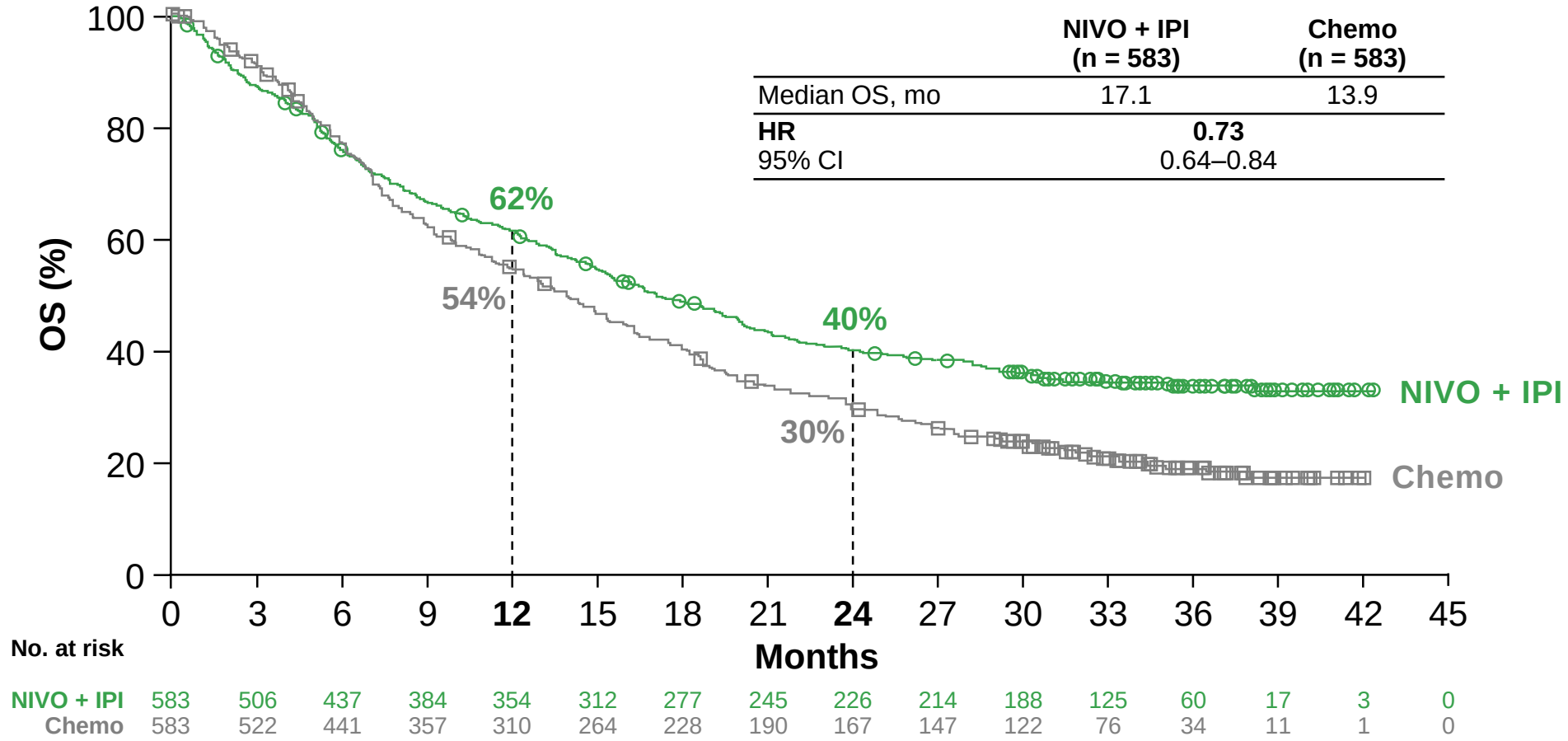
	NIVO + IPI (n = 51)	NIVO + chemo (n = 67)	Chemo (n = 43)
Median DOR, mo	18.0	8.3	4.8
95% CI	12.4–28.6	5.9–9.4	3.7–5.8

No. at risk													
NIVO + IPI	51	45	37	32	28	24	19	16	15	12	6	4	0
NIVO + chemo	67	59	40	26	19	13	11	10	7	7	4	1	0
Chemo	43	29	11	9	9	5	3	2	1	0	0	0	0

Adapted from Peters S et al ESMO 2019

OS With NIVO + IPI vs Chemo in
All Randomized Patients (Regardless of PD-L1)

Part 1 (1a and 1b)
NIVO + IPI
Chemo



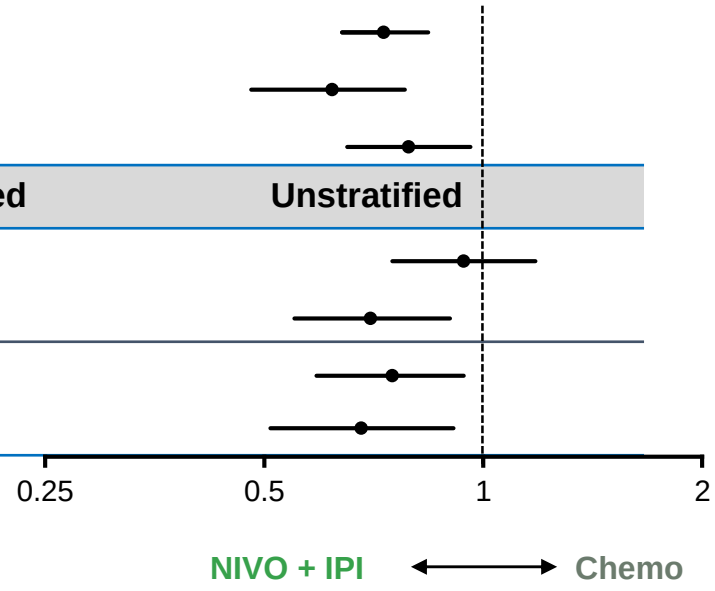
	NIVO + IPI (n = 583)	Chemo (n = 583)
Median OS, mo	17.1	13.9
HR	**0.73**	
95% CI	0.64–0.84	

No. at risk

NIVO + IPI	583	506	437	384	354	312	277	245	226	214	188	125	60	17	3	0
Chemo	583	522	441	357	310	264	228	190	167	147	122	76	34	11	1	0

OS for NIVO + IPI vs Chemo by Tumor PD-L1 Expression, TMB Status, and Combined Subgroups in All Randomized Patients

		Median OS, months NIVO + IPI n = 583	Chemo n = 583	HR	HR (95% CI)
Randomized groups				**Stratified**	**Stratified**
PD-L1	All randomized (N = 1166)	17.1	13.9	0.73	
	PD-L1 < 1% (n = 373)	17.2	12.2	0.62	
	PD-L1 ≥ 1% (n = 793)	17.1	14.9	0.79[a]	
Additional exploratory subgroups analyses[b,c]				**Unstratified**	**Unstratified**
PD-L1	1–49% (n = 396)	15.1	15.1	0.94	
	≥ 50% (n = 397)	21.2	14.0	0.70	
TMB[d] (mut/Mb)	low, < 10 (n = 380)	16.2	12.6	0.75	
	high, ≥ 10 (n = 299)	23.0	16.4	0.68	



- No consistent correlation was observed between survival outcomes with NIVO + IPI vs chemo and PD-L1 or TMB alone or in combination[1]

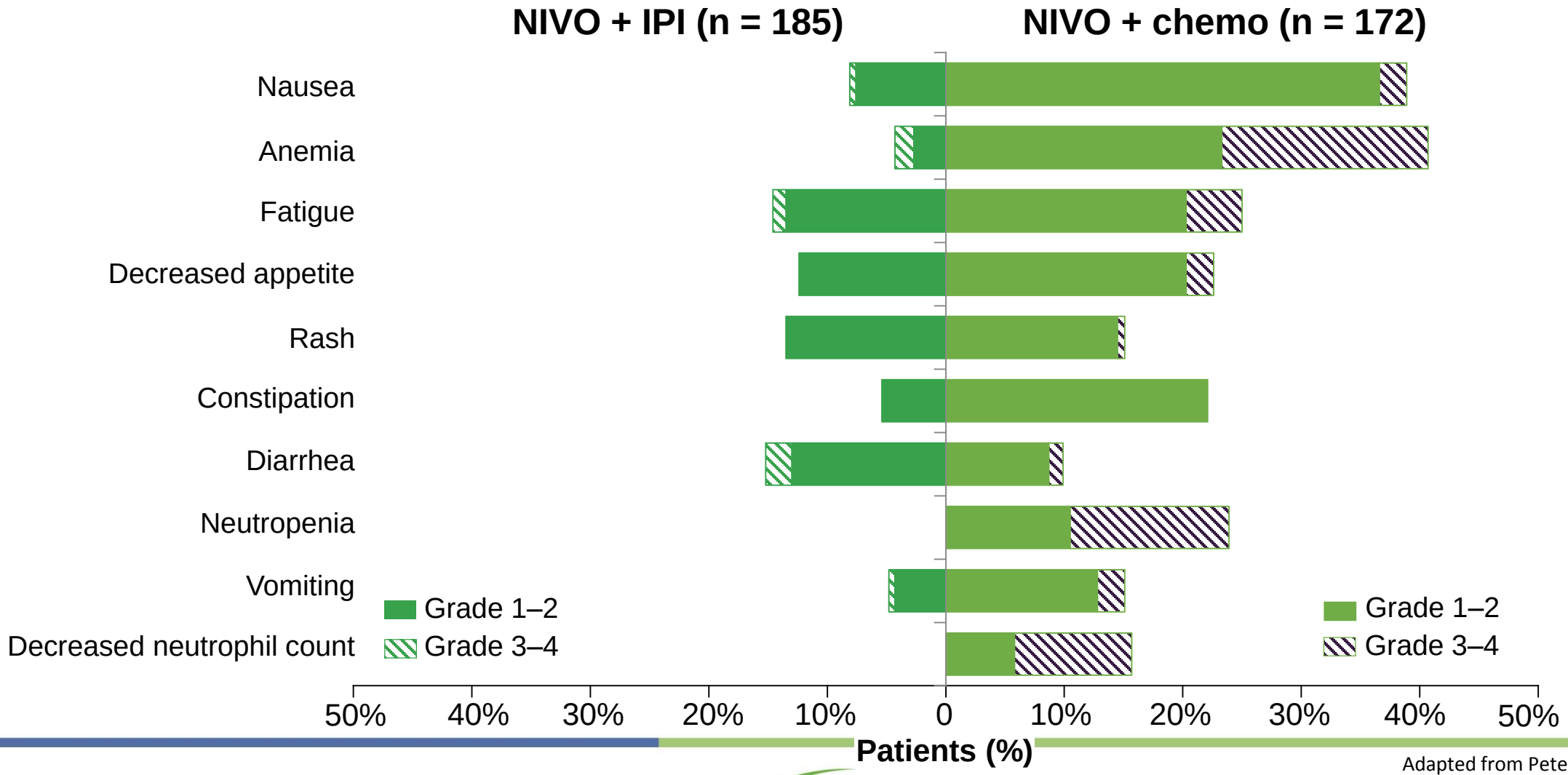
Safety Summary of Treatment-Related AEs in All Patients Treated With NIVO + IPI, Chemo, or NIVO

TRAE,[a] %	NIVO + IPI (n = 576)		Chemo (n = 570)		NIVO[b] (n = 391)	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Any TRAE	77	33	82	36	66	19
TRAE leading to discontinuation[c]	18	12	9	5	12	7
Most frequent TRAEs (≥ 15%)						
Diarrhea	17	2	10	1	12	< 1
Rash	17	2	5	0	11	1
Fatigue	14	2	19	1	11	< 1
Decreased appetite	13	1	20	1	7	0
Nausea	10	< 1	36	2	6	< 1
Anemia	4	1	33	12	3	< 1
Constipation	4	0	15	< 1	2	0
Neutropenia	< 1	0	17	10	< 1	0
Treatment-related deaths[d]	1		1		< 1	

- With 18 months more follow-up, safety was consistent with the previous report[1] and did not increase
- Median duration of therapy (range) was 4.2 mo (0.03–25.5) with NIVO + IPI, 2.6 mo (0.03–37.6+) with chemo, and 4.6 mo (0.03–26.5) with NIVO

Adapted from Peters S et al ESMO 2019

Most Frequent TRAEs (≥ 15%) With NIVO + IPI and NIVO + Chemo in Patients With Tumor PD-L1 Expression < 1%[a]



Adapted from Peters S et al ESMO 2019

First Line Studies: Comparison in PD-L1 High (> 50%) Advanced NSCLC – RR, PFS, OS, AEs

	KEYNOTE 024	KEYNOTE 042	KEYNOTE 189	KEYNOTE 407	CheckMate 227
RR	45%	39.5%	62%	60.3%	44.4%
Median PFS (mo)	10.3	7.1	9	8	6.7
1yr PFS	48%	37.4%	38.8%	Not Reported	41%
OS HR	0.65	0.69	0.59	0.64	0.70
1yr OS	70.3%	Not Reported	73.3%	~70%	67%
2yr OS	51.7%	45%	51.9%	Not Reported	48%
Rx related AEs Grade 3-5*	31%	18%	67.2%	69.8%	33%
Immune mediated AEs Grade 3-5*	13.6%	8%	10.9%	10.8%	Not reported

*ITT group regardless of PD-L1 for KN 042,189,407, CM 227

Reck M et al JCO 2019, Mok T et al Lancet 2018, Gadgeel S et al ASCO 2019, Paz-Ares L et al NEJM 2018, Hellmann M et al NEJM 2019

First Line Studies: Comparison in PD-L1 Negative Disease Advanced NSCLC – RR, PFS, OS

	KEYNOTE 189	KEYNOTE 407	CheckMate 227
RR	32.3%	63.2%	27.3%
Median DOR (mo)	10.8	Not reported	18
Median PFS (mo)	6.2	6.3	Not Reported
1yr PFS	25%	~25%	Not Reported
Median OS (mo)	17.2	15.9	17.2
1yr OS	63.4%	~70%	60%
2yr OS	38.5%	Not Reported	40%

*ITT group regardless of PD-L1 for KN 189,407, CM 227

Reck M et al JCO 2019, Mok T et al Lancet 2018, Gadgeel S et al ASCO 2019, Paz-Ares L et al NEJM 2018, Hellmann M et al NEJM 2019

Conclusions

- Nivolumab + Ipilimumab significantly improves overall survival in patients with NSCLC PD-L1 positive disease.
- Nivolumab + Ipillimumab also improves overall survival in patients with NSCLC PD-L1 negative disease.
- Nivolumab + Ipilimumab compared to chemotherapy has a trend towards less TRAEs but more TRAEs leading to treatment discontinuation.
- Nivolumab + Ipilimumab is a viable treatment option for patients with NSCLC regardless of PD-L1 status.

Clinical Conclusions: Which patients would I use or not use PD-1/CTLA-4 combination in?

- I would use the combination in patients with minimal symptoms or lower burden of disease. IO/chemotherapy may be clinically helpful for patients with high burden of disease where you need the increased response rate.
- I would use the combination in patients were I don't think they would tolerate chemotherapy or those who don't want to undergo chemotherapy.
- I would not use the combination in patients with a history of autoimmune disease. I would stick with either single agent IO or IO chemotherapy if I felt it was safe to use IO.
- I would not use this combination in patients with EGFR or ALK positive disease as these patients were not included in CM-227.
- I would use the combination in patients with PD-L1 negative disease over IO chemotherapy, but would love a head to head comparison.