Clinical outcomes in patients with tumor PD-L1 < 1% with first-line nivolumab + ipilimumab + 2 cycles of chemotherapy vs chemotherapy alone for metastatic non-small cell lung cancer: results from CheckMate 9LA

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Objective

- To report an exploratory analysis of clinical outcomes in patients with tumor programmed death ligand 1 (PD-L1) expression < 1% from CheckMate 9LA according to histology and baseline brain metastases

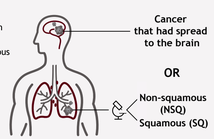
Conclusions

- With a 3-year minimum follow-up, first-line (1L) nivolumab (NIVO) + ipilimumab (IPI) + chemotherapy (chemo) for metastatic non-small cell lung cancer (NSCLC) showed long-term, durable overall survival (OS) benefit vs chemo in this exploratory analysis in patients with tumor PD-L1 expression < 1%, regardless of histology or baseline brain metastases
- A trend favoring NIVO + IPI + chemo vs chemo alone for progression-free survival (PFS) was observed in histology subgroups, as well as in patients with or without baseline brain metastases
  - Duration of response (DOR) was also improved by NIVO + IPI + chemo in histology subgroups; for the baseline brain metastases subgroup, data interpretation was limited by the small sample size
- The safety profile was consistent with previous reports, and no new safety signals were seen in patients with baseline brain metastases
- These data further support NIVO + IPI + chemo as a 1L treatment option for patients with metastatic NSCLC, including those with a high unmet need

Plain Language Summary

Unmet Needs and Objectives

- There are limited long-term benefits from the use of immunotherapy in people with non-small cell lung cancer (NSCLC) whose cancer cells do not express a specific protein called PD-L1
- Additionally, a high unmet need for effective therapies remains in people with squamous cancers (based on how the cancer cells look under a microscope), or in people whose cancer had already spread to the brain
- This exploratory analysis from CheckMate 9LA was designed to further understand treatment outcomes of an immunotherapy combination, NIVO + IPI + chemo, vs chemo alone in people whose cancer cells do not express PD-L1, based on:
  - two different types of lung cancer cells (NSQ vs SQ) or
  - whether the cancer had spread to the brain



Findings

Clinical outcomes

- Among people without PD-L1 on cancer cells, more were alive overall (OS) at 3 years if treated with NIVO + IPI + chemo compared with those treated with chemo alone, regardless of the type of cancer cells or whether the cancer had spread to the brain

- A higher proportion of people in the NIVO + IPI + chemo group vs chemo were alive at 3 years without their cancer getting worse (PFS), regardless of the type of cancer cells or whether the cancer had spread to the brain
  - 16% vs 2% (NSQ) and 19% vs 4% (SQ)
  - 7% vs 0% (with cancer spread to the brain) and 18% vs 3% (without cancer spread to the brain)
- Regardless of the type of cancer cells, tumor shrinkage lasted longer in people who responded to NIVO + IPI + chemo vs chemo (2x longer [NSQ]; nearly 7x longer [SQ])
  - At 3 years, 36% (NSQ) and 39% (SQ) of people who responded to NIVO + IPI + chemo have kept this response; none who initially responded to chemo remained in response
- For people whose cancer had spread to the brain and responded to treatment, there is limited information available

Side effects

- Consistent with all people enrolled in the study, those whose cancers do not express PD-L1 had no new side effects, including those related to the nervous system, which could be more relevant for people whose cancer had spread to the brain

Conclusions

- NIVO + IPI + chemo could be used as a treatment option for people with previously untreated NSCLC that has spread or come back, regardless of the type of cancer cells or whether the cancer had spread to the brain

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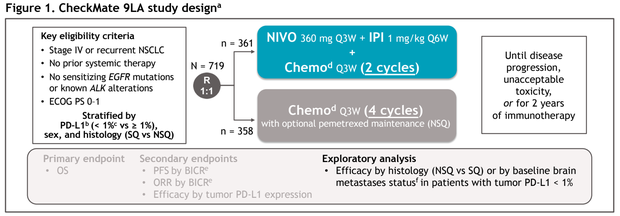
Introduction

- 1L immunotherapy + chemo regimens have limited long-term efficacy in patients with metastatic NSCLC and PD-L1 expression < 1%[1-3]
- Dual immunotherapy with NIVO + IPI has shown clinical activity in this patient population[4,5]
- A particularly high unmet need also remains in patients with squamous (SQ) metastatic NSCLC or with baseline brain metastases[6,7]
- In CheckMate 9LA, 1L NIVO + IPI + 2 cycles of chemo showed long-term, durable survival benefit vs chemo (4 cycles) in patients with metastatic NSCLC, regardless of tumor PD-L1 expression[8-10]
  - 3-year OS rates were 28% vs 19% (PD-L1 ≥ 1%) and 25% vs 15% (PD-L1 < 1%), respectively
- NIVO + IPI + chemo is indicated in the United States, European Union, and several other countries as 1L treatment for adult patients with metastatic NSCLC and no *EGFR* or *ALK* genomic tumor aberrations[11-14]

Methods

- Adults with previously untreated stage IV or recurrent NSCLC were enrolled in CheckMate 9LA (NCT03215706); the study design, key eligibility criteria, and study endpoints are shown in **Figure 1**
- Exploratory analyses included subgroup analyses of patients with tumor PD-L1 < 1% by histology (non-SQ [NSQ] or SQ) or by the presence of baseline brain metastasis (as determined by blinded independent central review [BICR])
- Treatment-related adverse events (TRAEs), including nervous system TRAEs, were assessed in all treated patients

Figure 1. CheckMate 9LA study design[a]



Database lock: February 15, 2022; minimum/median follow-up for OS: 36.1/42.6 months.

Adapted from *Lancet Oncology*, 22, Paz-Ares L, et al, First-line nivolumab plus ipilimumab combined with 2 cycles of chemotherapy in patients with non-small cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial, 198-211, Copyright 2021, with permission from Elsevier.

[a]NCT03215706. [b]Determined using the PD-L1 IHC 28-8 pharmDx assay (Dako). [c]Patients unevaluable for PD-L1 status were included in the tumor PD-L1 < 1% subgroup and capped at 10% of all randomized patients. [d]NSQ: pemetrexed + cisplatin or carboplatin; SQ: paclitaxel + carboplatin. [e]Statistically tested hierarchically. [f]Brain metastases determined by BICR at baseline.
ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; ORR, objective response rate; Q3W, every 3 weeks; Q6W, every 6 weeks; R, randomized.

Results

Patients

- Baseline characteristics in patients with tumor PD-L1 < 1% were generally similar to all randomized patients (**Table 1**)

Efficacy

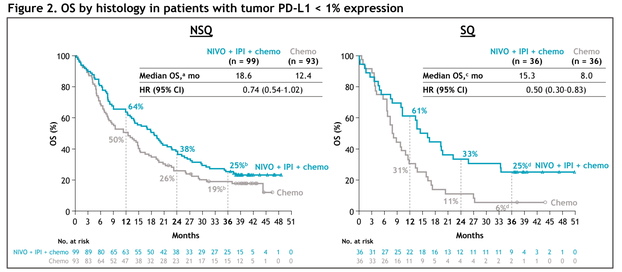
- In patients with tumor PD-L1 < 1%, survival and efficacy outcomes were improved with NIVO + IPI + chemo vs chemo alone, regardless of histology (**Figure 2, Figure 3, Table 2**)
- Survival outcomes were also generally improved with NIVO + IPI + chemo vs chemo alone in patients with tumor PD-L1 expression < 1% with or without baseline brain metastases (**Figure 4, Figure 5**)

Table 1. Baseline characteristics

	All randomized		PD-L1 < 1%		PD-L1 ≥ 1%	
	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)	NIVO + IPI + chemo (n = 135)	Chemo (n = 129)	NIVO + IPI + chemo (n = 204)	Chemo (n = 204)
Median age, years (range)	65 (35-81)	65 (26-86)	65 (39-78)	63 (30-79)	65 (35-81)	66 (26-86)
Female, %	30	30	29	30	29	29
ECOG PS, %						
0	32	32	35	34	30	31
1	68	68	65	66	69	69
Not reported	< 1	< 1	0	0	< 1	< 1
Smoking status, %						
Current/former	87	86	85	87	90	85
Never smoked	13	14	15	13	10	15
Histology, %						
NSQ	68	69	73	72	64	64
SQ	32	31	27	28	36	36
Metastases, %						
CNS[a]	18	16	17	14	18	17
Liver	19	24	15	22	21	26
Bone	27	31	30	32	25	31

[a]Includes metastases in the brain and spinal cord, as assessed by the investigator. CNS, central nervous system.

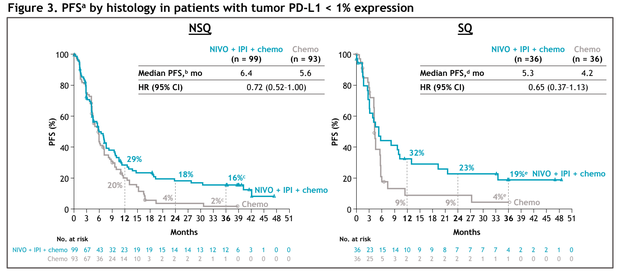
Figure 2. OS by histology in patients with tumor PD-L1 < 1% expression



Minimum follow-up: 36.1 months.

[a]95% CI, 13.2-22.7 (NIVO + IPI + chemo); 7.7-15.2 (chemo). [b]95% CI, 17-34 (NIVO + IPI + chemo) and 12-27 (chemo). [c]95% CI, 9.9-22.2 (NIVO + IPI + chemo) and 6.6-11.5 (chemo). [d]95% CI, 12-40 (NIVO + IPI + chemo) and 1-16 (chemo). CI, confidence interval; HR, hazard ratio.

Figure 3. PFS[a] by histology in patients with tumor PD-L1 < 1% expression



Minimum follow-up: 35.2 months.

[a]PFS assessed per BICR. [b]95% CI, 4.2-7.7 (NIVO + IPI + chemo) and 4.2-6.9 (chemo). [c]95% CI, 9-24 (NIVO + IPI + chemo) and < 1-8 (chemo). [d]95% CI, 3.0-10.2 (NIVO + IPI + chemo) and 4.0-5.6 (chemo). [e]95% CI, 8-34 (NIVO + IPI + chemo) and < 1-18 (chemo).

Table 2. Tumor response[a] by histology in patients with tumor PD-L1 < 1% expression

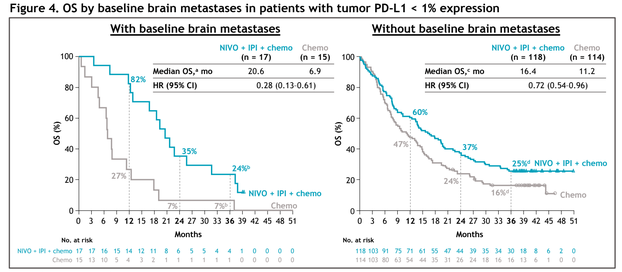
	NSQ		SQ	
	NIVO + IPI + chemo (n = 99)	Chemo (n = 93)	NIVO + IPI + chemo (n = 36)	Chemo (n = 36)
ORR, n (%) [95% CI]	26 (26) [18-36]	14 (15) [8-24]	17 (47) [30-64]	12 (33) [19-51]
BOR, n (%)				
Complete response	1 (1)	1 (1)	4 (11)	0
Partial response	25 (25)	13 (14)	13 (36)	12 (33)
Stable disease	57 (58)	54 (58)	10 (28)	17 (47)
Progressive disease	9 (9)	13 (14)	3 (8)	3 (8)
Median DOR, months (95% CI)	17.5 (4.4-38.9)	7.1 (3.0-9.7)	18.7 (6.0-NR)	2.8 (2.6-4.6)
Ongoing response ≥ 3 years, % (95% CI)	36 (16-56)	0	39 (17-61)	0

Minimum follow-up: 35.2 months.

BOR could not be determined in 7 and 11 patients treated with NIVO + IPI + chemo and chemo alone, respectively, in the NSQ group, and in 6 and 4 patients in the SQ group. BOR was not reported in 1 patient treated with chemo in the NSQ group.

[a]Tumor response assessed per BICR. BOR, best overall response; NR, not reached.

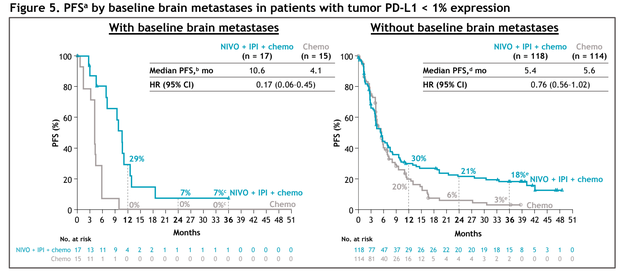
Figure 4. OS by baseline brain metastases in patients with tumor PD-L1 < 1% expression



Minimum follow-up: 36.1 months.

[a]95% CI, 12.3-31.6 (NIVO + IPI + chemo) and 3.1-11.4 (chemo). [b]95% CI, 7-45 (NIVO + IPI + chemo) and < 1-26 (chemo). [c]95% CI, 12.4-20.0 (NIVO + IPI + chemo) and 7.9-14.8 (chemo). [d]95% CI, 18-34 (NIVO + IPI + chemo) and 10-24 (chemo).

Figure 5. PFS[a] by baseline brain metastases in patients with tumor PD-L1 < 1% expression



Minimum follow-up: 35.2 months.

[a]Systemic PFS assessed per BICR. [b]95% CI, 6.8-12.6 (NIVO + IPI + chemo) and 1.4-5.8 (chemo). [c]95% CI, < 1-28 (NIVO + IPI + chemo) and 0 (chemo). [d]95% CI, 4.1-7.2 (NIVO + IPI + chemo) and 4.3-6.0 (chemo). [e]95% CI, 11-26 (NIVO + IPI + chemo) and 1-9 (chemo).

Safety

- Safety was consistent with previous reports,[8-10,15] and no new safety signals were detected (**Table 3**)
- Median duration of therapy was 5.7 months (range, 0·24.4) in patients treated with NIVO + IPI + chemo and 2.8 months (range, 0·43.0) in those treated with chemo in the PD-L1 < 1% subgroup
- Grade 3-4 nervous system TRAEs were observed in 6% vs 0% of patients treated with NIVO + IPI + chemo vs chemo in patients with baseline brain metastases, and in 1% each in those without baseline brain metastases in the PD-L1 < 1% subgroup

Table 3. Safety summary

	All treated				PD-L1 < 1%			
	NIVO + IPI + chemo (n = 358)		Chemo (n = 349)		NIVO + IPI + chemo (n = 134)		Chemo (n = 125)	
	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
TRAEs[a], %	92	48	88	38	90	48	87	36
Treatment-related SAEs[a], %	30	26	18	15	32	28	21	16
TRAEs leading to discontinuation[a], %	22	18	9	5	23	18	13	6
Treatment-related death[b], %	2[c]		2[c]		1[d]		4[d]	

Minimum follow-up: 35.2 months for safety.

[a]Includes events reported between the first dose and 30 days after the last dose of study drug. [b]Includes deaths related to study drug toxicity occurring at any time. [c]Treatment-related deaths in the NIVO + IPI + chemo arm (n = 8): acute renal failure, thrombocytopenia, pneumonitis, hepatic toxicity, hepatitis, sepsis (n = 1 each), and diarrhea (n = 2); treatment-related deaths in the chemo arm (n = 6; 1 for each event): sepsis, anemia, pancytopenia, respiratory failure, pulmonary sepsis, and febrile neutropenia. [d]Treatment-related deaths in the NIVO + IPI + chemo arm (n = 2; 1 for each event): hepatitis and sepsis; treatment-related deaths in the chemo arm (n = 5; 1 for each event): sepsis, anemia, pancytopenia, respiratory failure, and pulmonary sepsis.
SAE, serious adverse event.

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Declaration of Interests

T John reports advisory roles with Amgen, AstraZeneca, Bristol Myers Squibb, Gilead, Merck, MSD, Novartis, Pharmakar, Puma, Roche, and Specialised Therapeutics.

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