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ORIGINAL ARTICLE

# Immune checkpoint inhibitor use and the incidence of hepatitis B virus reactivation or immune-related hepatitis in non–small cell lung cancer patients with chronic hepatitis B

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## Abstract

**Background:** The safety of immune-checkpoint inhibitors (ICIs) has not been thoroughly investigated in non–small cell lung cancer (NSCLC) patients with chronic hepatitis B (CHB) or occult hepatitis B infection (OBI). The authors analyzed the incidence of hepatitis B virus (HBV) reactivation, immune-related hepatitis and jaundice in NSCLC patients in a real-world setting.

**Methods:** A total of 1277 NSCLC patients treated with ICIs were analyzed. Among them, 52 patients were hepatitis B surface antigen (HBsAg) (+) (group A, CHB), 759 patients were HBsAg (–)/hepatitis B core antibody immunoglobulin G (anti-HBc IgG) (+) (group B, OBI), and 466 patients were HBsAg (–)/anti-HBc IgG (–) (group C). Among the 52 patients with CHB, 38 (73.1%) were receiving antiviral therapy. The primary end point was HBV reactivation, immune-related hepatitis, and jaundice. The secondary end points included other immune-related adverse events and efficacy.

**Results:** HBV reactivation was observed in two patients (0.2%) who were both in group A (CHB). Among CHB patients who were not receiving antiviral therapy, HBV reactivation was observed in 14.3% (2 of 14 patients). The incidences of immune-related hepatitis and jaundice were comparable among the three groups. The incidence of ≥grade 3 other immune-related adverse events and efficacy were all comparable among the three groups ($p > .05$ for all comparisons).

**Conclusions:** In this large, real-world cohort study, the safety and efficacy of ICIs were comparable in patients with CHB and OBI. HBV reactivation was observed in patients with CHB without antiviral therapy indicating antiviral prophylaxis should be required for them. For patients with OBI, the risk of HBV reactivation was minimal.

KEYWORDS

hepatitis B virus reactivation, immune checkpoint inhibitor, non–small cell lung cancer

## INTRODUCTION

Non–small cell lung cancer (NSCLC) still remains the leading cause of cancer death worldwide.[1] Although the prognosis of advanced NSCLC is poor, there have been tremendous improvements in the clinical outcomes through the use of immune-checkpoint inhibitors (ICIs), especially in patients with non-oncogenic drivers. ICIs including pembrolizumab, atezolizumab, nivolumab, ipilimumab and durvalumab with or without chemotherapy have shown efficacy in various settings of NSCLC. In particular, ICIs have shown efficacy as neoadjuvant or adjuvant therapy in the early stage, as consolidation in locally advanced and as palliative treatment in metastatic advanced NSCLC.[2–5] Although ICIs have better safety profiles than do cytotoxic chemotherapy, they can cause immune-related adverse events (irAEs) in nearly any organ system (including immune-related hepatitis, pneumonitis, thyroiditis, colitis, etc.).[6]

Chronic hepatitis B (CHB) infection remains a huge burden in Asia, where it is unevenly prevalent compared to other regions in the world.[7] Several treatment modalities for cancers can lead to hepatitis B virus (HBV) reactivation. These treatments include anti-CD 20 agents, corticosteroids, cytotoxic chemotherapy, anti-TNF agents, radiotherapy, transarterial chemoembolization, or surgery.[8–11] Therefore, prophylaxis with antiviral agents is recommended for patients at high-risk of HBV reactivation.[12]

The increasing use of ICIs also posed the question if they would be safe for CHB patients. Although several reports have described the safe use of ICIs in CHB patients, a higher prevalence of serious hepatitis has also been reported in CHB patients treated with ICIs.[13–15] In contrast, another study reported that the HBV DNA titer decreased from baseline after administering ICIs due to their immune tolerance inhibitory effect.[16] Moreover, ICIs might be an effective treatment option for CHB by restoring antiviral T-cells, which have immune checkpoint overexpression.[17]

The relationship between ICI and HBV, with regard to safety and efficacy, has not yet been fully investigated in NSCLC. For this reason, CHB patients are usually excluded from clinical trials of ICIs. Several retrospective studies are available for the safety and efficacy of ICIs in cancer patients with hepatitis B; however, there are limited data comparing the incidence of reactivation of hepatitis B or immune related hepatitis and jaundice among CHB patients and patients with hepatitis B surface antigen (HBsAg) (−)/hepatitis B core antibody immunoglobulin G (anti-HBc IgG) (+) (occult hepatitis B infection [OBI]), or HBsAg (−)/anti-HBc IgG (−). Here, we investigate the hepatic adverse events including HBV reactivation, immune-related hepatitis, and jaundice in NSCLC patients with chronic HBV infection treated with ICIs compared to other patient populations (OBI and HBsAg (−)/anti-HBc IgG (−)) in a real-world setting.

## MATERIALS AND METHODS

We retrospectively collected clinicopathologic data from NSCLC patients who were treated with ICIs between January 2015 and December 2020 at Samsung Medical Center (Figure 1). The Clinical Data Warehouse DARWIN-C of Samsung Medical Center was used to extract data for this study. The ICIs included pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, ipilimumab, and tremelimumab. We collected the following clinicopathologic data: sex, age, histology, serologic status of HBV, HCV, and HIV, follow-up data of HBV serology, liver cirrhosis, smoking, Eastern Cooperative Oncology Group (ECOG) performance status, baseline and follow-up data of laboratory tests including complete blood count, liver and kidney function, types of ICIs, antiviral agents administered, response of ICIs, and irAEs. The data cutoff date was August 31, 2022.

A total of 2390 NSCLC patients treated with ICIs were enrolled from the Clinical Data Warehouse DARWIN-C. The following

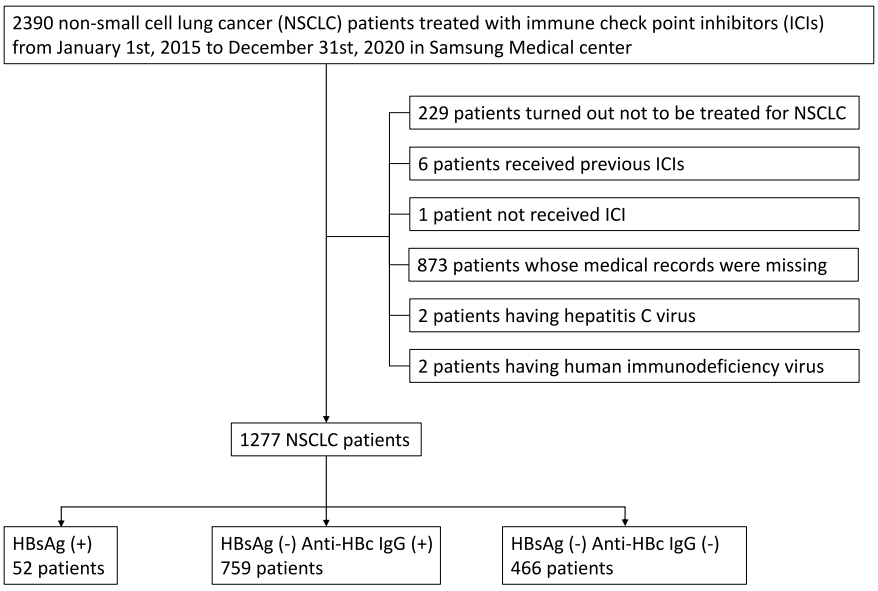


**FIGURE 1** Patient flow.

patients were excluded: 229 patients whose diagnosis was not NSCLC; six patients who received previous ICIs; one patient who did not receive an ICI; 873 patients whose medical records were not available; two patients with hepatitis C virus; and two patients with human immunodeficiency virus. Ultimately, 1277 patients were included in the analysis. Among them, 52 patients were HBsAg (+) (group A, CHB), 759 patients were HBsAg (–)/anti-HBc IgG (+) (group B, OBI), and 466 patients were HBsAg (–)/anti-HBc IgG (–) (group C) who were HBV-susceptible or HBV vaccinated patients. Two, 606, and 274 patients among each group were anti-HBs antibody-positive, respectively. Patients who were treated with ICIs as a palliative treatment ($n = 1013$) were analyzed for progression-free survival (PFS) and overall survival (OS).

The primary end point was to compare the incidence of HBV reactivation or immune-related hepatitis and jaundice among the three groups. The secondary end points included other irAEs, the objective response rate, and survival including PFS and OS. HBV reactivation was defined according to the American Association for the Study of Liver Diseases (AASLD) guidelines.[18] Adverse events including immune-related hepatitis and jaundice were assessed according to Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. In case of hepatic dysfunction, the clinical context and electronic medical record were reviewed to rule out etiologies such as liver metastases, drug-induced liver injury, or other causes beside ICI use. The PFS was defined as the duration from the date of initial ICIs to the date of disease progression. The OS was defined as the duration from the date of initial ICIs to the date of death or last follow-up, whichever occurs first. The response evaluation criteria in solid tumors (RECIST) version 1.1 and iRECIST were used to assess the response to ICIs.[19,20]

The Kruskal–Wallis rank-sum test and post hoc analysis using the Bonferroni correction were used to compare age among the three groups. Pearson's $\chi^2$ test or Fisher exact test and post hoc analysis using pairwise comparison were used to compare frequencies among the three groups. Kaplan–Meier survival curves were used to estimate PFS and OS. The log-rank test was used to analyze the survival differences between groups. R software (version 4.2.0; The R Project for Statistical Computing) was used for statistical analysis.

The present study was approved by the institutional review board of the Samsung Medical Center (approval no. 2023-02-026-001; February 14, 2023). The requirement for informed consent was waived due to the retrospective nature of the study.

## RESULTS

### Patient characteristics

The baseline patient characteristics are shown in Table 1. The median age was 62 years and 72% were male. The most common histology was adenocarcinoma (60.8%), followed by squamous cell carcinoma (27.9%). Most patients had ECOG 0–2 (99.6%), except 48 patients whose medical records were unavailable. Although 58% of patients had stage IV disease, 11.4% had stage I–III and 30.5% had recurrent disease. During the study period in Korea, ICI monotherapy was only reimbursed as a subsequent therapy rather than first-line treatment. We found that 56.5% of patients were treated with ICIs as a first- or second-line treatment and 32.2% of patients as a third-line or beyond therapy. Pembrolizumab (43.1%) was the most commonly administered ICI, followed by atezolizumab (34.4%) and nivolumab (15.9%).

Comparing the three groups, there were significantly more men in group B ($p < .001$), significantly younger patients in group A ($p < .001$), and more never smokers in group C ($p < .001$). Otherwise, there were no significant differences in other patient characteristics between the three groups.

Of the 52 patients from group A, 38 patients received antiviral therapy during treatment, as specified: 31 received antiviral therapy 3 months before, during, and 3 months after ICI administration; two patients received antiviral therapy starting 3 months before initial ICI administration but discontinued it before the last ICI administration; and five patients started antiviral therapy in the midst of ICI administration and received it until 3 months after last ICI administration. The remaining 14 patients did not receive any antiviral therapy during ICI administration (Table 2). Entecavir (57.7%) was the most frequently administered antiviral agent during ICI treatment, followed by tenofovir (13.5%) and lamivudine (1.9%). In this group, 28 patients had undetectable HBV DNA level, whereas the baseline HBV DNA level was not measured in nine patients. Four patients had HBV DNA baseline titer level <100 IU/mL, and three patients had HBV DNA baseline titer levels between 100 and 1000 IU/mL. Another three patients had HBV DNA titer between 1000 and 10,000 IU/mL. One patient had an HBV DNA titer of 33,900 IU/mL. Two patients had HBV DNA baseline titer levels between 100,000 and 1,000,000 IU/mL, and another two patients had HBV DNA baseline titer level of >10,000,000 IU/mL. A total of 134 among 759 of group B patients and 79 among 466 of group C patients had tested HBV DNA baseline level, all of which were undetected.

### Incidence of HBV reactivation

Twenty-five patients were tested for HBV DNA follow-up and evaluated for HBV reactivation in group A (Table 3). Of these, only two patients (0.2%) developed HBV reactivation, both of whom were HBsAg (+). In contrast, there were no cases of HBV reactivation in group B or group C.

One patient was treated with pembrolizumab for 9 months. After 2 months of pembrolizumab, the HBV DNA titer increased to 23,072 IU/mL (although there was no baseline HBV DNA titer level). At the time of HBV reactivation, the total bilirubin was 0.3 mg/dL, and AST and ALT were 33 and 55 U/L, respectively. The HBV DNA titer decreased to 50 IU/mL and became undetectable after entecavir treatment. Another patient was treated with pembrolizumab for a month. Before pembrolizumab, entecavir was administered during

**TABLE 1** Baseline characteristics.

| Variables | Levels | HBsAg (+) (*N* = 52) (%) | HBsAg (–), anti-HBc IgG (+) (*N* = 759) (%) | HBsAg (–), anti-HBc IgG (–) (*N* = 466) (%) | Total (*N* = 1277) (%) |
|---|---|---|---|---|---|
| Sex | Male | 34 (65.4) | 591 (77.9) | 301 (64.6) | 926 (72.5) |
| | Female | 18 (34.6) | 168 (22.1) | 165 (35.4) | 351 (27.5) |
| Age, years | Median | 58.5 | 64.0 | 60.0 | 62.0 |
| Histology | ADC | 27 (51.9) | 443 (58.4) | 307 (65.9) | 777 (60.8) |
| | SqCC | 20 (38.5) | 231 (30.4) | 105 (22.5) | 356 (27.9) |
| | Pleomorphic | 1 (1.9) | 11 (1.4) | 7 (1.5) | 19 (1.5) |
| | Others | 4 (7.7) | 74 (9.7) | 47 (10.1) | 125 (9.8) |
| LC | Yes | 3 (5.8) | 4 (0.5) | 4 (0.9) | 11 (0.9) |
| | No | 49 (94.2) | 755 (99.5) | 462 (99.1) | 1266 (99.1) |
| Smoking[a] | Current smoker | 21 (40.4) | 257 (34) | 129 (27.7) | 407 (31.9) |
| | Ex-smoker | 10 (19.2) | 250 (33.1) | 119 (25.5) | 379 (29.7) |
| | Never smoker | 21 (40.4) | 249 (32.9) | 218 (46.8) | 488 (38.3) |
| ECOG[a] | 0 | 2 (4) | 48 (6.5) | 28 (6.3) | 78 (6.3) |
| | 1 | 42 (84) | 624 (84.6) | 384 (87.1) | 1050 (85.4) |
| | 2 | 6 (12) | 62 (8.4) | 29 (6.6) | 97 (7.9) |
| | 3 | 0 (0) | 4 (0.5) | 0 (0) | 4 (0.3) |
| Stage | I–III | 3 (5.8) | 83 (10.9) | 60 (12.9) | 146 (11.4) |
| | IV | 28 (53.8) | 438 (57.7) | 275 (59) | 741 (58.0) |
| | Recurrent | 21 (40.4) | 238 (31.4) | 131 (28.1) | 390 (30.5) |
| Lines of ICI | Neoadj. or Adj. | 3 (5.8) | 84 (11.1) | 58 (12.4) | 145 (11.4) |
| | ≤ 2 line | 31 (59.6) | 448 (59.0) | 242 (51.9) | 721 (56.5) |
| | ≥ 3 line | 18 (34.6) | 227 (29.9) | 166 (35.6) | 411 (32.2) |
| ICIs | Pembrolizumab | 24 (46.2) | 325 (42.8) | 201 (43.1) | 550 (43.1) |
| | Nivolumab | 9 (17.3) | 128 (16.9) | 66 (14.2) | 203 (15.9) |
| | Atezolizumab | 20 (38.5) | 252 (33.2) | 167 (35.8) | 439 (34.4) |
| | Durvalumab | 2 (3.8) | 71 (9.4) | 47 (10.1) | 120 (9.4) |
| | Avelumab | 0 (0) | 15 (2) | 8 (1.7) | 23 (1.8) |
| | Ipilumab | 3 (5.8) | 12 (1.6) | 7 (1.5) | 22 (1.7) |
| | Tremelimumab | 0 (0) | 18 (2.4) | 6 (1.3) | 24 (1.9) |
| Antiviral agents | Entecavir | 30 (57.7) | 3 (0.4) | 0 (0) | 33 (2.6) |
| | Tenofovir | 7 (13.5) | 0 (0) | 0 (0) | 7 (0.5) |
| | Lamivudine | 1 (1.9) | 1 (0.1) | 0 (0) | 2 (0.2) |

Abbreviations: ADC, adenocarcinoma; Adj, adjuvant; anti-HBc IgG, hepatitis B core antibody immunoglobulin G; ECOG, Eastern Cooperative Oncology Group; HBsAg, hepatitis B surface antigen; ICIs, immune checkpoint inhibitors LC, lung cancer; Neoadj, neoadjuvant; Pleomorphic, pleomorphic carcinoma; SqCC, squamous cell carcinoma.

[a]Some patients were missing due to unavailable medical records.

adjuvant concurrent chemoradiotherapy and palliative chemotherapy. However, the patient stopped the entecavir 2 months before pembrolizumab was administered. After 2 months of pembrolizumab, the HBV DNA titer increased from undetectable at baseline to 1484 IU/mL. The patient's total bilirubin and liver function tests were within the normal ranges despite the detectable HBV DNA. After retreatment with entecavir for 1 month, the HBV DNA titer again became undetectable.

**TABLE 2** Baseline characteristics of chronic hepatitis B patients (group A).

| Variables | HBsAg (+) (N = 52) (%) |
|---|---|
| Antiviral treatment | |
| During ICI administration (3 months before initial and after last ICI administration) | 31 (59.6) |
| 3 months before initial ICI administration to before last ICI administration | 2 (3.8) |
| In the midst of ICI administration to 3 months after last ICI administration | 5 (9.6) |
| No treatment | 14 (26.9) |
| Baseline HBV DNA | |
| No baseline | 9 (17.3) |
| Undetectable | 28 (53.8) |
| –100 IU/mL | 4 (7.7) |
| 100–1000 IU/mL | 3 (5.8) |
| 1000–10,000 IU/mL | 3 (5.8) |
| 10,000–100,000 IU/mL | 1 (1.9) |
| 100,000–1,000,000 IU/mL | 2 (3.8) |
| 1,000,000–10,000,000 IU/mL | 0 (0) |
| 10,000,000 IU/mL – | 2 (3.8) |

Abbreviations: HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; ICI, immune checkpoint inhibitor.

**TABLE 3** HBV reactivation, immune-related hepatitis and jaundice.

| Variables | Levels | HBsAg (+) (N = 52) (%) | HBsAg (–), anti-HBc IgG (+) (N = 759) (%) | HBsAg (–), anti-HBc IgG (–) (N = 466) (%) | p |
|---|---|---|---|---|---|
| HBV reactivation | Yes | 2 (3.8) | 0 (0) | 0 (0) | |
| | No | 23 (44.2) | 131 (17.3) | 83 (17.8) | |
| Immune-related hepatitis | Grade ≥3 | 2 (3.8) | 22 (2.9) | 10 (2.1) | .406[a] |
| | Grade 1–2 | 9 (17.3) | 208 (27.4) | 132 (28.3) | |
| | No | 39 (75.0) | 503 (66.3) | 318 (68.2) | |
| Immune-related jaundice | Grade ≥3 | 1 (1.9) | 6 (0.8) | 3 (0.6) | .510[a] |
| | Grade 1–2 | 1 (1.9) | 24 (3.2) | 10 (2.1) | |
| | No | 48 (92.3) | 703 (92.6) | 447 (95.9) | |

Abbreviations: anti-HBc IgG, hepatitis B core antibody immunoglobulin G; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.
[a]Fisher exact test.

## Incidence of immune-related hepatitis and immune-related jaundice

Any grade of immune-related hepatitis was observed in 21.2% of group A, 30.3% of group B, and 30.5% of group C ($p > .05$). Grade ≥3 immune-related hepatitis occurred in 3.8% of group A, 2.9% of group B, and 2.1% of group C ($p > .05$).

Any grade of immune-related jaundice was observed in 3.8% of group A, 4.0% of group B, and 2.8% of group C ($p > .05$). Grade ≥3 immune-related jaundice occurred in 1.9% of group A, 0.8% of group B, and 0.6% of group C ($p > .05$).

Three patients died from immune-related hepatitis and jaundice.

## Other irAEs

Cutaneous adverse events (of any grade) were the most common (11.7%), followed by thyroid dysfunction (7.4%), rheumatologic (5.8%), pulmonary (5.2%), and gastrointestinal symptoms (3.7%). In contrast, pulmonary adverse events (2.0%) were the most common serious adverse events of grade ≥3 (Table 4). The incidences of other serious irAEs of grade ≥3 were two (3.8%) in group A, 38 (5.0%) in group B, and 16 (3.4%) in group C ($p > .05$) (Table 5). There were four patients with grade 5 irAE. Three of these five patients died from pulmonary irAE and one died from gastrointestinal irAE.

**TABLE 4** Other immune-related adverse events in the total population (1277 patients).

| | Grade 1 (%) | Grade 2 (%) | Grade ≥3 (%) | Any grade (%) |
|---|---|---|---|---|
| Cutaneous | 111 (8.7) | 31 (2.4) | 8 (0.6) | 150 (11.7) |
| Gastrointestinal | 33 (2.6) | 9 (0.7) | 5 (0.4) | 47 (3.7) |
| Pulmonary | 3 (0.2) | 38 (3.0) | 26 (2.0) | 67 (5.2) |
| Thyroid | 17 (1.3) | 74 (5.8) | 3 (0.2) | 94 (7.4) |
| Cardiac | 0 (0) | 1 (0.1) | 1 (0.1) | 2 (0.2) |
| Rheumatologic | 48 (3.8) | 25 (2.0) | 1 (0.1) | 74 (5.8) |
| Renal | 0 (0) | 0 (0) | 2 (0.2) | 2 (0.2) |
| Hematologic | 1 (0.1) | 0 (0) | 7 (0.5) | 8 (0.6) |
| Pancreas | 1 (0.1) | 15 (1.2) | 3 (0.2) | 19 (1.5) |
| Adrenal | 0 (0) | 12 (0.9) | 4 (0.3) | 16 (1.3) |
| Ocular | 0 (0) | 1 (0.1) | 0 (0) | 1 (0.1) |
| Others | 72 (5.6) | 45 (3.5) | 3 (0.2) | 120 (9.4) |

**TABLE 5** Other immune-related adverse events ≥grade 3 by group.

| Grade ≥3 | HBsAg (+) (N = 52) (%) | HBsAg (−), anti-HBc IgG (+) (N = 759) (%) | HBsAg (−), anti-HBc IgG (−) (N = 466) (%) | p |
|---|---|---|---|---|
| Yes | 2 (3.8) | 38 (5.0) | 16 (3.4) | .477[a] |
| No | 50 (96.2) | 721 (95.0) | 450 (96.6) | |

Abbreviations: anti-HBc IgG, hepatitis B core antibody immunoglobulin G; HBsAg, hepatitis B surface antigen.
[a]Fisher exact test.

## Objective response rate and survival

The overall response evaluation was available for 1013 patients treated with immunotherapy for palliation. In the HBsAg (+) group, six (15.0%) patients achieved partial response (PR), 11 (27.5%) stable disease (SD), and 23 (57.5%) progressive disease (PD). In the HBsAg (−) and anti-HBc IgG (+) group, 171 (28.5%) patients had complete response (CR) and PR, 148 (24.7%) SD, and 280 (46.7%) PD. In the HBsAg and anti-HBc IgG (−) group, 104 (27.8%) achieved CR and PR, 101 (27.0%) SD, and 169 (45.2%) PD. The objective response rates were comparable across the three groups (Table 6).

Over a median of 34 months of follow-up, the median PFS was 2 months in group A, 3 months in group B, and 3 months in group C (Figure 2A). There were no differences in PFS between the three groups ($p$ = .079). The median OS was 19 months in group A, 21 months in group B, and 22 months in group C (Figure 2B). There were no differences in the OS among the three groups ($p$ = .99).

## DISCUSSION

In this study, there was an extremely low (0.2%) rate of HBV reactivation in HBsAg (+) NSCLC patients treated with an ICI. In addition, the incidence of immune related-hepatitis and jaundice was not increased, which was comparable to those with HBsAg (−)/anti-HBc IgG (+) or HBsAg (−)/anti-HBc IgG (−). Moreover, the incidence of immune-related hepatitis and jaundice ≥ grade 3 in the HBsAg (+) group was similar to that of other groups. In terms of clinical outcomes, there were no significant differences in the objective response rate, PFS, or OS among the three groups.

HBV reactivation was only found in two patients, both of whom were in the HBsAg (+) group. This result is consistent with previous reports.[21–28] The two patients who developed HBV reactivation did not receive antiviral prophylaxis. Fortunately, both patients responded well to treatment with an additional antiviral agent for treatment of HBV reactivation. These findings suggest that the low incidence of HBV reactivation is attributable to the prophylactic use of antiviral agents and emphasize the importance of antiviral prophylaxis in CHB patients. According to the AASLD guidelines, HBV DNA titer or HBsAg serology should be monitored carefully during anticancer treatment to detect HBV reactivation. However, the appropriate frequency of this testing has not been defined, given that most patients receive antiviral agents as prophylaxis during anticancer treatment (including with ICIs). Prior research suggests that pembrolizumab is more strongly associated with HBV reactivation than are other ICIs such as atezolizumab, nivolumab, durvalumab, avelumab, and ipilimumab.[29] Although both patients who developed HBV reactivation in our study were treated with pembrolizumab, further

**TABLE 6** Objective response rates in evaluable NSCLC patients treated with immunotherapy for palliation.

| Best response | HBsAg (+) ($N$ = 40) (%) | HBsAg (−) anti-HBc IgG (+) ($N$ = 599) (%) | HBsAg (−), anti-HBc IgG (−) ($N$ = 374) (%) | Total ($N$ = 1013) (%) |
|---|---|---|---|---|
| CR | 0 (0) | 14 (2.3) | 7 (1.9) | 21 (2.1) |
| PR | 6 (15.0) | 157 (26.2) | 97 (25.9) | 260 (25.7) |
| SD | 11 (27.5) | 148 (24.7) | 101 (27.0) | 260 (25.7) |
| PD | 23 (57.5) | 280 (46.7) | 169 (45.2) | 472 (46.6) |

Abbreviations: anti-HBc IgG, hepatitis B core antibody immunoglobulin G; CR, complete response; HBsAg, hepatitis B surface antigen; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease.

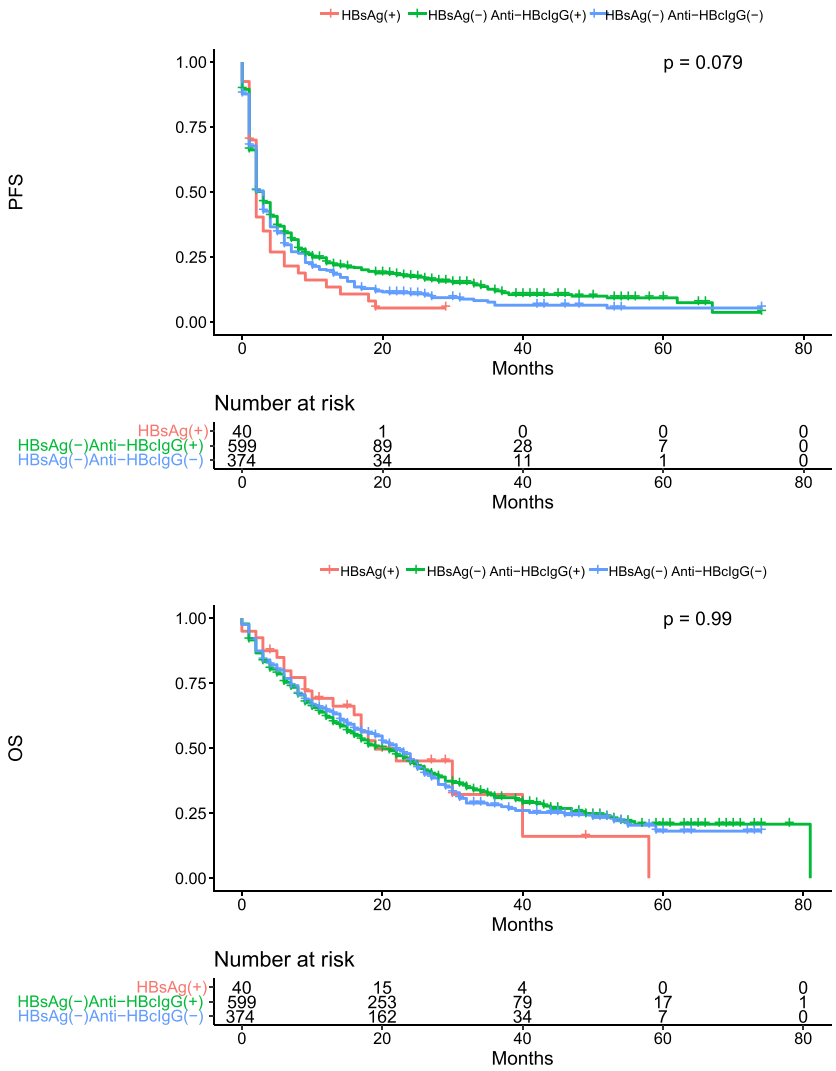


**FIGURE 2** Progression-free survival (A) and overall survival (B) of patients treated with ICIs for palliative aim.

investigation is needed to determine which ICI is most associated with this adverse effect.

Interestingly, there were no cases of HBV reactivation in groups B or C, even though only 17.3% (131 of 759) of patients in group B and 17.8% (83 of 466) in group C had follow-up HBV serology data. These data suggest that patients within these groups can be safely administered ICI without a prophylactic antiviral agent.

We also found that the incidence of immune-related hepatitis was not significantly increased in patients with HBsAg (+) (21.2%) compared to those without it (30.3% in group B and 30.5% in group

C). Furthermore, the rate of ≥grade 3 immune-related hepatitis was comparable among the three groups. Similarly, immune-related jaundice was not significantly increased in patients with HBsAg (+) (3.8%) compared to that in other patient groups (4.0% in group B and 2.8% in group C). Furthermore, the rate of ≥grade 3 immune-related jaundice was not different across the three groups. Even though the rates of ≥grade 3 immune-related hepatitis and jaundice were not significant among three groups, group A showed numerically higher rates of ≥grade 3 immune-related hepatitis and jaundice. This resulted in ICI therapy interruption, dose reduction, steroid or other immunosuppressive treatments. These immunosuppressive treatments to treat immune-related hepatitis and jaundice might increase the risk of HBV reactivation in turn. Nevertheless, the number in this study was too small to have a firm conclusion. Immune-related hepatitis and jaundice were diagnosed based on laboratory findings and consideration of the clinical context and electronic medical record review. Liver metastases, drug-induced liver injury, and other causes of liver injury (aside from ICIs) were excluded after clinical and record review.

Similarly, the rate of other irAEs was also comparable with those of other populations of non-CHB patients. The most common adverse events were cutaneous, followed by thyroid dysfunction and pulmonary events. However, we did not observe a high incidence of any specific ≥grade 3 irAEs in the HBsAg (+) group.

In terms of clinical outcomes, the objective response rates, PFS, and OS were quite similar among the three groups and comparable with other populations of non-CHB patients (especially considering the heterogeneous clinical settings and use of ICI treatment in later lines of treatment in this study).[30]

Patients with HBsAg (+) are usually excluded from most clinical trials due to their potentially high risk of HBV reactivation or immune-related hepatitis. However, given the high incidence of HBsAg (+) NSCLC in Asia, ICIs should still be administered in real clinical settings. Considering the low incidence of HBV reactivation, immune-related hepatitis, and comparable clinical outcomes between the groups in our study, we believe that patients with HBsAg (+) may be eligible for clinical trials as long as they receive prophylactic antiviral agents.

There are some limitations in this study. Its retrospective nature and single-center design might have introduced bias. There are missing data regarding follow-up HBV DNA titers and HBV serology, especially for patients who were not chronic hepatitis B carriers, because these tests were not routinely performed. The two patients with HBV reactivation in this study were discovered accidentally; therefore, the rate of HBV reactivation may be underestimated despite routine laboratory testing (including for liver function tests). In addition, we did not verify the diagnoses of immune-related hepatitis and jaundice with liver biopsies; therefore, bias may have been introduced despite clinical and medical record review.

Despite these limitations, this is one of the largest studies that investigated HBV reactivation, immune-related hepatitis and jaundice in NSCLC patients treated with ICIs. This study also evaluated the clinical outcomes not only in patients with HBsAg (+), but also in those with HBsAg (–)/anti-HBc IgG (+) and patients with HBsAg (–)/anti-HBc IgG (–). Another strength of this study was its analysis of patients with OBI (defined as HBsAg (–)/anti-HBc IgG (+)), which is a group with very limited data in terms of HBV reactivation and immune-related hepatitis.

We found that there were no differences in HBV reactivation, immune-related hepatitis, or jaundice among the three groups. Our findings suggest that ICIs can be effectively administered not only in patients with past HBV infections but also in those with chronic HBV as long as they receive antiviral prophylaxis. Antiviral prophylaxis should be recommended in chronic HBV patients receiving ICIs. A well-designed prospective study is needed to provide more evidence.

In conclusion, NSCLC patients with chronic HBV who take prophylactic antiviral agents and those with a history of past HBV infection can be treated safely with ICIs.

## AUTHOR CONTRIBUTIONS

**Joohyun Hong**: Conceptualization, methodology, formal analysis, investigation, resources, data curation, writing–original draft, writing–review and editing, and visualization. **Jiyun Lee**: Resources, data curation, and writing–review and editing. **Sehhoon Park**: Data curation, resources, and writing–review and editing. **Hyun-Ae Jung**: Data curation, resources, and writing–review and editing. **Jong-Mu Sun**: Writing–review and editing, resources, and data curation. **Se-Hoon Lee**: Data curation, resources, and writing–review and editing. **Jin Seok Ahn**: Writing–review and editing, resources, and data curation. **Dong Hyun Sinn**: Data curation, resources, writing–review and editing, conceptualization, and methodology. **Myung-Ju Ahn**: Conceptualization, methodology, data curation, resources, writing–review and editing, project administration, and supervision.

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The present study was approved by the institutional review board of the Samsung Medical Center (approval no. 2023-02-026-001; February 14, 2023). The requirement for informed consent was waived due to the retrospective nature of the study.

## CONFLICT OF INTEREST STATEMENT

Jin Seok Ahn reports fees for professional activities from Amgen, AstraZeneca Korea, Bayer Korea, BC World, Boehringer Ingelheim, Boryung, Daiichi Sankyo Korea, Eli Lilly and Company, F. Hoffmann-La Roche, Hanmi, Immuneoncia, Kyowa Kirin, Menarini Korea, Novartis, Pfizer, Pharmbio Korea, Samyang, Takeda Pharmaceutical, Therapex, Yooyoung, and Yuhan. Se-Hoon Lee reports fees for professional activities from Janssen Pharmaceuticals and Merck Sharp and Dohme; and grant and/or contract funding from AstraZeneca, Lunit, and Merck Sharp and Dohme. The other authors declare no conflicts of interest.

## DATA AVAILABILITY STATEMENT

Data are available on request due to restrictions of privacy.

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