Nefrologische toxiciteit bij chemo/immuuntherapie

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Longarts

Erasmus MC
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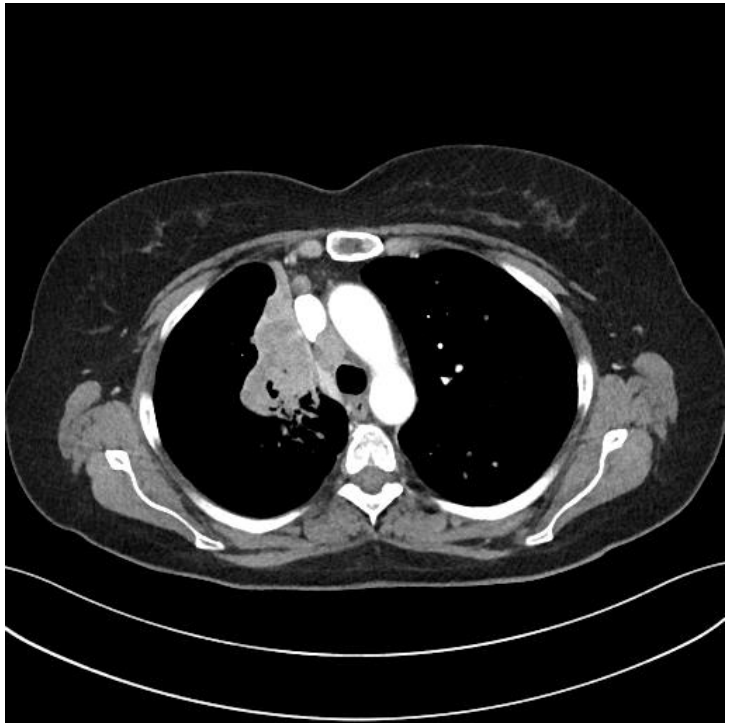
NO CONFLICTS OF INTEREST TO DECLARE

CASUS

- Vrouw, 66 jaar
- Stadium IV niet-kleincellig longcarcinoom (NSCLC)
- PD-L1 30%
- Geen targetable mutaties
- WHO performance score 0
- Medicatie: paracetamol, lisinopril



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CASUS

- Welke behandeling bij gemetastaseerd NSCLC?

- In afwezigheid van targetable mutatie

- Immuuntherapie is onderdeel van eerstelijns behandeling
  - Monotherapie immuuntherapie
  - Chemo/immuuntherapie

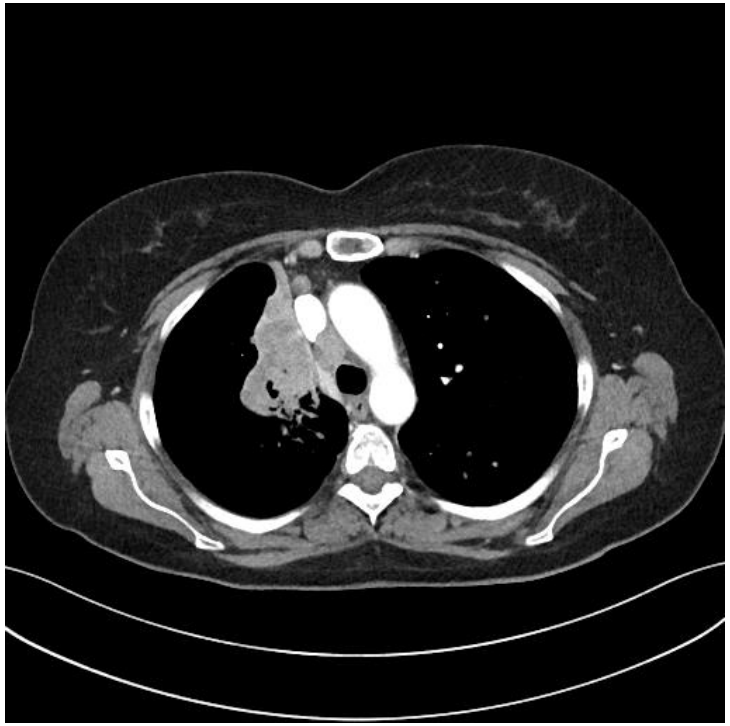


Table 1. Approved indications for ICPis

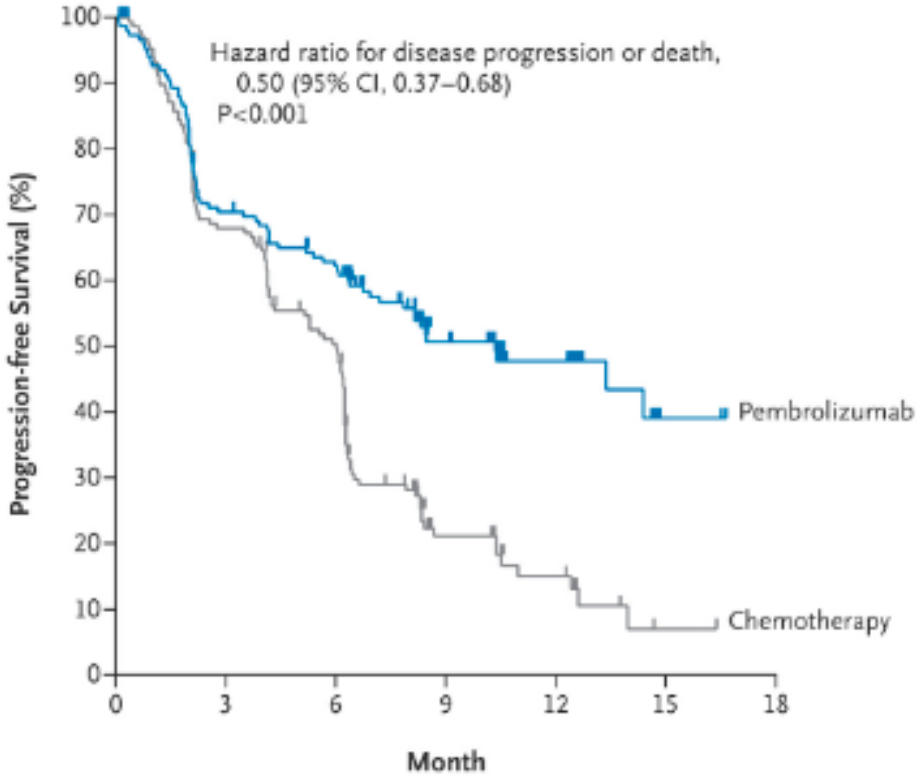
Drug	Indications	EMA/FDA approval
Ipilimumab	Metastatic melanoma	EMA + FDA
	Adjuvant therapy stage III melanoma	FDA
Nivolumab	Metastatic melanoma	EMA + FDA
	2nd line metastatic NSCLC	EMA + FDA
	2nd line metastatic RCC	EMA + FDA
	Classical Hodgkin's disease[a]	EMA + FDA
	Recurrent or metastatic SCCHN[b]	EMA + FDA
	Locally advanced or metastatic UCC[c]	EMA + FDA
Pembrolizumab	Metastatic melanoma	EMA + FDA
	2nd line metastatic NSCLC (PD-L1 ≥ 1%)	EMA + FDA
	1st line metastatic NSCLC (PD-L1 ≥ 50%)	EMA + FDA
	1st line metastatic NSCLC in combination with pemetrexed + carboplatin	FDA
	Classical Hodgkin's disease	EMA[a] + FDA[d]
	Locally advanced or metastatic UCC[c]	FDA
	MSI-H or MMR deficient metastatic malignancies[e]	FDA
Atezolizumab	Locally advanced or metastatic UCC[c]	FDA
	2nd line metastatic NSCLC	FDA
Avelumab	Locally advanced or metastatic UCC[c]	FDA
	Metastatic Merkel cell carcinoma	FDA
Durvalumab	Locally advanced or metastatic UCC[c]	FDA
Ipilimumab + nivolumab	Metastatic melanoma	EMA + FDA

Longkanker, mesothelioom

Haanen et al. Annals of Oncology 28 (Supplement 4): i119–i142, 2017. ESMO Clinical Practice Guidelines.

KEYNOTE-024

Pembrolizumab vs chemotherapie bij NSCLC st. IV, PD-L1 ≥ 50%



Reck N Engl J Med 2016;375:1823-33

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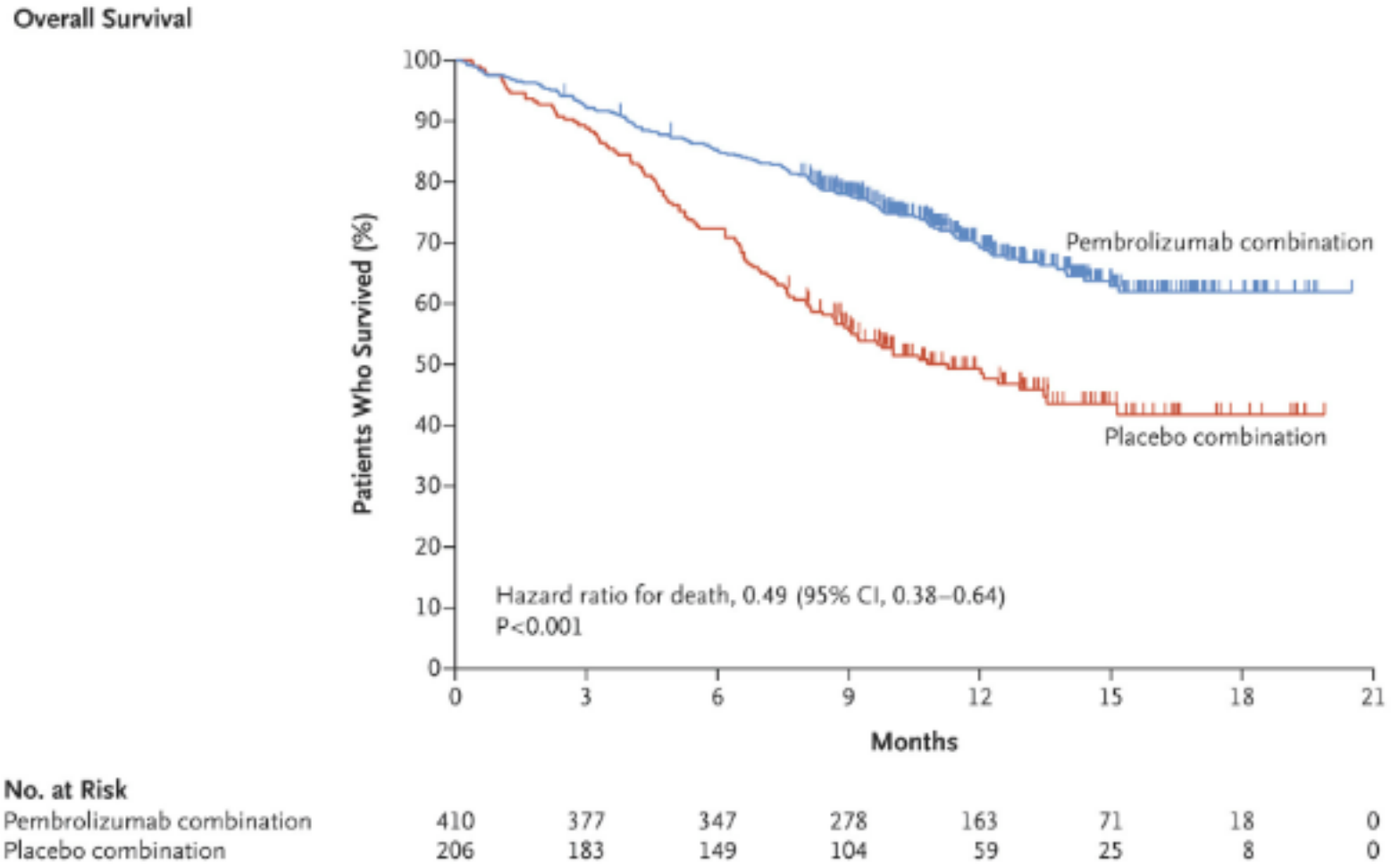
KEYNOTE-189

Pembro/chemo vs placebo/chemo bij NSCLC st. IV, ongeacht PD-L1



Gahndi N Engl J Med 2018;378:2078-92

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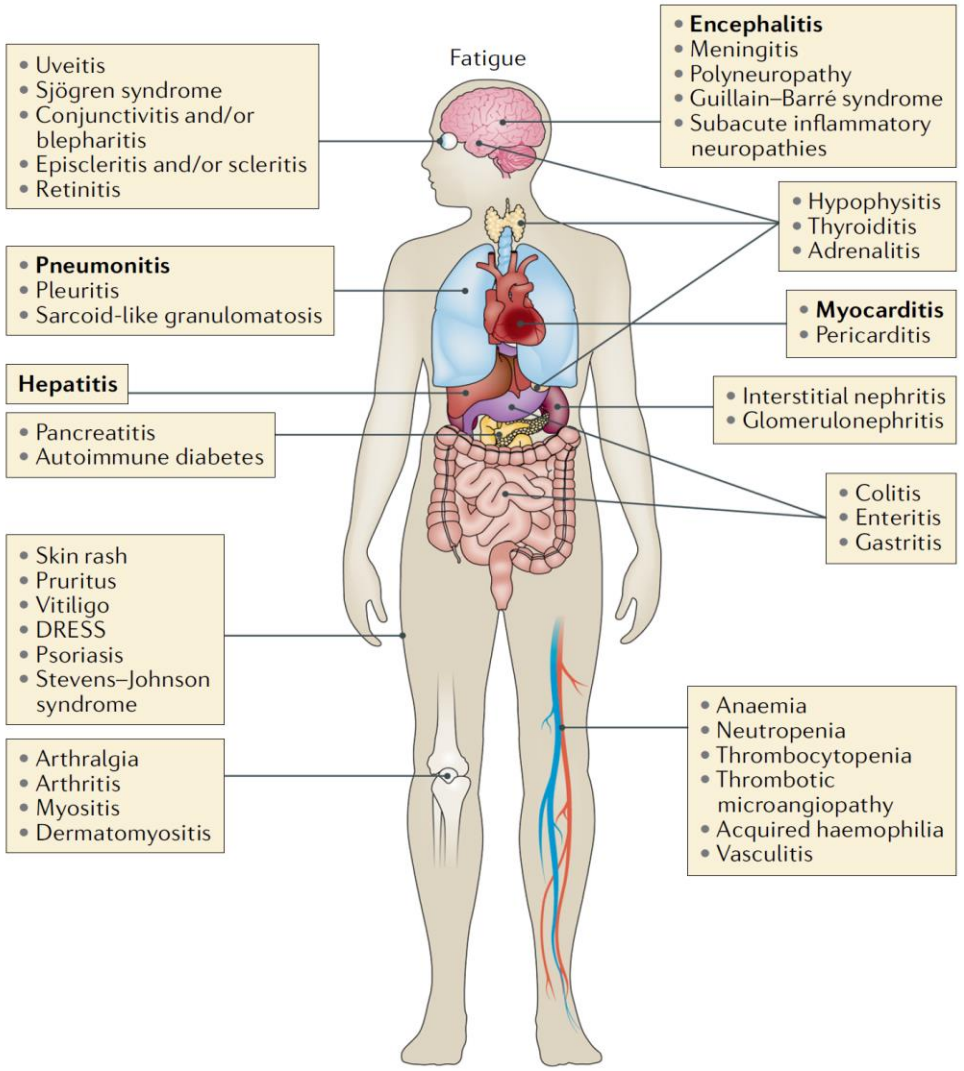
TOXICITEIT



Martins Nature Reviews Clinical Oncology volume 16, pages563–580 (2019)

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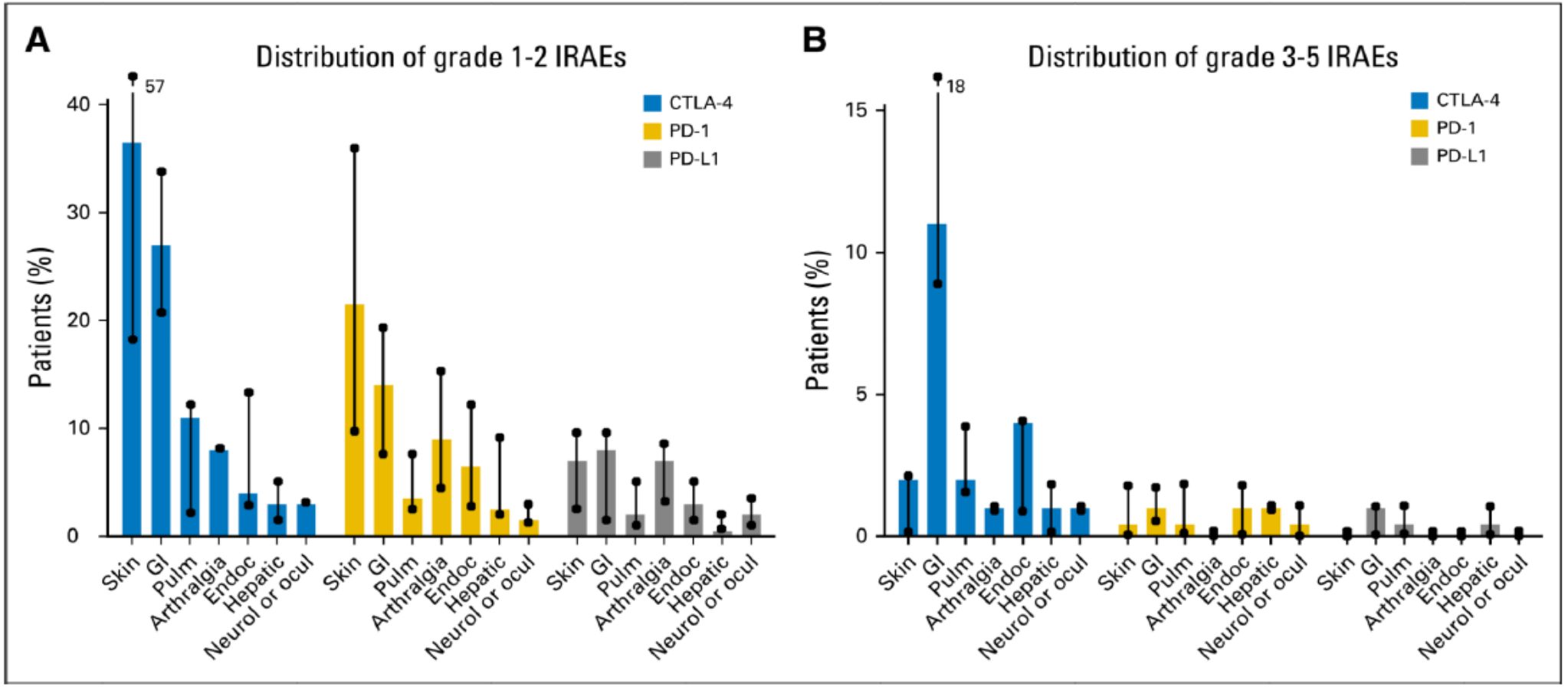

Brahmer et al J Clin Oncol. 2018 June 10; 36(17): 1714–1768

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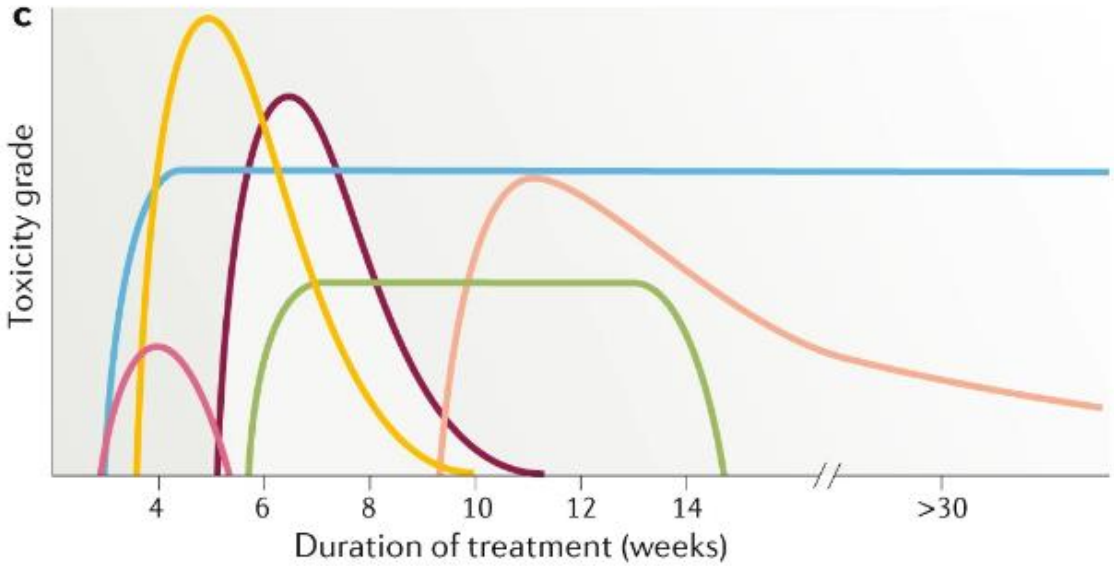
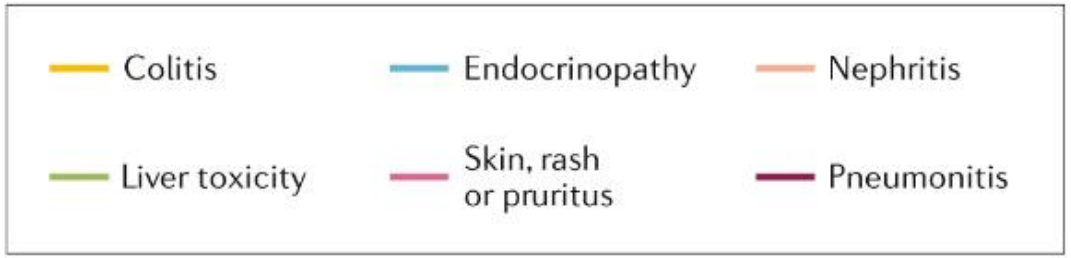
Wanneer te verwachten?





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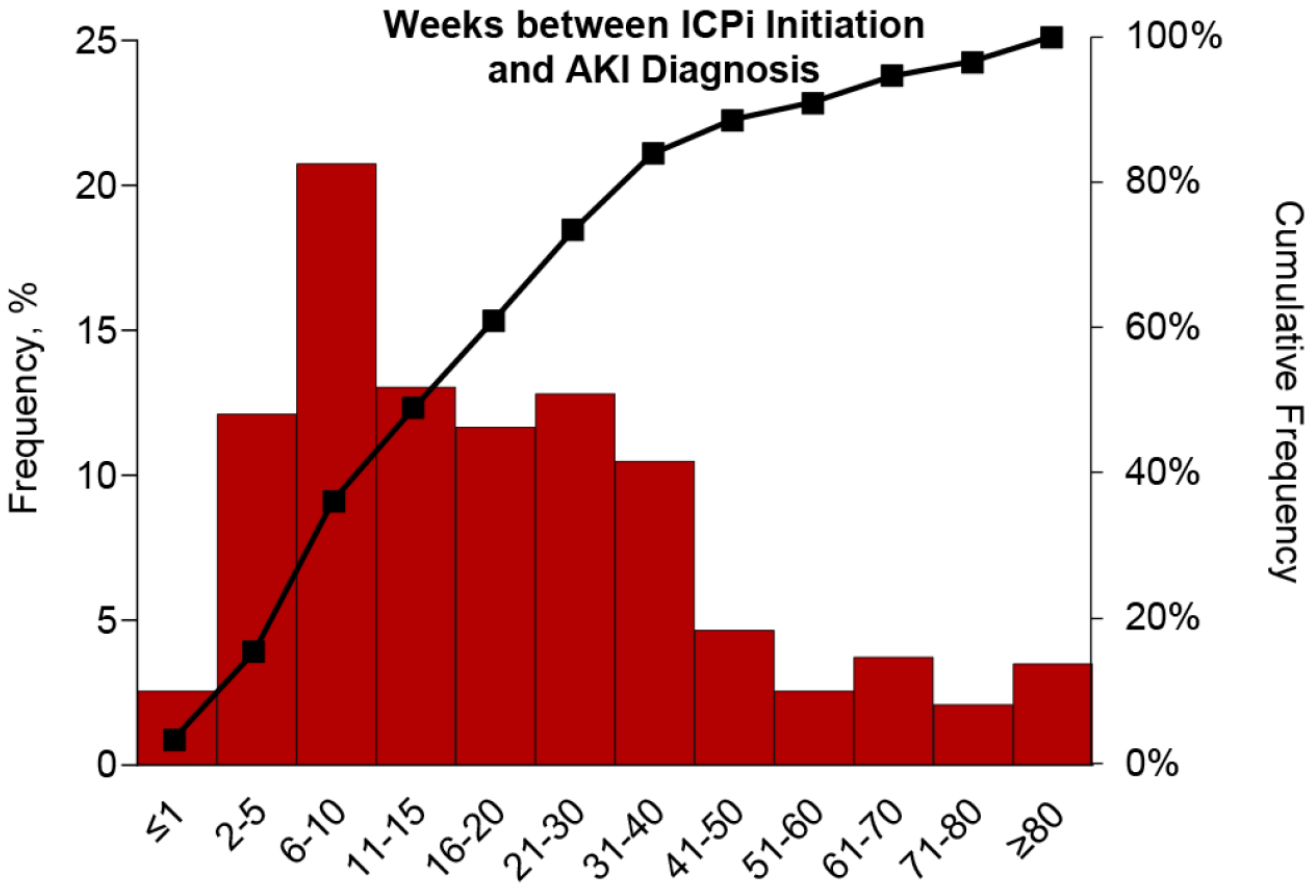

Gupta S, *et al*. *J Immunother Cancer* 2021;9:e003

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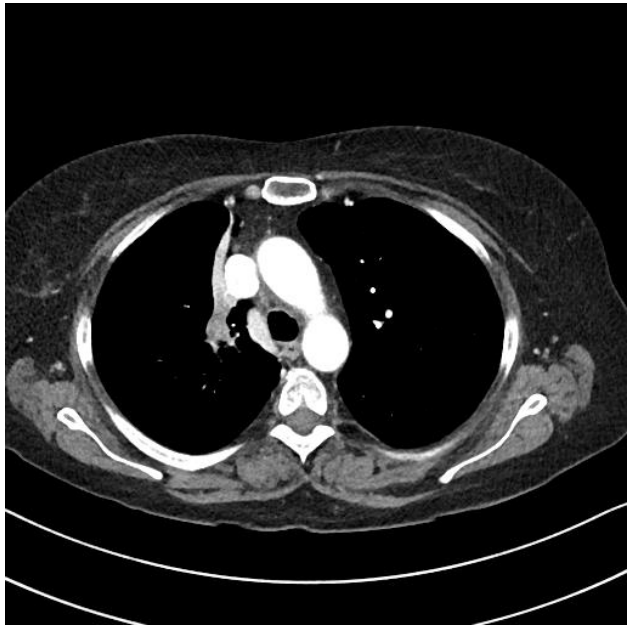
CASUS

- Vrouw, 66 jaar
- Stadium IV NSCLC, adenocarcinoom, PD-L1 30%
- WHO performance score 0
- Medicatie: paracetamol, lisinopril

Na 4 kuren carboplatin-pemetrexed-pembrolizumab partiële respons. Gevolgd door onderhoud pemetrexed-pembrolizumab.

voor

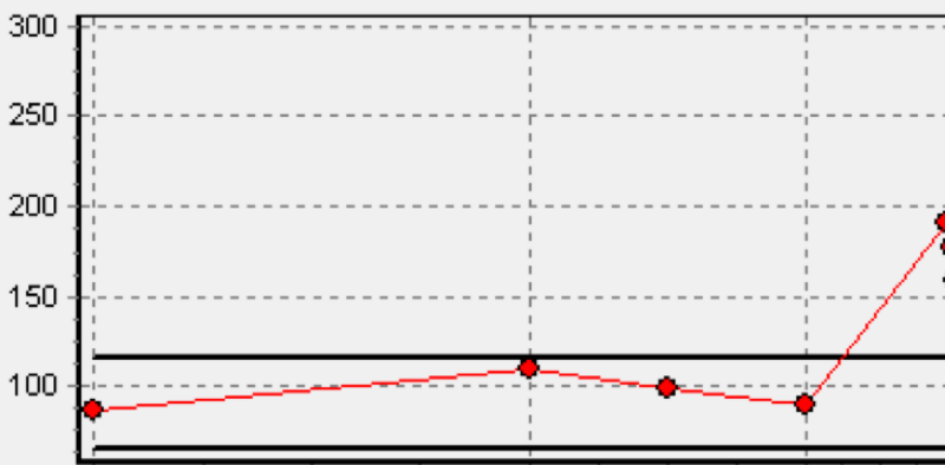


na

CASUS

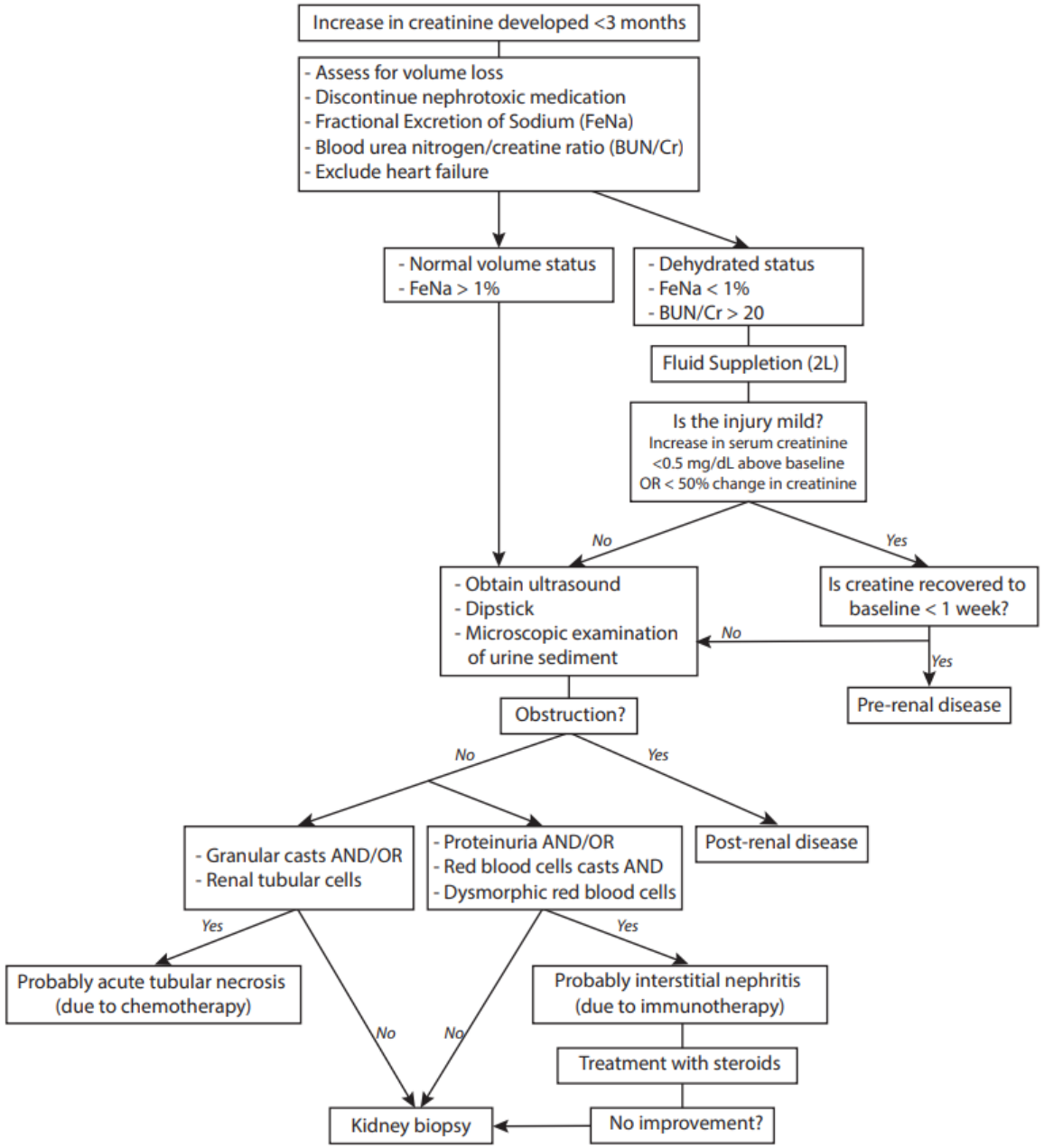
- Na 4 kuren onderhoud pemetrexed-pembrolizumab: stijging kreatinine

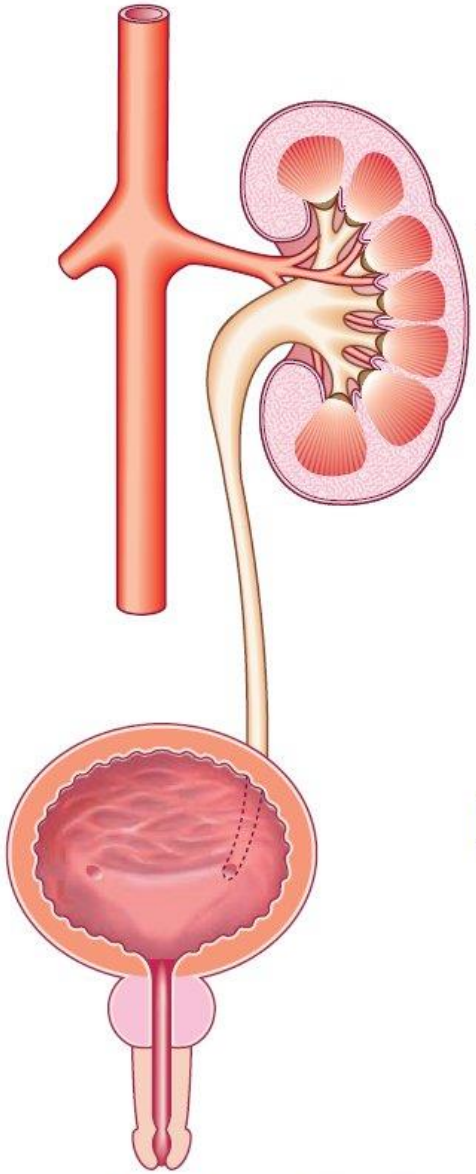
- Anamnese:
  - Normaal dieet, normaal gedronken
  - Geen diarree
  - Medicatie: diclofenac
  - CT met iv contrast



Wat is de diagnose?

1. t.g.v. NSAID i.c.m. ACE-remming
2. t.g.v. iv contrast
3. Interstitiele nefritis t.g.v. pembrolizumab
4. t.g.v. chemotherapie
5. Postrenale obstructie


Increase in creatinine developed <3 months
- Assess for volume loss
- Discontinue nephrotoxic medication
- Fractional Excretion of Sodium (FeNa)
- Blood urea nitrogen/creatine ratio (BUN/Cr)
- Exclude heart failure
- Normal volume status
- FeNa > 1%
- Dehydrated status
- FeNa < 1%
- BUN/Cr > 20
Fluid Suppletion (2L)
Is the injury mild?
Increase in serum creatinine
<0.5 mg/dL above baseline
OR < 50% change in creatinine
No
Yes
- Obtain ultrasound
- Dipstick
- Microscopic examination of urine sediment
Is creatine recovered to baseline < 1 week?
No
Yes
Pre-renal disease
Obstruction?
No
Yes
- Granular casts AND/OR
- Renal tubular cells
- Proteinuria AND/OR
- Red blood cells casts AND
- Dysmorphic red blood cells
Post-renal disease
Yes
Yes
Probably acute tubular necrosis (due to chemotherapy)
Probably interstitial nephritis (due to immunotherapy)
No
No
Treatment with steroids
Kidney biopsy
No improvement?



PRE-RENAL

Impaired perfusion:
- Cardiac failure
- Sepsis
- Blood loss
- Dehydration
- Vascular occlusion

RENAL

Glomerulonephritis
Small-vessel vasculitis
Acute tubular necrosis
- Drugs
- Toxins
- Prolonged hypotension

Interstitial nephritis
- Drugs
- Toxins
- Inflammatory disease
- Infection

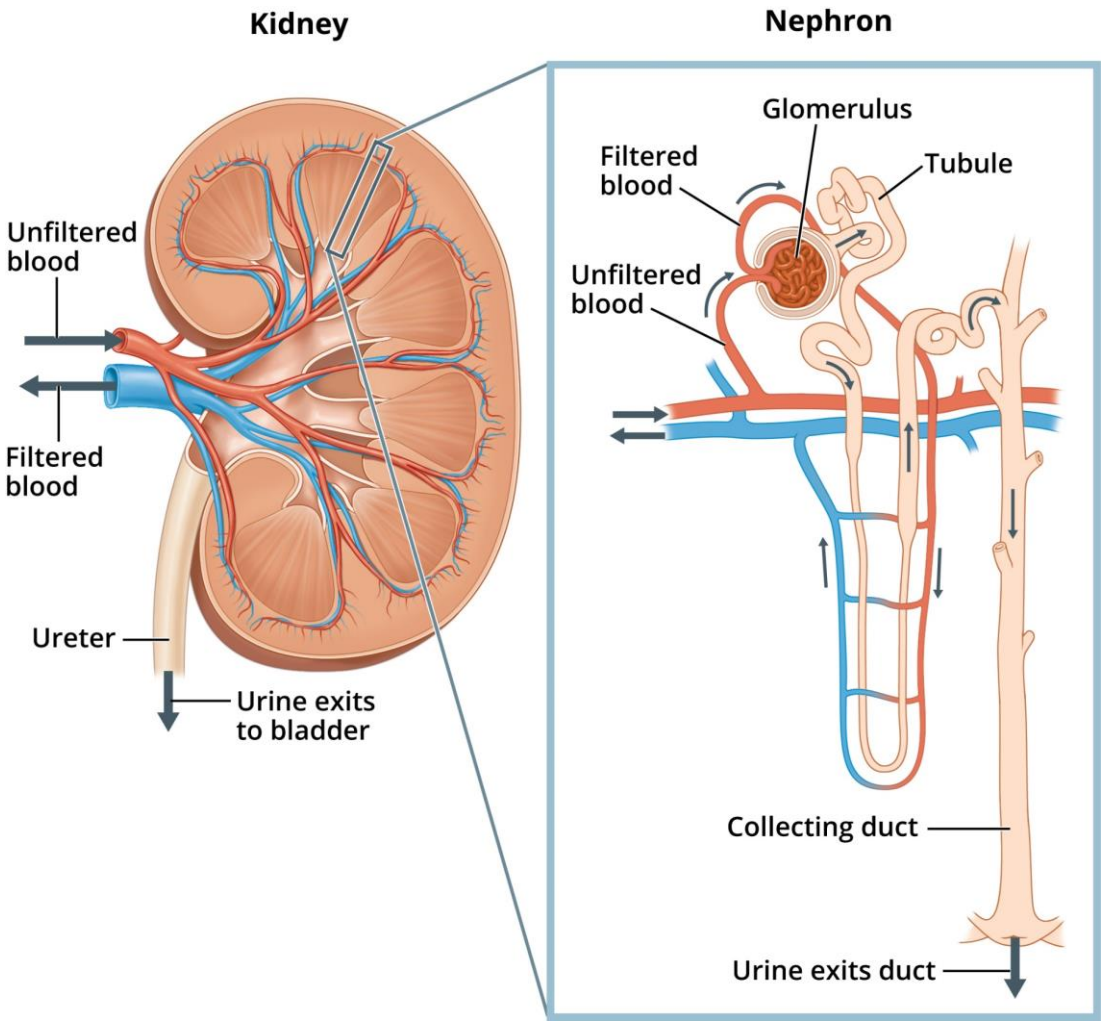
POST-RENAL

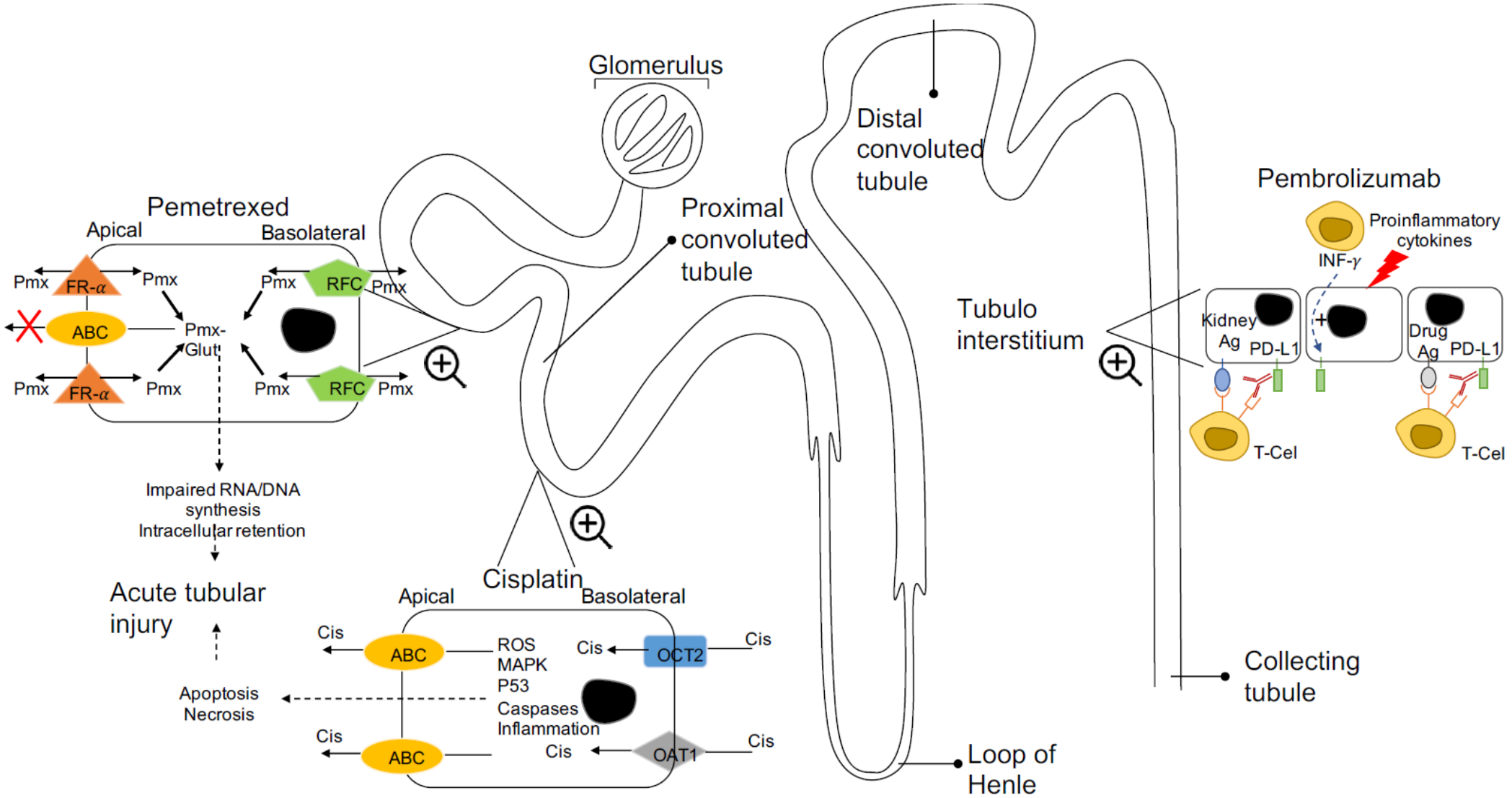
Urinary calculi
Retroperitoneal fibrosis
Benign prostatic enlargement
Prostate cancer
Cervical cancer
Urethral stricture/valves
Meatal stenosis/phimosis

Causes of acute kidney injury.

Source : Davidsons Essentials of Medicine, 2e

VAN DE NIER NAAR HET NEFRON





Dumoulin et al. Journal of Thoracic Oncology Vol. 15 No. 9: 1472–83

Urinary patterns associated with different kidney diseases

Urinary pattern	Kidney disease suggested by pattern
Hematuria with dysmorphic red blood cells, red blood cell casts, varying degrees of albuminuria	Proliferative glomerulonephritis (eg, IgA nephropathy, ANCA-associated vasculitis, lupus nephritis)
Heavy albuminuria with minimal or absent hematuria	Nonproliferative glomerulopathy (eg, diabetes, amyloidosis, membranous nephropathy, focal segmental glomerulosclerosis, minimal change)
Multiple granular and epithelial cell casts with free epithelial cells	Acute tubular necrosis in a patient with underlying acute kidney injury
Isolated pyuria	Infection (bacterial, mycobacterial) or tubulointerstitial disease
Abnormal kidney function with normal dipstick and sediment containing few cells, no casts, and no or minimal proteinuria	▪ Prerenal acute kidney injury due to either volume contraction or an effective decrease in circulating volume (eg, heart failure, liver disease) ▪ Hypercalcemia ▪ Light chain cast nephropathy in multiple myeloma ▪ Tumor lysis syndrome ▪ Vascular disease that produces glomerular ischemia but not infarction (eg, hypertensive emergency, scleroderma, thrombotic microangiopathies) or that affects extraglomerular vessels (eg, cholesterol atheroemboli, polyarteritis nodosa) ▪ Urinary tract obstruction

IgA: immunoglobulin A; ANCA: antineutrophil cytoplasmic antibody.

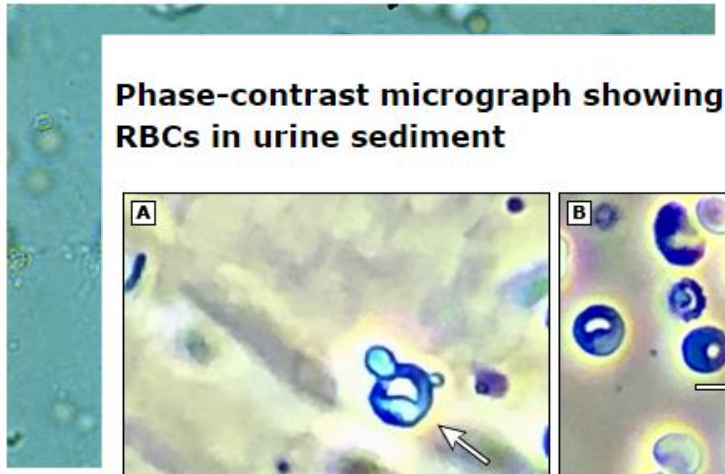
UpToDate®

Photomicrograph showing urine sediment with muddy brown granular casts

Urine sed
casts. Th
necrosis

Courtesy o

Photomicrograph of urine sediment with white blood cell cast (II)



A white
leukocy

Courtesy

Phase-contrast micrograph showing dysmorphic RBCs in urine sediment

Phase-contrast microscopy showing dysmorphic red blood cells (RBCs) and acanthocytes in the urinary sediment of a patient with glomerular hematuria. Acanthocytes (arrows) can be recognized as ring forms with vesicle-shaped protrusions.

Courtesy of Juan Carlos Q Velez, MD.

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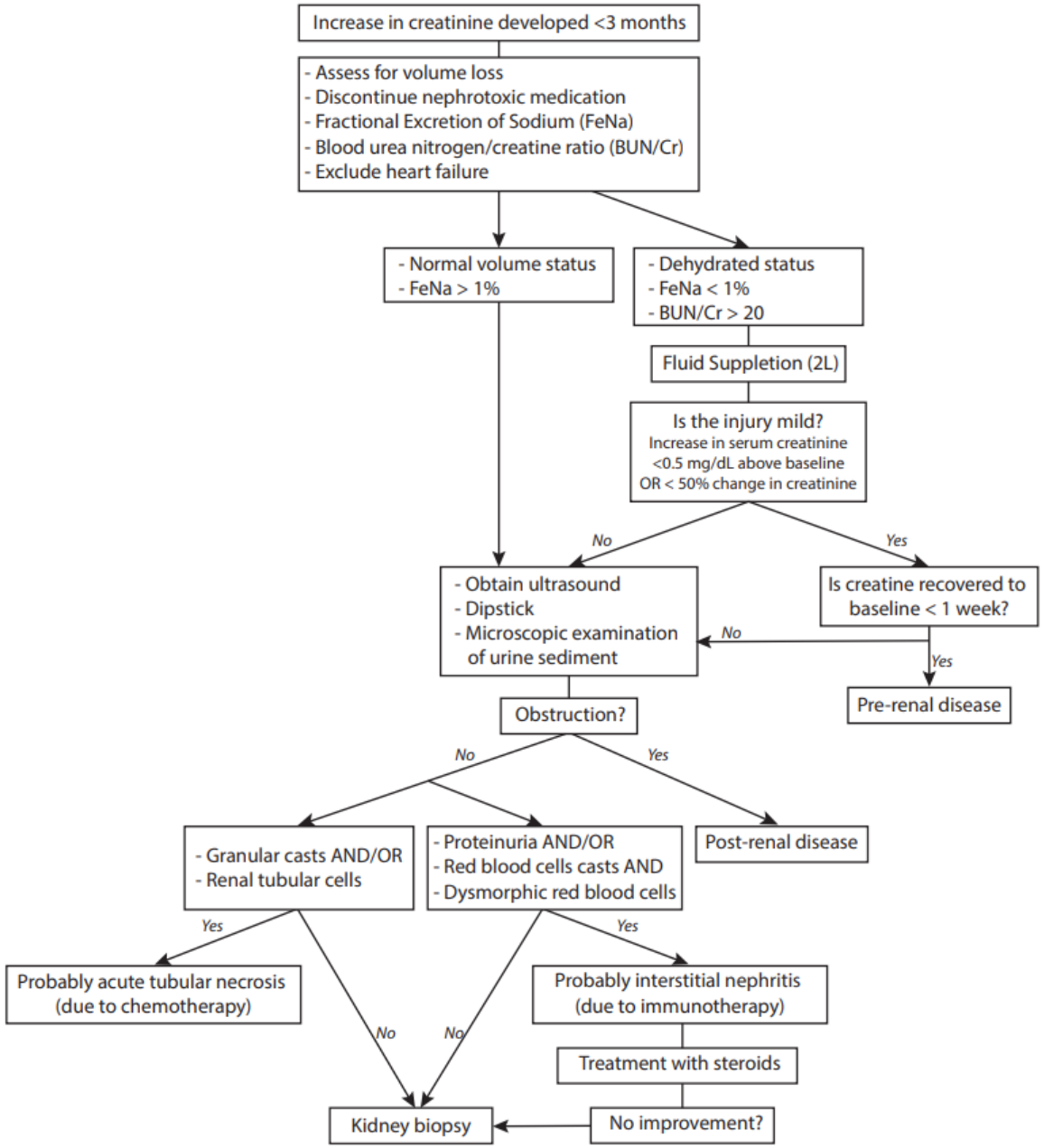
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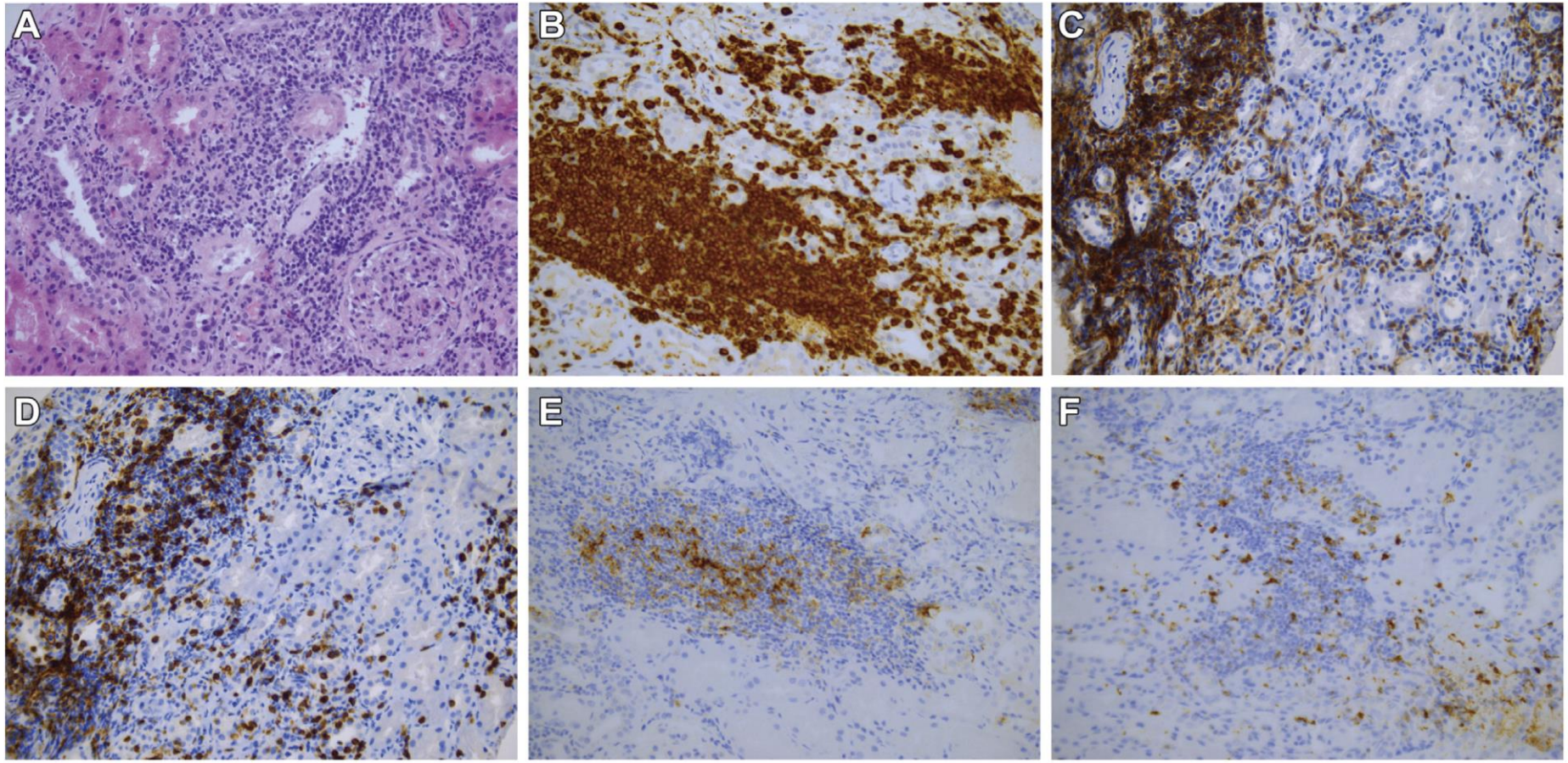
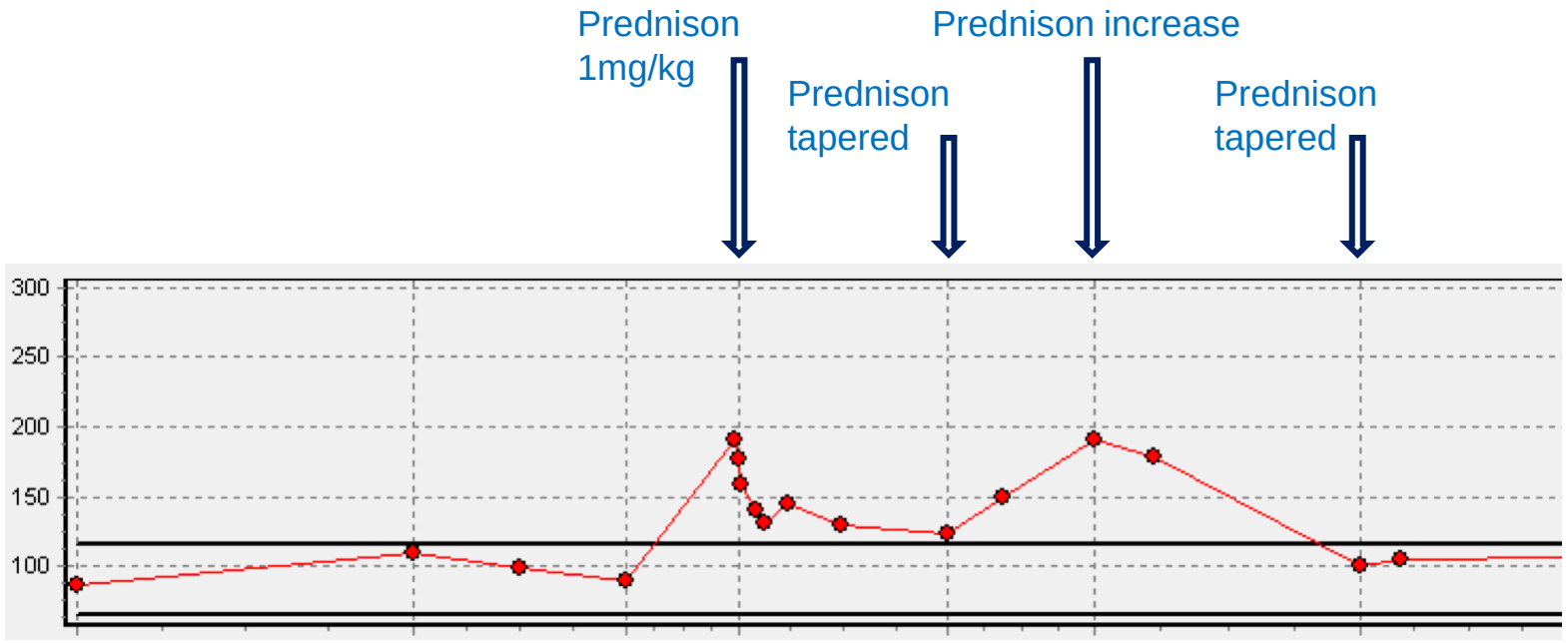
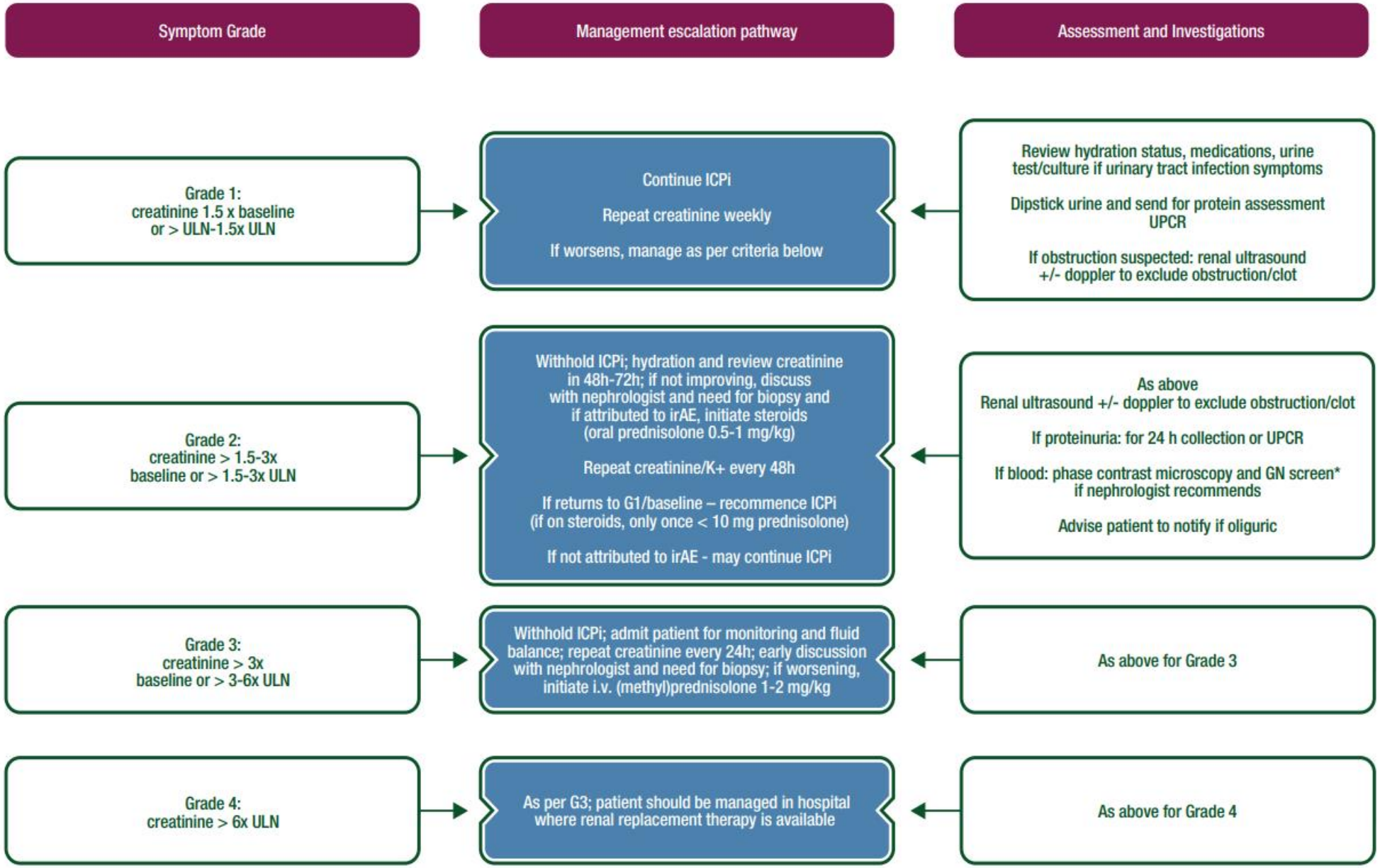


CASUS

Echo: geen post-renale obstructie

Urine microscopie: proteinurie en dysmorfe erythrocyten: TIN t.g.v. pembrolizumab





Haanen et al. Annals of Oncology 28 (Supplement 4): i119–i142, 2017. ESMO Clinical Practice Guidelines.

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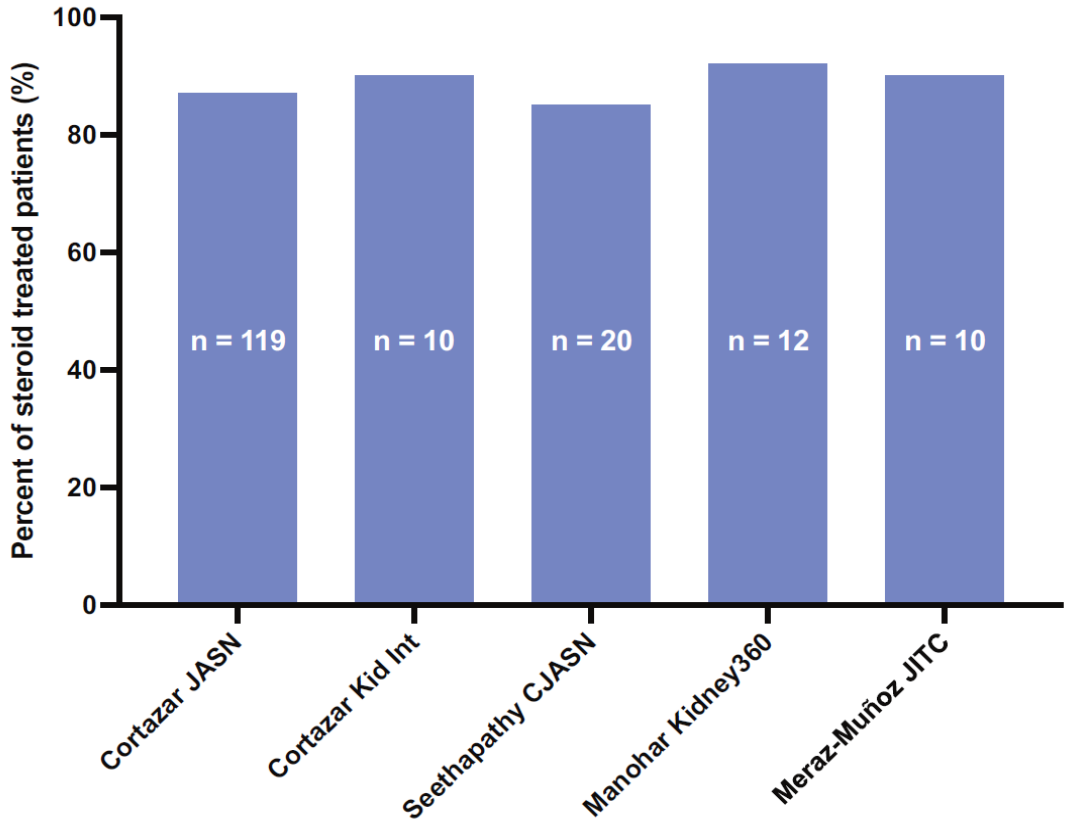
BEHANDELING

- PREDNISOLON
  - Retrospectieve studies

- Bij falen prednisolon?
  - mycofenolaat
  - cyclofosfamide
  - azathioprine
  - ciclosporine
  - infliximab



Seethapathy Kidney Med 2021. 3(6):1074-1081.

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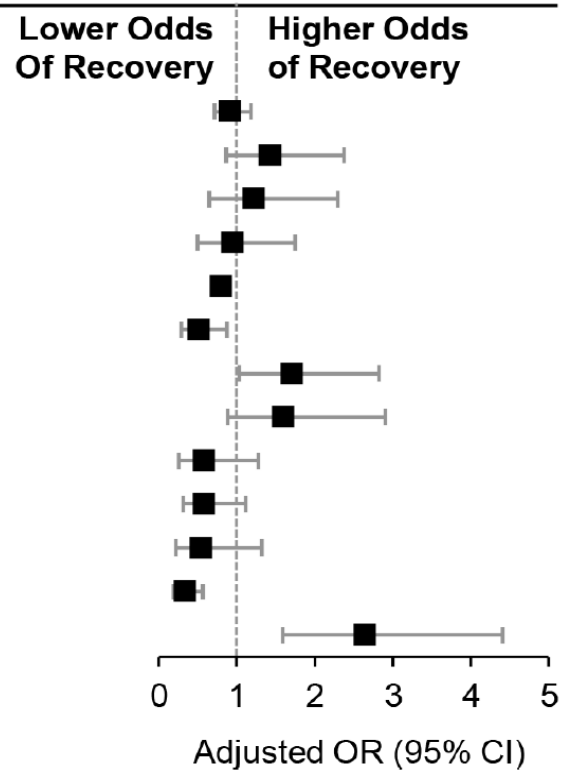
HERSTEL

Voorspellers voor herstel nierfunctie

C

Predictors of Renal Recovery after ICPi-AKI

Variable	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age (per 10 years)	1.10 (0.92-1.34)	0.92 (0.71-1.18)
Male sex	1.80 (1.18-2.75)	1.43 (0.86-2.38)
White	1.57 (0.93-2.67)	1.22 (0.64-2.30)
Combination Therapy	1.65 (0.98-2.77)	0.94 (0.50-1.75)
Baseline eGFR (per 10 points)	0.74 (0.66-0.82)	0.79 (0.69-0.91)
Lung cancer	0.38 (0.25-0.60)	0.51 (0.29-0.87)
Concomitant ATIN-causing medication*	1.50 (0.98-2.29)	1.70 (1.03-2.82)
Concomitant extrarenal irAEs**	2.01 (1.20-3.39)	1.60 (0.88-2.90)
≥2+ Blood on urinalysis	0.49 (0.26-0.90)	0.58 (0.26-1.28)
≥2+ Leukocyte esterase on urinalysis	0.42 (0.24-0.73)	0.58 (0.31-1.12)
≥1 g/g UPCR	0.40 (0.20-0.81)	0.54 (0.22-1.32)
Stage 3 AKI	0.30 (0.20-0.47)	0.33 (0.19-0.57)
Treated with corticosteroids***	2.27 (1.48-3.48)	2.64 (1.58-4.41)



Gupta S, *et al*. *J Immunother Cancer* 2021;9:e003

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NA HERSTEL

En dan?

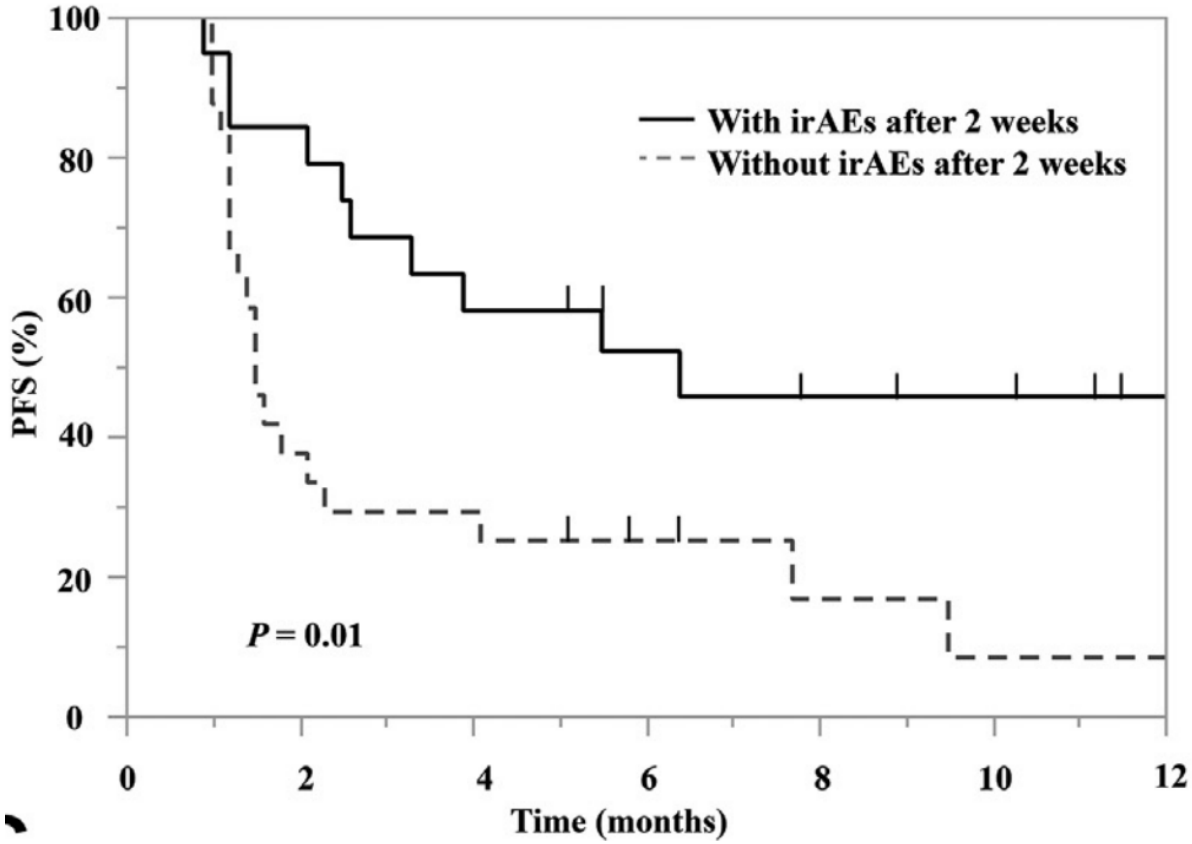
- Wordt de immuuntherapie weer herstart?
- Wanneer hervat je?
- Wat wordt hervat?
  - Nivolumab/ipilimumab
- Immuuntoxiciteit MDO

Table 1. Comparison of Guidelines Based Recommendations for Management of ICI-Induced AKI

Management	NCCN	SITC	ASCO
Immunotherapy	G1 & G2: Hold; G3 & G4: Permanently discontinue	G1 & G2: Hold; G3 & G4: Permanently discontinue	G1 & G2: Hold; G3 & G4: Permanently discontinue
Kidney Biopsy	Consider for G3	No recommendation	Consider kidney biopsy if alternative causes cannot be ruled out
Corticosteroid Taper	G1: None; G2: 0.5-1 mg/kg/day; G3/G4: 1-2 mg/kg/day; Taper over 4-6 weeks once Cr <=G1; Monitor Cr weekly	Dose/schedule to be individualized and based on grade	G1: None; G2: 0.5-1 mg/kg/day; G3/G4 or no improvement or worsening in G2: 1-2 mg/kg/day; Taper over 4-6 weeks once Cr <=G1; Monitor Cr weekly
Other immunosuppression	Add immunosuppression (cyclophosphamide, mycophenolate, azathioprine, infliximab) if Cr> G2 after 1 week	No recommendation	Add immunosuppression(e.g. Mycophenolate) of worsening or no improvement in: 7 days (G2)/3-5 days (G3)/2-3 days (G4)

Note: Recommendations by major societies or expert working groups on the management of checkpoint inhibitor related acute kidney injury.[43,44,63] Grading of renal immune-related adverse event is based on CTCAE (Common Terminology Criteria for Adverse Events) v5.0 criteria and is defined by elevation of creatinine above baseline.[54] Mild (G1): 1.5-2× baseline Cr or 0.3 mg/dL elevation above baseline; Moderate (G2): 2-3× baseline Cr; Severe (G3): >3× baseline Cr; Life-threatening (G4): >6× baseline Cr or dialysis indicated.
Abbreviations: ASCO, American Society of Clinical Oncology; Cr, creatinine; NCCN, National Comprehensive Cancer Network; SITC, Society for Immunotherapy of Cancer.

TOXICITEIT EN TUMOR RESPONS



Teraoka et al. *Early Immune-Related Adverse Events and Association with Outcome in Advanced Non–Small Cell Lung Cancer Patients Treated with Nivolumab: A Prospective Cohort Study* Journal of Thoracic Oncology Vol. 12 No. 12: 1798-1805

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TAKE HOME MESSAGE

- Immuuntherapie is een gevestigde behandeling bij thoracale oncologie
- Combinatie met chemotherapie maakt differentiëren in aard etiologie lastiger
- Multidisciplinair overleg en benadering m.b.t. behandeling en rechallenge
- Ruimte voor individueel plan voor patiënt

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VRAGEN?