
# Eventi avversi Immunomediati:

## Diagnosi precoce e gestione

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Desenzano, 14 Marzo 2017

# ADVERSE EVENT IN ONCOLOGY

- Impact on **quality of life** of patients

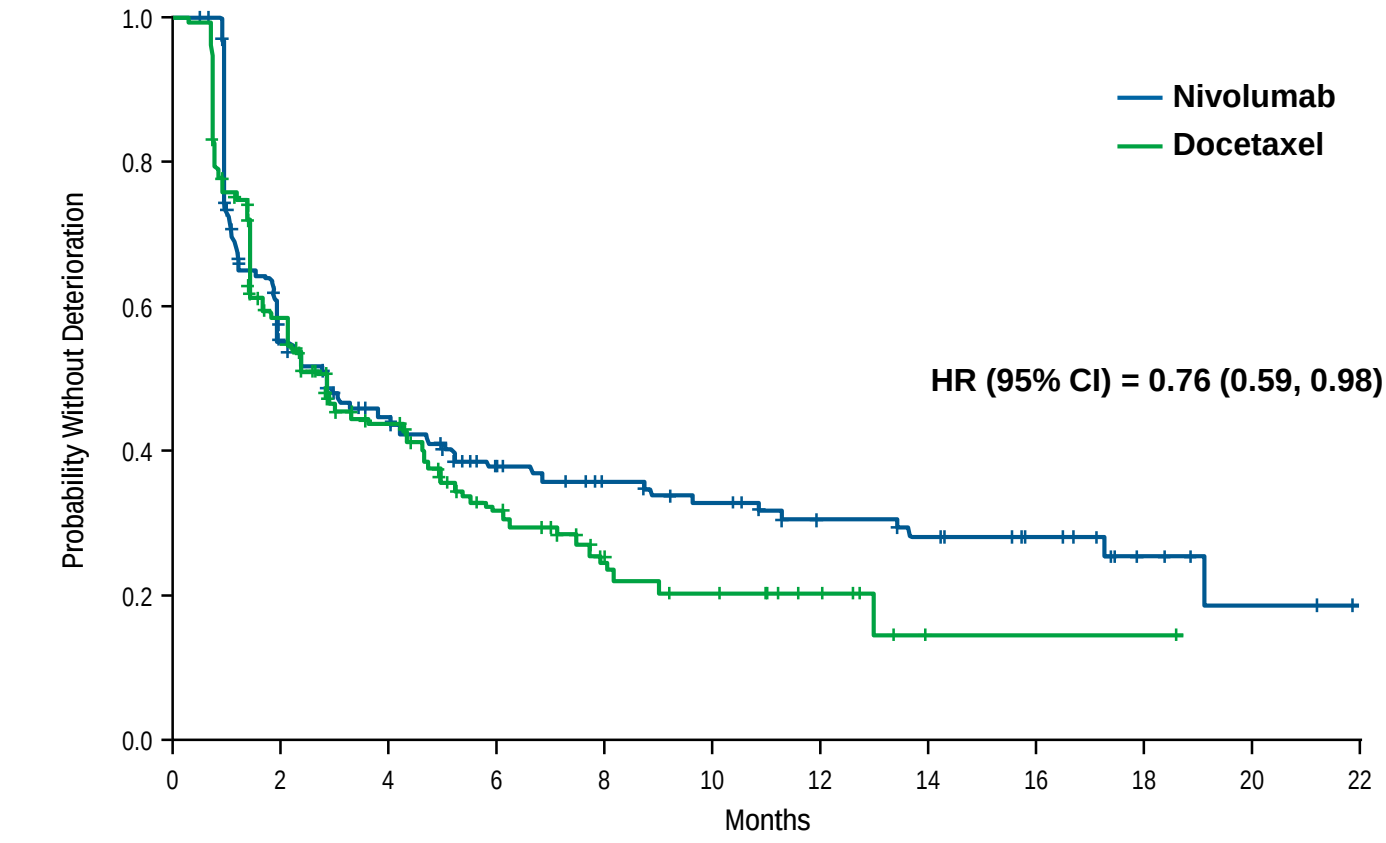
- Impact on **efficacy of treatment**
  (dose reduction and discontinuation)

- Impact on cost

- Impact on what oncologists need to know

# IMMUNOTHERAPY AND QUALITY OF LIFE

## Time to first deterioration (EQ5D VAS- Second-line-Checkmate 057)




| No. of patients: | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivolumab | 208 | 94 | 66 | 45 | 39 | 33 | 25 | 22 | 15 | 6 | 3 | 0 |
| Docetaxel | 212 | 104 | 59 | 33 | 15 | 12 | 6 | 1 | 1 | 1 | 0 | 0 |

Reck M et al, ESMO 2016

# IMMUNOTOXICITY AND EFFICACY-discontinuation

## Second-line: Checkmate 017-057 long-term results > 2 year fu

| Disposition (treated patients) | CheckMate 017 (SQ NSCLC) | | CheckMate 057 (non-SQ NSCLC) | |
|---|---|---|---|---|
| | Nivolumab (n = 131) | Docetaxel (n = 129) | Nivolumab (n = 287) | Docetaxel (n = 268) |
| **Continuing on treatment, %** | 8 | 0 | 9 | 0 |
| **Discontinued treatment, %** | 92 | 100 | 91 | 100 |
| **Reasons for discontinuation, %** | | | | |
| Disease progression | 72 | 62 | 70 | 67 |
| Study drug toxicity | 7 | 10 | 7 | 16 |
| AE unrelated to study drug | 5 | 10 | 8 | 4 |
| Death | 0 | 0 | <1 | <1 |
| Other[a] | 8 | 18 | 5 | 13 |
| **Subsequent therapy (all randomized patients)** | **Nivolumab (n = 135)** | **Docetaxel (n = 137)** | **Nivolumab (n = 292)** | **Docetaxel (n = 290)** |
| **Crossover to nivolumab, %** | NA | 4 | NA | 6 |
| **Received subsequent systemic therapy,[b] %** | 41 | 32 | 46 | 52 |

Barlesi F et al, ESMO 2016

# IMMUNOTOXICITY AND EFFICACY-discontinuation

## After the first-line: EAP

| Discontinuations | CNS metastases (n = 37) | All patients (N = 371) |
|---|---|---|
| **Discontinued treatment, n (%)** | 27 (73) | 281 (76) |
| **Reason for discontinuation, n (%)** | | |
| Progressive disease | 16 (59) | 160 (57) |
| Death | 6 (22) | 64 (23) |
| AEs/Serious AEs | 1 (4) | 21 (7) |
| Other[a] | 4 (15) | 36 (13) |

Bidoli P et al, ESMO 2016

# IMMUNOTOXICITY AND EFFICACY-

## How discontinuation and steroids use affect outcome

CHECKMATE 069

AE leading to discontinuation: 30% (NIVO+IPI) and 9% (IPI)

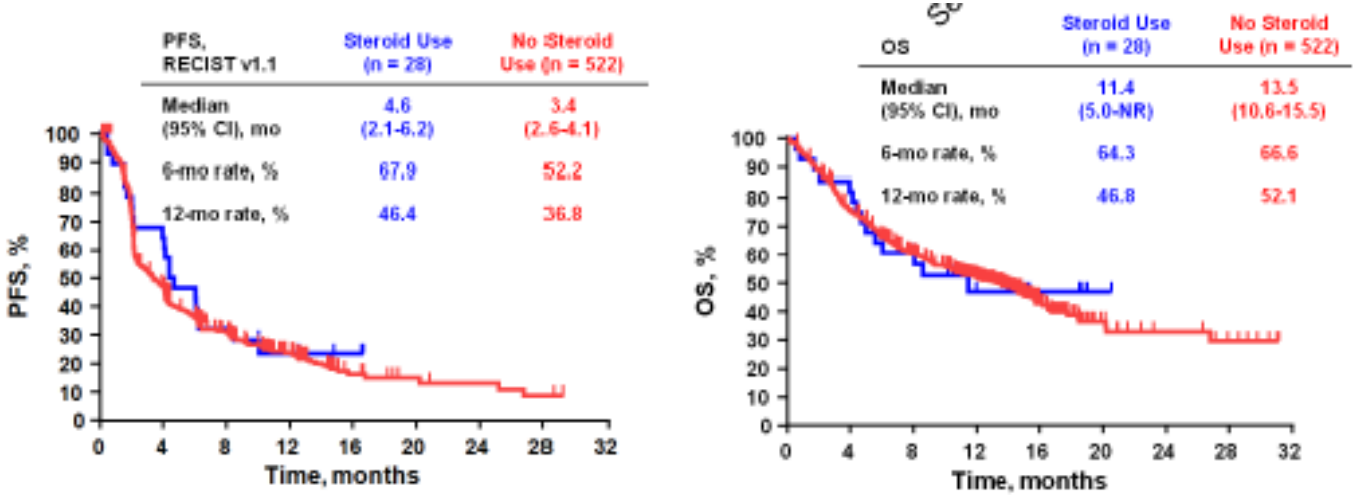
| | All randomized discontined due to toxicity | | All randomized (BRAF wt) | |
|---|---|---|---|---|
| | NIVO+IPI (N:44) | IPI (N:10) | NIVO+IPI (N:72) | IPI (N:37) |
| **Median OS, months (95% CI)** | NR | 11.2 (2.2-NR) | NR | NR |
| **18-month OS rate (%)** | 79.5 | 40 | 73.2 | 56 |

Hodi FS et al, ASCO 2016

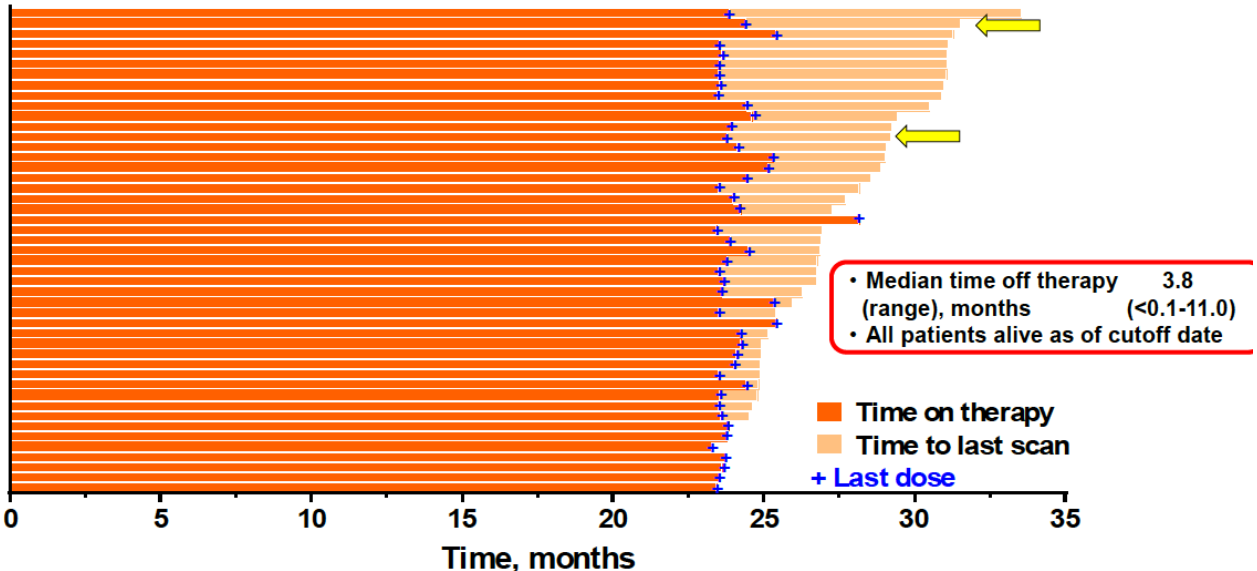
# IMMUNOTOXICITY AND EFFICACY-

## How discontinuation and steroids use affect outcome

## Keynote 01

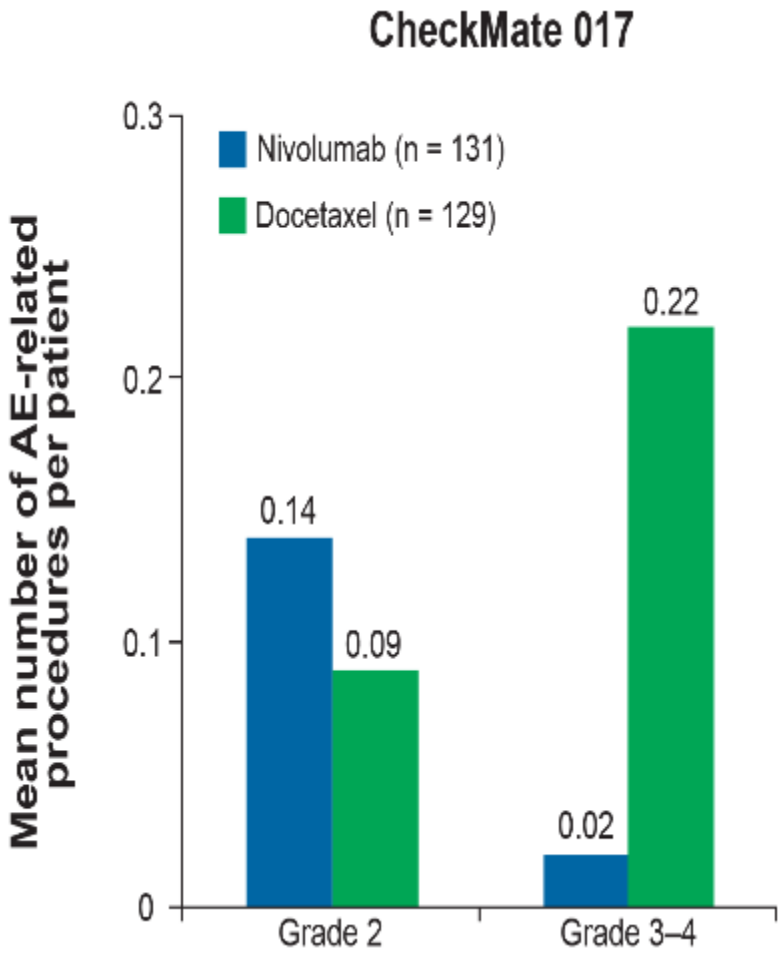


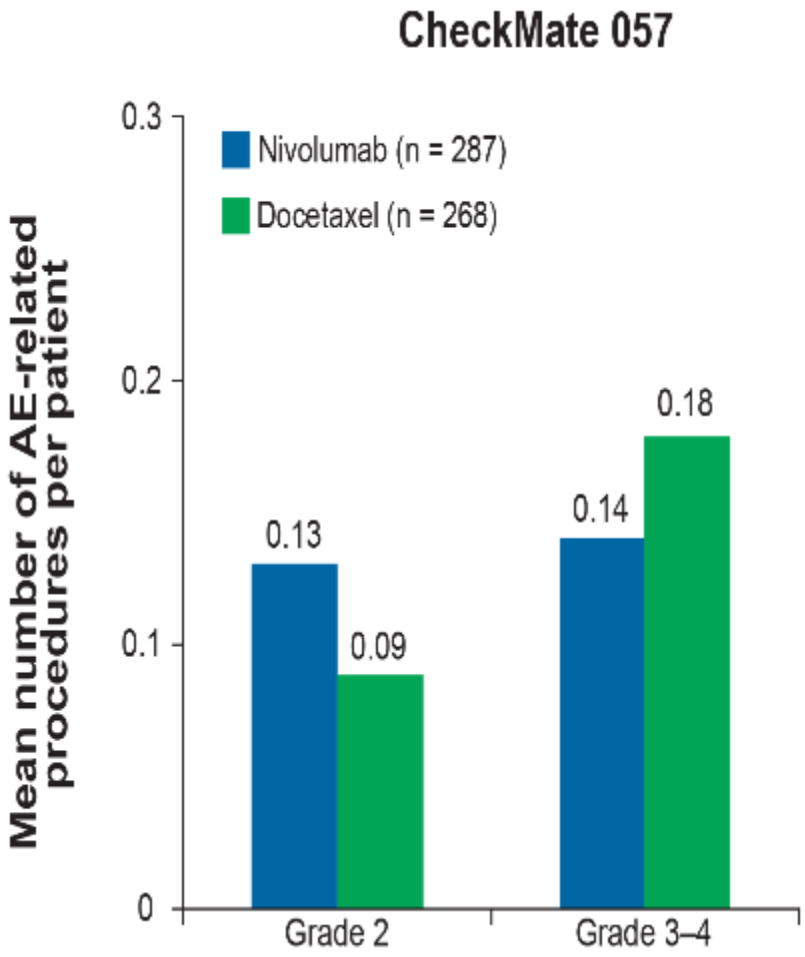

Leighl N et al, WCLC 2016




Herbst RS et al, WCLC 2016

# IMMUNOTOXICITY AND COST




Barlesi F et al, ESMO 2016

# IMMUNOTOXICITY: WHAT WE NEED TO KNOW EVERYDAY

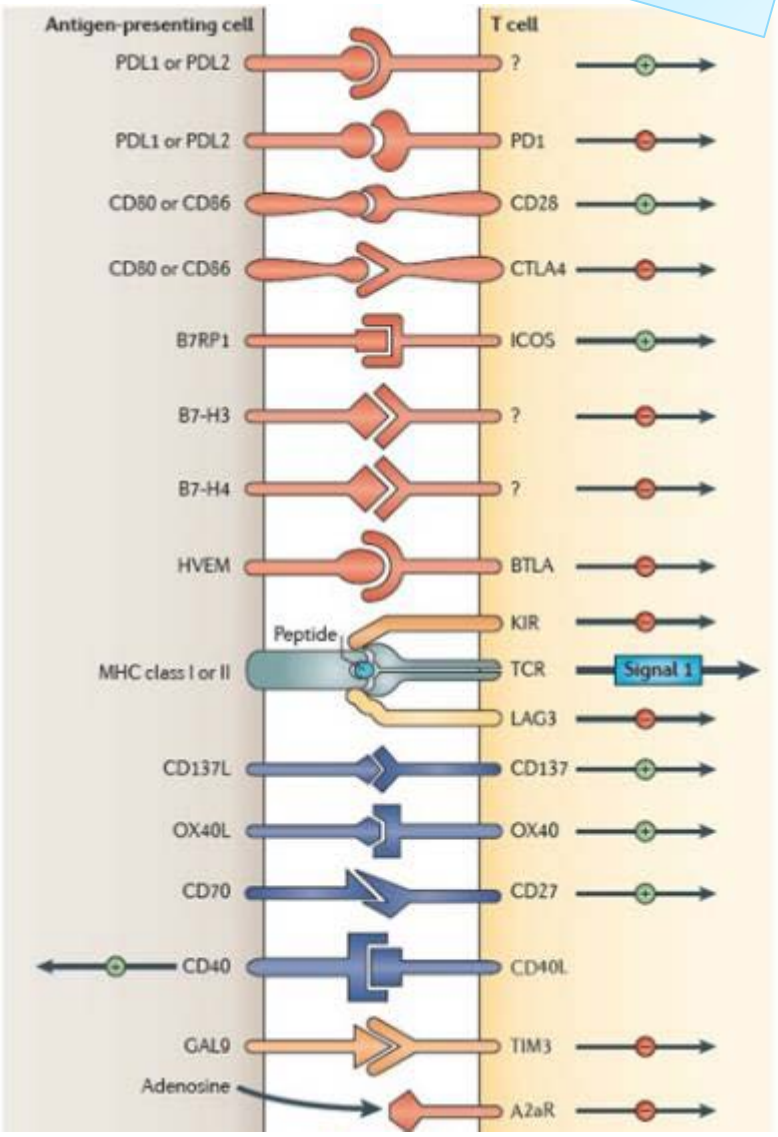
- ✓ **WHY**
- ✓ **WHAT**
- ✓ **WHEN**
- ✓ **HOW TO TREAT**

# Immune checkpoints

WHY

- Maintain self-tolerance
- Modulate the duration and amplitude of immune responses in peripheral tissues

**The blockade of immune checkpoints unleashes the antitumor immune response**



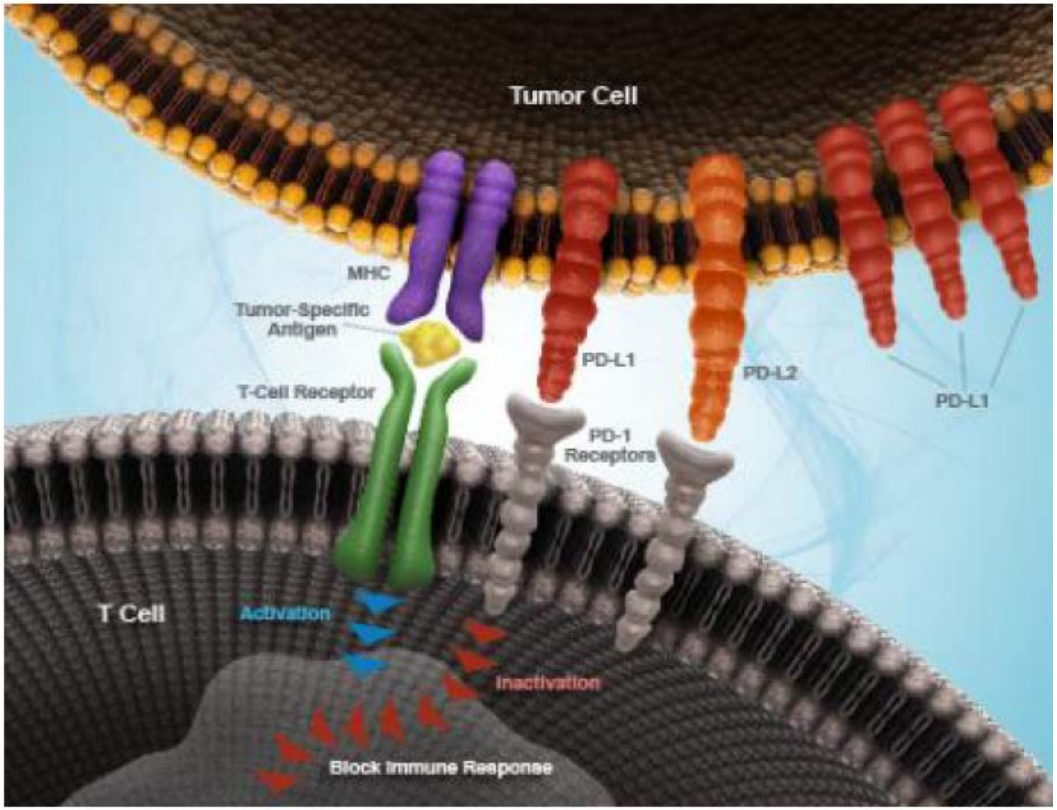

Pardoll et al, Nature Reviews Cancer 2012

WHY

## CTLA-4 regulate T-cell activation in lymphoid tissue

## PD-1/PDL-1 limits T-cell activity in peripheral tissue

**Anti-PDL1 do not block the interaction PDL2-PD1**



# ANTI-PD1 vs ANTI-PDL1: toxicity in phase III trials

| | | Nivolumab | Pembrolizumab | Atezolizumab | Docetaxel |
|---|---|---|---|---|---|
| TR AEs | Any grade | 58-69% | 63-66% | 64% | 81-88% |
| | Grade ≥3 | 7-10% | 13-16% | 37% | 35-57% |
| | Discontinued | 2-4% | 4-5% | 8% | 7% |
| Pneumonitis | Any grade | 5% | 4-5% | | 0% |
| | Grade ≥3 | 1% | 2% | 1% | 0% |
| Colitis | Any grade | 1% | 1% | | 0% |
| | Grade ≥3 | 1% | 0.5% | 0.3% | 0% |

Mitchell P, wclc 2016
Pillai R et al, wclc 2016

# Immune-Related Adverse Events (irAEs)

WHAT

Anti CTLA-4
- 10% → Hypophysitis and hypothyroidism

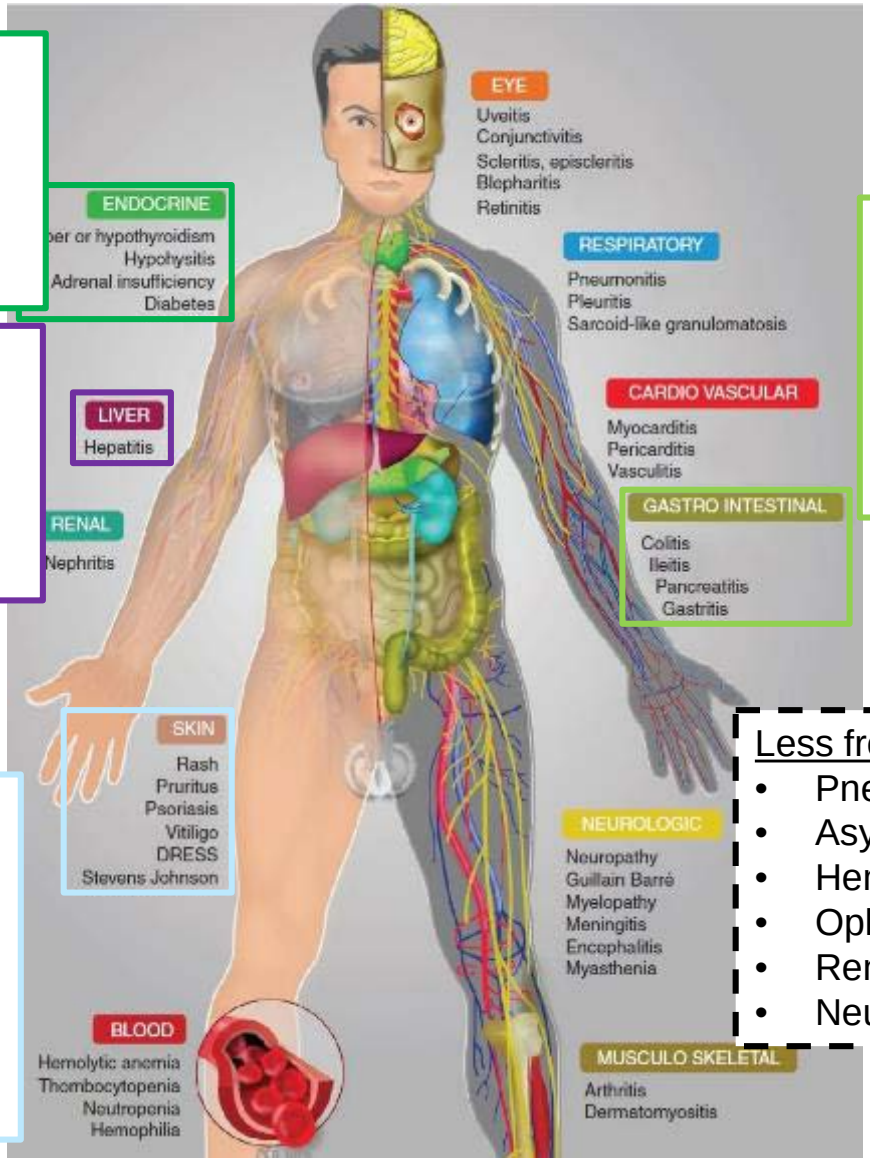
Anti PD-1
- <10% → Hypothyroidism

Anti CTLA-4
- 2.5% → Hepatotoxicity G2
- 2% → Hepatotoxicity G3-4

Anti PD-1
- <5% → Hepatotoxicity

Anti CTLA-4
- 50% → Rash and pruritus (trunk and extremities)

Anti PD-1
- 37% → skin toxicity of all grades
- 6,5% → dry mouth



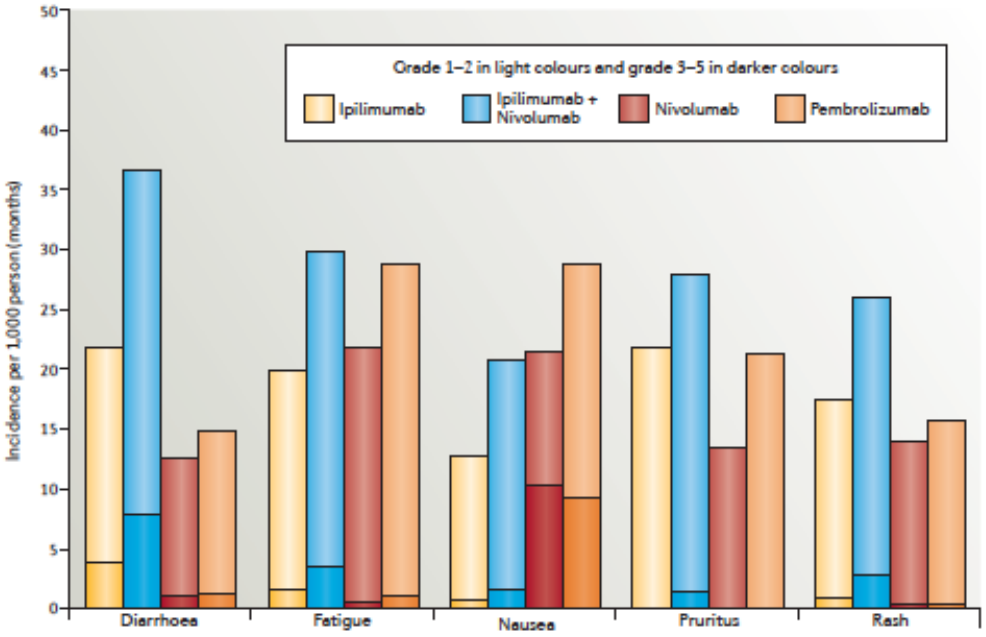

Anti CTLA-4
- 30% → Diarrhoea (only 10% G3-4)
- 5% → Colitis G3-4

Anti PD-1
- 1-2% → Diarrhoea G3-4

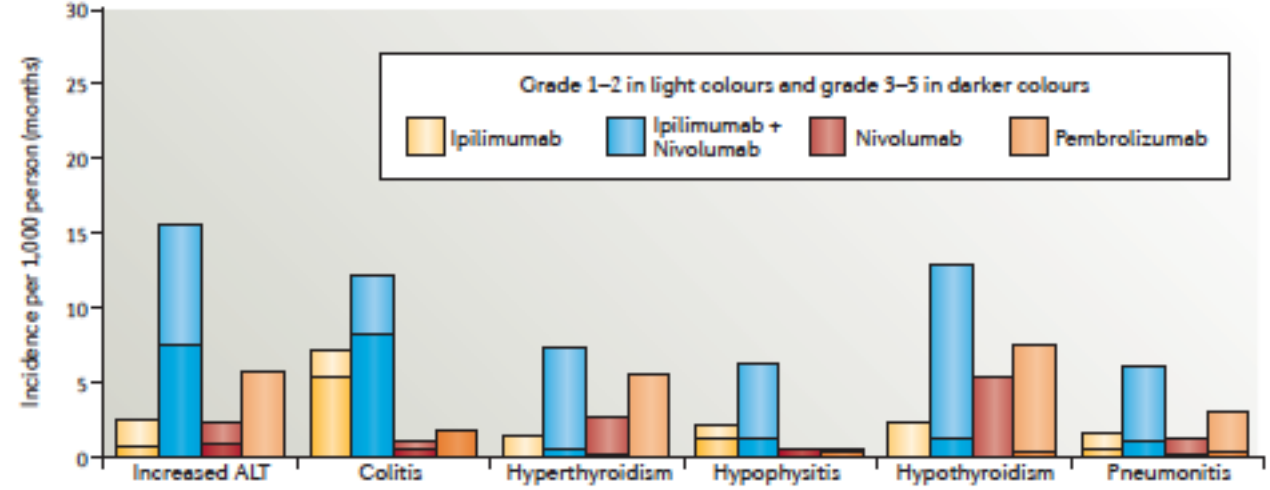
Less frequent irAEs:
- Pneumonitis
- Asymptomatic pancreatitis
- Hematologic syndromes
- Ophthalmologic disorders
- Renal insufficiency
- Neurologic syndromes

Champiat S. et al, Annals of Oncology 2015

WHAT




FREQUENT AE (> 10%)




RARE AE
(</= 10%)

Boutros C et al, Nat Rev Clin Onc 2016

# EVERYTHING MAY HAPPEN…..

WHAT

**Table 1.** Immune checkpoint blockade (ICB) toxicities

Frequent (>10%) ICB toxicities
- Ipilimumab (anti-CTLA4): diarrhea, rash, pruritus, fatigue, nausea, vomiting, decreased appetite and abdominal pain
- Nivolumab (anti-PD1): fatigue, rash, pruritus, diarrhea and nausea
- Pembrolizumab (anti-PD1): diarrhea, nausea, pruritus, rash, arthralgia and fatigue

Rare (<10%) life-threatening ICB toxicities
- Colitis and risk of gastrointestinal perforation
- Pneumonitis including acute interstitial pneumonia/acute respiratory distress syndrome
- Infusion reaction and anaphylactic shock
- Type 1 diabetes and risk of diabetic ketoacidosis
- Severe skin reactions, DRESS, Stevens Johnson syndrome
- Hemolytic anemia or immune thrombocytopenia and hemorrhagic risk
- Neutropenia and sepsis risk
- Encephalopathy and neurological sequelae
- Guillain–Barré syndrome and respiratory risk
- Myelitis and motor sequelae
- Myocarditis and cardiac insufficiency
- Acute adrenal insufficiency and hypovolemic shock
- Pleural and pericardial effusion
- Nephritis

COLITIS

PNEUMONITIS

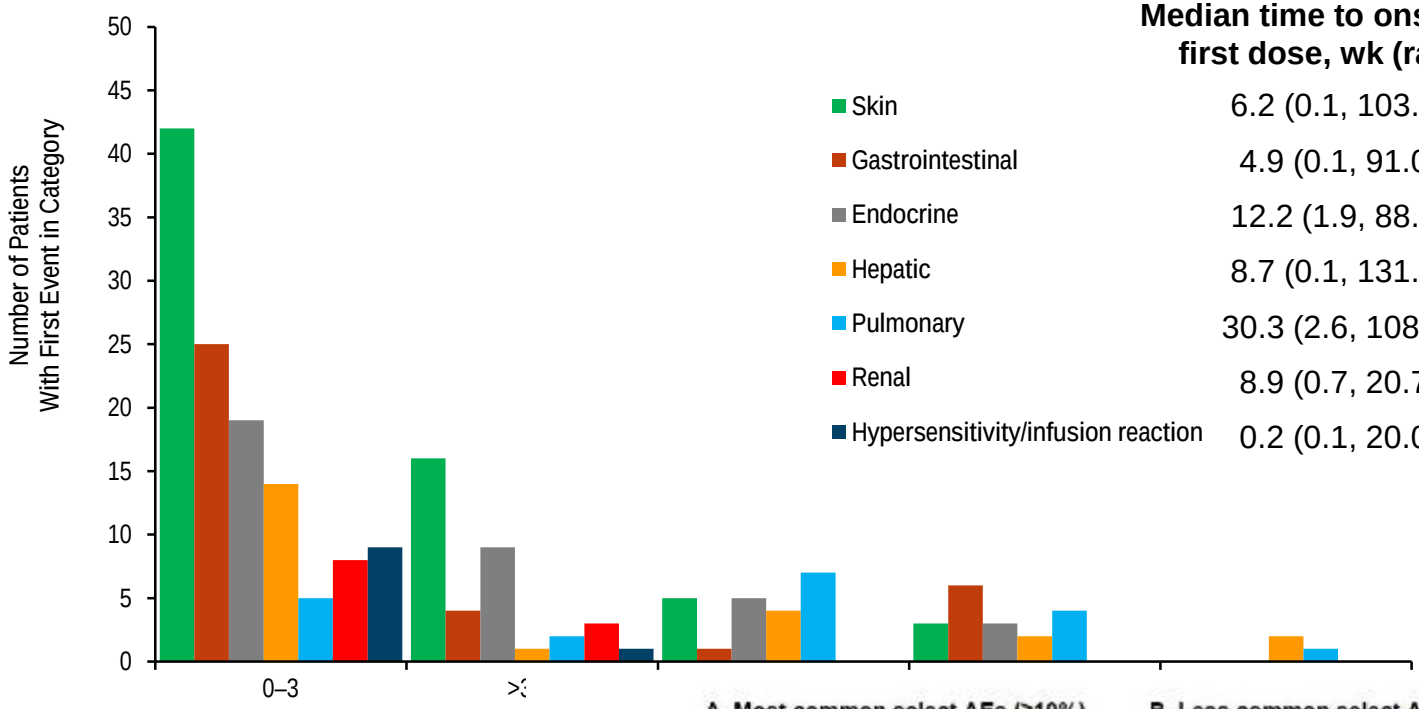
HEPATITIS

ENDOCRINOPATHY

SKIN RASH

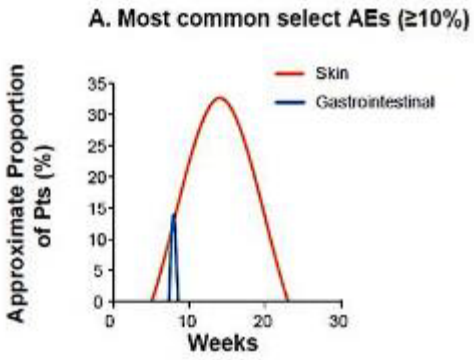
Champiat S. et al, Annals of Oncology 2015

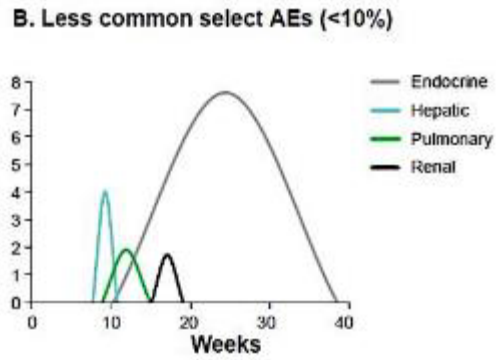
# WHEN?... AND HOW LONG?




| Median time to onset from first dose, wk (range) | |
|---|---|
| Skin | 6.2 (0.1, 103.3) |
| Gastrointestinal | 4.9 (0.1, 91.0) |
| Endocrine | 12.2 (1.9, 88.1) |
| Hepatic | 8.7 (0.1, 131.1) |
| Pulmonary | 30.3 (2.6, 108.1) |
| Renal | 8.9 (0.7, 20.7) |
| Hypersensitivity/infusion reaction | 0.2 (0.1, 20.0) |

| | | |
|---|---|---|
| **Patients on study, n** | 418 | 3 |
| **Patients on treatment, n** | 418 | 2 |
| **Patients with a first event,[a] n** | 106 | 1 |



# HOW LONG?

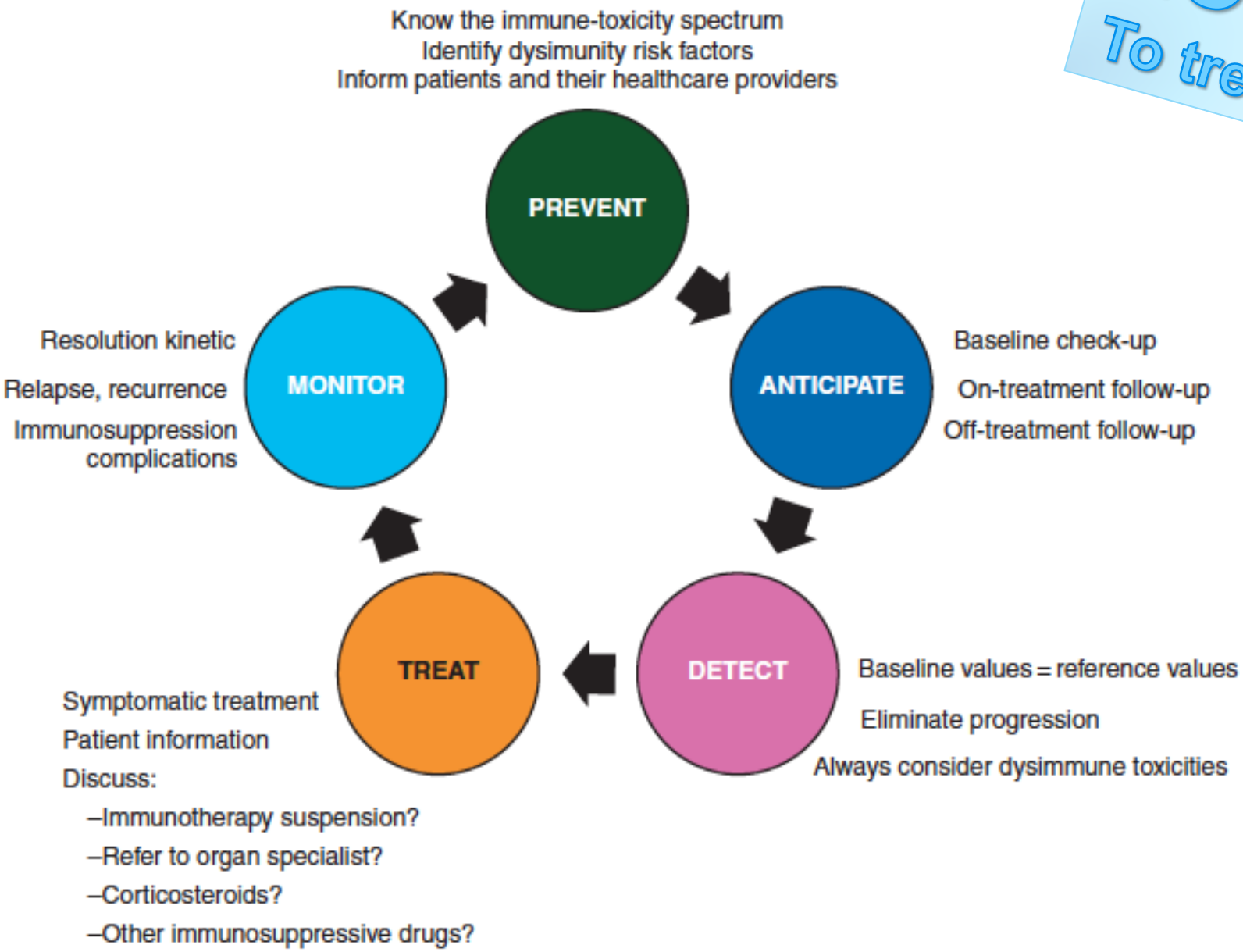
| Select AE category (total cases, n) | All patients with select AEs | | Patients with select AEs receiving immune-modulating medications[a] | | |
|---|---|---|---|---|---|
| | Cases resolved, n (%) | Median time to resolution, wk (range) | Patients,[b] n (%) | Median duration of immune-modulating medications, wk (range) | Cases resolved, n (%) |
| **Skin (n = 66)** | 58 (87.9) | 10.1 (0.1, 132.3+) | 23 (34.8) | 9.1 (0.1, 106.1) | 20 (87.0) |
| **Gastrointestinal (n = 36)** | 34 (94.4) | 2.3 (0.1, 84.3+) | 7 (19.4)[c] | 6.8 (2.3, 41.6) | 7 (100) |
| **Endocrine (n = 36)** | 17 (47.2)[d] | NE (1.3+, 130.9+)[e] | 3 (8.3) | 6.1 (0.6, 10.9) | 3 (100) |
| **Hepatic (n = 23)** | 17 (73.9) | 4.0 (0.1, 68.6+) | 3 (13.0) | 9.6 (1.0, 13.0) | 3 (100) |
| **Pulmonary (n = 19)** | 16 (84.2) | 5.9 (0.6, 58.1+) | 14 (73.7) | 6.1 (0.1, 37.0) | 13 (92.9) |
| **Renal (n = 11)** | 6 (54.5)[f] | 10.5 (0.3+, 104.1+) | 2 (18.2) | 11.8 (0.9, 22.7) | 2 (100) |
| **Hypersensitivity/ infusion reaction (n = 10)** | 10 (100) | 0.1 (0.1, 2.1) | 3 (30.0) | 0.9 (0.1, 1.9) | 3 (100) |

Barlesi F et al, ESMO 2016

# WHEN

- The majority of AE occur within 3 months (but not only)
  nivo: 11/418 after 1 year
- irAEs may happen also after discontinuation of drugs
- With the exception of treatment-related endocrine AEs (often requiring continued hormone replacement therapy) most irAEs resolve (within some weeks)

HOW
To treat




Champiat S. et al, Annals of Oncology 2015

# 1- PREVENT

HOW
To manage

**Table 2.** Immunotherapy baseline checklist

Physical examination
- Performance status
- Weight, size, body mass index
- Heart rate and blood pressure
- General symptoms such as asthenia or appetite should be evaluated as they are frequently affected
- Particularly pay attention to pre-existing symptoms regarding: intestinal transit, dyspnea and coughing, rash, nausea, headaches, signs of motor or sensory neuropathy and arthralgia
- History of fever or recent infection must be checked and investigated appropriately
- Baseline electrocardiogram
- Ongoing treatment

Laboratory test
- Complete CBC
- Serum electrolytes: Na, K, alkaline reserve, calcium, phosphorus, uric acid, urea, creatinine with estimated GFR (MDRD or CKD EPI)
- Glycemia
- Total bilirubin, AST, ALT, GGT, PAL
- Albuminemia, CRP
- TSH, T4
- Cortisol and ACTH at 8 am
- LH FSH estradiol testosterone
- Proteinuria: morning sample, fasting if possible (g/l with concomitant dosing creatinine in mmol/l)—better than an urine dipstick to detect low levels of proteinuria and tubular proteinuria
- Urinary sediment
- Quantiferon tuberculosis or TST in case of anterior exposure
- Virology: HIV, HCV and HBV serology
- Antibody: ANA, TPO Ab, Tg Ab
- If doable, we recommend a plasma/serum biobanking before the beginning of immunotherapy to retrospectively titrate at baseline any other factor of interest in case of development of toxicity with biological marker.

Imaging
- X-ray chest imaging reference is recommended at baseline
- The conventional pretherapeutic thoracic CT scan should be performed with thin sections with and without injection to have a baseline reference in case a pulmonary toxicity occurs.

Any other evaluation may also be necessary before starting immunotherapy depending on patient's history, symptoms or diseases detected at baseline.

Champiat S. et al, Annals of Oncology 2015

**Table 4**
Diagnosis and prevention of AEOSI: recommendations for routine laboratory testing.

| Test | Prior therapy | Prior cycle |
|---|---|---|
| *Blood count* | | |
| Differential blood count | x | x |
| *Clinical chemistry* | | |
| Electrolytes (Na, K, Ca) | x | x |
| Creatinine | x | x |
| Blood urea nitrogen | (x) | (x) |
| Bilirubin | x | x |
| Liver transaminases (AST, ALT, GGT) | x | x |
| LDH | x | (x) |
| Lipase | x | x |
| C-reactive protein | (x) | (x) |
| Glucose[a] | (x) | (x) |
| TSH[b] | x | x |
| Free triiodothyronine & thyroxine | x | (x) |
| Cortisol | (x) | (x) |
| *Serologic tests* | | |
| Hepatitis A/B/C | (x) | |
| Cytomegalovirus | (x) | |
| HIV | (x) | |
| Epstein-Barr virus | (x) | |

Eigentler T H et al, Cancer Treatment Rev 2016

# 2-ANTICIPATE:

## MONITOR AND INFORM

✓ LISTEN TO SYMPTOMS
(and not only…)

✓ MONITOR LAB TEST
(remember glycemia, serume electrolytes and TSH and…)

✓ VISIT

✓ WATCH CT-SCAN

HOW
To manage

## 3-DETECT:

**ANY NEW SYMPTOM AND LAB ABNORMALITIES MAY BE IMMUNORELATED**

- ✓ STUDY AND MONITOR
- ✓ CONSIDER OTHER CAUSES (1st PROGRESSION)
- ✓ CONSIDER TIMING

# 4-TREAT:

HOW To treat

| Grade (CTCAE v4) | Management | Follow-up monitoring |
|---|---|---|
| Grade 1 | • Continue immunotherapy<br>• Treatment of symptoms | • Frequent monitoring<br>• If worsening: treat as grade 2 or 3/4 |
| Grade 2 | • Delay immunotherapy<br>• Treatment of symptoms | • Resume immunotherapy when symptoms improve to grade 1<br>• Consider glucocorticosteroids 0.5–1 mg/kg per day if symptoms persist more than 5–7 days<br>• If worsening with steroids: treat as grade 3/4 |
| Grade 3–4 | • Discontinue immunotherapy except in patients with skin or endocrine toxicities<br>• Initiate glucocorticosteroids 1–2 mg/kg per day<br>• Consider hospitalization | • Continue glucocorticosteroids until grade 1<br>• Taper dose of steroids over at least one month<br>• If persistent or worsening: consider alternative immunosuppressive therapy |

**NO PANIC,**
**DELAY AND USE STEROIDS**

Boutros C et al, Nat Rev Clin Onc 2016

| | Examinations | Management | & Follow-up |
|---|---|---|---|
| **Skin events** | | | |
| °1 | | Topical steroid [b] | |
| °2 | | Topical steroid [b] | |
| °3-4 | (⊙Skin biopsy) | ▲ or ■ 1.0-2.0 mg/kg/d | ↗ : ● |
| **Diarrhea/Colitis** | | | |
| °1 | Stool test on pathogens | --- [c] | |
| °2 | (⊙ Colonoscopy) | ▲ 0.5-1.0 mg/kg/d | → : ■ |
| °3-4 | Colonoscopy | ■ 1.0-2.0 mg/kg/d | → / ↘ : Infliximab |
| **Hepatic events** | | | |
| °1 | Control for signs of hepatitis | ● --- | |
| °2 | Frequent controls [transaminases] | ▲ 0.5-1.0 mg/kg/d | ↗ : ● |
| °3-4 | Very frequent contr. [q1-2d]; (⊙Biopsy) | ■ 1.0-2.0 mg/kg/d | → / ↘ : Immunosuppr. therapy [e] |
| **Endocrine events** | | | |
| Asymptomatic °1 | Regular controls; (⊙ Imaging) | ● --- | |
| Symptomatic °2 | Regular controls; (⊙ Imaging; ⊙ Further diagnostics) | ▲ (⊙HRT); 1.0-2.0 mg/kg/d | ↗ : ● → : Start/maintain HRT |
| °3-4 | | ▲ (⊙ HRT); i.v. steroids [g] | ↗ : ● Regular controls |
| **Pneumonitis** | | | |
| °1 | Frequent controls [q2-3d] | ● --- | |
| °2 | Daily symptom contr.; (⊙ Bronchoscopy) | ▲ 1.0-2.0 mg/kg/d | ↗ : ● |
| °3-4 | Bronchoscopy/biopsy | ■ 2.0-4.0 mg/kg/d | → / ↘ : Immunosuppr. therapy [e] |

Legend: ● continue therapy
▲ delay therapy
■ stop therapy

In case of: ↗ Improvement
→ No change
↘ Worsening

Eigentler T.K. Et al, Cancer Treatment Reviews 2016

# AFTER RESOLUTION

# GRADUAL STEROID TAPERING

## At least 1 month

HOW To treat

| Temporary suspension | Permanent discontinuation |
|---|---|
| - IrAEs stabilized < G1<br>- Steroid dose reduced to < 10 mg/d prednisone | - IrAEs G4<br>- IrAEs G3 and recurring<br>- IrAEs G2 not resolutive in 3 months |

- ✓ Immunotherapy dose reduction not recommended
- ✓ No clear correlation between dose density and efficacy of immunecheckpoints inhibitors:
  - → <u>not influenced</u> by delaying immunotherapy

# And Combination treatment???

IMMUNOMODULATORS COMBINATIONS

CT+ anti-PD1-PDL1

anti-PD1-PL1 + TARGETED THERAPY

anti-PD1-PL1 + ANTIANGIOGENIC TREATMENT

# IMMUNOTOXICITY AND EFFICACY-discontinuation

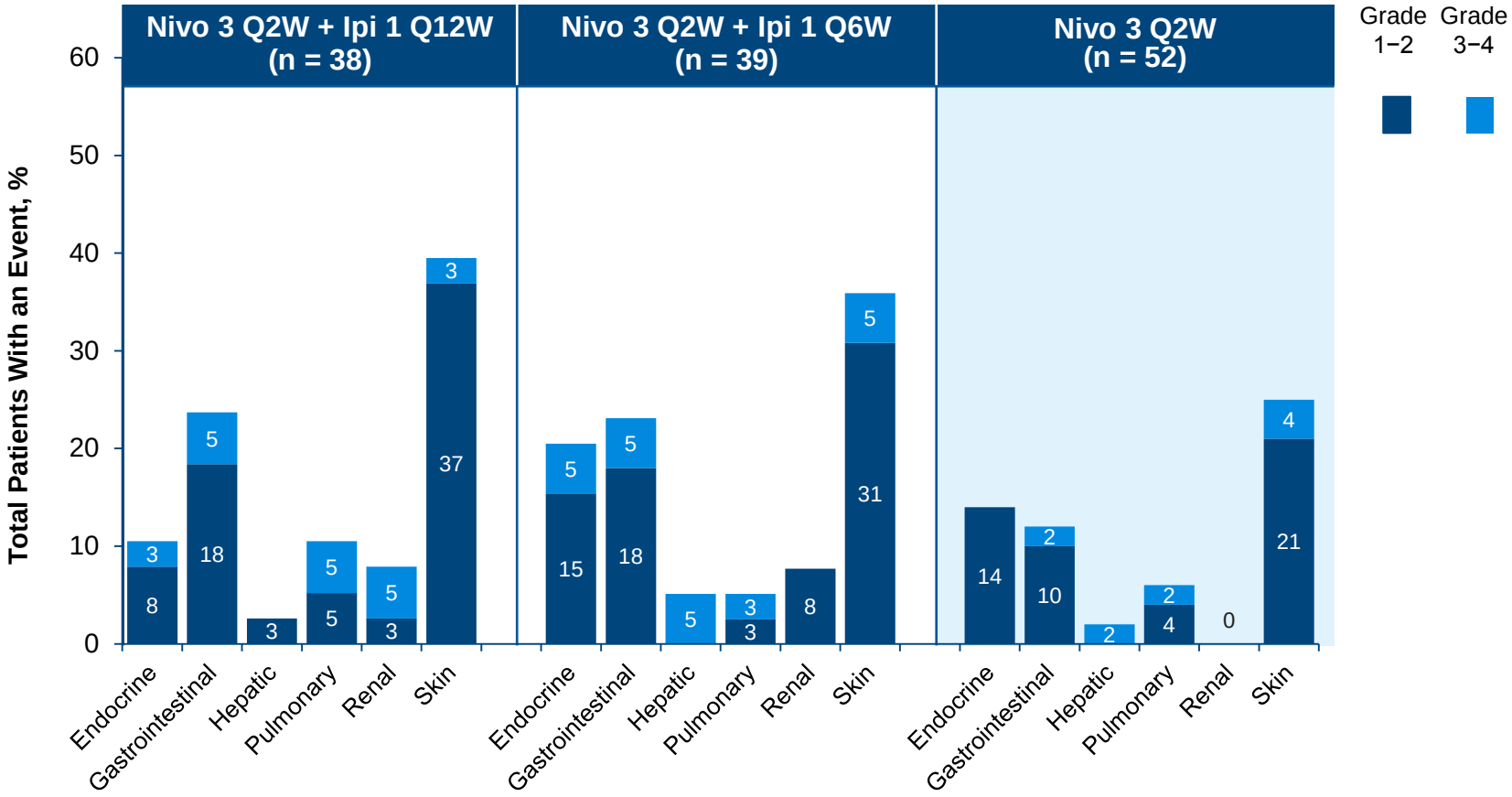
## Combination treatment-checkmate 012

| | Nivo 3 Q2W + Ipi 1 Q12W (n = 38) | | Nivo 3 Q2W + Ipi 1 Q6W (n = 39) | | Nivo 3 Q2W (n = 52) | |
|---|---|---|---|---|---|---|
| | Any grade | Grade 3–4 | Any grade | Grade 3–4 | Any grade | Grade 3–4 |
| **Treatment-related AEs, %** | 82 | 37 | 72 | 33 | 71 | 19 |
| **Treatment-related AEs leading to discontinuation, %** | 11 | 5 | 13 | 8 | 10 | 10 |

Treatment-related AEs leading to discontinuation:
1/3 than older combination arms

Hellman MD et al, ASCO 2016
Hellmann MD et al, Lancet Oncol 2017

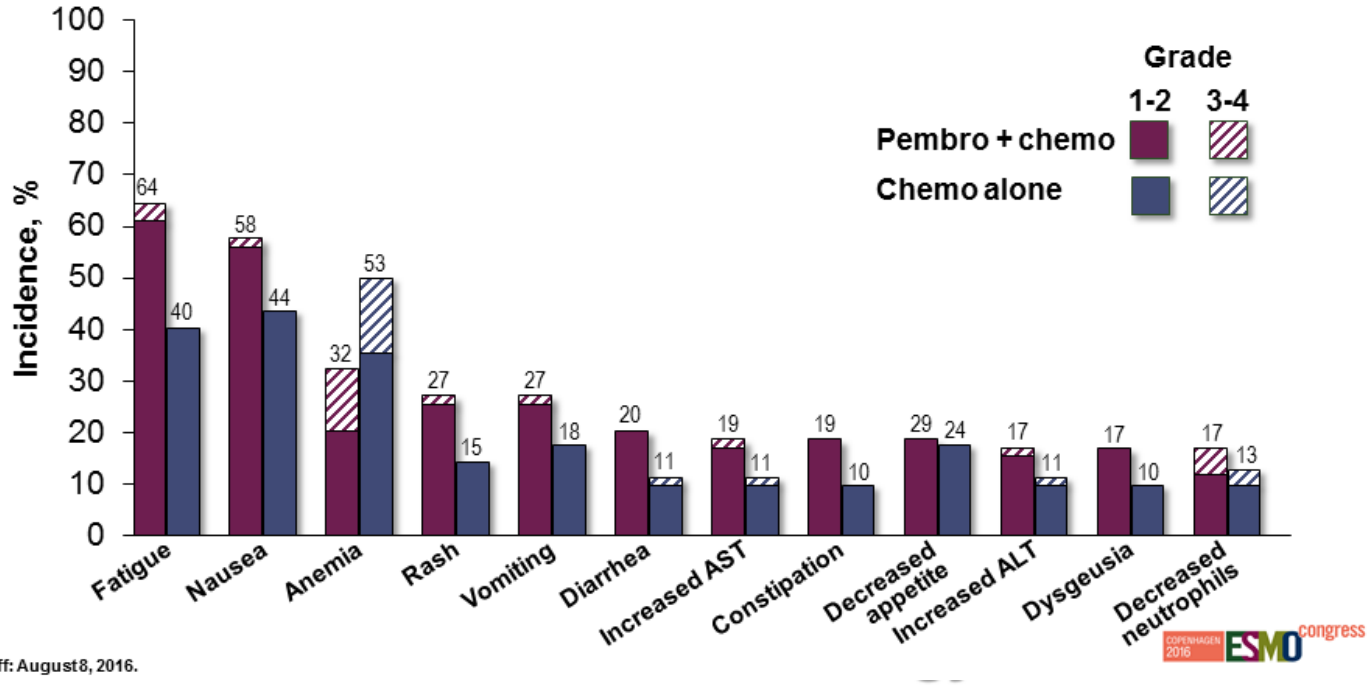
# Toxicity of combination (anti-PD1+anti-CTLA4)



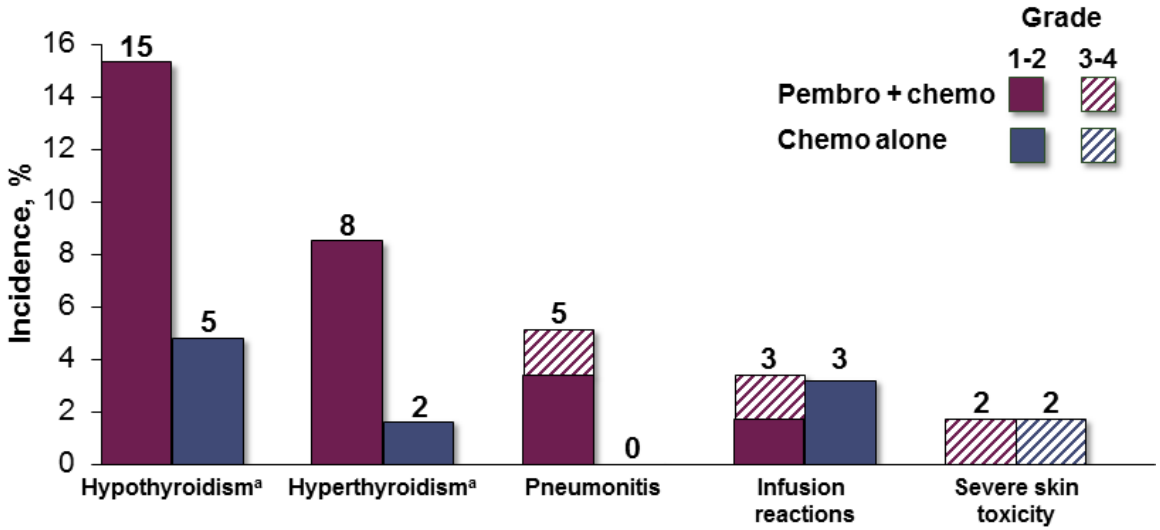

- All treatment-related pulmonary events were pneumonitis
- Grade 1–2 hypersensitivity/infusion reaction occurred in 5% and 6% of patients in the nivo 3 Q2W + ipi 1 Q12W and monotherapy groups, respectively

Hellman MD et al, ASCO 2016
Hellmann MD et al, Lancet Oncol 2017

# Toxicity of combination (anti-PD1+CT- Keynote 021)



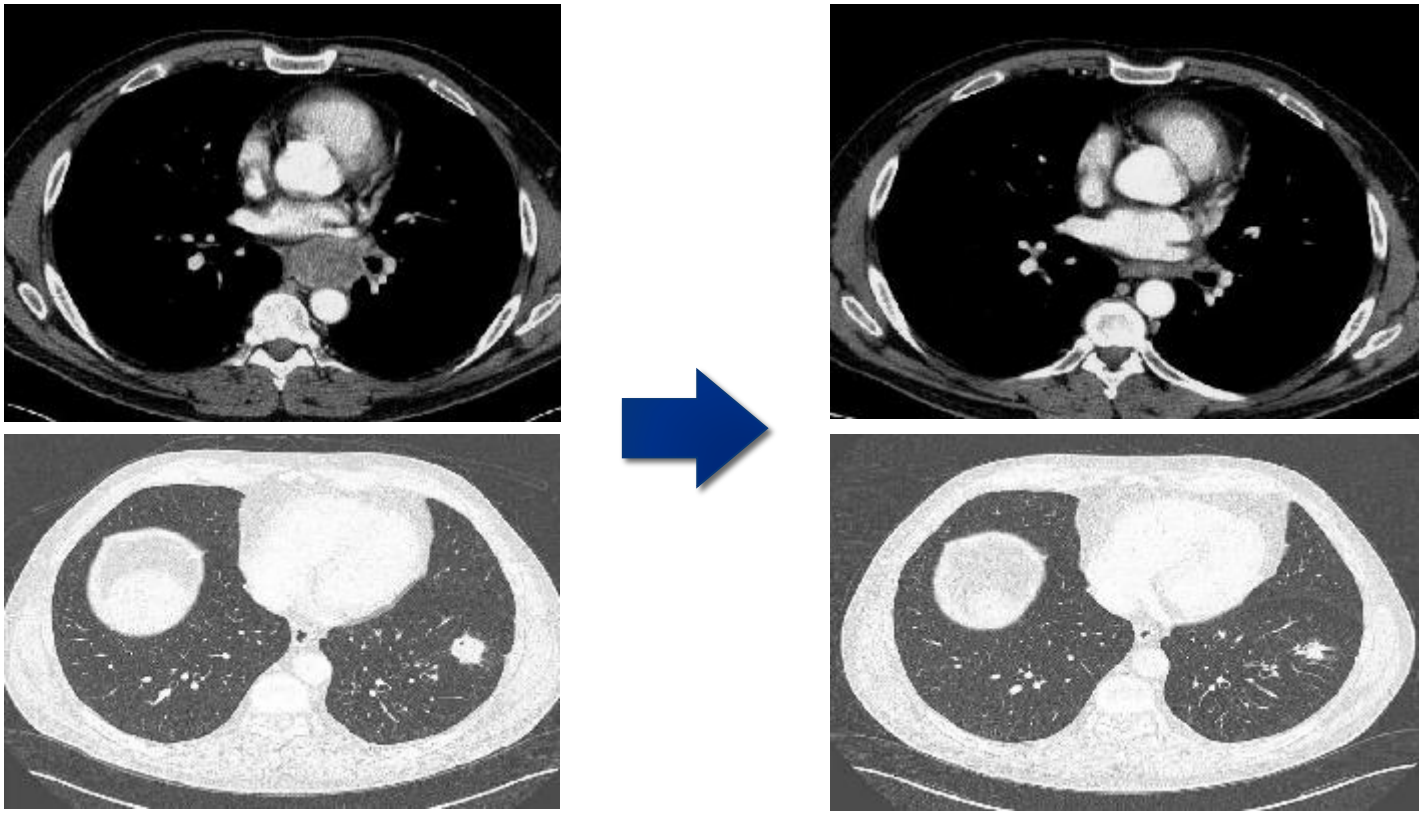

Data cut-off: August 8, 2016.




Langer CJ et al, ESMO 2016
Langer CJ et al, Lancet Oncol 2016

# Case 1- second-line atezolizumab


Phase III **OAK trial**: Atezolizumab *vs* Docetaxel



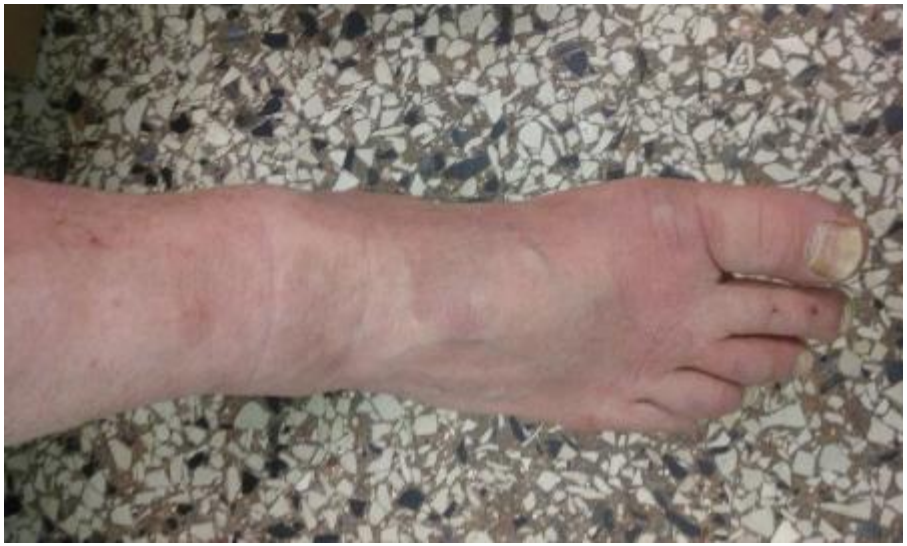
Oct 2014

Jul 2015

# TOXICITY-1


**PRURITUS G1**

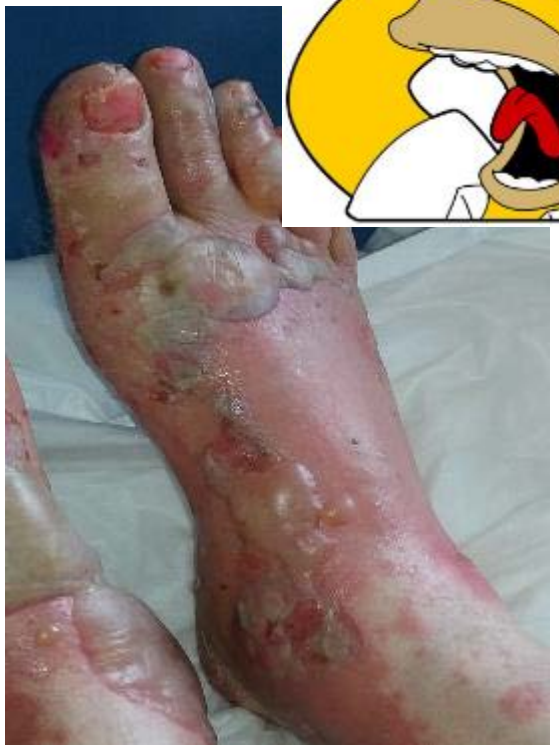
**JOINT PAIN G1**

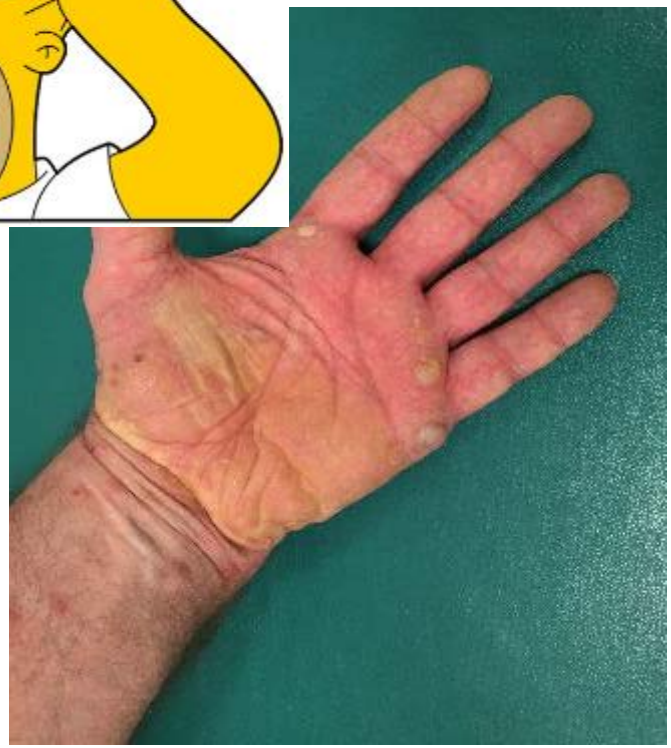


**TOPICAL STEROIDS**

**NO TREATMENT DELAY**

## TOXICITY

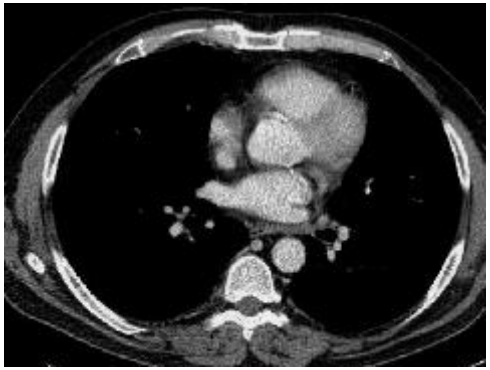




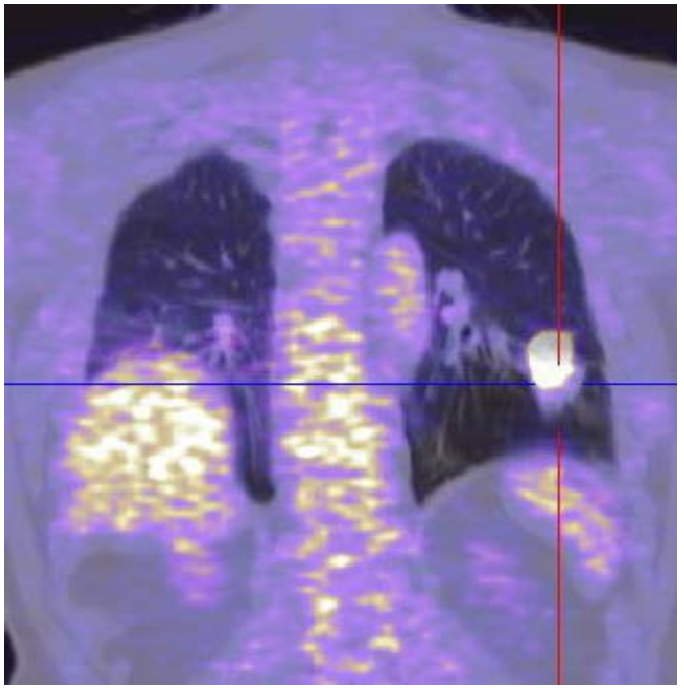

**BOLLOUS DERMATITIS**

**HOSPITALIZATION**
**SYSTEMIC STEROIDS**
**TREATMENT DISCONTINUATION**


ECOG PS 0



Jun 2016



Oct 2016

Single-site progression

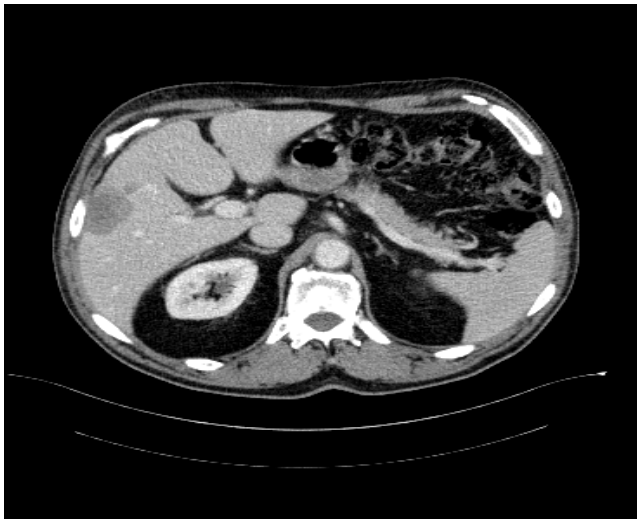
→ **Nov 2016: cyberknife RT on lung lesion**

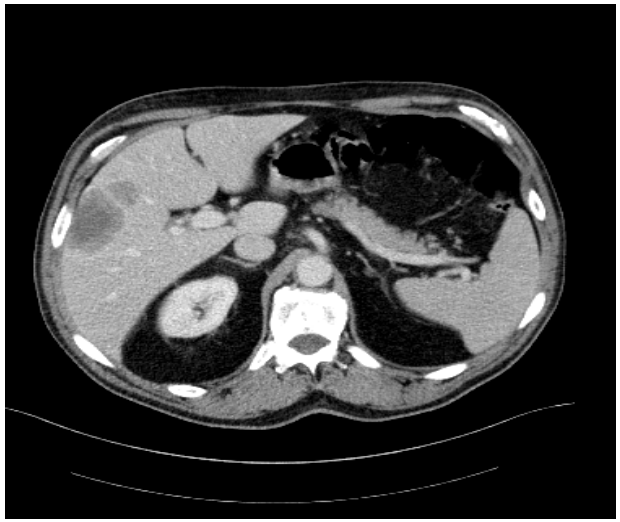
# Case 1, 2nd line SCLC, 69 year-old , nivolumab

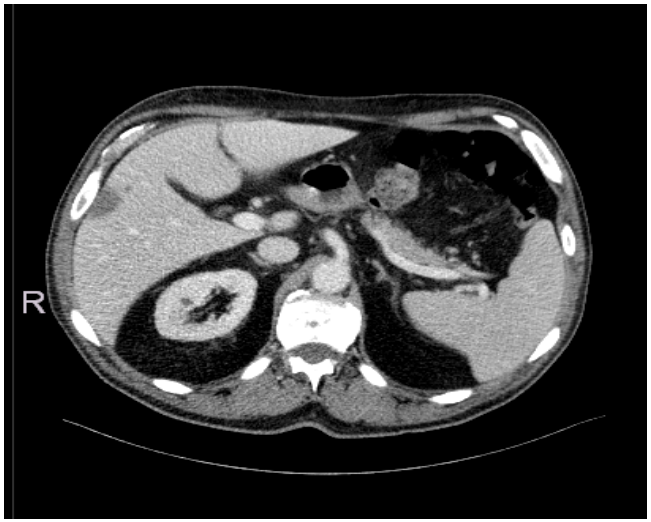
Aug 2016

Sept 2016

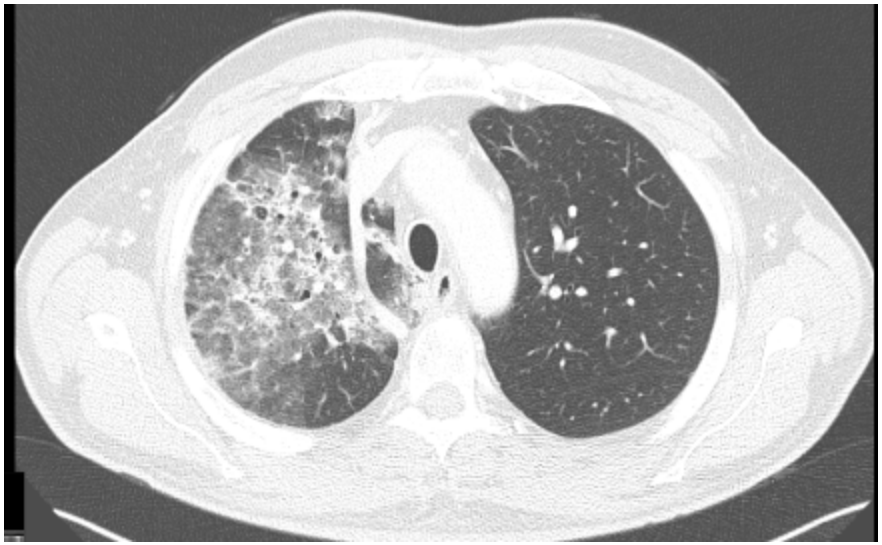
Nov 2016

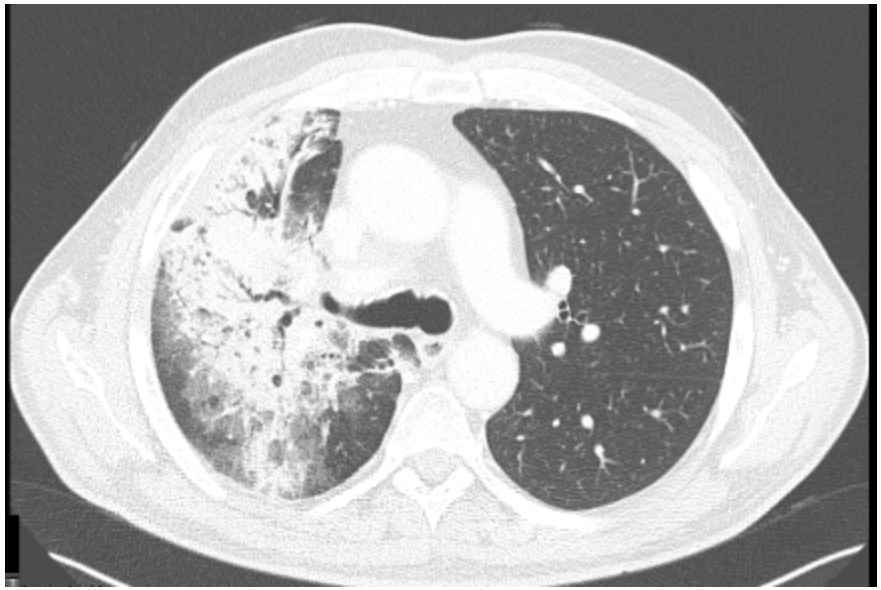


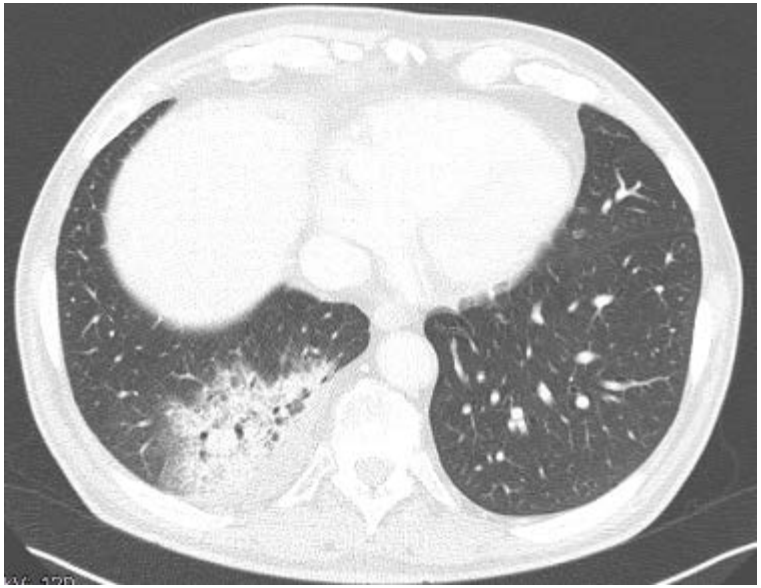




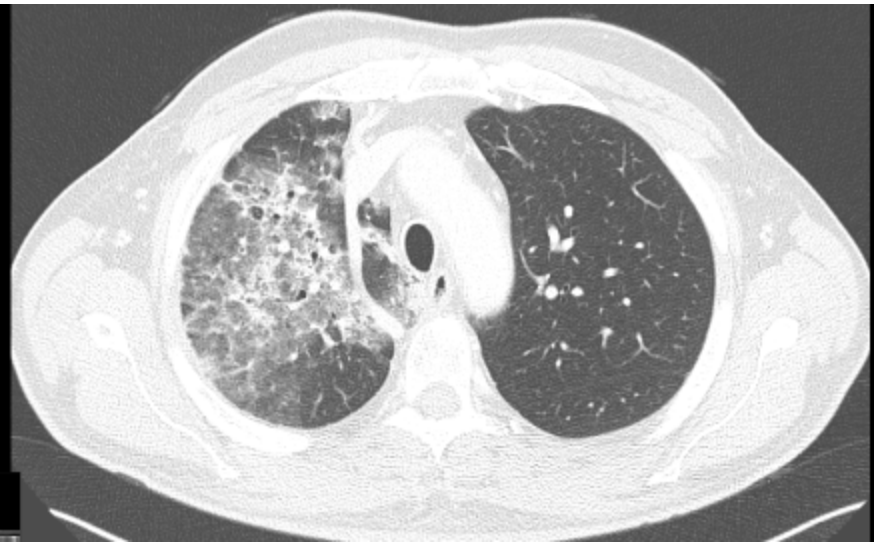

**Checkmate 032**








- **Previous RT (6 months before)**
- **Previous bacterial pulmonary infection**
- **asymptomatic**



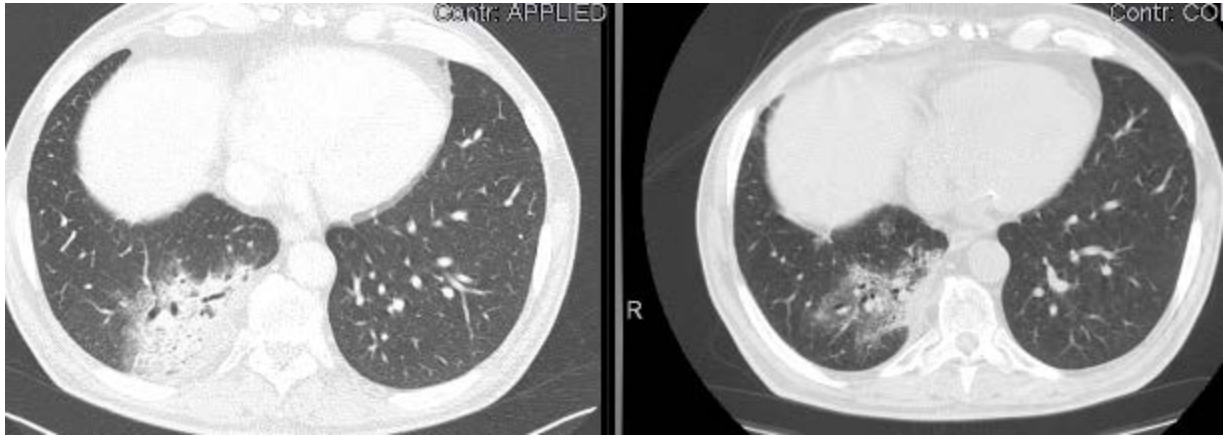
## Suspected immunorelated toxicity

**Grade 1**
Radiographic changes only

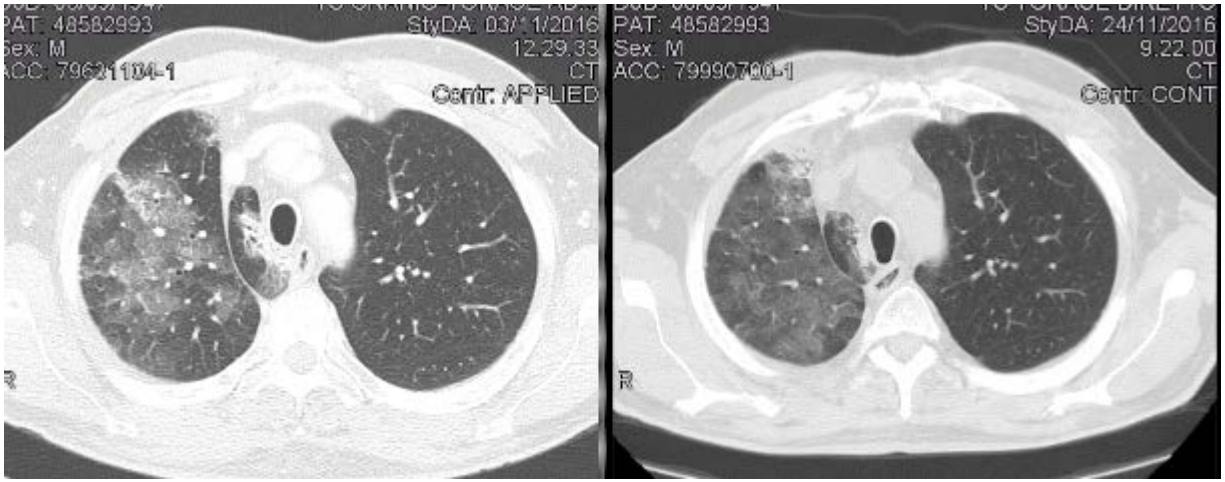
- **Consider delay of I-Therapy**
- **Monitor symptoms every 2–3 days**

**Re-image at least q3w**
**If worsens: treat as grade 2–4**

## DELAY AND OBSERVE








DELAY, OBSERVE AND FURTHER STUDY


BRONCHOSCOPY (AND LUNG BIOPSY):

→ ASPERGILLUS

CT-SCAN:

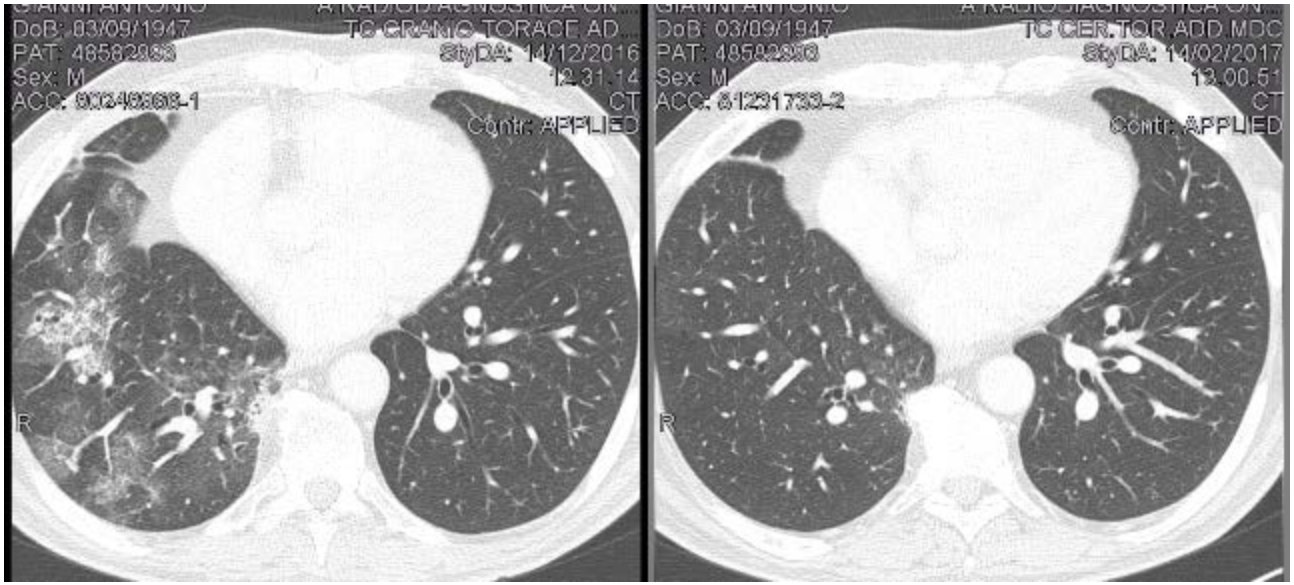
→ WORSENING OF POTENTIALLY IMMUNORELATED ASPECTS

MULTIDISCIPLINARY DISCUSSION:

- **NO SYMPTOMS**

- NO RADIOLOGICAL LESIONS TYPICAL FOR ASPERGILLUS (and other exams: fundus onculi, AG, repeat bronchoscopy)


START STEROIDS AND VORICONAZOLE
(STOP IMMUNOTHERAPY)




STILL MANTAING RESPONSE
STILL ASYMPTOMATIC

## WAITING FOR DISCUSSION

- Immunomodulators are generally well tollerated
- Toxicity requiring special management is rare (< 10%)
- irAE are generally reversible
- Early detection and correct monitoring is essential
- Delay in use of steroids may be dangerous and tapering should be over 4-6 weeks

# BACKUP FOR DISCUSSION: ALGRORYTHMS FOR GI TOX

| Evaluation | Treatment Indication | Simplified Management |
|---|---|---|
| **Grade 1**<br>Diarrhoea: <4 stools/ day over baseline;<br>Colitis: asymptomatic | • Continue I- Therapy<br>• Symptomatic treatment (Loperamide / Budesonide) | Close monitoring for worsening symptoms<br><br>Educate patient to report worsening immediately<br><br>If worsens: treat as grade 2 or 3–4 |
| **Grade 2**<br>Diarrhoea: 4-6 stools/day over baseline; IV fluids indicated <24 hrs; not interfering with ADL<br>Colitis: abdominal pain; blood in stool | • Delay I-Therapy<br>• If improves to grade 1: resume I-Therapy<br>• Symptomatic treatment<br>  • 0.5–1.0 mg/kg/day methylprednisolone or oral equivalent | If persists >5-7 days or recurs: 0.5–1.0 mg/kg/day methylprednisolone or oral equivalent;<br><br>When grade 1 symptoms, taper steroids ≥1 month, consider prophylactic antibiotics for opportunistic infections and resume I-Therapy per protocol<br><br>If worsens or persists > 3-5 days with oral steroids: treat as grade 3–4 |
| **Grade 3-4**<br>Diarrhoea (G3): ≥7 stools/day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL<br>Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation | • Discontinue I-Therapy<br>• If improves to grade 1: resume I-Therapy<br>• Consider endoscopy | If improves: continue steroids until grade 1, then taper ≥1 month<br>If > 7 stools baseline, or refractory to steroids:<br>  • Hospitalise for High dose of steroids IV<br>  • Consider colonscopy and CT scan<br>  • Consider Infliximab 5mg/kg<br>  • Add prophylactic antibiotics for opportunistic infection |

# PRACTICAL TIPS

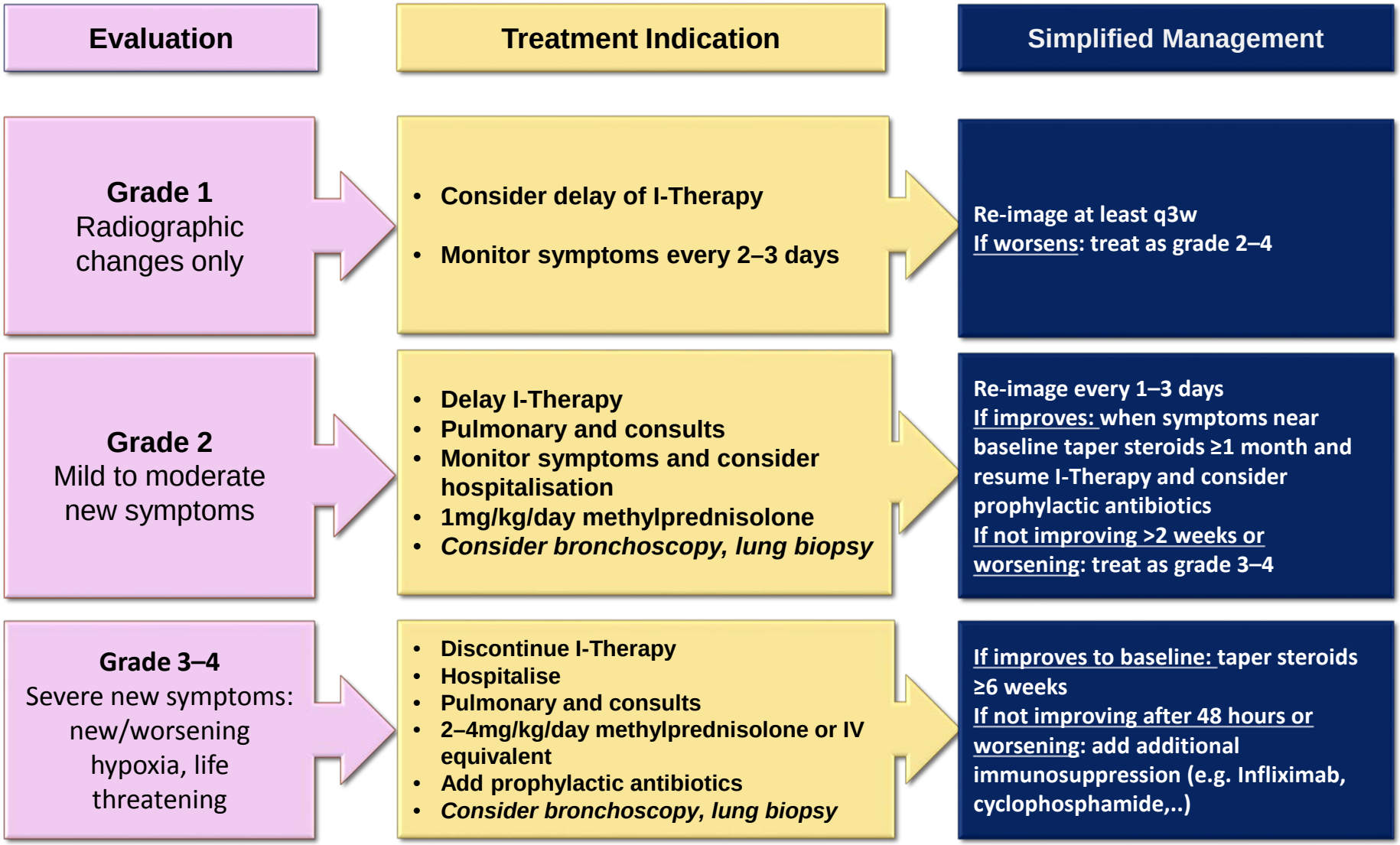
G1 DIARRHEA:
Be careful about drugs
C. difficile…

G2 DIARRHEA:
consider clinical condition, compliance, other treatments
Peritoneal signs

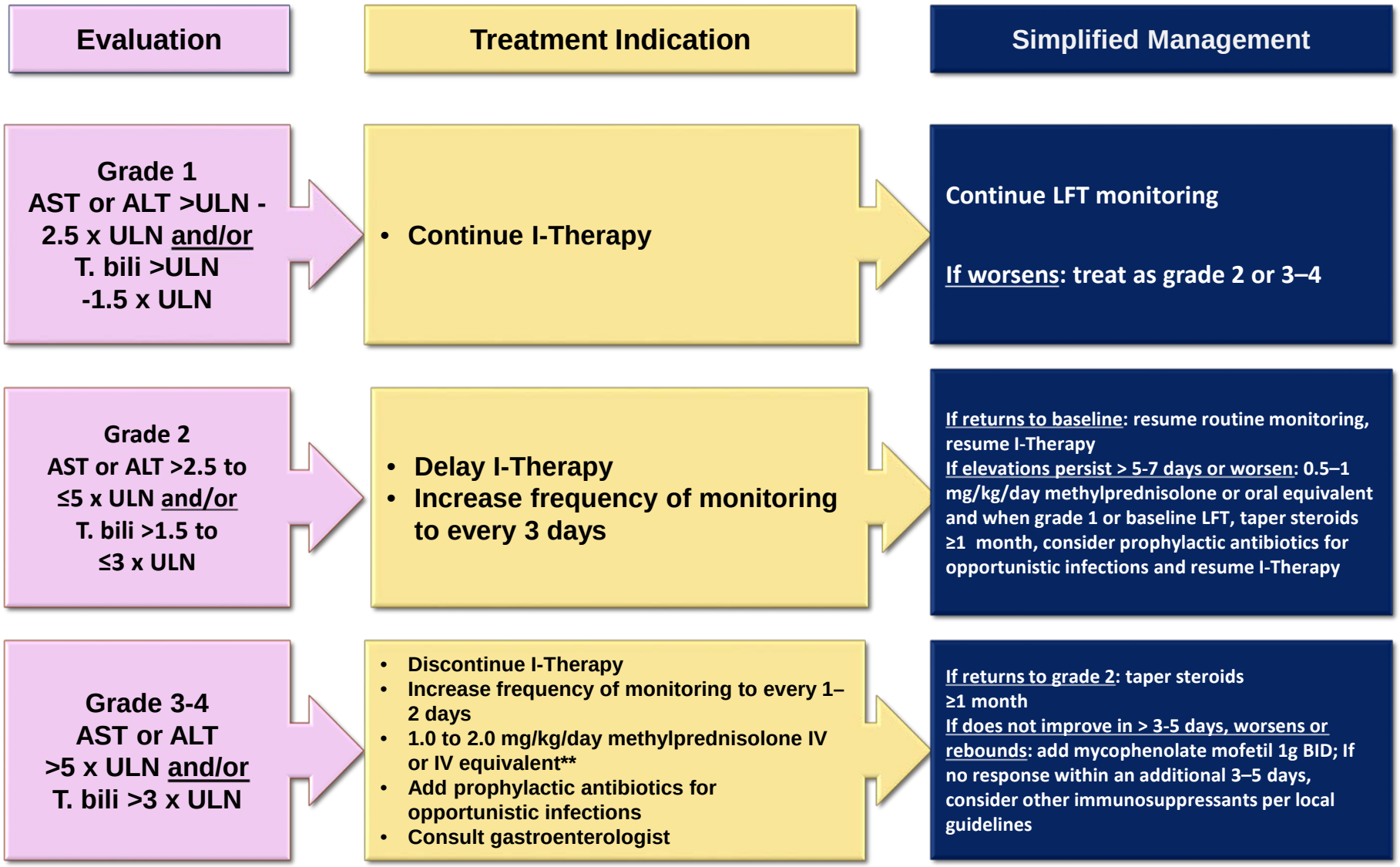
UNSTABLE: hospitalization, methylprednisolone 125 mg iv for 3 days

AFTER 5-7 DAYS OF STEROIDS: INFLIXIMAB 5 mg/kg
(repeat after 2 weeks if needed)
Selected cases: mycophenolate mofetil

# BACKUP FOR DISCUSSION: ALGRORYTHMS FOR PULMONARY TOX



# BACKUP FOR DISCUSSION: ALGRORYTHMS FOR LIVER TOX



# BACKUP FOR DISCUSSION: ALGRORYTHMS FOR ENDOCRINOPATHY

| | Asymptomatic Endocrinopathy (eg. Hypo/hyperthyroidism) | Symptomatic Endocrinopathy (eg. Hypo/hyperthyroidism) | Suspicion of Adrenal Crisis (eg. Severe dehydratation, hypotension, shock out of proportion to current illness) |
|---|---|---|---|
| Monitoring | If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: include fT4 at subsequent cycles as clinically indicated; consider endocrinology consult | Evaluate endocrine function<br>Consider pituitary scan.<br>Repeat labs in 1 to 3 weeks<br>MRI in 1 month if symptoms persist but normal lab/pituitary scan | Rule out sepsis |
| Consult | Consider endocrinology | Consider endocrinology | Endocrinology |
| I-Therapy | Continue I-Therapy | Continue Therapy for hypo or hyperthyroidism | |
| | | Withhold Therapy for other endocrinopathies with abdormal lab / pituitary scan | Withhold I-Therapy |

## HYPHOPHYSITIS: practical tips

Symptomatic→ start high-dose steroids
Prednisone 1 mg/kg/day
(methylprednisolone 125 mg/die iv or desametasone 6 mg x 4/die)

Long-term replacement

Acute adrenal insufficiency→
Hospitalization
Supportive care
Prednisone 60-80 mg/die

Long-term replacement

## BACKUP FOR DISCUSSION: SKIN TOX

Steven-Johnson syndrome and toxic epidermal necrosis <1%

G1-2: < 30% body→ local treatment, continue immunotp
if highly symptomatic consider G3 management

G3 >/= 50% body→ stop treatment,
start steroids 0,5 mg/kg/die prednisone