# ORIGINAL RESEARCH Effectiveness and Safety of the PD-I Inhibitor Lenvatinib Plus Radiotherapy in Patients with HCC with Main PVTT: Real-World Data from a Tertiary Centre

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Background: Patients with hepatocellular carcinoma (HCC) with portal vein tumour thrombus (PVTT), especially type Vp-4, usually have a poor prognosis. However, the vast majority of Phase III clinical trials exclude this population based on the inclusion criteria. Lenvatinib plus a PD-1 inhibitor has shown promising antitumour activity and tolerable safety in patients with unresectable HCC in Asian populations. Radiotherapy has also demonstrated high response rates and favourable survival for HCC patients with PVTT. This study aimed to explore the preliminary clinical efficacy and safety of lenvatinib plus the PD-1 inhibitor combined with radiotherapy for HCC patients with main portal vein tumour thrombus.

Methods: Between 1 March 2018 and 31 October 2020, HCC patients with main PVTT who received lenvatinib plus a PD-1 inhibitor (pembrolizumab, nivolumab or sintilimab) combined with radiotherapy from Beijing Tsinghua Changgung Hospital in China were reviewed for eligibility. The efficacy was evaluated by the survival and PVTT response rate, and the safety was evaluated by the frequency of key adverse events (AEs).

**Results:** In total, 39 eligible HCC patients with type Vp-4 PVTT who received triple therapy were included in this study. The 2-year OS rate was 15.4%, which was the primary end-point of our study. The median overall survival (OS) and progression-free survival (PFS) were 9.4 months (range 2.3 to 57.1) and 4.9 months (range 1.4 to 36.1), respectively. The objective response rate (ORR) of PVTT based on mRECIST was 61.5%. AFP dropped to normal 3 months after radiotherapy and was an independent risk factor associated with OS. All AEs were controlled, and no treatment-related deaths occurred.

Conclusion: Lenvatinib plus PD-1 inhibitor combined with radiotherapy had a significant therapeutic effect and manageable AEs in HCC patients with type Vp-4 PVTT and may be a potential treatment option for advanced HCC.

**Keywords:** hepatocellular carcinoma, portal vein tumour thrombus, lenvatinib, PD-1 inhibitor, radiotherapy

#### Introduction

Portal vein tumour thrombus (PVTT) occurs very frequently in patients with hepatocellular carcinoma (HCC) because the biological behaviour of HCC results in a strong likelihood of vascular invasion. PVTT incidence varies across countries and regions, and ranges from 13% to 45%.<sup>1</sup> HCC patients with PVTT have poor prognosis, with a median survival time associated with the best supportive care of only 4 to 6 months.<sup>2,3</sup> The American and ESMO guidelines for the diagnosis and treatment of HCC, which is based on the Barcelona Clinical Liver Cancer (BCLC) staging

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system, recommend systematic treatment regimens such as targeted drugs and immune drugs.<sup>4,5</sup> However, guidelines for the diagnosis and treatment of HCC in Asia such as Asian-Pacific guidelines<sup>6</sup> and guidelines from mainland China,<sup>7</sup> Korea<sup>8</sup> and Taiwan<sup>9</sup> all indicate that local therapies (eg, hepatic resection, radiotherapy, TACE and HAIC) may be used as an optional regimen for patients with PVTT in addition to targeted drugs and immunotherapy as the first-line treatment.

In recent years, more treatment options have been developed for patients with HCC with PVTT which has led to significant improvements in patient prognosis.<sup>10–13</sup> For example, advancements in radiotherapy technology have realized the use of local radiotherapy as an effective treatment option for PVTT. A study by a Chinese research team confirmed that, compared with surgery alone, surgery after radiotherapy prolonged the progression-free survival (PFS) and overall survival (OS) of liver cancer patients with PVTT.<sup>14</sup> Another study from South Korea showed that radiotherapy combined with immunotherapy was associated with longer OS than immunotherapy alone.<sup>15</sup> Given these promising results, the Chinese Expert Consensus on cases of HCC with PVTT and the CSCO HCC Treatment Guidelines both regard radiotherapy as the recommended method for PVTT.

New clinical data on antiangiogenic targeted drugs combined with immunotherapy for PVTT have been published. Since the publication of the 2008 SHARP study, there has been a rapid development of systematic drugs for advanced or unresectable HCC. The IMbrave150 study<sup>16</sup> included 501 patients with unresectable HCC who received atezolizumab plus bevacizumab or sorafenib. In the subgroup of people with PVTT, the objective response rate (ORR) of the combined treatment regimen reached 23%, and the median PFS and OS were 5.4 months and 7.6 months, respectively, which were superior to the results achieved by sorafenib monotherapy. In addition, some real-world studies have also shown that antiangiogenic targeted drugs combined with PD-1 inhibitors improve the efficacy and survival of HCC patients with PVTT.

However, clinical benefits in patients with type Vp-4 PVTT is unsatisfactory. A real-world study from Japan reported that the postoperative recurrence-free survival according to the degree of PVTT and Vp-4 was only 0.38 years (Vp-1, Vp-2 and Vp-3 were 1.23 years, 0.82 years and 0.56 years, respectively).<sup>17</sup> In the IMbrave 150 study, 129 patients with macrovascular invasion demonstrated that the median OS (mOS) was 14.2 months vs 9.7 months (HR: 0.68), which confirmed the effectiveness of immune checkpoint inhibitors (ICIs) combined with VEGF inhibitors in patients with PVTT. However, in 73 patients with Vp-4 PVTT, the OS was 7.6 months.<sup>18</sup>

An evaluation of radiotherapy combined with lenvatinib plus a PD-1 inhibitor as a treatment regimen for patients with HCC with main PVTT has not yet been conducted. Herein, we aimed to explore the efficacy and safety of triple therapy as the first-line treatment in HCC with main PVTT (type Vp-4).

## **Materials and Methods**

#### Study Design and Participants

This real-world study investigated the activity and safety of the PD-1 inhibitor lenvatinib plus radiotherapy in patients with HCC with main PVTT at the Beijing Tsinghua Changgung Hospital. The trial protocol, which is available in Figure 1, was approved by the Research Ethics Board of Beijing Tsinghua Changgung Hospital (No. 23223-6-01). All participants provided written informed consent. The primary inclusion criteria were as follows: aged eighteen years or older; HCC a diagnosis based on the American Association for the Study of Liver Diseases practice guideline;<sup>19</sup> PVTT diagnosis with Vp4 classification system of Japan, and a Child–Pugh score≤7. Patients with lymph node and extrahepatic metastases were not excluded. The primary exclusion criteria were as follows: hypersensitivity to Lenvatinib or PD-1 inhibitor components; patients with myocardial ischemia or myocardial infarction of grade II or above and poorly controlled arrhythmias; abnormal coagulation function (prothrombin time>ULN+4 seconds or activated partial thromboplastin time>1.5 ULN, with bleeding tendency or receiving thrombolytic or anticoagulation therapy); pregnant or breastfeeding women; have a history of mental illness or abuse of psychotropic substances; combined HIV-infected; history of liver transplantation; patients with active infection; with contraindications to radiotherapy.



Figure I Protocol of this study. Abbreviations: OS, overall survival; PFS, progression-free survival; ORR, objective response rate; PVTT, portal vein tumour thrombus; AE, adverse event.

### Procedures

All participants underwent treatment with external beam radiation therapy at the beginning of study enrolment. A CT scan (Discovery 590 RT, GE, USA) was performed with the patient in the supine position using chest-abdominal thermoplastic mask immobilization to reduce uncertainty and to restrain organ motion caused by abdominal breathing. Monaco 5.11 treatment planning systems (Elekta, Sweden) were used to optimize target and normal structure delineation. External RT with volumetric modulated arc therapy (VMAT) treatment plans were used to target the PVTT and primary tumour. The gross tumour volume (GTV) of the PVTT was defined as the tumour volume that was shown as a filling defect in the portal venous phase of the CT scan. The planning target volume (PTV) of the PVTT was expanded to include a margin of 5 mm in the transaxial direction and abdominal-dorsal direction and 10 mm in the cranio-caudal direction. The GTV of the primary tumour was defined as the liver tumour volume that was enhanced in the arterial phase of the CT scan. The clinical tumour volume (CTV) of the primary tumour was generated by adding 5 mm to the GTV in all directions. The PTV of the primary tumour was expanded to include a 5- to 10-mm margin from the CTV to compensate for internal physiologic movements and variations in the size, shape, and position of the CTV. The total dose to the PTV was 32.4–50 Gy, with a fractional size of 1.8–3.0 Gy in 36 participants, and another 3 participants were given 24–30 Gy to PTV with a fractional size of 8–10 Gy using 6-MV X-rays with a linear accelerator (Synergy; Elekta, Sweden). The mean dose to the normal liver (volume of total liver minus GTV) was limited to  $\leq 23$  Gy. The maximum allowable point dose to the duodenum and stomach was less than 54 Gy. The maximum allowable point dose to the colon was less than 55 Gy. The maximum point dose of the spinal cord was less than 45 Gy. The kidney volume receiving a dose  $\geq 20$  Gy (V20) was  $\leq 20\%$ .

Participants received the first cycle of PD-1 inhibitor (pembrolizumab, nivolumab or sintilimab) at a fixed dose of 200 mg within 3 days after the completion of radiotherapy. The PD-1 inhibitor was then given every 3 weeks until disease progression, the development of grade 3 or worse immune-related adverse events (AEs), or if the patient withdrew consent. Lenvatinib was started on the first day the PD-1 inhibitor was given after radiotherapy. The daily dose was determined according to body weight (8 mg for bodyweight < 60 kg and 12 mg for bodyweight  $\geq$  60 kg) until disease progression, the development of grade 3 or worse targeted-related AEs, or withdrawal of consent. Lenvatinib was used until disease progression or the patients reported the symptoms were intolerable, and the PD-1 inhibitors were used for up to 2 years.

All patients underwent baseline contrast-enhanced abdominal MRI or CT. The treatment response evaluation was assessed with MRI/CT after cycle 3 and cycle 6 of the PD-1 inhibitor and every 3 months thereafter (plus or minus 7 days). The Modified Response Evaluation Criteria in Solid Tumours (mRECIST) was used to report

radiological imaging. Safety assessments were documented throughout the treatment period. AEs were graded according to the US National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE; version 4.01). AFP concentration and the Child–Pugh score were measured at baseline, after radiotherapy and every 4 weeks thereafter.

### Outcomes

The primary endpoint was the OS rate at 2 years, which was defined as the proportion of participants alive at 2 years. The secondary endpoints were OS, PFS, ORR, and AEs. Tumour and PVTT assessments were evaluated by two independent radiologists according to the mRECIST, and the best responses were documented. The responses were confirmed by assessment after 9 weeks of radiotherapy. OS was defined as the time from radiotherapy to the date of death from any cause; PFS was defined as the time from radiotherapy to the first documented disease progression according to the mRECIST or death from any cause; the ORR was expressed as the percentage of patients who had a complete response or partial response of PVTT 2 months after radiotherapy. Safety was evaluated according to NCI CTCAE, version 4.01. Immune-related AEs were evaluated according to the consensus recommendations from the Society for Immunotherapy of Cancer Toxicity Management Working Group.

### Statistical Analysis

Tumour response, survival, and AEs were assessed and analysed in patients who received at least one cycle PD-1 inhibitor after radiotherapy. Baseline characteristics and response rates are expressed in terms of frequencies and percentages, and variables are indicated as either the mean (standard deviation) or median (range). The Kaplan–Meier method was used to estimate PFS, and univariate and multivariate regression analyses were used to analyse the prognostic factors of PFS. All analyses were performed using SPSS version 25.0.

## Results

Between 1st March 2018 and 31st October 2020, 50 participants were screened. Eight participants did not meet the eligibility criteria, and 3 participants withdrew consent. Thirty-nine of 50 (78.0%) screened patients were enrolled and received the study treatment (Figure 1). The baseline characteristics of the study participants are shown in Table 1. Most of the patients recruited were male and were Child–Pugh class A. All participants had main PVTT, and 25.6% of

Characteristics	Patients (n=39)	
Gender		
Male	37 (94.9%)	
Female	2 (05.1%)	
Age		
Median	56 (32–73)	
ECOG score		
0	7 (17.9%)	
I	28 (71.8%)	
2	4 (10.3%)	
Child-Pugh grade		
Α	29 (74.4%)	
В	10 (25.6%)	
PVTT position		
PVTT trunk combined with left and right branch	16 (41.1%)	
PVTT trunk combined with left or right branch	23 (58.9%)	

 Table I Patient Demographics and Clinical Characteristics

(Continued)

Characteristics	Patients (n=39)	
Extrahepatic spread		
No	29 (74.4%)	
Yes	10 (25.6%)	
AFP (ng/mL)		
≤400	17 (43.6%)	
>400	22 (56.4%)	
Hepatitis		
HBV	36 (92.3%)	
HCV	I (02.6%)	
Alcoholic	2 (05.1%)	
Previously treated		
No	10 (25.6%)	
Yes	29 (74.4%)	

 Table I (Continued).

participants had extrahepatic spread. Participants infected with hepatitis B virus (92.3%) were given preemptive antiviral therapy.

At the time of the enrolment period cut-off (Oct 31st, 2022), all patients had completed study treatment. Three patients received a median dose of 24.0 Gy (range 24.0–30.0) in 3 fractions with stereotactic body radiotherapy (SBRT). Thirty-six patients received VMAT with a single dose from 1.8 Gy to 3.0 Gy, and the median biological effective dose (BED) and equivalent dose in 2 Gy/f (EQD2) were 48.0 Gy (range 39.0–78.0) and 40 Gy (range 32.5–65.0), respectively. There were 16, 10 and 13 patients who received pembrolizumab, nivolumab and sintilimab, respectively. The median number of cycles that patients received PD-1 inhibitors was 11 (range 2–34). The median duration that participants received lenvatinib was 33 weeks (range 6–94).

#### Efficacy

Among 39 participants, the OS of 6 participants was longer than 2 years, and the 2-year OS rate was 15.4%, which was the primary endpoint of our study. The 6 months, 1-year and 2-year OS rates were 71.8%, 33.3% and 15.4%, respectively. The median OS and PFS were 9.4 months (range 2.3 to 57.1) and 4.9 months (range 1.4 to 36.1), respectively (Figures 2 and 3). The PVTT response is shown in Table 2. The confirmed ORR of PVTT was 61.5%, according to a per investigator review. The complete response rate was 5.1%, and the partial response rate was 56.4%. Eight (15.4%) patients had stable disease, and 9 (23.1%) patients had progressive disease. The disease control rate of



Figure 2 OS and PFS.



Figure 3 Patients survival information. Abbreviations: PFS, progression-free survival; OS, overall survival.

PVTT was 76.9%. Two patients were evaluated as CR based on the mRECIST criteria after treatment with radiotherapy combined with lenvatinib plus a PD-1 inhibitor, and the results of one patient is shown in Figure 4.

## Safety

We analysed safety data for all 39 patients. Thirty-seven patients (94.9%) experienced at least one treatment-related AE. The main treatment-related AEs (TRAEs) of patients are shown in Table 3. The most common treatment-related AEs of any grade were lymphopenia (84.6%), fatigue (53.8%), nausea/anorexia (43.6%), elevated aminotransferases (38.5%) and leukopenia (35.9%). Treatment-related grade 3 or 4 AEs occurred in 7 (17.9%) participants, and the most common AE was lymphopenia (10.3%). No treatment-related deaths occurred. Immune-related AEs of any grade were observed in 12 (30.8%) of patients. The most common immune-related AE was immune-related hypothyroidism (12.8%).

According to mRECIST					
	CR	2 (5.1%)			
	PR	22 (56.4%)			
	SD	6 (15.4%)			
	PD	9 (23.1%)			
	ORR (CR+PR)	24 (61.5%)			
	DCR (CR+PR+SD)	30 (76.9%)			

Table 2 Radiological Response of PVTT

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; DCR, disease control rate; ORR, objective response rate; mRECIST, modified Response Evaluation Criteria in Solid Tumors.



Figure 4 Typical case demonstration. A 69-year-old male HCC patient with main PVTT achieved complete response (mRECIST) after receiving Lenvatinib plus Pembrolizumab combined with Radiotherapy. Sub-figure A B C show the pre-treatment images and sub-figure D E F show the post-treatment images. Sub-figure G H show the radiotherapy target area. The red arrows in the sub-figure A and C indicate the range of PVTT before treatment. The red arrow in the sub-figure B indicate the range of Iver tumor before treatment. The red arrows in the sub-figure D and F indicate the range of PVTT after treatment. The red arrow in the sub-figure E indicate the range of Iver tumor after treatment. After treatment, the liver tumor and PVTT had shrunk and there was no enhancement on the enhanced image. Abbreviations: HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombus; mRECIST, modified response evaluation criteria in solid tumors.

#### Prognostic Factor Analysis

The prognostic factors for OS and PFS are shown in Table 4. Univariate analysis showed that GTV and AFP levels returning to normal 3 months after radiotherapy, and that a reduction in AFP by half 1 month after radiotherapy were factors that influenced OS A multivariate analysis showed that AFP returning to normal 3 months after radiotherapy was an independent risk factor for OS (Figure 5). Patients whose AFP levels returned to normal 3 months after radiotherapy had longer OS than those whose AFP remained higher than normal.

Adverse Event	Any Grade(%)	Grade I	Grade 2	Grade 3
Lymphopenia	33(84.6%)	16(41.0%)	3(33.3%)	4(10.3%)
Fatigue	21(53.8%)	20(51.3%)	l (2.5%)	0
Nausea/Anorexia	17(43.6%)	17(43.6%)	0	0
Elevated aminotransferases	15(38.5%)	11(28.2%)	3(7.7%)	I (2.5%)
Leukopenia	14(35.9%)	12(30.8%)	2(5.1%)	0
Elevated bilirubin	12(30.8%)	12(30.8%)	0	0
Thrombocytopenia	11(28.2%)	10(25.6%)	l (2.5%)	0
Proteinuria	10(25.6%)	8(20.5%)	2(5.1%)	0
Hypertension	10(25.6%)	10(25.6%)	0	0
Hypoproteinemia	7(17.9%)	5(12.8%)	2(5.1%)	0
Hand and foot skin reactions	7(17.9%)	6(15.4%)	l (2.5%)	0
Diarrhoea	6(15.4%)	6(15.4%)	0	0
Rash	5(12.8%)	4(10.3%)	0	l (2.5%)
Gastric ulcer	l (2.5%)	0	0	l (2.5%)
Immune-related adverse event	12(30.8%)			
Immune-related Adrenal hypofunction		3(7.7%)	0	0
Immune-related myocarditis		2(5.1%)	l (2.5%)	0
Immune-related hypothyroidism		2(5.1%)	3(7.7%)	0
Immune-related pneumonitis		l (2.5%)	0	0

#### Table 3 Treatment Related Adverse Events

Notes: Listed are adverse events, as defined by the National Cancer Institute Common Terminology Criteria (version 4.01).

Variable	Univariate Cox Analysis			Multivariate Cox Analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Sex (male vs female)	2.528	0.589–10.854	0.196			
Age(<55 vs ≥55)	0.875	0.441-1.736	0.703			
ECOG PS (0 vs.1/2)	2.331	0.107-4.907	0.720			
Extrahepatic metastasis (yes vs no)	0.705	0.305-1.631	0.364			
BED (<50Gy vs ≥50Gy)	0.792	0.399-1.567	0.502			
GTV (<544mL vs ≥544mL)	1.370	0.678-2.768	0.358			
Child-Pugh (Grade A vs Grade B)	0.736	0.322-1.686	0.430			
AFP (<400ng/mL vs ≥400ng/mL)	1.104	0.557-2.189	0.776			
*AFP dropped to normal (yes vs no)	0.141	0.068-0.295	0.0009	0.145	0.032-0.648	0.011
#AFP reduced by half (yes vs no)	2.468	1.201-5.071	0.011	0.629	0.303-1.303	0.212
Previously treated with TACE (yes vs no)	0.888	0.448–1.762	0.731			

Table 4 Univariate and Multivariate Analyses of Prognostic Factors Affecting OS

Notes: \*AFP dropped to normal 3 months after radiotherapy. #AFP reduced by half I month after radiotherapy. Statistically significant data has been highlighted in red according to multivariate cox analysis.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; BED, Equivalent Biological Dose; GTV, Gross Tumor Volume; AFP, a-fetoprotein; TACE, Transcatheter arterial chemoembolization/.

## Discussion

PVTT is a common phenomenon in HCC patients and usually shows a poor prognosis, particularly in the Vp-4 type patient population. Radiotherapy-antiangiogenesis-immune checkpoint blockade (RAICB) combination therapy has shown apparent clinical efficacy in HCC with PVTT. This real-world study investigated the OS rate at 2 years after a triple combination regimen of systemic therapy (lenvatinib plus PD-1 inhibitor) and locoregional therapy (radio-therapy). The OS was observed to be 15.4%, and there was no serious adverse reactions.

More recently, immune checkpoint blockade (ICB) has emerged as a promising therapeutic option for advanced HCC patients.<sup>19</sup> Phase III ICB trials, such as the IMbrave 150 rial and the HIMALAYA trials, which have used antibodies against programmed cell death protein 1 (PD-1), programmed cell death-Ligand 1 (PD-L1) and cytotoxic T-lymphocyte– associated antigen-4 (CTLA-4), have demonstrated clinical benefit and a lower incidence of serious treatment-related AEs in patients with advanced HCC.<sup>20,21</sup> Despite the initial success observed with ICB therapies across a broad range of



Figure 5 Independent risk factor for OS.

Abbreviations: AFP,  $\alpha$ -fetoprotein; HR, Hazard Ratio; CI, Confidence Interval.

Radiotherapy (RT) for treating HCC has traditionally been linked to suboptimal results due to limited tolerance of whole liver irradiation and the inability to conform radiation doses to tumours.<sup>24</sup> However, recent improved techniques allow for high doses of radiation to be delivered to the tumour while limiting the damage to surrounding healthy tissues. Meanwhile, clinical studies have shown that radiotherapy is sensitive to PVTT. A 2007 clinical study in Japan concluded that preoperative RT applied to PVTT in the main trunk or first branch improves patient prognosis in cases of HCC with PVTT and could be a promising new modality in the treatment of these patients.<sup>25</sup> RT has demonstrated good tumour control with 2-year local control rates between 84% and 95%.<sup>26,27</sup> However, OS is limited by out-of-field intra- and extrahepatic disease progression,<sup>28</sup> highlighting the need for concurrent systemic disease control.

Numerous findings have shown that RT can convert an otherwise "cold" tumour that has low immunogenicity and poorly infiltrated immune cells to an immune-reactive "hot" tumour, which is well infiltrated by immune cells. Traditionally, the rationale behind RT for cancer treatment is to induce lethal DNA damage to tumour cells with high-energy particles, leading to subsequent cell death.<sup>29</sup> However, the ability of RT to elicit an immune-mediated antitumour response, a phenomenon known as the "abscopal effect" denoted by the downsizing of nontargeted distant tumours following ionizing radiation treatment, has gained increased prominence in the last decade.<sup>30</sup> RT causes immunogenic cell death and cellular stress, which increases the pool of tumour-associated antigens and damage-associated molecular patterns (DAMPs).<sup>31</sup> These in turn activate dendritic cells, professional antigen-presenting cells (APCs) that prime tumour-specific CD8+ T cells to further enhance antitumour responses and promote immune cell infiltration into the tumor micro-environment (TME).<sup>32</sup>

In addition, the VEGF pathway is also an important mechanism for resistance to anti-PD-1 therapy, as it could hamper tumour infiltration and the functions of T effector cells.<sup>33,34</sup> Tumours with higher transcriptomic diversity were associated with worse OS in patients treated with ICB, and these tumour cells also expressed a significantly higher level of VEGF-A in patients with HCC.<sup>35</sup> A phase Ib clinical study showed that ensartinib, which can block VEGF, combined with a PD-1 inhibitor, has demonstrated good efficacy in the treatment of advanced HCC.<sup>36</sup> Although the phase III randomized controlled study (Leap-002) failed to meet the study endpoint, lenvatinib in combination with pembrolizumab resulted in the longest first-line treatment OS (21.2 m) observed to date,<sup>37</sup> and remains an important systematic option for treating advanced liver cancer in clinical settings in China.

In this real-world study, we combined radiotherapy with lenvatinib plus PD-1 inhibitors in HCC patients with main PVTT, and observed an objective response rate at 3 months of 63.8%, which showed good local tumour control. The median OS and PFS were 9.4 months and 4.9 months, respectively, which demonstrated good long-term survival. Patients whose AFP returned to normal 3 months after radiotherapy had longer OS. In addition, adverse effects of the triple therapy regimen were acceptable The most serious adverse reactions were lymphopenia, fatigue, nausea/anorexia, elevated aminotransferases and leukopenia.

To our knowledge this is the first study which reports real-world clinical results of treatment using lenvatinib + PD-1 inhibitors combined with radiotherapy for HCC with Vp4 PVTT. The results may provide clinical evidence for future prospective trials. However, there were some limitations to this study. First, this study was conducted in China at a single institution, with a limited sample size and, thus, the findings may be influenced by potential bias. Therefore, further study is required in larger populations in China or other countries and regions. Second, the types of PD-1 inhibitors, the dose of radiotherapy and the radiation pattern were not uniform, which required the results of this study to be validated using well-designed prospective multicentre randomized clinical trials. Third, this study mainly focused on HBV-related HCC, and whether triple therapy can be applied to patients with HCC with other aetiologies needs further research.

In summary, lenvatinib plus PD-1 inhibitors combined with radiotherapy had a significant therapeutic effect and resulted in manageable AEs in HCC patients with main PVTT and, thus, this particular combination therapy may be a promising alternative treatment for this specific subpopulation of HCC patients.

#### Abbreviations

PD-1, programmed cell death-1; RT, radiotherapy; HCC, hepatocellular carcinoma; PVTT, portal vein tumour thrombus; AEs, adverse events; OS, overall survival; PFS, progression-free survival; ORR, objective response rate; mRECIST,

modified response evaluation criteria in solid tumours; AFP, α-fetoprotein; ESMO, European society for medical oncology; BCLC, Barcelona clinical liver cancer; TACE, transcatheter arterial chemoembolization; HAIC, hepatic artery infusion chemotherapy; CSCO, Chinese society of clinical oncology; HR, hazard ratio; ICIs, immune checkpoint inhibitors; VEGF, vascular endothelial growth factor; ULN, upper limit of normal; HIV, human immunodeficiency virus; CT, computed tomography; VMAT, volumetric modulated arc therapy; GTV, gross tumour volume; PTV, planning target volume; CTV, clinical tumour volume; MRI, Magnetic resonance imaging; NCI CTCAE, National cancer institute common terminology criteria for adverse events; SBRT, stereotactic body radiotherapy; BED, biological effective dose; EQD2, equivalent dose in 2 Gy/f; CR, complete response; TAREs, treatment-related adverse events; RAICB, radio-therapy-antiangiogenesis-immune checkpoint blockade; PD-L1, programmed cell death-Ligand 1; CTLA-4, cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4), ICB, immune checkpoint blockade; DNA, Deoxyribonucleic acid; DAMPs, damage-associated molecular patterns; APCs, antigen-presenting cells; TME, tumour micro-environment.

## **Ethics Statement**

This study has been approved by the ethics committee of Beijing Tsinghua Changgung Hospital (No. 23223-6-01). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

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## **Author Contributions**

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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