Seminars in Oncology 52 (2025) 152348

Contents lists available at ScienceDirect

Seminars in Oncology

journal homepage: www.elsevier.com/locate/seminoncol

Atezolizumab plus bevacizumab versus Lenvatinib for patients with Barcelona clinic liver cancer stage B (BCLC-B) hepatocellular carcinoma (HCC): A real-world population

Francesco Vitiello[a,#], Toshifumi Tada[b], Goki Suda[c], Shigeo Shimose[d], Masatoshi Kudo[e], Jaekyung Cheon[f], Fabian Finkelmeier[g], Ho Yeong Lim[h], José Presa[i], Gianluca Masi[j], Changhoon Yoo[f], Sara Lonardi[k], Francesco Tovoli[l], Takashi Kumada[m], Mario Scartozzi[n], Emiliano Tamburini[o], Francesco Giuseppe Foschi[p], Mara Persano[n], Federico Rossari[a], Silvia Foti[a], Silvia Camera[a], Francesco De Cobelli[q], Luca Aldrighetti[r], Stefano Cascinu[a], Andrea Casadei-Gardini[a,#,*], Margherita Rimini[a,#]

[a] Department of Oncology, Vita-Salute San Raffaele University, IRCCS San Raffaele Scientific Institute Hospital, Milan, Italy
[b] Department of Internal Medicine, Japanese Red Cross Himeji Hospital, Himeji, Japan
[c] Department of Gastroenterology and Hepatology, Graduate School of Medicine, Hokkaido University, North 15, West 7, Kita-ku, Sapporo, Hokkaido, 060-8638, Japan
[d] Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, Kurume 830-0011, Japan
[e] Department of Gastroenterology and Hepatology, Kindai University, Faculty of Medicine
[f] Department of Medical Oncology, CHA Bundang Medical Center, CHA University, Seongnam 13496, South Korea
[g] Department of Internal Medicine 1, University Hospital Frankfurt, Goethe University, Frankfurt am Main, Germany
[h] Department of Medicine, Samsung Medical Center, School of Medicine, Sungkyunkwan University, Seoul, South Korea
[i] Liver Unit, Centro Hospitalar de Trás-os-Montes e Alto Douro (CHTMAD), Vila Real, Vila Real District, Portugal
[j] Unit of Medical Oncology 2, University Hospital of Pisa, Pisa, Italy; Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy
[k] Department of Oncology Unit 1, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy
[l] Department of Internal Medicine, Hepatobiliary and Immunoallergic diseases, IRCCS Azienda Ospedaliero-Universitaria di Bologna, via Albertoni 15 Bologna- Italy
[m] Department of Nursing, Gifu Kyoritsu University, Ogaki, Japan
[n] Department of Oncology, Azienda Ospedaliera Universitaria (AOU) Cagliari, University of Cagliari, Cagliari, Sardinia, Italy
[o] Department of Oncology and Palliative Care, Cardinale G Panico, Tricase City Hospital, Tricase, Italy
[p] Department of Internal Medicine, Ospedale per gli Infermi di Faenza, Faenza, Ravenna, Italy
[q] Department of Radiology, IRCCS San Raffaele Hospital, Milan, Italy; Experimental Imaging Center, IRCCS San Raffaele Scientific Institute, Milan, Italy; Universita Vita-Salute San Raffaele, Milan, Italy
[r] Department of Hepatobiliary Surgery Division, IRCCS San Raffaele Hospital, Milan, Italy

ARTICLE INFO

Article history:
Received 13 August 2024
Revised 11 December 2024
Accepted 27 March 2025

ABSTRACT

Background: The aim of the present study was to perform a real-world analysis on a large patient cohort with Barcelona Clinic Liver Cancer stage B (BCLC-B) hepatocellular carcinoma (HCC) treated with atezolizumab plus bevacizumab ($A+B$) or with Lenvatinib.
Methods: The study population included patients affected with Barcelona Clinic Liver Cancer stage B (BCLC-B) hepatocellular carcinoma not suitable for locoregional therapies (LRTs) from eastern and west-

Abbreviations: : BCLC- B, Barcelona clinic liver cancer stage B; HCC, Hepatocellular carcinoma; LRT s, locoregional therapies; OS, overall Survivor; TTP, time to progression; mOS, median overall survivor; HRs, hazard ratio; mTTP, median time to progression; ORR, objective response rate; Plt, platelets; NASH/NAFLD, nonalcoholic steatohepatitis/nonalcoholic fatty liver disease; PD-1, programmed cell death-1; 95% CI, 95% confidence interval; HFSR, hand-foot skin reaction; TACE, trans arterial chemoembolization; NLR, neutrophil-to-lymphocyte ratio; BCLC-B, Barcelona clinic liver cancer; TKI, tyrosin kinase inhibitor; RTC, randomized clinical trial; PFS, progression free survivor; pdl-1, programmed death ligand; AEs, adverse events; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for adverse events; CI, confidence interval; DCR, disease control rate; SD, stable disease; RP, partial response; CR, complete response; AUC, area under the curve; AFP, A-fetoprotein; ECOG-PS, Eastern Cooperative Oncology Group performance status; AST, aspartate aminotransferase; ALT, alanine amino transferase; BMI, body mass index; ICI, immune checkpoint inhibitors; TGF-b, transforming growth factor beta; NK, natural killer; PLR, platelet-lymphocyte ratio; DFS, disease free survivor; TGF-β, transforming growth factor-β; IPTW, inverse probability of treatment weights.

* Corresponding author. San Raffaele Hospital-IRCCS, Università Vita-Salute San Raffaele, via Olgettina 60 20132, Milano, Italy.
E-mail address: casadeigardini@gmail.com (A. Casadei-Gardini).
Co-last authors.

https://doi.org/10.1016/j.seminoncol.2025.152348

Keywords:
Hepatocellular carcinoma
BCLC-B
Lenvatinib
Atezolizumab plus bevacizumab
Predictors factor
BCLC-B heterogeneity

ern populations, who received atezolizumab plus bevacizumab ($A+B$) or Lenvatinib as first-line treatment. Univariate and multivariate analyses were used to evaluate predictive factors for overall survival (OS) and time to progression (TTP) while prognostic factors were analyzed by univariate and multivariate analysis using Cox regression model.

Results: 919 patients with BCLC-B HCC were analyzed in the study. Lenvatinib was administered to 561 (61%) patients while 358 (39%) received $A+B$. The median overall survival (mOS) for patients receiving Lenvatinib was 21.3 months compared to 15.8 months for patients receiving $A+B$ as first-line treatment (Lenvatinib *v* $A+B$), hazard ratio (HRs) 0.84 $P=0.22$. The median time to progression (mTTP) for patients receiving Lenvatinib was 7.3 months compared to 8.7 months for patients receiving $A+B$ as first-line treatment (Lenvatinib *v* $A+B$): HR 1.15 $P=0.10$. Multivariate analysis confirmed no different in terms of mOS and mTTP between the two treatments. Objective response rate (ORR) was 47.1% for patients receiving Lenvatinib and 27.1% for patients receiving $A+B$ $P<0.000001$. Patients receiving Lenvatinib experienced a significantly higher incidence of hand-foot skin reaction (HFSR), hypertension, diarrhea, fatigue, decrease appetite, hypothyroidism, and other toxicity compared to patients receiving $A+B$. Favorable prognostic factors for OS in Lenvatinib group were platelets (PLT) >100.000 (HR 0.68 $P=0.02$), HCC nonalcoholic steatohepatitis/nonalcoholic fatty liver disease (NASH/NAFLD) related (HR 0.53, $P=0.03$). No favorable prognostic factors were found for $A+B$ group. Favorable prognostic factors for TTP in the $A+B$ group were in TACE refractory patients (HR 0.76, $P=0.02$), PLT <100.000 (HR 0.62, $P=0.0067$), and neutrophil-to-lymphocyte ratio (NLR) < 3 (HR 0.78, $P=0.04$).

Conclusion: Although Lenvatinib had a higher response rate, the study showed no statistically significant differences between Lenvatinib and $A+B$ in terms of efficacy, in patients with BCLC-B HCC.

Introduction

Hepatocellular carcinoma (HCC) is the most frequent primary liver cancer, ranking sixth in prevalence amongst cancers globally and third amongst causes of cancer-related mortality worldwide [1]. The Barcelona Clinic Liver Cancer (BCLC) staging system, introduced in 1999, is widely used to stage primary liver cancer [2]. Treatment of patients with HCC depends mainly on the stage of disease. In the BCLC staging system, multifocal HCC characterized by preserved liver function, absence of cancer-related symptoms (PS 0), and lack of vascular invasion or extrahepatic dissemination is identified as the intermediate stage (BCLC-B). To date, transarterial chemoembolization (TACE) is the only standard treatment for patients with BCLC-B HCC. Nevertheless, the intermediate stage includes heterogeneous conditions, with significant differences in terms of tumor burden and functional liver reserve. For this reason, the 2022 update of the BCLC version stratifies patients in the BCLC-B stage into three distinct groups based on liver function and tumor burden [3].

The third subgroup of BCLC-B comprises patients with extensive, infiltrative, or severe involvement of HCC in the liver. This subgroup experiences limited benefits from TACE [4], thus systemic therapy has emerged as a possibly better treatment option for this group of patients [5,6]. Additionally, the promising outcomes achieved with systemic therapies in patients with advanced stage hepatocellular carcinoma (HCC) imply a potential advantage in the intermediate stage context, particularly among patients with substantial tumor burden. This prompted an exploration of the role of systemic therapies in this patient population. Indeed, in the last years, the therapeutic armamentarium for unresectable HCC has seen a dramatic expansion with the addition of several tyrosine kinase inhibitors and checkpoint inhibitors (Table 1).

Beginning with sorafenib, that showed a modest survival benefit in a population with advanced or unresectable HCC, respect to placebo [7].

Subsequently, the REFLECT trial demonstrated that Lenvatinib another tyrosine kinase inhibitor (TKI), was noninferior to sorafenib in terms of OS, and subgroup analyses from the same study suggested a benefit from TKIs as first line treatment also in patients with intermediate stages of HCC [8].

The IMBRAVE 150 study, demonstrated the superiority in terms of progression-free-survival (PFS) and OS of the combination of atezolizumab, an antibody against programmed death ligand (PDL-1), and bevacizumab, an anti-VEGF antibody, compared with sorafenib [9].

In the same way, the HIMALAYA study demonstrated the superiority in terms of OS of the combination of durvalumab, another anti-PDL-1 antibody, and tremelimumab, a human antibody that inhibits cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), compared with sorafenib [10]. All three of these studies reported response rates of up to 40%.

In the last ASCO meeting, the findings from the CheckMate-9DW trial showed that the combination of nivolumab and ipilimumab as first-line therapy improves mOS compared to Lenvatinib or sorafenib in patients with advanced, untreated HCC, the objective response rate with combination therapy was 36%, significantly higher than the 13% observed in patients treated with Lenvatinib or sorafenib [11]. Finally another programmed cell death protein 1 (PD-1) inhibitor, Tislelizumab demonstrated OS benefit that was noninferior versus sorafenib [12].

Moreover, several studies have also proposed therapeutic options for patients who experience disease progression following first-line therapy [13–16]

A study comparing Lenvatinib versus atezolizumab plus bevacizumab as first-line treatments for patients with intermediate hepatocellular carcinoma (HCC) (BCLC-B) who are not suitable candidates for loco-regional therapies or are refractory rto TACE has not been conducted. Tada and colleagues conducted a comparative study of atezolizumab plus bevacizumab versus Lenvatinib in real-world clinical settings for patients with BCLC-B HCC. The study revealed a median progression-free survival of 10.2 months in the atezolizumab plus bevacizumab group compared to 6.9 months in the Lenvatinib group ($P=0.02$). However, no significant difference was observed in terms of overall survival [17]. The aim of the present study was to perform a real-world analysis on a large number of patients with BCLC-B stage HCC not eligible for loco-regional therapies or refractory to TACE treated in first-line with either atezolizumab plus bevacizumab or Lenvatinib. As a secondary endpoint our aim was to identify a subcategory of patients in whom either Lenvatinib or atezolizumab plus bevacizumab arm was more effective.

Table 1
Summarizes clinical trials in HCC.

Drug/drug combination and comparator	Patient population and study	Results	Brief analysis/interpretation
Sorafenib (nexavar) vs. placebo [7]	*SHARP Trial* (Sorafenib HCC Assessment Randomized Protocol)	Median OS: 10.7 months (sorafenib) vs. 7.9 months (placebo), HR 0.69 ($P < 0.001$)	Sorafenib was the first systemic therapy approved for advanced HCC, showing a modest survival benefit in a population with advanced, unresectable HCC. It remains a standard of care for first-line treatment, despite the development of newer agents.
Lenvatinib (lenvima) vs. sorafenib [8]	*REFLECT Trial* (Randomized Phase III study)	Median OS: 13.6 months (Lenvatinib) vs. 12.3 months (sorafenib), HR 0.92 ($P = 0.043$)	Lenvatinib demonstrated noninferiority to sorafenib in overall survival, with better progression-free survival and objective response rates. It is now an accepted first-line therapy option for patients with advanced HCC, offering a different safety profile.
Bevacizumab (avastin) + atezolizumab (tecentriq) vs. sorafenib [9]	*IMbrave150 Trial* (Phase III, first-line)	Median OS: 19.2 months (bevacizumab + atezolizumab) vs. 13.4 months (sorafenib), HR 0.58 ($P < 0.001$)	The combination of an anti-VEGF (bevacizumab) and PD-L1 inhibitor (atezolizumab) significantly improved overall survival compared to sorafenib, establishing it as the new standard of care for first-line treatment of advanced HCC.
Durvalumab (Imfinzi) + tremelimumab (imjudo) vs. sorafenib [10]	*HIMALAYA Trial* (Phase III, first-line)	Median OS: 16.4 months (durvalumab + tremelimumab) vs. 13.8 months (sorafenib), HR 0.78 ($P = 0.017$)	The combination of durvalumab (PD-L1 inhibitor) and tremelimumab (CTLA-4 inhibitor) showed a meaningful survival benefit compared to sorafenib, and it is considered a promising treatment for patients with advanced HCC, especially those with immune-activated tumors.
Nivolumab and ipilimumab vs sorafenib/Lenvatinib [11]	*CheckMate-9DW* (Phase III, first-line)	Median OS: 23.7 months (Nivolumab plus ipilimumab) vs 20.6 months (sorafenib/Lenvatinib), HR 0.79($P = 0.018$).	The combination of anti-PD-1 Nivolumab with anti CTLA-4 Ipilimumab showed to improve survival outcomes in patients with previously untreated unresectable HCC compared with former standard-of-care Lenvatinib or sorafenib
Tislelizumab vs. sorafenib [12]	*RATIONALE-301* (Phase III, first-line)	Median OS: 15.4 months (tislelizumab) vs. 13.8 months (sorafenib), HR 0.85 ($P = 0.03$)	Tislelizumab, a PD-1 inhibitor, demonstrated comparable efficacy to sorafenib with a trend toward improved survival, suggesting it is a viable alternative for first-line treatment in advanced HCC.
Regorafenib (stivarga) vs. placebo [13]	*RESORCE Trial* (Phase III, second-line postsorafenib failure)	Median OS: 10.6 months (regorafenib) vs. 7.8 months (placebo), HR 0.63 ($P < 0.0001$)	Regorafenib, a multi-kinase inhibitor, offers a survival benefit in patients who have progressed on sorafenib. It is now a standard option for second-line treatment after sorafenib failure in advanced HCC.
Cabozantinib (Cabometyx) vs. Placebo [14]	*CELESTIAL Trial* (Phase III, second-line postsorafenib failure)	Median OS: 10.2 months (cabozantinib) vs. 8.0 months (placebo), HR 0.76 ($P < 0.001$)	Cabozantinib, another multi-kinase inhibitor, showed a significant survival benefit in patients progressing on sorafenib, and it is now a second-line treatment option in advanced HCC. It has shown efficacy in patients with both vascular invasion and extrahepatic spread.
Ramucirumab (cyramza) vs. placebo [15]	*REACH-2 Trial* (Phase III, second-line in AFP ≥400 ng/mL after sorafenib failure)	Median OS: 8.5 months (ramucirumab) vs. 7.3 months (placebo), HR 0.71 ($P = 0.017$)	Ramucirumab demonstrated survival benefits in a specific population with high AFP levels (≥ 400 ng/mL) after sorafenib failure, offering an option for second-line therapy in this subset of patients with advanced HCC.
Nivolumab (opdivo) vs. placebo [16]	*CheckMate 459* (Phase III, second-line postsorafenib failure)	Median OS: 16.4 months (nivolumab) vs. 14.7 months (placebo), HR 0.85 ($P = 0.05$)	Nivolumab, an anti-PD-1 therapy, showed a modest survival benefit compared to placebo in second-line treatment, and it is FDA-approved for HCC patients who have failed sorafenib. It offers a promising immune-based approach with manageable side effects.

Materials and methods

Study population

This was a retrospective observational study comparing two cohorts of patients with BCLC-B HCC not suitable for LRTs or refractory to TACE who received systemic treatment with either Lenvatinib or atezolizumab plus bevacizumab between March 2019 and May 2022. The overall cohort included Western and Eastern populations from 42 centers in five countries (Italy, Germany, Portugal, Japan, and the Republic of Korea). The c study was approved by the ethics committees at each center, and it followed the Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws, as well as the European Parliament and Council Regulation (EU) 2016/679 on the protection of natural persons with regard to the processing of personal data, which was enacted on April 27, 2016.

Treatments and definitions

Patients included received Lenvatinib or atezolizumab plus bevacizumab as first line therapy. In particular, all patients had been treated with Lenvatinib, until the approval of atezolizumab plus bevacizumab. After the approval of the combination of atezolizumab plus bevacizumab in 2020, the choice between the two therapies was left to the treating physician. Lenvatinib was administered following the protocol outlined in the REFLECT trial, where patients received a dosage of 12 mg if their baseline bodyweight was ≥60 kg or 8 mg if it was <60 kg, once daily via oral route. Atezolizumab in combination with bevacizumab was administered according to the regimen specified in the IMbrave150 trial, with all patients receiving 1200 mg of atezolizumab plus 15 mg/kg of body weight of bevacizumab intravenously every 3 weeks. Management of adverse events (AEs) permitted treatment interruptions and/or dose reductions. AEs were evaluated and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. Patients were followed every 2-3 months with multiphasic scanning technique. Tumor assessment was carried out regardless of dose interruption until radiological disease progression or imaging had become clinically irrelevant. When progression was diagnosed according to mRECIST 1.1 criteria, the adoption of any subsequent anticancer medication depended on the local physician decision.

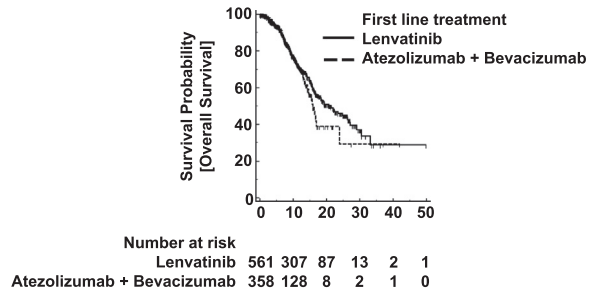

Fig. 1. The univariate analysis of overall survival (OS) comparing Lenvatinib against atezolizumab plus bevacizumab. The solid line represents the median OS for Lenvatinib, which is higher than the dashed line indicating the median OS for atezolizumab plus bevacizumab.

Statistical analysis

Categorical variables were reported as the number of cases and percentage, continuous variables were expressed as median and (95% CI). OS was computed as the interval between the date of therapy start until the date of death for any reason. Time to progression (TTP) was defined as the time from the start date of studied treatment to the date of progression or last follow-up. OS and TTP were reported as median values expressed in months, with 95% CI Disease control rate (DCR) was defined as the percent of patients with decreasing disease or stable disease (SD), objective response rate (ORR) was defined as the percent of patients with partial response (RP) or complete response (CR). Survival curves were estimated using the product-limit method of Kaplan–Meier. Hazard ratios (HRs) in multivariate analysis of baseline characteristics were calculated using the Cox proportional-hazards regression model.

Differences in baseline characteristics between groups were estimated with Mann-Whitney test or Fisher exact test. Continuous variables were dichotomized using receiver operating characteristic (ROC) curves applying the survival either above or below the mean OS as a classification variable to identify a possibly prognostic cutoff value based on the Youden's index in case of area under the curve (AUC) $>$ 0.5 and $P < 0.05$ unless a cutoff value with a prognostic role has already been described. About the latter case, cutoff for albumin was set at 3.5 g/dL and a-fetoprotein (AFP) at 400 mg/mL, PLT at 100.000 and NLR at 3, ALBI $<$ −2.6 for score 1 according [17–20], respectively. A MedCalc package (MedCalc® version 16.8.4) was used for statistical analysis.

Results

The study population included 919 patients with intermediate HCC BCLC-B, of whom 561 (61%) received Lenvatinib as first line and 358 (39%) received atezolizumab plus bevacizumab. Basal patients characteristics of the two populations were different for viral etiology, Eastern Cooperative Oncology Group performance status (ECOG PS), CHILD-PUGH, surgical intervention, and patients refractory to TACE (Table 2). Amongst patients receiving atezolizumab plus bevacizumab arm, the median follow-up time was 9.2 months (95% CI 8.7- 10.7 months), while amongst those treated with Lenvatinib, the median follow-up time was 14.8 months (95% CI 13.4–15.8).

In univariate analysis, mOS was 21.3 months (95% CI 17.5–26.3) in patients receiving Lenvatinib versus 15.9 months (95% CI 14.6–23.9) for patients treated with atezolizumab plus bevacizumab (Fig. 1), with a 14% reduction in the risk of death in favor of Lenvatinib compared to atezolizumab plus bevacizumab (Table 3), a reduction in risk that did not achieve statistical significance (Lenvatinib *v* atezolizumab plus bevacizumab, HR 0.86, 95% CI 0.90 −1.50 $P = 0.2347$).

Table 2
The baseline characteristics of the two patient populations treated with Lenvatinib or with atezolizumab plus bevacizumab.

Variable	Total ($n = 919$)	Atezolizumab +bevacizumab ($n = 358$)	Lenvatinib ($n = 561$)	*P*-value
Clinical				
Sex				
Male	726 (79%)	281 (78%)	445 (79%)	0.80
Female	193 (21%)	77 (22%)	116 (21%)	
Age				
>70	619 (67.3%)	253 (70%)	366 (65%)	0.09
<70	300 (32.7%)	105 (30%)	195 (35%)	
Etiology				
Viral	512 (55%)	172 (48%)	340 (60%)	**0.000231**
Nonviral	407 (45%)	186 (52%)	221 (40%)	
At least one surgery before				
Yes	269 (29%)	119 (33%)	150 (27%)	**0.03**
No	650 (70%)	239 (67%)	411 (73%)	
At least one radiofrequency before				
Yes	269 (29%)	104 (29%)	165 (29%)	0.28
No	607 (71%)	211 (71%)	396 (71%)	
TACE refractory				
Yes	535 (58%)	151 (42%)	384 (68%)	**<0.000001**
No	341 (37%)	164 (46%)	177 (32%)	
Child Pugh				
A	845 (92%)	339 (95%)	506 (90%)	**0.01**
B	74 (8%)	19 (5%)	55 (10%)	
ECOG				
>0	54 (6%)	42 (20%)	12 (2%)	**<0.000001**
0	865 (94%)	316 (80%)	549 (98%)	
Laboratory				
AFP				
<400	182 (20%)	68 (19%)	114 (20%)	0.67
≥400	731 (80%)	286 (31%)	445 (79%)	
Albumin				
≤3.5	309 (34%)	114 (32%)	195 (35%)	0.31
>3.5	594 (65%)	240 (67%)	354 (38.5%)	
NLR				
≥3	230 (25%)	91 (25%)	139 (25%)	0.47
<3	521 (57%)	221 (62%)	300 (53%)	
Creatinine				
≤0.76	338 (37%)	152 (42%)	186 (33%)	0.11
>0.76	517 (56%)	204 (57%)	313 (56%)	
AST (aspartate amino transferase)				
>40	449 (49%)	178 (50%)	271 (48%)	0.68
<40	467 (51%)	180 (50%)	288 (51%)	
ALT (alanine amino transfgerase)				
≤24	352 (38%)	147 (41%)	205 (36.5%)	0.18
>24	564 (61%)	210 (59%)	354 (63%)	
Bilirubin				
>0.8	283 (31%)	194 (54%)	89 (16%)	0.54
≤0.8	429 (47%)	163 (45.5%)	266 (47%)	
Platelets				
≤100	255 (28%)	86 (24%)	169 (30%)	0.05
>100	658 (72%)	268 (75%)	390 (69.5%)	
ALBI				
1	817 (89%)	323 (90%)	494 (88%)	0.56
2	86 (9%)	31 (9%)	55 (10%)	

Univariate analysis was utilized to identify statistically significant differences in baseline characteristics between the two populations. Statistically significant *P*-values are highlighted in bold.

In univariate analysis, mTTP was 7.3 months (95% CI 6.6–8.5 months) in patients receiving Lenvatinib and 8.7 months (95% CI 7.9–10.0) for patients treated with atezolizumab plus bevacizumab (Fig. 2), with a 14% reduction in the risk of progression, with atezolizumab plus bevacizumab compared to Lenvatinib that also did not achieve statistical significance (atezolizumab plus bevacizumab *v* Lenvatinib, HR 0.86, 95% CI 0.72–1.03 $P = 0.1056$) (Table 4).

Table 5.

In univariate analysis of the entire population, the risk of death was reduced in patients with Child-Pugh A compared to B (HR

Table 3
The results of univariate and multivariate analysis of OS for potential prognostic factors in the two patient populations treated with Lenvatinib or atezolizumab plus bevacizumab.

	Univariate		Multivariate analysis					
			Model 1		Model 2		Model 3	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
First line treatment Lenvatinib vs. Atezolizumab + bevacizumab	0.86 (0.90–1.50)	0.2347	1.25 (0.95–1.66)	0.1157	1.35 (0.99–1.83)	0.0562	1.34 (0.98–1.83)	0.0624
SEX Female vs. male	0.81 (0.58–1.09)	0.1291	–	–	–	–	–	–
AGE >70 vs. ≤70	0.89 (0.70–1.14)	0.3460	–	–	–	–	–	–
Viral etiology Yes vs. No	0.99 (0.78–1.25)	0.9052	0.97 (0.76–1.24)	0.8080	–	–	–	–
NASH/NAFLD Yes vs. no	0.87 (0.65–1.16)	0.3566	–	–	–	–	–	–
Previous surgery Yes vs. no	0.80 (0.62–1.04)	0.1074	0.88 (0.66–1.16)	0.3605	0.86 (0.64–1.17)	0.3352	0.91 (0.67–1.23)	0.53
Previous RFA Yes vs. No	0.97 (0.75–1.25)	0.8191	–	–	–	–	–	–
Previous TACE yes vs. no	0.82 (0.64–1.06)	0.1195	0.84 (0.65–1.09)	0.1980	0.86 (0.65–1.15)	0.3223	0.85 (0.64–1.14)	0.2816
Child Pugh class A vs. B	0.38 (0.23–0.64)	**<0.0001**	2.22 (1.53–3.22)	**<0.0001**	–	–	–	–
ECOG PS 0 vs. >0	0.96 (0.55–1.69)	0.8898	1.03 (0.55–1.93)	0.9212	0.90 (0.46–1.76)	0.7513	1.07 (0.55–2.11)	0.8356
AFP <400 vs. ≥400	0.67 (0.49–0.90)	**0.0033**	0.75 (0.56–0.99)	**0.0437**	0.79 (0.57–1.08)	0.1342	0.76 (0.56–1.04)	0.0836
NLR <3 vs. ≥3	0.66 (0.49–0.87)	**0.0035**	–		1.55 (1.18–2.04)	**0.0018**	1.51 (1.14–1.99)	**0.0037**
AST ≤NV vs. >NV	0.47 (0.37–0.59)	**<0.0001**	1.71 (1.26–2.32)	**0.0006**	1.87 (1.34–2.60)	**0.0002**	1.75 (1.26–2.44)	**0.0010**
ALT ≤NV vs. >NV	0.64 (0.49–0.83)	**0.0002**	1.28 (0.97–1.69)	0.0864	1.09 (0.80–1.47)	0.5861	1.07 (0.79–1.44)	0.6715
Bilirubin <2 mg/dl vs. ≥2 mg/dl	0.29 (0.1–0.87)	**<0.0001**	–	–	–	–	2.62 (1.21–5.70)	**0.0149**
Albumin >3.5 g/dl vs. ≤3.5 g/dl	0.45 (0.34–0.58)	**<0.0001**	–	–	–	–	2.04 (1.55–2.68)	**<0.0001**
Platelets >100,000 vs. ≤100,000	0.74 (0.57–0.96)	**0.0168**	1.22 (0.94–1.69)	0.1340	1.17 (0.87–1.56)	0.2931	1.35 (0.85–1.5	0.3879
ALBI 1 vs. 2	0.38 (0.24–0.59)	**<0.0001**	–	–	1.93 (1.32–2.83)	**0.0008**	–	–

Firstly, the results of univariate analysis are displayed, followed by those of the three multivariate analysis models. Statistically significant *P*-values are highlighted in bold.

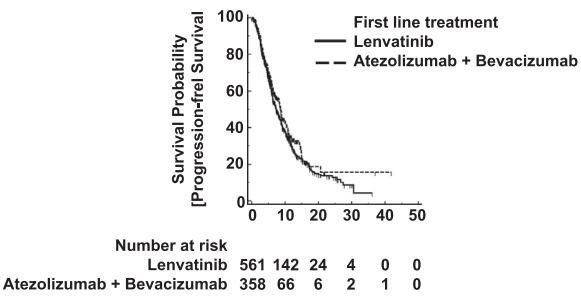

Fig. 2. The univariate analysis of time to progression (TTP) comparing Lenvatinib (solid line) against atezolizumab plus bevacizumab (dashed line). In contrast to Fig. 1, here atezolizumab plus bevacizumab shows a better TTP.

0.38, 95% CI 0.23–0.64 $P < 0.0001$), AFP <400 ng/ml (HR 0.67, 95% CI 0.49–0.90 $P = 0.0033$), albumin >3,5 g/dl (HR 0.45, 95% CI 0.34–0.58 $P < 0.0001$),NLR < 3 (HR 0.66, 95% CI 0.49–0.87 $P = 0.0035$), aspartate aminotransferase (AST) <Normal Value (NV) (HR 0.47, 95% CI 0.37–0.59 $P < 0.0001$), alanine amino transferase (ALT) ≤NV (HR 0.64, 95% CI 0.49–0.83 $P = 0.0002$), bilirubin <2 mg/dl (HR, 0.29, 95% CI 0.10–0.87 $P < 0.0001$), PLT≥100.000 (HR 0.74, 95% CI 0.57–0.96 P=.0168), ALBI score 1 (HR 0.38, 95% CI 0.24–0.59 $P < 0.0001$) (Table 3).

In univariate analysis of the entire population, the risk of progression was reduced in patients with Child-Pugh A compared to Child-Pugh B (HR 0.63,95% CI 0.44–0.91 $P = 0.0128$), AFP >400 ng/mL (HR 0.75, 95% CI 0.60–0.94 $P = 0.0128$), albumin >3.5 g/dl (HR 0.62, 95% CI 0.51–0.75 $P < 0.0001$), NLR<3 (HR 0.79, 95% CI 0.65-0.97, $P = 0.0246$), ALBI score 1 (HR 0.46, 95% CI 0.32–0.65 $P < 0.0001$) (Table 4).

To test all these variables in a multivariate analysis without incurring the bias of multicollinearity, three models were constructed: multivariate analysis confirmed no differences in terms of OS and TTP between Lenvatinib and atezolizumab plus bevacizumab (Tables 3 and 4). Forest plot highlighted that Lenvatinib had a better OS compared to atezolizumab plus bevacizumab in patients with NASH/NAFLD-related HCC (HR 0.24, 95% CI 0.08–0.74) and PLT>100.000 (HR 0.69, 95% CI 0.50–0.95). On the other hand, no significant predictors of OS were found in subgroups of atezolizumab plus bevacizumab (Fig. 3A). In terms of TTP, the forest plot did not show any predictors of TTP for patients who received Lenvatinib while patients who had undergone a previous surgery benefited more from treatment with atezolizumab plus bevacizumab compared to those who did not undergo surgery; in addition, atezolizumab plus bevacizumab had a better TTP in patients with NLR < 3 (HR 1.27, 95% CI 1.01–1.60) and platelets <100000 (HR 1.6, 95% CI 1.14–2.24).

Table 4
The results of univariate and multivariate analysis for time to progression (TTP) for potential prognostic factors in the two patient populations treated with Lenvatinib or atezolizumab plus bevacizumab.

	Univariate		Multivariate analysis					
			Model 1		Model 2		Model 3	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
First line treatment Lenvatinib vs. Atezolizumab + bevacizumab	0.86 (0.72–1.03)	0.1056	0.93 (0.75–1.15)	0.4837	0.89 (0.73–1.11)	0.3262	0.91 (0.74–1.13)	0.4214
SEX Female vs. male	0.97 (0.79–1.20)	0.7995	–	–	–	–	–	–
AGE >70 vs. ≤70	0.97 (0.81–1.16)	0.7132	–	–	–	–	–	–
Viral etiology Yes vs. no	0.89 (0.75–1.05)	0.1740	1.20 (0.99–1.45)	0.0690	1.19 (0.98–1.45)	0.0772	1.22 (1.00–1.48)	**0.0487**
NASH/NAFLD Yes vs. no	0.91 (0.63–1.31)	0.6009	–	–	–	–	–	–
Previous surgery Yes vs. No	0.93 (0.78–1.12)	0.4574	1.05 (0.85–1.30)	0.6601	1.06 (0.86–1.31)	0.5820	1.10 (0.89–1.36)	0.3941
Previous RFA Yes vs. No	0.84 (0.70–1.01)	0.0628	–	–	–	–	–	–
Previous TACE Yes vs. No	0.94 (0.79–1.13)	0.5379	1.05 (0.85–1.28)	0.6707	1.05 (0.86–1.29)	0.6348	1.10 (0.89–1.36)	0.6120
Child Pugh class A vs. B	0.63 (0.44–0.91)	**0.0128**	1.41 (0.98–2.05)	0.0675	–	–	–	–
ECOG PS 0 vs. >0	0.95 (0.64–1.40)	0.7779	0.87 (0.51–1.47)	0.5943	1.01 (0.59–1.72)	0.9745	1.13 (0.67–1.92)	0.6459
AFP <400 vs. ≥400	0.75 (0.60–0.94)	**0.0128**	0.76 (0.60–0.96)	**0.0228**	0.79 (0.62–1.00)	**0.0496**	0.78 (0.62–0.98)	**0.0383**
NLR <3 vs. ≥3	0.79 (0.65–0.97)	**0.0246**	1.29 (1.05–1.58)	**0.0145**	1.28 (1.04–1.57)	**0.0190**	1.24 (1.01–1.53)	**0.0411**
AST ≤NV vs. >NV	0.76 (0.64–0.90)	**0.0018**	1.24 (1.01–1.52)	**0.0355**	1.25 (1.02–1.52)	**0.0317**	1.19 (0.97–1.45)	0.0992
ALT ≤NV vs. >NV	0.85 (0.70–1.03)	0.0928	–	–	–	–		
Bilirubin <2 mg/dl vs. ≥2 mg/dl	0.54 (0.27–1.08)	0.0797	–	–	–	–	1.06 (0.52–2.14)	0.8763
Albumin >3.5 g/dl vs. ≤3.5 g/dl	0.62 (0.51–0.75)	**<0.0001**	–	–	–	–	1.53 (1.25–1.87)	**<0.0001**
Platelets >100,000 vs. ≤100,000	0.92 (0.76–1.12)	0.4095	–	–	–	–	–	–
ALBI 1 vs. 2	0.46 (0.32–0.65)	**<0.0001**	–	–	1.65 (1.20–2.26)	**0.0020**	–	–

Firstly, the results of univariate analysis are displayed, followed by those of the three multivariate analysis models. Statistically significant *P*-values are highlighted in bold.

Table 5
The frequencies of different treatment responses in the two patient populations treated with Lenvatinib or atezolizumab plus bevacizumab.

	Lenvatinib ($N=561$)	Atezolziumab plus bevacizumab ($N=358$)	*P*-value
CR	46 (8%)	17 (5%)	–
PR	215 (38%)	79 (22%)	–
SD	220 (39%)	195 (54.5%)	–
ORR	261 (46.5%)	96 (26.8%)	**<0.000001**
DCR	481 (86%)	291 (81%)	0.079656

Lenvatinib achieved a higher ORR than did atezolizumab plus bevacizumab. Statistically significant *P*-values are highlighted in bold.

Finally, Lenvatinib showed a higher percentage of response rate compared to patients treated with atezolizumab plus bevacizumab (46.5% *v* 26.8% respectively, $P<0.000001$); without differences in disease control rates (86% *v* 81% prespectively, $P=0.079656$); (Table 4).

Table 6 summarizes the AEs observed. The main drug-related AEs in patients treated with Lenvatinib were fatigue (34.1%), decreased appetite (34%), hypertension (33.8%) while the main drug-related AEs amongst those receiving atezolizumab plus bevacizumab were proteinuria (28.5%), hypertension (24.1%) and fatigue (21.5%). Data highlighted that HFSR ($P<0.000001$), diarrhea ($P<0.000001$), hypertension ($P=0.001$), fatigue ($P=0.000042$), decrease appetite ($P<0.000001$), and hypothyroidism ($P<0.000001$), occurred significantly more frequently in patients treated with Lenvatinib, while immune related toxicity ($P<0.000001$) was found significantly more frequently in patients treated with atezolizumab plus bevacizumab.

Discussion

We report a large sample-size study on the prognostic impact of first line treatment with Lenvatinib versus atezolizumab plus bevacizumab in a cohort of patients affected by intermediate stage (BCLC-B) HCC. In particular, in the present study, no significant differences in terms of both OS and TTP were reported in patients with BCLC-B HCC who received Lenvatinib or atezolizumab plus bevacizumab. While Lenvatinib exhibited a tendency toward a better OS and a higher ORR compared to atezolizumab plus bevacizumab, this did not reach statistical significance.

In recent years, several advances have been made in terms of systemic treatment for advanced HCC, thanks to the positive results of several randomized prospective trials, which led to the approval of a number of new drugs and combinations as therapeutic options for this setting of patients [21–23]. Moving from these, a special interest has been focused on the intermediate stage accord-

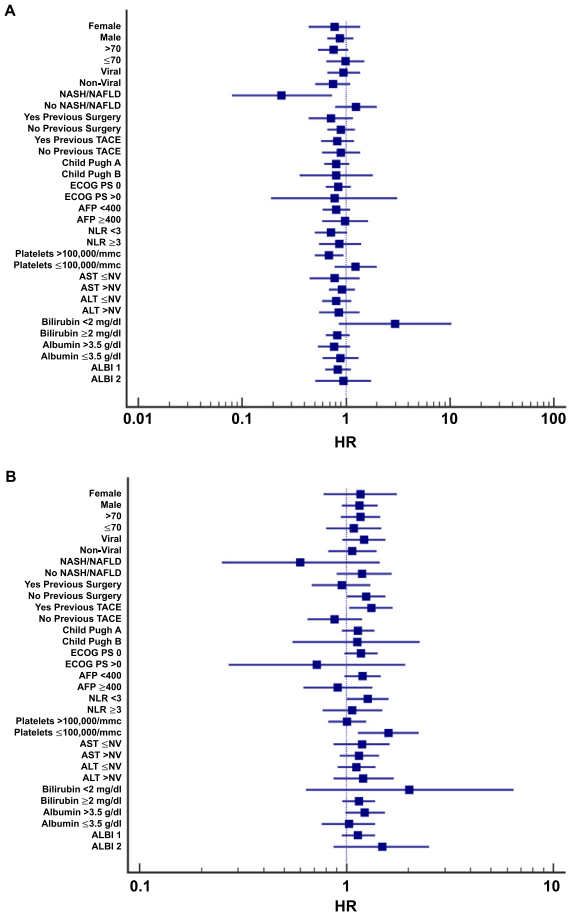

Fig. 3. The forest plot for overall survival (OS) (A) and time to progression (TTP) (B) comparing Lenvatinib and atezolizumab plus bevacizumab ($A + B$) across various subgroups.

Table 6
The percent frequency of different adverse reactions in the two treatment groups.

Toxicity of any grade	Atezolizumab plus bevacizumab N (%)	Lenvatinib N (%)	*P*-value
HFSR			
Yes	6 (1.6)	123 (21.9)	**$P < 0.000001$**
No	352 (98.4)	438 (78.1)	
Diarrhea			
Yes	27 (7.5)	126 (22.4)	**$P < 0.000001$**
No	331 (92.5)	435 (77.6)	
Hypertension			
Yes	86 (24.1)	190(33.8)	**$P = 0.001$**
No	272 (75.9)	371(66.2)	
Fatigue			
Yes	77 (21.5)	191 (34.1)	**$P = 0.000042$**
No	281 (78.5)	370 (65.9)	
Decreased appetite			
Yes	62 (17.3)	194(34.6)	**$P < 0.000001$**
No	296 (82.7)	367(65.4)	
Proteinuria			
Yes	102 (28.5)	145 (25.8)	$P = 0.40$
No	256 (71.5)	416 (74.2)	
Hypothyroidism			
Yes	22 (6.2)	183 (32.6)	**$P < 0.000001$**
No	336 (93.8)	378 (67.4)	
Immune-related toxicities			
Yes	41 (11,5)		**$P < 0.000001$**
No	317 (88,5)	561 (100)	
Other toxicities			
Yes	64 (17.8)	235 (41.8)	**$P < 0.000000001$**
No	294 (82.1)	326 (58)	

Statistical significance is indicated in bold.

ing to the BCLC staging system, in which setting the only approved therapeutic option is TACE. Indeed, the intermediate stage presents a heterogeneous population in terms of both residual liver function and tumor burden, and TACE alone has already demonstrated limited efficacy in the subgroup of BCLC B patients with multiple nodules and high tumor burden. Given this, interest in administering systemic treatments in patients intermediate HCC stage is growing, especially given the efficacy of systemic treatments like Lenvatinib and atezolizumab plus bevacizumab. A new dynamic therapeutic paradigm is currently emerging in the HCC setting, which is characterized by the shift from a treatment allocation strictly based on pretreatment staging features towards a more personalized approach based on a multiparametric therapeutic hierarchy, in which all the treatment options are ordered according to the survival benefit and their conversion or adjuvant abilities [24]. If the positive results achieved with new systemic treatments could be replicated in patients with BCLC-B HCCs, one could envision a so-called stage migration which would open the way to improved treatments in patients which, accordingly to the traditional BCLC model, might only be considered candidates for palliative treatments. In addition, another important aspect has to be taken in count. Results from the randomized EMERALD-1 trial (NCT03778957), a double-blind, global, phase 3 study demonstrated benefit in terms of PFS and TTP for patients eligible for embolization with the combination of TACE plus the anti-PDL1 antibody, durvalumab, and bevacizumab compared to TACE alone, and a recent sub-analysis highlighted a 60% ORR according to the modified RECIST criteria for patients who received these new combinations, thus opening the possibility of combining locoregional and systemic treatments for this setting of patients. EMERALD-1 reported higher ORRs, but already with Lenvatinib, atezolizumab, bevacizumab, or the regimen termed STRIDE consisting of a single, high priming dose of tremelimumab (anti-cytotoxic T lymphocyte–associated antigen 4) plus durvalumab (anti–programmed cell death ligand-1), we have already witnessed numerous patients experiencing stage migration.

The optimal efficacy results obtained in the present real-l analysis, mainly in the group of patients who received Lenvatinib, corroborates that concept. Recently, Tada and colleagues performed a similar analysis on 358 patients with BCLC-B HCC receiving Lenvatinib or atezolizumab plus bevacizumab. After propensity score matching, a significantly higher PFS was found in the group of patients who received atezolizumab plus bevacizumab; the benefit of atezolizumab plus bevacizumab was also confirmed after considering a subgroup of patients with HCC beyond the up-to-seven criteria [10]. Differences in sample size and baseline characteristics of the two cohorts of BCLC-B patients, along with the different ethnicities, may explain the different results from our analysis and those performed by Tada and his Japanese colleagues. The forest plot analysis performed in the present study deserves attention. In terms of OS, Lenvatinib appeared to better performs in patients with a NASH/NAFLD-related HCC and in those with platelets 100,000, whereas no significant predictors of OS were highlighted for patients who received atezolizumab plus bevacizumab. Several preclinical and clinical data sustain the different pathophysiology underlying viral and nonviral HCC, which could lead to different responses to different treatments [25]. In particular, a significant amount of preclinical and clinical real-world data demonstrated a possible higher benefit for patients with NASH/NAFLD with Lenvatinib compared to atezolizumab plus bevacizumab [13–17]. Why in the present cohort of patients with BCLC-B HCC those with platelets >100000/mmc benefit more from Lenvatinib compared

to atezolizumab plus bevacizumab is more difficult to explain. A possible role of the thrombophilic effect of bevacizumab could be hypothesized. Alternately, it could be speculated that the immunosuppressive effect exerted by platelets on the tumor microenvironment through the production of transforming growth factor- β (TGF-β) [26] could make patients with high platelet counts less likely to respond to immunotherapy. Further investigations will be needed in order to better understand this result. In terms of TTP, the forest plot we performed highlighted better outcomes in favor of atezolizumab plus bevacizumab for patients with NLR<3. NLR is already known as a marker of systemic inflammation, since is calculated as the ratio of the two main immune populations: neutrophils and lymphocytes. A large amount of evidence sustains a correlation between high NLR and poor prognosis in several oncologic settings, including HCC [27]. In patients with cancer who receive immunotherapy, therapeutic response has been linked to increased infiltration of CD3+ and CD8+ *T* cells [28], and elevated effector T cells [29]; high NLR has been associated with a proinflammatory immune-microenvironment characterized by tumor necrosis and low tumor-infiltrating lymphocytes (TILs), potentially helping to explain why low levels of NLR emerged as prognostic of TTP in patients with HCC who received atezolizumab plus bevacizumab.

Finally, the present analysis confirms the safety profiles of both Lenvatinib and atezolizumab plus bevacizumab in patients with BCLC-B HCC, with results comparable to to those reported in the prospective trials.

Several limitations could be ascribed to the present work. First of all, the multicentric retrospective nature could not exclude selection biases. Indeed, the two cohorts of patients, those received Lenvatinib and those administered atezolizumab plus bevacizumab, presented several differences in terms of sample size, median follow up and baseline characteristics. Cognizant of this we performed three multi-variate analyses with adjustment for the unbalanced characteristics in order to reduce the bias. Interestingly, in all the three models, no differences were found in terms of survival outcomes in patients affected by BCLC-B HCC according to the first line treatment used Lenvatinib versus atezolizumab plus bevacizumab, reinforcing the result. Secondly, the multicentric nature of the work need to take in count slight differences in tumor assessment modalities and time-points, which could have partially affected the TTP data.

We believe the present work addresses an important clinical query regarding the value of two first line systemic treatments in patients with BCLC-B HCC, by showing no significant differences in terms of both OS and TTP between Lenvatinib and atezolizumab plus bevacizumab, with a better ORR for Lenvatinib in a large and multinational study. Future prospective validations will be necessary in order to confirm our results, but the present analysis conducted on a large sample size could add a little piece to the puzzle of the best systemic choice for patients affected by unresectable HCC, which will be of particular interest in the growing scenario of therapeutic options for this clinical presentation.

Informed consent statement

Written informed consent for treatment was obtained for all patients.

IRB approval

The Ethical Review Board of each Institutional Hospital approved the present study. This study was performed in line with the principles of the Declaration of Helsinki.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Francesco Vitiello: Writing – original draft, Methodology, Formal analysis, Data curation. **Toshifumi Tada:** Supervision. **Goki Suda:** Supervision. **Shigeo Shimose:** Supervision. **Masatoshi Kudo:** Supervision. **Jaekyung Cheon:** Supervision. **Fabian Finkelmeier:** Supervision. **Ho Yeong Lim:** Supervision. **José Presa:** Supervision. **Gianluca Masi:** Supervision. **Changhoon Yoo:** Supervision. **Sara Lonardi:** Supervision. **Francesco Tovoli:** Supervision. **Takashi Kumada:** Supervision. **Mario Scartozzi:** Supervision. **Emiliano Tamburini:** Supervision. **Francesco Giuseppe Foschi:** Supervision. **Mara Persano:** Supervision. **Federico Rossari:** Supervision. **Silvia Foti:** Supervision. **Silvia Camera:** Supervision. **Francesco De Cobelli:** Supervision. **Luca Aldrighetti:** Supervision. **Stefano Cascinu:** Supervision. **Andrea Casadei-Gardini:** Supervision, Conceptualization. **Margherita Rimini:** Supervision.

Acknowledgments

The present work received no financial support.

References

[1] H Sung, J Ferlay, RL Siegel, et al. 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Global Cancer Statistics.
[2] Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999;19(3):329–38. doi:10.1055/s-2007-1007122.
[3] Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. J Hepatol 2022;76(3):681–93. doi:10.1016/j.jhep.2021.11.018.
[4] Weinmann A, Koch S, Sprinzl M, et al. Survival analysis of proposed BCLC-B subgroups in hepatocellular carcinoma patients. Liver Int 2015;35(2):591–600. doi:10.1111/liv.12696.
[5] Peck-Radosavljevic M, Kudo M, Raoul JL, et al. Outcomes of patients (pts) with hepatocellular carcinoma (HCC) treated with transarterial chemoembolization (TACE): global OPTIMIS final analysis. J Clin Oncol 2018;36(15_suppl):4018.
[6] Kudo M, Ueshima K, Chan S, et al. Lenvatinib as an initial treatment in patients with intermediate-stage hepatocellular carcinoma beyond up-to-seven criteria and child-Pugh A liver function: a proof-of-concept study. Cancers (Basel). 2019;11(8):1084. doi:10.3390/cancers11081084.
[7] Llovet JM, Ricci S, Mazzaferro V, et al. Jordi Bruix; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359(4):378–90. doi:10.1056/NEJMoa0708857.
[8] Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018;391(10126):1163–73. doi:10.1016/S0140-6736(18)30207-1.
[9] Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 2020;382(20):1894–905. doi:10.1056/NEJMoa1915745.
[10] Abou-Alfa GK, Chan SL, Kudo M, et al. Phase 3 randomized, open-label, multicenter study of tremelimumab and durvalumab as first-line therapy in patients with unresectable hepatocellular carcinoma: HIMALAYA. J Clin Oncol 2022;40:379. doi:10.1200/JCO.2022.40.4_suppl.379-.
[11] Robert Galle P, Decaens T, Kudo M, et al. Nivolumab (NIVO) plus ipilimumab (IPI) vs Lenvatinib (LEN) or sorafenib (SOR) as first-line treatment for unresectable hepatocellular carcinoma (uHCC): first results from CheckMate 9DW. J Clin Oncol 2024;42(Number 17_suppl). doi:10.1200/JCO.2024.42.17_suppl.LBA400.
[12] Qin S, Kudo M, Meyer T, et al. Tislelizumab vs Sorafenib as first-line treatment for unresectable hepatocellular carcinoma: a phase 3 randomized clinical trial. JAMA Oncol 2023;9(12):1651–9. doi:10.1001/jamaoncol.2023.4003.
[13] Bruix J, Qin S, Merle P, et al. RESORCE investigators. Lancet 2017;389(10064):56–66. doi:10.1016/S0140-6736(16)32453-9.
[14] Abou-Alfa GK, Meyer T, Cheng A-L, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. N Engl J Med 2018;379(1):54–63. doi:10.1056/NEJMoa1717002.
[15] Zhu AX, Kang Y-K, Yen C-J, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concen-

trations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trialù. Lancet Oncol 2019;20(2):282–96. doi:10.1016/S1470-2045(18)30937-9.
[16] Yau T, Park J-W, Finn RS, et al. Lancet Oncol 2022;23(1):77–90. doi:10.1016/S1470-2045(21)00604-5.
[17] Tada T, Kumada T, Hiraoka A, et al. Real-life practice experts for HCC (RELPEC) Study Group and the Hepatocellular Carcinoma Experts from 48 clinics in Japan (HCC 48) Group. Comparison of prognostic impact of atezolizumab plus bevacizumab versus Lenvatinib in patients with intermediate-stage hepatocellular carcinoma. Liver Int 2024;44(1):113–24. doi:10.1111/liv.15753.
[18] Vitale A, Cabibbo G, Iavarone M, et al. HCC Special Interest Group of the Italian Association for the Study of the Liver. Personalised management of patients with hepatocellular carcinoma: a multiparametric therapeutic hierarchy concept. Lancet Oncol 2023;24(7):e312–22. doi:10.1016/S1470-2045(23)00186-9.
[19] Llovet JM, Zucman-Rossi J, Pikarsky E, et al. Hepatocellular carcinoma. Nat Rev Dis Primers 2016;2:16018. doi:10.1038/nrdp.2016.18.
[20] Pfister D, Núñez NG, Pinyol R, et al. NASH limits anti-tumour surveillance in immunotherapy-treated HCC. Nature 2021;592(7854):450–6. doi:10.1038/s41586-021-03362-0.
[21] Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018;391(10126):1163–73. doi:10.1016/S0140-6736(18)30207-1.
[22] Finn RS, Qin S, Ikeda M, et al. IMbrave150 Investigators. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 2020;382(20):1894–905. doi:10.1056/NEJMoa1915745.
[23] Abou-Alfa GK, Chan SL, Kudo M, et al. Phase 3 randomized, open-label, multicenter study of tremelimumab and durvalumab as first-line therapy in patients with unresectable hepatocellular carcinoma: HIMALAYA. J Clin Oncol 2022;40:379. doi:10.1200/JCO.2022.40.4_suppl.379-.
[24] Vitale A, Cabibbo G, Iavarone M, et al. HCC Special Interest Group of the Italian Association for the Study of the Liver. Personalised management of patients with hepatocellular carcinoma: a multiparametric therapeutic hierarchy concept. Lancet Oncol 2023;24(7):e312–22. doi:10.1016/S1470-2045(23)00186-9.
[25] Llovet JM, Zucman-Rossi J, Pikarsky E, et al. Hepatocellular carcinoma. Nat Rev Dis Primers 2016;2:16018. doi:10.1038/nrdp.2016.18.
[26] Schmied L, Höglund P, Meinke S. Platelet-mediated protection of cancer cells from immune surveillance–possible implications for cancer immunotherapy. Front Immunol 2021;12:640578. doi:10.3389/fimmu.2021.640578.
[27] Johnson PJ, Dhanaraj S, Berhane S, et al. The prognostic and diagnostic significance of the neutrophil-to-lymphocyte ratio in hepatocellular carcinoma: a prospective controlled study. Br J Cancer 2021;125(5):714–16. doi:10.1038/s41416-021-01445-3.
[28] Wu YL, Fulgenzi CAM, Alessio A, et al. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios as prognostic biomarkers in unresectable hepatocellular carcinoma treated with atezolizumab plus bevacizumab. Cancers (Basel) 2022;14(23):5834. doi:10.3390/cancers14235834.
[29] Zhu AX, Abbas AR, de Galarreta MR, et al. Molecular correlates of clinical response and resistance to atezolizumab in combination with bevacizumab in advanced hepatocellular carcinoma. Nat Med 2022;28(8):1599–611. doi:10.1038/s41591-022-01868-2.