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Efficacy and Safety of Lenvatinib Versus Atezolizumab plus Bevacizumab as First-Line Systemic Therapies for Hepatocellular Carcinoma : Experience from a Single UK Centre

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Introduction

Atezolizumab plus Bevacizumab (Atezo/Bev) and Lenvatinib (Len) are approved as first-line systemic therapies for unresectable or metastatic hepatocellular carcinoma (HCC) based on the results of benchmark studies which compared them with Sorafenib.[1-2] However, there had been no head-to-head comparison between these two therapies in any randomized controlled clinical trials. Three systematic reviews and meta-analyses found no significant difference in the overall survival between patients treated with Atezo/Bev or Len.[3-5] However, most had included studies from Asia, and all of them are retrospective cohort studies. Such results may not be generalisable to Western European populations, where the etiology and clinical presentation of HCC differ.

In the United Kingdom, HCC is the 17th most common cancer, but the eighth most common cause of cancer-related death.[6] More than 90% of patients with HCC have underlying liver

diseases, such as alcoholic cirrhosis, metabolic dysfunction-associated steatotic liver disease (MASLD), or less commonly chronic viral hepatitis (CVH) infection from hepatitis B (HBV) and hepatitis C (HCV). Current 5-year survival of HCC in England is less than 20%, which can be variable in different cancer centres according to their social determinants.

Colchester General Hospital (East Suffolk and North Essex Foundation Trust, ESNEFT) is part of the health care network of East England. All patients with a diagnosis of HCC were reviewed centrally at either the HCC Multidisciplinary Teams of Addenbrooke's Hospital in Cambridge University or Royal Free Hospital in London, before they were referred back to receive systemic anti-cancer treatment locally. We report our experience of using Atezo/Bev and Len as first-line systemic therapies for HCC in the real world setting.

Methods

Patients

This retrospective study included 16 consecutive patients with unresectable or metastatic HCC who received first-line systemic therapy with either Len (n=5) or Atezo/Bev (n=11) between January 2022 and December 2025 at Colchester General Hospital, ESNEFT, UK. Eligible patients met the following criteria: (1) Adults aged 18 years or older with a confirmed diagnosis of unresectable or metastatic HCC, based on typical imaging or histology, who received either Len or Atezo/Bev as first-line systemic therapy; (2) Child-Pugh A liver function; (3) an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. We excluded patients with: (1) an ECOG performance status of 3-4; (2) Child-Pugh score B or above ; (3) patients with significant cardiovascular disease or high bleeding or thromboembolic risk. Patients who had rheumatological or autoimmune diseases were excluded from Atezolizumab and they were treated with Len. Inclusion and exclusion criteria followed the NHS England Cancer Drugs Fund (CDF) eligibility criteria.

This study did not obtain informed consent from participants because it was conducted retrospectively using data extracted from the hospital's electronic medical records. This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Data were extracted from the hospital's electronic medical records. To protect confidentiality, the final research dataset was fully de-identified, and no personal identifiers were included in

the analysis or reporting.

Treatment

In the Atezo/Bev group, patients received a combination Bevacizumab (15mg/kg) administered intravenously and Atezolizumab (1,200mg intravenously / 1875mg subcutaneously) every three weeks. In the Len group, patients received oral Lenvatinib (12 mg/day for those with a body weight ≧ 60kg or 8 mg/day for those with body weight < 60kg). Dose reduction of oral Len to 8mg/day was allowed if patients had grade 2 or above treatment-related toxicities.

Statistical analysis

Categorical variables were expressed as numbers and percentages. Overall survival (date of starting treatment to date of death, or censored at the last date of follow up) was estimated using the Kaplan-Meier method, with differences assessed by the log-rank method. Statistical analyses were performed using IBM SPSS Statistics version 22 (Armonk, NY, USA), with two-sided p-values < 0.05 considered statistically significant.

Results

Baseline patient and tumour characteristics

The baseline characteristics of the 16 patients are presented in Table 1. Of these, 14 (87.5%) were male, with mean age of 70.2 (range: 53-83 years). The mean baseline body weight was 84.8 kg. The most common comorbidities include hypertension (9), liver cirrhosis (10), type 2 diabetes mellitus (7), COPD or interstitial lung diseases (4), ischaemic heart disease (2). Three patients had history of pulmonary embolism on anticoagulation therapy, three patients had history of another cancer, three patients had history of stroke or transient ischaemic attack, and three patients had significant rheumatological or autoimmune diseases.

Table 1. Patient and tumour characteristics

	Len (n=5)	Atezo+Beva (n=11)
Male :Female	4:1	10:1
Liver cirrhosis	5	5
BCLC stage B/C	1/4	4/7

PS 0/1/2	1/3/1	1/9/1
Biopsy Yes/No	4/1	9/2
OGD varices Yes/No/NA	0/3/2	2/4/5
Dental assessment Y/N	1/4	7/4

According to the BCLC staging system, 5 patients were classified as stage B and 11 patients as stages C. Extrahepatic metastasis was observed in 6 patients, with sites of metastasis including lymph nodes (2), adrenal (2), bone (2), lung (2) and peritoneum (1). Macrovascular invasion (MVI) in the form of hepatic, portal vein or inferior vena cava thrombosis was present in 6 (37.5%) patients.

Regarding prior or concomitant therapies, radiofrequency ablation (RFA) was applied in two patients. Other treatments included transarterial chemoembolization (TAE) in two, SIRT in one and external radiation therapy (XRT) to bone metastasis in two patients.

Treatment delivery

Five patients received Lenvatinib as first treatment. Four patients discontinued treatment, while one remained on therapy. Among the 4 patients who stopped Lenvatinib, 2 stopped treatment due to disease progression, while the other two stopped treatment due to toxicity or intolerance. All patients who discontinued treatment subsequently died, with one died of acute heart failure after receiving only 2 days of Lenvatinib. The median duration of therapy was 4 months (range, 2 days - 15 months). Dose reduction from 12 mg OD to 8 mg OD had occurred in three out of five patients.

11 patients received Atezolizumab and Bevacizumab as first line treatment. 9 had stopped treatment while two patients were still receiving treatment. Among the 9 patients who stopped treatment, 5 stopped treatment due to disease progression and 4 stopped treatment due to toxicity or intolerance. One stopped treatment due to seizure and one patient stopped treatment because of acute cardiac failure which were possibly related to Bevacizumab. The median cycles of therapy delivered was 5 (range 2-38). No dose reduction was made in all delivered cycles.

Tumour response

Partial response was observed in two patients in the Lenvatinib group and four patients in the

Atezo/Bev group. (40% Vs 36%, χ^2 test, p=0.366). One of the responders in the Lenvatinib group also received TAE to a target lesion but unfortunately this progressed 8 months later so treatment was stopped. Another responders in the Lenvatinib presented with bone metastases which were irradiated before Lenvatinib. He had continued treatment for more than one year with recent imaging demonstrated a sustained response.

One responders in the Atezo/Bev had pseudoprogression on MRI scan because of tumour haemorrhage after Bevacizumab. He remained clinically well so he continued treatment with subsequent MRI liver scans showed shrinkage of all target lesions. Another responder had pseudoprogression in the mediastinal lymph nodes due to Atezolizumab. He continued treatment with subsequent CT / MRI confirmed decrease in size in the mediastinal lymph nodes and liver primary. Two patients whose follow up scans showed good partial response had stopped treatment, one due to Bevacizumab related seizure and the other due to patient's refusal.

Survival

After a median follow up of 10.5 months, 4 out of 5 patients in the Len group and 8 of 11 patients in the Atezo/Bev group had died. One patient in Len group and another patient in the Atezo/Bev group died of acute heart failure without cancer progression. All the other patients had died with evidence of disease progression. Median overall survival was 7 months in the Len group and 15 months in the Atezo/Bev group (p=0.48). (Figure 1)

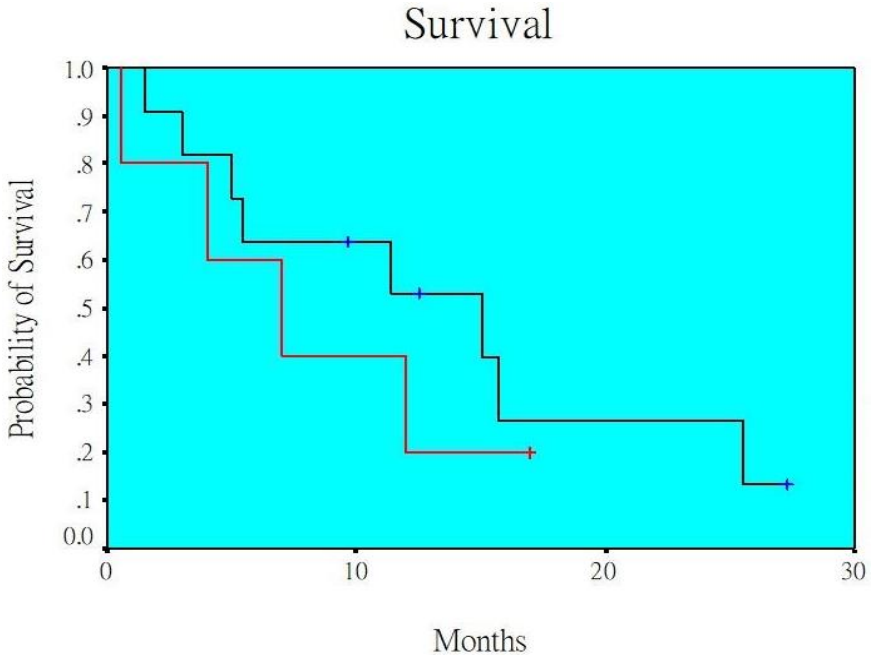

Figure 1. Overall Survival Comparison

Treatment related toxicity

Treatment related toxicity was summarised in table 2. Most of the toxicities were of low grade. Of note, acute cardiac failure occurred in two patients, one in the Len group and the other in the Atezo/Bev group, resulting in death. One patient developed Bevacizumab-related seizure so treatment had to be stopped. Another patient succumbed to liver failure in the presence of both cancer progression in liver and immunotherapy-related hepatitis, despite high dose steroid treatment.

Table 2. Treatment related adverse effects

	Len (n =5)	Atezo + Bev (n=11)
Myalgia (Grade 1-2)		1
GI Bleeding (Grade 1-2)		2
Tinnitus (Grade 1-2)		1
Anorexia (Grade 1-2)		3
Dysgeusia (Grade 1-2)		1
Sickness (Grade 1-2)		4
Constipation (Grade 1-2)	1	1
Fatigue (Grade 1-2)	1	2
Mucositis (Grade 1-2)	2	1
HFS (Grade 1-2)	1	
Dysphonia (Grade 1-2)	1	1
Hypothyroidism (Grade 1-2)	1	1
Proteinuria (Grade 1-2)		2
Hypertension (Grade 1-2)	1	1
Seizure (Grade 3)		1
Heart failure (Grade 5)	1	1
Hepatitis (Grade 5)		1

Discussion

IMbrave 150 trial and REFLECT trial are the pivotal trials to provide survival outcomes in patients treated with Atezo/Bev and Len, with median survival 19.2 months and 13.6 months respectively. [1-2] In this study, we compared the efficacy and safety of Atezo/Bev versus Len as first-line therapies for unresectable / metastatic HCC in a real world setting. Our results with Atezo/Bev and Len (median survival 15 months and 7 months) were comparable with the other real world study results such as Boonkaya et al.[7] The shorter survival observed in our cohort and other real world studies compared to IMBRAVE 150 and REFLECT study might be attributable to the more advanced baseline liver disease and tumour burden, as well as more medical comorbidities such as cardiovascular diseases. Most of our treated patients had BCLC stage C diseases, as well as extrahepatic metastases and macrovascular invasion. Moreover, all patients in our cohort were having one or more other significant medical conditions, which also increased their risk of treatment related toxicities.

Both Lenvatinib and Bevacizumab are vascular endothelial growth factor (VEGF) inhibitors which could cause exacerbation of patients' pre-existing cardiovascular conditions such as hypertension, cardiac failure (CHF), thromboembolism and cerebrovascular events. We observed two patients dying of heart failure (one after Lenvatinib and one after Bevacizumab), without evidence of cancer progression. Yuan et al also identified 15 cases of CHF in 221 patients (7%) who received Sorafenib / Lenvatinib / Bevacizumab for HCC in a multi-center cohort. 7/15 (47%) were associated with reduced left ventricular ejection fraction (LVEF).[8] The higher incidence of cardiovascular adverse events in the real world setting compared with the benchmark studies was likely due to the fact that a majority of patients who had baseline major cardiovascular events (MACE) would have been excluded from clinical trials. They suggested that uncontrolled hypertension, history of smoking, and previous history of MACE are associated with a higher risk of MACE following VEGF inhibitor treatment initiation. Nagumo et al also suggested when treating patients with unresectable HCC by Atezo/Bev, caution should be taken in older patients because they are vulnerable to decrease in skeletal muscle mass and deterioration of cardiac function.[9] Cardio-oncology evaluation with echocardiogram and electrocardiogram at baseline and regular intervals would be recommended for such patients, in addition to the other usual assessments such as dental review and endoscopic surveillance for oesophageal varices.

Our results show that Atezolizumab is a generally well tolerated treatment, except for one possible case of immunotherapy-related hepatitis. In patients with significant cardiovascular

comorbidities and bleeding risks such as oesophageal varices, Lenvatinib or Bevacizumab may not be the appropriate treatment. The dual checkpoint inhibitors combination Durvalumab and Tremelimumab (Durva/Treme) has been approved as first-line systemic therapy for unresectable and metastatic HCC patients.[10] This regimen can be offered as the safer option to these patients. In a real world study of unresectable HCC, Kournoutas et al reported no significant difference in clinical outcomes in terms of overall survival and time to treatment discontinuation between Atezo/Bev and Durva/Treme in the first line setting.[11] Nonetheless, patients with advanced HCC are at risk of liver decompensation which can mimic the occurrence of immunotherapy related hepatitis. Close liaison with hepatology and immunology is recommended.

Dawson et al[12] demonstrated in a randomized phase 3 study that adding stereotactic body radiation therapy (SBRT) improved overall survival in patients with advanced HCC, compared to Sorafenib alone. Similarly, a recent meta-analysis of Li et al[13] demonstrated that Sorafenib plus radiotherapy was more effective than Sorafenib monotherapy. Combining systemic treatment with external radiotherapy may also extend survival in HCC patients with bone metastasis.[14,15] Two of our patients were presented with bone metastasis and they were treated with external radiotherapy to their metastatic bone lesions with good response. They also had long survival after Len (13 months) and Atezo/Bev (12 months) respectively. Radiotherapy can elicit two different biological phenomenon in HCC: the abscopal effect and the bystander effect.[16] While the bystander effect is a local phenomenon that takes place in areas near the irradiated ones, the abscopal effect is a systemic, immune-mediated response which can lead to regression in non-irradiated tumour sites. The abscopal effect is of particular interest in HCC when integrating radiotherapy with immunotherapy, and their combination is still under the investigation in many clinical trials. [17-18]

The limitations of our study included its retrospective nature and the small number of patients in each group (n=5 and n=11 respectively) which limited its statistical power to detect any significant survival difference between the two groups. Nevertheless, HCC is a fatal disease and patients usually have very short life expectancy. After a median follow up of 10.5 months with 13 deaths, we had observed a trend of better survival outcome in patients who received Atezo/Bev than those who received Lenvatinib.

Conclusion

The survival outcomes of patients with advanced / metastatic HCC treated with Len or Atezo/ Bev in the real world setting were generally inferior to those reported in the benchmark studies. Better patient and treatment selection would be helpful to improve their outcomes. A multidisciplinary team approach is warranted, although this may be difficult to implement in many community hospitals.

References

[1] RS Finn, S Qin, M Ikeda, PR Galle, M Ducreux, T-Y Kim, M Kudo, V Breder, P Merle, AO Kaseb, D Li, W Verret, D-Z Xu, S Hernandez, J Liu, C Huang, S Mulla, Y Wang, HY Lim, AX Zhu, A-L Cheng, for the IMbrave 150 Investigators. Atezolizumab plus Bevacizumab for Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020; 382 (20): 1894-905

[2] M Kudo, RS Finn, S Qin, KH Han, K Ikeda, F Piscaglia, A Baron, J-W Park, G Han, J Jassem, JF Blanc, A Vogel, D Komov, TRJ Evans, C Lopez, C Dutcus, M Guo, K Saito, S Kraljevic, T Tamai, M Ren, A-L Cheng. Lenvatinib versus sorafenib in first-line treatment for unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018; 391:1163-73

[3] S Du, K Cao, Z Wang, D Lin. Clinical efficacy and safety of atezolizumab plus bevacizumab versus lenvatinib in the treatment of advanced hepatocellular carcinoma. A systematic review and meta-analysis. Medicine 2023;102: 23

[4] G Zhu, L Zeng, L Yang, X Zhang, J Tang, Y Pan, B Li, M Chen, T Wu.Is atezolizumab plus bevacizumab as first-line therapy for unresectable hepatocellular carcinoma superior to lenvatinib ? A systemic review and meta-analysis. European Journal of Clinical Pharmacology 2024; 80:1425-1434

[5] NPSI Remitha, NPRP Dewi, KWA Kusuma, IGAP Sasmana, IGP Supadmanaba, DA Sindhughosa, IK Mariadi. Efficacy and safety of lenvatinib versus atezolizumab plus bevacizumab in the treatment of unresectable hepatocellular carcinoma: a systematic review and meta-analysis. Asian Pac J Cancer Prev. 2025; 26(5) : 1529-1542

[6] A Burton, D Tataru, RJ Driver, TG Bird, D Huws, D Wallance, TJS Cross, IA Rowe, G Alexander, A Marshall, on behalf of the HCC-UK/BASL/NCRAS Partnership Steering

Group. Primary liver cancer in the UK: Incidence, incidence-based mortality, and survival by subtype, sex, and nation. JHEP Reports 2021;3:1-11

[7] S Boonkaya, C Pattarawongpaiboon, P Thaimai, P Ananchuensook, S Sriphoosanaphan, S Tanasanvimon, N Teeyapun, N Pakvisal, N Siripon, S Treeprasertsuk, P Komolmit, K Thanapirom. Efficacy and safety of atezolizuab plus bevacizumab and lenvatinib as first-line systemic therapies for hepatocellular carcinoma : A real-world study. PLOS One. 2025; 20(12) : 1-11

[8] F Yuan, C Lenneman, R Krone, GR Williams, D Outlaw Jr, M Katsnelson, S Lirette. Cardiovascular adverse events in patients with hepatocellular carcinoma receiving vascular endothelial growth factor inhibitors. Pharmacotherapy. 2025 ; 44(3) : 214-223

[9] H Nagumo, H Nagai, K Higai, T Matsuda, Y Igarashi. Effects of Atezolizumab plus Bevacizumab on skeletal muscle volume and cardiac function in patients with hepatocellular carcinoma. Oncology. 2025; 103 (5): 369-379

[10] GK Abou-Alfa, G Lau, M Kudo, S Chan, RK Kelley, J Furuse, W Sukeepaisarnjaroen, Y-K Kang, T Van Dao, EN De Toni, L Rimassa, V Breder, A Vasilyev, A Heurgue, VC Tam, K Mody, SC Thungappa, Y Ostapenko, T Yau, S Azeve do, M Varela, A-L Cheng, S Qin, P Galle, S Ali, M Marcovitz, M Makowsky, P He, JF Kurland, A Negro, B Sangro. Tremelimumab and Durvalumab in unresectable hepatocellular carcinoma. NEJM Evid 2022; 1(8):1-12

[11] I Kournoutas, P Marell, J Gile, A Peersen, P Shah, K VanDommelen, SD Kamath, G Gupta, M Akce, J DongYang, P-J Chen, N Naleid, A Mahipal, N Peterson, V Sahai, W Ma, Z Jin, T Halfdanarson, LF Kankeu, LA Washburn, CB Conboy, M Torbenson, A Goenka, S Thompson, SK Venkatesh, P Starlinger, L Roberts, GJ Gores, H Babiker, D Ahn, M Borad, T Bekaii-Saab, A Jatoi, R R McWilliams, F-S Ou, NH Tran. First-line atezolizumab/bevacizumab or durvalumab/tremelimumab in advanced hepatocelluar carcinoma: a real world, multicenter retrospective study. The Oncologist 2025; 30 (11): 1-12

[12] LA Dawson, K Winter, J Knox, AX Zhu, S Krishnan, C Guha, LA Kachnic, M Gillin, TS Hong, T Craig, et al. NRG / RTOG 1112 : Randomized Phase III study of Sorafenib vs. Stereotactic Body Radiation therapy (SBRT) followed by Sorafenib in Hepatocellular Carcinoma (HCC) (NCT01730937). Int J Radiat Oncol Biol Phys 2022 , 114, 1057

[13] H Li, Z Wu, J Chen, K Su, L Guo, K Xu, T Gu, Y Jiang, P Wang, H Zeng, et al. External

radiotherapy combined with sorafenib has better efficacy in unresectable hepatocellular carcinoma : A systematic review and meta-analysis. Clin Exp Med 2022.

[14] S Hayashi, H Tanaka, H Hoshi. External Beam Radiotherapy for painful bone metastases from hepatocellular carcinoma : multiple fractions compared with an 8-Gy single fraction. Nagoya J Med Sci 2014; 76 : 91-99

[15] L Ielasi, B Stefanini, F Piscaglia, A Granito, F Tovoli. A case of advanced hepatocellular carcinoma with bone metastases managed with tyrosine kinase inhibitors and aggressive palliative radiation therapy : role of combination therapy for extending survival. Gastroenterology Insights 2023 ; 14 : pp38-44

[16] L Cerrito, M Pallozzi, I Urbani, S Archilei, S Miliani, E Creta, L Stella, A Gasbarrini, FR Ponziani. Unexpected Therapeutic Implications : The Abscopal Effect in the Management of Hepatocellular Carcinoma. Cancers 2026; 18 (408)

[17] SMN Wong. Comparison of SBRT and SIRT with combination IO for locally-advanced, unresectable HCCs (BIIRTH). ClinicalTrials.gov (accessed in March 2026)

[18] ACY Chan, CL Chiang. Downstaging Unresectable Hepatocellular Carcinoma to Resectable disease with combined Immunotherapy and Stereotactic Beamed Radiotherapy : A Pilot Study 2025.ClinicalTrials.gov (accessed in March 2026)