Review

*For reprint orders, please contact: reprints@futuremedicine.com*

Melanoma Management

# Checkpoint inhibitor use in two heart transplant patients with metastatic melanoma and review of high-risk populations

Michael J Grant*[,1], Nicholas DeVito[2] & April K S Salama[2]

[1]Department of Medicine, Duke University Medical Center, Durham, NC 27710, USA

[2]Duke Cancer Institute, Duke University Medical Center, Durham, NC, USA

*Author for correspondence: Tel.: +1 919 681 9509; Michael.grant@duke.edu

## Practice points

- Three groups that were excluded or under-represented in major clinical trials involving immune checkpoint inhibitors were patients with autoimmune disease, solid and hematopoietic stem cell transplants, and chronic viral infections.
- Retrospective studies on patients with autoimmune disease treated with immune checkpoint inhibitors show that about 50% of patients will experience either a flare of their pre-existing autoimmune disease or immune-related adverse event that is grade 3 or higher.
- Most autoimmune disease flares were well-controlled with corticosteroids and rates of checkpoint inhibitor discontinuation and mortality rates were very low in the studies.
- Checkpoint inhibitor therapy seems to be associated with a decrease or at least a stable suppression of viral load/viral antigens in patients with chronic hepatitis B virus and hepatitis C virus infection and this may be related to abrogation of an 'exhaustive' T-cell phenotype associated with these infections.
- Emerging data on patients with HIV infection and malignancy allude to a promising safety profile in these patients as well as the possible beneficial effect of diminishing HIV reservoirs.
- In the solid organ transplant population, inhibitors of PD-1 and sequential treatment with PD-1 and CTLA-4 inhibitors seem to be more prone to cause rejection.
- Case reports support the use of sirolimus for immunosuppression in transplant patients with malignancy (usually in conjunction with low-dose prednisone) and this is further supported by literature on the drug's mechanistic properties.
- Patients from all populations discussed in this review should be closely monitored for both disease- and immune checkpoint inhibitor-specific complications that may arise.
- It will be crucial to involve respective specialists in treating these patients including, but not limited to, neurologists, dermatologists, rheumatologists, infectious disease and transplant physicians among many others. A multidisciplinary approach will be invaluable.
- Patients should be made aware of possible, even if rare, complications related to therapy and their respective comorbidities. Treatment should only ensue after proper education, and discussions have taken place.
- There is a need for larger retrospective analyses, prospective cohort studies and randomized controlled trials to study the safety and efficacy of immune checkpoint inhibitor use in these populations.

Due to the unique side-effect profile of immune checkpoint inhibitors (ICIs), groups of patients deemed to be at high risk of complications were excluded from trials that proved the efficacy and safety of these agents in patients with various malignancies. Among these excluded patients were those with prior solid organ transplantation, chronic viral infections and pre-existing autoimmune diseases including paraneoplastic syndromes. We present follow-up on a patient from a previously published case report with an orthotopic heart transplantation who was treated with both cytotoxic T-lymphocyte antigen 4 and PD-1 inhibition safely, without organ rejection. Additionally, we describe the case of a patient with a cardiac allograft who also did not experience organ rejection after treatment with pembrolizumab. Through smaller trials, retrospective analyses, case series and individual case reports, we are accumulating initial data on how these agents are tolerated by the aforementioned groups. Our survey of the literature has found more evidence of organ transplant rejection in patients treated with PD-1 inhibitors than those treated with inhibitors of cytotoxic T-lymphocyte antigen 4. Patients with chronic viral infections, espe-

Future Medicine

cially hepatitis C, seem to have little to no risk of treatment-related increase in serum RNA levels. The literature contains few documented cases of devastating exacerbations of pre-existing autoimmune disease during treatment with ICIs, and flares seem to be easily controlled by immunosuppression in the vast majority of cases. Last, several cases allude to a promising role for disease-specific antibodies and other serum biomarkers in identifying patients at high risk of developing certain immune-related adverse events, detecting subclinical immune-related adverse event onset, and monitoring treatment response to immunosuppressive therapy in patients treated with ICIs. Though these excluded populations have not been well studied in randomized placebo-controlled trials, we may be able to learn and derive hypotheses from the existing observational data in the literature.

First draft submitted: 15 February 2018; Accepted for publication: 3 August 2018; Published online: 26 October 2018

**Keywords:** autoimmune • challenging • checkpoint inhibitor • CTLA-4 • hepatitis B virus • hepatitis C virus • human immunodeficiency virus • PD-1 • transplant

Immune checkpoint inhibitors, including inhibitors of CTLA-4, PD-1 and the ligand to PD-1 (PD-L1) comprise a class of immunotherapeutic agents that have become widely used in the treatment of several common malignancies. These medications work by inhibiting negative regulators (checkpoints) of T-cell function that exist in both immune and tumor cells to enhance antitumor activity of the immune system [1]. Three immune checkpoint inhibitors that are currently US FDA-approved and indicated in the treatment of metastatic melanoma are ipilimumab (anti-CTLA-4), nivolumab and pembrolizumab (anti-PD-1) [85,86,87]. Ipilimumab has been FDA approved for the treatment of metastatic melanoma, and in the adjuvant setting to reduce the risk of recurrence after melanoma resection [85]. In addition to melanoma, nivolumab has been approved for metastatic non-small-cell lung cancer (NSCLC), renal cell carcinoma, classical Hodgkin lymphoma, squamous cell carcinoma of the head and neck, and microsatellite instability high or mismatch repair deficient metastatic colorectal cancer [86]. Likewise, pembrolizumab is currently also FDA-approved for recurrent or metastatic head and neck cancer and NSCLC as well as unresectable or metastatic, microsatellite instability high or mismatch repair deficient solid tumors [87]. This class of agents has a unique side-effect profile that is directly related to the immune-modulating mechanisms of action. Side effects are often referred to as 'immune-related adverse events (irAE)', which result from blocking negative regulators of immunity. This mimics autoreactivity by inciting inflammatory reactions in certain tissues through unchecked immune activation [1]. Several groups have been excluded or under-represented in major clinical trials that demonstrated the efficacy and safety of these agents. This includes patients with autoimmune disease, solid and hematopoietic stem cell transplantation, chronic viral infections (hepatitis C virus [HCV], hepatitis B virus [HBV], HIV), elderly patients, pregnant patients, patients on immune suppression for other reasons, and patients who have developed irAEs with another immune checkpoint inhibitor (ICI). Thus, when clinicians are presented with a patient who has one of these comorbid conditions, only small trials and case reports can assist in directing management. We previously presented a patient with a history of orthotopic heart transplantation who developed metastatic melanoma and was treated with ipilimumab followed by pembrolizumab [4]. In this report, we present follow-up on this case, a new case of a similar patient, and a review of the literature of ICIs in a subset of less well-studied populations: those with previously diagnosed autoimmune disease, chronic viral infections and prior solid organ transplants. Due to the paucity of clinical trial data in patients with cancer and certain immune-related co-morbidities, further study is needed to evaluate the safety of immune checkpoint blockade in these populations.

## Case 1: follow-up

We previously reported a 62-year-old male patient, who had undergone orthotopic heart transplantation, was maintained on chronic immunosuppression, and subsequently developed *BRAF* wild-type, *NRAS* wild-type metastatic melanoma. He was treated with ipilimumab for four cycles with interval increase in size of a fluorodeoxyglucose-avid left subpectoral lymph node as well as two new pulmonary metastases. A repeat PET/CT scan 2 months later showed further increase in size of several subpectoral nodes as well as the pulmonary nodules. At this time, he was initiated on pembrolizumab. After three cycles of pembrolizumab, he had slight enlargement of existing nodes and interval appearance of one subpectoral lymph node. He also had enlargement of previously documented pulmonary nodules. He received an additional four cycles of pembrolizumab, with continued disease progression. During this time, he had no significant adverse events and no signs or symptoms of organ rejection. He then received two cycles

of temozolomide; however, scans again showed progressive disease. Because of concern of local symptoms in the axilla, he received a course of radiation therapy to the right axilla, followed by re-initiation of pembrolizumab for four cycles. Scans continued to demonstrate progression, and his overall performance status continued to decline. He ultimately succumbed to metastatic melanoma with pulmonary involvement nearly 2 years after initiation of pembrolizumab. Throughout his melanoma treatment, he was continued on tacrolimus for chronic immunosuppression with no evidence of transplant rejection or impaired cardiac function. An echocardiogram shortly before the patient expired showed only mild left ventricular dysfunction with ejection fraction of 45% with normal right ventricular function consistent with pre-ipilimumab cardiac function. Ultimately, this patient did not have a clinical response to either ipilimumab or pembrolizumab, but demonstrated tolerance to both agents without evidence of significant allograft compromise.

## Case 2: new report

Our second patient is a 67-year-old male who underwent an orthotopic heart transplant in 2008 for ischemic cardiomyopathy who was maintained on tacrolimus and mycophenolate mofetil with a single episode of acute graft rejection in 2011. At this time he was treated with high-dose steroids and antithymocyte globulin with resolution of rejection and preservation of cardiac transplant function. He presented to our institution in 2016 for evaluation of metastatic melanoma.

The patient was initially diagnosed with melanoma of his right scalp in October 2013 and underwent a wide excision and sentinel lymph node biopsy with 0/7 nodes positive. Three years later, during routine follow-up for his cardiac transplant, he was found to have a new pulmonary nodule on x-ray. He underwent computed tomography (CT) imaging which showed multiple pulmonary nodules and bilateral hilar lymphadenopathy. A lung biopsy was performed in April 2016 and pathology was consistent with metastatic melanoma. PET/CT imaging showed multifocal metastatic disease with both pulmonary and osseous involvement. He presented to the Duke Melanoma Clinic in May 2016 to discuss treatment options. Mutational analysis revealed the presence of an *NRASQ61L* mutation. Trametinib was initiated, but treatment was complicated by severe rash and the patient was found to have progressive disease on imaging after one cycle. After discussion of the risks and benefits, the patient was initiated on therapy with pembrolizumab. His previous immunosuppression regimen, tacrolimus and mycophenolate mofetil, was maintained throughout the pembrolizumab treatment course. After three cycles, PET/CT showed evidence of progressive disease. Shortly thereafter, the patient's clinical status deteriorated due to disease progression with mediastinal, hilar and pulmonary metastatic disease leading to admission for postobstructive pneumonia. He was ultimately transitioned to comfort care and passed away approximately 5 months after his presentation with metastatic disease. He did not have evidence of cardiac allograft rejection, and echocardiography demonstrated a normal ejection fraction after two cycles of pembrolizumab.

## Discussion

### Checkpoint inhibitor therapy in patients with autoimmune diseases

#### *Systemic autoimmune disease*

Patients with malignancy and previously diagnosed autoimmune disease were excluded from trials leading to the approval of CTLA-4 and PD-1-inhibiting agents. The case for excluding these patients was based on the theoretical risk of causing an exacerbation of an existing autoimmune disease by blocking innate negative regulators of immunity [1]. Based on the mechanisms of action of these medications, it is not surprising that the clinical presentation of many irAEs mirrors that of common autoimmune syndromes. Polymorphisms of PD-1 and CTLA-4 are associated with various autoimmune conditions [5]. Autoimmune conditions are common in the general population, but also comprise a significant proportion of patients with malignancy. More than a quarter of patients diagnosed with lung and renal cancer were found to have a comorbid autoimmune condition (25 and 30%, respectively) [6]. There is also observational evidence that patients with chronic inflammation from systemic autoimmune conditions are at risk for subsequent development of malignancy [7]. As immune checkpoint inhibitors continue to define cancer treatment algorithms in an increasing number of tumor types, there will undoubtedly be a substantial number of patients with autoimmune disease and malignancy who are considered for immunotherapy.

At the time of writing this review, there were three larger retrospective analyses and a number of other case reports/case series describing outcomes of patients with known autoimmunity treated with ICIs for metastatic melanoma. Johnson *et al.* conducted a retrospective analysis of 30 patients with pre-existing autoimmune conditions diagnosed prior to ipilimumab initiation for advanced melanoma [8]. 43% of these patients were being actively


10.2217/mmt-2018-0004

Table 1. Summary of key findings from retrospective analyses of patients with pre-existing autoimmune conditions treated with checkpoint inhibitors for advanced melanoma.

| Study | Number of patients | Type of checkpoint inhibitor | % patients experiencing AD flare | % patients experiencing irAE (grade ≥3) | % patients with AD flare or grade ≥3 irAE | % patients with death associated with AD flare or irAE | % patients with discontinuation of therapy due to flare/irAE |
|---|---|---|---|---|---|---|---|
| Johnson *et al.* | 30 | Anti-CTLA-4 | 27 | 33 | 50 | 3 | not reported |
| Menzies *et al.* | 52 | Anti-PD-1 | 38 | 10 | 48 | 0 | 12 |
| Gutzmer *et al.* | 19 | Anti-PD-1 | 42 | 5 | 47 | 0 | 0 |

AD: Autoimmune disease; CTLA: Cytotoxic T-lymphocyte antigen; irAE: Immune-related adverse event; PD-1: Programmed cell death 1.

treated for their conditions with immunosuppressive therapy at the time of ipilimumab treatment. 27% experienced exacerbations of their autoimmune condition, 33% experienced grades 3–5 irAEs and 40% experienced either outcome (10% experienced both outcomes). The 33% grade ≥3 irAE rate seen in this study is similar to the overall 20–30% incidence of grades 3–5 irAEs quoted in ipilimumab monotherapy trials conducted on the general population [1,9]. However, it is important to note that exacerbations of pre-existing conditions experienced in this patient group were treated successfully with corticosteroids or infliximab [8]. 20% of the patients who received ipilimumab in this study experienced a partial or complete response. With respect to more high-risk autoimmune conditions, six patients in this review had inflammatory bowel disease, two had multiple sclerosis, two had systemic lupus erythematosus and two had sarcoidosis. In another retrospective analysis, 119 patients treated with pembrolizumab or nivolumab for advanced melanoma were reviewed [10]. 52 of these 119 patients had pre-existing autoimmune diseases and 67 had experienced an irAE from previous ipilimumab treatment. Of the 52 patients with autoimmune diseases at baseline, 29% had active symptoms from these conditions and 38% were on immunosuppressive therapy before receiving nivolumab. 38% of patients had symptoms consistent with a flare of their autoimmune condition, which required immunosuppression. Most flares tended to be recurrence/worsening of symptoms they had previously experienced as opposed to new manifestations of an existing condition (i.e., joint manifestations if they had already experienced this rather than new pulmonary disease in a patient with rheumatoid arthritis). The vast majority (85%) of patients who experienced a flare had symptoms consistent with a mild flare (grades 1–2). Only 4% of patients had to discontinue therapy as a direct result of severity of a flare. Of these 52 patients, 29% experienced conventional irAEs, 10% experienced ≥grade 3 toxicities and 8% discontinued treatment due to irAEs (Table 1). Clinical responses of melanoma to nivolumab therapy occurred in 17 of 52 patients (33%). The patients with flares of autoimmune disease (AD) were equally likely to respond to therapy as patients who did not experience a flare of AD. Of note, the majority of patients in this review had clinically inactive autoimmune disease prior to anti-PD-1 therapy. The authors conclude that although these cohorts may have a selection bias toward patients with less severe autoimmune disease, ICIs can be used cautiously in patients with pre-existing autoimmune disease. A third retrospective analysis by Gutzmer *et al.* looked at 19 patients with pre-existing autoimmune disease treated with PD-1 inhibitor therapy for advanced melanoma [11]. These patients had a wide variety of autoimmune diseases including Churg–Strauss vasculitis, sarcoidosis, ulcerative colitis and Guillain–Barré syndrome and 64% of patients were on baseline hormone supplementation or immunosuppressive therapy for their conditions. 42% of patients suffered from a flare of their disease and 16% of patients experienced an irAE unrelated to their autoimmune disorder. These numbers are comparable to the retrospective analyses discussed above [8,10]. 16% of these flares or new irAEs were grade ≥3 and all of these events were controlled by immunosuppression and symptomatic therapy, and no patients terminated therapy as a result [11]. Use of immunosuppressive medications at baseline, exacerbation of pre-existing AD, and whether or not the patient experienced an irAE all did not correlate with disease response outcomes. This is in contrast to the findings of Menzies *et al.* [10].

These analyses lacked a significant percentage of patients with autoimmune conditions associated with higher risk for potentially devastating exacerbations. Case reports demonstrate examples of patients with high-risk autoimmune conditions treated with ICI therapy. In contrast, two patients with metastatic melanoma and autoimmune disease, Behcet's disease and ulcerative colitis, treated with ipilimumab and IL-2 experienced an improvement in symptoms related to autoimmune disease [12]. The patient with ulcerative colistis achieved partial remission of metastatic melanoma while the patient with Behcet's disease achieved a complete remission. One patient with Churg–Strauss syndrome with stage 3 involvement (vasculitis) and metastatic melanoma was treated with ipilimumab with progression of disease and development of immunotherapy-induced colitis. Ipilimumab was switched to

pembrolizumab and after 16 cycles the patient had sustained partial response with no increase in Churg–Strauss disease activity or colitis [13]. In the literature, there are clear examples of all outcomes, from devastating irAEs to apparent autoimmune disease mitigation and from no treatment response to complete and sustained responses in some patients. Prospective data are needed to confirm that these medications are safe and effective in the autoimmune disease population.

### *Paraneoplastic autoimmune conditions*

Certain malignancies with high rates of paraneoplastic autoimmune complications such as small-cell lung cancer (SCLC) may theoretically see these complications triggered or enhanced by treatment with immunotherapy agents. Recent case reports allude to this phenomenon in patients who experienced treatment-related syndromes suspected to be paraneoplastic in nature. In one case, a patient with squamous NSCLC developed anti-Hu antibody-associated encephalitis when treated with nivolumab [14]. Another patient with melanoma treated with ipilimumab and nivolumab combination therapy developed paraneoplastic acral vascular syndrome [15]. In a preliminary analysis of an ongoing phase II study (NCT01331525) of ipilimumab with carboplatin and etoposide in SCLC, 61% of patients experienced grade 3 or higher adverse effects, 42% of which were deemed possibly ipilimumab related [16]. This is higher than the 31% rate of greater than or equal to grade 3 toxicity determined by a recent meta-analysis of 48 trials [17]. Two patients in the prelim analysis had ipilimumab-related neurological events. One of these was fatal, presenting like an anti-Hu-mediated paraneoplastic syndrome [16]. A phase I/II multicenter, open-label trial, Checkmate-032, demonstrated a durable response in patients with relapsed SCLC treated with nivolumab ± ipilimumab [18]. However, 8% of patients discontinued therapy due to treatment-related adverse events and there were three immune-related deaths in patients who experienced severe pneumonitis, myasthenia gravis and renal failure. Of note, all three deaths were in the combined checkpoint inhibitor arms where patients received combination ipilimumab and nivolumab therapy at variable doses. These findings lend credence to the theoretical concern that life-threatening paraneoplastic syndromes, such as immune-related encephalitis or myasthenia gravis, can be provoked by treatment with checkpoint inhibitors in patients with SCLC. Another phase II trial examined patients with extensive stage SCLC treated with ipilimumab and paclitaxel/carboplatin or paclitaxel/carboplatin alone [19]. Although treatment-related grade 3–4 adverse events were more frequent in the ipilimumab-containing arms than in the control arm, rates of discontinuation due to adverse events were similar across treatment arms. In this trial, patients treated with ipilimumab experienced only mild immune-related adverse events including rash, pruritus and diarrhea. Similarly, the phase Ib KEYNOTE-028 trial, which included 24 patients with PD-L1-expressing SCLC treated with pembrolizumab, showed a safety profile similar to that of other tumor types treated with ICIs [20]. Both the rate and severity of irAEs have implications for treatment tolerance if immunotherapy agents are proven efficacious for SCLC and other malignancies associated with paraneoplastic complications. These trials demonstrate that paraneoplastic complications can be particularly devastating and may be more likely to occur in patients on combination ICI therapy.

Patients with chronic lymphocytic leukemia (CLL) tend to be older and sometimes have comorbid melanoma, renal cell carcinoma, or NSCLC malignancies that may make them candidates for immune checkpoint inhibitors. However, CLL is frequently complicated by secondary autoimmune cytopenias; namely autoimmune hemolytic anemia, immune thrombocytopenia, pure red cell aplasia and autoimmune granulocytopenia. To our knowledge, there are no reports of worsening autoimmune cytopenias in patients with CLL undergoing ICI therapy for a co-existing malignancy. The small and limited trials that have been done on patients treated with checkpoint inhibitors for CLL itself reported no increased rate of irAEs compared with trials in other cancer types [21,22]. The adverse events reported were most commonly immune-related liver enzyme elevation and thyroiditis with no cases of autoimmune cytopenias noted.

## Checkpoint inhibitor therapy in patients with chronic viral infections

Patients with chronic viral infections, namely HCV, HBV and HIV, were another important group excluded from many immune checkpoint inhibitor trials to date. The role of immune checkpoints in patients with chronic viral infections is incompletely understood, and there is concern that checkpoint inhibitors could potentially cause viral reactivation of latent infection or contribute to ongoing hepatitis in these patients. This could be an important consideration in patients with underlying liver disease from chronic hepatitis. Traditional chemotherapy regimens are associated with a significant rate of HCV reactivation. This has an impact on viral-induced end-organ damage, and is associated with chemotherapy regimen modifications or interruptions in therapy, which can negatively affect

clinical outcomes [23]. Reactivation has also been reported in patients treated with targeted tyrosine kinase inhibitors such as imatinib [24]. With respect to irAEs, we know that the gastrointestinal system is significantly impacted, with sequelae including diarrhea, colitis or hepatitis [25]. The incidence of immune-related hepatic adverse events with ICI therapy varies, and can be as high as 15–20% with dual ICI treatment. These usually manifest as asymptomatic elevations of aspartate aminotransferase & alanine aminotransferase. Rarely, symptomatic adverse effects related to the liver also arise and these include fulminant hepatitis and death. Many *in vitro* studies allude to viral manipulation of the CTLA-4 and PD-1 pathways to promote unchecked replication. For instance, chronic hepatitis B and C infections are associated with an 'exhaustive' $CD8^+$ T-cell phenotype mediated by upregulation of CTLA-4 and PD-1. Exhausted T-cells exhibit a loss of IL-2 production, reduced proliferative capacity, reduced cytotoxic capacity and impaired production of proinflammatory cytokines [26]. In theory, this effector T-cell exhaustion may be abrogated by immune checkpoint inhibition, and this is supported by *ex vivo* and *in vitro* studies [27–33]. Similarly, in addition to $CD4^+$ T-cell depletion in HIV, increased PD-1 expression has been demonstrated on HIV-specific $CD8^+$ T-cells leading to a similar 'exhaustive' effect and this correlates with disease progression [34]. There may be a promising role for PD-1 inhibition in restoring normal immune mechanisms in these chronic viral infections; however, additional studies are needed to establish this.

With these theoretical sequelae in mind, large-scale data in patients with chronic viral infections undergoing ICI therapy are lacking. Patients with HCV and no underlying malignancy who were treated with nivolumab and tremelimumab have exhibited a decrease in viral load (VL) [35,36]. In a phase II, noncontrolled trial of patients with inoperable hepatocellular carcinoma (HCC) and chronic HCV infection, 20 patients were treated with a maximum of four cycles of tremelimumab (a CTLA-4 inhibitor) [37]. At baseline, 43% of these patients had some degree of liver dysfunction. No patients received systemic steroids and there were no treatment-related deaths; however, 45% of patients experienced transient grade 3 or higher transaminitis without associated decline in liver function. Interestingly, treatment with tremelimumab was associated with a significant decrease in average VL and three patients had a complete viral response during follow-up. A recent trial including 32 patients with advanced HCC treated with tremelimumab and radiofrequency ablation or chemoablation demonstrated an approximately 25% partial response rate [38]. Because HCC is often associated with chronic viral infection (namely HBV and HCV), this study can shed some light on the safety of immune checkpoint inhibition in chronically infected individuals. 12 of 14 patients with evaluable HCV VL achieved a VL reduction. The two patients who did not experience a VL reduction derived no antitumor benefit from ICI treatment. Similarly, three of the patients who initially responded had a concurrent reduction in VL until their malignancy progressed, at which point their VL also increased. These elevations clearly coincided with the time of disease progression. In the five patients with HBV infection who were enrolled in this trial, quantitative hepatitis B antigen, a reflection of the number of cells infected, decreased over time in all patients. Overall, this study demonstrated the safety and potential benefit of checkpoint inhibitor treatment in patients with HCC with HBV or HCV infection. Moreover, it alludes to the interesting correlation between HCV VL and HCC disease response. In a case series of nine patients with chronic HBV or HCV and metastatic melanoma (five with HBV, four with HCV) treated with ipilimumab, two out of nine patients experienced elevated transaminase levels during follow-up. The majority of patients had their VLs decrease or remain suppressed throughout the course of therapy although one patient had an increased VL after treatment with IL-2, ipilimumab and temozolomide [39]. Interim analysis from the Phase I/II trial of nivolumab in patients with advanced HCC (CA209-040 trial) showed that monotherapy with nivolumab had a favorable safety profile in patients with HCC compared with patients with other types of cancer [40,41]. Although this is an interim analysis, it alludes to the safety of nivolumab in patients with HBV and HCV infection. One patient with untreated HCV and metastatic merkel cell carcinoma was treated with pembrolizumab and saw a marked tumor response as well as HCV VL reduction [42]. Sharma *et al.* described a patient with chronic hepatitis B (patient 1) and one with chronic hepatitis C (patient 2) who were treated with ipilimumab for advanced melanoma. Patient 1 was treated with ipilimumab and tenofovir, and achieved reduction in VL to undetectable levels; unfortunately, this patient also had progression of melanoma and expired after receiving only one cycle of ipilimumab. Patient 2 was treated with four cycles of ipilimumab with overall progression of disease and transaminitis, and subsequently had a significant increase in VL months after discontinuing ipilimumab, corresponding with progression of metastatic melanoma. Based on the time course, it was not clear what role ipilimumab played in HCV control or transaminitis, but the elevated transaminase levels were ultimately attributed to an immune-related process [43]. There are currently several ongoing trials and analyses investigating patients with chronic HIV/HCV/HBV infection with and without malignancy being treated with immune checkpoint inhibitors [40]. Davar *et al.* reported on two patients, one with

HCV and one with HIV/HCV coinfection, who were treated with pembrolizumab for metastatic melanoma [44]. The patient with HIV/HCV coinfection progressed after two doses of pembrolizumab but had no increase in HIV or HCV VL, and the patient with HCV infection remained with a stable VL throughout nine cycles of pembrolizumab.

Recently, there has been more literature alluding to the safe treatment of HIV-infected patients. One case report demonstrates a decrease in the HIV reservoir in an HIV-positive patient with NSCLC treated with nivolumab and discusses the mechanisms that may be playing a role [45]. In short, checkpoint inhibitors may transiently reverse the blockade of HIV transcription in memory T-cells serving as reservoirs for chronic infection [46]. Similar to that postulated for chronic infectious hepatitides, checkpoint inhibitors might restore function in 'exhausted' HIV-specific T-cells ultimately leading to a 'drastic and durable diminution of the reservoir'. So far, there are several case reports demonstrating successful viral control and tumor response in HIV-infected patients with malignancies [47–51]. Future considerations should focus on risk of Immune Reconstitution Inflammatory Syndrome in these patients and ICI efficacy in treating malignancy in patients with disease-related defects in T-cell activity. In conclusion, a review of the existing literature of patients treated with HIV, HBV or HCV reveals that there has been no reported direct toxicity from these medications relating to their chronic viral infections.

## Checkpoint inhibitor therapy in patients with solid organ transplants

Skin cancers are the most common malignancies to affect patients who are chronically immunosuppressed in the setting of organ transplantation. There is a 3.6 relative risk for developing melanoma in this population compared with age-matched controls [52]. Similar to some of the other specific populations also discussed, patients with prior solid organ transplantation were excluded from the safety and efficacy trials on immune checkpoint inhibitors. The PD-1/PDL-1 and CTLA-4 pathways are essential for graft acceptance and their blockade results in accelerated organ rejection [53–61]. The mechanisms by which PD-1 blockade leads to graft rejection have been demonstrated in an elegant series of experiments by Thangavelu *et al.* [61]. Overall, PD-1 was shown to be important for induction and maintenance of tolerance. PD-1 -/- mice had an increase in donor-specific cytotoxic T-cells when compared with wild-type mice after islet cell transplantation. The authors hypothesized that this increase in $CD8^+$ T-cells could be due to reduced PD-1 signals in these cytotoxic T-cells themselves, reduced PD-1 signals in antidonor T-helper cells that lead to expansion of cytotoxic T-cells, or a reduced ability to generate Tregs. Additionally, blocking the PD-1/PD-L1 interaction on the target of rejection, the transplanted organ, may promote anti donor T-cell activity. Both of these mechanisms lead to loss of spontaneous tolerance. Thangavelu *et al.* did not identify an effect whereby CTLA-4 blockade-mediated rejection but concluded that their studies using CTLA-4 were too limited to completely exclude a role for this pathway in graft acceptance. However, it has been shown that in murine cardiac allografts, CTLA-4 plays a vital role in promoting graft acceptance, peripheral tolerance and intragraft $Foxp3^+$ Tregs [53]. Blazar *et al.* showed in a murine model that blockade of PD-1 led to severe acute graft-versus-host disease (GvHD) while blockade of CTLA-4 did not. There exists a theory that blockade of PD-1 pathway may lead to increased graft rejection and stronger T-cell alloreactivation than blockade of the CTLA-4 pathway [62]. Though both molecules function as immune checkpoints, their precise mechanisms of action differ and therefore it is entirely plausible that they have differential roles in allograft acceptance and tolerance. With respect to solid organ transplantation, the literature only consists of case reports of patients with a history of renal, hepatic and cardiac transplantation that underwent treatment with ICIs primarily for metastatic melanoma.

### *CTLA-4 inhibitors in patients with solid organ transplants*

There have been several case reports of patients treated with ipilimumab that experienced preservation of engrafted organs [63–65] (summarized in Table 2). Lipson described two patients with renal transplants treated with ipilimumab for metastatic melanoma who had partial responses to therapy and no evidence of rejection [66]. We presented a patient with an orthotopic heart transplant who was treated with ipilimumab for metastatic melanoma who also did not have evidence of rejection, although he had no response to therapy [4]. To our knowledge, there is one reported case of acute rejection after treatment with ipilimumab. One patient with a renal allograft for IgA nephropathy developed metastatic choroidal melanoma and was treated with two cycles of ipilimumab before having failure of his graft [67]. Interestingly, a biopsy of the renal transplant showed evidence of T-cell-mediated rejection but also showed evidence of recurrent IgA nephropathy, which the authors speculated may have been a complication of ipilimumab therapy. Therefore, it is unclear what role acute rejection played in graft failure. Case reports comprise the body of evidence for the safety of ipilimumab treatment in patients with organ transplantation and malignancy.


10.2217/mmt-2018-0004

Table 2. Summary of reported immune checkpoint inhibitors experience in patients with solid organ transplants.

| Patient | Study | Transplant | Cancer | ICI agent | Rejection (Y/N) | Immunosuppression prior to ICI | Immunosuppression during ICI treatment | Outcome |
|---|---|---|---|---|---|---|---|---|
| 1 | Lipson *et al.* | Kidney | MM | Ipilimumab | N | Prednisone/tacrolimus | Prednisone | Response |
| 2 | Lipson *et al.* | Kidney | MM | Ipilimumab | N | Prednisone/tacrolimus/mycophenolate | Prednisone | Response |
| 3 | Ranganath *et al.* | Liver | MM | Ipilimumab | N | Tacrolimus | Tacrolimus | POD |
| 4 | Morales *et al.* | Liver | MM | Ipilimumab | N | Rapamycin/mycophenolate | Rapamycin | Response |
| 5 | Jose *et al.* | Kidney | Metastatic Choroidal Melanoma | Ipilimumab | Y | Tacrolimus | Prednisolone | Not Reported |
| 6 | Herz *et al.* | Kidney | MM | Ipilimumab | N | Prednisone/tacrolimus | Prednisone/tacrolimus | POD |
| | | | | Nivolumab (after ipilimumab) | | | | |
| 7 | Spain *et al.* | Kidney | MM | Ipilimumab | N | Prednisone/tacrolimus | Prednisone | POD |
| | | | | Nivolumab (after ipilimumab) | Y | Prednisone | | Response |
| 8 | Alhamad *et al.* | Kidney | Metastatic SCC of skin | Ipilimumab | N | Cyclosporine/prednisone | Prednisone | POD |
| | | | | Nivolumab (after ipilimumab) | Y | Prednisone | | Not reported |
| 9 | Qin *et al.* | Heart | MM | Ipilimumab | N | Tacrolimus | Tacrolimus | POD |
| | | | | Pembrolizumab (after ipilimumab) | | | | |
| 10 | Grant *et al.* | Heart | MM | Pembrolizumab | N | Tacrolimus/mycophenolate | Tacrolimus/mycophenolate | POD |
| 11 | Ong *et al.* | Kidney | MM | Nivolumab | Y | Prednisone/tacrolimus/mycophenolate | Prednisone | Response |
| 12 | Lipson *et al.* | Kidney | Metastatic SCC of skin | Pembrolizumab | Y | Cyclosporine/prednisone | Prednisone | Response |
| 13 | Owonikoko *et al.* | Heart | Metastatic SCC of skin | Nivolumab | Y | Tacrolimus/sirolimus | Prednisone/tacrolimus | Not reported |
| 14 | Barnett *et al.* | Kidney | Metastatic Adenocarcinoma of the Duodenum | Nivolumab | N | Prednisone/tacrolimus/mycophenolate | Prednsione/sirolimus | Response |
| 15 | Boils *et al.* | Kidney | Stage IV NSCLC | Nivolumab | Y | Cyclosporine/prednisone | Reduced dose cyclosporine/prednisone | Not reported |
| 16 | Kittai *et al.* [68] | Kidney | Metastatic SCC of skin | Nivolumab | N | Prednisone/tacrolimus/mycophenolate | Prednisone/sirolimus | Response |
| 17 | Kittai *et al.* | Orthotopic Heart Transplant | Stage IV NSCLC | Nivolumab | N | Prednisone/cyclosporine/mycophenolate | Reduced dose cyclosporine/reduced dose mycophenolate | Response |

ICI: Immune checkpoint inhibitor; MM: Metastatic melanoma; N: No; NSCLC: Non-small-cell lung cancer; POD: Progression of disease; SCC: Squamous cell carcinoma; Y: Yes.

Nine such patients have been reported including kidney (n = 6), liver (n = 2) and heart (n = 1) transplant recipients. Eight out of these nine patients demonstrated no rejection during their ipilimumab treatment course and three out of nine had initial response of their respective malignancies, either metastatic melanoma or metastatic cutaneous squamous cell carcinoma. One patient who had an initial response to therapy went on to have progression of disease [66].

### *PD-1 inhibitors in patients with solid organ transplants*

The body of existing case reports suggests a less promising safety profile for anti-PD-1 antibody therapy (Table 2), though our patients received anti-PD-1 therapy without evidence of rejection. Our review of the literature revealed 13 solid organ transplant patients treated with PD-1 inhibitors, 4 of whom had already been treated and experienced progression of disease with ipilimumab [4,63,69,70]. Pembrolizumab was used in three cases while nivolumab was used in ten patients. Transplanted organs included kidney (n = 9) and heart (n = 4). Malignancies for which PD-1 inhibitor treatment was used included stage IV NSCLC, metastatic melanoma, squamous cell carcinoma of the skin and metastatic adenocarcinoma of the duodenum. Seven out of 13 patients experienced organ rejection and six out of 13 patients had disease response to PD-1 inhibitor therapy. Two patients with renal transplantation underwent treatment with nivolumab for metastatic squamous cell carcinoma and shortly thereafter developed acute rejection and graft failure [71,72]. One of these patients had their graft explanted and was maintained on hemodialysis with continued nivolumab treatment after experiencing a marked response to therapy. This patient had a substantial improvement in performance status and quality of life [71]. A patient with cardiac allograft for familial dilated cardiomyopathy, who suffered from chronic cardiac allograft vasculopathy, was diagnosed with metastatic cutaneous squamous cell carcinoma 16 years post-transplant. The patient was treated with nivolumab after failure of frontline cytotoxic chemotherapy and developed acute rejection precipitating cardiogenic shock. This improved with high doses of immunosuppression. He was ultimately not retreated with nivolumab and passed away 8 months later [73]. Another patient with a renal allograft was treated with nivolumab for metastatic melanoma [74]. She had graft failure and had to be transitioned to hemodialysis, but, due to the response of her disease to nivolumab, treatment was reinitiated. At the time of publication she maintained a response 8 months after restarting nivolumab [74]. There are two examples of patients with solid organ transplants and malignancy who progressed but did not experience rejection on ipilimumab, and were subsequently treated with anti-PD-1 antibodies, and experienced graft failure shortly after [69,70]. However, our patient is an example of one who did not experience rejection with PD-1 inhibition. Last, one patient with a renal allograft who was treated with ipilimumab then nivolumab for metastatic melanoma showed no evidence of rejection or graft failure but ultimately did not respond to either form of immunotherapy [63]. It is difficult to draw conclusions with the limited number of organ transplant patients treated with ICI therapy; however, there have been more reported cases of organ rejection with PD-1 inhibitors than with CTLA-4 inhibitors. As more patients are treated with these agents, different classes of ICIs may demonstrate a better safety profile in patients with transplanted organs and this may have implications for first-line management. Although they admit their analyses are limited, one particular study alludes to a more profound role of PD-1 blockade than CTLA-4 blockade in transplant rejection [61]. Our review of the existing case report literature agrees with this and may suggest a more important role of the PD-1 pathway in allograft tolerance. This will need to be explored in a more controlled setting.

### *Other considerations*

There have been several patients reported with prior kidney transplants that have had rejection and were transitioned to hemodialysis, but have had long-term survival attributed to ICI therapy [71,74]. Considering that metastatic melanoma is a life-limiting condition, the possible survival benefit associated with ICI treatment may be worth the risk of graft rejection in certain patients. Of course, this will depend on the organ transplanted. For instance, considering transplant rejection in the face of impending malignancy-related mortality, renal transplant patients may choose to be treated with ICIs and accept the risk of organ failure and transition to dialysis [75]. Unfortunately, liver transplant patients do not have an analogous option for emergent replacement of organ function. These scenarios will undoubtedly require expert communication between the patient, oncologist and multidisciplinary transplant team. Last, as more physicians consider using these agents in transplant patients with malignancy, they will be faced with decisions regarding the handling of immunosuppression for transplant tolerance.

There is a large difference between the immunosuppression used in patients with active autoimmune disease and that used in patients with organ transplants. In a systematic review of all reported cases of immune checkpoint

inhibitor use in patients with cancer and pre-existing autoimmune disease, it was found that 27% (27/107) of patients with autoimmune disease were on immunosuppressive medications for their condition prior to initiation of a checkpoint inhibitor [76]. 21% of these patients were on corticosteroids and 14% were on disease-modifying antirheumatic drugs including methotrexate, hydroxychloroquine, sulfasalazine, azathioprine, leflunomide and mycophenolate mofetil. A report on whether or not patients responded to immunotherapy is lacking in this study, but a smaller percentage of patients on immunosuppressive therapy suffered exacerbations of existing autoimmune disease or *de novo* irAEs than patients with autoimmune disease not on immunosuppressive therapy. In terms of whether concomitant systemic corticosteroids attenuate the anticancer response of immune checkpoint inhibitors, the verdict is still out but there is little evidence to suggest this. Several studies conclude that corticosteroid use, when the indication is treatment of irAEs, has no effect on overall survival or time to treatment failure [77–79].

Unlike in patients being treated for autoimmune disease, calcineurin inhibitor therapy is a mainstay of maintainance immunosuppression regimens for transplant patients. Calcineurin inhibitors (CNIs) prevent synthesis of IL-2 and other cytokines that would otherwise be produced by T-cells activated by allografts [80]. Just as there is a theoretical concern for attenuation of anticancer response to checkpoint inhibition with concomitant corticosteroid use, this concern is even greater for T-cell-specific immunosuppression such as calcineurin inhibitors. Unfortunately, what we know about patients being treated simultaneously with ICIs and CNIs is solely from isolated case reports. In these reports, treatment with ICI in the setting of immunosuppression with a calcineurin inhibitor was only associated with malignancy response in one out of nine cases. This includes both of our cases, patients who were left on a calcineurin inhibitor and neither had rejection nor tumor response when treated with an ICI. In the one responder, reduced dose cyclosporine (compared with pre-ICI treatment immunosuppression regimen) was used in addition to reduced-dose mycophenolate mofetil [68]. Two patients who remained on CNI therapy still had the undesired outcome of allograft rejection. They received a PD-1 inhibitor, nivolumab, and malignancy response was either not seen or not reported [72,73]. It is possible that treatment with checkpoint inhibitors cannot overcome the potent suppression of T-cell cytokine production resulting from calcineurin inhibition. PD-1 and CTLA-4 inhibitors in essence 'remove the brakes' on the adaptive immune system, but T-cell function is still required for these drugs to work. These complex interactions need to be further investigated in the lab and in a larger cohort before firm conclusions are drawn.

Interestingly, several transplant patients have had tumor response without rejection when their immunosuppressive regimen contains sirolimus [65,68,81]. Sirolimus, an mTOR inhibitor, exerts its immunosuppressive effects by blocking signal transduction from many cell surface cytokine receptors including IL-2 [80]. Moreover, the antitumor activity of sirolimus is well described [82]. This agent has also been shown to selectively preserve the development of Tregs, which are important for graft tolerance [83]. This is particularly relevant in the setting of PD-1 pathway inhibitor use as blockade of the PD-1/PD-L1 interaction has been shown to impair Treg cells in the renal allograft [84]. An ideal immunosuppression regimen in the transplant patient with malignancy has two main features: it preserves graft tolerance in the transplant patient while allowing the immune antitumor effects promoted by checkpoint inhibitors. With case reports alluding to success in this arena, sirolimus may be an agent uniquely poised to mediate the battle between immune suppression and activation [65,68,81].

## Conclusion

This review touches on only a subset of the challenging, poorly studied populations treated with immunotherapy agents. Other populations that need to be better studied in the context of ICIs before subjected to widespread use are elderly patients, pregnant patients, patients on immune suppression for other reasons than those mentioned, and patients who have developed serious irAEs with other class of immunotherapy agents. The use of these medications in certain patient populations raises concerns based on immunological mechanisms related to immune checkpoint inhibition and limited clinical trial experience. However, with the successful treatment of many patients with otherwise terminal disease, these medications need to be explored clinically in challenging patients as well before excluding them based on theoretical mechanisms. So far, based on limited clinical evidence, it seems that cautious use in patients with certain autoimmune diseases can be considered, while acknowledging that there is a risk of disease exacerbation. Overall, the risk of severe or treatment-refractory exacerbations appears to be low, but further study is needed. It will be important to weigh the risks and benefits of treatment with immune checkpoint inhibitors in these patients and involve patients in decision making. When considering the care of these patients, it will be essential to involve consultants from rheumatology, endocrinology, neurology, and all other possible intersecting subspecialties for extended risk/benefit discussions. We will need to study differential responses and side-effect

profiles with different classes (PD-1 vs PD-L1 vs CTLA-4) of checkpoint inhibitors in each of the high-risk groups that were excluded from the initial clinical trials. In patients with chronic hepatitis, ICIs have been well tolerated with very few accounts of increased viral activity, fulminant hepatitis or death. While patients with HCV seem to be more susceptible to immune-related elevations in transaminases than the general population, these generally are self limited, asymptomatic and unrelated to viral activity [37]. There is also mounting clinical evidence that ICI treatment causes VL suppression in HCV and that response of malignancy to ICI therapy corresponds with HCV VL reduction [35,37,38]. These are very promising findings which need further investigation. The transplant community represents arguably the most complex group of patients to be considered for use of immunotherapy agents. From the data collected to date, it seems that CTLA-4 inhibitors have been better tolerated in transplant patients treated with ICIs, demonstrating less risk of rejection than PD-1/PD-L1 inhibitors. Our review of the existing case report literature agrees with this and may suggest a more important role of the PD-1 pathway in allograft tolerance. There is a need for larger retrospective analyses, prospective cohort studies, as well as RCTs to study the safety and efficacy of ICI use in patients with autoimmune disease, chronic viral infections and solid organ transplants. Until then, we must extract what we can from anecdotal evidence, knowing the limitations of utilizing this information to draw conclusions and direct management.

## Future perspective

Immunotherapy, especially checkpoint inhibitor therapy, is a subset of cancer treatment that is advancing on a daily basis making it difficult to foresee changes in standard practice. Although excluded from most of the clinical trials demonstrating the efficacy of ICIs in certain malignancies, patients with chronic viral infections including HIV, HCV and HBV will benefit from inclusion in upcoming trials. Similarly, although at risk for flares or significant irAEs, most patients with autoimmune disease with sensitive malignancies can be safely treated with ICIs and may also be included in future clinical trials. On the other hand, the intricate immune interactions involving checkpoint inhibitors and patients with transplanted organs will need to be further studied before physicians are comfortable treating them on a larger scale. Until then, it will be interesting to see if sirolimus and low-dose prednisone for immunosuppression in transplant patients are used effectively as immunosuppression to prevent rejection but permit antitumor activity of ICIs. In the future, prospective and retrospective trials will both be useful to identify risk factors and other patient characteristics that will predict low adverse event profiles (such as irAEs, autoimmune flares, other irAEs) in patients treated with ICIs. Moreover, isolated cases suggest a promising role for disease-specific antibodies and other serum biomarkers for this purpose. Last, we will hopefully identify other interventions that can augment antitumor effects of ICIs while preventing the adverse effects. Some ideas on the horizon to boost the cancer-specific T-cell repertoire are the clinical use of tumor infiltrating lymphocytes, vaccines, adoptive T-cells, and adjunctive radiation, cytotoxic chemotherapy, or targeted therapy.

### Financial & competing interests disclosure

AKS Salama has the following conflicts of interest to disclose: Research Funding (paid to institution): Bristol-Myers Squibb, Celldex, Dynavax, Genentech, Immunocore, Merck, Reata. Consultant for the following: Array, Merck. Speaker for the following: Bristol-Meyers Squibb. Other authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

### Informed Consent Disclosure:

The authors affirm that they are in compliance with institutional standards regarding informed consent.

## References

Papers of special note have been highlighted as: • of interest; •• of considerable interest


1. Friedman CF, Proverbs-Singh TA, Postow MA. Treatment of the immune-related adverse effects of immune checkpoint inhibitors: a review. *JAMA Oncol.* 2(10), 1346–1353 (2016).
2. Kumar V, Chaudhary N, Garg M, Floudas CS, Soni P, Chandra AB. Current diagnosis and management of immune related adverse events (irAEs) induced by immune checkpoint inhibitor therapy. *Front. Pharmacol.* 8, 49 (2017).

• **An outstanding review on the immune-related adverse events of immune checkpoint inhibitors with emphasis on incidence management algorithms.**

3. Overman MJ, Mcdermott R, Leach JL *et al.* Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, Phase II study. *Lancet Oncol.* 18(9), 1182–1191 (2017).
4. Qin R, Salama A. Report of ipilimumab in a heart transaplant patient with metastatic melanoma on tacrolimus. *Melanoma Manag.* 2(4), 311–314 (2015).
5. Michot JM, Bigenwald C, Champiat S *et al.* Immune-related adverse events with immune checkpoint blockade: a comprehensive review. *Eur. J. Cancer* 54, 139–148 (2016).
6. El-Refai SM, Brown JD, Black EP, Talbert JC. Immune checkpoint inhibition and the prevalence of autoimmune disorders among patients with lung and renal cancer. *Cancer Inform.* 16 1176935117712520 (2017).
7. Franks AL, Slansky JE. Multiple associations between a broad spectrum of autoimmune diseases, chronic inflammatory diseases and cancer. *Anticancer Res.* 32(4), 1119–1136 (2012).
8. Johnson DB, Sullivan RJ, Ott PA *et al.* Ipilimumab therapy in patients with advanced melanoma and preexisting autoimmune disorders. *JAMA Oncol.* 2(2), 234–240 (2016).

•• **The retrospective analysis provides much insight into treating patients with autoimmune conditions with immune checkpoint inhibitors.**

9. Donia M, Pedersen M, Svane IM. Cancer immunotherapy in patients with preexisting autoimmune disorders. *Semin. Immunopathol.* 39(3), 333–337 (2017).
10. Menzies AM, Johnson DB, Ramanujam S *et al.* Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. *Ann. Oncol.* 28(2), 368–376 (2017).

•• **The retrospective analysis provides much insight into treating patients with autoimmune conditions with immune checkpoint inhibitors.**

11. Gutzmer R, Koop A, Meier F *et al.* Programmed cell death protein-1 (PD-1) inhibitor therapy in patients with advanced melanoma and preexisting autoimmunity or ipilimumab-triggered autoimmunity. *Eur. J. Cancer* 75, 24–32 (2017).
12. Pedersen M, Andersen R, Norgaard P *et al.* Successful treatment with ipilimumab and interleukin-2 in two patients with metastatic melanoma and systemic autoimmune disease. *Cancer Immunol. Immunother.* 63(12), 1341–1346 (2014).
13. Maul LV, Weichenthal M, Kahler KC, Hauschild A. Successful anti-PD-1 antibody treatment in a metastatic melanoma patient with known severe autoimmune disease. *J. Immunother.* 39(4), 188–190 (2016).
14. Raskin J, Masrori P, Cant A *et al.* Recurrent dysphasia due to nivolumab-induced encephalopathy with presence of Hu autoantibody. *Lung Cancer* 109, 74–77 (2017).
15. Gambichler T, Strutzmann S, Tannapfel A, Susok L. Paraneoplastic acral vascular syndrome in a patient with metastatic melanoma under immune checkpoint blockade. *BMC Cancer* 17(1), 327 (2017).
16. Ottensmeier C, Galea I, Cross N *et al.* A novel Phase II trial of ipilimumab, carboplatin and etoposide (ICE) for the first line treatment of extensive stage small cell lung cancer (SCLC). *Ann. Oncol.* 25(Suppl. 4), iv511–iv516 (2014).
17. Khoja L, Day D, Wei-Wu Chen T, Siu LL, Hansen AR. Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: a systematic review. *Ann. Oncol.* 28(10), 2377–2385 (2017).
18. Antonia SJ, Lopez-Martin JA, Bendell J *et al.* Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, Phase I/II trial. *Lancet Oncol.* 17(7), 883–895 (2016).
19. Reck M, Bondarenko I, Luft A *et al.* Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter Phase II trial. *Ann. Oncol.* 24(1), 75–83 (2013).
20. Ott PA, Elez E, Hiret S *et al.* Pembrolizumab in patients with extensive-stage small-cell lung cancer: results from the Phase Ib KEYNOTE-028 study. *J. Clin. Oncol.* 35(34), 3823–3829 (2017).
21. Jain N, Basu S, Thompson PA *et al.* Nivolumab combined with ibrutinib for CLL and Richter transformation: a Phase II trial. *Blood* 128, 59 (2016).
22. Ding W, Laplant BR, Call TG *et al.* Pembrolizumab in patients with CLL and Richter transformation or with relapsed CLL. *Blood* 129(26), 3419–3427 (2017).

23. Torres HA, Davila M. Reactivation of hepatitis B virus and hepatitis C virus in patients with cancer. *Nat. Rev. Clin. Oncol.* 9(3), 156–166 (2012).
24. Voican CS, Mir O, Loulergue P *et al.* Hepatitis B virus reactivation in patients with solid tumors receiving systemic anticancer treatment. *Ann. Oncol.* 27(12), 2172–2184 (2016).
25. Cramer P, Bresalier RS. Gastrointestinal and hepatic complications of immune checkpoint inhibitors. *Curr. Gastroenterol. Rep.* 19(1), 3 (2017).
26. Dyck L, Mills KHG. Immune checkpoints and their inhibition in cancer and infectious diseases. *Eur. J. Immunol.* 47(5), 765–779 (2017).
27. Reignat S, Webster GJ, Brown D *et al.* Escaping high viral load exhaustion: CD8 cells with altered tetramer binding in chronic hepatitis B virus infection. *J. Exp. Med.* 195(9), 1089–1101 (2002).
28. Owusu Sekyere S, Suneetha PV, Kraft AR *et al.* A heterogeneous hierarchy of co-regulatory receptors regulates exhaustion of HCV-specific CD8 T cells in patients with chronic hepatitis C. *J. Hepatol.* 62(1), 31–40 (2015).
29. Moreno-Cubero E, Larrubia JR. Specific CD8($^{+}$) T cell response immunotherapy for hepatocellular carcinoma and viral hepatitis. *World J. Gastroenterol.* 22(28), 6469–6483 (2016).
30. Harding JJ, El Dika I, Abou-Alfa GK. Immunotherapy in hepatocellular carcinoma: primed to make a difference? *Cancer* 122(3), 367–377 (2016).
31. Fisicaro P, Valdatta C, Massari M *et al.* Antiviral intrahepatic T-cell responses can be restored by blocking programmed death-1 pathway in chronic hepatitis B. *Gastroenterology* 138(2), 682–693, 693 e681–e684 (2010).
32. Wherry EJ. T cell exhaustion. *Nat. Immunol.* 12(6), 492–499 (2011).
33. Nakamoto N, Cho H, Shaked A *et al.* Synergistic reversal of intrahepatic HCV-specific CD8 T cell exhaustion by combined PD-1/CTLA-4 blockade. *PLoS Pathog.* 5(2), e1000313 (2009).
34. Day CL, Kaufmann DE, Kiepiela P *et al.* PD-1 expression on HIV-specific T cells is associated with T-cell exhaustion and disease progression. *Nature* 443(7109), 350–354 (2006).
35. Gardiner D, Lalezari J, Lawitz E *et al.* A randomized, double-blind, placebo-controlled assessment of BMS-936558, a fully human monoclonal antibody to programmed death-1 (PD-1), in patients with chronic hepatitis C virus infection. *PLoS ONE* 8(5), e63818 (2013).
36. Grosso JF, Jure-Kunkel MN. CTLA-4 blockade in tumor models: an overview of preclinical and translational research. *Cancer Immun.* 13, 5 (2013).
37. Sangro B, Gomez-Martin C, De La Mata M *et al.* A clinical trial of CTLA-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C. *J. Hepatol.* 59(1), 81–88 (2013).
38. Duffy AG, Ulahannan SV, Makorova-Rusher O *et al.* Tremelimumab in combination with ablation in patients with advanced hepatocellular carcinoma. *J. Hepatol.* 66(3), 545–551 (2017).

- **Aside from demonstrating safety of tremelimumab with ablation in advanced hepatocellular carcinoma, Duffy *et al.* allude to safety of immune checkpoint inhibitor use in the hepatitis C virus population and suggest possible hepatitis C virus viral load reduction as a possible surrogate for clinical antitumor activity.**

39. Ravi S, Spencer K, Ruisi M *et al.* Ipilimumab administration for advanced melanoma in patients with pre-existing hepatitis B or C infection: a multicenter, retrospective case series. *J. Immunother. Cancer* 2(1), 33 (2014).
40. Kudo M. Immune checkpoint inhibition in hepatocellular carcinoma: basics and ongoing clinical trials. *Oncology* 92(Suppl. 1), 50–62 (2017).
41. El-Khoueiry A, Melero I, Crocenzi TS *et al.* Phase I/II safety and antitumor activity of nivolumab in patients with advanced hepatocellular carcinoma (HCC): CA209-040. *J. Clin. Oncol.* 33(Suppl.): abstr (LBA101), (2015).
42. Jang S, Venna S. Antitumor and anti-hepatitis C viral response after administration of the anti-programmed death 1 antibody pembrolizumab. *J. Oncol. Pract.* 13(7), 462–464 (2017).
43. Sharma A, Thompson JA, Repaka A, Mehnert JM. Ipilimumab administration in patients with advanced melanoma and hepatitis B and C. *J. Clin. Oncol.* 31(21), e370–e372 (2013).
44. Davar D, Wilson M, Pruckner C, Kirkwood JM. PD-1 blockade in advanced melanoma in patients with hepatitis C and/or HIV. *Case Rep. Oncol. Med.* 2015, 737389 (2015).
45. Guihot A, Marcelin AG, Massiani MA *et al.* Drastic decrease of the HIV reservoir in a patient treated with nivolumab for lung cancer. *Ann. Oncol.* 29(2), 517–518 (2018).
46. Deeks SG, Lewin SR, Ross AL *et al.* International AIDS Society global scientific strategy: towards an HIV cure 2016. *Nat. Med.* 22(8), 839–850 (2016).
47. Wightman F, Solomon A, Kumar SS *et al.* Effect of ipilimumab on the HIV reservoir in an HIV-infected individual with metastatic melanoma. *AIDS* 29(4), 504–506 (2015).

48. Le Garff G, Samri A, Lambert-Niclot S *et al.* Transient HIV-specific T cells increase and inflammation in an HIV-infected patient treated with nivolumab. *AIDS* 31(7), 1048–1051 (2017).
49. Heppt MV, Schlaak M, Eigentler TK *et al.* Checkpoint blockade for metastatic melanoma and Merkel cell carcinoma in HIV-positive patients. *Ann. Oncol.* 28(12), 3104–3106 (2017).
50. Morris VK, Salem ME, Nimeiri H *et al.* Nivolumab for previously treated unresectable metastatic anal cancer (NCI9673): a multicentre, single-arm, Phase II study. *Lancet Oncol.* 18(4), 446–453 (2017).
51. Yanik EL, Kaunitz GJ, Cottrell TR *et al.* Association of HIV status with local immune response to anal squamous cell carcinoma: implications for immunotherapy. *JAMA Oncol.* 3(7), 974–978 (2017).
52. Zwald FO, Christenson LJ, Billingsley EM *et al.* Melanoma in solid organ transplant recipients. *Am. J. Transplant.* 10(5), 1297–1304 (2010).
53. Zhang T, Fresnay S, Welty E *et al.* Selective CD28 blockade attenuates acute and chronic rejection of murine cardiac allografts in a CTLA-4-dependent manner. *Am. J. Transplant.* 11(8), 1599–1609 (2011).
54. Morita M, Fujino M, Jiang G *et al.* PD-1/B7-H1 interaction contribute to the spontaneous acceptance of mouse liver allograft. *Am. J. Transplant.* 10(1), 40–46 (2010).
55. Pike R, Thomas N, Workman S *et al.* PD1-expressing T cell subsets modify the rejection risk in renal transplant patients. *Front. Immunol.* 7, 126 (2016).
56. Waldron-Lynch F, Deng S, Preston-Hurlburt P, Henegariu O, Herold KC. Analysis of human biologics with a mouse skin transplant model in humanized mice. *Am. J. Transplant.* 12(10), 2652–2662 (2012).
57. Tanaka K, Albin MJ, Yuan X *et al.* PDL1 is required for peripheral transplantation tolerance and protection from chronic allograft rejection. *J. Immunol.* 179(8), 5204–5210 (2007).
58. Ito T, Ueno T, Clarkson MR *et al.* Analysis of the role of negative T cell costimulatory pathways in CD4 and CD8 T cell-mediated alloimmune responses *in vivo*. *J. Immunol.* 174(11), 6648–6656 (2005).
59. Lin H, Rathmell JC, Gray GS, Thompson CB, Leiden JM, Alegre ML. Cytotoxic T lymphocyte antigen 4 (CTLA4) blockade accelerates the acute rejection of cardiac allografts in CD28-deficient mice: CTLA4 can function independently of CD28. *J. Exp. Med.* 188(1), 199–204 (1998).
60. Li W, Zheng XX, Kuhr CS, Perkins JD. CTLA4 engagement is required for induction of murine liver transplant spontaneous tolerance. *Am. J. Transplant.* 5(5), 978–986 (2005).
61. Thangavelu G, Murphy KM, Yagita H, Boon L, Anderson CC. The role of co-inhibitory signals in spontaneous tolerance of weakly mismatched transplants. *Immunobiology* 216(8), 918–924 (2011).
62. Blazar BR, Carreno BM, Panoskaltsis-Mortari A *et al.* Blockade of programmed death-1 engagement accelerates graft-versus-host disease lethality by an IFN-γ-dependent mechanism. *J. Immunol.* 171(3), 1272–1277 (2003).
63. Herz S, Hofer T, Papapanagiotou M *et al.* Checkpoint inhibitors in chronic kidney failure and an organ transplant recipient. *Eur. J. Cancer* 67, 66–72 (2016).
64. Ranganath HA, Panella TJ. Administration of ipilimumab to a liver transplant recipient with unresectable metastatic melanoma. *J. Immunother.* 38(5), 211 (2015).
65. Morales RE, Shoushtari AN, Walsh MM, Grewal P, Lipson EJ, Carvajal RD. Safety and efficacy of ipilimumab to treat advanced melanoma in the setting of liver transplantation. *J. Immunother. Cancer* 3, 22 (2015).
66. Lipson EJ, Bodell MA, Kraus ES, Sharfman WH. Successful administration of ipilimumab to two kidney transplantation patients with metastatic melanoma. *J. Clin. Oncol.* 32(19), e69–e71 (2014).
67. Jose A, Yiannoullou P, Bhutani S *et al.* Renal allograft failure after ipilimumab therapy for metastatic melanoma: a case report and review of the literature. *Transplant. Proc.* 48(9), 3137–3141 (2016).
68. Kittai AS, Oldham H, Cetnar J, Taylor M. Immune checkpoint inhibitors in organ transplant patients. *J. Immunother.* 40(7), 277–281 (2017).

•• **Highlights the key concepts in treating transplant patients with malignancy with immune checkpoint inhibitors.**

69. Spain L, Higgins R, Gopalakrishnan K, Turajlic S, Gore M, Larkin J. Acute renal allograft rejection after immune checkpoint inhibitor therapy for metastatic melanoma. *Ann. Oncol.* 27(6), 1135–1137 (2016).

• **Highlights the key concepts in treating transplant patients with malignancy with immune checkpoint inhibitors.**

70. Alhamad T, Venkatachalam K, Linette GP, Brennan DC. Checkpoint inhibitors in kidney transplant recipients and the potential risk of rejection. *Am. J. Transplant.* 16(4), 1332–1333 (2016).
71. Lipson EJ, Bagnasco SM, Moore J Jr *et al.* Tumor regression and allograft rejection after administration of anti-PD-1. *N. Engl. J. Med.* 374(9), 896–898 (2016).
72. Boils CL, Aljadir DN, Cantafio AW. Use of the PD-1 pathway inhibitor nivolumab in a renal transplant patient with malignancy. *Am. J. Transplant.* 16(8), 2496–2497 (2016).

73. Owonikoko TK, Kumar M, Yang S *et al.* Cardiac allograft rejection as a complication of PD-1 checkpoint blockade for cancer immunotherapy: a case report. *Cancer Immunol. Immunother.* 66(1), 45–50 (2017).

74. Ong M, Ibrahim AM, Bourassa-Blanchette S, Canil C, Fairhead T, Knoll G. Antitumor activity of nivolumab on hemodialysis after renal allograft rejection. *J. Immunother. Cancer* 4, 64 (2016).

75. Pham PT, Everly M, Faravardeh A, Pham PC. Management of patients with a failed kidney transplant: dialysis reinitiation, immunosuppression weaning, and transplantectomy. *World J. Nephrol.* 4(2), 148–159 (2015).

76. Abdel-Wahab N, Shah M, Lopez-Olivo MA, Suarez-Almazor ME. Use of immune checkpoint inhibitors in the treatment of patients with cancer and preexisting autoimmune disease: a systematic review. *Ann. Intern. Med.* 168(2), 121–130 (2018).

77. Horvat TZ, Adel NG, Dang TO *et al.* Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at Memorial Sloan Kettering Cancer Center. *J. Clin. Oncol.* 33(28), 3193–3198 (2015).

78. Yang JC, Hughes M, Kammula U *et al.* Ipilimumab (anti-CTLA4 antibody) causes regression of metastatic renal cell cancer associated with enteritis and hypophysitis. *J. Immunother.* 30(8), 825–830 (2007).

79. Downey SG, Klapper JA, Smith FO *et al.* Prognostic factors related to clinical response in patients with metastatic melanoma treated by CTL-associated antigen-4 blockade. *Clin. Cancer Res.* 13(22 Pt 1), 6681–6688 (2007).

80. Chinen J, Buckley RH. Transplantation immunology: solid organ and bone marrow. *J. Allergy Clin. Immunol.* 125(2 Suppl. 2), S324–S335 (2010).

81. Barnett R, Barta VS, Jhaveri KD. Preserved renal-allograft function and the PD-1 pathway inhibitor nivolumab. *N. Engl. J. Med.* 376(2), 191–192 (2017).

- **Highlights the key concepts in treating transplant patients with malignancy with immune checkpoint inhibitors.**

82. Law BK. Rapamycin: an anti-cancer immunosuppressant? *Crit. Rev. Oncol. Hematol.* 56(1), 47–60 (2005).

83. Coenen JJ, Koenen HJ, Van Rijssen E, Hilbrands LB, Joosten I. Rapamycin, and not cyclosporin A, preserves the highly suppressive $CD27^+$ subset of human $CD4^+CD25^+$ regulatory T cells. *Blood* 107(3), 1018–1023 (2006).

84. Riella LV, Paterson AM, Sharpe AH, Chandraker A. Role of the PD-1 pathway in the immune response. *Am. J. Transplant.* 12(10), 2575–2587 (2012).

85. YERVOY (ipilimumab) [package insert]. Bristol-Meyers Squibb Company, Princeton, NJ. (2015). Accessed January 20, 2018

86. OPDIVO (nivolumab) [package insert]. Bristol-Meyers Squibb Company, Princeton, NJ. (2017). Accessed: January 20, 2018

87. KEYTRUDA (pembrolizumab) [package insert]. Merck Sharpe & Dohme Corp., Whitehouse Station, NJ. (2016). Accessed: January 20, 2018