Toxicity of immunotherapies with anti-CTLA-4 and anti-PD-1

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Drugs

- Anti-CTLA-4 ipilimumab
- Anti-PD-1 nivolumab, pembrolizumab
- Combination of ipilimumab + nivolumab

Adverse Event	Ipilimumab plus gp100 (N = 380)			Ipilimumab Alone (N = 131)			gp100 Alone (N = 132)		
	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4
	number of patients (percent)								
Any event	374 (98.4)	147 (38.7)	26 (6.8)	127 (96.9)	49 (37.4)	11 (8.4)	128 (97.0)	54 (40.9)	8 (6.1)
Any drug-related event	338 (88.9)	62 (16.3)	4 (1.1)	105 (80.2)	25 (19.1)	5 (3.8)	104 (78.8)	15 (11.4)	0
Gastrointestinal disorders									
Diarrhea	146 (38.4)	16 (4.2)	1 (0.3)	43 (32.8)	7 (5.3)	0	26 (19.7)	1 (0.8)	0
Nausea	129 (33.9)	5 (1.3)	1 (0.3)	46 (35.1)	3 (2.3)	0	52 (39.4)	3 (2.3)	0
Constipation	81 (21.3)	3 (0.8)	0	27 (20.6)	3 (2.3)	0	34 (25.8)	1 (0.8)	0
Vomiting	75 (19.7)	6 (1.6)	1 (0.3)	31 (23.7)	3 (2.3)	0	29 (22.0)	3 (2.3)	0
Abdominal pain	67 (17.6)	6 (1.6)	0	20 (15.3)	2 (1.5)	0	22 (16.7)	6 (4.5)	1 (0.8)
Other									
Fatigue	137 (36.1)	19 (5.0)	0	55 (42.0)	9 (6.9)	0	41 (31.1)	4 (3.0)	0
Decreased appetite	88 (23.2)	5 (1.3)	1 (0.3)	35 (26.7)	2 (1.5)	0	29 (22.0)	3 (2.3)	1 (0.8)
Pyrexia	78 (20.5)	2 (0.5)	0	16 (12.2)	0	0	23 (17.4)	2 (1.5)	0
Headache	65 (17.1)	4 (1.1)	0	19 (14.5)	3 (2.3)	0	19 (14.4)	3 (2.3)	0
Cough	55 (14.5)	1 (0.3)	0	21 (16.0)	0	0	18 (13.6)	0	0
Dyspnea	46 (12.1)	12 (3.2)	2 (0.5)	19 (14.5)	4 (3.1)	1 (0.8)	25 (18.9)	6 (4.5)	0
Anemia	41 (10.8)	11 (2.9)	0	15 (11.5)	4 (3.1)	0	23 (17.4)	11 (8.3)	0
Any immune-related event	221 (58.2)	37 (9.7)	2 (0.5)	80 (61.1)	16 (12.2)	3 (2.3)	42 (31.8)	4 (3.0)	0
Dermatologic	152 (40.0)	8 (2.1)	1 (0.3)	57 (43.5)	2 (1.5)	0	22 (16.7)	0	0
Pruritus	67 (17.6)	1 (0.3)	0	32 (24.4)	0	0	14 (10.6)	0	0
Rash	67 (17.6)	5 (1.3)	0	25 (19.1)	1 (0.8)	0	6 (4.5)	0	0
Vitiligo	14 (3.7)	0	0	3 (2.3)	0	0	1 (0.8)	0	0
Gastrointestinal	122 (32.1)	20 (5.3)	2 (0.5)	38 (29.0)	10 (7.6)	0	19 (14.4)	1 (0.8)	0
Diarrhea	115 (30.3)	14 (3.7)	0	36 (27.5)	6 (4.6)	0	18 (13.6)	1 (0.8)	0
Colitis	20 (5.3)	11 (2.9)	1 (0.3)	10 (7.6)	7 (5.3)	0	1 (0.8)	0	0
Endocrine	15 (3.9)	4 (1.1)	0	10 (7.6)	3 (2.3)	2 (1.5)	2 (1.5)	0	0
Hypothyroidism	6 (1.6)	1 (0.3)	0	2 (1.5)	0	0	2 (1.5)	0	0
Hypopituitarism	3 (0.8)	2 (0.5)	0	3 (2.3)	1 (0.8)	1 (0.8)	0	0	0
Hypophysitis	2 (0.5)	2 (0.5)	0	2 (1.5)	2 (1.5)	0	0	0	0
Adrenal insufficiency	3 (0.8)	2 (0.5)	0	2 (1.5)	0	0	0	0	0

Hodi et al NEJM 2010

Adverse Event	Ipilimumab plus Dacarbazine (N=247)			Placebo plus Dacarbazine (N=251)		
	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4
	number of patients (percent)					
All adverse events, regardless of cause†						
Any event	244 (98.8)	99 (40.1)	40 (16.2)	236 (94.0)	45 (17.9)	24 (9.6)
Gastrointestinal: diarrhea	90 (36.4)	10 (4.0)	0	62 (24.7)	0	0
Dermatologic						
Pruritus	73 (29.6)	5 (2.0)	0	22 (8.8)	0	0
Rash	61 (24.7)	3 (1.2)	0	17 (6.8)	0	0
Hepatic						
Increase in alanine aminotransferase	82 (33.2)	40 (16.2)	14 (5.7)	14 (5.6)	2 (0.8)	0
Increase in aspartate aminotransferase	72 (29.1)	36 (14.6)	9 (3.6)	14 (5.6)	3 (1.2)	0
Other						
Pyrexia	91 (36.8)	0	0	23 (9.2)	0	0
Chills	28 (11.3)	0	0	10 (4.0)	0	0
Weight loss	27 (10.9)	1 (0.4)	0	13 (5.2)	1 (0.4)	0
Immune-related adverse events						
Any event	192 (77.7)	78 (31.6)	25 (10.1)	96 (38.2)	8 (3.2)	7 (2.8)
Dermatologic						
Pruritus	66 (26.7)	5 (2.0)	0	15 (6.0)	0	0
Rash	55 (22.3)	3 (1.2)	0	12 (4.8)	0	0
Gastrointestinal						
Diarrhea	81 (32.8)	10 (4.0)	0	40 (15.9)	0	0
Colitis	11 (4.5)	4 (1.6)	1 (0.4)	0	0	0
Hepatic‡						
Increase in alanine aminotransferase	72 (29.1)	37 (15.0)	14 (5.7)	11 (4.4)	2 (0.8)	0
Increase in aspartate aminotransferase	66 (26.7)	34 (13.8)	9 (3.6)	8 (3.2)	1 (0.4)	0
Hepatitis	4 (1.6)	3 (1.2)	0	0	0	0

Robert et al NEJM 2011

Summary of Exposure[a] and Treatment-Related AEs by Prior IPI

	IPI-N n = 190	IPI-T n = 221	Total N = 411
Time on therapy, weeks, mean (range)	34 (0.1-97)	28 (0.1-90)	30 (0.1-97)
Number of doses, median (range)	11 (1-47)	9 (1-46)	10 (1-47)
Grade 3-5 treatment-related AE, n (%)	26 (14)	25 (11)	51 (12)
Serious treatment-related AE, n (%)	20 (11)	12 (5)	32 (8)
Treatment-related AE leading to discontinuation, n (%)	7 (4)	10 (5)	17 (4)
Treatment-related death, n (%)	0 (0)	0 (0)	0 (0)

[a]Patients were treated with 10 mg/kg Q2W, 10 mg/kg Q3W, or 2 mg/kg Q3W.
Analysis cut-off date: October 18, 2013.

Presented by: Antoni Ribas

Treatment-Related AEs With Incidence >5%

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

- No treatment-related deaths
- Similar safety profiles in IPI-N and IPI-T patients

Analysis cut-off date: October 18, 2013.

Presented by: Antoni Ribas

Pembrolizumab: Immune-Mediated Adverse Events

Adverse Event	Any Grade, n (%)	Grade 3-4, n (%)
Hypothyroidism	32 (8)	1 (<1)
Hyperthyroidism	4 (1)	1 (<1)
Pneumonitis*	11 (3)	1 (<1)
Colitis	3 (<1)	2 (<1)
Hepatitis†	2 (<1)	1 (<1)

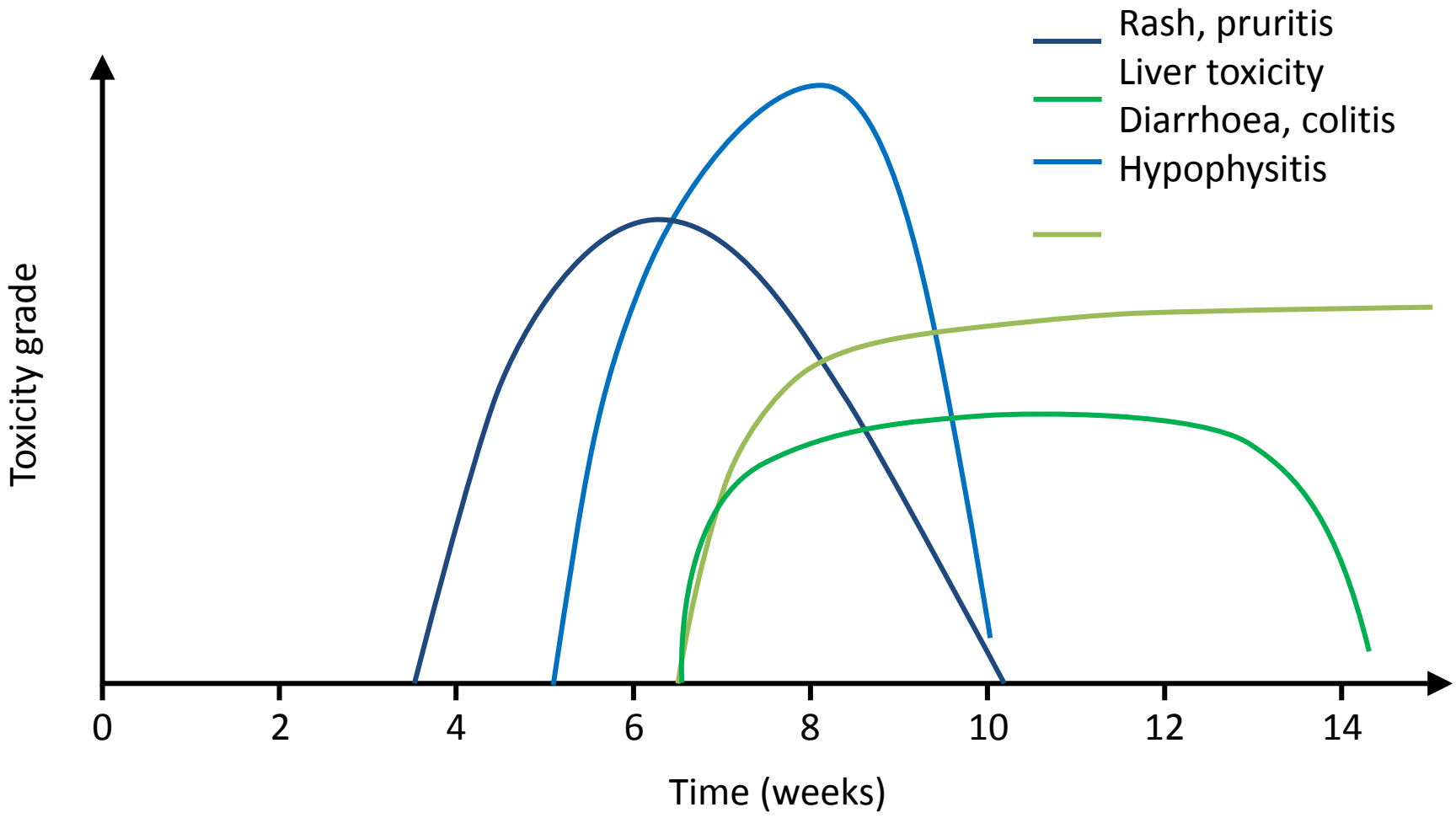
Nivolumab
Select Drug-Related Adverse Events

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)

Nivolumab + Ipilimumab

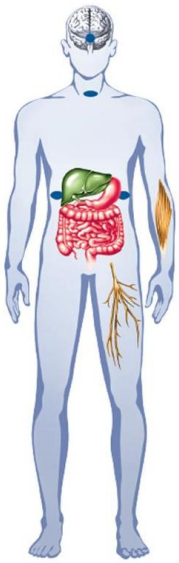
Adverse events	Concurrent Cohorts 1-3, % (n=53)		Cohort 8, % (n=41)		All Concurrent, % (n=94)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
All related AEs	96	62	95	61	96	62
Select AEs						
Gastrointestinal	43	9	34	20	39	14
Hepatic	30	15	12	12	22	14
Skin	79	4	73	15	77	9
Endocrine	17	4	22	2	19	3
Renal	6	6	0	0	3	3
Other						
Uveitis	6	4	2	2	4	3
Pneumonitis	6	2	2	2	4	2
Lipase increased	26	19	15	10	21	15
Amylase increased	21	6	12	7	17	6

Ipi: Kinetics of irAEs



Weber et al. JCO 2012; published ahead of print

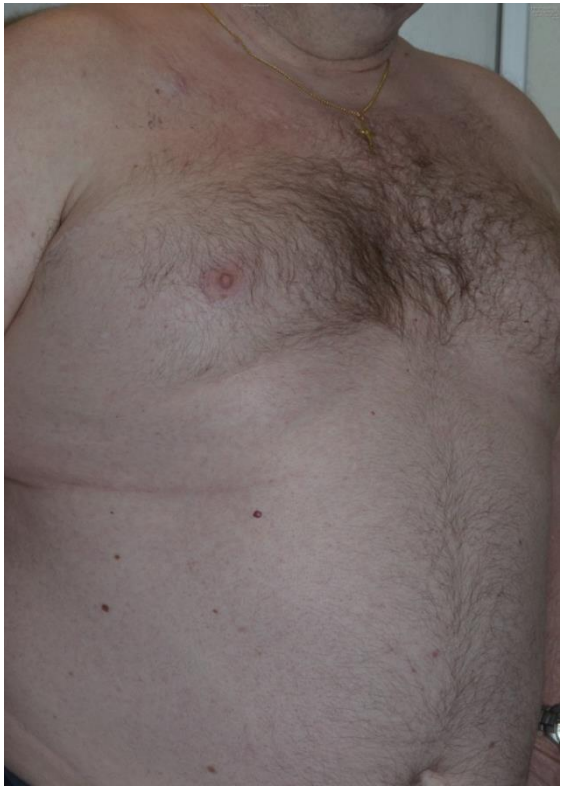
Treatment Guidelines

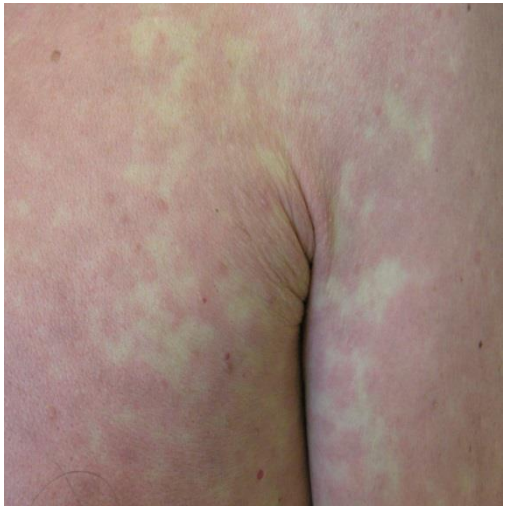


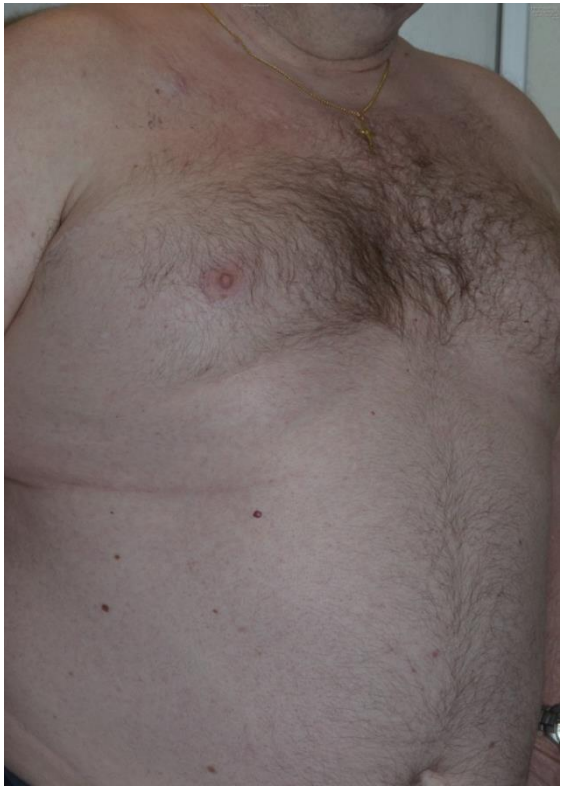
Mild	• Treat symptomatically
Persistent mild or moderate	• Treat with oral corticosteroids (prednisone 1mg/kg daily or equivalent) • Omit next dose of ipilimumab until symptoms resolve or return to baseline
Symptoms worsen, are severe, or life threatening	• Treat with high-dose IV corticosteroids (methylprednisolone 2mg/kg daily or equivalent) • If symptoms improve then consider a gradual steroid taper over at least 4 weeks • If symptoms do not respond within 5–7 days, consider alternative immunosuppressive therapies • Permanently discontinue ipilimumab

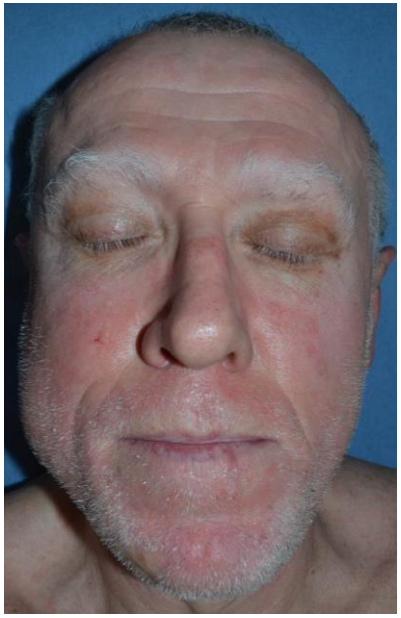
ipilimumab SmPC July 2011.

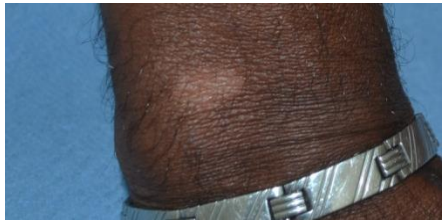
Skin AE

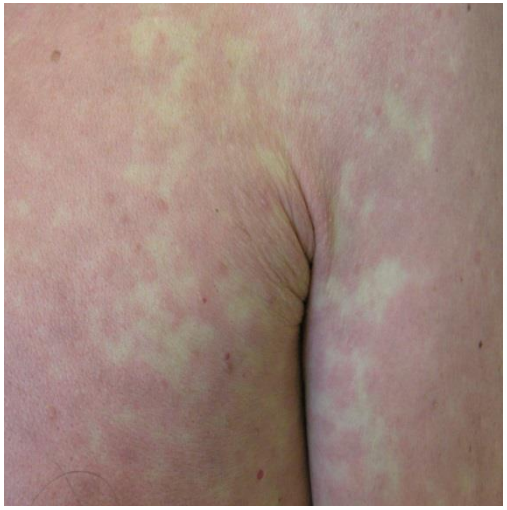


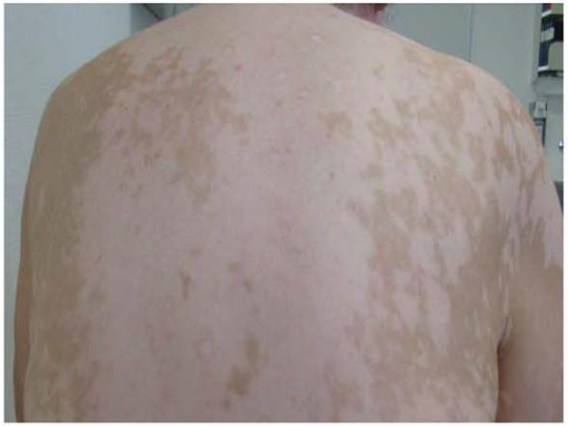


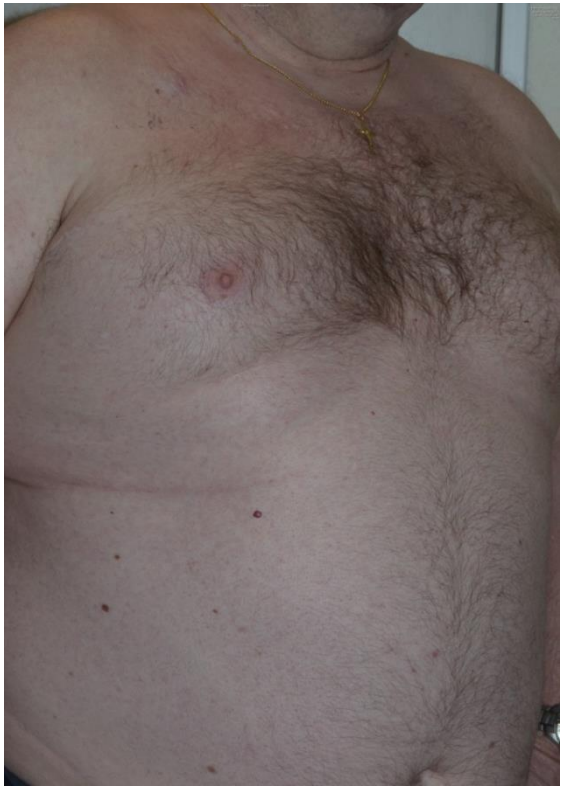


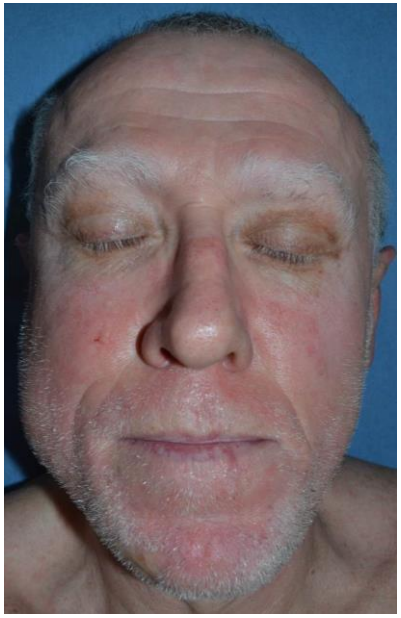


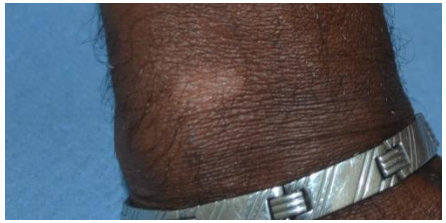


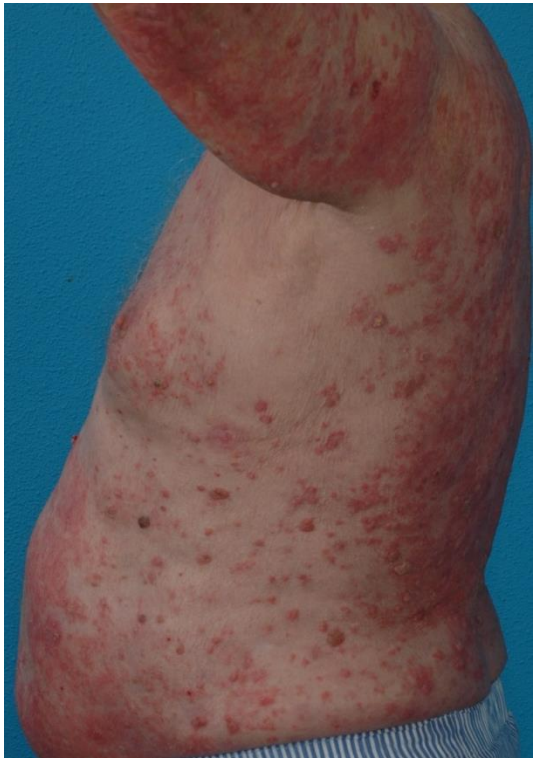


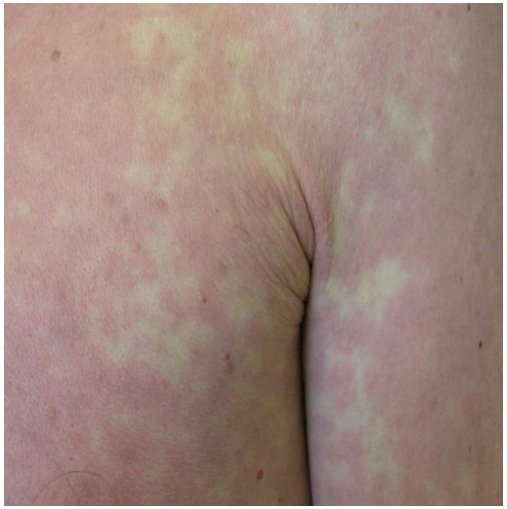


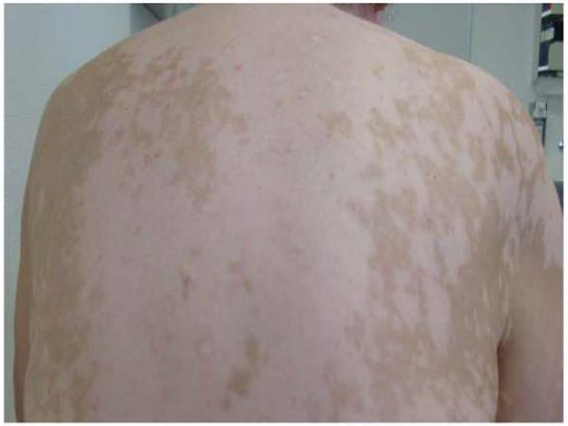


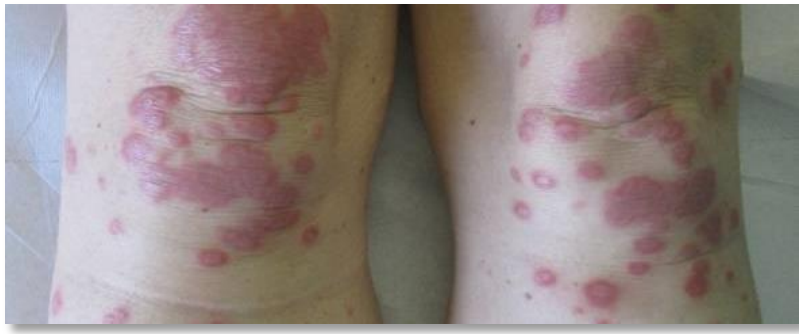






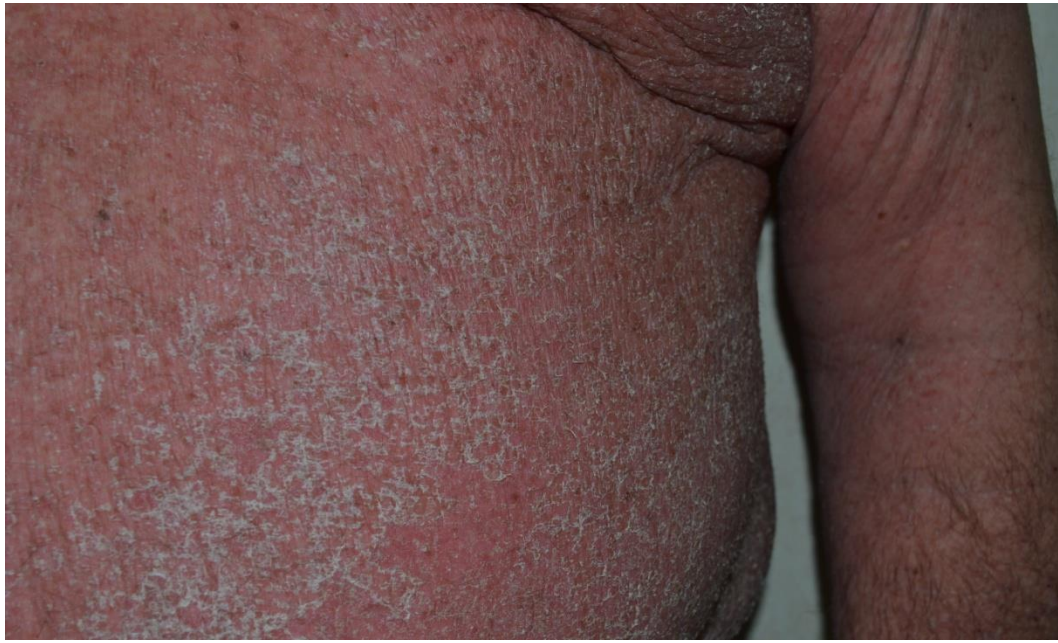




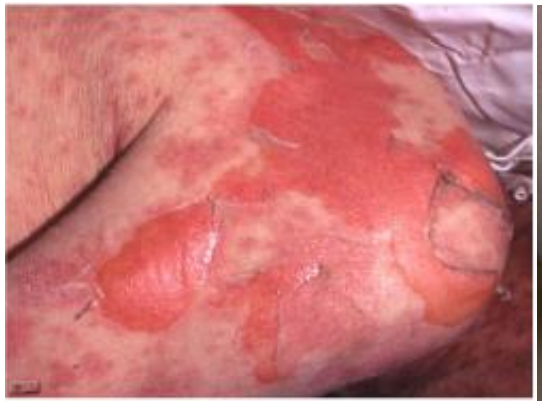


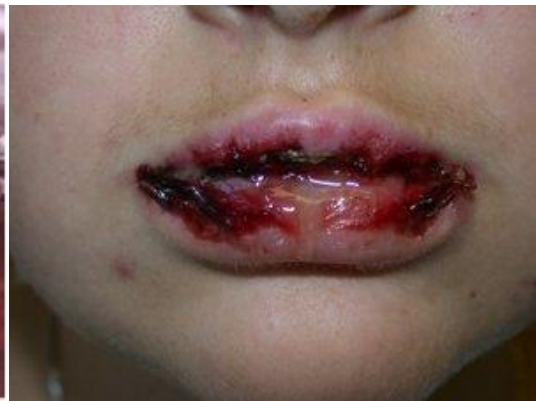
Severity evaluation: When to refer?

- DRESS: Drug Rash with Eosinophilia and Systemic Symptoms
  - Diffuse rash
  - Eosinophils > 1500
  - Systemic signs:
    - Fever +Lymphadenopathy
    - Hepatitis, nephritis, neurologic signs…

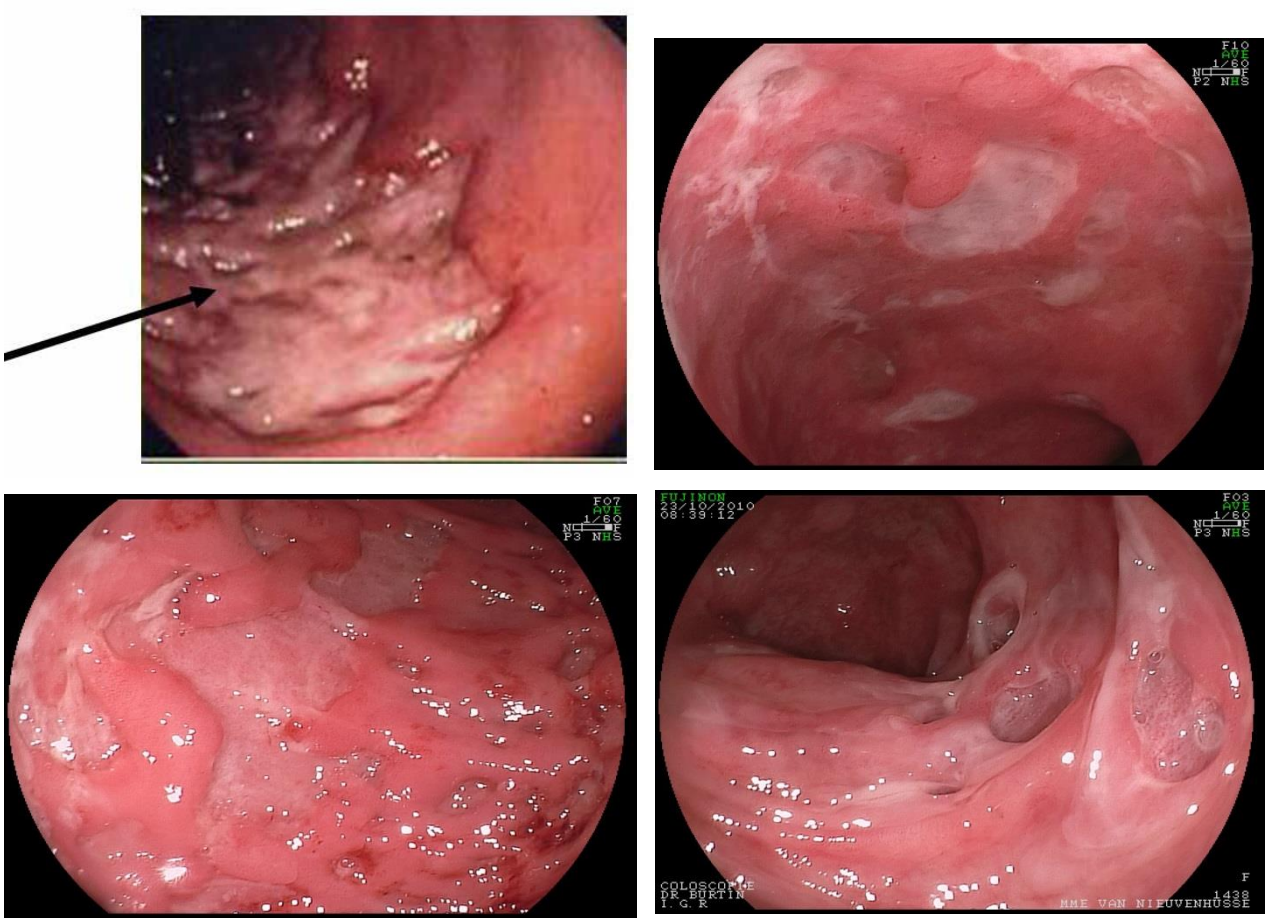


- SJS; TEN
  - Bullous lesions
  - Mucosal lesions
  - Systemic signs

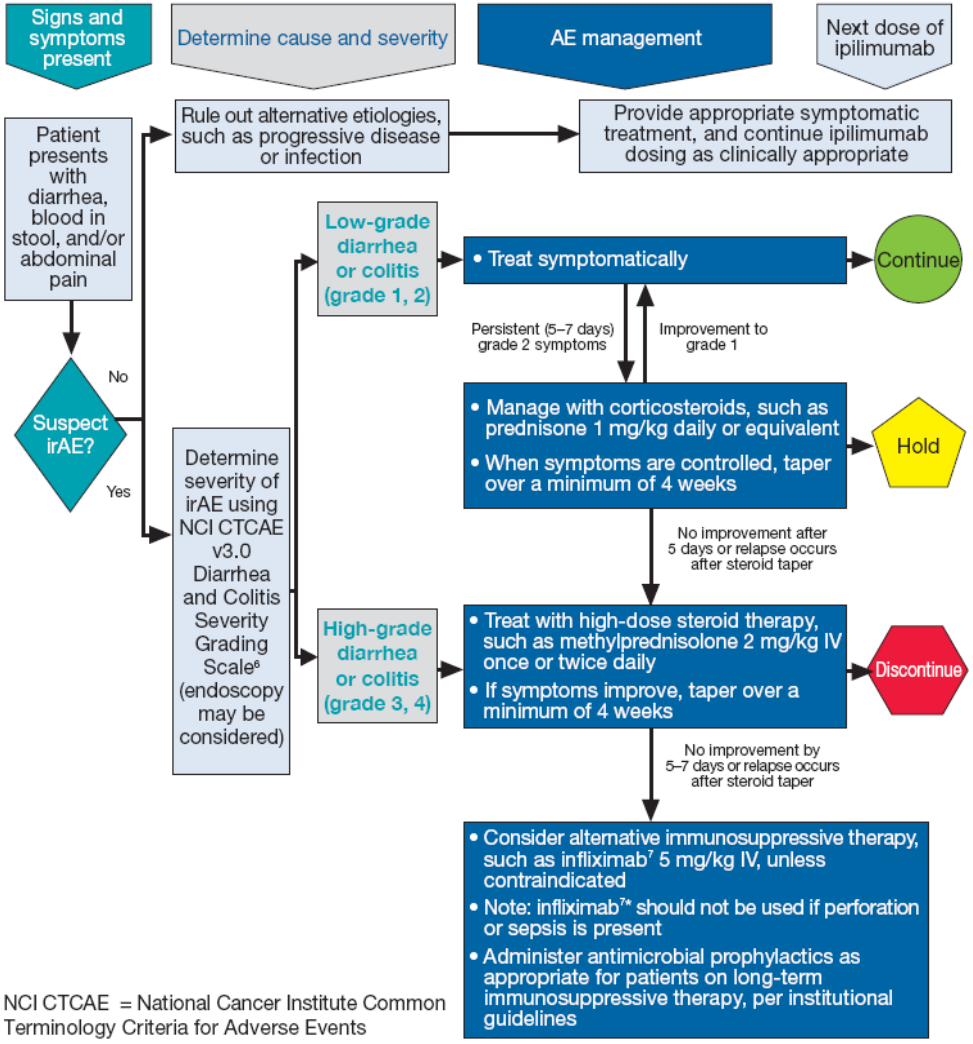




Colitis



Colitis Management Guidelines



Chin K et al. ESMO 2008, poster presentation Abstract #787P

Severity Evaluation
When to refer?

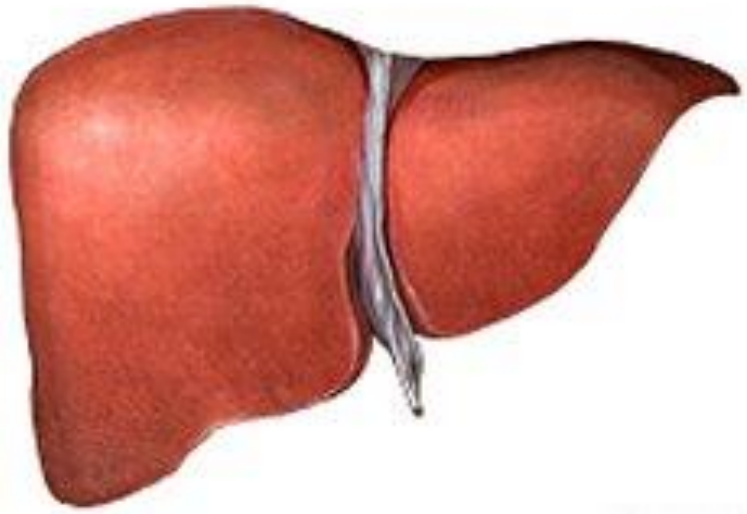
Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by frequent and watery bowel movements.					

Questions to identify patients requiring referral

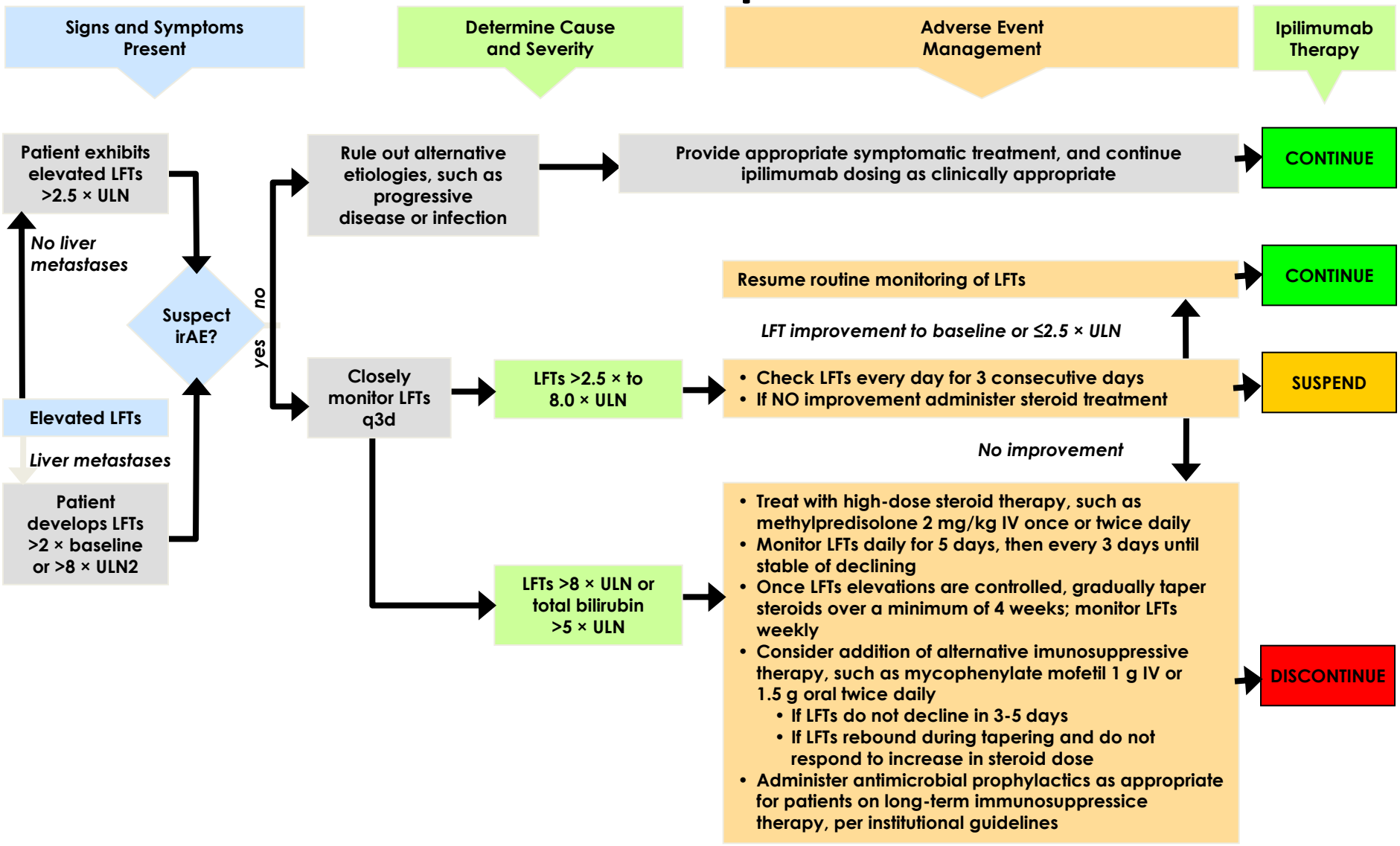
- Are they woken from sleep to defaecate?
- Do they have troublesome urgency of defaecation and /or faecal leakage/ soiling/incontinence?
- Do they have any GI symptoms preventing them from living a full life?

Jervoise Andreyev ESMO 2014

Hepato-related AE

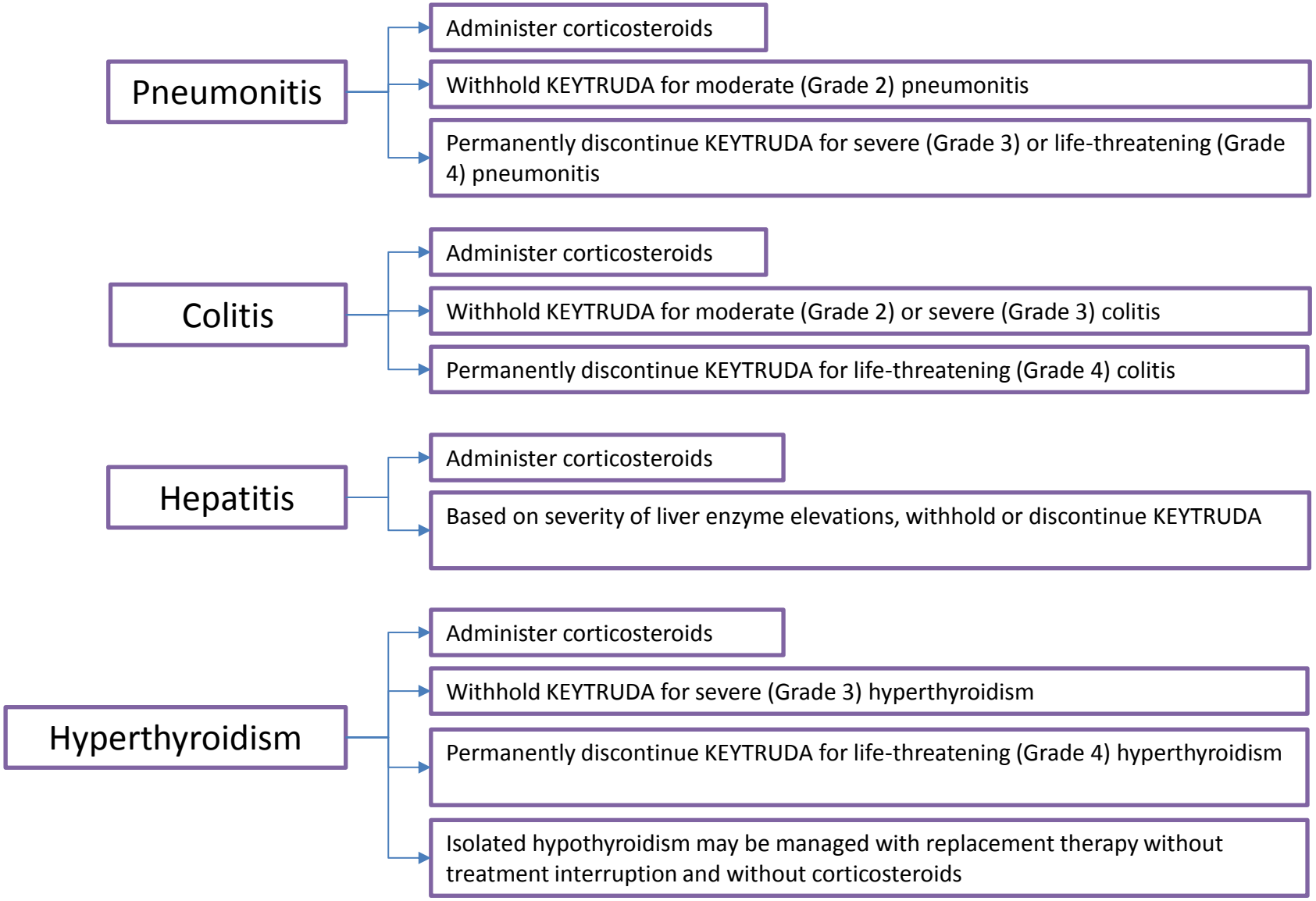


Guidelines for Hepato-related irAEs



BMS data on file, IB V12

KEYTRUDA Safety
irAEs Management Algorithms



KEYTRUDA (pembrolizumab)[package insert – United States]. Whitehouse Station, NJ: Merck & Co., Inc.; 2014.

Pembrolizumab: irAE Management Guidance

Adverse Reaction	Management Guidance			
	Grade 1	Grade 2	Grade 3	Grade 4
Pneumonitis	• Continue pembrolizumab with monitoring • If pneumonitis is suspected, evaluate with radiographic imaging	• Withhold pembrolizumab • Consider pulmonary consultation with bronchoscopy and biopsy, along with ID consult • Conduct an in-person evaluation approx. twice per week and consider frequent chest x-rays • Administer corticosteroids • Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month • Discontinue pembrolizumab if upon re-challenge patient develops a second episode of Grade 2 or higher pneumonitis	• Discontinue pembrolizumab • Consider pulmonary function tests with pulmonary consultation • Bronchoscopy with biopsy and/or BAL is recommended • Ireat with IV steroids; when symptoms improve to Grade 1 or less, administer oral steroids, then initiate taper over at least 1 month • Add prophylactic antibiotics for opportunistic infections • If IV steroids followed by oral steroids does not reduce initial symptoms within 48 to 72 hours, treat with infliximab at 5 mg/kg once every 2 weeks; discontinue upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days	
Colitis	• Supportive care • Continue treatment and monitor	• Withhold pembrolizumab • Administer corticosteroids • Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month	• Withhold pembrolizumab • Administer corticosteroids • Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month • Permanently discontinue pembrolizumab for any adverse reaction that recurs	• Discontinue pembrolizumab

Discontinue pembrolizumab if corticosteroid dose cannot be reduced to ≤10 mg prednisone or equivalent per day.
If a treatment-related toxicity does not resove to Grade 0-1 within 12 weeks after last dose of pembrolizumab, discontinue treatment.
Discontinue pembrolizumab if another episode of any severe toxicity occurs.

Pembrolizumab: irAE Management Guidance

Adverse Reaction	Management Guidance			
	Grade 1	Grade 2	Grade 3	Grade 4
Pneumonitis	• Continue pembrolizumab with monitoring • If pneumonitis is suspected, evaluate with radiographic imaging	• Withhold pembrolizumab • Consider pulmonary consultation with bronchoscopy and biopsy, along with ID consult • Conduct an in-person evaluation approx. twice per week and consider frequent chest x-rays	• Discontinue pembrolizumab • Consider pulmonary function tests with pulmonary consultation • Bronchoscopy with biopsy and/or BAL is recommended • Ireat with IV steroids; when symptoms improve to Grade 1 or less, administer oral steroids, then initiate taper over at least 1 month • Add prophylactic antibiotics for opportunistic infections • If IV steroids followed by oral steroids does not reduce initial symptoms within g/kg once every 2 weeks; discontinue ed steroid taper over 45 to 60 days	
Colitis	• Supportive care • Continue treatment and monitor	• Withhold pembrolizumab • Administer corticosteroids • Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month	• Withhold pembrolizumab • Administer corticosteroids • Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month • Permanently discontinue pembrolizumab for any adverse reaction that recurs	• Discontinue pembrolizumab

- Rule out infection immediately
- When to perform a lavage? How to interpret it?
- Are Chest-x rays really useful vs CT-scan?
- Anti-TNF?

Discontinue pembrolizumab if corticosteroid dose cannot be reduced to ≤10 mg prednisone or equivalent per day.
If a treatment-related toxicity does not resove to Grade 0-1 within 12 weeks after last dose of pembrolizumab, discontinue treatment.
Discontinue pembrolizumab if another episode of any severe toxicity occurs.

Pembrolizumab: irAE Management Guidance

Adverse Reaction	Management Guidance			
	Grade 1	Grade 2	Grade 3	Grade 4
Pneumonitis	• Continue pembrolizumab with monitoring • If pneumonitis is suspected, evaluate with radiographic imaging	• Withhold pembrolizumab • Consider pulmonary consultation with bronchoscopy and biopsy, along with ID consult • Conduct an in-person evaluation approx. twice per week and consider frequent chest x-rays • Administer corticosteroids • Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month • Discontinue pembrolizumab if upon re-challenge patient develops a second episode of Grade 2 or higher pneumonitis	• Discontinue pembrolizumab • Consider pulmonary function tests with pulmonary consultation • Bronchoscopy with biopsy and/or BAL is recommended • Ireat with IV steroids; when symptoms improve to Grade 1 or less, administer oral steroids, then initiate taper over at least 1 month • Add prophylactic antibiotics for opportunistic infections • If IV steroids followed by oral steroids does not reduce initial symptoms within 48 to 72 hours, treat with infliximab at 5 mg/kg once every 2 weeks; discontinue upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days	
Colitis	• Supportive care • Continue treatment and monitor	• Withhold pembrolizumab • Administer corticosteroids • Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month	• Withhold pembrolizumab • Administer corticosteroids • Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month • Permanently discontinue pembrolizumab for any adverse reaction that recurs	• Discontinue pembrolizumab

Discontinue pembrolizumab if corticosteroid dose cannot be reduced to ≤10 mg prednisone or equivalent per day.
If a treatment-related toxicity does not resove to Grade 0-1 within 12 weeks after last dose of pembrolizumab, discontinue treatment.
Discontinue pembrolizumab if another episode of any severe toxicity occurs.

Pembrolizumab: irAE Management Guidance

Adverse Reaction	Management Guidance			
	Grade 1	Grade 2	Grade 3	Grade 4
Pneumonitis	• Continue pembrolizumab with monitoring • If pneumonitis is suspected, evaluate with radiographic imaging	• Withhold pembrolizumab • Consider pulmonary consultation with bronchoscopy and biopsy, along with ID consult • Conduct an in-person evaluation approx. twice per week and consider frequent chest x-rays • Administer corticosteroids • Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month • Discontinue pembrolizumab if upon re-challenge patient develops a second episode of Grade 2 or higher pneumonitis	• Discontinue pembrolizumab • Consider pulmonary function tests with pulmonary consultation • Bronchoscopy with biopsy and/or BAL is recommended • Ireat with IV steroids; when symptoms improve to Grade 1 or less, administer oral steroids, then initiate taper over at least 1 month • Add prophylactic antibiotics for opportunistic infections • If IV steroids followed by oral steroids does not reduce initial symptoms within 48 to 72 hours, treat with infliximab at 5 mg/kg once every 2 weeks; discontinue upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days	
	• Supportive care	• Withhold pembrolizumab	• Withhold pembrolizumab pembrolizumab for any adverse reaction that recurs	• Discontinue pembrolizumab

- Monitoring K+ and Mg+ blood level
- Do we sometimes need anti-TNF?
- Can we prescribe pembro in a pt with an history of ipi-induced severe colitis?

Discontinue pembrolizumab if corticosteroid dose cannot be reduced to ≤10 mg prednisone or equivalent per day.
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Pembrolizumab: irAE Management Guidance

Adverse Reaction	Management Guidance			
	Grade 1	Grade 2	Grade 3	Grade 4
Hepatitis	• Monitor liver function tests more frequently (consider weekly)	• Withhold pembrolizumab for AST or ALT >3 to 5 times ULN and/or total bilirubin >1.5 to 3 times ULN • Administer corticosteroids • Monitor liver function tests more frequently (consider weekly) • Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month • Discontinue pembrolizumab for patients with liver metastases who begin treatment with moderate (Grade 2) elevation of AST or ALT, and AST or ALT increases ≥50% relative to baseline and lasts ≥1 week	• Discontinue pembrolizumab when AST or ALT >5 times ULN and/or total bilirubin >3 times ULN • Consider appropriate consultation and liver biopsy to establish etiology of hepatic injury • Administer corticosteroids • Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month	• Discontinue pembrolizumab • Consider appropriate consultation and liver biopsy to establish etiology of hepatic injury • Administer corticosteroids • Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month
Hyperthyroidism	• For symptomatic hyperthyroidism, prescribe beta-blockers	• Administer corticosteroids • Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month	• Withhold pembrolizumab • Administer corticosteroids • Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month • Permanently discontinue pembrolizumab for any adverse reaction that recurs	• Discontinue pembrolizumab • Administer corticosteroids • Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month

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Rule out virus infection
Biopsy important

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Does early corticotherapy decrease the risk of secondary hypothyroidism?

1

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Discontinue pembrolizumab if another episode of any severe toxicity occurs.

Pembrolizumab: Managing Select Adverse Events

Adverse Reaction	Management Guidance			
	Grade 1	Grade 2	Grade 3	Grade 4

Diarrhea	• Mild diarrhea can be treated with electrolytes, rehydration, and loperamide	• Withhold pembrolizumab
		• Provide symptomatic treatment
		• For Grade 2 diarrhea that persists >1 week, and for diarrhea with blood and/or mucus:
		  • Consider GI consultation and endoscopy to rule out colitis
		  • Administer oral corticosteroids
		• If symptoms worsen or persist >3 days, treat as Grade 3
			• Withhold pembrolizumab
			• Consider GI consultation and endoscopy to rule out colitis
			• Administer corticosteroids
			• Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month
				• Withhold pembrolizumab
				• GI consultation and endoscopy
				• Treat with IV steroids, followed by high dose oral steroids
				• If symptoms persist, administer additional anti-inflammatory drugs

Fatigue	• Nonpharmacologic interventions: Energy conservation; physical therapist referral for patients with comorbidities, recent major surgery, specific functional/anatomical deficits, substantial deconditioning; psychosocial interventions; nutritional consultation; sleep therapy. Limit naps to less than 1 hour; distractions (games, music, reading, socializing, etc.). Labor-saving techniques to not exhaust energy. Encourage moderate level of physical activity • Pharmacologic interventions: Consider psychostimulants (methylphenidate or modanfinil) after ruling out other causes. Treat for pain, emotional distress, and anemia as indicated. Optimize treatment for sleep dysfunction, nutritional deficiency, and comorbidities			• Discontinue pembrolizumab
Renal	• Supportive care • Continue treatment and monitor	• Withhold pembrolizumab • Administer corticosteroids • Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month	• Discontinue pembrolizumab • Renal consultation with consideration of ultrasound and/or biopsy as appropriate • Administer corticosteroids • Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month	

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Pembrolizumab: Managing Select Adverse Events

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		  • Consider GI consultation and endoscopy to rule out colitis
		  • Administer oral corticosteroids
		• If symptoms worsen or persist >3 days, treat as Grade 3
			• Withhold pembrolizumab
			• Consider GI consultation and endoscopy to rule out colitis
			• Administer corticosteroids
			• Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month
				• Withhold pembrolizumab
				• GI consultation and endoscopy
				• Treat with IV steroids, followed by high dose oral steroids
				• If symptoms persist, administer additional anti-inflammatory drugs

Fatigue	• Nonpharmacologic interventions: Energy conservation; physical therapist referral for patients with comorbidities, recent major surgery, specific functional/anatomical deficits, substantial deconditioning; psychosocial interventions; nutritional consultation; sleep therapy. Limit naps to less than 1 hour; distractions (games, music, reading, socializing, etc.). Labor- activity • Pharmacologic interventions: Co causes. Treat for pain, emotional distress, and anemia as indicated. Optimize treatment for sleep dysfunction, nutritional deficiency, and comorbidities			• Discontinue pembrolizumab
Renal	• Supportive care • Continue treatment and monitor	• Withhold pembrolizumab • Administer corticosteroids • Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month	• Discontinue pembrolizumab • Renal consultation with consideration of ultrasound and/or biopsy as appropriate • Administer corticosteroids • Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month	

Can we administer low dose steroids?

Discontinue pembrolizumab if corticosteroid dose cannot be reduced to ≤10 mg prednisone or equivalent per day.
If a treatment-related toxicity does not resove to Grade 0-1 within 12 weeks after last dose of pembrolizumab, discontinue treatment.
Discontinue pembrolizumab if another episode of any severe toxicity occurs.

How to monitor and manage anti-PD-1 associated thyroiditis?

- Thyrotoxicosis (Don't forget Graves hyperthyroidism!)
  - Thyroid uptake test and/or TSI (thyroid stimulating immunoglubulin).
  - Monitor TSH, T4 and T3 every 2-3 weeks.
  - Treat with Beta-blocker if young and no heart disease. Consider high dose glucocorticoids in patients with CAD and arhythmia.
- Overt hypothyroidism,
  - start levothyroxine replacement.
    - If patient has both adrenal insufficiency and hypothyroidism, replace with hydrocortisone for 2-3 days before initiating levothyroxine
    - Elderly patients or patients with heart diseases, start low and increase slow

Pembrolizumab: Managing Select Adverse Events

Adverse Reaction	Management Guidance			
	Grade 1	Grade 2	Grade 3	Grade 4
Infusion-related reaction	• Increase monitoring of vital signs as appropriate until the patient is deemed stable	• Stop infusion of pembrolizumab • Additional appropriate medical therapy may include IV fluids, antihistamines, NSAIDS, acetaminophen, narcotics • Increase monitoring of vital signs as appropriate until the patient is deemed stable • If symptoms resolve within 1 hour of stopping infusion, restart at 50% the original infusion rate; otherwise, hold dosing until symptoms resolve or the next scheduled dose	• Discontinue pembrolizumab • Additional appropriate medical therapy may include IV fluids, antihistamines, NSAIDS, acetaminophen, narcotics, oxygen, pressors, corticosteroids, epinephrine • Increase monitoring of vital signs as appropriate until the patient is deemed stable	
Nausea	• Proton pump inhibitors and histamine-2 (H2) receptor antagonists; dopamine receptor antagonists or benzodiazapines (anxiety-related nausea) • For persistent nausea, titrating dopamine receptor antagonists • Consider adding 5-HT3 receptor antagonists and/or anticholinergic agents and/or antihistimines, corticosteroids, continuous or subcutaneous infusion of antiemetics, antipsychotics, and/or cannabinoids		• Discontinue pembrolizumab for any adverse reaction that recurs	• Discontinue pembrolizumab
Pruritis/Rash	• Topical corticosteroids such as 0.1% betamethasone, urea-based topical lotions and oral antipruritic agents	• Topical corticosteroids such as 0.1% betamethasone, urea-based topical lotions and oral antipruritic agents • Oral steroids may be considered	• Withhold pembrolizumab • Consider dermatology consultation and biopsy for confirmation of diagnosis • Administer corticosteroids • Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month	• Discontinue pembrolizumab • Dermatology consultation and consideration of biopsy and clinical dermatology photograph • Administer corticosteroids • Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month

Discontinue pembrolizumab if corticosteroid dose cannot be reduced to ≤10 mg prednisone or equivalent per day.
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Pembrolizumab: Managing Select Adverse Events

Adverse Reaction	Management Guidance			
	Grade 1	Grade 2	Grade 3	Grade 4
Neuropathy	• Supportive care	• Consider withholding pembrolizumab • Administer corticosteroids • Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month • Consider Neurology consultation and biopsy	• Discontinue pembrolizumab • Administer corticosteroids • Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month • Obtain Neurology consultation and biopsy for confirmation of diagnosis	
Hypothyroidism	• Frequently monitor thyroid function and hormone levels	• Frequently monitor thyroid function and hormone levels • Consider consultation with endocrinologist • Continue pembrolizumab therapy while treating thyroid disorder • Treat with thyroid hormone and/or steroid replacement therapy	• Withhold pembrolizumab • Treat with IV methylprednisolone followed by oral prednisone • Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month • Replacement of appropriate hormones may be required as the steroid dose is tapered	• Discontinue pembrolizumab • Consider endocrine consultation • Rule out infection and sepsis with culture assay and imaging • Treat with IV methylprednisolone followed by oral prednisone • Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month • Replacement of appropriate hormones may be required as the steroid dose is tapered

Discontinue pembrolizumab if corticosteroid dose cannot be reduced to ≤10 mg prednisone or equivalent per day.
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Pembrolizumab: Managing Select Adverse Events

Adverse Reaction	Management Guidance			
	Grade 1	Grade 2	Grade 3	Grade 4
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Hypothyroidism	• Frequently monitor thyroid function and hormone levels	• Frequently monitor thyroid function and hormone levels • Consider consultation with disorder • Treat with thyroid hormone and/or steroid replacement therapy	• Withhold pembrolizumab • Treat with IV methylprednisolone followed by oral prednisone month • Replacement of appropriate hormones may be required as the steroid dose is tapered	• Discontinue pembrolizumab • Consider endocrine consultation • Rule out infection and sepsis with culture assay and imaging • Treat with IV methylprednisolone followed by oral prednisone • Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month • Replacement of appropriate hormones may be required as the steroid dose is tapered

Are steroids really useful?

Discontinue pembrolizumab if corticosteroid dose cannot be reduced to ≤10 mg prednisone or equivalent per day.
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Discontinue pembrolizumab if another episode of any severe toxicity occurs.

Management of Pneumonitis

Grade 1

- Anti-PD-1 can be continued with close monitoring

Grade 2 :

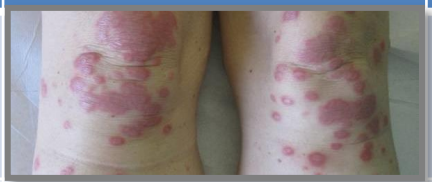
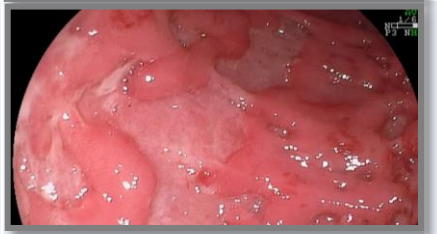
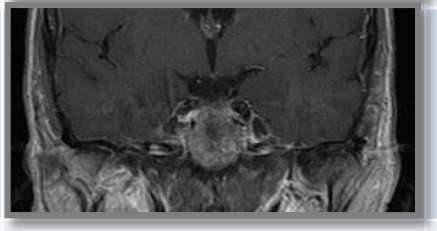
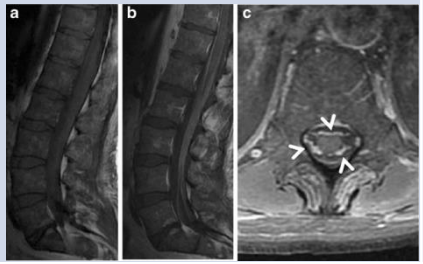
- Hold anti-PD-1 tt.
- Consider pulmonary consultation with bronchoscopy and biopsy/BAL, pulmonary function tests..
- Systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent.
- When back to Grade 1 or less, steroid taper over no less than 4 weeks.
- Anti-PD-1 may be resumed if the event improves to grade 0 or 1 within 12 weeks and corticosteroids have been reduced to the equivalent of methylprednisolone 10 mg po daily or less.

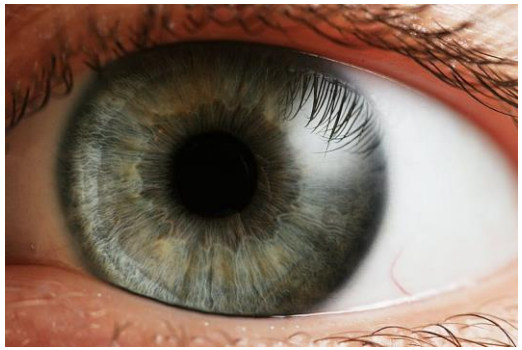
Second episode of pneumonitis – discontinue anti-PD-1 if upon rechallenge the patient develops a second episode of Grade 2 or higher pneumonitis

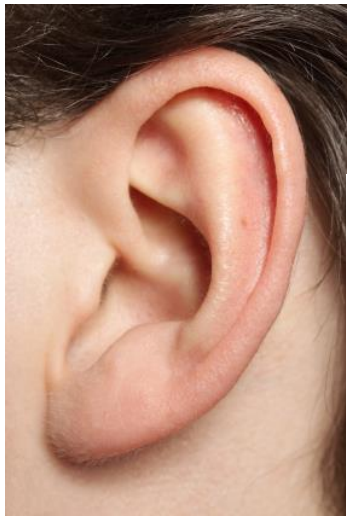
Grade 3 and 4:

- Permanently Discontinue anti-PD-1
- Pulmonary function tests with pulmonary consult., bronchoscopy with biopsy and/or BAL recommended.
- Intravenous steroids (methylprednisolone 125 mg), then oral and
- When symptoms improve to Grade 1 or less, taper over no less than 4 weeks.
- If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider more potent immunosuppressor

Merck recommendations

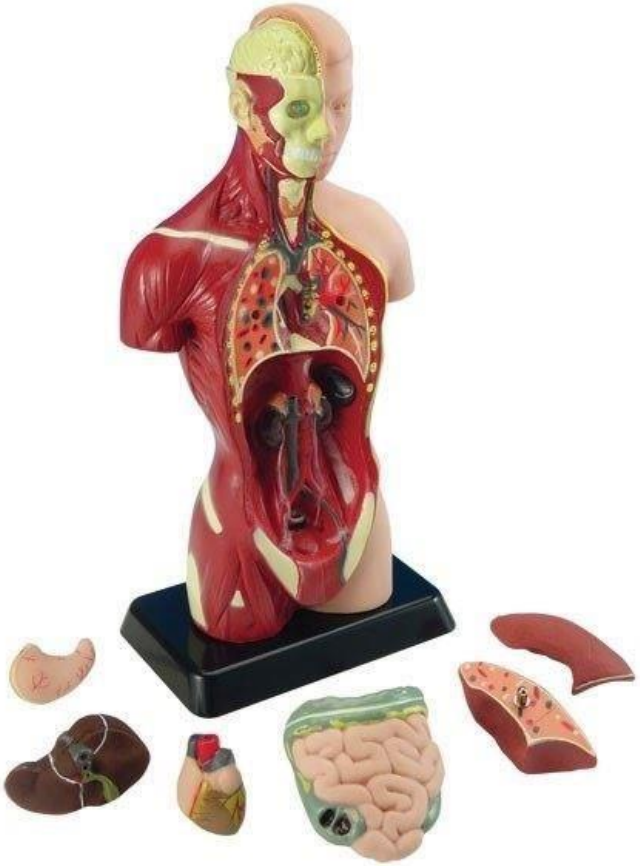
AE	presentations	anamnestic/ Clinical Diagnosis	Confirmatory explorations	Requirements
Skin AE		Clinical exam.	+/-biopsy	Listen to/observe pts
Colitis		Pt report diarrhea, pain, blood in tools	colonoscopy	Listen to pts prescribe endoscopy if needed
Endocrine		Pt report fatigue, frilosity..	Blood test imaging	Listen to pts Prescribe tests
hepatitis	AST, ALT	Monitoring liver function	Blood test +/- biopsy	Prescribe tests Look at the results +/- biopsy
neurological		Pt report pain, deficit Clinical exam.	Imaging Lumbar puncture	Listen to/observe pts Prescribe imaging and LP

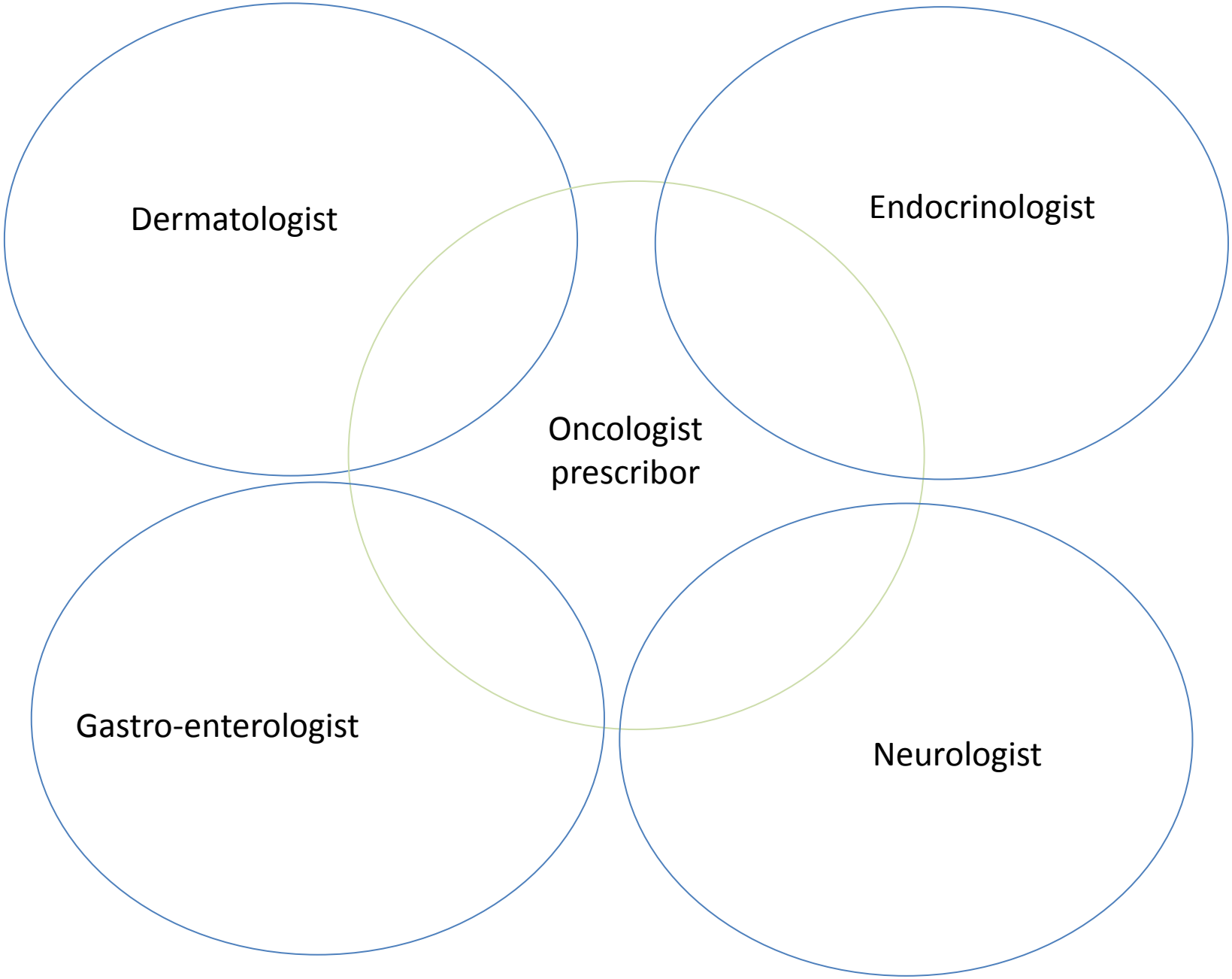




Treating irAE

- Following guidelines:
  - Prescribing symptomatic treatments
  - Prescribing steroids
- Remaining vigilant ie potential new AE
- Knowing when to refer patients with severe AE

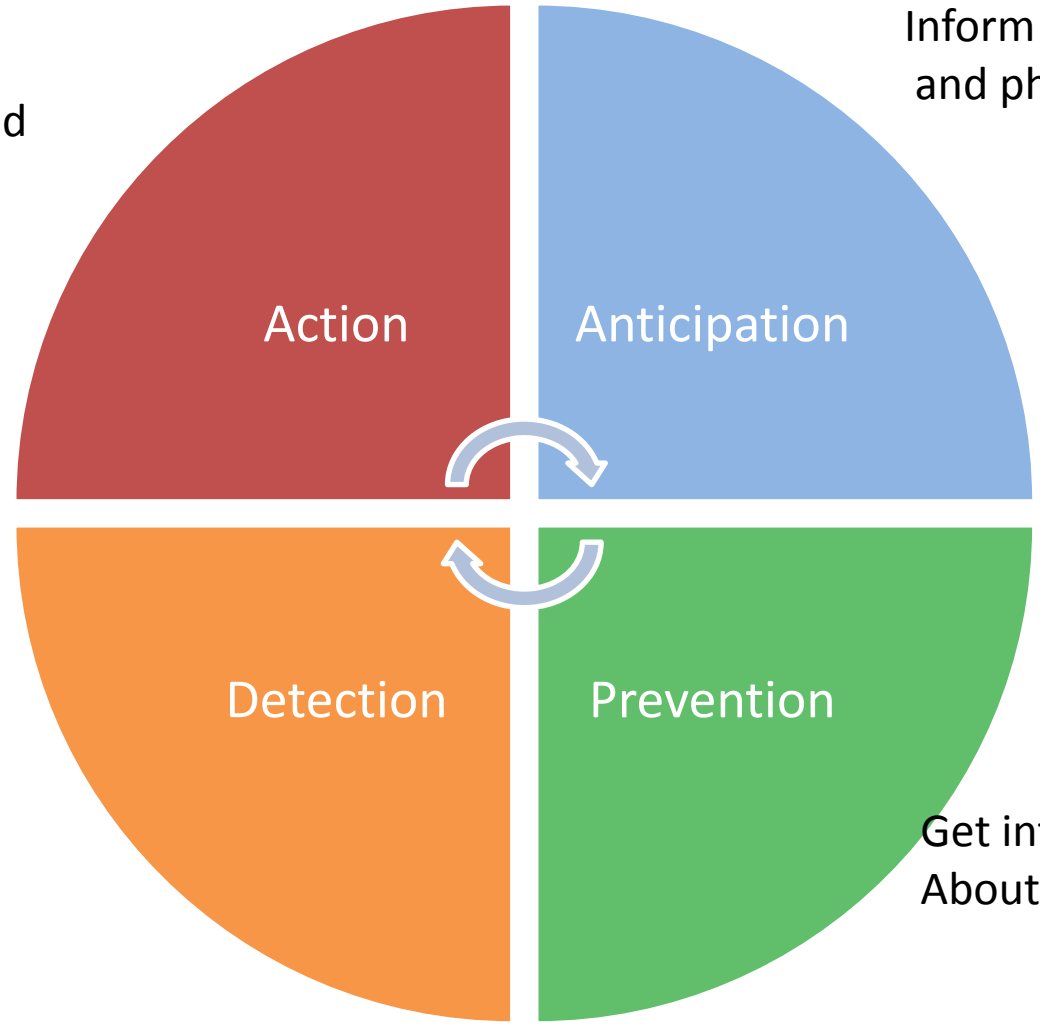



Dermatologist
Endocrinologist
Oncologist
prescribor
Gastro-enterologist
Neurologist

Risk management

Get information
Inform the patients
and physiciens

Treat and
refer when needed



Get information
About risk factors

Diagnose AE

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

CASE 1

Medical History

- 67 year-old-man
- October 2006: Primary melanoma stage IB
- December 2013: Progression to stage IV , M1c: liver, and subcutaneous metastases

→ - clinical trial MK3575-001 with pembrolizumab
- 10 mg/Kg Q2
- cycle 1: 30th/01/2014
- CT evaluation W12: partial response

Recent History

June - July 2014

- Diarrhea persistent grade 2
- Stool culture: positive for campylobacter jejuni
- Antibiotics and symptomatic treatments
- Discontinuation of pembrolizumab (last injection: July 1st 2014)

End of July - August 2014

- Diarrhea grade 3
- Hypokaliemia grade 4
- weight loss grade 2 (-13 Kg in 3 weeks)
- Coloscopy + gastroscopy:

→ **colitis grade 3 attributed to anti-PD-1 and moderate gastro-duodenitis, after six months of treatment**

Management and Follow-up

- Hospitalization
- Potassium supplementation
- **HD IV Corticosteroids** with progressive tapering
- **Permanent discontinuation of pembrolizumab**

→ - Quick normalization of bowel function

- last imaging evaluation (Oct 10th 2014): **complete response (irRC and RECIST 1.)**

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

CASE 2

Medical History

- 76-year-old-man
- January 1997: diagnosis of stage IB melanoma
- December 2013: disease progression stage IV distant lymph nodes

→

- clinical trial with pembrolizumab:MK3475-001
- 10 mg/Kg Q3
- cycle 1: 30th January 2014
- regular CT-scans: partial response

Recent History

August – September 2014

- Acute elevation of creatinine (renal clearance 35 ml/min)
- Proteinuria +
- Normal renal and pelvic ultrasonography
- Discontinuation of pembrolizumab (last injection: 1st Sept2014)

October 2014

- Renal biopsy:

→ **tubulointerstitial nephritis attributed to anti-PD-1, after 9 months of treatment**

Management and Follow-up

- Ongoing management with corticosteroids

→ - Discontinuation of pembrolizumab (last injection in september 2014)

- last imaging evaluation (10/09/2014): **partial response (-92% irRC); complete response (RECIST 1.1)**

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

CASE 3

Mr D, 78 years old was treated for melanoma on the cervix in 2009

Stade IV on december 2011 : T3aN3M1c

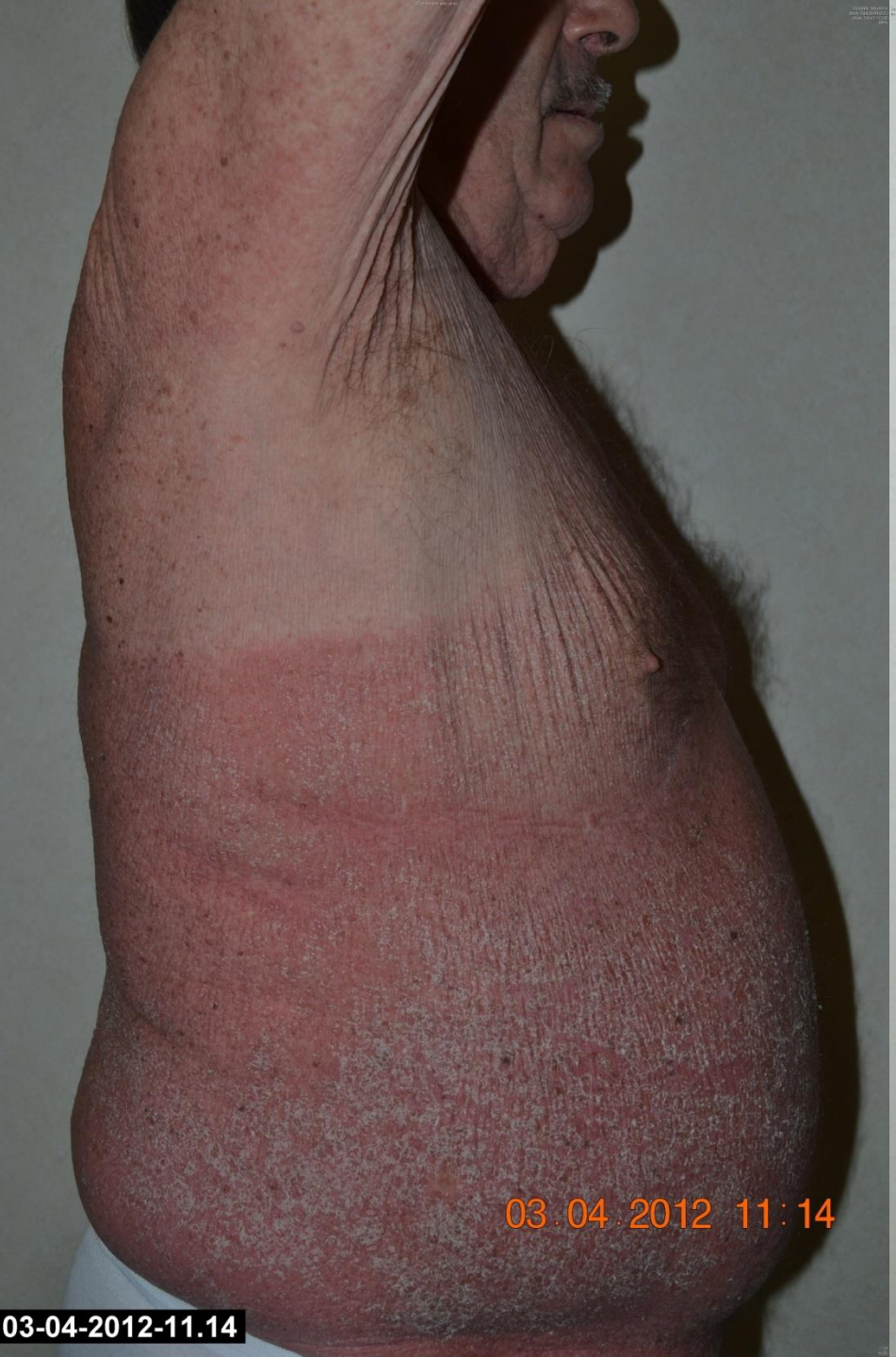
First line of treatment in the trial MelIpiRx

- 4 infusion ipilimumab 10mg/kg/ 3 weeks
- Radiotherapy 9 Gy in 3 fractions at week4 on axillar lymph node

At week5, 8 days after the second infusion and radiotherapy:

- diffuse maculo-papular rash evolving to an erythrodermia except axillar zone
- increase of eosinophils 2300/mm3
- renal failure with intertitial nephritis confirmed by biopsy

DRESS Syndrome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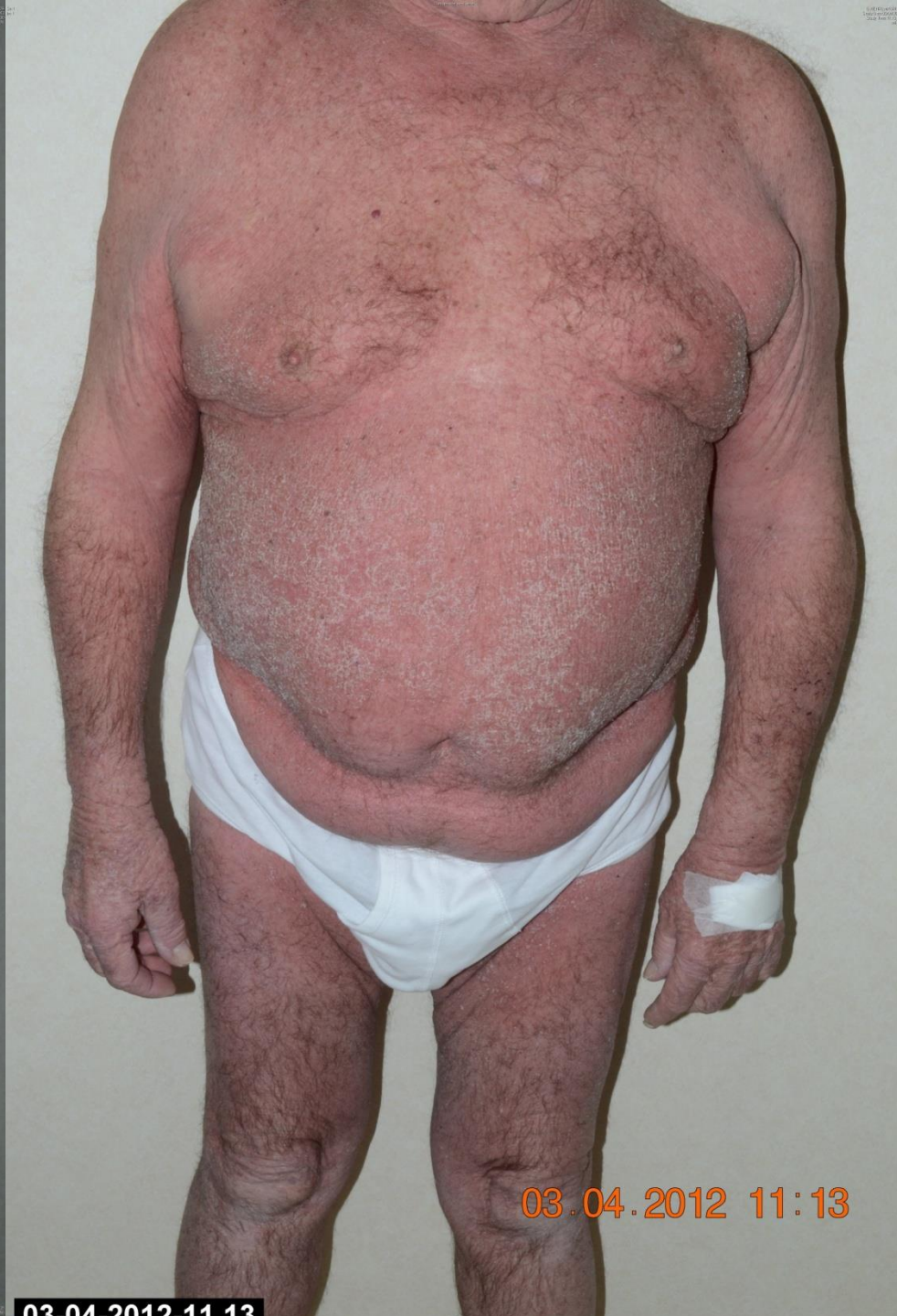
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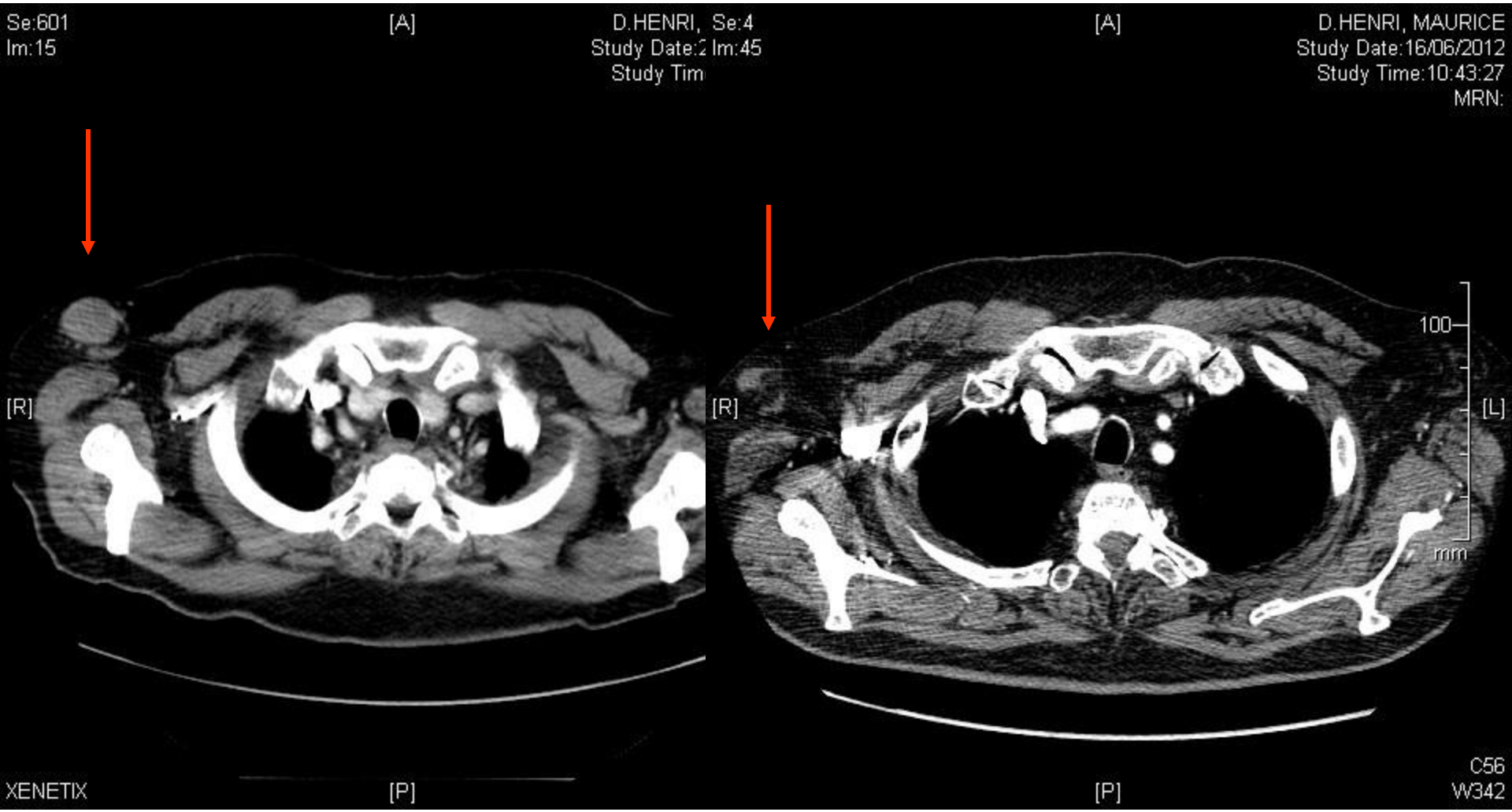
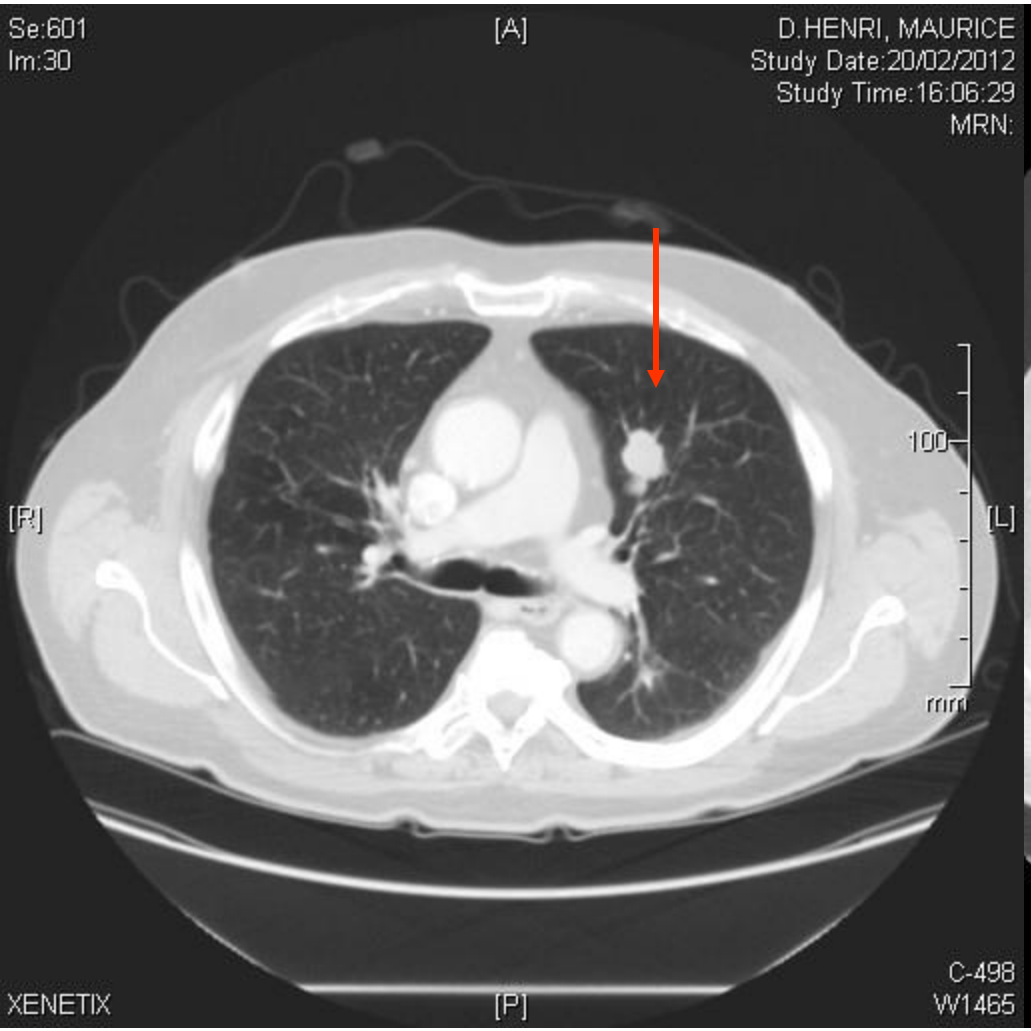


BEFORE IPILIMUMAB

AFTER IPILIMUMAB



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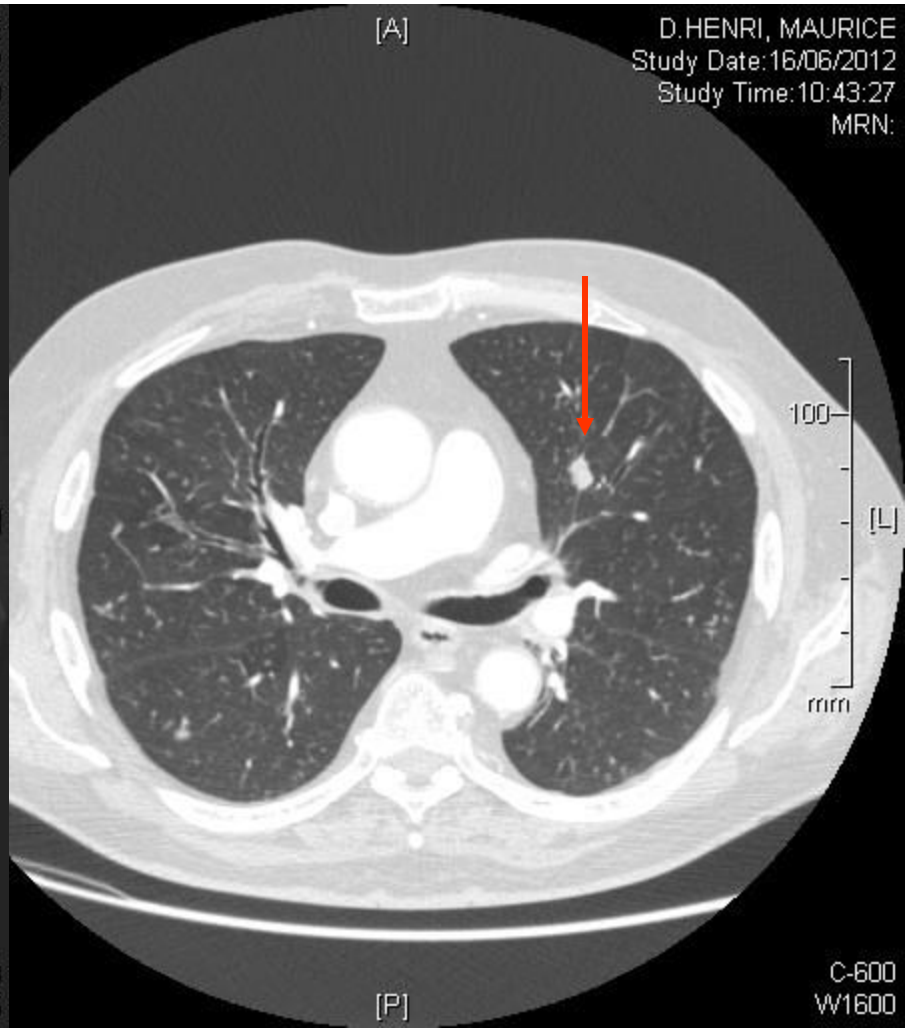

AFTER IPILIMUMAB

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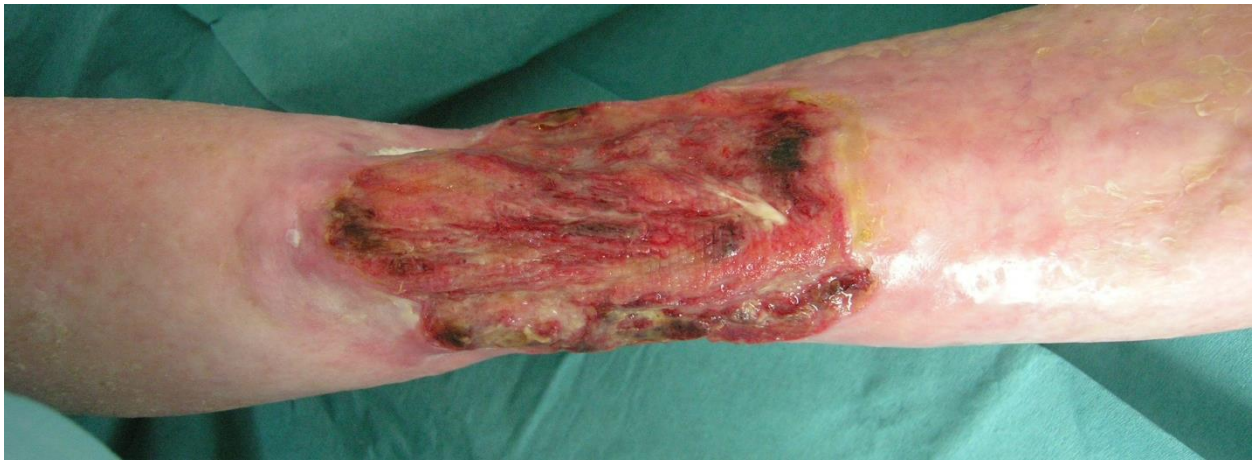
GRAND PARIS

CASE 4

Mrs V, 70 years old, primary melanoma in 2000

- Multiple locoregional relapses treated by surgery since 2003
- 3 ILP in sept 2005, december 2006, april 2009
- Last one complicated by neutrophilic dermatosis steroid dependent



-Included in a vaccination trial (MEL004) with Mage A3 vaccination between may and august 2010 → progression

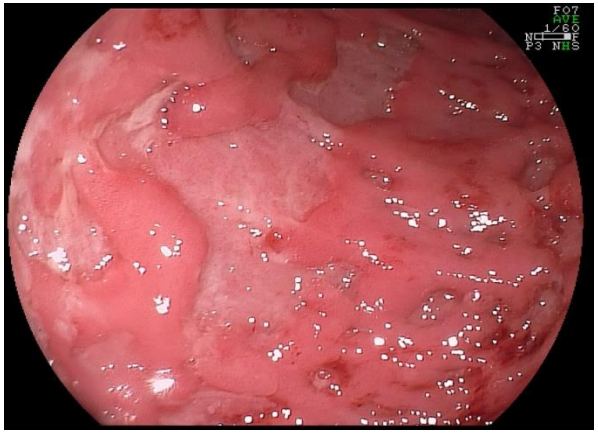
- Treatment by ipilimumab in the expanded access program

  - 1°infusion 12/08/2010

  -Colitis after the 3rd infusion grade 3

  -iv Steroids bolus > 120 mg 10 days

  -Infliximab one infusion



Complete remission

- 2 relapses since then:
- july 2011 : relapse with a unique brain metastasis → radiosurgery
- September 2011: relapse with unique digestive metastasis

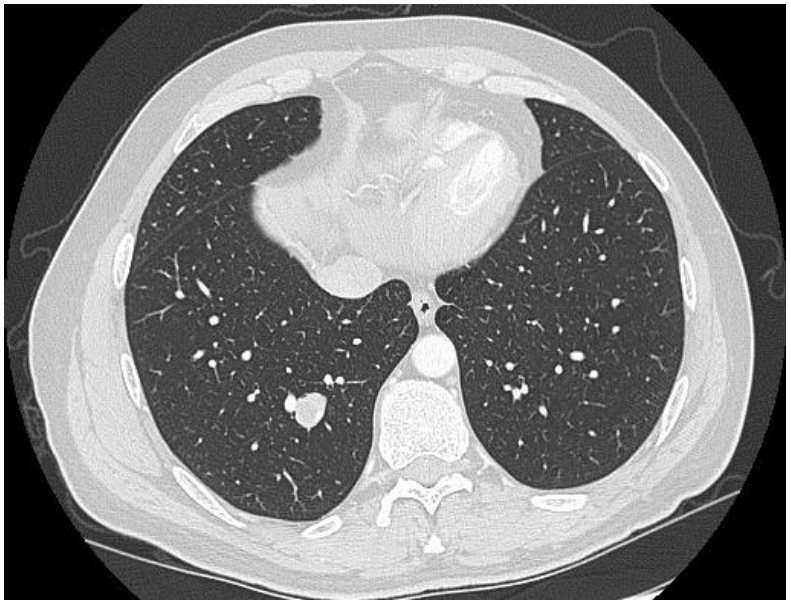
May 2012 still in Complete remission

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

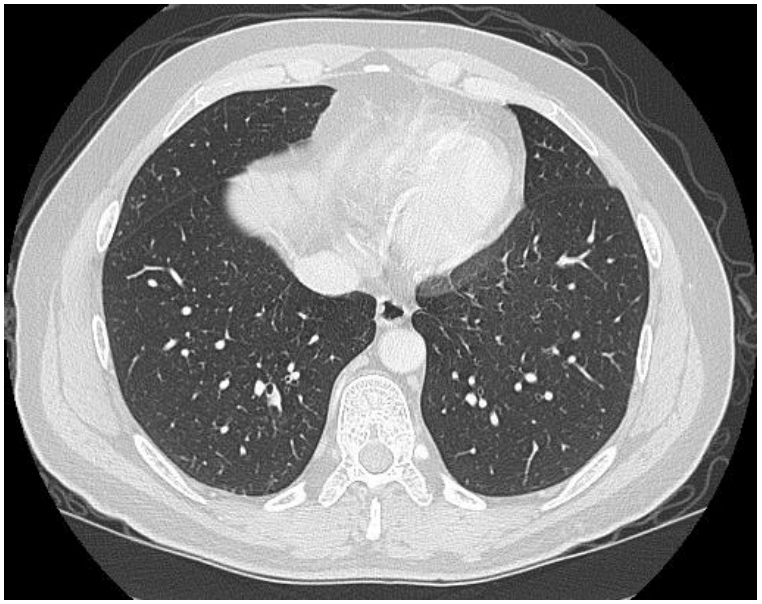
CASE 5

Mr P 47 years old

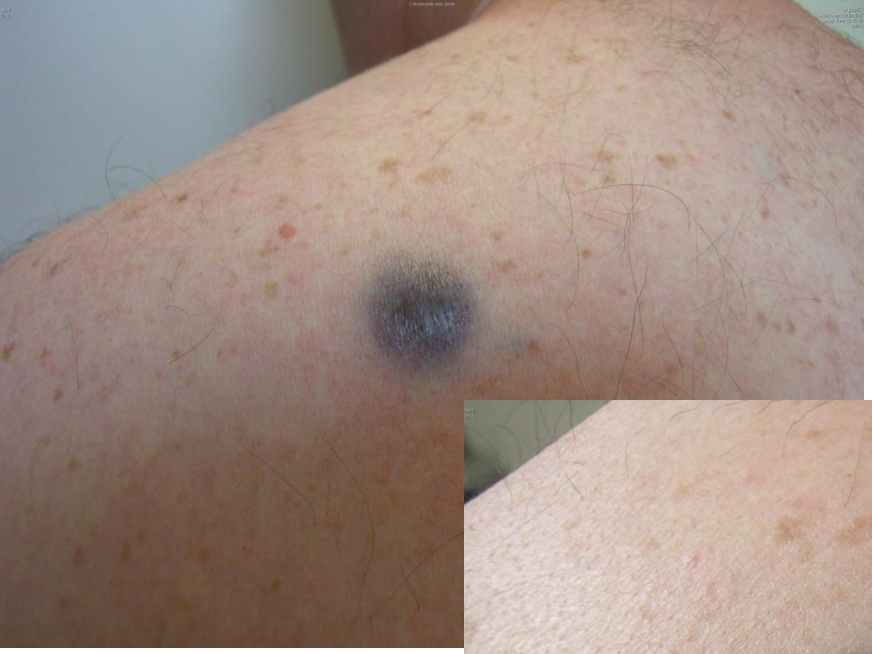
- May 2005: melanoma T4b: surgery + interferon (3 millions x 3 / week)
- Local relapse after few weeks: surgery and radiotherapy
- Diffuse skin relapses stade IV in sept 2006
    - 6 cycles of dacarbazine+fotemustine+cisplatine
    - july 2007 st M1b inclusion in Medarex trial
        - -4 infusions between july and sept 2007 → PR
        - -4 infusions between january and march 2008 → PR
        - -stereotatic radiotherapy in feb 2009
        - -4 infusions between march and may 2009 → PR
        - -4 infusions between april and june 2010 → *CR*



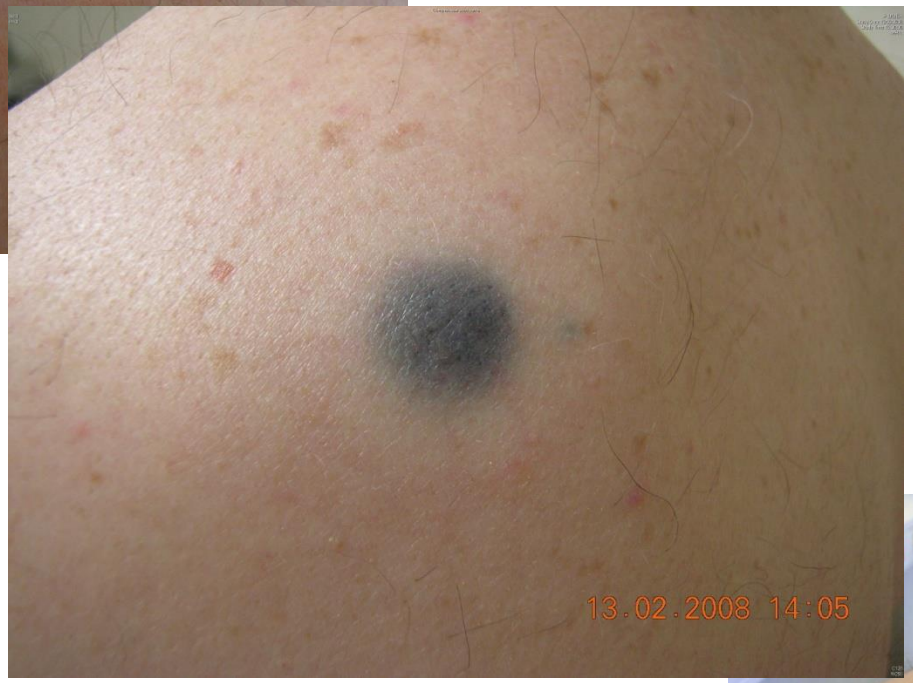
Before ipilimumab



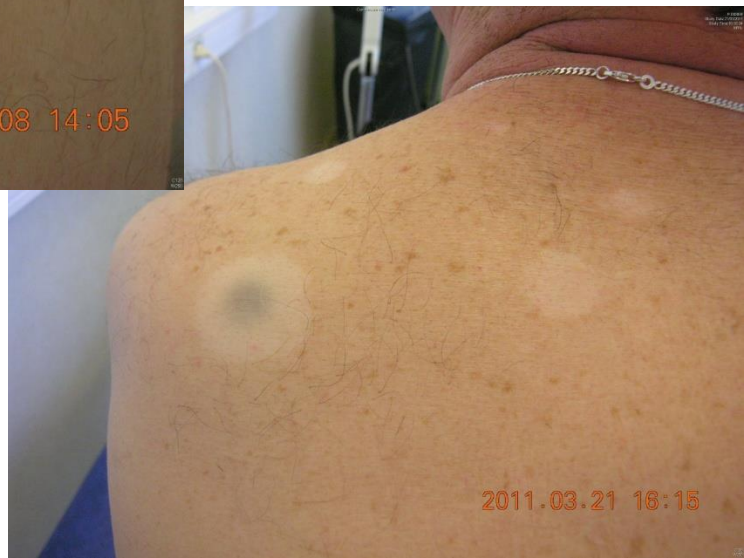
After 6 months



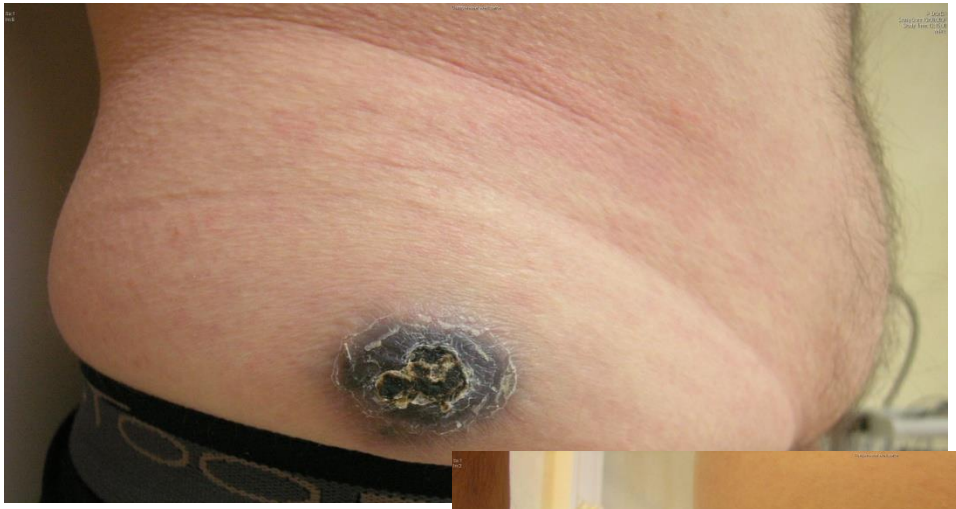
2007 : before ipilimumab



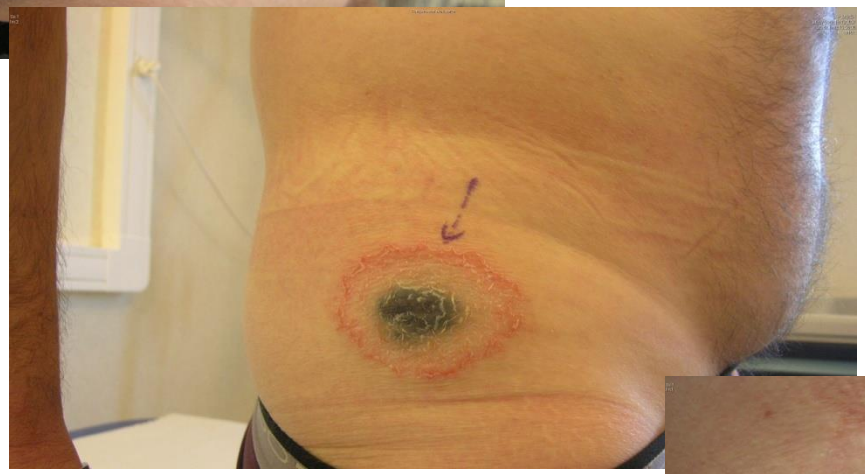
2008 : the second induction ipilimumab



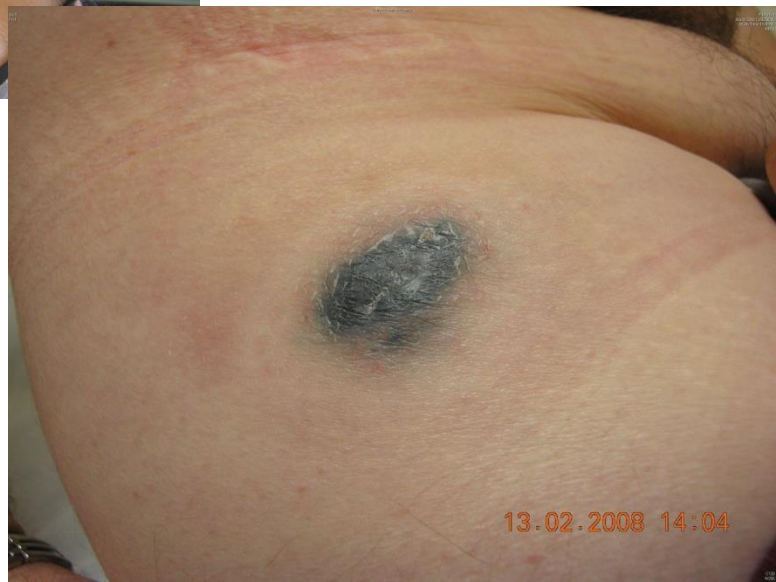
2011 : after 4 inductions



2007 : before ipilimumab

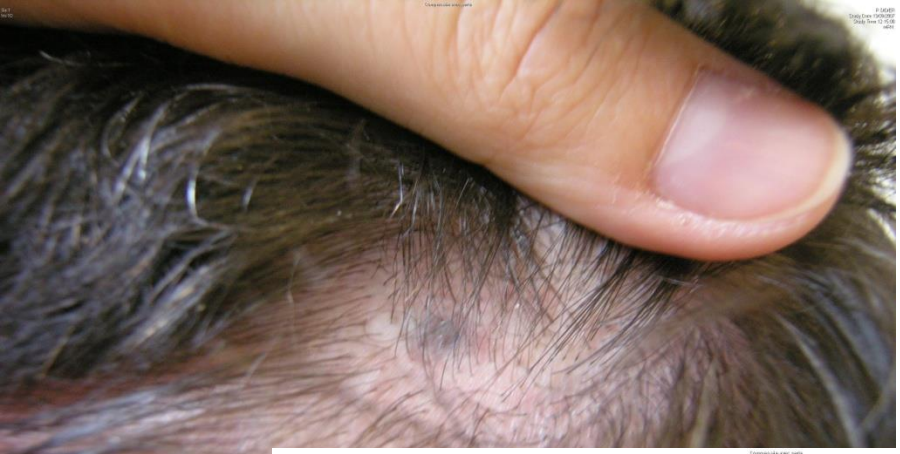


2007 : after the first induction

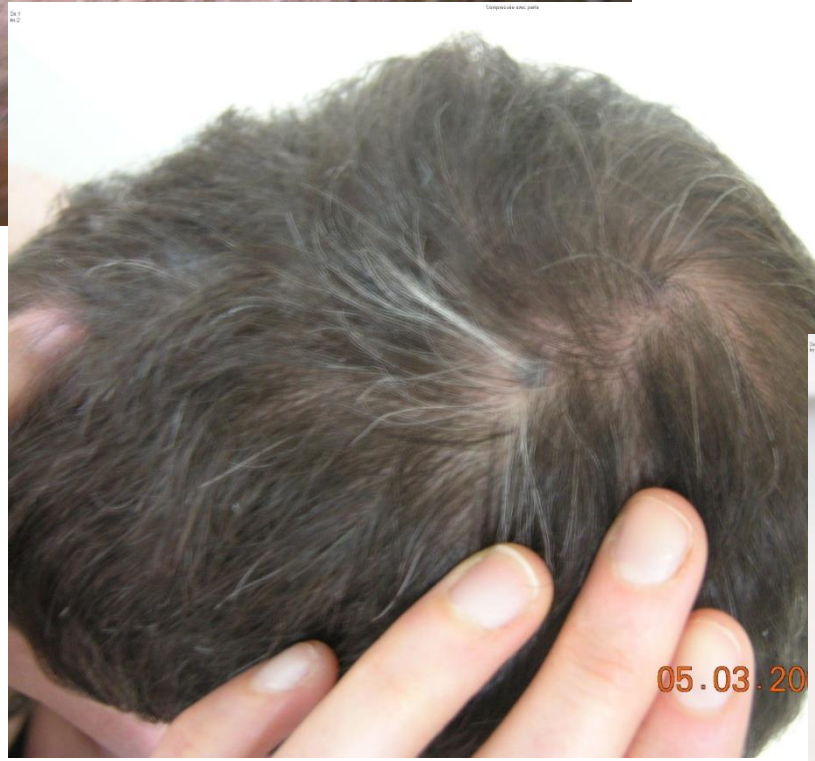


2008 : after 2 inductions

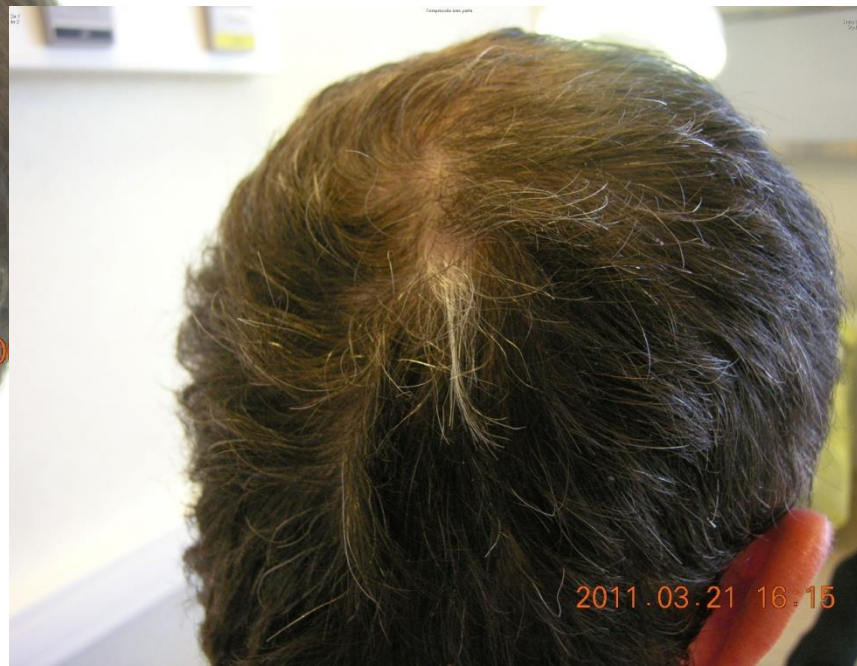
Excision=sterilization



2007: after 1 induction



2008: after 2 inductions



2011: after 4 inductions