ILCA Systemic Therapy Guidance

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Introduction

Systemic therapy for hepatocellular carcinoma (HCC) has evolved rapidly over the past few years and it is likely that the coming years will witness further advances. Consequently, the therapeutic algorithm for systemic therapy has become increasingly complex and existing guidelines are rapidly outdated. To address this, ILCA has developed an online guidance which can be continuously updated in response to new data. The ILCA systemic therapy guidance aims to provide the most up to date recommendations based on currently available evidence. This document has been developed by the ILCA Education Committee with input from external experts and peer review. The authorship and review process is described at the end of the document. The guidance is designed to be interactive and easy to navigate, allowing the reader to rapidly access relevant data though internal and external links. Each page is dated according to the most recent update.

We anticipate that this ‘live’ guidance will be of value to all clinicians involved in the treatment of patients with HCC and welcome comments via the feedback forum page.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>DCR</td>
<td>Disease control rate</td>
</tr>
<tr>
<td>DR</td>
<td>Duration of response</td>
</tr>
<tr>
<td>EHS</td>
<td>Extrahepatic spread</td>
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<tr>
<td>ICI</td>
<td>Immune Checkpoint Inhibitor</td>
</tr>
<tr>
<td>MVI</td>
<td>Macrovascular invasion</td>
</tr>
<tr>
<td>NCI CTC</td>
<td>National Cancer Institute Common Terminology Criteria for Adverse Events</td>
</tr>
<tr>
<td>ORR</td>
<td>Objective response rate</td>
</tr>
<tr>
<td>OS</td>
<td>Overall survival</td>
</tr>
<tr>
<td>PFS</td>
<td>Progression free survival</td>
</tr>
<tr>
<td>PPE</td>
<td>Palmar Plantar Erythema</td>
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<tr>
<td>PVI</td>
<td>Portal vein invasion</td>
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<tr>
<td>QOL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>TKI</td>
<td>Tyrosine Kinase Inhibitor</td>
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<tr>
<td>TTP</td>
<td>Time to progression</td>
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</tbody>
</table>
Systemic therapy

First line
- **First choice**
  - Atezolizumab plus Bevacizumab

Second line
- **First line alternatives**
  - Sorafenib
  - Cabozantinib
- **Second line alternatives**
  - Regorafenib
  - Ramucirumab

If AFP ≥400 ng/mL

- In patients who tolerated sorafenib

Level 1, A evidence

Level V, C evidence

*Click on box to navigate to further details*
<table>
<thead>
<tr>
<th>Trial</th>
<th>SHARP trial (<a href="https://clinicaltrials.gov/ct2/show/NCT00105443">ClinicalTrials.gov number, NCT00105443.</a>)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design (n)</td>
<td>Multicentre randomised double-blind phase 3 trial (602 1:1)</td>
</tr>
<tr>
<td>Control</td>
<td>Placebo</td>
</tr>
<tr>
<td>Experimental arm</td>
<td>Sorafenib 400mg BD</td>
</tr>
<tr>
<td>Key eligibility criteria</td>
<td>Histologically confirmed advanced HCC, no prior systemic therapy, ECOG PS ≤ 2, Child-Pugh A, measurable disease by RECIST 1.1</td>
</tr>
<tr>
<td>Stratification factors</td>
<td>Region, ECOG PS 0 vs 1 or 2, macroscopic vascular invasion or extrahepatic spread</td>
</tr>
<tr>
<td>Primary outcome</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>mOS 10.7 vs. 7.9 months; HR, 0.69; 95% CI, 0.55 to 0.87; P&lt;0.001</td>
</tr>
<tr>
<td>Time to symptomatic progression (FHSI8)</td>
<td>4.1 vs 4.9 months; HR 1.08; 95% CI, 0.88 to 1.31; P = 0.77</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
</tr>
<tr>
<td>TTP (RECIST)</td>
<td>5.5 vs 2.8 months; HR, 0.58; 95% CI, 0.45 to 0.74; P&lt;0.001</td>
</tr>
<tr>
<td>ORR and DCR</td>
<td>CR 0% vs 0%, PR; 2% vs 1%, SD; 71% vs 67%, DCR; 43% vs 32% (p=0.02)</td>
</tr>
<tr>
<td>Toxicity (NCI CTC V3.0)</td>
<td>Incidence of TRAEs 80% vs 52%. Grade 3-4 AEs for sorafenib; low phosphate 11%, diarrhoea (8%), hand-foot skin reaction (8%), thrombocytopenia (4%) hypertension (2%). Rate of discontinuation due to AEs 38% vs 37%, Dose reductions due to AEs 26% vs 7%.</td>
</tr>
</tbody>
</table>

Additional publications


IMbrave 150 (ClinicalTrials.gov number, NCT03434379.)

Multicentre open-label, randomised phase 3 trial (501 2:1)

Sorafenib 400mg BD

Atezolizumab 1200mg IV plus Bevacizumab 15mg/Kg IV both three weekly

Histological or cytological or meeting AASLD criteria for HCC, no prior systemic therapy, ECOG PS ≤ 2, Child-Pugh A, measurable disease by RECIST 1.1. Excluding those with untreated or incompletely treated esophageal or gastric varices (assessed with esophagogastroduodenoscopy within 6 months)

Region (Asia excluding Japan vs rest of world), MVI or EHS (presence or absence), baseline AFP (<400 vs ≥ 400ng/ml), PS 0 vs 1

OS
mOS NE vs 13.2m; HR 0.58; 95% CI, 0.42–0.79; P<0.001

PFS
mPFS 6.8 vs 4.3m; HR 0.59; 95% CI, 0.47-0.76, P<0.001

ORR
RECIST 1.1 27.3% vs 11.9% (P<0.001), mRECIST 33.2% vs 13.3% (P<0.001), CR 5.5% vs 0%

DR > 6month
RECIST 1.1 87.6% vs 59.1%

Time to reduced QOL
11.2 vs 3.6 months

Grade 3-4 TRAEs for Atezo/Bev: Hypertension (10.3%), Fatigue (1.5%), Proteinurea (2.7%), AST increase (4.3%). Treatment discontinuation due to AEs: 15.5% (either drug) 7% (both) vs 10.3%. Treatment interruption or modification 49.5% vs 60.9%

Publication: Finn RS et al NEJM 2020 May 14;382(20):1894-1905
Trial REFLECT (ClinicalTrials.gov number NCT01761266)

Design (n) Multicentre, open label, non-inferiority, randomised phase 3 trial (954 1:1)

Control Sorafenib 400mg BD

Experimental arm Lenvatinib 12 mg/day for bodyweight ≥60 kg or 8 mg/day for bodyweight <60 kg

Key eligibility criteria Histological or cytological or meeting AASLD criteria for HCC, no prior systemic therapy, ECOG PS ≤ 2, Child-Pugh A, measurable disease by mRECIST. Excluded patients with ≥ 50% liver involvement and invasion of bile duct or main portal vein.

Stratification factors Region (Asia Pacific or Western), MVI or EHS (presence or absence), ECOG PS (0 or 1), Bodyweight (<60 kg or ≥60 kg)

Primary outcome OS mOS 13.6 vs 12.3 months; HR 0.92; 95% CI, 0·79–1·06

Secondary outcomes PFS (mRECIST) 7.4 vs 3.7 months; HR 0·66; 95% CI, 0·57–0·77 P <0·0001

TTP (mRECIST) 8·9 vs 3·7 months; HR 0·63; 95% CI, 0·53–0·73 P <0·0001

ORR and DCR (mRECIST) 24·1% vs 9·2%; OR 3·13; 95% CI, 2·15–4·56 P<0·0001 DCR 75.5% vs 60.5%

QOL Between-group comparison, summary score HR 0·87, 95% CI 0·754–1·013,

Toxicity (NCI CTC V4.0) Grade 3-4 TRAEs 57% vs 49% Serious TRAEs 18% vs 10%. Grade 3-4 AEs for Lenvatinib; Hypertension (23%), decreased weight (8%), increased bilirubin (7%), Proteinuria (6%). TRAEs leading to dose reduction 37% vs 38%, and discontinuation: 9% vs 7%.

Additional publications

RESORCE trial ([ClinicalTrials.gov number, NCT01774344](https://clinicaltrials.gov/ct2/show/NCT01774344))

**Design (n)**
Multicentre randomised double-blind phase 3 trial (573, 2:1 randomisation)

**Experimental arm**
Regorafenib 160 mg p.o. QD days 1-21 out of every 28-day cycle

**Control**
Placebo

**Key eligibility criteria**
Histologically- or radiographically-confirmed BCLC stage B or C HCC, not amenable to resection or local therapies, radiographic progression on sorafenib as the only prior line of therapy, prior sorafenib tolerated at dose of ≥400 mg daily for at least 20 of last 28 days prior to discontinuation, ECOG PS ≤ 1, Child-Pugh A, measurable disease by mRECIST and RECIST 1.1

**Stratification factors**
Region, ECOG PS 0 vs 1, macroscopic vascular invasion, extrahepatic spread, AFP <400 vs ≥ 400 ng/mL

**Primary outcome**
Overall survival 10.6 vs. 7.8 months; HR, 0.63; 95% CI, 0.50 to 0.79; P<0.0001

**Secondary outcomes**
- Median PFS (mRECIST) 3.1 vs 1.5 months, HR 0.46; 95% CI, 0.37 to 0.56; P<0.0001
- Median TTP (mRECIST) 3.2 vs 1.5 months, HR 0.44; 95% CI, 0.36 to 0.55; P<0.0001
- ORR, DCR (mRECIST) PR 10% vs 4%; OR 11% vs 4%, one-sided P=0.0047; DCR 65% vs 36%, one-sided P<0.0001
- Safety (NCI CTC V4.03) Incidence of TRAEs: 93% vs 52%; G3-4 AEs for regorafenib: hypertension (15%), hand-foot skin reaction (13%), fatigue (9%), diarrhoea (3%); related SAEs: 10%; treatment-related G5 events: 2%; dose reductions in regorafenib: 51%

**Publication:** [Bruix et al, Lancet 2017;389:56-66](https://www.lancet.com/journals/lancet/article/PIIS0140-6736(16)32352-2)
Additional publications


CELESTIAL trial (ClinicalTrials.gov number, NCT01908426)

Design (n)
Multicentre randomised double-blind phase 3 trial (707, 2:1 randomisation)

Experimental arm
Cabozantinib 60 mg p.o. QD

Control
Placebo

Key eligibility criteria
Histologically-confirmed HCC not amenable to curative treatment, radiographic progression on or after 1-2 prior systemic therapies, received prior sorafenib therapy, ECOG PS ≤ 1, Child-Pugh A

Stratification factors
Etiology (HBV vs HCV vs other), region (Asia vs other), and extrahepatic spread and/or macrovessel invasion (yes vs no)

Primary outcome
OS
10.2 vs. 8.0 months; HR, 0.76; 95% CI, 0.63 to 0.92; P=0.005

Secondary outcomes
Median PFS (RECIST 1.1)
5.2 vs 1.9 months, HR 0.44; 95% CI, 0.36 to 0.52; P<0.001

ORR, DCR (RECIST 1.1)
PR 4% vs <1%, P=0.009; DCR 64% vs 33%

Safety (NCI CTC V4.0)
Incidence of all-cause G3-4 AEs: 68% vs 36%; common G3-4 AEs for cabozantinib: hypertension (16%), hand-foot skin reaction (17%), diarrhoea (10%), elevated aminotransferase level (12%), fatigue (10%); all-cause SAEs: 50%; treatment-related G5 events: 1.2%; dose reductions in cabozantinib: 62%

Additional publications


**Trial**  
REACH-2 trial ([ClinicalTrials.gov, number NCT02435433](https://clinicaltrials.gov/ct2/show/NCT02435433))

**Design (n)**  
Multicentre randomised double-blind phase 3 trial (292, 2:1 randomisation)

**Experimental arm**  
Ramucirumab 8 mg/kg intravenously every 2 weeks

**Control**  
Placebo

**Key eligibility criteria**  
Histologically- or cytologically-diagnosed HCC or cirrhosis with clinically-diagnosed HCC, BCLC stage B or C, received prior sorafenib therapy, ECOG PS ≤ 1, Child-Pugh A, AFP ≥ 400 ng/mL

**Stratification factors**  
Macrovessel invasion (yes vs no), ECOG (0 vs 1), region

**Primary outcome**  
OS  
8.5 vs. 7.3 months; HR, 0.710; 95% CI, 0.531 to 0.949; P=0.0199

**Secondary outcomes**  
- **Median PFS (RECIST 1.1)**  
  2.8 vs 1.6 months, HR 0.452; 95% CI, 0.339 to 0.603; P<0.0001
- **ORR (RECIST 1.1)**  
  PR 5% vs 1%, P=0.1697
- **Safety (NCI CTC V4.0)**  
  G3-4 AEs for ramucirumab: hypertension (13%), hyponatremia (6%), AST elevation (3%); all-cause SAEs: 35%; treatment-related G5 events: 1.5%; treatment discontinuation of ramucirumab due to AE: 18%. Treatment reductions due to AEs: 5%

Additional publications


## Positive Randomised Trials

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Phase</th>
<th>No Patients</th>
<th>Experimental arm</th>
<th>Control</th>
<th>Primary Endpoint(s)</th>
<th>median OS (m)</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
<th>reference</th>
</tr>
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<tbody>
<tr>
<td>SHARP</td>
<td>III</td>
<td>602</td>
<td>Sorafenib</td>
<td>Placebo</td>
<td>OS</td>
<td>10.7 vs. 7.9</td>
<td>0.69</td>
<td>0.55 to 0.87</td>
<td>&lt;0.001</td>
<td>Llovet et al, N Engl J Med 2008;359:378-90</td>
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<tr>
<td>Asia-Pacific</td>
<td>III</td>
<td>271</td>
<td>Sorafenib</td>
<td>Placebo</td>
<td>OS</td>
<td>6.5 vs 4.2</td>
<td>0.68</td>
<td>0.50 to 0.93</td>
<td>0.014</td>
<td>Cheng et al A-L, Lancet Oncol, 2009 10: 25-34</td>
</tr>
<tr>
<td>RESORCE</td>
<td>III</td>
<td>573</td>
<td>Regorafenib</td>
<td>Placebo</td>
<td>OS</td>
<td>10.6 vs 7.8</td>
<td>0.63</td>
<td>0.50 to 0.79</td>
<td>&lt;0.0001</td>
<td>Bruix et al, Lancet 2017;389:56-66</td>
</tr>
<tr>
<td>CELESTIAL</td>
<td>III</td>
<td>707</td>
<td>Cabozantinib</td>
<td>Placebo</td>
<td>OS</td>
<td>10.2 vs. 8.0</td>
<td>0.76</td>
<td>0.63 to 0.92</td>
<td>0.005</td>
<td>Abou-Alfa et al, N Engl J Med 2018;379:54-63</td>
</tr>
<tr>
<td>REFLECT</td>
<td>III</td>
<td>954</td>
<td>Lenvatinib</td>
<td>Sorafenib</td>
<td>OS</td>
<td>13.6 vs 12.3</td>
<td>0.92</td>
<td>0.79 to 1.06</td>
<td>&lt;0.0001</td>
<td>Kudo M et al, Lancet 2018; 391(10126):1163-1173</td>
</tr>
<tr>
<td>REACH 2</td>
<td>III</td>
<td>292</td>
<td>Ramucirumab</td>
<td>Placebo</td>
<td>OS</td>
<td>8.5 vs. 7.3</td>
<td>0.71</td>
<td>0.531 to 0.949</td>
<td>0.0199</td>
<td>Zhu et al, Lancet Oncol 2019;20(2):282-296</td>
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<tr>
<td>IMbrave 150</td>
<td>III</td>
<td>501</td>
<td>Atezolizumab / Bevacizumab</td>
<td>Sorafenib</td>
<td>OS</td>
<td>NE vs 13.2</td>
<td>0.58</td>
<td>0.42 to 0.79</td>
<td>&lt;0.001</td>
<td>Finn RS et al NEJM 2020; 382(20):1894-1905</td>
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<td></td>
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<td>PFS</td>
<td>6.8 vs 4.3</td>
<td>0.59</td>
<td>0.47 to 0.76</td>
<td>&lt;0.001</td>
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</tr>
</tbody>
</table>
First-Line Systemic therapy

1. First choice fist-line therapy
   - The IMbrave 150 trial met both co-primary endpoints and demonstrated that the combination of atezolizumab and bevacizumab is superior to sorafenib in terms of overall survival (HR 0.58; 95% CI, 0.47-0.76) and progression free survival (0.59; 95% CI, 0.42–0.79) (1)
   - The combination was also associated with a higher response rate, duration of response and longer duration to reduced QOL
   - Because of the increased risk of variceal haemorrhage with bevacizumab, gastroscopic assessment and treatment of varices within six months of therapy is recommended in those at risk.

2. Alternative first-line therapy
   - In patients for whom atezolizumab or bevacizumab are contraindicated or not acceptable to patient, sorafenib(2, 3) and lenvatinib are alternative options
   - The REFLECT trial met its primary endpoint and demonstrated that lenvatinib was non-inferior to sorafenib in terms of overall (HR 0.92; 95% CI, 0.79–1.06)(4)
   - In considering the option of lenvatinib or sorafenib, the following should be taken into account
     - Lenvatinib is associated with a superior PFS, TTP, ORR and disease control rate compared with sorafenib
     - Patients with Vp4 were and ≥ 50% liver involvement were excluded from REFLECT trial
     - There is no evidence-based second-line therapy after lenvatinib
     - Regorafenib, cabozantinib and ramucirumab have level 1A evidence as second line therapy after sorafenib
     - Hypertension, weight loss, proteinuria, hypothyroidism and vomiting are more common with lenvatinib
     - PPE, diarrhoea, alopecia and rash are more common with sorafenib

Second-Line Systemic Therapy

1. After Atezolizumab and Bevacizumab
   • There is no evidence-based standard of care after Atezo/Bev
   • Progressive disease was the best response in 20% patients treated with Atezo/Bev and the median PFS was 6.8 months. There is therefore a significant need for second line therapy in this setting(1)
   • In the IMbrave 150 trial 63 (19%) patients received a TKI post Atezo/Bev but no data on outcome published to date
   • Patients who are fit (PS <2 and Child-Pugh A) may benefit from a multi-kinase inhibitor and should ideally be offered this in the context of a randomised trial
   • There is no data to support one TKI over another and sorafenib, lenvatinib and cabozantinib may be considered
   • The rational for ramucirumab in patients progressing on bevacizumab is weaker than that for a TKI
   • Regorafenib is not appropriate in patients who have not had sorafenib but may be considered third line after sorafenib

2. After Sorafenib
   • Placebo controlled randomised trials support the use of regorafenib(2) in those that tolerated sorafenib, ramucirumab(3) in those with AFP ≥400 ng/mL and cabozantinib(4). HR for OS were 0.63, 0.71 and 0.76 respectively. In the CELESTIAL trial, 27% received cabozantinib as 3rd line therapy and for those that received cabozantinib as second line therapy, the HR was 0.70
   • There are no predictive biomarkers to inform decision making in this setting and cross-trial comparisons are not robust in terms of differentiating toxicity or secondary outcomes
   • The FDA granted conditional approval for nivolumab and pembrolizumab as second line therapy after sorafenib. These approvals were based on single arm phase II trials (5, 6) but the phase III trial of nivolumab in the first-line failed to meet its primary endpoint (7)and the phase III trial of pembrolizumab in the second line also failed to meet its endpoint(8). Therefore these options are not generally recommended.
   • The FDA also granted conditional approval for the combination of nivolumab 1mg/kg and ipilimumab 3mg/kg both three weekly for three cycles followed by single agent nivolumab 240mg 2 weekly. This was based on date from 49 patients treated in the CheckMate 040 trial (9) where response rate of 33% was reported. The phase three trial of this combination is ongoing and, in the absence of data from this trial, the combination is not generally recommended.
Second-Line Systemic Therapy (Cont)

3. After Lenvatinib
   - There is no evidence based standard of care following lenvatinib
   - In the REFLECT trial 156 patients (33%) received post-study medication and of these, 121 (25%) received sorafenib. The outcome of these patients has not been reported to date.
   - The benefit and toxicity second line therapy is not known and patients should ideally be treated in the context of clinical trials

Hepatitis B virus and systemic therapy for hepatocellular carcinoma

Introduction
Chronic HBV infection is featured by the persistence of hepatitis B surface antigen (HBsAg) positivity for more than 6 months, and this poses a strong risk of developing cirrhosis and hepatocellular carcinoma (HCC). Globally, chronic HBV infection accounts for more than half of HCC, and frequently complicates the management of HCC during systemic therapy. The impact of HBV on the management of HCC and related guidance on management of HBV is discussed below:

1. Management of HBV during systemic therapy for HCC
2. HBV as a predictor of efficacy of systemic therapy
3. Areas of research on HBV in ICI treatment
4. Summary of recommendations
5. References
Management of HBV during systemic therapy for HCC

Screening and monitoring
All patients with the diagnosis of HCC should be tested for HBsAg prior to commencement of systemic therapy. For patients who are positive for HBsAg, HBV DNA should be determined at baseline and monitored every 1-3 months during systemic therapy. Liver biochemistry, particularly alanine aminotransferase (ALT), should also be monitored at least every 4-6 weeks along the course of systemic therapy. For patients who are negative for HBsAg, hepatitis B core antibody (anti-HBc) may be tested according to local practice to identify patients with prior HBV exposure. In case of HBsAg-negative and anti-HBc-positive, patients should be monitored with ALT, HBV DNA and HBsAg regularly. The above monitoring measures should be continued for at least 12 months after cessation of systemic therapy or until clinically not indicated (e.g. terminal stage of HCC).

Prevention of HBV reactivation
HBV reactivation refers to loss of immune control of HBV in patients with chronic HBV infection or prior exposure to HBV after immunosuppressive treatment. The reactivation of HBV activity is followed by hepatitis flare which is reflected by an elevation of ALT. Heterogeneous definitions of HBV reactivation and hepatitis flare have been described in literatures. The American Association for the Study of Liver Diseases provides a detailed and updated definition: In HBsAg-positive, anti-HBc-positive patients, HBV reaction is defined: 1) ≥2 log (100-fold) increase in HBV DNA compared to the baseline; or 2) HBV DNA ≥3 log (1,000) IU/mL in a patient with previously undetectable HBV level; or 3) HBV DNA ≥4 log (10,000) IU/mL if the baseline value is not available. For patients who are HBsAg-negative, Anti-HBc-positive, the definition of HBV reactivation is: 1) HBV DNA is detectable; or 2) reappearance of HBsAg. A hepatitis flare is defined as an ALT rise to ≥ 3 times of baseline level and > 100 U/L.

In the old era of cytotoxic chemotherapy, HBV reactivation occurred in up to 40% of HCC patients without antiviral therapy. However, HBV reactivation is less commonly encountered in the modern era of tyrosine kinase inhibitors (TKIs), likely due to less immunosuppressive property of approved TKIs for HCC and common use of antiviral therapy for HBV in patients with HCC. Regarding immune checkpoint inhibitors (ICIs), initial experiences came from clinical trials whereas all patients with HBsAg positivity are required to have extremely low HBV viral load (<100 IU/ml) and prophylactic antiviral therapy prior to recruitment. Under these circumstances, although fluctuation of HBV viral load has been observed during the treatment, significant HBV reactivation and/or hepatitis is rarely observed. For HBsAg-positive patients, antiviral therapy is essential during ICIs because multiple case series showed that HBV reactivation could occur when antiviral therapy was not administered. In the real-world setting, it is less clear whether HBV reactivation remains uncommon in patients with higher baseline HBV viral load and higher tumour burden. Further, hepatic events, including the elevation of ALT, frequently occur during ICIs treatment, and HBV reactivation should always be an important differential diagnosis during work-up.

The detailed HBV prophylaxis treatment has been described in various guidelines. For HBsAg-positive patients, if antiviral therapy is not commenced prior to diagnosis of HCC, prophylactic antiviral should be commenced at least 7 days prior to systemic therapy. Either entecavir or tenofovir is preferred because of higher potency and resistance barriers compared to other nucleos(t)ide analogues. Currently, there is no consensus on the optimal timing of stopping anti-HBV prophylaxis after completion of anti-cancer treatment for HCC. For general cancers, it was recommended that prophylaxis should be continued for at least 6 months after completion of immunosuppressive therapy. For HCC, most patients have comorbid significant liver fibrosis and/or cirrhosis, which is an indication for long-term antiviral therapy. Also, most patients require multiple lines of systemic therapy with short drug-free interval, hence it is reasonable for clinicians to continue antiviral therapy without interruption in the remaining course of advanced disease.
**HBV as a predictor of efficacy of systemic therapy**

**Targeted therapy**
Understanding on the influence of HBV on outcomes of systemic therapy mainly comes from subgroup analyses of prospective clinical trials. For sorafenib, according to subgroup analyses of both SHARP and the AP-SHARP studies, the survival benefits of sorafenib were less noticeable in subpopulations of HBV infection as the aetiology of HCC.\(^{19,20}\) These observations were further confirmed by an individual patient meta-analysis on three other phase III clinical trials comparing sorafenib to competitor small molecules, namely linifanib, sunitinib and brivanib.\(^{21}\) A total of 3256 patients, with 50% receiving first-line sorafenib, were analysed, and it was found that survival benefits of sorafenib were demonstrated in the HBV-negative/HCV-positive subgroup but not in the HBV-positive/HCV-negative subgroup, as compared to other TKIs.\(^{21}\) The above findings were not observed with other targeted agents. For lenvatinib, as shown by the REFLECT study, survival benefits were similarly observed in HCC of HBV or HCV aetiology.\(^{22}\) For cabozantinib, pre-planned subgroup analyses of the CELESTIAL study in sorafenib-treated population showed that the HBV subgroup tended to benefit more from the drug than the HCV subgroup.\(^{23}\) For regorafenib, the RESORCE study showed that survival benefits persisted regardless of the presence of hepatitis B status or not.\(^{24}\) For ramucirumab, REACH2 study indicated that survival benefits were observed in HCC of all aetiologies, including HBV.\(^{25}\)

**Immune check-point inhibitors**

The influence of viral aetiology on the outcomes of ICIs is less understood. The Checkmate 459 study suggested that HCC of HBV or HCV aetiology had trends of more OS benefits from nivolumab than the patients with non-B-non-C aetiology.\(^{26}\) For pembrolizumab, subgroup analyses of the Keynote 240 clinical trial showed that pembrolizumab benefitted HCC of all aetiologies in terms of OS, but there was a trend of more benefits in the HBV subgroup than the HCV and non-B-non-C aetiology.\(^{8}\) In the IMBRAVE150 study, the regimen of atezolizumab plus bevacizumab benefitted patients of all aetiologies but there was a trend of more benefit in the HBV or HCV-subgroup than the non-B-non-C subgroup.\(^{27}\)

In summary, the findings on the impact of HBV on outcomes of sorafenib are supported by two phase III clinical trials and meta-analyses on another three phase III clinical trials. Therefore, the aetiology of HCC should be one of the considerations for clinicians planning to administer sorafenib for patients. For other targeted agents and ICIs, the association of viral aetiology with treatment outcomes is less clear. Caution should be exercised when interpreting subgroup analyses of single clinical trials, which are prone to bias.
Areas of research on HBV in ICI treatment

Optimal baseline HBV NDA
The optimal cut-off HBV DNA for enrolment to clinical trials on ICIs is unknown. Currently, most sponsored clinical trials have adopted a conservative approach of using undetectable or extremely low HBV DNA cut-off ranging from 100 to 500 IU/ml as inclusion criteria. According to one retrospective study on 6 out 141 patients who developed HBV reactivation during ICIs for treatment of various cancer types, multivariate analysis showed that the prophylactic antiviral therapy, but not baseline HBV DNA level, to be the single independent predictor for HBV reactivation. This study gives a clue that baseline HBV viral load may be less crucial than prophylactic antiviral therapy on the development of HBV reactivation during ICI treatment. However, more robust data are required to determine the optimal cut-off of HBV viral load prior to commencement of ICIs.

Population of HBsAg-negative, anti-HBc-positive
In general, patients who are HBsAg-negative, anti-HBc-positive have a lower risk of HBV reactivation than HBsAg-positive counterparts. For HCC, most clinicians prefer monitoring instead of prophylactic antiviral treatment in this population. However, HBV reactivation may still occur in this population who undergo biologics with immunomodulatory effects (e.g. rituximab, infliximab) for other diseases, or undergo ICIs in the presence of human immunodeficiency viruses infection. When ICI use becomes more popular with more novel immunotherapeutic agents in future, safety data of immunotherapy in HBsAg-negative, anti-HBc-positive will be important.
Summary of Recommendations

1. Definition of HBV reactivation
   - HBsAg +ve
     • $\geq 2 \log (100\text{-fold})$ increase in HBV DNA compared to the baseline OR
     • HBV DNA $\geq 3 \log (1,000)$ IU/mL in a patient with previously undetectable HBV level OR
     • HBV DNA $\geq 4 \log (10,000)$ IU/mL if the baseline value is not available.
   - HBsAg –ve ; Anti-HBc +ve
     • HBV DNA is detectable OR
     • Reappearance of HBsAg

2. Definition of hepatitis flare
   • ALT $\geq 3$ times of baseline level and $> 100$ U/L.

3. Screening (prior to systemic therapy)
   • HBsAg should be tested in all patients. This is usually accompanied with Anti-HCV to determine the aetiology of HCC.
   • If HBsAg is negative, Anti-HBc may be tested according to local practice.
Summary of Recommendations (Cont)

4. Monitoring (during systemic therapy)
   • HBsAg +ve
     • Monitor ALT every 4-6 weeks (or more frequently if clinically indicated)
     • Monitor HBV DNA every 3 months
   • HBsAg –ve/Anti-HBc +ve
     • Monitor ALT every 4-6 weeks (or more frequently if clinically indicated)
     • Monitor HBV DNA and HBsAg every 3 months

5. Prophylactic antiviral therapy
   • Population: All HBsAg +ve patients who are scheduled to undergo systemic therapy
   • Type of anti-cancer treatment: cytotoxic chemotherapy, TKI, ICIs
   • Time: Antiviral therapy should be commenced at least 7 days prior to systemic therapy
   • Antiviral therapy: Entecavir or Tenofovir is preferred
   • Duration
     - Till at least 6 months after completion of anti-cancer treatment
     - Long-term in patients who have cirrhosis/significant liver fibrosis/short drug-free period
     - May be stopped in patients with terminal-stage HCC
   • Consult hepatologist if clinically indicated


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