Emergency management of immune-related toxicities

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Post MASCC Brussels, Brussels, Nov 2019

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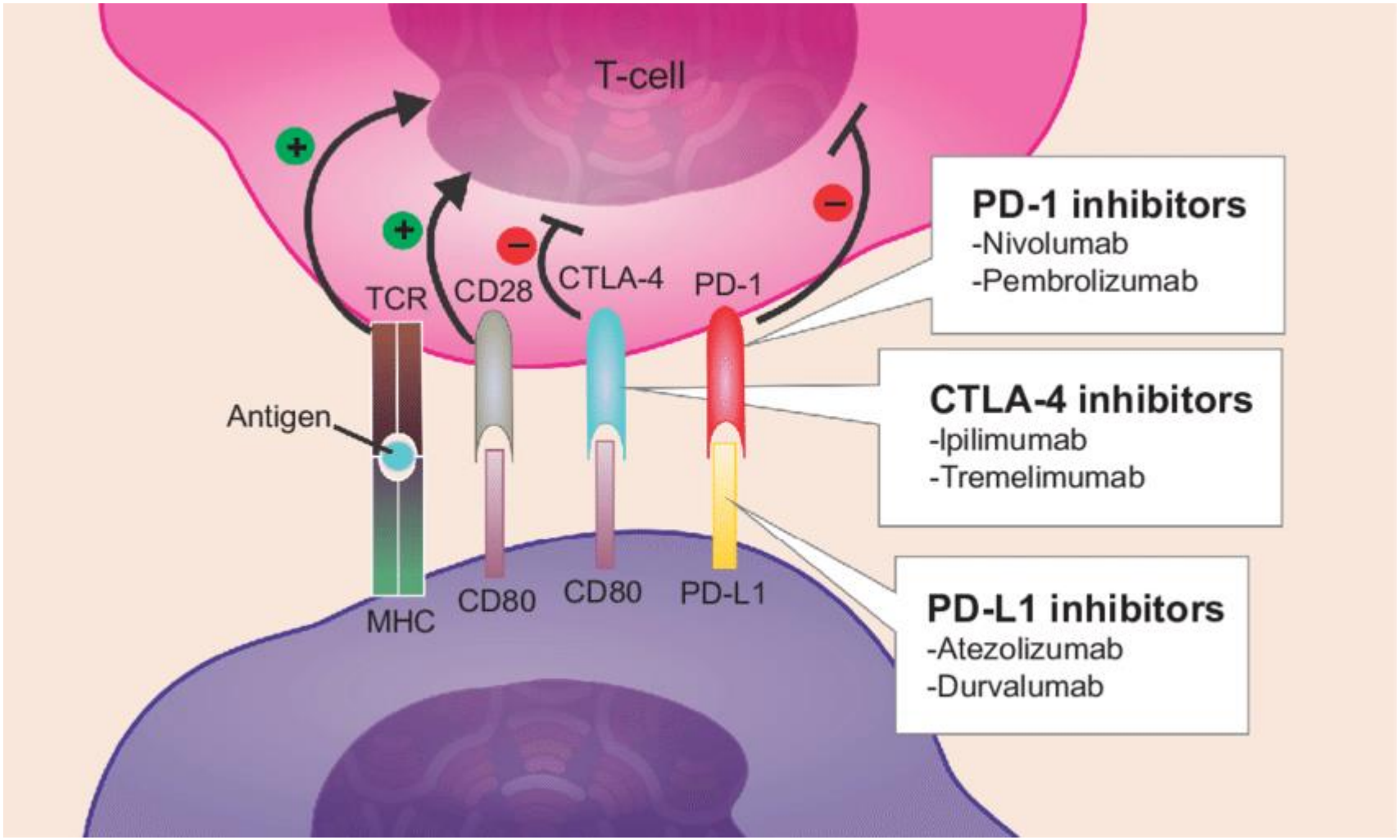
Overview

- Description of immune-related toxicities
- Current guidelines
- Approach to an unwell patient on checkpoint inhibition
- Case studies

Mechanism of checkpoint inhibitors



Postow et al 2018 Uptodate

Evidence for checkpoint inhibitors

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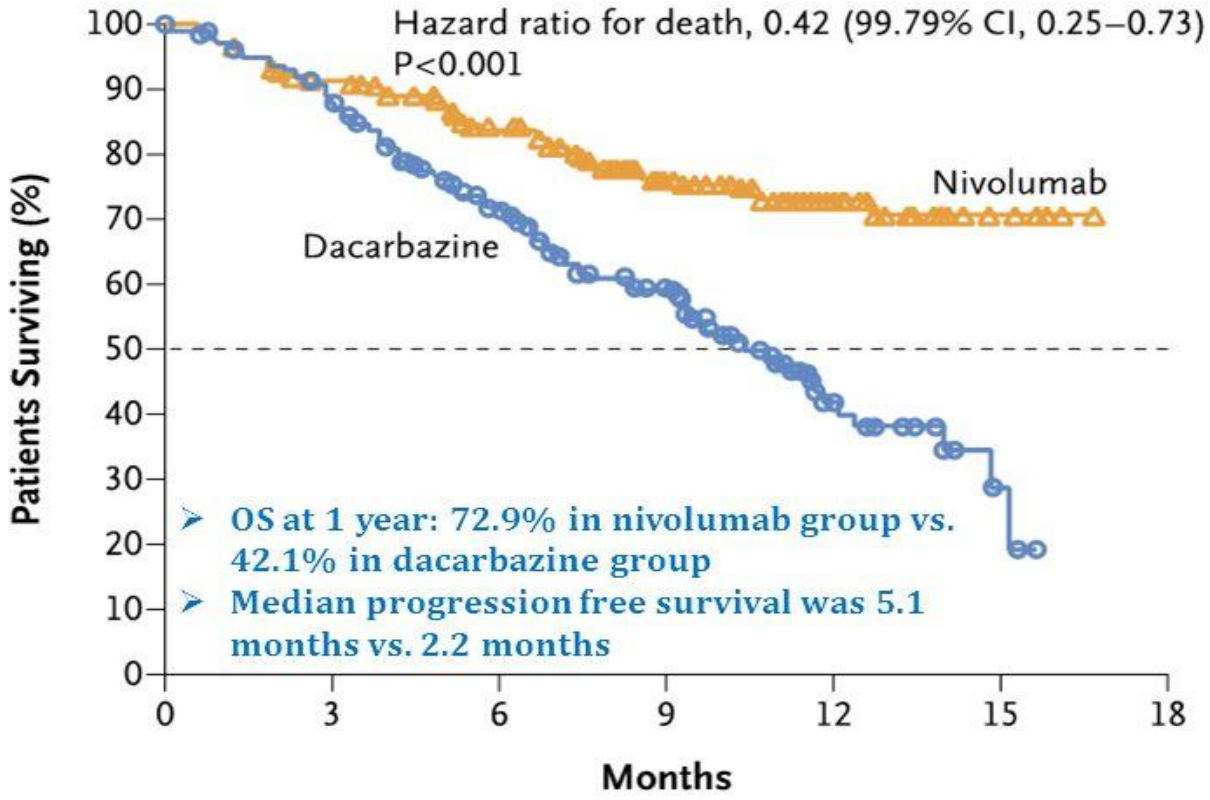
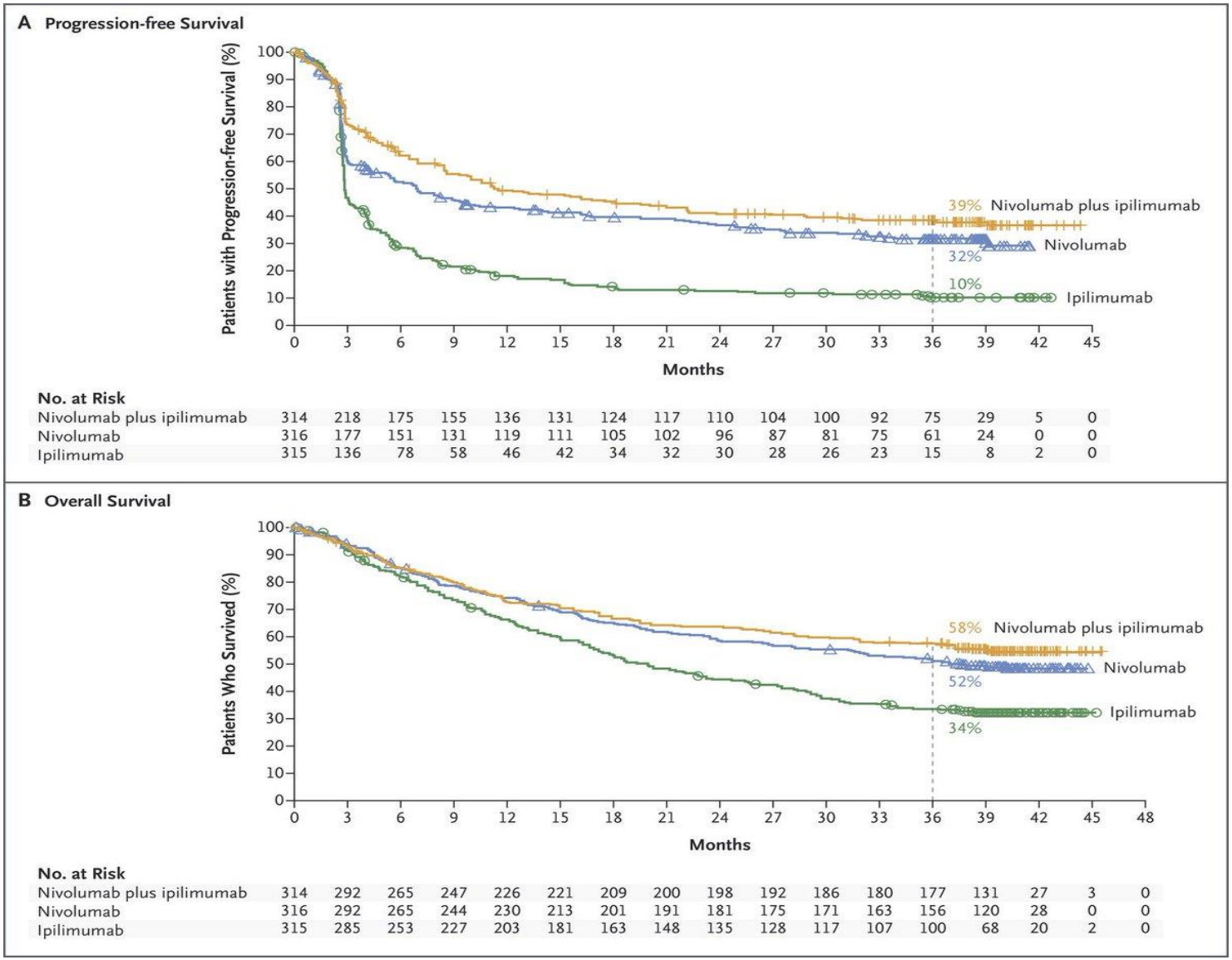
Overall Survival Rates: Nivolumab vs. Dacarbazine



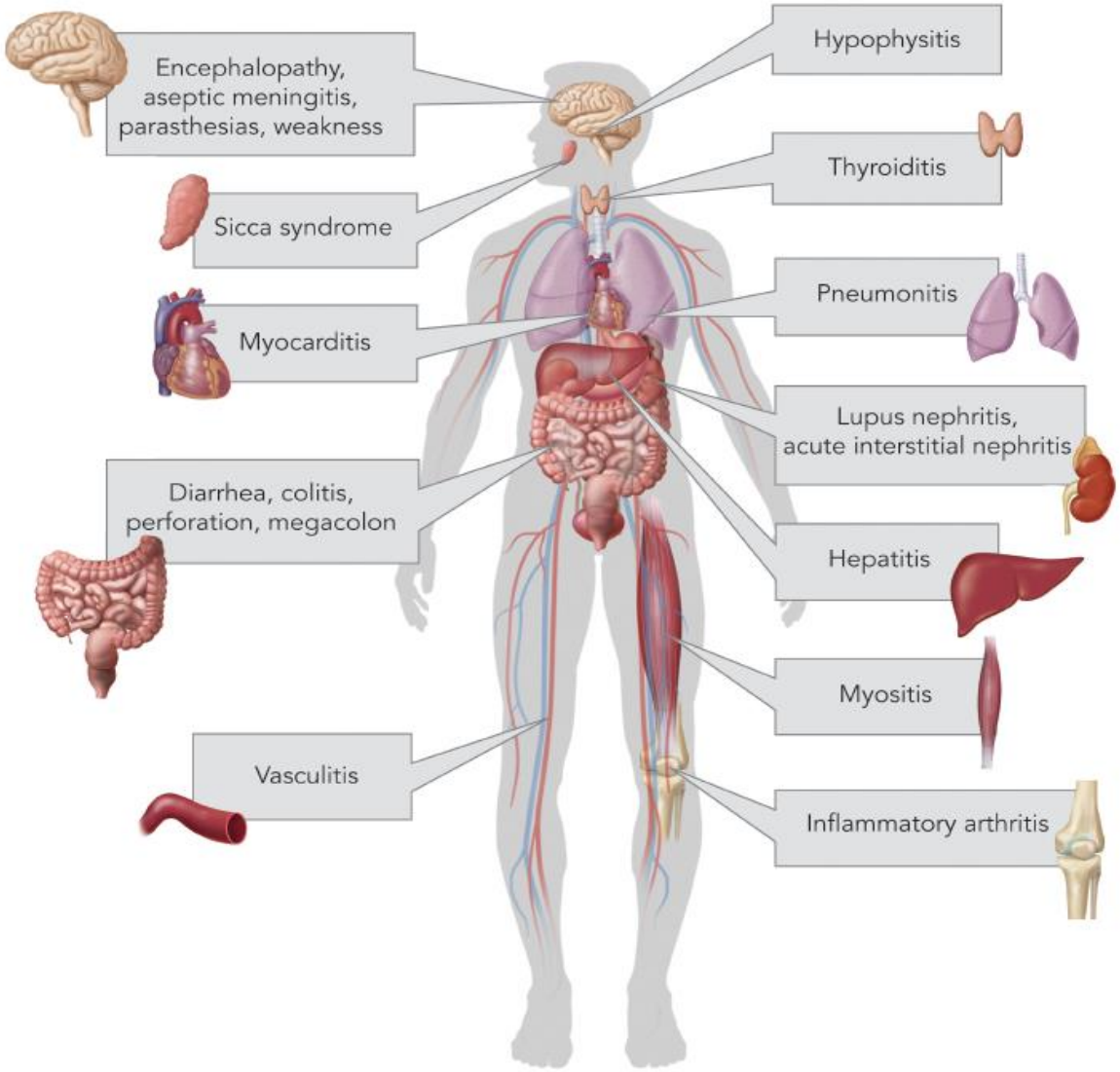
Robert C et al. Nivolumab in previously untreated melanoma with BRAF mutation. NEJM. 2015; 372:320-30.

Combination Checkpoint Inhibition



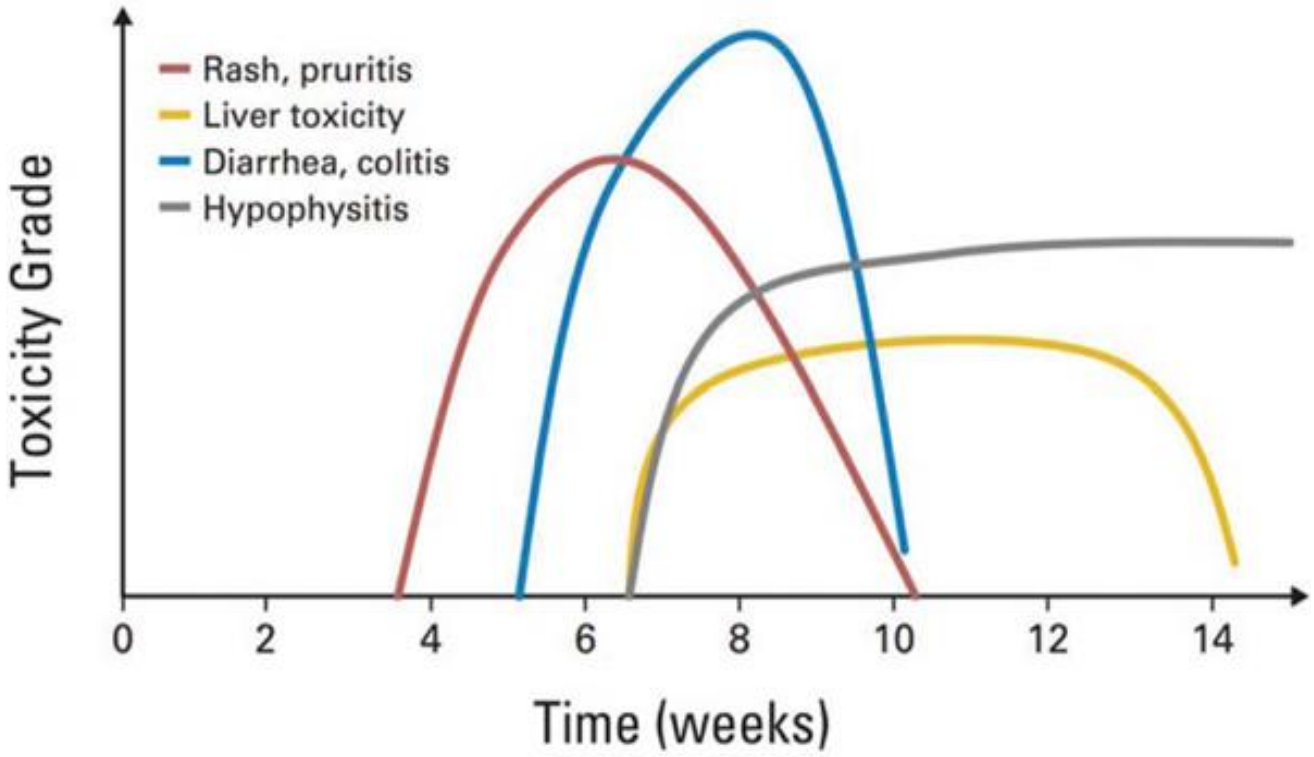
Wolchok et al. NEJM 2017

Immune-related toxicities

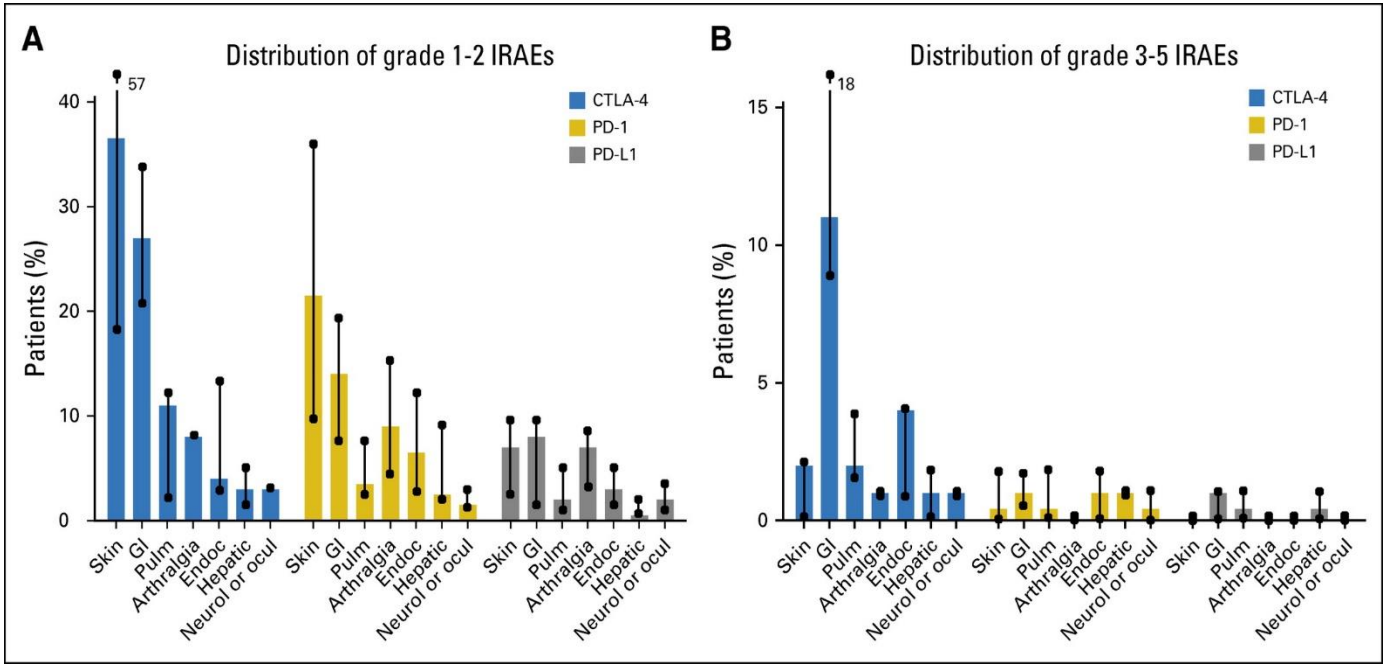


Dirzeno et al. The Rheumatologist

Timing of IR toxicities



Frequency of IR Toxicities



Brahmer et al 2018. ASCO

Guidelines

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Annals of Oncology 28 (Supplement 4): iv119–iv142, 2017
doi:10.1093/annonc/mdx225

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

CLINICAL PRACTICE GUIDELINES

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

J. B. A. G. Haanen[1], F. Carbonnel[2], C. Robert[3], K. M. Kerr[4], S. Peters[5], J. Larkin[6] & K. Jordan[7], on behalf of the ESMO Guidelines Committee*

[1]Netherlands Cancer Institute, Division of Medical Oncology, Amsterdam, The Netherlands; [2]Department of Gastroenterology, Kremlin Bicêtre Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France; [3]Department of Medicine, Dermatology Unit, Gustave Roussy Cancer Campus, Villejuif, France; [4]Department of Pathology, Aberdeen University Medical School & Aberdeen Royal Infirmary, Aberdeen, UK; [5]Oncology Department, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland; [6]Royal Marsden Hospital NHS Foundation Trust, London, UK; [7]Department of Medicine V, Hematology, Oncology and Rheumatology, University Hospital of Heidelberg, Heidelberg, Germany

*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland. E-mail: clinicalguidelines@esmo.org

†Approved by the ESMO Guidelines Committee: May 2017.

General approach to IR toxicities

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CTCAE Grade	Management
1	Supportive treatment Close monitoring Investigations to exclude other cause of symptoms Patient advice and education
2	As per grade with the addition of:- Withhold checkpoint inhibitor until symptoms settle/resolve If symptoms persist for >5 days consider oral prednisolone Liaison with Oncology and Organ-related specialist
3/4	Supportive treatment Commence high dose steroids (1-2mg/kg OD IV Methylprednisolone) Withhold checkpoint inhibitor Investigations to exclude other cause of symptoms and assess severity Liaison with Oncology and Organ-related specialist If symptoms persist despite steroids consider additional immunosuppressive agent

Case Study

- 54 year old male
- Metastatic melanoma
- Completed 3 cycles of Ipilimumab
- 4 day history of generalized headache, extreme fatigue and nausea
- Seen 2 days earlier at local Uni hospital
    - CT brain – NAD
    - Diagnosed migraine and discharged

Case Study (Examination)

- Drowsy but easily rousable
- BP = 100/60mmHg. Pulse = 90bpm
- Chest clear
- No focal neurology
- BM = 2.1mmols

Case Study (Pituitary Profile)

- Cortisol < 50
- TSH = 0.03
- LH < 1
- FSH < 2
- ACTH = 10
- Prolactin = 150

Guidelines

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Endocrine CONNECTIONS | C E Higham *et al.* | Acute management of CKI endocrinopathies | 7:5 | G1–G7

PROOF ONLY

EMERGENCY GUIDANCE

SOCIETY FOR ENDOCRINOLOGY ENDOCRINE EMERGENCY GUIDANCE

Acute management of the endocrine complications of checkpoint inhibitor therapy

C E Higham[1], A Olsson-Brown[2,3], P Carroll[4], T Cooksley[5], J Larkin[6], P Lorigan[7], D Morganstein[8] and P J Trainer[1] the Society for Endocrinology (SfE) Clinical Committee[9]

[1]Department of Endocrinology, Christie Hospital NHS Foundation Trust, Manchester, Centre for Endocrinology and Diabetes, Institute of Human Development, Faculty of Medical and Human Sciences, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK
[2]The Clatterbridge Cancer Centre, Bebbington, Wirral, UK
[3]The University of Liverpool, Brownlow Hill, Liverpool, UK
[4]Department of Endocrinology, Guy's & St. Thomas' NHS Foundation Trust, London, UK
[5]Department of Acute Medicine, UHSM and Christie Hospital NHS Foundation Trust, Manchester, UK
[6]Skin Unit, Royal Marsden Hospital, London, UK
[7]Department of Medical Oncology, Christie Hospital NHS Foundation Trust, Manchester, UK
[8]Department of Endocrinology, Chelsea and Westminster Hospital, London, UK
[9]The Society for Endocrinology, Woodlands, Bradley Stoke, Bristol, UK

Guidance for life-threatening immune-mediated HPA toxicity

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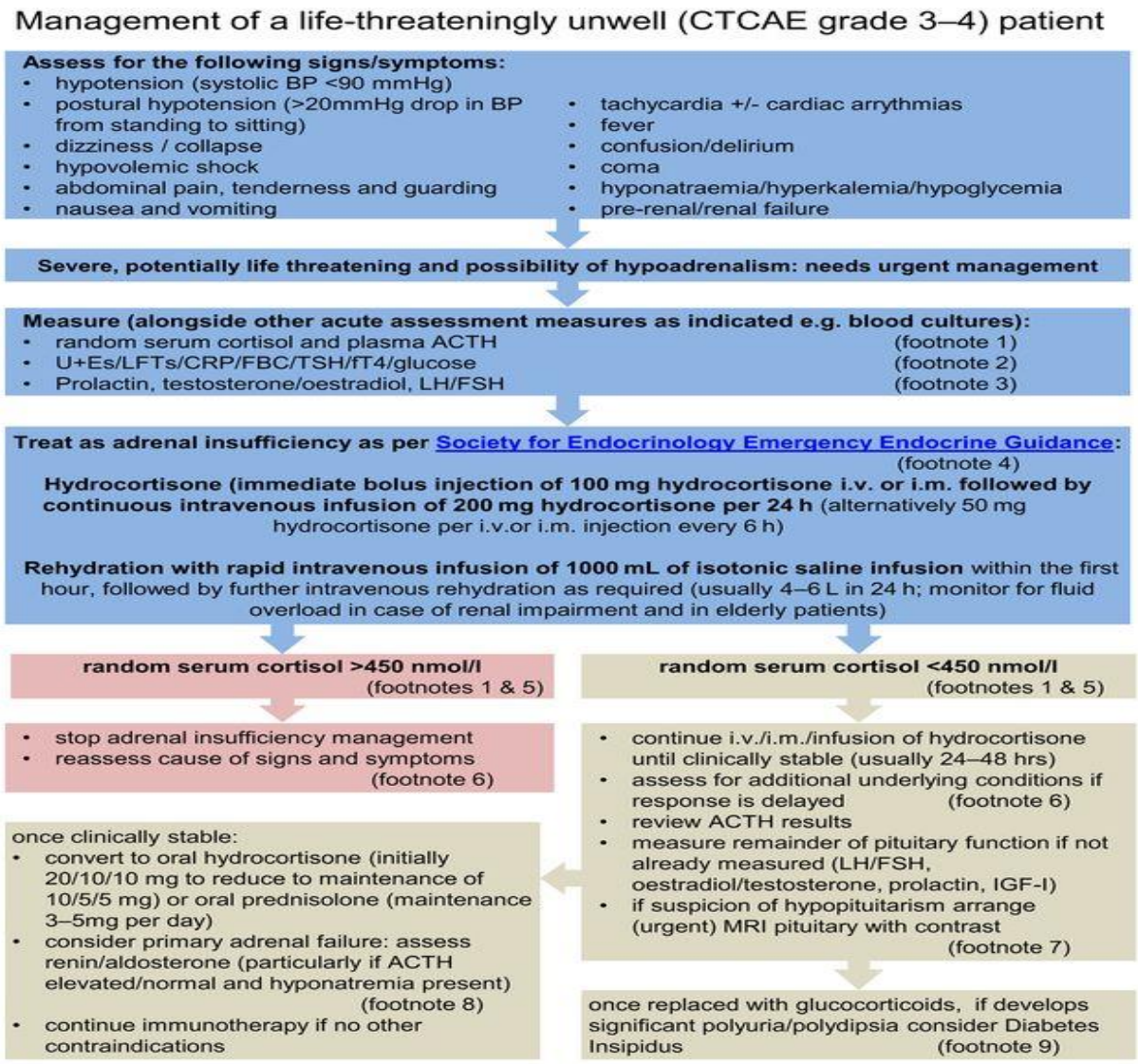

Guidance for possible mild/moderate immune-mediated HPA toxicity

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Management of patient with mild/moderate symptoms (CTCAE grade 1–2) compatible with cortisol deficiency

- tiredness/fatigue
- weight loss
- susceptibility to infection
- normal BP with no postural drop

↓

mild/moderate: non life-threatening
(may become life-threatening if intermittent illness/physical stress occurs)

↓

measure serum cortisol (ideally at 9 am), and ACTH (footnote 1)

9 am cortisol <200 nmol/l or random cortisol <100 nmol/l **adrenal insufficiency likely**	9 am cortisol 200–450 nmol/l or random cortisol 100–450 nmol/l **adrenal insufficiency possible**	9 am or random cortisol >450 nmol/l **adrenal insufficiency unlikely**
• start oral hydrocortisone (10, 5, 5 mg) or prednisolone (3–5mg) • refer to specialist services (Endocrinology) • measure remainder of pituitary profile IGF-1/TSH/fT4/LH+FSH/T2orE2/prolactin For TFT abnormalities see Algorithm 3 • if suspicion of primary adrenal failure or ACTH elevated measure plasma renin and aldosterone • give emergency advice about H/C: https://www.endocrinology.org/adrenal-crisis/ https://doi.org/10.1530/EC-16-0054 • continue immunotherapy if no other contraindications	• refer to Endocrinology • measure remainder of pituitary profile IGF-1/TSH/fT4/LH+FSH/TorE2/prolactin For TFT abnormalities see Algorithm 3 • consider SST (but interpret with caution if ACTH low as may be falsely reassuring in recent onset pituitary disease – discuss with Endocrinology) • continue immunotherapy if no other contraindications • if delay in Endocrine referral anticipated start oral hydrocortisone (10, 5, 5 mg) or prednisolone (3–5mg)	• consider other causes of symptoms • continue immunotherapy if no other contraindications

Footnotes:

Footnote 1 Review patient information for evidence of recent steroid use:

- any supraphysiological dose of glucocorticoid can suppress the adrenal axis.
- patients receiving doses of dexamethasone >0.75 mg or prednisolone >3mg daily will likely have a supressed endogenous HPA axis and may have a serum cortisol measurement of <50 nmol/l. If the glucocorticoid treatment is ongoing they are not adrenally insufficient but may need higher doses of glucocorticoids when clinically unwell. Seek specialist advice from endocrinology.

Steroid management of IR HPA toxicity

Cancer

Original Article

High-dose glucocorticoids for the treatment of ipilimumab-induced hypophysitis is associated with reduced survival in patients with melanoma

Alexander T. Faje MD ✉, Donald Lawrence MD, Keith Flaherty MD, Christine Freedman RN, Riley Fadden NP, Krista Rubin NP, Justine Cohen MD, Ryan J. Sullivan MD

First published: 05 July 2018 | https://doi.org/10.1002/cncr.31629 | Cited by: 4

High dose steroids for IR HPA toxicity associated with reduced survival

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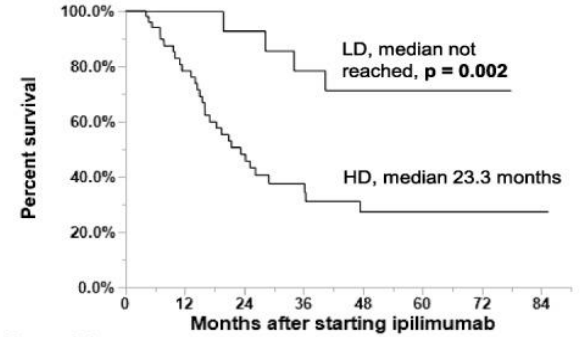
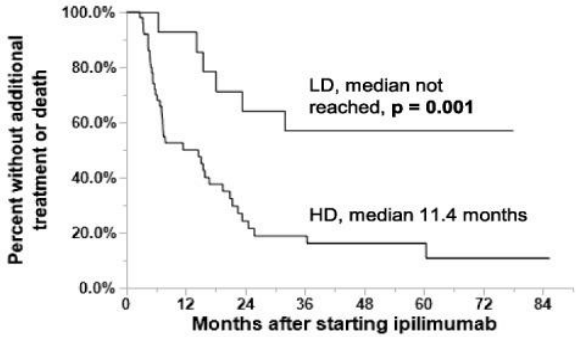
A)



No. at risk:

LD	14	14	13	11	8	3	2	
HD	50	34	20	12	7	3	2	1

B)

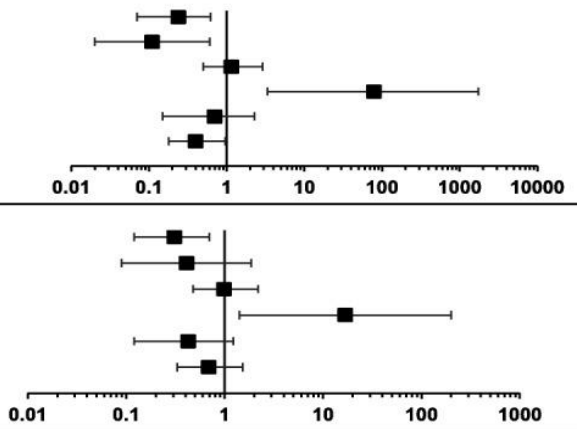


No. at risk:

LD	14	13	9	8	7	3	2	
HD	50	20	9	7	5	3	2	1

C)

	n	HR	95% CI	P value	Forest Plot
Death					
LD vs HD	64	0.24	0.07-0.62	0.002	
Age	64	0.11	0.02-0.61	0.01	
Gender (male vs female)	64	1.15	0.50-2.91	0.75	
LDH[a]	60	78.61	3.34-1736.77	0.008	
Resected NED (yes vs no)	64	0.70	0.15-2.28	0.58	
ECOG (0 vs 1 or 2)	64	0.40	0.18-0.96	0.04	
Treatment Failure					
LD vs HD	64	0.31	0.12-0.70	0.004	
Age	64	0.41	0.09-1.86	0.26	
Gender (male vs female)	64	0.99	0.48-2.18	0.97	
LDH[a]	60	16.75	1.41-199.38	0.04	
Resected NED (yes vs no)	64	0.43	0.12-1.22	0.12	
ECOG (0 vs 1 or 2)	64	0.69	0.33-1.52	0.34	



[a] log transformed

Collaboration is key

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Cancer

Correspondence

Emergency management of immune-related hypophysitis: Collaboration between specialists is essential to achieve optimal outcomes

Tim Cooksley MBChB (Hons), MRCP (Acute), Claire Higham MBBS, DPhil, Paul Lorigan MBBCH, FRCP, Peter Trainer MBChB, MD

First published: 23 October 2018 | https://doi.org/10.1002/cncr.31789

Case Study

- 65 year old male
- Metastatic ureteric carcinoma
- Completed 4 cycles of Pembro
- Presents with:
  - Fatigue
  - Fever
  - Osmotic symptoms

Clinical examination

- Alert
- Temp = 38^{o}C
- Dry
- BP = 110/70mmHg Pulse =130bpm
- RR = 28 O_2 SATS = 98% (AIR)
- Chest clinically clear
- Abdo and neuro examination unremarkable

Immune-related DKA

- BM = 29.8mmols
- pH = 7.29, BE = -10.7

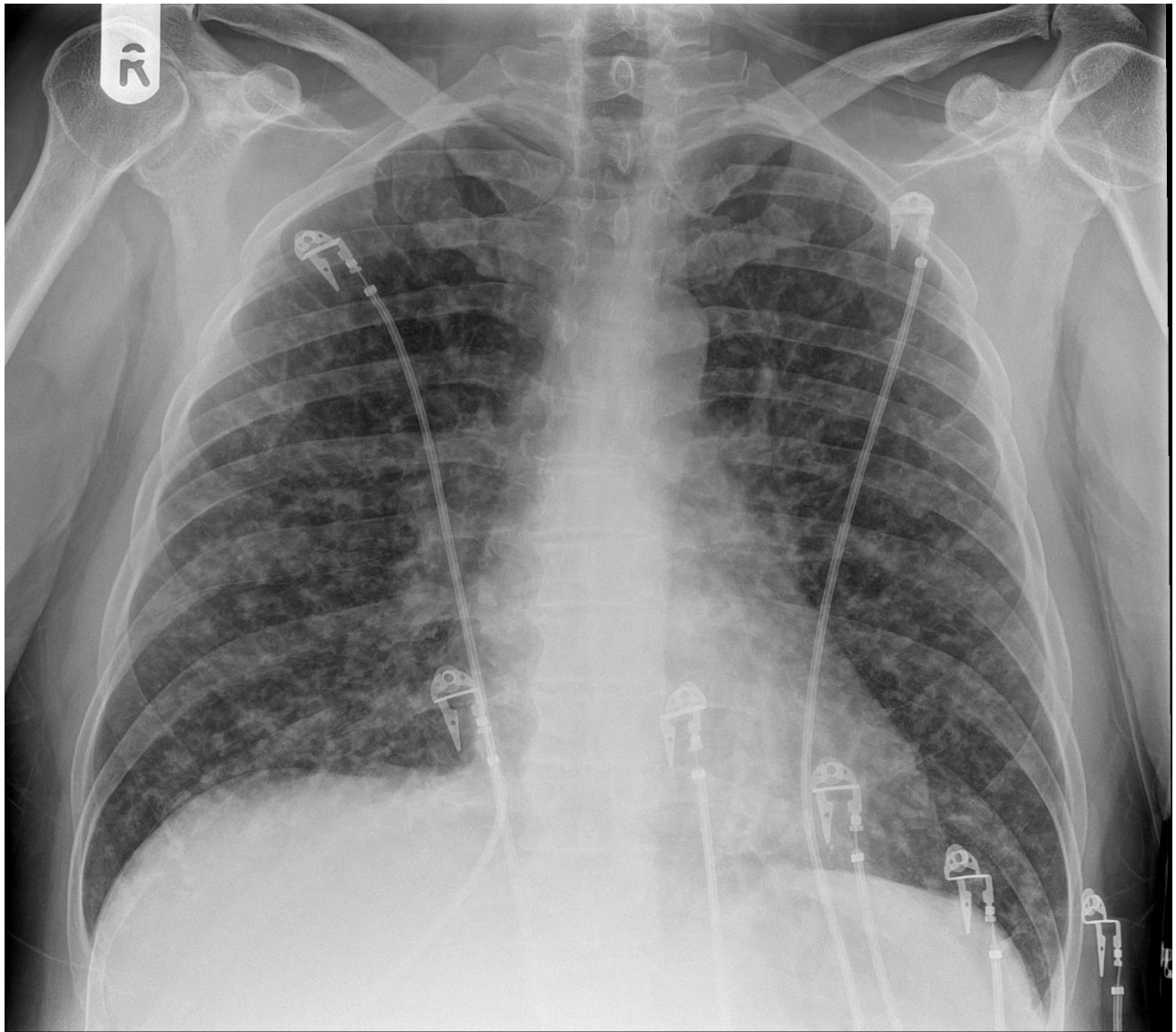
- IV insulin infusion
- Bolus of basal insulin
- Judicious fluid resuscitation
- Careful K^+ management
- No role for steroids
- Need long term insulin management

Case Study

- 47 year old male
- Metastatic melanoma
- Completed 2 cycles of Ipi/Nivo
- Presents with:
  - Severe and rapidly progressively dyspnoea
  - Dry cough
  - Myalgia/fatigue

Clinical examination

- Unwell. Extremely dyspnoeic
- Apyrexial
- BP = 140/70mmHg Pulse =130bpm
- RR = 40 O_2 SATS = 82% (AIR)
- Chest clinically clear
- Abdo and neuro examination unremarkable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Emergency management

- Cultures – including Viral N+T swabs, PCP screen and β-Glucan
- Urgent HRCT
- Too unwell for bronchoscopy

- High flow Oxygen
- IV Methylprednisolone 2mg/kg - PPI and antimicrobial prophylaxis
- IV Co-Amoxiclav
- Chest physio
- Agreement with ICU colleagues for IPPV if required
- Given IV infliximab (5mg/kg) at 24 hours given severity of illness

Immune-mediated granulomatous pneumonitis

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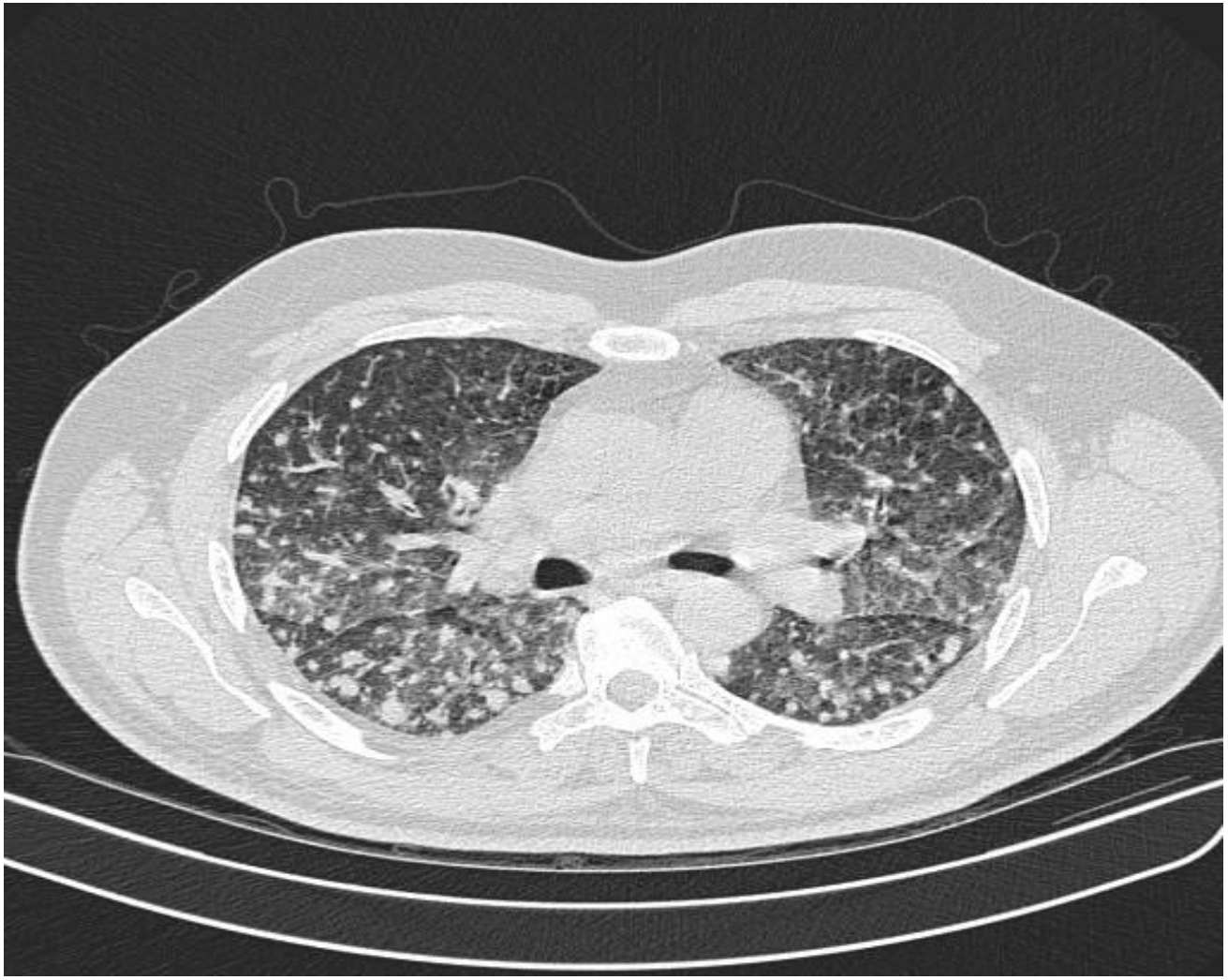

Clinical progress

- Excellent clinical progress over 72 hours
- High flow oxygen weaned
- 3 days of IV methylprednisolone (2mg/kg)

- Cultures and β – Glucan negative

- Weaned to oral prednisolone
- Commenced on Mycophenolate Mofetil 500mg BD

- Discharged at 5 days with early clinic follow up

1 week later

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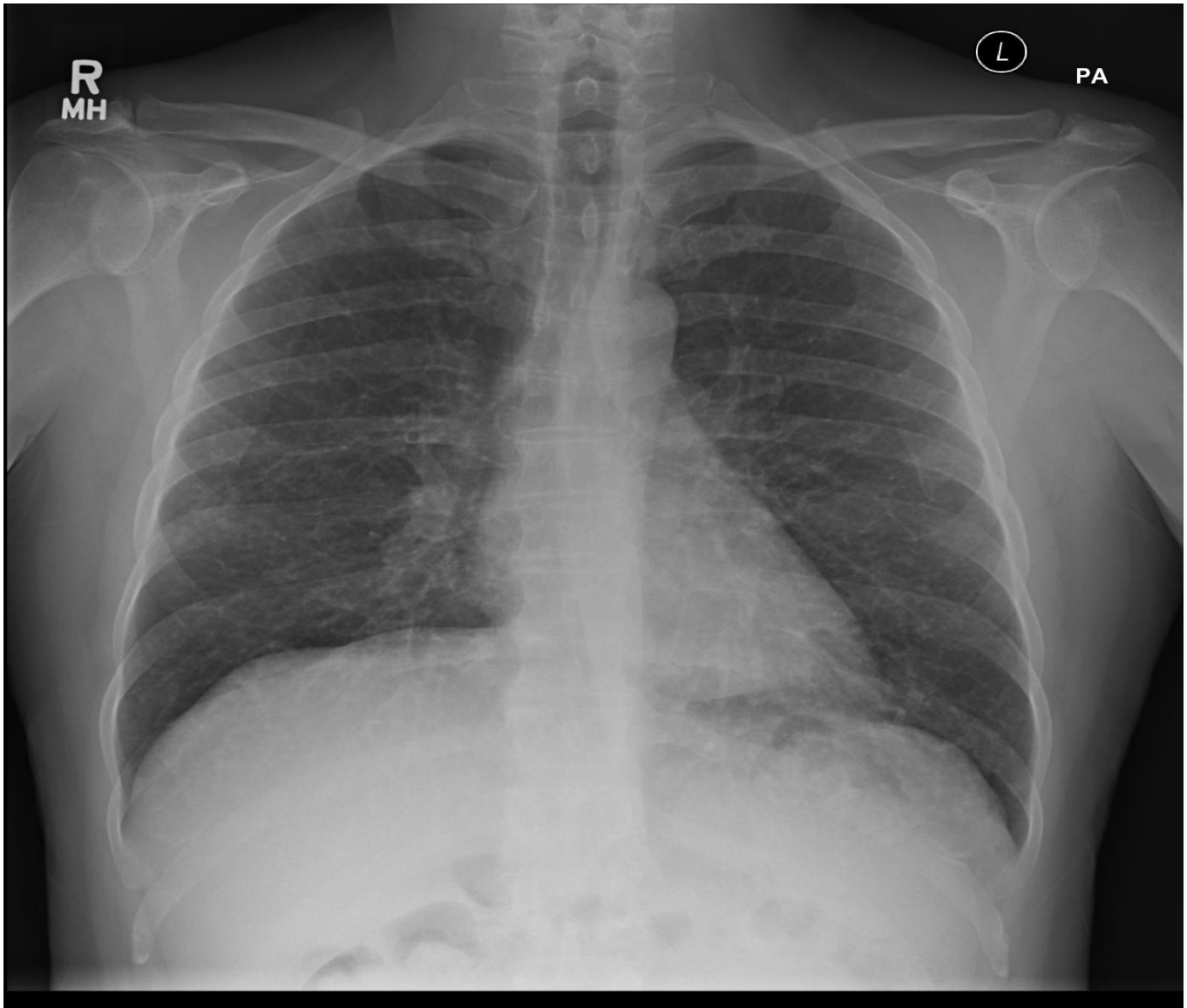

Case presentation

- 57 year old male with metastatic papillary renal cell carcinoma
- C1 Ipi/Nivo
- Presents with rapid onset of diplopia

Case presentation

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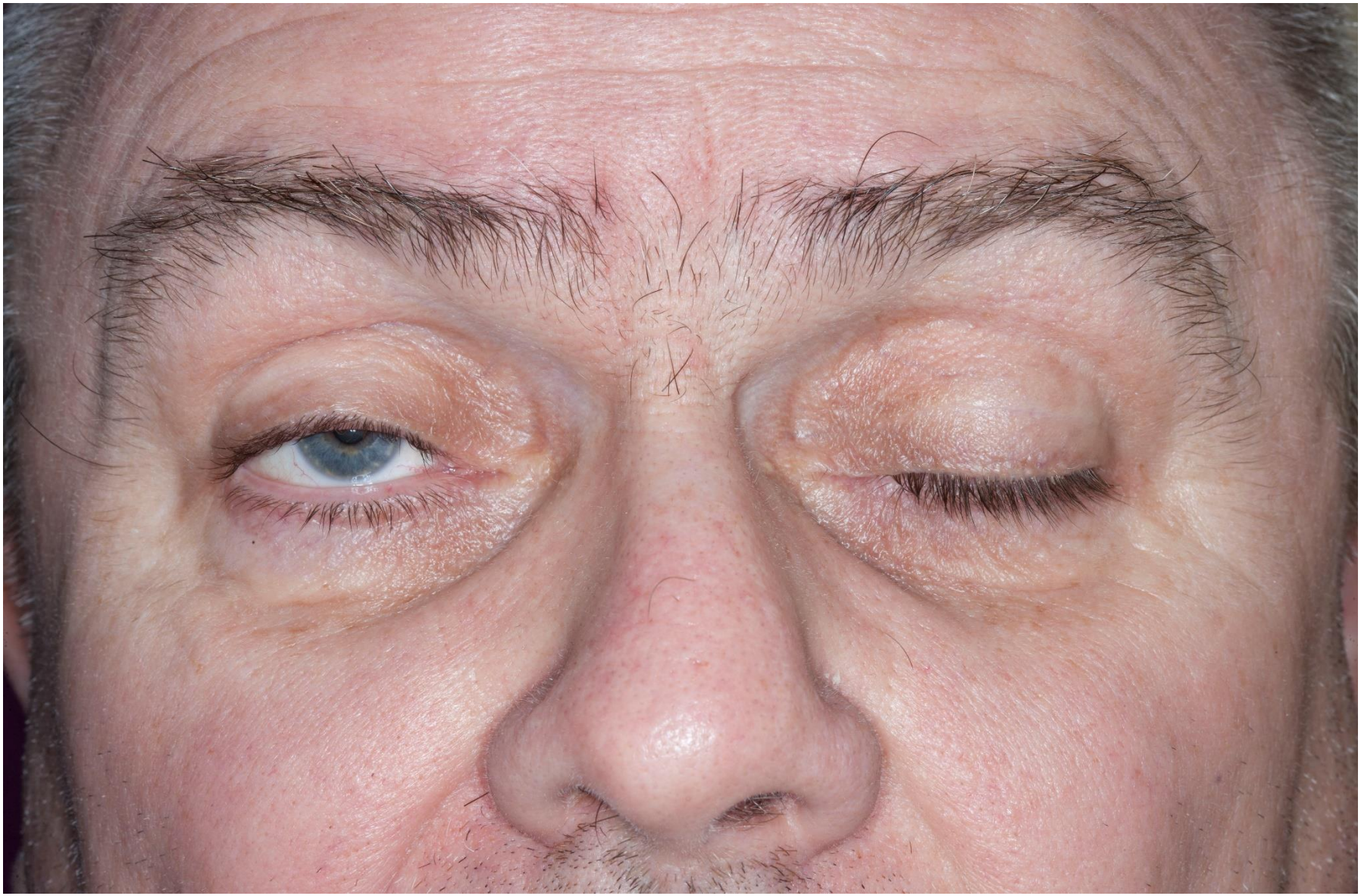

Emergency management

- Commenced on IV methylprednisolone (1mg/kg)
- Pyridostigmine 60mg TDS
- Monitoring FEV1

- EMG – Abnormal jitter analysis in facial muscles

- IV Immunoglobulins (1g/kg)

- Excellent clinical progress
- Converted to weaning oral prednisolone and MMF 500mg BD

Myasthenia and Myocarditis

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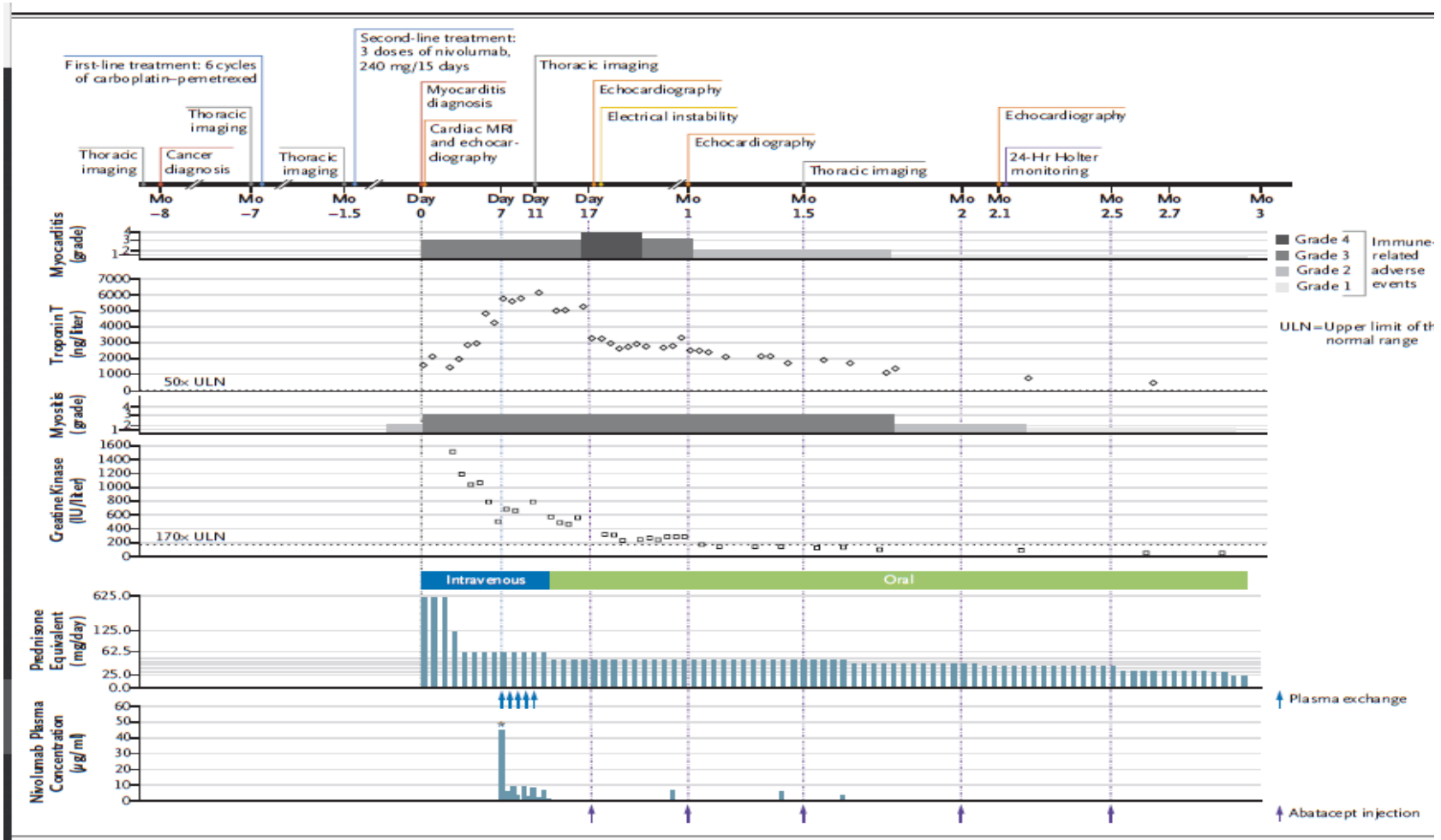
September 12, 2017; 89 (11) ARTICLE

Nivolumab-related myasthenia gravis with myositis and myocarditis in Japan

Shigeaki Suzuki, Nobuhisa Ishikawa, Fumie Konoeda, Nobuhiko Seki, Satoshi Fukushima, Kikuko Takahashi, Hisashi Uhara, Yoshikazu Hasegawa, Shinichiro Inomata, Yasushi Otani, Kenji Yokota, Takashi Hirose, Ryo Tanaka, Norihiro Suzuki, Makoto Matsui

Abatacept for severe IR myocarditis



Salem et al NEJM 2019

Emergency presentation data

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Article in Press

Adverse Effects of Immune Checkpoint Therapy in Cancer Patients Visiting the Emergency Department of a Comprehensive Cancer Center

Presented at the National Comprehensive Cancer Network 22nd annual conference, Orlando, FL, March 23-24, 2017.

Imad El Majzoub, MD, Aiham Qdaisat, MD, Kyaw Z. Thein, MD, Myint A. Win, MD, Myat M. Han, MD, Kalen Jacobson, MD, Patrick S. Chaftari, MD, Michael Prejean, RN, Cielito Reyes-Gibby, PhD, Sai-Ching J. Yeung, MD, PhD

Emergency Oncology Models

Support Care Cancer
DOI 10.1007/s00520-016-3470-1

COMMENTARY

Emergency oncology: development, current position and future direction in the USA and UK

Tim Cooksley[1] · Terry Rice[2]

Cooksley T, Rice T. *Supportive Care in Cancer* 2017

Ambulatory Care of IR toxicities

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PERSPECTIVE

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE WILEY

Ambulatory emergency oncology: A key tenet of future emergency oncology care

Antibiotics and ICIs

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Annals of Oncology 29: 1437–1444, 2018
doi:10.1093/annonc/mdy103
Published online 30 March 2018

ORIGINAL ARTICLE

Negative association of antibiotics on clinical activity of immune checkpoint inhibitors in patients with advanced renal cell and non-small-cell lung cancer

L. Derosa[1,2,3†], M. D. Hellmann[4,5,6†], M. Spaziano[7], D. Halpenny[8], M. Fidelle[1,2,3], H. Rizvi[9], N. Long[8], A. J. Plodkowski[8], K. C. Arbour[4], J. E. Chaft[4,5], J. A. Rouche[10], L. Zitvogel[1,2,3,11], G. Zalcman[12], L. Albiges[1,3,13,14], B. Escudier[1,13,14] & B. Routy[1,2,3,15,16*]

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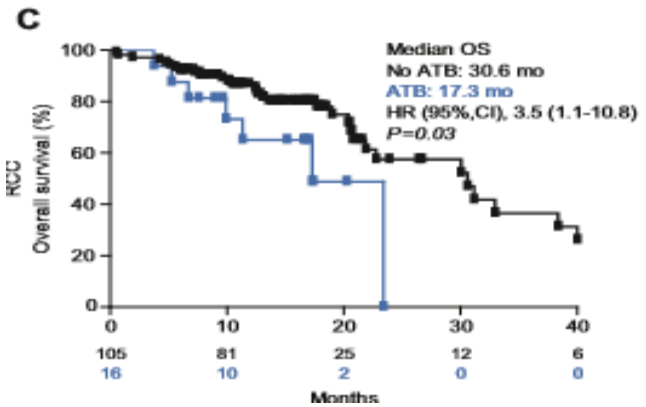

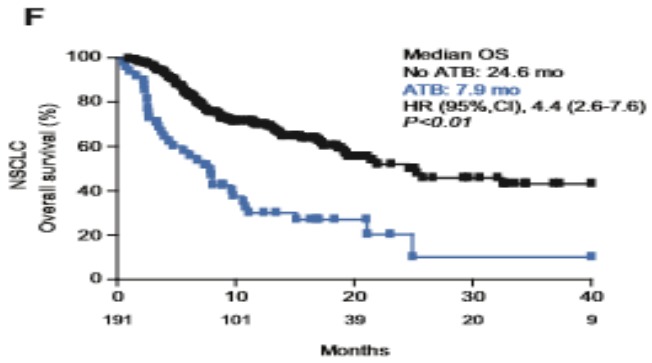

Emergency Workup

- Low threshold for considering IR toxicities
- Need thorough clinical work up
- Need to exclude important non-IR related diagnoses

- Early initiation of high dose steroids in those with high clinical suspicion
- Role for early infliximab (anti-TNF) to minimize long-term steroid exposure and reduce morbidity/mortality in life-threatening IR toxicity?
- Novel therapies for severe life-threatening toxicity

Conclusions

- Emergency presentations in patients on checkpoint inhibition are a challenge
- Need to distinguish IR and non-IR presentations
- Research needed into management and pathways of IR toxicities
- Ambulatory management of IR toxicities
- Education of patients and health care professionals