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Second-Line Treatment after Failure of Immune Checkpoint Inhibitors in Hepatocellular Carcinoma: Tyrosine Kinase Inhibitor, Retrial of Immunotherapy, or Locoregional Therapy?

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Keywords
Hepatocellular carcinoma · Immune checkpoint inhibitor · Second-line treatment · Tyrosine kinase inhibitor · Locoregional therapy

Abstract
Background: Immune checkpoint inhibitor (ICI)-based therapy such as atezolizumab plus bevacizumab or durvalumab plus tremelimumab became mainstream first-line systemic treatment in advanced hepatocellular carcinoma (HCC) patients since remarkably superior efficacy of ICI-based therapy compared to tyrosine kinase inhibitors (TKIs) was reported in two recent randomized controlled trials (RCTs) (IMbrave150, HIMALAYA). However, the optimal second-line therapy after treatment failure of first-line ICI-based therapy remains unknown as no RCT has examined this issue. ***Summary:*** Therefore, at present, most clinicians are empirically treating patients with TKIs or retrial of ICI or locoregional treatment (LRT) modality such as transarterial therapy, radiofrequency ablation, and radiation therapy in this clinical setting without solid evidence. In this review, we will discuss current optimal strategies for second-line treatment after the failure of first-line ICI-based therapy by reviewing published studies and ongoing prospective trials. ***Key Messages:*** Clinicians should consider carefully whether to treat the patients with TKI, other ICI-based therapy, or LRT in this situation by considering several factors including liver function reserve, performance status, adverse events of previous therapy, and presence of lesion that can consider LRT such as oligoprogression and vascular invasion. In the meantime, we await the results of ongoing prospective trials to elucidate the best management options.

Introduction

Hepatocellular carcinoma (HCC) is the most frequent primary malignant tumor of the liver and also accounts for the second-most cancer-related deaths worldwide [1, 2]. Unfortunately, curative treatment options such as surgical resection, transplantation, and local ablation often cannot be applied for advanced HCC patients because of poor liver function reserve and distant metastasis; therefore, systemic therapy is recommended for those patients according to several international guidelines [2–4].

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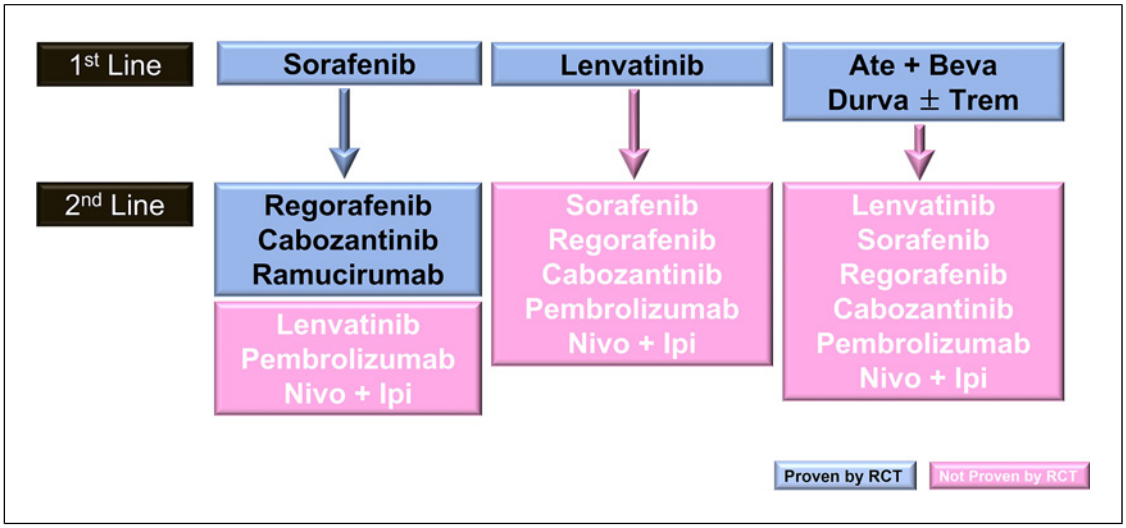

Fig. 1. Systemic treatment strategy of advanced HCC. Ate + Beva, atezolizumab + bevacizumab; Durva ± Trem, durvalumab ± tremelimumab; Nivo + Ipi, nivolumab + ipilimumab; RCT, randomized controlled trial.

Recently, systemic treatment of HCC has made remarkable progress, especially in some randomized controlled trials (RCTs) on immune checkpoint inhibitor (ICI)-based treatment for HCC, and investigators have published superior results of ICI-based therapy compared to tyrosine kinase inhibitors (TKIs). The IMbrave150 trial demonstrated that patients receiving the combination therapy of atezolizumab plus bevacizumab had better overall survival (OS) (19.2 vs. 13.4 months, hazard ratio [HR] 0.66) and median progression-free survival (PFS) (6.9 vs. 4.3 months, hazard ratio 0.65) than patients treated with sorafenib [5]. In the HIMALAYA trial, combination therapy of durvalumab-tremelimumab also demonstrated improved OS (16.4 vs. 13.8 months, HR 0.78) compared to sorafenib [6].

However, second therapy after treatment failure of first-line ICI-based therapy has not been firmly established due to lack of well-designed RCTs (Fig. 1). Therefore, most clinicians are treating patients by using TKIs or retrial of ICI or locoregional therapy (LRT) after treatment failure of ICI-based therapy. However, these patterns of treatment are based on clinician's preference and experience without concrete evidence.

In this review, we will discuss strategies for second-line treatment after the failure of first-line ICI-based therapy by looking at published studies and ongoing prospective trials aimed to overcome the resistance of immunotherapy.

Second-Line Treatment versus Best Supportive Care

To continue further treatment after failure of ICI-based therapy may not be best option for patients who already have advanced disease as further deterioration in liver function is common after treatment failure. Moreover, if hyper-progressive disease occurs after failure of ICI-based therapy, it becomes more difficult to choose further treatment. Hyper-progressive disease is defined as a phenomenon of hyper-accelerated tumor growth and clinical deterioration after failure of previous therapy [7, 8]. Several studies have shown that the incidence of hyper-progressive disease after ICI-based therapy is 9–29% in various cancer types, and this status itself is a poor prognostic factor [9–11]. Recently, a few studies reported that the incidence of hyper-progressive disease in HCC patients after failure of ICI-based therapy was 10.2–12.7% [12, 13]. However, Talbot et al. [14] reported that the post-progression survival of HCC patients treated by both continuation of ICI and switching to TKIs after failure of ICI-based therapy was significantly longer than that of patients with only best supportive care (10.3 vs. 1.9 months, $p < 0.0001$). Sharma et al. [15] analyzed patterns and outcomes of subsequent therapy after ICI discontinuation in 420 HCC patients and showed that patients receiving post-ICI therapy were associated with longer median OS compared with those who had received best supportive care (12.1 vs. 3.3 months; HR: 0.4, $p < 0.001$). Although these studies are somewhat limited by their retrospective approach, these global multicenter

trials support the use of ICI in the second-line setting in patients with good liver functional reserve and ECOG performance status.

Tyrosine Kinase Inhibitor

TKIs could be selected as a further treatment after failure of ICI-based therapy for the following reasons: (1) there are some theoretical and clinical reasons that efficacy of TKIs after failure of ICI-based therapy might be promising, (2) clinicians can use third-line therapy with confidence after second-line sorafenib failure because efficacy of several TKIs such as regorafenib, cabozantinib, and ramucirumab after sorafenib failure was already well demonstrated in RCTs, and (3) adverse reactions to TKIs are manageable.

Kudo [16] suggested that TKIs may be effective after failure of ICI-based therapy because TKIs such as lenvatinib, sorafenib, regorafenib, and cabozantinib are stronger vascular endothelial growth factor-A inhibitors than bevacizumab. Osa et al. [17] showed that the binding of nivolumab to programmed death (PD)-1 receptors on lymphocytes can be sustained for around 20 weeks after administration of nivolumab in lung cancer patients. On the basis of that report, Kudo postulated that these TKIs may have more therapeutic efficacy through synergism with the persistent effect of PD-1 or PD ligand-1 (PD-L1) antibodies even though ICI administration has ceased. Another study reported that the median OS, PFS, objective response rate (ORR), and disease control rate (DCR) of lenvatinib after failure of ICI therapy are 15.8 months, 10 months, 55.6%, and 86.1%, respectively [18]. Kudo [16] postulated that Wingless and Int-1 (WNT)/β-catenin mutations are found in approximately 20–30% of all HCC, and these might be considered as immunologically cold subclasses, and therefore HCC with resistance to ICI-based therapy may have WNT/β-catenin mutations. He mentioned additionally that fibroblast growth factor receptor 4 (FGFR4) expression has a positive correlation with WNT/β-catenin mutations and lenvatinib is a potent inhibitor of FGFR4 [19]; therefore, lenvatinib might be good option for patients with progression on ICI therapy.

Yamauchi et al. [20] demonstrated that PFS of patients treated with lenvatinib was longer in groups with high FGFR4 expression than in those without FGFR4 (5.5 vs. 2.5 months, $p = 0.01$). Similar phenomena were observed in the study mentioned previously [14]; post-progression survival of subsequent therapy after failure of ICI therapy was 10.4 months in the group immediately switched to TKIs. Interestingly, post-progression survival was longer (15.3 months) in the group that received ICI beyond progression followed by TKIs; therefore, one could postulate that subsequent TKIs might be more effective because of synergism with continued ICI beyond progressive disease.

Efficacy of further line treatments after failure of sorafenib is well established in several RCTs. Median OS of ramucirumab (only if AFP ≥400 ng/mL) [21], regorafenib [22], and cabozantinib [23] compared to placebo after failure of sorafenib were 8.5 versus 7.3 months ($p = 0.0199$), 10.6 versus 8.0 months ($p < 0.001$), and 10.2 versus 8.0 months ($p = 0.005$), respectively. Moreover, adverse events of TKIs such as hand-foot skin reaction, general weakness, and hypertension, proteinuria were manageable.

There is no strong evidence regarding which specific TKI is better as a subsequent treatment after failure of ICI-based therapy in HCC. If clinicians choose sorafenib as a second-line treatment, they can use third-line treatment with strong evidence after failure of sorafenib based on several RCTs [21–23]. If clinicians choose lenvatinib as a second-line treatment, they may expect a more potent PFS and ORR than sorafenib; however, there are no further treatments with strong evidence after failure of lenvatinib. Yoo et al. [24] reported retreatment of 49 patients with subsequent TKIs (sorafenib, lenvatinib, and cabozantinib) after failure of atezolizumab plus bevacizumab therapy, and median PFS was significantly longer in the lenvatinib group than in the sorafenib group, respectively (6.1 vs. 2.5 months, $p = 0.004$). Armstrong et al. [25] analyzed efficacy of subsequent TKIs (6 sorafenib, 12 lenvatinib, 6 regorafenib, 4 cabozantinib, 1 ramucirumab) in 29 patients among 77 overall patients after failure of previous ICI-based therapy and showed improved median OS compared to patients that did not receive TKIs (19 vs. 5 months, $p = 0.0024$). Recently, Cabibbo et al. [26] compared the efficacy and safety of five TKIs (sorafenib, lenvatinib, regorafenib, cabozantinib, and ramucirumab) after failure of atezolizumab plus bevacizumab therapy using Markov simulation modeling. They reported that lenvatinib was the most effective compared to other TKIs (median OS 24 vs. 18–23 months), whereas sorafenib had the best safety profile (with the least severe adverse events) compared to other TKIs (63 vs. 67.8–70%). However, RCTs on subsequent TKI treatment after failure of ICI-based therapy are necessary because all these studies are retrospective.

Retrial of ICI-Based Therapy

Several studies reported that the ORR of nivolumab plus ipilimumab therapy after failure of anti-PD-1(L1) treatment in those with melanoma [27], non-small cell lung cancer (NSCLC) [28], and renal cell carcinoma [29, 30] was 10–20%. However, studies on retrial of ICI after failure of prior ICI-based therapy in HCC patients are scarcer than those on TKIs.

Roessler et al. [31] analyzed HCC patients who received nivolumab plus ipilimumab therapy after failure of ICI-based treatment and reported that median OS and PFS were 7.4 months and 2.9 months, respectively, and that ORR and DCR were 30% and 40%, respectively. Wong et al. [32] analyzed patients who received ipilimumab with nivolumab/pembrolizumab after failure of prior ICI-based therapy. They reported that median OS and time to progression were 10.9 months and 3.0 months, respectively, and ORR was 16%. These authors [32] suggested that combination with anti-cytotoxic T-lymphocyte-associated protein (CTLA)-4 inhibitor (ipilimumab) might be an important modality in retrials of ICI-based therapy after failure of anti-PD-1(L1) inhibitor therapy for the following reasons: (1) immune phases that two immune checkpoints work on are different (the PD-1 pathway affects the effector phase whereas the CTLA-4 pathway affects the immune priming and proliferation phase) [33], (2) combination of anti-PD-1(L1) and anti-CTLA-4 inhibitors might stimulate the immune tumor microenvironment by decreasing the fraction of regulatory T cells and increasing CD8+ T cell to myeloid-derived suppressor cell ratio [34], (3) upregulation of alternative immune checkpoints such as CTLA-4 occurs in the condition of acquired resistance to single anti-PD-1 inhibition, and therefore anti-CTLA-4 inhibition would be more effective [35], and (4) CTLA-4 blockade may provide long term tumor control because anti-CTLA-4 inhibitors activate proliferation of transition memory T cells while anti-PD-1(L1) inhibitor does not act on memory T cells [36, 37]. On the basis of the above, Wong et al. [32] concluded that ipilimumab with anti-PD-1(L1) inhibitors might be effective salvage therapy in patients with advanced HCC after failure of prior anti-PD-1(L1) inhibitors. However, retrial of ICI-based therapy must be considered cautiously in patients with good liver function reserve because 12% of patients experienced treatment-related severe adverse events (grade ≥3), and poor Child-Pugh class and ALBI (albumin-bilirubin) grade were significantly associated with poor prognosis [32]. Sangro et al. [38] mentioned that the incidence of severe immune-related adverse events was 6% in anti-PD-1(L1) inhibitors, 24% in anti-CTLA-4 inhibitors, and higher with both ICIs combined. Therefore, we must pay attention to adverse events when both ICIs are combined. RCTs are necessary to guide the use of second-line ICI-based combination therapy.

Locoregional Therapy

LRT such as transarterial chemoembolization (TACE), radiofrequency ablation (RFA), and radiation therapy can be a potential strategy for overcoming resistance to immunotherapy because LRT-induced cell death may induce the liberation of tumor-associated antigens and activation of antigen-presenting cells that can convert the tumor microenvironment to become immune-sensitive [39]. (Fig. 2). Ding et al. [40] showed in a meta-analysis (1,174 patients, 3 databases, and 19 individual studies) that the patients treated by combination of cellular immunotherapy with LRT (TACE being the predominant modality) significantly improved DCR (OR = 5.91, p = 0.007), over 1-year PFS (OR = 3.56, $p < 0.00001$), 24-month OS (OR = 3.52, $p < 0.0001$) compared to those treated by LRT only. Duffy et al. [41] reported in 32 patients treated by combination of tremelimumab and LRT (TACE, RFA, cryoablation) that partial response rate was 26.3%, and the 6-month and 12-month PFS rates were 57.1% and 33.1%, respectively. Median OS was 12.3 months. Recently, Kudo et al. [42] analyzed the clinical results of 110 unresectable or TACE unsuitable intermediate-stage HCC patients who were treated by atezolizumab plus bevacizumab at seven Japanese centers. They showed that 28 patients (25%) achieved CR by LRT (ablation, 13; superselective TACE, 15) in patients who became able to try treatment with a curative intent by atezolizumab plus bevacizumab therapy. However, LRT may not be suitable in cases with disseminated tumor progression after previous ICI-based therapy.

Conventionally, it was thought that systemic therapy should be changed if existing lesions are significantly increased or new lesions (including metastases) occur. Recently, it was suggested that if there are a few progressive sites in the context of overall stability of other tumor sites, treating these "oligoprogression sites" by local ablative therapy (LAT) and maintaining the existing systemic treatment might be helpful in select patients. Although there is no strict definition of oligoprogression, disease progression of 3–5 lesions in 1–3 organs after achieving at least stable disease of other sites for a minimum of 3 months on ICIs is generally suggested as a definition [43, 44].

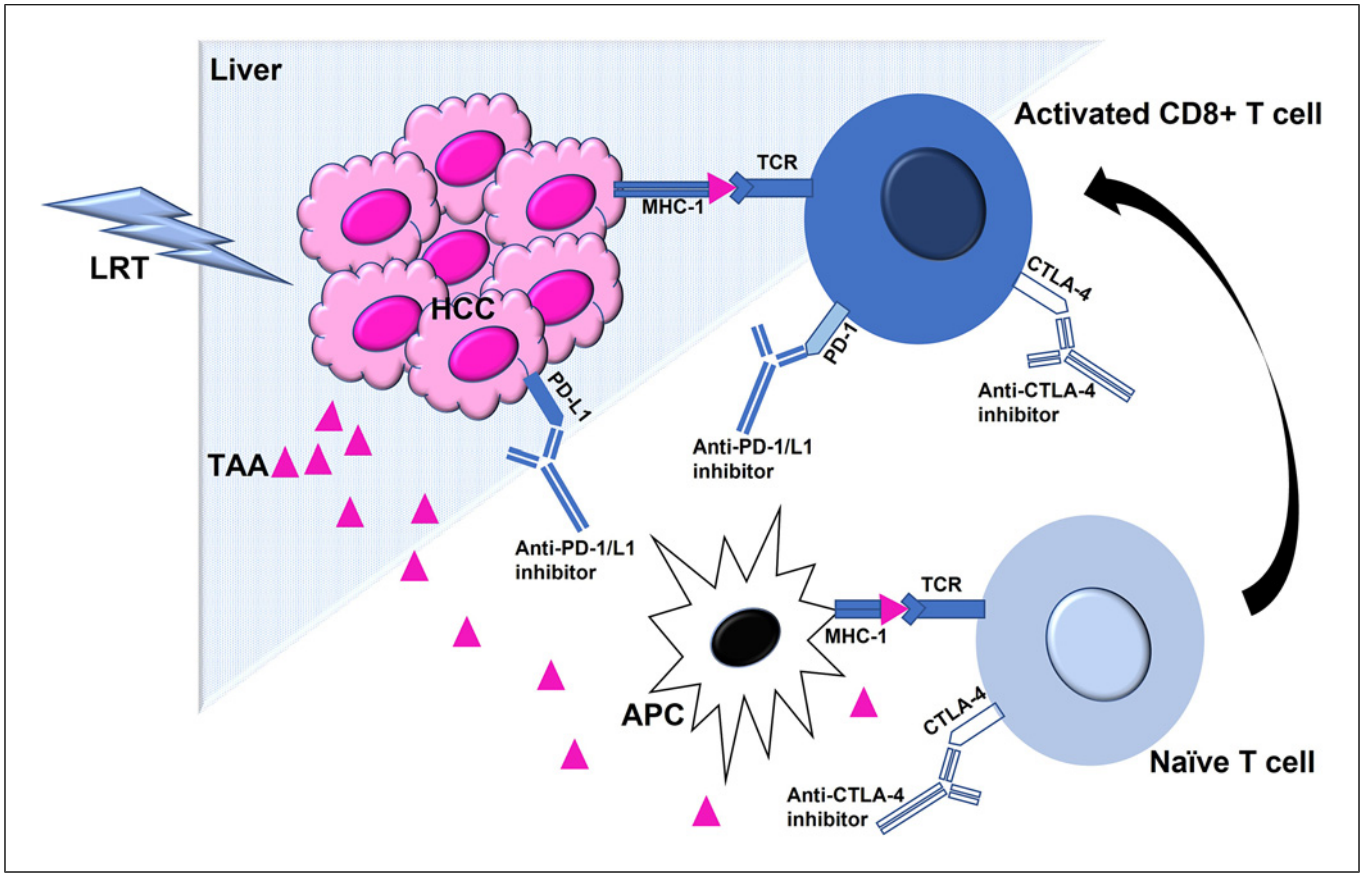

Fig. 2. Mechanism of immunostimulatory effect of LRT and ICI therapy. LRT enhances local immunogenicity by damaging HCC cells and releasing immunostimulatory molecules like TAA, followed by inducing conversion from naïve T cell to activated CD8+ T cell. This results in synergic antitumor immune response by combination of anti-PD-1/L1 and CTLA-4 inhibitors. LRT, locoregional therapy; ICI, immune checkpoint inhibitor; HCC, hepatocellular carcinoma; TAA, tumor-associated antigen; PD-1/L1, programmed death-1/ligand-1; CTLA-4, cytotoxic T-lymphocyte associated protein-4; APC, antigen presentation cell; MHC, major histocompatibility complex class; TCR, T cell receptor.

Differentiating between oligoprogression and true progression may be important because clinicians can try continuing with ICI therapy if the oligoprogression sites can be well controlled by LAT. The incidence of oligoprogression was reported as 10–20% with ICI-based therapy [45, 46], and a few studies have been reported the role of LAT in oligoprogression [47, 48] in mainly NSCLC patients. In particular, stereotactic body radiation therapy (SBRT) is an attractive LAT option for oligoprogression because not only can it be performed with no or minimal interruption of ICI therapy, but it also has the potential for immune stimulation [39]. Wang et al. [49] analyzed 24 patients with NSCLC that received SBRT after oligoprogression during ICI therapy and reported that OS was 34 months, PFS was 11 months, and 2-year local control rate was 81.8%. Tsai et al. [50] reported a RCT of SBRT in 59 patients with oligoprogressive metastatic NSCLC after prior immunotherapy. They showed that median PFS of the SBRT group was markedly superior to that of the supportive care control group (10 vs. 2.2 months, $p = 0.002$), although there was no difference in OS between the two groups.

We can expect a possible role for combination of SBRT and systemic therapy in HCC patients because a few studies suggest that this combination can be effective. Dawson et al. [51] reported in a phase III RCT that OS of two groups (SBRT followed sorafenib vs. sorafenib monotherapy) was 15.8 versus 12.3 months, respectively (HR = 0.72, 95% CI: 0.52–0.99, 2-sided Cox $p = 0.042$), and PFS was 9.2 versus 5.5 months, respectively (HR = 0.55, 95% CI: 0.40–0.75, 2-sided $p = 0.0001$). Juloori et al. [52] showed in a phase 1 randomized trial that median OS of two groups (SBRT plus nivolumab/ipilimumab vs. SBRT plus nivolumab) was 41.6 versus 4.7 months,

Table 1. Ongoing trials investigating second-line treatment in patients with HCC beyond ICI-based therapy

Number of clinical trial	Phase	Type	Arm and drug	*N*	Enrollment criteria	Treatment	Primary endpoint	Completion date
NCT04770896	III	Interventional Randomized (open label) Multicenter	Two arms (Ate + Lenva or Sora vs. Lenva or Sora)	554	Advanced HCC Failure of AteBeva	Ate 1,200 mg q3w iv Lenva 8 mg or 12 mg po every day for 3 w Sora 800 mg po every day for 3 w	OS	5 Feb 2025
NCT05178043	II	Interventional Non-randomized (open label) Multicenter	Single arm (Nivo + GT90001)	105	Advanced HCC Failure of prior ICIs	Nivo 240 mg q2w iv GT90001 (anti-ALK-1 mAb) 7 mg/kg q2w iv	ORR	31 Dec 2024
NCT05199285	II	Interventional Non-randomized (open label) Multicenter	Single arm (Nivo + Ipi)	40	Unresectable HCC Failure of AteBeva	Nivo + Ipi q3w iv for 4 cycles After that, Nivo q4w iv up to 24 cycles	ORR	31 Jan 2027
NCT03970616	Ib/II	Interventional Non-randomized (open label)	Single arm (Durva + Tivo)	42	Advanced HCC Untreated HCC and failure of AteBeva	Durva 1,500 mg iv q4w Tivo 1 mg po daily for 21 days followed by 7 days rest	TEAEs	Mar 2023
NCT05101629	II	Interventional Non-randomized (open label) Multicenter	Single arm (Pembro + Lenva)	32	Unresectable HCC Failure of prior ICIs	Pembro 200 mg iv q3w Lenva 8 mg or 12 mg po every day for 3 w	ORR	Dec 2024
NCT04430452	II	Interventional Non-randomized (open label)	Two arm (Durva + hypofractionated RT versus. Durva + Treme + hypofractionated RT	30	Advanced HCC Failure of prior ICIs (except prior Durva)	Hypofractionated RT for 5 days Within 3–10 days after completion of RT, Durva + Treme iv q4w up to 2 years	ORR	28 Feb 2027

N, number of patients; Ate, atezolizumab; Lenva, lenvatinib; Sora, sorafenib; AteBeva, atezolizumab plus bevacizumab; iv, intravenous; q, once every; w, week; OS, overall survival; Nivo, nivolumab; Ipi, ipilimumab; ORR, objective response rate; mAb, monoclonal antibody; Durva, durvalumab; Tivo, tivozanib; TEAEs, treatment-emergent adverse events; Pembro, pembrolizumab; Treme, tremelimumab; RT, radiotherapy; ICI, immune checkpoint inhibitor.

respectively ($p < 0.05$). Median PFS was 11.6 versus 2.7 months, respectively ($p < 0.05$), and ORR was 57% versus 0%, respectively ($p < 0.05$). Chen et al. [53] reported in a prospective trial that median PFS of 20 HCC patients treated with SBRT followed by toripalimab plus anlotinib was 7.4 months, ORR was 15.0%, DCR was 50.0%, and 2-year survival rate was 50.9%.

Studies of SBRT for oligoprogression during ICI therapy in HCC patients are extremely rare. Sindhu et al. [43] analyzed 30 patients with solid tumor including 16 HCC patients (53%) who received SBRT after oligoprogression during ICI therapy. They showed that median (for 30 patients) PFS was 7.1 months, and 2-year OS was 82.8%. No patients experienced grade III or higher acute toxicities, and all HCC patients continued ICI therapy for at least 4 months (maximum duration of 38 months) after SBRT (total dose 40–60 Gray in 5 fractions). RCTs are

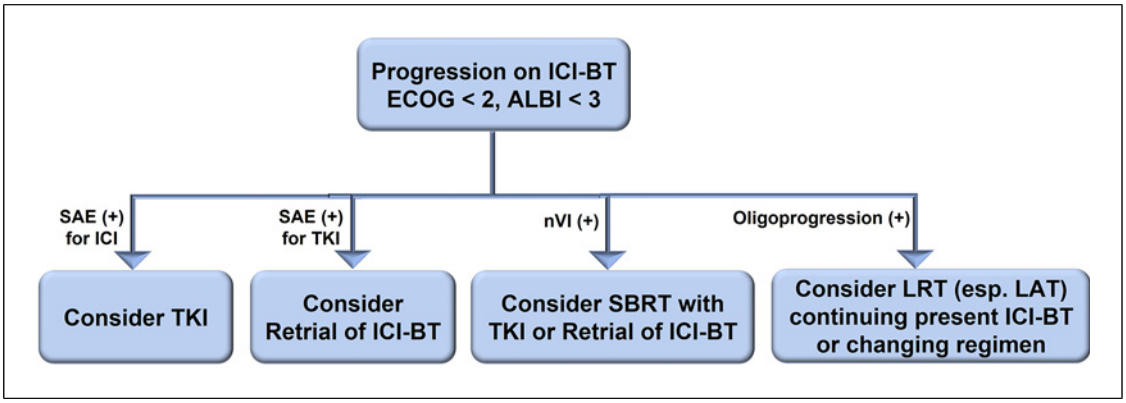

Fig. 3. Algorithm of second-line treatment options after failure of first-line ICI-based therapy. ICI-BT, immune checkpoint inhibitor-based therapy; ECOG, Eastern Cooperative Oncology Group; ALBI, albumin-bilirubin; SAE, severe adverse event; TKI, tyrosine kinase inhibitor; SBRT, stereotactic body radiation therapy; nVI, new onset vascular invasion; LRT, locoregional therapy; LAT, local ablative therapy.

needed to guide the use of LAT including SBRT in patients with oligoprogression during ICI-based therapy.

SBRT can also be applied to cases with vascular invasion after progression with prior ICI-based therapy. Talbot et al. [14] reported that new vascular invasion was a representative pattern of post-ICI therapy progression associated with shorter OS (HR 2.15 [95% CI: 1.38–3.35]; $p = 0.0007$), and actually median OS was only 0.4 months. Therefore, SBRT can play an important role to control new vascular invasion in patients with progression after prior ICI-based therapy. Jiang et al. [54] suggested that the HCC patient with macrovascular invasion is an ideal candidate for SBRT plus ICI. Dutta et al. [55] prospectively analyzed 72 HCC patients with portal vein tumor thrombus treated by SBRT and showed that mean OS was 11.4 months, 1-year OS rate was 38%, and radiologic ORR of portal vein tumor thrombus was 30%. They also reported that median OS between responders and non-responders was 14.4 versus 7.4 months ($p = 0.022$), respectively, and 4 patients (4%) had hepatic decompensation.

TKI versus ICI versus LRT

The final results of currently ongoing clinical trials will be needed to definitively determine which strategy (TKI vs. retrial of ICI-based therapy vs. LRT) is the best second-line treatment after failure of first-line ICI-based therapy. The ongoing trials concerning this question are summarized in Table 1. However, only one study (NCT04770896, IMbrave251) is a phase III, open-label, multicenter, randomized, two-arm study designed to evaluate the efficacy and safety of atezolizumab plus either lenvatinib or sorafenib versus lenvatinib or sorafenib alone in patients with advanced HCC who have progressed on prior atezolizumab plus bevacizumab therapy. Interestingly, the investigators selected the continuation of atezolizumab with other TKIs (lenvatinib or sorafenib) instead of switching to other ICIs. We can infer that the investigators chose this study design from immune biology pathways (efficacy of TKIs after failure of ICI-based therapy might be promising) as mentioned above.

Definitive answers about these issues should be available when the results of IMbrave251 or other trials are presented. However, to date, based on results of the studies currently available, a strategy of switching to TKI (especially lenvatinib) seems to have more supporting evidence than other options such as retrial of ICI therapy or LRT. We suggest that if patients experienced autoimmune adverse events such as pneumonitis, hepatitis, thyroiditis, adrenalitis, or others during first-line ICI-based therapy, a switch to TKI should be more strongly preferred as a second-line treatment. However, if patients experienced more common adverse event of TKIs (bevacizumab) such as gastrointestinal bleeding during first-line combination therapy of atezolizumab plus bevacizumab, a retrial of ICI-based therapy without TKI would be the preferred second-line choice.

Additionally, LRT, especially LAT with systemic therapy (continuation of present ICI or changing to TKI/other ICI), can be considered in patients with oligoprogression and in patients who have progressed with new vascular invasion. In the remaining cases, clinicians

will have to make management decisions based on individual situations such as patient's preference, liver function, and financial considerations. Finally, there are special considerations regarding second-line treatment in patients with good liver function reserve and performance status after progression on first line.

ICI-based therapy warrant mentioning. Talbot et al. [14] reported that poor performance state (ECOG ≥2) at disease progression was strongly associated with poor OS (HR 2.04 [1.31–3.17], p = 0.0015) on multivariate analysis. Poor liver function (albumin-bilirubin [ALBI] grade ≥3) at disease progression was also associated with poor OS (HR 1.51 [1.04–2.21], p = 0.0334), but only on univariate analysis. Therefore, the possibility exists that further treatment itself might accelerate clinical deterioration in these situations; thus, the risk-benefit balance needs to be carefully weighed. On the basis of all the above considerations, we propose a suggested algorithm about second-line treatment after failure of first-line ICI-based therapy (Fig. 3).

Conclusion

ICI-based therapy (atezolizumab plus bevacizumab, durvalumab plus tremelimumab) has become the first-line systemic treatment in advanced HCC patients due to a remarkable improvement in survival outcomes compared to TKI therapy in recent RCTs (IMbrave150, HIMALAYA). However, there are no phase III RCT data to support second-line treatment after first-line ICI-based therapy. Clinicians should decide carefully whether to treat the patients with TKI, other ICI-based therapy, or LRT in this situation by considering several factors such as performance status, liver function reserve, adverse events of therapy, and presence of vascular invasion. In the meantime, we await the results of ongoing prospective trials to elucidate the best management options.

Statement of Ethics

This manuscript is a review of published studies, and no new research activities involving human subjects were performed. Therefore, an institutional or ethical review was not considered necessary by the authors.

Conflict of Interest Statement

Samuel S. Lee has consulted for AbbVie, Gilead, Grifols, Jazz, Novartis, and Oncoustics. The other authors have no disclosures.

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Author Contributions

Conception and manuscript preparation: Sang Y. Hwang, Sangjune L. Lee, and Samuel S. Lee; critical revision: Sang Y. Hwang, Sangjune L. Lee, Hongqun Liu, and Samuel S. Lee. All authors reviewed the manuscript and approved the final version.

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