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A multicenter, open-label, single-arm, phase Ib clinical trial of HH2853 treatment in patients with relapsed and/or refractory peripheral T-cell lymphoma

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Abstract

Background Peripheral T-cell lymphoma (PTCL) is an aggressive malignancy with limited treatment options and poor prognosis, particularly for relapsed or refractory (r/r) patients. HH2853, a novel dual inhibitor of EZH1/2, has previously demonstrated clinical benefits in solid tumors. Here, we report safety and efficacy data from a phase Ib trial of HH2853 in r/r PTCL.

Methods A phase Ib clinical trial in PTCL was conducted from July 2022–August 2023 at 15 sites in China. The study employed a dose-escalation phase (300 mg, 400 mg, and 600 mg BID) to determine the recommended phase II dosage (RP2D), followed by a dose expansion phase (300 mg and 400 mg BID). The primary endpoints were safety and the overall response rate (ORR).

Results Thirty-four patients with various r/r PTCL histology types, a median age of 58 years, and a median of 2 prior systemic therapies were enrolled. Treatment-related adverse events (TRAEs) were observed in 92.1% of the patients, with 20.6% experiencing grade 3 TRAEs. The most common TRAEs included anemia (67.6%), thrombocytopenia (52.9%), leukopenia (44.1%), and diarrhea (38.2%). One patient (2.9%) receiving 600 mg BID experienced dose-limiting toxicity due to grade 4 thrombocytopenia. The dose of 400 mg BID was selected as the RP2D. The ORR was 67.6%, comprising 29.4% complete remission and 38.2% partial remission. As of the data cutoff in September 2024, the median follow-up period was 15.7 months, with a median duration of response of 14.8 months; overall survival had not yet been reached.

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Conclusions The selective EZH1/2 dual inhibitor HH2853 demonstrated acceptable and manageable safety profiles and promising efficacy in r/r PTCL patients, indicating its therapeutic potential for this difficult-to-treat patient population.

Trial registration NCT04390737

Keywords Peripheral T-cell lymphoma, EZH1/2, HH2853

Background

Peripheral T-cell lymphomas (PTCLs) encompass a heterogeneous group of aggressive lymphoid malignancies with generally poor outcomes [1, 2]. The most prevalent subtypes include peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), anaplastic large cell lymphoma (ALCL), and angioimmunoblastic T-cell lymphoma (AITL), now renamed nodal T-follicular helper cell lymphoma, angioimmunoblastic type [3]. Despite the use of multiagent chemotherapeutic regimens as standard induction therapy, the prognosis for PTCLs remains significantly worse than that for B-cell lymphomas, with many patients experiencing relapse or disease progression [4, 5]. The median overall survival (OS) for patients with relapsed and refractory (r/r) PTCL is only 6 months [6, 7]. Although new agents, including JAK/STAT pathway inhibitors, histone deacetylase (HDAC) inhibitors, and immunotherapies, are expanding treatment options for relapsed or refractory (r/r) disease [8–12], there is a pressing need for more effective therapies for this high-risk disease.

The enhancer of zeste homolog 2 (EZH2), a critical component of the polycomb repressive complex 2 (PRC2), catalyzes the trimethylation of lysine 27 on histone H3 (H3K27me3), leading to transcriptional silencing [13]. The overexpression of EZH2 has been implicated in various cancers, including PTCL, where it drives tumor progression [14, 15]. Several EZH2 inhibitors, such as GSK126 and tazemetostat, have shown promising therapeutic efficacy in solid tumors and various types of lymphomas [16–18]. Nevertheless, the clinical efficacy of EZH2 inhibitors is hindered by compensatory upregulation of EZH1, which plays a critical role in maintaining H3K27me3 levels. Previous studies have demonstrated that dual inhibition of EZH1 and EZH2 is more effective in reducing H3K27me3 levels compared to EZH2-selective inhibitors [15, 19, 20], establishing it as a promising therapeutic strategy. Valemetostat, a potent dual EZH1/2 inhibitor, has shown encouraging efficacy and tolerability in r/r T-cell leukemia and lymphoma [21, 22], supporting further investigations of dual inhibitors for PTCL treatment.

HH2853 is a selective dual EZH1/2 inhibitor that effectively reduces H3K27me3 levels and demonstrates potent antitumor activity. HH2853 outperforms the FDA-approved EZH2-specific inhibitor tazemetostat in terms of its antitumor efficacy at equipotent dosing across preclinical models [23]. Moreover, HH2853 has demonstrated a clinical benefit with an acceptable safety profile in phase I/II trials in solid tumors [24]. On the basis of these encouraging results, we performed a phase Ib trial to assess the safety, efficacy, pharmacokinetics and pharmacodynamics of twice-daily oral HH2853 in patients with r/r PTCL.

Methods

Participants

This study was a multicenter, open-label, phase Ib trial conducted from July 2022 to August 2023 at 15 sites in China. The eligible participants had confirmed r/r PTCL with at least 1 line of prior systemic treatment (maximum ≤ 5 lines). Relapsed disease was defined as the recurrence or progression of disease following complete remission (CR) or partial remission (PR) after prior treatment. Refractory disease was defined as the need for a treatment change following stable disease (SD) or disease progression within one year of completing adequate treatment. Other essential inclusion criteria included an age ≥ 18 years, an anticipated life expectancy of at least 3 months, an Eastern Cooperative Oncology Group performance score of 0 or 1, and sufficient bone marrow, liver and renal functions in the absence of treatment with cell growth factor. Patients were excluded if they met any of the following criteria: prior treatment with EZH2 or EZH1/2 inhibitors, central nervous system (CNS) involvement, a history or concurrent presence of other primary malignancies, active infections (including hepatitis B and C), recent major surgery or severe traumatic injury, receipt of anticancer treatment within the required interval between the last antitumor therapy and the first administration of HH2853, clinically significant cardiovascular disease, inability to take oral medication, malabsorption syndrome, or any other uncontrolled gastrointestinal condition that could impair the bioavailability of HH2853. Additionally, patients were excluded if they had taken potent CYP3A4 inducers/inhibitors within 1 week or had received inactivated or live attenuated vaccines within 2 weeks before the first dose. Patients were also excluded if any prior treatment-related clinically significant toxicities had not resolved or remained unstable at the time of enrollment.

Study design

The study was structured into two phases: dose escalation and dose expansion. In the dose-escalation part for HH2853, a 3 + 3 design was employed to identify the recommended phase II dosage (RP2D). Initial oral doses of 300 mg, 400 mg, and 600 mg, administered twice daily, were assessed for monitoring dose-limiting toxicities (DLTs). Moreover, the safety monitoring committee, composed of medical experts from both the investigators and the sponsor, were responsible for choosing additional doses on the basis of the data collected throughout the study. According to the available data from dose escalation, one or two dose levels could continue to be used for dose expansion, and another 10–15 patients for each dose could be enrolled to further evaluate the safety and efficacy profile of HH2853.

Patients participating in both the dose-escalation and dose-expansion phases commenced oral HH2853 treatment twice daily. Treatment persisted in 28-day cycles until intolerable toxicity, investigator- or patient-initiated withdrawal, disease progression, loss to follow-up, death, or study termination. Patients who demonstrated continued clinical benefit without signs of clinical deterioration were allowed to continue treatment beyond documented disease progression. For these patients, the duration of response was determined based on the date of first documented disease progression.

The primary objective of this study was to determine the RP2D of HH2853 for PTCLs, with the primary endpoint being the evaluation of its safety and overall response rate (ORR), which was defined as the proportion of patients who achieved a PR or CR. The secondary objectives included assessing the preliminary efficacy and characterizing the pharmacokinetic profile. The secondary endpoints were the investigator-assessed complete response rate (CRR), duration of response (DoR), disease control rate (DCR), and time to response (TTR). Additional secondary endpoints involved evaluating pharmacokinetic parameters such as the maximum concentration (Cmax), time to reach the maximum concentration (Tmax), elimination half-life (t1/2), clearance (CL/F), and area under the concentration–time curve (AUC).

Outcomes

DLTs, which were meticulously monitored during the observation period, included a grade 4 decreased neutrophil count that was accompanied by fever or lasted at least 7 days; grade 3 decreased platelet count lasting at least 7 days or with evident clinical hemorrhage symptoms; grade 4 decreased platelet count; grade 4 anemia lasting at least 7 days; grade 3 or higher cardiotoxicities; grade 3 or higher fatigue lasting over 3 days; grade 3 or higher nausea, vomiting, or diarrhea persisting for at least 5 days despite symptomatic treatment; a grade 3 (lasting > 7 days) or grade 4 increase in the alanine aminotransferase (ALT) or aspartate aminotransferase (AST) concentration; and grade 3 or higher nonhematological toxicities resulting in a greater than 7-day treatment interruption; other inability to start cycle 2 within 2 weeks of the scheduled time due to > grade 2 drug-related toxicity. DLTs were assessed within the first treatment cycle (the initial 28 days) following study drug administration, with intensive monitoring conducted throughout this period.

Treatment-emergent adverse events (TEAEs) were assessed in compliance with the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0). Vital signs, laboratory abnormalities, and 12-lead ECG were regularly evaluated. These assessments were performed at baseline, on days 1 and 15 of the first two treatment cycles, and on day 1 of the third cycle and thereafter. A final assessment was conducted within 7 days following the last administered dose.

The adverse events of each patient were tabulated on the basis of the coded preferred term, considering the strongest causality and most severe impact. The planned safety assessments encompassed the compilation of data associated with diverse dosage levels, offering a comprehensive perspective. Interim safety evaluations took place before dose-level escalations and expansion of the study. Treatment-related adverse events (TRAEs) were ascertained through the treating physician's assessment, considering their potential association as possibly linked to the treatment.

All patients underwent a baseline 18 F-FDG PET-CT scan along with CT or MRI imaging of the chest, neck, abdomen, and pelvis. Tumor assessments were conducted every two cycles using CT or MRI. When a possible PR or CR was first recorded on CT or MRI, a PET/CT scan was subsequently performed to confirm the response status. Tumor responses were evaluated by investigators in accordance with the 2014 Lugano criteria for lymphomas. The HH2853 in the plasma samples was analyzed via validated liquid chromatography–tandem mass spectrometry (LC–MS-MS), with a quantitation limit of 1 ng/mL. Standard pharmacokinetic parameters were obtained via Phoenix WinNonlin (version 8.2) with noncompartmental analysis. Furthermore, for pharmacodynamics analysis, the level of H3K27me3 in peripheral blood mononuclear cells (PBMCs) was measured via flow cytometry. Whole-blood samples for PBMCs were collected on C1D1 before dosing and on C1D15 at 8 h after dosing.

Statistical analysis

The sample size for the dose-escalation portion of the study was determined according to the 3 + 3 design

principles, which involved enrolling 3–6 patients per dose level. Following safety confirmation on the basis of the 3 + 3 design, an additional 15 patients for each dose were allowed to be enrolled in the dose expansion phase on the basis of safety and efficacy data from the dose-escalation phase. The overall safety and efficacy profiles were subsequently analyzed on the basis of these two sets of data. Safety and efficacy analyses included all full analysis set (FAS) patients, which included individuals who had received at least one dose of the HH2853 drug.

The objective response rate point estimates, along with their two-sided 95% CIs, were determined via the Clopper–Pearson method. The Kaplan–Meier method was used to estimate the median DoR, progression-free survival (PFS) and OS, along with their corresponding two-sided 95% CIs. The pharmacokinetic parameters were computed via Phoenix WinNonlin (version 8.2). SAS 9.4 (SAS Institute, Cary, North Carolina, USA) was employed for safety and efficacy assessments. The study protocols received approval from the ethics committees at each participation center. All patients provided written informed consent, and the study adhered to the principles outlined in the Declaration of Helsinki. This study has been registered with ClinicalTrials.gov under the identifier NCT04390737.

Results

Patients

Between July 2022 and August 2023, 34 patients diagnosed with r/r PTCL participated in the trial (Supplementary Fig. 1), including 15 (44.1%) patients with AITL, 11 (32.4%) with PTCL-NOS, 3 (8.8%) with ALK-ALCL, 2 (5.9%) with natural killer T-cell lymphoma (NKTCL), 2 (5.9%) with nodal T-follicular helper cell lymphoma, not otherwise specified (TFH-NOS), and 1 (2.9%) with primary cutaneous T-cell lymphoma. All participants received at least one dose of HH2853. Among the enrolled patients, 25 (73.5%) patients were men, and the median age was 58.0 years (range, 34–79 years), with 21 patients (61.7%) having advanced-stage disease at baseline. Patients were pretreated with a median of 2 prior lines of therapy (range, 1–5). Most patients (91.2%) had previously received CHOP or CHOP-like regimens, and 13 patients (38.2%) had been treated with the HDAC inhibitor chidamide. Additionally, some patients had previously received thalidomide (17.6%), JAK inhibitors (2.9%), or brentuximab vedotin (5.9%) as part of drug therapy or clinical trials. Twenty-six patients (76.5%) exhibited refractory characteristics to their last treatment. One patient (2.9%) had previously undergone autologous stem cell transplantation. Baseline characteristics of patients in the 300 mg, 400 mg, and 600 mg dose cohorts, as well as the overall cohort, were summarized in Table 1.

Safety

In the 300 mg and 400 mg groups, no DLTs were observed. However, when we increased the dosage to 600 mg, DLTs were reported in one out of three patients (33.3%). The 400 mg administered twice daily was determined to be the RP2D.

All 34 patients who received HH2853 experienced TEAEs. The incidence of Grade 3 or higher TEAEs per CTCAE was 52.9%. The most common hematologic TEAEs included anemia (76.5%), thrombocytopenia (58.8%), leukopenia (47.1%), neutropenia (44.1%), and lymphopenia (38.2%). Common nonhematologic TEAEs included diarrhea (41.2%), elevated lactate dehydrogenase (38.2%), hyperuricemia (35.3%), hypokalemia (32.4%), elevated ALT (29.4%), elevated AST (29.4%) and hypoalbuminemia (26.5%). The grade ≥ 3 TEAEs, which were reported in ≥ 10% of the patients, comprised thrombocytopenia (23.5%), neutropenia (23.5%), leukopenia (20.6%), lymphopenia (11.8%) and anemia (11.8%) (Fig. 1A). The TEAEs observed in each dose cohort were summarized in Supplementary Fig. 2.

The most common hematologic TRAEs included anemia (67.6%), thrombocytopenia (52.9%), leukopenia (44.1%), neutropenia (38.2%), and lymphopenia (35.3%). Common nonhematologic TRAEs included diarrhea (38.2%), elevated lactate dehydrogenase (29.4%), hyperuricemia (26.5%), hypokalemia (26.5%), increased AST (23.5%), increased ALT (20.6%), and hypoalbuminemia (20.6%). The grade ≥ 3 TRAEs, which were reported in ≥ 10% of the patients were thrombocytopenia (20.6%), neutropenia (20.6%), leukopenia (17.6%) and anemia (11.8%) (Fig. 1B). The TRAEs observed in each dose cohort were summarized in Supplementary Fig. 3.

Eighteen patients (52.9%) experienced TEAEs resulting in dose interruption, and 14 patients (41.2%) experienced TEAEs related to treatment, including thrombocytopenia (17.6%), neutropenia (14.7%), and elevated blood bilirubin (5.8%). Eight patients (23.5%) experienced TEAEs causing a dose reduction, with three patients in the 600 mg cohort, three in the 400 mg cohort, and two in the 300 mg cohort. And all of these events, including thrombocytopenia (8.8%), diarrhea (5.8%), pneumonia (5.8%), anemia (2.9%), increased blood bilirubin (2.9%) and rash (2.9%), were considered to be treatment related. Except for one case of thrombocytopenia that did not resolve after dose reduction, the TEAEs in most of the remaining seven patients were transient and eventually resolved. One patient (2.9%) permanently discontinued HH2853 due to TEAEs, which ultimately led to death. This patient was a 75-year-old male with r/r AITL who developed hemophagocytic lymphohistiocytosis and subsequently died from multiorgan failure after receiving more than one month of HH2853 treatment. The median dose intensities of HH2853 in the 300 mg, 400 mg, and

Table 1 Patient demographics and baseline characteristics

	300 mg (*N* = 15)	400 mg (*N* = 16)	600 mg (*N* = 3)	Total (*N* = 34)
Median Age in Years (range)	59 (44, 75)	60 (37, 79)	52 (34, 57)	58 (34, 79)
Gender				
Male	10 (66.7%)	13 (81.3%)	2 (66.7%)	25 (73.5%)
Female	5 (33.3%)	3 (18.8%)	1 (33.3%)	9 (26.5%)
Pathological Type				
AITL	7 (46.7%)	8 (50.0%)	0	15 (44.1%)
PTCL-NOS	5 (33.3%)	5 (31.3%)	1 (33.3%)	11 (32.4%)
ALK-ALCL	2 (13.3%)	0	1 (33.3%)	3 (8.8%)
NKTCL	0	2 (12.5%)	0	2 (5.9%)
TFH-NOS	1 (6.7%)	1 (6.3%)	0	2 (5.9%)
SKIN-PTCL	0	0	1 (33.3%)	1 (2.9%)
ECOG performance status				
0	2 (13.3%)	5 (31.3%)	2 (66.7%)	9 (26.5%)
1	13 (86.7%)	11 (68.8%)	1 (33.3%)	25 (73.5%)
Ann-Arbor Stage				
I	0	0	0	0
II	0	2 (12.5%)	0	2 (5.9%)
III	6 (40.0%)	4 (25.0%)	1 (33.3%)	11 (32.3%)
IV	9 (60.0%)	10(62.5%)	2(66.7%)	21 (61.8%)
Autologous hematopoietic stem cell transplantation	1 (6.7%)	0	0	1 (2.9%)
Median Number of Prior Lines (range)	2 (1, 2)	2 (1, 3)	2 (2, 5)	2 (1, 5)
Previous systemic therapies				
CHOP/CHOP-like regimen	15 (100.0%)	13 (81.3%)	3 (100.0%)	31 (91.2%)
including chidamide regimen	5 (33.3%)	6 (37.5%)	2 (66.7%)	13 (38.2%)
including thalidomide regimen	3 (20.0%)	3 (18.8%)	0	6 (17.6%)
including brentuximab regimen	1 (6.7%)	1 (6.3%)	0	2 (5.9%)
including azacitidine regimen	1 (6.7%)	0	1 (33.3%)	2 (5.9%)
including PD-1 regimen	0	2 (12.5%)	0	2 (5.9%)
Other drugs[#]	2 (13.3%)	2 (13.3%)	0	4 (11.7%)
Refractory to last regimen	10(66.7%)	14(87.5%)	2(66.7%)	26(76.5%)

AITL, angioimmunoblastic T-cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma not otherwise specified; ALK-ALCL, ALK-negative anaplastic large cell lymphoma; NKTCL, natural killer T-cell lymphoma; TFH-NOS, nodal T-follicular helper cell lymphoma, not otherwise specified; SKIN-PTCL, primary cutaneous T-cell lymphomas

CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone;

Other drugs[#] included mitoxantrone, lenalidomide, ADZ4205 (a highly selective JAK1 inhibitor) and YY-20,394 (PI3Kδ inhibitor)

ECOG, Eastern Cooperative Oncology Group;

600 mg groups were 596.9, 770.4, and 723.8 mg/day, respectively.

Efficacy

A final data cutoff on September 2024 was conducted for efficacy assessments, and the median follow-up duration was 15.7 months. Among the 34 enrolled patients, 23 patients (67.6%, 95% CI: 49.5-82.6%) exhibited an overall response, including 29.4% (10 patients) with CR, 38.2% (13 patients) with PR and 5.9% (2 patients) with SD, contributing to 73.5% (25 patients) with DCR. The ORRs were comparable across the 300 mg, 400 mg, and 600 mg dose cohorts, at 66.7%, 68.8%, and 66.7%, respectively (Fig. 2A).

At the cutoff timepoint, eight individuals (23.5%) were still receiving treatment with HH2853, whereas 26 patients (76.5%) had discontinued their treatment. Among them, 19 patients discontinued due to disease progression, while the remaining 7 discontinued for other reasons, including toxicity ($n = 3$), patient withdrawal ($n = 3$), and physician's decision ($n = 1$). The median TTR was 2.1 months (1.7–5.6). In addition, 12 (52.2%) of the 23 responders continued to exhibit ongoing responses (Fig. 2B).

Notably, among the 21 patients (61.8%) who had previously received treatment with novel antitumor agents—including chidamide, pralatrexate, brentuximab vedotin, or other targeted immunotherapy drugs—HH2853 continued to demonstrate significant efficacy. These patients achieved an ORR of 61.9% (95% CI: 38.4–81.9), a CR rate of 23.8%, and a mPFS of 3.7 months (95% CI: 1.8–9.5). By comparison, among the 13 patients (38.3%) who had only

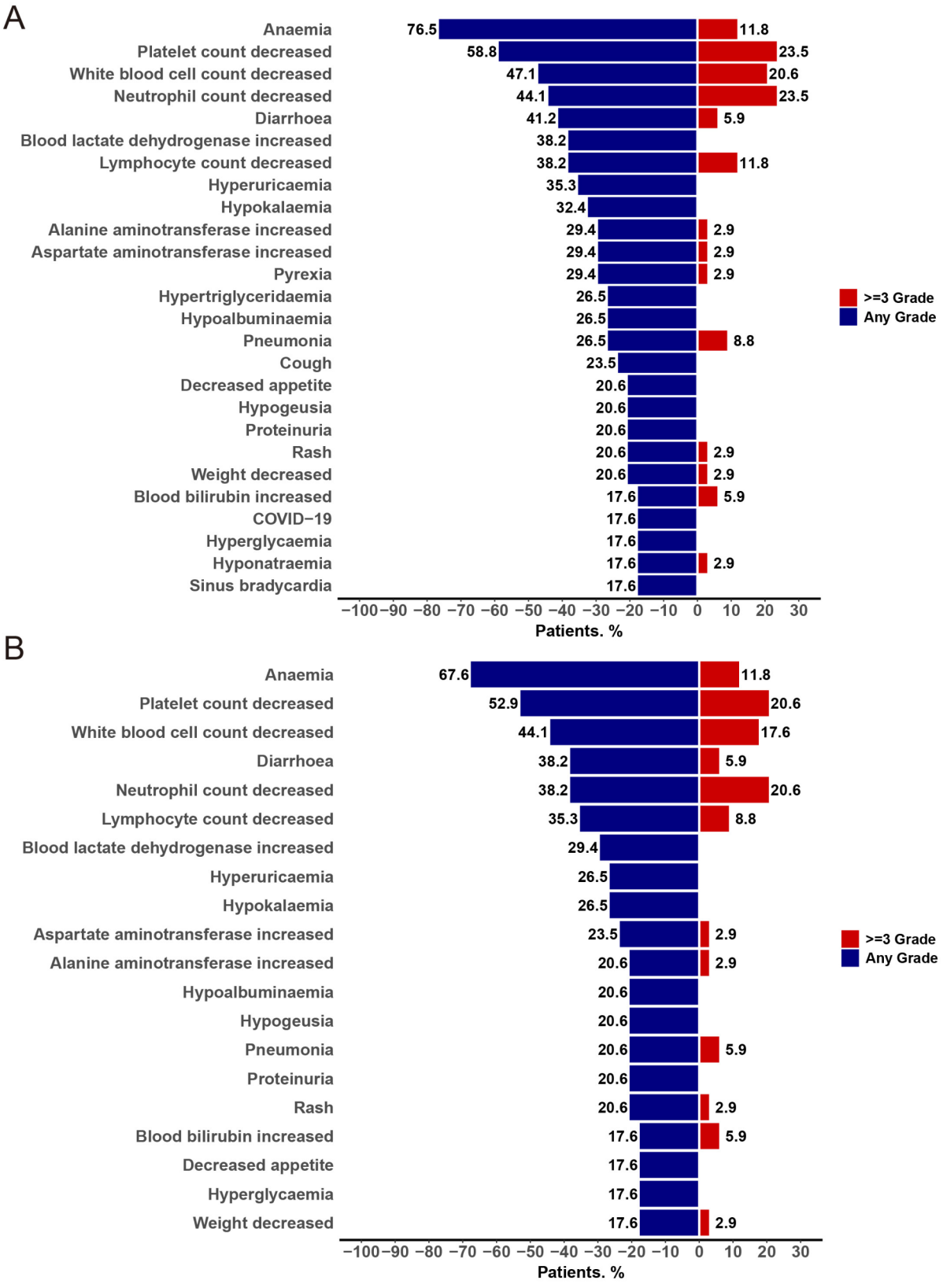

Fig. 1 Summary of adverse events in patients treated with HH2853. (**A**) Treatment-emergent adverse events (TEAEs); (**B**) Treatment-related adverse events (TRAEs). The bars represent the percentage of patients experiencing adverse events, with light blue indicating any grade and red representing grade ≥ 3 events

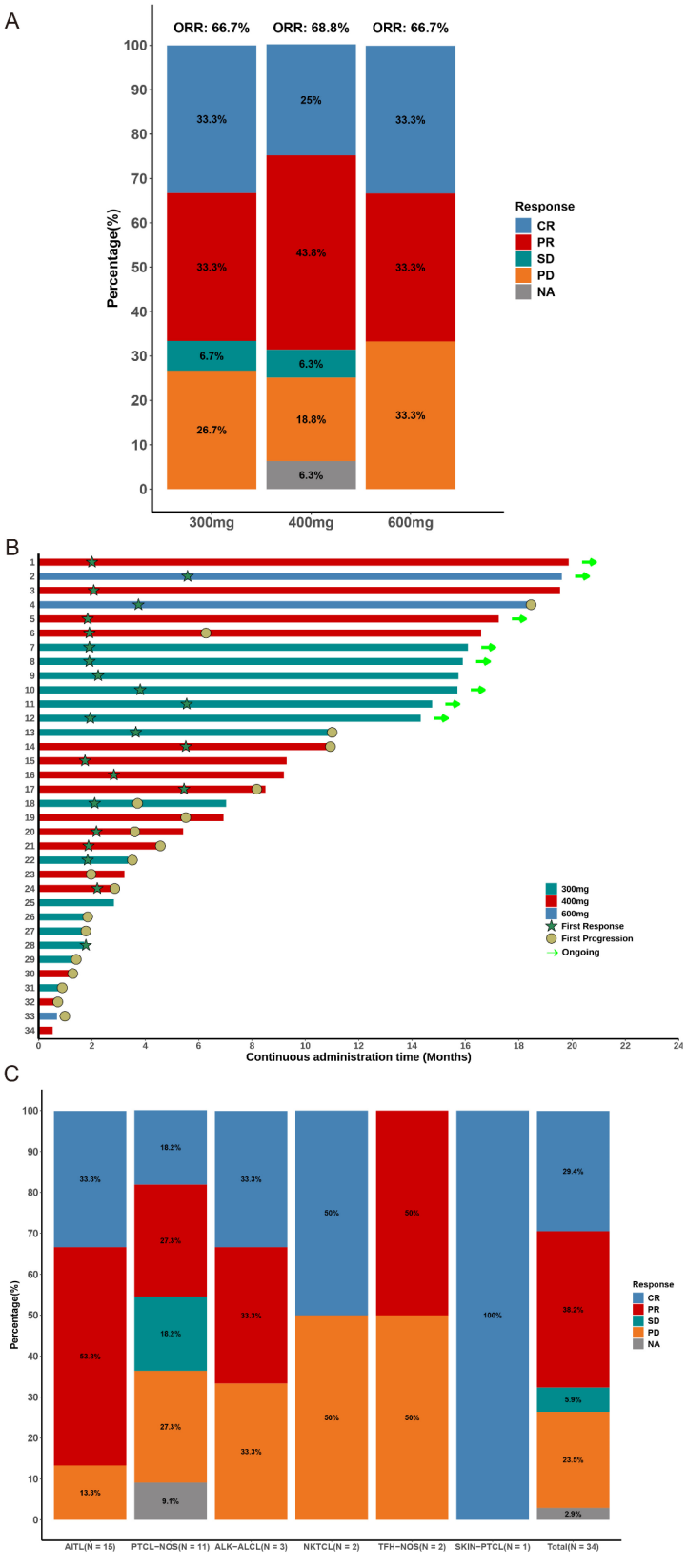

Fig. 2 Treatment response in patients treated with HH2853. (**A**) Best overall response by different dose levels in patients treated with HH2853. (**B**) Swimmer plot summarizing treatment duration and best response for patients on different doses of HH2853, with green arrows indicating ongoing patients. (**C**) Best overall response by pathological subtype in patients treated with HH2853

received systemic chemotherapy but no novel agents, HH2853 showed even greater efficacy, with an ORR of 76.9% (95% CI: 46.2–95.0), a CR rate of 38.5%, and a significantly longer mPFS of 18.5 months (95% CI: 3.6–NE). In a subgroup of 15 patients with the AITL pathological subtype, the treatment efficacy was notably greater than that in patients with other subtypes, with an ORR of 86.7% and a CR rate of 33.3% (Fig. 2C).

The estimated mDoR for the 23 responders was 14.8 months (95% CI: 2.8–not reached) (Fig. 3A). For the overall cohort of 34 patients, the estimated mPFS was 6.3 months (95% CI: 2.9–18.5) (Fig. 3B), while the mOS had not yet been reached (Fig. 3C).

Pharmacokinetics and pharmacodynamics

In this study, 34 R/R PTCL patients received multiple doses of HH2853 twice daily (300 mg, 400 mg, and 600 mg) under fasting conditions. Plasma PK samples at three dose levels were available for PK evaluation.

After multiple oral administrations, HH2853 was rapidly absorbed, with a median peak time (Tmax) of 2.0 h and no significant dose-dependent effect (Fig. 4A). HH2853 exposure levels (Cmax and AUC) exhibited high interindividual variation. Within the dose range of 300–600 mg, the exposure of HH2853 (Cmax and AUC) increased with an increasing dose and showed a certain absorption saturation trend. The exposure level of HH2853 resulted in mild accumulation at steady state: the mean accumulation ratios ranged from 0.6 to 2.1 and 1.2–2.7 for Cmax and AUC0-12 h, respectively.

Available samples from 30 PTCL patients were evaluated for pharmacodynamics following the oral administration of HH2853. Robust inhibition of H3K27me3 was observed in peripheral monocytes at different doses, which demonstrated HH2853 target (EZH1/2) engagement in PTCL patients (Fig. 4B).

Discussion

This study revealed the safe administration of HH2853 at doses of 300 mg, 400 mg and 600 mg twice daily in patients with r/r PTCL. The most frequently observed TEAEs predominantly involved hematological events, which was consistent with the safety profiles of other EZH1/2 inhibitors, such as valemetostat [21]. Most TEAEs were successfully addressed with supportive care and/or dose adjustments, underscoring the safe and well-tolerated profile of HH2853 in patients with r/r PTCL.

Patients with r/r PTCL have limited therapeutic options and bleak outcomes. Pralatrexate, an innovative antifolate, exhibited only a 29% ORR in patients with r/r PTCL [25]. The ORR for the PI3K inhibitor copanlisib in patients with relapsed/refractory PTCL was approximately 30% [26]. The JAK/STAT pathway is activated in various PTCL subtypes, but the response rate to the JAK1/2 inhibitor ruxolitinib in r/r PTCL remains limited to only 25% [27]. Similarly, HDAC inhibitors have produced ORRs between 25% and 46% [28–30]. In this context, the ORR of 67.6% achieved by patients receiving HH2853 is notably promising. This high response rate was consistent with findings for another selective EZH1/2 inhibitor, valemetostat, in other cases of relapsed or refractory hematologic malignancies [21, 22]. Notably, in r/r PTCL, HH2853 demonstrated an even higher ORR and CR rate, along with a longer median duration of response. Moreover, HH2853 exhibited lower rates of severe hematologic toxicity and treatment discontinuation due to adverse events, suggesting potential differences in both efficacy and tolerability that warrant further investigation. Furthermore, even in patients previously treated with novel antitumor agents, HH2853 exhibited considerable efficacy, yielding an ORR of 61.9% and a CR rate of 23.8%. These findings suggest that HH2853 may serve as a potential salvage therapy in patients who experience treatment failure after novel drugs are administered. For patients who had received only systemic chemotherapy, the ORR was 76.9%, and the mPFS reached 18.5 months, significantly outperforming currently approved single agents mentioned above for r/r PTCL. These results suggest that HH2853 may potentially delivering substantial clinical benefits to patients with earlier lines of r/r PTCL. On the basis of these promising results, we initiated a phase II study to further evaluate the efficacy and safety of HH2853 in patients who had received at least one prior line of combination chemotherapy, as well as treatment with at least one novel agent (such as chidamide, pralatrexate, or brentuximab vedotin).

The emergence of immune checkpoint inhibitors has transformed the treatment landscape for r/r NKTCL [31, 32]. However, the efficacy of anti-PD-1 or anti-PD-L1 antibodies in other PTCL subtypes has been less impressive [33]. Preclinical research indicates that combining EZH2 inhibition with anti-PD-1 therapy can alter the tumor microenvironment, enhancing the response to immunotherapy and generating synergistic antitumor effects [34]. Moreover, preclinical studies have shown that combining EZH2 inhibitors with HDAC inhibitors results in promising synergistic effects. Given the potent inhibition of EZH1/2 by HH2853, combining it with immunotargeted therapy may further enhance clinical outcomes in PTCL patients.

Interestingly, patients with AITL in this study had a higher ORR than those with the other subtypes did. This intriguing phenomenon was also observed in research involving the EZH2 inhibitor SHR2554 [35]. These findings suggest that sensitivity to EZH1/2 inhibitors may differ among PTCL subtypes and that a more precise molecular subtyping system may help identify patients most likely to benefit from these targeted therapies.

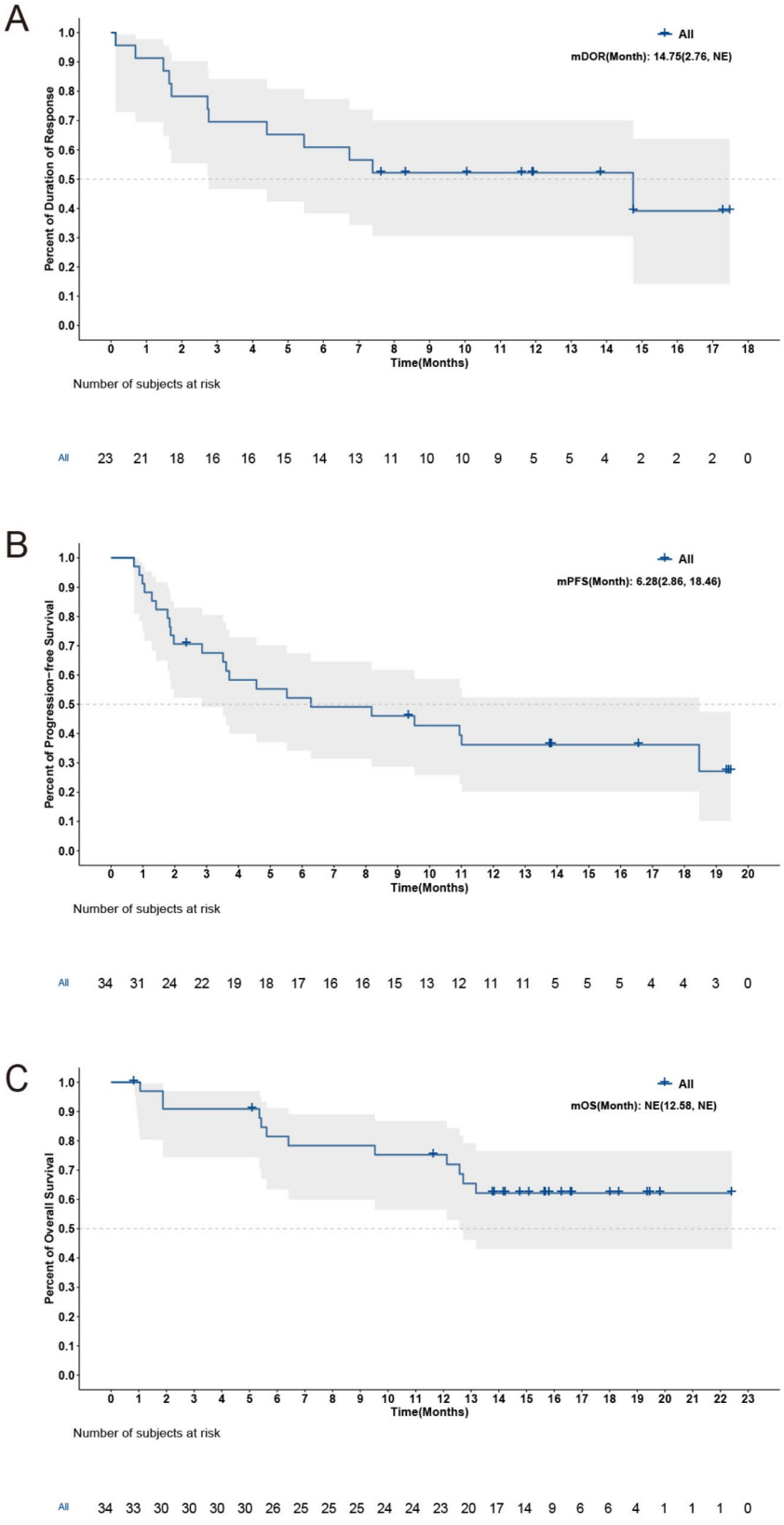

Fig. 3 Kaplan–Meier survival curves of patients treated with HH2853. (**A**) Duration of response (DoR) for the overall 23 responders; (**B**) Progression-free survival (PFS) for the overall 34 patients; (**C**) Overall survival (OS) for the overall 34 patients

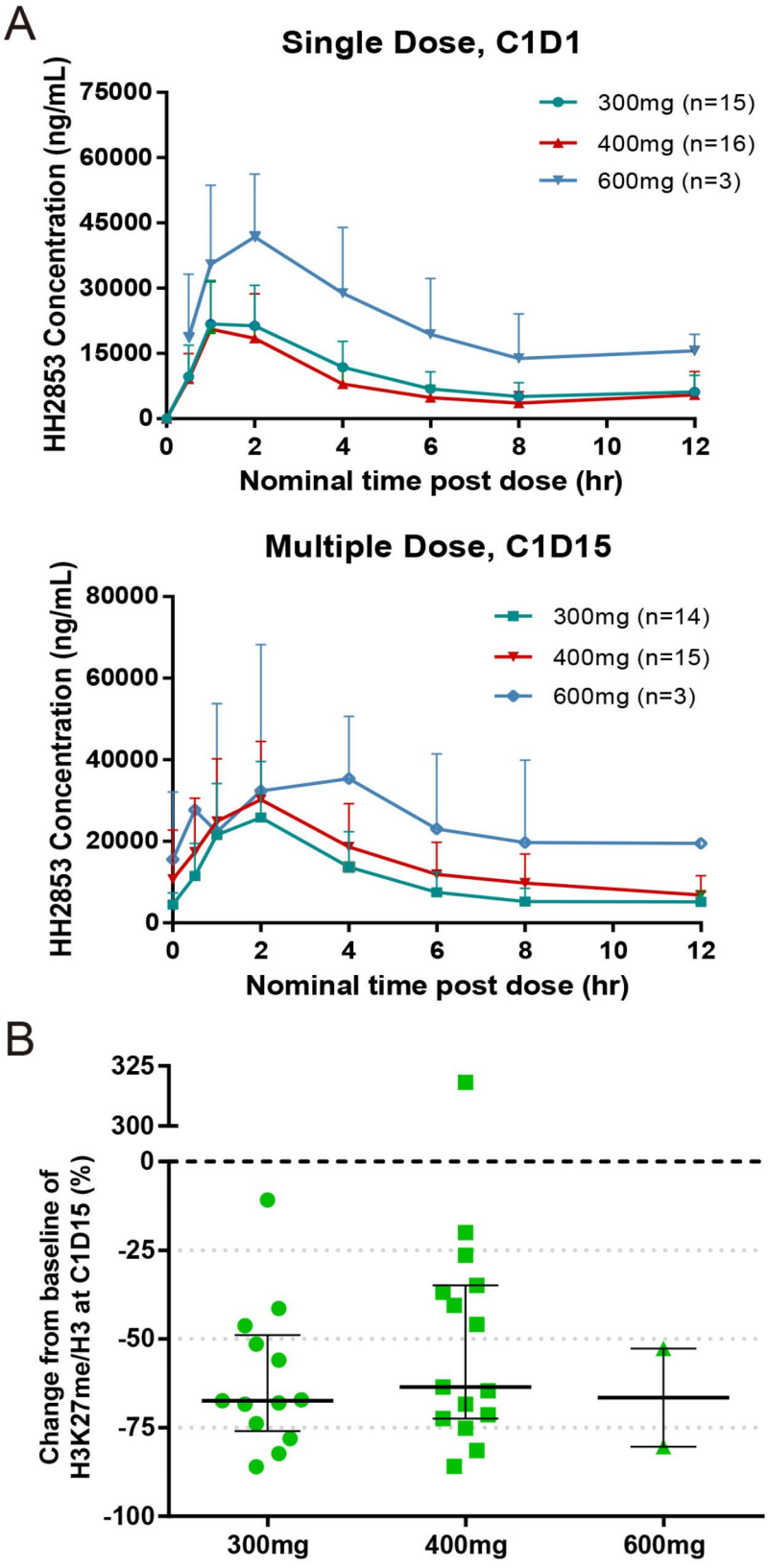

Fig. 4 HH2853 pharmacokinetics and pharmacodynamics. (**A**) Plasma concentration of HH2853 over time across various dose cohorts (300 mg, 400 mg, and 600 mg). (**B**) Percentage change from baseline of H3K27me3 in peripheral monocytes in PTCL patients. Observed data are represented by median with interquartile range

However, given the limited sample size in this study, additional research is necessary to confirm these findings.

There are several limitations in this study. First, the relatively short follow-up duration necessitates an extended observation to fully evaluate the long-term safety and efficacy of HH2853. Moreover, this investigation was limited by the characteristics typical of a phase I clinical trial, including the absence of randomization, the open-label design, and the lack of a control group. Furthermore, despite the sufficient sample size to meet the study's objectives, future studies should aim to include larger patient populations and assess the impact of HH2853 across various PTCL subgroups.

Conclusions

In summary, our findings indicate that HH2853 has a favorable safety profile and shows promise for promoting antitumor activity in individuals with r/r PTCL. These findings support further research into HH2853 as a potential treatment option for this challenging disease.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13045-025-01697-z.

Supplementary Material 1

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Author contributions
Conception and design: Tongyu Lin, Huangming Hong, Mingzhi Zhang. Provision of study materials or patients: Tongyu Lin, Huangming Hong, Mingzhi Zhang, Zhigang Peng, Jianzhen Shen, Yuerong Shuang, Hui Zhou, Hongqiang Guo, He Huang, Fei Li, Zhengzi Qian, Lihong Liu, Liang Wang, Wei Yang, Liling Zhang, Pengcheng He. Collection and assembly of data: Huangming Hong, Zegeng Chen, Mingzhi Zhang, Jianzhen Shen, Hui Zhou, Hongqiang Guo, Shen Qian, Fugen Li. Data analysis and interpretation: Tongyu Lin, Huangming Hong, Zegeng Chen, Zhigang Peng, Jianzhen Shen, Yuerong Shuang, Meng Li. Manuscript writing: All authors. Final approval of manuscript: All authors.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study protocols received approval from the ethics committees at each participation center. All patients provided written informed consent, and the study adhered to the principles outlined in the Declaration of Helsinki. This study has been registered with ClinicalTrials.gov under the identifier NCT04390737.

Competing interests
The authors declare no competing interests.

Clinical trial information
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