Role of Immunotherapy in Patients with Solid Organ Transplants

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Objectives

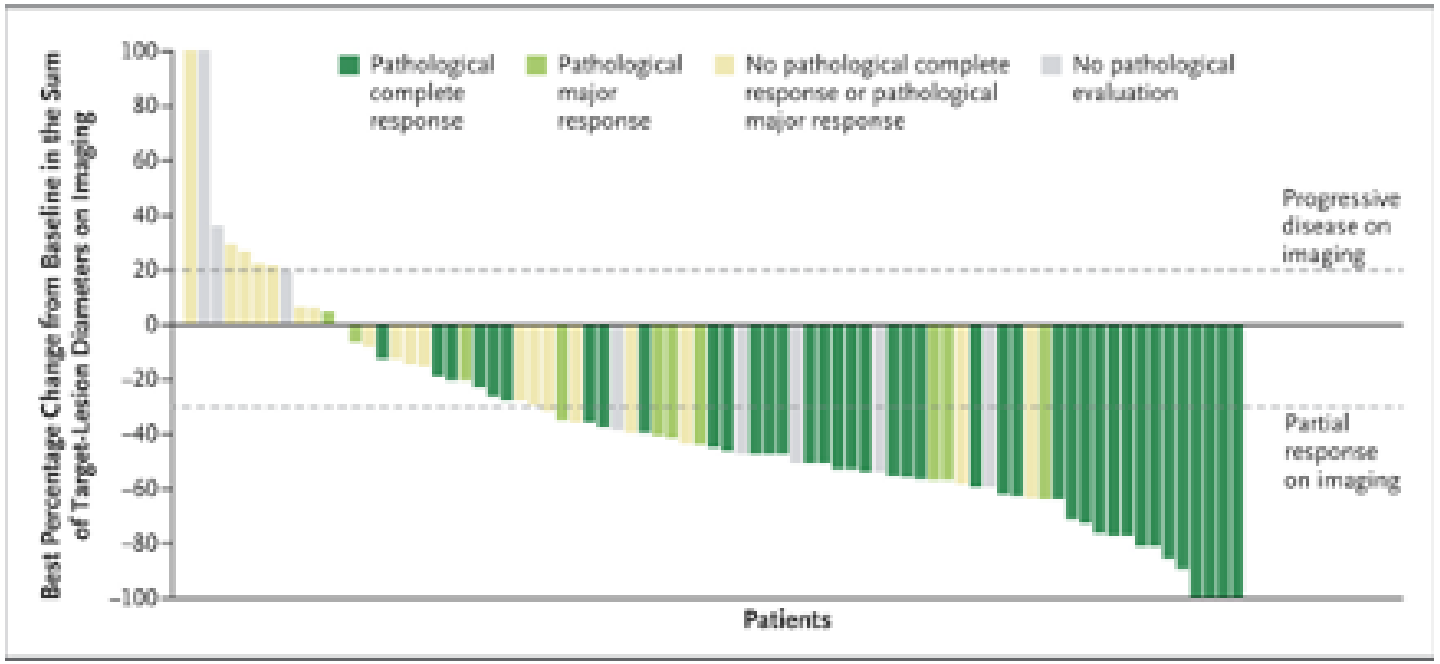
1. Evaluate emerging data for immune checkpoint inhibitors in solid organ transplant recipients with advanced cutaneous squamous cell carcinomas

2. Discuss appropriate patient selection, including identification of risk factors and use in various organ transplant types

3. Recommend appropriate monitoring parameters and multidisciplinary care for this high-risk population

Neoadjuvant cemiplimab in surgically resectable, LA-cSCC is highly effective

- 79 patients enrolled; surgical candidates at baseline
- Stage: II (n=4), III (n=38), IV (n=36)
- Intervention: 4 cycles of Cemiplimab 350mg q3 weeks
- Key Outcomes: ORR (68%), pCR (50%) MPR (13%)
- Toxicities: Grade ≥3: 18%



Potential Benefits of Neoadjuvant PD1 Blockade

- Decrease tumor burden for subsequent surgical resection
- Preserve functional structures
- Decrease intensity of adjuvant therapy
- Determine responsiveness of tumor to ICI
- Improve long-term disease control

Can these data be replicated in immunocompromised patients?

How to categorize immunocompromised patients?

CLL and other heme malignancies

HIV/AIDS and other chronic inflammatory disorders

Transplant Patients

Autoimmune Disease

Long-term steroid use

Diabetics

Response Rates with ICI in R/M cSCC:
Immunocompetent vs. Immunocompromised

Response Rate	Immunocompetent	Immunocompromised
1L or 2L[1]	48%	32%
2L only[2]	33%	
2L Renal Tx[3]		36%

1. Hanna GJ, et al. *Br J Cancer*. 2020 Nov;123(10):1535-1542.
2. Hughes BGM, et al. *Ann Oncol.* 2021 Oct;32(10):1276-1285.
3. Murakami N, et al. *Kidney Int*. 2021 Jul;100(1):196-205.

Emerging Data in Renal Transplant

Original Reports | Skin Cancer

Cemiplimab for Kidney Transplant Recipients With Advanced Cutaneous Squamous Cell Carcinoma

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ABSTRACT

PURPOSE Cemiplimab is approved for treating locally advanced or metastatic cutaneous squamous cell carcinoma (CSCC). Solid organ transplant recipients have been excluded from immunotherapy trials, given concern for allograft rejection despite their increased risk of skin cancers. Chronic immunosuppression is necessary to prevent organ rejection but may attenuate antitumor response with PD-1 inhibitors.

METHODS We report a phase I study of cemiplimab for kidney transplant recipients (KTRs) with advanced CSCC. After cross-taper to a mammalian target of rapamycin (mTOR) inhibitor and pulsed dose corticosteroids (prednisone 40 mg once daily, the day before and on days 1-3 of each cycle, followed by 20 mg once daily on days 4-6, then 10 mg once daily until the day before each subsequent cycle), patients received cemiplimab 350 mg intravenously once every 3 weeks for up to 2 years and were assessed for response every 8 weeks. The primary end point was the rate of kidney rejection, with key secondary end points including rate and duration of response, and survival.

RESULTS Twelve patients were treated. No kidney rejection or loss was observed. A response to cemiplimab was observed in five of 11 evaluable patients (46%; 90% CI, 22 to 73), including two with durable responses beyond a year. Median follow-up was 6.8 months (range, 0.7-29.8). Treatment-related grade 3 or greater adverse events occurred in five patients (42%), including diarrhea, infection, and metabolic disturbances. One patient died of angioedema and anaphylaxis attributed to mTOR inhibitor cross-taper.

CONCLUSION mTOR inhibitor and corticosteroids represent a favorable immunosuppressive regimen for KTRs with advanced CSCC receiving immunotherapy. This combination resulted in durable antitumor responses with no kidney rejection events (funded by Regeneron Pharmaceuticals [ClinicalTrials.gov identifier: NCT04339062]).

ACCOMPANYING CONTENT

Editorial, p. 981

Appendix

Protocol

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View Online Article

Study Design

- Single center study (DFCI)
- Key inclusion criteria: ≥ 18-year-old, locally advanced unresectable or metastatic cSCC
- Primary endpoint: safety and toxicity
- 12 KTR enrolled from 11/2020 to 3/2023

Transplant History/Prior IS Regimen

Time since kidney transplant, years, median (range)[b]	7.2 (2.8-21.1)
No. of IS agents before enrollment, (%)	
2	6 (50)
3	6 (50)
IS regimen before enrollment, No. (%)[c]	
Calcineurin inhibitors	7 (58)
mTOR inhibitors	6 (50)
Antiproliferative	6 (50)
Prednisone	10 (83)
Baseline renal allograft function, median (range)	
Baseline creatinine, mg/dL	1.51 (0.95-1.86)
Estimated GFR, mL/min[d]	49 (32-60+)

Can we extrapolate this data to other transplanted organ types?

Case reports/series in other transplanted organs

Transplant Type	Efficacy	Safety
Heart		
- 4 pt case series, all treated with PD-1[1]	- Not reported	- 3 (**75%**) had rejection; 2 died 2/2 cancer, 1 from tx complication
- 3 pt case series; 2 treated with PD-1, one with ipilimumab[2]	- 2 responses; one stopped after 1 dose for rejection	- 2 (**66%**) had rejection; 1 died 2/2 cancer, 1 from tx complication
Lung		
- 2 pt case series, all treated with PD-1[1]	- Not reported	- Neither had biopsy-proven rejection but both developed acute graft dysfunction, died 2/2 complications
- Case report of 1 pt treated with PD-1[3]	- CR	- No rejection

1. Daud A, et al. J Heart Lung Transplant. 2020 Jun;39(6):604-606.
2. Yeung T, et al. JACC CardioOncol. JACC CardioOncol. 2022 Dec; 4(5): 717–721.
3. Tsung I, et al. Oncologist. 2021 Feb;26(2):133-138.

Case reports/series in other transplanted organs

Transplant Type	Efficacy	Safety
Liver		
- Systematic review of 52 patients, majority with HCC and most treated with PD-1 alone[1]	- 34% response, 44% disease control rate	- Rejection in **29%**; 13% died due to graft loss
- 4 pt case series, all treated with PD-1 ± bevacizumab (all for GI malignancies)[2]	- All progressed	- 1 rejection (**25%**); death likely 2/2 transplant complications

- Rejection rates appear higher in heart transplant patients, lower in liver
- Too few reports to draw conclusions for lung
- Although data is sparse, ipilimumab may have lower rates of graft rejection but risk of reduced efficacy vs PD-1 inhibitors

1. Kayali S, et al. Liver Int. 2023 Jan; 43(1): 8–17.
2. Rudolph M, et al. J Gastrointest Oncol. 2023 Apr 29; 14(2): 1141–1148.

Monitoring based on specific organ transplant

Kidney	Heart	Liver	Lung
Per DFCI study protocol[1] • Weekly labs for renal function and urine protein levels • mTOR inhibitor troughs at least every other week • Plasma donor-derived cell free DNA (dd-cfDNA) at least every other week for first 2-3 months)	Per Yeung, et al[2] • Weekly troponin levels • NT-proBNP, TTE, and endomyocardial biopsy 1-2 weeks after each cycle for 3 months then q6w if stable then q3m • At UNC: added weekly BNP; utilized dd-cfDNA testing instead of biopsy; added DSA on week 9 along with biopsy	No formal recommendations published Have not yet treated at UNC	No formal recommendations published At UNC: • Non-contrast CT chest 1-2 days prior to each PD-1 infusion • Frequent PFTs

If rejection occurs, it is often early -- median time in systematic review of 39 pts: 21 days (95% CI 19.3-22.8 days)

Monitor FREQUENTLY and monitor EARLY

1. Schenk KM, et al. J Clin Oncol. 2024 Mar 20;42(9):1011-1020.
2. Yeung T, et al. JACC CardioOncol. JACC CardioOncol. 2022 Dec; 4(5): 717–721.

Medication Management is Highly Complex

Immunosuppression regimen based on organ transplant

- Higher immunogenicity with lung vs other organs, liver least immunogenic
- Some may need triplet vs doublet regimen (ie lung) or if prior rejection episodes

Immunosuppression regimen based on treatment intent

- Bigger consideration for mTOR in neoadjuvant setting where response is crucial
- If palliative, can balance risk with use of low-dose CNI

mTOR inhibition key for balancing risks/benefits

- Prospective study of eight kidney transplant recipients with advanced cutaneous cancers treated with nivolumab + tacrolimus + prednisone ± ipilimumab[1]
  - All patients had PD on nivolumab with one developing treatment-related allograft loss (TRAL)
  - Six patients then received ipilimumab + nivolumab with two CR (one with TRAL) and four PD (one with TRAL)

- Systematic review of 39 SOT patients[2]

- DFCI protocol with mTOR + pulse pred[3]
  - 46% tumor response
  - 0% rejection events

Immunosuppression regimen	Allograft rejection	Tumor response
All patients	15/28 (40%)	15/32 (47%)
Single-agent IS therapy		
Prednisone (≤10 mg/day)	7/9 (78%)	5/8 (63%)
MTOR inhibitors	2/3 (67%)	1 /2 (50%)
Calcineurin inhibitors	**1/9 (11%)**	**2/8 (25%)**
Combination IS therapy	**5/17 (29%)**	**7/14 (50%)**

1. Schenk KM, et al. J Clin Oncol. 2024 Mar 20;42(9):1011-1020.
2. Abdel-Wahab N, et al. J Immunother Cancer. 2019 Apr 16;7(1):106
3. Hanna GJ, et al. J Clin Oncol. 2024 Mar 20;42(9):1021-1030.

Who is at risk?

- Appears there is no increased risk for[1]:
  - Patients with prior rejection episode
  - Patients who change IS regimen just prior to ICI treatment

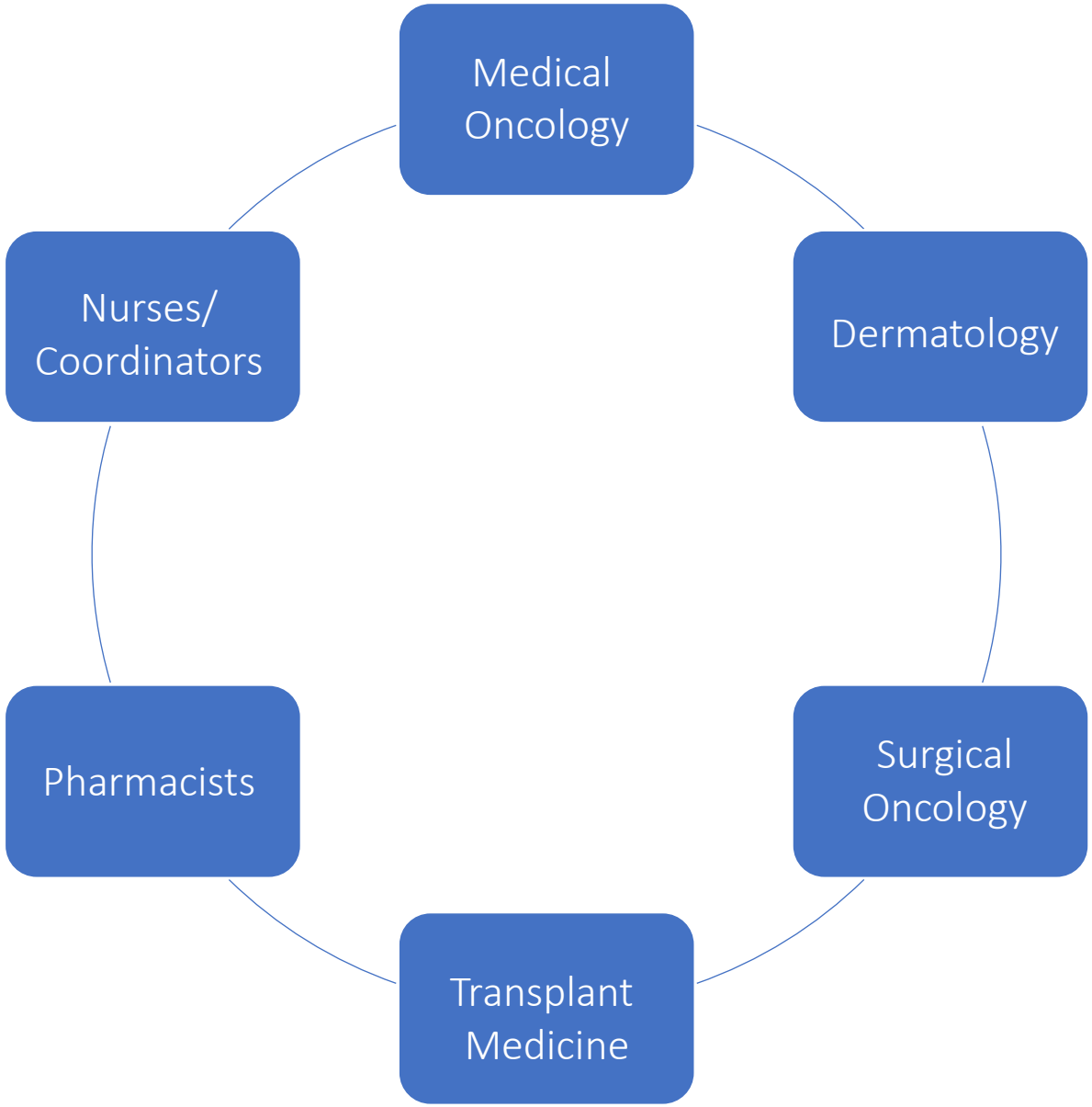
- Increased risk for:
  - Patients on single-agent immunosuppression
  - Lung and heart transplants (vs liver/kidney)

- Data is conflicting on risk of rejection based on time from transplant, but most data favors no increased risk[1,2]

- Risk of immune-related adverse events does not seem to be increased in SOT patients compared to immunocompetent patients

1. Abdel-Wahab N, et al. J Immunother Cancer. 2019 Apr 16;7(1):106
2. Kayali S, et al. Liver Int. 2023 Jan; 43(1): 8–17.

Multidisciplinary Care is Essential



How to identify the ideal SOT patient?

There isn’t an ideal patient.

Identifying which SOT patients with cSCC to treat with ICI:

1. **Need strong patient buy-in**
   - ⬆ Office visits, lab appointments, imaging

2. **Need strong multidisciplinary team buy-in**
   - Who will own which piece of the management?
   - Ideally 1 quarterback
   - Pharmacy/NN support is critical
   - Referral to academic centers (for now)

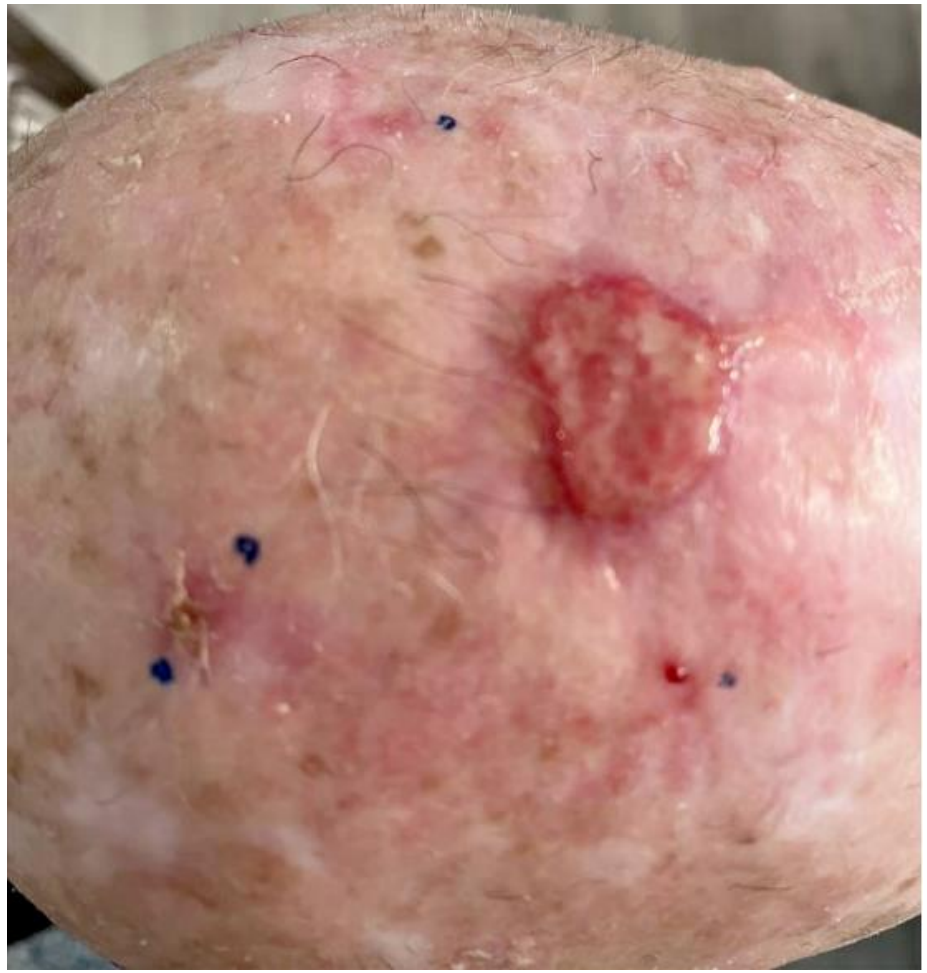
3. **For now, prioritize renal transplant**
   - Dialysis is a backup

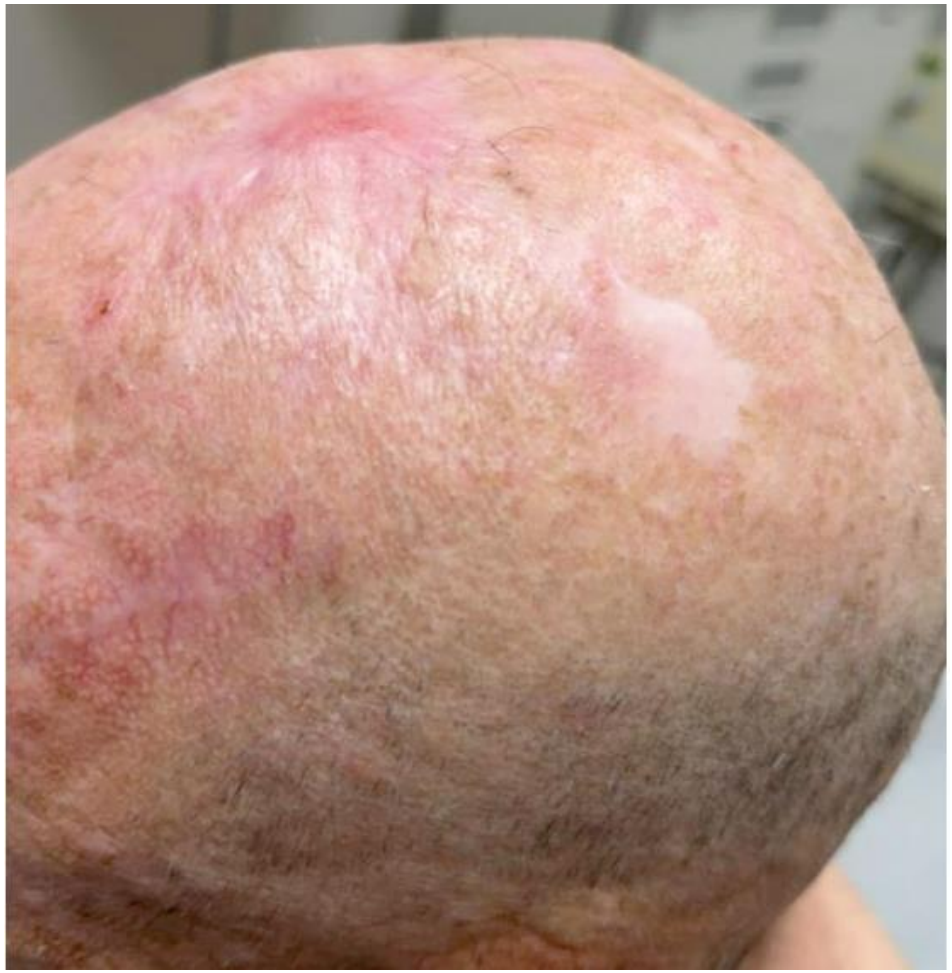
4. **Follow the science**
   - Our current data is limited → use it and try not to chart your own path
   - We need prospective data

UNC Experience

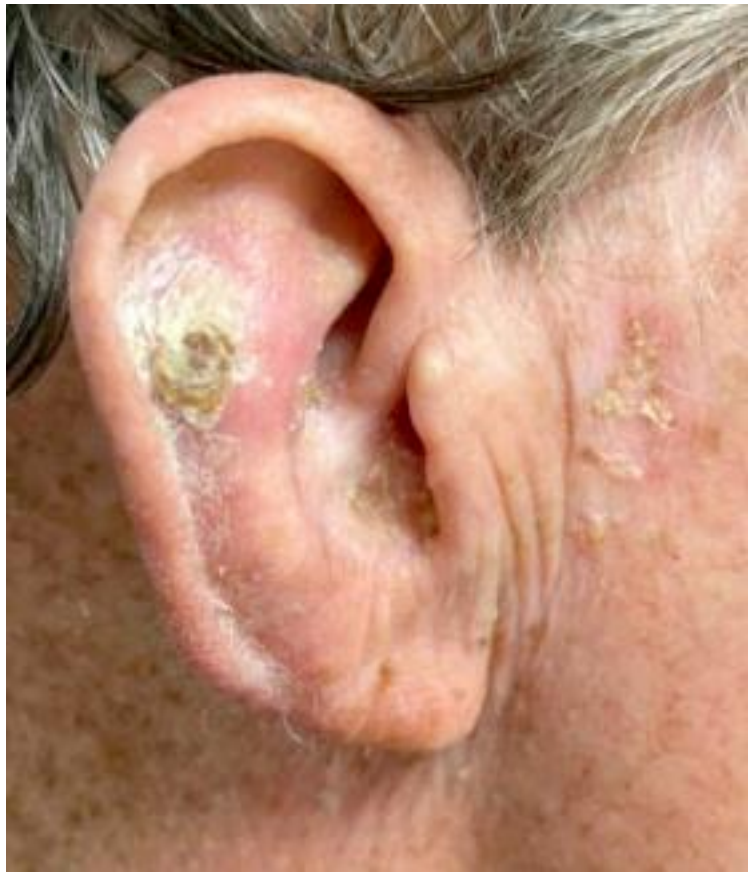
Transplant Type	Kidney #1	Kidney #2	Kidney #3	Lung	Heart
Disease State	• LA-cSCC of scalp	• LA-cSCC of EAC	• Multiply recurrent, unresectable cSCC	• LA- cSCC of parotid	• LA- cSCC of ear
ICI Received	• 6 cycles of cemiplimab	• 6 cycles of cemiplimab	• 4 cycles of cemiplimab	• 4 cycles of cemiplimab	• 3 cycles of cemiplimab
Toxicity	• Developed G2 irAE (pneumonitis) after C6; holding ICI + on steroids	• Developed grade 2 irAE (rash) after 2C after cycle 2, improved with steroids; no delay	• No immune-related toxicities	• No immune-related toxicities	• No immune-related toxicities
Rejection	• No evidence of organ rejection	• No evidence of organ rejection	• No evidence of organ rejection	• No evidence of organ rejection	• No evidence of organ rejection
Response Status	• NED	• Partial response	• Partial response	• Partial response	• Partial response

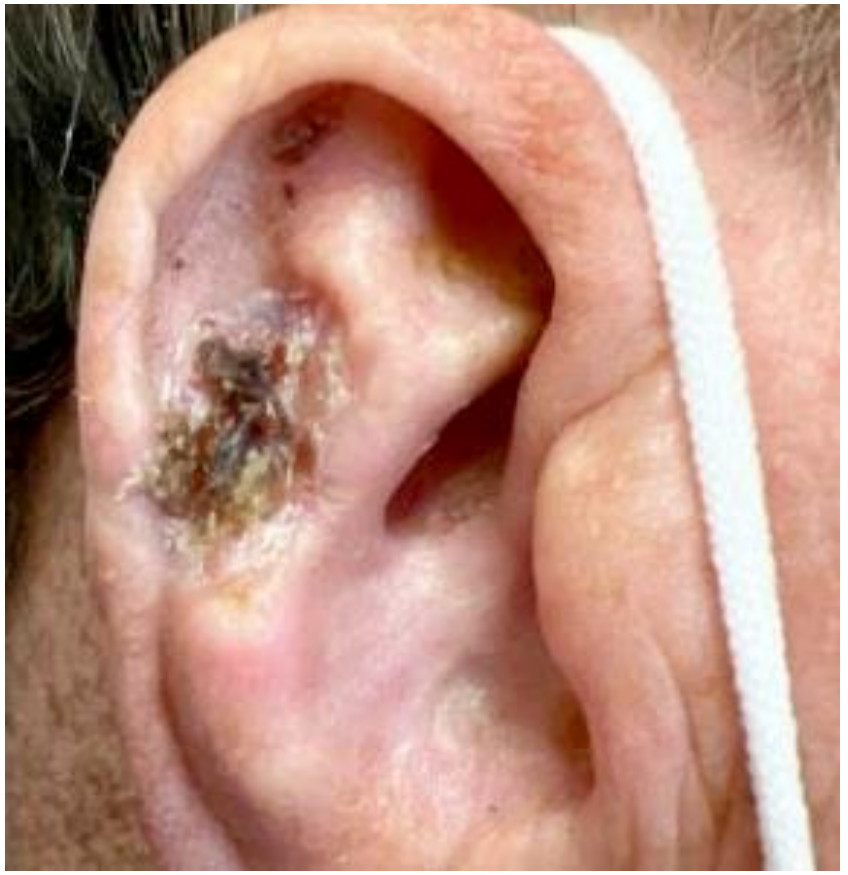
Scalp cSCC: Pre-treatment vs. after 3 cycles





Ear cSCC: Pre-treatment vs. after 3 cycles





Outstanding questions:

1. **What is the role of pulse-dose steroids?**
   - Can we maintain safety and improve efficacy with lower (<10 mg/day) prednisone

2. **What is the utility and timing of donor-derived cell-free DNA for rejection monitoring in ICI patients?**

3. **What are the benefits of testing organ graft for PD-L1 to assess risk for rejection?**
   - Small study of 5 patients showed those with negative PD-L1 expression (4/5) had no rejection while those with positive expression experienced rejection (1/5)[1]

4. **Prospective data and monitoring parameters in other solid organ transplant types?**

1. Shi GM, et al. Liver Transpl. 2021 Feb;27(3):444-449

Key Takeaways

- The use of immune checkpoint inhibitors is safe and has promising efficacy in solid organ transplant patients with advanced cutaneous squamous cell carcinomas

- Treatment is more complex compared to immunocompetent patients, requiring more intensive monitoring and medication management

- Multidisciplinary care is essential

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