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Primary analysis of HBI-8000-303: A randomized phase 3 trial of nivolumab plus HBI-8000 or placebo in advanced melanoma

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Background

Outcome for patients with advanced melanoma has improved significantly with immunotherapy and targeted therapy. In a phase 1b/2 study in anti-PD(L)-1 naïve advanced melanoma, HBI-8000, an oral selective histone deacetylase (HDAC) inhibitor combined with nivolumab (NIVO) achieved an objective response rate (ORR) of 66%. HBI-8000-303 is a global, randomized, double-blind, placebo-controlled phase 3 study of NIVO with HBI-8000/placebo in unresectable or metastatic melanoma not previously treated with PD(L)-1 inhibitors.

Methods

Patients with advanced, non-uvéal melanoma with measurable disease, ECOG 0-1, and adequate organ function were randomized to receive oral HBI-8000 30 mg or placebo twice weekly in combination with NIVO 480 mg intravenously every 4 weeks, stratified by tumor PD-L1 expression and serum LDH. The primary endpoint was progression-free survival (PFS) assessed by a Blinded Independent Review Committee. Secondary endpoints were ORR, overall survival, and safety.

Results

Between July 2021 and April 2024, 404 patients were randomized to HBI-8000 + NIVO (n=203) or placebo + NIVO (n=201). Patient characteristics were well balanced; 33.7% (136/404) with ↑ LDH. Median follow up was 37 months. The median PFS in the HBI-8000 + NIVO arm was 11.7 months (95% CI, 7.3, 21.1), significantly higher than 7.4 months (95% CI, 4.5, 10.1) in the placebo + NIVO arm; hazard ratio 0.73 (96% CI, 0.56 – 0.95, P=0.0141). Confirmed ORR was 41.4% (95% CI, 34.5, 48.5) for HBI-8000 + NIVO, and 32.3% (95% CI, 25.9, 39.3) for placebo + NIVO. The incidence of > G3 treatment related adverse events (TRAEs) was 55% and 18% in the HBI-8000 and placebo arms respectively; 14% and 5% respectively discontinued therapy for any grade TRAEs. Diarrhea, nausea, fatigue, thrombocytopenia, asthenia, and neutropenia were the most common (> 20%) TRAEs for HBI-8000 + NIVO.

Conclusions

HBI-8000 in combination with NIVO results in a significant improvement in PFS compared with NIVO alone in anti-PD(L)-1 naïve advanced melanoma. The toxicity profile is consistent with class effect of HDAC inhibitors and typically reversible. This combination offers a new standard of care for this patient population.

Clinical trial identification

NCT04674683.

Legal entity responsible for the study

HUYABIO International.

Funding

HUYABIO International.

Disclosure

N.I. 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