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Immuno-Oncology

A Pilot Study of Checkpoint Inhibitors in Solid Organ Transplant Recipients with Metastatic Cutaneous Squamous Cell Carcinoma

Irene Tsung,[a] Francis P. Worden,[a] Robert J. Fontana[b]

[a]Division of Hematology and Oncology and [b]Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, Michigan, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Transplant recipient • Checkpoint inhibitor • Squamous cell carcinoma

Abstract

Background. Immune checkpoint inhibitors (ICIs) are increasingly used in various solid organ malignancies. However, there are limited data regarding their safety and efficacy in solid organ transplant (SOT) recipients. The aim of this study was to review our experience with ICIs in SOT recipients with advanced head and neck cutaneous squamous cell carcinoma (cSCC).

Methods. A retrospective review of ICIs used in SOT recipients from April 2011 to September 2019 was undertaken. Patient clinical and demographic features, ICI regimen, immunosuppression, treatment efficacy, and adverse events were reviewed.

Results. The seven SOT recipients (four kidney, two liver, one lung) were diagnosed with metastatic head and neck cSCC. All had undergone prior locoregional surgery and adjuvant radiation therapy. At a median of 10.8 years (range, 6.6–18.1) post-transplant, six were treated with cemiplimab and one with pembrolizumab after minimizing calcineurin inhibitors (CNIs) or conversion of CNI to mammalian target of rapamycin (mTOR) inhibitors. During a median follow-up of 7.1 months, overall tumor response rate was 57.1% with one complete responder and three partial responders. Four patients died at a median of 135 days after starting ICI with two dying from tumor progression and two dying from other causes. Regarding adverse events, one lung transplant recipient developed severe pneumonitis that resolved with high-dose steroids, and one renal transplant patient developed progressive renal injury and died of unrelated causes. The three patients who received prophylactic prednisone all responded to cemiplimab with preserved allograft function and no adverse events.

Conclusion. Our data suggest that minimization of CNI and conversion of CNI to mTOR inhibitors along with judicious use of prophylactic steroids may allow for the safe use of ICIs in SOT recipients with advanced cSCC. Short-term efficacy appears promising, but prospective studies with further follow-up and a standardized protocol for prophylactic steroids are needed. ***The Oncologist*** 2021;26:133–138

Implications for Practice: Solid organ transplant (SOT) recipients are at increased risk of developing malignancy because of long-term post-transplant immunosuppression. Although immune checkpoint inhibitors (ICIs) are increasingly shown to be successful in treating multiple types of cancer, SOT recipients have been excluded from clinical trials because of concerns regarding potential allograft rejection. This pilot study provides evidence that ICIs along with prophylactic steroids may be a safe and efficacious treatment option for selected SOT recipients with advanced cutaneous squamous cell carcinoma. However, further prospective studies using ICIs in this high-risk patient population are needed.

Introduction

Oncologists are increasingly using immune checkpoint inhibitors (ICIs) such as antibodies targeting programmed cell death 1 (PD-1) in numerous advanced solid organ malignancies. However, the safety and efficacy of anti–PD-1 therapy in solid organ transplant (SOT) recipients are largely unknown, as these patients are routinely excluded from clinical trials because of their risk for severe and irreversible allograft rejection [1–3].

As SOT recipients remain on lifelong immunosuppressive regimens to prevent allograft rejection, they are at

Correspondence: Francis P. Worden, M.D., Med Inn Building, Room 369, 1500 East Medical Center Drive, Ann Arbor, Michigan 48109, USA. Telephone: 734-615-6633; e-mail: fworden@med.umich.edu Received May 29, 2020; accepted for publication September 11, 2020; published Online First on October 15, 2020. http://dx.doi.org/10.1002/onco.13539

increased risk of developing various solid organ tumors as well as cutaneous malignancies. Cutaneous squamous cell carcinoma (cSCC) is the most common post-transplant malignancy that arises in 10% to 27% of SOT recipients at 10 years of follow-up and increases to 40% to 60% at 20 years of follow-up [4]. These patients have high tumor mutational burdens (TMBs) because of ultraviolet-induced carcinogenesis from cumulative lifetime sun exposure [5]. cSCC tends to be more aggressive in SOT recipients compared with immunocompetent patients with increased risk of local recurrence, regional and distant metastasis, and mortality [4]. Initial management of high-risk cSCC in SOT recipients usually involves minimization of immunosuppression, aggressive surgical therapy, and possible adjuvant radiation therapy after an incomplete resection or if extensive lymph node or perineural involvement is present [6].

Systemic treatments for metastatic or unresectable advanced cSCC have traditionally involved more toxic treatments with less durable response rates such as chemotherapy and epidermal growth factor receptor (EGFR) targeted therapy [7]. However, because tumors with high mutational burdens are more likely to respond to immunotherapy, a phase I–II trial of cemiplimab (PD-1 inhibitor) was conducted in nonimmunosuppressed patients with advanced cSCC. The response rate was almost 50% with 75% having a duration of response for greater than 1 year [8]. Herein, we review our preliminary experience regarding the potential safety and efficacy of ICIs in SOT recipients with advanced cSCC of the head and neck region who have failed attempts at immunosuppression minimization as well as prior surgical, radiation, and other systemic therapies.

Materials and Methods

All solid organ transplant recipients at the University of Michigan were identified using the institution's Organ Transplantation Information System. This database included 9,435 unique SOT recipients who had undergone a total of 10,244 transplant surgeries (1,090 heart, 1 heart/liver, 13 heart/lung, 5,834 kidney, 30 kidney/heart, 86 kidney/liver, 2,424 liver, 766 lung). There were 5,274 patients still alive in September 2019 for potential inclusion in this study. All SOT recipients treated with ICIs from April 1, 2011, to September 1, 2019, were identified through the Data Office for Clinical and Translational Research. The search included all U.S. Food and Drug Administration–approved ICI treatments for malignancy (atezolizumab, avelumab, cemiplimab, durvalumab, ipilimumab, pembrolizumab, nivolumab). Only patients with a minimum of 30 days of follow-up after starting ICI therapy were included. One additional patient who started ICI after September 2019 was also included because he was identified and treated by the same clinical team. Patient clinical and demographic features, ICI regimen, immunosuppression, allograft function, efficacy, and outcome were reviewed through May 15, 2020, using the electronic medical record system. A waiver from the institutional review board was obtained to conduct this chart review study.

Results

This study identified seven SOT recipients receiving ICIs for metastatic head and neck cutaneous squamous cell carcinoma (Fig. 1). All patients had measurable stage IV disease based on the American Joint Committee on Cancer TNM Staging System (Table 1). There were four kidney, two liver, and one lung SOT recipients. The median patient age was 75 years, 85.7% were male, and 100% were White. The median time since SOT was 10.8 years, and immunosuppression was minimized in all of the patients by their transplant physicians including the conversion from tacrolimus to everolimus based treatment in three patients combined with low-dose steroids. All of the patients had prior surgery and radiation therapy, and four received prior systemic therapy with either chemotherapy, EGFR inhibitor, or tyrosine kinase inhibitor. Tumor genetic profiling was available in five patients, and all tested samples demonstrated high TMBs.

Six patients were treated with cemiplimab for a median of six infusion cycles (range, 2–13), and one patient was treated with two infusions of pembrolizumab. Three SOT recipients treated with cemiplimab received a prophylactic steroid regimen consisting of prednisone 40 mg on the day prior to ICI infusion, 20 mg daily from day of ICI infusion through day 5, and 10 mg daily until day 20. The other four patients did not receive additional immunosuppression after the minimization of their calcineurin inhibitors (CNIs), although three were still receiving low-dose prednisone (≤7.5 mg per day) as part of their baseline immunosuppression regimen (Table 2).

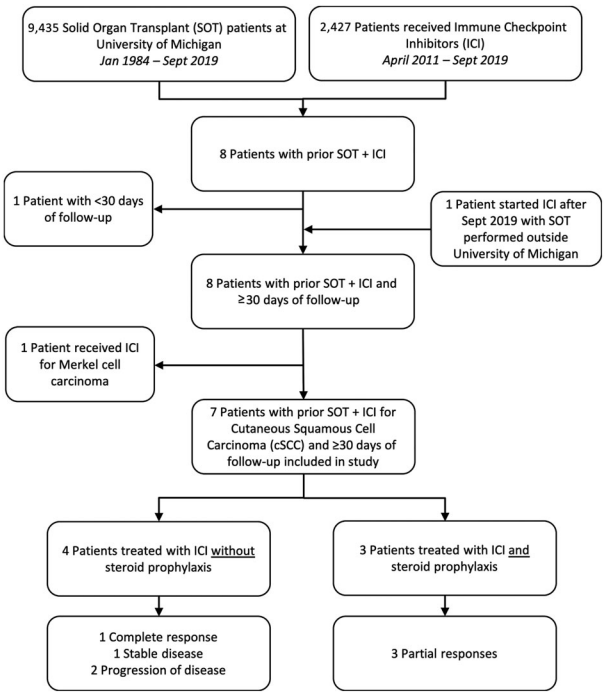

Figure 1. Study flow chart.
Abbreviations: cSCC, cutaneous squamous cell carcinoma; ICI, immune checkpoint inhibitor; SOT, solid organ transplant.

Tumor Response

At a median follow-up of 7.1 months (range, 1.2–13.3), the overall tumor response rate was 57.1%. One patient had a complete response, three were partial responders (one had clinical improvement, but follow-up imaging is pending), one had stable disease, and two patients had progression of disease.

All three SOT recipients (two kidney, one liver) receiving cemiplimab and prophylactic steroids attained partial responses. Two of these patients are alive and continuing treatment at 88 days (case #4) and 323 days (case #1). The third patient (case #6) died from cardiopulmonary disease, but prior to his terminal hospitalization, he had completed 12 cycles of cemiplimab and achieved a partial response.

Of the four patients who did not receive prophylactic steroids, there was one complete responder, one with stable disease, and two who died of tumor progression. The patient who had stable disease (case #3) died of cardiovascular disease at 214 days.

Safety

Two of the seven patients (28.6%) experienced an immune-related adverse event (irAE) during treatment. Case #3 was an 84-year-old woman who was 14.3 years post–kidney transplant without a prior history of rejection. After three cycles of cemiplimab, she experienced an increase of her baseline creatinine level of 0.8 mg/dL to 1.0–1.1 mg/dL, which was presumed to be due to possible rejection, although no biopsy was performed. Imaging after cycle 3 also showed evidence of tumor progression, but therapy was continued for two more cycles because of the patient's improved quality of life and symptom profile. After withholding cemiplimab for 2 months, her creatinine stabilized at 1.2 mg/dL, and follow-up imaging showed stable disease, so two additional cycles of cemiplimab were completed. After resuming therapy, her creatinine level rose to 3.1 mg/dL prior to her terminal hospitalization, when she died of multiple strokes and debilitation.

Case #7 was a 71-year-old man who was 10.8 years post–lung transplant without a prior history of rejection. After two cycles of cemiplimab, he was found to have dyspnea and hypoxemia, requiring intubation. A chest computed tomography showed diffuse bilateral ground glass opacities with nodular consolidations. He was treated with antibiotics for multifocal pneumonia and high-dose steroids for presumed immune mediated pneumonitis. After treatment, he improved and was discharged home on a steroid taper. He remains well at 1 year of follow-up with complete tumor response.

Of the three patients treated with steroid prophylaxis, none experienced any evidence of immune-related adverse events nor acute allograft rejection. Two of these patients remain on cemiplimab after 5 and 13 infusion cycles without any evidence of renal allograft dysfunction.

Table 1. Baseline clinical characteristics of SOT recipients prior to immune checkpoint inhibitor therapy

	SOT recipients (n = 7), n (%)
Age, median (range), years	75 (50–84)
Male	6 (85.7)
White	7 (100)
Non-Hispanic/Latino	7 (100)
SOT type	
Kidney	4 (57.1)
Liver	2 (28.6)
Lung	1 (14.3)
ECOG performance status 0–1	7 (100)
Time since transplant, median (range), years	10.8 (6.6–18.1)
Cancer type: cutaneous SCC	7 (100)
Prior treatments	
Systemic therapy	
Chemotherapy	2 (28.6)
Cetuximab	1 (14.3)
Axitinib	1 (14.3)
None	3 (42.9)
Locoregional surgery	7 (100)
Locoregional radiation	7 (100)
Immunosuppression	
Tacrolimus alone	1 (14.3)
Tacrolimus and prednisone	3 (42.9)
Everolimus and prednisone	3 (42.9)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; SCC, squamous cell carcinoma; SOT, solid organ transplant.

Discussion

This pilot study provides evidence that ICIs along with prophylactic steroids may be a safe and efficacious treatment option for selected SOT recipients with advanced cutaneous squamous cell carcinoma. Three of our patients obtained partial responses to therapy without evidence of irAEs when prophylactic steroids were given.

ICI therapy is well known to cause irAEs in up to 70% of treated patients, with skin and colon more commonly affected than lung or liver. Management of irAEs usually involves withholding of the ICI and initiation of corticosteroids for grade 3 to 4 events [9]. Because of the potential for increased toxicity, patients with a history of autoimmune disorders as well as transplant recipients have been excluded from clinical trials [10]. Therefore, use of ICIs in SOT recipients requires special consideration regarding the potential risk of not only irAEs but also irreversible allograft rejection. In our pilot study, our data suggest that ICIs may be safe and efficacious in a select population of SOT recipients with advanced cSCC and adequate performance status who are carefully monitored by an experienced oncologist in collaboration with the transplant team. To date, the overall tumor response rate has been 57.1%, and the incidence of immune-related allograft injury has been 28.6%.

cSCCs in SOT recipients often have higher TMB because of a combination of lifelong immunosuppressants and photocarcinogenesis from chronic ultraviolet radiation exposure, which is evident in all five of our patients who completed

Table 2. Characteristics and outcomes of SOT recipients receiving ICIs for cSCC

Case	Sex/Age	Organ transplant	Hx of prior rejection	cSCC stage[a]	ICI, # infusions	Mutational burden (mut/Mb)	Pre-ICI immunosuppression	Steroid prophylaxis	Allograft rejection after ICI	iRECIST	Post-ICI F/U (days)	Outcome
1	M/50	Kidney ×3	Yes	T4b N0 M1	Cemiplimab, 13[b]	156.1	Everolimus 0.75 mg BID, prednisone 5 mg daily	Yes	No	PR	323[b]	Alive
2	M/66	Kidney	No	T2 N0 Mx, now with locoregional failure and distant metastases	Pembrolizumab, 2	82.5	Everolimus 0.5 mg BID, prednisone 5 mg daily	No	No	N/A	35	Death – tumor progression
3	F/84	Kidney	No	T3 N0 M0, now with locoregional failure and distant metastases	Cemiplimab, 7	N/A	Tacrolimus 1.5 mg qAM and 0.5 mg qPM, prednisone 7.5 mg daily	No	Yes (no biopsy)	SD	214	Death – multiple falls, stroke
4	M/84	Kidney	No	Tx Nx M1	Cemiplimab, 5[b]	121.8	Everolimus 0.75 mg BID, prednisone 5 mg daily	Yes	No	N/A	88[b]	Alive
5	M/75	Liver	No	Tx Nx M1	Cemiplimab, 2	N/A	Tacrolimus 1 mg BID	No	No	N/A	55	Death – tumor progression
6	M/77	Liver	No	T4b N3 M0, now with locoregional failure and distant metastases	Cemiplimab, 12	98.1	Tacrolimus 0.5 mg BID	Yes	No	PR	245	Death – influenza A, cardiac arrest
7	M/71	Lung	No	Tx Nx M0, now with locoregional failure	Cemiplimab, 2	107.5	Tacrolimus 1 mg BID, prednisone 5 mg daily	No	No	CR	400	Alive

[a]Based on American Joint Committee on Cancer TNM Staging System for cSCC of the Head and Neck (eighth edition).
[b]Ongoing treatment.
Abbreviations: BID, twice a day; CR, complete response; cSCC, cutaneous squamous cell carcinoma; F, female; F/U, follow-up; Hx, history; ICI, immune checkpoint inhibitor; iRECIST, immune response evaluation criteria in solid tumors; M, male; mut/Mb, mutations per megabase; N/A, not available; PR, partial response; qAM, every morning; qPM, every evening; SD, stable disease; SOT, solid organ transplant.

tumor sequencing. Studies have correlated high TMB with better tumor response rates from ICI treatment [11]. In addition to cemiplimab, pembrolizumab has also yielded promising results in the treatment of unresectable, advanced, or metastatic cSCC. In the phase II CARSKIN trial evaluating first-line treatment with pembrolizumab, the 15-week response rate was 38.5% [12]. Additionally, results of the phase II KEYNOTE-629 study showed an overall response rate of 34.3% and a median progression-free survival of 6.9 months [13]. Furthermore, published practice guidelines suggest that the use of mammalian target of rapamycin inhibitors and minimizing CNIs can reduce the risk and rate of post-transplant skin cancer development [14]. Case reports also suggest a prophylactic conditioning regimen of corticosteroids may allow for allograft protection during ICI treatment without decreasing the efficacy of ICI therapy [15]. Whether this approach may also prevent other irAEs is not well known at this time, although there is a large ongoing study addressing this in patients with autoimmune disorders. All three of our SOT recipients managed with careful modification of their immunosuppressants prior to receiving corticosteroids and ICI therapy had tumors that showed partial responses and no evidence of allograft rejection or other irAEs.

Much of the literature in ICIs for SOT recipients focuses on renal transplant patients because of the availability of renal replacement therapy should allograft injury be encountered. However, three of our patients had received a prior liver (two) or lung (one) transplant, and two of them (one liver and one lung) had partial and complete responses, respectively, without evidence of allograft rejection. Limitations of our study include the small number of patients treated and the limited duration of follow-up. However, all of the patients were treated by a single experienced medical oncologist using a standardized dose and frequency of ICI administration along with serial labs that were monitored in collaboration with the on-site transplant team to maximize patient safety. Serum chemistry panels and complete blood counts were followed weekly for the first two cycles of ICI and then every 3 weeks thereafter with ICI if the bloodwork remained stable. Interestingly, none of our patients experienced diarrhea or rash, which is reported in at least 20% of nontransplant patients treated with cemiplimab and pembrolizumab [16, 17]. The lower rate of irAE may be, in part, due to the long-term use of immunosuppression in these patients.

Conclusion

Currently, there are no guidelines or consensus on how and when to use ICIs in SOT recipients with advanced malignancies such as cSCC of the head and neck region, which can be very aggressive and fatal despite standard therapies. As a result, clinicians are often faced with the challenging decision of treating an aggressive tumor versus preserving the transplanted organ. In this special population, progression of aggressive head and neck cSCC is frequently the cause of mortality rather than allograft failure. Our pilot study provides additional evidence that ICIs may be feasible in a variety of SOT recipients with advanced cSCC. Although short-term efficacy and safety appear promising, further prospective studies using a standardized approach with prophylactic steroids are needed. In addition, serial monitoring of noninvasive biomarkers of allograft tolerance such as cell-free DNA may prove useful in SOT recipients with advanced cSCC to minimize the risk of inadvertent allograft injury while maximizing tumor response [18].

Author Contributions

Conception/design: Irene Tsung, Francis P. Worden, Robert J. Fontana
Provision of study material or patients: Irene Tsung, Francis P. Worden, Robert J. Fontana
Collection and/or assembly of data: Irene Tsung, Francis P. Worden, Robert J. Fontana
Data analysis and interpretation: Irene Tsung, Francis P. Worden, Robert J. Fontana
Manuscript writing: Irene Tsung, Francis P. Worden, Robert J. Fontana
Final approval of manuscript: Irene Tsung, Francis P. Worden, Robert J. Fontana

Disclosures

Francis P. Worden: Merck Sharp & Dohme, Eisai, Bristol-Myers Squibb, LOXO, Bayer, CUE Biopharma (H), Eisai, Bayer, CUE Biopharma, Rakuten, Merck, Loxo (C/A), Bristol-Myers Squibb, Loxo, Oragenics, Eli Lilly & Co., Pfizer, Merck, Eisai (RF—institution), Merck Sharp & Dohme, Bayer (other—travel); **Robert J. Fontana:** Gilead, Abbvie (RF), Sanofi (C/A). Irene Tsung indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

References

1. Abdel-Wahab N, Safa H, Abudayyeh A et al. Checkpoint inhibitor therapy for cancer in solid organ transplantation recipients: An institutional experience and a systematic review of the literature. J Immunother Cancer 2019;7:106.

2. DeLeon TT, Salomao MA, Aqel BA et al. Pilot evaluation of PD-1 inhibition in metastatic cancer patients with a history of liver transplantation: The Mayo Clinic experience. J Gastrointest Oncol 2018;9:1054–1062.

3. Kumar V, Shinagare AB, Rennke HG et al. The safety and efficacy of checkpoint inhibitors in transplant recipients: A case series and systematic review of literature. ***The Oncologist*** 2020; 25:1–10.

4. O'Reilly Zwald F, Brown M. Skin cancer in solid organ transplant recipients: Advances in therapy and management: Part I. Epidemiology of skin cancer in solid organ transplant recipients. J Am Acad Dermatol 2011;65:253–261.

5. Madan V, Lear JT, Szeimies RM. Non-melanoma skin cancer. Lancet 2010;375:673–85.

6. O'Reilly Zwald F, Brown M. Skin cancer in solid organ transplant recipients: Advances in therapy and management: Part II. Management of skin cancer in solid organ transplant recipients. J Am Acad Dermatol 2011;65:263–279.

7. Guminski A, Stein B. Immunotherapy and other systemic therapies for cutaneous SCC. Oral Oncol 2019;99:104459.

8. Migden MR, Rischin D, Schmults CD et al. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. N Engl J Med 2018;379:341–351.

9. Michot JM, Bigenwald C, Champiat S et al. Immune-related adverse events with immune checkpoint blockade: A comprehensive review. Eur J Cancer 2016;54:139–148.

10. Kennedy LC, Bhatia S, Thompson JA et al. Preexisting autoimmune disease: Implications for immune checkpoint inhibitor therapy in solid tumors. J Natl Compr Canc Netw 2019;17: 750–757.

11. Yarchoan M, Hopkins A, Jaffee EM. Tumor mutational burden and response rate to PD-1 inhibition. N Engl J Med 2017;377:2500–2501.

12. Maubec E, Boubaya M, Petrow P et al. Pembrolizumab as first-line therapy in patients with unresectable cutaneous squamous cell carcinoma (cSCC): Phase II results from CARSKIN. J Clin Oncol 2019;37(suppl 15): 9547a.

13. Grob JJ, Gonzalez R, Basset-Sequin N et al. KEYNOTE-629: Phase 2 study of pembrolizumab for recurrent/metastatic or locally advanced unresectable cutaneous squamous cell carcinoma (cSCC). J Clin Oncol 2019;37(suppl 15):TPS9598a.

14. Kuschal C, Thoms KM, Schubert S et al. Skin cancer in organ transplant recipients: Effects of immunosuppressive medications on DNA repair. Exp Dermatol 2011;21:2–6.

15. Barnett R, Barta VS, Jhaveri KD. Preserved renal-allograft function and the PD-1 pathway inhibitor nivolumab. N Engl J Med 2017;376:191–192.

16. Libtayo (cemiplimab) [package insert]. Tarrytown, NY and Bridgewater, NJ: Regeneron Pharmacceuticals/Sanofi-Aventis U.S., 2018.

17. Keytruda (pembrolizumab) [package insert]. Whitehouse Station, NJ: Merck and Company, 2020.

18. Knight SR, Thorne A, Lo Faro ML. Donor-specific cell-free DNA as a biomarker in solid organ transplantation: A systematic review. Transplantation 2019;103:273–283.

For Further Reading:
Vivek Kumar, Atul B. Shinagare, Helmut G. Rennke et al. The Safety and Efficacy of Checkpoint Inhibitors in Transplant Recipients: A Case Series and Systematic Review of Literature. ***The Oncologist*** 2020;25:505–514.

Implications for Practice:
Transplant recipients are at higher risk of developing cancers. Although immune checkpoint inhibitors have been shown to improve the outcome in more than one cancer type, transplant recipients were excluded from these trials. Most of the data on the safety and efficacy of immune checkpoint inhibitors in transplant patients are based upon case series and case reports. The pooled data from these reports suggest that anti-programmed death-ligand 1 inhibitors have reasonable safety and efficacy among organ transplant patients, which warrants testing in clinical trials.