Update in immunotherapy and the kidneys

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Medical Oncologist

General dogsbody in a fancy translational research lab

Contents

- Advances in the treatment of metastatic melanoma with immune checkpoint inhibitors
- Renal toxicity with immune checkpoint inhibitors
- Immune checkpoint inhibitors in “special populations”
  - Chronic kidney disease/end stage renal failure
  - Allogeneic kidney transplant
  - Autoimmune disease
- What about BRAF inhibitors?

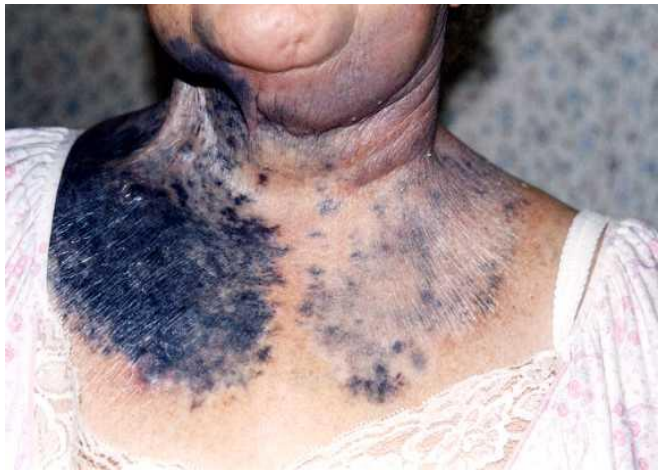
Melanoma Institute Australia

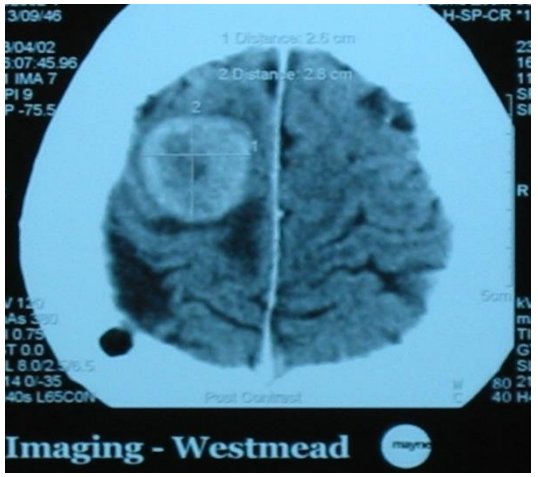
Update in immunotherapy and the kidneys

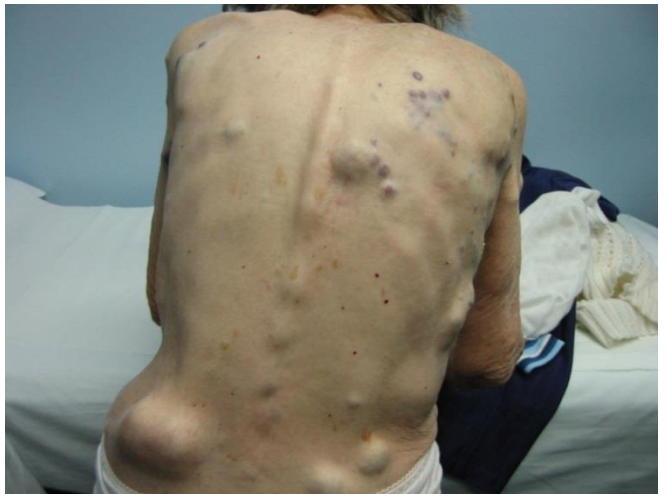
IMMUNE CHECKPOINT INHIBITORS SAVE THE DAY

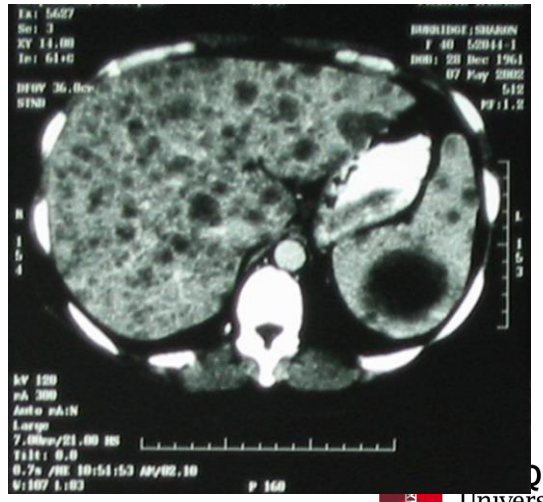
Metastatic melanoma in Australia

- >1500 Australian deaths yearly
- Most common cancer causing death in young adults
- Brain metastases present in a fifth at presentation
  - Contributing to death in the majority
- Chemotherapy resistant with a particularly poor prognosis
  - Median OS < 12 months









Photos curtesy of Rick Kefford

Randomised phase III trial: Temozolomide vs Dacarbazine

TEMOZOLOMIDE OR DTIC FOR METASTATIC MELANOMA

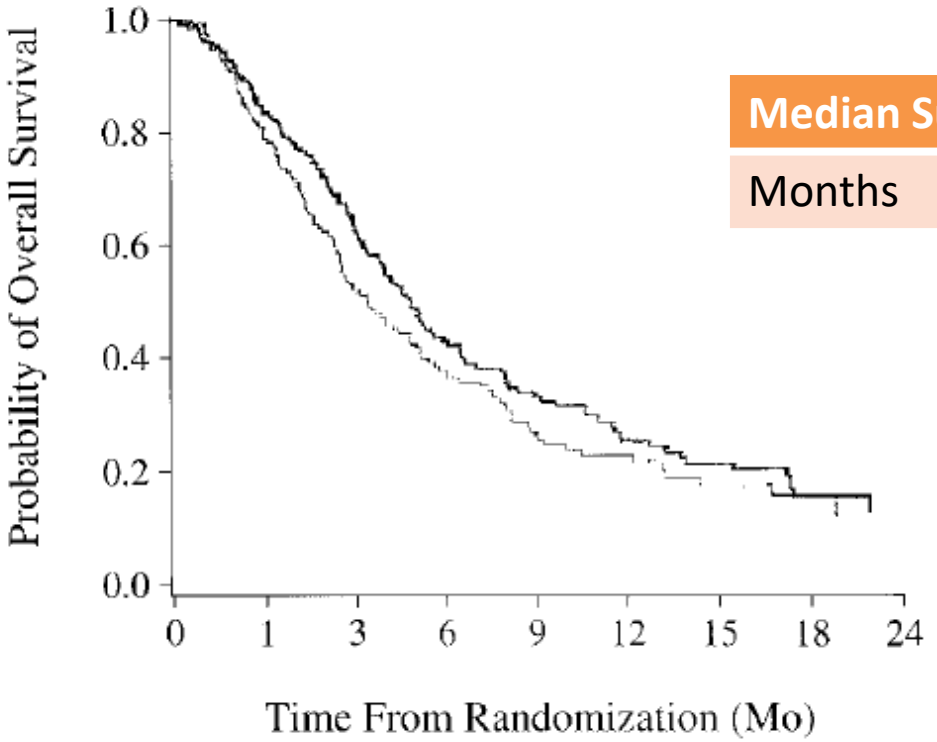


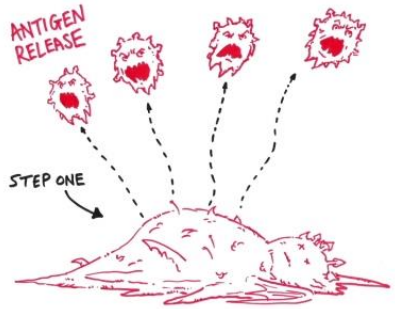
Fig 1. Overall survival in the temozolomide (thick line) and DTIC (thin line) treatment groups.

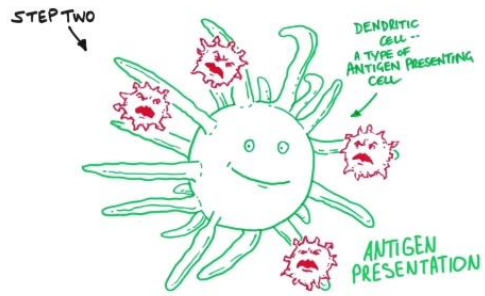
Median Survival	DTIC	Tem.
Months	6.4m	7.7m

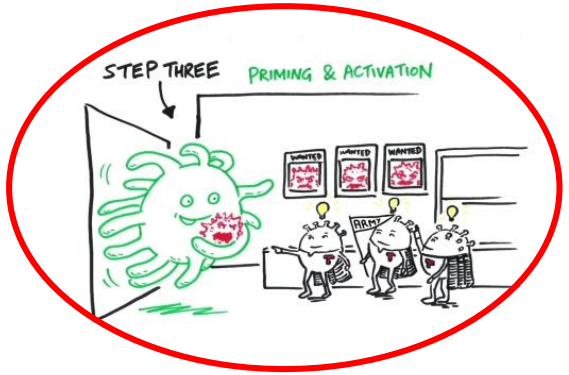
1. Middleton, et al., J Clin Oncol 18:158-166

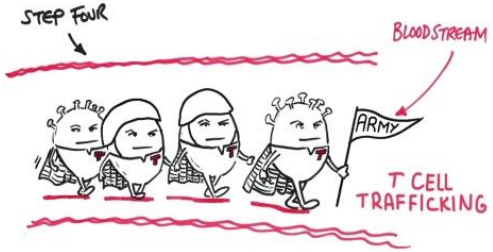
A very immunological cancer

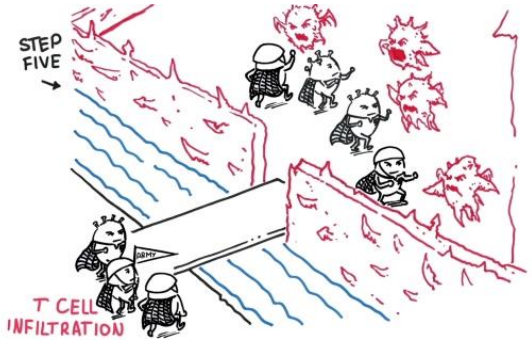
- Melanoma antigens are being recognised by T-cells
  - One of the highest mutation rate and genomic alteration
- Prognostic significance of immune infiltrates in primary tumours
  - Spontaneous regression of primary melanomas
- Association between vitiligo and melanoma regression with treatment
- Highest solid organ response to immune checkpoint inhibitors

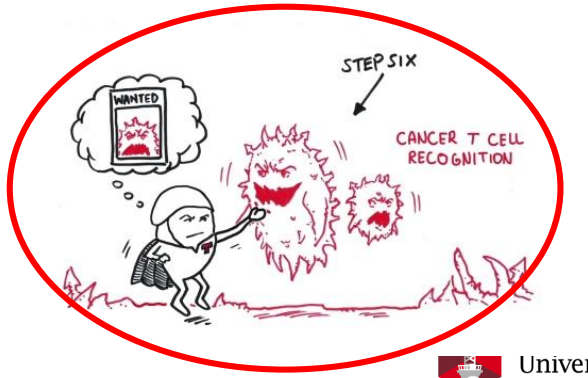








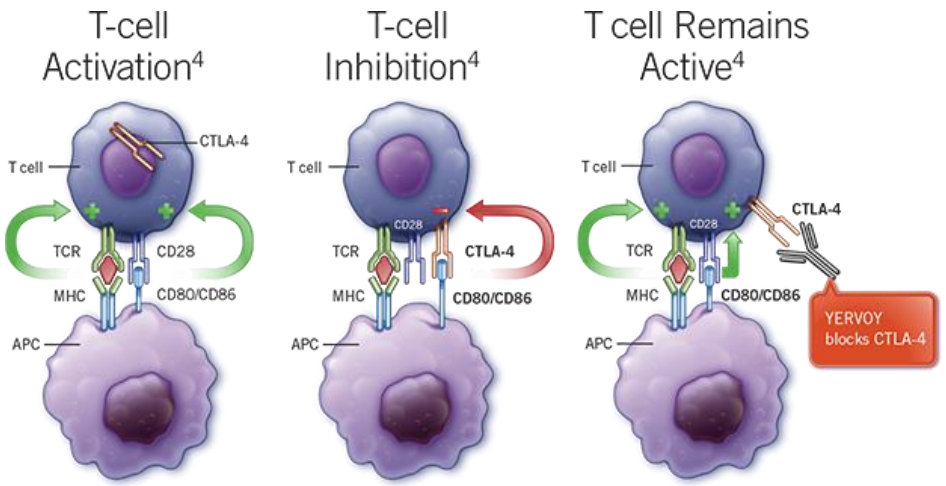


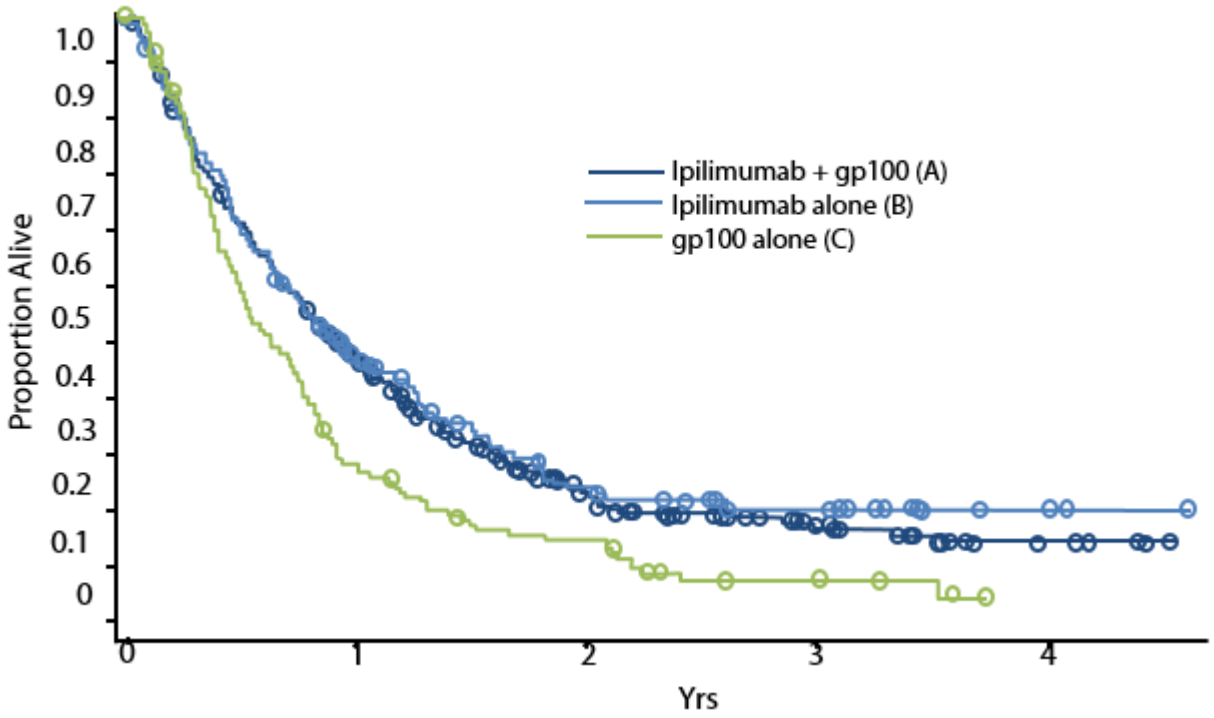


May KF Jr et al. Cancer Immunotherapy. 2nd ed. Elsevier; 2013:101–113.

Ipilimumab (anti-CTLA-4): the first drug to show improvement in overall survival

3. The priming phase

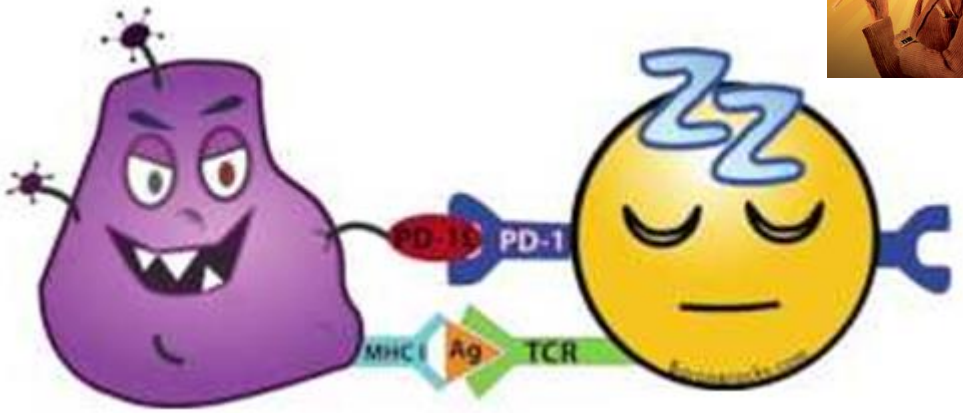




Hodi FS, et al. N Engl J Med. 2010;363:711-723.

PD-1/PD-L1 interaction: What's really happening…

6. Immune activation through interferon gamma signalling

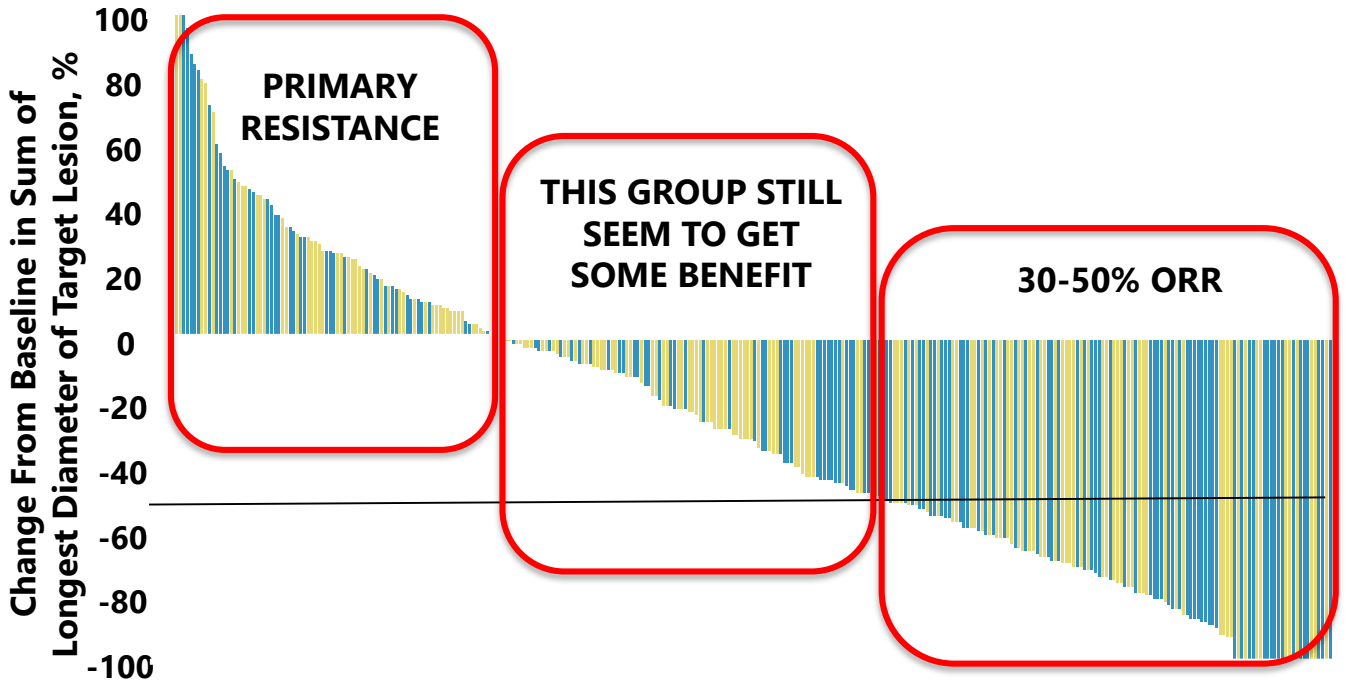


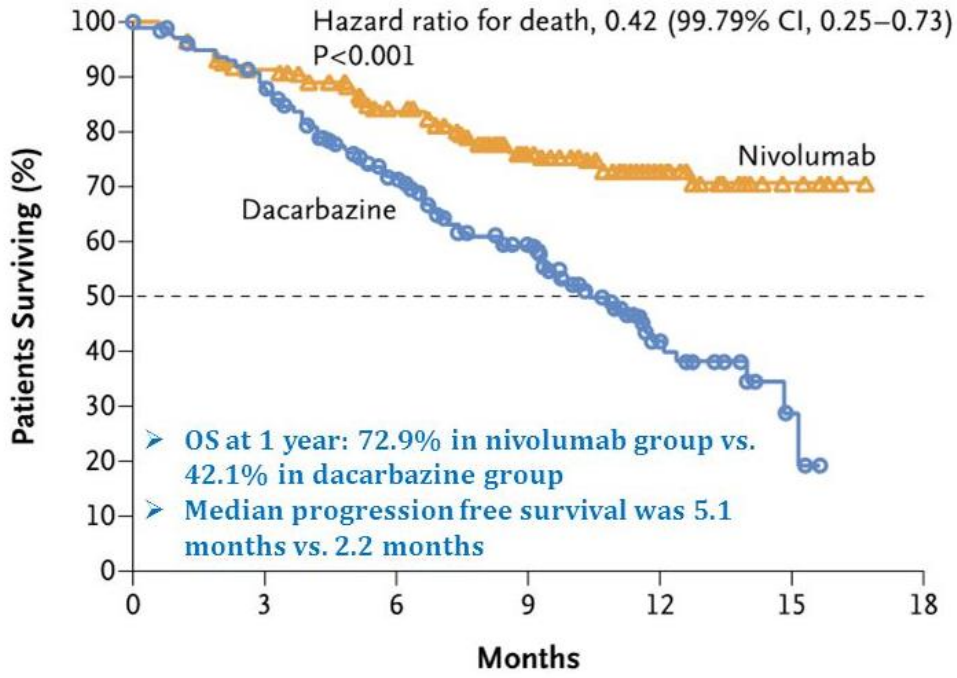
Melanoma Cell

Cytotoxic T cell

Anti-PD1 works (but not on everyone…)

Individual Patients Treated With Pembrolizumab KEYNOTE 001





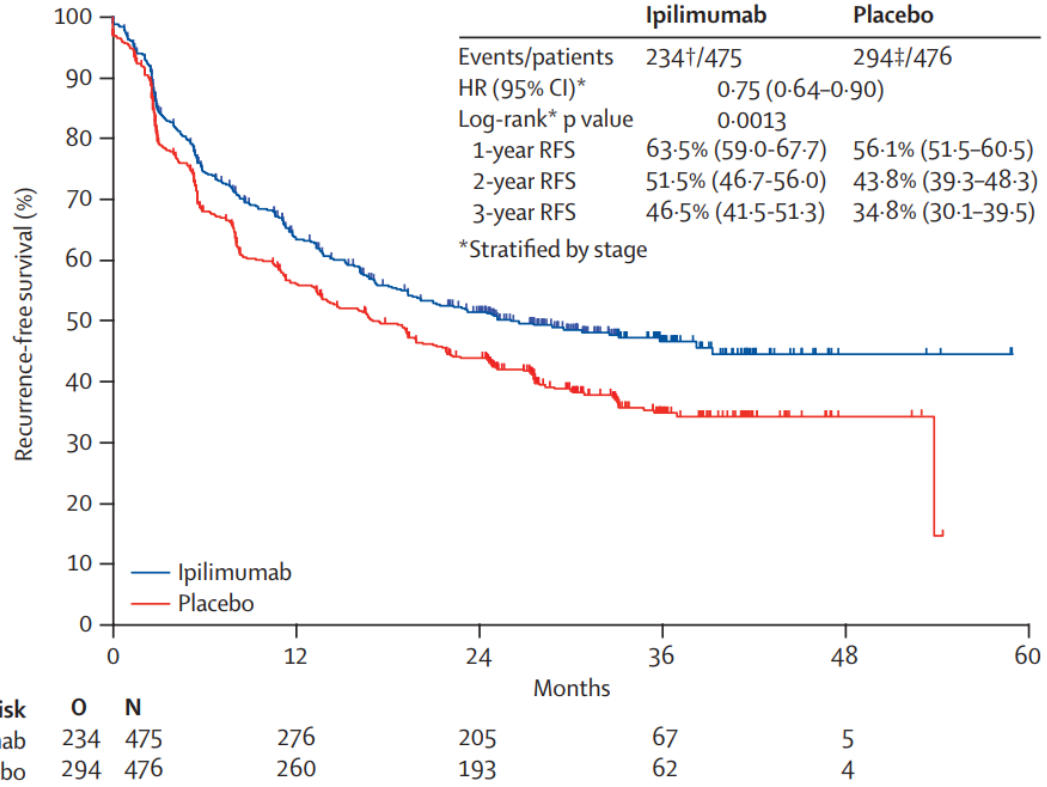
1. Ribas A, et al. ASCO 2014. 2. Robert C, et al. N Engl J Med. 2015 Jan;372:320-30

Complete response to PD-1 antibodies are sustained

MK3475-001 Trial, M1c disease, Westmead Hospital Sydney
Commenced treatment Feb 2012 – complete remission off treatment Sept 2015

MK3475-006 Trial, M1c disease, Westmead Hospital Sydney
Commenced treatment April 2013 –

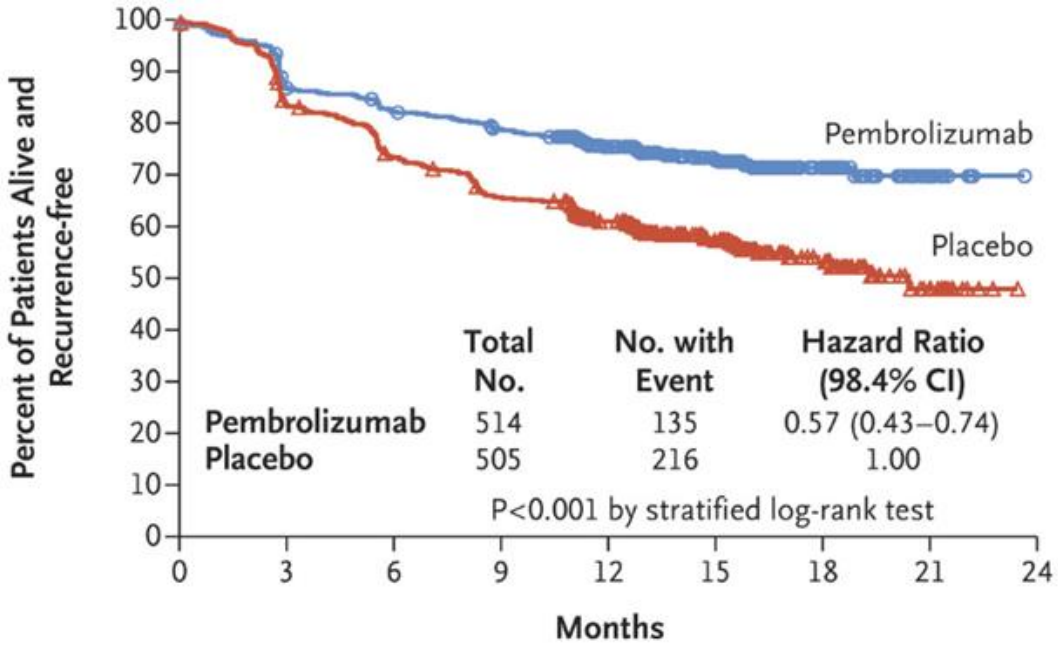
Immune checkpoint inhibitors in the adjuvant setting



	Ipilimumab	Placebo
Events/patients	234†/475	294‡/476
HR (95% CI)*	0·75 (0·64–0·90)	
Log-rank* p value	0·0013	
1-year RFS	63·5% (59·0-67·7)	56·1% (51·5–60·5)
2-year RFS	51·5% (46·7-56·0)	43·8% (39·3–48·3)
3-year RFS	46·5% (41·5-51·3)	34·8% (30·1–39·5)

*Stratified by stage

Number at risk	O	N				
Ipilimumab	234	475	276	205	67	5
Placebo	294	476	260	193	62	4



	Total No.	No. with Event	Hazard Ratio (98.4% CI)
Pembrolizumab	514	135	0.57 (0.43–0.74)
Placebo	505	216	1.00

No. at Risk									
Pembrolizumab	514	438	413	392	313	182	73	15	0
Placebo	505	415	363	323	264	157	60	15	0

1. Eggermont A, et al. N Engl J Med. 2016;375:1845-1855. 2. Eggermont A, et al. N Engl J Med. 2018;378:1789-1801

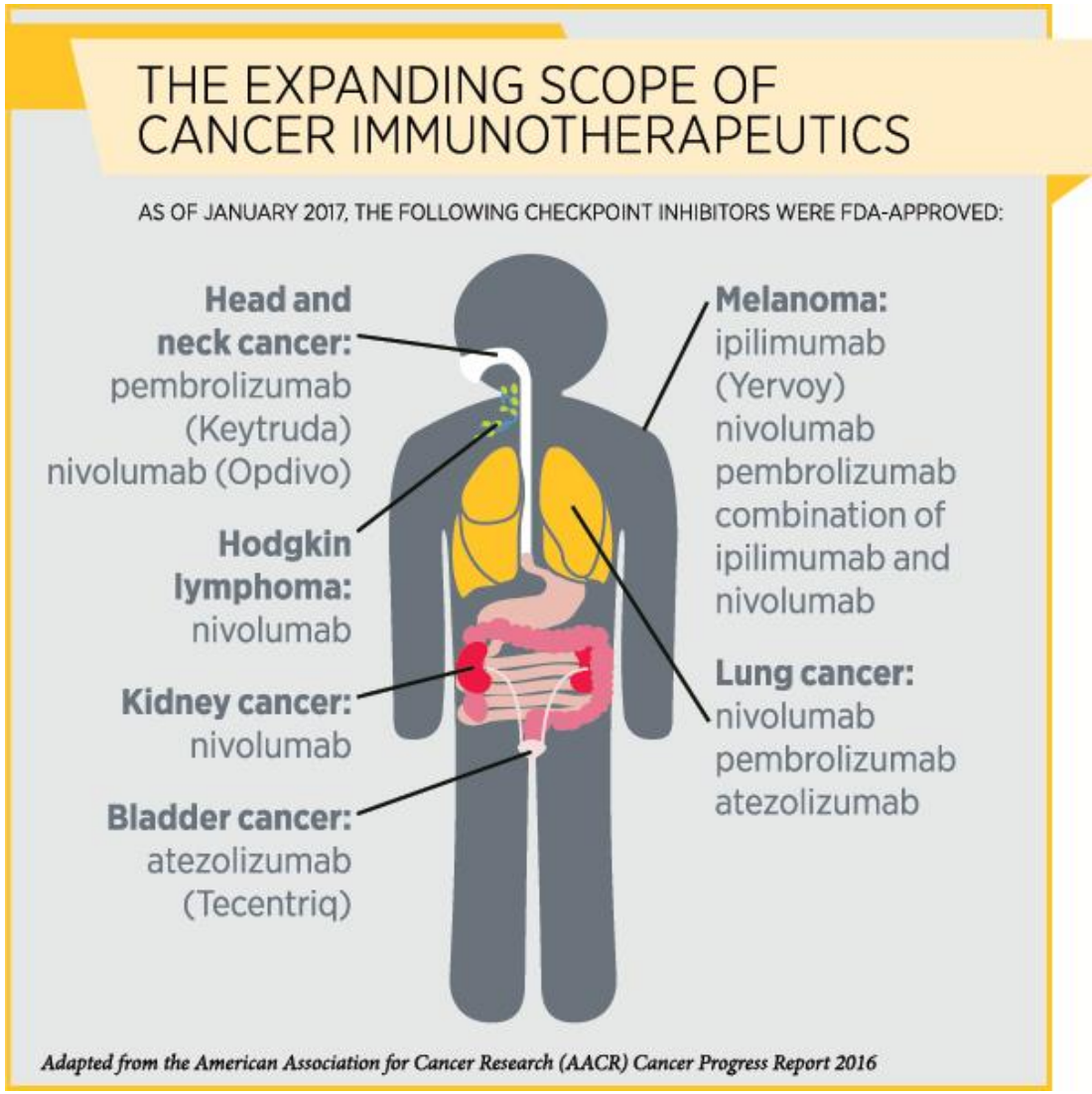
Immunotherapy, here to stay

18th common (1 in 47)

6th common (1 in 36)

9th common (1 in 65)

12th common (1 in 68)



4th common (1 in 17)

5th common (1 in 17)

PBS The Pharmaceutical Benefits Scheme

Melanoma Institute Australia

Immune checkpoint inhibitor	Ipilimumab	Nivolumab	Pembrolizumab
PBS listed indications	- Unresectable stage III/IV melanoma	- Unresectable stage III/IV melanoma - Locally advanced or metastatic non-small cell lung cancer - Clear cell variant renal cell carcinoma - Recurrent/metastatic SCC of the head and neck	- Unresectable stage III/IV melanoma - Treatment refractory Hodgkin's lymphoma

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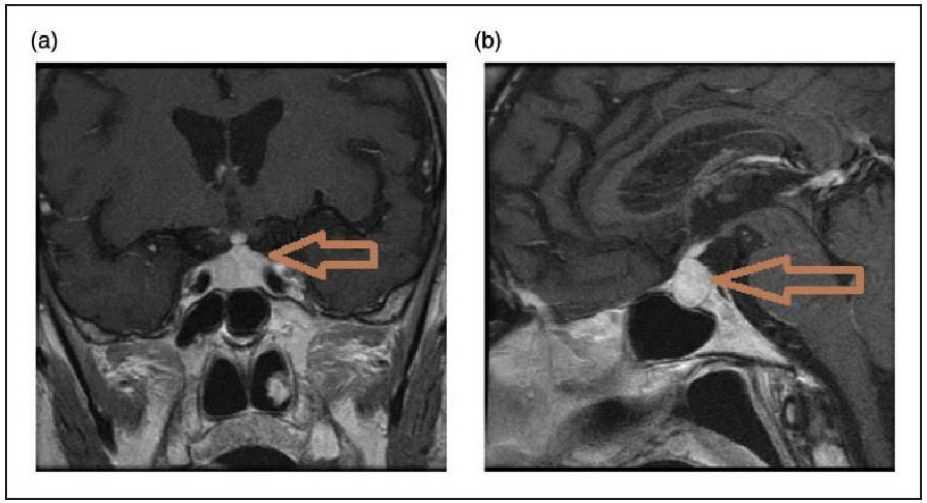
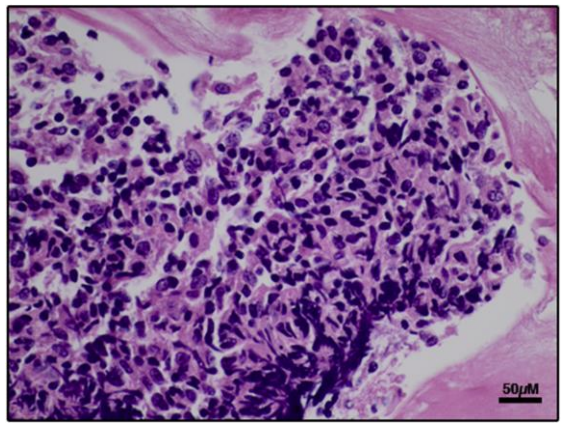
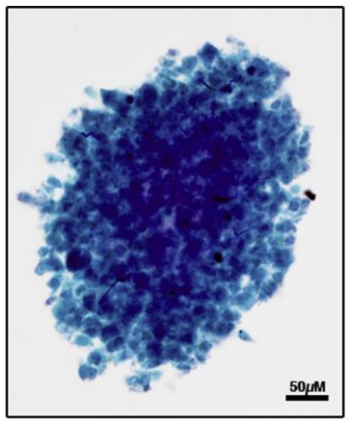
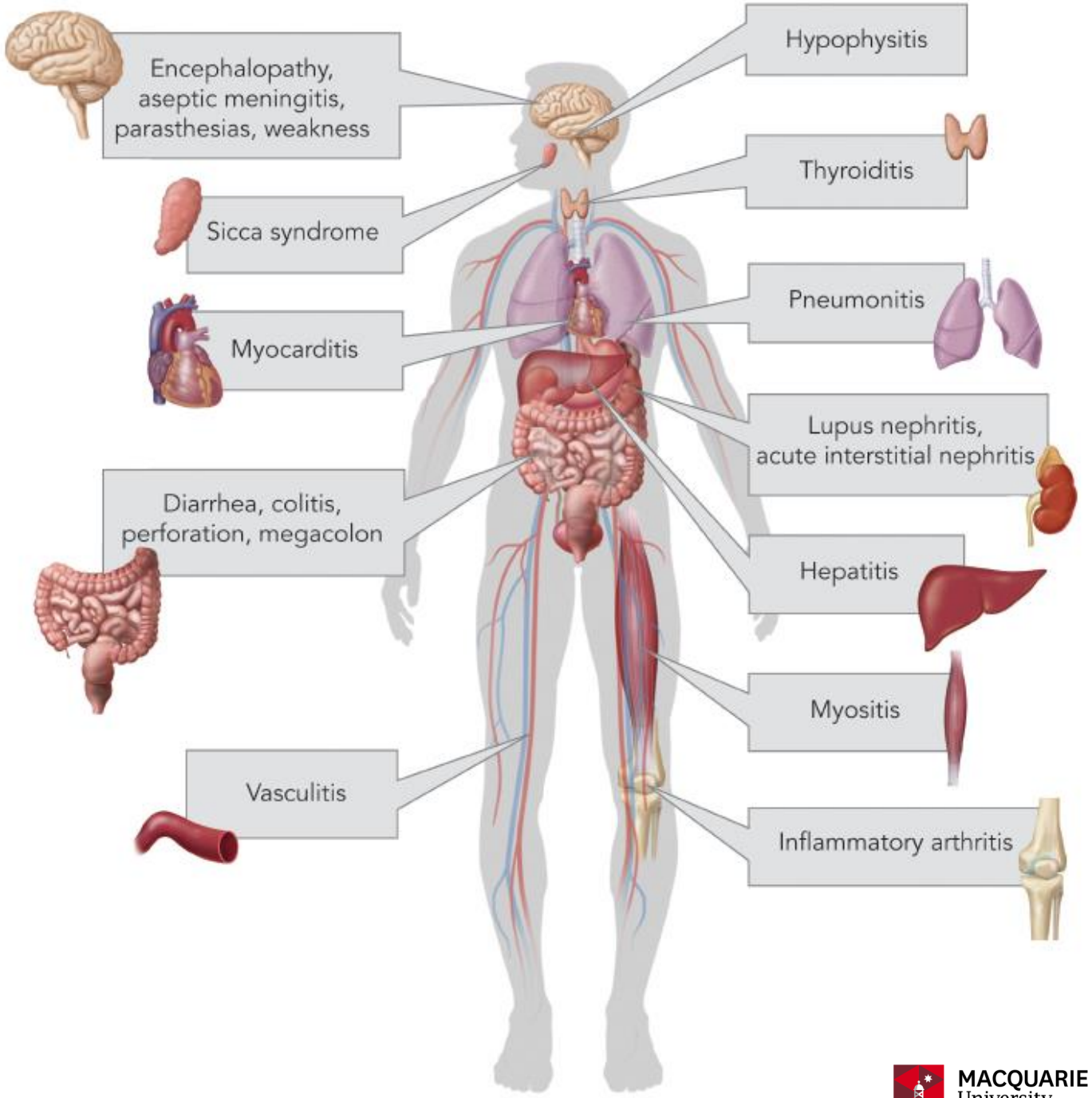
Immune Mediated Adverse Events



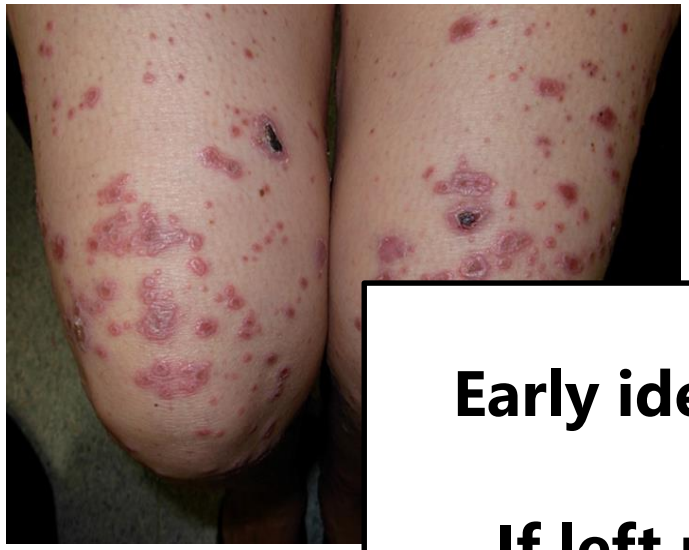


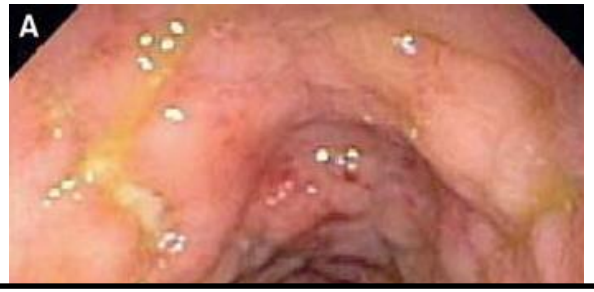


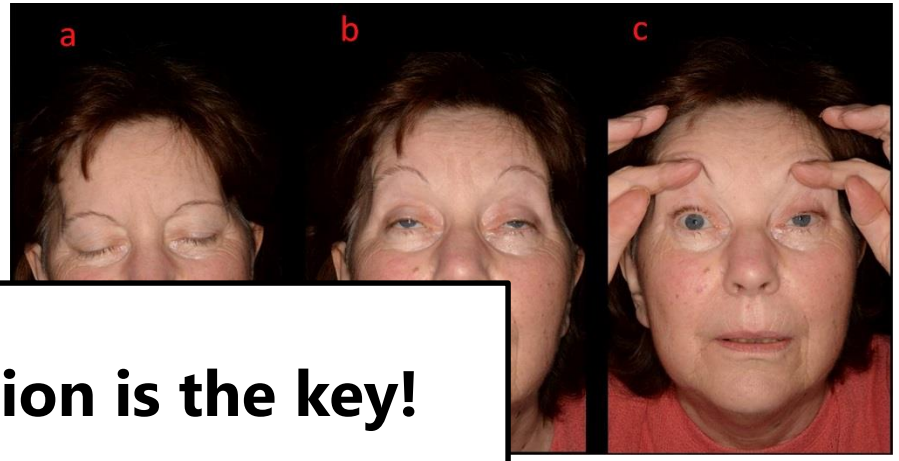


1. Valecha G, et al. J Oncol Pharm Pract. 2017:1078155217727142. 2. Angell T, et al. Genes Dis. 2018;5(1):46-48.

Clinical presentations of irAE

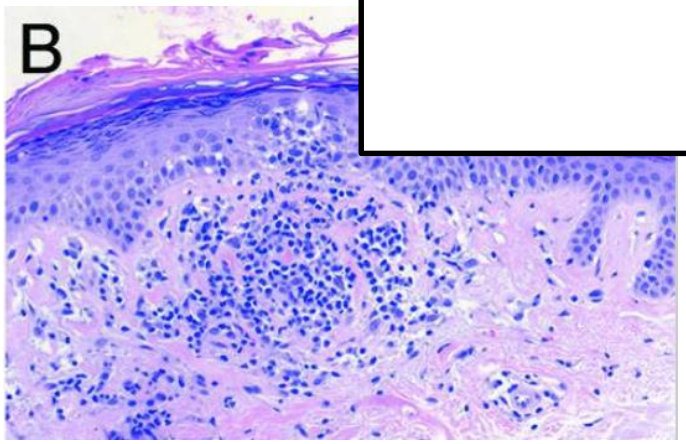


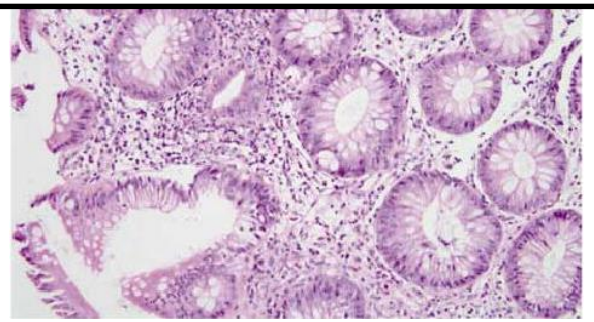


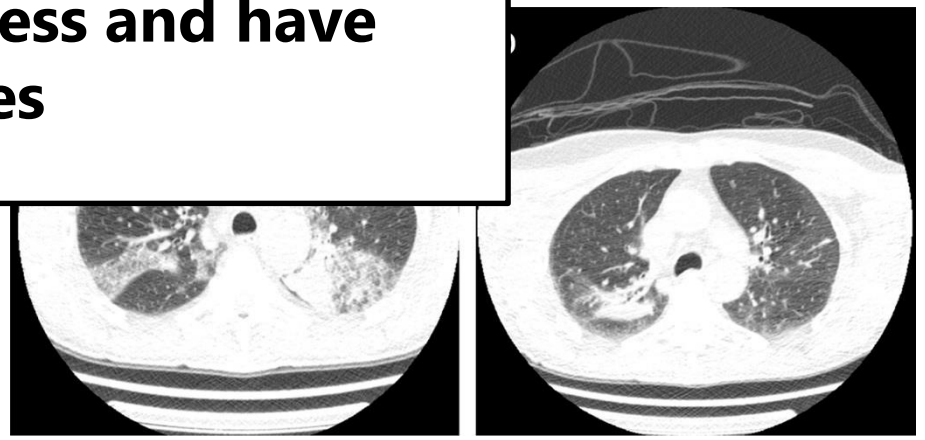


Early identification and intervention is the key!

If left untreated, irAE can progress and have devastating outcomes







1. Hodi F, et al. Proc Natl Acad Sci USA. 2003;100:4712-4717. 2. Maker A, et al. Ann Surg Oncol. 2005;12:1005-1016. 3. Zimmer L, et al. Eur J Cancer. 2016;60:210-225.

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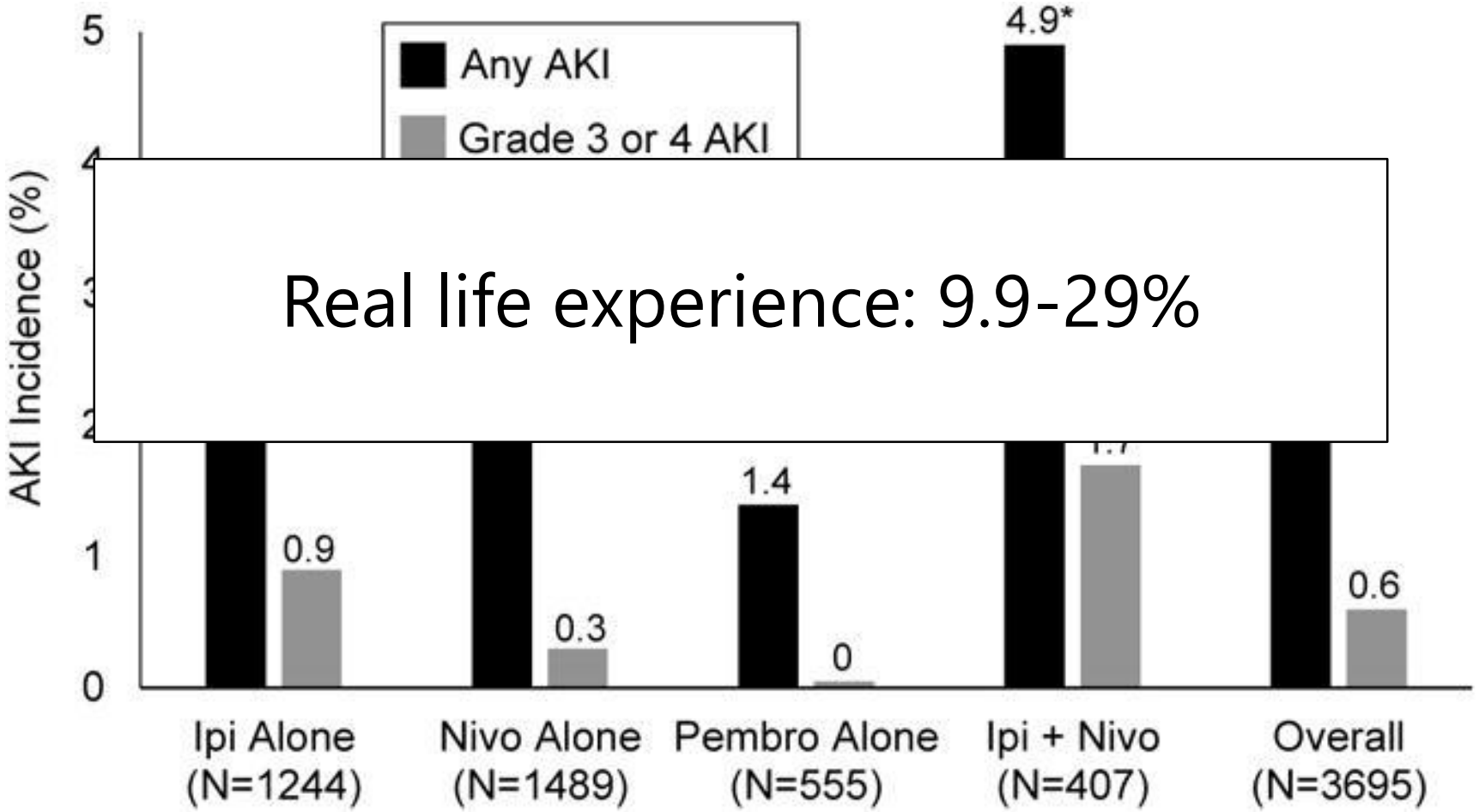
Update in immunotherapy and the kidneys

IMMUNE-MEDIATED KIDNEY INJURY

What is the risk of developing immune related nephritis with immune checkpoint inhibitors?

1. <5%
2. 5-10%
3. 10-20%
4. >20%
5. It depends

Estimated incidence of ICI-associated AKI



Real life experience: 9.9-29%

1. Cortazar F, et al. Kidney Int. 2016 Sep;90(3):638-47. 2. Wanchoo R, et al. Am J Nephrol. 2017;45(2):160-169.

Clinical features

- Usually asymptomatic
  - Hypertension 11%
  - Haematuria 11% (usually microscopic)
  - Pyuria 68%
  - Rise in serum creatinine 100% (duh..that's the definition..)
  - Eosinophilia 21%
  - Nephrotic syndrome is rare

- Onset from start of drug treatment variable
  - Ipilimumab: 6-12 weeks but up to 6 months
    - Delayed onset association with worse outcome (steroid refractory, need to dialysis)
  - Anti-PD1: 3-12 months
    - Outcome not association with timing of onset

Wanchoo R, et al. Am J Nephrol. 2017;45(2):160-169.

Mechanism of injury

- CTLA-4: primer phase
  - Uncontrolled activation of auto-reactive T cells
- PD-1/PD-L1 axis: effector phase
  - Normal up-regulation of PD-L1 by renal cells
  - Essential in preventing inflammatory responses in target organs such as the kidney
- Acute interstitial nephritis most common
  - But not your typical drug induced hypersensitivity AIN
  - Heterogeneity of time course, delayed response and need for immunosuppression
    - Renal function did not improve in patients who did not receive corticosteroids (small case series)
  - Renal injury exacerbated nephrotoxic drugs (NSAIDs, PPI)
    - Exhausted drug specific T cells primed by these drugs can be reactivated, causing damage
- Glomerulonephritis can occur with ipilimumab
  - Case reports of minimal change or membranous GN has been reported

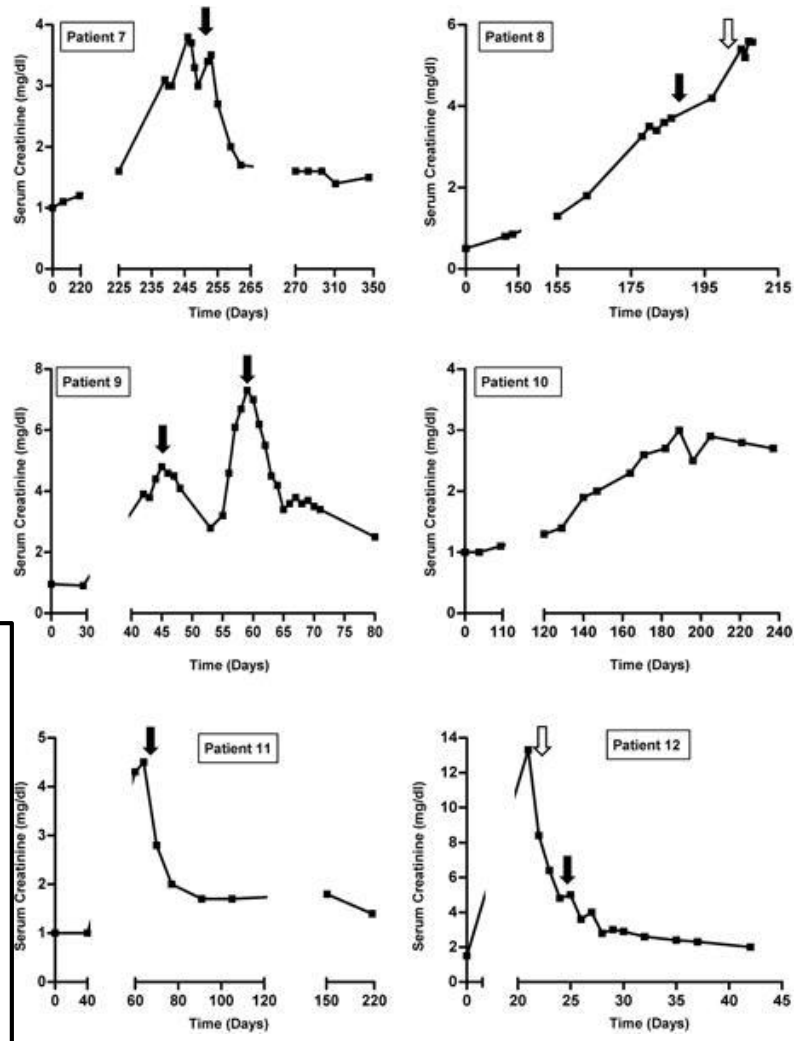
Wanchoo R, et al. Am J Nephrol. 2017;45(2):160-169.

Case series of ICI-nephritis (n = 13)

Age: median (range)	66 (32-75)
Malignancy: - Melanoma, n (%) - Other*, n (%)	 9 (69) 4 (31)
Immune checkpoint regimen: - Ipilimumab, n (%) - Anti-PD1, n (%) - Combination ipi + anti-PD1, n (%)	 6 (46) 3 (23) 4 (31)
Nephrotoxic drug use, n (%)	7 (54)
Day of AKI: median (range)	91 (21-245)
Days since last dose of ICI: median (rang	
Extra-renal irAE, n (%)	
Requirement for HD, n (%)	
Renal function: - Complete recovery, n (%) - Partial recovery, n (%) - No recovery, n (%)	

Response to steroid (n = 22)

No recovery n = 2 (9%)
Partial recovery: n = 8 (36%)
Complete recovery: 12 (54%)

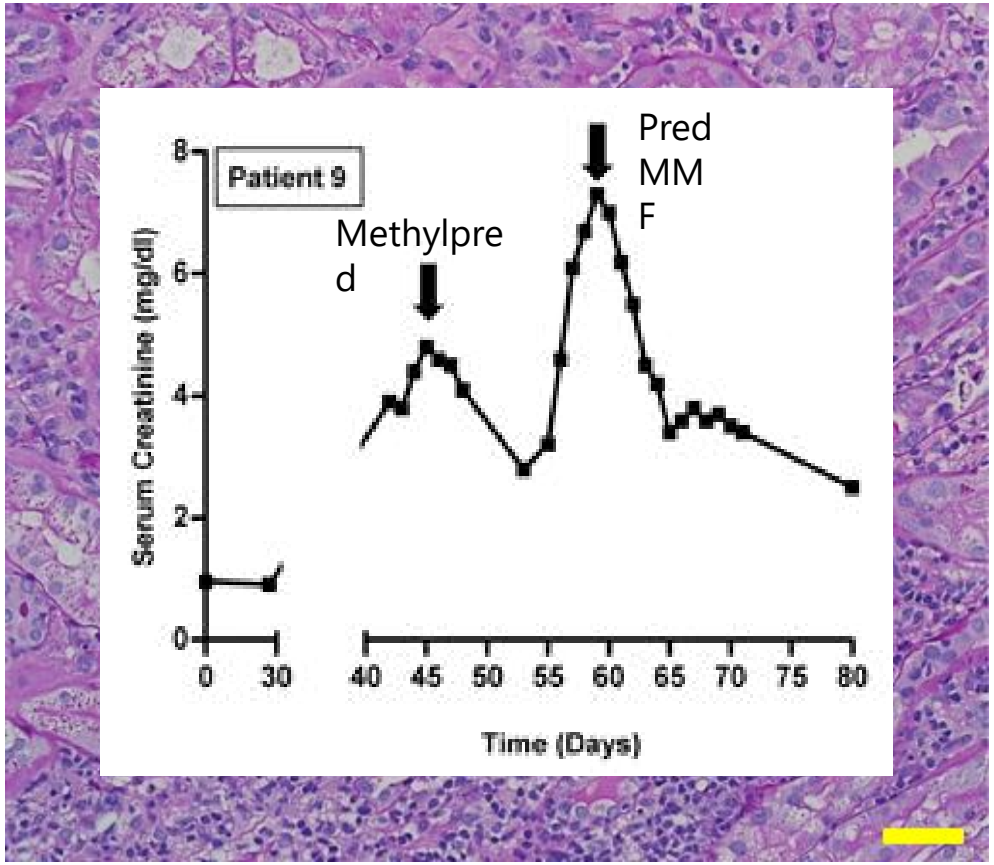


Cortazar F, et al. Kidney Int. 2016 Sep;90(3):638-47.

Patient 9

- 75 yo male with metastatic melanoma
- BGHx: BPH
- Medications: none
- Treatment: Ipi + nivo
- Onset of AKI: day 42 (off drug for 21 days)
  - Other irAE: dermatitis, colitis

- Diagnosis: acute interstitial nephritis
  - Predominant lymphocyte infiltration with tubilitis
- Methylprednisolone 500mg IV for 3 days, followed by 60mg prednisolone daily
- Prednisolone increased to 80mg BD and MMF 1g BD added
  - Partial recovery only

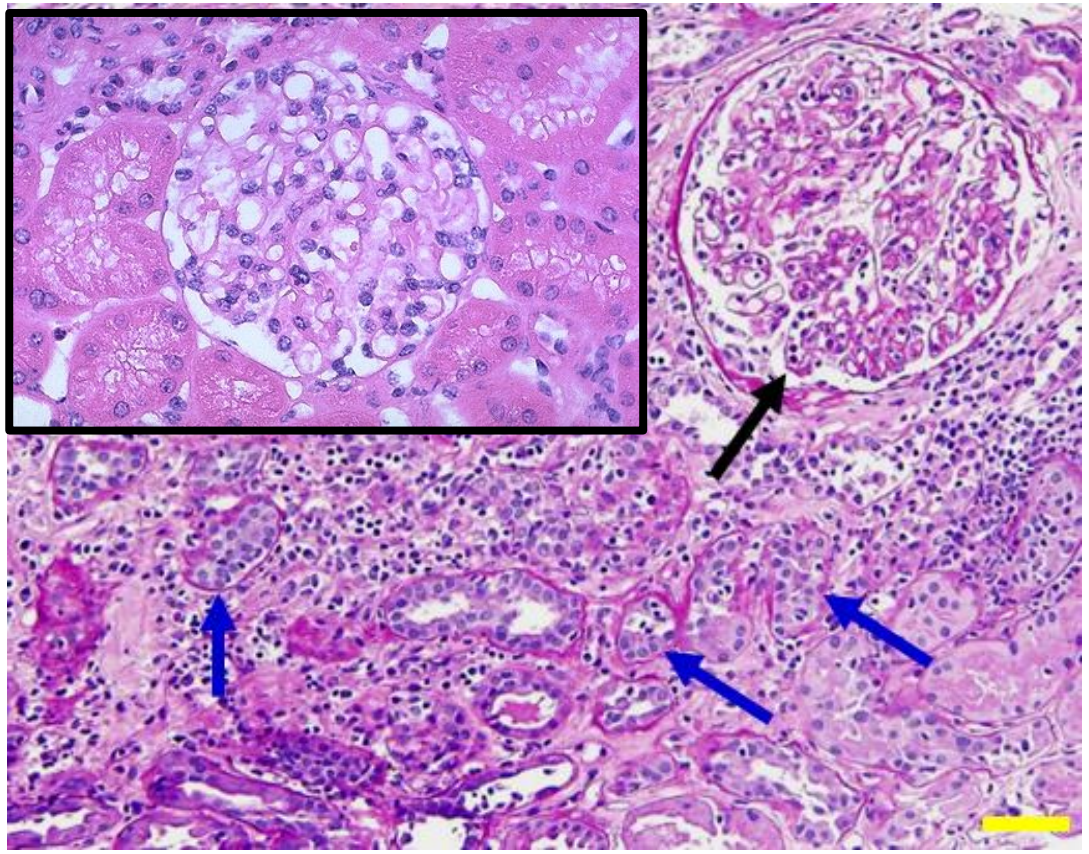


Cortazar F, et al. Kidney Int. 2016 Sep;90(3):638-47.

Patient 2

- 64 yo male with metastatic melanoma
- BGHx: CKD, hypertension, BPH
- Medications: albuterol, fluticasone, oxycodone
- Treatment: ipi + anti-PD1
- Onset of AKI: day 91 (off drug for 49 days)
  - Other irAE: thyroiditis, ileitis

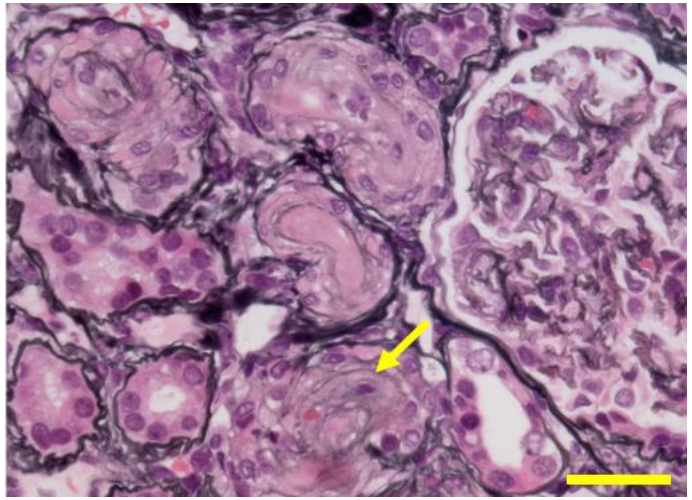
- Diagnosis: granulomatous acute interstitial nephritis
- Prednisolone 60mg daily, tapered over 6 weeks
  - Complete recovery (to baseline)



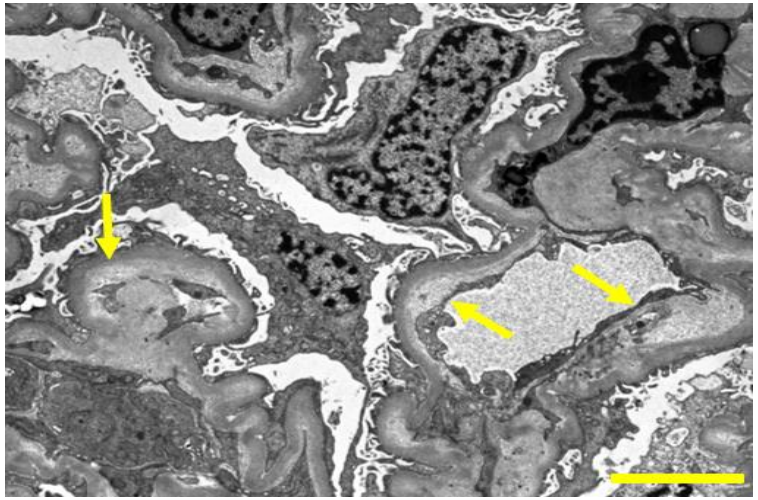
Cortazar F, et al. Kidney Int. 2016 Sep;90(3):638-47.

Patient 8

- 58 yo male with metastatic melanoma
- BGHx: hypertension
- Medications: ibuprofen
- Treatment: ipilimumab
- Onset of AKI: day 154
  - Other irAE: none



- Diagnosis: acute thrombotic microagngiopathy
- Prednisolone 60mg daily, tapered over 2 weeks
- Haemodialysis dependent starting day 210



Cortazar F, et al. Kidney Int. 2016 Sep;90(3):638-47.

Management of toxicities (ASCO guidelines)

Grade	CTCAE Description	Management
1	- Cr level increase of 25µmol/L - Cr 1.5-2.0x above baseline	- Consider temporarily holding ICPi, pending consideration of potential alternative etiologies (recent IV contrast, meds, fluid status) and baseline renal function
2	- Cr 2-3x above baseline	- Hold ICPi temporarily and consults nephrology - If other etiologies ruled out, administer 0.5 – 1mg/kg prednisolone equivalent - If no improvement or worsening, 1 – 2mg/kg prednisolone equivalent and permanently discontinue treatment - If improved to G1 or less, taper corticosteroids over 4-6 weeks
3	- Cr >3x baseline or 350µmol/L - Hospitalisation indicated	- Permanently discontinue ICPi - Same as above
4	- Life-threatening consequences - Dialysis indicated	- Consult nephrology - Administer corticosteroids (initial dose 1 – 2mg/kg/day prednisolone equivalent)

Additional considerations
- Monitor creatinine weekly
- Reflect kidney biopsy should be discouraged until corticosteroids treatment has been attempted
- If no recurrence of chronic renal insufficiency, discuss resumption of ICPi with patient after taking into account the risks and benefits

Puzanov I, et al. J Immunother Cancer. 2017 Nov 21;5(1):95

Abbreviations: CTCAE: Common Terminology Criteria for Adverse Events, ICI: immune checkpoint

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Update in immunotherapy and the kidneys

AT RISK POPULATION: IS IT SAFE TO PROCEED?

At risk population groups

- Clinical trials exclude patients with:
  - Organ dysfunction
  - Autoimmune disease
  - Solid organ transplantation
  - Concurrent immunosuppression

- Increased risk of developing melanoma and other malignancies

- Underlying renal impairment common in patients with bladder cancer (cisplatin induced, comorbidities etc.) and creatinine clearance lower in patients with RCC following nephrectomy
  - PD1 antibodies approved for use in both bladder (FDA but not PBS) and kidney cancer (PBS listed)

- Best data currently available in this population: small case series at best

When would you be comfortable with giving a metastatic melanoma patient with an allogenic renal transplant immune checkpoint inhibitors?

1. When the risk of rejection is 80% but response rate is 40%
2. When the risk of rejection is 60% but response rate is 20%
3. When the risk of rejection is < 50% but response rate is 10%
4. Never

Case study: history

- 63 y.o. female with longstanding T1DM and hypertension diagnosed with CKD in 2002
  - Renal allograft transplant (husband's kidney)
  - Immunosuppression: MMF, prednisolone and tacrolimus
  - Kidney function stable (cr = 80)

- Primary melanoma diagnosed in May 2015
  - Breslow 2.59mm, mitoses 5/mm^2, no ulceration, 1 sentinel LN positive with extranodal extension
  - No adjuvant treatment

- Stage IV recurrence in October 2015
  - Lungs and hilar LN mets
  - BRAF WT

Ong M, et al. J Immunother Cancer. 2016;4:64.

Case study: management

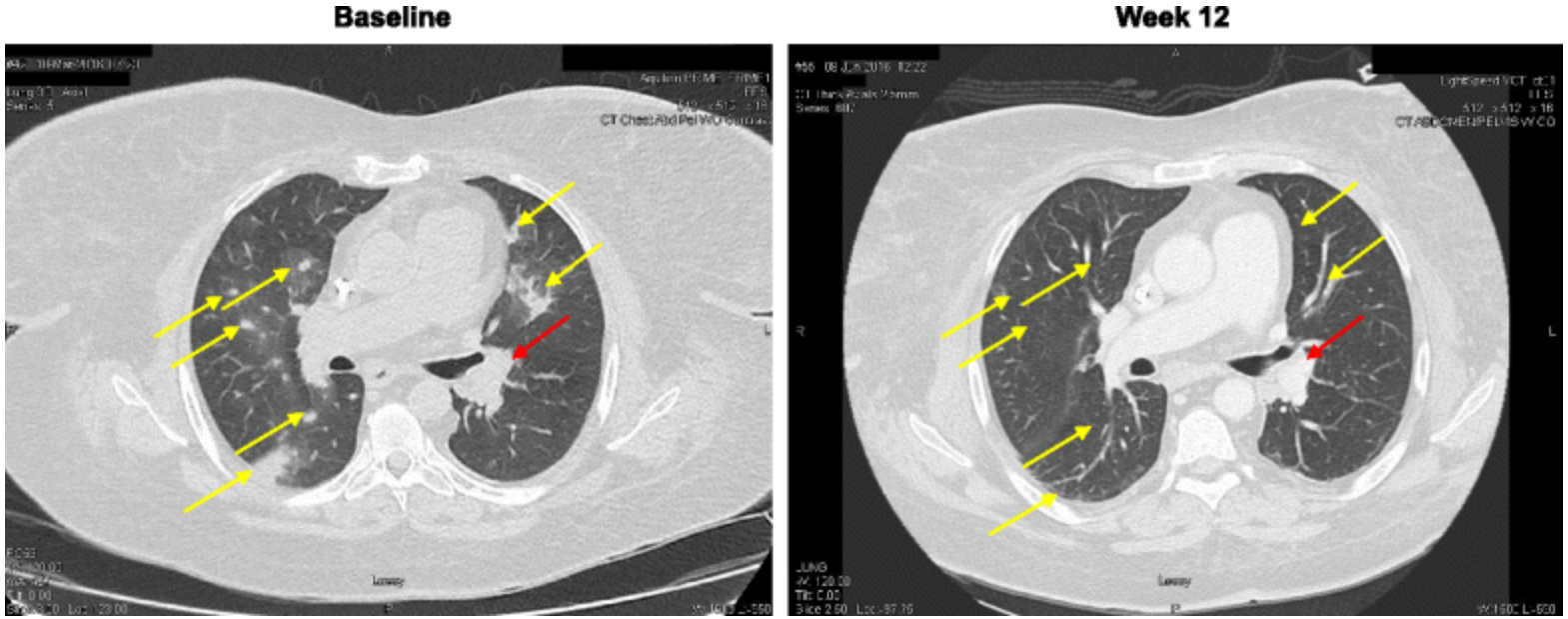
- Immunosuppressive meds titrated (eventually ceased) and prednisolone maintained at 10mg daily
  - No deterioration of renal function prior to nivolumab
- 8 days following first dose of nivolumab: lethargy, abdominal pain, nausea, vomiting, diarrhoea, malaise, anorexia, fatigue
- Investigations
  - EUC: Cr 577
  - Doppler US of kidney: evidence of medical renal disease, poor perfusion, elevated resistive indices concerning for transplant dysfunction
- Treatment of acute transplant rejection
  - Methylprednisolone 500mg IV
  - Renal allograft function did not return, commenced haemodialysis

Ong M, et al. J Immunother Cancer. 2016;4:64.

Case study: haemodialysis

- Significant PD after 2 months following first dose of nivolumab
  - Multiple new lung nodules

- Re-challenge with nivolumab…



This patient had ongoing treatment response after 8 months

Ong M, et al. J Immunother Cancer. 2016;4:64.

Chronic kidney disease: case series I put together…

Case	1	2	3	4	5
Age at diagnosis	46				56
Medical history	MG hae wit				Hypertension, T2DM
Cause of renal insufficiency	Lig nep				Diabetic nephropathy – haemodialysis
Stage	IIIC				IV melanoma
PD1 antibody received	Per				Ipilimumab
Response to PD1 Ab	Pro				Mixed response then partial response
Baseline creatinine	160				Not reported
Change in Cr with treatment	No				No renal complications
Toxicity	Well tolerated	Well tolerated	Respiratory complications (multifactorial)	Well tolerated	Bullous pemphigoid

Summary

In population pharmacokinetic studies, renal function did not affect clearance of ICI antibodies, and dose adjustments are not recommended for chronic kidney disease.

According to case reports, ICI appear to be safe in patients on haemodialysis with similar efficacy (high molecular weight so probably not cleared by dialysis)

1. Herz S, et al. Eur J Cancer. 2016;67:66-72. 2. Cavalcante L, et al. Cancer Manag Res. 2015;7:47-50. 3. Guilfoyle MR, et al. J Urol. 2016;70(6):1082-1083.

Risk and timing of allograft rejection in renal transplant patients

ICI used	% of total rejected	Change in immunosuppression	Time until rejection	Outcome
Ipilumumab monotherapy	1/3 (33%)	Tacrolimus and MMF ceased, pred 5mg	8 weeks	Haemodialysis. Died from metastatic melanoma.
Pembrolizumab monotherapy	2/2 (100%)	Cyclosporine ceased and prednisolone 5mg.	Pt 1: 6 weeks Pt 2: 8 weeks	Pt 1: Haemodialysis dependent. Metastatic cutaneous SCC excellent response. Pt 2: Declined haemodialysis. Rapid melanoma progression and death.
Nivolumab monotherapy	2/3 (66%)	Low dose Cyclosporine and prednisolone Tac/cyclo ceased, prednisolone 10mg	Pt 1: 6 weeks Pt 2: 6 weeks	Pt 1: Haemodialysis dependent. Pt 2: Haemodialysis dependent. Metastatic melanoma excellent response
Ipilimumab followed by nivolumab	1/2 (50%)	Tacrolimus ceased, pred 5mg	6 days	Haemodialysis dependent. Metastatic melanoma excellent response.
Ipilimumab followed by pembrolizumab	1/1 (100%)	Cyclosporine ceased, pred continued	3 weeks	Haemodialysis dependent.

What would you do for a transplant patient's immunosuppression if they require ICPi?

1. Continue low dose prednisolone at 5-10mg daily and cease all other immunosuppressants
2. Continue low dose prednisolone 5-10mg daily and reduce all other immunosuppressants
3. Continue all immunosuppressants at maximum dose
4. Continue low dose prednisolone 5-10mg daily, start (or continue) MTOR inhibitor and cease immunosuppressants
5. Panic and ring a transplant physician

Take-home message for transplant patients

- Significant risk of rejection in kidney transplant recipients with the use of checkpoint inhibitors (usually acute cellular rejection)
  - Rejection rate higher for PD1 inhibitors compared with CTLA4 inhibitors
  - Mechanism: disruption of immune tolerance
- ICPis should be used with extreme caution and in an MDT setting with full disclosure to the patient surrounding the risks
- The decrease in immunosuppression prior to administration of ICPi probably a contributing factor
  - Consider switching immunosuppression to mTOR inhibitors in combination with low dose steroids as an alternative (although no evidence…)
- ICPi re-challenge is recommended for kidney transplant patients 12 weeks after the rejection process once they are on haemodialysis
- Other immune mediated adverse events was not necessarily higher in this cohort

Autoimmunity

- Hallmark toxicities of ICI, immune related adverse events (irAE), result from aberrant activation of autoreactive T cells against host tissues
  - Clinically, these irAE closely resemble various autoimmune disease

- Pre-clinical models that raised concerns:
  - CTLA-4 knockout mice: fulminant autoimmune activation with multi-organ involvement and diffuse lypmphoproliferative process (early death)
  - PD1 knockout mice: SLE, myocarditis

- Concerns around clinically unacceptable immune re-activation in patients with pre-existing autoimmunity
  - Patients with active autoimmune disease excluded from all clinical trials

- Problematic as autoimmune disease is common
  - One study showed 13.5% of lung cancer patients had concurrent diagnosis of autoimmune disease
  - 20-50 million people in the US alone
  - Although autoantigens are non-renal in most cases, the kidneys are still involved frequen

Johnson D, et al. Cancer. 2017;123(11):1904-1911.

Pre-existing autoimmune disease and ipilimumab

- 30 patients with melanoma and pre-existing autoimmune disease
  - Inflammatory bowel disease, rheumatoid arthritis, multiple sclerosis most common
- 20% patients managed with steroids or other immunosuppressants prior to commencing ipilimumab
- 27% had exacerbation of their own autoimmune disease and 33% experienced irAE from drug, requiring treatment
- All but 1 event resolved quickly with standard steroid treatment
  - One patient who had psoriasis died from colitis (late presentation)
- Response rate 20%, consistent with ipilimumab clinical trials

Pre-existing autoimmune disease and PD1 antibodies

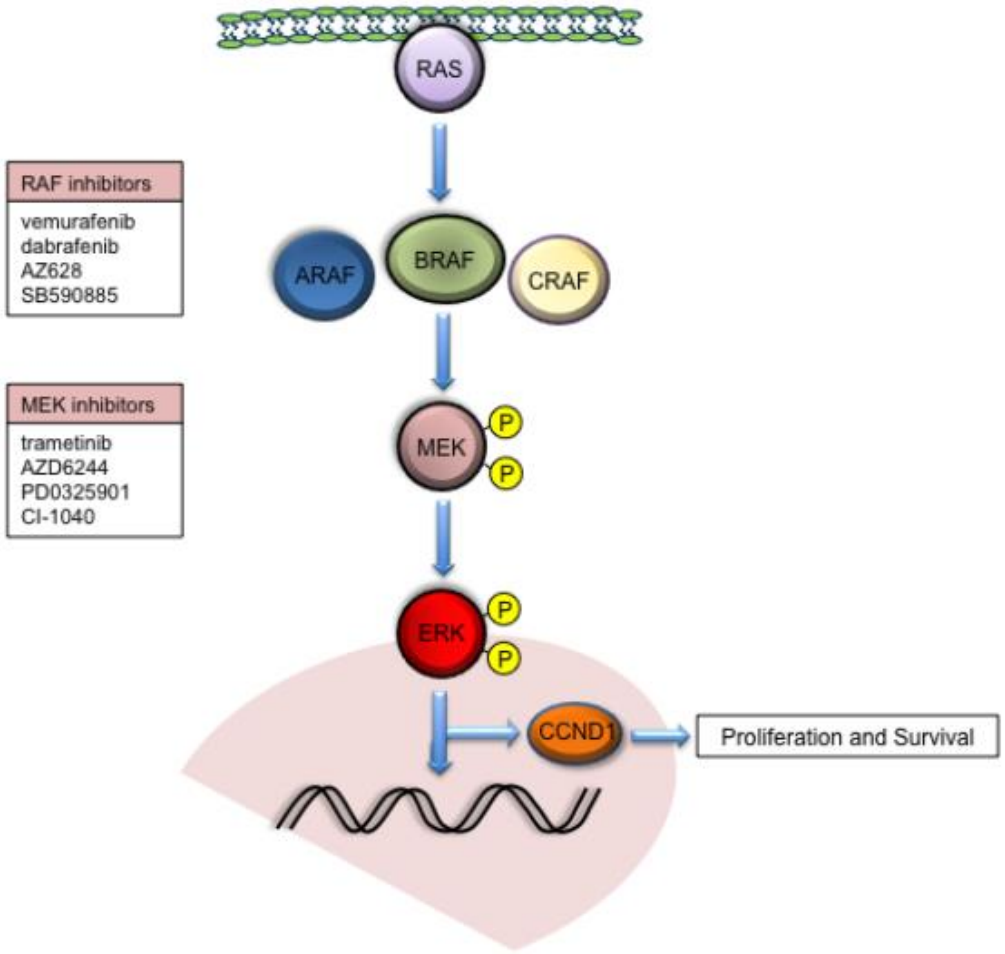
- 52 patients with melanoma and pre-existing autoimmune disease
- 30% had exacerbation of their own autoimmune disease
  - Typically low grade and only 4% required treatment discontinuation
  - Usually observed in patients with rheumatological disorders (RA, SLE, psoriasis)
  - No patients with GI or neurological disorders experienced flares
- 29% experienced irAE from drug, with 8% requiring treatment discontinuation
- Both autoimmune flares and irAEs responded to standard treatment algorithms
- Response rate 33%, consistent with PD1 antibody trials

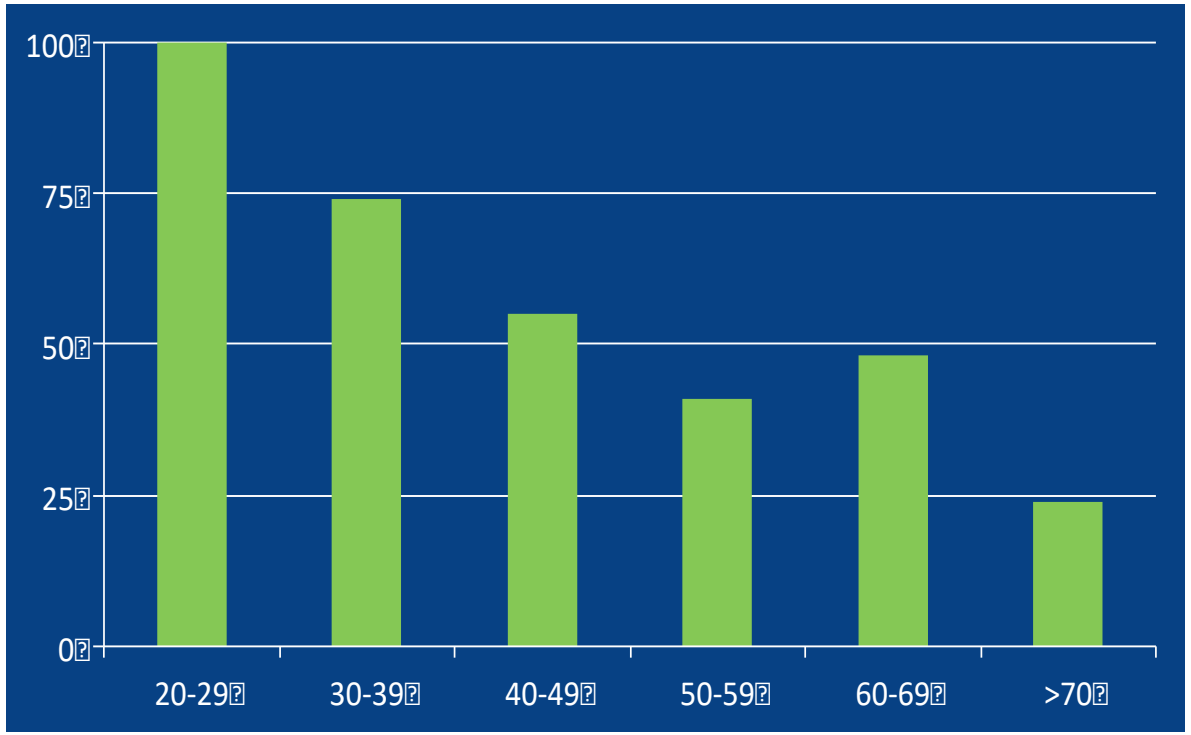
Melanoma Institute Australia

Update in immunotherapy and the kidneys

WHAT ABOUT BRAF INHIBITORS?

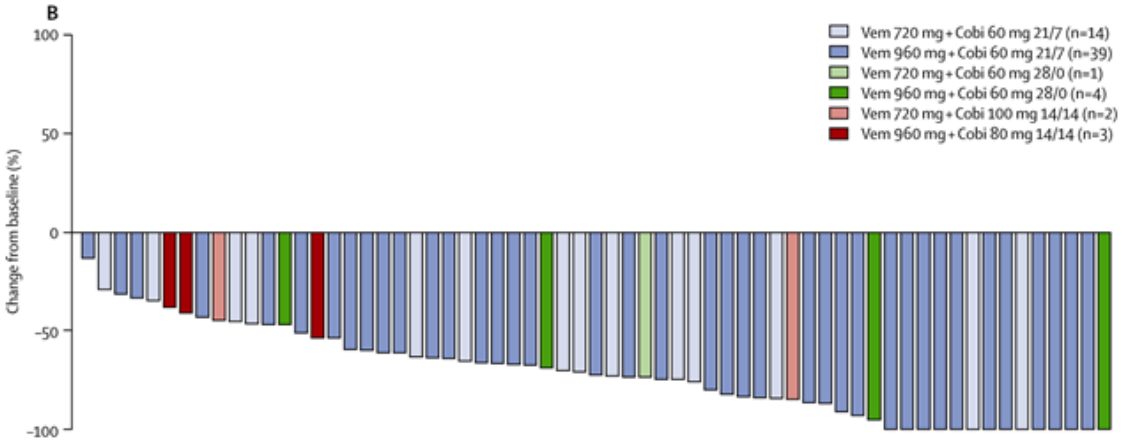
MAPK (BRAF) signaling cascade

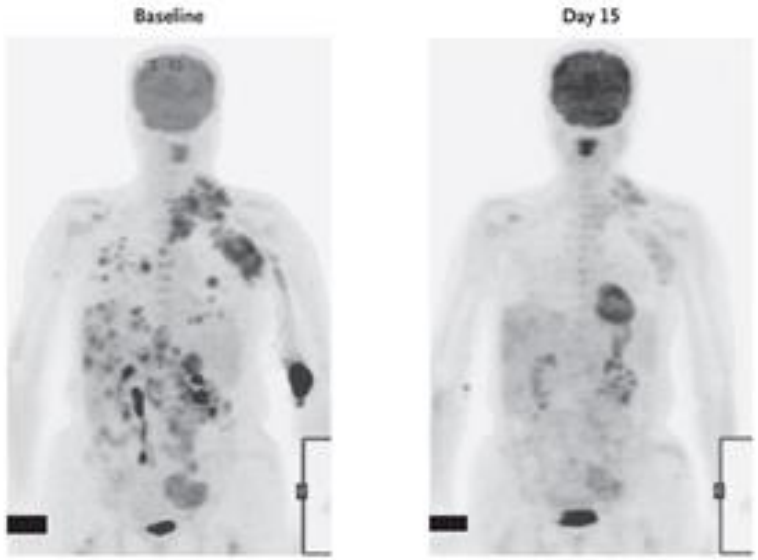


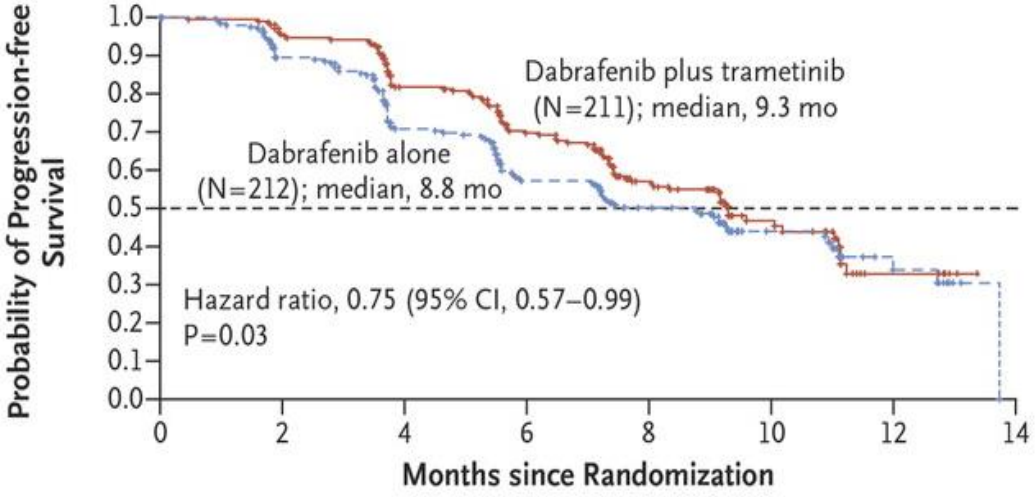


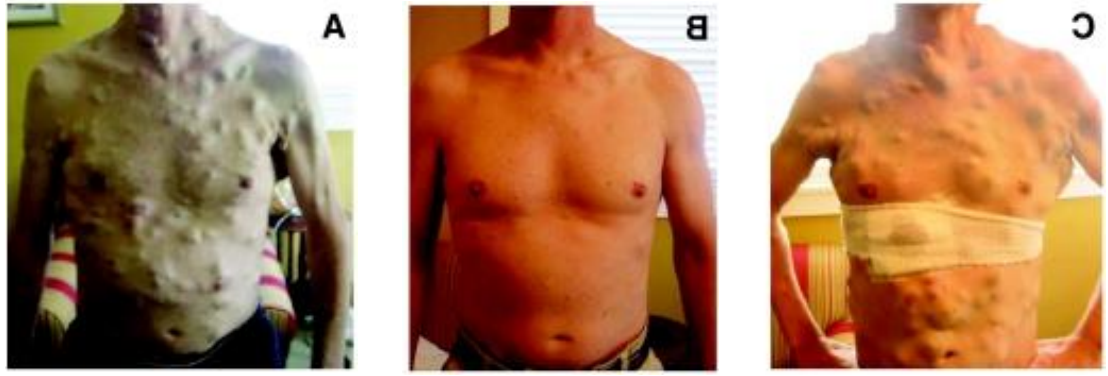
1. Gowrishankar et al., 2013

Miracles of MAPK inhibitors









1. Ribas et al. Lancet Oncol. 2014 Aug;15(9):954-65. 2. Long et al. N Engl J Med. 2014 Nov 13;371(20):1877-88. 3. Flaherty et al. N Engl J Med. 2010 Aug

BRAF inhibitor toxicity

BRAF-SPECIFIC SKIN REACTIONS

BRAF inhibitors cause a rash over the whole body (left), as well as stem warts (centre), which can be burnt with nitrogen, and squamous cell carcinoma (right), which must be excised.

Courtesy of the Netherlands Cancer Institute

AKI reported with vemurafenib: a systematic review

Publication	Total no. of patients	Onset of renal dysfunction	Cancer	Mean age (years)	Males/ females	Outcome
Uthurriague et al	16	After 1 month	Melanoma	Not reported	10/6	Decrease in renal function persisted for 3 months. In patients with the longest follow-up (8 months), CKD persisted.
Regnier-Rosencher et al	4	After 1-2 weeks	Melanoma	76	4/0	All patients had underling CKD (stage 2-3A). Improvement in renal function following drug cessation but AKI relapsed after re-introduction. All patients had an excellent response in their cancer.
Launa-Vacher et al	8	50% after 1-2 months 50% after 1-2 weeks	Melanoma	66	6/2	All patients had underling CKD (stage 2-3A). Cr stabilised (but did not improve) with dose reduction in 3 patients. Cr improved to baseline in 2 patients who maintained full dose. Drug stopped and Cr improved in 2 patients. Cr continued to worsen in 1 patient; dialysis indicated but refused. Patient died.

Wanchoo R, et al. Clin Kidney J. 2016;9(2):245-51.

BRAF inhibitor-related toxicity summary

- Allergic interstitial disease
- Acute tubular necrosis
- Proximal tubular damage (Fanconi's syndrome)
- Electrolyte disturbance: hypophosphataemia, hyponatraemia, hypokalaemia
- Subnephrotic-range proteinuria
- Acute/subacute decrease in GFR by 20-40%
- Urinalysis may have haematuria, proteinuria and white blood cells
- Urinary sediment may show granular casts or while blood cell casts

- Lower rates of kidney disease and cutaneous lesions seen with dabrafenib compared to vemurafenib
- Management: a trial of drug cessation with gradual reintroduction at lower dose

Wanchoo R, et al. Clin Kidney J. 2016;9(2):245-51.

BRAF agents in CKD and ESKD

- Vemurafenib
  - Highly protein bound, metabolised in the liver and excreted via faces
    - Excretion via urine 1%
  - No dose reduction required in mild to moderate renal impairment
    - Limited data in severe impairment so use with caution
  - One patient on peritoneal dialysis required a dose reduction follow QT prolongation

- Dabrafenib
  - Renal excretion is higher than vemurafenib (71% faecal, 23% urinary excretion)

Wanchoo R, et al. Clin Kidney J. 2016;9(2):245-51.

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ANY QUESTIONS?