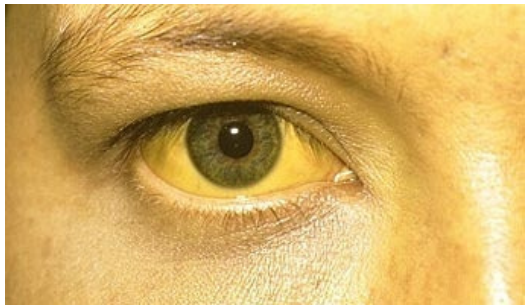
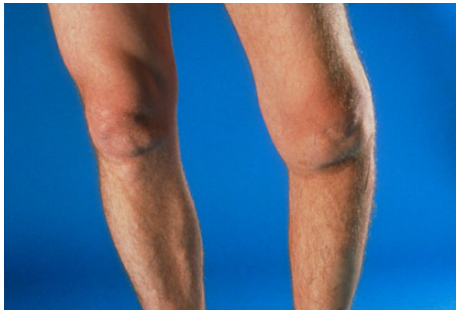
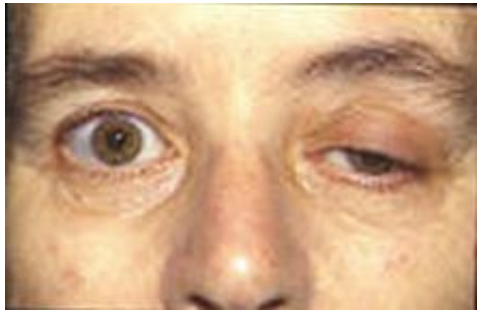
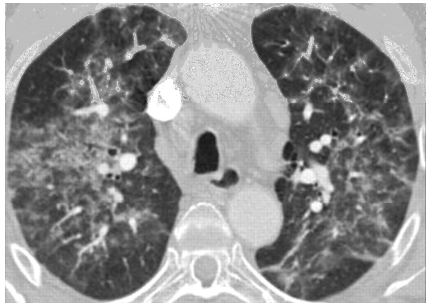
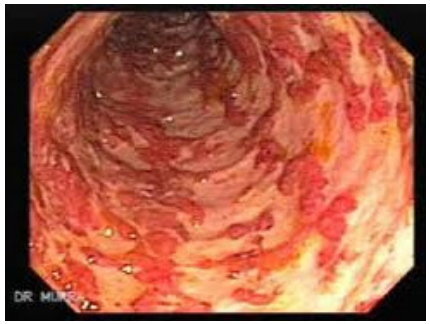






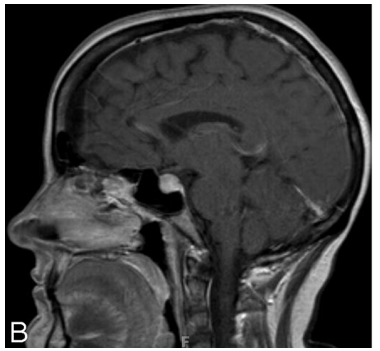


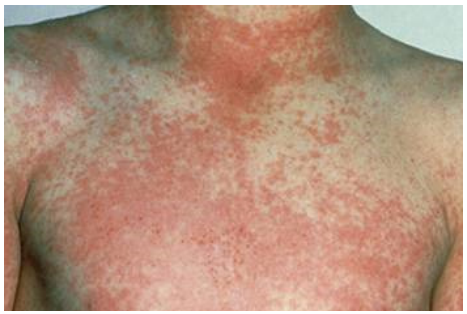
Managing immune related toxicity



Karijn Suijkerbuijk

May 27th 2017





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Disclosures

- Advisory role: BMS, Merck
- Travel support: Amgen, Novartis, Roche

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Why bother?

- Patients are dying from toxicity
  - Eggermont ipilimumab adjuvant stage III melanoma 1% (5 patients)

-> Early recognition is key!

Eggermont 2016

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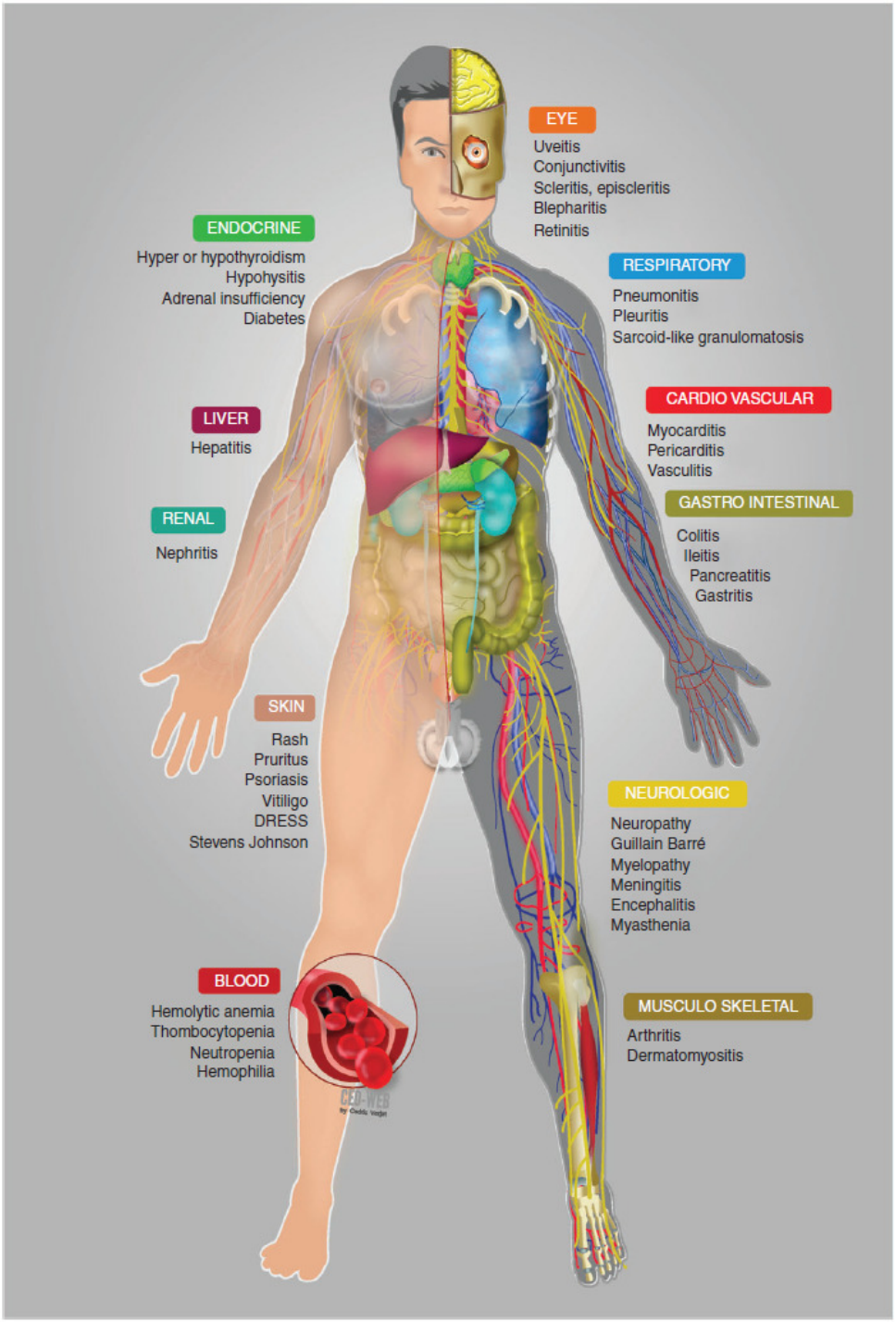
During checkpoint inhibitor treatment, consider toxicity for each new symptom, until proven otherwise



Champiat Ann Oncol 2016

????????

1. **Most irAEs occur during the first 16 weeks of treatment** *True/False*
2. **The majority of severe irAEs is reversible after steroid treatment** *True/False*
3. **Toxicity during ICPI treatment predicts response** *True/False*
4. **Steroid treatment for toxicity negatively affects response** *True/False*
5. **Influenza vaccination during checkpoint inhibitor treatment is safe** *True/False*

Immune related toxicity (irAE)

Common
Fatigue
Pruritus/rash
Loss/change of appetite
Myalgia/arthralgia
Hypo-/hyperthyroidism

Severe, potentially life-treatening	Symptoms
Colitis	Diarrhea
Hepatitis	Jaundice
Hypophysistis	Headache, confusion, lethargy
Pneumonitis	Cough, dyspnea
Myocarditis	Chest pain, heart faillure
Guillain-Barré **Myasthenia Gravis** **Encephalitis**	Weakness Paresthesia Confusion/lethargy

Increased response comes at a price
Severe toxicity rate triples in combination therapy

	Ipilimumab	Nivolumab	Nivolumab +ipilimumab
Grade 3/4 irAEs	**27%**	**16%**	**55%**
Discontinue for toxicity	**15%**	**8%**	**36%**
ORR	**19%**	**44%**	**58%**

Larkin NEJM 2015
AACR data

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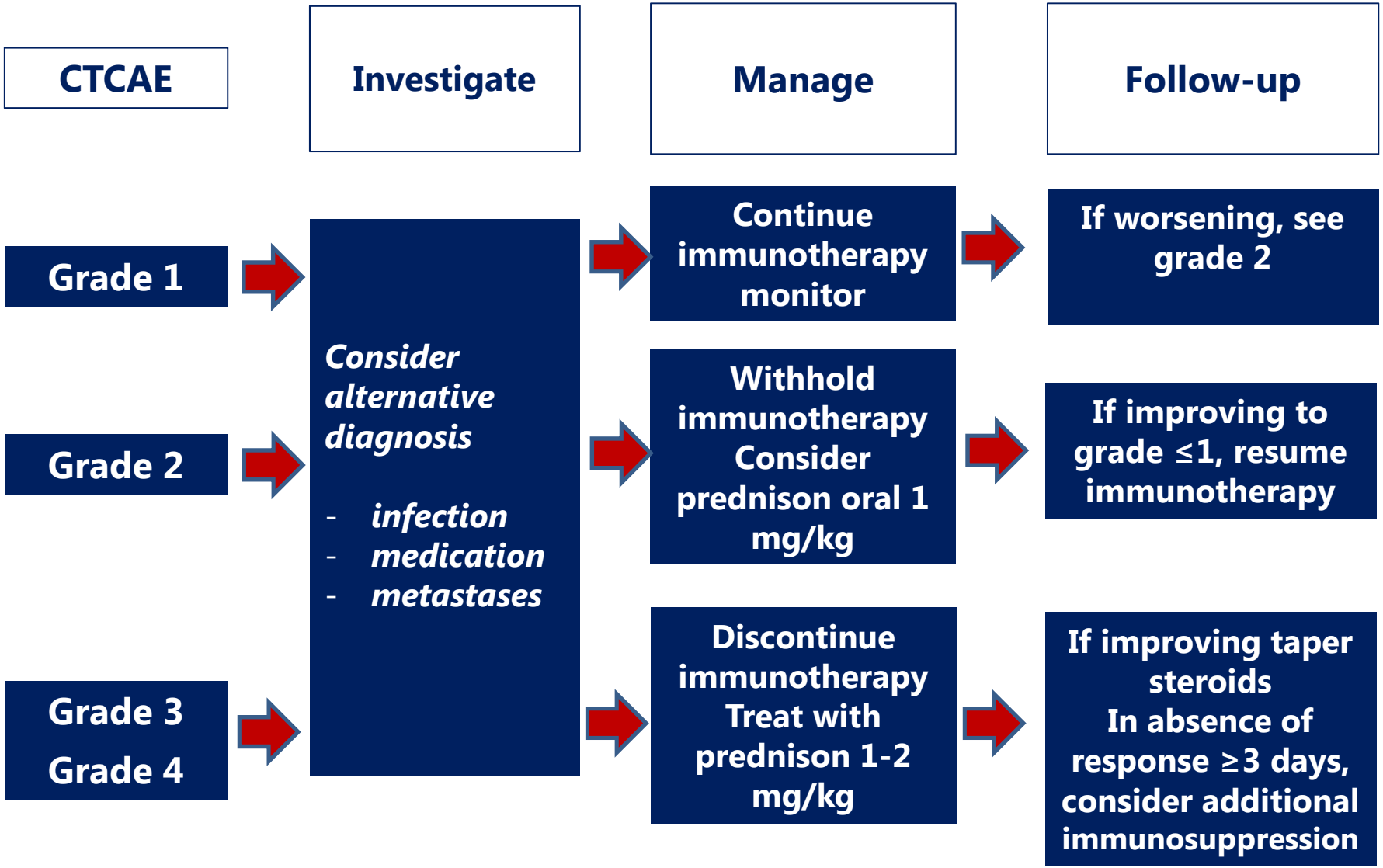
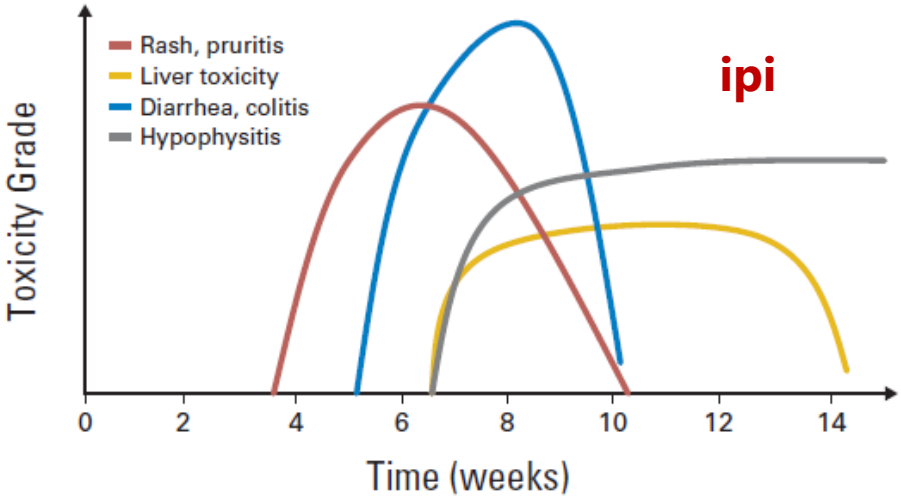
Management

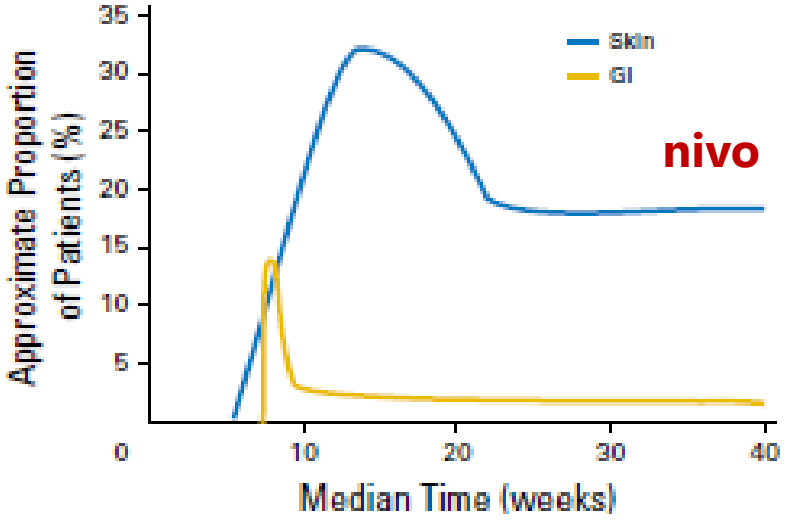

CTCAE
Investigate
Manage
Follow-up
Grade 1
Grade 2
Grade 3
Grade 4
Consider alternative diagnosis
- infection
- medication
- metastases
Continue immunotherapy monitor
Withhold immunotherapy Consider prednison oral 1 mg/kg
Discontinue immunotherapy Treat with prednison 1-2 mg/kg
If worsening, see grade 2
If improving to grade ≤1, resume immunotherapy
If improving taper steroids
In absence of response ≥3 days, consider additional immunosuppression

Second line immunomodulatory agents

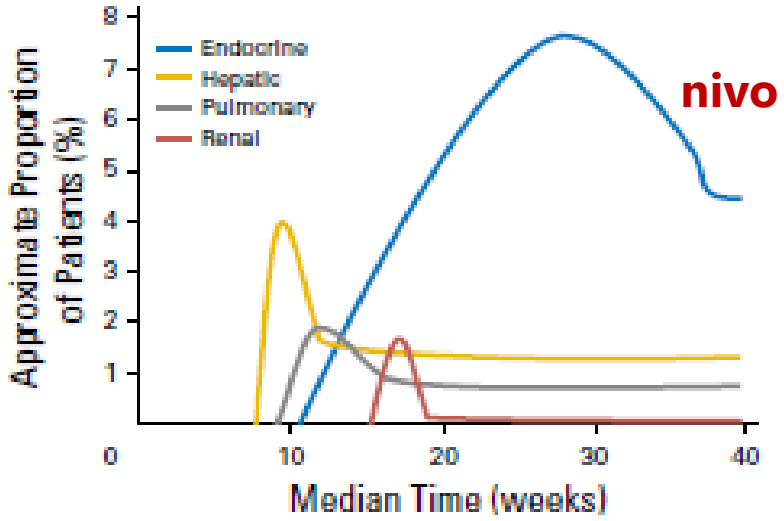
- Infliximab
- Mycophenolate
- Tacrolimus
- Cyclophosphamide
- Immunoglobulins
- …….
- ……

Onset of toxicity





85% occuring in first 16 weeks



Weber JCO 2012/2016

Reversibility

- 58%-85% of toxicity is reversible after steroid treatment

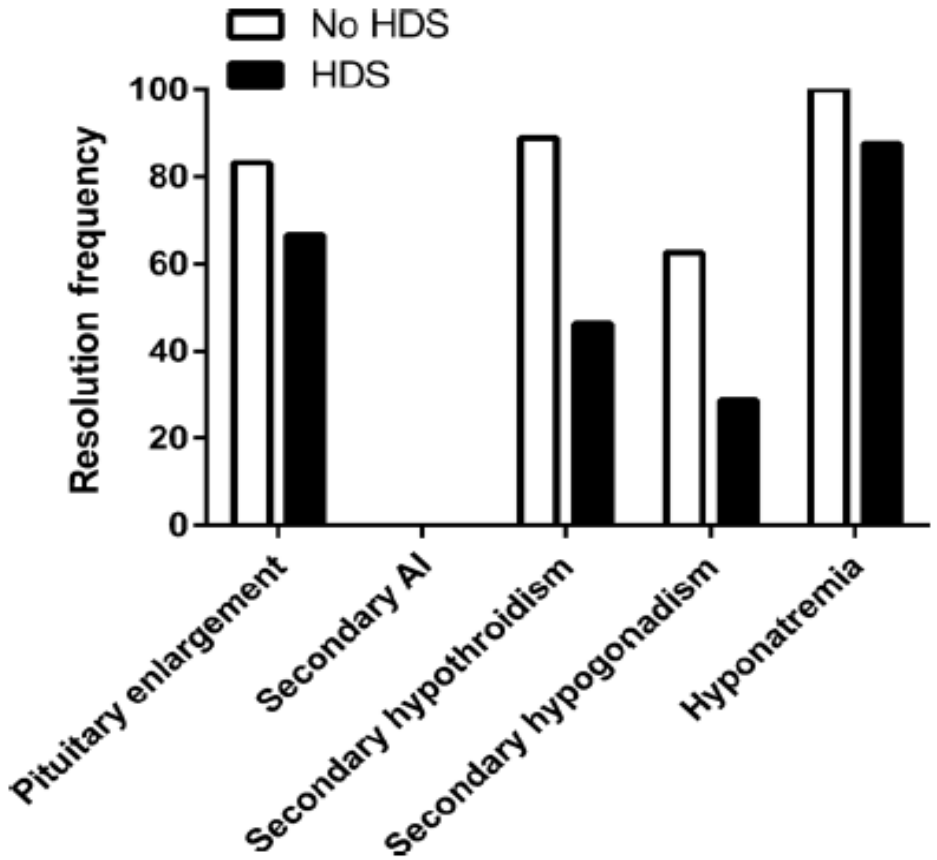
- Irreversible:
  - Endocrine insufficiency after hypophysitis
  - Hypothyroidism
  - Diabetes mellitus
  - Uveitis/arthritis

Weber JCO 2016
Larkin NEJM 2015

Clinical Cancer Research

Systemic High-Dose Corticosteroid Treatment Does Not Improve the Outcome of Ipilimumab-Related Hypophysitis: A Retrospective Cohort Study

Le Min[1], Frank Stephen Hodi[2], Anita Giobbie-Hurder[2], Patrick A. Ott[2], Jason J. Luke[2,3], Hilary Donahue[2], Meredith Davis[2], Rona S. Carroll[1], and Ursula B. Kaiser[1]



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Does toxicity predict response?

- Checkmate 069:

  ORR for patients that discontinued treatment for toxicity 66%

  (vs 59% for all patients on ipi/nivo)

Hodi Lancet Oncol 2016

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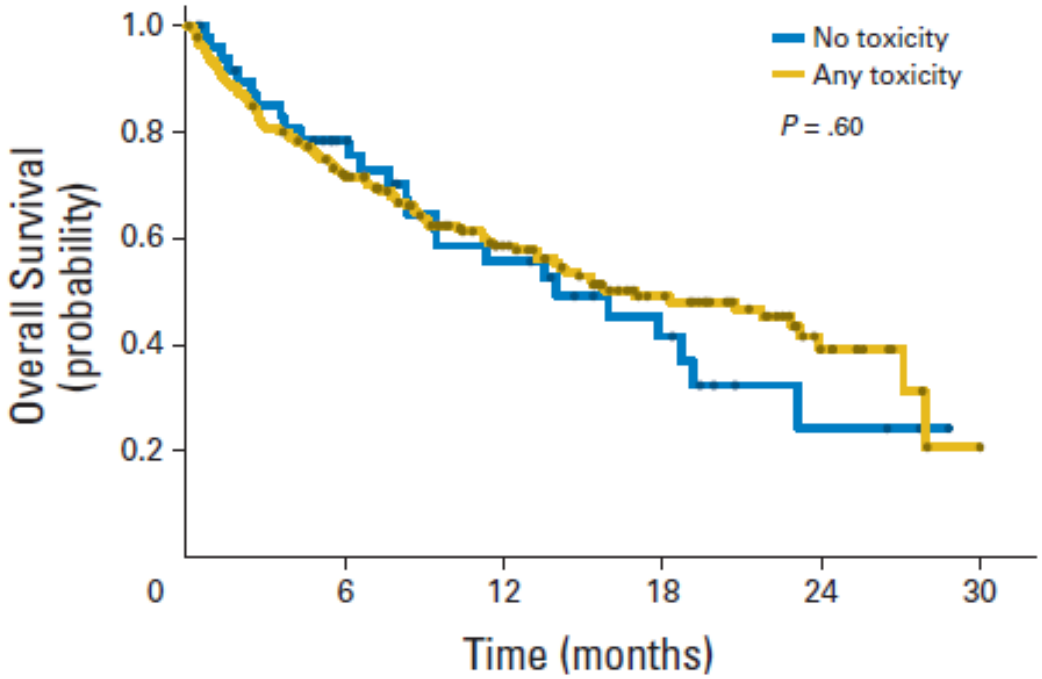
Does toxicity predict response?



- 298 melanoma patients treated with ipilimumab, retrospective analysis
- 85% experienced any irAE

Horvat JCO 2015

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Does toxicity predict response?

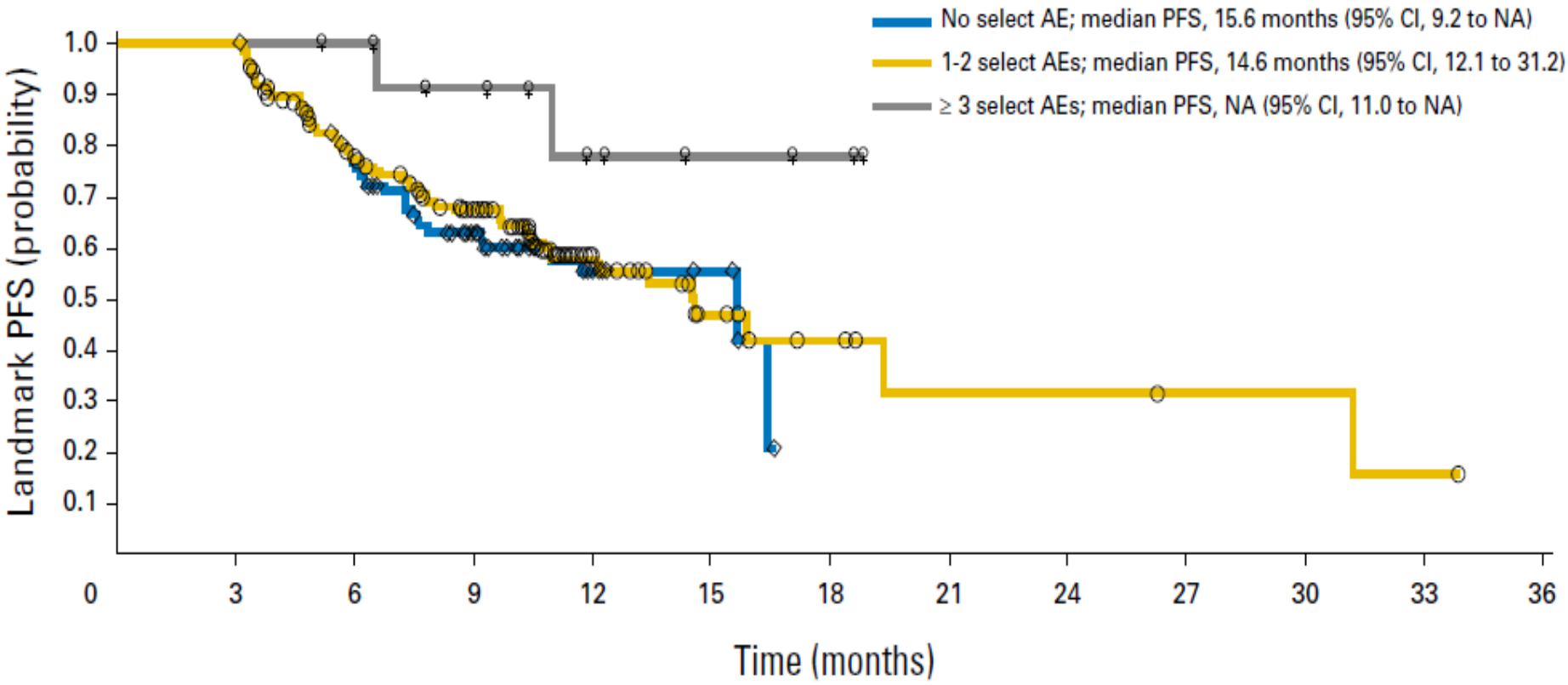
- pooled data nivolumab
- 4 studies, 576 melanoma patients

	Any-Grade Treatment-Related Select AEs			
	Any (n = 255)	None (n = 321)	1-2 (n = 242)	≥ 3 (n = 13)
ORR, No. of patients (%)	124 (48.6)	57 (17.8)	113 (46.7)	11 (84.6)
95% CI	42.3 to 54.9	13.7 to 22.4	40.3 to 53.2	54.6 to 98.1
P	< .001		< .0001*	< .001*

- No significant difference for grade 3/4

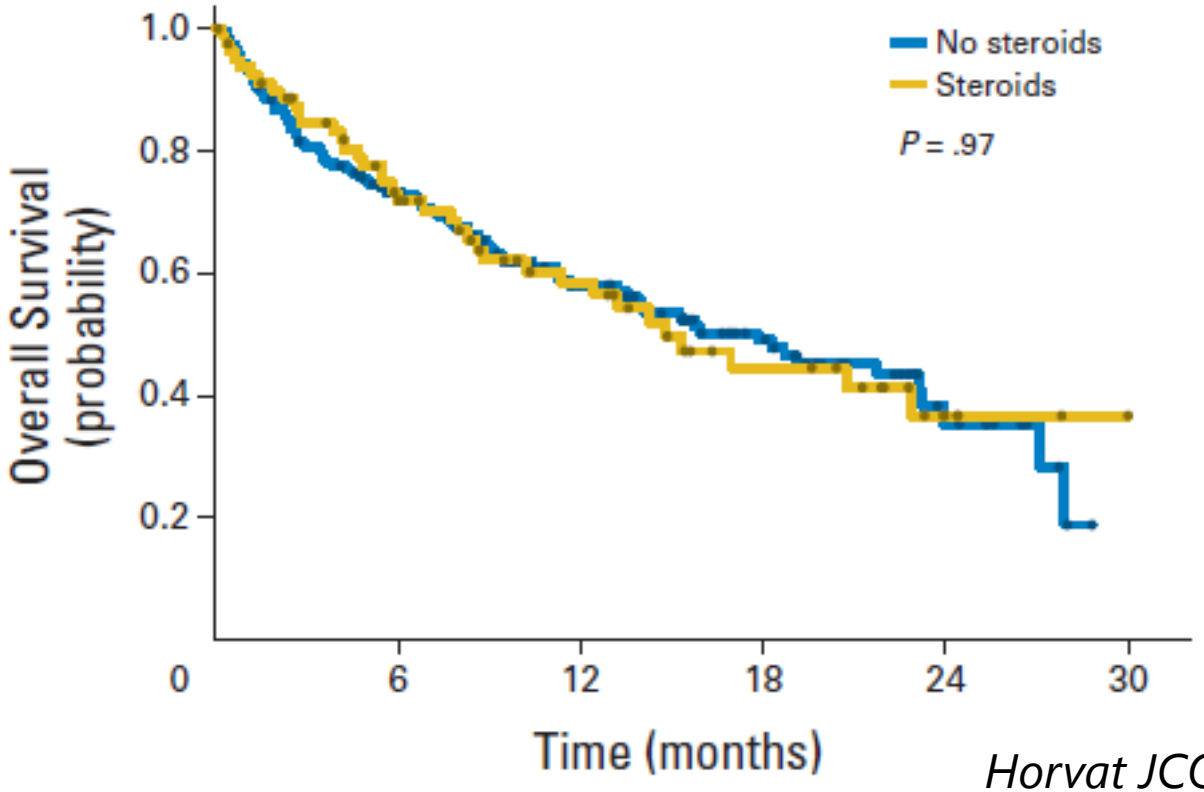
Weber JCO 2016

Does toxicity predict response?



Weber JCO 2016

Does steroid-treatment affect response?



Horvat JCO 2015

- 298 patients, treated with ipilimumab
- 35% required steroids for irAE

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Does steroid-treatment affect response?

	Patients Receiving Systemic IM	
	Yes (n = 114)	No (n = 462)
ORR, No. of patients (%)	34 (29.8)	147 (31.8)
95% CI	21.6 to 39.1	27.6 to 36.3
P	.736	

Weber JCO 2016

Anti-PD1 toxicity in patients with autoimmune disorders or previous irAEs

119 melanoma patients treated with anti-PD1:

- **Preexisting AD (n=52)**
  - 38% flare requiring immunosuppression (no IBD, or neurological sequellae)
  - 5% discontinued

- **Prior ipilimumab-related toxicity** requiring immunosuppression (n=67)
  - 3% same irAE; 34% other irAEs
  - 12% discontinued

Menzies Ann Oncol 2017

ELCC 2017 Press Release: Annual Flu Jab May Pose Greater Risk for Lung Cancer Patients Under Immunotherapy

Date: 26 Apr 2017

Topic: **Lung and other thoracic tumours / Cancer Immunology and Immunotherapy**

Geneva, Switzerland – Lung cancer patients treated with PD-1/PD-L1 checkpoint inhibitors may be at increased risk of adverse events after receiving the seasonal influenza vaccination, according to the first study measuring this effect[1].

- 23 patients monotherapy anti-PD1
- 52% irAEs, 26% grade 3/4

- Activation of immune system bij vaccination?

Rothschild ELCC abstract 2017

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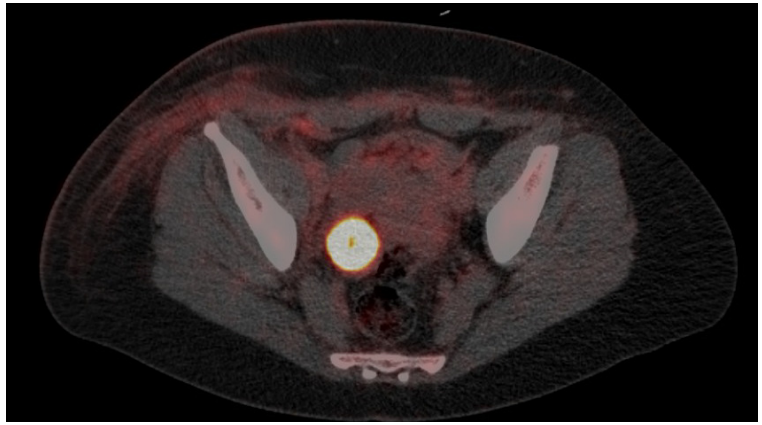
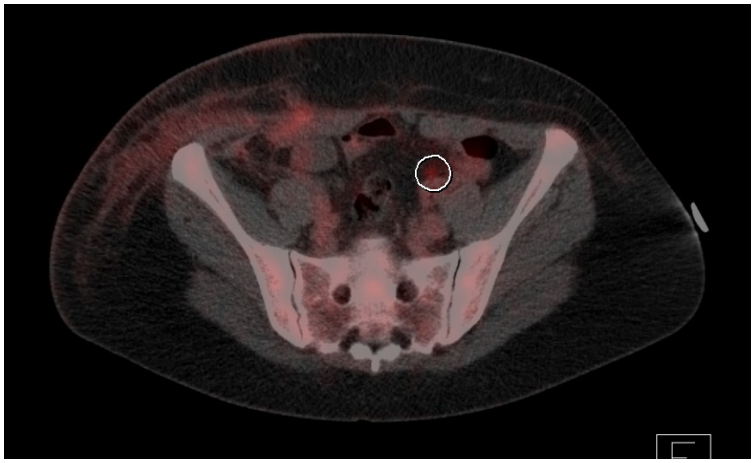
Patient X, 42 years

- Stage IV M1c melanoma (normal LDH, low tumor load)
- Started pembrolizumab treatment





Just before 3rd cycle

- Upper abdominal pain radiating to the back. Moderately ill. No fever.
- Examination: no abdominal tenderness

☐	Bilirubine Totaal	5		6		3 - 21	µmol/L
☐	Alkalische fosfatase	81		92		0 - 120	U/L
☐	gamma-GT	31		37		0 - 40	U/L
☐	ASAT	20		24		0 - 30	U/L
☐	ALAT	28		33		0 - 35	U/L
☐	LD	186		169		0 - 250	U/L
☐	Amylase			278	H	0 - 100	U/L
☐	Lipase			849	H	0 - 67	U/L
☐	Albumine	34.0	L	36.8		35.0 - 50.0	g/L
☐	CRP	26	H	22	H	0 - 10	mg/L

- Withhold pembrolizumab?
- Start steroids?

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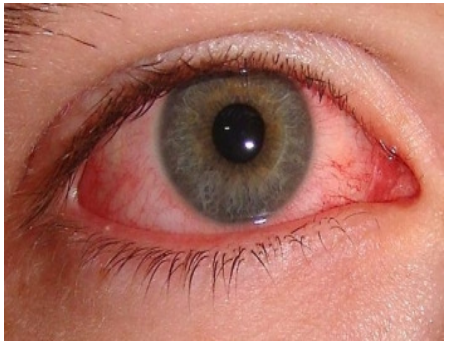
2 weeks later



- Abdominal pain has subsided
- Red eyes….
- No visual impairment, pain or photophobia

TSH	2.4	0.71	0.030	L	0.35 - 5.0	mIU/L
Vrij T4	13	17	26	H	10 - 22	pmol/L

- Ophthalmologist: bilateral anterior uveitis (no signs of Graves' ophthalmopathy)
- No symptoms of hyperthyroidism

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- Restart pembrolizumab?
- Start steroids?

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Again 2 weeks later

- Diarrhea 5 times a day with (lower) abdominal discomfort
- No upper abdominal pain
- Weight loss (2 kg)

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- Colonoscopy?
- Start steroids?
- Anything else?

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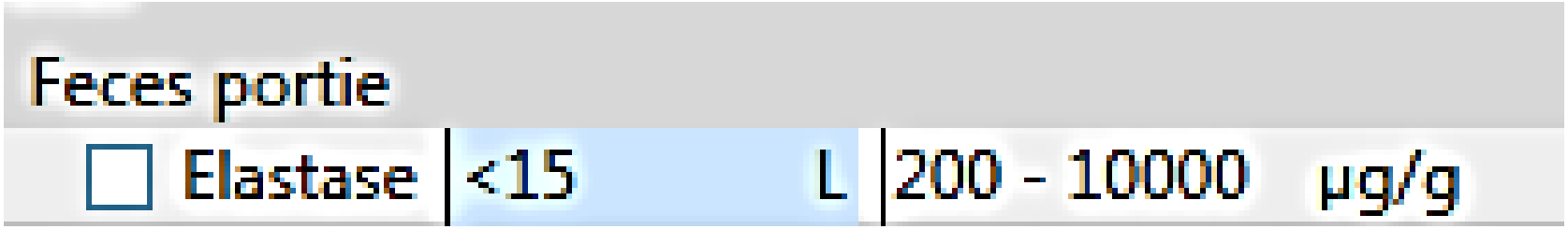

- Started pancreatic enzymes

  -> resolution of symptoms

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3 months after starting pembrolizumab

- Hypothyroidism -> replacement therapy
- PET-CT: CR

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What would YOU DO?

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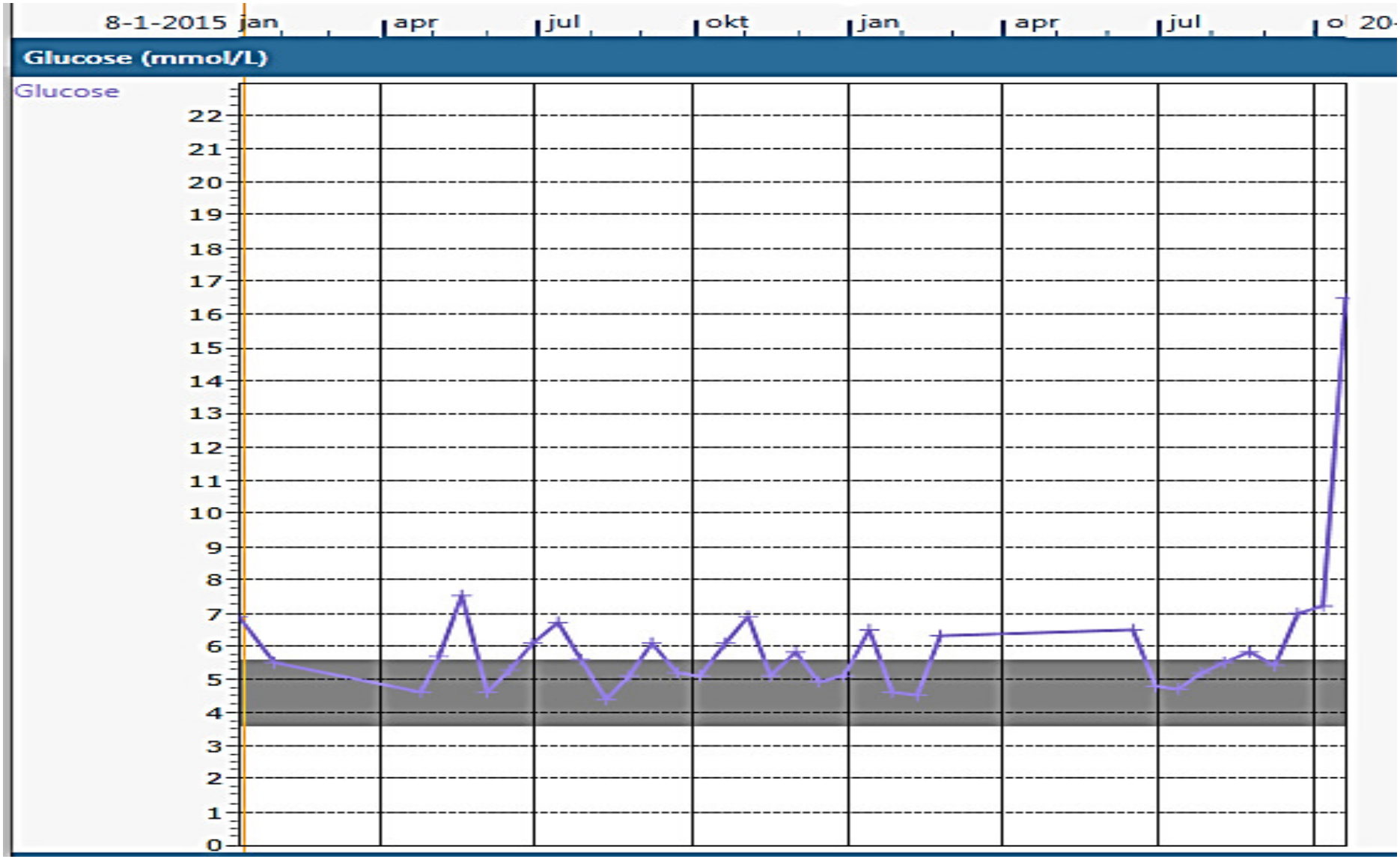
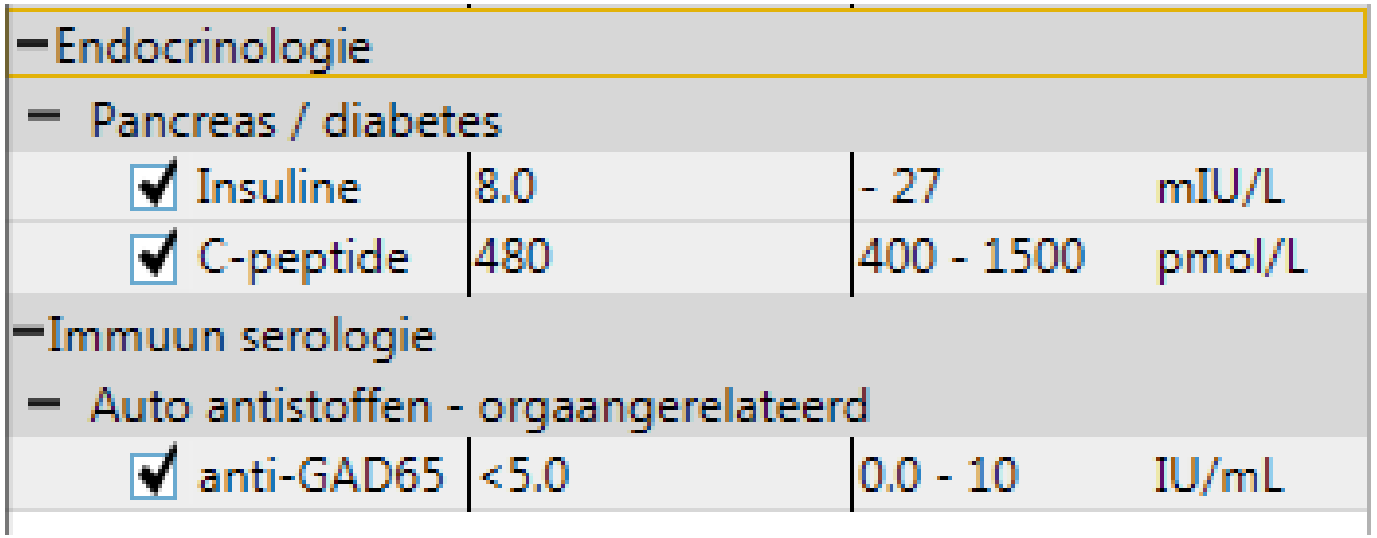
Patient Y, 61 year old

- Stage IV (M1c) metastatic melanoma treated with nivolumab after progression on 1rst line ipilimumab (checkmate 172)
- Partial respons after 10 cycles
- After 21 cycles resection growing axillairy lymphnode metastasis
- Continued nivolumab with stable disease

After nivolumab cycle 39 (19 months)



After nivolumab cycle 39 (19 months)



Endocrinologie			
Pancreas / diabetes			
Insuline	8.0	- 27	mIU/L
C-peptide	480	400 - 1500	pmol/L
Immuun serologie			
Auto antistoffen - orgaangerelateerd			
anti-GAD65	<5.0	0.0 - 10	IU/mL

- Bicarbonate: normal
- BMI: 37

- Treat for type 2 diabetes?
- Admit the patients and monitor glucoses?
- Anything else?

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One week later....

Bloedgassen					
Zuurgraad (Art.)	7.35	L		7.37 - 7.45	
Koolzuurspanning (Art.)	27	L		35 - 45	mm Hg
Zuurstofspanning (Art.)	113	H		70 - 100	mm Hg
Actueel Bicarbonaat (Art.)	14.3	L		22.0 - 29.0	mmol/L
Base Excess (Art.)	-11.3	L		-3.0 - 3.0	mmol/L
Glucose					
Glucose	21.9	H		3.6 - 5.6	mmol/L
Urine					
Screening					
Ketonen			st.pos	neg	

Pancreas / diabetes				
C-peptide	132	L	400 - 1500	pmol/L

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- Start steroids?
- Continue nivolumab?

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BMJ

CASE REPORT

Glucocorticoids did not reverse type 1 diabetes mellitus secondary to pembrolizumab in a patient with metastatic melanoma

Jasna Aleksova,[1] Peter K H Lau,[2] Georgia Soldatos,[2,3] Grant McArthur[4,5]

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Take home

- Checkpoint inhibitor toxicity can be unpredictable in many ways
- Consider pancreatic insufficiency as a cause of diarrhea
- Steroid treatment for irAEs does not affect respons
- Data suggest a correlation between irAEs and response in anti-PD1

Future

- Adjuvant treatment → (long term) toxicity even more important
- Better understand toxicity to be able to more efficiently treat it
- Other immunosuppression (e.g. anti-TNF) in first line?

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Predicting nivolumab toxicity?

	Any irAE	Grade 3/4 irAE
All patients	71%	10%
≥65 years	73%	15%
≥75 years	72%	18%
Prior ipilimumab	69%	8%
Brain metastases	61%	8%
Stage M1c	71%	9%
LDH increased	67%	8%
PD-L1 expression >5%	80%	14%

Weber JCO 2016

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Ipilimumab toxicity in patients with autoimmune disorders

Patients excluded from trials

30 melanoma patients with preexisting autoimmune disorders treated with ipilimumab:

- 27% flare
- 33% other irAEs
- 1 patient with reumatoid arthritis died of colitis

Johnson JAMA oncol 2016

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Eur J Cancer. 2017 Apr;75:24-32. doi: 10.1016/j.ejca.2016.12.038. Epub 2017 Feb 16.

Programmed cell death protein-1 (PD-1) inhibitor therapy in patients with advanced melanoma and preexisting autoimmunity or ipilimumab-triggered autoimmunity.

Gutzmer R[1], Koop A[2], Meier F[3], Hassel JC[4], Terheyden P[5], Zimmer L[6], Heinzerling L[7], Ugurel S[8], Pföhler C[9], Gesierich A[10], Livingstone E[11], Satzger I[12], Kähler KC[13]; German Dermatooncology Group (DeCOG).

⊕ Author information

Abstract

AIM: Programmed cell death protein 1 (PD-1) inhibitors are a common treatment strategy for metastatic melanoma and other tumour entities. Clinical trials usually exclude patients with preexisting autoimmune diseases, thus experience with PD-1 inhibitor (PD-1i) in this patient population is limited.

PATIENTS AND METHODS: Metastatic melanoma patients with preexisting autoimmune disorders or previous ipilimumab-triggered immune-related adverse events (irAE) undergoing treatment with PD-1i from seven German skin cancer centres were evaluated retrospectively with regard to flare of the preexisting autoimmunity and development of new, not preexisting irAE as well as response to PD-1i therapy.

RESULTS: In total, 41 patients had either preexisting autoimmunity (n=19, group A, including two patients with additional ipilimumab-triggered autoimmune colitis) or ipilimumab-triggered irAE (n=22, group B). At PD-1i therapy initiation, six patients in group A and two patients in group B required immunosuppressive therapy. In group A, a flare of preexisting autoimmune disorders was seen in 42% of patients, new irAE in 16%. In group B, 4.5% of patients showed a flare of ipilimumab-triggered irAE and 23% new irAE. All flares of preexisting autoimmune disorders or irAE were managed by immunosuppressive and/or symptomatic therapy and did not require termination of PD-1i therapy. tumour responses (32% in group A and 45% in group B) were unrelated to occurrence of autoimmunity.