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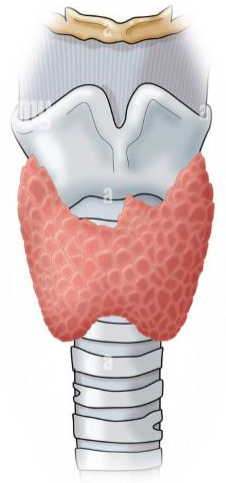
Prise en charge des toxicités des immunothérapies aux urgences

Toxicité endocrinienne



Jeroen de Filette, MD, PhD
Clinique d'Endocrinologie
CHU Brugmann

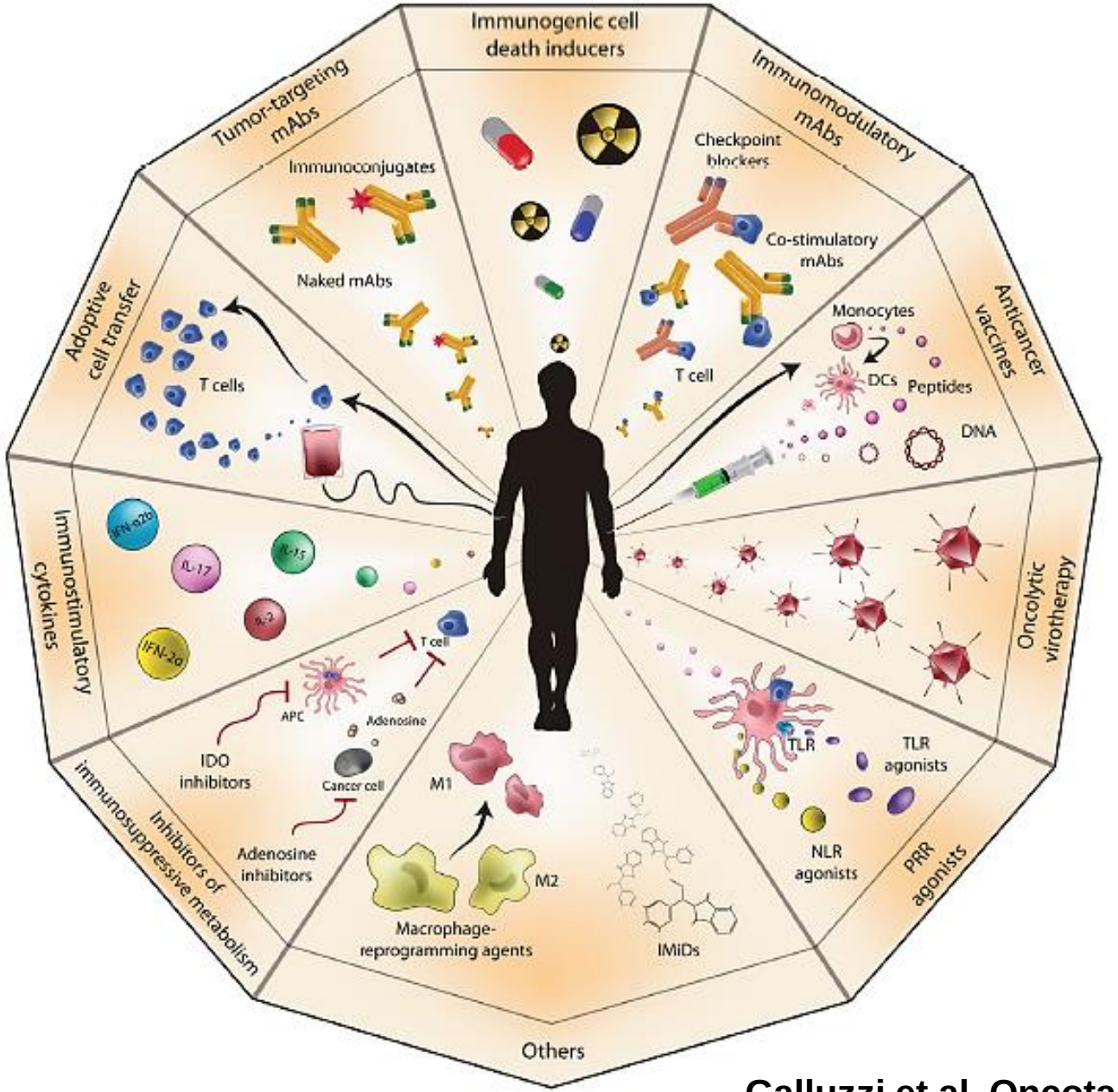
Learning Objectives

- Diagnosis and management of endocrine adverse events of immune checkpoint inhibitors (ICI) with clinical cases

- Novel therapies (LAG-3)

Immunotherapy?

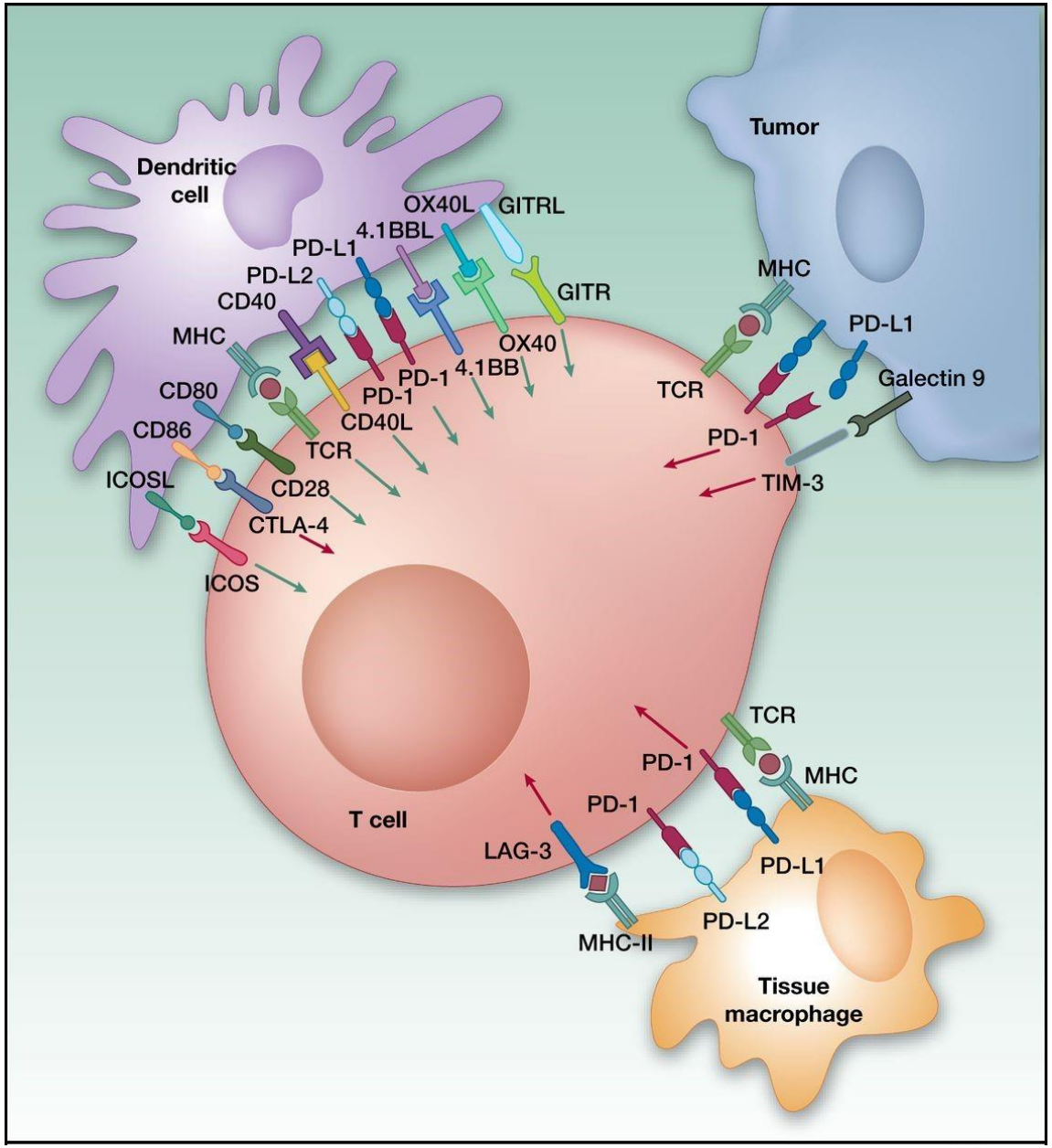
Types of immunotherapy



Galluzzi et al. Oncotarget 2015

C H U | U V C
B R U G M A N N

Immune checkpoints keep the immune system *"in check"*



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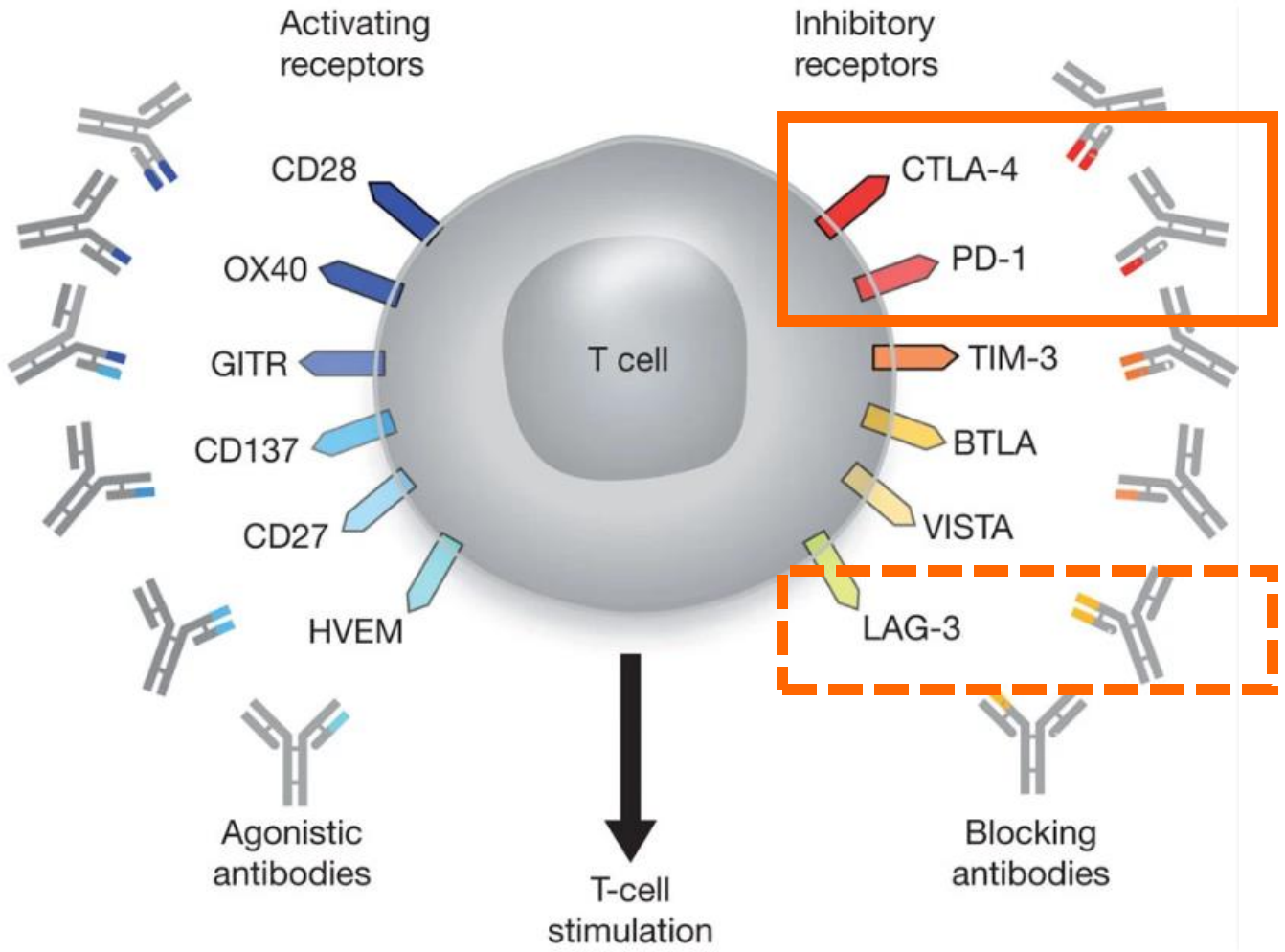
Immune checkpoint inhibitors (ICI) are the standard for many cancers



Mellman et al. Nature 2011

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› Nieuw
› 2024
› 2023
› 2022
› 2021
› 2020
› 2019
› 2018
› 2017

Nieuwigheden in de oncologie

nivolumab + relatlimab (Opdualag® ▼)

De associatie nivolumab + relatlimab (Opdualag® ▼, hoofdstuk 13.3.1, intraveneus, voor gebruik in het ziekenhuis) is een associatie van twee monoklonale antilichamen (immuuncheckpoint-inhibitoren van PD-1 en LAG-3) met als indicatie de behandeling van bepaalde gevorderd **melanomen** bij personen vanaf 12 jaar (synthese van de SKP).
De associatie nivolumab + relatlimab verbeterde de mediane progressievrije overleving met 6 maanden ten opzichte van enkel nivolumab (primair eindpunt), maar niet de totale overleving (secundair eindpunt). De associatie werd niet vergeleken met de combinatie nivolumab + ipilimumab, waarvan werd aangetoond dat ze de totale overleving kan verlengen.
De associatie nivolumab + relatlimab geeft een risico op ernstige immunologische ongewenste effecten, waaronder sterfgevallen (zie 13.3.1. Immuuncheckpoint-inhibitoren).[1-3]

Kostprijs: € 6111 voor een flacon van 240 mg + 80 mg, terugbetaald in al op 1 maart 2024 (zie voorwaarden en formulieren)

Most commonly used drugs

CTLA-4 inhibitors

- Ipilumumab
- Tremelimumab

PD-1 inhibitors

- Cemipilimab
- Dostarlimab
- Pembrolizumab
- Nivolumab

PD-L1 inhibitors

Atezolizumab

Avelumab

Durvalumab

LAG-3 inhibitor

Relatlimab (*03-2024*)

In development

Vopratelimab (ICOS)

Spartalizumab, Camrelizumab, Sintilimab, Tislelizumab, Toripalimab, Acrixolimab (PD-1)

Cosibelimab (PD-L1)

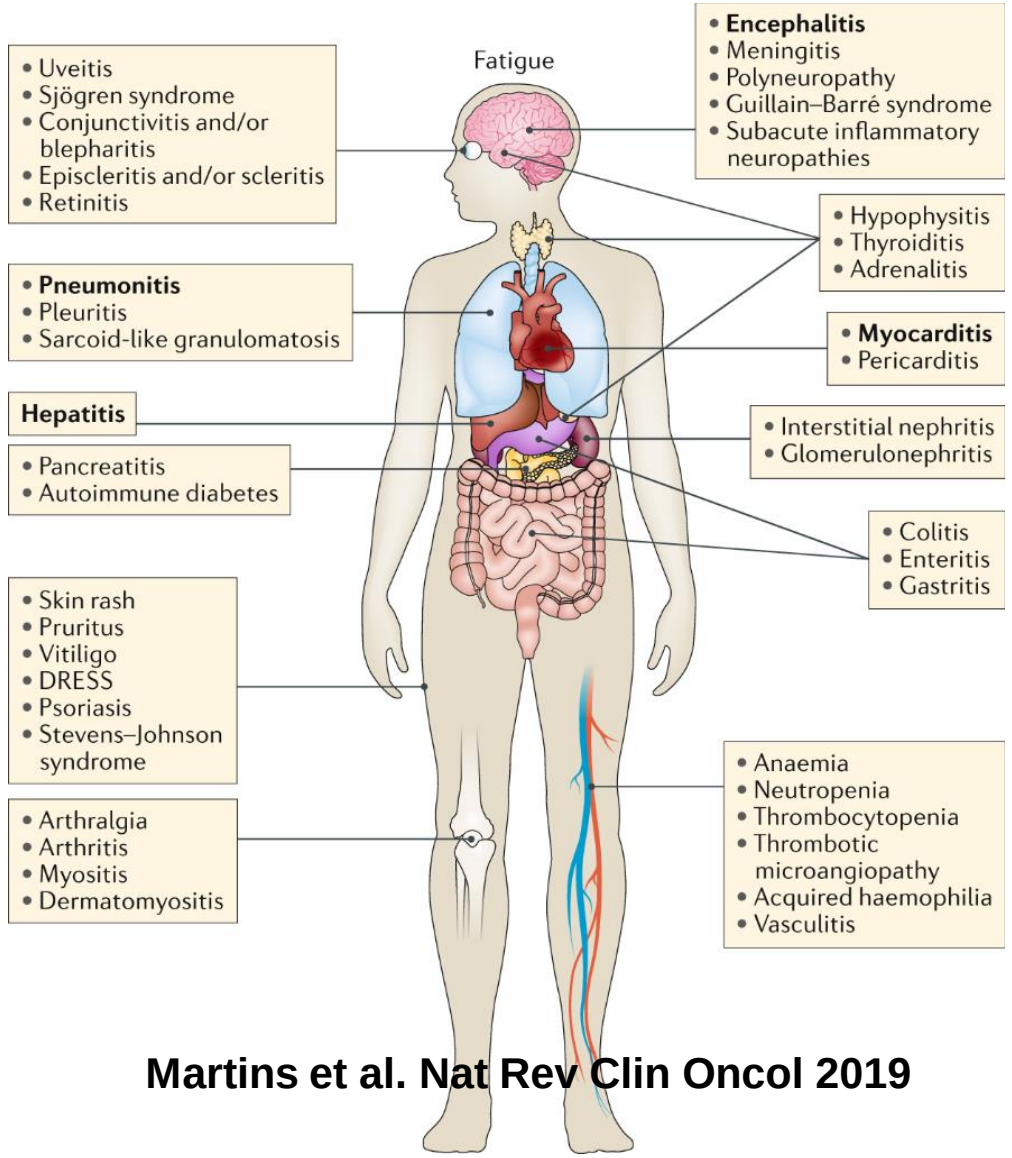
Ieramilimab (LAG-3 inh)

Eftilagimod alpha (sLAG-3)

Tebotelimab (PD-1 x LAG-3)

…

The immune response, however, is not specific…



Martins et al. Nat Rev Clin Oncol 2019

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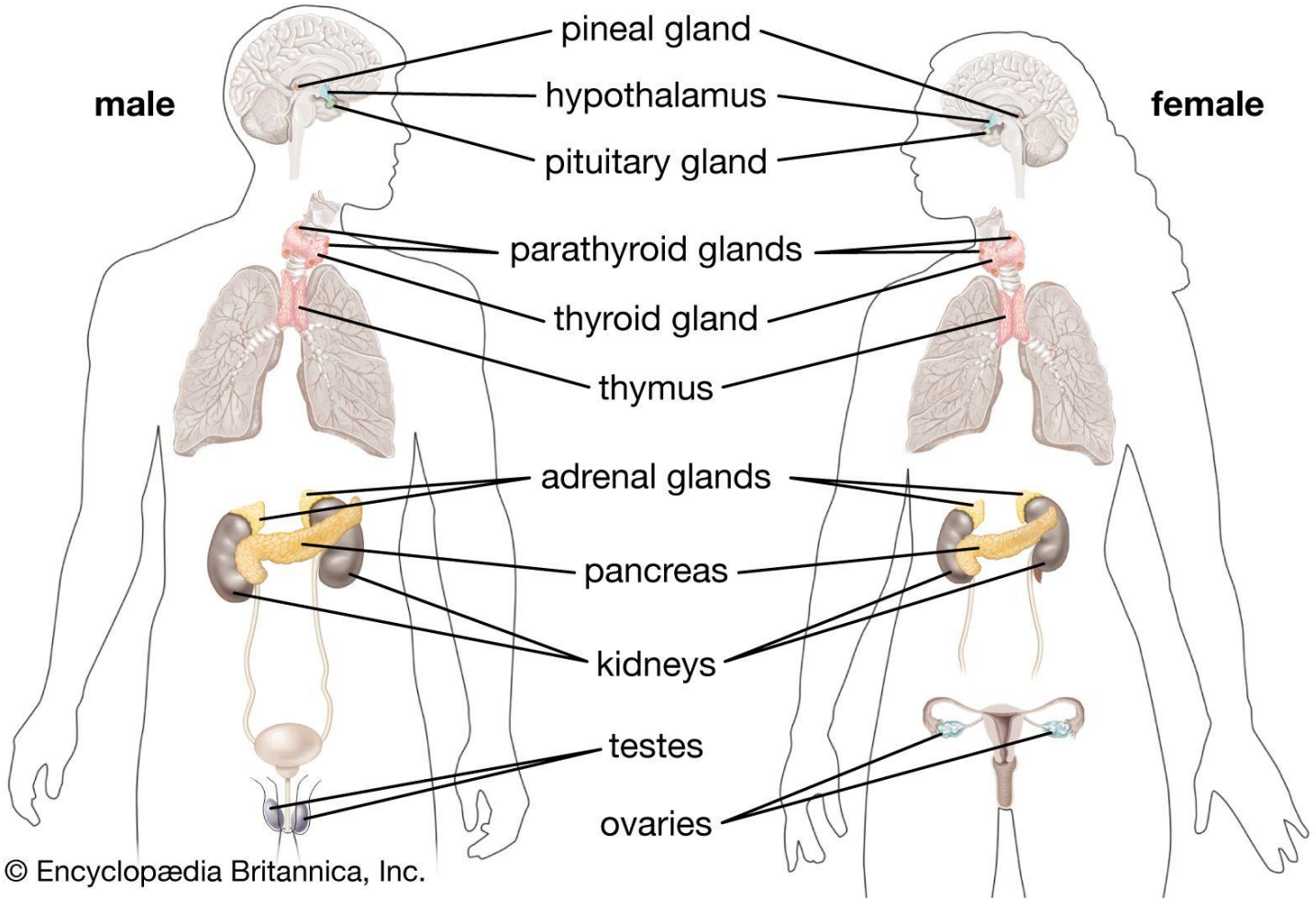
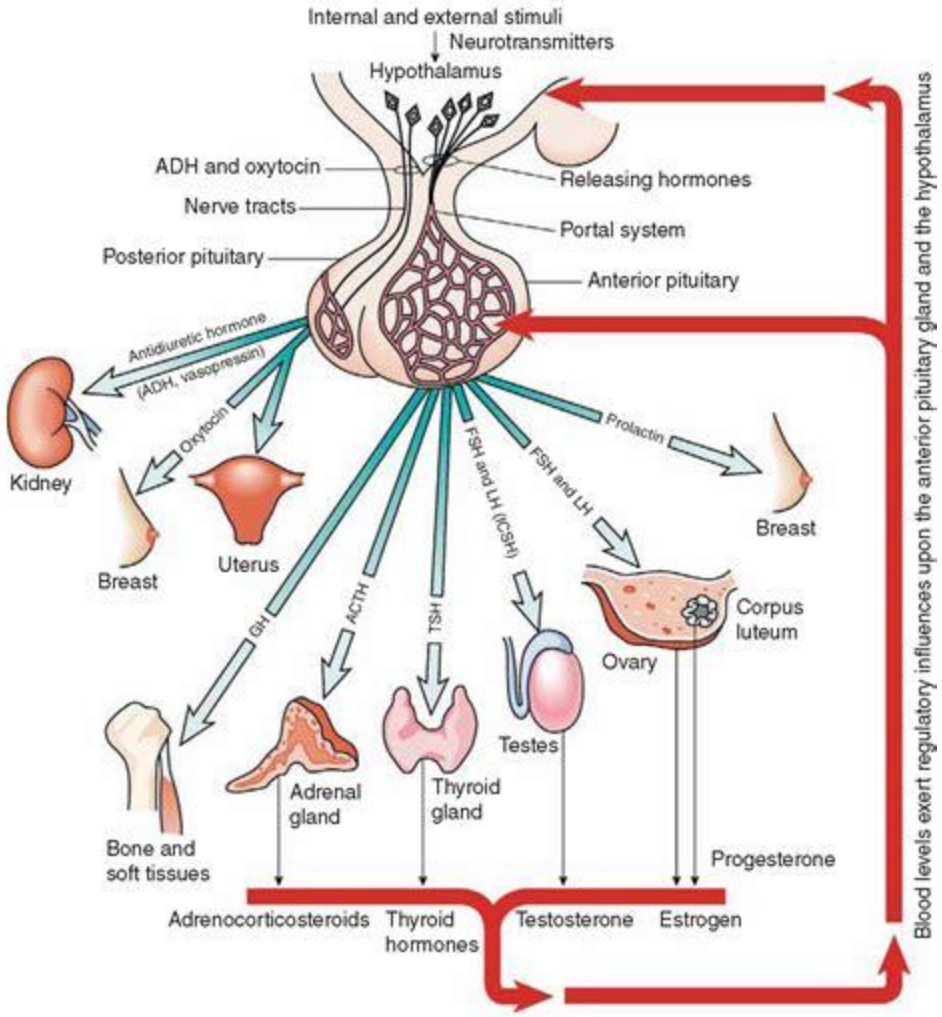
	CTLA-4	PD-1	Combo
Dermatologic *dry mouth, mucositis, rash, pruritis, and vitiligo*	44-68%	37-42%	58-71%
Colitis	10-25%	1-5%	~20%
Endocrine *thyroid dysfunction*	1-5%	5-10%	~20%
Hepatitis	3,9%	3,8%	17,6%
Pulmonary pneumonitis, sarcoidosis, pleural effusions, and reactive airway disease		3,8%	9,6%
Cardiac asymptomatic biomarker (troponin, NT-proBNP) elevation or acute decompensated heart failure, cardiac arrest, or hemodynamically significant complete heart block		0,5%	2,4%

C H U | U V C
B R U G M A N N

Adapted from **Darnell et al. Curr Oncol Rep. 2020**

Endocrine system





Endocrine adverse events

Hypophysitis

- Silent hypophysitis
- Secondary adrenal insufficiency
- Isolated ACTH-def.

Adrenalitis

- Primary adrenal insufficiency

Thyroid

Thyroiditis

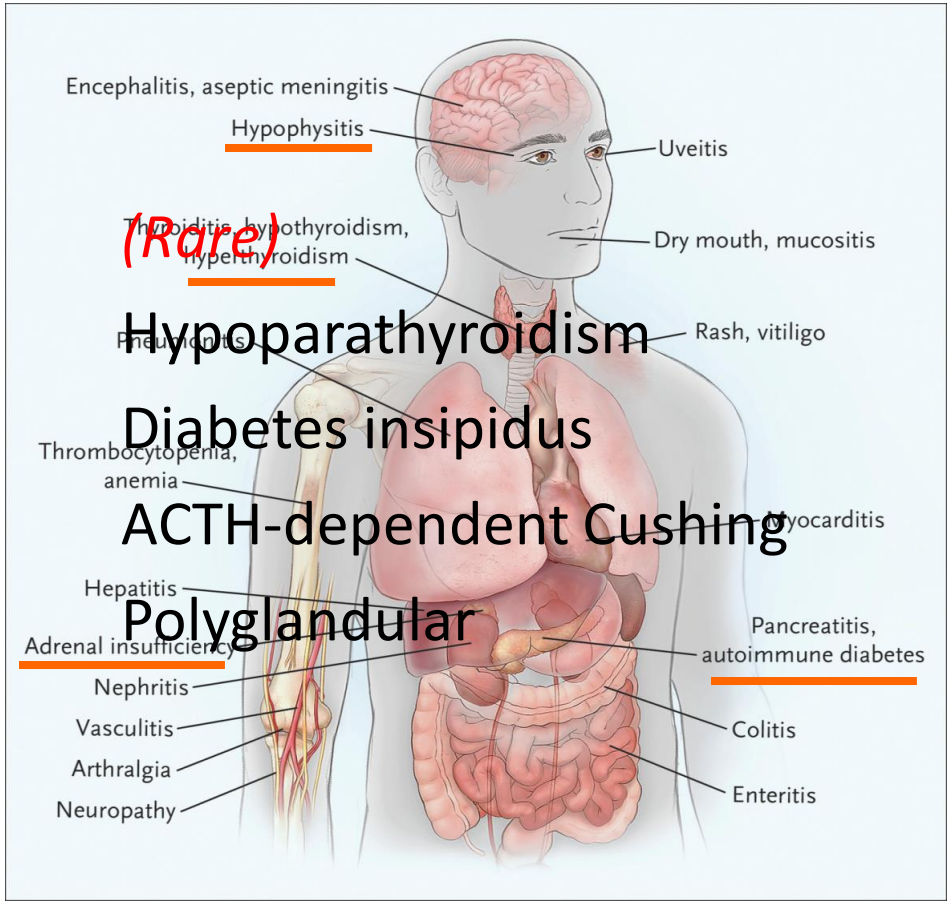
Isolated hyper-hypothyroidism

m.Graves w/o TED

Diabetes mellitus

Type-1 like (fulminant)

Type 2 diabetes (worsening)



(Rare)

Hypoparathyroidism

Diabetes insipidus

ACTH-dependent Cushing

Polyglandular

Postow et al. NEJM 2018

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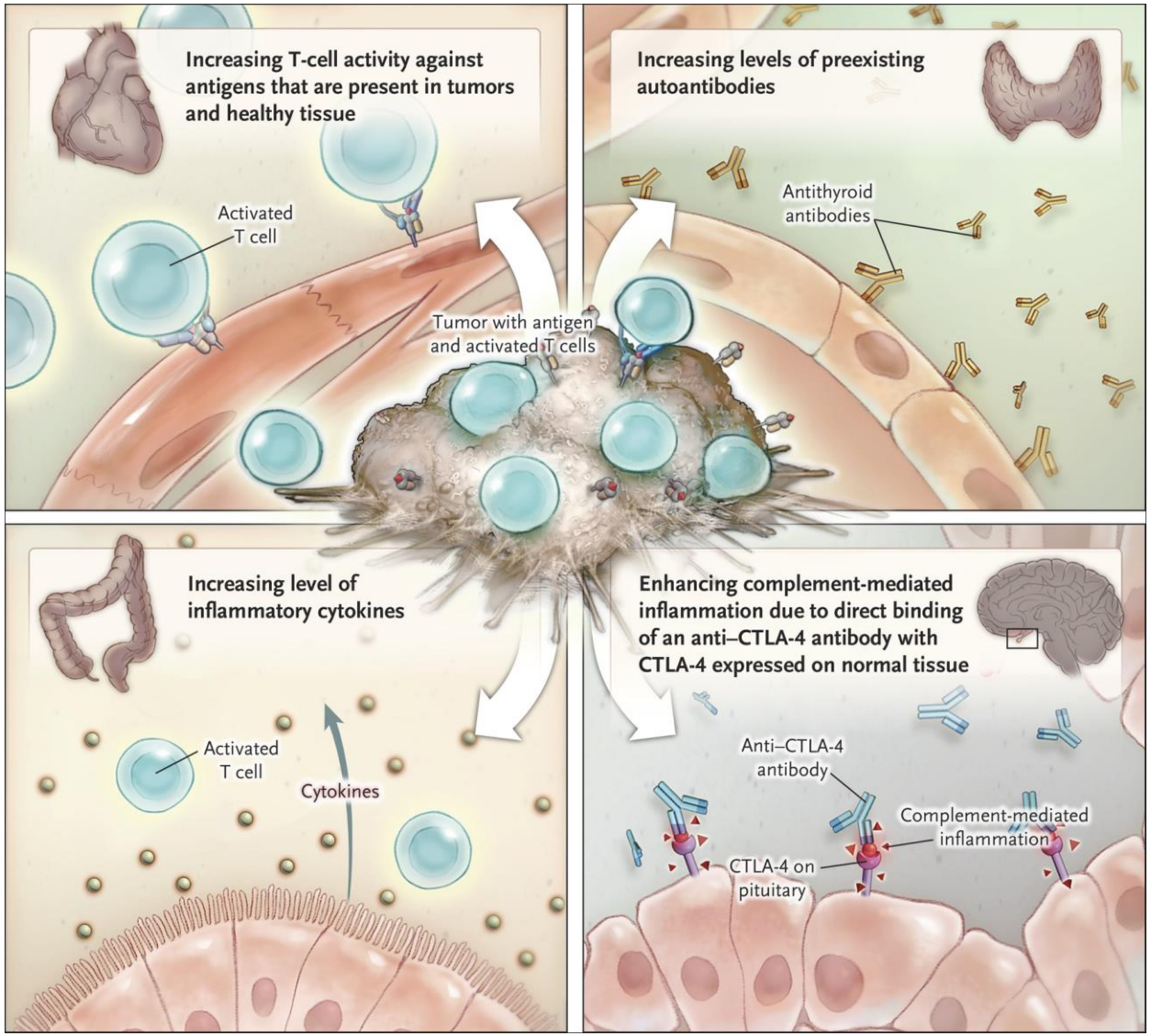
Mechanisms of ICI toxicity

Removal of self-tolerance

Factors

- Demographics
- Environmental triggers
- Pre-existing autoimmunity?



Postow et al. NEJM 2018

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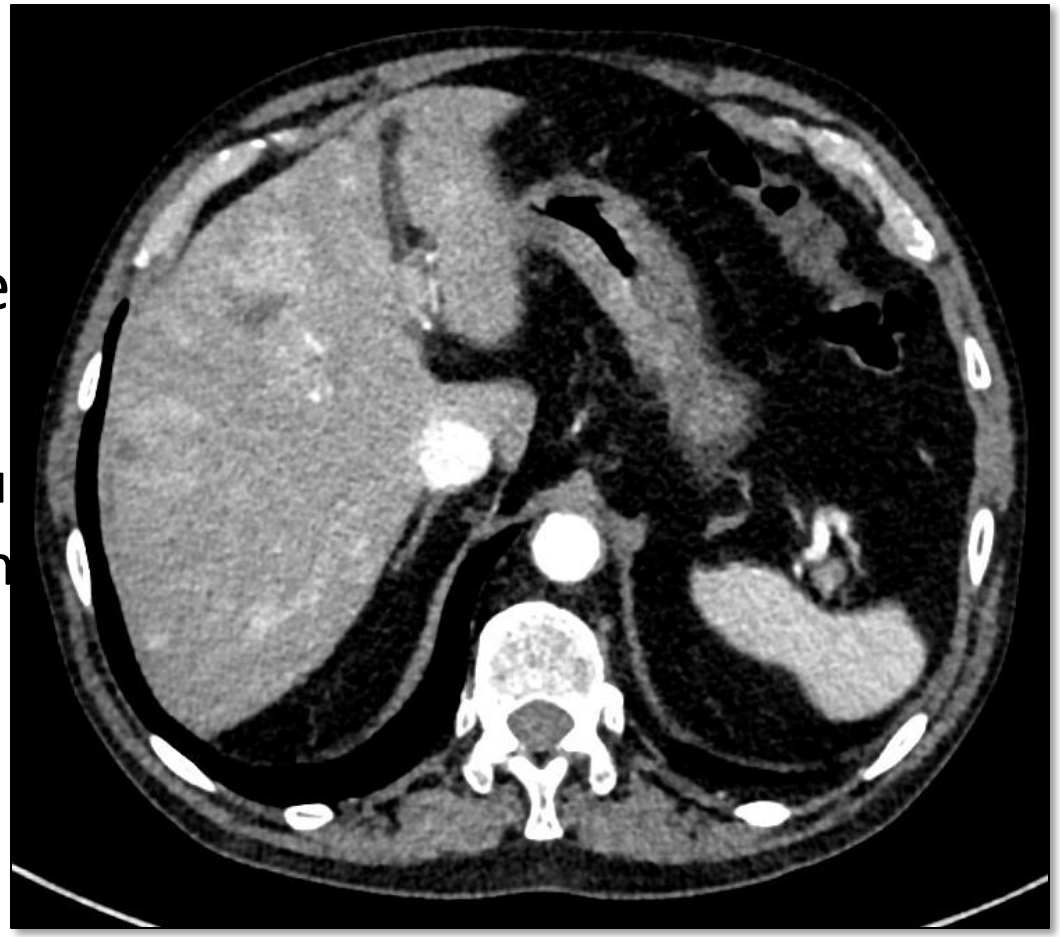
Spectrum of endocrine adverse events

- Up to 40% of patients
- Thyroid > pituitary > others
- Often unpredictable onset (even after cessation)
- Subclinical <-> overt disease
- Permanent and irreversible
- (!) Immunotherapy may be continued

Case 1

- 68-year old male
- Cirrhosis, treated for HCV (?) with inte
- Bilan :
  - CT : multiple hepatic lesions, hypervascu
  - Alpha-foetoproteine + 23,9 mcg/L; CEA n
  - HCV RNA indetectable



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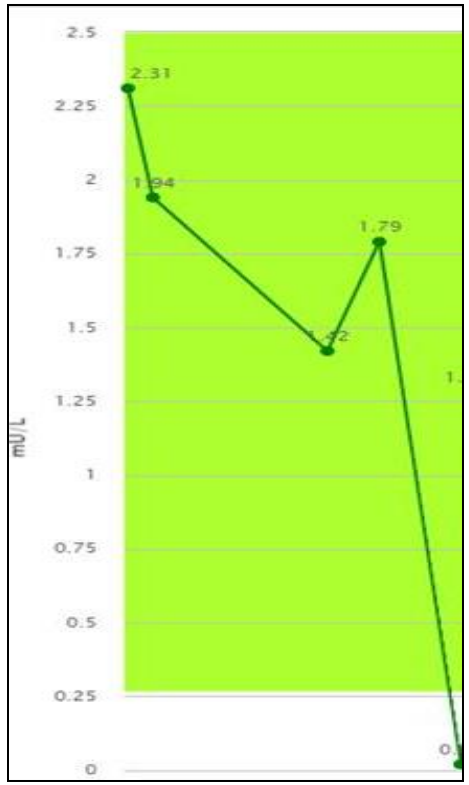
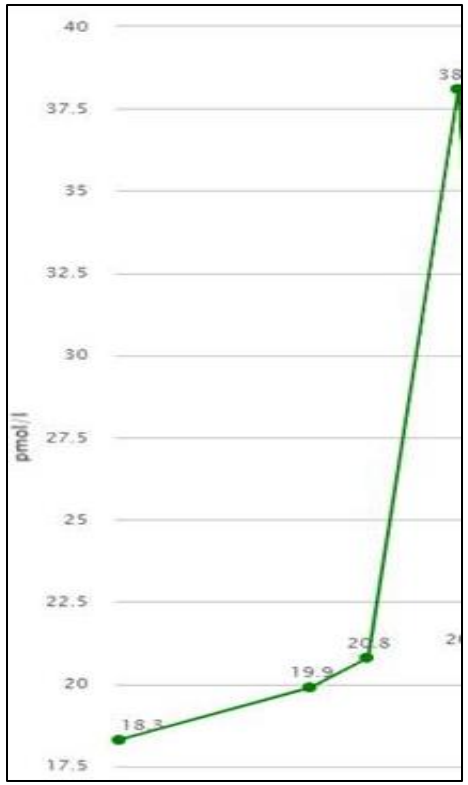
Case 1

- 68-year old male
- Cirrhosis, treated for HCV (?) with interferon (2014), alcohol
- Bilan :
  - CT : multiple hepatic lesions, hypervascular with late phase washout
  - Alpha-foetoproteine + 23,9 mcg/L; CEA nl
  - HCV RNA indetectable
- Hepatocarcinoma stage BCLC C (advanced)
- 10/2022 : Atezolizumab (PD-L1 inhibitor) et bevacizumab (anti-VEGF-A)

After 4 cycles of atezo-beva…



TSH à 0,02



fT4 à 38

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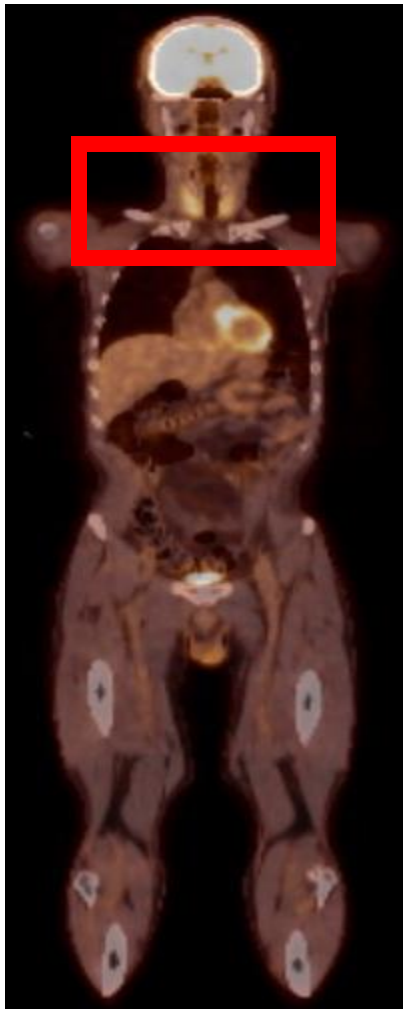
What to do next ?

- **A** Thyroid autoantibodies
- **B** Ultrasonography
- **C** Thyroid scintigraphy
- **D** PET-CT
- **E** Start thyroid blocking drug, i.e. strumazole

What to do next ?

- **A** Thyroid autoantibodies – **TRAb = TSI ?**
- **B** **Ultrasonography ?**
- **C** Thyroid scintigraphy
- **D** **PET-CT**
- **E** Start thyroid blocking drug, i.e. strumazole



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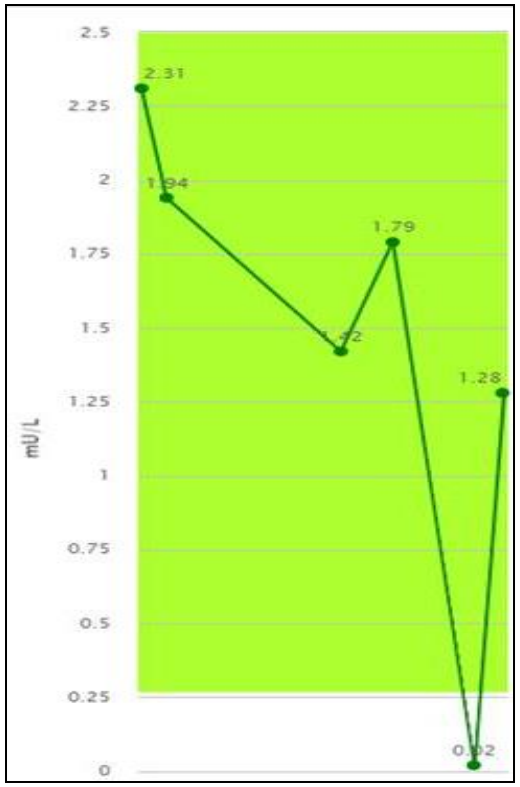
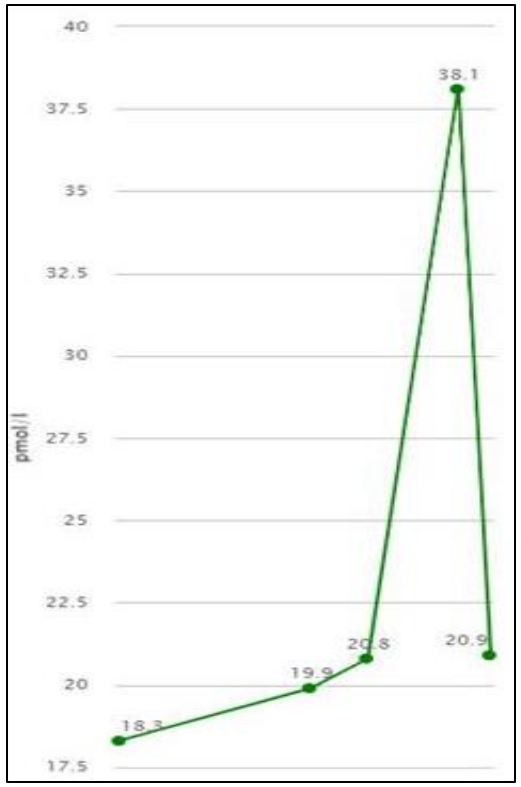
Case 1



TSH à 1,28



fT4 à 20,9

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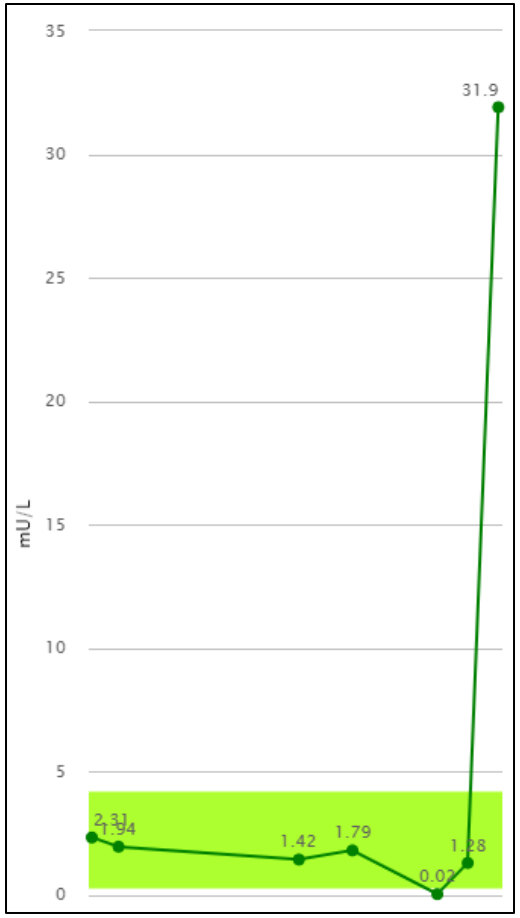
What to do next ?

- **A** Follow-up of thyroid function tests in 3 weeks
- **B** Follow-up of thyroid function tests in 3 months
- **C** Thyroid autoantibodies
- **D** Start thyroid hormone therapy
- **E** If thyroid hormone therapy is started...
  could it be stopped in the future ?

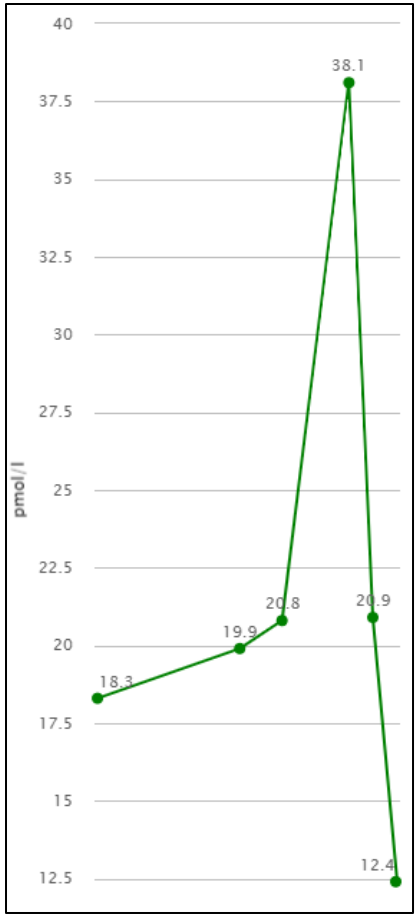
What to do next ?

- **A** **Follow-up of thyroid function tests in 3 weeks**
- **B** Follow-up of thyroid function tests in 3 months
- **C** Thyroid autoantibodies – *BASELINE ?*
- **D** Start thyroid hormone therapy
- **E** If thyroid hormone therapy is started...
  could it be stopped in the future ?

Case 1



TSH à 31,9



fT4 à 12,4

+ L-thyroxine

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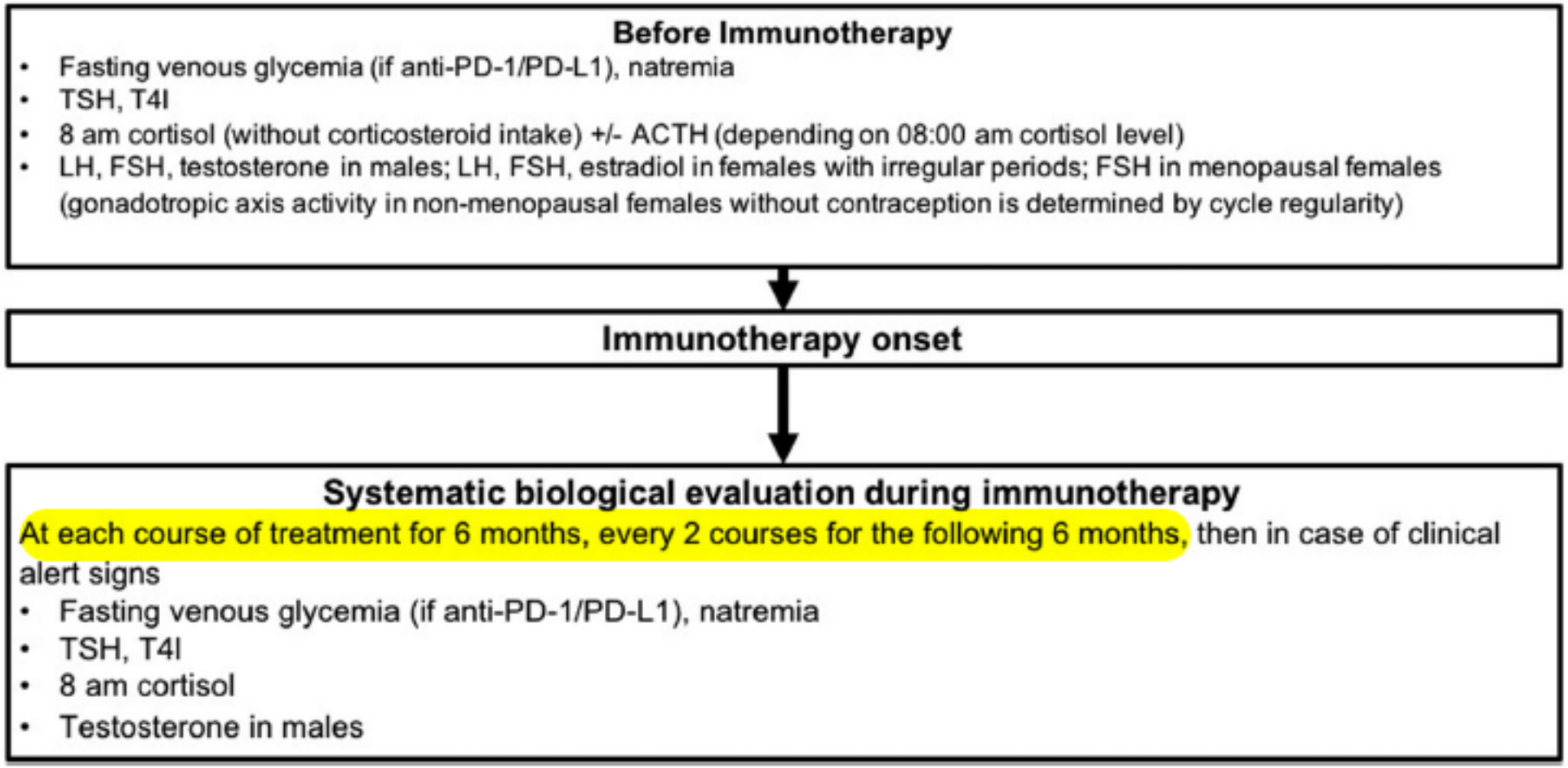
Thyroiditis

- Most common endocrinopathy
- Mild or asymptomatic
- Biphasic or only hypothyroidism
- Combination ICI > PD-1/L1 > CTLA-4
- Low uptake on scintigraphy and absent TRAb/TSI; FDG-PET+
- No specific treatment, watchful waiting (beta-blockers)

Risk factors : women, higher baseline TSH, thyroid autoAb+ and prior exposure to tyrosine kinase inhibitors



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Castinetti et al. Endocr Relat Cancer. 2019

Screening Monitoring	ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY	ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE	European Society of Endocrinology The voice for endocrinology
GI toxicity	AST, AST and bili : before every cycle	AST, AST, **ALP, *GGT** and bili : before every cycle *Amylase and lipase : every 6 wk	NA
Endocrine: thyroid	TSH (+fT4) : **every 4-6 weeks** **on ICI therapy**	TSH, fT4 : before every cycle **first 3 months** every 2nd cycle thereafter	TSH, fT4 : before every cycle **first 6 months** every 2-3 mo for 6 mo every 6 mo thereafter
Diabetes	glycemia : before every cycle *& up to 6 mo	*glycemia : every 4-6 weeks on ICI therapy	NS
Renal	serum creatinine : before every cycle *urinalysis: not necessary	*eGFR & urine sediment : Before every cycle	NA
Hemato	NS	*CBC, fibrinogen	NA
Cardiac	NS	*Troponin T, NT-proBNP and CK : before every cycle	

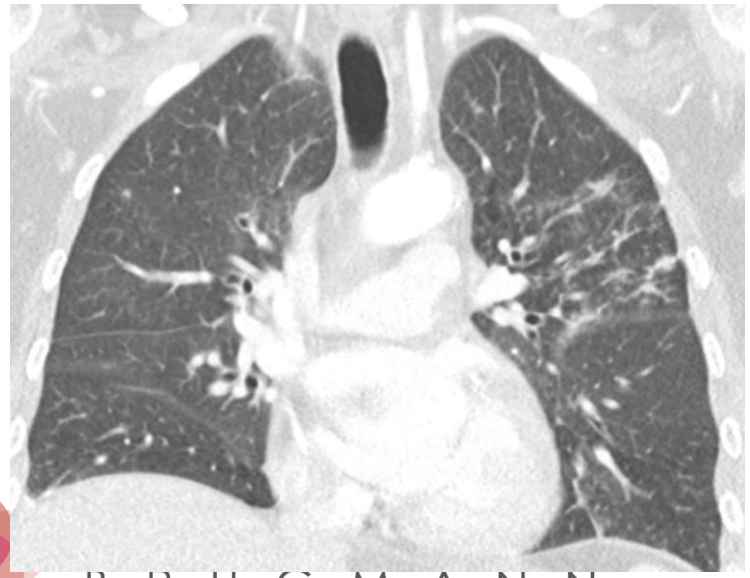
***supplementary data; NS, not specified; NA, not applicable**

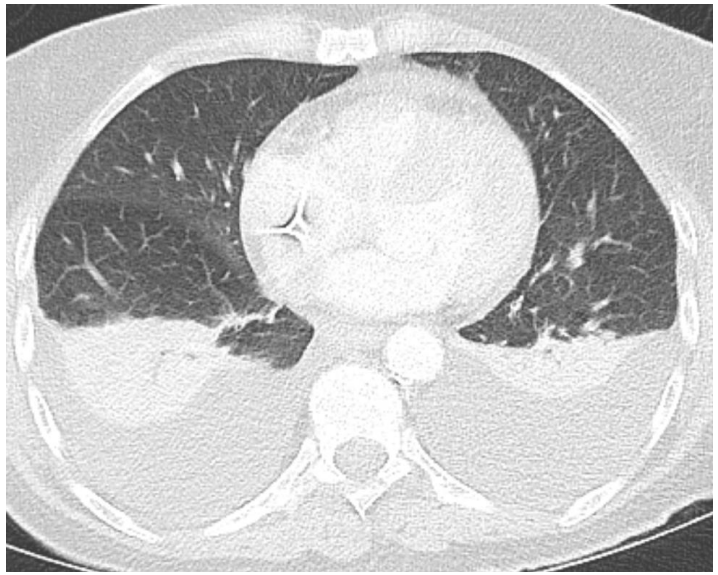
Case 2

- 60-year old female
- Invasive triple-negative breast carcinoma on the right, cT2 cN0 M0
- Neoadjuvant chemo (taxol + carbo) with pembrolizumab Q3W for 4 cycles
- Hospitalization two weeks after last immuno …

Case 2

- ER : Fatigue, asthenia, myalgia, chills, coughing … for a few days
- T 38,5°, desaturation
- Labs : WBC 5.9 x10^3/µL, neutro’s 83%, CRP 443 mg/L
- ABG : pH 7.48, pO2 56 mmHg, pCO2 28 mmHg





Case 2

- ER : Fatigue, asthenia, myalgia, chills, coughing … for a few days
- T 38,5°, desaturation
- Labs : WBC 5.9 x10^3/µL, neutro's 83%, CRP 443 mg/L
- ABG : pH 7.48, pO2 56 mmHg, pCO2 28 mmHg

- Empiric treatment with Tazocin-Amukin

>>> Meropenem-Biclar >>> Biclar (*Mycoplasma pneumoniae*)

Case 2

- Persisting fatigue …

- ACTH < 3.0 ng/L
- TSH 4.77 mU/L
- FSH 68.0 UI/L
- IGF-1 74.1 mcg/L
- Prolactin 34.8 mcg/L

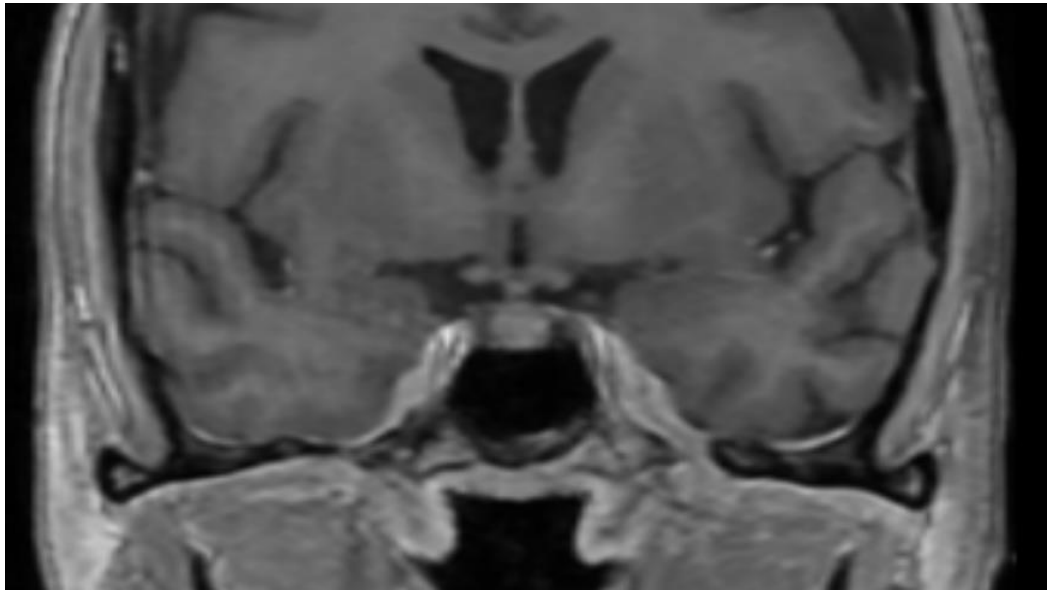
Morning cortisol 5 nmol/L (*confirmed*)

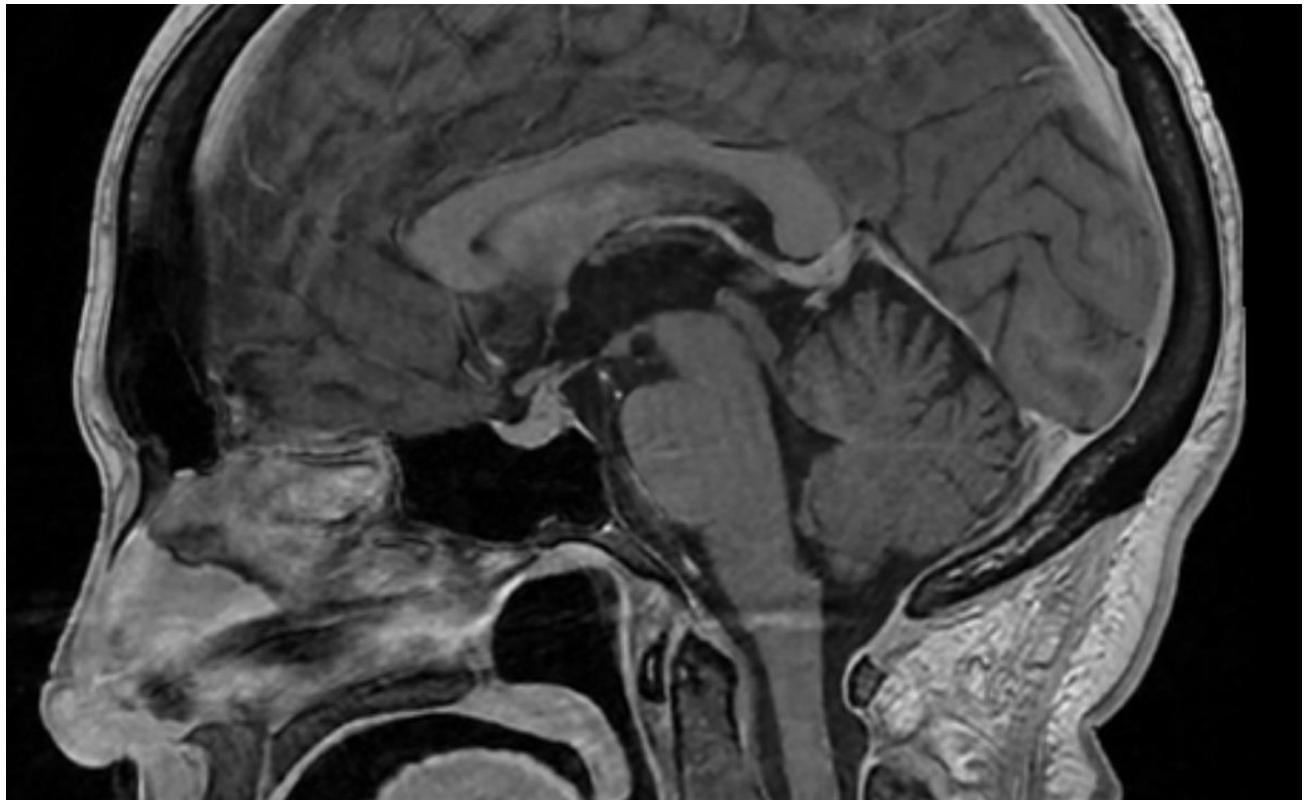
fT4 13.1 pmol/L

LH 18.4

Case 2

- Severe corticotropic insufficiency due to isolated ACTH-deficiency
- Hydrocortisone supplementation led to spectacular improvement





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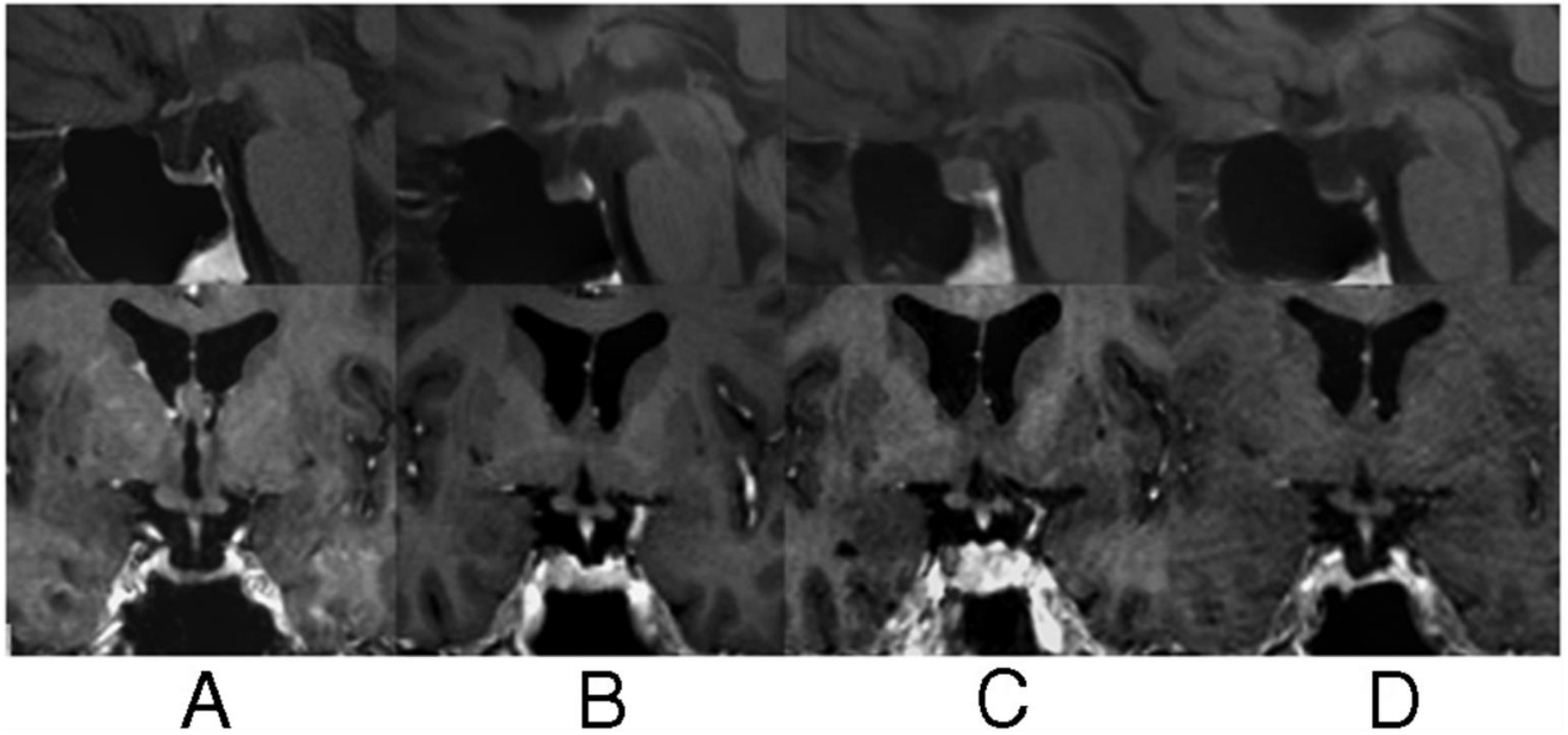
Hypophysitis

- Most common cause of autoimmune hypophysitis
- Male and age >60
- Onset: < 3 months (CTLA-4) up to >6 months (PD-1)
- Dose-dependent for CTLA-4 inhibitors (3 vs 10mg/kg)
- Role of circulating pituitary autoantibodies ?

Hypophysitis

- Symptoms of adrenal insufficiency (fatigue, nausea) and compression (headache)
- Adrenal crisis possible (concurrent disease, start of thyroid hormone therapy)
- Panhypopituitarism <-> isolated ACTH deficiency (PD-1/L1)
- Treatment depends on initial presentation
- MRI for initial diagnosis AND exclude metastasis

Hypophysitis - Imaging



-1 month | After 2nd cycle | After 3rd cycle | +1 month

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Faje et al., JCEM 2014

Hypophysitis associated with immune checkpoint inhibitors (ICIs)

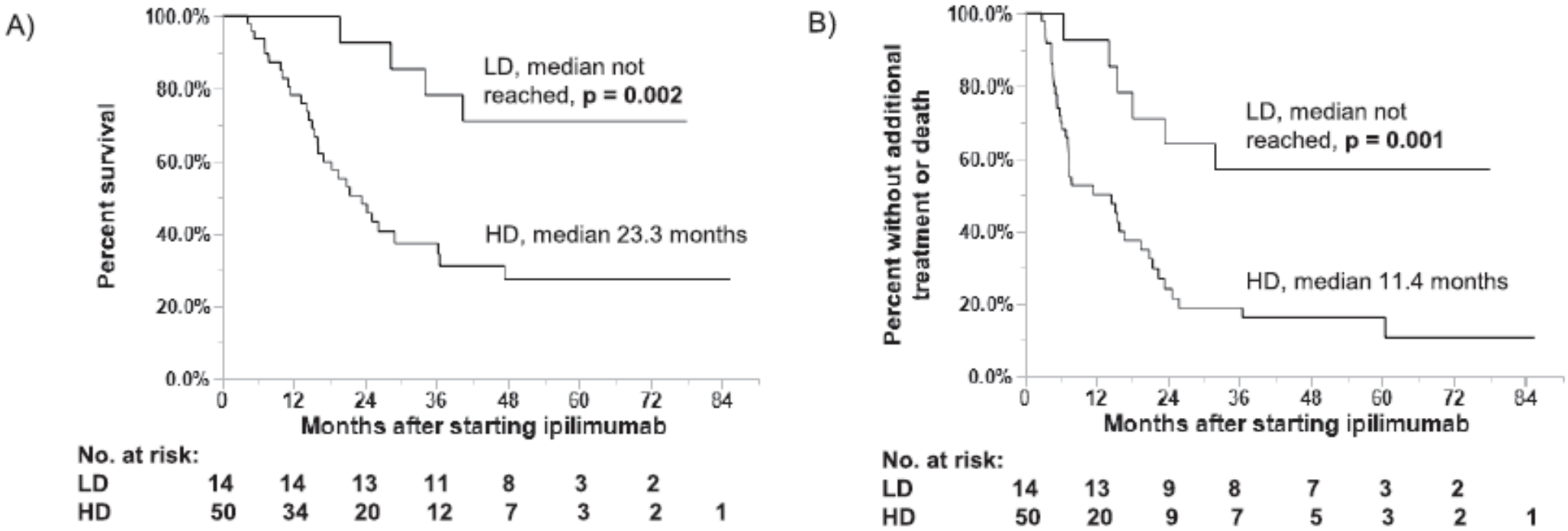
	Ipilimumab (anti CTLA-4 Ab)	Pembrolizumab (anti PD-1 Ab)
Prevalence among treated patients	10% (64 cases)	0.5% (22 cases)
Onset after start of therapy	9.3 wk (7.2-11.1)	25.8 wk (18.4-44.0)
Pituitary enlargement on MRI	Almost universal (60/61 pts)	Uncommon (5/18 pts)
Headache	48 patients (75%)	5 patients (23%)
Pituitary function at diagnosis	Multiple anterior pituitary hormone deficiencies are present in most patients	Central AI is universal (other deficits are uncommon)
Pituitary function on follow-up	Partial recovery of pituitary function in a minority of patients	Persistent AI occurs
Hormone replacement	Physiologic endocrine replacement (including glucocorticoids)	Physiologic endocrine replacement (including glucocorticoids)

Compression of the optic chiasm is rare in hypophysitis associated with ICIs

Faje A et al, JCEM, 2014; Faje A et al, EJE, 2019

High-Dose Glucocorticoids for the Treatment of Ipilimumab-Induced Hypophysitis Is Associated With Reduced Survival in Patients With Melanoma

Median
5.5 mg
vs
22.4 mg



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Faje et al. Cancer. 2018

Pituitary autoantibodies

Table 1. Serum pituitary antibodies in 20 cancer patients with or without a clinical diagnosis of hypophysitis before and after administration of ipilimumab (Ipi). na, sera that were "not assessed" for cell-specific antibodies because the overall pituitary antibodies were negative.

ID	Sex	Age (years)	Cancer type	Clinical hypophysitis	Overall pituitary antibodies		Cell-specific pituitary antibodies				
					Before Ipi	After Ipi	SH-secreting cells	FSH-secreting cells	ACTH-secreting cells	GH-secreting cells	PRL-secreting cells
1	M	53	Melanoma	Yes	Absent	Present	Positive	Positive	Negative	Negative	Negative
2	M	68	Melanoma	Yes	Absent	Present	Positive	Positive	Negative	Negative	Negative
3	M	59	Melanoma	Yes	Absent	Present	Positive	Negative	Positive	Negative	Negative
4	F	34	Melanoma	Yes	Absent	Present	Positive	Positive	Positive	Negative	Negative
5	F	58	Melanoma	Yes	Absent	Present	Positive	Negative	Negative	Negative	Negative
6	M	72	Melanoma	Yes	Absent	Present	Positive	Positive	Positive	Negative	Negative
7	M	65	Prostate	Yes	Absent	Present	Positive	Positive	Negative	Negative	Negative
8	M	58	Prostate	No	Absent	Absent	na	na	na	na	na
9	M	63	Prostate	No	Absent	Absent	na	na	na	na	na
10	M	65	Melanoma	No	Absent	Absent	na	na	na	na	na
11	F	57	Melanoma	No	Absent	Absent	na	na	na	na	na
12	F	54	Melanoma	No	Absent	Absent	na	na	na	na	na
13	F	50	Melanoma	No	Absent	Absent	na	na	na	na	na
14	M	57	Prostate	No	Absent	Absent	na	na	na	na	na
15	M	64	Prostate	No	Absent	Absent	na	na	na	na	na
16	M	74	Prostate	No	Absent	Absent	na	na	na	na	na
17	M	78	Prostate	No	Absent	Absent	na	na	na	na	na
18	M	66	Prostate	No	Absent	Absent	na	na	na	na	na
19	M	63	Melanoma	No	Absent	Absent	na	na	na	na	na
20	M	62	Melanoma	No	Absent	Absent	na	na	na	na	na

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Iwama et al. Sci Transl Med 2014

Hypophysitis - treatment

- Oral hydrocortisone
  <-> high-dose hydrocortisone or methylprednisolone IV

(!) Teaching

- Levothyroxine : after corticoids, start low and go slow
- Testosterone or estrogen replacement : only if persisting
- No GH replacement therapy

Teaching adrenal insufficiency

1. ‘Sick days’ – mild or moderate stress
2. Severe stress – Solu-Cortef ‘rescue’ injection
3. Emergency ‘bracelet – card’
   + informing relatives

BijnierNET

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Why hydrocortisone?

- Cortisol = endogenous corticosteroid
- Synthetic:
  - Short duration (8-12h) : hydrocortisone = bioactive
  - Intermediate (12-36h) : prednisone, prednisolone, methylprednisolone (Medrol)
  - Long duration (>24h) : dexamethasone

} + anti-inflammatory

Addison crisis : treatment

- Hydrocortisone 20-25mg / day, in multiple doses
- Prevention (!) = adaptation to the stress situation
  - Mild stress : extra dose
  - Moderate stress : temporary doubling of dose (e.g., flu, heavy labor)
  - Severe stress : trauma, surgery, severe illness : up to 10x higher (!)
    → emergency injection

Case 3

- 58-year old female
- Triple-negative breast carcinoma, cT3 N1 M0
- Neoadjuvant chemo (taxol + carbo) with pembrolizumab Q3W for 4 cycles

- Glycemia 124 mg/dL (before chemo-immuno)
- 4 weeks after 1st cycle, she says "*she drinks a lot and is always thirsty*"
- Glycemia 556 mg/dL
- pH 7.46, bicarbonate 28 mmol/L

What to do next ?

- **A** HbA1c ?
- **B** c-peptide ?
- **C** lipase ?
- **D** islet cell antibodies ?
- **E** CT abdomen ?

What to do next ?

- **A** **HbA1c**
- **B** **c-peptide**
- **C** lipase
- **D** **islet cell antibodies**
- **E** CT abdomen

Case 3

- No ketoacidosis, rather phenotype of preserved beta-cell function
- HbA1c 9.8%; c-peptide 0.590 nmol/L, anti-GAD negative
- Start basal-bolus insulin therapy

- +1 month : HbA1c 7.6%; c-peptide 1.020 nmol/L
- Gradual reduction of basal-bolus insulin

- +4 months: HbA1c 6.3%; c-peptide 0.898 nmol/L
- Metformin monotherapy

Diabetes mellitus

- Less frequent – 1-2%
- PD-1 or PD-L1 inhibitors

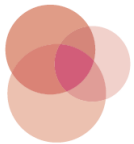
- Age >60 and male
- +-75% ketoacidosis at diagnosis = fulminant
- Early onset < 12 weeks

Diabetes mellitus

- Classic symptoms

- Random blood glucose, U&E, blood pH and ketones
- HbA1c ? **C-peptide ?** Lipase ?
- Islet cell autoantibodies – GAD in ½
- HLA-DR4

- Treat as type 1 diabetes



Novel combination of immunotherapy PD-1 inhibitor with LAG-3 inhibitor

= Lymphocyte-Activation Gene-3

Mechanism : interaction with antigen-MHC Class II on APCs

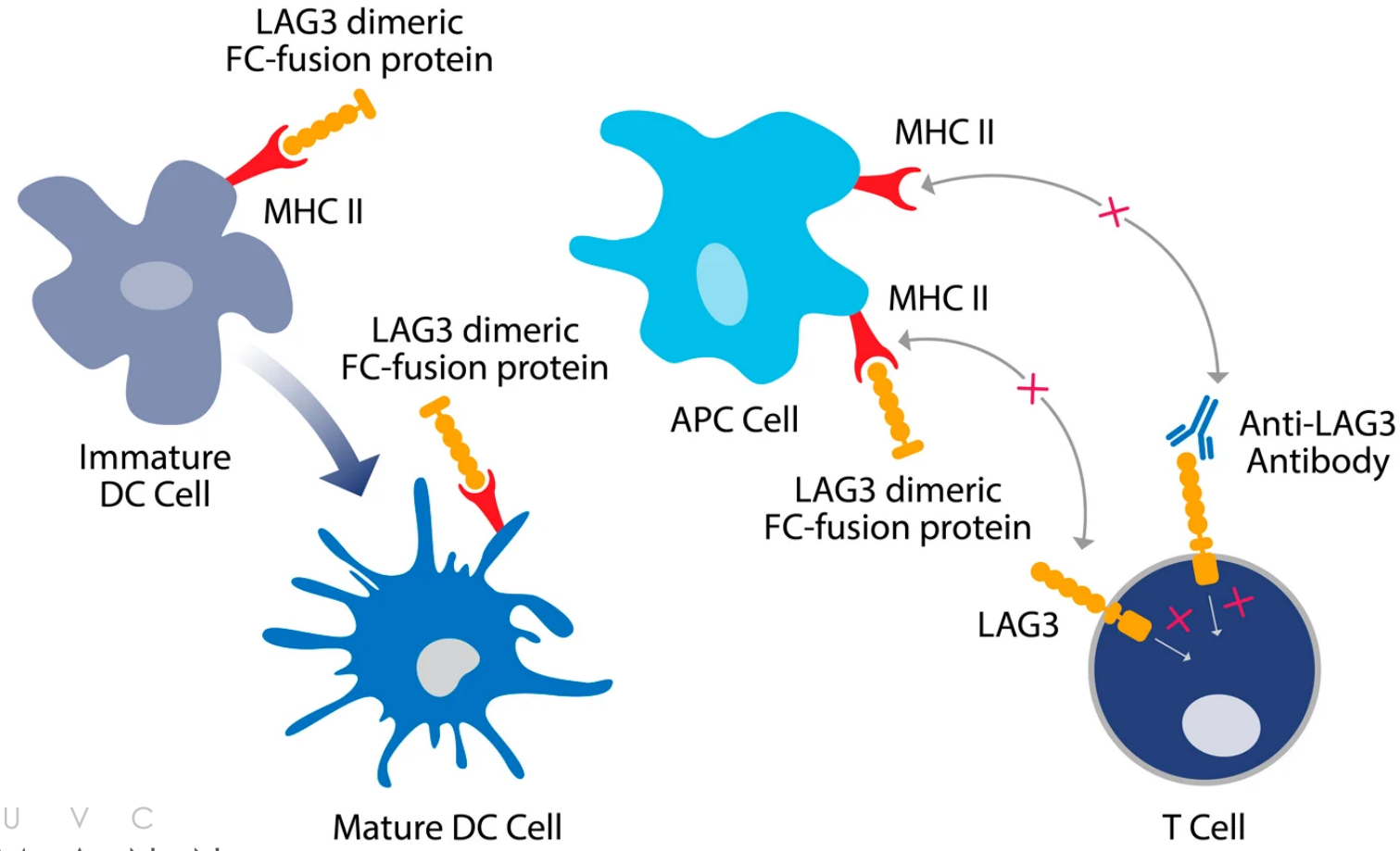
Therapeutic strategy :

Block LAG-3 (inhibitor) on cytotoxic and regulatory T-cells (relatlimab)

or stimulate MHC Class II on dendritic cells (e.g. soluble LAG-3)

Synergy with PD-1/L1 inhibitors?

Novel combination of immunotherapy PD-1 inhibitor with LAG-3 inhibitor



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PD-1 inhibitor with LAG-3 inhibitor

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma

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Tawbi et al. NEJM 2022

PD-1 inhibitor Nivolumab with LAG-3 inhibitor Relatlimab

- Metastatic or unresectable melanoma
- Improvement in PFS compared to monotherapy with Nivolumab (12m PFS :47,7% vs 36%)

BACKGROUND

Lymphocyte-activation gene 3 (LAG-3) and programmed death 1 (PD-1) are distinct inhibitory immune checkpoints that contribute to T-cell exhaustion. The combination of relatlimab, a LAG-3–blocking antibody, and nivolumab, a PD-1–blocking antibody, has been shown to be safe and to have antitumor activity in patients with previously treated melanoma, but the safety and activity in patients with previously untreated melanoma need investigation.

METHODS

In this phase 2–3, global, double-blind, randomized trial, we evaluated relatlimab and nivolumab as a fixed-dose combination as compared with nivolumab alone when administered intravenously every 4 weeks to patients with previously untreated metastatic or unresectable melanoma. The primary end point was progression-free survival as assessed by blinded independent central review.

RESULTS

The median progression-free survival was 10.1 months (95% confidence interval [CI], 6.4 to 15.7) with relatlimab–nivolumab as compared with 4.6 months (95% CI, 3.4 to 5.6) with nivolumab (hazard ratio for progression or death, 0.75 [95% CI, 0.62 to 0.92]; P=0.006 by the log-rank test). Progression-free survival at 12 months was 47.7% (95% CI, 41.8 to 53.2) with relatlimab–nivolumab as compared with 36.0% (95% CI, 30.5 to 41.6) with nivolumab. Progression-free survival across key subgroups favored relatlimab–nivolumab over nivolumab. Grade 3 or 4 treatment-related adverse events occurred in 18.9% of patients in the relatlimab–nivolumab group and in 9.7% of patients in the nivolumab group.

CONCLUSIONS

The inhibition of two immune checkpoints, LAG-3 and PD-1, provided a greater benefit with regard to progression-free survival than inhibition of PD-1 alone in patients with previously untreated metastatic or unresectable melanoma. Relatlimab and nivolumab in combination showed no new safety signals. (Funded by Bristol Myers Squibb; RELATIVITY-047 ClinicalTrials.gov number, NCT03470922.)

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PD-1 inhibitor Nivolumab with LAG-3 inhibitor Relatlimab

- Hypothyroidism (18 vs 13.9%)
- Adrenal insufficiency (4.2 vs 0.8%)
- Hypophysitis (2.5 vs 0.8%)

Table 2. Summary of Adverse Events.

Adverse Event	Relatlimab–Nivolumab (N=355)		Nivolumab (N=359)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
	number of events (percent)			
Any adverse event	345 (97.2)	143 (40.3)	339 (94.4)	120 (33.4)
Treatment-related adverse event	288 (81.1)	67 (18.9)	251 (69.9)	35 (9.7)
Led to discontinuation of treatment	52 (14.6)	30 (8.5)	24 (6.7)	11 (3.1)
Treatment-related adverse event in ≥10% of patients in the relatlimab–nivolumab group				
Pruritus	83 (23.4)	0	57 (15.9)	2 (0.6)
Fatigue	82 (23.1)	4 (1.1)	46 (12.8)	1 (0.3)
Rash	55 (15.5)	3 (0.8)	43 (12.0)	2 (0.6)
Arthralgia	51 (14.4)	3 (0.8)	26 (7.2)	1 (0.3)
Hypothyroidism	51 (14.4)	0	43 (12.0)	0
Diarrhea	48 (13.5)	3 (0.8)	33 (9.2)	2 (0.6)
Vitiligo	37 (10.4)	0	35 (9.7)	0
Immune-mediated adverse event*				
Hypothyroidism or thyroiditis	64 (18.0)	0	50 (13.9)	0
Rash	33 (9.3)	2 (0.6)	24 (6.7)	5 (1.4)
Diarrhea or colitis	24 (6.8)	4 (1.1)	11 (3.1)	5 (1.4)
Hyperthyroidism	22 (6.2)	0	24 (6.7)	0
Hepatitis	20 (5.6)	14 (3.9)	9 (2.5)	4 (1.1)
Adrenal insufficiency	15 (4.2)	5 (1.4)	3 (0.8)	0
Pneumonitis	13 (3.7)	2 (0.6)	6 (1.7)	2 (0.6)
Hypophysitis	9 (2.5)	1 (0.3)	3 (0.8)	1 (0.3)
Nephritis and renal dysfunction	7 (2.0)	4 (1.1)	5 (1.4)	4 (1.1)
Hypersensitivity	4 (1.1)	0	4 (1.1)	0

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PD-1 inhibitor with LAG-3 inhibitor

Original Reports | Gastrointestinal Cancer

First-Line Nivolumab and Relatlimab Plus Chemotherapy for Gastric or Gastroesophageal Junction Adenocarcinoma: The Phase II RELATIVITY-060 Study

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PD-1 inhibitor Nivolumab with LAG-3 inhibitor Relatlimab

- Untreated advanced gastric cancer or gastro-esophageal junction cancer

ABSTRACT

PURPOSE Open-label phase II study (RELATIVITY-060) to investigate the efficacy and safety of first-line nivolumab, a PD-1–blocking antibody, plus relatlimab, a lymphocyte-activation gene 3 (LAG-3)–blocking antibody, plus chemotherapy in patients with previously untreated advanced gastric cancer (GC) or gastro-esophageal junction cancer (GEJC).

METHODS Patients with unresectable, locally advanced or metastatic GC/GEJC were randomly assigned 1:1 to nivolumab + relatlimab (fixed-dose combination) + chemotherapy or nivolumab + chemotherapy. The primary end point was objective response rate (ORR; per RECIST v1.1 by blinded independent central review [BICR]) in patients whose tumors had LAG-3 expression ≥1%.

RESULTS Of 274 patients, 138 were randomly assigned to nivolumab + relatlimab + chemotherapy and 136 to nivolumab + chemotherapy. Median follow-up was 11.9 months. In patients with LAG-3 expression ≥1%, BICR-assessed ORR (95% CI) was 48% (38 to 59) in the nivolumab + relatlimab + chemotherapy arm and 61% (51 to 71) in the nivolumab + chemotherapy arm; median progression-free survival (95% CI) by BICR was 7.0 months (5.8 to 8.4) versus 8.3 months (6.9 to 12.1; hazard ratio [HR], 1.41 [95% CI, 0.97 to 2.05]), and median overall survival (95% CI) was 13.5 months (11.9 to 19.1) versus 16.0 months (10.9 to not estimable; HR, 1.04 [95% CI, 0.70 to 1.54]), respectively. Grade 3 or 4 treatment-related adverse events (TRAEs) occurred in 69% and 61% of all treated patients, and 42% and 36% of patients discontinued because of any-grade TRAEs in the nivolumab + relatlimab + chemotherapy and nivolumab + chemotherapy arms, respectively.

CONCLUSION RELATIVITY-060 did not meet its primary end point of improved ORR in patients with LAG-3 expression ≥1% when relatlimab was added to nivolumab + chemotherapy compared with nivolumab + chemotherapy. Further studies are needed to address whether adding anti–LAG-3 to anti–PD-1 plus chemotherapy can benefit specific GC/GEJC patient subgroups.

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PD-1 inhibitor Nivolumab with LAG-3 inhibitor Relatlimab

- Hypothyroidism (14 vs 11%)
- Hyperthyroidism (6 vs 2%)
- Adrenal insuff. (3 vs <1%)
- Hypophysitis (2 vs 0%)
- Diabetes mellitus (2 vs 1%)

TABLE 3. Summary of AEs in All Treated Patients

	NIVO + RELA + Chemo (n = 136), No. (%)		NIVO + Chemo (n = 135), No. (%)	
Patient	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Any AE[a]	135 (99)	118 (87)	135 (100)	115 (85)
Serious AEs	95 (70)	84 (62)	82 (61)	71 (53)
AEs leading to discontinuation[b]	72 (53)	44 (32)	56 (41)	28 (21)
Any TRAE[a]	124 (91)	94 (69)	129 (96)	82 (61)
Serious TRAEs[a]	52 (38)	46 (34)	38 (28)	35 (26)
TRAEs leading to discontinuation[b]	57 (42)	29 (21)	48 (36)	25 (19)
TRAEs reported in ≥15% of patients in either arm				
Nausea	53 (39)	2 (1)	63 (47)	5 (4)
Fatigue	52 (38)	10 (7)	58 (43)	9 (7)
Diarrhea	41 (30)	5 (4)	45 (33)	8 (6)
Neutropenia	36 (26)	28 (21)	37 (27)	23 (17)
Neuropathy peripheral	30 (22)	5 (4)	43 (32)	10 (7)
Vomiting	28 (21)	0	34 (25)	4 (3)
Anemia	26 (19)	5 (4)	16 (12)	5 (4)
Peripheral sensory neuropathy	24 (18)	3 (2)	29 (21)	1 (<1)
Decreased appetite	23 (17)	3 (2)	23 (17)	0
Hypothyroidism	21 (15)	0	16 (12)	1 (<1)
Thrombocytopenia	18 (13)	1 (<1)	24 (18)	3 (2)
Platelet count decreased	12 (9)	1 (<1)	22 (16)	2 (1)
Immune-mediated AE[c]				
Hypothyroidism	19 (14)	0	15 (11)	1 (<1)
Rash	13 (10)	3 (2)	6 (4)	1 (<1)
Hyperthyroidism	8 (6)	1 (<1)	3 (2)	0
Diarrhea/colitis	5 (4)	4 (3)	5 (4)	3 (2)
Hepatitis	5 (4)	3 (2)	3 (2)	3 (2)
Adrenal insufficiency	4 (3)	2 (1)	1 (<1)	0
Pneumonitis	4 (3)	0	9 (7)	5 (4)
Hypophysitis	3 (2)	2 (1)	0	0
Diabetes mellitus	3 (2)	2 (1)	2 (1)	1 (<1)
Thyroiditis	2 (1)	1 (<1)	0	0

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