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Nivolumab plus ipilimumab vs lenvatinib or sorafenib as first-line treatment in Chinese patients with unresectable/advanced hepatocellular carcinoma: CheckMate 9DW expanded analyses

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Background

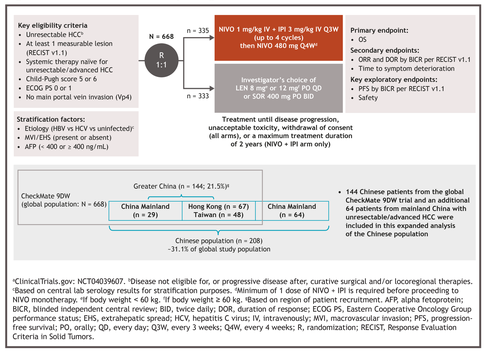
- China has the highest incidence and overall mortality rate from primary liver cancer globally, with chronic hepatitis B virus (HBV) infection as the leading cause of hepatocellular carcinoma (HCC)[1]
- Regimens containing programmed death (PD-1)/programmed death ligand 1 (PD-L1) inhibitors are standard first-line treatments for unresectable/advanced HCC; however, prognosis remains poor and alternative therapies with long-term survival benefits remain an unmet need for these patients[2-6]
- Nivolumab (NIVO) and ipilimumab (IPI) are immune checkpoint inhibitors with distinct but complementary mechanisms of action.[7,8] Combination treatment with NIVO + IPI has shown durable responses and long-term overall survival (OS) benefit in the treatment of several advanced cancers, including HCC[9-12]
- In the global phase 3 CheckMate 9DW study (NCT04039607), NIVO + IPI has shown a statistically significant OS benefit vs lenvatinib or sorafenib (LEN/SOR) (median, 23.7 vs 20.6 months; hazard ratio [HR], 0.79; 95% confidence interval [CI], 0.65-0.96; log-rank $P = 0.018$) as first-line treatment in patients with unresectable HCC. Objective response rate (ORR) was also significantly higher with NIVO + IPI than LEN/SOR (36% vs 13%; $P < 0.0001$)[13]
- Consistent with the findings from the global study, NIVO + IPI also showed clinically meaningful OS benefit vs LEN/SOR in the Chinese population (median, 23.5 vs 20.1 months; HR, 0.82; 95% CI, 0.57-1.18), with higher ORR (37% vs 14%; difference between groups, 23.2%; 95% CI, 11.4-34.3) **(Figure 2)**[14]
- In this expanded analysis, we report ORR by subgroups and additional efficacy and safety analyses in the Chinese population

Methods

Study design

- This is an expanded analysis of the Chinese population from the phase 3, randomized, open-label CheckMate 9DW study. In the study, combination treatment with NIVO + IPI was compared with LEN/SOR as first-line treatment in patients with unresectable HCC (NCT04039607) **(Figure 1)**
- At data cutoff (January 31, 2024), the median (range) follow-up was 31.3 (15.4-46.5) months for the Chinese population

Figure 1. CheckMate 9DW study design[a]



[a]ClinicalTrials.gov: NCT04039607. [b]Disease not eligible for, or progressive disease after, curative surgical and/or locoregional therapies. [c]Based on central lab serology results for stratification purposes. [d]Minimum of 1 dose of NIVO + IPI is required before proceeding to NIVO monotherapy. [e]If body weight < 60 kg. [f]If body weight ≥ 60 kg. [g]Based on region of patient recruitment. AFP, alpha fetoprotein; BICR, blinded independent central review; BID, twice daily; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EHS, extrahepatic spread; HCV, hepatitis C virus; IV, intravenously; MVI, macrovascular invasion; PFS, progression-free survival; PO, orally; QD, every day; Q3W, every 3 weeks; Q4W, every 4 weeks; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors.

Results

Baseline patient characteristics

- A total of 208 Chinese patients (98 randomized to NIVO + IPI and 110 randomized to LEN/SOR) were included in the analysis. Among the 110 patients assigned to the LEN/SOR arm, 102 (93%) received LEN and 6 (5%) received SOR
- Baseline characteristics were generally balanced between the 2 treatment groups **(Table 1)**, except for a greater proportion of patients with an ECOG PS of 1 (35% vs 13%) and a lower proportion of patients with prior locoregional therapy in the NIVO + IPI group vs the LEN/SOR group (43% vs 58%)

Table 1. Baseline characteristics of the Chinese population

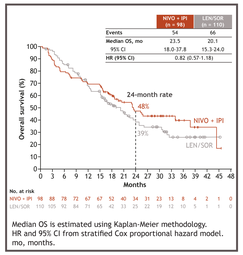
Characteristics	NIVO + IPI (n = 98)	LEN/SOR (n = 110)
Median age (range), years	63.5 (37-84)	62 (26-81)
≥ 65 years, n (%)	41 (42)	46 (42)
Male, n (%)	78 (80)	89 (81)
Etiology, n (%)[a,b]		
HBV	77 (79)	77 (70)
HCV	11 (11)	13 (12)
Uninfected	10 (10)	19 (17)
Child-Pugh score, n (%)[c]		
5	74 (76)	87 (79)
6	22 (22)	22 (20)
ECOG PS 1, n (%)	34 (35)	14 (13)
BCLC stage, n (%)		
≤ B	22 (22)	29 (26)
C	76 (78)	81 (74)
MVI/EHS, n (%)[a]		
MVI	29 (30)	34 (31)
EHS	51 (52)	61 (55)
MVI/EHS	65 (66)	79 (72)
AFP ≥ 400 ng/mL, n (%)	41 (42)	43 (39)
Prior locoregional therapy, n (%)	42 (43)	64 (58)

[a]Per CRF. [b]LEN/SOR, n = 1 HBV/HCV. [c]Child-Pugh score ≥ 7: NIVO + IPI, n = 2; LEN/SOR, n = 1 in the Chinese population. BCLC, Barcelona Clinic Liver Cancer; CRF, case report form.

Tumor response by subgroups

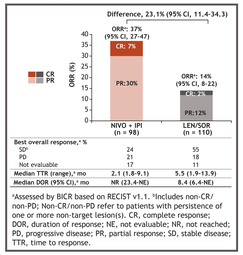
- NIVO + IPI resulted in a greater ORR versus LEN/SOR, with a higher complete response rate (7% vs 2%, respectively) and longer median DOR **(Figure 3)**, as assessed by BICR
- A deeper tumor response was also observed with NIVO + IPI vs LEN/SOR, with a greater median tumor reduction and more patients achieving > 50% and > 75% best reduction from baseline in target lesion diameter **(Figure 4)**
- The favorable ORR with NIVO + IPI vs LEN/SOR was seen across all subgroups, including those by etiology (HBV, 32.5% vs 13.0%; HCV, 63.6% vs 15.4%), BCLC stage (stage ≤ B: 27.3% vs 17.2%; stage C: 39.5% vs 12.3%), and AFP levels (< 400 ng/mL: 38.6% vs 16.4%; ≥ 400 ng/mL: 34.1% vs 9.3%) at baseline **(Figure 5)**

Figure 2. Overall survival in the Chinese population[14]



Median OS is estimated using Kaplan-Meier methodology. HR and 95% CI from stratified Cox proportional hazard model. mo, months.

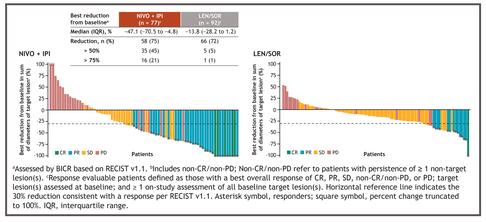
Figure 3. Objective response in the Chinese population



Best overall response,[a] %		
SD[b]	24	55
PD	21	18
Not evaluable	17	11
Median TTR (range),[c] mo	2.1 (1.8-9.1)	5.5 (1.9-13.9)
Median DOR (95% CI),[c] mo	NR (23.4-NE)	8.4 (6.4-NE)

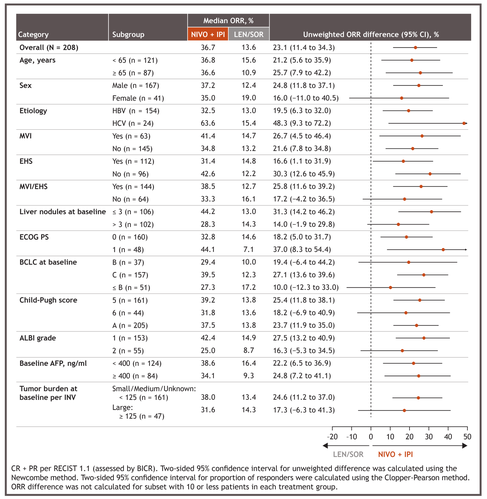
[a]Assessed by BICR based on RECIST v1.1. [b]Includes non-CR/non-PD; Non-CR/non-PD refer to patients with persistence of one or more non-target lesion(s). CR, complete response; DOR, duration of response; NE, not evaluable; NR, not reached; PD, progressive disease; PR, partial response; SD, stable disease; TTR, time to response.

Figure 4. Depth of tumor response in the Chinese population



[a]Assessed by BICR based on RECIST v1.1. [b]Includes non-CR/non-PD; Non-CR/non-PD refer to patients with persistence of ≥ 1 non-target lesion(s). [c]Response evaluable patients defined as those with a best overall response of CR, PR, SD, non-CR/non-PD, or PD; target lesion(s) assessed at baseline; and ≥ 1 on-study assessment of all baseline target lesion(s). Horizontal reference line indicates the 30% reduction consistent with a response per RECIST v1.1. Asterisk symbol, responders; square symbol, percent change truncated to 100%. IQR, interquartile range.

Figure 5. ORR analysis by subgroups in the Chinese population

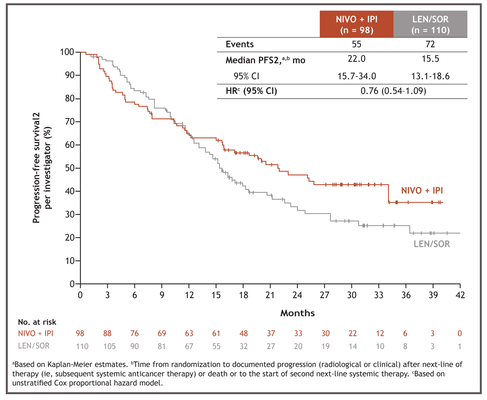


CR + PR per RECIST 1.1 (assessed by BICR). Two-sided 95% confidence interval for unweighted difference was calculated using the Newcombe method. Two-sided 95% confidence interval for proportion of responders were calculated using the Clopper-Pearson method. ORR difference was not calculated for subset with 10 or less patients in each treatment group.

PFS2 and subsequent anticancer therapies

- Median PFS2 (assessed by investigator) was numerically longer with NIVO + IPI vs LEN/SOR, with a 24% reduction in the risk of death or disease progression on subsequent systemic therapy **(Figure 6)**
- Subsequent systemic anticancer therapies were received by 40 (41%) vs 57 (52%) patients in the NIVO + IPI vs LEN/SOR arm, including anti-PD-1/PD-L1 therapies (n = 5 [5%] vs n = 16 [15%]) and anti-VEGF agents (n = 29 [30%] and n = 17 [16%]) **(Table 2)**

Figure 6. Progression-free survival on next-line therapy (PFS2) in the Chinese population



[a]Based on Kaplan-Meier estmates. [b]Time from randomization to documented progression (radiological or clinical) after next-line of therapy (ie, subsequent systemic anticancer therapy) or death or to the start of second next-line systemic therapy. [c]Based on unstratified Cox proportional hazard model.

Table 2. Subsequent anticancer therapies in the Chinese population

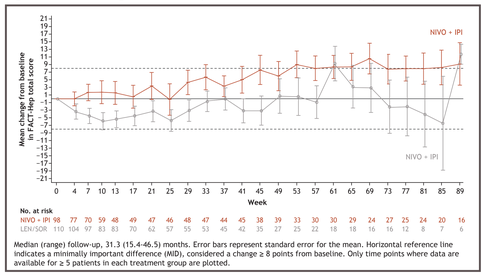
Subsequent therapy,[a] n (%)	Chinese population	
	NIVO + IPI (n = 98)	LEN/SOR (n = 110)
Any subsequent therapy	46 (47)	61 (55)
Subsequent radiotherapy	6 (6)	5 (5)
Subsequent surgery	4 (4)	3 (3)
Subsequent locoregional therapy	14 (14)	13 (12)
Subsequent systemic therapy[b]	40 (41)	57 (52)
Anti-PD-1/PD-L1	5 (5)	16 (15)
Combination regimen of anti-CTLA-4 + anti-PD-1/PD-L1	0	3 (3)
Combination regimen of anti-PD-1/PD-L1 + VEGF	12 (12)	21 (19)
Platinum-based chemotherapy	1 (1)	0
Anti-VEGF agents	29 (30)	17 (15)

Subsequent therapy was defined as therapy started on or after first dosing date (randomization date if patient never treated). [a]Patients may have received more than 1 type of subsequent therapy. [b]Combination regimen of anti-CTLA-4 + anti-PD-1/PD-L1 + VEGF: NIVO + IPI, n = 2; LEN/SOR, n = 4 in the Chinese population. Combination regimen of anti-PD-1/PD-L1 + other systemic anticancer therapy: NIVO + IPI, n = 1; LEN/SOR, n = 0 in the Chinese population. Combination regimen of anti-PD-1/PD-L1 and LAG-3: NIVO + IPI, n = 0; LEN/SOR, n = 7 in the Chinese population. Investigational anti-neoplastic agents: NIVO + IPI, n = 0; LEN/SOR, n = 3 in the Chinese population. Other systemic anticancer therapy: NIVO + IPI, n = 0; LEN/SOR, n = 2 in the Chinese population. CTLA-4, cytotoxic T lymphocyte antigen-4; LAG-3, lymphocyte-activation gene 3; VEGF, vascular endothelial growth factor.

Health-related quality of life (HRQoL)

- Patients in the NIVO + IPI group had numerical improvements in HRQoL throughout the course of treatment (except week 25); in particular, the mean changes from baseline in Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) total score exceeded the minimal important difference (MID) of 8 points from week 53 to 89 **(Figure 7)**
- By contrast, patients in the LEN/SOR group had worsening FACT-Hep total score at several timepoints, with the mean change exceeding MID at week 61

Figure 7. Mean changes in FACT-Hep total score in the Chinese population



Median (range) follow-up, 31.3 (15.4-46.5) months. Error bars represent standard error for the mean. Horizontal reference line indicates a minimally important difference (MID), considered a change ≥ 8 points from baseline. Only time points where data are available for ≥ 5 patients in each treatment group are plotted.

Table 3. Safety summary in the Chinese population

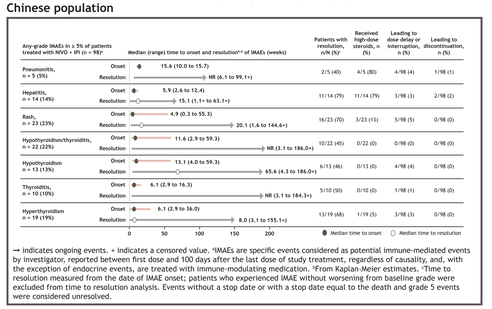
All treated patients, n (%)	NIVO + IPI (n = 98)		LEN/SOR (n = 108)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any TRAEs[a]	88 (90)	42 (43)	103 (95)	41 (38)
Treatment-related hepatic events				
Hepatobiliary disorders	15 (15)	12 (12)	7 (6)	3 (3)
Hepatobiliary investigations				
AST increased	23 (23)	1 (1)	17 (16)	0
ALT increased	18 (18)	3 (3)	11 (10)	1 (< 1)
Bilirubin increased	11 (11)	0	18 (17)	2 (2)
Treatment-related cardiovascular events	6 (6)	0	55 (51)	11 (10)
Treatment-related hemorrhagic events	3 (3)	0	13 (12)	1 (< 1)
Serious TRAEs	30 (31)	26 (27)	18 (17)	16 (15)
TRAEs leading to discontinuation	20 (20)	16 (16)	14 (13)	10 (9)
Treatment-related deaths[b]	3 (3)[c]		1 (< 1)[d]	

[a]Includes events reported between first dose and 30 days after last dose of study therapy. [b]Treatment-related deaths were reported regardless of time frame. [c]Included myocarditis (n = 1), hepatic failure (n = 1), immune myositis and nephritis (n = 1). [d]Included hepatorenal syndrome (n = 1). ALT, alanine aminotransferase; AST, aspartate aminotransferase; TRAE, treatment-related adverse event.

Safety

- In the NIVO + IPI group, 98 patients received treatment, with a median duration of treatment of 6.6 months (IQR, 1.4-15.7), and 59% of the patients received 4 cycles of NIVO + IPI treatment; 90% of patients received > 1 dose of IPI and 72% received 3 or 4 doses of IPI. In the LEN/SOR group, 108 subjects received treatment, with a median duration of treatment of 7.4 months (IQR, 3.5-14.0)
- Most TRAEs were grade 1 or 2 and did not result in treatment discontinuation **(Table 3)**
- The most common any-grade TRAEs under hepatobiliary disorders were immune-mediated hepatitis with NIVO + IPI (4%) and hyperbilirubinemia with LEN/SOR (5%)
- Any-grade immune mediated adverse events (IMAEs) occurred in 61% of patients treated with NIVO + IPI; grade 3/4 IMAEs occurred in 25% of patients, with hepatitis (4%) and rash (3%) being the most commonly reported grade 3/4 IMAEs. Most IMAEs were manageable and did not lead to treatment delay, interruption, or discontinuation **(Figure 8)**

Figure 8. Summary of common IMAEs (≥ 5% patients) of any grade in the Chinese population



→ indicates ongoing events. + indicates a censored value. [a]IMAEs are specific events considered as potential immune-mediated events by investigator, reported between first dose and 100 days after the last dose of study treatment, regardless of causality, and, with the exception of endocrine events, are treated with immune-modulating medication. [b]From Kaplan-Meier estimates. [c]Time to resolution measured from the date of IMAE onset; patients who experienced IMAE without worsening from baseline grade were excluded from time to resolution analysis. Events without a stop date or with a stop date equal to the death and grade 5 events were considered unresolved.

Conclusions

- NIVO + IPI showed clinically meaningful OS and ORR benefit vs LEN/SOR (whereby 93% of patients were on LEN and 5% on SOR) in the Chinese population,[14] with deeper and more durable tumor response in the NIVO + IPI group
- ORR benefit was seen across clinically relevant subgroups by baseline characteristics
- Efficacy of NIVO + IPI was also supported by numerically longer PFS2 vs LEN/SOR; therefore, the PFS benefit was seen during the next line of anticancer therapy, which supports long-term clinical benefit of the combination treatment
- Safety profile of NIVO + IPI in the Chinese population was manageable and consistent with the global results, with no new safety concerns identified
- The majority of IMAEs were manageable without leading to treatment discontinuation
- The results further support NIVO + IPI as a potential new first-line standard-of-care therapy for patients with unresectable HCC in China, a region with the highest HCC incidence and overall mortality rate from HCC globally

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Disclosures

- Shukui Qin has no competing interest to declare.

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