

Nivolumab (NIVO) plus ipilimumab (IPI) vs lenvatinib (LEN) or sorafenib (SOR) as first-line treatment for unresectable hepatocellular carcinoma (uHCC): First results from CheckMate 9DW.

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Background: First-line therapies based on programmed death ligand 1 (PD-L1) inhibitors are standard of care (SOC) in uHCC and demonstrate improved outcomes over SOR; however, prognosis remains poor and there is an unmet need for alternative therapies with long-term benefits. Second-line NIVO + IPI demonstrated clinically meaningful efficacy and manageable safety in SOR-treated patients (pts) with HCC in CheckMate 040, leading to its accelerated approval in the United States. We report first results from the preplanned interim analysis of the phase 3, open-label, randomized CheckMate 9DW trial evaluating the efficacy and safety of NIVO + IPI vs LEN or SOR as first-line therapy for pts with uHCC (NCT04039607). **Methods:** Adult pts with previously untreated HCC not eligible for curative surgical or locoregional therapies, Child-Pugh score 5–6, and ECOG performance status 0–1 were included. Pts were randomly assigned 1:1 to receive NIVO 1 mg/kg + IPI 3 mg/kg Q3W (up to 4 cycles) followed by NIVO 480 mg Q4W or investigator's choice of LEN 8 mg or 12 mg QD or SOR 400 mg BID until disease progression or unacceptable toxicity. NIVO was given for a maximum of 2 years. The primary endpoint was overall survival (OS). Secondary endpoints included objective response rate (ORR) and duration of response (DOR) per blinded independent central review (BICR) using RECIST v1.1. **Results:** In total, 668 pts were randomized to NIVO + IPI (n = 335) or LEN/SOR (n = 333); among 325 pts treated in the LEN/SOR arm, 275 (85%) received LEN. After a median (range) follow-up of 35.2 (26.8–48.9) months (mo), median OS was 23.7 mo with NIVO + IPI vs 20.6 mo with LEN/SOR (HR, 0.79; 95% CI, 0.65–0.96; P = 0.0180) (Table), with respective 24-mo OS rates (95% CI) of 49% (44–55) vs 39% (34–45). ORR was higher with NIVO + IPI (36%) vs LEN/SOR (13%; P < 0.0001); complete response was observed in 7% of pts with NIVO + IPI vs 2% with LEN/SOR. Median DOR was 30.4 mo with NIVO + IPI vs 12.9 mo with LEN/SOR (Table). A summary of treatment-related adverse events (TRAEs) is shown in the Table. **Conclusions:** NIVO + IPI demonstrated statistically significant OS benefit vs LEN/SOR in pts with previously untreated uHCC, as well as higher ORR and durable responses with a manageable safety profile. These results support this combination as a potential new first-line SOC for uHCC. Clinical trial information: NCT04039607. Research Sponsor: Bristol Myers Squibb.

Efficacy	NIVO + IPI (n = 335)	LEN/SOR (n = 333)
Median OS (95% CI), mo	23.7 (18.8–29.4)	20.6 (17.5–22.5)
HR (95% CI); P value ^a	0.79 (0.65–0.96); 0.0180	
ORR, ^b n (%) ; 95% CI	121 (36); 31–42	44 (13); 10–17
P value ^a	< 0.0001	
Median DOR ^b (95% CI), mo	30.4 (21.2–NE) (n = 332)	12.9 (10.2–31.2) (n = 325)
Safety, n (%)		
Any-grade/grade 3–4 TRAEs	278 (84)/137 (41)	297 (91)/138 (42)
Any-grade/grade 3–4 TRAEs leading to discontinuation	59 (18)/44 (13)	34 (10)/21 (6)

^aTwo-sided P value. ^bPer BICR using RECIST v1.1.