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SYSTEMIC TREATMENT FOR ADVANCED HEPATOCELLULAR CARCINOMA

M. BOUATTOUR,[1] N. MEHTA,[2] A.R. HE,[3]
E.I. COHEN,[4] AND J. NAULT[5,6]

SELECTED HIGHLIGHTS

[1]Department of Digestive Oncology, Hôpital Beaujon, APHP Hôpitaux Universitaires Paris Nord Val de Seine., Clichy, France;
[2]UCSF Medical Center. San Francisco, USA;
[3]Department of Medical Oncology, MedStar Georgetown University Hospital, Washington DC, USA;
[4]Department of Radiology, MedStar Georgetown University Hospital, Washington DC, USA;
[5]Liver Unit, Hôpital Jean Verdier, APHP Hôpitaux Universitaires Paris-Seine-Saint-Denis, Paris, France;
[6]Department of Functional Genomics of Solid Tumors, INSERM UMR 1162, Paris, France

Bouattour M, et al. Liver Cancer. March 6, 2019 [Epub]. doi.org/10.1159/000496439

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BACKGROUND

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- Hepatocellular carcinoma (HCC) is the 2nd most common cause of cancer-related death[1]
  - HCC is almost invariably associated with underlying risk factors, such as chronic infections with hepatitis B (HBV) or C (HCV), metabolic syndrome, and alcohol abuse[2]
- Many HCC patients present with advanced-stage disease and have a poor prognosis
  - Advanced disease is defined as Barcelona-Clínic Liver Cancer (BCLC) stage C[2, 3]
- Sorafenib has been the global standard of care for advanced HCC for a decade[4, 5]
  - In 2017, regorafenib was registered as 2nd-line treatment in the US and Europe[6]
  - Nivolumab and pembrolizumab were registered for 2nd-line use in the US[7, 8]
- **This review covers current data on systemic treatment of advanced HCC and their practical implications, aiming to assist physicians in making treatment decisions for these patients**

1. Ervik M, et al. http://gco.iarc.fr/today, accessed 23 February 2018. 2. EASL. J Hepatol 2018;69:182-236. 3. Forner A, et al. Lancet 2018;391:1301-1314. 4. Llovet JM, et al. N Engl J Med 2008;359:378-390. 5. Cheng AL, et al. Lancet Oncol 2009;10:25-34. 6. Bruix J, et al. Lancet 2017;389:56-66. 7. El-Khoueiry AB, et al. Lancet 2017;389:2492-2502. 8. Zhu AX, et al. Lancet Oncol 2018:19:940-952

QUESTIONS AND ANSWERS ON THE SYSTEMIC TREATMENT OF ADVANCED HCC

WHAT IS THE IMPACT OF PATIENT CHARACTERISTICS ON OUTCOMES WITH SORAFENIB?

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IMPACT OF LIVER FUNCTION

Sorafenib is **extensively studied** in **Child-Pugh A** patients

- The sorafenib trials only included Child-Pugh A patients[1, 2]

Sorafenib should be **used with caution** in **Child-Pugh B** patients

- There is a narrow margin between an unknown clinical benefit and the risk of toxicities and liver decompensation[3]
- In cohort studies, Child-Pugh B patients had a lower OS benefit[4, 5]
- A phase-2 trial showed more severe liver toxicities in Child-Pugh B patients[6]

Sorafenib is still **contraindicated** in **Child-Pugh C** patients

- Limited life expectancy and low magnitude of benefit
- Although in the GIDEON study some Child-Pugh B and C patients were treated with sorafenib without obvious deleterious effects on liver function, this study was not designed to assess this issue[7]

HCC, hepatocellular carcinoma; OS, overall survival

1. Llovet JM, et al. N Engl J Med 2008;359:378-390. 2. Cheng AL, et al. Lancet Oncol 2009;10:25-34. 3. Wörns MA, et al. Dig Liver Dis 2013;45:408-13. 4. Pinter M, et al. Oncologist 2009;14:70-76. 5. Ozenne V, et al. Eur J Gastroenterol Hepatol 2010;22:1106-1110. 6. Abou-Alfa GK, et al. J Clin Oncol 2006;24:4293-4300. 7. Marrero JA, et al. J Hepatol. 2016;65:1140-1147

WHAT IS THE IMPACT OF PATIENT CHARACTERISTICS ON OUTCOMES WITH SORAFENIB?

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IMPACT OF MACROVASCULAR INVASION (MVI) AND EXTRA-HEPATIC SPREAD (EHS)

- Many patients with advanced HCC have MVI and/or EHS
- MVI and EHS impact OS
  - In the SHARP trial, the median OS was 8.9 months in patients with MVI and/or EHS versus 14.5 months in those without[1]
  - A combined analysis of the SHARP and Asia-Pacific trials confirmed that patients with EHS have a smaller absolute OS benefit from sorafenib[2]
    - HR = 0.84 with EHS versus 0.55 without EHS
- **More data are needed about the prognostic value of MVI and EHS in patients treated with TKIs**

HCC, hepatocellular carcinoma; HR, hazard ratio; OS, overall survival

1. Bruix J, et al. J Hepatol 2012;57:821-829. 2. Bruix J, et al. J Hepatol 2017;67:999-1008

WHAT IS THE IMPACT OF PATIENT CHARACTERISTICS ON OUTCOMES WITH SORAFENIB?

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IMPACT OF ETIOLOGY

- HBV-positive patients in the Asia-Pacific trial had a lower median OS than patients in the SHARP trial[1]
- HCC patients with HBV may have lower OS than those with HCV[2]
- A meta-analysis of three randomized controlled trials suggested that the effect of sorafenib was not significant in patients with HBV[3]
  - However, the Asia-Pacific trial also showed a significantly increased OS for sorafenib versus placebo (HR 0.74), while more than 70% of patients were HBV positive[1]
- The phase-3 REFLECT trial has shown somewhat more survival benefit from lenvatinib versus sorafenib in patients with HBV (HR 0.83)[4]
  - However, superiority over sorafenib was not reached
- **Treatment decisions cannot be solely based on the etiology of the underlying liver disease, as these data are derived from post-hoc subgroup analyses**

EHS, extra-hepatic spread; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; OS, overall survival

1. Bruix J, et al. J Hepatol 2017;67:999-1008. 2. Cantarini MC, et al. Am J Gastroenterol 2006;101:91-98. 3. Jackson R, et al. J Clin Oncol 2017;35:622-628. 4. Kudo M, et al. Lancet. 2018;391(10126):1163-1173.

WHAT IS THE IMPACT OF PATIENT CHARACTERISTICS ON OUTCOMES WITH SORAFENIB?

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IMPACT OF ALPHA-FETOPROTEIN (AFP) LEVELS

- **AFP < 200 ng/mL has prognostic value for sorafenib and lenvatinib**
  - A subgroup analysis showed AFP levels > 200 ng/ml are a strong prognostic factor of poor OS with sorafenib[1]
  - In both arms of the REFLECT study, patients with baseline AFP levels < 200 ng/mL had a longer OS than those with AFP levels ⩾ 200 ng/mL[2]
    - This confirms the prognostic value of AFP < 200 ng/mL for lenvatinib and sorafenib
- **AFP ⩾ 400 ng/ml seems to be predicting response to ramucirumab**
  - Initial data from the REACH-2 trial indicate an increased OS with second-line ramucirumab versus placebo in patients with a serum AFP ⩾ 400 ng/ml[3]
  - This suggests that the AFP level is a predictive marker of response to ramucirumab

OS, overall survival

1. Bruix J, et al. J Hepatol 2017;67:999-1008. 2. Kudo M, et al. Lancet. 2018;391(10126):1163-1173. 3. Zhu AX, et al. Lancet Oncol. 2019;20:282-296.

PHASE-3 TRIALS ON THE 1ST-LINE TREATMENT OF HCC

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Treatment	S/NI	N per arm	Median OS, months	Median TTP, months	Median PFS, months	ORR, %	Comments
Sorafenib vs placebo[1]	S	299/303	10.7 vs 7.9 (P < 0.001)	5.5 vs 2.8 (P < 0.001)	NR	2 vs 1* RECIST	
Sorafenib vs placebo[2]	S	150/76	6.5 vs 4.2 (P = 0.014)	2.8 vs 1.4 (P = 0.005)	NR	3.3 vs 1.3*	Patients from the Asia-Pacific region
FOLFOX4 vs doxorubicin[3]	S	184/187	6.4 vs 4.97 (NS)	NR	2.93 vs 1.77 (P < 0.001)	8.2 vs 2.7* (P = 0.02)	Open-label study
Sunitinib vs sorafenib[4]	S	530/544	7.9 vs 10.2 (P = 0.0014)	4.1 vs 3.8 (P = 0.3082)	3.6 vs 3 (P = 0.22)	7.2 vs 6.9*	More AEs in the sunitinib arm
Brivanib vs sorafenib[5]	NI	577/578	9.5 vs 9.9 (NI not met)	4.2 vs 4.1 (P = 0.85)	NR	12 vs 9** (P = 0.56)	
Sorafenib + erlotinib vs sorafenib[6]	S	362/358	9.5 vs 8.5 (NS)	3.2 vs 4 (P = 0.18)	NR	6.6 vs 3.9* (P = 0.102)	Higher OS in patients with HBV
Linifanib vs sorafenib[7]	NI	514/521	9.1 vs 9.8 (NI not met)	5.4 vs 4 (P = 0.001)	NR	13 vs 6.9*	More AEs in the linifanib arm
Lenvatinib vs sorafenib[8]	NI	478/476	13.6 versus 12.3 (NI met)	8.9 vs 3.7 (P < 0.0001)	7.4 vs 3.7 (P < 0.0001)	24.1 vs 9.2** (P < 0.0001)	
Doxorubicin + sorafenib vs sorafenib[9]	NR	173/173	9.3 vs 10.5 (NS)	NR	3.6 vs 3.2 (NS)	NR	Unpublished data Study halted for futility

ORR was assessed at imaging, either using traditional RECIST (*) or mRECIST (**) criteria.

AE, adverse event; AFP, alpha-fetoprotein; FOLFOX4, oxaliplatin, folinic acid and 5-fluorouracil; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; mRECIST, modified RECIST; NI, non-inferiority; NR, not reported; NS, not significant; OS, overall survival; RECIST, Response Evaluation Criteria In Solid Tumors; S, superiority

1. Llovet JM, et al. N Engl J Med 2008;359:378-390. 2. Cheng AL, et al. Lancet Oncol 2009;10:25-34. 3. Qin S,, et al. J Clin Oncol 2013;31:3501-3508. 4. Cheng AL, et al. J Clin Oncol 2013;31:4067-4075. 5. Johnson PJ, et al.. J Clin Oncol 2013;31:3517-3524. 6. Zhu AX, et al. J Clin Oncol 2015;33:559-566. 7. Cainap C, et al. J Clin Oncol 2015;33:172-179. 8. Kudo M, et al. Lancet. 2018;391(10126):1163-1173. 9. Abou-Alfa GK, et al. J Clin Oncol. 2016;34:Suppl:4003

PHASE-3 TRIALS ON THE 2ND-LINE TREATMENT OF HCC

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Treatment	S/NI	N per arm	Median OS, months	Median TTP, months	Median PFS, months	ORR, %	Comments
Brivanib vs placebo[1]	S	263/132	9.4 vs 8.2 (NS)	4.2 vs 2.7 (P < 0.001)	NR	10 vs 2* (P = 0.003)	
Everolimus vs placebo[2]	S	362/184	7.6 vs 7.3 (NS)	3 vs 2.6 (NS)	NR	2.2 vs 1.6*	Increased survival in patients with HBV
Ramucirumab vs placebo[3]	S	283/282	9.2 vs 7.6 (NS)	3.5 vs 2.6 (P < 0.0001)	2.8 vs 2.1 (P < 0.0001)	8 vs 1* (P < 0.0001)	Higher OS in patients with AFP ⩾ 400 ng/ml
Ramucirumab vs placebo[4]	S	197/95	8.5 vs 7.3 (P = 0.0199)	3.0 vs 1.6† (P < 0.0001)	2.8 vs 1.6 (P < 0.0001)	4.6 vs 1.1* (NS)	Patients with elevated AFP (⩾ 400 ng/ml)
Regorafenib vs placebo[5]	S	379/194	10.6 vs 7.8 (P < 0.0001)	1.4 vs 1.4	3.1 vs 1.5 (P < 0.0001)	11 vs 4** (P < 0.0001)	Patients tolerant to sorafenib
Cabozantinib vs placebo[6]	S	470/237	10.2 vs 8.0 (P = 0.0049)	NR	5.2 vs 1.9 (P < 0.0001)	4 vs 0.4 (P = 0.0086)*	
S-1 vs placebo[7]	S	223/111	11.1 vs 11.2 (NS)	2.6 vs 1.4 (P < 0.0001)	2.6 vs 1.4 (P < 0.0001)	5 vs <1 (NS)	Patients from Japan
Tivantinib vs placebo[8]	S	226/114	8.4 vs 9.1 (NS)	2.4 vs 3.0 (NS)	2.1 vs 2.0 (NS)	0 vs 0*	Patients with high MET expression (staining intensity score ⩾2 in ⩾50% of tumor cells)
ADI-PEG 20 vs placebo[9]	S	424/211	7.8 vs 7.4 (NS)	NR	2.6 vs 2.6 (NS)	NR	

ORR was assessed at imaging, either using traditional RECIST (*) or mRECIST (**) criteria.
†Data updated after publication of Bouattour M, et al. Liver Cancer. March 6, 2019 [Epub]. doi.org/10.1159/000496439.

AFP, alpha-fetoprotein; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; mRECIST, modified RECIST; NI, non-inferiority; NR, not reported; NS, not significant; OS, overall survival; RECIST, Response Evaluation Criteria In Solid Tumors; S, superiority

1. Llovet JM, et al. J Clin Oncol 2013;31:3509-3516. 2. Zhu AX, et al. JAMA 2014;312:57-67. 3. Zhu AX, et al. Lancet Oncol 2015;16:859-870. 4. Zhu AX, et al. Lancet Oncol. 2019;20:282-296. 5. Bruix J, et al. Lancet 2017;389:56-66. 6. Kelley RK, et al. Ann Oncol 2017;28:528-534. 7. Kudo M, et al. Lancet Gastroenterol Hepatol. 2017;2:407-417. 8. Rimassa L, et al. Lancet Oncol. 2018;19:682-693. 9. Abou-Alfa GK, et al. Ann Oncol. 2018;29:1402-1408.

WHAT ARE THE APPROVED 2ND-LINE TREATMENT OPTIONS FOR ADVANCED HCC?

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REGORAFENIB

- Regorafenib is approved by FDA and EMA and currently is the **recommended 2nd-line treatment in Child-Pugh A patients with an ECOG-PS score of 0-1 who tolerated sorafenib**
  - The RESORCE trial showed regorafenib increased the OS by 2.8 months versus placebo (HR 0.63) in patients with radiological progression on sorafenib[1]
  - Sequential sorafenib followed by regorafenib lead to a median OS of 26 months[2]
  - The main AEs of regorafenib were similar to sorafenib[1]
- Patients with Child-Pugh B cirrhosis, significant comorbidities or sorafenib intolerance should not be treated by regorafenib[3]
- Real-world evaluation of second-line regorafenib is required
  - A non-interventional study is currently ongoing (NCT03289273)

AE, adverse event; EMA, European Medicines Agency; FDA, US Food and Drug Administration; HCC, hepatocellular carcinoma; HR, hazard ratio; OS, overall survival

1. Bruix J, et al. Lancet 2017;389:56-66. 2. Finn RS, et al. J Hepatol. 2018;69:353-358. 3. Gyawali B, et al. Nat Rev Clin Oncol. 2017;14:653-654.

WHAT ARE THE APPROVED 2ND-LINE TREATMENT OPTIONS FOR ADVANCED HCC?

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NIVOLUMAB AND PEMBROLIZUMAB

Nivolumab and pembrolizumab were approved by the FDA (not EMA) for the 2nd-line treatment of advanced HCC, based on early-stage studies

Phase-1/2 CheckMate-040 study[1] with **nivolumab** in sorafenib-naive and pre-treated patients	Phase-2 Keynote-224 study[2] with **pembrolizumab** (ongoing)	CheckMate-040 and Keynote-224 did not include a control arm
• ORR 19% • Median duration of response 9.9 months • Median OS 15 months	• ORR 17%, • Median PFS 4.9 months • Median OS 12.9 months	

Continued approval may depend on confirmation of the results and clinical benefit in the phase-3 trials expected for 2019

EMA, European Medicines Agency; FDA, US Food and Drug Administration; HCC, hepatocellular carcinoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival

1. El-Khoueiry AB, et al. Lancet 2017;389:2492-2502. 2. Zhu AX, et al. Lancet Oncol 2018:19:940-952.

WHAT WILL BE THE PLACE OF NOVEL COMPOUNDS IN THE TREATMENT OF ADVANCED HCC?

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LENVATINIB

The open-label phase-3 study REFLECT compared 1st-line lenvatinib with sorafenib in patients with advanced HCC without MVI

Lenvatinib was non-inferior to sorafenib	**Improvement in secondary endpoints** with lenvatinib versus sorafenib	**Increased rate of treatment interruptions and discontinuations** due to AEs with lenvatinib versus sorafenib
•Median OS 13.6 versus 12.3 months (HR 0.92)	•PFS 7.4 versus 3.7 months (P < 0.00001) •Time to progression 8.9 versus 3.7 months (P < 0.0001) •ORR 24.1% versus 9.2% (P < 0.00001)	•Interruptions 40% versus 32% •Discontinuations 9% versus 7%

- In 2018, lenvatinib was approved in the US, Europe and Japan
- **Further analysis of the phase-3 data will be needed to elucidate the potential of lenvatinib as an alternative for sorafenib and to decide how to choose between lenvatinib and sorafenib**

AE, adverse event; HCC, hepatocellular carcinoma; MVI, macrovascular invasion; ORR, overall response rate; OS, overall survival; PFS- progression-free survival

Kudo M, et al. Lancet. 2018;391:1163-1173.

WHAT WILL BE THE PLACE OF NOVEL COMPOUNDS IN THE TREATMENT OF ADVANCED HCC?

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CABOZANTINIB

- In 2018 and 2019, cabozantinib was **approved by FDA and EMA** for the treatment of HCC after progression to sorafenib
  - The phase-3 CELESTIAL study showed an OS of 10.2 versus 8.0 months (HR 0.76; P = 0.005) for cabozantinib versus placebo in 2nd or 3rd line
  - PFS was 5.2 versus 1.9 months (HR 0.44; P < 0.0001)
  - Although the ORR was relatively limited in both groups (4% versus 0.4%; P < 0.001), cabozantinib almost doubled the disease control rate (64% versus 33%)

AFP, alpha-fetoprotein; EMA, European Medicines Agency; FDA, US Food and Drug Administration; HCC, hepatocellular carcinoma; HR, hazard ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival

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

WHAT WILL BE THE PLACE OF NOVEL COMPOUNDS IN THE TREATMENT OF ADVANCED HCC?

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TARGETED THERAPIES

Ramucirumab

- Second-line ramucirumab failed to increase OS compared with placebo in the phase-3 **REACH study**[1]
  - A post-hoc analysis suggested that patients with AFP levels ⩾ 400 ng/ml could benefit from ramucirumab
- A new phase-3 trial (**REACH-2**) showed and increased OS with ramucirumab vs placebo in patients with AFP levels ⩾ 400 ng/ml[2]

Apatinib

- Apatinib is currently tested in the placebo-controlled phase-3 **AHELP study** in Asia (NCT02329860)

AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; HR, hazard ratio; OS, overall survival

1. Zhu AX, et al. Lancet Oncol 2015;16:859-870. 2. Zhu AX, et al. Lancet Oncol. 2019;20:282-296

WHAT WILL BE THE PLACE OF NOVEL COMPOUNDS IN THE TREATMENT OF ADVANCED HCC?

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IMMUNOTHERAPY

Many novel compounds are being tested, as well as regimens combining immunotherapy with chemotherapy, targeted therapy, radiation, or another immunotherapy

A phase-3 study comparing **1st-line nivolumab** to sorafenib in patients without major portal vein invasion is ongoing (NCT02576509)	A phase-3 study comparing **2nd-line pembrolizumab** to placebo is ongoing (NCT02702401)	**Pembrolizumab + lenvatinib** is tested in a 2-part, phase 1b trial in patients with unresectable HCC (NCT03006926)[1] •Confirmed ORR of 27% •Unconfirmed ORR: 42% •A phase-3 trial of pembrolizumab + lenvatinib in 1st line is ongoing (NCT03713593)	In a phase-2 study in patients with HCV-related HCC, **tremelimumab** showed[2] •PR rate of 18% •TTP of 6.5 months •A phase 3 study comparing **tremelimumab + durvalumab** with sorafenib is underway (NCT032988451)	In phase 1, **atezolizumab + bevacizumab** was safe and well tolerated, with promising early efficacy (NCT02715531)[3] The phase-3 trial IMbrave150, comparing atezolizumab + bevacizumab with sorafenib has recently closed enrolment (NCT03434379)[4]

HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ORR, overall response rate; PR, partial response; TTP, time to progression

1. Ikeda M, et al. :J Clin Oncol. 2018;36:Suppl:4076. 2. Sangro B, et al. J Hepatol 2013;59:81-88. 3. Stein S, et al. J Clin Oncol 2018;36:Suppl:4074. 4. Finn RS, et al. J Clin Oncol. 2018;36:Suppl:TPS4141.

WHAT TOXICITY PROFILES CAN BE EXPECTED WHEN USING TARGETED THERAPY OR IMMUNOTHERAPY?

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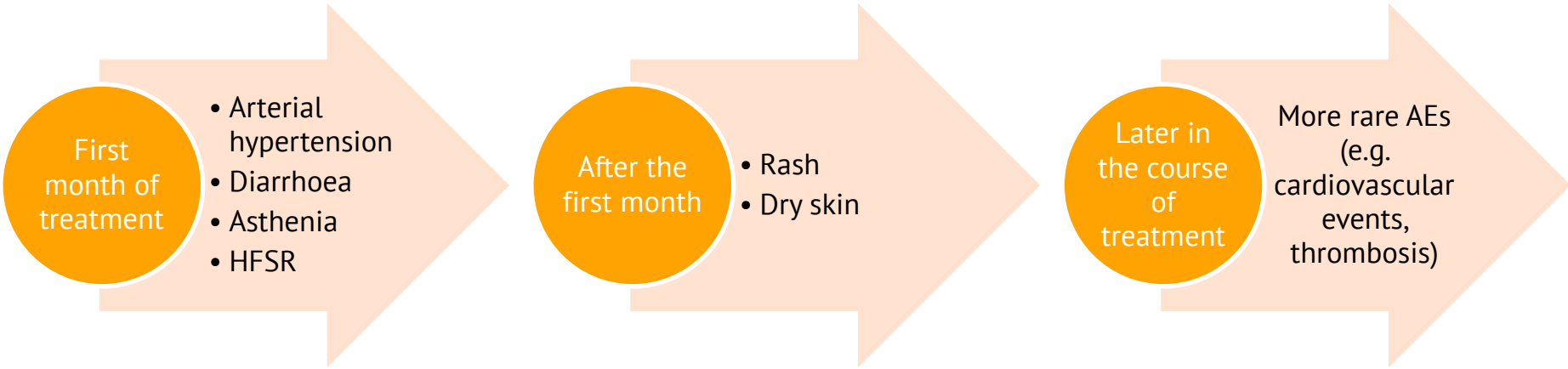
Targeted therapy



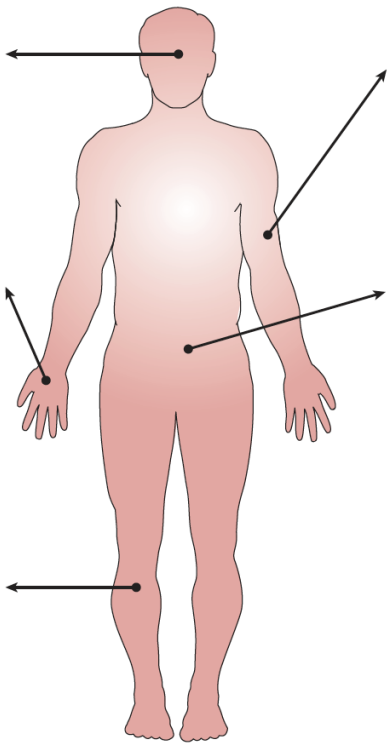
Immunotherapy

- Rash
- Immune-mediated AEs
  - Rare, but can be severe
  - Including hypothyroidism, adrenal insufficiency, colitis, hepatitis and acute renal injury

AE, adverse event; HFSR, hand-foot-skin reaction

GENERAL MANAGEMENT OF AEs

Grade 1: symptomatic treatment
Grade 2: symptomatic treatment, dose reduction, and dose interruption
Grade 3/4: symptomatic treatment and dose interruption



Asthenia
Regorafenib 40%/*9%*
Sorafenib 25%/*4%*
Lenvatinib 30%/*4%*
Anti-PD1 23%/*1%*

Nutritional support

HFSR
Regorafenib 53%/*13%*
Sorafenib 45%/*11%*
Lenvatinib 27%/*3%*
Anti-PD1 0%/*0%*

Prophylactic urea cream
Therapeutic urea cream
Topical corticosteroid

Rash
Regorafenib NA/*NA*
Sorafenib 20%/*1%*
Lenvatinib 10%/*0%*
Anti-PD1 15%/*1%*

Therapeutic urea cream
Topical corticosteroid

Arterial hypertension
Regorafenib 31%/*15%*
Sorafenib 19%/*2%*
Lenvatinib 42%/*23%*
Anti-PD1 0%/*0%*

Anti hypertensive treatment

Diarrhea
Regorafenib 41%/*3%*
Sorafenib 39%/*8%*
Lenvatinib 39%/*4%*
Anti-PD1 13%/*1%*

Loperamide

Immune-mediated AE
Anti-PD1/PD-L1
Hypothyroidism 4%/*0%*
Adrenal insufficiency 2%/*0%*
Hepatitis 4%/*4%*
Acute renal injury 4%/*2%*
Hypersensitivity 4%/*2%*

Discuss corticosteroids

The purple boxes contain the main AEs related to sorafenib, lenvatinib, regorafenib and anti-PD1 antibodies, with the percentages of any-grade AEs/grade 3-4 AEs (italics). The blue boxes contain suggestions for the management of the AEs.

AE, adverse event; NA, not applicable; HFSR, hand-foot-skin reaction; PD-1, programmed-cell-death protein; PD-L1, programmed-cell-death protein ligand

WHAT IS THE ROLE OF DRIVER MUTATIONS AND PRECISION MEDICINE IN THE FIELD OF HCC?

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- Compared to other types of solid tumours, precision medicine in HCC is still at the embryonical stage
- Precision medicine in HCC has several limitations
  - Potential targetable alterations have a frequency of less than 5-10%[1]
  - The most frequent genetic alterations have no available treatment options[2]
  - Tumor heterogeneity could decrease the efficacy of targeted therapy[2]
  - Primary or secondary resistance invariably occurred[3]
- **Additional knowledge about tumour heterogeneity and plasticity of cancer cells and further efforts on drug development will be required to lead HCC into the era of precision medicine**
- In the design of new clinical trial in HCC, biomarker enrichment and tumour biopsies should be mandatory prior inclusion in order to give access to material that can be used to identify biomarkers of response

HCC, hepatocellular carcinoma

1. Schulze K, et al. J Hepatol 2016;65:1031-1042. 2. Le Tourneau C, et al. Lancet Oncol 2015;16:1324-1334. 3. Prasad V, et al. Lancet Oncol 2016;17:e81-e86.

WHAT IS THE ROLE OF DRIVER MUTATIONS AND PRECISION MEDICINE IN THE FIELD OF HCC?

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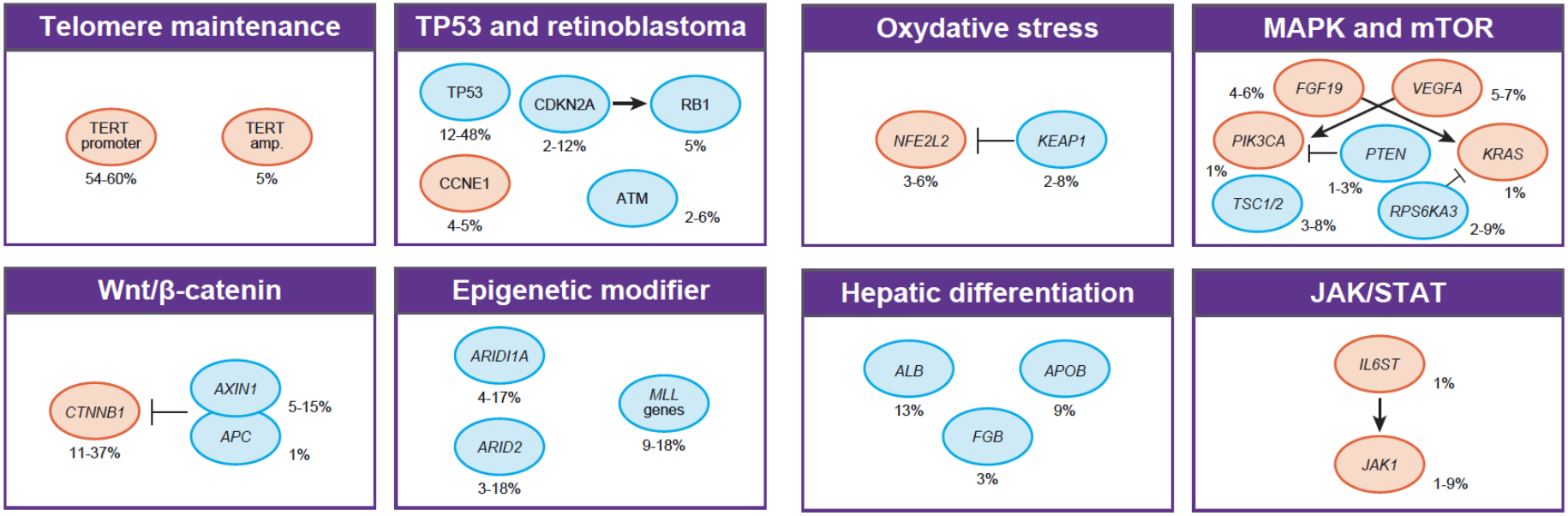
Main signaling pathways mutated in liver carcinogenesis

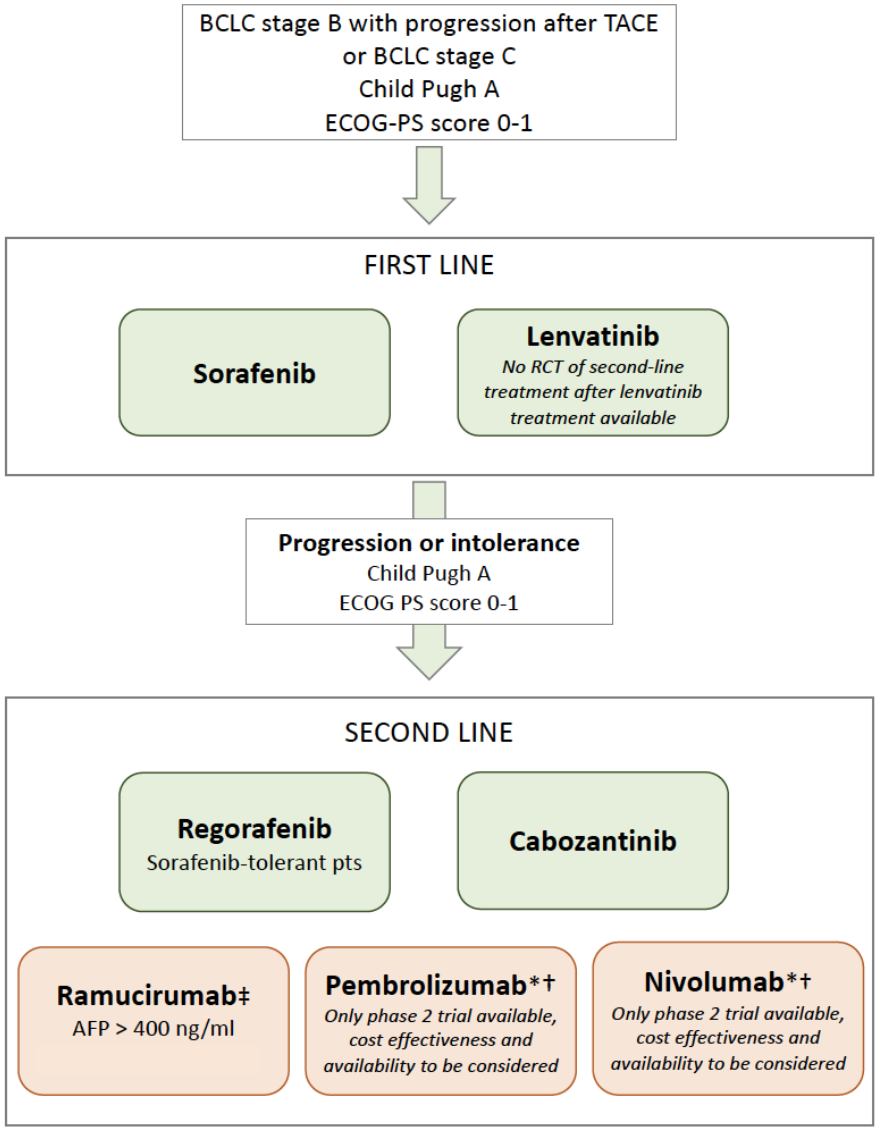


- The main driver genes mutated in HCC in each signaling pathway are shown with the percentages of somatic mutations in each gene
- Oncogenes are presented in red and tumor-suppressor genes in blue
- *TERT, CCNE1* and *MLL4* are also targeted by recurrent somatic HBV insertions. The *TERT* gene was either mutated in its promoter or amplified (*TERT* amp.)

ALB, albumin; APC, adenomatosis polyposis coli tumor suppressor; APOB, apolipoprotein B; ARID2, AT-rich interactive domain-containing protein 2; ARIDI1A, AT-rich interactive domain-containing protein 1A; ATM, ataxia-telangiectasia mutated; CCNE1, cyclin E1; CDKN2A, cyclin-dependent kinase inhibitor 2A; CTNNB1, Catenin (cadherin-associated protein) beta 1; FBG, fibrinogen beta chain; FGF19, fibroblast growth factor 19; HCC, hepatocellular carcinoma; IL6ST, glycoprotein 130; JAK, janus kinase; KEAP1, kelch-like ECH-associated protein 1; MLL, mixed-lineage leukemia; mTOR, mechanistic target of rapamycin; NFE2L2, nuclear factor (erythroid-derived 2)-like 2; RB1, retinoblastoma protein; PIK2CA, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; PTEN, phosphatase and tensin homolog; RPS6KA3, ribosomal protein S6 kinase, 90kDa, polypeptide 3; STAT, signal transducer and activator of transcription; TERT, telomerase reverse transcriptase; TP53, tumor protein p53; TSC1/2, tuberous sclerosis 1/2; VEGFA, vascular endothelial growth factor A

PATIENT SCENARIOS AND TREATMENT PROPOSALS

CURRENT AND FUTURE TREATMENT OPTIONS



Current and future treatment options by line of therapy and patient subgroup

- The green boxes contain recommended (future) therapies
- The orange boxes contain alternative future treatments, not recommended as 1st choice based on the current knowledge
- No studies on 2nd-line treatment after progression/ intolerance to lenvatinib are currently available

*Insufficient data for robust recommendation. † Only registered in the US. ‡ Not registered
BCLC, Barcelona-Clínic Liver Cancer; ECOG-PS, Eastern Cooperative Oncology Group performance status; pts, patients; RCT, randomized controlled trial; TACE, transarterial chemoembolization

1ST-LINE TREATMENT OF ADVANCED HCC

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HCV-INFECTED PATIENTS

- **Sorafenib** could be suggested as a 1st-line option in this population
  - Sorafenib has shown a clear efficacy and safety benefit in HCV-infected patients with advanced HCC[1]
  - A subgroup analysis of the SHARP and Asia-Pacific trials showed that HCV-positive patients were more likely to benefit from sorafenib[2]
- **Nivolumab** showed impressive efficacy results in a phase 1/2 study in 2nd-line, but adequate data is lacking to recommend nivolumab as a 1st-line treatment option[3]

HBV-INFECTED PATIENTS

- The subgroup analysis of the REFLECT trial could permit starting with 1st-line **lenvatinib** in HBV-positive patients with advanced HCC, to optimize their chance of response, survival, and treatment cost[1]
- It is also possible to treat HBV-positive patients with **sorafenib**, as the Asia-Pacific trial included a large proportion of HBV-infected patients and showed benefit[2, 3]
- While awaiting the final phase-3 data, **nivolumab** will be not suggested in 1st-line

HCC, hepatocellular carcinoma; HCV, hepatitis C virus

1. Jackson R, et al. J Clin Oncol 2017;35:622-628. 2. Bruix J, et al. J Hepatol 2017;67:999-1008. 3. El-Khoueiry AB, et al. Lancet 2017;389:2492-2502

1ST-LINE TREATMENT OF LOCALLY ADVANCED HCC

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- Locally-advanced HCC is defined as:
  - BCLC stage C with portal vein invasion, without metastases
  - BCLC stage B progressive after TACE

- Two open-label phase-3 trials (SARAH and SIRVENIB) evaluated sorafenib versus selective internal radiation therapy (SIRT)
  - Despite a lower rate of AEs, a better quality of life and higher ORR, survival benefit was not significantly higher in the SIRT groups
  - OS was slightly lower in the SIRT group compared with the sorafenib arm in patients with portal vein thrombosis

- **Sorafenib remains the standard of care in this setting**

AE, adverse event; BCLC, Barcelona-Clínic Liver Cancer; HCC, hepatocellular carcinoma; ORR, overall response rate; OS, overall survival; TACE, transarterial chemoembolization

1. Vilgrain V, et al. Lancet Oncol 2017;18:1624-1636. 2. Chow PHW, et al. J Clin Oncol 2018; 36:1913-1921.

2ND AND FURTHER LINES OF TREATMENT

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PATIENTS WITH PROGRESSION UNDER SORAFENIB

- **Regorafenib** has shown a clear benefit in progressive patients, provided sorafenib was well tolerated[1]
  - In our opinion, **regorafenib** and **cabozantinib** should be the **2nd-line treatment options of choice.** The choice between of these drug will be at the physician's discretion
- A small proportion of patients will be eligible for **3rd-line treatment**
  - **Cabozantinib** may be a future treatment option in this subgroup
  - As no data are available for 2nd-line treatment after lenvatinib, a robust recommendation in this setting is lacking

SORAFENIB-INTOLERANT PATIENTS

- **Cabozantinib is the first choice**
- **Nivolumab** and **pembrolizumab** could be considered in the US
- **Ramucirumab** (in patients with AFP ⩾ 400 ng/mL) may present a **future alternative**
- Regorafenib should generally be avoided in sorafenib-intolerant patients

AE, adverse event; AFP, alpha-fetoprotein

1. Bruix J, et al. Lancet 2017;389:56-66.

CONCLUSION

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- After 10 years, **sorafenib** is still the **1st-line standard of care** for many patients with advanced HCC, including patients with locally advanced HCC and HCV-related advanced HCC
  - **Lenvatinib** may present an **alternative in 1st-line**
- **Cabozantinib and regorafenib** are the **treatment of choice for progressive patients**
  - Although nivolumab and pembrolizumab are available in the US based on the results of a phase 2 study
- **Ramucirumab** may be a **future 2nd-line treatment option** in patients with AFP ⩾ 400 ng/mL
- In the near future, more data will be published on immunotherapy that will possibly affect the herein proposed recommendations
  - In the more distant future, precision medicine may come into play in the treatment of advanced HCC

AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; HCV, hepatitis C virus

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HCC CONNECT

Email
froukje.sosef@cor2ed.com

HCC CONNECT
Bodenackerstrasse 17
4103 Bottmingen
SWITZERLAND

Dr. Antoine Lacombe
Pharm D, MBA
Phone: +41 79 529 42 79
antoine.lacombe@cor2ed.co

Dr. Froukje Sosef
MD
Phone: +31 6 2324 3636
froukje.sosef@cor2ed.com