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REVIEW

Immunotherapy use outside clinical trial populations: never say never?

K. Rzeniewicz[1,2], J. Larkin[3], A. M. Menzies[4,5†] & S. Turajlic[2,3*†]

[1]Warwick Medical School, University of Warwick, Warwick; [2]Cancer Dynamics Laboratory, The Francis Crick Institute, London; [3]Renal and Skin Units, The Royal Marsden NHS Foundation Trust, London, UK; [4]Melanoma Institute Australia and The University of Sydney, Sydney, Australia; [5]Royal North Shore and Mater Hospitals, Sydney, Australia

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Background: Based on favourable outcomes in clinical trials, immune checkpoint inhibitors (ICIs), most notably programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitors, are now widely used across multiple cancer types. However, due to their strict inclusion and exclusion criteria, clinical studies often do not address challenges presented by non-trial populations.

Design: This review summarises available data on the efficacy and safety of ICIs in trial-ineligible patients, including those with autoimmune disease, chronic viral infections, organ transplants, organ dysfunction, poor performance status, and brain metastases, as well as the elderly, children, and those who are pregnant. In addition, we review data concerning other real-world challenges with ICIs, including timing of therapy switch, relationships to radiotherapy or surgery, re-treatment after an immune-related toxicity, vaccinations in patients on ICIs, and current experience around ICI and coronavirus disease-19. Where possible, we provide recommendations to aid the often-difficult decision-making process in those settings.

Conclusions: Data suggest that ICIs are often active and have an acceptable safety profile in the populations described above, with the exception of PD-1 inhibitors in solid organ transplant recipients. Decisions about whether to treat with ICIs should be personalised and require multidisciplinary input and careful counselling of patients with respect to potential risks and benefits. Clinical judgements need to be carefully weighed, considering factors such as underlying cancer type, feasibility of alternative treatment options, or activity in trial-eligible patients.

Key words: immunotherapy, checkpoint inhibitors, PD-1, CTLA-4, special populations

INTRODUCTION

Immune checkpoint inhibitors (ICIs) are now widely used across multiple tumour types. They work by blocking inhibitory checkpoint molecules responsible for attenuating T-cell-mediated immune responses, most notably programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte antigen-4 (CTLA-4) (Figure 1).[1] This results in restoration of cellular immunocompetence to recognise and destroy cancerous cells.[1] However, this shift in the immune system balance can result in immune-related adverse events (irAEs), toxicities that are unique for the class and generally manageable, but that occasionally cause significant morbidity and mortality.[2] Given the strict trial enrolment criteria, many patients were ineligible for the initial clinical studies of ICIs, including those with autoimmune disease (AID), chronic viral infections, organ transplants, organ dysfunction, poor performance status (PS), and brain metastases (BrM), as well as the elderly, paediatric, and pregnant patients. This review aims to summarise current knowledge of the efficacy and safety of ICIs in those non-trial populations, which represent a substantial proportion of patients seen in the clinic. In addition, we review data regarding pertinent questions around timing of therapy switch and in relation to radiotherapy (RT) or surgery, re-treatment after toxicity, and current knowledge regarding ICI and vaccinations, and ICI and coronavirus diease-19 (COVID-19).

AUTOIMMUNE CONDITIONS

Patients with pre-existing AIDs were typically excluded from ICI clinical studies due to safety concerns about AID exacerbation. This concern relates to the role that both checkpoint molecules play in the maintenance of self-tolerance (Figure 1), with CTLA-4 having an early role during priming of T-cells in lymphatic tissues, and PD-1 modulating

*Correspondence to: Dr Samra Turajlic, Cancer Dynamics Laboratory, The Francis Crick Institute, 1 Midland Rd, Somers Town, London NW1 1AT, UK. Tel: +44-020-3796-1111

E-mail: samra.turajlic@crick.ac.uk (S. Turajlic).

† These authors contributed equally.

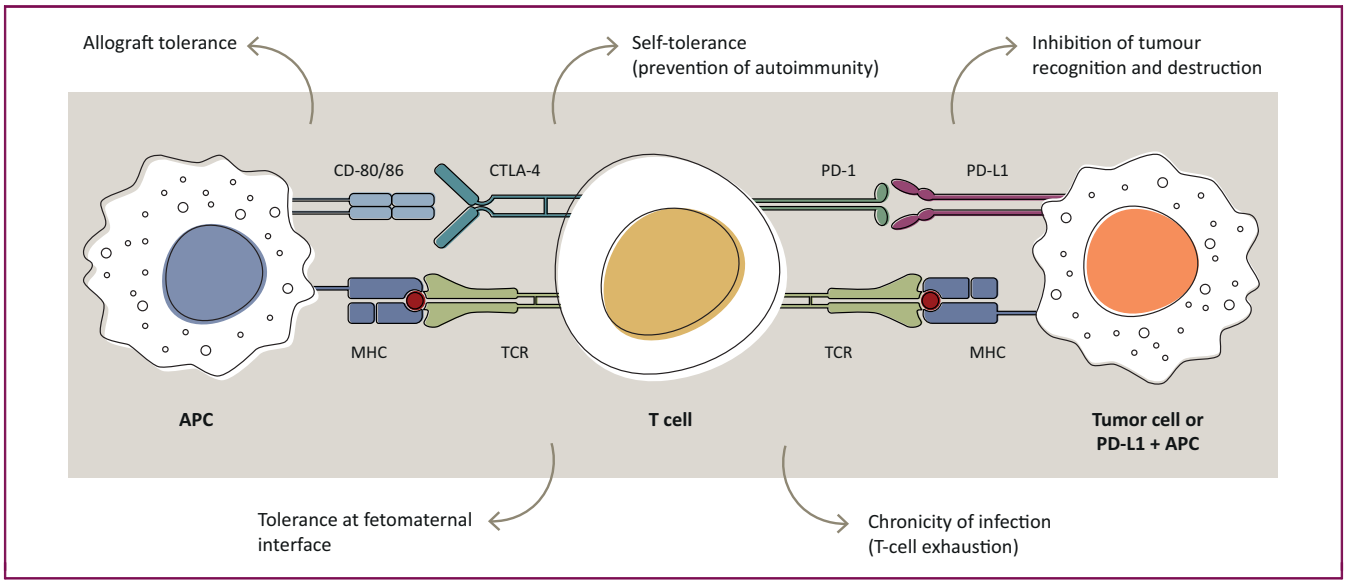

Figure 1. Schematic of CTLA-4 and PD-1 involvement in physiological and pathological T-cell-mediated processes.
Immune checkpoint molecules CTLA-4 and PD-1 are responsible for attenuating T-cell-mediated immune responses important in several physiological and pathological processes as shown. CTLA-4 functions primarily at sites of T-cell priming (i.e. secondary lymphoid organs) but can also attenuate T-cell function at peripheral sites. The primary function of PD-1 is to dampen T-cell activation in the periphery. APC, antigen-presenting cell; CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte antigen 4; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TCR, T-cell receptor. The figure was developed based on Wei et al.[1] and created with BioRender.com.

T-cell effector function in peripheral tissues,[3] issues especially relevant in established AID. Additionally, patients with AID often require immunosuppressive treatment, which may compromise ICI efficacy.[4]

Regarding the efficacy and overall toxicity of ICI in the AID population, in the first retrospective study of anti-PD-1 in AIDs, the objective response rate (ORR) was 33% in patients with melanoma, AID flares were common at 38% (6% grade 3) but otherwise 'conventional' irAEs occurred at rates similar to those previously reported in clinical studies (29% overall, 10% grade 3).[5] Subsequent retrospective studies of agents blocking PD-1 or its ligand (PD-L1) [primarily in melanoma and non-small-cell lung cancer (NSCLC)] reported similar findings (ORR: 22%-54%; AID flares: 6%-42%; irAEs: 16%-38%).[6-11] In the only prospective study to date (atezolizumab in urinary tract carcinoma), patients with AIDs ($n = 35$) had increased rates of irAEs (i.e. dermatological, hepatic, endocrine, and respiratory events and any AID flares) versus non-AID patients ($n = 962$) (46% versus 30%; 14% versus 6% grade $\geq$3).[12] AID flares occurred in 11%, but were manageable and rarely led to ICI discontinuation; ORR was 11% versus 14% in non-AID patients.[12] In a systematic review of 49 publications ($N = 123$, mainly melanoma and NSCLC), 50% of patients experienced AID flares, and 34% had new unrelated irAEs, most of which were manageable with corticosteroids and improved without discontinuing ICI.[13] Clinical activity of ICI appeared similar in AID and non-AID populations.[13] A phase Ib study of nivolumab in patients with unresectable/metastatic cancers and AIDs is ongoing (NCT03816345; estimated recruitment: $N = 264$).

Overall, considerations for treatment of AID patients with ICI are multifactorial. Firstly, the type of AID is of critical importance. As the majority of studies cover multiple AIDs each, it is difficult to paint a condition-specific picture. However, available reports suggest that rheumatological AIDs flare most frequently (44%)[5,8-11,14,15] psoriasis flares also appear common (43%),[5,7-9,11,14] while thyroid AID flares seem less frequent (13%)[5,7-9,14] (Table 1); all are easily managed with standard treatments. Inflammatory bowel disease (IBD) flares, in particular following CTLA-4 targeting, can result in significant clinical deterioration and morbidity,[5,6,8,9,11,14] and vigilance is warranted. Neurological AID experience is very limited but substantial flares of myasthenia gravis[5,7,9,16-20] and multiple sclerosis[7,9,12,14,21-23] occurred with anti-PD-(L)1. Secondly, baseline AID severity/level of disease activity and the required level of immunosuppression for adequate control of AID symptoms need consideration. The majority of patients in the available reports were generally asymptomatic or had mild/well-controlled disease at baseline. Data on those with severe active disease or those requiring high doses of immunosuppression for maintaining AID remission are lacking, which likely reflects the treating physician's reluctance to initiate ICI in those patients. Those with active symptoms and requiring immunosuppressants at baseline were shown to flare more frequently in one study,[5] but this was not confirmed in a systematic review of 123 patients.[13] A recent review found optimal anticancer activity without severe AID exacerbations when ICIs were administered with selective immunosuppressants (e.g. infliximab, tocilizumab, vedolizumab) in patients with active AIDs.[24]

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Table 1. Summary of findings from retrospective studies and case series/reports of ICI use in patients with cancer and specific AID groups[a]

AID type	Refs
Rheumatoid arthritis and other rheumatic diseases • Flares occurred in 44% of patients across studies (ranging from 6% to 67%) and were more common than in patients with other AIDs (40% versus 10% in one study); conventional irAEs occurred in 29% (13% grade >2) • Flares usually presented as reappearance of prior symptoms rather than new AID manifestations, were mild (grade >2 events in ~8%), and were generally easily managed with NSAIDs, low-dose oral, intraarticular, or topical corticosteroids	5,8-11,14,15
Skin and autoimmune thyroid dysfunction • Skin conditions (predominantly psoriasis) flared quite frequently (43%) but grade >2 events were uncommon (~7%); 45% had other conventional irAEs (19% grade >2) • Flares of thyroid AID were less frequent (13%) and all were mild (grade 1-2); 28% of patients had other conventional irAEs (6% grade >2) • Generally, flares and irAEs were amenable to standard treatment algorithms	5,7-9,11,14
Inflammatory bowel disease • In a study of 102 patients receiving ICI [anti-PD-(L)1, $n = 85$; anti-CTLA-4, $n = 17$]: ○ Any-grade colitis was higher than in patients without IBD (41% versus 11%); grade 3/4 colitis occurred in 36% of patients, and four (4%) had bowel perforations (versus ~2% published risk of colonic perforation with immune-mediated enterocolitis); anti-CTLA-4 antibodies were of particular risk ○ Most patients (76%) were treated with corticosteroids, 29% had treatment escalation to include infliximab or vedolizumab, and 52% required hospitalisation; gastrointestinal irAEs led to ICI discontinuation in 23% • Across other reports, 9 of 32 (28%) patients with IBD (majority asymptomatic or mild symptoms) experienced AID flares (seven severe)	6 5,8,9,11,14
Neurological conditions • Multiple sclerosis: 2 of 10 patients had MS relapses (both were treated with ipilimumab); 1 of 10 (with co-existing ulcerative colitis) experienced grade 1/2 pneumonitis that eventually necessitated permanent anti-PD-(L)1 discontinuation • Transverse myelitis: 1 of 1 patient experienced colitis whilst on ipilimumab, which was successfully managed with prednisone • Myasthenia gravis: 5 of 8 patients treated with anti-PD-(L)1 had disease flares (including one severe myasthenic crisis necessitating initiation of hospice care); 1 of 8 patients developed grade 3 pneumonitis • Others: no AID flares or other irAEs were reported for three patients with Guillain–Barré syndrome, one with chronic inflammatory demyelinating polyneuropathy and one with Bell's palsy	7,9,12,14,21-23 5,7,9,16-20 5,8

AID, autoimmune disease; CTLA-4, cytotoxic T-lymphocyte antigen 4; IBD, inflammatory bowel disease; ICI, immune checkpoint inhibitor; irAEs, immune-related adverse events; MS, multiple sclerosis; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio; PD-(L)1, programmed cell death (ligand) 1.
[a] Data on specific AIDs were extracted from individual studies where available and summary rates across studies are presented.

In summary, pre-existing mild-to-moderate AID does not necessarily prohibit ICI treatment, and many patients (~60%-90%) experience no or mild flares, not requiring ICI discontinuation or even corticosteroid initiation.[5,7-11,14,15] Those who do experience irAEs/flares can be often successfully managed with standard therapeutic algorithms. However, there are many areas where experience is lacking; e.g. little is known about ICI treatment of patients with moderate-to-severe AIDs or those with neurological AIDs specifically. In addition, severe and life-threatening exacerbations have been reported [e.g. severe cases of IBD with anti-CTLA-4,[6,11,14] severe myasthenic crisis with anti-PD-1[16]]. Thus, a personalised multidisciplinary management of such patients is required. An AID-tailored risk-based strategy was published recently, centred around the use of corticosteroid-sparing selective immunosuppression before ICI initiation where possible.[24]

PATIENTS WITH HIV OR HBV/HCV

Chronic infections, such as human immunodeficiency virus (HIV) or hepatitis B/C virus (HBV/HCV) infections, not only lead to immunosuppression but—just like cancer—are characterised by T-cell exhaustion, with abrogation of effector function (Figure 1).[25] This raises a theoretical concern of exceedingly blunted immune responses driving reduced ICI efficacy in cancer patients with co-existing chronic infections. However, it also creates a rationale for ICI use as a treatment for chronic infections, aimed at T-cell reinvigoration.[26]

In studies of HIV-infected patients with cancer, ICI treatment resulted in favourable antitumour activity with a safety profile similar to that reported previously in non-HIV populations (Table 2; Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2021.03.199), with the majority of irAEs being grade 1/2, and with no evidence of increased risk of immune reconstitution syndrome.[27-36] The majority of patients were on concomitant anti-retroviral therapy throughout ICI treatment, with no apparent detrimental changes to HIV viral load or CD4+ T-cell counts.[27-36] Responses occurred across multiple tumour types and were observed in patients with low baseline CD4+ counts, high baseline HIV viral load, or metastatic disease.[27-36] Findings regarding the effect of ICI on HIV latency (i.e. the ability to influence the persisting HIV reservoir within CD4+ cells) have been inconsistent.[37-41] However, immunological and virological features of HIV infection in ICI-treated cancer patients are under prospective investigation (NCT02408861, NCT03354936). Overall, available data suggest that HIV infection should not preclude ICI treatment as good clinical efficacy can be achieved with no increase in toxicity or impact on HIV control.

Similarly, in studies of ICI in HBV/HCV-infected patients, clinical activity and safety profile of ICIs appeared similar to that in non-infected patients across multiple tumour types (Table 2; Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2021.03.199).[29,30,42-46] In the largest-to-date retrospective study, HBV reactivation/flare was 5.3% (6/114).[45] Some patients experienced decreases in HCV RNA when on ICI,[30,42,43,47-50] consistent with the

Table 2. Summary of findings from prospective and key retrospective studies of ICI therapy in patients with HIV and HBV/HCV

Chronic viral infection type	Refs
HIV • In two phase I/II studies (mainly NSCLC, anal cancer, KS, NHL), response rates were 11%-17%, with grade ≥3 irAEs ranging from 0% to 20% • In nine retrospective reviews/case series (mainly lung cancer and melanoma), response rates varied from 21% to 67%, with grade ≥3 irAEs ranging from 0% to 25%	27-36
HBV/HCV • In two phase I/II studies in HCC, ORR was 7%-14% for those with concurrent HBV, and 17.6%-30% for those with HCV, with no new safety issues reported (grade ≥3 TRAEs: 6%-30%)[a] • In five retrospective studies across multiple cancer types (most commonly RCC, NPC, HCC, melanoma, NSCLC), response rates varied from 21% to 27%, with grade ≥3 irAEs ranging from 12.5% to 29% • Across studies, where data were available for HBV specifically, response rates varied from 6% to 23%, with grade ≥3 irAEs ranging from 9% to 13% • Across studies, where data were available for HCV specifically, response rates varied from 18% to 30%, with grade ≥3 irAEs ranging from 23% to 30%	29,30,42-46 42,45,46 42-44

HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; irAEs, immune-related adverse events; KS, Kaposi sarcoma; NHL, non-Hodgkin's lymphoma; NPC, nasopharyngeal cancer; NSCLC, non-small-cell lung cancer; RCC, renal cell carcinoma; TRAEs, treatment-emergent adverse events.

[a] Transaminitis after the first dose occurred in >50% patients (grade 3/4 in 45%) in a study of tremelimumab but was not associated with a decline in liver function, and did not recur in the subsequent cycles.

potential mechanism for viral control via ICI. In a systematic review of 186 ICI-treated patients with HBV/HCV and cancer [mainly hepatocellular carcinoma (HCC), melanoma, NSCLC], the overall rate of hepatitis was 1.9%, which was similar to that seen in patients without viral hepatitis.[51] The overall incidence of grade 3/4 transaminitis was 10.8% (HBV: 3.4%, HCV: 17.3%).[51] Although it is unclear as to why the grade 3/4 transaminitis rate was relatively high in HCV patients, all the grade 3/4 transaminitis events in HBV/HVC patients were reversible with antiviral treatment or steroids, and without the need for increased ICI treatment cessation.[51] Overall, 2.8% of patients without antiviral therapy experienced increased virus load.[51] In summary, ICI appeared to be effective and have a good safety profile, and treatment should not be contraindicated in patients with cancer and HBV/HCV infection. Although the risk of virus reactivation and virus-related hepatotoxicity appears to be low, patients with active HBV/HCV should routinely be monitored and treated with antiviral agents if indicated in close cooperation with hepatology and infectious disease experts.[51,52]

IMMUNODEFICIENCY, INCLUDING TRANSPLANT RECIPIENTS

Cancer patients may have a co-existing immunodeficiency, e.g. those with skin cancers often have chronic lymphocytic leukaemia (CLL). ICI experience in those patients is limited; however, in a recent retrospective study of ICI in patients with non-resectable skin cancer and concomitant haematological malignancy [most commonly CLL (38%)], ORR was 31.8% (14/44) for melanoma, 18.8% (3/16) for Merkel cell carcinoma, and 26.7% (4/15) for squamous cell carcinoma (SCC), with survival outcomes similar to those observed in a real-world immune-competent cohort, except for SCC, where they were lower.[53] ICIs are also an emerging treatment strategy for CLL itself, with early trials of anti-PD-1 suggesting activity in patients with Richter transformation, with overall acceptable toxicity.[54,55]

Immunocompromised state can also result from chronic immunosuppressive treatments, such as those received by transplant recipients. Furthermore, considering the role of CTLA-4 and PD-1 in the induction and maintenance of allograft tolerance (Figure 1),[56] ICI use may risk breaking tolerance and graft rejection. In allogeneic haematopoietic stem cell transplant (allo-HSCT), ICI may enhance allogeneic T-cell responses, improving graft-versus-tumour effect, but also potentially increasing graft-versus-host disease (GVHD).

ICI experience in solid organ transplant recipients is mainly derived from analyses of case reports/series, the largest of which is a systematic review of 83 cases (melanoma, HCC, cutaneous SCC) who were predominantly treated with anti-PD-(L)1 (73.5%).[57] Allograft rejection rate was 39.8% [kidney 43.4% (23/53), liver 37.5% (9/24), heart 16.7% (1/6)]. This resulted in end-stage organ failure in 71% of cases [kidney 72.7% (16/22), liver 75.0% (6/8), heart 0% (0/1)]; the ORR was 27.7%.[57] Increased risk with PD-(L)1-based versus CTLA-4-containing regimens was observed, although it was not statistically significant [hazard ratio (HR): 2.35; $P = 0.177$].[57] In the second largest review of 64 ICI-treated transplant recipients (mainly melanoma, HCC, lung cancer), 41% experienced graft rejection.[58] ORR in this population was 36%, with graft rejection rate similar in responders (36%) and non-responders (35%).[58] The highest rejection risk was observed with PD-1 inhibitors [48% (20/42) overall; 54% (13/24) nivolumab, 39% (7/18) pembrolizumab], and the lowest with ipilimumab [23% (3/13)].[58] Relatively high risk of rejection with anti-PD-1 was also shown in other reports,[58-66] and rates by organ type for this class are shown in Table 3. Renal transplant was the most common allograft type, with rejection rates of 42%-63% with anti-PD-1-based therapy[58-65] and a median time to rejection of 21-24 days from ICI start.[59,61] Underscoring

Table 3. Rate of allograft rejection with anti-PD-(L)1-based therapy in patients with cancer and solid organ transplants[a]

Organ	PD-(L)1 monotherapy	Anti-PD-(L)1 following ipilimumab	Ipilimumab + nivolumab	Refs
Kidney	42%-63%	50%[b]	25%-100%	58-65
Liver	25%-33%	0%-50%		58,59,62,64,66
Heart	0%-33%[b]	0%[c]		58,59,62
Lung	0%[c]			64
Cornea	100%[c]	0%[c]		58

PD-(L)1, programmed cell death (ligand) 1.

[a] Included patients may overlap across reviews of case studies/series.

[b] Based on <5 patients.

[c] Based on one patient only.

the potentially life-threatening consequences of anti-PD-1 use around transplant, a recent report detailed a case of an HCC patient who underwent liver transplant after 2 years of nivolumab treatment (last dose 8 days before transplantation) and subsequently suffered fatal acute hepatic necrosis in the immediate post-operative period resulting from a profound immune reaction likely enabled by nivolumab.[67] The main risk factors for graft rejection are yet to be clearly understood, but the use of $\geq$1 immunosuppressants other than steroids, longer time (>8 years) since transplant, and no history of prior rejection were found to confer lower risk.[57] It is unclear as to which immunosuppressive treatment adequately reduces rejection risk without significantly reducing ICI activity. Peri-infusional prednisone and mechanistic target of rapamycin inhibitors may aid allograft preservation,[24,59,60,68,69] but experience is limited (reviewed in Supplementary Text S1, available at https://doi.org/10.1016/j.annonc.2021.03.199) and prospective studies are needed. Because dialysis is an option following renal transplant failure, treatment with ICI is feasible in this setting if patients fully understand the risks and implications of possible renal failure. However, if the patient is not prepared to accept the risk of graft rejection and dialysis, anti-PD-1 should not be used. Unfortunately, no replacement alternatives exist in case of liver or heart allograft failure, and so anti-PD-1 treatment in those patients is not advisable.

Regarding ICI use around allo-HSCT, data exist mainly for Hodgkin's lymphoma (HL) and suggest that severe immune-related complications are frequent. In a systematic review of seven studies, receiving ICI [nivolumab (n = 91), pembrolizumab (n = 11), ipilimumab (n = 8)] before allo-HSCT was associated with high rate of disease control (ORR: 68%) but also high rates of hyperacute (7%), acute (56%), and chronic (29%) GVHD, with the overall GVHD mortality risk of 11%.[70] Accordingly, the nivolumab label carries Food and Drug Administration (FDA) warnings for allo-HSCT complications.[71] Data from two small studies of anti-PD-1 suggest that prophylactic cyclophosphamide post-transplant may improve GVHD-related outcomes in this population.[72,73] In a systematic review of 19 studies, receiving ICI [ipilimumab (n = 85), nivolumab (n = 76), pembrolizumab (n = 16)] after allo-HSCT had high efficacy (ORR: 54%) and risk of GVHD (14% acute, 11% chronic), with a GVHD mortality risk of 7%.[70] Incidentally, historical rates of GVHD in patients without any ICI exposure (before or after) were found to be 30%-50% for acute[70,74] and up to 28% for *de novo* chronic GVHD.[75] In the first prospective study of anti-PD-1 post-allo-HSCT (nivolumab, N = 28), irAEs and GVHD (two fatal) occurred, requiring dose de-escalation, with only modest antitumour activity (ORR: 32%), suggesting that this approach may require specific toxicity mitigation strategies.[76] Overall, published reports suggest that history of GVHD and shorter time between ICI and allo-HSCT may increase GVHD risk. Expert recommendations exist for ICI use before and after allo-HSCT in HL, offering guidance on patient selection, transplant strategy, ICI dose, and management in case of GVHD.[77]

ORGAN DYSFUNCTION, POOR PERFORMANCE STATUS, AND BRAIN METASTASES

Patients with organ dysfunction have limited treatment options and are typically excluded from clinical studies. Due to their unique pharmacological properties (e.g. independence of hepatic/renal clearance), ICI may be safer to use in such patients than other systemic therapies.[78] Experience is limited; however, some clinical studies permitted inclusion of patients with mild organ dysfunction. For example, two phase II studies of atezolizumab in urothelial carcinoma {one included patients with creatinine clearance of <60 ml/min, and one those with renal impairment [glomerular filtration rate (GFR): 30-60 ml/min]} demonstrated low incidence of clinically relevant treatment-related AEs (TRAEs), no renal function deterioration specifically,[79] and no meaningful impact on median overall survival (OS) (14.1 versus 15.9 months for all patients).[80] Regarding hepatic impairment, in the phase I/II CheckMate 040 study, nivolumab achieved durable responses with a good safety profile in patients with advanced HCC and cirrhosis, of whom 43% were categorised as Child—Pugh class B.[42] Grade 3-4 TRAEs occurred in 25% in the dose-escalation phase (n = 48) and in 19% in the dose-expansion phase (n = 214), with no treatment-related deaths. Data from these studies did not suggest increased susceptibility to specific irAEs of nephritis or hepatitis, respectively. A retrospective study of 27 patients with organ dysfunction (cardiac: left ventricular ejection fraction $\leq$45%; renal: creatinine $\geq$2mg/dl or GFR $\leq$30ml/min; hepatic: imaging consistent with cirrhosis or aspartate aminotransferase/alanine aminotransferase/bilirubin $\geq$3 $\times$ upper limit of normal) showed worsening organ dysfunction in eight patients; however, this was not immune-mediated and resolved with supportive care. Two patients had grade 3 irAEs, and the disease control rate was 48%.[81] Recently, a real-world analysis of ICI-treated melanoma patients with baseline renal (n = 46) or hepatic (n = 48) dysfunction (as per the Common Terminology Criteria for Adverse Events' laboratory values) suggested both shorter OS and real-world time to treatment discontinuation (rwTTD) versus patients without organ dysfunction.[82] Shortened OS and rwTTD were thought to possibly reflect toxicity, disease progression, or patient/physician preference for treatment discontinuation,[82] although this was not formally assessed. Overall, ICI use in patients with mild-to-moderate organ dysfunction appears safe and should not be contraindicated. As data on severe organ dysfunction are lacking, treatment of such patients should be approached with more caution and those patients need close monitoring.

Seven prospective studies of ICI monotherapy in NSCLC and urinary tract carcinoma have now included patients with Eastern Cooperative Oncology Group (ECOG) PS 2 (N = 712 total), showing good tolerability and safety profiles and antitumour activity comparable to the overall population

(especially in those whose tumours expressed PD-L1), although with evidence of shortened survival relative to the overall population (as expected based on poor PS)[80,83-88] (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2021.03.199). However, in a meta-analysis of 19 retrospective NSCLC studies, patients with ECOG $\geq$2 had worse outcomes versus ECOG 0-1 [OS HR: 2.72, $P < 0.001$; progression-free survival HR: 2.39, $P < 0.0001$; ORR odds ratio (OR): 0.25, $P = 0.001$].[89] In other tumour types, data are limited and come from retrospective analyses or case series/reports. For example, in 27 patients with microsatellite instability-high solid tumours and ECOG 2-3, response rate with anti-PD-(L)1 was 33% (versus up to 50% with good PS, historically), but 52% of patients had an improvement of PS.[90] However, in 24 anti-PD-1-treated melanoma patients with ECOG 2-3, outcomes were poor (ORR: 12% versus 39% ECOG 0-1), and those patients were also more likely to be treated and hospitalised within the last month of life and die in the hospital.[91] Another analysis of 157 patients with solid tumours showed that 27% received an ICI dose in the last 30 days of life, which was associated with ECOG $\geq$3, lower hospice enrolment, and dying in the hospital.[92] Overall, although ICI appear safe in patients with poor PS, activity evidence is mixed. This is a heterogeneous population, where poor PS may be driven by cancer burden, cancer progression rate (either of which may co-exist/overlap with mechanisms of primary ICI resistance), unrelated comorbidities, or a combination of all these factors. Thus, each patient's suitability for ICI treatment should be considered individually.

Finally, in patients with BrM, data from four phase II ICI studies, mainly in melanoma, have shown an intracranial benefit rate of up to 57% which is generally on par with extracranial benefit rate.[93-96] Available data suggest that anti-PD-1 + anti-CTLA-4 combinations achieve higher intracranial response rates (ICRs) than single-agent anti-PD-1. For example, ICR was 46% with ipilimumab + nivolumab versus 20% with nivolumab alone in one study,[94] and single-agent pembrolizumab achieved a relatively low ICR of 26% in another.[97] Furthermore, lower response rates were shown in symptomatic versus asymptomatic BrM, e.g. ICR of 16.7% versus 54.5% with ipilimumab + nivolumab,[98] or 5% versus 16% with ipilimumab alone.[95] Overall, we believe patients with asymptomatic/locally treated BrMs should be considered in the same way as those without BrMs and receive ICIs (anti-PD-1 + anti-CTLA-4 combination, where possible) as standard of care, and be able to participate in clinical studies of these agents, whether in melanoma, lung, kidney, or other cancers in which ICIs are active.[99] The efficacy of ICI in active symptomatic BrMs, including the exact sequencing with other treatment modalities, and in patients with leptomeningeal disease requires ongoing investigation.[99]

ICI IN CHILDREN AND THE ELDERLY

Children and adolescents

The 2020 Paediatric Strategy Forum by the multistakeholder organisation ACCELERATE and the European Medicines Agency stated that ICI monotherapy has limited activity in paediatric oncology apart from HL and some hypermutant tumours.[100] However, ICIs may still be relevant in children and adolescents with typically adult tumours, where efficacy and safety of these agents is well established, e.g. melanoma. Although the early clinical studies showed that the safety profile of ICIs in children was like that seen in adults,[101-105] the implications of endocrine toxicities such as thyroiditis or hypophysitis carry a different burden in paediatric patients, with wide-reaching implications for growth, puberty, and fertility, and, by extension, psychological well-being. Therefore, relevant screening tests at appropriate stages of growth and development should be carried out, ideally in close cooperation with paediatric endocrinologists.[106] Additionally, as many of those patients will be treated with curative intent and will be expected to live for decades, systematic follow-up well into adulthood will be crucial to detect any significant/unexpected late toxicities and to understand any impact ICIs may have on quality of life.[107]

Elderly

In a meta-analysis of nine randomised controlled trials (RCTs) of anti-PD-(L)1 across four tumour types [five NSCLC, two melanoma, one renal cell carcinoma (RCC), one head and neck cancer], survival was comparable in patients aged $\geq$65 and <65 years (HR: 0.64 versus 0.68), but the data were insufficient to draw any conclusions for patients aged $\geq$75 years.[108] In NSCLC, an FDA meta-analysis of four RCTs of anti-PD-(L)1 and two recently published post-approval nivolumab studies showed similar survival benefits regardless of age (using <65-, $\geq$65-, $\geq$70-, or $\geq$75-year cut-offs).[83,84,109] In RCC, a recent review of five studies concluded that, although data are poor because of low accrual and events for elderly patients, ICIs appear to provide benefit in patients aged $\geq$65 years.[110] In melanoma, there is evidence of better efficacy in older versus younger patients,[111,112] which may result from chronic sun exposure and increased tumour mutational burden and the fact that younger patients have a higher proportion of intratumoural regulatory T cells, which constrains antitumour immunity.[112] Regarding the safety and tolerability of ICI in the elderly, studies suggest that this is similar to that reported for overall population, and overall toxicity is less than that reported with chemotherapy.[83,84,109,113-116] Real-world data suggest that, rather than age, toxicities and worse outcomes with ICI in the elderly are more likely associated with poor PS or comorbidities.[115,117,118]

Overall, the available data suggest that ICIs have a good safety profile and show activity in elderly patients. Comprehensive geriatric assessment, rather than chronological age alone, should guide treatment in this population.[119] Individual assessment of comorbidities, concurrent medications, and functional reserve will be helpful to balance the benefits of ICI therapy with risks of irAEs, which may have a more profound impact in the older versus younger patients.

PREGNANCY

Although malignancies are generally more common in the elderly, conditions such as melanoma or lymphoma disproportionally affect the young, melanoma being one of the most frequent gestational cancers.[120] Checkpoint molecules are implicated in the immune tolerance of semiallogeneic fetus (Figure 1), and their blockade resulted in spontaneous abortions, premature deliveries, and fetal deaths in animal studies.[121-123] Preclinical studies of nivolumab showed no teratogenic effects in surviving offspring, but some congenital abnormalities were noted with ipilimumab; however, these were judged of unclear relation to the drug.[123,124] Product labels necessitate effective contraception during treatment and for up to 5 months after the last ICI dose,[123-130] and human data are scarce. A total of five cases have been reported (all in metastatic melanoma) of ICI administration in pregnancy: one introduced at week 9 of pregnancy, one in the second trimester, and in three cases conception occurred whilst the patient was receiving ICI (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2021.03.199).[131-134] Obstetric complications occurred in three cases [one placental insufficiency and fetal bradycardia (ICI started at the ninth week; discontinued in the second trimester),[132] two intrauterine growth restrictions (in both, conception occurred on ICI; one discontinued in the first trimester and one continued until elective delivery at week 32)[131,135]]; upon follow-up, all infants were meeting developmental milestones and/or were in good health. These limited cases illustrate that favourable outcomes can be achieved in fetuses with *in utero* ICI exposure and offer some experience for the management of pregnancies in patients on ICI, but the knowledge is extremely limited. Because of evidence suggesting that gestation beyond 36 weeks may increase transplacental melanoma risk, elective delivery at 34-36 weeks should be considered in those diagnosed with gestational melanoma,[131] followed by systemic therapy. Generally, the approach should involve a multidisciplinary team of obstetricians, paediatricians/fetal medicine specialists, and oncologists, aiming to deliver as early and safely as possible in order to start systemic therapy for the mother and reduce the possibility of transplacental spread, with examination of the placenta and close follow-up of the child.

SEQUENCING TREATMENT BEFORE AND AFTER ICI

As sequencing of anticancer therapy in clinical studies is dictated by strict wash-out periods, limited data exist to guide real-life sequencing to/from ICI, with no standardised switch points. A retrospective study of melanoma patients switching to ICI whilst deriving benefit (sDR, $n = 37$) or at progression (sPD, $n = 37$) on BRAF/MEK targeted therapy (TT), showed a trend towards survival benefit for the sDR group (median OS: 30.8 versus 14.1 months sPD, HR: 0.48).[136] In a pooled analysis of data from three pembrolizumab studies, patients with BRAF-mutant melanoma and prior TT had baseline characteristics with worse prognosis and worse tumour outcomes versus the TT-naive group, albeit safety was similar.[137] Regarding switching from ICI, 11 of 18 (61%) melanoma patients initiated on TT at a median of 28 days after anti-PD-1 therapy developed toxicities requiring dose modifications/delays, including four grade 3 rash and two cytokine release syndrome cases.[138] Responses occurred in 8 of 10 patients requiring and 4 of 7 not requiring TT dose modifications.[138] In another retrospective melanoma study ($N = 78$), the standard dose and schedule of the TT regimen (initiated after a median of 34 days after the last ICI dose) did not appear to be tolerated, as well as in the front-line setting, with 65 patients (83%) needing $\geq$1 dose modification.[139] Fever was a common AE (73%) that tended to be severe and occur early (median: 1.9 weeks), followed by rash (36%, median: 4.4 weeks).[139] Cytopenia, an AE not described in the prospective TT trials, occurred in 13%, and 25 regimens (32%) resulted in $\geq$1 hospitalisations.[139] However, it is difficult to ascertain whether the observed safety profile was reflective of the potentiation of TT AEs by prior ICI exposure, progressing disease/disease burden, or both. In RCC, retrospective studies of second-line vascular endothelial growth factor (receptor)-tyrosine kinase inhibitors [VEGF(R)-TKIs], initiated at a median of ~4-5 weeks after ICI-based regimens, showed ORRs of 29%-41% and a safety profile generally typical for the class, with a potential toxicity signal for transaminitis suggested in one small series (grade 3/4, 9%).[140-142] However, the impact on AEs that overlap between classes, e.g. diarrhoea with ICI and VEGF(R)-TKIs, cannot be distinguished unless specifically investigated. In NSCLC, an increased pneumonitis risk has been reported for endothelial growth factor receptor (EGFR)-TKIs and ICI combination versus either agent alone, and when EGFR-TKIs (especially osimertinib) were used post-ICI (but not before ICI).[143-145] Collectively, there may be an increased propensity for toxicity after a switch from ICI, consistent with long receptor occupancy of ICI, and vigilance is recommended.

TIMING OF ICI TREATMENT WITH SURGERY OR RADIOTHERAPY

As immunotherapy becomes more widely used, it may lead to a close temporal association with surgery, including as a neoadjuvant agent or in the setting of metastasectomies, bringing a new set of challenges regarding safety and feasibility of ICI around resection. Clinical data from neoadjuvant studies in melanoma[146-149] and NSCLC[150-152] showed evidence of effective pathological remission and prolonged survival, with no indications of increased complications reported to date. A series of 17 patients who underwent various resections without interrupting their ICI regimen also suggested no safety concerns perioperatively.[153] Although ICI toxicities may lead to steroid use, currently there is no evidence for concern regarding ICI and surgery. Considering RT, in a retrospective study of 53 melanoma patients on anti-PD-1 who received either extracranial or intracranial RT, response rate was 64% with

concurrent versus 44% sequential stereotactic treatment ($P = 0.448$). There was no excessive anti-PD-1 or RT toxicity with extracranial RT, and anti-PD-1 and whole-brain radiation were generally well tolerated albeit with rare toxicities of uncertain aetiology.[154] NSCLC studies of concurrent stereotactic body RT and anti-PD-1 showed improved activity with acceptable toxicity (with one study reporting toxicities to predominantly occur in the irradiated region).[155,156] In melanoma BrM, two systematic reviews of retrospective data suggest that RT and ICI can be used concurrently for improved efficacy.[157,158] In small retrospective studies (predominantly of ipilimumab), radionecrosis rates ranged from 0% to 20.7%.[157] In a large retrospective analysis of brain RT received during or within 1 year before anti-PD-1, the cumulative incidence of radionecrosis at 2 years was 18%, suggesting that it may represent an emerging long-term complication.[159]

RE-TREATMENT AFTER TOXICITY

Trials typically mandate permanent ICI discontinuation after grade $\geq$3 toxicity, with 38% of patients discontinuing for this reason in studies of ipilimumab + nivolumab in melanoma.[160,161] Despite evidence for improved survival in some patients who were re-challenged with ICI after a toxicity,[162,163] physicians are understandably hesitant to resume treatment with the same agent because of the risk of repeat toxicity, especially in patients who experienced a grade 3/4 irAE.

A number of retrospective studies have examined ICI re-challenge. By far the largest is the World Health Organization's pharmacovigilance data analysis, which contains case reports from 130 countries and across multiple tumour types.[164] In this analysis, 25% of the total 24 079 identified irAEs were associated with ICI re-treatment.[164] Of 452 informative irAEs [81.9% anti-PD-(L)1, 13.3% anti-PD-(L)1 + anti-CTLA-4, 4.9% anti-CTLA-4], 130 (28.8%) were recurrences [most commonly colitis (27.7%), pneumonitis (22.8%), and thyroiditis (13.5%)] and 4.4% were new irAEs.[164] The recurrence rate was 28.6% after anti-PD-(L)1 monotherapy, 43.5% after combination therapy, and 47.4% after anti-CTLA-4 monotherapy resumption.[164] In the multivariate analysis, factors associated with a higher irAE recurrence rate were anti-CTLA-4 regimen (OR: 3.5; $P = 0.04$), age, colitis (OR: 2.99; $P < 0.001$), hepatitis (OR: 3.38; $P = 0.01$), and pneumonitis (OR: 2.26; $P = 0.01$).[164] In other retrospective studies of ICI re-treatment/resumption, the incidence of flares was 18%-44%, but more new irAEs were observed (12.5%-26%).[163,165-167] In two studies of switching (ipilimumab to anti-PD-1 and vice versa), increased irAE rates were also seen versus front-line setting for the individual agents.[5,168] Findings of those studies are summarised in the Supplementary Text S2, available at https://doi.org/10.1016/j.annonc.2021.03.199.

Overall, re-challenge may be clinically beneficial and feasible in select patients, particularly those who had mild and easily manageable irAEs and/or who have limited alternative treatment options. Ideally, any re-challenge should be attempted: (i) with a single agent; (ii) only in patients with non-life-threatening, immunosuppression-sensitive, and resolved/well-controlled irAEs; and (iii) after a personalised risk assessment in a multidisciplinary centre experienced in the treatment of irAEs.[169] A possible prophylactic algorithm has been recently published,[169] although its feasibility will vary by country, and ICI efficacy in this setting has not been well established.

VACCINATIONS

In principle, inactive vaccines (e.g. influenza, pneumococcal) should be safe to administer alongside ICIs, whilst live vaccines (e.g. shingles) should be avoided. Current experience on vaccination in ICI-treated cancer patients comes from studies of influenza, and generally suggests efficacy of influenza vaccination with seroprotection rates of ~70%, no negative effects on cancer outcomes, and, apart from one study, no increased toxicity (Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2021.03.199).[170-173] Curiously, one retrospective study suggested that influenza vaccine may not be effective but may prolong survival in vaccinated versus non-vaccinated lung cancer patients on ICIs.[174] Regarding possible factors affecting the frequency of irAEs, no difference was observed with trivalent versus quadrivalent vaccines or with different timing of vaccination and ICI initiation (prior, on the day, after).[171]

Experience with vaccines other than influenza is limited; however, an observational study of pneumococcal vaccine in ICI-treated cancer patients is planned (NCT03989050). Finally, it will also be important to understand how safe any severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine will be in cancer patients undergoing ICI treatment, whether it will induce long-term immunity, and whether it may influence tumour response and irAE rates. Regarding SARS-CoV-2 infection, so far there is evidence of humoral immunity wane after mild disease,[175] induction of SARS-CoV-2-specific T cells with stem cell-like memory phenotype,[176] and a crucial role for adequate coordination of adaptive immune responses.[177] It remains to be seen whether these findings will be confirmed in cancer patients, and whether ICI exposure will have any effect on SARS-CoV-2 immunity. Prospective studies, such as COVID-19 antiviral response in a pan-tumour immune monitoring study (CAPTURE), evaluating peripheral immune response following SARS-CoV-2 infection or vaccination, will provide more concrete evidence.[178]

COVID-19

Theoretically, ICIs could be seen as a double-edged sword with regard to COVID-19, with restoration of immunocompetence on the one hand, and immune overdrive and ICI toxicities exacerbating the hyperinflammation-driven pathology behind severe COVID-19 on the other.[179] The largest published study on cancer and COVID-19 (COVID-19 and Cancer Consortium, $N = 928$) found no association between anticancer therapy type and mortality risk; however, the majority of patients (60%) were not on active

Box 1. Key findings of ICI use in non-trial populations

- Treatment of special cancer populations with ICIs requires personalised approach with multidisciplinary involvement of specialists from relevant areas of medicine
- Pre-existing mild-to-moderate AID is not an absolute contraindication to ICI treatment and flares can be often successfully managed with standard treatment algorithms
- With appropriate use of antiviral medication, HIV, HBV, or HCV infection should not be a barrier to ICI treatment as good clinical efficacy can be achieved with no increase in toxicity and generally no impact on viral control
- Treatment of solid organ transplant recipients with PD-(L)1 inhibitors is generally not recommended, with the exception of renal transplant patients if prepared to convert to dialysis
- ICI use in patients with mild-to-moderate organ dysfunction appear to be safe and should not be contraindicated
- ICIs have a good safety profile and show activity in elderly patients and appropriateness of use will depend on the individual ability to tolerate irAEs
- ICIs may be relevant in paediatric patients with typically adult tumours (e.g. melanoma) but screening at appropriate stages of growth and development should be employed to monitor for effects of any endocrine toxicities
- There may be an increased propensity for toxicity after a switch from ICI to a targeted agent and vigilance is recommended
- Data suggest that combining ICI and RT improves tumour outcomes but radionecrosis may be an emerging long-term side-effect
- Re-challenge with ICI after an irAE may be clinically beneficial and feasible in select patients, particularly those who had mild and easily manageable irAEs and/or who have limited alternative treatment options
- In general, non-live vaccines (e.g. influenza, pneumococcal) should be safe to administer alongside ICIs, whilst live vaccines (e.g. shingles) should be avoided
- Available data suggest that ICIs do not appear to increase the risk of COVID-19 severity or death in cancer patients

AID, autoimmune disease; COVID-19, coronavirus disease-19; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICIs, immune checkpoint inhibitors; irAE, immune-related adverse event; PD-L(1), programmed cell death (ligand) 1; RT, radiotherapy.

treatment, and only <4% were on ICIs.[180] In another single-centre retrospective review ($N = 423$), ICIs were associated with severe COVID-19 outcomes; however, only 31 patients were receiving ICI, of whom 10 had lung cancer (which itself was an independent risk factor for severe outcomes).[181] In fact, a report of 69 lung cancer patients from the same centre found no association between anti-PD-1 and increased risk of COVID-19 severity.[182] Furthermore, data from the Thoracic Cancers International COVID-19 Collaboration (TERAVOLT) registry ($N = 200$) showed that, although patients with thoracic malignancies and COVID-19 had a high mortality rate (33%), this was not associated with any specific anticancer treatment.[183] Finally, in the UK Coronavirus Cancer Monitoring Project registry, analysis of 800 patients did not find a significant effect of immunotherapy received within the past 4 weeks on mortality [$n = 44$; OR: 0·59 (95% confidence interval: 0.27-1.27); $P = 0.177$],[184] and a multicentre retrospective analysis found that COVID-19 mortality among 113 cancer patients on ICI was similar to that reported for the general cancer population (8% versus 7.6%-12%).[185] Overall, evidence suggests that ICIs independently do not appear to increase the risk of COVID-19 severity or death in cancer patients, and remain a suitable treatment option during the current pandemic. Furthermore, SARS-CoV-2 status should likely be confirmed via large-scale screening before receiving any systemic anticancer therapy.

LIMITATIONS

The aim of this review was to provide an overview of data on ICI use outside clinical trials. This represents a limitation on its own as the majority of such data were collected retrospectively. Additionally, certain amount of bias is unavoidable in this setting, e.g. publication bias is unfortunately expected when efficacy is disappointing and/or safety concerning. We have striven to evaluate available evidence in a careful and balanced manner but also explicitly advocated caution when we believed it was due. Furthermore, most of the experience with ICI in those challenging scenarios was acquired in specialised, tertiary cancer centres that benefit from a high level of expertise and multidisciplinary input. This may represent a selection bias in the available publications, and similar ICI experience may not be replicable in less specialised institutions. Therefore, especially in institutions with limited ICI experience, caution is warranted when considering ICI use outside of approved indications, and challenging cases should be treated in, or supported by, experienced centres. Although a

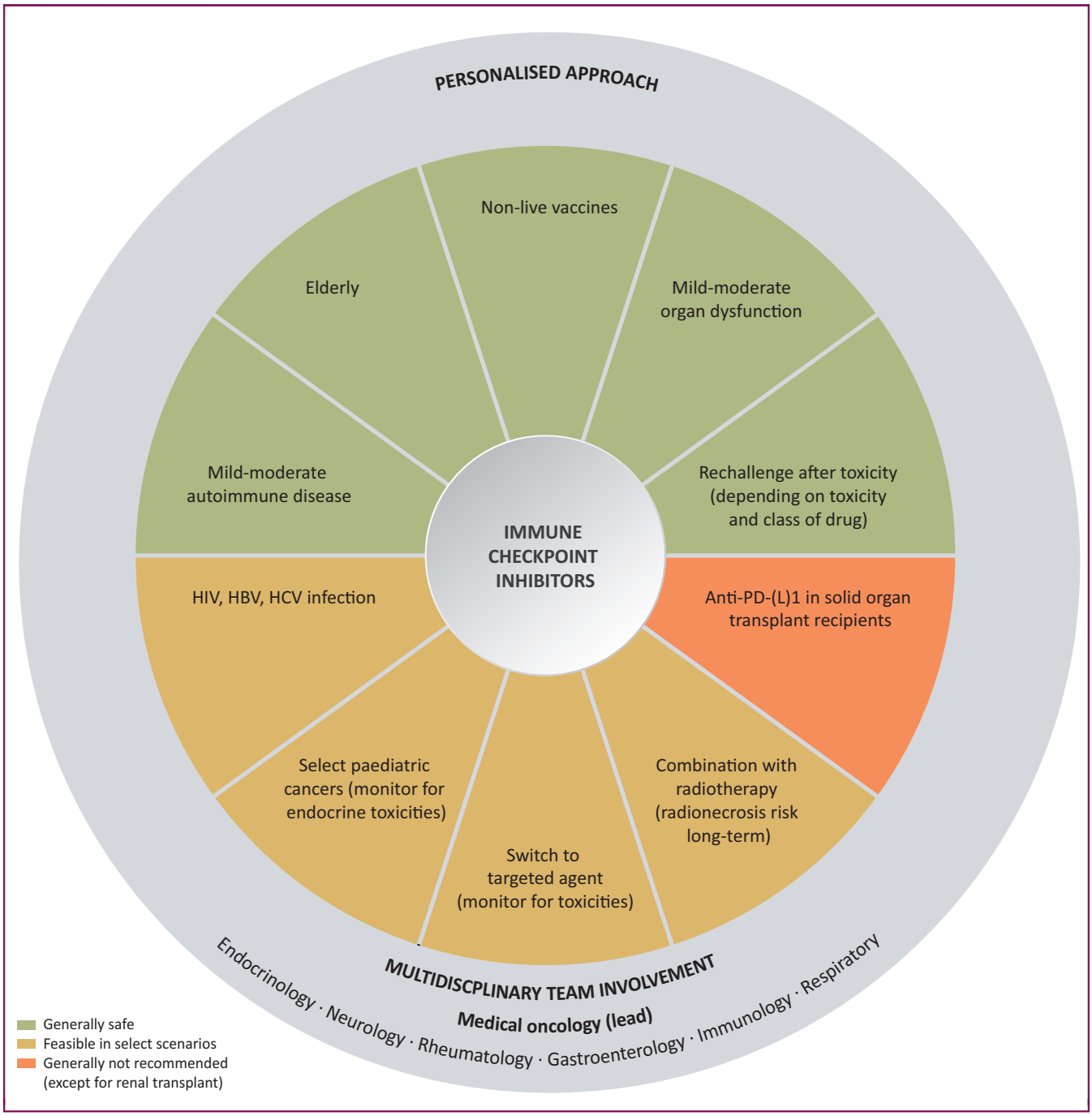

Figure 2. Summary of findings on immune checkpoint inhibitor (ICI) treatment in non-trial populations.
HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

higher level of uncertainty or risk may be acceptable when considering ICI treatment in patients who ultimately have no other options, all the above limitations should be borne in mind when making the decision to treat.

CONCLUSIONS

A growing number of patients are being treated with ICIs in the real world, including those traditionally considered trial-ineligible. Available evidence suggests that ICIs are often active in those populations and have an acceptable safety profile in most settings; key findings are summarised in Box 1 and Figure 2. Ultimately, clinicians must balance the risks of toxicity with potential benefits, considering factors such as underlying cancer type, alternative treatment options, or activity in trial-eligible patients. Decision-making should be personalised and supported by multidisciplinary teams, including specialists from relevant medical fields outside of oncology where needed. Toxicity prophylaxis could be put in place where possible and vigilance is advised to allow early recognition of AEs.

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