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Immunotherapy for advanced hepatocellular carcinoma: a focus on special subgroups

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ABSTRACT

Following the success of immune checkpoint blockers (ICBs) in different cancer types, a large number of studies are currently investigating ICBs in patients with hepatocellular carcinoma (HCC), alone or in combination with other treatments. Both nivolumab and pembrolizumab, as well as the combination of nivolumab plus ipilimumab have been granted accelerated approval by the United States Food and Drug Administration for sorafenib-pretreated patients. While nivolumab and pembrolizumab both failed to meet their primary endpoints in phase III trials, the combination of atezolizumab plus bevacizumab eventually improved overall and progression-free survival compared with sorafenib in a front-line phase III trial, and thus, will become the new standard of care in this setting. Despite this breakthrough, there are patient populations with certain underlying conditions that may not be ideal candidates for this new treatment either due to safety concerns or potential lack of efficacy. In this review, we discuss the safety of ICBs in patients with pre-existing autoimmune disease, IBD or a history of solid organ transplantation. Moreover, we summarise emerging preclinical and clinical data suggesting that ICBs may be less efficacious in patients with underlying non-alcoholic steatohepatitis or HCCs with activated Wnt/β-catenin signalling.

INTRODUCTION

The multi-tyrosine kinase inhibitor (mTKI) sorafenib has been the standard of care for patients with advanced hepatocellular carcinoma (HCC) for more than a decade.[1 2] Efforts to expand the systemic treatment options for HCC have been complicated by numerous failed clinical trials.[2] Only recently, four additional targeted therapies have been approved for HCC based on positive results in phase III studies: lenvatinib in first line, and regorafenib, cabozantinib and ramucirumab—all in sorafenib-pretreated patients.[3–6]

Fuelled by the success of immune checkpoint blockers (ICBs) in melanoma,[7] these agents have been extensively tested in numerous cancer types, including HCC, and the list of approvals of ICBs for different malignancies is steadily increasing.[8] In HCC, nivolumab and pembrolizumab, both monoclonal antibodies against programmed cell death protein 1 (PD-1), as well as the combination of nivolumab plus ipilimumab (monoclonal antibody against cytotoxic T lymphocyte antigen-4 (CTLA-4)) have been granted accelerated approval for sorafenib-experienced patients in the USA (but not in Europe), based on encouraging response data from phase I/II studies.[9–11] Real-world data confirmed the efficacy and safety of PD-1-targeted immunotherapy in HCC, including in patients with Child-Pugh stage B or intensive pretreatment.[12] However, subsequent phase III trials testing nivolumab versus sorafenib in first line and pembrolizumab versus placebo in second line both failed to meet their primary survival endpoints (table 1).[13 14]

The evaluation of the combination of nivolumab plus ipilimumab in phase III is currently ongoing (NCT04039607). In addition, vascular endothelial growth factor (VEGF)–targeted therapies are currently being investigated in combination with ICBs. Mechanistically, these agents may reverse the immunosuppressive effects of VEGF in the tumour microenvironment and thereby boost the efficacy of ICBs (figure 1).[15 16] The combination of lenvatinib plus pembrolizumab as well as bevacizumab (monoclonal antibody against VEGF) plus atezolizumab (monoclonal antibody against programmed cell death 1 ligand 1 (PD-L1)) have both received breakthrough therapy designation from the United States Food and Drug Administration based on encouraging results from phase Ib studies.[17 18] The latter combination finally succeeded in a front-line phase III trial (IMbrave150)[19]: atezolizumab plus bevacizumab improved both co-primary endpoints overall survival (OS; median, not evaluable vs 13.2 months; HR 0.58) and progression-free survival (PFS; median, 6.8 vs 4.3; HR 0.59) compared with sorafenib, and showed a good safety profile and improved quality of life (table 1). Hypertension and proteinuria—typical side effects of bevacizumab—were among the top three adverse events in the combination arm. Upper GI bleeding, another known side effect of bevacizumab and a main concern in cirrhotic patients, occurred in 7% of patients in this group,[19] which is well within the range of previous studies evaluating bevacizumab in HCC.[20 21] An increase in transaminases and pruritus were common side effects attributable to atezolizumab.[19] As only patients with Child-Pugh class A were included in this study—a common practice in HCC trials—no data are available regarding efficacy and safety of this combination in patients with more advanced liver function impairment.[19]

The implementation of atezolizumab plus bevacizumab as the new standard of care in front line will have significant implications on the treatment sequencing of HCC (figure 2), as none of the currently approved therapies was tested in ICB-experienced patients. It also poses the important question if every patient with advanced stage HCC

Table 1 Main results from phase III trials testing immune checkpoint blockers in hepatocellular carcinoma

	IMbrave150[19]		CheckMate 459[14]		KEYNOTE-240[13]	
	Atezolizumab/bevacizumab (n=336)	Sorafenib (n=165)	Nivolumab (n=371)	Sorafenib (n=372)	Pembrolizumab (n=278)	Placebo (n=135)
Inclusion criteria	Locally advanced or metastatic, no prior systemic therapy, Child-Pugh A, ECOG PS 0–1		Advanced HCC not amenable to surgery/LRT, no prior systemic therapy, Child-Pugh A, ECOG PS 0–1		Intermediate or advanced HCC not amenable to LRT; prior sorafenib treatment; Child-Pugh A; ECOG PS 0–1	
Primary endpoint(s)	Overall survival, progression-free survival		Overall survival*		Overall survival, progression-free survival*	
BCLC A/B/C, n (%)	8 (2)/52 (15)/276 (82)	6 (4)/26 (16)/133 (81)	15 (4)/53 (14)/303 (82)	18 (5)/63 (17)/291 (78)	0/56 (20)/222 (80)	0/29 (22)/106 (79)
Overall survival						
Median (95% CI), months	NE	13.2 (10.4 to NE)	16.4 (13.9 to 18.4)	14.7 (11.9 to 17.2)	13.9 (11.6 to 16.0)	10.6 (8.3 to 13.5)
HR (95% CI)	0.58 (0.42 to 0.79)		0.85 (0.72 to 1.02)		0.781 (0.611 to 0.998)	
P value	<0.001		0.0752		0.0238	
Progresion-free survival						
Median (95% CI), months	6.8 (5.7 to 8.3)	4.3 (4.0 to 5.6)	3.7 (3.1 to 3.9)	3.8 (3.7 to 4.5)	3.0 (2.8 to 4.1)	2.8 (1.6 to 3.0)
HR (95% CI)	0.59 (0.47 to 0.76)		0.93 (0.79 to 1.10)		0.718 (0.570 to 0.904)	
P value	<0.001		NR		0.0022	
Radiological response†						
CR, n (%)	18 (6)	0	14 (4)	5 (1)	6 (2)	0
PR, n (%)	71 (22)	19 (12)	43 (12)	21 (6)	45 (16)	6 (4)
SD, n (%)	151 (46)	69 (43)	130 (35)	180 (48)	122 (44)	66 (49)
PD, n (%)	64 (20)	39 (25)	136 (37)	105 (28)	90 (32)	57 (42)
ORR, n (%)	89 (27)	19 (12)	57 (15)	26 (7)	51 (18)	6 (4)
DCR, n (%)	240 (74)	88 (55)	203 (55)	215 (58)	173 (62)	72 (53)
Duration of response						
Median, months	NE	6.3 (95% CI 4.7 to NE)	23.3 (range, 3.1–34.5)	23.4 (range, 1.9–28.7)	13.8 (range, 1.5–23.6)	NE (2.8–20.4)
Treatment duration						
Median, months	7.4/6.9	2.8	4.2	3.7	3.5	2.8
Treatment-related adverse events						
All-grade, n (%)	276 (84)	147 (94)	NR	NR	170 (61)	65 (49)
Grades 3–4, n (%)	117 (36)	71 (46)	81 (22)	179 (49)	51 (18)	10 (7)
Grade 5, n (%)	6 (2)	1 (<1)	1 (<1)	1 (<1)	NR‡	NR‡
Common adverse events	Hypertension, proteinuria, diarrhoea, fever	Diarrhoea, PPE, anorexia, hypertension	Fatigue, pruritus, rash, AST increase	PPE, diarrhoea, anorexia, fatigue	AST increase, bilirubin increase, fatigue, pruritus	Fatigue, cough, AST increase, diarrhoea, anorexia
Quality-of-life assessment	Atezolizumab+bevacizumab delayed time to deterioration		Nivolumab improved QoL and reduced treatment burden		NR	

*Failed to meet prespecified threshold of significance for primary endpoints.
†Independent review according to RECIST version 1.1.
‡No grade 5 events occurred in ≥1.0% of patients.
AST, aspartate aminotransferase; CR, complete response; DCR, disease control rate; HCC, hepatocellular carcinoma; LRT, locoregional therapy; NE, not estimable; NR, not reported; ORR, overall response rate; PD, progressive disease; PPE, palmar-plantar erythrodysesthesia; PR, partial response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; SD, stable disease.

should receive this combination in first line from now on or if there is still a place for mTKIs in this setting.

In this review, we discuss the use of ICBs (and bevacizumab) in certain subgroups of patients that may not derive a clinical benefit from these treatments or could even be harmed. Specifically, we elaborate on the safety of these new treatment options in patients with pre-existing autoimmune disease, IBD or a history of solid organ transplantation. We discuss emerging data raising concerns regarding the efficacy of ICBs in patients with underlying non-alcoholic steatohepatitis or Wnt/β-catenin-activated HCCs.

AUTOIMMUNE DISEASE

ICBs can cause autoimmune-mediated adverse events (irAEs), whose pathogenesis and histological characteristics may resemble those of autoimmune diseases.[22–24] Depending on the organ affected, these can be severe, irreversible and even lethal.[22 25] A large proportion of patients with cancer suffer from underlying autoimmune diseases (AIDs). For example, in patients with lung and renal cancer, around 13%–30% have a concomitant AID—hypothyroidism, rheumatoid arthritis, type 1 diabetes and psoriasis representing the most common ones.[26 27] Patients with HCC may suffer from hepatobiliary AIDs (eg, autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC)), as these are known risk factors for HCC.[28 29] While only a low proportion of patients with PSC develop HCC,[29] the risk is higher in patients with AIH, especially in those with concomitant cirrhosis.[30]

Based on concerns regarding severe immune activation and disease exacerbation, patients with AID have routinely been excluded from clinical trials. Thus, data on the safety of ICBs in individuals with pre-existing AID are limited and restricted to case reports and retrospective cohorts. These studies included patients with a large variety of AIDs, which makes it impossible to draw firm conclusions on any specific subgroups (including patients with hepatobiliary disorders).

Several studies evaluated the safety and efficacy of ICBs in patients with cancer with pre-existing AIDs.[31–38] Most data are available on the use of PD-(L)1–directed ICBs, which came from retrospective studies with sample sizes of 45–85 patients (table 2).[32 33 36 37]

Most common AIDs included rheumatoid arthritis, psoriasis and thyroid disorders. Flares of these AIDs are usually not associated with life-threatening consequences. AIDs with a potentially higher mortality on reactivation, such as neurological or neuromuscular disorders (eg, myasthenia gravis, Guillain-Barre syndrome), were fairly underrepresented, as were those with hepatobiliary disorders (only one patient with PSC). According to these reports, up to 57% of patients had active/symptomatic AID at time of ICB initiation and 16%–38% were on treatment for their AID. The rate of flares of any grade ranged from 23% to 47%, but less than 10% experienced high-grade (grades 3–4) flares. The rate of irAEs not judged as flares was 10%–38% (high-grade, ~10%). Most flares and irAE could be well managed with immunosuppressive drugs and only up to 14% of patients required permanent discontinuation of ICBs due to flares of irAEs (table 2).[32 33 36 37]

There were some other interesting observations regarding the safety and efficacy of anti-PD-(L)1–directed therapy in patients with AID, especially when compared with those without pre-existing AID. First, the incidence of irAEs was higher in patients with versus without underlying AID.[32 33] Both active and inactive concomitant AID were independently associated with higher occurrence of any irAEs,[32] but no differences were

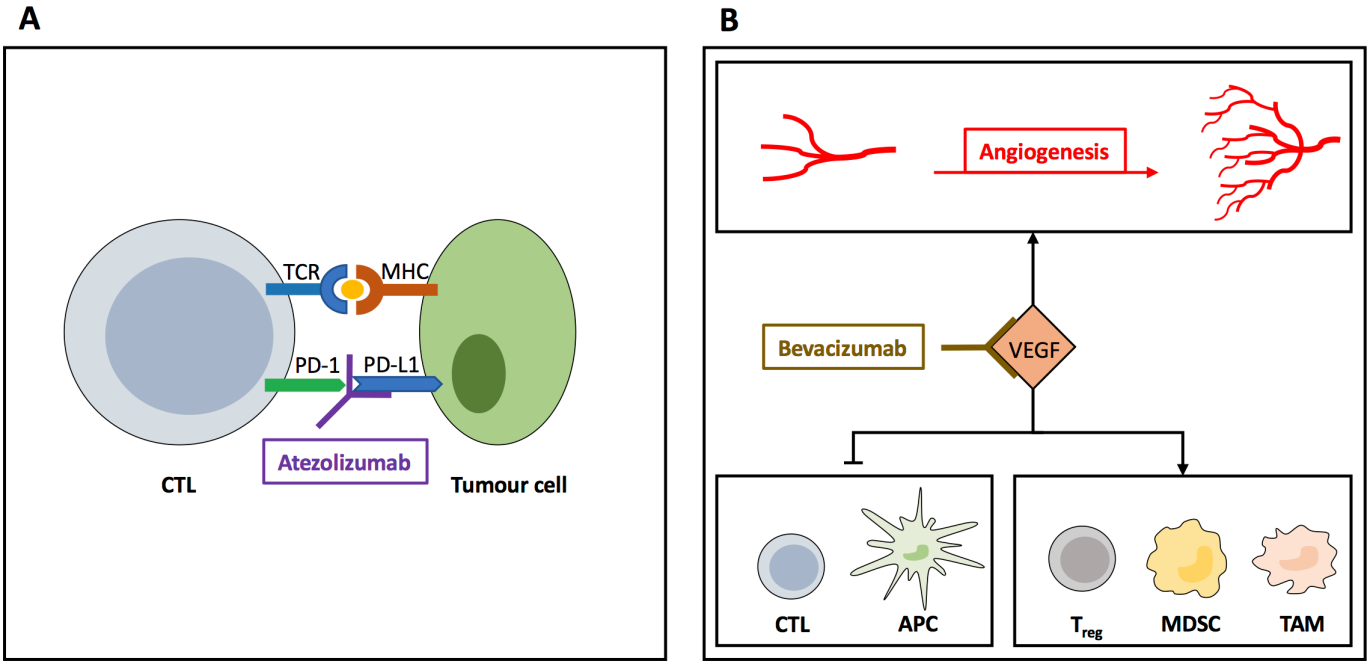

Figure 1 Mechanisms of action of atezolizumab and bevacizumab. (A) Atezolizumab is a monoclonal antibody against PD-L1. It reverses T-cell suppression by preventing interaction between the inhibitory immune checkpoint molecules PD-1 and PD-L1. (B) Besides inducing tumour angiogenesis, VEGF also mediates immunosuppression within the tumour microenvironment by promoting immunosuppressive cells such as T_{regs}, MDSCs and TAMs, while suppressing antigen-presenting cells and CTLs. Bevacizumab is a monoclonal antibody against VEGF and reverses its angiogenic and immunosuppressive effects in the tumour microenvironment. APC, antigen-presenting cell; CTL, cytotoxic T lymphocyte; MDSC, myeloid-derived suppressor cell; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1, programmed cell death 1 ligand 1; TAM, tumour-associated macrophage; TCR, T-cell receptor; T_{reg}, regulatory T cell; VEGF, vascular endothelial growth factor.

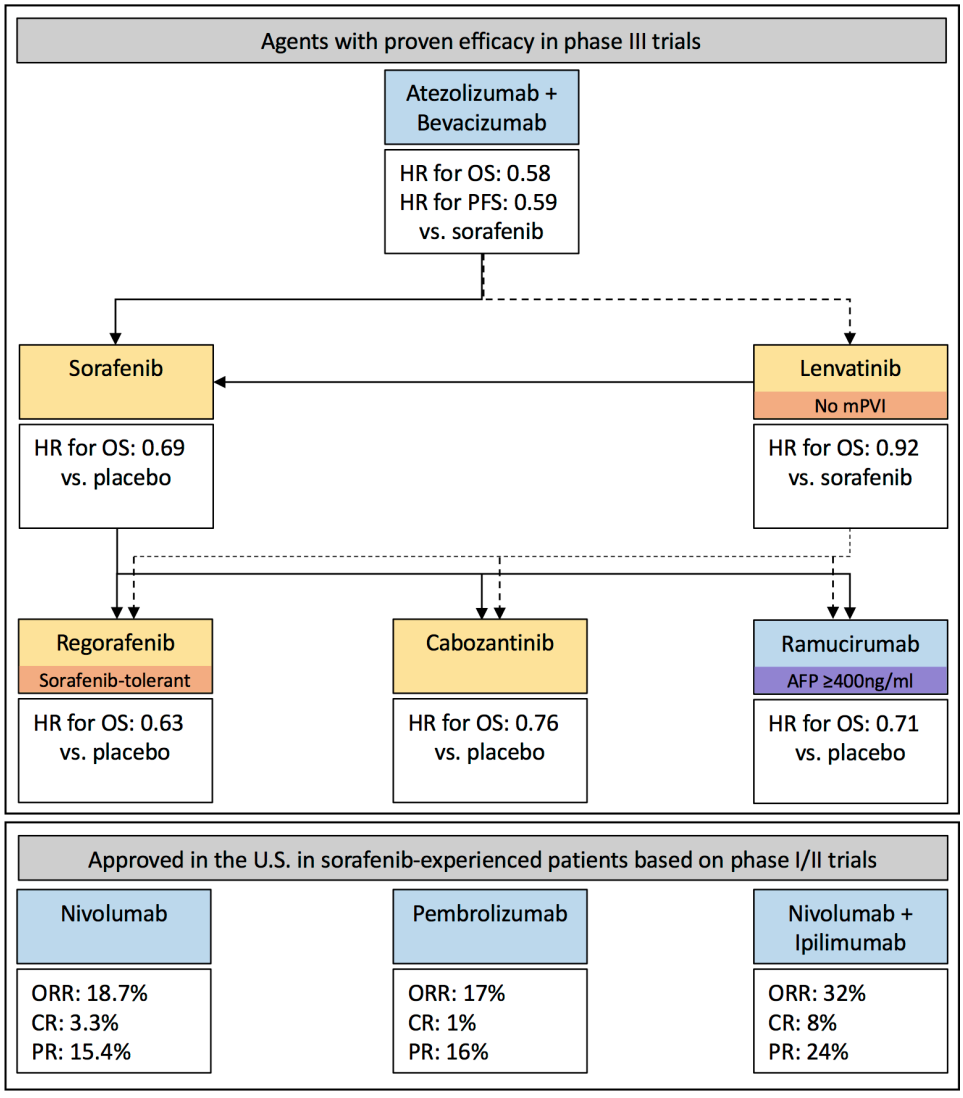

Figure 2 Proposed treatment sequence for patients with advanced hepatocellular carcinoma. Atezolizumab plus bevacizumab, sorafenib, lenvatinib (all tested in first line), regorafenib, cabozantinib and ramucirumab (all tested in sorafenib-pretreated patients) have demonstrated efficacy in phase III trials. Boxes indicate main study inclusion criteria that separate them from the other studies and HRs for the primary survival endpoints. A blue background marks monoclonal antibodies, yellow background labels multi-tyrosine kinase inhibitors. In contrast to continuous lines, dotted lines represent treatment sequences that are not in accordance with drug labels but may also be considered in clinical practice. Nivolumab, pembrolizumab and nivolumab plus ipilimumab have been granted accelerated approval for sorafenib-experienced patients in the USA (but not in Europe) based on promising response rates from phase I/II trials. However, their role in patients previously treated with atezolizumab plus bevacizumab is unclear. AFP, alpha-fetoprotein; CR, complete response; mPVI, main portal vein invasion; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; U.S, United States.

observed regarding high-grade irAEs compared with patients without AID.[32 33] Second, the rate of permanent discontinuation of ICBs due to irAEs was not different between patients with versus without pre-existing AID.[32] Third, flares occurred more often in patients with symptomatic AID compared with those with inactive disease, but the rate of flares was not significantly different between patients on immunosuppression at the time of ICB initiation and those who were not.[36 37] Finally, the efficacy of ICBs in terms of overall response rate, PFS and OS did not differ between patients with versus without underlying AID.[32 33] However, there were conflicting reports regarding the response rate according to concomitant immunosuppressive therapy at the time of ICB initiation: while it was lower in patients on immunosuppressants in one study,[37] no association between immunosuppression and treatment response was found in another.[36]

Data on CTLA-4–targeted ICBs are limited to smaller cohorts. For instance, two studies analysed the use of the anti-CTLA-4 antibody ipilimumab in patients with melanoma and concomitant AID. Around 30% of the patients experienced an AID flare, and high-grade adverse events occurred in up to 33%.[34 35]

Taken together, the incidence of irAEs seems to be higher in patients with pre-existing AID compared with those without an AID. Flares and irAEs can usually be managed with steroids or other immunosuppressants and only a minority of patients requires permanent discontinuation of the ICB. Concomitant AID seems not to be associated with worse outcome in terms of response and survival. However, data on the safety of ICBs in patients with severe neurological, neuromuscular or hepatobiliary disorders, in whom exacerbation can be lethal, are very limited. Taking into account benefits and potential risks, every

Table 2 Selected retrospective studies of PD-(L)1-targeted immune checkpoint blockers in patients with cancer and pre-existing autoimmune disease

	Menzies[37]	Danlos[33]	Leonardi[36]	Cortellini[32]
Total no of patients	119	397	56	751
No of patients with pre-existing AID	52*	45†	56 ‡‡	85‡
Predominant cancer	Melanoma (100%)	Melanoma (80%), NSCLC (13%), others (7%)	NSCLC (100%)	NSCLC (66%), melanoma (21%), RCC (13%), others (<1%)§
Pre-existing AIDs (n)	RA (13), sarcoidosis (3), PMR (3), SLE (2), scleroderma (2), PsA (2), SjS (2), PsO (6), eczema (1), EN (1), CD (3), UC (2), CelD (1), GBS (2), CIDP (1), MG (1), Bell's palsy (1), GD (4), asthma (2), ITP (2)	Vitiligo (17), PsO (11), PsA (1), HT/GD (7), SjS (4), RA (2), ITP (1), SpA (1), MS (2), hidradenitis suppurativa (1), MG (1), PMR (1), PAN (1), sarcoidosis (1), CCL (1), T1D (1)	RA (11), PMR (5), SNRA (4), scleroderma (2), PsA (2), SLE (1), SjS (1), temporal arteritis (1), PsO (14), alopecia areata (1), discoid lupus (1), GD (5), HT (4), UC (3), CD (3), MG (1), MS (2), rheumatic fever (2), AIHA (1)	GD/AIT (54), PsO (13), vitiligo (2), lichen planus (1), PMR (2), SLE (2), RA (4), vasculitis (1), CD (3), PSC (1), autoimmune optic neuritis (1), MGN (1), GBS (1), MG (1), scleroderma (1)
Active/symptomatic AID	15 (29%)	30 (57%)¶	10 (18%)	15 (18%)
AID treatment at ICB start	20 (38%)	7 (16%)	11 (20%)	15 (18%)
Any AID flare	20 (38%)	11 (24%)	13 (23%)	40 (47%)
High-grade (≥3) AID flare	3 (6%)	NR	2 (4%)	8 (9%)
Median time to AID flare or irAE (months)	1.2 (flare)	2.1 (flare or irAE)	Range: 0.03–8.5 (flare) 1–17.5 (irAE)	1.9–3.5 (grade 3/4 flare or irAE)**
Any irAE††	15 (29%)	10 (22%)	21 (38%)	16 (19%)
High-grade (≥3) irAE††	5 (10%)	NR	6 (11%)	0
Systemic IS for flare or irAE	Flare: 20 (38%) irAE: 7 (13%)	Flare/irAE: 6 (13%)	Flare: 4 (7%) irAE: 7 (13%)	NR
ICB interruption	Flare: 8 (15%) irAE: 3 (6%)	Flare/irAE: 1 (2%)	Flare: 2 (4%) irAE: 3 (5%)	NR
Permanent ICB discontinuation	Flare: 2 (4%) irAE: 4 (8%)	Flare/irAE: 4 (9%)	Flare: 0 irAE: 8 (14%)	Flare/irAE: 6 (7%)
Treatment-related deaths	0	0	0	NR
ORR	33%	38%	22%	38% (inactive AID), 50% (active AID)

*Two patients had 2 concomitant AIDs.
†Eight patients had 2 concomitant AIDs.
‡Four patients had 2 concomitant AIDs.
§Percentages refer to the total cohort (n=751).
¶Percentage refers to 53 AIDs (8 patients had 2 concomitant AIDs).
**Median time to grade 3/4 irAE or flare was 1.9 months for inactive and 3.5 months for active AID.
††Excludes irAEs that were judged as AID flares.
‡‡Seven patients had more than 1 AID (6 had 2 AIDs, 1 had 3 AIDs).
§§
AID, autoimmune disease; AIHA, autoimmune hemolytic anaemia; AIT, autoimmune thyroiditis; CCL, chronic cutaneous lupus; CD, Crohn's disease; CelD, coeliac disease; CIDP, chronic inflammatory demyelinating polyneuropathy; EN, erythema nodosum; GBS, Guillain-Barre syndrome; GD, Grave's disease; HT, Hashimoto thyroiditis; ICB, immune checkpoint blocker; irAE, immune-related adverse event; IS, immunosuppression; ITP, immune thrombocytopenic purpura; MG, myasthenia gravis; MGN, membraneous glomerulonephritis; MS, multiple sclerosis; NR, not reported; NSCLC, non-small cell lung cancer; ORR, overall response rate; PAN, polyarteritis nodosa; PMR, polymyalgia rheumatica; PsA, psoriatic arthritis; PSC, primary sclerosing cholangitis; PsO, psoriasis; RA, rheumatoid arthritis; SjS, Sjogren's syndrome; SLE, systemic lupus erythematosus; SNRA, seronegative RA; SpA, spondyloarthritis; T1D, type 1 diabetes.

patient considered for ICBs should be individually discussed and managed within a multidisciplinary team.[24] It is recommended to avoid ICBs (1) whenever AID reactivation may be life threatening, (2) in patients with neurological or neuromuscular disorders, and (3) in patients with poorly controlled AID or on high doses of immunosuppression[24]; TKIs should still be considered the first choice in these patients (figure 3). Moreover, a recently published position paper on the use of ICBs in patients with AID suggests to replace non-selective immunosuppressants with selective immunosuppressive drugs before ICB initiation, as they seem less likely to negatively impact ICB efficacy; they provide specific recommendations and algorithms for several common AIDs.[39]

ORGAN TRANSPLANTATION

Liver transplantation is a potential curative treatment option for patients with early-stage HCC.[40] However, around 8% to 21% of patients experience HCC recurrence, depending on tumour size and number as well as biological factors such as alpha-fetoprotein.[41 42] Recurrent HCC after liver transplantation is considered a systemic disease. Thus, these patients often receive systemic treatment, either alone or in addition to surgical and locoregional procedures, even though high-level evidence is missing. Data from retrospective cohorts suggest that TKIs such as sorafenib and regorafenib are safe and moderately effective in these patients.[43 44] However, there is considerable concern about the use of ICBs in patients with prior solid organ transplantation, as immune checkpoint molecules, particularly PD-(L)1, play an important role in establishing graft tolerance.[45 46] Boosting the immune system with ICBs may lead to organ rejection, while concomitant immunosuppressive therapy may hamper efficacy of ICBs at the same time. As patients with a history of prior organ transplantation are usually excluded from clinical trials investigating ICBs, data

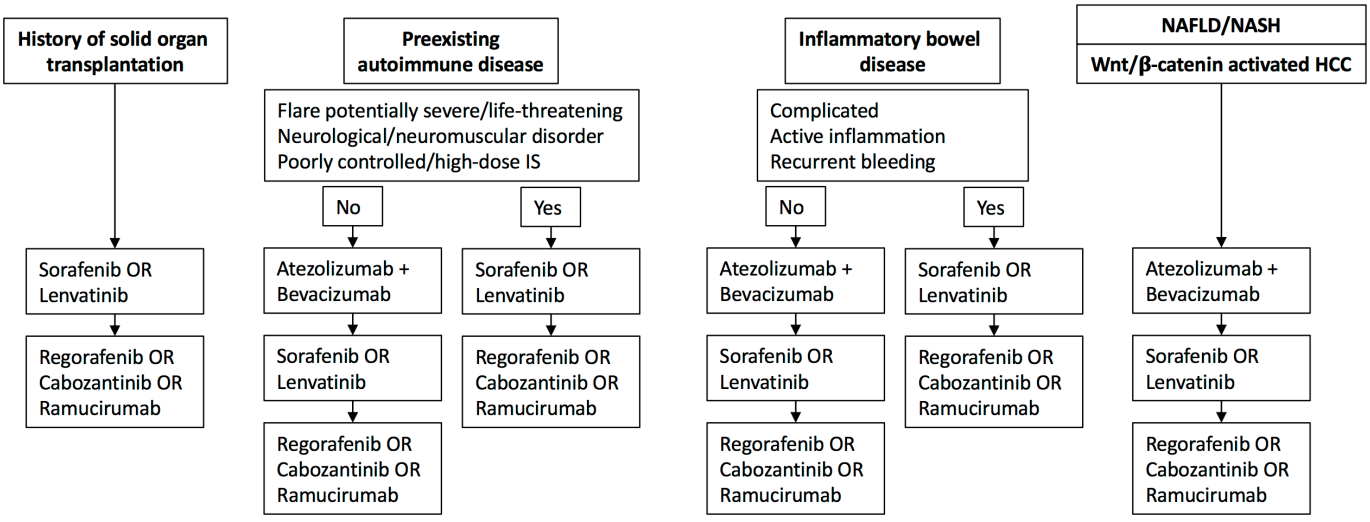

Figure 3 Proposed treatment algorithms for special populations. Patients with prior solid organ transplantation, severe or poorly controlled autoimmune disease, or complicated IBD should not receive an immune checkpoint blocker (ICB)–based regimen due to considerable safety concerns. The potential use of ICBs as an *ultima ratio* in selected patients (eg, history of kidney transplantation) needs to be evaluated carefully on a case-by-case basis within a multidisciplinary team and the patient must be comprehensively informed about potential risks. Immunotherapy should not be withheld in patients with non-alcoholic fatty liver disease or Wnt/β-catenin activated hepatocellular carcinoma, as concerns regarding efficacy are based on preliminary evidence. Note that lenvatinib is approved for patients who have received no prior systemic therapy. Regorafenib, cabozantinib and ramucirumab are approved in sorafenib-experienced patients. HCC, hepatocellular carcinoma; IS, immunosuppression; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

on their use in transplant recipients are mainly derived from case reports and case series.

Munker and De Toni[47] summarised 14 published cases of patients with prior liver transplantation, who received ICBs to treat a malignancy (HCC, n=7; melanoma, n=5; fibrolamellar HCC, n=2). Four patients (29%) experienced organ rejection which was lethal in three patients (21%). All four rejections occurred in patients treated with an ICB directed against PD-1, while none of the three patients under anti-CTLA-4 treatment developed graft rejection. Responses were reported in four (29%) patients (melanoma, n=3; HCC, n=1).[47]

Other studies reported their own patients alone or together with published cases or case series reporting on ICB use after organ transplantation.[48 49] The largest study, a systematic review, identified and analysed a total of 83 published cases,[50] including those from the aforementioned studies.[47–49] Accordingly, the most common cancer types were melanoma (55%), HCC (14%) and skin squamous cell carcinoma (12%). The majority of patients had a history of kidney transplantation (64%), while 29% and 7% underwent prior liver and heart transplantation, respectively. Seventy-three per cent received anti-PD-(L)1 antibodies, 16% had anti-CTLA-4 treatment and 11% were treated with a combination of both. Mean time from transplantation to ICB initiation was shorter in liver recipients (5.6 years) compared with patients with prior kidney (10.8 years) and heart (12.2 years) transplantation. Allograft rejection occurred in 40% of the patients (kidney, 43%; liver, 38%; heart, 17%) after a mean time of 5.6 weeks. The concomitant immunosuppressive regimen had no impact on the risk of rejection. Factors independently associated with lower risk of rejection included ≥1 concomitant immunosuppressant other than steroids as well as time since transplantation ≥8 years; history of prior rejection was associated with an increased risk of rejection. Only a few patients showed complete (6%) or partial (23%) recovery with salvage immunosuppressive therapy (mostly methylprednisolone), but the majority (71%) developed end-stage organ failure (75% in liver recipients). Out of 48 patients with a reported cause of death, 19% died from organ rejection. Overall, 28% of the patients showed a response to ICB treatment, and 19% of cases were still alive without signs of rejection and tumour progression.[50]

In conclusion, around one-third of patients with a history of solid organ transplantation respond to ICB treatment. However, they have a high risk of experiencing allograft rejection, which leads to end-stage organ failure in the majority of patients and is often lethal. Thus, despite a variety of opinions,[47–50] we believe that according to the current evidence, ICBs are contraindicated in transplant recipients where organ rejection may be life-threatening and organ replacement therapy is not available (eg, liver). As sorafenib and regorafenib seem to be safe in patients with recurrent HCC after liver transplantation, TKIs or potentially anti-VEGFR antibodies are the drugs of choice in this setting. In kidney recipients, ICBs may be considered but should be used with extreme caution and only as *ultima ratio* (figures 3 and 4).

INFLAMMATORY BOWEL DISEASE

Patients with IBD (ie, Crohn's disease (CD) and ulcerative colitis (UC)) have an increased risk for the development of extraintestinal malignancies, including liver and biliary cancers.[51] IBD is often associated with hepatobiliary disorders, including PSC, autoimmune hepatitis/PSC overlap syndrome, PBC and non-alcoholic fatty liver disease (NAFLD),[52] and some of them can lead to biliary tract cancer or HCC, either directly or via the development of liver cirrhosis.[28 29] In addition, like the general population, patients with IBD may also acquire other risk factors for cirrhosis and HCC, including viral hepatitis or alcohol abuse.[28] Thus, some patients with HCC, who will become candidates for atezolizumab plus bevacizumab, may suffer from concomitant IBD.

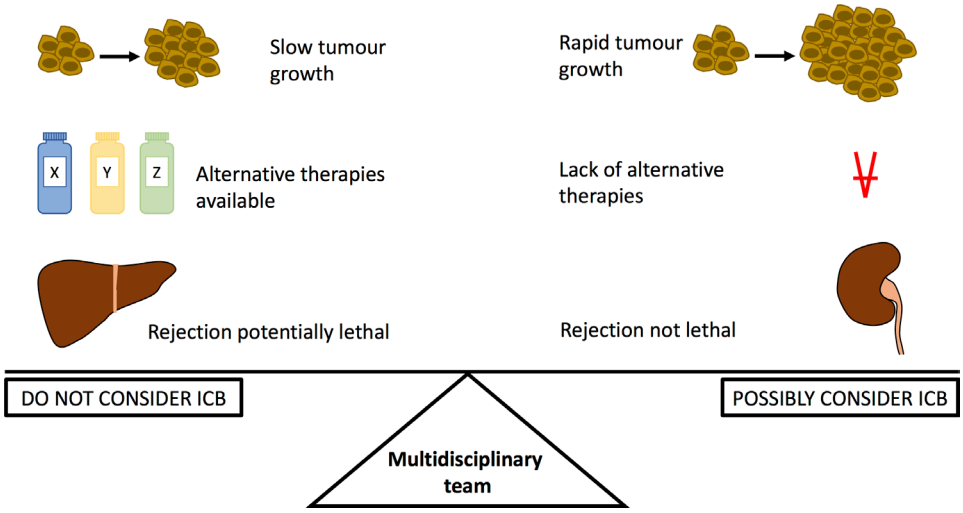

Figure 4 Considerations before initiation of immune checkpoint blockers in patients with a history of solid organ transplantation. The decision to use immune checkpoint blockers (ICBs) in patients with prior organ transplantation should only be made after careful evaluation within a multidisciplinary team. Some key points need to be addressed. This includes whether a potential organ rejection during ICB treatment will be life threatening due to lack of organ replacement therapy (ie, liver) or not (ie, kidney). History of prior organ rejection also needs to be incorporated into the risk–benefit analysis as it may be associated with an increased risk of rejection during ICB treatment. It is important to preferentially use alternative treatment option that have a better safety profile in transplant recipients. Tumour extent and growth rate and potentially associated imminent organ dysfunction should also be taken into account as a measure of urgency for using ICBs. ICB, immune checkpoint blocker.

There are concerns about the safety of bevacizumab in patients with IBD due to the risk of GI perforation (~2.4%) and severe bleeding (~3.1%) associated with bevacizumab treatment.[53 54] Only few data are available about its use in patients with IBD. According to a report on two cases with CD and metastatic colorectal cancer (mCRC), bevacizumab was safe and did not cause any acute CD exacerbation, bleeding or perforation.[55] One of these patients had a 2-year history of CD under steroids and 5-aminosalicylate treatment, with two exacerbations per year, the other had a 14-year history of CD and prior colectomy due to pancolitis.[55] In a large phase III trial of patients with advanced ovarian cancer (n=1873), history of IBD treatment (<1% of study population) and bevacizumab exposure independently increased the risk (estimated odds, 13.4 and 2.15, respectively) of developing GI AEs (grade ≥2 perforation, fistula, necrosis or haemorrhage). However, based on a logistic model with a treatment–factor interaction term, bevacizumab did not further increase the risk of a GI AE in patients with a history of IBD diagnosis or treatment.[56] Only recently, a retrospective study reported on the safety of bevacizumab in 28 patients with IBD (6 UC, 22 CD) and metastatic solid tumours, who received bevacizumab-based chemotherapy. Three patients were on steroids and four received 5-aminosalicylates. IBD was well controlled and no patient had complications such as fistula, bleeding or abscess formation when bevacizumab was initiated. Only one patient developed rectorrhagia after 6 months of bevacizumab plus FOLFIRI treatment, which was considered as CD flare. Re-challenge with bevacizumab after irinotecan withdrawal did not lead to further bleeding complications in this patient.[57]

Patients with IBD may also be at increased risk of developing disease flares or severe GI AEs if treated with ICBs. Although CTLA-4 seems to be more important for gut homeostasis,[58] PD-1/PD-L1 signalling is also crucial for intestinal tolerance, as its blockade leads to $CD8^+$ T cell–mediated autoimmune enteritis in murine models.[59] In line, immune-mediated enterocolitis and diarrhoea are common side effects in patients treated with ICBs.[25] Immune checkpoint molecules may also play a role in the pathophysiology of IBD, as polymorphisms in the CTLA-4 gene were associated with increased risk of UC in Asians,[60] and expression of PD-1 and PD-L1 on the intestinal epithelium is higher in patients with IBD compared with healthy controls.[61]

Small series reported an IBD exacerbation or colitis in two of six ipilimumab (anti-CTLA-4)-treated patients,[34] while no IBD flares were reported in 11 subjects receiving anti-PD-(L)1 antibodies.[36 37] In another retrospective series of 14 patients with cancer and IBD receiving either ICBs against PD-(L)1 (n=13) or CTLA-4 (n=1), 7 (50%) had a flare which was severe (grades 3–4) in 6 patients (43%), and 5 patients (36%) discontinued ICBs permanently due to immunotoxicity.[38]

A recently published multicentre study investigated the use of ICBs in 102 patients with underlying IBD (UC, n=49; CD, n=49; unclassified, n=4).[62] Patients received either monotherapy with PD-(L)1 (n=85) or CTLA-4 (n=7) antibodies or a combination of both (n=10). Forty-three (42%) patients were not receiving IBD treatment, and the median time from last active IBD episode until ICB start was 5 (IQR, 3–12) years. Moreover, most patients with available endoscopic information had normal findings. Together, these data indicate that the majority of patients had well-controlled disease. Patients with underlying IBD had a higher rate of GI AEs than patients without IBD (41% vs 11%, p<0.001). Three-fourths (n=32) of patients with GI AEs received glucocorticoids, and 12 patients required an escalation to infliximab/vedolizumab. Overall, 23 patients discontinued ICBs due to GI AEs. Even though no fatal GI events were observed, 21 patients had high-grade diarrhoea, and four patients experienced colonic perforation (3 on anti-PD-(L)1 and 1 on combined anti-PD-(L)1/CTLA-4 treatment)—two of them requiring surgery.[62] Notably, the rate of perforation in this study was higher than that previously reported for subjects with immune-mediated enterocolitis (~2%).[63]

Taken together, limited data with a low evidence level are available on the use of bevacizumab and ICBs in patients with IBD. Bevacizumab seems to be safe in patients with quiescent or well-controlled IBD, while ICBs may increase the risk of GI

events even in patients with controlled disease. However, caution is warranted in patients with complicated disease (ie, fistulating CD) due to the risk of perforation. ICBs were associated with a higher rate of high-grade GI AEs and colonic perforation in patients with IBD (figure 3). It is currently unclear if the combination of atezolizumab and bevacizumab may even potentiate the GI risk in patients with IBD. As mentioned previously in the context of AIDs, it was recently proposed to use a selective immunosuppressive regimen as they seem less likely to impair ICB efficacy than non-selective immunosuppressants. For IBD, the authors recommend switching to vedolizumab, or alternatively to anti-TNF-α–targeted agents, tofacitinib or ustekinumab before starting ICBs.[39]

NON-ALCOHOLIC FATTY LIVER DISEASE

NAFLD is the most common liver affection worldwide with an estimated global prevalence of 25%. The HCC incidence among patients with NAFLD is low (0.44 per 1000 person-years), but increases by more than 10-fold (5.29 per 1000 person years) in those who have already progressed to non-alcoholic steatohepatitis (NASH).[64] NAFLD/NASH is a main aetiological risk factor for HCC in the USA,[65] and the incidence of NAFLD/NASH-associated HCC is expected to further increase globally.[66 67] Different from other aetiologies of liver disease, up to 50% of patients with NAFLD/NASH-associated HCC do not have underlying liver cirrhosis,[68] and HCC surveillance for individuals with NAFLD but without severe fibrosis/cirrhosis is not universally recommended.[40] Considering the prevalence of NAFLD, regular HCC surveillance of all affected individuals would also be logistically impossible with currently available resources. Thus, HCC in patients with NAFLD is usually diagnosed incidentally outside specific surveillance programmes or in symptomatic patients, and consequently at more advanced tumour stages, resulting in lower probability of receiving curative treatment and shorter survival.[64 68] Thus, a significant proportion of patients with NAFLD-related HCC will eventually become candidates for systemic front-line therapy with atezolizumab plus bevacizumab.

Pathophysiologically, NAFLD reshapes the local immune microenvironment, as it leads to a decrease of anti-tumour $CD4^+$ T cells and induces tumour-promoting functions in $CD8^+$ T cells, natural killer T cells and Th17 cells.[69–71] This may have implications for immunotherapy. Indeed, subgroup analysis of the CheckMate 459 phase III trial demonstrated that nivolumab was less effective in terms of OS in patients with HCC with non-viral aetiology (vs sorafenib: HR 0.95; 95% CI 0.74 to 1.22).[14] Similar results were reported for the combination of atezolizumab plus bevacizumab in patients with non-viral HCC (vs sorafenib: HR 0.91; 95% CI 0.52 to 1.60) in the IMbrave150 trial.[19] Even though both studies did not differentiate between NAFLD and alcoholic liver disease, emerging preclinical data suggest that immunotherapy may be less effective in NAFLD/NASH[72]: mice fed with a NASH-inducing diet showed reduced efficacy of $CD4^+$ T cell–dependent immunotherapy against intrahepatic metastases from melanoma. Mechanistically, this was associated with a loss of $CD4^+$ T cells and a more immunosuppressive immune phenotype in the tumour microenvironment.[72]

NAFLD as underlying aetiology of HCC could also have implications on the efficacy of bevacizumab. More than half of patients with NAFLD are obese,[64] and obesity may be associated with resistance to anti-VEGF treatment. In preclinical models of breast cancer, obesity impaired the anti-angiogenic and anti-tumour effects of anti-VEGF antibody treatment by increasing the expression of inflammatory and angiogenic factors (ie, interleukin-6, fibroblast growth factor 2).[73] In line, visceral fat area (VFA) and obesity (body mass index >30) were associated with poorer outcome in patients with mCRC treated with first-line bevacizumab-based treatment.[74 75] However, a pooled analysis of individual patient data from eight first-line mCRC trials found no interaction between obesity and bevacizumab in terms of survival.[76]

In patients with HCC, high VFA was associated with shorter OS and linked with primary resistance to sorafenib and brivanib according to a small retrospective study.[77] In contrast, individual components of the metabolic syndrome (ie, obesity, type 2 diabetes, arterial hypertension, dyslipidaemia) were not linked to OS in patients with HCC treated with sorafenib; patients with two or more individual components even had a longer survival.[78] Data in patients with renal cell carcinoma treated with VEGF-targeted therapy (ie, sorafenib, sunitinib, axitinib, bevacizumab) are also conflicting.[79 80] However, in contrast to bevacizumab, multi-tyrosine kinase inhibitors such as sorafenib, brivanib or sunitinib also block other molecular targets. Thus, they may be less prone to potential obesity-induced resistance to anti-VEGF therapy.

Taken together, NAFLD reshapes the immune microenvironment and may hamper the efficacy of immunotherapy. Also, obesity—often prevalent in patients with NAFLD—could be implicated in resistance to anti-VEGF therapy, even though clinical data are conflicting and were obtained retrospectively. Based on the current data, aetiology should not be used to decide whether or not to use atezolizumab/bevacizumab in front line (figure 3). Prospective evaluation is needed to obtain better understanding of the efficacy of atezolizumab/bevacizumab in this patient population.

WNT/B-CATENIN ACTIVATION

As of today, no biomarker to predict response or resistance to immunotherapy exists in HCC. Tumorous expression of PD-L1—an established biomarker in other solid tumours[81]—failed to predict response to nivolumab and pembrolizumab in HCC.[11 14] Other potential biomarkers, including high tumour mutational burden or microsatellite instability, are less useful due to their low prevalence in HCC.[82 83]

Emerging evidence suggests that activated Wnt/β-catenin signalling is enriched in non-T cell–infiltrated ('cold') tumours across multiple cancer types and may be implicated in primary resistance to immunotherapy.[84] This is also reflected by a recently proposed immunological classification of HCC, which divides HCCs into three subclasses—(1) immune (30%), (2) immune intermediate (45%) and (3) immune excluded class (25%).[85 86] While tumours of the immune class, characterised by immune cell infiltrates and expression of immune checkpoint molecules, may be good candidates for immunotherapy, tumours of the immune excluded class showed activated Wnt/β-catenin signalling and a lack of intratumoral T cells. Thus, they may not be sensitive to ICBs.[85 86] This hypothesis is supported by preclinical and clinical data[87 88]: in a murine model of HCC, upregulation of the β-catenin pathway was associated with immune escape and failure of anti-PD-1 treatment.[88] In a small cohort of patients with HCC treated with ICBs (n=31), tumours with activating mutations in Wnt/β-catenin (n=10) were resistant to ICBs, which resulted in poorer PFS and OS.[87]

Taken together, activated Wnt/β-catenin signalling is associated with a lack of T-cell infiltrates, which are the main target of PD-(L)1 antibodies, including atezolizumab. Data from preclinical and small clinical studies support the notion that tumours

Box 1 Safety and efficacy concerns associated with immune checkpoint blockers (and bevacizumab) in special subgroups

- The combination of atezolizumab plus bevacizumab will become the new reference standard in systemic front-line treatment of advanced hepatocellular carcinoma.
- Alternative systemic therapies should be preferred over immune checkpoint blockers (ICBs) in patients with prior organ transplantation and uncontrolled pre-existing autoimmune disease (AID) due to safety concerns (organ rejection rate with ICBs: ~40%; high-grade flares and immune-related adverse events in AID: up to 9% and ~10%–33%, respectively).
- Bevacizumab seems to be safe in patients with quiescent or well-controlled IBD, while immune checkpoint blockers may increase the risk of GI adverse events even in patients with controlled disease (high-grade diarrhoea/colitis/perforation with ICBs in IBD: 21%/17%/4%, respectively).
- Non-alcoholic fatty liver disease reshapes the immune microenvironment and may hamper the efficacy of immune checkpoint blockers.
- Tumours with activated Wnt/β-catenin signalling may have a primary resistance to immunotherapy.

with upregulated Wnt/β-catenin pathway may have a primary resistance to ICBs. If proven in large prospective studies, this would have implications for the use of atezolizumab plus bevacizumab in front line (figure 3) and also needs to be considered in the future trial design of studies investigating ICBs. Another question is if these 'cold' tumours can be turned into 'hot', T cell–inflamed tumours in order to make them sensitive to ICBs.

CONCLUSIONS AND FURTHER PERSPECTIVES

The combination of atezolizumab and bevacizumab will become the new reference standard in advanced HCC, and is currently being evaluated in earlier stages as adjuvant treatment after resection or ablation (NCT04102098) and in combination with transarterial chemoembolisation (NCT04224636).[89] However, patients with prior organ transplantation and uncontrolled pre-existing AID (including IBD) should not receive atezolizumab plus bevacizumab due to safety concerns, as long as there are other treatment options available. In case of mild or well-controlled AID and whenever disease flares are not life threatening, ICBs may be considered based on safety data from retrospective analyses. High-level evidence to back these decisions is missing. Therefore, every patient should be evaluated on a case-by-case basis within a multidisciplinary team. Moreover, emerging data suggest that ICBs may be less effective in patients with underlying NASH or Wnt/β-catenin-activated tumours. Since these data largely come from experimental studies and retrospective analysis, they can be considered as hypothesis-generating, but further prospective evaluation is needed before they can be incorporated into clinical decision-making (box 1).

Patients with a chronic viral disease represent a special subgroup that has not been discussed in detail in this review. While flares during ICB treatment in patients with chronic hepatitis C virus infection are very unlikely, there have been reports of reactivation in patients with hepatitis B virus (HBV) infection.[90 91] Hence, only patients under antiviral treatment and with a HBV viral load below a certain cut-off (<100 IU/mL or <500 IU/mL) could be included into clinical trials with ICBs, while no antiviral therapy was required for patients with chronic hepatitis C.[92]

ICBs also seem to be safe and effective in patients with HIV. According to a systematic review including 73 cases with advanced cancer and HIV, ICBs were efficacious and well tolerated without causing any new safety signals. HIV viral load remained suppressed with undetectable viral loads in almost all cases.[93]

Finally, it is also important to mention that patients intended to receive the combination of atezolizumab plus bevacizumab should undergo endoscopic variceal screening, if the current status is unknown. Given the increased bleeding risk associated with bevacizumab, patients with gastro-oesophageal varices should receive adequate prophylactic medical or endoscopic treatment.[94] A practical approach could be the use of beta-blockers in patients with small varices without signs of increased bleeding risk, while endoscopic interventions may be considered in those with large varices or red wale marks.

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