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RESEARCH

Cadonilimab, a PD-1/CTLA-4 bispecific antibody in unresectable hepatocellular carcinoma: a real-world study

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Abstract

Objective This study retrospectively evaluated the safety and efficacy of cadonilimab combined with tyrosine kinase inhibitors (TKI) for the treatment of unresectable hepatocellular carcinoma (uHCC).

Patients and methods Seventy-eight patients who received cadonilimab + TKI were included; 42 and 36 received it as first-line (1 L) and second-line and above (≥ 2 L) systemic treatment, respectively. Besides, ninety-five patients who received PD-1 inhibitor + TKI as first-line treatments were included. Safety was the primary endpoint; secondary endpoints were overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and disease control rate (DCR).

Results Treatment-related adverse events (TRAEs) of any grade occurred in 84.6% of the patients, with grade ≥ 3 in 20.5%. In patients with a Child-Pugh score of ≥ 8 (CP ≥ 8), any grade TRAEs occurred in 88.2%, and grade ≥ 3 in 20.6%. The overall cohort's median progression-free survival (mPFS) was 3.6 months, whereas the median overall survival (mOS) was 8.8 months. In the 1 L group, mPFS was 6.7 months versus 2.3 months in ≥ 2 L. In the 1 L group, mOS was 13.7 months versus 3.2 months in ≥ 2 L. For CP < 8, 1 L mPFS was 7.6 months, mOS not reached; CP ≥ 8 had mPFS of 5.2 months, mOS of 5.6 months. For CP < 8 in ≥ 2 L, mPFS was 3.1 months, mOS 8.8 months; CP ≥ 8 had mPFS of 1.4 months, mOS of 2.2 months. After propensity score matching (PSM), the incidence of TRAEs of any grade was 77.1%, with grade ≥ 3 accounting for 17.1% in the PD-1 group. In the PD-1/CTLA-4 group, the incidence of TRAEs of any grade was 80.0%, and that of grade ≥ 3 TRAEs was 17.1%. The mPFS was 6.7 months in the PD-1/CTLA-4 group versus 3.3 months in the PD-1 group. The mOS was 13.7 months in the PD-1/CTLA-4 group versus 6.7 months in the PD-1 group.

Conclusion Cadonilimab + TKI showed a favorable trend in safety and efficacy, especially when applied as first-line systemic therapy for uHCC. This study offers a clinical reference for its use in systemic uHCC therapy, particularly in patients with advanced liver dysfunction.

Keywords Unresectable hepatocellular carcinoma · Cadonilimab · Bispecific antibody · Real-world data

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Introduction

Liver cancer is one of the most common malignant tumors worldwide, ranking sixth in incidence and third in cancer-related mortality [1]. Primary liver cancer includes various pathological types, such as hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC), and mixed types of HCC and ICC, with HCC accounting for approximately 90% of all primary liver cancers [2]. Key risk factors for HCC include hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, long-term alcohol consumption, and non-alcoholic steatohepatitis (NASH) associated with diabetes or obesity. In China, chronic HBV infection remains the leading cause of HCC [3, 4]. Treatment options for HCC include liver resection, transplantation, and local ablation for early-stage liver cancer; transarterial chemoembolization (TACE) for intermediate stages; and systemic therapy for advanced stages [5]. However, HCC often has an insidious onset, and 70% of patients present at advanced stages, precluding curative or localized treatments.

Since the introduction of Sorafenib in 2007 [6], targeted therapies including lenvatinib, regorafenib, cabozantinib, and ramucirumab for advanced HCC have emerged as first-line and subsequent treatments [7–10]. Immune checkpoint inhibitors (ICIs) further revolutionized systemic therapy for advanced liver cancer. However, the tumor microenvironment (TME) of liver cancer is usually more complex [11]. To break through the bottleneck of tumor drug resistance, various combination regimens, including targeted - immune combination therapy and targeted - immune combination with local therapy, have been widely applied in the treatment of unresectable hepatocellular carcinoma (uHCC) [12–14]. Meanwhile, an increasing number of investigational studies focusing on predictive biomarkers for assessing immunotherapeutic efficacy have been progressively reported [15–18]. Programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) are common immune checkpoints; however, their monotherapy shows only a 15–20% objective response rate in HCC [19, 20]. Multi-target combinations, such as nivolumab with ipilimumab or durvalumab with ramucirumab, demonstrate superior efficacy but increase adverse events [21–23], hindering their clinical application. Given the limitations of both single- and dual-agent therapies, the use of PD-1/CTLA-4 bispecific antibodies is expected to be an effective strategy for treating advanced liver cancer.

Cadonilimab, developed by Akesobio, is a humanized bispecific antibody that simultaneously targets PD-1 and CTLA-4. Its IgG1 backbone exhibits a more stable structural profile and modifications to the Fc region effectively eliminate its effector functions, suggesting improved safety for clinical treatment. Additionally, cadonilimab selectively binds to tumor-infiltrating lymphocytes more effectively than to peripheral lymphocytes and inhibits CTLA-4 binding in the peripheral blood and normal tissues, reducing off-target effects and further enhancing its efficacy and safety [24].

Multiple clinical trials of cadonilimab for the treatment of intermediate-to-advanced HCC have been successfully conducted, all of which have shown encouraging results [25, 26]. However, most of the studied populations included patients with relatively good liver function who were selected based on strict inclusion and exclusion criteria, and the available data have primarily focused on its efficacy and safety as a first-line systemic therapy. In this study, we aimed to comprehensively evaluate the safety and efficacy of cadonilimab for the treatment of uHCC in a real-world setting.

Patients and methods

Patients

This retrospective study included patients with uHCC treated with cadonilimab at the Fifth Medical Center of the PLA General Hospital between September 2022 and October 2024. cadonilimab was administered at 6 mg/kg once every 2 weeks. This study was approved by the Ethics Committee of the Fifth Medical Center of the PLA General Hospital and conducted in accordance with the Declaration of Helsinki (KY-2024-10-153-1). As this was a retrospective study, the requirement for informed consent was waived.

The inclusion criteria for this study were: ① a confirmed diagnosis of uHCC; ② received at least one cycle of cadonilimab; ③ presence of at least one measurable lesion in the liver. The exclusion criteria for this study were: ① uncollectable or incomplete clinical information; ② inability to undergo enhanced CT or MRI scans of the liver; ③ severe or uncontrolled progressive chronic diseases; ④ history of progressive neurological disorders or mental illness; ⑤ pregnant, breastfeeding, or planning pregnancy within 6 months.

Endpoints and assessment

The primary endpoint was safety. Secondary endpoints included progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and disease control rate (DCR). OS was measured from the initiation of treatment to death. PFS was defined as the time from treatment initiation to disease progression or death from any cause, whichever occurred first. ORR was defined as the proportion of patients with partial response (PR) or complete response (CR). DCR

was defined as the proportion of patients achieving PR, CR, or stable disease (SD). Safety was assessed according to version 5.0 of the Common Terminology Criteria for Adverse Events (CTCAE) [27]. The response was evaluated based on the RECIST guidelines (version 1.1) for HCC.

Statistical analyses

Descriptive statistics were used to summarize the baseline data and treatment-related adverse events (TRAEs). Continuous variables were presented as mean ± standard deviation (normally distributed data) or median and interquartile range (non-normally distributed data). Independent samples *t*-test was used for data with normal distribution, while Mann-Whitney U test was applied to data with non-normal distribution to compare characteristics among groups. Categorical variables were expressed as frequencies and percentages, with comparisons between groups using the chi-square or Fisher's exact test. To minimize selection bias and potential confounders, propensity score matching (PSM) analysis was employed. Survival analysis was performed using the Kaplan–Meier method and log-rank tests. The impact of survival prognostic factors was analyzed using univariate and multivariate Cox regression models. Statistical significance was set at $P < 0.05$. Statistical analyses were conducted using IBM SPSS 26.0, GraphPad Prism 9.0, and R 4.4.0.

Results

Patient characteristics

A total of 78 patients received cadonilimab treatment (Fig. 1). Table 1 summarizes the patients' demographic and clinical information. Among the patients, 42 cases (53.8%) received cadonilimab combined with tyrosine kinase inhibitors (TKI) as first-line (1 L) systemic therapy, while 36 cases (46.2%) received it as second-line and above (≥ 2 L) systemic treatment and no significant differences were observed in baseline characteristics between the two groups. The mean age at the start of treatment was 57.2 ± 11.1 years. There were 71 males (91.0%) and 7 females (9.0%). Hepatitis B virus infection was present in 78.2% of the patients. The majority of patients were in advanced stages, with 63 patients (80.8%) in stage C by Barcelona Clinic Liver Cancer criteria (BCLC) and 9 patients (11.5%) in stage D. Alpha-fetoprotein (AFP) levels were equal to or greater than 400 μg/L in 41 patients (52.6%). Among the patients, 22 patients (28.2%) received local therapy. The average maximum tumor diameter was 9.5 ± 5.0 cm. The liver function of the patients in the overall cohort was generally poor: 46 patients (59.0%) were Child-Pugh grade B, and 9 (11.5%) were grade C. 34 (43.6%) had a Child-Pugh score of ≥ 8. The modified albumin-bilirubin (mALBI) grade was predominantly 2b (44.9%) or 3 (29.5%). The score of the model for end-stage liver disease (MELD) was 11.2 ± 5.2. The total bilirubin (TBIL), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels were elevated.

Safety

Among the 78 patients, TRAEs of any grade occurred in 66 patients (84.6%); grade ≥ 3 occurred in 16 patients (20.5%) (Table 2). Common TRAEs of any grade included fever in 25 patients (32.1%), elevated aspartate aminotransferase levels in 18 patients (23.1%), elevated bilirubin levels in 17 patients (21.8%), decreased platelet count in 15 patients (19.2%), increased thyroid-stimulating hormone levels in 14 patients (17.9%), hypoalbuminemia in 10 patients (12.8%), anemia in 8 patients (10.3%), rash in 7 patients (9.0%).

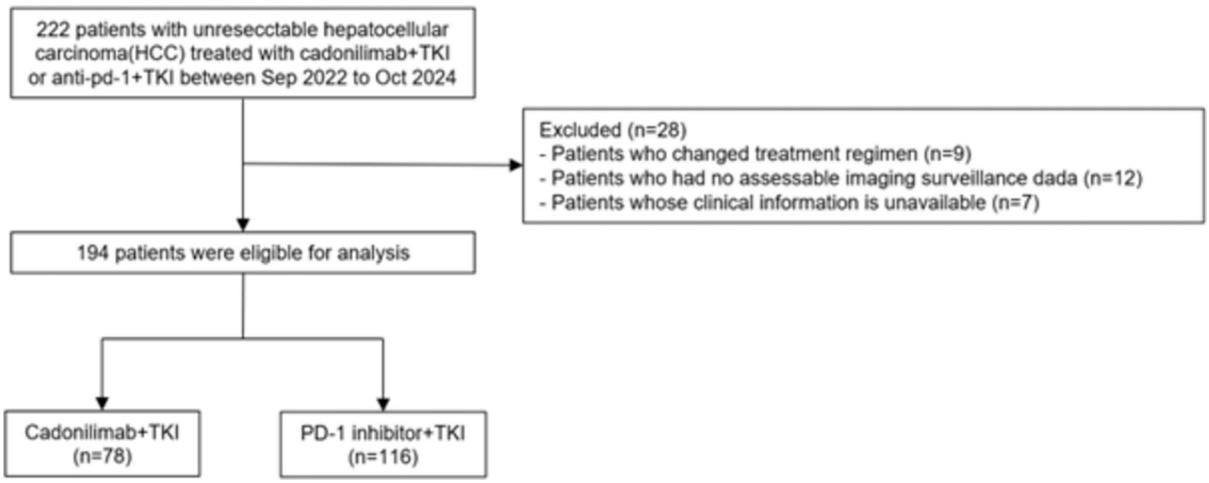

Fig. 1 Flowchart for patient screening

Table 1 Baseline demographics and clinical characteristics of the cadonilimab cohort

Characteristics	Overall (n = 78)	1 L (n = 42)	≥2 L (n = 36)	*P*
Age, year	57.2 ± 11.1	58.9 ± 11.29	55.31 ± 10.76	0.156
Sex				
Male	71 (91.0%)	38 (90.5%)	33 (91.7%)	
Female	7 (9.0%)	4 (9.5%)	3 (8.3%)	
Basics of hepatitis				0.381
Viral hepatitis B	61 (78.2%)	31 (73.8%)	30 (83.3%)	
Viral hepatitis C	3 (3.8%)	3 (7.1%)	0 (0.0%)	
Alcoholic hepatitis	6 (7.7%)	3 (7.1%)	3 (8.3%)	
Other	8 (10.3%)	5 (11.9)	3 (8.3%)	
BCLC stage				0.977
B	6 (7.7%)	3 (7.1%)	3 (8.3%)	
C	63 (80.8%)	34 (81.0%)	29 (80.6%)	
D	9 (11.5%)	5 (11.9%)	4 (11.1%)	
mALBI				0.938
1	7 (9.0%)	4 (9.5%)	3 (8.3%)	
2a	13 (16.7%)	6 (14.3%)	7 (19.4%)	
2b	35 (44.9%)	19 (45.2%)	16 (44.4%)	
3	23 (29.5%)	13 (31.0%)	10 (27.8%)	
Child-Pugh stage				0.938
A	23 (29.5%)	13 (31.0%)	10 (27.8%)	
B	46 (59.0%)	24 (57.1%)	22 (61.1%)	
C	9 (11.5%)	5 (11.9%)	4 (11.1%)	
Child-Pugh score				0.349
5	6 (7.7%)	1 (2.4%)	5 (13.9%)	
6	17 (21.8%)	12 (28.6%)	5 (13.9%)	
7	21 (26.9%)	10 (23.8%)	11 (30.6%)	
8	8 (10.3%)	4 (9.5%)	4 (11.1%)	
9	17 (21.8%)	10 (23.8%)	7 (19.4%)	
10	6 (7.7%)	4 (9.5%)	2 (5.6%)	
11	3 (3.8%)	1 (2.4%)	2 (5.6%)	
MELD	11.2 ± 5.2	11.2 ± 4.8	11.2 ± 5.7	0.973
AFP, μg/L				0.517
< 400	37 (47.4%)	18 (42.9%)	19 (52.8%)	
≥ 400	41 (52.6%)	24 (57.1%)	17 (47.2%)	
Combined locoregional therapy				0.065
No	56 (71.8%)	26 (61.9%)	30 (83.3%)	
Yes	22 (28.2%)	16 (38.1%)	6 (16.7%)	
Extrahepatic metastasis				0.985
No	25 (32.1%)	14 (33.3%)	11 (30.6%)	
Yes	53 (67.9%)	28 (66.7%)	25 (69.4%)	
Tumor diameter, cm	9.5 ± 5.0	10.0 ± 4.6	9.0 ± 5.4	0.353
TBIL, μmol/L	30.2 (17.1, 72.9)	30.55 (19.8, 66.1)	26.65 (13.6, 74.0)	0.780
ALT, U/L	39.5 (24.8, 66.5)	43.5 (30.3, 67.5)	33 (19.0, 61.3)	0.644
AST, U/L	76.0 (42.0, 117.5)	85.5 (46.0, 113.8)	68 (35.8, 115.3)	0.955

BCLC: barcelona clinic liver cancer; mALBI: modified albumin-bilirubin; MELD: model for end-stage liver disease; AFP: alpha fetoprotein; TKI: tyrosine kinase inhibitor; TBIL: total bilirubin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; 1 L: first-line; ≥ 2 L: second-line and above

Common grade ≥ 3 TRAEs included decreased platelet count in 4 patients (5.1%), elevated bilirubin levels in 4 patients (5.1%), rash in 2 patients (2.6%), and anemia in 2 patients (2.9%) (Supplementary Table 1). No fatal TRAEs were reported. We also analyzed the occurrence of TRAEs in patients with a Child-Pugh score of ≥ 8 (CP ≥ 8). Among

Table 2 Summary of TRAEs in the cadonilimab cohort

	Total (n = 78) no. (%)	CP ≥ 8 (n = 34) no. (%)	*P*
Any	66 (84.6%)	30 (88.2%)	0.609
Grade ≥ 3	16 (20.5%)	7 (20.6%)	0.993

TRAEs: treatment-related adverse events; CP ≥ 8: Child-Pugh score of ≥ 8

the 34 patients, TRAEs of any grade were observed in 30 patients (88.2%), with grade ≥ 3 TRAEs occurring in 7 patients (20.6%) (Table 2).

Efficacy

Among the 78 patients, the median progression-free survival (mPFS) was 3.6 months (95% CI: 1.7, 5.5) with 55 endpoint events (Fig. 2a), while the median overall survival (mOS) was 8.8 months (95% CI: 2.5, 15.1) with 41 endpoint events (Fig. 2b). In the 1 L treatment group, 24 PFS events and 17 OS events were observed, whereas in the ≥ 2 L treatment group, 31 PFS and 24 OS events were recorded. The mPFS was 6.7 months (95% CI: 4.6, 8.8) in the 1 L treatment group and 2.3 months (95% CI: 1.5, 2.9) in the ≥ 2 L treatment group (Fig. 2c). The mOS was 13.7 months (95% CI: 6.1, 21.3) in the 1 L treatment group and 3.2 months (95% CI: 1.8, 4.6) in the ≥ 2 L treatment group (Fig. 2d).

Of the 78 enrolled patients, 32 were evaluated for efficacy. Among the 32 patients, no patient achieved a CR, 4 patients (12.5%) achieved a PR, 19 patients (59.4%) had SD, and 9 patients (28.1%) experienced PD. The ORR was 12.5%, and the DCR was 71.9%. Of the 32 evaluable patients, 21 received 1 L of treatment. In this group, none of the patients achieved CR, 4 (19.0%) achieved PR, 14 (66.7%) had SD, and 3 (14.3%) experienced PD. The ORR was 19.0% and the DCR was 85.7%, respectively. In the 11 patients who received ≥ 2 L treatment, no patients achieved CR or PR, 5 patients (45.5%) had SD, and 6 patients (54.5%) experienced PD. The DCR rate in this group was 45.5% (Supplementary Table 2).

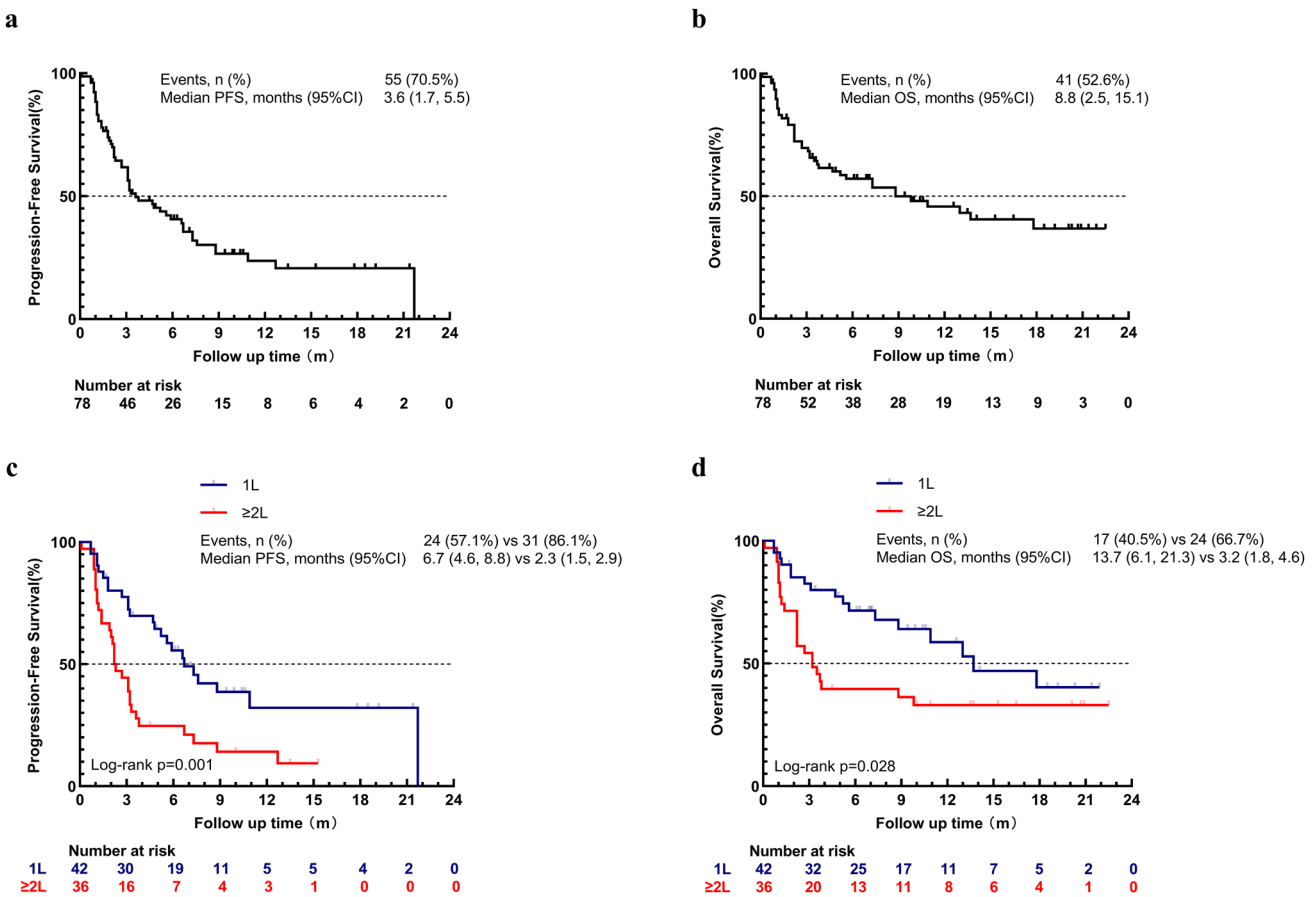

Fig. 2 Kaplan–Meier survival curves of the the cadonilimab cohort. **a** PFS of the overall cohort. **b** OS of the overall cohort. **c** PFS by lines of therapy (1 L vs ≥ 2 L). **d** OS by lines of therapy (1 L vs ≥ 2 L)

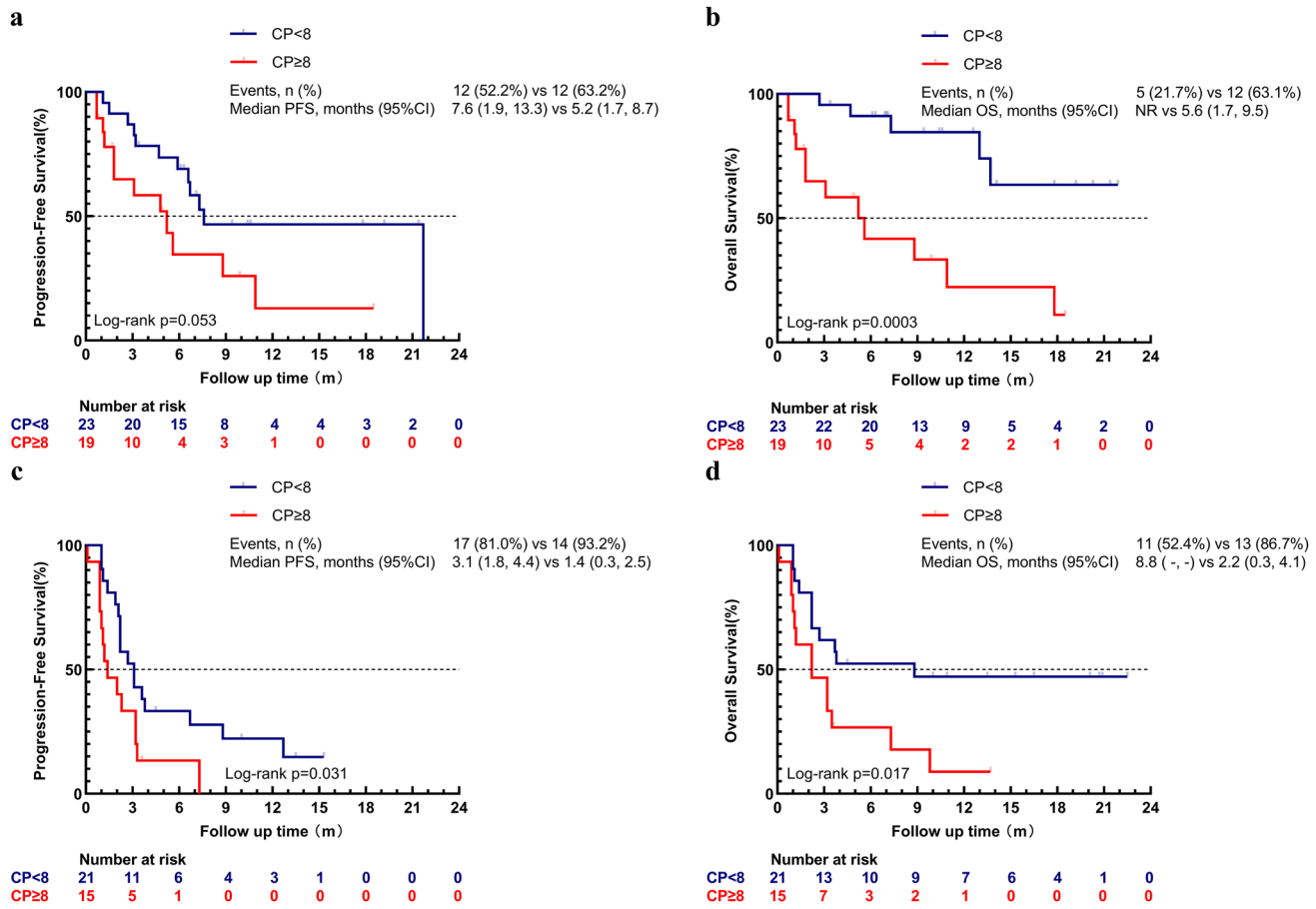

Fig. 3 Kaplan–Meier survival curves of the the cadonilimab cohort. **a** PFS by Child-Pugh liver status (CP < 8 vs CP ≥ 8) in 1 L cohort. **b** OS by Child-Pugh liver status (CP < 8 vs CP ≥ 8) in 1 L cohort. **c** PFS by Child-Pugh liver status (CP < 8 vs CP ≥ 8) in ≥ 2 L cohort. **d** OS by Child-Pugh liver status (CP < 8 vs CP ≥ 8) in ≥ 2 L cohort

OS and PFS in patients with CP < 8 vs CP ≥ 8

In the 1 L treatment group, 23 patients were CP < 8, and 19 patients were CP ≥ 8. The mPFS for patients with CP < 8 in this group was 7.6 months (95% CI: 1.9–13.3) (Fig. 3a), while the mOS was not reached (Fig. 3b). The mPFS for patients with CP ≥ 8 was 5.2 months (95% CI: 1.7–8.7) (Fig. 3a), and the mOS was 5.6 months (95% CI: 1.7–9.5) (Fig. 3b).

In the ≥ 2 L treatment group, 21 patients were CP < 8, and 15 patients were CP ≥ 8. The mPFS for patients with CP < 8 in this group was 3.1 months (95% CI: 1.8–4.4) (Fig. 3c), and the mOS was 8.8 months (95% CI: -, -) (Fig. 3d). The mPFS for patients with CP ≥ 8 was 1.4 months (95% CI: 0.3–2.5) (Fig. 3c), and the mOS was 2.2 months (95% CI: 0.3–4.1) (Fig. 3d).

Independent prognostic factors for PFS and OS

Cox univariate and multivariate analyses were performed, and the results showed that ≥ 2 L treatment and CP ≥ 8 were associated with poorer PFS and OS (Supplementary Table 3).

Comparison of safety and efficacy between Cadonilimab + TKI and PD-1 inhibitor + TKI

To compare the safety and efficacy of cadonilimab with other ICIs, we screened 95 contemporaneous patients who received PD - 1 inhibitor + TKI as first-line systemic therapy from 116 patients as comparators (PD-1 group). Compared to the PD-1 group, patients treated with cadonilimab + TKI as first-line systemic therapy (PD/CTLA-4

Table 3 Summary of TRAEs in the PD-1 group and the PD-1/CTLA-4 group

	PD-1 (n = 35) no. (%)	PD-1/CTLA-4 (n = 35) no. (%)	*P*
Any	27 (77.1%)	28 (80.0%)	0.569
Grade ≥ 3	6 (17.1%)	6 (17.1%)	1.000

TRAEs: treatment-related adverse events

group) had a higher proportion of individuals with AFP ≥ 400 μg/L and extrahepatic metastases. After PSM, there were no significant differences in the baseline characteristics between the two groups (Supplementary Table 4).

In the PD-1 group, TRAEs of any grade were observed in 27 patients (77.1%), with grade ≥ 3 in 6 patients (17.1%). In the PD-1/CTLA-4 group, TRAEs of any grade were observed in 28 patients (80.0%), with grade ≥ 3 in 6 patients (17.1%). There were no statistically significant differences between the two groups (Table 3). Common TRAEs of any grade in the PD-1 group included increased thyroid-stimulating hormone levels in 14 patients (25.7%), elevated bilirubin levels in 8 patients (22.9%), elevated aspartate aminotransferase levels in 8 patients (22.9%) (Supplementary Table 5).

In the PD-1 group and the PD-1/CTLA-4 group, 26 and 22 PFS endpoint events were observed respectively, and 23 and 16 OS endpoint events were observed. The mPFS in the PD-1 group was 3.3 months (95% CI: 2.5, 4.1), while that in the PD-1/CTLA-4 group was 6.7 months (95% CI: 4.0, 9.4) (Fig. 4a). The mOS in the PD-1 group was 6.7 months (95% CI: 2.2, 11.2), and in the PD-1/CTLA-4 group was 13.7 months (95% CI: 5.8, 21.6) (Fig. 4b). There were no statistically significant differences between the two groups.

Discussion

This was the first real-world investigation to administer 6 mg/kg cadonilimab fortnightly for the treatment of uHCC, and was the first to compare the safety and efficacy of cadonilimab + TKI and PD-1 inhibitor + TKI in the first-line systemic application for uHCC. It also includes relevant data on second-line therapy and patients with CP ≥ 8 in the cadonilimab cohort. The findings demonstrated that cadonilimab exhibited favorable trend in safety and efficacy, especially when applied as first-line systemic therapy for uHCC.

In this study, most TRAEs were grade 1 or 2, and no fatal adverse were observed. The majority of adverse events were transient and resolved or improved following symptomatic treatment. The overall incidence of any grade TRAEs was 84.6%, while that of grade ≥ 3 TRAEs was 20.5%. Even in patients with poor liver function (CP ≥ 8), the incidence of any grade TRAEs was 88.2%, and the incidence of grade ≥ 3 TRAEs was 20.6%, aligning closely with the overall cohort. Comparatively, in the low-dose group (6 mg/kg Q2W intravenous injection) of a phase Ib/II clinical trial (COMPASSION-08) investigating the combination of cadonilimab and lenvatinib as first-line treatment for uHCC, the incidence of TRAEs of any grade was 100%, whereas the incidence of grade ≥ 3 TRAEs was 67.7%. Our study indicated combining cadonilimab with TKI did not increase toxicity in clinical practice, irrespective of liver function status.

In the CheckMate 9DW trial, the combination of the PD-1 inhibitor nivolumab and the CTLA-4 inhibitor ipilimumab as a first-line treatment for uHCC achieved a mPFS of 9.1 months and an ORR of 36%, with grade 3 or 4 TRAEs in 41% of patients [28]. The STRIDE cohort of the phase III HIMALAYA study combined the CTLA-4 inhibitor, tremelimumab, with the PD-L1 inhibitor, durvalumab. Although reducing the dosage of CTLA-4

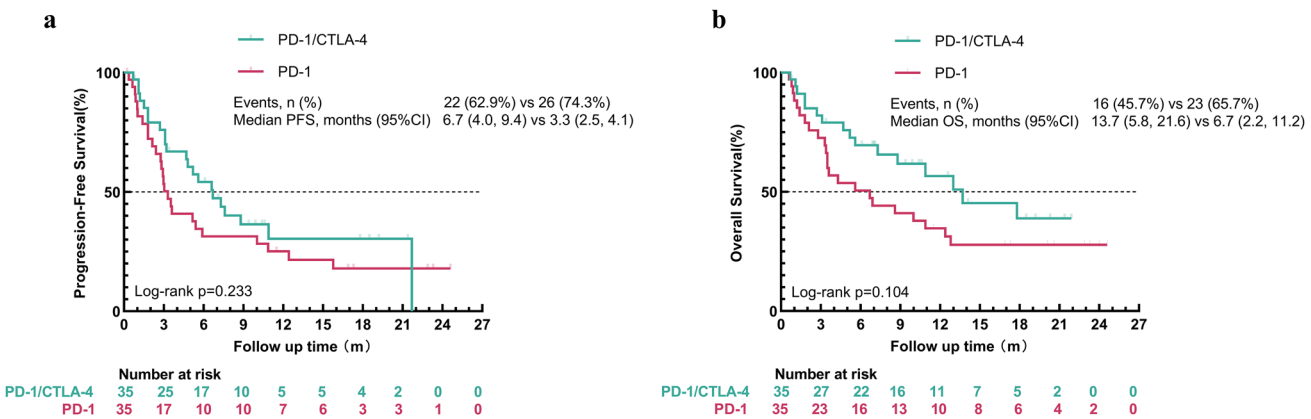

Fig. 4 Kaplan–Meier survival curves between the PD-1 Group and the PD-1/CTLA-4 Group. **a** Kaplan–Meier survival curves of PFS. **b** Kaplan–Meier survival curves of OS

inhibitor decreased grade 3/4 TRAEs to 25.8%, this came at the cost of efficacy, with an mPFS of 3.8 months [29]. Our findings demonstrate that cadonilimab combined with TKI, as a first-line treatment, achieved an mPFS of 6.7 months surpassing the mPFS of the STRIDE cohort of the HIMALAYA study. Survival outcomes were analyzed based on different liver function statuses according to the Child-Pugh score. Among 1 L treatment patients, those with CP ≥ 8 had an mPFS of 5.2 months and a mOS of 5.6 months. In another study involving the combination of atezolizumab and bevacizumab as a first-line treatment for uHCC, patients with CP ≥ 8 demonstrated an mPFS of 2.7 months and an mOS of 4.7 months [30].

It can be inferred that cadonilimab combined with TKI shows a favorable trend in efficacy as the first-line treatment of uHCC. In addition to targeting two immune checkpoints simultaneously, cadonilimab's tetravalent structural design enhances its binding affinity within TME where PD-1 and CTLA-4 antigens are highly co-expressed, allowing it to preferentially accumulate in the TME rather than in normal peripheral tissues. Furthermore, cadonilimab is designed with an Fc null backbone, eliminating Fc-mediated effector functions that could damage PD-1-expressing T-cells and reducing the production of pro-inflammatory cytokines, such as IL-6 and IL-8. These characteristics may contribute to the improved efficacy and reduced toxicity of cadonilimab [24]. However, the observed advantages in efficacy were not significant and fell short of those reported in the CheckMate 9DW and COMPASSION-08 studies. Several factors may have accounted for this discrepancy. First, in the COMPASSION-08 study [25], 64.4% of the enrolled patients were at stage C of the BCLC staging system, whereas 80.8% of the patients in our study were at stage C, with an additional 11.5% at the terminal stage. The more advanced tumor stage in our cohort likely contributed to faster disease progression and shorter survival. Moreover, most published studies predominantly included patients with Child-Pugh grade A liver function, whereas our cohort predominantly consisted of grade B patients, with nearly half of the patients with CP ≥ 8. As shown in the univariate and multivariate Cox analyses, differences in liver function significantly affected prognosis. In view of this situation, we collected 95 contemporaneous patients who received PD-1 inhibitor + TKI as first-line systemic therapy as comparators. To minimize selection bias and potential confounders, PSM analysis was employed. After PSM, there was no significant difference in the incidence of TRAEs between the PD-1 group and the PD-1/CTLA-4 group. The mPFS of the PD-1 group and the PD-1/CTLA-4 group was 3.3 months and 6.7 months respectively, and the mOS was 6.7 months and 13.7 months respectively. Although there were no statistically significant differences in both mPFS and mOS between the two groups, we could still observe a trend that the survival of patients in the PD-1/CTLA-4 group was better than that in the PD-1 group.

Overall, the core potential of this study lies in providing a new perspective for the immunotherapy of advanced liver cancer. Firstly, the structural advantages of this novel PD-1/CTLA-4 bispecific antibody and the favorable efficacy trend of its combination with TKI suggest that bispecific ICIs are expected to replace traditional single-target antibodies as a new option for uHCC immunotherapy. Additionally, this study fills the data gap for Child-Pugh B/C patients. Such patients account for 30–40% of the real-world liver cancer population but are often excluded from clinical trials. However, the research on bispecific antibodies in the treatment of liver cancer is still in its infancy. We anticipate that in the next five years, more optimized combination regimens of bispecific antibodies with different targeted drugs and local therapies, as well as more scientific regimen selection for different patient populations, will emerge. Moreover, with the continuous development of antibody engineering technology, we believe that more bispecific or even multispecific antibodies targeting other antigens will be developed and widely applied.

While this study provides a relatively comprehensive presentation of real-world data on the clinical use of cadonilimab combined with TKI for uHCC, it has some limitations. First, survival data and adverse event data were extracted from the Electronic Medical Record system and online follow-up, which may introduce potential human errors in data accuracy. However, as less than 10% of patients were lost to follow-up in OS and PFS analyses, the risk of bias was minimal. Additionally, to ensure comprehensive and accurate reporting of all TRAEs, clinical indicators during patient follow-up were recorded and evaluated collaboratively by investigators and department physicians through multidisciplinary discussions. Second, the small sample size constrained more in-depth stratified analyses. Specifically, patients who died within three months or did not undergo follow-up assessments at our institution were excluded from ORR and DCR calculations, resulting in a limited number of cases available for 3-month efficacy evaluation. To address this limitation, future studies will focus on extending the patient cohort to improve the reliability of outcomes. Finally, this study is retrospective, selection bias is inevitable. We have attempted to minimize this limitation through comparing baseline information between groups and PSM analysis. However, prospective studies targeting specific populations or subgroups remain indispensable.

Conclusions

Through the stratified analysis of the cadonilimab cohort and the comparison with the PD-1 inhibitor cohort, the results showed that the combination of cadonilimab with TKI for the treatment of uHCC has a favorable safety profile,

with no increase in toxicity, even in patients with CP ≥ 8. Additionally, its application as first-line systemic therapy for uHCC demonstrated a favorable trend in terms of efficacy. In summary, this study provides data to support the clinical application of this innovative bispecific antibody in uHCC, offering additional therapeutic options for patients with uHCC, particularly those in advanced stages and those with impaired liver function.

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Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare no competing interests.

Ethics approval This study was approved by the Ethics Committee of the Fifth Medical Center of the PLA General Hospital and was conducted in accordance with the Declaration of Helsinki (KY-2024-10-153-1) on October 12, 2024.

Consent to participate As this was a retrospective study, the requirement for informed consent was waived.

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