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LETTERS TO THE EDITOR

Updated treatment recommendations for hepatocellular carcinoma (HCC) from the ESMO Clinical Practice Guidelines

The following ESMO Clinical Practice Guideline has been recently updated with new treatment recommendations for hepatocellular carcinoma:

Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[1]

EUPDATE

View the eUpdate here: https://www.esmo.org/guidelines/gastrointestinal-cancers/hepatocellular-carcinoma/eupdate-hepatocellular-carcinoma-treatment-recommendations

https://www.esmo.org/guidelines/gastrointestinal-cancers/hepatocellular-carcinoma/eupdate-hepatocellular-carcinoma-algorithm

STAGING AND RISK ASSESSMENT

The original Table 4 is updated.

MANAGEMENT OF EARLY AND INTERMEDIATE HEPATOCELLULAR CARCINOMA (HCC), SELECTIVE INTERNAL RADIOTHERAPY

The text has been updated to include a level of evidence and grade of recommendation for selective internal radiotherapy (SIRT):

Thus, in exceptional circumstances, for patients with liver-confined disease and good liver function in whom neither transarterial chemoembolisation (TACE) nor systemic therapy is possible, SIRT may be considered [III, C].

MANAGEMENT OF ADVANCED DISEASE, SYSTEMIC THERAPIES FOR ADVANCED HCC

New text to replace subsections 'Targeted first-line therapies' and 'Targeted second-line therapies':

Table 4. BCLC staging and treatment options according to level of evidence and approval status

BCLC stage		Treatment (standard of care)	Indication constraints based on tumour burden and liver function	Alternative treatment
0-A	Single tumour any size or up to three nodules ≤3 cm Preserved liver function ECOG PS 0	Resection [III, A] Transplantation [III, A] Thermal ablation [III, A] TACE [I, A]	Adequate size and function of remnant liver Size ≤5 cm, number of nodules ≤3 Size ≤3 cm, not adjacent to vessels or bile duct Contraindications against resection and thermal ablation. Bridging to transplantation	SBRT [III, C] HDR brachytherapy [III, C] SIRT [III, C]
B	Multinodular Preserved liver function ECOG PS 0	TACE [I, A]	Size 5-10 cm, tumour nodules accessible to supra-selective catheterisation	Transplantation [III, A] Resection [III, A] Systemic therapy (not suitable for local therapies) [I, A] SIRT (liver confined, good liver function, no systemic therapy feasible)
C	Portal invasion Extrahepatic spread Preserved liver function ECOG PS 0-2	Atezolizumab plus bevacizumab (first line) [I, A; ESMO-MCBS v1.1 score: 5] Option: Sorafenib (first line) [I, A; ESMO-MCBS v1.1 score: 4] Lenvatinib (first line) [I, A][a] Standard after sorafenib: Cabozantinib [I, A; ESMO-MCBS v1.1 score: 3] Regorafenib[b] [I, A; ESMO-MCBS v1.1 score: 4] Ramucirumab[c] [I, A; ESMO-MCBS v1.1 score: 1] Option after atezolizumab plus bevacizumab/lenvatinib: Sorafenib [V, C] Lenvatinib [V, C] Cabozantinib [V, C] Regorafenib[b] [V, C] Ramucirumab[c] [V, C]	Child–Pugh A Child–Pugh A Tolerability to sorafenib, (regorafenib) AFP ≥400 ng/ml for ramucirumab	SIRT (liver confined, good liver function, no systemic therapy feasible)
D	End-stage liver function ECOG PS 3-4	BSC [III, A]		

AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; HDR, high dose rate; PS, performance status; SBRT, stereotactic body radiotherapy; SIRT, selective internal radiotherapy; TACE, transarterial chemoembolisation; TKI, tyrosine kinase inhibitor.

[a] Noninferiority to sorafenib established; no evaluable benefit.

[b] Regorafenib is not recommended in TKI-naïve patients.

[c] Ramucirumab is only recommended in patients with an AFP level ≥400 ng/ml.

Treatment sequencing

In recent years, several first- and second-line treatment options have been approved for advanced HCC and recommended in ESMO Clinical Practice Guidelines. Exploratory analyses of the reported first- and second-line trials indicate that a cumulative median overall survival (OS) of >20 months can be reached in patients with maintained liver function, and sequential systemic therapy is therefore strongly recommended.

Atezolizumab plus bevacizumab is the first treatment to demonstrate a significant OS benefit compared with sorafenib with a hazard ratio for death of 0.66 [95% confidence interval (CI) 0.52-0.85; $P = 0.0009$] in data reported from a recent abstract.[2] Consequently, atezolizumab plus bevacizumab will become the standard of care in first-line systemic therapy for HCC. However, 20% of patients do not respond to atezolizumab plus bevacizumab and the median progression-free survival is only 6.8 months, raising the need to define options for second-line therapy.[3] Drugs in the second-line setting have so far only been tested after sorafenib failure/intolerance and there are currently no phase III trial data to inform the choice of second-line therapy in HCC patients that received alternative front-line therapies. There is, however, a clear rationale for offering a multikinase inhibitor given the existing evidence for efficacy in first and second line. See ESMO-Magnitude of Clinical Benefit Scale (MCBS) (Table 8). As there is no evidence for any drug in particular, it is recommended that all the currently approved first- and second-line agents could be considered as second-line therapy (see Figure 1; efficacy data are summarised in a new Table 9).

Current evidence base:

- Sorafenib: sorafenib has only been evaluated in the first-line setting. Phase IV/observational studies have not revealed new safety signals in patients with Child–Pugh B cirrhosis[4] [I, A; ESMO-MCBS v1.1 score: 4].
- Lenvatinib: lenvatinib has only been evaluated in the first-line setting. The drug has shown a higher response rate compared with other tyrosine kinase inhibitors (TKIs) and ramucirumab in HCC[5] [I, A], with noninferiority to sorafenib established and no evaluable benefit.
- Regorafenib: regorafenib has only been evaluated in the second-line setting after progression on sorafenib. One main inclusion criterion for the RESORCE study was the tolerance to sorafenib; therefore the drug is preferably recommended in patients that have tolerated sorafenib and not in TKI-naïve patients[6] [I, A; ESMO-MCBS v1.1 score: 4].
- Cabozantinib: cabozantinib has been evaluated in the second- and third-line (28% of patients in the CELESTIAL trial) setting after intolerance to or progression under sorafenib treatment. Efficacy and safety of cabozantinib is independent of the duration of sorafenib pretreatment[7] [I, A; ESMO-MCBS v1.1 score: 3].
- Ramucirumab: ramucirumab has only been evaluated in the second-line setting after intolerance to/progression under sorafenib treatment. Ramucirumab has only shown efficacy in patients with an α-fetoprotein (AFP) level ≥400 ng/ml[8] [I, A; ESMO-MCBS v1.1 score: 1].

The majority of ESMO Guideline authors recommend considering all approved agents (sorafenib, lenvatinib, regorafenib, cabozantinib and ramucirumab) in the second-line setting after atezolizumab plus bevacizumab. A minority of the authors (3/14) recommended that only sorafenib or lenvatinib should be used in second line after atezolizumab plus bevacizumab and that regorafenib, cabozantinib and ramucirumab should be used in third line.

The ESMO-MCBS Table 8 is updated to include scores for ramucirumab and atezolizumab plus bevacizumab.

Table 8. ESMO-MCBS table for new therapies/indications in HCC[a]

Therapy	**Lenvatinib versus sorafenib in first-line treatment**
Disease setting	First-line advanced or unresectable hepatocellular carcinoma
Trial	A multicentre, open-label, phase III trial to compare the efficacy and safety of lenvatinib (E7080) versus sorafenib in first-line treatment of participants with unresectable hepatocellular carcinoma (REFLECT)[5] NCT01761266
Phase	III
Control	Sorafenib OS control: 12.3 months PFS control: 3.7 months
Absolute survival gain	OS gain: 1.3 months OS noninferiority, inferiority margin: 1.08 PFS gain: 3.7 months
HR (95% CI)	OS HR: 0.92 (0.79-1.06) PFS HR: 0.66 (0.57-0.77)
QoL/toxicity	No evaluable benefit
ESMO-MCBS score[b]	Noninferiority to sorafenib established, no evaluable benefit. Not scorable.
Therapy	**Cabozantinib versus placebo in second-line treatment**
Disease setting	Second-line unresectable hepatocellular carcinoma after TKI
Trial	Study of cabozantinib (XL184) versus placebo in patients with hepatocellular carcinoma who have received prior sorafenib (CELESTIAL)[7] NCT01908426
Phase	III
Control	Placebo OS control: 8.0 months PFS control: 1.9 months
Absolute survival gain	OS gain: 2.2 months PFS gain: 3.3 months
HR (95% CI)	OS HR: 0.76 (0.63-0.92) PFS HR: 0.44 (0.36-0.52)
QoL/toxicity	Increased toxicity
ESMO-MCBS score[b]	3 (Form 2a)
Therapy	**Regorafenib after sorafenib in second-line treatment**
Disease setting	Second-line unresectable hepatocellular carcinoma after TKI
Trial	Study of regorafenib after sorafenib in patients with hepatocellular carcinoma (RESORCE)[6] NCT01774344
Phase	III
Control	Placebo OS control: 7.8 months PFS control: 1.5 months
Absolute survival gain	OS gain: 2.8 months 2-year survival gain >10% PFS gain: 1.6 months
HR (95% CI)	OS HR: 0.63 (0.50-0.79) PFS HR: 0.46 (0.37-0.56)
QoL/toxicity	Increased toxicity
ESMO-MCBS score[b]	4 (Form 2a)

Table 8. Continued

Therapy	Ramucirumab versus placebo in advanced HCC
Disease setting	Patients with advanced HCC that cannot be removed by surgery with a high blood level of AFP and previously treated with sorafenib
Trial	A study of ramucirumab (LY3009806) versus placebo in participants with hepatocellular carcinoma and elevated baseline alpha-fetoprotein (REACH-2)[8,12] NCT02435433
Phase	III
Control	Placebo OS control: 7.3 months
Absolute survival gain	OS gain: 1.2 months
HR (95% CI)	OS HR: 0.71 (0.53-0.95)
QoL/toxicity	Benefit for delayed deterioration in global QoL not significant
ESMO-MCBS score[b]	1 (Form 2a)
Therapy	**Atezolizumab plus bevacizumab versus sorafenib in first-line treatment**
Disease setting	First-line advanced or unresectable hepatocellular carcinoma
Trial	A study of atezolizumab in combination with bevacizumab compared with sorafenib in patients with untreated locally advanced or metastatic hepatocellular carcinoma (IMbrave150)[3] NCT03434379
Phase	III
Control	Sorafenib OS control: 13.2 months
Absolute survival gain	OS gain: 9.6[c] months
HR (95% CI)	OS HR 0.58 (0.42-0.79) $P < 0.001$ crossed the first interim boundary of 0.0033
QoL/toxicity	Delayed deterioration
ESMO-MCBS score[b]	5 (Form 2a)

AFP, α-fetoprotein; CI, confidence interval; EMA, European Medicines Agency; ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; HCC, hepatocellular carcinoma; HR, hazard ratio; OS, overall survival; PE, point estimate; PFS, progression-free survival; QoL, quality of life; TKI, tyrosine kinase inhibitor.

[a] EMA approvals since January 1, 2016.

[b] ESMO-MCBS v1.1[13] The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/scale-evaluation-forms-v1.0-v1.1/scale-evaluation-forms-v1.1).

[c] Estimation of gain based on the PE HR 0.58.

MANAGEMENT OF ADVANCED DISEASE, IMMUNOTHERAPIES

The text has been updated:

Atezolizumab plus bevacizumab, which showed superior efficacy compared with sorafenib, is recommended as standard of care in first-line therapy of patients with advanced HCC and received European Medicines Agency (EMA) approval in late 2020[3,9] [I, A; ESMO-MCBS v1.1 score: 5].

Immunotherapy in the form of monotherapy has been evaluated in patients in two phase III studies. The first-line phase III CheckMate 459 trial, comparing sorafenib with nivolumab as a first-line treatment option, failed to meet the primary endpoint of OS.[10] The second-line phase III KEYNOTE-240 trial of pembrolizumab versus placebo also failed to meet its co-primary endpoints of OS and progression-free survival.[11] Neither drug has received EMA approval and they are not recommended as monotherapy for the treatment of advanced HCC.

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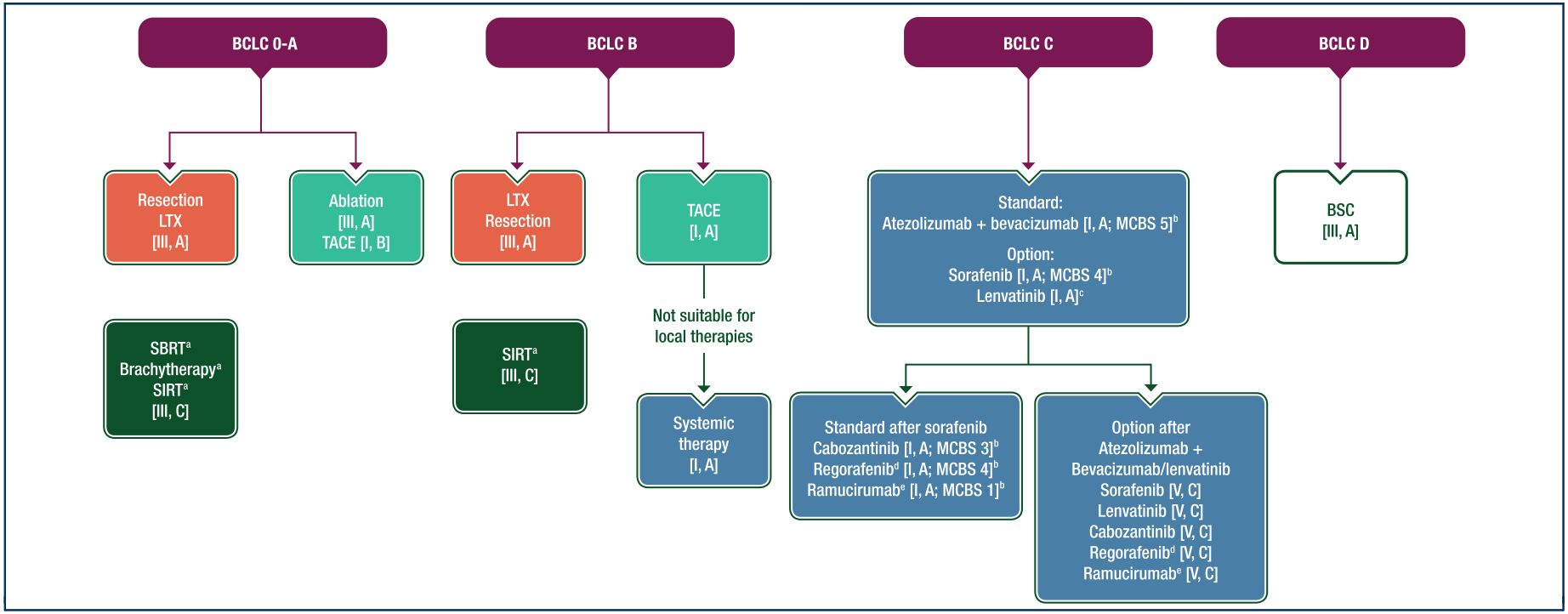

Figure 1. HCC treatment options depending on BCLC stage.
Purple: general categories or stratification; red: surgery; green: radiotherapy; blue: systemic anticancer therapy; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.
AFP, a-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; EMA, European Medicines Agency; HCC, hepatocellular carcinoma; LTX, liver transplantation; ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; SBRT, stereotactic body radiotherapy; SIRT, selective internal radiotherapy; TACE, transarterial chemoembolisation; TKI, tyrosine kinase inhibitor.
[a] Nonstandard, alternative treatment.
[b] ESMO-MCBS v1.1 score for new therapy/indication approved by the EMA since January 1, 2016. The score has been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/scale-evaluation-forms-v1.0-v1.1/scale-evaluation-forms-v1.1).
[c] Noninferiority to sorafenib established; no evaluable benefit.
[d] Regorafenib is not recommended in TKI-naïve patients.
[e] Ramucirumab is only recommended in patients with an AFP level ≥400 ng/ml.

Table 9. Summary of efficacy data for HCC

Study	IMbrave150[2]		Sharp[14]		Reflect[5]		Resorce[6]		Celestial[7]		Reach-2[8]	
Phase	III		III		III		III		III		III	
Drug/Control	Atezolizumab/ Bevacizumab N=336	Sorafenib N=165	Sorafenib N=299	Placebo N=303	Lenvatinib N=478	Sorafenib N=476	Regorafenib N=379	Placebo N=194	Cabozantinib N=470	Placebo N=237	Ramucirumab N=197	Placebo N=95
mOS, months	19.2	13.4	10.7	7.9	13.6	12.3	10.6	7.8	10.2	8.0	8.5[a]	7.3[a]
PFS, months	6.9	4.3	5.5	2.8	7.3	3.6	3.1	1.5	5.2	1.9	2.8	1.5
Absolute survival gain	OS gain: 5.8 months PFS gain: 2.6 months		OS gain: 2.8 Months PFS gain: 2.7 months		OS gain: 1.3 months PFS gain: 3.7 months		OS gain: 2.8 months 2-year survival gain >10% PFS gain: 1.6 months		OS gain: 2.2 months PFS gain: 3.3 months		OS gain: 1.2 months PFS gain: 1.3 months	
HR (95% CI)	OS HR: 0.66 (0.52-0.85) $P = 0.0009$ PFS HR: 0.65 (0.53-0.81) $P = 0.0001$		OS HR: 0.69 (0.55-0.87) $P < 0.001$ PFS HR: 0.58 (0.45-0.74) $P < 0.001$		OS HR: 0.92 (0.79-1.06) Noninferiority PFS HR: 0.66 (0.57-0.77) $P < 0.001$		OS HR: 0.63 (0.50-0.79) $P < 0.001$ PFS HR: 0.46 (0.37-0.56) $P < 0.001$		OS HR: 0.76 (0.63-0.92) $P = 0.005$ PFS HR: 0.44 (0.36-0.52) $P < 0.001$		OS HR: 0.71 (0.53-0.95) OS HR: 0.69[a] (0.57-0.84) $P = 0.0002$ PFS HR: 0.45 (0.34-0.60) $P < 0.001$	
ORR[b]	30	11	N/A	N/A	19	7	N/A	N/A	4	1	5	1
ORR[c]	35	14	N/A	N/A	41	12	11	4	N/A	N/A	N/A	N/A
CR[b]	8	0.6	0	0	<1	<1	1	0	0	0	0	0
PR[b]	22	11	2	1	18	6	10	4	4	1	5	1
SD[b]	44	43	71	67	54	53	54	32	60	33	55	35
DCR[b]	74	55	43	32	73	59	65	36	64	33	60	39
PD[b]	19	25	N/A	N/A	18	32	N/A	N/A	21	55	33	51
PD[c]	20	25	N/A	N/A	17	32	23	56	N/A	N/A	N/A	N/A
Albi 1	NR	NR	NR	NR	66	72	43	42	39	43	43	44
Albi 2	NR	NR	NR	NR	34	28	56	58	61	57	57	56

Albi, albumin—bilirubin score; CI, confidence interval; CR, complete response; DCR, disease control rate; HCC, hepatocellular carcinoma; HR, hazard ratio; mOS, median overall survival; NA, not available; NR, not reached; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

[a] Pooled data.

[b] Response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1).

[c] Modified RECIST.

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Complete pathological and serological response to immunotherapy in a patient with MMR-deficient early rectal cancer

Randomized trials have demonstrated the importance of preoperative radiotherapy or chemoradiotherapy in reducing local recurrence rate in patients with high-risk rectal cancer.[1] However, there is a paucity of data and contradictory results in rectal cancer patients presenting