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the therapeutic algorithm for systemic therapy has become increasingly complex and existing guidelines are rapidly outdated.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.

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Abbreviations

DCR	Disease control rate
DR	Duration of response
EHS	Extrahepatic spread
ICI	Immune Checkpoint Inhibitor
MVI	Macrovascular invasion
NCI CTC	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Objective response rate
OS	Overall survival
PFS	Progression free survival
PPE	Palmar Plantar Erythema
PVI	Portal vein invasion
QOL	Quality of life
TKI	Tyrosine Kinase Inhibitor
TTP	Time to progression

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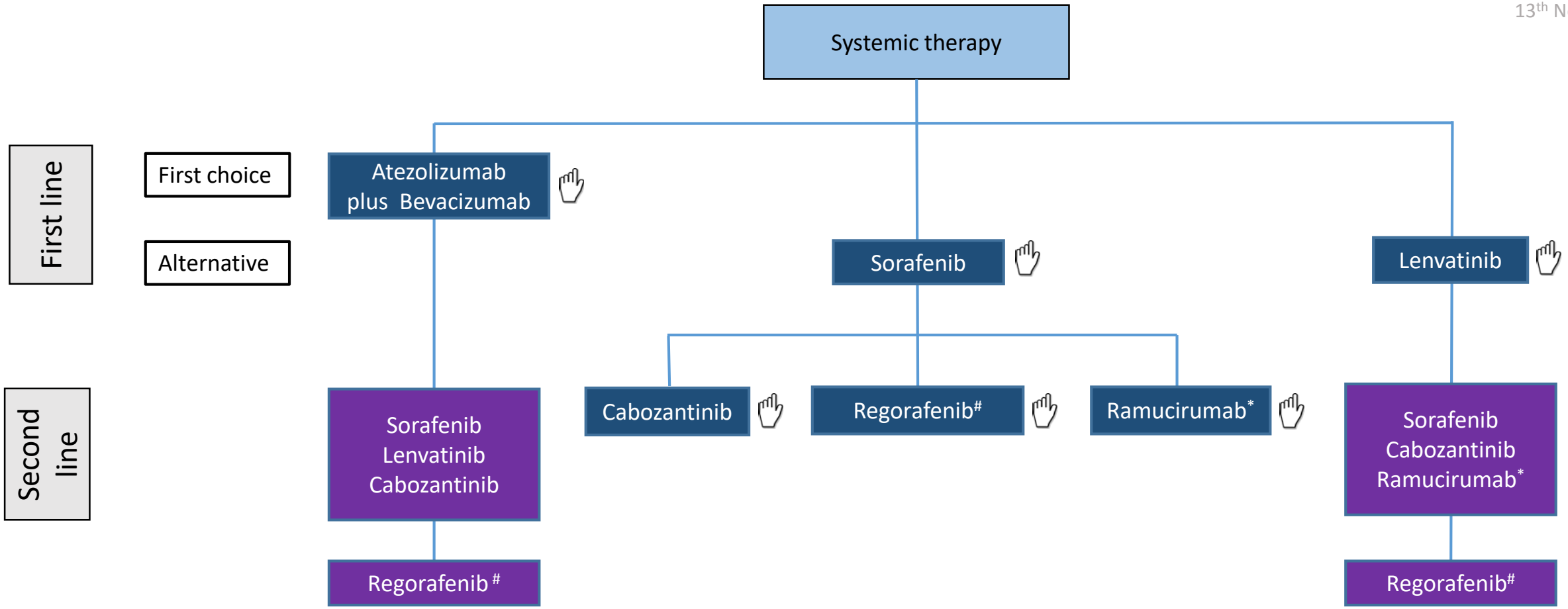

Level 1,A evidence

Level V,C evidence

*If AFP ≥400 ng/mL

#In patients who tolerated sorafenib

Click on box to navigate to further details

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Trial	SHARP trial (ClinicalTrials.gov number, NCT00105443.)
Design (n)	Multicentre randomised double-blind phase 3 trial (602 1:1)
Control	Placebo
Experimental arm	Sorafenib 400mg BD
Key eligibility criteria	Histologically confirmed advanced HCC, no prior systemic therapy, ECOG PS ≤ 2, Child-Pugh A, measurable disease by RECIST 1.1
Stratification factors	Region, ECOG PS 0 vs 1 or 2, macroscopic vascular invasion or extrahepatic spread
Primary outcome	
OS	mOS 10.7 vs. 7.9 months; HR, 0.69; 95% CI, 0.55 to 0.87; P<0.001
Time to symptomatic progression (FHSI8)	4.1 vs 4.9 months; HR 1.08; 95% CI, 0.88 to 1.31; P = 0.77
Secondary outcomes	
TTP (RECIST)	5.5 vs 2.8 months; HR, 0.58; 95% CI, 0.45 to 0.74; P<0.001
ORR and DCR	CR 0% vs 0%, PR; 2% vs 1%, SD; 71% vs 67%, DCR; 43% vs 32% (p=0.02)
Toxicity (NCI CTC V3.0)	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%.

Publication; Llovet et al, N Engl J Med 2008;359:378-90

Additional Publications

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Additional publications

- 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. 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. Lancet Oncol. 2009 Jan;10(1):25-34. doi: 10.1016/S1470-2045(08)70285-7.
- Observational registry of sorafenib use in clinical practice across Child-Pugh subgroups: The GIDEON study. Marrero JA, Kudo M, Venook AP, Ye SL, Bronowicki JP, Chen XP, Dagher L, Furuse J, Geschwind JH, de Guevara LL, Papandreou C, Takayama T, Sanyal AJ, Yoon SK, Nakajima K, Lehr R, Heldner S, Lencioni R. J Hepatol. 2016 Dec;65(6):1140-1147. doi: 10.1016/j.jhep.2016.07.020
- Relationship between baseline hepatic status and outcome, and effect of sorafenib on liver function: SHARP trial subanalyses. Raoul JL, Bruix J, Greten TF, Sherman M, Mazzaferro V, Hilgard P, Scherubl H, Scheulen ME, Germanidis G, Dominguez S, Ricci S, Nadel A, Moscovici M, Voliotis D, Llovet JM. J Hepatol. 2012 May;56(5):1080-8. doi: 10.1016/j.jhep.2011.12.009.
- Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. Bruix J, Raoul JL, Sherman M, Mazzaferro V, Bolondi L, Craxi A, Galle PR, Santoro A, Beaugrand M, Sangiovanni A, Porta C, Gerken G, Marrero JA, Nadel A, Shan M, Moscovici M, Voliotis D, Llovet JM. J Hepatol. 2012 Oct;57(4):821-9. doi: 10.1016/j.jhep.2012.06.014.
- Plasma biomarkers as predictors of outcome in patients with advanced hepatocellular carcinoma. Llovet JM, Peña CE, Lathia CD, Shan M, Meinhardt G, Bruix J; SHARP Investigators Study Group. Clin Cancer Res. 2012 Apr 15;18(8):2290-300. doi: 10.1158/1078-0432.CCR-11-2175.

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Trial	IMbrave 150 (ClinicalTrials.gov number, NCT03434379.)
Design (n)	Multicentre open-label, randomised phase 3 trial (501 2:1)
Control	Sorafenib 400mg BD
Experimental arm	Atezolizumab 1200mg IV plus Bevacizumab 15mg/Kg IV both three weekly
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 RECIST 1.1. Excluding those with untreated or incompletely treated esophageal or gastric varices (assessed with esophagogastroduodenoscopy within 6 months)
Stratification factors	Region (Asia excluding Japan vs rest of world), MVI or EHS (presence or absence), baseline AFP (<400 vs $\geq 400\text{ng/ml}$, PS 0 vs 1
Primary outcome	
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
Secondary outcomes	
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
Toxicity (NCI CTC V4.0)	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

Additional Publications

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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%.

Publication; Kudo M et al, Lancet Mar 24;391(10126):1163-1173.

Additional Publications

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Additional publications

- Urine protein:creatinine ratio vs 24-hour urine protein for proteinuria management: analysis from the phase 3 REFLECT study of lenvatinib vs sorafenib in hepatocellular carcinoma. Evans TRJ, Kudo M, Finn RS, Han KH, Cheng AL, Ikeda M, Kraljevic S, Ren M, Dutcus CE, Piscaglia F, Sung MW. Br J Cancer. 2019 Jul;121(3):218-221. doi: 10.1038/s41416-019-0506-6.

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Trial	RESORCE trial (ClinicalTrials.gov number, 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

Additional Publications

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Additional publications

- Regorafenib in Patients With Advanced Child-Pugh B Hepatocellular Carcinoma: A Multicenter Retrospective Study. Liver Int. Kim H-D, Bang Y, Lee MA, et al. 2020 Jun (e-pub). DOI: 10.1111/liv.14573.
- Preliminary Experience on Safety of Regorafenib After Sorafenib Failure in Recurrent Hepatocellular Carcinoma After Liver Transplantation. Iaverone M, Invernizzi F, Czauderna C, et al. Am J Transpl. 2019 Nov;19(11):3176-3184. DOI: 10.1111/ajt.15551.
- Biomarkers Associated With Response to Regorafenib in Patients With Hepatocellular Carcinoma. Teufel M, Seidel H, Kochert K, et al. Gastroenterol. 2019 May;156(6):1731-1741. DOI: 10.1053/j.gastro.2019.01.261.
- Outcomes of Sequential Treatment With Sorafenib Followed by Regorafenib for HCC: Additional Analyses From the Phase III RESORCE Trial. Finn RS, Merle P, Granito A, et al. J Hepatol. 2018 Aug;69(2):353-358. DOI: 10.1016/j.jhep.2018.04.010.
- Exposure-response Relationship of Regorafenib Efficacy in Patients With Hepatocellular Carcinoma. Solms A, Reinecke I, Fiala-Buskies S, et al. Eur J Pharm Sci. 2017 Nov;15(109S):S149-S153. DOI: 10.1016/j.ejps.2017.05.050.

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Trial	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%

Publication: Abou-Alfa et al, N Engl J Med 2018;379:54-63

Additional Publications

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Additional publications

- Serum alpha-fetoprotein levels and clinical outcome in the phase 3 CELESTIAL study of cabozantinib versus placebo in patients with advanced hepatocellular carcinoma. Kelley RK, Meyer T, Rimassa L, et al. Clin Cancer Res. 2020; in press. DOI: 10.1158/1078-0432.CCR-19-3884.
- Comparative Efficacy of Cabozantinib and Regorafenib for Advanced Hepatocellular Carcinoma. Kelley RK, Mollon P, Blanc J-F, et al. Adv Ther. 2020 Jun;37(6):2678-2695. DOI: 10.1007/s12325-020-01378-y.
- Cabozantinib Exposure-Response Analyses of Efficacy and Safety in Patients With Advanced Hepatocellular Carcinoma. Nguyen L, Chapel S, Tran BD, Lacy S. J Pharmacokinet Pharmacodynam. 2019 Dec;46(6):577-589. DOI: 10.1007/s10928-019-09659-y.

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Trial	REACH-2 trial (ClinicalTrials.gov, number 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 of ramucirumab due to AE: 18%. Treatment reductions due to AEs; 5%

Publication: Zhu et al, Lancet Oncol 2019;20(2):282-296

Additional Publications

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Additional publications

- Ramucirumab in Elderly Patients With Hepatocellular Carcinoma and Elevated Alpha-Fetoprotein After Sorafenib in REACH and REACH-2. Kudo M, Galle PR, Llovet JM, et al. Liver Int. 2020 Apr (e-pub). DOI: 10.1111/liv.14462.
- Alpha-fetoprotein Kinetics in Patients With Hepatocellular Carcinoma Receiving Ramucirumab or Placebo: An Analysis of the Phase 3 REACH Study. Chau I, Park JO, Ryoo B-Y, et al. Br J Cancer. 2018 Jul;119(1):19-26. DOI: 10.1038/s41416-018-0103-0.
- Ramucirumab as Second-Line Treatment in Patients With Advanced Hepatocellular Carcinoma: Analysis of REACH Trial Results by Child-Pugh Score. Zhu AX, Baron AD, Malfertheiner P, et al. JAMA Oncol. 2017 Feb;3(2):235-243. DOI: 10.1001/jamaoncol.2016.4115.

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Positive Randomised Trials

Trial Name	Phase	No Patients	Experimental arm	Control	Primary Endpoint(s)	median OS (m)	HR	95% CI	P	reference
SHARP	III	602	Sorafenib	Placebo	OS	10.7 vs. 7.9	0.69	0.55 to 0.87	<0.001	Llovet et al, N Engl J Med 2008;359:378-90
Asia-Pacific	III	271	Sorafenib	Placebo	OS	6.5 vs 4.2	0.68	0·50 to 0·93	0.014	Cheng et al A-L, Lancet Oncol, 2009 10: 25-34
RESORCE	III	573	Regorafenib	Placebo	OS	10.6 vs 7.8	0.63	0.50 to 0.79	<0.0001	Bruix et al, Lancet 2017;389:56-66
CELESTIAL	III	707	Cabozantinib	Placebo	OS	10.2 vs. 8.0	0.76	0.63 to 0.92	0.005	Abou-Alfa et al, N Engl J Med 2018;379:54-63
REFLECT	III	954	Lenvatinib	Sorafenib	OS	13.6 vs 12.3	0.92	0·79 to 1·06		Kudo M et al, Lancet 2018; 391(10126):1163-1173
REACH 2	III	292	Ramucirumab	Placebo	OS	8.5 vs. 7.3	0.71	0.531 to 0.949	0.0199	Zhu et al, Lancet Oncol 2019;20(2):282-296
IMbrave 150	III	501	Atezolizumab / Bevacizumab	Sorefenib	OS	NE vs 13.2	0.58	0.42 to 0.79	<0.001	Finn RS et al NEJM 2020; 382(20):1894-1905
					PFS	6.8 vs 4.3	0.59	0.47 to 0.76	<0.001	

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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

1. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020;382(20):1894-905.
2. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378-90.
3. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. 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(1):25-34.
4. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018;391(10126):1163-73.

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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.

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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

1. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020;382(20):1894-905.
2. Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;389(10064):56-66.
3. Zhu AX, Kang YK, Yen CJ, Finn RS, Galle PR, Llovet JM, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased alpha-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019;20(2):282-96.
4. Abou-Alfa GK, Meyer T, Cheng AL, El-Khoueiry AB, Rimassa L, Ryoo BY, et al. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. N Engl J Med. 2018;379(1):54-63.
5. El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet. 2017;389(10088):2492-502.
6. Zhu AX, Finn RS, Edeline J, Cattan S, Ogasawara S, Palmer D, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol. 2018;19(7):940-52.
7. Yau T, Park JW, Finn RS, Cheng AL, Mathurin P, Edeline J, et al. CheckMate 459: A randomized, multi-center phase III study of nivolumab (NIVO) vs sorafenib (SOR) as first-line (1L) treatment in patients (pts) with advanced hepatocellular carcinoma (aHCC). Annals of Oncology. 2019;30:874-+.
8. Finn RS, Chan SL, Zhu AX, Knox JJ, Cheng AL, Siegel AB, et al. KEYNOTE-240: Randomized phase III study of pembrolizumab versus best supportive care for second-line advanced hepatocellular carcinoma. Journal of Clinical Oncology. 2017;35(4).
9. Yau T, Kang YK, Kim TY, El-Khoueiry AB, Santoro A, Sangro B, et al. Nivolumab (NIVO) plus ipilimumab (IPI) combination therapy in patients (pts) with advanced hepatocellular carcinoma (aHCC): Results from CheckMate 040. Journal of Clinical Oncology. 2019;37(15).

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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).[1] Globally, chronic HBV infection accounts for more than half of HCC, and frequently complicates the management of HCC during systemic therapy.[2] The impact of HBV on the management of HCC and related guidance on management of HBV is discussed below:

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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.[3,4] For patients who are positive for HBsAg, HBV DNA should be determined at baseline and monitored every 1-3 months during systemic therapy.[3] 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.[3] 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).[3]

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:[3] 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[5] and common use of antiviral therapy for HBV in patients with HCC.[6] 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.[7-9] Under these circumstances, although fluctuation of HBV viral load has been observed during the treatment, significant HBV reactivation and/or hepatitis is rarely observed.[10] 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.[11-13] 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,[14] and HBV reactivation should always be an important differential diagnosis during work-up.[15]

The detailed HBV prophylaxis treatment has been described in various guidelines.[3,4] 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.[16,17] 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.[3] For HCC, most patients have comorbid significant liver fibrosis and/or cirrhosis, which is an indication for long-term antiviral therapy.[18] 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.

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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.

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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.[11] 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 immuno-modulatory effects (e.g. rituximab, infliximab) for other diseases,[28,29] or undergo ICIs in the presence of human immunodeficiency viruses infection.[30] 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.

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Summary of Recommendations

1. Definition of HBV reactivation
   -HBsAg +ve
   - ≥2 log (100-fold) increase in HBV DNA compared to the baseline OR
   - HBV DNA ≥3 log (1,000) IU/mL in a patient with previously undetectable HBV level OR
   - HBV DNA ≥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 ≥ 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.

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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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