



**Brigham and Women's Hospital**  
Founding Member, Mass General Brigham

# Use of Checkpoint Inhibitors in Kidney Transplant Recipients

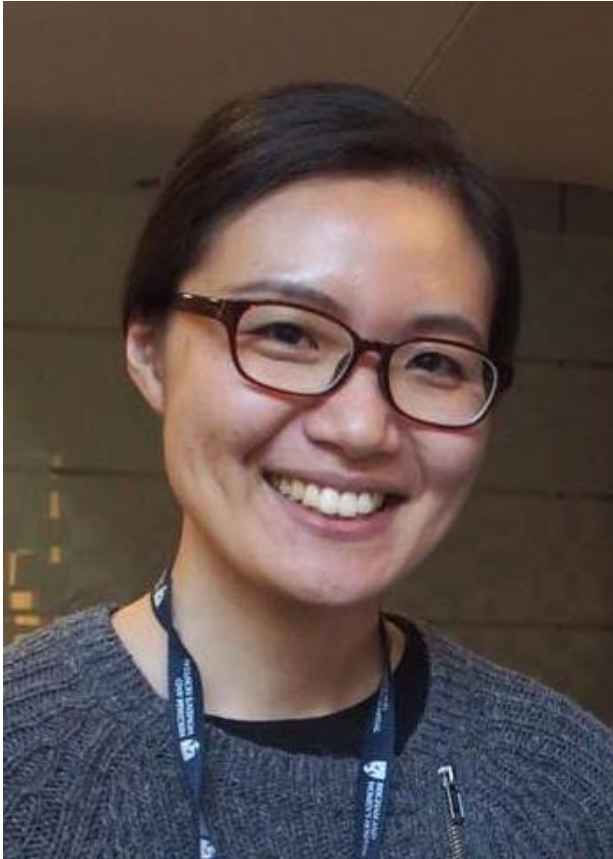
Naoka Murakami, MD PhD

Transplant Nephrology, Renal Division, Brigham and Women's Hospital

Assistant Professor of Medicine, Harvard Medical School



# Naoka Murakami, MD PhD



- Medical school: University of Tokyo
- Medicine residency at Mount Sinai Beth Israel (New York)
- Nephrology fellowship at BWH/MGH
- Assistant Professor of Medicine at HMS
  - Clinical focus: cancer in kidney transplant recipients
  - Research focus: roles of immunotherapy associated acute kidney injury and acute rejection

# Disclosure

- Honoraria:
  - Akebia Inc.
  - Sanofi Canada

# Key learning objectives

- Understand the increased risk of cancer in kidney transplant patients
- Learn evidence-based prevention and treatment options for cancers in kidney transplant patients
- Learn considerations in using novel cancer-targeted therapies in transplant patients

# Case 1

- A 66-year-old man with history of ADPKD and living related kidney transplant 16 years ago, presented with multiple skin lesions. Biopsy of skin lesions revealed invasive cutaneous squamous cell carcinoma. He likes gardening and often does outdoor activities.
- Immunosuppression: mycophenolic acid 180 mg twice a day, tacrolimus 4 mg twice a day (trough level ~6 ng/ml).
- Other medications: hydrochlorothiazide
- Laboratory values: Cr 0.9 mg/dL, urine protein/creatinine 0.2 g/gCr. Electrolytes and liver function tests were normal. CBCs are normal limit.

The following management helps prevent non-melanoma skin cancer EXCEPT?

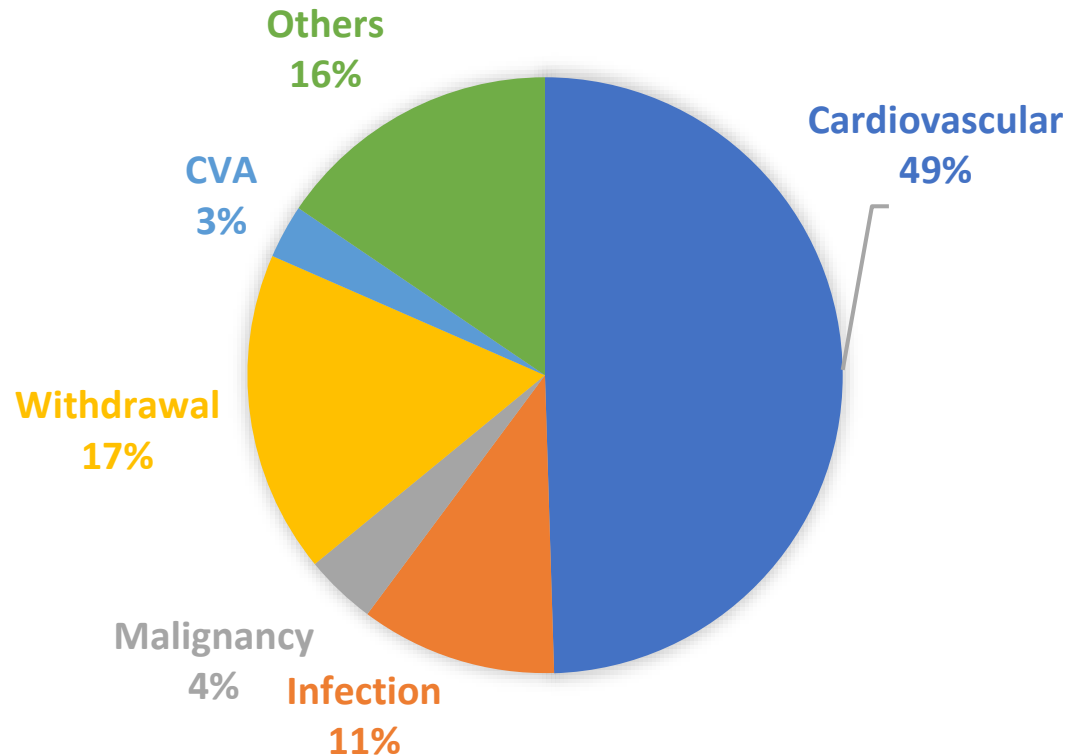
- A. Switch mycophenolic acid to azathioprine
- B. Switch tacrolimus to sirolimus or everolimus
- C. Discontinue hydrochlorothiazide
- D. Annual full body skin examination by dermatologist
- E. Recommend sunscreen use at outdoor activities

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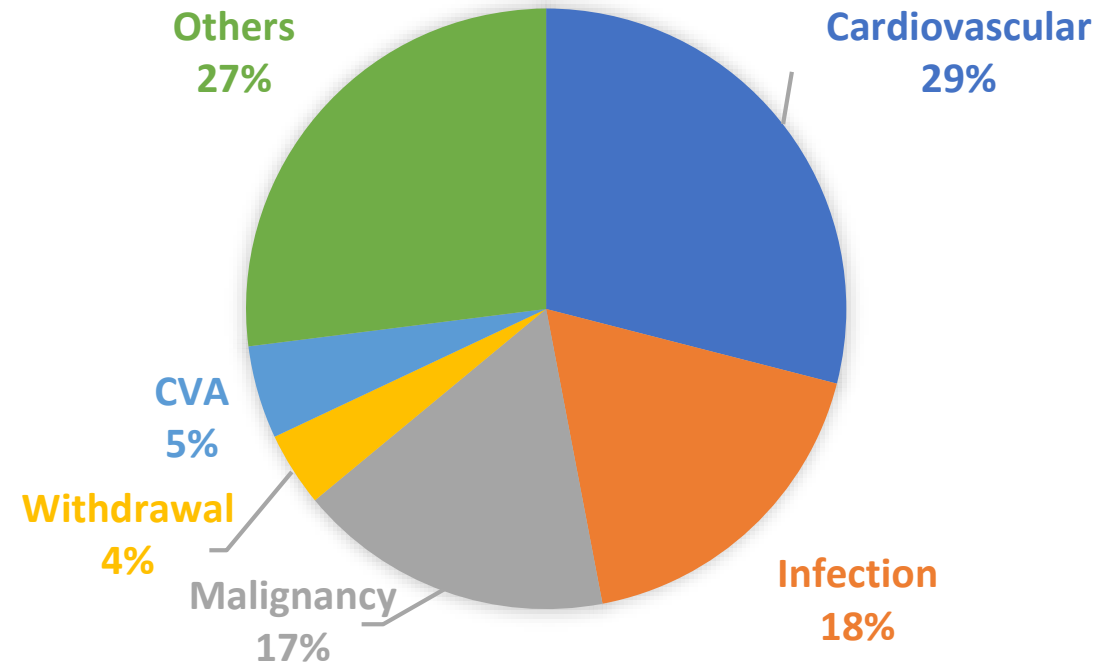
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# Malignancy is a major cause of death after kidney transplantation

**DIALYSIS**



**TRANSPLANT**

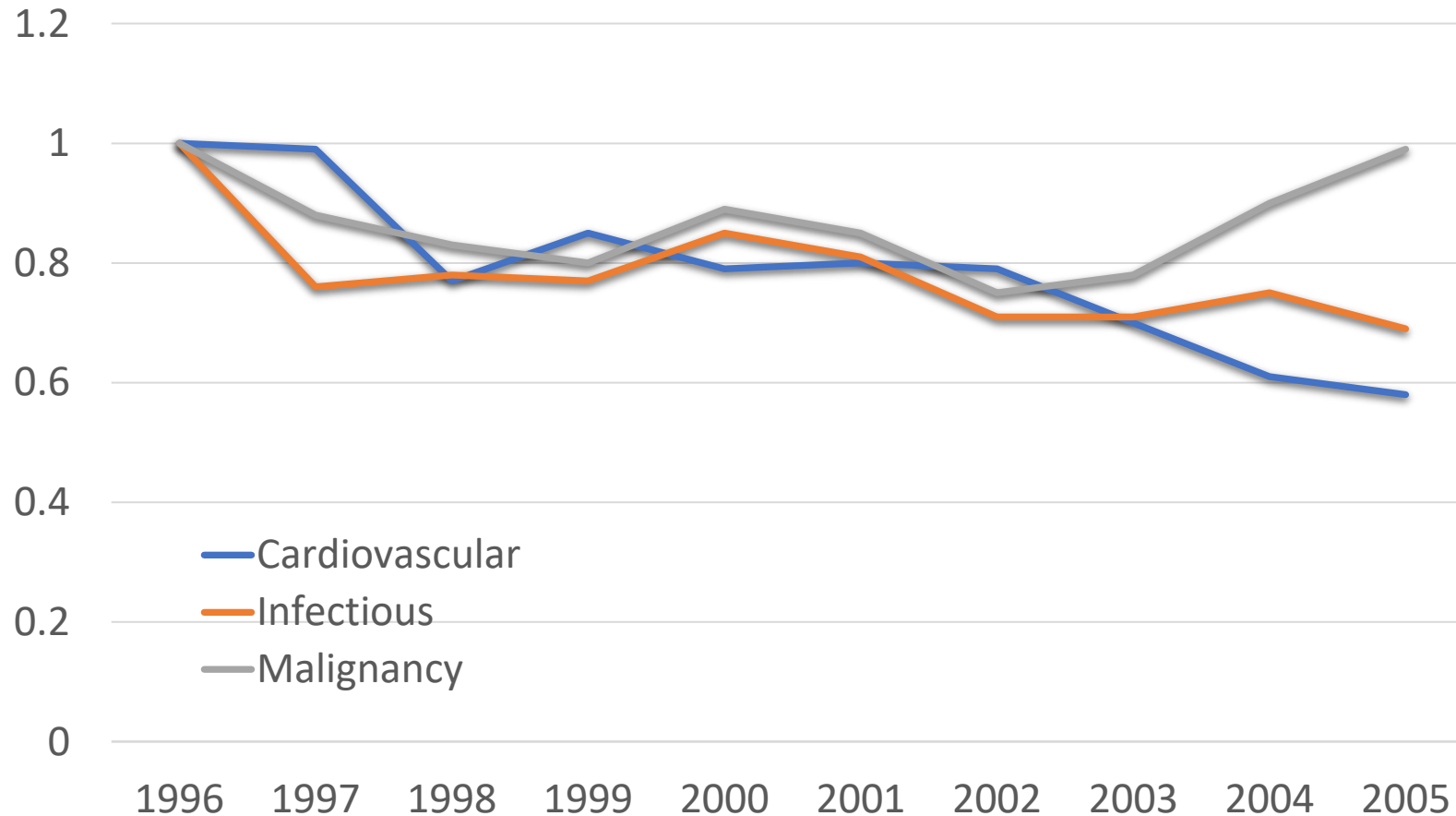


Adapted from USRDS (2018)

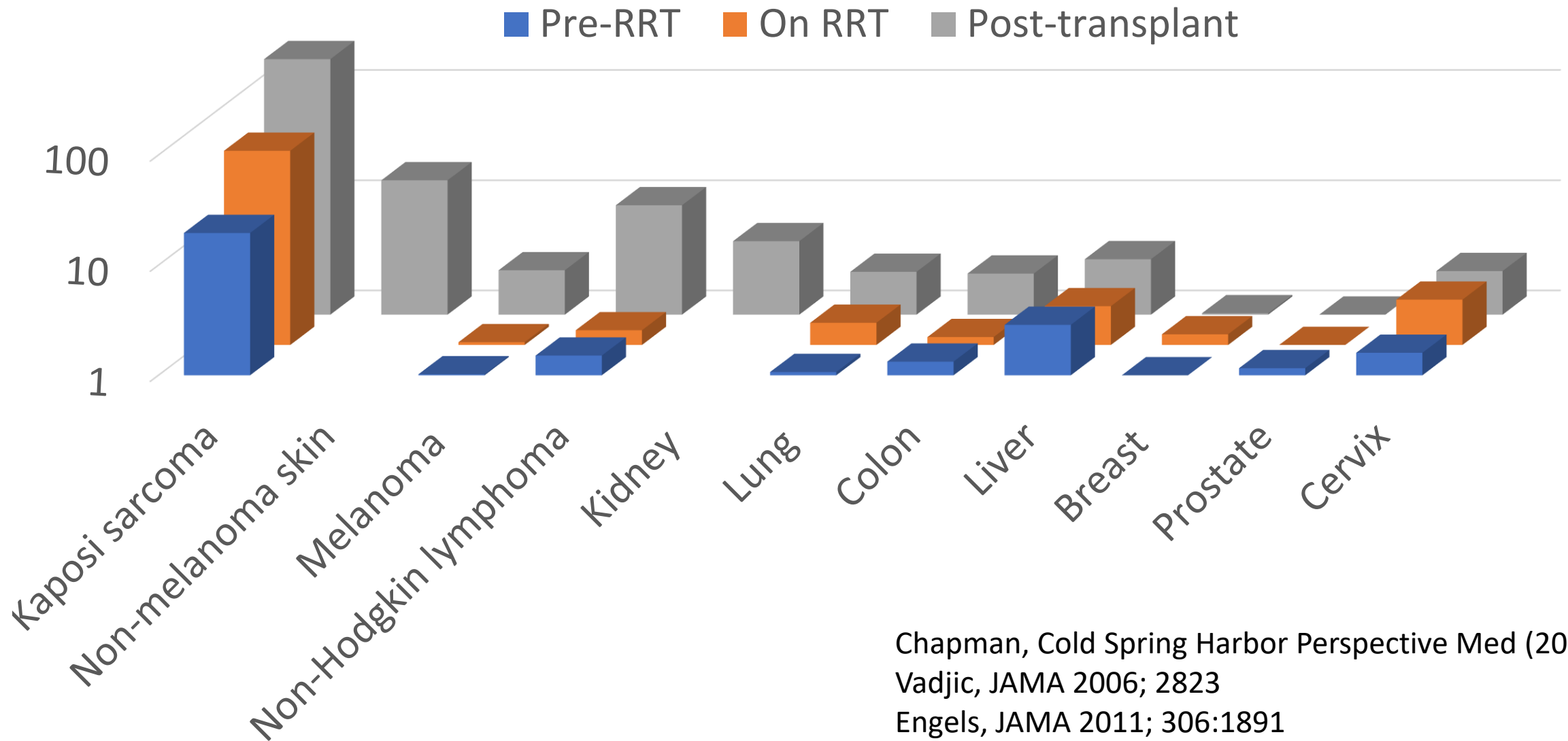


# Death due to malignancy didn't decline

10-year cause-specific mortality hazard ratio (reference year=1996)



# Cancer incidence is higher after transplant

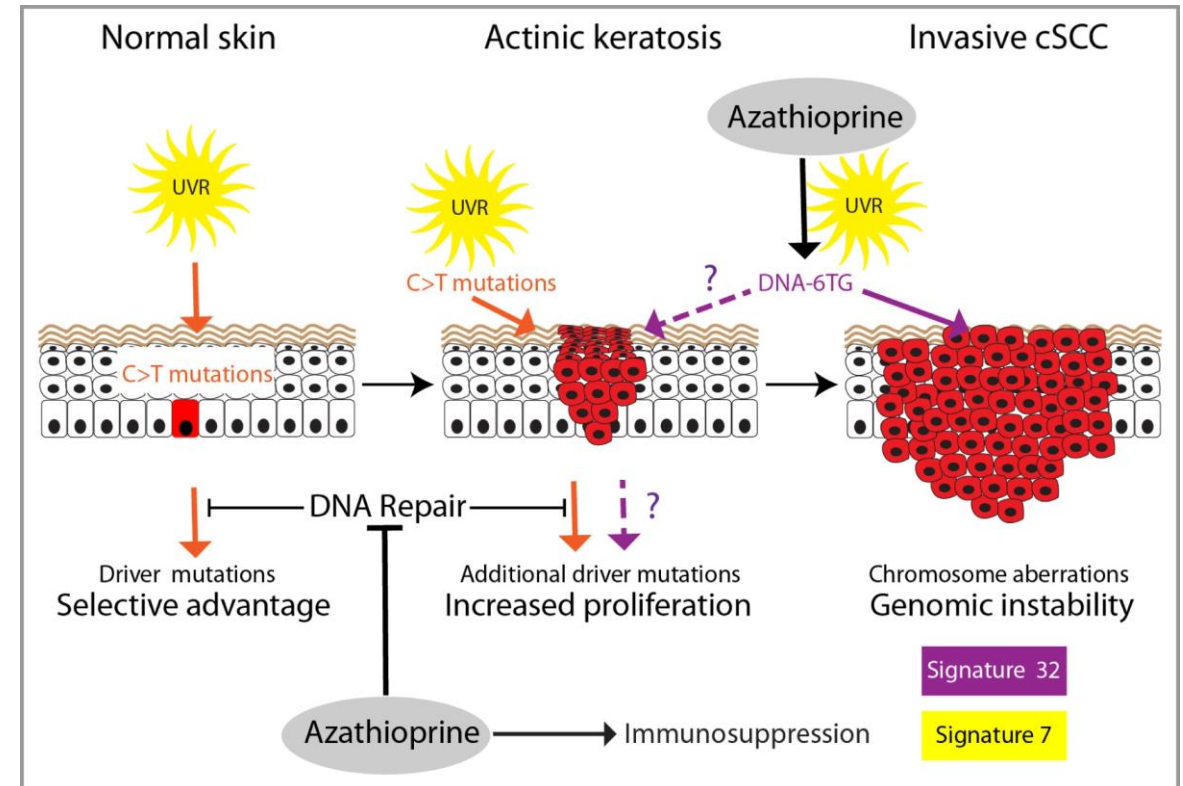


# Cancer screening post-transplant (*de novo*)

Cancer species	Screening method	Frequency	Who to screen
Skin Cancer	Total body skin exam (preferably by specialist)	Annually	All
Cervical Cancer	Pap smear	Every 1-3 years	>20-year-old female
Breast Cancer	Mammography	Every 1-2 years	>50-year-old female
Prostate Cancer	Not recommended/ PSA	Annually	>50-year-old male
Colorectal Cancer	FOBT/ Flex sig/ Colonoscopy	1, 5, and 10 years	>50-year-old
Lung	Not recommended		
Liver	AFP and/or Ultrasound	Every 6-12 mo	High risk group (HBV, HCV, cirrhosis)
Kidney	Not recommended		

# Azathioprine is associated with increased risk of squamous cell carcinoma (SCC)

- Relative risk of SCC is 1.56 [1.11-2.18] on azathioprine (Aza) vs non-Aza regimen in kidney tx patients (Metanalysis by Jiyad et al Am J Transplant 2016; 16:3490)
- Aza use in other autoimmune disease are shown to increase NMSC risks to 3-5 times:
  - HR 5.9 [2.1-16.4] in inflammatory bowel disease (Peyrin-Birouet, Gastroenterology, 2011; 141:1621)
- Aza increases photosensitivity to UVA, contributing to SCC development
- Switching from Aza to mycophenolate mofetil (MMF) helps reduce the risk of SCC with HR 0.24 [0.10-0.56] (Vos, JHLT 2018; 37: 857)



# HCTZ is associated with increased risk of NMSC

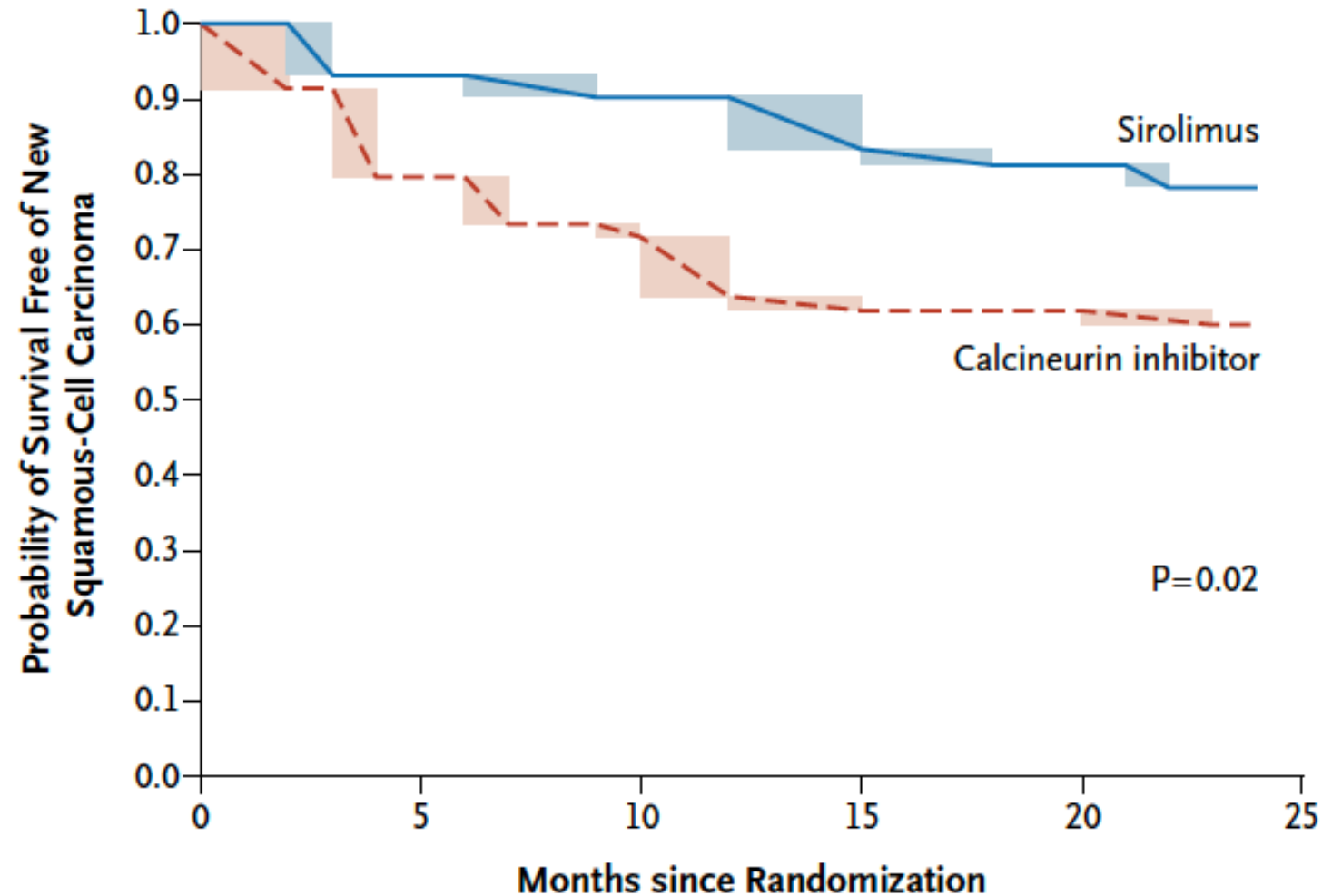
- Post-marketing study suggested a small increase of SCC with HCTZ use
  - OR 2.0-3.3, higher in long-term use (Shin, J Clin Med Res, 2019; 11:247)
  - OR 4.0 in case-control study in 80,000 cases vs 16 million controls (Pedersen, JAAD 2018; 78:673)
- FDA package insert warning on SCC risk
  - Absolute risk is small, increase by 1 case per 16,000 patients per year.
- Sunscreen >SPF30 provides protection for both UVA and UVB and recommended for all kidney transplant patients

Conversion to  
mammalian target of  
rapamycin (mTOR)  
inhibitor is  
associated with  
lower skin cancer  
recurrence

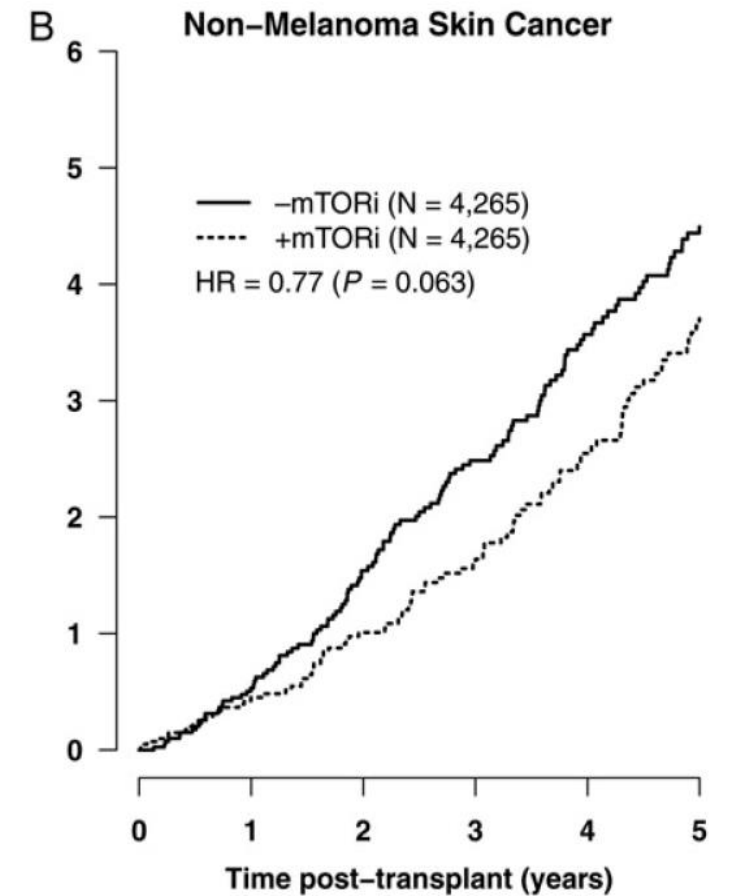
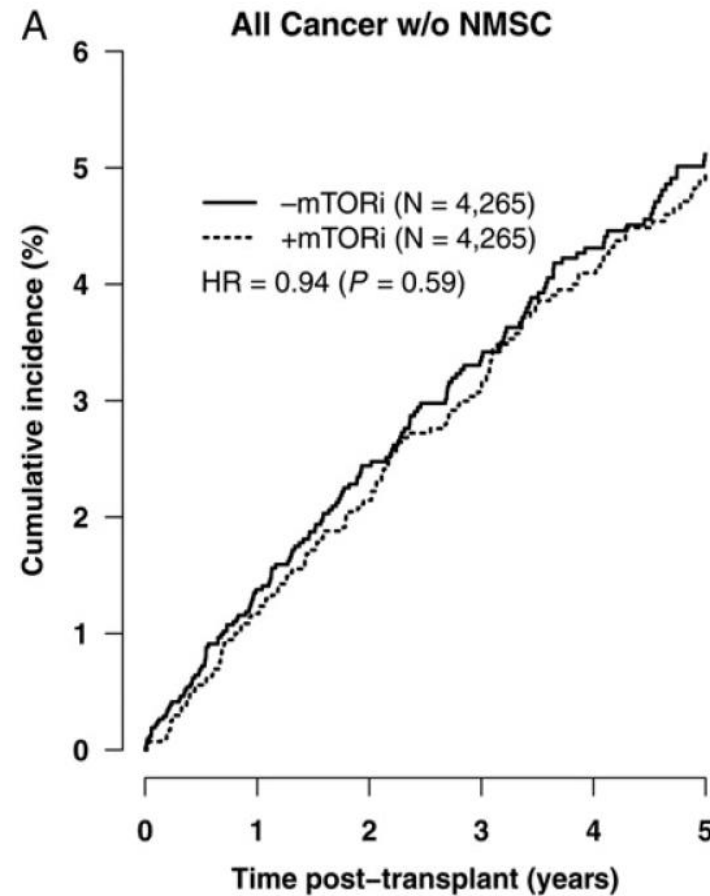
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TUMORAPA Study Group, NEJM  
2012; 367:329

**A All Patients**



mTORi  
conversion did  
not reduce non-  
skin cancer risk



## Case 2

- A 58-year-old woman s/p living kidney transplant 24 years ago for reflux uropathy, recently started treatment for metastatic melanoma. She presented to clinic with decreased urine output and hematuria.
- Immunosuppression: prednisone 5 mg daily.
- Other medications: carvedilol, omeprazole. Ipilimumab (anti-CTLA4) and Nivolumab (anti-PD-1), started 3 weeks ago.
- Labs: Cr 3.4 mg/dL (baseline 1.2), urine protein/creatinine 1.0 g/gCr. Urinalysis: SG 1.014, 1+ protein, 1+ blood, 2+ leukocyte esterase.
- Urine sediment: >182 RBCs and 20-30 WBCs/hpf, 2-4 WBC casts/lpf.
- Kidney biopsy is performed.



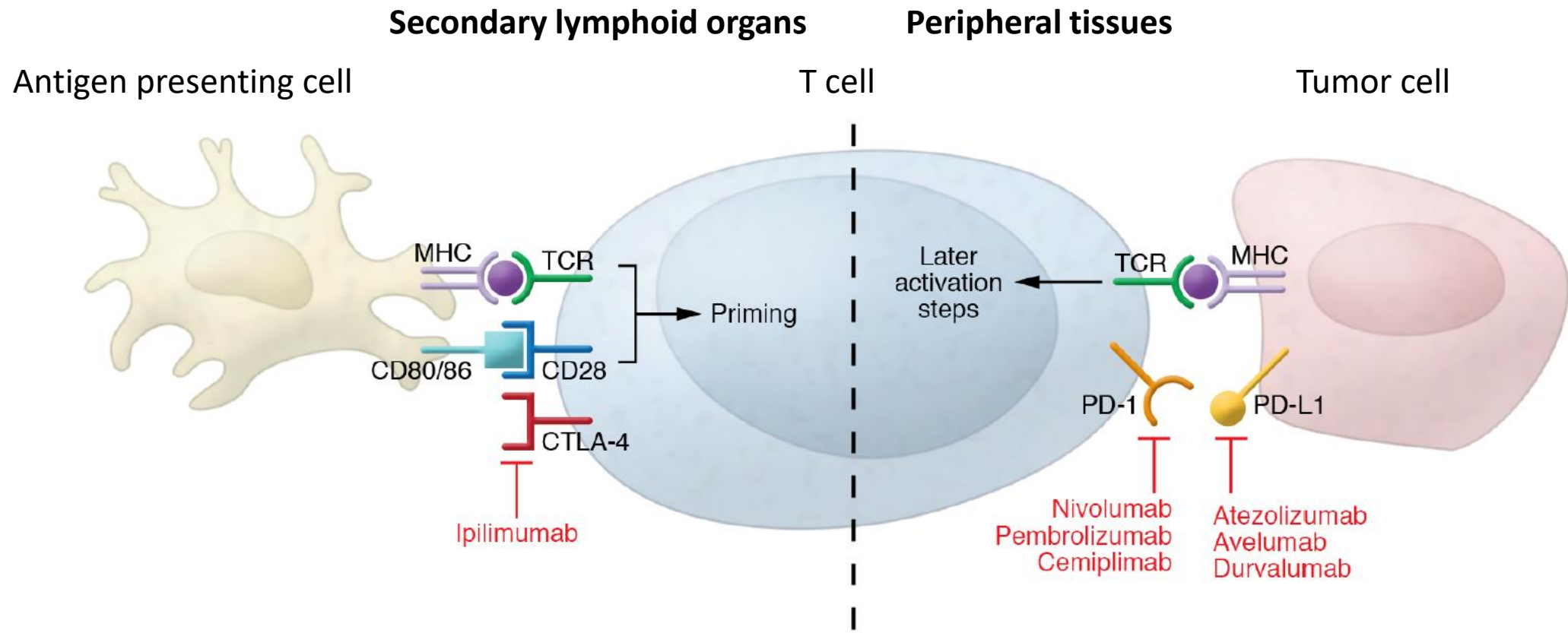
What is the most likely kidney lesion that will be seen in this patient?

- A. Acute cellular rejection
- B. BK nephropathy
- C. IgA nephropathy
- D. De novo membranous nephropathy
- E. Metastasis of melanoma to the allograft

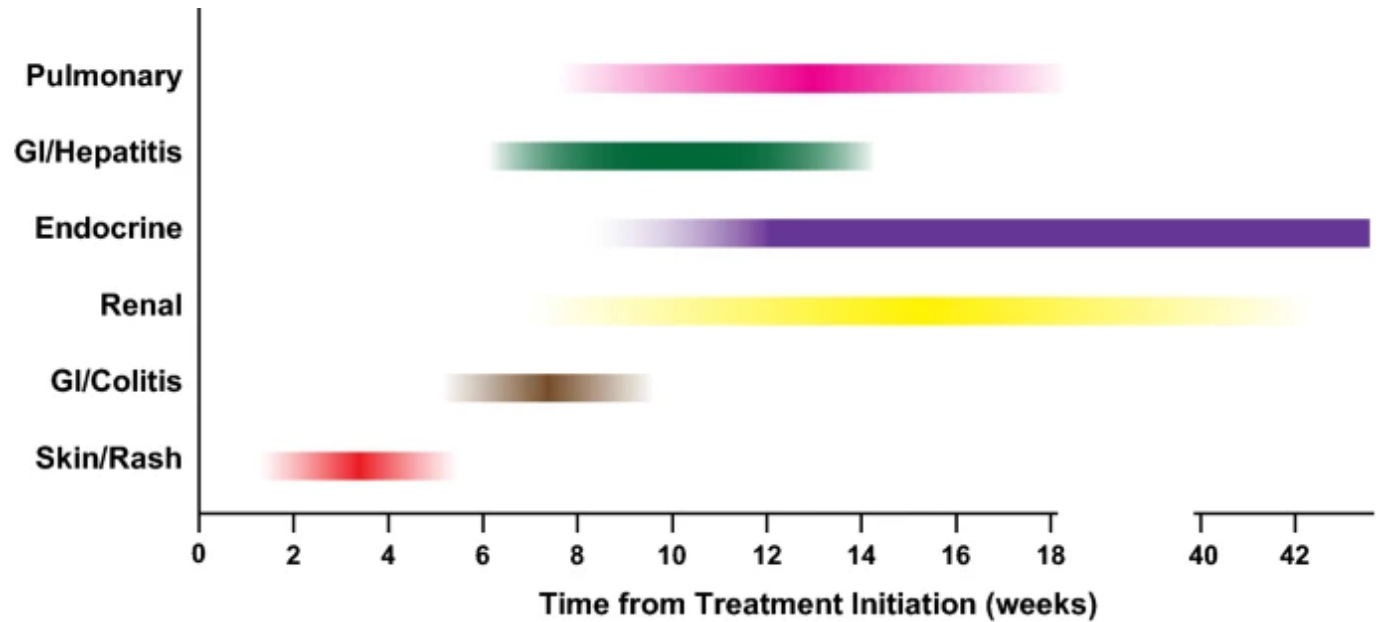
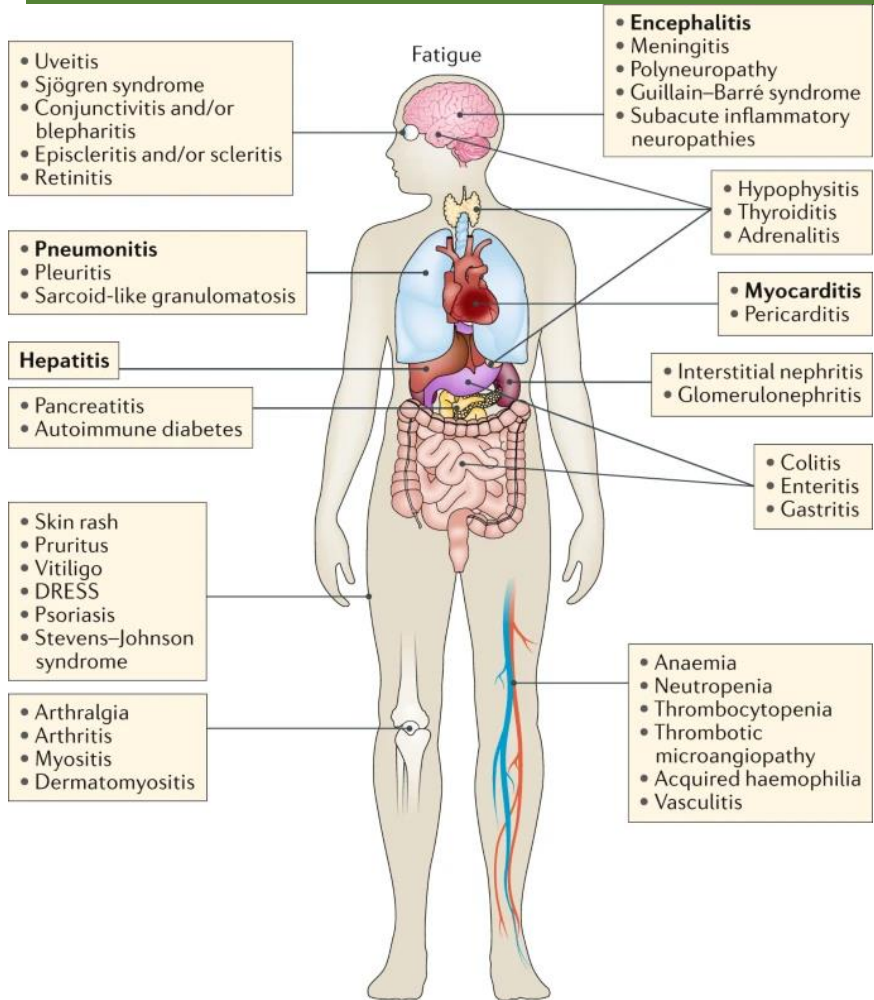
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# Immune checkpoint inhibitors unleash the “brake” against cancer immunity



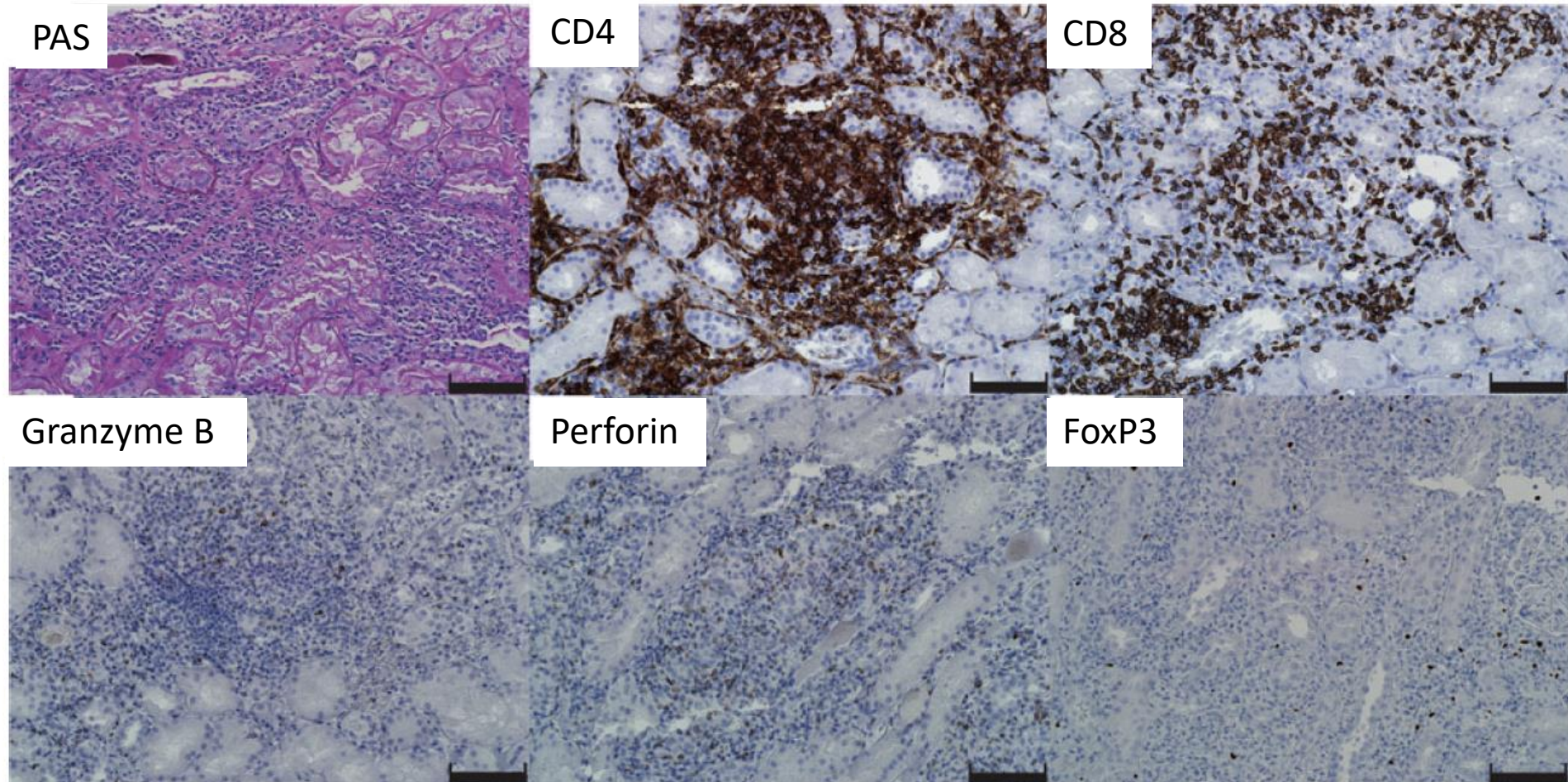
# Immune-related adverse events (irAE) with different tempo and severity



Martins, Nat Reviews Clin Oncol. 2019; 16:563  
Helmink, Annals Surg Oncol. 2020; 27:1533



# Severe acute tubulointerstitial nephritis after combination treatment of aCTLA-4 and aPD-1



# Prevalence of ICI-associated AKI

- All AKI: single center studies
  - 17% (Cr >1.5-fold) Seethapathy, CJASN (2019)
  - 16.5% (Cr >1.5-fold) Meraz-Munoz, JITC (2020)
- ICI-associated AKI
  - 2-5% Seethapathy, CJASN (2019), KI Reports (2020)
  - 1.8% Izzedine CKJ (2019)
- Less frequent in PD-L1 use Seethapathy, KI Reports (2020)

What is the frequency & etiology of AKI and what are its risk factors in patients on checkpoint inhibitors?

CJASN  
Clinical Journal of American Society of Nephrology

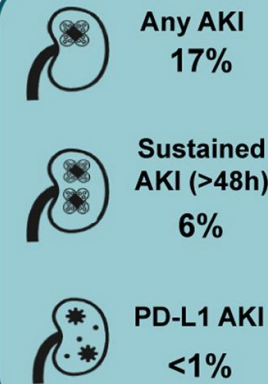
## Incidence and clinical features of immune-related acute kidney injury in patients receiving Programmed Cell Death Ligand-1 Inhibitors

### PATIENTS & METHODS



- Single-center, retrospective
- 599 patients with cancer
- Received PD-L1 inhibitors (Durvalumab, Atezolizumab, Avelumab)
- Followed Cr-kinetics for 12 months for KDIGO AKI outcomes

### RESULTS



### CONTEXT

#### INCIDENCE OF CHECKPOINT INHIBITOR RELATED AKI

CTLA4 inhibitors	2-5%	PD-1 inhibitors	~2%
Cortazar et al (2016) Seethapathy et al (2019)		Cortazar et al (2016) Seethapathy et al (2019) Manohar et al (2019)	
Combined CTLA4/PD-1	~5%	PD-L1 inhibitors	<1%
Cortazar et al (2016)		Current Study	

#### CONCLUSION:

ICI-related AKI may be less common with PD-L1 inhibitors compared to other ICIs

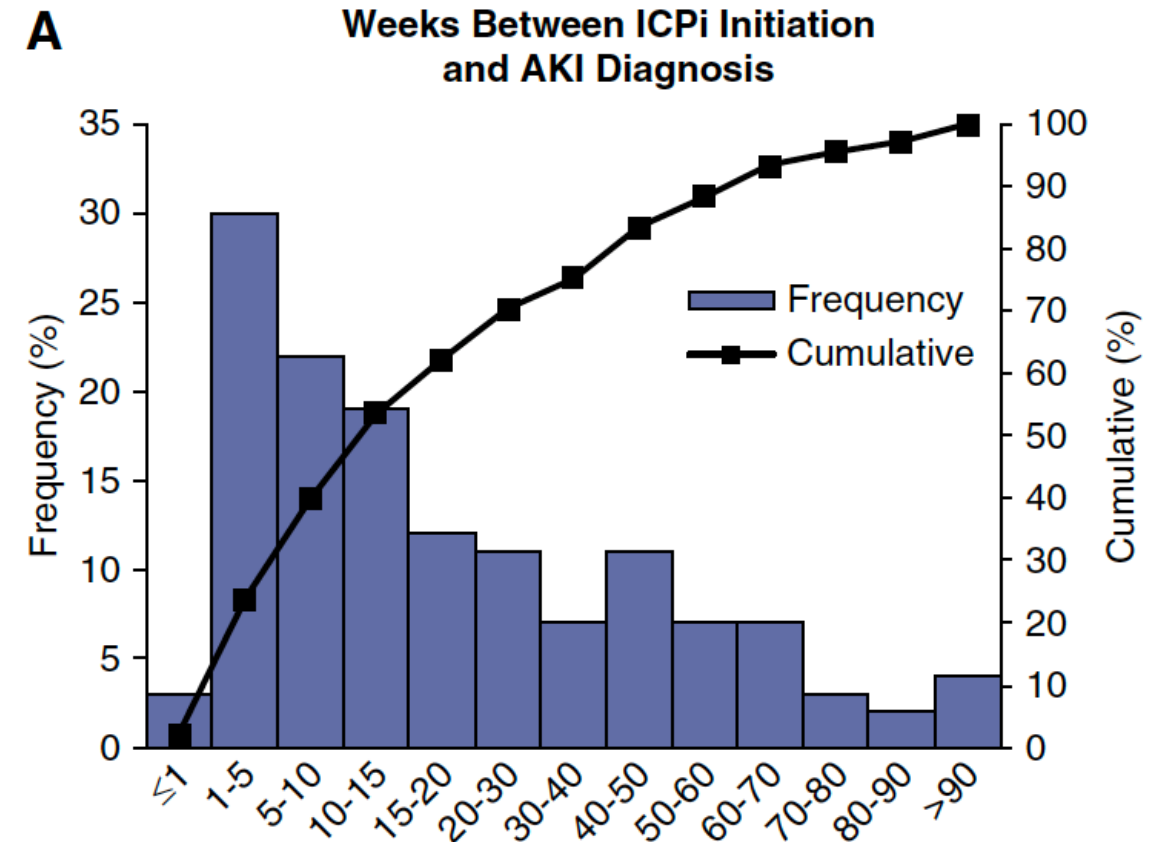
KI REPORTS  
KIReports.org

Seethapathy et al, 2020



# Clinical characteristics of ICI-AKI

- Multicenter retrospective cohort study
  - 26 institutions
  - 138 AKI cases (Stage 2 or above), 276 control cases (random)
- AKI onset: median 14 weeks from ICI initiation [IQR 6-37 weeks]
  - Stage 2: 43%
  - Stage 3: 57%
  - RRT dependence: 9%

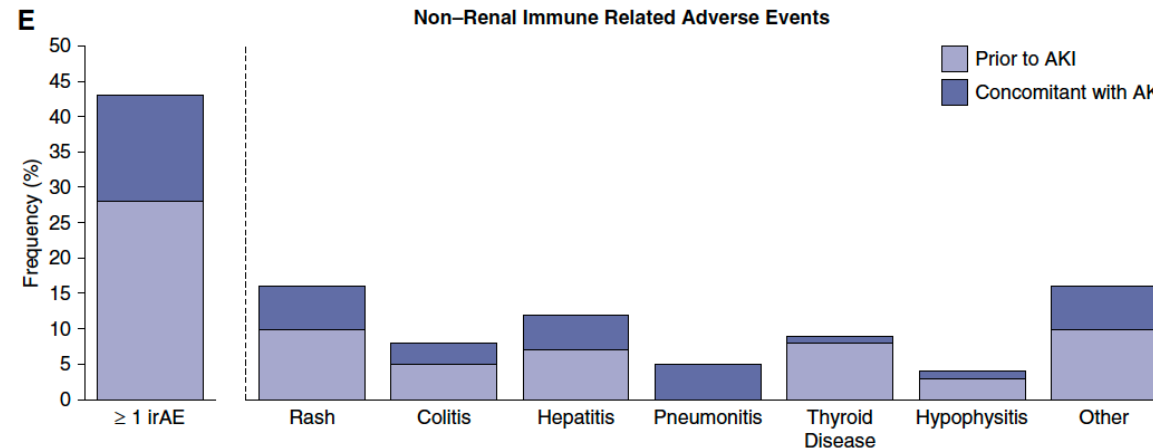


# Risk factors of ICI-AKI

Table 2. Risk factors for ICPI-AKI

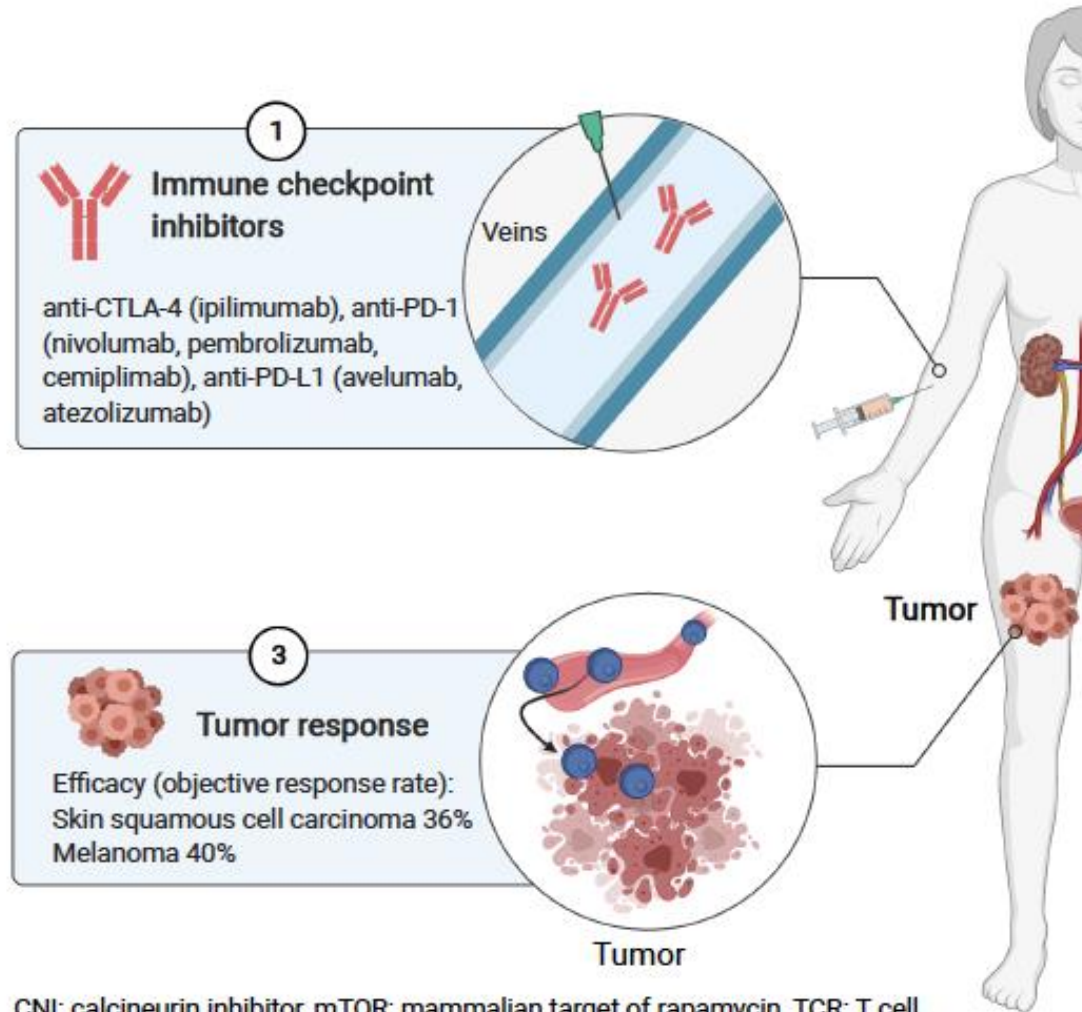
Baseline Variables	Odds Ratio (95% Confidence Interval) for ICPI-AKI		
	Univariate	Multivariate	Forest Plot
Age (per 10 years)	1.08 (0.92 to 1.26)	0.91 (0.75 to 1.11)	
Female	1.08 (0.71 to 1.64)	1.05 (0.67 to 1.65)	
Prior autoimmune disease	1.15 (0.61 to 2.18)	1.08 (0.55 to 2.11)	
eGFR, per 30 ml/min per 1.73 m <sup>2</sup> decline	1.67 (1.27 to 2.17)	1.99 (1.43 to 2.76)	
PPI use	2.38 (1.57 to 3.62)	2.85 (1.81 to 4.48)	
Combination ICPI therapy	2.71 (1.62 to 4.53)	3.88 (2.21 to 6.81)	

The full multivariable model was adjusted for the covariates listed in the table.





## Immune checkpoint inhibitors in patients with kidney transplant



CNI: calcineurin inhibitor, mTOR: mammalian target of rapamycin, TCR: T cell receptor, PD1: programmed cell death protein-1, CTLA-4: cytotoxic T-lymphocyte-associated protein-4 (figure prepared with BioRender.com)

# Immune checkpoint inhibitors in kidney transplant patients

## 1. Safety

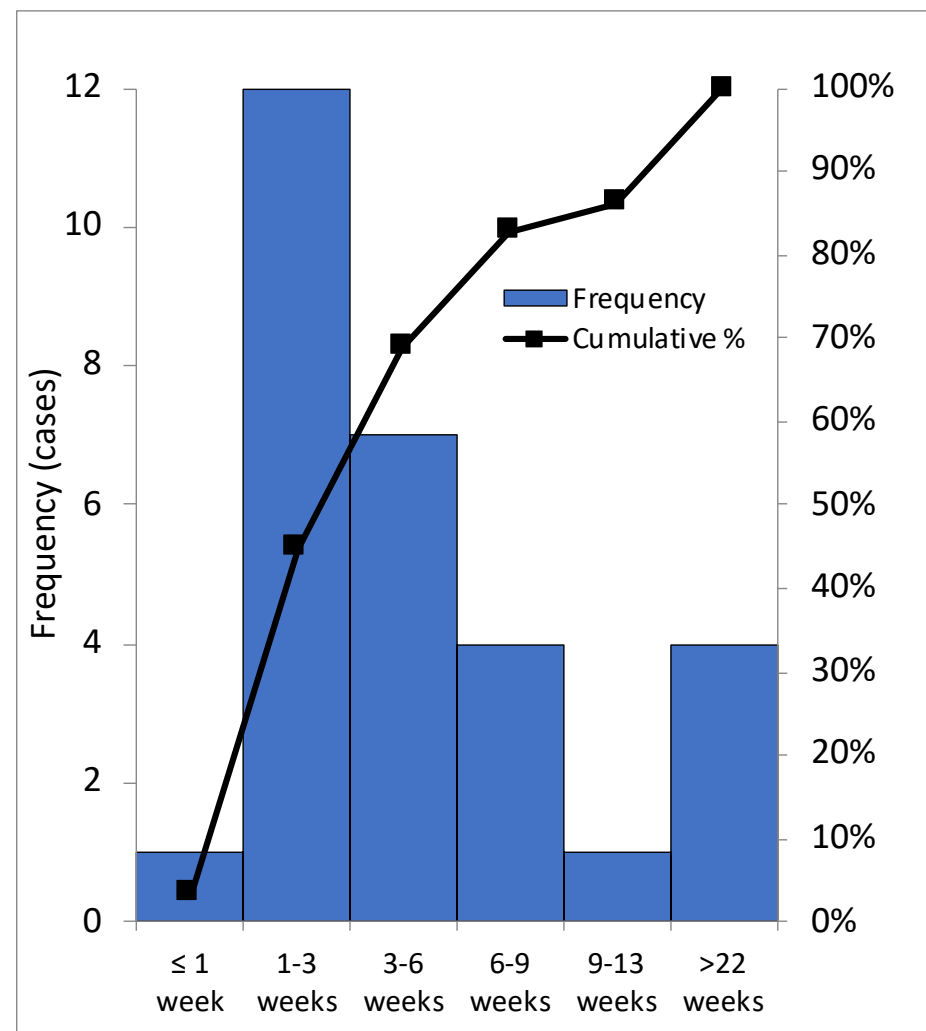
- Ipilimumab (anti-CTLA-4): No rejection (Lipson et al. JCO 2014)
- Nivolumab (anti-PD-1): Rejection (Lipson et al. NEJM 2016)
- Pooled case series and meta-analysis:
  - Rate of acute rejection: 30-40%
  - Association between rejection episode and overall survival is unclear(Abdel-Wahab et al. JITC 2019, Manohar et al. KI reports 2020, d'Izarny-Cargas et al. AJT 2020, Saberianfar et al, Annals Oncol 2020)

## 2. Efficacy

- No study has tested the clinical efficacy of ICIs in kidney transplant population

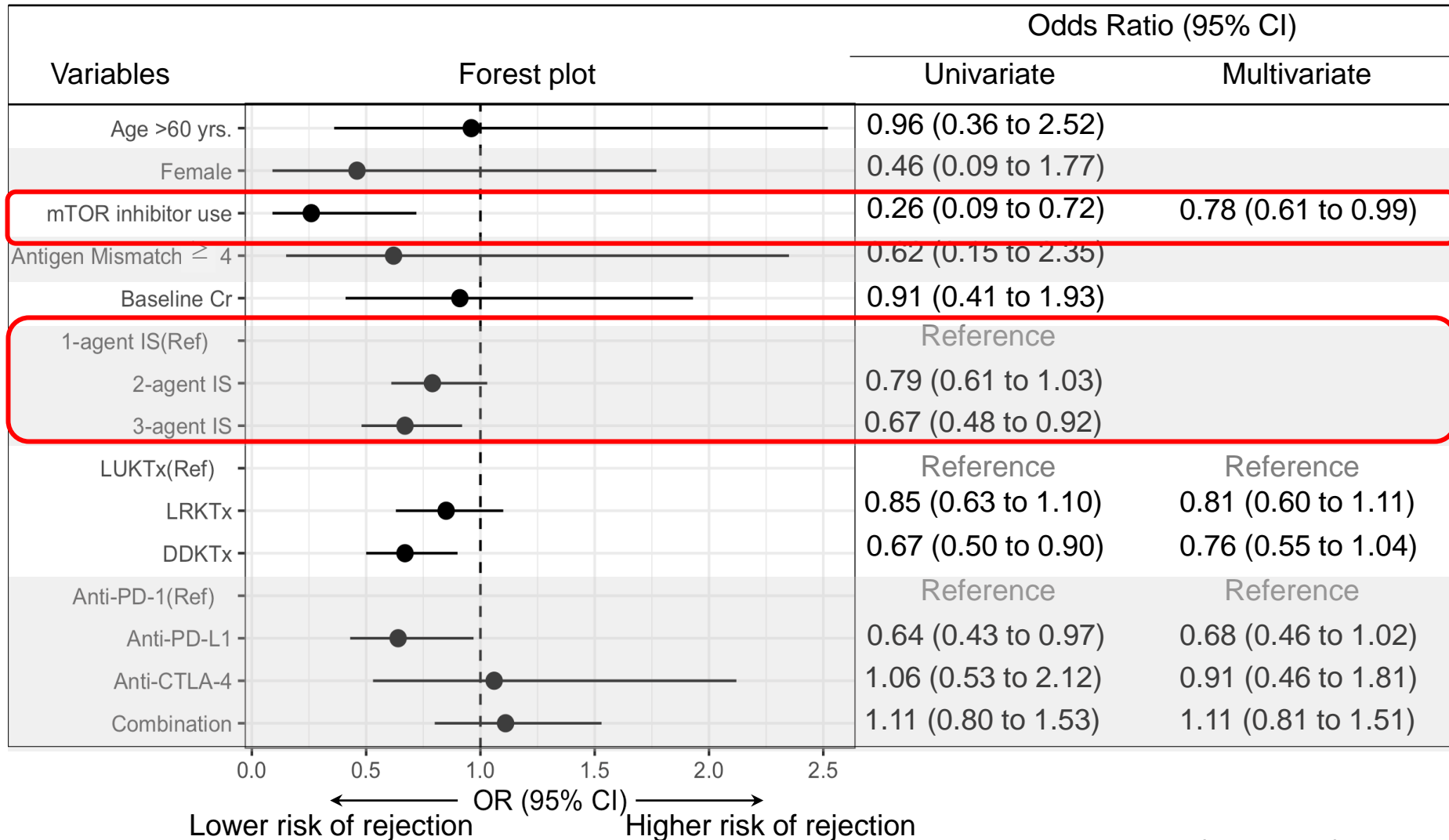
# Clinical characteristics of acute rejection

Variable	Total (n=29)
Age at ICI initiation, yr	63 (54-70)
Transplant to ICI, yr	9.3 (4.1-15.6)
ICI (rejection rate %)	
aPD-1: Pembrolizumab	14 (48.3)
Nivolumab	4 (36.3)
Cemiplimab	4 (40.0)
aPD-L1: Atezolizumab	0 (0.0)
Avelumab	0 (0.0)
aCTLA-4: Ipilimumab	1 (50.0)
aPD-1/aCTLA-4 combination	6 (54.5)
ICI to rejection, day	24 (20-56)
Type of rejection, <i>n</i> (%)	
Mixed TCMR/ABMR*	7 (24.1)
TCMR*	7 (24.1)
Not biopsied	15 (51.7)
Graft loss, <i>n</i> (%)	19 (65.5)



TCMR: T cell-mediated rejection, ABMR: antibody-mediated rejection

# Risk factors of allograft rejection



# Can we mitigate rejections?

## Preserved Renal-Allograft Function and the PD-1 Pathway Inhibitor Nivolumab

**TO THE EDITOR:** Inhibition of immune checkpoints with the use of antibodies targeting programmed cell death 1 (PD-1) or monoclonal anti-therapy and discontinuation of mycophenolate mofetil, decreased doses of tacrolimus, and intestinal stenting.

**Table 1. Immunosuppressive Regimen in a Patient Who Had Undergone Kidney Transplantation.**

Timing*	Drug and Dosage
1 Wk before	Prednisone — 40 mg daily
Concurrent	Prednisone — 20 mg daily; sirolimus — target goal, 4–6 ng per milliliter
1 Wk after	Prednisone — 20 mg
>2 Wk and ≤6 mo after	Prednisone — 10 mg/day; sirolimus — target goal, 10–12 ng per milliliter
>6 Mo after	Glucocorticoid — gradually decreased to 5 mg/day; sirolimus — continued to maintain goal of 10–12 ng per milliliter

\* Timing represents the initiation of the immunosuppressive regimen in relation to the administration of nivolumab.

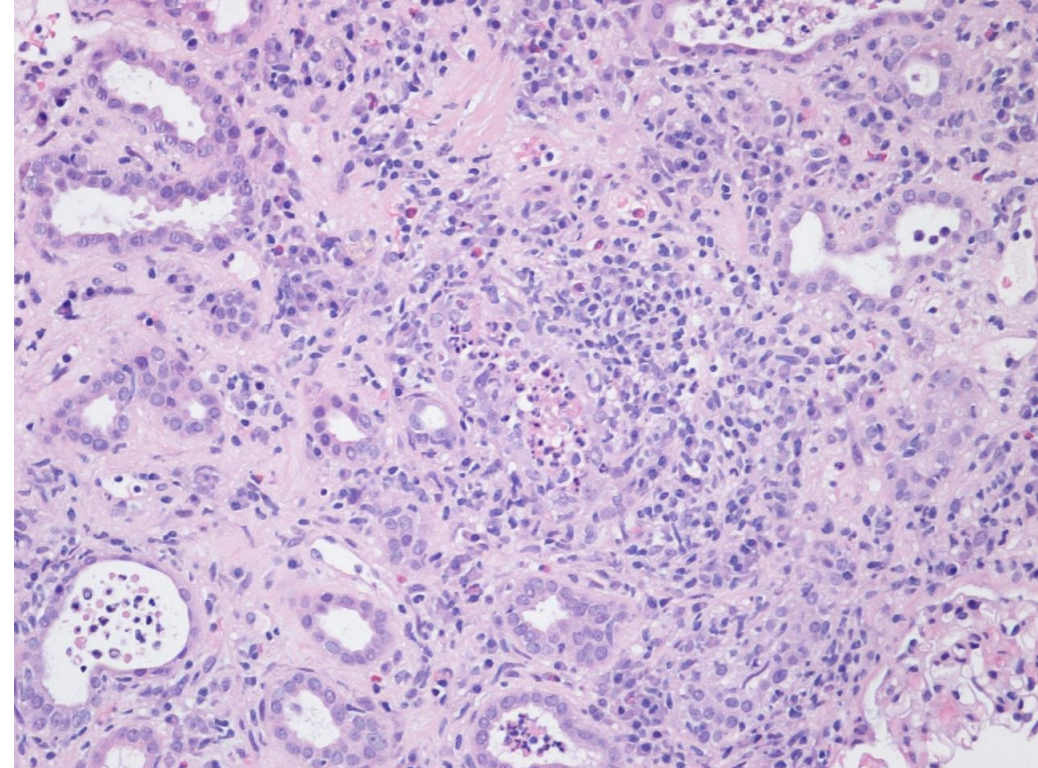
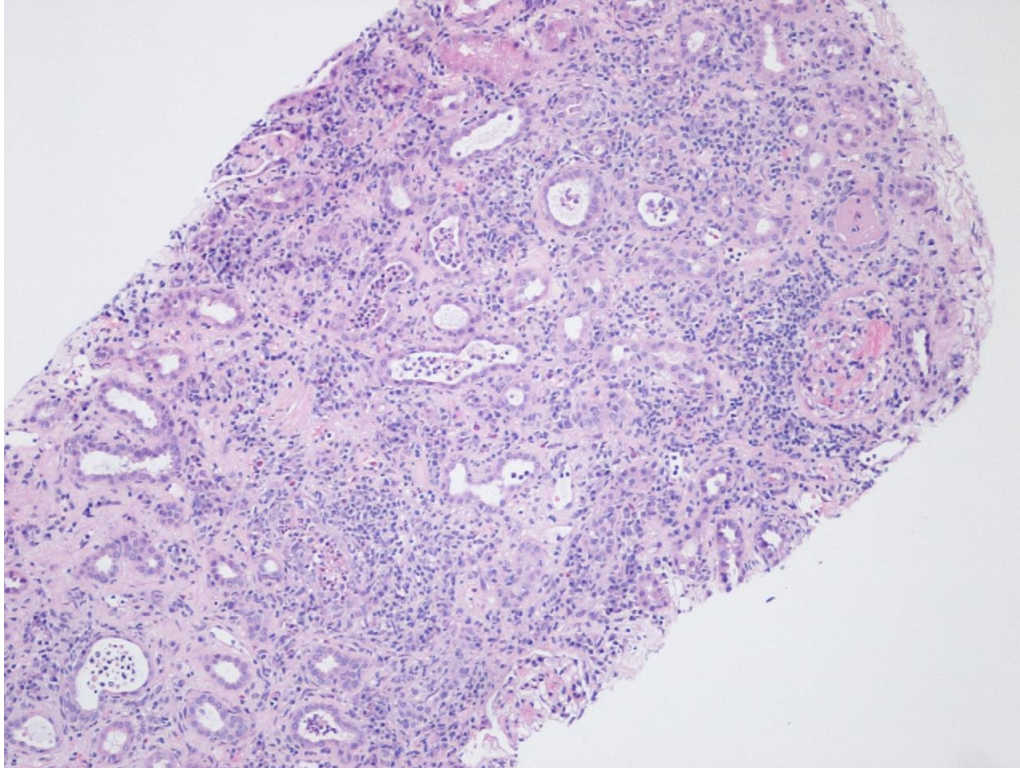
Barnett, NEJM 2017; 376:191

# Summary of clinical trials on ICI and kidney transplant

Study name	Nivolumab in tx patients	Tacrolimus and ICI	CONTRAC-1
Cancer type	Any cancers (incurable, metastatic solid tumors)	Skin cancers (Melanoma, cSCC, BCC, Merkel cell carcinoma)	cSCC
Transplant	Kidney	Kidney	Kidney
ICI	Nivolumab*	Nivolumab +/- Ipilimumab	Cemiplimab
Immunosuppression	Keep the same dose	Tac (2-5 ng/ml), pred 5 mg/d	mTORi + dynamic pred
Patient #	17	8	12
Rejection	2 (11.7%)	2 (25%)	0 (0%)
ORR (CR+PR)	53%	33%	45%
Registry	ANZCTR CA209-993ISR	NCT03816332	NCT03565783
Primary institution	Royal Adelaide Hospital, multicenter	Johns Hopkins Hospital	Dana Farber Cancer Institute
	Australia	USA	USA
Ref.	Lancet Oncol (2022)	J Clin Oncol (2024)	J Clin Oncol (2024)



## Case 2: Allograft biopsy



Severe mononuclear cell infiltration, focal tubulitis, neutrophil casts, eosinophil infiltrates.

Courtesy of BWH pathology team (Drs. Rennke and Weins)

# Clinical characteristics of ICI-associated AKI

	Non-transplant patients	Kidney transplant patients
<b>Frequency of ICI-associated AKI</b>	2-3%	30-40%
<b>Timing of ICI to AKI (median)</b>	14 weeks	24 days
<b>Histology of kidney biopsy</b>	Mononuclear cell infiltrations (T, B cells and eosinophils).	Mononuclear cell infiltrations (T, B cells), TCMR and mixed TCMR/ABMR
<b>Steroid therapy response</b>	Good (85% achieved recovery)	Refractory
<b>Requirement of renal replacement therapy</b>	5-10%	60-70%
<b>Risk factors</b>	Low baseline kidney function, PPI	mTOR inhibitor and 3-agent immunosuppression (lower risk)

ICI: immune checkpoint inhibitor, AKI: acute kidney injury, PPI: proton pump inhibitor, mTOR: mammalian target of rapamycin



# Summary

- Kidney transplant patients are at higher risk of developing cancer after transplant
- Reduction and change of immunosuppression regimen, can prevent and treat cancers
- Novel cancer-targeted therapies may be associated with risk of acute rejection and patient-centered decision making is necessary

# Reference

- Guidelines for cancer screening for kidney transplant candidates
  - **Pre-Transplant Solid Organ Malignancy and Organ Transplant Candidacy: A Consensus Expert Opinion Statement**, Al-Adra, AJT (2021) 21:460
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- Guidelines for cancer screening post-kidney transplant
  - **KDIGO clinical practice guideline for the care of kidney transplant recipients: a summary**, Kasiske, Kidney Int (2009)
  - **Cancer Screening Recommendations for Solid Organ Transplant Recipients: A Systematic Review of Clinical Practice Guideline** Acuna, AJT 2017; 17:103
- Checkpoint inhibitors and acute kidney injury
  - **Clinical Features and Outcomes of Immune Checkpoint Inhibitor–Associated AKI: A Multicenter Study**, Cortazar, JASN (2020) 31: 435
  - **Checkpoint inhibitor therapy for cancer in solid organ transplantation recipients: an institutional experience and a systematic review of the literature**, Abdel-Wahab et al. JITC 2019; 7:106
  - **Efficacy and tolerance of immune checkpoint inhibitors in transplant patients with cancer: A systematic review**, d'Izarny-Cargas, AJT (2020); <https://doi.org/10.1111/ajt.15811>
  - **A multi-center study on safety and efficacy of immune checkpoint inhibitors in cancer patients with kidney transplant**, Murakami, Kidney Int (2021) 100:196
  - **Cemiplimab for kidney transplant recipients with advanced cutaneous squamous cell carcinoma**. Hanna GJ, J Clin Oncol 2024; 42:1021
  - **Nivolumab + Tacrolimus + prednisone +/- Ipilimumab for kidney transplant recipients with advanced cutaneous cancers**. Schenk, J Clin Oncol 2024; 42:1011.
- Email: nmurakami1@bwh.harvard.edu