Novel oncologic therapies: what radiologists have learned so far

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Learning Objectives

- The **objectives** of this work are:
  - Brief overview of new oncology drugs: targeted drugs and immunotherapy
  - Key points of response patterns according iRECIST
  - Examples and discussion of events related to new oncologic treatments, including clinical and imaging findings

- **Imaging findings**:
  - Treatment response patterns according iRECIST - partial response, complete response, stable disease, unconfirmed progression and confirmed progression
  - Targeted-related adverse events: fistulas, pneumatosis, bleeding
  - Immune-related adverse events: pneumonitis, hepatitis, pancreatitis, diarrhea and nephritis

Background

- **Traditional cytotoxic chemotherapies** destroy rapidly growing cells, and act on the mechanism of cell division

- **Targeted drugs** are intended to interfere with specific aberrant molecular mechanisms involved in the development of tumors, for example, associated with tumor antiangiogenesis

- **Immunotherapy** uses immune system responses to treat cancer

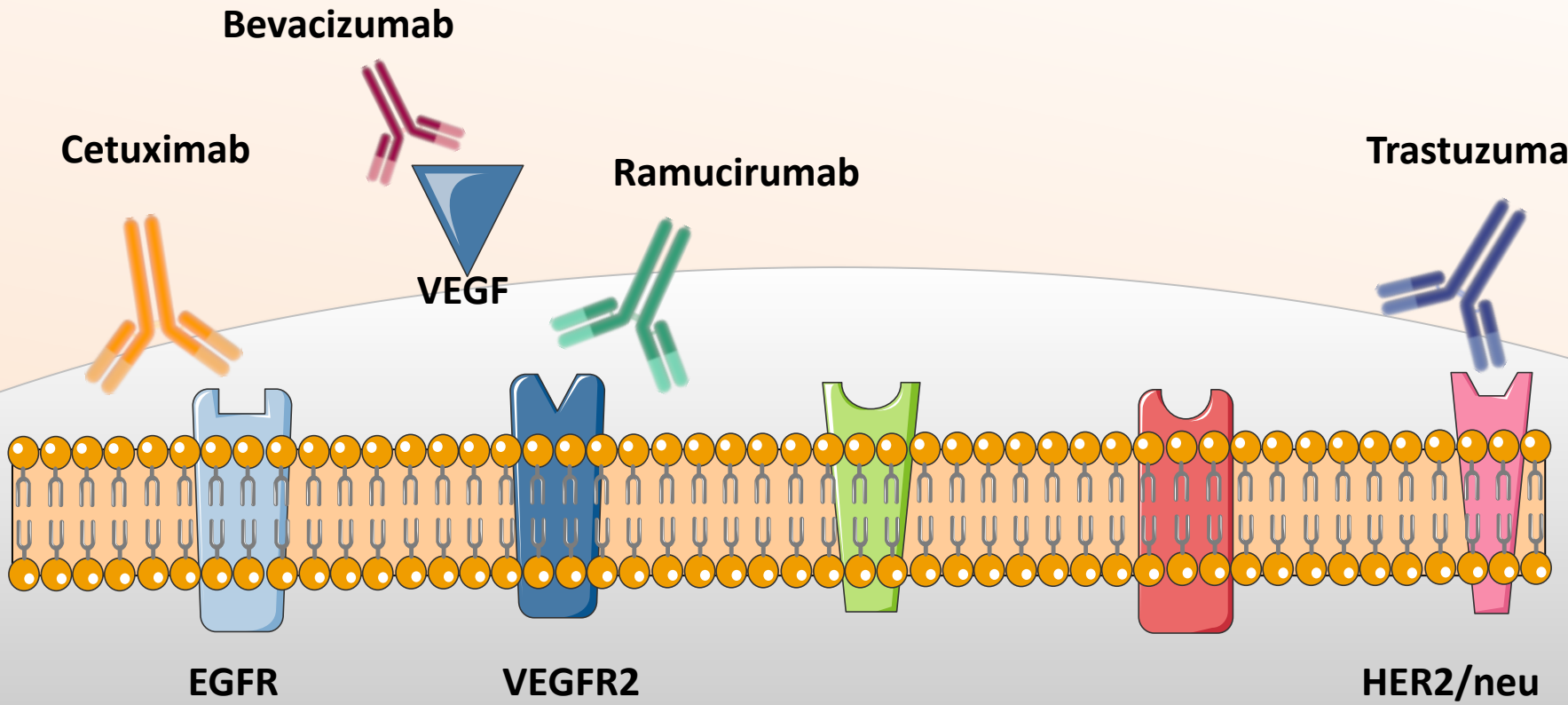
Targeted drugs

- The advantage of target drugs is to act more accurately and with fewer side effects

- In general, these drugs are classified into:
  - monoclonal antibodies (e.g. bevacizumab, cetuximab)
  - tyrosine kinase inhibitors (e.g. sorafenib, imatinib)

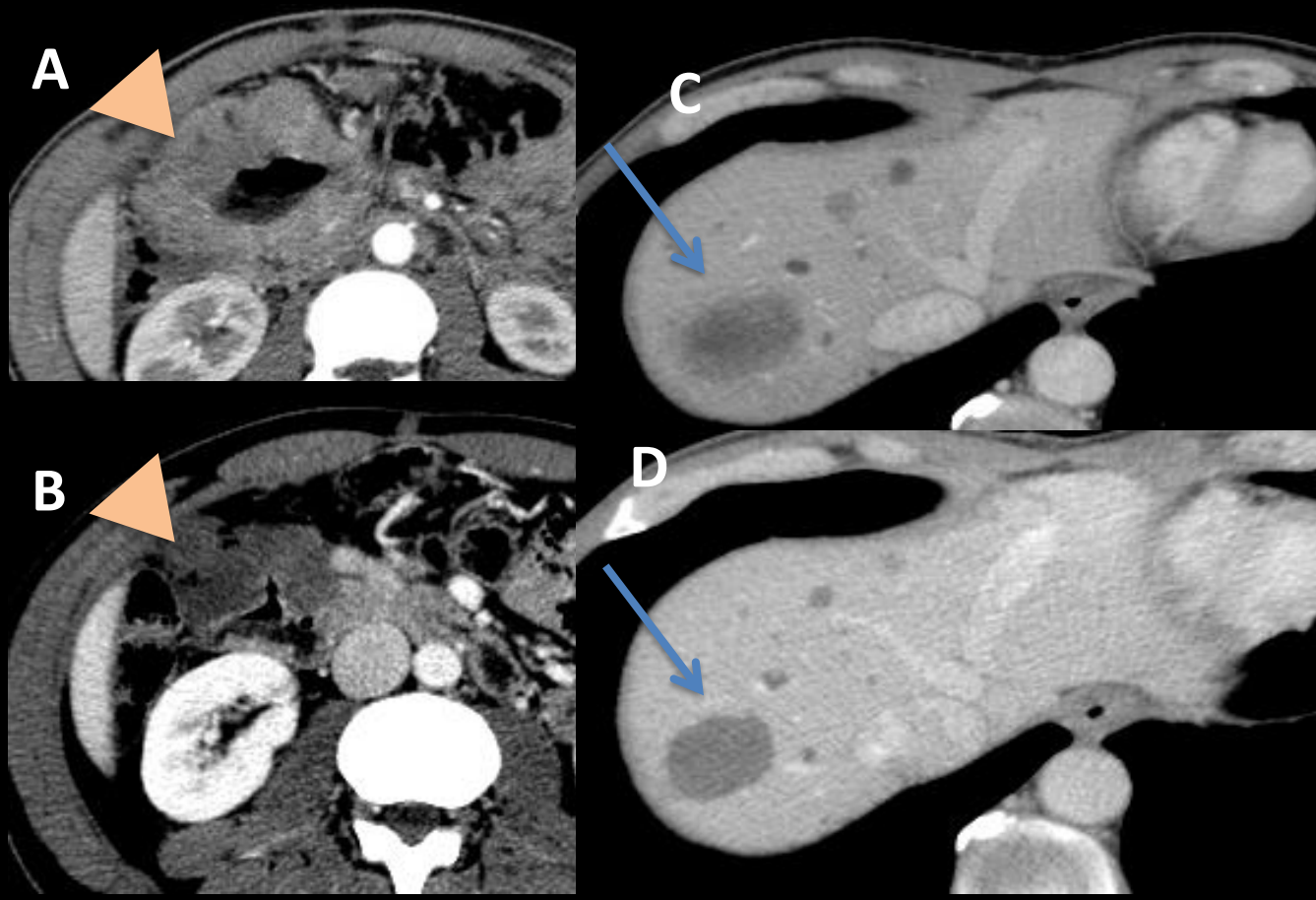
- Are currently used in various tumor therapy, such as:
  - breast, colorectal, renal cells, glioblastoma multiforme, neuroendocrine, melanoma, gastrointestinal stromal tumors (GIST) and leukemia.

Targeted drugs



Response to targeted drugs

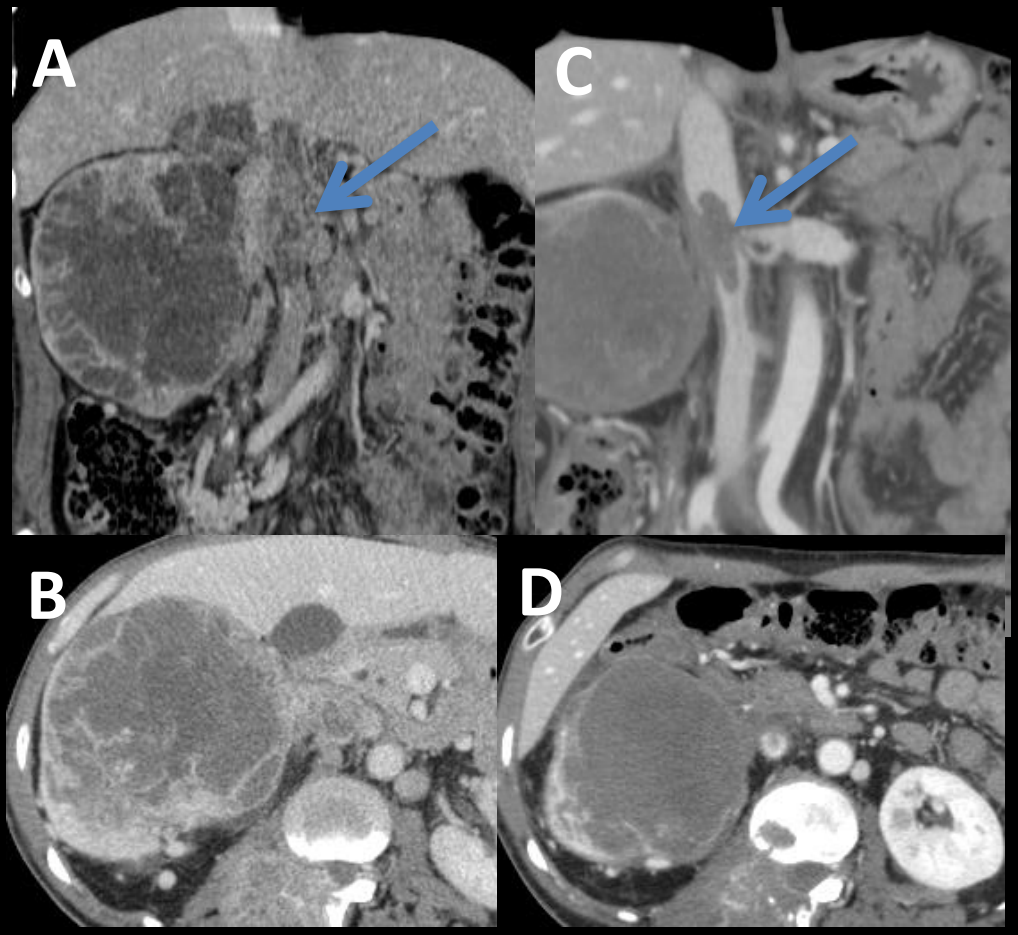
- Imatinib is the first-line treatment for metastases, unresectable lesions or recurrence of GISTs
- Mean survival of patients with advanced GIST increased from 18 to 57 months with the use of Imatinib
- After treatment, the lesions may reduce in size or remain stable, acquiring a "cystic" appearance



Patient with duodenal GIST (**orange** arrowheads) and hepatic metastases (**blue** arrows) under treatment with imatinib. Contrast-enhanced CT images obtained before (A and C) and after (B and D) treatment showed good response, with reduction of dimensions and significant reduction of lesion attenuation of both primary and secundary lesions.

Response to targeted drugs

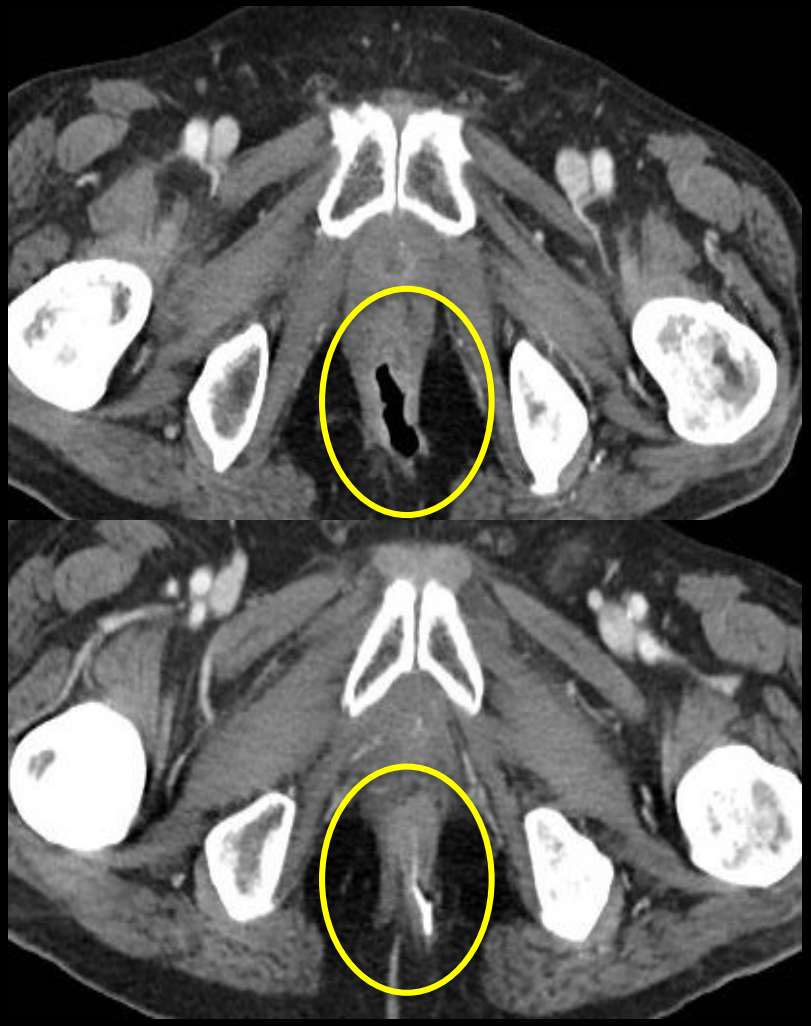
- Sunitibib is an inhibitor of tyrosine kinases (VEGF) related to angiogenesis pathway
- First choice treatment for metastatic renal cell carcinoma (clear cells)
- The response pattern associated to sunitinib is related to the intense vascularization of clear cell tumors, by an overexpression of VEGF receptors.



Metastatic clear renal cell carcinoma. Contrast-enhanced CT images from before (A and B) and 2 months after (C and D) treatment show response to therapy, with reduction of lesion dimensions and attenuation, including tumor thrombus in the vena cava (**blue** arrow). This response reflects impaired tumor vascularization by therapy.

Targeted drug adverse effects

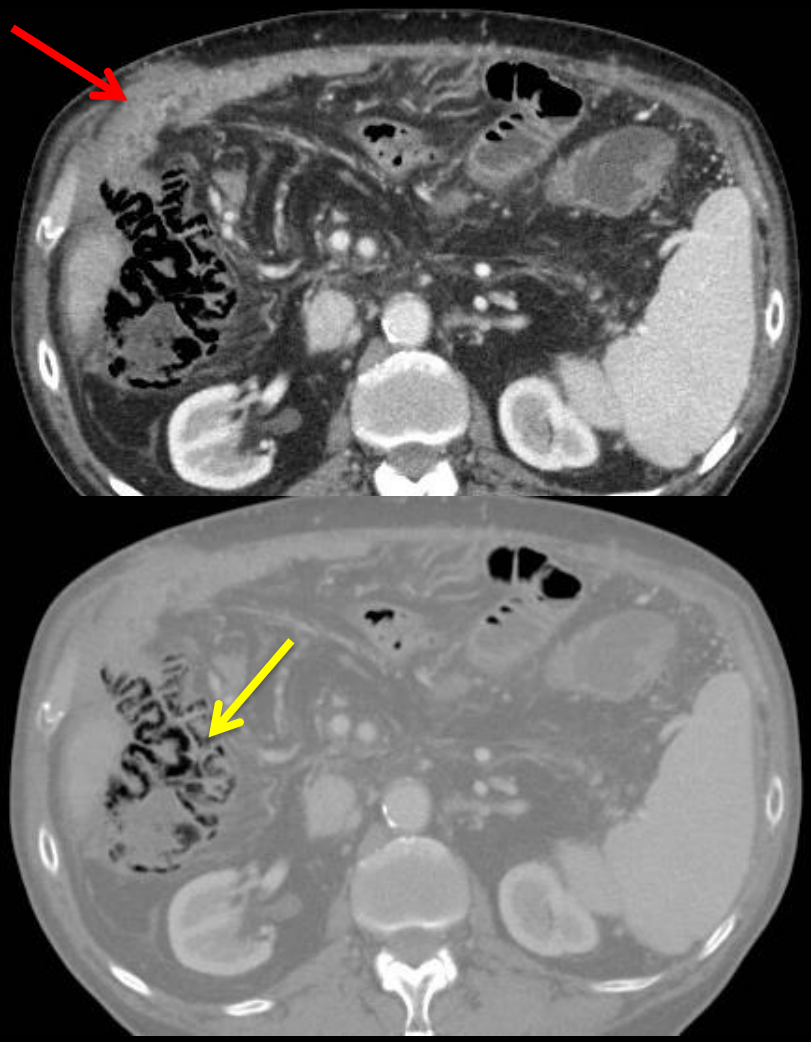
- Antiangiogenic target drugs, such as those that act to inhibit the vascular endothelial growth factor (VEGF) pathway, are associated with intestinal perforation and formation of fistulas
- The drugs interfere with the intestinal microvasculature, leading to vessel thrombosis, ischemia, ulceration and poor healing of the mucosa, leading to perforation.



Patient with adenocarcinoma of the prostate with bone metastases under treatment with cabozatinib, a targeted drug that acts by inhibiting the VEGF pathway. CT images after treatment show perianal fistula formation.

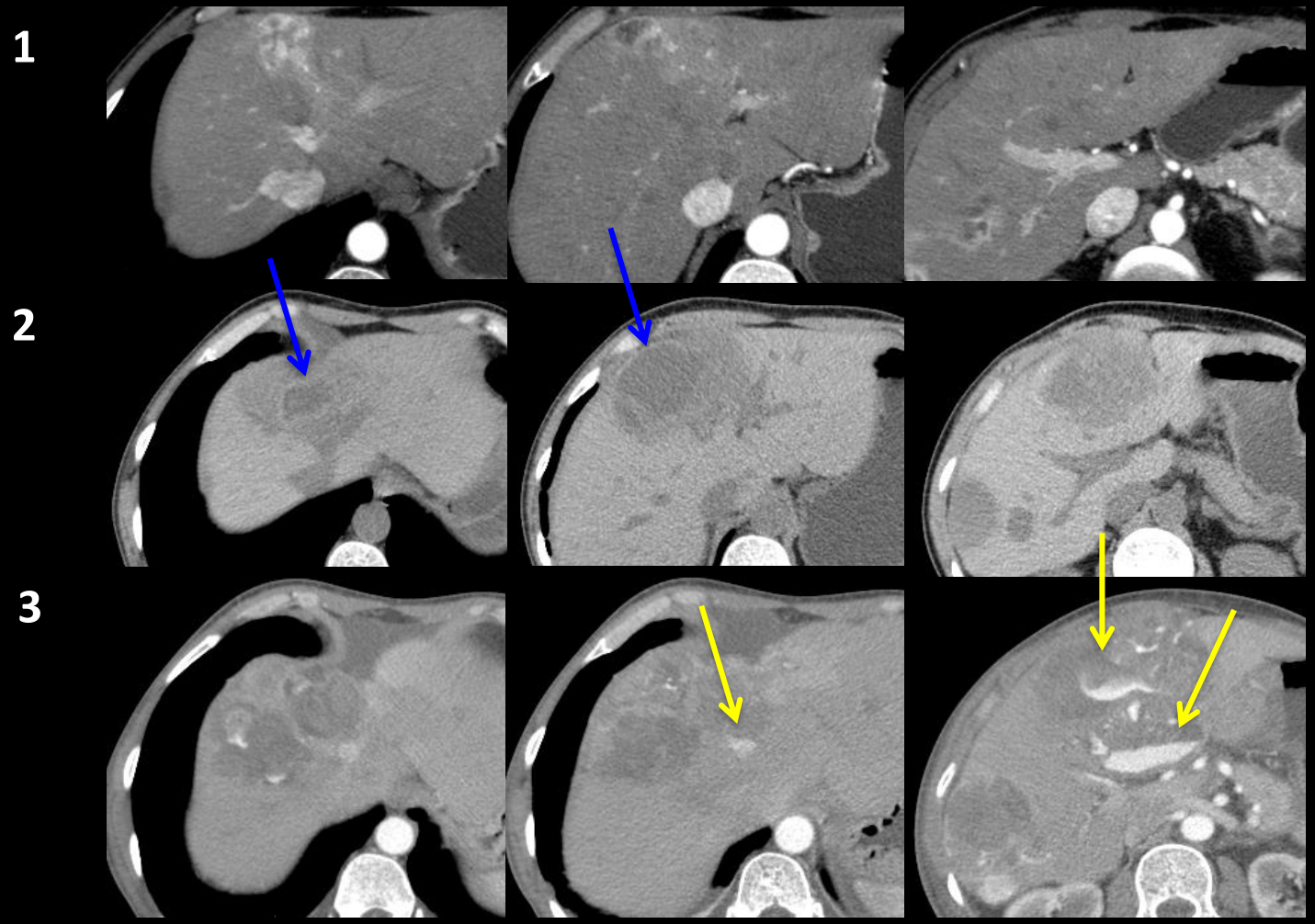
Targeted drug adverse effects

- Bevacizumab is a targeted drug widely used in the treatment of colorectal, renal, ovarian and lung cancer
- Antiangiogenic target drug, which inhibits the VEGF pathway
- The incidence of perforation in patients receiving bevacizumab ranged from 0.9% to 1.7%, with a mortality rate of 21.7%, in a meta-analysis of 12,294 patients (Risk of gastrointestinal perforation in patients with cancer treated with bevacizumab: the meta-analysis Lancet Oncol 2009).



Patient with advanced colorectal adenocarcinoma under treatment with bevacizumab. CT images during treatment show signs of intestinal pneumatosis in the right colon (**yellow** arrow), with is also infiltrated by a secundary peritoneal (**red** arrow) implant.

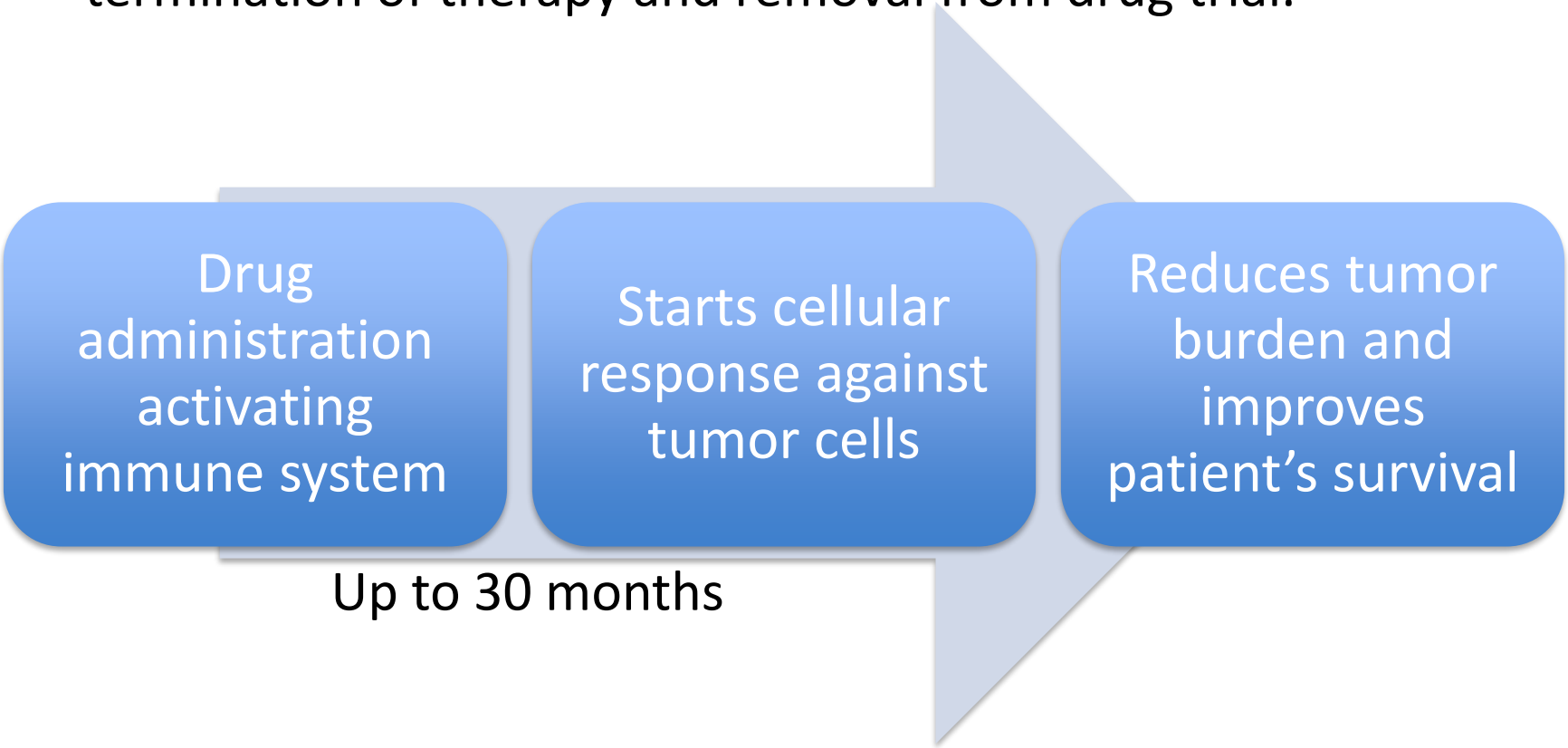
Targeted drug adverse effects



Intratumoral haemorrhage as an adverse effect of imatinib in a patient with metastatic GIST to the liver. 1 - Pre-treatment images. 2 - Follow-up images with increased lesion attenuation (**blue** arrow). 3 - CT images demonstrate active hemorrhage in multiple sites (**yellow** arrows).

Immunotherapy

- Immunotherapy treatment response takes time
- Inaccurate interpretation of response may lead to premature termination of therapy and removal from drug trial.



Immunotherapy - basics

- Strategies for activating anti-tumor immunity

- Include vaccines, oncolytic viruses, the transfer of activated T cells and NK ex vivo, or administration of antibodies or recombinant proteins that stimulate or block so-called **immune checkpoints**

Immune Checkpoints

- Immune Checkpoints are physiological inhibitory mechanisms in the immune system, essential for the maintenance of **"self-tolerance", avoiding autoimmunity**

- Tumors have ability to activate immune checkpoints, which is one of the most important mechanisms of immune resistance, particularly inactivating T cells

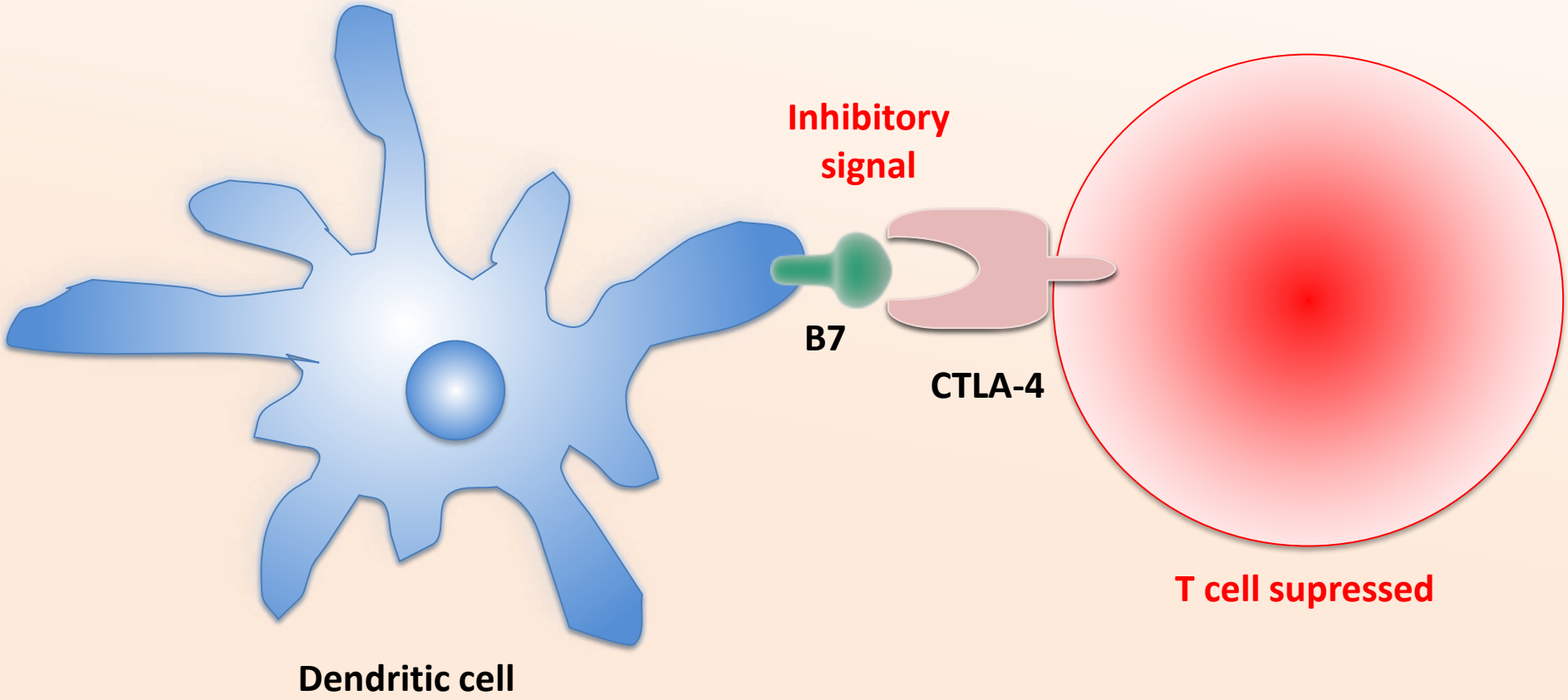
Immune Checkpoints

- CTLA4 and PD1 are receptors normally present in T cells which act inhibiting T cell activation. These are mechanisms of tumor escape

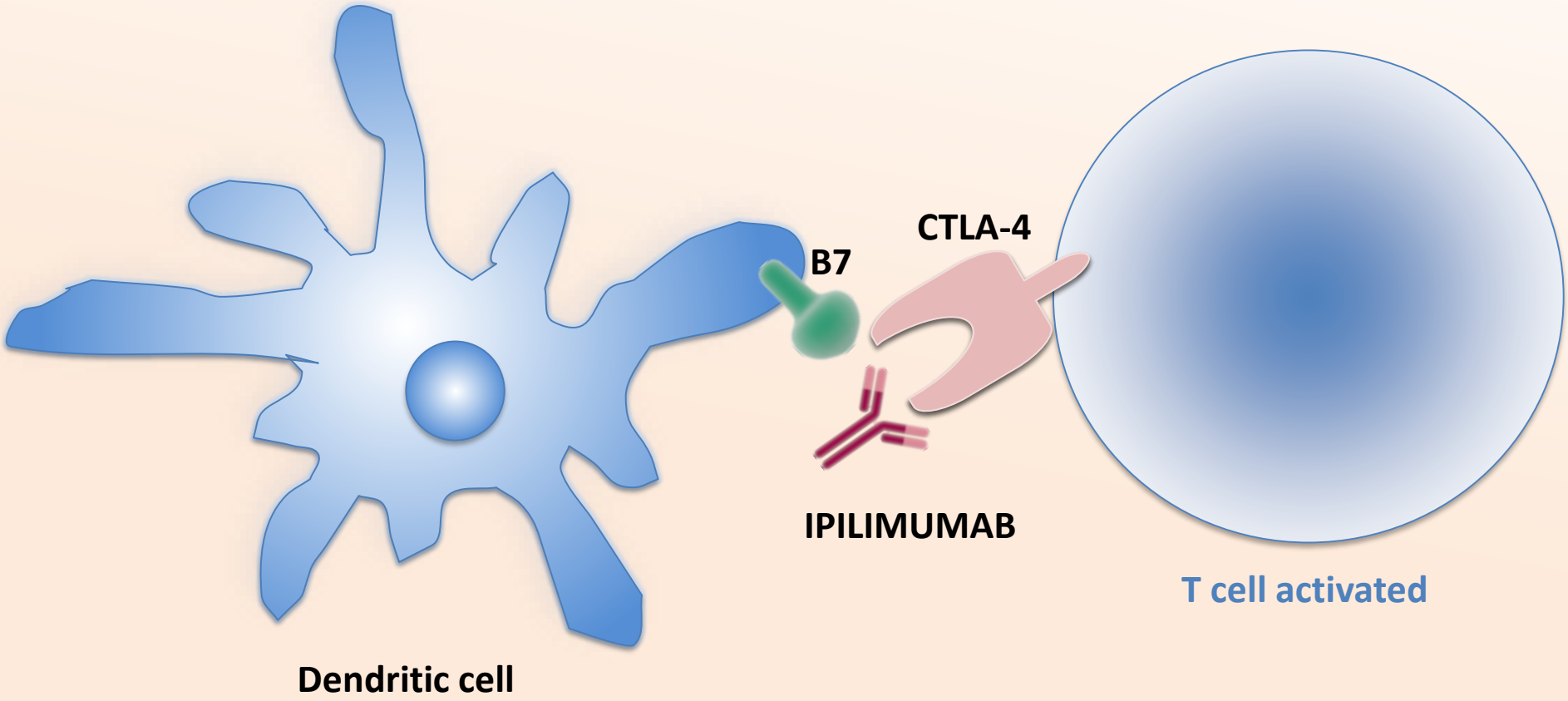
- Blocking these receptors with antibodies would prevent their binding to ligants, preventing T cell inactivation and amplifying the antitumor action

- The FDA approved in 2011 one anti-CTLA-4 antibody (ipilimumab) and, in 2014, anti-PD1 antibodies (nivolumab and pembrolizumab) for the treatment of melanoma

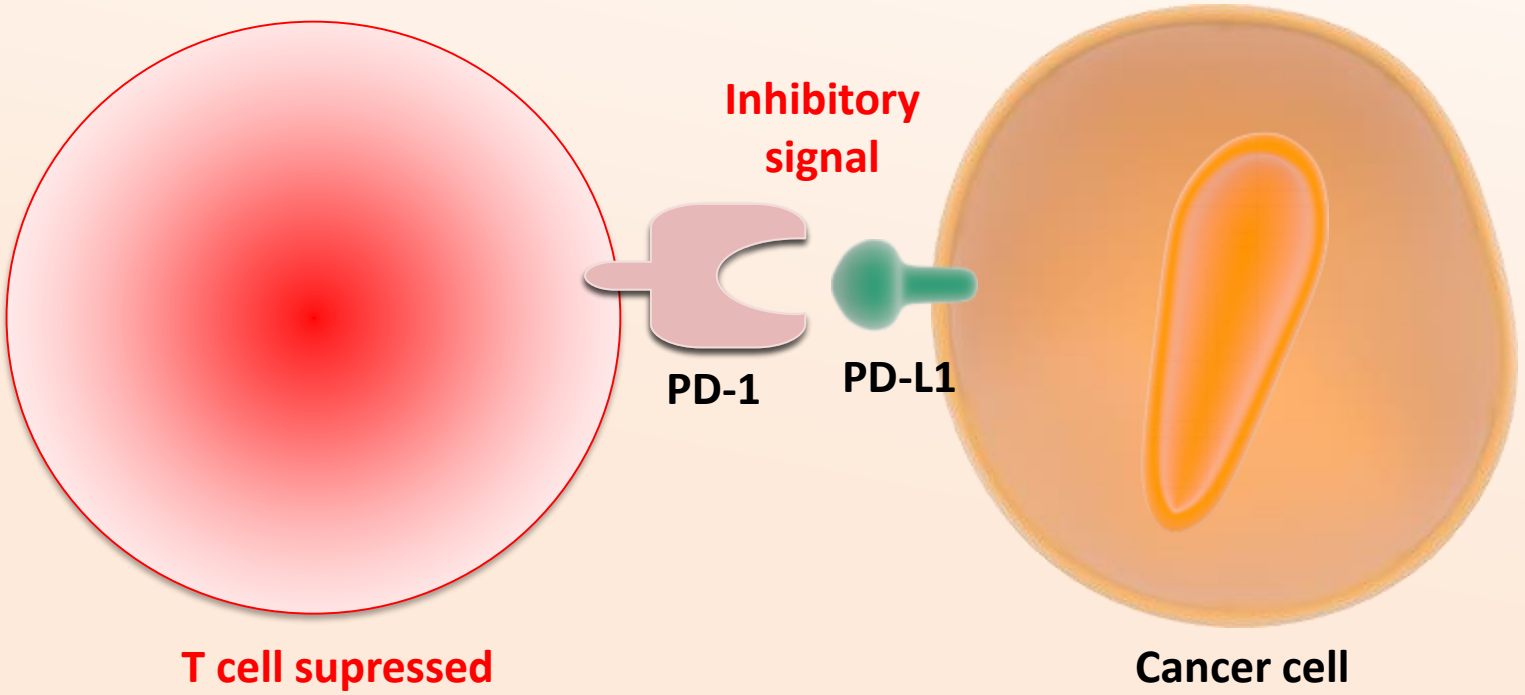
Immunotherapy – priming phase



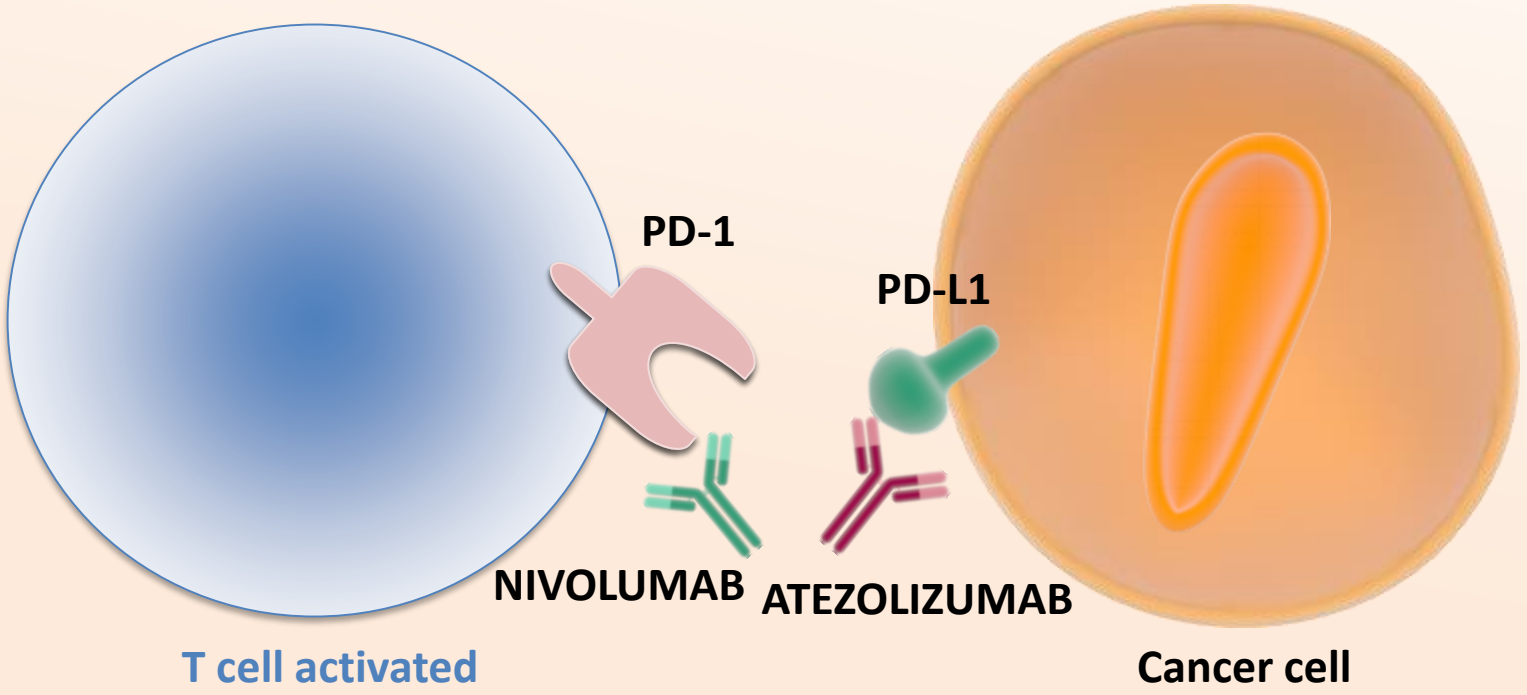
Immunotherapy – priming phase



Immunotherapy – effector phase



Immunotherapy – effector phase



Immune response criteria

- Need for new response criteria
  - irRC 2009 (immune-related response criteria)
  - irRECIST 2013 (immune-related RECIST)
  - **iRECIST** mar/2017 (immune RECIST)

- They all account for new patterns of response observed in immunotherapies

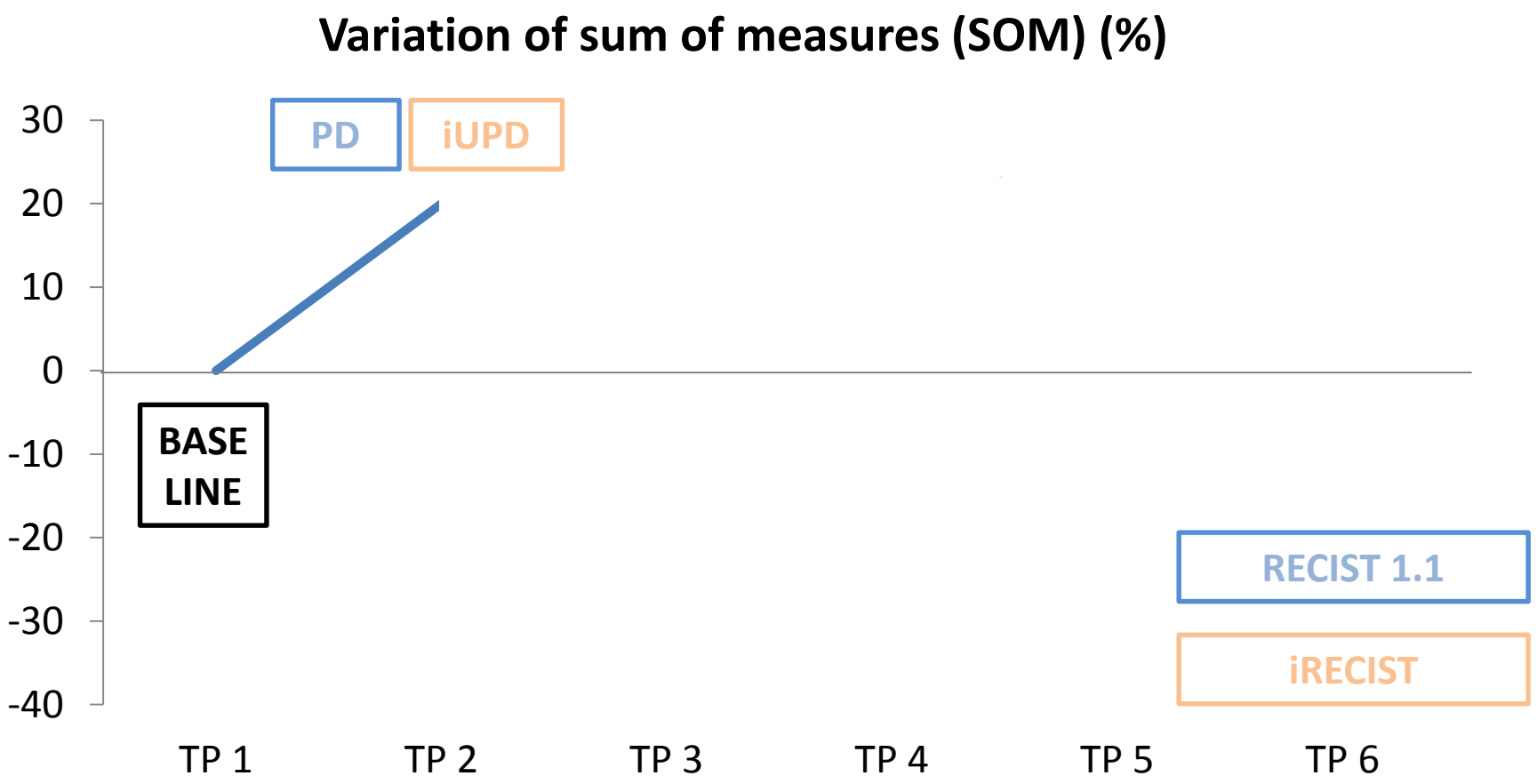
Background - iRECIST

- Seymour el al. Lancet Oncol 2017;18,e143–e152
  - Developed by RECIST working group
  - Standardizes and validates immune response criteria
  - **Key points**
    - New overall response called iUPD - immune unconfirmed progressive disease
    - Resetting the bar if Progressive Disease (PD) is followed in the next time point by tumor shrinkage

Background - iRECIST

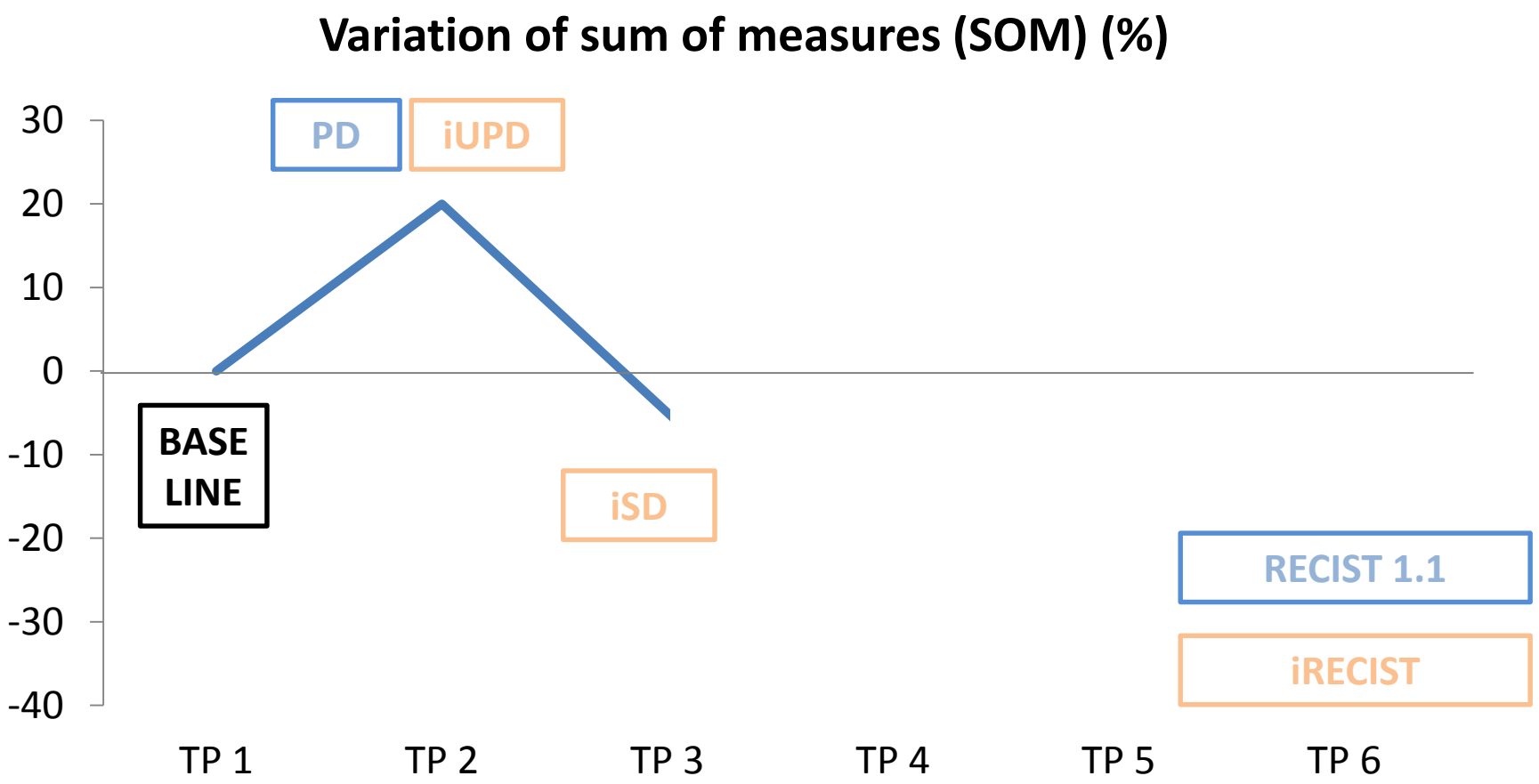
- Time point (TP) response
  - First RECIST 1.1 progressive disease (PD) is "**unconfirmed**" for iRECIST – iUPD
  - Must be confirmed at the next assessment, in 4 to 8 weeks
  - After iUPD, it's possible to have:
    - Confirmed progression (iCPD)
    - Stable (iSD)
    - Partial response (iPR) or
    - Complete response (iCR)

iRECIST - example



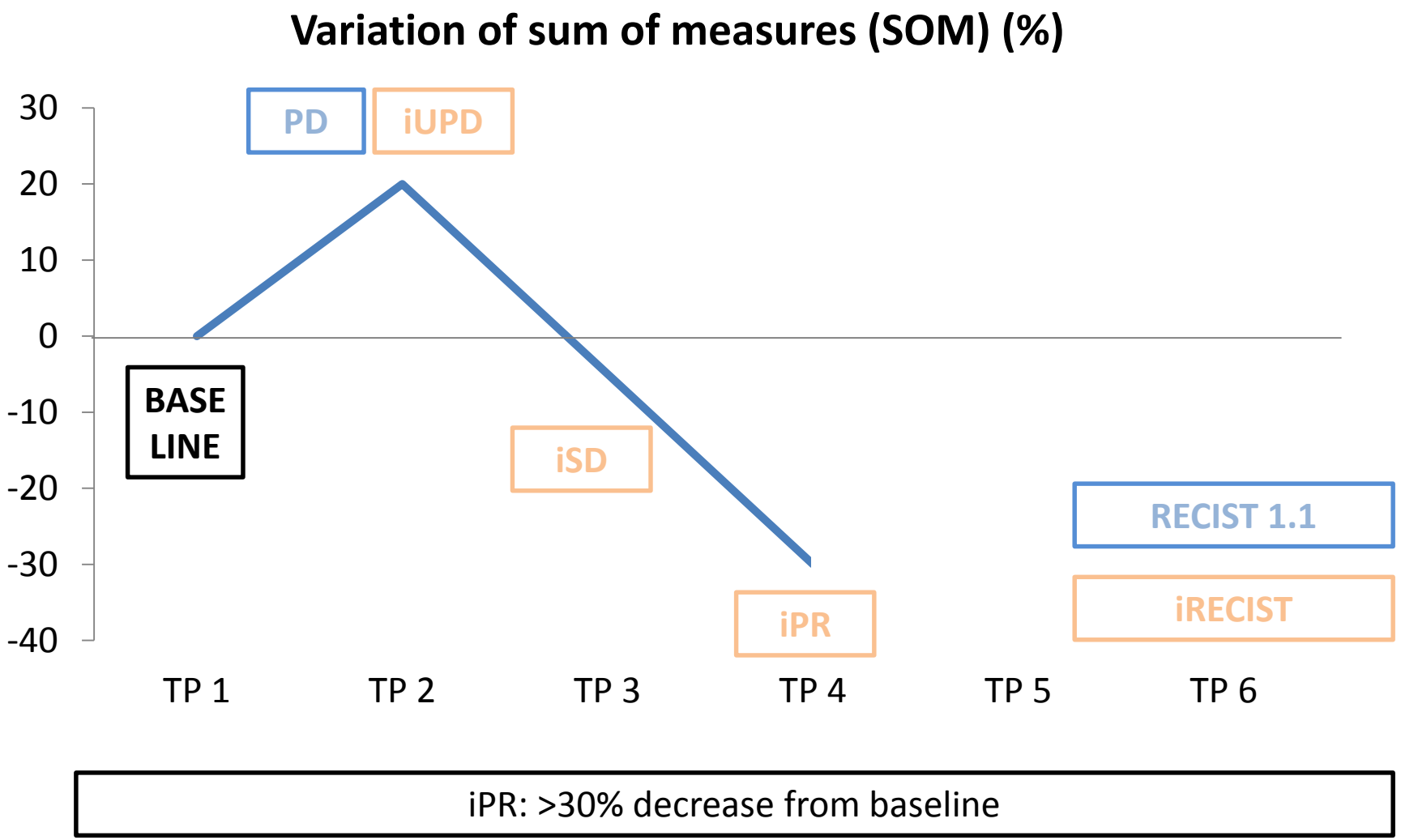
TPD: >20% increase in SOM or appearance of new lesion. So this became iUPD

iRECIST - example



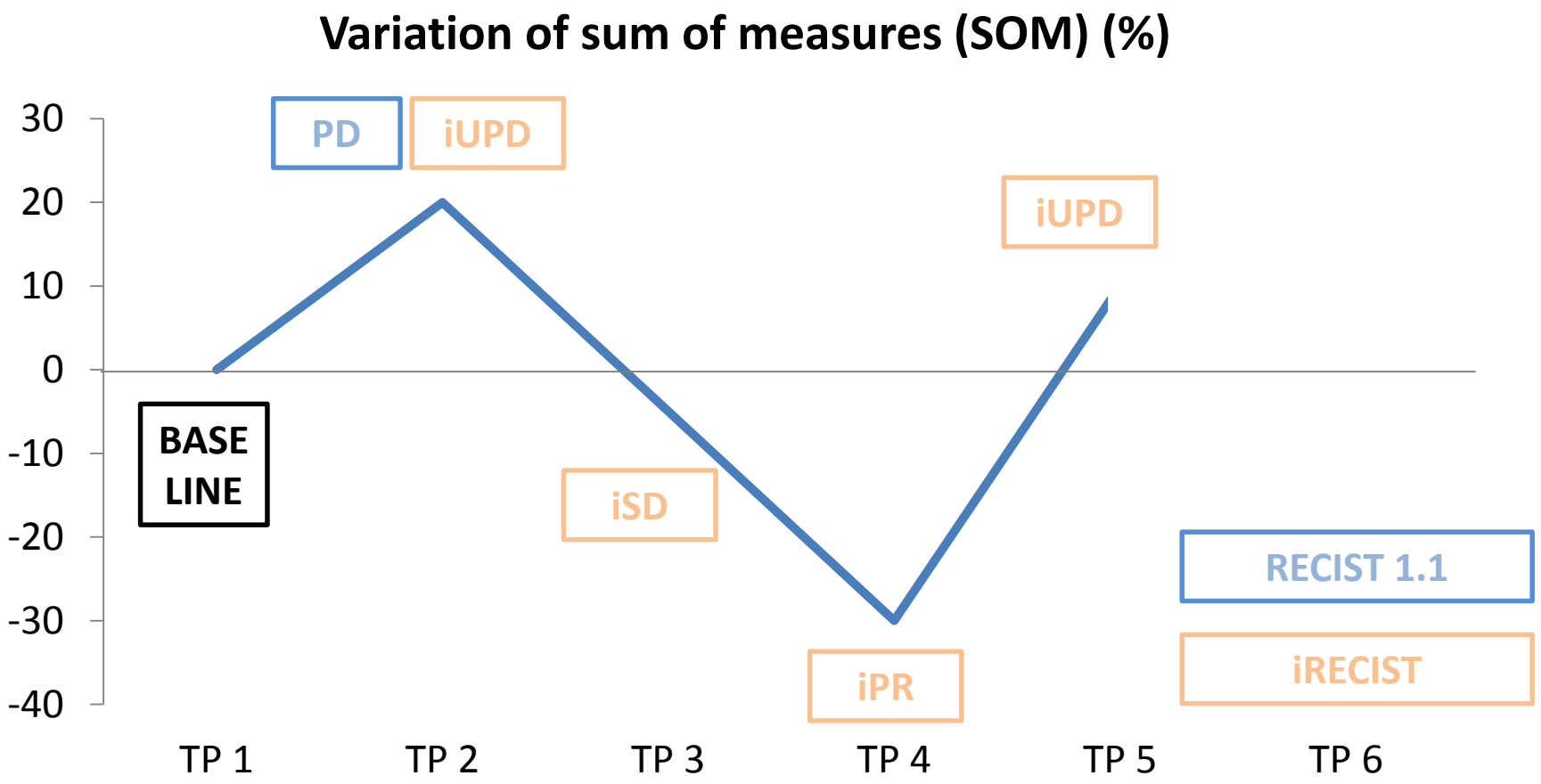
iSD: stable from baseline. PD not confirmed (pseudoprogression)

iRECIST - example



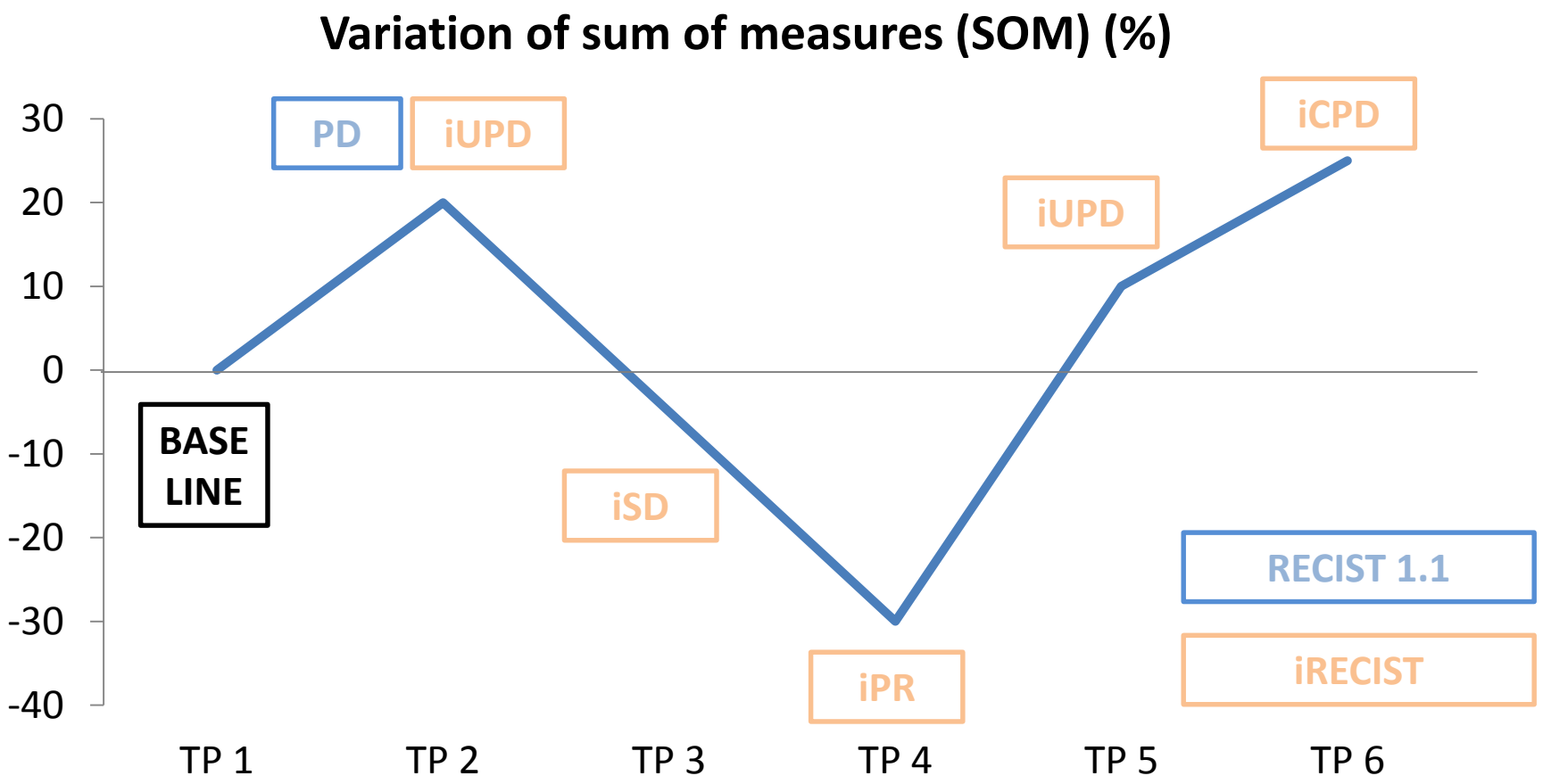
iPR: >30% decrease from baseline

iRECIST - example



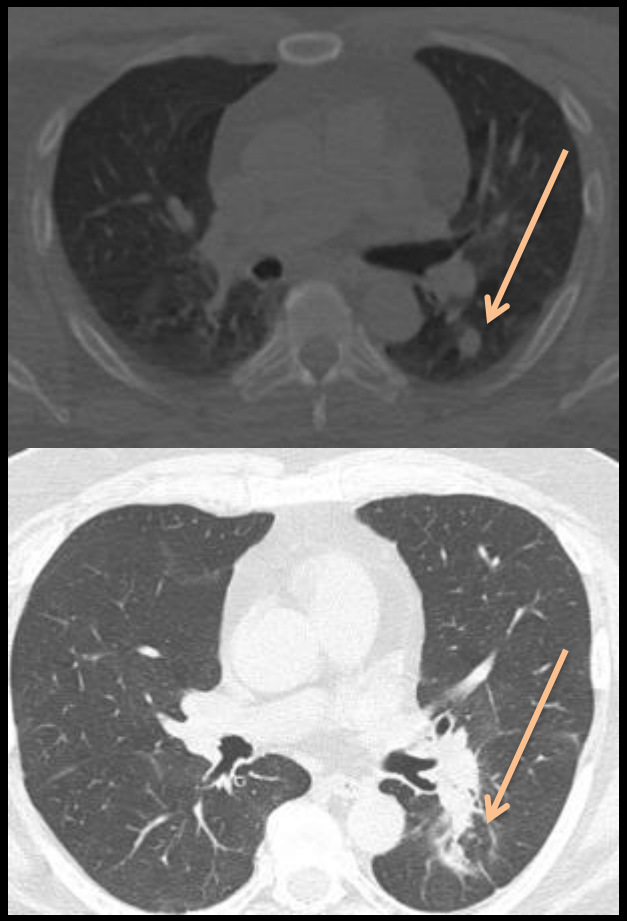
iUPD: >20% increase from NADIR. iUPD not iCPD (confirmed progression) because SD/PR has intervened and so bar is reset

iRECIST - example

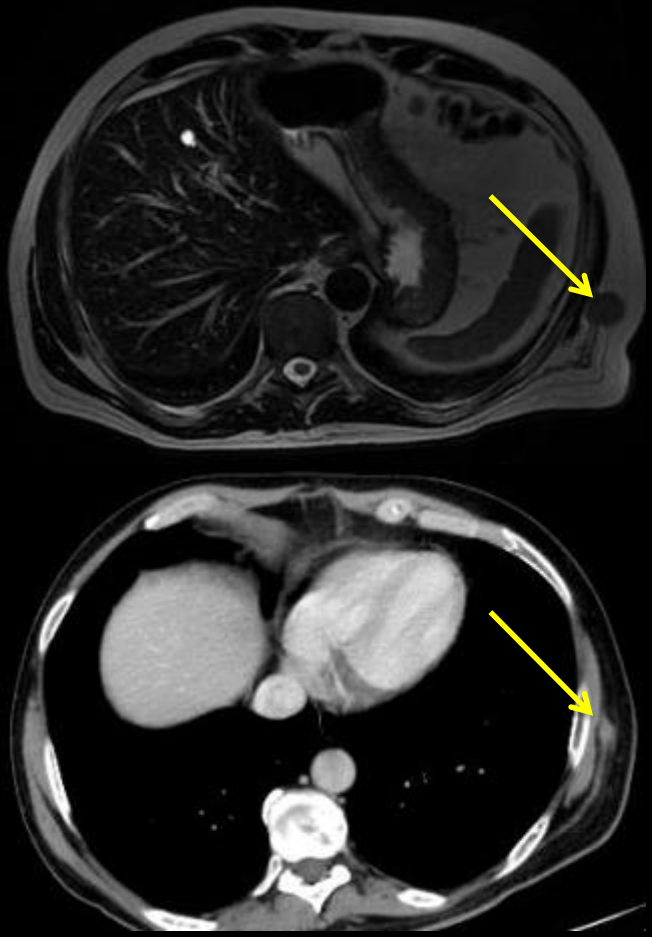


iCPD: now confirmed progression (>20% from NADIR)

Immunotherapy response patterns

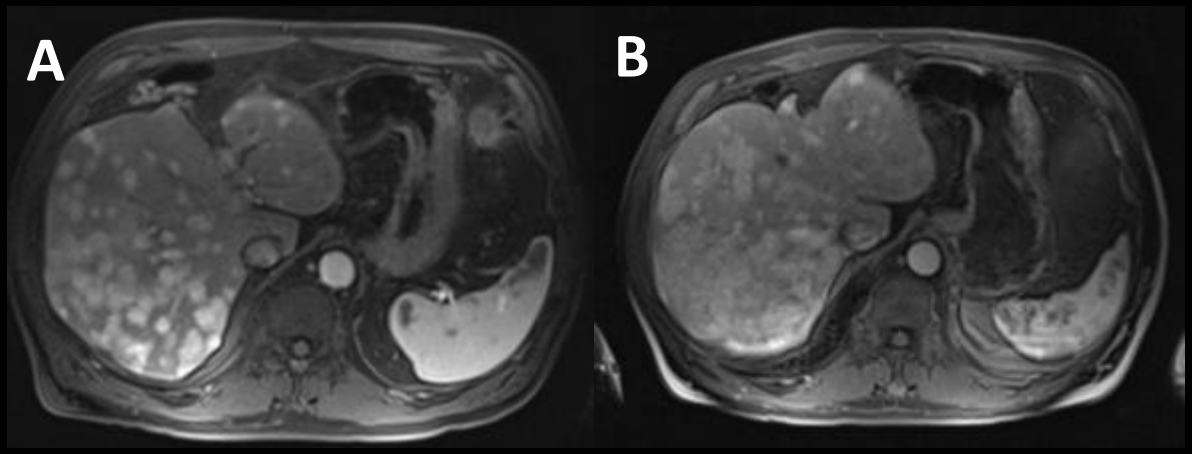


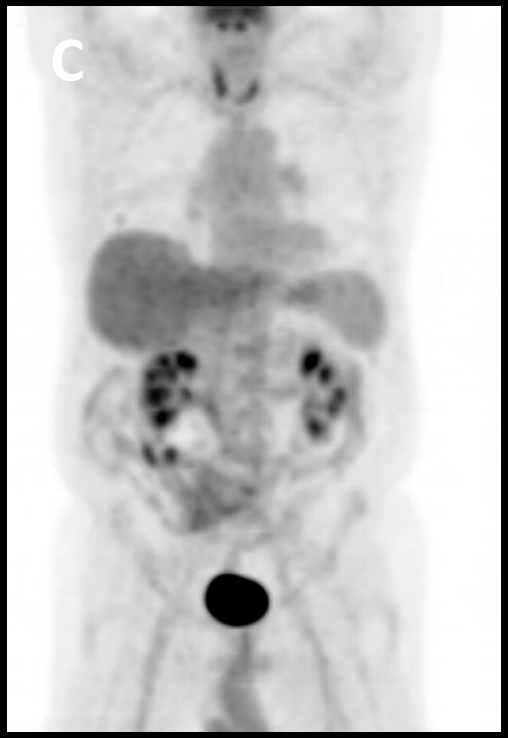
Patient with melanoma and lung metastasis. Complete response (iCR) after 2-year treatment with nivolumab and pulmonary SBRT, with remaining atelectasic opacities at the site.



Metastatic melanoma under treatment with atezolizumab. Partial response (iPR) with significant reduction of the implant in the subcutaneous of the thoracoabdominal wall.

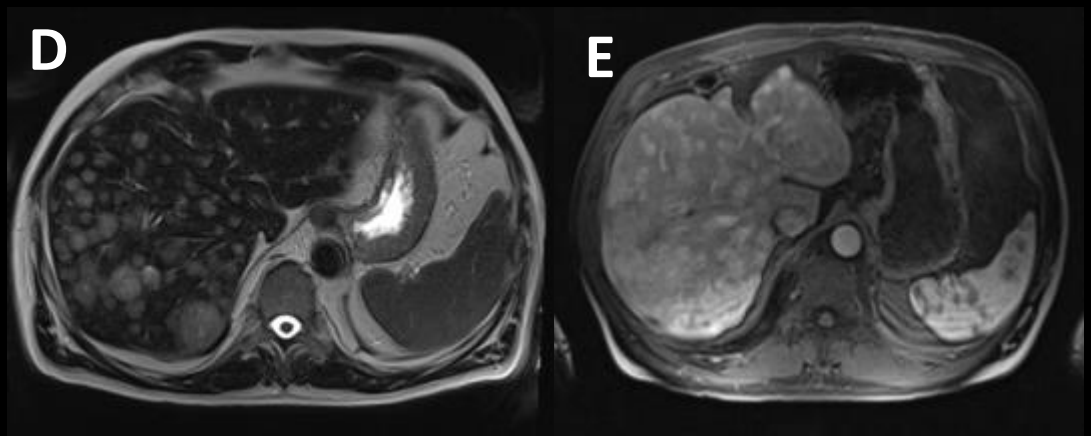
Immunotherapy response patterns





Patient with pulmonary neuroendocrine neoplasia with hepatic metastasis under treated with nivolumab [baseline]. The MRI images before (A) and 2 months [TP 2] after (B) the treatment evidenced an increase in the hypervascular liver lesions (iUPD). Glycolytic hypermetabolism in the lesions was not characterized in PET / CT (C) also performed during follow-up, characterizing **pseudoprogression**.

MRI images (D and E) after 3 more months of treatment [TP 3] show stability of the lesions.



Immunomediated adverse effects

- Serious adverse events were observed in up to 36% of patients receiving ipilimumab
- Combined therapy with more than one agent also led to a greater incidence in immunomediated adverse effects
- Other inhibitors of immune checkpoint have shown lower rates of severe toxicity.

The NEW ENGLAND JOURNAL of MEDICINE

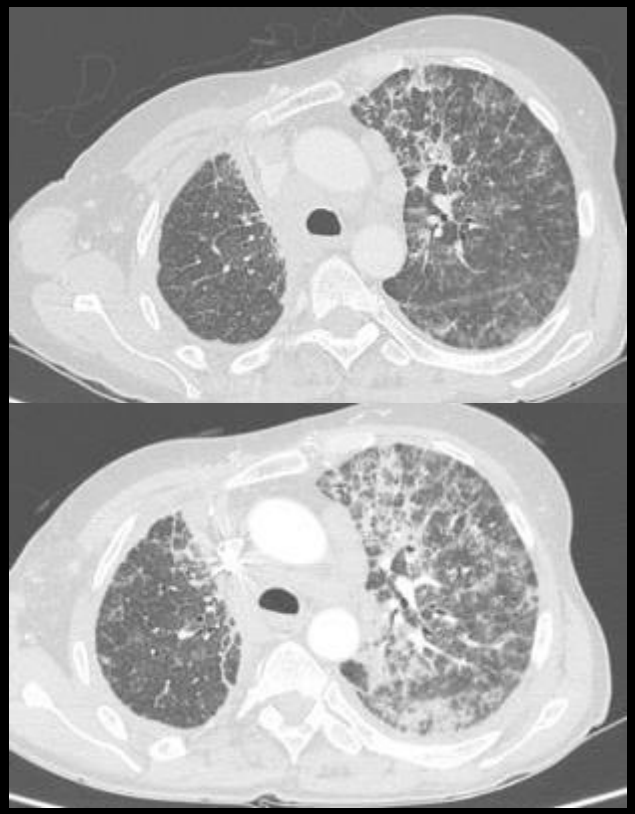
ORIGINAL ARTICLE

Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

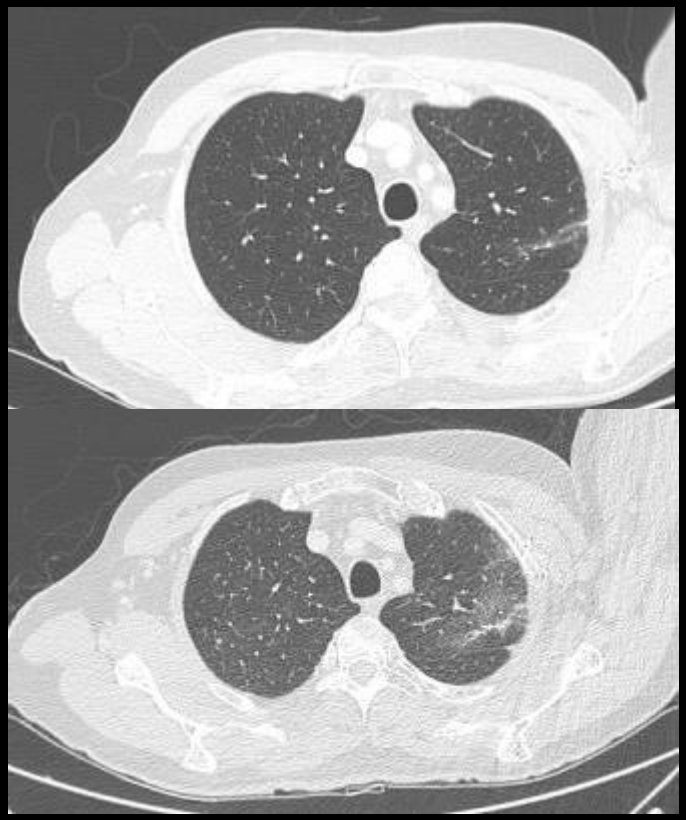
Special thanks to Carolina Victor, MD oncologist

Event	Nivolumab alone (N=313)		Nivolumab plus Ipilimumab (N=313)		Ipilimumab alone (N=311)	
	Total	Grade 3 or 4	Total	Grade 3 or 4	Total	Grade 3 or 4
	no. of patients with event (%)					
Any select adverse event	194 (62.0)	24 (7.7)	275 (87.9)	124 (39.6)	229 (73.6)	58 (18.6)
Treatment-related select adverse event[†]						
Skin	131 (41.9)	5 (1.6)	185 (59.1)	18 (5.8)	168 (54.0)	9 (2.9)
Pruritus	59 (18.8)	0	104 (33.2)	6 (1.9)	110 (35.4)	1 (0.3)
Rash	68 (21.7)	1 (0.3)	89 (28.4)	9 (2.9)	65 (20.9)	5 (1.6)
Rash maculo-papular	13 (4.2)	1 (0.3)	37 (11.8)	6 (1.9)	37 (11.9)	1 (0.3)
Vitiligo	23 (7.3)	1 (0.3)	21 (6.7)	0	12 (3.9)	0
Gastrointestinal	61 (19.5)	7 (2.2)	145 (46.3)	46 (14.7)	114 (36.7)	36 (11.6)
Diarrhea	60 (19.2)	7 (2.2)	138 (44.1)	29 (9.3)	103 (33.1)	19 (6.1)
Colitis	4 (1.3)	2 (0.6)	37 (11.8)	24 (7.7)	36 (11.6)	27 (8.7)
Hepatic	20 (6.4)	8 (2.6)	94 (30.0)	59 (18.8)	22 (7.1)	5 (1.6)
Increase in alanine aminotransferase	12 (3.8)	4 (1.3)	55 (17.6)	26 (8.3)	12 (3.9)	5 (1.6)
Increase in aspartate aminotransferase	12 (3.8)	3 (1.0)	48 (15.3)	19 (6.1)	11 (3.5)	2 (0.6)
Endocrine	45 (14.4)	2 (0.6)	94 (30.0)	15 (4.8)	34 (10.9)	7 (2.3)
Hypothyroidism	27 (8.6)	0	47 (15.0)	1 (0.3)	13 (4.2)	0
Hyperthyroidism	13 (4.2)	0	31 (9.9)	3 (1.0)	3 (1.0)	0
Hypophysitis	2 (0.6)	1 (0.3)	24 (7.7)	5 (1.6)	12 (3.9)	6 (1.9)
Pulmonary	5 (1.6)	1 (0.3)	22 (7.0)	3 (1.0)	6 (1.9)	1 (0.3)
Pneumonitis	4 (1.3)	1 (0.3)	20 (6.4)	3 (1.0)	5 (1.6)	1 (0.3)

Pneumonitis

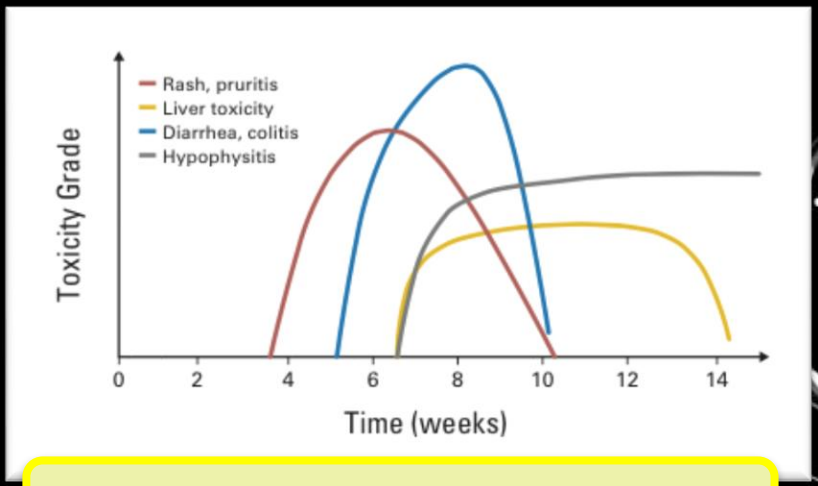


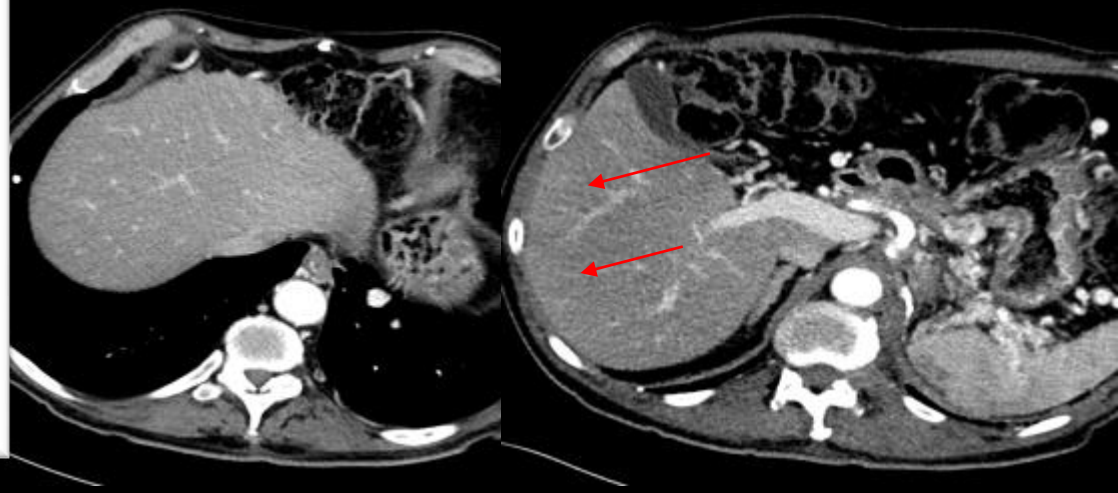
Patient with pleural mesothelioma under treatment with ipilimumab + nivolumab, presented G1 pneumonitis and subsequent worsening with need for ICU admission. Bilateral pulmonary infiltrate, characterized by septal thickening with reticular and ground glass opacities. Imunotherapy was suspended.



Patient with melanoma under treatment with atezolizumab presented G1 pneumonitis during treatment. TC appearance of discrete ground glass opacities in the upper lobes. In this patient, the oncologist chose to continue with immunotherapeutic treatment.

Hepatotoxicity





Hepatotoxicity after 6th week

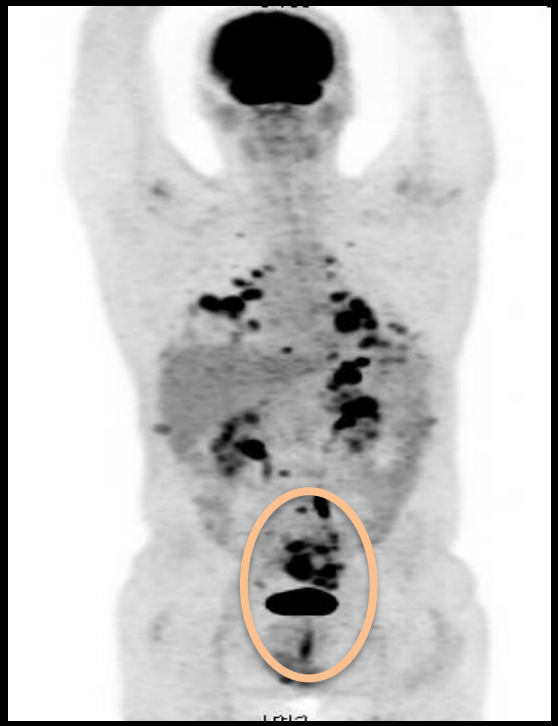
Patient with metastatic renal cell carcinoma, presenting with abdominal pain and jaundice, during the second month of treatment with nivolumab, after the third dose

Laboratory tests: TGO 979; TGP 1487; Total bilirubin: 3.02; Direct bilirubin: 2.89

Contraste-enhanced CT images show areas of tenuous peripheral arterial hypervascularization, suggestive of a mild perfusion disorder. **Images with minimal alterations, despite an important clinical and laboratory scenario.**

Abscopal Effect

a



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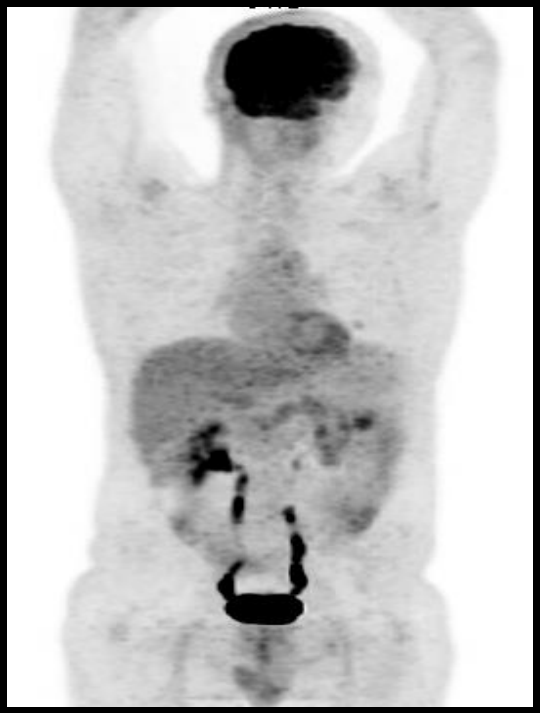

Patient with gastric adenocarcinoma under treatment with nivolumab and radiotherapy for secundary pelvic implants.

PET-CT before treatment (figure *a*) delimitating the area of radiotherapy. After 4 cycles of radiotherapy in the pelvis, a complete response was achieved on other sites (figure *b*).