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Analysis of Immune-Related Adverse Events of Atezolizumab and Bevacizumab in Patients with Hepatocellular Carcinoma: A Multicentre Cohort Study

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Keywords
Hepatocellular carcinoma · Atezolizumab · Bevacizumab · Immune-related adverse events · Time-to-treatment discontinuation

Abstract
Introduction: Despite the emergence of atezolizumab and bevacizumab (A + B) as standard first-line systemic therapy for unresectable hepatocellular carcinoma (HCC), a comprehensive understanding of the clinical significance of immune-related adverse events (irAEs) remains limited. We aimed to assess the impact of irAEs on patients with HCC undergoing A + B treatment. ***Methods:*** This multicentre retrospective study included consecutive patients with HCC who were treated with the A + B regimen from September 2020 to December 2022. Patients were categorized into three groups based on the severity of irAEs, ranging from those without any experience of irAEs to those with severe irAEs. ***Results:*** This study included 150 patients with HCC, with a mean age of 63.3 years. Among them, 93.3% of

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patients were classified as Barcelona Clinic Liver Cancer stage C, 52.0% had portal vein tumour thrombosis (PVTT), and 60.7% extrahepatic spread. Patients were classified as follows: group 1 (n = 84) had no irAEs, group 2 (n = 37) had mild irAEs (grade 1-2), and group 3 (n = 29) had severe irAEs (grade ≥3). The median overall survival (OS), progression-free survival (PFS), and time-to-treatment discontinuation (TTD) were 13.6, 5.7, and 3.6 months, respectively. Group 2 demonstrated significantly superior OS compared to group 1 (9.5 months) and group 3 (5.6 months), with a median OS of 23.0 months ($p < 0.001$). Furthermore, group 2 demonstrated significantly better outcomes in terms of PFS and TTD compared to both group 1 and group 3 ($p < 0.001$ for both). Multivariate analysis identified mild irAEs (hazard ratio [HR], 0.353; $p = 0.010$), ALBI grade 1 (HR, 0.389; $p = 0.006$), Child-Pugh class A (HR, 0.338; $p = 0.002$), and the absence of PVTT (HR, 0.556; $p = 0.043$) as independent predictors of better OS. ***Conclusion:*** Our study highlights the significant impact of irAE severity on the outcomes of patients with HCC receiving A + B. Notably, the occurrence of mild irAEs was independently associated with favourable survival, suggesting their potential role as surrogate indicators of HCC prognosis.

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumours worldwide and a leading cause of cancer-related mortality globally [1]. Over the past decade, several tyrosine kinase inhibitors, including lenvatinib, regorafenib, and cabozantinib, have been introduced for the treatment of advanced HCC. However, these target therapies have shown limited efficacy and tolerability in clinical practice and have failed to meet the expected outcomes. In 2020, IMbrave 150 trial was the first to demonstrate the superior effectiveness of an immuno-oncological regimen over sorafenib in advanced HCC, exerting a substantial influence in the field. The trial demonstrated that the combination of atezolizumab plus bevacizumab (A + B) resulted in superior overall survival (OS) with median of 19.2 months compared to 13.6 months with sorafenib [2, 3]. Atezolizumab, an immune checkpoint inhibitor (ICI) targeting programmed death ligand 1 for T-cell restoration, is combined with bevacizumab, which is a monoclonal antibody for anti-vascular endothelial growth factor-A, with the expectation of generating a synergistic effect through pathophysiological mechanisms that foster a more immunoactive tumour microenvironment [4]. Post hoc analyses of the IMbrave 150 trial have also revealed consistent trends favouring the superior outcomes of A + B compared to sorafenib, irrespective of age and ethnicity [5, 6]. Subsequently, several real-world data studies on A + B treatment for HCC have been published, further demonstrating promising treatment efficacy and an acceptable safety profile [7–12].

Following the A + B treatment, various ICI-based treatments have demonstrated therapeutic efficacy in the treatment of HCC and are recommended as the standard of care in most guidelines. With the expanding application of ICI-based treatments, clinical awareness of immune-related adverse events (irAEs) has become increasingly important, drawing attention to their prominence [13]. These irAEs can present in a variety of forms across multiple organs, including thyroiditis, pneumonitis, hepatitis, and enteritis [13]. Emerging data in lung cancer and melanoma have shown that patients who experience early irAEs tend to exhibit improved clinical outcomes and prolonged OS [14–16]. However, the precise mechanisms underlying these results are not yet fully understood, and the question of whether irAEs could be truly associated with favourable outcomes in individuals treated with ICIs remains a subject of debate. In addition, it is important to note that the occurrence of severe irAEs can necessitate the early discontinuation of ICI treatment, potentially limiting available treatment options and leading to a poorer prognosis [17, 18]. Taking into account the association between fatalities related to ICI treatments and hepatitis [19], it is crucial to be vigilant about such incidents in HCC treatment. Furthermore, the precise impact of irAEs on patients with HCC has not yet been fully established, underscoring the significance of meticulous analyses.

Recently, the time-to-treatment discontinuation (TTD) has been recognized as a reliable endpoint for evaluating the anticancer efficacy of drugs in real-world experience studies [20]. TTD offers several advantages in this context: it can be easily obtained from electronic medical records, has a lower likelihood of containing censored data, and has demonstrated a strong correlation with progression-free survival (PFS) [20]. Furthermore, response evaluation based on the modified Response Evaluation Criteria in Solid Tumours (mRECIST) is frequently characterized by irregular time intervals and may be susceptible to subjective biases brought on by physicians during the assessment of response. Therefore, TTD is considered a suitable and practical endpoint for real-world data studies [21].

It has been hypothesized that irAEs could serve as surrogate markers for prognosis. Nevertheless, irAEs encompass a broad spectrum, affect nearly every organ,

and exhibit varying degrees of severity. While mild irAEs are common and manageable, severe irAEs are frequently associated with organ dysfunction and reduced quality of life [22]. Consequently, a more thorough evaluation and characterization of irAEs is essential for assessing their role in ICI-based therapy. In this real-world study, we aimed to investigate the impact of irAEs and their severity on treatment outcomes in patients with HCC treated with A + B, while also assessing the potential role of irAEs as surrogate markers for prognosis. We used TTD and OS as surrogate endpoints to evaluate treatment efficacy.

Materials and Methods

Patients

We conducted a retrospective multicentre study involving 150 patients with unresectable HCC who received A + B treatment at six affiliated hospitals in Korea between September 2020 and December 2022. The diagnosis of HCC was based on histological and/or radiological examinations such as computed tomography and/or magnetic resonance imaging. The inclusion criteria were as follows: (1) Patients diagnosed with unresectable HCC; (2) age ≥18 years; (3) Eastern Cooperative Oncology Group (ECOG) performance status ≤2; (4) patients treated with A + B as first-line systemic therapy; (5) BCLC stage B or C; and (6) patients who had at least one follow-up visit at the clinic after receiving the A + B treatment. Patients with concurrent extrahepatic malignancies or liver function deterioration classified as Child-Pugh class C were excluded. This study was approved by the Institutional Review Board of the Catholic University of Korea (approval number: KC22EASI0342) and was performed in accordance with the Declaration of Helsinki.

Treatment Protocol

A + B was administered using the standard dosing regimen described in the IMbrave 150 trial, which involved the intravenous administration of 1,200 mg of atezolizumab and 15 mg/kg of body weight of bevacizumab every 3 weeks. Tumour response was evaluated at intervals of approximately three-four treatment cycles using imaging tools and tumour markers, and the assessment of response followed the mRECIST guidelines. Treatment with A + B was continued until disease progression, death, or occurrence of unacceptable adverse events. The decision to interrupt the A + B treatment was made by the treating clinicians, taking into consideration the occurrence and severity of adverse events. In case of disease progression, physicians considered second-line therapy based on the recently published Korean practice guidelines for HCC management [23, 24].

Assessment of IrAEs

Adverse events were evaluated in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, which uses a severity scale ranging from grade 1 to grade 5, with grade 5 representing an adverse event leading to death (grade 0 refers to the absence of any symptoms or problems). Within the broad spectrum of adverse events, irAEs were defined as those with a pathophysiology likely to be associated with an immunological response or those for which the treating physicians used corticosteroids as rescue therapy. Two independent researchers assessed adverse events in guidance of a recently published review article explaining the diagnosis and management of irAEs [25]. Agreement between the researchers was reached to identify the presence of irAEs using the diagnostic algorithm proposed by Sangro et al. [25] to ascertain their classification as irAEs. To evaluate their influence on HCC prognosis, irAEs were categorized as mild if they displayed grade 1 or 2 severity and severe if they manifested grade 3 or higher severity.

Study Objectives and Endpoints

The primary endpoint of this study was OS defined as the period from the initiation of A + B treatment to death from any cause. In cases in which patients were lost to follow-up or remained alive at the end of the study period, OS was considered censored. Additionally, survival outcomes were comprehensively assessed by measuring TTD and PFS. TTD was defined as the duration between the first administration of A + B and either the last administration of the drug or death [20]. PFS was defined as the time from the initiation of A + B treatment to disease progression or death from any cause. To evaluate liver function at the start of the A + B treatment, the albumin-bilirubin (ALBI) score was used. An ALBI score below −2.60 indicated grade 1, signifying optimal liver function. Conversely, a score above −1.39 denoted grade 3, indicating impaired liver function. Scores falling between these values were classified as grade 2.

Statistical Analysis

Statistical analyses were conducted using appropriate methods for different variables. Continuous variables with normal distributions are presented as means with standard deviations, while those with non-normal distributions are presented as medians with interquartile ranges. An analysis of variance was used to compare the differences in means between more than two groups. Categorical variables were compared using either the χ^2 test or Fisher's exact test depending on the sample size and assumptions. The Kaplan-Meier method was used to visualize the survival curve of patients treated with A + B. The log-rank test was used to compare survival rates among the different groups. Cox regression analysis was performed to identify factors associated with OS, PFS, and TTD. The Pearson's correlation test was used to investigate the correlation between TTD and other endpoint markers. Variables with a p value <0.05 in the univariate analysis were included in the multivariate analysis. All statistical analyses were performed using Stata/IC 17 software (StataCorp LLC, TX, USA).

Results

Baseline Characteristics

A total of 150 patients were included in the analysis. Table 1 shows the baseline characteristics of patients. The mean age of the patients was 63.3 ± 11.3 years, with a

Table 1. Baseline characteristics of enrolled patients

	Total (n = 150)	No irAEs, group 1 (n = 84)	Mild irAEs (1-2), group 2 (n = 37)	Severe irAEs (≥3), group 3 (n = 29)	p value
Male sex	128 (85.3)	76 (90.5)	31 (83.8)	21 (72.4)	0.057
Age, years	63.3±11.3	62.0±11.5	64.1±10.2	65.9±11.9	0.240
BMI, kg/m^2	23.2±3.5	23.4±3.4	23.0±3.4	22.8±4.0	0.650
Aetiology					0.370
Viral	104 (69.3)	61 (72.6)	26 (70.3)	17 (58.6)	
Non-viral	46 (30.7)	23 (27.4)	11 (29.7)	12 (41.4)	
WBC, /μL	5,585.9±2,523.4	5,607.1±2,372.4	5,174.6±1,760.5	6,049.3±3,573.1	0.380
NLR	3.8±3.3	4.0±3.7	2.8±1.7	4.6±3.3	0.069
AST, IU/L	79.2±82.8	77.4±78.8	55.9±40.8	114.1±118.2	0.016
ALT, IU/L	36.6±33.0	38.9±39.0	31.1±18.5	37.1±27.9	0.480
TB, mg/dL	0.9±0.6	0.9±0.7	0.8±0.6	1.1±0.6	0.086
Albumin, mg/dL	3.8±0.5	3.8±0.5	3.8±0.5	3.6±0.5	0.150
PT (INR)	1.1±0.1	1.1±0.1	1.1±0.1	1.2±0.2	0.043
Cr, mg/dL	0.9±0.6	0.9±0.7	0.8±0.3	0.9±0.7	0.990
ALBI grade					0.220
1	61 (40.7)	35 (41.7)	18 (48.7)	8 (27.6)	
2	89 (59.3)	49 (59.3)	19 (51.3)	21 (72.4)	
Child-Pugh class					0.810
A/B	134 (89.3)/16 (10.7)	76 (90.5)/8 (9.5)	33 (89.2)/4 (10.8)	25 (86.2)/4 (13.8)	
PVTT	78 (52.0)	47 (56.0)	15 (44.1)	16 (55.2)	0.270
EHS	91 (60.7)	52 (61.9)	21 (60.3)	18 (62.1)	0.850
Tumour number (single)	41 (27.3)	22 (26.2)	11 (29.7)	8 (27.6)	0.920
Tumour size, cm	7.6±5.7	6.0±5.4	8.0±5.7	8.2±5.9	0.160
mUICC stage					0.630
III	16 (10.7)	7 (8.3)	4 (10.8)	5 (17.2)	
IVa	43 (28.7)	25 (29.8)	12 (32.4)	6 (20.7)	
IVb	91 (60.7)	52 (61.9)	21 (56.8)	18 (62.1)	
BCLC stage					0.540
B/C	10 (6.7)/140 (93.3)	4 (4.8)/80 (95.2)	3 (8.1)/34 (91.9)	3 (10.3)/26 (89.7)	
AFP, ng/mL	184.0 (8.5, 4,587.6)	245.9 (14.9, 15,258.3)	124.0 (8.0, 2,303.0)	70.7 (5.7, 1,031.6)	0.210
PIVKA, mAU/mL	1,255.0 (158.7, 16,418.0)	1,532.7.0 (231.5, 12,072.0)	925.5 (70.5, 6,391.0)	3,827.0 (33.0, 41,760.0)	0.560

Values are presented as mean ± SD, median (IQR), or number (%). AFP, alpha fetoprotein; ALBI, albumin to bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona clinic liver cancer; BMI, body mass index; Cr, creatinine; EHS, extrahepatic spread; INR, international normalized ratio; irAEs, immune-related adverse events; NLR, neutrophil-to-lymphocyte ratio; PIVKA, protein induced by vitamin K absence; PT, prothrombin time; PVTT, portal vein tumour thrombus; TB, total bilirubin; WBC, white blood cell.

predominance of male patients (85.3%). Viral aetiology was more prevalent (69.3%) than non-viral aetiology (30.7%). Regarding liver function, 134 patients (89.3%) had Child-Pugh class A, and 61 (40.7%) had ALBI grade 1. The mean tumour size was 7.6 cm, and 41 patients (27.3%) had solitary tumours. In addition, 78 patients had portal vein tumour thrombosis (PVTT), and 91 had extrahepatic spread (EHS), resulting in 93.3% of patients being classified as BCLC stage C. Based on the presence and severity of irAEs, patients were categorized into three groups: group 1 (n = 84) comprised patients who did not experience irAEs, group 2 (n = 37) included patients who exhibited mild irAEs, and group 3 (n = 29) consisted of patients who experienced irAEs graded 3 or higher (Fig. 1). The detailed baseline characteristics of the groups are presented in Table 1. Notably, no statistically significant differences were detected among the three groups in terms of age, underlying aetiological factors, Child-Pugh classification, ALBI grading, and HCC status parameters (tumour size, tumour number, EHS, PVTT, and tumour staging). In terms of sex distribution, group 3 had a higher proportion of female subjects compared to other

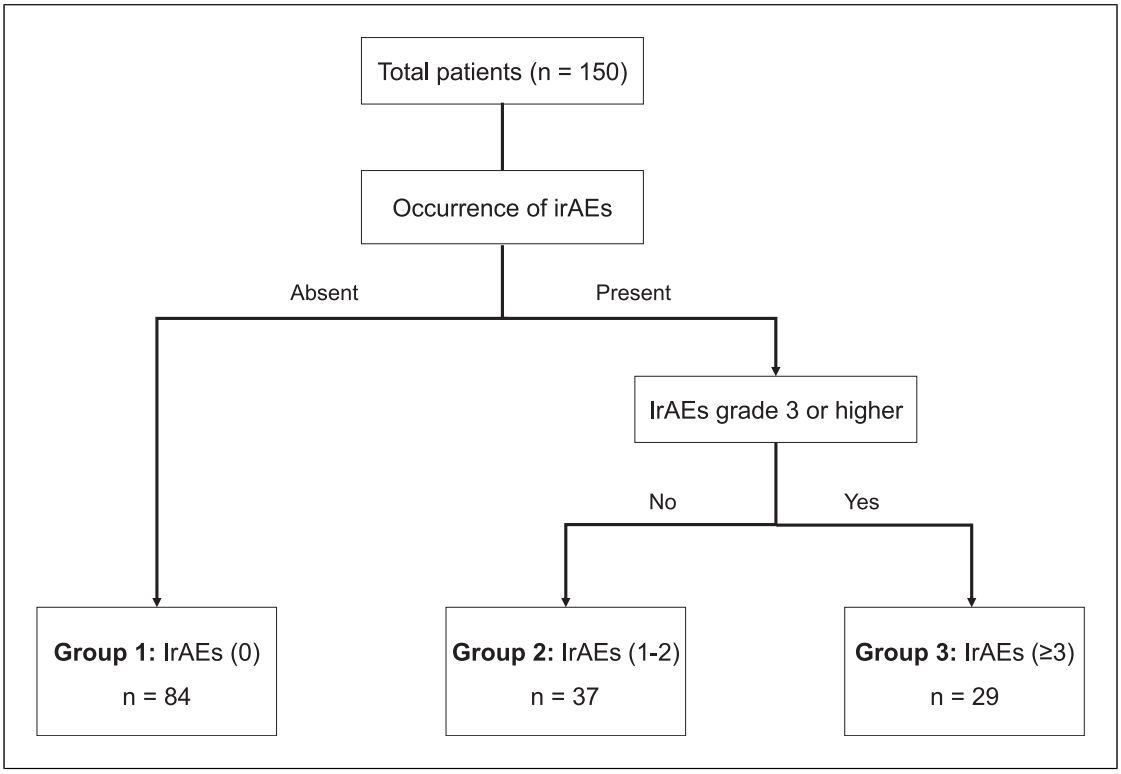

Fig. 1. Flow diagram illustrating the allocation of patients based on the occurrence and severity of irAEs. IrAEs, immune-related adverse events.

groups, although statistical significance was unreached (p = 0.057). Regarding laboratory findings, distinct differences were observed in the levels of aspartate aminotransferase (AST) among these groups (group 1: 77.4 IU/L vs. group 2: 55.9 IU/L vs. group 3: 114.1 IU/L, p = 0.016).

Immune-Related Adverse Events

Table 2 provides an overview of the types and severity levels of irAEs experienced by the patients. A total of 37 patients (24.7%) have experienced mild irAEs (grade 1–2), while 29 patients (19.3%) suffered severe irAEs (grade ≥3). The median time to irAE development was 2.4 months (95% confidence interval [CI]: 1.0–4.3). In terms of mild irAEs (grades 1-2), endocrine-related irAEs (n = 27) were predominant, followed by hepatitis (n = 5), colitis (n = 4), and skin rashes (n = 1). In this study, all endocrine-related irAEs were associated with the thyroid gland, and their frequencies were as follows: hypothyroidism (n = 13), subclinical hypothyroidism (n = 11), thyrotoxicosis (n = 2), and subclinical thyrotoxicosis (n = 1). Immune-related hepatitis was the most frequent severe irAE observed, with 12 patients experiencing alanine aminotransferase (ALT) elevation exceeding 5-fold of the upper limit of normal. The median time of immune-related hepatitis was 1.3 months. The median values of laboratory findings of patient with immune-related hepatitis were as follows: AST 402 IU/L (95% CI: 348–488), ALT 167 IU/L (95% CI: 97–298), total bilirubin 3.8 mg/dL (95% CI: 2.4–4.8), albumin 3.3 mg/dL (95% CI: 3.0–3.6), and international normalized ratio (INR) 1.23 (95% CI: 1.16–1.37). Colitis was the second most common severe irAE (n = 5), followed by fatigue (n = 3), pneumonitis (n = 3), cholangitis (n = 2), and skin rash (n = 1). Additionally, individual cases of anaphylactic shock (n = 1), myositis (n = 1), hepatic encephalopathy (n = 1), and asthma (n = 1) were documented as irAEs following A + B treatment. Among all patients, we identified 10 fatal events (6.7%) attributed to severe irAEs, which included hepatitis (n = 8), pneumonitis (n = 1), and myositis (n = 1).

Treatment Disruptions and Time to Events

The mean follow-up duration for the entire patient population was 7.2 months. At the end of the study period, 40 patients continued to receive treatment with

Table 2. IrAEs associated with A + B treatment

Grade 1-2	
Total	37 (24.7)
Endocrine	27 (18.0)
Hepatitis	5 (3.3)
Colitis	4 (2.7)
Skin rash	1 (0.7)
Grade ≥3	
Total	29 (19.3)
Endocrine	0 (0.0)
Hepatitis	12 (8.0)
Colitis	5 (3.3)
Pneumonitis	3 (2.0)
Fatigue	3 (2.0)
Cholangitis	2 (1.3)
Skin rash	1 (0.7)
Hepatic encephalopathy	1 (0.7)
Anaphylactic shock	1 (0.7)
Myositis	1 (0.7)
Asthma	1 (0.7)

Data are presented as *n* (% in total patients). A + B, atezolizumab plus evacizumab; irAEs, immune-related adverse events.

A + B regimen, whereas 110 patients discontinued the A + B regimen for various reasons (online suppl. Table 1; for all online suppl. material, see https://doi.org/10.1159/000535839). Among the 110 patients, 59 (39.3%) discontinued treatment owing to disease progression and 38 (25.3%) discontinued the regimen owing to adverse events. Additionally, 4 patients discontinued treatment after achieving a complete response (CR). In the overall population, the median OS was 13.6 months (95% CI: 8.0–20.6 months), and the median PFS was 5.7 months (95% CI: 4.0–12.5 months) (Fig. 2a, b). The TTD, which was shorter than PFS, had a median value of 3.6 months (95% CI: 2.6–5.1 months) (Fig. 2c).

Survival Analysis according to IrAEs

At the end of the follow-up period, a total of 62 mortality cases were observed (group 1 = 35, group 2 = 8, group 3 = 19). Within group 3, 10 out of 19 cases resulted in death due to fatal toxicities of irAEs, 4 cases were attributed to disease progression, and others were due to sepsis (n = 1), pneumonia (n = 1), and unknown causes. Further survival analyses were conducted to compare the outcomes across the three groups. In terms of OS, group 2 exhibited superior outcomes compared to both group 1 and group 3, (group 1: 9.5 months, 95% CI: 7.0–19.7; group 2: 23.0 months, 95% CI: 13.6–NA; group 3: 5.6 months, 95% CI: 2.9–9.5; $p < 0.001$) (Fig. 3a). Furthermore, group 2 demonstrated better results than group 1 and group 3 in terms of PFS (group 1: 4.2 months, 95% CI: 2.8–14.7; group 2: 23.0 months, 95% CI: 22.9–NA; group 3: 5.3 months, 95% CI: 2.3–6.0; $p < 0.001$) and TTD (group 1: 2.8 months, 95% CI: 1.8–4.0; group 2: 8.7 months, 95% CI: 5.6–NA; group 3: 2.2 months, 95% CI: 0.7–3.7; $p < 0.001$) (Fig. 3b, c). When comparing group 1 and group 3, group 1 showed higher median OS compared to group 3 (median OS 9.5 months [95% CI: 7.0–19.7] vs. 5.6 months [95% CI: 2.9–9.5]), although statistical significance was not achieved ($p = 0.075$). No significant differences were found in terms of PFS ($p = 0.338$) and TTD ($p = 0.109$) between group 1 and group 3.

Landmark Analysis of Patient Survival

Considering the potential immortal time bias associated with irAEs, a PFS analysis was conducted using a landmark approach. The PFS outcome was divided into two sections using 4 months threshold, and a Kaplan-Meier curve was generated. The results revealed significant differences in PFS among the three distinct groups both before ($p = 0.020$) and after ($p = 0.002$) the designated landmark time (online suppl. Fig. 1). In addition, individual pairwise comparisons were conducted between the groups. Prior to reaching the landmark time, group 2 exhibited significantly better PFS outcomes in comparison to group 1 ($p = 0.005$) and group 3 ($p = 0.028$). Notably, no substantial differences in PFS were observed between group 1 and group 3 before the landmark time ($p = 0.830$). In the landmark analysis, group 2 demonstrated extended PFS compared to group 1 ($p = 0.048$) and group 3 ($p = 0.001$) after the landmark time. Furthermore, landmark analysis revealed that group 3 exhibited significantly inferior PFS outcomes compared to group 1 ($p = 0.033$).

Treatment Responses

The treatment response was determined based on the best response observed during all visits from the initiation of treatment until the first occurrence of disease progression (online suppl. Table 2). In total, 132 patients were eligible for evaluation. Among them, six (4.5%) achieved CR, while 41 (31.1%) achieved partial response (PR), resulting in an objective response rate (ORR: CR + PR) of 35.6%. Stable disease was observed in 47 patients (35.6%) with a disease control rate of 71.2% (DCR: CR + PR + SD).

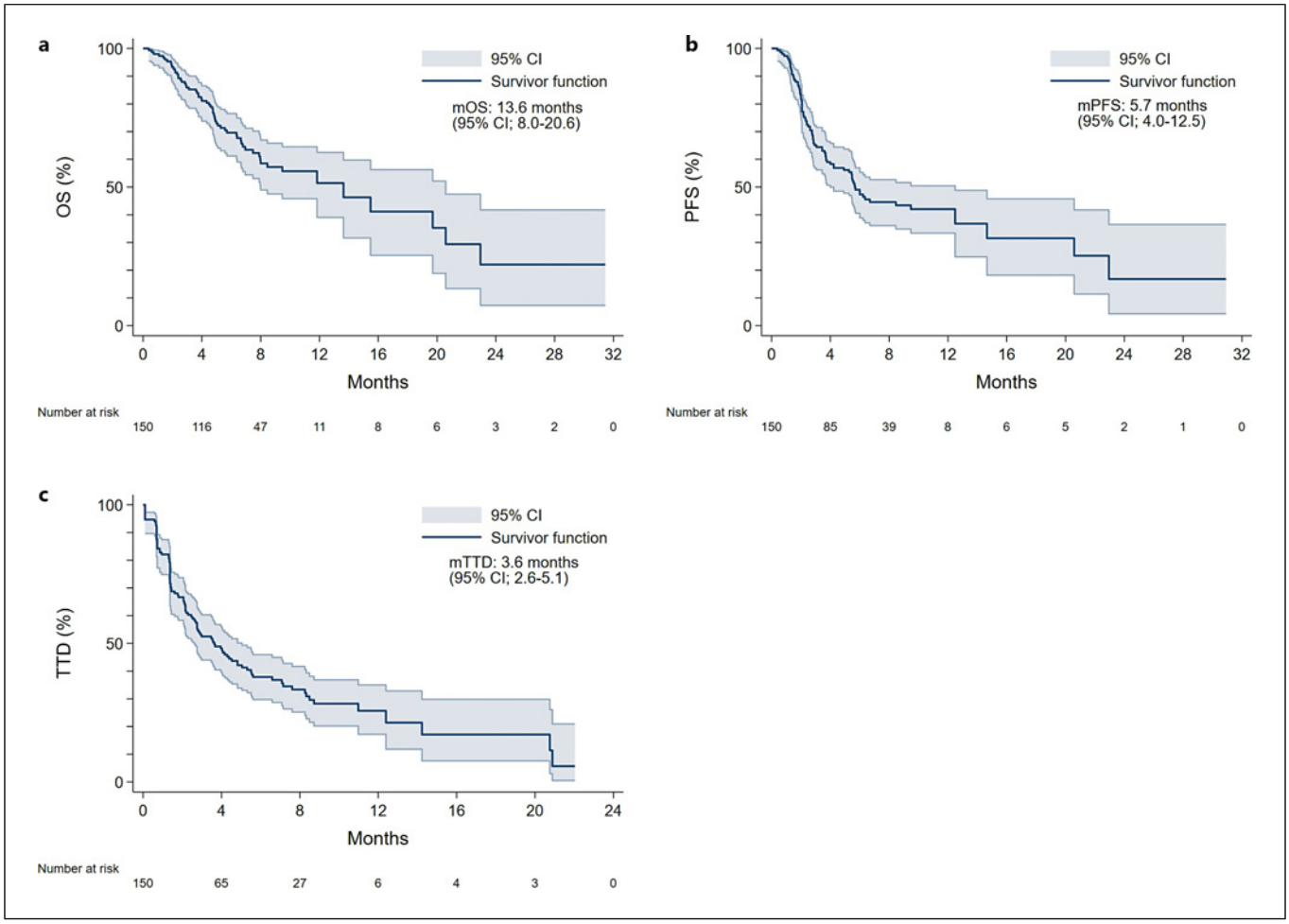

Fig. 2. Kaplan Meier survival curves of the patients. **a** OS. **b** PFS. **c** TTD.

Factors Associated with Outcome Measures

Various factors that could affect the survival outcomes were included in the analysis (Table 3). In terms of OS, univariate analysis revealed significant associations with neutrophil-to-lymphocyte ratio (NLR) <3.0, ALBI grade 1, Child-Pugh class A, tumour size <7 cm, the absence of PVTT, and mild irAEs. Factors that demonstrated significance in univariate analysis were subsequently included in multivariate analysis. Consequently, ALBI grade 1 (hazard ratio [HR] 0.389, 95% CI: 0.198–0.763, $p = 0.006$), Child-Pugh class A (HR 0.338, 95% CI: 0.173–0.663, $p = 0.002$), absence of PVTT (HR 0.556, 95% CI: 0.314–0.983, $p = 0.043$), and mild irAEs (HR 0.353, 95% CI: 1.313–4.102, $p = 0.004$) were all identified as independent predictors of favourable OS. Severe irAEs showed a tendency towards worse outcomes, although statistical significance was not achieved (HR 1.701, 95% CI: 0.934–3.098; $p = 0.082$). Regarding TTD, univariate analysis revealed significant associations with male sex, NLR <3.0, ALBI grade 1, Child-Pugh class A, and mild irAEs. In the multivariate analysis, male sex (HR 0.537, 95% CI: 0.321–0.899; $p = 0.018$), ALBI grade 1 (HR 0.596, 95% CI: 0.383–0.927; $p = 0.022$), and mild irAEs (HR 0.343, 95% CI: 0.196–0.599; $p < 0.001$) were indicative of a good prognosis in terms of TTD. For PFS, Child-Pugh class A (HR 0.478, 95% CI: 0.254–0.897; $p = 0.022$), absence of EHS (HR 0.546, 95% CI: 0.341–0.876; $p = 0.012$), and mild irAEs (HR 0.318, 95% CI: 0.165–0.612; $p = 0.001$) were predictive factors for favourable outcomes in the multivariate analysis (online suppl. Table 3).

Subgroup Analysis of Male Subjects

A subgroup analysis focusing on male patients was conducted owing to the notable sex disparity, with males exhibiting a considerably higher median TTD

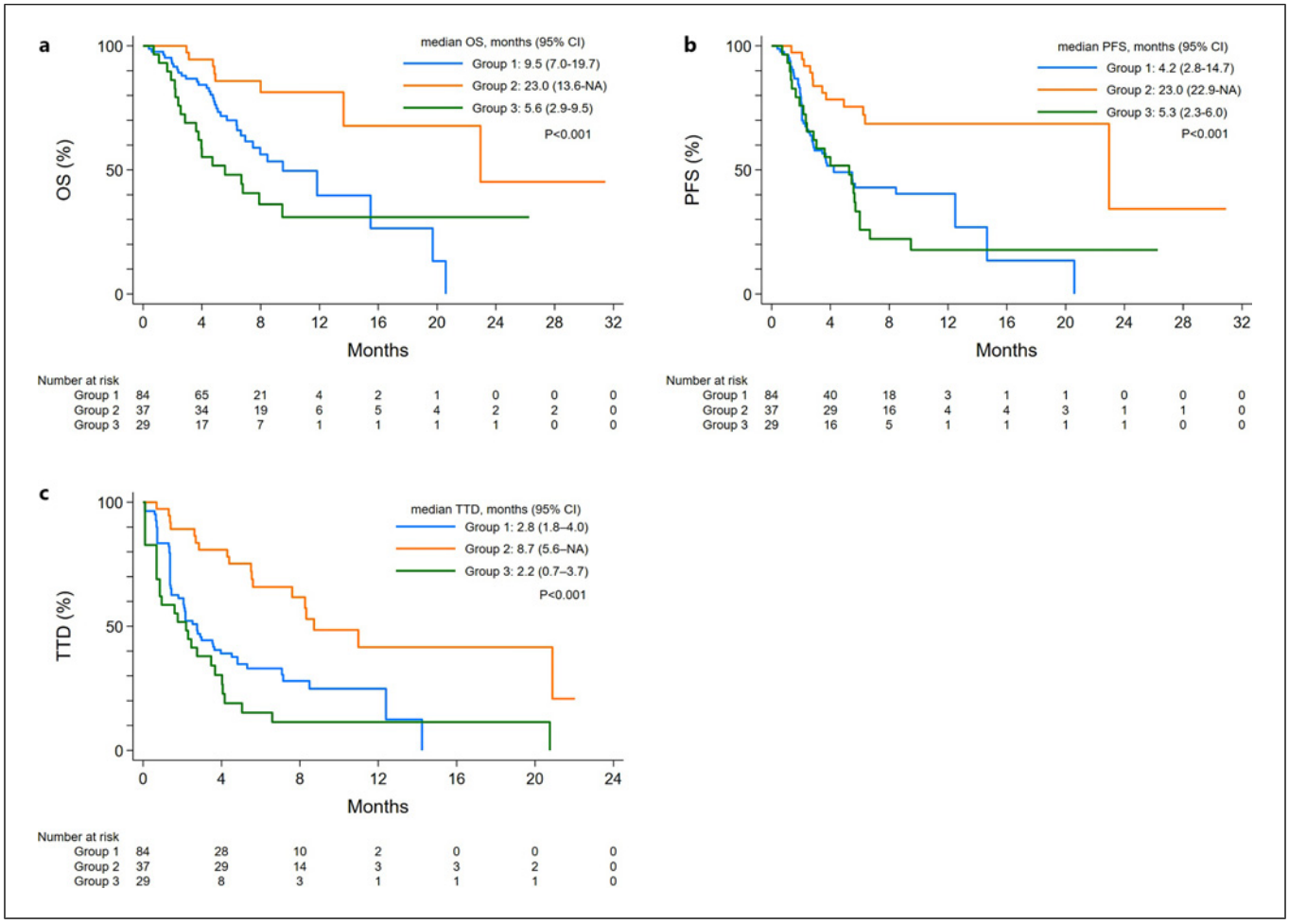

Fig. 3. Kaplan Meier survival curves of OS, PFS, and TTD in groups 1, 2, and 3. **a** OS. **b** PFS. **c** TTD. OS, overall survival; PFS, progression free survival; TTD, time-to-treatment discontinuation.

compared to female subjects (4.2 months vs. 2.4 months, $p = 0.019$) (Fig. 4a). When comparing the three groups of male subjects, group 2 showed better outcomes than both group 1 and group 3 in terms of OS and TTD ($p = 0.002$ and $p < 0.001$, respectively) (Fig. 4b, c). The factors associated with survival outcomes were also assessed (online suppl. Table 4). In the multivariate analysis, ALBI grade 1 (HR 0.336, 95% CI: 0.156–0.723, $p = 0.005$), Child-Pugh class A (HR 0.349, 95% CI: 0.166–0.736, $p = 0.006$), and mild irAEs (HR 0.274, 95% CI: 0.111–0.680, $p = 0.005$) were identified as independent factors for favourable OS outcomes. For TTD, ALBI grade 1 (HR 0.531, 95% CI: 0.331–0.853, $p = 0.009$) and mild irAEs (HR 0.293, 95% CI: 0.151–0.570, $p < 0.001$) were the two factors associated with favourable outcomes.

Sensitivity Analysis in Patients with/without EHS

Furthermore, a sensitivity analysis was conducted among patients with and without EHS. For patients with EHS, 91 individuals were included in the analysis (group 1 = 52, group 2 = 21, group 3 = 18) (online suppl. Fig. 2a–c). Regarding OS, significant differences were observed among the three groups, with group 2 demonstrating the most favourable outcomes (median OS: 7.5, NA, and 6.8 months for groups 1, 2, and 3, respectively, $p = 0.019$). In terms of PFS (median PFS: 2.9, NA, and 5.7 months for groups 1, 2, and 3, respectively, $p = 0.004$) and TTD (median TTD: 2.2, 8.3, and 2.5 months for groups 1, 2, and 3, respectively, $p = 0.003$), group 2 consistently demonstrated most favourable outcomes, with no significant differences observed between groups 1 and 3 in these outcome measures.

Table 3. Univariate and multivariate analysis of factors influencing OS and TTD

	OS			TTD		
	univariate analysis	multivariate analysis		univariate analysis	multivariate analysis	
	p value	HR (95% CI)	*p* value	*p* value	HR (95% CI)	*p* value
Age ≥65 years	0.325			0.419		
Sex (male)	0.457			**0.019**	**0.537 (0.321, 0.899)**	**0.018**
Aetiology (viral)	0.425			0.248		
NLR <3.0	<**0.001**	0.602 (0.351, 1.034)	0.066	**0.042**	0.777 (0.513, 1.177)	0.233
ALBI grade 1	<**0.001**	**0.389 (0.198, 0.763)**	**0.006**	**0.005**	**0.596 (0.383, 0.927)**	**0.022**
Child-Pugh class A	<**0.001**	**0.338 (0.173, 0.663)**	**0.002**	**0.032**	0.700 (0.365, 1.343)	0.283
AFP <400 ng/mL	0.059			0.188		
Tumour size <7 cm	**0.009**	0.847 (0.490, 1.462)	0.550	0.752		
BCLC stage C	0.872			0.405		
mUICC stage III	0.984			0.344		
Absence of PVTT	**0.040**	**0.556 (0.314, 0.983)**	**0.043**	0.630		
Absence of EHS	0.088			0.342		
IrAEs	Reference (absence of irAEs)			Reference (absence of irAEs)		
Mild irAEs	<**0.001**	**0.353 (0.159, 0.783)**	**0.010**	<**0.001**	**0.343 (0.196, 0.599)**	<**0.001**
Severe irAEs	0.075	1.701 (0.934, 3.098)	0.082	0.109	1.276 (0.779, 2.092)	0.333

Values with statistical significance are highlighted in bold. AFP, alpha fetoprotein; ALBI, albumin to bilirubin; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; EHS, extrahepatic spread; HR, hazard ratio; irAEs, immune-related adverse events; mUICC, modified Union for International Cancer Control; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PVTT, portal vein tumour thrombus; TTD, time-to-treatment discontinuation.

In the analysis of patients without EHS, consistent results were observed, with group 2 exhibiting the best outcomes across all measures, namely, OS (median OS: 11.8, 23.0, and 4.0 months for groups 1, 2, and 3, respectively, $p = 0.008$), PFS (median PFS: 20.6, 23.0, and 3.6 months for groups 1, 2, and 3, respectively, $p = 0.009$), and TTD (median TTD: 3.6, 11.0, and 1.8 months for groups 1, 2, and 3, respectively, $p = 0.003$) (online suppl. Fig. 2d–f). Notably, when comparing groups 1 and 3, group 1 was revealed to be superior in all three outcomes (OS: $p = 0.010$, PFS: $p = 0.008$, and TTD: $p = 0.032$).

Correlation between TTD and Other Endpoint Measures

To evaluate the utility of TTD as a surrogate marker for survival outcomes in patients with HCC, its correlation with OS and PFS was evaluated (online suppl. Fig. 3). Using Pearson's correlation test, a correlation coefficient between TTD and OS was calculated to be 0.735 (95% CI: 0.625–0.845, $p < 0.001$), indicating a strong positive correlation between the two outcome measures. Notably, TTD showed a strong correlation with PFS as well, with a correlation coefficient of 0.833 (95% CI: 0.743–0.923, $p < 0.001$). Taken together, TTD exhibited a strong correlation with both OS and PFS, suggesting its potential as a reliable surrogate indicator of HCC outcomes.

Discussion

IrAEs that occur during ICIs therapy can involve various organs and manifest with varying degrees of severity. It has been recently suggested that endocrine, dermatologic, and low-grade irAEs can serve as independent prognostic markers for favourable cancer outcomes in various malignancies [26, 27]. In this study, we

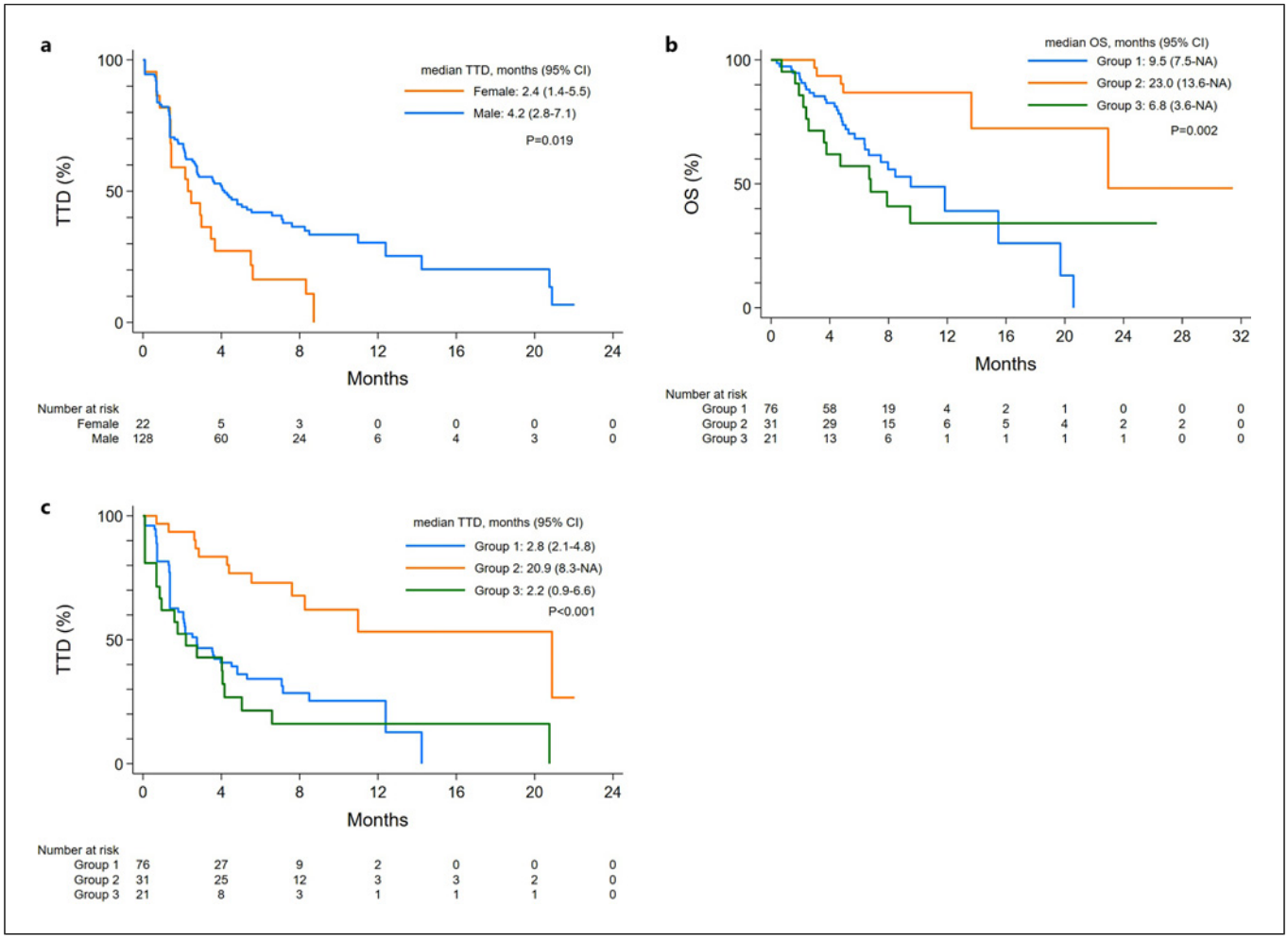

Fig. 4. Kaplan Meier survival curves of OS and TTD in the male subgroup. **a** TTD in the male and female subjects. **b** OS in the male subgroup. **c** TTD in the male subgroup. OS, overall survival; TTD, time-to-treatment discontinuation.

meticulously explored the frequency and severity of various types of irAEs that can be encountered in real clinical practice among patients with HCC treated with A + B. In this regard, a recent study suggested an association between thyroid-related irAEs and favourable outcomes in HCC patients treated with A + B [28]. Our study further extends this finding by revealing that the occurrence of mild-grade irAEs, encompassing thyroid-related irAEs, is independently associated with favourable outcomes in terms of OS, PFS, and TTD. Additionally, the study has shown a potential association between severe irAEs and worse outcomes. The occurrence of mild irAEs was identified as a favourable indicator of patient outcomes in terms of OS, TTD, and PFS, suggesting that mild irAEs hold promise as potential surrogate markers for the prognosis of A + B-treated HCC. Our study, with its rigorous analysis, is the first to comprehensively investigate the effect of irAEs in patients with HCC who underwent A + B therapy as a first-line systemic therapy.

The most commonly documented irAE in our study was an endocrinological disorder, which mainly comprised thyroid-related irAEs. A recent study showed that thyroid-related irAEs occurred in 19.7% of the A + B-treated patients with HCC, which closely aligns with our results of 18% [28]. Given that thyroid-related irAEs require hospitalization to be classified as grade 3 according to the CTCAE criteria, all occurrences of endocrine disorders in our study were categorized as mild irAEs. The most commonly observed severe irAE was transaminase elevation, which is known to occur more frequently in HCC compared to other malignancies due

to the underlying liver disease [25]. To distinguish immune-related hepatitis from transaminase elevation caused by other factors, we used a stepwise algorithmic assessment of irAEs for hepatitis, as introduced by Sangro et al. [25]. Immune-related hepatitis usually manifests within 4–12 weeks after ICI administration, which is in line with our results showing median time to immune-related hepatitis of 1.3 months [25]. Additionally, we documented other severe irAEs such as colitis, fatigue, skin rash, and pneumonitis, which have also been reported in previous real-world studies involving A + B-treated patients with HCC [29, 30]. Fatal irAEs observed in our study included hepatitis, pneumonitis, and myositis, all of which have also been presented as potentially life-threatening irAEs in other studies [19].

The underlying mechanisms of irAEs are believed to involve nonspecific upregulation of the immune system [13]. Multiple studies have proposed various potential mechanisms for irAEs, including an imbalance in regulatory T cells and type 17 T-helper cells, cross-reactivity of T cells with normal tissues, and B-cell-mediated production of autoantibodies [31, 32]. However, the identification of patients at higher risk for developing irAEs and factors associated with the occurrence of irAEs remain poorly established [33]. Several studies have investigated the prognostic role of irAEs in cancers treated with ICIs. Despite these efforts, controversy remains regarding their impact on survival outcomes [34].

We comprehensively assessed the diverse effects of irAEs on HCC outcomes. Our study revealed that mild irAEs were independently associated with favourable outcomes. Although not completely understood, the occurrence of irAEs is thought to indicate a robust immune reaction targeting both healthy and tumour tissues, thereby enhancing antitumour activity [27, 35]. Furthermore, mild irAEs can be effectively managed without the need to interrupt planned treatment, thus preserving the anticancer efficacy during the course of irAEs. Conversely, severe irAEs were associated with significantly worse outcomes. Although robust immune reactions coupled with severe irAEs might have been generated, presumably as a beneficial event for killing cancer cells, it is equally important for the reactions to be balanced against harmful events as an excessive immune response can be detrimental. Therefore, patients with severe irAEs may have suffered the consequences of increased mortality from toxicities rather than obtaining treatment benefits. Furthermore, impaired ECOG performance status or deterioration in liver function caused by severe irAEs could restrict patients' suitability for subsequent therapies [22]. These results emphasize that the impact of irAEs on cancer prognosis might vary depending on their severity and highlight the need for meticulous monitoring of irAE symptoms and tailored therapeutic approaches.

In our study, the TTD was chosen as the endpoint for assessing treatment efficacy. Although PFS is commonly used as an endpoint in studies evaluating the effectiveness of anticancer drugs, it overlooks treatment discontinuation due to adverse effects. Moreover, the risk of disease progression after drug cessation potentially delays the clinical course when using PFS. In contrast, TTD seems to be a useful tool for real-world studies as it reflects various reasons for drug cessation and potentially facilitates the early identification of disease progression. Furthermore, considering the recent introduction of multiple systemic treatment options for advanced HCC, TTD can aid in formulating appropriate treatment strategies because it can proactively predict patient prognosis. TTD also showed a strong correlation with OS and PFS in our study, further emphasizing its utility as a surrogate marker for predicting survival outcomes in real-world studies.

For patients encountering irAEs, disease progression often requires a considerable period, even after the cessation of immuno-oncological drugs, thus introducing immortal time bias. To mitigate this bias concerning irAEs, we conducted a landmark analysis of PFS at 4 months after treatment initiation, considering that the median time to the occurrence of irAEs in this study was 2.4 months. The results of our landmark analysis further reinforced the impact of irAEs on HCC outcomes. The group that experienced mild irAEs exhibited notably superior PFS outcomes both at the 4-month landmark and before the landmark time. This finding substantiates that the superior outcomes associated with mild irAEs may not be attributable to immortal time bias but rather to the inherent nature of irAEs. Notably, patients with severe irAEs demonstrated inferior PFS outcomes compared to those without irAEs in the landmark analysis, highlighting that severe irAEs could serve as unfavourable prognostic indicators of outcomes in patients with HCC undergoing A + B treatment.

Consistent with the results of previous studies, our findings did not reveal significant correlations between sex and survival outcomes (OS or PFS). However, in terms of TTD, females demonstrated significantly poorer TTD outcomes. We hypothesize that the fixed dose of 1,200 mg atezolizumab, regardless of patient weight, may have prompted these outcomes. Given the comparatively lower body weights of Asian women compared to those of other races and sexes, it is plausible that this dosage of atezolizumab might result in increased toxicity. This can lead to early treatment discontinuation, as demonstrated

in the present study. This study has several limitations that need to be acknowledged. First, the retrospective design of the study may restrict comprehensive investigation of all irAEs that developed during the treatment course. Second, the number of enrolled patients was insufficient to fully determine the impact of irAEs with different aetiologies, especially in women. Even though we conducted a subgroup analysis involving male subjects to rectify the potential influence of sex bias on the results, a more comprehensive investigation, encompassing a larger female population, would provide a clearer understanding of this matter. Additionally, it is worth noting that this study was conducted solely in Korea, and therefore the assessment of diverse ethnicities could not be performed. As the majority of the study population was chronically infected with hepatitis B virus, the reproducibility of the study results in Caucasians or patients with non-alcoholic steatohepatitis is uncertain, given the differences in host immunity between patients with chronic hepatitis B virus infection and those with non-alcoholic steatohepatitis. Lastly, the present study relied solely on clinical variables and proposed algorithms to define irAEs, lacking any data regarding immune profiling. Although histological data are not easily accessible in routine clinical practice, its inclusion might have provided a more profound understanding of the results derived from our study.

With the increasing prominence of ICI-based treatments in cancer therapy, irAEs have become a major concern for physicians. We provide pioneering evidence that the severity of irAEs independently affects survival outcomes, offering impactful insights into the management of ICI. In our study, the impact of irAE severity exhibited duality. Although mild irAEs can be considered favourable prognostic factors for HCC outcomes, severe irAEs can yield worse outcomes than those observed without irAEs. This duality emphasizes the importance of close monitoring and proper assessment of irAEs when administering A + B regimen for HCC. Furthermore, it highlights the need to implement appropriate management strategies for patients experiencing irAEs as this can significantly prolong treatment duration and ultimately improve cancer outcomes.

Statement of Ethics

This study was approved by the Institutional Review Board of the Catholic University of Korea (approved number: KC22EASI0342). The need for informed consent was waived by the Institutional Review Board of the Catholic University of Korea.

Conflict of Interest Statement

None to declare.

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Author Contributions

Jeong Won Jang: study design, data collection, data analysis, data interpretation, manuscript writing, and manuscript approval. Heechul Nam and Jaejun Lee: study design, data collection, data analysis, data interpretation, and manuscript writing. Ji Won Han, Soon Kyu Lee, Hyun Yang, Hae Lim Lee, Pil Soo Sung, Hee Yeon Kim, and Seok-Hwan Kim: data collection. Myeong Jun Song, Jung-Hyun Kwon, Chang Wook Kim, Soon Woo Nam, Si Hyun Bae, Jong Young Choi, and Seung Kew Yoon: data interpretation and manuscript approval.

Data Availability Statement

The original contributions presented in the study are included in the article and its online supplementary material files; further enquiries can be directed to the corresponding author.

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