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REVIEW ARTICLE

Immune checkpoint inhibition (ICI) in current systemic therapies for hepatocellular carcinoma (HCC)

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Immune checkpoint inhibition (ICI) has revolutionized cancer therapy, including treatment of hepatocellular carcinoma (HCC) which comprises 80%-90% of all liver cancers, the third most common cause of cancer-related death worldwide. The main targeted pathways are the cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and the programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) checkpoints. Blockade of CTLA-4 with monoclonal antibodies leads to an activation and increase in effector T cells that can interact with tumor cells. Additionally, inhibitory regulatory T cells are reduced, leading to an immunosupportive tumor microenvironment. PD-1/PD-L1 inhibition reduces immunosuppression directly within the tumor tissue and reactivates the immune response to tumor cells. Recently, the HIMALAYA trial has shown that dual ICI with the CTLA-4-blocking antibody tremelimumab and the PD-L1-directed antibody durvalumab (STRIDE regimen) is superior to sorafenib regarding efficacy and safety in advanced HCC and has shown unprecedented long-term survival data for these patients. The combination of PD-L1-directed ICI (atezolizumab) and anti-vascular endothelial growth factor (bevacizumab) significantly improved outcomes compared to sorafenib and has been in clinical use since 2020. Looking at outcome measures for ICI, radiologically assessed endpoints such as progression-free survival and objective response rate only modestly correlate with overall survival. The modified RECIST criteria seem to better identify ICI responders in HCC compared to conventional imaging evaluation criteria. So far, predictive biomarkers in HCC and a robust understanding of the impact of underlying liver diseases are largely lacking. An accurate stratification of patients based on biomarkers and etiology has the potential to further improve outcomes in HCC.

Key words: immune checkpoint inhibition, CTLA-4, PD-1/PD-L1, systemic therapy, HCC, advanced hepatocellular carcinoma, long-term survival

INTRODUCTION

Liver cancer is the sixth most common cancer and third most common cause of cancer-related death worldwide.[1,2] By 2040, incidences of liver cancer are expected to increase to ∼1.4 million.[3] Hepatocellular carcinoma (HCC) comprises 80%-90% of all liver cancers[4,5] and highest incidence rates are found in Africa and Asia where the majority of HCC cases are caused by hepatitis B virus (HBV).[1,6] In Western populations, non-viral etiologies and chronic hepatitis C virus (HCV) infection are prominent risk factors.[7] The overall prognosis for patients with HCC is poor, especially when patients are diagnosed at an advanced stage.[8] For a long period, no major therapeutic progress was achieved since the approval of the tyrosine kinase inhibitor (TKI) sorafenib for systemic therapy of unresectable HCC (uHCC) in 2008.[7]

Immune checkpoint inhibition (ICI) has been one of the most successful improvements of cancer treatments of the last decade in regard to efficacy and safety, greatly improving outcomes and long-term survival chances for cancer patients.[9] Since the marketing authorization of the cytotoxic T-lymphocyte-associated protein-4 (CTLA-4)-directed monoclonal antibody ipilimumab in 2011 for the treatment of metastatic melanoma,[10] several ICIs have been developed and authorized, including additional antibodies targeting CTLA-4 such as tremelimumab[11] as well as antibodies targeting programmed cell death protein 1 (PD-1) (such as nivolumab) and programmed death-ligand 1 (PD-L1) (such as atezolizumab and durvalumab).[9] ICIs are now leading the field of cancer therapy, as they are currently

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being used in numerous cancer indications, with increasing use in adjuvant or neoadjuvant settings.[9,12] The impact of ICIs on cancer medicine is reflected in the 2018 Nobel Prize in Medicine awarded to the two immunologists who were decisively involved in developing the concept of ICI therapy, James Allison (USA) and Tasuku Honjo (Japan).[13]

Among other tumor entities, ICIs targeting both PD-1/PD-L1 and CTLA-4 pathways have found their way into the treatment of HCC. In this article, we describe the current role of ICIs in the treatment of HCC and discuss their potential future development.

PRINCIPLES OF ICIS

For adequate immune function and to prevent autoimmunity, it is paramount that the immune system can differentiate between the endogenous and exogenous cells such as infectious microbes, or neoplastic altered body cells such as cancer cells. Within the immune system, there are molecules known as checkpoints that help maintain a balance between immune activation and suppression. These checkpoints prevent excessive immune responses that can lead to autoimmune diseases, but they can also be exploited by cancer cells to evade immune recognition and attack. The concept of cancer immunotherapy is to inhibit those checkpoints and thus to release the 'brakes' on the immune system, enabling T cells and other immune cells to recognize and attack cancer cells more effectively. An overview over phases of the cancer-immunity cycle and cancer therapies that modulate the respective phases is presented in Figure 1 (modified after Chen and Mellman, 2013).[14]

The initial phase of the immune recognition process is the binding of the T-cell receptor (TCR), located on the surface of a T cell, to an antigen displayed by the major histocompatibility complex on the surface of an antigen-presenting cell (APC) (Figure 1, phase 2).[15] Binding between T cells and APCs is facilitated by CD28 on the T cell and B7 ligands (CD80/86) on APCs; this binding leads to effector T-cell activation and proliferation (Figure 1, phase 3). Subsequently, there are several pathways in place that are involved in the regulation of immune responses, the most prominent being the CTLA-4 and the PD-1 checkpoints.[15]

CTLA-4

CTLA-4 can be considered to be a leading regulator of cellular immune response pathways, as it regulates T-cell activation and response at an initial stage, within the lymph nodes.[15] CTLA-4 is a receptor on the T-cell surface; however, in resting naïve T cells, CTLA-4 is located primarily in the intracellular compartment.[16] Upon binding of a TCR to a

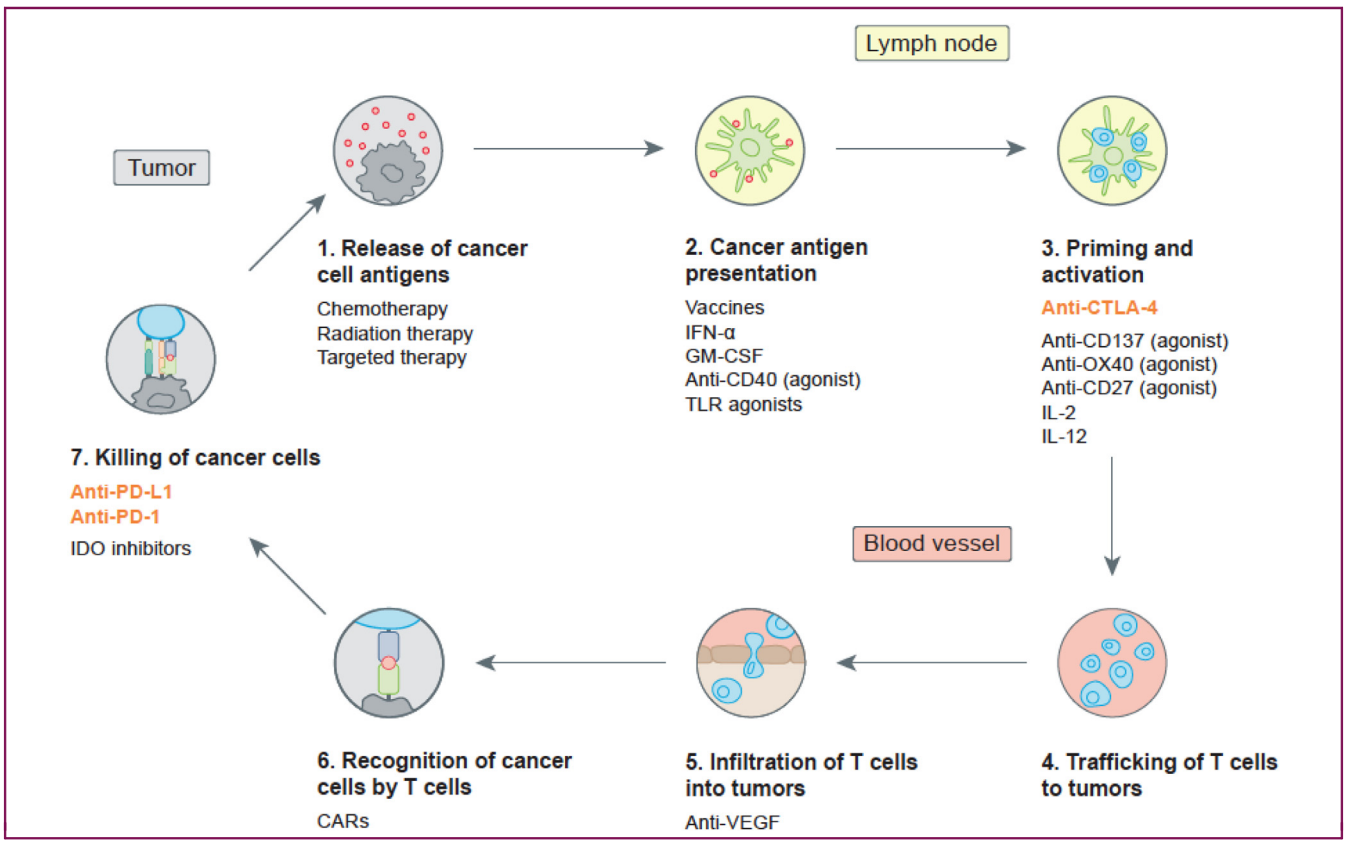

Figure 1. Phases of the cancer-immunity cycle and therapies that modulate them, modified after Chen and Mellman (2013).[14] The cancer-immunity cycle can be subdivided into phases that take place in different compartments, i.e. tumor tissue (phases 1, 6, 7), lymph nodes (phases 2, 3) and blood vessels (phases 4, 5). Cancer therapies that modulate the respective phases are depicted accordingly, anti-CTLA-4 and anti-PD-L1/anti-PD-1 are highlighted in orange.
CARs, chimeric antigen receptors; CD27/40/137, cluster of differentiation 27/40/137; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; GM-CSF, granulocyte—macrophage colony-stimulating factor; IDO, indoleamine 2,3-dioxygenase; IFN-α, interferon-α; IL-2/12, interleukin 2/12; OX40 (CD134), cluster of differentiation 134; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TLR, Toll-like receptor; VEGF, vascular endothelial growth factor.

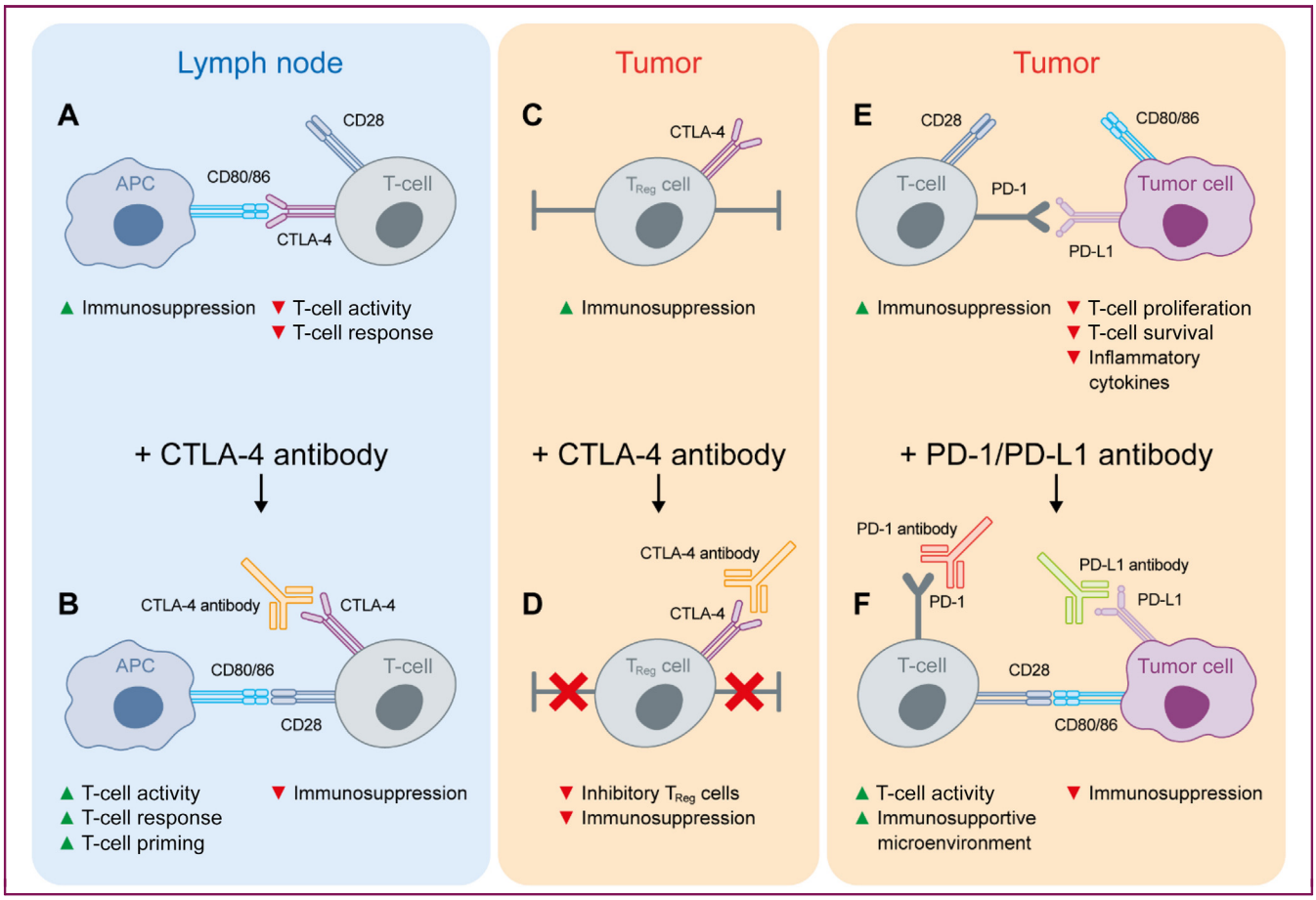

Figure 2. Effects of CTLA-4-directed and PD-1/PD-L1-directed therapies on T cells in lymph nodes and tumor tissue as well as effects on regulatory T cells (T_{Reg} cells). (A) Once CTLA-4 is expressed on the surface of T cells within the lymph node, it can bind to CD80/86, thereby reducing T-cell activity and response. (B) When CTLA-4 is blocked by an antibody, CD80/86 is free to bind to CD28 again, thereby reactivating the immune response by increasing T-cell activity and T-cell response. (C) Inhibitory T_{Reg} cells can promote an immunosuppressive tumor microenvironment. (D) When CTLA-4 on the surface of T_{Reg} cells is blocked, they no longer exert their immunosuppressive effects. (E) Within the tumor tissue, the interaction between PD-1 (on the surface of immune cells) and PD-L1 (on the surface of cancer cells) can reduce T-cell proliferation, T-cell survival and inflammatory cytokines, causing an immunosuppressive tumor microenvironment. (F) When PD-1 or PD-L1 is blocked by an antibody, the inhibitory effects are reversed, leading to an immunosupportive microenvironment.

APC, antigen-presenting cell; CD28/80/86, cluster of differentiation 28/80/86; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

respective antigen on an APC, CTLA-4 expression on the surface of the activated T cell is rapidly up-regulated. Thus, CTLA-4 is an important and early contributor to the development of immune tolerance.[17] Once CTLA-4 is abundant on the T-cell surface, it can bind to B7 ligands with a higher affinity than CD28 and antagonize the activation signals by limiting co-stimulatory signaling through CD28. This terminates the T-cell response and inhibits further effector T-cell activity (see Figure 2A).[17] When CTLA-4 is blocked, e.g. by an antibody such as tremelimumab or ipilimumab, B7 ligands are again free to bind to CD28, so effector T-cell activity and response is maintained and potentiated (see Figure 2B). In cancer, this reactivation can confer immunity on a secondary response to tumor cells and subsequent tumor rejection.[17] Besides increasing effector T-cell activity, CTLA-4-directed therapies can also deplete local inhibitory intratumoral regulatory T cells (T_{Reg} cells), thereby directly changing the tumor microenvironment, in particular reducing immunosuppression (Figure 2D).[18] It has also been shown that a single dose of a CTLA-4 antibody can enhance formation of CD8+ memory T cells as well as their function and maintenance.[17,19] Memory T cells are key to establishing long-term immunological memory.[18] Furthermore, CTLA-4 blockade can broaden the peripheral TCR repertoire.[20,21]

PD-1/PD-L1

Another major immune pathway is the PD-1/PD-L1 checkpoint. PD-1 is a receptor located on T cells as well as on other immune cells such as B cells and myeloid cells that regulates T-cell function.[15] Binding of PD-1 to its receptor PD-L1, which is expressed both on APCs and tumor cells, inhibits T-cell activation/proliferation, reduces T-cell survival and reduces production of inflammatory cytokines such as interferon-γ, tumor necrosis factor, and interleukin 2 (Figure 2E).[22] Therefore, prolonged interaction between PD-1 and PD-L1 can deliver a surplus of inhibitory signals that can cause a shift to an immunosuppressive environment. In various tumor types, PD-L1 can be widely expressed on the surface of cancer cells.[23] Also, PD-1 overexpression on T cells is a hallmark of T-cell exhaustion that occurs in cancers.

Taken together, the increased interaction between PD-1 and PD-L1 in cancer results in immunosuppression and impaired immunological tumor control.[15]

PD-1-directed antibodies (such as pembrolizumab or nivolumab) and/or PD-L1-directed antibodies (such as durvalumab and atezolizumab) disrupt binding of PD-1 and PD-L1, thereby preventing immunosuppression and reshaping tumor microenvironment back to an immunosupportive microenvironment (see Figure 1, phase 7 and Figure 2F).

Synergistic/complementary effects of combined CTLA-4 and PD-1/PD-L1 blockade

The blockade of both CTLA-4 and PD-1/PD-L1 with monoclonal antibodies has stimulatory effects on T-cell activity and can reduce immunosuppression. However, the timing and compartments where these effects are triggered differ. CTLA-4 blockade stimulates T-cell activity in the priming phase within the lymph nodes, where new activated effector T cells are created, thereby increasing activation of T cells and creating a more diverse T-cell response.[15] Within the tumor microenvironment, CTLA-4 can be expressed on infiltrating T_{Reg} or tumor cells. The inhibitory effects of intratumoral T_{Reg} cells on cytotoxic T lymphocytes can lead to the suppression of effector T cells.[24]

Blocking PD-1/PD-L1 affects the effector phase primarily in the peripheral tumor microenvironment to restore/enhance the function of already existing effector T cells that have been inactivated/exhausted.[15] Therefore, a simultaneous blockade of CTLA-4 and PD-1/PD-L1 can work synergistically and have strong additive and longer-lasting immune effects. Cell profiling of T cells has indeed revealed that the effects of a combined CTLA-4 and PD-1/PD-L1 blockade on T cells are largely additive in nature.[25] Additionally, there are effects that only result from a combination of the two, e.g. a unique modulation of terminally differentiated effector CD8+ T cells.[25] In a clinical phase Ib/II study, combined CTLA-4 and PD-1/PD-L1 produced an initial burst of peripheral T cells within patients receiving a single high dose of tremelimumab followed by durvalumab monotherapy.[26] The additive and synergistic mechanistic effects are also reflected in clinical outcomes, as combined CTLA-4 and PD-1/PD-L1 blockade has been proven to increase long-term survival for patients, e.g. as shown for metastatic melanoma, metastatic non-small-cell lung cancer and uHCC.[11,27-29]

EVOLUTION OF ICI THERAPIES IN uHCC

The liver plays a central role in the sensing of potential pathogens absorbed from the gut and the response to systemic inflammation.[30,31] In HCC, several dysregulations of immune responses and inflammatory activity have been identified.[30,32] These include immune escape/evasion of tumor cells, e.g. by antigen-presenting inhibition, tumor-associated macrophage proliferation, overexpression of CTLA-4 and PD-L1 and increased immunosuppressive cytokines.[31,33,34] Therefore, it was hypothesized that stimulating the immune response may be effective in HCC, facilitate tumor clearance and inhibit tumor progression.[33,34] Indeed, immune-stimulatory therapies, e.g. blockade of CTLA-4 and PD-1/PD-L1 with monoclonal antibodies and ICI combination therapies with antiangiogenic compounds, have shown improved outcomes in uHCC in recent years and were subsequently approved.[35] The next paragraphs and Table 1 give a selected overview of pivotal trials in ICI-based treatments for uHCC (Figure 3).

ICI monotherapy

In first-line (1L) therapy of uHCC, the phase III CheckMate 459 trial investigated nivolumab versus sorafenib in patients with uHCC (Figure 3). Median overall survival (OS) was similar in the nivolumab and sorafenib groups (16.4 versus 14.7 months, P = not significant).[36,37] The randomized controlled phase III HIMALAYA three-arm study evaluated the efficacy and safety of durvalumab plus tremelimumab combination and durvalumab monotherapy versus sorafenib in the 1L treatment of patients with uHCC. Durvalumab monotherapy was non-inferior to sorafenib, hereby meeting a secondary endpoint, but no superiority (median OS 16.6 versus 13.8 months).[11] Similarly, the RATIONALE-301 phase III trial met its primary endpoint of median OS non-inferiority of treatment with the PD-1 antibody tislelizumab versus sorafenib (15.9 versus 14.1 months).[38]

In the second-line treatment of uHCC, the PD-1 antibody pembrolizumab showed a median OS of 13.2 months for uHCC patients previously treated with sorafenib in the phase II trial KEYNOTE-224.[39] Based on these results, pembrolizumab was approved by the Federal Drug Administration (FDA) for previously treated uHCC patients, however not in the European Union (EU) as the results did not meet the regulatory requirements for approval. The phase III KEYNOTE-240 trial with pembrolizumab + best supportive care (BSC) versus placebo + BSC confirmed numerically higher median OS for pembrolizumab without reaching statistical significance.[40] The PD-1 antibody camrelizumab showed a comparable median OS with 13.8 months in later lines of uHCC in a phase II trial.[41]

In the nivolumab monotherapy arm of the phase I/II CheckMate 040 trial, a subgroup of previously treated uHCC patients showed favorable responses to treatment which resulted in accelerated FDA approval of nivolumab for previously treated uHCC patients.[42] The approval was however withdrawn in 2021. Taken together, ICI monotherapy does not seem to convey a statistically significant OS benefit for patients with uHCC when compared with sorafenib in the 1L, although the use of ICI monotherapy in earlier and later lines of uHCC may convey OS prolongation.

ICI plus ICI combinations

A combination of two ICIs targeting different immune checkpoint pathways has also been evaluated in clinical trials. Thus, the combination of the CTLA-4 antibody ipilimumab with nivolumab was evaluated in the above-mentioned CheckMate 040 trial in patients previously treated with sorafenib.[43] In arm A with higher initial

Table 1. Selected trials involving ICI in the treatment of uHCC

Study (year[a])	Population	Treatment	mOS, months (95% CI)	OS rate months, %	mPFS, months (95% CI)	TRAEs grade ≥3, %	irAEs requiring immunosuppressive treatment (%)
ICI monotherapies							
CheckMate 459 (2019)[36,37] $N = 743$	uHCC, Child—Pugh A, no prior systemic therapy	Nivolumab (NIVO) versus sorafenib (SORA)	16.4 for NIVO (13.9-18.4) versus 14.7 for SORA (11.9-17.2) (HR 0.85)	N/A	3.7 for NIVO (3.1-3.9) versus 3.8 for SORA (3.7-4.5) (HR 0.93)	21.8 for NIVO versus 49.6 for SORA	8 (hepatitis), 3 (rash) for NIVO versus <1 (rash) for SORA
HIMALAYA (2022)[11,29] $N = 1171$	uHCC, Child—Pugh A, BCLC stage B/C, no prior systemic therapy	Durvalumab (DURVA) versus sorafenib (SORA)	16.6 for DURVA (14.1-19.1) 13.8 for SORA (12.3-16.1) (HR 0.86)	18-month OS 47.4 for DURVA 41.5 for SORA 24-month OS 39.6 for DURVA 32.6 for SORA 36-month OS 24.7 for DURVA 20.2 for SORA 48-month OS 19.3 for DURVA 15.1 for SORA	3.7 for DURVA (3.2-3.8) 4.1 for SORA (3.8-5.5) (HR 1.02)	12.9 for DURVA 36.9 for SORA	10.9 for DURVA
RATIONALE-301 (2022)[38] $N = 674$	uHCC, Child—Pugh A, no prior systemic therapy	Tislelizumab (TIS) versus sorafenib (SORA)	15.9 for TIS (13.2-19.7) versus 14.1 for SORA (12.6-17.4) (HR 0.85)	N/A	2.2 for TIS versus 3.6 for SORA (HR 1.1)	48.2 for TIS versus 65.4 for SORA	N/A
Double ICI combinations							
CheckMate 040 (2020)[43,45] $N = 148$	Previously treated uHCC, Child—Pugh A	Ipilimumab (IP) + nivolumab (NI) Arm A: 4× (3 mg/kg IP + 1 mg/kg NI q3w) → 240 mg NI q2w versus arm B: 4× (1 mg/kg IP + 3 mg/kg NI q3q) → 240 mg NI q2w versus arm C: 1 mg/kg IP + 3 mg/kg NI q6w	22.2 for arm A (9.4-54.8) versus 12.5 for arm B (7.6-16.4) versus 12.7 for arm C (7.4-30.5)	12-month OS 61.0 for arm A versus 56.0 for arm B versus 51.0 for arm C versus 24-month OS 48.0 for arm A versus 30.0 for arm B versus 42.0 for arm C versus 36-month OS 42.0 for arm A versus 26.0 for arm B versus 30.0 for arm C versus 60-month OS 29.0 for arm A versus 19.0 for arm B versus 21.0 for arm C versus	N/A	53.0 for arm A versus 29.0 for arm B versus 31.0 for arm C	20 (hepatitis), 35 (rash) for arm A versus 12 (hepatitis), 29 (rash) for arm B versus 6 (hepatitis), 17 (rash) for arm C
HIMALAYA (2022)[11,29] $N = 1171$	uHCC, Child—Pugh A, BCLC stage B/C, no prior systemic therapy	Tremelimumab + durvalumab (STRIDE) versus sorafenib (SORA)	16.4 for STRIDE (14.2-19.6) 13.8 for SORA (12.3-16.1) (HR1 0.78, $P = 0.0035$)	18-month OS 48.7 for STRIDE 41.5 for SORA 24-month OS 40.5 for STRIDE 32.6 for SORA 36-month OS 30.7 for STRIDE 20.2 for SORA 48-month OS 25.2 for STRIDE 15.1 for SORA	3.8 for STRIDE (3.7-5.3) 4.1 for SORA (3.8-5.5) (HR 0.90)	25.8% for STRIDE 36.9% for SORA	20.1 for STRIDE

Continued

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Table 1. Continued

Study (year[a])	Population	Treatment	mOS, months (95% CI)	OS rate months, %	mPFS, months (95% CI)	TRAEs grade ≥3, %	irAEs requiring immunosuppressive treatment (%)
ICI combinations with antiangiogenesis							
IMbrave150 (2020)[48,49] $N = 501$	uHCC, Child–Pugh A, no prior systemic therapy	Atezolizumab + bevacizumab (ATBE) versus sorafenib (SORA)	19.2 for ATBE (17.0-23.7) versus 13.4 for SORA (11.4-16.9) (HR 0.66, $P < 0.001$)	12-month OS 67.2 for ATBE versus 54.6 for SORA 18-month OS 52.0 for ATBE versus 40 for SORA	6.9 for ATBE (5.7-8.6) versus 4.3 for SORA (4.0-5.6) (HR 0.65, $P < 0.001$)	43 for ATBE versus 46 for SORA	12.2 for ATBE versus NE for SORA
COSMIC-312 (2021)[50] $N = 837$	uHCC, Child–Pugh A, no prior systemic therapy	Atezolizumab + cabozantinib (ATCA) versus sorafenib (SORA)	15.4 for ATCA (13.7-17.7) versus 15.5 for SORA (12.1-NE) (HR 0.90)	12-month OS 61.8 for ATCA versus 58.2 for SORA	6.8 for ATCA (5.6-8.3) versus 4.2 for SORA (2.8-7.0) (HR 0.63, $P = 0.0012$)	75.5 for ATCA versus 57.0 for SORA	7 for ATCA versus NE for SORA
LEAP-002 (2022)[51] $N = 794$	uHCC, Child–Pugh A, no prior systemic therapy	Pembrolizumab + lenvatinib (PELE) versus lenvatinib (LENV)	21.2 for PELE (19.0-23.6) versus 19.0 for LENV (17.2-21.7) (HR 0.84)	24-month OS 43.7 for PELE versus 40.0 for LENV	8.2 for PELE (6.3-8.3) versus 8.1 for LENV (6.3-8.3) (HR 0.834)	62.5 for PELE versus 57.5 for LENV	N/A
SHR-1210-III-310 (2022)[52] $N = 543$	uHCC, Child–Pugh A, BCLC stage B/C, no prior systemic therapy	Camrelizumab + rivoceranib (CARI) versus sorafenib (SORA)	22.1 for CARI (19.1-27.2) versus 15.2 for SORA (13.0-18.5) (HR 0.62, $P < 0.0001$)	12-month OS 76.5 for CARI versus 60.8 for LENV	5.6 for CARI (5.5-6.3) versus 3.7 for SORA (2.8-3.7) (HR 0.52, $P < 0.0001$)	80.9 for CARI versus 52.4 for SORA	

P values are only given in case of (prespecified) statistical significance.
HR, hazard ratio; irAEs, Immune-related adverse events; mOS, median overall survival; mPFS, median progression-free survival; NA, not available; NE, not estimable; NR, not reached; TRAEs, treatment-related adverse events.
[a]Date refers to most recent published data.

ipilimumab doses (3 mg/kg q3w) added to nivolumab, median OS was considerably higher (22.2 months) than in arms B and C with lower initial ipilimumab doses (1 mg/kg q3w and 1 mg/kg q6w, respectively) added to nivolumab (12.5 and 12.7 months, respectively). Based on these results, the combination of ipilimumab and nivolumab was approved by the FDA for uHCC patients previously treated with sorafenib.[44] Recently, 5-year follow-up data for the CheckMate 040 trial were published. The ipilimumab/nivolumab combination regimen showed sustained OS and long-term survival rates, especially for the regimen with the higher initial ipilimumab dose (60-month OS: arm A: 29%; arm B: 19%; arm C: 21%).[45]

The above-mentioned phase III HIMALAYA trial investigated the combination of the CTLA-4 inhibitor tremelimumab and PD-L1 inhibitor durvalumab (STRIDE: Single Tremelimumab Regular Interval Durvalumab) versus sorafenib.[11] The addition of a single priming dose of tremelimumab to regular interval durvalumab monotherapy had already shown a numerical median OS benefit in a phase I/II study.[26] In HIMALAYA, the STRIDE regimen lead to a statistically significant median OS benefit over sorafenib [16.4 versus 13.8 months, hazard ratio (HR) 0.78, $P = 0.0035$] with a median follow-up time of 33.2 months. Based on these findings, the combination of durvalumab and tremelimumab has been approved for the treatment of uHCC by the FDA in October 2022 and by the European Medicines Agency (EMA) in February 2023.[46,47] Recently published exploratory 4-year follow-up data of HIMALAYA revealed unprecedented long-term survival rates for tremelimumab and durvalumab versus sorafenib (48-month survival rate: 25.2% versus 15.1%).[29]

ICI combinations with antiangiogenic drugs

The phase III IMbrave150 trial evaluated the combination of the PD-L1 inhibitor atezolizumab and the anti-vascular endothelial growth factor (VEGF) antibody bevacizumab versus sorafenib.[48,49] With an OS of 19.2 versus 13.4 months (HR 0.66, $P < 0.001$) and a median follow-up duration of 15.6 months,[49] the combination of atezolizumab and bevacizumab was significantly superior to sorafenib. Based on these results, atezolizumab and bevacizumab was approved by the FDA and the EMA in 2020 for 1L treatment of uHCC. Further trials investigated the combination of PD-1/PD-L1 and VEGF antibodies or PD-1/PD-L1 ICIs combined with antiangiogenic TKIs. The combination of atezolizumab with cabozantinib in the phase III COSMIC-312 trial did not show median OS benefit versus sorafenib (15.4 versus 15.5 months, $P = 0.44$).[50] In the phase III LEAP-002 trial, the combination of pembrolizumab and lenvatinib failed to show a statistically significant longer median OS over lenvatinib alone (21.2 versus 19 months).[51] On the contrary, the interim analysis of a global phase III trial (SHR-1210-III-310) with a predominantly Asian population showed significantly longer median OS for the combination of the PD-1 antibody camrelizumab with the VEGF receptor 2-targeted inhibitor rivoceranib as compared to

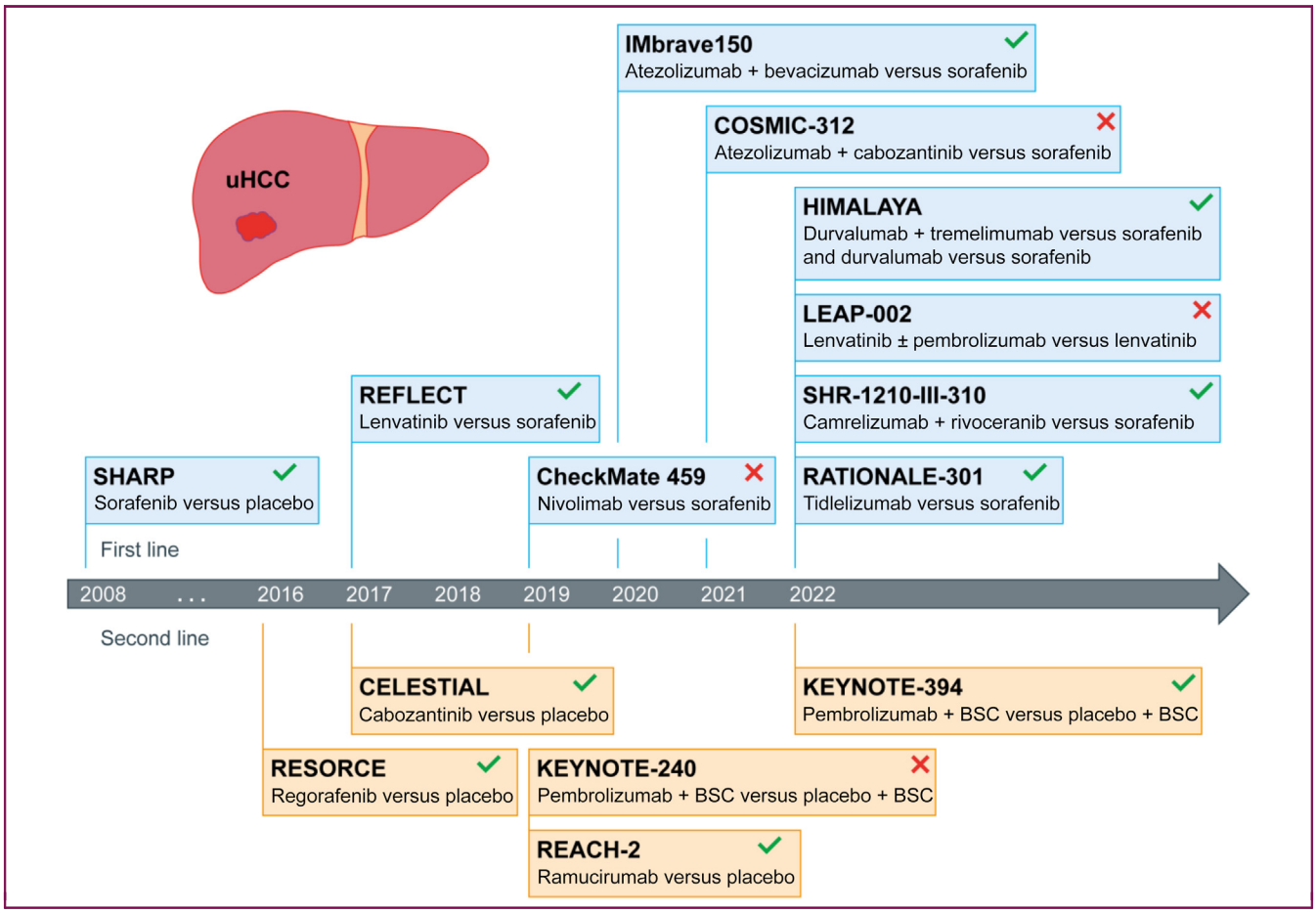

Figure 3. Evolution of uHCC therapy from 2008 to today. Pivotal phase III trials (dates denote first published results) for first-line therapy of HCC are depicted above the time beam, and pivotal phase III trials for second (and further)-line therapy of HCC are depicted beneath the time beam. Green checkmarks denote if the trial was statistically superior or non-inferior to the comparator, and red crosses denote if the trial failed to show statistically significant superiority to the comparator.
uHCC, unresectable hepatocellular carcinoma.

sorafenib {22.1 [95% confidence interval (CI) 19.1-27.2] versus 15.2 [13.0-18.5] months; HR 0.62 [95% CI 0.49-0.80]; one-sided $P < 0.0001$}.[52] Based on these results, a new drug application has been submitted to the FDA in May 2023, seeking approval of rivoceranib in combination with camrelizumab for the frontline treatment of patients with uHCC. As 75% of the patients treated with rivoceranib and camrelizumab had chronic hepatitis B, it will be of great interest to learn how this combination treatment will work in Western or African patients.

ICI in adjuvant setting and in combination with locoregional treatment

Several trials testing adjuvant ICI and ICI combinations are currently running, e.g. CheckMate 9DX,[53] EMERALD-2,[54] IMbrave050[55] and KEYNOTE-937.[56] The open-label IMbrave050 trial recently reported superiority of atezolizumab and bevacizumab regarding recurrence-free survival in an adjuvant setting in patients at high risk of recurrence following resection or ablation (HR 0.72, $P = 0.012$).[55]

In locoregional therapy of HCC, the combination of durvalumab and bevacizumab with transarterial chemoembolization (TACE) is currently being investigated in the EMERALD-1 trial.[57] Pembrolizumab ± lenvatinib with concurrent TACE is being investigated in the LEAP-012 trial.[58] Another development in ICI therapy for HCC is the combination of three agents. The EMERALD-3 trial is evaluating double ICI therapy (tremelimumab and durvalumab) ± lenvatinib with concurrent TACE in intermediate HCC.[59] The MORPHEUS-Liver phase Ib/II study showed that the combination of atezolizumab and bevacizumab with tiragolumab, a novel ICI targeting TIGIT (T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains), can lead to improved antitumor responses compared to atezolizumab + bevacizumab alone.[60] Remarkably, objective response rate (ORR) for atezolizumab + bevacizumab in MORPHEUS-Liver was only 11% compared to 30% in Imbrave150, which further shows that radiologically assessed endpoints can vary substantially.

CLINICAL ASPECTS OF ICI THERAPIES IN uHCC

Responses and safety in ICI therapies

A recent meta-analysis of 29 studies has shown that ICI monotherapies with PD-1/PD-L1 inhibitors lead to improved ORR, DCR, progression-free survival (PFS) and OS compared

to sorafenib and ICI combination therapies (both ICI + anti-VEGF and double ICI) lead to improved ORR, DCR, PFS and OS compared to ICI monotherapy.[61]

In regard to ICI + anti-VEGF, in the IMbrave150 trial, responses were higher with atezolizumab + bevacizumab than with sorafenib, the ORR was 3× higher (30% versus 11%) and the DCR was 74% versus 55%.[49] After 18 months, survival rate was 52% for patients on atezolizumab + bevacizumab and 40% for patients on sorafenib. The incidence of treatment-related adverse events (TRAEs) grade ≥3 was similar in both groups 43% versus 46% and the incidence of immune-related adverse events (irAEs) that required immunosuppressive treatment was 12.2% for atezolizumab + bevacizumab.[62] When looking at subgroups of IMbrave150, there was a trend that patients with α-fetoprotein (AFP) <400 ng/ml at baseline and viral HCC etiology profited more from atezolizumab + bevacizumab versus sorafenib. An additional analysis of the IMbrave150 trial showed that for patients stratified by age group (<65 years, ≥65-<75 years and ≥75 years), median OS was longer for all patients receiving atezolizumab + bevacizumab versus sorafenib.[63] The IMbrave150 trial results regarding ORR, OS and PFS were also recently confirmed in a real-world setting in German HCC patients.[64]

In the phase III HIMALAYA trial, the ORR was 4× higher in the dual ICI group compared to the sorafenib group (20.1% versus 5.1%).[11] While the DCR was similar in both arms (60.1% versus 60.7%), survival rates were nearly 45% at 3 years and 36% at 4 years in participants who achieved disease control with tremelimumab and durvalumab compared to sorafenib (27.9% and 20.3%).[29] After 18 months, survival rate was 48.7% for patients on tremelimumab and durvalumab and 41.5% for patients on sorafenib; the prespecified 36-month survival rate was 30.7% in the tremelimumab and durvalumab cohort and 20.2% in the sorafenib cohort. In June 2023, the 4-year OS follow-up of HIMALAYA was reported. After 48 months, 25.2% of tremelimumab and durvalumab patients were still alive compared to 15.1% of patients treated with sorafenib.[29] The incidence of TRAEs was lower for the tremelimumab and durvalumab regimen compared to sorafenib, with TRAEs grade ≥3 of 25.8% for tremelimumab and durvalumab and 36.9% for sorafenib. The incidence of irAEs that required immunosuppressive treatment was 20.1% for tremelimumab and durvalumab and ∼10% for durvalumab monotherapy. The majority occurred within the first 3 months of treatment and few irAEs led to treatment discontinuation (5.7% for tremelimumab and durvalumab and 2.6% for durvalumab monotherapy).[65] While irAEs were correlated with numerically improved OS for patients treated with tremelimumab and durvalumab, this dual ICI therapy benefitted patients regardless of irAEs.[66] Long-term survival (≥3 years) was achieved in patients treated with tremelimumab and durvalumab irrespective of irAE occurrence versus sorafenib.[29] In the subgroup analysis, there was a trend in OS benefit for tremelimumab and durvalumab versus sorafenib (HR <1) in all etiology subgroups (HBV, HCV and non-viral) when subsets were adjusted for prognostic factor imbalances in the HCV cohort.[67] At 4-year update, all subgroups favored tremelimumab and durvalumab regarding OS, including the HCV cohort.[29] A *post hoc* analysis of the HIMALAYA trial showed that the STRIDE regimen showed a favorable benefit—risk profile compared with sorafenib across all albumin—bilirubin (ALBI) score subgroups, including patients with moderate/severe liver function impairment (ALBI 2/3).[68] The ALBI score gives an estimate of liver function and can allow for a more detailed prognostic classification of HCC.[69] Treatment with tremelimumab and durvalumab was associated with a delayed time to deterioration of patient-reported quality of life, role functioning or disease-related symptoms compared with sorafenib.[70]

Clinical endpoints in the era of immune therapies

Median OS (mOS) is the gold standard for assessing efficacy in oncological clinical trials.[71,72] However, OS is characterized by the survival curve over the entire follow-up time, not just the median, as mOS only describes the outcome at a single timepoint and may not adequately represent the treatment benefit with ICIs which are characterized by their ability to induce a durable response.[71-74] Compared to immunotherapies, cytotoxic and molecularly targeted agents often show direct antitumor effects with early clinical response. ICIs demonstrate unique kinetics that involve building a cellular immune response before influencing tumor burden or patient survival and therefore start to show in long-term follow-up.[71,75] This leads to a plateau in the tail of the OS curve, which is not accurately captured by the endpoint mOS.

Indeed, both the CheckMate 040 trial with ipilimumab and nivolumab and the HIMALAYA trial with tremelimumab and durvalumab have reported high rates of long-term survival with double ICI (CheckMate 040: 5-year survival rate: 29.0; HIMALAYA: 4-year survival rate: 25.2%). Long-term survival is an important endpoint that complements mOS, especially for ICI therapies.

Radiological evaluation criteria and outcomes

In many cancers including HCC, disease progression is assessed radiologically and measured in endpoints such as PFS, time to progression (TTP) or ORR. How accurate these endpoints are as surrogates for OS is under debate. Several studies have investigated the relationship between PFS, TTP and ORR to OS in HCC. A meta-analysis of 21 phase III trials found only a modest correlation between PFS and TTP with OS in systemic HCC therapy.[76]

The commonly used RECIST criteria (v. 1.1) are used to assess radiological endpoints such as PFS and TTP and radiological responses such as ORR and DCR. To better address the particularities of HCC, the RECIST criteria were modified in 2010.[77] Using these modified RECIST (mRECIST) criteria can result in higher registered ORRs in tumors treated with molecular therapies, and those responses were shown to be associated with improved survival.[78] However, in light of novel treatments for HCC such as ICI combination

therapies, it has been proposed that there is a need to further refine some concepts of mRECIST performance.[78,79] To specifically evaluate responses for ICI, the immune RECIST (iRECIST) 1.1 criteria have been established.[80] In early trials of ICI, unique response patterns termed 'pseudoprogressions' were reported using the RECIST criteria, although some patients who showed progression based on RECIST actually showed late but deep and durable responses.[80] However, a comparison of using mRECIST criteria versus RECIST 1.1 versus iRECIST 1.1 criteria for the evaluation of responses and outcomes in HCC patients receiving PD-1 antibody therapy has revealed that mRECIST was more powerful in discriminating between responders and non-responders.[79] ORRs were numerically but not significantly higher with mRECIST versus RECIST 1.1 and iRECIST 1.1.

In conclusion, the surrogacy of radiologically assessed endpoints such as PFS and ORR to OS in HCC remains uncertain. Although these endpoints are useful to accelerate drug approval and to potentially capture OS benefit early, they are subjective and there is also heterogeneity between different radiological criteria.[81] For ICI therapies, there is also the problem that late responses, as described before as being inherent to ICI, may not be captured by endpoints such as median PFS although they may be durable and deep. Also, depending on the used RECIST criteria, pseudoprogressions might falsely reflect the actual response to treatment.

Prediction of response to ICI-based treatment for HCC

To date, there is no (genetic) biomarker recommended by guidelines that can reliably predict susceptibility to HCC and predictive biomarkers play almost no role in HCC therapy.[82] AFP is one of the very few diagnostic markers used in HCC, but it has clear limitations such as a low sensitivity and specificity. Several studies showed disappointing or even contradictory results.[82] The most common mutations in HCC (e.g. in the *TERT* promoter, *CTNNB1* and *TP53*) are not druggable and only ∼25% of liver tumors contain potentially targetable drivers.[83]

HCC can have viral and non-viral etiologies. Infection with HBV or HCV is a major risk factor.[7] Non-viral etiology of HCC is however often multifactorial and cannot easily be attributed to a single cause, for intrinsic and extrinsic factors that can trigger HCC development and influence response to therapy, see Figure 4.

For example, metabolic dysfunction-associated steatotic liver disease (MASLD) that can result from metabolic syndrome or diabetes mellitus is an important etiology of HCC, particularly in the West.[7] Also, alcohol-related liver disease (ALD) caused by excessive alcohol consumption can trigger HCC.[84] The distinction between MASLD and ALD can however be challenging, as excessive alcohol consumption has been observed in ∼30% of obese patients.[85] In regard to ICI therapies in HCC, a meta-analysis has shown that both ICI + anti-VEGF as well as double ICI in HCC lead to significant survival advantage over control for non-viral as well as viral etiologies.[86] However, after a paper published by Pfister et al. in 2021, which reported reduced response of metabolic dysfunction-associated steatohepatitis-triggered HCC to ICI,[87] the discussion on the influence of HCC etiology on response to ICI therapy is controversial.

CONCLUSION AND FUTURE DIRECTIONS

Two different combination therapies have recently become available as systemic 1L treatment options for patients with HCC. Accordingly, a current consultation version of the German guideline for the treatment of HCC recommends that a 1L therapy with either the combination of atezolizumab and bevacizumab or the combination of durvalumab and tremelimumab should be offered to HCC patients in Child—Pugh stage A and Barcelona Clinic Liver Cancer (BCLC) B or C, with distant metastases or tumor location that cannot be controlled or resected locoregionally.[88] The individual benefit of these two treatment options may be related to the specific adverse effects of these therapies, but remains to be clarified in future studies. The recommended second-line therapy after failure to the approved ICI-containing regimens is based on TKI treatment, but the optimal second-line therapy after ICI-based 1L therapy for HCCs and the potential role of ICI are unclear and subject to ongoing studies. The ICI monotherapy with pembrolizumab has been approved by the FDA as second-line therapy for HCC, in which a previous sorafenib treatment failed, but not in the EU. Camrelizumab was reported as a second-line therapy for advanced HCC, in which a previous systemic treatment approved by the China FDA (CFDA) had failed.

There is still a high medical need for safe and effective therapies for patients with cirrhosis in stages Child—Pugh B or C, which represents a sizable portion of patients presenting in clinical practice. Unfortunately, clinical trials on ICI-containing treatment regimens in those patients are rare. The phase II trial CheckMate 040 included 49 patients with Child—Pugh B7-8 cirrhosis in which treatment with nivolumab did not lead to unexpected toxicities.[89] Although in patients with Child B (or C) cirrhosis survival is strongly determined by liver function and less by tumor disease than in patients in Child—Pugh A stage, the treatment of HCCs in patients with advanced cirrhosis should be clarified in future studies.

Due to the rising incidence of HCC worldwide, the scarcity of mutational drivers and the lack of druggable mutations, host-intrinsic as well as host-extrinsic factors that cause HCC and influence therapeutic outcomes (as depicted in Figure 4) have to be deciphered.[7] Further, robust predictive biomarkers that can guide therapeutic decision in HCC are still lacking. Therefore, it is still unclear which patients will benefit best from which therapy. Considering the diversifying ICI combination therapy landscape in HCC, e.g. ICI + anti-VEGF or double ICI, a thorough understanding of predictive biomarkers and a corresponding accurate stratification of patients have the potential to further improve outcomes.

Besides mOS, double ICI with CTLA-4 and PD-1/PD-L1 antibodies has shown remarkable long-term survival rates

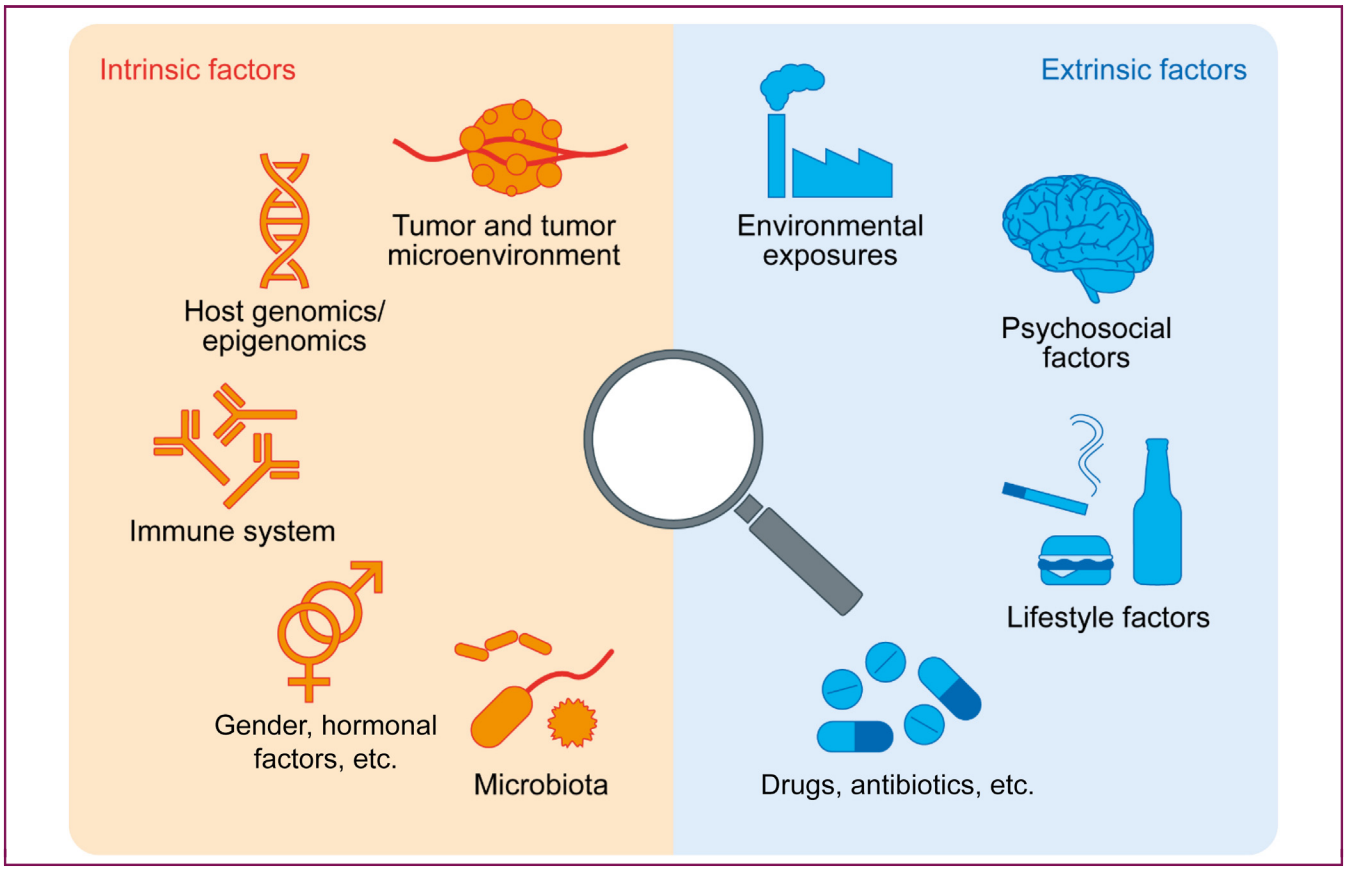

Figure 4. Intrinsic and extrinsic factors that can trigger HCC development and influence response to therapy. Intrinsic factors include genomics, tumor microenvironment, immune system, gender/hormonal factors as well as microbiota. Extrinsic factors include environmental factors (such as exposure to toxins/pollutants), psychosocial factors, lifestyle factors (such as poor diet, alcohol and lack of physical activity) as well as exposure to drugs (such as antibiotics).

that are not accurately captured by the median OS. These survival rates need to be followed up and verified in long-term studies, but they give reason to hope that patients with uHCC have the opportunity for long-term survival after treatment with ICI-based therapies in the future.

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