Management of Toxicity during Immunotherapy

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TÜV SÜD ISO 9001

Universitätsklinikum Essen

Disclosures

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- During the last two years I was either a member of the advisory board/consultant or received speakers´ honoraria from the following companies:
  - Amgen, BMS, GSK, Merck, Novartis, Roche
- Received research funding from Merck

PD 1 Antibodies

- Nivolumab
- Pembrolizumab

Ipilimumab

Grading: side effects

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Grading	Clinical severity index
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or non invasive intervention indicated; limiting age appropriate instrumental ADL
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL*
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

Select Drug-Related Adverse Events (≥1%) Occurring in Melanoma Patients Treated with Nivolumab[1]

- Select AE: AE with potential immunologic etiologies that require more frequent monitoring and/or unique intervention
- All patients have ≥1 year of follow-up
- Safety analyses were not updated and were recently published[1]

Category	Any Grade % (n)	Grade 3-4 % (n)
Any select AE	54 (58)	5 (5)
Skin	36 (38)	0
Gastrointestinal	18 (19)	2 (2)
Endocrinopathies	13 (14)	2 (2)
Hepatic	7 (7)	1 (1)
Infusion reaction	6 (6)	0
Pulmonary	4 (4)	0
Renal	2 (2)	1 (1)

[1]Topalian S, et al. *J Clin Oncol*. 2014 ;32:1020-30

Treatment-Related AEs With Incidence >5% by Pembrolizumab

Adverse Event, %	Total N = 411	
	Any Grade	Grade 3/4
Fatigue	36	2
Pruritus	24	<1
Rash	20	<1
Diarrhea	16	<1
Arthralgia	16	0
Nausea	12	<1
Vitiligo	11	0
Asthenia	9	0
Cough	9	0

Adverse Event, n (%)	Total N = 411	
	Any Grade	Grade 3/4
Myalgia	9	0
Headache	8	<1
Hypothyroidism	8	<1
Decreased appetite	7	<1
Dyspnea	7	<1
Chills	6	0
Pyrexia	6	0
ALT increased	5	<1
Total	83	12

- Similar safety profiles in IPI-N and IPI-T patients

Presented by: Antoni Ribas at ASCO 2014

immune-related AEs by Pembrolizumab

Adverse Event, n (%)	Any Grade	Grade 3-4
Hypothyroidism	32 (8)	1 (<1)
Hyperthyroidism	4 (1)	1 (<1)
Pneumonitis[a]	11 (3)	1 (<1)
Colitis	3 (<1)	2 (<1)
Hepatitis[b]	2 (<1)	1 (<1)

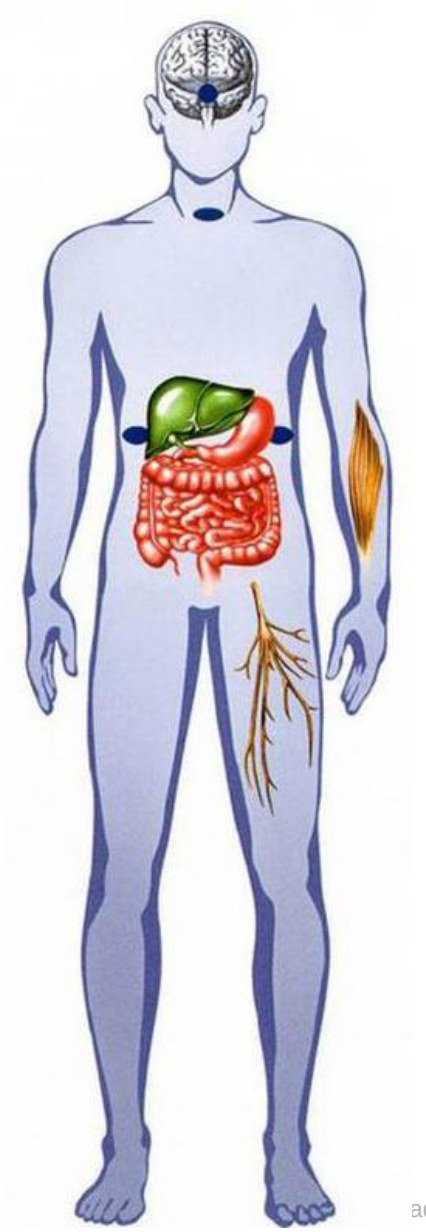
- Some reported skin rashes may have been immune-mediated
- The following potentially immune-mediated AEs were reported in <1% of patients: nephritis, hypophysitis, and uveitis

[a]1 additional patient experienced interstitial lung disease of grade 1-2.
[b]Includes autoimmune hepatitis.
Analysis cut-off date: October 18, 2013.

Presented by: Antoni Ribas at ASCO 2014

Ipilimumab

irAE (immune-related adverse events)



Most Common Immune-Related Adverse Events* (irAEs; all Grades)

% of Patients*			
irAE	**Ipi + gp100 N=380**	**Ipi + placebo N=131**	gp100 + placebo N=132
All grades			
Any	58.2	**61.1**	31.8
Dermatologic	40.0	**43.5**	16.7
GI	32.1	**29.0**	14.4
Endocrine	3.9	**7.6**	1.5
Hepatic	2.1	**3.8**	4.5
Treatment-related deaths	2.1	**3.1**	1.5

*Across entire study duration

Hodi, FS. et al., N Engl J Med 2010;363:711-23.

adendorf

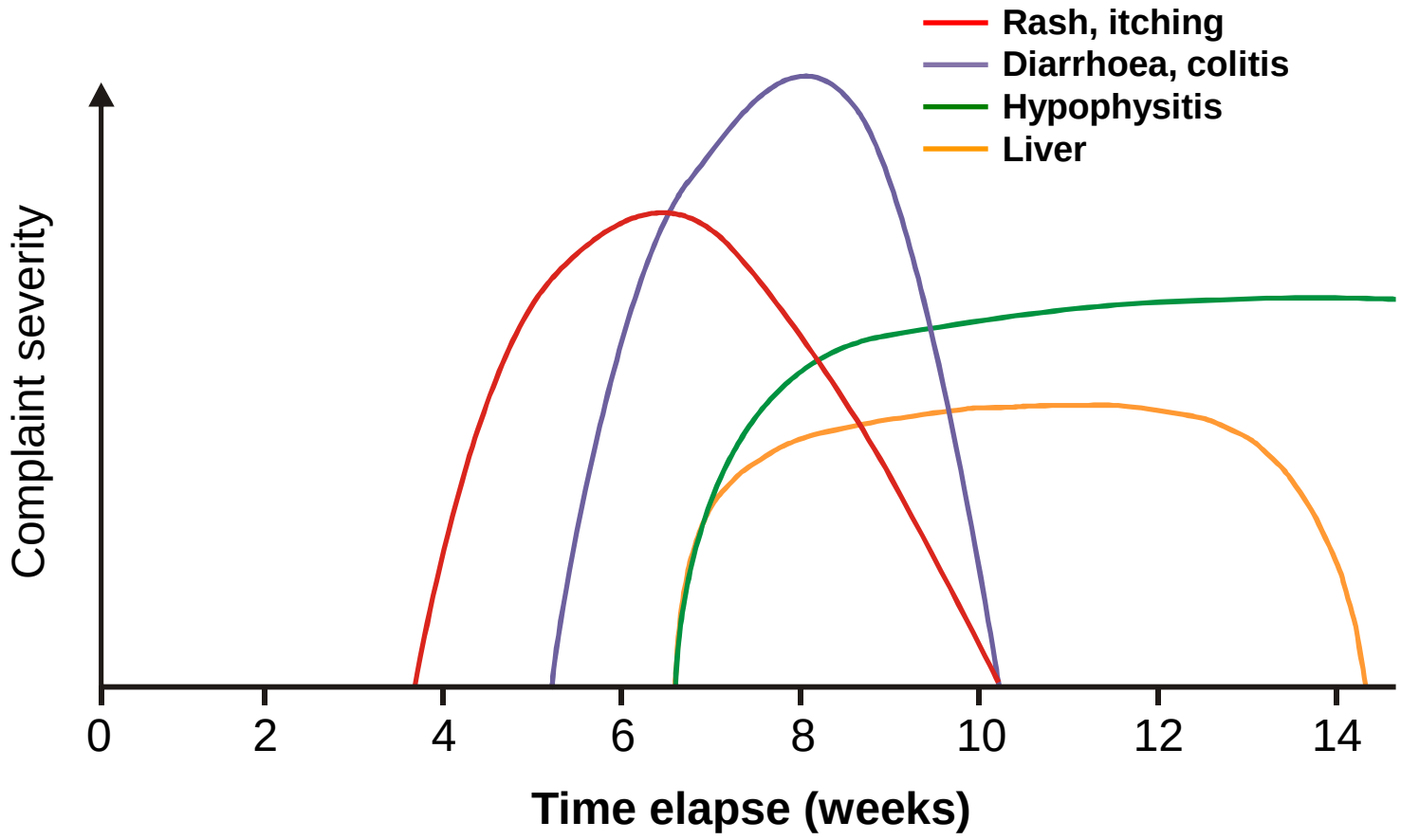
Most common immune-related adverse events* (grades 3, 4 & 5)

% of Patients						
irAE	Ipi + gp100 N=380		Ipi + pbo N=131		gp100 + pbo N=132	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Any	9.7	0.5	12.2	2.3	3.0	0
Dermatologic	2.1	0.3	1.5	0	0	0
GI	5.3	0.5	7.6	0	0.8	0
Endocrine	1.1	0	2.3	1.5	0	0
Hepatic	1.1	0	0	0	2.3	0
Treatment-related deaths	1.3		1.5		0	

*** Across entire study duration**

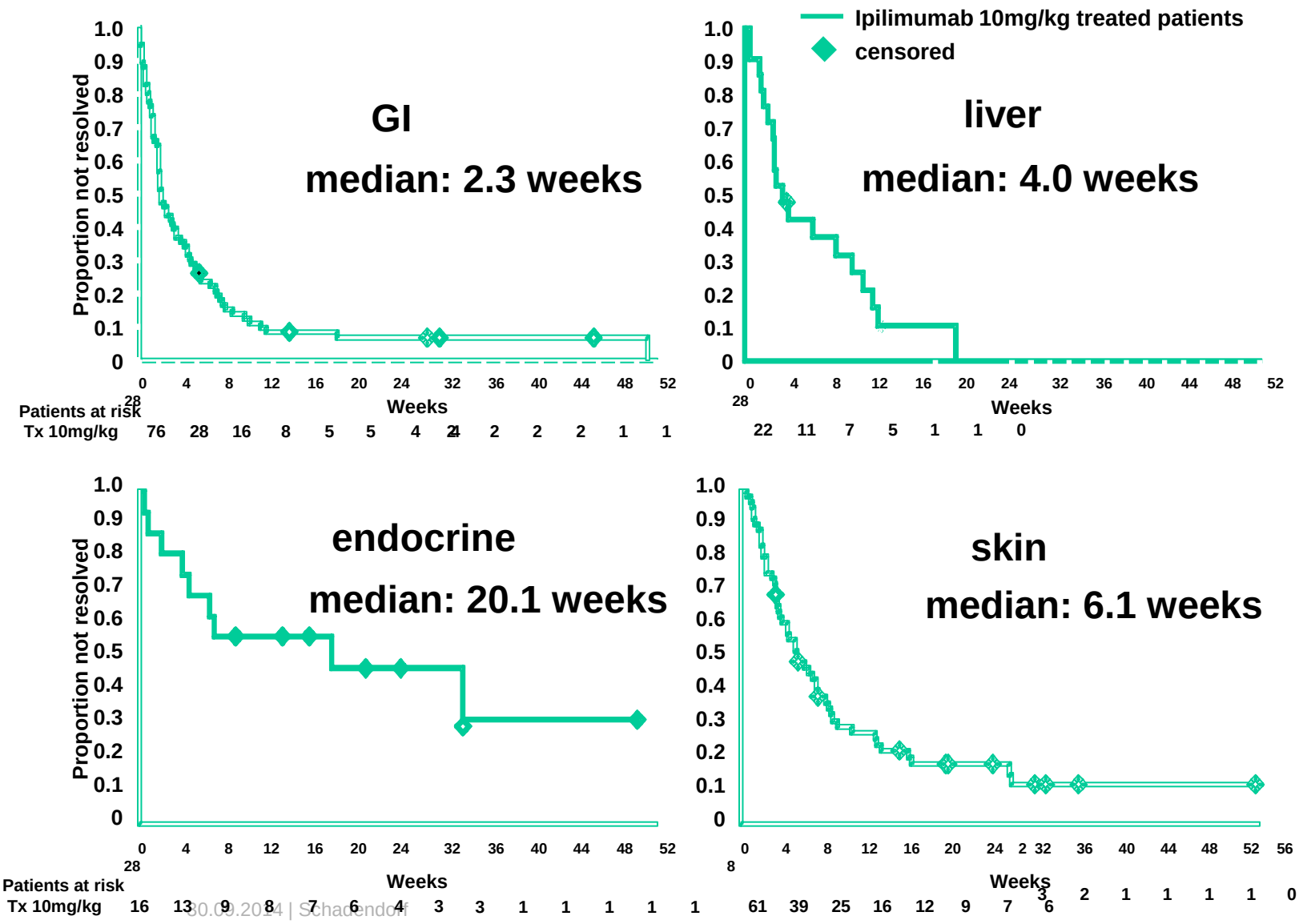
Hodi FS, et al. *N Engl J Med* 2010;363:711–723

Chronological sequence of typical side effects



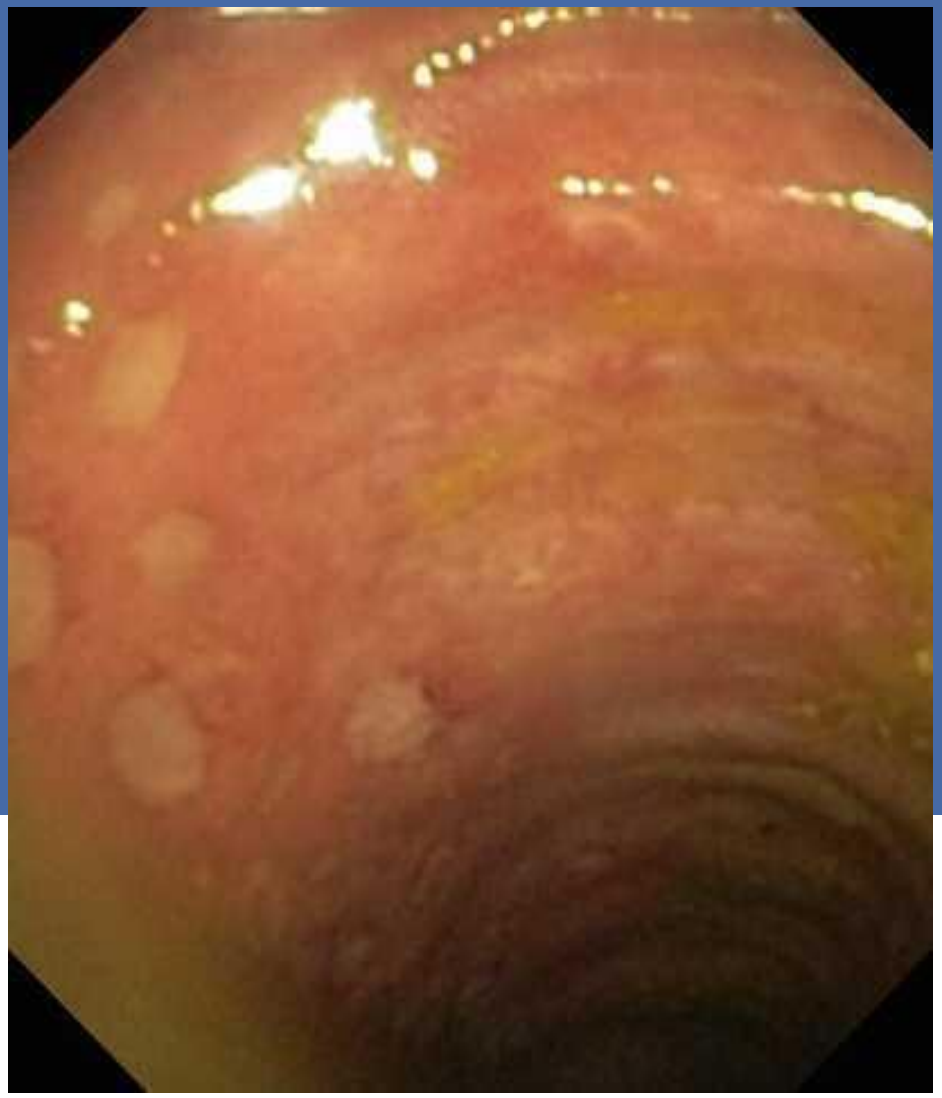
Kaehler et al., 2010

Time to Improvement of Grade 2-4 irAEs



Lebbe, Perspectives in Melanoma XII 2008, Abstract O-015

Immune-mediated enterocolitis



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irEnterocolitis (~30%)

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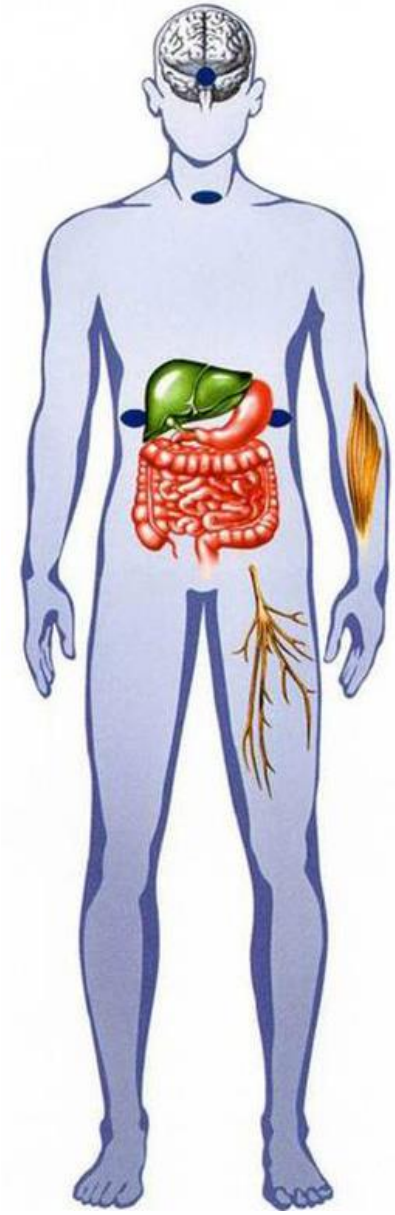
Signs and symptoms

- Diarrhea (frequency, blood/mucus) ± fever
- Abdominal pain
- Peritonitis
- Ileus
- Electrolyte imbalance
- Weakness
- Weight loss

→ 5-8% Grade 3/4



CTC: diarrhea/colitis

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4–6 stools per day over baseline; IV fluids indicated <24 hours moderate increase in ostomy output compared to baseline; not interfering with ADL	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24hours hospitalisation; severe increase in ostomy output compared to baseline; interfering with ADL	Life-threatening consequences (e.g. haemodynamic collapse)	Death

Colitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death

Definition: a disorder characterised by inflammation of the colon

irEnterocolitis

Management

Grade 1: ∅ specific Dx, symptomatic Tx
Loperamide, fluid replacement, e´lyte replacement if required.

From grade 2: Exclude other GI infections/CIBD
(stool diagnostics: leucocytes, calprotectin, stool culture, *Clostridium difficile titre*, endoscopy [+ biopsy] if required.)

Therapy:

1. Budesonide 9 mg/day
2. Prednisolone 1 mg/kg

CAVEAT: anticoagulants

Grade 3/4 irEnterocolitis (>5%)

Management

- Discontinue therapy
- IV replenishment of fluid and electrolytes
- IV: methylprednisolone 2 mg/kg BW daily or dexamethasone 0.33 mg/kg BW daily

Grade 3/4 irEnterocolitis

Management

- Improvement in initial symptoms within 48–72 hours?
  - YES: taper over at least 30 days
  - **NO: infliximab 5 mg/kg single dose, followed by methylprednisolone (slow tapering)**

- Re-start of symptoms during tapering?
  - ↑ corticosteroid, slower tapering, infliximab 5 mg/kg single dose

Case

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Case ♀ * 1935

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- 03/2009: Sentinel lymph node dissection, right groin (5/5 LN pos.)
- 04/2009: Radical lymphadenectomy, right groin (5/7 LN pos.)
- 14/07/2009: Start adjuvant study therapy with ipilimumab
- 05/08/2009: Admitted as in-patient suffering from watery diarrhoea for 8 days 7–10x daily, in addition nausea and a rash with fine spots all over the skin

Diagnostics: what would you do?

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Diagnostic procedures & results

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- **Colonoscopy**: Evidence of non-specific colitis including ulcer and sigma diverticulitis and also no indication of malignancy in the biopsy of the colon
- **Skin biopsy**: superficial perivascular dermatitis, consistent with a drug-induced rash
- **Staging**: CT thorax/abdomen and MRI skull: no evidence of metastases
- **Stool diagnosis:** no evidence of entamoeba histolytica, giardia intestinalis or cryptosporidium EIA, furthermore no worm eggs or protozoa
- Classification according to **CTCAE criteria** 7–10 watery stools/day: grade 3 (≥=7 stools/day, incontinence, in-patient admission indicated)

Diagnostics 2

- **Stool diagnosis:** no evidence of entamoeba histolytica, giardia intestinalis or cryptosporidium EIA, furthermore no worm eggs or protozoa

- Classification according to **CTCAE criteria** 7–10 watery stools/day: grade 3 (≥=7 stools/day, incontinence, in-patient admission indicated)

Diagnosis

Autoimmune colitis grade 3 and drug-induced rash grade 3 on ipilimumab therapy

Therapy: what would you do?

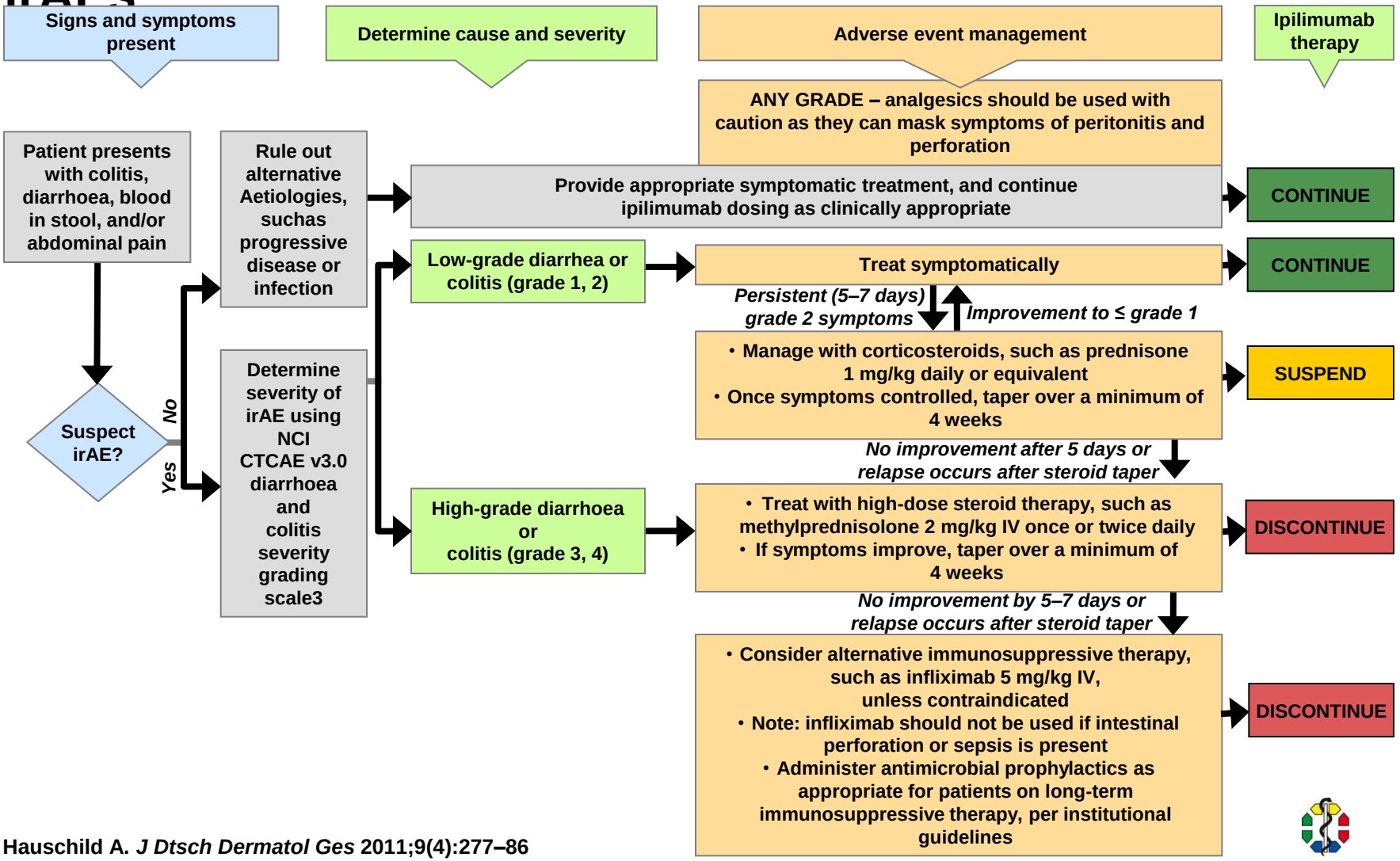
1. Wait & see

2. Discontinue therapy with ipilimumab

3. Symptomatic therapy and continue therapy with ipilimumab

4. Symptomatic therapy; there is no correlation with ipilimumab therapy

Management guidelines for gastrointestinal-related irAEs



Hauschild A. *J Dtsch Dermatol Ges* 2011;9(4):277–86

Therapy 1

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- 05/08/2009–24/08/209 hospital admission
- SDH initially 60 mg 1x daily IV
- Reduction to 45 mg until time of discharge
- Then, as outpatient, 5 mg reduction every 3 days
- Ranitidine 150 mg 2x daily and Salofalk 1000 mg 3x daily
- Adjust insulin regimen for existing diabetes *mellitus*
- As inpatient initially antibiotic therapy with metronidazole and ciprofloxacin – discontinued during the course

Therapy 2

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- 08/09/2009–09/10/2009 another in-patient admittance for recurrent colitis, grade 3 according to CTCAE
- Administered SDH 150 mg/day over 8 days, insufficient improvement

→ Single dose of infliximab (5 mg/kg BW)

- Within several days of this, diarrhoea cleared up
- Administration of prednisolone could be reduced to 115 mg at time of discharge
- Followed by 5 mg reduction every 3 days as outpatient

Conclusion

- Autoimmune colitis when on ipilimumab should be considered at an early stage and treated accordingly to management guidelines!

Immune-mediated hepatotoxicity

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irHepatotoxicity (<5%)

Signs and symptoms

- Asymptomatic elevated transaminases (GOT/GPT >2.5, ULN) bilirubin (>1.5 x ULN)
- Fever, sickness
- Jaundice

irHepatotoxicity

Management: diagnostics

- Transaminases (ALT, AST), bilirubin, SAP, albumine, coagulation values (Quick)
- Hepatitis serology
- Autoantibodies: ANA, SMA
- Grade 3–4: imaging, liver biopsy if required, gastroenterological consultation

irHepatotoxicity

Management

ALT/AST >5 to ≤8 x ULN, gbili >3 to ≤5 x ULN	ALT/AST >8 x ULN, gbili >5 x ULN

Excluded: progressive liver metastases, hepatitis (viral), tox drug reactions

• Ipilimumab pause • Monitor liver parameters • Continue treatment with ALT/AST <5 x ULN and gbili <3 x ULN	• Discontinue ipilimumab • Begin IV methylprednisolone immediately 2 mg/kg BW daily • Monitor liver parameters • Reduce steroids over at least 4 weeks after LFT normalised

irHepatotoxicity

Management I

- Transaminase: monitoring
  - LFTs <8 x ULN/gbili <5 x ULN: every 3 days until stabilised/decrease, then weekly
  - LFTs >8 x ULN/gbili >5 x ULN: daily until decrease, then weekly
- If LFT increases again during reduction: increase steroids, very slow tapering >4 week schedule

irHepatotoxicity

Management II

- No improvement after 5–7 days on steroids
  - Additional mycofenolate mofetil (1 g IV/1.5 g 2 x daily PO.)
  - Tacrolimus 0.1–0.25 mg/kg BW daily
  - Infliximab 5 mg/kg, single dose
  - Antibiotic prophylaxis for long-term immune-suppressed patients in accordance with the guidelines

Case

Make sure that your patients are being treated in your center…….

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Case history

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- Male patient, age 57
- Superficial spreading malignant melanoma presternal right, TD 1.4 mm, ED 06/2010
- 06/10 Sentinel lymph node axilla right positive (2+/2 LN)
- 07/10 Lymphadenectomy axillary right. Tumour-free (0/12 LN)
- 08/10 Inclusion in the adjuvant ipilimumab therapy study BMS-CA184029 (EORTC 18071)
  - 23/08/2010 1. Administration study drug
  - 13/09/2010 2. Administration study drug

Lab diagnostics

- Serology, Clin chemistry – normal at start of treatment
- HCV – negative
- HBV – negative
- HAV – titre indicative of current or past infection
- HIV – negative

Clinical course

- From 27/09/10: fever
- 30/9/10 admission to non-surgical department of a basic care hospital far away (2 weeks after 2nd ipi infusion)
- Initial lab findings GOT at 584

Clinical course

What would you do?

A. With suspected cholecystitis, appropriate treatment in accordance with guidelines and continue study medication

B. With suspected autoimmune hepatitis further diagnosis and stop study medication

C. Initiate steroid therapy 1 mg/kg BW

CTCAE* Metabolic/Laboratory

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Grade 1	
ALT, SGPT (serum glutamic pyruvic transaminase)	>ULN–2.5 x ULN
AST, SGOT (serum glutamic oxaloecetic transaminase)	>ULN–2.5 x ULN
Bilirubin	>ULN–1.5 x ULN
Grade 2	
ALT, SGPT (serum glutamic pyruvic transaminase)	>2.5–5.0 x ULN
AST, SGOT (serum glutamic oxaloecetic transaminase)	>2.5–5.0 x ULN
Bilirubin	>1.5–3.0 x ULN
Grade 3	
ALT, SGPT (serum glutamic pyruvic transaminase)	>5.0–20.0 x ULN
AST, SGOT (serum glutamic oxaloecetic transaminase)	>5.0–20.0 x ULN
Bilirubin	>5.0–20.0 x ULN
Grade 4	
ALT, SGPT (serum glutamic pyruvic transaminase)	>20.0 x ULN
AST, SGOT (serum glutamic oxaloecetic transaminase)	>20.0 x ULN
Bilirubin	>10.0 x ULN
Grade 5	–

*National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0 (NCI-CTCAE v3)

Procedure/diagnosis

- Algorithm faxed to colleagues, in-depth telephone consultation re further diagnosis (liver biopsy, ANA, SMA, hepatitis serology) and immediate initiation of treatment (120 mg methyprednisolone IV/d)

Procedure/diagnosis (cont‘d)

- **SMA** (smooth muscle antibody), **LNM-1** (anti-liver-kidney microsome antibody), **anti-SLA** (anti-soluble liver antigen antibody) negative, ANA 1:80
- **Liver biopsy 5/10/10:** severe acute to subacute hepatitis with 30% hepatocyte necrosis, perivenulitis, concomitant cholangitis, no fibrosis, suspected medically toxic liver parenchymal damage DD viral hepatitis
- **Hepatitis serology** (A/B/C), **EBV and CMV serology** negative
- **Abdominal sonography 1/10 + 6/10:** hepatomegaly, clear thickening of gall bladder wall, no ascites
- **Abdominal sonography 11/10:** suspected cholecystitis, no intra or extra-hepatic bile duct dilatation
- **MRI liver 14/10:** assessment: marginal thickening of gall bladder wall surrounded by free fluid, from morphological image analysis does not correlate with clinically recognised subacute liver failure

Clinical course

01/10/10 **GOT 881, GPT 678, GGT 862, Bili 2.93**

→ **CTCAE Grade III**

04/10/10 **GOT 3063, GPT 1569, GGT 744, Bili 5.31**
Fulminant increase in liver values within 3 days

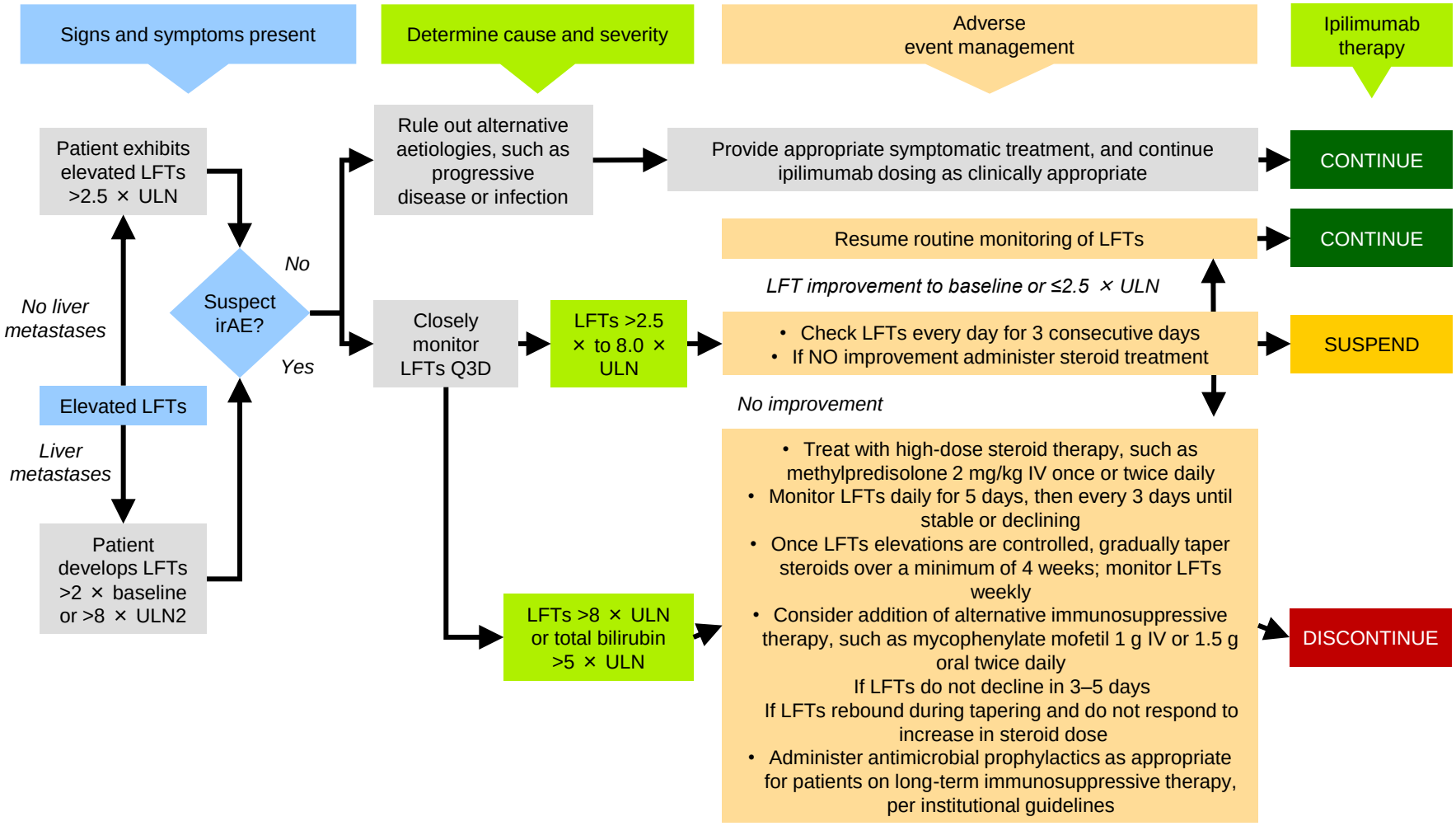
→ **CTCAE Grade IV**

Problem: liver biopsy delayed because of fever and thus no steroids

05/10/10 **GOT 6169, GPT 2661, GGT 934, Bili 7.79**
Liver puncture, then initiate Urbason [*Medrone*] 120 mg IV

→ **CTCAE Grade IV**

Management guidelines for hepato-related irAEs



Hauschild A. *J Dtsch Dermatol Ges* 2011;9(4):277–86

Clinical course (cont‘d)

- 07/10/10 **GOT 4141, GPT 2871, GGT 1142, Bili 10.9, AP 881**

  Patient transferred to Skin Cancer Unit Essen with jaundice, US and UA-oedema, increase Urbason [*Medrone*] to 2 x 125 mg IV with gastric protection and osteoporosis prophylaxis

- 08/10/10 GOT 2642, GPT 2428, GGT 1035, Bili 10.4, AP 685

- 11/10/10 GOT 476, GPT 1354, GGT 1103, Bili 12.0

Clinical course cont‘d

- 19/10/10 **GOT 60, GPT 341, GGT 407, Bili 3.5**

  Reduced Urbason [*Medrone*] on 20/10/ to 180 mg IV 1x/day for 2 days, then 180 mg oral 1xday – 150 mg p.o. – 125 mg p.o. – 100 mg p.o., then 5 mg every 3 days

- 24/10/10 GOT 44, GPT 183, GGT 260, Bili 2.4

- 04/01/11 GOT 27, GPT 36, GGT 44 (Urbason [*Medrone*] at 55 mg/day)

→ Normal liver values after....weeks

Conclusion

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- Quick action indicated in suspected autoimmune hepatitis according to present algorithms
- Clinical picture largely unknown by internists and hepatologists. Caveat: premature reduction of steroid dose or insufficiently high steroid dose a frequent problem at the beginning
- Essential that patient transferred to ward familiar with management of side effects
- Close consultation with BMS monitors (in our case: daily follow-up, very good care from BMS re therapy)

Immune-mediated endocrinopathies

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irEndocrinopathies (~8%)

- Hypophysitis
- Adrenal gland failure (including adrenal crisis)
- Hypopituitarism
- Hypo (or hyper)thyroidism

irEndocrinopathies

Before initiating Ipi

FT3, FT4, TSH

irEndocrinopathies (cont'd)

Signs and symptoms

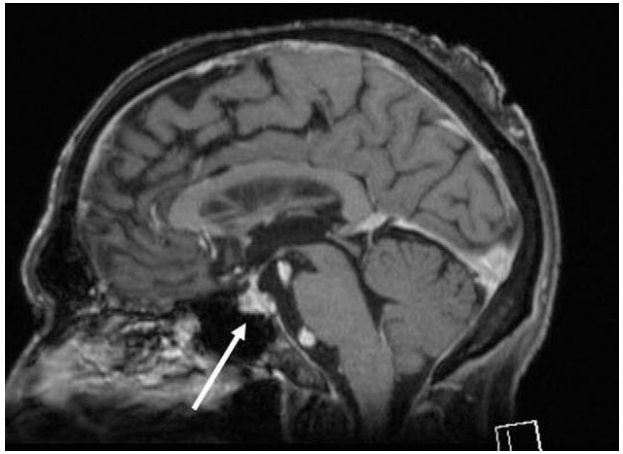
- Fever
- Hypoglycaemia
- Hyponatraemia
- Unusual bowel habits
- Hypotension
- Non specific symptoms which may resemble other causes such as brain mets or underlying disease

irEndocrinopathies (cont'd)

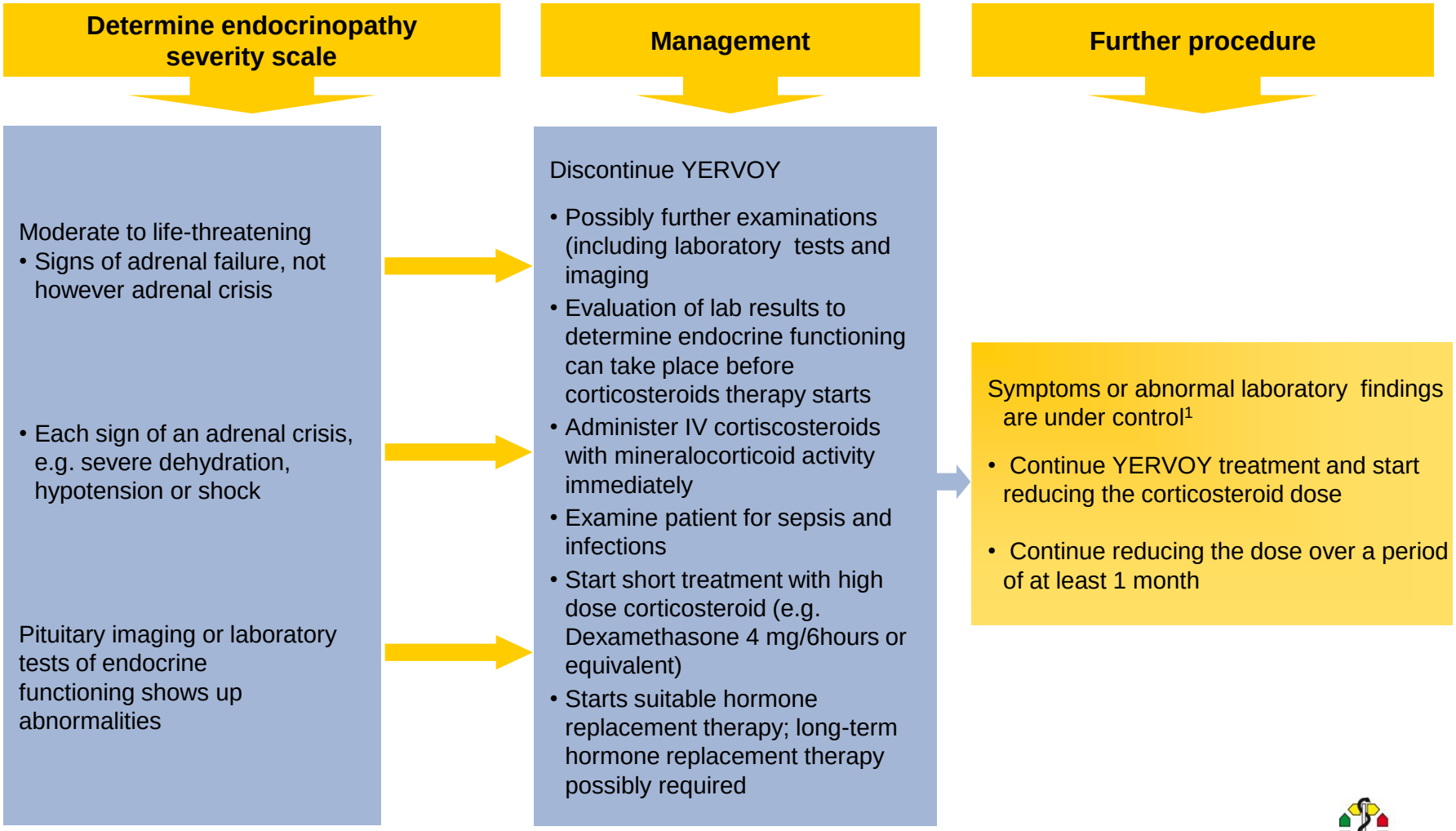
Suspicion while on ipilimumab therapy

- FT3, FT4, TSH, anti-TPO
- Serum cortisol (morning)
- ACTH (corticotropin)
- Testosterone (men)
- FSH, LH (women)

Skull – MRI/cross-sections of pituitary



irEndocrinopathy



Other immune-mediated adverse reactions <1% incidence, including ocular manifestations

- Nephritis
- Pneumonitis
- Meningitis
- Pericarditis
- Uveitis, iritis, conjunctivitis, blepharitis, epi-/scleritis
- Haemolytic anaemia
- Myocarditis
- Angiopathy
- Temporal arteritis
- Vasculitides
- Polymyalgia rheumatica
- Erythema multiforme
- Psoriasis
- Pancreatitis
- Arthritis

The Price of Tumor Control: An Analysis of Rare Side Effects of Anti-CTLA-4 Therapy in Metastatic Melanoma from the Ipilimumab Network Voskens et al. PLOS One 2013

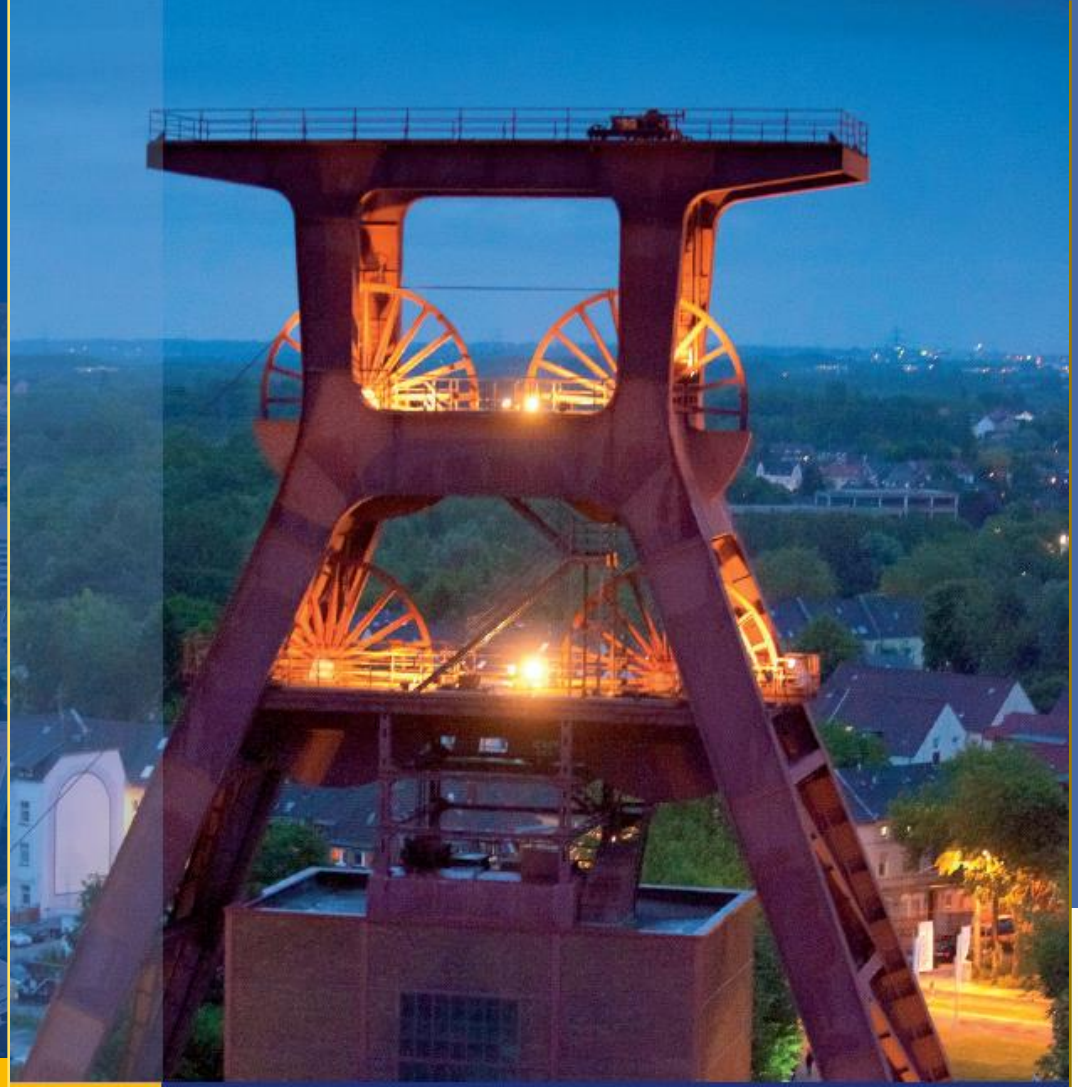
Management adverse reactions: summary

Mild[2]	• Treat systematically
Persistently mild or moderate[2]	• Treat with oral corticosteroids (prednisone 1 mg/kg BW or equivalent daily) • Stop the next dose of YERVOY until the symptoms subside or return to the original condition
Symptoms worsen, are severe or life-threatening	• Treat with high-dose IV corticosteroids (methylprednisolone 2 mg/kg BW or equivalent daily); when symptoms subside, consider gradually tapering the steroid dose over at least 4 weeks • If the symptoms do not respond to treatment within 5–7 days, other immunosuppressive therapies should be considered • Discontinue YERVOY permanently*

*With dermatological immune-mediated adverse reactions: scale 3: drop next dose of YERVOY; scale 4: rash or scale 3 pruritus: discontinue YERVOY permanently

Discontinuation of therapy

- irDermatitis grade 4
- Severe or life-threatening (grade 3/4) irAE GI tract, neurological
- ≥3 endocrinopathies + insufficient hormone replacement therapy
- GOT/GPT >8 x ULN, total bilirubin >5 x ULN
- irEye diseases ≥2 that do NOT respond to topical corticosteroid therapy
- Persistent moderate ARs (grade 2) or continuous prednisone dose of 7.5 mg/day



Thank you for your attention

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