

# A Comparative Efficacy of Atezolizumab plus Bevacizumab Versus Sorafenib in Advanced Hepatocellular Carcinoma: A Review

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## Abstract

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Hepatocellular carcinoma (HCC) ranks sixth as the most common cancer and fourth as the most common cause of cancer-related death globally. The standard treatment for advanced HCC is by prescribing sorafenib, a tyrosine kinase inhibitor. Despite its moderate efficacy and concerning side effects, there is no better alternative to sorafenib to treat HCC. However, a new combination of atezolizumab (an inhibitor of PD-L1) and bevacizumab (an inhibitor of vascular endothelial growth factor), has shown a potential to surpass the efficacy of sorafenib. This review was written to provide an insight into pharmacodynamics of sorafenib and atezolizumab plus bevacizumab, effectiveness of sorafenib and the one of atezolizumab plus bevacizumab, utilization of atezolizumab plus bevacizumab in the clinical practice, as well as to argue that this combination can replace sorafenib as the standard palliative treatment for HCC.

## Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy globally, in which its cases has been growing exponentially since 1980 and it is one of the leading cancer-related mortality.<sup>1</sup> HCC is often diagnosed in advanced stages because its signs and symptoms are usually unnoticeable until it already reached advanced stages. Advanced HCC are unresectable, however, since the cancerous cells are located near to a large blood vessel or might have invaded a vasculature. Thus, patients diagnosed with advanced HCC only receive palliative treatment. Currently, the standard palliative treatment of HCC is through the administration of sorafenib (SFB), an oral multi-kinase inhibitor.<sup>2</sup> However, SFB only prolongs life expectancy by 4.3 months, while it also induces moderate drug-related adverse

events.<sup>3</sup> Thus, a more effective treatment is needed.

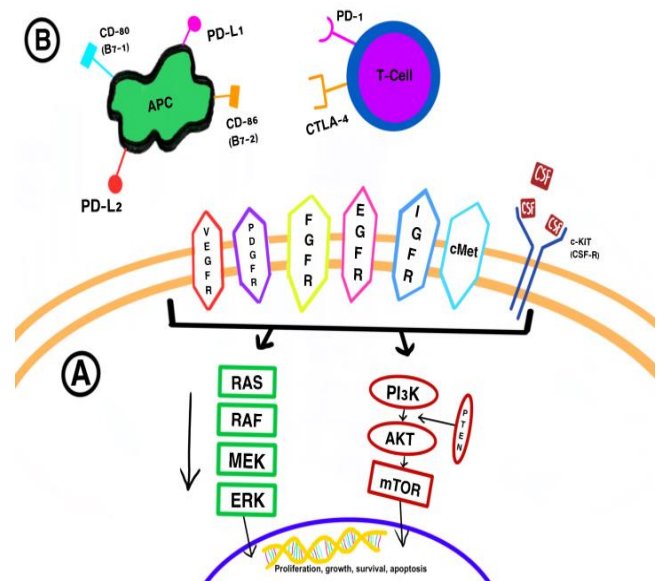
Over the years, cancer drugs that target tumor angiogenesis, such as anti-angiogenic drugs, have been developed. Moreover, cancer immunotherapy such as immune checkpoint inhibitors (ICI) has been available as well to treat various cancers. The combination of ICI with anti-angiogenic drugs could be useful to treat certain cancers. A particular example is the combination of atezolizumab (ATZ), the programmed death-ligand 1 (PD-L1) inhibitor, and bevacizumab (BVZ), the vascular endothelial growth factor (VEGF) inhibitor. This review was thus written to compare ATZ+BVZ with SFB in terms of its pharmacodynamics, general efficacy, and consideration in the real-world clinical practice to determine its likelihood of replacing SFB as the standard palliative care for advanced HCC.

## Signaling Pathways as Target of HCC Drugs

The development of cancer-inhibiting drugs began when proto-oncogenes had been discovered in the 1980s.<sup>4</sup> Proto-oncogenes are genes that have the potential to cause cancer. Mutated versions of these genes are called oncogenes, which usually affect growth of mutated cells.

Growth factors in the liver are most active during the embryonic stage of life, when growth factors, such as the epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), insulin-like growth factors (IGF), hepatocyte growth factor (HGF), platelet-derived growth factor (PDGF) and transforming growth factors - $\alpha$  and - $\beta$  (TGF- $\alpha$  and TGF- $\beta$ ), are produced to support the liver development. In contrast, these growth factors are produced minimally or not at all in the liver of an adult.<sup>5</sup> In a case of liver injury or damage, however, hepatocytes could upregulate growth factors, such as EGF, VEGF, IGF and TGF- $\alpha$ . Those are the growth factors that oncogenes target as well. A dysregulation of growth factor production and growth factor receptor signaling pathways within adult's liver might lead to uncontrolled division and metastasis.

Critical growth factor signaling pathways in HCC include the Ras/Raf/MEK/ERK (MAPK/ERK), Phosphoinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) and the Wnt/catenin pathway.<sup>6</sup> The Ras/Raf/MEK/ERK (MAPK/ERK) pathway is especially critical for HCC initiation and progression. It transduces extracellular signals from tyrosine kinase receptors, such as EGF-receptor (EGFR), VEGF-receptor (VEGFR), IGF-receptor (IGFR) and the PDGF-receptor (PDGFR), into the nucleus.<sup>6</sup> This pathway is most frequently hyper-activated in HCC and occurs in about 50% of early-stage and most advanced cases.<sup>7</sup>



**Figure 1. Major signaling pathways responsible for hepatocellular carcinoma and its progression.** (A) The Ras/Raf/MEK/ERK (MAPK) and PI3K/Akt/mTOR pathways can be activated through receptors of VEGF, PDGF, FGF, EGF, or IGF as well as other receptor tyrosine kinases (including c-MET and c-Kit). The activation results in either proliferation, growth, survival or apoptosis. (B) The immune checkpoint inhibitor mechanism between antigen-presenting cells (APCs) and T cells.

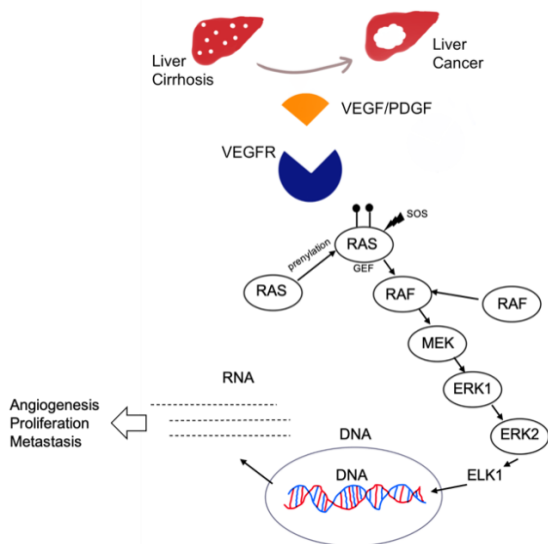
There is a series of phosphorylation events within the Ras/Raf/MEK/ERK (MAPK) pathway (**Figure 1**).<sup>6</sup> First, Ras will be activated and activate the serine-threonine kinase of the Raf family. Raf in turn phosphorylates the mitogen-activated kinase (MEK) 1/2 kinases, activating the extracellular regulated kinases (ERK) 1/2. ERK 1/2 kinase will migrate into the nucleus and subsequently regulates protein expression responsible for cell cycle progression, apoptosis resistance, cellular motility, angiogenesis and drug resistance. The oncogenic transformation of the Ras/Raf isoforms or gene upregulation will dysregulate this pathway, causing abnormal cell growth, proliferation and migration.<sup>7</sup>

In addition to Ras/Raf/MEK/ERK (MAPK) signaling pathway, a receptor called the VEGF receptor (VEGFR) is also important for angiogenesis. **Figure 2** depicts a role of VEGFR in HCC progression. Among three types of VEGF receptors (VEGFR-1, VEGFR-2 and VEGFR-3), VEGFR-2 mediates most of cellular responses for the angiogenesis.<sup>6</sup> Angiogenesis is critical for cancer cells since tumor growth in the liver induces hypoxia for cancer cells.<sup>8,9</sup> Therefore, new blood vessels are required to provide oxygen. Growth factors such as hypoxia-inducible factors 1 and 2 (HIF-1 and HIF-2) and insulin-like growth factor 2 (IGF-2) will be induced in hypoxic hepatocytes, stimulating VEGF expression.<sup>6</sup> High levels of VEGF in HCC patients result in tumor progression, poor prognosis after resection, disease recurrence, vascular invasion and portal vein embolism.<sup>6</sup> During the formation of new blood vessels, PDGFR is responsible for forming pericytes and smooth muscle cells around the new blood vessel.

VEGFR would activate the Ras/Raf/MEK/ERK signaling pathway. This would induce angiogenesis, proliferation and metastasis of hepatocellular carcinoma.

Aside from those growth factors, immune checkpoints, such as PD-1 and CTLA-4, could also be activated during HCC development (**Figure 1**).<sup>6,8</sup> In normal conditions, these checkpoints regulate the immune system by preventing the immune system from over-activation and from attacking normal cells. Thus, immune checkpoints may render immune cells, such as cytotoxic CD8<sup>+</sup> T cells, to be inactive. Malignant cells unfortunately could hijack these mechanisms to suppress the proper activation of immune system.<sup>9</sup>

It is obvious therefore that those mentioned growth factors and signaling pathways as well as the immune checkpoints are potential targets for treating HCC. Most cancer drugs target the VEGFR growth factor and/or the Ras/Raf/MEK/ERK (MAPK) pathway, in which a particular cancer drug could target a single pathway or multiple pathways at once. Such is the case for SFB and ATZ+BVZ drugs, which this paper will discuss further. For instance, SFB targets two pathways, i.e., the VEGFR and the Ras/Raf/MEK/ERK (MAPK) pathways, to mitigate the impact of dysregulated pathways. In contrast, certain drugs might target a single pathway, such as the ATZ (inhibiting PD-L1) and BVZ (inhibiting VEGF).



**Figure 2. Role of VEGF/VEGFR in the hepatocellular carcinoma.** During the progression of liver cirrhosis to liver cancer, an interaction of VEGF and

### Parameters to Consider for Determining Drug Efficacy

To determine the efficacy of HCC drugs, various common parameters are used, including alpha-fetoprotein (AFP) level, Child-Pugh (C-P) score, albumin-bilirubin (ALBI) level, whether a patient is a molecular-targeted agent (MTA) naïve or experienced, as well as whether the cause of HCC is viral or non-viral.

Firstly, AFP serves as a diagnostic marker in AFP-positive HCC.<sup>10</sup> AFP is produced by neoplastic or regenerating hepatocytes. As AFP is made in the liver of infants, healthy adults should have very low levels of AFP, in which AFP levels exceeding 400 ng/mL could be a sign of malignancy. The significant decrease in AFP levels among clinical subjects suggests the good potency of the tested drug for HCC treatment.

Secondly, the C-P score acts to predict the mortality rate of HCC patients.<sup>11</sup> There are three categories: grade A indicates a good hepatic function; grade B indicates a moderately impaired hepatic function; and grade C indicates advanced hepatic dysfunction. The C-P score needs to be evaluated before treatment to analyze the suitability of the antineoplastic drug.

Thirdly, the albumin-bilirubin (ALBI) score uses objective parameters, i.e., albumin and total bilirubin levels, which supposedly provide a better evaluation than the C-P score.<sup>12</sup> There are three grades: grade 1 classifies 25% of patients with the lowest risk of death; grade 3 classifies 10% of patients with the highest risk of death; and grade 2 classifies patients in between.

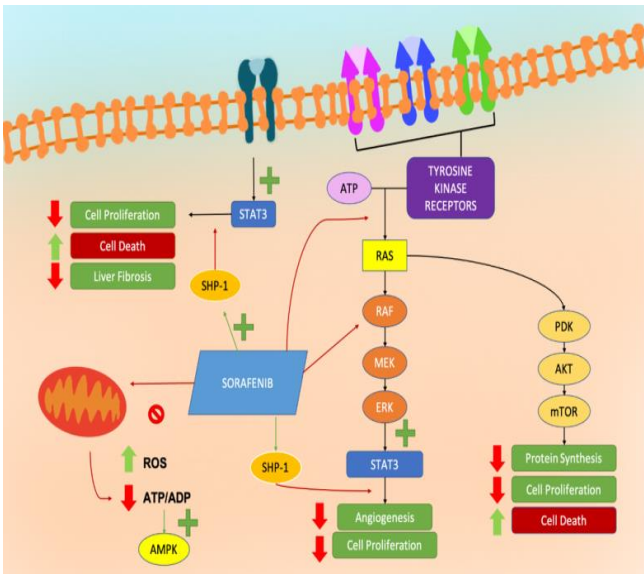
Fourthly, the MTA-naive and experienced patients may present different responses toward drugs. Therefore, it is also critical to consider this as a parameter.<sup>13</sup> Finally, the HCC causes could be divided into viral, caused by hepatitis B (HBV) or hepatitis C (HCV) virus, and non-viral, due to excessive alcohol consumption, smoking, and obesity. This parameter is significant since, according to past studies, non-viral HCC presents a poorer prognosis.<sup>14,15</sup>

## Sorafenib to Treat Advanced HCC

Sorafenib (SFB) is a multi-kinase inhibitor. Although it was initially identified as a Raf-1 kinase inhibitor, it is known now to target multiple tyrosine kinase receptors, including VEGF receptors 1-3, PDGFR- $\beta$ , stem cell factor receptor (KIT), FMS-related tyrosine kinase 3 receptor (FLT3), FGFR1, RET proto-oncogene and downstream serine/threonine kinase, such as BRAF (mediating signals from RAS to MEK). SFB has been widely used since 2010 as the main palliative treatment option for advanced HCC. Upon ingestion, SFB will be metabolized mainly in the liver through two pathways, producing eight metabolites. Among those eight, M2 (N-oxidation), M4 (demethylation), and M5 (oxidative metabolite) are identified to inhibit VEGF, PDGFR, and members of the MAPK pathway.<sup>16</sup>

As mentioned (**Figure 3**), SFB inhibits tumor cell proliferation by blocking the B-RAF, RAF-1 and the kinase activity within the Ras/Raf/MEK/ERK signaling pathways.<sup>17</sup> It also prevents tumor-associated angiogenesis by targeting the PGFR- $\beta$ , VEGFR-1,2,3, and c-KIT. Lastly, SFB could induce apoptosis of tumor cells by reducing eIF4E phosphorylation and downregulating Mcl-1 levels.<sup>18</sup>

The current problem of using SFB to treat advanced HCC is its modest efficacy, the growing numbers of resistance, and the side effects of SFB. Only 30% of patients are estimated to benefit from SFB, and usually, the drug resistance occurs within six months of treatment.<sup>19</sup> Furthermore, SFB might induce side effects, including diarrhea, fatigue, and hand-foot-mouth disease. In some patients, SFB even could cause an elevated blood pressure and abdominal pain. These adverse events may be caused by disruptions of multiple signaling pathways such as VEGF, PDGF, RAF1, B-RAF, KIT and FLT3 in normal organs.<sup>17</sup>



**Figure 3. Responsible mechanisms of SFB-targeting signaling pathways for treating hepatocellular carcinoma<sup>19</sup>.** SFB induces antitumoral effects by inhibiting tyrosine kinase receptors and TGF- $\beta$  receptor, as well as altering mitochondrial function. SFB inhibits tyrosine kinase receptors (e.g., VEGFR, PDGFR, c-KIT) and downstream kinases (e.g., Raf), thus influencing key cellular pathways, such as Raf/MEK/ERK and PI3K/Akt/mTOR. The regulation of STAT3 activity leads to an increase in cell death and a decrease in proliferation, protein synthesis and angiogenesis within the tumor. SFB increases Tyr dephosphorylation activity of SHP-1, which in return decreases STAT3 activity. Furthermore, SFB-disrupted TGF- $\beta$  pathway promotes cell death while suppressing liver fibrosis and cell proliferation. SFB alters AMPK activity by lowering the ATP/AMP ratio and/or eventually producing ROS, which inhibits the mTORC1 signaling pathway. Green arrow denotes an increase of cellular activity. Red arrow denotes a decrease of cellular activity. Stop sign denotes an inhibition of cellular activity. A plus sign denotes an upregulation of a particular molecule.

### A combination of Atezolizumab and Bevacizumab to Treat HCC

Atezolizumab (ATZ) and bevacizumab (BVZ) are novel inhibitors utilized to target HCC (**Figure 4**). ATZ is an ICI for the programmed death-ligand 1 (PD-L1).<sup>8</sup> PD-L1 is expressed in tumor cells, while programmed death 1 (PD-1) is expressed on cytotoxic CD8<sup>+</sup> T cells. The interaction of PD-1 and PD-L1 suppresses the activation of cytotoxic CD8<sup>+</sup> T cells. Thus, ATZ will inhibit the PD-1 and PD-L1 interaction and subsequently prevent T-cell suppression.<sup>3</sup>

BVZ is a monoclonal antibody that targets VEGF (i.e., the anti-VEGF antibody).<sup>9</sup> Thus, this drug primarily induces anti-angiogenic effects since VEGF is most known for its angiogenic capability. However, VEGF could induce immunosuppressive activities within the tumor microenvironment (TME), including an inhibition of dendritic cell maturation, promotion of immune-suppressive cell infiltration and enhancement of the expression of immune checkpoint molecules.<sup>23</sup>

The immunosuppressive activity of VEGF is possible through three main mechanism.<sup>23</sup> First, VEGF can inhibit dendritic cells maturation. VEGF inhibit dendritic cells since it secretes enzyme (2,3-dioxygenase), which inhibits immune response. Second, VEGF promotes regulatory T cell infiltration and myeloid-derived suppressor cell. Regulatory T cell suppresses immune response and myeloid-derived suppressor cell can inhibit antigen presentation and CD8+ cytotoxic T cell (CTL) activity. Third, VEGF increases immune checkpoint molecules expression on CTL, thereby, suppresses CTL activity.

BVZ can promote ATZ efficacy as the addition of BVZ could prevent the immunosuppression of immune cells. This therapy might also recruit cytotoxic CD8<sup>+</sup> T cells to the tumor microenvironment. Thus, BVZ can both act as an anti-angiogenic and immunomodulatory drug.<sup>3</sup>

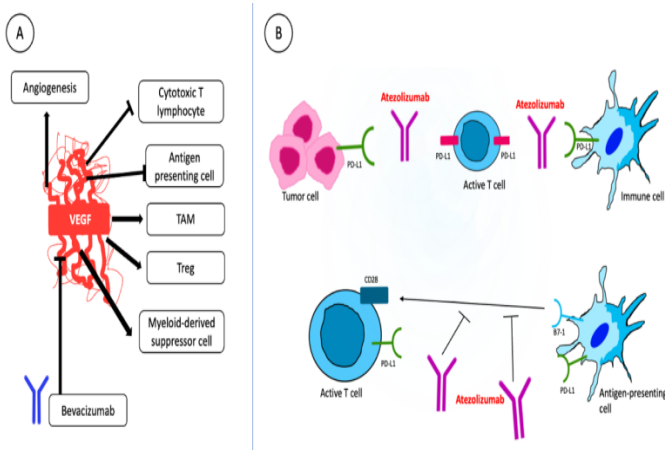
normalization of the TME with anti-angiogenic drug such as BVZ, which targets VEGF, might increase ICI efficacy and reduce serious AE from occurring.

### Real-world Clinical Practice Considerations

Due to the recent usage of this combination, comparable real-world data between ATZ+BVZ and SFB are still limited. Clinical trial results for the ATZ+BVZ combination from the phase III IMbrave150 study demonstrated that ATZ+BVZ increased the survival time by 2.5 months as compared to SFB, reduced the risk of death by 42% as compared to SFB, and induced minor AE.<sup>3</sup> However, the enrolled patients were MTA-naïve and were C-P class A. A further study on ATZ-BVZ will need to be conducted to clarify whether this drug combination is safe for MTA-experienced patients and those with other C-P scores.

A study by Iwamoto et al.<sup>21</sup> described an observational trial result of ATZ+BVZ in patients with previous MTA history or other than ALBI grade 1. However, due to the small sample size of patients with C-P class B, a conclusion on the drug's safety for C-P class B patients could not be reached. The median progression-free survival of this study was 5.4 months. It was concluded that ATZ+BVZ could be safely administered to MTA-experienced and ALBI grade 1-3 patients.

Another study evaluated the safety and efficacy of using ATZ+BVZ in patients with viral/non-viral HCC and other C-P classes as well as other serious AE caused by ATZ+BVZ.<sup>13</sup> The findings indicated that ATZ+BVZ performed better on HCC patients of viral origin than those with non-viral HCC. Also, ATZ+BVZ had a lower efficacy on patients with C-P class B and C. Aside from the well-known AE such as hypertension and proteinuria, variceal bleeding was a common AE of ATZ+BVZ.



**Figure 4. Mechanism of bevacizumab and atezolizumab.**<sup>20</sup> (A) Bevacizumab inhibits VEGF and reverses the impact of VEGF signaling in HCC, i.e., suppressing angiogenesis, activating antigen-presenting cells and cytotoxic T lymphocytes, as well as inhibiting tumor-associated macrophages (TAM), regulatory T ( $T_{reg}$ ) cells and myeloid-derived suppressor cells. (B) Atezolizumab inhibits the interaction between PD-L1 and PD-1, preventing T-cell suppression.

A combination of ATZ and BVZ would provide a synergistic effect in treating HCC. Several studies indicate that a combination of anti-angiogenic and ICI could promote an immunity against cancerous cells.<sup>24,25</sup> It should be clear that immunotherapy efficacy is greatly affected by the immune effector cells within the TME. This claim is backed up by the data that shows 50-80% of patients who receives ICI are indicated to not benefit from the drug and many experiences adverse events (AE).<sup>26</sup> This occur because unsupportive TME such as low pH, hypoxia, and high interstitial fluid pressure, can reduce ICI efficacy.<sup>25</sup> Therefore,

An interesting study by Sho et al.<sup>22</sup> reported the early response of ATZ+BVZ among patients who were ineligible for the IMbrave150 clinical trial. The results of this study reinforced the exemplary safety and effectiveness in the usage of ATZ+BVZ.

Based on the various studies above, it could be concluded that, in general, ATZ+BVZ is safe for use by patients with advanced HCC, and proves to presents a higher efficacy compared to SFB. However, its efficacy might decrease in patients with C-P class B and C, as well as with HCC of non-viral origin.<sup>21,13</sup> However, due to the limited data, more studies are required to strengthen this hypothesis.

### **Safety and Clinical Guideline of Utilizing Atezolizumab and Bevacizumab**

An updated data on the IMbrave150 study, 12 months after the clinical cut-off date of August 31, 2020, showed a consistent clinically successful treatment benefit and safety.<sup>27</sup> First, follow-up at a median of 8.6 months presents data that meets co-primary endpoints, overall survival (OS), and progression-free survival (PFS). Clinically meaningful improvements were also seen for OS (hazard ratio (HR), 0.58 [95% CI, 0.42, 0.79];  $P < 0.001$ ) and independently-assessed PFS (PFS; per RECIST 1.1; HR, 0.59 [95% CI, 0.47, 0.76];  $P < 0.001$ ). The second follow-up after 15.6 months was conducted on 156 patients (ATZ+BVZ,  $n=336$ ; SFB,  $n=165$ ). The OS for ATZ+BVZ patients was 19.2 months, while OS for SFB was only 13.4 months. Thus, the survival rate at 18 months for ATZ+BVZ 52%, and 40% for SFB (HR, 0.66 [95% CI, 0.52, 0.85];  $P=0.0009$ ).

Overall, ATZ+BVZ increases patients' quality of life, and AE.<sup>3</sup> Patients

who receive ATZ+BVZ experience delayed deterioration of patient-reported quality of life (ATZ+ BVZ=median of 11.2 months; SFB=3.6 months). AE of any group in ATZ+BVZ patients were lower (98.2%,  $n=323$ ) than in SFB patients (98.7%,  $n=154$ ). The most frequent AE was hypertension, fatigue, and proteinuria. However, serious AE did occur more frequently in patients receiving ATZ+BVZ (38%,  $n=125$ ) than SFB (30.8%,  $n=48$ ). However, there was no specific incident that caused serious AE.

As of May 2020, ATZ+BVZ for patients who have not received systemic therapy has been approved by the Food and Drug Administration (FDA).<sup>28</sup> The recommended dose is 1,200 mg of ATZ and 15 mg/kg of BVZ, both intravenously. However, the dosing of each drug should be discussed further with the attending physician. Accordingly, ATZ+BVZ is better standard therapy than SFB, as seen from scores of OS, PFS, and AE of patients.

### **Conclusion**

The combination of ATZ+BVZ presents a higher efficacy than SFB, according to the pharmacodynamics of ATZ+BVZ and the IMbrave150 study, as a palliative treatment for patients with advanced HCC. This notion is supported by real-world clinical findings from various studies. The pharmacodynamics of ATZ+BZ proves to be crucial to treat HCC as this combination targets both the PD-1/PD-L1 and VEGFR pathway. The incidence of adverse events were relatively low in most patients as well. However, parameters such as C-P score, ALBI score and type of HCC (viral/non-viral) would need to be considered in future studies, as data of patients with various HCC types are required. It is likely that this combination could replace sorafenib as the standard palliative care treatment of advanced HCC.

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