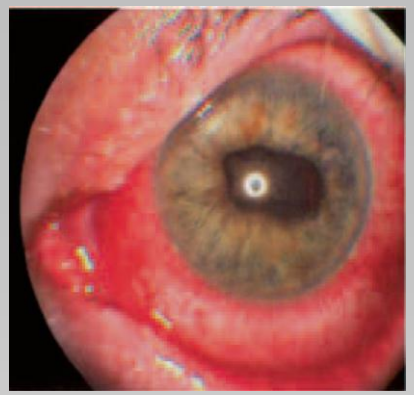

The handling of toxicity in newly approved melanoma therapies: anti-CTLA4 toxicity

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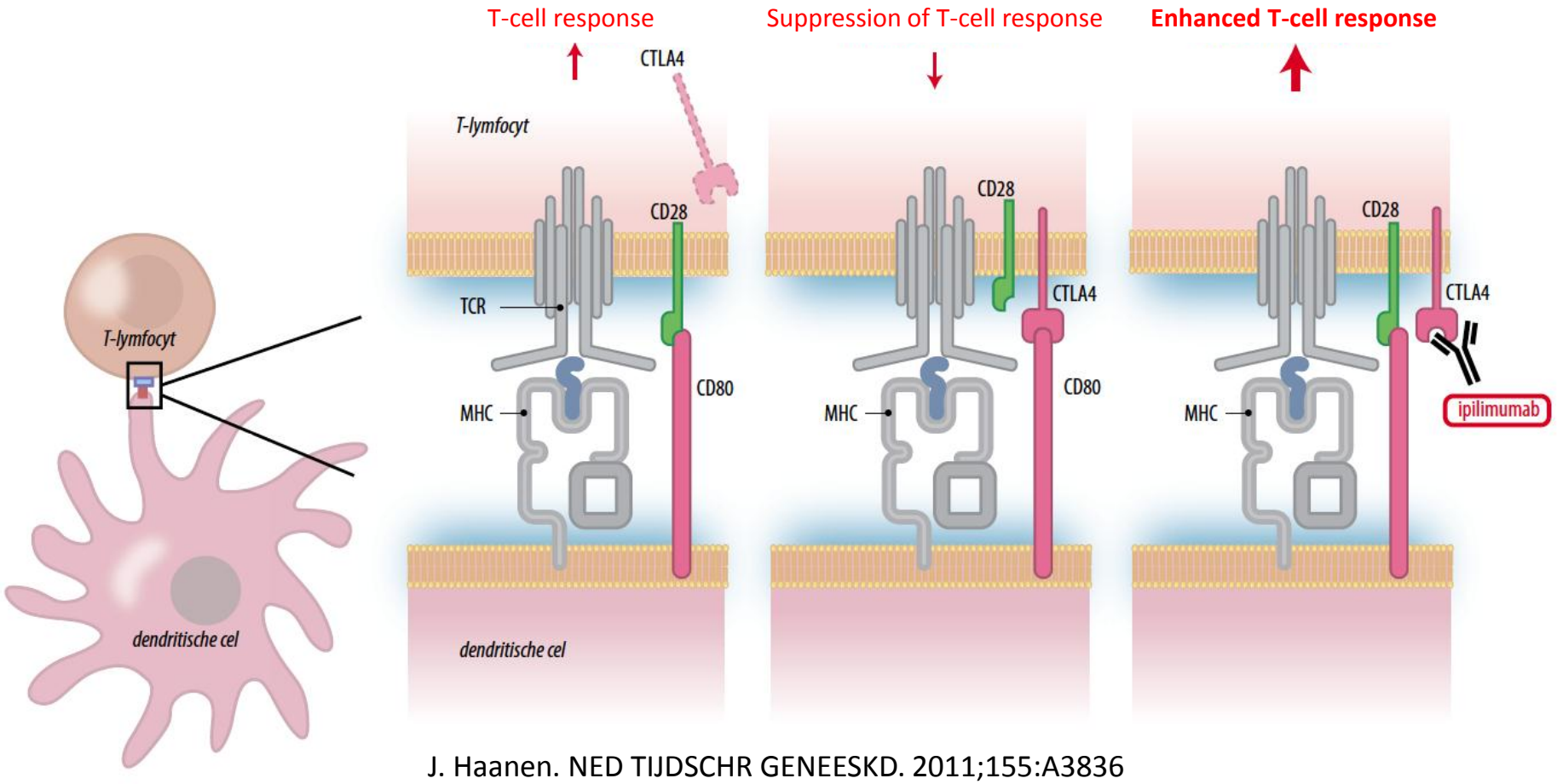
Disclosure slide

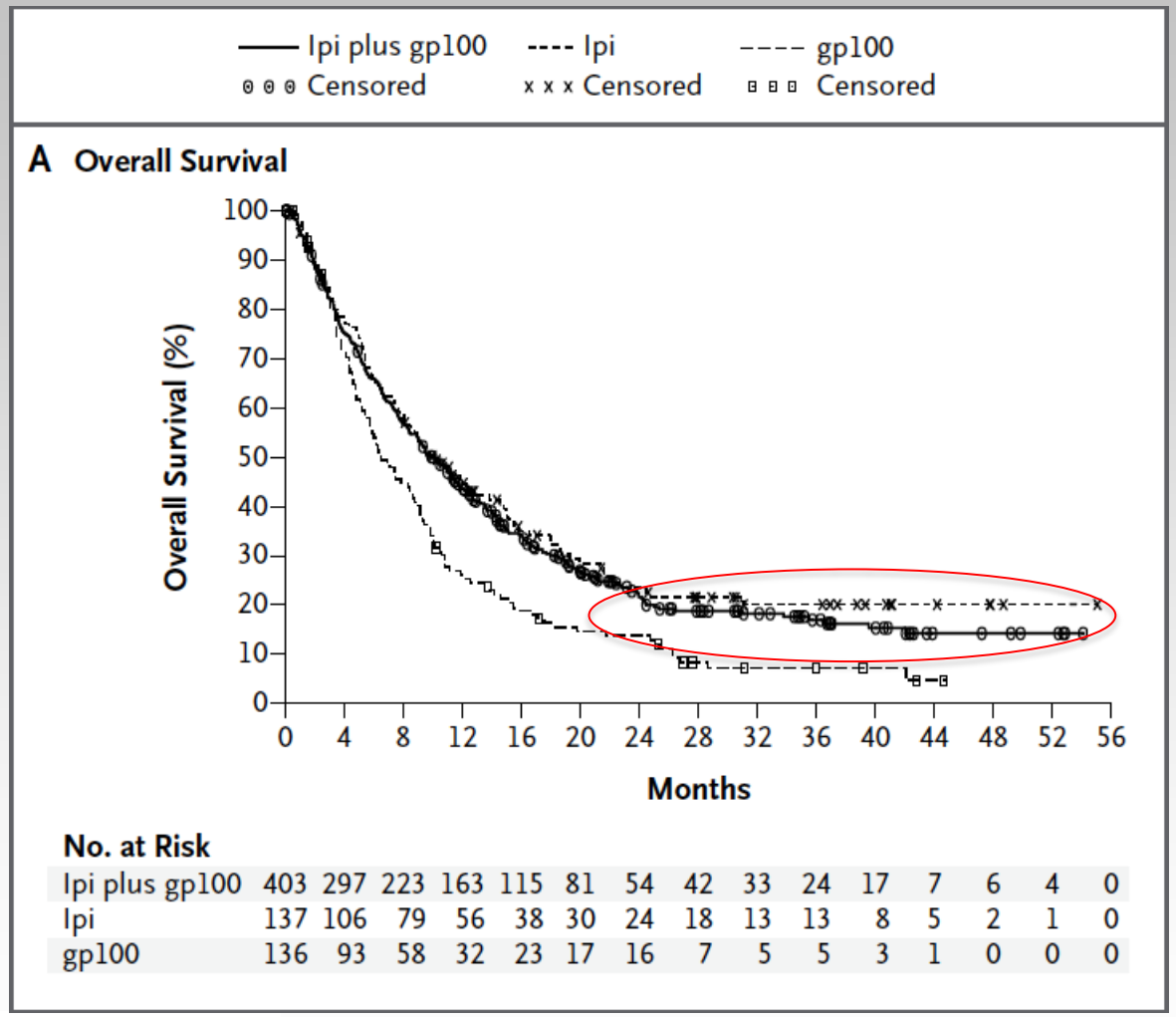
- JH has received honoraria from BMS, Roche, GSK for participation in advisory boards
- JH received research grant from BMS

Ipilimumab mechanism of action



J. Haanen. NED TIJDSCHR GENEESKD. 2011;155:A3836

Overall survival in pivotal trial



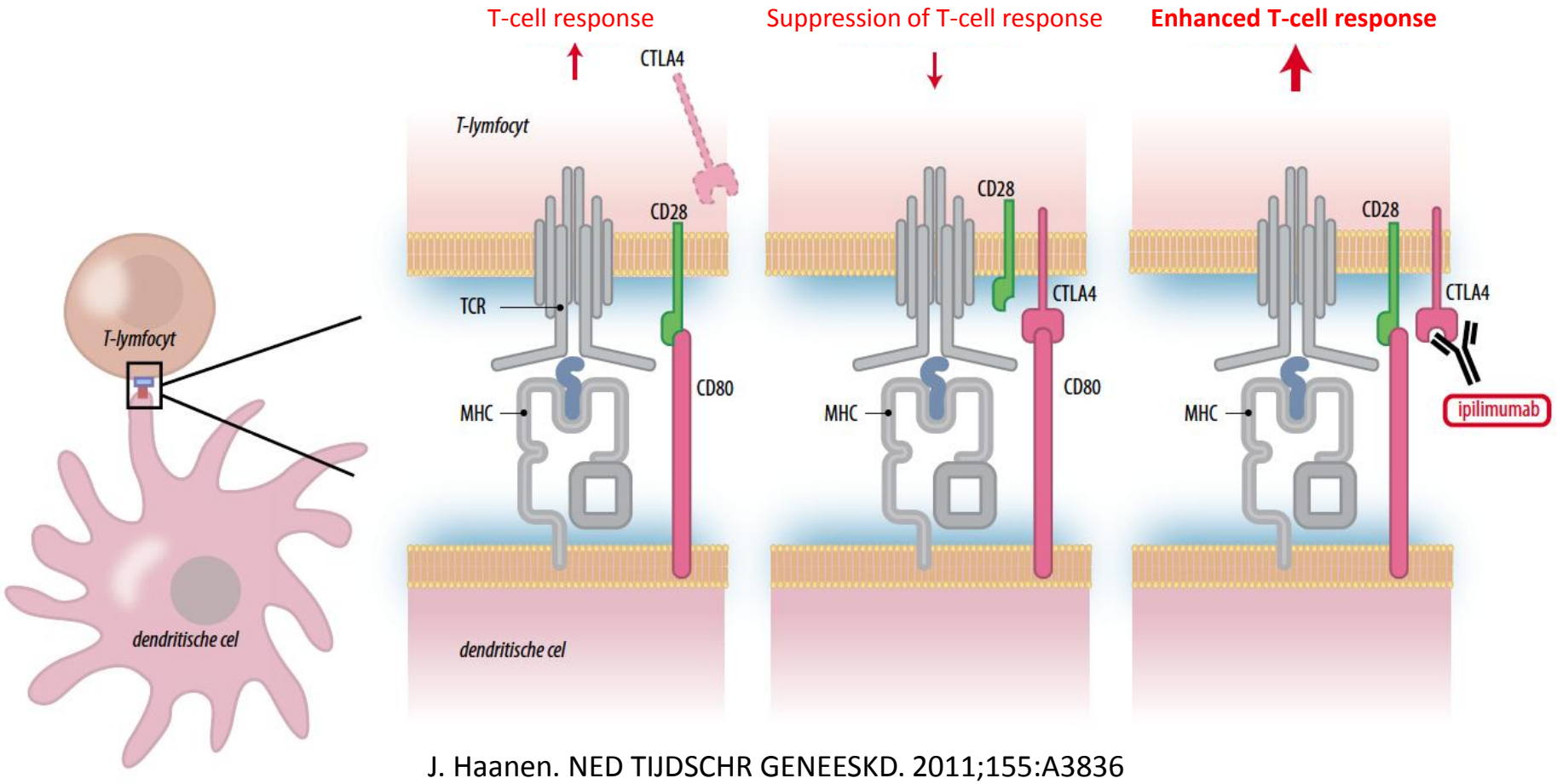
Hodi et al., NEJM 2010

Hodi et al., NEJM 2010

Efficacy of ipilimumab treatment

	Ipilimumab plus gp100 (N=403)	Ipilimumab Alone (N=137)	gp100 Alone (N=136)
Evaluation of therapy			
Induction			
Best overall response — no. (%)			
Complete response	1 (0.2)	2 (1.5)	0
Partial response	22 (5.5)	13 (9.5)	2 (1.5)
Stable disease	58 (14.4)	24 (17.5)	13 (9.6)
Progressive disease	239 (59.3)	70 (51.1)	89 (65.4)
Not evaluated	83 (20.6)	28 (20.4)	32 (23.5)
Best overall response rate — % (95% CI)	5.7 (3.7–8.4)	10.9 (6.3–17.4)	1.5 (0.2–5.2)
P value for comparison with gp100 alone	0.04	0.001	—
P value for comparison with ipilimumab alone	0.04	—	—
Disease control rate — % (95% CI)†	20.1 (16.3–24.3)	28.5 (21.1–36.8)	11.0 (6.3–17.5)
P value for comparison with gp100 alone	0.02	<0.001	—
P value for comparison with ipilimumab alone	0.04	—	—

Ipilimumab mechanism of toxicity



J. Haanen. NED TIJDSCHR GENEESKD. 2011;155:A3836

AEOSI

- **A**dverse **E**vents **O**f **S**pecific **I**nterest in stead of immune related Adverse Events (irAE)

Infusion-related AEs and AEOSI

- Infusion-related AE
  - Allergic reaction
    - Nausea, rash, dyspnea, diarrhea
    - During or shortly after end of infusion

- AEOSI
  - Colitis, dermatitis, hepatitis, thyreoiditis etc.
    - Days, weeks or months after infusion

Ipilimumab related AEOSI

Hodi et al., NEJM 2010

Adverse Event	Ipilimumab plus gp100 (N=380)			Ipilimumab Alone (N=131)		
	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4
	number of patients (percent)					
Any immune-related event	221 (58.2)	37 (9.7)	2 (0.5)	80 (61.1)	16 (12.2)	3 (2.3)
Dermatologic	152 (40.0)	8 (2.1)	1 (0.3)	57 (43.5)	2 (1.5)	0
Pruritus	67 (17.6)	1 (0.3)	0	32 (24.4)	0	0
Rash	67 (17.6)	5 (1.3)	0	25 (19.1)	1 (0.8)	0
Vitiligo	14 (3.7)	0	0	3 (2.3)	0	0
Gastrointestinal	122 (32.1)	20 (5.3)	2 (0.5)	38 (29.0)	10 (7.6)	0
Diarrhea	115 (30.3)	14 (3.7)	0	36 (27.5)	6 (4.6)	0
Colitis	20 (5.3)	11 (2.9)	1 (0.3)	10 (7.6)	7 (5.3)	0
Endocrine	15 (3.9)	4 (1.1)	0	10 (7.6)	3 (2.3)	2 (1.5)
Hypothyroidism	6 (1.6)	1 (0.3)	0	2 (1.5)	0	0
Hypopituitarism	3 (0.8)	2 (0.5)	0	3 (2.3)	1 (0.8)	1 (0.8)
Hypophysitis	2 (0.5)	2 (0.5)	0	2 (1.5)	2 (1.5)	0
Adrenal insufficiency	3 (0.8)	2 (0.5)	0	2 (1.5)	0	0
Increase in serum thyrotropin level	2 (0.5)	0	0	1 (0.8)	0	0
Decrease in serum corticotropin level	0	0	0	2 (1.5)	0	1 (0.8)
Hepatic	8 (2.1)	4 (1.1)	0	5 (3.8)	0	0
Increase in alanine aminotransferase	3 (0.8)	2 (0.5)	0	2 (1.5)	0	0
Increase in aspartate aminotransferase	4 (1.1)	1 (0.3)	0	1 (0.8)	0	0
Hepatitis	2 (0.5)	1 (0.3)	0	1 (0.8)	0	0
Other	12 (3.2)	5 (1.3)	0	6 (4.6)	2 (1.5)	1 (0.8)

AEOSI (I)

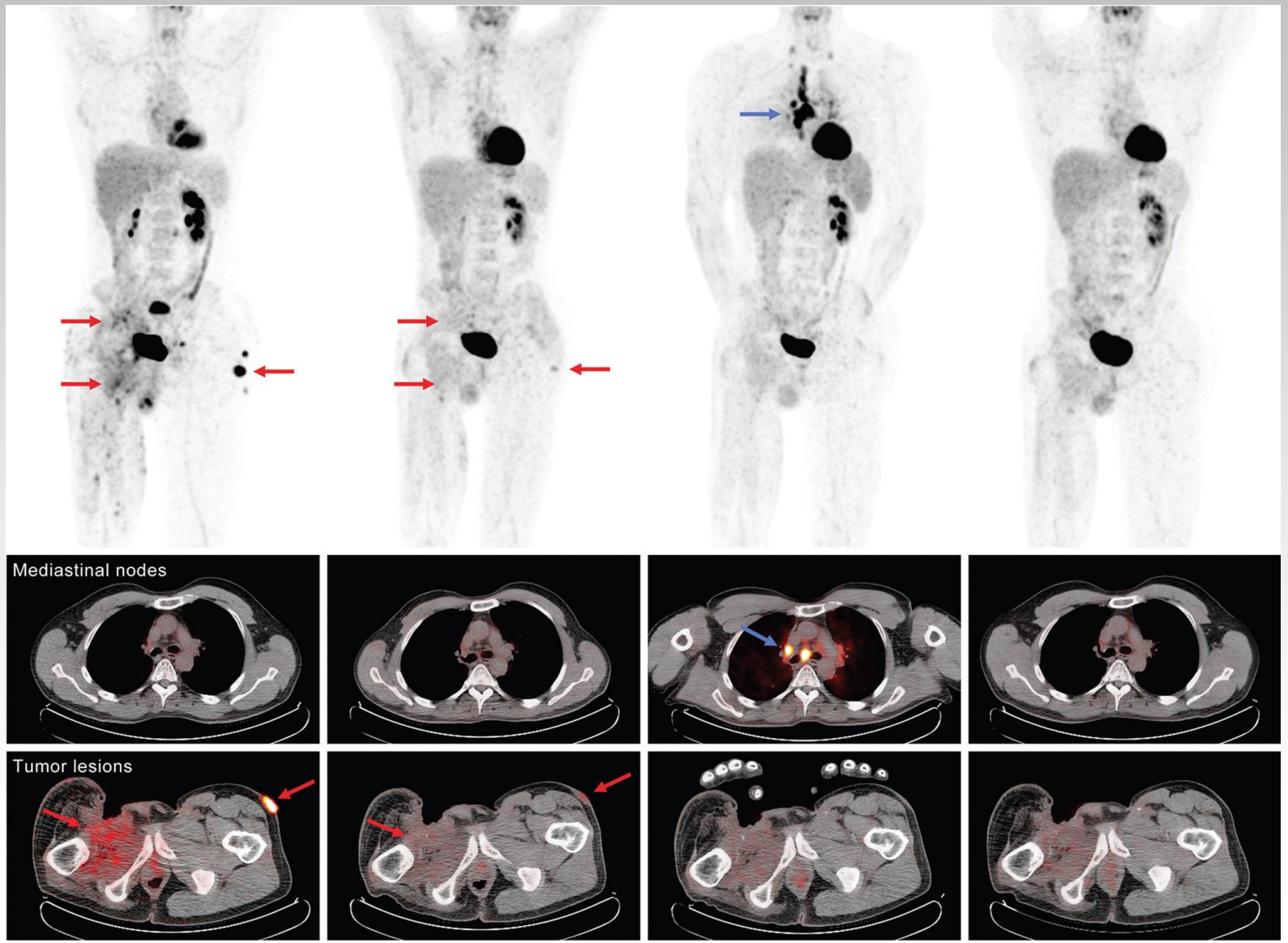
Case: 49-year old male patient with metastatic melanoma was treated with ipilimumab in EAP (3mg/kg; x 4).

Received 4 courses without side effects

After 4 courses PET-scan showed near complete metabolic response of known lesions but also new mediastinal ^{18}FDG-uptake.

EBUS- biopsy was performed showing non-caseous granulomatous inflammation typical for sarcoidosis. Also serum ACE was elevated.

Sarcoidosis grade I as toxicity of ipilimumab



Vogel et al. J Clin Oncol 2012

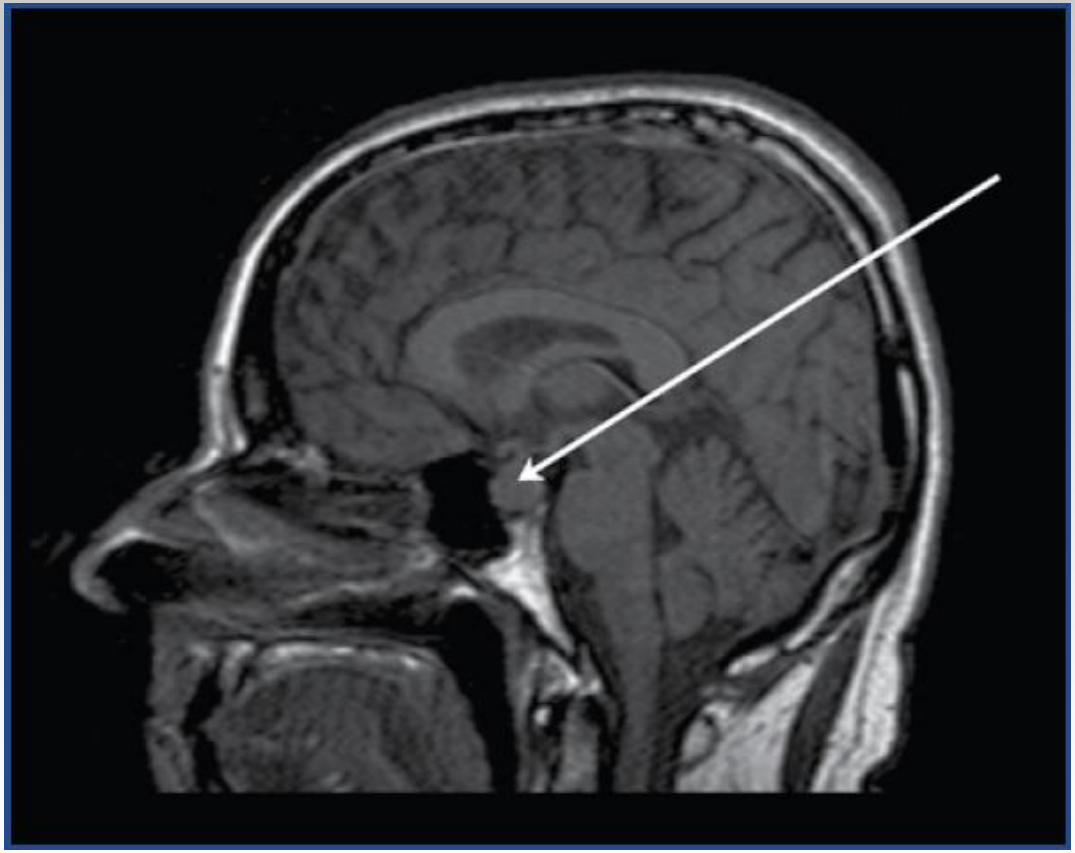
AEOSI (II)

Case: a 60-year old male started adjuvant treatment in E18071 (10 mg/kg x4, followed by maintenance) for stage III melanoma. After course 2 he developed intermittend headaches for which he was seen by a neurologist. Brain-CT did not reveal any abnormalities (no brain mets). He was treated with painkillers and presented himself 2 weeks later with continuous headaches.

Lab test showed: Low FT4 and TSH and LH and testosterone.

MRI-brain showed enlarged hypophysis

Hypophysitis as ipilimumab related toxicity



Kapiteijn & Blank, NTvO 2011

TSH: 0.03 mIU/L
T4: 7.3 pmol/L ↓

LH: 0.5 IU/L
Testosterone: 0.2 nmol/L ↓

Cortisol, ACTH: normal
Prolactine: normal

Patient was put on steroids, levothyroxine and testosterone and recovered (normal MRI) with 4 weeks after which prednisone could be tapered

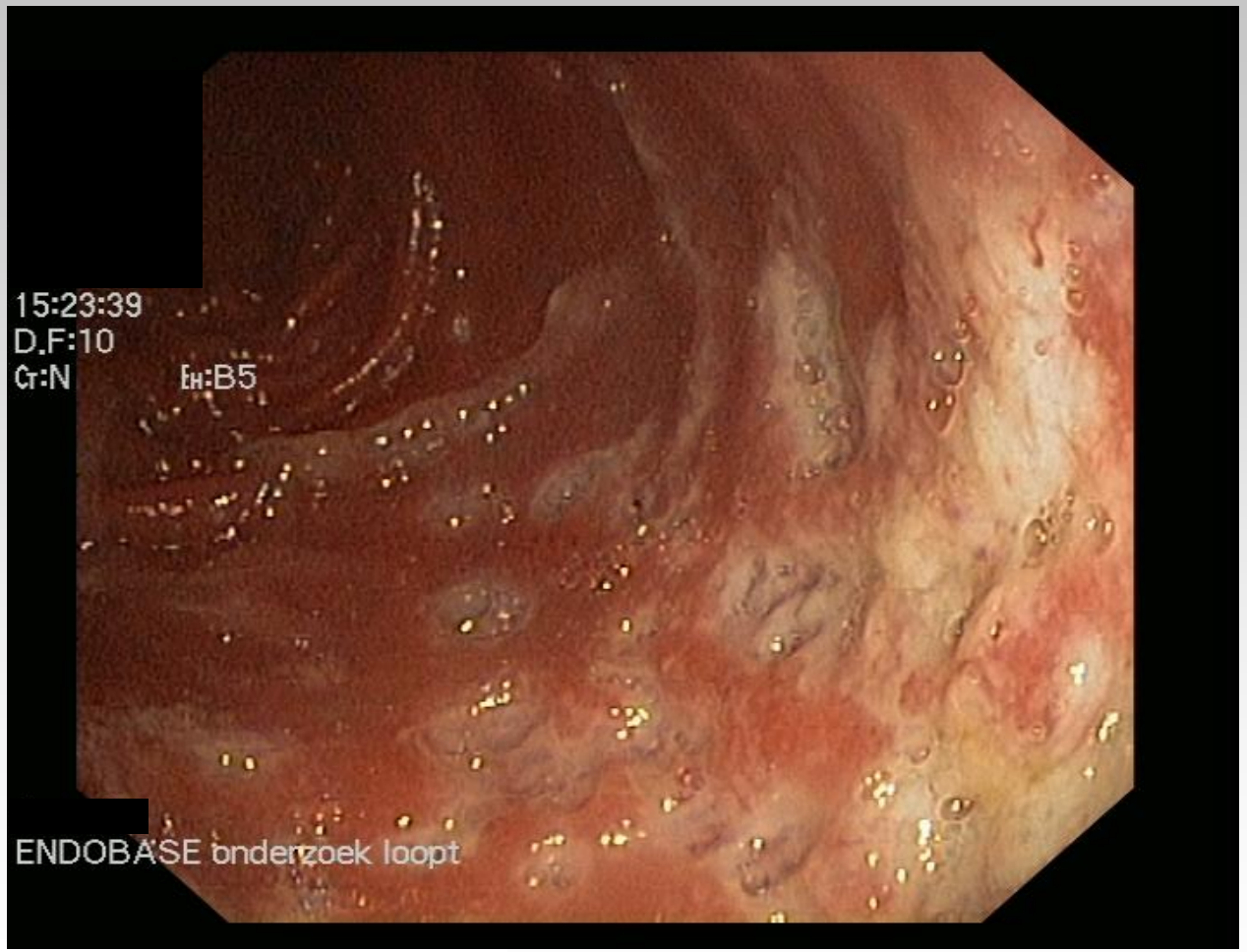
AEOSI (III)

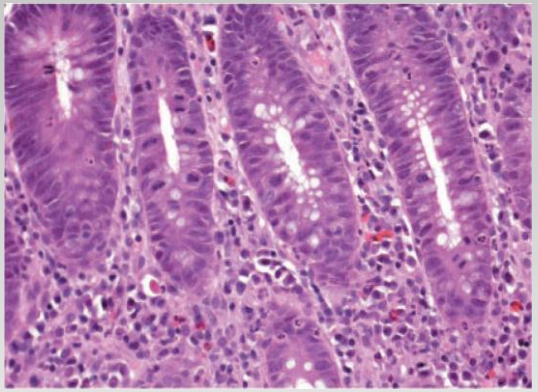
Case: a 65-year old man started ipilimumab for metastatic melanoma because of disease progression under dacarbazine. He had several subcutaneous, lymph node and intra-abdominal metastases.

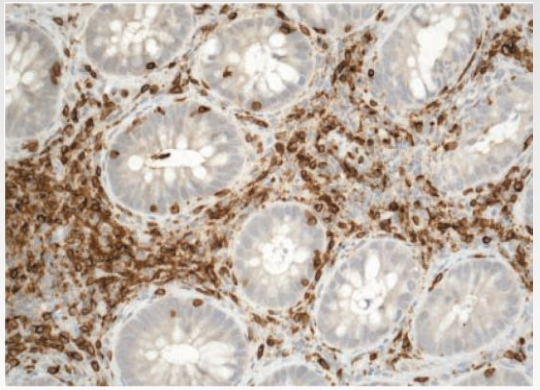
Shortly after the 4th infusion he developed severe diarrhea for which he was admitted to the hospital. A coloscopy was performed showing grade 3 colitis.

The patient was put on high dose prednison, but developed an intestinal perforation for which acute surgery was required. A sigmoidectomy was performed and a temporary AP was generated. After surgery he was treated with infliximab, resolving the diarrhea.

Grade 3 colitis as ipilimumab toxicity

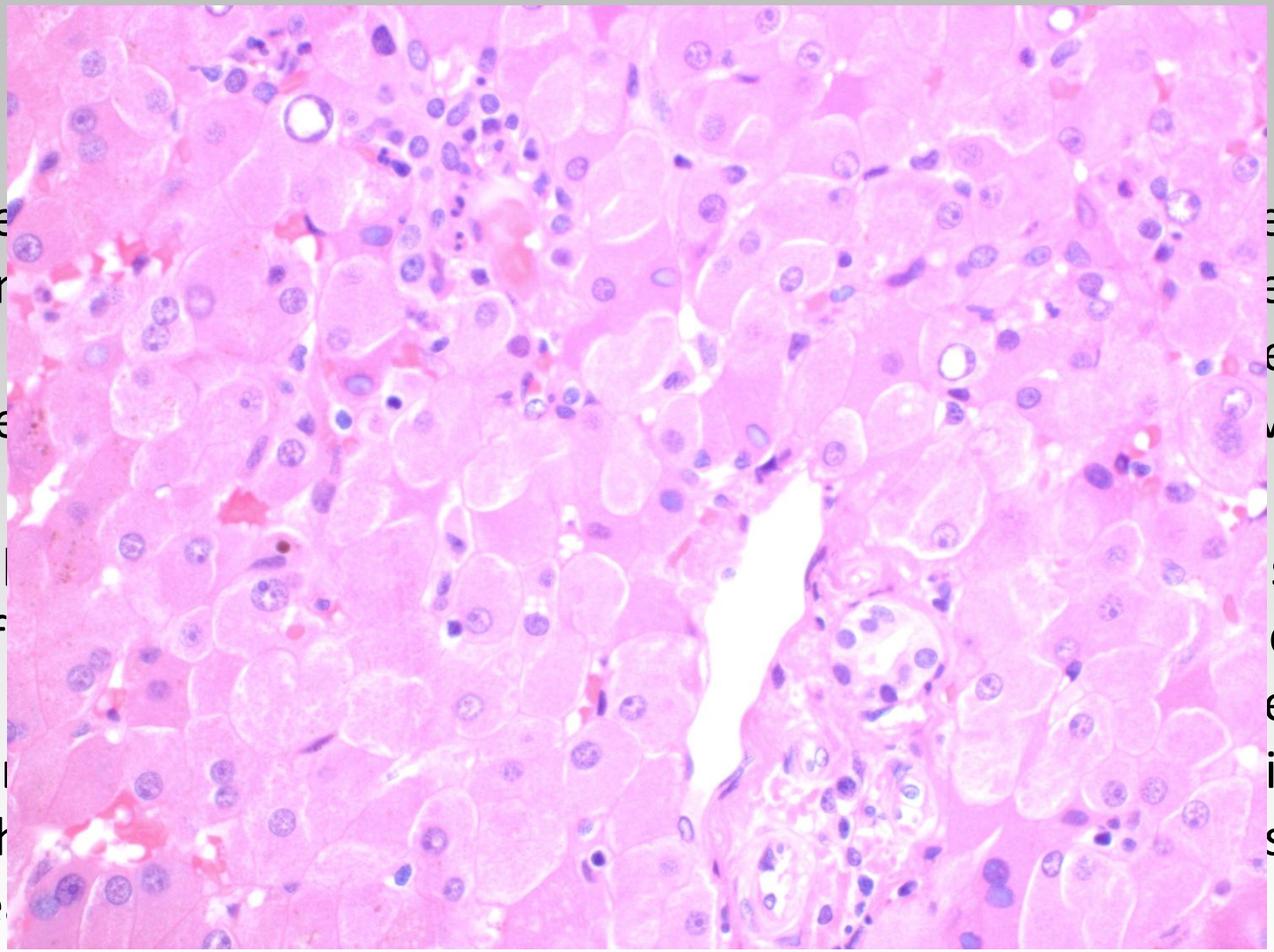






AEOSI (IV)

- Case: A 63 year old man was treated for metastatic melanoma with ipilimumab (3 mg/kg; x4). The patient had lung, liver and cervical node metastases. After 4 courses, he was evaluated with CT-scan showing progressive disease at all sites. Shortly thereafter he was admitted elsewhere because of muscle weakness of upper legs and arms, and based on an EMG Guillain-Barre syndrome was diagnosed. He was transferred to our hospital, but despite high doses of steroids, his condition deteriorated requiring mechanical ventilation. The patient refused further treatment and died of progressive disease and Guillain-Barre syndrome.



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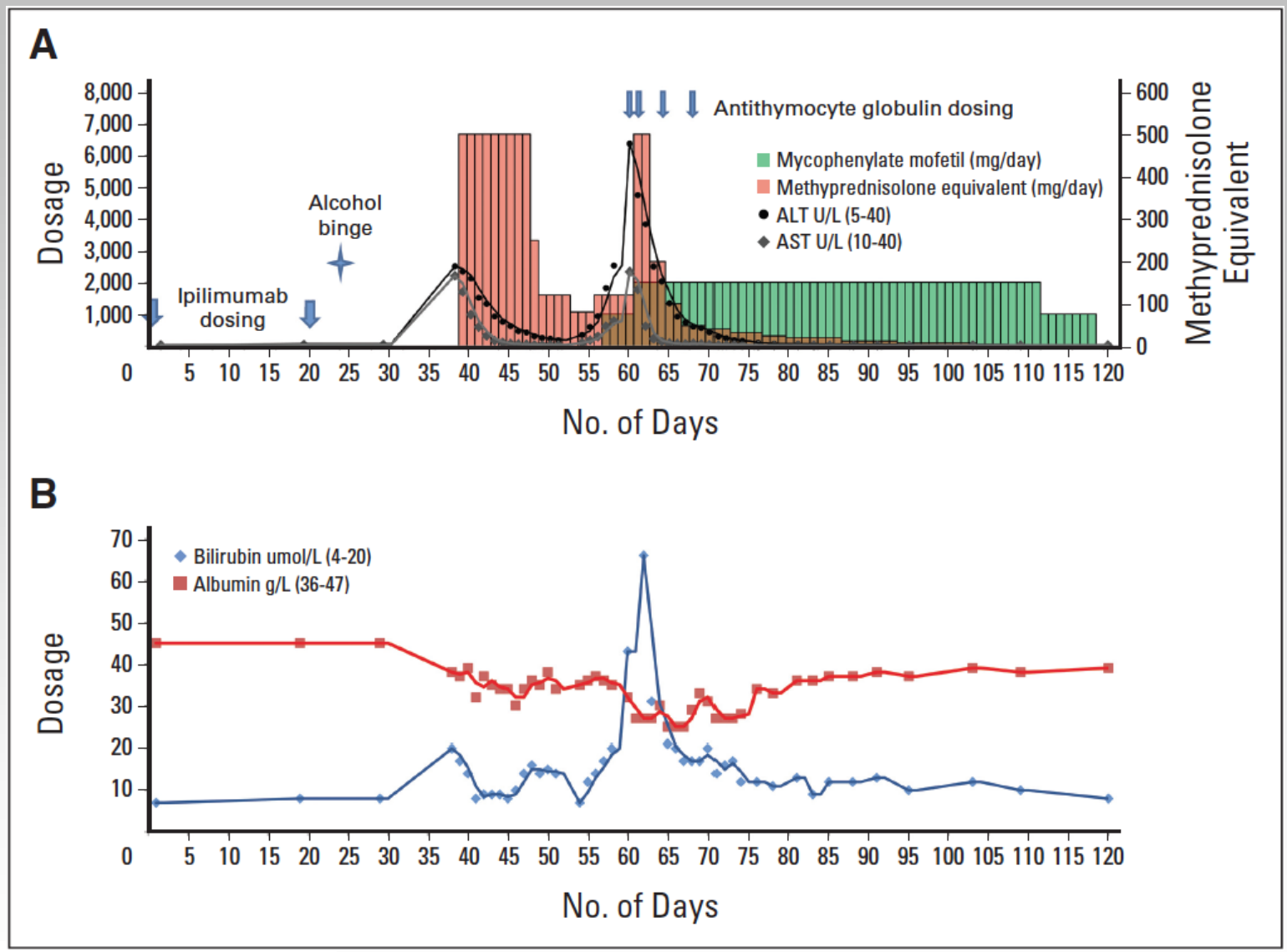
Severe ipi-induced hepatitis responding to antithymocyte globulin



Chmiel et al., J Clin Oncol 2011

Summary

- AEOSI occur in about 50-60% of patients treated with ipilimumab
- 10% or less develop grade 3/4 toxicity requiring high doses of steroids, infliximab, mycophenolate or other immunosuppressive drugs
- Most common side effects are colitis, dermatitis, hepatitis and endocrinopathies
- Make use of the management algorithms of AEOSI
- Instruct patients to respond to you in case of side effects
- Be on the outlook for rare toxicities!