Hepatocellular carcinoma (HCC) is the third leading cause of death worldwide with increasing incidence and mortality in the United States. High HCC-associated mortality is in part due to the high proportion of patients diagnosed with advanced stage HCC and historical lack of effective systemic therapies for HCC.

HCC staging is unique because liver function and functional status, in addition to tumor burden, are integral determinants of stage and prognosis. Although staging systems vary, parameters that define advanced stage HCC eligible for therapy include presence of portal vein tumor invasion and/or extrahepatic metastases, with relatively preserved liver function and functional status. Generally, systemic therapy trials excluded patients with Child Pugh class B and C cirrhosis, largely because of the competing risk for mortality with cirrhosis. Thus, for many therapies, there are little data on efficacy and tolerability in patients with more advanced liver disease. Systemic therapies may also be appropriate in those patients with unresectable HCC who are not eligible for or are unlikely to benefit from locoregional therapies, although the decision on timing of when to initiate systemic therapy in a patient with intermediate HCC who is eligible for recurrent locoregional therapy remains an open question. In this review, we discuss contemporary approaches and ongoing studies for the treatment of patients with advanced HCC.
Multikinase Inhibitors

Until recently, sorafenib has been the only US Food and Drug Administration (FDA)-approved first-line agent for advanced HCC. Sorafenib has been associated with modest improvement in overall survival (OS) as compared with placebo in patients with Child-Pugh A cirrhosis and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 in both a trial setting (10.7 versus 7.9 months [hazard ratio (HR), 0.73; 95% confidence interval (CI), 0.58-0.92]) in the phase 3 sorafenib hepatocellular carcinoma assessment randomized protocol (SHARP) trial and 6.5 versus 4.2 months in the Asia-Pacific trials, respectively) and in multiple real-world observational cohorts that included patients with varying liver function. Adverse events (AEs), including diarrhea, fatigue, and palmar-plantar erythrodysthesia, are frequent (80%) and led to drug discontinuation in approximately 20% of patients in the global investigation of therapeutic decisions in hepatocellular carcinoma and of its treatment with sorafenib (GIDEON) observational cohort study. Lenvatinib was recently shown to be noninferior to sorafenib (13.6 versus 12.3 months; HR, 0.92; 95% CI, 0.79-1.06) in the REFLECT study with similar side effects (hypertension, diarrhea, fatigue, weight loss, palmar-plantar erythrodysthesia) and frequency of grade ≥3 AEs (75%), resulting in the recent first-line approval of lenvatinib for HCC by the FDA. Compared with sorafenib, lenvatinib is also associated with higher rates of proteinuria (25%) and dysphonia (24%). Secondary endpoints of time to progression (HR, 0.60; 95% CI, 0.51-0.71) and objective response (HR, 3.13; 95% CI, 2.15-4.56) were superior in the lenvatinib arm; however, in subgroup analysis, this effect appears to be mostly driven by the impact in Asian patients.

Until 2017, there were no approved agents for patients who did not respond positively to sorafenib. The results of the phase 3 RESORCE trial (OS for regorafenib: 10.6 versus 7.8 months in placebo; HR, 0.63; 95% CI, 0.50-0.79) led to FDA approval of regorafenib as a second-line therapy for patients with advanced HCC who progressed with sorafenib. (Fig. 1) Notably, patients enrolled in the RESORCE trial were required to have tolerated sorafenib at a dose of at least 400 mg daily and maintain Child-Pugh A cirrhosis and an ECOG status of 0 despite progression with sorafenib, which, when applied in clinical practice, is a highly selected population. Forty-six percent of patients experienced grade ≥3 AEs in the trial; however, there was no meaningful difference in quality of life compared with placebo.

Cabozantinib, another tyrosine kinase inhibitor, was shown to improve OS in patients who did not respond positively to first- and/or second-line therapies in the phase 3 CELESTIAL trial. Cabozantinib also showed increased OS compared with placebo in patients with Child-Pugh A with an ECOG of 0 to 1 (10.2 versus 8.0 months; HR, 0.76; 95% CI, 0.63-0.92) and will be considered for approval as a second- or third-line agent. Finally, the phase 3 REACH-2 trial showed that ramucirumab improved OS as a second-line agent in patients with preserved liver function and functional status who progressed or were intolerant to sorafenib with an alpha-fetoprotein >400 ng/mL (OS, 8.5 versus 7.3 months; HR, 0.71; 95% CI, 0.53-0.95) and thus will also be considered for approval in this setting in the coming months.

Checkpoint Inhibitors

Checkpoint inhibitors, a form of immunotherapy, are increasingly being used in several solid malignancies, and they have been studied in HCC, with several trials scheduled to report results in the coming months. Nivolumab, a programmed death receptor-1 (PD-1) inhibitor, was studied in sorafenib-naive and experienced patients in the phase 1/2 CheckMate-040 trial with Child-Pugh A liver function and an ECOG status of 0 to 1, which led to its FDA approval as a second-line treatment for advanced HCC in 2017. The observed overall tumor response rate was 16%, with three or more AEs reported in 25% of patients. Nivolumab and other immunotherapy agents have the potential to induce immune-mediated AEs, including autoimmune hepatitis, colitis, pneumonitis, and uveitis; however, the incidence of severe immune-mediated reactions in the CheckMate-040 was less than 5%. Nivolumab is not currently approved for use for patients with HCC in other countries, including throughout Europe, because of surrogate endpoint reporting in CheckMate-040. A phase 3 clinical trial comparing nivolumab and sorafenib as first-line therapy (CheckMate-459) in patients with advanced HCC has enrolled and is pending full reporting (NCT02576509). Notably, the second-line approval of nivolumab is contingent on the results of this trial showing superiority to sorafenib.

Pembrolizumab is another PD-1 inhibitor that has recently attained conditional approval from the FDA for use as...
a second-line treatment for advanced HCC (NCT02702401) (Table 2). Finally, a large phase 3 study of another checkpoint inhibitor, durvalumab, with and without tremelimunab (CTLA-4 inhibitor), compared with sorafenib in the first-line setting is currently recruiting (NCT03298451).

**LOCOREGIONAL THERAPY**

Systemic therapy is recommended as the standard of care for advanced HCC in practice guidelines worldwide. However, liver-directed locoregional therapies have been explored in advanced stage patients with portal vein tumor thrombus without extrahepatic disease. Observational cohort studies and early-phase clinical trials with transarterial chemoembolization (TACE; with/without concurrent radiation therapy), hepatic arterial infusion chemotherapy (HAIC), and transarterial radioembolization with $^{90}$Y-loaded resin microspheres (selective internal radiation therapy [SIRT]) showed improvement in patient survival as compared with sorafenib.12 (Table 2) However, the recently completed phase 3 sorafenib versus radioembolization in advanced hepatocellular carcinoma (SARAH)
### TABLE 1. STUDIES FOR FIRST- AND SECOND-LINE TREATMENT FOR ADVANCED HCC

| Author (Year)     | Trial          | Intervention | Control | Design | Patients (n) | Child-Pugh Class A/B Score (%) | BCLC A/B/C (%) | Outcome       | Outcome       | P Value       |
|-------------------|----------------|--------------|---------|--------|--------------|--------------------------------|----------------|---------------|---------------|---------------|
| **First-Line Treatment** |                |              |         |        |              |                                |                |               |               |               |
| Llovet3 (2008)    | SHARP          | Sorafenib    | Placebo | RCT, phase 3 | 299 versus 303 | 95/5 | 0/17/83 | Median OS | 10.7 versus 7.9; HR, 0.69 (95% CI, 0.55-0.87) | <0.001 |
| Cheng15 (2009)    | Asia-Pacific   | Sorafenib    | Placebo | RCT, phase 3 | 150 versus 76  | 97/3 | 0/5/95 | Median OS | 6.5 versus 4.2; HR, 0.68 (95% CI, 0.50-0.93) | 0.014 |
| Cheng16 (2013)    | Sunitinib      | Sorafenib    | Sunitinib | RCT, phase 3 | 530 versus 544 | 100/0 | 0/13/87 | Median OS | 7.9 versus 10.2; HR, 1.3 (95% CI, 1.13-1.5) | 0.99 |
| Johnson17 (2013)  | BRISK-FL       | Brivanib     | Sorafenib | RCT, phase 3 | 577 versus 578 | 92/8 | 6/17/77 | Median OS | 9.5 versus 9.9; HR, 1.06 (95% CI, 0.93-1.22) | 0.37 |
| Cairap18 (2015)   | Lenvatinib     | Sorafenib    | Lenvatinib | RCT, phase 3 | 514 versus 521 | 95/5 | 0/15/85 | Median OS | 9.1 versus 9.8; HR, 1.046 (95% CI, 0.89-1.22) | NS |
| Kudo6 (2018)      | REFLECT       | Lenvatinib   | Sorafenib | RCT, phase 3 | 478 versus 476 | 99/1 | 0/21/79 | Median OS | 13.6 versus 12.3; HR, 0.92 (95% CI, 0.79-1.06) | NS |
| **In process**    |                |              |         |        |              |                                |                |               |               |               |
| CheckMate 459     | Nivolumab      | Sorafenib    | RCT, phase 3 | 726 | 100/0 | Pending | Median OS | In process | In process | In process |
| CheckMate 459     | Durvulomab     | Sorafenib    | RCT, phase 3 | 1200* | 100/0 | Pending | Median OS | In process | In process | In process |
| **Second-Line Treatment (Sorafenib Failure or Intolerance)** |                |              |         |        |              |                                |                |               |               |               |
| Llovet3 (2013)    | BRISK-PS       | Brivanib     | Placebo | RCT, phase 3 | 263 versus 162 | 92/8 | 3/9/88 | Median OS | 9.4 versus 8.2 months; HR, 0.89 (95% CI, 0.69-1.15) | 0.104 |
| Zhu19 (2014)      | EVOLVE-1       | Everolimus   | Placebo | RCT, phase 3 | 362 versus 184 | 98/2 | 0/14/86 | Median OS | 7.6 versus 7.3 months; HR, 0.93 (95% CI, 0.75-1.15) | 0.68 |
| Zhu20 (2015)      | REACH          | Ramucirumab  | Placebo | RCT, phase 3 | 283 versus 282 | 98/2 | 0/12/88 | Median OS | 9.2 versus 7.6 months; HR, 0.87 (95% CI, 0.72-1.05) | 0.14 |
| Bruix7 (2017)     | RESORCE        | Regorafenib  | Placebo | RCT, phase 3 | 379 versus 194 | 98/2 | 0/14/86 | Median OS | 10.6 versus 7.8 months; HR, 0.63 (95% CI, 0.50-0.79) | <0.0001 |
| El-Khoueiry11     | CheckMate-040  | Nivolumab    | Sorafenib | Phase 1/2 | 262 | 98/2 | BCLC-C | ORR | 15%-20% | NA |
| Rimassa21 (2018)  | Metiv-HCC      | Tivantinib   | Placebo | RCT, phase 3 | 226 versus 114 | 95/5 | 7/12/81 | Median OS | 8.4 versus 9.1 months; HR, 0.97 (95% CI, 0.75-1.25) | 0.81 |
| Abou-Alfa9 (2018) | CELESTIAL      | Cabozantinib | Placebo | RCT, phase 3 | 311 versus 466 | 100/0 | BCLC-C | Median OS | 10.2 versus 8 months; HR, 0.76; 95% CI, 0.63-0.92 | 0.005 |
| Zhu10 (2018)      | REACH-2        | Ramucirumab  | Placebo | RCT, phase 3 | 197 versus 95 | 100/0 | NR | Median OS | 8.5 versus 7.3 months; HR 0.71; 95% CI, 0.53-0.95 | 0.02 |
| **In process**    |                |              |         |        |              |                                |                |               |               |               |
| KEYNOTE-240       | Pembrolizumab  | Placebo      | RCT, phase 3 | 408 (21) | A, B7 | BCLC-C | Median OS | In process | In process | In process |

*Projected.
†Sorafenib failure only.
| Author (Year) | Intervention | Control | Design | Patients (n) | Child-Pugh Score (%) | BCLC A/B/C (%) | MVI/EHS (%) | Survival, HR (95% CI) | P Value | Disease Control, HR (95% CI) | P Value |
|--------------|--------------|---------|--------|--------------|----------------------|----------------|-------------|------------------------|---------|----------------------------|---------|
| Yang22 (2012) | Cryo+ Sorafenib | Sorafenib | RCT | 52 versus 52 | 79/21 | 0/0/100 | 100/NA | Median OS 12.5 versus 8.6 months; Median OS 7.1 versus 4.1 months; | 0.01 | TTP 9.5 versus 5.3 months | 0.02 |
| Luo23 (2011) | TACE | Conservative | Observational | 84 versus 80 | 100/0 | 0/0/100 | 100/15 | Median OS 9.2 versus 7.4 months; NA | <0.001 | NA | NA |
| Pinter24 (2012) | TACE | Sorafenib | Observational | 34 versus 63 | 59/41 | 0/0/100 | 32/41 | Median OS 5.9 versus 4.4 months; 0.57 (0.39-0.83) | 0.377 | TTP 5.3 months | 0.73 |
| Kim25 (2015) | TACE | Sorafenib | Observational | 295 versus 66 | 83/17 versus 66/34 | 0/0/100 | 100/11-50 | Surv. rate 12.8 versus 10.0 months; 0.61; (0.38-0.98) | 0.003 | TTP 3.4 versus 1.8 months; 0.32 (0.19-0.55) | <0.001 |
| Yoon26 (2018) | TACE/RT | Sorafenib | Randomized, phase 2 | 45 versus 45 | 0 | 0/0/100 | 100/0 | Median OS 12.8 versus 10.0 months; 0.61; (0.38-0.98) | 0.04 | TTP 7.2 versus 2.7 months; 0.28 (0.17-0.46) | <0.001 |
| Kulik27 (2008) | TACE | Conservative | Phase 2 | 108 | 54/27 | 0/66/33 | 37/12 | Median OS 16 months | NA | Partial response rate 42%-70% | NA |
| D’Aoola28 (2009) | TACE | Control | Observational | 35 versus 43 | 94/6 | 3/51/46 | 46/NA | Median OS 16 versus 8 months; 0.377 | <0.001 | NA | NA |
| Mazzaferro29 (2013) | TACE | Sorafenib | Observational | 34 versus 107 | 82/18 | 0/0/100 | 53/NA | Median OS 26.2 versus 8.7 months; 0.4 (0.19-0.82) | 0.054 | Response rate 78% versus 27% | 0.003 |
| Vilgrain13 (2017) | TACE | Sorafenib | Observational | 237 versus 222 | 84/16 | 4/28/68 | 60/0 | Median OS 8 versus 9 months; 1.15 (0.94-1.41) | 0.18 | PFS 4.1 versus 3.7 months; 1.03 (0.85-1.25) | 0.76 |
| Chow14 (2018) | TACE | Sorafenib | Observational | 182 versus 178 | NA | NA | NA | Median OS 8.8 versus 10 months; 1.1 (0.9-1.4) | 0.36 | NA | NA |
| Song31 (2015) | TACE | HAIC (LFP) | Control | 60 versus 50 | 84/16 | 0/0/100 | 100/33 | Median OS 7.1 versus 5.5 months | 0.011 | TTP 3.2 versus 2.1 months | 0.034 |
| Moriguchi12 (2017) | TACE | HAIC (LFP) + Sorafenib | Observational | 32 versus 14 | 100/0 | 0/0/100 | 100/22-35 | Median OS 10.3 versus 4 months | 0.009 | TTF 3.6 versus 1.2 months | 0.002 |
| Bujold34 (2013) | TACE | Sorafenib | Observational | 55 | 80/20 | 0/33/67 | 69/89 | Median OS 19.9 months | NA | NA | NA |
| Nakazawa35 (2014) | 3D CRT | Sorafenib | Observational | 36 versus 28 | 59/41 | 0/0/100 | 19/19 | Median OS 4.3 versus 5.9 months; NA | 0.12 | Local control at 1 year 87% | NA |

* SARAH study. ** SIRveNIB study.
and selective internal radiation therapy versus sorafenib in locally advanced hepatocellular carcinoma (SIRveNIB) trials failed to demonstrate OS benefits of SIRT as compared with sorafenib in patients with Child-Pugh A liver function and advanced HCC.\textsuperscript{13,14} (Table 2) Even though these studies were negative, limitations related to the study designs (e.g., main portal vein invasion, limited ability to provide boosted radiation) may allow for further study of radioembolization in select patients with advanced stage HCC.

**SURGERY**

Surgical resection can be an effective curative option in highly selected patients with portal vein tumor thrombus and preserved liver function. In observational studies from Asia, resection in patients with segmental or branch portal vein tumor thrombus show that 5-year recurrence-free survival rate can exceed 75\%.\textsuperscript{36,37} This approach warrants further study.

**BEST SUPPORTIVE CARE**

Advanced HCC in the setting of decompensated cirrhosis and/or poor performance is terminal stage disease, and systemic therapies have not shown to be effective or safe in this population. Palliative care with the goal of symptom control should be discussed with all patients with advanced HCC and in particular in those patients without options for therapy.

**CONCLUSIONS AND FUTURE DIRECTIONS**

Systemic therapies with sorafenib or lenvatinib are first-line options in patients with advanced HCC, with several medications available or pending FDA review in the second and third line for first-line failures (Fig. 1). We lack serum or tissue biomarkers to aid in therapy selection and lack adequate information on lines of therapy. Numerous clinical trials are due to report in the coming months that may expand treatment options for advanced HCC. In addition, there are planned or recently opened trials using combination therapy, including lenvatinib + pembrolizumab (NCT03713593) and cabozantinib + nivolumab. Finally, several adjuvant trials currently accruing are combining resection, ablation, or radiation therapy with immunotherapy to determine whether immunotherapy can enhance the effectiveness of these therapies or improve recurrence-free survival. An open question remains whether immunotherapy can be safely used in patients who are being considered for liver transplantation and, if so, the optimal timing between receipt of immunotherapy and transplant.

Further understanding of comparative effectiveness of these therapies alone and possibly in combination will aid in developing evidence-based treatment algorithms for patients with advanced HCC. Ultimately, precision medicine with development of biomarkers that can better direct therapy selection will be critical in the treatment of advanced HCC.

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