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Atezolizumab plus bevacizumab in advanced hepatocellular carcinoma after treatment failure with multikinase inhibitors

Vincent Haghnejad[a,b], Marie Muller[a,b,1], Lorraine Blaise[c], Rene Gerolami[d], Mohamed Bouattour[e], Eric Assenat[f], Sylvain Manfredi[g,h], Jean-Marie Peron[i], Adriano Burcheri-Curatolo[j], Anthony Lopez[a,b], Emmnanuelle Ressiot[d], Pierre Nahon[c,k], Jean-Pierre Bronowicki[a,b,*]

[a] Department of Hepatology and Gastroenterology, Nancy University Hospital, University of Lorraine, 54500 Vandœuvre-lès-Nancy, France
[b] INSERM U1256, NGERE, Faculty of Medicine, University of Lorraine, 54500 Vandœuvre-lès-Nancy, France
[c] Liver Unit, Bobigny; University of Sorbonne Paris Nord, F-93000 Bobigny, France
[d] Department of Hepatology, La Timone University Hospital, Marseille, France
[e] Liver Cancer Unit, Assistance-Publique Hôpitaux de Paris, Beaujon University Hospital, Clichy, France
[f] Department of Oncology, St-Eloi University Hospital, Montpellier, France
[g] Department of Hepatology and Gastroenterology, Dijon University Hospital, France
[h] INSERM U 1231, University of Bourgogne Franche Comté, Dijon, France
[i] Hepatology Unit, Rangueil University Hospital, Toulouse, France
[j] Department of Biopathology, CHRU Nancy, Faculty of Medicine, Université de Lorraine, Vandoeuvre-lès-Nancy, France
[k] Inserm, UMR-1138 "Functional Genomics of Solid Tumors", Centre de recherche des Cordeliers, University of Paris, Paris, France.

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ABSTRACT

Background and aims: Data on the effectiveness of atezolizumab plus bevacizumab (atezo-bev) after failure of multikinase inhibitor (MKI) therapy in patients with advanced hepatocellular carcinoma are scarce.
Methods: This retrospective multicentre study included all consecutive patients treated with atezo-bev after failing one or more MKI treatments in the setting of an early access program. The primary endpoint was the objective response rate (ORR) by investigator assessment (using Response Evaluation Criteria in Solid Tumors v1.1). Overall survival (OS) and progression-free survival (PFS) were assessed using the Kaplan–Meier method.
Results: Fifty patients were included in this analysis. Atezo-bev was started between April 2020 and November 2021 (median follow-up, 18.21 months). The investigator-assessed ORR was 14% (95% CI 5.37–22.63%), with 7 patients displaying a tumour response, and the disease control rate was 56% (95% CI 51.21–60.8%). After starting atezo-bev, the median OS was 17.1 months (95% CI 10.58–22.01), and the median PFS was 7.99 months (95% CI 4.78–10.50). Treatment-related adverse events led to treatment discontinuation in 7 patients.
Conclusions: Atezo-bev every three weeks showed clinical benefit for a proportion of patients previously treated with one or multiple lines of MKIs.

1. Introduction

Hepatocellular carcinoma (HCC) is a leading cause of cancer death worldwide [1]. The prognosis is poor for patients with advanced, unresectable disease [2]. For more than a decade, sorafenib, an antiangiogenic multikinase inhibitor (MKI), was the only systemic agent available with a survival benefit for the treatment of advanced HCC (aHCC) [3]. MKIs, including regorafenib, cabozantinib, and the monoclonal antibody ramucirumab, have been approved for patients previously treated with sorafenib, and pivotal phase 3 trials report median overall survival (OS) times ranging from 8.5 months to 10.6 months [4–6]. The anti-programmed cell death protein-1 (anti PD-1) immune checkpoint inhibitors (ICIs) nivolumab and pembrolizumab were approved in some countries, such as the United States, as second-line therapy for aHCC, with median OS times ranging from 12.9 months to 13.1 months [7,8]. More recently, atezolizumab plus bevacizumab (atezo-bev) showed a significant benefit in OS and progression-free survival (PFS) compared with sorafenib in patients with sys-

* Corresponding author at: Hépato-gastroentérologie, INSERM U1256 CHRU Nancy, 54500 Vandoeuvre-lès-Nancy, France.
E-mail address: jp.bronowicki@chru-nancy.fr (J.-P. Bronowicki).
[1] Co-first author.

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temic treatment-naïve aHCC [9]. Based on these findings, atezo-bev is now approved for the treatment of aHCC without previous systemic therapy. The French early access program allows physicians to implement new innovative and approved molecules before their reimbursement. In 2020, atezo-bev was approved for use in France at a time when most patients were under or failed to respond to multiple lines of MKI. However, no data were available at this time regarding the safety and efficacy of this therapeutic sequence, and the current literature on this situation remains scarce [10–13]. The objectives of this retrospective multicentre study were to assess the objective response rate (ORR), OS and PFS in patients with aHCC treated with atezo-bev following previous lines of treatment with one or several MKIs.

2. Patients and methods

2.1. Study design and participants

This retrospective study included all patients recruited from 7 French university hospitals between April 2020 and November 2021. Patients were over 18 years of age, had an established diagnosis of aHCC, and were treated with the combination of atezolizumab 1200 mg plus bevacizumab 15 mg/kg intravenously every three weeks as a second- or nth-line therapy after MKI failure. Each treatment indication was validated by the respective hospital tumour board, taking into account the national guidelines as well as the opportunity allowed by the French early access program. Tumours were assessed by computed tomography or magnetic resonance imaging at baseline and then every three courses of treatment (every 9–12 weeks) until the treatment was stopped. The best radiological response was classified as complete response (CR), partial response (PR), stable disease, or progressive disease based on investigator assessment using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [14]. Patients who were previously treated with immunotherapy were excluded from the final analysis. Survival data were censored as of October 1, 2022.

2.2. Statistical analysis

Patients' baseline characteristics are described using median and interquartile range (IQR) for quantitative variables and numbers and percentages for categorical variables. The ORR was defined as the proportion of all treated patients whose best overall response was CR or PR. Both the median OS and PFS were computed using Kaplan–Meier curves and compared with the log-rank (Mantel–Cox) test. Hazard ratios (HRs) for events were estimated using the log-rank method. The modified albumin-bilirubin grade (mALBI) with 4 grades ($1 \leq 2.60$, $2a > -2.60$ to ≤ -2.27, $2b > -2.27$ to ≤ -1.39, and $3 > -1.39$) was calculated using the formula (log10bilirubin (µmol/L) × 0.66) + (albumin (g/L) × –0.085) [15].

2.3. Statement of ethics

This study was approved by the institutional review board of the CHRU in Nancy under the reference 2021PI23. The study used the reference methodology MR004 defined by the French National Commission on Informatics and Liberty and has thus been granted an exemption from requiring ethics approval from an independent ethics committee. Subjects provided written informed consent to collect data based on the principles of the Declaration of Helsinki. The information collected was strictly limited to the purpose of this study. The data were extracted from patient electronic medical records. The management of the electronic dataset was realized under conditions guaranteeing the confidentiality of the data and the anonymity of the patients.

3. Results

3.1. Patients

We identified 60 patients who received atezo-bev as second- or nth-line therapy. Ten patients (16.4%) were excluded from the final analysis because they received previous immunotherapy agents. The patient characteristics are described in Table 1. Forty-three patients were classified as Child–Pugh A (86%). The aetiology of the liver disease was viral in 21 patients (42%) and strictly nonviral in 29 patients (58%). Macrovascular invasion was noted in 20 patients (40%), and extrahepatic metastasis was noted in 31 patients (62%). Seventeen patients (34%) had an α-fetoprotein (AFP) level above 400 ng/ml (range 1.3–200000 ng/ml). The median time from diagnosis of HCC to combination therapy initiation was 2.86 years (IQR 1.77–3.86 years). Before atezo-bev initiation, 48% of patients received one line of MKI, and 52% received two or more lines of MKIs. Sorafenib was the most frequently administered MKI (98%), followed by cabozantinib (38%). The median exposure time to MKIs was 11.4 months. The switch from MKI to atezo-bev was attributed to progression for 41 patients (82%) and toxicity for 9 patients (18%). None of the patients were shifted to combination therapy while they were stable under MKI therapy.

3.2. Patient outcomes

The mean and median exposure times to atezo-bev were 8.79 months and 7.99 months, respectively (IQR: 3.26–12.53). The median follow-up time was 18.1 months. At the date of censorship, 29 patients (58%) had stopped atezo-bev due to either clinical (n=1) or tumour progression (n=28). Clinical progression was due to an intestinal bowel obstruction that was later attributed to the progression of peritoneal carcinomatosis. Two patients (4%) were lost to follow-up before radiological assessment. Two patients (4%) had a liver decompensation preluding a radiological progression that led to the permanent discontinuation of the treatment. Median time to decompensation was 2.61 months. One patient initially Child-Pugh score A6 - mALBI grade 2b has further aggravated to Child-Pugh score B7 with ascites -mALBI grade still 2b. He received one more infusion of atezo-bev before further aggravation of the Child-Pugh score from B7 to B8 and a mALBI grade 3. The other patient had an initial Child-Pugh score A5 and a mALBI grade 2b that has aggravated to B8 with jaundice and a mALBI grade 3. Radiological assessment confirmed the associated morphological progression in both cases. Six patients (12%) permanently stopped the combination treatment due to drug toxicity: one case of arterial pulmonary hypertension attributed to bevacizumab; two cases of hypertension attributed to bevacizumab, of which one case with grade 3 urine proteins; one case of myocarditis attributed to atezolizumab; one case of anaphylaxis and one case of rectal bleeding indistinctively attributed to both drugs. Altogether, treatment discontinuation for drug-related toxicity occurred for four patients with mALBI grade 2b, one patient with mALBI grade 2a and one patient with mALBI grade 1. No treatment-related deaths were reported. The most common adverse event reported was asthenia (8.0%). Eleven patients (22.0%) were still under combination therapy at the censoring date. Table 2 summarizes the disposition of the patients at the time of the analysis. Table 3 summarizes the treatment-emergent adverse events.

The ORR by investigator assessment using RECIST v1.1 was 14% (n=7) (95% CI 5.37–22.63), and the disease control rate (DCR) was 56% (n=28) (95% CI 51.21–60.8) (Table 4).

After initiating atezo-bev, the median OS was 17.1 months (95% CI 10.58–22.01, range 1.15–22.82) (Fig. 1 a), and the median PFS for all patients was 7.99 months (95% CI 4.78–10.50) (Fig. 1 b). The median OS times were 21.57 months (95% CI 15.77–22.53)

Table 1
Baseline clinical characteristics of patients with advanced hepatocellular carcinoma treated with atezolizumab plus bevacizumab after failure of a multikinase inhibitor.

Characteristic	Total (n=50)
Age, years	
Median	65
IQR	60-71
Sex, Male, n (%)	38 (76)
ECOG performance status, n (%)	
0	28 (56)
1	17 (34)
2	2 (4)
Missing	3 (6)
Aetiology of HCC, n (%) †	
Alcohol	17 (34)
Viral hepatitis B	10 (20)
Viral hepatitis C	13 (26)
MAFLD[a]	14 (28)
Multiple etiologies[b]	2 (4)
Unknown[c]	5 (10)
Child–Pugh grade, n (%)	
A5	31 (62)
A6	12 (24)
B7	5 (10)
B8	1 (2)
B9	1 (2)
mALBI grade	
1	11 (22.0)
2a	13 (26.0)
2b	19 (38.0)
3	7 (14.0)
AFP >400 ng/ml, n (%)	17 (34.0)
Vascular invasion, n (%)	20 (40.0)
Extrahepatic metastasis, n (%)	31 (62.0)
Previous antiviral therapies	
Entecavir	6 (12.0)
Tenofovir	1 (2.0)
Direct-acting antiviral agents	12 (24.0)
Interferon	3 (6.0)
Ribavirine	2 (4.0)
Previous treatments before MKI treatment, n (%)	
Resection	16 (32.0)
Percutaneous ablation	10 (20.0)
Stereotactic radiotherapy	7 (14.0)
Transarterial chemoembolization	26 (52.0)
Transarterial radioembolization	9 (18.0)
Previous MKI treatments before atezolizumab plus bevacizumab, n (%)	
Sorafenib	49 (98)
Lenvatinib	12 (24)
Regorafenib	13 (26)
Cabozantinib	19 (38)
Number of MKI lines before atezolizumab plus bevacizumab, n (%)	
1 line	24 (48)
2 lines	14 (28)
3 lines	7 (14)
4 lines	5 (10)
Exposure to MKIs, months	
Median	11.4
IQR	6.3-22

HCC, Hepatocellular Carcinoma; MKI, multikinase inhibitor; ECOG, Eastern Cooperative Oncology Group; AFP, α-fetoprotein. † Some patients had >1 disease aetiology category; a: metabolic dysfunction-associated fatty-liver disease b: 1 haemochromatosis and one hepatic vascular disease; c: no aetiology was found, and the viral serologies were negative.

for patients with stable disease or PR and 10.57 months (95% CI 4.94–11.92 months) for patients with progressive disease (HR 0.27, 95% CI of ratio 0.10–0.73, $p = 0.0005$) (Fig. 2). The median OS times were 14.83 months (95% CI 7.19–22.01) for patients with only one line of MKI pre-exposure and 17.1 months (95% CI 10.53–not reached) for patients with $\geq$ 2 MKI treatments (HR 1.05, 95% CI of ratio 0.51–2.25, $p = 0.84$). Patients with a MKI pre-exposure time above 12 months had a median OS of 17.1 months (95% CI 9.95-not reached) and a median PFS of 10.06 months (95% CI 3.35-17.56). Patients with a MKI pre-exposure time below 12 months had a median OS of 15.62 months (95% CI 7.21-21.99) and a median PFS of 6.375 months (95% CI 3.45-9.73). OS and PFS were not significantly different between these two subgroups (HR 1.20, 95% CI of ratio 0.57–2.54, $p = 0.62$ for OS and HR 1.23 0.65-2.30, $p = 0.51$ for PFS) (shown in Supplementary 1). OS was not significantly different based on AFP level and HCC aetiology, although the median survival times were 20.84 months for patients with an AFP level below 400 ng/ml (95% CI 11.04–22.46) and 11.87 months for patients with an AFP level above 400 ng/ml (95% CI 5.78–21.55) (HR 0.57, 95% CI of ratio 0.24–1.31, $p = 0.13$) (shown in Supplementary 2). OS and PFS were significantly different depending on the mALBI grade ($p = 0.0129$ and 0.0001, respectively). Eleven pa-

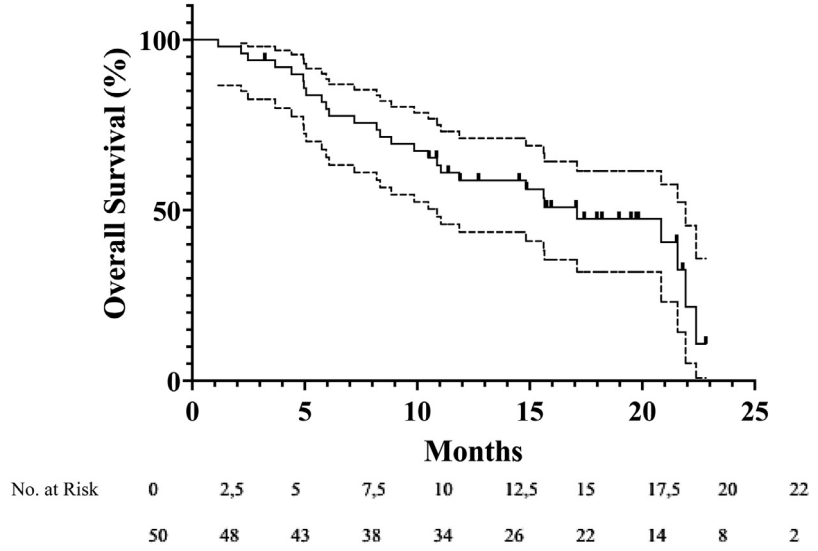


Fig. 1. a. Overall survival from the initiation of atezolizumab plus bevacizumab. The confidence interval is represented by dotted lines b. Progression-free survival from the initiation of atezolizumab plus bevacizumab.

Table 2
Patient disposition.

	Total (n=50)
Continuing treatment, n (%)	11 (22.0)
Treatment discontinuation, n (%)	39 (78.0)
Reasons for discontinuation	29 (58.0)
Progression†	6 (12.0)
Adverse effects	2 (4)
Liver decompensation with progression	0 (0)
Liver decompensation without progression	0 (0)
Death	2
Loss to follow-up	(4.0)
Treatment duration, months	
Mean	8.79
Median	7.99
IQR	3.26–12.53

† Either clinical (n=1) or radiological (n=28).

Table 4
Response and disease control rate.

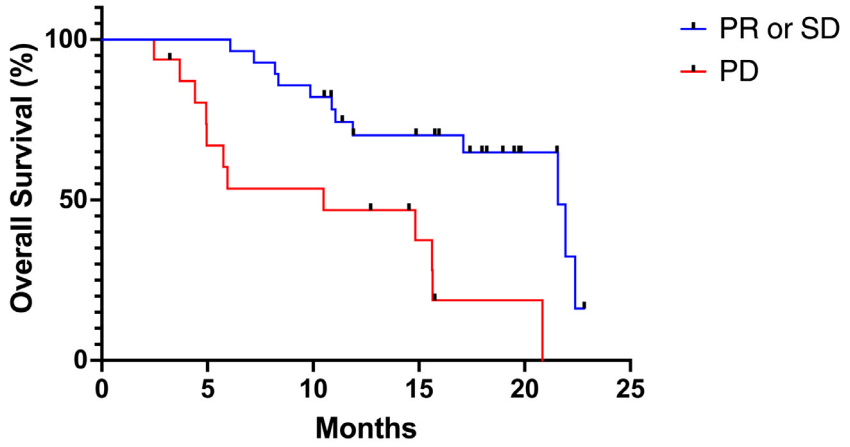
	Total (n=50)
Objective response rate using RECIST v1.1, n (%)	7 (14.0)
Best overall response using RECIST v1.1	
Complete response, n (%)	0 (0)
Partial response, n (%)	7 (14.0)
Stable disease, n (%)	21 (42.0)
Progressive disease, n (%)	16 (32.0)
Undetermined, n (%)†	6 (12.0)
Disease control rate, n (%)	28 (56.0)

† Two patients were lost to follow-up before radiological assessment, one patient had a treatment-related adverse event leading to discontinuation (myocarditis), two patients had clinical worsening before radiological assessment, of which one had intestinal bowel obstruction and one had worsening of liver function, and one patient had missing data.

Table 3
Summary of treatment-emergent adverse events.

	Teae		Teae Drug-related	
Teae, N (%)	Any grade	Grade 3/4	Any grade	Grade 3/4
Liver Decompensation	2 (4)	1 (2)	0 (0)	0 (0)
Hypertension†	4 (8)	2 (4)	4 (8)	2 (4)
Proteinuria	3 (6)	1 (2)	3 (6)	1 (2)
Rectal Bleeding	3 (6)	1 (2)	3 (6)	1 (2)
Myocarditis	1 (2)	1 (2)	1 (2)	1 (2)
Arterial pulmonary hypertension	1 (2)	1 (2)	1 (2)	1 (2)
Anaphylaxis	1 (2)	1 (2)	1 (2)	1 (2)
Asthenia	4 (8)	0 (0)	0 (0)	0 (0)
Pruritus	2 (4)	0 (0)	1 (2)	0 (0)
Nausea – vomiting	2 (4)	0 (0)	0 (0)	0 (0)
Epistaxis	2 (4)	0 (0)	2 (4)	0 (0)
Erythema	2 (4)	0 (0)	2 (4)	0 (0)
Dysthyroidism	2 (4)	0 (0)	2 (4)	0 (0)
Atrial fibrillation	1 (2)	0 (0)	0 (0)	0 (0)
Uveitis	1 (2)	0 (0)	1 (2)	0 (0)
Loss of appetite	1 (2)	0 (0)	0 (0)	0 (0)
Abdominal pain	1 (2)	0 (0)	0 (0)	0 (0)
Xerostomia	1 (2)	0 (0)	1 (2)	0 (0)
Palmoplantar hyperkeratosis	1 (2)	0 (0)	1 (2)	0 (0)
Lower limb oedema	1 (2)	0 (0)	0 (0)	0 (0)

TEAE, treatment-emergent adverse event; † One patient had grade 3 proteinuria associated with grade 3 hypertension.



No. at Risk - Progressive	0	2,5	5	7,5	10	12,5	15	17,5	20	20,8
	16	16	11	9	9	8	5	2	2	0
No. at Risk – SD or PR	0	2,5	5	7,5	10	12,5	15	17,5	20	22
	28	28	28	27	24	17	16	12	6	2

Fig. 2. Overall survival according to tumoral response (PR, partial response; SD, stable disease; PD, progressive disease).

tients with mALBI grade 1 had a median survival of 22.39 months (95% CI 4.96–22.82) and a PFS of 12.43 months (95% CI 9.63–not reached). Thirteen patients with mALBI grade 2a had a median survival of 15.62 months (95% CI 8.19–not reached) and a PFS of 9.17 months (95% CI 2.74–not reached). Nineteen patients with mALBI grade 2b had a median survival of 15.65 months (95% CI 5.95–21.72) and a PFS of 7.2 months (95% CI 3.42–10.96). Seven patients with mALBI grade 3 had a median survival of 8.84 months (95% CI 4.41–14.8) and a median PFS of 2.27 months (95% CI 1.51–4.78) (shown in Supplementary 3). Post-discontinuation survival was significantly different based on the reasons for discontinuation of the treatment ($p = 0.0010$). Two patients with a liver decompensation had a median post-discontinuation survival of 0.65 months (95% CI not estimated-1.26). Six patients with drug-related toxicities had a median post-discontinuation survival of 2.47 months (95% CI not estimated-13.59). 29 patients with a tumour progression had a median post-discontinuation survival of 7.27 months (95% CI 2.10-10.68) (shown in supplementary 4).

4. Discussion/conclusion

To our knowledge, this study is one of the largest cohorts with the longest median follow-up time of 18.21 months for aHCC patients treated with atezolizumab plus bevacizumab after prior exposure to one or multiple lines of MKIs. The atezo-bev combination provided a clinical benefit in patients pre-exposed to MKI, with an ORR of 14% (per RECIST v1.1) and a DCR of 56%. The patients had a median OS of 17.1 months from the date of treatment initiation and a PFS of 7.99 months. Patients with PR or stable disease had an improved median OS compared with those with progressive disease. Interestingly, our results showed that survival was neither influenced by the number of lines nor the pre-exposure time of MKIs used before. A few studies have reported early results of atezo-bev after MKI failure, usually after a very short follow-up period. Hiraoka et al reported the experience of 96 Japanese patients treated with atezo-bev after prior MKI exposure. After a median observation period of 2.25 months, the ORR and DCR were 9.7% and 77.8%, respectively, at 6 weeks [10]. In a second Japanese cohort, 44 patients with a history of systemic therapy were treated with atezo-bev [11]. The ORRs and DCRs observed using RECIST 1.1 were 5.2% and 82.8% at 6 weeks and 10.0% and 84.0% at 12 weeks, respectively. Portal vein invasion was the only factor associated with progressive disease, and there was a tendency for patients with underlying viral hepatitis B to have a better ORR ($p = 0.05$). A third Japanese study prospectively included 31 patients treated with lenvatinib [13]. The ORR and DCR were 17% and 60%, respectively. The median OS was 11.4 months, and the median PFS was 3.5 months. A German and Austrian multicentric retrospective study included 19 patients previously treated with sorafenib and three patients treated with lenvatinib before atezo-bev [12]. In their cohort, prior systemic treatment did not significantly affect the median OS, which was 8.2 months (3.6–12.7). Similarly, neither underlying liver disease nor AFP was identified as an independent prognostic factor. Likewise, in our study, neither baseline AFP levels nor the aetiology of liver disease significantly influenced the outcome, but this might be due to a lack of power since the median OS times were 20.84 months and 11.87 months for patients with AFP levels below or over 400 ng/ml, respectively.

No new safety signals were observed in our study. The rate of adverse events leading to treatment discontinuation was low. Recently, a modified albumin-bilirubin grade (mALBI grade) with 4 grades was reported to be a more useful assessment tool for hepatic function in aHCC patients undergoing systemic treatments [15]. Despite a mean follow-up of 2.5 months, they suggested that mALBI grade 2a might be the minimum hepatic function required to introduce atezo-bev to anticipate the postprogression treatment. In line with this assertion, OS and PFS were significantly correlated with mALBI grade in our study. One half of our cohort had a mALBI grade of 2b or 3. Patients with mALBI grade 2b still had an honourable OS of 13.35 months, but at the same time, 4 out of 6 treatment discontinuation cases for toxicity occurred in this subgroup. Moreover, 2 (4 %) patients with an initial mALBI

grade 2b had a median time to decompensation of 2.6 months and a significantly impaired post-discontinuation survival. Our results are in line with the Italian Association for the Study of the Liver who have recently highlighted the importance of evaluating appropriately the liver function before the onset and during systemic therapies [16]. This position paper suggests using atezo-bev in second-line, after sorafenib or lenvatinib, according to the concept of "drug class change". Accordingly, decision-making should be based on specific contraindications, patient's characteristics and reasons for first-line discontinuation. Distinction between discontinuation due to progression, intolerance or liver decompensation was already proposed for sorafenib and is known to have survival correlates [17]. However, current evidence on the use of ICIs has not yet demonstrated a liver toxicity profile significantly different from that of MKIs [18]. Future well-conducted real-world studies are advocated to unravel the risks of liver decompensation during therapy with MKIs and ICIs. Given the lack of evidence of properly designed randomized controlled trials, choosing the best sequential treatment is difficult and remains conditioned by country regulatory policies.

In Europe, MKIs, including regorafenib, cabozantinib and the monoclonal antibody ramucirumab, are the only approved therapies after sorafenib. Indirect comparisons suggest that atezo-bev may provide improved efficacy in terms of the ORR. Indeed, the CELESTIAL and RESORCE trials with cabozantinib and regorafenib demonstrated ORRs of 4% and 7%, respectively [5,6]. Ramucirumab, a direct VEGFR2 antagonist, showed an ORR of 4.6% in the REACH-2 trial for patients with a baseline AFP level of over 400 µg/l [4]. In these phase 3 studies, the median OS after sorafenib ranged from 8.5 months to 10.6 months. The Keynote 224 and CheckMate 040 studies led to FDA approval of nivolumab and pembrolizumab as second-line therapy after prior exposure to sorafenib [7,8,19]. The median OS times were 12.9 months and 13.1 months, respectively. ORRs of 17% and 18% were reported. The consecutive phase 3 Keynote-240 study did not reach a significant difference in OS, with median OS times of 13.9 months for pembrolizumab and 10.6 months for placebo [20]. The ORRs were 18.3% for pembrolizumab and 4.4% for placebo in the final analysis. Even though our study showed a better median OS, direct comparisons are difficult since half the population in our study included patients with two or more lines of MKIs. More recently, different combinations of nivolumab and ipilimumab have been evaluated in patients not responding to sorafenib [21]. The combination of nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every three weeks (4 doses), followed by nivolumab 240 mg every two weeks, was tested in 49 patients and resulted in an objective response in 32% of patients and a 54% DCR. The median OS was 22.8 months. However, 18% of patients had to stop treatment because of adverse events that were classified as grade 3-4 in more than half of the cases and often related to an immune-mediated effect. Overall, the optimal sequential first and second-line treatment strategy remains unanswered. To answer this question, an Italian team has developed a model based on randomized controlled trials for patients with aHCC [22]. Lenvatinib followed by nivolumab was the most effective sequence while atezo-bev followed by nivolumab was the safest sequence. Nonetheless, atezo-bev was not computed as a potential second-line treatment. Also, MKIs as first-line therapeutic agents might not have given their last words considering the role of liver aetiology [23], liver function [16], specific contraindications and more recently, antidrug antibodies against atezolizumab [24]. Transcriptomic analyses of 111 cases of aHCC treated by anti PD-1 revealed a gene expression signature capable of discriminating responders from nonresponders patients in terms of ORR, OS and PFS [25]. The study suggests that MKIs could reshape the tumoral microenvironment to render either sensitive or resistant to anti PD-1 depending on tumours biologies. In our study, preexposure time with MKIs did not significantly influence OS and PFS but it is unknown whether atezo-bev could overcome a tumoral microenvironment remodeling.

Our study has several limitations: 1) the retrospective design; 2) the limited number of patients; 3) a potentially selected population with an overall good condition and a low AFP level, which allowed the use of several lines of MKIs in more than half of them; and 4) the absence of patients pre-exposed to lenvatinib due to the non-reimbursement of this treatment in France.

Nevertheless, the median follow-up was twice as high as that in the Imbrave150 study (8.6 months), which confirmed the results after an additional 12 months of follow-up [9].

In conclusion, atezolizumab plus bevacizumab every three weeks may be a therapeutic option for patients previously treated with one or multiple lines of MKIs. Efficacy and side effects seemed related to liver function.

Author contributions

VH and JPB conceived and designed the study. VH, MM, LB, GR, MB, EA, JMP, ABC, AL, ER, PN, and JPB collected the data. VH and JPB analysed the data. All authors interpreted the data and were involved in the development, review and approval of the final version of the manuscript.

Conflict of Interest Statement

Pierre Nahon has received honouraria from and/or consults for AstraZeneca, Abbvie, Bayer, Bristol-Myers Squibb, Eisai, Gilead, Ipsen, MSD and Roche. He received research grants from AstraZeneca, AbbVie, Bristol-Myers Squibb and Eisai.

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Supplementary materials

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