Efficacy and safety of HBM4003 combined with toripalimab in refractory neuroendocrine neoplasms: a multicenter, phase II study

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Summary

Background High-grade neuroendocrine neoplasms (NENs) have limited treatment options following first-line platinum-based chemotherapy, often resulting in poor clinical outcomes. Dual immune checkpoint blockade targeting CTLA-4 and PD-1 offers a synergistic approach by enhancing T-cell activation and amplifying anti-tumor immune responses. This study evaluates the efficacy and safety of HBM4003, a novel fully human anti-CTLA-4 monoclonal antibody, in combination with toripalimab, a PD-1 inhibitor, in patients with high-grade, refractory NENs.

Methods This multicenter, open-label, phase II study enrolled patients with neuroendocrine carcinomas (NECs), grade 3 NETs (NETs G3), and mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs) who had progressed on first-line therapy. Patients received HBM4003 at either 0.3 mg/kg or 0.45 mg/kg in combination with toripalimab (240 mg) every three weeks. The primary endpoint was the objective response rate (ORR). The study was registered on ClinicalTrials.gov (NCT05167071).

Findings Between December 2021 and May 2024, a total of 29 patients were enrolled (NECs, n = 22; NETs G3, n = 3; MiNENs, n = 4). All patients had previously undergone chemotherapy, with 11 receiving ≥2 lines of therapy. Thirteen (13) patients had lung metastasis and 18 had liver metastasis. Patients were assigned to the HBM4003 0.3 mg/kg cohort (n = 13) or the 0.45 mg/kg cohort (n = 16), with 26 patients forming the efficacy analysis set. The overall ORR was 34.6% (95% confidence intervals [CI], 17.2–55.7), and the disease control rate (DCR) was 65.4% (95% CI, 44.3–82.8). Median progression-free survival (PFS) and overall survival (OS) were 4.0 months (95% CI, 1.6–5.1) and 21.8 months (95% CI, 16.7-not estimated [NE]), respectively. For 19 NEC patients in the efficacy analysis set, the ORR and DCR were 36.8% (95% CI, 16.3–61.6) and 68.4% (95% CI, 43.4–87.4), respectively. The median PFS was 4.0 months (95% CI, 1.6–5.4), while the median OS was not reached (95% CI, 13.5-NE). Of the 29 NEN patients receiving at least one dose of study treatment, all patients experienced at least one treatment-related adverse event (TRAE), with 10 (34.5%) experiencing grade ≥3 TRAE and eight (27.6%) experiencing grade ≥3 immune-related adverse events.

Interpretation HBM4003 combined with toripalimab demonstrated promising anti-tumor activity and manageable safety in patients with refractory NENs, supporting further investigation of this combination therapy.

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Research in context

Evidence before this study

To evaluate the efficacy and safety of HBM4003 combined with toripalimab for refractory neuroendocrine neoplasms (NENs), we conducted a comprehensive search of the literature on PubMed. Studies were included if they examined dual immune checkpoint inhibitors targeting CTLA-4 and PD-1/PD-L1 pathways in high-grade NENs, particularly after first-line therapy. The search period covered publications from December 2014 to December 2024, without language restrictions. Key search terms included "neuroendocrine neoplasms," "neuroendocrine tumors," "CTLA-4," "PD-1," "PD-L1," and "dual immunotherapy." Evidence from prior clinical trials indicated that combinations including ipilimumab plus nivolumab and durvalumab plus tremelimumab yielded objective response rates (ORRs) of 9.1–31% in high-grade NENs, while safety remains a critical consideration. Therefore, it is imperative to evaluate the efficacy and safety of novel CTLA-4 inhibitors such as HBM4003 as potential treatment options for these patients.

Added value of this study

This multicenter, open-label, phase II study represents the first clinical trial of dual immunotherapy in Chinese patients with NENs. The results revealed a promising ORR of 34.6% and a median overall survival of 21.8 months. Additionally, this study is among the first to provide subgroup analyses within a regimen combining a CTLA-4 inhibitor with a PD-1/PD-L1 inhibitor, offering preliminary insights into the efficacy in different patient populations. The safety profile of HBM4003 combined with toripalimab was generally consistent with the known adverse events (AEs) associated with immune checkpoint inhibitors, and most of the immune-related adverse events (irAEs) were manageable and recoverable during the study period.

Implications of all the available evidence

This study supported the hypothesis that HBM4003 plus toripalimab may be effective and safe in patients with refractory NENs, a population with historically poor outcomes. Future research should focus on larger-scale randomized controlled trials to validate these results and identify specific subpopulations that may benefit from this treatment.

Introduction

Neuroendocrine neoplasms (NENs) represent a heterogeneous group of tumors that primarily arise in the gastrointestinal tract, including the stomach, intestines, and pancreas.[1] Although NENs have a relatively low age-standardized incidence rate of 1.14 cases per 100,000 individuals in China, there has been a steady annual increase in incidence in recent years.[2] NENs are broadly classified based on histopathological differentiation and proliferation rate, with most falling under well-differentiated neuroendocrine tumors (NETs). However, approximately 10–20% of cases comprise poorly differentiated, highly proliferative neuroendocrine carcinomas (NECs), along with rare occurrences of mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs).[3–5] While many NENs exhibit indolent behavior, a substantial subset demonstrates aggressive, invasive, or metastatic tendencies.[6] This is particularly concerning in grade 3 NETs (NETs G3) and NECs, where treatment options remain limited.[7–9] Despite first-line treatment with platinum-based chemotherapy, these patients continue to face a poor prognosis,[10] underscoring an urgent need for novel and effective therapeutic approaches.

Recent advancements in dual immune checkpoint blockade have focused on combining CTLA-4 and PD-1/PD-L1 monoclonal antibodies across various tumor types.[11] CTLA-4 inhibits early T-cell activation, predominantly in lymph nodes, whereas PD-1 primarily regulates T-cell cytotoxic activity within tumors. Targeting both CTLA-4 and PD-1/PD-L1 in combination therapy offers a synergistic effect, enhancing anti-tumor immune responses.[12] Studies investigating CTLA-4 inhibitors (e.g., ipilimumab) in combination with PD-1 inhibitors have shown promising efficacy in high-grade NENs, achieving objective response rates (ORRs) of approximately 26–31%.[13,14] Despite growing interest in dual immune checkpoint blockade, current research has not sufficiently examined how clinical factors such as metastatic sites and the number of prior treatment lines influence treatment outcomes. This gap holds substantial clinical implications in NENs, particularly in NECs, where over 80% of patients present with metastatic disease at diagnosis.[15]

HBM4003 is a fully human, recombinant, monoclonal heavy-chain-only antibody that differs structurally from conventional CTLA-4 inhibitors such as ipilimumab. Specifically, HBM4003 consists of a single heavy-chain variable region and two constant domains (CH2 and CH3), but lacks the CH1 domain. This structural design confers high affinity binding to CTLA-4 and significantly enhances regulatory T-cell (Treg) depletion via antibody-dependent cell-mediated cytotoxicity (ADCC). Depletion of intratumoral Tregs is believed to

play a critical role in restoring anti-tumor immune surveillance.[16] Unlike ipilimumab, which primarily increases CD4+ and CD8+ T-cell infiltration but does not significantly reduce FOXP3+ Tregs,[17] HBM4003 has demonstrated superior Treg clearance, which may translate into more potent anti-tumor activity. Toripalimab, an anti-PD-1 monoclonal antibody, complements HBM4003 by further promoting T-cell activation and contributing to Treg modulation, thereby enhancing overall immune-mediated tumor control.[18] A recent phase I study (n = 40) demonstrated that the combination of HBM4003 (0.3 mg/kg) and toripalimab (240 mg), administered every three weeks, has a manageable safety profile in patients with advanced melanoma and other solid tumors.[19] Building on this rationale, the present study aims to evaluate the efficacy and safety of HBM4003 in combination with toripalimab in patients with refractory high-grade NENs.

Methods

Study design and population

This multicenter, open-label, phase II study was conducted across four centers in China from December 2021 to May 2024 to evaluate the efficacy and safety of HBM4003 plus toripalimab in patients with refractory NENs. The study adhered to Good Clinical Practice (GCP) guidelines, relevant regulatory requirements, and the principles of the Declaration of Helsinki, with approval from the Ethics Committee of Peking University Cancer Hospital & Institute (approval number: 2021YW203). Written informed consent was obtained from all patients prior to enrollment. The study was registered on ClinicalTrials.gov (NCT05167071).

Eligible patients included adults aged 18 years or older with unresectable, histopathologically confirmed, locally advanced, or metastatic NENs (Ki-67 index >20%), including NETs G3, NECs, and MiNENs. Classification criteria follow *the 2019 WHO classification of tumours of the digestive system*.[20] Patients had either progressed following first-line systemic therapy or were unable to tolerate it. Specific treatment requirements included at least one prior systemic therapy for NETs G3 patients, which could involve somatostatin analogs, mTOR inhibitors, anti-angiogenesis agents, or chemotherapy, with documented disease progression during treatment or within six months post-treatment. For NEC patients, progression must have occurred during or within six months after at least one line of systemic treatment, and prior treatment must include platinum-based chemotherapy. Similarly, MiNEN patients were required to show progression during or within six months following first-line systemic treatment. Disease recurrence during adjuvant therapy or within six months following the last dose of adjuvant therapy was also considered treatment failure. For patients unable to tolerate first-line therapy, documentation of adverse events (AEs) was required. Additional inclusion criteria included an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of ≤1, sufficient bone marrow function, no coagulopathy, an expected survival of at least three months, and at least one measurable lesion at baseline as per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1). Patients with NECs originating from the lung or prostate, prior exposure to immune checkpoint inhibitors (anti-CTLA-4, anti-PD-1, anti-PD-L1, or anti-PD-L2), or active systemic autoimmune disease were excluded. Those with symptomatic or active central nervous system metastases, or those requiring urgent treatment were also ineligible. Further details regarding eligibility are provided in the Supplementary materials.

Procedures

This study initially included a dose-escalation phase (part 1). However, following the Safety Review Committee (SRC) evaluation of results from the parallel study (Study 4003.1, NCT04135261)[21] on December 07, 2021, HBM4003 0.3 mg/kg plus toripalimab 240 mg every three weeks (Q3W) was determined to be the expansion dose. On April 22, 2022, after reviewing data from another Phase I study (Study 4003.3, NCT04866485), which investigated safety of HBM4003 0.45 mg/kg plus pembrolizumab 200 mg in patients with non-small cell lung cancer and other solid tumors,[22] as well as available safety data of the six NEN patients enrolled in this study, the SRC recommended HBM4003 0.45 mg/kg plus toripalimab 240 mg Q3W as the recommended phase II dose (RP2D). Consequently, this study adopted two dose levels for HBM4003: 0.3 mg/kg and 0.45 mg/kg.

On the first day of each 21-day cycle, toripalimab was administered initially, followed by HBM4003 infusion if no clinically significant infusion-related reactions (IRRs) occurred; should any grade ≤2 IRR emergent and resolved within 3 h after toripalimab administration, HBM4003 can be given or otherwise study treatment will be discontinued. Study treatment could be suspended in case of immune-related AEs (irAEs) or discontinued if deemed necessary by the investigator (see Supplementary materials for details). Dose reduction was not permitted for a single administration. Patients would be continued with study treatment for a maximum of two years, or until disease progression, no longer benefit from study treatment, intolerance to toxicity, or voluntarily withdrawal, whichever occurs first.

Tumor responses were assessed by the investigators via computed tomography (CT) or magnetic resonance imaging (MRI) every six weeks for the first 12 months and subsequently every 12 weeks, following RECIST v1.1 criteria. Patients would be followed up for safety from signing the informed consent form until 84 days after the last administration. Survival follow-up

commenced 84 days post-treatment, continuing until study withdrawal, loss to follow-up, death, or study completion, with assessments every 12 weeks.

Biomarkers analysis of blood and tumor tissue samples

In order to better elucidate the mechanism of tumor immunotherapy for NENs, exploratory research was performed by profiling tumor biopsies and analyzing pharmacodynamic effects from serial patient blood samples. Formalin-fixed paraffin-embedded (FFPE) tumor tissue samples underwent multiplex immunofluorescence (mIF) profiling (Leica Bond RX). Stained slides were digitally scanned by Aperio Versa 8 scanner (Leica). Image analysis was conducted using HALO software, version 3.1.1 (Indica Labs, Corrales, NM, USA). Blood samples were analyzed using flow cytometry (BD FACS Canto TM II) and serum cytokine quantification (MSD V-PLEX proinflammatory panel 1 [human] kit).

Endpoints

The primary endpoint of this study was the ORR, defined as the proportion of patients achieving either a complete response (CR) or partial response (PR) according to RECIST 1.1. Secondary endpoints included disease control rate (DCR), the duration of objective response (DOR), overall survival (OS), progression-free survival (PFS), and time to objective response (TTR). The severity of AEs was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and the relationship of AEs to study treatment was assessed as either related or not related. Definitions of endpoints were detailed in the Supplementary materials.

As for the exploratory analysis, blood samples were collected from eligible patients and sent to a central laboratory for biomarker analysis. Evaluated biomarkers included cytokines, as well as biomarkers of peripheral immune cells such as CD4+ Ki-67+ T cells, CD8+ Ki-67+ T cells, Ki-67+ CD8+ T cells and Treg.

Statistical analysis

This was an exploratory trial. No formal statistical hypotheses were pre-specified. The sample size in each dose cohort was calculated based on an assumed true ORR of 35%, yielding a 75.5% probability of observing at least six objective responses (CR or PR) in a cohort of 20 patients. If the true ORR were 40%, the probability of observing six or more objective responses would increase to 87.4%; conversely, with a true ORR of 20%, the probability would drop to below 20%.

Time-to-event data were analyzed and presented using Kaplan–Meier curves. Efficacy data derived from imaging results, including best-overall-all (BOR) response, DOR, and maximum tumor shrinkage, were summarized descriptively for patients with both baseline and post-baseline imaging data (referred to as evaluable efficacy set). The 95% confidence intervals (CIs) for binary efficacy endpoints were calculated using the Clopper-Pearson exact method.

Subgroup efficacy analyses were performed for the NEC subgroup. Due to the small sample sizes of patients with NETs G3 and MiNENs, only ORR was reported for these subgroups. Safety analysis was conducted for all patients who received at least one dose of the study treatment. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Role of the funding source

The funder was partially involved in trial design; data collection, analysis, and interpretation; and paper writing and submission.

Results

Patient disposition and baseline characteristics

Between December 2021 and May 2024, a total of 34 patients with refractory NEN were screened and 29 met eligibility criteria and were enrolled. Thirteen patients were assigned to the HBM4003 0.3 mg/kg combined with toripalimab 240 mg cohort (referred to as '0.3 mg/kg cohort' thereafter) and 16 to the HBM4003 0.45 mg/kg combined with toripalimab 240 mg cohort (referred to as '0.45 mg/kg cohort' thereafter). As of the data cut-off date (December 06, 2024), 25 patients (11 in the 0.3 mg/kg cohort and 14 in the 0.45 mg/kg cohort) had discontinued treatment; the most common reasons for HBM4003 discontinuation were disease progression (14 patients), adverse events (five patients) and loss of clinical benefit (three patients). A total of four patients (two in each cohort) were still receiving both HBM4003 and toripalimab by the cut-off date (Fig. 1).

The median age of enrolled patients was 54.0 years old, and 65.5% were male. Most (69.0%) patients had an ECOG PS score of one at baseline. Histopathological evaluation indicated that the majority of patients (75.9%) had NECs, with similar distributions between the 0.3 mg/kg and 0.45 mg/kg cohorts (76.9% vs. 75.0%, respectively). The median time since the initial diagnosis was 8.54 months. All patients had previously undergone chemotherapy, including 11 (37.9%) patients who had received ≥2 prior lines of therapy. Primary tumor locations were predominantly gastrointestinal (24.1%) and other locations (65.5%). At the time of screening, 13 (44.8%) patients had lung metastasis, and 18 (62.1%) patients had liver metastasis (Table 1).

Efficacy

A total of 26 patients were included in the efficacy analysis set, as three (all in 0.45 mg/kg cohort) of the 29 patients were excluded because of no baseline tumor assessment result. The median follow-up time was 17.5

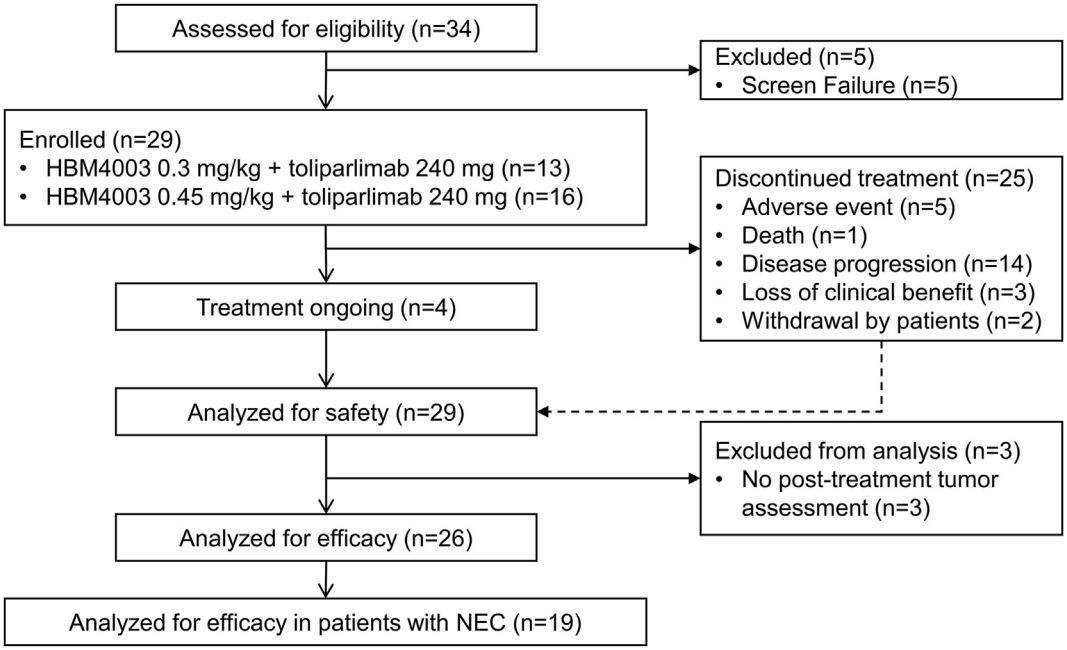

Fig. 1: Flowchart of patient enrollment and analysis.

months (range, 3.0–25.7). PR was observed in nine patients (34.6%), while stable disease (SD) was achieved in eight patients (30.8%) (Table 2). The ORR was 34.6% (95% CI, 17.2–55.7), with the ORR in the HBM4003 0.3 mg/kg cohort at 38.5% (95% CI, 13.9–68.4), and 0.45 mg/kg cohort at 30.8% (95% CI, 9.1–61.4). The DCR was 65.4% (95% CI, 44.3–82.8). The median DOR was 12.2 months (95% CI, 2.8-not estimated [NE]), with three patients achieving PR for > one year (Fig. 2). The median PFS of all patients was 4.0 months (95% CI, 1.6–5.1) and the median OS was 21.8 months (95% CI, 16.7, NE). The OS rates at 6 months, 12 months, and 18 months were 88%, 79%, and 69%, respectively (Fig. 3).

Nineteen NEC patients were included in the NEC efficacy analysis set, the ORR and DCR were 36.8% (95% CI, 16.3–61.6) and 68.4% (95% CI, 43.4–87.4), respectively. The median PFS was 4.0 months (95% CI, 1.6–5.4), while the median OS was not reached (95% CI, 13.5-NE) (Table 2, Supplementary Figs. S1 and S2). In subgroups with characteristics such as age over 65 years, received one-line prior therapy, absence of liver metastasis, and PD-L1-positive status, the ORR appeared higher compared to their complements (Fig. 4). Similarly, in the NEC subgroup, patients who received only one-line prior therapy had an ORR of 46.2%, which appeared numerically higher than those with two or more prior therapies (16.7%). PD-L1-positive patients achieved an ORR of 57.1%, compared to 25.0% in PD-L1-negative patients. Absence of liver metastasis was associated with an ORR of 62.5%, numerically greater than the ORR of 18.2% observed in those with liver metastasis. Interestingly, patients with lung metastasis had an ORR of 50.0%, compared to 27.3% in those without lung metastasis. Of note, the differences observed between subgroups were based on small sample sizes.

After progression, a total of 16 patients (55.2%) received subsequent treatments. The details of subsequent therapies are listed in Table 3.

Safety

For 29 patients who received at least one dose of study treatment, the median duration of treatment exposure for all patients was 88.0 days, with a median of 109.0 days for the 0.3 mg/kg cohort and 53.5 days for the 0.45 mg/kg cohort. The median number of infusions was six in the 0.3 mg/kg cohort (range, 1–33) and three in the 0.45 mg/kg cohort (range, 1–32). Nine patients in the 0.3 mg/kg cohort had received ≥5 infusions and five patients in the 0.45 mg/kg cohort. All 29 patients experienced at least one treatment-emergent AE (TEAE) and treatment-related AE (TRAE) of any grade (Note: if not elsewhere specified, TRAE refers to AE that is considered as related to either HBM4003 or toripalimab by the investigator). Five (38.5%) patients in the 0.3 mg/kg cohort and eight (50.0%) in the 0.45 mg/kg cohort experienced serious AEs (SAEs), and by Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT), the SAEs reported by more than two patients were hyperglycaemia and pyrexia. The majority of patients (92.3% in 0.3 mg/kg and 87.5% in 0.45 mg/kg) experienced irAEs, including 27.6% (38.5% in 0.3 mg/kg and 18.8% in 0.45 mg/kg) irAEs were of grade ≥3

Characteristics	All			NEC		
	HBM4003 0.3 mg/kg + Toripalimab 240 mg (N = 13)	HBM4003 0.45 mg/kg + Toripalimab 240 mg (N = 16)	Total (N = 29)	HBM4003 0.3 mg/kg + Toripalimab (N = 10)	HBM4003 0.45 mg/kg + Toripalimab (N = 12)	Total (N = 22)
Sex, n (%)						
Male	8 (61.5)	11 (68.8)	19 (65.5)	8 (80.0)	8 (66.7)	16 (72.7)
Female	5 (38.5)	5 (31.3)	10 (34.5)	2 (20.0)	4 (33.3)	6 (27.3)
Age, years, median (range)	55.0 (41.0–68.0)	52.0 (30.0–72.0)	54.0 (30.0–72.0)	59.5 (41.0–68.0)	49.0 (30.0–72.0)	56.5 (30.0–72.0)
ECOG performance score at baseline, n (%)						
0	4 (30.8)	5 (31.3)	9 (31.0)	3 (30.0)	5 (41.7)	8 (36.4)
1	9 (69.2)	11 (68.8)	20 (69.0)	7 (70.0)	7 (58.3)	14 (63.6)
Tumor classification, n (%)						
NET G3	1 (7.7)	2 (12.5)	3 (10.3)	–	–	–
NEC	10 (76.9)	12 (75.0)	22 (75.9)	10 (100.0)	12 (100.0)	22 (100.0)
MiNEN	2 (15.4)	2 (12.5)	4 (13.8)	–	–	–
Time since first diagnosis, months, median (range)	12.62 (6.2–110.8)	7.39 (3.2–30.6)	8.54 (3.2–110.8)	10.45 (6.2–110.8)	6.49 (3.2–30.6)	7.87 (3.2–110.8)
Differentiation, n (%)						
Well differentiated	1 (7.7)	2 (12.5)	3 (10.3)	0 (0.0)	0 (0.0)	0 (0.0)
Poorly differentiated	12 (92.3)	13 (81.3)	25 (86.2)	10 (100.0)	11 (91.7)	21 (95.5)
Unknown	0 (0.0)	1 (6.3)	1 (3.4)	0 (0.0)	1 (8.3)	1 (4.5)
Ki-67 labelling index, %, median (range)	70.0 (25.0–90.0)	80.0 (35.0–90.0)	80.0 (25.0–90.0)	70.0 (30.0–90.0)	80.0 (50.0–90.0)	80.0 (30.0–90.0)
Location of primary site, n (%)						
Gastrointestinal	5 (38.5)	6 (37.5)	11 (37.9)	5 (50.0)	6 (50.0)	11 (50.0)
Uterus	3 (23.1)	4 (25.0)	7 (24.1)	1 (10.0)	4 (33.3)	5 (22.7)
Hepatobiliary	1 (7.7)	4 (25.0)	5 (17.2)	1 (10.0)	1 (8.3)	2 (9.1)
Pancreas	1 (7.7)	1 (6.3)	2 (6.9)	1 (10.0)	0 (0.0)	1 (4.6)
Others[a]	3 (23.1)	1 (6.3)	4 (13.8)	2 (20.0)	1 (8.3)	3 (13.6)
Location of metastasis at the time of screening, n (%)						
Brain	1 (7.7)	1 (6.3)	2 (6.9)	0 (0.0)	1 (8.3)	1 (4.5)
Lung	5 (38.5)	8 (50.0)	13 (44.8)	4 (40.0)	6 (50.0)	10 (45.5)
Liver	9 (69.2)	9 (56.3)	18 (62.1)	7 (70.0)	6 (50.0)	13 (59.1)
Bone	1 (7.7)	1 (6.3)	2 (6.9)	1 (10.0)	0 (0.0)	1 (4.5)
Other	12 (92.3)	11 (68.8)	23 (79.3)	9 (90.0)	7 (58.3)	16 (72.7)
Previous therapies, n (%)						
Chemotherapies	13 (100.0)	16 (100.0)	29 (100.0)	10 (100.0)	12 (100.0)	22 (100.0)
Targeted therapies	5 (38.5)	9 (56.3)	14 (48.3)	3 (30.0)	5 (41.7)	8 (36.4)
Hormone	1 (7.7)	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)
Number of lines of previous therapies, n (%)						
<2	7 (53.8)	11 (68.8)	18 (62.1)	6 (60.0)	10 (83.3)	16 (72.7)
≥2	6 (46.2)	5 (31.3)	11 (37.9)	4 (40.0)	2 (16.7)	6 (27.3)
PD-L1 expression CPS at screening, n (%)						
Positive	4 (30.8)	6 (37.5)	10 (34.5)	4 (40.0)	4 (33.3)	8 (36.4)
Negative	6 (46.2)	6 (37.5)	12 (41.4)	4 (40.0)	4 (33.3)	8 (36.4)
Missing	3 (23.1)	4 (25.0)	7 (24.1)	2 (20.0)	4 (33.3)	6 (27.3)

ECOG: Eastern Cooperative Oncology Group; NET G3: grade 3 neuroendocrine tumor; NEC: neuroendocrine carcinoma; MiNEN: mixed neuroendocrine-non-neuroendocrine neoplasm; CPS: combined positive score. [a]Others: Other primary sites included urinary bladder (n = 1), lung (n = 1) and unknown site (n = 2) in all patients.

Table 1: **Baseline characteristics of patients in the safety set.**

severity. Six and seven patients from the 0.3 mg/kg and 0.45 mg/kg cohort experienced TEAEs leading to temporary interruption of study treatment; two and four patients from the 0.3 mg/kg and 0.45 mg/kg cohort experienced TEAEs leading to permanent discontinuation of study treatment, which were grade 3 immune-mediated lung disease and grade 1 blood glucose increased (patients in 0.3 mg/kg cohort), grade 3 immune-mediated myocarditis, grade 2 immune-mediated enterocolitis, grade 3 biliary tract infection, grade 1 pneumonia, and grade 4 infection and renal failure (patients in 0.45 mg/kg cohort). One patient from 0.3 mg/kg cohort had a fatal TEAE of sudden cardiac death, which was assessed as treatment-related because the investigator could not completely rule out the possibility of casual relationship between study treatment and the event given that the event occurred after receipt of study treatment.

Endpoints	All			NEC		
	HBM4003 0.3 mg/kg + Toripalimab 240 mg (N = 13)	HBM4003 0.45 mg/kg + Toripalimab 240 mg (N = 13)	Total (N = 26)	HBM4003 0.3 mg/kg + Toripalimab (N = 10)	HBM4003 0.45 mg/kg + Toripalimab (N = 9)	Total (N = 19)
Best overall response, n (%)						
CR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PR	5 (38.5)	4 (30.8)	9 (34.6)	3 (30.0)	4 (44.4)	7 (36.8)
SD	4 (30.8)	4 (30.8)	8 (30.8)	3 (30.0)	3 (33.3)	6 (31.6)
PD	4 (30.8)	5 (38.5)	9 (34.6)	4 (40.0)	2 (22.2)	6 (31.6)
ORR, n (%) [95% CI]	5 (38.5) [13.9, 68.4]	4 (30.8) [9.1, 61.4]	9 (34.6) [17.2, 55.7]	3 (30.0) [6.7, 65.2]	4 (44.4) [13.7, 78.8]	7 (36.8) [16.3, 61.6]
DCR, n (%) [95% CI]	9 (69.2) [38.6, 90.9]	8 (61.5) [31.6, 86.1]	17 (65.4) [44.3, 82.8]	6 (60.0) [26.2, 87.8]	7 (77.8) [40.0, 97.2]	13 (68.4) [43.4, 87.4]
TTR, days, median (range)	46.0 (42.0–63.0)	67.0 (42.0–89.0)	50.0 (42.0–89.0)	51.7 (46.0–63.0)	66.3 (42.0–89.0)	60.0 (42.0–89.0)
DOR, months [95% CI]	12.2 [3.5, NE]	NA [2.8, NE]	12.2 [2.8, NE]	3.6 [3.5, NE]	NA [2.8, NE]	4.1 [2.8, NE]
PFS events, n (%)	13 (100.0)	13 (100.0)	26 (100.0)	10 (100.0)	9 (100.0)	19 (100.0)
PFS, months, median [95% CI]	4.1 [1.5, 5.5]	3.0 [1.5, 5.4]	4.0 [1.6, 5.1]	3.4 [0.6, 5.1]	4.1 [1.4, NE]	4.0 [1.6, 5.4]
OS events, n (%)	7 (53.8)	4 (30.8)	11 (42.3)	6 (60.0)	1 (11.1)	7 (36.8)
OS, months, median [95% CI]	18.8 [7.2, NE]	NR [11.4, NE]	21.8 [16.7, NE]	18.3 [3.0, NE]	NR [16.7, NE]	NR [13.5, NE]
OS rate, %						
6 months [95% CI]	85 (51, 96)	92 (57, 99)	88 (68, 96)	80 [41, 95]	100 [100, 100]	89 [64, 97]
12 months [95% CI]	76 (NE, NE)	83 (47, 96)	79 (56, 91)	69 [NE, NE]	100 [NE, NE]	84 [NE, NE]
18 months [95% CI]	63 (28, 85)	74 (39, 91)	69 (45, 84)	51 [14, 80]	86 [33, 98]	69 [39, 86]

NEC: neuroendocrine carcinoma; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: objective response rate; DCR: disease control rate; TTR: time to objective response; DOR: duration of objective response; PFS: progression-free survival; OS: overall survival; CI: confidence interval; NE: not estimated; NR: not reached.

Table 2: **Efficacy endpoints in the efficacy analysis set.**

A total of 44.8% of patients experienced grade ≥3 TEAEs, with a higher incidence in the 0.3 mg/kg cohort (61.5%) compared to the 0.45 mg/kg cohort (31.3%). Similarly, the incidence of grade ≥3 TRAEs was 34.5%, with a higher incidence observed in the 0.3 mg/kg cohort (46.2%) than in the 0.45 mg/kg cohort (25.0%). irAEs by PT ≥ 20% in either 0.3 or 0.45 mg/kg cohort were alanine aminotransferase increased (30.8% vs. 50.0%), aspartate aminotransferase increased (15.4% vs. 50.0%), rash (38.5% vs. 56.3%), hyperthyroidism (38.5% vs. 37.5%), blood bilirubin increased (30.8% vs. 12.5%), blood creatine phosphokinase increased (30.8% vs. 0), hypothyroidism (23.1% vs. 25.0%), bilirubin conjugated increased (23.1% vs. 18.8%). Most of irAEs were managed by routine clinical practice such as oral/intravenous steroids therapy which was consistent with the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for Management of Immunotherapy-Related Toxicities. Detailed summary of overall safety, TEAE, TRAE and irAE categories are shown in Tables 4 and 5 and Supplementary Tables S1 and S2.

Biomarker analysis

In 19 patients with IFNγ biomarker analysis results, an increase in IFNγ levels was observed 24 h post-treatment, with concentrations surpassing 50 pg/mL. Response analysis revealed that IFNγ concentrations were higher in patients achieving PR compared to those with SD or disease progression (Supplementary Fig. S3).

A total of 26 patients were evaluated for peripheral blood T cell. A decline was observed on Cycle one, Day four (C1D4), with a subsequent rebound by C1D15 in both cohorts, which may suggest enhanced Treg clearance following HBM4003 treatment. An increase in proliferating Ki-67+CD8+ and Ki-67+CD4+ T cells on-treatment was observed, on C1D8 indicating that HBM4003 plus toripalimab could effectively activate the patients' T cells and induce T cells to proliferate in large numbers (Supplementary Fig. S4).

Results of mIF revealed that the response with PR patients showed higher intensity ratio of positive Foxp3+/CD4+ T cell than SD and PD patients. The Foxp3+/CD4+ T cell ratio should be a potential biomarker to benefit from the administration. The detailed results are provided in Supplementary Fig. S5.

Discussion

This multicenter, open-label, phase II study represents the first clinical trial of dual immunotherapy in Chinese patients with NENs. The findings provided preliminary evidence that the combination of HBM4003 and toripalimab has therapeutic potential in refractory NENs across various subtypes. The safety profile of HBM4003 combined with toripalimab was generally similar to the known AEs for immune checkpoint inhibitors, most of the irAEs are manageable and recoverable during study participation. These results supported the hypothesis that HBM4003 plus toripalimab is effective in a population with limited treatment options and historically

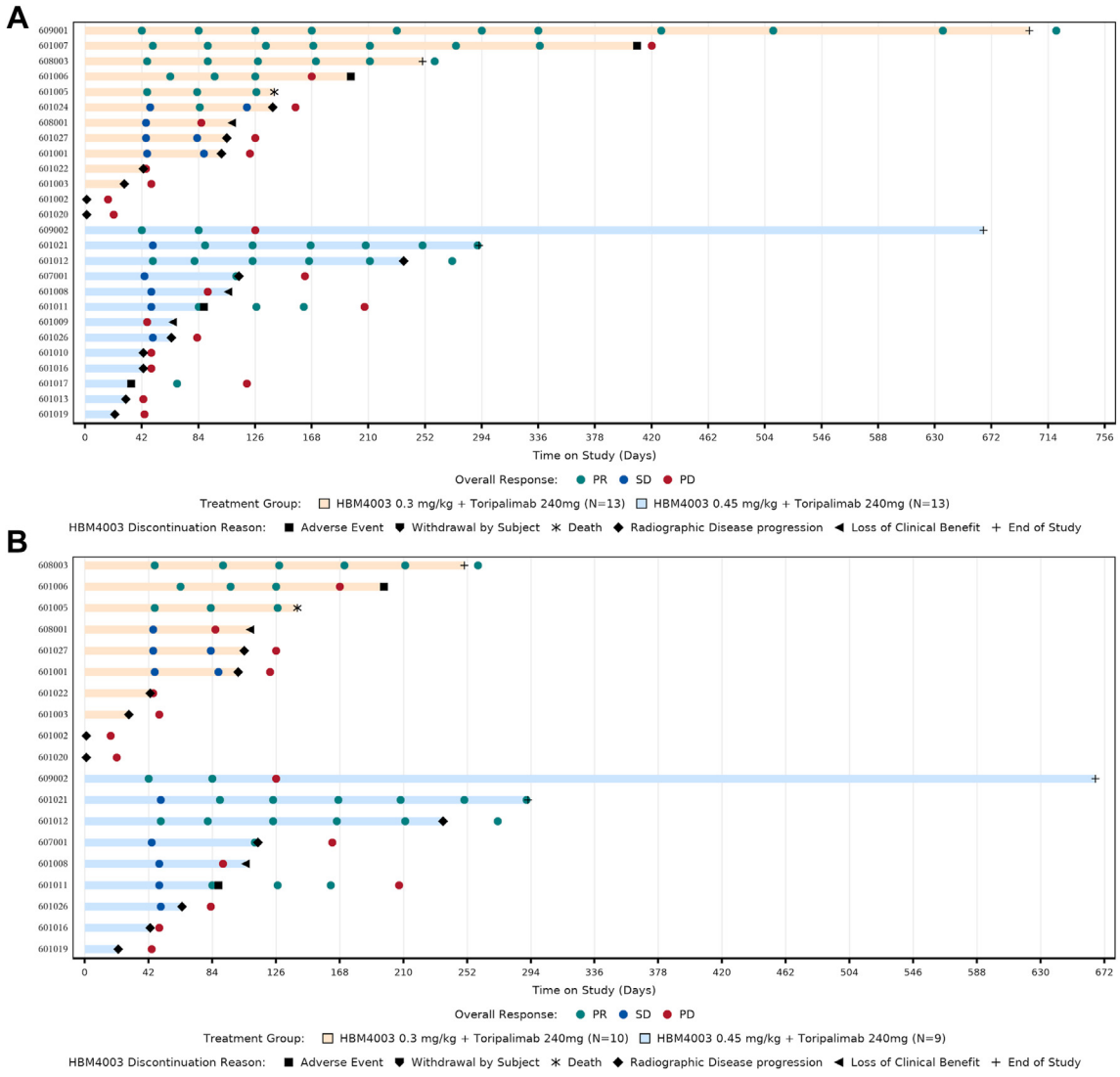

Fig. 2: Swimmer plots of treatment duration and response in the efficacy analysis set. A) Swimmer plot of neuroendocrine neoplasm (NEN) patients. B) Swimmer plot of neuroendocrine carcinoma (NEC) patients.

poor prognosis. Notably, subgroup analyses indicate that early introduction of dual immunotherapy may enhance therapeutic benefit; patients with <2 prior lines of therapy exhibited a higher ORR compared to those with two or more prior treatments. This suggests that initial lines of treatment may influence tumor immune characteristics and responsiveness, highlighting the importance of treatment timing in the therapeutic strategy for NENs.

Both dose cohorts exhibited similar efficacy. The ORR in the HBM4003 0.3 mg/kg cohort was numerically higher than in the 0.45 mg/kg cohort (38.5% vs. 30.8%). In terms of safety, the incidence of grade ≥3 TRAEs was higher in the 0.3 mg/kg cohort compared with the 0.45 mg/kg cohort (46.2% vs. 25.0%). This difference may potentially be attributed to the longer median treatment exposure in the lower-dose cohort (109.0 days vs. 53.5 days) and the small sample size. Despite longer median exposure in the 0.3 mg/kg cohort, the incidence of TRAEs leading to discontinuation of either treatment was similar (15.4% vs. 18.8%), suggesting that HBM4003 0.3 mg/kg dose level may be more tolerable to NEN patients while maintaining comparable efficacy.

The combination of HBM4003 and toripalimab has demonstrated efficacy in treating refractory NENs. Currently, the NCCN guidelines suggest that dual immune checkpoint blockade, such as the combination of ipilimumab and nivolumab, may be considered for patients with advanced NENs, including NETs G3, NECs,

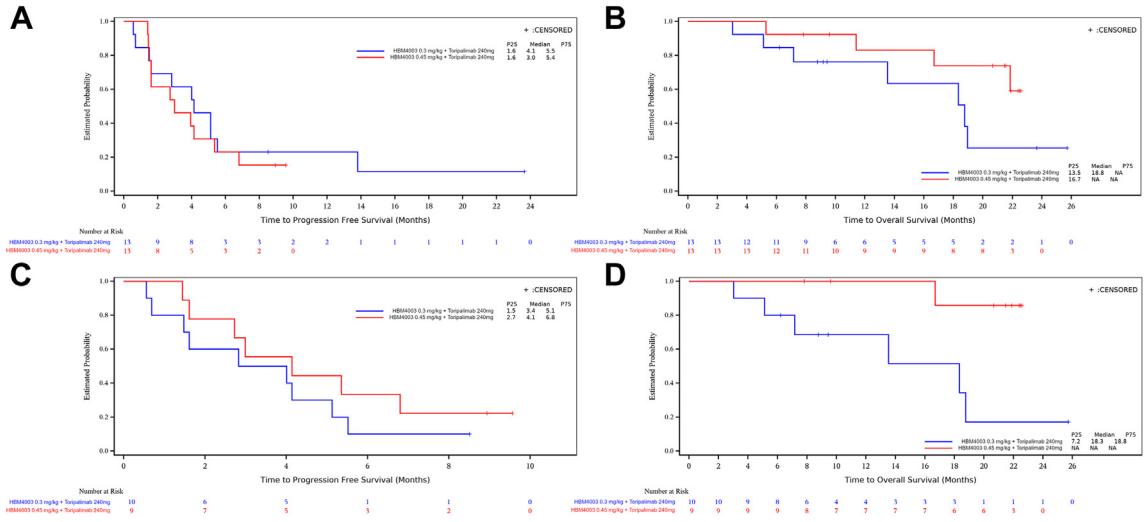

Fig. 3: Kaplan–Meier curves for progression-free survival (PFS) and overall survival (OS) in the efficacy analysis set. A) Kaplan–Meier curve for PFS in neuroendocrine neoplasm (NEN) patients. B) Kaplan–Meier curve for OS in NEN patients. C) Kaplan–Meier curve for PFS in neuroendocrine carcinoma (NEC) patients. D) Kaplan–Meier curve for OS in NEC patients.

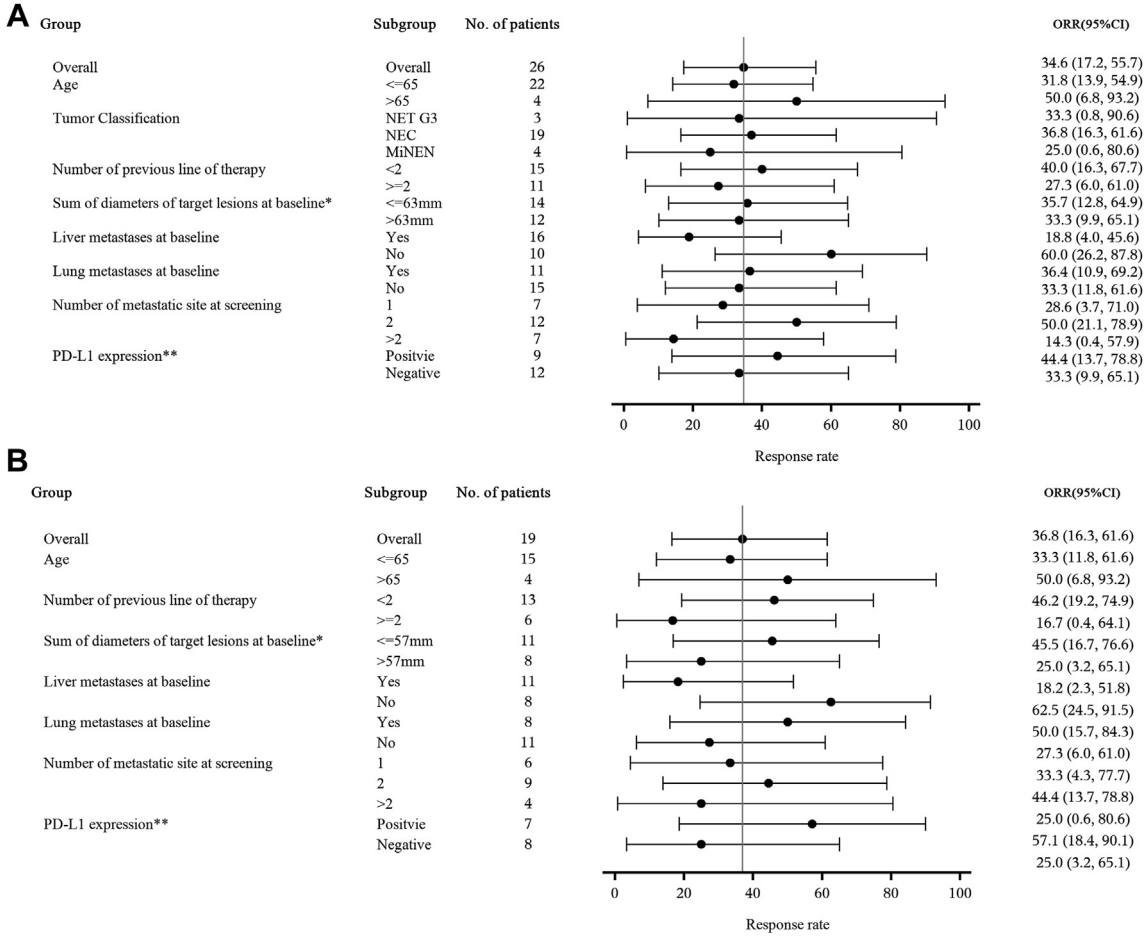

Fig. 4: Subgroup analysis of objective response rate (ORR). A) Subgroup analysis in neuroendocrine neoplasm (NEN) patients. B) Subgroup analysis in neuroendocrine carcinoma (NEC) patients. **PD-L1 expression refers to PD-L1 combined positive score (CPS); Positive: CPS $\geq$ 1, Negative: CPS < 1.

	HBM4003 0.3 mg/kg + Toripalimab 240 mg (N = 13)	HBM4003 0.45 mg/kg + Toripalimab 240 mg (N = 16)	Total (N = 29)
Any subsequent anti-cancer therapies, n (%)	7 (53.8)	9 (56.3)	16 (55.2)
Subsequent surgeries	0 (0.0)	1 (6.3)	1 (3.4)
Subsequent systemic chemotherapies	6 (46.2)	8 (50.0)	14 (48.3)
Subsequent radiotherapies	2 (15.4)	1 (6.3)	3 (10.3)
Subsequent targeted therapies	3 (23.1)	5 (31.3)	8 (27.6)
Subsequent hormone, immunotherapy and vaccines	0 (0.0)	2 (12.5)	2 (6.9)
Subsequent other therapy	0 (0.0)	0 (0.0)	0 (0.0)

Table 3: **Subsequent anti-cancer therapies in the safety set.**

and MiNENs.[23] Previous studies have reported efficacy outcomes of the combination of ipilimumab and nivolumab, such as the SWOG S1609 DART phase II study, which showed an ORR of 26%, a median PFS of 2 months, and a median OS of 8.9 months in high-grade NEN patients.[13] Similarly, the CA209-538 phase II study in advanced NET patients showed an ORR of 24%, median PFS of 4.8 months, and median OS of 14.8 months, with a 31% ORR observed in high-grade NEN subpopulations.[14] Another dual immune checkpoint blockade under investigation included the combination of durvalumab plus tremelimumab, which showed an ORR of 9.1%, median PFS of 2.4 months, and median OS of 5.9 months in the subpopulations with high-grade gastroenteropancreatic NENs.[24]

Variables	HBM4003 0.3 mg/kg + Toripalimab 240 mg (N = 13)	HBM4003 0.45 mg/kg + Toripalimab 240 mg (N = 16)	Total (N = 29)
Drug exposure			
Total duration of HBM4003, days, median (range)	109.00 (1.0–700.0)	53.50 (1.0–666.0)	88.00 (1.0–700.0)
Number of infusions of HBM4003, median (range)	6.0 (1.0–33.0)	3.0 (1.0–32.0)	4.0 (1.0–33.0)
Total duration of toripalimab, days, median (range)	109.00 (1.0–700.0)	53.50 (1.0–666.0)	88.00 (1.0–700.0)
Number of infusions of toripalimab, median (range)	6.0 (1.0–33.0)	3.0 (1.0–32.0)	4.0 (1.0–33.0)
AE summary			
TEAEs, n (%)	13 (100.0)	16 (100.0)	29 (100.0)
Grade ≥3	8 (61.6)	5 (31.3)	13 (44.8)
Serious	5 (38.5)	8 (50.0)	13 (44.8)
Leading to discontinuation	2 (15.4)	4 (25.0)	6 (20.7)
Leading to death	1 (7.7)	1 (6.3)	2 (6.9)
TRAEs, n (%)	13 (100.0)	16 (100.0)	29 (100.0)
Grade ≥3	6 (46.2)	4 (25.0)	10 (34.5)
Serious	4 (30.8)	4 (25.0)	8 (27.6)
Leading to discontinuation	2 (15.4)	3 (18.8)	5 (17.2)
Leading to death	1 (7.7)	0	1 (3.4)
irAE, n (%)	12 (92.3)	14 (87.5)	26 (89.7)
Grade ≥3	5 (38.5)	3 (18.8)	8 (27.6)

TEAEs: treatment-emergent adverse events; TRAEs: treatment-related adverse events; irAE: immune-related adverse events.

Table 4: **Safety overview (safety set).**

The combination of HBM4003 and toripalimab in our study resulted in a median OS that was numerically longer than that reported in previous studies involving similar patient populations. This observation is particularly notable given that the cohort predominantly comprised patients with pretreated NECs, a group typically associated with poor prognosis. One potential contributing factor is that 48.3% of patients received systemic chemotherapy following disease progression on study treatment, which was numerically higher than those reported in the real-world NORDIC NEC study.[25] The ability to proceed to subsequent therapy may reflect the relatively preserved performance status of these patients at the time of progression, possibly due to disease stabilization or favorable tolerability of the immunotherapy regimen. Furthermore, it is increasingly recognized that prior exposure to immune checkpoint inhibitors may enhance the efficacy of subsequent chemotherapy by modulating the tumor microenvironment or reprogramming immune responsiveness.[26] This immunomodulatory effect may have contributed to prolonged survival in patients who were able to receive additional lines of treatment. The apparent disconnect between a modest PFS of 4.0 months and a longer OS is also consistent with known patterns of response to immunotherapy. Unlike cytotoxic agents, immune checkpoint inhibitors can produce delayed yet durable responses in a subset of patients, leading to sustained disease control not fully captured by PFS metrics.[27,28] It is also important to acknowledge that approximately half of the patients did not receive further systemic therapy after disease progression. This may have been due to rapid clinical deterioration, lack of available treatment options, or other patient- or system-related factors. Future studies are needed to better understand the interplay between immunotherapy and subsequent treatments, including the potential priming effect of immune checkpoint blockade and its implications for optimizing treatment sequencing and survival outcomes in patients with refractory NENs.

This study is among the first to provide subgroup analyses within a CTLA-4 inhibitor plus PD-1/PD-L1 inhibitor regimen, offering preliminary efficacy insights for distinct patient subpopulations. Subgroup analyses in our study indicate that the combination of HBM4003 and toripalimab demonstrates antitumor activity across diverse types of NENs, with the highest ORR observed in NEC patients (36.8%). This finding aligns with previous research, such as the study evaluating surufatinib plus toripalimab in advanced NENs, which reported ORRs of 21.1% in NENs (including

Events by preferred terms, n (%)	HBM4003 0.3 mg/kg + Toripalimab 240 mg (N = 13)				HBM4003 0.45 mg/kg + Toripalimab 240 mg (N = 16)				Total (N = 29)			
	Any grade	Grade 1/2	Grade ≥3	Grade 4	Any grade	Grade 1/2	Grade ≥3	Grade 4	Any grade	Grade 1/2	Grade ≥3	Grade 4
Alanine aminotransferase increased	5 (38.5)	5 (38.5)	0 (0.0)	0 (0.0)	9 (56.3)	7 (43.8)	2 (12.5)	0 (0.0)	14 (48.3)	12 (41.4)	2 (6.9)	0 (0.0)
Rash	5 (38.5)	5 (38.5)	0 (0.0)	0 (0.0)	9 (56.3)	9 (56.3)	0 (0.0)	0 (0.0)	14 (48.3)	14 (48.3)	0 (0.0)	0 (0.0)
Aspartate aminotransferase increased	4 (30.8)	4 (30.8)	0 (0.0)	0 (0.0)	9 (56.3)	8 (50.0)	1 (6.3)	0 (0.0)	13 (44.8)	12 (41.4)	1 (3.4)	0 (0.0)
Hyperthyroidism	6 (46.2)	6 (46.2)	0 (0.0)	0 (0.0)	6 (37.5)	6 (37.5)	0 (0.0)	0 (0.0)	12 (41.4)	12 (41.4)	0 (0.0)	0 (0.0)
Anaemia	5 (38.5)	5 (38.5)	0 (0.0)	0 (0.0)	6 (37.5)	5 (31.3)	1 (6.3)	0 (0.0)	11 (37.9)	10 (34.5)	1 (3.4)	0 (0.0)
Neutrophil count decreased	6 (46.2)	5 (38.5)	1 (7.7)	0 (0.0)	4 (25.0)	4 (25.0)	0 (0.0)	0 (0.0)	10 (34.5)	9 (31.0)	1 (3.4)	0 (0.0)
White blood cell count decreased	4 (30.8)	4 (30.8)	0 (0.0)	0 (0.0)	6 (37.5)	6 (37.5)	0 (0.0)	0 (0.0)	10 (34.5)	10 (34.5)	0 (0.0)	0 (0.0)
Pyrexia	2 (15.4)	2 (15.4)	0 (0.0)	0 (0.0)	7 (43.8)	7 (43.8)	0 (0.0)	0 (0.0)	9 (31.0)	9 (31.0)	0 (0.0)	0 (0.0)
Hypothyroidism	3 (23.1)	3 (23.1)	0 (0.0)	0 (0.0)	4 (25.0)	4 (25.0)	0 (0.0)	0 (0.0)	7 (24.1)	7 (24.1)	0 (0.0)	0 (0.0)
Platelet count decreased	3 (23.1)	3 (23.1)	0 (0.0)	0 (0.0)	4 (25.0)	4 (25.0)	0 (0.0)	0 (0.0)	7 (24.1)	7 (24.1)	0 (0.0)	0 (0.0)
Blood creatine phosphokinase increased	4 (30.8)	3 (23.1)	1 (7.7)	0 (0.0)	2 (12.5)	2 (12.5)	0 (0.0)	0 (0.0)	6 (20.7)	5 (17.2)	1 (3.4)	0 (0.0)
Lipase increased	3 (23.1)	2 (15.4)	1 (7.7)	0 (0.0)	3 (18.8)	3 (18.8)	0 (0.0)	0 (0.0)	6 (20.7)	5 (17.2)	1 (3.4)	0 (0.0)
Bilirubin conjugated increased	3 (23.1)	3 (23.1)	0 (0.0)	0 (0.0)	3 (18.8)	3 (18.8)	0 (0.0)	0 (0.0)	6 (20.7)	6 (20.7)	0 (0.0)	0 (0.0)
Blood glucose increased	5 (38.5)	5 (38.5)	0 (0.0)	0 (0.0)	1 (6.3)	1 (6.3)	0 (0.0)	0 (0.0)	6 (20.7)	6 (20.7)	0 (0.0)	0 (0.0)
Hyperglycaemia	2 (15.4)	0 (0.0)	2 (15.4)	1 (7.7)	3 (18.8)	3 (18.8)	0 (0.0)	0 (0.0)	5 (17.2)	3 (10.3)	2 (6.9)	1 (3.4)
Amylase increased	2 (15.4)	1 (7.7)	1 (7.7)	0 (0.0)	3 (18.8)	3 (18.8)	0 (0.0)	0 (0.0)	5 (17.2)	4 (13.8)	1 (3.4)	0 (0.0)
Hyponatraemia	2 (15.4)	2 (15.4)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (6.3)	0 (0.0)	3 (10.3)	2 (6.9)	1 (3.4)	0 (0.0)
Hepatic failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (6.3)	1 (6.3)	1 (3.4)	0 (0.0)	1 (3.4)	1 (3.4)
Infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (6.3)	1 (6.3)	1 (3.4)	0 (0.0)	1 (3.4)	1 (3.4)
Renal failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (6.3)	1 (6.3)	1 (3.4)	0 (0.0)	1 (3.4)	1 (3.4)
Diabetic ketoacidosis	1 (7.7)	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)	0 (0.0)	1 (3.4)	0 (0.0)
Immune-mediated hepatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (6.3)	0 (0.0)	1 (3.4)	0 (0.0)	1 (3.4)	0 (0.0)
Immune-mediated lung disease	1 (7.7)	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)	0 (0.0)	1 (3.4)	0 (0.0)
Immune-mediated myocarditis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (6.3)	0 (0.0)	1 (3.4)	0 (0.0)	1 (3.4)	0 (0.0)
Sudden cardiac death	1 (7.7)	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)	0 (0.0)	1 (3.4)	0 (0.0)

TRAE: Treatment-related adverse event.

Table 5: **TRAEs with an incidence of ≥20%, or any TRAE with grade ≥3 (safety set).**

grades 1–3), 33.3% in NECs, and 0 in MiNENs, suggesting particularly favorable outcomes in NEC patients.[29] While these results are encouraging, larger randomized controlled trials are essential to validate the observed efficacy and better delineate the specific benefits of dual immunotherapy in NEN subtypes.

The analysis of prior treatment lines within the NEC cohort suggests that early use of immunotherapy may improve outcomes. Patients who received fewer than two lines of prior therapy exhibited an ORR of 46.2%, compared with 16.7% in those who had undergone two or more lines. Furthermore, the metastatic profile appears to influence treatment response. In our NEC cohort, patients without liver metastasis had an ORR of 62.5%, markedly higher than the 18.2% observed in those with liver metastasis. Previous basic research has indicated the association between liver metastasis and poorer response to immunotherapy in cancer patients.[30] Additionally, this trend aligns with data from a study on HBM4003 in melanoma and other solid tumors, which demonstrated poorer PFS outcomes associated with liver metastasis (HR = 2.53, P = 0.15).[19] Interestingly, patients with lung metastasis in our study achieved a higher ORR (50.0%) than those without lung metastasis (27.3%), suggesting that HBM4003 plus toripalimab may retain efficacy in patients with lung metastatic involvement.

HBM4003 (0.3 or 0.45 mg/kg) combined with toripalimab 240 mg demonstrated a well-tolerated safety profile in NEN patients, and the AE categories observed in this study were generally similar to the known AEs for immune checkpoint inhibitors, with no new safety signals identified. Safety remains a critical consideration when applying dual immunotherapy in patients with advanced cancer, as irAEs often occur more frequently and severely when CTLA-4 is combined with PD-1/PD-L1 inhibitors. Prior studies have shown a relatively higher incidence of irAEs (such as diarrhea and colitis) with ipilimumab, which limited its clinical dosage and treatment cycles. These factors can lead to excessive T-cell activation, which may result in unintended targeting of healthy tissues and subsequent irAEs.[31] A meta-analysis reported that gastrointestinal risk such as diarrhea and colitis was the second highest risk for patients (N = 3970) with malignant tumors dosing with ipilimumab plus nivolumab in 23 different clinical studies,[32] with risk ratio of grade 1 and 2 diarrhea 23.58%, grade 3 diarrhea 5.72% and grade 3 colitis

6.39%. In contrast, despite there was no maximum number of HBM4003 doses to be administrated for each patient, diarrhea was only observed from 17.2% of patients, and no grade ≥3 diarrhea was noted, suggesting that the combination of HBM4003 and toripalimab may offer a favorable tolerability profile in comparison to other dual immune checkpoint inhibitors. These findings suggested that the distinct design of HBM4003 may mitigate some of the adverse effects typically seen with CTLA-4 inhibition, supporting its potential as a safer dual immunotherapy option for patients with refractory NENs.

This study has several limitations that should be considered when interpreting the results. The absence of a contemporaneous control group limits the ability to directly compare the efficacy of HBM4003 combined with toripalimab against standard therapies. Furthermore, the small sample size, particularly within specific NEN subtypes, constrains the statistical power to accurately evaluate efficacy across diverse patient subgroups. A randomized phase III trial is being planned to validate these findings, incorporating immune RECIST (iRECIST) criteria, longitudinal biomarker analysis, tissue re-biopsy, and stratified subgroup evaluation to further elucidate the clinical and biological predictors of response to dual immune checkpoint blockade in high-grade NENs.

In conclusion, the findings from this phase II study suggest that HBM4003 combined with toripalimab demonstrates promising anti-tumor activity and manageable safety in patients with refractory NENs. These results warrant further investigation in larger, randomized trials to establish its therapeutic potential in this challenging patient population.

Contributors

Panpan Zhang and Kai Chen contributed to this work as co-first authors. They have directly accessed and verified the underlying data reported in this manuscript and were primarily responsible for the original draft writing, data curation, and investigation. Ming Lu, Lin Shen and Xiaolu Tao supervised the entire study, primarily responsible for the conceptualization, investigation, funding acquisition and administration of the study. Jianwei Yang and Lijie Song contributed to data curation and investigation. Fei Zheng, Ruixuan Luo, Yebo He, Feng Li, Di Yang, Nan Cao and Xiaolu Tao contributed to the methodology, validation, and writing, review & editing of the manuscript. All authors have read, critically revised, and approved the final manuscript.

Data sharing statement

De-identified patient-level data required for replication of the study's endpoints are available from the corresponding author (M.L.) upon reasonable request, as well as the study protocol and statistical analysis plan, from publication date onwards.

Declaration of interests

Fei Zheng, Ruixuan Luo, Yebo He, Feng Li, Di Yang, Nan Cao and Xiaolu Tao are employees of Harbour BioMed (Shanghai) Co. Ltd. Other authors declared no conflicts of interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103249.

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