Management of toxicities of immune checkpoint inhibitors.

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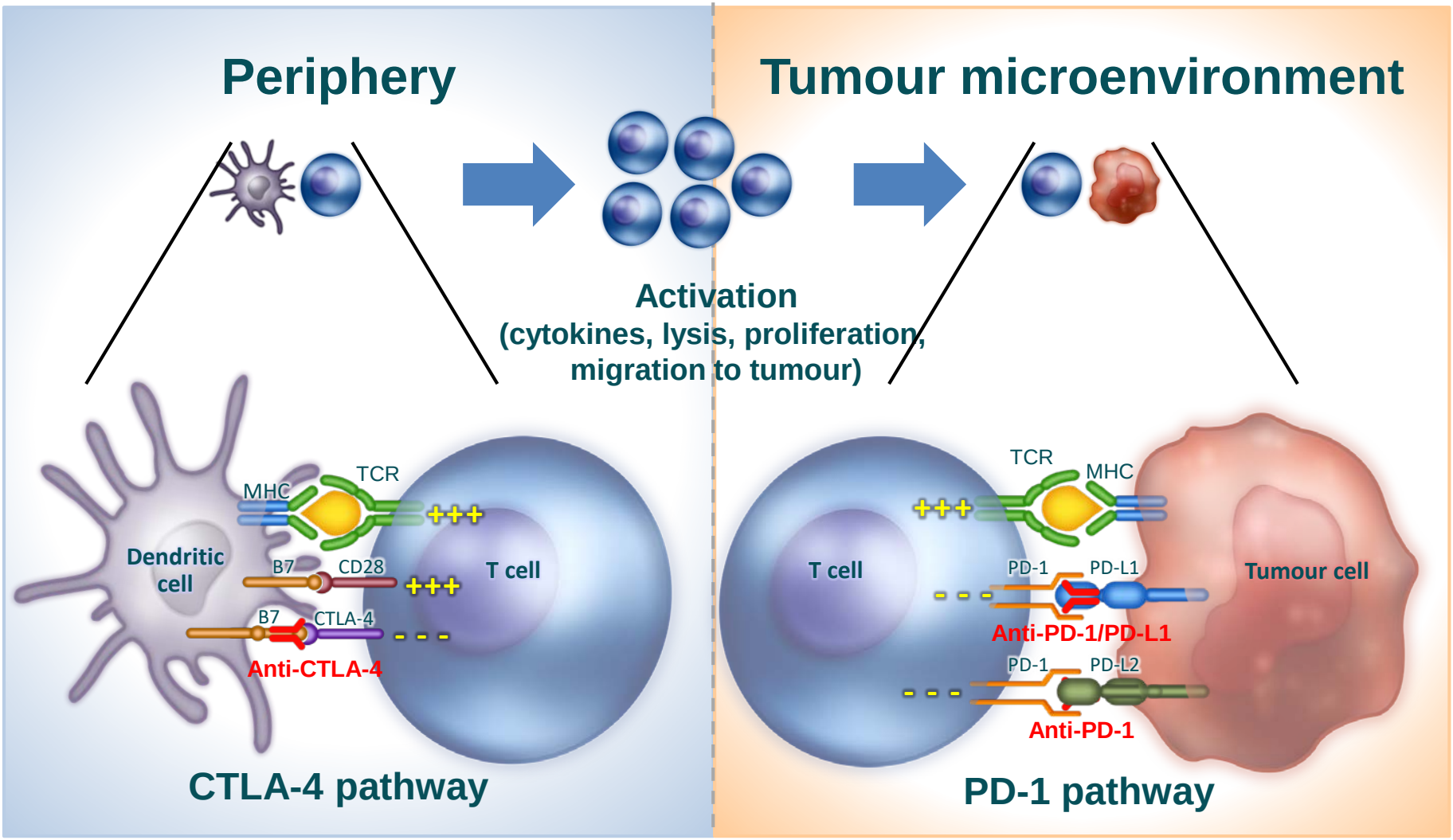
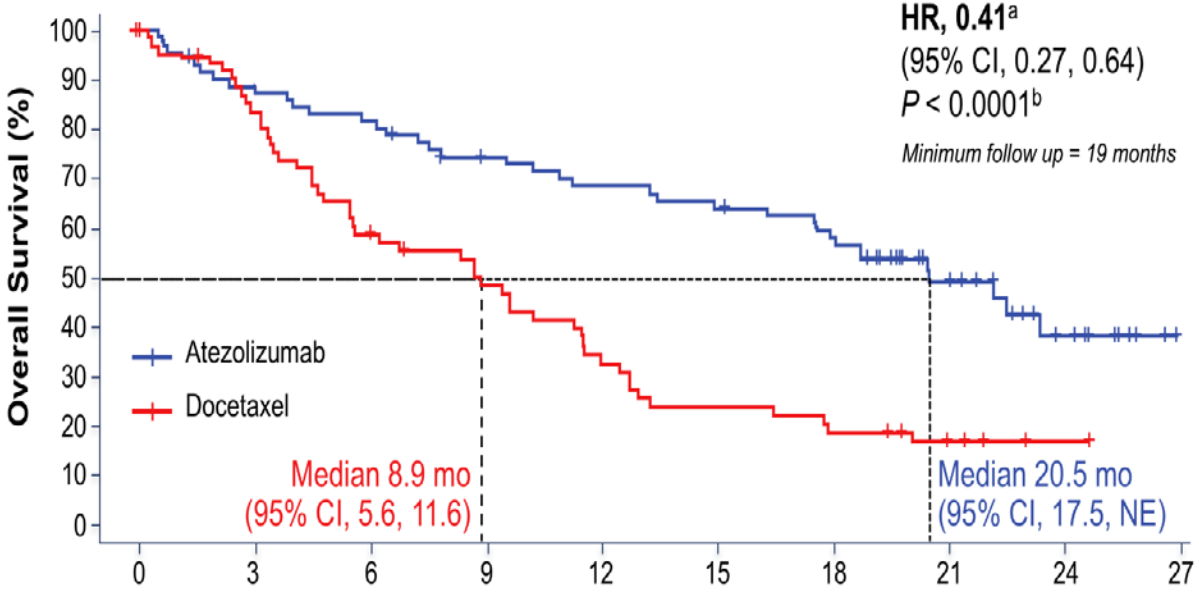
The Most Promising Pathways



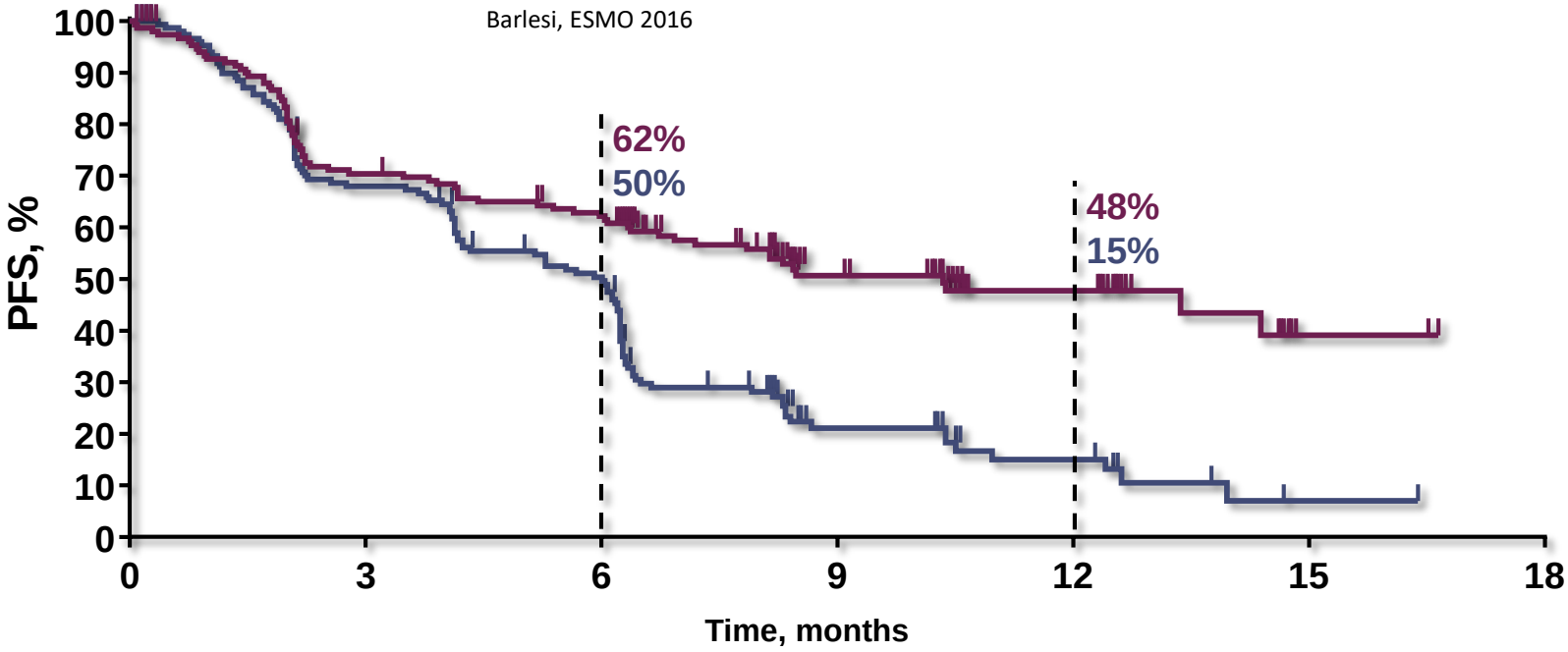
Wolchock J, et al. *J Clin Oncol* 2013;31(Issue 15_suppl); abstr 9012^

Several PD-1/PD-L1 inhibitors are being evaluated in NSCLC

PD-1	***Nivolumab BMS-936558***	***Fully human IgG4 mAb***	***Bristol-Myers Squibb***	***Phase III***
	Pembrolizumab MK-3475	***Humanized IgG4 mAb***	***Merck***	***Phase III***
	Pidilizumab CT-011	Humanized IgG1 mAb	CureTech	Phase II
	PDR001	Humanized IgG4 mAb	Novartis	Phase II
	AMP-224	Recombinant PD-L2-Fc fusion protein	GlaxoSmithKline	Phase I
	MEDI-0680	Humanized IgG4 mAb	Medimmune - AZ	Phase I
	REGN2810	Humanized IgG4 mAb	Regeneron/Sanofi	Phase I
PD-L1	***Durvalumab MedI-4736***	***Engineered human IgG1 mAb***	***MedImmune - AZ***	***Phase III***
	Atezolizumab MPDL-3280A	***Engineered human IgG1 mAb***	***Genentech***	***Phase III***
	Avelumab MSB0010718C	Engineered human IgG1 mAb	EMD Serono	Phase III
	BMS-936559	Fully human IgG4 mAb	Bristol-Myers Squibb	Phase II



Barlesi, ESMO 2016



Reck M et al. N Engl J Med 2016

Basis for AEs

- Immune checkpoint inhibitors promote T cell activity
- Amplification of immune system: auto-immunity
- Common side effects: fatigue, anorexia, arthralgia
- Immune related adverse events (irAEs):
  - “-itis” or “-opathy”
- Where can irAEs appear?

Side effects of immune checkpoint inhibitors

Everywhere!

Pulmonary
Dyspnoea
Pneumonitis

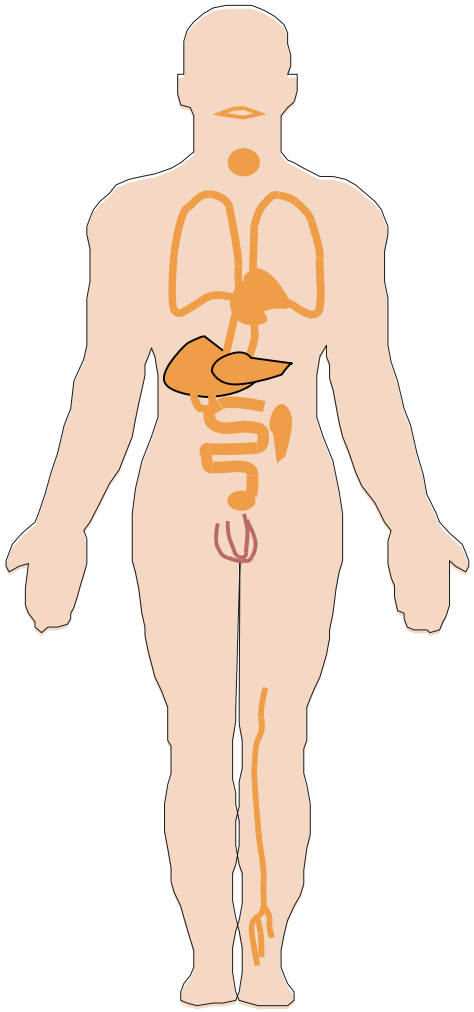
Cardiovasc
Pericarditis
Myocarditis
Vasculitis

Gastro-intestinal
Diarrhea, nausea
Pancreatitis. colitis

Hepatic
Transaminitis
Hepatitis

MSK
Arthralgia, myalgia, arthritis, myositis

Renal
Nephritis



Dermatologic
Rash, pruritus
Vitiligo
PPE
Ulcers

Endocrine
Hypothyroidism
hyperthyroidism
Hypophysitis
Hypopituitarism
Thyroiditis
Adrenal insufficiency

Neurologic
Neuropathy
Meningitis
Guillain-Barre

Ocular
Dry eyes, Iritis
Uveitis, conjunctivitis

General
Fatigue, asthenia, fever, chills, infusion related reaction

Overview of immune checkpoint TRAEs

Population	Drug	Incidence, %		Author
		Any grade	G3-4	
NSCLC	Pembrolizumab	71	9.5	Garon, NEJM 2015
SCC	Nivolumab Docetaxel	58 86	7 55	Brahmer, NEJM 2015
Non-SCC	Nivolumab Docetaxel	69 88	10 54	Borghaei NEJM 2015
SCC	Nivolumab	74	17	Rizvi Lancet Oncol 2015
RCC	Nivolumab Everolimus	79 88	19 37	Motzer NEJM 2015
Melanoma	Nivo/ Ipi Ipilumumab	91 93	54 24	Postow NEJM 2015
Melanoma	Nivolumab Nivo/ Ipi Ipilumumab	82.1 95.5 86.2	16.3 55 27.3	Larkin NEJM 2015
NSCLC	Nivolumab	41	4.7	Gettinger JCO 2015
Solid tumors	Atezolizumab	70	12.6	Herbst Nature 2014
NSCLC	Atezolizumab Docetaxel	67 88	11 39	Spira ASCO 2015
NSCLC	Atezolizumab	64	11	Besse ECC 2015

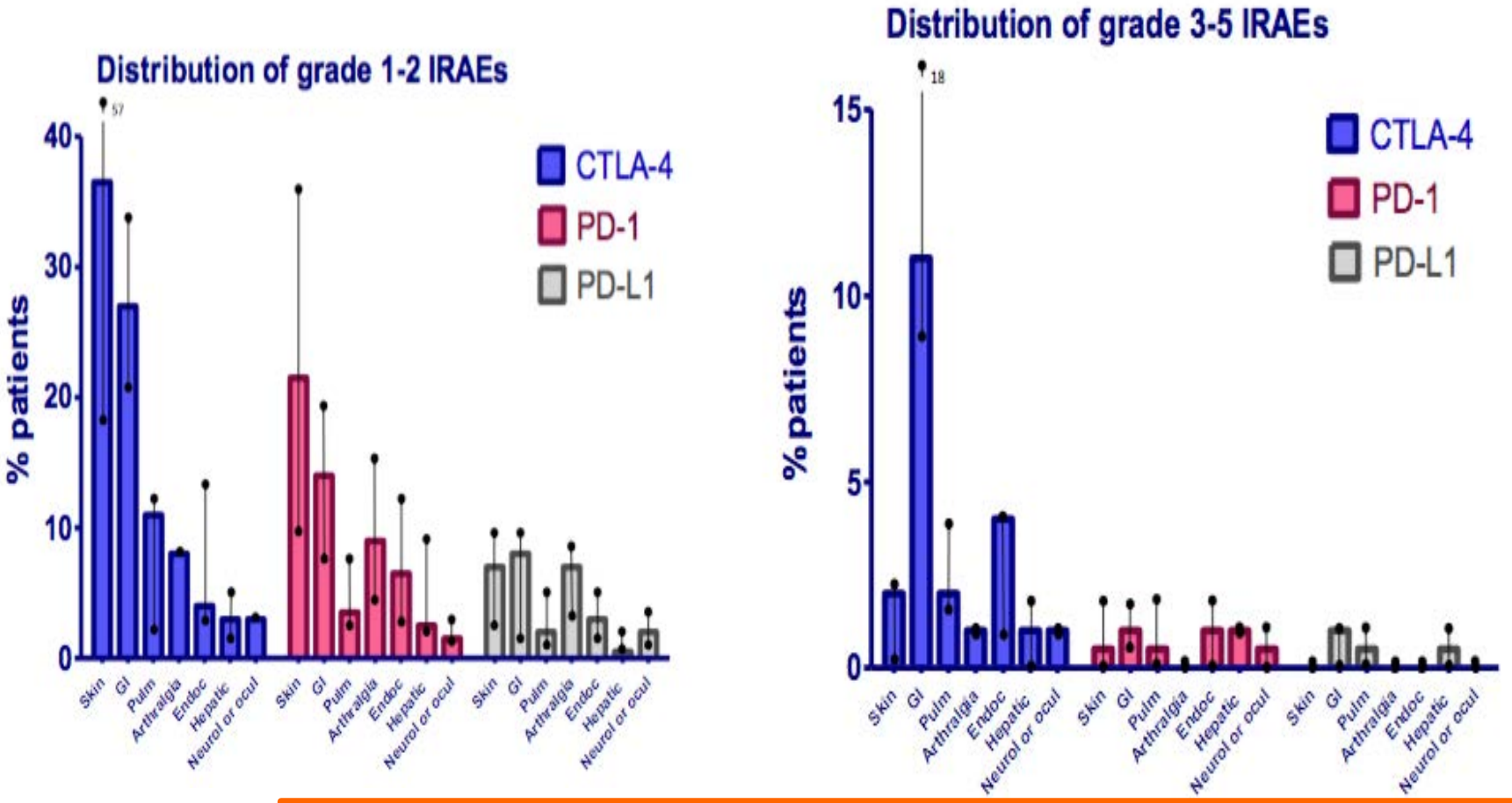
Checkmate 017: nivolumab had less TRAEs vs docetaxel

Table 3. Treatment-Related Adverse Events Reported in at Least 5% of Patients.*

Event	Nivolumab (N=131)		Docetaxel (N=129)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with an event (percent)			
Any event	76 (58)	9 (7)	111 (86)	71 (55)
Fatigue	21 (16)	1 (1)	42 (33)	10 (8)
Decreased appetite	14 (11)	1 (1)	25 (19)	1 (1)
Asthenia	13 (10)	0	18 (14)	5 (4)
Nausea	12 (9)	0	30 (23)	2 (2)
Diarrhea	10 (8)	0	26 (20)	3 (2)
Arthralgia	7 (5)	0	9 (7)	0
Pyrexia	6 (5)	0	10 (8)	1 (1)
Pneumonitis	6 (5)	0	0	0
Rash	5 (4)	0	8 (6)	2 (2)
Mucosal inflammation	3 (2)	0	12 (9)	0
Myalgia	2 (2)	0	13 (10)	0
Anemia	2 (2)	0	28 (22)	4 (3)
Peripheral neuropathy	1 (1)	0	15 (12)	3 (2)
Leukopenia	1 (1)	1 (1)	8 (6)	5 (4)
Neutropenia	1 (1)	0	42 (33)	38 (30)
Febrile neutropenia	0	0	14 (11)	13 (10)
Alopecia	0	0	29 (22)	1 (1)

Brahmer NEJM 2015

IRAEs anti CTLA-4 and anti PD-1/ anti PD-L1



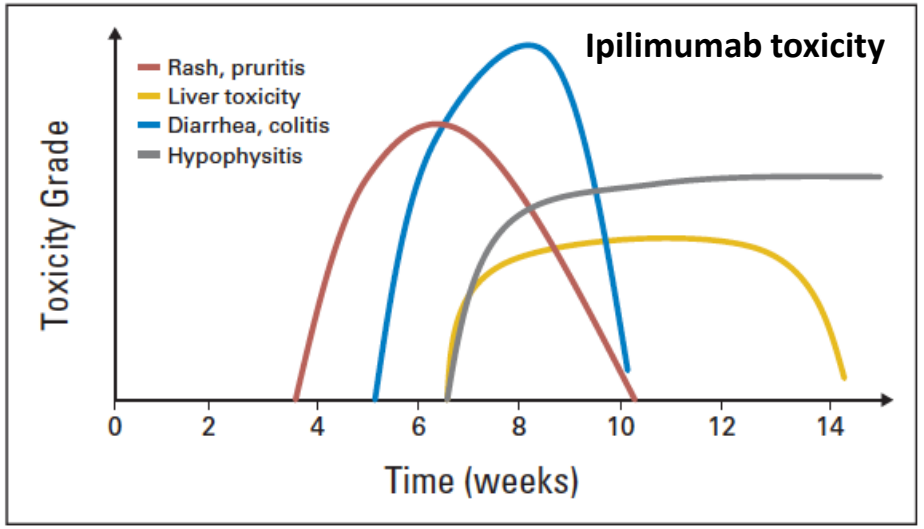
Anti-CTLA-4 Antibodies: More IRAEs, More severe IRAES (GI, Skin, Endocrine IRAES)

Michot JM EJC (2016) 54: 139-148

Patterns of irAEs:

- Onset:
  - 6-12 weeks post initiation
  - Variable:
    - Within days
    - After months
    - Post discontinuation
- Increased in combination with other immunotherapy agents, chemotherapy, RT

AE	Av. onset
Skin rash, pruritus	2-3w
GI and hepatic	6-7w
Endocrinologic	After 9w



Weber JCO 2012, Gangadhar Nat Rev Clin Oncol. 2014

More AEs with combination immune checkpoint inhibitors

CheckMate 067	Combination	Nivolumab	Iplilimumab
G3-4 TRAEs	55%	16%	27%
TRAE discontinuation	36%	8%	15%

CheckMate 012	Combination*	Nivolumab 3mg q2w
G3-4 TRAEs	28-35%	19%
TRAE discontinuation	5-13%	10%

*Combination: nivolumab + ipilimumab at 4 different doses & schedules

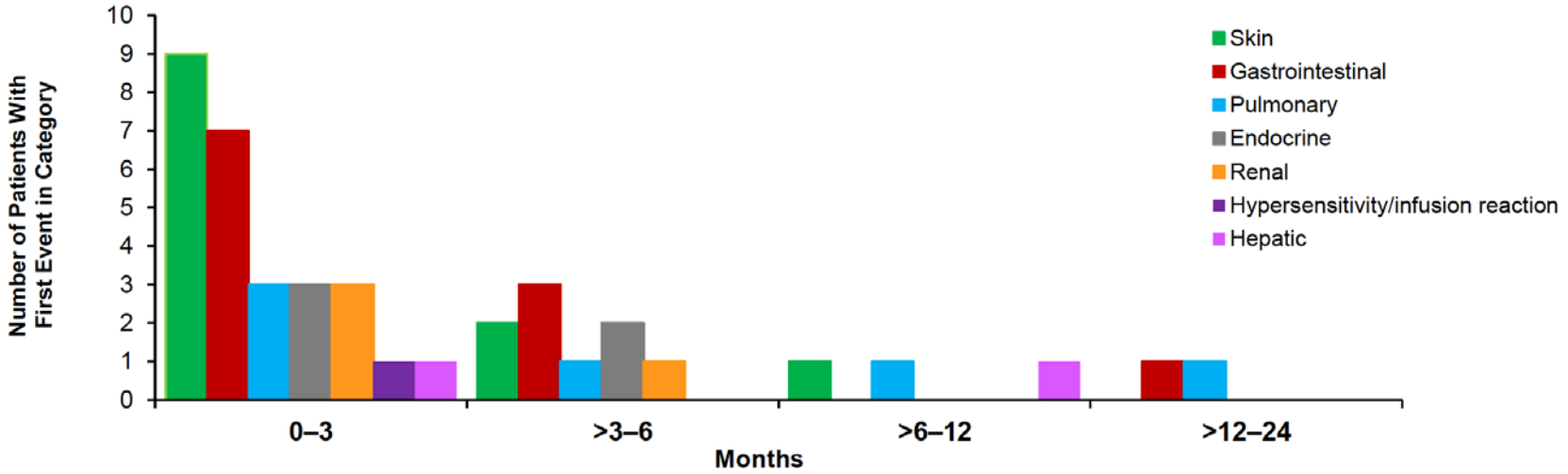
Larkin NEJM 2015, Rizvi WCLC 2015

1st onset of treatment related select AEs usually within 3 months of initiation

IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

16TH WORLD CONFERENCE ON LUNG CANCER
SEPTEMBER 6–9, 2015 → DENVER, COLORADO, USA

Time to Onset of First Treatment-related Select AE With Nivolumab by Category (Any Grade)



Pts still on study, n	131	112	85	52
Pts still on treatment, n	131	73	51	25
Total pts with first event,[a] n	24	6	2	1

- The majority of patients who experienced treatment-related select AEs with nivolumab experienced their first event within the first 3 months of treatment

Select AEs: AEs with potential immunologic etiology that require frequent monitoring/intervention.
Based on December 2014 DBL. Includes events reported between first dose and 30 days after last dose of study therapy.
Within each time interval, patients with ≥1 event were counted only once in each category but could be classified into more than one category

Reckcamp WCLC 2015

Side effects

Autoimmune:

1. Pulmonary
2. Cutaneous
3. Gastrointestinal
4. Hepatic
5. Endocrine
6. Rare: Neurological, pancreatic, renal, ocular

General:

1. Capillary leak syndrome
2. Cytokine release syndrome
3. Hemophagocytic lymphohistiocytosis

Infusion related reaction

Pulmonary irAE

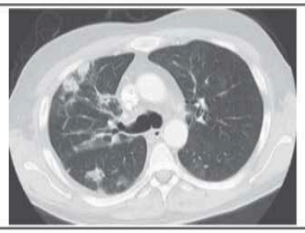
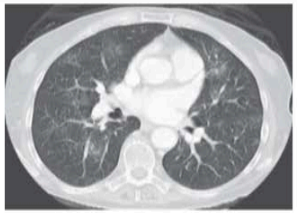
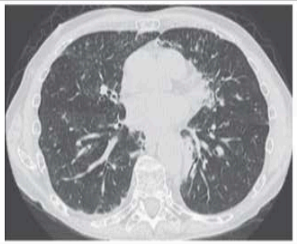
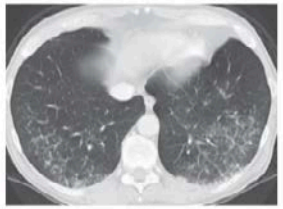
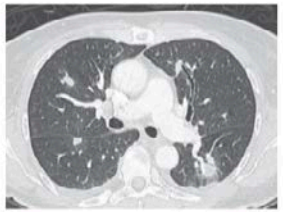
PNEUMONITIS AFTER ANTI PD-1/PD-L1 ANTIBODIES

- Incidence: 5% (greater after combination therapy – no difference between anti PD-1/PD-L1 antibodies)
- Incidence independent from tumor type:More common in patients with lung cancer
- Incidence independent from smoking status (Smoker 56% vs Never Smoker 44%)
- Incidence independent from treatment line
- Median time to onset : 2.8 months – however range: 9 days – 19.2 months!
- Common symptoms: Dyspnea, cough – however 33% of the patients were asymptomatic!
- 58% of the patients had additional IRAEs

Naidoo JN, J Clin Oncol 2016 e-published

PNEUMONITIS AFTER ANTI PD-1/PD-L1 ANTIBODIES

A heterogeneous picture..

Radiologic Subtypes	Representative Image	Description
Cryptogenic organizing pneumonia-like (n = 5, 19%)		Discrete patchy or confluent consolidation with or without air bronchograms Predominantly peripheral or subpleural distribution
Ground glass opacities (n = 10, 37%)		Discrete focal areas of increased attenuation Preserved bronchovascular markings
Interstitial (n = 6, 22%)		Increased interstitial markings, interlobular septal thickening Peribronchovascular infiltration, subpleural reticulation Honeycomb pattern in severe patient cases
Hypersensitivity (n = 2, 7%)		Centrilobular nodules Bronchiolitis-like appearance Tree-in-bud micronodularity
Pneumonitis not otherwise specified (n = 4, 15%)		Mixture of nodular and other subtypes Not clearly fitting into other subtype classifications

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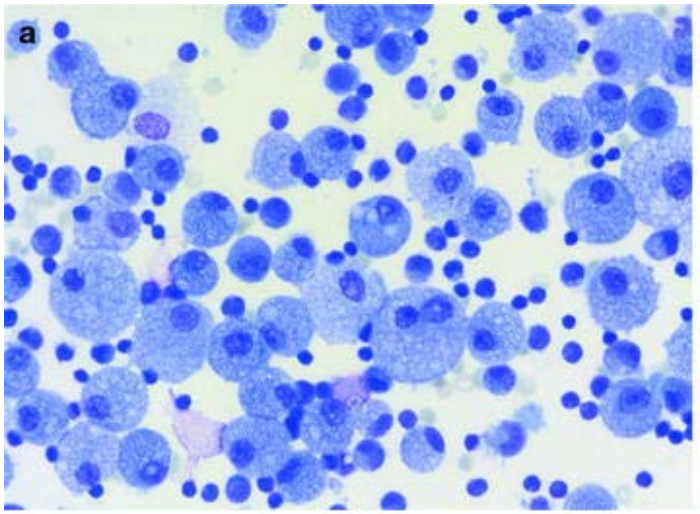
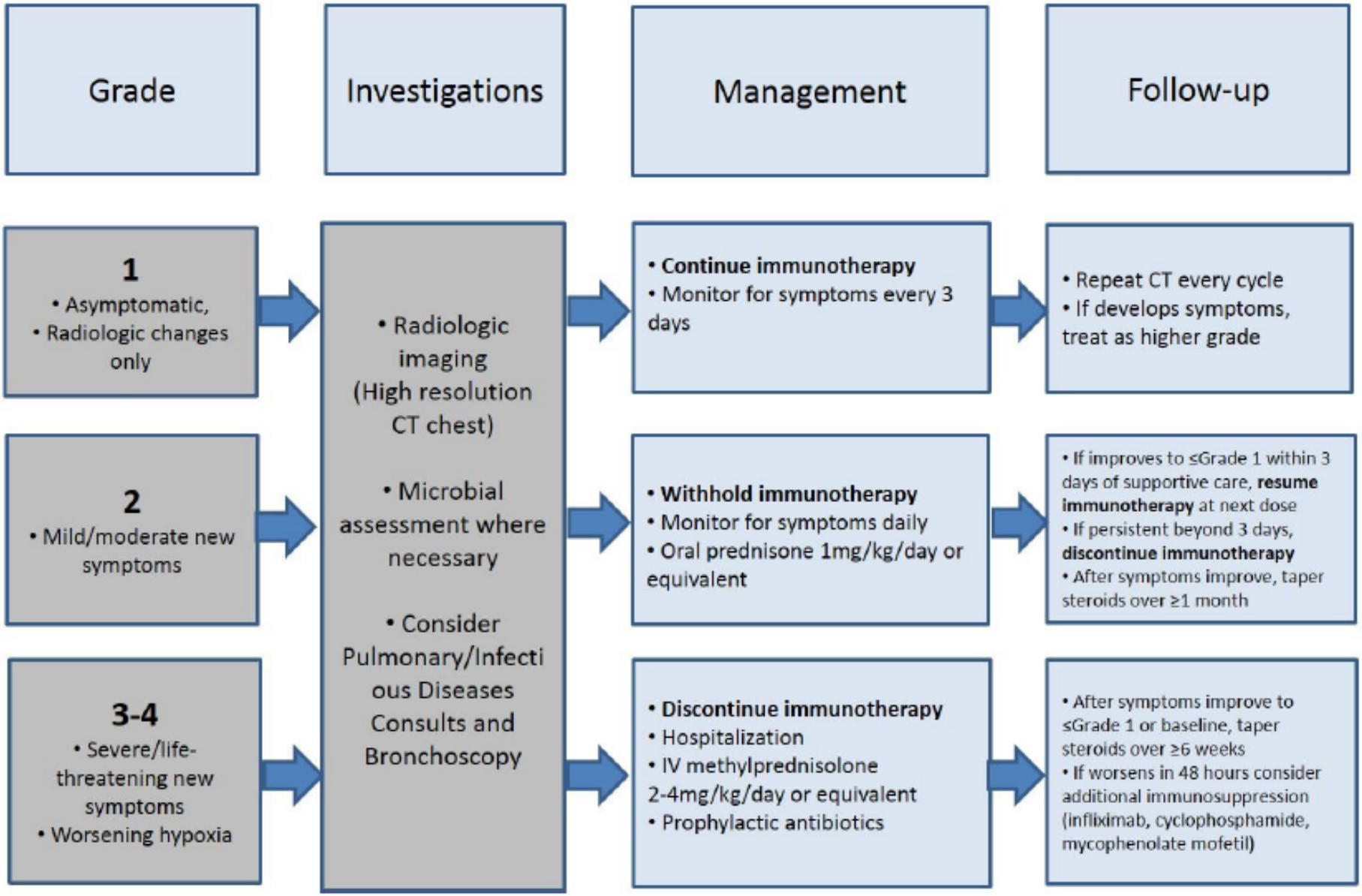
BAL



Répartition cellulaire :	%	*Normes* **
macrophages	51	*> 85*
neutrophiles	3	*< 3*
éosinophiles		*< 0,5*
lymphocytes	46	*< 12*
cellules bronchiques		*< 10*
cellules pavimenteuses		
cellules mal conservées		
autres		

Microbiology: no germ

Pulmonary irAE management



PNEUMONITIS AFTER ANTI PD-1/PD-L1 ANTIBODIES

- 88% improved/resolved (100% Grade 1, 93% Grade 2, 64% =/> Grade 3)
- Treatment:
    - Grade 1: 88% Treatment interruption, 12% steroids
    - Grade 2: 100% Steroids
    - Grade =/>3: 100% Steroids + additional immunosuppression in 42%
- Worsening more common in smokers or patients with prior lung diseases
- Median duration of steroids: 68 days (20 – 154 days!)
- Reexposition to immunotherapy in 12 patients:
    - 9 patients without recurrent pneumonitis
    - 3 patient with recurrent pneumonitis

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Cutaneous irAE

- **Clinical presentations**: maculopapular, papulopustular, acute febrile neutrophilic dermatosis (Sweet's syndrome), follicular or urticarial dermatitis

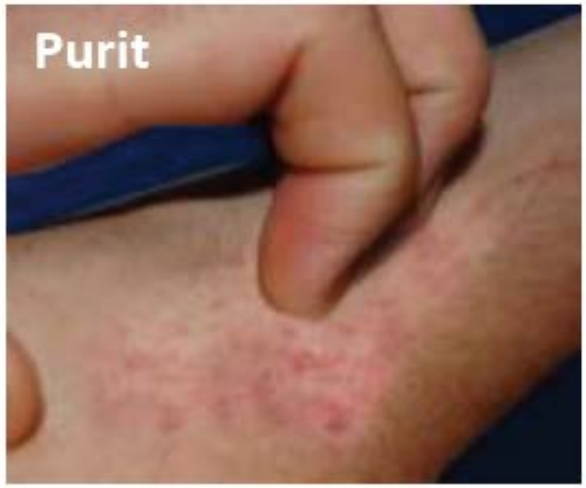
- **Severe irAEs:** bullous phemphigoid, Stevens Johnson syndrome, toxic epidermic necrolysis (Lyell's syndrome)

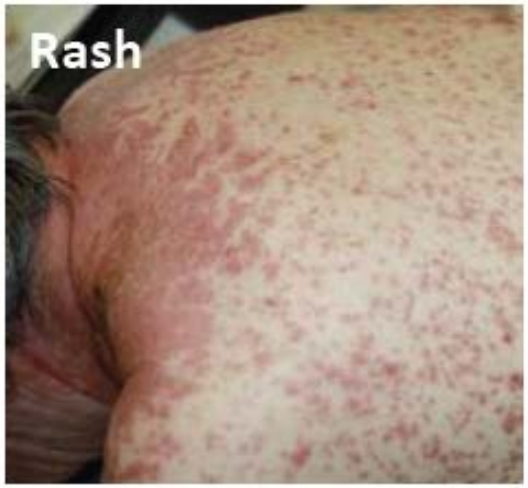
- **Mucosal toxicity:** lichenoide mucositis, oral mucositis, gingivitis, sicca syndrome-like

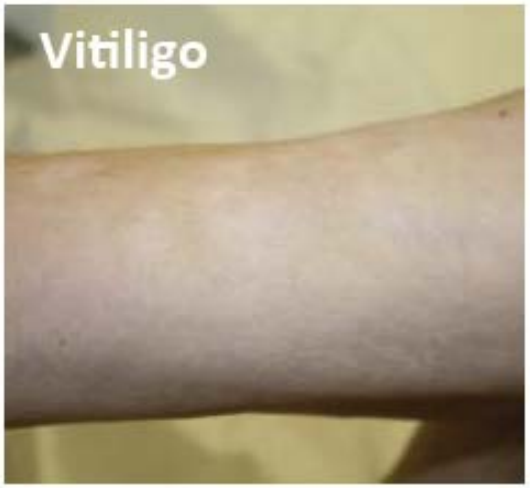
-> Rash is More frequent with pembrolizumab (39%) followed by nivolumab (34%) and ipiilimumab at 21%.

-> Vitiligo 10% with pembrolizumab and 2% with ipilimumab

Cutaneous irAE

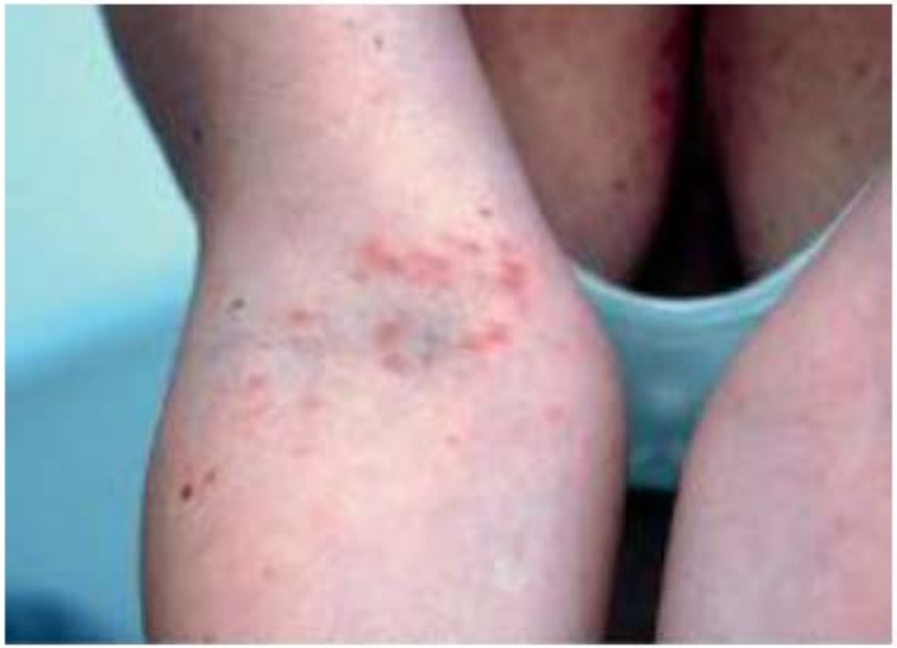




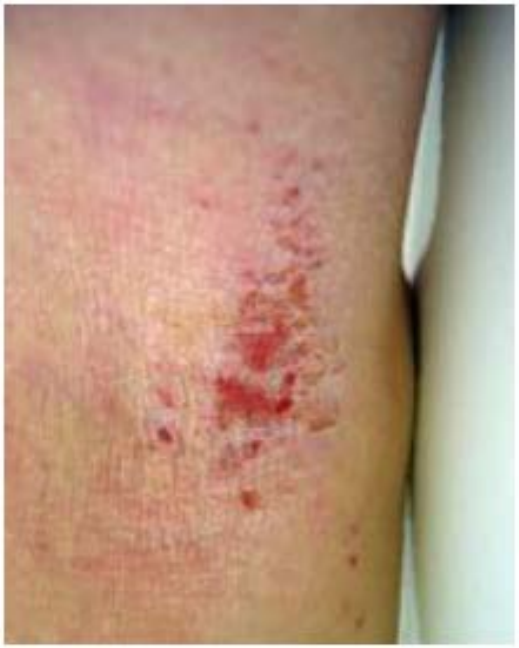


Cutaneous irAE

Anti-CTLA-4 / Skin Rash



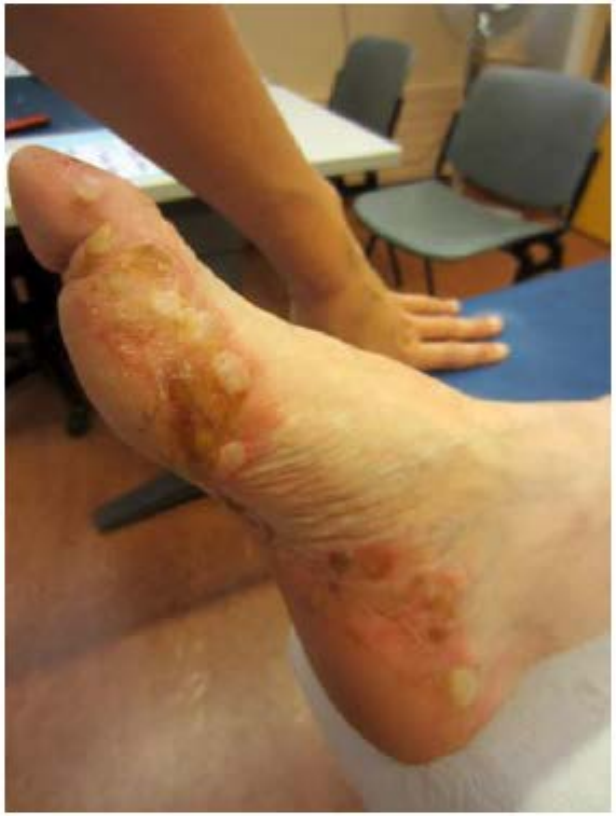
Erythematous papilles,
confluent plaques,
predominantly in regions with fine skin

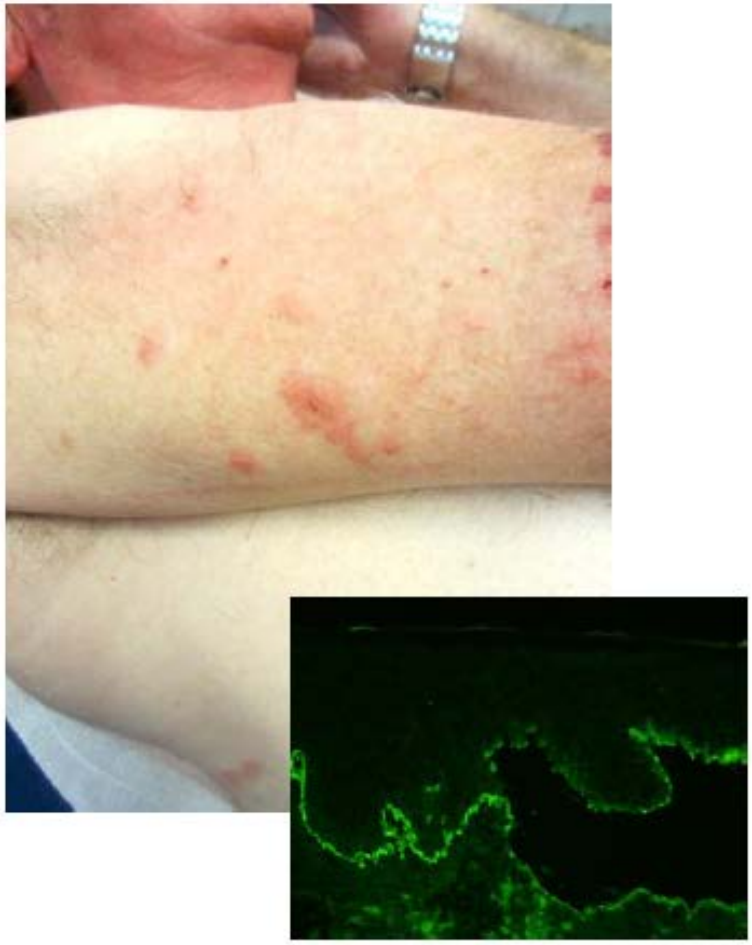


Eczema

Cutaneous irAE

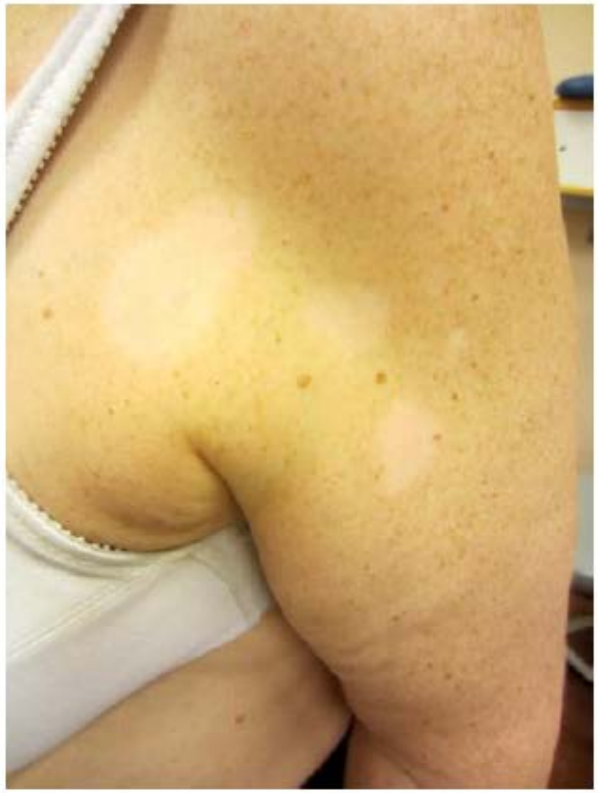
Anti-CTLA-4 / Pemphigoid bulleuse

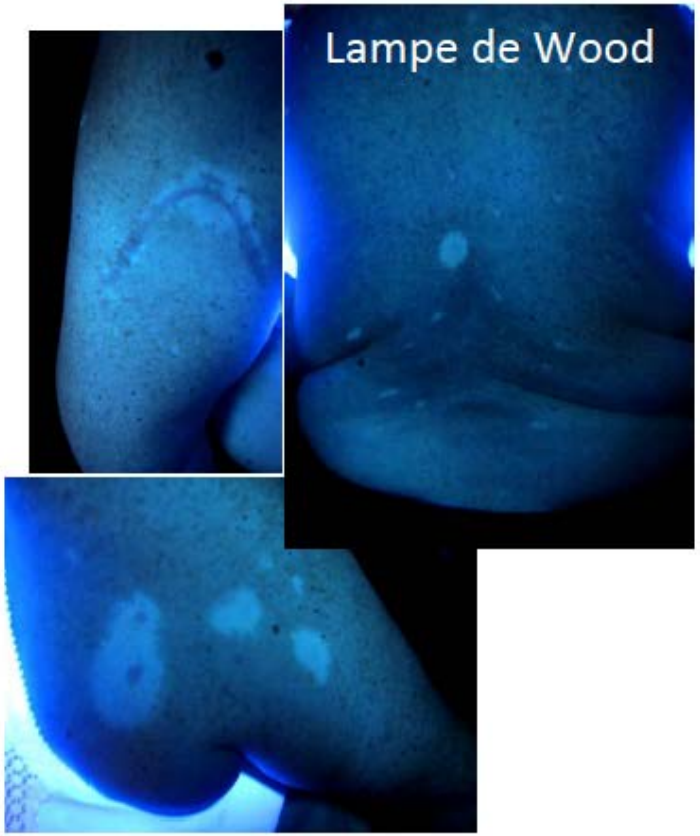




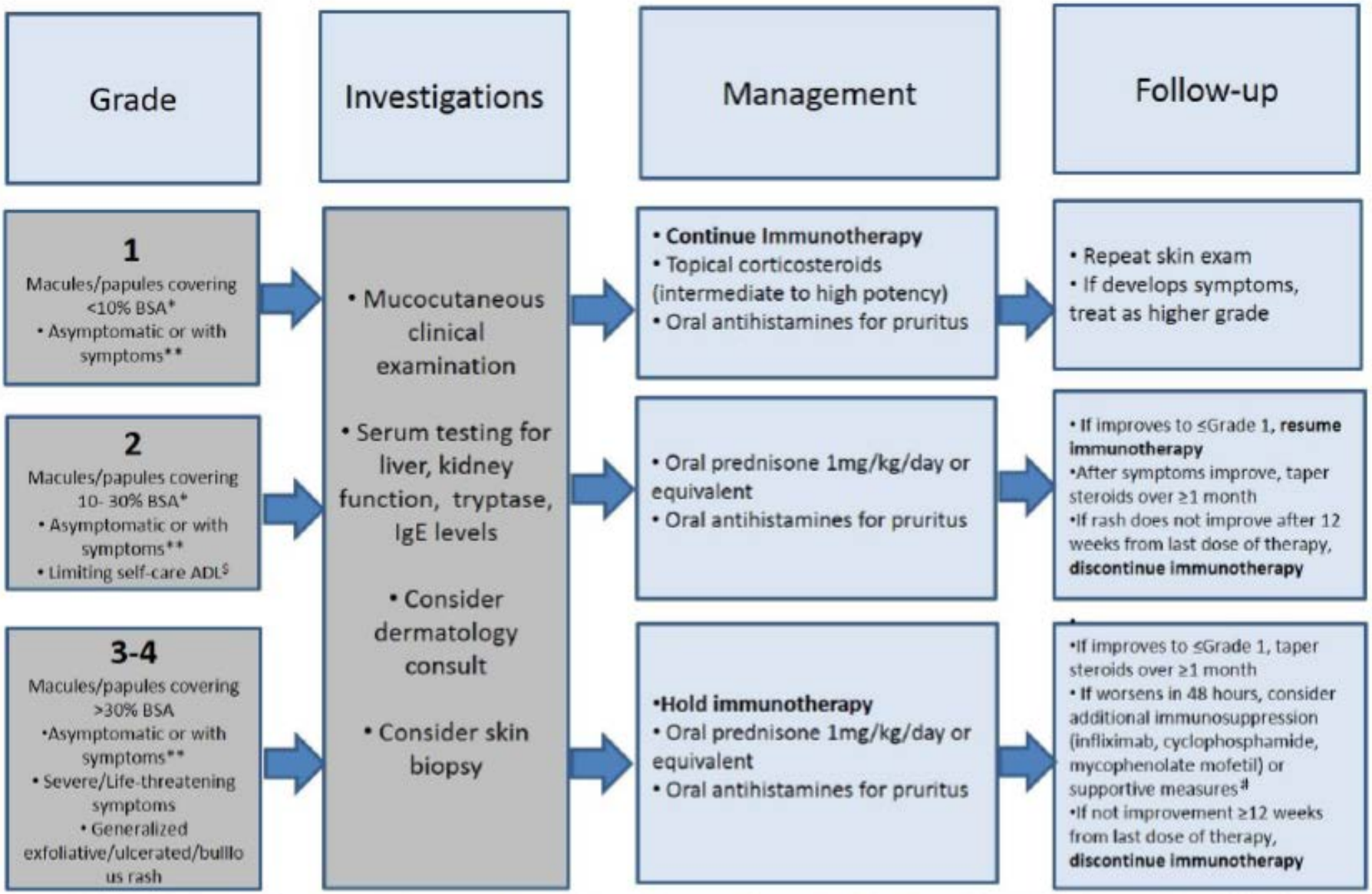
Cutaneous irAE

Anti-CTLA-4 / Vitiligo





Management of Cutaneous irAE

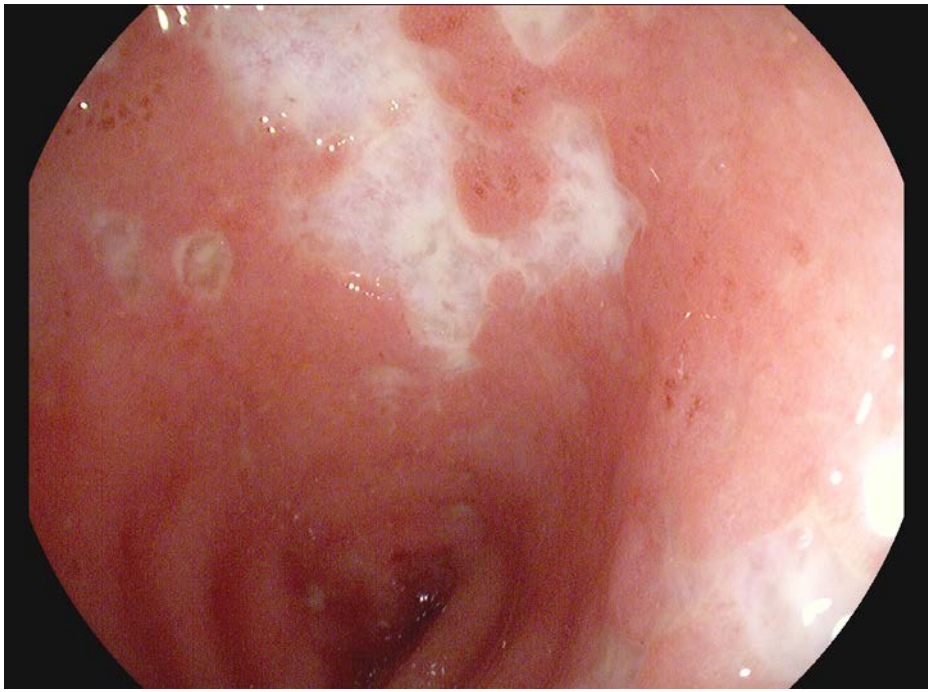


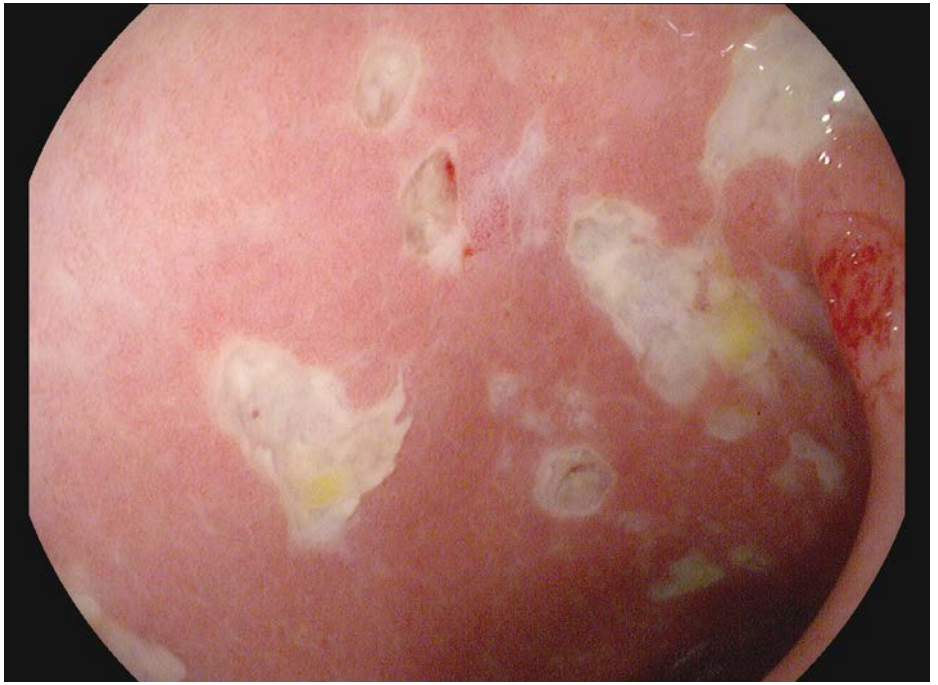
*BSA= Body surface area, **Symptoms: As per CTCAE version 4.0. For example: pruritus, burning, tightness. $ADL= activities of daily living, # Additional supportive measures= prophylactic antibiotics, management in the burns unit.

Colonic irAE

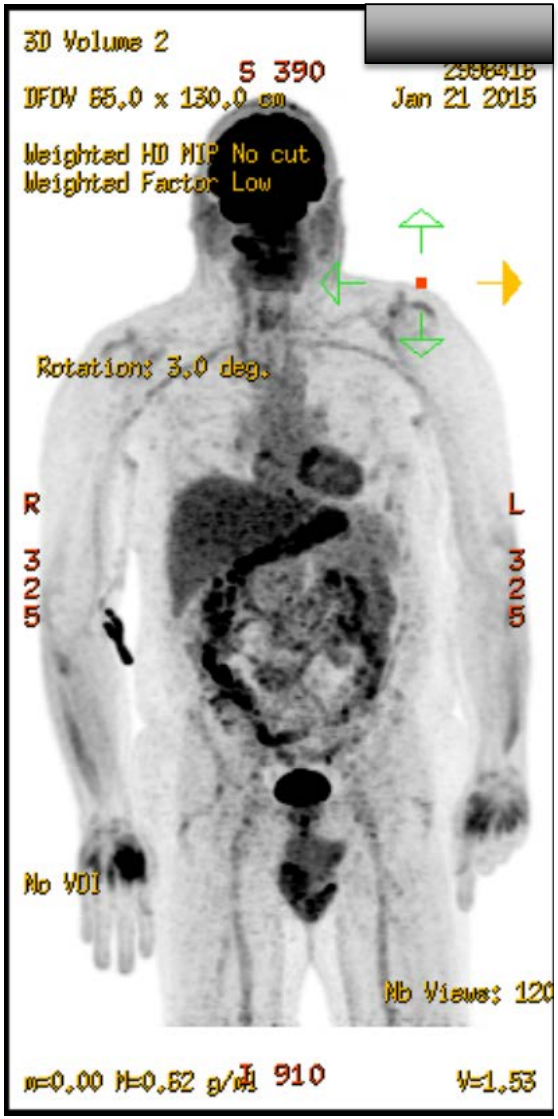
- **Symptoms:** 1. Diarrhea as increased stool frequency 2. colitis: abdominal pain, descending colon is the most common site
- **Examinations**: colonoscopy with biopsies for every grade 2 diarrhea or rectal bleeding, CT Imaging only if severe abdominal pain and/or peritonitis signs, persistent or > grade 2 diarrhea. Rule out infection. C. Difficile, stool cultures, parasites
- **More frequent** with CTLA4 blockade (5-8%), less with PD-1/PD-L1 blockade 1-3%.
- **Pathology:** neutrophilic and lymphocytic infiltration
- **Severity**: could lead to perforation

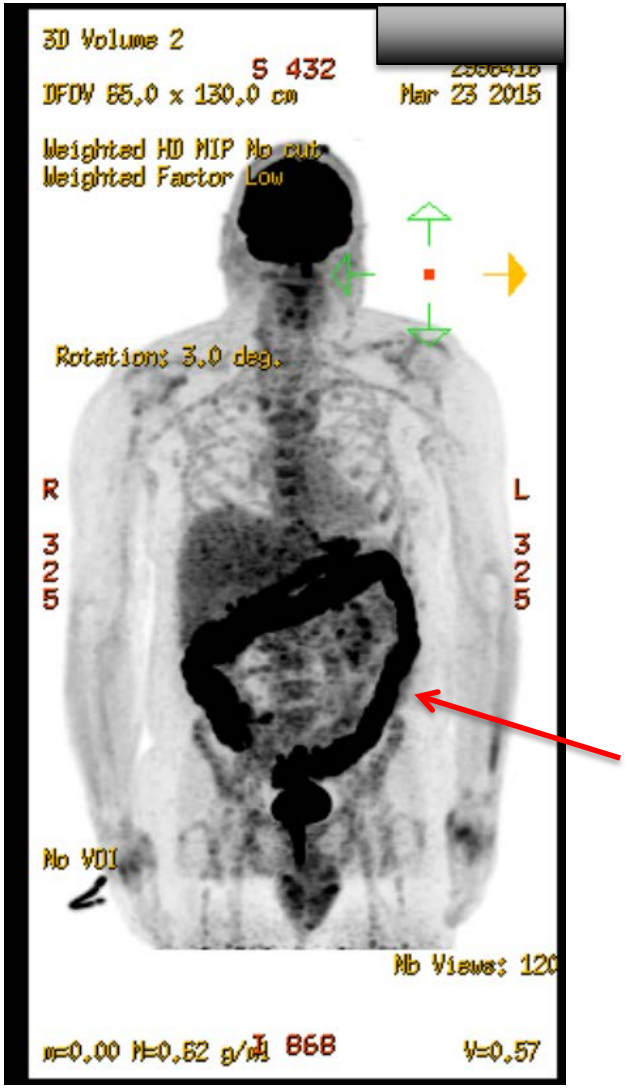
Colonic irAE: endoscopy showing deep ulcers





Pet-CT J-3 C3 (protocol IPI-Bio)





Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

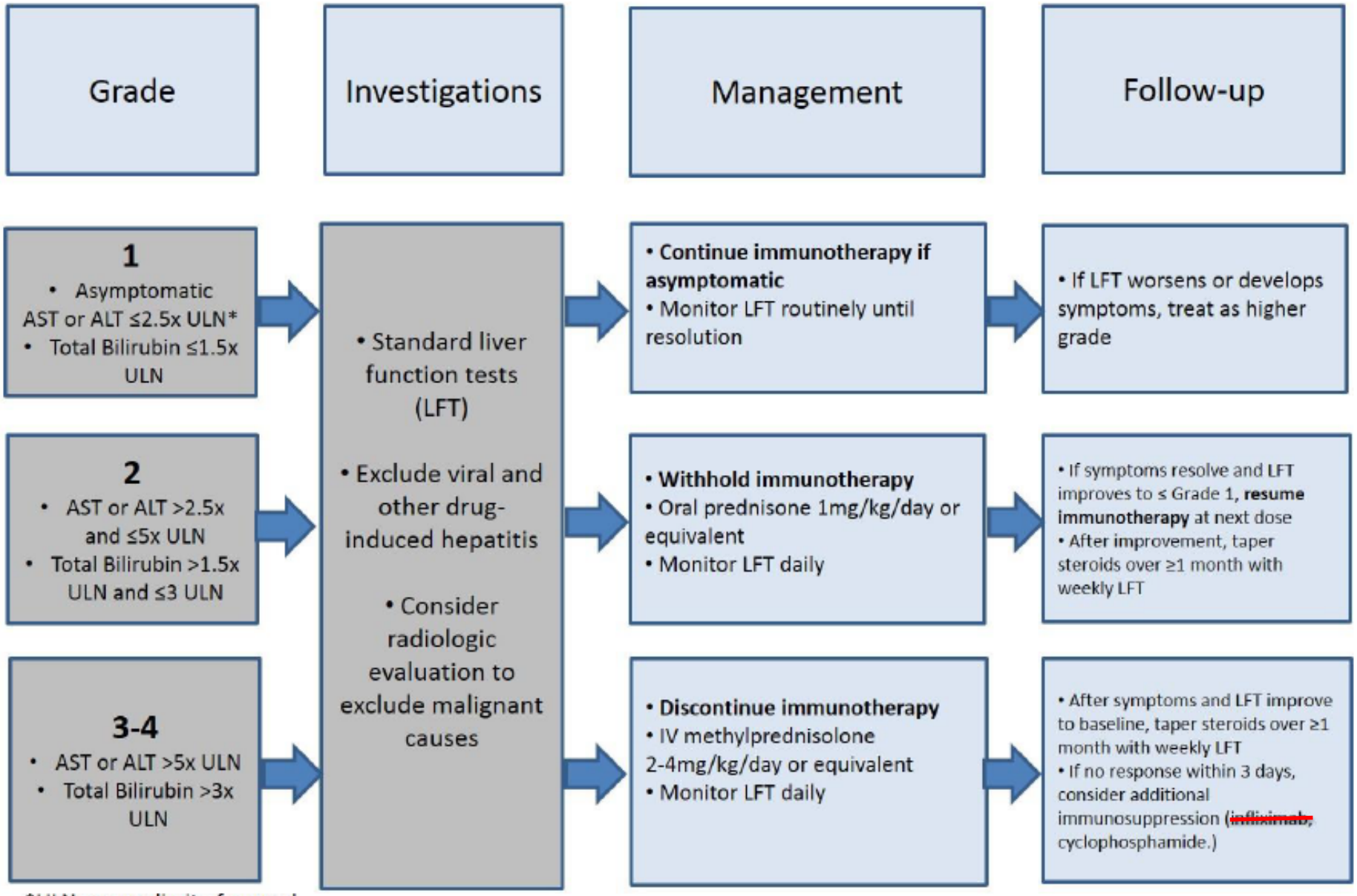
Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Hepatic irAE

- **Symptoms:** 1. Mostly asymptomatic especially if only transaminitis (autoimmune hepatitis), 2. Fever 3. Malaise 4. if bilirubin is also increased symptoms could be linked hyperbilirubinemia (drug induced liver injury, DILI = AST/ALT plus bilirubin increase)
- **Examinations**: US, CT scan /PET, laboratory tests, virology including rare viruses (EBV, CMV), biopsies (repeat if needed),
- **More frequent** with CTLA4 blockade (10%), less with PD-1/PD-L1 blockade 5%.
- **Anti PD1/PD-L1** therapy of HCC results in increased hepatitis (20%)
- **Nivolumab + pazopanib or sunitinib** resulted in increased grade 3/4 irAE of 9 and 20 %.
- **Pathology:** panlobular hepatitis, perivenular infiltrates, or lymphocytic infiltrates around ducts
- **Evolution:** can evolve chronically

Hepatic irAE

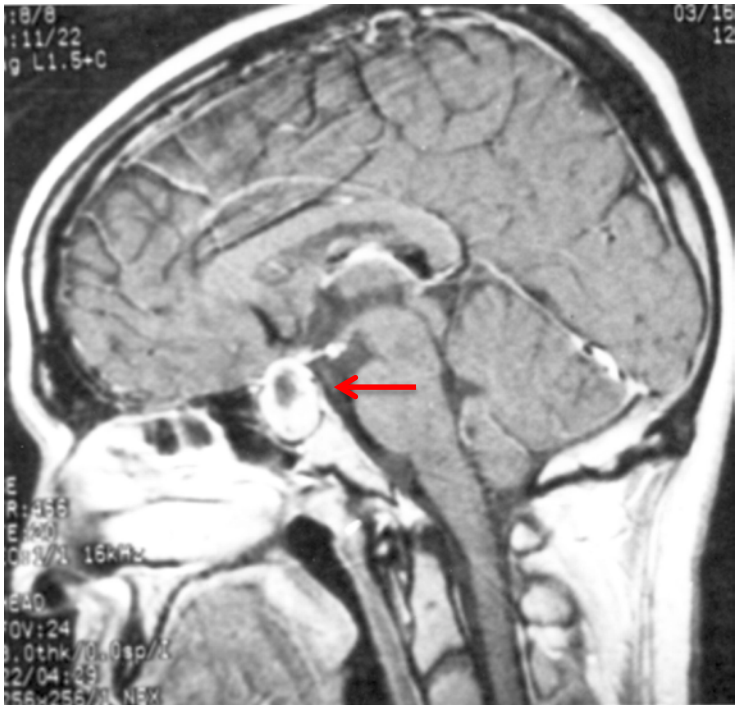


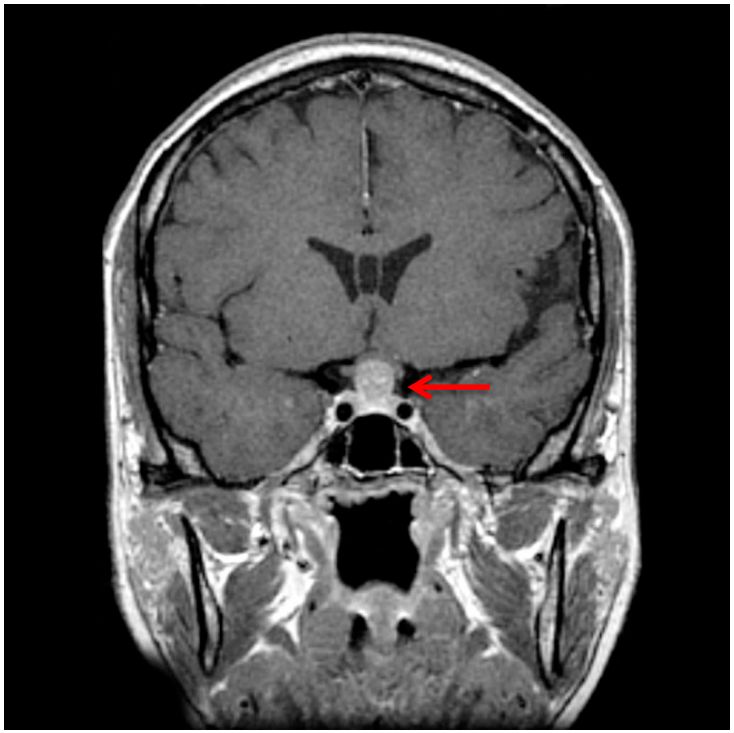
*ULN= upper limit of normal

Endocrine irAE

- **Symptoms**: fatigue, headache, diagnosis can be challenging as symptoms could be non-specific
- **Differential diagnoses**: 1 Disease progression, 2. brain metastases 3. pituitary metastases, 4. pituitary bleeding, 5. meningitis
- **Examinations**: Hormonal tests: TSH, free T4, LH, FSH, ACTH, cortisol, for pituitary gland: MRI, anti-thyroglobulin antibodies, anti-thyroid peroxidase antibodies
- **Thyroid toxicities** more frequent with PD-1/PD-L1 (10%) therapy than with CTLA4 (5%)
- **Hypophysitis** similar incidence between classes
- Complete recovery of gonadal axis has been reported in 57% of men and recovery of the thyroid axe in 37-50% of cases

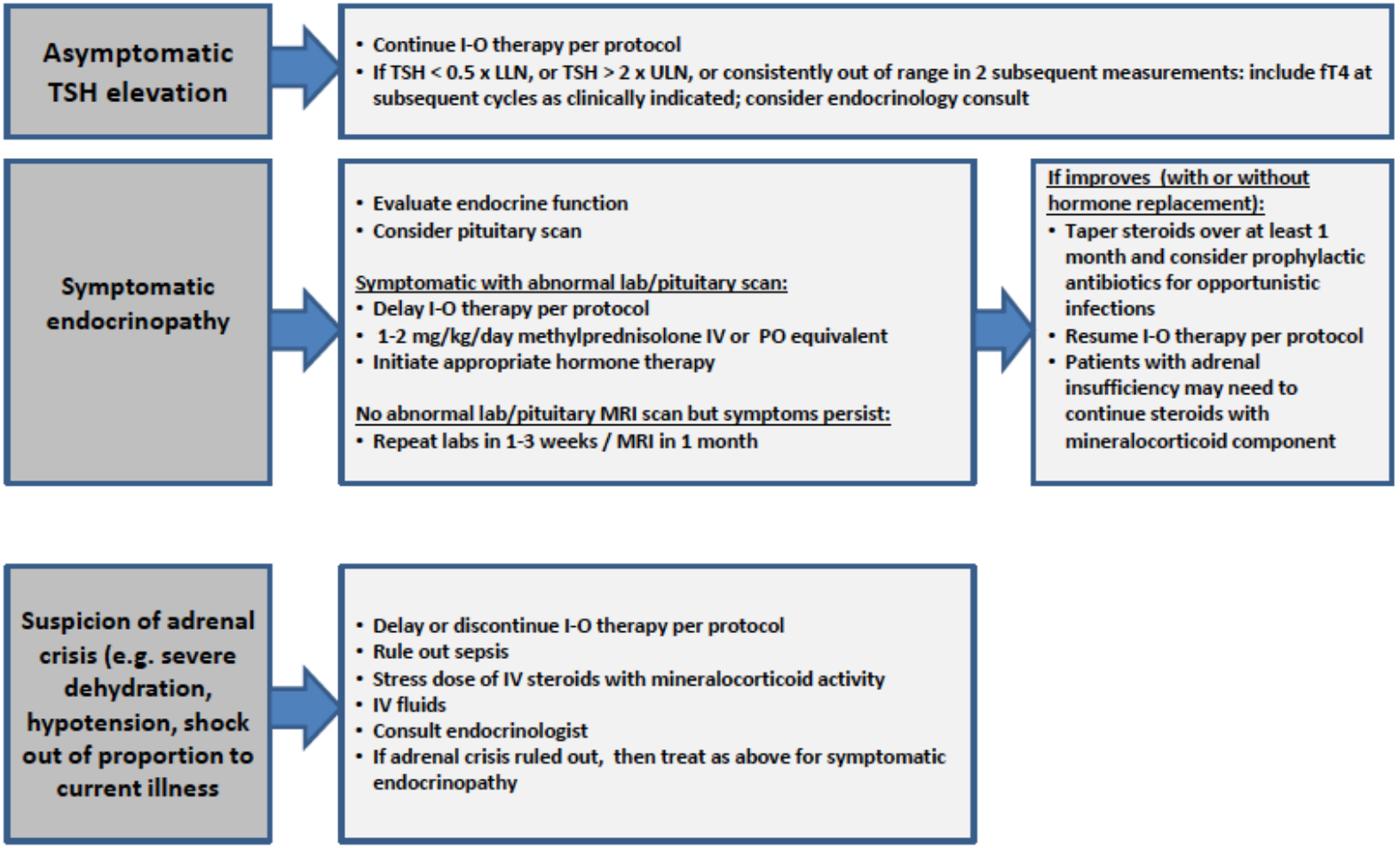
Endocrine irAE





Endocrine irAE

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Rare irAEs

- **Neurological autoimmune disease:**

  1. more frequent with CTLA4 than with PD1/PDL1.

  2. PD1: cases of myasthenia gravis

  3. CTLA4: transverse myelitis, enteric neuropathy, aseptic meningitis, rare cases of Guillain-Barre 6 limbic encephalitis (SCLC)

  4. Therapy: High dose corticoids, IV immunoglobulins, plasmapheresis

- **Pancreatitis**

  1. Asymptomatic increase of lipase and amylase with both CTLA4 and PD1/ PDL1 therapies

  2. Amylase and lipase should not be checked routinely only in case of suspected pancreatitis

- **Renal toxicity**

  1. Interstitial nephritis could occur

  2. Pathological appearances so far only described for CTLA4 in form of lupus nephritis or granulomatous nephritis

  3. Asymptomatic gradual increase of creatinin, which responds well to steroids after exclusion of other causes of renal failure

- **Ocular toxicity**

  1. Uveitis with both classes of agents

  2. Generally treated with topical steroids

  3. Should receive systemic corticoids in case of grade 3/4 toxicity

What if steroids fail?

- Steroids work in most (>99%) of cases. Choose the right dose and start early
- In case steroids fail key is to understand the potential reasons. Talk to a team of experts including: immunologists, organ specialist, infectious disease, clinical pharmacologist

- Colitis: 1st choice is anti-TNF alfa infliximab 5 mg/kg IV, should be given up to max 3 days with lack of improvement, could be repeated every two weeks, exclude infections
- Hepatitis: Infliximab cannot be given since hepatotoxic
- Other options:

1. Mycophenolat mofetil, (CELLCEPT)
2. Tacrolimus
3. Cyclophosphamide
4. IVIG
5. Anti-thymocyte globulin

Take home messages

1. Always look for side effects
2. Treat early proactively even grade 2 toxicity
3. Do not fear of negative impact on outcome
4. Adapt the therapy to the individual (if grade 4 toxicity with no change in 48 hours do not wait until 72 hours)
5. More combinations potentially more side effects
6. Education of non-oncologists in collaborations

Readings:

Naidoo at al. Ann Oncol. 2015 Sep 14. PMID: 26371282

Fecher et al. Oncologist. 2013 Jun;18(6):733-43. PMID: 23774827

Weber et al. J Clin Oncol. 2015 Jun 20;33(18):2092-9. PMID: 25918278

Patient education

What you should know about your treatment

How you are given KEYTRUDA

KEYTRUDA will be given to you in a hospital or clinic under the supervision of an experienced doctor. KEYTRUDA will be administered through an infusion into a vein.

The infusion will last for 30 minutes. The amount of KEYTRUDA you receive depends on how much you weigh. The recommended dose is 2 mg of KEYTRUDA per kilogram of your body weight.

KEYTRUDA is usually given once every 3 weeks. Your doctor will decide how many treatments you need.

Sometimes the tumour may get bigger, in the first few months after starting treatment with KEYTRUDA, before it starts to shrink or new tumours may appear. Your doctor may continue your treatment if your health condition is stable, and will check again to see if you are responding.

It is important that you visit your doctor for your scheduled appointments so your doctor can check your progress and administer KEYTRUDA. If you are unable to keep an appointment, call your doctor right away to reschedule.

Possible side effects

Like all medicines, KEYTRUDA can cause side effects, although not everyone gets them. When you take KEYTRUDA, you can have some serious side effects that need to be treated straight away. It is very important to tell your doctor about any symptoms you notice while taking KEYTRUDA. Your doctor may give you other medicines in order to prevent more severe complications and reduce your symptoms. Your doctor may withhold the next dose of KEYTRUDA or stop your treatment.

Getting your treatment

About OPDIVO® (nivolumab) infusions

OPDIVO is given intravenously (IV) through a needle placed in a vein while under medical supervision. OPDIVO infusions take approximately 60 minutes. Your healthcare provider will decide how many treatments you need.

Dosing frequency

Recommended OPDIVO treatment is usually every 2 weeks. It is recommended that you stay on OPDIVO unless the melanoma grows or you have unacceptable side effects. If you do experience side effects, your oncologist may decide to delay or stop OPDIVO, or give you other medicines to treat your symptoms. Be sure to talk with your healthcare team about any side effects. Your healthcare provider will do blood tests to check you for side effects.

Scheduling your treatments

Scheduling your treatments in advance may help you stay on top of your appointments and also give you one less thing to worry about. Try to schedule your appointments for the same day of the week and the same time of day to make it easier to remember. It is important for you to keep all appointments with your healthcare provider. If you miss one, call your healthcare provider as soon as possible to reschedule your appointment.

What should I tell my healthcare provider before receiving OPDIVO?

Before receiving OPDIVO, tell your healthcare provider about:

- Health problems, if you:
  - have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
  - have had an organ transplant
  - have lung or breathing problems
  - have liver problems
  - have any other medical conditions
  - are pregnant or plan to become pregnant
    - OPDIVO can harm your unborn baby
    - females who are able to become pregnant should use an effective method of birth control during and for at least 5 months after the last dose of OPDIVO. Talk to your healthcare provider about birth control methods that you can use during this time
    - tell your healthcare provider right away if you become pregnant during treatment with OPDIVO
  - are breastfeeding or plan to breastfeed
    - it is not known if OPDIVO passes into your breast milk
    - do not breastfeed during treatment with OPDIVO
- All the medicines they take, including all prescription and non-prescription medicines; vitamins; and herbal supplements

Before starting a new medicine, patients should talk with their oncologist who prescribed OPDIVO.

Antitumor Response and Corticosteroid Use To Manage Immune-Mediated AEs

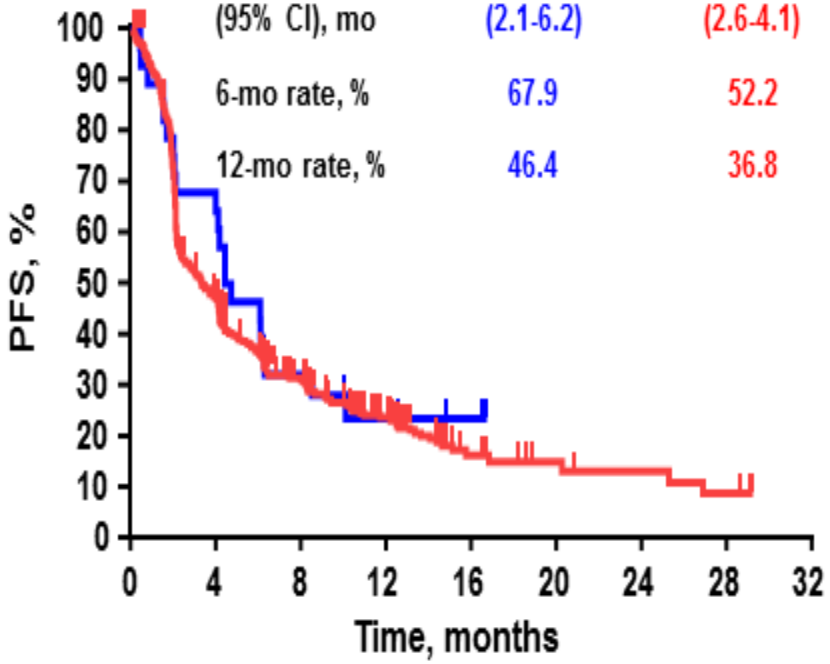
	Steroid Use (n = 28)	No Steroid Use (n = 522)
CR,[a] % (95% CI)	0.0 (0.0-12.3)	0.8 (0.2-2.0)
ORR,[a] % (95% CI)	32.1 (15.9-52.4)	19.5 (16.2-23.2)
DCR,[a] % (95% CI)	64.3 (44.1-81.4)	49.6 (45.2-54.0)
Time to response, median (range), months	2.0 (1.8-3.9)	2.1 (1.4-19.4)
Duration of response, median (range), months	NR (4.2-14.5+)	23.3 (1.0+-23.3)

[a]Assessed per RECIST v1.1 by central review.
Data cutoff date: January 23, 2015.

N. Leighl
Presented at WCLC 2015

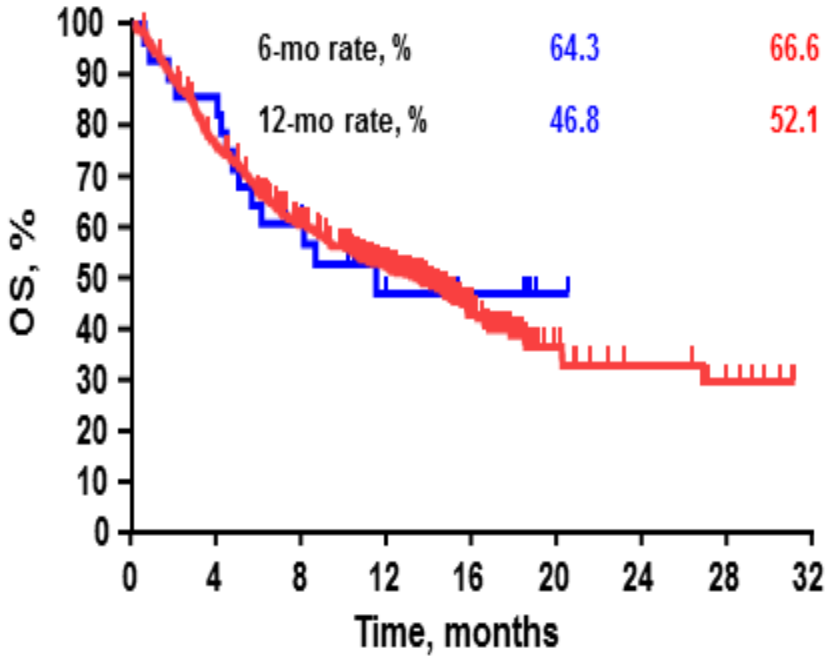
Survival and Corticosteroid Use To Manage Immune-Mediated AEs

PFS, RECIST v1.1	Steroid Use (n = 28)	No Steroid Use (n = 522)
Median (95% CI), mo	4.6 (2.1-6.2)	3.4 (2.6-4.1)
6-mo rate, %	67.9	52.2
12-mo rate, %	46.4	36.8



No. at risk									
Steroid use	28	18	8	4	2	0	0	0	0
No steroid use	522	239	127	65	17	8	6	4	0

OS	Steroid Use (n = 28)	No Steroid Use (n = 522)
Median (95% CI), mo	11.4 (5.0-NR)	13.5 (10.6-15.5)
6-mo rate, %	64.3	66.6
12-mo rate, %	46.8	52.1

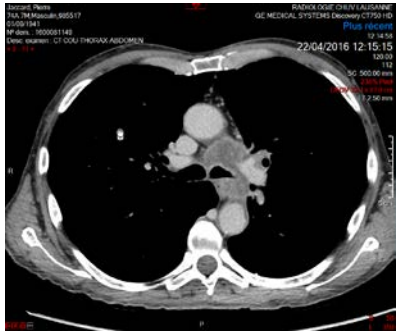


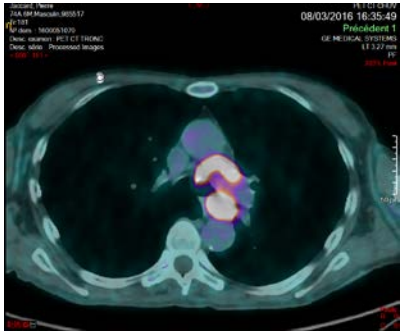
No. at risk									
Steroid use	28	23	15	7	5	1	0	0	0
No steroid use	522	388	285	195	63	21	11	7	0

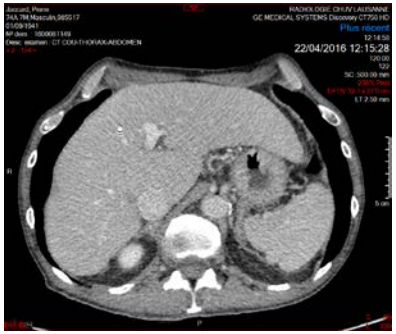
Data cutoff date: January 23, 2015.

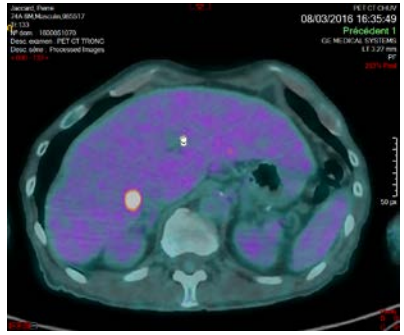
N. Leighl
Presented at WCLC 2015

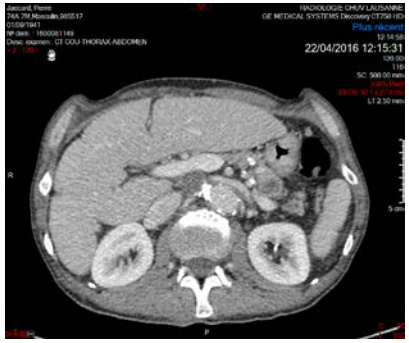
A 74-year-old Caucasian man, heavy smoker, diagnosed with stage IV (cT1a cN2 cM1b (liver, pancreas, parotid, muscle and bone)
NSCLC (ADC) on February 2016.

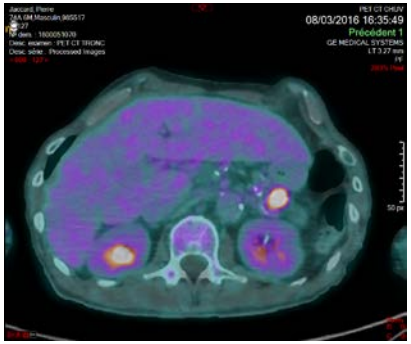


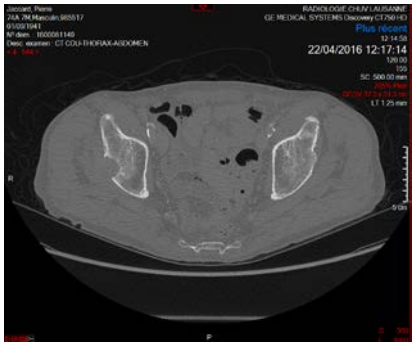


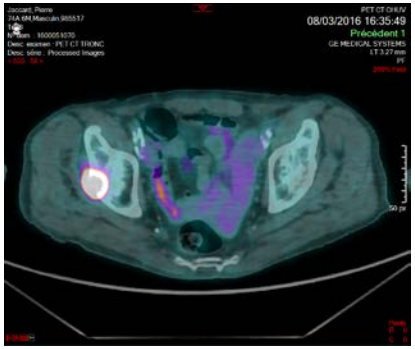




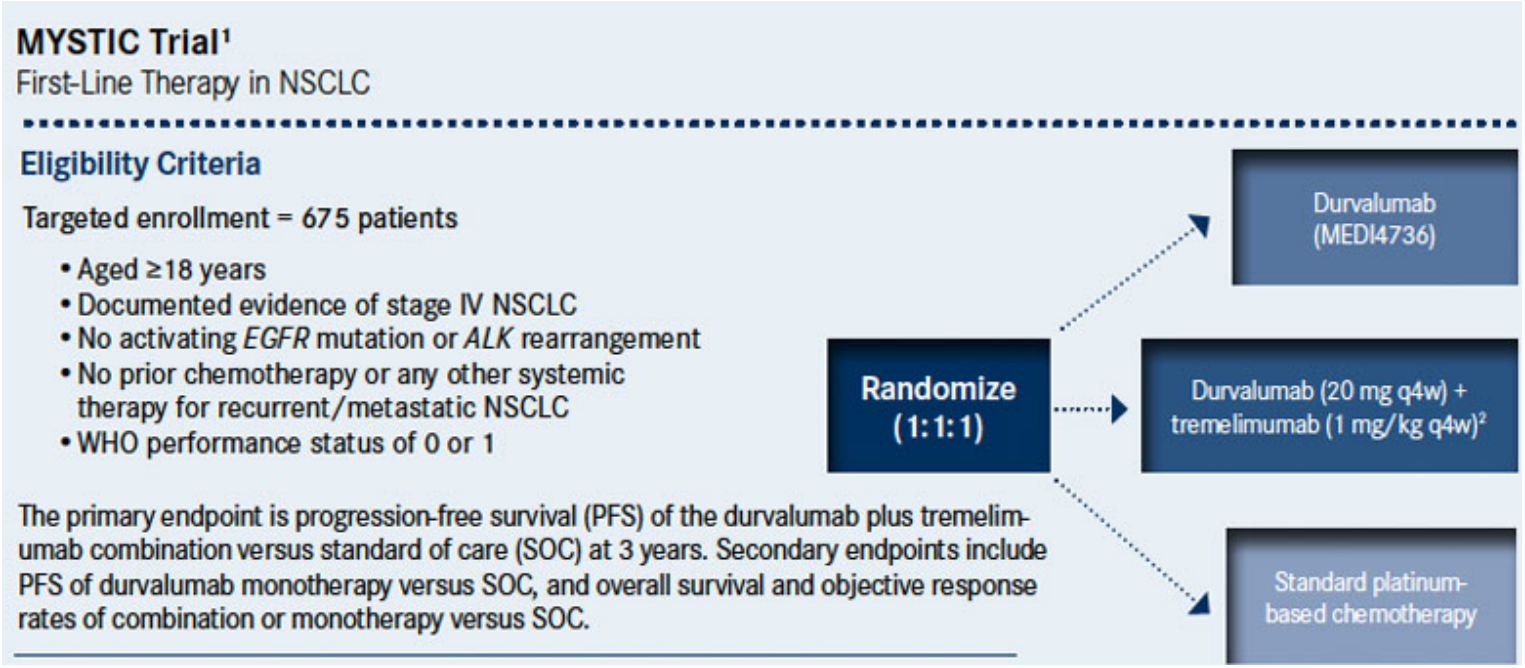




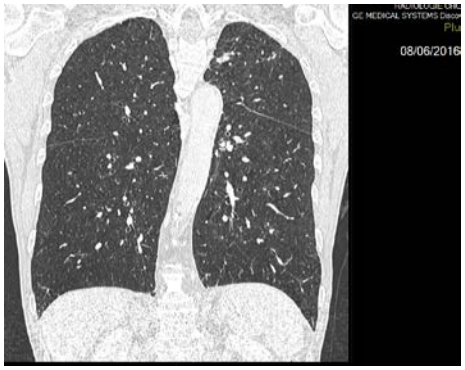




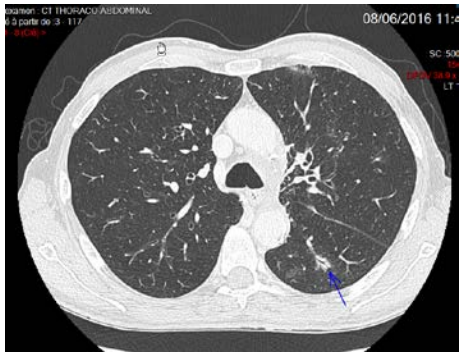
27.04.2016: Inclusion in Phase III trial “MYSTIC” with durvalumab + tremelimumab

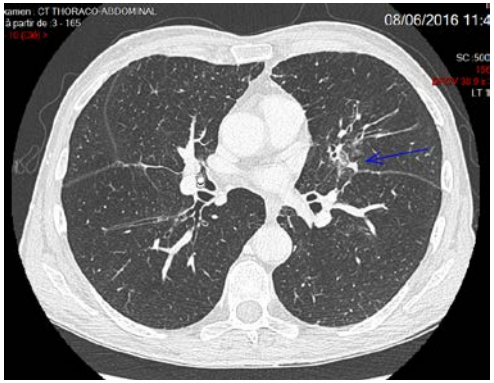


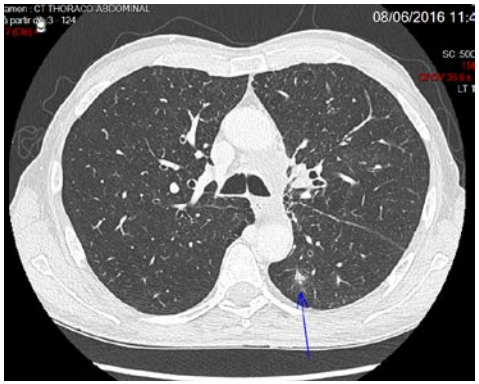
7 weeks later, after 2 cycles



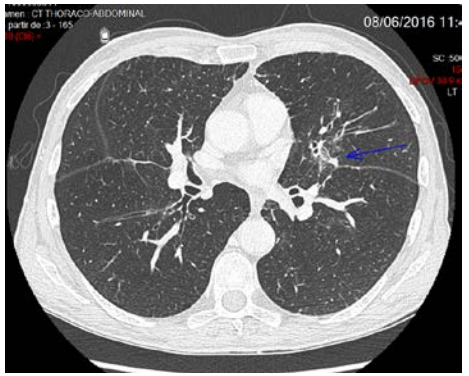
Slight increasing of dyspnea associated to cough



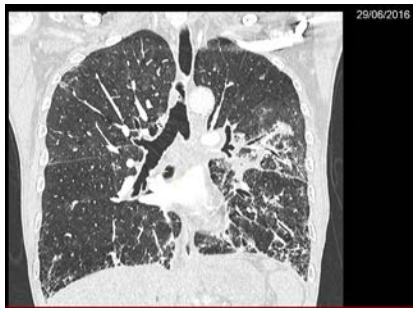


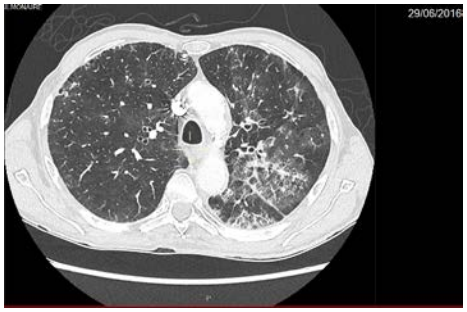


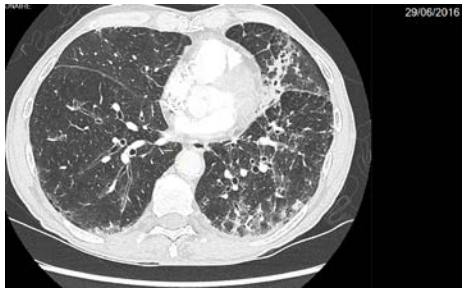
Empirical antibiotherapy

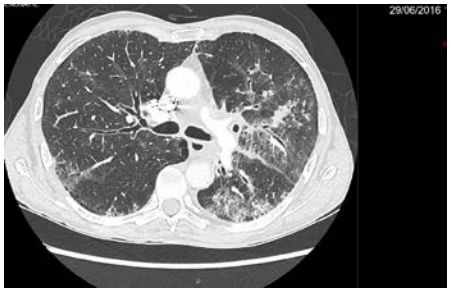


10 weeks later, after 3 cycles







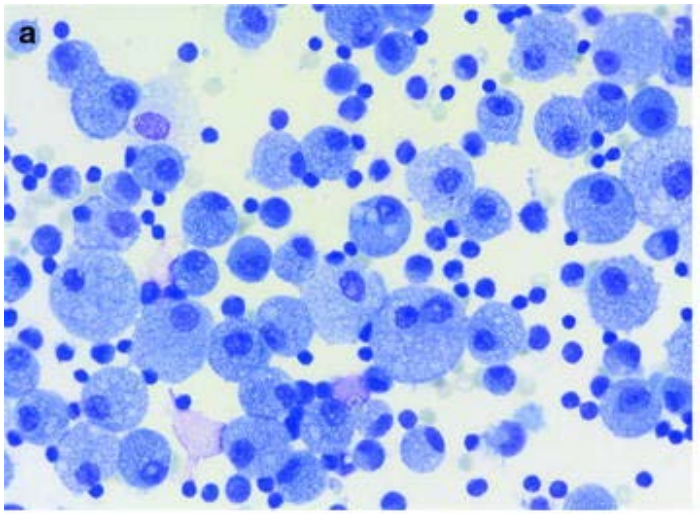


Biologie délocalisée (P.O.C.T.) — 01.07.16 09:34

Gazométrie (P.O.C.T.)

		Artériel
Prélèvement		
Fraction inspirée d'O2	%	21.0
Température	°C	37.0
Hémoglobine	(133 - 177) g/l	134
pH	(7.35 - 7.45)	7.476 H
Pression CO2	(35 - 45) mmHg	28.7 L
Pression O2	(73 -103) mmHg	54.1 L
Bicarbonate	(22 - 26) mmol/l	20.9 L
CO2 total	(23 - 27) mmol/l	
ABE	(-2-+2) mmol/l	-1.1
SBE	(-2-+2) mmol/l	
Bicarbonate standard	(22 - 26) mmol/l	23.3
Saturation en O2	(95 - 99) %	88.9 L
Contenu en O2	(23 - 27) vol%	16.4 L
p50	(24.7 - 28.6) mmHg	25.39
Carboxyhémoglobine	(0.0 - 0.8) %	1.9 H
Méthémoglobine	(0.2 - 0.6) %	-0.2 L
Oxyhémoglobine	(94 - 98) %	87.4 L
Hémoglobine réduite HB	(0 - 6) %	
Sodium	(135 - 145) mmol/l	
Potassium	(3.5 - 4.6) mmol/l	
Chlorure	mmol/l	
Calcium ionisé(pH 7.4)	mmol/l	
Glucose	(4.2 - 6.1) mmol/l	
L-lactate	(0.63 - 2.44) mmol/l	2.00

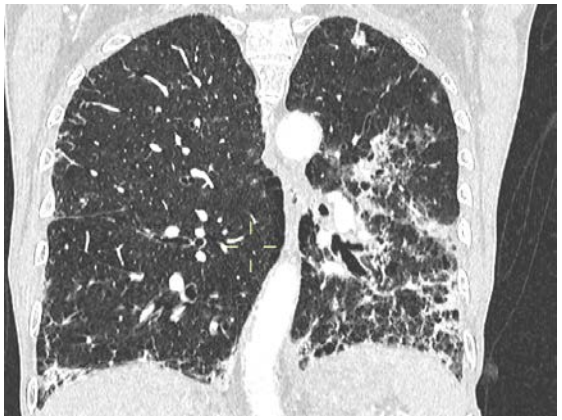
BAL

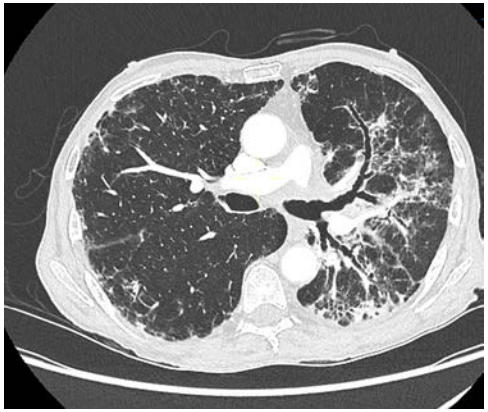


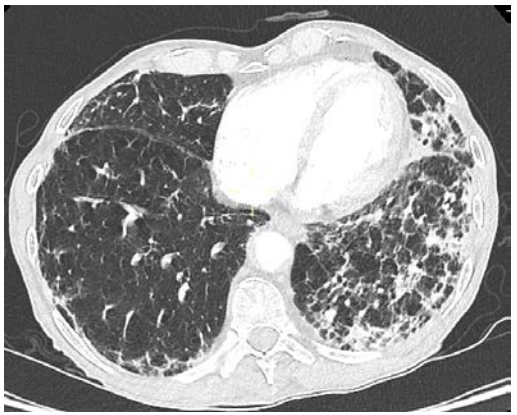
Répartition cellulaire :	%	*Normes* **
macrophages	51	*> 85*
neutrophiles	3	*< 3*
éosinophiles		*< 0,5*
lymphocytes	46	*< 12*
cellules bronchiques		*< 10*
cellules pavimenteuses		
cellules mal conservées		
autres		

Microbiology: no germ

Diagnosis	Immunotherapy-induced interstitial lung disease
Treatment	Prednisone without clinical improvement therefore: Methylprednisolone
Clinical response	Persistent dyspnea Abrupt decrease of oxygen saturation







Treatment

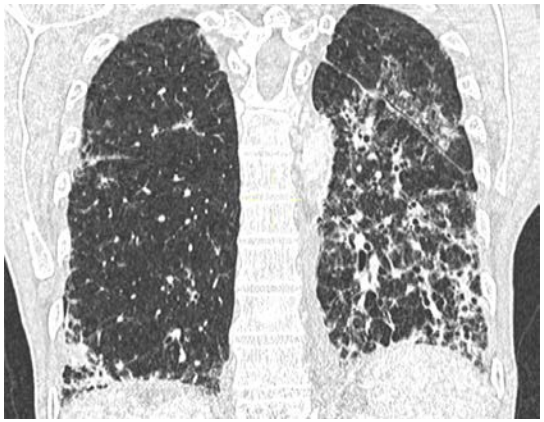
Infliximab

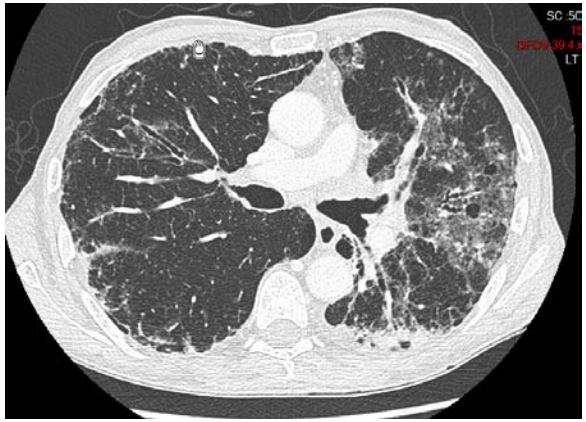
Bactrim prophylaxis

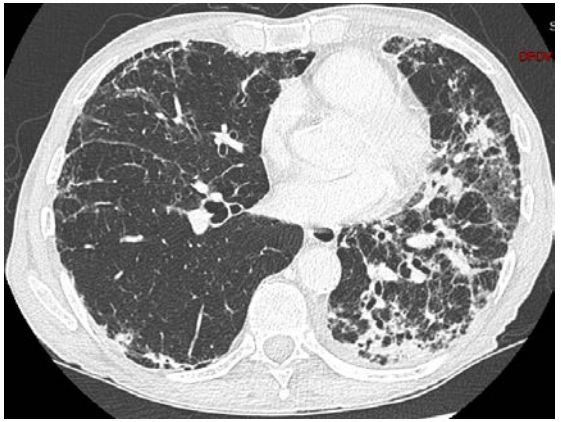
Four days after Infliximab

Decrease of dyspnea

Oxygen saturation 92-96%





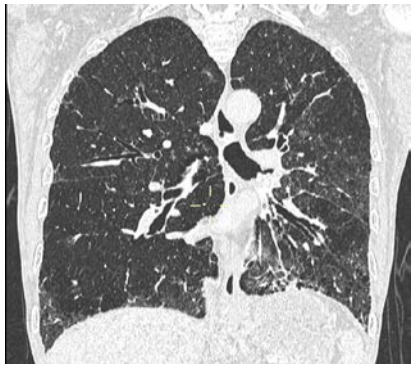


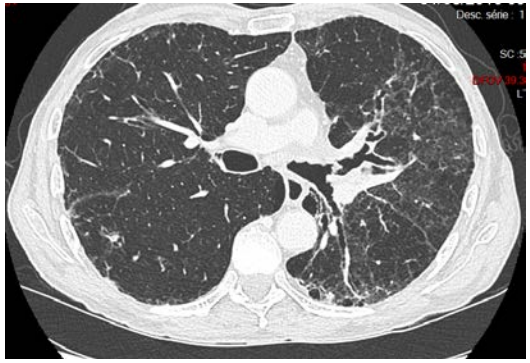
Treatment

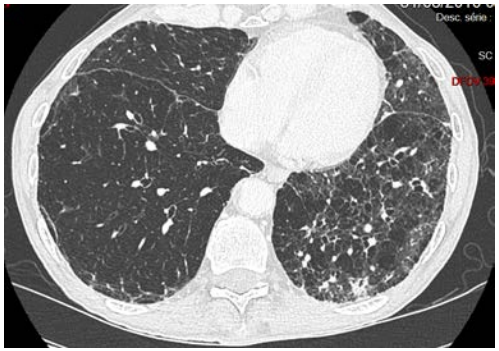
Prednisone ongoing

Bactrim ongoing

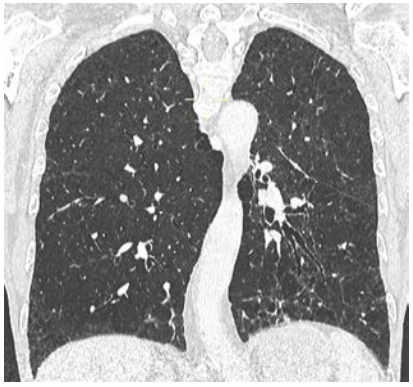
Six weeks after Infliximab

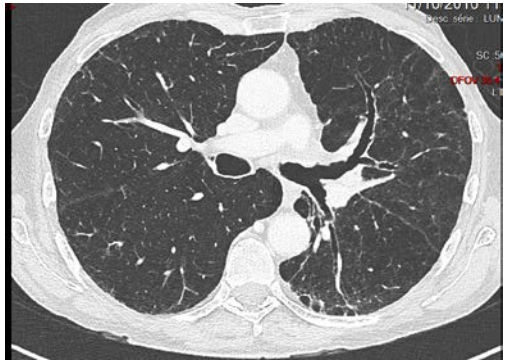


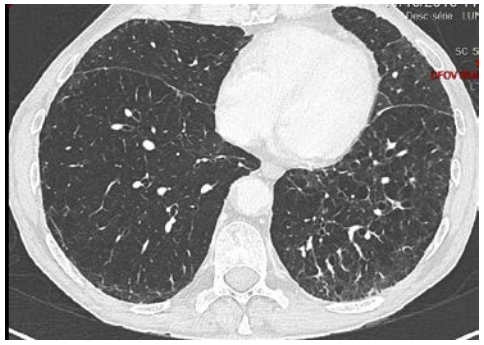




Three months after Infliximab







Thank you!