Patterns & Response to Immunotherapy

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BASICS

Basis of Immunotherapy

- Malignant cells often undergo modification to escape the native immune response
- Immunotherapy by using ICIs aims to facilitate recognition of the tumor antigen by the T cells, thereby resulting in tumor regression
- Enables T cells to mount an antitumor immune response that bypasses the regulatory mechanisms in the tumor cells
- Knowledge of these mechanisms is evolving, with new pathways for immunomodulation continually emerging

Pathways

- The CTLA-4 Pathway

- The Programmed Cell Death Protein 1 Pathway (PD1 & PDL1)

- Other Pathways for Cancer Immunotherapy
  - **Chimeric antigen receptor (CAR) T-cell therapy**
  - **natural killer cell–mediated immunotherapy**
  - **human epidermal growth factor receptor 2–directed monoclonal antibody T-cell immunoglobulin,**
  - **immunoreceptor tyrosine- based inhibitory motif domain,**
  - **Lymphocyte activation gene 3, and**
  - **cytokine-mediated immunotherapy**

The CTLA-4 Pathway

- Earliest to be identified
- Chronic inflammation or induction by tumor cells, resulting in decreased effectiveness of the T-cell immune response
- Downregulates the CD28 protein expressed on T-cells, which provides costimulatory signals for T-cell activation
- CTLA-4 binds to the closely related CD80 and CD86 B7 membrane proteins that are involved in T-cell activation with a higher affinity than CD28, thereby decreasing the availability for CD28 binding
- CTLA-4 can decrease CD80 and CD86 expression through endocytosis

The Programmed Cell Death Protein 1 Pathway

- PD-1 - a cell surface protein with inhibitory effects on immune response with two ligands, PD-L1 and PD-L2
- Tumor-specific T cells and tumor-infiltrating lymphocytes have high PD-1 expression, resulting in decreased T-cell function with impaired cytokine production and upregulation in the tumor microenvironment
- Better safety profile with decreased side effects in comparison with CTLA-4 inhibitors
- Multiple preclinical and early clinical studies have shown the feasibility of in vivo PD-L1 imaging using different radiolabeled agents.
- Further studies required to assess their clinical translation and evolution of next generation of imaging biomarkers.

Other Pathways for Cancer Immunotherapy

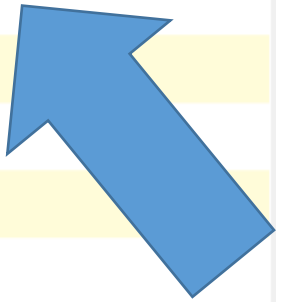
- **Chimeric antigen receptor (CAR) T-cell therapy is one of the** most effective adoptive T-cell therapies. CAR T cells are created from CD4+ and CD8+ T cells that are modified to identify specific antigens on the tumor cell surface by expressing the CAR on the T-cell surface; T-cell proliferation and cytokine release kill the target tumor cells.

- Potential application of in vivo PET and tracking of activated T cells to monitor the response to CAR T-cell therapy.

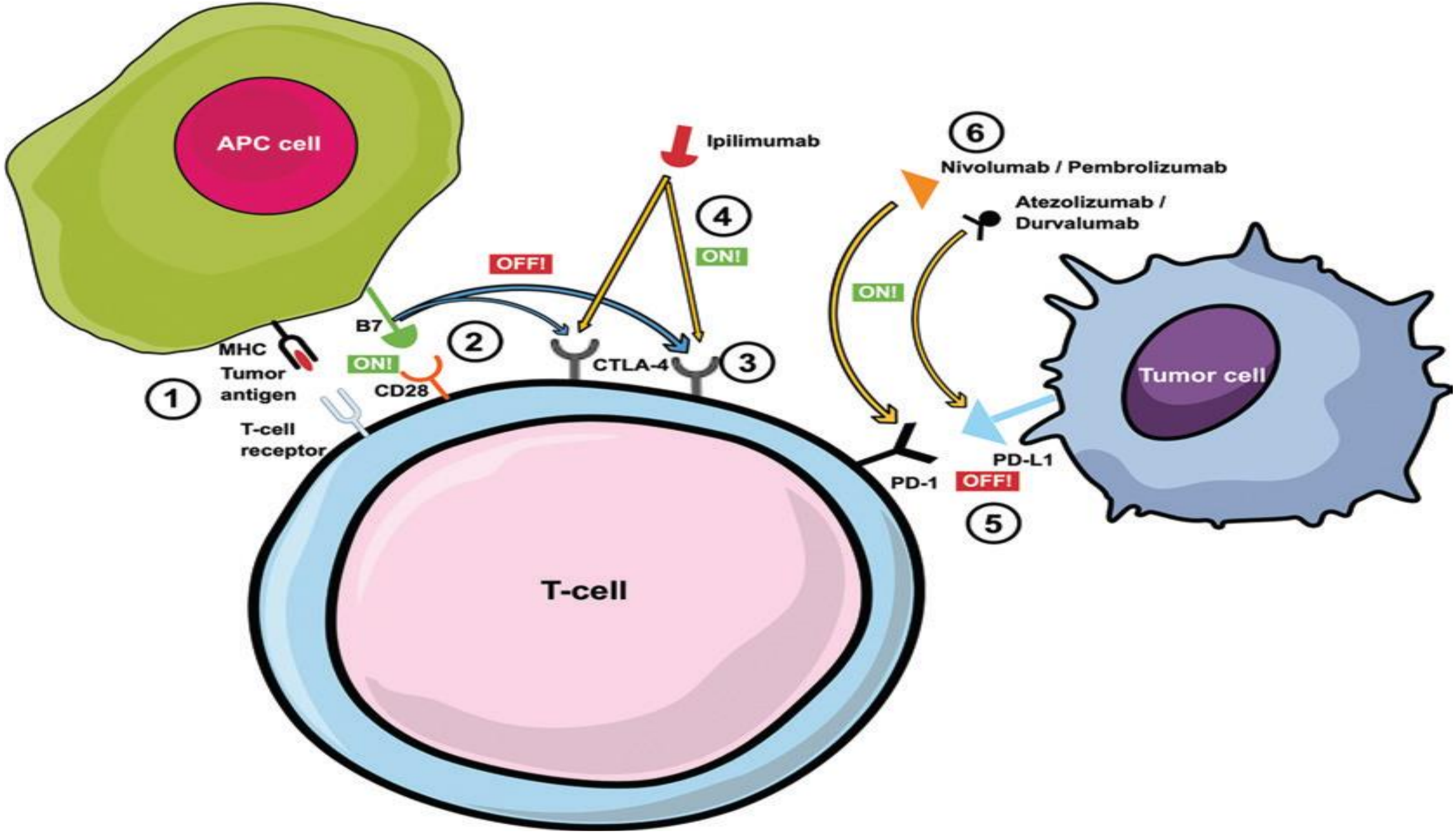
- PET agents, if successful, can improve patients' risk stratification and enhance the efficacy and safety of CAR T-cell therapy.

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.


APC cell
Ipilimumab
6
Nivolumab / Pembrolizumab
Atezolizumab /
Durvalumab
4
ON!
OFF!
ON!
B7
2
MHC
Tumor
antigen
1
ON!
CD28
CTLA-4
3
Tumor cell
T-cell
receptor
PD-L1
PD-1
OFF!
5
T-cell

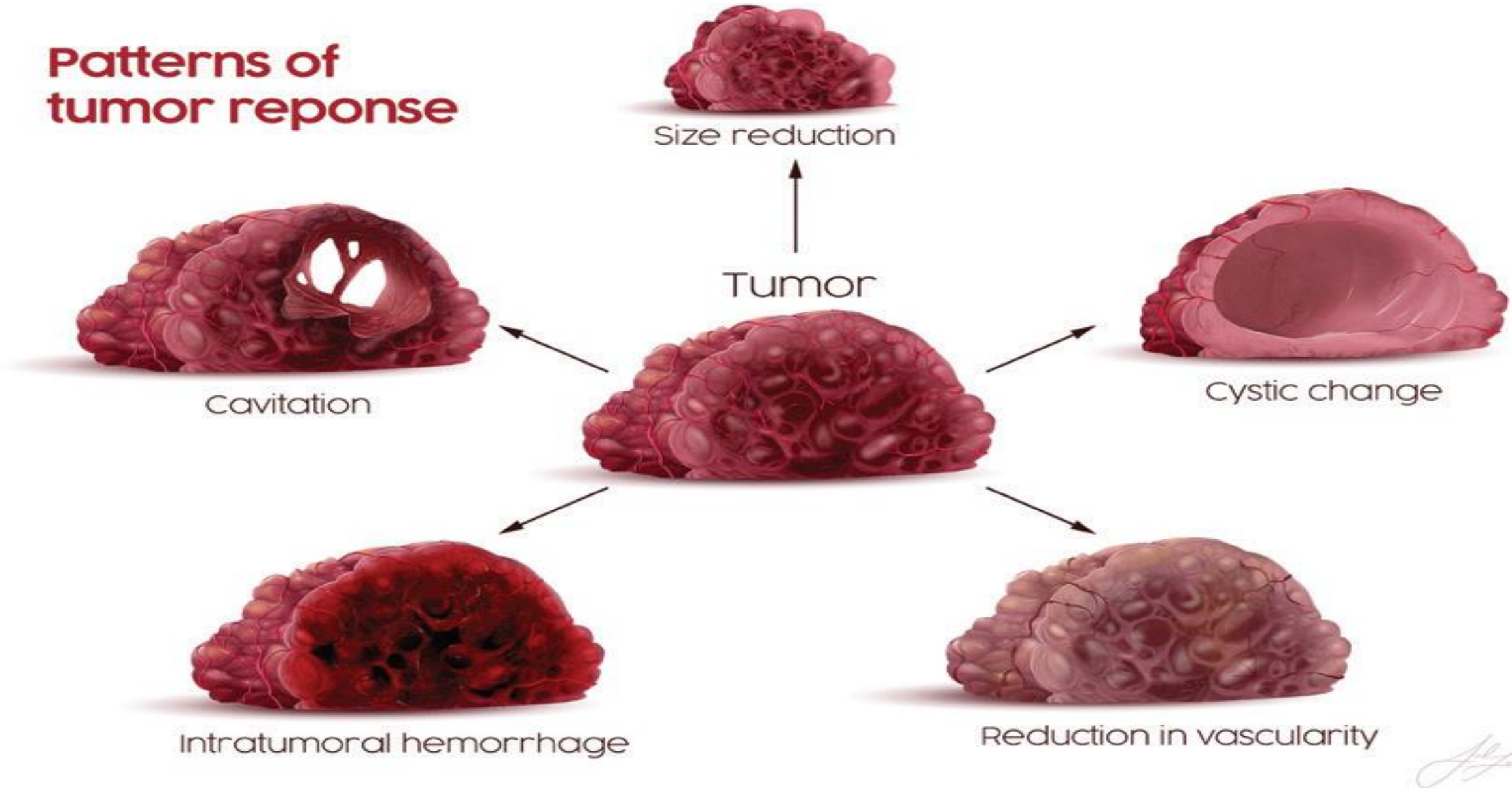
Checkpoint Inhibitors Approved by the FDA as of January 2020

Drug	Target	Approved Use (FDA)
Ipilimumab	CTLA-4	Advanced tumors: melanoma, RCC
Nivolumab	PD-1	Advanced tumors: melanoma, NSCLC, RCC, urothelial carcinoma, classic Hodgkin lymphoma, HNSCC, SCLC, HCC, dMMR colorectal cancer Adjuvant: melanoma
Pembrolizumab	PD-1	Advanced tumors: melanoma, NSCLC, HNSCC, urothelial carcinoma, classic Hodgkin lymphoma, RCC, dMMR tumors, gastric cancer, PMLBCL, Merkel cell carcinoma, cervical cancer, SCLC esophageal cancer, endometrial cancer Adjuvant: melanoma Localized: NMIUC
Cemiplimab	PD-1	Cutaneous squamous cell carcinoma
Durvalumab	PD-L1	Advanced tumors: urothelial carcinoma Stage III: NSCLC
Atezolizumab	PD-L1	Advanced tumors: urothelial carcinoma, NSCLC, SCLC
Avelumab	PD-L1	Advanced tumors: urothelial carcinoma, Merkel cell carcinoma, RCC

Source.—Reference 14.
Note.—CTLA-4 = cytotoxic T-lymphocyte–associated protein 4, dMMR = defective mismatch repair, FDA = U.S. Food and Drug Administration, HCC = hepatocellular carcinoma, HNSCC = head and neck squamous cell carcinoma, NMIUC = non–muscle-invasive urothelial cancer, NSCLC = non–small cell lung cancer, PD-L1 = programmed cell death ligand 1, PD-1 = programmed cell death protein 1, PMLBCL = primary mediastinal large B-cell lymphoma, RCC = renal cell carcinoma, SCLC = small cell lung cancer.

RESPONSES AND CRITERIA

Patterns of tumor reponse



Need of specialized assessment criteria

- Confounding imaging features after immunotherapy
- Some instances of good clinical response discordant with obvious progression on imaging, which when persisted with same Rx in some cases demonstrated response on follow up imaging - ? Treat beyond progression
- Occasional instances of unusually rapid progression of disease with clinical deterioration to death
- Delayed onset of response on imaging
- Durable response even after cessation of Rx
- Dissociate response and oligoprogression
- Distinct adverse events

Types of response

- CR
- PR
- SD
- PD
- iUPD
- iCPD
- iSD
- Pseudoprogression
- Hyperprogression
- Dissociative response
- Durable response
- Adverse events

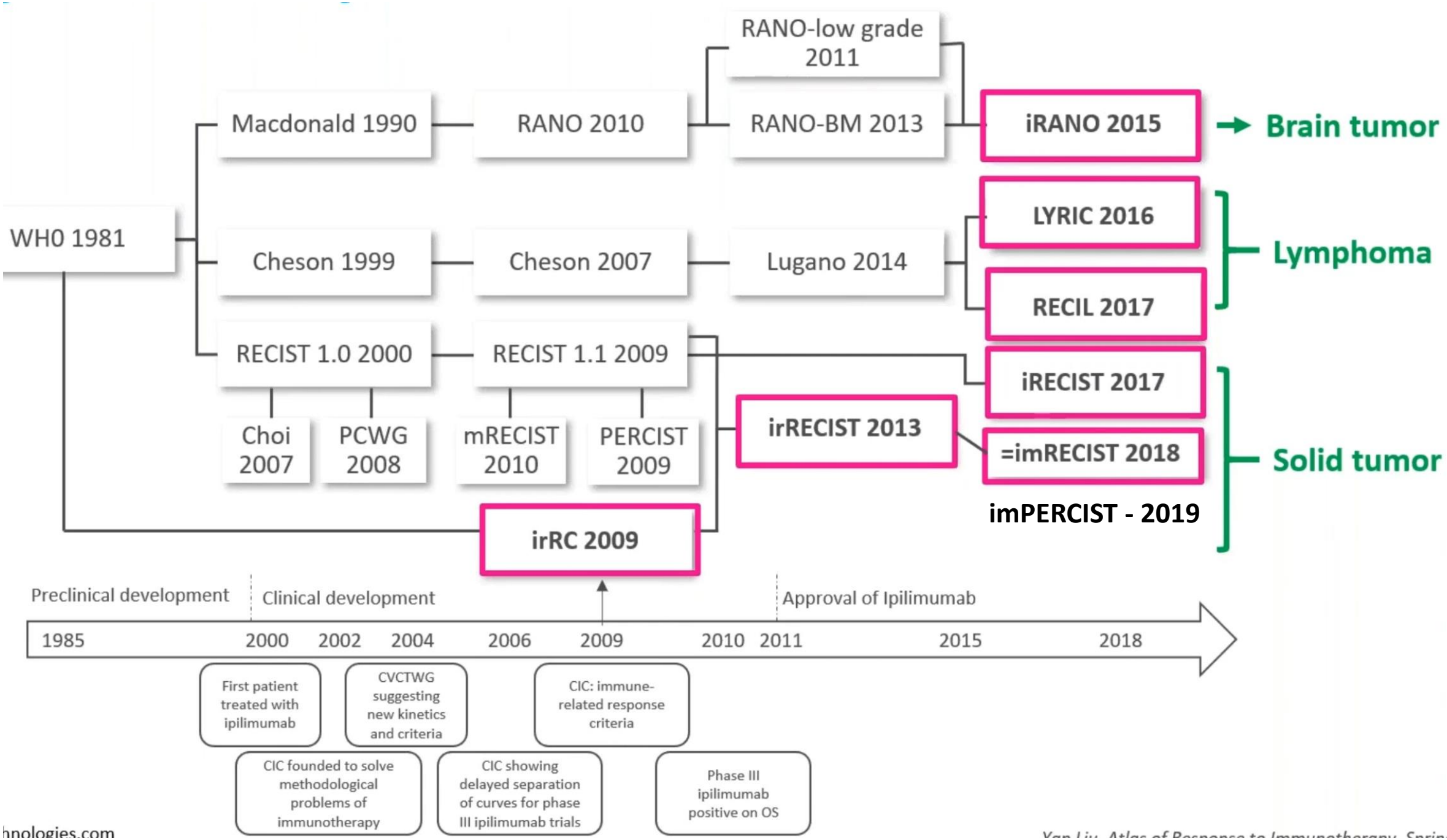

RANO-low grade 2011
Macdonald 1990
RANO 2010
RANO-BM 2013
iRANO 2015
Brain tumor
WH0 1981
LYRIC 2016
Cheson 1999
Cheson 2007
Lugano 2014
Lymphoma
RECIL 2017
RECIST 1.0 2000
RECIST 1.1 2009
iRECIST 2017
irRECIST 2013
Choi 2007
PCWG 2008
mRECIST 2010
PERCIST 2009
=imRECIST 2018
Solid tumor
imPERCIST - 2019
irRC 2009
Preclinical development
Clinical development
Approval of Ipilimumab
1985
2000
2002
2004
2006
2009
2010
2011
2015
2018
First patient treated with ipilimumab
CVCTWG suggesting new kinetics and criteria
CIC: immune-related response criteria
CIC founded to solve methodological problems of immunotherapy
CIC showing delayed separation of curves for phase III ipilimumab trials
Phase III ipilimumab positive on OS

TABLE 2: Overview of RECIST 1.1 and Criteria for Anatomic Response Evaluation to Immunotherapy

Characteristic	RECIST 1.1 (2009)	irRC (2009)	irRECIST (2014) and imRECIST (2018)	iRECIST (2017)	mChoi (2010)[a]
Spatial assessment	Unidimensional	Bidimensional	Unidimensional	Unidimensional	Unidimensional (incorporates changes in size and attenuation)
Target lesions	Five lesions (2 per organ)	15 Lesions (5 per organ)	Five lesions (2 per organ)	Five lesions (2 per organ)	10 Lesions
CR	Complete resolution of nonnodal lesions; reduction of pathologic nodes to < 1 cm	Disappearance of all target lesions or lymph nodes in 2 consecutive observations ≥ 4 wk apart	Similar to RECIST 1.1	Similar to RECIST 1.1	Disappearance of all target lesion
PR	≥ 30% Reduction in tumor burden; no new lesions	≥ 50% Reduction in tumor burden in 2 observations ≥ 4 wk apart	Similar to RECIST 1.1	Similar to RECIST 1.1	> 10% Decrease in size AND > 15% decrease in tumor density (expressed as Hounsfield units); no new lesions
SD	Not meeting criteria for CR, PR, or PD	Not meeting criteria for CR, PR, or PD	Not meeting criteria for CR, PR, or PD	Not meeting criteria for CR, PR, or PD	Not meeting criteria for CR, PR, or PD
PD	≥ 20% Increase in the SPD relative to nadir or minimum absolute increase of 5 mm; new target or nontarget lesions	≥ 25% Increase in tumor burden compared with nadir (at any single time point) in 2 consecutive observations ≥ 4 wk apart	≥ 20% Increase in SPD relative to nadir or minimum absolute increase of 5 mm; new target or nontarget lesions	iUPD: ≥ 20% increase in SPD relative to nadir or minimum absolute increase of 5 mm; new target or nontarget lesions iCPD: new lesions, ≥ 5 mm increase in size of target or any increase in nontarget lesions on subsequent imaging	> 10% Increase in tumor size and does not meet criteria of partial response by tumor density
Confirmation of PD	Not required (unless equivocal)	Required (≥ 4 wk apart)	Required (≥ 4 wk apart)	Required (4–8 wk apart)	Not determined
New lesions	Always PD	PD if confirmed; incorporated for calculating tumor burden	PD if confirmed; incorporated for calculating the SPD	iUPD, becomes iCPD if confirmed; not included in SPD calculation	Always PD

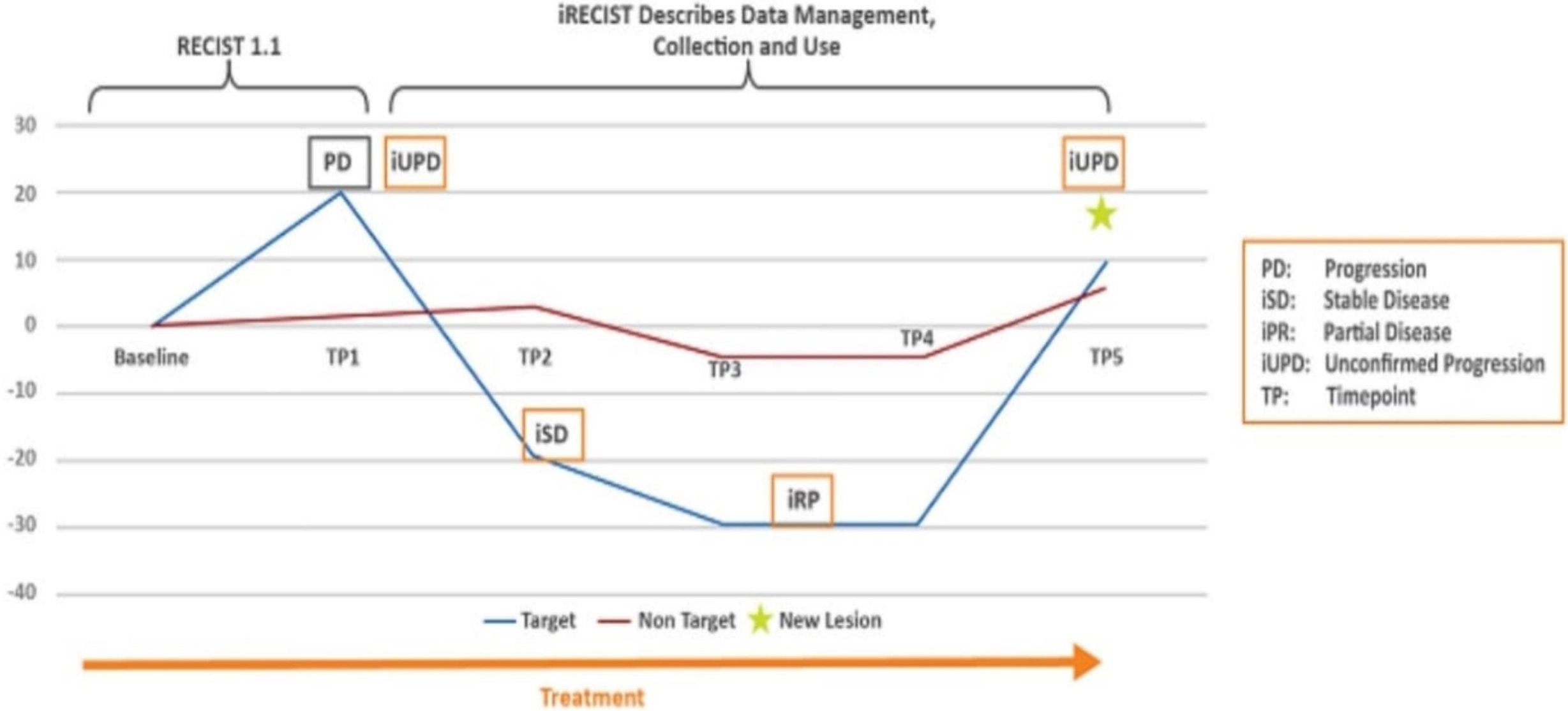
Note—Portions of this table were previously presented in Sheikhbahaei S, Verde F, Hales RK, Rowe SP, Solnes LB. Imaging in therapy response assessment and surveillance of lung cancer: evidenced-based review with focus on the utility of ^{18}F-FDG PET/CT. *Clinical Lung Cancer* 2020; 21:485–497 (© 2020 Elsevier Inc., used with permission). Values in parentheses in the column headings indicate the year in which the criteria were introduced. irRC = immune-related response criteria, irRECIST = immune-related RECIST, imRECIST = immune-modified RECIST, iRECIST = immune RECIST, mChoi = modified Choi, CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, SPD = sum of products of diameters, iUPD = immune unconfirmed progressive metabolic disease, iCPD = immune confirmed progressive disease.

[a]Initially proposed for therapy response assessment in patients with gastrointestinal stromal tumor.

Overview of PERCIST 1.0 and FDG PET/CT–Based Criteria for Metabolic Response Evaluation to Immunotherapy

Characteristic	PERCIST 1.0 (2009)	PERCIMT (2018)	imPERCIST (2019)	LYRIC (2016)
CR	Complete resolution of uptake of all FDG-avid lesions	Complete resolution of uptake of all FDG-avid lesions; no new lesions	Similar to PERCIST 1.0	PET: resolution of FDG uptake (uptake below or equal to liver, Deauville score of 1–3) CT: reduction of lesions to normal size
PR	≥ 30% Reduction in the SUL_{peak} and ≥ 0.8 absolute decrease in SUL_{peak}	Complete resolution of uptake of some FDG-avid lesions; no new lesions	Similar to PERCIST 1.0	PET: reduced FDG uptake (uptake higher than liver, Deauville score of 4–5) CT: ≥ 50% reduction in SPD of up to six lesions
SD	Not meeting criteria for CR, PR, or PD	Not meeting criteria for CR, PR, or PD	Not meeting criteria for CR, PR, or PD	Not meeting criteria for CR, PR, or PD
PD	≥ 30% Increase in SUL_{peak} and > 0.8 absolute increase in SUL_{peak}; new FDG-avid lesions	No clinical benefit Appearance of ≥ 4 new lesions with functional diameter < 1 cm, ≥ 3 new lesions with functional diameter > 1 cm, or ≥ 2 new lesions with functional diameter > 1.5 cm	iUPD: ≥ 30% Increase in the SUL_{peak} and > 0.8 absolute increase in SUL_{peak}; new FDG-avid lesions iCPD: increase in SUL_{peak} or appearance of new FDG-avid lesions on subsequent examination	Indeterminate response (IR): IR1: ≥ 50% Increase in SPD in 12 wk without clinical deterioration IR2: < 50% increase in SPD with new lesion(s), or ≥ 50% increase in SPD of lesion or set of lesions at any time during treatment IR3: increase in FDG uptake without increase in lesion size meeting criteria for PD
Confirmation of PD	Not required (unless equivocal)	Required (subsequent imaging)	Required (subsequent imaging at least 4–8 wk apart)	Required (biopsy or subsequent imaging within 12 wk)

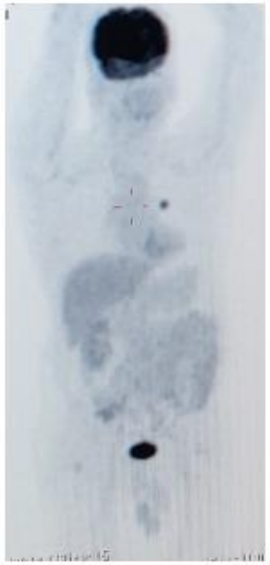
Note—Portions of this table were previously presented in Sheikhbahaei S, Verde F, Hales RK, Rowe SP, Solnes LB. Imaging in therapy response assessment and surveillance of lung cancer: evidenced-based review with focus on the utility of ^{18}F-FDG PET/CT. *Clinical Lung Cancer* 2020; 21:485–497 (© 2020 Elsevier Inc., used with permission). Values in parentheses in header row indicate year in which criteria were introduced. PERCIST = PET RECIST, PERCIMT = PET Response Evaluation Criteria for Immunotherapy, imPERCIST = immunotherapy-modified PERCIST, LYRIC = Lymphoma Response to Immunomodulatory Therapy Criteria, CR = complete response, PR = partial response, SUL_{peak} = peak SUV corrected for lean body mass, SPD = sum of the products of diameters, SD = stable disease, PD = progressive disease, iUPD = immune unconfirmed progressive metabolic disease, iCPD = immune confirmed progressive disease.

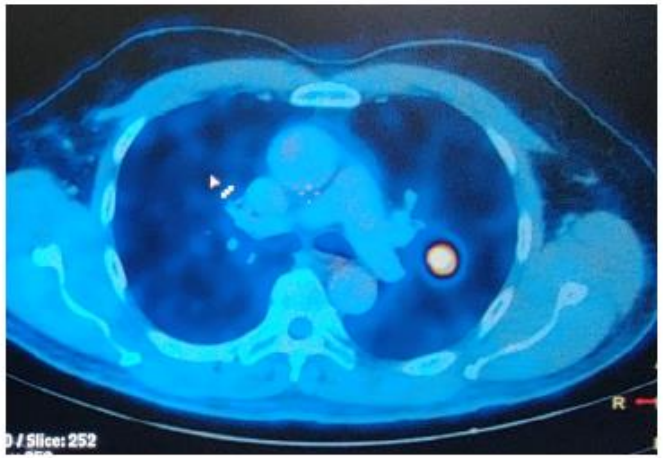


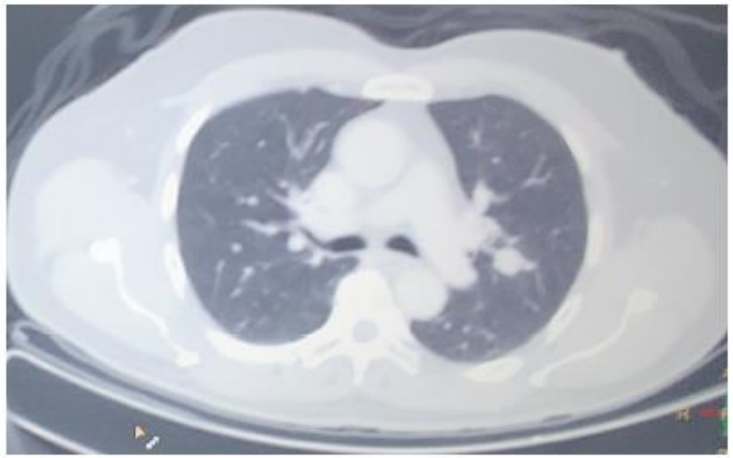
Adapted from Seymour L, et al. on behalf of the RECIST working group. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet. 2017;18(3):e142-152.

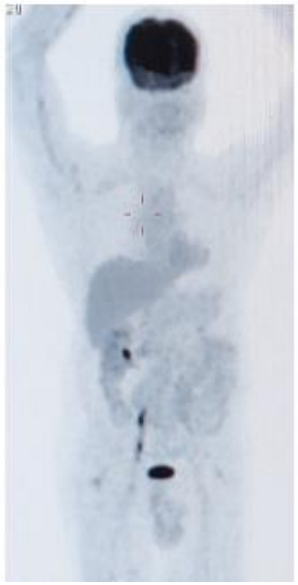
Examples

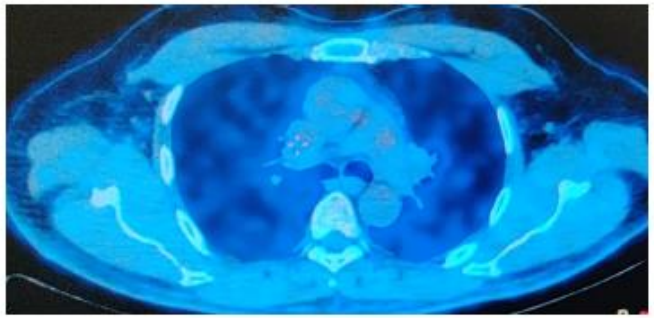
Left renal cell carcinoma metastasis to left lung; complete resolution after 3 months of nivolumab treatment – response.

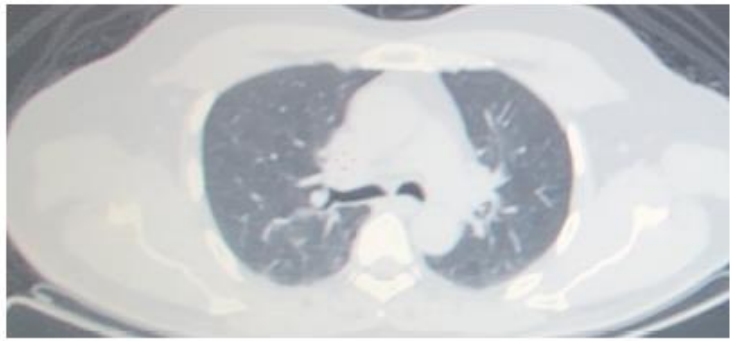






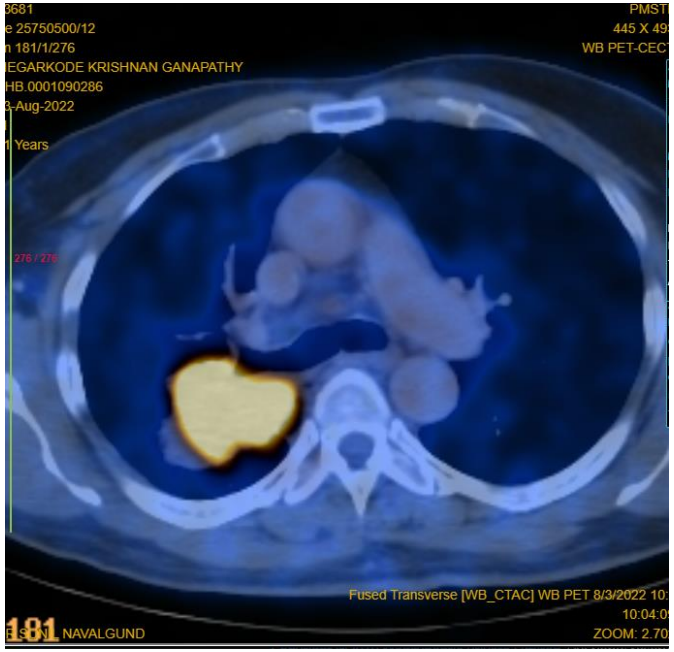


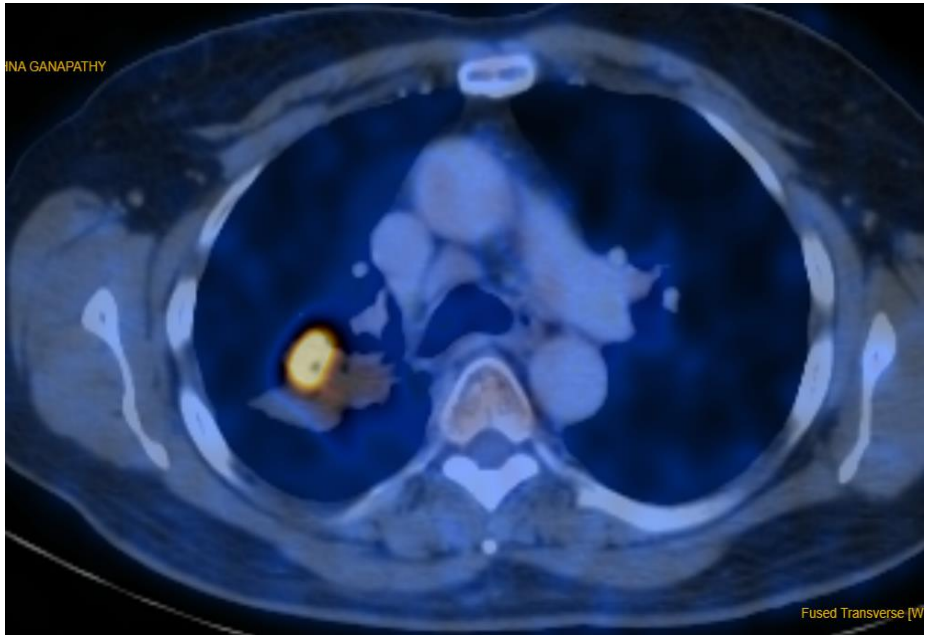




CR

Ca. lung on Immunotherapy - PR





PD

- Assigned iUPD at first instance of progression on imaging
- Requires confirmation on follow up scan after a few weeks
- If confirmed – iCPD
- If regression or stabilization on follow up – iPR or iSD - pseudoprogression

Pseudoprogression

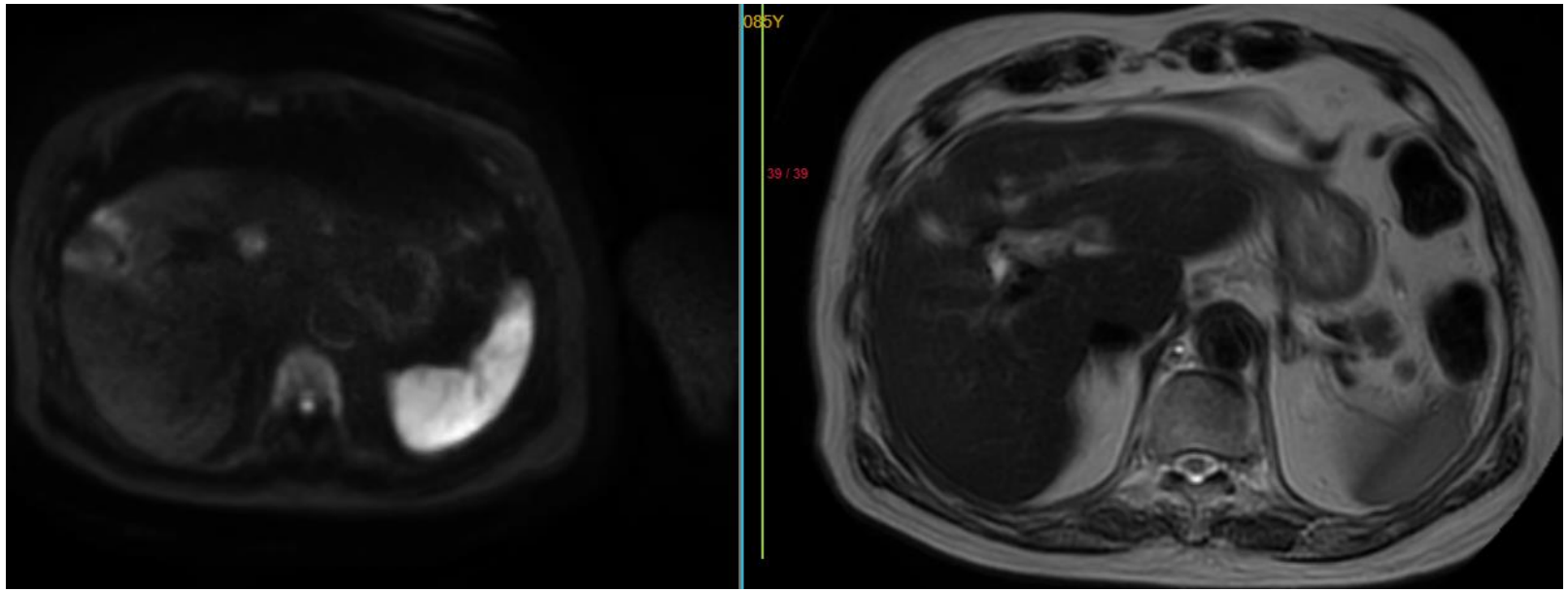
- Important pitfall

- PD as per criteria
  - an increase in tumor size or metabolism
  - the appearance of new lesions

- Followed by a decrease in tumor burden or stabilization of disease on subsequent examinations

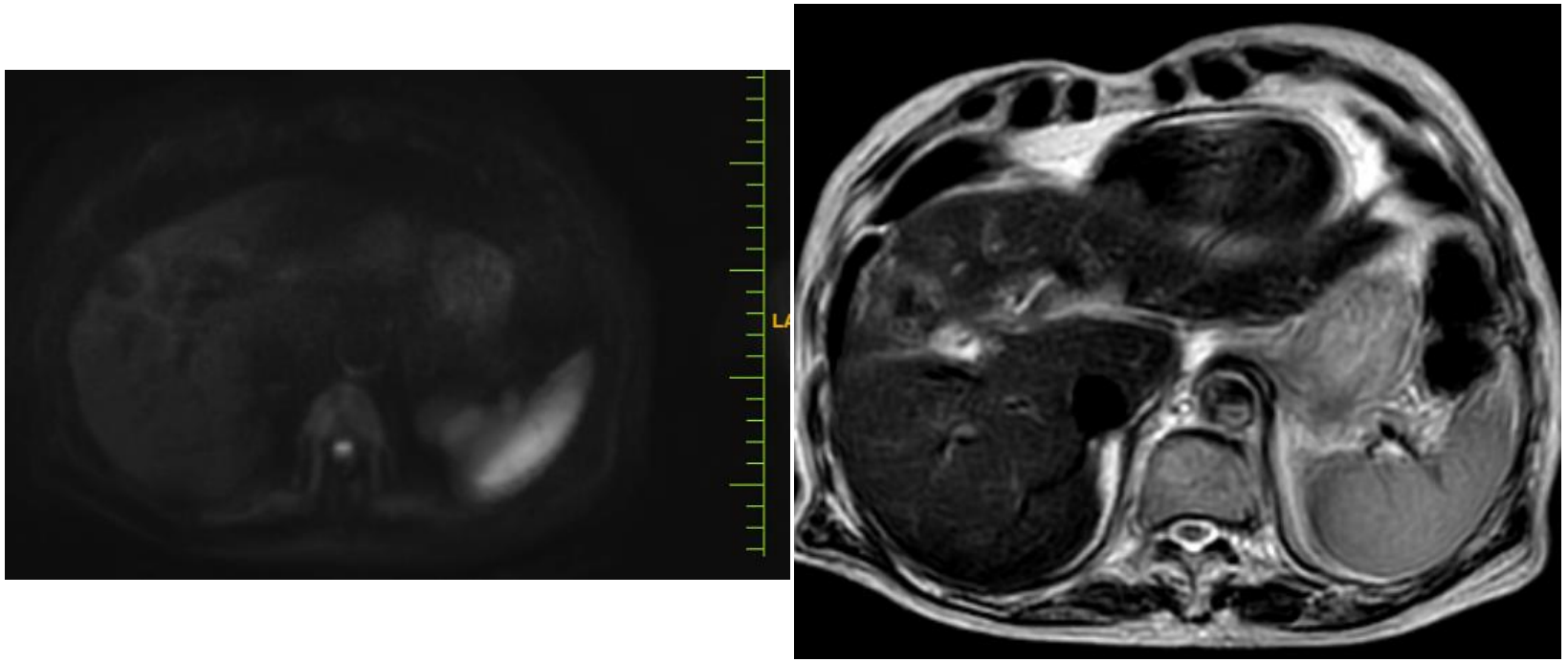
Pseudoprogression

- first described in patients with metastatic melanoma (5–15%)
- 6.9% in non–small cell lung cancer,
- 5–7% in renal cell carcinoma, and
- 1% in head and neck cancer
- Progression at the first response assessment is **usualy the true progression except when patient's clinical condition shows concurrent improvement**

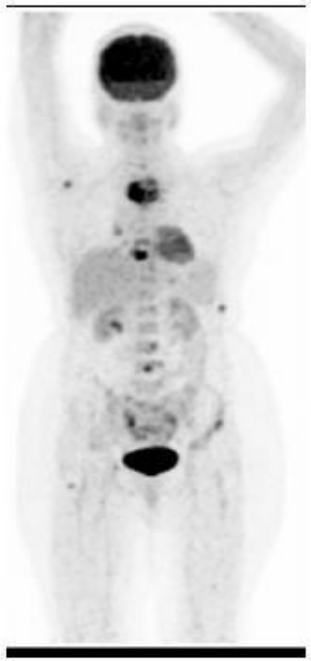


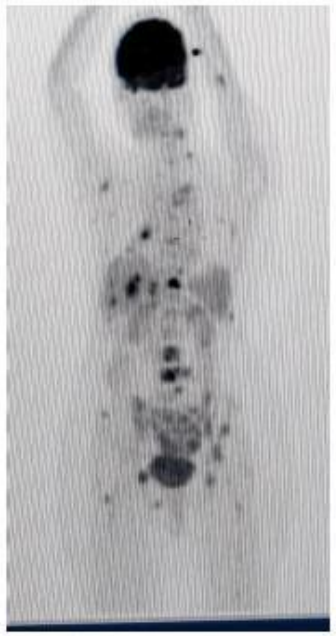
iUPD

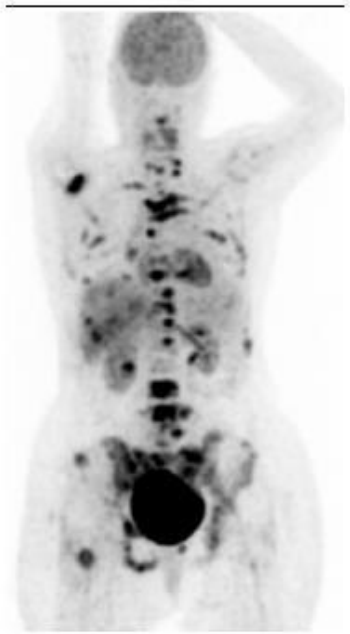
HCC on Immunotherapy

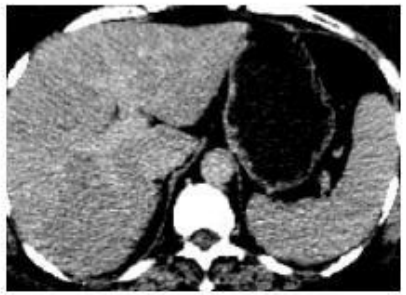


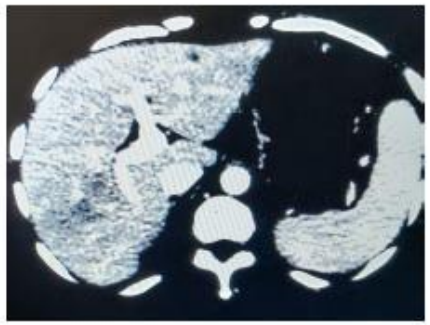
iSD

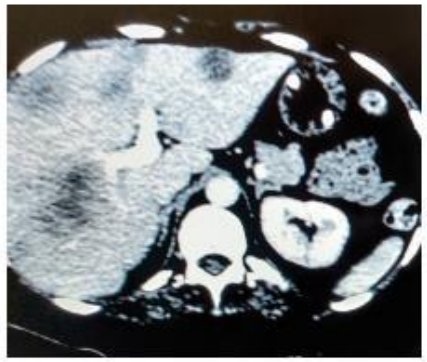












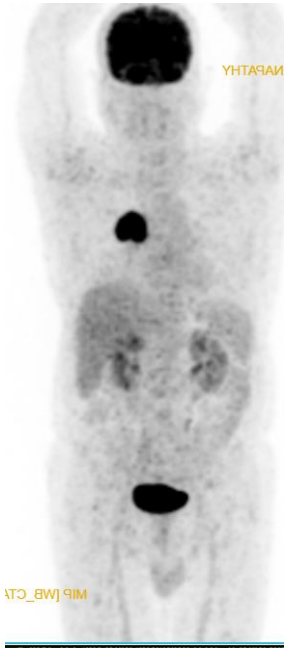
PET CT images - NSCLC right lung metastases to liver, shows progression after 3 months of nivolumab treatment and assigned IUPD, which worsened 8 weeks later confirming progression.

True PD

iCPD

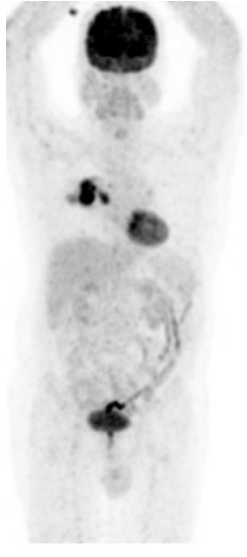
SD

3rd Aug 2022



17th Nov 2022

CT



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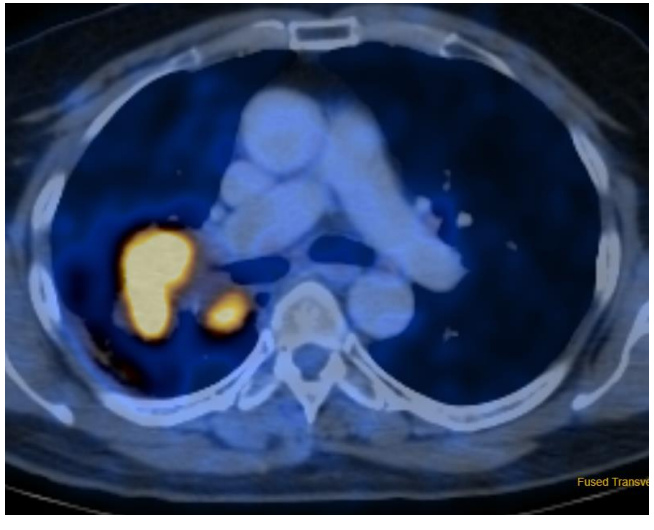
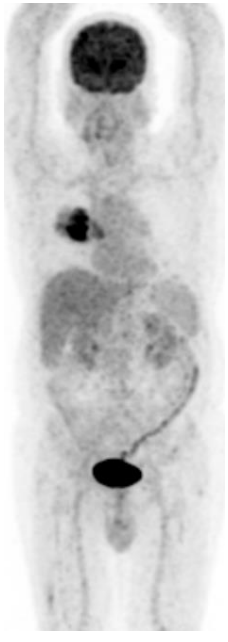
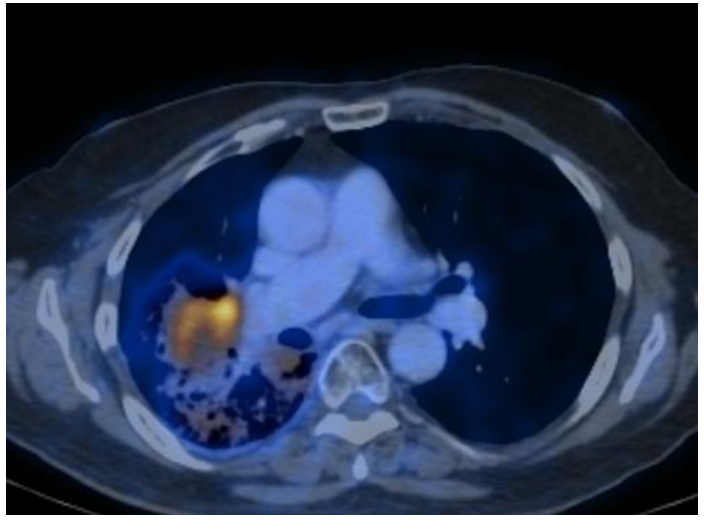


Immuno therapy



6th June 2023

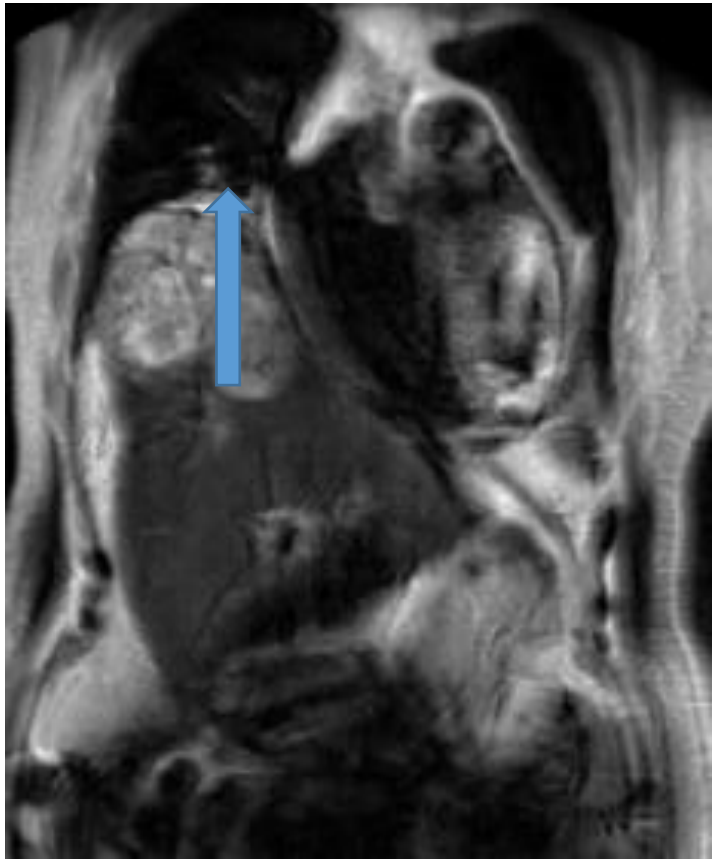
SD



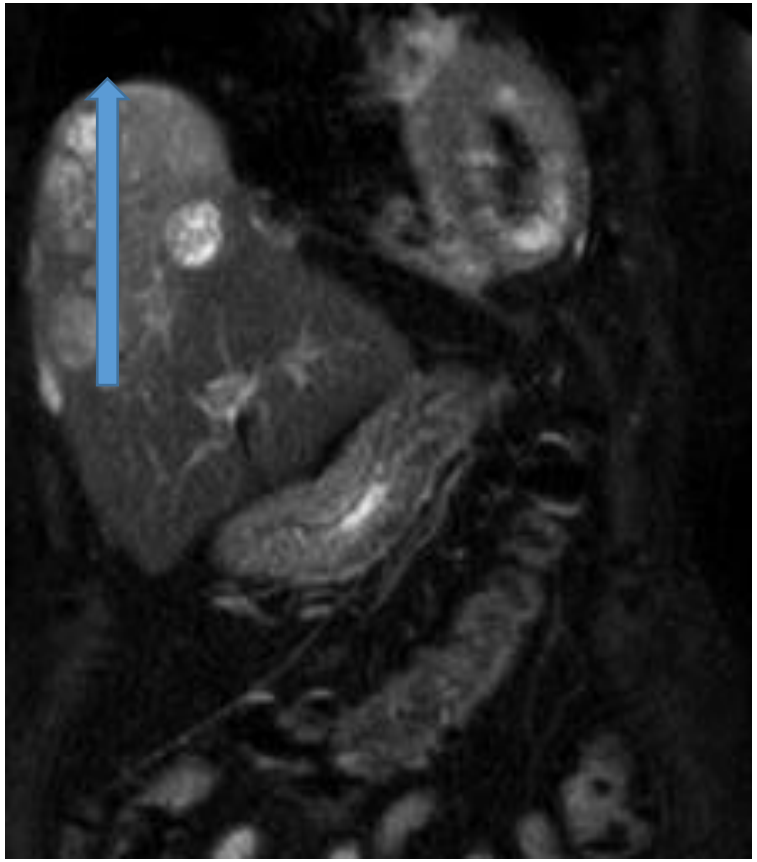
Hyperprogression

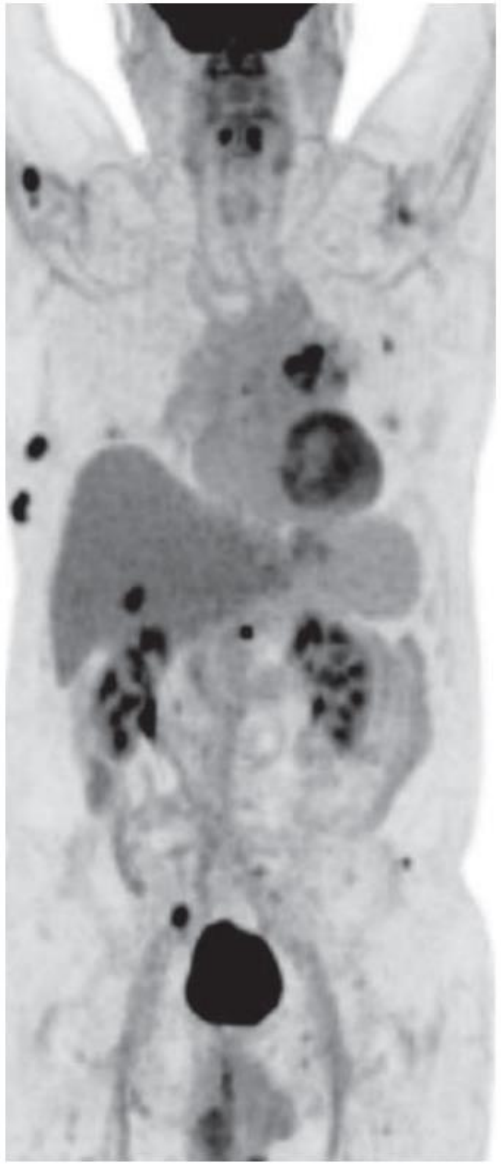
- A twofold or greater increase in the tumor volume growth rate during immunotherapy, time to treatment failure of less than 2 months, and clinical deterioration
- 4–28% of patients treated with immunotherapy
- More common with anti–PD-1/PD-L1 agents than anti–CTLA-4 therapy
- Possible mechanisms include changes in the tumor immune microenvironment during Rx, exacerbation of the suppression of innate immunity, activation of oncogenic signaling, and tumor-promoting cytokines

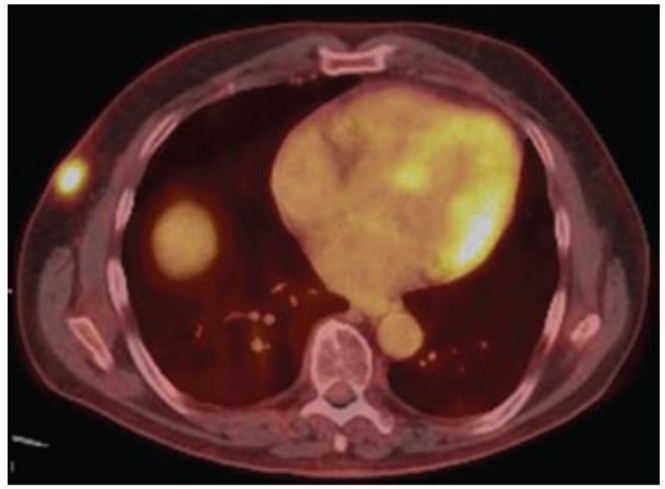
Hyperprogression

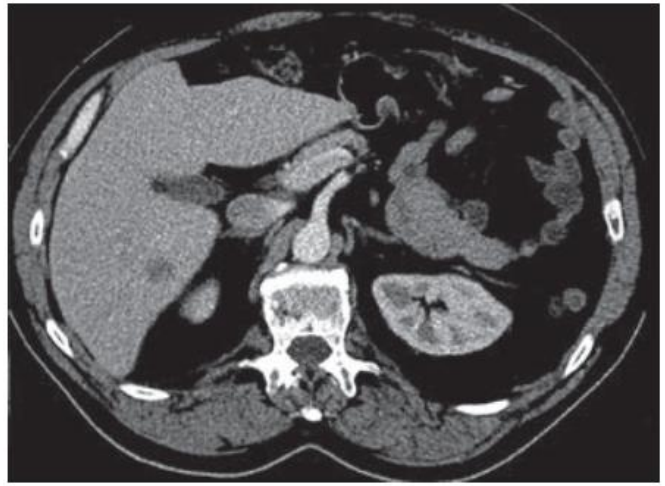


HCC progressed on CT and started on immunotherapy – worsened clinically and tumor burden almost doubled on 1st follow up imaging and died 1 month later

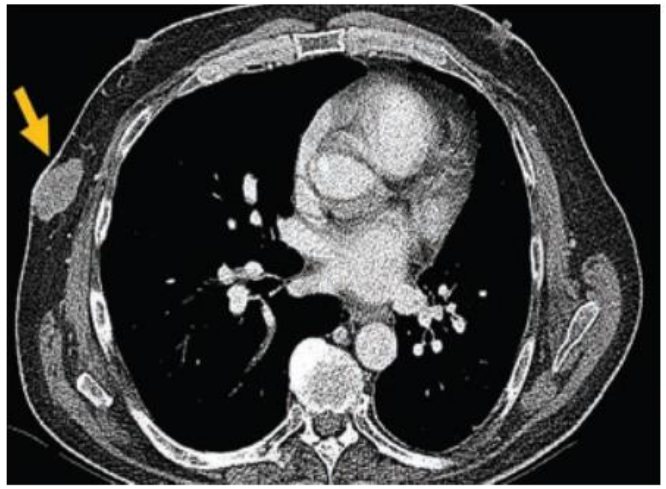


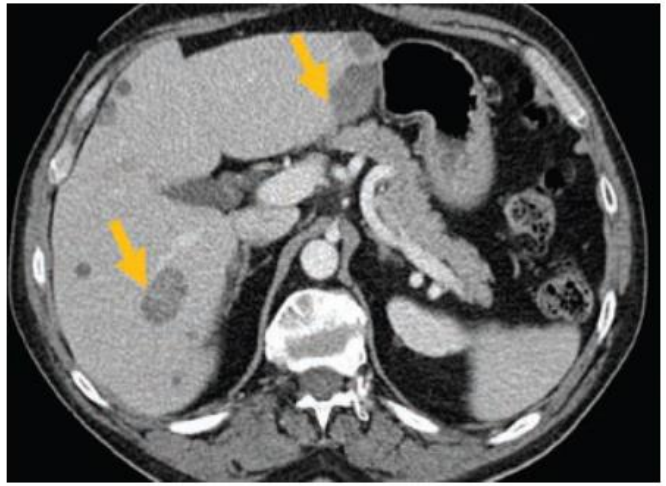




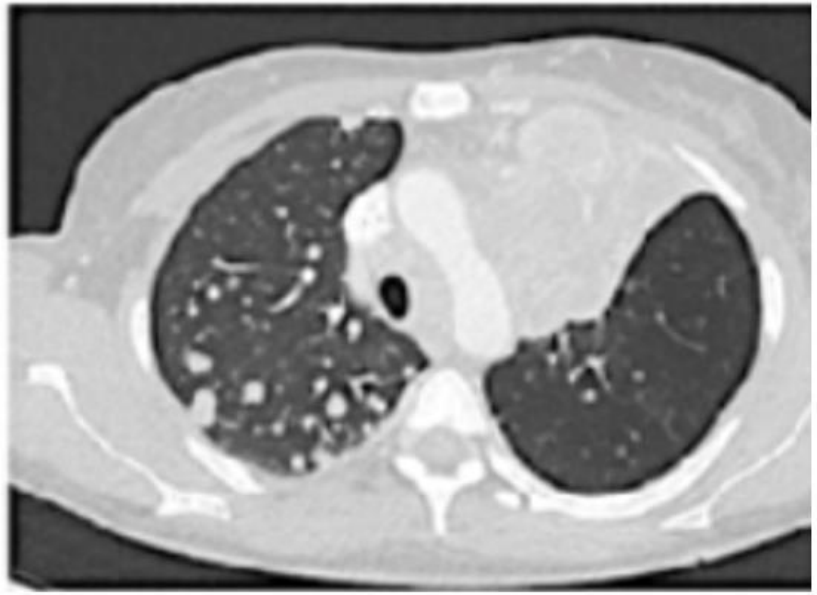


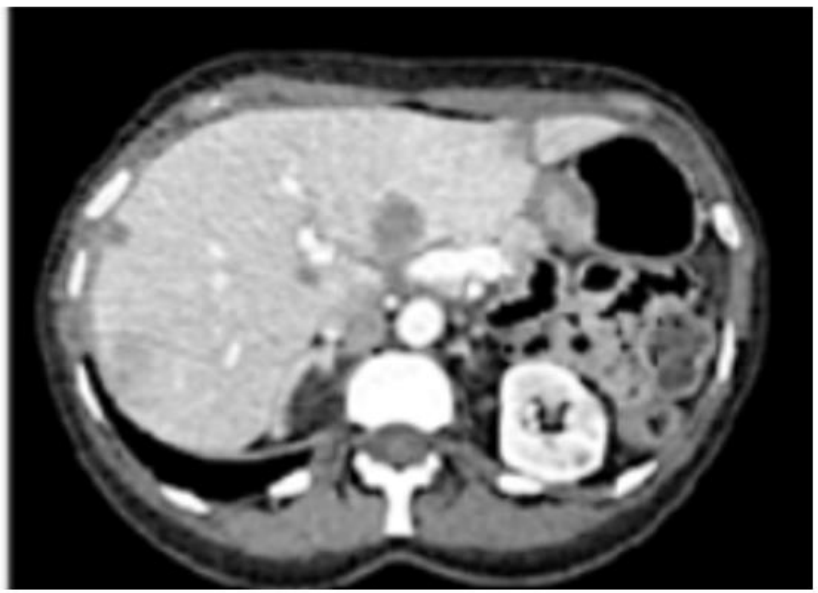
Melanoma
-
nivolumab
&
ipilimumab



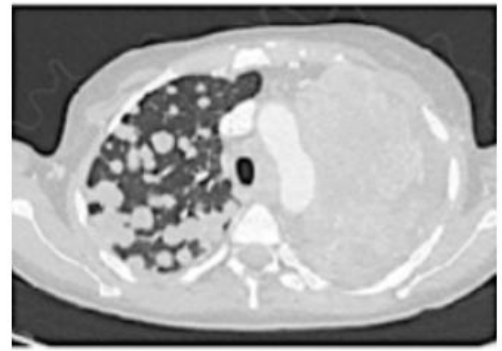


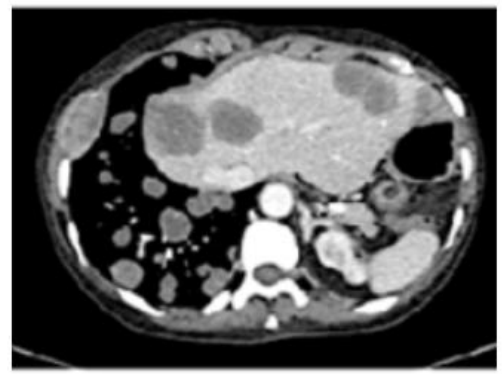
Scan after 4 weeks - hyperprogression

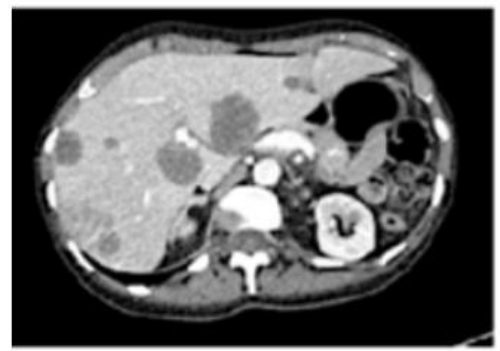




Nivolumab started as 4th line after PD with chemo – metastatic lung cancer - hyperprogression within 6 weeks – died after a couple of months

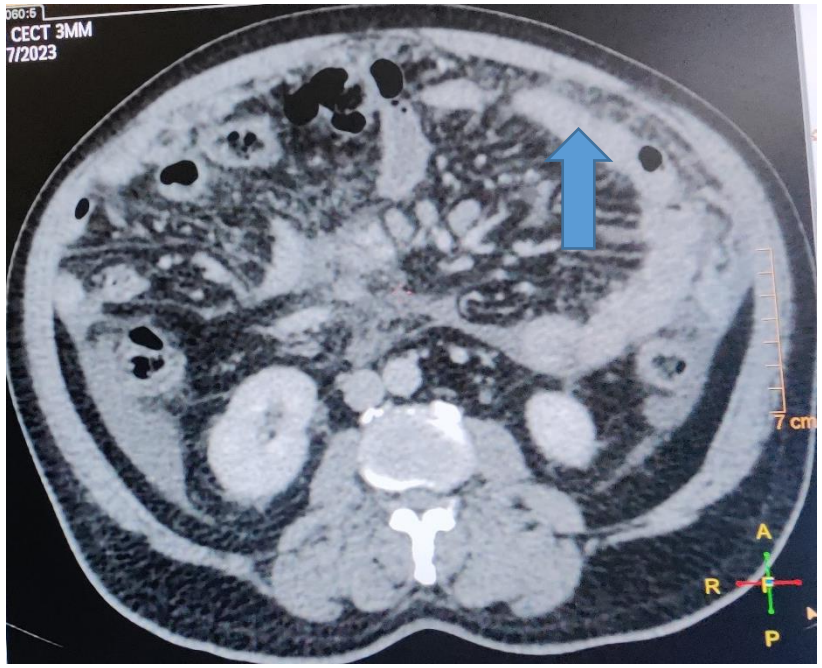




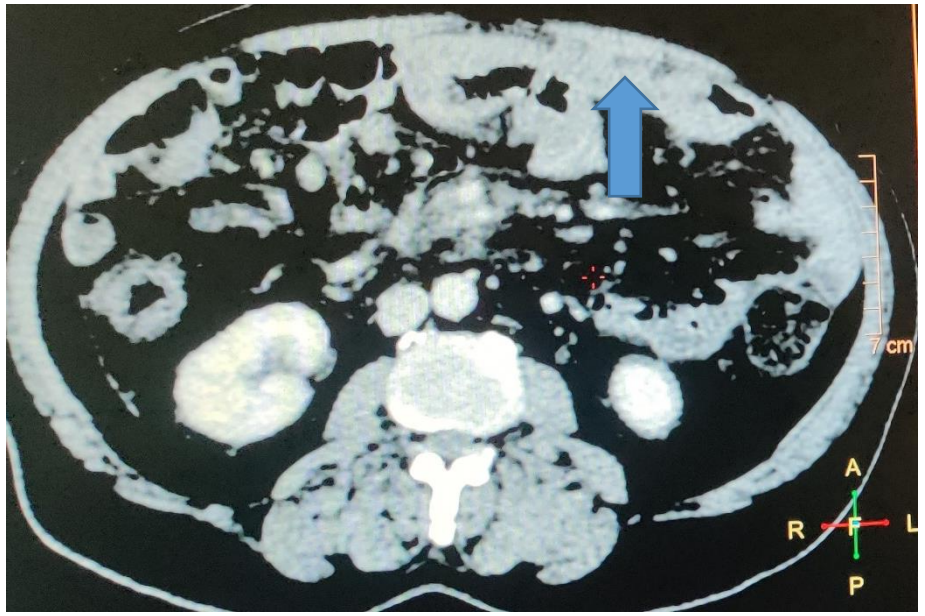


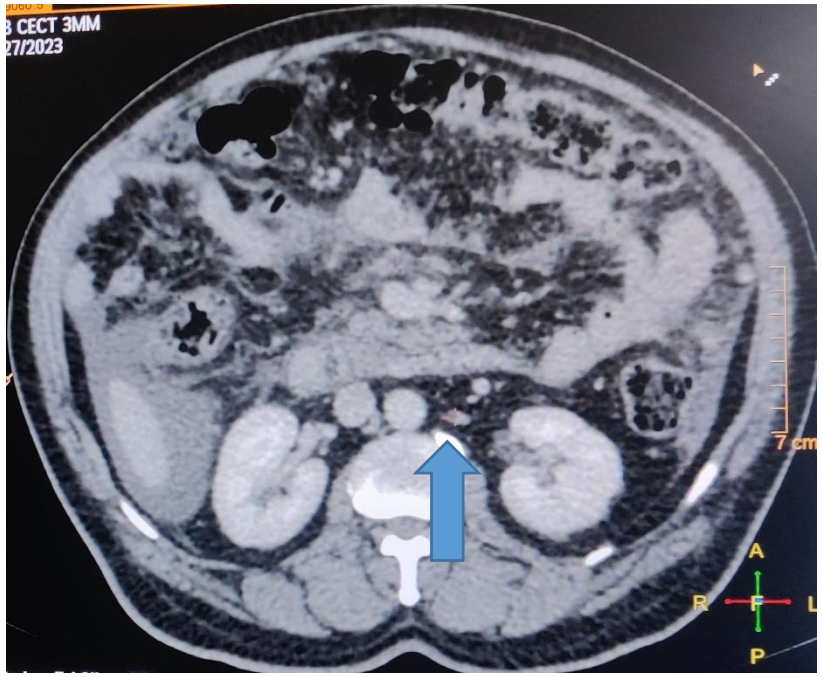
Dissociative response

- up to 10% of patients with coexistence of responding lesions and nonresponding lesions; oligoprogression – increase of only a few lesions
- first detected with pts of NSCLC on anti-PD-1/PDL-1 therapy
- benefit from continuation of ICI therapy and local ablative treatments to the growing lesions
- To be assigned at later time points of disease progression, rather than on the first follow-up examination only

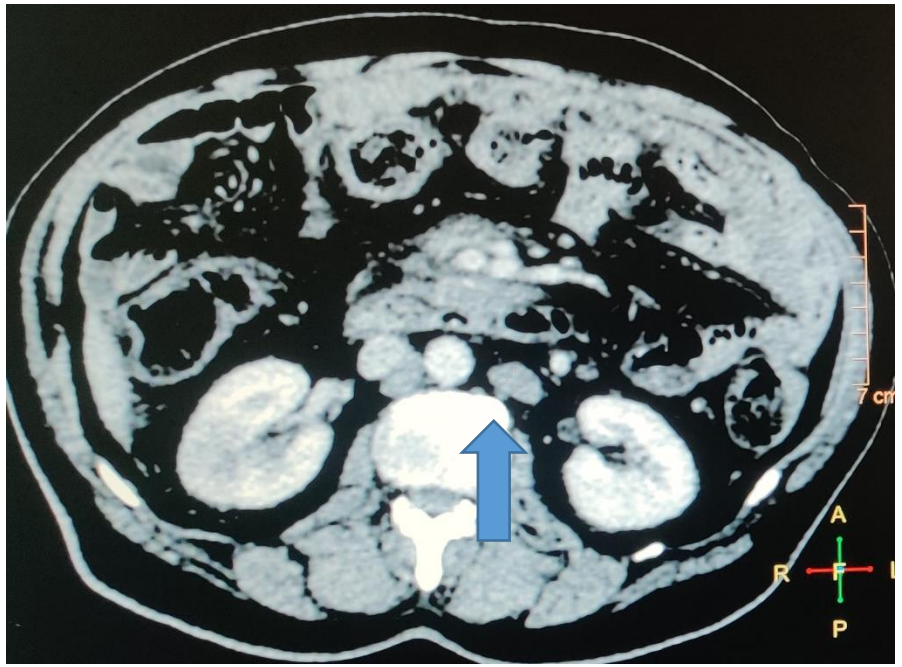


Advanced metastatic carcinoma on immunotherapy





First follow up scan reveals regression of peritoneal disease and ascites BUT increase in the retroperitoneal nodes – assigned iUPD



Durable response

- Delayed but durable response even after treatment cessation; progression-free survival (PFS) exceeds three times the median PFS of the patients receiving the same therapy

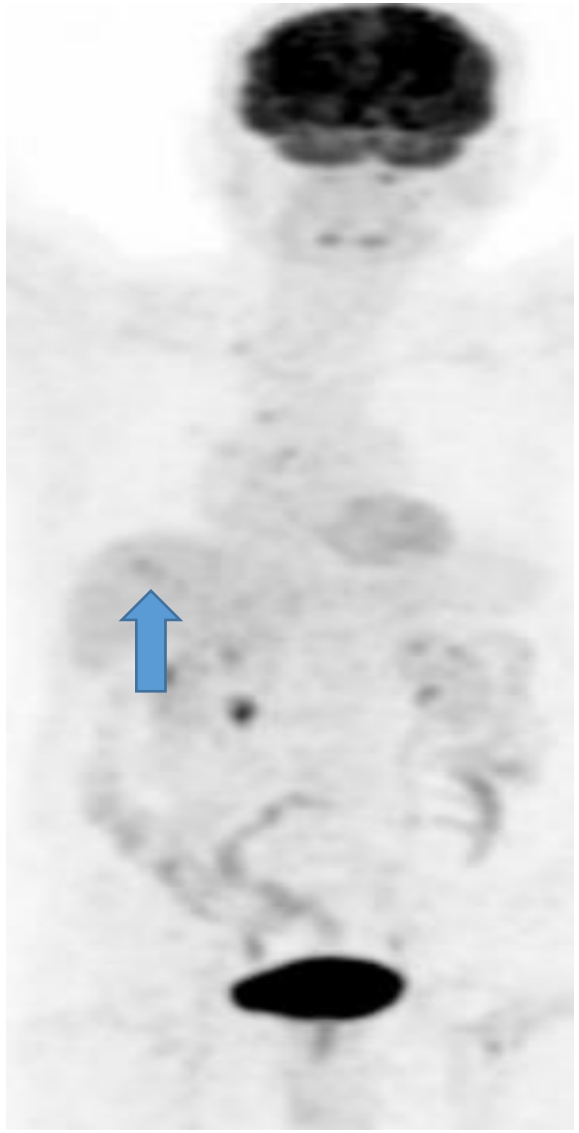
- ICIs - 2.3 times more likely to achieve durable response compared to chemotherapy or targeted therapy

- Controversial whether immunotherapy should be interrupted after a certain treatment duration or whether it should be continued until disease progression.

- Future studies to investigate predictors of durable response to immunotherapy

85 y M

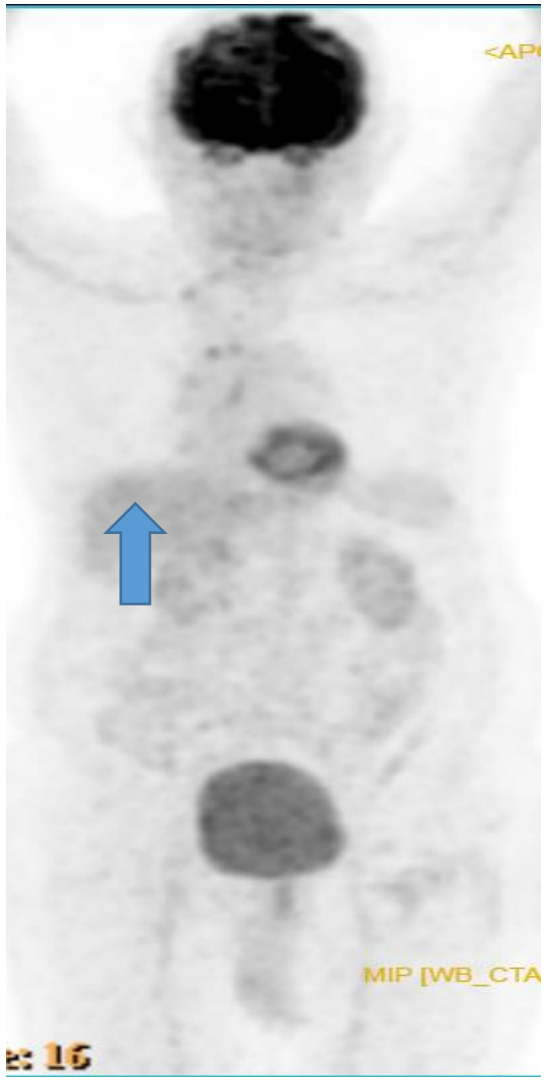
Progressive HCC 18th May 2020

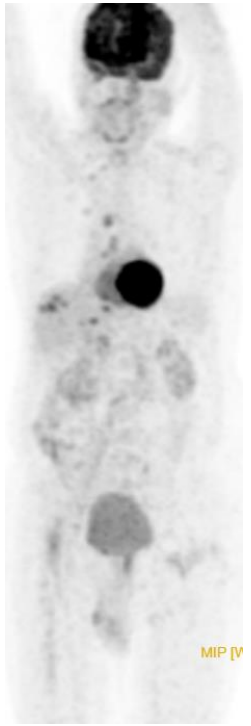


On bevacizumab plus atezolizumab-

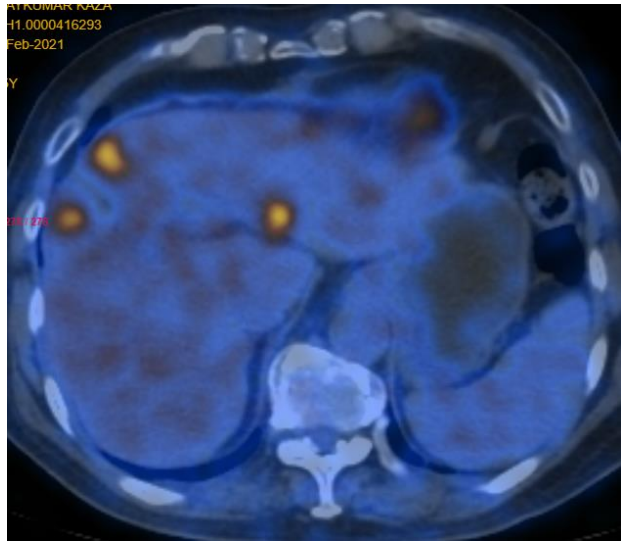
PR

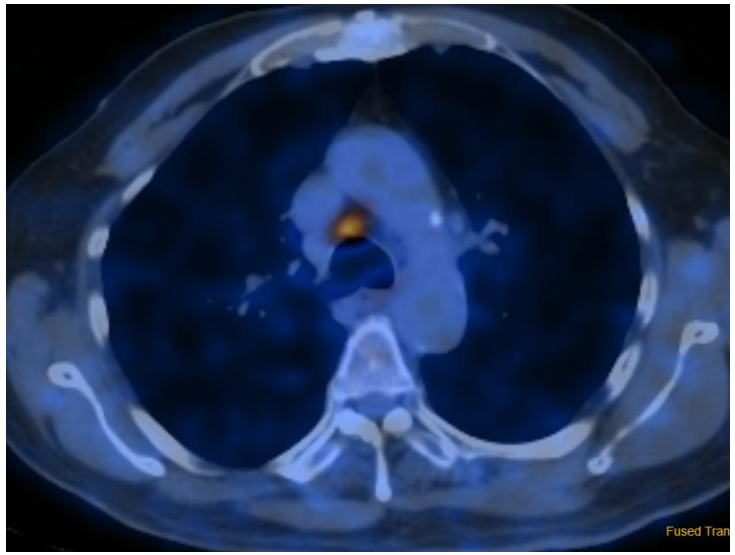
7th Sep 2020

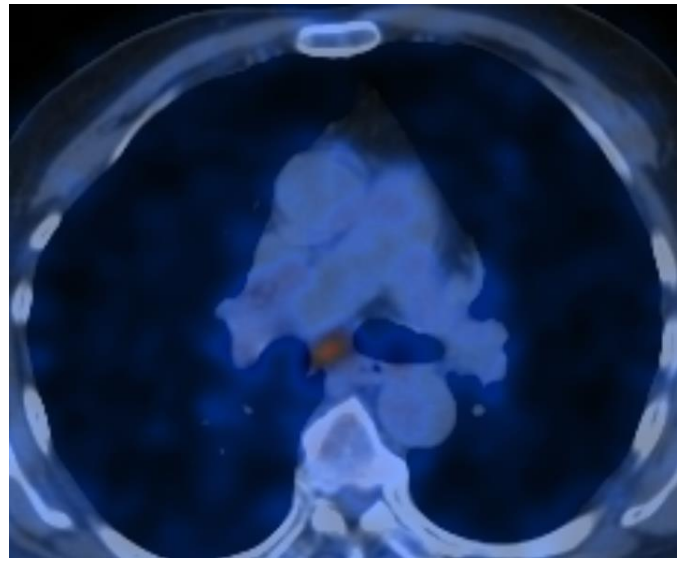


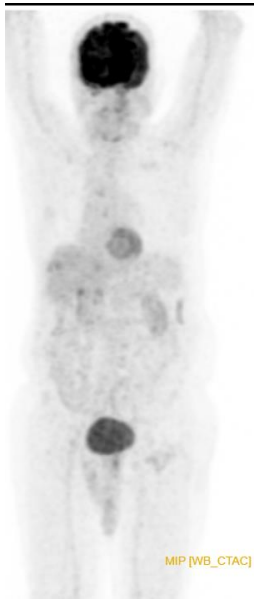


23rd Feb 2021 iUPD

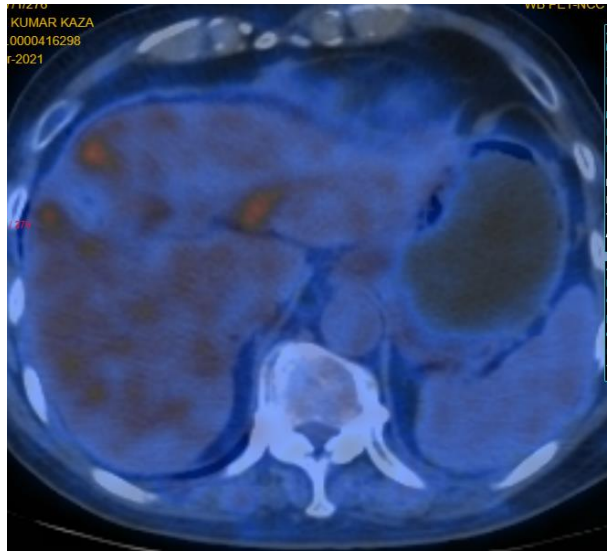


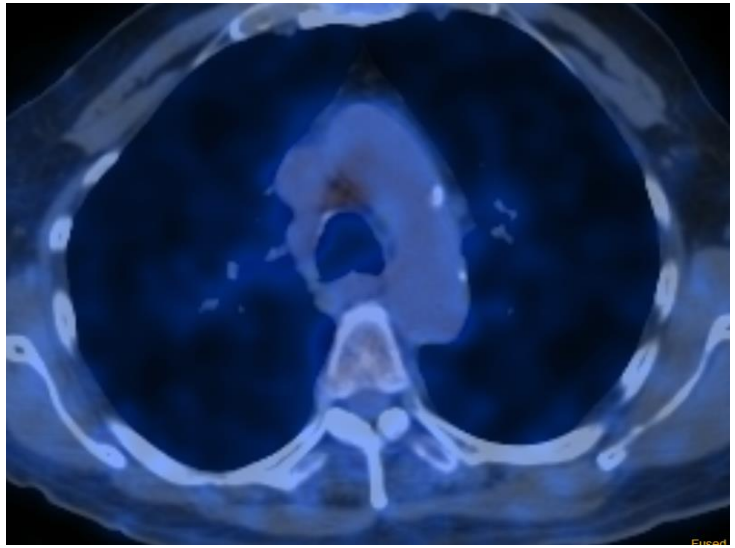


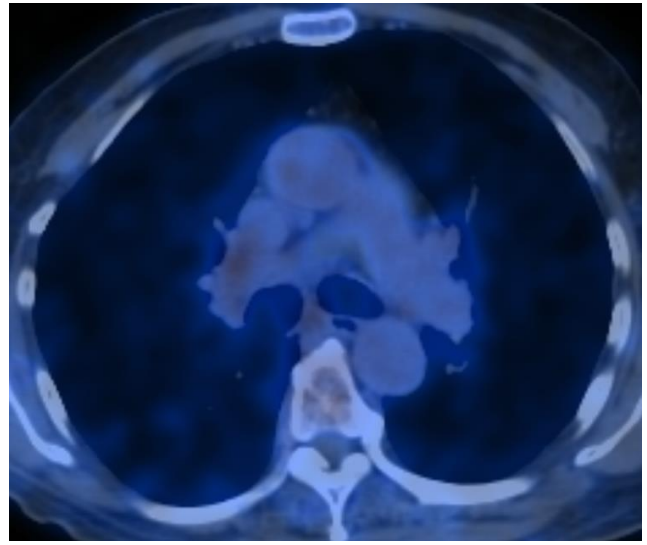


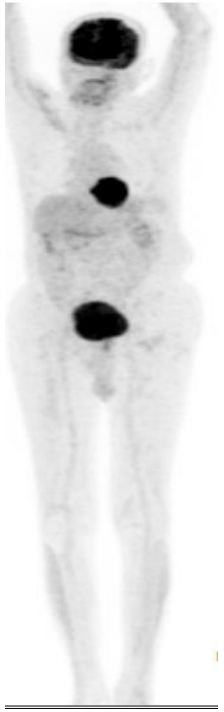


26th Apr 2021 iSD

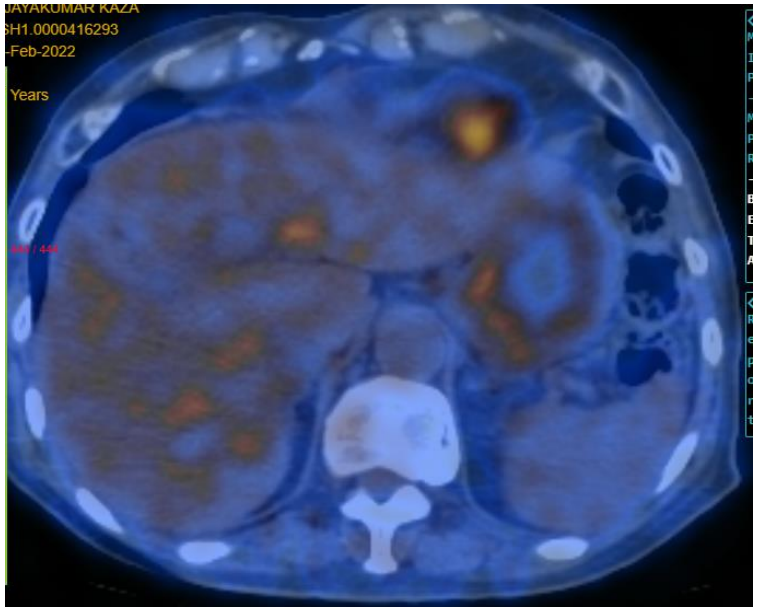


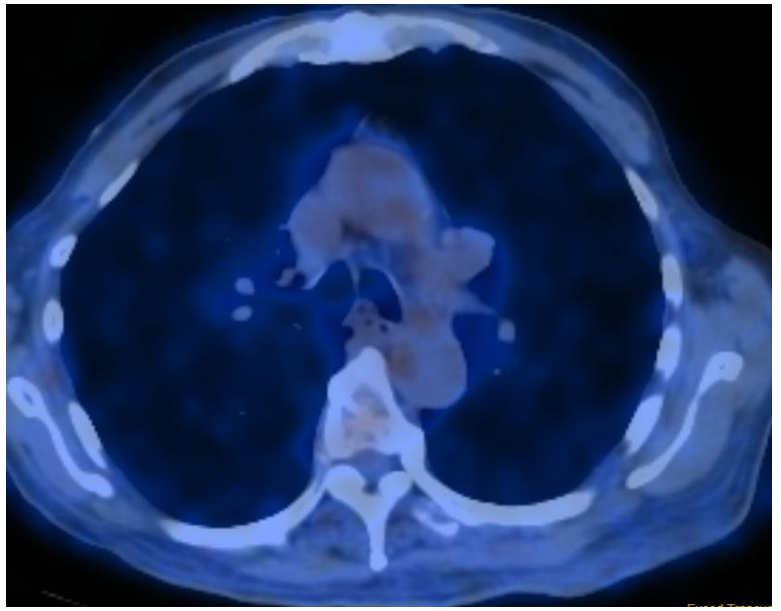


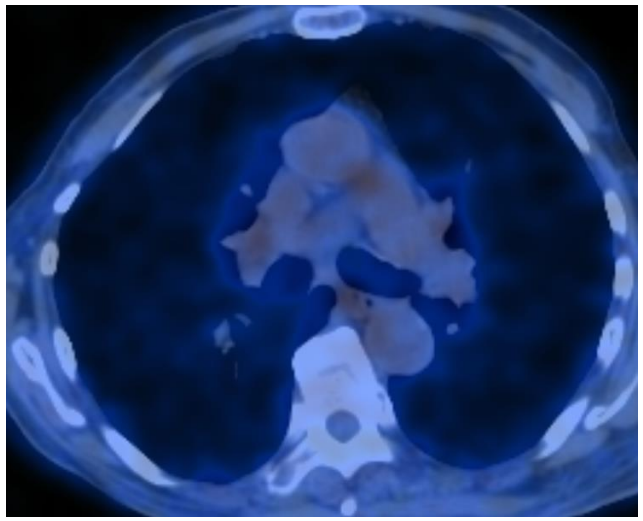


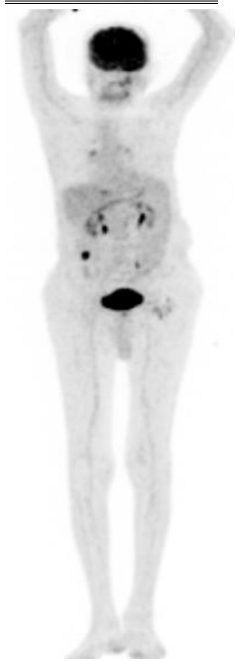


11th Feb 2022 - SD – cessation of therapy

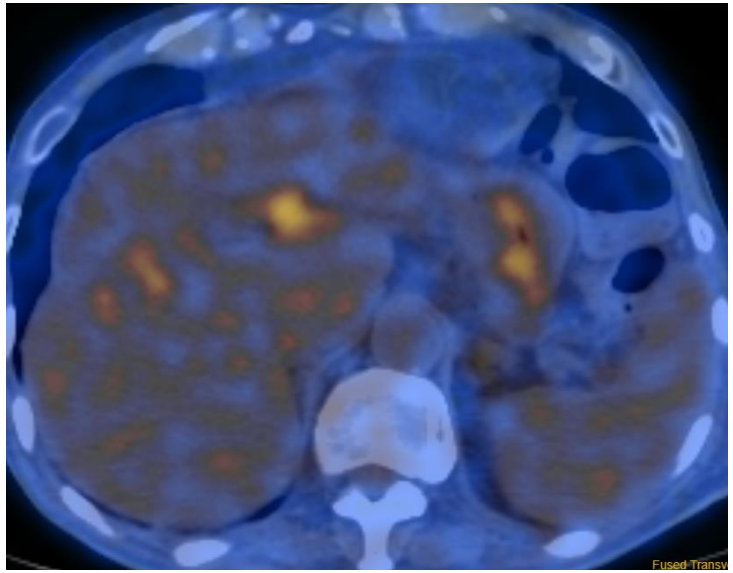


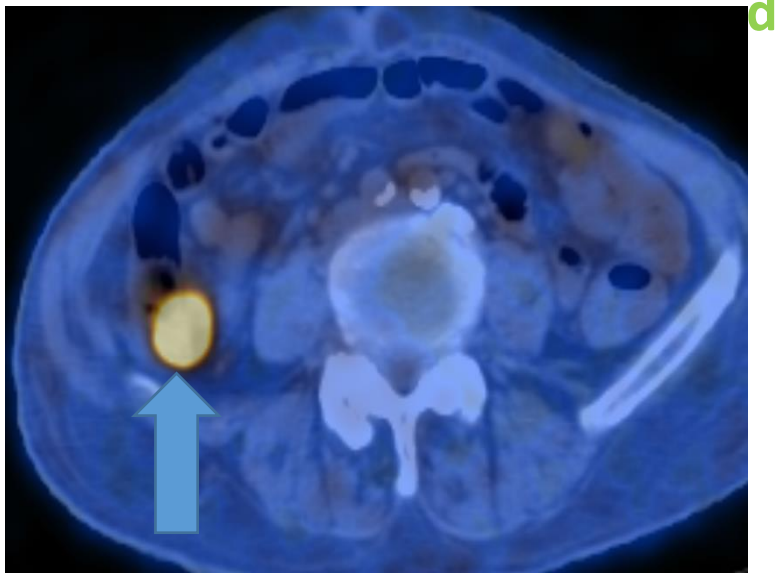




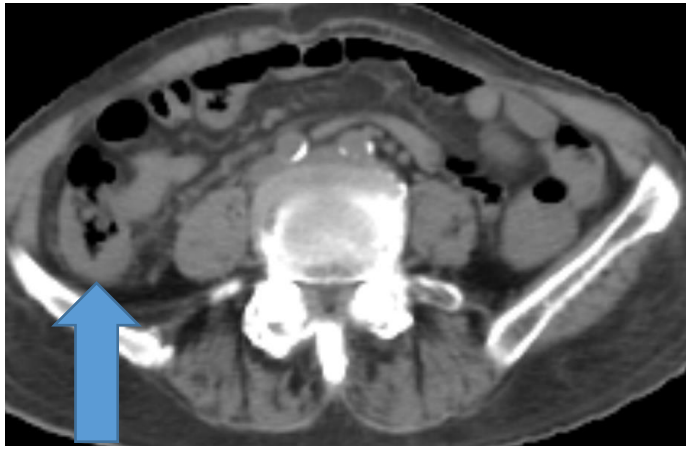


5th Nov 2022 - SD





Operated for Ca. Cecum and doing well !!!!

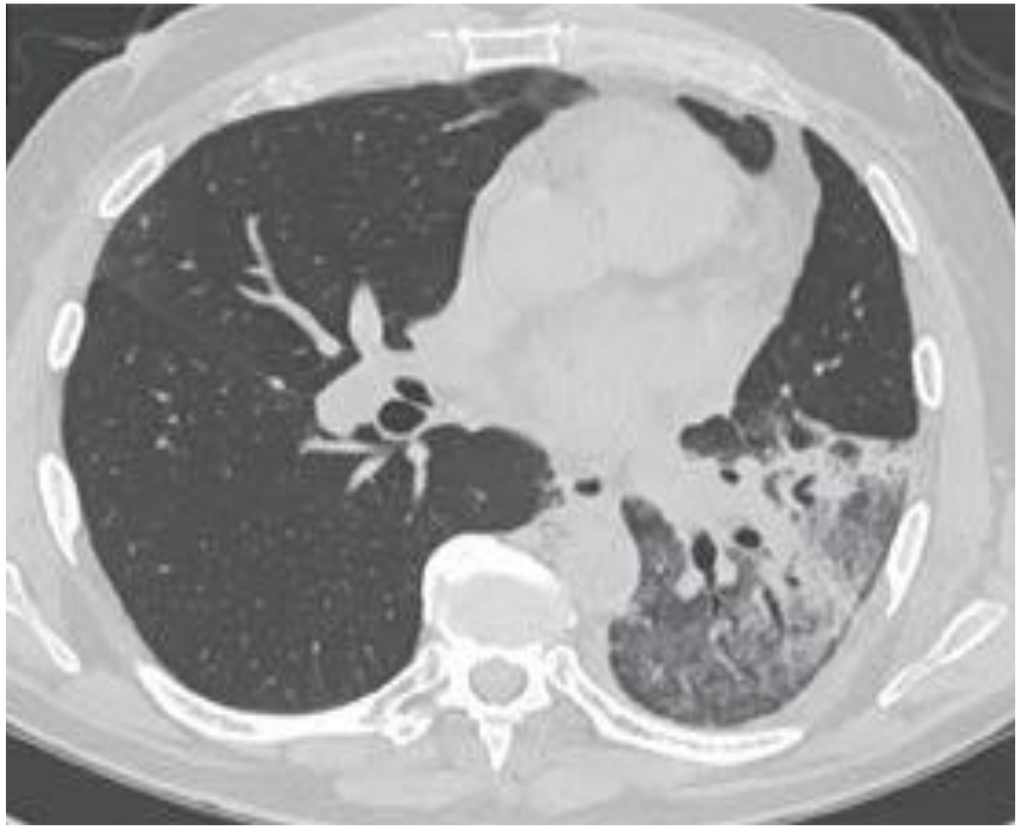


AEs

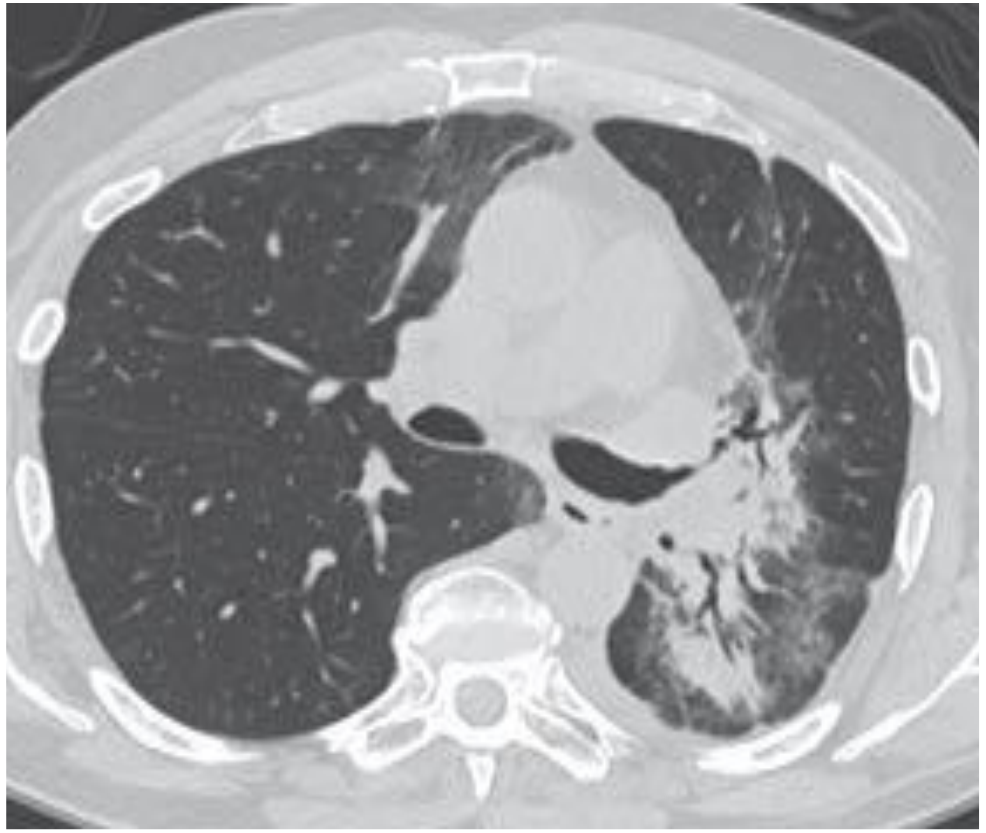
- dose dependent
- skin, gastrointestinal tract, and lung - more vulnerable
- pneumonitis and thyroid disorders more common with anti–PD-1/PDL-1 therapy,
- hypophysitis and colitis more common with anti–CTLA- 4 antibodies
- Pneumonitis first detected by imaging, before symptom onset
- Prompt identification needed

Organ System	Reported Time to Onset (wk)[a]			irAE	Incidence (%)		Radiologic Manifestation
	Monotherapy (PD-1/PD-L1)	Monotherapy (CTLA-4)	Combined Therapy		Monotherapy	Combined Therapy	
Skin	6.1	3.6	2.4	Pruritis, rash	Up to 12.1	Up to 24.0	NR
Gastrointestinal	8.9	5.0	5.0	Diarrhea Colitis	11.2 0.8	27.9 7.3	Bowel wall edema with adjacent mesenteric stranding Colitis patterns: diffuse colitis (most common, up to 75%), segmental colitis associated with diverticulosis (25%), and isolated rectosigmoid colitis without diverticulosis
Pulmonary	10.7	10.0	10.0	Pneumonitis Infection	1.5–3.0[b] 4.6	7.5–10.0[b] 2.6	Pneumonitis patterns: cryptogenic organizing pneumonia (most common pattern), NSIP, and diffuse alveolar damage
Hepatobiliary	12.3	8.9	6.1	Increased AST or ALT Increased amylase Pancreatitis	4.8 3.9 NR	13.4 10.7 NR	Hepatitis or cholangitis: nonspecific, normal or may show hepatomegaly, periportal edema, diffuse decreased parenchymal attenuation, or biliary ductal dilation without obstruction Pancreatic edema with peripancreatic fatty stranding, intense FDG uptake in pancreas
Musculoskeletal	NR	NR	NR	Myalgia Arthralgia	3.2–4.9[b] 6.2–9.4[b]	11.9 14.6	Inflammatory myositis or arthritis: thickening or hyperenhancement of the fascia or muscles, increased FDG uptake within muscles, fascia, or joints
Endocrine	12.0	9.0	8.0	Hypothyroidism Hyperthyroidism Adrenal insufficiency Pituitary hypophysitis	6.5 2.3 1.0 0.5	15.2 10.6 5.7 8.4	Thyroiditis: nonspecific, diffuse homogeneous increased uptake in thyroid gland Adrenalitis: bilateral enlargement of the adrenal glands with mild increased FDG uptake Hypophysitis: enlarged pituitary gland and stalk with heterogeneous enhancement, subtle increased FDG uptake
Neurologic	NR	NR	NR	CNS: aseptic meningitis, encephalitis, myelitis PNS: peripheral neuropathy including Guillain-Barré syndrome, myasthenia gravis	3.8–6.1[b]	12.0	Wide spectrum of imaging findings; may be normal or may show leptomeningeal enhancement or abnormal signal on MRI involving basal ganglia, limbic system, splenium of the corpus callosum; posterior reversible encephalopathy; demyelinating lesions; thickening and enhancement of the nerve roots and cauda equina
Cardiac	4–9	4–9	4–9	Myocarditis, pericarditis, ventricular arrhythmia	Up to 0.4	Up to 1.1	MRI showing edema (i.e., T2 hyperintensity) and late gadolinium enhancement involving the subepicardial myocardium or pericardium; regional or global wall motion abnormalities Reference standard: endomyocardial biopsy

Metastatic NSCLC, developed SOB after 2 months of nivolumab and ipilimumab



Pneumonitis - COP



Improvement after steroids

GIT:

Diarrhea or colitis; 5–10 weeks

Colitis - most common cause of death among all individuals with irAEs

Diffuse colitis (most common; up to 75% of cases), segmental colitis associated with diverticulosis, and isolated rectosigmoid colitis without diverticulosis

CT scan - extent and severity of colitis and evaluation of possible perforation

Rx - depends on the rate of toxicity

Less common are ileitis, upper gastrointestinal tract involvement, hepatitis (hepatocellular and cholestatic patterns), and pancreatitis

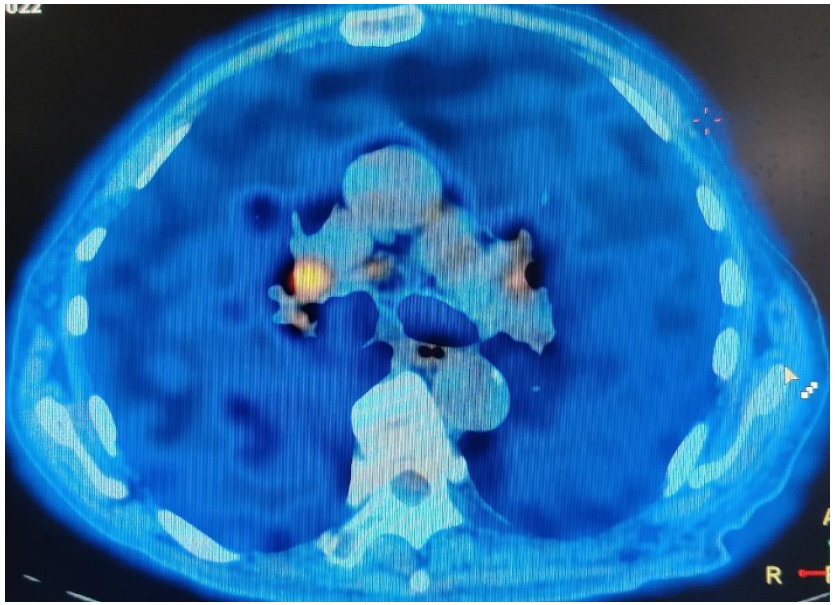
Lymphadenopathy and Sarcoidlike Reaction

Rare; 3–36 weeks

Mediastinal lymphadenopathy, pulmonary involvement, skin rashes, and, rarely, renal disease

New mediastinal and hilar lymphadenopathy can mimic disease progression

Treatment includes interruption of ICI treatment and corticosteroid initiation if there are significant symptoms or evidence of organ damage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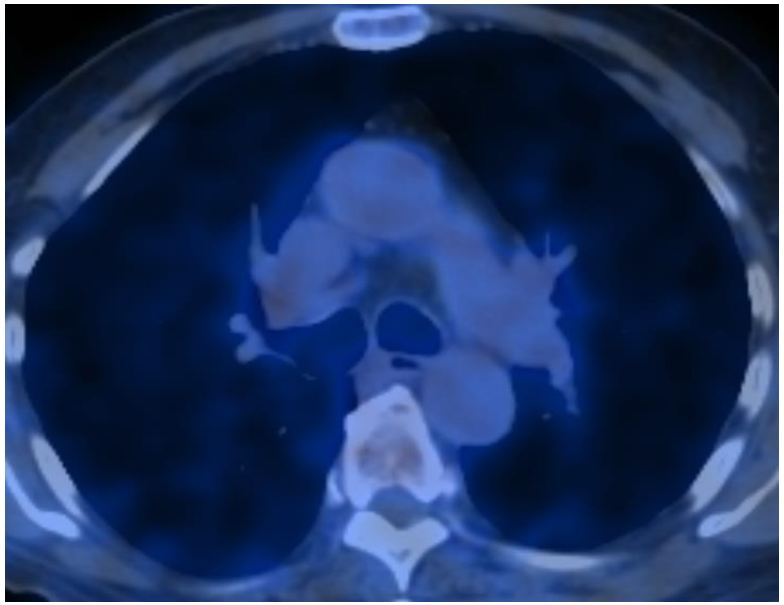
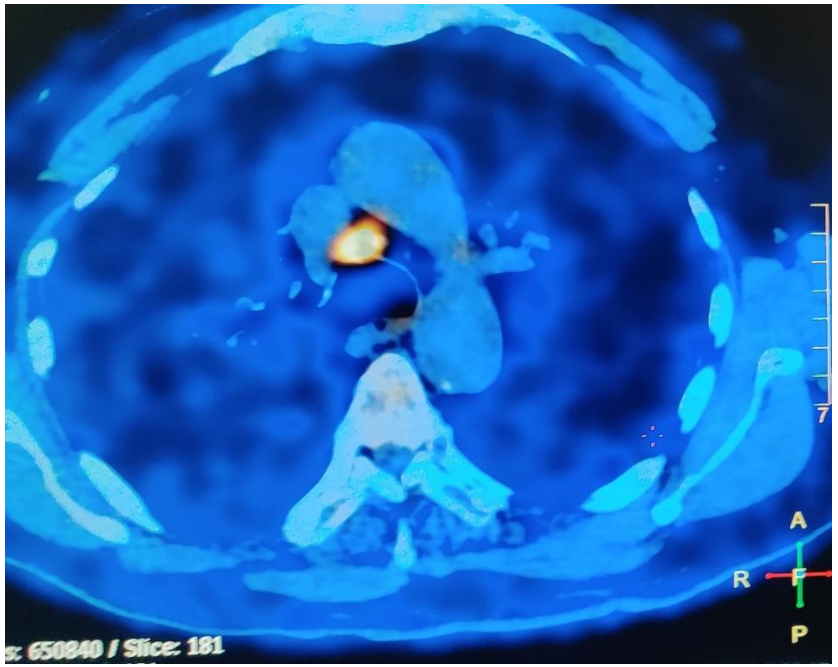
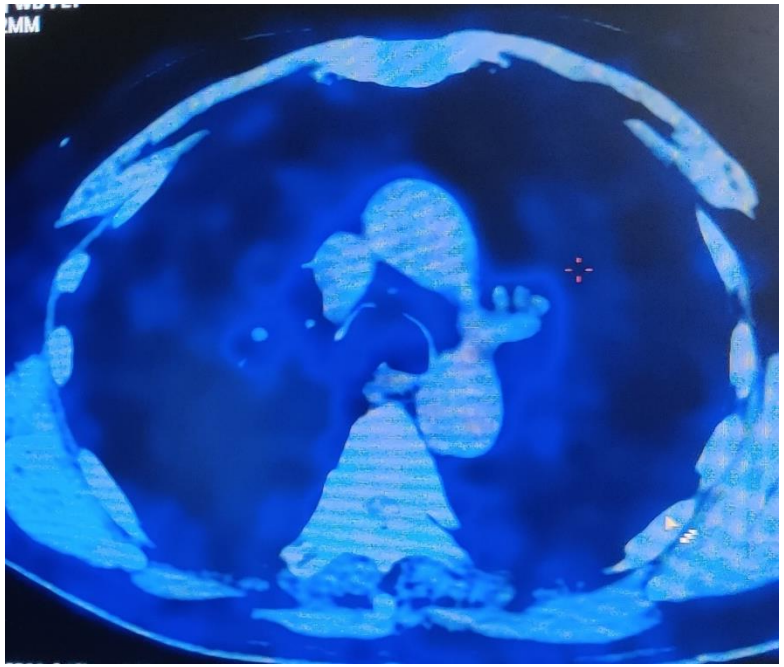



A
R
P
Slice: 181



Summary

- atypical response patterns - pseudoprogression, hyperprogression, dissociated response and durable response
- iRECIST, imPERCIST, LYRIC and mChoi
- PD requires confirmation at least 4 weeks later by imaging, to rule out pseudoprogression or delayed response
- Treat beyond progression ONLY if clinical improvement
- adverse events
- **However, “imaging progression is true progression more often than not”**

- THANK YOU