Nivolumab + Ipilimumab + 2 Cycles of Platinum-Doublet Chemotherapy vs 4 Cycles Chemotherapy as First-Line Treatment for Stage IV/Recurrent NSCLC: CheckMate 9LA

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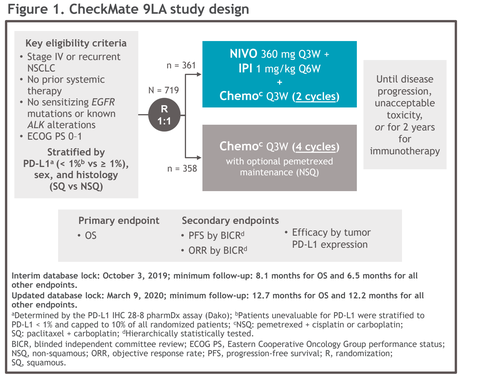
Introduction

- Nivolumab (NIVO) + ipilimumab (IPI) have distinct but complementary mechanisms of action, and have shown improved long-term survival in melanoma, renal cell carcinoma, and non-small cell lung cancer (NSCLC)[1-3]
  - IPI induces de novo anti-tumor T-cell responses, including an increase in memory T cells, while NIVO restores anti-tumor T-cell function[4-7]
- CheckMate 227 showed durable response and overall survival (OS) benefit with NIVO + IPI vs chemo in first-line (1L) advanced NSCLC, regardless of histology or programmed death ligand 1 (PD-L1) expression[8]
- Adding a limited course of chemo to NIVO + IPI could potentially provide rapid disease control while building on the durable OS benefit observed with NIVO + IPI in CheckMate 227; CheckMate 568 part 2 showed that this regimen was tolerable[9]
- CheckMate 9LA (NCT03215706) is a phase 3, randomized, open-label study evaluating NIVO + IPI + chemo (2 cycles) vs chemo (4 cycles) in 1L stage IV or recurrent NSCLC
  - NIVO + IPI + chemo is now indicated in several countries including the United States as 1L treatment of patients with metastatic/recurrent NSCLC with no epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) genomic tumor aberrations[10-13]

Methods

Figure 1. CheckMate 9LA study design



Interim database lock: October 3, 2019; minimum follow-up: 8.1 months for OS and 6.5 months for all other endpoints.
Updated database lock: March 9, 2020; minimum follow-up: 12.7 months for OS and 12.2 months for all other endpoints.
[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 committee review; ECOG PS, Eastern Cooperative Oncology Group performance status; NSQ, non-squamous; ORR, objective response rate; PFS, progression-free survival; R, randomization; SQ, squamous.

- A sample of ~700 randomized patients with 402 deaths would provide 81% power to detect hazard ratio (HR) of 0.75 with a 5% type I error (2-sided)
- Planned interim analysis (reviewed by external, independent data monitoring committee [DMC])
  - Planned to occur after 322 deaths (80% of total deaths)
  - 351 observed events; minimum follow-up, 8.1 months
  - α boundary: ≤ 0.033
- The DMC confirmed superiority for NIVO + IPI + 2 cycles of chemo vs chemo for OS at the pre-planned interim analysis
- PFS and ORR were tested hierarchically if OS was statistically significant

Results

Patients

- Overall, 719 patients were randomized
- Baseline characteristics were well-balanced between arms for subgroups (**Table 1**)
  - Approximately 40% of patients had PD-L1 < 1%

Table 1. Baseline characteristics

	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
Age, median (range), years	65 (35-81)	65 (26-86)
Female, %	30	30
ECOG PS,[a] %		
0	31	31
1	68	68
Smoking status, %		
Never smoker	13	14
Current / former smoker	87	86
Histology, %		
Squamous	31	31
Non-squamous	69	69
Metastases, %		
Bone	27	31
Liver	19	24
CNS	18	16
Tumor PD-L1 expression,[b] %		
< 1%[c]	40	39
≥ 1%[c]	60	61
1-49%[c]	38	32
≥ 50%[c]	22	29

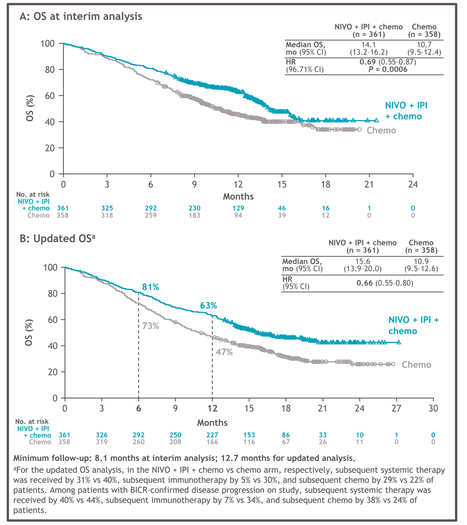
[a]ECOG PS was not reported for 1 patient (0.3%) in each of the NIVO + IPI + chemo and chemo arms; [b]6% and 7% of patients in the NIVO + IPI + chemo and chemo arms, respectively, were unevaluable for PD-L1; [c]Calculated as a percentage of quantifiable patients.

Efficacy

OS

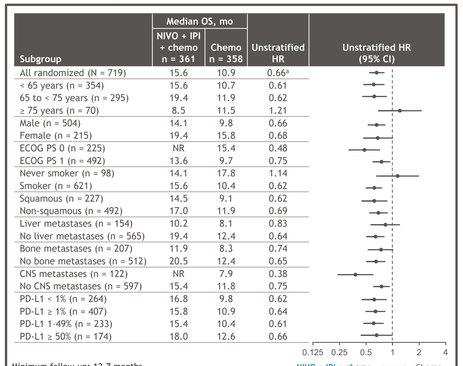
- At the interim analysis (minimum follow-up, 8.1 months), OS was significantly improved for NIVO + IPI + chemo (2 cycles) vs chemo; HR, 0.69 (96.61% CI: 0.55-0.87; *P* = 0.0006) (**Figure 2A**)
- With an additional minimum follow-up of 4.6 months, NIVO + IPI + chemo continued to demonstrate longer OS vs chemo (**Figure 2B**)
- NIVO + IPI + chemo demonstrated OS benefit in the majority of subgroups assessed, including in patients with CNS metastasis, and across histologies (**Figure 3**)
- NIVO + IPI + chemo showed similar magnitude of OS benefit across PD-L1 expression levels (**Figure 4**)

Figure 2. Primary endpoint



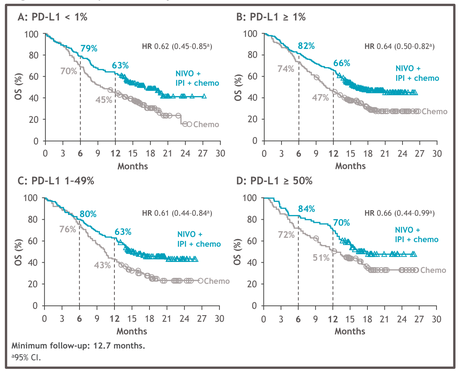
Minimum follow-up: 8.1 months at interim analysis; 12.7 months for updated analysis.
[a]For the updated OS analysis, in the NIVO + IPI + chemo vs chemo arm, respectively, subsequent systemic therapy was received by 31% vs 40%, subsequent immunotherapy by 5% vs 30%, and subsequent chemo by 29% vs 22% of patients. Among patients with BICR-confirmed disease progression on study, subsequent systemic therapy was received by 40% vs 44%, subsequent immunotherapy by 7% vs 34%, and subsequent chemo by 38% vs 24% of patients.

Figure 3. OS subgroup analysis



Minimum follow-up: 12.7 months.
[a]Stratified HR; unstratified HR was 0.67 (95% CI, 0.55-0.81).
NR, not reached.

Figure 4. OS by PD-L1 expression level



Minimum follow-up: 12.7 months.
[a]95% CI.

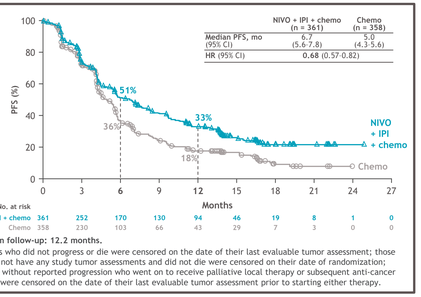
PFS per BICR

- At interim analysis (minimum follow-up, 6.5 months), PFS was significantly improved with NIVO + IPI + chemo vs chemo (**Figure 5**); HR, 0.70 (97.48% CI, 0.57-0.86; *P* = 0.0001)
- NIVO + IPI + chemo continued to demonstrate improved PFS with a longer follow-up (**Figure 5**)

ORR per BICR and duration of response (DOR)

- At interim analysis (minimum follow-up, 6.5 months), ORR was significantly improved with NIVO + IPI + chemo vs chemo, ORR rates were 38% vs 25%, respectively (*P* = 0.0003)
- ORR at the updated analysis was similar to that at interim (**Table 2**)
  - Progressive disease (PD) as best overall response (BOR) was observed in a lower proportion of patients in the NIVO + IPI + chemo arm (9%) vs chemo arm (13%)
- At the updated analysis, median DOR for NIVO + IPI + chemo vs chemo was 11.3 vs 5.6 months, respectively (**Figure 6**)

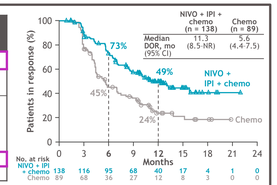
Figure 5. PFS per BICR[a]



Minimum follow-up: 12.2 months.
[a]Patients who did not progress or die were censored on the date of their last evaluable tumor assessment; those who did not have any study tumor assessments and did not die were censored on their date of randomization; patients without reported progression who went on to receive palliative local therapy or subsequent anti-cancer therapy were censored on the date of their last evaluable tumor assessment prior to starting either therapy.

Table 2. ORR per BICR and Figure 6. DOR

	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
ORR, n (%)	138 (38)	89 (25)
Odds ratio (95% CI)	1.9 (1.4-2.6)	
BOR, n (%)		
CR	8 (2)	4 (1)
PR	130 (36)	85 (24)
SD	164 (45)	185 (52)
PD	32 (9)	45 (13)
DCR, n (%)	302 (84)	274 (76)



Minimum follow-up: 12.2 months.
CR, complete response; DCR, disease control rate; PD, progressive disease; PR, partial response; SD, stable disease.

Safety

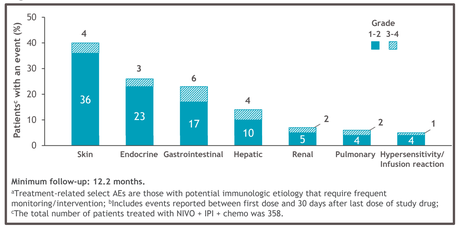
- Median (range) duration of therapy was 6.1 (0-23.5) months and 2.4 (0-24.0) months for NIVO + IPI + chemo (2 cycles) vs chemo, respectively
  - 74 (28%) and 28 (8%) patients were still receiving treatment of NIVO + IPI + chemo and chemo, respectively
  - Most patients (93%) in the experimental arm received 2 cycles of chemo
- Safety summary of NIVO + IPI + chemo and chemo is summarized in **Table 3**
  - Most common any-grade treatment-related adverse events (TRAEs) occurring in at least 15% of patients were nausea, anemia, asthenia, and diarrhea
- TRAEs typically associated with chemo were generally lower with NIVO + IPI + chemo vs chemo, with most common being anemia (23% vs 38%), neutropenia (10% vs 17%), and thrombocytopenia (5% vs 10%)
- Treatment-related select adverse events (AEs, those with immunological etiology) in the NIVO + IPI + chemo arm are shown in **Figure 7**

Table 3. Safety summary of TRAEs

TRAE,[a] %	NIVO + IPI + chemo (n = 358)		Chemo (n = 349)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any TRAE	92	47	88	38
TRAEs leading to discontinuation of any component of the regimen	19	16	7	5
Serious TRAEs	30	25.4	18	15
Treatment-related deaths[b]	2		2	

Minimum follow-up: 12.2 months.
[a]Includes events reported between first dose and 30 days after last dose of study drug.
[b]Treatment-related deaths in the NIVO + IPI + chemo arm (n = 7; 1 for each event) were due to acute renal failure due to chemo, thrombocytopenia, pneumonitis, hepatic toxicity, hepatitis, diarrhea, sepsis, and acute renal insufficiency; treatment-related deaths in the chemo arm (n = 6; 1 for each event) were due to sepsis, anemia, pancytopenia, respiratory failure, pulmonary sepsis, and febrile neutropenia (1 grade 5 AE was reported [sudden death due to fall] as potentially treatment-related but cause of death was recorded as unknown).

Figure 7. Treatment-related select AEs with NIVO + IPI + chemo[a,b]



Minimum follow-up: 12.2 months.
[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 + chemo was 358.

Summary

- CheckMate 9LA met its primary endpoint of OS at the pre-planned interim analysis (HR 0.69, *P* = 0.0006)
- Clinically meaningful improvement of all efficacy endpoints was observed and increased with longer follow-up
  - With a minimum follow-up of 12 months, OS benefit was further improved (HR 0.66)
- Magnitude of benefit with NIVO + IPI + 2 cycles of chemo vs chemo was consistent across histologies and all PD-L1 expression levels, including PD-L1 < 1% and 1-49% populations
- No new safety signals were observed for NIVO + IPI + 2 cycles of chemo
- With early separation of OS curves and lower PD rates as BOR, the hypothesis for CheckMate 9LA study design was validated
- Based on these results, NIVO + IPI + 2 cycles of chemo is indicated in the United States as 1L treatment of adult patients with metastatic or recurrent NSCLC without *EGFR* or *ALK* genomic tumor aberrations

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