Review Article

# The Hong Kong consensus statements on unresectable hepatocellular carcinoma: narrative review and update for 2021

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**Background and Objective:** Hong Kong, like many parts of Asia, faces a high burden of hepatocellular carcinoma (HCC) caused by high endemic rates of hepatitis B virus infection. Hong Kong clinicians have developed a high level of expertise in HCC treatment across surgical, transarterial, ablative, radiotherapeutic and systemic modalities. This publication summarizes the latest evidence-based recommendations on how these modalities should be used.

**Methods:** In two meetings held in 2020, a multidisciplinary panel of surgeons, oncologists and interventional radiologists performed a narrative review of evidence on the management of HCC, with an emphasis on treatment of HCC not amenable to surgical resection. Close attention was paid to new evidence published since the previous version of these statements in 2018.

**Key Content and Findings:** The expert panel has formulated 60 consensus statements to guide the staging and treatment of unresectable HCC. Since the previous version of these statements, considerable additions have been made to the recommendations on use of targeted therapies and immunotherapies because of the large volume of new evidence.

**Conclusions:** Our consensus statements offer guidance on how to select HCC patients for surgical or non-surgical treatment and for choosing among non-surgical modalities for patients who are not candidates for

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resection. In particular, there is a need for more evidence to aid physicians in the selection of second-line systemic therapies, as currently most data are limited to patients with disease progression on first-line sorafenib.

**Keywords:** Hepatocellular carcinoma (HCC); Hong Kong; guidelines; consensus

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## Introduction

Liver cancer, predominantly hepatocellular carcinoma (HCC), imposes a great burden in Asia. Because of the high endemic rates of hepatitis B virus (HBV) infection, more than 70% of all new liver cancer cases are diagnosed in the Asia-Pacific region (1), and HCC is the third most common cause of cancer death (2). Hong Kong is no exception; according to local registry data from 2018, HCC was the fifth most common type of cancer by incidence and third most common cause of cancer death in the territory (3).

In Hong Kong, liver cancer is treated with both surgical and nonsurgical approaches. Non-surgical modalities include transcatheter arterial chemoembolization (TACE), transcatheter arterial radioembolization (TARE), stereotactic body radiation therapy (SBRT), systemic chemotherapy, and more recently immunotherapy and targeted agents. The surgical treatments for HCC are liver resection and transplantation, and because of the high case load and high level of expertise in Asia, surgical resection is recommended for a broader population of HCC patients than elsewhere (4-6).

The high level of experience with HCC in Hong Kong has resulted in the creation and evolution of several documents to guide specialists who treat HCC patients. The Hong Kong Liver Cancer (HKLC) staging system is a locally developed and validated algorithm that can identify HCC patients suited to more aggressive treatment approaches that maximize overall survival (OS) (4). The HKLC staging system is complemented by consensus statements, first published in 2015 (7) and updated in 2018 (8), that provide additional guidance for the treatment of unresectable HCC. Since 2018, there has been a considerable volume of new data published, particularly on the use of targeted therapies and immunotherapy for unresectable HCC. Therefore, the objective of this publication is to update the consensus statements, with an emphasis on incorporating these new data.

The recommendations in this publication were formulated during two online meetings held in September and October 2020. A group of Hong Kong clinicians including surgeons, medical oncologists, clinical oncologists, and interventional radiologists convened to review and update consensus statements on the management of unresectable HCC. The group was selected to comprise local experts with a high level of clinical experience in HCC treatment from universities and hospitals, forming a panel that was representative of local institutions and specialties. The consensus statements were developed using the same process as the previous statements published in 2018 (8). Designated specialists reviewed the literature, prepared summary presentations of relevant clinical data and formulated consensus statements ahead of the meetings. During the meetings the supporting evidence was presented to the panel, and evaluated by the panel using a Likert scale (1—accept completely; 2—accept with some reservations; 3—accept with major reservations; 4—reject with reservations; 5—reject completely). Voting was performed anonymously to encourage independent responses and acceptance was defined as 80% of the group accepting a statement completely or with some reservations. If a consensus was not met, statements were revised and voted on until a consensus was met. The group evaluated each statement's level of evidence as per the Oxford Centre for Evidence-Based Medicine's 2011 Levels of Evidence (9). To assist readers' understanding of the changes to the statements since the previous version, revised statements are presented alongside the 2018 versions. As there are few new data on systemic chemotherapy in HCC, we have not covered this topic in this update; our recommendations for systemic chemotherapy can be found in the 2018 consensus statements (8). We present this article in accordance with the Narrative Review reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-405/rc).

## Consensus statements

### *The role of staging systems*

(I) *The BCLC staging system is not conventionally used to stratify HCC patients for treatment in Hong Kong (accepted without revision from 2018).*

(II) *The HKLC staging system provides a better prognostic classification and treatment algorithm than BCLC (Level 2).*

*Original 2018 statement*: *the HKLC staging system provides a better prognostic classification and treatment algorithm than BCLC in a HBV-predominant population*.

(III) *In patients with intermediate and locally advanced HCC, HKLC is better than BCLC in stratifying patients into various treatment modalities (Level 2).*

*Original 2018 statement*: *in patients from an HBV-predominant population with intermediate and locally advanced HCC, HKLC staging is better than BCLC in stratifying patients into various treatment modalities*.

(IV) *With a rapidly evolving landscape in HCC treatment, an updated staging system which incorporates all the new treatments is necessary (new statement).*

The challenge in HCC is that physicians must simultaneously treat both a highly malignant tumor as well as associated cirrhosis and impaired liver function. To meet this challenge, various systems for staging and management have been devised. The most commonly used of these in Western countries is the Barcelona Clinic Liver Cancer (BCLC) (10). The BCLC staging system was originally developed in populations where hepatitis C virus (HCV) infection, alcohol-related cirrhosis, and non-alcoholic fatty liver disease (NAFLD) are the predominant etiologies of HCC, whereas in Asia, HBV infection is the predominant cause (8). The tumor, node, metastasis (TNM) system is widely used in the USA for HCC patients, but has some disadvantages including a lack of homogeneity in outcomes for patients within certain current TNM categories, and poor stratification of survival at intermediate stages (11). As the recommended treatments, particularly the indications for surgery, from BCLC staging are perceived as too conservative in Asia, expert groups in Asia-Pacific have devised alternate staging systems incorporating local experience. The Hong Kong Liver Cancer (HKLC) staging system was developed using patient data from 3,856 patients treated for HCC in Hong Kong between 1995 and 2008 (4). The HKLC staging system allocates patients to resection, ablation, transplantation, TACE, systemic therapy, or supportive care based on tumor characteristics, presence of venous invasion and Child-Pugh status. Compared to BCLC, HKLC uses more 'granular' data regarding tumor size, nodules and vascular invasion and identifies patients with intermediate or advanced HCC who may benefit from more aggressive treatments (12). In a validation study in 668 Chinese HCC patients who were treated at the Hospital of Nanjing University, HKLC had a better discriminatory ability and higher predictive power than BCLC (13). In another validation study in North America, the HKLC was validated for determining prognosis in 881 patients who had unresectable HCC and underwent intra-arterial therapy (IAT) at the Johns Hopkins Hospital (14). In this study, the HKLC system consistently demonstrated significantly improved calibration, discrimination, monotonicity/homogeneity, and survival curve separation over the BCLC system (14). The HKLC system is recognized as a step forward from the BCLC (12), especially in Asian populations, and further validation in non-Asians may help refine its use for other patient populations. However developing staging systems that appropriately balance the complexity of allocating patients to an expanding variety of treatment options, in particular the recent advent of immunotherapy treatment, while maintaining ease of use will be an ongoing challenge.

### *The role of liver resection*

(V) *Liver resection should be considered as a first-line curative treatment for solitary or multifocal HCC confined to the liver, anatomically resectable, and with satisfactory liver function reserve (accepted without revision from 2018).*

(VI) *Liver resection should be considered in HKLC locally advanced HCC when adequate function of future liver remnant (FLR) is anticipated.*

*Original 2018 statement*: *liver resection should be considered in locally advanced tumor when adequate function of FLR is anticipated*.

(VII) *Resection may be considered in patients with intrahepatic portal vein or hepatic vein branch invasion; resection of such patients should only be considered in specialized centers (accepted without revision from 2018).*

(VIII) *Resection of primary hepatic tumor and resection/ablation of isolated extrahepatic metastasis can be considered in selected patients.*

*Original 2018 statement*: *resection of both isolated extrahepatic metastasis and hepatic resection can be considered in selected patients*.

(IX) *Patients with bilobar tumor (a predominant large mass in one lobe and one or two small tumor nodules in the other lobe) may benefit from combined resection of the predominant tumor and*

*resection or ablation of the contralateral nodules (Level 4) (accepted without revision from 2018).*

Outcomes of hepatectomy are influenced by three key factors including patient and tumor characteristics and liver function (15). The size of the tumor and extent of extrahepatic involvement, presence of cirrhosis or fatty liver, and age of the patient and any existing comorbidities are known to affect the outcomes of hepatectomy (4,16-19).

In addition to the parameters specified in the HKLC staging system, assessment of liver function by indocyanine green (ICG) retention and computed tomography (CT) assessment of the volume of the FLR are useful for assessing candidates for resection. Experience suggests that a FLR ≥20% may be appropriate for patients with normal liver function (20,21), but this should be increased for patients exposed to chemotherapy (FLR >30%) or those with cirrhosis (FLR >40%) (22,23).

Portal vein thrombosis (PVT)—occlusion of the portal vein by a tumor—is driven by the high propensity of HCC for veinous invasion and is a common complication in advanced HCC (24). If the thrombus extends extrahepatically into the main portal vein, circulation to the entire liver is reduced (24). Thrombi may also occur in the inferior vena cava (IVC), but at a lower incidence than PVT (25). Historically, HCC patients with venous invasion have had a poor prognosis (24-26), but their treatment options are evolving. In Asia, vascular invasion is not considered an absolute contradiction to HCC resection, and a growing body of evidence supports the use of surgery in selected patients with PVT or IVC thrombosis (24-26). However, patients with thrombi in the main portal vein or IVC require complex surgery including vascular reconstruction or resection in addition to hepatectomy (26). Therefore, such patients must be referred to expert centers.

Partial hepatectomy is indicated for unilobar HCC with no venous invasion in patients with no severe chronic illness and acceptable liver function (Child-Pugh A and 15-minute ICG retention <14%). The safety and efficacy of partial hepatectomy combined with radiofrequency ablation (RFA) was demonstrated in a case comparison study of HCC patients in Hong Kong, including patients with bilobar disease, treated with RFA and resection (n=19) or resection alone (n=54) (27). Combined RFA and resection was found to be effective for treatment of multifocal HCC, with similar rates of complications to resection alone (27). Similar conclusions on the efficacy of RFA combined with resection were reached in a Korean study of 53 patients with multifocal HCC, 29 of whom had bilobar disease (28).

### *The role of portal vein embolization (PVE), ALPPS, and liver transplantation*

(X) *For patients with inadequate FLR, PVE may increase the chance of resection (Level 3) (accepted without revision from 2018).*

(XI) *The application of ALPPS may be considered as an alternative option to increase resectability in patients with inadequate FLR reserve (Level 5) (new statement).*

(XII) *Liver transplantation is a treatment option for HCC patients with poor liver function, following local transplant criteria (Level 4) (new statement).*

In selected patients with HCC and inadequate FLR, PVE can be used to induce hypertrophy of the liver and thus increase FLR and improve their eligibility for surgery (29). A meta-analysis that included 2,144 patients concluded that PVE was safe and effective with low perioperative morbidities and good long-term outcomes (29).

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) is an alternative method of inducing liver hypertrophy, although initial data suggested it was associated with a higher risk of postoperative mortality than PVE (approximately 8% *vs.* 4%, respectively, after procedure and liver resection) (29,30). However, emerging evidence suggests that ALPPS can be performed safely in HCC if the patient selection criteria are followed rigorously (31-33). For example, a case review of 148 HCC patients found no difference in hospital mortality rate for PVE compared with ALPPS (6.5% *vs.* 5.8%, respectively) (31). Not all HCC patients are eligible for ALPPS, but it can potentially increase the number of HCC patients who are eligible for resection.

Liver transplantation has a theoretical advantage over resection in that it would treat both HCC and liver disease (34). Selection for liver transplantation in Hong Kong is based on the University of California San Francisco (UCSF) criteria of a solitary tumor <6.5 cm, or <3 nodules with the largest lesion <4.5 cm and total tumor diameter <8 cm (35). An analysis of 175 propensity score matched cases found that primary liver transplant may be a better treatment option than salvage transplant (36). While availability of donor grafts limits the use of liver transplantation, living donor liver transplant (LDLT) can improve this situation. A study of patients with HCC ≤8 cm treated with LDLT (n=50) or liver resection (n=350) found that LDLT had better survival outcomes, notably an OS rate 1.5 times as high and a 10-year disease-free survival (DFS) rate twice as high as resection (34).

### *The role of local ablation in HCC 3–5 cm*

(XIII) *Local ablation is an acceptable alternative to resection for small HCC (<3 cm) in Child-Pugh A/B patients (Level 1). Choice of ablation or resection should be individualized based on tumor location, liver function reserve and patient comorbidity.*

*Original 2018 statement*: *Local ablation is an acceptable alternative to resection for small HCC (<3 cm) in Child-Pugh A/B patients.*

(XIV) *For resectable tumors 3–5 cm in patients with Child-Pugh A liver function, resection is the preferred option over ablation (Level 1) (accepted without revision from 2018).*

Several studies published since the 2018 consensus statements have added to the body of evidence guiding the use of RFA for smaller HCC. A single-center randomized controlled trial (RCT) in Hong Kong of 218 HCC patients who were randomized to RFA or resection found that although 5-year survival and disease recurrence rates were similar between both groups the RFA group had shorter treatment duration, less blood loss and shorter hospitalization than the resection group (37). A meta-analysis of five RCTs including 742 patients concluded that RFA and resection had similar OS rates at 1 and 3 years; RFA resulted in lower OS at 5 years but complications may be less frequent than with resection (38). The authors noted that to conclusively demonstrate a survival advantage for RFA, additional, well-designed trials using clearer indications for RFA are needed (38). A meta-analysis of 15 studies concluded that RFA and resection were equivalent for OS in patients with solitary tumors <3 cm (39). A recent meta-analysis of 23 studies (3 RCTs and 20 observational comparative studies) found that while resection was generally better than RFA for improving OS, based on subanalyses by tumor size, the authors noted that RFA or resection could be equally recommended for patients with a single tumor ≤3 cm, and RFA or transplantation could be recommended for patients with multiple lesions (40).

### *The role of RFA combined with TACE*

(XV) *For HCC nodules 3–5 cm in diameter, the combination of TACE and ablation may be more beneficial than ablation alone (Level 1). However, surgical resection remains the preferred treatment over combined RFA and TACE for resectable tumors (Level 2).*

*Original 2018 statement*: *For HCC nodules 3–5 cm in diameter, the combination of TACE and ablation may be more beneficial than ablation alone.*

(XVI) *For solitary tumors 5–7 cm, ablation combined with TACE may be beneficial in selected patients (Level 1) (accepted without revision from 2018).*

The combination of TACE and RFA is an important option for patients with larger HCC. Chen and colleagues performed a meta-analysis of eight RCTs and concluded that RFA + TACE confers advantages in recurrence-free survival (RFS) and OS compared with RFA alone (41). RFA + TACE has been compared to resection in a RCT of 200 patients which found that resection was associated with better OS and RFS, but with a higher incidence of complications than RFA + TACE (42). A meta-analysis of seven case-control studies and one RCT of patients meeting the Milan criteria also compared RFA + TACE to resection and found that neither 3- and 5-year OS nor 1-, 3- and 5-year RFS differed significantly between them, but RFA + TACE had fewer complications (43).

### *The selection of ablation modalities*

(XVII) *RFA via the surgical approach is preferred when tumor location incurs a high risk of biliary or visceral injury by percutaneous approach, and may offer a survival benefit for patients with large HCC >3 cm (Level 3) (accepted without revision from 2018).*

(XVIII) *Percutaneous ethanol injection is associated with lower complete ablation rate and higher local tumor recurrence rate than thermal ablation, but it still has a role in small HCC <2 cm not suitable for thermal ablation (Level 1).*

*Original 2018 statement*: *Percutaneous ethanol injection still has a role in small HCC <2 cm not suitable for thermal ablation.*

(XIX) *Microwave ablation (MWA) is a safe and equally effective alternative modality for treatment of HCC (Level 1).*

*Original 2018 statement*: *Microwave ablation is a safe and effective modality for treatment of HCC. It is an alternative option to RFA.*

(XX) *High-intensity focused ultrasound (HIFU) ablation is a safe and effective alternative to RFA in the treatment of small HCCs, and it may have some advantage in selected patients (Level 1).*

*Original 2018 statement*: *HIFU ablation is safe and effective in the treatment of small HCCs. It can achieve survival outcomes comparable to those of RFA and thus serves as a good alternative treatment.*

(XXI) *Cryoablation is an equally effective alternative to thermal ablation for treatment of small HCC (Level 3) (new statement).*

The preference for surgical ablation over percutaneous is based on a study of 162 patients with HCC in dangerous locations which found local tumor progression was better and severe postoperative complications were lower with surgical RFA compared with percutaneous RFA (44). A large meta-analysis has compared RFA to other ablative techniques including percutaneous ethanol injection (PEI; 6 RCTs, 4 cohort studies), MWA (3 RCT and 6 cohort studies), cryoablation (1 RCT, 4 cohort studies) and HIFU ablation (1 cohort study) (45). Identical effects to RFA were found in MWA and cryoablation groups; complete tumor ablation rate was significantly lower in the PEI group than in the RFA group (45). Similar therapeutic effects and rates of complications were reported for RFA and HIFU groups (45), and HIFU may be advantageous in patients with lesions that are difficult to treat with RFA (e.g., those with ascites or tumors close to bile ducts) (46). Additionally, a meta-analysis of four RCTs and 24 observational studies comparing MWA and RFA in both HCC and colorectal liver metastases found no significant differences in outcomes between these modalities (47).

### *Recommendation for ablative margin size*

(XXII) *An ablation margin of ≥10 mm should be targeted if feasible. An ablative margin of <10 mm was significantly correlated with tumor recurrence in HCC (Level 4).*

*Original 2018 statement*: *An ablative margin of <5 mm was significantly correlated with local recurrence in HCC.*

A retrospective study of 281 patients with single HCC tumors of 3.1–5.0 cm compared patients with an ablative margin of 0.5–1.0 to those with a margin of >1.0 cm and found that local tumor progression-free survival (PFS) rates were significantly higher in the >1.0 cm group (48). This recommendation is further supported by an RCT including patients with HCC ≤3.0 cm who were randomized to wide (≥1.0 cm) or narrow (≥0.5 to <1.0 cm) ablative margins, which found that the wider margin was associated with a reduced risk of local progression and recurrence (49).

### *The role of RFA as a bridge to liver transplantation*

(XXIII) *Local ablation can be used as a first-line bridge therapy to liver transplantation (Level 4).*

*Original 2018 statement*: *HIFU may be used as an alternative bridging therapy for HCC patients awaiting liver transplantation.*

A study of 121 patients with HCC (mean tumor size 2.4 cm) treated with RFA as an initial stand-alone bridge therapy to liver transplant concluded this approach achieved excellent long-term and overall tumor-specific survival, with a low dropout rate from tumor progression, despite long wait list times (50).

### *The role of RFA combined with resection*

(XXIV) *Combined resection and RFA allows curative treatment for multifocal HCCs for patients with bilobar tumors, marginal liver function or complicated tumor distribution not suitable for resection alone (Level 1).*

*Original 2018 statement*: *Patients with a predominant large mass in one lobe and one or two small tumor nodules in the other lobe may benefit from combined resection of the predominant tumor and resection or ablation of the contralateral nodules*

Combining resection and RFA in patients with multifocal HCC is supported by a meta-analysis of four retrospective studies which found that RFA combined with resection could achieve similar long-term survival outcomes to resection alone, and may be a promising option in patients with marginal liver function or complex tumor distribution (51).

(XXV) *Ablation is an equally effective treatment as re-resection for recurrent HCC. It has the advantage of higher repeatability and safety, and may be preferred in selected patients (Level 1) (new statement).*

A small retrospective cohort study at a single center in Hong Kong compared outcomes in 29 patients who underwent resection and 45 who had RFA for recurrent HCC (52). Both treatments were found to have similar survival benefits, and the high repeatability and ability for percutaneous treatment render RFA to be a preferable option in selected patients (52). In a meta-analysis of five retrospective studies comparing a repeated resection to RFA in recurrent HCC, neither was found to be superior for DFS or OS (53). However, RFA was found to have a significantly lower morbidity rate (2% *vs.* 17%; P<0.001) (53).

### *The role of TACE*

(XXVI) *TACE can be considered in patients with unresectable HCC with segmental portal vein invasion. The survival benefit of TACE in patients with segmental PVT is greater than that in patients with major PVT (Level 2).*

*Original 2018 statement*: *TACE can be considered in patients with unresectable HCC with segmental portal vein invasion (Level 4).*

(XXVII) *TACE combined with external beam radiotherapy (EBRT) may be considered in selected patients with advanced,*

**Table 1** Definition of TACE-unsuitability from the APPLE consensus statement 2020

| Clinical conditions | Patient characteristics |
|---|---|
| TACE-unsuitability is defined as each one of the following 3 clinical conditions that prevent a survival benefit from TACE or conditions where TACE is even harmful: | |
| (I) Unlikely to respond to TACE | Confluent multinodular type, massive or infiltrative type, simple nodular type with extranodular growth, poorly differentiated type, intrahepatic multiple disseminated nodules, or sarcomatous changes after TACE |
| (II) Likely to develop TACE failure/refractoriness | Up-to-7 criteria out nodules |
| (III) Likely to become Child-Pugh B or C after TACE | Up-to-7 criteria out nodules (especially, bilobar multifocal HCC), mALBI grade 2b |

Based on Kudo *et al.* 2020 (62). TACE, transcatheter arterial chemoembolization; APPLE, Asia-Pacific Primary Liver Cancer Expert; HCC, hepatocellular carcinoma; mALBI, modified albumin-bilirubin.

*non-metastatic HCC with venous invasion (Level 2) (new statement)*.

(XXVIII) *The existing prognostic scores regarding TACE-suitability and TACE-unsuitability are lacking specific predictive values and currently not recommended for guiding decisions on TACE treatment (new statement)*.

While TACE for HCC has been previously been contraindicated in patients with PVT, cohort studies have found that selective TACE can be used in these patients to improve OS (54). More recently, a meta-analysis of 13 studies concluded that TACE was safe in selected HCC patients and that the survival benefit was greater in patients with segmental rather than major PVT (55). A small study (n=42) comparing TACE and TACE + RFA in HCC with inferior vena cava thrombosis found TACE + RFA to achieve better OS (56). Combination therapy of TACE with EBRT has been evaluated in comparison to sorafenib in a RCT including 90 subjects with HCC; the study found TACE + EBRT improved OS, PFS and time to progression versus sorafenib (57). As there is considerable heterogeneity among the intermediate HCC patients who are potential candidates for TACE, patient selection should be highly individualized as not all patients may benefit equally (58,59). Although there have been attempts at developing prognostic scores to identify candidates for initial or repeated TACE (60), these scores have shown limited predictive value and are currently not recommended for selection of candidates (61). The Asia-Pacific Primary Liver Cancer Expert (APPLE) consensus statement has defined a set of three clinical conditions that define TACE unsuitability based on (i) characteristics of HCC unlikely to respond to TACE, (ii) criteria associated with TACE failure, and (iii) criteria associated with hepatic function of Child-Pugh categories B or C following TACE (*Table 1*) (62).

### *Options in TACE-refractory HCC*

(XXIX) *TACE with drug-eluting beads (DEB-TACE) is an alternative treatment for HCC after conventional TACE fails. The non-superiority of DEB-TACE over conventional TACE regarding OS, objective response (OR), and adverse events (AEs) has been confirmed (Level 1)*.

*Original 2018 statement*: *TACE with drug-eluting beads (TACE-DEB) is an alternative treatment for HCC after conventional TACE fails, but there is no evidence of survival benefit over conventional TACE.*

(XXX) *Transarterial ethanol ablation (TEA) as well as ablative chemoembolization (ACE) can be considered as an alternative to TACE in selected cases or when TACE fails (Level 1 and Level 2, respectively) (new statement)*.

(XXXI) *TACE should be stopped when there is liver impairment, other serious complications, or TACE refractoriness (Level 5). The decision whether to stop TACE due to ineffectiveness/toxicity or to move on to systemic therapy can be challenging and can be made on a case-by-case basis at a multidisciplinary cancer conference, if possible.*

*Original 2018 statement, with proposed additional text*: *TACE should be stopped when there is liver impairment, other serious complications, or TACE refractoriness, or radiologic tumor progression, despite adequate drug administration (Level 5)*.

(XXXII) *TACE refractoriness is defined when one of the following conditions occur after two or more sessions of TACE within 6 months from the first TACE: (i) consecutive insufficient tumor response (viable lesion>50%); (ii) two or more consecutive progressions in tumor number; (iii) continuous elevation of tumor markers; (iv) new development of vascular invasion; or (v) development of extrahepatic spread (new statement)*.

(XXXIII) *Systemic therapy instead of repeat-TACE should be considered for patients with TACE refractoriness (Level 3). Early*

*switching is preferred before the conversion to systemic therapy becomes impossible due to suboptimal liver function (Level 3) (new statement)*.

(XXXIV) *The clinical benefit of adding sorafenib to TACE is minimal. Routine combination of targeted therapy and TACE is not recommended (Level 1)*.

*Original 2018 statement*: *The clinical benefit of additional sorafenib to TACE is minimal. Routine combination of sorafenib and TACE is not recommended (Level 1)*.

A meta-analysis of four RCTs and eight observational studies of DEB-TACE versus conventional TACE found a nonsignificant trend in 1-, 2-, and 3-year survival in favor of DEB-TACE, and concluded DEB-TACE to be non-superior to conventional TACE (63). An RCT evaluated TEA in comparison to TACE in 200 HCC patients and, although terminated early, interim analysis showed that while there was no significant difference in OS, TEA demonstrated better complete tumor response and longer PFS than TACE (64). A 2018 case-control study compared outcomes of ACE (study group) and TACE (control group) in 44 HCC patients, and median time to progression and median PFS were significantly longer in the study group than in the control group (65). The authors concluded ACE was safe and effective and may be more effective than TACE in achieving complete response (65). While TEA and ACE are probably more effective than TACE, a high level of clinician experience and careful patient selection is required for successful use of TEA and ACE.

The decision whether to stop TACE due to ineffectiveness/toxicity or to switch to systemic therapy can be challenging, and in concurrence with other clinical guidelines we recommend a case-by-case approach, preferably discussed at a multidisciplinary cancer conference (66,67). We recommend a pragmatic approach that considers liver function, tumor status and events such as extrahepatic spread or venous invasion, and clinicians must be vigilant to ensure that the temporary liver impairment known to occur following TACE does not become chronic (68). Various definitions of TACE refractoriness have been proposed (66); the definition included here aligns closely with that of the Japanese Society of Hepatology/Liver Cancer Study Group of Japan (69). The switching of TACE-refractory HCC patients to systemic treatment with sorafenib is supported by two retrospective studies that show longer survival and better preservation of liver function in those who switched compared with those receiving repeated TACE (70,71).

In line with other guidelines we recommend switching from TACE to systemic therapy when refractoriness becomes apparent (67,72). A growing evidence base suggests that physicians should be aware of the importance of switching while liver function is still well preserved, and observational data demonstrate improved survival in patients who switch to sorafenib earlier compared with those who switch later (73,74).

Evidence does not support addition of sorafenib to TACE; in five RCTs, TACE combined with several systemic agents, including sorafenib, orantinib and brivanib, failed to demonstrate any clinical advantage over TACE alone, with the exception of the TACTICS trial that demonstrated significantly improved PFS, but with longer sorafenib pretreatment durations compared to the negative trials (75-79). Combinations of TACE and systemic agents are also under investigation in advanced HCC, although data so far are ambiguous (80,81).

(XXXV) *Assessment of response for TACE should follow mRECIST criteria using dynamic contrast enhanced CT or magnetic resonance imaging (Level 1) (new statement)*.

Several clinical investigations and a meta-analysis of seven trials have shown OR according to modified Response Evaluation Criteria in Solid Tumors (mRECIST) predicts survival in patients receiving loco-regional therapies (82,83). Compared to RECIST, mRECIST has higher sensitivity for capturing response (82), and use of mRECIST has been endorsed by European and Asia-Pacific expert groups for assessing response to loco-regional therapy (6,62).

### *The role of TARE*

(XXXVI) *TARE can be considered as a bridge therapy to liver transplantation in selected patients (Level 4)*.

*Original 2018 statement*: *TARE is useful as a bridge therapy to liver transplantation in suitable candidates (Level 4)*.

(XXXVII) *TARE can be considered for Child-Pugh A patients with multifocal or large burden HCC (Level 5)*.

*Original 2018 statement*: *TARE is useful for Child-Pugh A patients with multifocal or large burden HCC (Level 5)*.

(XXXVIII) *For unresectable or unablatable HCC >5 cm, TARE can be considered (Level 5) (accepted without revision from 2018)*.

(XXXIX) *TARE can be considered for Child-Pugh A and selected Child-Pugh B patients (≤7) with small burden HCC but fail to respond to conventional TACE (Level 5)*.

*Original 2018 statement*: *TARE is useful for Child-Pugh A and selected Child-Pugh B patients with small burden HCC but fail to respond to conventional TACE (Level 5)*.

(XL) *If a tumor is confined to 1 to 2 segments, radiation segmentectomy may be considered for potential complete response and better survival (Level 3) (new statement).*

In a multicenter study of 102 subjects with solitary unresectable HCC ≤5 cm not amenable to RFA, Vouche and colleagues found radiation segmentectomy (RS; a segmental, high-dose radioembolization) to be effective, with a favorable risk profile (84). A retrospective case series comparing TACE plus MWA and RS in patients with unresectable HCC ≤3 cm found these modalities to have similar CR and OS (85), and the same investigators when comparing RS and TACE alone found, after propensity score matching, CR rates of 92% and 53% for RS and TACE respectively (86). Another retrospective study comparing TACE and RS also found RS to compare favorably to TACE (87), and in a retrospective study in 93 patients with HCC secondary to HBV infection, TARE showed low toxicity and good survival outcomes (88). When stratified by Child-Pugh status, median OS was 17.5 months for Child-Pugh A and 14.5 months for Child-Pugh B (88).

In summary, if a tumor is <8 cm in size and confined to 1 or 2 segments, RS can be considered to achieve complete pathological necrosis in the tumor. Complete tumor targeting and dose to tumor are independent factors associated with tumor control in patients treated with yttrium-90 (Y-90) TARE (89), and commercially available software can assist with personalized dosimetry planning (90,91).

(XLI) *In patients with right or left portal vein tumor thrombus, Child-Pugh class ≤B7, Eastern Cooperative Oncology Group (ECOG) score ≤1, ablative TARE (ablative liver radiation dose to tumor bearing lobe) may prolong median OS compared to conventional TARE (Level 4).*

*Original 2018 statement*: *TARE is useful for HCC with vascular invasion, and disease is liver-dominant, and patients have bilirubin <2 mg/dL and Child-Pugh score ≤7 (Level 4).*

Ablative TARE—a form of TARE that delivers a high dose of radioactivity to kill the tumor-adjacent normal parenchyma in the treatment zone—was evaluated for HCC with portal vein invasion in a recent retrospective cohort study (92). Compared to conventional TARE, ablative TARE was associated with longer median OS, lower risk of death and improved 4-year survival (92).

(XLII) *After unilobar TARE, it is advised to follow up the patient for at least 3 months, for possible disease downstaging and curative resection (Level 5).*

*Original 2018 statement*: *After unilobar TARE, it is advised to follow up the patient for at least 6 months, for possible disease downstaging and curative resection (Level 5).*

Following TARE, we recommend patients should be followed up clinically and with imaging to evaluate the possibility of disease downstaging and curative resection.

(XLIII) *TARE is not shown to have survival benefit in inoperable HCC when compared with sorafenib (Level 2). TARE + sorafenib has similar survival benefit when compared with TARE alone (new statement).*

Two recent phase III trials (SARAH and SIRveNIB) have compared TARE with sorafenib and found consistent results in patients with advanced HCC, a population with poor prognosis (93). In both trials, Y-90 TARE showed a higher tumor response rate in the initial phase and a better AE profile than sorafenib, but neither trial showed a statistically significant difference in survival between treatment arms (93). Similarly, a meta-analysis which included these two trials, a trial comparing lenvatinib and sorafenib, and studies of TARE, concluded that there was no difference in OS among any of these treatments (94). In both the SARAH and SIRveNIB studies, AEs, particularly grade ≥3 events, were more frequent in the sorafenib groups (95,96). In the PREMIERE study, HCC patients were randomized to TARE + sorafenib or sorafenib alone as a bridge to transplant, with similar outcomes reported in both treatment groups (97). An analysis of 175 propensity score matched HCC cases treated with sorafenib + TARE or TARE alone found there were no significant differences in median OS, median PFS, toxicity, or liver decompensation rates between the two treatments (98).

### *The role of SBRT*

(XLIV) *SBRT is a viable option for Child-Pugh A patients with unresectable HCC. It may be considered as an alternative to other liver-directed therapies (Level 4). The choice of treatment should preferably be determined by the expertise and preferences of the treating team in a MDT meeting.*

*Original 2018 statements*: *SBRT is an acceptable option for unresectable HCC (up to 5 lesions) (Level 4) and SBRT can be considered for patients with limited liver reserve (up to Child-Pugh Grade B8 and platelet count ≥50×10$^9$/L).*

(XLV) *SBRT with individualized doses is safe and effective for large HCC (>5 cm). It may convert initially unresectable HCC to resectable (Level 5) (new statement).*

(XLVI) *SBRT combined with planned TACE may be considered for large (>5 cm) unresectable HCC, Child-Pugh A, in view of possibly superior response rate, local control, and OS (Level 3) (new statement).*

The use of SBRT in HCC is supported by a growing

**Table 2** Summary of phase III studies of targeted therapies for treatment of HCC

| Study and population | Comparators | Median OS |
|---|---|---|
| REFLECT: Advanced HCC with no previous systemic treatment (116) | Lenvatinib *vs.* sorafenib | Lenvatinib: 13.6 months; Sorafenib: 12.3 months; (HR 0.92; 95% CI: 0.79–1.06; non-inferiority criteria met) |
| CELESTIAL: Advanced HCC, previously treated with sorafenib (113) | Cabozantinib *vs.* placebo | Cabozantinib: 10.2 months; Placebo: 8.0 months; (HR 0.76; 95% CI: 0.63–0.92; P=0.005) |
| REACH-2: Advanced HCC, previously treated with sorafenib and AFP ≥400 ng/mL (118) | Ramucirumab *vs.* placebo | Ramucirumab: 8.5 months; Placebo: 7.3 months; (HR 0.710; 95% CI: 0.531–0.949; P=0.0199) |
| RESORCE: Advanced HCC, previously treated with sorafenib (114) | Regorafenib *vs.* placebo | Regorafenib: 10.6 months; Placebo: 7.8 months; (HR 0.63; 95% CI: 0.50–0.79; P<0.0001) |
| SHARP: Advanced HCC with no previous systemic treatment (117) | Sorafenib *vs.* placebo | Sorafenib: 10.7; Placebo; 7.9 months; (HR 0.69; 95% CI: 0.55–0.87; P<0.001) |
| IMBrave150: Advanced HCC with no previous systemic treatment (115) | Atezolizumab plus bevacizumab *vs.* sorafenib | Atezolizumab plus bevacizumab: 19.2 months; Sorafenib: 13.4 months; (HR 0.66; 95% CI: 0.52–0.85; P=0.0009) |

HCC, hepatocellular carcinoma; OS, overall survival; AFP, α-fetoprotein; CI, confidence interval; HR, hazard ratio.

evidence base, with numerous retrospective and prospective studies demonstrating rates of local control of 66–95% at 2 to 3 years and OS of 60–78% at 2 or 3 years (99-104), and an acceptable safety profile. However, at the time of writing, SBRT has not been evaluated in a randomized study comparing it to resection or other liver-directed therapies.

While much of these data are from subjects with small tumors (<5 cm), many patients in Hong Kong present with larger tumors. Several studies have evaluated SBRT in patients with larger HCC with good results (105-107). Treatment of larger HCC with SBRT was evaluated in a 2020 study that included 55 patients with median tumor size of 15.3 cm, 25.5% and 32.7% of whom had vascular invasion and extrahepatic metastases, respectively, and administered combined TACE and HIGRT (hypofractionated image-guided radiotherapy) (108). Of the 37 patients without extrahepatic disease at baseline, 27% (10 out of 37) were subsequently treated with curative resection (108).

Support for SBRT combined with TACE in unresectable HCC is found in a meta-analysis of 25 studies (including 11 RCTs and various forms of radiotherapy, including 3-dimensional conformal and stereotactic) which concluded TACE + radiotherapy had better 1-year survival than TACE alone, and this benefit progressively increased for 2-, 3-, 4-, and 5-year survival (109). In a retrospective study of 77 HCC patients with median tumor size of 8.5 cm, SBRT alone, or as an adjunct to transarterial embolization (TAE) or TACE, was effective, with the TAE/TACE + SBRT combination achieving better median OS and 5-year survival than SBRT alone (110). A retrospective study of 103 patients comparing those who received planned adjuvant DEB-TACE after SBRT with those receiving salvage SBRT, found that the combination produced high OR and local control rates and might produce superior outcomes to salvage SBRT (111). A retrospective study in Hong Kong of patients with non-resectable HCC treated with TACE + SBRT (n=49) or TACE alone (n=98) found the 1- and 3-year OS were better in the TACE + SBRT group than in the TACE-alone group (112).

### *The role of targeted therapy*

(XLVII) *For TKI monotherapy, lenvatinib or sorafenib are both options for first-line treatment of advanced HCC (Level 1).*

*Original 2018 statement*: *Sorafenib is currently the standard first-line systemic treatment for HCC with Child-Pugh A liver function who are not suitable for surgery, locoregional therapy or transarterial therapy (Level 2).*

Since the 2018 consensus statements, lenvatinib has joined sorafenib as an option for first-line systemic treatment of unresectable HCC, and the evidence base to support treatment decisions post-sorafenib has grown (113-118) (*Table 2*). In the multicenter, phase III REFLECT trial, patients with HCC (99% Child-Pugh A) were randomized to lenvatinib or sorafenib (116). Noninferiority for OS, the primary outcome, was established by a median OS of 13.6 and 12.3 months for lenvatinib and sorafenib, respectively (116). Disease control rate (DCR) was higher

 

for lenvatinib than for sorafenib (73% *vs.* 59%), and overall response rate (ORR; masked independent imaging review according to mRECIST criteria) was also significantly higher for lenvatinib (40.6% *vs.* 12.4%; P<0.0001) (116). Based on these data the US Food and Drug Administration (FDA) approved lenvatinib for first-line treatment of unresectable HCC in August 2018 (119). The 2021 guidelines from the National Comprehensive Cancer Network (NCCN) and the Japan Society of Hepatology (JSH) recommend atezolizumab plus bevacizumab as the preferred first-line option for systemic treatment of unresectable HCC, with sorafenib and lenvatinib as options for patients with disease progression, contraindication or unacceptable AEs on atezolizumab plus bevacizumab (120,121).

(XLVIII) *Regorafenib*, *cabozantinib*, *ramucirumab and immunotherapy*, *are options for subsequent lines of treatment for patients who develop progressive disease to first-line sorafenib (Level 2)*.

*Original 2018 statement*: *Regorafenib is an option for second-line treatment for patients who developed progressive disease to sorafenib treatment (Level 2)*.

Cabozantinib was evaluated in a randomized, double-blind, placebo-controlled, phase III trial of 707 patients with advanced HCC (all Child-Pugh A) as a second- (70% of patients) or third-line (30%) therapy (113). The median OS was 10.2 and 8.0 months, and median PFS was 5.2 and 1.9 months, with cabozantinib and placebo, respectively (113). Cabozantinib was approved by the US FDA for treatment of HCC following sorafenib in January 2019 (122).

Ramucirumab as a second-line therapy to sorafenib was evaluated in the placebo-controlled, phase III REACH-2 study, which enrolled 292 patients with Child-Pugh A liver function and α-fetoprotein (AFP) concentrations ≥400 ng/mL (118). At a median follow-up of 7.6 months, median OS (8.5 *vs.* 7.3 months; P=0.0199) and PFS (2.8 *vs.* 1.6 months; P<0.0001) were significantly improved in ramucirumab-treated patients compared with placebo (118). The ORR in the ramucirumab and placebo groups was 4.6% *vs.* 1.1%, respectively, and the DCR was 59.9% *vs.* 38.9% (118). Ramucirumab was approved by the US FDA for treatment of HCC patients with AFP ≥400 ng/mL and previous treatment with sorafenib in May 2019 (123).

The efficacy of regorafenib in sorafenib-refractory HCC patients was demonstrated in the phase III, placebo-controlled RESORCE study (114). Compared with placebo, regorafenib improved survival, with a median OS of 10.6 versus 7.8 months in the placebo group (114). Approval for the use of regorafenib in HCC patients treated with sorafenib was granted in April 2017 (124).

Most of the second-line agents have been evaluated in sorafenib-treated patients as sorafenib was once the only approved first-line agent for HCC. There are no clinical trials to support the possible use of first-line agents in second-line settings, or the use of second-line agents after lenvatinib. Therefore, we recommend that the selection of second-line therapy should be based on the judgement of the treating clinician.

(XLIX) *For patients who develop progressive disease on lenvatinib (non-sorafenib first-line regimen)*, *regorafenib*, *cabozantinib*, *ramucirumab or unused TKI, and immunotherapy could be considered in subsequent lines of treatment (Level 5) (new statement)*.

Data to guide the selection of therapy after disease progression on agents other than sorafenib are scarce. Currently available options are regorafenib, cabozantinib ramucirumab, pembrolizumab and nivolumab (with or without ipilimumab). Several analyses of HCC patients who have progressed on sorafenib treatment have identified predictors of post-sorafenib survival, the most notable of which is the use of additional therapies post sorafenib (125-127). Therefore, in agreement with recent American Association for the Study of Liver Disease (AASLD) guidelines (72), we recommend that additional lines of systemic therapy with previously unused agents be considered in patients who progress after first-line lenvatinib.

(L) *TKI should preferably be commenced in patients with optimal hepatic function to achieve maximal benefits (Level 2) (new statement)*.

A growing body of evidence suggests that patients with better hepatic function benefit more from systemic therapies than patients with hepatic impairment. For example, an analysis of patients in the REFLECT trial of lenvatinib stratified by baseline liver function found that median OS was longer for patients with albumin-bilirubin grade 1 (ALBI-1) versus grade 2 (or for Child-Pugh 5 *vs.* Child-Pugh 6) in both lenvatinib and sorafenib arms (128). Similar conclusions were reached in another analysis of lenvatinib-treated patients (129) and an analysis of cabozantinib-treated patients in the CELESTIAL trial (130). Furthermore, retrospective studies of sorafenib-treated patients have found better ALBI grade to predictive of better survival post-sorafenib (131,132).

(LI) *For patients with high-burden hepatic disease load*, *systemic therapy may be better than TACE in terms of preservation of hepatic function and improvement of survival*

 

*outcomes (Level 3)* (*new statement*).

The 'up-to-seven' criteria [seven being the result of the sum of maximum size (cm) and number of tumors] can serve as a threshold for defining patients with high tumor burden (133,134). An analysis of the OPTIMIS study of TACE in unresectable HCC found that a higher proportion of patients exceeding the up-to-seven criteria experienced deterioration of liver function after first TACE than those within this limit (135), and the 2020 APPLE consensus statements includes the up-to-seven criteria as part of its definition of TACE unsuitability (62). The option of lenvatinib as an alternative to TACE in unresectable intermediate-stage HCC was evaluated in a proof-of-concept study in which, after propensity score matching, 30 patients treated with lenvatinib were compared to 60 patients treated with TACE (136). Lenvatinib was associated with better preservation of liver function; reported ALBI score changes from baseline to the end of treatment were –2.61 to –2.61 (P=0.254) in the lenvatinib group and –2.66 to –2.09 in the cTACE group (P<0.01) (136). Lenvatinib was also associated with a significantly longer OS (37.9 *vs.* 21.3 months; P<0.01), significantly longer median PFS (16.0 *vs.* 3.0 months; P<0.001) and significantly higher ORR per mRECIST criteria (73.3% *vs.* 33.3%; P<0.001) than TACE (136). Therefore, lenvatinib may be preferable to TACE in patients with high-burden hepatic disease load.

### *The role of immunotherapy*

(LII) *Patients with advanced, unresectable HCC can be considered for immunotherapy irrespective of ethnicity or viral hepatitis etiology (Level 2).*

*Original 2018 statement*: *Anti-PD1 therapy is potentially a second-line or subsequent line of treatment in patients with sorafenib-refractory disease.*

(LIII) *It is advisable that, during immunotherapy, HBV patients be on concomitant antiviral medication (Level 2) (new statement).*

The evidence base for immunotherapy has expanded considerably since the previous consensus statements were formulated. In the phase I/II CheckMate 040 trial, advanced HCC patients, many pre-treated with sorafenib, showed durable OR to nivolumab, including those with HBV and HCV infection (137). Additional data are found in a cohort analysis of Asian patients in the CheckMate 040 study where median OS was found to be similar among the Asian and overall populations (14.9 *vs.* 15.1 months, respectively) (138). The most common AEs with nivolumab in both cohorts were skin rash and gastrointestinal toxicity, and derangement of liver function was rare (138). Antiviral therapy was a requirement for subjects with HBV (but not HCV) in CheckMate 040, and no significant liver dysfunction due to HBV reactivation was reported during the study (137).

(LIV) *The combination of anti-PD-1/anti-PD-L1 with anti-CTLA-4 agents showed promising antitumor activity with acceptable safety profile in phase I/II studies and needs to be confirmed by ongoing phase III studies (Level 2) (new statement).*

(LV) *For patients with good performance status who have progressed on TKI and have not received prior immunotherapy, nivolumab monotherapy, pembrolizumab monotherapy, and nivolumab in combination with ipilimumab, are all possible immunotherapeutic options (new statement).*

The randomized, placebo-controlled, phase III KEYNOTE 240 study compared pembrolizumab with best supportive care as second-line therapy in advanced HCC (139). The OR rates were 18.3% and 4.4% for pembrolizumab and control groups, respectively (139). Numerical, but not statistically significant improvements in OS and PFS with pembrolizumab compared to control group were reported (139).

Combination therapy with agents targeting cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) is thought to induce a synergistic antitumor response (140), and this strategy has been evaluated for advanced HCC (post sorafenib) in a cohort of the CheckMate 040 trial (141). Nivolumab + ipilimumab was evaluated in three comparator arms with different dosing regimens, and good response was seen in all groups (141). Notably, in arm A where subjects received the high dose (3 mg/kg) ipilimumab regimen approved by the US FDA (142), median OS was 23 months and four out of 50 patients had a complete response. In the recent updated analysis , the 36-month OS rates were 42% in the high dose ipilimumab arm with 8% of the randomized patients in arm A achieving complete remission (143). A phase I/II study of the programmed cell death ligand 1 (PD-L1)-binding antibody durvalumab and anti-CTLA-4 antibody tremelimumab has also shown promising clinical activity in HCC patients with progression on sorafenib, and further clinical development of this combination is ongoing (144).

(LVI) *Nivolumab monotherapy has been demonstrated to be safe and has demonstrated activity for second-line treatment of patients with Child-Pugh B HCC (Level 2) (new statement).*

A cohort analysis of patients with Child-Pugh B liver function (n=48; 75% B7, 22% B8; half with prior sorafenib)

in the CheckMate 040 study found nivolumab achieved good tumor shrinkage in nearly half of the cohort, and the safety profile of nivolumab in patients with Child-Pugh B status was comparable to patients with Child-Pugh A status (145).

(LVII) *Single agent nivolumab demonstrated meaningful clinical benefits with better tolerability and quality of life when compared with single agent sorafenib as first-line treatment in an advanced HCC population (Level 2) (new statement)*.

(LVIII) *For first-line treatment of patients with advanced Child-Pugh A HCC, atezolizumab plus bevacizumab is the preferred option, unless bevacizumab is contraindicated (Level 2) (new statement)*.

(LIX) *More mature long-term data are needed to assess durability, survival benefit, and tolerability of atezolizumab and bevacizumab as a first-line treatment option for advanced HCC patients (new statement)*.

(LX) *For patients who do not prefer or have a contraindication to antiangiogenic therapies or TKIs, first-line treatment with nivolumab may be considered (Level 2) (new statement)*.

The randomized, phase III CheckMate 459 study compared nivolumab and sorafenib as first-line therapy for advanced HCC (146). The primary endpoint of OS in the study did not achieve statistical significance versus sorafenib, yet nivolumab showed clinically meaningful improvements in OS, ORR, and CR rate as first-line treatment for advanced HCC (146). Consistent OS benefit was observed with nivolumab irrespective of baseline PD-L1 expression, and nivolumab demonstrated an improved safety profile, with fewer grade 3/4 treatment-related AEs, and fewer AEs leading to discontinuation, versus sorafenib (146).

IMbrave150 was an open-label, phase III, randomized study to evaluate atezolizumab plus bevacizumab or sorafenib in patients with unresectable HCC who had not received prior systemic therapy (147). Although median follow-up was only 8.6 months, statistically significant and clinically meaningful improvements with atezolizumab plus bevacizumab over sorafenib for OS and ORR were achieved and responses with atezolizumab plus bevacizumab were durable (147). The safety and tolerability profile of atezolizumab plus bevacizumab was consistent with those of the individual components, and the most common treatment-related AE with atezolizumab plus bevacizumab was hypertension (147). A recent update of the phase III IMbrave150 trial of atezolizumab plus bevacizumab showed an impressive effect on survival in the front-line setting (115). After a median follow-up of 15.6 months, median OS was 19.2 months with the combination, compared with 13.4 months with sorafenib [hazard ratio (HR) =0.66; P=0.0009] (115). The rate of confirmed responses was 30% with atezolizumab plus bevacizumab *vs.* 11% with sorafenib, and 7% of patients receiving atezolizumab plus bevacizumab achieved complete response (115). Moreover, no new safety signals were reported (115). These favorable data on atezolizumab plus bevacizumab have led to the National Comprehensive Cancer Network (NCCN) and the JSH recommending this combination as the preferred regimen for first-line systemic therapy (120,121).

## Conclusions

These consensus statements capture the latest insights into clinical practice for HCC based on experience in Hong Kong and evidence from international clinical studies. In line with our previous consensus document we advocate a broader use of surgical resection in HCC and we continue to advocate use of the HKLC staging system, based on its validation in both Asian and non-Asian populations. Compared to the previous version of these consensus statements we have substantially updated our guidance on the use of targeted therapies and immunotherapies; we hope that these statements encourage use of these promising new modalities in HCC patients unsuitable for resection.

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