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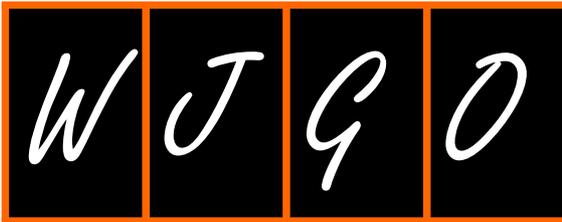
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## Recent update on comprehensive therapy for advanced hepatocellular carcinoma

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### Abstract

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors in the world. The treatment methods for HCC are diverse, mainly including surgical resection, ablation, and liver transplantation. The curative effect can be achieved only for early stage HCC, and it is easy to recur and metastasize after surgery, with a 5-year recurrence rate as high as 70%. Most patients with HCC are in the middle and advanced stage at the time of diagnosis and lose the chance of surgical resection. In recent years, with the in-depth study of the pathogenesis of HCC and the progress of medical science and technology, the systemic treatment of advanced HCC has made a breakthrough. At present, multidisciplinary comprehensive treatment including targeted therapy and immunotherapy has become an effective strategy and inevitable trend for the treatment of advanced HCC. Combined therapy has greatly improved the prognosis of HCC patients and opened up a new milestone in the treatment of this malignancy. In this article, we focus on the treatment progress of advanced HCC to further guide clinical practice.

**Key Words:** Hepatocellular carcinoma; Local treatment; Targeted therapy; Immunotherapy; Comprehensive therapy; Multidisciplinary therapy

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**Core Tip:** Hepatocellular carcinoma (HCC) is one of the most common malignant tumors in the world. The curative effect can be achieved only for early stage HCC, and it is easy to recur and metastasize after surgery, with a 5-year recurrence rate as high as 70%. Recently, the systematic treatment of advanced HCC has made a breakthrough. Multidisciplinary comprehensive treatment including targeted therapy and immunotherapy has become an effective strategy and inevitable trend for the treatment of

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## INTRODUCTION

At present, primary liver cancer (PLC) is still one of the most common malignant tumors in the world, ranking sixth among all kinds of tumors, and the third leading cause of death[1]. According to the latest statistics, in 2020, there were more than 900000 new PLC cases and 830000 deaths worldwide, mainly in the East[2]. Hepatocellular carcinoma (HCC) accounts for 75%-85% of PLC cases. The onset of HCC is insidious, and it is not easy to be detected early. Most patients with HCC are in the middle and late stages at the time of diagnosis and lose the opportunity of surgical treatment, and the postoperative recurrence and metastasis rates are high. The 5-year recurrence rate is as high as 70%[3] and 5-year overall survival (OS) rate is 15%-19% in North America, but only 12.1% in China[4,5]. In recent years, with the in-depth study of the pathogenesis of liver cancer and the progress of medical science and technology, the advent of targeted drugs represented by sorafenib and immunotherapeutic drugs represented by pembrolizumab has made a breakthrough in the systemic treatment of advanced HCC. Multidisciplinary comprehensive treatment including surgical resection, transarterial chemoembolization (TACE), or radiofrequency ablation (RFA) combined with systemic targeted and immunotherapy has become an effective strategy and inevitable trend for the treatment of advanced HCC. Combined therapy has greatly improved the prognosis and opened up a new milestone in the treatment of HCC. In this article, we review the latest progress in the treatment of advanced HCC based on the literature reports, National Comprehensive Cancer Network (NCCN), and Chinese Society of Clinical Oncology (CSCO) guidelines, in order to further guide clinical practice.

## LOCAL TREATMENT OF HCC

### Surgical resection

Surgical resection is still the most effective treatment method for HCC. However, the resection rate is less than 30% and all patients are faced with the risk of further disease progression and liver function deterioration or even failure. It has been reported that if the intraoperative blood transfusion rate is less than 10%, the treatment-related mortality is less than 1%-3%, and the 5-year survival rate is more than 50%[6]. The recurrence rate post-surgical resection is high, most patients have tumor recurrence within 2 years after resection, and the 5-year recurrence rate is as high as 70%[3,7]. The surgical resection has been developed to the stage of anatomical hepatectomy, and the concept of minimally invasive and precise surgery has dominated the current treatment methods. At present, indocyanine green fluorescent staining and a 3D laparoscopic augmented reality navigation system are mainly used to help define the resection boundary. It makes up for the defects of lack of touch and limited vision in laparoscopic surgery, which improves the accuracy and safety of surgery to a certain extent[8].

Laparoscopic liver resection for malignant tumors was controversial, but a recent meta-analysis pointed out that compared with open hepatectomy, laparoscopic hepatectomy had no significant difference in OS and recurrence-free survival rate[9]. Generally, laparoscopic hepatectomy has the advantages of less bleeding, fewer postoperative complications, less pain, and quicker recovery in the short-term effect, but the long-term recurrence rate and OS are similar to those of open hepatectomy[10, 11]. At present, laparoscopic hepatectomy has accounted for 77% of all liver cancer operations[12]. Instead of laparoscopic surgery, robot-assisted hepatectomy has a

clearer vision, higher flexibility, and higher accuracy, and has incomparable advantages in a special location and the more complex anatomic environment as well. However, a meta-analysis indicated that robotic hepatectomy can greatly increase intraoperative blood loss, operation duration, and cost, and there is no difference in postoperative mortality, complication rate, and tumor prognosis. Compared with laparoscopic hepatectomy, robotic hepatectomy cannot significantly benefit patients [13].

Recently, the establishment of two-step hepatectomy method, associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), has made it possible for patients with huge liver mass with insufficient future liver remnant. In the first stage, portal vein ligation and hepatic parenchyma disconnection were performed. After the reserved liver volume increased to more than 40% of the standard liver volume, the second stage operation was performed to remove the liver lesions, which greatly improved the chance of resection of huge liver tumors or multiple tumors. However, it is undeniable that there are many problems with the operation of ALPPS. Postoperative liver failure is the most serious problem after ALPPS. At present, there are a variety of improved operation methods for ALPPS, which can improve the success rate to a certain extent [14-17]. 3D visualization, 3D printing, virtual reality technology, intraoperative navigation system, and augmented reality technology are also in fully developing.

### **Ablation**

Only 10%-20% of HCC patients can receive surgery [18]. Ablation is also an extremely important treatment for HCC patients. At present, RFA and microwave ablation (MA) are the most widely recognized [19]. For patients having a single lesion diameter less than 5 cm and 2-3 lesions with the largest lesion diameter less than 3 cm, no invasion of blood vessels, bile ducts, or adjacent organs, no distant metastasis at the same time, and the liver function at A or B level, either ablation or surgical resection can achieve a radical effect. RFA has certain advantages in terms of safety, patient experience, tolerance, postoperative complications, and recovery speed, and has become the preferred local ablation technology for the treatment of HCC. Studies have shown that the 3-year and 5-year OS rates have reached 65.7% and 51.6%, respectively [20].

There was no significant difference in the incidence of complications and long-term survival rate between MA and RFA. When the tumor diameter was more than 3 cm or close to the large blood vessels, MA should be considered better. The incidence of infection, pleural effusion, and abdominal bleeding after RFA was lower than that of surgical resection, but there was no significant difference in the incidence of postoperative fever and pain between RFA and surgical resection. Lee *et al* [21] conducted a 10-year study to follow the patients who received RFA therapy before liver transplantation, and to evaluate the effect of ablation therapy on the patients after liver transplantation. They found that the 5-year and 10-year OS rates of patients after liver transplantation were 75.8% and 42.2%, respectively, and the disease free survival rates were 71.1% and 39.6%, respectively [21]. These indicated that RFA could be used before liver transplantation and improve the therapeutic effect. RFA technology in combination with TACE or systemic drug therapy plays a significant role in the treatment of HCC now.

### **Liver transplantation**

Liver transplantation is one of the most ideal methods for the treatment of small HCC. However, patients often lose the chance of transplantation due to the donor shortage. Moreover, the application of systemic immunosuppressants post-transplantation can easily lead to a series of severe complications such as systemic infection, tumor recurrence, and metastasis. The criteria for liver transplantation are varied for HCC. European countries mostly refer to Milan standard [22], North American countries mostly refer to UCSF standard [23], and Chinese academician Zheng *et al* [24] put forward Hangzhou standard according to their national conditions [24]. In recent years, Xu *et al* [25] subdivided Hangzhou criteria into subtypes A and B again and found that the postoperative survival rate of type A patient was significantly better than that of type B [25].

For HCC patients who are not in the range of various standards, many scholars have proposed the down-stage treatment before liver transplantation. At present, there is no significant difference in the OS rate or tumor-free survival rate between the patients with successful down-stage treatment and those who meet the Milan standard [26,27]. Certainly, bridging therapy is also very necessary. It is generally believed that candidate patients should be given bridging therapy when the expected waiting time is more than 6 mo [28]. Bridging therapy can effectively reduce the withdrawal rate of

patients during the waiting period, but whether it can improve the prognosis of patients is still unclear. Right now, the 1, 2, and 3-year cumulative survival rates of liver transplantation for HCC are 82.04%, 72.45%, and 65.43%, respectively. However, once the tumor recurred, the median survival time was only 12.97 mo[29].

How to make the inclusion criteria more perfect, manage an ideal balance between immune rejection and defense, find a better postoperative adjuvant therapy, and reduce recurrence rate remains the hot issues of liver transplantation for HCC in the future.

### TACE

TACE is the most commonly used treatment in patients with advanced HCC. It is recommended to be used in stages Ib-IIIb, and as the first line treatment in stages IIB and IIIa according to the Chinese guidelines for the diagnosis and treatment of liver cancer[30]. At present, TACE treatment alone has some limitations due to the tortuous and complex of hepatic artery branches, which could not make the embolization and chemotherapy drugs accurately reach the tumor site. Second, repeated TACE treatment is easy to induce TACE resistance and liver function damage. It has been proposed that TACE is performed before ablation to block the blood supply and to reduce the tumor size. At the same time, the lesion can be more easily located due to the role of the contrast medium, which can largely improve the positioning accuracy and success rate of ablation[31]. TACE combined with surgery, ablation, chemotherapy, targeted or immunotherapy has shown promising good results in HCC patients.

### Radiotherapy

With the progress of radiotherapy technology, the application of stereotactic body radiotherapy (SBRT) has made significant progress and showed potential good results in the treatment of HCC. It is composed of three-dimensional conformal radiotherapy (3DCRT), intensity-modulated radiation therapy (IMRT), and volumetric intensity-modulated arc therapy (VMAT). A phase II clinical study of Mornex *et al*[32] has shown that high-dose 3DCRT is suitable for patients with unresectable small HCC with cirrhosis[32]. Kimura *et al*[33] found that SBRT combined with TACE was an effective and safe local treatment for small isolated primary HCC, with a complete response rate even reaching 96%[33]. However, the most severe adverse effect of radiation liver disease can be fatal in severe cases[34]. IMRT, like 3DCRT, can benefit in all stages of HCC. A study conducted by Kim *et al*[35] showed that the 2-year local control rate and OS rate were 80.9% and 81.3%, respectively[35]. IMRT is currently considered a promising radiotherapy technique with an objective relative risk of 43%-74% and 1-year survival rate of 45%-85% for HCC. However, more attention should be paid to hepatotoxicity and gastrointestinal toxicity when IMRT combined with targeted drug therapy is used[36].

Besides, the application of iodine-125 particles in the treatment of HCC has drawn more and more attention in recent years. The seeds were implanted directly into the tumor for early stage HCC, while implanting the seeds stent has achieved better results for late-stage HCC patients with portal vein tumor thrombus. Chen *et al* have reported that RFA combined with iodine-125 seed implantation showed more survival benefits than RFA treatment alone. The tumor recurrence rates at 1, 2, and 5 years in the combined group were significantly lower than those with RFA treatment alone (4.5%, 22.1%, and 39.8% *vs* 14.8%, 35.3%, and 57.4%, respectively), while the 1, 3, and 5-year survival rates were significantly higher in the combined group than in the RFA alone group (100%, 86.7%, and 66.1% *vs* 95.6%, 75.0%, and 47.0%, respectively)[37]. TACE combined with iodine-125 seed implantation also showed more survival benefits than TACE treatment alone. The median survival rate of the combined group was significantly higher than that of the TACE alone group (30 mo *vs* 18 mo), and the 1 and 3-year survival rate was also significantly higher in the combined group than that of the TACE alone group (89.1% and 65.5% *vs* 51.0% and 7.4%, respectively)[38]. Yang *et al*[39] have studied the effect of TACE combined with iodine 125 seed implantation in the treatment of HCC with portal vein tumor thrombosis. The median survival time of the combined group was significantly higher than that of the simple TACE group (210 d *vs* 154 d), and the survival rates at 90 d, 180 d, and 360 d in the combined group were significantly higher than those of the simple TACE group (97.6%, 58.9%, and 12.3% *vs* 92.5%, 30.7%, and 0%, respectively)[39].

Therefore, either iodine-125 seed internal or SBRT external radiotherapy combined with TACE or RFA and other local treatments for unresectable HCC has achieved encouraging results and significantly prolonged the OS time.

## SYSTEMIC TREATMENT OF HCC

### ***Molecular targeted therapy***

The advent of molecular targeted drugs is called the second revolution in cancer treatment, and it is a major breakthrough in the history of HCC therapy. Molecular targeted therapy has shown positive anti-tumor effects and brought hope to patients with advanced HCC. At present, a variety of targeted drugs for HCC have been used in the clinic, including sorafenib, regorafenib, lenvatinib, cabozantinib, *etc.* They mainly are multi-target tyrosine kinase inhibitors (TKI) targeting vascular endothelial growth factor receptor, platelet-derived growth factor receptor, fibroblast growth factor receptor, and receptor with tyrosine molecules.

Sorafenib has been used in HCC since 2017 as the first targeted drug. Among a number of global multicenter clinical studies such as the SHARP trial (Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol), sorafenib has shown good efficacy in the treatment of unresectable advanced HCC, the median survival time has been extended by more than 2.8 mo, and the adverse reactions are within the acceptable range[40,41]. Another study also showed that the median OS (mOS) of patients with Barcelona Clinic Liver Cancer B stage HCC treated with sorafenib was 15-20 mo[42]. Sorafenib, as the first multi-target molecular targeted drug approved for systemic treatment of liver cancer, is still widely recognized as the first-line treatment drug for advanced HCC.

Regorafenib is another multi-point TKI developed by Bayer company after sorafenib. Its targeted inhibitory effect is stronger than that of sorafenib, and the adverse reactions are similar. It is used for sequential therapy of disease progression after sorafenib treatment[43]. RESORCE study has shown that treatment with regorafenib could prolong the survival by 2-8 mo compared to the control group when the disease progresses[44]. Another study has showed that sequential therapy with sorafenib and regorafenib increased the mOS of patients with advanced HCC to 26 mo[45].

Lenvatinib was introduced in 2017. In a phase III clinical study[46], compared with sorafenib, it can prolong the OS by 1.3 mo, progression free survival (PFS) by 3.7 mo, disease progression time by 5.2 mo, and objective remission rate by 15%. This study also found that the mOS in China, including Taiwan and Hong Kong, was 4.8 mo longer than that in the sorafenib group. Lenvatinib has been approved by the Food and Drug Administration (FDA) of the United States and China authorization for the treatment of advanced HCC patients who had not received systematic treatment since 2019, and it was also listed as the first-line drug.

Also, cabozantinib, apatinib (Etam), and ramucirumab have been successful in clinical trials of HCC recently, and have been approved as second-line treatment drugs for HCC by FDA. CELESTIAL[47] found that cabozantinib was associated with a longer OS (2.2 mo longer) and PFS (3.3 mo longer) than the control group, but the incidence of adverse events doubled.

Ramucirumab is mainly used in patients with advanced HCC who have not been successfully treated with sorafenib. Patients with serum alpha-fetoprotein of 400 ng/mL or higher can benefit from ramucirumab[48].

So far, either sorafenib or lenvatinib, as the first line targeted therapy for HCC, has shown definite curative effects and potential application prospects, which is obviously superior to traditional chemotherapy. The combination of targeted drug with TACE or local ablation is the trend. As a sequential treatment of sorafenib resistance, regorafenib has been proved to have a significant rescue effect to further prolong the OS of HCC patients. How to prevent drug resistance and serious adverse reactions remains to be further studied.

### ***Immunotherapy***

Immunotherapy is the latest breakthrough in the treatment of advanced HCC and is called the third revolution in the history of cancer therapy, which is expected to cure HCC completely. Anti-programmed death 1 (PD-1) antibodies represented by pembrolizumab and nivolumab, and programmed cell death 1 ligand 1 (PD-L1) monoclonal antibodies represented by atezolizumab are currently the most studied and the fastest developed immunotherapy in the clinic.

Nivolumab is the first immune checkpoint inhibitor for advanced HCC approved by FDA. The CHECKMATE 040[49] trial showed that 22.5% of HCC patients had an objective response, and the mOS was 29 mo. Although subsequent phase III data did not show a statistically significant improvement in OS, clinically significant results were observed. The combination of nivolumab and ipilimumab resulted in an average sustained response time of 17.5 mo, 56% of patients lasted no less than 12 mo, and 31%

of patients lasted no less than 24 mo[50]. Based on this study, the FDA accelerated approval of the combination in March 2020.

Pembrolizumab is the second immunotherapy drug approved by FDA for advanced HCC. In the KEYNOTE-224[51] trial, pembrolizumab was safe and effective for HCC patients who had previously received sorafenib treatment. The adverse reactions were tolerable, with a response rate of 17% and median survival time of 13 mo. In the subsequent phase III trial of KEYNOTE-240[52], pembrolizumab was better than the control group in OS (13.9 mo *vs* 10.6 mo) and median PFS (3.0 mo *vs* 2.8 mo).

At present, there are more and more PD-1 mAbs in research and development around the world. Toripalimab, as the first PD-1 inhibitor independently developed in China, has been approved in December 2018. Since then, clinical trials in a variety of solid tumors have been carried out and achieved gratifying results. Camrelizumab is another PD-1 inhibitor produced in China, and a phase II trial[53] showed that in patients who had received at least one course of systemic therapy, camrelizumab achieved an objective response of 14.7% and 6-mo OS rate of 74.4%. Compared with other immune drugs, the disease control rate of camrelizumab is relatively low, and the PFS is slightly short. However, even with the poor baseline characteristics, camrelizumab still achieves a similar objective response rate. Reactive cutaneous capillary hyperplasia is a very common immune-related adverse reaction. But it is mild or moderate and clinically controllable. Camrelizumab has shown antitumor activity, preliminary survival benefits, and manageable safety in Chinese patients with advanced HCC, and may be a potential second-line or beyond treatment for patients with advanced HCC.

### Combination therapy

The combination of antiangiogenic and immune checkpoint inhibitor has shown a variety of synergistic anti-tumor effects and has opened the 2.0 era of tumor immunotherapy. Sorafenib or lenvatinib targeted therapy combined with PD-1 inhibitors is the commonly used combination therapy strategy for HCC presently. In a real case, the application of reduced lenvatinib combined with pembrolizumab for 8 mo resulted in continuous shrinkage of liver tumor, complete remission of the disease, and rapid reversal of liver failure caused by the huge liver tumor, and PFS reached as much as 19 mo with no sign of recurrence[54]. This combination plays a trump role in the treatment of advanced HCC. Based on the data from KEYNOTE-524[55] [overall response rate (ORR): 46%; CR: 11%; median PFS (mPFS): 9.3 mo; DCR: 88%] to the data of Chinese Professor Sun's real-world study[56] (ORR: 55.9%; CR: 15.30%; mPFS: 4.8 mo), we can see that the combination of lenvatinib and pembrolizumab improves the curative effect of advanced HCC significantly.

Most recently, IMbrave150[57], the world's first successful phase III clinical study of immunotherapy for HCC, has attracted extensive international attention and discussion. This study has showed that the OS and PFS rates of the atezolizumab and bevacizumab (T+A) combination group were significantly better than those of the sorafenib group in unresectable HCC patients who had not received previous treatment. Not only the risk of death was reduced by 42% and the OS was extended by 2.5 mo, but also the risk of disease progression or death was reduced by 41% and 27.3%, respectively. At the same time, in the combination group, the median time of deterioration of quality of life and function was significantly longer than that of PFS. Considering this excellent result, both FDA and American Society of Clinical Oncology (ASCO) guidelines recommend the T+A regimen as the superior first-line treatment for advanced HCC[58,59]. This combination is also recommended by CSCO as the first-line treatment for advanced HCC (version 2020).

Moreover, the ORIENT-32[60] study led by Chinese Dr. Fan has indicated that the combination of sintilimab and bevacizumab showed significant advantages over sorafenib in terms of OS (NR *vs* 10.4 mo) and mPFS (4.6 mo *vs* 2.8 mo). At the same time, the risk of disease progression and death was reduced by 43%, and the objective response rate was 5 times higher than that of sorafenib. The adverse effect of the combination group was controllable and well-tolerated, which was equivalent to sorafenib monotherapy. This is also the first phase III clinical study of PD-1 combined with antiangiogenic drugs in the first-line treatment of advanced HCC.

Besides, nivolumab combined with tremelimumab was authorized by FDA in 2019 to be used in patients with advanced HCC who had previously received sorafenib treatment. Compared with the single drug, the combined treatment of nivolumab and tremelimumab can prolong the mOS by 22.8 mo, and the safety is acceptable. At the same time, the combination of the two drugs can induce pathological complete remission in 29% of patients with resectable advanced HCC within 6 wk according to 2019 ASCO data. In January 2021, devaruzumab and tremelimumab were approved by

**Table 1 First and second-line treatments for advanced hepatocellular carcinoma**

Systemic treatment	Drug selection	
	First-line drugs	Second-line drugs
Targeted therapy	Sorafenib; Lenvatinib; Donafenib	Regorafenib; Cabozantinib; Apatinib
Immunotherapy	Nivolumab; Pembrolizumab	Camrelizumab; Ramucirumab; Durvalumab
Combination therapy	Atezolizumab + Bevacizumab (Preferred)	Camrelizumab + Apatinib (Phase Ia/Ib)
	Sintilimab + Bevacizumab analogs (Phase III)	Nivolumab + Ipilimumab (Phase II)
	Camrelizumab + Apatinib (Phase II)	Nivolumab + Ipilimumab + Cabozantinib (Phase II)
	Sintilimab + Anlotinib (Phase II)	
	Tremelimumab + Durvalumab (Phase II)	
	Pembrolizumab + Lenvatinib (Phase Ib)	
	Anlotinib + Penpulimab (Phase Ib/II)	

FDA for the treatment of patients with advanced HCC too. However, both of them remain to be further studied with a larger sample size (Table 1).

### **Multidisciplinary therapy**

Due to the complexity of HCC itself and the diversity of treatment methods, multidisciplinary therapy (MDT), including local treatment combined with targeted therapy and immunotherapy, is a new trend to guide the individualized comprehensive treatment. At present, HCC treatment has entered the 3.0 era. The overall goal of HCC therapy is to prolong the OS and maximize the quality of life of patients.

Although traditional surgery, ablation, and liver transplantation, as well as targeted therapy, immunotherapy, and multi-mode combination therapy, have constantly brought patient benefits, we cannot avoid the adverse reactions and drug selection problem, and even drug resistance. At present, there is no clinically useful marker to drive the choice of the treatment regimen, and it is impossible to predict the response to drugs and the effectiveness of treatment. In addition, we must consider the quality of life of the patients while considering the curative effect, to minimize the occurrence of adverse events. Therefore, it is particularly important to strengthen the whole process management of HCC patients and individualized comprehensive treatment under the guidance of MDT consultation. MDT mode is the general trend of malignant tumor treatment, and it is essential for liver cancer patients. This mode can quickly integrate the high-quality resources of different departments, and organically integrate the advantages of treatment methods of different disciplines to quickly develop the optimal individualized treatment plan for patients, so as to make the treatment of HCC toward the true individualization. With the promotion and application of MDT mode, not only can the treatment plan of patients be more standardized, accurate, and efficient, but it can also enable different disciplines to make common progress through mutual communication, deepen the basic research on the clinical and application of liver cancer, and standardize the diagnosis and treatment behavior of medical worker to ensure the quality and safety of medical treatment.

### **CONCLUSION**

In summary, it remains a great challenge in the treatment of HCC, in particularly for real time individualized therapy. The principle of HCC therapy is multidisciplinary comprehensive treatment based on surgery. The outcome may varies depends on the status of patient's primary liver disease, tumor stage, liver function reserve, surgeon's skills, drug or equipment availability, financial support, *etc.* Thus, a MDT consultation is very necessary to make a best treatment regimen and maximize the prognosis of HCC patients. According to the recent two major guidelines of NCCN and CSCO, surgical resection is first applied for patients with stages I and IIa HCC patients, TACE or ablation first for stage IIb, and TKI targeted drug and PD-1 or PD-L1 inhibitors apply for all unresectable HCC without liver function failure. Sorafenib and lenvatinib are equally divided as first-line target drugs, while A+T combination appears superior to other targeted drugs or combinations. Regorafenib as second-line sequen-

tial treatment after sorafenib has been affirmed. In the meantime, many new drugs are being constantly produced and more second-line and third-line drugs are being developed (Table 1). It can be predicted that besides surgical resection, ablation/TACE plus immunotherapy combined with targeted therapy may become the main first-line treatment in the near future, and the era of complete cure of liver cancer is not far off.

## REFERENCES

- 1 **Bangaru S**, Marrero JA, Singal AG. Review article: new therapeutic interventions for advanced hepatocellular carcinoma. *Aliment Pharmacol Ther* 2020; **51**: 78-89 [PMID: 31747082 DOI: 10.1111/apt.15573]
- 2 **Sung H**, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; **71**: 209-249 [PMID: 33538338 DOI: 10.3322/caac.21660]
- 3 **Lai E**, Astara G, Ziranu P, Pretta A, Migliari M, Dubois M, Donisi C, Mariani S, Liscia N, Impera V, Persano M, Tolu S, Balconi F, Pinna G, Spanu D, Pireddu A, Saba G, Camera S, Musio F, Puzzone M, Pusceddu V, Madeddu C, Casadei Gardini A, Scartozzi M. Introducing immunotherapy for advanced hepatocellular carcinoma patients: Too early or too fast? *Crit Rev Oncol Hematol* 2021; **157**: 103167 [PMID: 33271389 DOI: 10.1016/j.critrevonc.2020.103167]
- 4 **Allemani C**, Weir HK, Carreira H, Harewood R, Spika D, Wang XS, Bannon F, Ahn JV, Johnson CJ, Bonaventure A, Marcos-Gragera R, Stiller C, Azevedo e Silva G, Chen WQ, Ogunbiyi OJ, Rachet B, Soeberg MJ, You H, Matsuda T, Bielska-Lasota M, Storm H, Tucker TC, Coleman MP; CONCORD Working Group. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). *Lancet* 2015; **385**: 977-1010 [PMID: 25467588 DOI: 10.1016/S0140-6736(14)62038-9]
- 5 **Chen W**, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ, He J. Cancer statistics in China, 2015. *CA Cancer J Clin* 2016; **66**: 115-132 [PMID: 26808342 DOI: 10.3322/caac.21338]
- 6 **Bruix J**, Llovet JM. Prognostic prediction and treatment strategy in hepatocellular carcinoma. *Hepatology* 2002; **35**: 519-524 [PMID: 11870363 DOI: 10.1053/jhep.2002.32089]
- 7 **Llovet JM**, Schwartz M, Mazzaferro V. Resection and liver transplantation for hepatocellular carcinoma. *Semin Liver Dis* 2005; **25**: 181-200 [PMID: 15918147 DOI: 10.1055/s-2005-871198]
- 8 **Fang CH**, Zhang P, Luo HL, Zhu W, Zeng SL, Hu HY, Xiang N, Yang J, Zeng N, Fan YF, Jia FC, Liu LX. [Application of augmented-reality surgical navigation technology combined with ICG molecular fluorescence imaging in laparoscopic hepatectomy]. *Zhonghua Wai Ke Za Zhi* 2019; **57**: 578-584 [PMID: 31422626 DOI: 10.3760/cma.j.issn.0529-5815.2019.08.004]
- 9 **Jiang S**, Wang Z, Ou M, Pang Q, Fan D, Cui P. Laparoscopic Versus Open Hepatectomy in Short- and Long-Term Outcomes of the Hepatocellular Carcinoma Patients with Cirrhosis: A Systematic Review and Meta-Analysis. *J Laparoendosc Adv Surg Tech A* 2019; **29**: 643-654 [PMID: 30702362 DOI: 10.1089/lap.2018.0588]
- 10 **Jarnagin W**, Chapman WC, Curley S, D'Angelica M, Rosen C, Dixon E, Nagorney D; American Hepato-Pancreato-Biliary Association; Society of Surgical Oncology; Society for Surgery of the Alimentary Tract. Surgical treatment of hepatocellular carcinoma: expert consensus statement. *HPB (Oxford)* 2010; **12**: 302-310 [PMID: 20590903 DOI: 10.1111/j.1477-2574.2010.00182.x]
- 11 **Parks KR**, Kuo YH, Davis JM, O'Brien B, Hagopian EJ. Laparoscopic versus open liver resection: a meta-analysis of long-term outcome. *HPB (Oxford)* 2014; **16**: 109-118 [PMID: 23672270 DOI: 10.1111/hpb.12117]
- 12 **Cai XJ**, Zheng Q, Jiang GY. [Current status and prospect of surgical treatment of liver cancer]. *Zhonghua Wai Ke Za Zhi* 2019; **57**: 494-499 [PMID: 31269609 DOI: 10.3760/cma.j.issn.0529-5815.2019.07.003]
- 13 **Hu L**, Yao L, Li X, Jin P, Yang K, Guo T. Effectiveness and safety of robotic-assisted versus laparoscopic hepatectomy for liver neoplasms: A meta-analysis of retrospective studies. *Asian J Surg* 2018; **41**: 401-416 [PMID: 28912048 DOI: 10.1016/j.asjsur.2017.07.001]
- 14 **Petrowsky H**, Györi G, de Oliveira M, Lesurtel M, Clavien PA. Is partial-ALPPS safer than ALPPS? *Ann Surg* 2015; **261**: e90-e92 [PMID: 25706390 DOI: 10.1097/SLA.0000000000001087]
- 15 **Robles R**, Parrilla P, López-Conesa A, Brusadin R, de la Peña J, Fuster M, García-López JA, Hernández E. Tourniquet modification of the associating liver partition and portal ligation for staged hepatectomy procedure. *Br J Surg* 2014; **101**: 1129-34; discussion 1134 [PMID: 24947768 DOI: 10.1002/bjs.9547]
- 16 **Xiao L**, Li JW, Zheng SG. Totally laparoscopic ALPPS in the treatment of cirrhotic hepatocellular carcinoma. *Surg Endosc* 2015; **29**: 2800-2801 [PMID: 25515978 DOI: 10.1007/s00464-014-4000-1]
- 17 **Schadde E**, Raptis DA, Schnitzbauer AA, Ardiles V, Tschuur C, Lesurtel M, Abdalla EK, Hernandez-Alejandro R, Jovine E, Machado M, Malago M, Robles-Campos R, Petrowsky H, Santibanes ED, Clavien PA. Prediction of Mortality After ALPPS Stage-1: An Analysis of 320 Patients From the International ALPPS Registry. *Ann Surg* 2015; **262**: 780-5; discussion 785-6 [PMID: 26583666 DOI: 10.1097/SLA.0000000000001450]
- 18 **Minami Y**, Kudo M. Radiofrequency ablation of hepatocellular carcinoma: Current status. *World J Radiol* 2010; **2**: 417-424 [PMID: 21179308 DOI: 10.4329/wjr.v2.i11.417]

- 19 **Lencioni R**, Crocetti L. Local-regional treatment of hepatocellular carcinoma. *Radiology* 2012; **262**: 43-58 [PMID: [22190656](#) DOI: [10.1148/radiol.11110144](#)]
- 20 **Choi D**, Lim HK, Rhim H, Kim YS, Lee WJ, Paik SW, Koh KC, Lee JH, Choi MS, Yoo BC. Percutaneous radiofrequency ablation for early-stage hepatocellular carcinoma as a first-line treatment: long-term results and prognostic factors in a large single-institution series. *Eur Radiol* 2007; **17**: 684-692 [PMID: [17093964](#) DOI: [10.1007/s00330-006-0461-5](#)]
- 21 **Lee MW**, Raman SS, Asvadi NH, Siripongsakun S, Hicks RM, Chen J, Worakitsitatorn A, McWilliams J, Tong MJ, Finn RS, Agopian VG, Busutil RW, Lu DSK. Radiofrequency ablation of hepatocellular carcinoma as bridge therapy to liver transplantation: A 10-year intention-to-treat analysis. *Hepatology* 2017; **65**: 1979-1990 [PMID: [28170115](#) DOI: [10.1002/hep.29098](#)]
- 22 **Mazzaferro V**, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693-699 [PMID: [8594428](#) DOI: [10.1056/NEJM199603143341104](#)]
- 23 **Yao FY**, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology* 2001; **33**: 1394-1403 [PMID: [11391528](#) DOI: [10.1053/jhep.2001.245663](#)]
- 24 **Zheng SS**, Xu X, Wu J, Chen J, Wang WL, Zhang M, Liang TB, Wu LM. Liver transplantation for hepatocellular carcinoma: Hangzhou experiences. *Transplantation* 2008; **85**: 1726-1732 [PMID: [18580463](#) DOI: [10.1097/TP.0b013e31816b67e4](#)]
- 25 **Xu X**, Lu D, Ling Q, Wei X, Wu J, Zhou L, Yan S, Wu L, Geng L, Ke Q, Gao F, Tu Z, Wang W, Zhang M, Shen Y, Xie H, Jiang W, Wang H, Zheng S. Liver transplantation for hepatocellular carcinoma beyond the Milan criteria. *Gut* 2016; **65**: 1035-1041 [PMID: [25804634](#) DOI: [10.1136/gutjnl-2014-308513](#)]
- 26 **Yao FY**, Mehta N, Flemming J, Dodge J, Hameed B, Fix O, Hirose R, Fidelman N, Kerlan RK Jr, Roberts JP. Downstaging of hepatocellular cancer before liver transplant: long-term outcome compared to tumors within Milan criteria. *Hepatology* 2015; **61**: 1968-1977 [PMID: [25689978](#) DOI: [10.1002/hep.27752](#)]
- 27 **Kulik L**, Heimbach JK, Zaiem F, Almasri J, Prokop LJ, Wang Z, Murad MH, Mohammed K. Therapies for patients with hepatocellular carcinoma awaiting liver transplantation: A systematic review and meta-analysis. *Hepatology* 2018; **67**: 381-400 [PMID: [28859222](#) DOI: [10.1002/hep.29485](#)]
- 28 **Majno P**, Lencioni R, Mornex F, Girard N, Poon RT, Cherqui D. Is the treatment of hepatocellular carcinoma on the waiting list necessary? *Liver Transpl* 2011; **17** Suppl 2: S98-108 [PMID: [21954097](#) DOI: [10.1002/lt.22391](#)]
- 29 **de'Angelis N**, Landi F, Carra MC, Azoulay D. Managements of recurrent hepatocellular carcinoma after liver transplantation: A systematic review. *World J Gastroenterol* 2015; **21**: 11185-11198 [PMID: [26494973](#) DOI: [10.3748/wjg.v21.i39.11185](#)]
- 30 **Qiu G**, Jin Z, Chen X, Huang J. Interpretation of guidelines for the diagnosis and treatment of primary liver cancer (2019 edition) in China. *Glob Health Med* 2020; **2**: 306-311 [PMID: [33330825](#) DOI: [10.35772/ghm.2020.01051](#)]
- 31 **Yamagiwa K**, Shiraki K, Yamakado K, Mizuno S, Hori T, Yagi S, Hamada T, Iida T, Nakamura I, Fujii K, Usui M, Isaji S, Ito K, Tagawa S, Takeda K, Yokoi H, Noguchi T. Survival rates according to the Cancer of the Liver Italian Program scores of 345 hepatocellular carcinoma patients after multimodality treatments during a 10-year period in a retrospective study. *J Gastroenterol Hepatol* 2008; **23**: 482-490 [PMID: [18086115](#) DOI: [10.1111/j.1440-1746.2007.05262.x](#)]
- 32 **Mornex F**, Girard N, Beziat C, Kubas A, Khodri M, Trepo C, Merle P. Feasibility and efficacy of high-dose three-dimensional-conformal radiotherapy in cirrhotic patients with small-size hepatocellular carcinoma non-eligible for curative therapies--mature results of the French Phase II RTF-1 trial. *Int J Radiat Oncol Biol Phys* 2006; **66**: 1152-1158 [PMID: [17145534](#) DOI: [10.1016/j.ijrobp.2006.06.015](#)]
- 33 **Kimura T**, Aikata H, Doi Y, Imano N, Takeuchi Y, Takahashi I, Nishibuchi I, Katsuta T, Kenjo M, Murakami Y, Awai K, Chayama K, Nagata Y. Comparison of Stereotactic Body Radiation Therapy Combined With or Without Transcatheter Arterial Chemoembolization for Patients With Small Hepatocellular Carcinoma Ineligible for Resection or Ablation Therapies. *Technol Cancer Res Treat* 2018; **17**: 1533033818783450 [PMID: [29963972](#) DOI: [10.1177/1533033818783450](#)]
- 34 **Pan CC**, Kavanagh BD, Dawson LA, Li XA, Das SK, Miften M, Ten Haken RK. Radiation-associated liver injury. *Int J Radiat Oncol Biol Phys* 2010; **76**: S94-100 [PMID: [20171524](#) DOI: [10.1016/j.ijrobp.2009.06.092](#)]
- 35 **Kim JW**, Kim DY, Han KH, Seong J. Phase I/II trial of helical IMRT-based stereotactic body radiotherapy for hepatocellular carcinoma. *Dig Liver Dis* 2019; **51**: 445-451 [PMID: [30503296](#) DOI: [10.1016/j.dld.2018.11.004](#)]
- 36 **Bae SH**, Jang WI, Park HC. Intensity-modulated radiotherapy for hepatocellular carcinoma: dosimetric and clinical results. *Oncotarget* 2017; **8**: 59965-59976 [PMID: [28938697](#) DOI: [10.18632/oncotarget.19219](#)]
- 37 **Chen K**, Chen G, Wang H, Li H, Xiao J, Duan X, He J, He K, Xiang G. Increased survival in hepatocellular carcinoma with iodine-125 implantation plus radiofrequency ablation: a prospective randomized controlled trial. *J Hepatol* 2014; **61**: 1304-1311 [PMID: [25064436](#) DOI: [10.1016/j.jhep.2014.07.026](#)]

- 38 **Li M**, He J, Pan M, Yu Y, Pan Z, Xu B, Zhu J. Iodine-125 implantation plus transarterial chemoembolization for the treatment of hepatocellular carcinoma of 3-5cm: A propensity score matching study. *Dig Liver Dis* 2016; **48**: 1082-1087 [PMID: [27365224](#) DOI: [10.1016/j.dld.2016.06.007](#)]
- 39 **Yang M**, Fang Z, Yan Z, Luo J, Liu L, Zhang W, Wu L, Ma J, Yang Q, Liu Q. Transarterial chemoembolisation (TACE) combined with endovascular implantation of an iodine-125 seed strand for the treatment of hepatocellular carcinoma with portal vein tumour thrombosis versus TACE alone: a two-arm, randomised clinical trial. *J Cancer Res Clin Oncol* 2014; **140**: 211-219 [PMID: [24374800](#) DOI: [10.1007/s00432-013-1568-0](#)]
- 40 **Llovet JM**, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378-390 [PMID: [18650514](#) DOI: [10.1056/NEJMoa0708857](#)]
- 41 **Cheng AL**, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, Xu J, Sun Y, Liang H, Liu J, Wang J, Tak WY, Pan H, Burock K, Zou J, Voliotis D, Guan Z. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; **10**: 25-34 [PMID: [19095497](#) DOI: [10.1016/S1470-2045\(08\)70285-7](#)]
- 42 **Ganten TM**, Stauber RE, Schott E, Malfertheiner P, Buder R, Galle PR, Göhler T, Walther M, Koschny R, Gerken G. Sorafenib in Patients with Hepatocellular Carcinoma-Results of the Observational INSIGHT Study. *Clin Cancer Res* 2017; **23**: 5720-5728 [PMID: [28698202](#) DOI: [10.1158/1078-0432.CCR-16-0919](#)]
- 43 **Bruix J**, Tak WY, Gasbarrini A, Santoro A, Colombo M, Lim HY, Mazzaferro V, Wiest R, Reig M, Wagner A, Bolondi L. Regorafenib as second-line therapy for intermediate or advanced hepatocellular carcinoma: multicentre, open-label, phase II safety study. *Eur J Cancer* 2013; **49**: 3412-3419 [PMID: [23809766](#) DOI: [10.1016/j.ejca.2013.05.028](#)]
- 44 **Bruix J**, Qin S, Merle P, Granito A, Huang YH, Bodoky G, Pracht M, Yokosuka O, Rosmorduc O, Breder V, Gerolami R, Masi G, Ross PJ, Song T, Bronowicki JP, Ollivier-Hourmand I, Kudo M, Cheng AL, Llovet JM, Finn RS, LeBerre MA, Baumhauer A, Meinhardt G, Han G; RESORCE Investigators. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017; **389**: 56-66 [PMID: [27932229](#) DOI: [10.1016/S0140-6736\(16\)32453-9](#)]
- 45 **Finn RS**, Merle P, Granito A, Huang YH, Bodoky G, Pracht M, Yokosuka O, Rosmorduc O, Gerolami R, Caparello C, Cabrera R, Chang C, Sun W, LeBerre MA, Baumhauer A, Meinhardt G, Bruix J. Outcomes of sequential treatment with sorafenib followed by regorafenib for HCC: Additional analyses from the phase III RESORCE trial. *J Hepatol* 2018; **69**: 353-358 [PMID: [29704513](#) DOI: [10.1016/j.jhep.2018.04.010](#)]
- 46 **Kudo M**, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, Baron A, Park JW, Han G, Jassem J, Blanc JF, Vogel A, Komov D, Evans TRJ, Lopez C, Dutcus C, Guo M, Saito K, Kraljevic S, Tamai T, Ren M, Cheng AL. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018; **391**: 1163-1173 [PMID: [29433850](#) DOI: [10.1016/S0140-6736\(18\)30207-1](#)]
- 47 **Abou-Alfa GK**, Meyer T, Cheng AL, El-Khoueiry AB, Rimassa L, Ryoo BY, Cicin I, Merle P, Chen Y, Park JW, Blanc JF, Bolondi L, Klumpen HJ, Chan SL, Zagonel V, Pressiani T, Ryu MH, Venook AP, Hessel C, Borgman-Hagey AE, Schwab G, Kelley RK. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. *N Engl J Med* 2018; **379**: 54-63 [PMID: [29972759](#) DOI: [10.1056/NEJMoa1717002](#)]
- 48 **Kudo M**, Hatano E, Ohkawa S, Fujii H, Masumoto A, Furuse J, Wada Y, Ishii H, Obi S, Kaneko S, Kawazoe S, Yokosuka O, Ikeda M, Ukai K, Morita S, Tsuji A, Kudo T, Shimada M, Osaki Y, Tateishi R, Sugiyama G, Abada PB, Yang L, Okusaka T, Zhu AX. Ramucirumab as second-line treatment in patients with advanced hepatocellular carcinoma: Japanese subgroup analysis of the REACH trial. *J Gastroenterol* 2017; **52**: 494-503 [PMID: [27549242](#) DOI: [10.1007/s00535-016-1247-4](#)]
- 49 **El-Khoueiry AB**, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, Kim TY, Choo SP, Trojan J, Welling TH Rd, Meyer T, Kang YK, Yeo W, Chopra A, Anderson J, Dela Cruz C, Lang L, Neely J, Tang H, Dastani HB, Melero I. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet* 2017; **389**: 2492-2502 [PMID: [28434648](#) DOI: [10.1016/S0140-6736\(17\)31046-2](#)]
- 50 **He AR**, Yau T, Hsu C, Kang YK, El-Khoueiry AB. Nivolumab + ipilimumab combination therapy in patients with advanced hepatocellular carcinoma: subgroup analysis from CheckMate 040. *J Clin Oncol* 2020; **38** (4\_suppl): 512 [DOI: [10.1200/JCO.2020.38.4\\_suppl.512](#)]
- 51 **Zhu AX**, Finn RS, Edeline J, Cattani S, Ogasawara S, Palmer D, Verslype C, Zagonel V, Fartoux L, Vogel A, Sarker D, Verset G, Chan SL, Knox J, Daniele B, Webber AL, Ebbinghaus SW, Ma J, Siegel AB, Cheng AL, Kudo M; KEYNOTE-224 investigators. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. *Lancet Oncol* 2018; **19**: 940-952 [PMID: [29875066](#) DOI: [10.1016/S1470-2045\(18\)30351-6](#)]
- 52 **Finn RS**, Ryoo BY, Merle P, Kudo M, Bouattour M, Lim HY, Breder V, Edeline J, Chao Y,

- Ogasawara S, Yau T, Garrido M, Chan SL, Knox J, Daniele B, Ebbinghaus SW, Chen E, Siegel AB, Zhu AX, Cheng AL; KEYNOTE-240 investigators. Pembrolizumab As Second-Line Therapy in Patients With Advanced Hepatocellular Carcinoma in KEYNOTE-240: A Randomized, Double-Blind, Phase III Trial. *J Clin Oncol* 2020; **38**: 193-202 [PMID: 31790344 DOI: 10.1200/JCO.19.01307]
- 53 **Qin S**, Ren Z, Meng Z, Chen Z, Chai X, Xiong J, Bai Y, Yang L, Zhu H, Fang W, Lin X, Chen X, Li E, Wang L, Chen C, Zou J. Camrelizumab in patients with previously treated advanced hepatocellular carcinoma: a multicentre, open-label, parallel-group, randomised, phase 2 trial. *Lancet Oncol* 2020; **21**: 571-580 [PMID: 32112738 DOI: 10.1016/S1470-2045(20)30011-5]
- 54 **Liu Z**, Li X, He X, Xu Y, Wang X. Complete response to the combination of Lenvatinib and Pembrolizumab in an advanced hepatocellular carcinoma patient: a case report. *BMC Cancer* 2019; **19**: 1062 [PMID: 31703571 DOI: 10.1186/s12885-019-6287-8]
- 55 **Sun HC**, Zhu XD, Huang C, Shen YH, Fan J. Combination therapy with lenvatinib and anti-PD-1 antibodies for unresectable or advanced hepatocellular carcinoma: A real-world study. *J Clin Oncol* 2020; **38**: e16610-e16610 [DOI: 10.1200/JCO.2020.38.15\_suppl.e16610]
- 56 **Lee CH**, Shah AY, Hsieh JJ, Rao A, Pinto A, Bilen MA, Cohn AL, Simone CD, Shaffer DR, Sarrio RG. Phase II trial of lenvatinib (LEN) plus pembrolizumab (PEMBRO) for disease progression after PD-1/PD-L1 immune checkpoint inhibitor (ICI) in metastatic clear cell renal cell carcinoma (mccRCC). *J Clin Oncol* 2020; **38**: 5008-5008 [DOI: 10.1200/JCO.2020.38.15\_suppl.5008]
- 57 **Finn RS**, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Xu DZ, Hernandez S, Liu J, Huang C, Mulla S, Wang Y, Lim HY, Zhu AX, Cheng AL; IMbrave150 Investigators. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *N Engl J Med* 2020; **382**: 1894-1905 [PMID: 32402160 DOI: 10.1056/NEJMoa1915745]
- 58 **Casak SJ**, Donoghue M, Fashoyin-Aje L, Jiang X, Rodriguez L, Shen YL, Xu Y, Liu J, Zhao H, Pierce WF, Mehta S, Goldberg KB, Theoret MR, Kluetz PG, Pazdur R, Lemery SJ. FDA Approval Summary: Atezolizumab Plus Bevacizumab for the Treatment of Patients with Advanced Unresectable or Metastatic Hepatocellular Carcinoma. *Clin Cancer Res* 2021; **27**: 1836-1841 [PMID: 33139264 DOI: 10.1158/1078-0432.CCR-20-3407]
- 59 **Gordan JD**, Kennedy EB, Abou-Alfa GK, Beg MS, Brower ST, Gade TP, Goff L, Gupta S, Guy J, Harris WP, Iyer R, Jaiyesimi I, Jhaver M, Karippot A, Kaseb AO, Kelley RK, Knox JJ, Kortmansky J, Leaf A, Remak WM, Shroff RT, Sohal DPS, Taddei TH, Venepalli NK, Wilson A, Zhu AX, Rose MG. Systemic Therapy for Advanced Hepatocellular Carcinoma: ASCO Guideline. *J Clin Oncol* 2020; **38**: 4317-4345 [PMID: 33197225 DOI: 10.1200/JCO.20.02672]
- 60 **Ren Z**, Fan J, Xu J, Bai Y, Xu A, Cang S, Du C, Liu B, Li Q, Lu Y. LBA2 Sintilimab plus bevacizumab biosimilar vs sorafenib as first-line treatment for advanced hepatocellular carcinoma (ORIENT-32). *Ann Oncol* 2020; **31** [DOI: 10.1016/j.annonc.2020.10.134]



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