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HARNESSING THE IMMUNE SYSTEM AGAINST HEPATOCELLULAR CARCINOMA: A CLINICAL PERSPECTIVE

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ABSTRACT

Hepatocellular carcinoma, or HCC, is one of the most common and deadliest types of cancer worldwide. It accounts for nearly 90% of primary liver cancers and is the third leading cause of cancer-related deaths globally. For years, treatment options were pretty limited, especially for those diagnosed in the later stages when the disease is harder to tackle. But things have started to change thanks to immunotherapy—a new kind of treatment that helps the body's own immune system fight back against cancer. One of the biggest breakthroughs has been the combination of two drugs: atezolizumab, which helps "take the brakes off" the immune system, and bevacizumab, which cuts off the blood supply tumors need to grow. This combo is now the first choice for treating advanced HCC because it not only helps people live longer but also improves their quality of life. Researchers aren't stopping there, though. They're exploring exciting new approaches like oncolytic viruses, which are designed to infect and kill cancer cells directly, and adoptive T-cell therapy, which boosts the cancer-fighting power of a patient's own immune cells. Still, HCC tumors have a way of creating a kind of "immune shield" that makes it tough for treatments to work perfectly. That means there's a lot more we need to learn—like how to use immunotherapy earlier, what drug combinations work best, and how to overcome when tumors become resistant. This review takes a close look at why immunotherapy makes sense for HCC, what the clinical trials have shown so far, and where the research is headed next. For people facing this tough diagnosis, these advances bring fresh hope that better, more effective treatments are on the horizon.

KEYWORDS: Hepatocellular carcinoma (HCC), Immunotherapy, Immune checkpoint inhibitors, Tumor immune microenvironment, Adoptive T-cell therapy, Combination therapy.

INTRODUCTION

Liver cancer ranks as the sixth most common cancer around the world and is unfortunately the third leading cause of cancer-related deaths. The majority of these cases are due to hepatocellular carcinoma, or HCC, which is the most prevalent type of primary liver cancer.[1,2] In India, hepatocellular carcinoma (HCC) affects a small but significant portion of the population—estimates range from about 0.2% to 1.6%. One of the main drivers behind these cases is the hepatitis B virus (HBV), which is still quite common across the country. Unfortunately, because there isn't widespread or consistent monitoring, it's hard to get a clear picture of just how big the problem really is nationwide. Although treatments for HCC have improved over the years, many patients are still diagnosed at a late stage, which makes effective treatment much more difficult. To give patients the best chance possible, it's essential to take a team-based, multidisciplinary approach to care and to continue pushing forward with research to develop better therapies.[3] Recent breakthroughs in immunotherapy, especially when combined with other treatments, have changed how we approach hepatocellular carcinoma (HCC). Clinical trials are actively exploring these new strategies, pushing the field forward. By continuing to study how immunotherapy can be paired with current treatments—particularly for patients with early to mid-stage HCC—we have the potential to help more people benefit from these advances.[4] Immune checkpoint inhibitors (ICIs) have been tested as single agents in advanced hepatocellular carcinoma (HCC), showing objective response rates of 15–20%, but without significant overall survival (OS) benefit, and about 30% of HCC cases display intrinsic resistance to ICIs. Due to the lack of reliable biomarkers to predict which patients will benefit most from immunotherapy, research has focused on combination strategies to improve outcomes across broader patient groups. Early-phase studies and basket trials explored combinations of ICIs with anti-angiogenic agents, tyrosine kinase inhibitors (TKIs), or dual ICIs, leading to phase III trials based on promising preliminary results. The IMbrave150 trial demonstrated

that combining atezolizumab (anti-PD-L1) with bevacizumab (anti-VEGF) significantly improved survival compared to sorafenib, resulting in a practice-changing first-line approval. Similarly, the HIMALAYA trial showed that the STRIDE regimen—durvalumab (anti-PD-L1) plus a single priming dose of tremelimumab (anti-CTLA-4)—was superior to sorafenib, establishing another frontline option. However, combinations involving ICIs and TKIs have shown mixed results, with only one phase III trial showing a clear OS benefit. As the treatment landscape rapidly evolves, several key questions remain, including the optimal sequencing of therapies, identification of predictive biomarkers, integration with locoregional therapies, and the development of next-generation immunotherapies. This review explores the science behind using immunotherapy for advanced HCC and looks at the latest clinical evidence supporting its role in treatment.[5]

Immunotherapy for advanced stage HCC

Immunotherapy has become a key player in the treatment of advanced hepatocellular carcinoma (HCC). Among the most promising approaches are immune checkpoint inhibitors (ICIs), particularly those targeting PD-1 or PD-L1 pathways. These drugs have been the focus of several major clinical trials, showing encouraging results both on their own and when combined with other treatments. Today, they form an important part of systemic therapy for HCC. Researchers are also exploring newer options like adoptive cell therapy, which could potentially enhance the effectiveness of existing immunotherapies and offer more hope for patients facing this challenging disease.

Monotherapies with ICI's

Nivolumab, a monoclonal antibody that targets the PD-1 protein, was first tested in the CheckMate 040 phase 1/2 clinical trial. This study included 262 patients with advanced hepatocellular carcinoma (HCC), many of whom had already been treated with sorafenib. The findings showed that around 14% of patients responded to the treatment based on standard RECIST 1.1 criteria, and about 18% when using the modified RECIST scale. What stood out was the durability of the responses—lasting a median of 17 months. The median overall survival for patients was 15.6 months, and the side effects were in line with what had been observed in earlier nivolumab studies. These promising results led the U.S. FDA to grant nivolumab accelerated approval for patients with advanced HCC who had previously received sorafenib.[6] Following its early success, nivolumab was evaluated in the phase 3 CheckMate 459 trial, where it was directly compared to sorafenib as a first-line treatment for patients with advanced hepatocellular carcinoma who hadn't received any prior therapy. The results showed that nivolumab offered a slight improvement in median overall survival—16.4 months compared to 14.7 months with sorafenib. It also had a higher response rate, with 15% of patients showing tumor shrinkage versus 7% in the sorafenib group. However, these differences weren't large enough to reach the trial's main goal for statistical significance. Both treatments showed similar progression-free survival, but nivolumab had an edge when it came to tolerability, with fewer serious side effects reported among patients.[7]

Pembrolizumab showed encouraging results in the phase 2 KEYNOTE-224 trial, leading to FDA approval for advanced HCC patients previously treated with sorafenib. In 104 patients, it achieved a 17% response rate, with a median PFS of 4.9 months and OS of 12.9 months, and no unexpected safety concerns.[8] However, the phase 3 KEYNOTE-240 trial, which tested pembrolizumab versus placebo in the second-line setting, did not meet its pre-specified thresholds for OS and PFS despite modest improvements (OS: 13.9 vs. 10.6 months; PFS: 3.0 vs. 2.8 months). Adverse events were slightly more frequent with pembrolizumab.[9] The more recent KEYNOTE-394 trial in Asia confirmed pembrolizumab's benefit, showing significant gains in OS (14.6 vs. 13.0 months), PFS (2.6 vs. 2.3 months), and ORR (13.7% vs. 1.3%) over placebo, supporting its role as a second-line option, especially in Asian patients.[10]

The phase 3 HIMALAYA trial confirmed that PD-1/PD-L1 inhibitors have antitumor activity in advanced HCC. It compared sorafenib with durvalumab alone or in combination with a single high dose of tremelimumab (the STRIDE regimen) in treatment-naive patients. Durvalumab monotherapy proved to be non-inferior to sorafenib in overall survival (HR = 0.86) and was better tolerated, with significantly fewer severe side effects (12.9% vs. 36.9%).[11] Tislelizumab, an anti–PD-1 antibody, is being evaluated as a first-line treatment for unresectable HCC in the phase 3 RATIONALE 301 trial, comparing it to sorafenib. This may be the final major trial aiming to establish a single-agent checkpoint inhibitor for global approval. However, the focus in the field has largely moved toward combination therapies, which are showing greater promise.[12]

Dual therapies combining ICIs with anti-VEGF antibodies

The phase 3 IMbrave150 trial was a significant breakthrough in treating advanced hepatocellular carcinoma (HCC). It showed that combining atezolizumab, which blocks PD-L1, with bevacizumab, a drug that inhibits VEGF, could offer better results than previous standard treatments. Because of its improved effectiveness and tolerable side effects, this combination has become the new first-choice treatment, often replacing older drugs like sorafenib and lenvatinib in many cases.[13] Initially, a phase 1b study showed promising activity with this combination, but the IMbrave150 trial provided definitive evidence. In the trial, 501 patients with advanced, untreated HCC were randomized 2:1 to receive atezolizumab plus bevacizumab or sorafenib. At the primary analysis, the

combination significantly reduced the risk of death by 42% (HR = 0.58; p < 0.001), with a median overall survival (OS) not reached in the combination arm versus 13.2 months with sorafenib. Patients who received the combination treatment had a longer median progression-free survival—6.8 months compared to 4.3 months for those on sorafenib. The response rate was also significantly better, with over 27% of patients responding to the combo, versus about 12% with sorafenib alone. In terms of safety, both groups had a similar rate of severe side effects, with grade 3 or 4 adverse events occurring in just over half of the patients in each group—56.5% for the combination therapy and 55.1% for sorafenib. The strong performance of this treatment is believed to come from how the two drugs work together: blocking PD-L1 helps activate the immune system, while VEGF inhibition helps strip away the tumor's defenses, making it easier for immune cells to do their job.[14] In a similar vein, the ORIENT-32 trial carried out in China evaluated the combination of sintilimab, a PD-1 inhibitor, with a bevacizumab biosimilar (IBI305), compared to sorafenib in patients receiving systemic treatment for the first time. The results were encouraging—both overall survival and progression-free survival improved with the combination, and the safety profile remained manageable. These findings further support the growing evidence that pairing immunotherapy with VEGF inhibition can offer meaningful benefits in treating advanced HCC.[15]

Dual Immunotherapy Strategies: Checkpoint and Multikinase Inhibitor Combinations

Pairing immune checkpoint inhibitors (ICIs) with tyrosine kinase inhibitors (TKIs) is emerging as a promising option for treating advanced hepatocellular carcinoma—offering a potential alternative to the more common combination of ICIs with anti-VEGF therapies.

Several such combinations are currently under investigation. One notable example is the combination of cabozantinib and atezolizumab, being evaluated in the COSMIC-021 phase 1b trial. Early data suggest a significant improvement in progression-free survival (PFS) compared to control arms (HR = 0.63; p = 0.0012), although overall survival (OS) has not yet shown statistical significance.[16]

The lenvatinib and pembrolizumab combination has also shown encouraging results in a phase 1b study involving 104 treatment-naive patients with unresectable HCC. It achieved ORRs of 46% by mRECIST and 36% by RECIST 1.1, with a median OS of 22 months and a median PFS of 8.6–9.3 months. However, 67% of patients experienced grade 3 or higher adverse events. This combination is now being tested in the phase 3 LEAP-002 trial against lenvatinib alone.[17] Another promising approach is camrelizumab (anti–PD-1) with apatinib (a TKI), which showed an ORR of 50% in a phase 1 trial. It is currently in a phase 3 trial comparing it to sorafenib in the first-line setting.[18] Overall, these trials reflect a growing interest in ICI-TKI combinations as a potential new strategy in the treatment of advanced HCC.

Immunotherapy for Intermediate-Stage HCC

Transarterial chemoembolization (TACE) remains the standard of care for intermediate-stage hepatocellular carcinoma (HCC), classified as stage B in the Barcelona Clinic Liver Cancer (BCLC) staging system. This stage typically includes patients with preserved liver function (Child-Pugh A or B), good performance status (ECOG 0), and multinodular tumors without vascular invasion or distant spread. TACE has been shown to improve overall survival in this group.[19] In addition to its direct tumor-targeting effects, TACE may also modulate the immune environment by reducing regulatory T cells and exhausted effector T cells while promoting pro-inflammatory responses within the tumor.[20]

There's growing interest in pairing immunotherapy with local treatments like transarterial chemoembolization (TACE). A small study looked at the safety and practicality of combining tremelimumab, an anti–CTLA-4 antibody, with either ablation or TACE in patients who couldn't undergo surgery or liver transplantation. Out of 19 patients who could be evaluated, 5 showed a partial response, and the median overall survival was nearly 20 months. What's particularly encouraging is that biopsies from those who responded revealed a higher number of CD8+ T cells—immune cells known to fight cancer—providing strong support for combining immunotherapy with locoregional treatments in patients with intermediate-stage HCC.[21]

Combination treatments

Although the IMbrave150 trial included some patients with intermediate-stage hepatocellular carcinoma—about 15 percent of the total—it primarily focused on individuals with unresectable disease. As a result, it does not provide enough evidence to fully evaluate the effectiveness of the combination of atezolizumab and bevacizumab in this specific group, particularly when compared to the current standard treatment, transarterial chemoembolization (TACE).[22]

To explore this further, two large, investigator-initiated phase 3 trials are underway. The first, called the ABC-HCC trial, is comparing atezolizumab and bevacizumab directly with TACE in patients with intermediate-stage HCC. This study introduces a novel primary endpoint called "time to failure of treatment strategy," which measures the duration until a treatment must be stopped due to lack of effectiveness. The second trial, named RENOTACE, is testing the combination of regorafenib and nivolumab against TACE. It uses progression-free survival—measured according to modified criteria that account for changes in blood supply to the tumor—as its main outcome.[23]

Beyond comparing these two treatment approaches, another strategy being explored is combining systemic therapy with TACE, rather than choosing one over the other. Several ongoing phase 3 trials are investigating this combination approach. The TALENTACE trial is testing atezolizumab and bevacizumab with TACE The LEAP-012 trial combines lenvatinib and pembrolizumab with TACE. The EMERALD-1 trial is assessing durvalumab, with or without bevacizumab, alongside TACE. The CheckMate 74W trial is evaluating nivolumab, with or without ipilimumab, in combination with TACE. Additionally, the TACE-3 trial is comparing TACE or transarterial embolization with and without nivolumab.[24]

These studies reflect a growing effort to integrate systemic immunotherapy into the treatment of intermediate-stage HCC, with the potential to improve outcomes beyond what TACE alone can offer.

Immunotherapy for Early-Stage HCC

For patients with very early-stage (BCLC 0) and early-stage (BCLC A) hepatocellular carcinoma (HCC), the main treatment options are surgical resection, liver transplantation, and local ablation. The primary goal at these stages is a complete cure, and five-year survival rates after surgery can reach 70 to 80 percent. However, recurrence after surgical resection remains a major issue, with rates as high as 70 percent over five years. Risk factors for recurrence include the presence of satellite tumors, underlying cirrhosis, and low platelet counts.[25]

Immune-related factors also play a key role in recurrence risk. A tumor environment rich in immunosuppressive cells like regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), along with decreased activity of immune-stimulating elements such as interferon-gamma and increased PD-L1 expression, is linked to poorer outcomes. In contrast, high levels of CD3+ and CD8+ T cells in and around the tumor—quantified by what is known as the "Immunoscore"—are associated with a lower likelihood of recurrence.[26] These findings support the potential role of immunotherapy in both adjuvant (post-surgical) and neoadjuvant (pre-surgical) settings, aiming to improve long-term outcomes and reduce recurrence after curative-intent treatments for HCC.

Future directions

The introduction of immune checkpoint inhibitors (ICIs) has significantly transformed the treatment landscape for advanced hepatocellular carcinoma (HCC), but several key challenges remain. First, there is an ongoing effort to determine whether immunotherapy can offer meaningful benefits in earlier stages of the disease. Ongoing clinical trials are now exploring whether immunotherapy could be effective even in earlier stages of hepatocellular carcinoma. For patients with intermediate-stage HCC, studies like ABC-HCC and RENOTACE are taking a closer look. These trials are comparing immune-based treatments—such as atezolizumab combined with bevacizumab in ABC-HCC, and regorafenib paired with nivolumab in RENOTACE—against the current standard approach, which is transarterial chemoembolization (TACE). The goal is to see if these newer combinations can offer better outcomes than what's traditionally been used. These trials differ in focus: ABC-HCC includes a broader patient population, while RENOTACE targets those with more advanced tumor burden. Meanwhile, other studies like LEAP-012, EMERALD-1, and CheckMate 74W are exploring whether adding immunotherapy to TACE may further improve outcomes.

In early-stage HCC, research is centered on whether ICIs can reduce recurrence and enhance survival when given either after surgery or ablation (adjuvant therapy), or before treatment (neoadjuvant therapy). Trials involving combinations such as nivolumab, pembrolizumab, and atezolizumab with bevacizumab are underway and expected to provide critical insights into their role in curative settings.

Beyond current checkpoint targets, researchers are investigating next-generation immunotherapies. These include agents targeting alternative immune checkpoints like LAG-3, as well as cellular therapies using engineered immune cells—such as CAR-T and CAR-NK cells—and oncolytic viruses. These approaches aim to address a second major gap: expanding therapeutic options for patients who do not respond to standard ICIs. This also relates to the third challenge—managing resistance or lack of response to immunotherapy. Some tumors, particularly those with an “immune desert” microenvironment lacking immune cell infiltration, are less responsive to ICIs. For such cases, continued development of targeted therapies and new molecular strategies remains crucial. Ultimately, while immunotherapy has opened new possibilities, optimizing its use across all stages of HCC will depend on evidence from ongoing trials and a deeper understanding of tumor immunobiology.

CONCLUSION

Immunotherapy is quickly becoming one of the most promising tools in the fight against cancer. By tapping into the body’s own immune system, it offers a more targeted approach than traditional treatments like chemotherapy or radiation, often with fewer side effects. But when it comes to hepatocellular carcinoma (HCC)—the most common form of liver cancer—the results so far have been mixed.

One of the main challenges is the nature of the tumor environment in HCC. These tumors typically have low levels of immune cell infiltration, which makes it harder for immunotherapies to be effective. Immune checkpoint inhibitors (ICIs), for example, have shown encouraging signs in clinical trials across various cancers, and they’ve

made their way into HCC treatment as well. However, when used on their own, their impact tends to be limited.

To overcome this, researchers are increasingly turning to combination strategies. Using ICIs alongside other treatments—such as chemotherapy, anti-angiogenic agents (which cut off blood supply to tumors), or radiotherapy—has shown better outcomes, particularly in improving objective response rates. These combinations seem to help create a more favorable immune environment, giving the body a better chance to recognize and fight the cancer.

Beyond ICIs, other forms of immunotherapy are also under investigation. These include adoptive cell transfer (ACT), where a patient's own immune cells are modified and reinfused to better attack cancer; tumor vaccines designed to "train" the immune system; and therapies based on cytokines, which help regulate immune responses. While many of these are still in early research stages, they offer promising new directions.

The path forward likely involves combining different immunotherapies and tailoring treatment plans to individual patients. By understanding the specific immune landscape of each tumor, doctors may be able to design more effective, personalized approaches. With continued research and innovation, there's real hope that immunotherapy will become a more powerful and reliable option for patients with HCC.

REFERENCES

1. Kinsey E, Lee HMJC. Management of hepatocellular carcinoma in 2024: the multidisciplinary paradigm in an evolving treatment landscape, 2024; 16(3): 666.
2. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, 2024; 74(3): 229-63.
3. Chavda HJJIJoS. Hepatocellular carcinoma in India, 2021; 83(4): 959-66.
4. Zongyi Y, Xiaowu LJCl. Immunotherapy for hepatocellular carcinoma, 2020; 470: 8-17.
5. Sangro B, Sarobe P, Hervás-Stubbs S, Melero IJNrG, hepatology. Advances in immunotherapy for hepatocellular carcinoma, 2021; 18(8): 525-43.
6. El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. The Lancet, 2017; 389(10088): 2492-502.
7. Yau T, Park J, Finn R, Cheng A-L, Mathurin P, Edeline J, et al. CheckMate 459: A randomized, multi-center phase III study of nivolumab (NIVO) vs sorafenib (SOR) as first-line (1L) treatment in patients (pts) with advanced hepatocellular carcinoma (aHCC), 2019; 30: v874-v5.
8. Zhu AX, Finn RS, Edeline J, Cattan S, Ogasawara S, Palmer D, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial, 2018; 19(7): 940-52.
9. Finn RS, Ryoo B-Y, Merle P, Kudo M, Bouattour M, Lim HY, et al. Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in KEYNOTE-240: a randomized, double-blind, phase III trial, 2020; 38(3): 193-202.
10. Qin S, Chen Z, Fang W, Ren Z, Xu R, Ryoo B-Y, et al. Pembrolizumab plus best supportive care versus placebo plus best supportive care as second-line therapy in patients in Asia with advanced hepatocellular carcinoma (HCC): Phase 3 KEYNOTE-394 study. American Society of Clinical Oncology, 2022.
11. Abou-Alfa GK, Chan SL, Kudo M, Lau G, Kelley RK, Furuse J, et al. Phase 3 randomized, open-label, multicenter study of tremelimumab (T) and durvalumab (D) as first-line therapy in patients (pts) with unresectable hepatocellular carcinoma (uHCC): HIMALAYA. American Society of Clinical Oncology, 2022.
12. Qin S, Finn RS, Kudo M, Meyer T, Vogel A, Ducreux M, et al. RATIONALE 301 study: tislelizumab versus sorafenib as first-line treatment for unresectable hepatocellular carcinoma, 2019; 15(16): 1811-22.
13. Lee M, Ryoo B-Y, Hsu C-H, Numata K, Stein S, Verret W, et al. Randomised efficacy and safety results for atezolizumab (Atezo)+ bevacizumab (Bev) in patients (pts) with previously untreated, unresectable hepatocellular carcinoma (HCC), 2019; 30: v875.
14. Hegde PS, Wallin JJ, Mancao C, editors. Predictive markers of anti-VEGF and emerging role of angiogenesis inhibitors as immunotherapeutics. Seminars in cancer biology, 2018: Elsevier.
15. Ren Z, Xu J, Bai Y, Xu A, Cang S, Du C, et al. Sintilimab plus a bevacizumab biosimilar (IBI305) versus sorafenib in unresectable hepatocellular carcinoma (ORIENT-32): a randomised, open-label, phase 2–3 study, 2021; 22(7): 977-90.
16. Kelley RK, W Oliver J, Hazra S, Benzaghou F, Yau T, Cheng A-L, et al. Cabozantinib in combination with atezolizumab versus sorafenib in treatment-naive advanced hepatocellular carcinoma: COSMIC-312 Phase III study design, 2020; 16(21): 1525-36.
17. Ipsen PJPR. Exelixis and Ipsen announce cabozantinib in combination with an immune checkpoint inhibitor significantly improved progression-free survival in phase 3 COSMIC-312 pivotal trial in patients with previously untreated advanced liver cancer, 2021.
18. Xu J, Zhang Y, Jia R, Yue C, Chang L, Liu R, et al. Anti-PD-1 antibody SHR-1210 combined with apatinib for advanced hepatocellular carcinoma, gastric, or esophagogastric junction cancer: an open-

label, dose escalation and expansion study, 2019; 25(2): 515-23.
19. Lencioni R, de Baere T, Soulen MC, Rilling WS, Geschwind JFHJH. Lipiodol transarterial chemoembolization for hepatocellular carcinoma: a systematic review of efficacy and safety data, 2016; 64(1): 106-16.
20. Llovet JM, Bruix JJH. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival, 2003; 37(2): 429-42.
21. Pinato DJ, Murray SM, Forner A, Kaneko T, Fessas P, Toniutto P, et al. Trans-arterial chemoembolization as a loco-regional inducer of immunogenic cell death in hepatocellular carcinoma: implications for immunotherapy, 2021; 9(9): e003311.
22. Foerster F, Kloeckner R, Reig M, Chan SL, Chung JW, Merle P, et al. ABC-HCC: A phase IIIb, randomized, multicenter, open-label trial of atezolizumab plus bevacizumab versus transarterial chemoembolization (TACE) in intermediate-stage hepatocellular carcinoma. American Society of Clinical Oncology, 2022.
23. Kudo M, Guo Y, Hua Y, Zhao M, Xing W, Zhang Y, et al. TALENTACE: A phase III, open-label, randomized study of on-demand transarterial chemoembolization combined with atezolizumab+ bevacizumab or on-demand transarterial chemoembolization alone in patients with untreated hepatocellular carcinoma. American Society of Clinical Oncology, 2022.
24. Llovet JM, El-Khoueiry A, Vogel A, Madoff D, Finn R, Ogasawara S, et al. 1016TiP LEAP-012 trial in progress: Pembrolizumab plus lenvatinib and transarterial chemoembolization (TACE) in patients with intermediate-stage hepatocellular carcinoma (HCC) not amenable to curative treatment, 2020; 31: S702-S3.
25. Roayaie S, Obeidat K, Sposito C, Mariani L, Bhoori S, Pellegrinelli A, et al. Resection of hepatocellular cancer≤ 2 cm: results from two Western centers, 2013; 57(4): 1426-35.
26. Gabrielson A, Wu Y, Wang H, Jiang J, Kallakury B, Gatalica Z, et al. Intratumoral CD3 and CD8 T-cell densities associated with relapse-free survival in HCC, 2016; 4(5): 419-30.