REVIEW

Second-line treatment options in hepatocellular carcinoma

Donatella Marino MD1,2, Clizia Zichi MD1,2, Marco Audisio MD1,2, Elisa Sperti MD2, Massimo Di Maio MD1,2

1Department of Oncology, University of Turin, Turin, Italy; 2Division of Medical Oncology, Ordine Mauriziano Hospital, Torino, Italy

Abstract

For many years, sorafenib has been the only approved systemic treatment for advanced hepatocellular carcinoma (HCC). For over a decade, randomized controlled trials exploring the efficacy of new drugs both in first- and second-line treatment have failed to prove any survival benefit. However, in the past few years, several advances have been made especially in pretreated patients; phase III trials of regorafenib, cabozantinib, and ramucirumab in patients with elevated α-fetoprotein have demonstrated efficacy in patients progressing after or intolerant to sorafenib. In addition, early phase I and II trials have shown promising results of immunotherapy alone or in combination with tyrosine-kinase inhibitors or monoclonal antibodies in the same setting of patients. In this review, we will discuss the evidence on second-line options for HCC, focusing on the latest results that are currently refining the treatment scenario.

Keywords: cabozantinib, hepatocellular carcinoma, immunotherapy, ramucirumab, regorafenib, second line, treatment.

Citation

Marino D, Zichi C, Audisio M, Sperti E, Di Maio M. Second-line treatment options in hepatocellular carcinoma. Drugs in Context 2019; 8: 212577. DOI: 10.7573/dic.212577

Introduction

Hepatocellular carcinoma (HCC) is the most frequent primary liver tumor, and it is a worldwide leading cause of morbidity and mortality. According to recent statistics, about 40,000 HCC new cases and 30,000 deaths are expected in the United States alone in 2018.1

Chronic liver inflammation is a procarcinogenic condition that is associated to the majority of known HCC risk factors: hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol abuse/exposure to toxic agents, nonalcoholic fatty liver disease (NAFLD), and autoimmune hepatitis. In 30% of cases, no risk factor is identified and HCC is defined as cryptogenetic; however, it is important to point out that many of these risk factors are preventable (such as HBV infection prevented by active vaccination) or can be handled with habit modifications (alcohol abuse and nonalcoholic steatohepatitis [NASH] that is a precursor of NAFLD) or with effective treatment (direct-acting antiviral agents for HCV infection).2 Although this should hopefully lead to a drastic change in the epidemiology of HCC in the next decades, HCC currently remains a major health problem worldwide.3

Sorafenib, a multi-target tyrosine-kinase inhibitor (TKI), was the first drug to demonstrate efficacy in advanced HCC with well-preserved liver function (Child-Pugh A). Ten years ago, in the SHARP randomized trial and afterward in the Asia-Pacific randomized trial, the comparison of sorafenib to placebo led to a significant improvement in overall survival (OS) and time to progression (TTP).4,5 The drug was consequently approved for the treatment of advanced disease, and has remained the gold standard for over a decade. After the negative results of several randomized controlled trials (RCTs),6–10 in 2018 lenvatinib has proved to be noninferior to sorafenib in the first-line setting11 and has subsequently received approval by Food and Drugs Administration (FDA) and European Medicines Agency (EMA).12,13

Unfortunately, both adaptive resistance and intrinsic resistance represent crucial issues in the management of patients receiving first-line treatment of HCC. Disease progression or significant toxicity leading to first-line therapy discontinuation is a frequent event and further treatment options are eagerly needed. Disappointingly, the first attempt to provide a gold standard in the second-line treatment was unsuccessful. We performed a structured search on the PubMed database and on the proceedings of the main oncology and hepatology conferences, identifying clinical trials of second-line therapy in HCC between 1 January 2008 and 15 February 2019. We also searched Clinicaltrials.gov with the terms ‘hepatocellular carcinoma’ and ‘liver cancer’ to identify ongoing post-sorafenib clinical trials.
Hence, in this review, we will discuss the evidence on second-line options for HCC, focusing on the latest results that are currently referring the treatment scenario.

**Negative randomized control trials**

Following the publication of the SHARP trial and based on promising phase II trials, several drugs have been tested in RCTs in patients experiencing failure of first-line sorafenib. In these trials, given the absence of an active standard treatment, TKIs or monoclonal antibodies (MoAbs) with different target profiles were compared to placebo and best supportive care (BSC).

**Brivanib**

Brivanib is an oral inhibitor of vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) receptor that was tested in HCC patients both in first-line and in second-line therapy. It enrolled 546 patients with advanced HCC progressing on or intolerant to sorafenib were enrolled. Despite a benefit in TTP (median TTP was 4.2 months for brivanib and 2.7 months for placebo; p<0.001) and objective response rate (ORR) (10 and 2%, respectively) assessed with mRECIST criteria, there was no significant improvement in OS; median OS was 9.4 months for brivanib and 8.2 months for placebo (p=0.3307). The authors indicated numerical imbalances in some baseline factors such as α-fetoprotein (AFP) levels and the presence of vascular invasion, favoring placebo as possible explanation for brivanib failure.

**Everolimus**

On the basis of preclinical evidence supporting the role of the mTOR pathway in hepatocarcinogenesis and of the clinical experience of the mTOR inhibitor everolimus in HCC, the phase III trial EVOLVE-1 was designed. It enrolled 395 patients with advanced HCC progressing on or intolerant to sorafenib. The patients were randomized in a 2:1 ratio to receive everolimus 7.5 mg per day (n=362) or matched placebo (n=184). The treatment with everolimus did not confer any survival advantage: mOS 7.6 months for everolimus and 7.3 months for placebo (HR 0.97; 95% CI: 0.86–1.27; p=0.68). Prespecified subgroup analyses revealed similar results in most subgroups, except for HBV-positive patients who seemed to obtain some benefit from everolimus therapy. However, no differences were seen in secondary endpoints such as TTP, disease control rate (DCR), and health-related quality of life (HR-QoL).

**Ramucirumab**

Ramucirumab, a recombinant IgG1 MoAb directed against VEGFR-2, was tested as second-line treatment in the REACH trial, enrolling 565 HCC patients. Inclusion criteria and study design were similar to the RCTs already discussed. In this study population, ramucirumab achieved better TTP (median 3.5 versus 2.6 months; p<0.0001), ORR (7 versus 1%, p<0.0001), and DCR (56 versus 46%; p=0.011) at the cost of manageable toxicities. However, the primary endpoint was not met: mOS 9.2 months in the ramucirumab group compared with 7.6 months in the placebo group (HR 0.87; 95% CI: 0.72–1.05; p=0.14). In the prespecified subgroup analyses, patients with a baseline AFP concentration of 400 ng/mL or greater had a statistically significant survival benefit (mOS 7.8 versus 4.2 months; HR 0.67; 95% CI: 0.51–0.90; p=0.006). This subgroup also experienced a benefit from ramucirumab treatment in the deterioration of symptoms in FHSI-8 (HR 0.69; p=0.054) and PS (HR 0.642; p=0.057). These findings have led to the design of a population-enriched trial that will be discussed later.

**ADI-PEG 20**

ADI-PEG 20 is the pegylated form of the enzyme arginine deiminase (ADI) that converts arginine to citrulline. Arginine deprivation can induce HCC cell death, and it is therefore a potential target for cancer treatment. The development of ADI-PEG 20 has moved fast from phase II to a phase III trial that enrolled 635 patients worldwide. Unfortunately, similar to the previously listed studies, this trial did not reach its primary endpoint: mOS was 7.8 months for ADI-PEG 20 versus 7.4 months for placebo (HR 1.022; 95% CI: 0.847–1.233; p=0.884). Despite these negative results in the whole study population, post hoc analyses suggested improved survival in patients with prolonged arginine depletion (mOS 12.3 versus 7.3 months; p=0.0032) or citrulline increase (mOS 11.6 versus 3.5 months; p<0.0001) for >8 weeks.

**Tivantinib**

In the METIV-HCC trial, tivantinib, a selective TKI targeting MET receptor, was tested in a biomarker-enriched population. The HGF–MET pathway is involved in tumor development and metastasis and has a prognostic value. Moreover, MET is often overexpressed after sorafenib exposure. In a randomized phase II trial, interesting hints of efficacy of tivantinib were seen in MET-high tumors; therefore, only patients harboring this molecular characteristic (staining intensity score ≥2 in ≥50% of tumor cells) were enrolled in the subsequent randomized, double-blind, placebo-controlled trial. Unfortunately, efficacy outcomes were not significant between the groups, and the trial did not meet its primary endpoint (mOS was 8.4 months for tivantinib and 9.1 months for placebo; HR 0.97; 95% CI: 0.75–1.25; p=0.81). Although it is difficult to identify a clear reason for such a negative result, authors suggest that it may be due to the tivantinib formulation (capsules in the phase II study and tablets in the phase III study), different timing of tissue analysis (before sorafenib exposure or after sorafenib progression), unintentional selection of patients with less-aggressive disease, and importance of maintaining VEGF inhibition beyond first-line treatment. The lack of efficacy on
Regorafenib

Regorafenib is an oral multitarget inhibitor that is already approved for refractory colorectal cancer and gastrointestinal stromal tumors (GISTs). Although it is structurally similar to sorafenib, regorafenib shows a more potent pharmacological activity and a distinct molecular target profile, blocking the activity of several protein kinases involved in the regulation of tumor angiogenesis (VEGFR1, VEGFR2, VEGFR3, and TIE2), oncogenesis (KIT, RET, RAF1, BRAF, and BRAF\(^{V600E}\)), and the tumor microenvironment (PDGFR and FGFR). In a single-arm phase II trial, 36 patients with Barcelona Clinic Liver Cancer (BCLC) staging classification B or C HCC that would not benefit from treatments of established efficacy were enrolled.\(^3\)

Notably, patients who experienced discontinuation of previous sorafenib due to poor drug tolerability were excluded. The primary endpoint of the study was to assess the safety of regorafenib as second-line treatment in HCC patients who had disease progression after sorafenib; secondary endpoints included efficacy (including TTP and OS) and pharmacokinetics. In half of the cases, adverse events were the reasons for treatment discontinuation, but only in 19% it was deemed to be related to regorafenib. All the 36 patients experienced at least a treatment-related adverse event, and dose modifications were frequent (97%); nevertheless, the safety profile in this setting of patients was in line with the known safety from other indications, and it was globally deemed manageable, being diarrhea, fatigue, and hand-foot skin reaction (HFSR) the most frequent adverse events. Notably, in the efficacy analysis, mTTP was 4.3 months (95% CI: 2.9–13.1) and mOS was 13.8 months (95% CI: 9.3–18.3) with a DCR of 72%. On these bases, the drug was moved to a phase III RCT, the RESORCE study,\(^4\) that was planned as a double-blind, placebo-controlled, international trial. Randomization was stratified by geographical region (Asia versus rest of world), macrovascular invasion (yes versus no), extrahepatic disease (yes versus no), AFP concentration (<400 versus ≥400 ng/mL), and Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0 versus 1). As for the phase II study, eligible patients must have a BCLC stage B or C that is not amenable to locoregional treatments, a Child-Pugh A, and they had to be previously treated with sorafenib in first-line treatment. To select a study population that could more likely tolerate regorafenib, patients needed to be sorafenib-tolerant, meaning that they must have received ≥400 mg of sorafenib daily for at least 20 of the 28 days preceding discontinuation. As a consequence, all the patients enrolled in the RESORCE trial had discontinued sorafenib because of disease progression. The drug was administered at the recommended dosing schedule of 160 mg once daily in repeating cycles of 3 weeks on treatment followed by 1 week of treatment and the treatment needed to be initiated within 10 weeks of sorafenib discontinuation. After a median follow-up of 7 months, the benefit of regorafenib treatment was consistent for primary and secondary endpoints and in all prespecified subgroup analyses. Namely, mOS was 10.6 months with regorafenib and 7.8 months with placebo (HR 0.63; 95% CI: 0.50–0.79; \(p<0.0001\)). In addition, mTTP by mRECIST was 3.2 months with regorafenib and 1.5 months with placebo and more patients in the experimental arm experienced disease control (DCR 65 versus 36%; \(p<0.0001\)). For safety, more patients in the regorafenib arm had treatment interruptions or dose reductions (54 versus 10%) and discontinuation due to drug-related adverse events (10 versus 4%); however, no difference in grade 5 adverse events was recorded. HR-QoL was assessed using FACT-G, FACT-Hep, EQ-5D, and EQ-VAS questionnaires; globally, the scores were similar between the groups except for the FACT-Hep total score that favored placebo (\(p<0.001\)). Nevertheless, the difference did not meet the established minimally important threshold of 8–9 points (129.31 points for regorafenib and 133.17 points for placebo).\(^5\) The adverse events profile of regorafenib in this study is in line with the known drug safety profile from other indications, being hypertension (15%), HFSR (9%), and diarrhea (3%) the most common clinically relevant grade 3 or 4 events.

Based on the results of the RESORCE trial, regorafenib was the first drug to be approved by regulatory agencies as second-line treatment for HCC patients following first-line sorafenib. Subsequent analyses showed that, at least in this selected population of patients who well tolerated sorafenib and were subsequently eligible for a second-line treatment, the sequence sorafenib-regorafenib yields a mOS of 26 months versus 19.2 months of sorafenib-placebo, and that the survival benefit is independent of the pattern of the disease progression during prior sorafenib treatment and of their last sorafenib dose (800 or <800 mg/day).\(^6\) The development of new distant metastases or vascular invasion was confounded to be associated with worse survival irrespective of treatment.\(^7\) Similar to previous observation with sorafenib, also for regorafenib treatment the early onset of dermatological toxicity correlates with better outcome.\(^8\) As for molecular biomarkers, regorafenib benefit is independent of baseline AFP and cMET protein levels that are on the contrary negative prognostic factors.\(^9\) Initial evidence suggests that some single-nucleotide polymorphisms (SNPs) assessed in the RESORCE population may have a prognostic and predictive impact; however, to date, no predictive molecular biomarker of regorafenib benefit has been established.\(^10\)

Cabozantinib

Cabozantinib is an oral multitarget TKI that was initially identified as a potent dual inhibitor of VEGFR-2 and c-MET. Its target profile also includes the inhibition of VEGFR-1 and 3, AXL, RET, FLT3, and TIE-2. It is important to point out that both MET and AXL overexpression has a negative prognostic impact and that MET might be induced by sorafenib treatment and can be a mechanism of resistance.\(^31,32\) The first clinical experience...
of cabozantinib in HCC involved 41 patients (19 sorafenib naïve, 22 sorafenib pretreated) enrolled in 1 of the 9 cohorts of a phase II randomized discontinuation trial.\textsuperscript{33,34} Patients received a 12-week lead-in treatment with 100 mg per day of cabozantinib. After restaging, patients with stable disease (SD) were randomized to cabozantinib or placebo, patients with a partial response (PR) could continue open-label cabozantinib treatment, and patients with progressive disease (PD) at or before week 12 permanently discontinued treatment. The primary endpoint of the lead-in phase was ORR at week 12, and the primary endpoint of the randomized phase was PFS. Randomization was halted before the preplanned accrual was reached due to initial efficacy results. In the HCC cohort, cabozantinib demonstrated a week-12-ORR of 5% and a week-12-DCR of 66%. Among the patients who had SD at week 12 (n=22), 12 patients were randomized to placebo and 10 to cabozantinib. With the limitation of this small sample size, no significant difference in PFS was observed between the two groups. In the overall population of 41 treated patients, mPFS from the start of the study was 5.2 months and mOS 11.5 months. The most frequent adverse events (diarrhea, weight loss, and HFSR) were mainly mild to moderate.

Based on these preliminary signals of clinical activity, a phase III, randomized, double-blind, controlled trial comparing cabozantinib to placebo in patients with HCC who had received prior sorafenib therapy was conducted (the CELESTIAL trial).\textsuperscript{35} Study treatment accounted for either a 60-mg of cabozantinib or a matched placebo once per day administered as long as patients experienced clinical benefit or, until they had unacceptable toxicity. Patients were allowed to receive cabozantinib or placebo beyond radiographic progression, as long as they continued to have clinical benefit. Randomization was stratified according to etiologic factor (HBV+HCV versus HCV without HBV versus other), geographic region (Asia versus other), and evidence of extrahepatic disease, macrovascular invasion, or both (yes versus no). Eligible patients had a diagnosis of HCC not amenable to curative treatment but with preserved liver function (Child-Pugh A) and had received previous sorafenib, but they could have received up to two previous systemic treatments and should have progressed on at least one of them (27% of cases). A total of 707 patients were randomized, in a 2:1 ratio, to receive cabozantinib (470), or placebo (237) in 95 centers worldwide during 4 years. The trial reached its primary endpoint of improving survival at the second preplanned interim analysis: median OS was 10.2 months in the cabozantinib group and 8.0 months in the placebo group (HR for death 0.76; 95% CI: 0.63–0.92; p=0.005). In the subgroup of patients whose only previous systemic therapy was sorafenib, the mOS was 11.3 months with cabozantinib and 7.2 months with placebo (HR for death 0.70; 95% CI: 0.55–0.88). In addition, the secondary endpoints favored the experimental arm; cabozantinib yielded a DCR of 64% as compared with 33% in the placebo group. mPFS was 5.2 months in the cabozantinib group and 1.9 months in the placebo group (HR 0.44; 95% CI: 0.36–0.52; p<0.001).

Of note, 47% of patients on cabozantinib had a reduction in target lesions, and 23% of AFP-high patients on cabozantinib experienced ≥50% reduction in AFP levels.\textsuperscript{36,37} Overall, patients with AFP levels >400 ng/mL experienced a larger treatment benefit from cabozantinib if compared with those with AFP <400 ng/mL (HR for OS 0.71 versus 0.81). Other analyses have shown that the benefit of cabozantinib is independent of the presence of macrovascular invasion, extrahepatic disease, disease extension, previous TACE treatment, and age (<65 or ≥65 years).\textsuperscript{38–40}

As for safety, more patients in the experimental arm needed dose reductions (62 versus 13%) or treatment discontinuation due to drug-related adverse events (16 versus 3%). Adverse events were consistent with the known safety profile of the drug, being the most common grade 3 or 4 adverse events palmar-plantar erythrodysesthesia (17 versus 0% with placebo), hypertension (16 versus 2%), increased aspartate aminotransferase (AST) level (12 versus 7%), fatigue (10 versus 4%), and diarrhea (10 versus 2%). HR-QoL was assessed using the EQ-5D-5L questionnaire at baseline, every 4 weeks through week 25, then every 8 weeks, but these results have not been reported yet. Based on the CELESTIAL trial results, cabozantinib has been approved by the EMA for the treatment of patients previously treated with sorafenib and is under evaluation by the FDA.

### Ramucirumab

We have already discussed the initial clinical development of the MoAb ramucirumab in HCC. Following the results of the REACH trial\textsuperscript{16} in the subgroup of patients with baseline AFP concentration of 400 ng/mL or greater, the REACH-2 trial was designed to assess the benefit of ramucirumab specifically in this subgroup of patients. The results of this trial were presented at the 2018 ASCO Meeting.\textsuperscript{41} There were 292 previously treated patients with BCLC-B or C HCC, Child-Pugh A who were randomized 2:1 to receive ramucirumab 8 mg/kg (n=197) or matched placebo (n=95) intravenously (I.V.) every 2 weeks. Treatment was continued until PD or unacceptable toxicity, and patients were stratified according to macrovascular invasion (yes versus no), ECOG PS (0 versus 1), and geographic region (Japan versus rest of Asia versus other regions). The primary endpoint of the study was OS, and the secondary objectives included PFS, ORR per RECIST v1.1, and safety.

In the efficacy analysis, OS benefit favored ramucirumab over placebo: mOS was 8.5 versus 7.3 months (HR for death 0.71; p=0.0199). Secondary endpoints were improved as well; mPFS was 1.6 months in the placebo arm and 2.8 months in the ramucirumab arm (p<0.0001), and DCR was 38.9 and 59.9%, respectively (p=0.0006). Although the absolute benefit seems inferior if indirectly compared to the other studies we have already discussed, it is important to point out that elevated AFP is a recognized negative prognostic factor in HCC and consequently patients included in the REACH-2 trial had a worse survival expectancy. In addition, for the first time in the clinical development of a drug in this disease, a
predictive marker of response (AFP ≥ 400 ng/mL) was validated. Ramucirumab toxicity was globally manageable with no unexpected adverse events recorded. The most common grade ≥ 3 adverse events of interest were hypertension (12.7%), bleeding events (5.1%), proteinuria (2%), and liver injury (18.3%).

Data from the REACH-2 and from the AFP-high patients enrolled in the REACH trial were recently pooled together. In a population of 542 patients (292 patients from the REACH-2 and 250 patients from the REACH trial), 316 were treated with ramucirumab and 226 with placebo. The results of the pooled analysis are consistent with the individual studies, with a significant improvement in survival favoring ramucirumab (median OS 8.1 months versus 5.0 months; HR 0.694; p = 0.0002). Improvements in PFS (mPFS 2.8 months versus 1.5 months; HR 0.572; p < 0.0001), ORR (5.4% versus 0.9%; p = 0.0040), and DCR (56.3% versus 37.2%; p < 0.0001) were observed. In another recent analysis on patients reported outcomes assessed in the same pooled population, ramucirumab demonstrated a consistent trend for a benefit in disease-related symptoms as measured by FACT-FHSI-8. The results of phase III trials in second-line treatment for HCC are summarized in Table 1.

### Immunotherapy and future perspectives

Immunotherapy has been the breakthrough in cancer treatment in the last few years, and it has completely revolutionized the cure strategy, with continuous advances and evidence of efficacy in several types of cancer. The possibility of unleashing T cells activation against cancer cells produces durable responses at the cost of limited toxicity. Although the knowledge of predictive factors is far from being optimal, efficacy of immunotherapy is often correlated to specific features that are independent of the site of primary tumor, such as PD-1/PD-L1 expression, tumor mutational burden (TMB), or presence of microsatellite-instable phenotype (MSI-H). In HCC etiology, the role of chronic liver injury is prevalent and it is associated with inflammation and establishment of a suppressed immune environment. In addition, high expression of PD-L1 in tumors correlates with a poorer prognosis in patients with HBV-related HCC, and upregulation of PD-1 on CD8(+) T cells could predict a poorer disease progression and postoperative recurrence. Within HCC, current evidence suggests the presence of three immunogenic subgroups that show different patterns of immune cell infiltration, PD-1/PD-L1 expression, IFNγ signaling activation, and chromosomal aberrations and may consequently show a different potential of response to immunotherapy. Currently, clinical evidence of efficacy of immunotherapy in HCC is available for two anti-PD-1 MoAbs, nivolumab and pembrolizumab.

### Nivolumab

The CheckMate-040 was designed as a multicenter, open-label, phase I/II study, to evaluate the safety and efficacy of nivolumab in 262 patients with advanced HCC. Eligible

---

**Table 1. Results of phase III trials in second-line treatment for HCC.**

| Study     | Author (year) | Randomization | Child-Pugh score | Patients (n)  | Survival (months) | Significance | TTP or PFS* (months) | Significance |
|-----------|---------------|---------------|------------------|---------------|-------------------|--------------|----------------------|--------------|
| BRISK-PS  | Llovet et al.24 | Brivanib versus placebo | A-B7             | 263 versus 132 | 9.4 versus 8.2    | p = 0.33     | 4.2 versus 2.7       | p = 0.001    |
| EVOLVE-1  | Zhu et al.25   | Everolimus versus placebo | A               | 362 versus 184 | 7.6 versus 7.3    | p = 0.68     | 3.0 versus 2.6       | p = 0.01     |
| REACH     | Zhu et al.9    | Ramucirumab versus placebo | A               | 283 versus 282 | 9.2 versus 7.6    | p = 0.14     | 3.5 versus 2.6       | p < 0.0001   |
| ADI-PEG 20| Abou-Alfa et al.29 | ADI-PEG 20 versus placebo | A-B7             | 424 versus 211 | 7.8 versus 7.4    | p = 0.88     | 2.6 versus 2.6*      | p = 0.075    |
| METIV-HCC | Rimassa et al.39 | Tivantinib versus placebo• | A               | 226 versus 114 | 8.4 versus 8.1    | p = 0.81     | 2.4 versus 3         | p = 0.076    |
| RESORCE   | Bruix et al.25 | Regorafenib versus placebo | A               | 379 versus 194 | 10.6 versus 7.8   | <0.0001      | 3.9 versus 1.5       | <0.0001      |
| CELESTIAL | Abou-Alfa et al.35 | Cabozantinib versus placebo | A               | 470 versus 237 | 10.2 versus 8.0   | p = 0.005    | 5.2 versus 1.9*      | p = 0.001    |
| REACH-2   | Zhu et al.41   | Ramucirumab versus placebo• | A               | 197 versus 95  | 8.5 versus 7.3    | p = 0.0199   | 2.8 versus 1.6*      | p < 0.0001   |

• In patients with baseline MET-high tumor.
• In patients with baseline α-fetoprotein ≥ 400 ng/mL.
* TTP is not reported, only PFS is available.
patients were required to have Child-Pugh A or B7 for the dose-escalation phase and Child-Pugh A for the dose-expansion phase and were enrolled into three cohorts on the basis of etiology (without viral hepatitis, HCV infection, and HBV infection). Although the majority of the patients were heavily pretreated, 56 were sorafenib-naive or intolerant patients. Patients received I.V. nivolumab every 2 weeks at 0.1–10 mg/kg in the dose-escalation phase (48 patients), and 3 mg/kg in the dose-expansion phase (214 patients). Overall, the DCR was reached in 64% of the cases (complete response [CR] 1%, PR 18%, and SD 45%). Responses occurred early in treatment, generally within 3 months, and were durable in time (median duration of response [DoR] 9.9 months). Survival outcomes were encouraging with a 6- and 9-month survival of 83 and 74%, respectively, and an mTTP of 4 months. In recent updates of the study, 18-month OS rates were 57% in sorafenib-naive patients and 44% in sorafenib-experienced patients, mOS was 28.6 months and 15.6 months, respectively, and survival was correlated with the degree of nivolumab antitumor activity.51,52

As for safety, the most common adverse events of any grade were fatigue (23%), pruritus (21%), and rash (15%) and grade 3/4 AST and alanine aminotransferase (ALT) increase occurred in 4 and 2%, respectively. Symptomatic treatment-related adverse events were comparable in patients with and without HCV or HBV infection. As a secondary endpoint, PD-L1 expression levels were retrospectively assessed as a potential biomarker for nivolumab therapy. Using a cut-off of at least 1% of membrane expression of PD-L1 on tumor cells, no correlation with outcome was demonstrated. On the basis of the Checkmate-040 study, the FDA granted accelerated approval for the use of nivolumab in patients previously treated with sorafenib. More recently, at the 2018 AASLD meeting, results of the Child-Pugh B cohort of the Checkmate-040 study were presented: 25 patients were sorafenib naïve and 24 were sorafenib experienced, 37 had a B7 Child-Pugh score, while 11 had a B8. As for efficacy, ORR was 10.2% and DCR was 55.1%, with a median DOR of 9.9 months; mOS was 7.6 months. The safety profile of nivolumab in patients with Child-Pugh B status was comparable to patients with Child-Pugh A status. Drug-related adverse events led to discontinuation in 2 patients (grade 3 hepatic function disorder; grade 2 hyperbilirubinemia plus grade 3 transaminase increase, respectively).53

**Pembrolizumab**

Pembrolizumab was assessed in patients with advanced HCC who had progressed on (80%) or were intolerant to (20%) sorafenib in the KEYNOTE-224, a nonrandomized, multicenter phase II trial. A total of 104 eligible patients were enrolled and treated with pembrolizumab 200 mg I.V. every 3 weeks for up to 35 cycles.54 After a median follow-up of 12.3 months, an ORR was recorded in 18 (17%) of the patients (CR 1% and PR 16%). Moreover, 44% of patients had SD as best response on treatment. Similar to nivolumab, also for pembrolizumab responses generally occurred at the first radiological assessment and were durable. The mTTP was 4.9 months, while mOS was 12.9 months. The most frequent serious adverse events were increased AST concentration in four (4%) participants, increased ALT concentration in two (2%), and adrenal insufficiency in two (2%) participants. The association with tumor proportion score was not significant, consistently with Checkmate 040 conclusions. However, to explore potential predictive biomarkers, investigators used a combined positive score (a measure of PD-L1-positive immune and tumor cell number) that was found to be associated with response to pembrolizumab.55 Based on the KEYNOTE-224 results, the FDA granted accelerated approval for the use of pembrolizumab in patients previously treated with sorafenib. Merck has recently published a press release about the final analysis of the phase III trial KEYNOTE-240 (NCT02702401) evaluating pembrolizumab versus placebo as second-line treatment in Western population; although the co-primary endpoints OS and PFS were improved, these differences did not meet the statistical significance.56

**Ongoing and future trials**

Final considerations about the role of anti-PD-1 monotherapy in HCC will be drawn as soon as other RCTs will be completed; the results of the CheckMate-459 and the BGB-A317-301 trials (nivolumab or tislelizumab compared with sorafenib in the frontline setting, NCT02576509, NCT03412773) and of the KEYNOTE 394 (pembrolizumab versus placebo as second-line setting in Asian population, NCT03062358) are eagerly awaited.

In addition, other strategies are being pursued to maximize the potential of immunotherapy; in particular, some trials are exploring the combination of anti-PD-1/PD-L1 with TKIs, anti-VEGF, or anti-CTLA-4. Some results from phase I trials are already available, and they show a potential benefit compared to anti-PD-1 monotherapy. In a group of 18 subjects (6 previously treated and 12 treatment-naive), lenvatinib and pembrolizumab yielded high rates of ORR (46% PR) and a 92% DCR.57 The combination of two checkpoint inhibitors, the anti-PD-L1 durvalumab and the anti-CTLA-4 tremelimumab given at the dose of 20 and 1 mg/kg I.V., respectively, for four doses followed by 20 mg/kg durvalumab alone every 4 weeks, was tested in a safety run-in cohort with 40 patients. No unexpected safety signals were seen in this unresectable HCC population that included 30% of sorafenib-naive patients. Clinical activity was observed predominantly in uninfected patients (DCR 70 versus 44.4 and 45.5% of HCV and HBV infected),58 Taking the advantage of the immunomodulatory effects of anti-VEGF therapy, the combination of atezolizumab 1200 mg and bevacizumab 15 mg/kg every three weeks is being explored. Among the 73 patients enrolled in a phase Ib trial, ORR was 32% with responses observed in all clinical significant subgroups and adverse events were consistent with the established safety profile of each agent.59 Atezolizumab is also being tested in combination with the anti-glypican-3 codrituzumab. In the preliminary analyses on 18 patients recently reported, the combinations obtained 1 PR and 10 SD,
Table 2. Ongoing immunotherapy studies in HCC.

| Phase | Title                                                                                                                                   | ClinicalTrials.gov identifier | Status                      |
|-------|----------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|-----------------------------|
| III   | Phase 3 Study of BGB-A317 versus Sorafenib in Patients with Unresectable HCC                                                           | NCT03412773                  | Recruiting                  |
| III   | An Investigational Immuno-therapy Study of Nivolumab Compared to Sorafenib as a First Treatment in Patients with Advanced Hepatocellular Carcinoma | NCT02576509                  | Active, not recruiting      |
| III   | Study of Pembrolizumab (MK-3475) versus Best Supportive Care in Participants with Previously Systemically Treated Advanced Hepatocellular Carcinoma (MK-3475-240/KEYNOTE-240) | NCT02702401                  | Active, not recruiting      |
| III   | Study of Pembrolizumab (MK-3475) or Placebo Given with Best Supportive Care in Asian Participants with Previously Treated Advanced Hepatocellular Carcinoma (MK-3475-394/KEYNOTE-394) | NCT03062358                  | Recruiting                  |
| I/II  | An Immuno-therapy Study to Evaluate the Effectiveness, Safety and Tolerability of Nivolumab or Nivolumab in Combination with Other Agents in Patients with Advanced Liver Cancer (CheckMate040) | NCT01658878                  | Active, not recruiting      |
| II    | Study of BGB-A317 in Patients with Previously Treated Unresectable HCC                                                                     | NCT03419897                  | Recruiting                  |
| III   | Safety and Effect of Lenvatinib (E7080/MK-7902) in Combination with Pembrolizumab (MK-3475) versus Lenvatinib as First-line Therapy in Participants with Advanced Hepatocellular Carcinoma (MK-7902-002/LEAP-002) | NCT03713593                  | Not yet recruiting          |
| III   | Study of Durvalumab and Tremelimumab as First-line Treatment in Patients with Unresectable Hepatocellular Carcinoma (HIMALAYA)                      | NCT03298451                  | Recruiting                  |
| III   | A Study of Atezolizumab in Combination with Bevacizumab Compared with Sorafenib in Patients with Untreated Locally Advanced or Metastatic Hepatocellular Carcinoma (IMbrave150) (IMbrave150) | NCT03434379                  | Recruiting                  |
| I/II  | A Trial to Evaluate the Safety and Effect of the Combination of the Oncolytic Immunotherapy Pexa-Vec with the PD-1 Receptor Blocking Antibody Nivolumab in the First-line Treatment of Advanced HCC | NCT03071094                  | Recruiting                  |
| I/II  | CBT-501 or Nivolumab in Combination with CBT-101 in Locally Advanced or Metastatic HCC and RCC                                              | NCT03655613                  | Recruiting                  |
| II    | A Study of MEDI4736 with Tremelimumab, MEDI4736 or Tremelimumab Monotherapy in Unresectable Hepatocellular Carcinoma                         | NCT02519348                  | Recruiting                  |
| I     | Study of Safety and Tolerability of PDR001 in Combination with Sorafenib and to Identify the Maximum Tolerated Dose and/or Phase 2 Dose for This Combination in Advanced Hepatocellular Patients | NCT02988440                  | Recruiting                  |
| II    | A Trial of SHR-1210 (an Anti-PD-1 Inhibitor) in Combination with Apatinib in Patients with Advanced HCC(RESCUE)                                     | NCT03463876                  | Recruiting                  |
| I/II  | A Study of Galunisertib (LY2157299) in Combination with Nivolumab in Advanced Refractory Solid Tumors and in Recurrent or Refractory NSCLC, or Hepatocellular Carcinoma | NCT02423343                  | Recruiting                  |

(Continued)
### Table 2. (Continued)

| Phase | Title                                                                 | ClinicalTrials.gov identifier | Status                  |
|-------|-----------------------------------------------------------------------|------------------------------|-------------------------|
| I/II  | Exploratory Clinical Study of Apatinib and SHR-1210 in Treating Advanced Hepatocellular Carcinoma or Gastric Cancer | NCT02942329                  | Recruiting              |
| I/II  | Phase Ib/II Study of INC280 + PDR001 or PDR001 Single Agent in Advanced HCC | NCT02795429                  | Recruiting              |
| I/Ib  | Phase I/Ib Study of NIS793 in Combination with PDR001 in Patients with Advanced Malignancies | NCT02947165                  | Recruiting              |
| I     | A Study of Ramucirumab (LY3009806) Plus MEDI4736 in Participants with Advanced Gastrointestinal or Thoracic Malignancies | NCT02572687                  | Active, not recruiting  |
| I/II  | Study of Cabozantinib in Combination with Atezolizumab to Subjects with Locally Advanced or Metastatic Solid Tumors | NCT03170960                  | Recruiting              |
| I     | Regorafenib Plus Pembrolizumab in First Line Systemic Treatment of HCC | NCT03347292                  | Recruiting              |
| I/II  | A Phase I/II Study of Regorafenib Plus Avelumab in Digestive Tumors (REGOMUNE) | NCT03475953                  | Recruiting              |
| I     | A Study of Avelumab in Combination with Axitinib in Advanced HCC (VEGF Liver 100) | NCT03289533                  | Recruiting              |

#### Early stage disease (BCLC A or B)

| II    | Neoadjuvant and Adjuvant Nivolumab in HCC Patients Treated by Electroporation (NIVOLEP) | NCT03630640                  | Recruiting              |
| II    | CTLA-4 /PD-L1 Blockade Following Transarterial Chemoembolization (DEB-TACE) in Patients with Intermediate Stage of HCC(Hepatocellular Carcinoma) Using Durvalumab and Tremelimumab | NCT03638141                  | Not yet recruiting      |
| I     | Stereotactic Body Radiotherapy (SBRT) Followed by Immunotherapy in Liver Cancer | NCT03203304                  | Recruiting              |
| I     | Feasibility and Ef cacy of Neoadjuvant Cabozantinib Plus Nivolumab (CaboNivo) Followed by Def nitive Resection for Patients with Locally Advanced Hepatocellular Carcinoma (HCC) | NCT03299946                  | Recruiting              |
| III   | A Study of Nivolumab in Patients with Hepatocellular Carcinoma Who Are at High Risk of Recurrence after Curative Hepatic Resection or Ablation (CheckMate 9DX) | NCT03383458                  | Recruiting              |
| II    | Study Evaluating Nivolumab (Anti-PD-1 Antibody) Alone versus Nivolumab Plus Ipilimumab (Anti-CTLA-4 Antibody) in Patients with Resectable and Potentially Resectable Hepatocellular Carcinoma (HCC) (CA209-956) | NCT03222076                  | Recruiting              |
| II    | Transarterial Chemoembolization in Combination with Nivolumab Performed for Intermediate Stage Hepatocellular Carcinoma (IMMUTACE) | NCT03572582                  | Recruiting              |
| II    | A Study of the Safety and Antitumoral Ef cacy of Nivolumab After SIRT for the Treatment of Patients with HCC (NASIR-HCC) | NCT03380130                  | Recruiting              |
| II    | A Pilot Study of Combined Immune Checkpoint Inhibition in Combination with Ablative Therapies in Subjects with Hepatocellular Carcinoma (HCC) or Biliary Tract Carcinomas (BTC) | NCT02821754                  | Recruiting              |
| I     | Pembrolizumab Plus Y90 Radioembolization in HCC Subjects | NCT03099564                  | Recruiting              |
some of which are durable. The ongoing immunotherapy studies, both for advanced and for early-intermediate stage disease, are reported in Table 2.

Discussion

Advanced HCC still is a medical unmet need; for over a decade, sorafenib had been the only approved treatment in this setting, with several drugs failing to show a benefit both in first- and second-line setting in RCTs. Trials conducted in the last decade have been generally characterized by an underestimation of driving mechanisms of HCC pathogenesis and progression; thus, many studies enrolled a heterogeneous population regardless of potential biomarkers of response. Similarly, promising drugs were moved from phase II to phase III on the basis of very small, single-arm trials and relying on surrogate endpoints such as ORR, PFS, and TTP that are not predictors of OS in HCC. In patients with compromised baseline liver function due to chronic liver disease, the toxicity of certain drugs might strongly impact on treatment compliance and efficacy. In addition, it has to be pointed out that trials generally enroll patients with Child-Pugh A liver function that are not representative of all HCC patients. As a consequence, scientific evidence of safety for Child-Pugh B patients that could be treated in clinical practice is always limited to observational or retrospective series. In a recently presented real-life experience after first-line sorafenib, investigators remarked that only a small proportion of patients (13.1%) met the criteria used for enrollment in RESORCE, CELESTIAL, and REACH-2 trials. By using modified eligibility criteria (such as including patients with ECOG PS 2 or with Child-Pugh score B7), the percentage of eligible patients would increase to 31.7%, but at the cost of a worse survival outcome (mOS 6.2 versus 9.4 months of strict eligibility criteria).

Although the molecular underpinnings of HCC are being unveiled, the majority of recurrent somatic genetic alterations are not directly druggable; unsurprisingly, the larger part of the recently approved drugs were tested in a ‘all-comers’ setting and block, among the others, the VEGF pathway. Ramucirumab is actually the only drug that has proven efficacy in a biomarker-selected population, thanks to an initial preplanned subgroup analysis from the REACH trial that was negative for the primary endpoint; in this case, indeed, the predictive biomarker, AFP elevation, is a clinical and not a molecular biomarker.

It has already been pointed out that the effect of anti-angiogenic drugs has reached an efficacy ceiling with a mOS of first-line treatments constantly below 1 year. Although much progress has been made, especially in the second-line treatment after sorafenib, it is mandatory for clinical research to focus on optimizing a treatment algorithm, rather than introducing into the market ‘me-too’ drugs. In the absence of a direct comparison between second-line options, some aspects of the RCTs that we have discussed may be used to help clinicians; for example, regorafenib should not be offered to patients who are sorafenib intolerant, whereas cabozantinib may be used also in third-line treatment. Ramucirumab differs from the other treatment options for the route of administration (I.V.) and for the presence of a predictive biomarker (AFP>400 ng/mL).

In this context, immunotherapy has drawn considerable interest for its potential under many issues. First, its mechanism of action is completely different from the other approved drugs. Second, although a minority of patients could experience severe and even potentially life-threatening toxicities, immunotherapy has a more favorable profile. In addition, immunotherapy may produce early and durable responses that are already being investigated in other disease settings, such as neoadjuvant treatment or combination with local treatments increasing tumor antigens exposure. The recent announcement of the negative results of the KEYNOTE-240 trial might hamper the enthusiasm for immunotherapy, but it will be important to analyze the whole data to draw definitive conclusions.

Hopefully, with the advances in understanding tumor microenvironment and immune reactivity, we will be able to select patients for their potential response to these new drugs.

Contributions: Donatella Marino performed the literature research and writing. Massimo Di Maio conceived the topic of the review and provided support in writing. All other authors reviewed all drafts of this manuscript and approved the final version. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their version for this article to be published.

Disclosure and potential conflicts of interest: Donatella Marino, Clizia Zichi, Marco Audisio, and Elisa Sperti report no conflicts of interest. Massimo Di Maio received honoraria and had roles as consultant or advisor for AstraZeneca, Lilly, Roche, Bristol Myers Squibb, Merck Sharp & Dohme, and Janssen. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors are available for download at http://www.drugsincontext.com/wp-content/uploads/2019/03/dic.212577-COI.pdf

Acknowledgements: None.

Funding declaration: None.
References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68(1):7–30. http://dx.doi.org/10.3322/caac.21442

2. Mak LY, Cruz-Ramon V, Chinchilla-Lopez P, et al. Global epidemiology, prevention, and management of hepatocellular carcinoma. Am Soc Clin Oncol Educ Book. 2018;38:262–279. http://dx.doi.org/10.1200/EDBK_200939

3. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet. 2018;391(10127):1301–1314. http://dx.doi.org/10.1016/S0140-6736(18)30010-2

4. Llovet JM, Ricci S, Mazzaferrro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378–390. http://dx.doi.org/10.1056/NEJMoa0708857

5. Cheng AL, Kang YK, Chen Z, 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. http://dx.doi.org/10.1016/S1470-2045(08)70285-7

6. Cheng AL, Kang YK, Lin DY, et al. Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. J Clin Oncol. 2013;31(32):4067–4075. http://dx.doi.org/10.1200/JCO.2012.45.8372

7. Johnson PJ, Qin S, Park JW, et al. Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III brisk-f study. J Clin Oncol. 2013;31(28):3517–3524. http://dx.doi.org/10.1200/JCO.2012.48.4410

8. Cainap C, Qin S, Huang WT, et al. Linifanib versus sorafenib in patients with advanced hepatocellular carcinoma: results of a randomized phase III trial. J Clin Oncol. 2015;33(6):559–566. http://dx.doi.org/10.1200/JCO.2013.54.3298

9. Zhu AX, Rosmorduc O, Evans TR, et al. Search: a phase III, randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with advanced hepatocellular carcinoma. J Clin Oncol. 2015;33(6):559–566. http://dx.doi.org/10.1200/JCO.2013.53.7746

10. Abou-Alfa GK, Niedzwiecki D, Knox JJ, et al. Phase III randomized study of sorafenib plus doxorubicin versus sorafenib in patients with advanced hepatocellular carcinoma (hcc): Calgb 80802 (alliance). J Clin Oncol. 2016;34(15_suppl):4003–4003. http://dx.doi.org/10.1200/JCO.2016.34.15_suppl.4003

11. 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(10126):1163–1173. http://dx.doi.org/10.1016/S0140-6736(18)30207-1

12. US FDA. FDA approves lenvatinib for unresectable hepatocellular carcinoma. https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm617185.htm. Accessed March 27, 2019.

13. EMA. EMA recommends extension of indications for lenvatinib. https://www.esmo.org/Oncology-News/EMA- Recommends-Extension-Of-Indications-for-Lenvatinib. Accessed March 27, 2019.

14. Llovet JM, Decaens T, Raoul J L, et al. Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: results from the randomized phase III brisk-ps study. J Clin Oncol. 2013;31(28):3509–3516. http://dx.doi.org/10.1200/JCO.2012.47.3009
15. Zhu AX, Kudo M, Assenat E, et al. Ef ect of everolimus on survival in advanced hepatocellular carcinoma after failure of sorafenib: the evolve-1 randomized clinical trial. *JAMA.* 2014;312(1):57–67. http://dx.doi.org/10.1001/jama.2014.7189

16. 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(7):859–870. http://dx.doi.org/10.1016/S1470-2045(15)00050-9

17. Chau I, Peck-Radosavljevic M, Borg C, et al. Ramucirumab as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib: patient-focused outcome results from the randomised phase III reach study. *Eur J Cancer.* 2017;81:17–25. http://dx.doi.org/10.1016/j.ejca.2017.05.001

18. Glazer ES, Piccirillo M, Albino V, et al. Phase II study of pegylated arginine deiminase for nonresectable and metastatic hepatocellular carcinoma. *J Clin Oncol.* 2010;28(13):2220–2226. http://dx.doi.org/10.1200/JCO.2009.26.7765

19. Abou-Alfa GK, Qin S, Ryoo BY, et al. Phase III randomized study of second line adi-peg 20 plus best supportive care versus placebo plus best supportive care in patients with advanced hepatocellular carcinoma. *Ann Oncol.* 2018;29(6):1402–1408. http://dx.doi.org/10.1093/annonc/mdy101

20. Rimassa L, Assenat E, Peck-Radosavljevic M, et al. Tivantinib for second-line treatment of met-high, advanced hepatocellular carcinoma (metiv-hcc): a final analysis of a phase 3, randomised, placebo-controlled study. *Lancet Oncol.* 2018;19(5):682–693. http://dx.doi.org/10.1016/S1470-2045(18)30146-3

21. Santoro A, Rimassa L, Borbath I, et al. Tivantinib for second-line treatment of advanced hepatocellular carcinoma: a randomised, placebo-controlled phase 2 study. *Lancet Oncol.* 2013;14(1):55–63. http://dx.doi.org/10.1016/S1470-2045(12)70490-4

22. Kobayashi S, Ueshima K, Moriguchi M, et al. Jet-hcc: a phase 3 randomized, double-blind, placebo-controlled study of tivantinib as a second-line therapy in patients with c-met high hepatocellular carcinoma. *Ann Oncol.* 2017;28(suppl_5):v209-v268. http://dx.doi.org/10.1093/annonc/mdx369

23. Bruix J, Tak WY, Gasbarrini A, et al. Regorafenib as second-line therapy for intermediate or advanced hepatocellular carcinoma: multicentre, open-label, phase II safety study. *Eur J Cancer.* 2013;49(16):3412–3419. http://dx.doi.org/10.1016/j.ejca.2013.05.028

24. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (res escaped), a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2017;389(10064):56–66. http://dx.doi.org/10.1016/S0140-6736(16)32453-9

25. Bruix J, Merle P, Granito A, et al. Ef cacy, safety, and health-related quality of life (hrqol) of regorafenib in patients with hepatocellular carcinoma (hcc) progressing on sorafenib: results of the international, double-blind phase 3 resorce trial. *Ann Oncol.* 2016;27(suppl_6):LBA28-LBA28. http://dx.doi.org/10.1093/annonc/mdw435

26. Finn RS, Merle P, Granito A, et al. Outcomes of sequential treatment with sorafenib followed by regorafenib for hcc: additional analyses from the phase III resorce trial. *J Hepatol.* 2018;69(2):353–358. http://dx.doi.org/10.1016/j.jhep.2018.04.010

27. Bruix J, Merle P, Granito A, et al. Survival by pattern of tumor progression during prior sorafenib ( sor ) treatment in patients with hepatocellular carcinoma (hcc) in the phase III resorce trial comparing second-line treatment with regorafenib (reg) or placebo. *J Clin Oncol.* 2017;35(4_suppl):229–229. http://dx.doi.org/10.1200/JCO.2017.35.4_suppl.229

28. Bruix JMP, Granito A, Huang YH, et al; On Behalf of RESORCE Investigators. Hand-foot skin reaction (hfsr) and overall survival (os) in the phase 3 resorce trial of regorafenib for treatment of hepatocellular carcinoma (hcc) progressing on sorafenib. *J Clin Oncol.* 2018;36(no. 4_suppl):412–412. http://dx.doi.org/10.1200/JCO.2018.36.4_suppl.412

29. Teufel M, Köchert K, Meinhardt G, Bruix J. Ef cacy of regorafenib (reg) in patients with hepatocellular carcinoma (hcc) in the phase III resorce trial according to alpha-fetoprotein (afp) and c-met levels as predictors of poor prognosis. *J Clin Oncol.* 2017;35(15_suppl):4078–4078. http://dx.doi.org/10.1200/JCO.2017.35.15_suppl.4078

30. Köchert K, Meinhardt G, Bruix J, Teufel M. 701panalysis of single-nucleotide polymorphisms (snps) in the phase III resorce trial of regorafenib versus placebo in patients with hepatocellular carcinoma (hcc). *Ann Oncol.* 2018;29(suppl_8). http://dx.doi.org/10.1093/annonc/mdy282

31. Liu J, Wang K, Yan Z, et al. Axl expression strati es patients with poor prognosis after hepatectomy for hepatocellular carcinoma. *Plos One.* 2016;11(5):e015476. http://dx.doi.org/10.1371/journal.pone.0154767

32. Rimassa L, Abbadessa G, Personeni N, et al. Tumor and circulating biomarkers in patients with second-line hepatocellular carcinoma from the randomized phase II study with tivantinib. *Oncotarget.* 2016;7(45):72622–72633. http://dx.doi.org/10.18632/oncotarget.11621

33. Kelley RK, Verslype C, Cohn AL, et al. Cabozantinib in hepatocellular carcinoma: results of a phase 2 placebo-controlled randomized discontinuation study. *Ann Oncol.* 2017;28(3):528–534. http://dx.doi.org/10.1093/annonc/mdw651

34. Schof ski P, Gordon M, Smith DC, et al. Phase II randomised discontinuation trial of cabozantinib in patients with advanced solid tumours. *Eur J Cancer.* 2017;66:296–304. http://dx.doi.org/10.1016/j.ejca.2017.09.011

35. Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. *New Engl J Med.* 2018;379(1):54–63. http://dx.doi.org/10.1056/NEJMoa1717002
36. Yau T, van Vlierberghen H, Love C, et al. Assessment of tumor response, alpha-fetoprotein (afp) response, and time to progression (ttp) in the phase III celestial trial of cabozantinib (c) versus placebo (p) in advanced hepatocellular carcinoma (hcc). *Ann Oncol*. 2018;29(suppl_9). http://dx.doi.org/10.1093/annonc/mdy432
37. Kelley RK, Rimassa L, Ryoo B-Y, et al. Alpha fetoprotein (afp) response and ef cacy outcomes in the phase III celestial trial of cabozantinib (c) versus placebo (p) in advanced hepatocellular carcinoma (hcc). *J Clin Oncol*. 2019;37(4_suppl):423–423. http://dx.doi.org/10.1200/JCO.2019.37.4_suppl.423
38. Blanc J-F, Adriani J, Kelly RK, et al. 703assessment of disease burden in the phase III celestial trial of cabozantinib (c) versus placebo (p) in advanced hepatocellular carcinoma (hcc). *Ann Oncol*. 2018;29(suppl_8). http://dx.doi.org/10.1093/annonc/mdy282.086
39. Yau T, Patel M, El-Khoueiry AB, et al. 704outcomes by prior transarterial chemoembolization (tace) in the phase III celestial trial of cabozantinib (c) versus placebo (p) in patients (pts) with advanced hepatocellular carcinoma (hcc). *Ann Oncol*. 2018;29(suppl_8). http://dx.doi.org/10.1093/annonc/mdy282.087
40. Rimassa L, Cicin I, Blanc J-F, et al. Outcomes based on age in the phase 3 celestial trial of cabozantinib (c) versus placebo (p) in patients (pts) with advanced hepatocellular carcinoma (hcc). *J Clin Oncol*. 2018;36(15_suppl):4090–4090. http://dx.doi.org/10.1200/JCO.2018.36.15_suppl.4090
41. Zhu AX, Yen C, 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 f rst-line sorafenib. *J Clin Oncol*. 2018;36(suppl; abstr 4003). http://dx.doi.org/10.1200/JCO.2018.36.15_suppl.4003
42. Zhu A, Finn R, Galle P, et al. Lba-001ramucirumab as second-line treatment in patients with advanced hepatocellular carcinoma (hcc) and elevated alpha-fetoprotein (afp) following f rst-line sorafenib: pooled ef cacy and safety across two global randomized phase 3 studies (reach-2 and reach). *Ann Oncol*. 2018;29(suppl_5)mdy208-mdy208. http://dx.doi.org/10.1093/annonc/mdy208
43. Zhu AX, Gable J, Bowman L, et al. Ramucirumab as second-line treatment in patients with advanced hepatocellular carcinoma (hcc) and elevated alpha-fetoprotein (afp) following f rst-line sorafenib: patient reported outcome results across two phase III studies (reach-2 and reach). *Ann Oncol*. 2018;29(suppl_8). http://dx.doi.org/10.1093/annonc/mdy282.006
44. Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. *New Engl J Med*. 2018;378(22):2109–2104. http://dx.doi.org/10.1056/NEJMoai801946
45. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to pd-1 blockade. *Science*. 2017;357(6349):409–413. http://dx.doi.org/10.1126/science.aan6733
46. Herbst RS, Soria J, Kowanetz M, et al. Predictive correlates of response to the anti-pd-l1 antibody mpdl3280a in cancer patients. *Nature*. 2014;515(7528):563–567. http://dx.doi.org/10.1038/nature14011
47. Han X, Gu YK, Li SL, et al. Pre-treatment serum levels of soluble programmed cell death-ligand 1 predict prognosis in patients with hepatitis b-related hepatocellular carcinoma. *J Cancer Res Clin Oncol*. 2018. http://dx.doi.org/10.1007/s00432-018-2758-6
48. Shi F, Shi M, Zeng Z, et al. Pd-1 and pd-l1 upregulation promotes cd8(+) t-cell apoptosis and postoperative recurrence in hepatocellular carcinoma patients. *Int J Cancer*. 2011;128(4):887–896. http://dx.doi.org/10.1002/ijc.25397
49. Sia D, Jiao Y, Martinez-Quetglas I, et al. Identification of an immune-specific class of hepatocellular carcinoma, based on molecular features. *Gastroenterology*. 2017;153(3):812–826. http://dx.doi.org/10.1053/j.gastro.2017.06.007
50. 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(10088):2492–2502. http://dx.doi.org/10.1016/S0140-6736(17)31046-2
51. El-Khoueiry AB, Melero I, Yau TC, et al. Impact of antitumor activity on survival outcomes, and nonconventional benef t, with nivolumab (nivo) in patients with advanced hepatocellular carcinoma (ahcc): subanalyses of checkmate-040. *J Clin Oncol*. 2018;36(4_suppl):475–475. http://dx.doi.org/10.1200/JCO.2018.36.4_suppl.475
52. Crocenzi TS, El-Khoueiry AB, Yau TC, et al. Nivolumab (nivo) in sorafenib (sor)-naive and -experienced pts with advanced hepatocellular carcinoma (hcc): checkmate 040 study. *J Clin Oncol*. 2017;35(15_suppl):4013–4013. http://dx.doi.org/10.1200/JCO.2017.35.15_suppl.4013
53. Kudo M, Matilla AM, Santoro A, et al. Nivolumab in patients with child-pugh b advanced hepatocellular carcinoma (ahcc) in the checkmate-040 study. *Hepatology*. 2018;68, S1(Abstract LB-2).
54. 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(7):940–952. http://dx.doi.org/10.1016/S1470-2045(18)30351-6
55. Zhu AX, Finn RS, Edeline J, et al. Pembrolizumab (pembro) in patients with advanced hepatocellular carcinoma (hcc): keynote-224 update. *J Clin Oncol*. 2018;36(15_suppl):4020–4020. http://dx.doi.org/10.1200/JCO.2018.36.15_suppl.4020
56. Merck. Merck provides update on KEYNOTE-240, a phase 3 study of KEYTRUDA®(pembrolizumab) in previously treated patients with advanced hepatocellular carcinoma. https://investors.merck.com/news/press-release-details/2019/Merck-Provides-
Update-on-KEYNOTE-240-a-Phase-3-Study-of-KEYTRUDA-pembrolizumab-in-Previously-Treated-Patients-with-Advanced-Hepatocellular-Carcinoma/default.aspx. Accessed March 27, 2019.

57. Ikeda M, Sung MW, Kudo M, et al. A phase 1b trial of lenvatinib (len) plus pembrolizumab (pem) in patients (pts) with unresectable hepatocellular carcinoma (uhcc). J Clin Oncol. 2018;36(suppl; abstr 4076).
http://dx.doi.org/10.1200/JCO.2018.36.15_suppl.4076

58. Kelley RK, Abou-Alfa GK, Bendell JC, et al. Phase II study of durvalumab and tremelimumab in patients with unresectable hepatocellular carcinoma (hcc): phase I safety and efficacy analyses. J Clin Oncol. 2017;35(suppl; abstr 4073).
http://dx.doi.org/10.1200/JCO.2017.35.15_suppl.4073

59. Pishvaian MJ, Lee MS, Ryoo B-Y, et al. Lba26updated safety and clinical activity results from a phase Iib study of atezolizumab + bevacizumab in hepatocellular carcinoma (hcc). Ann Oncol. 2018;29(suppl_8). http://dx.doi.org/10.1093/annonc/mdy424.028

60. Cheng AL, Yen CJ, Okusaka T, et al. 697pa phase I, open-label, multi-center, dose-escalation study of codrituzumab, an anti-glypican-3 monoclonal antibody, in combination with atezolizumab in patients with locally advanced or metastatic hepatocellular carcinoma. Ann Oncol. 2018;29(suppl_8):mdy282.080-mdy282.080. http://dx.doi.org/10.1093/annonc/mdy282.080

61. Brizzi MP, Pignataro D, Tampellini M, Scagliotti GV, Di Maio M. Systemic treatment of hepatocellular carcinoma: why so many failures in the development of new drugs? Exp Rev Anticancer Ther. 2016;16(10):1053–1062.
http://dx.doi.org/10.1080/14737140.2016.1227706

62. Fung AS, Tam VC, Meyers DE, et al. Real world eligibility for cabozantinib (c), regorafenib (reg), and ramucirumab (ram) in hepatocellular carcinoma (hcc) patients after sorafenib (s). J Clin Oncol. 2019;37(4_suppl):422–422.
http://dx.doi.org/10.1200/JCO.2019.37.4_suppl.422

63. Cancer Genome Atlas Research Network. Electronic address wbe, Cancer Genome Atlas Research N. Comprehensive and integrative genomic characterization of hepatocellular carcinoma. Cell. 2017;169(7):1327–1341 e1323.
http://dx.doi.org/10.1016/j.cell.2017.05.046

64. Abou-Alfa GK, Venook AP. The antiangiogenic ceiling in hepatocellular carcinoma: does it exist and has it been reached? Lancet Oncol. 2013;14(7):e283–288. http://dx.doi.org/10.1016/S1470-2045(13)70161-X