First-line nivolumab + ipilimumab + chemotherapy vs chemotherapy alone in patients with metastatic non-small cell lung cancer from CheckMate 9LA: 4-year clinical update including subgroup analyses by tumor histology and PD-L1 level

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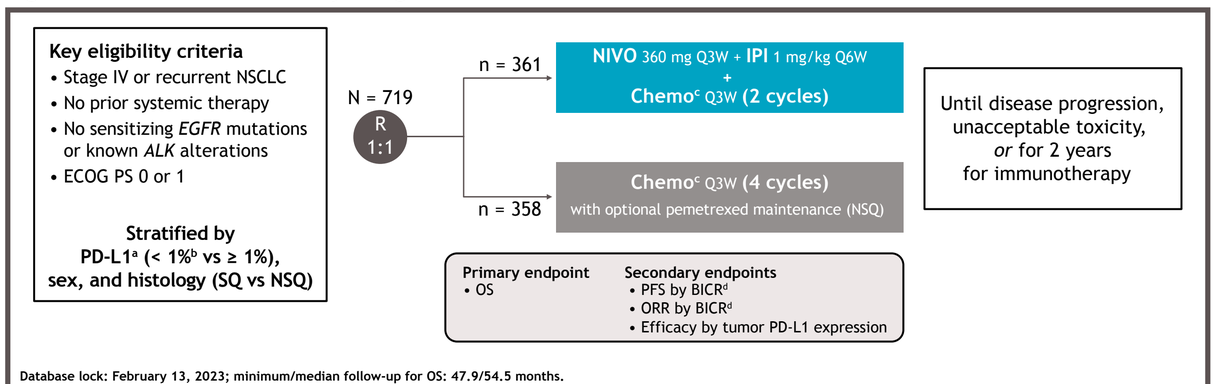
Background

- The combination of nivolumab plus ipilimumab (NIVO + IPI), immune checkpoint inhibitors with distinct but complementary mechanisms of action,[1,2] has shown long-term, durable overall survival (OS) benefit in the treatment of several advanced cancers,[3-5] including metastatic non-small cell lung cancer (NSCLC)[6-9]
- In the randomized phase 3 CheckMate 9LA study, first-line NIVO + IPI plus 2 cycles of chemotherapy (chemo) significantly improved OS vs chemo alone (4 cycles) in patients with metastatic NSCLC[6-8]
- Here, we present the updated efficacy and safety results of CheckMate 9LA, with a minimum follow-up of 4 years, including analyses of OS by histology and programmed death ligand 1 (PD-L1) levels

Methods

- Adults with stage IV/recurrent NSCLC (no known sensitizing epidermal growth factor receptor [*EGFR*]/anaplastic lymphoma kinase [*ALK*] alterations) and Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1 were enrolled in CheckMate 9LA (NCT03215706) and randomized 1:1 to NIVO + IPI + 2 cycles of chemo or to 4 cycles of chemo alone (**Figure 1**)
- OS, progression-free survival (PFS), objective response rate (ORR), and duration of response (DOR) were assessed in all randomized patients and in patients by PD-L1 or by histology
- Efficacy was also assessed in patients who discontinued all components of NIVO + IPI + chemo due to treatment-related adverse events (TRAEs)

Figure 1. CheckMate 9LA study design[7]



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[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.
BICR, blinded independent central review; IHC, immunohistochemistry; NSQ, non-squamous; Q3W, every 3 weeks; Q6W, every 6 weeks; R, randomized; SQ, squamous.

Results

Patients and analysis populations

- Baseline characteristics for the full randomized population have been previously reported and were balanced across all treatment groups[8,9]
  - Among all patients (n = 719), 492 (68%) had NSQ histology and 264 (37%) had PD-L1 tumor status < 1%

Subsequent therapy

- In all randomized patients, subsequent systemic therapy was received by 37% (NIVO + IPI + chemo) and 49% (chemo) of patients
  - Subsequent immunotherapy was received by 7% and 36% and subsequent platinum-doublet chemo by 20% and 6% of patients, respectively

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

- NIVO + IPI + chemo continued to improve all efficacy outcomes vs chemo at 4 years, regardless of tumor PD-L1 expression or histology (**Table 1** and **Figures 2-4**)
- A greater magnitude of efficacy benefit with NIVO + IPI + chemo was observed in patients with tumor PD-L1 expression < 1% (**Table 1**, and **Figures 3A** and **4B**) or SQ histology (**Table 1** and **Figure 3C**)
- Further efficacy analysis showed a trend for improved OS with NIVO + IPI + chemo vs chemo in each PD-L1 subgroup across SQ and NSQ histology (**Figure 5**)
- Among patients who discontinued all components of NIVO + IPI + chemo due to TRAEs (n = 61), the 4-year OS rate was 41% (**Figure 6**), median OS was 27.5 months, and ORR was 51%

Safety

- Safety in all treated patients was consistent with previous reports,[6,7] and no new safety signals were identified
- Grade 3-4 TRAEs occurred in 48% of patients in the NIVO + IPI + chemo arm and 38% in the chemo arm; any-grade TRAEs leading to discontinuation occurred in 22% and 9% of patients, respectively

Table 1. Efficacy in all randomized patients and subgroups by PD-L1 or histology

	ITT		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, mo (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 (0.59-0.83)		0.70 (0.53-0.92)		0.70 (0.56-0.87)		0.64 (0.48-0.86)		0.75 (0.61-0.91)	
4-y PFS rate, % (95% CI)	12 (8-15)	5 (3-8)	12 (7-19)	3 (0-8)	12 (8-17)	6 (3-11)	8 (4-15)	4 (1-11)	13 (9-18)	5 (3-10)
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]
Ongoing response at 4 y, % (95% CI)	25 (17-33)	12 (6-20)	29 (15-45)	0	24 (15-34)	15 (7-26)	17 (8-29)	6 (1-17)	30 (19-41)	16 (7-28)

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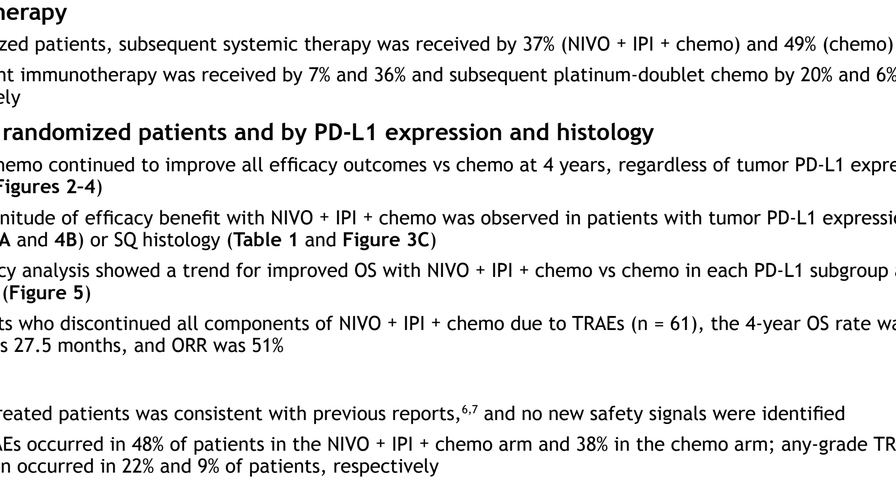
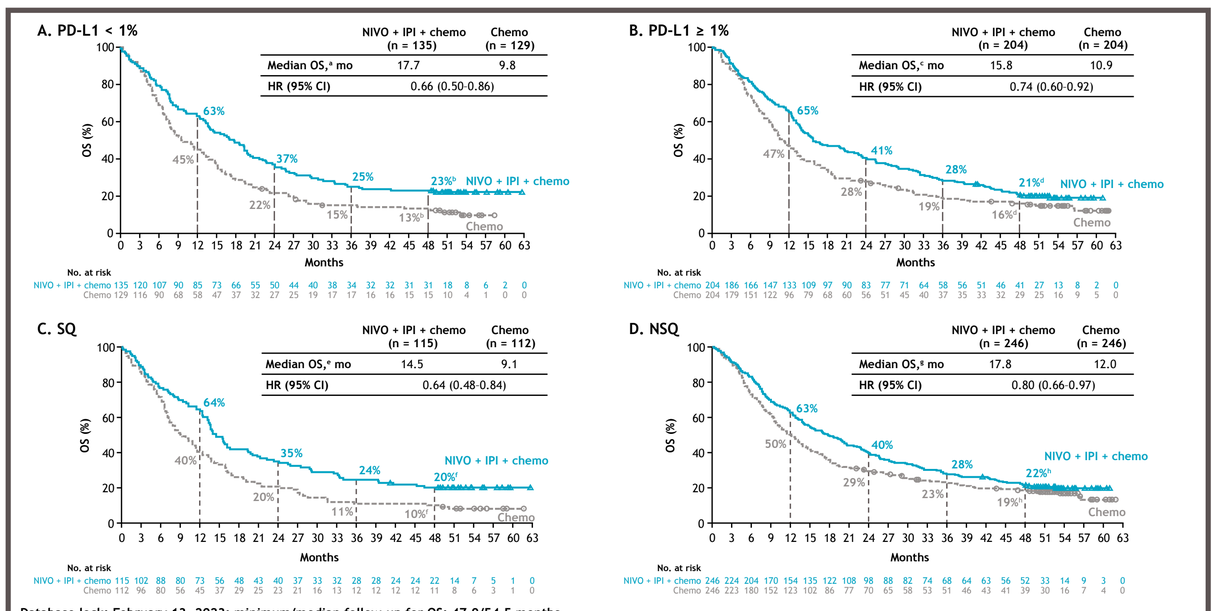
CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; mo, month; y, year.

Figure 2. OS in all randomized patients



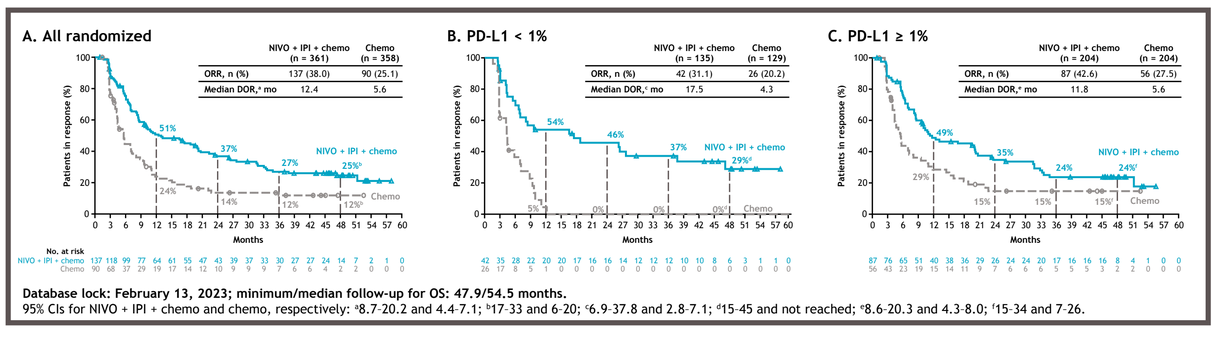
Database lock: February 13, 2023; minimum/median follow-up for OS: 47.9/54.5 months.
95% CIs for NIVO + IPI + chemo and chemo, respectively: [a]13.9-19.7 and 9.5-12.7; [b]17-25 and 12-20.

Figure 3. OS in subgroups by PD-L1 expression or histology



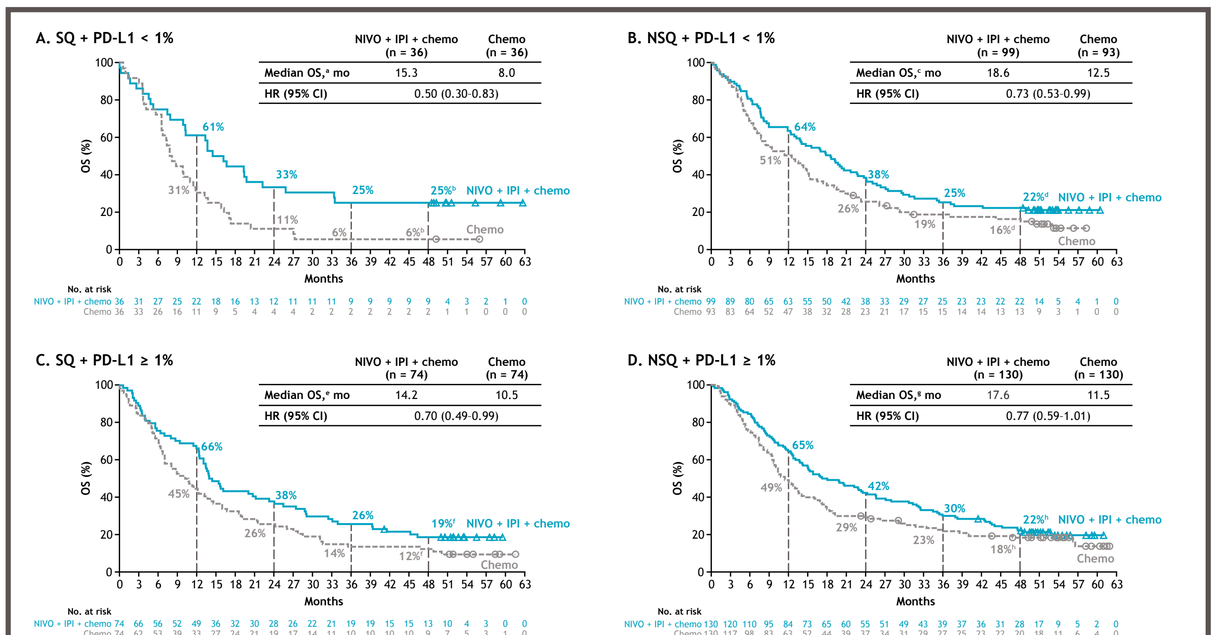
Database lock: February 13, 2023; minimum/median follow-up for OS: 47.9/54.5 months.
95% CIs for NIVO + IPI + chemo and chemo, respectively: [a]13.7-20.3 and 7.7-13.5; [b]16-30 and 8-20; [c]13.8-22.2 and 9.5-13.2; [d]16-27 and 11-22; [e]13.1-19.3 and 7.2-11.6; [f]13-28 and 5-16; [g]14.1-20.7 and 9.9-13.9; [h]17-27 and 14-24.

Figure 4. DOR in all randomized patients and subgroups by PD-L1 expression



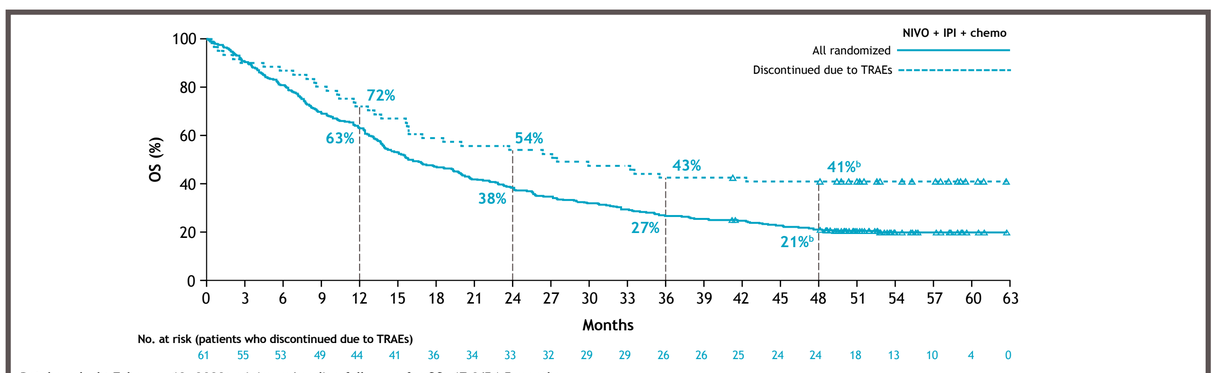
Database lock: February 13, 2023; minimum/median follow-up for OS: 47.9/54.5 months.
95% CIs for NIVO + IPI + chemo and chemo, respectively: [a]8.7-20.2 and 4.4-7.1; [b]17-33 and 6-20; [c]6.9-37.8 and 2.8-7.1; [d]15-45 and not reached; [e]8.6-20.3 and 4.3-8.0; [f]15-34 and 7-26.

Figure 5. OS in subgroups by PD-L1 expression and histology



Database lock: February 13, 2023; minimum/median follow-up for OS: 47.9/54.5 months.
95% CIs for NIVO + IPI + chemo and chemo, respectively: [a]9.9-22.2 and 6.6-11.5; [b]12.4-39.8 and 1.0-16.3; [c]13.2-22.7 and 7.7-15.2; [d]14.6-30.8 and 9.5-24.7; [e]12.5-23.3 and 7.1-14.1; [f]10.7-28.3 and 6.0-20.7; [g]13.8-24.3 and 9.7-13.9; [h]15.4-29.6 and 12.2-25.6.

Figure 6. Efficacy in patients who discontinued NIVO + IPI + chemo due to TRAEs[a]



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[a]Post hoc analysis includes patients with TRAEs (reported between first dose and 30 days after the last dose of study treatment) leading to the discontinuation of all components of study treatment.
[b]95% CIs for patients who discontinued due to TRAEs and all randomized, respectively: 29-53 and 17-25.

Conclusions

- With a 4-year minimum follow-up, patients treated with NIVO + IPI + chemo continued to derive long-term, durable OS benefit vs chemo alone regardless of tumor PD-L1 expression or histology
- OS benefit with NIVO + IPI + chemo compared with chemo alone was observed in all histology and PD-L1-level subgroups analyzed
  - Greater benefits were observed in the PD-L1 < 1% or SQ NSCLC populations
  - PFS and DOR benefit were also maintained in patients with tumor PD-L1 < 1% or SQ NSCLC
- Discontinuation of NIVO + IPI + chemo due to TRAEs did not negatively impact the long-term clinical or efficacy benefit, with a 4-year OS rate of 41%
  - Of these patients, 27% were alive and treatment-free 4 years after discontinuing study therapy
- No new safety signals were reported
- These data further support the use of NIVO + IPI + chemo as an efficacious first-line treatment option for patients with metastatic NSCLC, particularly for those with tumor PD-L1 < 1% or SQ histology, which are populations with high unmet needs

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