Identification of Atezolizumab plus BEvacizumab prognostic index via recursive partitioning analysis in advanced hepatocellular carcinoma: the ABE index

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Abbreviations: HCC: hepatocellular carcinoma; OS: overall survival; HR: hazard ratio; CI: confidence interval; PD-L1: programmed cell death ligand-1; PFS: progression-free survival; ALBI: albumin-bilirubin; NLR: neutrophil-lymphocyte ratio; RPA: recursive partitioning analysis; AE: adverse events; AFP: alpha-fetoprotein; AST: aspartate aminotransferase; PD: progressive disease.

Conflict of Interest:

A.C.G. has received grants and personal fees from MSD, Eisai, Bayer, and is an advisor for MSD, Eisai, Bayer, Bristol-Myers Squibb, AstraZeneca and GSK.

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The other authors declare no conflicts of interest.

Commentato [RLH2]: If you may add Tiziana Pressiani please ask her for her COIs

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Authors' contributions:

Conception and design: A. Casadei-Gardini, M. Persano, M. Rimini.

Acquisition of data (acquired and managed patients): All authors.

Analysis and interpretation of data: A. Casadei-Gardini, M. Persano, M. Rimini.

Writing, review, and/or revision of the manuscript: A. Casadei-Gardini, M. Persano, M. Rimini.

Final approval of manuscript: All authors.

Statement of Ethics

The study protocol was reviewed and approved by the local Ethics Committee (EC). In particular, the protocol was firstly approved by the San Raffaele Authority Hospital EC for the coordinating centre and subsequently approved by the remaining EC (number DSAN854-A-OS/5). A written

informed consent was obtained according to the EC's recommendations. The study was conducted according to the ethical guidelines of the 1975 Declaration of Helsinki.

Acknowledgments: nothing to declare.

ABSTRACT

BACKGROUND & AIMS: this study aims to identify a new prognostic index by applying recursive partitioning analysis (RPA) in hepatocellular carcinoma (HCC) patients treated with atezolizumab plus bevacizumab (AB).

METHODS: RPA was applied on 784 consecutive HCC patients treated with AB.

RESULTS: RPA allowed the identification of the Atezolizumab BEvacizumab prognostic (ABE) index, comprising three groups of patients: low risk, [(i) Child-Pugh A (CPA) patients without macrovascular invasion (MVI) but with Albumin-Bilirubin (ALBI) 1, aspartate aminotransferase (AST) normal value (NV), and alpha-fetoprotein (AFP) < 400 ng/mL, (ii) CPA patients without MVI but with ALBI 1, AST increased value (IV), and neutrophil-lymphocyte ratio (NLR) < 3, and (iii) CPA patients with MVI, ALBI 1, and AFP < 400 ng/mL]; intermediate risk, [(i) CPA patients without MVI but with ALBI 1, AST NV, and AFP ≥ 400 ng/mL, and (ii) CPA patients without MVI but with ALBI 1, AST IV, and NLR ≥ 3]; high risk [(i) CPA patients with ALBI 2, (ii) CPA patients with ALBI 1, MVI, and AFP ≥ 400 ng/mL, and (iii) CPB patients]. Overall survival was 22.5 months [95% confidence interval (CI) 17.0-22.5 months] in patients with low risk (60.1%), 14.2 months (95% CI 12.4-15.7 months) in intermediate risk (19.1%), and 7.0 months (95% CI 6.0-8.7 months) in high risk (20.8%); low risk hazard ratio (HR) 1, intermediate risk HR 1.76 (95% CI 1.26-2.46), high risk HR 3.99 (95% CI 2.76-5.77); P < 0.01.

CONCLUSIONS: the ABE index is an easy-to-use tool able to stratify HCC patients undergoing first-line therapy with AB.

Commentato [RLH3]: Why "but"? Same comment for other "but"

Commentato [RLH4]: It should be "within normal ranges"

Commentato [RLH5]: What is the advantage of this tool compared to consider just the high-risk features as in the IMbrave analysis? (from a reviewer point of you, not a criticism)

KEYWORDS: advanced hepatocellular carcinoma, atezolizumab plus bevacizumab, prognostic index, recursive partitioning analysis, ABE index

Lay summary: recursive partitioning analysis allowed the identification of the Atezolizumab BEvacizumab prognostic (ABE) index, comprising three groups of hepatocellular carcinoma patients: low risk, intermediate risk, and high risk. It is a useful tool because it can stratify patients who are candidates for atezolizumab plus bevacizumab from a prognostic point of view, identifying in an early manner those patients who could potentially benefit less from this therapeutic option.

INTRODUCTION

Hepatocellular carcinoma (HCC) remains the third leading cause of cancer death worldwide [1]. However, the therapeutic armamentarium available has expanded in recent years with the approval of new systemic treatments. Sorafenib was the only available first-line therapy for 10 years based on the results of the two trials, SHARP and Asia Pacific. In these two studies, overall survival (OS) was between 6.5 and 10.7 months, significantly longer than that obtained with placebo [2, 3]. Lenvatinib was the second drug approved in 2017 for the first-line treatment of HCC. The open-label, multicenter, phase III REFLECT trial demonstrated non-inferiority of lenvatinib in OS (13.6 months) compared to sorafenib (12.3 months; hazard ratio [HR] 0.92; 95% confidence interval [CI] 0.79-1.06) [4]. The combination of the anti-programmed cell death ligand-1 (PD-L1) atezolizumab plus the anti-vascular-endothelial growth factor bevacizumab represents the first therapeutic doublet approved for HCC treatment in the first-line setting. Indeed, the IMbrave150 trial demonstrated that this combination can obtain an advantage in OS (19.2 v.s 13.4 months; $P < 0.001$) and progression-free survival (PFS) (6.9 vs. 4.3 months; $P < 0.001$) compared to sorafenib [5]. Recently, the final data from the phase III HIMALAYA trial were published. The immunotherapeutic combination of

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the anti-PD-L1 durvalumab plus a single priming dose of the anti-cytotoxic T-lymphocyte antigen 4 tremelimumab was shown to significantly improve OS compared to sorafenib (16.4 vs. 13.8 months; P = 0.0035) in the first-line setting [6].

In light of these results, lenvatinib and atezolizumab plus bevacizumab represent the two options currently most used in first-line therapy in clinical practice. It has become crucial for clinicians to have prognostic tools available to correctly frame patients and be able to offer them the best treatment.

Literature data highlighted some prognostic factors for HCC patients treated with lenvatinib or atezolizumab plus bevacizumab, such as Child Pugh score, Albumin-Bilirubin (ALBI) grade, and neutrophil-lymphocyte ratio (NLR) [7-19]. As regards lenvatinib, relative dose intensity, prognostic nutritional index, body mass index, and muscle mass have also proved to be important prognostic factors [20-23]. Recently, a complex prognostic index derived from a recursive partitioning analysis (RPA), the lenvatinib prognostic (LEP) index, has been validated [24, 25]. Regarding atezolizumab plus bevacizumab, there are still few real-world studies that evaluate potential prognostic factors in patients treated with this therapeutic combination. This study aims to identify a new prognostic index by applying RPA in HCC patients treated with atezolizumab plus bevacizumab in first-line setting.

Commentato [RLH7]: You may want to mention also the camrelizumab-apatinb phase 3 trial and the tiszelizumab phase 3 trial

Commentato [RLH8]: This is not correct, if you mention lenvatinib you should mention also sorafenib as in all international guidelines

Commentato [RLH9]: If you mention lenvatinib you should mention also sorafenib, the two drugs have the same role in international guidelines, BCLC, EASL position paper

Commentato [RLH10]: There are analyses from IMbrave, according to high-risk features, Vp4, varices, ALBI. They should be mentioned, see below for the references

METHODS

Patients

The overall cohort of this multicentric study included 784 consecutive HCC patients from 4 countries (Italy, Germany, Japan, and the Republic of Korea) treated with atezolizumab plus bevacizumab between October 2018 and April 2022. The study population was treated with atezolizumab plus bevacizumab as first-line therapy for Barcelona Clinic Liver Cancer (BCLC) B or C HCC, deemed not eligible for first treatment or re-treatment with surgical or loco-regional

therapies. Eligible patients had HCC diagnosis confirmed histologically or confirmed clinically in accordance with international guidelines. None of them received previous systemic therapy. Due to the intent to build a real-word dataset of patients treated with atezolizumab plus bevacizumab, no specific inclusion and exclusion criteria were applied, except for the absence of previous systemic therapies for HCC. Atezolizumab plus bevacizumab was administered as described in the IMbrave150 trial, and all patients received 1200 mg of atezolizumab plus 15mg/kg of body weight of bevacizumab intravenously every 3 weeks [5]. Treatment interruptions and/or dose reductions were allowed to manage adverse events (AEs). AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 [26].

The present study was approved by the ethics committee at each center, complied with the provisions of the Good Clinical Practice guidelines and the Declaration of Helsinki and local laws, and fulfilled the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data.

Statistical analysis

Clinical features and hematologic blood tests were collected at baseline (the day before the start of treatment).

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We applied survival tree regression to identify risk groups in the overall cohort after dichotomizing each variable. Beginning by the overall cohort, we conducted univariate Cox proportional hazards regression for each predictor variable. The criteria to define groups at each level comprised the variable with the highest HR. We later dichotomized the cohort using the selected predictor variable and replicated the univariate Cox models among each group. We recursively replayed this process among each new group till no variable met the criteria for selection. After establishing initial groups or “nodes”, HRs for each node were calculated relative to the lowest risk node. Kaplan Meier methods were applied to estimate survival for each node, and an overall log-rank test was calculated for the model.

MedCalc package (MedCalc® version 16.8.4) was used for statistical analysis.

RESULTS

The clinical and laboratory characteristics of the study population are shown in Table 1.

The first node split by the Child-Pugh class states that the survival difference between Child-Pugh A versus Child-Pugh B patients is greater than the difference between any other patients' subset. The same process has been recursively implemented to the arising subpopulations, giving origin to the partitioning tree represented in Figure 1. Between the 725 Child-Pugh A patients, the most meaningful split was by ALBI grade, among patients with ALBI grade 1 (n = 692) and patients with ALBI grade 2 (n = 33). Between the 692 Child-Pugh A patients with ALBI grade 1, the most considerable split was among patients with macrovascular invasion (MVI) (n = 153) and patients without macrovascular invasion (n = 539). Between the 153 Child-Pugh A patients with ALBI 1 and macrovascular invasion, the closing split was among patients with alpha-fetoprotein (AFP) < 400 ng/mL (n = 82) and patients with AFP ≥ 400 ng/mL (n = 71). Between the 539 Child-Pugh A patients with ALBI 1 without macrovascular invasion, the most meaningful split was among patients with aspartate aminotransferase (AST) normal value (n = 223) and patients with AST increased value (n = 316). Within the latter patients' subset, the closing split was among patients with NLR < 3 (n = 199) and patients with NLR ≥ 3 (n = 117). Between the 223 Child-Pugh A patients with ALBI 1 and AST normal value without macrovascular invasion, the closing split was among patients with AFP < 400 ng/mL (n = 190) and patients with AFP ≥ 400 ng/mL (n = 33).

In accordance with the RPA tree, we have found three groups of patients with differing outcomes with regard to OS. The first group, named "low risk", comprises (i) Child-Pugh A patients without macrovascular invasion but with ALBI 1, AST normal value, and AFP < 400 ng/mL, (ii) Child-Pugh A patients without macrovascular invasion but with ALBI 1, AST increased value, and NLR < 3, and (iii) Child-Pugh A patients with macrovascular invasion, ALBI 1, and AFP < 400 ng/mL.

Commentato [RLH12]: Change the following into MVI as in the abstract; also in figures and tables

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The second group, named “intermediate risk”, comprises (i) Child-Pugh A patients without macrovascular invasion but with ALBI 1, AST normal value, and AFP ≥ 400 ng/mL, and (ii) Child-Pugh A patients without macrovascular invasion but with ALBI 1, AST increased value, and NLR ≥ 3. Finally, the third group, named “high risk”, comprises (i) Child-Pugh A patients with ALBI 2, (ii) Child-Pugh A patients with ALBI 1, macrovascular invasion, and AFP ≥ 400 ng/mL, and (iii) Child-Pugh B patients. We have denominated this score the Atezolizumab BEvacizumab prognostic index “ABE index”.

OS was 22.5 months (95% CI 17.0-22.5 months) in patients with low risk (n = 471, 60.1%), 14.2 months (95% CI 12.4-15.7 months) in intermediate risk (n = 150, 19.1%), and 7.0 months (95% CI 6.0-8.7 months) in high risk (n = 163, 20.8%); low risk HR 1 (reference group), intermediate risk HR 1.76 (95% CI 1.26-2.46), high risk HR 3.99 (95% CI 2.76-5.77); P < 0.01 (Figure 2A). Receiver operating characteristic (ROC) curve analysis displayed an area under the curve (AUC) of 0.72 (95% CI 0.68-0.76; P < 0.0001).

PFS was 9.4 months (95% CI 8.4-10.8 months) in patients with low risk, 6.1 months (95% CI 5.5-8.1 months) in intermediate risk, and 5.3 months (95% CI 3.7-5.8 months) in high risk; low risk HR 1 (reference group), intermediate risk HR 1.47 (95% CI 1.14-1.89), high risk HR 1.79 (95% CI 1.37-2.35); P < 0.01 (Figure 2B).

The three groups had a differing rate of progressive disease (PD) at the first computed tomography (CT) response assessment (low risk 16.1%; intermediate risk 24.0%; high risk 29.4%; P < 0.01) and of patients who received a second line therapy (low risk 54.7%; intermediate risk 52.7%; high risk 31.9%; P < 0.01) (Figure 3A). Median OS in subsequent anticancer treatments was 10.5 months (95% CI 8.6-15.4 months) in patients with low risk, 7.9 months (95% CI 4.6-9.4 months) in intermediate risk, and 3.1 months (95% CI 2.4-3.7months) in high risk; low risk HR 1.00 (reference group), intermediate risk HR 1.57 (95% CI 1.07-2.31), high risk HR 3.36 (95% CI 2.17-5.19); P < 0.01 (Figure 3B).

Commentato [RLH14]: Do you think that high-risk features may have an impact on response and not only on survival (OS and PFS)?

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In the three groups, differing profiles of toxicity have been highlighted, notably in terms of hypertension (low risk 27.4%; intermediate risk 22.7%; high risk 17.2%, P = 0.03), proteinuria (low risk 28.7%; intermediate risk 35.3%; high risk 22.7%, P < 0.05), and hypothyroidism (low risk 6.1%; intermediate risk 2.7%; high risk 1.8%; P = 0.03) (Table 2).

Commentato [RLH16]: Any explanation?

DISCUSSION

By applying RPA to a real-world population of HCC patients treated in first-line setting with atezolizumab plus bevacizumab, we have created an easy-to-use prognostic index, the ABE index.

In our analysis, low risk patients achieved better survival outcomes than the phase III IMbrave150 trial in terms of both OS (22.5 vs. 19.2 months) and PFS (9.4 vs. 6.9 months) [5]. The low risk group, therefore, allows us to identify patients who could potentially benefit most from this therapeutic combination even in terms of low percentages of PD at the first re-evaluation. This is also in line with literature data suggesting that HCC patients benefit most from systemic treatments if they are administered in the early stages of the disease when liver function is still well preserved [27-31]. This benefit also translates into median OS in subsequent anticancer treatments which in our data was 10.5 months in low risk patients and 3.1 months in high risk patients. Patients who had better outcomes from first-line therapy with atezolizumab plus bevacizumab maintained this greater benefit also in subsequent lines, most likely because they are those who, thanks to disease control, also maintained good liver function that allowed them to access the benefits of the following therapies. Low risk patients are also those who have received the therapeutic combination longer, resulting in greater exposure to the mechanisms determining the AEs' onset. Indeed, our data show that hypertension (typically caused by bevacizumab), as well as hypothyroidism (typically associated with immunotherapy), were more frequent in low risk patients than in the other groups. This phenomenon was also reported in a Japanese real-world study in which Child-Pugh A patients

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treated with atezolizumab plus bevacizumab reported a higher percentage of proteinuria than Child-Pugh B patients, most likely because the latter have received the therapy for a shorter time [32].

Of particular importance for clinical practice are the prognostic factors characterizing the high risk group because they allow the identification of patients who derive limited benefits from therapy with atezolizumab plus bevacizumab (OS 7.0 and PFS 5.3 months). These factors are represented by Child-Pugh B, ALBI 2, and AFP ≥ 400 ng/mL in patients with macrovascular invasion.

There is numerous evidence that the most important prognostic factors in HCC patients are those representatives of liver function [33-37]. In our analysis, the Child-Pugh score was the first split node that allowed us to stratify two populations. This is in line with literature data on this particular subset of patients treated with atezolizumab plus bevacizumab. In particular, a real-world study by D'Alessio and colleagues on 216 patients reported significant differences between patients with Child-Pugh A and patients with Child-Pugh B both in terms of OS (A 16.8 vs. B 6.7 months, P = 0.0003) and in terms of PFS (A 7.6 vs. B 3.4 months, P = 0.03) (38). Another real-world study conducted on 457 Japanese patients confirmed statistically significant differences in survival outcomes [OS: A not reached (NR) vs. B 6.4 months, P < 0.001; PFS: A 7.5 vs. B 6.0 months, P = 0.011]. Tanaka et al also analyzed the differences between the individual scores constituting the Child-Pugh classes, highlighting progressively worse OS and PFS as the score increased [32]. This type of correlation was also found in patients receiving the other currently available first-line therapies, sorafenib and lenvatinib [7, 11, 33-35, 37]. The second split node within RPA was the ALBI score. Patients with Child-Pugh A but ALBI 2 composed the high risk group, having achieved an OS of 8.0 months. Tanaka and colleagues found that in patients with Child-Pugh A, OS and PFS worsen significantly from ALBI 1 to ALBI 2b [32]. Our work confirms that even in patients treated with atezolizumab plus bevacizumab, as with other available first-line therapies, Child-Pugh class and ALBI score represent the most important prognostic factors capable of identifying patients who are likely to have a limited benefit from first-line therapy and for which it

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is necessary to carefully evaluate the relationship between possible benefits and risks associated with the treatment to be offered. Furthermore, the ABE index, being consistent with the literature data in real-world settings, is a reliable index to be used in clinical practice, even if further analyses on external cohorts of patients treated with atezolizumab plus bevacizumab are desirable for its validation.

Very interesting data is represented by the subsequent split node which helps to identify high risk patients. These are Child-Pugh A patients with ALBI 1 and macrovascular invasion. In these patients, the factor that caused the greatest difference in OS was the baseline AFP levels. Patients with AFP ≥ 400 ng/mL composed the high risk group and achieved an OS of 7.6 months. In contrast, patients with low baseline AFP levels were classified as low risk having achieved an OS of 22.5 months. AFP is a known prognostic factor for HCC patients in both localized and advanced disease settings [7, 37, 39-42] and is part of another prognostic score, the CRAFITY score [43]. This score was obtained from the univariate and multivariate analyses performed on 190 HCC patients treated with immunotherapy. In multivariate analysis, macrovascular invasion was not a factor influencing the prognosis of these patients, while AFP ≥ 100 ng/mL and C-reactive protein ≥ 1 mg/dL were independent prognostic factors for OS also in multivariate analysis and constituted, in fact, the CRAFITY score. Patients who had neither of these two elevated values had OS of 27.6 months, while for patients with at least one of these criteria, OS was 11.3 and 6.4 months, respectively. In contrast to our study, the population included in these analyses was highly heterogeneous because it included patients treated with immunotherapy in different lines and with different drugs. Furthermore, the cut-off used for AFP was not the one that has mostly been identified in the literature as a discriminant of the prognosis in patients with HCC [37].

A separate discussion deserves NLR, which represents the split node able to discriminate between Child-Pugh A without macrovascular invasion but with ALBI 1 and increased AST values, those intermediate risk (NLR ≥ 3: OS 13.9 months) from those low risk (NLR < 3: OS NR). NLR is a

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particularly interesting prognostic factor for patients being treated with immunotherapy because it is representative of the state of activation of the immune system [43-48]. Elevated NLR values can be determined by lymphopenia or neutrophilia. Lymphopenia can determine the ineffectiveness of the immune system's reaction to cancer cells [49]. Neutrophilia is associated with a high release of cytokines by macrophages recruited in the tumor microenvironment which contribute to the creation of a chronic inflammatory state, in which the perpetually active immune system undergoes functional exhaustion [50]. Regarding specifically HCC patients treated with atezolizumab plus bevacizumab, NLR was found to be an independent prognostic factor also in two Japanese real-world studies [18, 19].

Our study has some limitations, the most important being its retrospective nature so there are some gaps in the data collected. This limit is partly offset by the large sample size, the fact that the population is homogeneous from a therapeutic point of view, and that it is made up of both Western and Eastern patients. Another limitation is represented by the fact that it is needed to further validate this index in an external cohort of patients, and above all to investigate its predictive role, applying it to patients treated with other available first-line therapies, such as lenvatinib and sorafenib.

Commentato [RLH20]: You have to add and discuss the high-risk, Vp4, varices, and ALBI analyses from IMbrave, you cannot omit them in the discussion:
-Finn RS et al. AACR 2021, abstr 5080, Cancer Res 2021;81(13_Suppl):Abstract nr CT009
-Breder VV et al. ASCO 2021, abstract 4073 (I have the poster if needed)
-Merle P et al. APPLE 2021 (I have the slides if needed)
-Kudo M et al. ILCA 2021, abstr O-18

ha eliminato: could be useful

CONCLUSIONS

The "ABE index" is an easy-to-use tool because it is made up of factors widely used in clinical practice in HCC patients. It is also a useful tool because it can stratify HCC patients who are candidates for atezolizumab plus bevacizumab from a prognostic point of view, identifying in an early manner those patients who could potentially benefit less from this therapeutic option.

Commentato [RLH21]: As above, which is the advantage of this tool compared to consider high-risk features per se?

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Commentato [RLH22]: Add also the original publication in NEJM

Commentato [RLH23]: It is NEJM Evidence

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Legends:

Figure 1. Classification of patients treated with atezolizumab plub bevacizumab according to RPA. RPA identifies three risk group: low risk (in green), [(i) Child-Pugh A pt without MV

invasion but with ALBI 1, AST NV, and AFP < 400 ng/mL, (ii) Child-Pugh A pt without MV invasion but with ALBI 1, AST IV, and NLR < 3, and (iii) Child-Pugh A pt with MV invasion, ALBI 1, and AFP < 400 ng/mL;]; intermediate risk (in blue), [(i) Child-Pugh A pt without MV invasion but with ALBI 1, AST NV, and AFP ≥ 400 ng/mL, and (ii) Child-Pugh A pt without MV invasion but with ALBI 1, AST IV, and NLR ≥ 3]; high risk (in orange) [(i) Child-Pugh A pt with ALBI 2, (ii) Child-Pugh pt with ALBI 1, MV invasion, and AFP ≥ 400 ng/mL, and (iii) Child-Pugh B pt]. AFP: alpha-fetoprotein; ALBI: Albumin-Bilirubin; AST: aspartate aminotransferase; IV: increased value; mo: months; MV: macrovascular; NLR: neutrophil-lymphocyte ratio; NR: not reached; NV: normal value; OS: overall survival; pt: patients; RPA: recursive partitioning analysis.

Figure 2. Median OS (A) and PFS (B) of patients treated with atezolizumab plus bevacizumab based on risk groups identified with RPA. OS: overall survival; PFS: progression-free survival; RPA: recursive partitioning analysis.

Figure 3. DCR and median OS in subsequent anticancer treatments of patients treated with atezolizumab plus bevacizumab based on risk groups identified with RPA. DCR: disease control rate; OS: overall survival; PD: progressive disease; RPA: recursive partitioning analysis.

Table 1. Baseline characteristics of study population. AFP: alpha-feto-protein; ALBI: Albumin-Bilirubin; BCLC: Barcelona Clinic Liver Cancer; CP: Child Pugh; EHD: extrahepatic disease; MV: macrovascular; NLR: neutrophil-lymphocyte ratio; PS: performance status.

Table 2. Adverse events reported in patients treated with atezolizumab plus bevacizumab.