Original Article

Pilot evaluation of PD-1 inhibition in metastatic cancer patients with a history of liver transplantation: the Mayo Clinic experience

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Background: Patients with solid organ transplants (SOTs) have been excluded from programmed death protein-1 (PD-1)/programmed death ligand-1 (PD-L1) inhibitor clinical trials due to concern for allograft rejection. The use of immune checkpoint inhibitor therapy remains controversial in transplant patients.

Methods: A retrospective pilot evaluation was conducted to assess the safety and efficacy of PD-1 inhibitors in patients with liver transplantation (LT). The primary endpoint was the rate of allograft rejection. Secondary endpoints included overall response rate (ORR), progression free survival (PFS) and overall survival (OS). Translational objectives included evaluation of tumor PD-L1, tumor infiltrating lymphocytes (TILs) and allograft PD-L1 expression.

Results: Seven metastatic cancer patients with a history of LT who received PD-1 inhibitor therapy were included [hepatocellular carcinoma (HCC), n=5; melanoma, n=2]. Rejection was observed in 2 of 7 patients. When rejection occurs it appears to be an early event with a median time to rejection of 24 days in our cohort. One patient achieved a complete response (CR), 3 patients had progressive disease (PD) and 3 patients discontinued therapy prior to restaging assessments. Two of five patients with available tissue had PD-L1 expression in the allograft and both developed rejection. One of five evaluable patients had abundant TILs. Two of five evaluable patients had PD-L1 tumor staining. The single patient with both abundant TILs and PD-L1 staining obtained a response. The median OS and PFS were 1.1 (0.3–21.1) and 1.8 (0.7–21.1) months, respectively.

Conclusions: In this pilot evaluation both preliminary efficacy (1 of 4) and allograft rejection (2 of 7) were exhibited in evaluable patients. Larger, prospective trials are needed to elucidate optimal patient selection.

Keywords: Immunotherapy; liver transplantation (LT); hepatocellular carcinoma (HCC); melanoma; graft rejection

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Introduction

The success of programmed death protein-1 (PD-1) inhibitors in cancer therapy has led to an expanding relevance of immunotherapy in oncology (1). However, the safety and efficacy of PD-1 inhibitors in cancer patients with a solid organ transplant (SOT) has remained controversial. Preclinical models have demonstrated that PD-1 and its ligand programmed death ligand-1 (PD-L1) are essential components of both graft induction and maintenance of immune tolerance (2-4). Several murine models have shown that blockade of the PD-1/PD-L1 pathway leads to accelerated graft rejection in cardiac transplants among major histocompatibility complex (MHC) mismatched mice (3,5). Rejection following PD-1/PD-L1 blockade was associated with activation of cellular immunity through $CD8^+$ effector cells and downregulation of regulatory T cells (3). On the contrary, PD-L1 expression in the donor graft appeared to have a protective effect against graft rejection (2,6).

Given the valid concern for graft rejection, patients with a SOT have thus far been excluded from cancer immunotherapy clinical trials. Additionally, it is unclear if the effectiveness of cancer immunotherapy is dampened by immunosuppression therapy. Several studies have assessed the safety and efficacy of checkpoint inhibitors in bone marrow transplant patients and have demonstrated that both graft versus host disease and clinical benefit can occur after introduction of checkpoint inhibitors including PD-1 inhibitors (7-9).

Recent case reports have examined the safety of checkpoint inhibitors in SOT patients. A compilation of existing reports showed that graft rejection occurred in 4 out of 12 SOT patients who received checkpoint inhibitors including PD-1 inhibitors and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) inhibitors (10). The aforementioned literature review included 2 cases of liver transplantation (LT) patients who received CTLA-4 inhibitor therapy, but no LT patients who received PD-1 inhibitors.

According to United Network for Organ Sharing (UNOS) data, hepatocellular carcinoma (HCC) patients who undergo LT have a 5-year OS of 62% (11). However, HCC recurrence following LT occurs frequently with recurrence rates ranging from 6.9–35.9% at 5 years of follow up (12). The lack of safety data for the use of checkpoint inhibitors after LT deprives post-LT patients with HCC recurrence the opportunity to be considered for checkpoint inhibitors. Recently, the United States Food and Drug Administration (FDA) approved nivolumab, a PD-1 inhibitor, for advanced HCC who have previously received sorafenib (13). There is an urgent need to evaluate whether checkpoint inhibitors, such as PD-1 inhibitors, can safely salvage HCC that recurs after LT. There are 8 cases reported in which PD-1 inhibitors were used following a LT, of which 2 cases experienced graft rejection (14-16). So far there are only 3 cases that have examined the use of PD-1/PD-L1 inhibitors in HCC patients with a previous LT. This pilot study encompasses the largest single center compilation of LT patients who were treated with PD-1 inhibitors, including HCC patients.

Methods

Study design

Retrospective data for this single center pilot study were collected from Mayo Clinic Arizona from April 1, 2016 to April 3, 2018. Patients were identified through physician referral and queries through I2B2 (Informatics for Integrating Biology and the Bedside) and ACE (Advanced Cohort Explorer) search programs. The date ranges were set between March 1, 2007 to March 31, 2017 for both the I2B2 and ACE searches. Participants were required to have received a LT and subsequently, PD-1 or PD-L1 inhibitor therapy for advanced, recurrent or *de novo* malignancy. The primary objective was to evaluate the incidence of graft rejection with PD-1/PD-L1 inhibitor therapy. Secondary endpoints include the overall response rate (ORR) with PD-1/PD-L1 inhibitor therapy, the effect of immunosuppression therapy on rejection and response, clinical outcomes such as progression free survival (PFS), overall survival (OS) and duration of therapy. ORR was determined by RECIST v1.1 criteria. Patients were categorized as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) with regards to best response obtained. Exploratory endpoints included changes in liver function tests [aspartate aminotransferase (AST), alanine aminotransferase (ALT), international normalized ratio (INR), total bilirubin, albumin], tumor marker [alpha-fetoprotein (AFP)] and liver prognostic scores [Model for End Stage Liver Disease (MELD), Child-Turcotte-Pugh] with immunotherapy and the incidence of tumor infiltrating lymphocytes (TILs) and PD-L1 expression in the tumor and allograft. PD-L1 expression in the tumor and TILs were correlated

Table 1 Patient characteristics

ID	Malignancy	Gender	Race	Age (years)	ECOG PS	Initial stage	Pathologic grade	Number of metastatic sites	Organ transplant	Reason for transplant	Years from transplant	Donor type	Cold/ warm ischemia	Ischemia time
1	HCC	M	White	56.8	–	IVA	Moderately differentiated	2	Liver	HCC	2.7	DCD	Warm	27 min
2	Melanoma	M	White	54.5	1	IA	Not assessed	3	Liver	HCC	5.5	DDLT	Cold	5 h 30 min
3	HCC	M	White	55.9	1	–	Not assessed	1	Liver	HCC	7.8	DDLT	–	–
4	HCC	F	White	34.9	0	IIIB	Moderately differentiated	2	Liver	HCC	3.7	Living donor	–	3 h 24 min
5	HCC	M	White	63.6	1	I	Moderately differentiated	2	Liver	HCC	1.2	DDLT	Cold	8 h 45 min
6	HCC	M	White	68	1	II	Moderately differentiated	2	Liver	HCC	1.1	DDLT	–	–
7	Melanoma	M	White	63.4	0	IB	Poorly differentiated	4	Liver	Cholangiocarcinoma	3.1	DDLT	Cold	6 h 8 min
Median	N/A	N/A	N/A	56.8	1	N/A	N/A	2	N/A	N/A	3.1	N/A	N/A	4 h 27 min

–, denotes that data not available for evaluation. HCC, hepatocellular carcinoma; M, male; F, female; ECOG PS, Eastern Cooperative Oncology Group performance status; DCD, donor after cardiac death; DDLT, deceased donor liver transplantation; h, hours; min, minutes; N/A, not applicable; ID, patient identification.

with ORR to PD-1/PD-L1 inhibitors. PD-L1 staining in the liver allograft tissue was correlated with rates of graft rejection.

PD-L1 staining and TILs

Patients with sufficient pathologic specimen of their liver allograft tissue and tumor tissue underwent PD-L1 staining and evaluation for TILs. PD-L1 staining was performed with the Ventana PD-L1 antibody (SP263) according to the manufacturer's instructions. Tumor PD-L1 status was determined by the percentage of tumor cells with any membrane staining above background of tumor-associated immune cells. Similarly, allograft PD-L1 expression was determined by the percentage of allograft lymphocytes with membrane PD-L1 staining. PD-L1 positivity was defined as tumor or allograft lymphocyte staining ≥1%. TILs were measured as the percentage of TILs present above background tumor-associated lymphocytes. Given the exploratory nature of TILs in HCC there was no threshold for high versus low TILs.

Results

Patient characteristics

Seven metastatic cancer patients were identified who had a history of LT and subsequently received PD-1 inhibitor therapy and their characteristics are summarized in *Table 1*. The study cohort included patients with HCC (n=5) and melanoma (n=2). Patients received nivolumab (n=5) and pembrolizumab (n=2). All of the patients in this cohort received previous treatments. The median number of previous therapies was two. All HCC patients had previously received sorafenib. The immunosuppressive agents used in this study are shown in *Table 2*.

Clinical outcomes

Four patients were evaluable for response to PD-1 inhibitor therapy. Responses included PD (n=3) and CR (n=1). The patient with a CR (patient #2) had metastatic melanoma and discontinued therapy after 9.5 months because of clinical remission (*Figure 1*) and remains in remission. Three patients required early discontinuation of their therapies because of graft rejection (n=2) and development of multi-organ failure unrelated to PD-1 inhibition (n=1). Graft rejection was confirmed with a liver biopsy. Patient #2

Table 2 Immunotherapy outcomes

ID	Immunotherapy	Line of therapy	RECISTv1.1 response	DOT (months)	PFS (months)	OS (months)	Reason for stopping therapy	Graft rejection	Allograft PD-L1 staining	PD-L1 tumor staining	TILs	Prior sorafenib therapy	Immunosuppressive agent(s) used
1	Nivolumab	3	PD	1.2	2.2	1.2	Progression	No	–	10%	10%	Yes	Tacrolimus
2	Pembrolizumab	2	CR	9.5	21.1*	21.1	Complete response	No	0%	5%	50%	No	Everolimus, mycophenolate mofetil
3	Nivolumab	4	PD	1.1	0.7	1.1	Progression	No	0%	–	–	Yes	Mycophenolate mofetil, sirolimus
4	Nivolumab	5	PD	1.3	1.3	1.3	Progression	No	0%	0%	5–10%	Yes	Tacrolimus
5	Nivolumab	2	–	0.3	–	0.3	Multi-organ failure	No	–	0%	10%	Yes	Tacrolimus
6	Nivolumab	2	–	0.9	–	0.9	Graft rejection	Yes	30%	0%	–	Yes	Sirolimus
7	Pembrolizumab	2	–	0.7	–	0.7	Graft rejection	Yes	25%	–	–	No	Mycophenolate mofetil, prednisone
Median	N/A	2	N/A	1.1	1.8	1.1	N/A	N/A	0%	0%	10%	N/A	N/A

*, denotes ongoing response; –, denotes that data not available for evaluation. ID, patient identification; RECIST, response evaluation criteria in solid tumors; DOT, duration of therapy; PFS, progression free survival; OS, overall survival; PD-L1, programmed death ligand-1; TIL, tumor infiltrating lymphocyte.

Figure 1 PET/CT scans of patient #2. (A) PET/CT prior to immunotherapy in patient #2; (B) PET/CT scan showing radiographic complete response in patient #2 after completing pembrolizumab treatment.

received an mTOR inhibitor for immunosuppression. In the patients who experienced graft rejection, one patient was treated with mycophenolate mofetil and prednisone, while the other patient received sirolimus. The 3 patients who received tacrolimus did not have graft rejection or response to therapy. The median duration of therapy with PD-1 inhibitors [1.1 (range, 0.3–9.5) months], PFS [1.8 (range, 0.7–21.1) months] and OS [1.1 (range, 0.3–21.1) months] were all brief in this cohort reflective of the advanced nature of disease in these patients (*Table 2*). Patient #6 expired due to progression of his cancer. The natural history of his allograft rejection is unclear since he enrolled in hospice and did not have subsequent assessments. Patient #7 is still undergoing treatment for his allograft rejection, but at the time of this report the patient's acute cellular rejection appears to be improving with treatments of thymoglobulin, mycophenolate mofetil, tacrolimus and prednisone.

PD-L1 staining and TILs

Five patients were evaluable for liver allograft lymphocyte PD-L1 expression. All three patients without allograft rejection had 0% allograft PD-L1 staining. However, both cases of allograft rejection in this cohort were found to have allograft lymphocyte PD-L1 expression with a median

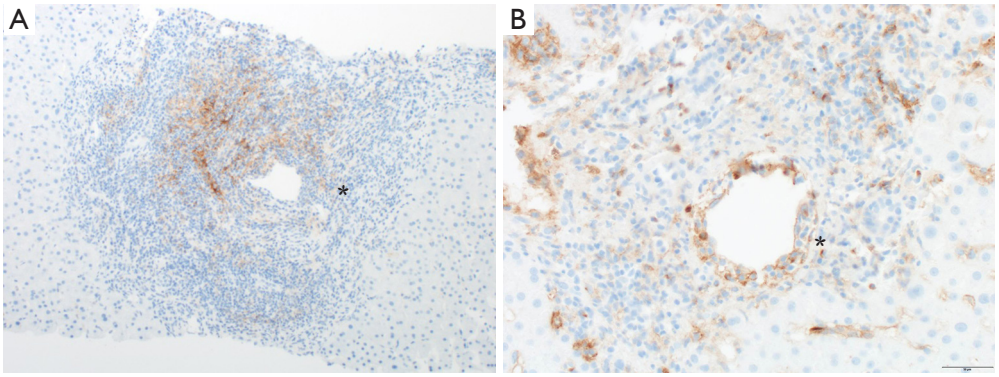

Figure 2 PD-L1 immunohistochemistry in liver allograft tissue near the portal vein in patient #6 (A) (magnification ×100) and patient #7 (B) (magnification ×200). Brown staining represents PD-L1 expression in portal lymphocytes. Image (B) shows enrichment of PD-L1 lymphocyte staining in areas of endotheliitis. *, denotes the portal vein. PD-L1, programmed death ligand-1.

PD-L1 lymphocyte expression of 27.5% (range, 25–30%) as shown in *Figure 2*. One case of allograft rejection (patient #7) demonstrated enrichment of lymphocytes with PD-L1 expression (>80%) in areas of endotheliitis.

Five patients had tumor samples that were evaluable for PD-L1 staining. Two of the five patients were found to have PD-L1 expression. The median tumor PD-L1 expression was 0% (range, 0–10%). The patient who responded to PD-1 inhibition (patient #2) had 5% PD-L1 tumor staining. However, patient #1 had 10% PD-L1 tumor expression, but had PD. Patient #4 did not have PD-L1 expression and had PD. Patient #5 and #6 did not have PD-L1 expression and were not evaluated for response to therapy.

Four patients had sufficient tumor tissue for TIL assessment. The median percentage of TILs was 10% (range, 0–50%). The patient who responded to PD-1 inhibitor therapy (patient #2) had both PD-L1 expression (5%) and a high percentage of TILs (50%). However, the patient who had PD-L1 expression (10%), but a lower percentage of TILs (10%) was found to have PD on PD-1 inhibitor therapy (patient #1). Patient #4 had no PD-L1 expression and a low percentage of TILs (5–10%) and had PD. Assessment of PD-L1 expression and TILs are summarized in *Table 2*.

Changes in liver laboratory studies, prognostic scores and tumor markers

Acute cellular rejection was seen in two patients. The diagnosis of rejection was established based on a significant elevation of transaminases and in one case elevation of total bilirubin, without any significant change in albumin, or INR as shown in *Table S1*. Patient #6 had grade 3 [Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 classification] elevation of AST [460 units (U)/liter (L)] and ALT (433 U/L) at baseline. Only one other patient (patient #1) started off with elevated AST (134 U/L) and ALT (253 U/L) levels, but these were lesser grades of AST (grade 0) and ALT (grade 2) elevations. All patients with HCC experienced an increase in AFP with a median rise of 1,000 nanograms (ng)/milliliter (mL) and ranged from 1,000 to 214,082 ng/mL.

Discussion

PD-1/PD-L1 inhibitor therapy in patients with a history of LT needs to be considered with a great deal of caution given the possibility of graft rejection. However, the effectiveness of immunotherapy in certain tumor types warrants the exploration of immunotherapy in LT patients. This small retrospective study provides preliminary insight into the possible outcomes of PD-1 inhibition in this population.

In this study, a single patient obtained a durable CR, while two patients developed graft rejection. The patient that responded was a patient with melanoma (patient #2) and has achieved a sustained CR for over 21 months. However, none of the 5 HCC patients derived clinical benefit from PD-1 inhibitor therapy. This is far lower than the response rate reported in the literature for patients with SOT (47.4%). However, the response rate reported in the literature is likely inflated due to publication bias towards positive results. There are several potential explanations

Table 3 Summary of literature results and study cohort results

Variables	Liver transplant (literature)	Renal & heart transplant (literature)	PD-1 inhibitors (literature)	CTLA-4 inhibitors (literature)	PD-1 & CTLA-4 inhibitor (literature)	All literature results	Study cohort (liver transplant)	Overall (all results)
Rate of graft rejection	25% (n=12)	43.8% (n=16)	33.3% (n=15)	25% (n=8)	40% (n=5)	32.1% (n=28)	28.6% (n=7)	31.4% (n=35)
Median time to graft rejection (days)	13 (n=2)	8 (n=5)	13.5 (n=6)	–	8 (n=1)	8 (n=7)	24 (n=2)	19 (n=9)
Response rate	33% (n=10)	55.6% (n=9)	66.7% (n=9)	28.6% (n=7)	33.3% (n=3)	47.4% (n=19)	25% (n=4)	43.4% (n=23)
Median PFS (months)	3.8 (n=10)	8 (n=11)	8 (n=11)	5 (n=7)	8 (n=3)	7 (n=21)	1.8 (n=4)	6 (n=25)
Median time to transplant (years)	6 (n=11)	11 (n=15)	9 (n=14)	8 (n=8)	11 (n=4)	8 (n=26)	3 (n=7)	8 (n=33)

PFS, progression free survival; PD-1, programmed death protein-1; CTLA-4, cytotoxic T-lymphocyte-associated protein-4.

for the lack of clinical benefit, which includes the use of immunosuppression. However, the effect these agents have in preventing therapeutic benefit from PD-1 inhibitors is not clear. Interestingly, mTOR inhibitors were used in one of the patients who experienced graft rejection and the patient who responded to immunotherapy, which may suggest less potent suppression of the PD-1/PD-L1 pathway. On the contrary, none of the patients on calcineurin inhibitors experienced a therapeutic response or graft rejection. Previous case reports have shown that patients can respond to cancer immunotherapy despite immunosuppression, including patient #2 from this cohort of patients. Many patients in this cohort had advanced disease at the time of receiving PD-1 inhibition, which likely influenced both the tolerance and duration of therapy. The median duration of therapy was 1.1 months with the longest duration of therapy in HCC patients being 1.3 months. The short duration of therapy, differences in efficacies of checkpoint inhibitors between HCC and more responsive tumors such as melanoma and the small size of this cohort are additional likely contributors to the lack of observed clinical benefit from PD-1 inhibitors.

PD-L1 staining alone did not consistently predict response to PD-1 inhibitor therapy. While the only patient in this cohort with a response to PD-1 inhibition (patient #2) had PD-L1 staining of 5%, there was also a patient with 10% PD-L1 tumor staining that did not respond to therapy (patient #1). Notably, patient #2 had both PD-L1 expression and a high percentage of TILs (50%). We speculate that abundant TILs and PD-L1 expression in combination may be a more reliable predictor of response to PD-1 inhibitors compared to PD-L1 expression alone.

There are 15 reported cases of patients with a history of SOT who received PD-1 inhibitors (10,14-25). The rejection rate in these case reports was 33.3% as shown in *Table 3*. The rejection rate was similar in the 5 patients whom received both PD-1 inhibitors and CTLA-4 inhibitors with a graft rejection rate of 40% (26-30). Eight patients had a history of LT and received PD-1 inhibitors; two of these patients developed graft rejection, which equates to a graft rejection rate of 25% (14-16). All case reports of PD-1 inhibitor therapy with SOT are summarized in *Tables S2* and *S3*. A similar rate of graft rejection occurred (25%) in the 8 patients treated with CTLA-4 inhibitors alone as shown in *Tables S4* and *S5*, including 4 patients with a history of LT (29,31-36). Preclinical models have suggested that CTLA-4 contributes to induction of graft tolerance, but not to maintenance of graft tolerance, which may suggest a lower predisposition to graft rejection in patients receiving CTLA-4 inhibitors with a remote history of SOT (37,38). All patients who received ipilimumab and experienced graft rejection were receiving only prednisone for immune suppression therapy. All patients on more potent immune suppression who received ipilimumab did not experience graft rejection. Therefore, inadequate immune suppression may have contributed to graft rejection in these ipilimumab cases.

The rate of graft rejection in our study was 28.6%, which is very similar to the 33.3% graft rejection rate reported in previous case reports that received PD-1 inhibitors. Unlike the response rates to immunotherapy the short duration of therapy did not appear to influence our observed rate

of rejection. Graft rejection appears to be an early PD-1 inhibitor adverse event and occurs earlier than most other autoimmune adverse events which typically peak between 6–14 weeks after initiating therapy (39). The median time to rejection reported in previous case reports is 8 days with a range of 5–63 days (14,18,19,23,25,27). Similarly, in our cohort the median time to graft rejection diagnosis was 24 days with a range of 20–28 days. The early occurrence of graft rejections likely mitigated the effect that the short duration of therapy had on graft rejection rates in this cohort.

It remains unclear which immunosuppression is most efficacious at reducing the risk for graft rejection with immune checkpoint inhibitor therapy. There were no graft rejections in the 3 patients who received calcineurin inhibitors. There were graft rejections in the patients who received mTOR inhibitors (1 out of 3) and mycophenolate mofetil (1 out of 3). The reported rates in the literature of graft rejection in patients treated with mTOR inhibitors (n=8), calcineurin inhibitors (n=6), mycophenolate mofetil (n=4) and glucocorticoids alone (n=8) are 12.5%, 18.2%, 0% and 75% respectively (10,14-35). However, many of these cases received combinations of immune suppression medications. Consequently, it is difficult to ascertain the degree in which each individual immune suppressive agent contributes to preventing graft rejection. However, glucocorticoids by themselves do not appear to be effective in preventing graft rejection when receiving immune checkpoint inhibitors.

A recent report described two case reports of allograft liver rejection after receiving PD-1 inhibition in patients whose allograft liver tissue demonstrated PD-L1 expression (14). However, our study is the first to observe clinical outcomes in LT patients with and without allograft PD-L1 expression who received PD-1 inhibitors. All reported LT cases, including our study, who lacked allograft lymphocyte PD-L1 expression (n=3) did not develop rejection while those with allograft lymphocyte PD-L1 expression (n=4) developed rejection. This finding should be confirmed in larger studies. However, if validated, allograft lymphocyte PD-L1 expression could function as a biomarker that predicts risk for graft rejection in SOT patients when using PD-1 inhibitors. A limitation of our assessment is that both patients who experienced rejection were tested for allograft lymphocyte PD-L1 expression after receiving PD-1 inhibitors.

Conclusions

There is very limited data for the use of PD-1/PD-L1 inhibitors in patients with LT and larger, prospective studies are needed to define the optimal patient selection and management of LT patients who receive PD-1 inhibitor therapy. In the meantime clinical benefit may be achieved with PD-1 inhibitor therapy despite immunosuppressive therapy. However, this benefit is counterbalanced by the risk of graft rejection and careful consideration of the risk-benefit ratio should occur prior to pursuing this option in patients with LT.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the Mayo Clinic Institutional Review Board (No. IRB00000020) and informed consent waiver was granted by the IRB under 45 CFR 46.116 given the retrospective, minimal risk nature of the study.

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Supplementary

Table S1 Change in laboratory data with immunotherapy

ID	Change in Child Pugh	Change in MELD	Change in AFP (ng/mL)	Change in albumin (g/dL)	Change in Tbili (mg/dL)	Change in AST (U/L)	Change in ALT (U/L)	Change in INR
1	0	+5	+1,000	−0.3	0	+162	+84	+0.08
2	0	0	N/A	+0.3	+0.1	−4	−7	−0.2
3	+1	0	+214,082	−0.1	0	+3	+26	+0.08
4	+1	+1	+8,480	−0.3	+0.1	+7	0	+0.08
5	0	+1	+206.1	+1.5	−0.1	+11	+1	+0.45
6	+2	+5	+64.6	−1.1	+0.2	+900	+846	0.18
7	+2	+6	+44,767	−0.1	+0.8	169	+151	+0.1
Median	+1	+1	+1,000	−0.3	+0.1	+11	+26	+0.08

ID, patient identification; MELD, model for end stage liver disease; AFP, alpha-fetoprotein; Tbili, total bilirubin; AST, aspartate transaminase; ALT, alanine transaminase; INR, international normalized ratio; ng/Ml, nanograms per milliliter; g/dL, grams per deciliter; mg/dL, milligrams per deciliter; U/L, units per liter.

Table S2 Previously reported cases of PD-1 inhibitor exposure in liver transplant patients

ID	Age	Transplant to immunotherapy (years)	Organ transplant	Malignancy	Immunotherapy	Number of immunotherapy doses	Time to graft rejection (days)	Immune suppression	Organ rejection	Response to immunotherapy	PFS (months)	Ref
1	62	6	Liver	Malignant peripheral nerve sheath tumor	Ipilimumab & pembrolizumab	4/25	–	Sirolimus, mycophenolate mofetil	No	PR	17*	(29)
2	20	4	Liver	FL-HCC	Nivolumab	2	19	Sirolimus	Yes	–	–	(14)
3	14	3	Liver	FL-HCC	Nivolumab	1	7	Tacrolimus	Yes	–	–	(14)
4	70	8	Liver	HCC	Pembrolizumab	–	N/A	Tacrolimus	No	PD	3	(15)
5	54	13	Liver	Non-small cell lung cancer	Nivolumab	3	N/A	Tacrolimus, everolimus, prednisone	No	PD	1.5	(16)
6	41	–	Liver	HCC	Nivolumab	15	N/A	Tacrolimus	No	PD	3.5	(20)
7	35	20	Liver	Melanoma	Pembrolizumab	2	N/A	Tacrolimus	No	CR	6*	(22)
8	57	3	Liver	HCC	Pembrolizumab & sorafenib	14	N/A	mTOR inhibitor, tacrolimus	No	CR	10*	(21)
Median	68	6	N/A	N/A	N/A	N/A	13	N/A	N/A	N/A	6	N/A

*, denotes ongoing response; –, denotes that data not available for evaluation. ID, patient identification; SCC, squamous cell carcinoma; FL-HCC, fibrolamellar hepatocellular carcinoma; PD, progressive disease; PR, partial response; Ref, references; N/A, not applicable.

Table S3 Previously reported cases of PD-1 inhibitor exposure in kidney and heart transplant patients

ID	Age	Transplant to immunotherapy (years)	Organ transplant	Malignancy	Immunotherapy	Number of immunotherapy doses	Time to graft rejection (days)	Immune suppression	Organ rejection	Response to immunotherapy	PFS (months)	Ref
13	77	8	Kidney	Melanoma	Ipilimumab & nivolumab	4/7	N/A	Prednisone, tacrolimus	No	PD	5	(26)
14	48	14	Kidney	Melanoma	Ipilimumab & nivolumab	2/1	8	Prednisolone	Yes	–	8	(27)
15	68	15	Kidney	Melanoma	Ipilimumab & pembrolizumab	4/1	–	Prednisone	Yes	–	–	(28)
16	62	–	Heart	Melanoma	Ipilimumab & pembrolizumab	–	–	–	No	PD	–	(30)
17	74	5	Kidney	SCC of lung	Nivolumab	3	63	Prednisone, cyclosporine	Yes	–	–	(18)
18	57	25	Kidney	Cutaneous SCC	Pembrolizumab	–	60	Prednisone	Yes	PR	8*	(19)
19	69	14	Kidney	Cutaneous SCC	Nivolumab	11	N/A	Prednisone, sirolimus	No	–	8	(10)
20	70	5	Kidney	Duodenum cancer	Nivolumab	16	N/A	Prednisone, sirolimus	No	PR	8*	(17)
21	72	10	Heart	SCC of lung	Nivolumab	12	N/A	Mycophenolate mofetil, cyclosporine	No	–	8*	(10)
22	63	11	Kidney	Melanoma	Nivolumab	17	8	Prednisone	Yes	PR	8*	(23)
23	61	8	Kidney	Urothelial cancer	Pembrolizumab, bevacizumab, cisplatin and gemcitabine	11	N/A	Mycophenolate mofetil, tacrolimus	No	PR	7*	(24)
24	49	19	Heart	Cutaneous SCC	Nivolumab	1	5	Prednisone, tacrolimus	Yes	–	–	(25)
Median	68	11	N/A	N/A	N/A	N/A	8	N/A	N/A	N/A	8	N/A

*, denotes ongoing response; –, denotes that data not available for evaluation. ID, patient identification; SCC, squamous cell carcinoma; PD, progressive disease; N/A, not applicable; PR, partial response; SD, stable disease; Ref, references.

Table S4 Previously reported cases of CTLA-4 inhibitor exposure in liver transplant patients

ID	Age	Transplant to immunotherapy (years)	Organ transplant	Malignancy	Immunotherapy	Number of immunotherapy doses	Time to graft rejection (days)	Immune suppression	Organ rejection	Response to immunotherapy	PFS (months)	Ref
9	59	8	Liver	Melanoma	Ipilimumab	4	N/A	Tacrolimus	No	SD	5	(33)
10	67	8	Liver	Melanoma	Ipilimumab	4	N/A	Sirolimus	No	PR	4*	(32)
11	62	6	Liver	Malignant peripheral nerve sheath tumor-like melanoma	Ipilimumab	4	N/A	Sirolimus, mycophenolate mofetil	No	PD	3	
12	67	1.5	Liver	Ocular melanoma	Ipilimumab	1	–	Prednisone	Yes	PD	3	(34)
Median	63	7	N/A	N/A	N/A	4	–	N/A	N/A	N/A	3.5	N/A

*, denotes ongoing response; –, denotes that data not available for evaluation. ID, patient identification; PD, progressive disease; N/A, not applicable; PR, partial response; SD, stable disease; Ref, references.

Table S5 Previously reported cases of CTLA-4 inhibitor exposure in kidney and heart transplant patients

ID	Age	Transplant to immunotherapy (years)	Organ transplant	Malignancy	Immunotherapy	Number of immunotherapy doses	Time to graft rejection (days)	Immune suppression	Organ rejection	Response to immunotherapy	PFS (months)	Ref
25	72	11	Kidney	Melanoma	Ipilimumab	–	N/A	Prednisone	No	PR	30*	(31)
26	58	8	Kidney	Melanoma	Ipilimumab	4	N/A	Prednisone	No	–	6	(31)
27	40	20	Kidney	Ocular Melanoma	Ipilimumab	2	–	Prednisone	Yes	PD	–	(35)
28	69	15	Heart	Melanoma	Ipilimumab	4	N/A	Tacrolimus	No	SD	10	(36)
Median	63	13	N/A	N/A	N/A	4	N/A	N/A	N/A	N/A	10	N/A

*, denotes ongoing response; –, denotes that data not available for evaluation. ID, patient identification; PD, progressive disease; N/A, not applicable; PR, partial response; SD, stable disease; Ref, references.