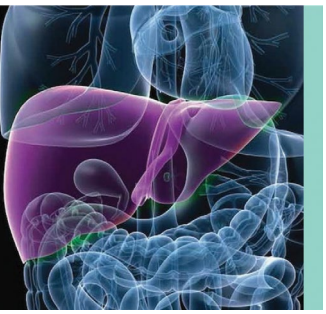

New Drugs Effective in the Systemic Treatment of Hepatocellular Carcinoma

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Liver cancer is a major health problem, being the second leading cause of cancer-related death worldwide,[1] with an annual incidence of more than 850,000 new cases globally.[2] Hepatocellular carcinoma (HCC) represents 85% to 90% of all primary liver cancers and occurs mainly in the setting of chronic inflammatory liver diseases.[2] Only 40% to 50% of patients with HCC are diagnosed at early stages (Barcelona Clinic Liver Cancer [BCLC] 0-A) amenable to potentially curative approaches.[2] However, up to 70% of patients present with disease recurrence within 5 years,[2] and no adjuvant therapies to prevent this complication are available to date. Patients diagnosed at an intermediate stage (BCLC B) are treated with transarterial chemoembolization,[2,3] whereas 40%

Abbreviations: AE, adverse event; AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CCR4, chemokine receptor 4; CI, confidence interval; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; DLTs, dose limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; EHS, extrahepatic spread; FDA, US Food and Drug Administration; FGFR, fibroblast growth factor receptor; FGFR4, fibroblast growth factor receptor 4; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; Hsp90, heat shock protein 90; IDO1, indolamine2,3-dioxygenase 1; IHC, immunohistochemistry; mRECIST, modified response evaluation criteria in solid tumors; MTD, maximum tolerated dose; ORR, objective response rate; OS, overall survival; PD-1, programmed death-1; PDGFR, platelet-derived growth factor receptor; PDGFRB, platelet-derived growth factor receptor β; PD-L1, programmed death ligand 1; RP2D, recommended phase II dose; TGF-βR1, transforming growth factor-β receptor 1; VEGFA, vascular endothelial growth factor A; VEGFR, vascular endothelial growth factor receptor; VEGFR2, vascular endothelial growth factor receptor 2; VEGFR3, vascular endothelial growth factor receptor 3.

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TABLE 1. SUCCESSFUL PHASE III TRIALS IN ADVANCED HCC

Trial	Arms	N	OS	
			Median (months)	HR (95% CI)
First-line				
SHARP	Sorafenib versus placebo	299 vs. 303	10.7 vs. 7.9	0.69 (0.55-0.87)
Asian-Pacific	Sorafenib versus placebo	150 vs. 76	6.5 vs. 4.2	0.68 (0.50-0.93)
REFLECT*	Lenvatinib versus sorafenib	478 vs. 476	13.6 vs. 12.3	0.92* (0.79-1.06)
Second-line				
RESORCE	Regorafenib versus placebo	379 vs. 194	10.6 vs. 7.8	0.63 (0.50-0.79)
CELESTIAL	Cabozantinib versus placebo	470 vs. 237	10.2 vs. 8	0.76 (0.63-0.92)
REACH-2	Ramucirumab versus placebo	197 vs. 95	8.5 vs. 7.3	0.71 (0.53-0.95)

*Positive study for noninferiority design.

of patients are diagnosed at an advanced stage (BCLC C) and can benefit from systemic therapies.[3] In this scenario, the approval of sorafenib in 2007 was followed by several unsuccessful phase III trials assessing novel targeted therapies and locoregional therapies, such as radioembolization,[4,5] that did not fulfill the primary overall survival (OS) endpoints. From 2016 to 2018, five new drugs (lenvatinib, regorafenib, cabozantinib, ramucirumab, and nivolumab) showed clinical efficacy and have been adopted by guidelines[3,6] (Table 1; Figs. 1 and 2). We herein review the systemic treatments available for advanced HCC that have revolutionized the management of this devastating cancer.

FIRST-LINE THERAPIES

Sorafenib

Sorafenib is a multikinase inhibitor that exerts antiproliferative (RAF1, BRAF, and KIT), antiangiogenic (vascular endothelial growth factor receptor [VEGFR] and platelet-derived growth factor receptor β [PDGFRB]), and proapoptotic effects. Sorafenib has shown antitumor activity in phase III trials in patients with advanced HCC. Both the SHARP trial[7] conducted in western countries and the Asian-Pacific trial[8] demonstrated survival benefits of sorafenib versus placebo (median OS 10.7 versus 7.9 months; SHARP trial: hazard ratio [HR] 0.69; 95% confidence interval [CI]: 0.55-0.87; $P < 0.001$; Asian-Pacific trial: 6.5 versus 4.2 months; HR 0.68; 95% CI: 0.50-0.93; $P = 0.014$). This represented a breakthrough in the management of advanced stage HCC. Sorafenib is indicated as a first-line treatment option for patients with advanced tumors (BCLC C) or tumors at an intermediate stage (BCLC B) with a well-preserved liver function (Child-Pugh A) that progressed upon locoregional therapies. A greater magnitude of benefit is obtained in patients without extrahepatic spread and with hepatitis C virus etiology.[8]

Lenvatinib

Lenvatinib is an oral multikinase inhibitor of VEGFRs 1 to 3, fibroblast growth factor receptors (FGFRs) 1 to 4, RET, KIT, and PDGFRα. A recent phase III trial in HCC (REFLECT[9]) demonstrated noninferiority OS benefit of lenvatinib versus sorafenib (median OS 13.6 versus 12.3 months; HR 0.92; 95% CI: 0.79-1.06) and showed an improvement in secondary efficacy endpoints, including objective response (24% lenvatinib versus 9% sorafenib as per modified response evaluation criteria in solid tumors [mRECIST]). Of note, patients with 50% of liver occupation, clear invasion

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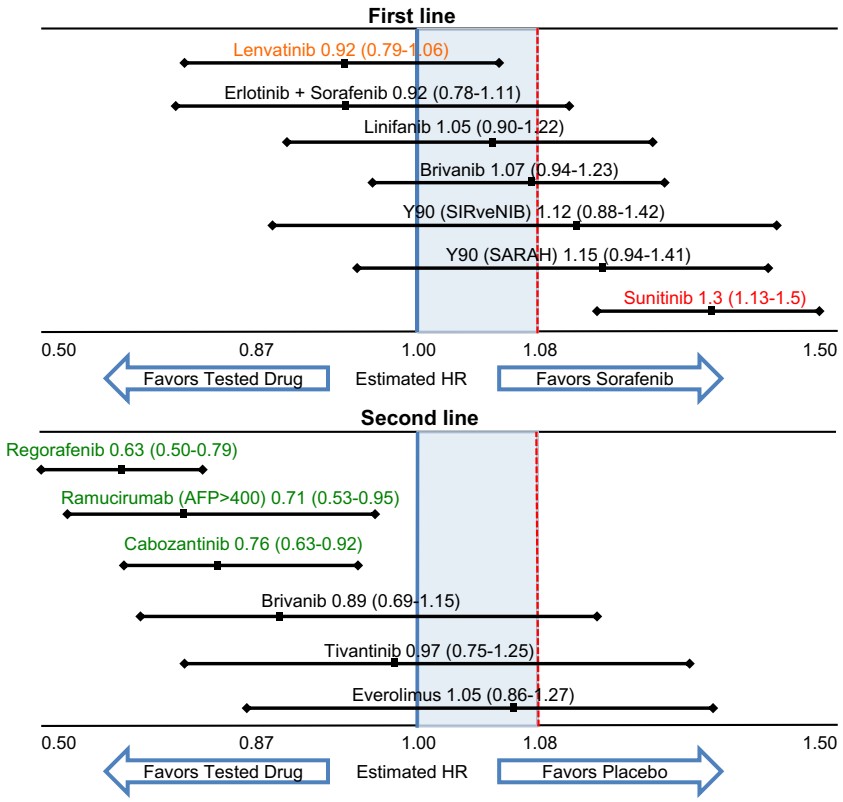

FIG 1 Overall survival outcomes of phase III clinical trials testing molecular targeted therapies or radioembolization in patients with advanced-stage hepatocellular carcinoma. Adapted from Llovet JM, et al. Nat Rev Clin Oncol 2018.[3] The figure illustrates the estimated overall survival hazard ratios (HRs) and 95% confidence intervals for the experimental drug (or combination) versus either sorafenib in the first-line setting or placebo in the second-line setting. Green text indicates positive results from trials with a superiority design. Orange text indicates positive results from trials with a non-inferiority design. Black text and red text represent negative results with a HR confidence interval crossing or not crossing 1, respectively. Blue and red lines refer to the upper limit for superiority and non-inferiority, respectively.

into the bile duct, and main portal vein invasion were not included in this trial.

SECOND-LINE THERAPIES

Regorafenib

Regorafenib is an oral multikinase inhibitor that has a similar mechanism of action to sorafenib but with a greater potency against the VEGFR kinases and a broader activity, for example, against angiopoietin 1 receptor (TIE2), KIT, and RET. A phase III trial (RESORCE) in patients with advanced HCC that progressed and were tolerant to sorafenib demonstrated an impact on survival with regorafenib (7.8 months with placebo to 10.6 months with regorafenib; HR 0.63; 95% CI: 0.50-0.79; $P < 0.0001$). Median treatment duration was 3.6 months with regorafenib and 1.9 months with placebo.[10] The precise mechanism by which regorafenib improves survival after sorafenib progression is unknown.

Cabozantinib

Cabozantinib is a small-molecule multitarget tyrosine kinase inhibitor that inhibits VEGFRs with a potent inhibitory effect against MET and AXL. CELESTIAL[11] was a global, randomized, placebo-controlled phase III trial of cabozantinib in patients who had HCC progression on prior sorafenib. The trial revealed a median OS of 10.2 months for cabozantinib versus 8.0 months in the placebo arm (HR 0.76; 95% CI: 0.63-0.92; $P = 0.0049$) and hence was stopped after a second interim analysis. The most frequent grade 3/4 adverse event (AE) observed in the cabozantinib group was palmar-plantar erythrodysesthesia (17% versus 0% in the placebo arm).

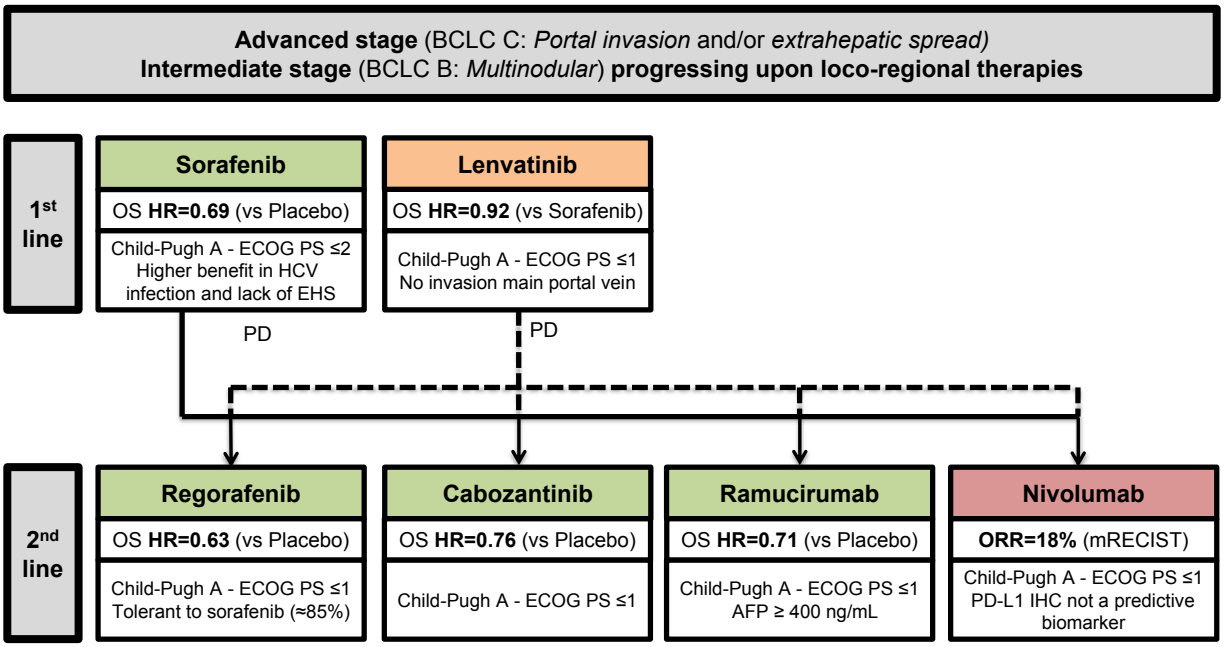

FIG 2 Treatment strategy for advanced hepatocellular carcinoma. Adapted from Llovet JM, et al. Nat Rev Clin Oncol 2018.[3] Drugs in green have positive results from phase III trials with a superiority design (sorafenib in the first-line setting and regorafenib, cabozantinib and ramucirumab in the second-line setting). Drugs in orange have positive results from phase III trials with a non-inferiority design (lenvatinib in the first-line setting). Drugs in red have received accelerated approval from the FDA on the basis of promising efficacy results in phase II trials (nivolumab in the second-line setting). Key details of the patient populations are provided.

Ramucirumab

Ramucirumab is an anti-VEGFR2 monoclonal antibody. A phase III trial (REACH[12]) involving patients with advanced stage HCC after prior treatment with sorafenib showed negative results for its primary endpoint of OS, although a subgroup of patients with a baseline serum alpha-fetoprotein (AFP) level ≥400 ng/mL demonstrated a significant improvement in median OS from 4.2 months with placebo to 7.8 months with ramucirumab. Based on this observation, a second phase III trial of ramucirumab in the second-line setting (REACH-2[13]) was performed incorporating biomarker-based enrichment for patients with baseline AFP concentrations ≥400 ng/dL. Results of this trial have demonstrated an improvement in OS of 8.5 months with ramucirumab versus 7.3 months for placebo (HR 0.710; 95% CI: 0.531-0.949; $P = 0.0199$). Therefore, ramucirumab represents the first agent with a demonstrated clinical benefit in a biomarker-selected population of patients with HCC.

Immune Checkpoint Inhibitors

Immunotherapies have changed the landscape of cancer treatment and have provided hope to patients with advanced tumors. Regulatory agencies have approved immune checkpoint inhibitors in several solid tumors including melanoma, lung cancer, renal cancer, and bladder cancer. These drugs enhance antigen-specific T cell responses, unleashing the potential of the preexisting antitumor immune response.

Nivolumab

Nivolumab is a monoclonal antibody directed against the negative immunoregulatory human cell surface receptor programmed death-1 (PD-1). A large phase I/II study[14] of nivolumab including 262 patients with HCC with or without previous exposure to sorafenib showed an objective response rate (ORR) of 14% by RECIST (18% by mRECIST). The median OS for patients in second-line therapy was 15.6 months.[15] Based on these results, the US Food and Drug Administration (FDA) granted accelerated approval to nivolumab for patients with advanced stage HCC previously treated with sorafenib. A confirmatory open-label, randomized phase III trial comparing sorafenib versus nivolumab in the front-line setting is ongoing (CheckMate 459; NCT02576509); patient accrual is complete, and the results are eagerly awaited.

TABLE 2. ONGOING TRIALS OF TARGETED AND IMMUNE THERAPIES COMBINATIONS FOR HCC*

Drugs	Targets	Clinical Stage	Enrichment	Phase (Comparator)	Endpoint	NCT
Atezolizumab + bevacizumab	PD-L1/VEGFA	Advanced first line	No	III (sorafenib)	OS	NCT03434379
Durvalumab +/– tremelimumab	PD-L1/CTLA-4	Advanced first line	No	III (sorafenib)	OS	NCT03298451
Nivolumab +/– ipilimumab	PD-1/CTLA-4	Neoadjuvant	No	II	AEs	NCT03222076
Galunisertib + sorafenib	TGF-βR1/VEGFRs, C-KIT, PDGFRB, RAF	Advanced first line	No	II	OS	NCT02178358
Mogamulizumab + nivolumab	CCR4/PD-1	Advanced second line	No	I-II	MTD	NCT02705105
Pembrolizumab + epacadostat	PD-1/IDO1	Advanced second line	No	I-II	DLTs	NCT02178722
Galunisertib + nivolumab	TGF-βR1/PD-1	Advanced second line	AFP > 200 ng/mL	I-II	MTD	NCT02423343
Apatinib + SHR1210	VEGFR2/PD-1	Advanced second line	No	I-II	OS	NCT02942329
Spartalizumab +/– capmatinib	PD-1/MET	Advanced second line	No	I-II	DLTs	NCT02795429
FGF401 +/– spartalizumab	FGFR4/PD-1	Advanced second line	$FGFR4^+$ KLB^+	I-II	DLTs	NCT02325739
Pembrolizumab + sorafenib	PD-1/VEGFRs, C-KIT, PDGFRB, RAF	Advanced first line	No	I-II	ORR	NCT03211416
Pembrolizumab + lenvatinib	PD-1/VEGFR2, VEGFR3	Advanced second line	No	I	DLTs	NCT03006926
Spartalizumab + sorafenib	PD-1/VEGFRs, C-KIT, PDGFRB, RAF	Advanced first line	No	I	AEs	NCT02988440
Regorafenib + pembrolizumab	VEGFRs, FGFRs, C-KIT, PDGFRs, RAF/PD-1	Advanced first line	No	I	AEs	NCT03347292
Cabozantinib + nivolumab	MET, VEGFRs/PD-1	Neoadjuvant	No	I	AEs	NCT03299946
Avelumab + axitinib	PD-L1/VEGFRs, C-KIT, PDGFRs	Advanced first line	No	I	AEs	NCT03289533
Ramucirumab + durvalumab	VEGFR2/PD-L1	Advanced second line	AFP > 1.5× upper limit of normal	I	DLTs	NCT02572687
XL888 + pembrolizumab	Hsp90/PD-1	Advanced second line	No	I	RP2D	NCT03095781

*Data were accessed in January 2018 on the ClinicalTrials.gov database. Keyword searches for "hepatocellular carcinoma" were used to identify active clinical trials that started in the last 5 years investigating combination systemic targeted therapies.

Pembrolizumab

Pembrolizumab is another anti–PD-1 monoclonal antibody that has shown antitumor activity with a safe profile in several cancers.[16] The efficacy and safety of this drug has been evaluated in a phase II clinical trial (KEYNOTE-224) in 104 patients with advanced HCC previously treated with sorafenib. This trial showed an overall response rate of 17% (according to RECIST version 1.1) with a median time to progression and progression-free survival of 4.9 months and a median OS of 12.9 months. However, a randomized phase III clinical trial (KEYNOTE-240; NCT02702401) that will assess pembrolizumab versus placebo as a second-line therapy in advanced HCC is ongoing in several countries.[16] Longer-term follow-up data on the former phase II as well as the results of the phase III trial are awaited.

FINAL CONCLUSIONS AND FUTURE PERSPECTIVES

There has been a revolution in the management of patients with advanced HCC. The efficacy of the seven drugs described in this review increases the antitumor armamentarium, which is being translated in encouraging outcomes with sequential therapies. However, up to date, apart from patients with high AFP level (>400 ng/dL) who could benefit from ramucirumab, there are no other available biomarkers to predict patient response or allow the choice of one drug over another for the treatment of HCC. In addition, programmed death ligand 1 (PD-L1) expression by immunohistochemistry did not show to be useful in HCC.

In the future and considering the possibility that the results of the phase III CheckMate-459 trial assessing nivolumab versus sorafenib are positive, this anti–PD-1 monoclonal antibody will become the standard of care in advanced HCC, causing the current front-line sorafenib and the recently approved lenvatinib to move to the second line, leaving, in this hypothetical scenario, the current second-line drugs as a third option for the treatment of this dismal disease.

Currently, combinations of kinase inhibitors and immunotherapies are emerging as tools to boost responses of the immune system against HCC-derived neoantigens (Table 2). These unprecedented outcomes (objective responses >45%) resulted in breakthrough therapy designation for bevacizumab and atezolizumab by the FDA.[17] Overall, major improvements are expected in the coming years, particularly if biomarkers of response or resistance to therapies are identified.

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REFERENCES

1) Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87-108.

2) Llovet JM, Zucman-Rossi J, Pikarsky E, et al. Hepatocellular carcinoma. Nat Rev Dis Primers 2016;2:16018.

3) Llovet JM, Montal R, Sia D, et al. Molecular therapies and precision medicine for hepatocellular carcinoma. Nat Rev Clin Oncol 2018;15:599-616.

4) Vilgrain V, Pereira H, Assenat E, et al.; SARAH Trial Group. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. Lancet Oncol 2017;18:1624-1636.

5) Chow PKH, Gandhi M, Tan SB, et al.;Asia-Pacific Hepatocellular Carcinoma Trials Group. SIRveNIB: selective internal radiation therapy versus sorafenib in Asia-Pacific patients with hepatocellular carcinoma. J Clin Oncol 2018;36:1913-1921.

6) Zucman-Rossi J, Villanueva A, Nault JC, et al. Genetic landscape and biomarkers of hepatocellular carcinoma. Gastroenterology 2015;149:1226-1239.

7) Llovet JM, Ricci S, Mazzaferro Z, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-390.

8) Bruix J, Cheng AL, Meinhardt G, et al. Prognostic factors and predictors of sorafenib benefit in patients with hepatocellular carcinoma: analysis of two phase III studies. J Hepatol 2017;67:999-1008.

9) Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018;391:1163-1173.

10) Bruix J, Qin S, Merle P, et al.; RESORCE Investigators. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017;389:56-66.

11) Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. N Engl J Med 2018;379:54-63.

12) Zhu AX, Park JO, Ryoo BY, et al. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol 2015;16:859-870.

13) Zhu AX, Kang Y-K, Yen C-J, et al. REACH-2: a randomized, double-blind, placebo-controlled phase 3 study of ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma (HCC) and elevated baseline alpha-fetoprotein (AFP) following first-line sorafe. J Clin Oncol 2018;36(Suppl. 15):4003.

14) El-Khoueiry AB, Sangro B, Yau T, 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;389:2492-2502.

15) El-Khoueiry AB, Melero I, Yau TC, et al. Impact of antitumor activity on survival outcomes, and nonconventional benefit, with nivolumab (NIVO) in patients with advanced hepatocellular carcinoma (aHCC): subanalyses of CheckMate-040. J Clin Oncol 2018; 36(Suppl. 4):475.

16) Zhu AX, Finn RS, Edeline J, 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;19:940-952.

17) Genentech. FDA grants breakthrough therapy designation for Genentech's TECENTRIQ in combination with avastin as first-line treatment for advanced or metastatic hepatocellular carcinoma (HCC). Available at: https://www.gene.com/media/press-releases/14736/2018-07-17/fda-grants-breakthrough-therapy-designat. Published July 17, 2018.