6-year outcomes with first-line nivolumab plus ipilimumab plus chemotherapy in patients with metastatic non-small cell lung cancer with and without brain metastases from CheckMate 9LA

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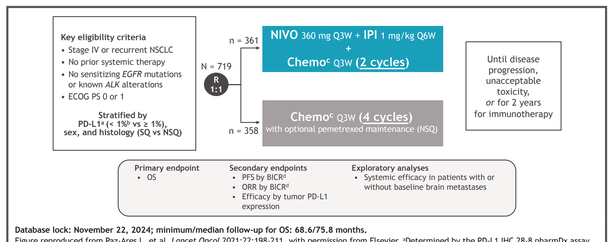
Introduction

- The global randomized phase 3 CheckMate 9LA study demonstrated long-term, durable overall survival (OS) benefit with first-line (1L) nivolumab (NIVO) + ipilimumab (IPI) with 2 cycles of chemotherapy (chemo) vs chemo alone (4 cycles) in patients with metastatic non-small cell lung cancer (mNSCLC)[1-5]
  - This regimen is approved as a 1L treatment option for eligible adult patients with mNSCLC and no *EGFR* or *ALK* genomic alterations in multiple countries, including the United States and across the European Union[6,7]
  - Notably, NIVO + IPI + chemo has shown durable efficacy in populations with high unmet needs, such as patients with tumor programmed death ligand 1 (PD-L1) expression < 1%,[5] squamous (SQ) cell histology,[5] or baseline brain metastases[3]
- Here, we present the final 6-year efficacy and safety outcomes, including subgroup analyses of patients with and without baseline brain metastases

Methods

- In CheckMate 9LA (NCT03215706), adults with stage IV/recurrent NSCLC and *EGFR*/*ALK* wild-type were randomized 1:1 to receive NIVO + IPI with 2 cycles of chemo or 4 cycles of chemo alone (**Figure 1**)
- Patients with treated brain metastases who were asymptomatic for ≥ 2 weeks before the first study treatment were eligible for enrollment
- OS, progression-free survival (PFS), objective response rate (ORR), and duration of response (DOR) were assessed in all randomized patients and in key patient subgroups based on
  - Tumor PD-L1 expression (< 1 vs ≥ 1%)
  - Histology (SQ vs non-squamous [NSQ])
  - Baseline brain metastases per blinded independent central review (BICR; with vs without)

Figure 1. CheckMate 9LA study design[1]



Database lock: November 22, 2024; minimum/median follow-up for OS: 68.6/75.8 months.

Figure reproduced from Paz-Ares L, et al. *Lancet Oncol* 2021;22:198-211, with permission from Elsevier. [a]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako). [b]Patients unevaluable for PD-L1 were stratified to PD-L1 < 1% and capped to 10% of all randomized patients. [c]NSQ: pemetrexed + cisplatin or carboplatin; SQ: paclitaxel + carboplatin. [d]Hierarchically statistically tested. ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; Q3W, every 3 weeks; R, randomized.

Results

Patients

- Baseline characteristics in all randomized patients have been reported previously and were generally well-balanced between treatment arms[1]
- 52 (14%) patients in the NIVO + IPI + chemo arm and 50 (14%) patients in the chemo alone arm had baseline brain metastases[5]
  - Baseline characteristics in patients with or without baseline brain metastases have been reported previously and were generally similar across both treatment arms (**Table 1**)

Table 1. Baseline characteristics by baseline brain metastasis status[5]

	With brain metastases		Without brain metastases	
	NIVO + IPI + chemo (n = 52)	Chemo (n = 50)	NIVO + IPI + chemo (n = 309)	Chemo (n = 308)
Median age, years (range)	60 (44-81)	64 (36-82)	66 (35-80)	65 (26-86)
Male, n (%)	34 (65)	37 (74)	218 (71)	215 (70)
Smoking status, n (%)				
Current/former	41 (79)	46 (92)	274 (89)	260 (84)
Never	11 (21)	4 (8)	35 (11)	48 (16)
ECOG PS, n (%)[a]				
0	17 (33)	13 (26)	97 (31)	100 (32)
1	34 (65)	37 (74)	212 (69)	207 (67)
Geographic region, n (%)				
Asia	5 (10)	4 (8)	23 (7)	26 (8)
Europe	30 (58)	29 (58)	182 (59)	184 (60)
North America	5 (10)	8 (16)	31 (10)	20 (6)
Rest of the world[b]	12 (23)	9 (18)	73 (24)	78 (25)
Tumor histology, n (%)				
Squamous	8 (15)	13 (26)	107 (35)	99 (32)
Non-squamous	44 (85)	37 (74)	202 (65)	209 (68)
Tumor PD-L1 expression, n (%)				
< 1% or non-quantifiable	21 (40)	20 (40)	136 (44)	134 (44)
> 1 %	31 (60)	30 (60)	173 (56)	174 (56)
1-49%	19 (36)	17 (34)	109 (35)	89 (29)
≥ 50%	12 (23)	13 (26)	64 (21)	85 (28)
Metastasis, n (%)				
Liver	8 (15)	20 (40)	60 (19)	66 (21)
Bone	14 (27)	10 (20)	83 (27)	101 (33)
Prior steroid use, n (%)	3 (6)	8 (16)	7 (2)	11 (4)
Prior radiotherapy, n (%)	47 (90)	45 (90)	58 (19)	44 (14)
Brain radiotherapy[c]	46 (88)	44 (88)	13 (4)	12 (4)
Whole brain radiotherapy	17 (33)	18 (36)	6 (2)	4 (1)
Brain tumor burden, median (range), mm	20.0 (10-113)	29.5 (12-71)	—	—

Percentages may not total 100 due to rounding. [a]ECOG PS not reported in 2% of patients with brain metastases (NIVO + IPI+ chemo) and < 1% of patients without brain metastases (chemo). [b]Includes Argentina, Australia, Brazil, and Chile. [c]SBRT that is focal and not whole brain radiotherapy. SBRT, stereotactic body radiation therapy.

Figure 2. OS in all randomized patients and in subgroups by tumor PD-L1 expression or histology

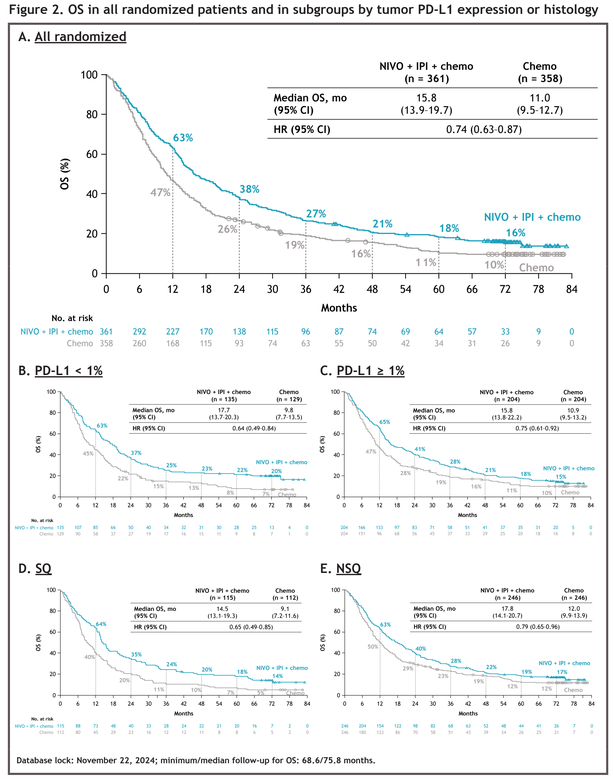


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Table 2. Efficacy in all randomized patients and by tumor PD-L1 expression or histology

	All randomized		PD-L1 < 1%		PD-L1 ≥ 1%		SQ		NSQ	
	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)	NIVO + IPI + chemo (n = 135)	Chemo (n = 129)	NIVO + IPI + chemo (n = 204)	Chemo (n = 204)	NIVO + IPI + chemo (n = 115)	Chemo (n = 112)	NIVO + IPI + chemo (n = 246)	Chemo (n = 246)
Median PFS, months (95% CI)	6.7 (5.6-8.0)	5.3 (4.4-5.6)	5.8 (4.4-7.7)	5.0 (4.2-5.8)	6.9 (5.6-8.9)	4.7 (4.2-5.6)	5.6 (4.3-9.7)	4.3 (4.2-5.2)	6.9 (5.5-8.4)	5.6 (4.6-5.8)
HR (95% CI)	0.70 (0.59-0.82)		0.71 (0.53-0.92)		0.69 (0.56-0.86)		0.65 (0.48-0.87)		0.74 (0.61-0.91)	
6-year PFS rate, % (95% CI)	9 (6-12)	3 (1-6)	9 (5-15)	NA[a]	8 (5-13)	4 (1-9)	7 (3-14)	4 (1-11)	9 (6-14)	2 (1-7)
ORR, n (%) [95% CI]	137 (38) [33-43]	90 (25) [21-30]	42 (31) [23-40]	26 (20) [14-28]	87 (43) [36-50]	56 (28) [22-34]	56 (49) [39-58]	35 (31) [23-41]	81 (33) [27-39]	55 (22) [17-28]
Median DOR, months (95% CI)	13.0 (8.7-20.2)	5.6 (4.4-7.1)	17.5 (6.9-37.8)	4.3 (2.8-7.1)	11.8 (8.6-20.3)	5.6 (4.3-8.0)	10.8 (8.4-18.7)	3.9 (2.8-4.6)	20.0 (8.0-27.7)	7.1 (5.6-11.0)
Ongoing response at 6 years, % (95% CI)	19 (12-26)	NA[a]	25 (12-40)	0 (NA)	16 (9-26)	NA[a]	15 (7-26)	NA[a]	21 (12-32)	NA[a]

Database lock: November 22, 2024; minimum/median follow-up for OS: 68.6/75.8 months.
[a]Rate is reported as NA because all patients with continuing response in the chemo arm were censored prior to 72 months. NA, not available.

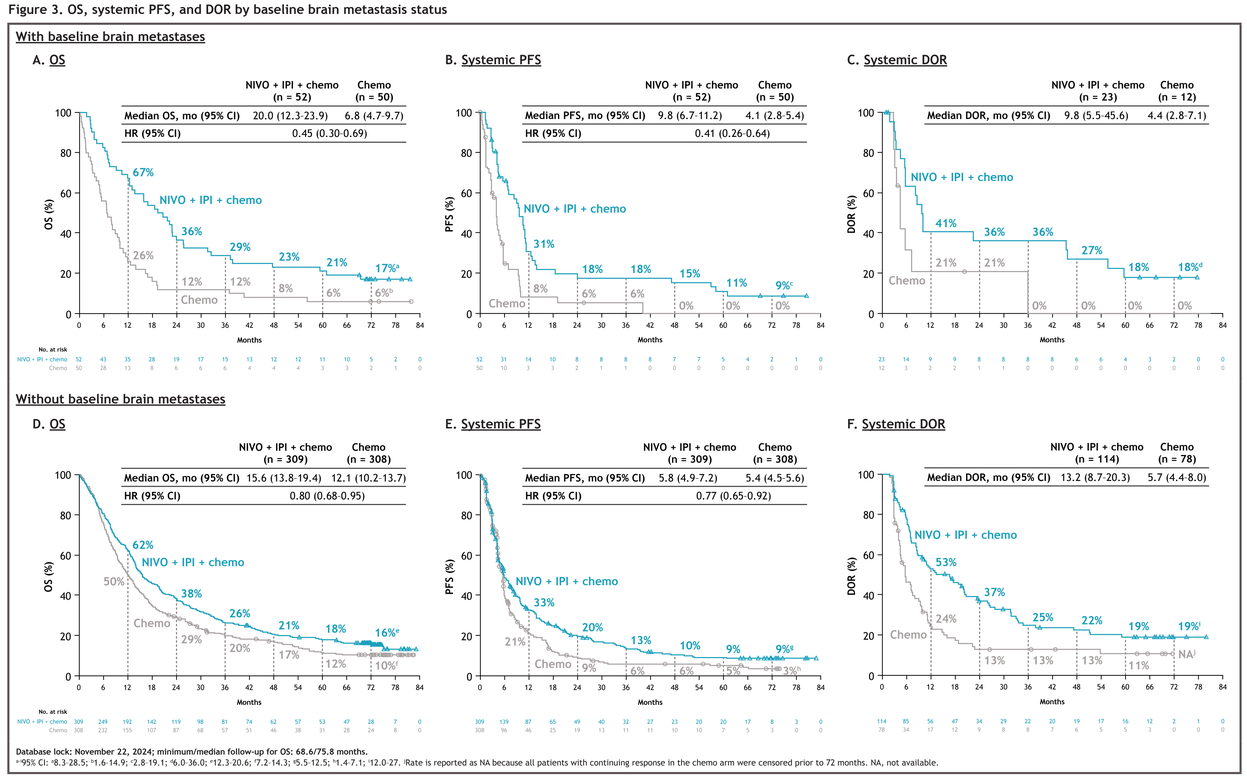
Efficacy in all randomized patients and by tumor PD-L1 expression or histology

- With a minimum follow-up of 68.6 months, NIVO + IPI + chemo continued to improve OS vs chemo alone in all randomized patients and regardless of tumor PD-L1 expression or histology (**Figure 2**)
  - A greater magnitude of OS benefit was observed with NIVO + IPI + chemo vs chemo alone in patients with tumor PD-L1 expression < 1% or SQ histology (**Figures 2B** and **2D**)
- PFS, ORR, and DOR favored NIVO + IPI + chemo vs chemo in all randomized patients and across patient subgroups (**Table 2**)

Subsequent therapy by baseline brain metastasis status

- Among patients with baseline brain metastases, 35% of patients in the NIVO + IPI + chemo arm and 50% in the chemo only arm received any subsequent therapy and among patients without baseline brain metastases, 45% of patients in the NIVO + IPI + chemo arm and 56% of patients in the chemo only arm received any subsequent therapy (**Table 3**)

Figure 3. OS, systemic PFS, and DOR by baseline brain metastasis status



Database lock: November 22, 2024; minimum/median follow-up for OS: 68.6/75.8 months.
[a]95% CI: [b]8.3-28.5; [c]1.6-14.9; [d]2.8-19.1; [e]6.0-36.0; [f]12.3-20.6; [g]7.2-14.3; [h]5.5-12.5; [i]1.4-7.1; [j]12.0-27. [k]Rate is reported as NA because all patients with continuing response in the chemo arm were censored prior to 72 months. NA, not available.

Table 3. Subsequent therapy by baseline brain metastasis status

	With baseline brain metastases		Without baseline brain metastases	
	NIVO + IPI + chemo (n = 52)	Chemo (n = 50)	NIVO + IPI + chemo (n = 309)	Chemo (n = 308)
Subsequent therapy, n (%)	18 (35)	25 (50)	140 (45)	174 (56)
Subsequent radiotherapy, n (%)	10 (19)	12 (24)	58 (19)	50 (16)
Subsequent brain radiotherapy,[a] n (%)	6 (12)	8 (16)	9 (3)	14 (4)
Subsequent systemic therapy, n (%)	15 (29)	18 (36)	122 (40)	160 (52)
Platinum-doublet chemo	9 (17)	1 (2)	64 (21)	22 (7)
Immunotherapy	2 (4)	14 (28)	27 (9)	119 (39)

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Patient may have received more than 1 type of subsequent therapy. Subsequent therapy was defined as therapy started on or after first dosing date (or randomization date if patient was not yet treated). [a]Includes any type of radiotherapy to the brain.

Exploratory analyses in patients with or without baseline brain metastases

- NIVO + IPI + chemo continued to provide OS benefit vs chemo regardless of baseline brain metastasis status (**Figures 3A** and **3D**)
  - In patients with baseline brain metastases, the median OS for NIVO + IPI + chemo vs chemo alone was 20 months vs 6.8 months, with 6-year rates of 17% vs 6%
- Patients with baseline brain metastases treated with NIVO + IPI + chemo had systemic PFS benefit (6-year PFS rates, 9% vs 0%; HR, 0.41 [95% CI, 0.26-0.64]) vs patients treated with chemo alone (**Figure 3B**)
  - Improvement in systemic PFS with NIVO + IPI + chemo vs chemo were also maintained in patients without baseline brain metastases (**Figure 3E**)
- Patients with baseline brain metastases treated with NIVO + IPI + chemo also had more durable responses (median systemic DOR, 10 months vs 4 months; 6-year DOR rates, 18% vs 0%) vs patients treated with chemo alone (**Figure 3C**)

Safety

- At the 6-year update, safety in all treated patients was consistent with previous reports and no new safety signals were reported

Conclusions

- With a minimum follow-up of 68.6 months, NIVO + IPI + chemo continued to show long-term, durable OS and consistent clinical response benefit vs chemo alone in patients with mNSCLC, including those with tumor PD-L1 expression < 1% or SQ histology
  - 6-year OS rates: all randomized, 16% vs 10%; PD-L1 < 1%, 20% vs 7%; SQ, 14% vs 5%
  - NIVO + IPI + chemo also maintained its consistent clinical response benefit across PFS, ORR, and DOR vs chemo alone
- Additionally, NIVO + IPI + chemo continued to deliver systemic efficacy benefit vs chemo in patients with or without brain metastases
- This 6-year update represents one of the longest reported follow-ups for a 1L dual immuno-oncology–based regimen in mNSCLC
- These long-term results reinforce NIVO + IPI + chemo as a durable and effective 1L treatment option for patients with mNSCLC, particularly those with high unmet needs, including patients with tumor PD-L1 expression < 1%, SQ histology, or baseline brain metastases

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