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Nofazinlimab combined with lenvatinib versus placebo plus lenvatinib as first-line therapy for unresectable or metastatic hepatocellular carcinoma: A phase III, randomized, double-blind, multiregional study (CS1003-305)

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Background

Nofazinlimab (NOFA) is a novel humanized, recombinant IgG4 anti-PD-1 monoclonal antibody. Here we report the final results of a randomized, double-blind, global phase 3 trial assessing NOFA + lenvatinib (LEN) vs. placebo (PBO) + LEN as first-line therapy for unresectable or metastatic hepatocellular carcinoma (HCC).

Methods

Eligible systemic therapy–naïve patients (≥ 18 years) with unresectable or metastatic HCC (BCLC stage B/C, Child-Pugh class A, and ECOG performance status ≤ 1) were randomized 2:1 to receive NOFA (200 mg IV Q3W) + LEN (12 mg [body weight ≥ 60 kg] or 8 mg [< 60 kg], PO QD) or PBO + LEN. The primary endpoint is overall survival (OS). Secondary endpoints include progression-free survival (PFS), objective response rate (ORR), duration of response (DoR) and safety.

Results

At this preplanned final analysis (data cutoff: 6 March 2025), a total of 534 patients were randomized to NOFA + LEN (N=353) or PBO + LEN (N=181) group, and median follow-up was 42.5 months. Median OS for NOFA + LEN was 21.6 months vs. 18.5 months for PBO + LEN (HR 0.86, 95% CI 0.69-1.06; two-sided *P*=0.1456). NOFA + LEN also demonstrated superior PFS (median 9.2 months vs 6.9 months; HR 0.72, 95% CI 0.58-0.88; two-sided nominal *P*=0.0017) and higher ORR (33.1% vs 18.8%; two-sided nominal *P*=0.0006), with more durable response (median DoR: 12.4 months vs 11.1 months) per RECIST v1.1 assessed by Blinded Independent Central Review. Grade 3-5 treatment-related adverse events (TRAEs) occurred in 56.5% (NOFA + LEN) vs. 49.2% (PBO + LEN) of patients, any-grade treatment-related SAEs in 23.0% vs. 17.7%, and fatal TRAEs in 1.7% vs. 2.2%. Subsequent systemic anti-cancer therapy was administered in 52.4% vs. 57.5% of patients, respectively.

Conclusions

The final analysis demonstrated a clinically compelling OS trend favoring NOFA + LEN despite not achieving statistical significance. Clinical meaningful improvements in PFS and ORR, alongside numerically competitive outcomes relative to current therapies, highlight the regimen's therapeutic value. Safety was manageable, with no new safety signals observed.

Clinical trial identification

NCT04194775.

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Legal entity responsible for the study

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Disclosure

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