

IMMUNOTHERAPY OVERVIEW



Gloria Roldan Urgoiti MD, MSc, FRCPC

Tom Baker Cancer Centre

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Faculty/Presenter Disclosure

- **Speaker:** Dr. Gloria Roldan Urgoiti
- **Relationships with commercial interests:**
 - Grants/Research Support: n/a
 - Speakers Bureau/Honoraria: n/a
 - Consulting Fees: AMGEN, Canadian Brain Tumor Consortium
 - Other: n/a

Disclosure of Commercial Support

- ❑ This Program is funded through AHS Operational Funding.
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- ❑ This Program has not received in-kind support.
- ❑ Dr. Gloria Roldan Urgoiti is presenting at this Program on a voluntary basis.
- ❑ **Potential for conflict(s) of interest: None**

Mitigating Potential Bias

- Consultancy not related to this presentation topic.

General Objective

- Family Physicians will be able to identify the most common side effects associated with immunotherapy currently used and know when sending the patient to ED and/or contacting Medical Oncology is warranted.

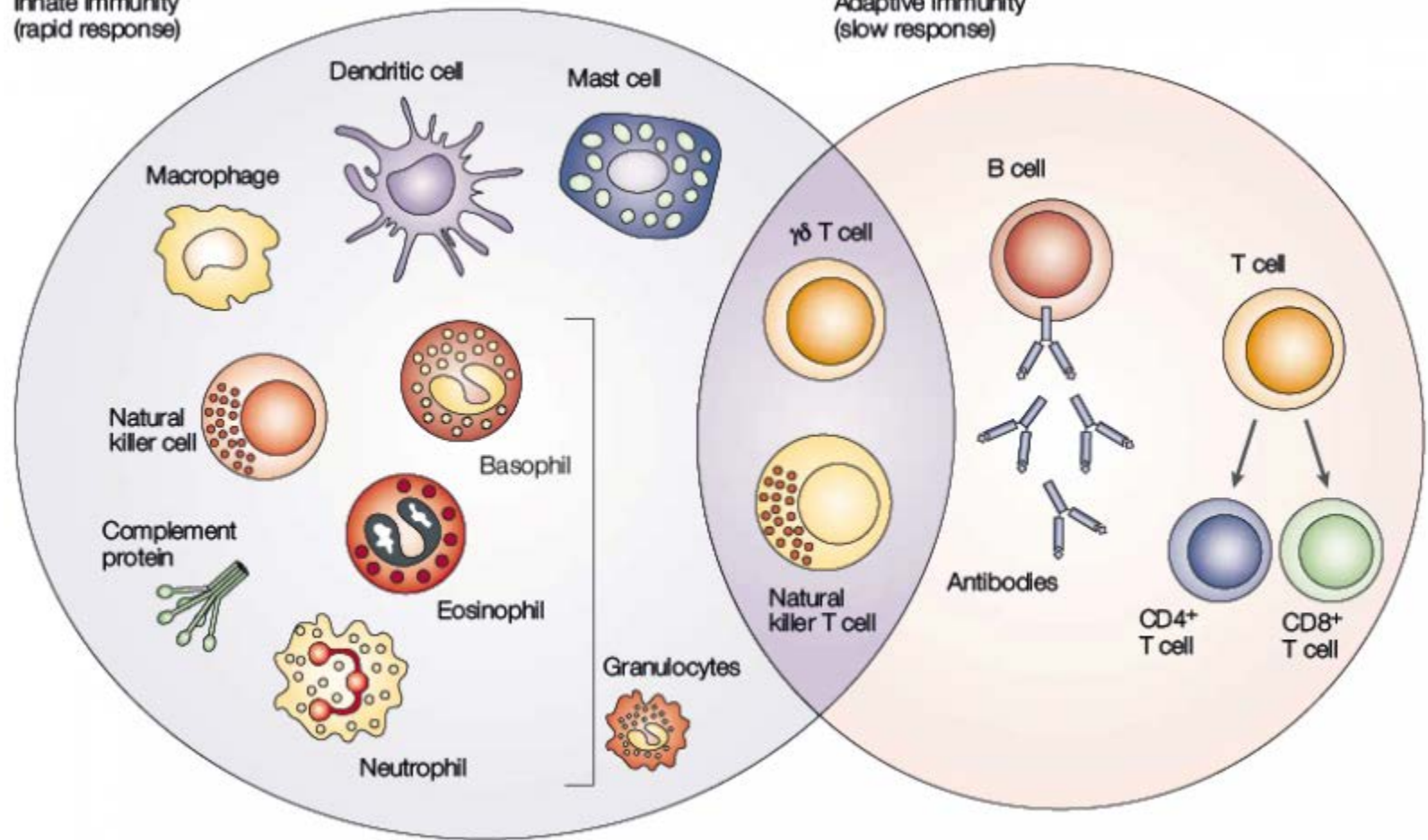
SPECIFIC OBJECTIVES

- ❑ General overview of immune response in the context of cancer
- ❑ Understand the mechanism of action of checkpoint inhibitors.
- ❑ Review most frequent adverse events from these drugs.

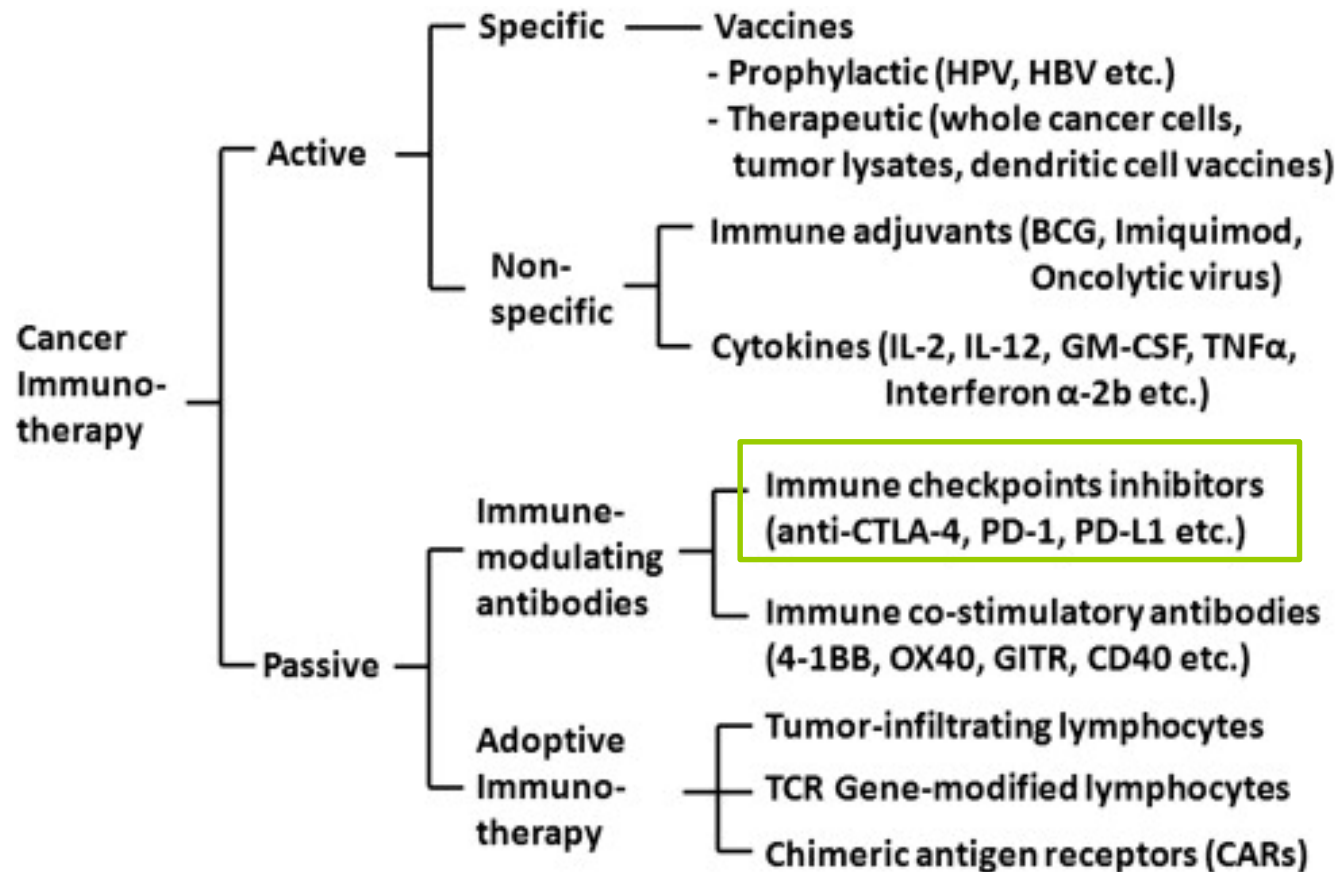
IMMUNE RESPONSE

Innate immunity
(rapid response)

Adaptive immunity
(slow response)



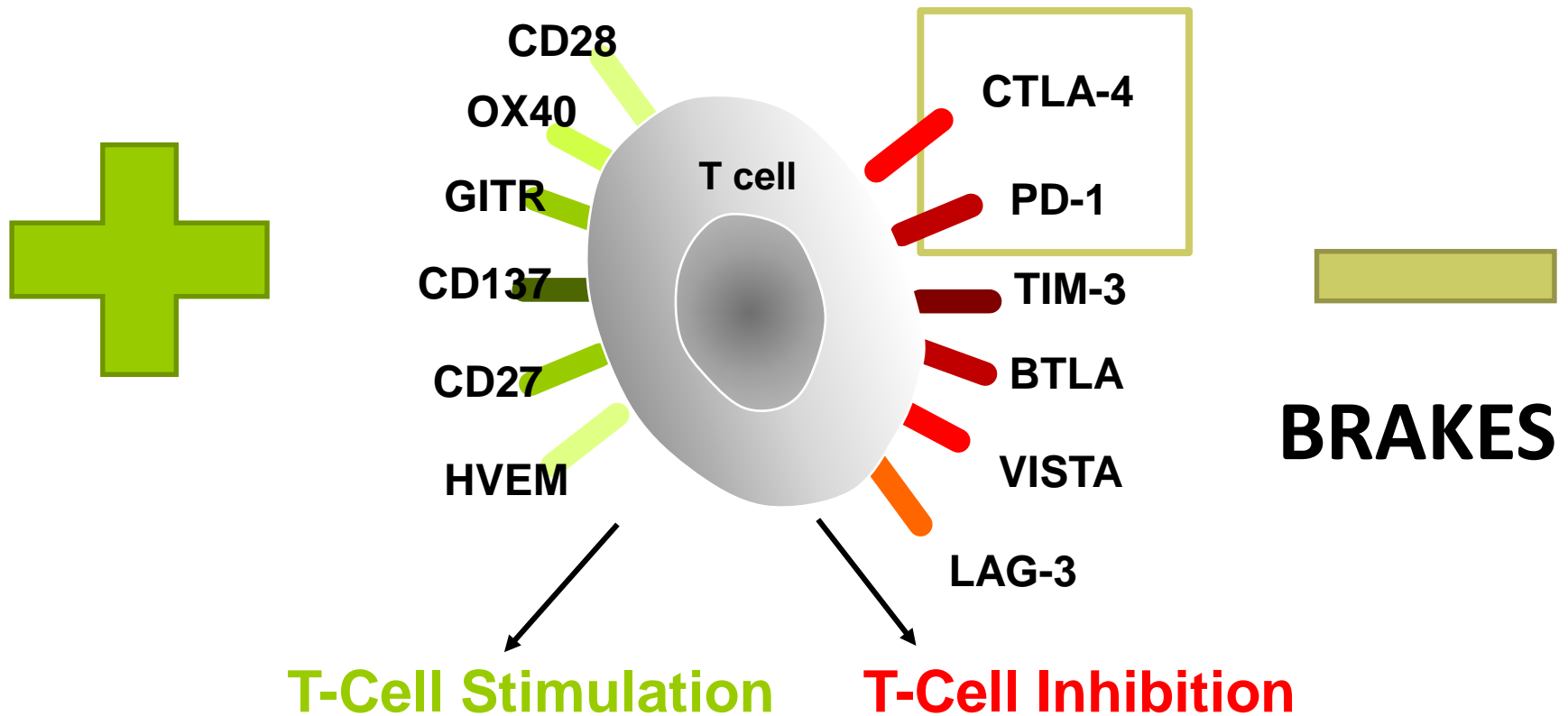
TYPES OF IMMUNOTHERAPY



WHAT ARE CTLA-4 and PD1/PDL1?

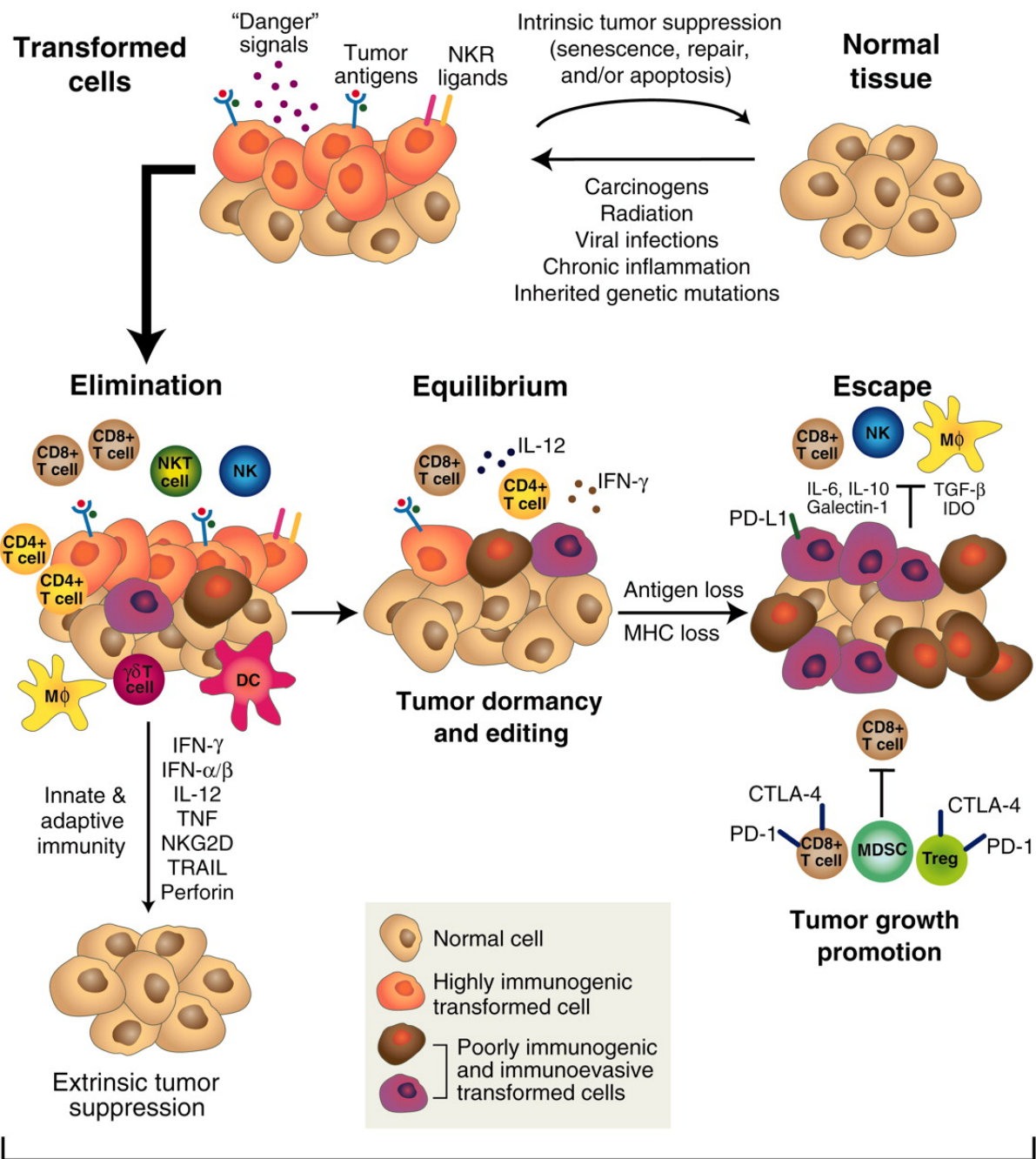


SIGNALS REGULATING T-CELLS

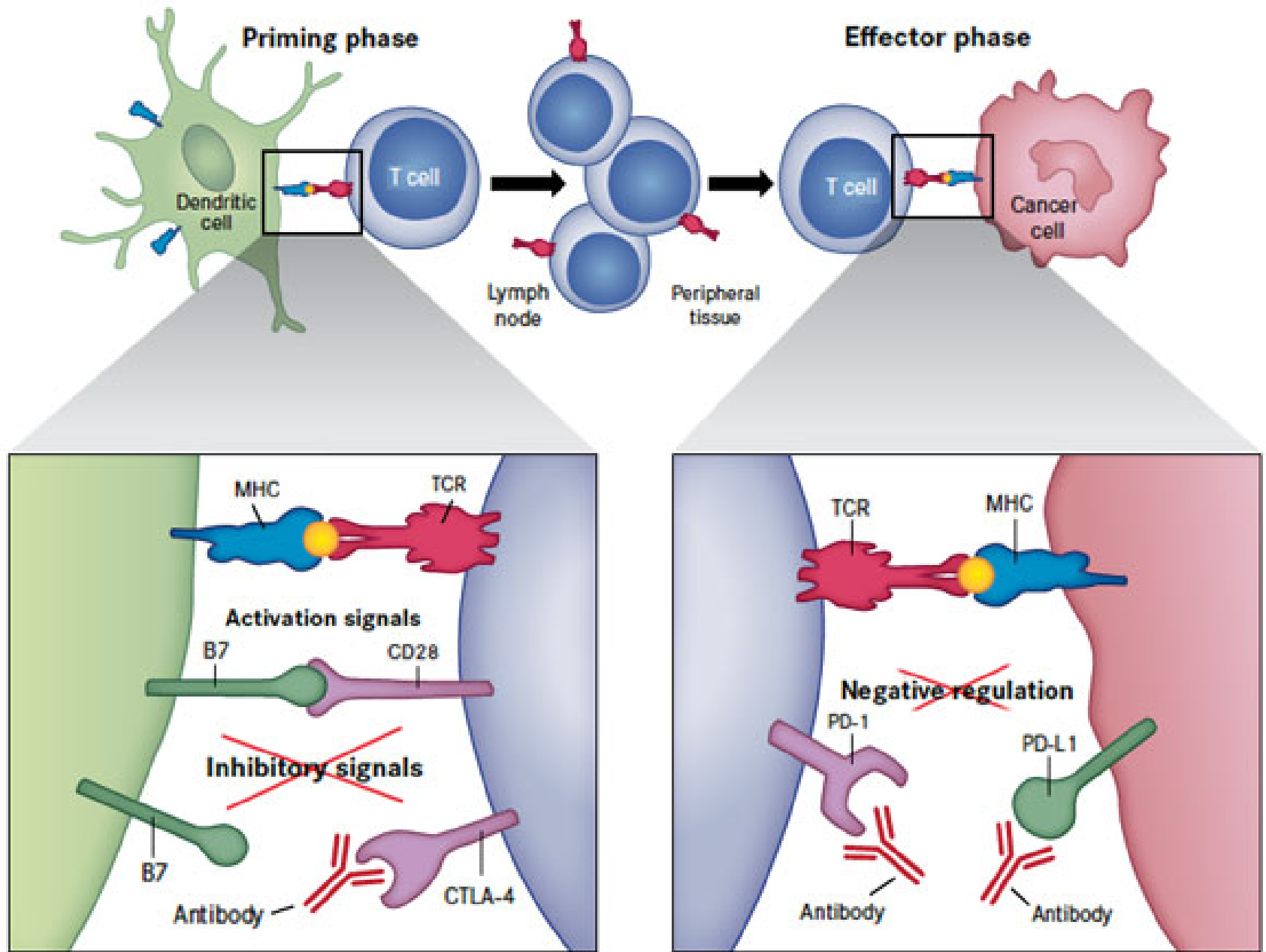


WHY THE IMMUNE SYSTEM DOES NOT ELIMINATE ALL CANCER CELLS?





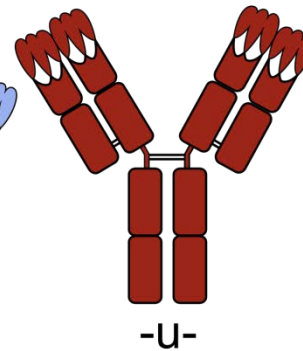
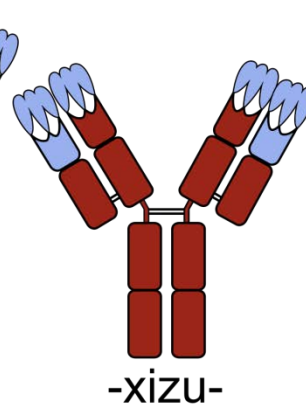
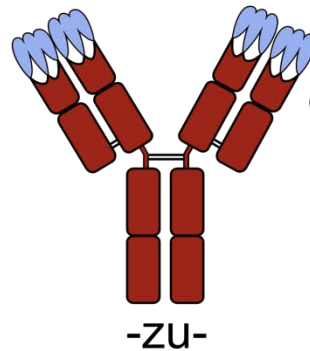
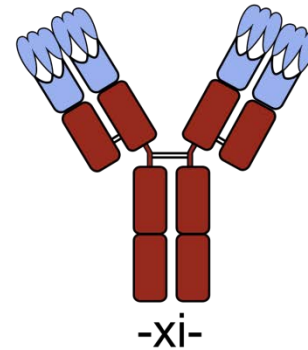
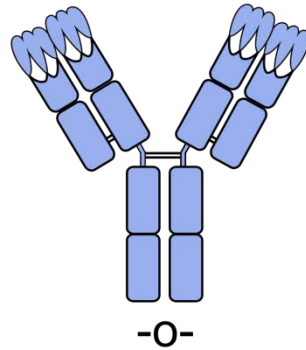
Cancer Immunoeediting



CTLA-4 mAbs:

Ipilimumab

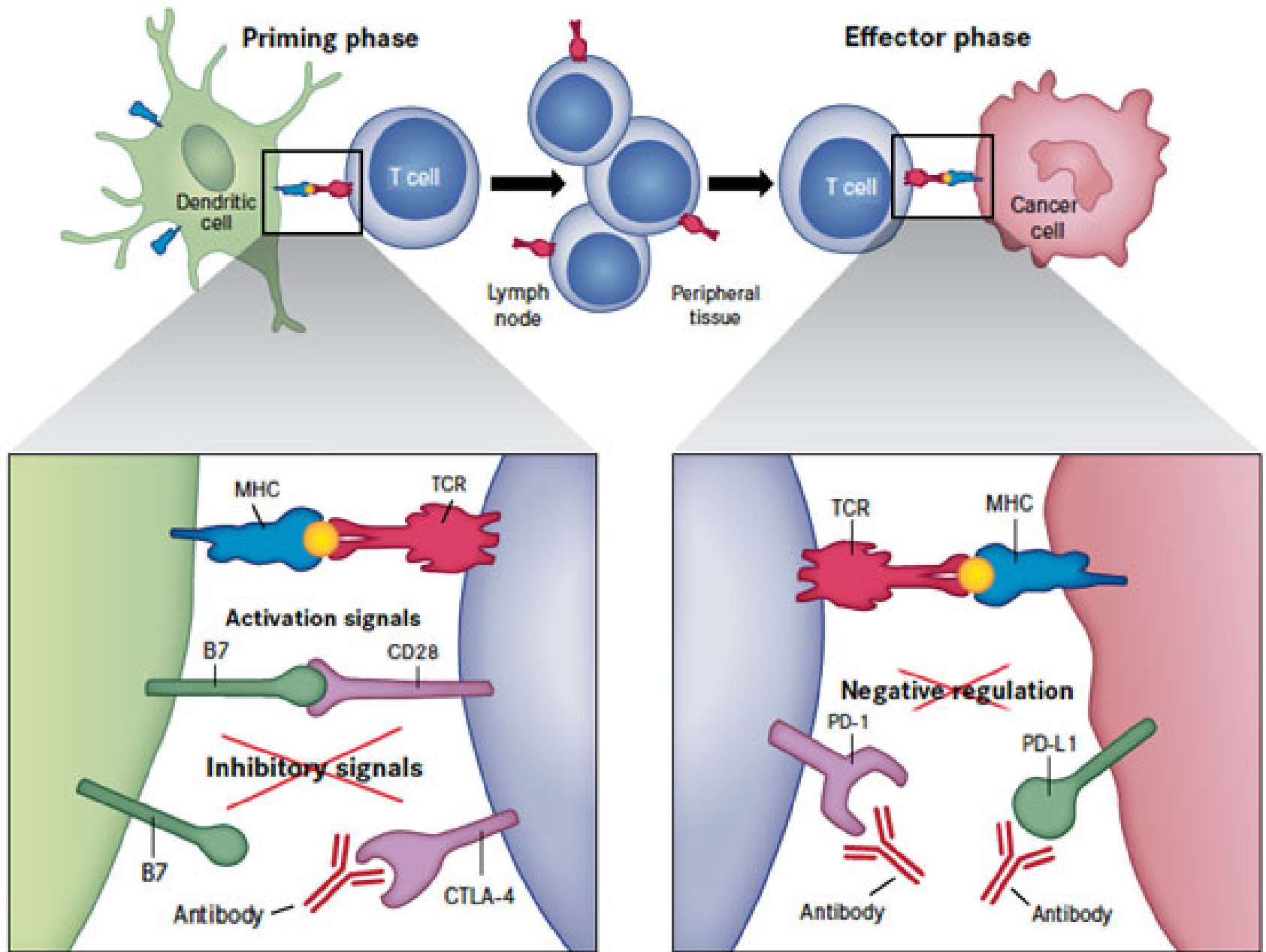
Tremelimumab



PD-1 mAbs:
Nivolumab
Pembrolizumab

PD-L1 mAbs:
Atezolizumab
Avelumab
Durvalumab

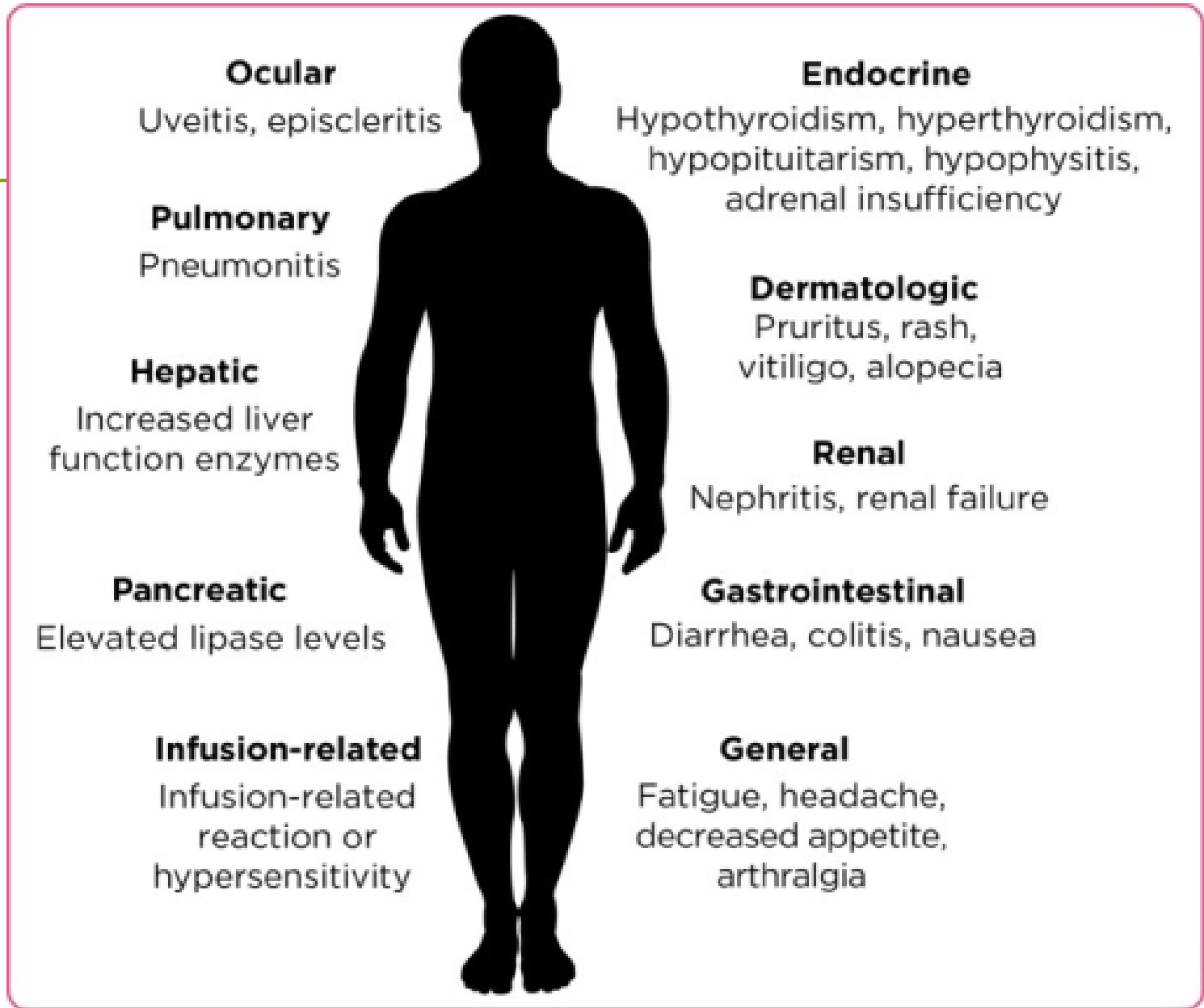
CHECKPOINT INHIBITORS



.... If you take out the brakes...



IMMUNE-RELATED AEs

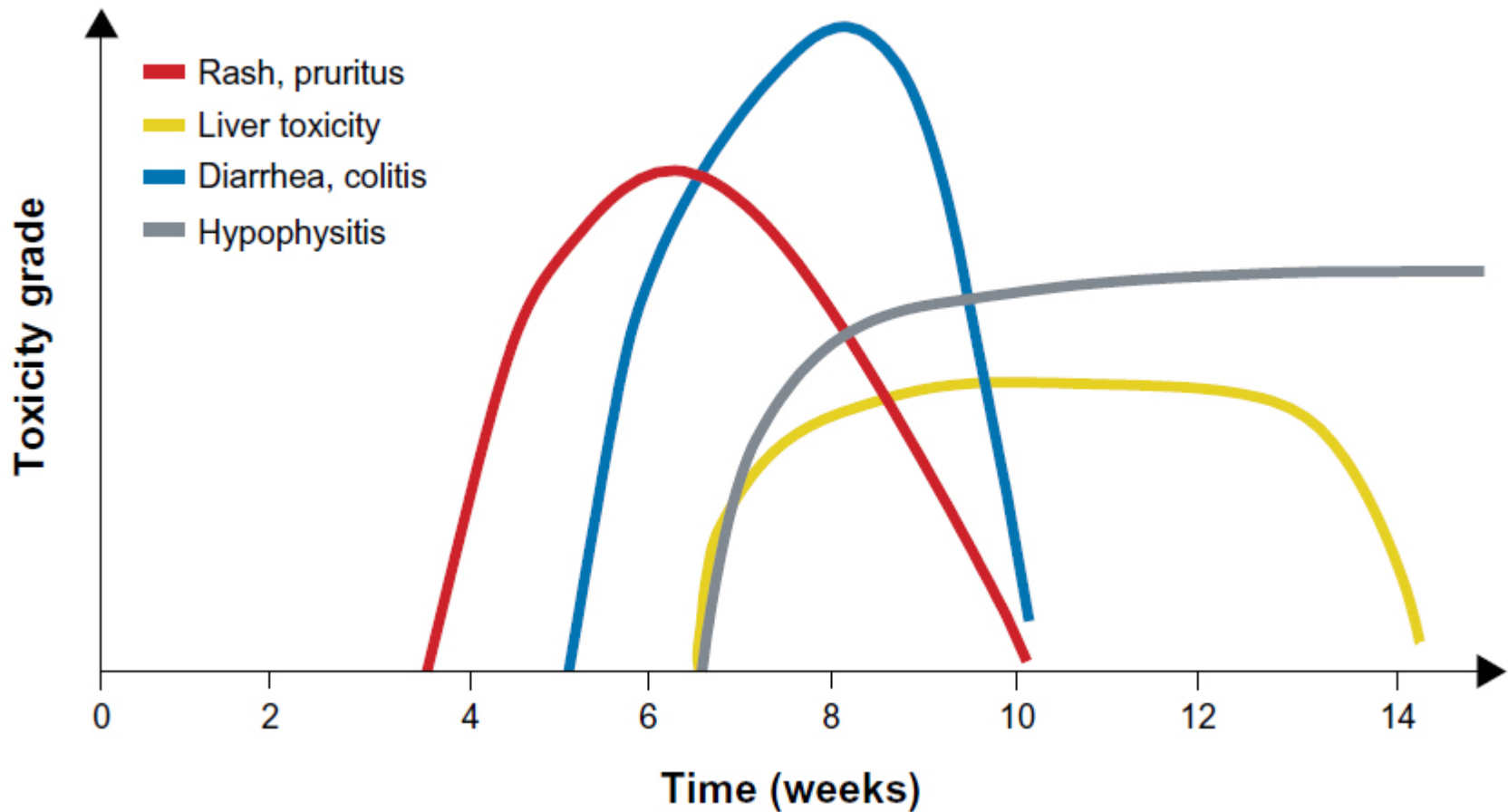


FREQUENCY - IPILIMUMAB

□ Any iAEs	64%
□ Dermatologic	45%
□ Gastrointestinal	32%
□ Endocrine	5%
□ Pulmonary	5%
□ Hepatic	2%



TIME OF ONSET



GRADE/GENERAL MANAGEMENT

- GRADE 1 - mild
- GRADE 2 - moderate

Outpatient

- GRADE 3 - severe
- GRADE 4 - life threatening

Inpatient

- GRADE 5 - death

DERMATITIS

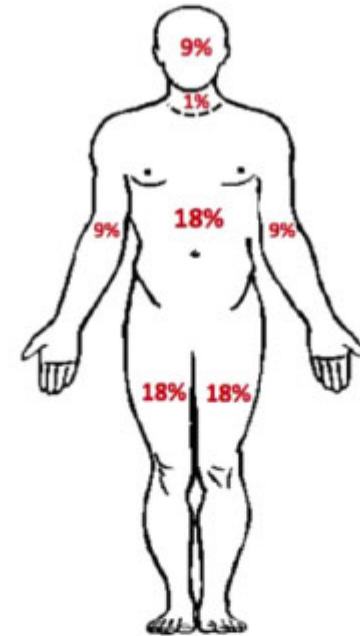
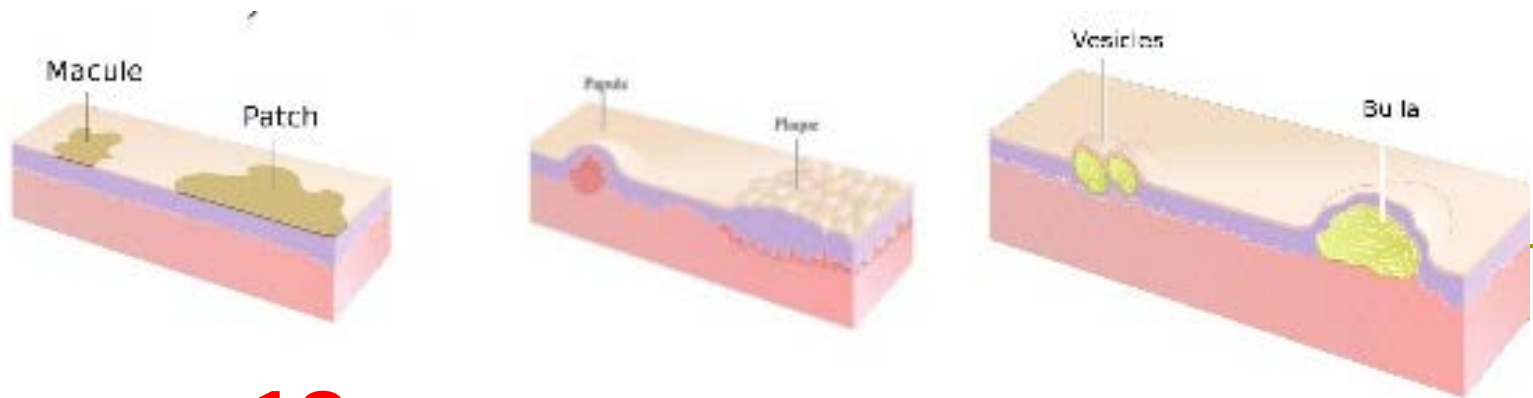


Fig. 1 – Practical scheme for determining percentages of body surface area (BSA) affected by skin reactions in adults.

Adult	Surface %
Arm	9
Head	9
Neck	1
Leg	18
Face/anterior trunk	18
Face/posterior trunk	18



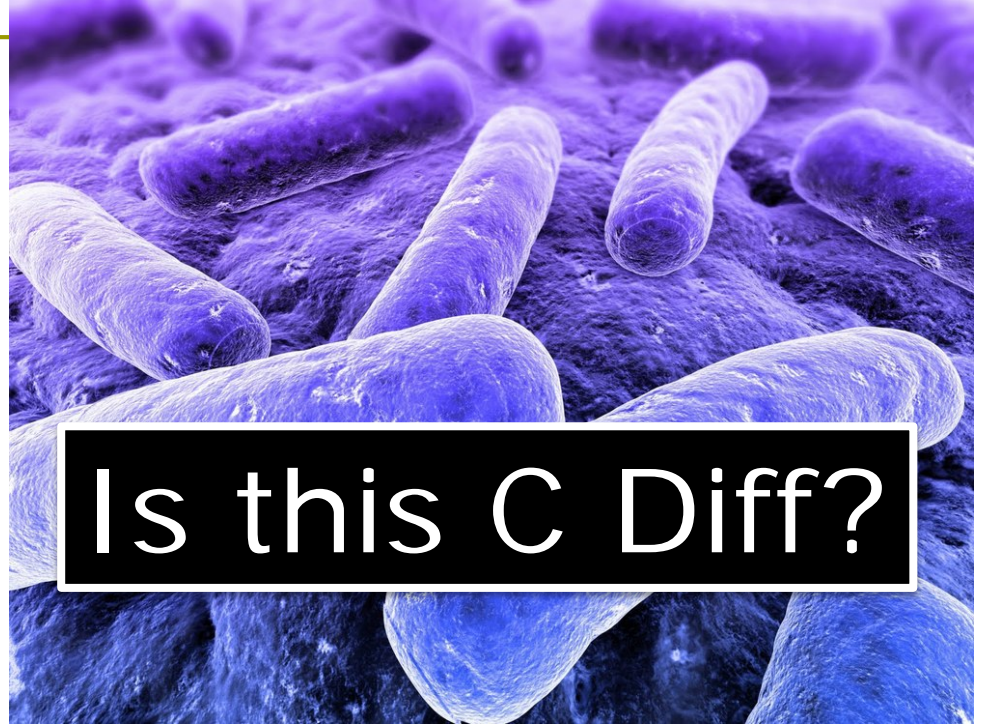
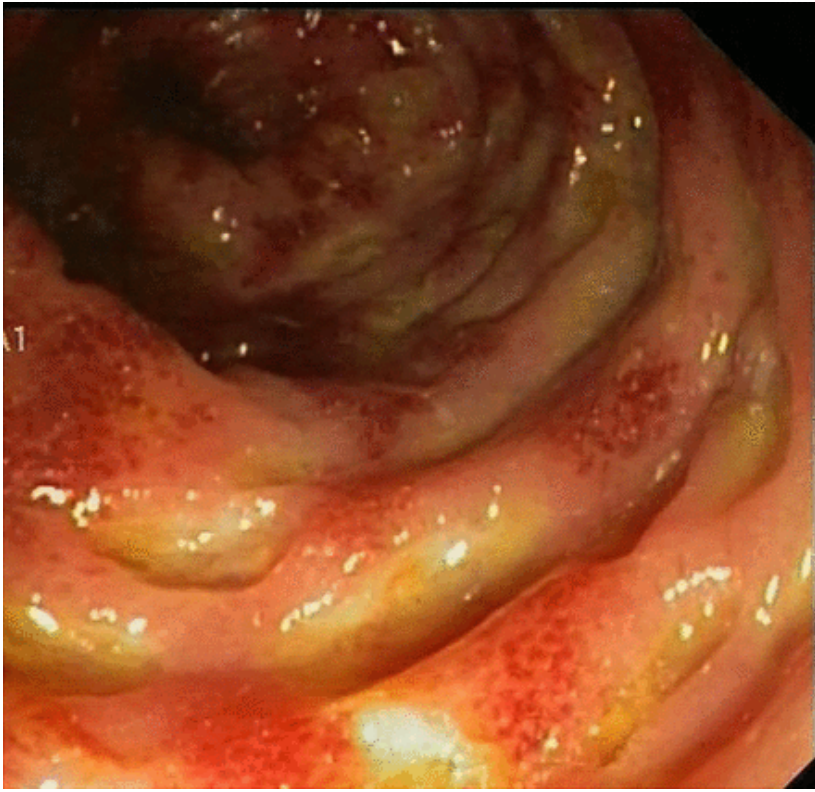
- **GRADE 1** **10** continue

- **GRADE 2** **10-30** hold/delay - prednisone 1 mg/kg/d
 oral antihistamines for pruritus

- **GRADE 3 - 4** **> 30** Derm consult;
 Glucocorticosteroids i/v → infliximab or mycophenolate
 mofetil.

**Toilet Paper
Wedding Dresses**

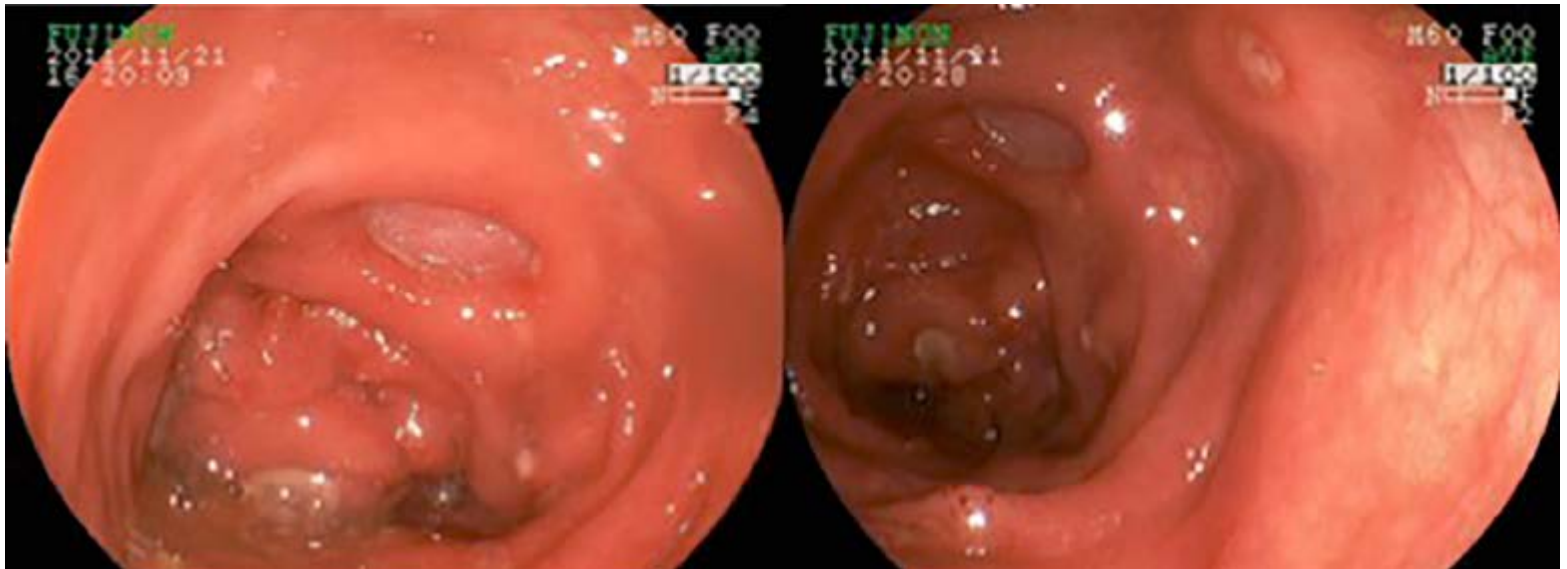




Is this C Diff?



- 10% Grade 3-4 (**7 or more stools above baseline, fever, ileus or peritoneal signs**)
- 1% intestinal perforation
- 1% treatment related death



Hypothalamus

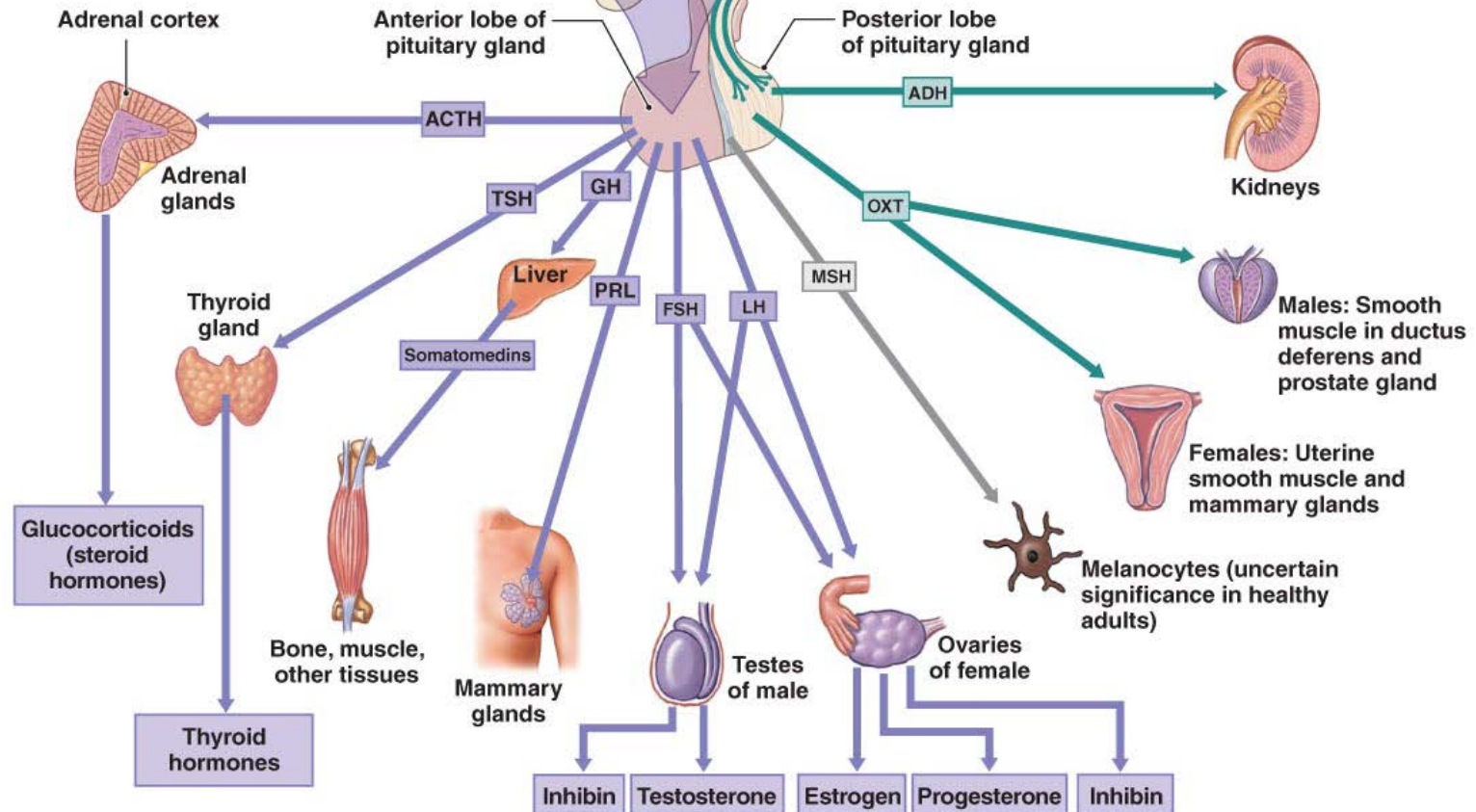
Indirect Control through Release of Regulatory Hormones

Corticotropin-releasing hormone (CRH)	Thyrotropin-releasing hormone (TRH)	Growth hormone-releasing hormone (GH-RH)	Growth hormone-inhibiting hormone (GH-IH)	Prolactin-releasing factor (PRF)	Prolactin-inhibiting hormone (PIH)	Gonadotropin-releasing hormone (GnRH)
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Direct Release of Hormones

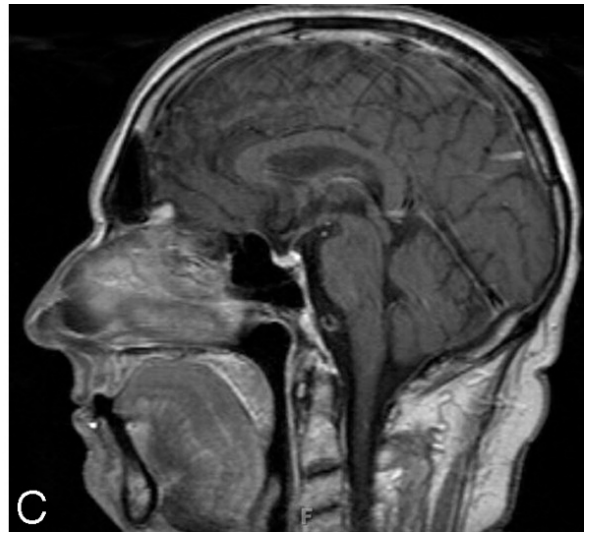
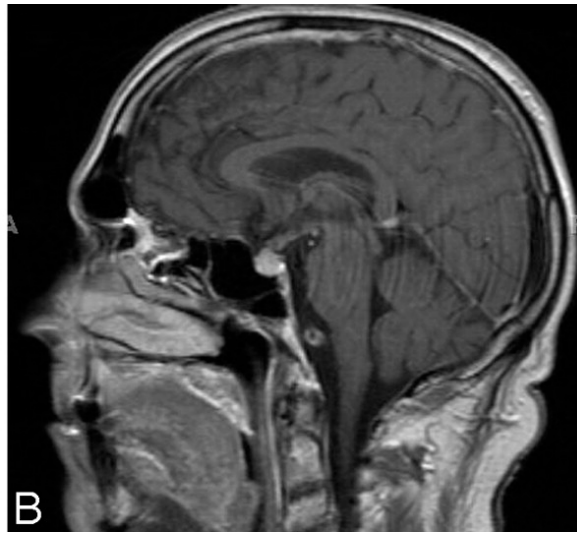
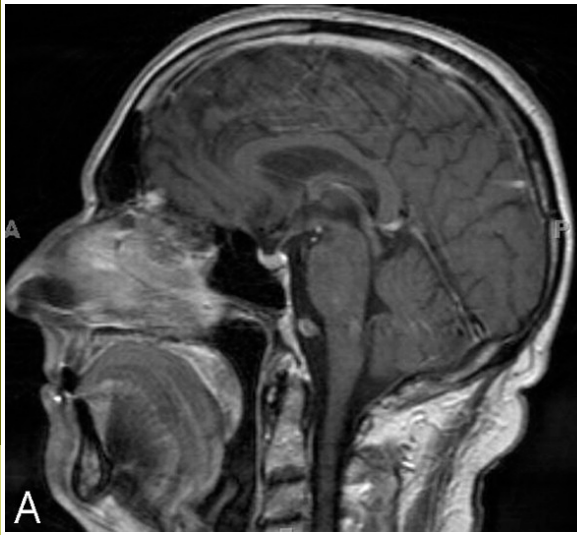
Sensory stimulation Osmoreceptor stimulation

Regulatory hormones are released into the hypophyseal portal system for delivery to the anterior lobe of the pituitary gland.



-
- Hypophysitis 9%
 - Adrenal insufficiency 5%
 - Hypothyroidism 7-22%





Headache

Visual changes

Nausea/vomiting

Secondary adrenal
insufficiency



LAB RESULT	GRADE
AST or ALT \leq 2.5 x ULN BT \leq 1.5 x ULN	GRADE 1
AST or ALT 2.5-5 x ULN BT 1.5 – 3 x ULN	GRADE 2
AST or ALT $>$ 5 x ULN BT $>$ 3 x ULN	Grade 3-4

hepatology / gastroenterology consultation +/- liver biopsy

COUGH AND FEVER!



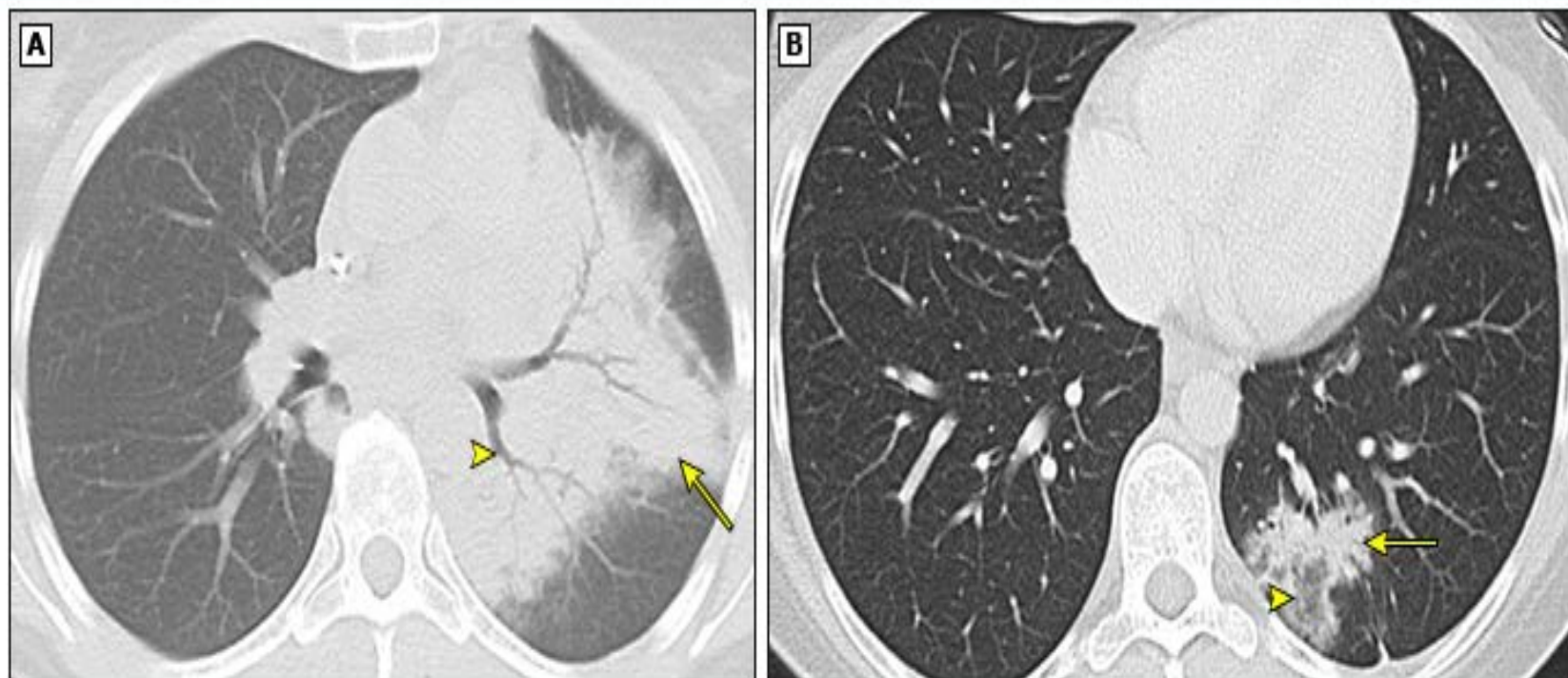
DRUG VS BUG

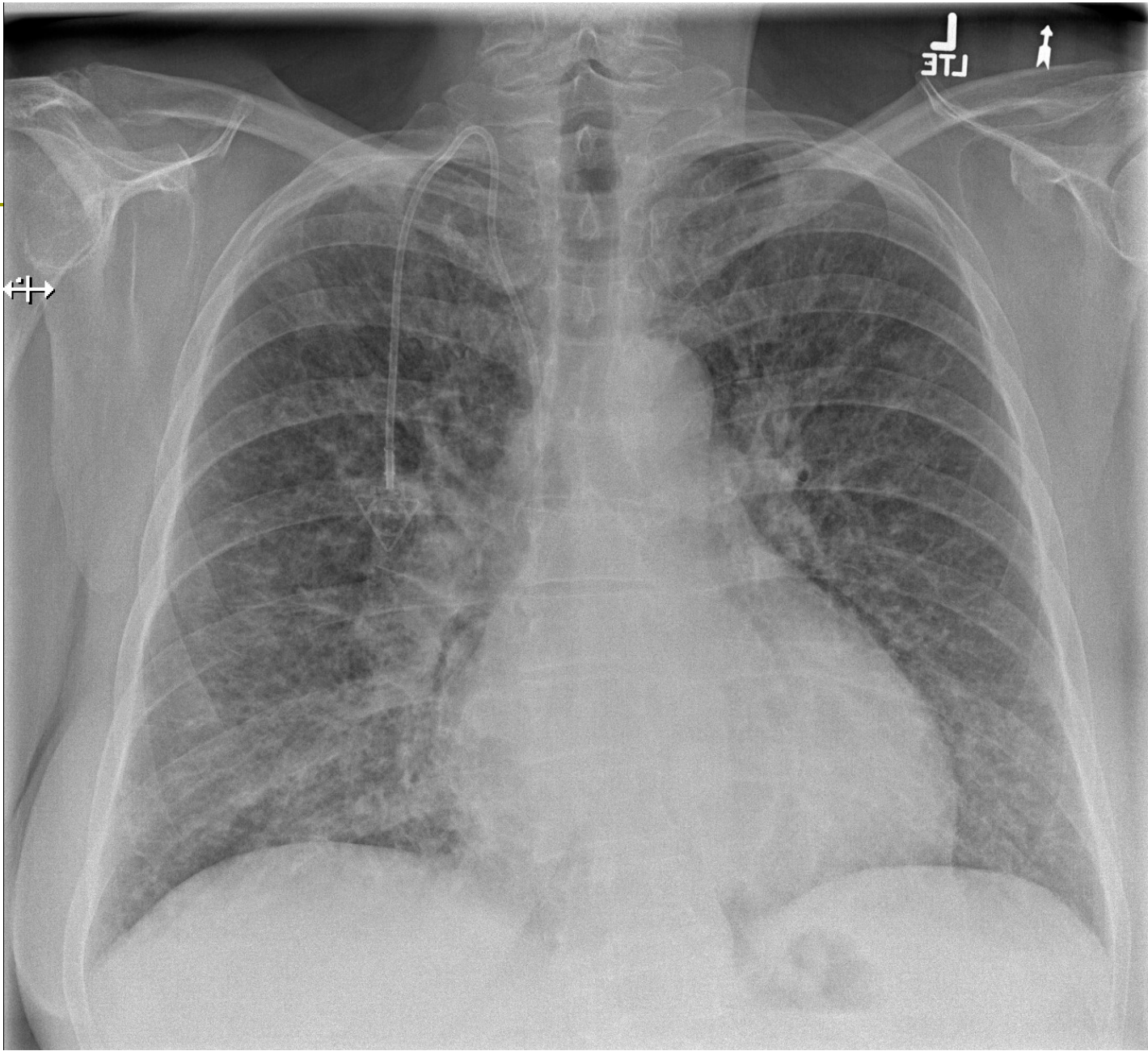


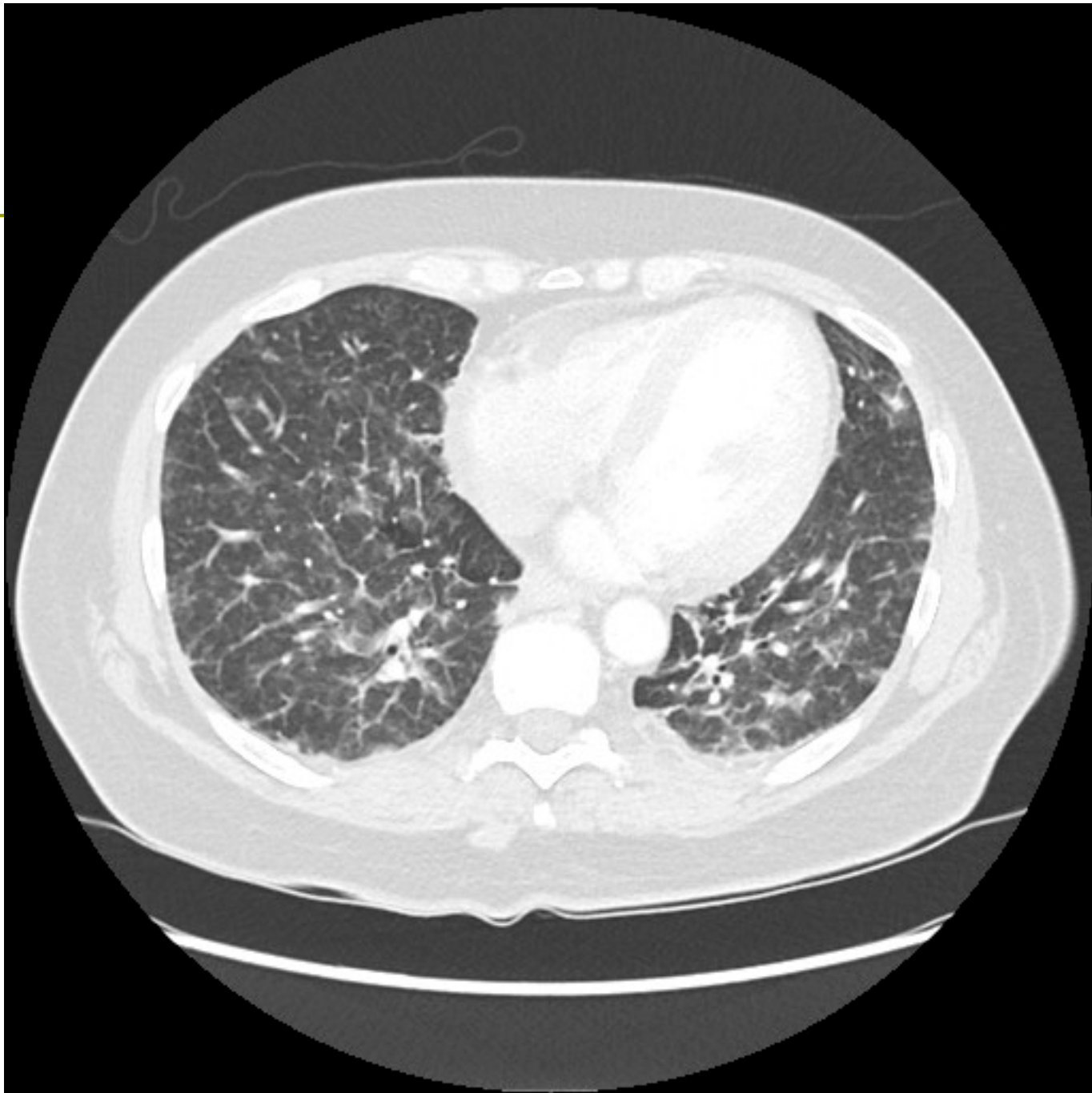
HYPOXIA

	Grade 1 (Radiographic changes only)	Grade 2 (Mild-to-moderate symptoms; worsens from baseline)	Grade 3-4 (Severe symptoms; new/worsening hypoxia; life-threatening); hospitalize
Treatment With OPDIVO or OPDIVO + YERVOY Regimen	Consider withholding treatment	Withhold treatment	Permanently discontinue treatment
Monitoring	Every 2 to 3 days	Daily	Daily
Consult	Consider pulmonary and infectious disease	Pulmonary and infectious disease	Pulmonary and infectious disease
Steroids	-	1-2 mg/kg/day prednisone equivalents	1-2 mg/kg/day prednisone equivalents [†]
Pulmonary Tests	-	Consider bronchoscopy, lung biopsy	Consider bronchoscopy, lung biopsy

Autoimmune pneumonitis complicating immunotherapy for metastatic melanoma with checkpoint inhibition







PROGRESSION OR PSEUDOPROGRESSION?



Medical & Science

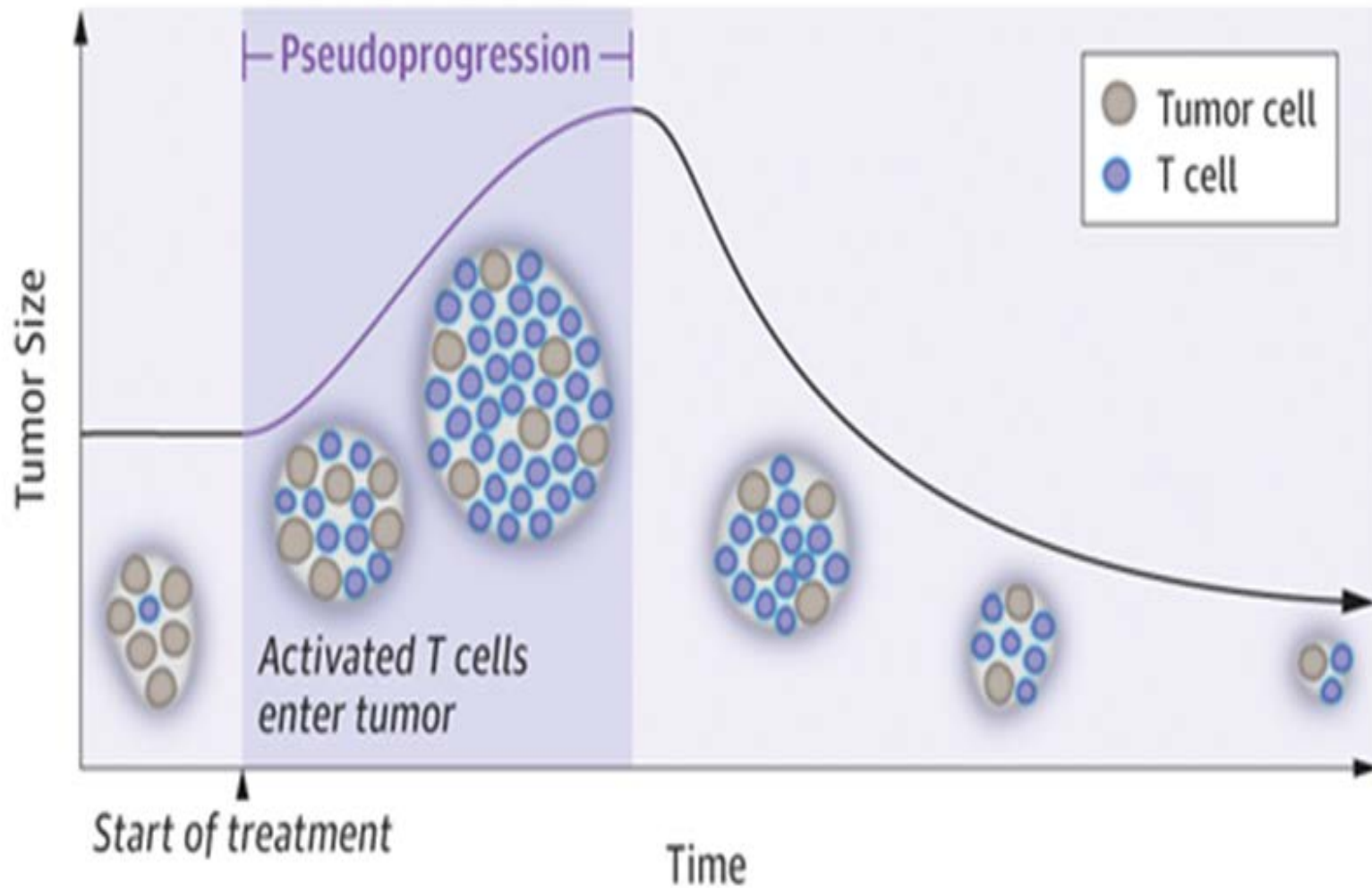
PSEUDO-

means

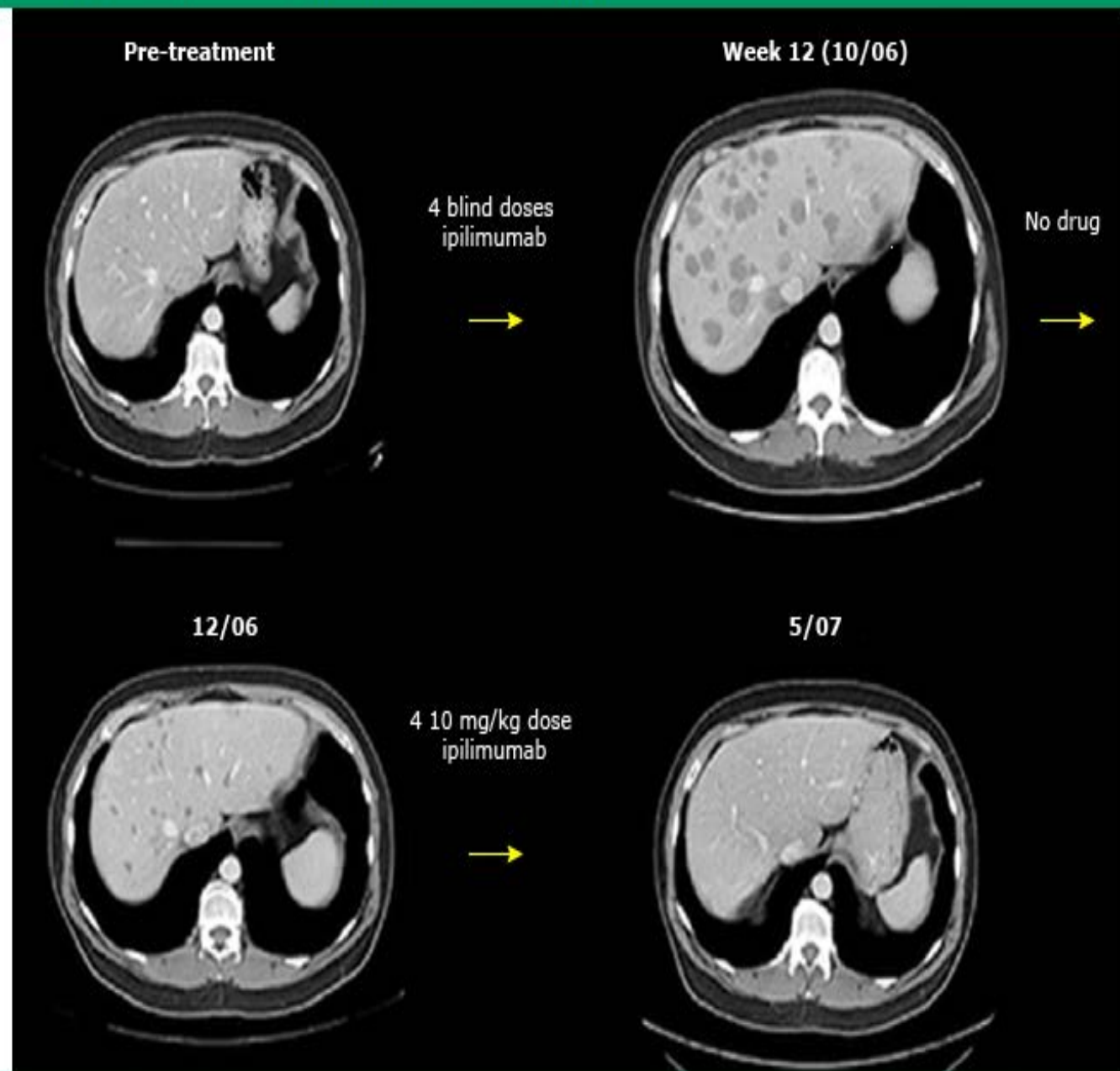
False

by [acronymsandslang.com](https://www.acronymsandslang.com)

Response to immune checkpoint inhibitor treatment with brief increase in tumor size (pseudoprogression)



Delayed response to ipilimumab therapy



TAKE HOME MESSAGES 1/3

- ❑ The most used modality of immunotherapy currently involve checkpoint inhibitors = antibodies against CTL-4, PD1 and PDL1.
- ❑ From inhibiting inhibitory mechanisms you expect “uncontrolled” T-cell response that can affect ANY organ.
- ❑ Holding agent +/- corticosteroids = treatment
- ❑ Specially for colitis and neumonitis ddx: infection!

TAKE HOME MESSAGES 2/3

- ❑ AES from immunotherapy can be as/more severe than those from chemotherapy
- ❑ Patients are very close monitored including pauci-symptomatic AEs.
- ❑ SEVERE = ADMISSION
- ❑ Prolonged moderate → admission; so call your friend the oncologist.

TAKE HOME MESSAGES 3/3

- ❑ Other types of immunotherapy in experimental phases or in isolated centres (US).
- ❑ Standard of care:
 - melanoma
 - non-small cell lung cancer
 - kidney cancer
 - bladder cancer
 - head and neck cancers
 - Hodgkin lymphoma
- ❑ + + + + + in clinical trials

SPECIFIC OBJECTIVES

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Thank you.

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