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Review

Immunotherapy in hepatocellular carcinoma: how will it reshape treatment sequencing?

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***Abstract*:** The treatment landscape of advanced hepatocellular carcinoma (HCC) has broadened with immune checkpoint inhibitors (ICIs) setting a novel standard of care. With the increased number of therapies either in first or in further line, disentangling the possible treatment sequences has become much more complex. Yet, all the second-line therapies have been evaluated after sorafenib. After ICIs, offering multikinase inhibitors is a widespread approach, either shifting forward sorafenib or lenvatinib, or choosing among regorafenib or cabozantinib, already approved in the refractory setting. Under specific circumstances, ICIs could be maintained beyond disease progression in patients with proven clinical benefit, as supported by some data emerging from phase III clinical trials with immunotherapy in HCC. Rechallenge with ICIs is an additional attractive alternative, although requiring careful and individual evaluation as efficacy and safety of such a strategy have not been yet clarified. Still, a considerable number of patients displays primary resistance to ICIs and might benefit from antiangiogenics either alone or in addition to ICIs instead. Hopefully, the ongoing clinical trials will enlighten regarding the most effective treatment pathways. The identification of predictive correlates of response to immunotherapy will help treatment allocation at each stage, thus representing an urgent matter to address in HCC research. With programmed death ligand 1 expression, tumor mutational burden, and microsatellite status being inadequate biomarkers in HCC, patient characteristics, drug safety profile, and regulatory approval remain key elements to acknowledge in routine practice. Despite the tissue remaining a preferred source, biomarkers discovery could take advantage of liquid biopsy to overcome the matter of tissue availability and track tumor changes. Lastly, tumor genetic phenotypes, tumor microenvironment features, gut microbiome, and markers of immune response and systemic inflammation are all potential emergent predictors of response to ICIs, pending validation in the clinical setting.

Keywords: hepatocellular carcinoma, immunotherapy, immune checkpoint inhibitors, liver cancer, multikinase inhibitors, rechallenge, sequencing, systemic therapy, targeted therapy, tyrosine kinase inhibitors

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Introduction

Liver cancer is one of the most common cancers worldwide and remains a global health challenge.[1] Although Africa and Asia are the most affected countries, its incidence is rising in Western countries as well and it is predicted that there will be over one million individuals affected annually by liver cancer by 2025.[2] Hepatocellular carcinoma (HCC) – which accounts for around 90% of the cases of primary liver cancer – generally arises on a cirrhotic liver as a result of hepatitis B virus or hepatitis C virus infection, excessive alcohol

consumption, metabolic syndrome, and exposure to toxic agents such as aflatoxin.[1] Its management is informed by the Barcelona Clinic Liver Cancer staging system, the most widely used system for the disease, which endorses the use of systemic therapy for patients diagnosed at an advanced stage and fit for treatment.[3]

The therapeutic landscape of advanced HCC has changed significantly over recent years. Multityrosine kinase inhibitors (MKIs) were the first class of agents showing an overall survival (OS) benefit with sorafenib being approved in 2007 following the positive results of two randomized phase III trials.[4,5] A decade later, lenvatinib was found to be non-inferior compared to sorafenib in the first-line setting.[6] In the refractory setting, regorafenib in a sorafenib-tolerant population and cabozantinib showed to be an effective second-line option when compared to placebo.[7,8] Of note, cabozantinib is also approved as a third-line option as 27% of the patients in the CELESTIAL trial received it in this setting, although the trial was not powered to demonstrate a survival difference according to the line of treatment.[8] In addition, ramucirumab, a recombinant immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that binds to vascular endothelial growth factor receptor 2 (VEGFR-2), demonstrated improved OS compared to placebo in patients with baseline alpha-fetoprotein (AFP) levels ⩾400 ng/mL.[9] The advent of immune checkpoint inhibitors (ICIs) has revolutionized the management of advanced HCC with the combination of atezolizumab–bevacizumab becoming the new front-line standard of care and durvalumab plus tremelimumab recently qualifying as another active front-line regimen.[10] Efficacy and safety data of the treatment options proven effective for advanced HCC are summarized in Tables 1 and 2.

Table 1. Efficacy and safety of first-line treatment options.

	SHARP[4]	REFLECT[6]	IMbrave150[11]	HIMALAYA[12]	
				STRIDE	Durvalumab
Median OS, months	10.7	13.6	19.2	16.4	16.6
HR (95% CI)	0.69 (0.55–0.87)	0.92 (0.79–1.06)	0.66 (0.52–0.85)	0.78 (0.65–0.93)	0.86 (0.73–1.03)
p Value	<0.001	–	0.0009	0.0035	0.0674[$]
Median PFS, months	5.5	7.4	6.0	3.8	3.7
HR (95% CI)	0.58 (0.45–0.74)	0.66 (0.57–0.77)	0.66 (0.52–0.85)	0.90 (0.77–1.05)	1.02 (0.88–1.19)
p Value	<0.001	<0.0001	<0.001	–	–
ORR per RECIST v1.1, %	2.0	24.1	29.8	20.1	17.0
Any grade TRAEs, %	80.0	94.0	86.0	75.8	52.1
Grade ⩾3 TRAEs, %	45.0	75.0	43.0	25.8	12.9
TRAEs leading to discontinuation, %	38.0[‡]	9.0	10.0[§]	8.2[§]	4.1
Most frequent any grade TRAEs	Diarrhea	Hypertension	Proteinuria	Rash	Increased AST
	Hand–foot skin reaction	Diarrhea	Hypertension	Pruritis	Rash
	Fatigue	Decreased appetite	Increased AST	Diarrhea	Diarrhea

[$]*p* value of superiority to sorafenib.
[‡]Due to AEs regardless of causality.
[§]Discontinuation of both components.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TRAEs, treatment-related adverse events; 95% CI, 95% confidence interval; –, not available.

Table 2. Efficacy and safety of second-line treatment options.

	RESORCE[7]	CELESTIAL*,[8]	REACH-2[9]	KEYNOTE-224[13]	CheckMate 040$,[14]
Median OS, months	10.6	10.2	8.5	13.2	22.8
HR (95% CI)	0.63 (0.50–0.79)	0.76 (0.63–0.92)	0.71 (0.53–0.95)	–	–
p Value	<0.0001	0.005	0.0199	–	–
Median PFS, months	3.1	5.2	2.8	4.9	–
HR (95% CI)	0.44 (0.36–0.55)	0.44 (0.36–0.52)	0.45 (0.34–0.60)	–	–
p Value	<0.0001	<0.001	<0.0001	–	–
ORR per RECIST v1.1, %	11.0	4.0	5.0	18.3	32.0
Any grade TRAEs, %	93.0	99.0‡	46.0	73.1	94.0
Grade ⩾3 TRAEs, %	50.0	68.0‡	35.0	26.0	53.0
TRAEs leading to discontinuation, %	10.0	16.0‡	11.0	4.8	18.0
Most frequent any grade TRAEs	Hand–foot skin reaction	PPE	Fatigue	Fatigue	Pruritus
	Hypertension	Hypertension	Nausea	Increased AST	Rash
	Diarrhea	Increased AST	Decreased appetite	Pruritus	Diarrhea

*Second line and third-line.
$4 doses nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks, then nivolumab 240 mg every 2 weeks.
‡Regardless of causality.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PPE, palmar-plantar erythrodysesthesia; TRAEs, treatment-related adverse events; 95% CI, 95% confidence interval; –, not available.

In this review, we will discuss treatment sequencing for advanced HCC after front-line immunotherapy, encompassing the relevant clinical and molecular markers that could help disentangle the treatment choice, and highlighting the future challenges to be addressed.

Immunotherapy in advanced HCC

Preclinical rationale

Cancer development and progression have been notoriously linked with evasion of the immune response *via* a plethora of mechanisms including the upregulation of immune checkpoints, namely programmed death-1 (PD-1) and its ligand (PD-L1) and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), that prevents immune system from overactivation.[15,16] By overexpressing PD-L1, tumor cells boost the negative feedback on the immune response exerted by PD-1/PD-L1 interaction, hindering the immune response against cancer-related epitopes. The liver acts as an 'immunological gatekeeper' modulating the immune response against a number of antigens originating from the gut, including bacterial nucleic acid, lipopolysaccharides, and toxins.[17,18] Arising within this peculiar immune-tolerant microenvironment, HCC further promotes immune escape *via* impaired antigen presentation, dysregulation of T-cell response, and upregulation of immunosuppressive myeloid cells. Thus, it offers a fascinating immunological background that supports the use of immunotherapy either alone or in combination with other agents to address possible mechanisms of resistance.[19,20]

ICI monotherapy

In the front-line setting, two PD-(L)1 inhibitors, namely durvalumab and tislelizumab have recently proven to be non-inferior compared to sorafenib in terms of OS (HR 0.86; 95.67% CI, 0.73–1.03; noninferiority margin, 1.08 for

durvalumab and HR 0.85, 95.003% CI, 0.712, 1.019 for tislelizumab) in the phase III HIMALAYA trial and RATIONALE-301, respectively.[12,21] However, despite showing encouraging clinical activity with an objective response rate (ORR) of 15–20% and a median OS surpassing 12 months in a pretreated population in early phase clinical trials, both nivolumab and pembrolizumab, two anti-PD-1 mAbs, failed to meet their primary endpoints in their respective global phase III trials.[22–25] Of note, in the phase III KEYNOTE-394 trial enrolling pretreated Asian patients, pembrolizumab performed significantly better in all the efficacy endpoints against placebo.[26] Lastly, camrelizumab, another PD-1 inhibitor, revealed encouraging antitumor activity (ORR: 14.7% with a 6-month OS of 74.4%) in pretreated Chinese patients in a single-arm phase II trial.[27]

Dual ICI blockade

With the aim to tackle some of the mechanisms of resistance to single-agent ICIs, a number of combinations offering a co-inhibition of PD-(L)1 and CTLA-4 were evaluated. Nivolumab plus ipilimumab is currently being tested in first-line against sorafenib or lenvatinib in the phase III CheckMate 9DW trial (NCT04039607), after proving its activity in the phase I/II CheckMate 040 trial in a post-sorafenib setting.[14] Of note, in the early phase study, which tested the combination in three different dosing regimens, the arm A (4 doses nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks, then nivolumab 240 mg every 2 weeks) was associated with the highest ORR of 32%, thus receiving accelerated US Food And Drug Administration (FDA) approval.[28]

Furthermore, in light of the promising activity seen in the phase I/II Study 22 in sorafenib-pretreated or intolerant patients, durvalumab with or without a single priming dose of tremelimumab [also known as the STRIDE regimen (tremelimumab 300 mg one dose plus durvalumab 1500 mg every 4 weeks)] was further evaluated in the phase III HIMALAYA trial against sorafenib in the first-line setting.[12,29] After a median follow-up of more than 30 months, the STRIDE regimen outperformed sorafenib in terms of median OS (HR: 0.78; 96.02% CI, 0.65–0.93; $p = 0.0035$), the primary endpoint of the study, showing a 36-month OS rate of 30.7% *versus* 20.2% and a manageable safety profile.[12] As such, the combination has been recently approved by the US FDA and, therefore, will implement the treatment options available in the first-line scenario.[30]

ICI combinations

Since the overactivation of the VEGF pathway, a hallmark of HCC, might further enhance the immune escape, PD-1 and PD-L1 inhibitors have been also evaluated in association with anti-VEGF agents and MKIs with an antiangiogenic effect.[20]

After showing promising results in the phase Ib GO30140 study, atezolizumab plus bevacizumab further confirmed its activity against sorafenib in treatment-naïve patients in the subsequent phase III IMbrave150 trial, reaching a median OS of 19.2 months (HR: 0.66; 95% CI, 0.52–0.85; $p = 0.0009$) and a median progression-free survival (PFS) of 6.9 months (HR: 0.65; 95% CI, 0.53–0.81; descriptive $p < 0.001$). The combination also demonstrated an ORR of 30% and a favorable safety profile.[11,31] Thus, it has become the new first-line standard of care for advanced HCC.[10] Similarly, the combination of the anti-PD-1 sintilimab with a bevacizumab biosimilar (IBI305) demonstrated a significant OS and PFS benefit compared to sorafenib in a phase III trial enrolling a Chinese population.[32]

Regarding the ICIs plus MKIs combinations, the phase III COSMIC-312 trial testing cabozantinib–atezolizumab *versus* sorafenib in the front-line setting met one of its dual primary endpoints, with the experimental combination yielding a significantly longer PFS (HR: 0.63; 99% CI, 0.44–0.91; $p = 0.0012$). However, even though an early separation of the survival curves was seen at the interim analysis, the difference in median OS did not reach the bound for statistical significance.[33] Furthermore, although the clinical activity shown in an early-phase clinical trial was encouraging, in the phase III LEAP-002 trial, the combination of pembrolizumab plus lenvatinib did not meet the primary endpoints (OS and PFS) of the study against lenvatinib.[34,35] Lastly, camrelizumab combined with rivoceranib confirmed the promising efficacy demonstrated in a phase II trial (ORR of 34.3%) outperforming sorafenib in both the survival outcomes (PFS: HR: 0.52, 95% CI, 0.41–0.65; one-sided $p < 0.0001$; and OS: HR,

0.62, 95% CI 0.49–0.80; one-sided $p < 0.0001$) in the front-line setting at the planned interim analysis of an international phase III trial.[36,37]

The reshaped therapeutic algorithm: how to inform treatment choice and sequencing

Comparison between treatment options

Over the past 5 years, the number of active first-line systemic treatment options for patients with unresectable HCC has dramatically increased, adding considerable complexity to the therapeutic scenario. Furthermore, all the phase III randomized clinical trials testing these novel options acknowledged sorafenib as the comparator arm, leaving to indirect analyses the task of informing on the most suitable front-line treatment and its best sequential strategy.

The most updated guidelines recommend atezolizumab plus bevacizumab as the standard of care for first-line unresectable HCC,[3,10,38] and a number of network meta-analyses consistently supported this recommendation by ranking atezolizumab plus bevacizumab as superior to all the other treatments evaluated in the front-line setting, including lenvatinib and nivolumab.[39,40] Moreover, atezolizumab plus bevacizumab led to better survival outcomes compared to lenvatinib (HR: 0.59; 95% CI, 0.46–0.75) and sorafenib (HR: 0.58, 95% CI, 0.42–0.79), according to some matched-adjusted indirect comparisons (MAICs).[41,42]

The lack of direct comparison also affects the refractory setting where all the available agents were compared against placebo.[17,18] Some specific features of the populations enrolled in the pivotal trials (tolerance to previous sorafenib for regorafenib, baseline AFP levels ≥ 400 ng/mL for ramucirumab, availability also as a third-line option for cabozantinib, and suitability for immunotherapy for ipilimumab–nivolumab and pembrolizumab) could provide some guidance as to how to unravel the choice in the clinical setting. However, the largely overlapping characteristics of the patients eligible for further-line treatments make the need for a formal comparison between these treatments of utmost importance. When indirectly compared, regorafenib, cabozantinib, and ramucirumab were all established as active options for pretreated patients, with ramucirumab confirming a significant advantage only in those with elevated AFP levels.[39] No survival differences between these agents were found, according to two MAICs comparing cabozantinib with regorafenib and ramucirumab, respectively.[43,44] Of note, a longer median PFS was observed for cabozantinib compared with regorafenib and ramucirumab in such analyses but intrinsic differences in the trial protocols regarding the timing of the assessments could have influenced these results.[43,44]

Biomarkers of response

The introduction of immunotherapy in the treatment scenario represented a paradigm shift in HCC care, showing a completely new response pattern as compared to MKIs. Among responders, the treatment benefit appears durable over time, even when only the PD-1/PD-L1 pathway is targeted.[13,22] On the other side, a sizeable group of patients are primary progressors, particularly when immunotherapy is not paired with antiangiogenic agents. Therefore, identifying biomarkers able to inform the best treatment approaches will be key to plan the continuum of care for such patients by a greater comprehension of the mechanisms of action and resistance to the available drugs.

The most extensively studied predictive biomarkers for immunotherapy, namely PD-L1 expression, microsatellite instability (MSI), and tumor mutational burden (TMB) are infrequently found in HCC and their correlation with tumor response remains largely unclear.[45–47] For HCC patients, the PD-L1 expression was not a mandatory entry criterion to access immunotherapy nor a preplanned stratification factor. Therefore, it was not uniformly reported across clinical trials with ICIs and substantial inter-assay heterogeneity in the assessment of PD-L1 expression was observed.[48] Moreover, apart from a significant association of PD-L1 combined positive score ≥ 1 with tumor response in an exploratory analysis of the KEYNOTE-224 trial, overall similar response rates were found in both PD-L1-positive and -negative patients in trials with ICIs.[13,14,31] Of note, a genomic signature of pre-existing immunity, including high expression of PD-L1 mRNA, was recently found to be significantly associated with better outcomes with a trend toward higher tumor responses as the PD-L1 cutoffs increase (≥ 1, 5 or 10%) in a translational study conducted on the GO30140 and IMbrave150 data.[49] Although more consistent data are being generated, the wide variability of the PD-L1 expression

resulting from the retrospective nature of such analyses, the lack of standardization of the assays employed, and the different scoring systems adopted across the trials limit the usefulness of PD-L1 as a predictive biomarker in this setting and require a more rigorous systematic evaluation.[48]

Mismatch repair deficiency (dMMR) or MSI and TMB-high are additional, agnostic predictive biomarkers of immunotherapy benefit across solid tumors.[46,47,50] In HCC, the dMMR signature has been correlated with better prognosis but the MSI-high status is overall rare (less than 3%).[51] Similarly, a TMB-high is found in nearly 5% of the cases but its association with the efficacy outcomes in HCC remains poorly defined.[52] Across a cohort of patients treated with atezolizumab–bevacizumab, the median TMB was around 5 mutations/Mb and tumor response was significantly associated with a TMB-high status in the phase Ib study but not in the IMbrave150 trial, according to a retrospective analysis.[49] However, the relatively low prevalence of the MSI-high and TMB-high signatures in HCC limits their utility as predictors of response.[46,47,53]

A great effort has been made to characterize some genomic, transcriptomic, and epigenetic signatures to postulate further potential biomarkers of response to immunotherapy.[52,54] High levels of immune cell infiltration, hyperexpression of PD-1 and/or PD-L1, activation of interferon-gamma (IFN-γ) signaling, and the absence of *CTNNB1* mutations – a gene that encodes for β-catenin – might predict an immune-active phenotype. On the other hand, the overactivation of transforming growth factor-beta and WNT/β-catenin signaling has been linked to an immune exhausted and immune excluded subtype, respectively. Nevertheless, similar survivals were observed in patients with *CTNNB1* wild-type or mutations in the IMbrave150 trial, suggesting that the addition of bevacizumab might overcome this mechanism of resistance to ICIs.[49]

Moreover, the identification of an HCC immune gene signature failed to anticipate a clinical response to such agents.[54] The understanding of the complex dynamic interactions among cancer cells, immune cells, and other immunomodulators in the tumor microenvironment (TME) will be essential to distinguish between active and exhausted or excluded immune subclasses, phenotypes that could benefit from different therapeutic approaches.[54,55] Other explored correlates of response to ICIs encompass cell surface protein expression, serum and stromal biomarkers, and even certain gut microbiome richness.[56] With this respect, a high serum concentration of the tumor necrosis factor family member CD137 and a high density of antitumoral M1 macrophage infiltration in the tumor stroma recently emerged as potential predictive biomarkers for the PD-1 inhibitor and anti-VEGF combination.[57] Further insights might be provided by a deeper understanding of the inflammatory milieu of liver cirrhosis in which HCC typically arises. An inflammatory signature has been correlated with an immune-enriched genomic profile and response to anti-PD-1 inhibitors.[52,54,58] However, the richness of pro-inflammatory cytokines in the TME fosters tumor-promoting signals and facilitates immune evasion *via* T-cell exhaustion and the promotion of M2-type macrophages, which ultimately is associated to a state of systemic inflammation and resistance to ICIs.[59] Different immune scores tried to recapitulate this state of systemic inflammation into novel biomarkers of potential clinical utility. The CRAFITY score was developed from a combination of baseline AFP and C-reactive protein levels, with lower levels being associated with better survival and radiological responses in patients receiving anti-PD-(L)1 agents.[60] Similarly, raised baseline neutrophil–lymphocyte ratio and platelet–lymphocyte ratio, reflecting a pro-inflammatory microenvironment, which promotes neoangiogenesis and metastases development, were found to retain negative prognostic significance.[59,61,62]

The most relevant biological determinants of response to ICIs are summarized in Figure 1.

Role of clinical features and drug safety profile

In the absence of validated molecular biomarkers of response, understanding the possible association of some clinical features with a potential benefit from immunotherapy is gaining certain recognition in the HCC research field. Although the treatment benefit across clinical subgroups or etiologies of the underlying liver disease was generally homogeneous across the phase III clinical trials with ICIs, some evidence suggests that the non-viral etiologies might derive less benefit from immunotherapy.[63–65] According to a meta-analysis evaluating more than 1600 advanced HCC patients, treatment with PD-(L)1 inhibitors was not associated with a significant survival improvement in patients with non-viral HCC, and

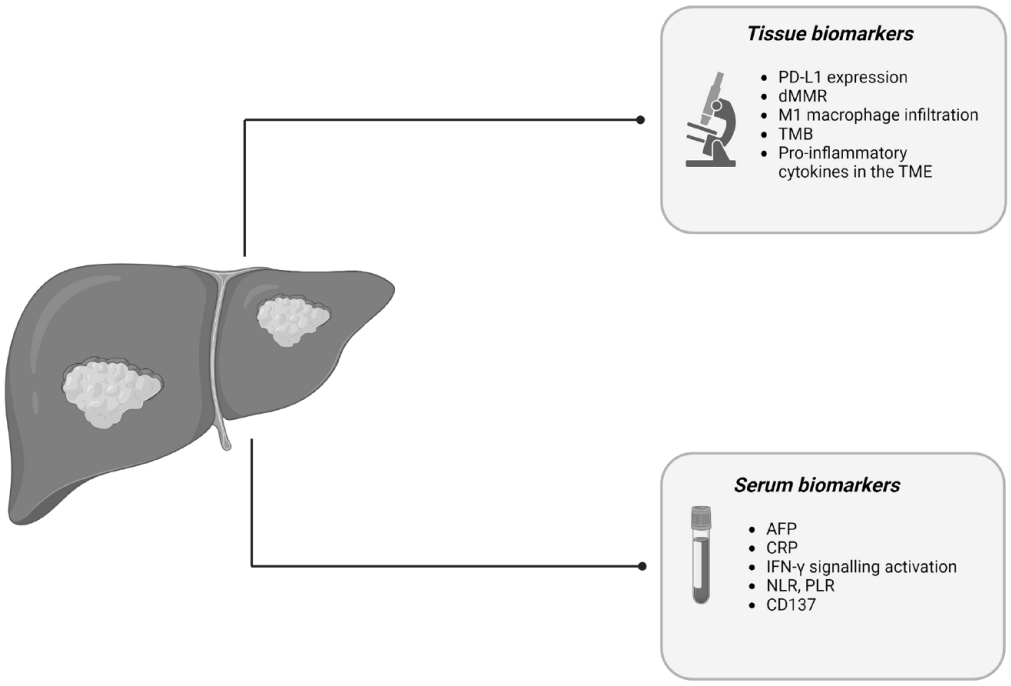

Figure 1. Biological determinants influencing ICIs response in advanced HCC.
Source: Created with BioRender.com.
AFP, alpha-fetoprotein; CRP, C-reactive protein; dMMR, mismatch repair-deficiency; HCC, hepatocellular carcinoma; ICIs, immune checkpoint inhibitors; IFN-γ, interferon-gamma; NLR, neutrophil–lymphocyte ratio; PD-L1, programmed death-ligand 1; PLR, platelet–lymphocyte ratio; TMB, tumor mutational burden; TME, tumor microenvironment.

nonalcoholic steatohepatitis (NASH)-related HCC independently predicted unfavorable outcomes.[64] Indeed, an accumulation of exhausted, dysfunctional CD8+ T cells might be responsible for this impaired immune surveillance in NASH-related HCC, according to a preclinical study.[64]

Furthermore, it has been suggested that immunotherapy benefit could be paired with the occurrence of immune-related adverse events (irAEs). The development of grade ⩾2 irAEs has successfully identified a subgroup of HCC patients more likely to derive better survival outcomes whilst on ICIs.[66] That treatment-related adverse events (TRAEs) could predict treatment benefit is no new concept in HCC, where a wide range of side effects have been linked to MKI benefit.[67–70] However, TRAEs appear of limited utility in the clinical setting as to assisting the treatment decision, not allowing an upfront selection of the optimal candidates for ICIs. Moreover, the promotion of a personalized therapeutic choice could not disregard the different safety profiles of ICIs and MKIs, and the development of severe AEs with a certain drug class should be carefully considered when the switch to a further-line option is planned.[71] Increased risk of bleeding, autoimmune conditions requiring immunosuppressive treatment, and liver transplantation can limit the use of atezolizumab–bevacizumab, limiting the choice to sorafenib or lenvatinib as first-line treatments.[10,72] With this respect, the future availability of antiangiogenic-free regimens, such as durvalumab with or without tremelimumab, will possibly widen the proportion of patients eligible for first-line treatment with ICIs allowing also the inclusion of those with significant cardiovascular comorbidities.[12] Moreover, real-life studies could add precious information to the decision-making process, providing evidence that a certain treatment might be suitable for a broader population than that enrolled in clinical trials, as recently shown by the reassuring safety of atezolizumab–bevacizumab in Child–Pugh B patients.[73]

Treatment sequences: potential approaches and unsolved challenges

The unprecedented number of therapeutic choices available for advanced HCC has made remarkably more complex the selection of the most adequate sequence of treatments for each patient. The

approval of a considerable number of active treatments and the availability of sequential lines of therapy led to an unprecedented survival prolongation from just over 6 months in the pre-sorafenib era to more than 2 years for patients suitable to multiple lines of therapy, and the outcomes will be probably even better for patients receiving the novel immunotherapy-based front-line options.[4,74–76] Yet, after disease progression (PD) on a front-line regimen, less than 50% of HCC patients treated with ICI-based approaches receive further lines of treatment.[12,24,31] Furthermore, all second- and further-line treatment options have been evaluated after sorafenib, whereas for patients who do not have contraindications, atezolizumab plus bevacizumab embodies now the front-line recommended treatment worldwide, and durvalumab with a single priming dose of tremelimumab represents a valid alternative option.[3,10,38]

MKIs after first-line immunotherapy-based treatments. Since no published prospective data are available so far, upon progression to ICIs, the choice of the most appropriate sequential treatment for the patients who are fit enough to receive it remains essentially empirical. In the absence of evidence-based interventions, patients' clinical features, tolerability of the prior therapy, and labeling and regulatory approvals in each country drive the decision-making process. Enrollment within a clinical trial is warmly encouraged, where available, and several studies are currently interrogating the role of single-agent MKIs after immunotherapy, a widespread approach in this setting (e.g. NCT05134532, NCT04435977, NCT04316182). However, if a clinical study is not accessible, there exists initial reassuring evidence regarding the use of MKIs after ICIs in routine clinical practice. Both sorafenib and lenvatinib showed to be effective options after atezolizumab plus bevacizumab with a tolerability profile in keeping with the literature data, according to a real-world retrospective analysis and a simulation model built on the data from pivotal phase III trials.[77,78] Interestingly, lenvatinib and sorafenib appeared as the most effective options in second line and the sequence sorafenib–cabozantinib after atezolizumab plus bevacizumab reached a median OS of 28 months in the previously mentioned simulation model.[78,79] Similarly, ramucirumab, regorafenib, and cabozantinib were proven effective and safe following immunotherapy, also when received beyond the second line of therapy.[80–82] Of note, ramucirumab was offered to a sorafenib-naïve population with baseline AFP levels ⩾400 ng/mL, 64% of whom received a prior line of therapy containing ICIs, whereas regorafenib and cabozantinib were given to a sorafenib-experienced population, 9% and 10% of whom, respectively, received prior immunotherapy. Therefore, either shifting forward sorafenib or lenvatinib, originally approved in the first-line setting, or adopting regorafenib, cabozantinib, or ramucirumab, approved as further-line options after sorafenib, are acceptable strategies recognized by most of the international guidelines.[3,10,38,83]

Immunotherapy beyond radiological progression. Maintaining treatments beyond progression in case of sustained clinical benefit might be a reasonable strategy with ICIs, a class of agents recognized for inducing unique patterns and timing of response. Delayed response and pseudoprogression are renowned phenomena in immune-oncology, although rather infrequent in the HCC field.[84–86] Indeed, around 30–60% of HCC patients show primary resistance to ICIs within clinical trials.[12,14,24,25,29] However, even in patients displaying PD as best response, ICIs could lead to unconventional benefit. In the IMbrave150 trial, more than half of the patients continued to receive atezolizumab plus/minus bevacizumab beyond PD with reported sustained benefit and prolonged survival.[11] A similar trend was observed in the HIMALAYA trial, where slightly less than half of the patients on an ICI-containing arm continued to receive treatment beyond PD, and 7.6% of the patients in the STRIDE arm were rechallenged with a second priming dose of tremelimumab at PD.[12] Disentangling in a timely fashion the subgroup of patients among progressors that could still benefit from treatment will be essential, and the pattern of progression might appear as an informative parameter in doing so. With this respect, nivolumab yielded durable survival benefit reaching a median OS of 18.8 months in patients with PD of target lesions followed by a formal response, PD with new lesions followed by ⩾10% decrease in target lesions, or PD of target lesions or new lesions followed by stabilization of the disease burden, compared with 8.4 months in the remaining progressors, according to a post-hoc analysis of the CheckMate 040 study.[87] Thus, the evidence of radiological PD should not always claim treatment failure and prompt to switch to a subsequent line of therapy. Although continuing treatment beyond progression is no new concept, the decision is usually made per investigator's choice in clinical trials in the absence

of well-established biomarkers of response and elucidated mechanisms of primary and acquired resistance to ICIs. Yet, while promising also in a real-world scenario, this approach seems much less adopted for unselected patients in a less rigorous setting like that of clinical practice.[88]

Immunotherapy rechallenge. Despite maintaining ICIs beyond progression might be considered in specific circumstances, immunotherapy discontinuation is usually advised upon tumor progression and/or after the occurrence of severe AEs in clinical trials, and limited evidence exists regarding the clinical outcomes at treatment resumption.[89] So far, only very few HCC patients (<2%) receiving ICIs within phase III clinical trials have been switched to another immune-oncology agent after PD and the effects of rechallenge with immunotherapy are largely unknown.[11,12,24] In the real-world setting, some evidence suggests that rechallenge with ICIs is associated with similar rates of radiological responses and irAEs compared to the first ICI-containing regimen.[90,91] Indeed, ORR ranged from 16% to 26% with responses seen also in the subgroup of primary progressors and grade 3–4 irAEs ranged from 8% to 17%, according to two retrospective studies. Of note, a new line of treatment with ICIs was offered in up to 6% of patients and tumor responses were observed regardless of the regimen type (monotherapy or combinations).[90]

Reoccurrence of severe irAEs after ICI rechallenge, however, remains to be elucidated for HCC patients. Across other tumor types, mostly melanoma and non-small-cell lung cancer, clinically significant irAEs were reported in 18–44% of patients (both new and recurrent AEs) with immunotherapy retreatment, and higher irAE rates happened with anti-CTLA-4 agents alone or in combinations.[89,92,93] In the HCC setting, no toxicity recurrence was observed across the patients retreated with nivolumab with or without ipilimumab – temporarily withheld due to irAEs – in the CheckMate 040 study.[14] Furthermore, only 5% of patients rechallenged in a real-world scenario developed again grade 3–4 irAEs, although the small sample size of the study limits the conclusions that can be drawn.[90] Although worth of further investigations, this strategy will serve a limited number of patients as treatment discontinuation due to irAEs did not exceed 15% for ICI combinations and 5% for ICI monotherapy in phase III trials in the front-line setting.[11,12,24,33] A more relevant issue might be posed by the subgroup of patients experiencing severe toxicity on combinations of ICIs with either anti-VEGF mAb or MKIs. Despite the treatment discontinuation rate is not much different from those receiving ICIs alone, grade 3 or higher AEs have been reported in 43–81% of patients receiving combinations with antiangiogenics, with most of the AEs falling within the spectrum of the expected side effects of the antiangiogenic compound.[11,33,35,37] Therefore, the choice of MKIs as a suitable further line of therapy – one of the most widespread approaches – would require a cautious evaluation in this setting.

For the vast majority of patients discontinuing ICIs for PD, either shifting to a different drug class with or without maintaining ICI or, in the frame of early phase clinical trials, exploring other treatment avenues with new immunotherapeutic agents (e.g. agonist immunostimulatory mAbs, bispecific antibodies, engineered cytokines, antibody–drug conjugates, adoptive T-cell therapy, and neoantigen vaccination) might represent more successful sequential strategies.

Changing companion in immunotherapy-based combinations. Another sequential approach considers the replacement of the anti-VEGF agent with an MKI with the hope that their broader mechanism of action could tackle some of the resistance pathways emerging during the treatment with atezolizumab plus bevacizumab. A number of clinical trials are questioning the added value of maintaining the ICI compound after PD when its anti-VEGF companion is substituted with an MKI (e.g. NCT04770896, NCT05168163). Further endorsing the relevant preclinical rationale that supported the development of combinations with ICIs and antiangiogenics, recent translational evidence shed light on some biological mechanisms driving the augmented antitumor activity seen co-targeting PD-(L)1 and the VEGF pathway in the clinical setting.[49] Indeed, PD rates were much lower with atezolizumab–bevacizumab (19%) and cabozantinib–atezolizumab (14%) as compared to nivolumab (37%) or durvalumab with (40%) or without tremelimumab (45%).[11,12,33] However, it remains to be elucidated whether or not the use of ICI-MKI combinations would restore sensitivity to immunotherapy even in the refractory setting by reigniting an immunosuppressive microenvironment, particularly for patients not previously exposed to antiangiogenics in the front-line

setting. Furthermore, pairing ICIs with MKIs would take advantage of a wider inhibition of several tyrosine kinase-mediated pathways – dysregulated in HCC development and progression – than targeting angiogenesis alone, hopefully reestablishing ICI susceptibility also in patients previously exposed to anti-VEGF agents. Moreover, these ongoing studies will also provide further hints on the optimal MKI to be used in the sequential strategy. A summary of the ongoing clinical trials for each proposed sequential approach is provided in Table 3 while the most relevant biological predictors of benefit from ICIs alone and combined with antiangiogenics are summarized in Figure 2.

Conclusions and future directions

After more than a decade of sorafenib monopoly, the therapeutic scenario for advanced HCC has grown at a sustained pace, leading to the approval of novel therapies and to an unprecedented survival prolongation in this setting. However, the advancement in terms of drug development has not been followed by a systematic understanding of how to redesign the therapeutic landscape. In the absence of head-to-head comparisons between these regimens nor validated predictive biomarkers other than elevated baseline AFP levels for ramucirumab, considerable uncertainty remains as to the most appropriate treatment choice.[9,94] Thus, nowadays, treatment selection and sequencing are still predominantly guided by a comprehensive assessment of patient and treatment characteristics altogether with regulatory approvals.

The entry of ICI-based combinations into the front-line armamentarium has imposed a thorough reflection on how to unravel the increased number of potential treatment sequences (Figure 3). Indeed, informed strategies for patients that have not been exposed to prior sorafenib remain to be elucidated. When offered after immunotherapy, preliminary data suggest that MKIs retain a drug profile in keeping with the literature data.[77,78] On the other side, when retreatment with ICIs is considered, balancing the potential benefits derived from the restored treatment efficacy with the concerns of irAE reoccurrence is crucial. Therefore, enrollment within a clinical trial or treatment in an experienced clinical setting should be endorsed, lacking rigorous evidence that supports this choice.

Furthermore, the criteria themselves guiding the shift to a further line of therapy are being revisited in certain circumstances. As for other cancer types, initial evidence suggests that maintaining treatment with ICIs beyond radiological disease progression could be an option in carefully selected patients as the survival benefit might not be always accurately recapitulated by the radiological metrics in immune-oncology.[84–86] Nevertheless, this approach needs further validation before a wider use in clinical practice could be advised as not switching to a further line of treatment in a timely manner might affect patient eligibility for further active treatments due to the concomitant potential deterioration of liver function. Hopefully, the ongoing clinical trials testing MKIs – as single agents or in combinations with ICIs – and novel immunotherapeutic strategies will generate data on the most effective sequential treatments after tumor progression on ICIs and provide some hints on how to optimize patient selection.

Despite the identification of different molecular subclasses of HCC has thrown light on some genetic, epigenetic, and immunological features that could act as potential predictors of response, precision medicine in HCC has not been a particularly successful path to follow so far, leaving behind the set-up of biomaker-enriched clinical trials to favor all-comers study designs.[95–97] Inappropriate target, patient, and treatment selection, intra and inter-tumor heterogeneity might have contributed to the failure of such tailored approaches. Furthermore, the limited number of correlative studies due to the paucity of available tumor samples clearly represented a major barrier in the understanding of the leading mechanisms of treatment response or resistance in this setting. In fact, particularly in the advanced stage where a radiological diagnosis does not necessarily require further histological confirmation in cirrhotic patients, the reduced number of tumor biopsies has hampered the discovery and validation of predictive biomarkers of clinical utility that could inform treatment choice at each time point.[54,98] With this respect, the studies evaluating neoadjuvant and perioperative approaches with ICIs will represent a privileged field for biomarkers discovery and validation.[99–101] Indeed, the availability of longitudinal, prospectively collected tissue samples will likely enable a comprehensive evaluation of the correlates of response to such treatments at a biological level that could

Table 3. Sequential strategies after immunotherapy explored in clinical trials.

Sequential strategy	Trial name/number	Phase/design	Regimens	Primary endpoint
Switching to MKIs	REGONEXT (NCT05134532)	Phase II – single arm, open label	Regorafenib after atezolizumab–bevacizumab	PFS
	Immunocabo (NCT04435977)	Single arm, open label	Cabozantinib after ICIs	PFS
	ACTION (NCT04316182)	Phase II – single arm, open label	Cabozantinib in sorafenib intolerant or after non-sorafenib-based first-line treatment	TTP
Switching to MKIs maintaining ICIs	IMbrave251 (NCT04770896)	Phase III – randomized, open label	Atezolizumab plus lenvatinib or sorafenib *versus* lenvatinib or sorafenib alone	OS
	NCT05168163	Phase II – randomized, open label	Atezolizumab plus MKIs (cabozantinib or lenvatinib) *versus* MKIs alone after ICIs	PFS and OS
	NCT05101629	Phase II – single arm, open label	Pembrolizumab plus lenvatinib after ICIs	ORR
	NCT04696055	Phase II – non-randomized, open label	Pembrolizumab plus regorafenib following anti-PD(L)1 therapy	ORR
	GOING (NCT04170556)	Phase I/II – single arm, open label	Regorafenib followed by nivolumab from week 8 after progression on sorafenib (cohort A) or atezolizumab–bevacizumab (cohort B)	Safety
ICIs beyond progression*	IMbrave150 (NCT03434379)	Phase III – randomized (2:1), open label	Atezolizumab plus bevacizumab *versus* sorafenib in treatment-naïve HCC patients	PFS and OS
	HIMALAYA (NCT03298451)	Phase III – randomized (1:1:1), open label	Durvalumab plus or minus tremelimumab *versus* sorafenib in treatment-naïve HCC patients	OS
	CheckMate 459 (NCT02576509)	Phase III – randomized (1:1), open label	Nivolumab *versus* sorafenib in treatment-naïve HCC patients	OS
Novel immunotherapies	NCT04374877	Phase I – open label	SRF388, a IgG1 antibody against IL-27, alone or in combination with pembrolizumab in advanced solid tumors including HCC	Safety and ORR
	NCT05003895	Phase I – single arm, open label	GPC3 targeted CAR-T Cell therapy in advanced GPC3+ HCC	Safety and feasibility
	NCT05070156	Early phase I – single arm, open label	B010-A Injection, a neoantigen vaccine, in advanced GPC3+ HCC	Safety
	NCT05293496	Phase I/Ib – open-label	MGC018, an ADC against B7-H3$, in combination with MGD019, a bispecific DART molecule that binds PD-1 and CTLA-4, in advanced solid tumors including HCC	Safety

*Phase III trials allowing treatment with ICIs beyond progression in the front-line setting.
$B7-H3 is an additional immune checkpoint potentially involved in resistance to anti-PD-1/PD-L1 blockade.
ADC, antibody–drug conjugate; B7-H3, B7 Homolog 3; CTLA-4, Cytotoxic T lymphocyte-associated antigen-4; DART, dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors; GPC3, glypican-3; HCC, hepatocellular carcinoma; ICIs, immune checkpoint inhibitors; IgG1, immunoglobulin G1, IL-27, interleukin-27; MKIs, multikinase inhibitors; ORR, objective response rate; OS, overall survival; PD(L)-1, programmed death (ligand)-1; PFS, progression-free survival; TTP, time to progression.

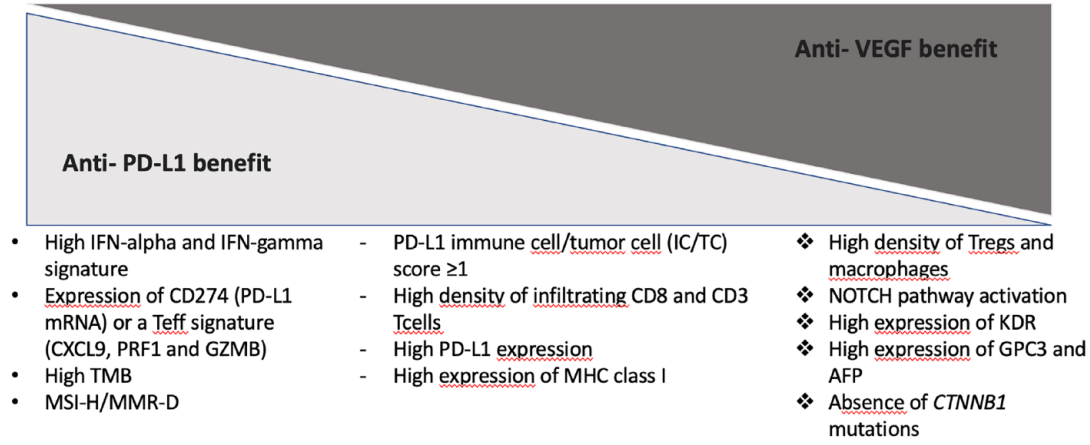

Figure 2. Biological predictors of benefit from ICIs alone and combined with antiangiogenics.
AFP, alpha-fetoprotein; ICIs, immune checkpoint inhibitors; IFN-alpha, interferon alpha; IFN-gamma, interferon-gamma; MHC, major histocompatibility complex; MMR-D, mismatch repair-deficiency; mRNA, messenger ribonucleic acid; MSI-H, microsatellite instability-high; PD-L1, programmed death-ligand 1; TMB, tumor mutational burden; Tregs, regulatory T cells; VEGF, vascular endothelial growth factor.

possibly be informative also for the advanced stage.

While tumor tissue remains the optimal source for identifying tumor-specific biomarkers, liquid biopsy is emerging as an attractive, non-invasive procedure that could overcome the matter of reduced tissue availability, capture tumor heterogeneity, and offer longitudinal treatment monitoring without the need for repeated tumor sampling.[102] Compared to other malignancies, still fewer data are available for HCC, but cell-free DNA, cell-free RNA, extracellular vesicles, and circulating tumor cells all appear promising candidates for identifying a biomarker of interest and tracking on-treatment tumor changes.[103–106] Prospective longitudinal studies have identified some predictive mutational signatures associated with responses to MKIs using circulating tumor DNA. However, the detection of activating mutations in WNT/β-catenin pathway as a feature associated with resistance to ICIs – as shown in previous studies on tissue samples – has not been confirmed with liquid biopsy so far.[107]

Moving forward, multi-omics data, including genomics, transcriptomics, proteomics, and metabolomics offer integrative insights into the molecular mechanisms of HCC development and progression, possibly suggesting reliable tumor biomarkers that could inform treatment selection and sequencing in clinical practice.[108] Even a certain gut microbiome richness is emerging as an intriguing predictor of response or resistance to ICIs and there is increasing interest in evaluating the modulation of the microbiome as a mechanism to regulate the immune composition of the TME.[109] Different plasma proteins and miRNAs with a role in HCC development, tyrosine kinase receptor signaling, and tumor angiogenesis were found to retain prognostic and sometimes predictive significance in retrospective analyses of pivotal trials with MKIs, despite being of limited clinical value in the therapeutic decision-making, lacking of further thorough validation.[110–115] For patients with HCC receiving immunotherapy, PD-L1 expression and TMB levels correlated poorly with clinical outcomes.[45–47] In its place, a genomic signature of pre-existing immunity, including high expression of PD-L1 mRNA, enrichment of inflammation response pathways, and high density of CD8+ T cells in the TME successfully predicted response to atezolizumab plus bevacizumab in a recent study, pointing out that a comprehensive assessment of the dynamic interactions between tumor cells and the TME can more accurately capture susceptibility to immunotherapy.[49] Interestingly, the addition of bevacizumab to atezolizumab was found to enhance the antitumor activity of the anti-PD-L1 agent by targeting VEGF-mediated angiogenesis, regulatory T cells proliferation, and myeloid cell inflammation, all features that promote resistance to ICIs. Therefore, further validation of these translational findings and their integration with the upcoming evidence from the ongoing studies and the relevant clinical data for each subject will hopefully help determine enriched subsets of

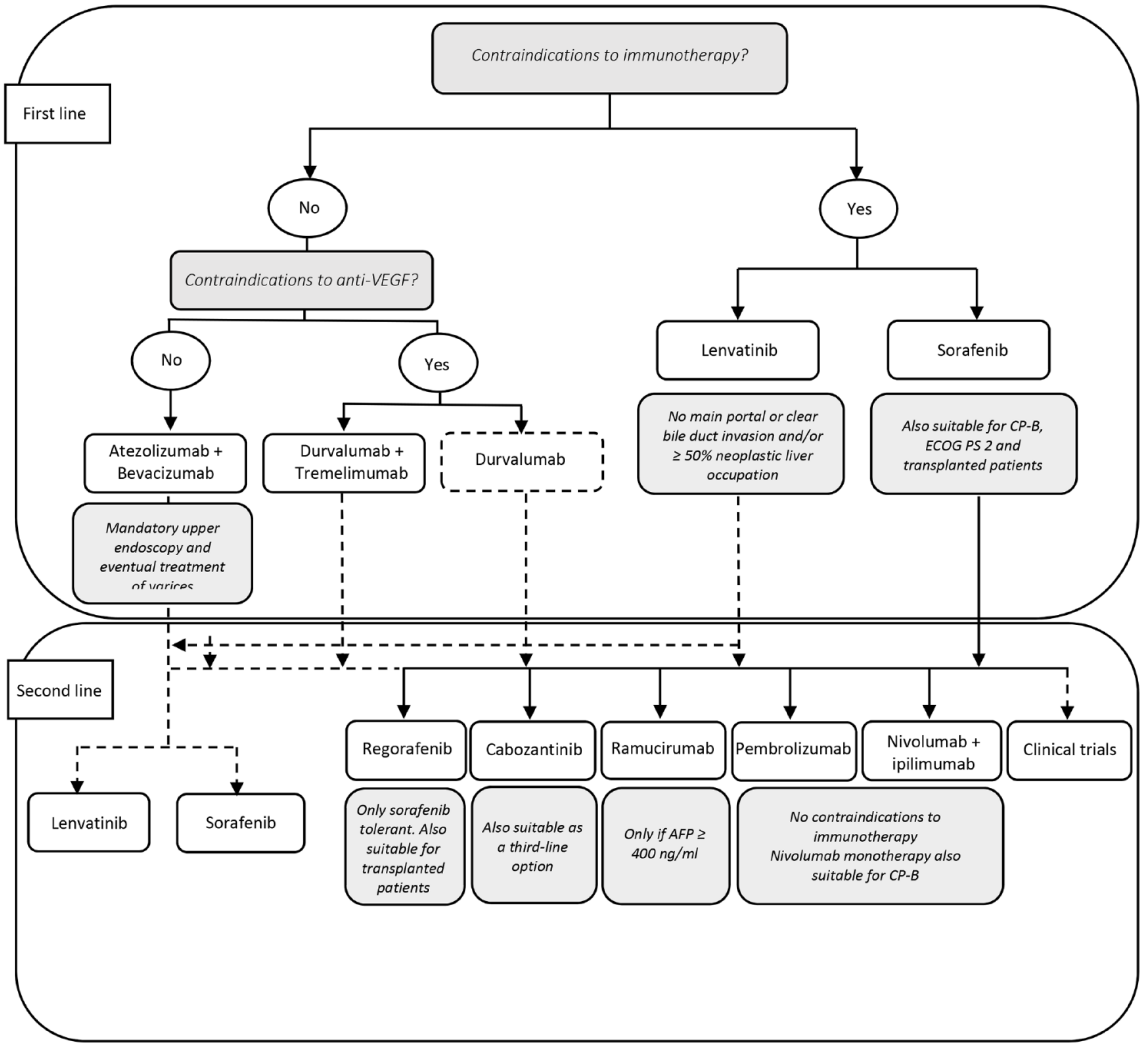

Figure 3. Current treatment algorithm and potential alternative sequences.

patients that could benefit from a specific treatment at each stage with the least toxicity, ultimately guiding the decision-making in routine practice.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contribution(s)

Antonella Cammarota: Conceptualization; Data curation; Methodology; Supervision; Writing – original draft; Writing – review & editing.

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Availability of data and materials
The data used in writing this review are reported in the references.

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