Toxicity of new Immunotherapies for Melanoma

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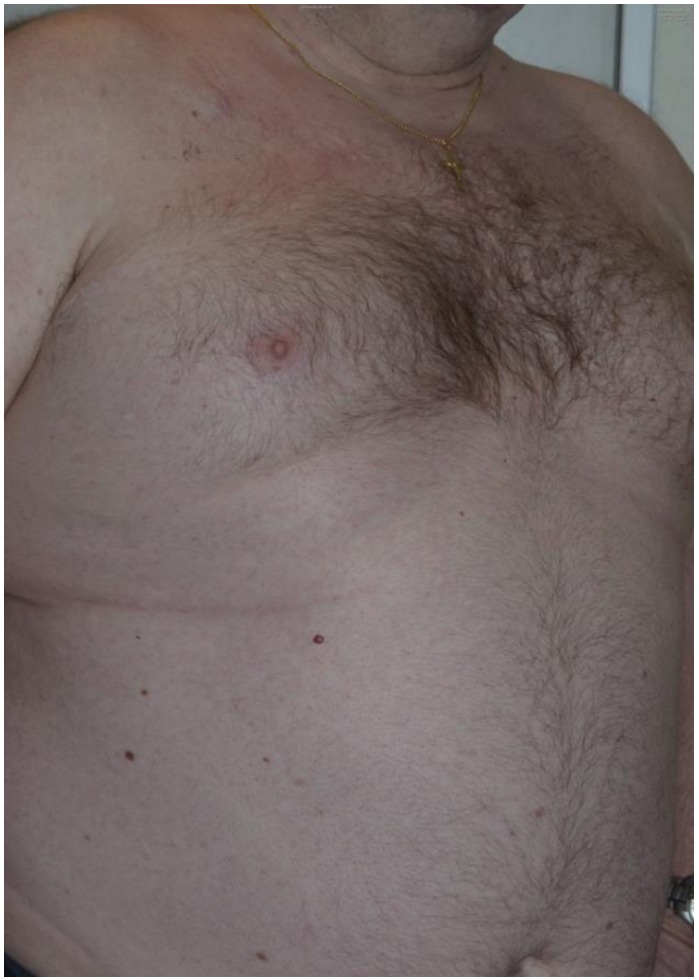
Disclosure slide

- Consultant for MSD, BMS, Amgen, Novartis, Amgen

- Mr I. 72
- 1.25 mm Melanoma on the back in December 2012
- Wide excision + SN in January 2013
  - One positive left cervical SN
- Lymphadenectomy February 2013
  - 34 negative LN: 1N+/35N
- June 2013: 3 Infracentimetric lung and skin metastases

- BRAF WT
- Wait until activation of a clinical trial with an anti-PD1 mAb
- Randomized in Keynote 006:
  - ipilimumab versus pembrolizumab (2 doses)
- Randomized in the ipi arm, and retracted
- Randomized in the BMS 069 trial October 31st 2013
  - ipilimumab versus ipilimumab + nivolumab

- After 4 weeks :
  - prurit grade 1
  - Disseminated grade 2 maculopapular erythematous rash



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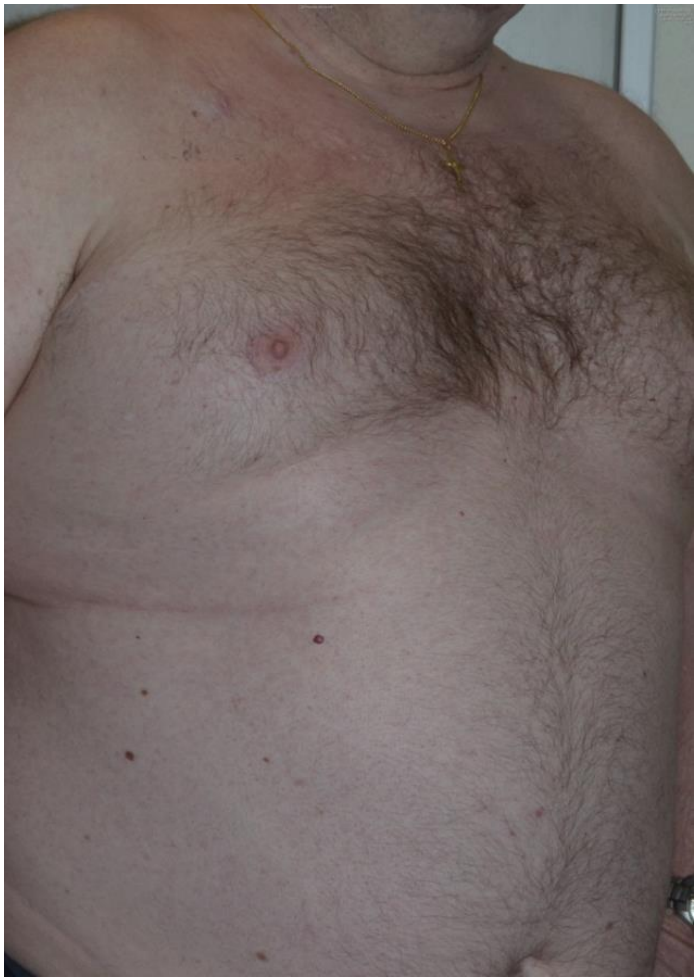
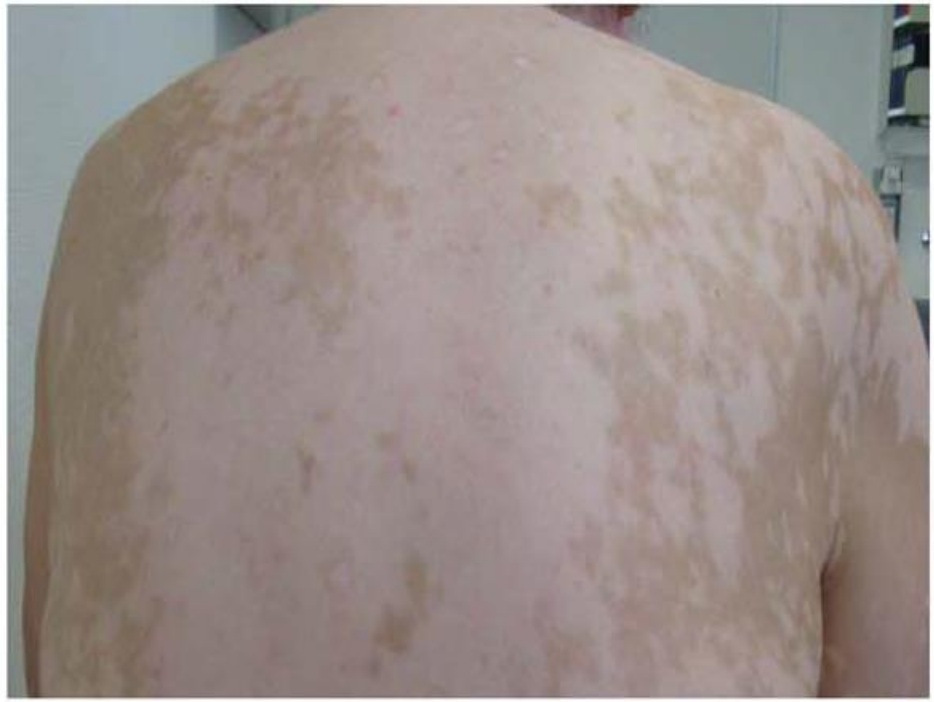
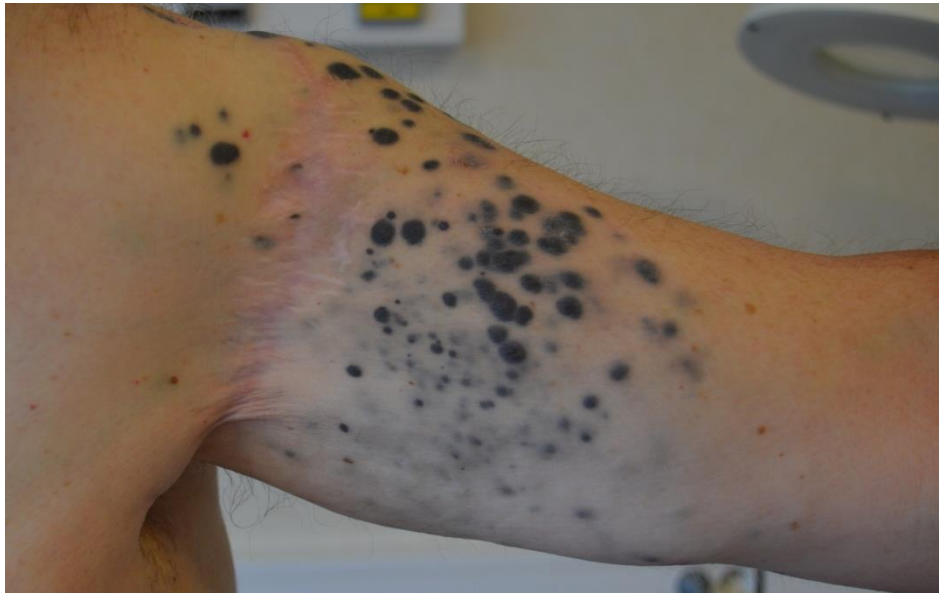
  - Disseminated grade 2 maculopapular erythematous rash

- Topical steroid and therapy continued



- After 8 weeks :
  - Vitiligo on the back and around the skin metastases





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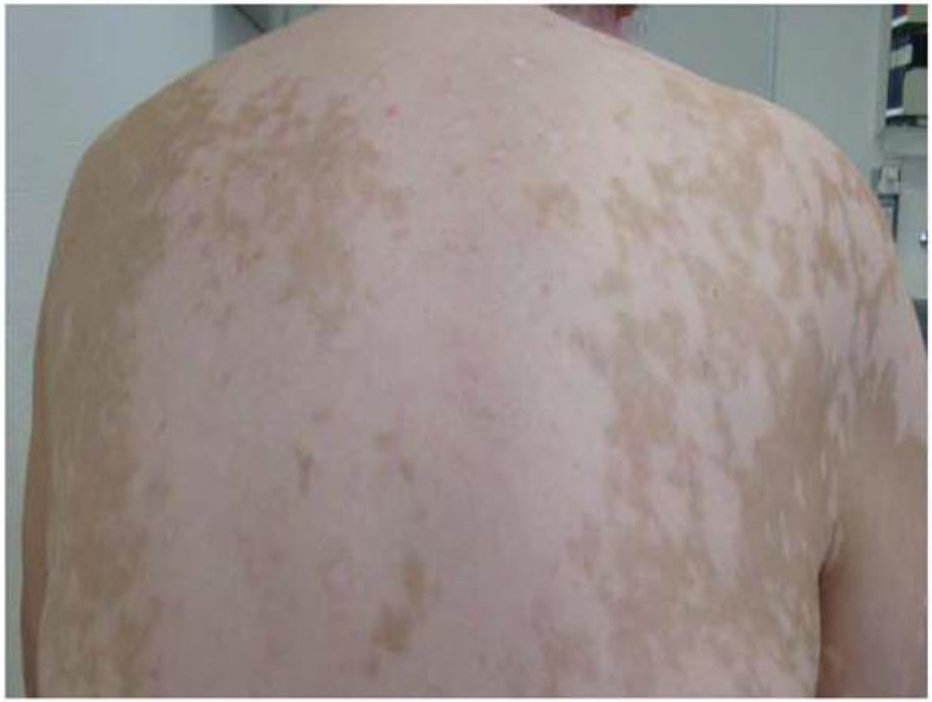
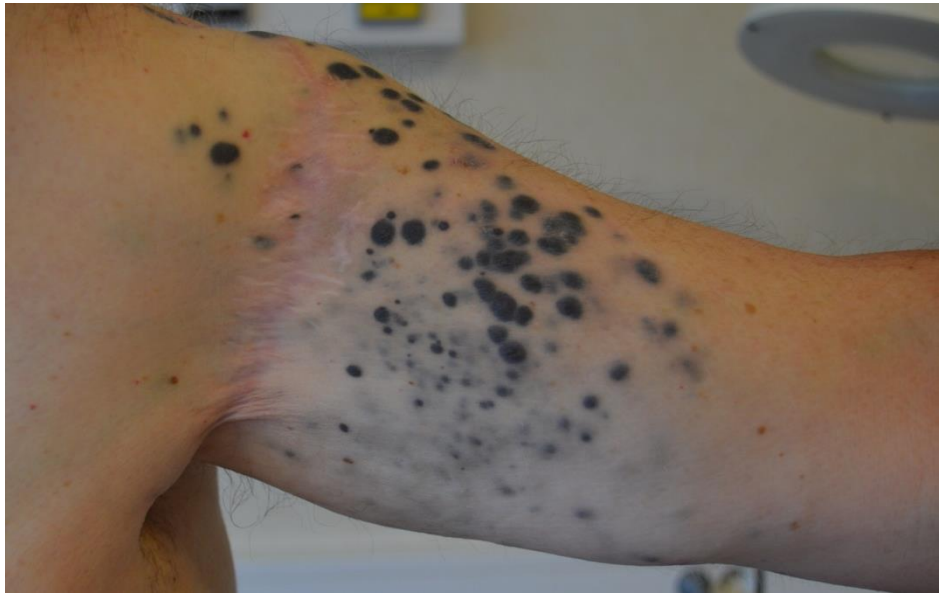


- Treatment continued



10 weeks

- Deep asthenia
- Headache
- nausea
- Blood pressure: 100/60 mmHg

- Biology
  - Hyponatremia
  - Low blood and urinary cortisol
  - Low ACTH, testosterone
  - T3, T4, TSH : normal
- Normal hypophyse MRI

- Hormonal compensation
  - hydrocortisone 30 mg/day
  - testosterone testosterone 250 mg/3 weeks

- Treatment continued

12 weeks

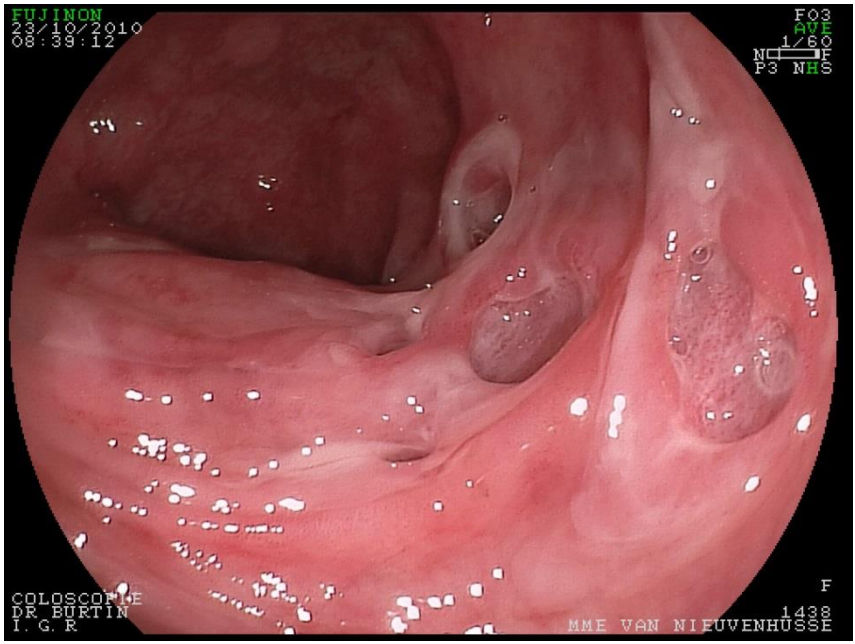
- Evaluation : Partial response with 75% decrease of the target lesions
- Abdominal pain and diarrhea with 7-9 stools/day last two days
- Colonoscopy

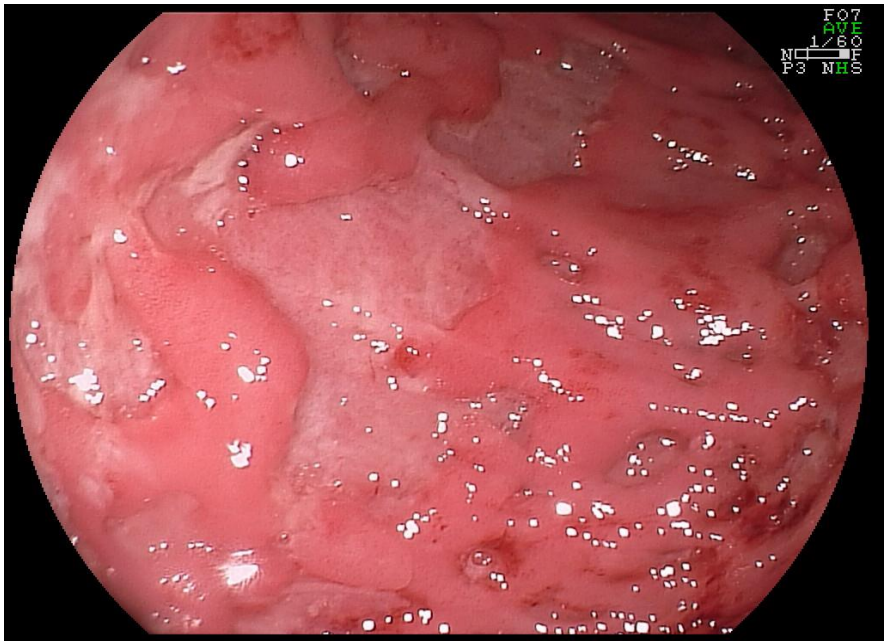
  Gr 3 colitis

  Pathology: epithelial ulceration,

  cryptitis, lymphytic and neutrophilic

  rare plasmocytes




F07
AVE
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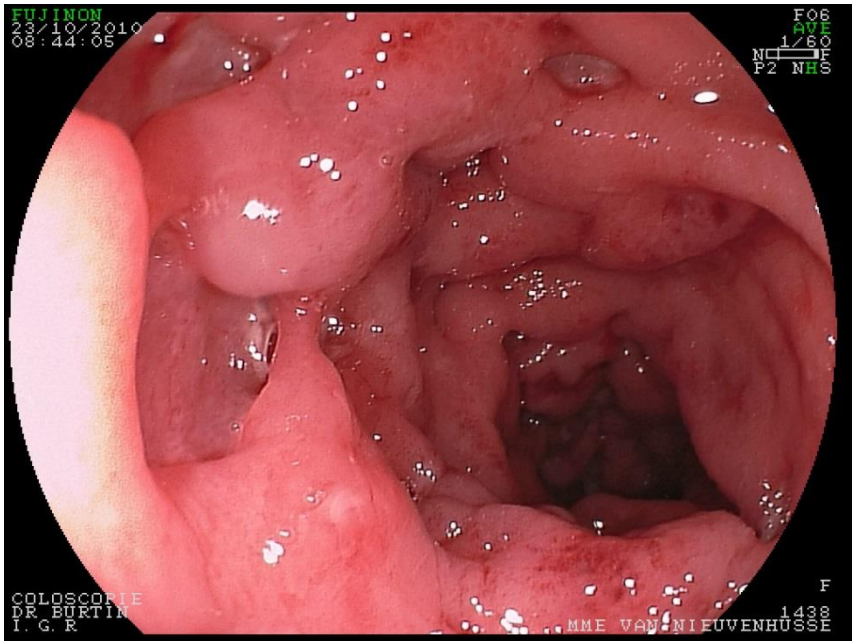
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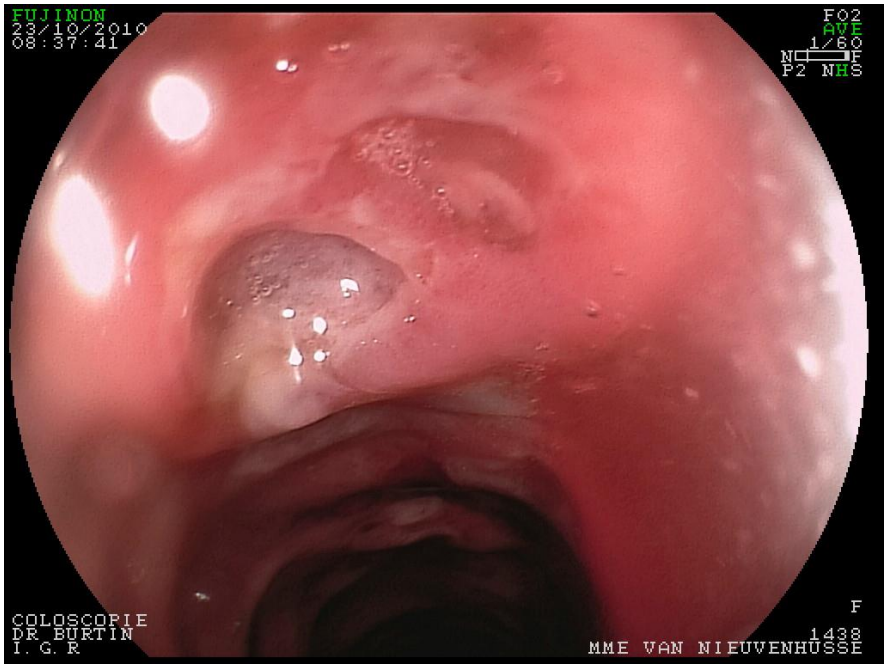
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MME VAN NIEUVENHUSSE

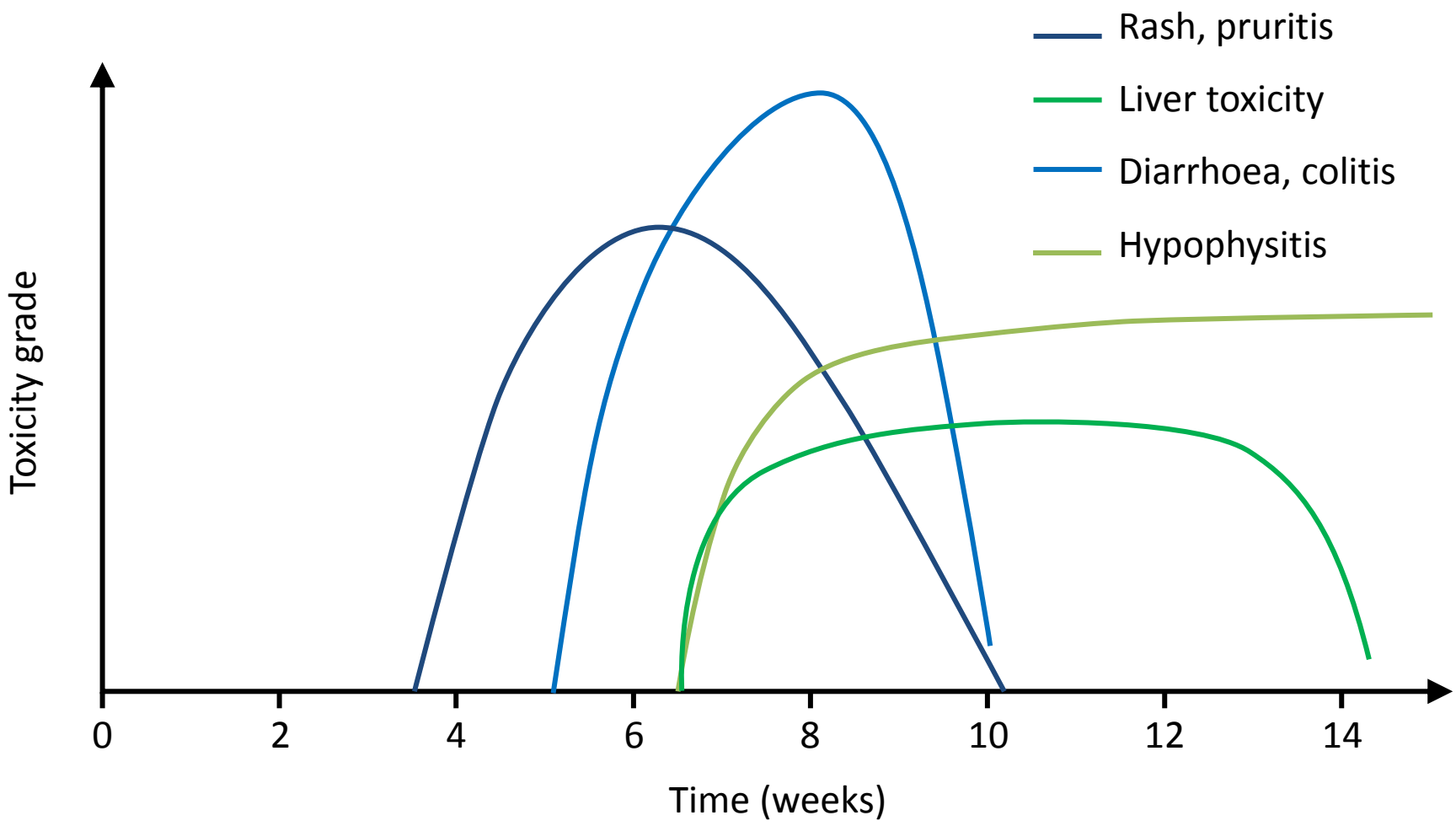
- Treatment interruption
- Steroids 1 mg/kg for 10 days
- Infliximab one infusion 5 mg/kg
- Steroids tapered in 8 weeks
- Normal colonoscopy after 10 weeks

Questions

- Can we give anti-PD1 mAb in patients who had severe irAE with ipilimumab?

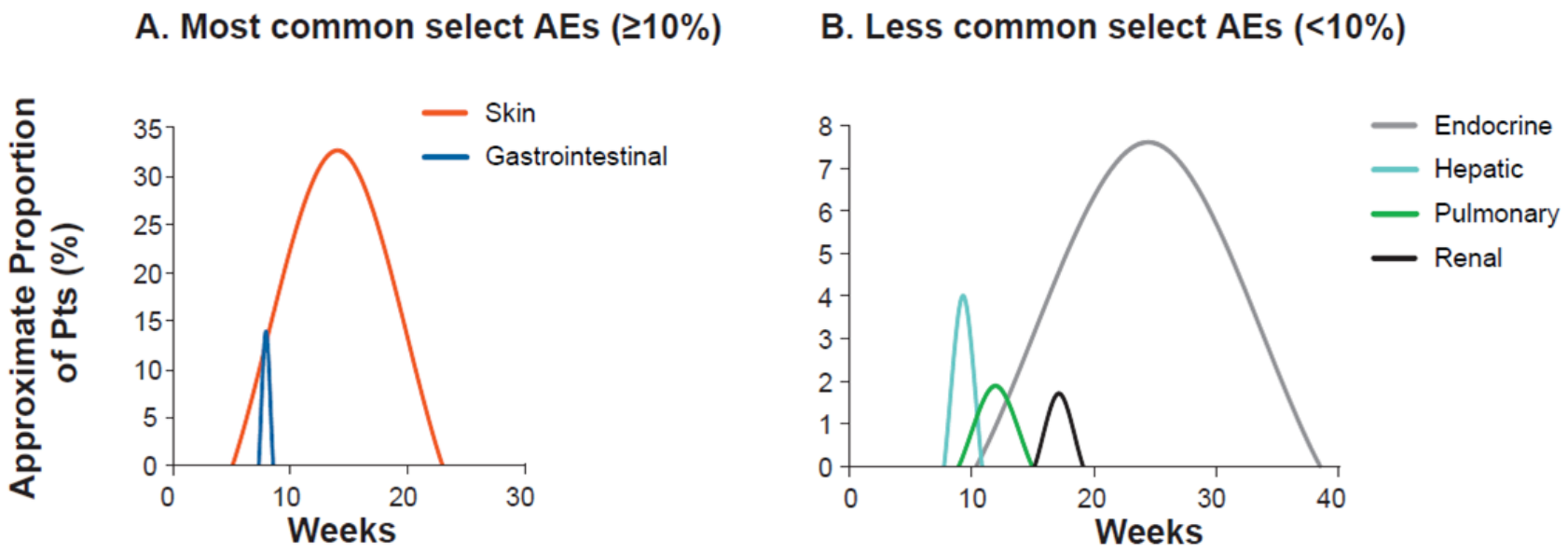
- Should we give anti-TNF earlier in case of severe colitis?

Ipilimumab Kinetics of irAEs



Weber et al. JCO 2012

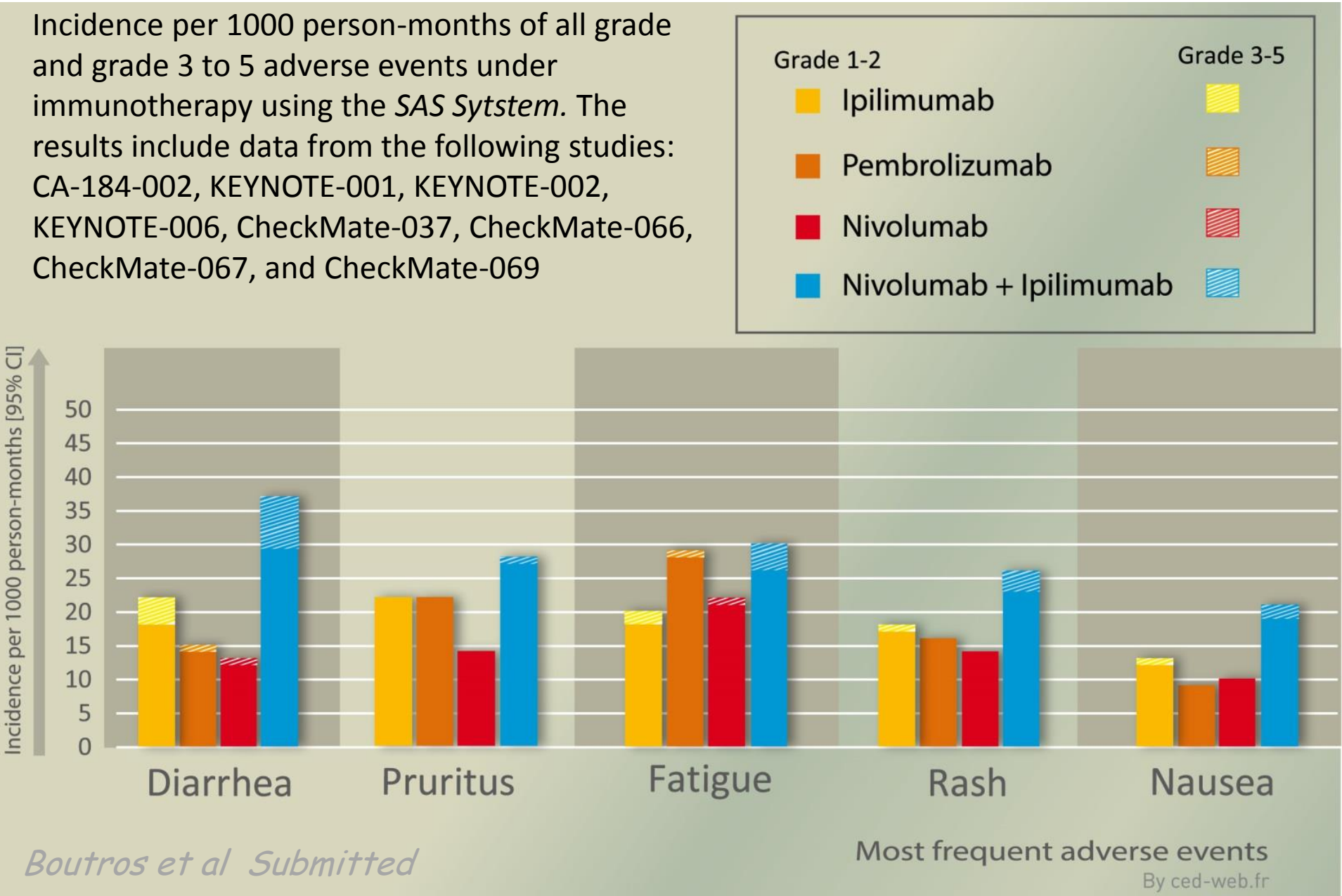
Nivolumab Kinetics of irAEs



Weber et al ASCO 2014

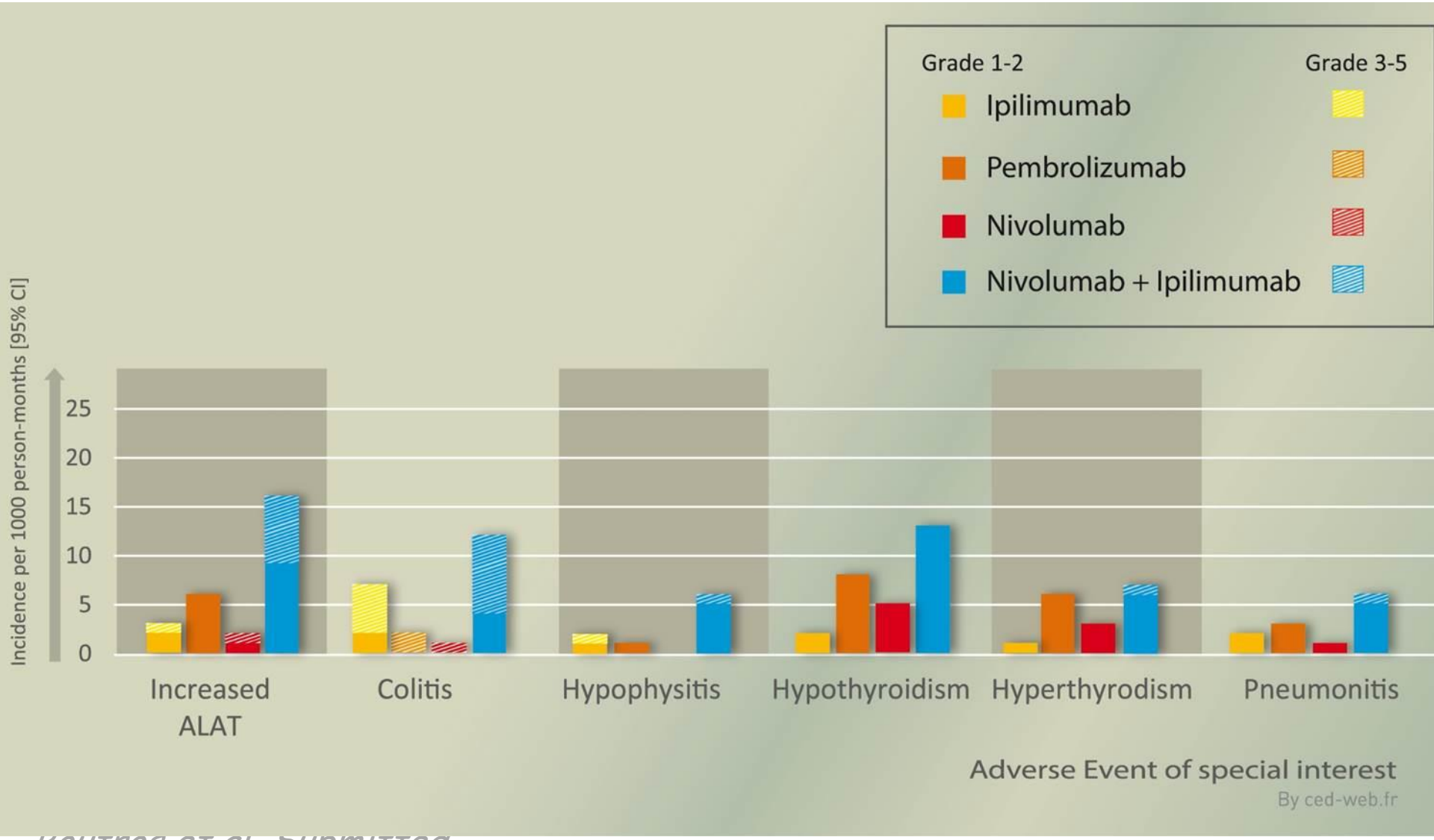
Frequent AE

Incidence per 1000 person-months of all grade and grade 3 to 5 adverse events under immunotherapy using the *SAS Sytstem.* The results include data from the following studies: CA-184-002, KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, CheckMate-037, CheckMate-066, CheckMate-067, and CheckMate-069



Boutros et al Submitted

AE « of special interest »



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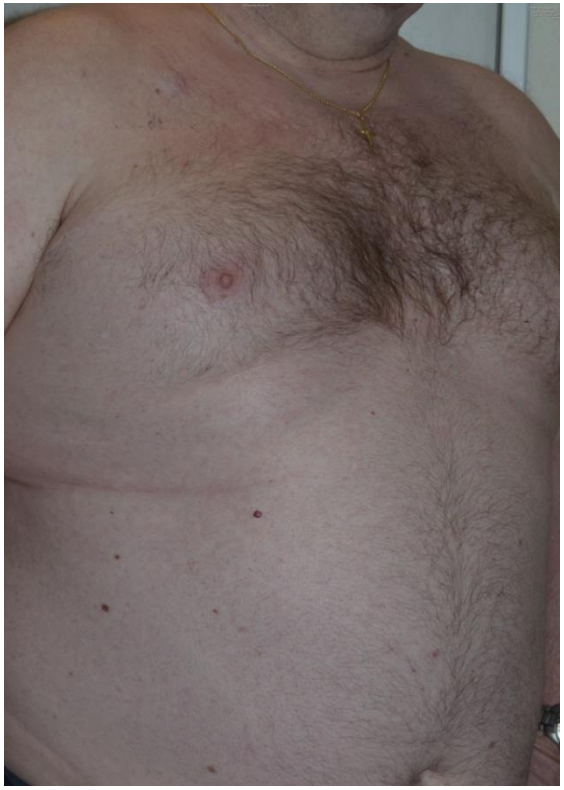
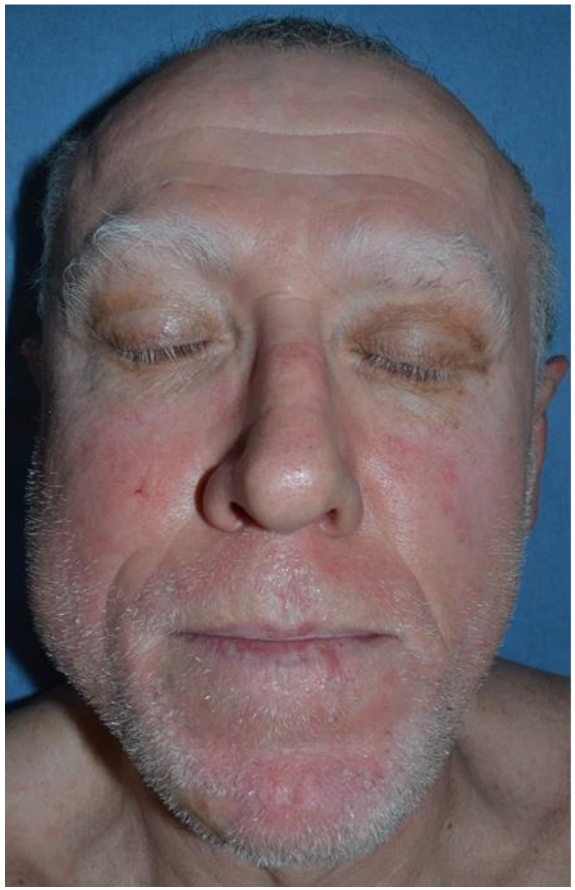
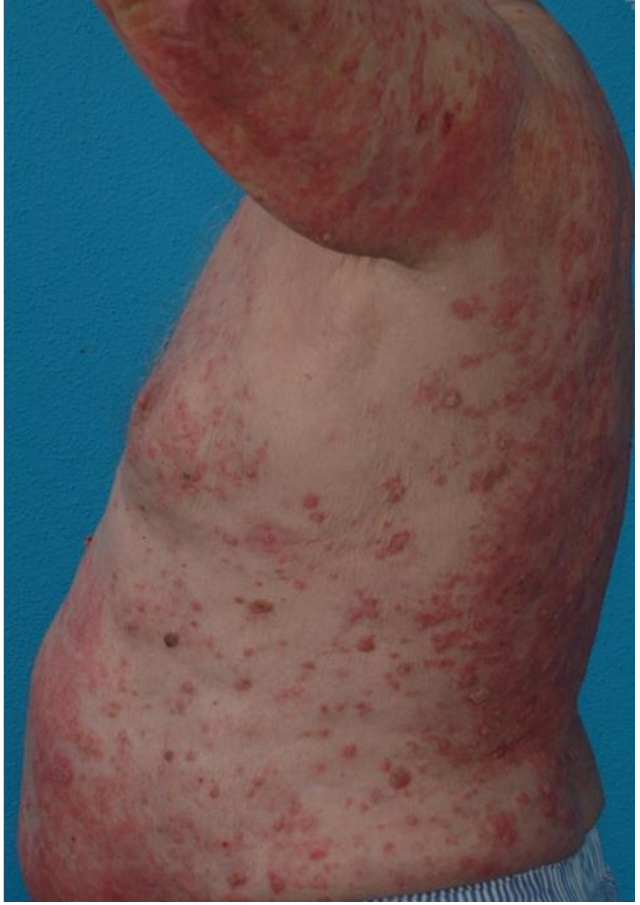
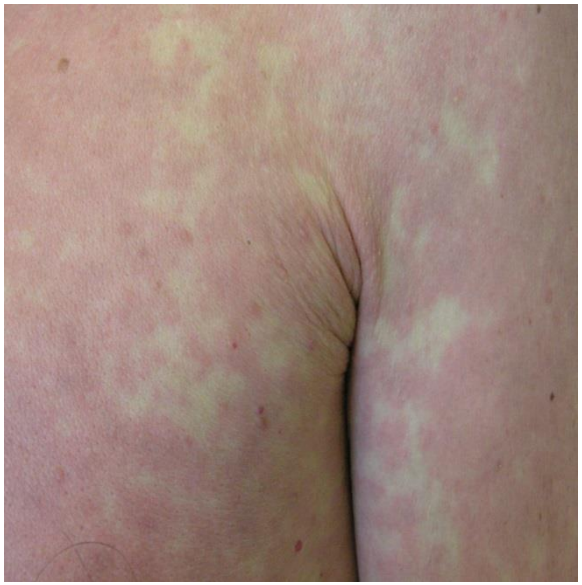
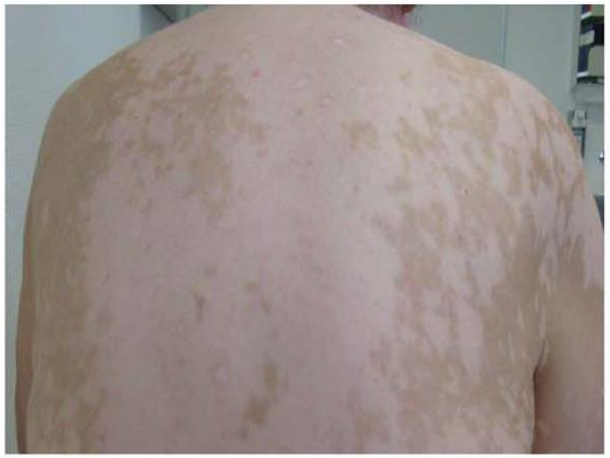
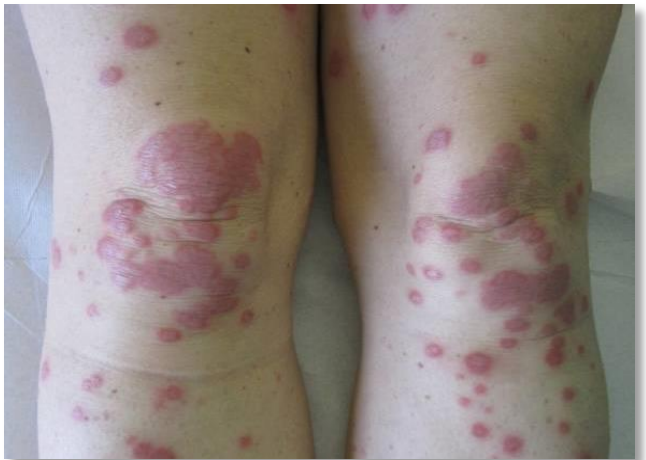








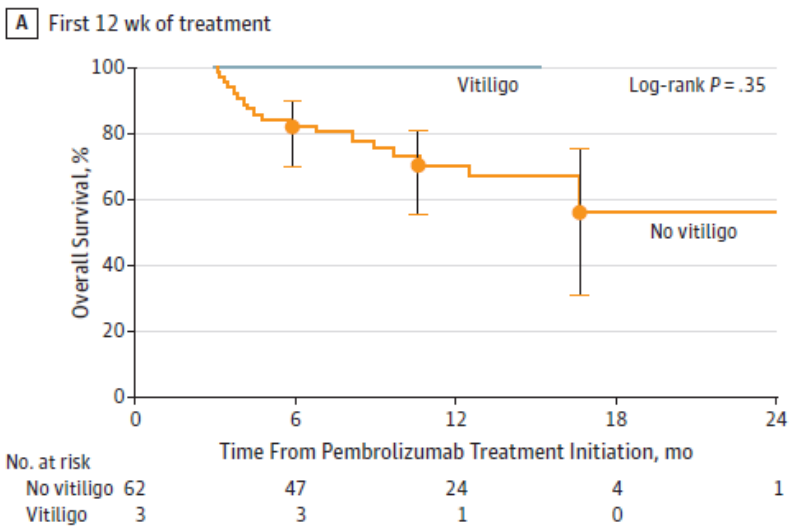


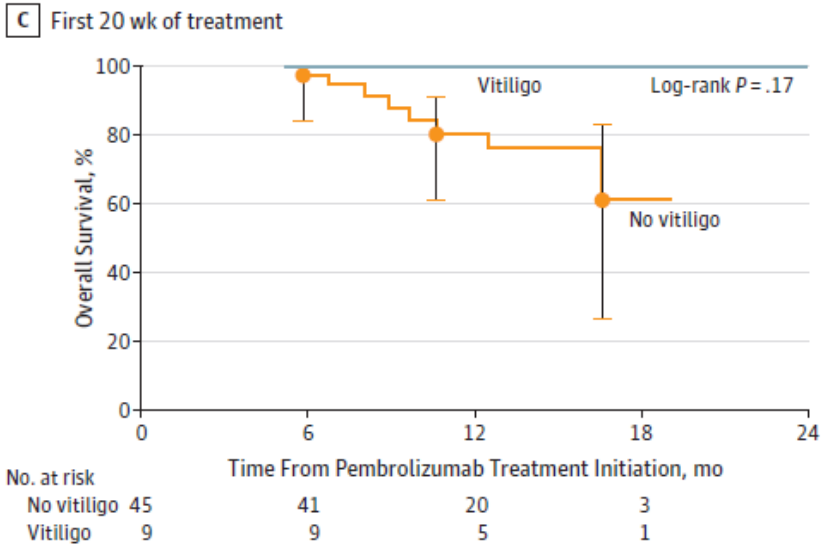


Vitiligo and clinical response to pembrolizumab

Patient	CR	PR	SD	PD	p*
Vitiligo (N=17)	3 (18)	9 (53)	3 (18)	2 (12)	0.002
Non vitiligo (N=50)	4 (8)	10 (20)	1 (2)	35 (70)	
Total (N=67)	7 (10)	19 (28)	4 (6)	36 (54)	

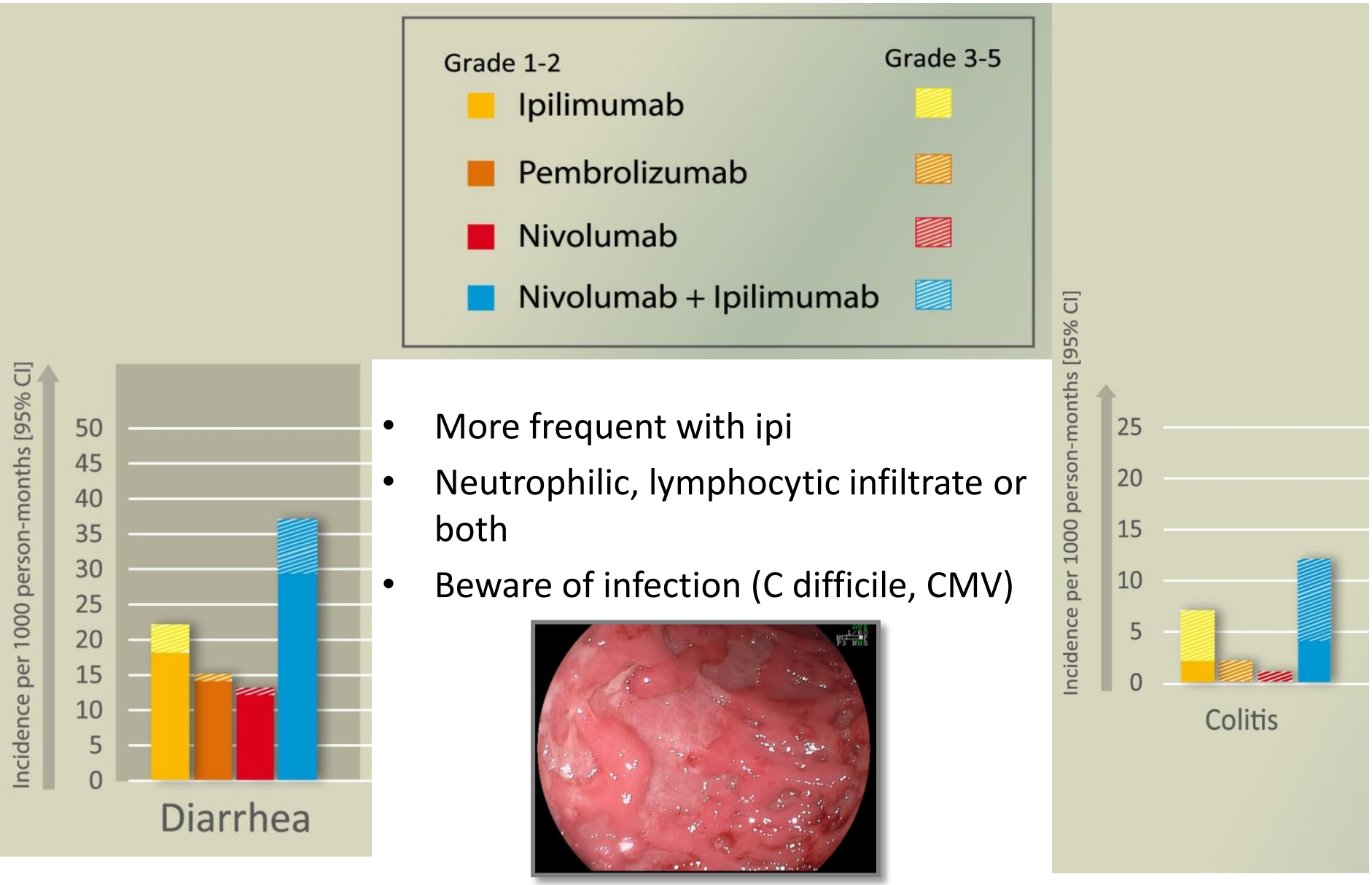
***Complete/partial response versus stable/ progressive disease/progression progression in patients disease/progression in patients with and without vitiligo, exact fisher test**





Hua et al JAMA Dermatol 20015

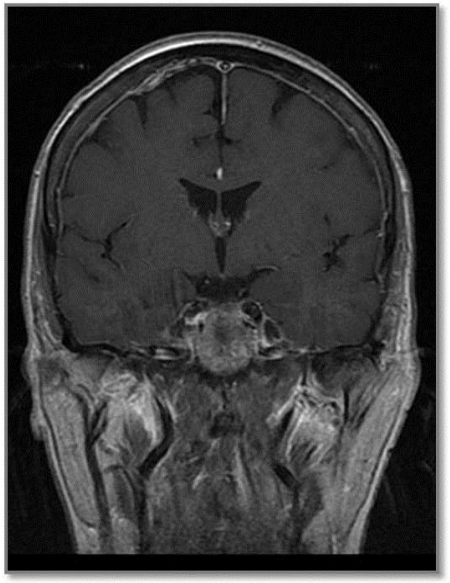
Diarhhea/colitis

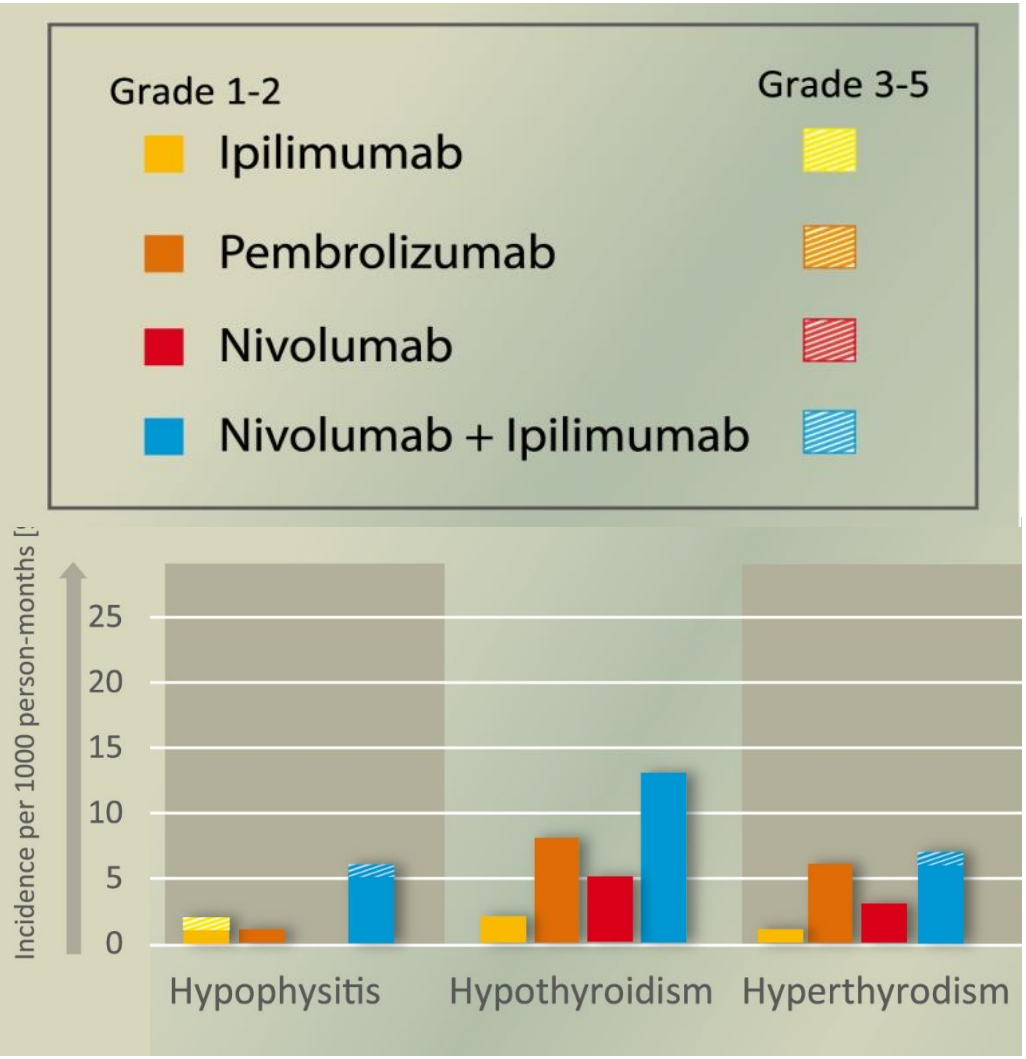


- More frequent with ipi
- Neutrophilic, lymphocytic infiltrate or both
- Beware of infection (C difficile, CMV)

Boutros et al Submitted

Endocrine AE

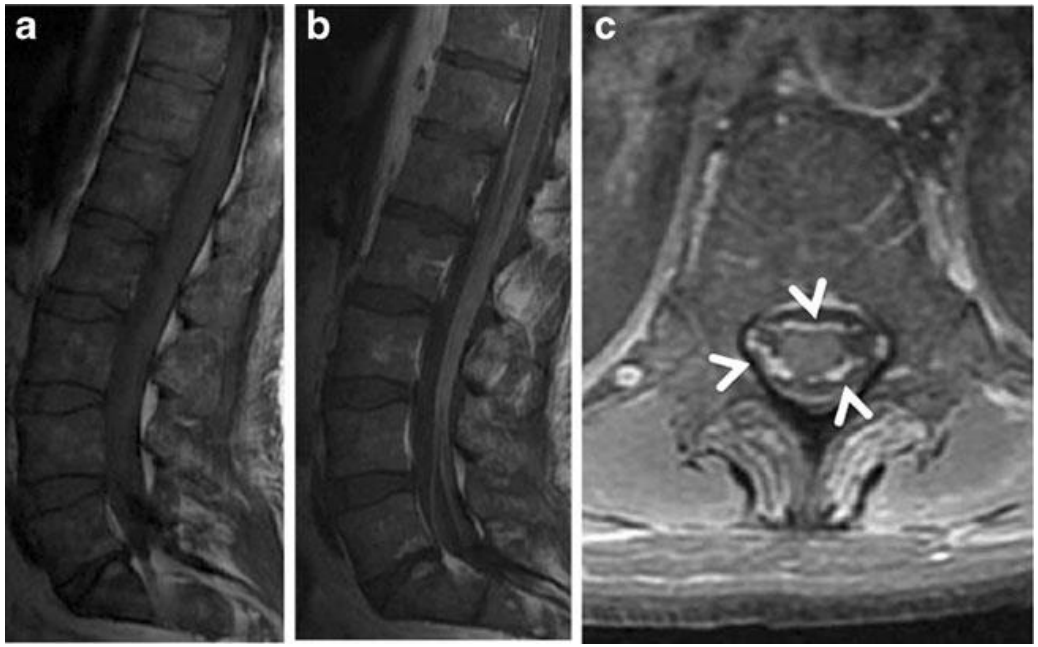




- Dysthyroidisms more frequent with anti-PD-1 than CTLA-4
- Hyper frequently precedes hypothyroidisms
- Hypophysitis induces pan or partial hypopituitaris, more frequent with anti-CTLA-4
- Long lasting AE requiring replacement therapy

Be aware of Rare and serious AE

- 56 year old man
- Anti-CTLA4 adjuvant for resected stage III disease
- One week after last ipi infusion progressive severe meningo-radiculo-nevritis with increased CD4+ Th1 and Th17 T cells in CSF
- HD steroids and iv-Ig
- Recovery after 2 years



Bompaire et al Invest New drugs 2012

General algorithm