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A pilot study of checkpoint inhibitors in solid organ transplant recipients with metastatic cutaneous squamous cell carcinoma

Short Title: Checkpoint inhibitors in transplant recipients

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Key Words: transplant recipient, checkpoint inhibitor, squamous cell carcinoma

Abbreviations

CNI	Calcineurin inhibitor
cSCC	Cutaneous squamous cell carcinoma
dL	Deciliter
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
FDA	Food and Drug Administration
ICI	Immune checkpoint inhibitor
irAE	Immune-related adverse event
mg	Milligram
mTOR	Mammalian target of rapamycin
OTIS	Organ Transplantation Information System
PD-1	Programmed cell death 1

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SOT	Solid organ transplant
TMB	Tumor mutational burden

Abstract

Background: Immune checkpoint inhibitors (ICI) are increasingly used in various solid organ malignancies. However, there is 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 7 SOT recipients (4 kidney, 2 liver, 1 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 [6.6-18.1] post-transplant, 6 were treated with cemiplimab and 1 with pembrolizumab after minimizing calcineurin inhibitors (CNI) or conversion of CNI to mTOR inhibitors. During a median follow-up of 7.1 months, overall tumor response rate was 57.1% with 1 complete responder and 3 partial responders. Four patients died at a median of 135 days after starting ICI with 2 dying from tumor progression and 2 dying from other causes. Regarding adverse events, 1 lung transplant recipient developed severe pneumonitis that resolved with high-dose steroids, and 1 renal transplant patient developed progressive renal injury and died of unrelated causes. The 3 patients who received prophylactic prednisone all responded to cemiplimab with preserved allograft function and no adverse events.

Conclusions: 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.

Implications for Practice

Solid organ transplant (SOT) recipients are at increased risk of developing malignancy due to long-term post-transplant immunosuppression. Although immune checkpoint inhibitors (ICI) are increasingly shown to be successful in treating multiple types of cancer, SOT recipients have been excluded from clinical trials due to 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 utilizing immune checkpoint inhibitors (ICI) 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 is largely unknown as these patients are routinely excluded from clinical trials due to their risk for severe and irreversible allograft rejection.[1,2,3]

As SOT recipients remain on lifelong immunosuppressive regimens to prevent allograft rejection, they are at 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 (TMB) due to ultraviolet-induced carcinogenesis from cumulative lifetime sun exposure.[5] Cutaneous SCC tend to be more aggressive in SOT recipients compared to 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 non-immunosuppressed 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.

Methods

All solid organ transplant recipients at the University of Michigan were identified using the institution's Organ Transplantation Information System (OTIS). This database included 9435 unique SOT recipients who had undergone a total of 10244 transplant surgeries (1090 heart, 1 heart/liver, 13 heart/lung, 5834 kidney, 30 kidney/heart, 86 kidney/liver, 2424 liver, 766 lung). There were 5274 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 FDA

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 since 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 7 SOT recipients receiving ICIs for metastatic head and neck cutaneous squamous cell carcinoma (Figure 1). All patients had measurable stage IV disease based on American Joint Committee on Cancer (AJCC) TNM Staging System (Table 1). There were 4 kidney, 2 liver, and 1 lung SOT recipients. The median patient age was 75 years, 85.7% were male, and 100% were Caucasian. 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 3 patients combined with low dose steroids. All of the patients had prior surgery and radiation therapy, and 4 received prior systemic therapy with either chemotherapy, EGFR inhibitor, or tyrosine kinase inhibitor. Tumor genetic profiling was available in 5 patients, and all tested samples demonstrated high TMBs.

Six patients were treated with cemiplimab for a median of 6 infusion cycles (range: 2-13), and 1 patient was treated with 2 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 4 patients did not receive additional immunosuppression after the minimization of their CNIs, although 3 were still receiving low-dose prednisone (≤7.5 mg per day) as part of their baseline immunosuppression regimen (Table 2).

Tumor Response

At a median follow-up of 7.1 months [1.2-13.3], the overall tumor response rate was 57.1%. One patient had a complete response, 3 were partial responders (1 had clinical improvement, but follow-up imaging is pending), 1 had stable disease, and 2 patients had progression of disease.

All 3 SOT recipients (2 kidney, 1 liver) receiving cemiplimab and prophylactic steroids attained partial responses. Two of these patients are alive and continuing treatment at 88 (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 4 patients who did not receive prophylactic steroids, there was 1 complete responder, 1 with stable disease, and 2 who died of tumor progression. The patient who had stable disease (case #3) died of cardiovascular disease at 214 days.

Safety

Two of the 7 patients (28.6%) experienced an 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 3 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 2 more cycles due to 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 2 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. Following 2 cycles of cemiplimab, he was found to have dyspnea and hypoxemia, requiring intubation. A chest CT 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. Following 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 3 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.

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] Due to 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 irreversible allograft rejection as well. 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%.

Cutaneous SCCs in SOT recipients often have higher TMB due to a combination of lifelong immunosuppressants and photocarcinogenesis from chronic ultraviolet radiation exposure, which is evident in all 5 of our patients who completed 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 mTOR 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 3 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 nor other irAE.

Much of the literature in ICIs for SOT recipients focuses on renal transplant patients due to the availability of renal replacement therapy should allograft injury be encountered. However, 3 of our patients had received a prior liver (2) or lung (1) transplant, and 2 of them (1 liver and 1 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 non-transplant 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 non-invasive 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]

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Table 1: Baseline clinical characteristics of SOT recipients prior to ICI therapy

	SOT Recipients (n=7)
Age (yrs)	75 [50-84]
Male	6 (85.7)
Caucasian	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 (yrs)	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)

Data presented as median [range] or n (%).
Abbreviations: SOT, solid organ tumor; ECOG, Eastern Cooperative Oncology Group; SCC, squamous cell carcinoma.

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

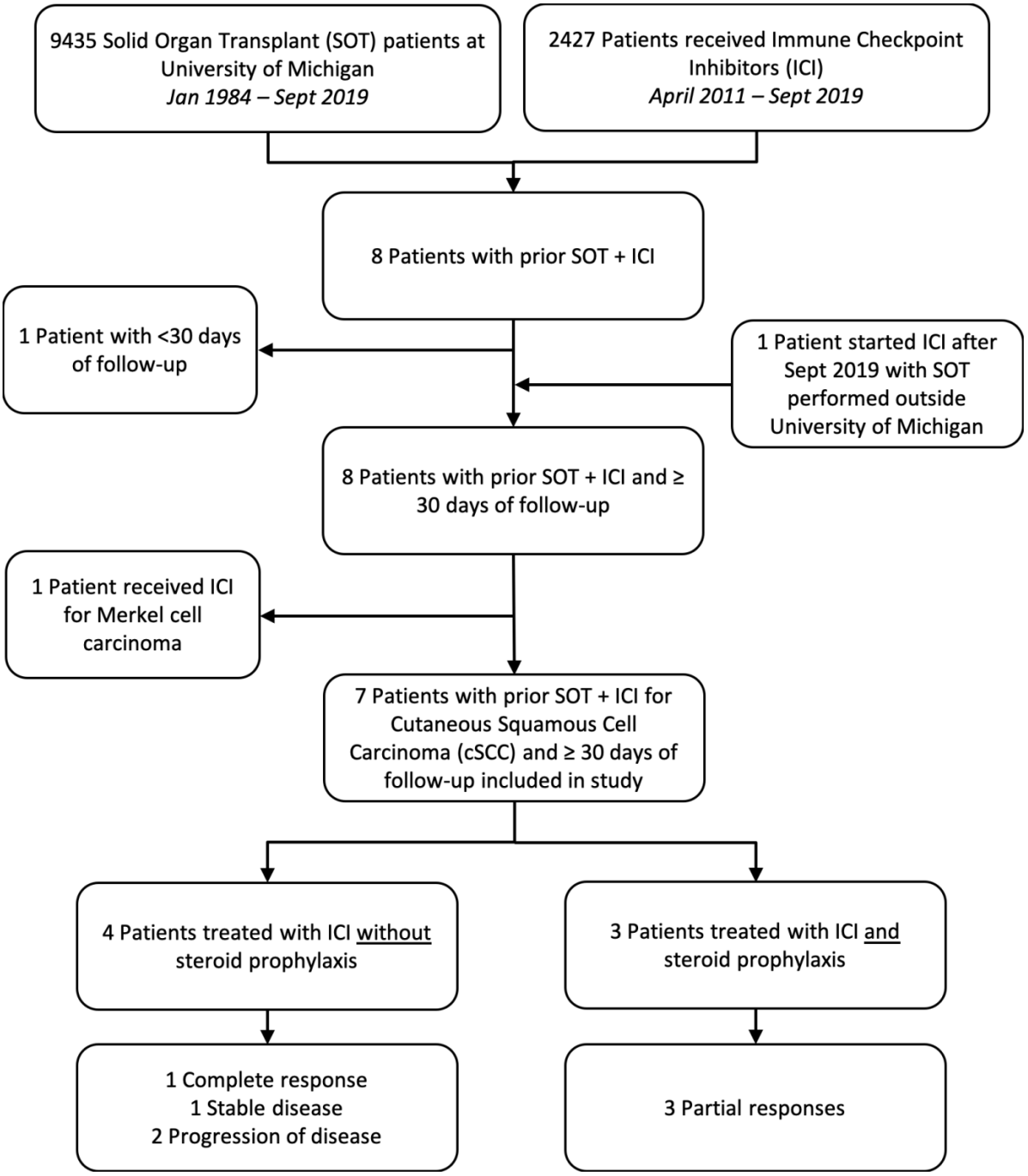
Case	Sex/Age	Organ Transplant	Hx of Prior Rejection	cSCC Stage[a]	ICI, # Infusions	Mutational Burden (mut/Mb)	Pre-ICI Immunosuppression	Steroid Prophylaxis	Allograft Rejection after ICI	iRECIST	Post-ICI F/U (days)	Outcome
1	M/50	Kidney x3	Yes	T4b N0 M1	Cemiplimab, 13[b]	156.1	Everolimus 0.75 mg BID, 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 (AJCC) TNM Staging System for cSCC of the Head and Neck (Eighth Edition)
[b]Ongoing treatment

Abbreviations: SOT, solid organ transplant; ICI, immune checkpoint inhibitor; cSCC, cutaneous squamous cell carcinoma; Hx, history; iRECIST, immune response evaluation criteria in solid tumors; F/U, follow-up; M, male; F, female; mg, milligram; BID, twice a day; qAM, every morning; qPM, every evening; PR, partial response; N/A, not available; SD, stable disease; PD, progression of disease; CR, complete response.

Figure 1: Study flow chart



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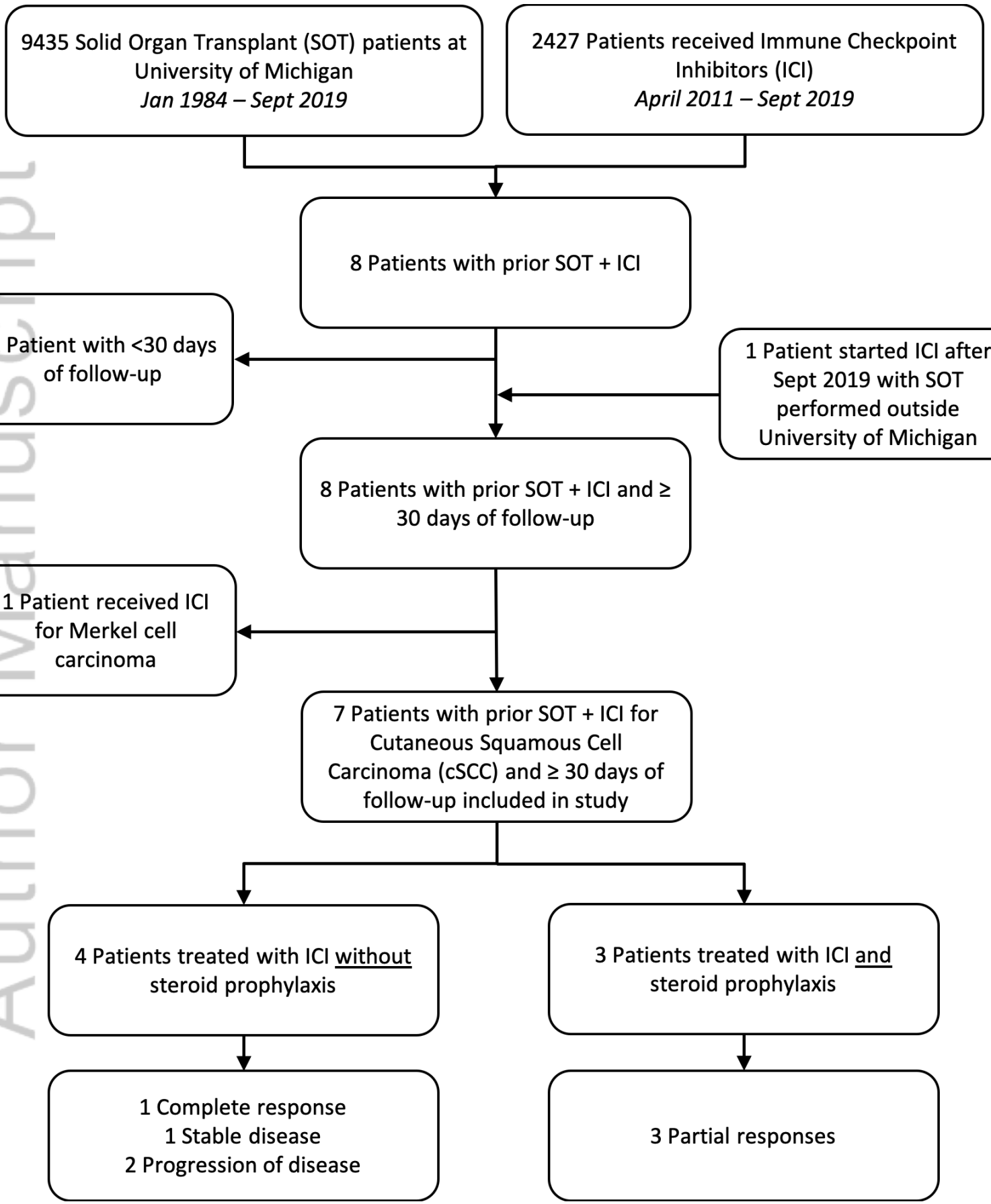

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