Editorial

Combination immunotherapy with anti-VEGF/TKI for hepatocellular carcinoma: present and future perspective

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The results of the Phase 3 IMbrave150 trial were published in the *New England Journal of Medicine* (1). The IMbrave150 trial is a global multicenter phase 3 comparative study conducted in patients with locally advanced or metastatic liver cancer and unresectable hepatocellular carcinoma (HCC). Patients were assigned, 2:1, to atezolizumab plus bevacizumab (Atezo + Beva) (n=336) and sorafenib (n=165) groups. The co-primary endpoints were progression-free survival (PFS) and overall survival (OS) using the independent review facility (IRF)-assessed Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Stratification factors were geographic region (Asia excluding Japan *vs.* rest of world), Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0 *vs.* 1), macrovascular invasion (MVI) and/or extrahepatic spread (EHS) (presence *vs.* absence), and serum alpha-fetoprotein (AFP) level (≤400 *vs.* >400 ng/mL). The proportion of patients with MVI was 38% (129/336), MVI and/or EHS was 78% (258/336), and AFP ≥400 ng/mL was 38% (126/336) in the IMbrave150 population and their prognosis was poor. Nevertheless, surprisingly good results were observed in the IMbrave150 trial. The OS in the Atezo + Beva group was not estimable (NE) and that in the sorafenib group was 13.2 months [95% confidence interval (CI), 10.4–NE]. Additionally, a surprising hazard ratio, of 0.58 (95% CI, 0.42–0.79, P=0.0006) was observed. It is worth noting that the α given to the OS for the 1st interim analysis of this trial was 0.0033 and the results in this study sufficiently cleared this value (1).

The PFS, by IRF-assessed RECIST v1.1, in the IMbrave150 trial was 6.8 months (95% CI, 5.7–8.3) in the Atezo + Beva group and 4.3 months (95% CI, 4.0–5.6) in the sorafenib group and the HR was 0.59 (95% CI, 0.47–0.76, P<0.0001). Although the Phase 1b Arm A (2) PFS value was lower at 7.3 months, this was considerably longer than the 5.6 months observed in Arm F (2). As the observation period for IMbrave150 (8.6 months) was shorter than that for Arm A (12.4 months) an extension of the observation period may result in a greater PFS.

The objective response rate (ORR), by IRF-assessed RECIST v1.1, was significantly higher in the Atezo + Beva group (27%; 95% CI, 23–33) than in the sorafenib group (12%; 95% CI, 7–18) (stratified P value <0.0001). The ORR in the Atezo + Beva group was superior in Phase 1b Arm A (36%) than in Arm F (20%), and this may be further improved in the final analysis, in which the observation period is extended. A complete response was observed in 18 patients (6%), which was a promising result. The median duration of response (DOR) was NE and DOR >6 months was observed in 80% of responders, which indicated a durable response.

A more favorable patient-reported outcome was observed in the Atezo + Beva group than in the sorafenib group. The decrease in quality of life (QOL) in the Atezo + Beva group was more favorable than that in the sorafenib group, with an HR of 0.63 (95% CI, 0.46–0.85, P=0.0028), which is comparable to that reported for a similar antibody, ramucirumab (3), and this cannot be achieved with tyrosine kinase inhibitors (TKIs), which induce adverse events (AEs). For example, time to symptomatic progression was examined in the SHARP trial but no improvements were observed. These favorable results observed in IMbrave150 may be caused by the delayed onset of symptoms owing to the drug and as this combination is an antibody-based

drugs, which cause minimal AEs and is well tolerated. A subset-analysis in IMbrave150 showed that the Atezo + Beva group was superior in both OS and PFS than the sorafenib group in all subsets except intermediate stage HCC.

In conclusion, Atezo + Beva produced promising results, outperforming sorafenib in all endpoints, OS, PFS, ORR, and safety, and categories in the planned interim analysis (OS, PFS by IRF-assessed RECIST v1.1, ORR by IRF RECIST v1.1, and ORR by IRF-assessed mRECIST v1.1) (1). This can be said to be an important result, in which the theory that proposes that enhanced programmed death-ligand 1 (PD-L1) antibody effects are induced by anti-vascular endothelial growth factor (VEGF) antitumor effects by changing the immune microenvironment from suppressive to responsive was supported in clinical trials (4,5). This Atezo + Beva combination is the only drug that has shown superiority compared with sorafenib since 2007 and, in this sense, is a landmark result. Surprisingly, cancer and the immune system responded as suggested by this theory. Thus, this could be a milestone in the development of systemic therapy for HCC (1,4,5).

The immune class of HCCs reported by Sia *et al.* (6) is important for understanding differences between a programmed cell death protein 1 (PD-1)/PD-L1 antibody monotherapy and PD-1/PD-L1 antibody plus anti-VEGF antibody/TKI combination therapy. Sia *et al.* showed that approximately 30% of all patients with HCC have immune hot tumors with lymphocyte infiltration, in which there is an abundance of interferon-γ, granzymes, immune cells, and PD-L1; therefore, immune checkpoint inhibitors (ICIs) may be effective. This corresponds to the Type I and IV tumor microenvironments (TMEs) reported by Teng *et al.* (7). ICI monotherapy is effective in 20% of the active immune class group, which corresponds to the Type I TME. However, 10% of the exhausted immune class is in a state in which T-cell activity is suppressed (i.e., immune exhausted) by various suppressive TMEs, which corresponds to the Type IV TME. Therefore, in Type IV TMEs, ICI monotherapy may not be effective. However, although effects may not be expected from PD-1/PD-L1 antibody monotherapy for tumors with an immunosuppressive TME (i.e., immune exhausted subclass), it is estimated that PD-1/PD-L1 antibodies will activate CD8-positive cells as a result of anti-VEGF antibody/TKI therapy by improving the TME. Furthermore, the Wnt/β-catenin mutation is an activating mutation, in which β-catenin is activated, with a frequency of approximately 20–30%. Sia *et al.* classified HCCs containing this Wnt/β-catenin mutation as the immune exclusion class and proposed that it is resistant to ICI treatment (i.e., primary resistance) (6).

PD-1/PD-L1 monotherapy only exerts (I) an inhibitory effect on the PD-1/PD-L1 pathway, and effects of the tumor, with immunosuppressive TME or β-catenin mutation cannot be expected. In contrast, in addition to inhibiting the PD-1/PD-L1 pathway, PD-1/PD-L1 antibody plus anti-VEGF/TKI combination therapies, for example, using bevacizumab or TKIs, may exert combined effects such as: (II) inhibiting the VEGF-A signaling pathway and killing the tumor cell irrespective of β-catenin mutation, (III) increasing cancer antigen release by HCC necrosis, (IV) activating the maturation of dendritic cells by anti-VEGF antibodies and improving the ability to recognize and present cancer antigens, (V) improving the ability to activate CD8-positive cells at the priming phase, (VI) increasing tumor infiltration by CD8-positive cells by normalizing abnormal tumor vessels (owing to the action of anti-VEGF antibodies), and (VII) improving the suppressive TME (owing to anti-VEGF effects). Thus, anti-PD-1/PD-L1 antibody plus anti-VEGF antibody/TKI combination therapy, with the inhibition of the PD-1/PD-L1 pathway, produces synergistic effects by acting in an immunostimulatory manner in every step of the cancer immunity cycle (*Table 1*) as a result of the (I) release of cancer antigens, (II) enhanced ability of dendritic cells to present cancer antigens, (III) antigen-specific T cell activation by enhanced priming capacity in lymph nodes, and (IV) stimulation of CD8-positive cell infiltration into the tumor, after which activated T cells attack cancer cells owing to the anti-PD-1/PD-L1 pathway blockade and improvement in the immunosuppressive TME.

The release of VEGF-A from the hypoxic tumor increases the number of suppressive molecules, such as tumor-associated macrophages, regulatory T cells, and myeloid-derived suppressor cells (8). Furthermore, immunosuppressive cytokines interleukin-10 and transforming growth factor-β are released to further suppress the TME. This inhibits the maturation of dendritic cells and the activation/proliferation of T-cells. However, the administration of anti-VEGF antibodies improves the immunosuppressive environment and T-cell activation/maturation by dendritic cells. Therefore, anti-VEGF antibodies exert their effects and contribute to the restoration of CD8-positive cell immune activity when CD8-positive activation is suppressed by the TME, even

Table 1 Synergistic effect of combination immunotherapy with PD-1/PD-L1 antibody and anti-VEGF/TKI

	PD-1/PD-L1 antibody monotherapy	PD-1/PD-L1 antibody plus anti-VEGF/TKI combination immunotherapy
Mode of action	PD-1·PD-L1 blockade	PD-1·PD-L1 blockade
		Direct antitumor effect by inhibiting signaling pathway
		Increased cancer antigen release by tumor necrosis
		Increased antigen presentation by maturation of dendritic cell
		Increased activation of CD8+ T cell at the priming phase
		Increased tumor infiltration of CD8+ T cell by normalization of abnormal tumor vessel
		Improvement of tumor microenvironment from immune suppressive to immune responsive

VEGF, vascular endothelial growth factor; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; TKI, tyrosine kinase inhibitor.

when CD8-positive cells infiltrate in the cancer, as in Type IV tumors.

In addition to the low immunogenicity of TMEs in Type II tumors, Type II cases include cancers with Wnt/β-catenin-activating mutations, as proposed by Llovet *et al.*; therefore, the Type II TME does not appear to be infiltrated by CD8-positive cells. As such, antitumor effects may be exerted by the direct antitumor and necrotic effects of HCCs by the anti-VEGF antibodies/TKIs themselves, even in Type II tumors, which do not originally have immune cell infiltration. Furthermore, CD8-positive cell infiltration and the exertion of ICI effects may be caused by the increased immunogenicity induced by necrosis. Among the clinical cases in Harding *et al.* (9), All of 10 patients with Wnt/β-catenin mutations had progressive disease (PD), whereas 17 patients without WNT/β-catenin mutation had a disease control rate of 71% (9). Furthermore, the PFS in patients with the Wnt/β-catenin mutation administered ICI monotherapy was 2.0 months, whereas the PFS in patients without this mutation reached 7.4 months (P<0.0001). The disease control rate value of 71% is in good agreement with the value of approximately 70% when the immune hot subclass (30%) and immune moderate subclass (40%) are combined. However, There was no relationship between effects of sorafenib and the presence or absence of Wnt/β-catenin mutations (9).

The Wnt/β-catenin mutation was originally considered to be present in 20–30% of all HCCs. Indeed, PD rates from single-agent nivolumab, single-agent pembrolizumab, and single-agent atezolizumab are as high as 37%, 32.4%, and 42.0%, respectively (2,10,11) (*Table 2*). However, combined PD-1/PD-L1 and anti-VEGF/TKI therapy reduces PD rates to 20% for the Atezo + Beva group (Phase 3 IMbrave150) (1), 28% for the Atezo + Beva group (Phase 1b Arm F), 24.0% for the Atezo + Beva group (Phase 1b Arm A) (2), 7.0% for the pembrolizumab + lenvatinib group (Phase 1b) (12), and 8.3% for the nivolumab + lenvatinib group (Phase 1b) (13) (*Table 2*). The ORR of bevacizumab is 13% in RECIST v1.0, whereas the ORR of lenvatinib is 18.8% in RECIST v1.1 and 40.6% in mRECIST, indicating a strong antitumor effect of lenvatinib (14). This may result in a lower PD rate because multikinase inhibitors, such as lenvatinib, have higher tumor-necrosis and cancer-antigen release effects than bevacizumab; therefore, the combination of lenvatinib and pembrolizumab exerts a greater anti-tumor effect on Type IV and probably Type II HCC than each drug alone (15). These combination therapies with ICIs and anti-VEGF antibody/TKIs may be effective in tumors with Wnt/β-catenin activating mutations such as Type II HCC. As a result, lower PD rates have led to prolonged PFS (*Table 2*).

These results suggest that combination immunotherapy would be more effective than ICI monotherapy owing to the synergistic effects brought about by: (I) anti-VEGF activity (improved TME, dendritic cell activation, and immune cell infiltration into the tumor), (II) direct anticancer activity (increased release of cancer antigens by a blockade of VEGF and multi-kinase pathways), (III) blockade of the PD-1/PD-L1 pathway (activation of CD8-positive cells), and (IV) effects on Wnt/β-catenin activated mutations.

A Phase 3 LEAP002 trial, which compares pembrolizumab + lenvatinib combination therapy with

Table 2 Efficacy results of ICI monotherapy and ICI + anti-VEGF/TKI combination therapy (RECIST 1.1)

	Monotherapy			Combination therapy (ICI + anti-VEGF, TKI)					
	Nivolumab (n=371)	Pembrolizumab (n=183)	Atezolizumab (n=59)	Atezolizumab + Bevacizumab (n=60)	Atezolizumab + Bevacizumab (n=336)	Atezolizumab + Bevacizumab (n=104)	Pembrolizumab + Lenvatinib (n=100)	Nivolumab + Lenvatinib (n=24)
	(CheckMate-459) (10)	(KEYNOTE 240) (11)	Phase 1b (2) (Arm F)	Phase 1b (2) (Arm F)	(IMbrave 150) (1)	Phase 1b (2) (Arm A)	(Phase 1b) (12)	(Phase 1b) (13)
ORR (%)	15.0	18.3	17.0	20	27.0	36.0	36.0	54.2
PD (%)	37.0	32.4	42.0	28	20.0	24.0	7.0	8.3
PFS (M)	3.7	3.0	3.4	5.6	6.8	7.1	8.6	7.4
OS (M)	16.4	13.9	N/A	N/A	NR	17.1	22.0	NR

ICI, immune checkpoint inhibitor; VEGF, vascular endothelial growth factor; TKI, tyrosine kinase inhibitor; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; OS, overall survival; NR, not reached; N/A, not available.

lenvatinib alone, is in progress and its results are greatly awaited.

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Footnote

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