IMAGING OF CANCER IMMUNOTHERAPY

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INTRODUCTION

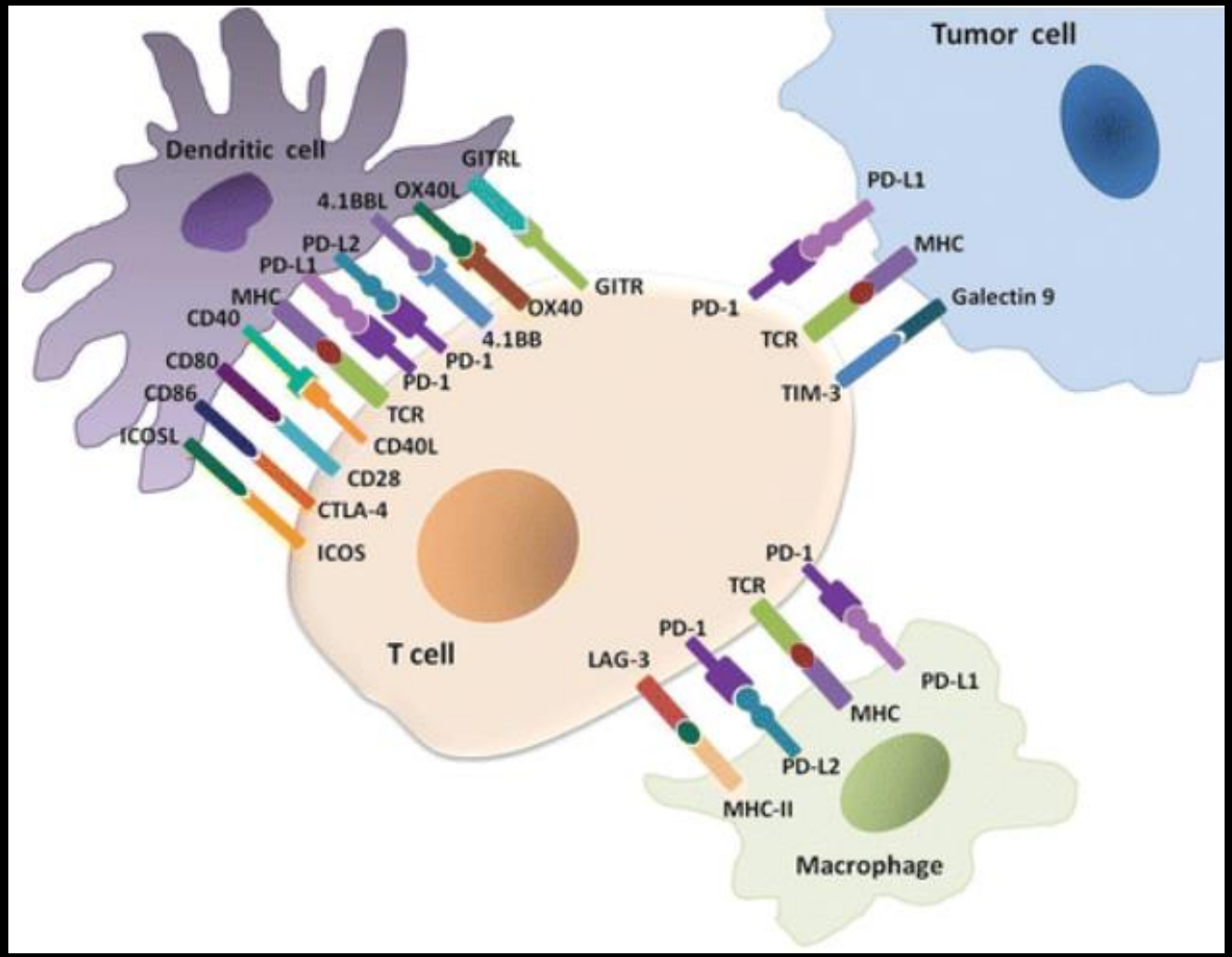
- The recent advances in cancer immunotherapy using **immune-checkpoint inhibitors** - a paradigm shift in advanced cancer treatments.

- Mechanism of Action

  - blockade of tumor-mediated inhibition of immune responses, which can be associated with novel types of tumor response patterns and toxicities.

IMMUNE CHECK POINT

- T cells have major roles in immune-mediated defence mechanisms against cancer.
- The stimulatory and inhibitory signals from the ligand-receptor pairs between tumor cells, T cells, dendritic cells, and macrophages in the tumor microenvironment are called “immune checkpoints.”
- These immune checkpoint molecules regulate T-cell activation specific to tumor cells as immune responses of the host against cancer.



IMMUNE-CHECKPOINT INHIBITORS

- Can interfere with the interaction and block the T-cell immune inhibition by tumors, leading to the activation of the immune response against cancer.

- Include:
- **Cytotoxic T-lymphocyte antigen 4 (CTLA-4)** inhibitors and

- **Programmed cell death protein 1 (PD-1)** and **programmed cell death protein ligand 1 (PD-L1)** inhibitors

IMMUNE-CHECKPOINT INHIBITORS

Class of Agent and Agent	Approved Tumor Types in the United States
CTLA-4 inhibitor	
Ipilimumab*	Melanoma†
PD-1 inhibitor	
Nivolumab*	Melanoma†, NSCLC†, RCC†, Hodgkin lymphoma†, UCC†, head and neck sqCC†, dMMR and MSI-H colorectal cancer, hepatoma
Pembrolizumab	Melanoma†, NSCLC†, Hodgkin lymphoma†, UCC†, head and neck sqCC, MSI-H or dMMR solid tumors, gastric and gastroesophageal junction cancers, cervical cancer
PD-L1 inhibitor	
Atezolizumab	UCC†, NSCLC†
Durvalumab	UCC, NSCLC (as consolidation after chemoradiotherapy for stage III)

ROLE OF IMAGING

1. Objectively defining tumor response and progression in patients treated with immunotherapy

2. Detecting and monitoring immune-related toxicities, which can involve various organs.

CONVENTIONAL TUMOR RESPONSE CRITERIA

- **World Health Organization criteria (1979)**
- **Response Evaluation Criteria in Solid Tumors (RECIST)**

❖ 2000- RECIST 1.0

❖ 2009- RECIST 1.1

- Due to the cytotoxic nature of treatment with chemotherapeutic agents, a decrease in tumor size indicates a decrease in the number of neoplastic cells.
- Response evaluation with the use of these methods is based on the percentage change in the size of target lesions (i.e., tumor burden) within a few weeks of treatment initiation.

CONVENTIONAL TUMOR RESPONSE CRITERIA

Categorized into four groups:

1. Complete response (CR)
2. Partial response (PR)
3. Progressive disease (PD)
4. Stable disease (SD)

CONVENTIONAL TUMOR RESPONSE CRITERIA

Type of Criteria and Criteria	Measurement	PR Criteria*	PD Criteria†	Confirmation of PD	New Lesion
WHO (1979) (18)	Bidimensional (LD×LPD)	≥50% reduction	≥25% increase, new lesion, or nontarget PD	Not required	Defines PD
RECIST 1.0 (2000) (19)	Unidimensional (LD)	≥30% reduction	≥20% increase, new lesion, or nontarget PD	Not required	Defines PD
RECIST 1.1 (2009) (20)	Unidimensional (LD for nonnodal lesions; LPD for lymph nodes)	≥30% reduction	≥20% and ≥ 5 mm increase, new lesion, or nontarget PD	Not required	Defines PD

IMMUNE-RELATED RESPONSE EVALUATIONS

- The unique mechanism of immune checkpoint inhibitors results in atypical patterns of tumor response.

- The atypical patterns of response that have been reported in clinical trials include

  pseudoprogression

  hyperprogression

  dissociated response and

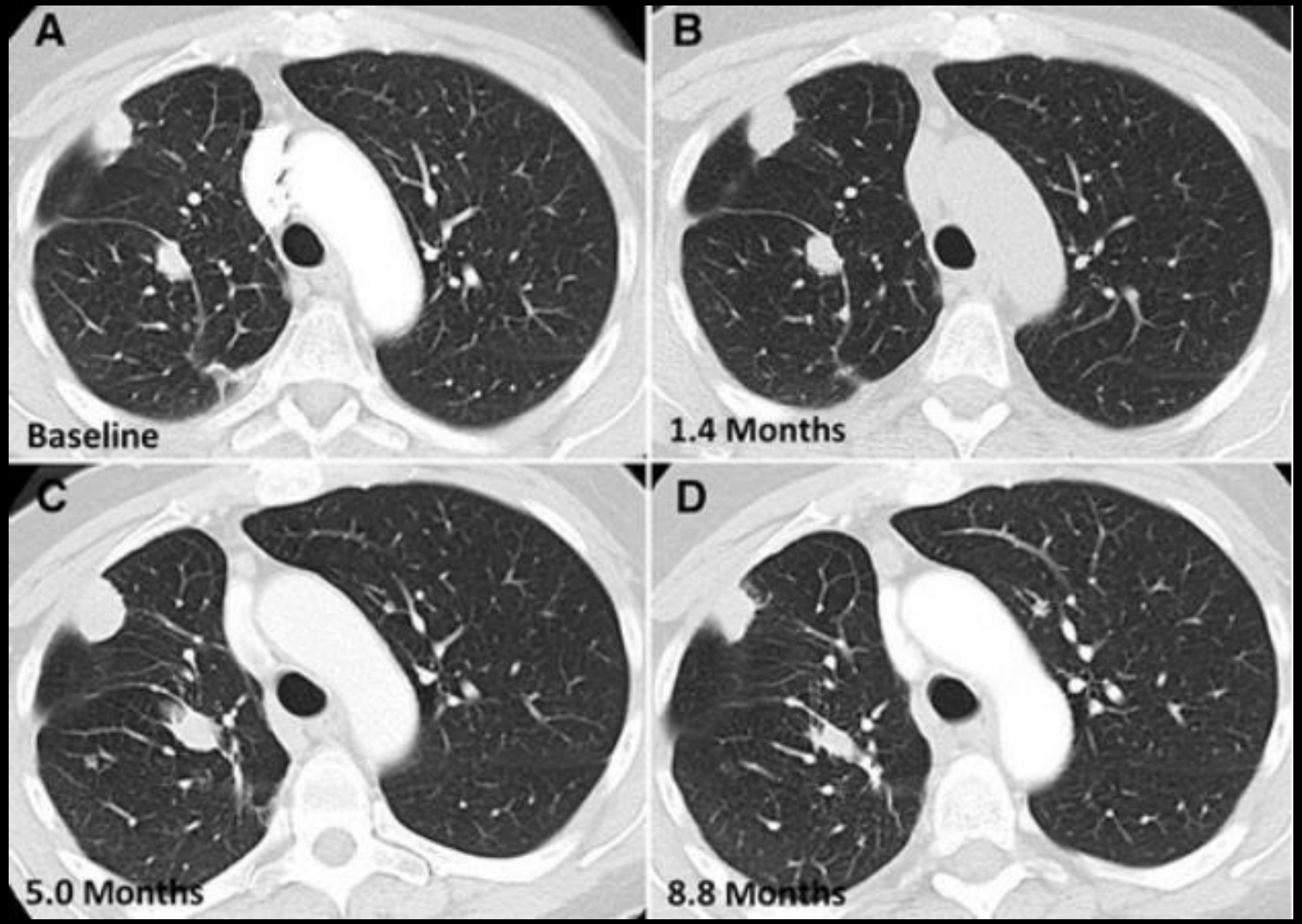
  durable response.

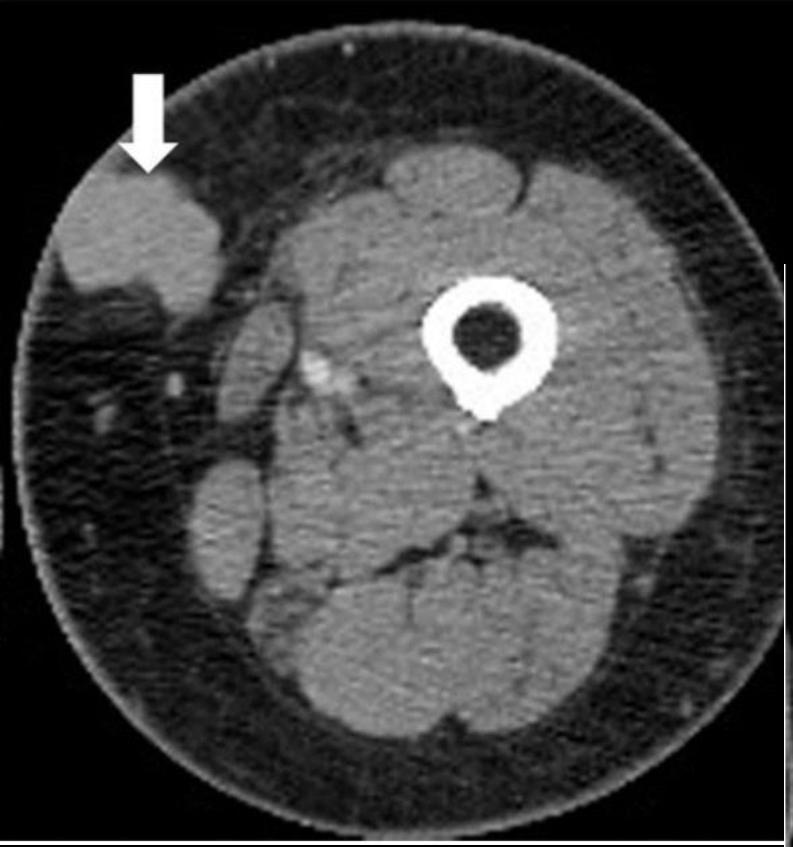
- The conventional response criteria could lead to mis-interpretation and underestimation of treatment response.

PSEUDOPROGRESSION

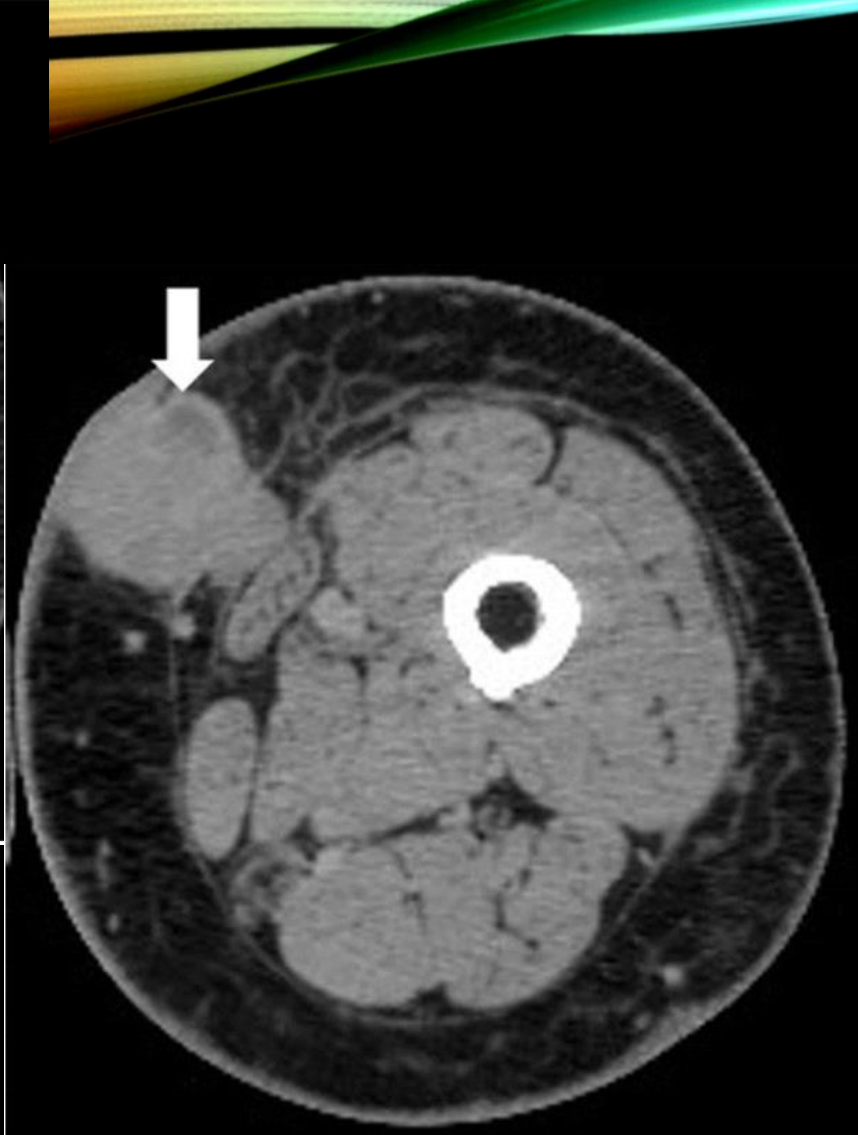
- It is a phenomenon of immune-related tumor response.
- It is defined as the presence of at least one of three observations on the initial follow-up examination,
  - ❖Increase in tumor size,
  - ❖the appearance of new lesions, or
  - ❖an increase in lesion metabolism [using FDG PET-based criteria],
  - ❖followed by a decrease in tumor burden or stabilization of disease on subsequent examinations.
- The mechanism of pseudo-progression is thought to be the infiltration of T cells into tumors, resulting in an initial apparent increase in tumor burden rather than true proliferation of tumor cells.
- Therefore, follow up is necessary to establish true progression.

PSEDOPROGRESSION FOLLOWING NIVOLUMA TREATMENT IN CASE OF PD-1 IN CASE OF NSCLC

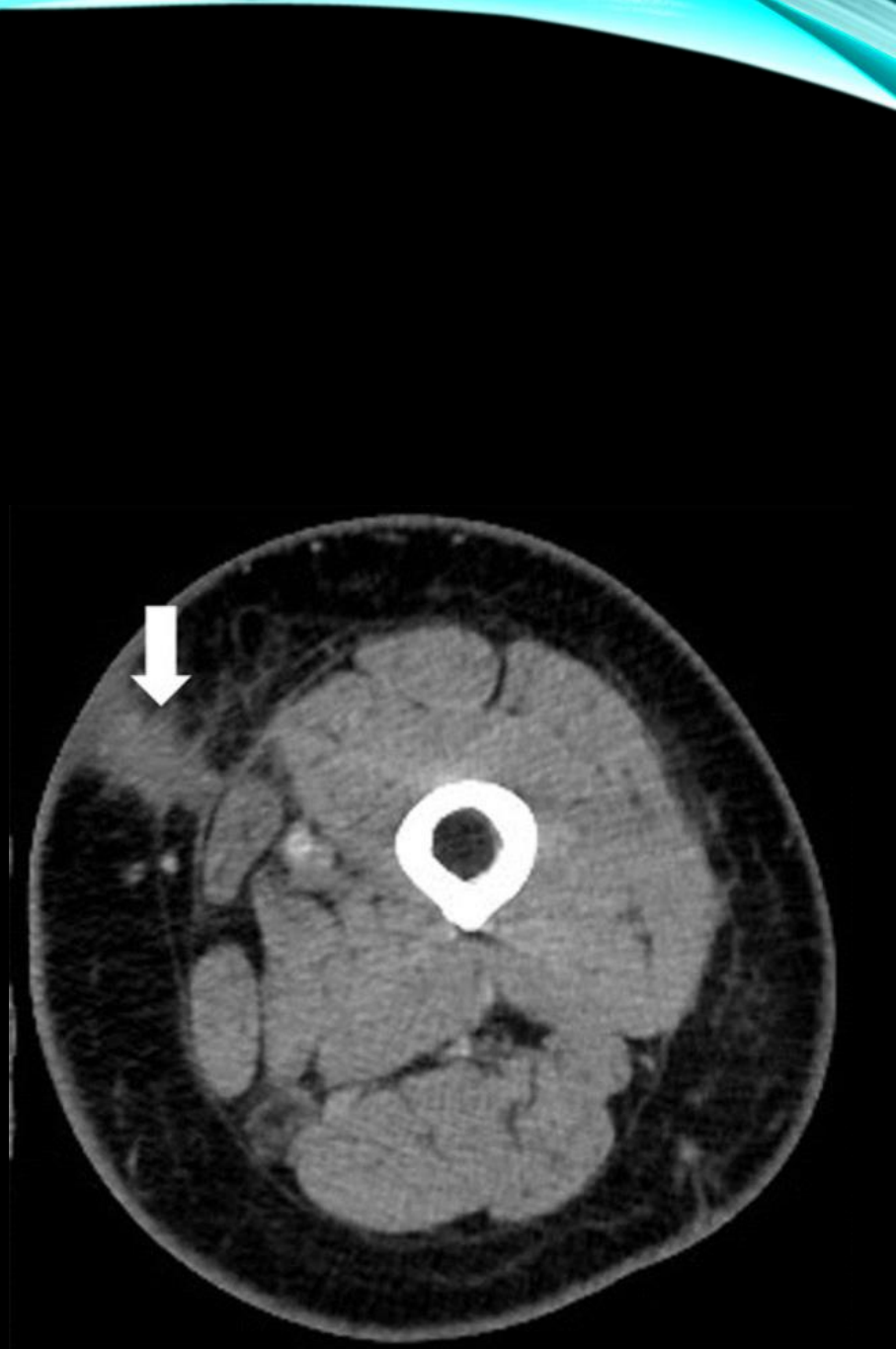




BASELINE



3 MONTHS



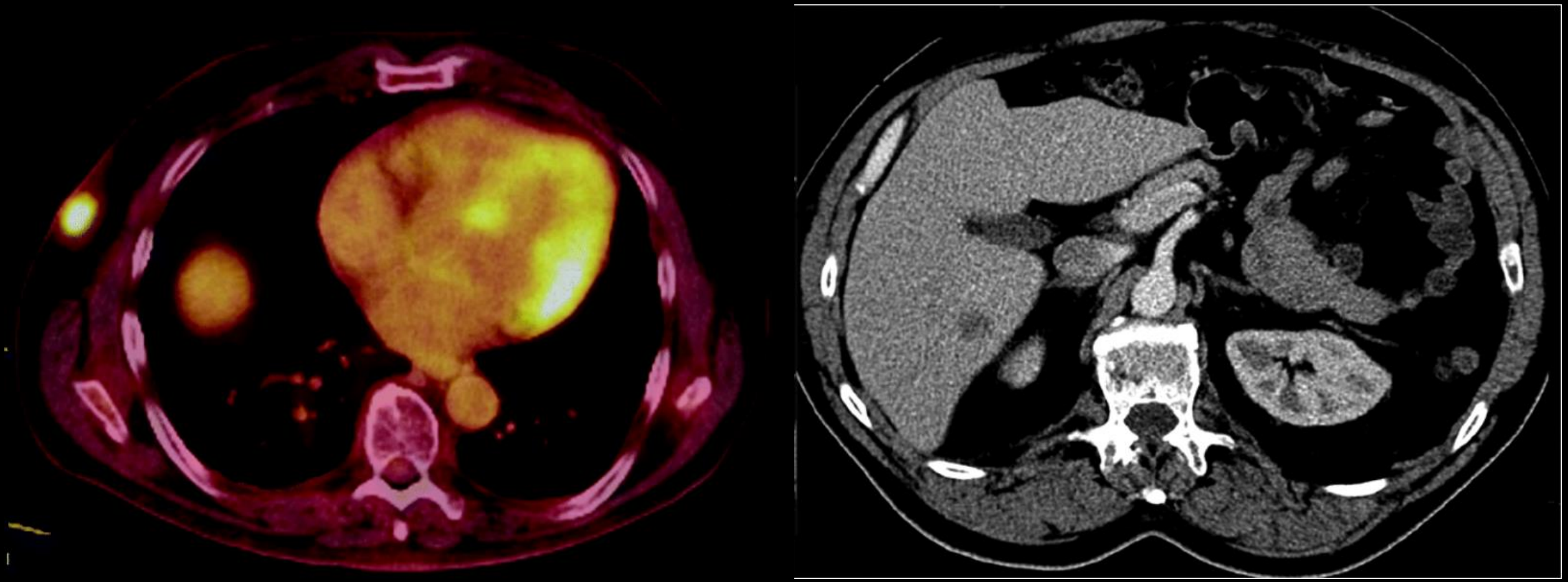
6 MONTHS

Pseudoprogression with initial increase in tumor burden followed by subsequent tumor shrinkage due to immune-related response in a 66-year-old woman with metastatic melanoma treated with nivolumab and ipilimumab.

HYPERPROGRESSION

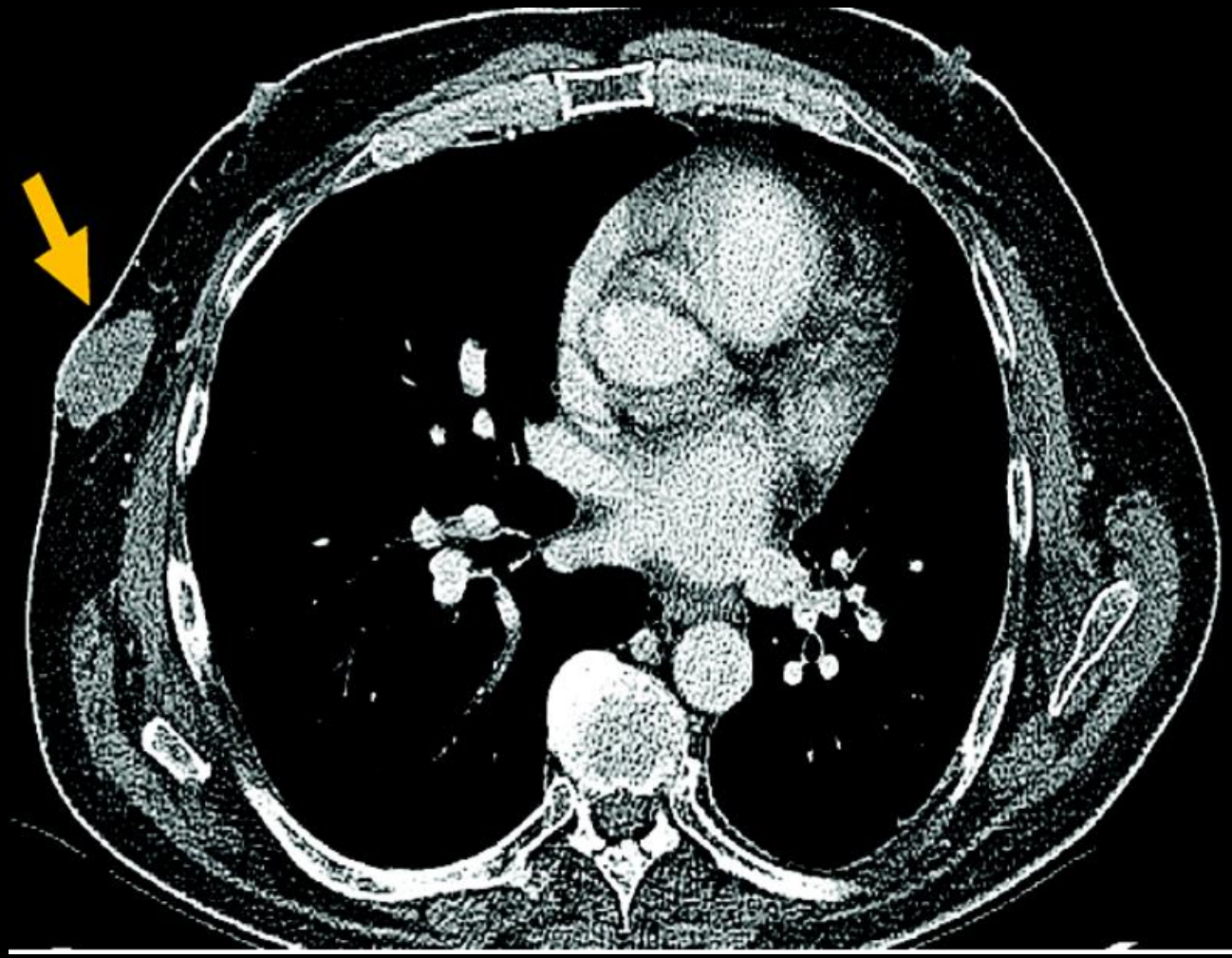
- Unfavourable pattern of atypical response characterized by a rapid increase in tumor growth kinetics early after initiation of immunotherapy.
- It occurs in 4–28% of patients treated with immunotherapy and is associated with a worse survival outcome.
- Hyper-progression more commonly occurs in patients treated with anti–PD-1/PD-L1 agents compared with anti–CTLA-4 therapy.
- Early clinical or imaging identification of hyperprogression is important to rapidly switch the treatment to another potential effective treatment.

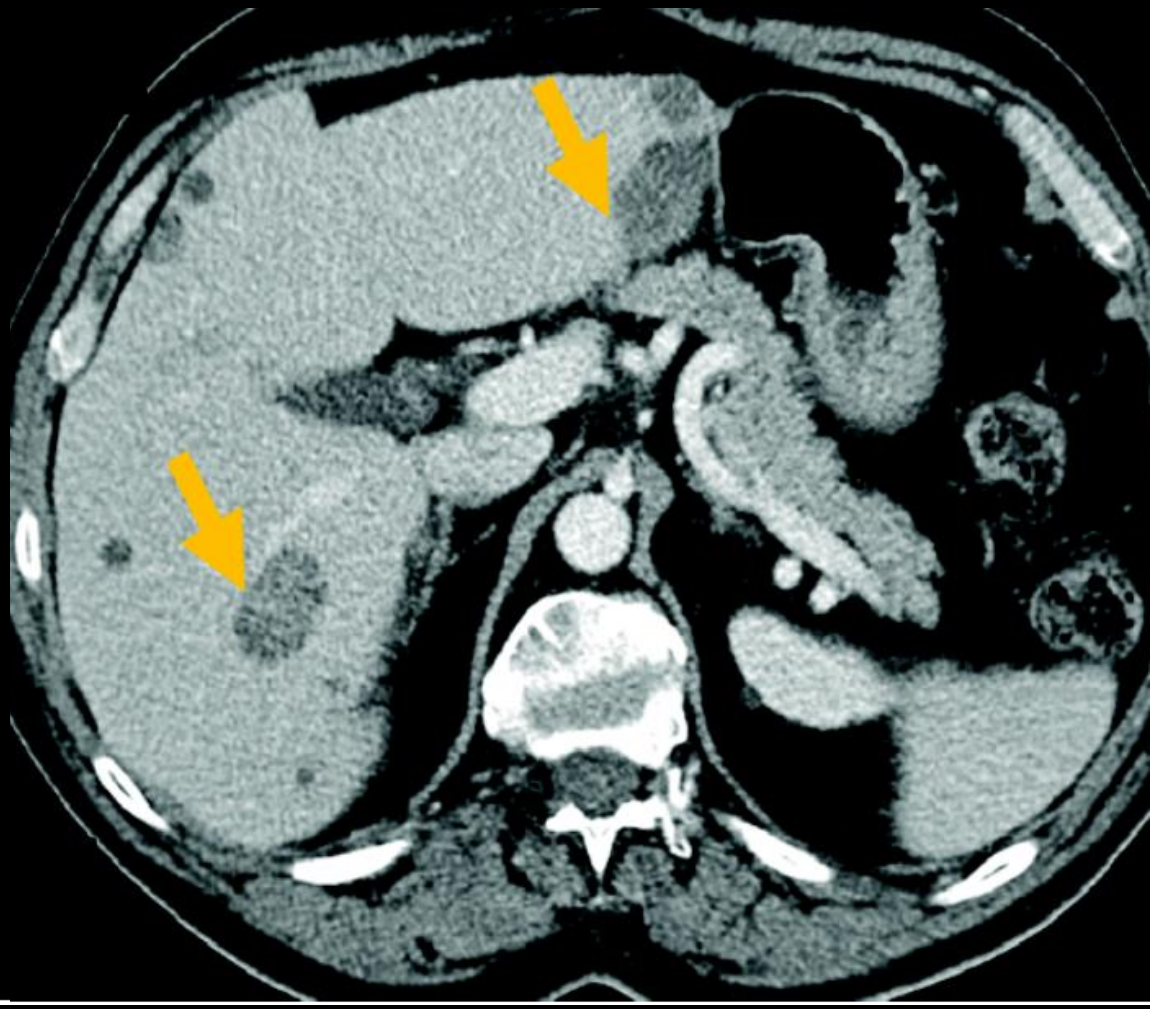
HYPERPROGRESSION



58-year-old man with stage IV lung neuroendocrine tumor. Base line PET CT shows right chest wall and liver metastases.

HYPERPROGRESSION





58-year-old man with stage IV lung neuroendocrine tumor. Follow-up CT after 4 weeks shows increase in size of right chest wall mass and increase size and number of liver metastases.

DISSOCIATED RESPONSE

- Defined as the coexistence of responding lesions and nonresponding lesions within the same patient.
- First reported in patients with non–small cell lung cancer receiving anti-PD-1/PDL-1 therapy.
- Associated with a favourable outcome & can be a sign of treatment efficacy.
- In contrast to pseudoprogression, a dissociated response pattern can be described at later time points of disease progression, rather than on the first follow-up examination only.

DURABLE RESPONSE

- Immunotherapy is associated with a delayed but durable response that can persist even after treatment cessation is observed in a subset of patients with advanced disease.

- A recent meta-analysis showed that patients treated with immunotherapy are 2.3 times more likely to achieve durable response compared with patients in control arms who received chemotherapy or targeted therapy.

- Durable response can be considered when progression-free survival (PFS) exceeds three times the median PFS of the patients receiving the same therapy in the same trial.

MODIFIED STRATEGIES FOR IMMUNE-RELATED RESPONSE EVALUATIONS

- **Immune-related response criteria (irRC)-** 2009
- **Immune-related RECIST (irRECIST)-** 2013, revised in 2017.

- The immune-related response assessment methods incorporate two main changes compared with RECIST.
  - 1. Classification of progressive disease requires two consecutive imaging assessments performed at least 4 weeks apart to capture pseudoprogression or delayed response. Further increase in a lesion's size or the appearance of new lesions denotes confirmed progressive disease (CPD).

  - 2. In patients with unconfirmed progressive disease (UPD), clinical status and clinical stability should be considered to guide therapeutic decisions.

MODIFIED STRATEGIES FOR IMMUNE-RELATED RESPONSE EVALUATIONS

Type of Criteria and Criteria	Measurement	PR Criteria*	PD Criteria†	Confirmation of PD	New Lesion
irRC (2009) (16)	Bidimensional (LD×LPD)	≥50% reduction	≥25% increase	Required on consecutive studies at least 4 weeks apart	Does not define PD; measurements of new lesions included in the total tumor burden
irRECIST (2013) (25–27,73)	Unidimensional (LD for nonnodal lesions; LPD for lymph nodes)	≥30% reduction	≥20% and ≥ 5 mm increase, new lesion, or nontarget PD	Required on a consecutive scan at least 4 weeks apart	Does not define PD; measurements of new lesions included in the total tumor burden
iRECIST (2017) (29)	Unidimensional (LD for nonnodal lesions; LPD for lymph nodes)	≥30% reduction	≥20% and ≥ 5 mm increase, new lesion, or nontarget PD	Required at the next assessment 4–8 weeks later	Defines unconfirmed PD; confirms PD if additional new lesions or size increase (≥ 5 mm for the sum of new target or any increase in new nontarget lesions) are noted on the next assessment

UNCONFIRMED PD

- PD according to RECIST 1.1 that remains to be confirmed.
- iUPD can become “confirmed PD” (iCPD) if the next imaging study in 4–8 weeks shows further increase.
- The concept can be helpful for further delineation of response assessment results, because patients with initial tumor burden increase may not necessarily be re-evaluated with a consecutive study for confirmation.
- Some patients may choose to start the next systemic therapy without waiting for 4 weeks or more to have the confirmation study.
- Others may not tolerate immunotherapy any further because of side effects or cannot return for the follow-up study because of clinical deterioration.

IMMUNE-RELATED ADVERSE EVENTS

- The mechanism of irAEs is presumed to be autoimmune effects resulting from misdirected stimulation of the immune system during immunotherapy.

Various reported manifestations include:

1. Hypophysitis
2. Pneumonitis
3. Sarcoid like lymphadenopathy and granulomatosis
4. Colitis
5. Hepatitis

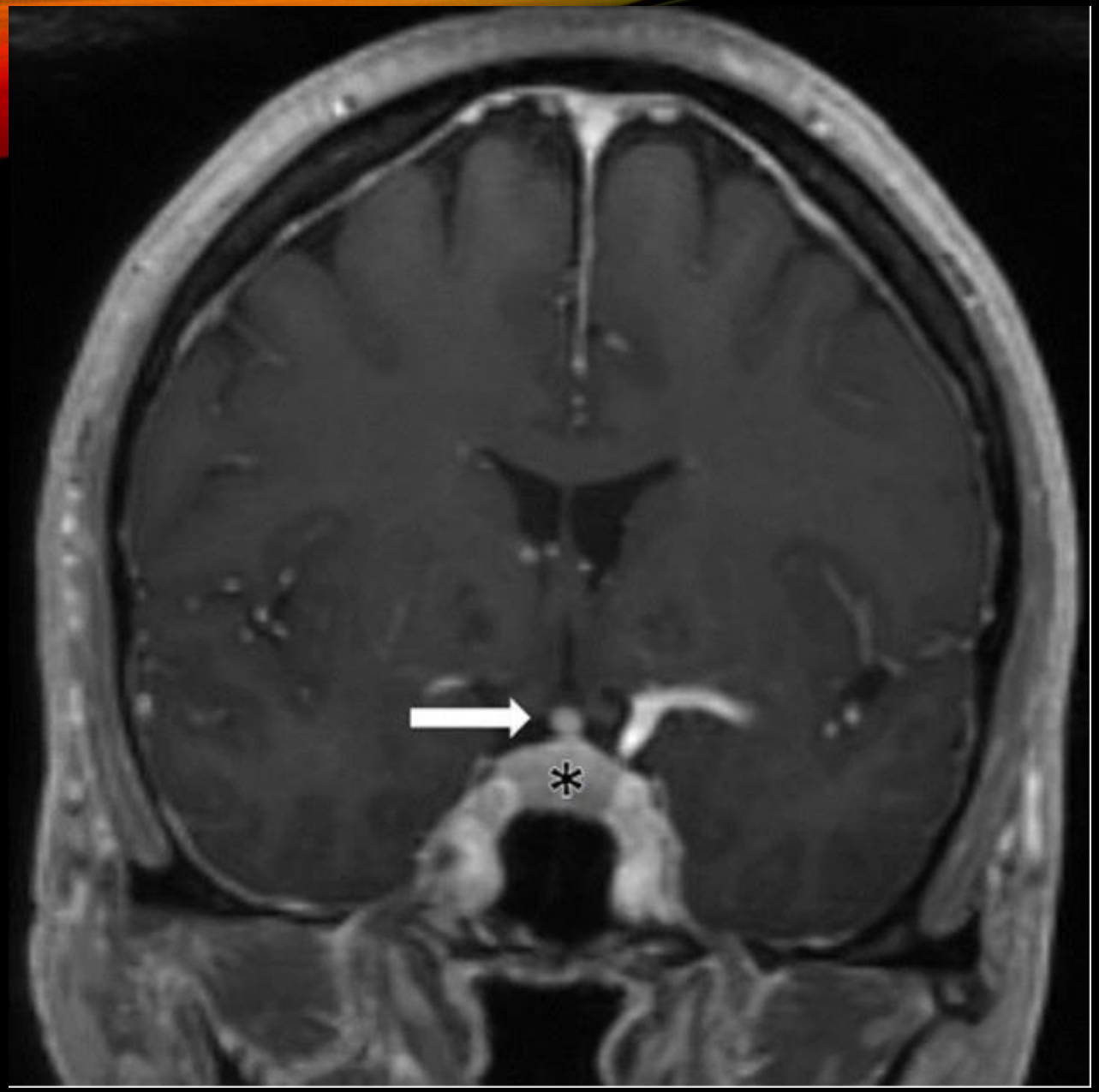
HYPOPHYSITIS

- One of the most common immune-related endocrinopathies.

- The diagnosis of immune-related hypophysitis is presumptive diagnosis
- It is generally based on the development of new hypopituitarism and pituitary enlargement at imaging after initiation of immunotherapy without an alternative etiology.

- At MRI, enlarged pituitary glands may demonstrate homogeneous or heterogeneous enhancement, and thickening of the pituitary stalk.

- Treatment strategies include systemic high-dose corticosteroid administration, while hormone replacement for hypophysitis-related hormone deficiencies is also useful.



Immune-related hypophysitis in a 56-year-old woman with metastatic melanoma receiving ipilimumab and nivolumab and with headaches at presentation.

Coronal MR image after 8 weeks of ipilimumab and nivolumab therapy shows an enlarged pituitary gland and infundibular thickening, representing immune-related hypophysitis.

The symptom and findings resolved after corticosteroid therapy.

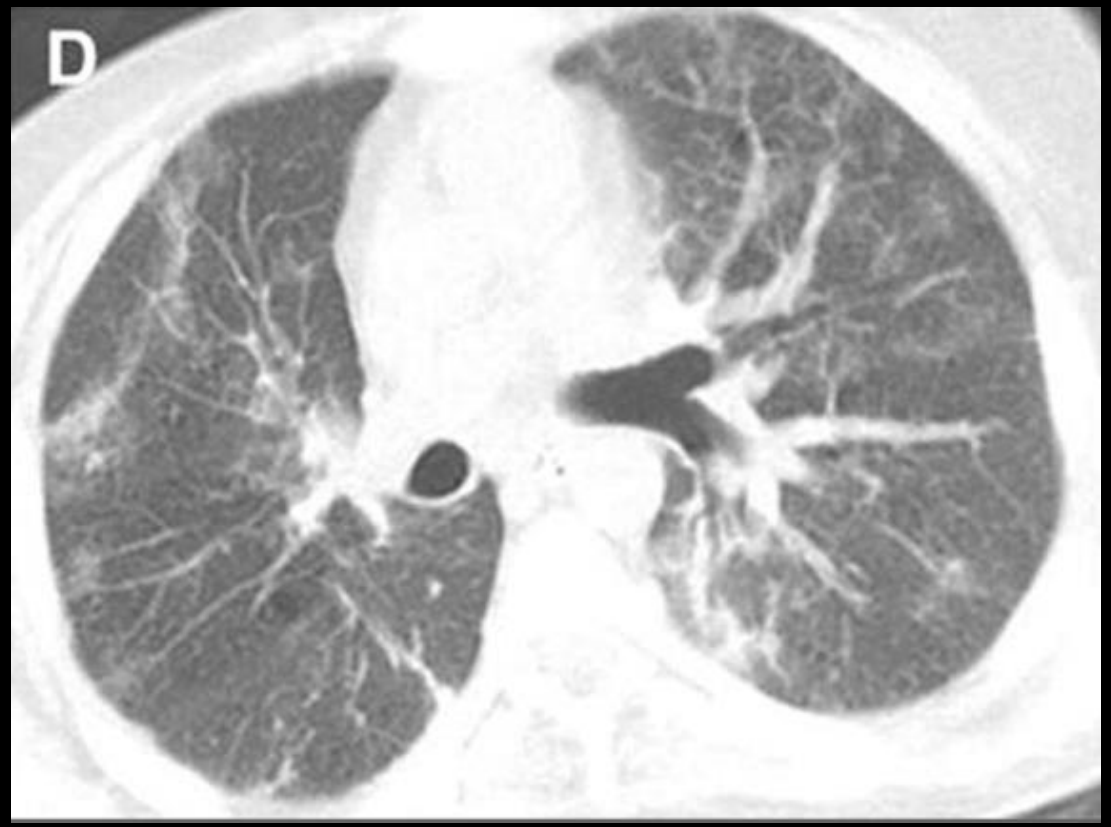
PNEUMONITIS

- Usually seen in patients treated with PD-1/PD-L1 inhibitors.
- clinically serious and potentially life-threatening toxicity of immune-checkpoint blockade.
- A prior meta-analysis of 20 clinical trials of PD-1 inhibitor therapy in melanoma, NSCLC, and renal cell carcinoma reported that higher odds of pneumonitis were noted in NSCLC, patients with a history of asthma or chronic obstructive pulmonary disease and in those with a history of thoracic radiation.

RADIOGRAPHIC PATTERNS OF PNEUMONITIS

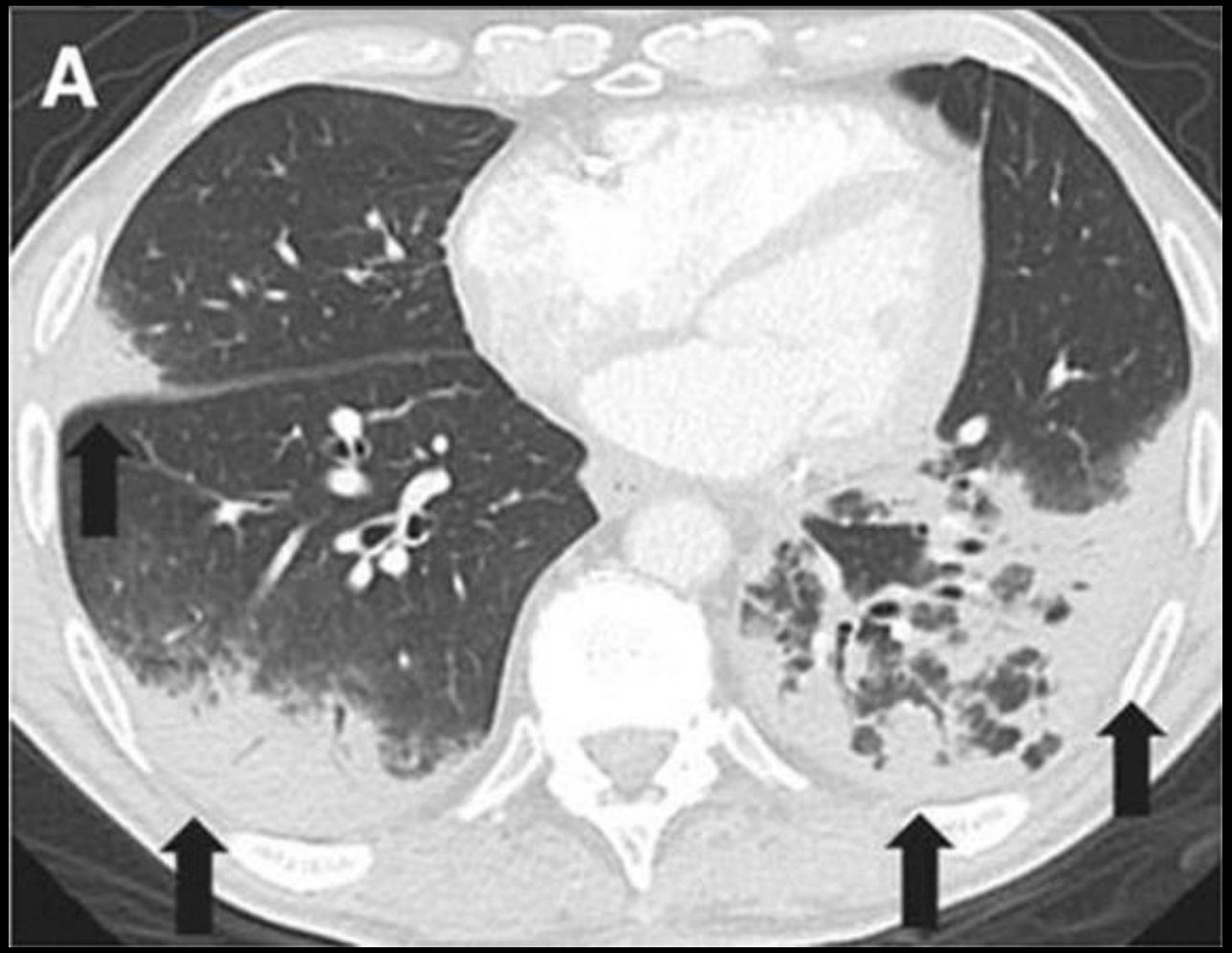
- **Acute interstitial pneumonia (AIP)/acute respiratory distress syndrome (ARDS) pattern (Grade III)-**

characterized by diffuse or multifocal GGOs or consolidations, along with lung volume loss and traction bronchiectasis.



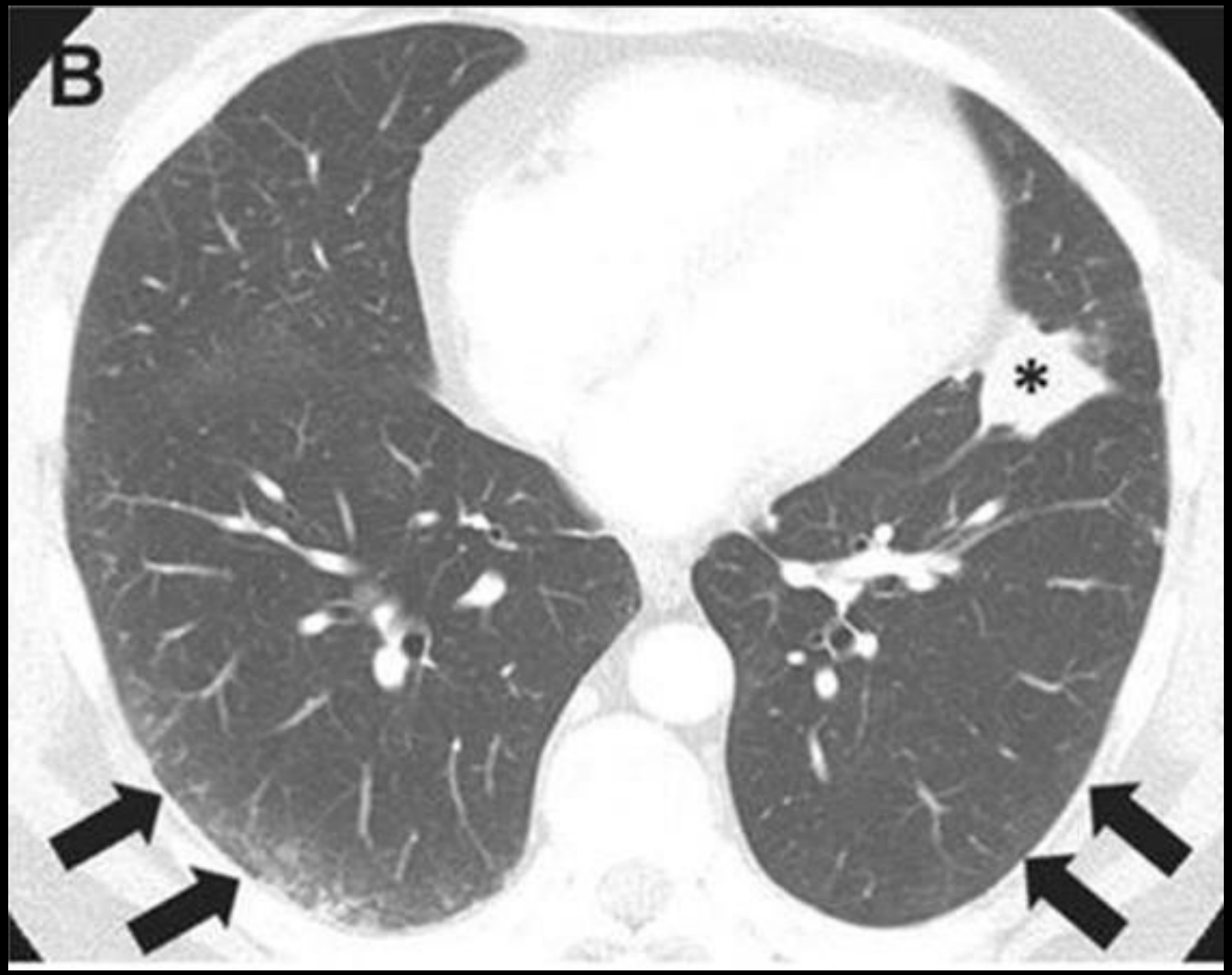
- **Cryptogenic organizing pneumonia (COP) pattern (Grade II)** – most common

Characteristics are multifocal bilateral parenchymal consolidations with peripheral and lower lung distribution, with ground-glass opacities (GGOs) and reticular opacities

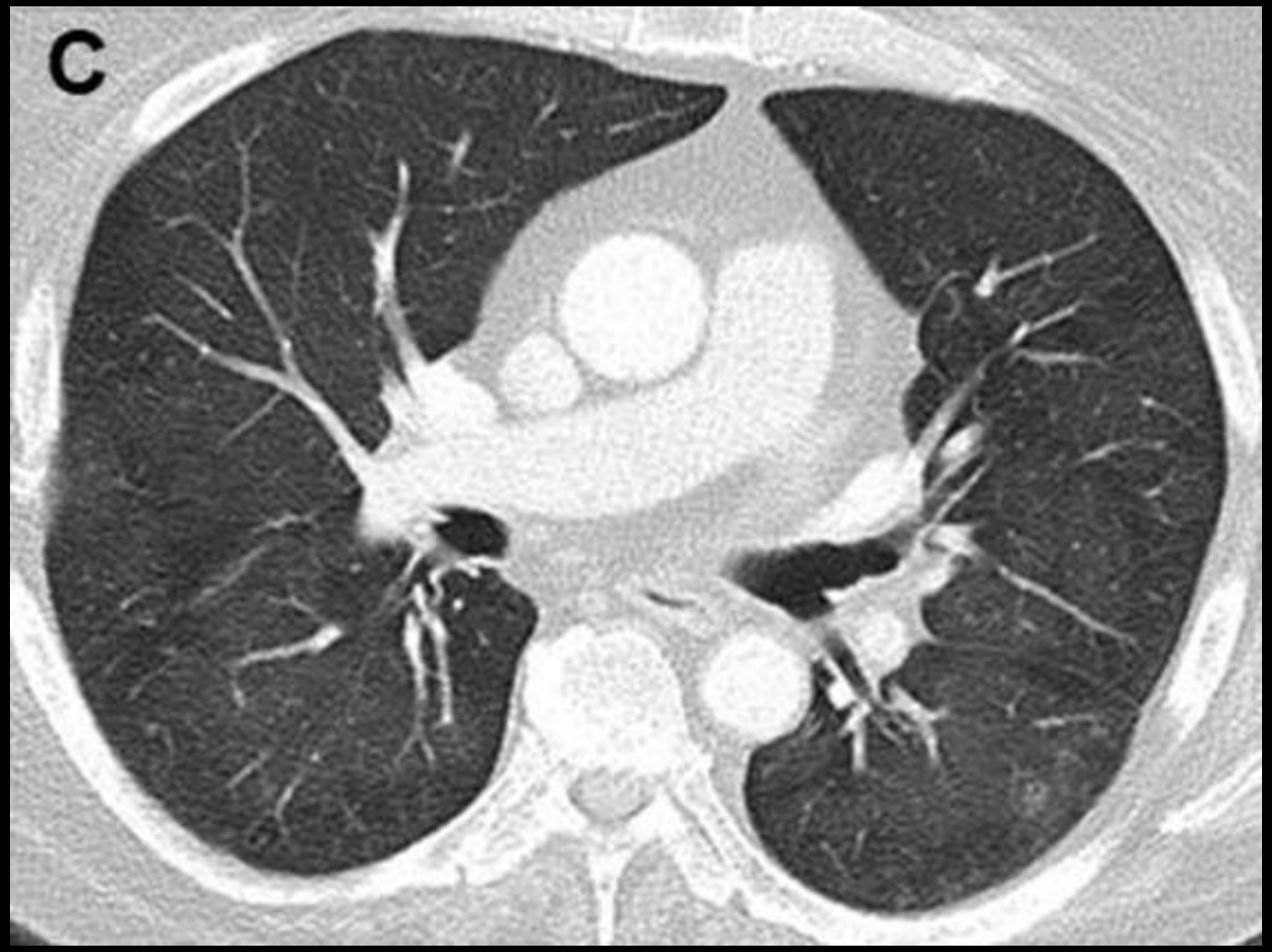


- **Nonspecific interstitial pneumonia (NSIP) pattern- Grade I.**

Characterized by GGOs and reticular opacities predominantly in a peripheral and lower lung distribution



- **Hypersensitivity pneumonitis (HP) pattern- Grade I.**
  Characterized by diffuse GGOs and centrilobular nodularities, with scattered areas of air trapping



TREATMENT OF PNEMONITIS

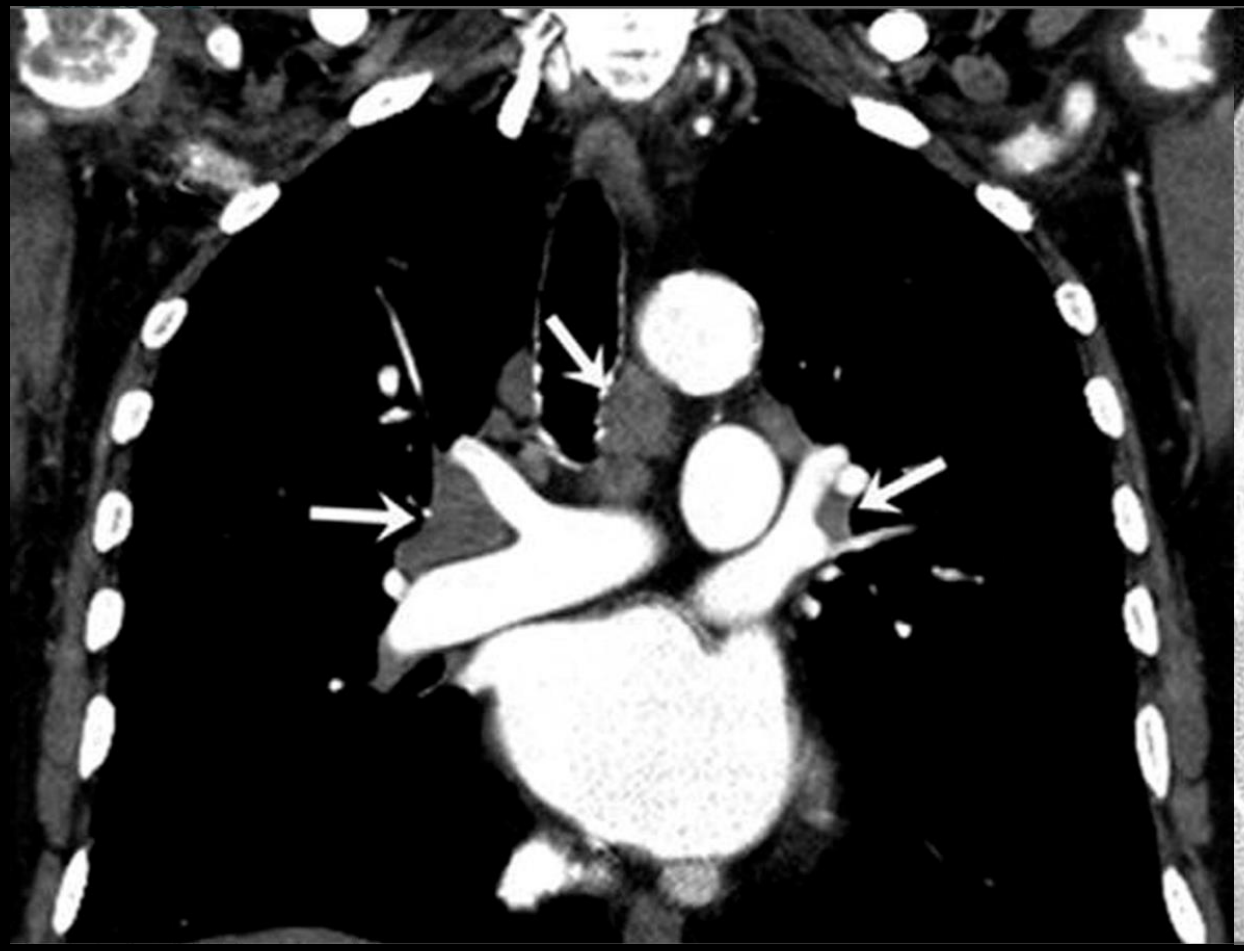
- consists of corticosteroids along with withholding the responsible immunotherapeutic agents for most cases.
- “Pneumonitis Flare” - in a small subset of patients, pneumonitis may recur after the completion of a corticosteroid taper without restarting immune-checkpoint inhibitors or any other systemic agents.
- Re-treatment with immunotherapy after episodes of pneumonitis is another challenging issue. We have limited data for this.

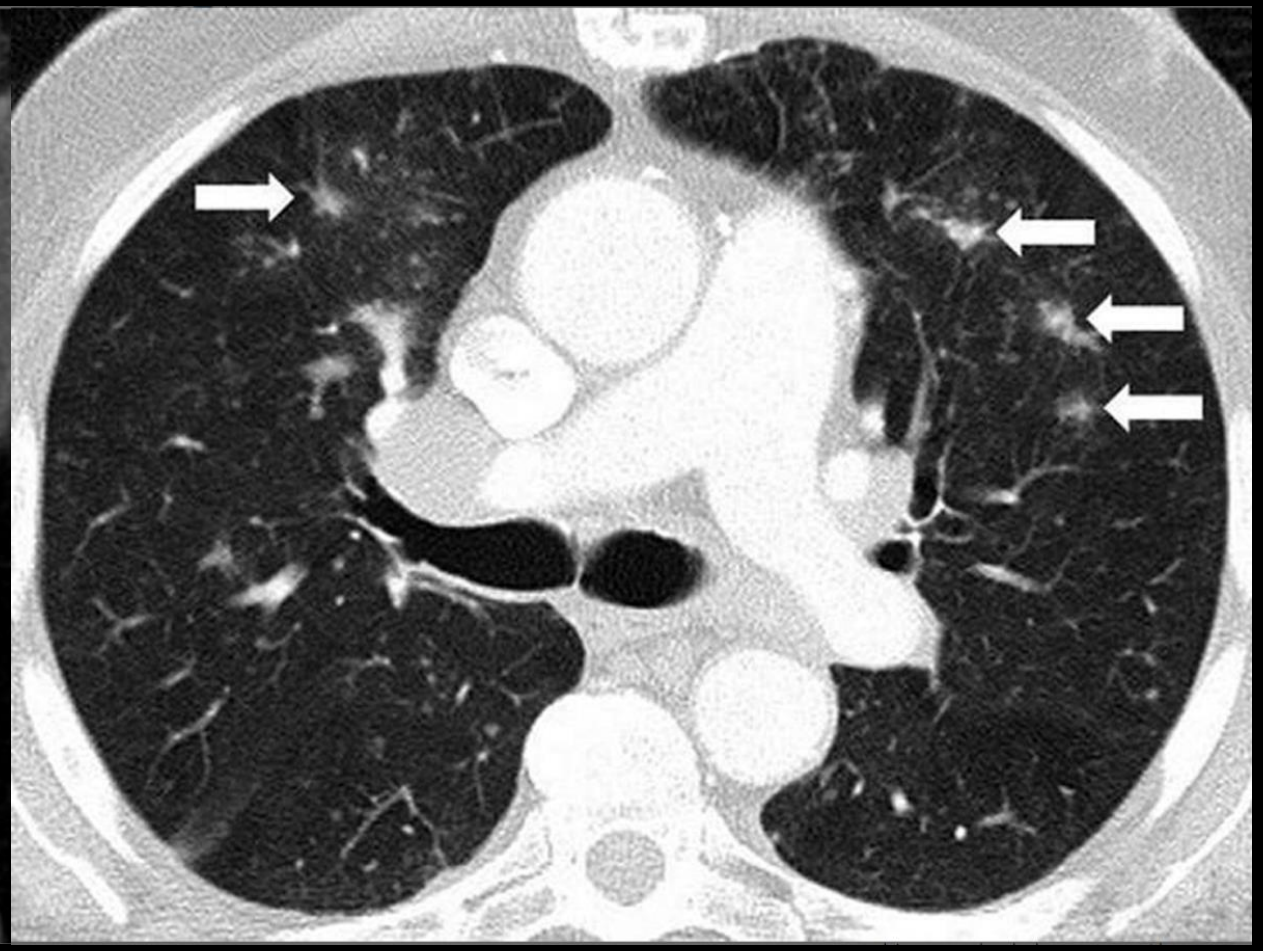
SARCOID LIKE LYMPHADENOPATHY AND GRANULOMATOSIS

- Incidence- up to 5%–7% of patients treated with immune-checkpoint inhibitors.
- Most Common Location- mediastinal and hilar lymph nodes.
- Imaging findings

  mediastinal and hilar lymphadenopathy with nodular thickening of peribronchovascular bundles and the interlobular septum in lung parenchyma
- Histologic sampling of these cases revealed granulomatous inflammation in an interlobular, peribronchiolar, and subpleural distribution resembling sarcoidosis.
- These findings resolve after immune-checkpoint inhibitors are withheld.

SARCOID LIKE LYMPHADENOPATHY AND GRANULOMATOSIS





COLITIS

- Incidence - 8% to 22%.
- Most common agent- Ipilimumab.

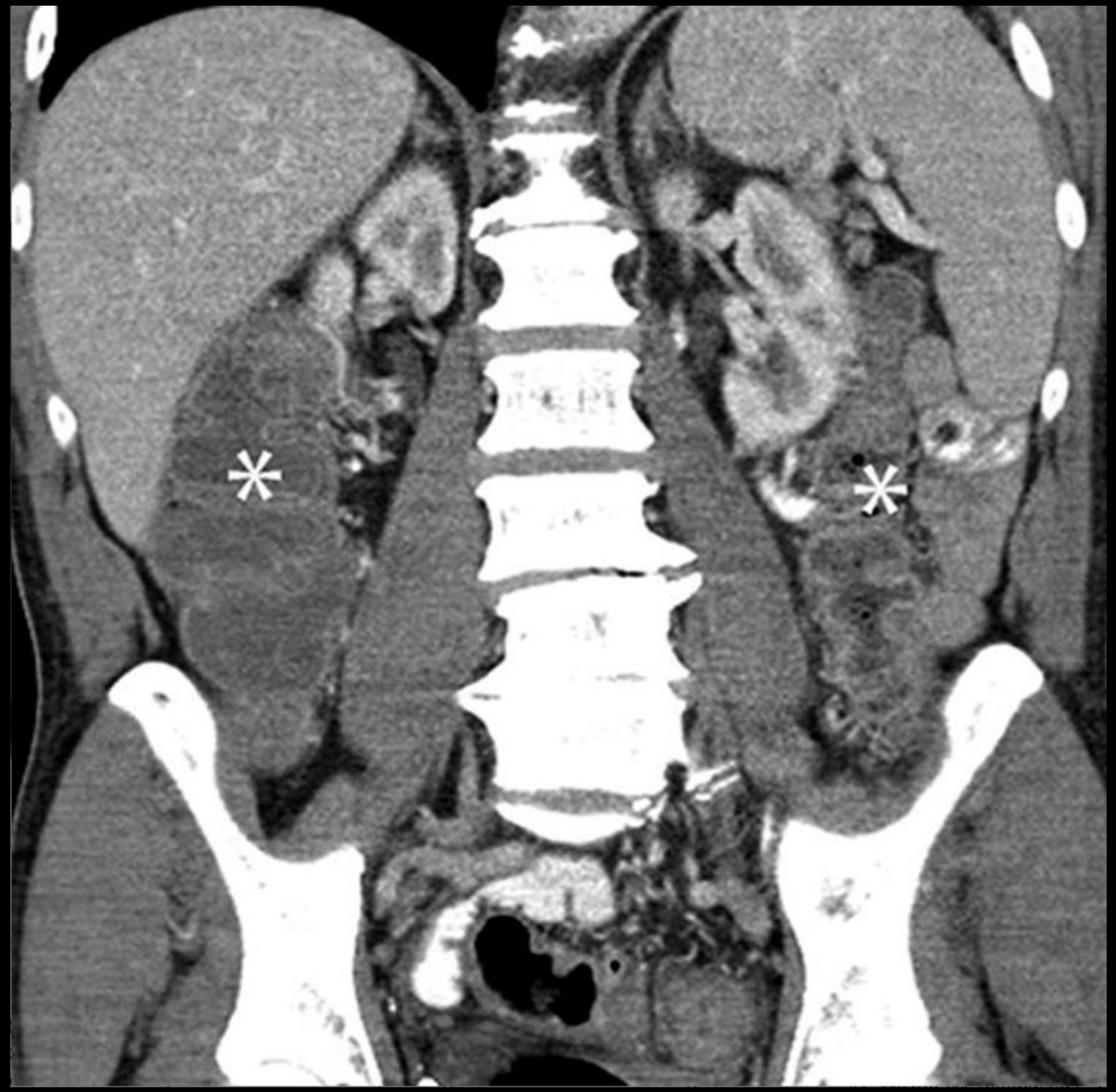
- In ipilimumab-treated patients, colitis usually develops 6–7 weeks after the initiation of treatment and resolves within 6–8 weeks.

- Two distinct patterns of colitis:

❖ **Diffuse** colitis pattern- seen in about 75% of cases, which is characterized by mild diffuse bowel wall thickening or a fluid-filled distended colon with mesenteric vessel engorgement.

❖**Segmental** colitis associated with diverticulosis (SCAD) pattern- noted in approximately 25% of cases, characterized by moderate wall thickening and associated pericolic fat stranding in a segment of pre-existing diverticulosis.

DIFFUSE COLITIS PATTERN



TREATMENT OF COLITS

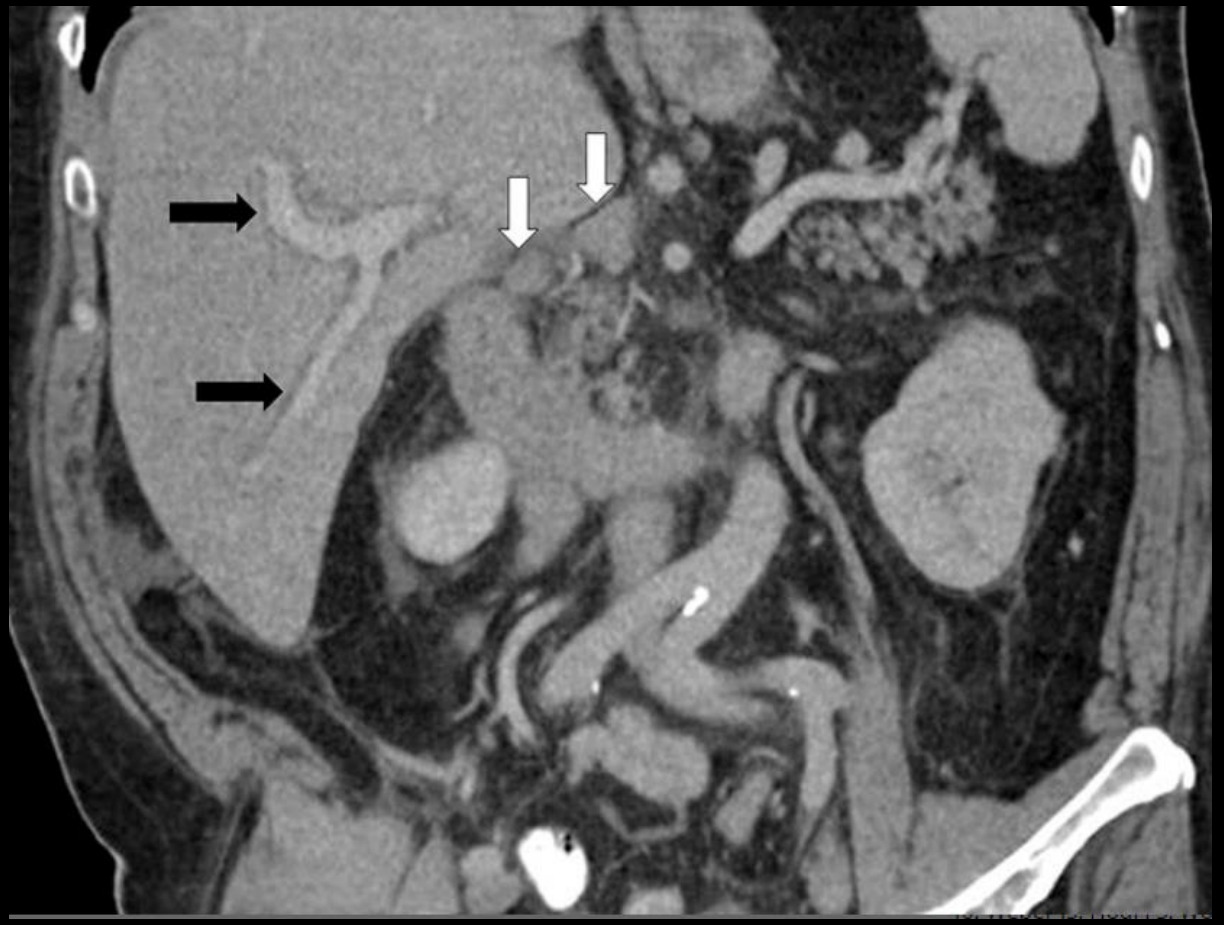
- A **diffuse colitis pattern manifests with profuse watery diarrhea**, whereas a **segmental colitis pattern manifests with mixed watery and bloody diarrhea with cramping pain.**

- **Diffuse colitis** cases can often be managed with **corticosteroids alone**, while **segmental colitis** cases are treated with **corticosteroids and antibiotics**.

HEPATITIS

- INCIDENCE- 1%–2% of patients.
- Most common agent- PD-1/PD-L1 or CTLA-4 inhibitor monotherapy.
- **Time between therapy initiation and hepatitis is 5 weeks in patients.**
- Spectrum of manifestations, ranging from mild asymptomatic cases with mildly increased liver function without imaging abnormalities, to severe cases with systemic symptoms and highly elevated liver function test results.
- Severe cases are often accompanied by hepatomegaly, periportal edema, and periportal lymphadenopathy at imaging.
- **Most cases are treated with corticosteroids**, while the addition of azathioprine or mycophenolate mofetil is considered in steroid-refractory cases according to the management guidelines of autoimmune hepatitis.

IMMUNE-CHECKPOINT INHIBITOR-RELATED HEPATITIS



EMERGING APPROACHES USING MOLECULAR IMAGING FOR IMMUNOTHERAPY

- Molecular imaging techniques using novel radioactive tracers that target the key molecules of immune-checkpoint pathways and cellular immune responses have been explored.
- Early efforts have focused on radiolabelling of antibodies against key molecules such as PD-1 and PD-L1.
- Recent advances - **high-affinity competitive non-antibody antagonist of PD-L1, conjugated with ^{64}Cu-DOTA (tetraazacyclododecane tetraacetic acid) and tested as a PET tracer.**

IMAGING AGENTS

TABLE 1: Common Immunotherapy Pathways and Therapeutic and Imaging Agents

Antigen Target	Common Therapeutic Agents	Clinical Applications	Imaging Agents
CTLA-4	Ipilimumab Tremelimumab	Melanoma	^{64}Cu-DOTA-anti-CTLA-4 ^{89}Zr-ipilimumab
PD-1/PD-L1	PD-1: pembrolizumab, nivolumab PD-L1: atezolizumab, avelumab, durvalumab, pidilizumab	Melanoma, RCC, HNSCC, NSCLC, ovarian cancer, Merkel cell carcinoma, B-cell lymphoma, follicular lymphoma, urothelial carcinoma	^{89}Zr-avelumab ^{89}Zr-nivolumab ^{64}Cu-atezolizumab ^{89}Zr-penbrolizumab ^{18}F-DK222 ^{89}Zr-atezolizumab (in humans)
CAR T cells	Axicabagene ciloleucel, tisangenlecleucel-T	Leukemia, lymphoma	In vivo: ^{8}F-TFB (sodium iodide symporter) ^{18}F-NOTA-octreotide (somatostatin receptor) ^{18}F-FEAU (human deoxycytidine kinase)
VEGF	Bevacizumab	CRC, NSCLC, RCC, glioblastoma, ovarian cancer, breast cancer	^{89}Zr-bevacizumab
EGFR	Cetuximab	HNSCC, CRC	^{89}Zr-cetuximab
CD20	Rituximab	B-cell lymphoma	^{89}Zr-rituximab
CD38	Daratumumab, isatuximab	Multiple myeloma	^{89}Zr-DFO-daratumumab
HER2	Trastuzumab	Breast cancer	^{89}Zr-trastuzumab

Note—CTLA-4 = cytotoxic T-lymphocyte antigen 4, DOTA = dodecane tetraacetic acid, PD-1 = programmed cell death protein-1, PD-L1 = programmed death-ligand 1, RCC = renal cell carcinoma, HNSCC = head and neck squamous cell carcinoma, NSCLC = non–small cell lung cancer, CAR = chimeric antigen receptor, TFB = tetrafluoroborate, NOTA = 1,4,7-triazacyclononane-N,N′,N″-triacetic acid, FEAU = 2-fluoro-2-deoxyarabinofuranosyl-5-ethyluracil, VEGF = vascular endothelial growth factor, CRC = colorectal cancer, EGFR = epidermal growth factor receptor, DFO = deferoxamine, HER2 = human epidermal growth factor receptor 2.

IMMUNE-RELATED METABOLIC RESPONSE ASSESSMENT CRITERIA

- Utilization of FDG PET/CT for monitoring immunotherapy response

- Include:

❖Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC, 2016)
❖PET Response Evaluation Criteria for Immunotherapy (PERCIMT, 2018)
❖Immunotherapy-modified PET RECIST (imPERCIST, 2019)

LYRIC

- adapted from the Lugano classification and is specific to lymphoma immunotherapy assessment.

- According to these criteria, imaging findings suggestive of progressive disease in the absence of clinical deterioration are classified as indeterminate response (IR) and require subsequent imaging within 12 weeks or biopsy for confirmation.

PERCIMT

- based on the size and number of new lesions and applies a threshold of four new FDG-avid lesions on a post-therapy examination as a reliable indicator of treatment failure.

- imPERCIST is a modification of the PERCIST criteria that uses the sum of the peak SUV corrected for lean body mass (SUL_{peak}) for up to five lesions.

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THANK YOU