Management of Renal Complications Encountered in Cancer Care

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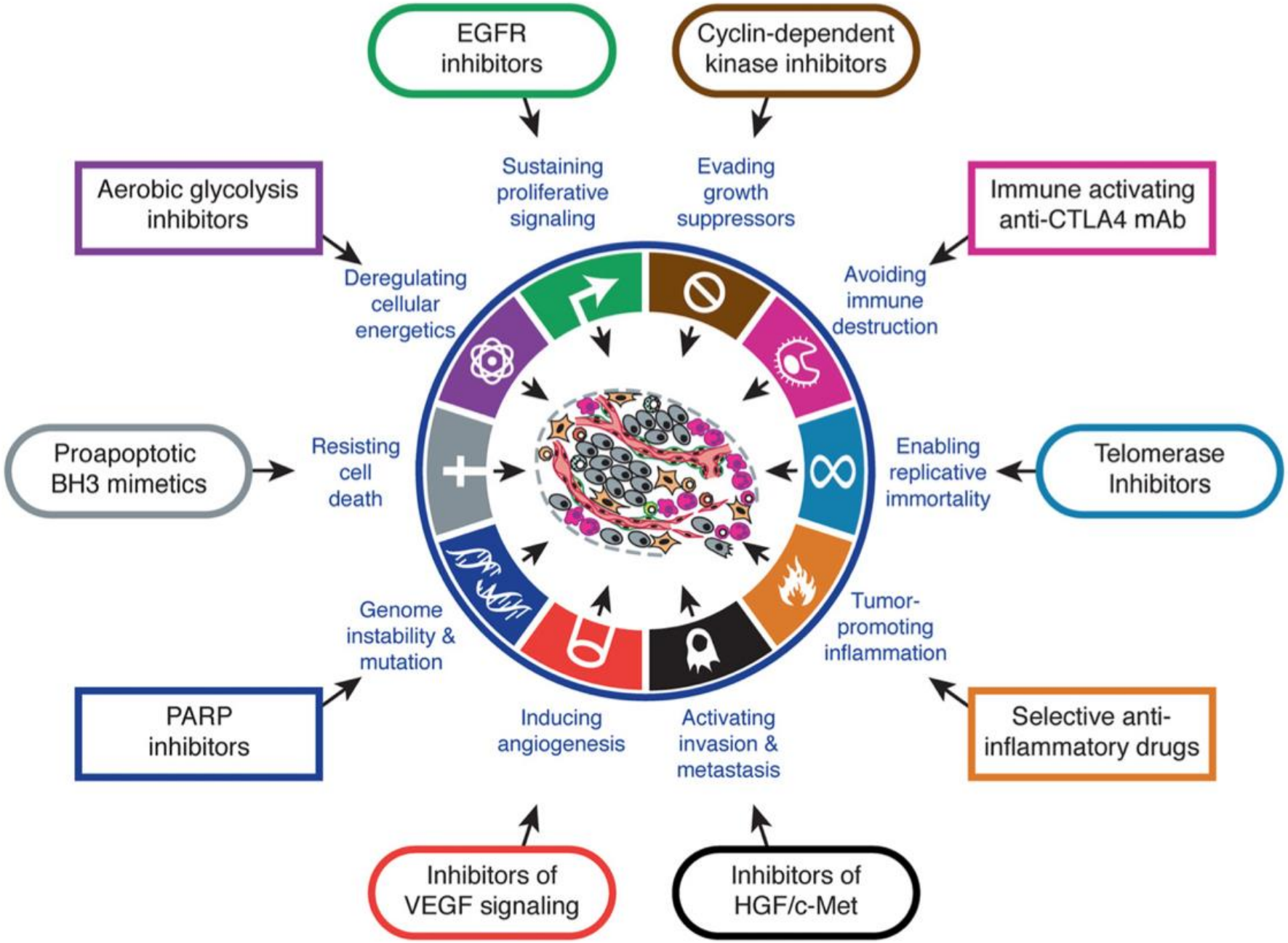
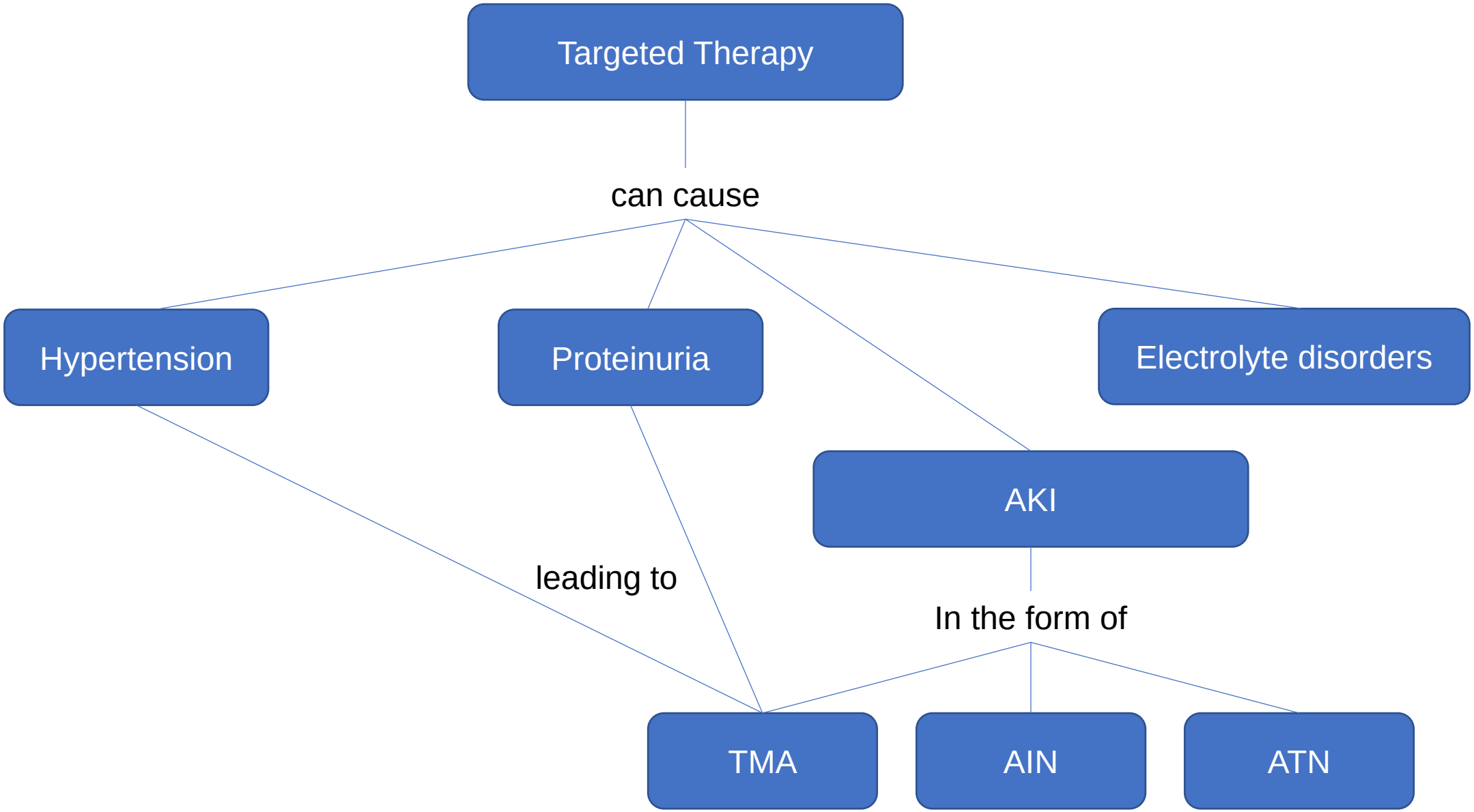
May 24th, 2019

Contents

- Acute kidney injury associated with targeted therapies
  - Anti-angiogenesis agents
  - Immune checkpoint inhibitors
  - Chimeric antigen receptor T cells
  - Tumor lysis syndrome with venetoclax



Hanahan D and Weinberg RA. Cell 2011



Jhaveri KD https://www.youtube.com/watch?v=prmaujWxWYM

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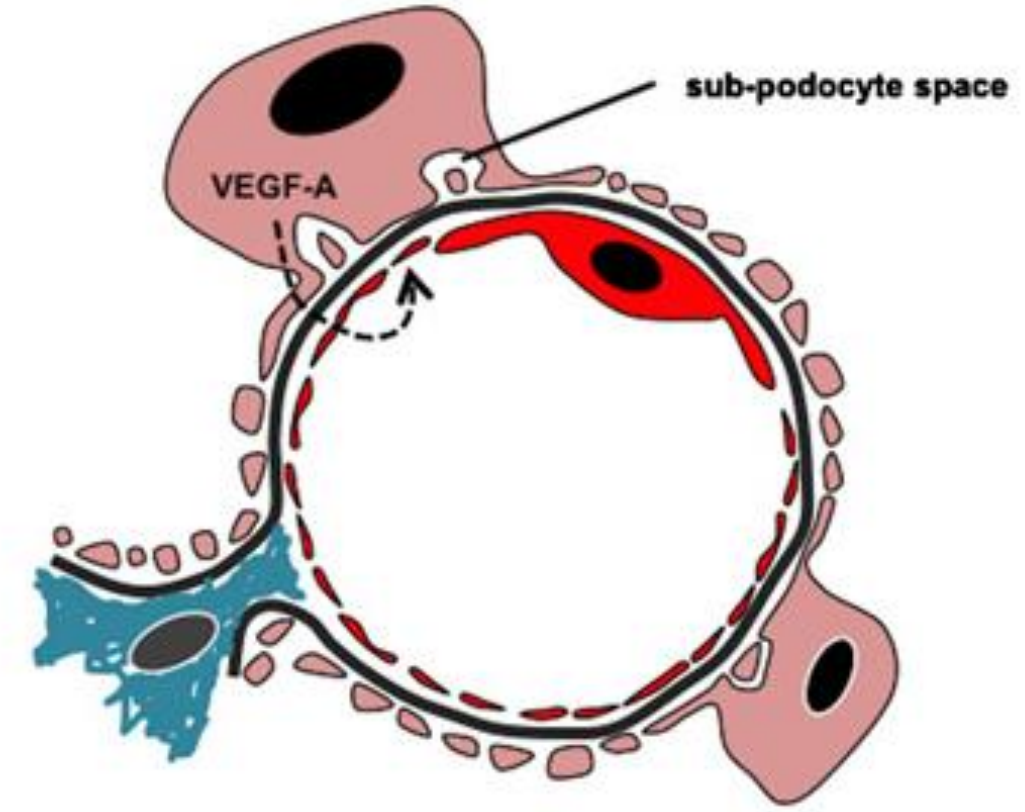
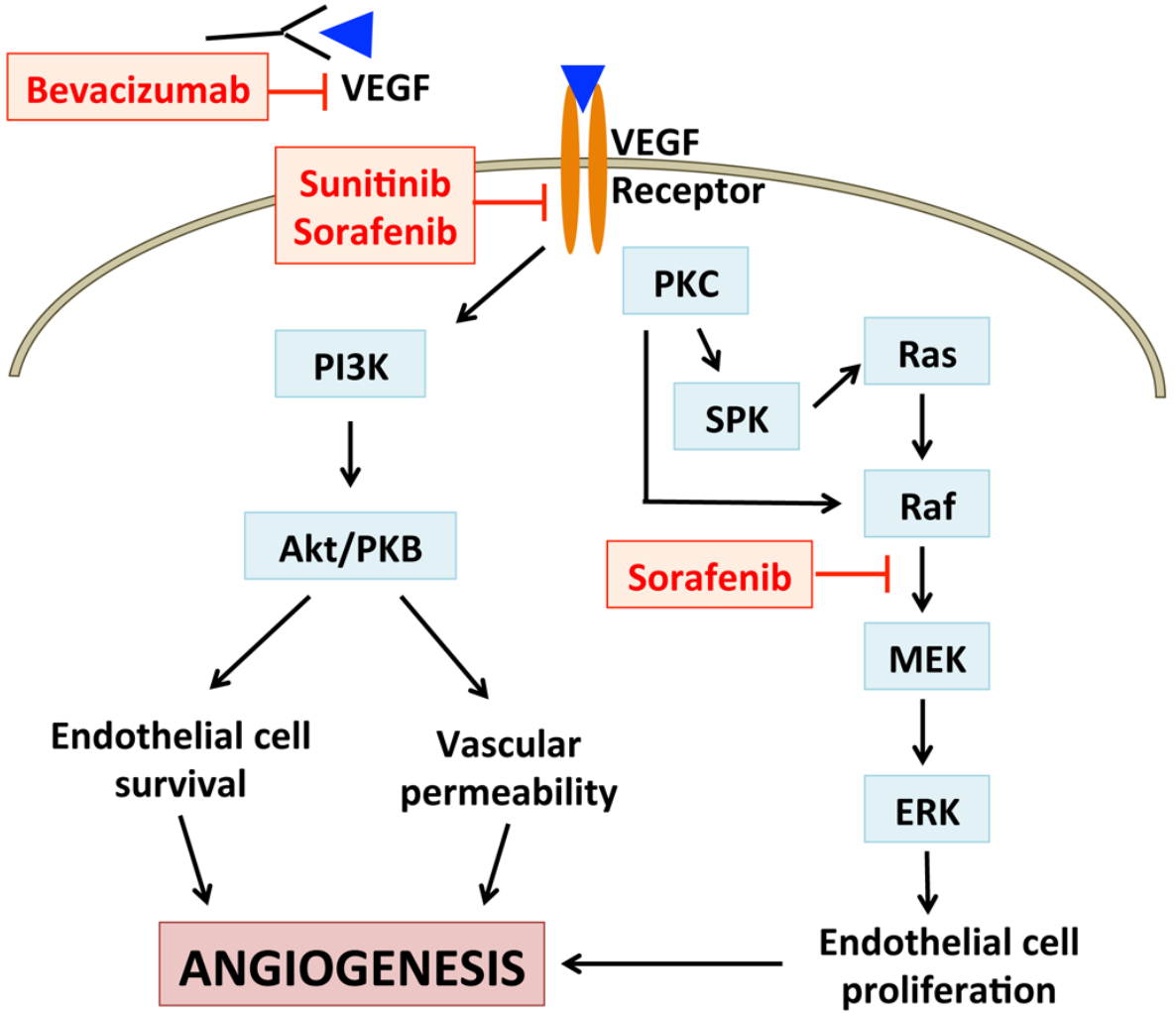
VEGF in the glomerulus

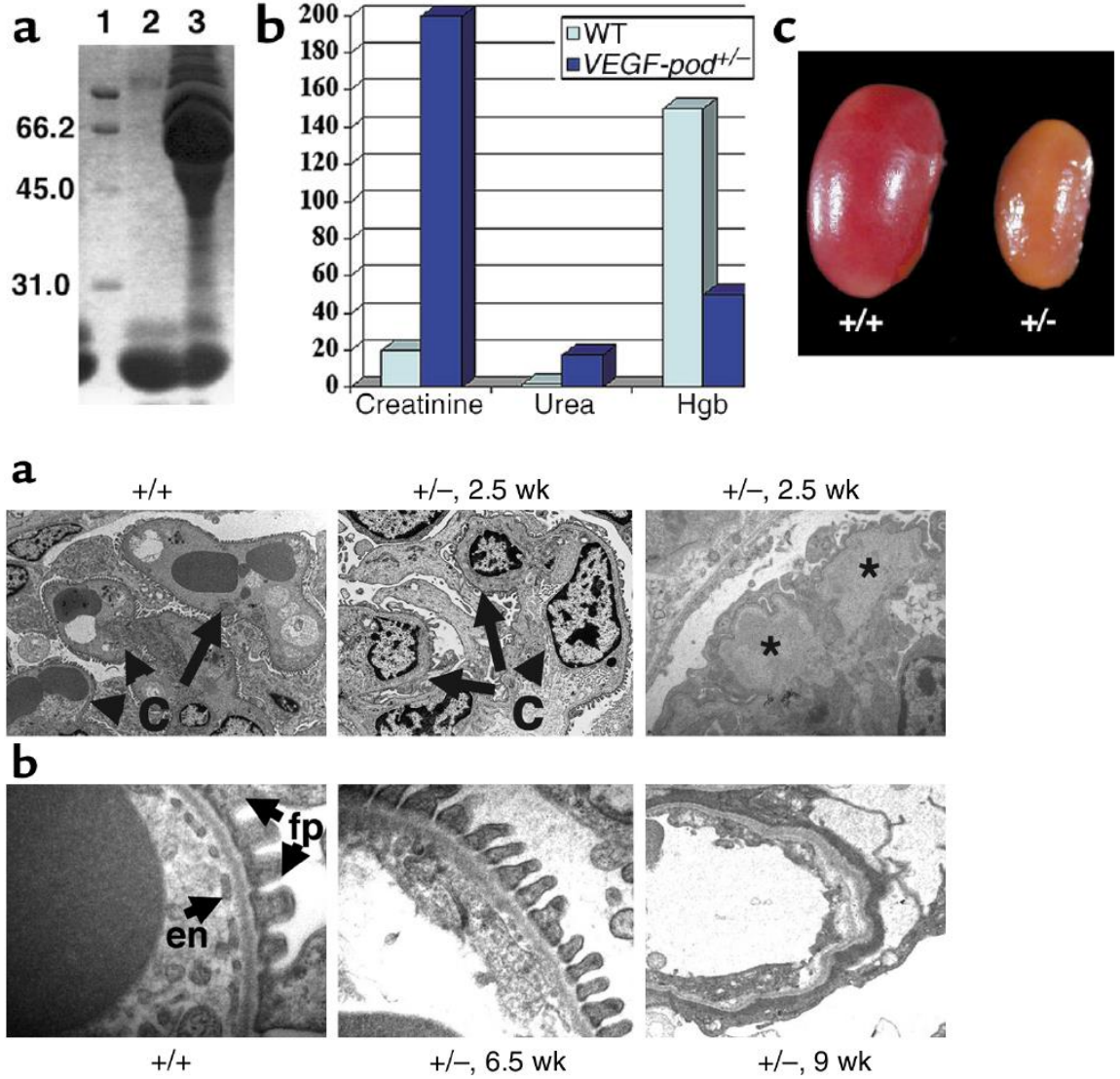




VEGF in the glomerulus

- Podocyte-specific heterozygous knockdown of VEGF leads to nephrotic syndrome and end-stage renal failure by 9 weeks of age.

- VEGF-null glomeruli do not form filtration barriers or fenestrations.



J Clin Invest 111: 707-716, 2003

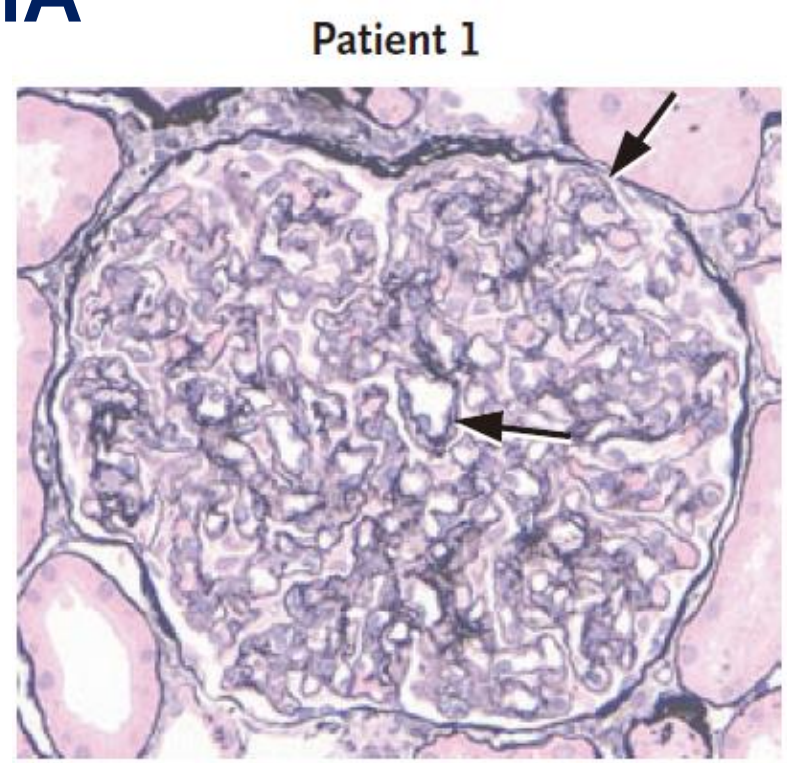
Bevacizumab and the risks of proteinuria and hypertension

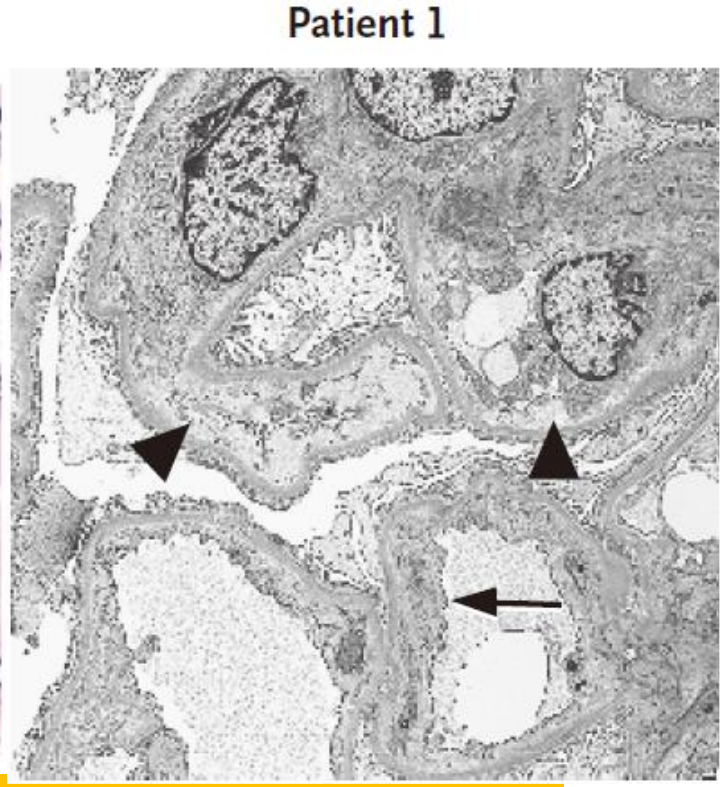
- Zhu et al. (2007)
  - A meta-analysis of 1,850 patients from 7 clinical trials
  - Increased risk of proteinuria (RR 1.4 with low dose; RR 2.2 with high dose)
  - Increased risk of hypertension (RR 3.0 with low dose; RR 7.5 with high dose)

- Ranpura et al. (2010)
  - 12,656 patients from 20 studies
  - RR for high-grade hypertension: 5.28 (6.1-10.2)
  - RR for hypertensive crisis: 3.16 (0.91-10.90)
  - RR for hypertension: 2.49 with mesothelioma; 14.80 with breast cancer

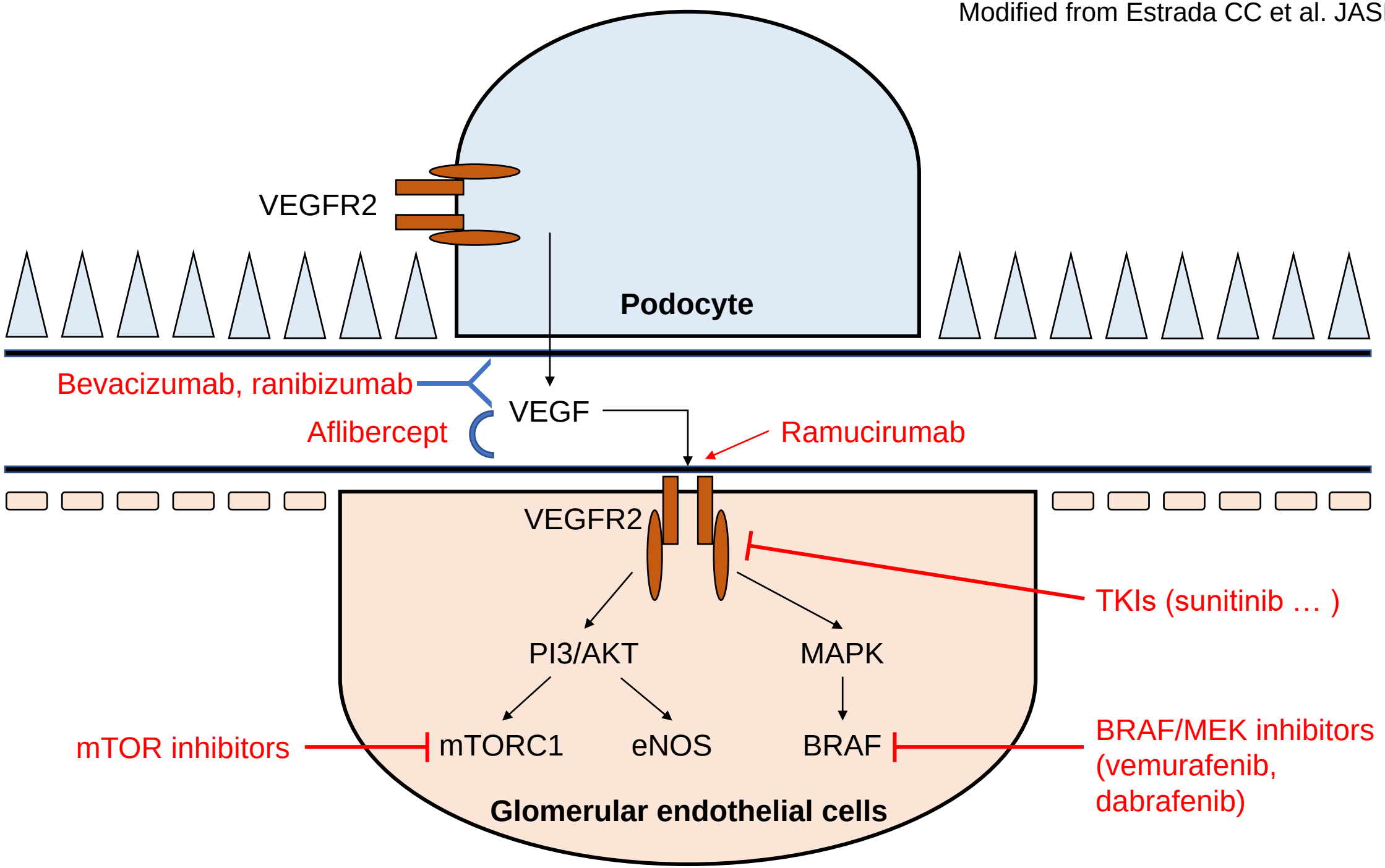
Bevacizumab and TMA

- Eremina V et al. (2008)
- 6 cases of bevacizumab-associated thrombotic microangiopathy
- Podocyte-specific VEGF deletion in mice recapitulated the renal effect of bevacizumab in humans.



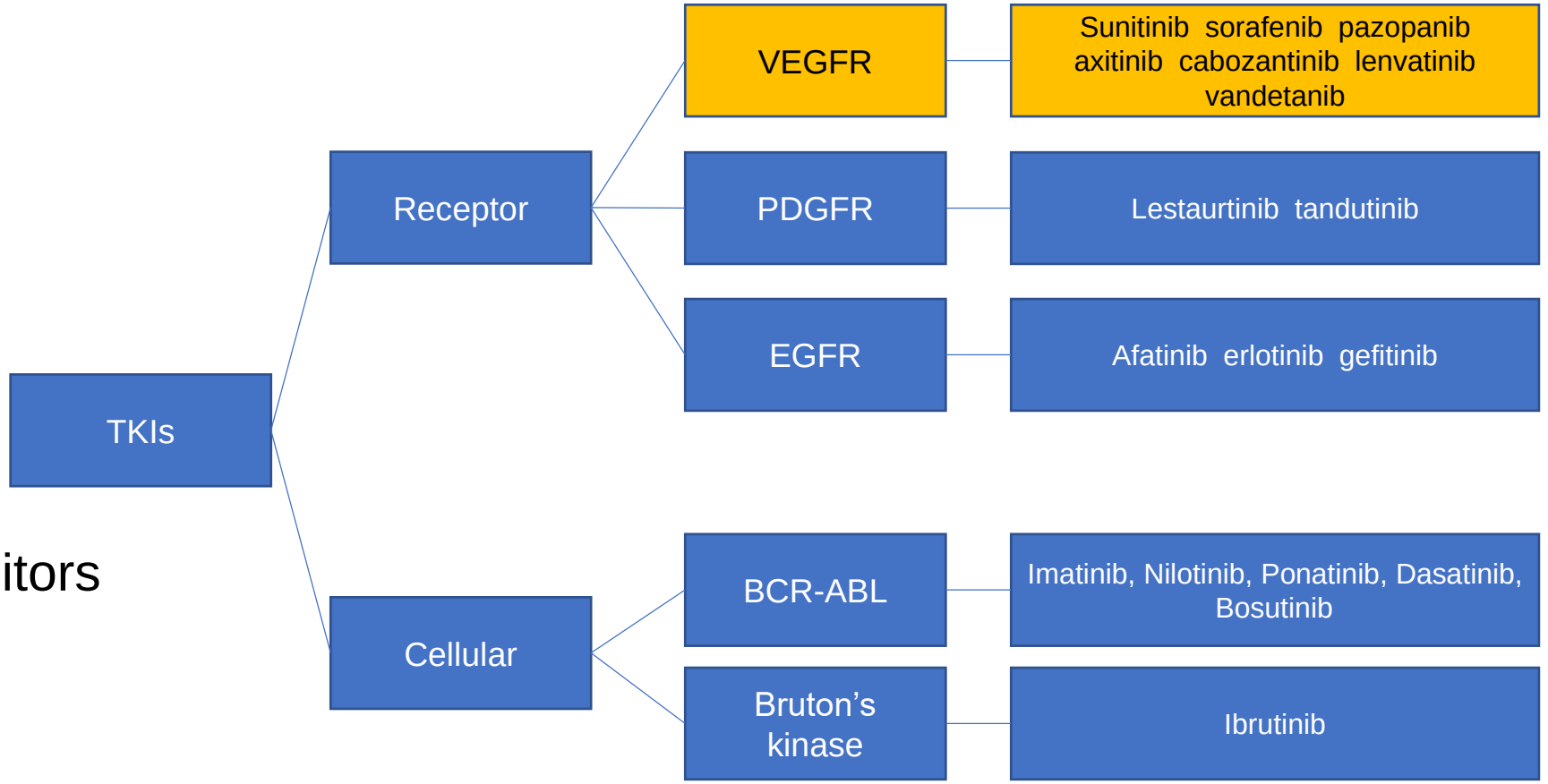


- 59/M with hepatocellular ca.
  - Bevacizumab for 24 doses
  - Proteinuria: 0.5 g/d → 3.4 g/d
  - Hypertension
  - Platelets: 103,000/mL
  - No schistocytes


VEGFR2
Podocyte
Bevacizumab, ranibizumab
Aflibercept
VEGF
Ramucirumab
VEGFR2
TKIs (sunitinib …)
PI3/AKT
MAPK
mTOR inhibitors
mTORC1
eNOS
BRAF
BRAF/MEK inhibitors
(vemurafenib,
dabrafenib)
Glomerular endothelial cells

Anti-VEGF agents

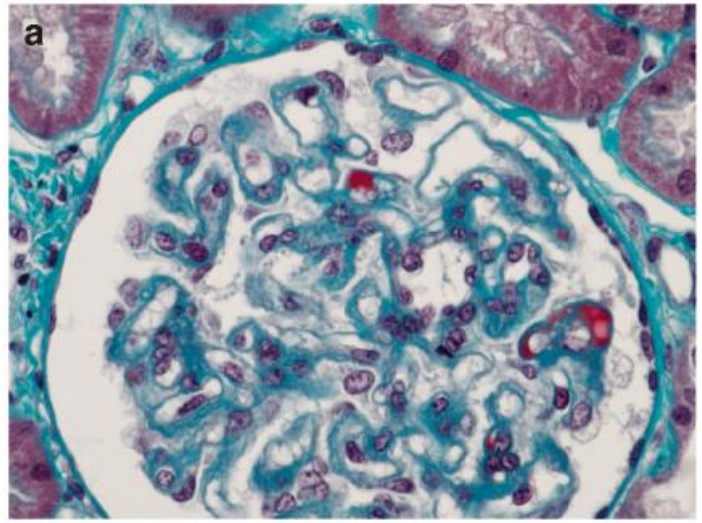
- Monoclonal Abs
  - Bevacizumab
  - Ramucirumab
- VEGF trap
  - Aflibercept
- Tyrosine kinase inhibitors
  - Sunitinib
  - Sorafenib
  - Pazopanib
  - Regorafenib
  - Axitinib

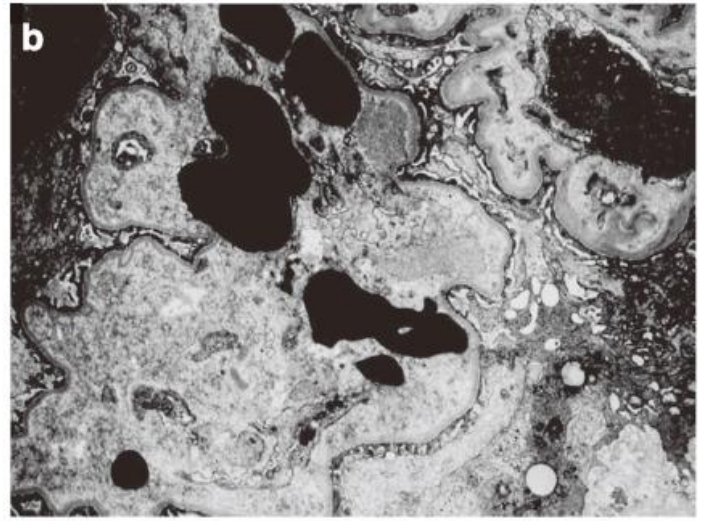


Jhaveri KD et al. KI Reports 2016

Nephrotoxicities of anti-angiogenesis agents

- Hypertension (common)
- Proteinuria / nephrotic syndrome (common)
- Thrombotic microangiopathy
- Acute interstitial nephritis (rare)





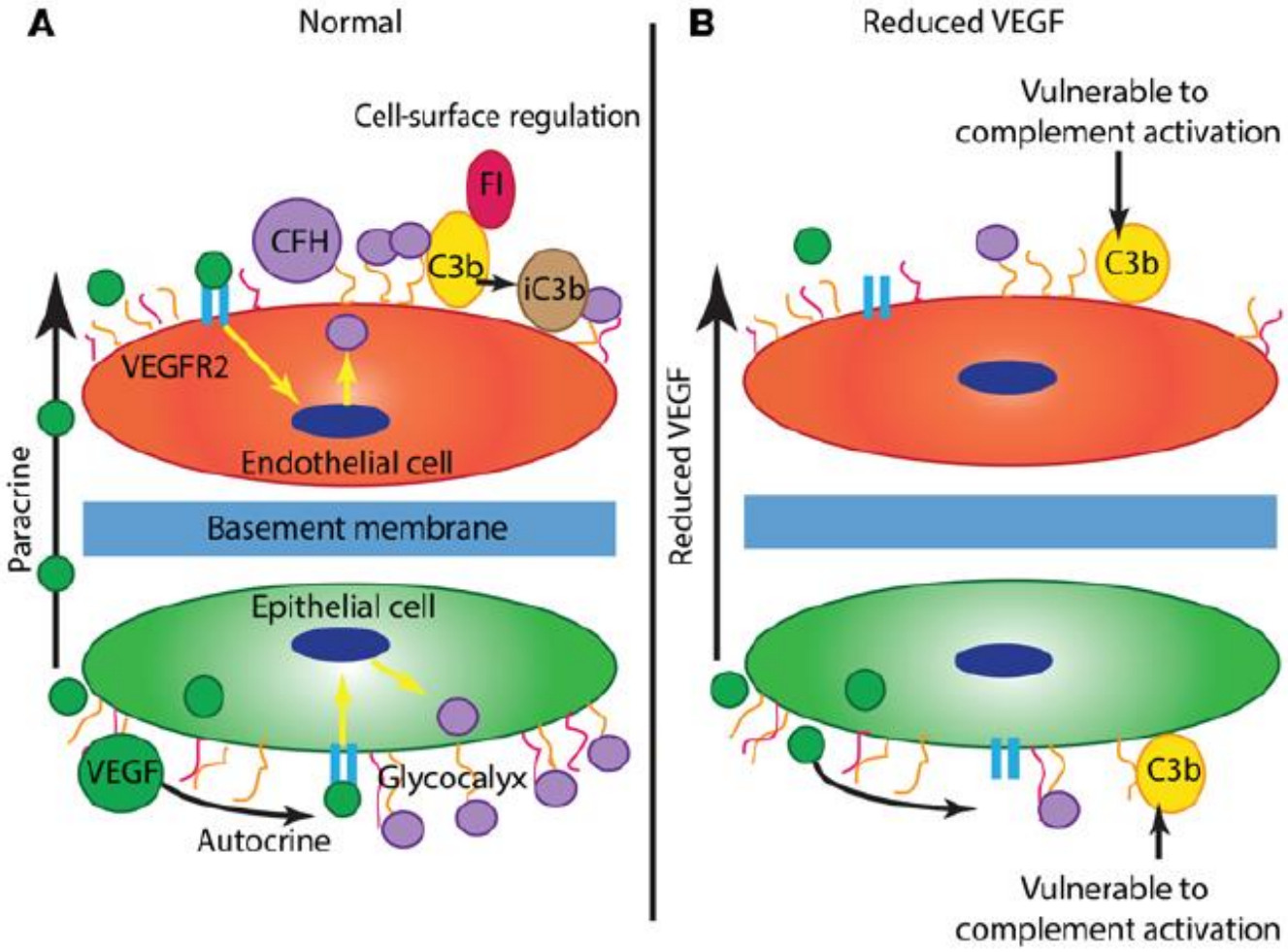
Perazella M et al. Kidney Int 2015

Renal complications associated with anti-VEGF

- Izzedine et al. (2014)
  - A series of 94 patients referred for anti-VEGF-associated kidney ds.
  - Median onset: 6.8 months
  - Proteinuria (100%)
  - Hypertension (74%)
  - Renal failure (40%; eGFR < 60)
  - TMA (n=73)
    - Bevacizumab in 61; aflibercept in 5
    - Hypertension in 83%
    - 71% female
  - MCN/FSGS-like (n=21)
    - Sunitinib in 13; sorafenib in 5
    - Hypertension in 48%
  - Renal function improved only following antihypertensive therapy and cessation of anti-VEGF therapy.

Izzedine H. et al. Medicine 93: 333-339, 2014

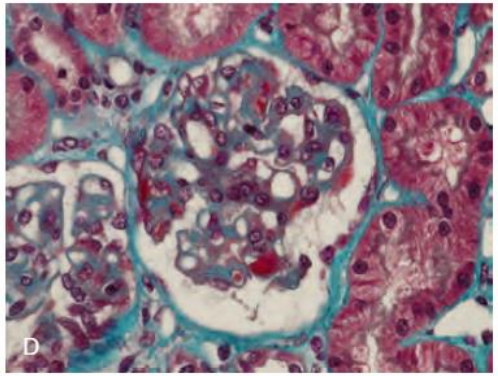
VEGF regulates local complement activity

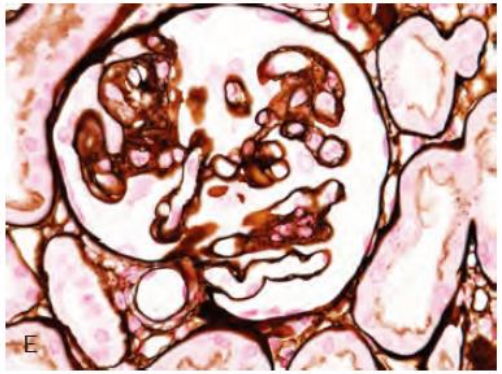


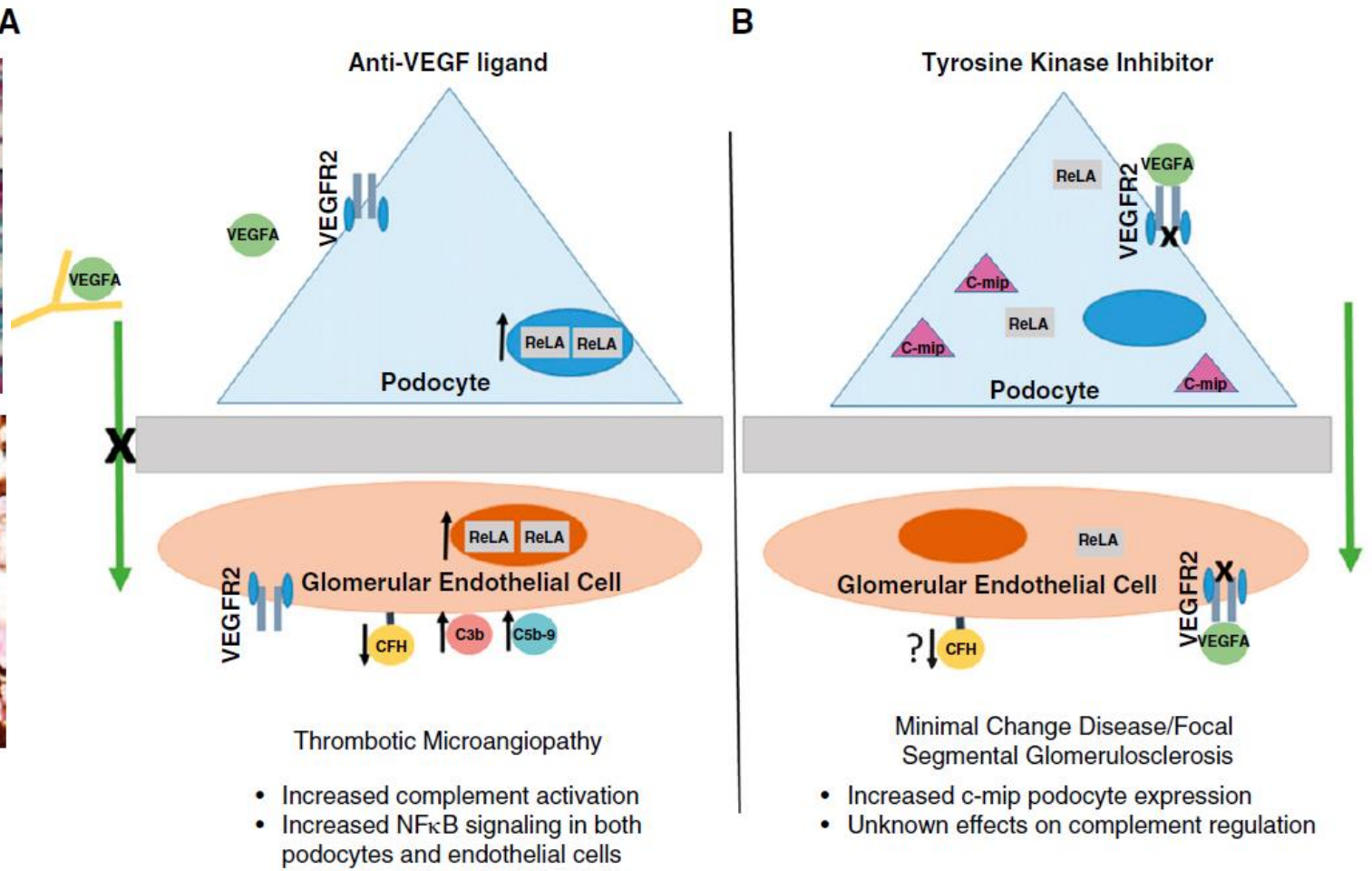
- VEGF increases CFH production.
- Anti-VEGF therapy reduces CFH production, making the cells vulnerable to complement activation.

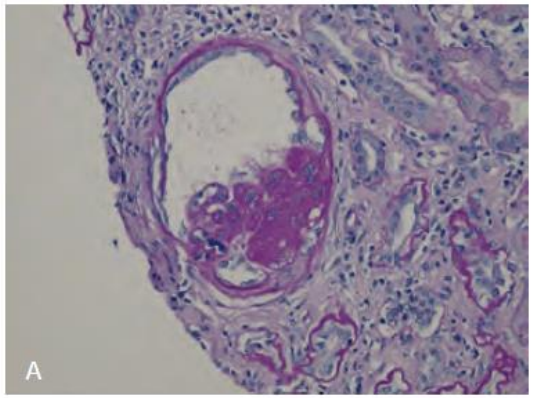
Keir L. et al. J Clin Invest 127(1):199-214, 2017

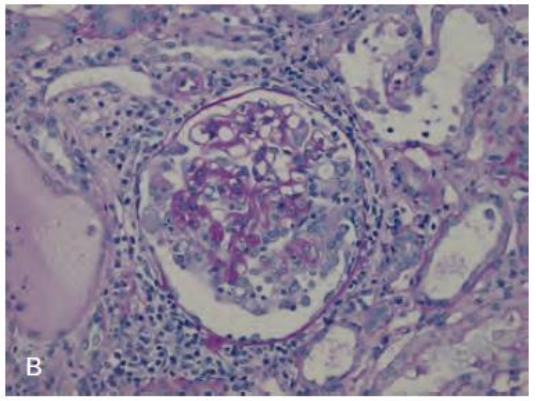
VEGF signaling and associated nephrotoxicities











Estrada CC et al. JASN 2019

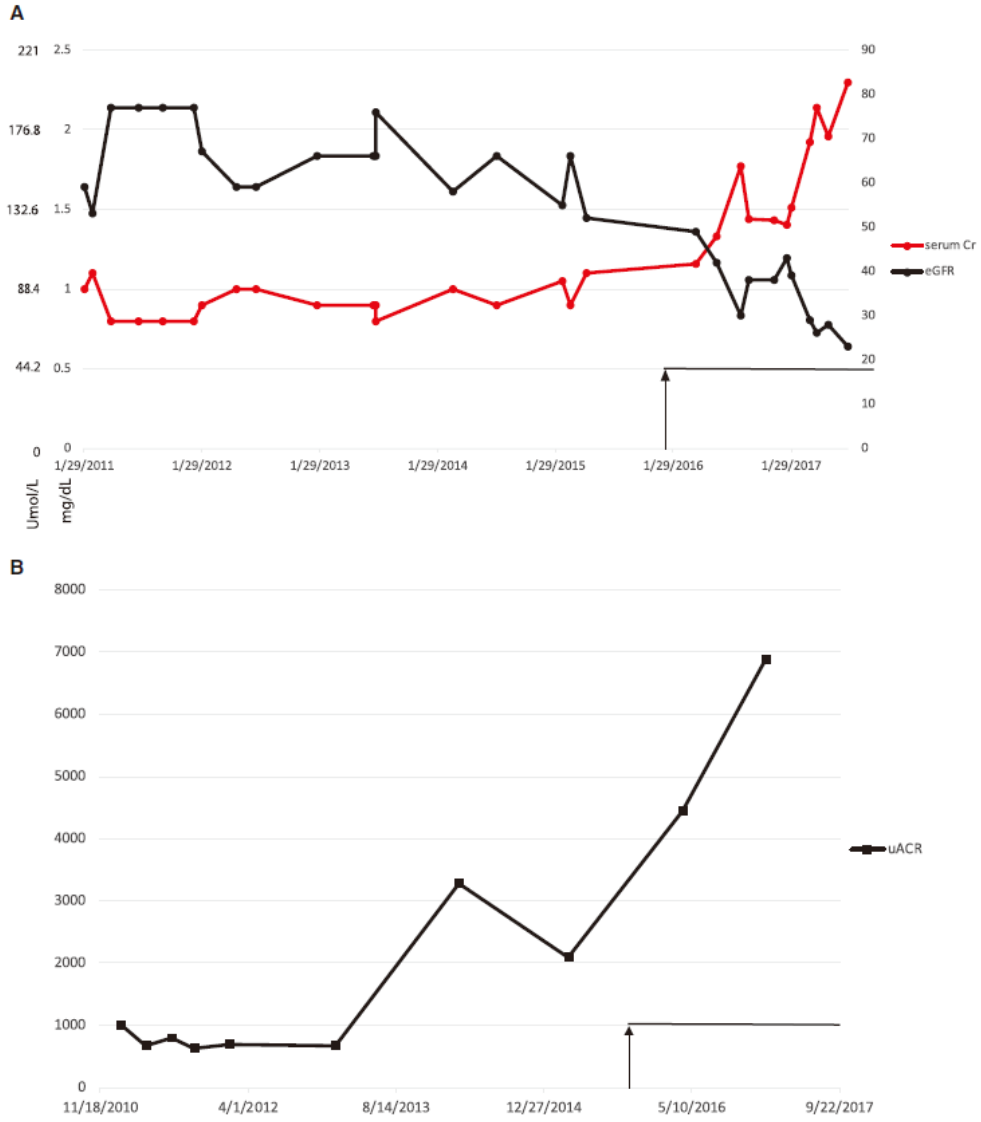
Clinical Kidney Journal, 2019, vol. 12, no. 1, 92–100

doi: 10.1093/ckj/sfy060
Advance Access Publication Date: 27 July 2018
Exceptional Case

EXCEPTIONAL CASE

Three patients with injection of intravitreal vascular endothelial growth factor inhibitors and subsequent exacerbation of chronic proteinuria and hypertension

- Intravitreal bevacizumab and/or aflibercept
- Worsening hypertension, proteinuria, and kidney injury
- Detectable in bloodstream up to 30 days post-intravitreal injection



BRAF inhibitors

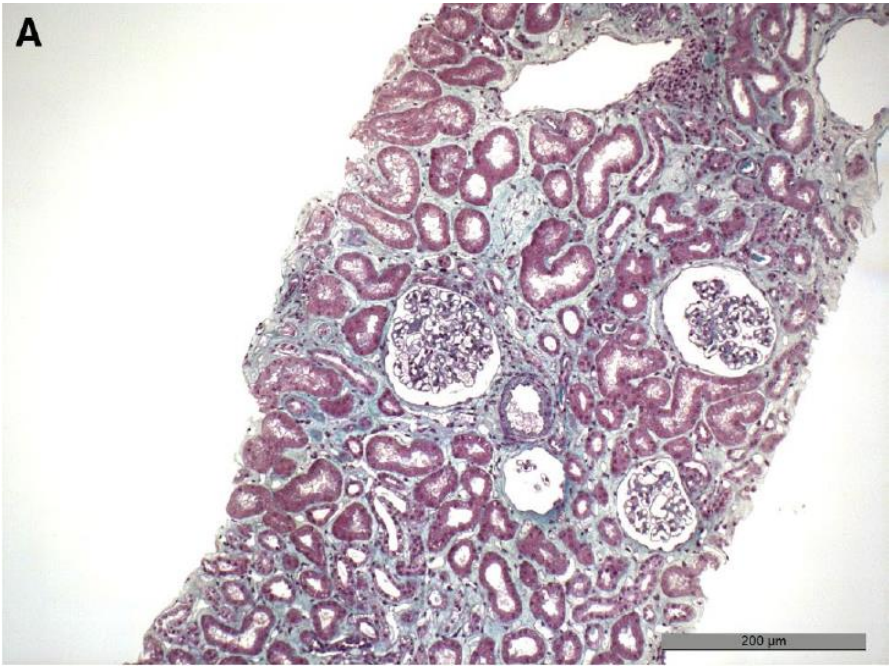
- BRAF-V600-mutant metastatic melanomas

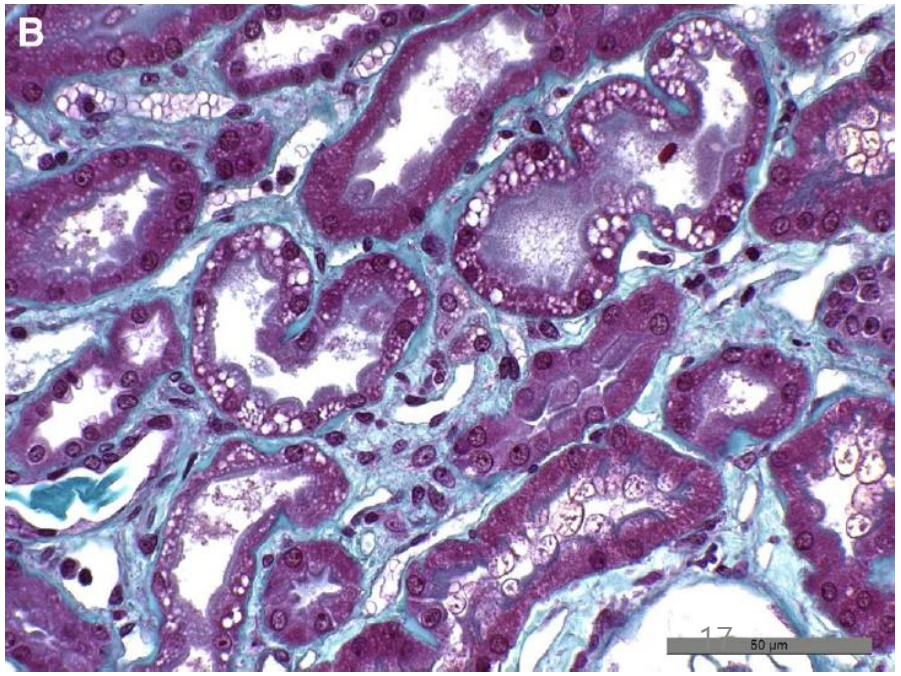
- Vemurafenib
  - 44/74 (59.5%) patients had a rise in serum Cr > 1.5 x baseline
  - Pathology: acute focal tubular damage, interstitial fibrosis
  - 80% reversible within 3 months of discontinuation

Teuma C et al. Cancer Chemother Pharmacol 2016

  - Inhibition of tubular secretion of Cr

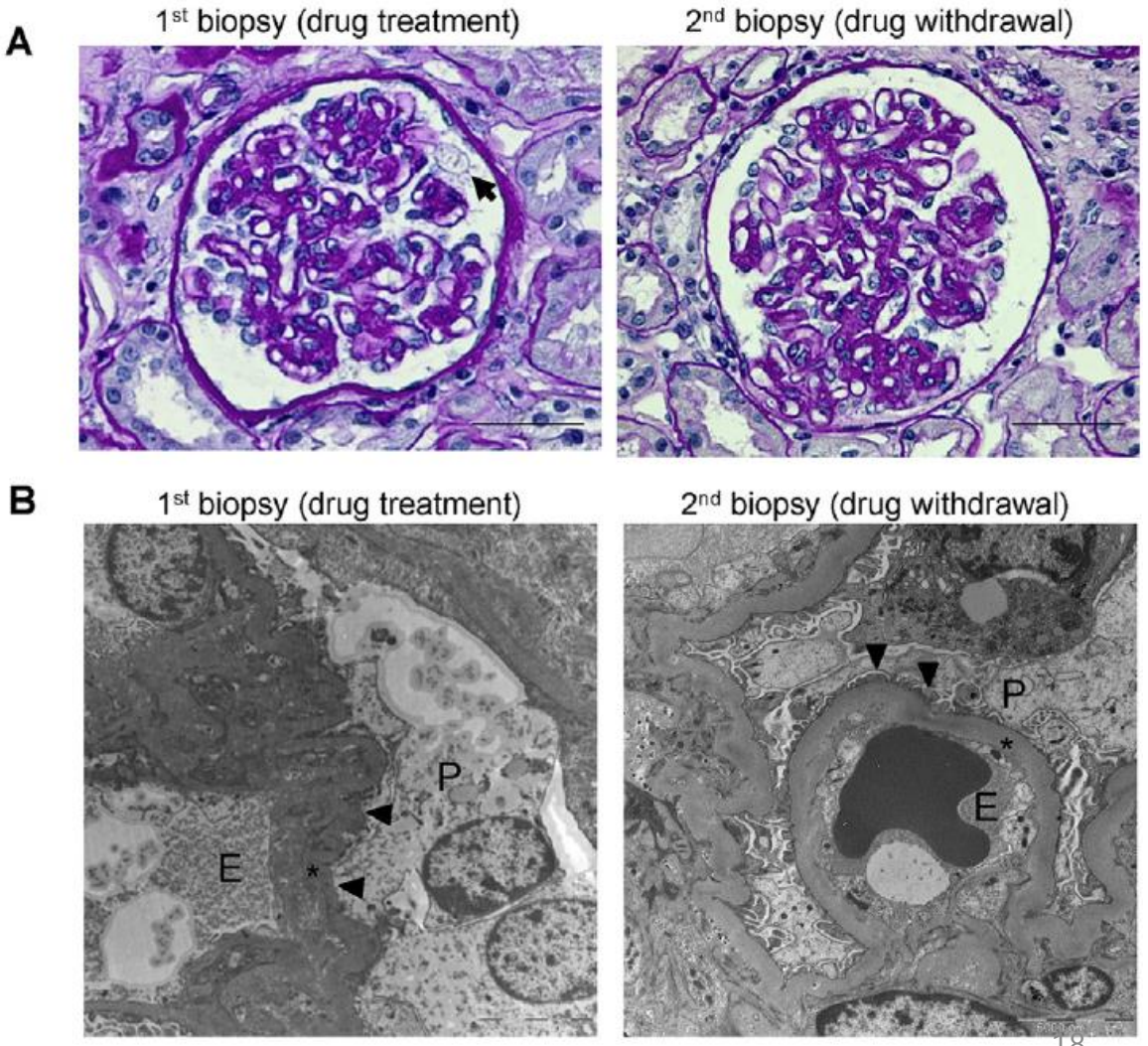
Hurabielle C et al. PLoS ONE 2016





BRAF/MEK inhibitors and the podocyte

- Nephrotic syndrome with dabrafenib and trametinib
  - Loss of podocytes
  - Glomerular endothelial injury
  - Reduction in PLCε1 and nephrin expression
  - Inhibition of VEGF system



Perico L. et al. Am J Kidney Dis 2017

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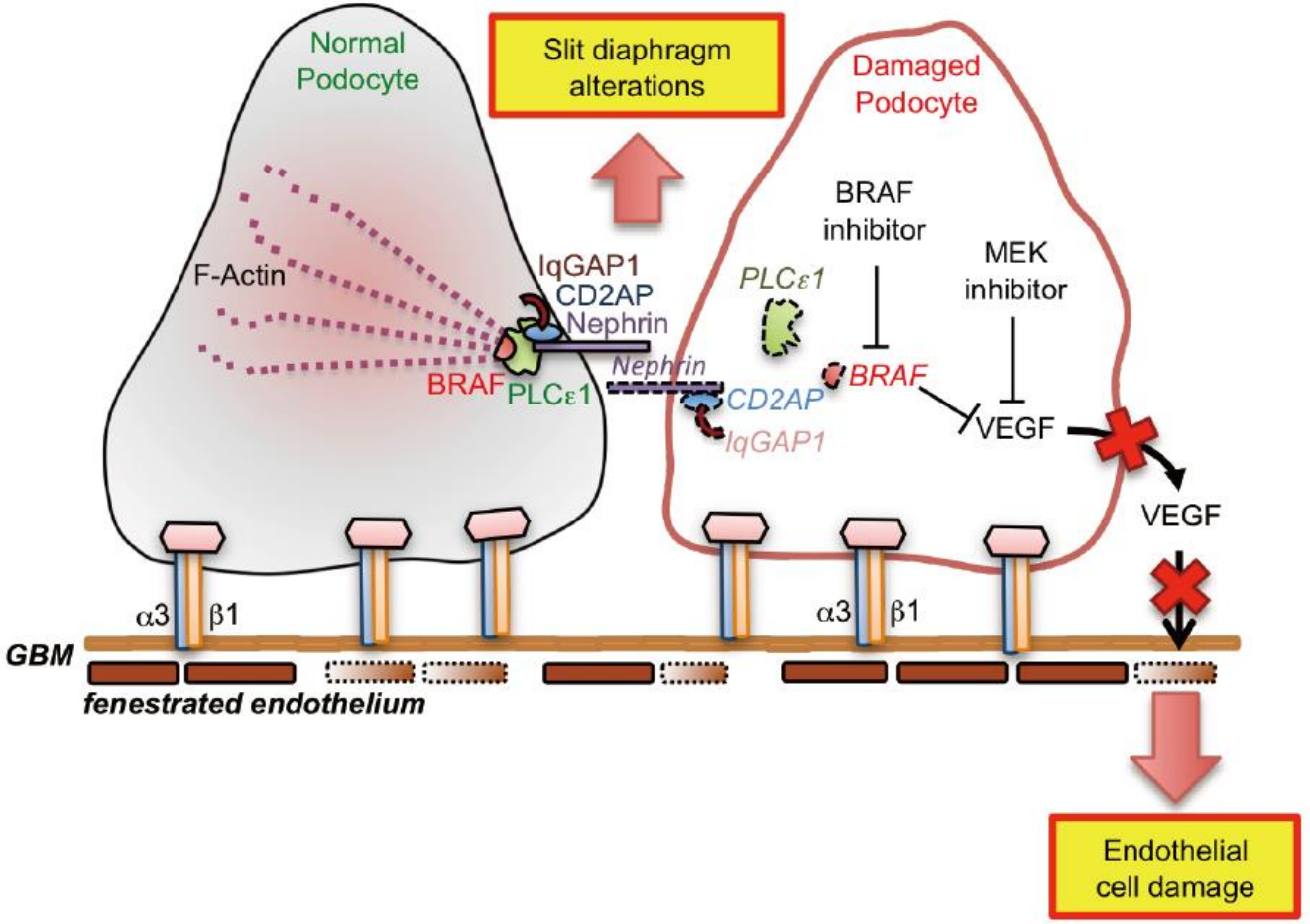

Perico L. et al. Am J Kidney Dis 2017

Clinical manifestations of VEGF inhibition

Drugs	Class	Renal Manifestations
Bevacizumab	mAb against VEGFA	Proteinuria 21-62%; HTN 23.7%; TMA, MCD, ABMR-intraocular
Ranibizumab (intraocular)	mAb against VEGFA	TMA, proteinuria, ABMR-intraocular
Aflibercept	Recombinant VEGF trap	HTN 42.4%; proteinuria, TMA, ABMR-intraocular
Ramucirumab	mAb against VEGFR2	HTN 21%; proteinuria 9%
Sunitinib	Multitargeted TKIs	HTN 14.9%; MCD/cFSGS
Pazofanib	Multitargeted TKIs	HTN 47%; proteinuria 13.5%
Sorafenib	Multitargeted TKIs	HTN 18.1%; MCD/cFSGS; TMA; proteinuria 11.6%
Vemurafenib	BRAF inhibitor	AKI, ATN
Dabrafenib	BRAF inhibitor	Nephrotic syndrome
Trametinib	MEK inhibitor	Nephrotic syndrome

Estrada CC et al. JASN 2019

Clinical considerations

- Optimize cardiovascular risk prior to anti-VEGF therapy
- BP < 140/90 mmHg
- Inhibition of renin-angiotensin system
- Stop anti-VEGF agents if frank AKI(+) or nephrotic-range proteinuria

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Immune Checkpoint Inhibitors

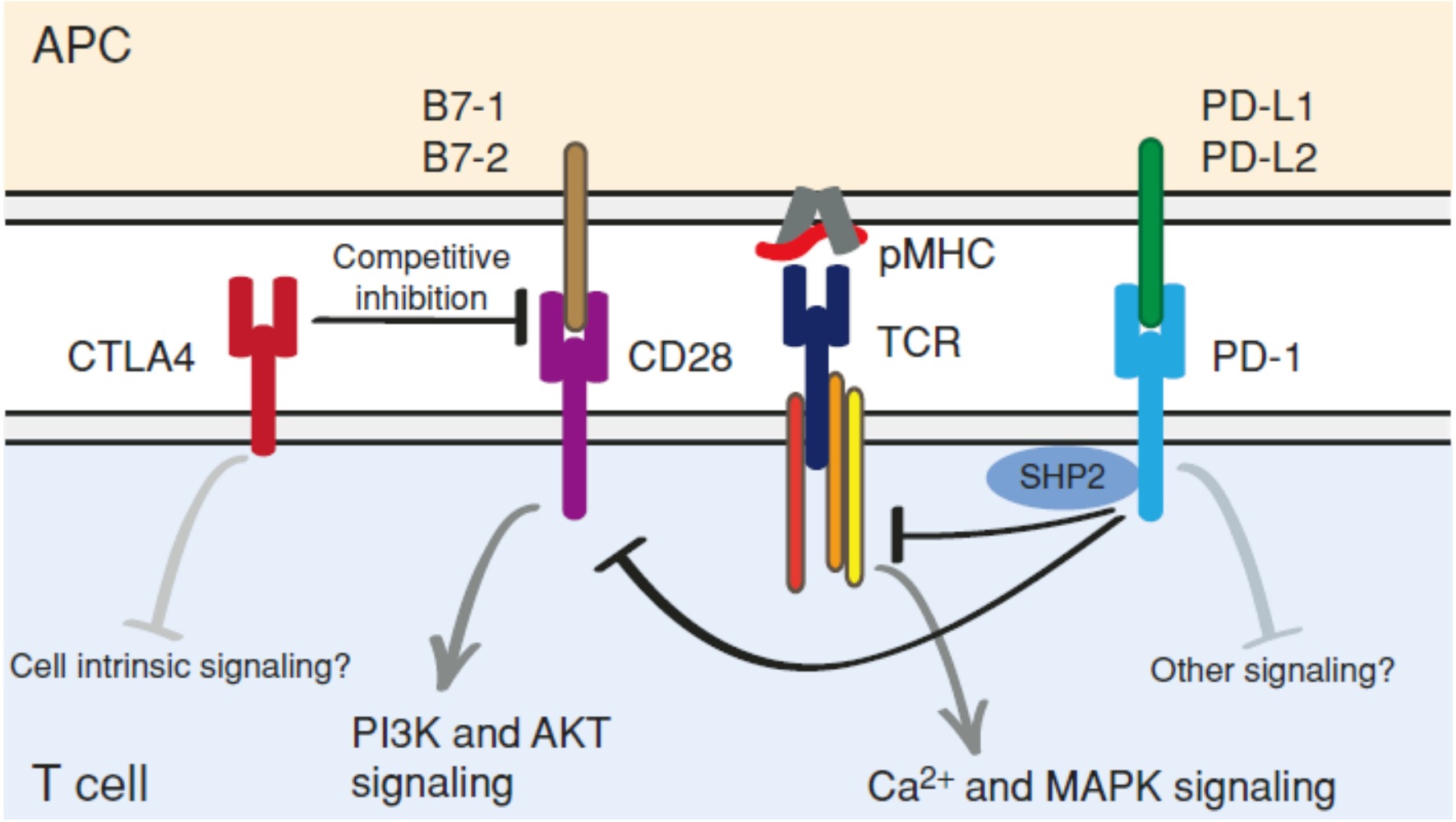
Immune checkpoints

- Protect tissues from an activated immune system
- Primary mechanism is a downregulation of T cell activation or effector functions.

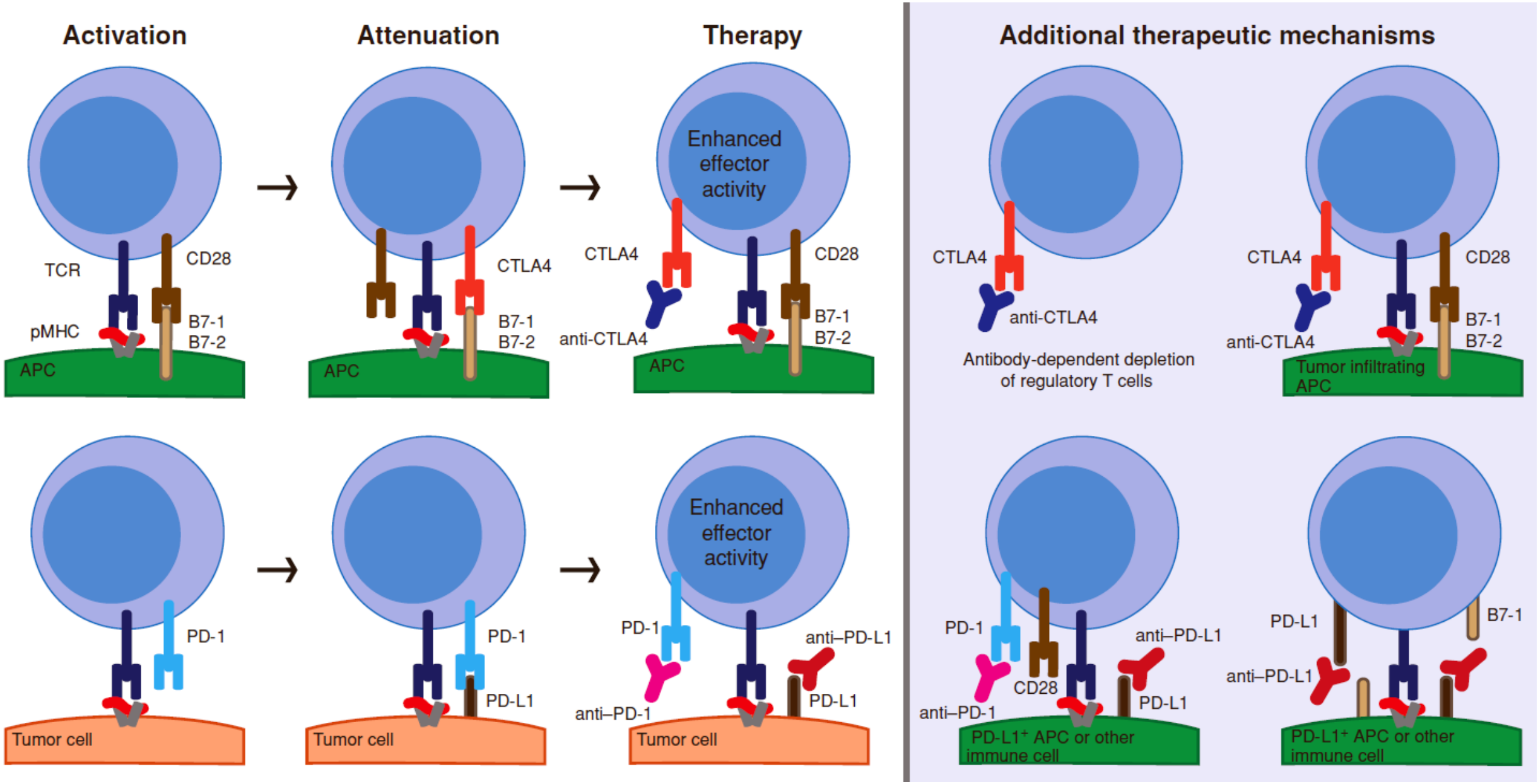
Molecular targets

- CTLA-4 (cytotoxic T lymphocyte-associated protein 4)
- PD-1/PD-1L (programmed cell death protein-1 / programmed cell death protein-1 ligand)

“Immune checkpoint”



Wei SC et al. Cancer Discovery 2018



Wei SC et al. Cancer Discovery 2018

Immune Checkpoint inhibitors

- Anti-CTLA4
  - Ipilimumab
  - Tremelimumab
- Anti-PD-1/PD-L1
  - nivolumab, pembrolizumab
  - atezolizumab, durvalumab, avelumab

Indications

- First-line treatment of :
  - Melanoma
  - Non-small cell lung cancer
- Pembrolizumab
  - Any solid tumor harboring microsatellite instability-high (MSH-H) or a deficient DNA mismatch repair system (dMMR)

Immune-related adverse events (irAEs)

- Of autoimmune nature
- Ipilimumab : 75%; high-grade (grade 3 or 4) irAEs in 43%
- Anti-PD-1/PD-L1 : 30%; high-grade in 20%
- Combined treatment : irAEs in 95%; 55% in grade 3 or 4

Immune-related adverse events (irAEs)

Common

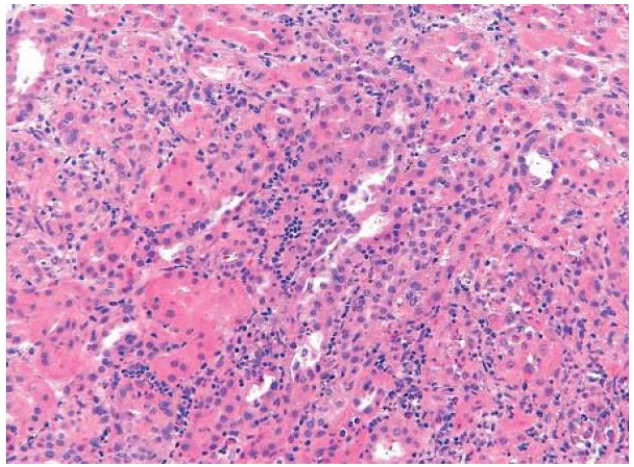
- Skin
- GI tract: colitis, hepatitis
- Endocrine: hypophysitis, thyroiditis

Uncommon

- Renal: AKI - AIN, ATN
  - 1-2% with monotherapy
  - 4.9% with combined therapy
- Pulmonary: pneumonitis
- Cardiovascular: myocarditis
- Neurological

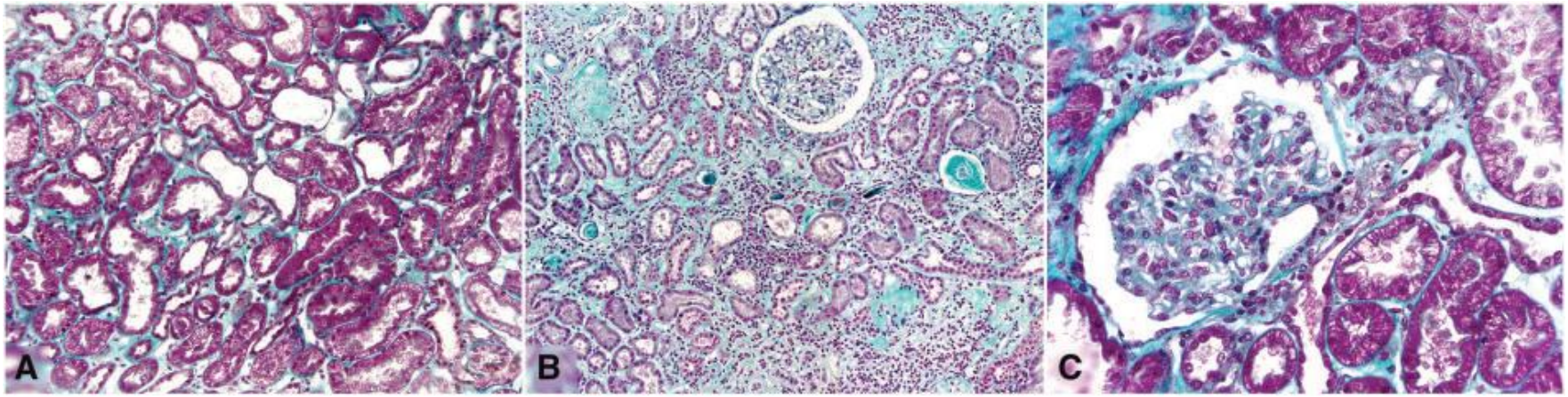
Renal irAEs

- Acute tubulointerstitial nephritis



Wanchoo R et al, Am J Nephrol 2016

- Acute tubular injury



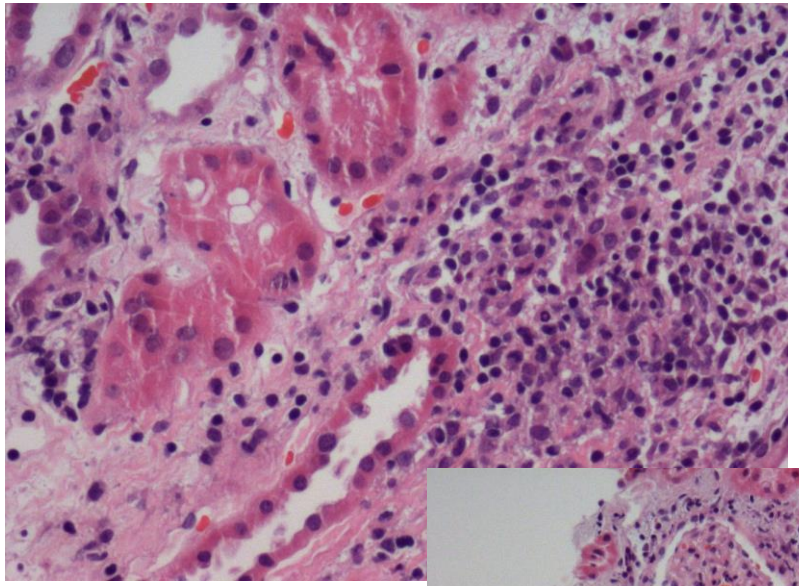
Izzedine H et al, Clin Kidney J 2019

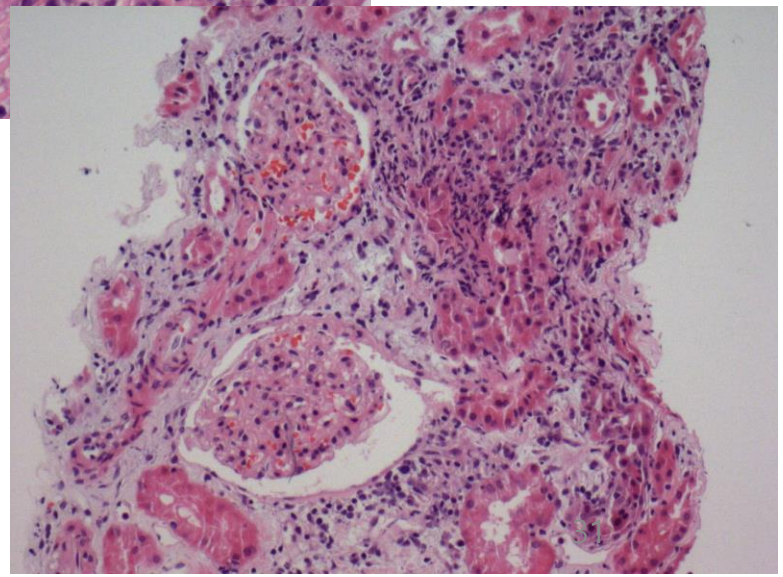
Pt	Urine sediment[a]	Proteinuria (dipstick/UPCR)	Day of AKI[b]	Days since last dose of CPI	Eos	HTN[c]	Oliguria[d]	Kidney size (cm)	Peak SCr (mg/dl)	Requirement for RRT	IRAEs
1	5–10 WBCs[e] 2 RBCs	1+/0.6	54	54	No	No	No	R 12.8 L 13.8	6.2	No	Hypophysitis
2	2–3 WBCs 3–5 RBCs	Trace/NA	91	49	No	No	No	R 12.2 L 13.2	4.1	No	Thyroiditis; ileitis
3	5–10 WBCs 0 RBCs 0–2 WBC casts	Trace/NA	69	14	No	No	No	R 11.6 L 12.6	9.7	3 HD treatments starting on day 130	Hepatitis
4	16–34 WBCs	NA/NA	70	28	NA	No	No	R 13.0 L 13.0	3.6	No	None
5	5 WBCs[e] 1 RBC	Neg/0.26	245	63	No	No	No	R 13.2 L 13.0	2.9	No	Hypophysitis; thyroiditis
6	0 WBC 0 RBC	Neg/0.74	183	36	No	Yes	Yes	R 10.9 L 13.5	11.7	HD-dependent starting on day 183	Hypophysitis;[f] colitis
7	0 WBC[e] 0 RBC	Neg/NA	224	14	No	No	No	R 11.8 L 12.2	3.8	No	Sicca syndrome with sialadenitis on lip biopsy; colitis
8	6–9 WBCs 0–3 RBCs	1+/0.98	154	7	No	No	Yes	R 12.8 L 11.8	5.6	HD-dependent starting on day 210	None
9	9 WBCs[e] 8 RBCs WBC casts	2+/0.12	42	21	No	Yes	No	R 12.4 L 13.0	7.3	No	Rash; colitis
10	3 WBCs[e] 3 RBCs WBC casts	1+/0.73	120	57	No	No	No	R 8.0 L 10.0	2.9	No	None
11	50–100 WBCs 0–2 RBCs	1+/0.18	60	18	14.7%	No	No	R 10.2 L 10.0	4.5	No	None
12	20–50 WBCs 0-2 RBCs	1+/NA	21	21	No	No	No	NA	13.3	3 HD treatments starting on day 21	None
13	11–20 WBCs 0 RBCs	Neg/0.36	231	21	No	No	No	R 10.7 L 11.9	2.5	No	Iritis; colitis
Median IQR		0.48 0.24–0.73	91 60–183	21 18–49				R 12.0, L 12.8 R 10.9–12.8 L 11.9-13.1	4.5 3.6–7.3		

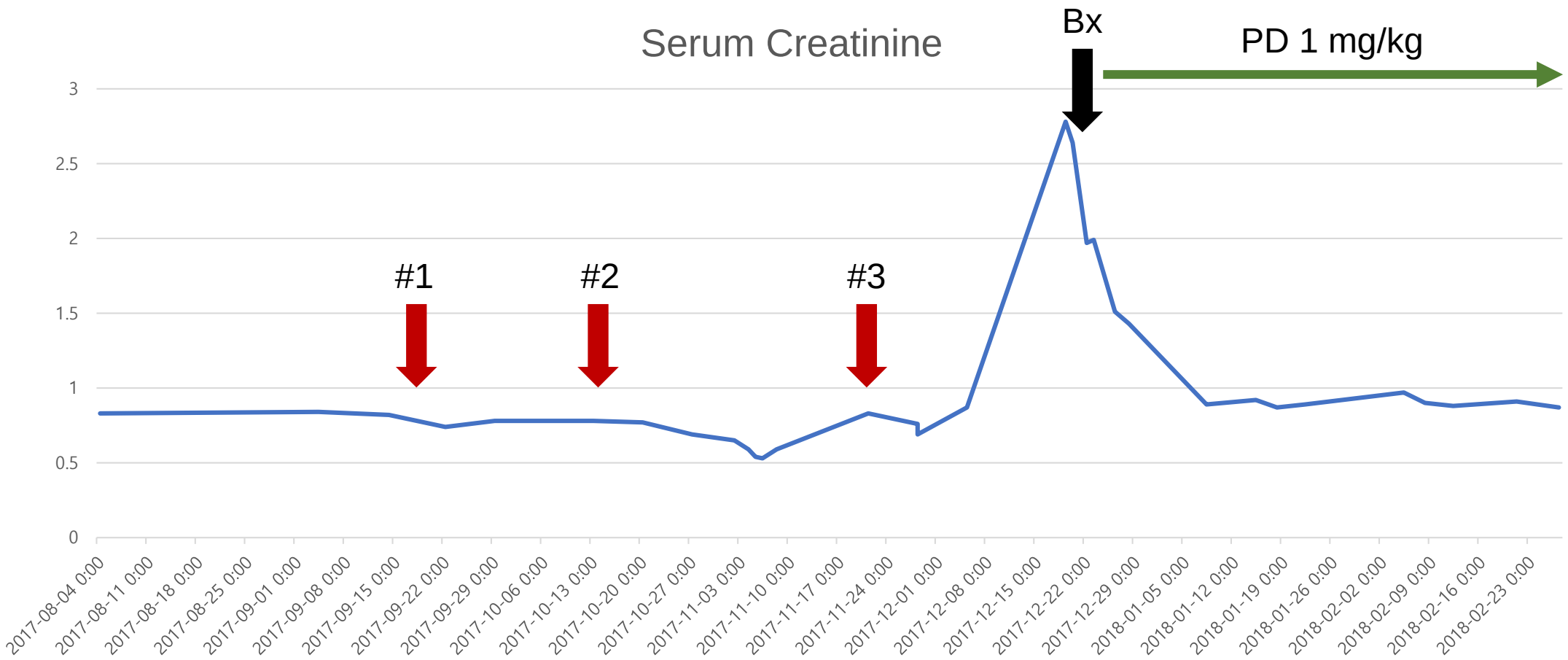
Cortazar F et al, Kidney Int 2016

A case of AKI associated with ICI treatment

- 64/M, Advanced gastric cancer
- Progressive azotemia over 2 weeks after cycle #3 of anti-CTLA4 (tremelimumab) and anti-PD-L1 (durvalumab)
- BUN/Cr 30/2.64 mg/dL
- U/A with microscopy: protein 1+, glucose -, RBC 5-9/HPF, WBC >100/HPF






Serum Creatinine
Bx
PD 1 mg/kg
#1
#2
#3
3
2.5
2
1.5
1
0.5
0
2017-08-04 0:00
2017-08-11 0:00
2017-08-18 0:00
2017-08-25 0:00
2017-09-01 0:00
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2017-09-15 0:00
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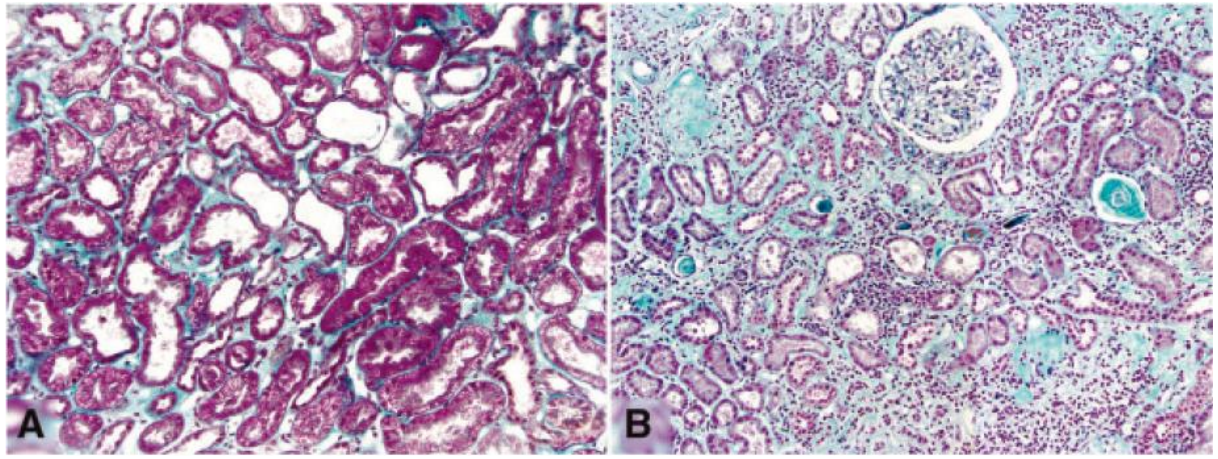
Tubular injury with pembrolizumab

- 12/676 (1.77%) cases in France

- 4 patients with AIN
- 5 patients with ATI
- 1 patient with MCD + ATI
- 1 patient with MCD

- Steroid + withdrawal of pembrolizumab



Izzedine H et al. Clin Kidney J 2019

VOLUME 36 · NUMBER 17 · JUNE 10, 2018

JOURNAL OF CLINICAL ONCOLOGY

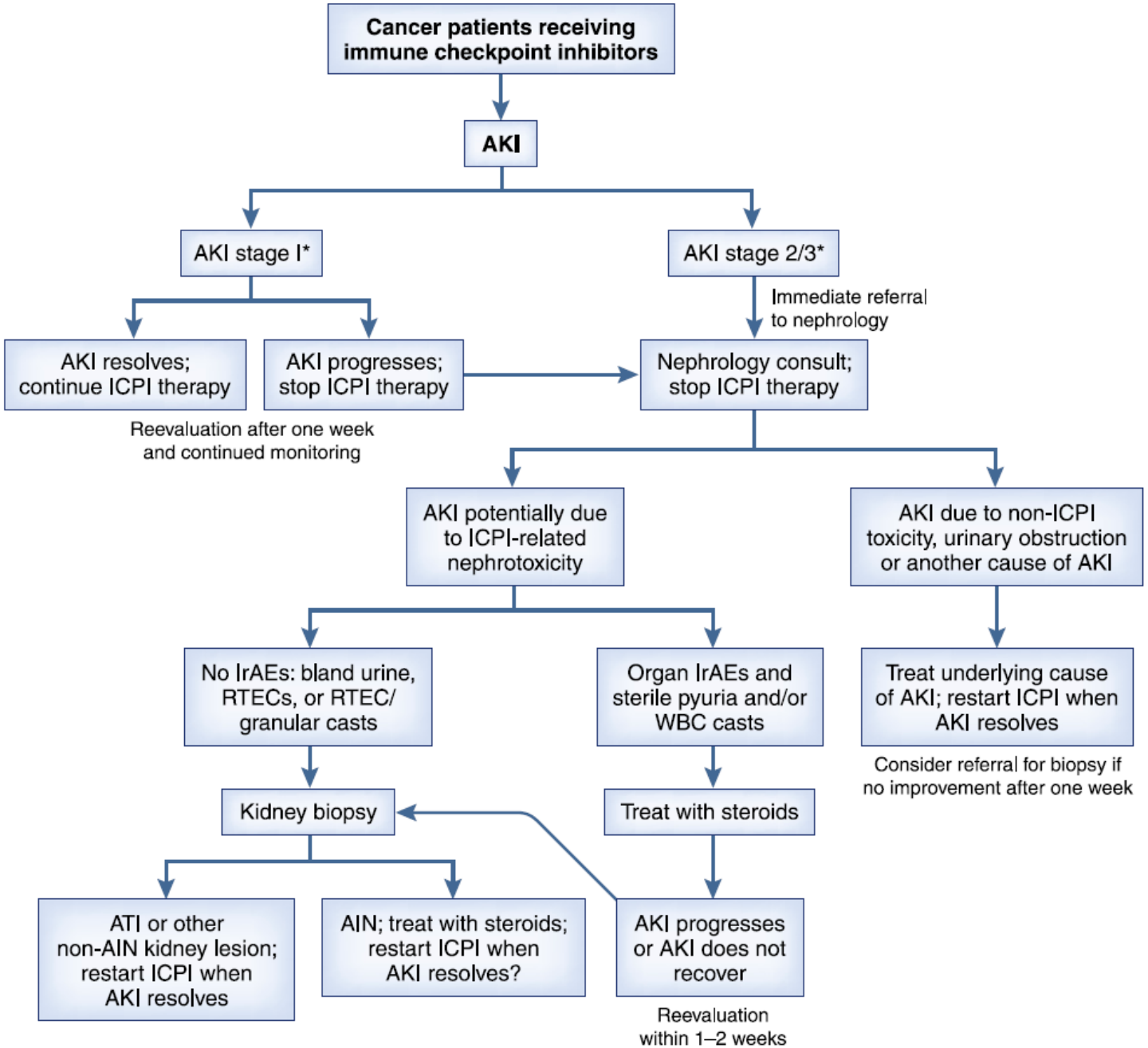
ASCO SPECIAL ARTICLE

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

6.1 Nephritis

Additional considerations
- Monitor creatinine weekly
- Reflex kidney biopsy should be discouraged until corticosteroid treatment has been attempted

Cr rise > 0.3 mg/dL; Cr 1.5-2.0 x over baseline	Consider temporarily holding ICPi
Cr 2-3 x above baseline	Hold ICPi temporarily; 1-2 mg/kg PD
Cr > 3 x baseline or > 4 mg/dL	Permanently discontinue ICPi



Perazella MA et al. CJASN 2019

Use of ICIs in a transplant recipient

- 70/M
- Bilateral RCC → Nx → KT
- GC + tacrolimus + MMF

- Duodenal ca. m/liver
- Nivolumab therapy

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 R et al. N Engl J Med 2017

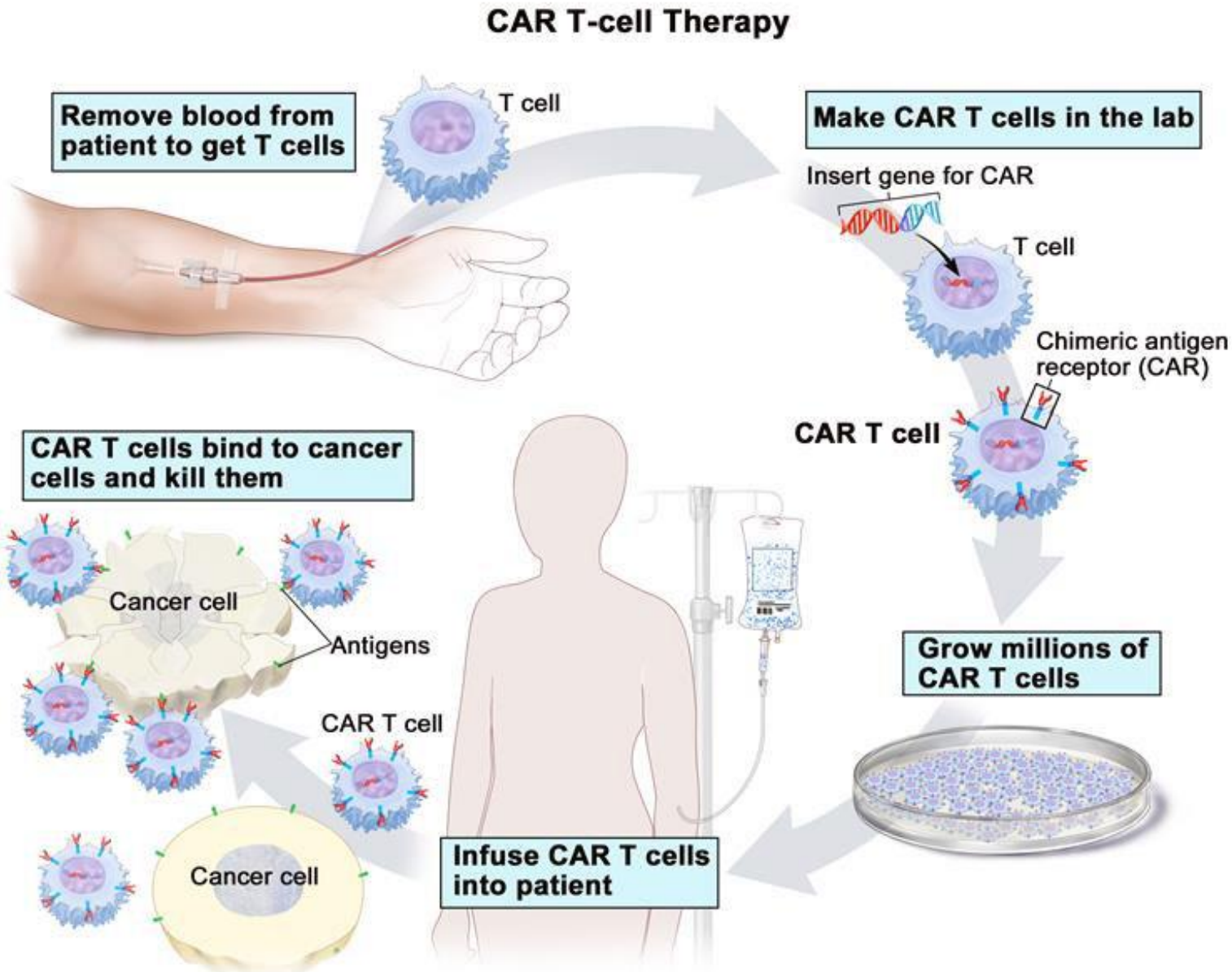
Summary of renal effects of ICIs

	CTLA-4 antagonists	PD-1 inhibitors
Most common toxicity	AIN in 10 patients	AIN in 16; 6 patients receiving combination CTLA-4 therapy
Timing of onset	6 to 12 wk after initiation Late onset related to severe AKI	3 to 12 mo after initiation
Glomerular findings	Membranous nephropathy in 1 TMA in 1 MCD in 2	MCD in 1 IgA nephropathy in 1
Outcomes after kidney transplantation	No transplant rejection reported in 2 patients	Transplant rejection reported in 7 of 10 patients including 3 who had received combination therapy with CTLA-4 antagonists

Jhaveri K. et al. N Engl J Med 2017

Contents

- Acute kidney injury associated with targeted therapies
  - Anti-angiogenesis agents
  - Immune checkpoint inhibitors
  - Chimeric antigen receptor T cells
  - Tumor lysis syndrome with venetoclax



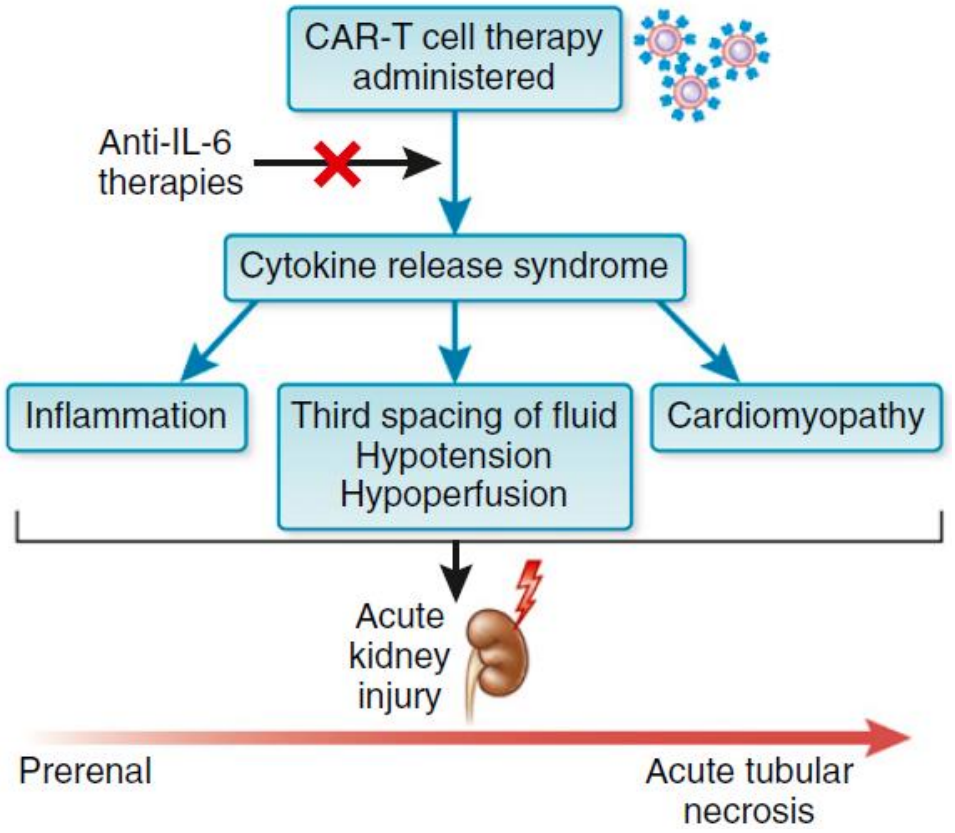
Disease	Response Rate
	percent
Leukemia	
B-cell acute lymphoblastic leukemia (in adults)	83–93
B-cell acute lymphoblastic leukemia (in children)	68–90
Chronic lymphocytic leukemia	57–71
Lymphoma	
Diffuse large B-cell lymphoma	64–86
Follicular lymphoma	71
Transformed follicular lymphoma	70–83
Refractory multiple myeloma	25–100
Solid tumors	
Glioblastoma	ND
Pancreatic ductal adenocarcinoma	17

https://www.cancer.gov/publications/dictionaries/cancer-terms/def/car-t-cell-therapy

June CH et al. N Engl J Med 2018

Chimeric Antigen Receptor T cell therapy and the kidney

- Cytokine release syndrome
- Tumor lysis syndrome
- Electrolyte disorders
  - Hypokalemia (47%)
  - Hypophosphatemia (37%)
  - Hyponatremia (5%)



Jhaveri KD et al. Clin J Am Soc Nephrol 2017

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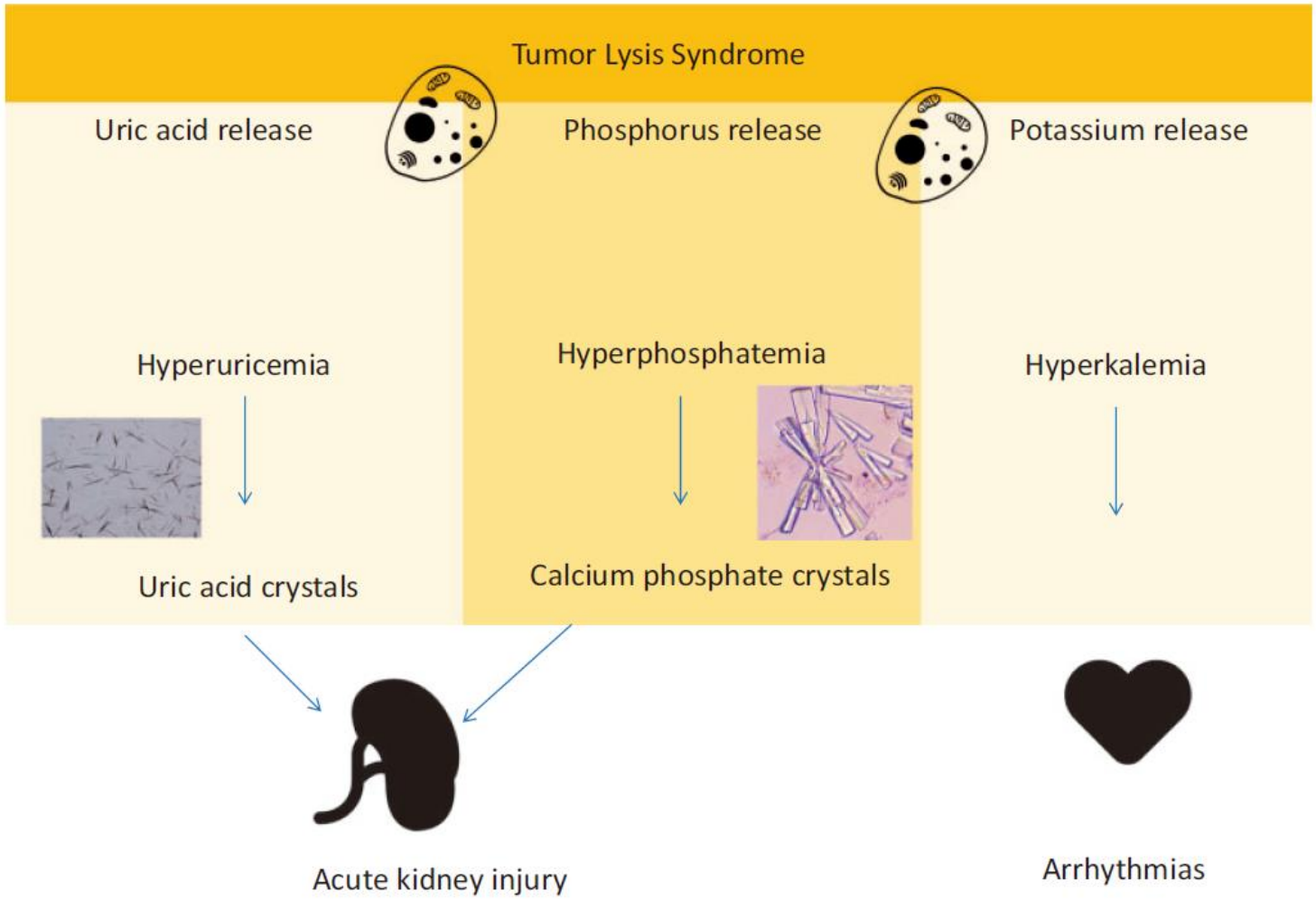
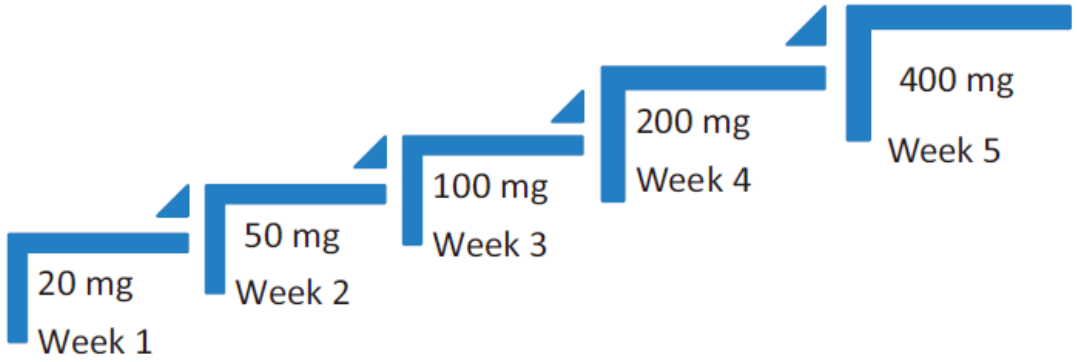
Tumor lysis syndrome



Wanchoo R et al. CKJ 2018

Venetoclax

- Anti-bcl-2 agent
- Second-line treatment for CLL (17p deletion)
- Can cause rapid-onset tumor lysis syndrome
- 6 TLS, 2 deaths during dose escalation; many TLS cases
- Other agents: dinaciclib, favopiridol, ibrutinib, idelalisib



- High risk of tumor lysis
  - Any LN > 10 cm
  - Lymphocytes > 25,000/microliter + LN > 5 cm
- First doses should be inpatient dosing
- TLS prophylaxis
- Labs at 0 4, 8, 12, and 24 h

Wanchoo R et al. CKJ 2018

Acknowledgment

- Glomerular Disease Study & Trial Consortium (GlomCon)
  - https://www.youtube.com/channel/UC7FG1vWfVQSwOcJHO35lOAg
  - https://www.youtube.com/watch?v=jqYq6kLR8Bs
  - https://www.youtube.com/watch?v=prmaujWxWYM (Dr. Kenah Jhaveri)
  - Twitter: @GlomCon