

CheckMate 6DW: first-line nivolumab + ipilimumab vs platinum + pemetrexed for pleural mesothelioma in Chinese patients

Shun Lu,¹ Yan Yu,² Zhen Zhou,¹ Weimin Mao,³ Wei Guo,⁴ Diansheng Zhong,⁵ Yinyin Li,⁶ Jun Zhao,⁷ Zhiwei Chang,⁸ Jiuiwei Cui,⁹ Jin Zhou,¹⁰ Jianying Zhou,¹¹ Yunchao Huang,¹² Hongcheng Wu,¹³ Lin Wu,¹⁴ Li Luo,¹⁵ Vamshidhar Raparathi,¹⁵ Fei Liu,¹⁵ Dongying Liu¹⁶

¹Shanghai Chest Hospital, Shanghai, China; ²Harbin Medical University Cancer Hospital, Harbin, China; ³Zhejiang Cancer Hospital, Hangzhou, China; ⁴Shanxi Cancer Hospital, Taiyuan, China; ⁵Tianjin Medical University General Hospital, Tianjin, China; ⁶The Shenyang Tenth People's Hospital - Shenyang Chest Hospital, Shenyang, China; ⁷Beijing Cancer Hospital, Beijing, China; ⁸The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; ⁹The First Hospital of Jilin University, Changchun, China; ¹⁰Sichuan Cancer Hospital, Chengdu, China; ¹¹The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; ¹²Yunnan Province Cancer Hospital, Kunming, China; ¹³Ningbo Medical Center Lihuili Hospital, Ningbo, China; ¹⁴Hunan Cancer Hospital, Changsha, China; ¹⁵Bristol Myers Squibb; ¹⁶Tianjin Medical University Cancer Institute & Hospital, Tianjin, China

Introduction

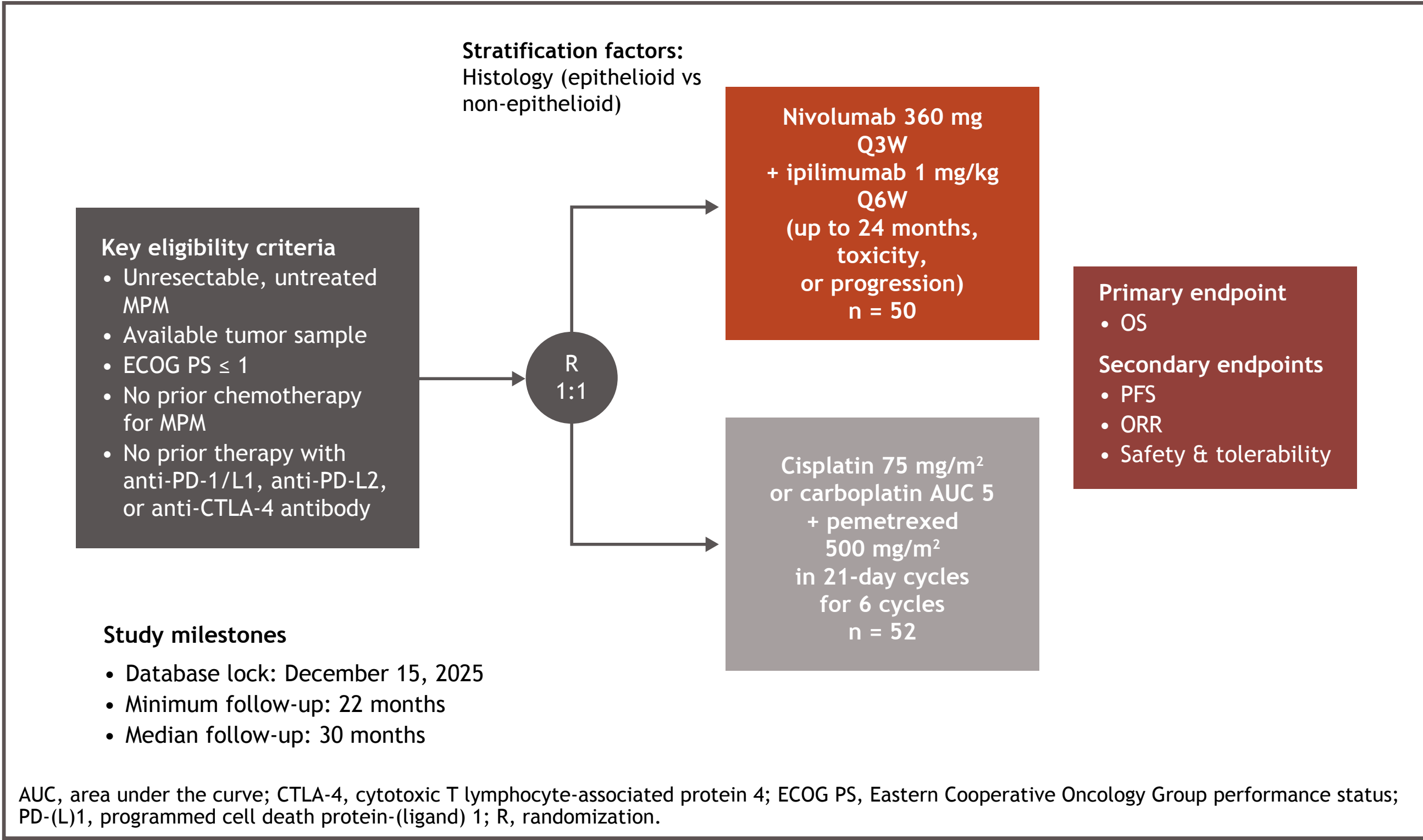
- Malignant pleural mesothelioma (MPM) is a rare locally invasive and highly aggressive cancer of the pleura membrane¹
- In the global pivotal phase 3 study CA209-743 (CheckMate 743), nivolumab + ipilimumab as the first-line treatment for patients with unresectable MPM demonstrated statistically significant and clinically meaningful improvements in overall survival (OS) compared with chemotherapy (median OS [mOS], 18.1 months vs 14.1 months; hazard ratio [HR], 0.74; 95% confidence interval [CI], 0.60-0.91)²
 - Based on the significant clinical efficacy, the United States Food and Drug Administration approved nivolumab + ipilimumab as the first and only immunotherapy treatment for previously untreated, unresectable MPM³
 - Conditional approval of nivolumab + ipilimumab as first-line treatment for non-epithelioid MPM was also granted by the China National Medical Products Administration
- CheckMate 6DW is a phase 2, randomized, open-label trial of nivolumab in combination with ipilimumab vs pemetrexed with cisplatin or carboplatin as first-line therapy for Chinese patients with unresectable MPM, including epithelioid and non-epithelioid MPM
- CheckMate 6DW evaluated whether the clinical benefit and safety of nivolumab + ipilimumab in Chinese patients with unresectable MPM are consistent with those observed in the CheckMate 743 study

Methods

Study design

- CheckMate 6DW is a phase 2, randomized, open-label bridging study in Chinese patients with previously untreated, unresectable MPM (**Figure 1**)
- Patients were stratified by histology (epithelioid vs non-epithelioid) and randomized (1:1) to nivolumab (360 mg every 3 weeks [Q3W]) + ipilimumab (1 mg/kg every 6 weeks [Q6W]) for ≤ 2 years or pemetrexed + cisplatin/carboplatin (Q3W) for ≤ 6 cycles
- The primary endpoint was OS (time from randomization to the date of death)
- The secondary endpoints included progression-free survival (PFS) and objective response rate (ORR) per investigator assessment, and safety/tolerability

Figure 1. CheckMate 6DW study design



Statistical analysis

- The study was planned to have formal data analysis after a minimum follow-up of approximately 22 months (similar minimum follow-up to the interim analysis in the pivotal CheckMate 743 study)
- OS, PFS, and duration of response (DOR) were assessed based on Kaplan-Meier estimates
- HRs were calculated using the stratified Cox proportional hazards model, and are expressed as nivolumab + ipilimumab over chemotherapy
- The threshold for consistency in OS benefit with the global CheckMate 743 study was defined as a HR of < 0.87

Results

Patients

- Overall, 102 patients were randomized (nivolumab + ipilimumab, n = 50; chemotherapy, n = 52)
- Baseline characteristics were generally balanced across treatment arms (epithelioid histology: 80.0% vs 78.8%; stage III: 66.0% vs 63.5%; stage IV: 30.0% vs 32.7%; PD-L1 expression ≥ 1%: 42.9% vs 40.6%) (**Table 1**)

Table 1. Key demographics and baseline characteristics

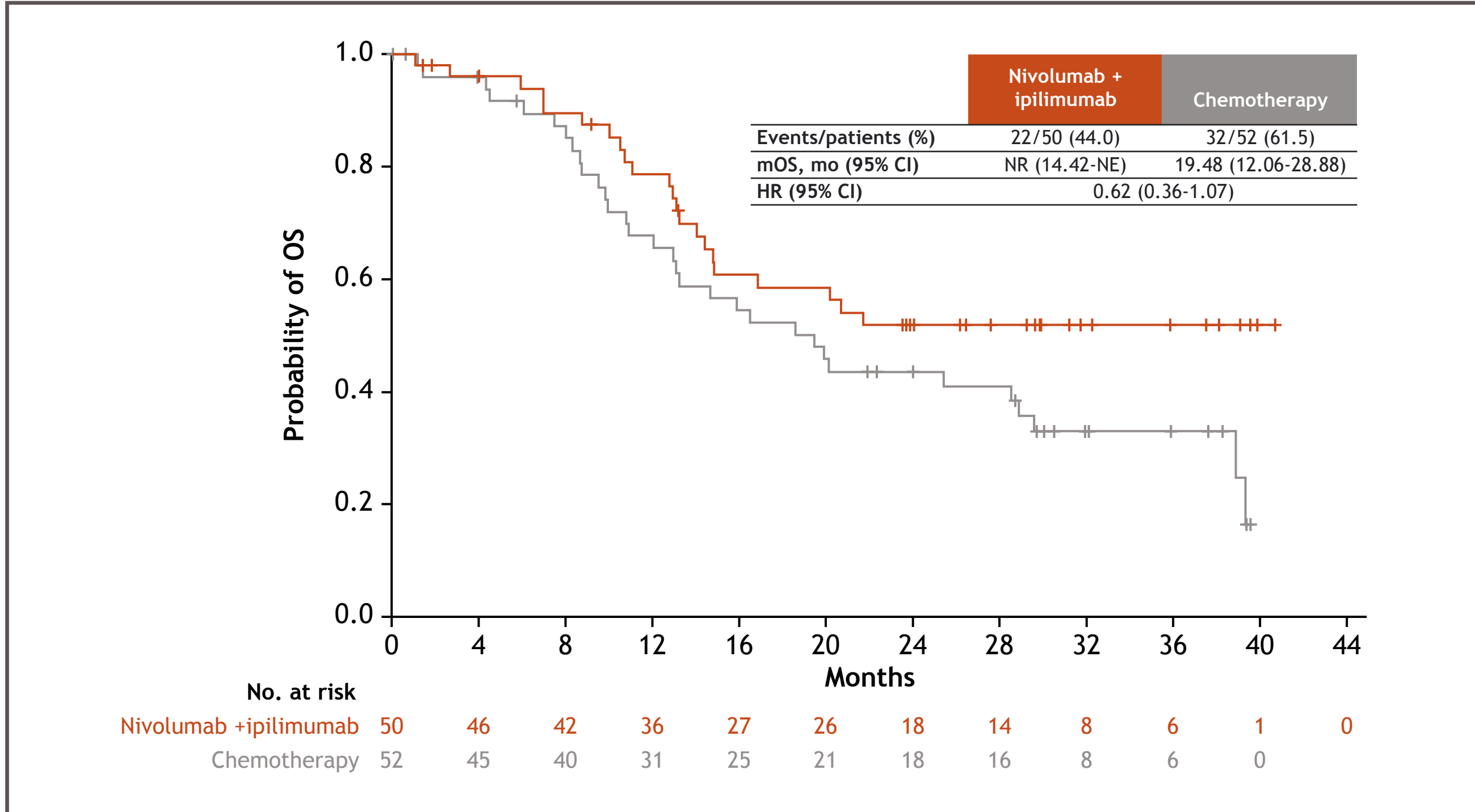
Demographic and baseline characteristics, n (%)	All randomized patients	
	Nivolumab + ipilimumab n = 50	Chemotherapy n = 52
Age (years)		
Median (range)	63.0 (31-83)	64.5 (20-74)
< 65	27 (54.0)	26 (50.0)
≥ 65	23 (46.0)	26 (50.0)
≥ 65 and < 75	19 (38.0)	26 (50.0)
≥ 75	4 (8.0)	0
Sex		
Male	27 (54.0)	22 (42.3)
Female	23 (46.0)	30 (57.7)
Race		
Chinese	50 (100.0)	52 (100.0)
Baseline histology cell type		
Epithelioid	40 (80.0)	41 (78.8)
Non-epithelioid	10 (20.0)	11 (21.2)
Disease stage at study entry		
Stage I	2 (4.0)	0
Stage II	0	2 (3.8)
Stage III	33 (66.0)	33 (63.5)
Stage IV	15 (30.0)	17 (32.7)
Tobacco use		
Never	35 (70.0)	38 (73.1)
Former	12 (24.0)	11 (21.2)
Current	3 (6.0)	3 (5.8)
Time from initial diagnosis to randomization		
< 1 year	50 (100.0)	52 (100.0)
≥ 1 year	0	0
ECOG PS		
0	14 (28.0)	5 (9.6)
≥ 1	36 (72.0)	47 (90.4)
PD-L1 TPS^a		
≥ 1%	15 (42.9)	13 (40.6)
< 1%	20 (57.1)	19 (59.4)

^aPD-L1 TPS % was calculated based on patients with quantifiable PD-L1 expression, while there were 35 patients (34.3%) with PD-L1 TPS undetermined/not evaluable/missing in CheckMate 6DW. TPS, tumor proportion score.

OS

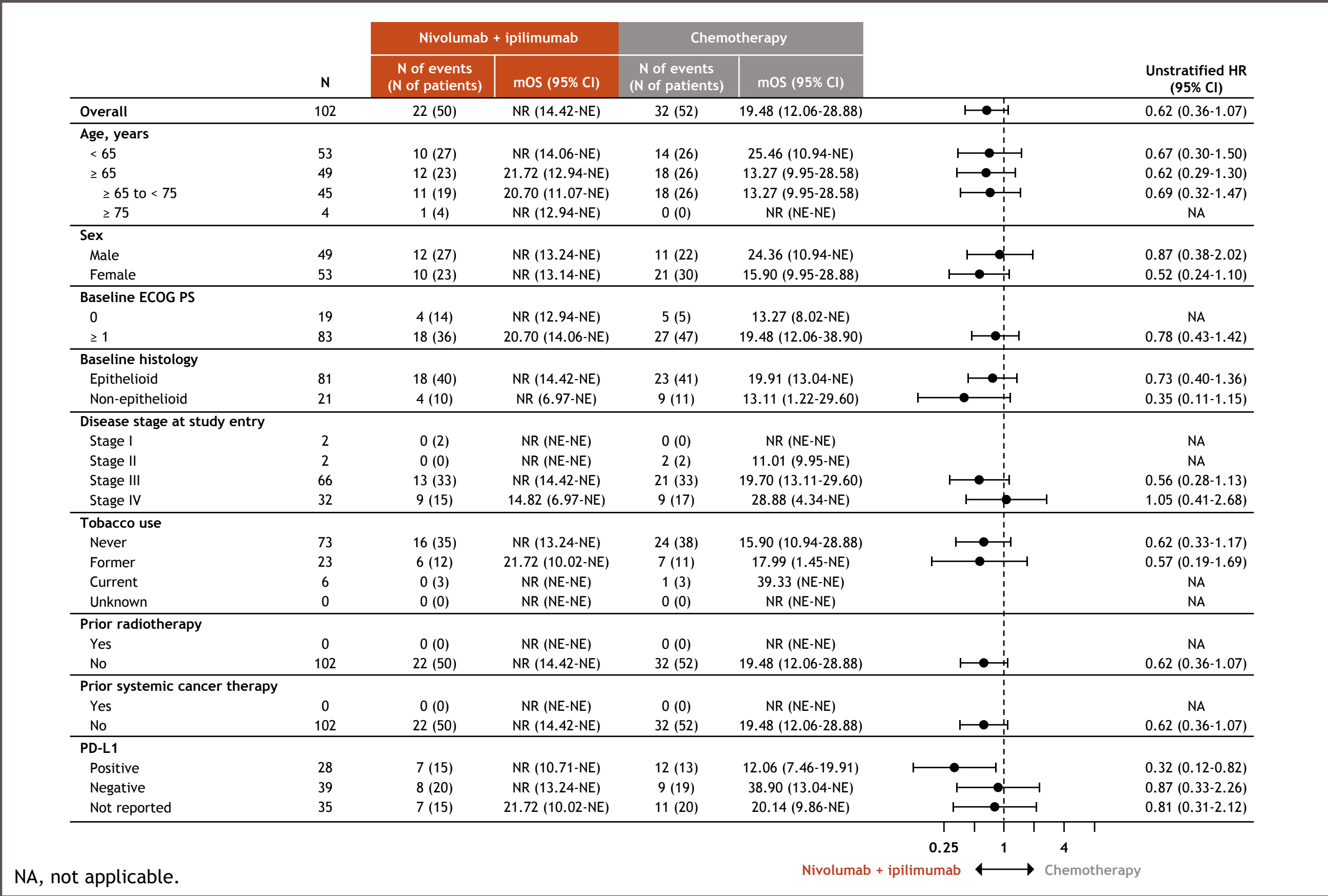
- With a median follow-up of 30 months, deaths occurred in 44.0% vs 61.5% of patients in the nivolumab + ipilimumab vs the chemotherapy arm; mOS (95% CI) was 19.48 months (12.06-28.88) in the chemotherapy arm, while this was not reached (NR; 14.42-not estimable [NE]) in the nivolumab + ipilimumab arm (**Figure 2**)
- OS favored nivolumab + ipilimumab with a HR of 0.62 (95% CI, 0.36-1.07), meeting the consistency criterion (HR, < 0.87) for successful bridging

Figure 2. OS in all randomized patients



- The OS benefit with nivolumab + ipilimumab vs chemotherapy was generally consistent across the subgroups
- Nivolumab + ipilimumab demonstrated an improvement in OS compared with chemotherapy in both non-epithelioid MPM (HR, 0.35; 95% CI, 0.11-1.15) and epithelioid MPM (HR, 0.73; 95% CI, 0.40-1.36) (**Figure 3**)

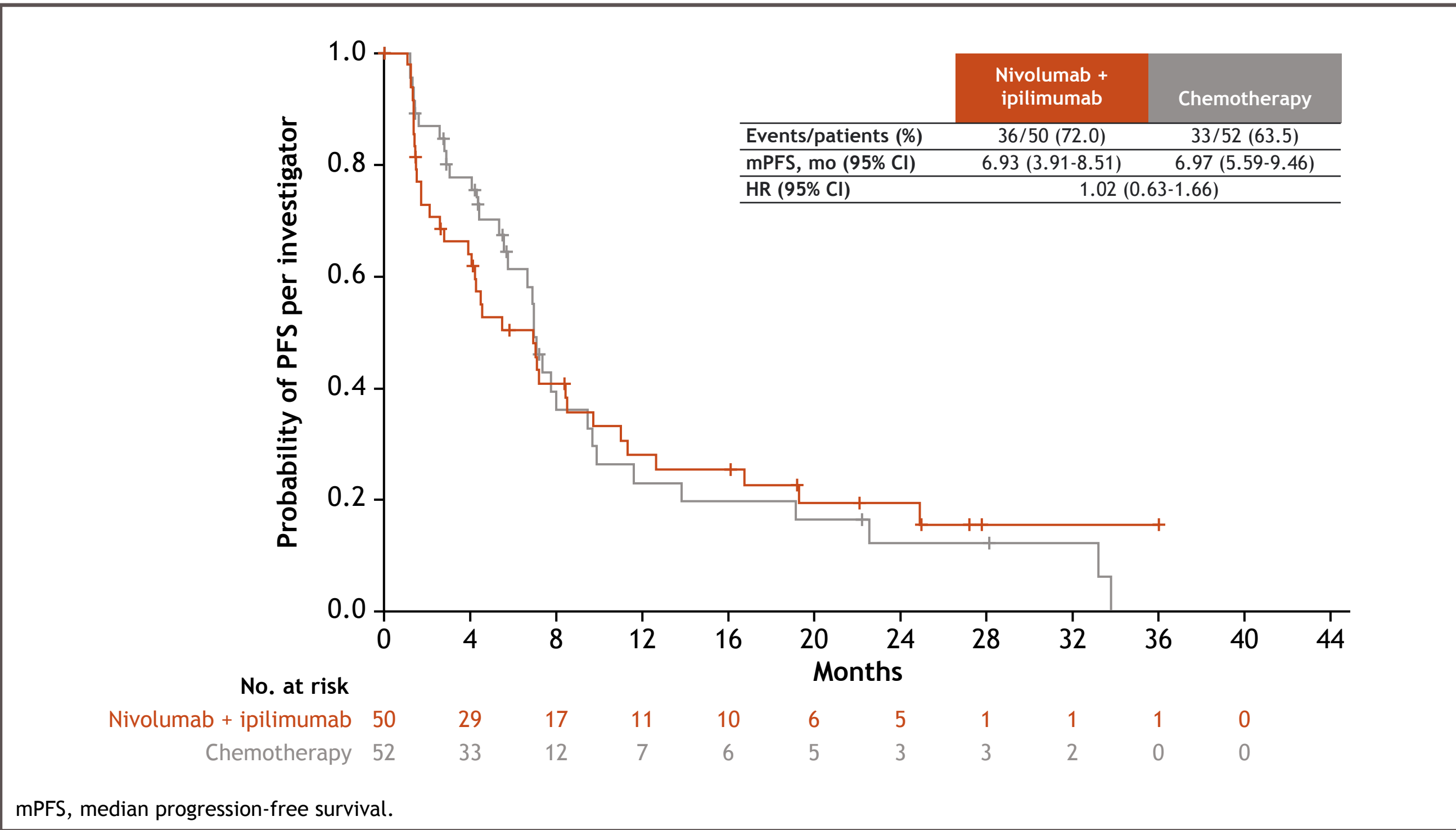
Figure 3. OS in predetermined subgroups



PFS

- PFS was similar between arms (median, 6.93 months nivolumab + ipilimumab arm vs 6.97 months chemotherapy arm; HR, 1.02; 95% CI, 0.63-1.66) (**Figure 4**)

Figure 4. PFS per investigator in all randomized patients



ORR and DOR

- A similar ORR was observed between the 2 treatment arms (34.0% nivolumab + ipilimumab arm vs 32.7% chemotherapy arm), with all responders achieving partial response (PR) (**Table 2**)
- A longer median DOR (mDOR) was observed in the nivolumab + ipilimumab arm than in the chemotherapy arm (20.1 months vs 6.9 months)

Table 2. ORR and DOR

	All randomized patients	
	Nivolumab + ipilimumab n = 50	Chemotherapy n = 52
ORR per investigator according to RECIST v1.1, n (%)	17 (34.0)	17 (32.7)
95% CI	(21.21-48.77)	(20.33-47.11)
Best overall response, n (%)		
CR	0	0
PR	17 (34.0)	17 (32.7)
SD	17 (34.0)	23 (44.2)
PD	13 (26.0)	4 (7.7)
Not evaluable	3 (6.0)	8 (15.4)
mDOR (95% CI), mo	20.1 (4.11-NR)	6.9 (5.42-17.77)

CR, complete response; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Subsequent therapy

- Subsequent therapy was given in 50.0% of patients in the nivolumab + ipilimumab arm and 63.5% of patients in the chemotherapy arm
- Subsequent systemic therapy with immune checkpoint inhibitors was received by 10.0% and 30.8% of patients in the nivolumab + ipilimumab and chemotherapy arms, respectively, and targeted therapy by 26.0% and 34.6%, respectively

Safety

- Of treated patients (n = 48 per arm), treatment-related adverse events (TRAEs) occurred in 83.3% vs 91.7% (grade 3/4: 41.7% vs 45.8%) and serious TRAEs in 39.6% vs 18.8% (**Table 3**)
- No deaths attributed to study drug toxicity occurred in either arm

Table 3. Safety summary

AE, n (%)	All treated patients			
	Nivolumab + ipilimumab n = 48		Chemotherapy n = 48	
	Any grade	Grade 3/4	Any grade	Grade 3/4
All-causality AEs				
AEs	44 (91.7)	24 (50.0)	46 (95.8)	23 (47.9)
SAEs	29 (60.4)	18 (37.5)	13 (27.1)	9 (18.8)
AEs leading to discontinuation ^a	6 (12.5)	4 (8.3)	1 (2.1)	1 (2.1)
TRAEs				
AEs	40 (83.3)	20 (41.7)	44 (91.7)	22 (45.8)
SAEs	19 (39.6)	14 (29.2)	9 (18.8)	8 (16.7)
AEs leading to discontinuation ^a	5 (10.4)	3 (6.3)	1 (2.1)	1 (2.1)
TRAEs^b occurring in ≥ 15% of treated patients in either group				
Aspartate aminotransferase increased	11 (22.9)	2 (4.2)	4 (8.3)	0
Alanine aminotransferase increased	10 (20.8)	4 (8.3)	7 (14.6)	0
Anemia	8 (16.7)	2 (4.2)	31 (64.6)	8 (16.7)
Pyrexia	8 (16.7)	0	0	0
Neutrophil count decreased	5 (10.4)	2 (4.2)	21 (43.8)	9 (18.8)
Platelet count decreased	5 (10.4)	2 (4.2)	13 (27.1)	8 (16.7)
Hyponatremia	5 (10.4)	0	9 (18.8)	0
White blood cell count decreased	3 (6.3)	0	24 (50.0)	5 (10.4)
Nausea	1 (2.1)	0	12 (25.0)	1 (2.1)
Non-endocrine IMAEs treated with IMMs^c				
Pneumonitis	3 (6.3)	1 (2.1)	0	0
Diarrhea/colitis	3 (6.3)	0	4 (8.3)	0
Hepatitis	22 (45.8)	6 (12.5)	10 (20.8)	0
Nephritis and renal dysfunction	3 (6.3)	0	5 (10.4)	0
Rash	8 (16.7)	2 (4.2)	5 (10.4)	0
Hypersensitivity	2 (4.2)	0	0	0
Endocrine IMAEs^c				
Adrenal insufficiency	4 (8.3)	3 (6.3)	0	0
Hypothyroidism/thyroiditis	7 (14.6)	0	2 (4.2)	0
Hypothyroidism	7 (14.6)	0	2 (4.2)	0
Hyperthyroidism	4 (8.3)	1 (2.1)	1 (2.1)	0
Hypophysitis	4 (8.3)	1 (2.1)	0	0

^aDiscontinuation of any component of the combination regimen was counted as a drug discontinuation event. ^bIncludes events reported between first dose and 30 days after last dose of study therapy. ^cIncludes events reported between first dose and 100 days after last dose of study therapy. AE, adverse event; IMAE, immune-mediated adverse event; IMM, immunomodulating medication; SAE, serious adverse event.

Conclusions

- The CheckMate 6DW study met the success criteria of the primary endpoint of OS with nivolumab + ipilimumab vs chemotherapy (success criteria of HR < 0.87), and OS favored nivolumab + ipilimumab in both epithelioid and non-epithelioid subgroups
 - This demonstrated consistent OS benefit with the global CheckMate 743 study
- PFS and ORR were similar with nivolumab + ipilimumab vs chemotherapy
 - Responses were durable and mDOR was longer with nivolumab + ipilimumab vs chemotherapy
- In CheckMate 6DW, the safety profile of nivolumab + ipilimumab in first-line MPM was similar to the known safety profile of the combination and generally consistent with that of the CheckMate 743 study, with no new safety signals identified
- Together, these findings support first-line nivolumab + ipilimumab for the treatment of Chinese patients with unresectable MPM

References

- Tedesco J, et al. *Cancers (Basel)*. 2022;14(18):4415.
- Baas P, et al. *Lancet*. 2021;397(10272):375-386.
- Nakajima E, et al. *Clin Cancer Res*. 2022;28(3):446-451.

Acknowledgments

- We thank the patients and families who made this study possible, the clinical study teams, and the global trial manager. All authors contributed to and approved the presentation. Professional medical writing and editorial assistance were provided by Jen Reinhold, PharmD, and Molly Yu, PhD, of Parexel, and was funded by Bristol Myers Squibb. The study was supported by Bristol Myers Squibb