British Geriatrics Society
Improving healthcare for older people

BGS Wales Autumn Meeting 2019

Oxwich Bay, 5-6 September

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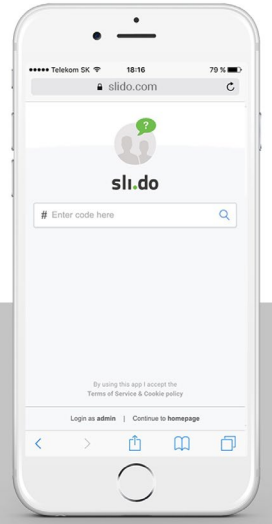

Go to www.slido.com
and insert code:

#BGSWales19

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Immunotherapy

An Overview for Non-Oncologists

British Geriatric Society

Wales Autumn Meeting

6th September 2019

Dr Owen Nicholas

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Swansea University
Prifysgol Abertawe
Medical School
Ysgol Feddygaeth

GIG CYMRU NHS WALES
Bwrdd Iechyd Prifysgol Bae Abertawe
Swansea Bay University Health Board
South West Wales Cancer Centre

Mudiad Canser GOLAU Cancer Foundation

Learning Objectives

By the end of the session:

- Gain a basic understanding of what immunotherapy is and how it works
- Understand the role it has to play in current oncological management
- Recognise common immunotherapy agents
- Diagnose common immunotherapy toxicities and;
- Grade the toxicity
- An overview on how to manage immunotherapy toxicities

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What is Immunotherapy?

- Agents that stimulates the host's immune system to attack cancer cells

N.b. In this talk, specifically referring to **Immune Checkpoint Inhibitors**

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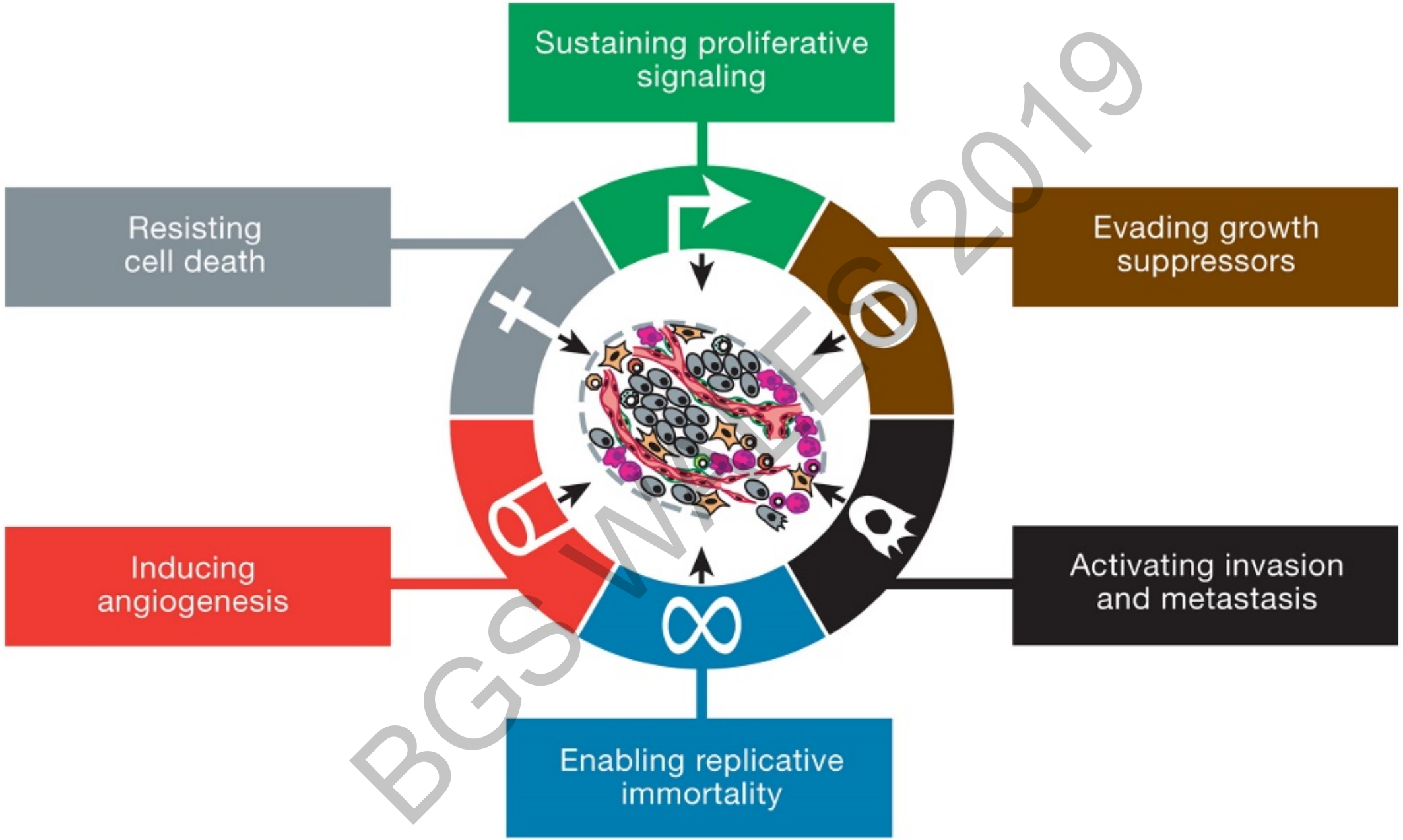

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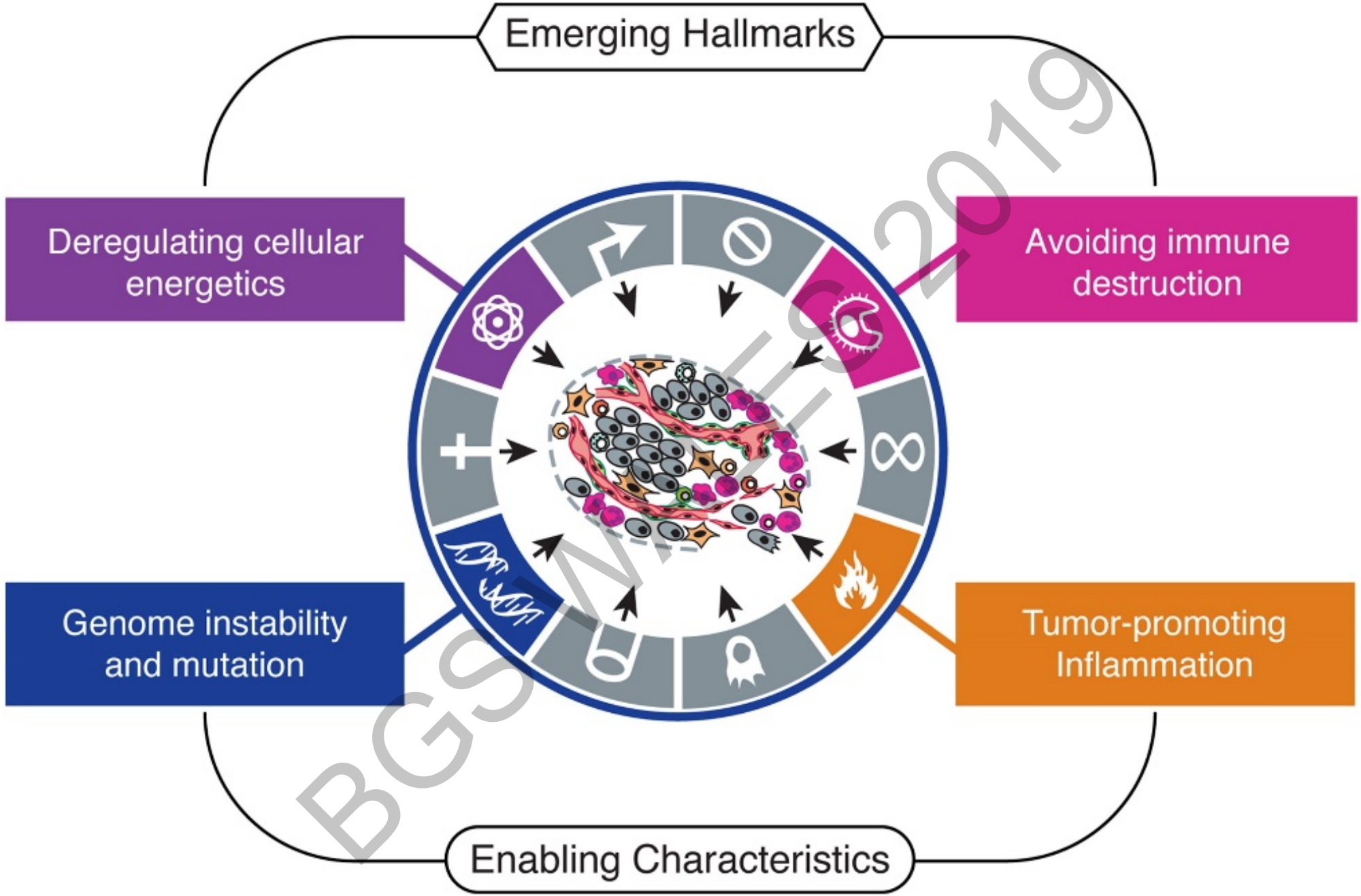
Hallmarks of Cancer *Hanahan and Weinberg Cell 2000*



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Hallmarks of Cancer *Hanahan and Weinberg Cell 2011*

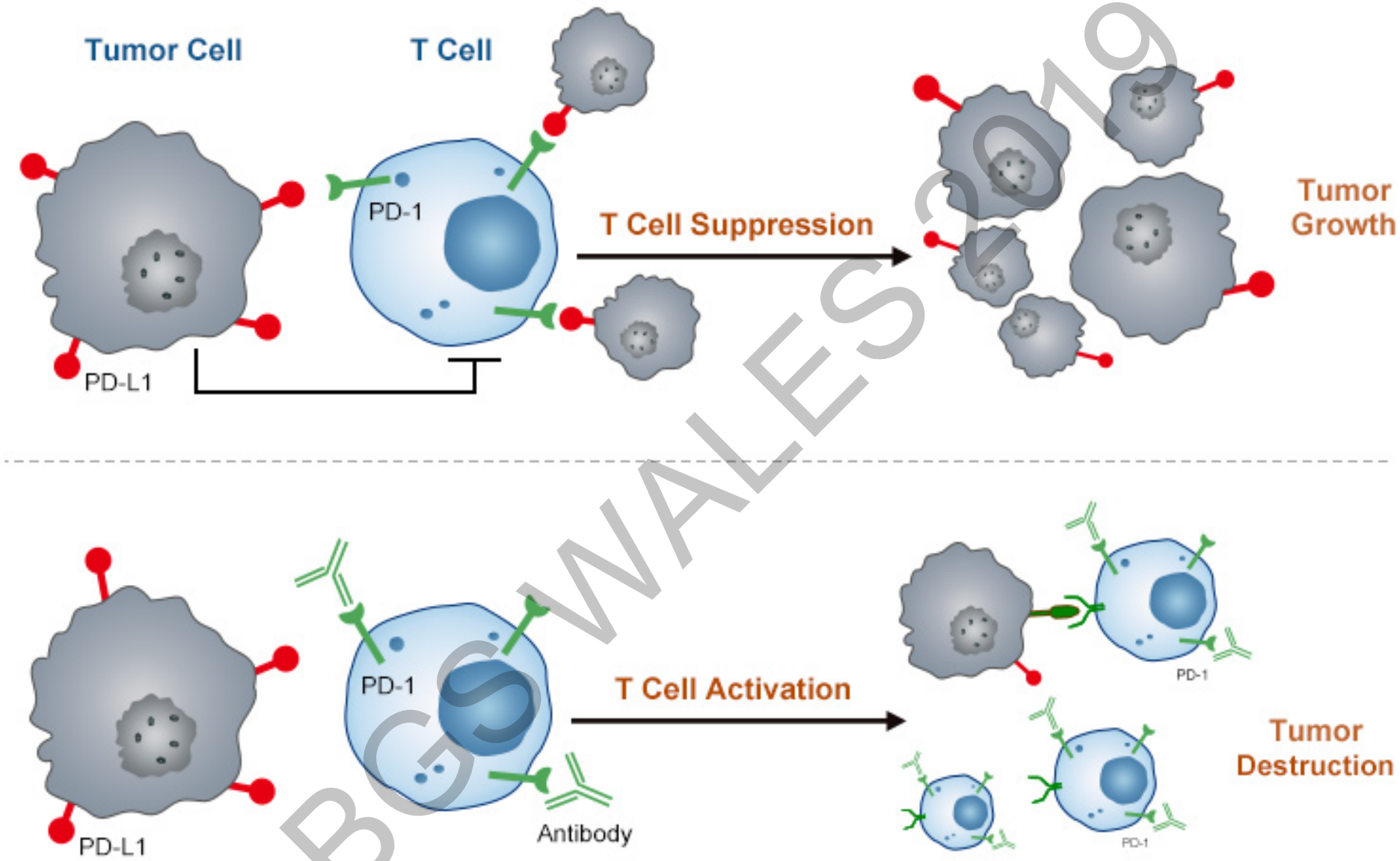

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Figure 1. PD-1 and corresponding antibodies mechanism of action.

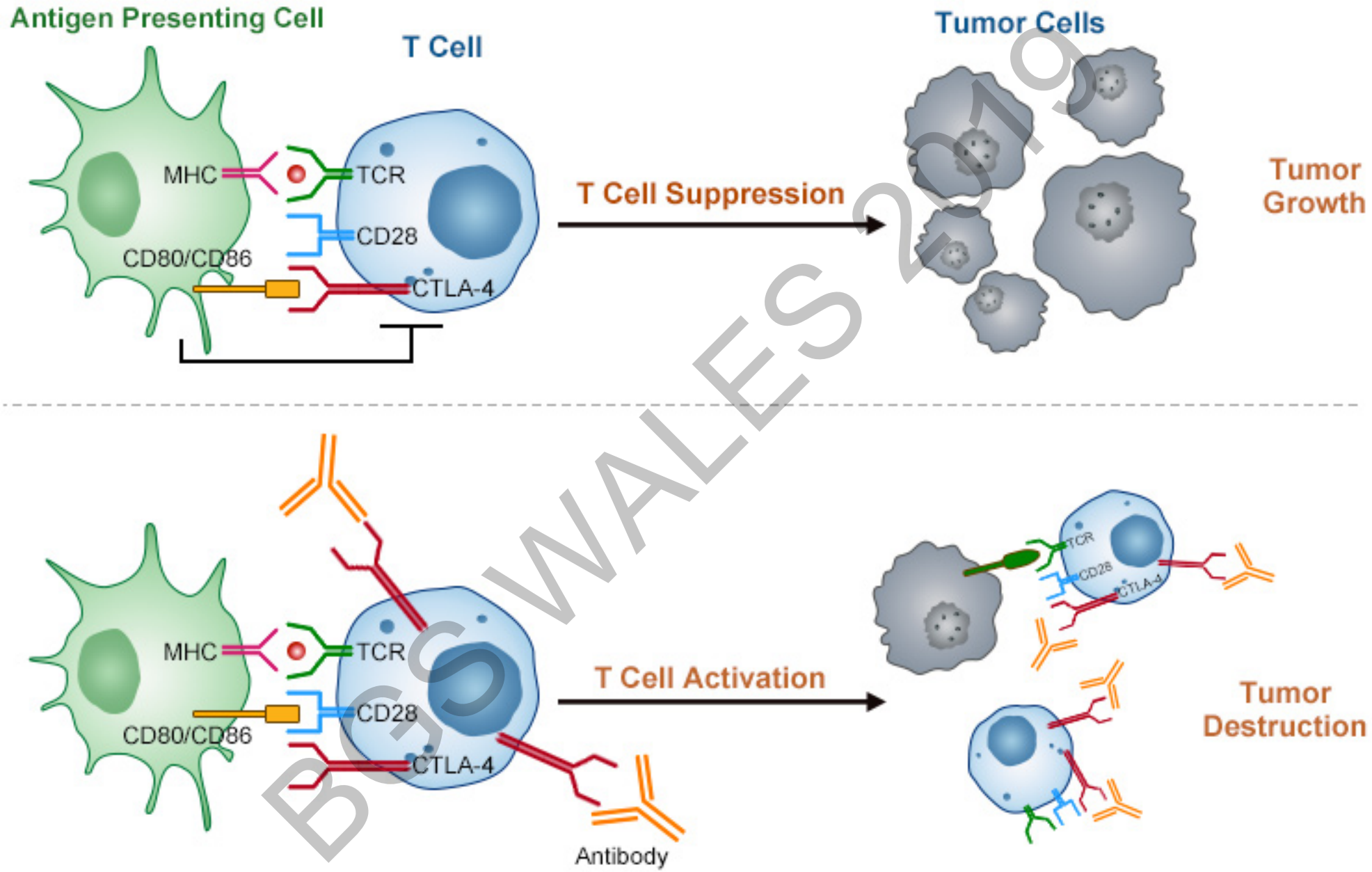

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Figure 2. CTLA-4 and corresponding antibodies mechanism of action.

Common Immunotherapy Agents

- Anti PD-1/PDL-1

Pembroluzimab (Pembro)
Nivolumab (Nivo)
Atezolizumab
Durvalumab

- Also used in combination - Nivo + Ipi

- Anti CTLA-4

Ipilimumab (Ipi)

All given by infusion

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In which cancers do they work?

- Melanoma
- Renal Cell Ca
- Lung Ca (Non small cell)
- Bladder Ca

Coming soon (likely)….

- Breast, Oesophagus, Brain, Pancreas, Colorectal etc.
- In combination with radiotherapy

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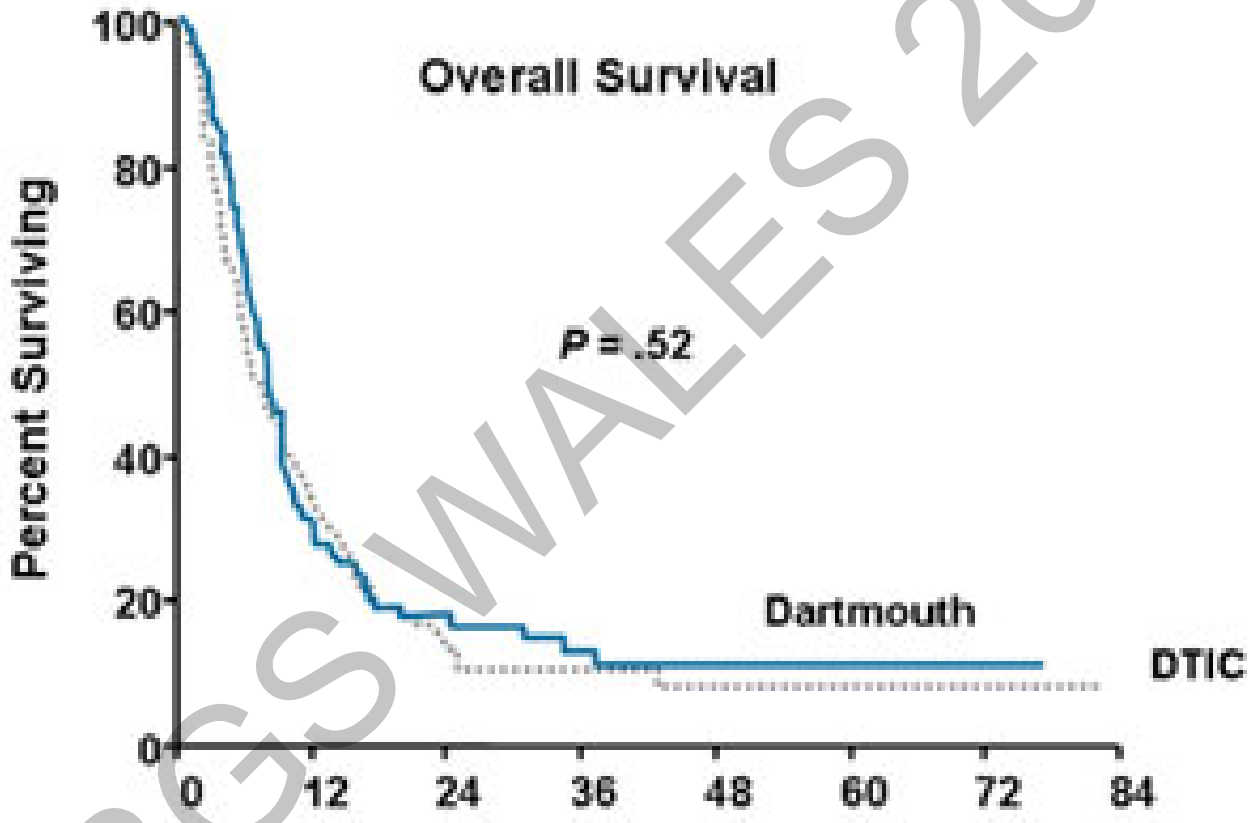
Dartmouth Regimen vs DTIC: No Survival Benefit



Chapman PB, et al. *J Clin Oncol.* 1999;17:2745-2751.

Medscape

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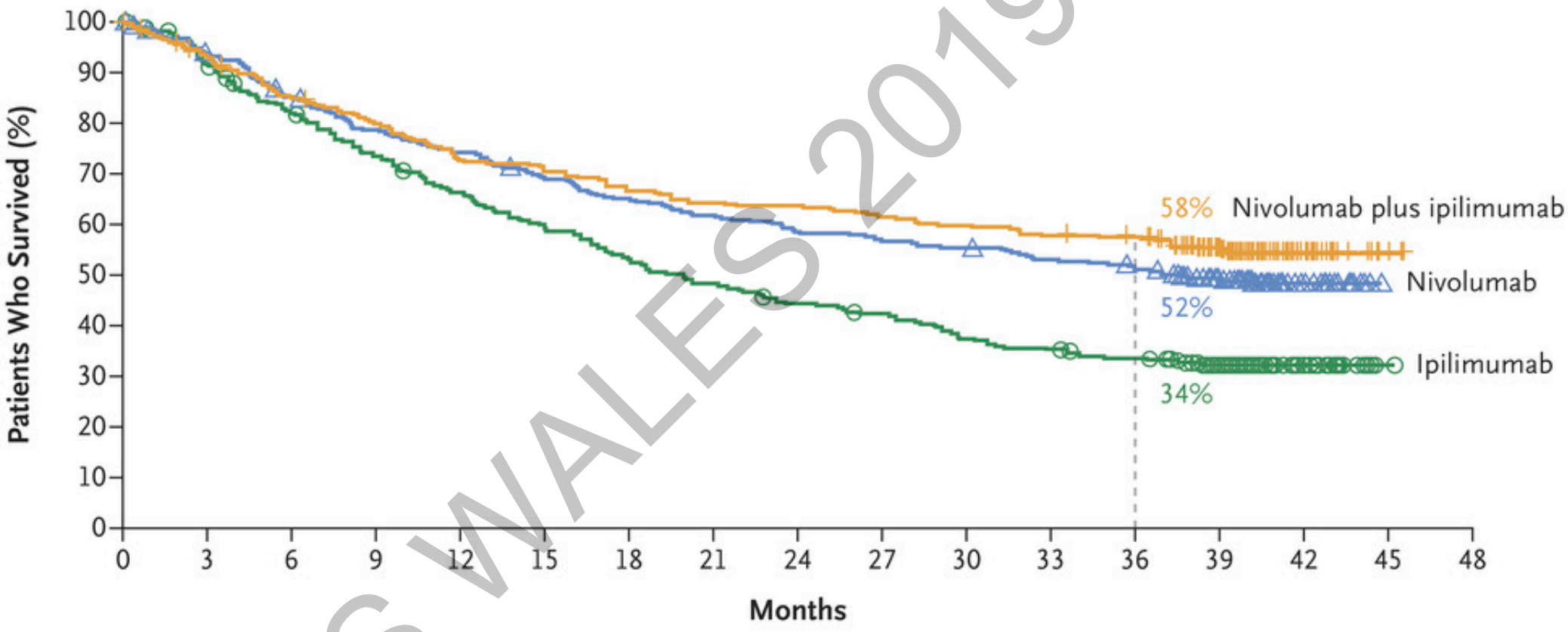
Ipilimumab	315	136	78	58	46	42	34	32	30	28	26	23	15	8	2	0

B **Overall Survival**



No. at Risk

Nivolumab plus ipilimumab	314	292	265	247	226	221	209	200	198	192	186	180	177	131	27	3	0
Nivolumab	316	292	265	244	230	213	201	191	181	175	171	163	156	120	28	0	0
Ipilimumab	315	285	253	227	203	181	163	148	135	128	117	107	100	68	20	2	0

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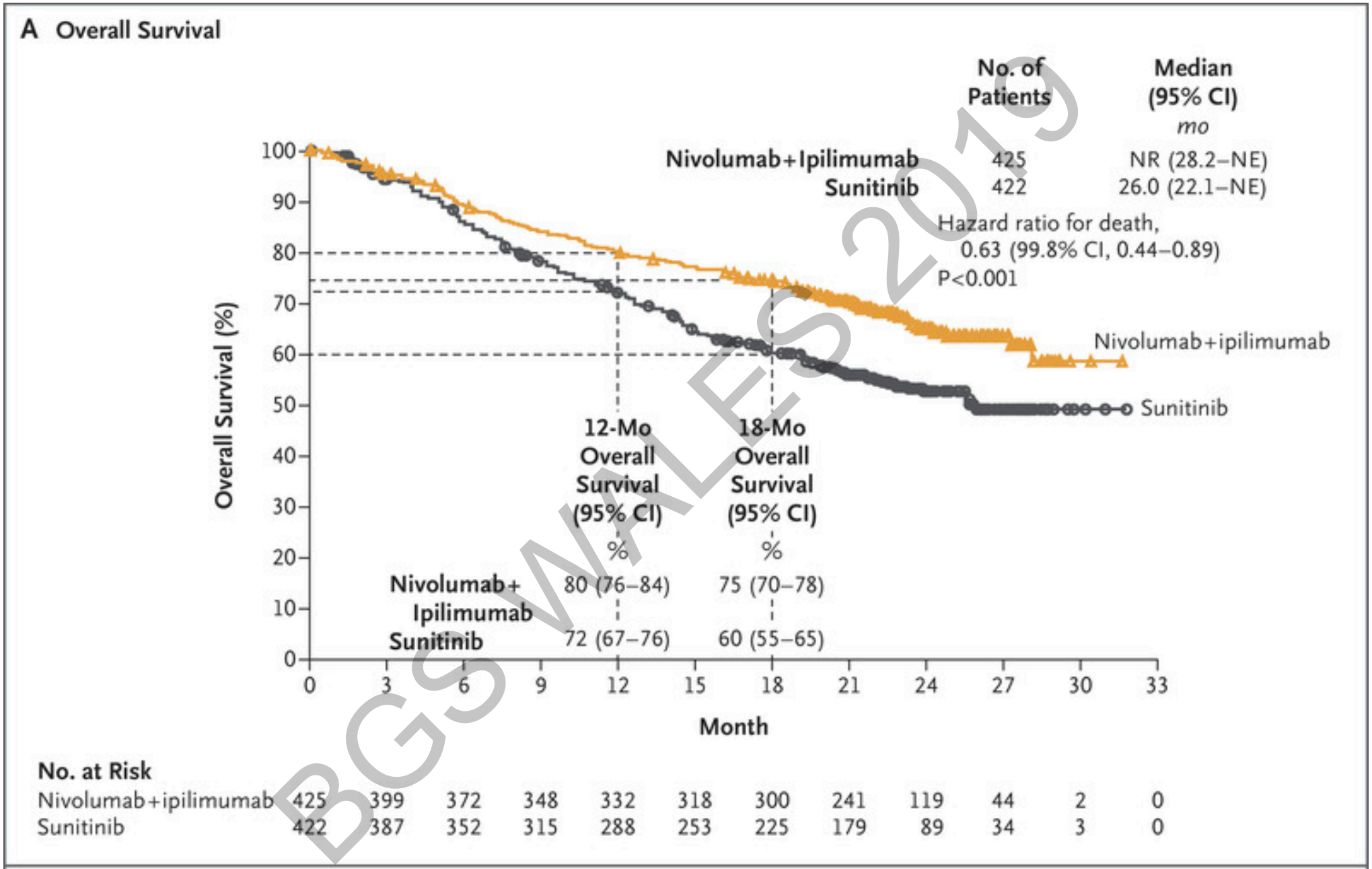
Checkmate 067 *Wolchok et al NEJM 2017*



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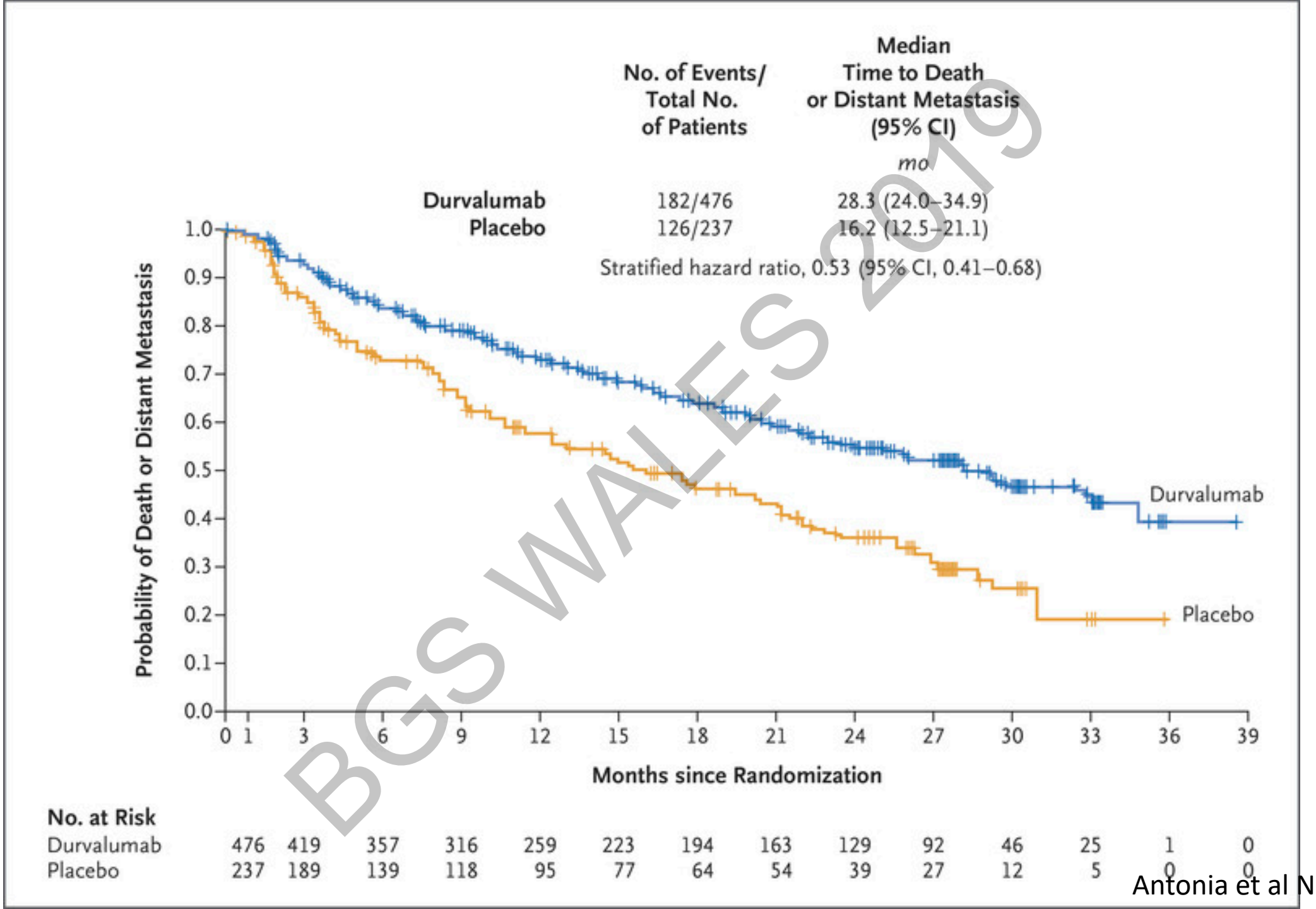
Motzer et al NEJM 2018



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Antonia et al NEJM 2018

Toxicities

- Name a body part then add - itis

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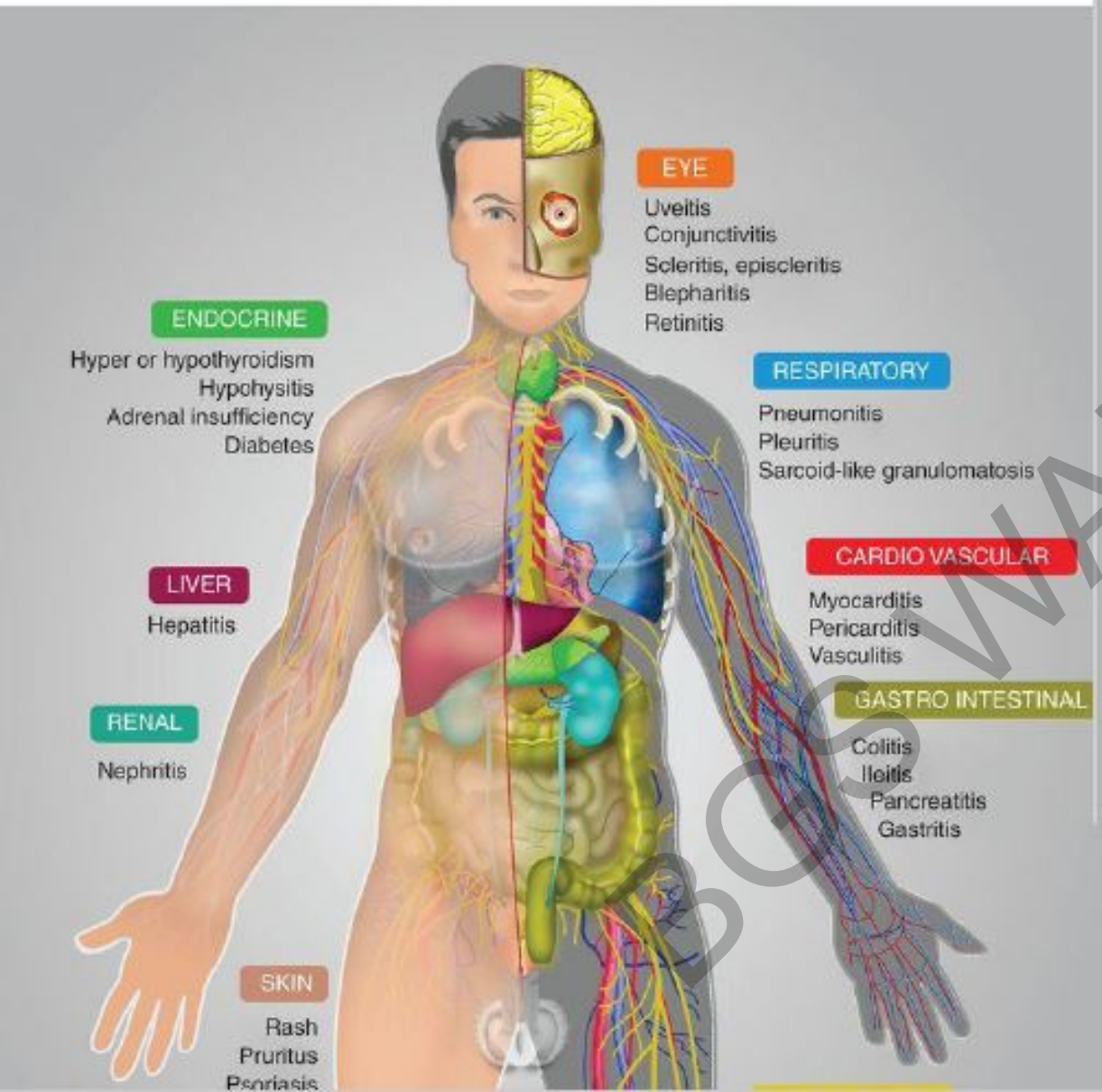
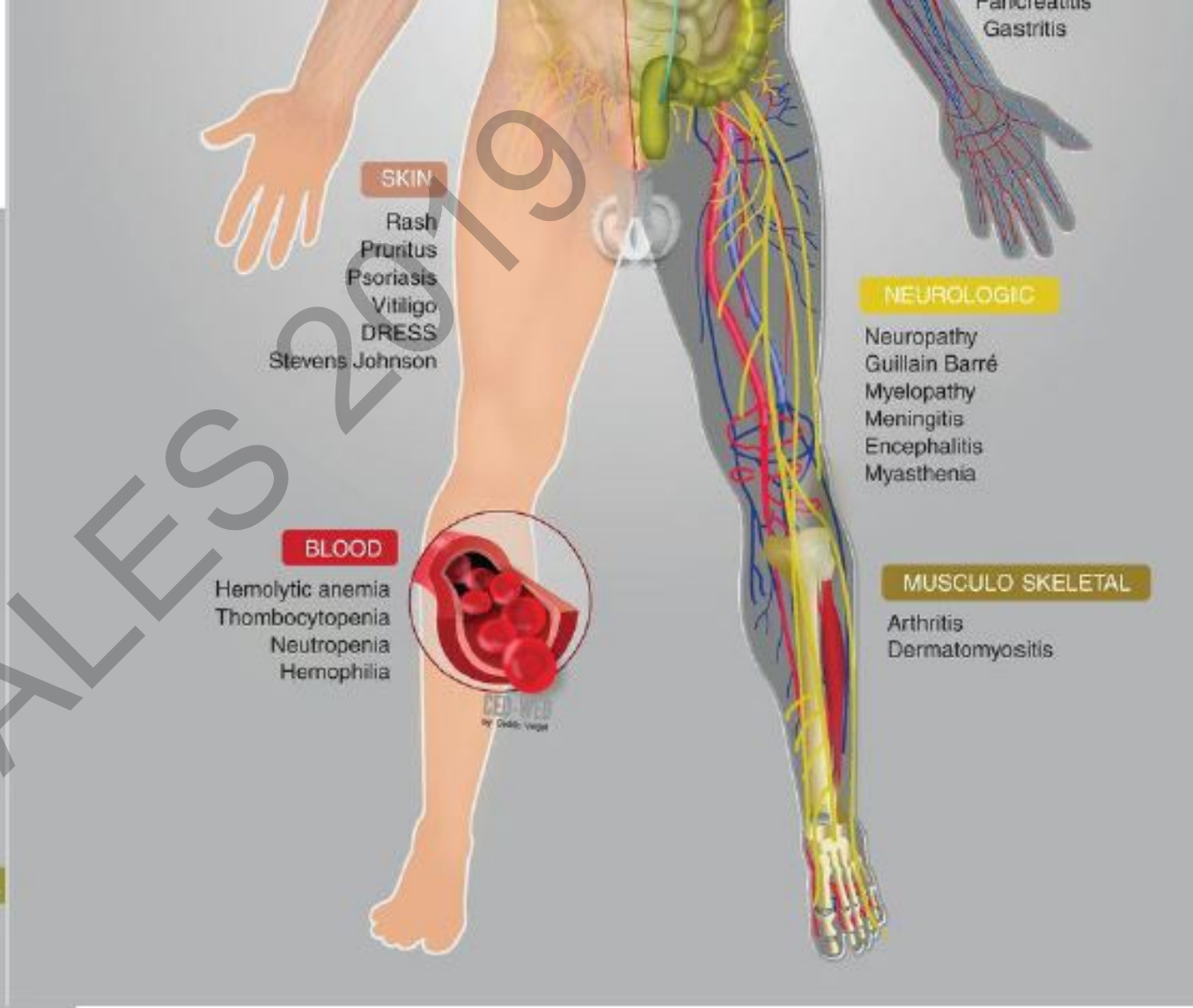
There is a broad spectrum of potential toxicities





Just about every part of the body...!

S. Champiat et al.
Ann Oncol 2016;27:559-574

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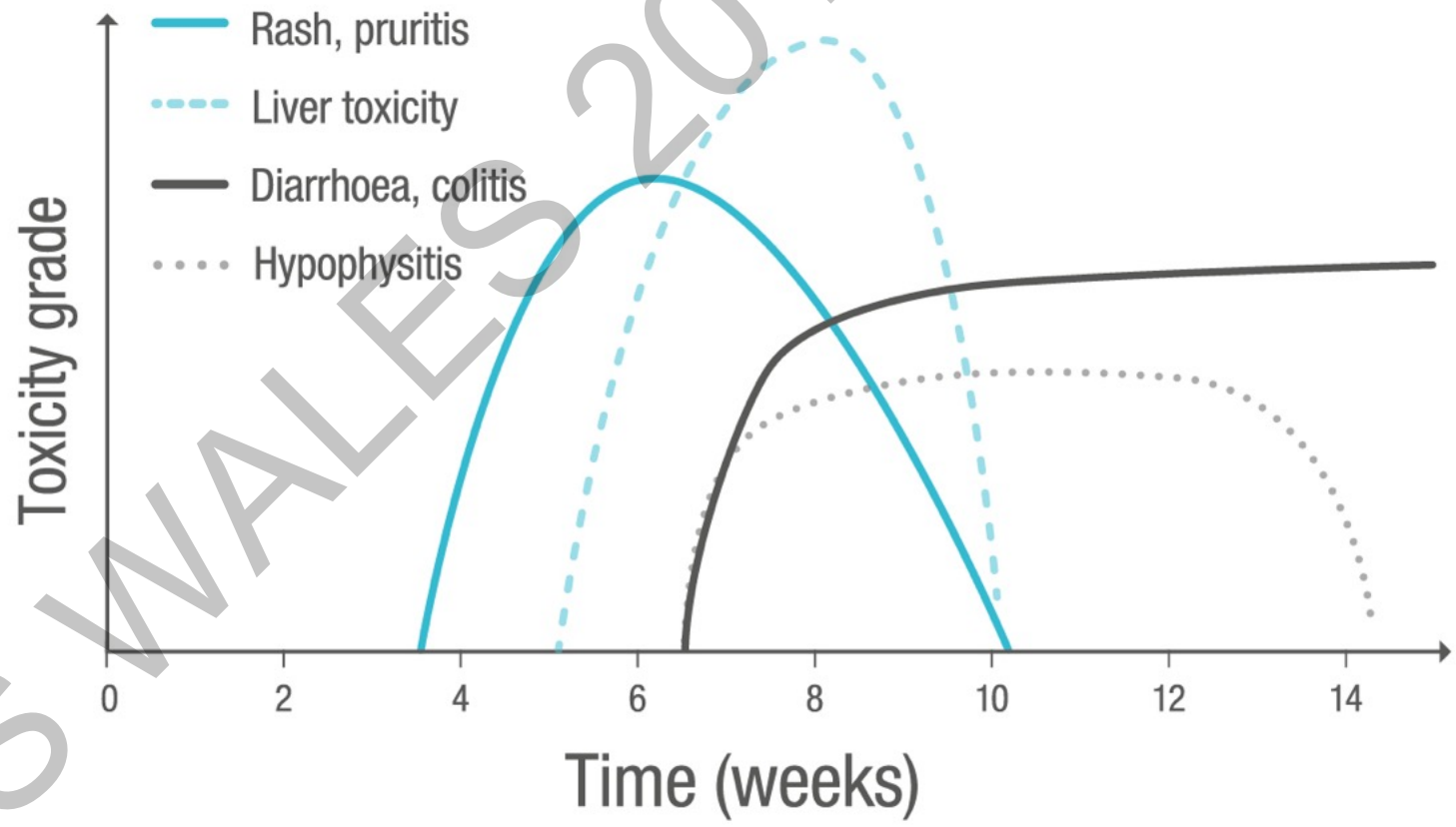
CLINICAL PRACTICE GUIDELINES

Incidence and epidemiology

Time to onset and resolution of occurrence of immuno-related adverse events following Ipilimumab treatment



Weber JS et al. J Clin Oncol 2012;30:2691–2697. Reprinted with permission. ©2012 American Society of Clinical Oncology. All rights reserved.

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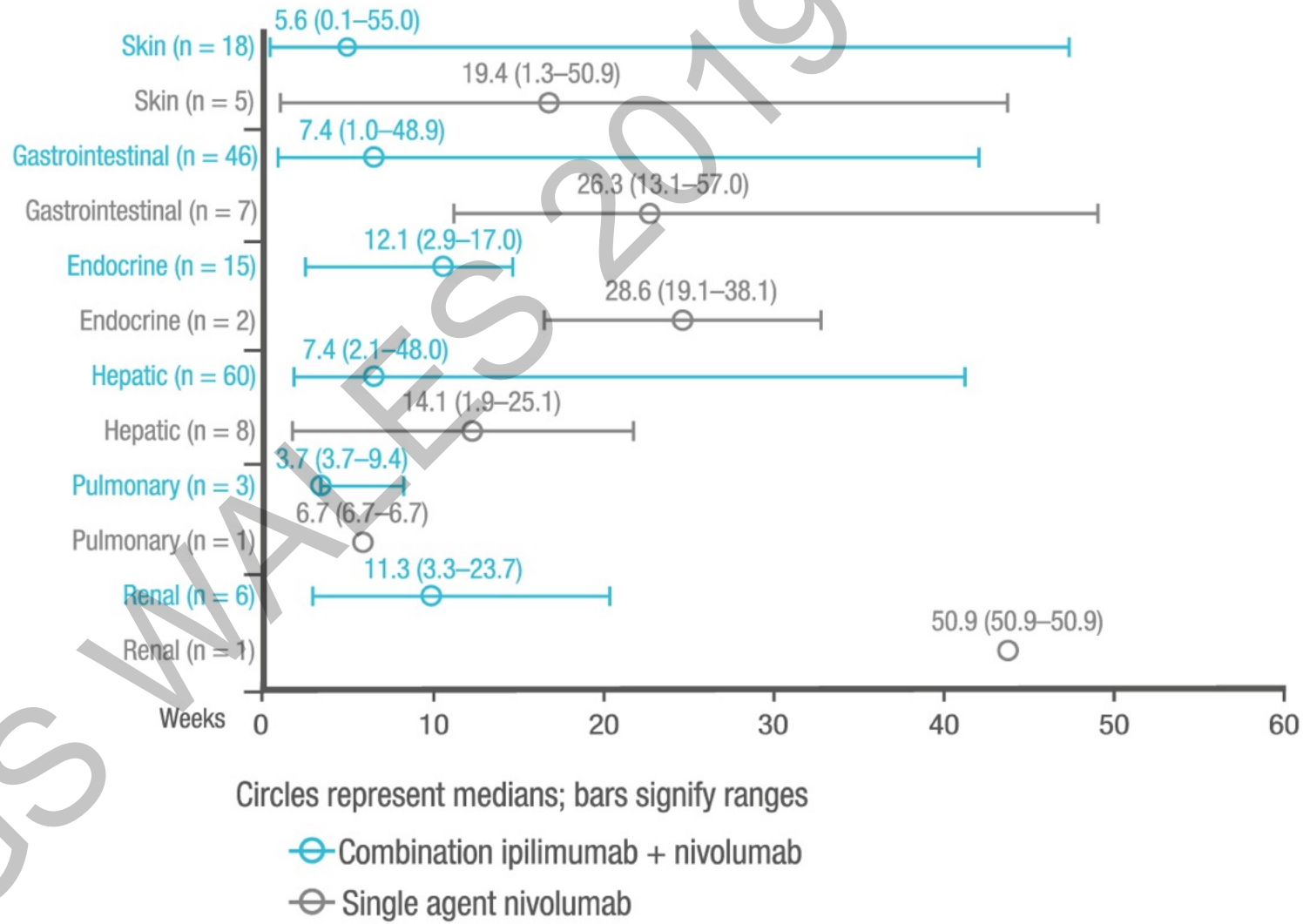
CLINICAL PRACTICE GUIDELINES

Incidence and epidemiology

Time to onset of grade 3-4 treatment-related select adverse events



Larkin J et al. Presented at ECC 2015;Abs330. Reprinted with permission.

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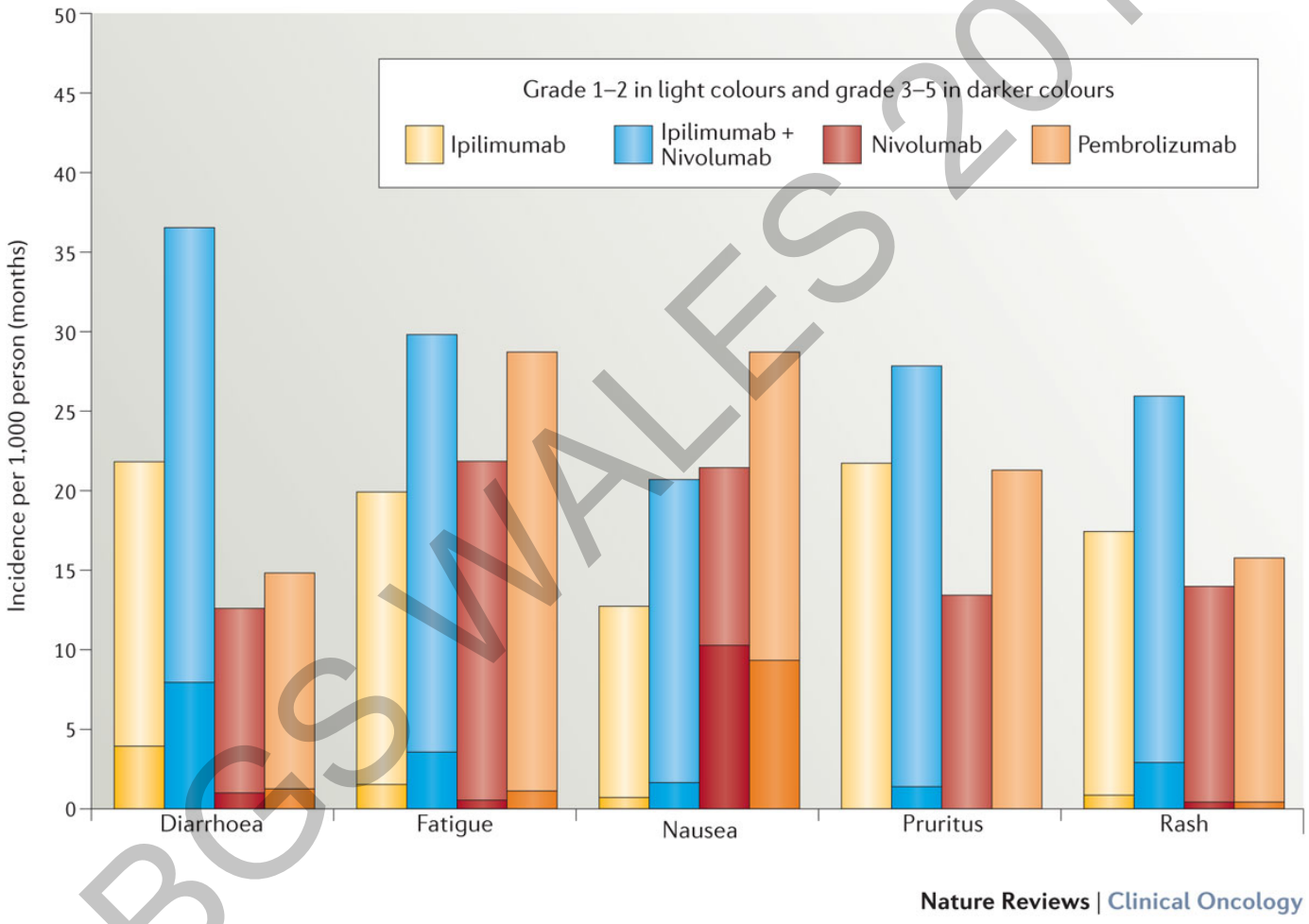
Figure 2 The most common adverse events in patients treated with ipilimumab, pembrolizumab, nivolumab, or ipilimumab plus nivolumab



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Boutros, C. *et al.* (2016) Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2016.58

General Principles of Managing Toxicities

- Recognise
- Grade it – CTCAE v4.0
- Investigate + exclude its Not other causes
- Steroids - PO if G2, IV if G3/4
- Specialist Advice
- Escalate/De-escalate

Algorithms Exist – Use Them!

RecoGNISSE *tm – O. Nicholas Sept 2019*

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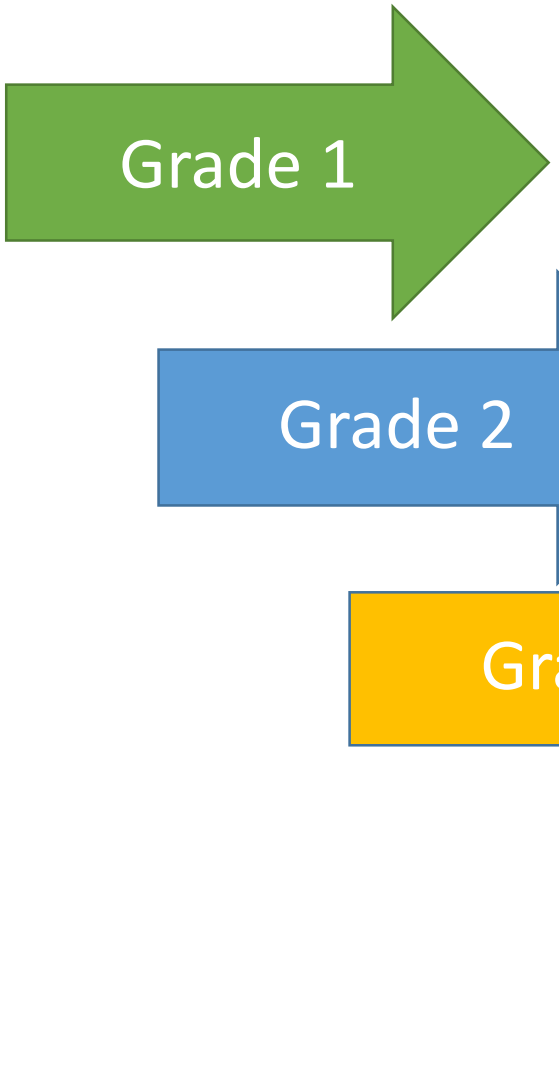
Grade the toxicity



Mild, manage as OP
Exclude other causes, monitor symptoms, supportive treatment (creams, loperamide etc), consider specialist advice

Moderate, consider IP
Exclude other causes, consider PO steroids, consider changing to IV if not improvement, consider specialist advice

Severe, IP admission
Exclude other causes, Commence IV steroids (1-2mg Methypred)
Seek specialist advice

Life threatening
Commence IV steroids (1-2mg Methypred)
Seek specialist advice

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Specific Toxicities

- Colitis
- Endocrinopathies

- Skin
- Hepatitis
- Nephritis
- Pneumonitis

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CLINICAL PRACTICE GUIDELINES

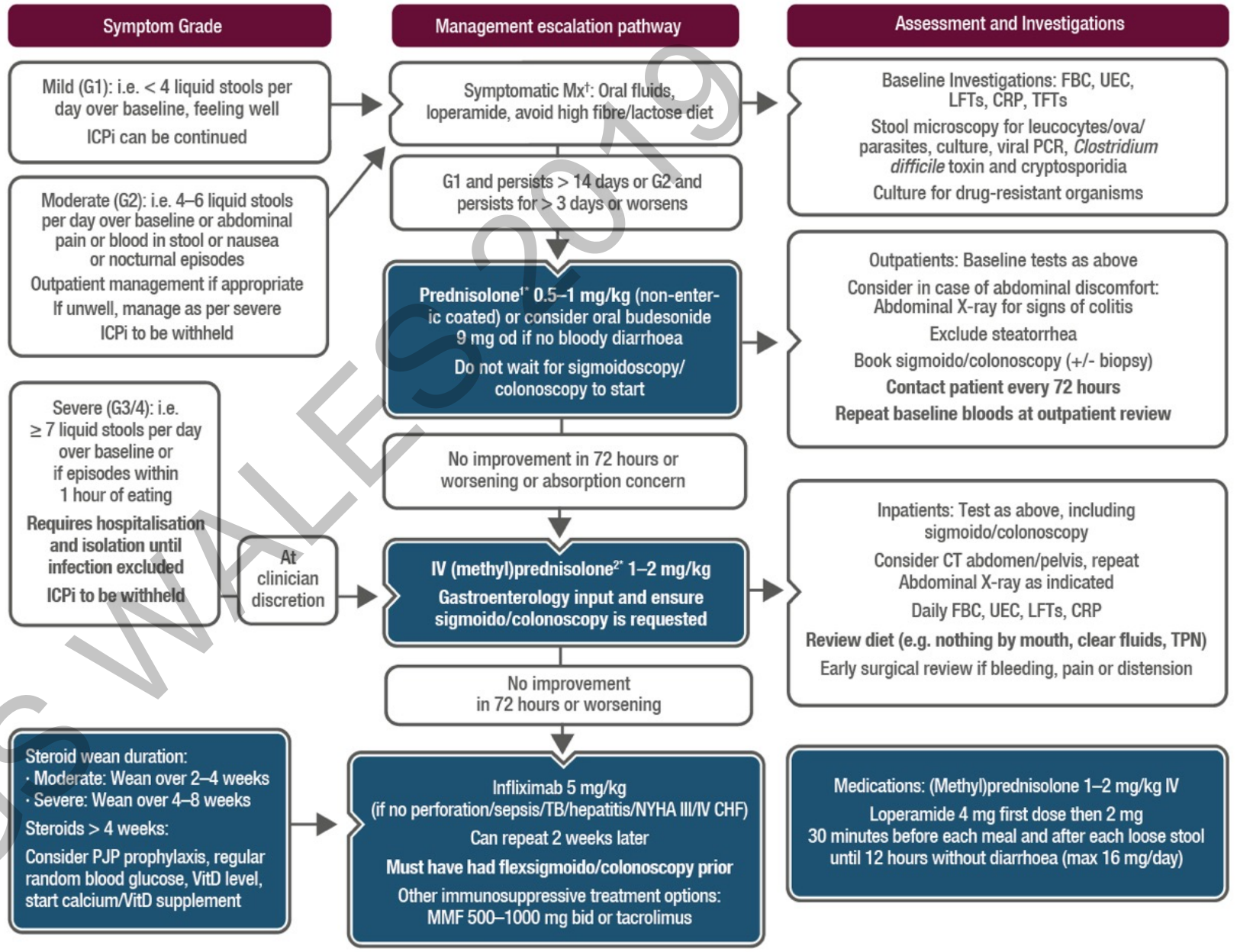
Immune related gastrointestinal toxicities

ICPi-related toxicity: Management of diarrhoea and colitis

†Loperamide 4 mg first dose then 2 mg 30 minutes before each meal and after each loose stool until 12 hours without diarrhoea (max 16 mg/day)

Steroid wean duration:
[1]Moderate: wean over 2–4 weeks
[2]Severe: wean over 4–8 weeks

*Steroids > 4 weeks: Consider PJP prophylaxis, regular random blood glucose, VitD level, start calcium/VitD supplement



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Colitis

- Recognise it
- Grade it! G1 - 0-3/day, G2- 4-6/day, G3/G4 - 7 and above/day
- Investigate + Exclude its Not other causes – FBC/UEs/LFTs/CRP/Bone/TFTs, stool cultures, AXR/CXR
- Steroids

G2 PO Prednisolone 0.5-1mg/kg,

G3/4 IV Methypred 1-2mg/kg

- Specialist advice – Gastro opinion, request flexi/sig, consider CT Abdo/Pelvis
- Escalate –

if G2 not improving – Change to IV Steroids,

If G3 not improving – Consider Infliximab 5mg/kg (also MMF/Tacrolimus)

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Endocrinopathies

- Hyper/Hypothyroid
- Hypopituitarism
- Hypoadrenalism

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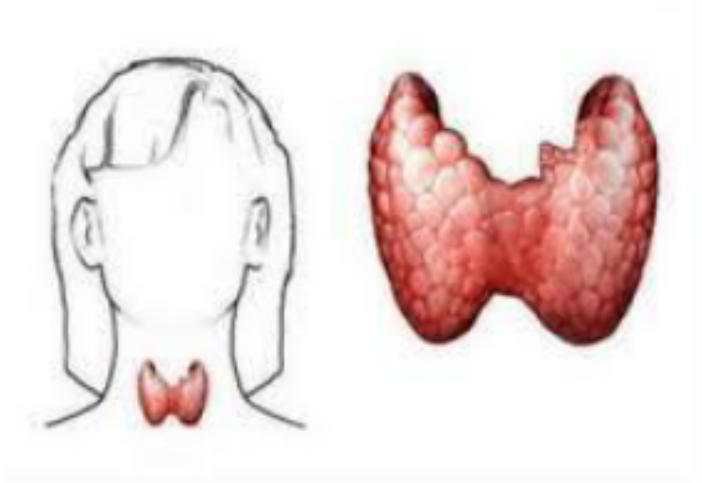

Thyroid dysfunction

More common with anti-PD1 agents (pembro, nivo) 4-10%

Grade 3 or 4 toxicities rare

Hypothyroidism

TSH >10 mU/L

Free T4 <12 pmoll

Hyperthyroidism

TSH <0.4 mU/L

Free T4 >22 pmol/L

Grade	Assessment	Management	Follow up
1 **Asymptomatic with biochemical changes**	Endocrine panel TSH, fT4, fT3, ACTH, LH, FSH, 9am cortisol, prolactin, blood glucose +/- testosterone, Oestradiol Thyroid autoantibodies Thyroglobulin Thyrotropin Receptor Anti TPO Abs If TSH low and T4 normal or low need to exclude pituitary dysfunction	Continue immunotherapy **Hyperthyroid** Monitor **Hypothyroid** Start levothyroxine 50mcg/day (if frailty or cardiovascular problems 25mcg)	**Hyperthyroid** recheck TFTs at 2 weeks then every 4-6 weeks (most become hypothyroid) **Hypothyroid** recheck TFTs each cycle Increase levothyroxine in 25mcg increments Endocrinology discussion re: long term management Endocrinology referral if unable to stabilise thyroid
2 **Symptomatic (tachycardia, tremor), Or intervention indicated**		Continue immunotherapy **Hyperthyroid** start propranolol 40-80mg daily Consider steroids 0.5mg-1mg/kg/day +PPI Carbimazole is rarely indicated unless anti-TSH antibodies present Endocrinology referral **Hypothyroid** start levothyroxine 50mcg/day	**Hyperthyroid** recheck TFTs 2 weekly as majority become hypothyroid in weeks **Hypothyroid** recheck TFTs with each cycle. Increase levothyroxine in 25mcg increments Endocrinology discussion re: long term management Endocrinology referral if unable to stabilise thyroid function
3 - 4 **Severe Or Life-threatening symptoms**		Hold immunotherapy Hospitalisation Oral prednisone 1-2mg/kg/day or IV equivalent Endocrinology Referral	Close monitoring as per Endocrinology If worried about thyroid storm or hypothyroid coma may need HDU

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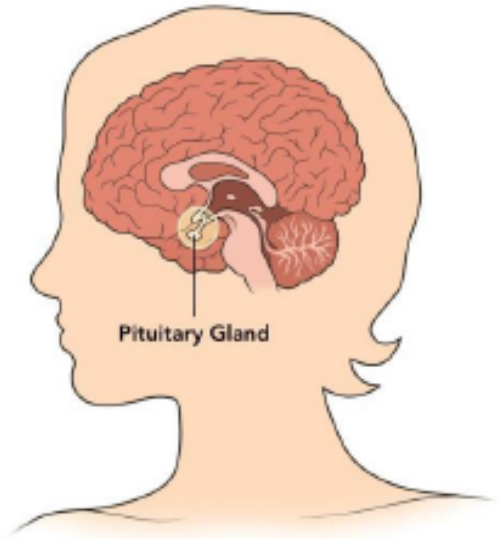
Credit: Sheffield Teaching Hospitals NHS Trust



Hypopituitarism

Combination 8%
Ipi 4%
PDL1 <1%

Commonly 6-13 weeks (up to 19 months)

Vague symptoms- fatigue, arthralgia, behavioural changes
Specific symptoms-headache, visual changes, dizziness, nausea

Grade	Assessment	Management	Follow up
1 Asymptomatic with biochemical changes	Endocrine panel TSH, fT4, fT3, ACTH, LH, FSH, 9am cortisol, prolactin, blood glucose +/- testosterone, Oestradiol IGF-1 **If Grade ≥ 2** MRI brain to image pituitary **Endocrinology Referral**	Continue immunotherapy Endocrinology Referral Replace cortisol for at least one week before thyroxine	Monitoring as per Endocrinology
2 Symptomatic (tachycardia, tremor), Or intervention indicated		Continue immunotherapy Endocrinology Referral Hormone Replacement Replace cortisol For at least one week before thyroxine Consider prednisolone 1mg/kg/day or IV equivalent Taper over 4 weeks followed by hormone replacement	Monitoring as per Endocrinology
3 - 4 Severe Or Life-threatening symptoms		Hold immunotherapy Endocrinology Referral Oral prednisone 1-2mg/kg/day or IV equivalent Taper over 4 weeks Followed by hormone replacement Replace cortisol for at least one week before thyroxine	Close monitoring as per Endocrinology Stop immunotherapy if Grade 4

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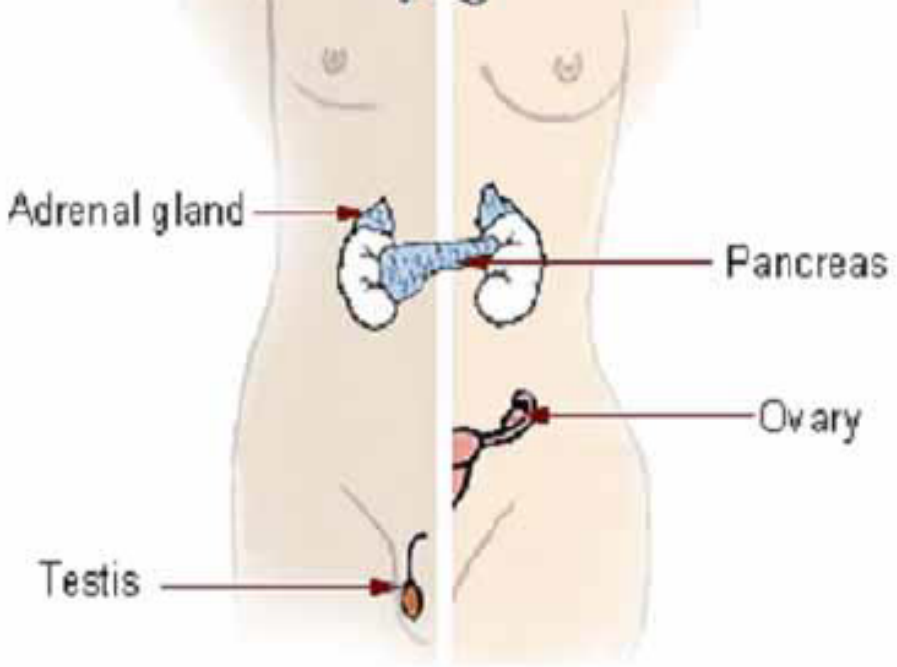

Hypoadrenalism

Likely if 9am cortisol <100 and possible if 100-400

Vague symptoms

Specific symptoms
dizzyness/collapse, nausea vomiting

Grade	Assessment	Management	Follow up
1 **Asymptomatic with biochemical changes**	Check 9am cortisol and ACTH Endocrine panel TSH, fT4, fT3, LH, FSH, prolactin, blood glucose +/- testosterone, Oestradiol IGF-1 **If Grade ≥2** MRI brain to image pituitary **Endocrinology Referral**	Continue immunotherapy If cortisol 100-400 nmol/L Monitor If cortisol <100 nmol/L Replace with hydrocortisone 10mg/5mg/5mg + Endocrinology referral	If cortisol 100-400 nmol/L Check 9am cortisol every cycle If cortisol <100 nmol/L Endocrinology discussion
2 **Symptomatic** Tachycardia, tremor Fatigue, Headache, Weight loss Normal BP **Or intervention indicated**		Hold immunotherapy Endocrinology Referral If cortisol <100 nmol/L Replace with hydrocortisone 10mg/5mg/5mg (discuss with endocrinology as may need weight related dosing)	If cortisol 100-400 nmol/L Check 9am cortisol every cycle If cortisol <100 nmol/L Endocrinology discussion
3 - 4 **Severe** **Or** **Life-threatening symptoms** Hypotension Postural hypotension Dizziness/Collapse Hypovolemia Nausea/ Vomiting Abdo pain/tenderness Fever, Confusion Coma, Hyponatraemia / Hyperkalaemia Hypoglycaemia AKI		Hold immunotherapy **ABCDE** Immediate IV/IM Hydrocortisone 100mg QDS Urgent Endocrionology Referral Rule out super-added infection Society for Endocrinology guidelines www.endocrineconnections.com/content/5/5/G1	Random cortisol >450nmol/L Stop insufficiency management and reassess Random cortisol <450nmol/L Continued endocrinology input **Adrenal crisis** Defined by severe dehydration, hypotensions or shock

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Summary of Endocrinopathies

- Recognise – symptoms can be vague
- Grade it!
- Investigate - Send Endocrine Panel – TFTs,FT4, 9am cortisol (or random), ACTH, LH/FSH, prolactin, testosterone, oestrodiol, IGF-1
- Steroids – Mild/moderate – PO Pred 0.5-1mg/kg, Severe IV Methypred 1-2mg/kg
- Specialist Advice – Endocrine opinion, consider MRI Pituitary
- Escalate/De-escalate – Advice from endocrine, taper steroids to maintenance dose

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Caveats

- Symptoms are vague, you have to suspect it to diagnose it!
- Check Endocrine profile BEFORE starting steroids.
- Don’t forget to replace cortisol for at least one week before thyroid replacement
- Wean steroids slowly – over period of 4-8 weeks, e.g. Pred 5mg-10mg/per week

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Don’t forget

- Skin toxicity

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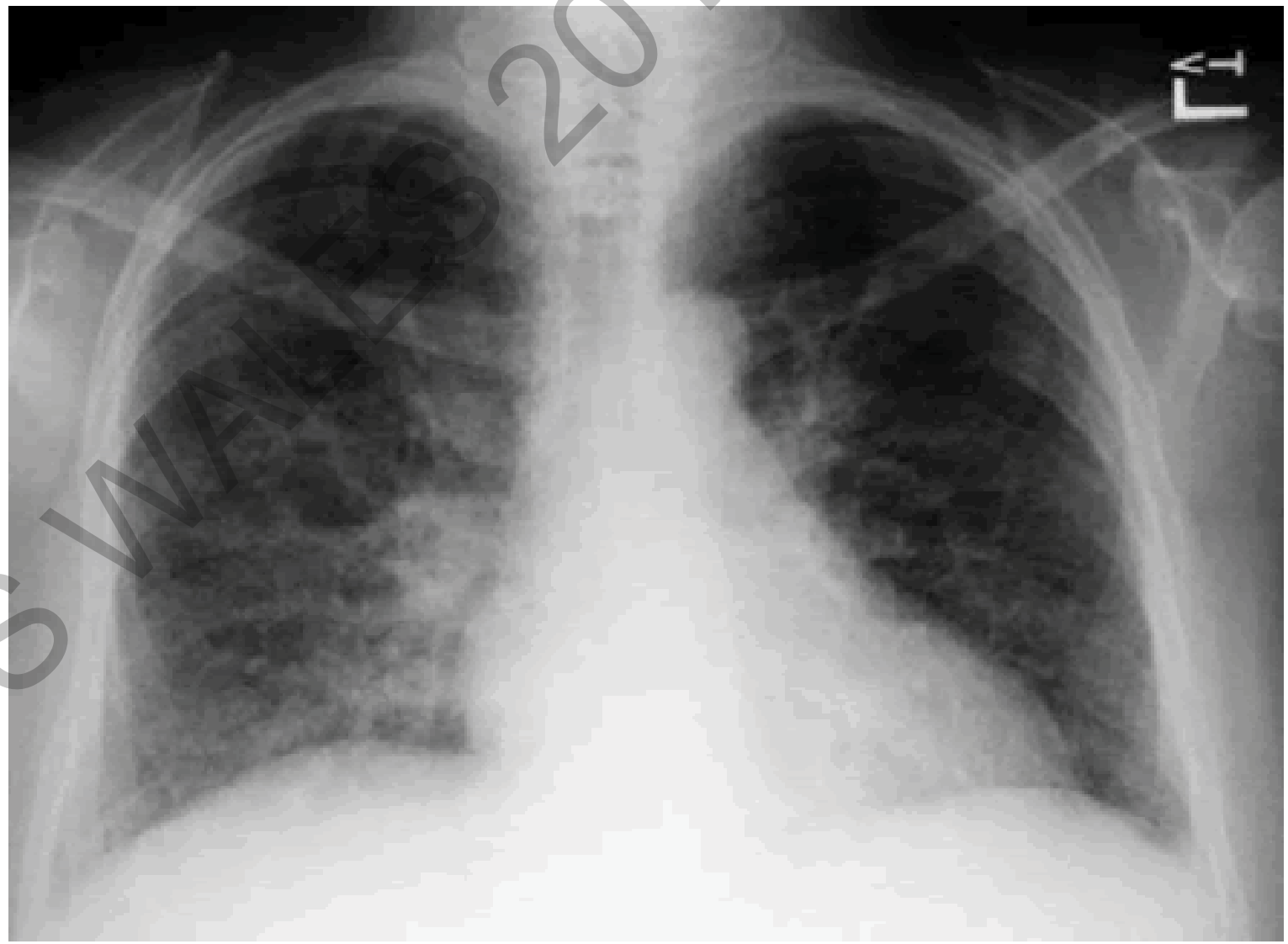
Don’t forget

- Pneumonitis



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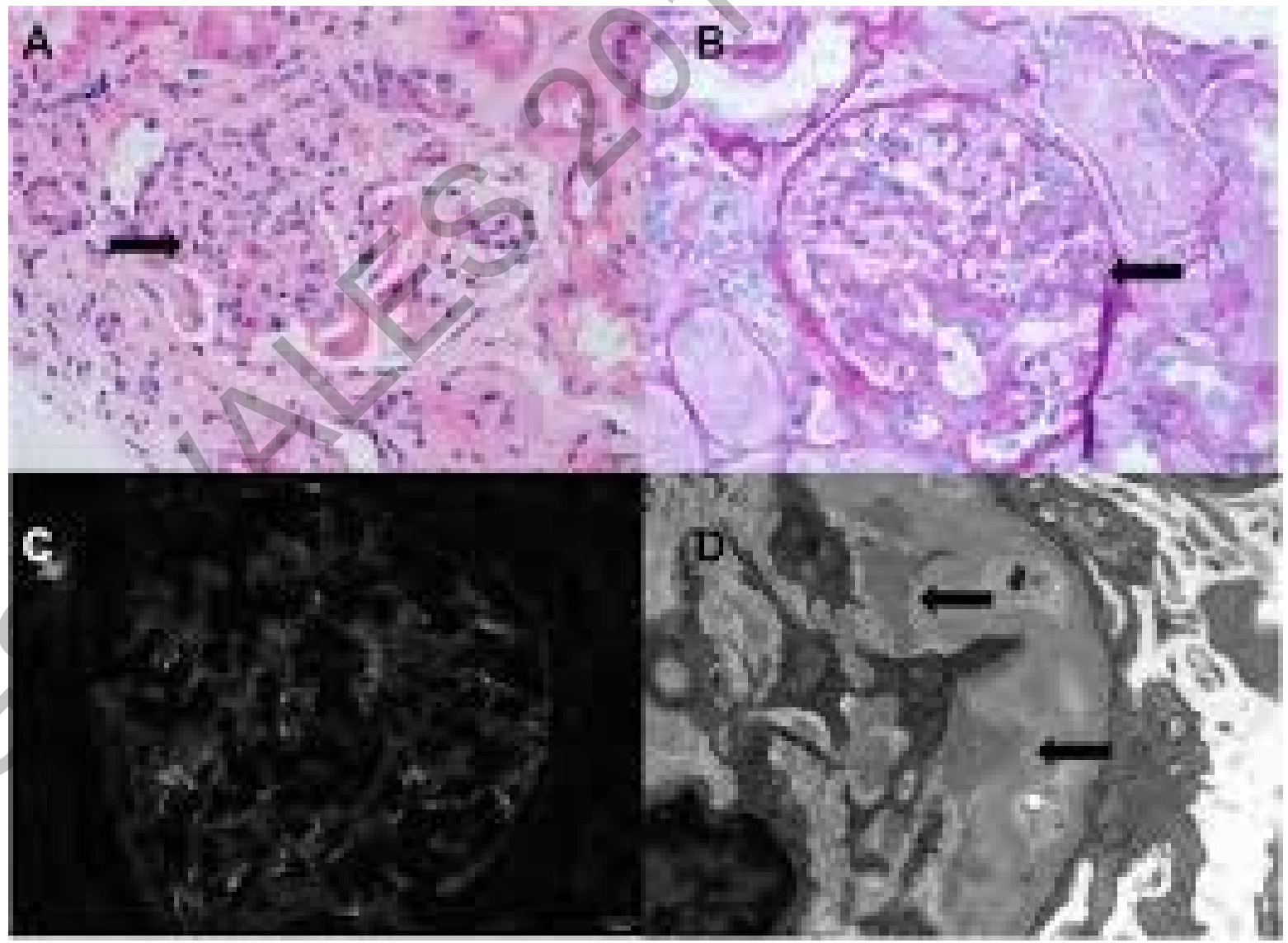
Don’t forget

- Nephritis



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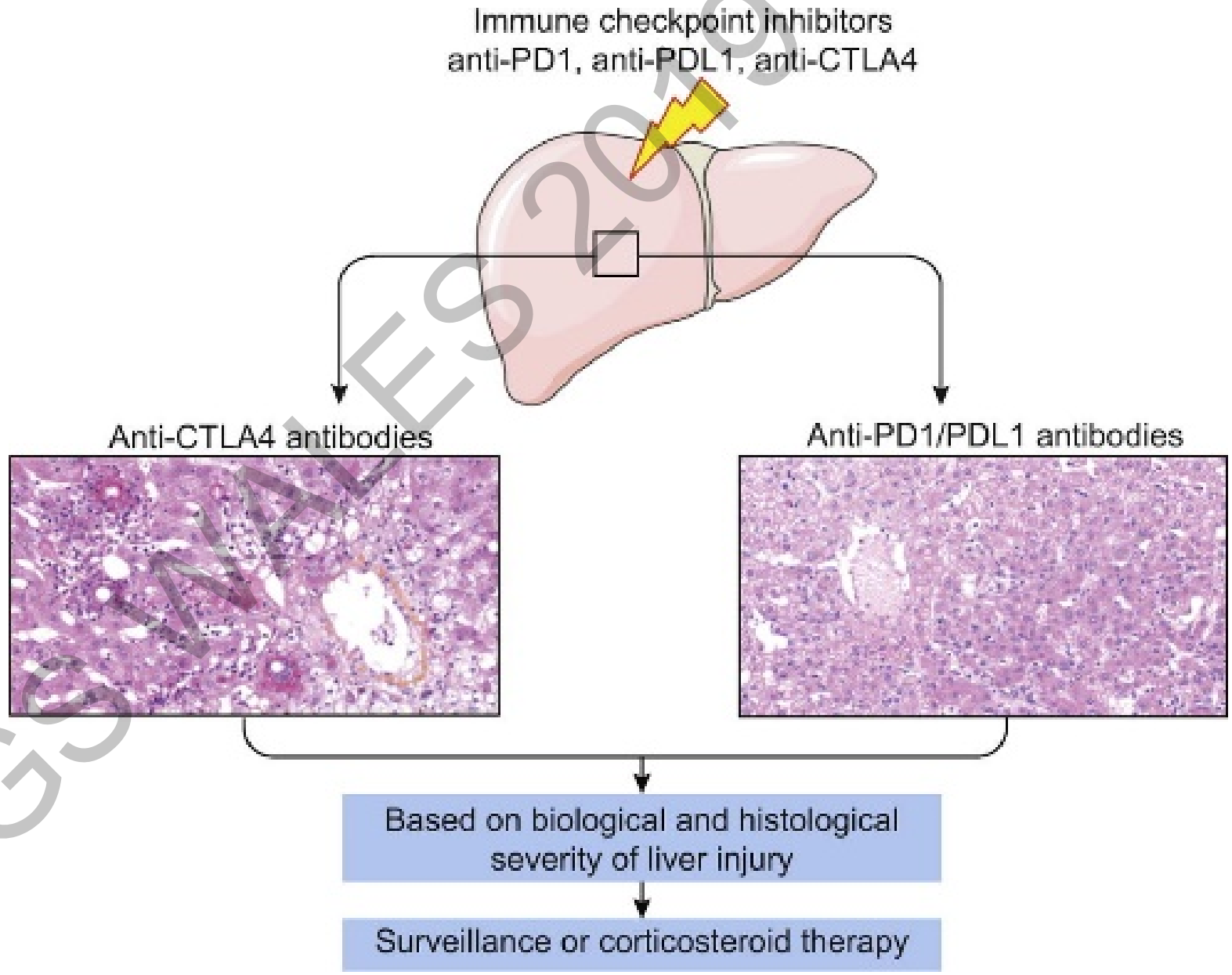
Don’t forget

- Hepatitis



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Don’t forget

- Rarer toxicities

Cardiac – e.g. pericarditis, myocarditis etc

Neurological – e.g. Guillain-Barre, Myasthenia Gravis, Cranial nerve palsies etc.

Rheumatological, incl. flare up of underlying autoimmune diagnoses

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Clinical Case

69yo, male, retired carpenter

PMHx - Melanoma Right Eye 11 years ago. Holiday home in Cyprus. Presents with Weight loss

Has CT at rapid diagnostic centre in NPT on 3/5/19.

CT – disseminated malignancy, lung, liver, bone, peritoneal mets

Bx 8/5/19 –Left flank superficial lesions – Melanoma

Has radiotherapy for soft tissue lesion near spine and acetabulum for pain- 21/5/19

Sees oncology 10/6/19 – PS – 0 starts combination Nivo + Ipi - 8th July 2019

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- 19/8/19 – Call triage helpline

Tired, poor appetite, sleeping all day, Diarrhoea 2-3 times/day.

Admitted to SAU

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- Initial history?
- Initial tests to send off?

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- Fatigue – Having to nap 2-3 day
- Bowels opening 6-8 times/day
- Mild general abdo tenderness. Looks tired but quite well. obs stable

- Bloods – routine bloods + endocrine panel (incl TFTs, random cortisol, ACTH, LH/FSH, testosterone,)
- Stool MC+S
- Imaging AXR

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- Bloods – AKI Creat 190, CRP 98

- Random cortisol 350, ACTH awaited
- TFTs normal

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Grade of toxicity?

Management?

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Grade 3 Colitis

Starts on 1mg/kg Methypred + loperamide/IV fluids

After 48 hours,

Feels better

Bowels opening 6 times still

Escalation?

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Escalation?

Methylpred – increased to 2mg/kg

Gastro opinion – flexi sig, CMV/quantiferon prior to starting infliximab

Remains on Infliximab, diarrhoea settling 2-3/day

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Learning Objectives

By the end of the session:

- Gain a basic understanding of what immunotherapy is and how it works
- Understand the role it has to play in current oncological management
- Recognise common immunotherapy agents
- Diagnose common immunotherapy toxicities and
- Grade the toxicity
- An overview on how to manage immunotherapy toxicities

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Common Immunotherapy Agents

- Anti PD-1/PDL-1

Pembroluzimab (Pembro)
Nivolumab (Nivo)
Atezolizumab
Durvalumab

- Also used in combination - Nivo + Ipi

- Anti CTLA-4

Ipilimumab (Ipi)

All given by infusion

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Grade the toxicity

Grade 1

Mild, manage as OP
Exclude other causes, monitor symptoms, consider specialist advice

Grade 2

der changing to IV if

RecoGNISSE™

Grade 3

Exclude other causes, Commence IV steroids (1-2mg Methypred)
Seek specialist advice

Grade 4

Life threatening
Commence IV steroids (1-2mg Methypred)
Seek specialist advice

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Useful Links

Use guidelines – plenty exist

https://www.esmo.org/content/download/151567/2718664/file/Clinical-Practice-Guidelines-Slideset-Toxicities-Immunotherapy.pdf

Common Terminology Criteria for Adverse Events (CT CAE 4.0)

https://www.eortc.be/services/doc/ctc/ctcae_4.03_2010-06-14_quickreference_5x7.pdf

Use local **Acute Oncology Service**

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Questions

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