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First-line nivolumab + ipilimumab vs chemotherapy in unresectable malignant pleural mesothelioma: CheckMate 743

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Disclosures

Commercial Interest	Relationship(s)
MSD	Advisory board
AstraZeneca	Advisory board
Takeda	Advisory board

Introduction

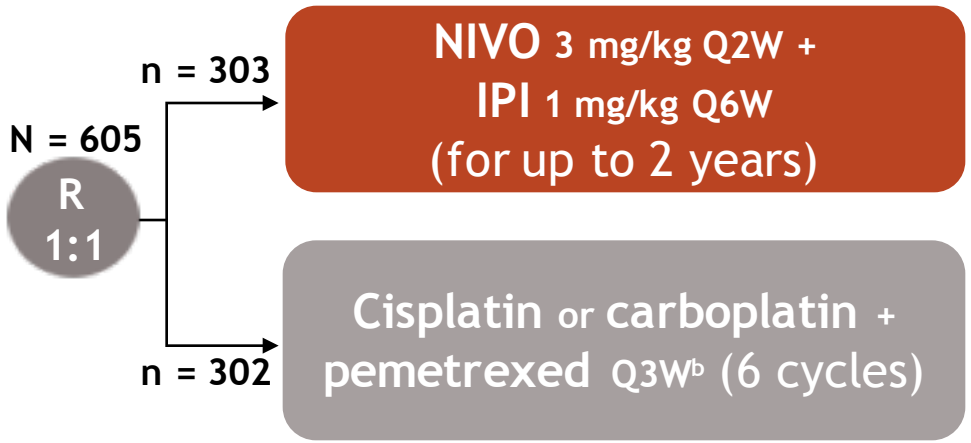
- Malignant pleural mesothelioma (MPM) is a highly aggressive cancer, with a 5-year survival rate of < 10%[1,2]
- Platinum doublet chemotherapy has been the approved standard of care for 1L unresectable MPM since 2004[1,3]
- Epithelioid histology has been associated with better outcomes than non-epitheliod histology[4,5]
- Nivolumab (NIVO) and ipilimumab (IPI) are immune checkpoint inhibitors (ICI) with distinct but complementary mechanisms of action
  - NIVO restores anti-tumor T-cell function, while IPI induces *de novo* anti-tumor T-cell responses[6]
  - NIVO + IPI has demonstrated an improved and durable survival benefit and is approved for multiple tumors[7-12]
- Randomized trials of single-agent ICI did not show significant benefits in 2L+ MPM settings,[13,14] although encouraging clinical activity of NIVO + IPI has been observed in single-arm MPM studies[15-18]
- CheckMate 743 is a phase 3, randomized, open-label study evaluating NIVO + IPI versus standard of care chemotherapy in 1L unresectable MPM

1. NCCN Clinical Practice Guidelines in Oncology. Malignant Pleural Mesothelioma. Published April 1, 2019. 2. Milano MT, Zhang H. *J Thorac Oncol* 2010;5:1841-1848; 3. Scherpereel A, et al. *Eur Respir J* 2020;55(6):1900953; 4. Verma V, et al. *Clin Lung Cancer* 2018;19:e901-e912; 5. Billé A, et al. *J Thorac Oncol* 2015;11:249-255; 6. Wei SC, et al. *Cancer Discov* 2018;8:1069-1086; 7. Larkin J, et al. *N Engl J Med* 2019;381:1535-1546; 8. Motzer RJ, et al. *Lancet Oncol* 2019;20:1370-1385; 9. Hellmann MD, et al. *N Engl J Med* 2019;381:2020-2031; 10. Ramalingam et al. Oral presentation at ASCO; May 29-31, 2020; Abstract 9500; 11. He AR, et al. *J Clin Oncol* 2020;38(suppl 4):abstr 512); 12. Overman MJ, et al. *J Clin Oncol* 2018;36:773-779; 13. Maio M, et al. *Lancet Oncol* 2017;18:1261-1273; 14. Popat S, et al. *Ann Oncol* 2019;30:v931; 15. Disselhorst MJ, et al. *Lancet Respir Med* 2019;7:260-270; 16. Quispel-Janssen J, et al. *J Thorac Oncol* 2018;13:1569-1576; 17. Okada M, et al. *Clin Cancer Res* 2019;25:5485-5492; 18. Scherpereel A, et al. *Lancet Oncol* 2019;20:239-253.

CheckMate 743 study design[a]

Key Eligibility Criteria
- Unresectable pleural mesothelioma
- No prior systemic therapy
- ECOG performance status 0–1

Stratified by:
histology (epithelioid vs non-epithelioid) and gender



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

Primary Endpoint
- OS

Secondary Endpoints
- ORR, DCR, and PFS by BICR
- PD-L1[c] expression as a predictive biomarker

Database lock: April 3, 2020; minimum follow-up for OS: 22.1 months; median follow-up: 29.7 months.

[a]NCT02899299; [b]Cisplatin (75 mg/m^2) or carboplatin (AUC 5) + pemetrexed (500 mg/m^2), Q3W for 6 cycles; [c]Determined by PD-L1 IHC 28-8 pharmDx assay from Dako.

Statistical considerations

- Analysis plan[a]:
  - To detect a HR of 0.72 with a power of 90% and 5% type-I error (2-sided)
  - Planned total: 600 randomized patients with 473 deaths
- Pre-specified interim analysis[b]:
  - Reviewed by external, independent data monitoring committee
  - 419 observed events (89% of total deaths); minimum follow-up, 22.1 months
  - α boundary: ≤ 0.0345
- The data monitoring committee confirmed the primary endpoint of improved OS for NIVO + IPI vs chemo at the pre-specified interim analysis

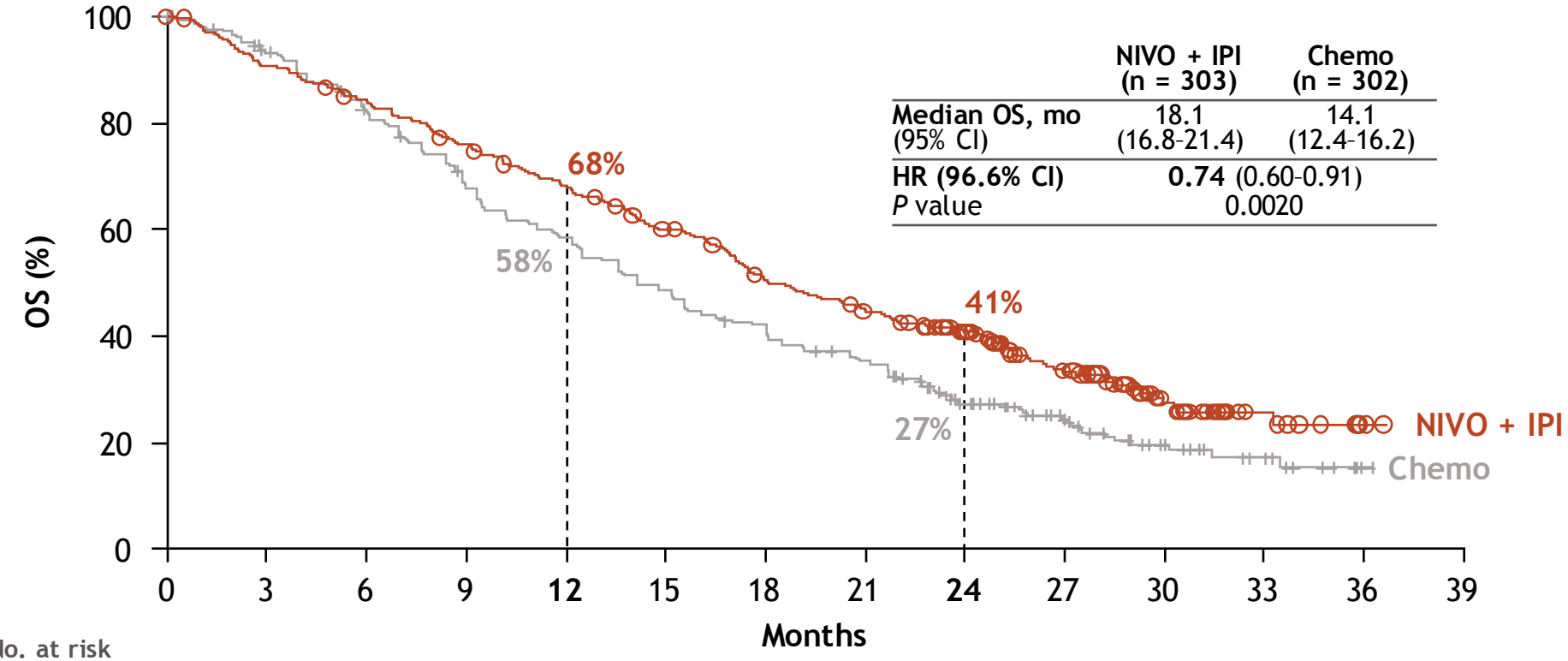
[a]Secondary endpoints were not formally tested; [b]Planned to occur after 403 deaths (85% of total deaths).The stopping boundary at the interim analysis was based on the actual number of deaths at the time of the analysis using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries.

Baseline characteristics: All randomized

	NIVO + IPI (n = 303)	Chemo (n = 302)
Age, median (range), years	69 (65-75)	69 (62-75)
Male, %	77	77
ECOG performance status		
0, %	38	42
1, %	62	57
Smoking status		
Never, %	42	40
Current / former, %	57	57
Histology,[a] %		
Epithelioid	76	75
Non-epithelioid[b]	24	25
Prior radiotherapy, %	10	9
PD-L1 quantifiable at baseline,[c] n	289	297
< 1%,[d] %	20	26
≥ 1%,[d] %	80	74

[a]Based on CRF source; [b]Included 47% sarcomatoid and 53% mixed/other in the NIVO + IPI arm and 48% and 52%, respectively, in the chemo arm; [c]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [d]Based on PD-L1 quantifiable at baseline, 95% and 98% of patients in the NIVO + IPI and chemo arms, respectively.

Primary endpoint: Overall survival



	NIVO + IPI (n = 303)	Chemo (n = 302)
Median OS, mo (95% CI)	18.1 (16.8-21.4)	14.1 (12.4-16.2)
HR (96.6% CI)	**0.74** (0.60-0.91)	
P value	0.0020	

No. at risk

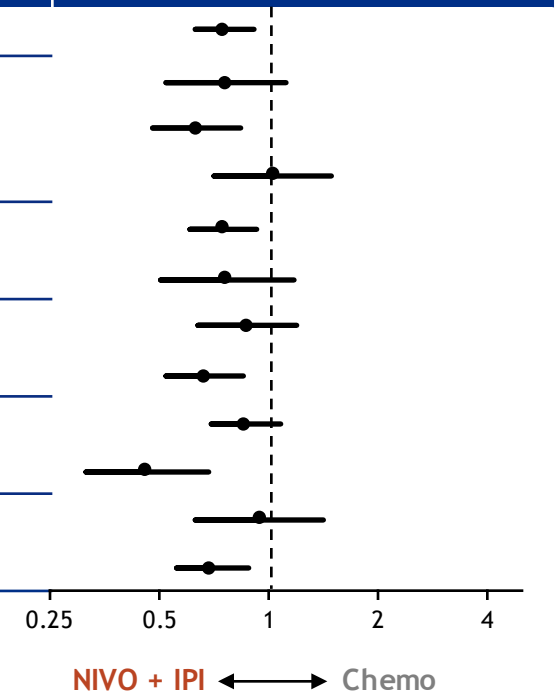
NIVO + IPI	303	273	251	226	200	173	143	124	101	65	30	11	2	0
Chemo	302	268	233	190	162	136	113	95	62	38	20	11	1	0

Minimum follow-up: 22.1 months; median follow-up: 29.7 months.

Subsequent systemic therapy was received by **44%** of patients in the NIVO + IPI arm and **41%** in the chemo arm; subsequent immunotherapy was received by 3% and 20%, and subsequent chemotherapy by 43% and 32%, respectively.

Overall survival: Subgroup analysis

Subgroup	Median OS, mo		Unstratified HR
	NIVO + IPI n = 303	Chemo n = 302	
All randomized (N = 605)	18.1	14.1	0.75[a]
< 65 years (n = 167)	17.2	13.3	0.76
≥ 65 to < 75 years (n = 281)	20.3	14.9	0.63
≥ 75 years (n = 157)	16.9	15.4	1.02
Male (n = 467)	**17.5**	**13.7**	**0.74**
Female (n = 138)	**21.4**	**18.0**	**0.76**
ECOG performance status 0 (n = 242)	20.7	19.5	0.87
ECOG performance status ≥ 1 (n = 363)	17.0	11.6	0.66
Epithelioid (n = 456)	**18.7**	**16.5**	**0.86**
Non-epithelioid (n = 149)	**18.1**	**8.8**	**0.46**
PD-L1 < 1% (n = 135)	17.3	16.5	0.94
PD-L1 ≥ 1% (n = 451)	18.0	13.3	0.69



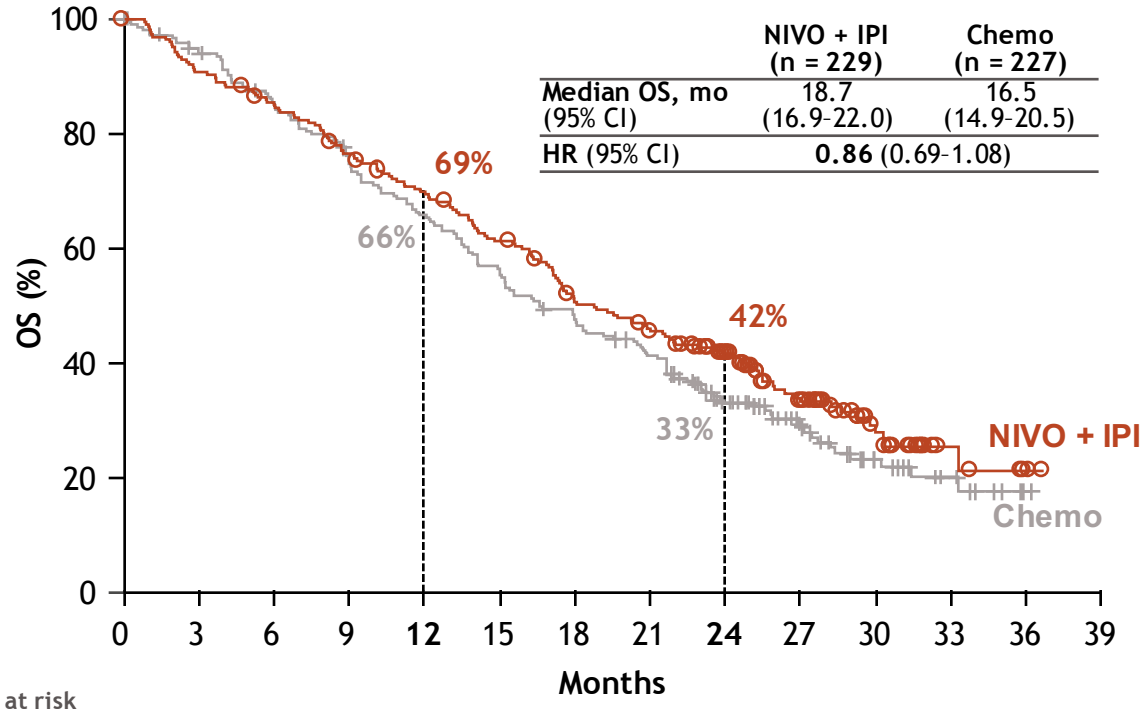
Minimum follow-up: 22.1 months; median follow-up: 29.7 months.

Bold text indicates study stratification factors.

[a]Stratified HR, 0.74.

Overall survival by histology[a]

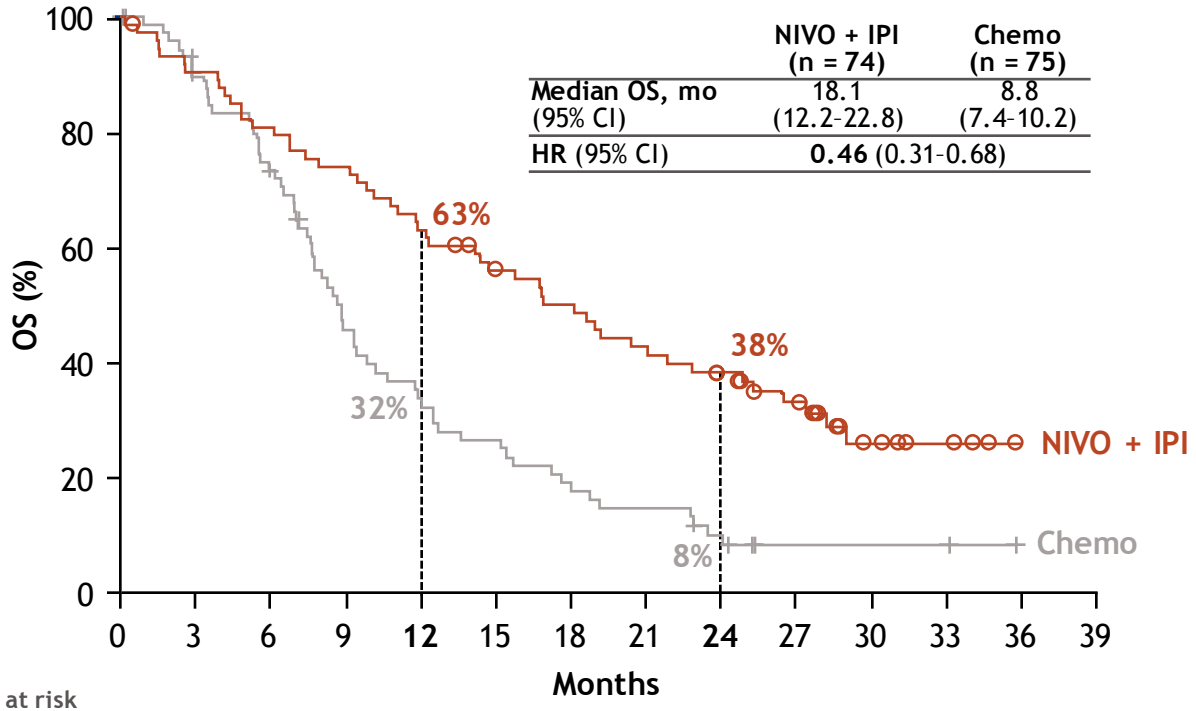
Epithelioid



	NIVO + IPI (n = 229)	Chemo (n = 227)
Median OS, mo (95% CI)	18.7 (16.9-22.0)	16.5 (14.9-20.5)
HR (95% CI)	**0.86** (0.69-1.08)	

No. at risk														
NIVO + IPI	229	207	192	172	154	135	109	96	77	47	22	6	2	0
Chemo	227	204	182	159	140	118	101	85	57	36	18	9	1	0

Non-epithelioid



	NIVO + IPI (n = 74)	Chemo (n = 75)
Median OS, mo (95% CI)	18.1 (12.2-22.8)	8.8 (7.4-10.2)
HR (95% CI)	**0.46** (0.31-0.68)	

No. at risk														
NIVO + IPI	74	66	59	54	46	38	34	28	24	18	8	5	0	0
Chemo	75	64	51	31	22	18	12	10	5	2	2	2	0	0

Minimum follow-up: 22.1 months; median follow-up: 29.7 months.

Patients were stratified by tumor histology: epithelioid vs non-epithelioid.

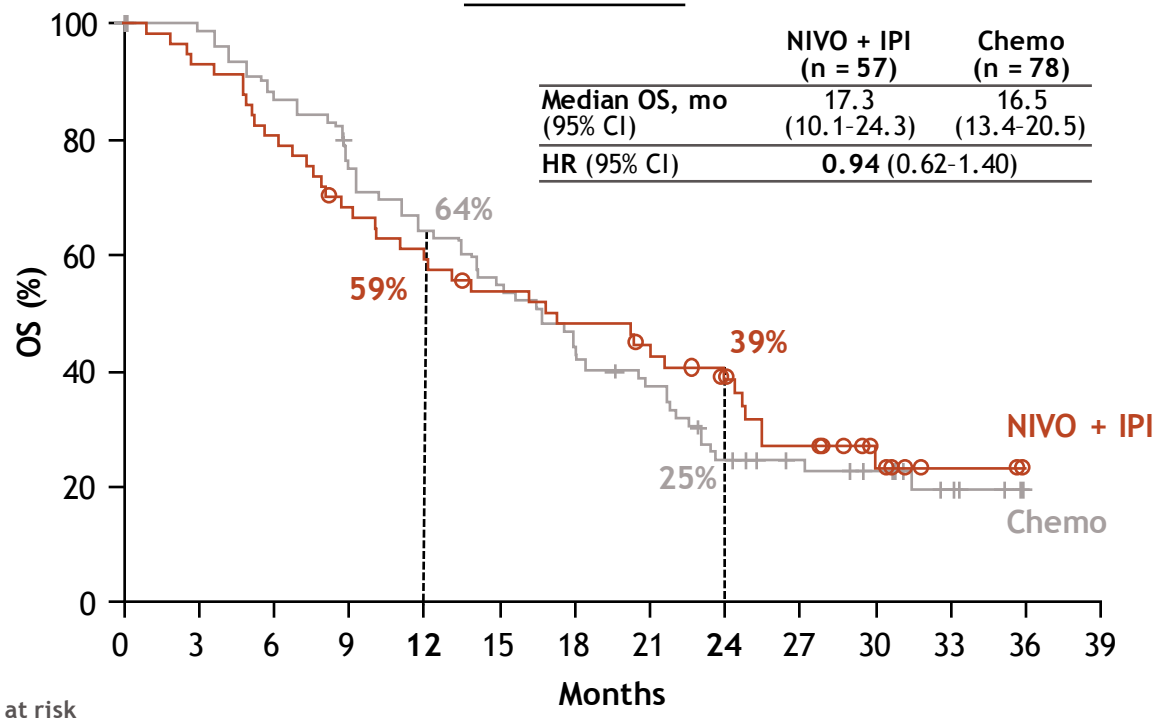
OS HR (95% CI) for epithelioid vs non-epithelioid were: NIVO + IPI, 0.93 (0.68-1.28); chemo, 0.47 (0.35-0.63).

[a]Histology per CRF source.

Overall survival by PD-L1 expression level

PD-L1 < 1%

	NIVO + IPI (n = 57)	Chemo (n = 78)
Median OS, mo (95% CI)	17.3 (10.1-24.3)	16.5 (13.4-20.5)
HR (95% CI)	**0.94** (0.62-1.40)	

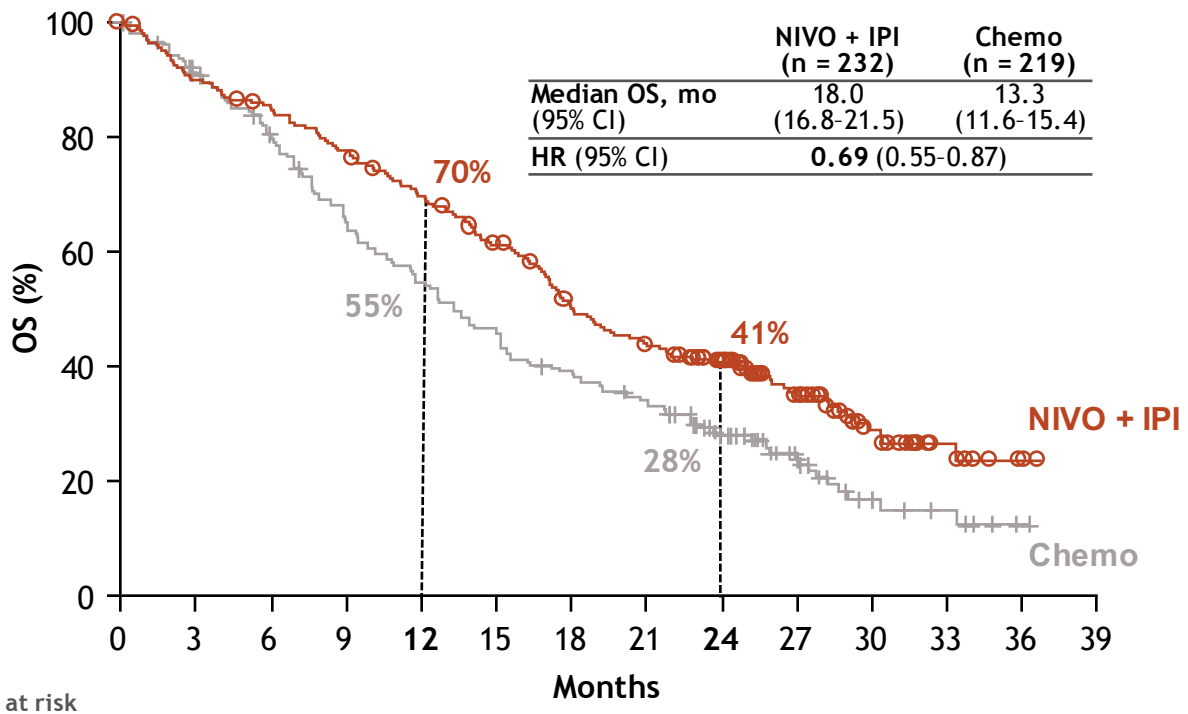


No. at risk

NIVO + IPI	57	53	46	38	33	29	26	22	18	12	6	2	0	0
Chemo	78	75	67	56	48	41	33	27	17	13	10	5	0	0

PD-L1 ≥ 1%

	NIVO + IPI (n = 232)	Chemo (n = 219)
Median OS, mo (95% CI)	18.0 (16.8-21.5)	13.3 (11.6-15.4)
HR (95% CI)	**0.69** (0.55-0.87)	



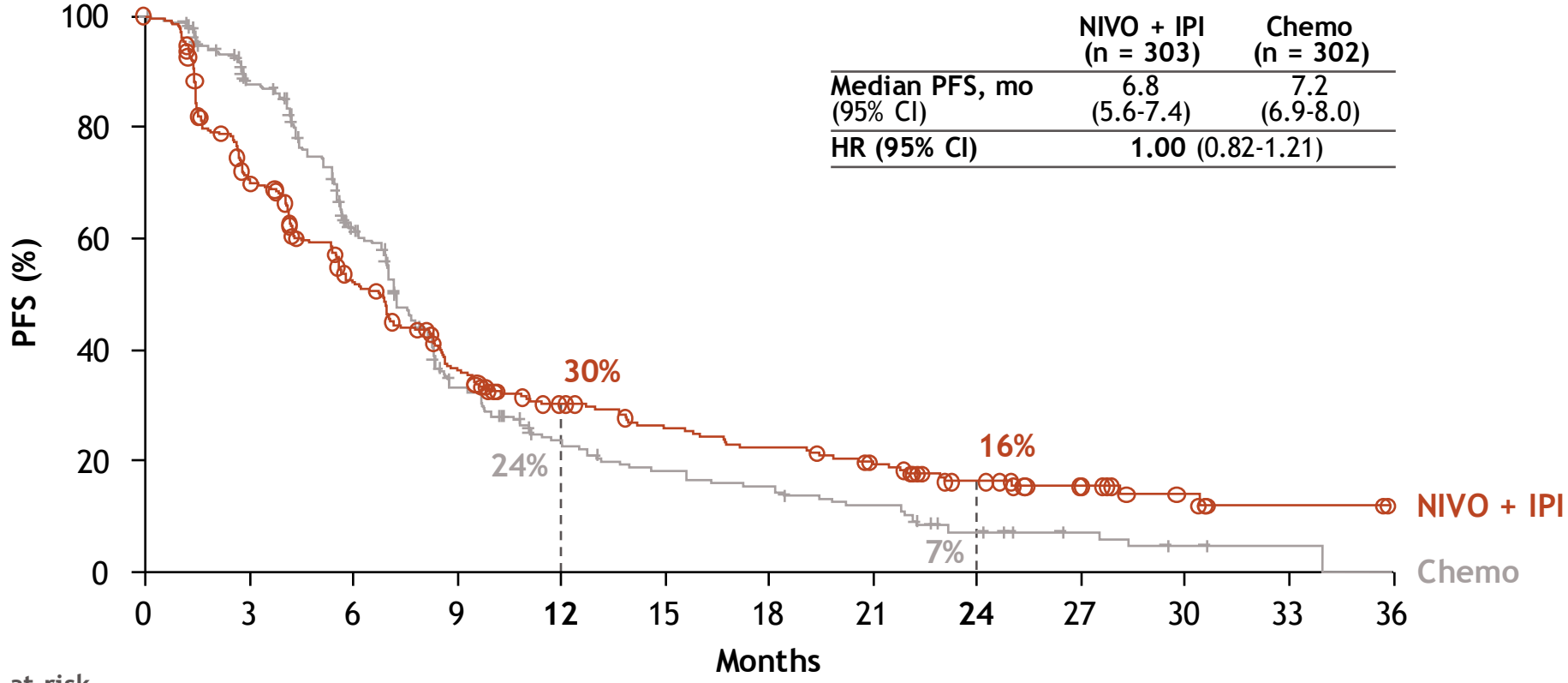
No. at risk

NIVO + IPI	232	207	194	177	157	135	108	93	76	50	24	9	2	0
Chemo	219	188	162	131	111	92	78	66	44	24	9	6	1	0

Minimum follow-up: 22.1 months; median follow-up: 29.7 months.
Patients were not stratified by PD-L1 expression level.
OS HR (95% CI) for PD-L1 ≥ 1% vs < 1% were: NIVO + IPI, 0.87 (0.61-1.23); chemo, 1.18 (0.87-1.60).

Progression-free survival by BICR[a]

	NIVO + IPI (n = 303)	Chemo (n = 302)
Median PFS, mo (95% CI)	6.8 (5.6-7.4)	7.2 (6.9-8.0)
HR (95% CI)	**1.00** (0.82-1.21)	



No. at risk

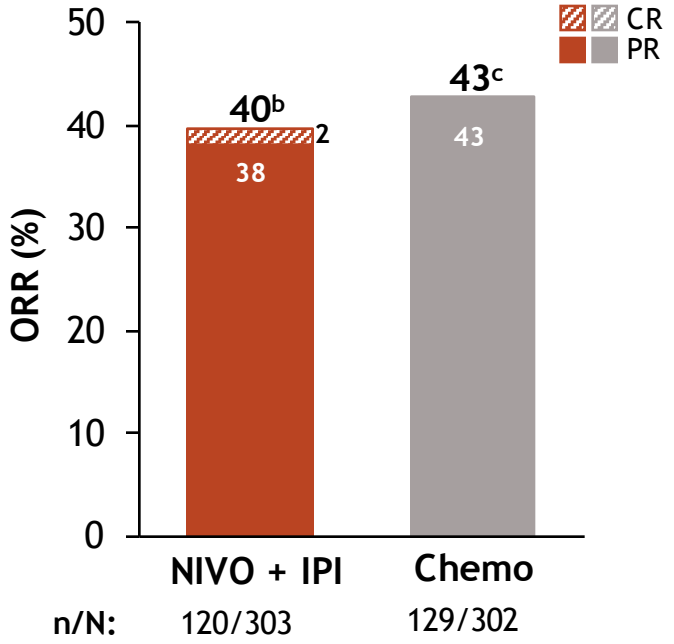
NIVO + IPI	303	198	135	89	64	52	45	36	22	15	7	2	0
Chemo	302	222	144	71	44	33	27	21	10	6	3	1	0

[a]Per adapted mRECIST for pleural mesothelioma lesions[1] and/or RECIST v1.1 for non-pleural lesions.

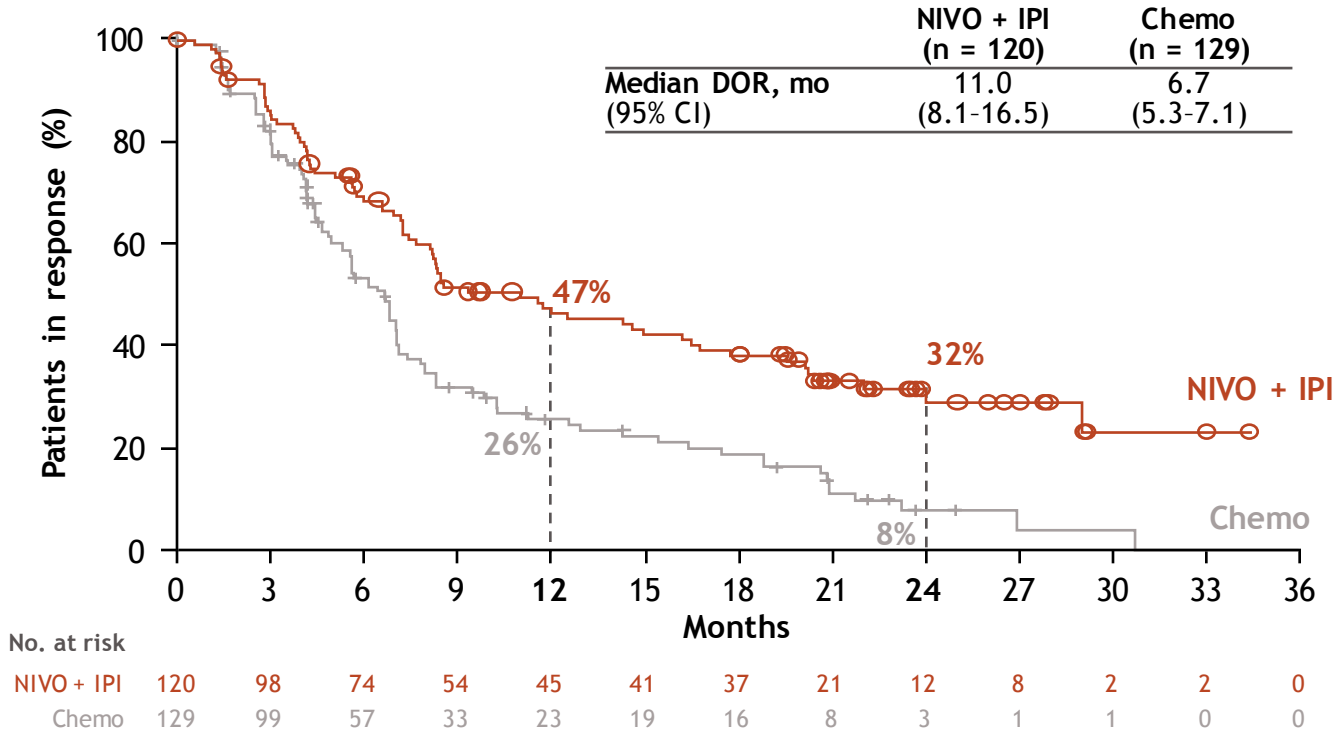
1. Byrne MJ, Nowak AK. *Ann Oncol* 2004;15(2):257-260.

Overall response rate per BICR[a] and duration of response

Response rates



Duration of response



- Disease control rate was 76.6% with NIVO + IPI and 85.1% with chemo

Median time to response was 2.7 months with NIVO + IPI and 2.5 months with chemotherapy.
[a]Per adapted mRECIST for pleural mesothelioma lesions[1] and/or RECIST v1.1 for non-pleural lesions; [b]95% CI, 34%-45%; [c]37%-49%.
1. Byrne MJ, Nowak AK. *Ann Oncol* 2004;15(2):257-260.

Safety summary of TRAEs

TRAE, %	NIVO + IPI[a] (n = 300)		Chemo[b] (n = 284)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Any TRAE[c]	80	30	82	32
TRAEs leading to discontinuation of any component of the regimen[c]	23	15	16	7
Serious TRAEs[c]	21	15	8	6
Treatment-related deaths	1[d]		0.4[e]	

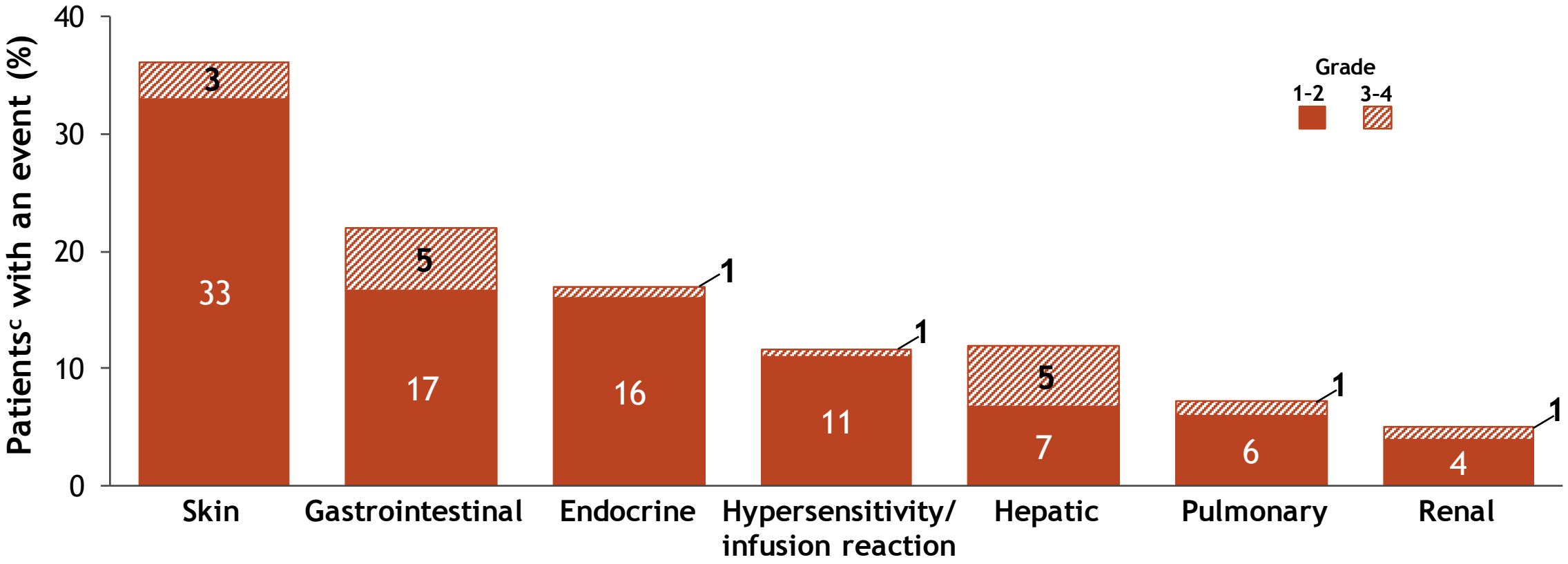
- Median (IQR) duration of therapy was 5.6 (2.0–11.4) months in the NIVO + IPI arm and 3.5 (2.7–3.7) months in the chemo arm
- The most common TRAEs (≥15%) were diarrhea and pruritus with NIVO + IPI, and nausea, anemia, neutropenia, fatigue, decreased appetite, and asthenia with chemo

Person-years of exposure: NIVO + IPI, 220.3; chemo, 94.5.

NIVO + IPI doses were NIVO 3 mg/kg Q2W + IPI 1 mg/kg Q6W.

[a]Median (IQR) doses for treated patients: NIVO, 12.0 (5.0–23.5); IPI, 4.0 (2.0–7.0); [b]Median (IQR) doses for treated patients: pemetrexed, 6.0 (4.0–6.0); cisplatin 5.0 (3.0–6.0); carboplatin 6.0 (4.0–6.0); [c]Includes events reported between first dose and 30 days after last dose of study drug; [d]3 deaths due to NIVO + IPI: pneumonitis, encephalitis, acute heart failure; [e]1 death due to chemo: myelosuppression.

Treatment-related select AEs with NIVO + IPI[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 was 300; 12/14 other events of special interest were resolved with immune-modulating medication treatment.

Summary: NIVO + IPI in first-line unresectable MPM

- CheckMate 743 met its primary endpoint of statistically improved OS with NIVO + IPI versus chemo at the pre-specified interim analysis (HR 0.74, *P* = 0.002); 2-year OS rates were 41% vs 27%
- Survival benefit with NIVO + IPI vs chemo was observed regardless of histology; NIVO + IPI performed similarly in both histologies while chemo performed better in epithelioid histology, as expected
- PD-L1 data was descriptive in nature, precluding firm conclusions
- The safety profile of NIVO + IPI was consistent with that previously seen at this dose and schedule; no new signals were observed
- This is the first positive randomized trial of dual immunotherapy in first line treatment of patients with unresectable MPM and therefore NIVO+ IPI should be considered as a new standard of care

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Abbreviations

1L = first-line

2L+ = second-line or later

AE = adverse event

AUC = area under the curve

BICR = blinded independent committee review

Chemo = chemotherapy

CI = confidence interval

CR = complete response

CRF = case report form

CTLA-4 = cytotoxic T lymphocyte antigen-4

DCR = disease control rate

DOR = duration of response

ECOG = Eastern Cooperative Oncology Group

HR = hazard ratio

IHC = immunohistochemistry

IPI = ipilimumab

IQR = interquartile range

mo = months

MPM = malignant pleural mesothelioma

mRECIST = modified Response Evaluation Criteria in Solid Tumors

NIVO = nivolumab

No. = number

ORR = objective response rate

OS = overall survival

PD-1 = programmed death-1

PD-L1 = programmed death ligand 1

PFS = progression-free survival

PR = partial response

PS = performance status

Q2W = every 2 weeks

Q3W = every 3 weeks

Q6W = every 6 weeks

R = randomized

TRAE = treatment-related adverse event