Efficacy Evaluation for Immune Checkpoint Blockade

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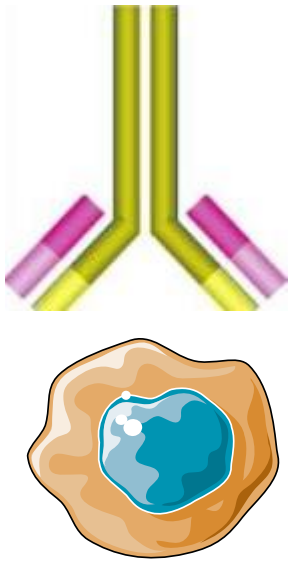
INSERM 1015

ESMO Advanced Course July 3rd 2019

GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS

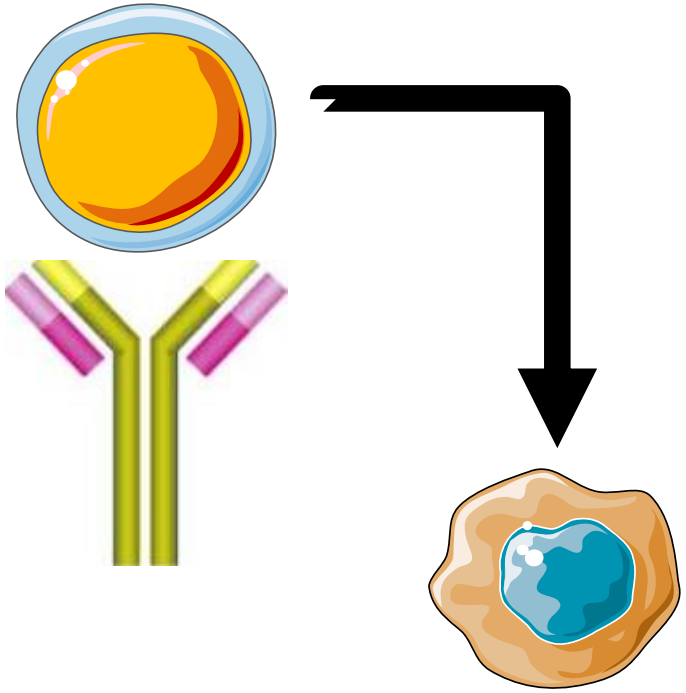
Paradigm Shift in Cancer Therapy

Historical Paradigm: Targeting Tumor Cells	New Paradigm: Targeting Immune Cells

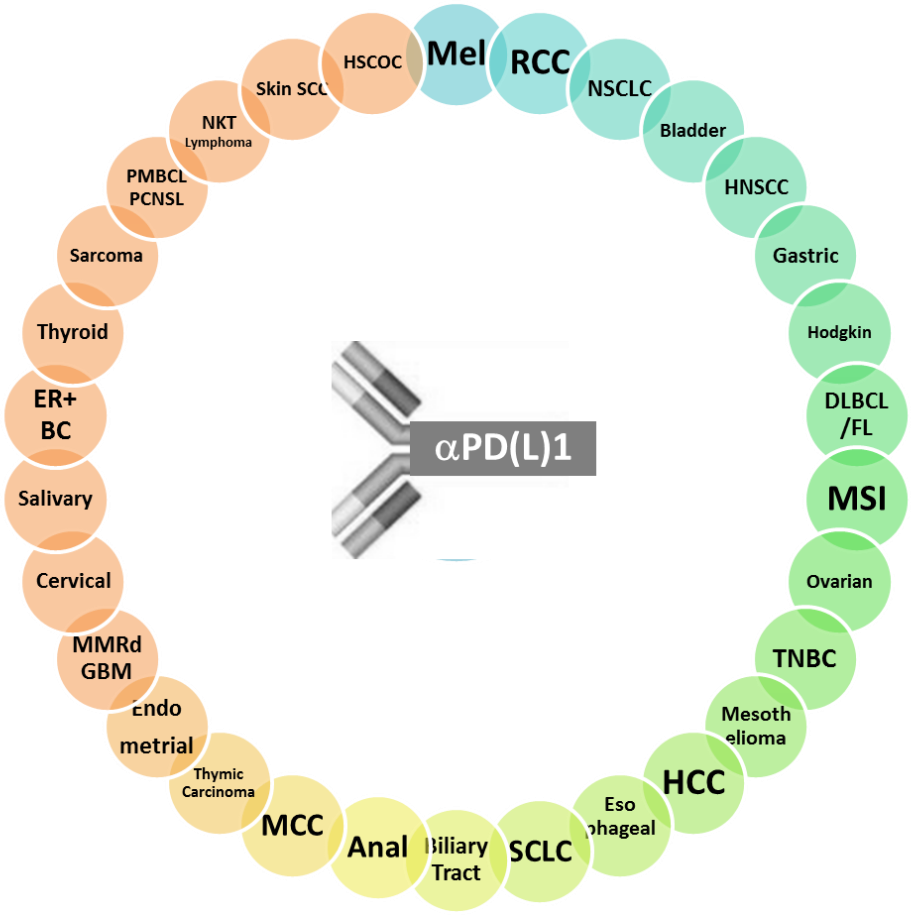


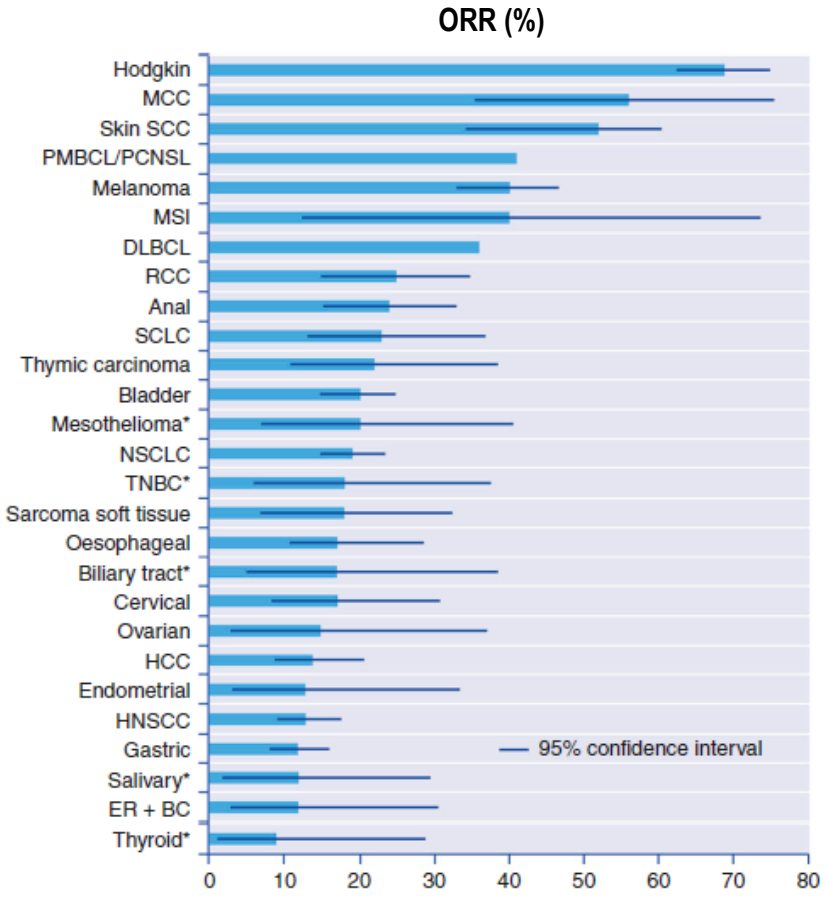
Tumor Cell

Lymphocyte



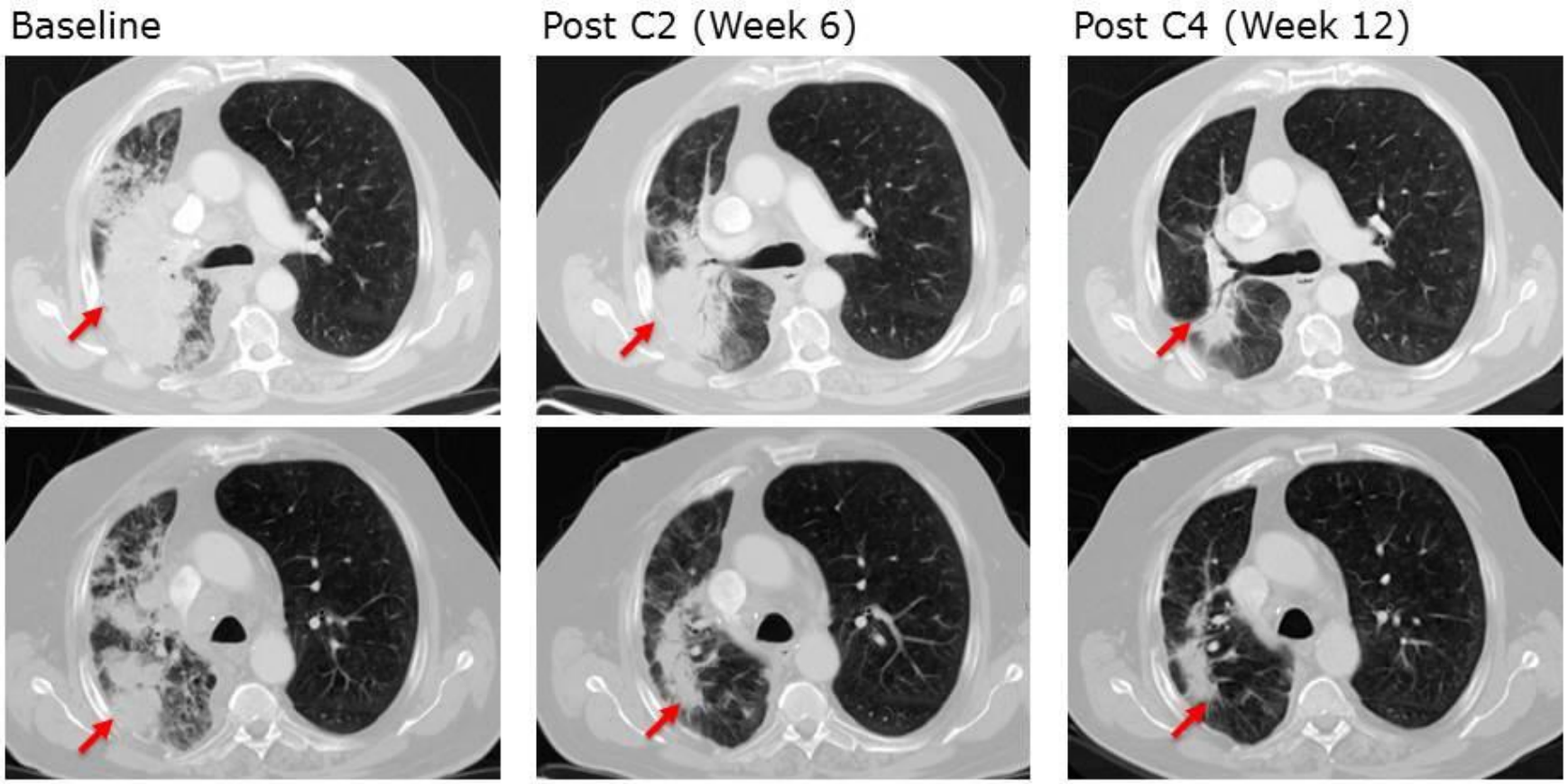
PD-Lomas





Hirsch L, Zitvogel L, Eggermont A, Marabelle A. Br J Cancer 2019;120:3–5.

Rapid Response in an NSCLC Patient Treated With MPDL3280A Monotherapy



64-year-old male with squamous NSCLC s/p R lobectomy, cisplatin + gemcitabine, docetaxel, erlotinib, PD-L1 positive

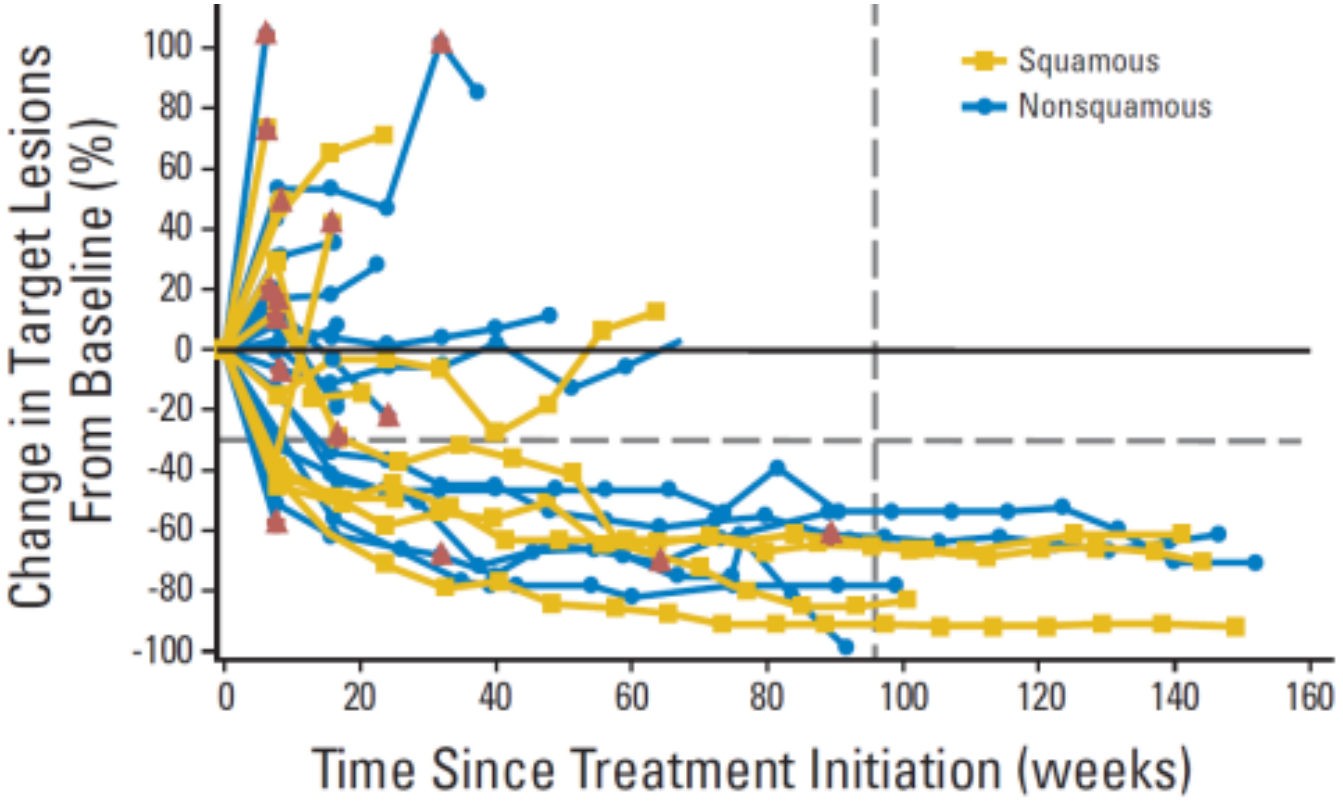
Images represent data from patient enrolled after Aug 1, 2012.
Hospital Universitario Vall D´Hebron (Cruz/Tabernero).

MPDL3280A Phase Ia

PRESENTED AT: ASCO Annual '13 Meeting

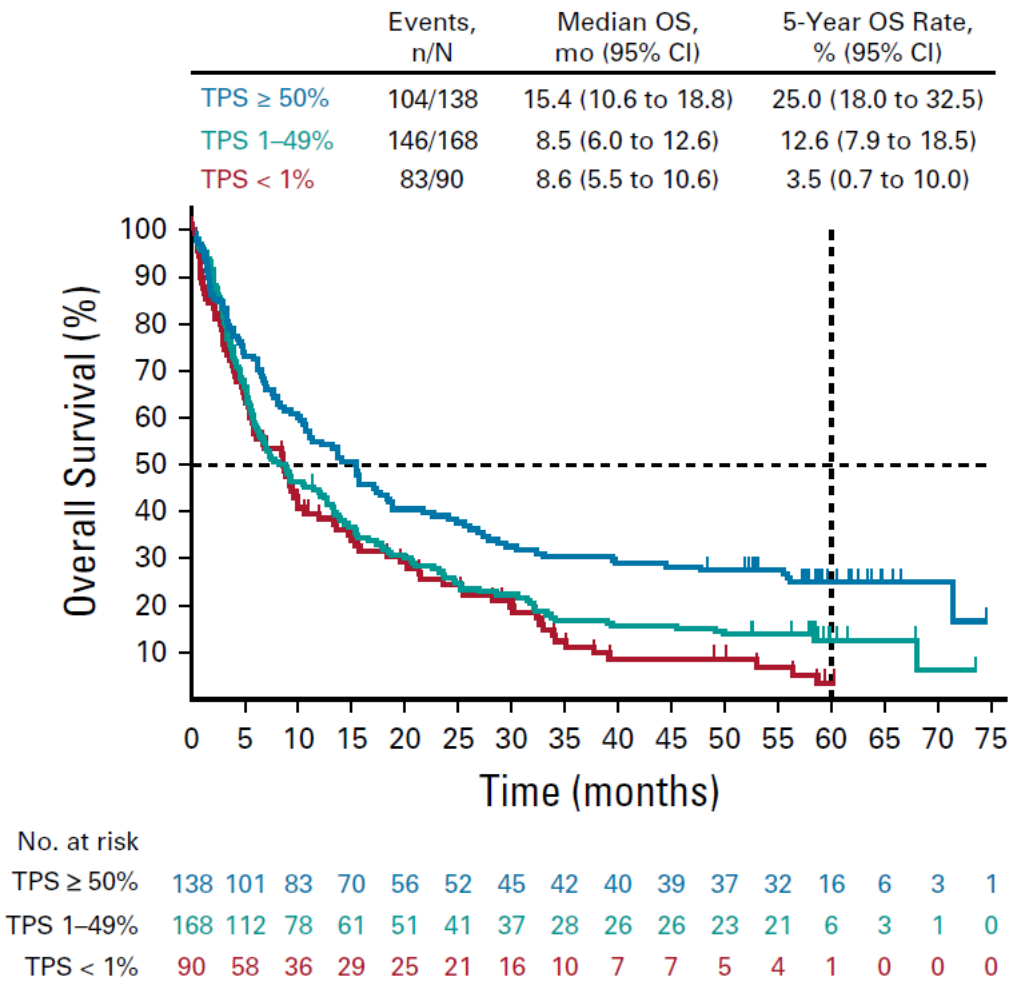
Presented By Roy S. Herbst, MD, PhD at 2013 ASCO Annual Meeting

Long Duration of Responses



JCO, April 20, 2015.

Five-Year Overall Survival for Patients With Advanced Non–Small-Cell Lung Cancer Treated With Pembrolizumab: Results From the Phase I KEYNOTE-001 Study



Garon EB, et al. J Clin Oncol 2019

Why Immune Targeted Therapies provide Survival Benefits?

Adaptive anti-tumor immunity is polyclonal:

➔ ***better control of tumor heterogeneity***

Adaptive anti-tumor immunity has memory:

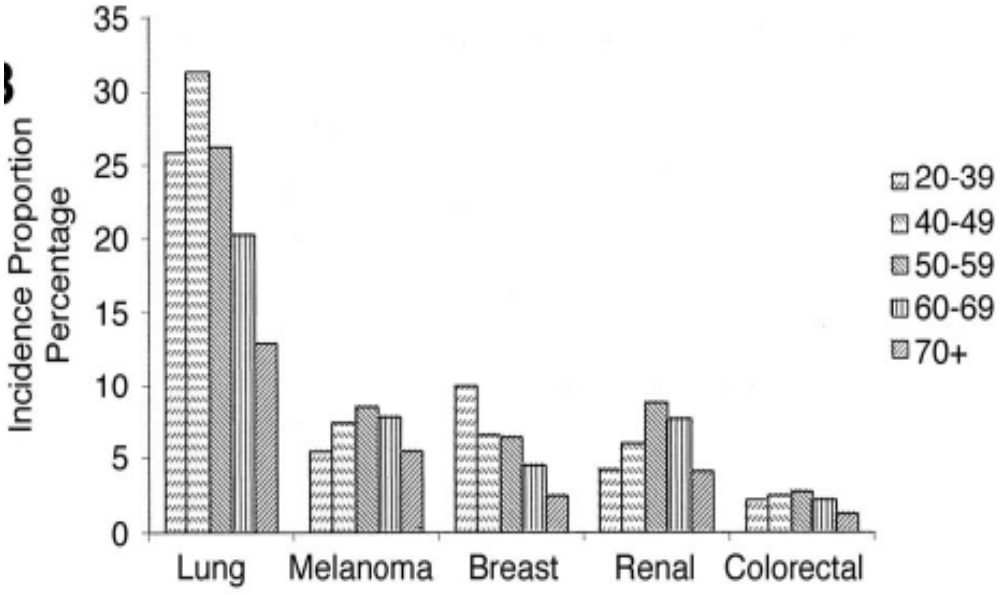
➔ ***durable remissions***

And immune cells can cross the BBB

(whereas most drugs can't)

Incidence of brain metastases

- Occur in 10-30% of all adult cancers
- Approx. 10 times more frequent than primary brain tumors
- Relative incidence increasing, due to
  - Effective systemic treatments → with longer survival
  - Improved imaging techniques and their increased availability
- Approx. half of all brain mets due to NSCLC, others:
  - Breast cancer
  - Melanoma
  - Unknown primary
  - Renal cell carcinoma



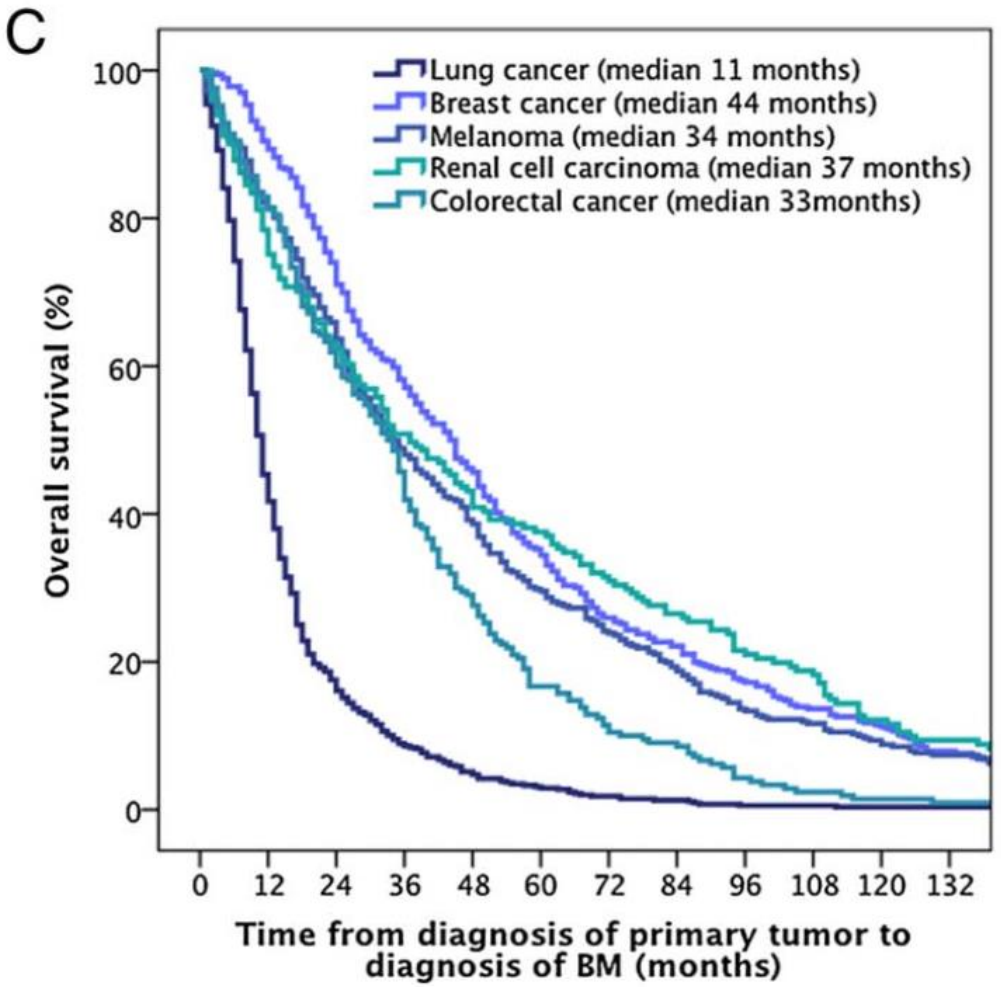
Barnholtz-Sloan… Sawaya RE. J Clin Oncol 22:2865-72, 2004

Courtsesy of Prof M.Preusser

ESMO Open
Cancer Horizons

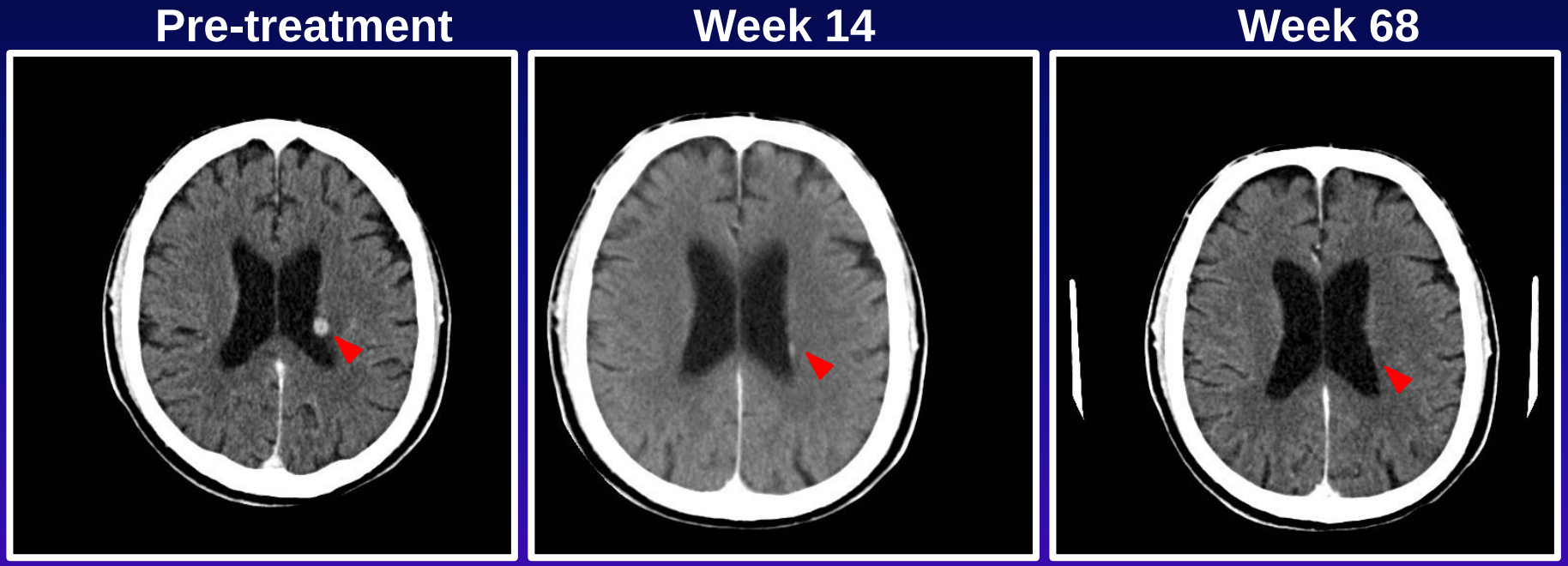
Descriptive statistical analysis of a real life cohort of 2419 patients with brain metastases of solid cancers

Anna S Berghoff,[1,2] Sophie Schur,[1,2] Lisa M Füreder,[1,2] Brigitte Gatterbauer,[2,3] Karin Dieckmann,[2,4] Georg Widhalm,[2,3] Johannes Hainfellner,[2,5] Christoph C Zielinski,[1,2] Peter Birner,[2,6] Rupert Bartsch,[1,2] Matthias Preusser[1,2]



Courtsesy of Prof M.Preusser

Response to Nivolumab in SQ NSCLC Brain Metastasis



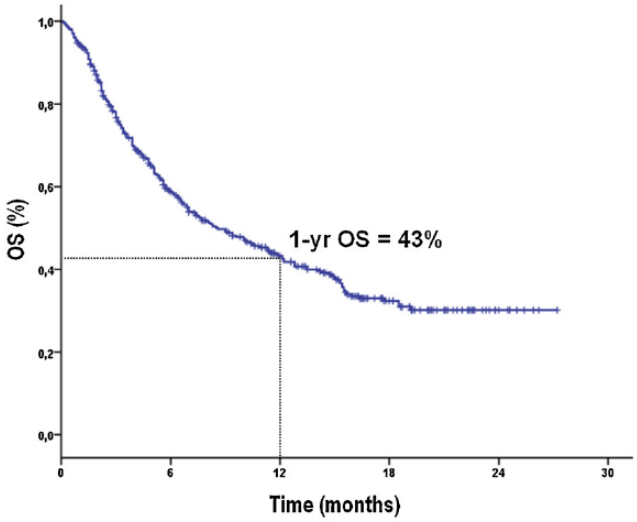
- 73 year-old male, stage IIIb, former smoker
- Prior radiotherapy (mediastinal), 3 prior systemic regimens (cisplatin/gemcitabine, docetaxel, vinorelbine)
- No prior CNS-directed radiotherapy

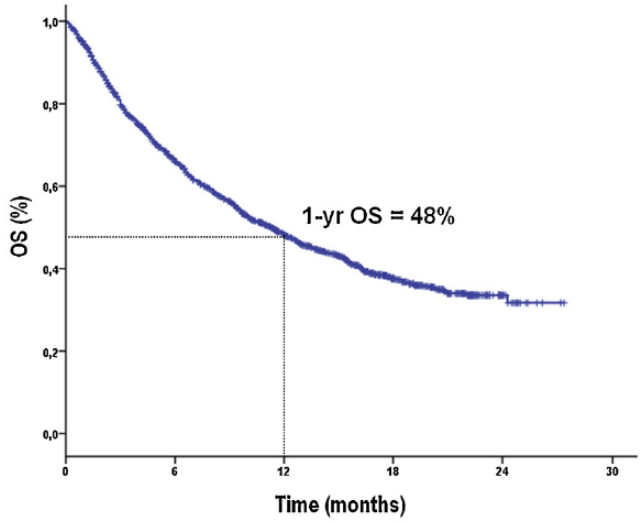
Ramalingam et al

Anti-PD-1 in NSCLC with Brain Mets

Response outcomes.

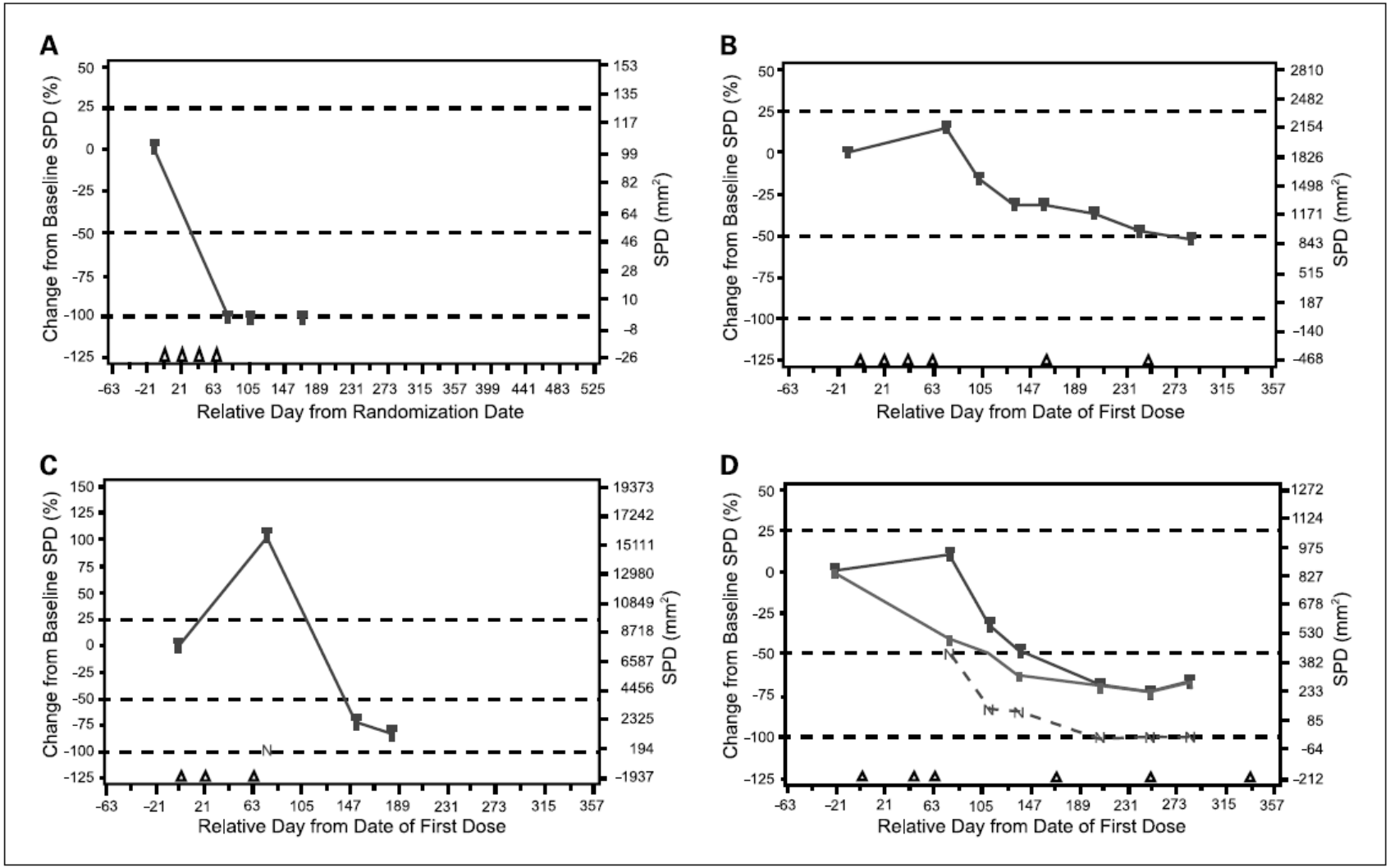
Response, n (%)	CNS metastasis (n = 409)	All patients (n = 1588)
Objective response rate	68 (17)	290 (18)
Disease control rate	164 (40)	704 (44)
Complete response	4 (1)	12 (1)
Partial response	64 (16)	278 (18)
Stable disease	96 (23)	414 (26)
Progressive disease	192 (47)	688 (43)
Death	35 (9)	130 (8)
Not determined	18 (4)	66 (4)





Crinò L, et al. Nivolumab and brain metastases in patients with advanced non-squamous non-small cell lung cancer. Lung Cancer 2019. doi:10.1016/j.lungcan.2018.12.025.

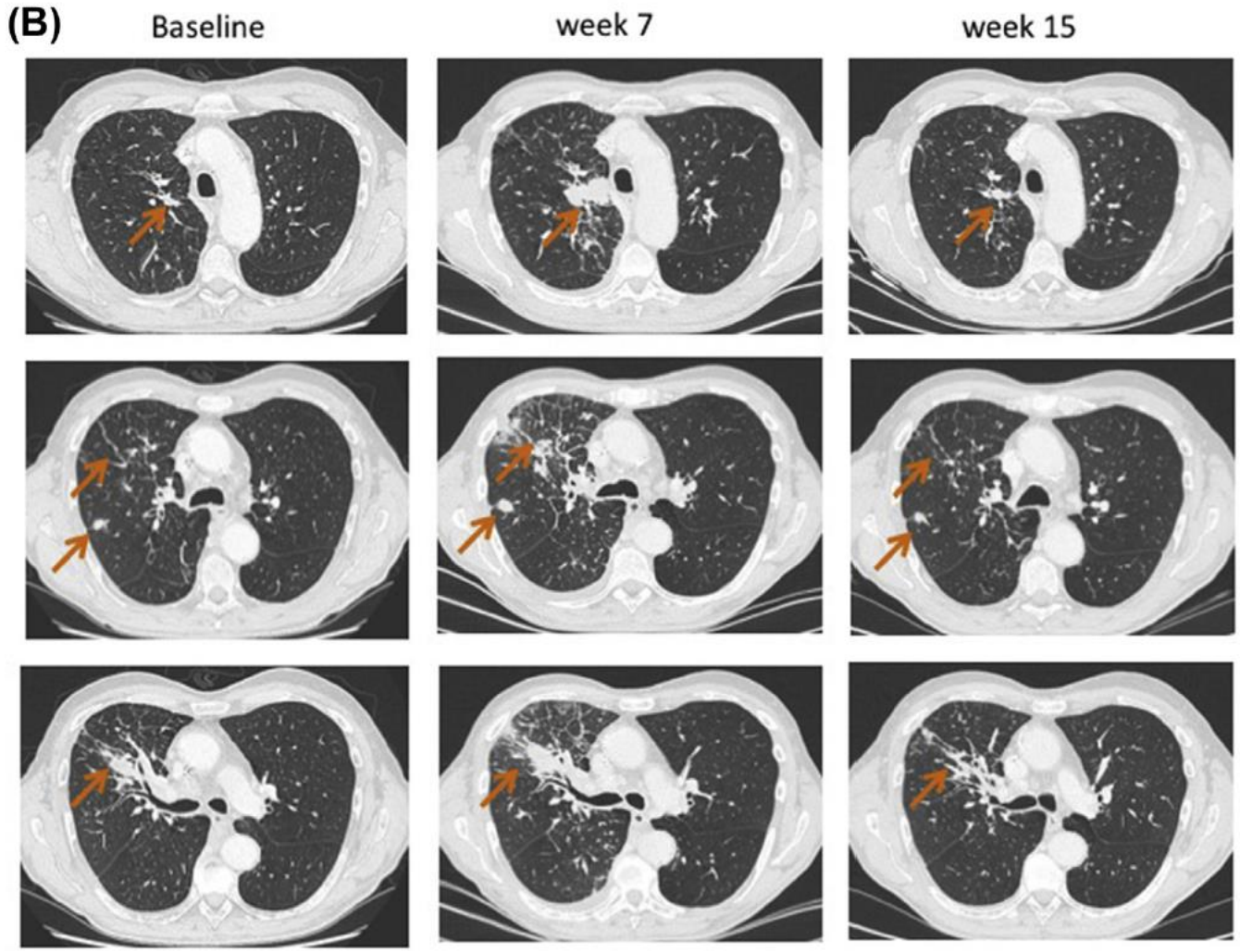
New Types of Responses in Oncology



Immune-Related Response Criteria

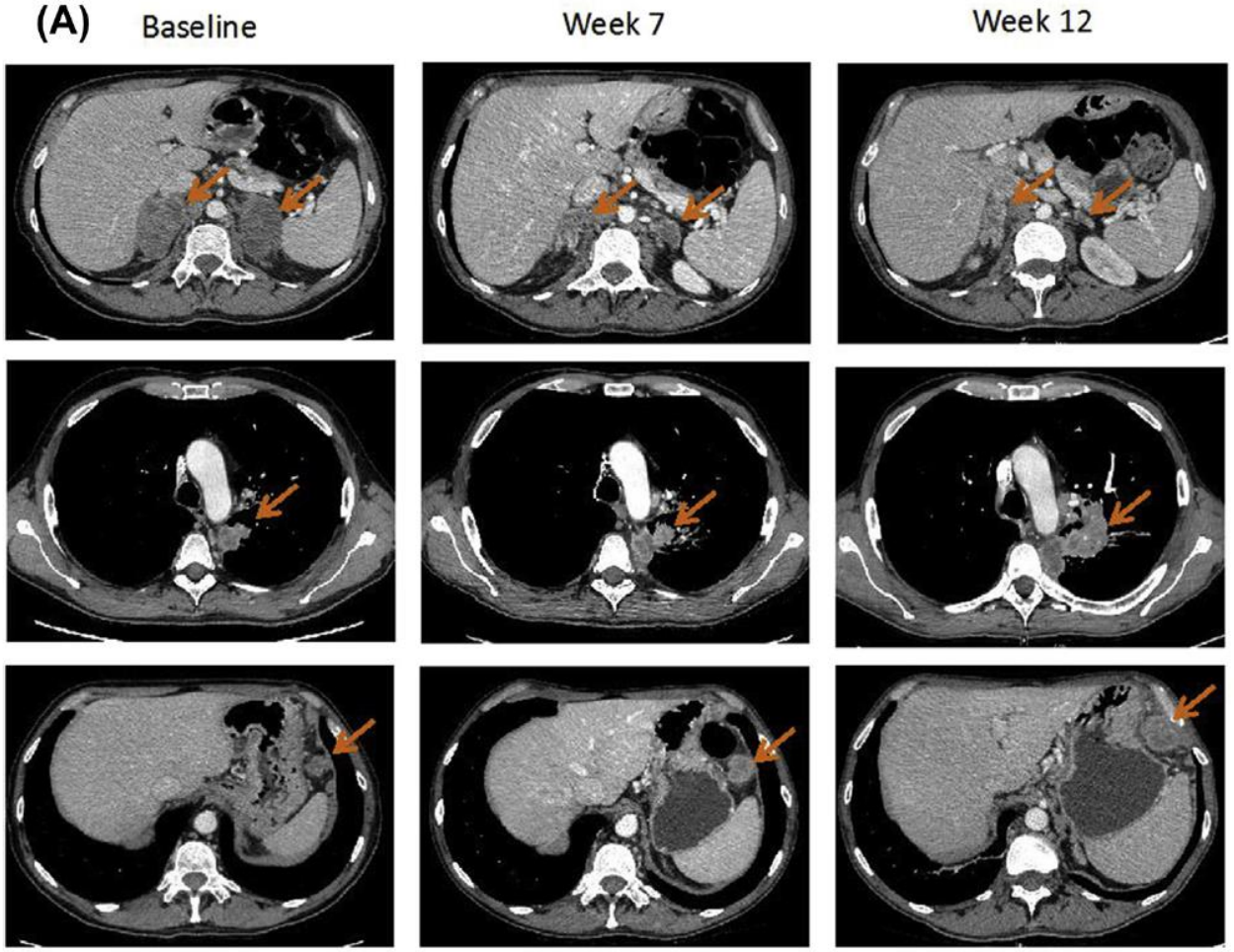
Clin Cancer Res 2009;15(23) December 1, 2009

Pseudo-Progression (PsPD) in NSCLC



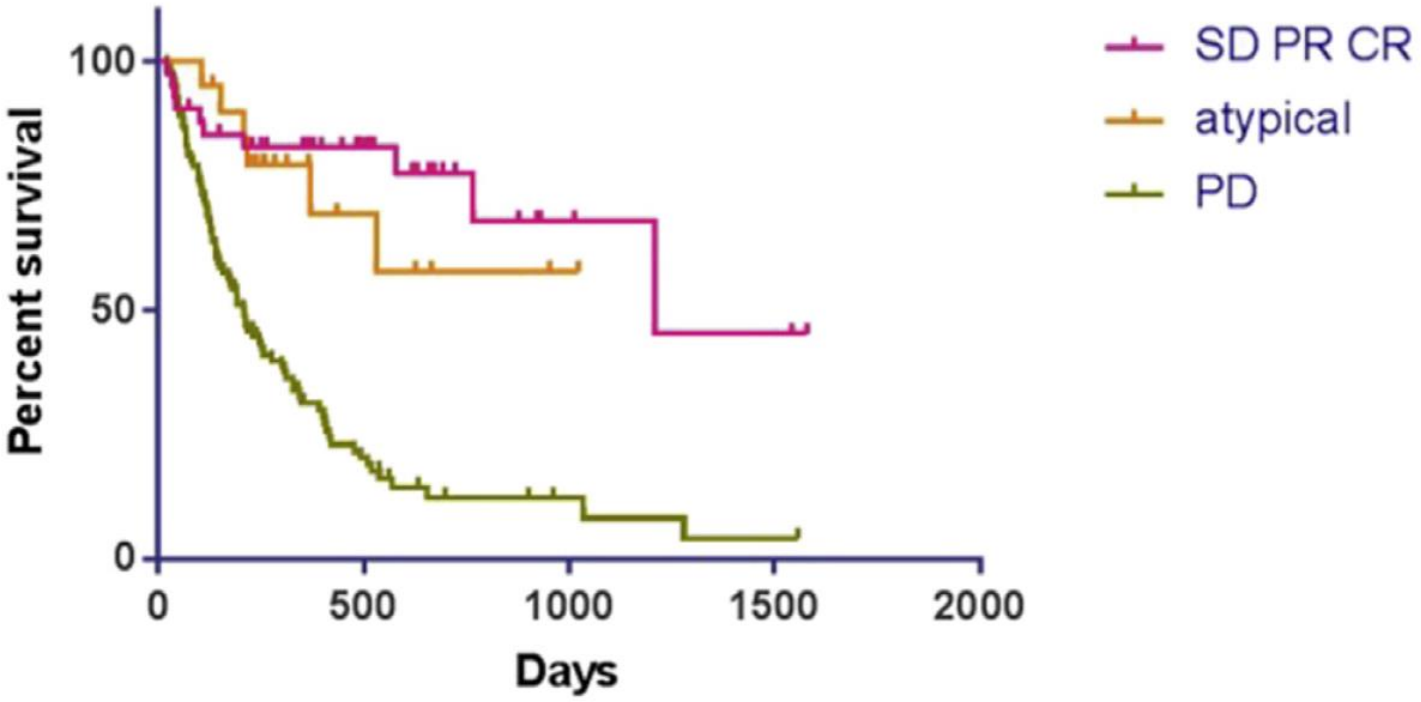
Tazdait M, et al. Patterns of responses in metastatic NSCLC during PD-1 or PDL-1 inhibitor therapy: Comparison of RECIST 1.1, irRECIST and iRECIST criteria. Eur J Cancer 2018;88:38–47.

Mixed Response in NSCLC



Tazdait M, et al. Patterns of responses in metastatic NSCLC during PD-1 or PDL-1 inhibitor therapy: Comparison of RECIST 1.1, irRECIST and iRECIST criteria. Eur J Cancer 2018;88:38–47.

Impact of Atypical Responses on Survival in NSCLC



Tazdait M, et al. Patterns of responses in metastatic NSCLC during PD-1 or PDL-1 inhibitor therapy: Comparison of RECIST 1.1, irRECIST and iRECIST criteria. Eur J Cancer 2018;88:38–47.

Baseline Tumor assessment

RECIST v1.1	irRC	irRECIST	iRECIST
• Sum of longest diameters of target lesions (unidimensional) • Max 5 lesions (2 per organ) • Measurable lesions defined as: ✓ 10 mm by CT ✓ 10 mm by caliper ✓ 20 mm chest X-ray ✓ Lymph nodes ≥15 mm short axis	• Sum of the products of the two largest perpendicular diameters (SPD) of each lesion ≥ 5 x 5 mm.	• Follows RECIST v1.1	• Follows RECIST v1.1

New Lesions

RECIST v1.1	irRC	irRECIST	iRECIST
• Represents PD	• Tumor Burden = $SPD_{\text{index lesions}} + SPD_{\text{new lesions}}$	• Does not correspond to a formal progression. • The longest diameter will be **added to the total measured tumour burden** of all target lesions at baseline	• Does not correspond to a formal progression • **Is not incorporated into tumor burden**

Complete Response (CR)

RECIST v1.1	irRC	irRECIST	iRECIST
• Disappearance of all target lesions • Lymph nodes must have reduction in short axis of <10mm • No new lesions	• Complete disappearance of all lesions • Confirm after 4 weeks	• Same as RECIST 1.1	• Same as RECIST 1.1

Partial Response (PR)

RECIST v1.1	irRC	irRECIST	iRECIST
• ≥30% decrease in sum of diameters of target lesions relative to baseline • Non progression of non-target lesions • No new lesions	• Decrease in tumor burden ≥50% relative to baseline • Confirm after 4 weeks	• Same as RECIST1.1	• Same as RECIST1.1

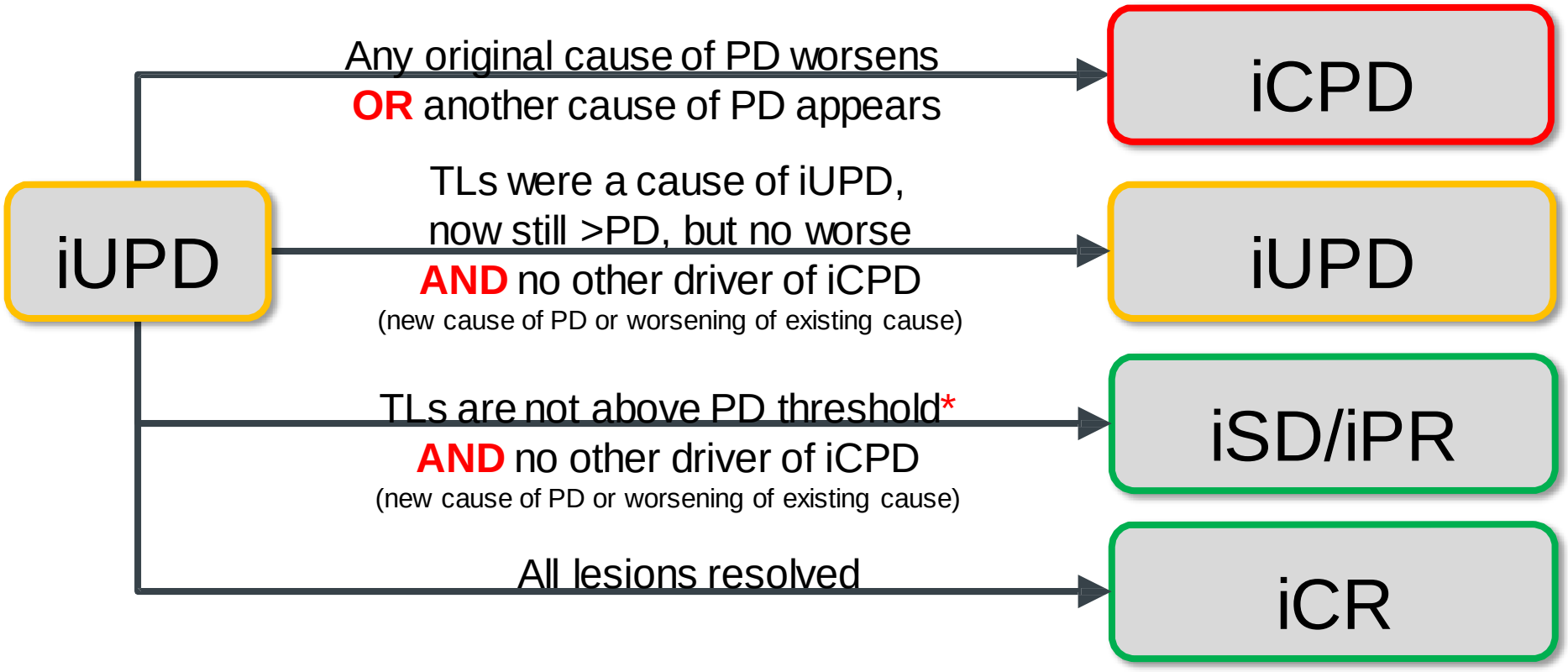
Stable Disease (SD)

RECIST v1.1	irRC	irRECIST	iRECIST
Neither PR or PD			

Progressive Disease (PD)

RECIST v1.1	irRC	irRECIST	iRECIST
• At least 20% increase in the sum of longest diameters of target lesions compared to nadir (absolute increase of at least 5mm) • Progression of non target lesions • New lesions • **Confirmation not required**	• Increase in tumor burden ≥25% relative to nadir • Confirm after 4 weeks.	**irPD** • Same as RECIST 1.1 **BUT** confirm after 4 weeks after the first irPD	**iUPD** • Same as RECIST 1.1 **BUT** confirm after 4 weeks after the first iUPD

Resolving Initial iUPD



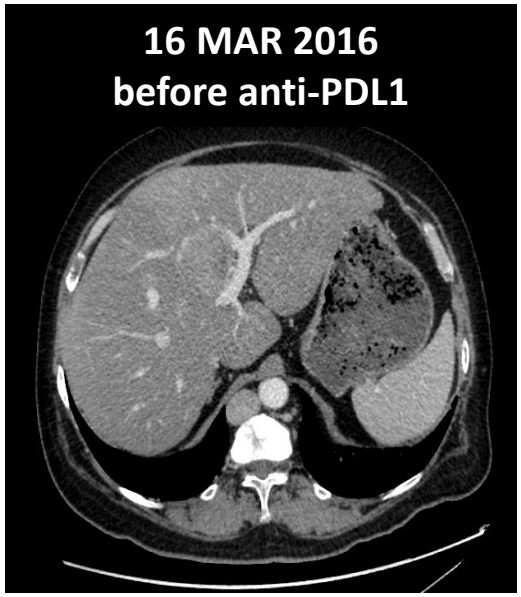
Note: Only target lesion PD, if present at iUPD, must resolve to achieve iSD/iPR.
e.g. PR in TLs + unequivocal PD of NTLs + new lesions → unchanged = iPR

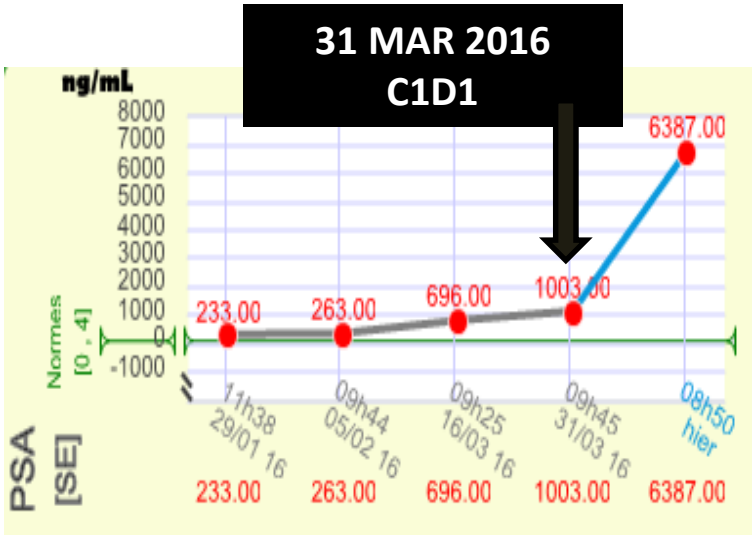
Courtesy of Gregory Goldmacher (MSD)

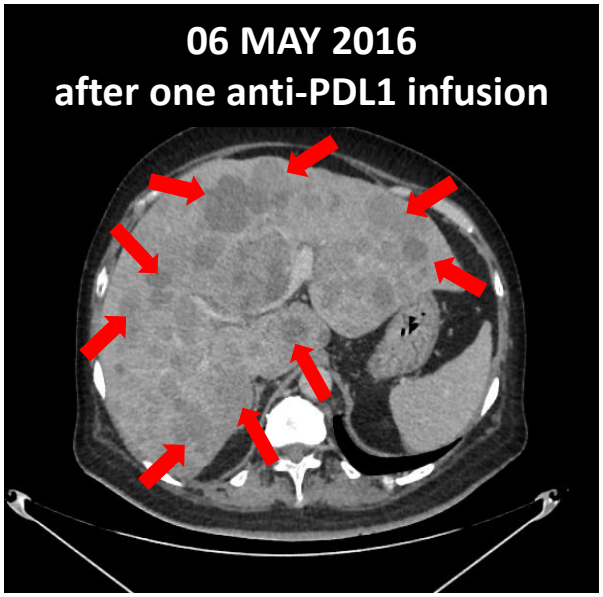
In Summary

- **RECIST 1.1 does not take atypical immune responses into account**
- **irRC**: more complex and no standardized definition of PsPD (threshold, timing)
- **irRECIST**: unidimensional, confirmation of PD at 4 weeks, *addition of new lesions to sum of target lesions*
- **iRECIST**: same as irRECIST *without addition of new lesions to sum of target lesions*

Could Anti-PD-(L)1 Immunotherapy be detrimental for some patients ?

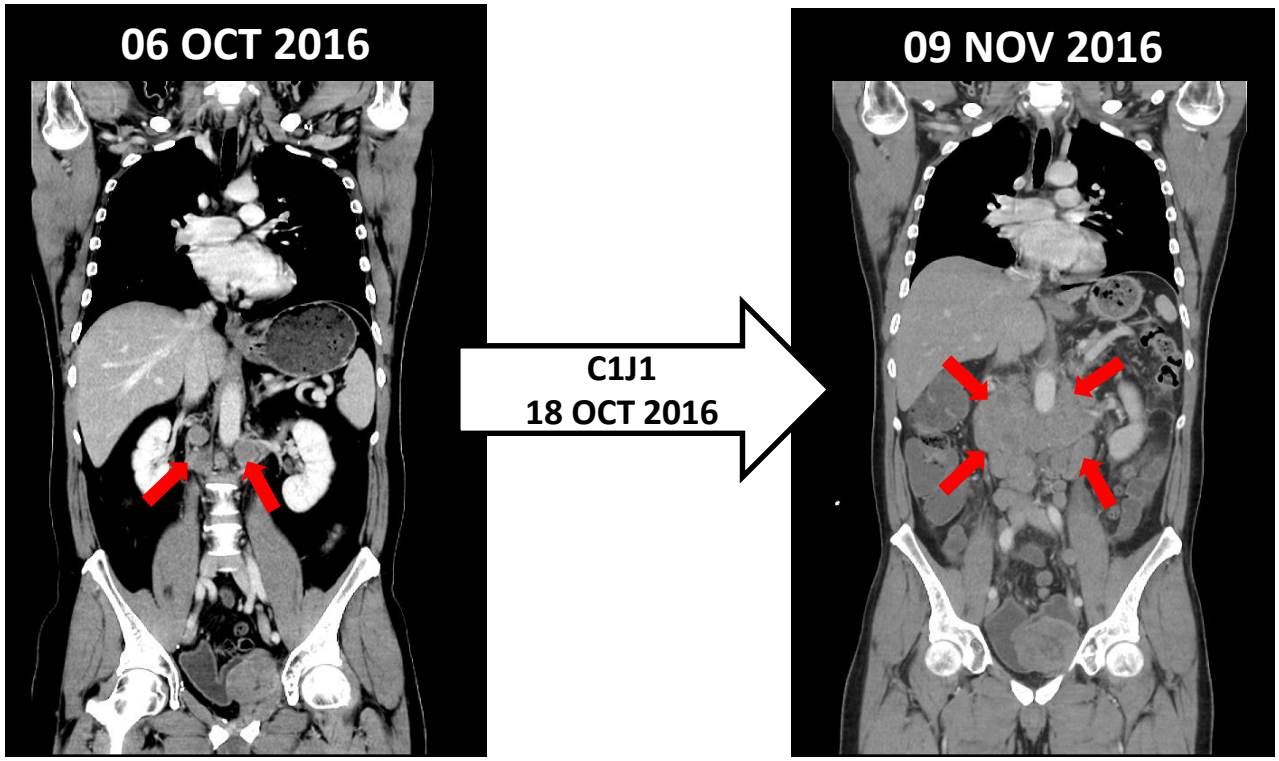






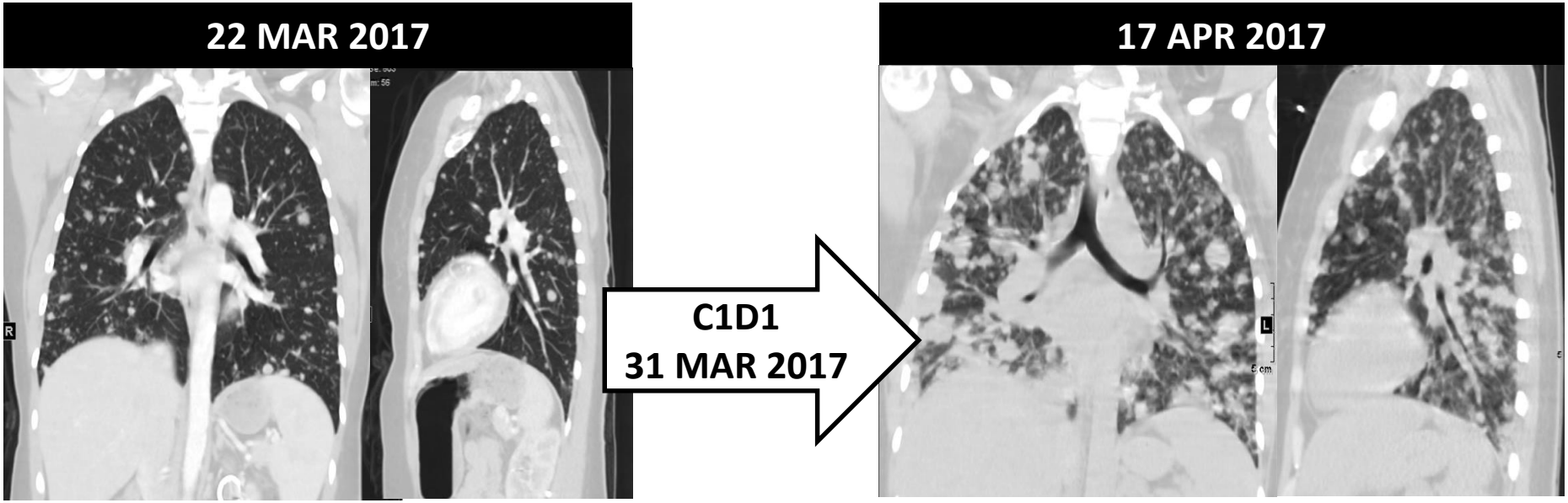
Hyperprogressive Prostate Cancer under Anti-PD-L1 Therapy

Urothelial carcinoma 49 yo male
anti-PDL1 combo with other immunotherapy



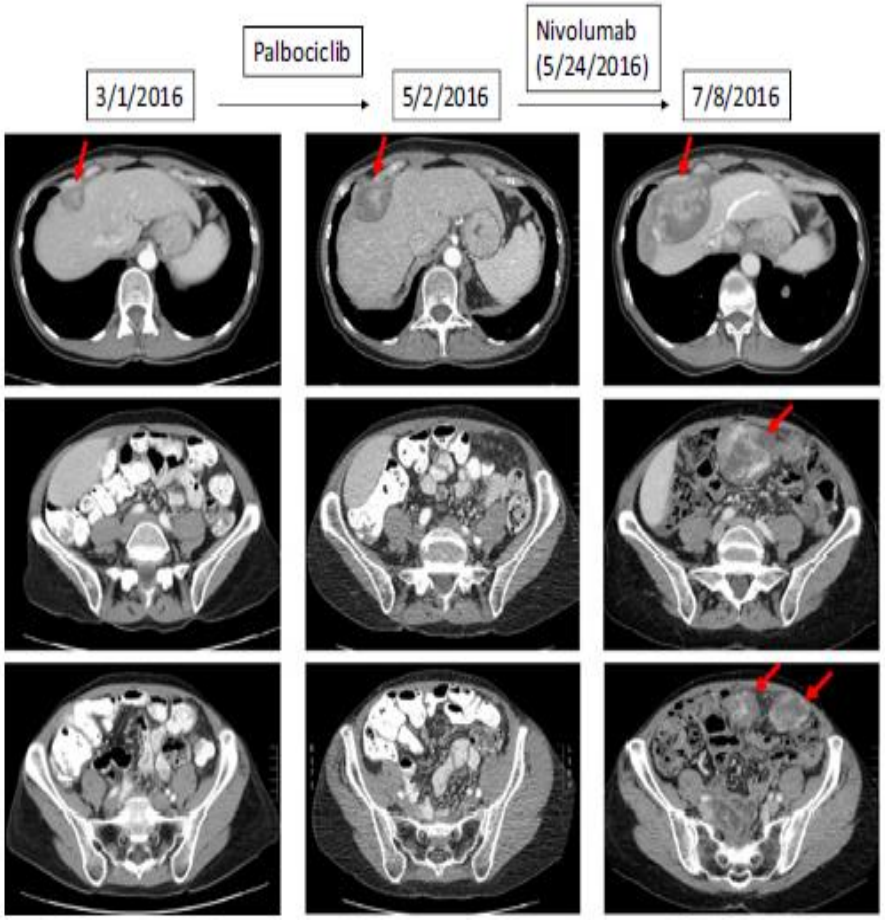
Aurélien Marabelle MD, PhD, Gustave Roussy

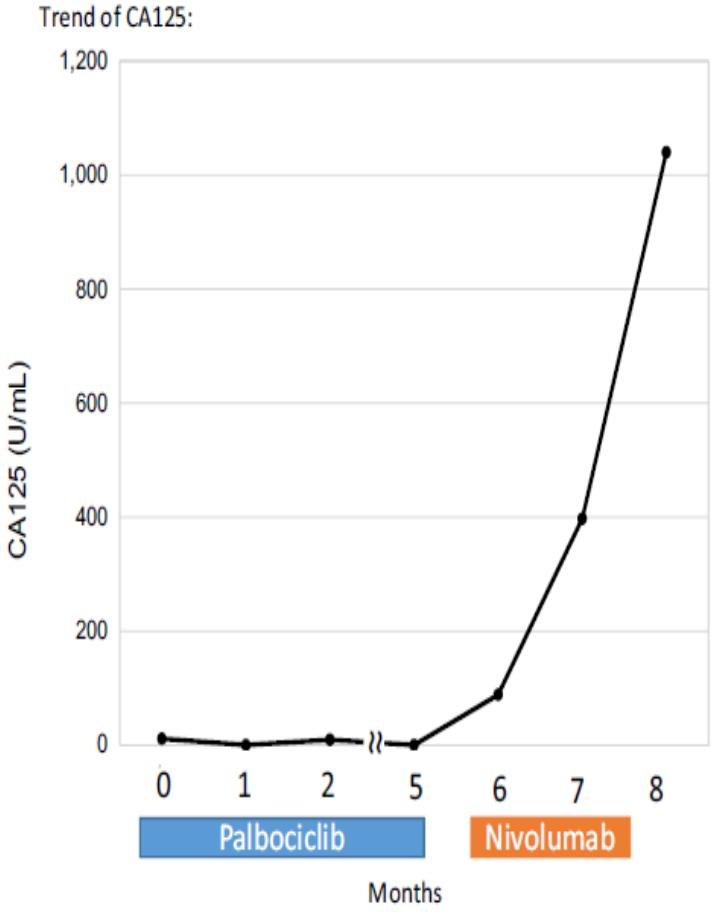
Urothelial carcinoma, 40yo female, anti-PD-1



Aurélien Marabelle MD, PhD, Gustave Roussy

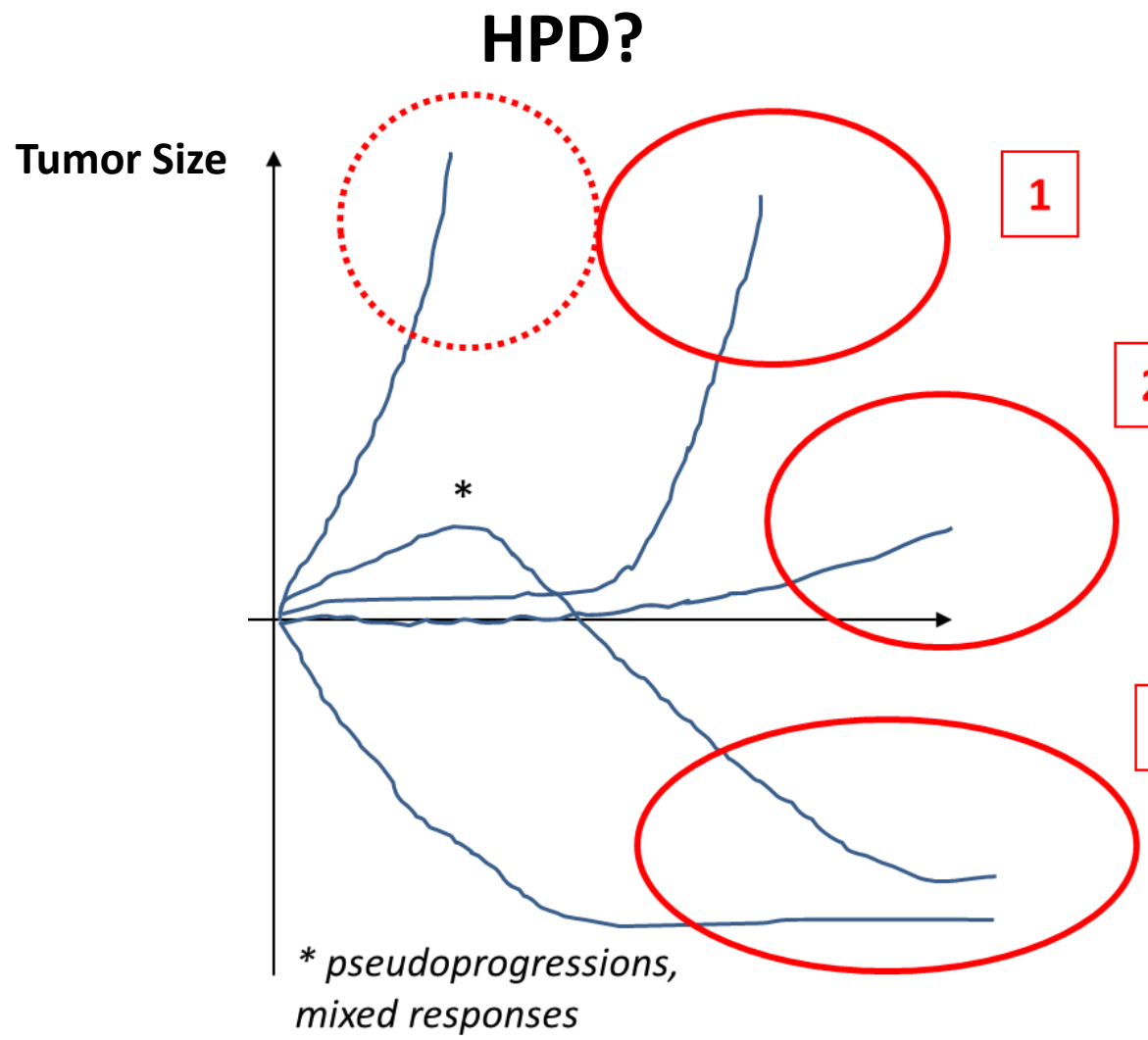
Endometrial Stromal Sarcoma, anti-PD-1





Kato S, et al. Hyper-progressors after Immunotherapy: Analysis of Genomic Alterations Associated with Accelerated Growth Rate. Clin Cancer Res 2017:clincanres.3133.2016.

Is HPD an unexpected pattern of progression?

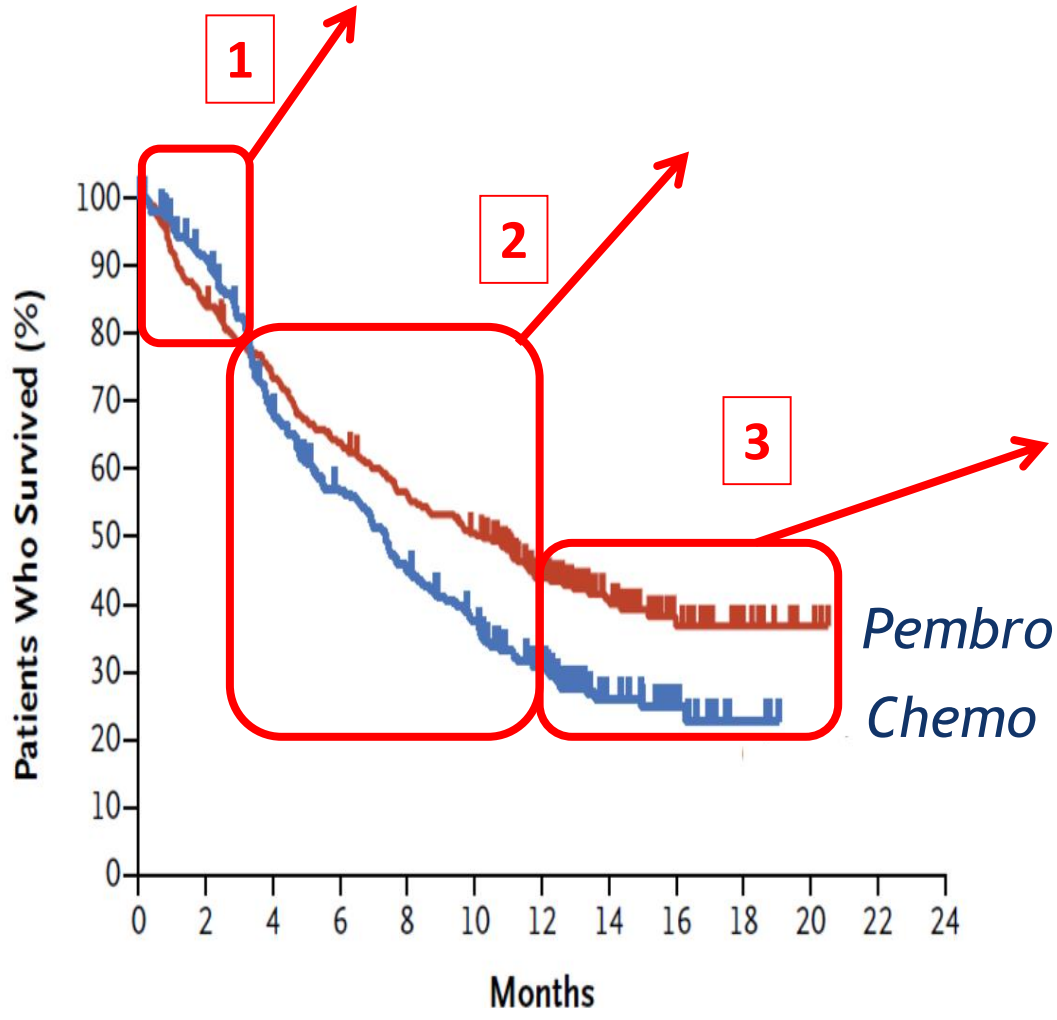


1 **Progressive Disease**

2 **Stable Disease**

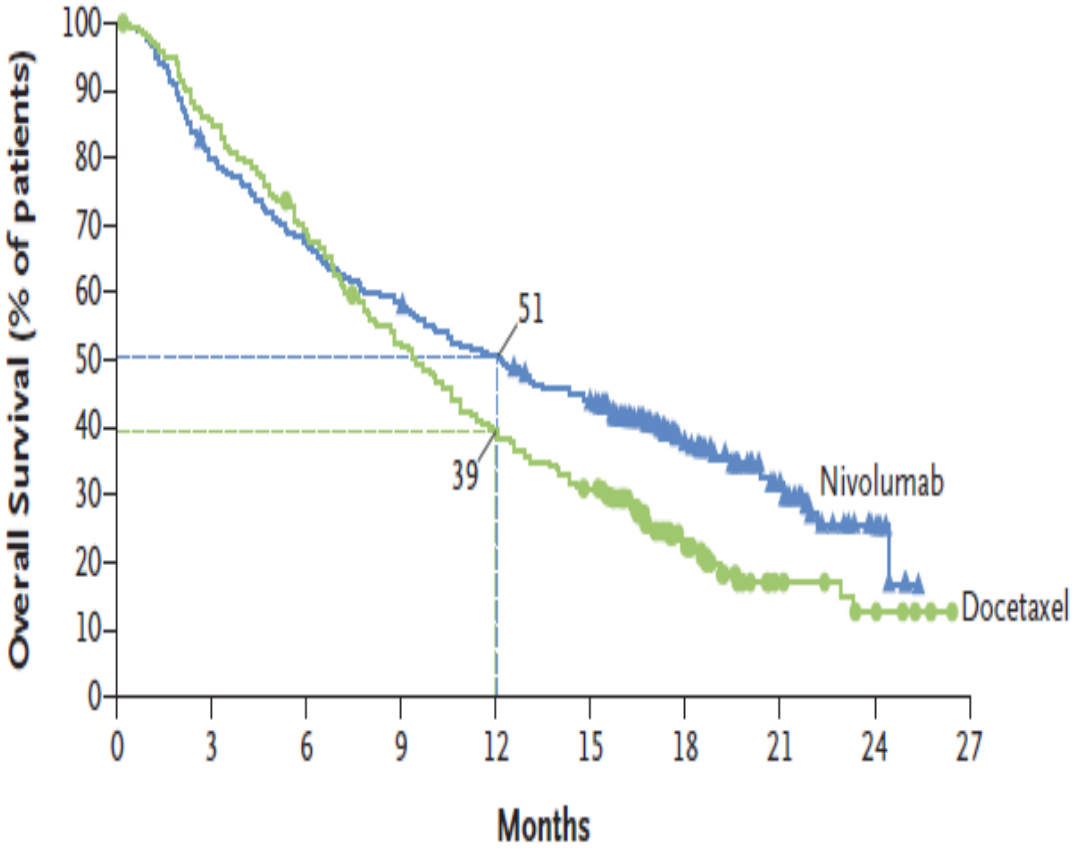
3 **Partial/Complete Responses**

Can HPD Explain Early Crossing of Survival Curves ?



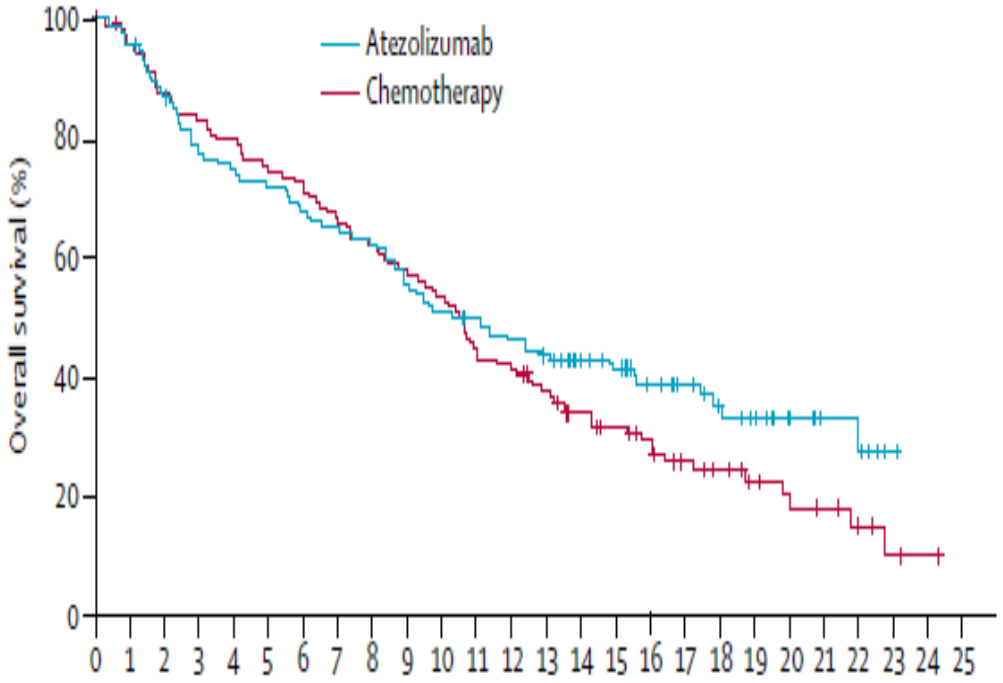
NEJM 2017; 376(11):1015–1026.

Excess of Death in first 3 months *nivolumab in NSCLC*



Borghaei H, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer. N Engl J Med 2015.

Excess of Death in first 3 months *atezolizumab in UC*



Powles T, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2018;391:748–57.

What is a Hyperprogression ?

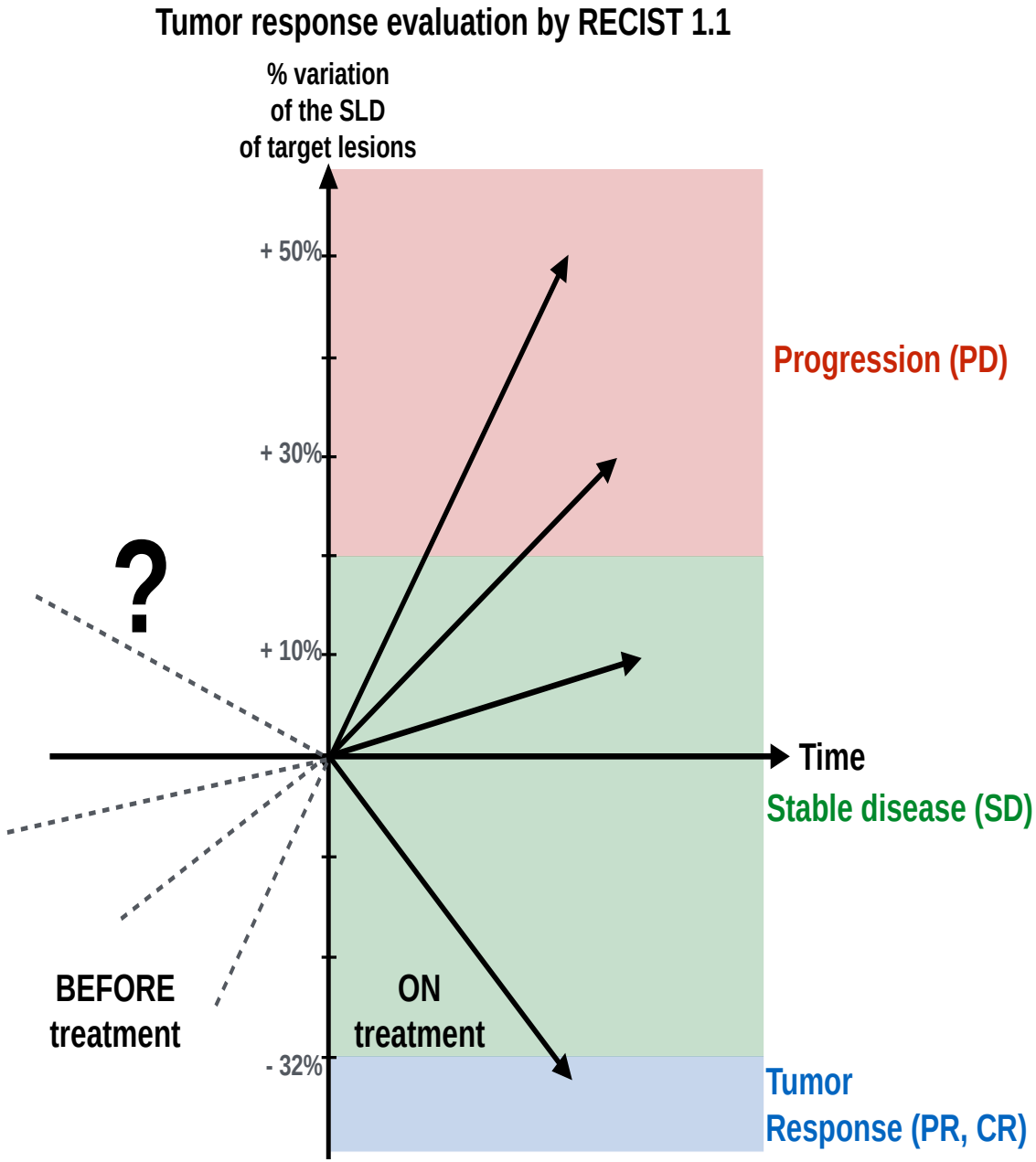
Acceleration of Cancer Growth

Triggered by the initiation of anti-PD(L)1 Treatment

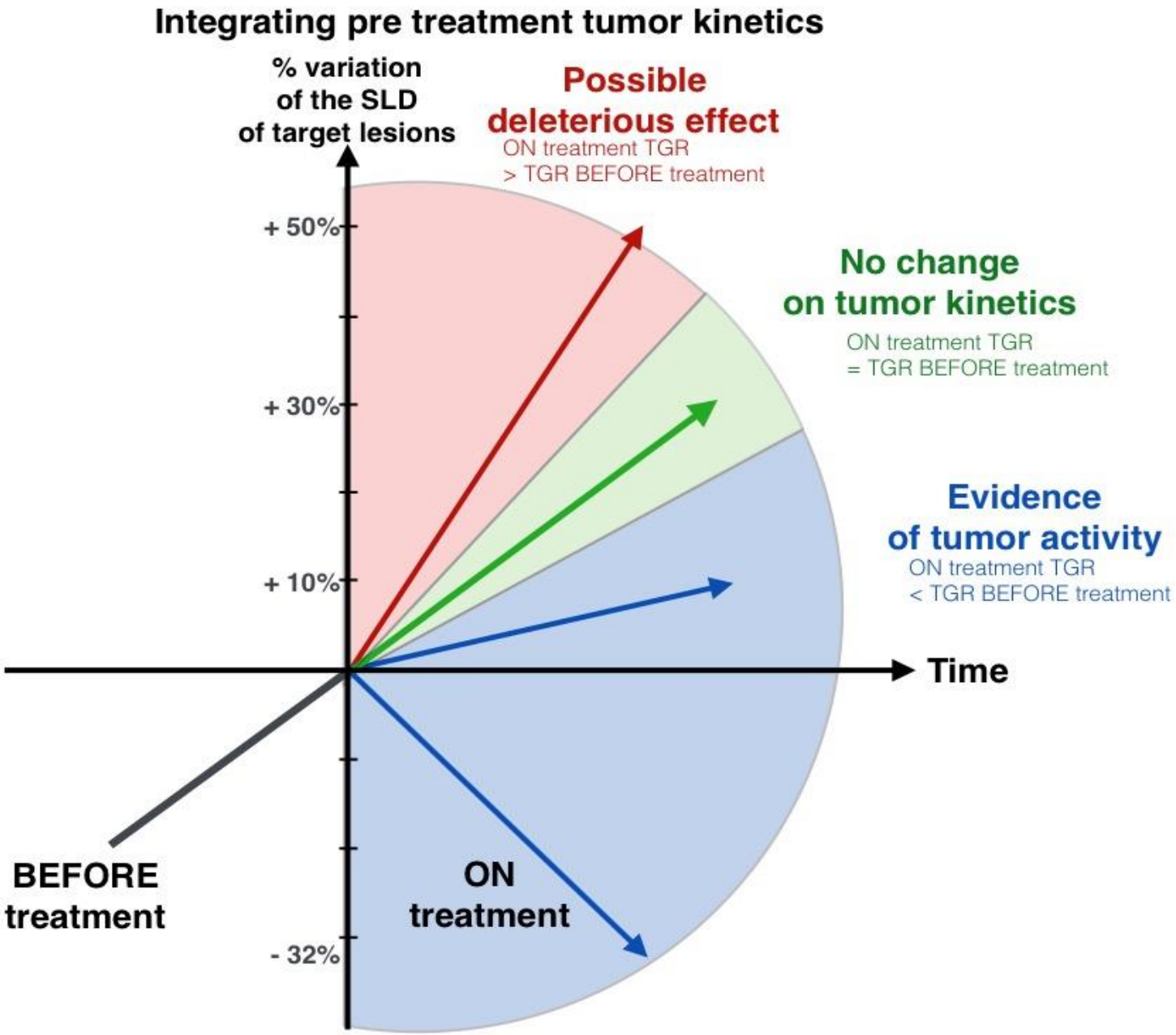
(Clinical Definition)

➔ *Detrimental effect*

➔ *At the beginning of the treatment*



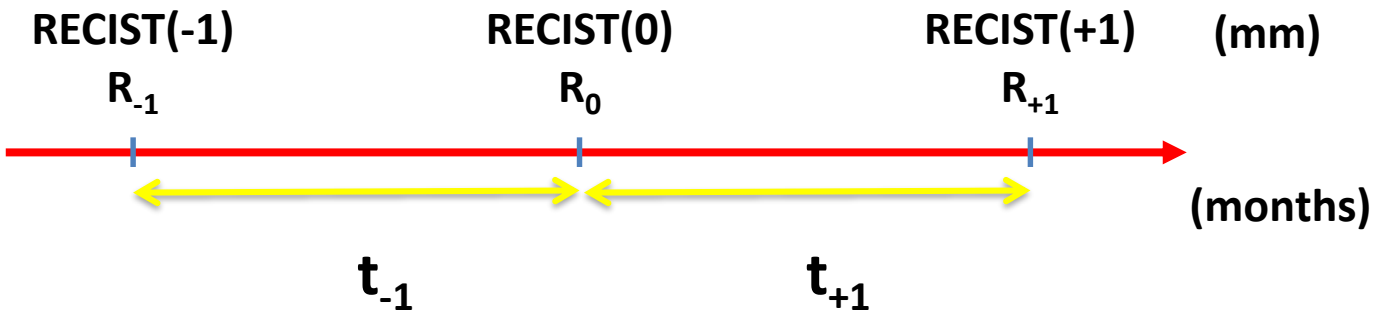
Champiat S, et al. Hyperprogressive disease: recognizing a novel pattern to improve patient management. Nat Rev Clin Oncol 2018;15:748–62.



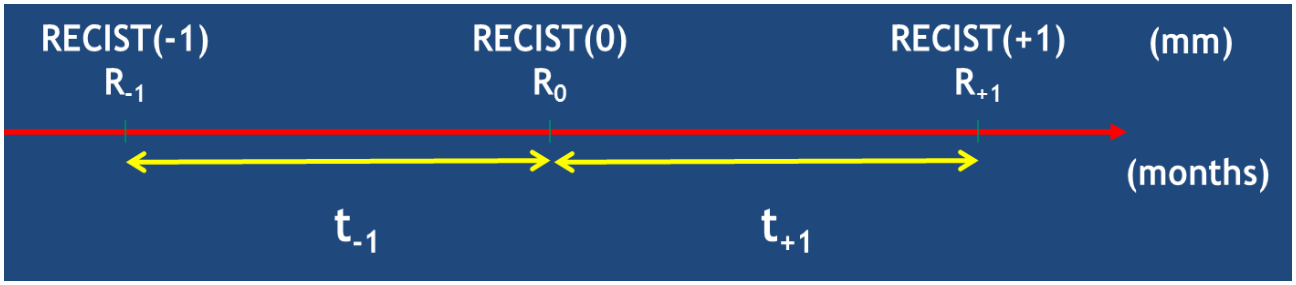
Champiat S, et al. Hyperprogressive disease: recognizing a novel pattern to improve patient management. Nat Rev Clin Oncol 2018;15:748–62.

Evaluating Tumor Kinetics in Clinical Practice

What is needed ?



Tumor Growth Rates (TGR) vs Kinetics (TGK)



TGR method :

$$TGR_{-1} = 100\left[\exp\left(\frac{3\log(R_0/R_{-1})}{t_{-1}}\right) - 1\right] \qquad TGR_{+1} = 100\left[\exp\left(\frac{3\log(R_{+1}/R_0)}{t_{+1}}\right) - 1\right]$$

TGK method :

$$TGK_{-1} = \frac{R_0 - R_{-1}}{t_{-1}} \qquad TGK_{+1} = \frac{R_{+1} - R_0}{t_{+1}}$$

$\frac{TGR_{+1}}{TGR_{-1}}$

Champiat et al.

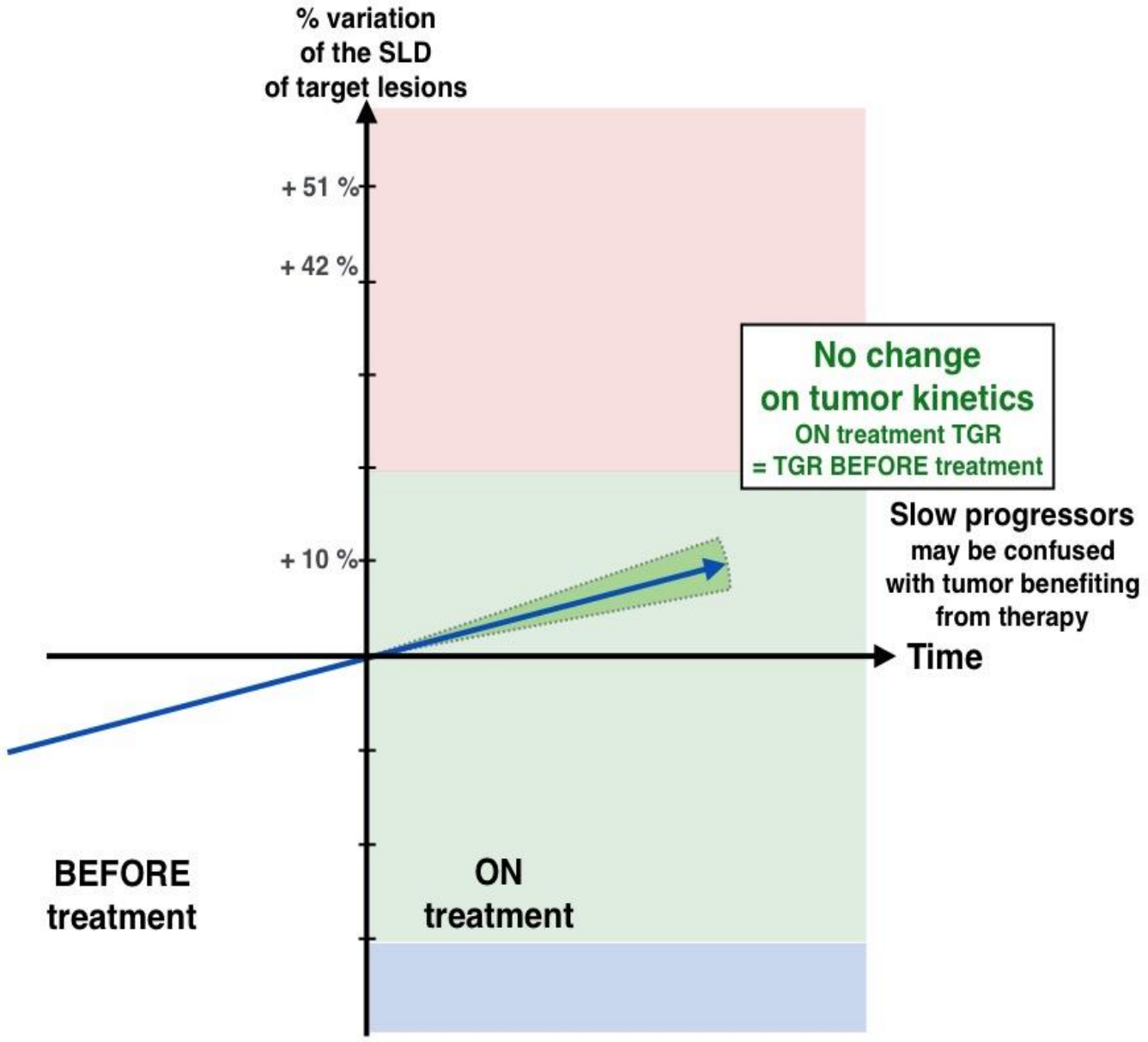
Delta TGR: $TGR_{+1} - TGR_{-1}$

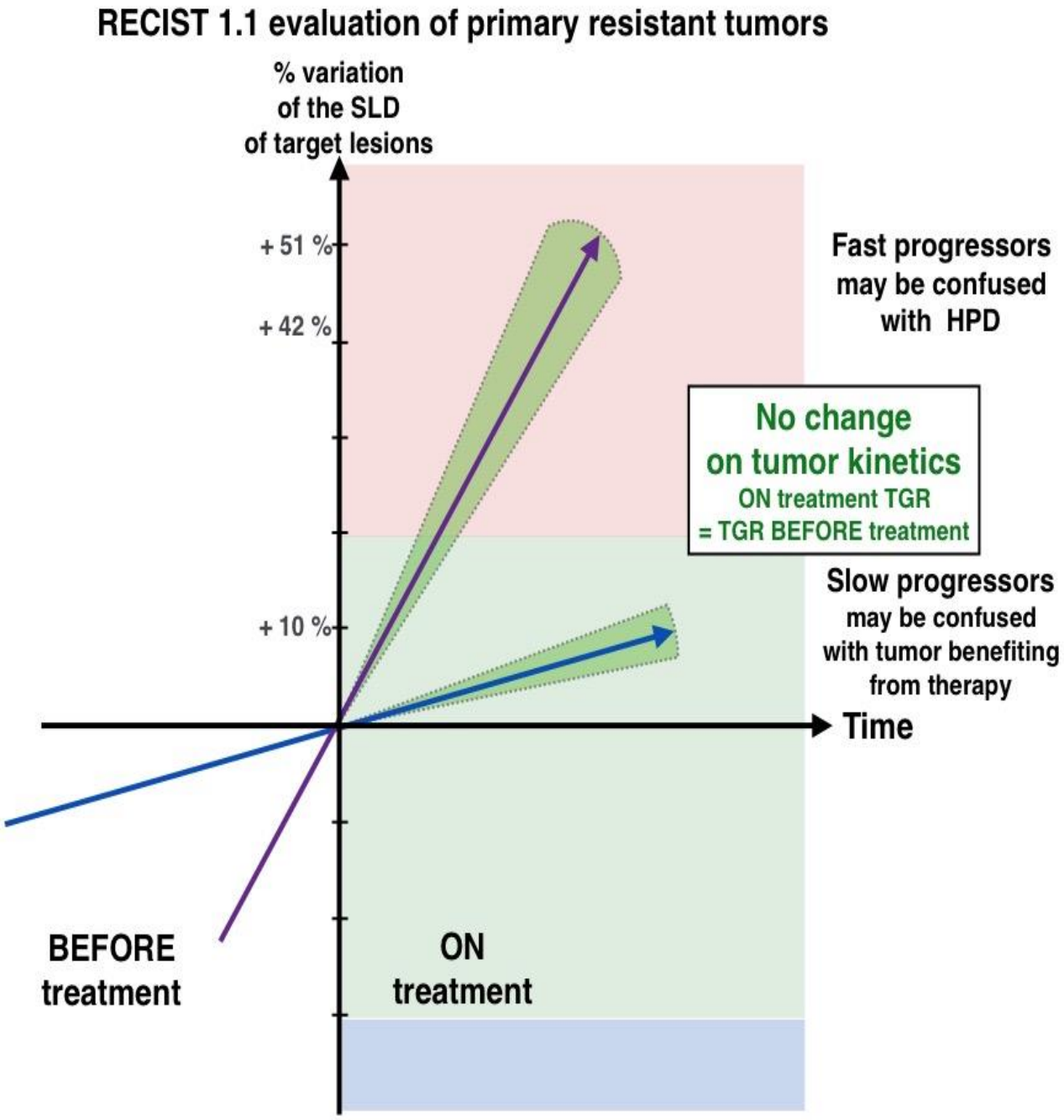
Ferrara et al.

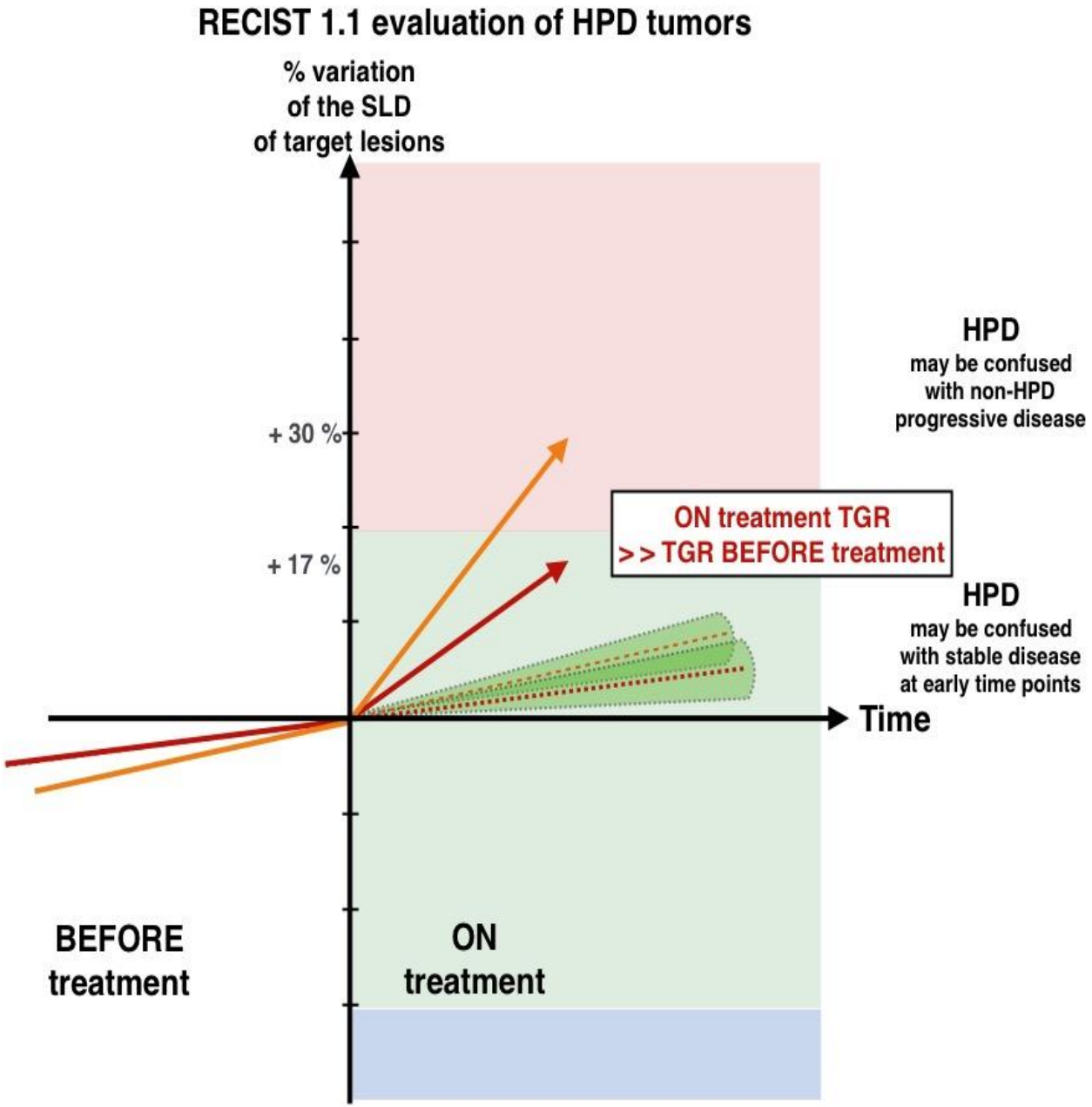
TGK ratio : $\frac{TGK_{+1}}{TGK_{-1}}$

Saada-Bouzid et al.

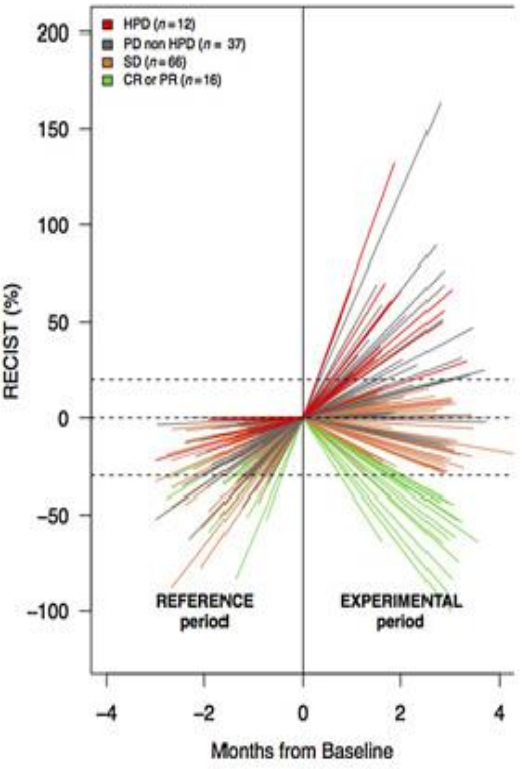
RECIST 1.1 evaluation of primary resistant tumors



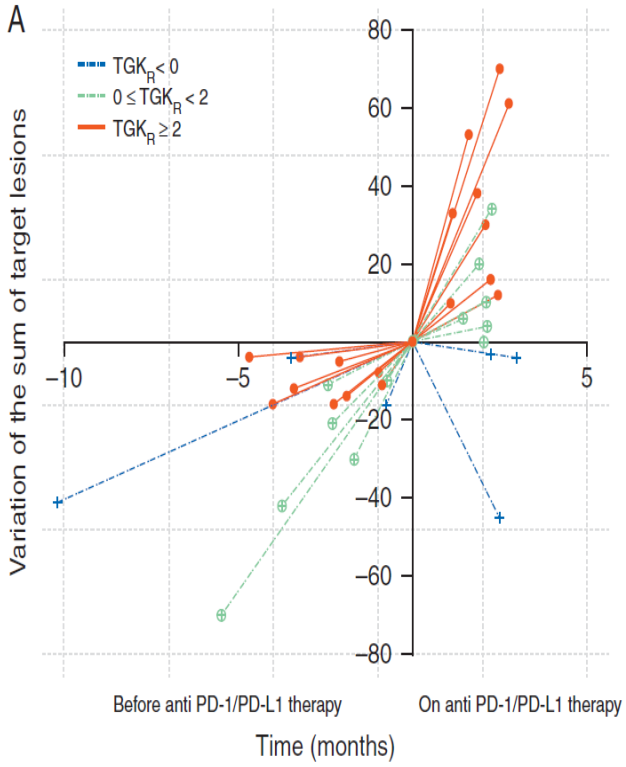



RECIST 1.1 evaluation of HPD tumors
% variation
of the SLD
of target lesions
+ 30 %
+ 17 %
HPD
may be confused
with non-HPD
progressive disease
ON treatment TGR
>> TGR BEFORE treatment
HPD
may be confused
with stable disease
at early time points
Time
BEFORE
treatment
ON
treatment

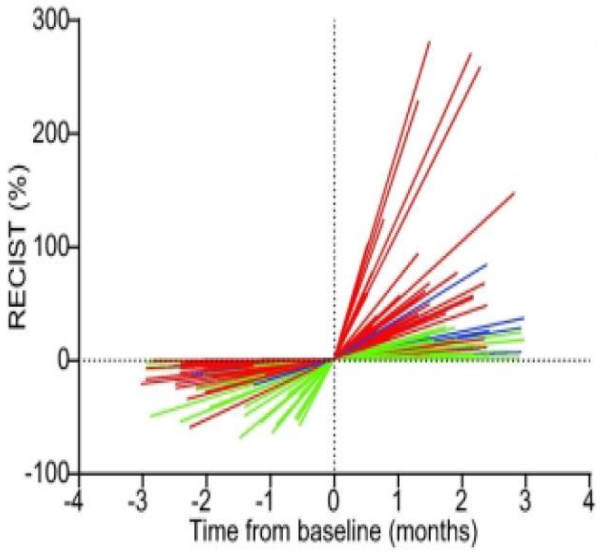
Some Patient Increase Their TGR/TGK Under Anti-PD(L)1



Champiat S, et al.
Clin Cancer Res 2017;23:1920–8.



Saâda-Bouzid E, et al. Ann Oncol 2017:1605–11.

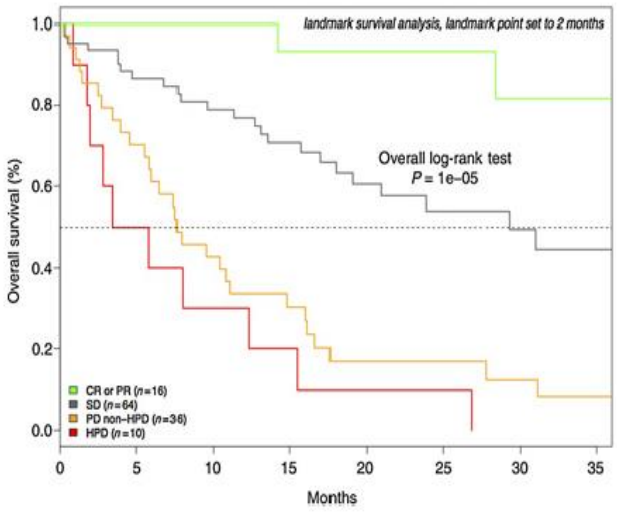


Kim CG, et al. Ann Oncol 2019. doi:10.1093/annonc/mdz123.

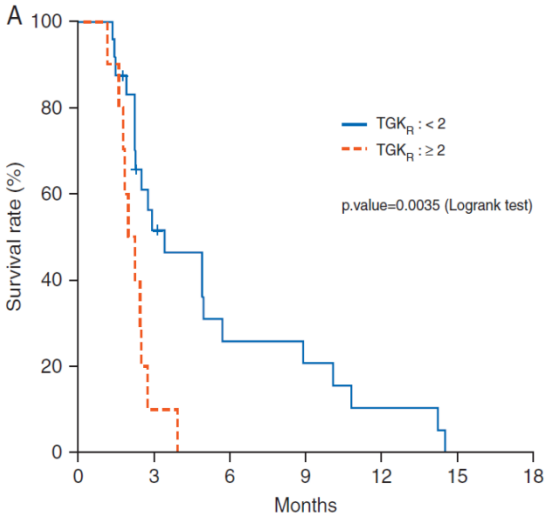
Incidence of HPD ?

	Champiat et al. Clin. Cancer Research 2016	Kato et al. Clin. Cancer Research 2017	Saâda-Bouzid et al. Annals of Oncol 2017	Ferrara et al. JAMA Oncol 2018	Kim et al. Annals of Oncol 2019
HPD definition	**RECIST PD at first evaluation** **and** **TGR EXP/TGR Ratio ≥ 2**	**time-to-treatment failure (TTF) <2 months** **>50% increase in tumor burden compared with pre-immunotherapy imaging** **>2-fold increase in "progression pace"**	acceleration of tumor growth kinetics (TGK) **TGK ratio (TGK_R) ≥2**	**RECIST PD at first evaluation** **and** **TGR EXP/TGR Ratio > 1,5**	**TGK, TGR, TTF**
Patients	**N = 131** **Metastatic cancers** phase 1 trials Anti-PD(L)1 monotherapy	**N = 155** **Metastatic cancers with molecular profiling** Anti-CTLA-4, PD-1/PD-L1 or other investigational agents	**N= 34** **Recurrent and/or Metastatic HNSCC** Anti-PD(L)1 monotherapy	**N= 406** **Advanced NSCLC** Anti-PD(L)1 +/- IO combo	N = 263 recurrent and/or metastatic NSCLC Anti-PD(L)1 monotherapy
HPD rate	**9% (12/131)**	**6% (6/102)**	**29% (10/34)**	**14% (56/406)**	**21% (55/263)**

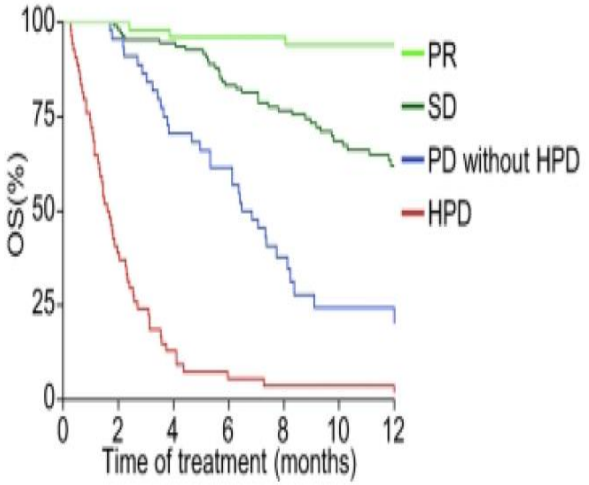
HPD Patients Have a Worse Prognosis



Champiat S, et al.
Clin Cancer Res 2017;23:1920–8.

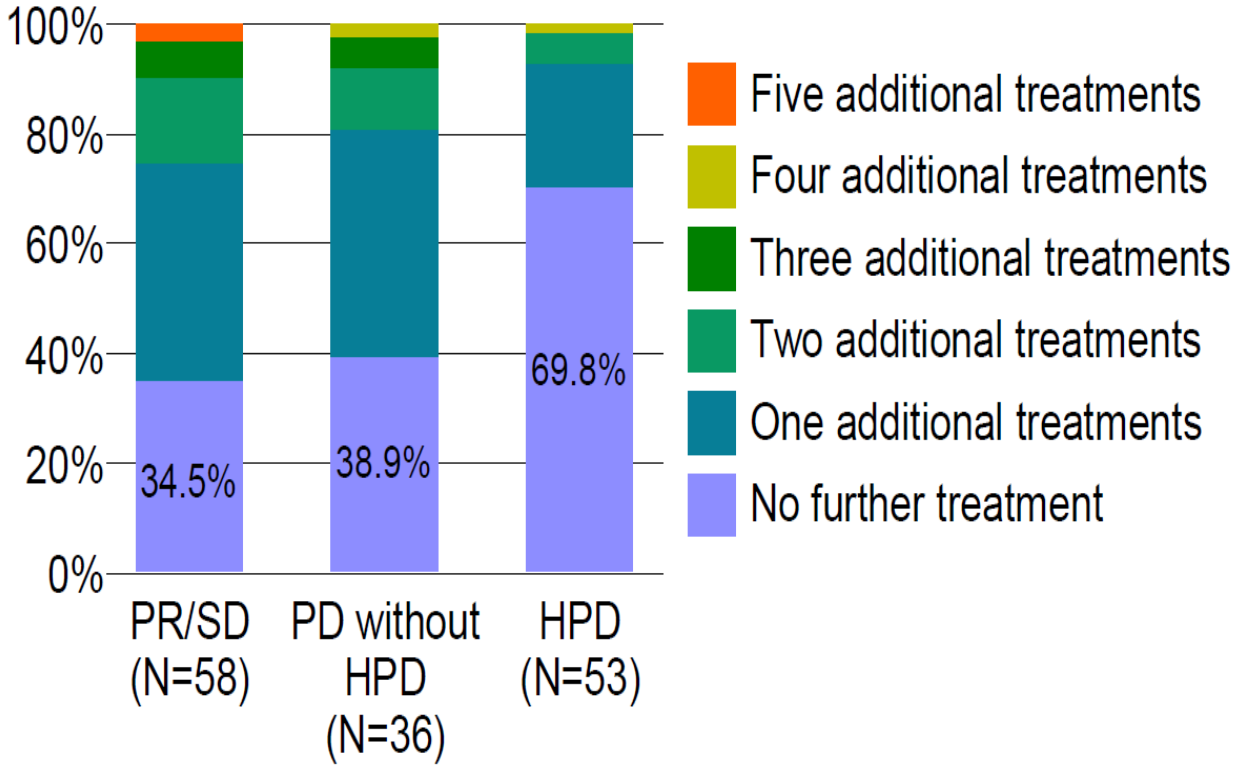


Saâda-Bouzid E, et al.
Ann Oncol 2017:1605–11.
doi:10.1093/annonc/mdx178.



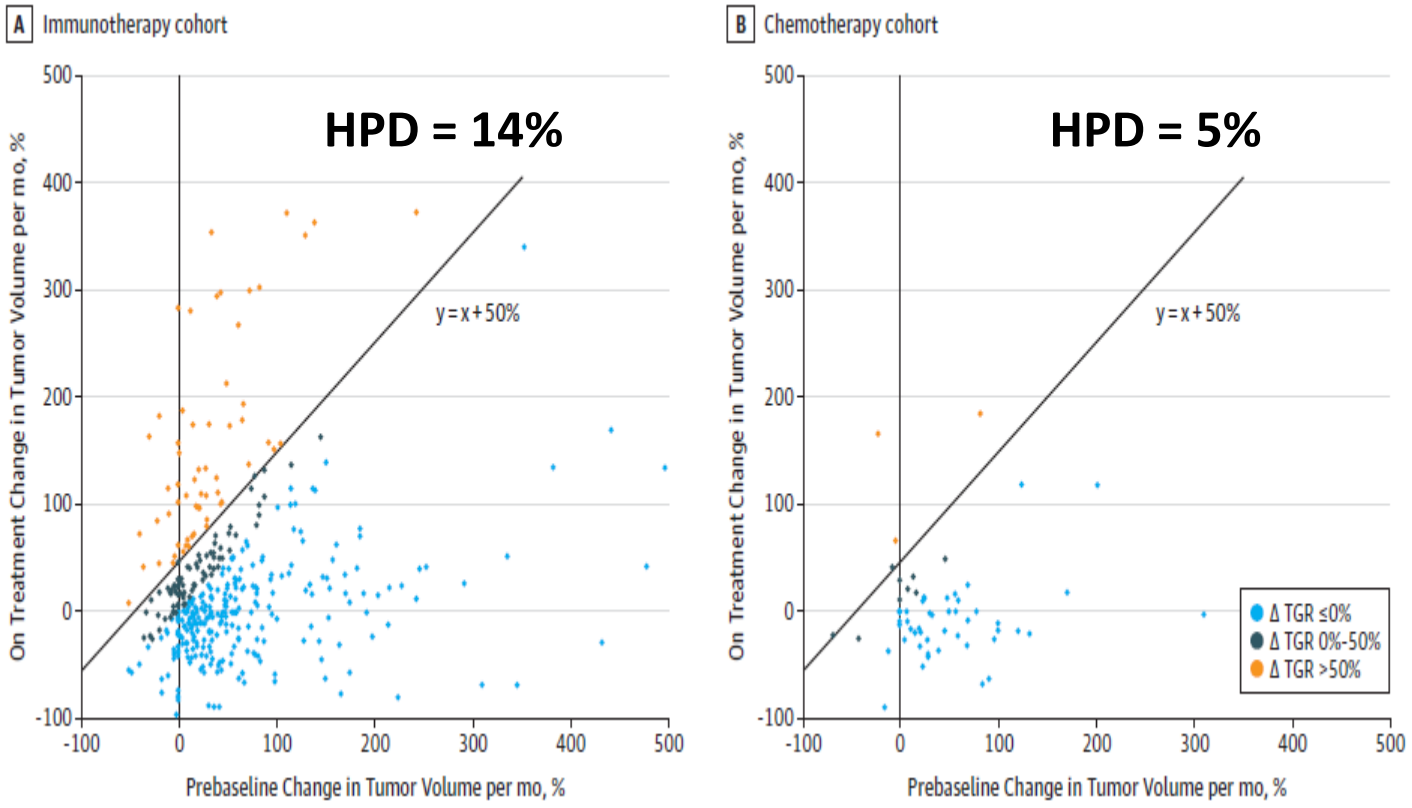
Kim CG, et al. Ann Oncol 2019.
doi:10.1093/annonc/mdz123.

HPD Patients Don’t Have Time For Next Line of Therapy



Kim CG, et al. Hyperprogressive disease during PD-1/PD-L1 blockade in patients with non-small-cell lung cancer. Ann Oncol 2019. doi:10.1093/annonc/mdz123.

HPD is not limited to anti-PD(L)1



(Pseudo-Prog = 5%)

Ferrara R, et al. Hyperprogressive Disease in Patients With Advanced Non-Small Cell Lung Cancer Treated With PD-1/PD-L1 Inhibitors or With Single-Agent Chemotherapy. JAMA Oncol 2018;4:1543–52.

HPD is Not Associated with :

sex, ECOG, smoking, histology, drug/isotype
albumin, NLR
tumor burden
tumor PD-L1, EGFR, ALK, ROS status
tumor mutational burden (TMB)
number or type of previous therapeutic lines
baseline corticosteroid use
presence of inflammatory markers at baseline

Champiat et al. Clin. Cancer Research 2016
Kato et al. Clin. Cancer Research 2017
Saâda-Bouzid et al.Annals of Oncology 2017
Ferrara R, et al. JAMA Oncol 2018;4:1543–52.
Kim CG, et al. Ann Oncol 2019. doi:10.1093/annonc/mdz123.

HPD has been associated with :

Age > 65y.o

LDH > ULN

Number of mets > 2

Liver mets

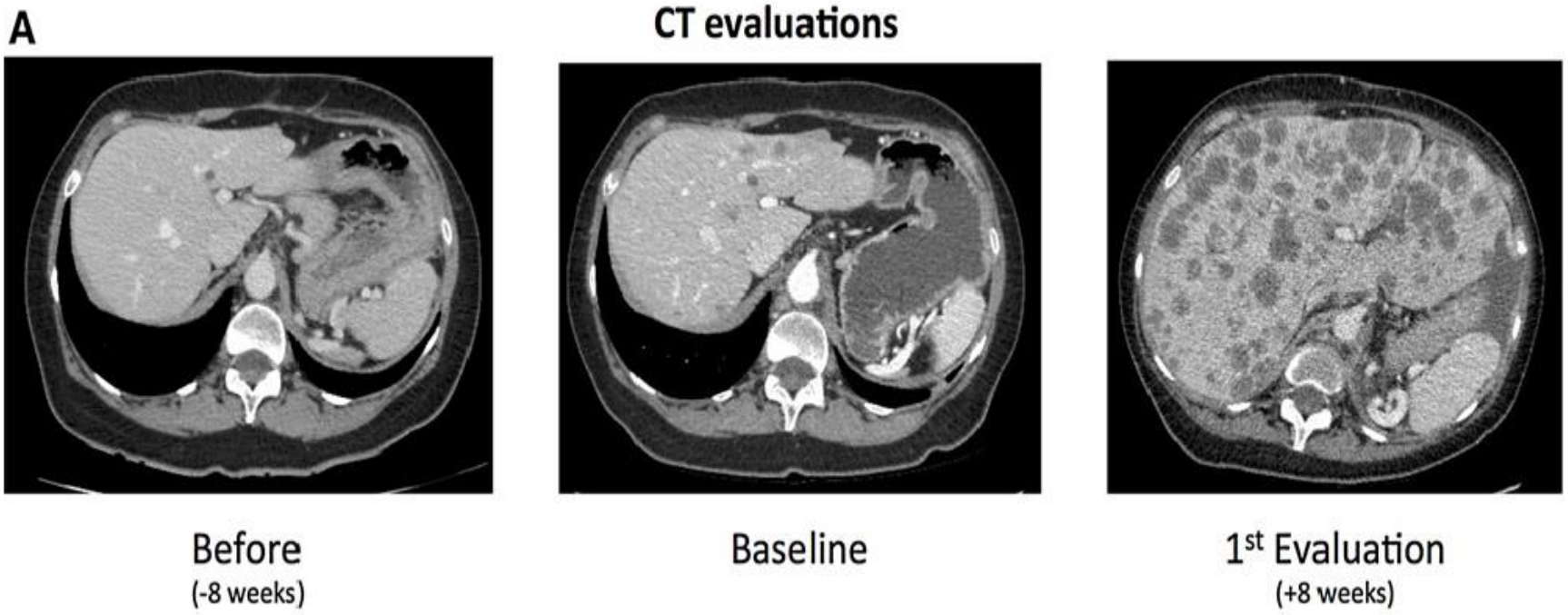
Champiat et al. Clin. Cancer Research 2016
Kato et al. Clin. Cancer Research 2017
Saâda-Bouzid et al.Annals of Oncology 2017
Ferrara R, et al. JAMA Oncol 2018;4:1543–52.
Kim CG, et al. Ann Oncol 2019. doi:10.1093/annonc/mdz123.

Limitations of TGR/TGK:

HPD on Metastatic Mode

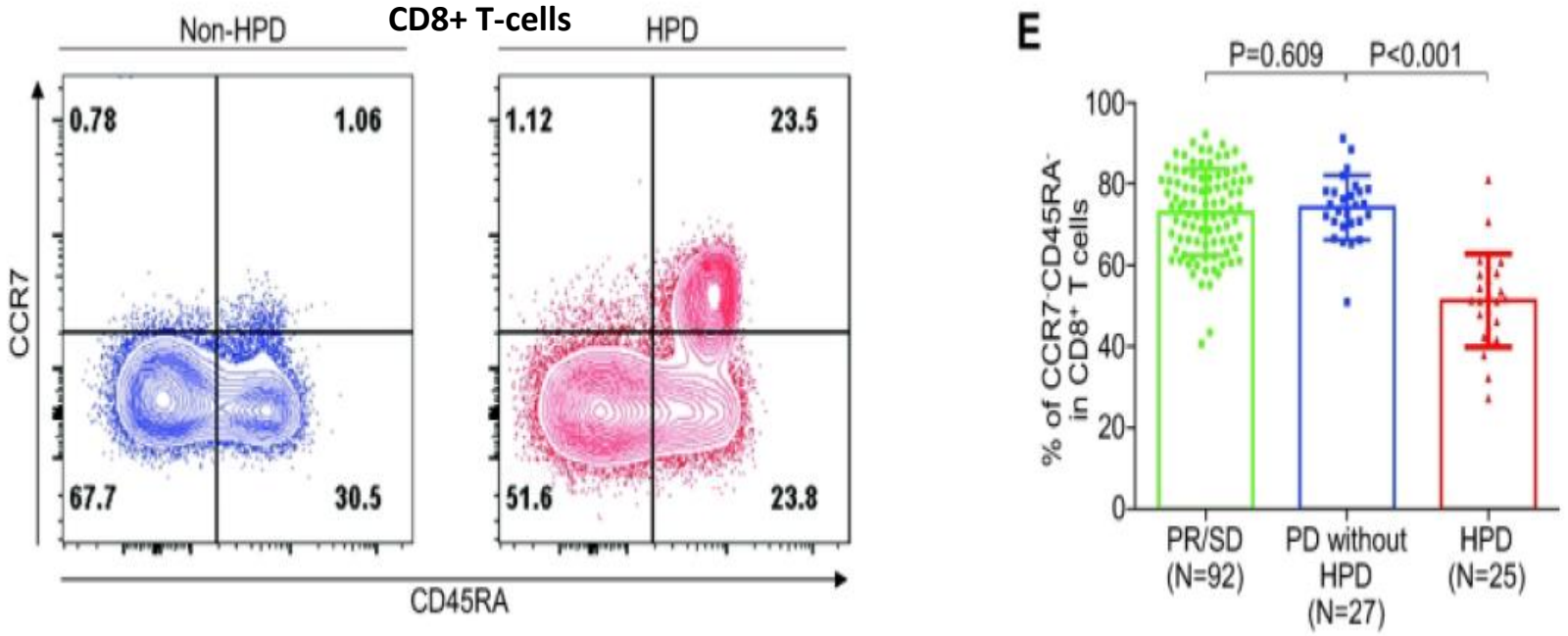
HPD on non target lesions

HPD in first line therapy



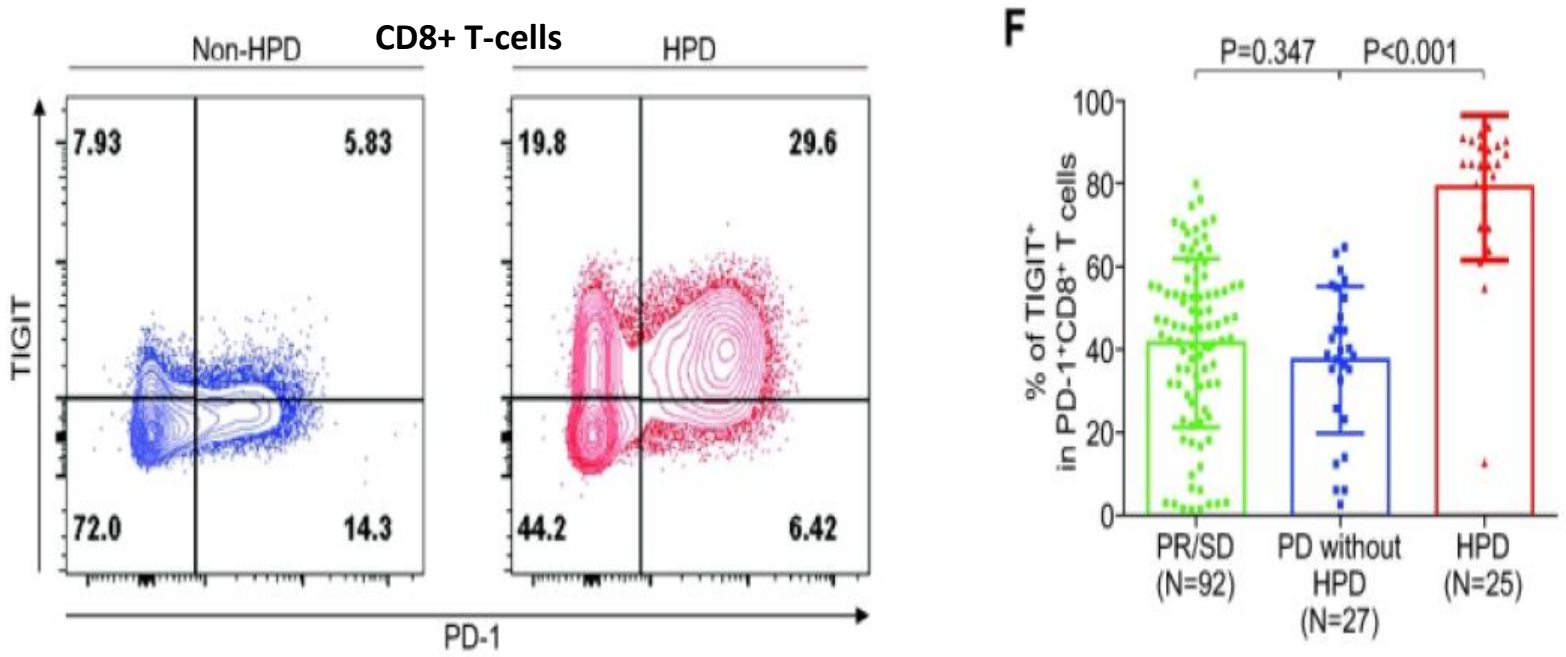
Champiat S, et al. Hyperprogressive Disease Is a New Pattern of Progression in Cancer Patients Treated by Anti-PD-1/PD-L1. Clin Cancer Res 2017;23:1920–8.

HPD patients have low circulating CCR7-CD45RA-CD8+ T-cells



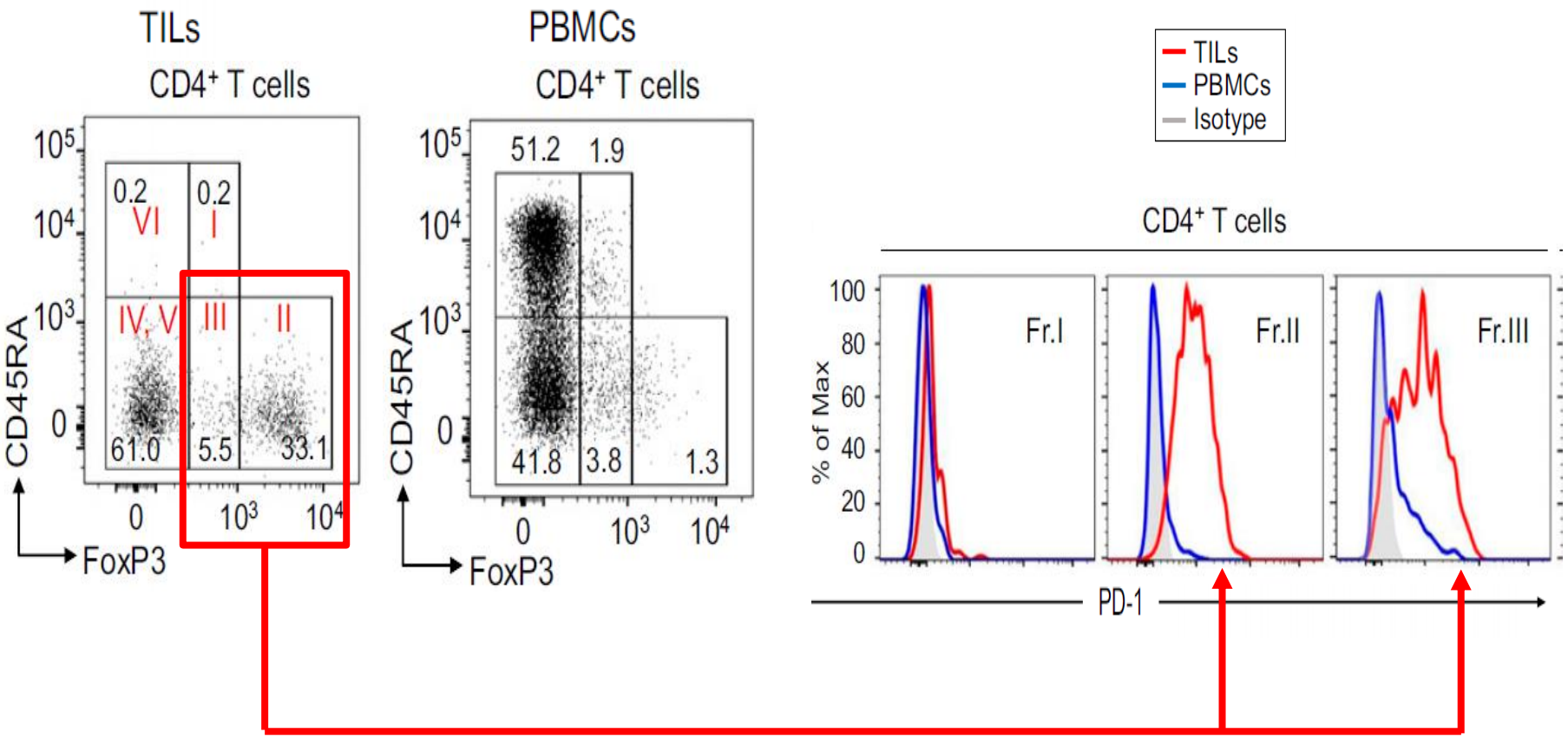
Kim CG, et al. Hyperprogressive disease during PD-1/PD-L1 blockade in patients with non-small-cell lung cancer. Ann Oncol 2019. doi:10.1093/annonc/mdz123.

HPD patients have high circulating TIGIT+PD-1+ CD8+ T-cells



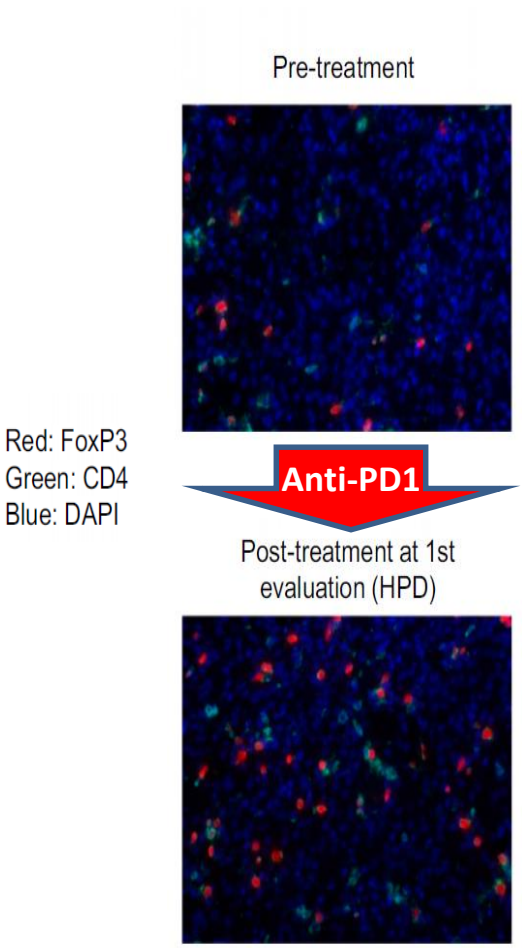
Kim CG, et al. Hyperprogressive disease during PD-1/PD-L1 blockade in patients with non-small-cell lung cancer. Ann Oncol 2019. doi:10.1093/annonc/mdz123.

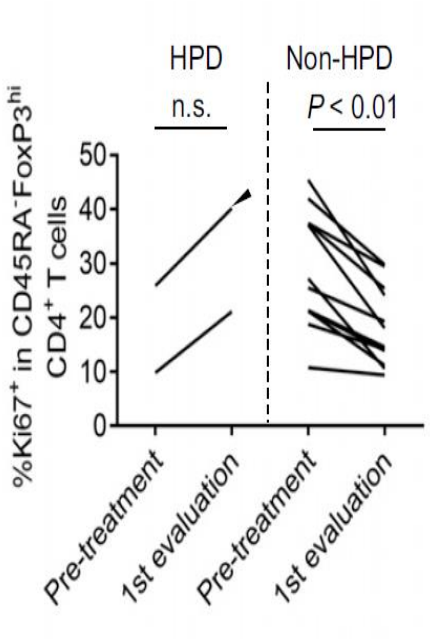
Impact of Intratumoral PD-1+ Tregs ?

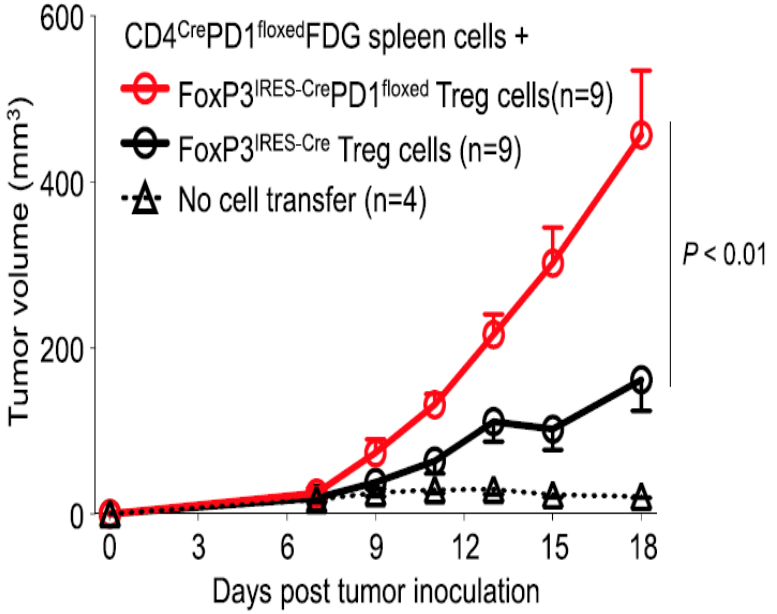


Kamada T, et al. PD-1 + regulatory T cells amplified by PD-1 blockade promote hyperprogression of cancer. PNAS 2019;116:201822001.

Intratumoral Tregs Proliferate in HPD Pts upon αPD1 therapy

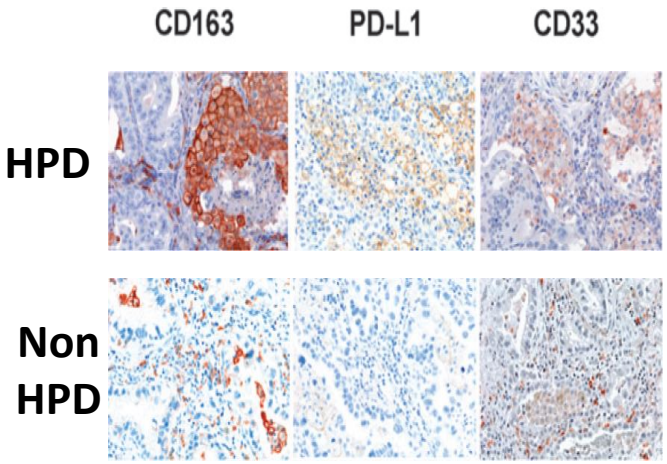


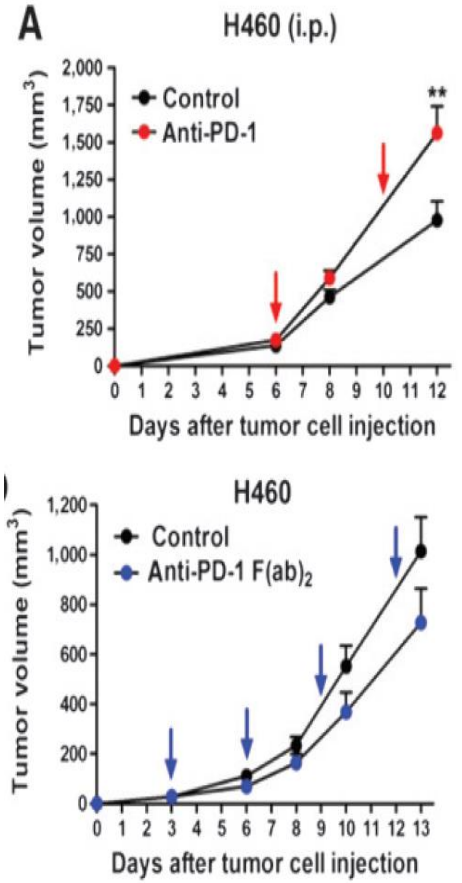


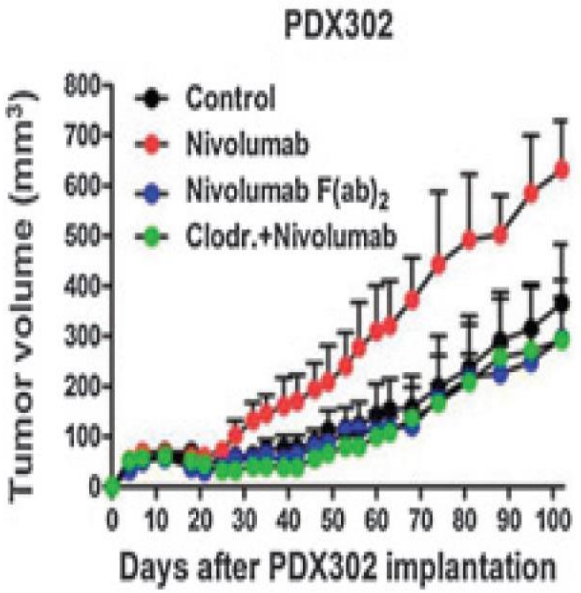


Kamada T, et al. PD-1 + regulatory T cells amplified by PD-1 blockade promote hyperprogression of cancer. PNAS 2019;116:201822001.

HPD by FcγR engagement by anti-PD-1 on TAMs

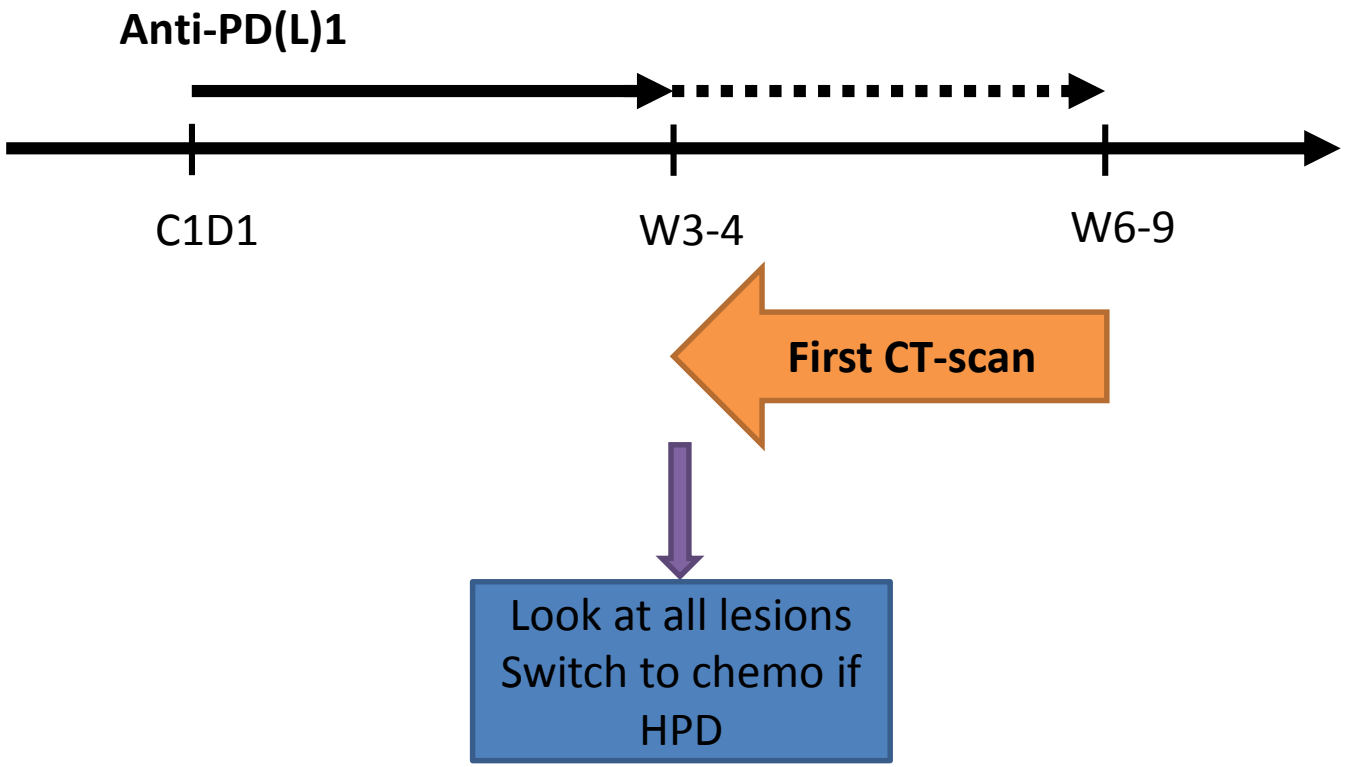






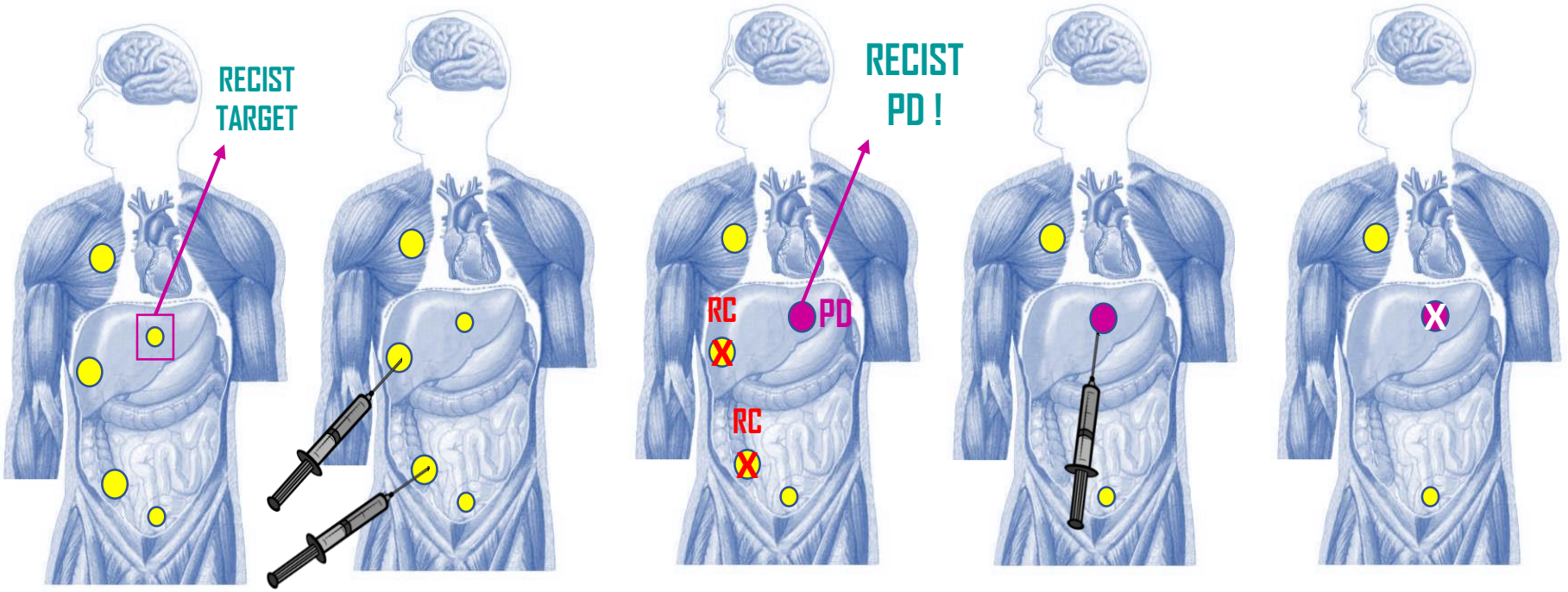
Lo Russo G, et al. Antibody–Fc/FcR Interaction on Macrophages as a Mechanism for Hyperprogressive Disease in Non–small Cell Lung Cancer Subsequent to PD-1/PD-L1 Blockade. Clin Cancer Res 2018:1–12.

Do we need HPD biomarkers or Better Clinical Practice ?

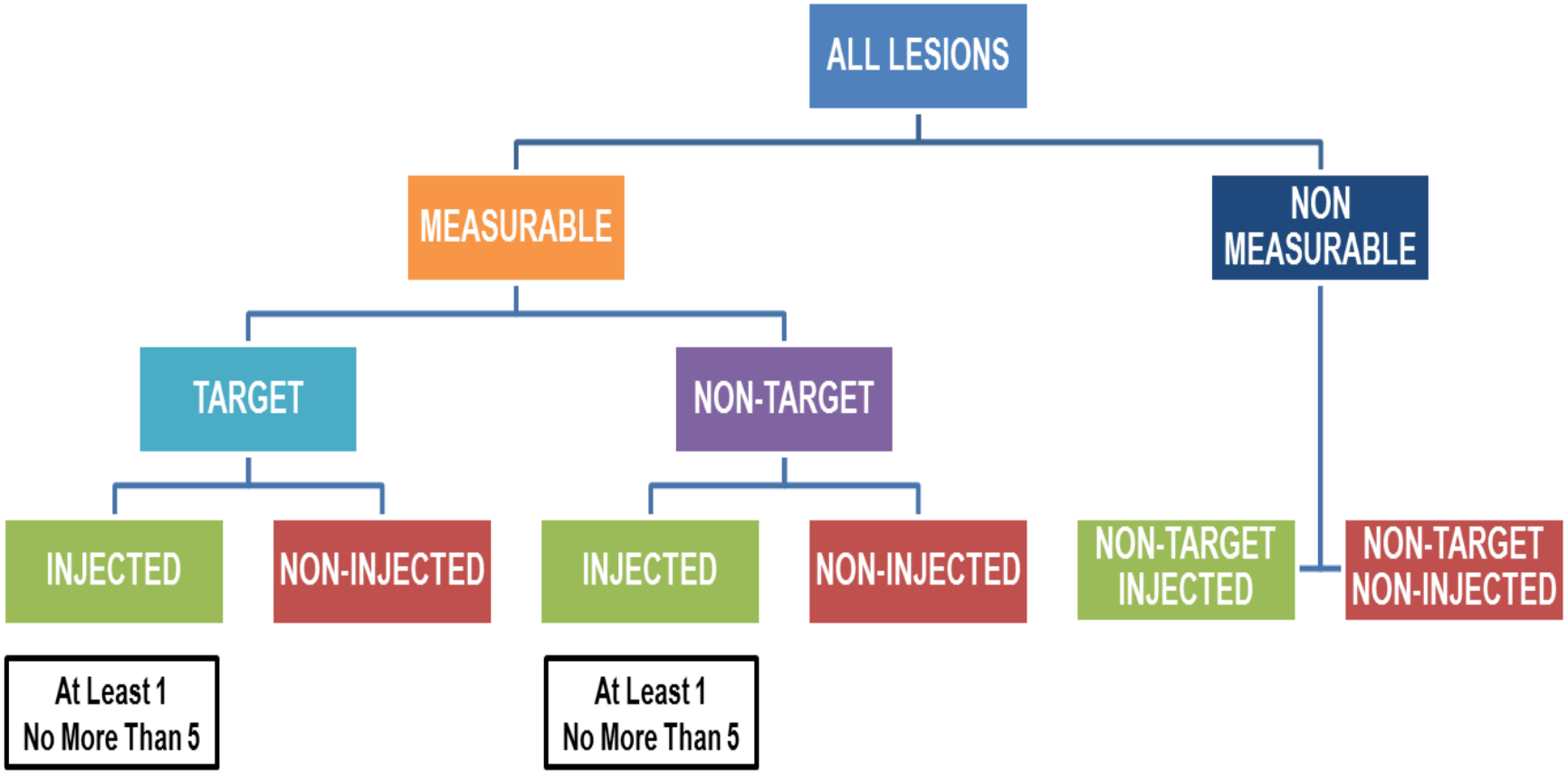


Imaging Assessment Criteria:
RECIST is not Adapted to Intratumoral Immunotherapy

Clinical Benefit ?

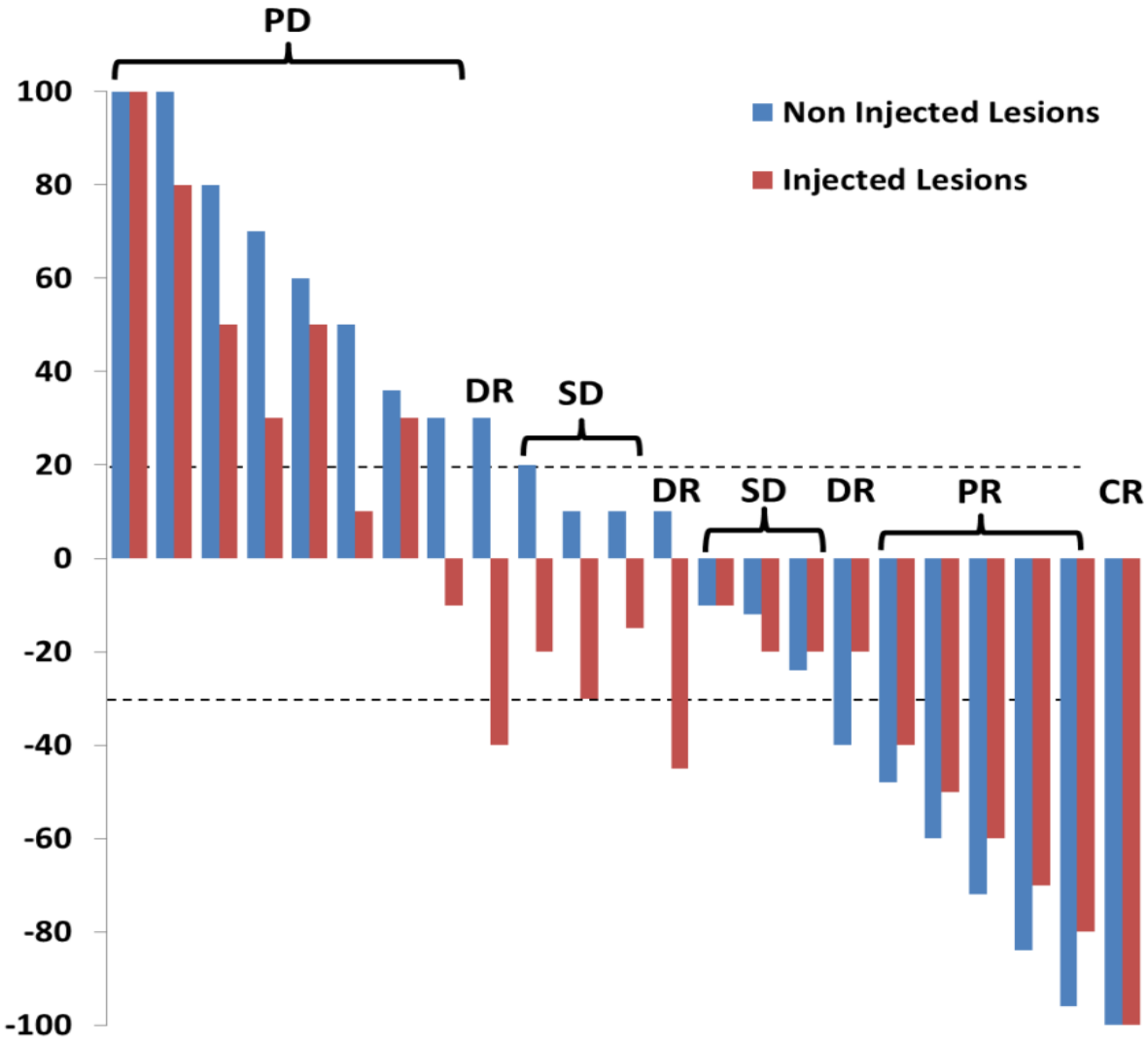


Intra Tumoral RECIST (itRECIST)



Goldmacher G et al. International Consensus Manuscript in Preparation

Waterfall Plots for Intratumoral Immunotherapy



Marabelle A, et al Ann Oncol. 2018;29:2163–74

Take Home Messages

- iRECIST criteria to confirm PD and take into consideration atypical responses
- Do not delay treatment onset if asymptomatic CNS mets
- Early CT-assessment to allow switch to chemo in case of fast/hyper-progression

Efficacy Evaluation for Immune Checkpoint Blockade

Aurélien Marabelle, MD, PhD
Clinical Director, Cancer Immunotherapy Pgm
Drug Development Dpt
INSERM 1015

ESMO Advanced Course July 3rd 2019

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