Molecular therapies and precision medicine for hepatocellular carcinoma

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Abstract | The global burden of hepatocellular carcinoma (HCC) is increasing and might soon surpass an annual incidence of 1 million cases. Genomic studies have established the landscape of molecular alterations in HCC; however, the most common mutations are not actionable, and only ~25% of tumours harbour potentially targetable drivers. Despite the fact that surveillance programmes lead to early diagnosis in 40–50% of patients, at a point when potentially curative treatments are applicable, almost half of all patients with HCC ultimately receive systemic therapies. Sorafenib was the first systemic therapy approved for patients with advanced-stage HCC, after a landmark study revealed an improvement in median overall survival from 8 to 11 months. New drugs — lenvatinib in the frontline and regorafenib, cabozantinib, and ramucirumab in the second line — have also been demonstrated to improve clinical outcomes, although the median overall survival remains ~1 year; thus, therapeutic breakthroughs are still needed. Immune-checkpoint inhibitors are now being incorporated into the HCC treatment armamentarium and combinations of molecularly targeted therapies with immunotherapies are emerging as tools to boost the immune response. Research on biomarkers of a response or primary resistance to immunotherapies is also advancing. Herein, we summarize the molecular targets and therapies for the management of HCC and discuss the advancements expected in the near future, including biomarker-driven treatments and immunotherapies.

Liver cancer is the second leading cause of cancerrelated death globally1 . Hepatocellular carcinoma (HCC) accounts for 90% of primary liver cancers and can be caused by chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), alcohol abuse, and metabolic syndrome related to diabetes and obesity2,3 . In developed countries, surveillance programmes lead to early HCC diagnosis in 40–50% of patients, at a stage amenable to potentially curative treatments2,4,5 . Patients with intermediate-stage HCC are treated with locoregional therapies, whereas those with advancedstage disease can benefit from systemic treatments2 . Overall, ~50% of patients receive systemic therapies at some point during the disease course2,4,5 . In a breakthrough study6 , the multi-target tyrosine kinase inhibitor (TKI) sorafenib, which has anti-angiogenic and anti-proliferative effects, extended the median overall survival of patients with advanced-stage HCC from 8 to 11 months and had a manageable toxicity profile. Sorafenib was the sole systemic therapy approved for the treatment of HCC between 2007 and 2016. In the past year or so, however, improvements in patient outcomes have been demonstrated in randomized phase III trials with lenvatinib7 in the frontline and regorafenib8 , cabozantinib9 , and ramucirumab10 in the second line after disease progression on sorafenib; regorafenib is currently FDA approved in the second-line setting. In addition, immunotherapy with nivolumab — a monoclonal antibody targeting the inhibitory immunecheckpoint molecule programmed cell death protein 1 (PD-1) — led to promising response rates and survival durations in a phase I–II study involving patients previously treated with sorafenib11 and has been granted accelerated approval by the FDA. By contrast, several kinase inhibitors (for example, sunitinib, brivanib, and erlotinib), doxorubicin, and radioembolization with yttrium 90 (90Y) -microspheres failed to improve overall survival in patients with unresectable HCC12.

Indeed, HCC is a highly therapy resistant and thus difficult to treat cancer; although systemic therapies have clinical benefits, the improvements in patient outcomes have been modest and incremental. Thus, novel therapies for HCC remain an unmet medical need. In this regard, important insights into the biology of the disease have been obtained through genomic, transcriptomic, and epigenomic studies2,3 . In this Review, we analyse the molecular targets and therapies for the management of HCC and highlight the advancements in biomarker-driven treatments and immunotherapies that are expected in the near future.

The molecular landscape of HCC

Molecular drivers

HCC development is a complex multistep process, with 70–80% of cases occurring in the context of established liver cirrhosis2,3 . The natural history of HCC in patients with cirrhosis progresses through a sequence of clinicopathological events starting with the appearance of pre-cancerous cirrhotic nodules (so-called dysplastic nodules), which can ultimately transform into HCC3 . Overall, one-third of patients with cirrhosis will develop HCC during their lifetime, with different rates per year observed according to aetiology2 . The median time between development of cirrhosis and the development of HCC is ~10 years13. In the non-cirrhotic liver, HCC can arise principally on a background of HBV infection or nonalcoholic steatohepatitis and more rarely through the malignant transformation of hepatocellular adenoma, a monoclonal and typically benign lesion14. Malignant transformation from adenomas occurs in <10% of cases and has been associated with TERT and CTNNB1 mutations14. Mature hepatocytes have been identified as the cell of origin for most HCCs; however, a subset of ~20% of HCCs with progenitor cell markers, such as epithelial cell adhesion molecule (EPCAM) and cytokeratin 19 (CK19), can arise from either progenitor cells or dedifferentiated mature hepatocytes15.

HCC results from the accumulation of somatic genomic and epigenomic alterations in the tissue of origin over time. In HCCs, an average of 40–60 somatic alterations are detected in protein-coding regions of the genome2,16. Most of these alterations occur in ‘passenger’ genes that are not directly implicated in neoplasia, but a few genomic alterations are considered to be ‘drivers’ involved in activating key signalling pathways for hepatocarcinogenesis. The identification of recurrently mutated genes and copy number alterations through integration of data from whole-exome sequencing (WES) studies and single-nucleotide polymorphism (SNP) array analyses has enabled deciphering of these pivotal pathways, which include telomere maintenance, cell cycle control, WNT–β-catenin signalling, chromatin modification, receptor tyrosine kinase (RTK)–RAS–PI3K cascades, and oxidative stress16–21 (Table 1). Unfortunately, most of the clonal, ‘trunk’ mutations and prevalent drivers (TERT, CTNNB1, TP53, AXIN1, ARID1A, and ARID1B) detected in HCCs are not clinically actionable16 — at least at present. Indeed, reports of WES studies indicate that only ~25% of HCCs harbour alterations that are potentially targetable with existing drugs16. DNA methylation profiling also enabled the discovery of IGF2 overexpression and CDKN2A silencing as epigenetic mechanisms of HCC tumorigenesis22.

Molecular classifications

Integrative molecular analyses involving genomic, transcriptomic, and/or epigenomic profiling of thousands of surgically resected tumours have provided the basis for the molecular classification of HCC subtypes21,23–26. These distinct molecular classes reflect different biological backgrounds with potential implications in patient prognostication and selection for therapies. Specifically, two major molecular subtypes of HCC, each encompassing ~50% of patients with this disease, have been proposed: a proliferation class and non-proliferation class3,27,28 (Fig. 1).

As their designation suggests, HCCs of the proliferation class are characterized by activation of signalling pathways involved in cell proliferation and survival, such as the PI3K–AKT–mTOR, RAS–MAPK, and MET

cascades21,23,24. Chromosomal instability seems to be a driving force in these tumours, with a particular enrichment of TP53 inactivation and FGF19 and/or CCND1 amplifications29. Our group and others3,27,28 have proposed that two subclasses exist within the proliferative class: a WNT–TGFβ group (also known as S1 tumours) characterized by non-canonical activation of WNT; and a progenitor cell group (also known as S2 tumours) characterized by overexpression of EPCAM, AFP, and IGF2, and a unique DNA hypermethylation signature30 (Fig. 1a). Overall, the proliferation class of HCC is associated with HBV-related aetiology and poor clinical outcomes.

The non-proliferation class is more heterogeneous than the proliferative class and might consist of at least three HCC subclasses3,21 (Fig. 1). One clear subclass has been delineated and is characterized by activation of the canonical WNT signalling pathway, often owing to mutation of CTNNB1 (encoding β-catenin)31, and is also associated with higher rates of TERT promoter mutations. From the clinical standpoint, non-proliferation class tumours are associated with alcohol-related and HCV-related aetiologies and better outcomes. These proposed molecular classes have been confirmed and further characterized in the comprehensive molecular analysis of 363 patients with HCC — the largest cohort published to date — reported by The Cancer Genome Atlas (TCGA) Research Network18. The integration of up to 5 other platforms — DNA copy number, DNA methylation, mRNA expression, microRNA (miRNA) expression, and reverse phase protein array (RPPA) assays — for 196 tumours yielded 3 subtypes, including a poor prognosis iClust1 subtype with a gene expression profile that closely resembles that of the progenitor cell subclass tumours and a lower-grade iClust2 subtype that shares molecular and pathological characteristics (for example, CTNNB1 mutations and less frequent microvascular invasion) with the non-proliferation class. The third TCGA cluster, iClust3, generated a TP53 signature associated with chromosomal instability and poor prognosis. Beyond tumour cell-intrinsic molecular aberrations, an altered tumour microenvironment (TME) is now recognized as a key enabling factor in the development of HCC32,33. In fact, HCC is a prototypical inflammationassociated cancer attributable to viral hepatitis or steatohepatitis (alcoholic or nonalcoholic). Multiple cell types interact with hepatocytes in the chronically inflamed liver, including lymphocytes, macrophages, stellate cells, and endothelial cells. In this regard, a novel molecular classification of HCC based upon immune status has been proposed34 (Fig. 1b). Through analyses of inflammatory gene-expression profiles, infiltrates, and regulatory molecules, 30% of HCCs could be classified into an ‘immune class’, with high levels of immune cell infiltration, expression of PD-1 and/or programmed cell death 1 ligand 1 (PD-L1), activation of IFNγ signalling, markers of cytolytic activity (such as granzyme B and perforin 1), and an absence of CTNNB1 mutations34. Within this class, two distinct ‘active immune’ and ‘exhausted immune’ subclasses, characterized by markers of an adaptive T cell response or exhausted immune response, respectively, have been identified34. The exhausted immune tumours express many genes regulated by TGFβ, which mediate immunosuppression and T cell exhaustion. An ‘immune excluded class’ accounting for ~25% of HCCs was characterized by T cell exclusion from the TME and CTNNB1 mutations34. The immune exhausted class mostly overlaps with the proliferative WNT–TGFβ subclass, whereas the immune excluded class overlaps with the CTNNB1 mutated non-proliferative class. Our group is currently exploring whether the immune active class is associated with responsiveness to immune-checkpoint inhibitors and whether, conversely, the immune exhausted and/ or the immune excluded classes are associated with primary resistance to these agents.

Clearly, further research is needed to translate the current knowledge of HCC biology into prognostic and predictive biomarkers in order to guide clinical decisionmaking and, ultimately, improve patient outcomes. In this regard, analysing the molecular landscape of tumour tissues obtained from patients with advancedstage HCC, predominantly through tumour-tissue and liquid biopsy procedures, is of crucial relevance because these are the patients who are actually treated with systemic therapies in clinical trials. Notably, the fact that systemic drugs with demonstrated survival benefits in patients with HCC (sorafenib, regorafenib, lenvatinib, cabozantinib, and ramucirumab) share an — at least partially —

anti-angiogenic mechanism of action highlights the importance of this hallmark of cancer, which is mainly promoted by endothelial cells35. Indeed, angiogenic signalling is prominent in all subclasses of HCC36,37 . Understanding how the distinct angiogenic signalling pathways interact with the immune component of HCCs and how mechanisms of resistance to antiangiogenic agents arise could potentially reveal novel therapeutic strategies.

Clinical management of HCC

Several HCC staging systems have been proposed during the past four decades38–41; however, the Barcelona Clinic Liver Cancer (BCLC) staging classification is the most widely recognized clinical algorithm used for patient stratification and treatment allocation4,5,42. As mentioned previously, in developed countries, 40–50% of patients with HCC are diagnosed at early stages (BCLC stage 0–A), when potentially curative treatments (resection, liver transplantation, or local ablation) are possible4 . These treatments can result in median overall survival durations >60 months4 . Nevertheless, up to 70% of patients undergoing HCC resection or ablation present with disease recurrence within 5 years2 , and no adjuvant therapies tested to date are able to prevent this complication43. Patients with intermediate-stage disease (BCLC stage B) with preserved liver function (Child–Pugh class A without any ascites) can benefit from transarterial chemoembolization (TACE), as reported in two randomized studies comparing this approach with best supportive care44,45 and one meta-analysis46, with estimated median overall survival durations of 25–30 months. No combination of kinase inhibitors (such as sorafenib or brivanib)47–49 with TACE has been shown to provide additive improvements in patient outcomes. Nevertheless, most patients with HCC (>50%) will eventually receive systemic treatments: patients with disease progression after TACE or those who are diagnosed with advanced-stage HCC (BCLC stage C) can benefit from sorafenib6 . More recently, first-line lenvatinib7 and second-line regorafenib8 , cabozantinib9 , and ramucirumab10 have also been demonstrated to provide survival benefits for patients with advancedstage disease. In clinical trials, the median overall survival durations achieved with these therapies are around 1 year. Nivolumab is another new option in the secondline setting on the basis of the promising response rates and durations observed in the phase I–II trial of this agent11. Patients with end-stage disease (BCLC stage D) should be considered for nutritional and psychological support and appropriate management of pain. In 2018, international guidelines4 have been revised to provide updated recommendations on the treatment of HCC based on levels of evidence, encompassing all major treatments tested in this cancer (Fig. 2).

Molecular targeted therapies

First-line treatments

Most patients with HCC are diagnosed at advanceddisease stages, at which the natural history of the disease carries a dismal prognosis. In this setting, conventional systemic chemotherapy lacks survival benefits. Phase III trials of doxorubicin alone, the PIAF regimen (cisplatin, IFNα2b, doxorubicin, and fluorouracil), and the FOLFOX4 regimen (fluorouracil, leucovorin (folinic acid), and oxaliplatin) all had negative results, in some instances with substantial toxicity50–52. Randomized studies also failed to prove any clinical effects of anti-oestrogen therapies or vitamin D derivatives53,54.

Sorafenib. In 2007, results of the phase III SHARP trial6 demonstrated survival benefits with sorafenib versus placebo (median overall survival 10.7 months versus 7.9 months; HR 0.69, 95% CI 0.55–0.87; $P < 0.001$), thus representing a breakthrough in the management of advanced-stage HCC. A similar magnitude of benefit was observed in another phase III study of sorafenib conducted in parallel in Asian patients, mostly with HBV-related HCC55. In these trials, treatment was generally associated with manageable adverse events (AEs), such as diarrhoea (grade 3 in 8–9%), hand–foot skin reactions (grade 3 in 8–16%), fatigue (grade 3 in 3%), and hypertension (grade 3 in 2%). Intolerance to sorafenib

(treatment discontinuation owing to AEs) typically occurs in 10–15% of patients6,55. The severity of toxicities — particularly hand–foot syndrome — has been associated with better survival outcomes in cohort studies56. A meta-analysis of the two phase III trials testing sorafenib revealed a consistent survival benefit across all clinical subgroups57. The greatest magnitude of the benefit was observed in patients with tumour confined to the liver, those who were HCV-positive, or those with a low neutrophil-to-lymphocyte ratio57. Sorafenib is indicated for patients with well-preserved liver function (Child–Pugh class A) and BCLC stage C disease or BCLC stage B disease that has progressed after locoregional therapy. Of note, the median overall survival of patients with BCLC stage B HCC treated with sorafenib is 15–20 months according to the findings of post-marketing studies58,59. Similarly, surveys conducted in >3,000 patients to evaluate the safety and tolerability of sorafenib in clinical practice reported median overall survival durations of 13.6 months for the Child–Pugh class A group and 5.2 months for a Child–Pugh class B group60,61. From the mechanistic standpoint, the efficacy of sorafenib probably results from a balance between targeting cancer cells and cells of the TME: this agent can inhibit up to 40 kinases, including mainly angiogenic RTKs (including VEGF receptors (VEGFRs) and PDGF receptor-β (PDGFRβ)) and drivers of cell proliferation (such as RAF1, BRAF, and KIT)62. Unfortunately, at least partially owing to this pharmacological complexity, no predictive biomarkers of a response to sorafenib have been identified; however, the companion biomarker study conducted within the SHARP trial showed a nonsignificant trend towards a greater survival benefit of sorafenib in patients with tumours harbouring high levels of KIT and low plasma HGF concentrations63. The efficacy of sorafenib in the advanced-stage setting has led to testing of this drug at earlier clinical stages. In the phase II SPACE and phase III TACE 2 placebo-controlled trials involving patients with intermediate-stage HCC47,48, sorafenib plus TACE was safe, but the combination did not improve time to progression (TTP) in a clinically meaningful manner. Similarly, in the adjuvant setting after surgical resection or local ablation (phase III STORM trial)43, sorafenib did not improve recurrence-free survival (RFS) compared with that observed with placebo. A thorough molecular analysis of resected tumours from this trial enabled the design of a multi-gene signature that could be used to identify patients who benefited from adjuvant sorafenib treatment64; however, this biomarker test requires prospective validation. The successful SHARP trial6 provided a framework for trial design that has been implemented in subsequent phase III studies65. The main traits of this design are the selection of an adequate target population: patients with well-preserved liver function (Child–Pugh class A), to minimize the risk of liver failure and death as a result of cirrhosis, and patients with either advanced-stage (BCLC stage C) or intermediate-stage (BCLC stage B) disease that has progressed following TACE, to provide clear results for this clinical stage. Moreover, overall survival was established as the most robust end point to assess efficacy in this population. Surrogate end points, such as TTP, have been associated with inconsistent results and are currently being revisited12. In this regard, use of the modified Response Evaluation Criteria in Solid Tumors (mRECIST), which are based on the concept of viable tumour, generally provides greater sensitivity in the assessment of response than the standard RECIST guidelines66; in phase III trials of sorafenib, objective response rates (ORRs) were 10–15% by mRECIST versus 2–6% by RECIST67. Several phase III trials have failed to demonstrate the superiority of a number of agents over sorafenib in the frontline setting (Fig. 3a). These therapies include brivanib (a selective VEGFR and FGF receptor (FGFR) TKI)68, sunitinib (a multi-target TKI with activity against VEGFRs, PDGFRs, and KIT)69, linifanib (a VEGFR and PDGFR TKI)70, and erlotinib (an EGFR inhibitor)71. The reasons for the disappointing phase III trial results include overinterpretation of marginal antitumour efficacy in small phase II studies, considerable liver toxicity, flaws in trial design, and the lack of biomarker-based enrichment12. Moreover, the results of the phase III SARAH72 and SIRveNIB73 superiority trials of internal radiation with 90Y resin microspheres versus sorafenib in patients with advanced-stage HCC (including >30% with main portal vein thrombosis) did not fulfil the primary overall survival end points. In these studies72,73, median overall survival was 8.0–8.8 months in the 90Y-microsphere arms compared with 9.9–10.0 months in the sorafenib arms, resulting in nonsignificant detriments in survival with radioembolization (HR 1.12–1.15) (Fig. 3a). Per-protocol subgroup analyses did not reveal any survival advantages72,73. The authors of

both trials highlighted the better response rates and quality of life (QOL) outcomes with radioembolization, thus suggesting this treatment as an alternative to sorafenib for selected patients. However, the indication of a therapy should be based upon the primary end point; therefore, the conclusion that the frontline treatment strategy can be decided on the basis of secondary end points is not sound. In addition, QOL outcomes typically have a negative correlation with time on therapy, which is clearly longer with sorafenib versus the one-time treatment with 90Y-microsphere radioembolization. Two additional phase III trials (STOP-HCC and SORAMIC) comparing combinations of 90Y glass microspheres plus sorafenib versus sorafenib alone have been initiated (NCT01556490 and NCT01126645). Preliminary results from the SORAMIC trial presented in abstract form in April 2018 indicate that this combination does not improve survival74.

Lenvatinib. Lenvatinib, an oral inhibitor of the VEGFRs, FGFR1–FGFR4, RET, KIT, and PDGFRα75, has been tested in phase II and phase III trials in patients with advanced-stage HCC7,76. In the phase III trial7 , lenvatinib was found to be non-inferior to sorafenib in terms of overall survival (median 13.6 months versus 12.3 months; HR 0.92, 95% CI 0.79–1.06) (Fig. 3a). Importantly, the ORR in the lenvatinib group according to mRECIST was 24.1% when evaluated by investigators but reached 40.6% (versus 18% by RECIST) upon masked independent imaging review7 . Of note, patients with ≥50% liver occupation, obvious invasion of the bile duct, and/or invasion at the main portal vein were excluded from this study7 . In a subgroup analysis, patients with baseline serum α-fetoprotein (AFP) levels of >200 ng/ml had a greater benefit from lenvatinib than sorafenib (HR 0.78, 95% CI 0.63–0.98). The frequency of grade ≥3 treatment-related AEs was higher with lenvatinib than with sorafenib (57% versus 49%). The most common treatment-emergent AEs of any grade associated with lenvatinib were hypertension (42%), diarrhoea (39%), decreased appetite (34%), and decreased bodyweight (31%); 9% and 7% of patients treated with lenvatinib and sorafenib, respectively, discontinued treatment owing to treatment-related AEs. Fatal AEs related to lenvatinib treatment, including hepatic failure, cerebral haemorrhage, and respiratory failure, occurred in 2% of patients versus 1% of patients in the sorafenib arm.

On the basis of these results, lenvatinib can be considered as an alternative first-line treatment option to sorafenib for patients with advanced-stage HCC (except those with main portal vein thrombosis or >50% liver involvement) or intermediate-stage disease after progression following TACE; FDA and European Medicines Agency (EMA) approvals are pending. Data from QOL studies suggest a similar overall profile for both drugs7 . No cost-effectiveness studies comparing both drugs have been reported to date. Similarly, no biomarkers predicting responses to either agent have been reported.

Second-line therapies

Since the approval of sorafenib in 2007, perhaps the largest unmet clinical need for patients with HCC has been in the second-line setting after disease progression on sorafenib. With therapies that improve overall survival without inducing high ORRs, such as sorafenib, identifying patients who are no longer benefiting from treatment is inherently challenging owing to difficulties in relating radiographic tumour measurements with clinical outcomes. Furthermore, in the pivotal phase III SHARP trial of sorafenib6 , patients were allowed to remain on treatment beyond radiological progression, ultimately adding additional layers of complexity. The decision to move novel therapies into phase III trials in the second-line setting has generally been based on findings from single-arm studies with small cohorts of patients; ultimately, most of the randomized phase III trials did not meet their end points, including studies of agents targeting the mTOR77, VEGF78 and/or FGF79, or HGF– MET80 signalling pathways (Fig. 3b). Since 2017, however, we have witnessed the reporting of positive results from three phase III trials in patients who had disease progression on, or were intolerant of, sorafenib8–10, as well as promising data from two phase II studies of different anti-PD-1 antibodies11,81. The results of these studies are now providing the clinicians with a number of secondline treatment options in the absence of comparative

studies. Thus, treatment choices will need to be based on the sound data that are available and clinical judgement. Given the increasingly rapid pace of approvals, data on sequencing of the available agents is also lacking. As in other diseases, clinical factors that can influence secondline treatment choices include the first-line therapy used, the duration of response to that therapy, how treatment was tolerated, the clinical condition of the patient upon progression, and the expected efficacy and AEs of the available treatments.

Regorafenib. Regorafenib has structural similarities to sorafenib, but the inhibitory profiles of these drugs differ slightly, with regorafenib having greater potency against the VEGFR kinases and a broader activity, for example, against angiopoietin 1 receptor (TIE2), KIT, and RET82. A small, single-arm phase II study of regorafenib provided some evidence of antitumour activity in the second-line setting83; however, the efficacy signals were not dissimilar from those obtained with other agents studied in this space. Nevertheless, the data led to the first positive phase III trial in patients with advanced-stage HCC for nearly a decade and the subsequent FDA approval of second-line regorafenib. The results of this global trial (RESORCE)8 demonstrated an improvement in the median overall survival of patients who had HCC progression on sorafenib from 7.8 months with placebo to 10.6 months with regorafenib (HR 0.63, 95% CI 0.50–0.79; P < 0.0001) (Fig. 3b). Unlike other studies in this setting77–80, this trial required that patients not only have documented progression on sorafenib (according to RECIST) but also to have tolerated sorafenib for a minimum period of time (≥400mg daily for at least 20 of the 28 days before discontinuation)8 . Regorafenib also significantly improved secondary end points, including TTP (HR 0.44, 95% CI 0.36–0.55; P< 0.0001). ORRs were higher with regorafenib versus placebo by both mRECIST and RECIST (10.6% versus 4.1% and 6.6% versus 2.6%, respectively). A subsequent evaluation of overall survival from the start of sorafenib treatment to death on study demonstrated a median duration of 26 months for regorafenib-treated patients versus 19 months for those in the placebo arm84. Toxicities were manageable in this sorafenib-tolerant population and were similar to those observed with sorafenib, including hand–foot skin reaction, diarrhoea, and hypertension.

Given the similarities between the two molecules, the exact mechanism of the benefit from regorafenib after progression on sorafenib is not clear. Besides continued suppression of VEGFR signalling and antiangiogenic effects, regorafenib has been hypothesized to directly inhibit pathways regulating tumour cell growth, proliferation, and metastasis and to modify the TME82.

Cabozantinib. Cabozantinib is a small-molecule multitarget TKI with an inhibitory profile that is unique among the molecules evaluated in phase III studies in patients with HCC to date; in addition to activity against VEGFRs, this drug also potently inhibits MET and AXL85,86. Of note, the HGF receptor MET has been implicated in the pathogenesis of HCC and sorafenib resistance87. Cabozantinib was initially evaluated in both patients with untreated HCC and those with progression on, or intolerance of, sorafenib in a randomized phase II discontinuation study, resulting in an overall median PFS of 5.5 months without substantial radiographical responses (2 of 41 patients had a partial response)86. CELESTIAL9 was a global, randomized, placebocontrolled, phase III trial of cabozantinib in patients who had HCC progression on prior sorafenib. Unlike in other studies, patients who had received up to two prior therapies for advanced-stage HCC were eligible for enrolment in CELESTIAL9 . This trial was stopped after a second interim analysis of data from the entire study population revealed a median overall survival of 10.2 months in the cabozantinib group versus 8.0 months in the placebo group (HR 0.76, 95% CI 0.63–0.92; P=0.0049) (Fig. 3b). Approximately 72% of patients had received only prior sorafenib treatment, and in this subpopulation, median overall survival was 11.3 months with cabozantinib versus 7.2 months with placebo (HR 0.70, 95% CI 0.55–0.88)9 . Cabozantinib did not have a notable ORR (4% by RECIST), but did improve PFS and TTP9 . AEs with cabozantinib were as seen in earlier studies of this agent; the most frequent grade 3–4 AEs were hand– foot syndrome (in 17% of

patients) and hypertension (in 16%)9 . Six grade 5 treatment-related AEs occurred with cabozantinib versus one with placebo9 .

Ramucirumab. Unlike the small-molecule TKIs discussed so far, ramucirumab is an antagonistic anti-VEGFR2 monoclonal antibody. On the basis of encouraging activity observed in a pilot study88, ramucirumab was compared with placebo in the phase III REACH trial involving patients with advanced-stage HCC and prior sorafenib treatment78. The study was negative for its primary end point of overall survival in the intentionto-treat population, although a subgroup of patients with a baseline serum AFP levels ≥400ng/ml had a significant improvement in median overall survival from 4.2 months with placebo to 7.8 months with ramucirumab (HR 0.67, 95% CI 0.51–0.90; P=0.006). This observation paved the way for a second phase III trial of ramucirumab in the second-line setting (REACH-2; NCT02435433), this time incorporating biomarker-based enrichment for patients with baseline AFP concentrations ≥400ng/ml. Results of this trial were reported in abstract form at the 2018 ASCO Annual Meeting10 and indicate a superior median overall survival duration of 8.5 months with ramucirumab versus 7.3 months with placebo (HR 0.71, 95% CI 0.53– 0.95; P=0.0199) (Fig. 3b) and a manageable safety profile (grade ≥3 hypertension and hyponatraemia in 12.2% and 5.6%, respectively). Thus, ramucirumab becomes the first agent with a demonstrated clinical benefit for a biomarker-selected population of patients with HCC. AFP is a plasma glycoprotein that is produced in the liver, predominantly during early fetal development, but also in few tumour types, including HCC, hepatoblastoma, and non-seminomatous germ cell tumours of the ovary and testis89. Of note, ~40% of patients with advanced-stage HCC have serum levels of AFP ≥400ng/ml, and this feature is associated with poor prognosis63. Some studies have linked high AFP levels with higher microvessel densities and VEGFA expression in HCCs90.

Immune-checkpoint inhibitors. The impact of treatments targeting immune checkpoints on oncology practice cannot be overstated: agents that target cytotoxic T lymphocyte protein 4 (CTLA-4), PD-1, or its ligand PD-L1 have revolutionized the management of many tumour types. A detailed description of the therapeutic mechanisms is beyond the scope of this Review, but in general, they involve blockade of negative feedback pathways of the immune system that mediate immunosuppression in the setting of malignancies91,92. For example, CTLA-4 is constitutively expressed in regulatory T cells but is also upregulated in cytotoxic T cells after T cell priming and is a dominant negative signalling molecule93. Monoclonal antibodies to CTLA-4, such as ipilimumab and tremelimumab, have been proven to block this negative feedback response and can lead to deep and durable responses in patients with cancer93. Similarly, PD-1 is a receptor expressed by T cells that provides negative regulatory signals predominantly during the effector phase of T cell responses. In the context of cancer pathogenesis, PD-1 on T cells can engage with its two known ligands, PD-L1 and PD-L2, in the TME to suppress anticancer immunity94. Monoclonal antibodies to either PD-1 (nivolumab and pembrolizumab) or PD-L1 (atezolizumab, avelumab, and durvalumab) are approved for the treatment of various malignancies95. HCC develops in an inflammatory milieu, and various studies have revealed a role for immune tolerance in the development of this cancer96, hinting at the potential of immune-checkpoint inhibition as an effective treatment strategy. Results of an initial phase II study of tremelimumab in a small cohort of patients with advanced-stage HCC (n = 20) demonstrated an ORR of 17.6% and a median TTP of 6.5 months97. Despite these signs of clinical efficacy, some safety concerns were raised, owing to transient but substantial increases in serum transaminase levels97. Notably, however, 43% of the patients enrolled had Child–Pugh class B liver disease97. More recently, nivolumab has been demonstrated to have single-agent activity in the much larger CheckMate 040 trial population, including patients with or without prior exposure to sorafenib11. In the phase I–II CheckMate 040 study11, a total of 262 eligible patients were treated with nivolumab, including 48 in the dose-escalation phase and another 214 in the dose-expansion cohort. Considering all patients included in the dose-expansion phase, the investigator-assessed ORR was 20%, with 3 complete responses and 39 partial responses11. Most impressive, though, was the duration of response of 9.9 months among the patients who had an objective

response11. Overall survival for patients in the secondline setting was 15.6 months98. Given the unmet needs in the second-line setting, the FDA granted accelerated approval to nivolumab for patients with advanced-stage HCC previously treated with sorafenib on the basis of the efficacy and safety data reported for a subpopulation comprising 154 sorafenib-treated patients included in CheckMate 040. In this subgroup, the ORR confirmed through blinded independent central review was 14.3% by RECIST 1.1 and 18.2% by mRECIST and the median duration of response was 16.6 months99. The toxicity data from the second-line population of CheckMate 040 seems manageable, with the most frequent AEs being fatigue, musculoskeletal pain, pruritus and rash, and diarrhoea. Treatment-emergent grade 3–4 AEs included elevations in serum aspartate transaminase (AST), alanine transaminase (ALT), and bilirubin levels in 18%, 11%, and 7% of patients, respectively99. Importantly, no patient had on-treatment hepatic failure, and only 11% of patients had to discontinue treatment owing to AEs. As for other indications, patients with HCC need to be monitored closely during immune-checkpoint inhibition, as this class of agents can affect essentially any organ system. A confirmatory open-label, randomized phase III trial comparing sorafenib to nivolumab in the frontline setting is ongoing (CheckMate 459; NCT02576509); patient accrual is complete and the results are eagerly awaited. Pembrolizumab seems to have similar activity to nivolumab in patients with HCC. In KEYNOTE-224 (ref. 100), a single-arm study of pembrolizumab for second-line treatment after frontline sorafenib, the ORR in 104 patients was 16.3%, including 1 complete response and 16 partial responses, and median overall survival was 12.9 months. Toxicities included fatigue, AST elevations, diarrhoea, and itching; seven patients discontinued treatment owing to AEs81. Longerterm follow-up data from this study are awaited, as are the results of KEYNOTE-240, a randomized, placebo-controlled phase III trial of pembrolizumab101. Durvalumab, an anti-PD-L1 monoclonal antibody, has also been tested in a phase I–II trial that included a dose-expansion cohort of patients with HCC102. In this study102, durvalumab had an acceptable safety profile and demonstrated antitumour activity (ORR 10%). The challenges to the development of immunecheckpoint inhibitors in patients with HCC are similar to those faced with other targeted therapies, most importantly, relating to the identification of predictive biomarkers of response. In other malignancies, several biomarkers have been proposed, including PD-L1 and/or PD-1 expression by immunohistochemistry (IHC)103, a high tumour mutational burden104, and tumour T cell infiltration105. To date, data presented on nivolumab and pembrolizumab therapy for HCC have not shown any correlation between PD-L1 expression or underlying aetiology of cirrhosis and clinical benefit11,106. The FDA has approved pembrolizumab for the treatment of microsatellite instability-high or mismatch repair-deficient advanced-stage cancers. This indication is agnostic to tumour histology and therefore includes HCC; however, the incidence of these defects in HCC is estimated to be low (~3%)107.

Combination strategies. The development of systemic therapies for HCC continues to benefit from knowledge gained in other tumour types. Combined CTLA-4 and PD-1 or PD-L1 blockade has been shown to improve survival outcomes, most notably in patients with melanoma108. In HCC, this approach is now being pursued in a phase III trial of durvalumab in combination with tremelimumab in the frontline setting (NCT03298451). The control arms of this trial include single-agent sorafenib and single-agent durvalumab. The trial is based on a phase I–II study evaluating the durvalumab–tremelimumab combination109, which resulted in a confirmed ORR of 15% among 40 evaluable patients included in the phase I component. AEs were manageable and most commonly included fatigue, ALT and AST elevations, and pruritus; no unexpected toxicities were observed109. The combination of molecularly targeted therapies with immunotherapies is another area of active interest. Again borrowing from experiences in other diseases, impressive responses have been seen in patients with renal cell carcinoma (RCC) using the combination of lenvatinib and pembrolizumab (two drugs that have meaningful activity as single agents in this disease), resulting in a ‘breakthrough therapy’ designation from the FDA. In a study involving patients with non-HCC malignancies, those with RCC had an ORR to the lenvatinib and pembrolizumab combination of 63%; the median PFS and overall survival durations had not been reached at the time of presentation110. Toxicities were in keeping with those of the single

agents, and no new safety signals were observed. This combination is now in development for the frontline treatment of HCC (NCT03006926), as is the combination of regorafenib and pembrolizumab (NCT03347292). These studies are building on the fact that these drugs have single-agent activity in patients with advanced-stage HCC, and as multi-target TKIs of VEGFRs and other kinases, lenvatinib and regorafenib have potential effects on the TME that might promote a response to immunotherapy36,37. Along those lines, monoclonal antibodies to VEGFA (bevacizumab) or VEGFR2 (ramucirumab) are being pursued in combination with PD-1 or PD-L1 inhibitors. Indeed, the combination of bevacizumab and atezolizumab is now being compared with sorafenib in a phase III study in the frontline setting (NCT03434379) and the FDA has granted this combination breakthrough designation on the basis of an ORR of 65% in 23 patients111 . Early phase studies evaluating the safety and efficacy of ramucirumab plus durvalumab in patients with HCC are underway (NCT02572687).

Proof of concept for precision medicine

As the above sections highlight, promising and robust clinical trial results have been presented in the past 2 years that are changing the treatment options for patients with advanced-stage HCC. All of the successful phase III studies yielded positive results without enriching for a biomarker-selected population, with the exception of REACH-2 (ref. 10). Despite the rapidly changing approach in other areas of oncology towards the development of molecularly targeted therapies in biomarkerselected populations112, this strategy is lacking in HCC. Nevertheless, attempts are being made at investigating this approach in patients with this disease (Fig. 4; Table 2).

MET The MET RTK has nonmalignant roles in liver physiology but has been implicated in the development of HCC. For example, elevated expression of MET and its ligand HGF has been associated with poor prognosis and resistance to sorafenib87. Subgroup analyses of a phase II study testing the small-molecule MET inhibitor tivantinib in 107 patients previously treated with sorafenib revealed a correlation of high MET expression by IHC (≥2+ in ≥50% of tumour cells) with an unfavourable prognosis but improved survival with tivantinib versus placebo113. This concept was then tested in a prospective, randomized, phase III study in the second-line setting in patients with MET-high HCC. This study did not meet its primary end point of an improvement in overall survival with tivantinib versus placebo80 (Fig. 3b). The placebo group of patients with MET-high HCC had a median overall survival of 9.1 months80. This survival duration is the longest ever reported for patients with advanced-stage HCC in the context of a second-line phase III trial, raising the question of whether or not a high level of MET expression is a negative prognostic marker in this setting. Alternatively, the assay and the cut-off used for defining MET-driven HCC might not have been appropriate. In addition, tivantinib has been postulated to have a mechanism of action that is independent of MET inhibition114. Nevertheless, studies evaluating the activity of more-specific MET inhibitors as single agents and in combination with immunotherapy (for example, the small-molecule MET inhibitor capmatinib alone (NCT01737827) or in combination with the anti-PD-1 antibody spartalizumab (NCT02795429)) are ongoing in patients with HCC. The relative contribution of MET inhibition by cabozantinib to the proven efficacy of this agent in the second-line treatment of HCC remains to be determined.

The FGF19– FGFR4 axis The FGF family consists of at least 5 RTKs and a large number of cognate ligands (at least 22) that have long been pursued as targets for anticancer treatments115. While FGFR2 alterations are being pursued as therapeutic targets in several cancers116,117, in HCC, FGFR4 — the predominant FGFR expressed in the liver118 — has been identified as a potentially important target. FGF19 can bind to and activate FGFR4 and induce hepatocyte proliferation119. FGF19 amplification occurs in ~5–10% of HCC and has been shown to be an oncogenic driver implicated in sorafenib resistance120 and a potential predictive marker of response to FGFR kinase inhibitors121–123. Specific FGFR4 kinase inhibitors are moving through the clinical development pathway, including BLU-554 (NCT02508467)124, H3B-6527 (NCT02834780)125, and FGF401 (NCT02325739). All these agents are

being evaluated using a biomarker-based approach, primarily on the basis of IHC for FGF19, FGFR4, and, in some cases, β-klotho, a transmembrane protein that enhances FGF19–FGFR4 interaction and signalling. BLU-554 has progressed furthest in clinical development, and preliminary data in patients with advanced-stage HCC have shown a response rate of 16% to this agent in an FGFR4-driven group (defined by ≥1% tumour expression of FGF19 by IHC) versus 0% in the FGFR4-negative group126. Responses occurred regardless of FGF19-amplification status, and toxicities were generally low grade, including diarrhoea, nausea, vomiting, and elevated AST and/or ALT levels (transaminase elevations had an increased tendency to be of grade 3–4). Mature data are awaited while this drug class moves through development as single agents and potentially in combination with other agents, particularly immune-checkpoint inhibitors (as in NCT02325739).

Intracellular kinases Clearly, most efforts in HCC drug development have been focused on RTKs. However, several clinical studies have examined intracellular kinases as targets on the basis of preclinical and laboratory evidence. mTOR is a central kinase involved in signalling downstream of many RTKs implicated in HCC tumorigenesis127,128. Everolimus, an allosteric inhibitor of mTOR complex 1 (mTORC1), has been evaluated in a phase III study as a second-line treatment of HCC77 but yielded negative results in an unselected patient population. A second-generation of mTOR pathway inhibitors (dual mTORC1 and mTORC2 inhibitors and mTOR–PI3K inhibitors) with a broader inhibitory action against PI3K–AKT signalling has been developed, and these agents are currently being investigated in early clinical trials (for example, NCT03059147)127,129. In contrast to everolimus, development of refametinib, a small-molecule MEK inhibitor, has been pursued in a biomarker-selected population. In a retrospective analysis of a single-arm phase II study evaluating refametinib plus sorafenib in patients with advanced-stage HCC, the best clinical responses were seen in patients with RAS mutations130. Two subsequent studies (NCT01915589 and NCT01915602) aimed to prospectively select patients on the basis of the presence of KRAS or NRAS mutations detected in serum circulating tumour DNA have been conducted using BEAMing technology; however, only 59 of 1,318 samples (4.4%) had detectable RAS mutations131 . A phase II combination trial enriched for RAS mutations testing refametinib plus sorafenib led to a median overall survival of 12.7 months in 16 patients131 .

Future prospects

Molecular characterizations have uncovered the most frequently mutated drivers (the TERT promoter, TP53, and CTNNB1), chromosomal aberrations (loss of 1q and 8p and high-level gains of 11q13 and 6p21), and deregulated pathways (RAS–MAPK, WNT, mTOR, or IGF2 signalling, among others)2,3,16,20 associated with HCC (Fig. 1; Table 1). Nonetheless, the advancements in the understanding of these molecular drivers have not yet been translated into biomarker-driven trials of precision medicine. In HCC, before the recently published REACH-2 trial10 , all effective drugs in phase III trials were multi-kinase inhibitors with no known predictive biomarkers (Fig. 5). Similarly, positive data from studies of immune-checkpoint inhibitors have not been accompanied by companion diagnostic tools. Thus, an urgent need exists to implement genome-based HCC therapies and to understand predictors of response to immunotherapies or identify agents that are able to boost immune response in primary resistant tumours.

Implementing driver-based therapies Molecular studies have already made great contributions to the understanding of HCC biology, but this knowledge has not been translated into clinical practice132. Strategic efforts are needed to foster precision medicine in this field. The co-development of predictive biomarkers together with novel targeted therapies is essential to overcome this issue133. In this regard, owing to the difficulties associated with the acquisition of biological samples of advanced-stage HCC, liquid biopsy — analyses of tumour cell-derived DNA and mRNA in cell-free plasma or circulating tumour cells — is envisioned as a useful tool to guide therapeutic decision-making in the near future134,135. A new drug development pathway has been established, consisting of positive proof-of-concept phase II

trials — leading to accelerated approval — followed by phase III randomized studies versus the standard of care to support conventional approval. In addition, 'monster' phase I trials have emerged in the field136, consisting of studies including 1,000–2,000 patients, which include multiple amendments for establishing the final well-selected population that will define the target patient cohort. This clear strategy is based upon the following concepts of precision medicine. First, driver mutations lead to oncogenic addiction loops; therefore, molecular therapies blocking these oncogenic drivers achieve substantial responses (in general, ORRs of ~50%) and survival advantages. Second, clonal founder or trunk mutations can be assessed with single biopsy samples. Currently, >25 molecular therapies in oncology have been approved for use based upon a predictive biomarker of efficacy112. The percentage of patients with tumours harbouring a biomarker that guides therapies approved by regulatory agencies ranges from 0% (for example, in those with HCC or prostate or pancreatic cancer) to >40% (in those with melanoma and gastrointestinal stromal tumours)137. However, the percentage of patients with a genomic alteration with compelling clinical evidence of an association with a response is much higher (>40% in those with non-small-cell lung, endometrial, breast, or thyroid cancer, and approaching 20% in those with HCC), although the corresponding drug is not yet standard of care owing to a lack of strong evidence137. In HCC, the landscape of mutations and targetable drivers has been defined, and ~25% of them are considered potentially actionable16. Unfortunately, therefore, most trunk mutations and prevalent drivers in HCC138 (affecting the TERT promoter, CTNNB1, TP53, AXIN1, ARID1A, and ARID1B) are not directly actionable at present16. Thus, driver-based trials are scarce in this field. A few studies, for instance, assessing refametinib plus sorafenib in patients with RAS-mutated HCC131 or FGFR4 inhibitors in patients with overexpression and/or amplification of FGF19 (refs124,125), have shown promise, whereas others failed (tivantinib in patients with METpositive HCC)80. According to the molecular pathogenesis and known pathways in HCC, drugs that block the effects of CTNNB1 mutations are expected to be relevant to precision medicine approaches.

Immunotherapies — new opportunities Increased understanding of the mechanisms that govern tumour–host interactions has accelerated the development of novel immunotherapies for cancer. Indeed, several immune-checkpoint inhibitors obtained regulatory approval for the treatment of melanoma and lung, renal, and bladder cancers139. Despite this unprecedented success, responses typically occur in a minority of patients, ranging from 20% to 50% depending on the tumour type. In a small proportion of patients, immunotherapy can cause severe and potentially permanent autoimmune AEs140; therefore, the identification of candidate biomarkers to target patients who are most likely to benefit is becoming crucial. Unfortunately, only PD-L1 expression by IHC has been approved as a companion diagnostic (for lung cancer) or complementary test (for melanoma and bladder cancer) for anti-PD-1 treatments141. The FDA has also approved pembrolizumab for the treatment of solid tumours with microsatellite instability ((on the basis of immune-specific gene signatures), and overexpression of PTK2, an oncogenic pathway associated with poor T cell infiltration into tumours143. These data are consistent with findings in melanoma showing that activation of the β-catenin (CTNNB1) pathway is associated with T cell exclusion and resistance to immunotherapy144, suggesting that the immune exclusion class of HCC encompasses patients with ineffective or suboptimal responses to immunotherapies. Importantly, if the results of the ongoing phase III CheckMate 459 trial comparing nivolumab to sorafenib are positive, this immune-checkpoint inhibitor will become the standardof-care frontline therapy; thus, biomarker-driven identification of responders will not only improve therapeutic decision-making in the advanced-stage setting but also help to move immunotherapies to earlier clinical stages. Conversely, if the study fails to hit the primary end point, a clear understanding of the biomarkers for predicting a response or primary resistance to these agents will be essential for future efforts to establish immunotherapy as a treatment strategy for patients with HCC.

Conclusions

The global disease burden of HCC is increasing and might surpass an incidence of 1 million cases annually in the near future. In this regard, primary and secondary prevention policies along with improved implementation of surveillance programmes will be essential to reduce the morbidity and mortality associated with this disease. In fact, few patients with HCC (<10%) are cured. Thus, the majority of patients ultimately develop advanced-stage HCC, at which point only systemic therapies are effective in delaying the natural history of the disease (Fig. 5); however, the median overall survival of these patients remains ~1 year with the use of efficacious multi-kinase inhibitors. Immune-checkpoint inhibitors are now entering HCC clinical practice on the basis of promising early data. New phase III studies are expected to demonstrate even more promising outcomes with these agents in the frontline. Similarly, combinations of molecularly targeted therapies and immunotherapies are emerging as tools to boost responses of the immune system against HCCderived neoantigens. Hopefully, these strategies might raise the bar for systemic HCC therapy by extending median overall survival beyond 2 years, particularly if predictors of responsiveness are identified. In this scenario, systemic therapies might start competing with locoregional therapies, such as chemoembolization, for intermediate-stage HCC.

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Author contributions

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