In the name of GOD

Nephrotoxicity Of Biologic Drugs

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Biologics

- ✓A substance that is made from a living organism or its products and is used in the prevention, diagnosis, or treatment of cancer and other diseases.

- ✓ **Biological products include a wide range of products such as :**
- ✓blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins **hormones**
- ✓Biological drugs include antibodies, cytokines, and vaccines

- ✓Biologic medications are drugs that target specific parts of immune system **to treat disease**.

Biologic medicines

cetuximab (Erbitux)
collagenase (Santyl)
collagenase clostridium histolyticum (Xiaflex)
daclizumab (Zenapax)
daclizumab (Zinbryta)
daratumumab (Darzalex)
darbepoetin alfa (Aranesp)
denileukin diftitox (Ontak)
denosumab (Prolia, Xgeva)
dinutuximab (Unituxin)
dornase alfa (Pulmozyme)

basiliximab (Simulect)
becaplermin (Regranex)
belatacept (Nulojix)
belimumab (Benlysta)
bevacizumab (Avastin)
bezlotoxumab (Zinplav
blinatumomab (Blincy
brentuximab vedotin (
canakinumab (Ilaris)
capromab pendetide (ProstaScint)
certolizumab pegol (Cin

aldesleukin (Proleukin)
alemtuzumab (Campath, Lemtrada)
alglucosidase alfa (Myozyme, Lumizyme)
alirocumab (Praluent)
alteplase, cathflo activase (Activase)
anakinra (Kineret)
asfotase alfa (Strensiq)
asparaginase (Elspar)
asparaginase erwinia chrysanthemi (Erwinaze)
atezolizumab (Tecentriq)

ulaglutide (Trulicity)
callantide (Kalbitor)
culizumab (Soliris)
osulfase alfa (Vimizim)
elotuzumab (Empliciti)
epoetin alfa (Epogen/Procrit
etanercept (Enbrel)
etanercept-szzs (Erelzi)
evolocumab (Repath
filgrastim (
filgras

follitropin alpha (Gonal f)
galsulfase (Naglazyme)
glucarpidase (Voraxaze)
golimumab (Simponi)
golimumab injection (Simponi Aria)
ibritumomab tiuxetan (Zevalin)
idarucizumab (Praxbind)
idursulfase (Elaprase)
incobotulinumtoxinA (Xeomin)
infliximab (Remicade)
imab-dyyb (Inflectra)

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omalizumab (Xolair)
onabotulinumtoxinA (Botox)
oprelvekin (Neumega)
palifermin (Kepivance)
palivizumab (Synagis)
panitumumab (Vectibix)
parathyroid hormone (Natpara)
pegaspargase (Oncaspar)
pegfilgrastim (Neulasta)
peginterferon alfa-2a (Pegasys)
peginterferon alfa-2b (PegIntron, Sylatron)
peginterferon beta-1a (Plegridy)
pegloticase (Krystexxa)

abatacept (Orencia)
abciximab (ReoPro)
abobotulinumtoxinA (Dysport)
adalimumab (Humira)
adalimumab-atto (Amjevita)
ado-trastuzumab emtansine (Kadcyla)
aflibercept (Eylea)
agalsidase beta (Fabrazyme)
albiglutide (Tanzeum)

interferon
interferon -2b (Intron A)
interferon alfa-n3 (Alferon N Injection)
interferon beta-1a (Avonex, Rebif)
interferon beta-1b (Betaseron, Extavia)
interferon gamma-1b (Actimmune)
ipilimumab (Yervoy)
ixekizumab (Taltz)
laronidase (Aldurazyme)
mepolizumab (Nucala)

follitropin alpha (Gonal f)
galsulfase (Naglazyme)
glucarpidase (Voraxaze)
golimumab (Simponi)
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infliximab-dyyb (Inflectra)

target specific cell types (such as B-cells or T-cells)

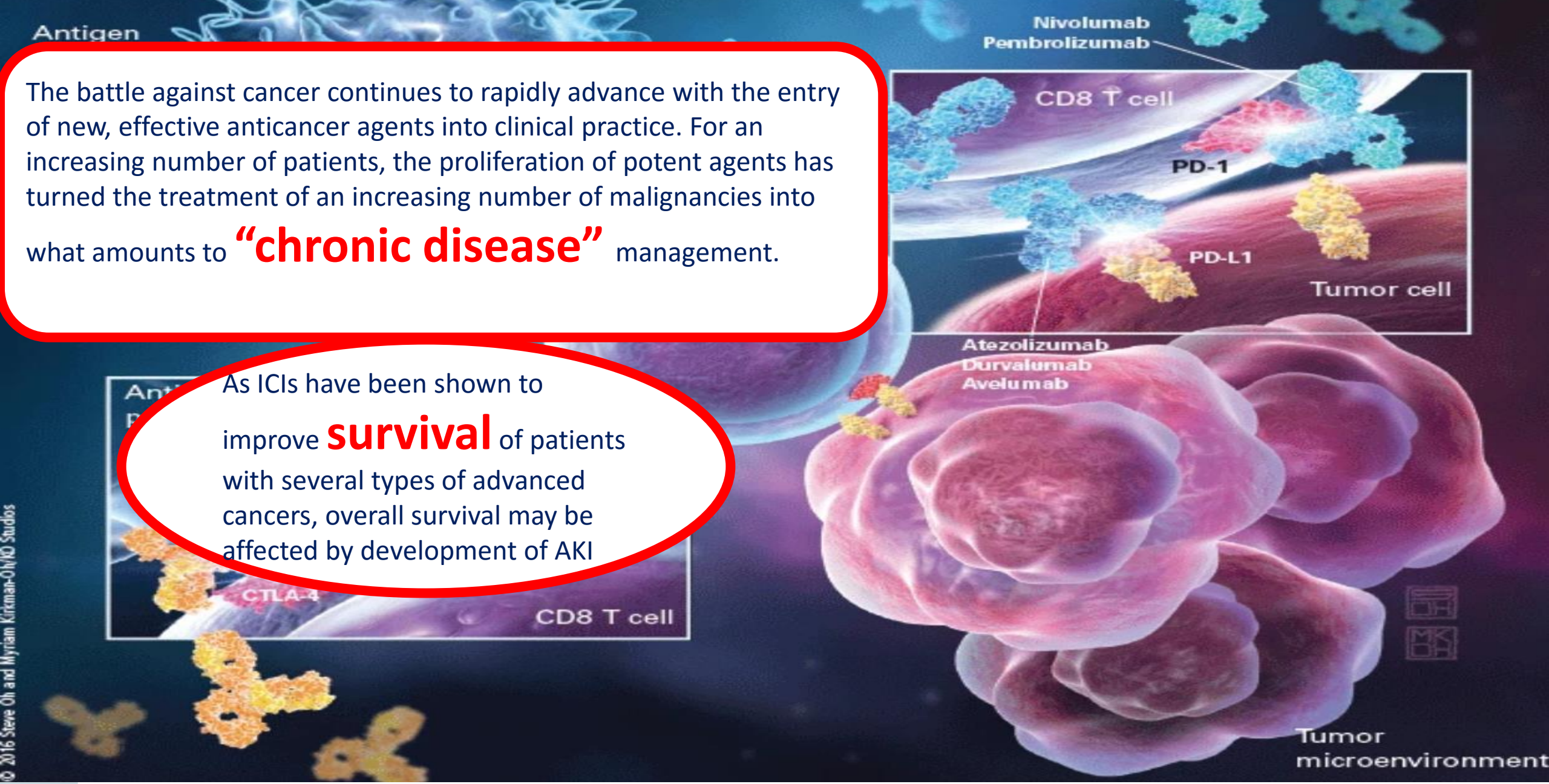
target cytokines (such as Tumour Necrosis Factor-α (TNFα) or Interleukin-6 (IL-6))

Biologics

target immunological pathway (such as complement activation or co-stimulatory signal)

They are novel agents that can target specific immune cell types, cytokines or immune pathways involved in the pathogenesis of these disorders.

Patients receive biologics mainly by injection under the skin (subcutaneously) or by intravenous infusion

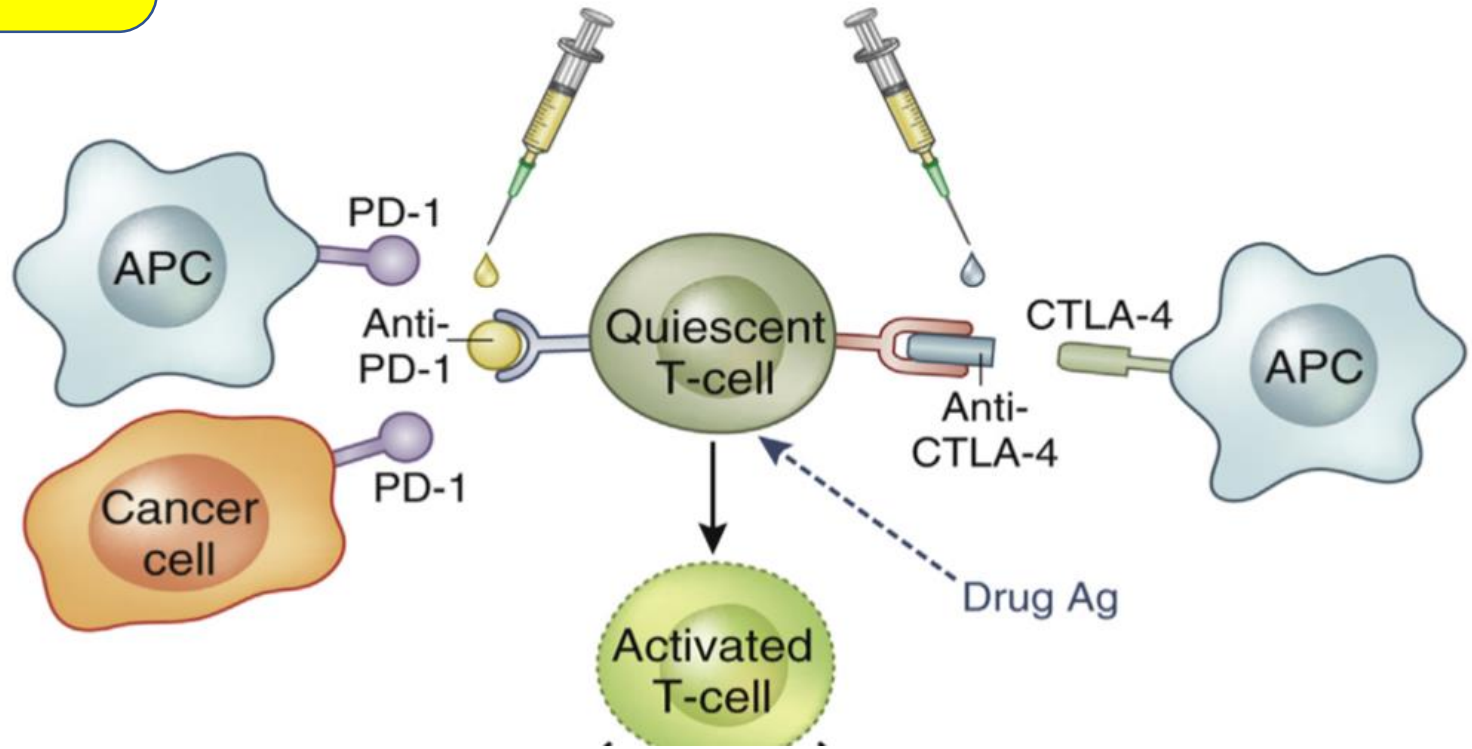


The battle against cancer continues to rapidly advance with the entry of new, effective anticancer agents into clinical practice. For an increasing number of patients, the proliferation of potent agents has turned the treatment of an increasing number of malignancies into what amounts to **"chronic disease"** management.

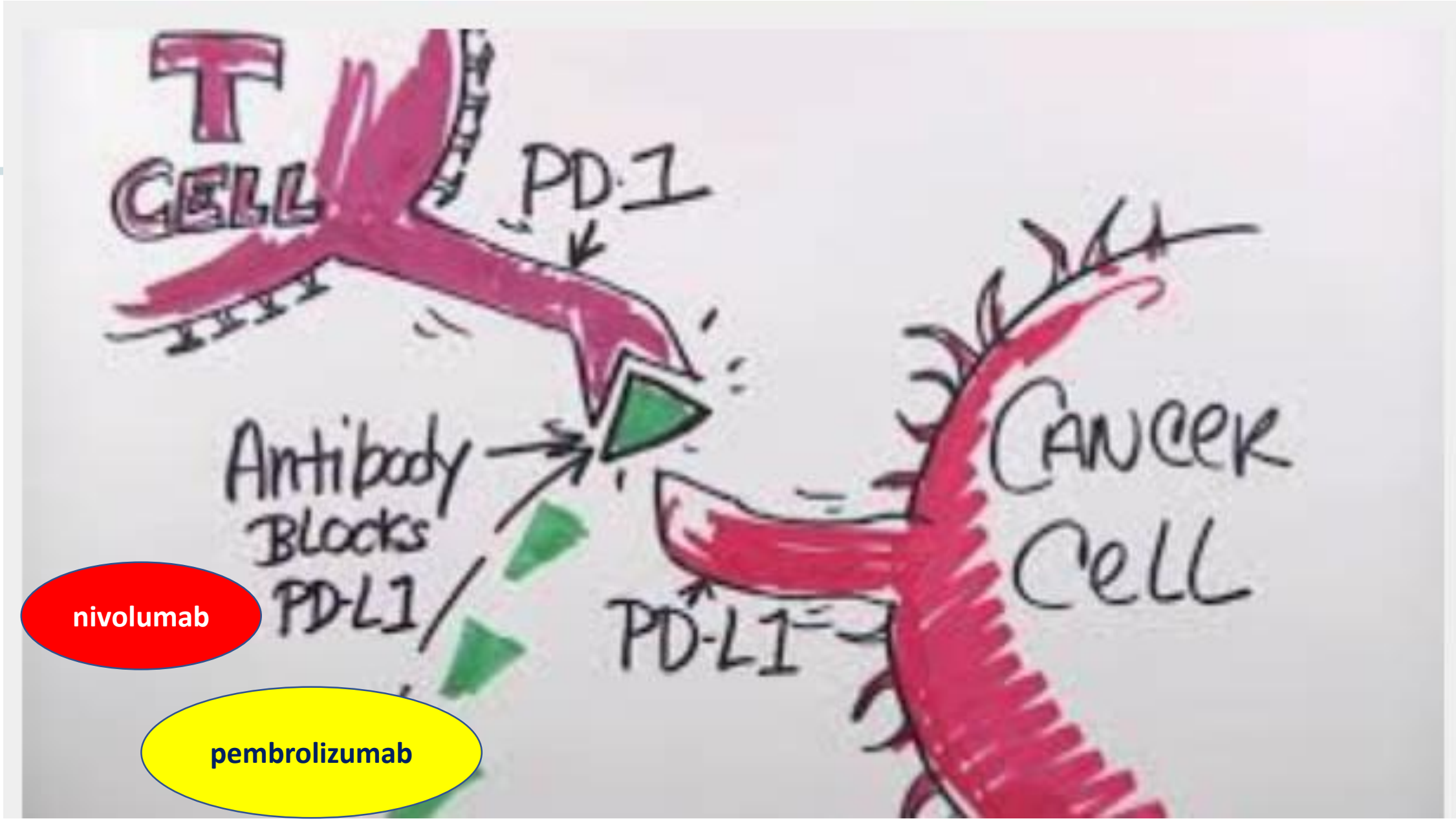
As ICIs have been shown to improve **survival** of patients with several types of advanced cancers, overall survival may be affected by development of AKI

CPIs

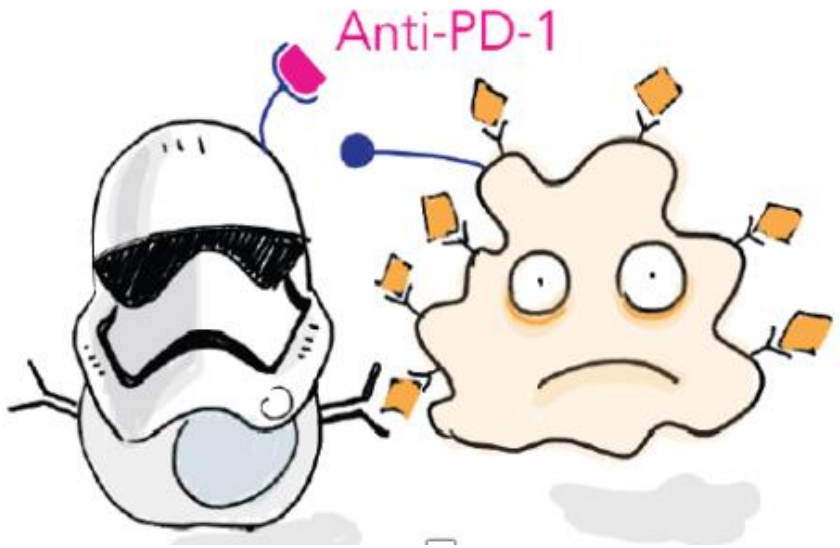
reprogram adaptive immunity



T-cells possess surface receptors such as pro- grammed death-1 protein (PD-1) and cytotoxic T lymphocyte-associated an- tigen-4 (CTLA-4), which when they are bound by ligands expressed by antigen- presenting cells down-regulate the cell. Consequently, an unwanted inflammatory response is suppressed by the action of these immune checkpoints.


T CELL
PD-1
Antibody Blocks PD-L1
PD-L1
CANCER Cell
nivolumab
pembrolizumab

Immune checkpoint inhibitors target proteins like PD-1 and PD-L1 to prevent cancer from "escaping" the immune system



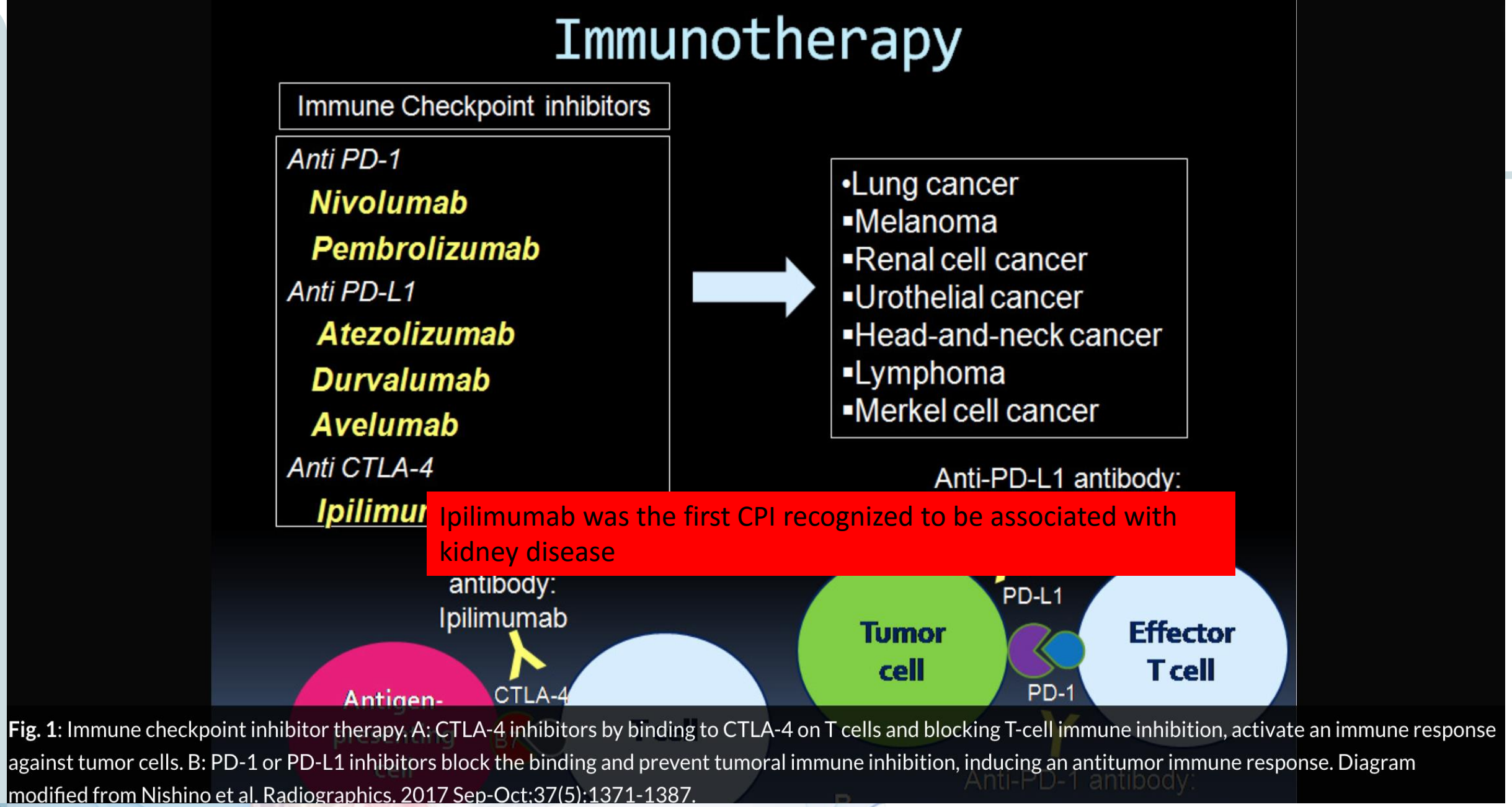
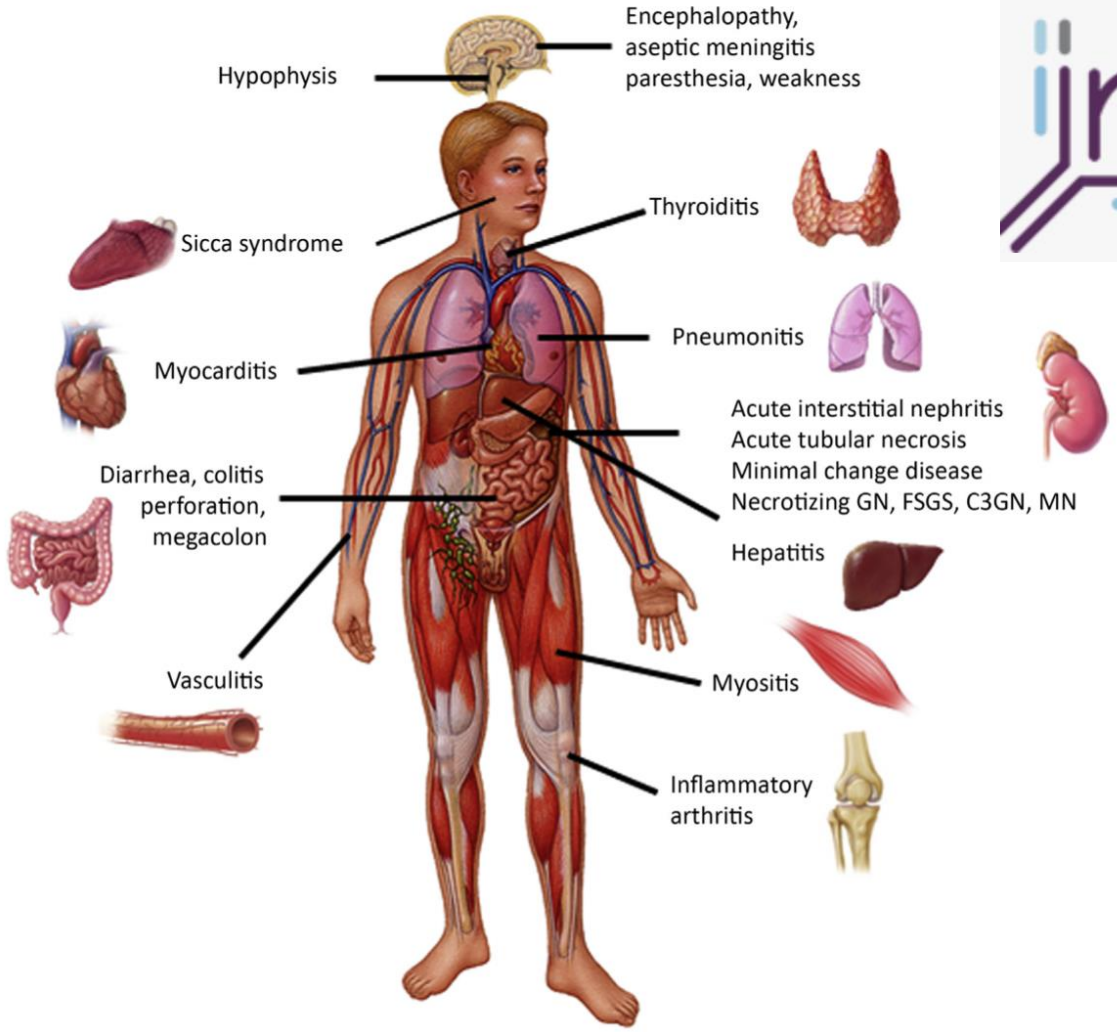


Fig. 1: Immune checkpoint inhibitor therapy. A: CTLA-4 inhibitors by binding to CTLA-4 on T cells and blocking T-cell immune inhibition, activate an immune response against tumor cells. B: PD-1 or PD-L1 inhibitors block the binding and prevent tumoral immune inhibition, inducing an antitumor immune response. Diagram modified from Nishino et al. Radiographics. 2017 Sep-Oct;37(5):1371-1387.

a potential concern of blocking immune check- points is that it risks the development of pathologic **autoimmunity** and **end organ injury.**



Immune-related adverse events. Various organs can be affected in immune-mediated injury caused by immune checkpoint inhibitors.

pneumonitis, colitis, endocrinopathies.
Now added to this list is AKI, primarily due to ATIN

AKI, proteinuria, and electrolyte abnormalities

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- ✓What Is the Incidence of ICPI-AKI?
- ✓What Are Possible Mechanisms of ICPI-AKI?
- ✓What Are the Key Clinical Features of ICPI-AKI?
- ✓What Are the Risk Factors for Development of ICPI-AKI?
- ✓Which Patients Should be Biopsied versus Treated Empirically?
- ✓What Are the Histopathologic Features of ICPI-AKI?
- ✓How Should Patients with Suspected or Confirmed ICPI-AKI be Treated?
- ✓Which Patients Can be Safely Rechallenged?

What Is the Incidence of ICPI-AKI?

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

Any AKI
17%

Sustained AKI (>48h)
6%

PD-L1 AKI
<1%

CONTEXT

INCIDENCE OF CHECKPOINT INHIBITOR RELATED AKI

CTLA4 inhibitors **2-5%**
Cortazar et al (2016)
Seethapathy et al (2019)

PD-1 inhibitors **~2%**
Cortazar et al (2016)
Seethapathy et al (2019)
Manohar et al (2019)

Combined CTLA4/PD-1 **~5%**
Cortazar et al (2016)

PD-L1 inhibitors **<1%**
Current Study

CONCLUSION:

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

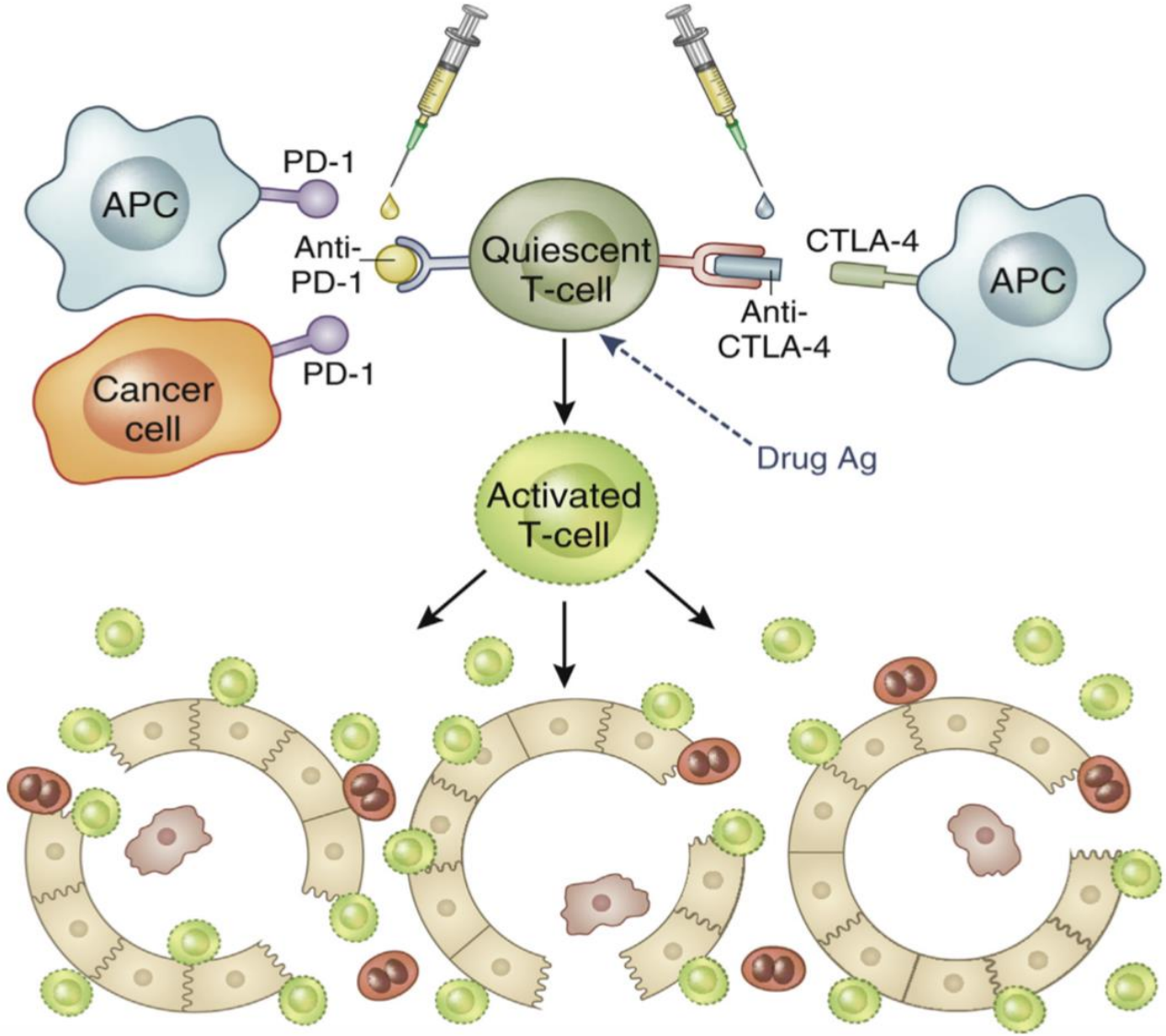
KI REPORTS
KIReports.org

Seethapathy *et al*, 2020

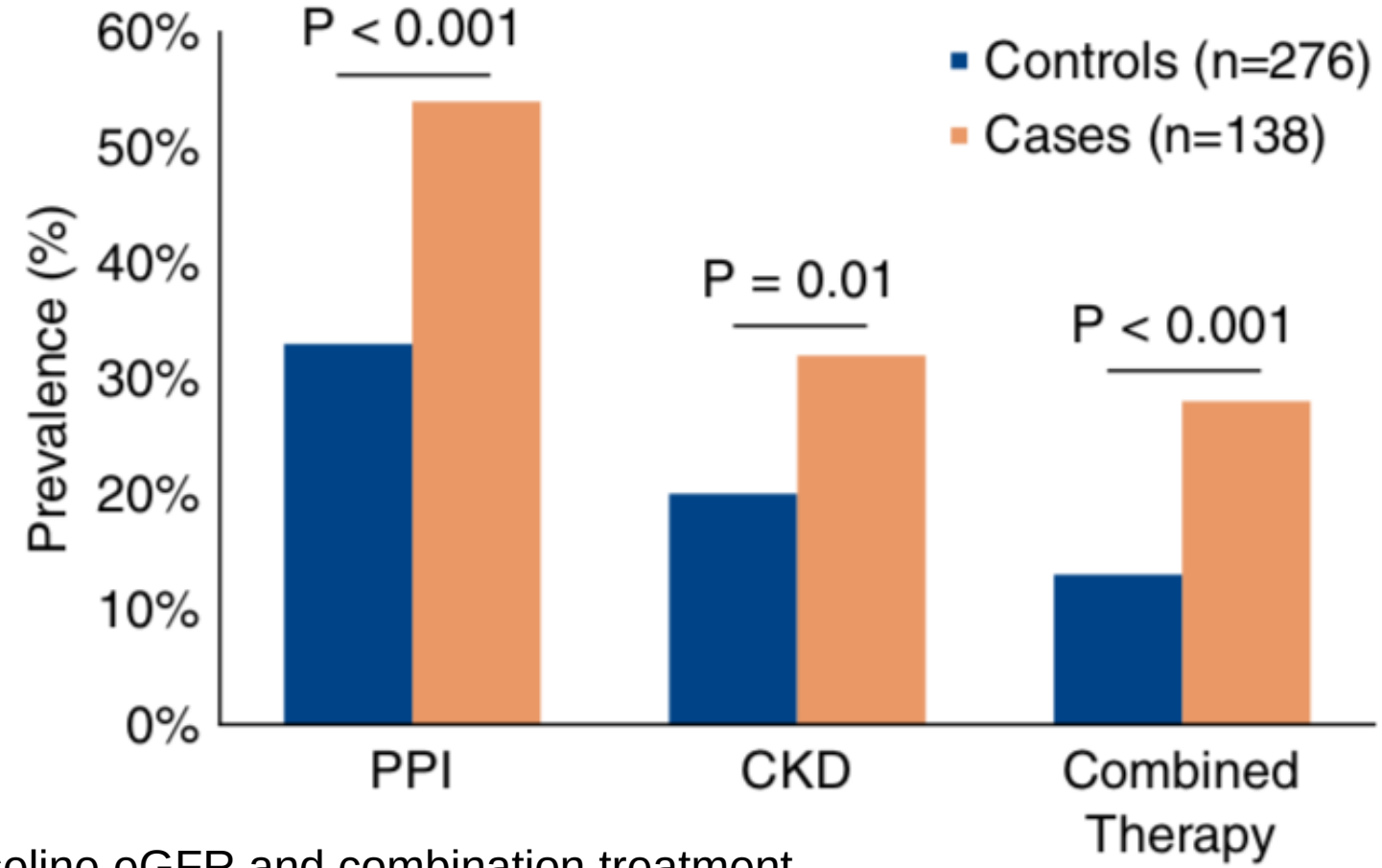
What Are Possible Mechanisms of ICPI-AKI?

Mechanisem of renal injury

CPIs disrupt CTLA-4 and PD-1 signaling that is critical to maintaining peripheral **self- tolerance**



What Are the Risk Factors for Development of ICPI-AKI?



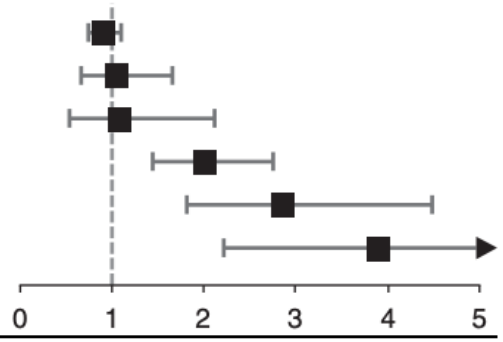
PPI use lower baseline eGFR and combination treatment with anti–CTLA-4 and anti–PD-1/PD-L1 agents are independently associated with ICPI-AKI.

Immune Checkpoint Inhibitor AKI, Gupta et al.

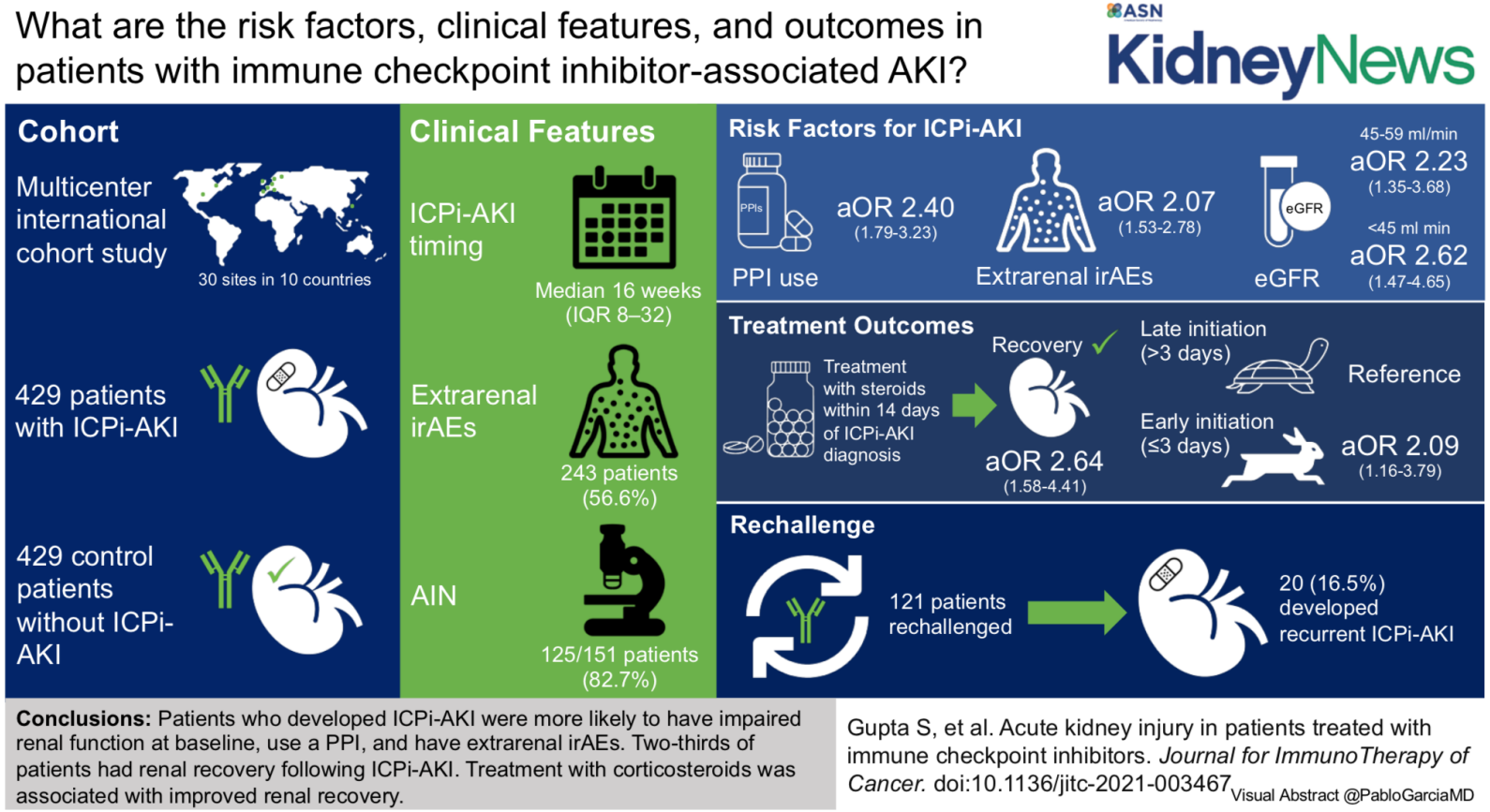
Clinical Features and Outcomes of Immune Checkpoint Inhibitor–Associated AKI: A Multicenter Study

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^2 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.



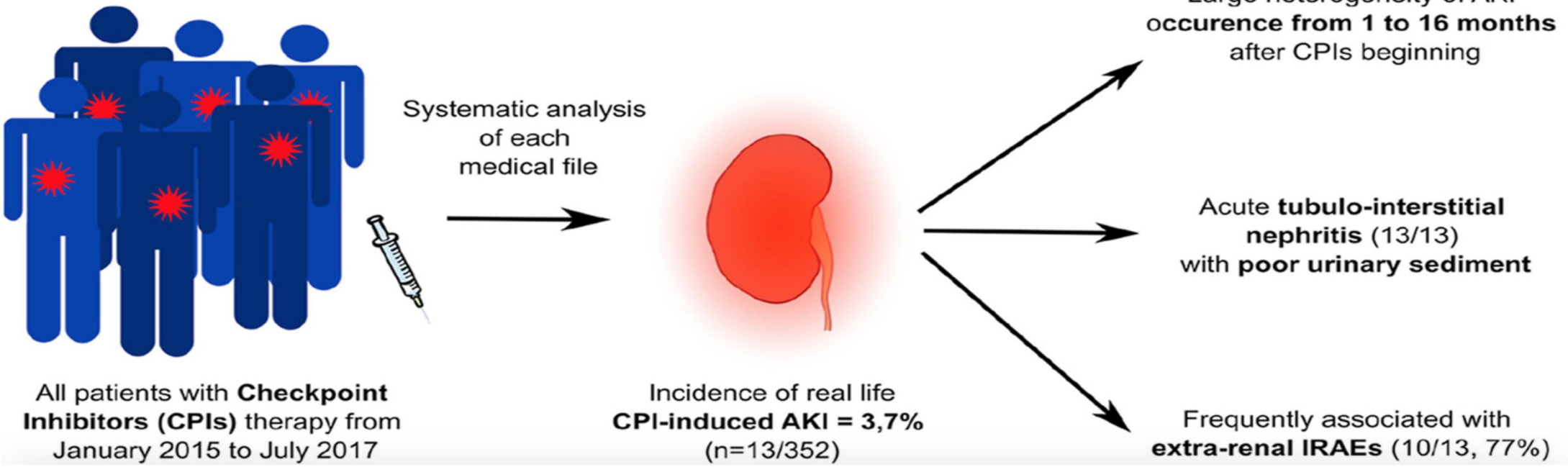
the presence of prior or coexisting irAEs was associated with a twofold higher risk of AKI.

IrAEs that develop with 1 class of immune checkpoint inhibitors (e.g., anti–CTLA-4) may not necessarily recur with exposure to another class (e.g., anti–PD-1).

What are the time of occurrence?

Renal adverse events of Immune Checkpoints Inhibitors in clinical practice : ImmuNoTox study

M.Espi, C.Teuma, E.Novel-Catin, D.Maillet, PJ.Souquet, S.Dalle, L.Koppe, D.Fouque, 2020



AKI developed at a median of approximately 3 months (range 21–245 days).

Patients should undergo some form of surveillance for the development of renal involvement while under treatment with these drugs, recognizing that occurrence of ATIN can be quite delayed (up to 18 months) after initial exposure.

(i) Observe patients for symptoms or signs of allergic reaction (i.e., rash, non-renal immune effects)
(ii) observe for eosinophilia and kidney injury (i.e., serum chemistry)
(iii) obtain urinalysis and urine microscopy checking for an active urine sediment (i.e., pyuria, hematuria, pro- teinuria) within a month of starting the drug, quarterly for the next 2 years and then every 6 months thereafter.

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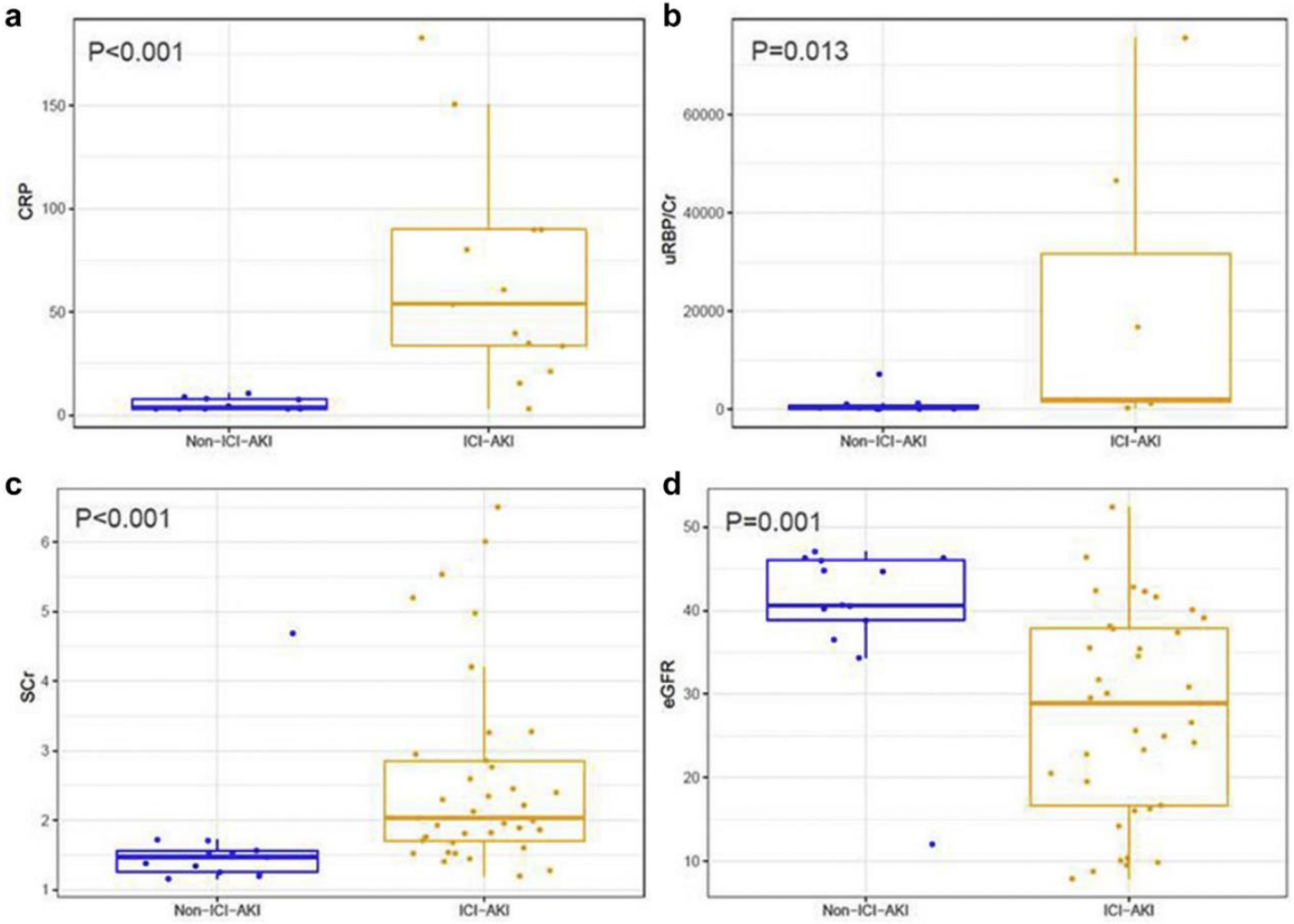
Biomarkers, Clinical Features, and Rechallenge for Immune Checkpoint Inhibitor Renal Immune-Related Adverse Events

patients with cancer treated with ICI therapy between 2014 and 2020 who developed AKI

First study to identify potential biomarkers

Conclusion: serum CRP and uRBP/Cr may help to differentiate AKI due to ICI from other causes.

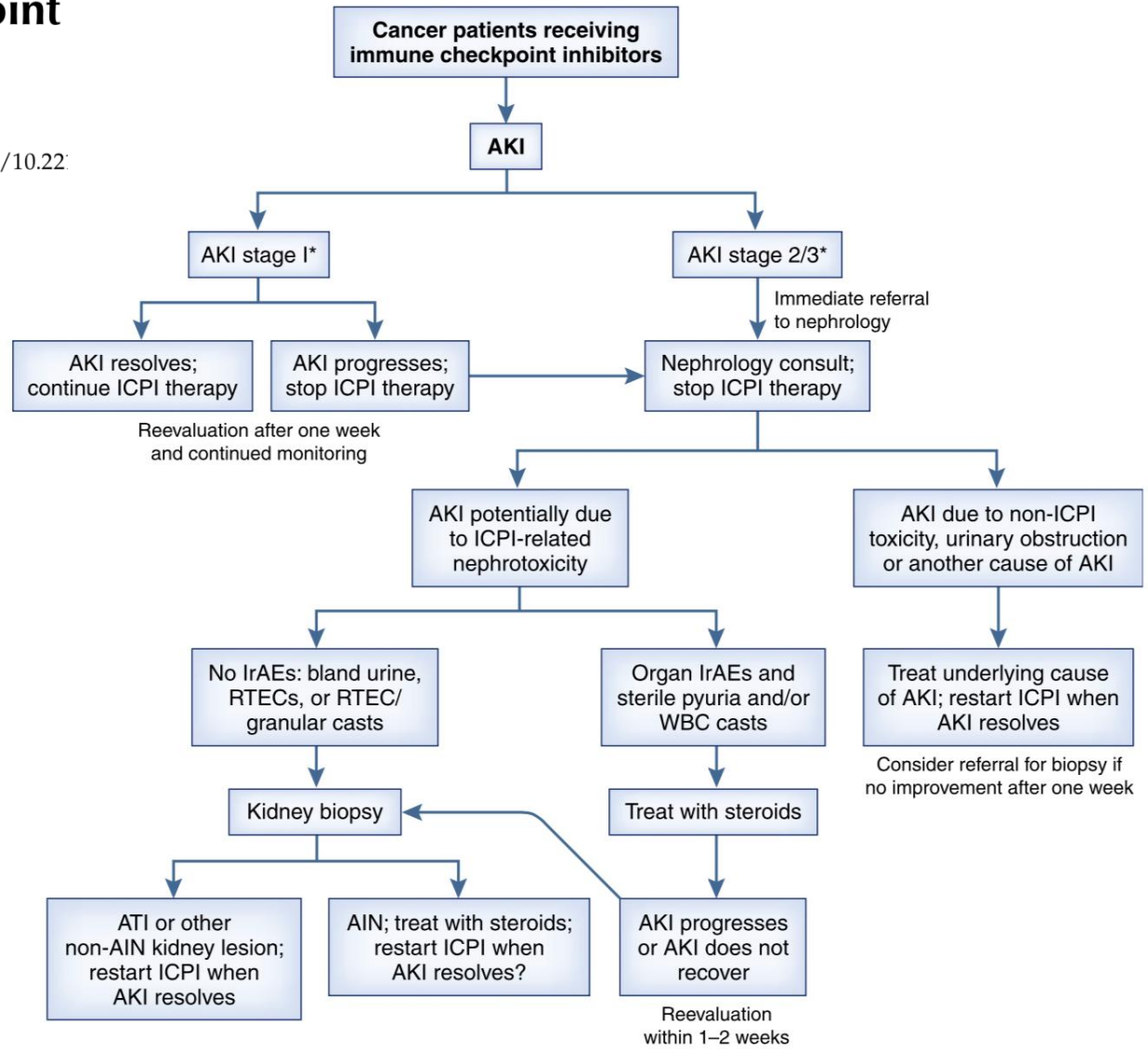


B Isik et al.: ICI-AKI Biomarkers Kidney International Reports (2021)

AKI in Patients Receiving Immune Checkpoint Inhibitors

Mark A. Perazella[1,2] *and Ben Sprangers*[3,4]

CJASN 14: 1077–1079, 2019. doi: https://doi.org/10.22



Algorithm for management of patients with cancer and AKI in the setting of immune checkpoint inhibitor therapy

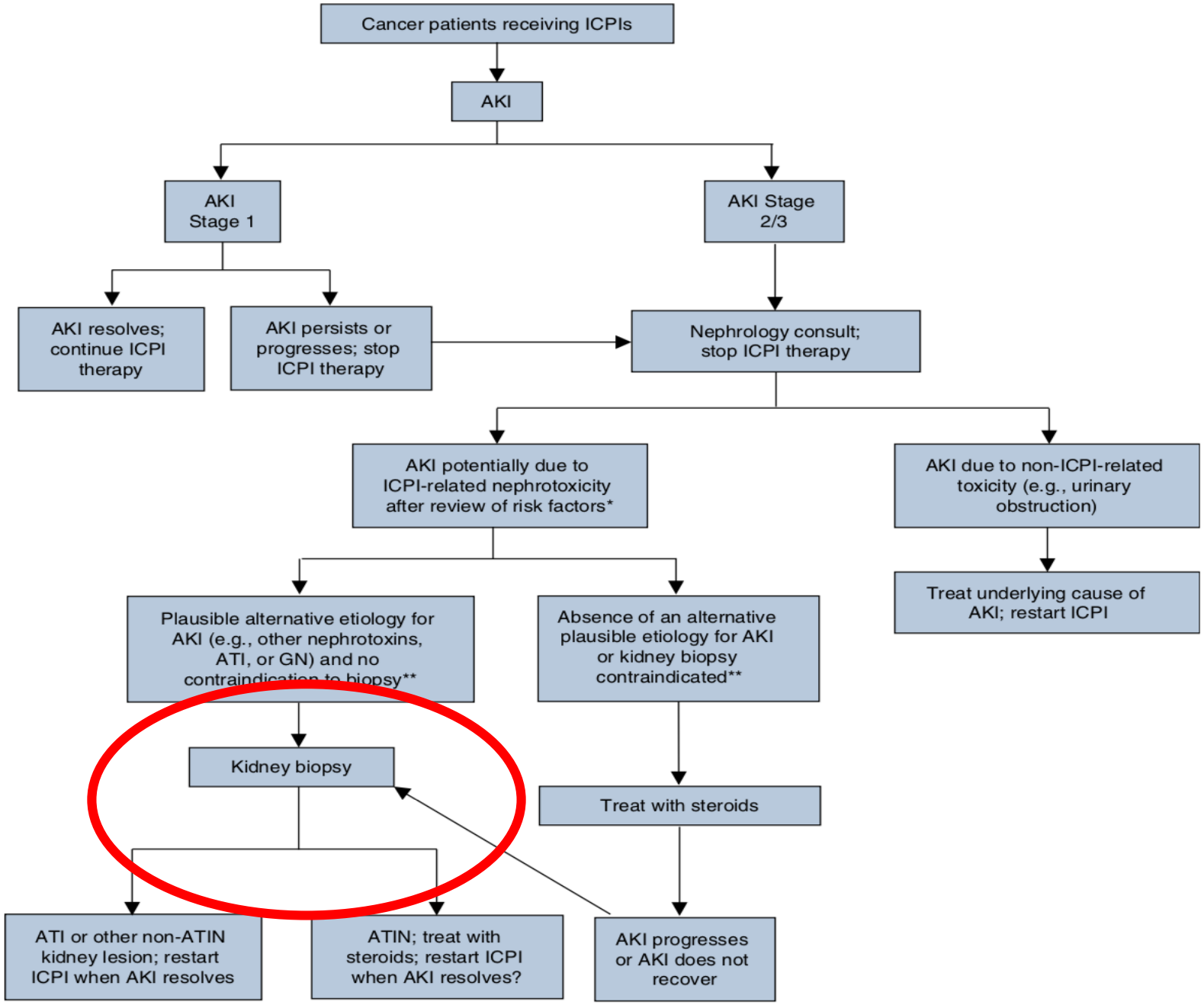
Which Patients Should be Biopsied versus Treated Empirically?

Review Article

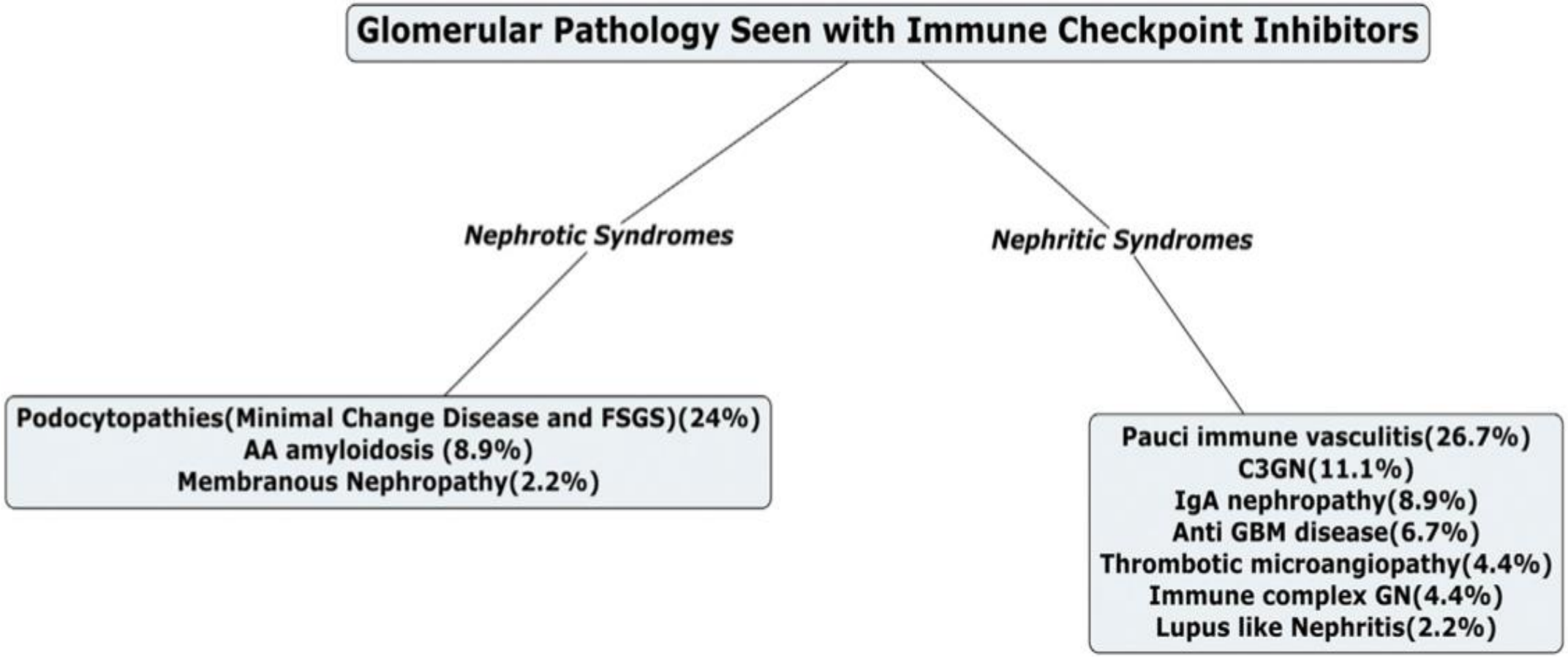
Immune Checkpoint Inhibitor Nephrotoxicity: Update 2020

Shruti Gupta,[1] Frank B. Cortazar,[2,3] Leonardo V. Riella,[1] and David E. Leaf[4]

- absence of an alternative etiology for AKI
- those with an absolute con traindication to kidney biopsy (e.g., solitary kidney, uncontrolled hypertension, or anticoagulation that cannot be safely held)



What Are the Histopathologic Features of ICPI-AKI?



A Kitchlu et al.: Immune Checkpoint Inhibitor–Associated Glomerular Disease

Immune checkpoint inhibitor nephrotoxicity: what do we know and what should we do?

Mark A. Perazella[1,2] and Anushree C. Shirali[1]

Table 2 | Kidney biopsy results in patients treated with immune checkpoint inhibitors[48–69]

Immune checkpoint inhibitor (n)	ATIN alone or with ATI (n)	ATIN + glomerular disease (n)	Glomerular disease (n)	ATI alone (n)	Other lesions (n)
Ipilimumab (n = 13)	ATIN (9)	MCD (1)	SLE-like MGN (1) MCD (1)		TMA (1)
Nivolumab (n = 20)	ATIN (11) ATIN/ATI (1)	FNGN (1) MGN (1) FSGS (1)	FSGS (1) IgAN (1) IgAN/ATI (1)	ATI (1)	IFTA/GScl (1)
Pembrolizumab (n = 27)	ATIN (12) ATIN/ATI (1)	IgAN (1) C3GN (1) AA amyloid (1)	MCD (2) MCD/ATI (2)	ATI (6)	NF (1)
Atezolizumab (n = 1) Tremelimumab (n = 1)	ATIN (1)	FNGN (1)			
Ipilimumab + nivolumab (n = 8)	ATIN (5) ATIN/ATI (1)	GPA (1) IgAN (1)			
Total (n = 70)	41	10	9	7	3

A Systematic Review of Immune Checkpoint Inhibitor-Associated Glomerular Disease

METHODS

Systematic review and meta-analysis

27 Studies

45 Cases of biopsy-proven ICI-associated glomerular diseases

HISTOPATHOLOGY

27% (12) Pauci-immune glomerulonephritis and renal vasculitis

24% (11) Podocytopathies

11% (5) C3 glomerulonephritis (C3 GN)

OUTCOMES

Recovery from AKI

31% Full recovery

42% Partial recovery

Remission of proteinuria

45% Complete Remission

38% Partial Remission

Dialysis dependence and death

19% Dialysis Dependence

34% Died

CONCLUSION:

Pauci-immune glomerulonephritis, podocytopathies and C3GN are the most frequently reported ICI-associated glomerular lesions and may be associated with poor kidney and mortality outcomes.

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Kitchlu, Kidney Int Rep.

Treatment

✓If the clinical picture strongly suggests ATIN or more preferably kidney biopsy demonstrates this lesion, **steroid administration** should be considered to suppress renal inflammation and reverse kidney injury.

early recognition is important to avoid development of significant tubulointerstitial **fibrosis**

Perazella ,Kidney International (2016)

Glucocorticoids are the mainstay of treatment for ICPI- AKI

- ✓ Although no randomized placebo-controlled trial has ever established the efficacy of steroids for treat- ment of ICPI-AKI, observational data supporting the efficacy of steroids in this setting are quite strong: in our multicenter study, 103 of 119 patients (87%) treated with steroids had complete or partial renal recovery

Prednisone 1 mg/kg daily as a starting dose, with a slow taper over 2–3 months

In patients with severe ICPI-AKI requiring intravenous steroids (e.g., methyl- prednisolone 250–500 mg daily for 3 days) may be used as initial therapy.

Other immunosuppressive agents

- ✓Mycophenolate mofetil
- ✓ Rituximab
- ✓Cyclophosphamide
- ✓Infliximab

New Data Highlight Acute Kidney Injury Associated with Immune Checkpoint Inhibitors

Reinitiation

Reinitiation of CPI therapy may be possible if steroid therapy is associated with renal recovery, but there is insufficient information to allow a definitive recommendation as the potential for kidney injury remains.

Last, and some- what surprising, was that rechallenge of patients who had AKI with immune checkpoint inhibitors was only associated with recurrent AKI in less than 20% of cases.

outcome

Outcomes of AKI associated with immune checkpoint inhibitors demonstrated that approximately two-thirds of patients had renal recovery, and this was associated with early initiation of corticosteroids.