ONCONEPHROLOGY:
OVERVIEW, CASES AND RESEARCH IN PROGRESS

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RENAL PHARMACISTS NETWORK EDUCATION DAY
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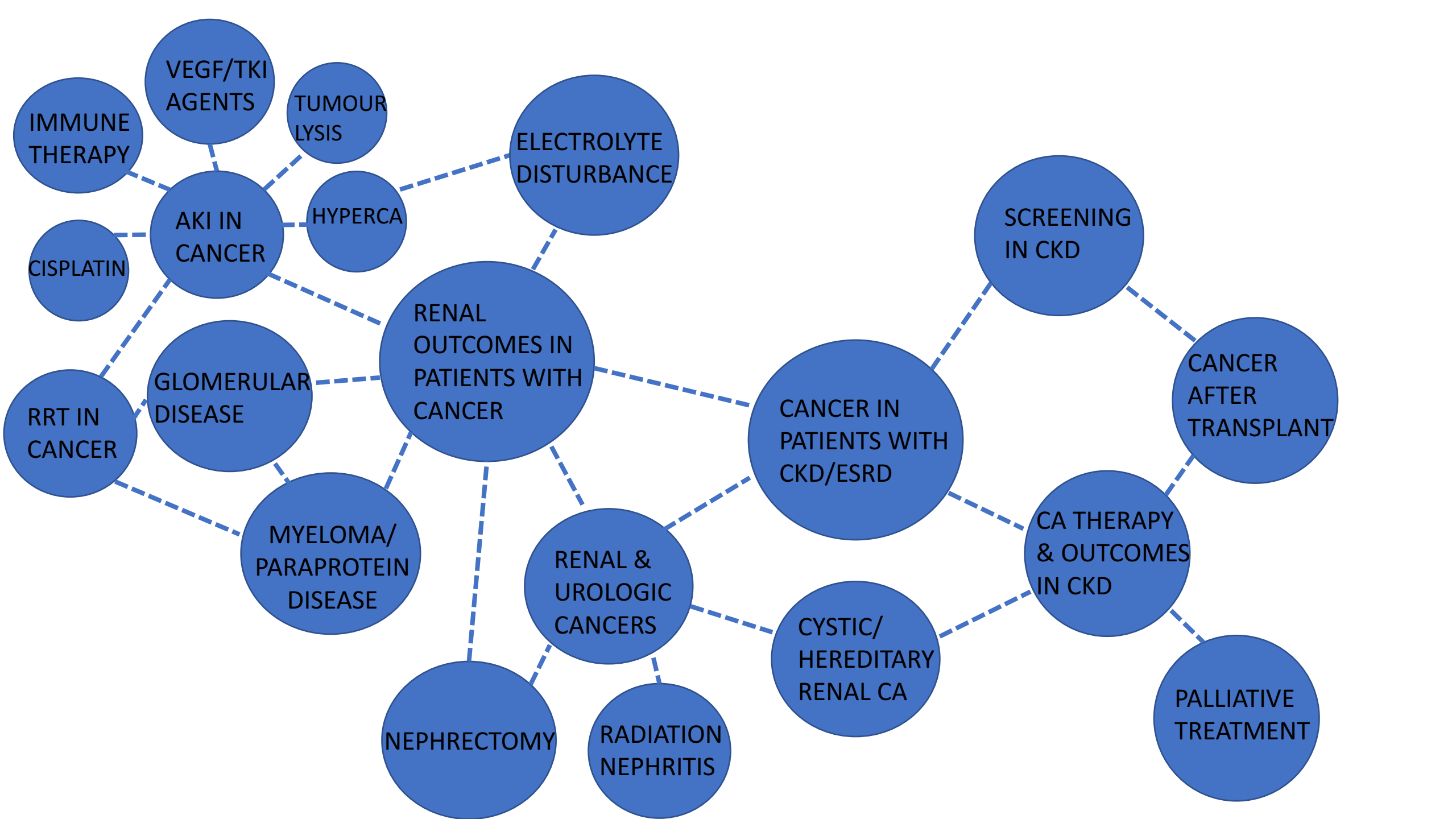
DISCLOSURES

- No conflicts of interest to declare
- A few caveats though – there will be:
  - Shameless plugging of our local work
  - Solicitation of guidance/input on future directions
  - Reminders: early days yet (18 months in – ‘Research *in Progress*’)

OUTLINE

- OVERVIEW OF ONCONEPHROLOGY
- KIDNEY INJURY IN PATIENTS WITH CANCER
  - CASES: TOXICITIES OF NOVEL THERAPIES
    - IMMUNOTHERAPIES, ANTI-ANGIOGENESIS AGENTS
  - EPIDEMIOLOGY
- CANCER IN PATIENTS WITH CHRONIC KIDNEY DISEASE
  - CANCER SCREENING
  - REPRESENTATION OF CKD PATIENTS IN CANCER TRIALS
- SUMMARY
- QUESTIONS


VEGF/TKI AGENTS
IMMUNE THERAPY
TUMOUR LYSIS
ELECTROLYTE DISTURBANCE
AKI IN CANCER
HYPERCA
CISPLATIN
RENAL OUTCOMES IN PATIENTS WITH CANCER
GLOMERULAR DISEASE
RRT IN CANCER
MYELOMA/ PARAPROTEIN DISEASE
CANCER IN PATIENTS WITH CKD/ESRD
SCREENING IN CKD
CANCER AFTER TRANSPLANT
CA THERAPY & OUTCOMES IN CKD
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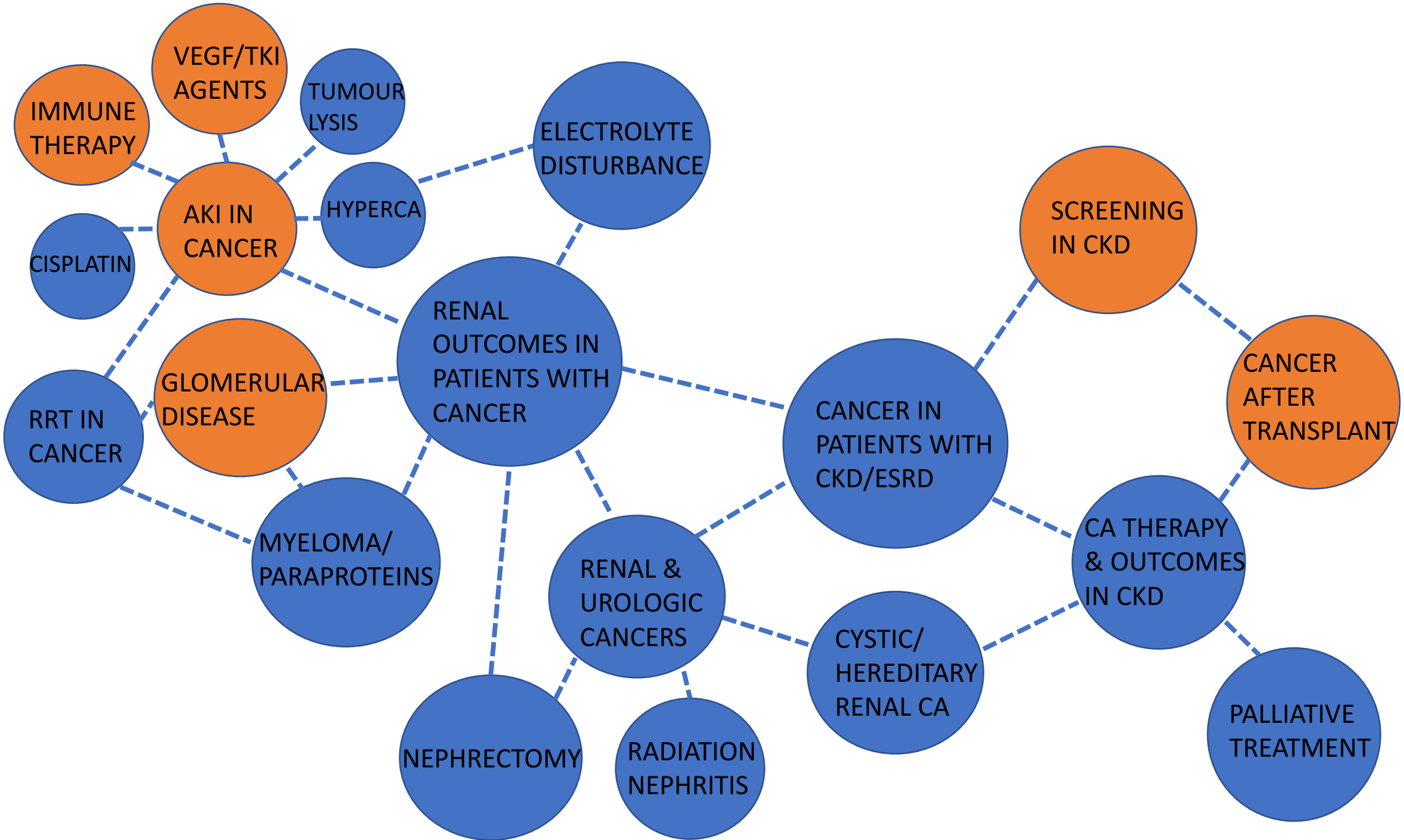
RADIATION NEPHRITIS
PALLIATIVE TREATMENT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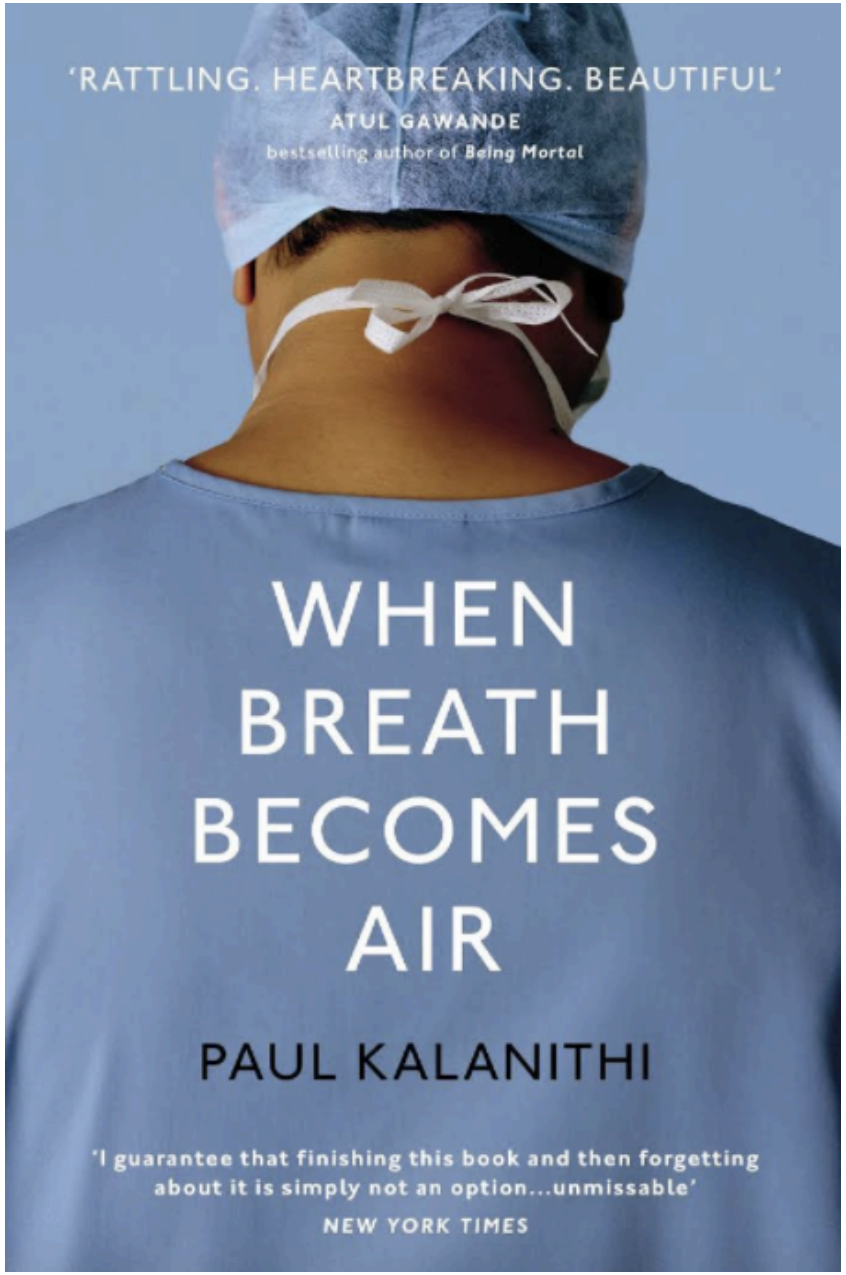


CASE '0'

"Paul Kalanithi's memoir, When Breath Becomes Air, written as he faced a terminal cancer diagnosis, is inherently sad. But it's an emotional investment well worth making: a moving and thoughtful memoir of family, medicine and literature."
—*The Washington Post*

36 yo M, metastatic NSCLC – treated with targeted therapy – developed AKI and decreased performance status → palliated and died

AKI IN PATIENTS WITH CANCER: NEPHROTOXICITY CASES

"My kidneys began to fail…my serum sodium reached a near-fatal level. The nephrologists disagreed with the ICU doctors, who disagreed with the oncologists, who disagreed with the endocrinologists…."

-- Paul Kalanithi, 'When Breath Becomes Air'

IMMUNOTHERAPY – CASE 1

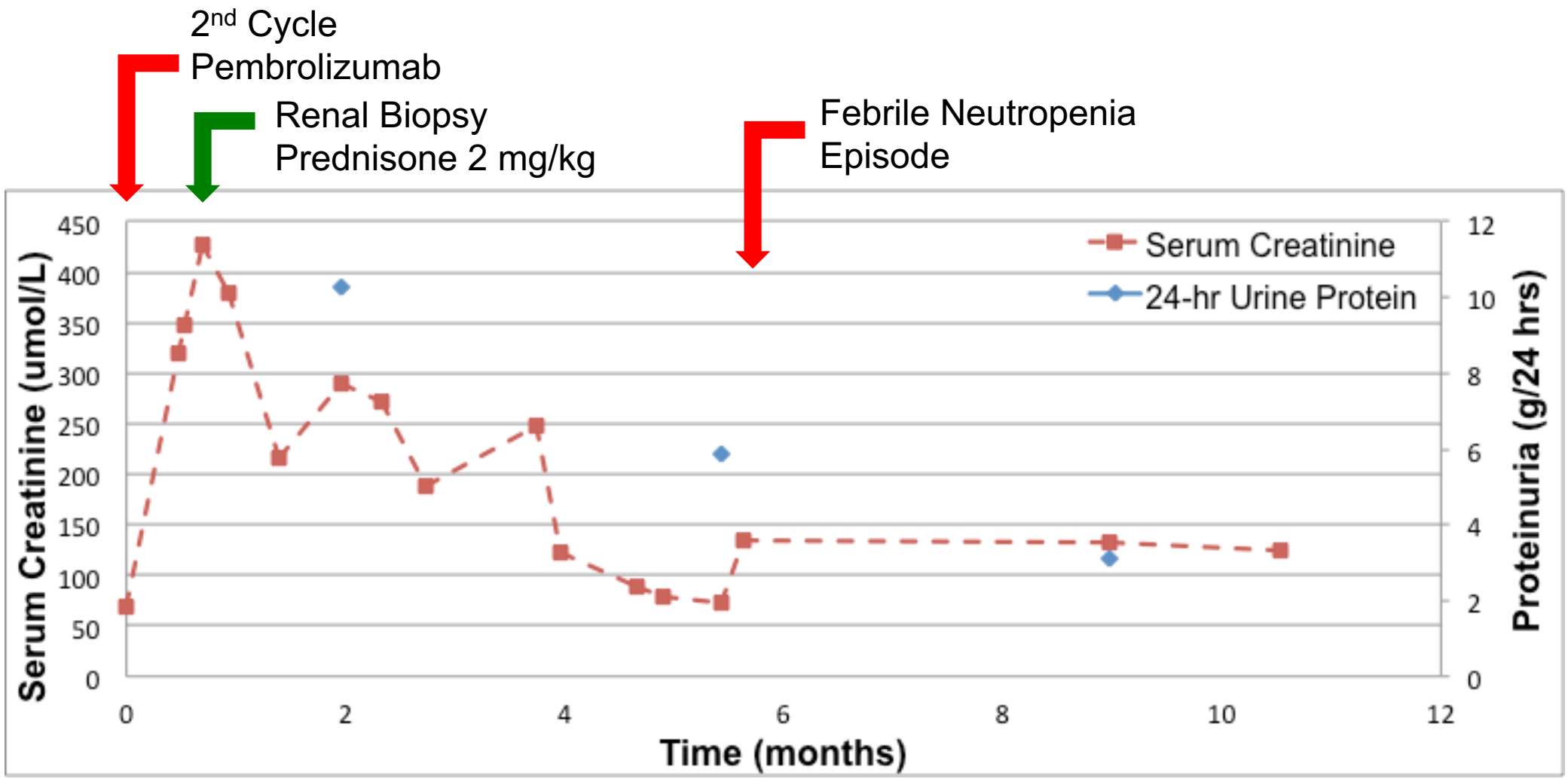
- **CASE 1:** 43 year old male, received 'anti PD-1 antibody', **pembrolizumab**, after a 9-year history of Hodgkin's lymphoma.
- Following 2nd dose: edema and nephrotic syndrome

- Investigations:
  - hypoalbuminemia (18 g/L)
  - nephrotic range proteinuria (10.3 g/day)
  - acute kidney injury (sCr 431 µmol/L)
  - Inflammatory serologies, SPEP/UPEP negative.

- Renal biopsy showed diffuse foot process effacement and mild acute tubular injury **(MINIMAL CHANGE DISEASE + ATN)**

Kitchlu *et al.* [Abstract] J Am Soc Neph 27, 2016: 374A *Manuscript accepted to AJKD*

IMMUNOTHERAPY – CASE 1



Kitchlu *et al.* [Abstract] J Am Soc Neph 27, 2016: 374A

IMMUNOTHERAPY – CASE 2

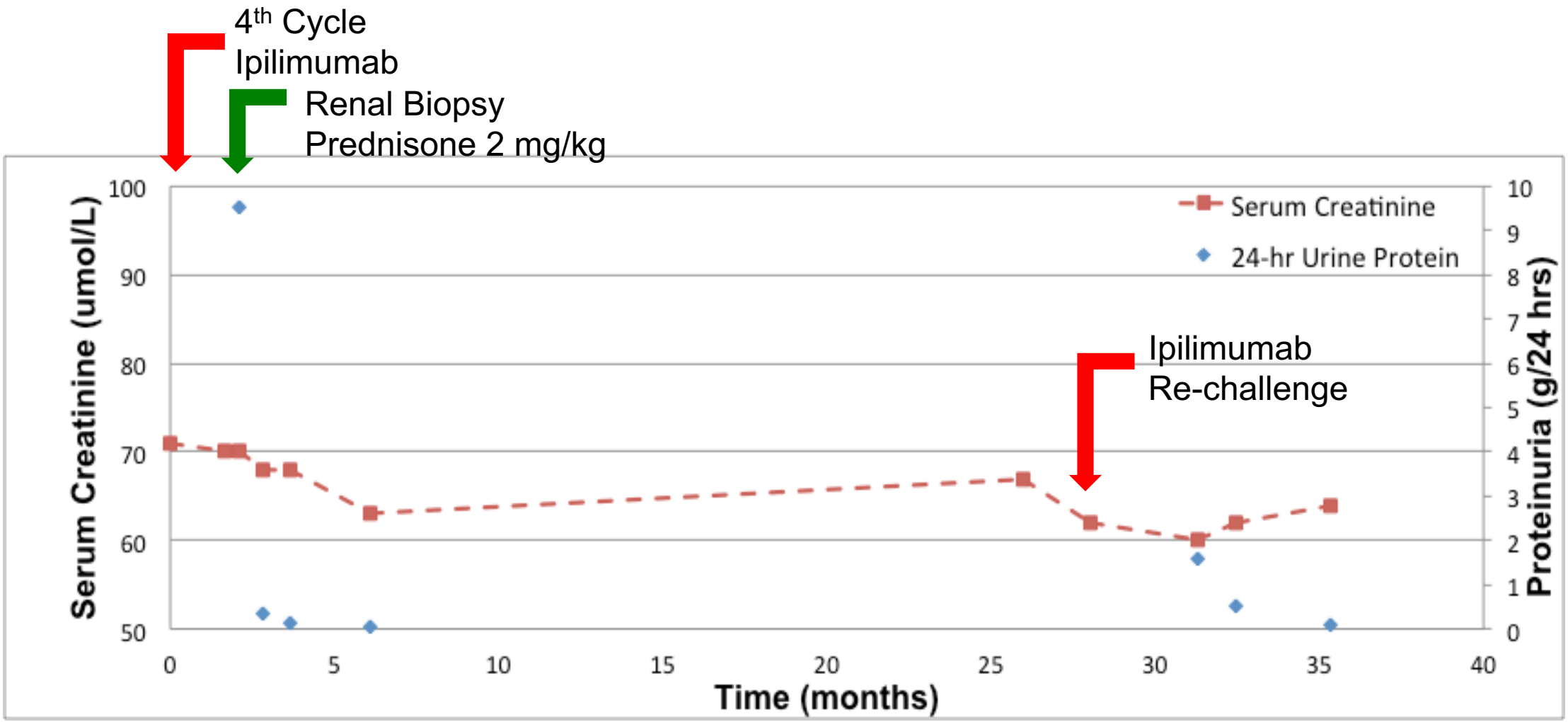
- **CASE 2:** 45 year old male with melanoma refractory to temozolamide and sorafenib who received the CTLA-4 antibody **ipilimumab**.

- Following four cycles: anasarca and nephrotic syndrome
- Laboratory findings:
  - hypoalbuminemia (26 g/L)
  - proteinuria of 9.5 g/day and
  - normal kidney function (sCr 79 µmol/L)

- Biopsy was again compatible with **minimal change disease (MCD)** Ipilimumab was stopped and proteinuria resolved following treatment with corticosteroids. Two years later ipilimumab restarted as salvage therapy

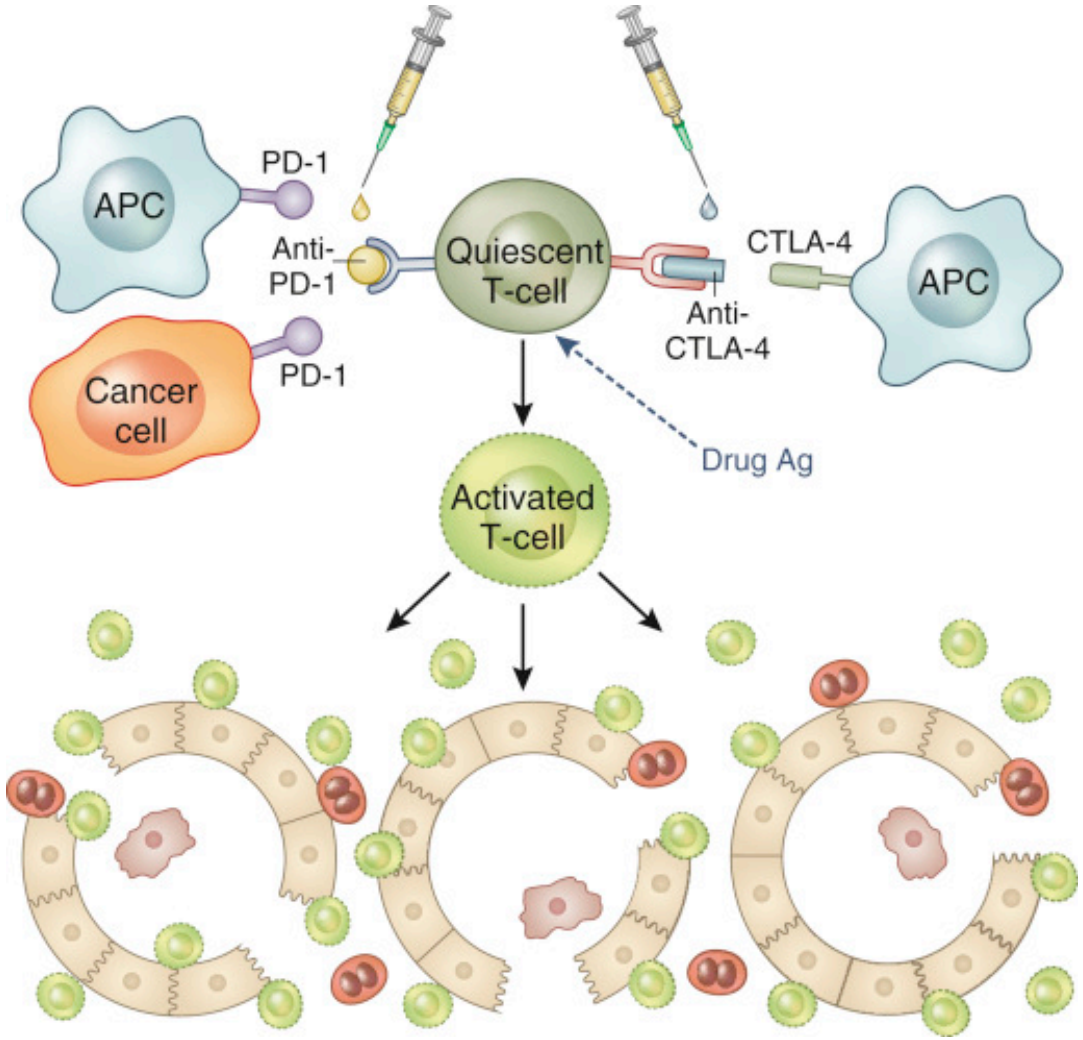
Kitchlu *et al.* [Abstract] J Am Soc Neph 27, 2016: 374A

IMMUNOTHERAPY – CASE 2



Kitchlu *et al.* [Abstract] J Am Soc Neph 27, 2016: 374A

IMMUNOTHERAPY: MECHANISM

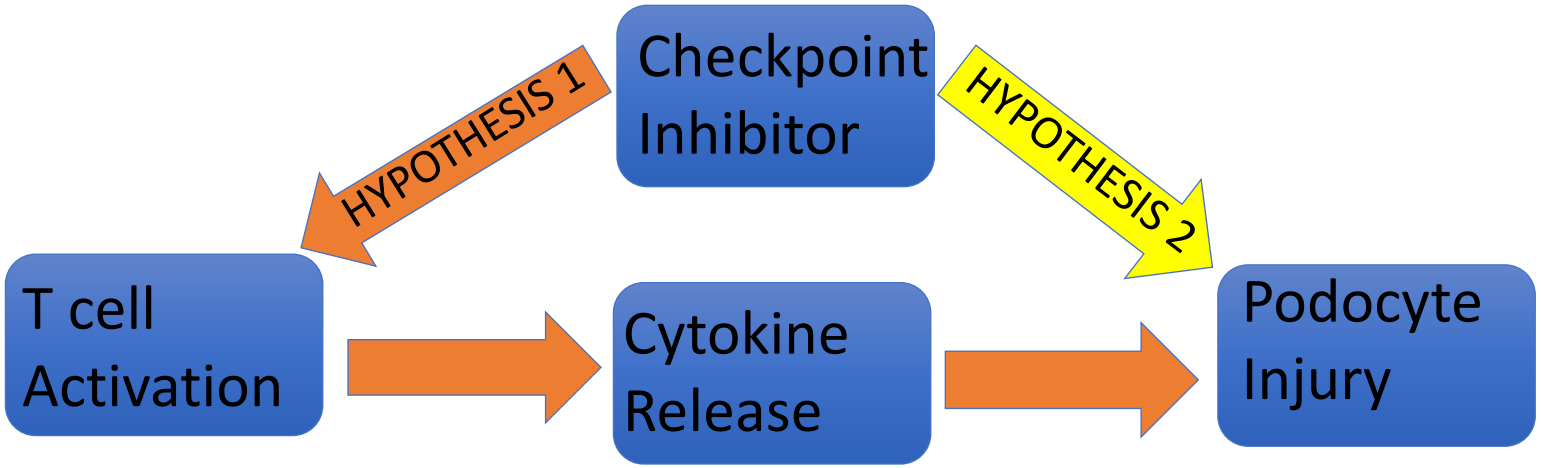


- Checkpoints on T-cell activation pathway
  - CTLA-4 (Ipilimumab)
  - PD-1/PD-L1 (Pembrolizumab)
- Dampen the immune response/prevent autoimmunity
- Inhibitors 'release the brakes' on immune response → increase T cell activation to target cancer cells

Perazella MA. Kidney Int. 2016. 90(3) 637-648.

IMMUNOTHERAPY: MINIMAL CHANGE DISEASE

- PODOCYTE INJURY MECHANISMS?
  - 1) Does T cell activation cause production of a 'permeability factor'?
    - T cell cytokines (?IL6-type) → disrupt glomerular barrier → podocyte injury
  - 2) Is there a more direct effect of Anti-CTLA-4/PD-1 on the podocyte?
    - Podocytes are known to express CD80/B7-1 (the ligand for CTLA-4/PD-1) → does inhibition destabilize podocytes?



IMMUNOTHERAPY: OTHER RENAL EFFECTS

- Checkpoint Inhibitor-associated AKI:
  - 9 case reports of **Acute Interstitial Nephritis** (2009 – 2015)
  - Case series of 13 patients at 7 US centers (2016); median (IQR) sCr peak: 396 µmol/L (319 – 642), 4 requiring dialysis (2 dialysis-dependent)

Cortazar *et al.* Kidney Int. 2016: 90(3), 637-48

IMMUNOTHERAPY: RENAL EFFECTS

Table 2| Clinical features of CPI-induced AKI

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		0.48	91	21				R 12.0, L 12.8	4.5		
IQR		0.24–0.73	60–183	18–49				R 10.9–12.8 L 11.9–13.1	3.6–7.3		

Pyuria/hematuria +/- WBC casts

Subnephrotic Proteinuria

2-8 weeks from last dose

Cortazar *et al.* Kidney Int. 2016: 90(3), 637-48

IMMUNOTHERAPY: SAFETY

- Immune-related adverse events (IRAEs):
  - Rash/vitiligo (40-50%)
  - diarrhea/colitis (2-9%)
  - hepatitis (<10%)
  - pneumonitis (<10%)
  - pancreatitis (<5%)
  - anemia/neutropenia (<5%)
  - neurologic (paresthesias, aseptic meningitis, Guillain-Barre Syndrome) (<5%)

Friedman CF *et al*. JAMA Oncol. 2016;2(10):1346-1353.

IMMUNOTHERAPY: RENAL EVENTS

- Incidence of AKI?
  - Analysis of phase II/III studies reporting renal outcomes (N = 3,695): AKI in 2.2%; combined ipilimumab + nivolumab: AKI in 4.9%
  - Single US center review of 99 with available sCr – AKI in 29%!

  - Risk factors are unknown
    - Combined immunotherapy, Dose/Frequency?
    - Specific cancers (melanoma)? Other comorbidities?

Cortazar *et al.* Kidney Int. 2016: 90(3), 637-48
Hirsch *et al.* [Abstract] J Am Soc Neph 27, 2016: 761A

IMMUNE CHECKPOINT INHIBITORS

Drug (Trade Name)	Pathway	Health Canada Approval (in trials)
Nivolumab (Opdivo)	Monoclonal Ab (IgG4) to PD-1	Metastatic Melanoma, NSCLC, Renal Cell Carcinoma, (Hodgkin's Lymphoma)
Pembrolizumab (Keytruda)	Monoclonal Ab (IgG4) to PD-1	Metastatic Melanoma, NSCLC, (Head and Neck, Triple-Negative Breast, Urothelial Cancers)
Ipilimumab (Yervoy)	Monoclonal Ab (IgG1) to CTLA-4	Metastatic Melanoma, (NSCLC, Prostate, Bladder Cancer)

NOVEL AGENTS: CASE 3

- **CASE 3:** 39 year old female, metastatic mesothelioma treated with decortication, **pembrolizumab** and **aflibercept**

- Following 5th cycle: frothy urine - urinalysis 3 g/L protein, trace blood
- Investigations:
  - hypoalbuminemia (32 g/L),
  - proteinuria (2.58 g/day)
  - preserved kidney function (creatinine 69 mg/L)
  - Serologic work-up negative.

- Renal biopsy showed chronic endothelial damage and thrombotic microangiopathy (TMA) – consistent with VEGF inhibitor toxicity

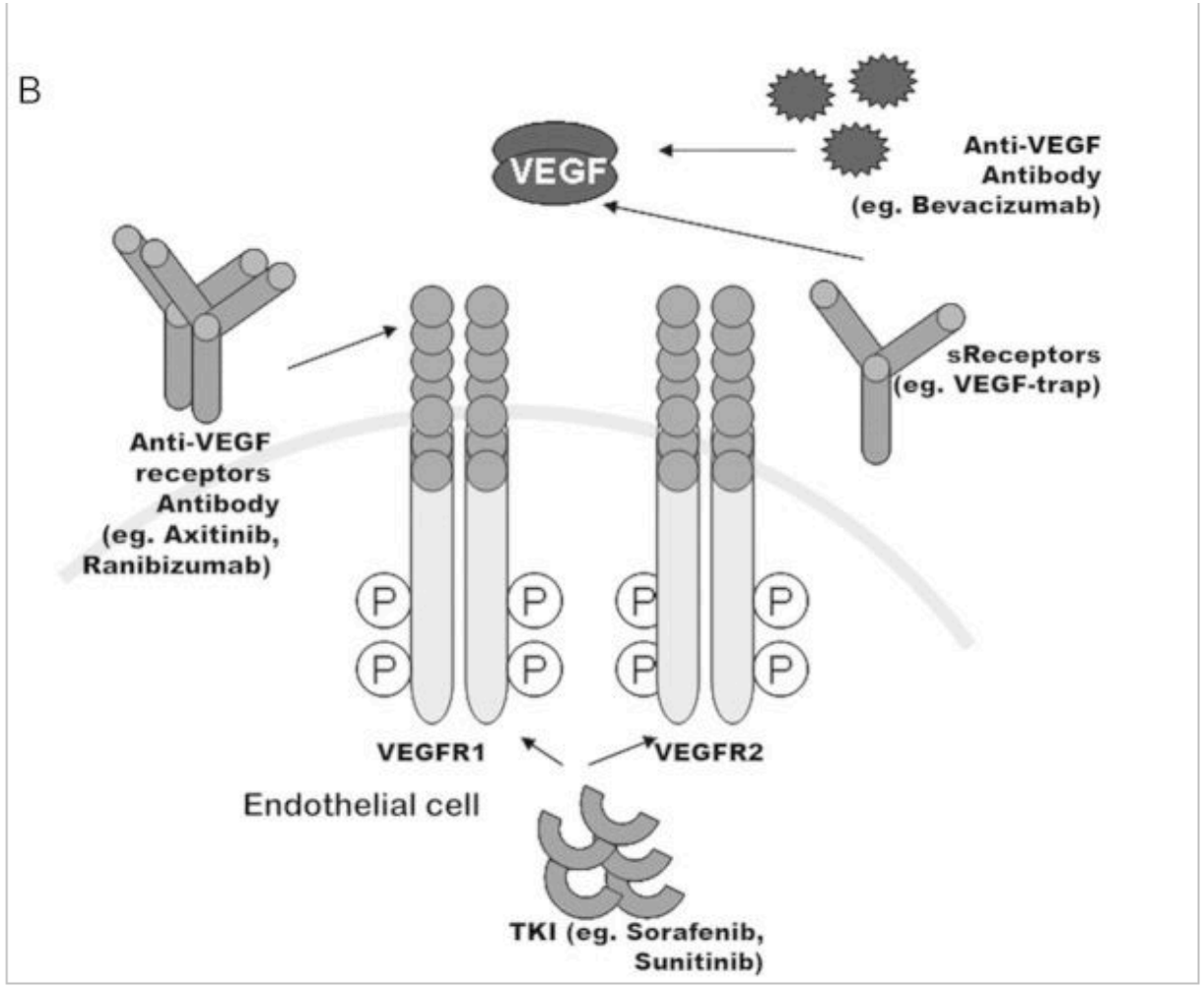
NOVEL AGENTS: CASE 3

aflibercept

Drug Monograph		
D - Adverse Effects		
Renal	Proteinuria (62%)	E
	Renal failure (rare)	E

Hypertension is common and may be severe. Blood pressure should be monitored regularly and treated appropriately. For a suggested treatment algorithm, see Appendix 8: Management of Angiogenesis Inhibitor (AI) Induced Hypertension.

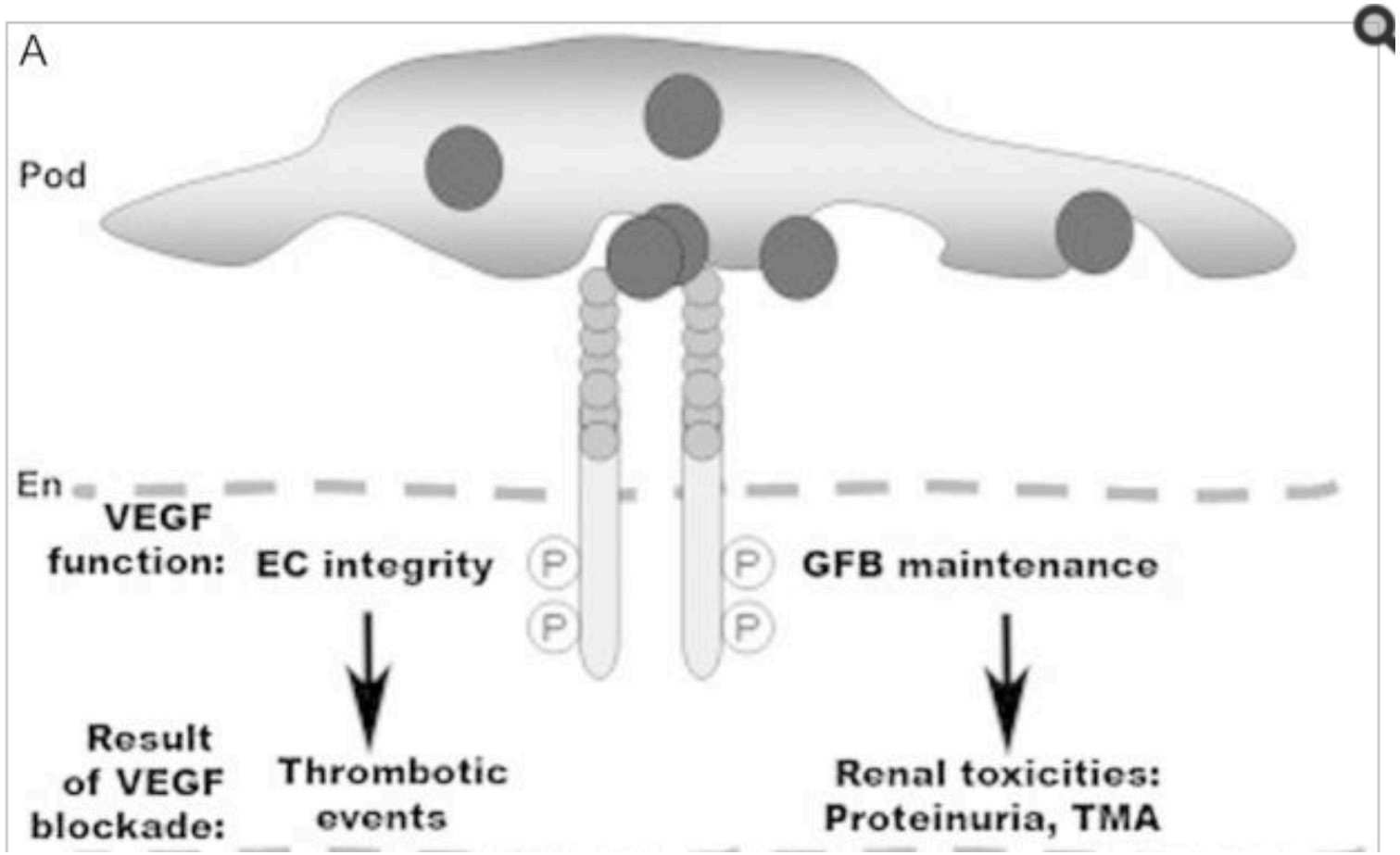
ANTI-ANGIOGENESIS AGENTS



- VEGF promotes angiognesis in tumours – can be blocked at multiple points

Lameire N. Clin Kidney J. 2014 Feb; 7(1): 11–22.

ANTI-VEGF AGENTS



- VEGF also released by podocytes – maintain endothelial cell/GBM integrity

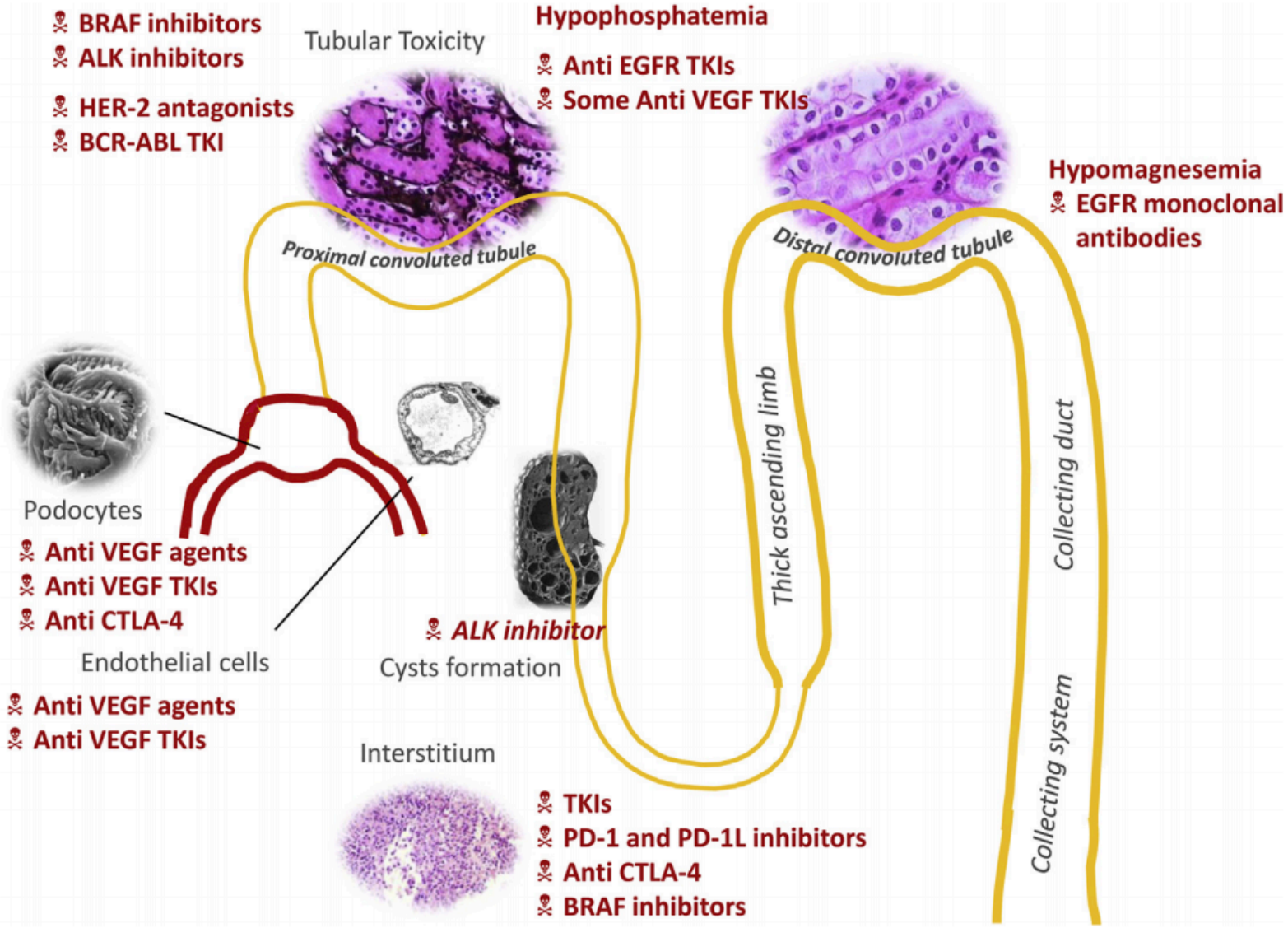
- Meta-analysis of 33 trials (n = 6,882)
- Any proteinuria: 18.7% (95% CI 13.3 – 25.6%)
- >3+ or >3.5 g/d: 2.4% (95% CI 1.6 – 3.7%)

Lameire N. Clin Kidney J. 2014 Feb; 7(1): 11–22.

ANTI-VEGF AGENTS

Drug (Trade Name)	Pathway	Health Canada Approval (in trials)
Bevacizumab (Avastin)* Aflibercept (Zaltrap)	Monoclonal/Fusion Ab (IgG1) to VEGF	Metastatic Colorectal, Renal, NSCLC, Ovarian Cancers, Glioblastoma, (Mesothelioma) *Macular Degeneration
Ramucirumab (Cyramza)	Monoclonal Ab (IgG1) to VEGFR2	Gastric/GEJ Adenocarcinoma, (Urothelial carcinoma)
Sunitinib (Sutent) Sorafenib (Nexavar) Pazopanib (Votrient) Ponatinib (Iclusig) Axitinib (Inlyta) Regarofenib (Stivarga)	Multi-target Tyrosine Kinase Inhibitor (mTKIs) → VEGFRs, FGFRs, PGFRs, BCR ABL	Metastatic Renal Cell, Colorectal, NETs, Sarcomas

NOVEL THERAPIES: OTHER TOXICITIES



Jhaveri K. Kidney Int Rep. 2017 Jan; 2(1): 108–123.

NOVEL THERAPIES: RENAL ADJUSTMENT

Table 1. Approved hematology and oncology indications for targeted therapies along with dosing in CKD and ESRD

Generic name of targeted therapy (trade name)	Target	Cancer	Renal excretion	Dose adjustment for GFR 30–90 ml/min/1.73 m^2	Dialysis dose adjustment
Afatineb (Gilotrif)	EGFR TKI	Metastatic NSCLC	<5%	No	No data
Axitinib (Inlyta)	Multi target TKI	Pancreatic cancer, RCC, CML	<25%	No	No
Aflibercept (Eylea or Zaltrap)	VEGF	Colorectal cancer	No	No	No
Bevacizumab (Avastin)	VEGF	Colorectal cancer, NSCLC, RCC, breast cancer, epithelial ovarian cancer, GBM	No	No	No
Bosutinib (Bosulif)	BCR-ABL TKI	CML	No	Reduce dose to 300 mg once daily	No data
Cetuximab (Erbitux)	EGFR	Colorectal cancer, head and neck SCC	No	No	No
Crizotinib (Xalkori)	ALK	NSCLC	No	No	No
Dabrafenib (Tafinlar)	BRAF	Melanoma	<25%	No	No data
Dasatinib (Sprycel)	BCR-ABL TKI	CML	<5%	No	No data
Erlotinib (Tarceva)	EGFR TKI	NSCLC, pancreatic cancer	<10%	No	No
Gefitinib (Iressa)	EGFR TKI	NSCLC	<5%	No	No
Ibrutinib (Imbruvica)	Bruton kinase TKI	CLL, mantle cell lymphoma	No	No data	No data
Imatinib (Gleevac)	BCR-ABL TKI	Gastrointestinal stromal tumors, CML	<15%	No	No
Ipilimumab (Yervoy)	CTLA4	Melanoma	No	No	No data
Lapatinib (Tykerb)	ERBB2	Breast cancer	<5%	No	No
Nivolumab (Opdivo)	PD-1	Melanoma, NSCLC, Hodgkin lymphoma, RCC	No	No	No data
Nilotinib (Tasigna)	BCR-ABL TKI	CML	No	No	No data
Panitumumab (Vectibix)	EGFR	Colorectal cancer	No	No	No
Pazopanib (Votrient)	Multitarget TKI	RCC, soft tissue sarcoma	<4%	No	No
Pembrolizumab (Keytruda)	PD-L1	Melanoma, NSCLC, Hodgkin lymphoma	No data	No	No
Pertuzumab (Perjeta)	ERBB2	Breast cancer	No	No	No data
Ponatanib (Iclusig)	BCR-ABL TKI	CML, ALL	No	No	No data
Regorafenib (Stivarga)	Multitarget TKI	Colorectal cancer, gastrointestinal stromal tumors	<20%	No	No
Sorafenib (Nexavar)	Multitarget TKI	RCC, hepatocellular carcinoma, thyroid carcinoma	<20%	No	No
Sunitinib (Sutent)	Multitarget TKI	RCC, gastrointestinal stromal tumors, pancreatic neuroendocrine tumors	<20%	No	No
Trametinib (Mekinist)	MEK	Melanoma	<20%	No	No data
Trastuzumab (Herceptin)	ERBB2	Breast cancer	No	No	No
Vandetanib (Caprelsa)	Multitarget TKI	Medullary thyroid cancer	<25%	No	No data
Vemurafenib (Zelboraf)	BRAF	Melanoma, thyroid cancer, colorectal cancer	<5%	No	No data

NOVEL THERAPIES: RESEARCH IN PROGRESS

- REB Approval to review all patients who received immune checkpoint inhibitors (2010 – 2016) at Princess Margaret Hospital
  - Data Sources: Oncology Pharmacy Information System (OPIS)
  - Automated EPR algorithm to report AKI using creatinine and urine protein data
  - Identified 353 patients, 4 different cancers, dates/dose administered:
    - AKI in 12%, KDIGO Stage 3 in 3%
    - chart review in progress: risk factors, other exposures

NOVEL THERAPIES: NEXT STEPS

- MANY new therapies in development – need for renal perspective in trial safety endpoints
- Development of a multicentre registry of renal toxicities from new therapies
- Identify high-risk patients/inclusion of patients with CKD in cancer trials

AKI IN PATIENTS WITH CANCER: EPIDEMIOLOGY

“How little do doctors know the hells through which we put our patients….”

-- Paul Kalanithi, ‘When Breath Becomes Air’

BACKGROUND

Renal Cell Cancer/Nephrectomy

Post-renal Obstruction

Hypercalcemia

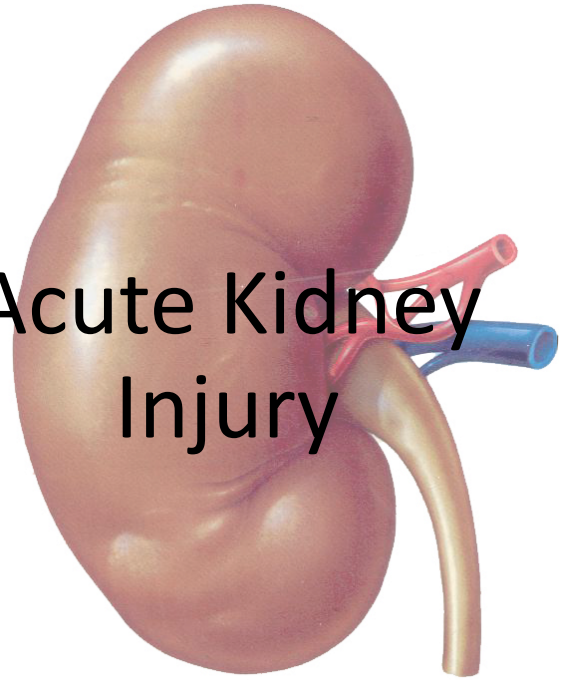
Paraprotein Disease

DISEASE RISKS

Patients with Cancer

WORSE CANCER OUTCOMES

Acute Kidney Injury



IATROGENIC RISKS

Chemotherapy

Nephrotoxins (IV Contrast, NSAIDs)

Volume Depletion

Sepsis

BACKGROUND: KNOWLEDGE GAP

- Predominantly hematologic cancer-specific
- Only one large cohort study (Denmark 1999 – 2006 data)
  - Kidney cancers at highest risk
- Limited data on risk factors and impact of therapy in current era of treatment

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Julie R. Ingelfinger, M.D., *Editor*

Acute Kidney Injury in Patients with Cancer

Mitchell H. Rosner, M.D., and Mark A. Perazella, M.D.

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original article

Incidence of acute kidney injury in cancer patients: A Danish population-based cohort study

Christian Fynbo Christiansen [a,*], Martin Berg Johansen [a], Wendy J. Langeberg [b], Jon P. Fryzek [b], Henrik Toft Sørensen [a]

METHODS

- **OBJECTIVES:**

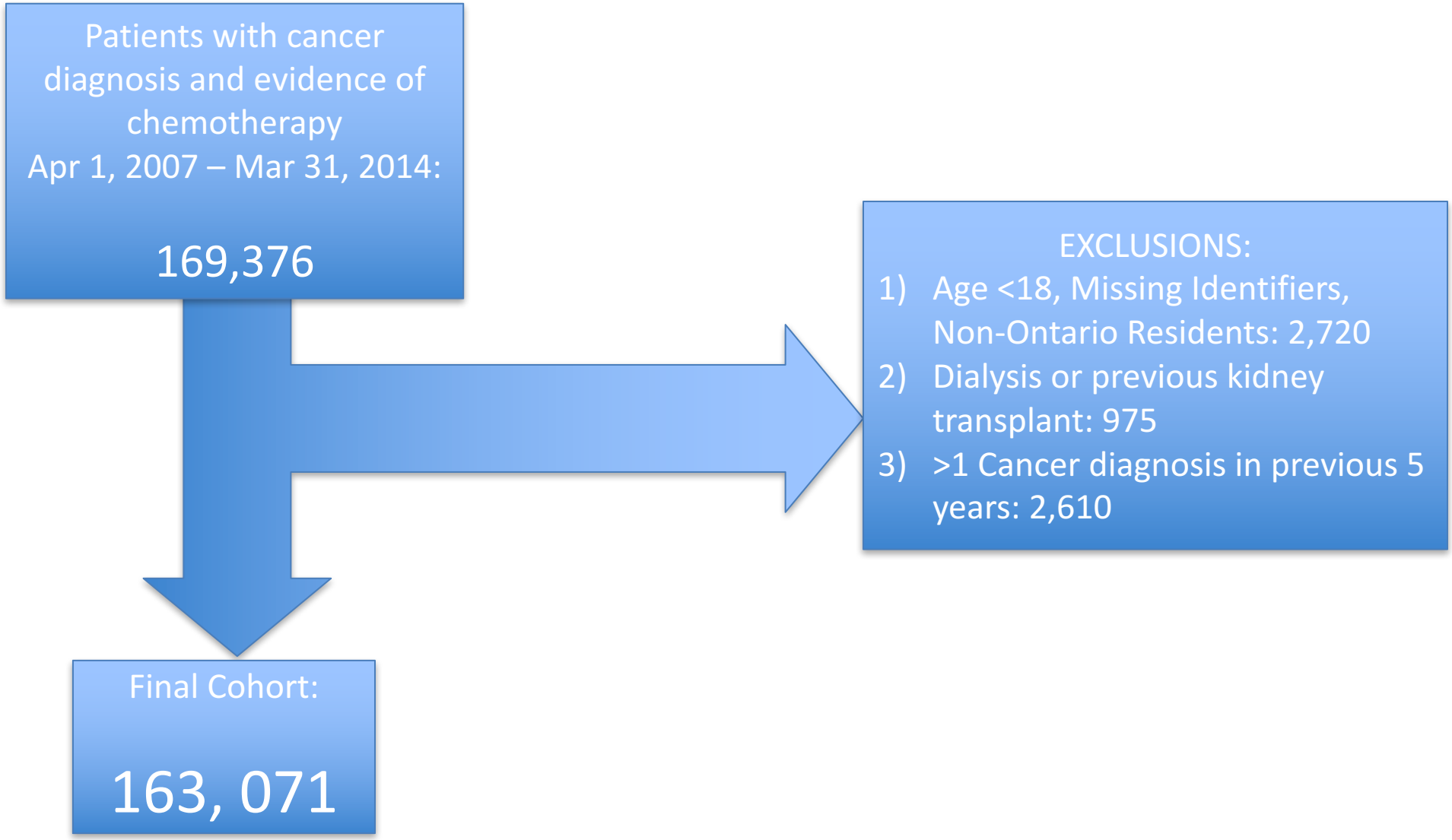
1) Determine incidence of hospitalizations/acute dialysis for AKI in patients treated for cancer in current era
2) Identify associated risk factors (cancer types, comorbidities, co-prescriptions) in this setting

- **POPULATION:** All patients, age > 18 years, *starting* therapy for incident cancer in Ontario between 2007 to 2014

- **DATA SOURCES:**
  - **Cancers** – Identified using the Ontario Cancer Registry (OCR)
  - **Systemic Therapy** – OHIP billing codes, National Ambulatory Care Reporting System (NACRS), Cancer Care Ontario – Activity Level Reporting*, New Drug Funding Plan*

**Provides drug/dose information*

RESULTS: STUDY FLOW DIAGRAM



RESULTS: BASELINE DATA

Baseline Characteristics	Acute Kidney Injury Status				Standardized Difference
	No		Yes		
	152,191		10,880		
	N	%	N	%	
Age at Index Date					
Mean (SD)	61.58	13.3	66.12	12.29	35%
Sex, Female	88,399	58.1%	4,635	42.6%	31%
Cancer Characteristics					
Stage at Diagnosis					
Missing	42,094	27.7%	4,497	41.3%	29%
1	19,157	12.6%	710	6.5%	21%
2	30,365	20.0%	1,386	12.7%	20%
3	31,409	20.6%	2,042	18.8%	5%
4	29,166	19.2%	2,245	20.6%	4%
Systemic Therapy (3 most common in AKI individuals)					
CCO Regimen 1 (*CHOP-RITUXIMAB)	25,898	17.0%	2,233	20.5%	9%
CCO Regimen 2 (*PACLICARBO)	26,282	17.3%	1,773	16.3%	3%
CCO Regimen 3 (*FOLFOX)	22,435	14.7%	1,270	11.7%	9%
NDFP Drug 1 (Rituximab)	10,522	6.9%	933	8.6%	6%
NDFP Drug 2 (Pamidronate)	4,019	2.6%	755	6.9%	20%
NDFP Drug 3 (Oxaliplatin)	10,658	7.0%	736	6.8%	1%

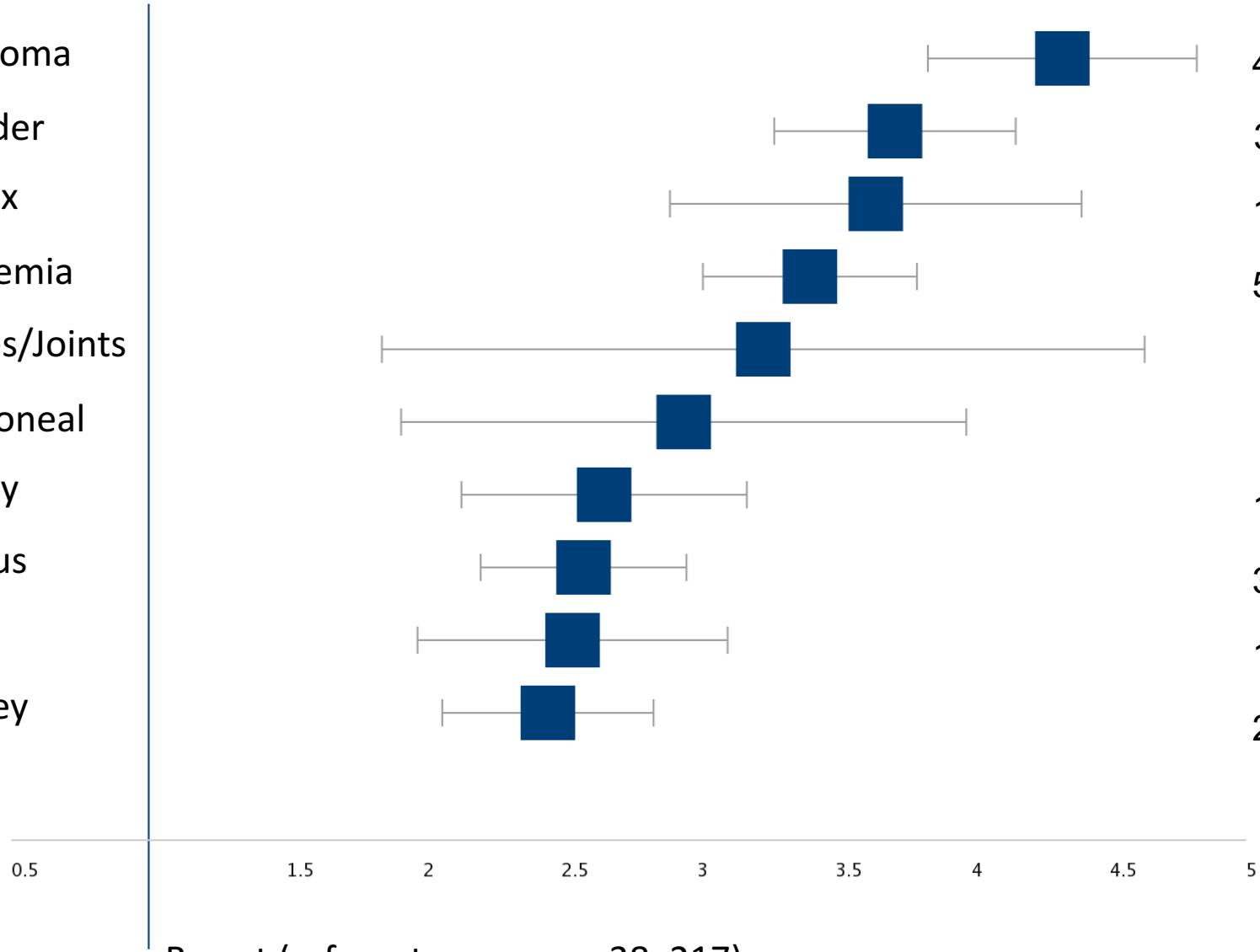
Baseline Characteristics	Acute Kidney Injury Status				Standardized Difference
	No 152,191		Yes 10,880		
	N	%	N	%	
Comorbidities					
Charlson Score Mean (SD)	1.80	2.43	2.23	2.61	17%
Acute Myocardial Infarction	3,040	2.0%	468	4.3%	13%
Congestive Heart Failure	8,211	5.4%	1,390	12.8%	26%
Cerebrovascular disease	6,872	4.5%	668	6.1%	7%
Diabetes with and without complications [Type 1 and 2]	29,118	19.1%	3,523	32.4%	31%
Chronic Liver Disease	2,267	1.5%	295	2.7%	8%
Peripheral Vascular Disease	3,270	2.1%	447	4.1%	12%
Cardiac Arrhythmia	14,167	9.3%	1,729	15.9%	20%
Ischemic Heart Disease	20,777	13.7%	2,479	22.8%	24%
Emphysema, Chronic Bronchitis, COPD	15,773	10.4%	1,420	13.1%	8%
HIV/AIDS	412	0.3%	42	0.4%	2%
Hypertension with and without major complications	61,088	40.1%	6,032	55.4%	31%
Chronic kidney disease	5,106	3.4%	1,464	13.5%	37%
Co-prescription within 60 days of Index Date					
# individuals > 66 years on index date	62,480	41.1%	6,001	55.2%	29%
ACE Inhibitor	18,891	30.2%	2,329	38.8%	18%
ARB	12,432	19.9%	1,465	24.4%	11%
Diuretics	17,585	28.1%	2,329	38.8%	23%
Beta-blockers	17,456	27.9%	2,202	36.7%	19%
Statins	28,034	44.9%	3,093	51.5%	13%

RESULTS: INCIDENCE

Cumulative Incidence of AKI in all cancers during follow-up:	9.3%
Median (IQR) time from initial therapy to AKI:	276 days (87, 704)
Median (IQR) time from most recent therapy to AKI:	33 days (9, 177)

	N	n	Frequency (%)	Total person-years f/u	Event rate per 1000-py	1-yr CI	5-yrs CI
Total Cohort	163,071	10,880	6.7%	403,538	27.0	3.9%	7.8%
Top 10 High Risk Cancers							
Myeloma	4,244	893	21.0%	9,833	90.8	10.1%	26.0%
Bladder	3,811	611	16.0%	7,925	77.1	10.7%	19.0%
Leukemia	5,766	740	12.8%	12,730	58.1	7.8%	15.4%
Kidney	2,021	223	11.0%	3,388	65.8	6.4%	13.9%
Peritoneal	311	30	9.6%	446	67.3	6.6%	13.8%
Liver	1,143	108	9.4%	1,326	81.4	7.4%	11.7%
Biliary	1,217	124	10.2%	1,657	74.9	7.0%	11.6%
Prostate	7,626	586	7.7%	16,939	34.6	4.5%	10.3%
Cervix	1,714	139	8.1%	5,359	25.9	4.4%	9.3%
Anal	1,031	83	8.1%	3,430	24.2	3.9%	9.1%

RESULTS: HIGH RISK CANCERS



	N	Adjusted HR	95% CI
Myeloma	4,244	4.30	(3.83, 4.82)
Bladder	3,811	3.69	(3.28, 4.16)
Cervix	1,714	3.47	(2.90, 4.14)
Leukemia	5,766	3.39	(3.02, 3.80)
Bones/Joints	242	2.93	(1.85, 4.63)
Peritoneal	311	2.77	(1.92, 3.98)
Biliary	1,217	2.61	(2.14, 3.18)
Uterus	3,239	2.55	(2.21, 2.96)
Anal	1,031	2.48	(1.98, 3.11)
Kidney	2,021	2.43	(2.07, 2.84)

1 Breast (referent group, n = 38, 217)

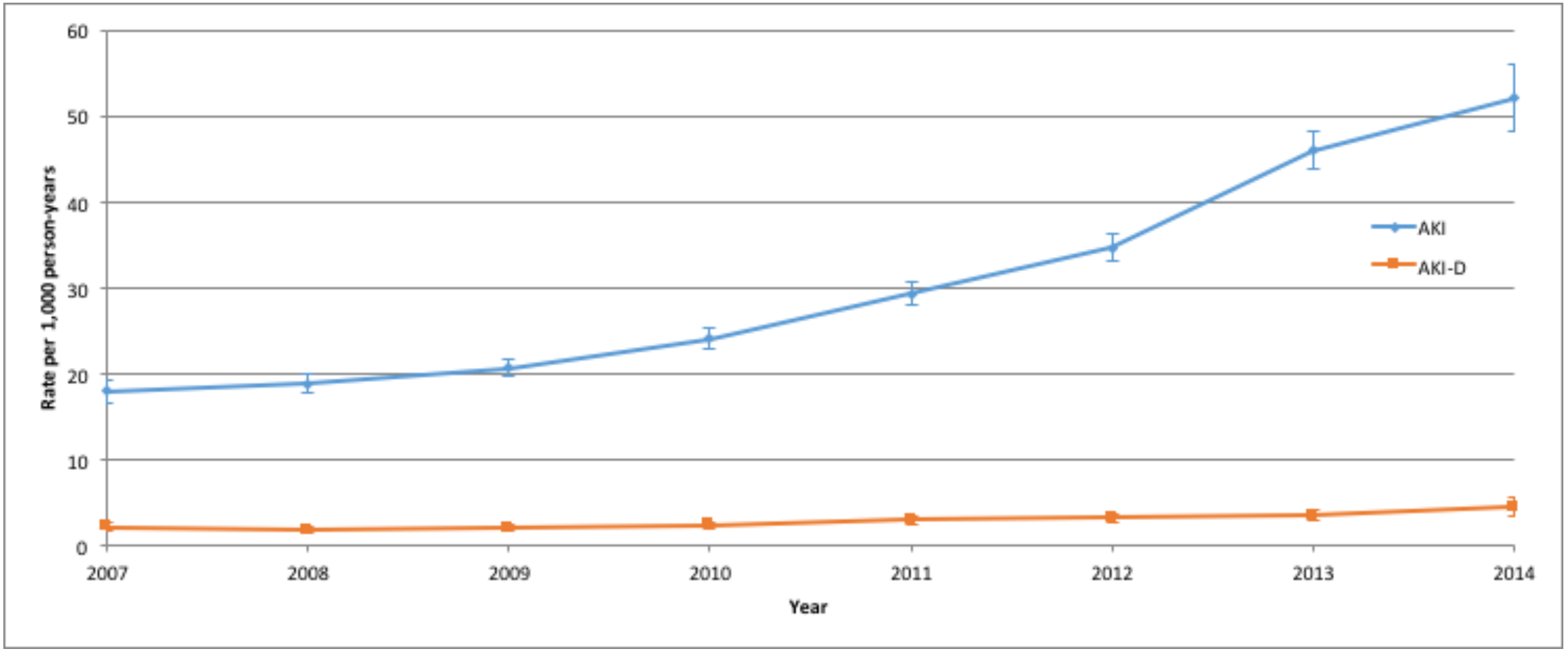
RESULTS: RISK FACTORS

Covariates	Adjusted Hazard Ratio	95% CI
Age (per year)	1.01	(1.01, 1.01)
Male vs Female	1.26	(1.20, 1.32)
Cancer Stage 4 vs 1	1.41	(1.28, 1.54)
Comorbidities		
Chronic Kidney Disease	1.80	(1.67, 1.93)
Diabetes Mellitus	1.43	(1.37, 1.50)
Congestive Heart Failure	1.36	(1.27, 1.45)
HIV/AIDS	1.36	(1.00, 1.84)
Chronic Liver Disease	1.30	(1.14,1.47)
Hypertension	1.28	(1.23,1.34)
Peripheral Vascular Disease	1.22	(1.11, 1.34)
Arrhythmia	1.09	(1.03,1.16)
Ischemic Heart Disease	1.06	(1.01, 1.12)
Previous Acute MI	1.05	(0.95,1.16)
COPD	1.05	(0.99, 1.11)
Cerebrovascular Disease	0.98	(0.91, 1.06)

RESULTS: SECONDARY ANALYSES

	Adjusted Hazard Ratio	95% CI
Chemotherapy exposure (90-day period following each treatment)	2.34	(2.24, 2.45)
Co-prescription within 60-days of chemotherapy start (patients aged >=66, n = 68,481)		
ACEi or ARB	1.30	(1.23, 1.38)
Diuretic	1.20	(1.14, 1.28)
Beta-blocker	1.10	(1.04, 1.17)
Calcium channel blocker	1.18	(1.07, 1.30)
Statin	1.02	(0.96, 1.07)

RESULTS: ANNUAL TRENDS IN AKI



AKI IN CANCER: KEY FINDINGS

- Hospitalization/acute dialysis for AKI is a common complication in patients treated for cancer (approximately 1 in 10)
- Myeloma, bladder cancer and leukemia patients at highest risk
  - Differs from previous data which reported renal cancers at greatest risk
- Consideration for holding diuretics, antihypertensives during chemotherapy, particularly in 90-day period after chemotherapy

AKI IN CANCER: NEXT STEPS

- Assess risk associated with select **treatment regimens** within single cancer subgroups

- Assess **mortality outcomes** and **delay in therapy** in patients with/without AKI (propensity matched analysis)

- Re-evaluate with OLIS (Laboratory Data)

CANCER IN CHRONIC KIDNEY DISEASE

“Yes, all patients with cancer are unlucky, but….”

-- Paul Kalanithi, ‘When Breath Becomes Air’

THE BURDEN OF CANCER IN CKD

Table 3. Cause-specific deaths among those with non–dialysis-dependent CKD

Causes of death (*n*, %)	Overall (*n*=6661)	eGFR 45–59 (*n*=3308)	eGFR 30–44 (*n*=2261)	eGFR<30 (*n*=1092)
Cardiovascular diseases	2311 (34.7)	1017 (30.7)	862 (38.1)	432 (39.6)
Ischemic heart disease	1227 (18.4)	532 (16.1)	457 (20.2)	238 (21.8)
Heart failure	163 (2.4)	61 (1.8)	75 (3.3)	27 (2.5)
Cerebrovascular diseases	255 (3.8)	123 (3.7)	94 (4.2)	38 (3.5)
Other cardiovascular diseases	666 (10.0)	301 (9.1)	236 (10.4)	129 (11.8)
Malignant neoplasms	2117 (31.8)	1282 (38.8)	616 (27.2)	219 (20.1)

Navaneethan SD *et al.* JASN. 2015; 26: 2512–2520.

CANCER SCREENING IN CKD

- **Non-dialysis CKD:**
  - **Higher cancer risk than the general population?** Wong *et al.* – prospective cohort (n = 3,554): for every 10 mL/min decrease in eGFR, cancer risk increased by 29%
  - **Higher cancer mortality?** Iff *et al.* – prospective cohort (n = 4,077): for every 10 mL/min decrease in eGFR, cancer mortality increased by 18%

- **Patients on Dialysis:**
  - **Choosing Wisely :** "Do not perform routine cancer screening for dialysis patients with limited life expectancy without signs or symptoms."
  - Chertow *et al.* – cancer screening in dialysis: net gain of 5 days in life expectancy and reduction in mortality rate of 0.02% **(1996)**

CANCER SCREENING IN CKD

- **Transplant Recipients (adults):**
  - **Higher cancer risk?:** Engels *et al.* – US SRTR data (n = 175, 178): 32 different cancer standardized incidence ratios (SIR) 1.97 – 7.54 times gen population
  - **Higher cancer mortality?:** Acuna *et al.* – ICES data (n = 11, 071): standardized mortality ratio (SMR) 2.84 times general population

Should we screen non-dialysis CKD and transplant recipients (at least) as per general population?

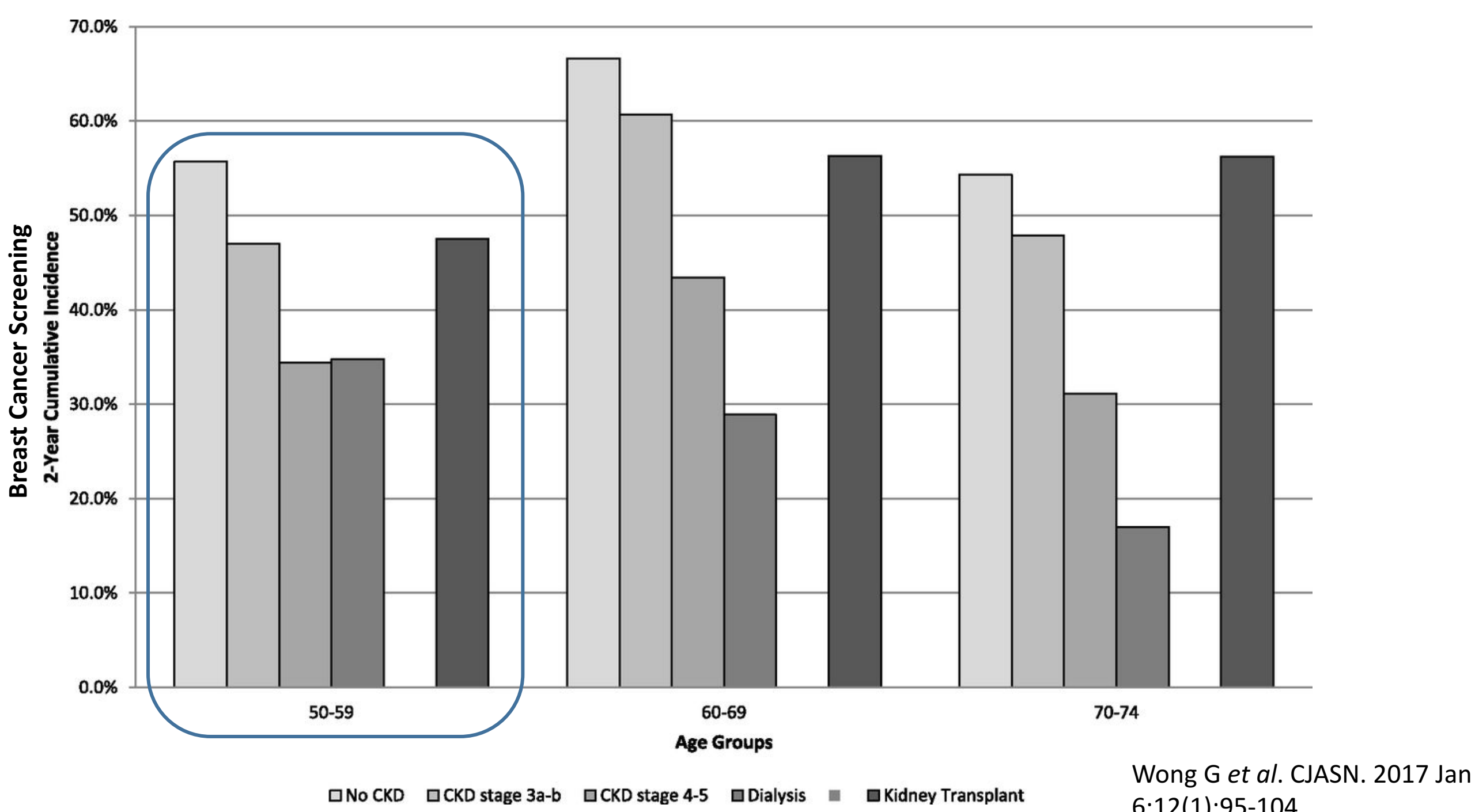
Engels EA *et al.* JAMA. 2011;306(17):1891-901.
Acuna SA *et al.* JAMA Oncol. 2016;2(4):463-469.

CANCER SCREENING IN CKD

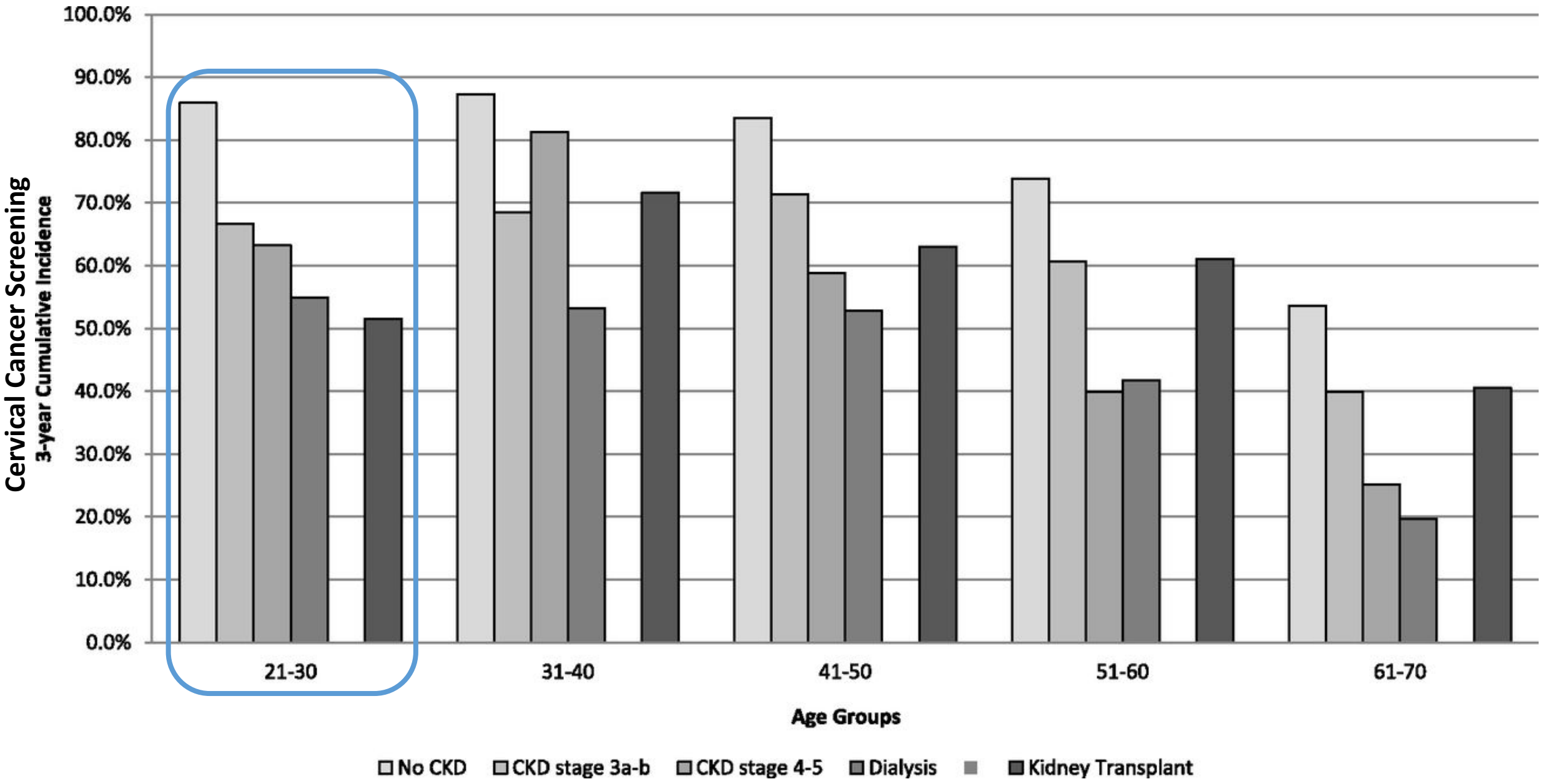
- 2 Retrospective cohort studies in Ontario to assess screening rates – CKD identified using Dynacare lab database (2002 – 2013):

- Breast Cancer (50 – 74 yo, n = 141, 326): 2-yr screening incidence
- Cervical Cancer (21 – 70 yo, n = 324, 548): 3 yr screening incidence

Wong G *et al*. Clin J Am Soc Nephrol. 2017 Jan 6;12(1):95-104.



Wong G *et al*. CJASN. 2017 Jan 6;12(1):95-104.


Cervical Cancer Screening
3-year Cumulative Incidence
100.0%
90.0%
80.0%
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
21-30
31-40
41-50
51-60
61-70
Age Groups
No CKD
CKD stage 3a-b
CKD stage 4-5
Dialysis
Kidney Transplant

HOW TO TREAT CANCER IN CKD?

- First-line chemotherapies for many solid cancers are contraindicated in CKD (e.g., platinum-based drugs – cisplatin, carboplatin, oxaliplatin) with eGFR < 50 – 60 mL/min

- May also be excluded from other therapies (e.g., hematopoietic cell transplant, VEGF agents/TKIs, surgery)

- Very limited data on dose adjustment in CKD and no clinical guidelines focused on this population

CANCER IN CKD: DOSE ADJUSTMENTS

- Very limited PK/PD data for most agents
- CKD potentiates renal and systemic toxicities

Onco-nephrology: an appraisal of the cancer and chronic kidney disease links

Hassan Izzedine[1] and Mark A. Perazella[2]

Nephrol Dial Transplant (2015) 30: 1979–1988
doi: 10.1093/ndt/gfu387
Advance Access publication 3 February 2015

American Society of Nephrology Onco-Nephrology Curriculum

Chapter 12: Pharmacokinetics of Chemotherapeutic Agents in Kidney Disease

Sheron Latcha, MD, FASN

HOW TO TREAT CANCER IN CKD?

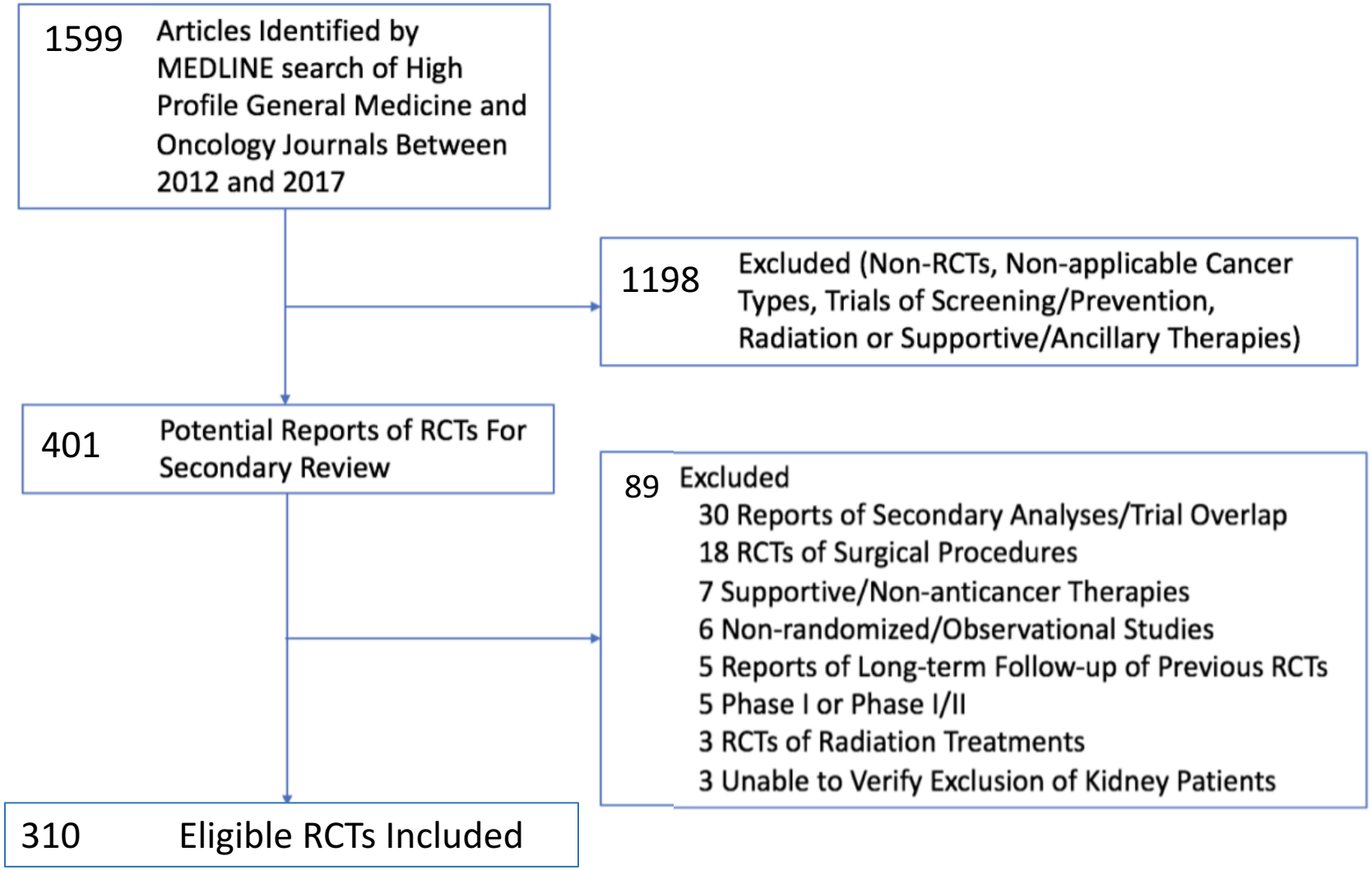
- *Are CKD patients even included in new cancer treatment trials?*
- SYSTEMATIC REVIEW:
  - RCTs of treatment 5 most common cancers
  - 6 high-profile GIM/Oncology journals (2012 – 2017)
  - Reviewed inclusion/exclusion criteria

Underrepresentation of Renal Disease in Randomized Controlled Trials of Cardiovascular Disease

Steven G. Coca, DO
Harlan M. Krumholz, MD
Amit X. Garg, MD, PhD
Chirag R. Parikh, MD, PhD

JAMA, September 20, 2006—Vol 296, No. 11

REPRESENTATION OF CKD PATIENTS IN CANCER TRIALS



EXCLUSION OF CKD PATIENTS FROM CANCER TRIALS

Trial Characteristics	Trials, n (%)	Patient Enrollment, n	Trials Excluding CKD, n (%)	*P* Value
Overall	310 (100)	282 889	264 (85)	
Publication, year*				
2012	58 (19)	46 567	50 (86)	
2013	60 (19)	73 745	55 (92)	
2014	46 (15)	35 264	37 (80)	0.16
2015	47 (15)	37 437	45 (96)	
2016	47 (15)	41 486	32 (68)	
2017	52 (17)	48 390	45 (87)	
Enrollment Start, year				
1995 – 2000	12 (4)	32 018	8 (67)	
2001 – 2006	91 (29)	122 789	77 (85)	0.24
2007 – 2012	176 (57)	113 061	154 (88)	
2013 – 2017	31 (10)	15 021	25 (81)	
Trial Enrollment, no. of patients				
<100	14 (5)	1 016	11 (79)	
100 – 200	35 (11)	5 282	29 (83)	0.52
201 – 500	85 (27)	28 269	77 (91)	
501 - 1000	89 (29)	61 893	75 (84)	
>1000	87 (28)	186 429	72 (83)	
Cancer Type				
Bladder	4 (1)	959	3 (75)	
Breast	111 (36)	144 052	87 (78)	
Colorectal	52 (17)	42 619	48 (92)	0.45
Lung	96 (31)	50 175	86 (90)	
Prostate	47 (15)	45 084	40 (85)	

EXCLUSION OF CKD PATIENTS FROM CANCER TRIALS

Trial Characteristics	Trials, n (%)	Patient Enrollment, n	Trials Excluding CKD, n (%)	*P* Value
Intervention Type				
Chemotherapy	78 (25)	60 986	68 (87)	
Biologic/Immunotherapy	87 (28)	81 802	78 (90)	
Endocrine Therapy	31 (10)	65 331	18 (58)	0.02
Targeted Agents	84 (27)	43 725	78 (86)	
Other Therapy	30 (10)	31 045	28 (93)	
Trial Phase				
Phase II	55 (18)	11 094	45 (82)	
Phase II/III	7 (2)	7 610	7 (100)	0.82
Phase III	246 (79)	263 735	210 (85)	
Phase IV	2 (1)	440	2 (100)	
Funding Source				
Industry	208 (67)	168 941	177 (85)	
Government	39 (13)	32 634	34 (87)	0.61
Both	63 (20)	81 314	53 (84)	
Journal				
JAMA	4 (1)	6 287	3 (75)	
Journal of Clinical Oncology	137 (44)	113 495	124 (91)	
Journal of the National Cancer Institute	5 (2)	4 786	4 (80)	0.09
Lancet	16 (5)	36 465	12 (75)	
Lancet Oncology	112 (36)	80 233	90 (80)	
New England Journal of Medicine	36 (12)	41 623	31 (86)	

EXCLUSION OF CKD PATIENTS FROM CANCER TRIALS

Table 2. Thresholds for Exclusion of Patients with Kidney Disease in Cancer Trials*

Measures Used for Exclusion Based on Kidney Function*	**No. (%)**
Trials excluding kidney disease with explicitly stated eligibility criteria	264 (85)
Trials excluding on the basis of serum creatinine value	162 (62)
Trials excluding on the basis of serum creatinine value relative to ULN	129 (49)
Serum creatinine > 5-times ULN	1 (0.4)
Serum creatinine >2.5-times ULN	6 (2)
Serum creatinine >2-times ULN	6 (2)
Serum creatinine >1.5-times ULN	93 (35)
Serum creatinine >1.25-times ULN	7 (3)
Serum creatinine > ULN	16 (6)
Trials excluding on the basis of creatinine clearance	115 (44)
Creatinine clearance <60 mL/min	38 (14)
Creatinine clearance <50 mL/min	44 (17)
Creatinine clearance <45 mL/min	10 (4)
Creatinine clearance <40 mL/min	12 (5)
Creatinine clearance <30 mL/min	11 (4)
Trials excluding on the basis of estimated GFR	14 (5)
eGFR <60 mL/min per 1.73 m^2	5 (2)
eGFR <50 mL/min per 1.73 m^2	4 (2)
eGFR <45 mL/min per 1.73 m^2	1 (0.4)
eGFR <30 mL/min per 1.73 m^2	4 (2)
Trials with a proteinuria-based exclusion	31 (12)
Non-specified renal exclusion (e.g., “adequate” or “intact” kidney function)	41 (16)
Trials with multiple renal exclusionary criteria (e.g. serum Cr, CrCl and/or proteinuria)	90 (34)

EXCLUSION OF CKD PATIENTS FROM CANCER TRIALS

- The majority of recent cancer trials explicitly exclude patients with CKD (85%)
- Thresholds for exclusion are typically ‘mild’ or ‘mild-moderate’ CKD
- Few trials used preferred/recommended measures of kidney function

CANCER IN CKD: NEXT STEPS

- Funding from Cancer Care Ontario/Ontario Renal Network for population-level studies assessing:
  - Cancer incidence/screening in CKD
  - Treatment patterns (receipt of systemic therapies, radiation, surgery)
  - Cancer outcomes (across varying severity of CKD)

Cancer Care Ontario

Ontario Renal Network
Réseau Rénal de L'Ontario

SUMMARY

- AKI IN CANCER:
  - AKI in cancer is common – ongoing work to identify high-risk patients/treatment regimens and modifiable risk factors
  - Novel cancer therapies are associated with significant renal adverse events – larger series are needed to characterize toxicities → registry/trial involvement

- CANCER IN CKD/ESRD:
  - Outcomes in patients with cancer and CKD are poor
  - Very limited data on treatment modification in CKD
  - Need for greater inclusion/partner trials of cancer treatment in CKD

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