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Editorial

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Challenges in Adjuvant Immunotherapy after Resection or Ablation for Hepatocellular Carcinoma at High-Risk of Recurrence

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Introduction

Recurrence of hepatocellular carcinoma (HCC) after resection or ablation is extremely common, with a recurrence rate of 70–80% at 5 years [1, 2]. Suppressing recurrence after curative resection or ablation is thus essential. The IMbrave050 trial [3] presented at AACR 2023 demonstrated, for the first time, that atezolizumab plus bevacizumab (Atezo/Bev) significantly improves recurrence-free survival (RFS) compared with active surveillance after surgery or ablation in patients at high risk for recurrence. However, the updated results of IMbrave050 presented at ESMO in 2024 showed that the hazard ratio (HR) of RFS was worse than that reported in the first interim analysis, indicating that the effect of adjuvant therapy on preventing recurrence was not sustained. This negative result highlights the difficulty in establishing adjuvant therapy regimens [4]. Many adjuvant therapy trials have been conducted to date, including the STORM trial [5], the NIK-333 trial [6, 7], and trials of vitamin-K2 [8] and interferon therapies [9]. These phase 3 trials all ended negatively [10]. In this editorial, The data from the primary and updated analyses of IMbrave050 and the future perspectives of adjuvant, neoadjuvant, and perioperative immunotherapy are discussed.

Prof. M. Kudo

Editor *Liver Cancer*

First Interim and Updated Analysis of the IMbrave050 Trial

The results of the first interim analysis showed that RFS, as assessed by an independent review facility, was not evaluable, with few events reported in both the Atezo/Bev and active surveillance groups. However, the HR was 0.72 (95% confidence interval [CI], 0.56–0.93, $p = 0.012$), indicating that Atezo/Bev significantly prolonged RFS, and the results were thus positive (Table 1). Overall

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Table 1. First interim analysis (primary analysis) primary endpoint

IRF-RFS	Atezo + Bev (*m* = 334)	Active surveillance (*n* = 334)
Patients with events, *n* (%)	110 (32.9)	133 (39.8)
Median RFS (95% CI), months	NE (22.1, NE)	NE (21.4, NE)
Stratified HR (95% CI)		0.72 (0.56, 0.93)
Stratified log-rank *p* value		0.012
OS		
Events, *n* (%)	27 (8)	20 (6)
OS, median (95% CI), months	NE (NA)	NE (NA)
Stratified HR (95% CI)		1.42 (0.80–2.54)

IRF-assessed RFS was significantly improved with Atezo + Bev versus active surveillance. Data cutoff date: Oct 21, 2022. Median follow-up duration: 17.4 month. IRF, independent review facility; RFS, recurrence-free survival; OS, overall survival; HR, hazard ratio; NE, not estimable.

survival (OS) data were immature, and the HR was 1.42 (Table 1).

In the updated analysis, the number of RFS events was 162 (49%) in the Atezo/Bev group and 164 (49%) in the active surveillance group, with a median RFS of 33.2 months in the Atezo/Bev group and 36.0 months in the active surveillance group (HR: 0.90 [95% CI], 0.72–1.12). The HR for OS improved slightly to 1.26 (95% CI: 0.85–1.87) because of a slight increase in events, but the HR remained >1 (Table 2) [4]. RFS as the primary endpoint was negative, and despite a positive primary endpoint in the first interim analysis (Table 1) [3], which was the primary analysis for the study, the FDA, EMA, and PMDA will not approve Atezo/Bev in the adjuvant setting. However, the results of the primary analysis showing suppression of the 1-year recurrence rate to 65% with Atezo/Bev versus 78% with active surveillance, together with those of the updated analysis showing that the 1-year recurrence rate was suppressed confirm that Atezo/Bev inhibits or delays recurrence [3, 4].

Possible Reasons for the Negative Results of the IMbrave050 Trial

Imamura et al. [11] reported that recurrence after surgery follows a bimodal pattern (Fig. 1). The first peak of recurrence occurs at approximately 1 year and consists of metastatic recurrence; the second peak occurs at approximately 4.5 years and is mainly due to secondary carcinogenesis. The design of the IMbrave050 trial specified discontinuation of Atezo/Bev after 12 months or 17 cycles, and the Kaplan-Meier curve may have thus overlapped between the Atezo/Bev and control arms. Conversely, if the treatment period had been >2 years, then the RFS could have been prolonged.

There are two possible explanations for the less favorable OS results. First, the number of events in the first interim analysis was too small, and the number of events in the updated analysis increased slightly to 54 in the Atezo/Bev group and 46 in the active surveillance group, but still small. Second, the active surveillance group was allowed to cross over to Atezo/Bev administration after recurrence; consequently, of the 156 recurrence cases in the active surveillance group, 61 (39%) were treated with Atezo/Bev after the active surveillance. Demonstrating favorable OS in clinical trials in which cross-over is allowed is extremely difficult, and although the IMbrave050 trial allowed cross-over for ethical reasons, further discussion is required to determine whether OS prolongation is required for approval by authorities in an adjuvant clinical trial [12].

Future Directions: Adjuvant, Neoadjuvant, or Perioperative Immunotherapy

The response and resistance to adjuvant immunotherapy in early-stage cancer follow the same principles as in advanced cancer [13]. In neoadjuvant immunotherapy, the primary lesion is the source of antigens for stimulating immune responses. Immunotherapy-induced antitumor immune responses depend on interactions between T cells, antigen-presenting cells, and tumor cells. Such interactions are more likely to occur when primary

Table 2. Updated analysis primary endpoint

IRF-RFS	Atezo + Bev (*m* = 334)	Active surveillance (*n* = 334)
Patients with events, *n* (%)	162 (49)	164 (49)
Median RFS (95% CI), months	33.2 (24.3, NE)	36.0 (22.7, NE)
Stratified HR (95% CI)		0.90 (0.72–1.12)
Stratified log-rank *p* value		NA; descriptive
OS		
Events, *n* (%)	54 (16)	46 (14)
OS, median (95% CI), months	NE (NA)	NE (NA)
Stratified HR (95% CI)		1.26 (0.85–1.87)

IRF-assessed was not significantly improved with Atezo + Bev versus active surveillance. Data cutoff date: May 3, 2024. Median follow-up duration: 35.1 month. IRF, independent review facility; RFS, recurrence-free survival; OS, overall survival; HR, hazard ratio; NE, not estimable.

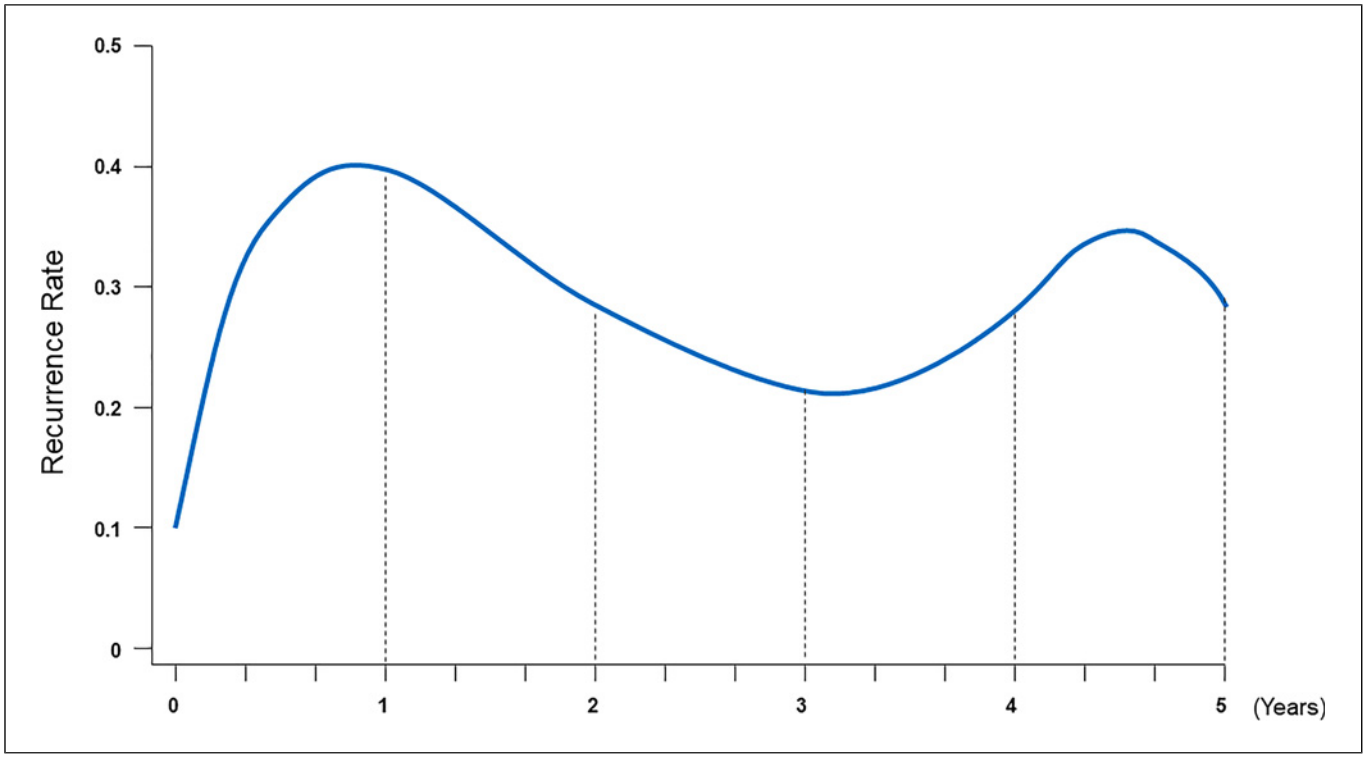

Fig. 1. Estimated recurrence rate (per year) of HCC over time after resection. Modified from Imamura et al. [11].

lesions containing antigens targeted by the immune system are still present in large numbers, a mechanistic reason why neoadjuvant immunotherapy may be preferable to adjuvant immunotherapy [14].

Accumulating preclinical evidence in various malignancies supports the use of neoadjuvant therapy over adjuvant therapy as a therapeutic strategy because of its superior efficacy and strong immune cell activation

effects [15–17]. Neoantigen recognition and dendritic cell priming are superior in active and measurable tumors, which ultimately improves immunologic clearance of micrometastatic disease.

The clinical benefits of preoperative immunotherapy are manifold. Primary reduction or downstaging of disease may lead to less extensive surgical resection and shorter recovery times. Neoadjuvant immunotherapy can induce antitumor immunity in patients with early-stage disease who have a limited tumor burden, a lower degree of immune exhaustion, and greater $CD8^+$ T-cell infiltration, which may result in more sustained and effective responses than those in advanced disease. Early treatment of micrometastatic lesions is an equally important goal. The persistence of neoplastic clones after resection or ablation is considered an essential determinant of recurrence after curative treatment.

Neoadjuvant therapy also offers a unique opportunity to study the dynamic changes occurring in the tumor immune microenvironment as a result of immunotherapy exposure through immunological analysis of resected specimens. Studies in other tumor types indicate that the increase in T cells is more pronounced when immunotherapies are administered prior to complete tumor resection than after surgery [18]. In patients receiving adjuvant immunotherapy, the micrometastases that may be present are less immunogenic than lesions detectable by imaging. Conversely, neoadjuvant immunotherapy in the presence of primary lesions can induce T-cell-mediated immunity, increase existing antitumor T cells, and promote a diverse tumor-specific T-cell repertoire more efficiently than after tumor resection [19]. A landmark study in breast cancer suggested that neoadjuvant immunotherapy can outperform adjuvant immunotherapy [17]. Preoperative administration of immunotherapy resulted in increased T cells and high antitumor activity with reduced toxicity [17]. These favorable outcomes were associated with increased numbers of tumor-specific $CD8^+$ T cells.

Unacceptable surgical delays or inability to perform surgery due to tumor progression or serious immune-related adverse events are important issues of concern for surgeons. However, published studies of neoadjuvant therapy, including anti-PD1 immunotherapy alone or in various combinations, have generally shown low rates of progression and surgical delay due to toxicity [19–22].

The safety and feasibility of neoadjuvant immunotherapy have recently been the subject of four independent, single-center trials [20–23]. In these trials, patients were treated with a PD1-based regimen 2–3 months before surgical resection. Of 86 treated patients, 6 (7%) had a progression event, and none of the patients was ineligible for surgical resection due to adverse events [24].

Pathologic response is used as a clinical endpoint for neoadjuvant therapy in some carcinomas and may be a surrogate endpoint for more clinically relevant endpoints (e.g., RFS, OS). In primary tumors that exhibit a pathologic response, the therapy is considered to have successfully induced systemic antitumor immunity and reduced tumor volume and micrometastatic lesions, thereby delaying or preventing recurrence. Pathologic response was the primary endpoint along with RFS in the first trials of neoadjuvant immunotherapy in triple-negative breast cancer and non-small cell lung cancer in studies conducted in the USA and Canada [25, 26].

Whether pathologic response is a valid surrogate measure of a clinically meaningful outcome in HCC remains to be established. In published studies of neoadjuvant immunotherapy [20–23], patients who showed a pathologic response achieved excellent clinical outcomes. In our seven-case series of patients treated with Atezo/Bev plus TACE prior to hepatic resection, we have not experienced a single case of post-resection recurrence [27].

The hypothesis that neoadjuvant-adjuvant immunotherapy (perioperative immunotherapy) provides better clinical outcomes than adjuvant immunotherapy was tested in a clinical trial of malignant melanoma [28]. Patients with stage III-IV malignant melanoma were randomized to receive the anti-PD-1 antibody pembrolizumab before and after resection (neoadjuvant-adjuvant strategy, $n = 154$) or only after surgery (adjuvant [standard therapy] strategy, $n = 159$). Both groups received the same number of doses of pembrolizumab for a total treatment period of 1 year. Patients in the neoadjuvant-adjuvant arm received three doses before surgery (approximately 9 weeks) and 15 doses after surgery, whereas patients in the control arm received all 18 doses after surgery. Event-free survival was significantly better in patients who received pembrolizumab both preoperatively and postoperatively (72% at 2 years vs. 49% in the adjuvant-only pembrolizumab group; HR: 0.58; 95% CI: 0.39–0.87; $p = 0.004$; median follow-up: 14.7 months) [28]. These results suggest that perioperative immunotherapy may be superior to adjuvant or neoadjuvant immunotherapy alone in HCC.

Conclusion

The success of the IMbrave050 trial, an adjuvant study of HCC published in 2023 [3], ended negatively after an updated analysis with an extended follow-up

failed to confirm sustained efficacy [4]. Three other global trials in the adjuvant setting with slightly different target populations, protocols, and dosing schedules from IMbrave050 are ongoing, and their results are eagerly awaited.

However, the results of the IMbrave050 trial suggest that a global phase 3 trial of neoadjuvant immunotherapy or neoadjuvant-adjuvant immunotherapy (perioperative immunotherapy), which is theoretically more effective than adjuvant immunotherapy alone [29], should be initiated soon. This is because the design of systemic therapy clinical trials for HCC has historically been improved based on "Lessons Learned from Negative Trials" [30].

Statement of Ethics

No statement is needed because this study was based exclusively on published data.

Conflict of Interest Statement

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Author Contributions

Masatoshi Kudo conceived, wrote, and approved the final manuscript.

Data Availability Statement

Data are not applicable because this is not a research article.

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