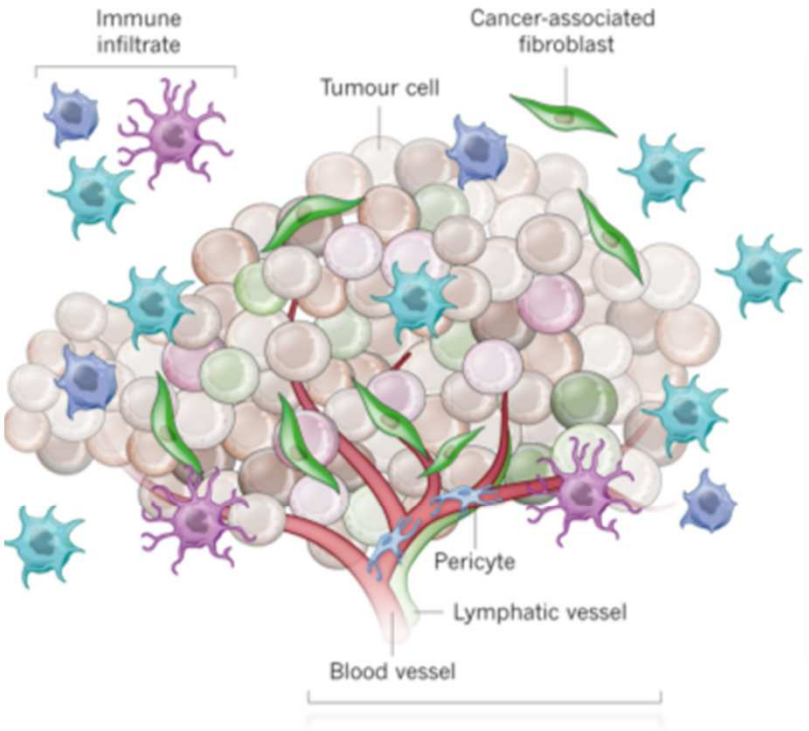
PET and immunotherapy in lymphoma:

how to report? interpret?



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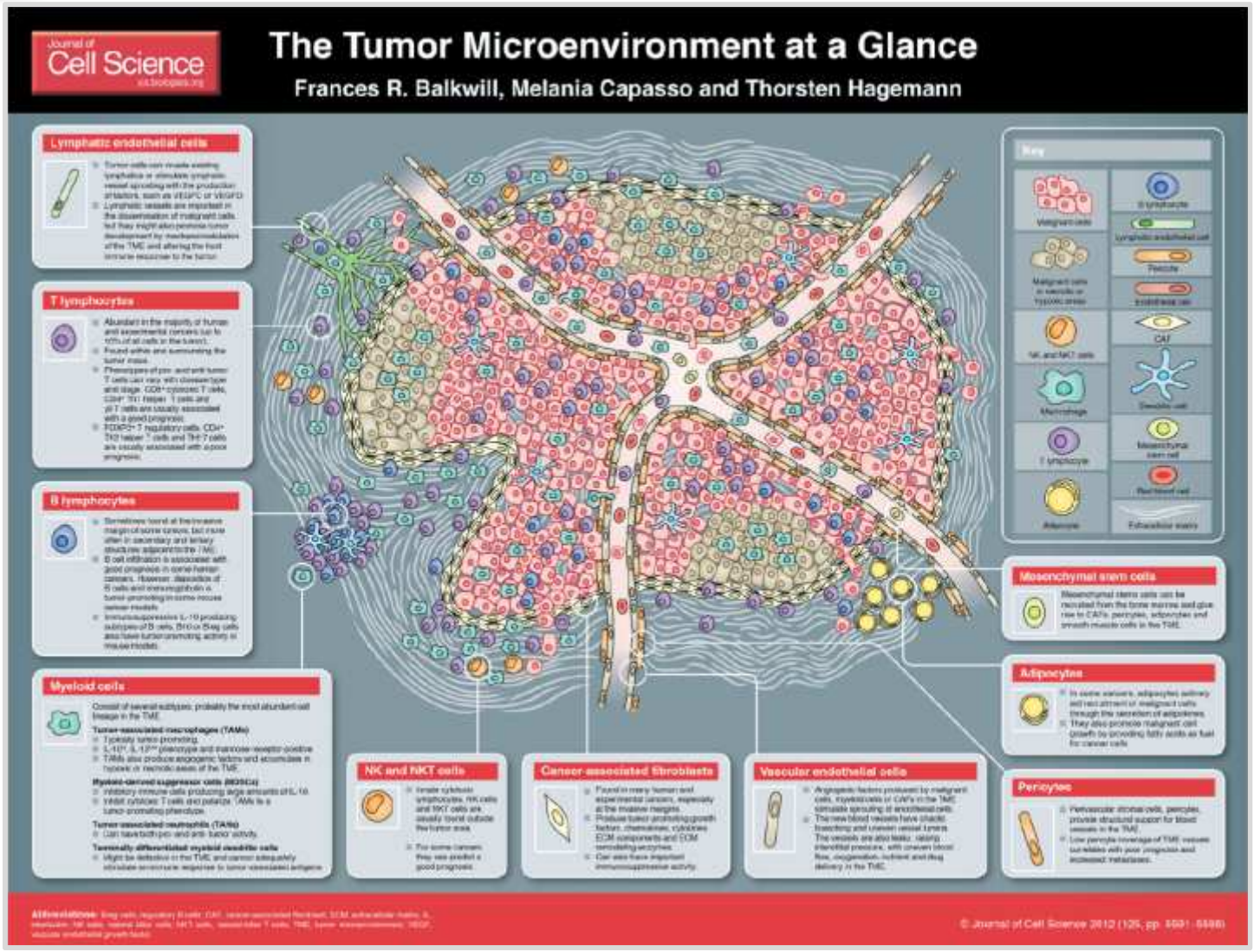
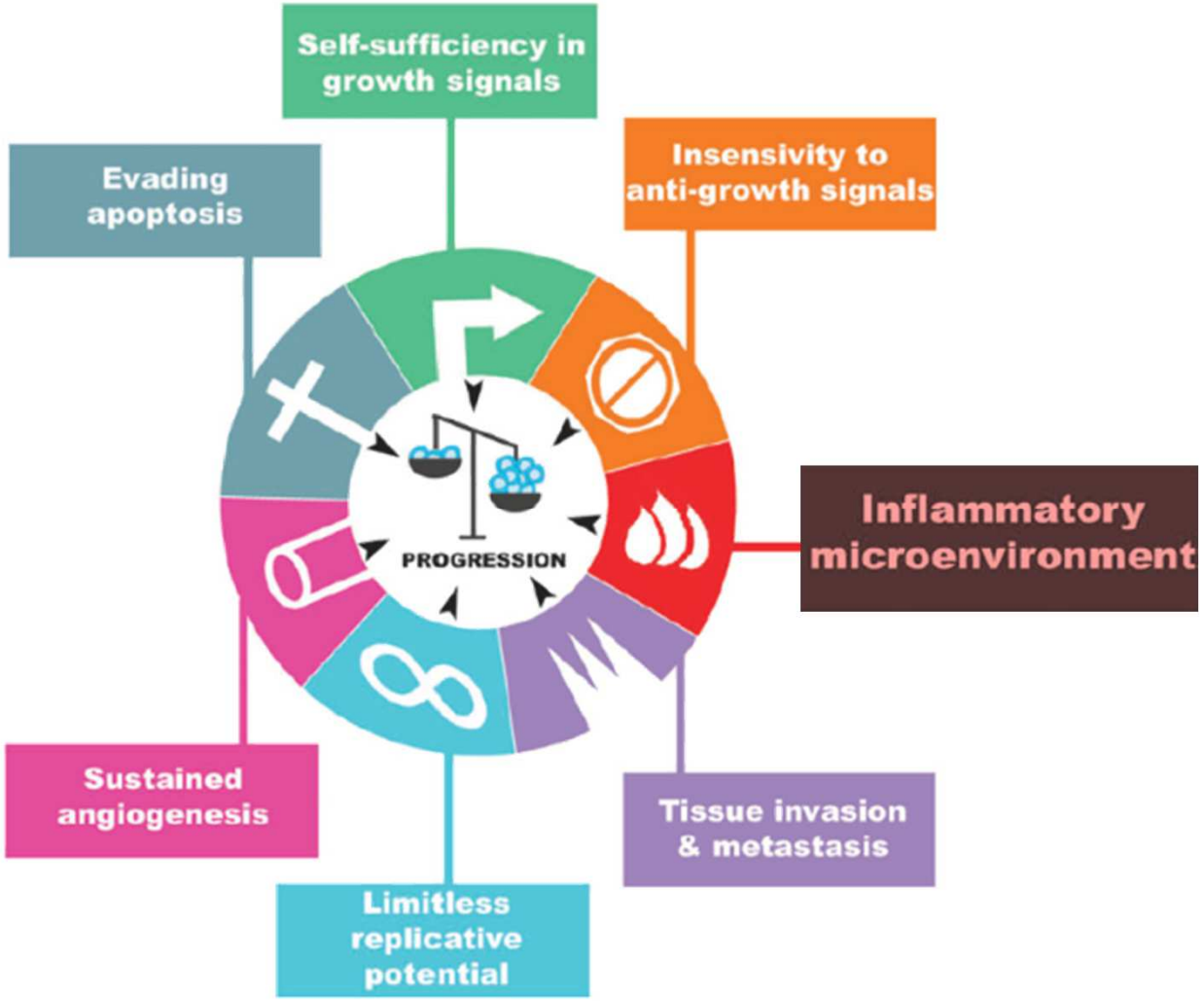
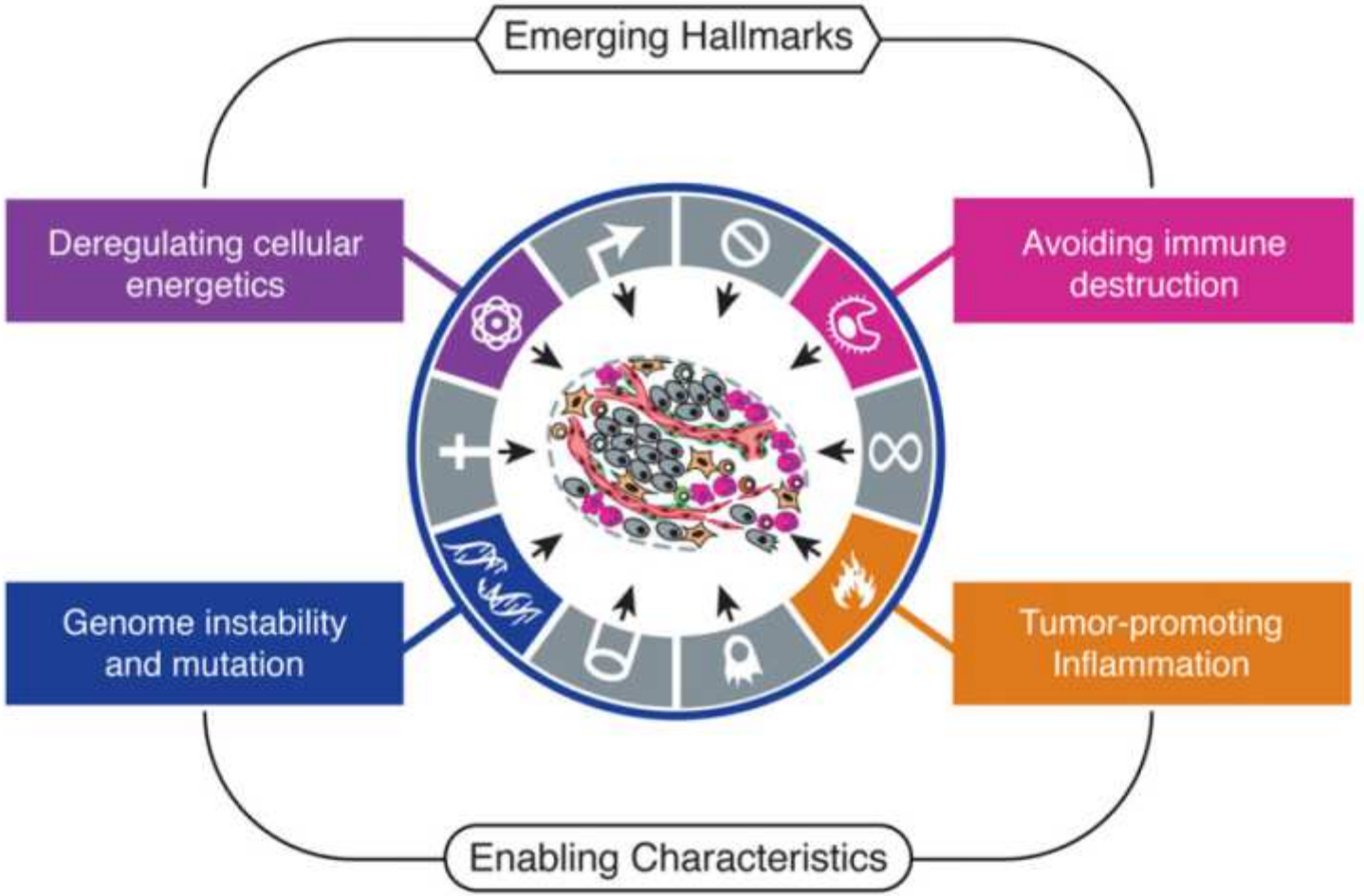

Journal of Cell Science
The Tumor Microenvironment at a Glance
Frances R. Balkwill, Melania Capasso and Thorsten Hagemann
Lymphatic endothelial cells
T lymphocytes
B lymphocytes
Myeloid cells
Tumor-associated macrophages (TAMs)
Myeloid-derived suppressor cells (MDSCs)
Tumor-associated neutrophils (TANs)
Terminally differentiated myeloid dendritic cells
NK and NKT cells
Cancer-associated fibroblasts
Vascular endothelial cells
Mesenchymal stem cells
Adipocytes
Pericytes
Key
Abbreviations



Carcinogenesis vol.30 no.7 pp.1073–1081, 2009



Cell *144*, March 4, 2011

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

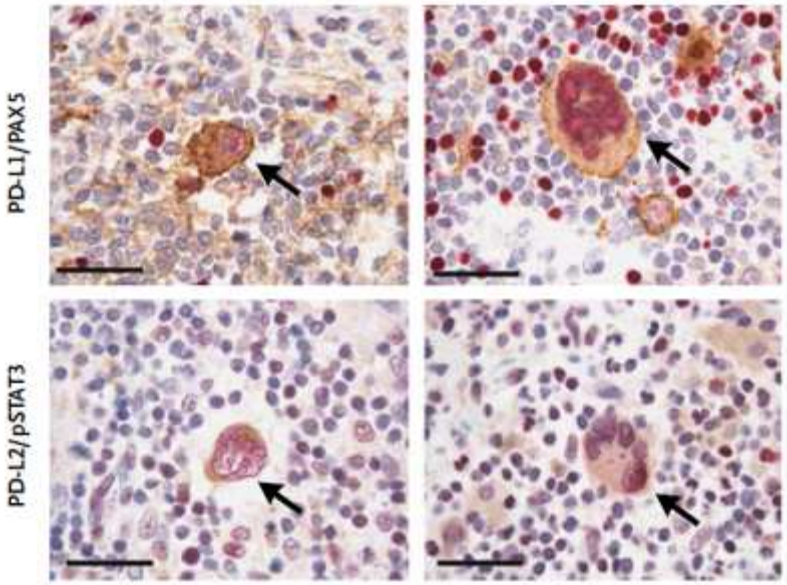
Release the Hounds! Activating the T-Cell Response to Cancer

Mario Sznol, M.D., and Dan L. Longo, M.D.

KEY POINTS

- The tumor microenvironment in lymphoma is highly immunosuppressive and inhibits the antitumor immune response.
- Immune checkpoints present a therapeutic target in non-Hodgkin lymphoma.
- Immune checkpoint inhibitors are clinically effective in patients with relapsed and refractory lymphoma.
- Patients with Hodgkin lymphoma have a very high response rate to PD-1 blockade and reponses in these patients appear durable.

Curr Opin Hematol 2015, 22:337–342



N Engl J Med 2015;372:311-9

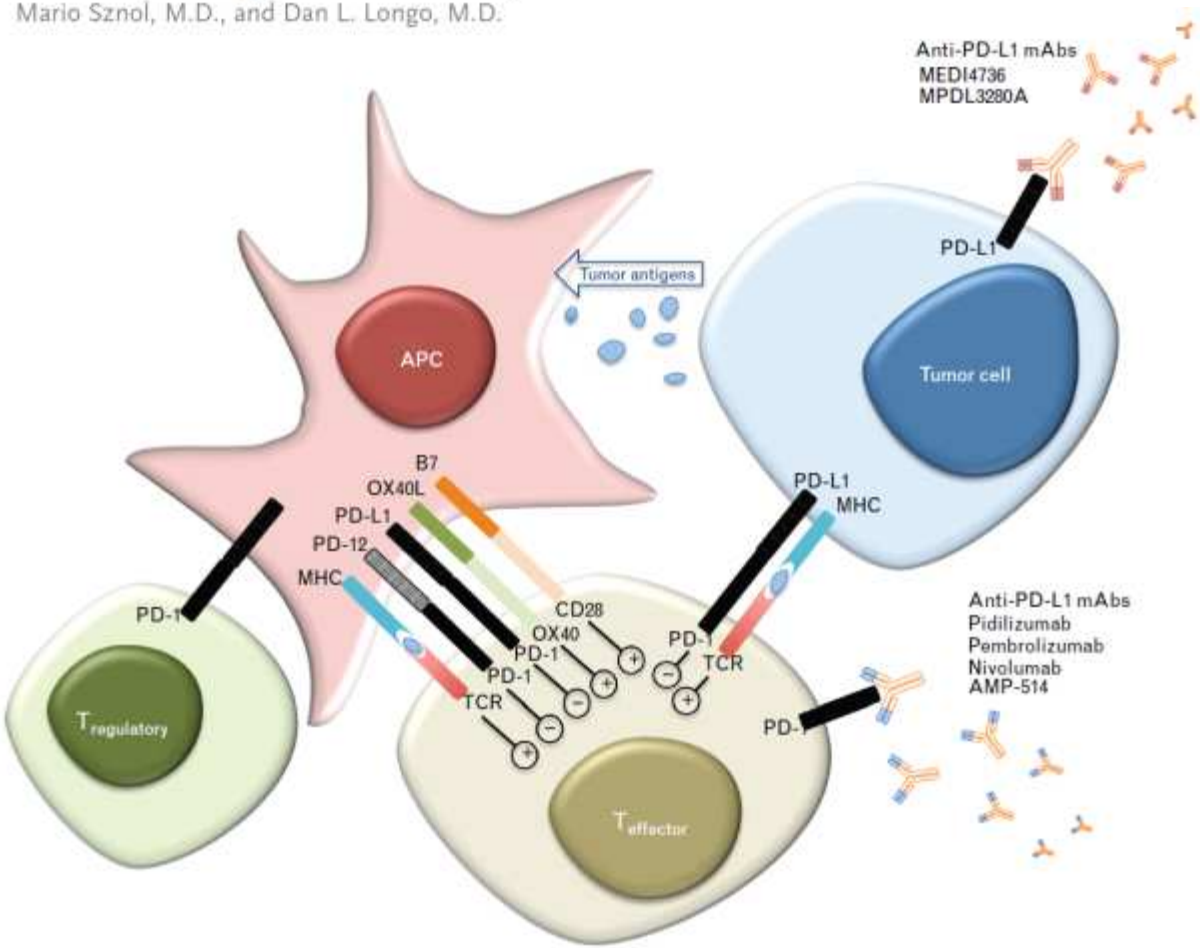
The NEW ENGLAND JOURNAL of MEDICINE

Release the Hounds! Activating the T-Cell Response to Cancer

Mario Sznol, M.D., and Dan L. Longo, M.D.

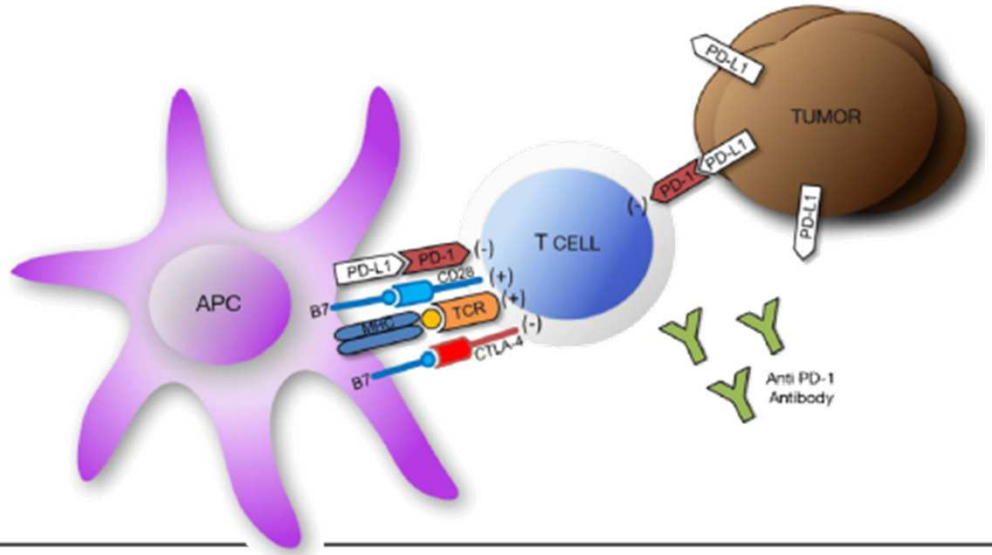
KEY POINTS

- The primary mechanism of action for mAbs targeting the PD-1 axis is reestablishment of the cytotoxic T-cell antitumor response.
- Two clinical trials using pidilizumab have demonstrated activity in relapsed diffuse large B-cell lymphoma (after autologous stem-cell transplantation) and follicular lymphoma.
- Nivolumab and pembrolizumab both have impressive single agent activity in relapsed/refractory Hodgkin lymphoma with objective response rates of 53–87%; the activity of nivolumab in other lymphoma subtypes also appears encouraging.
- A number of new agents targeting either PD-1 or programmed death-ligand 1 are under active development in early phase clinical trials.
- Future studies should incorporate correlative analyses to develop predictive biomarkers to identify patients unlikely to respond to therapy, and identify rational combination partners based on the immunologic properties of the tumor being treated.



Curr Opin Oncol 2015, 27:384–391

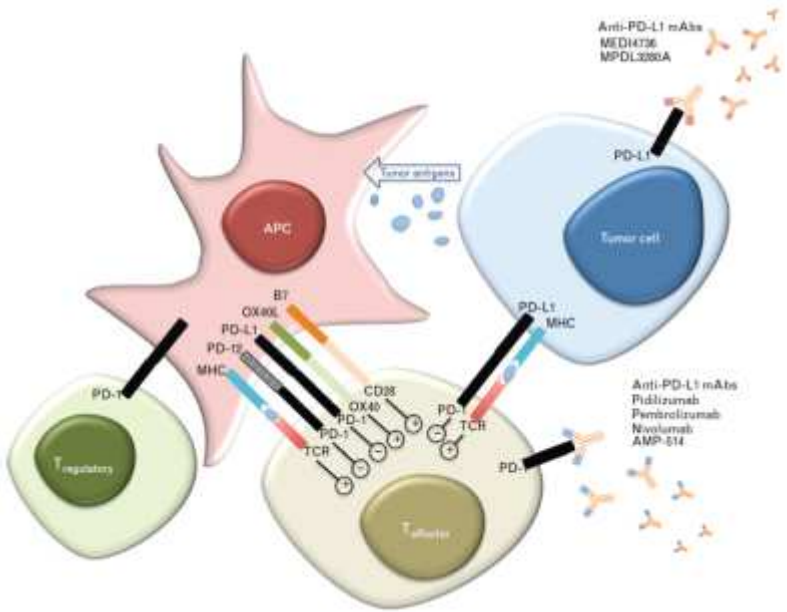
Checkpoint inhibitors in Lymphona



Agent	Phase	Additional therapy	Disease	Trial status	ClinicalTrials.gov ID
Nivolumab[c]	2	None	HL	Recruiting	NCT02181738
Nivolumab[c]	2	None	FL	Recruiting	NCT02038946
Nivolumab	2	None	DLBCL[a]	Recruiting	NCT02038933
Nivolumab[c]	1/2	Urelumab	B cell NHL	Recruiting	NCT02253992
Nivolumab	1	Ipilimumab or lirilumab	HL	Recruiting	NCT01592370
Nivolumab	2	Ibrutinib	CLL, FL, DLBCL	Not yet open	NCT02329847
Pembrolizumab	2	None	DLBCL, HL[b]	Not yet open	NCT02362997
Pembrolizumab	2	None	Low grade NHL	Not yet open	NCT02362997
Pembrolizumab[c]	1/2	ACP-196 (BTK inhibitor)	NHL, HL	Recruiting	NCT02362035
Urelumab[c]	1	Rituximab	B cell NHL	Recruiting	NCT01775631
Anti-LAG-3[c]	1	None	NHL, HL	Recruiting	NCT02061761
MEDI6469 (OX40 ligand)[c]	1/2	Rituximab	B cell NHL	Recruiting	NCT02205333

Curr Oncol Rep (2015) 17: 30

Checkpoint inhibitors in Lymphona



Original images

Agent	Phase	Number	Disease	Efficacy
Nivolumab [20•]	1	23	cHL	ORR 87 % (CR 17 %; PR 70 %)
Pembrolizumab [21]	1b	15	cHL	ORR 53 % (CR 20 %; PR 33 %)
Pidilizumab [27•]	2	32	FL	ORR 66 % (CR 52 %; PR 14 %)
Pidilizumab [34]	2	72	DLBCL, PMBCL	16-month PFS 72 %; ORR[a] 51 % (CR 34 %; PR 17 %)
Nivolumab [35]	1	13[b]	DLBCL, PMBCL	ORR 31 % (CR 8 %; PR 23 %)
Nivolumab [35]	1	10[b]	FL	ORR 40 % (CR 10 %, PR 30 %)

Curr Oncol Rep (2015) 17: 30

Revised Response Criteria for Malignant Lymphoma

Table 2. Response Definitions for Clinical Trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measuable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of [illegible]en	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain [illegible]	[illegible] on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

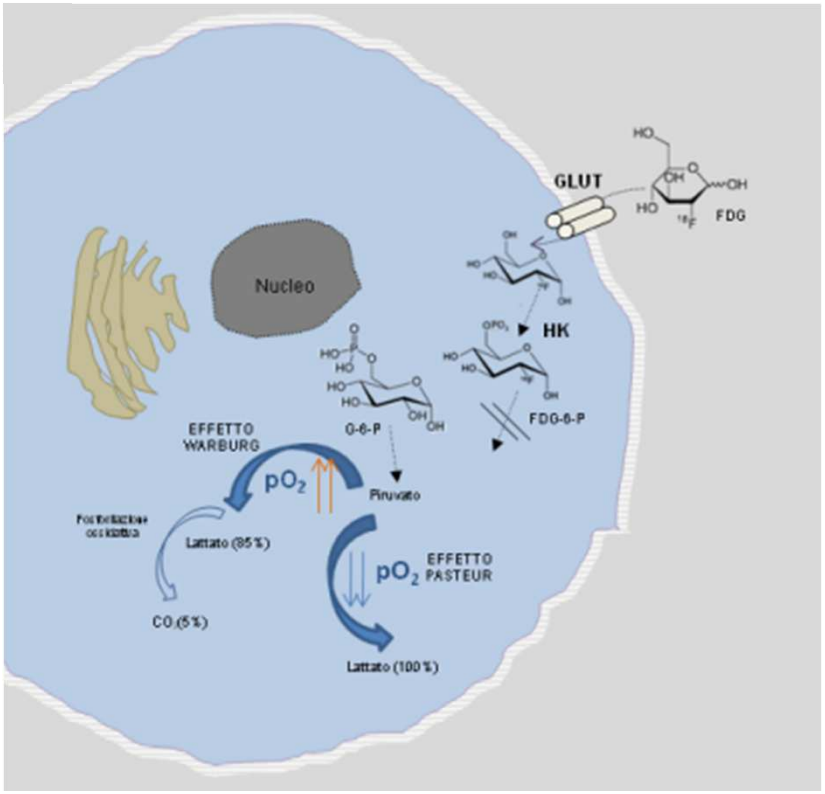
Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

Are we in need for defined irPET criteria?

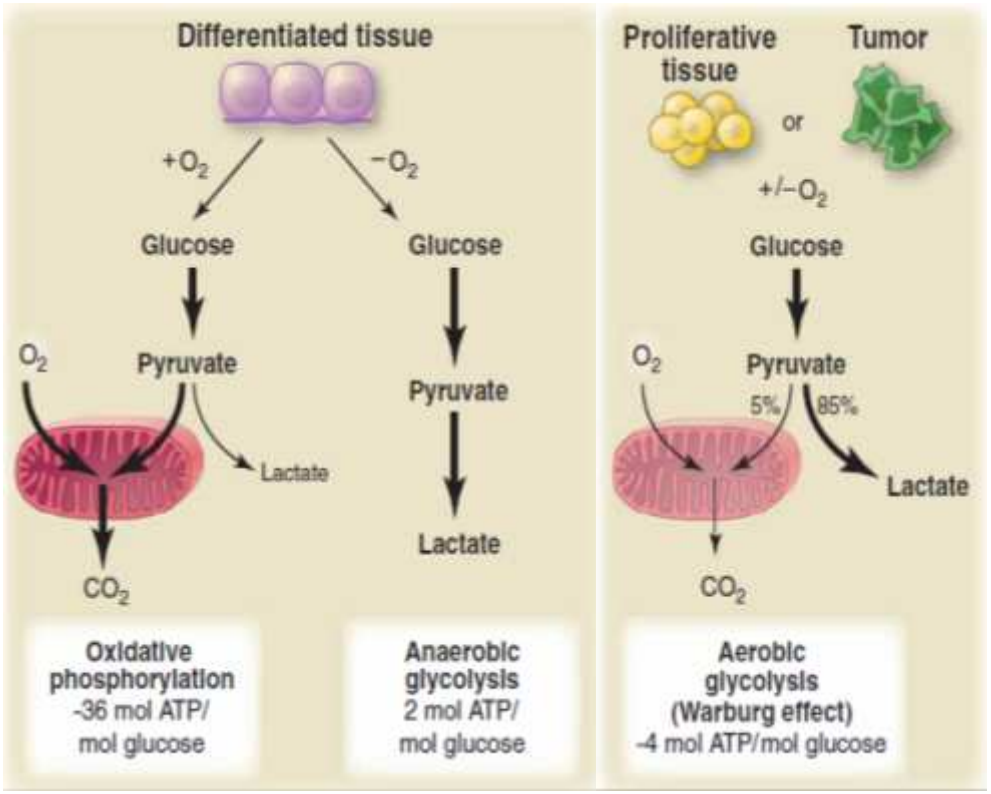
J Clin Oncol 25:579-586. © 2007

Metabolic and Immune markers

Am J Nucl Med Mol Imaging 2014;4(4):365-384



Science **324**, 1029 (2009)



Innate immune cells such as macrophages and granulocytes are critically dependent on HIF-1α-mediated induction of glycolytic genes to infiltrate inflamed tissue. Adaptive immune cells upregulate the expression of GLUTs and HK in response to mitogenic signals.

Curr Opin Genet Dev. 2010 February ; 20(1): 100–105

Table 1 Baseline epidemiologic and clinical characteristics of our study population

Characteristics	No. (%)
No. of patients	55
Age	68.9 years
Range	(49.4–89.9)
Gender	
Male	42 (76.4 %)
Female	13 (23.6 %)
Histology	
ADC	36 (65.5 %)
SCC	18 (32.7 %)
Sarcomatoid carcinoma	1 (1.8 %)
Stages	
IA	7 (12.7 %)
IB	13 (23.6 %)
IIA	9 (16.4 %)
IIB	10 (18.2 %)
IIIA	14 (25.5 %)
IIIB	2 (3.6 %)
Additional treatments	
Adjuvant chemotherapy	5 (9.1 %)
Radiation therapy	3 (5.5 %)

Abbreviations: *ADC* Adenocarcinoma, *SCC* Squamous Cell Carcinoma

*the sum of all values is superior to 100 % (more precisely, 100.1 %) because of the rounding of the percentages during computation

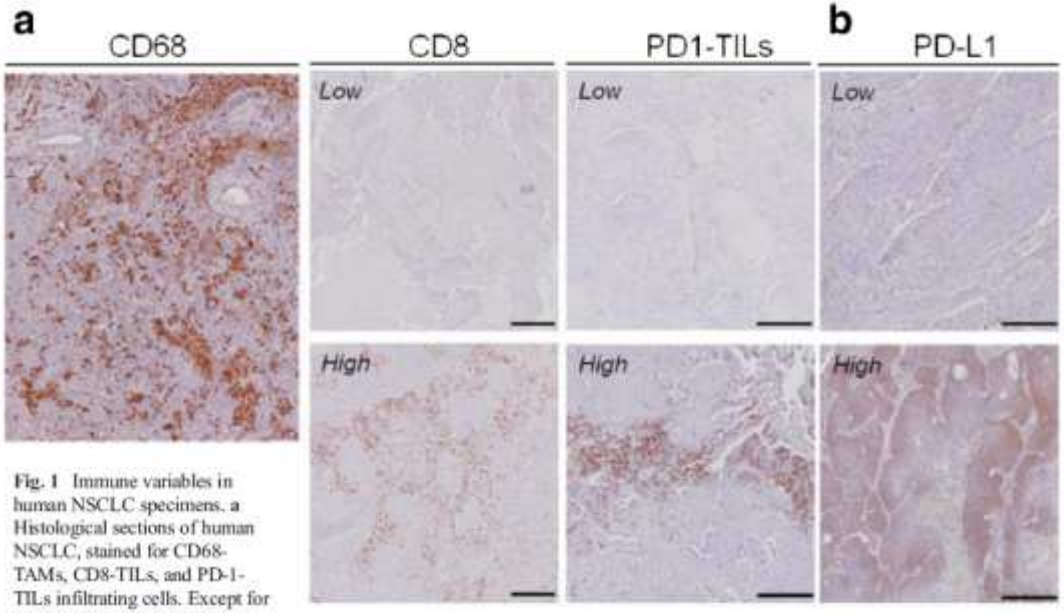
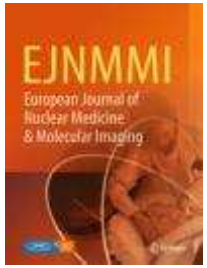
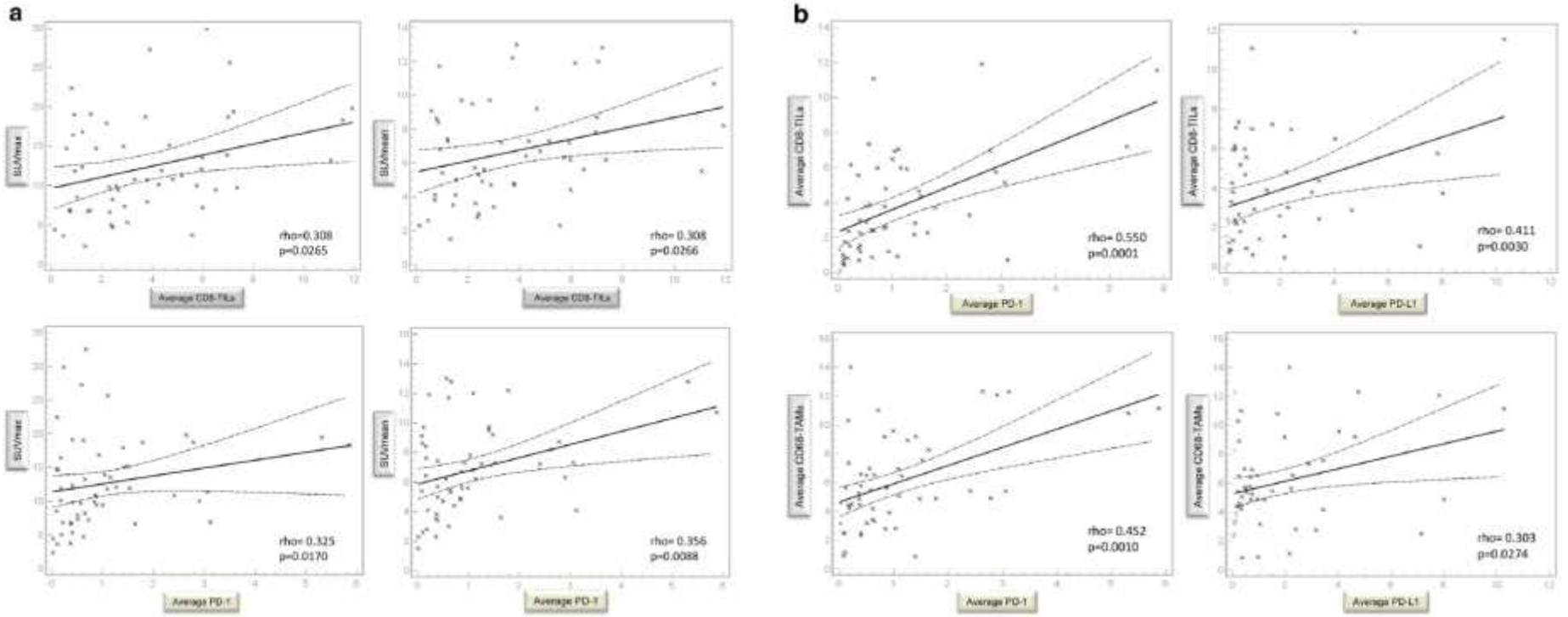


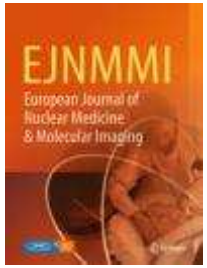
Fig. 1 Immune variables in human NSCLC specimens. **a** Histological sections of human NSCLC, stained for CD68-TAMs, CD8-TILs, and PD-1-TILs infiltrating cells. Except for CD68-TAMs, highly infiltrating in all the specimens analyzed, the density of immune variables is heterogeneous among specimens, with some scarcely infiltrated cases (*upper*) and some highly infiltrated cases (*lower*). **b** Similarly for PD-L1 expression in NSCLC cells



Eur J Nucl Med Mol Imaging. Oct 2016



Scatter plots with Spearman' correlation coefficient (*rho*) and linear regression tests. A) Correlation of semi-quantitative parameters on FDG-PET (i.e. SUVmax and SUVmean) with human NSCLC stained for CD8-TILs and PD-1-TILs (average values); B) Correlation for CD8-TILs and CD68-TAMs (average values) with respect to PD-1 and PD-L1 (average values).



Eur J Nucl Med Mol Imaging. Oct 2016

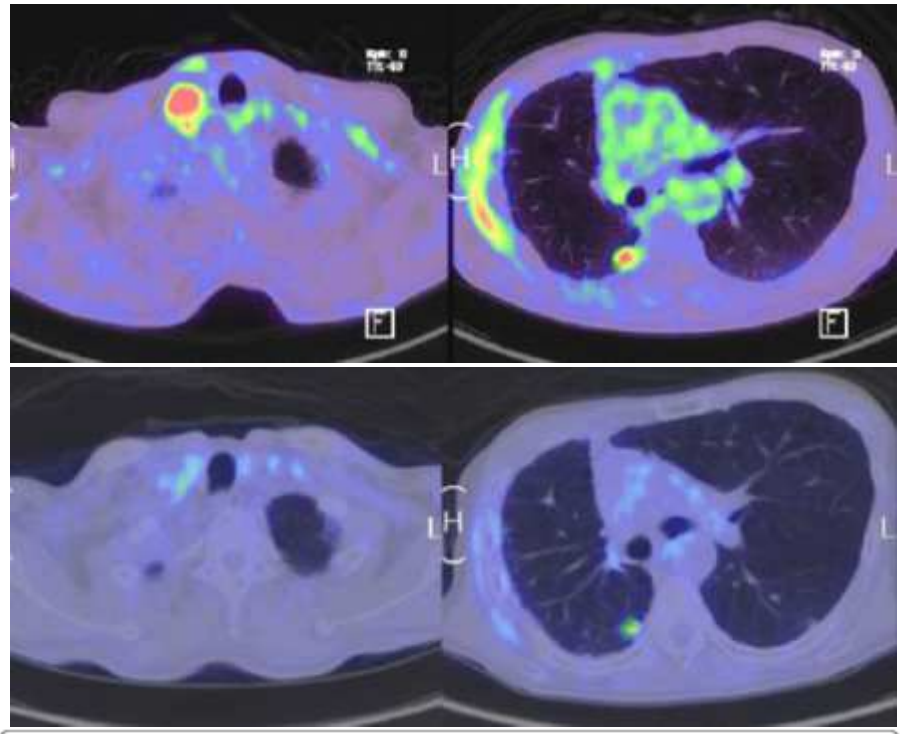


Fig. 2 FDG uptake before (**a**) and after (**b**) immunotherapy. Maximum standardized uptake value (SUVmax) of supraclavicular lymph node and disseminated lesions before and after immunotherapy decreased from 9.8 to no accumulation and 5.9 to 3.4, respectively. Each SUVmax was decreased after six courses of nivolumab treatment

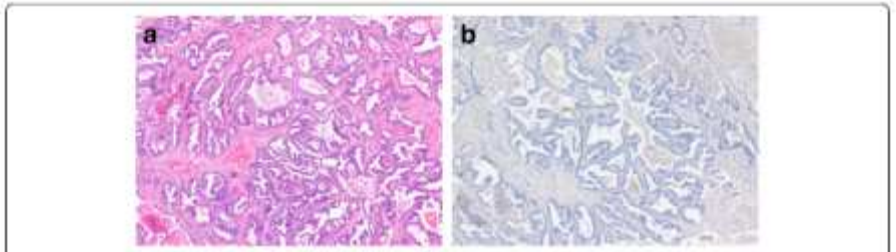


Fig. 1 Hematoxylin and eosin (H&E) staining (×100) (**a**) and immunohistochemical staining for PD-L1 (**b**) of surgically resected NSCLC tissue. H&E staining showed invasive adenocarcinoma papillary predominant type and immunohistochemical staining showed negative for PD-L1

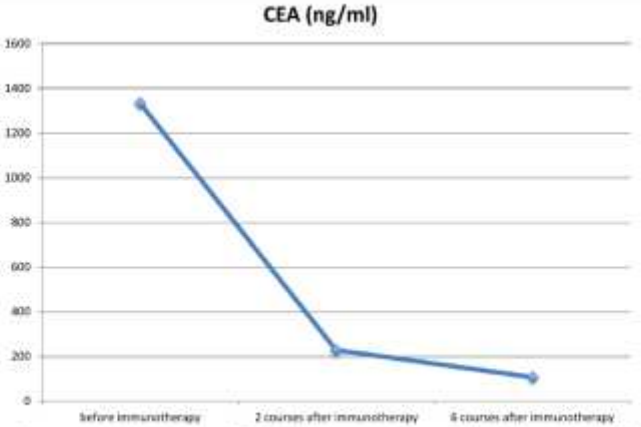
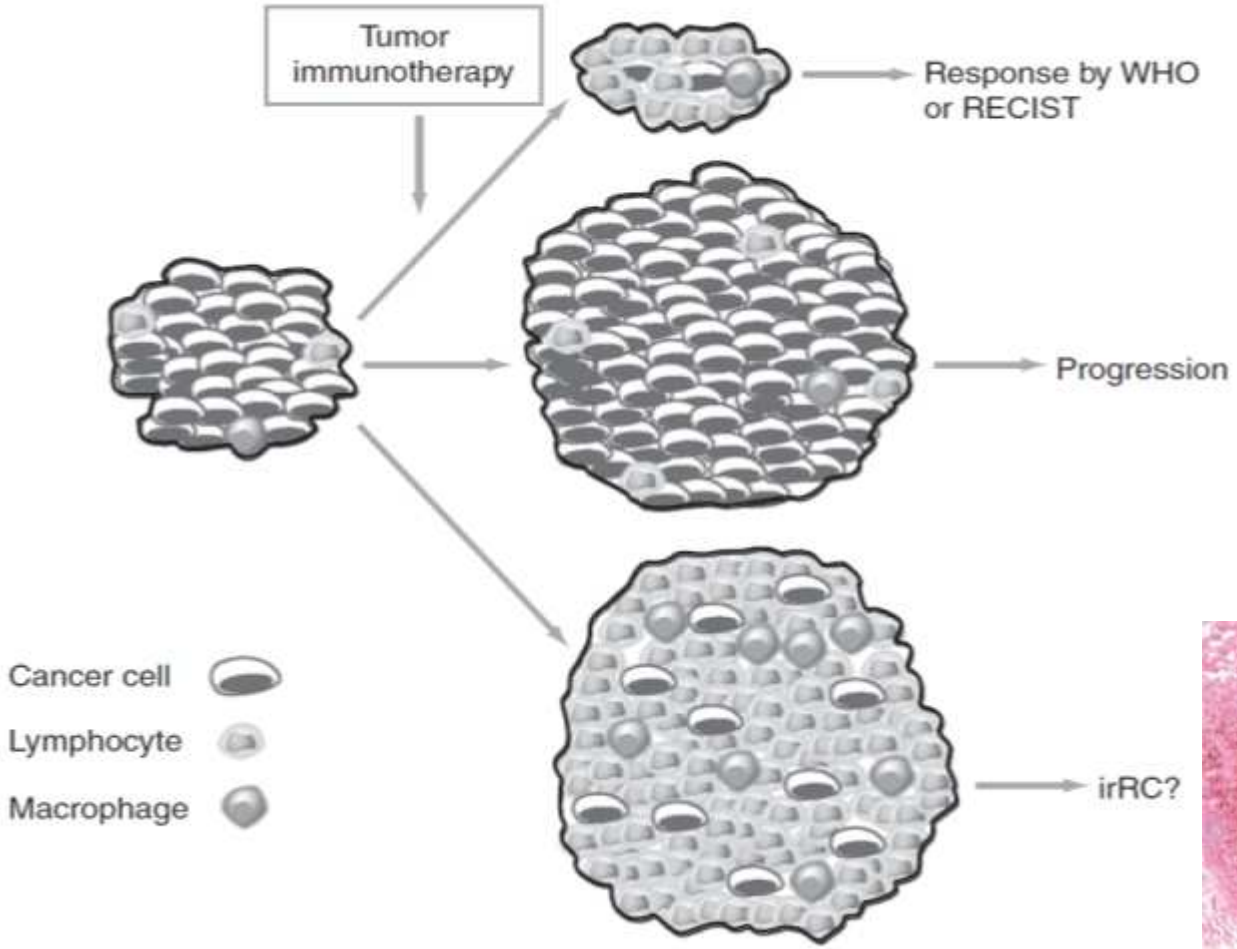


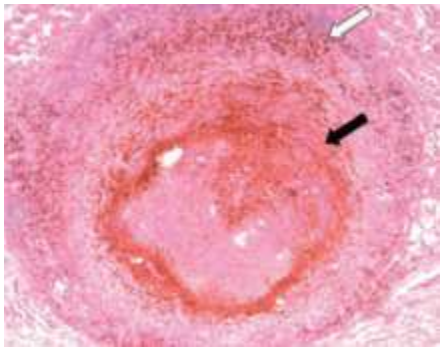
Fig. 3 Clinical course of serum carcinoembryonic antigen (CEA) levels during treatment. Serum CEA level decreased from 1335.0 to 108.4 ng/ml after six courses of nivolumab treatment

Higuchi *et al. World Journal of Surgical Oncology* (2016) 14:238

Response in Immunotherapy

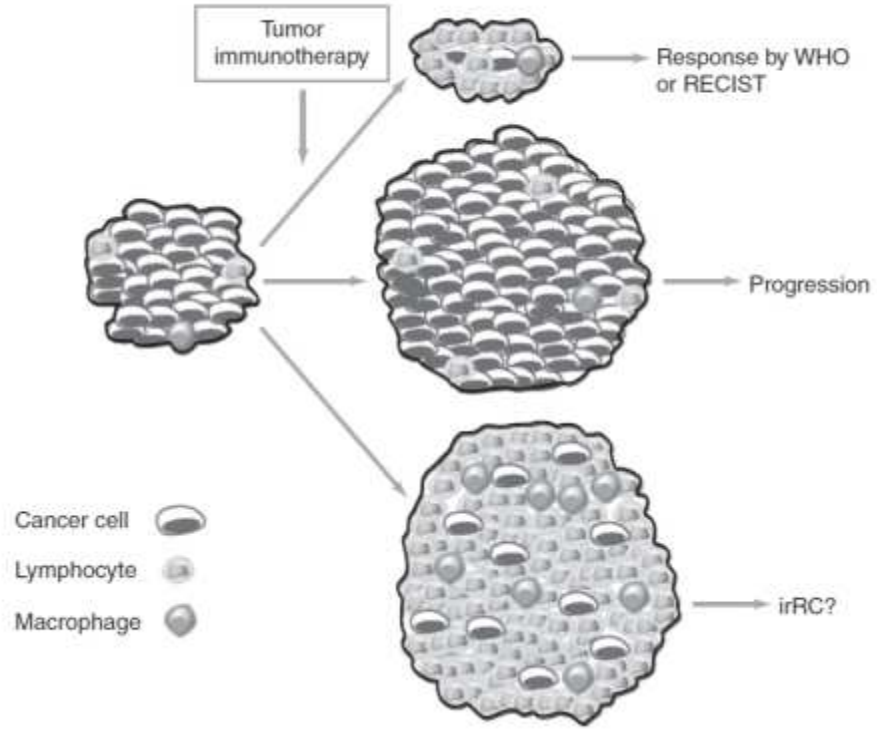


Am J Clin Oncol 2012;35:606–611
Adapted with permission from Ribas et al, *Clin Cancer Res.* 2009;15:7116–7118



Clin Cancer Res 2009;15(23):7412–20

Response in Immunotherapy



Am J Clin Oncol 2012;35:606-611
Adapted with permission from Ribas et al, *Clin Cancer Res.* 2009;15:7116-7118

Baseline	irRC 2009	irRC 2013	irRC 2014
Target Läsion (TL)	max. 15 TL (max. 10 viszeral + 5 kutan) max. 5 pro Organ	max. 10 TL, max. 5 pro Organ	max. 5 TL, max. 2 pro Organ
LAD / SAD	bi-dimensional (WHO) ≥ 5 x 5 mm (SAD x LAD)	uni-dimensional (RECIST 1.0) ≥ 10 mm (LAD)	uni-dimensional (RECIST 1.1) ≥ 10 mm (LAD) extranodal ≥ 15 mm (SAD) nodal
Non-Target Läsion (Non-TL)	alle anderen Läsionen, Nennung aller Tumorläsion, ggf. in Gruppen zusammengefasst	alle anderen Läsionen, Nennung aller Tumorläsion, ggf. in Gruppen zusammengefasst	alle anderen Läsionen, Nennung aller Tumorläsion, ggf. in Gruppen zusammengefasst
Follow-up			
Target Läsion (TL)	alle TL im LAD messen	alle TL im LAD messen	extranodale TL im LAD, nodale TL im SAD
Non-Target Läsion (Non-TL)	verschwunden, vorhanden oder eindeutig progredient	verschwunden, vorhanden oder eindeutig progredient	verschwunden, vorhanden oder eindeutig progredient
Neue Läsion (New TL)	Summiert zu den TL max. zusätzliche 15 TL, max. 5 pro Organ *(nicht direkt Progressive Disease)* ≥ 5 x 5 mm (SAD x LAD)	Summiert zu den TL max. zusätzliche 10 TL, max. 5 pro Organ *(nicht direkt Progressive Disease)* ≥ 10 mm (LAD)	Summiert zu den TL max. zusätzliche 5 TL, max. 2 pro Organ *(nicht direkt Progressive Disease)* ≥ 10 mm (LAD) extranodal ≥ 15 mm (SAD) nodal
Tumor-Response			
Progressive Disease (PD)	≥ 25% Zunahme *(Nadir)* und Bestätigung im FU nach mind. 4Wo	≥ 20% Zunahme *(Nadir)* und Bestätigung im FU nach mind. 4Wo	≥ 20% Zunahme *(Nadir)* und Bestätigung im FU nach mind. 4 Wo
Partial Response (PR)	≥ 50% Abnahme *(Baseline)*	≥ 30% Abnahme *(Baseline)*	≥ 30% Abnahme *(Baseline)*
Complete Response (CR)	verschwinden aller TL und Non-TL	verschwinden aller TL und Non-TL	verschwinden aller TL und Non-TL
Stable Disease (SD)	weder PD, PR oder CR	weder PD, PR oder CR	weder PD, PR oder CR

Radiologe 2015 · 55:127–135

- Confirmation of progression via a subsequent scans;
- Measuring new lesions to include them into the total tumor volume;
- Accounting for durable stable disease as benefit;
- Treating beyond conventional progression if the clinical situation allows.

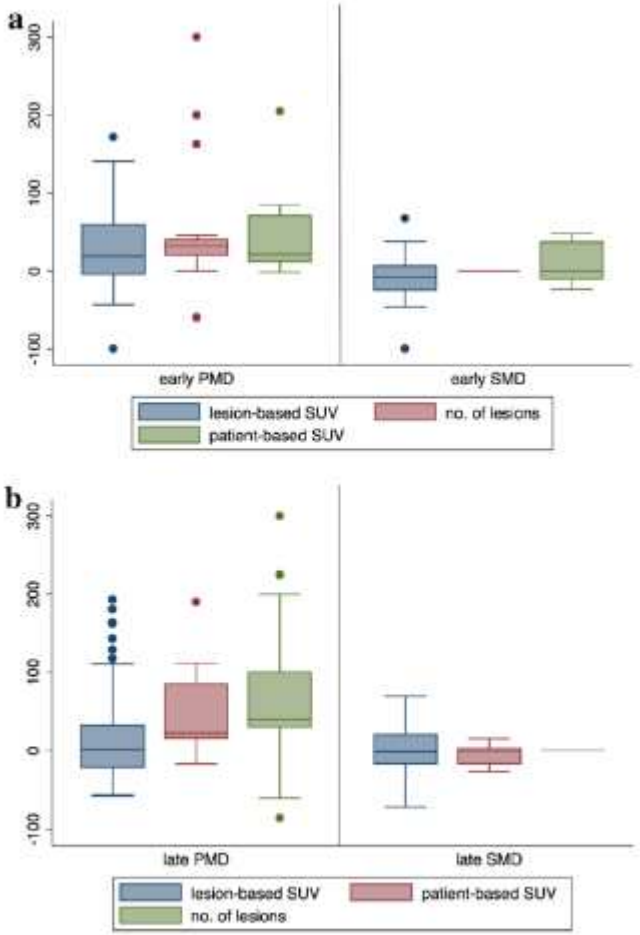


Fig. 6 Mean changes in lesion-based $SUV_{average}$, patient-based $SUV_{average}$ and number of metastatic lesions in patients with PMD and SMD (**a**) between the baseline and the first follow-up PET/CT scan (early response) and (**b**) between the baseline and the second follow-up PET/CT scan (late response)

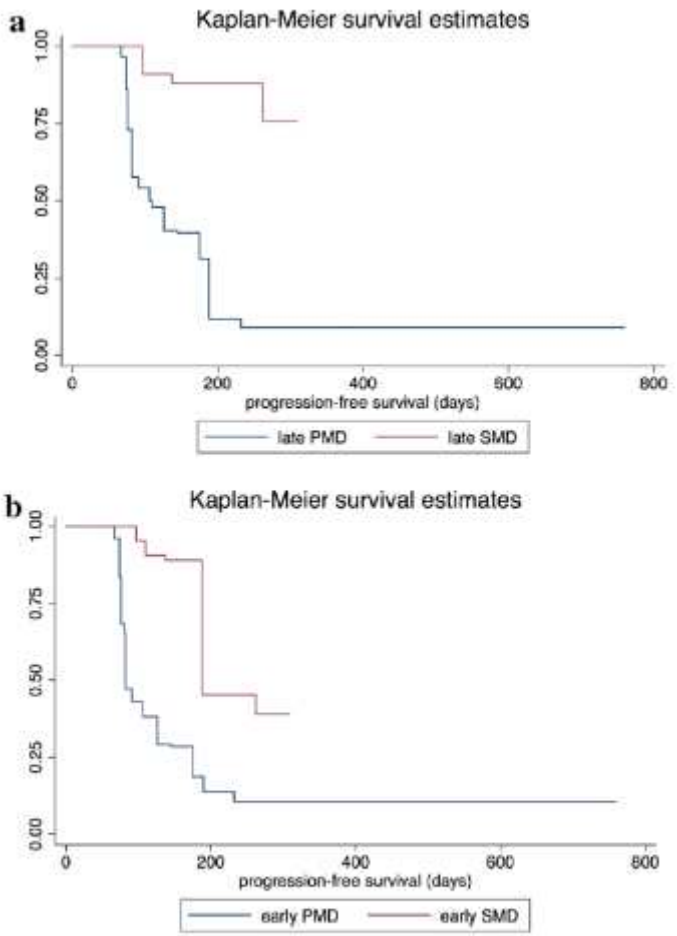
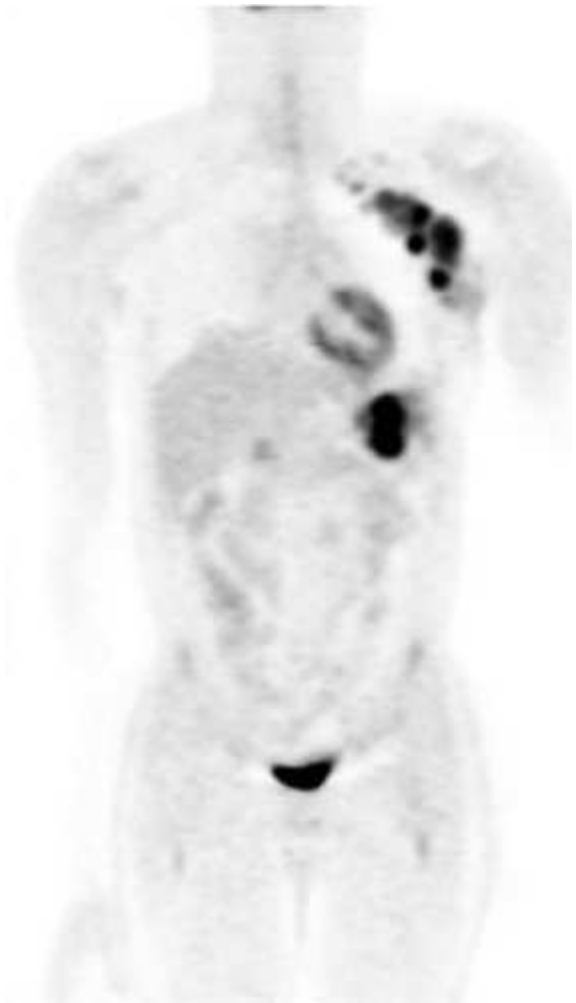


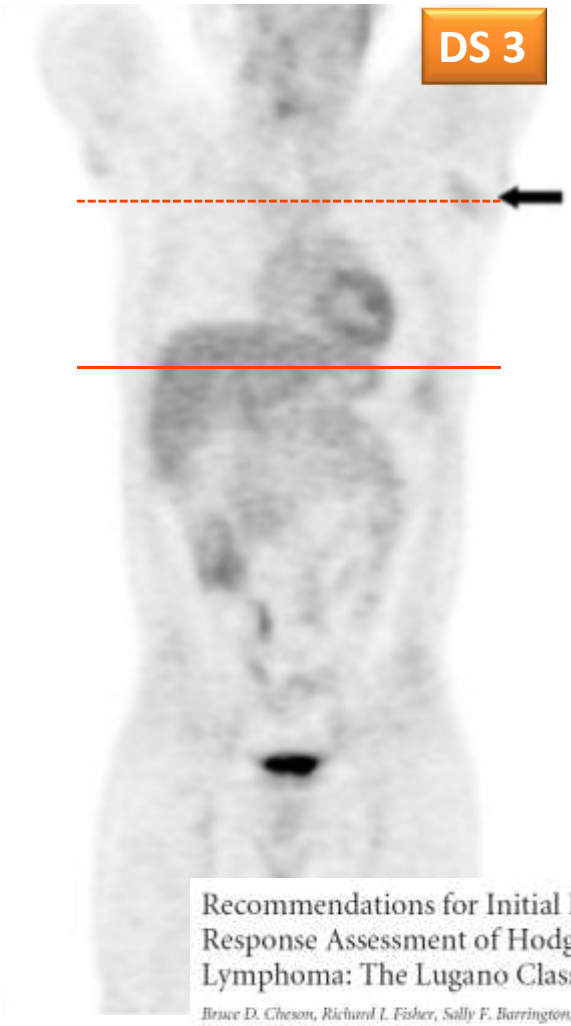
Fig. 5 Kaplan-Meier plots of PFS. **a** Patients with late PMD and late SMD. Patients with late SMD had a significantly longer PFS (log-rank $p < 0.001$). **b** Patients with early PMD and early SMD. Patients with early SMD had a significantly longer PFS (log-rank $p < 0.001$)

EORTC 1999

Eur J Nucl Med Mol Imaging (2015) 42:386–396

Current paradigm of response in lymphoma



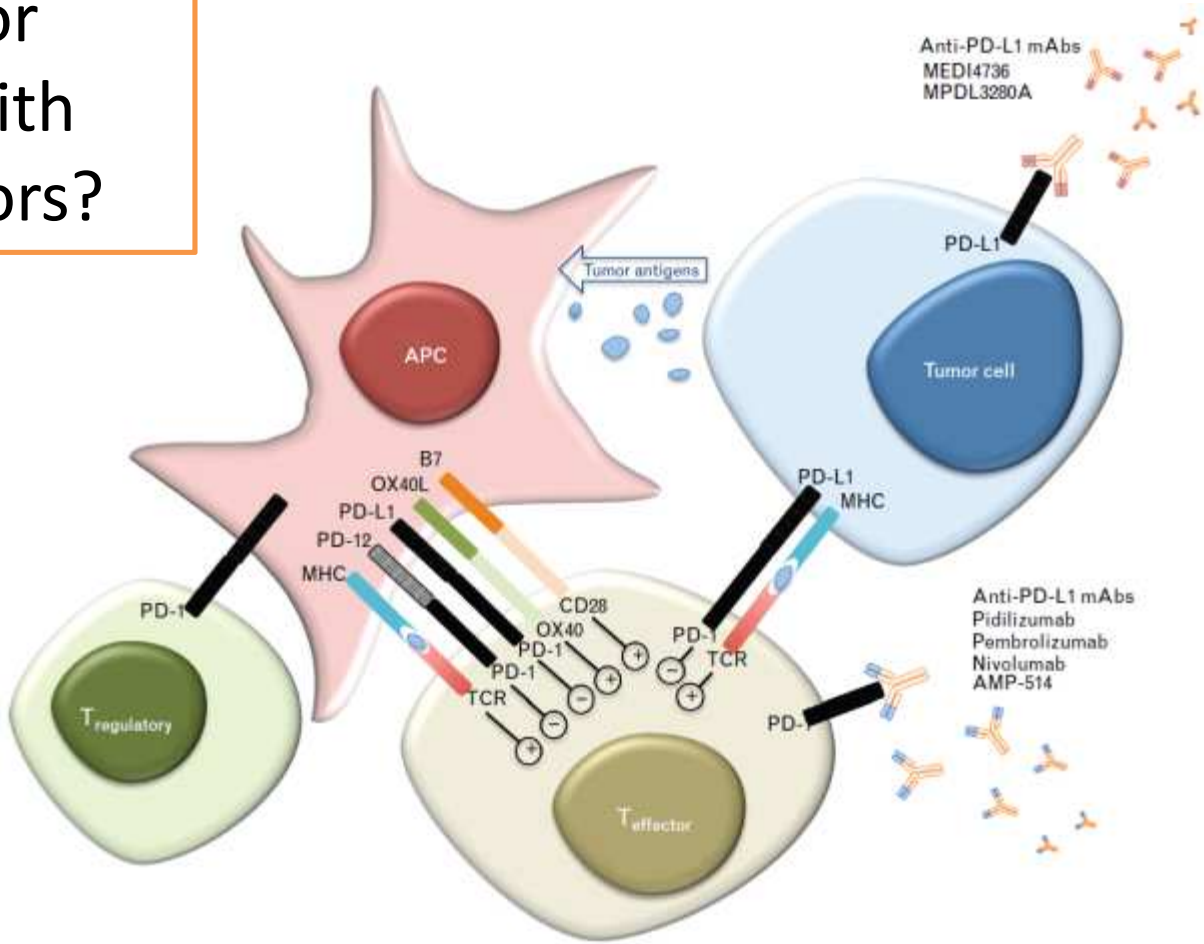


Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification

Bruce D. Cheson, Richard I. Fisher, Sally F. Barrington, Franco Cavalli, Lawrence H. Schwartz, Emanuele Zucca, and T. Andrew Lister

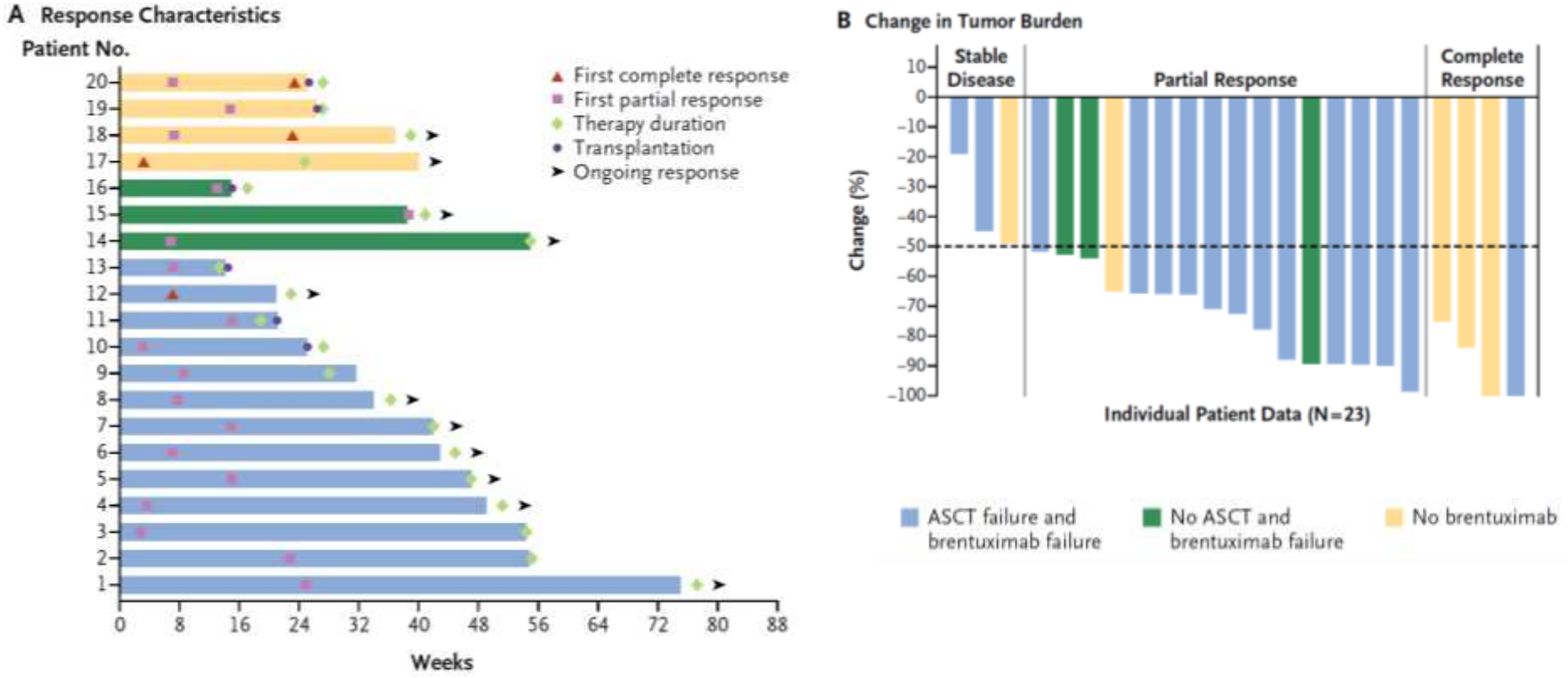
Eur J Nucl Med Mol Imaging (2010) 37:1824–1833
J Clin Oncol 32:3059-3067. © 2014

Is this applicable for Immunotherapy with checkpoint inhibitors?



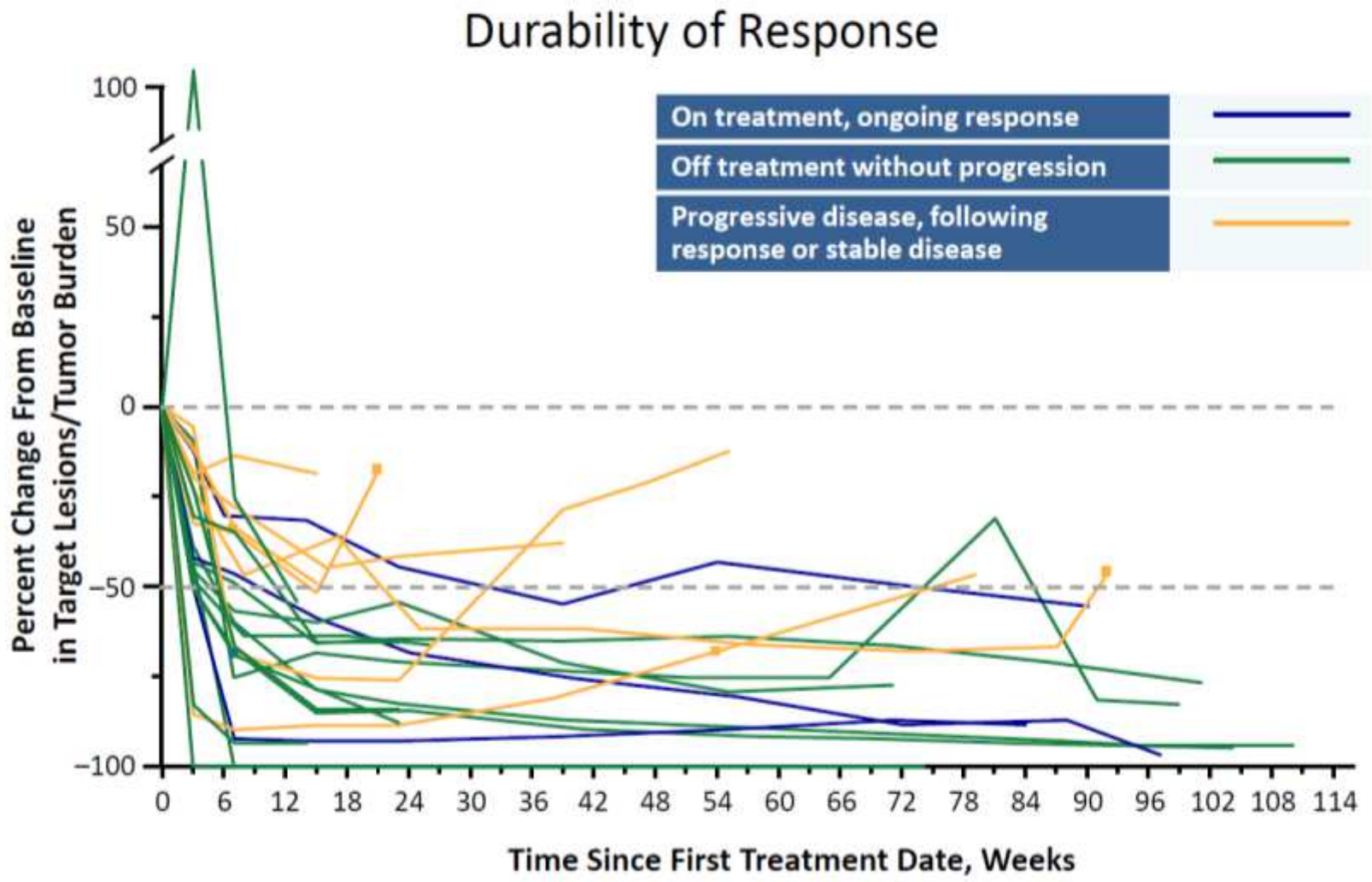
Curr Opin Oncol 2015, 27:384–391

PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma



Of the 20 patients who had a complete or partial response, 12 patients (60%) had the first response by 8 weeks (range, 3 to 39 weeks)

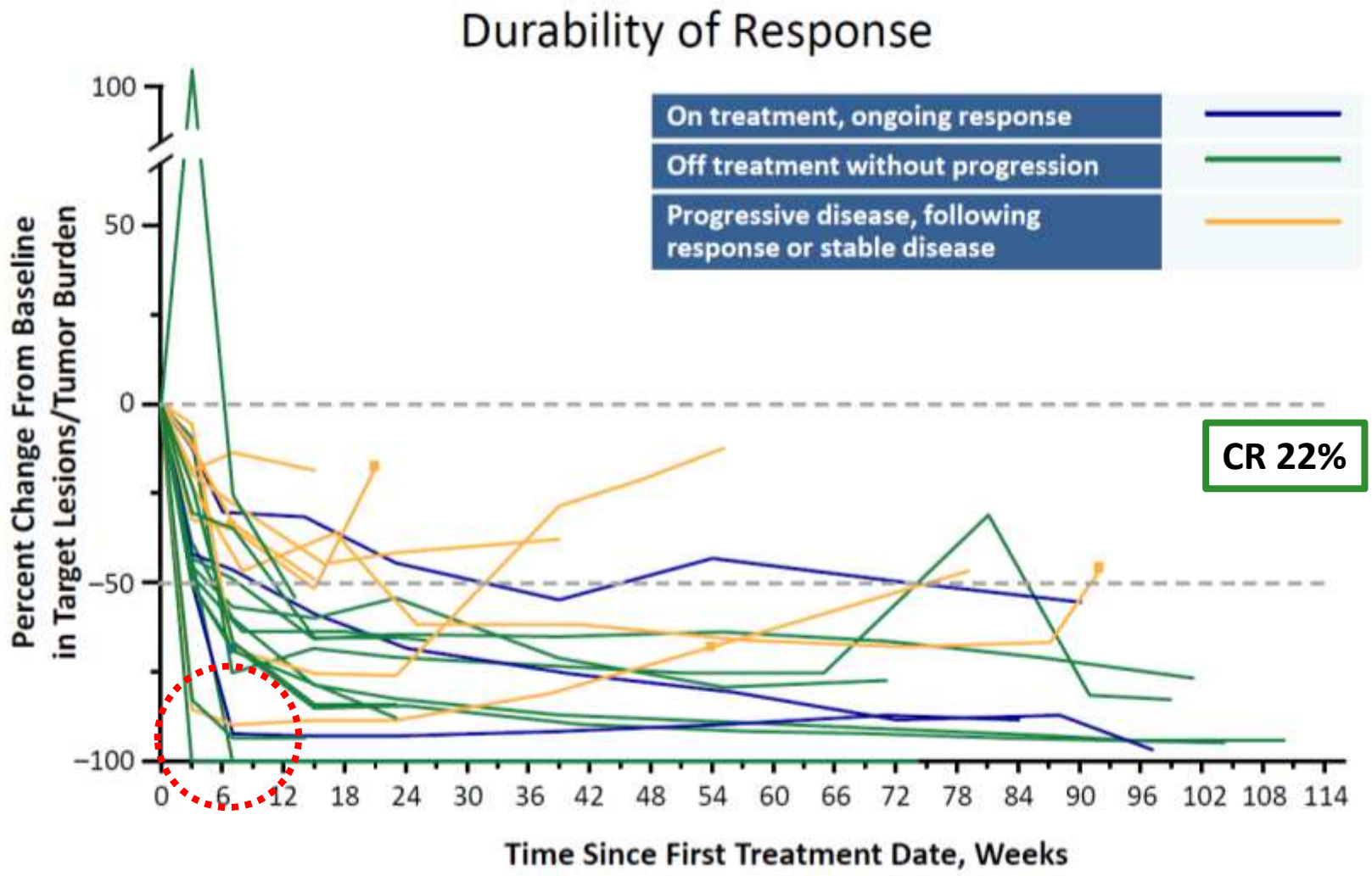
N Engl J Med 2015;372:311-9



Ansell et al ASH 2015

PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma

Early responder

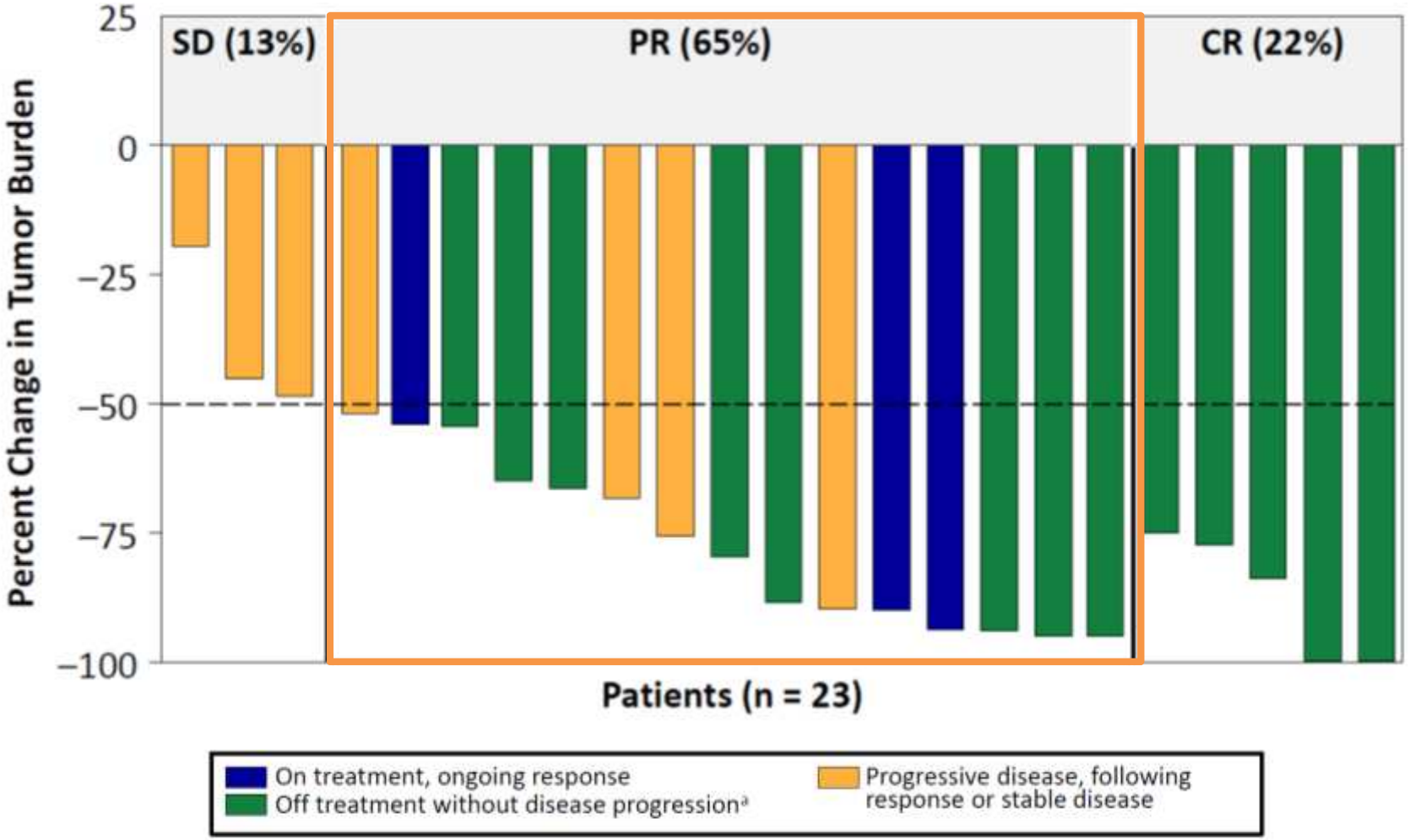


Ansell et al ASH 2015

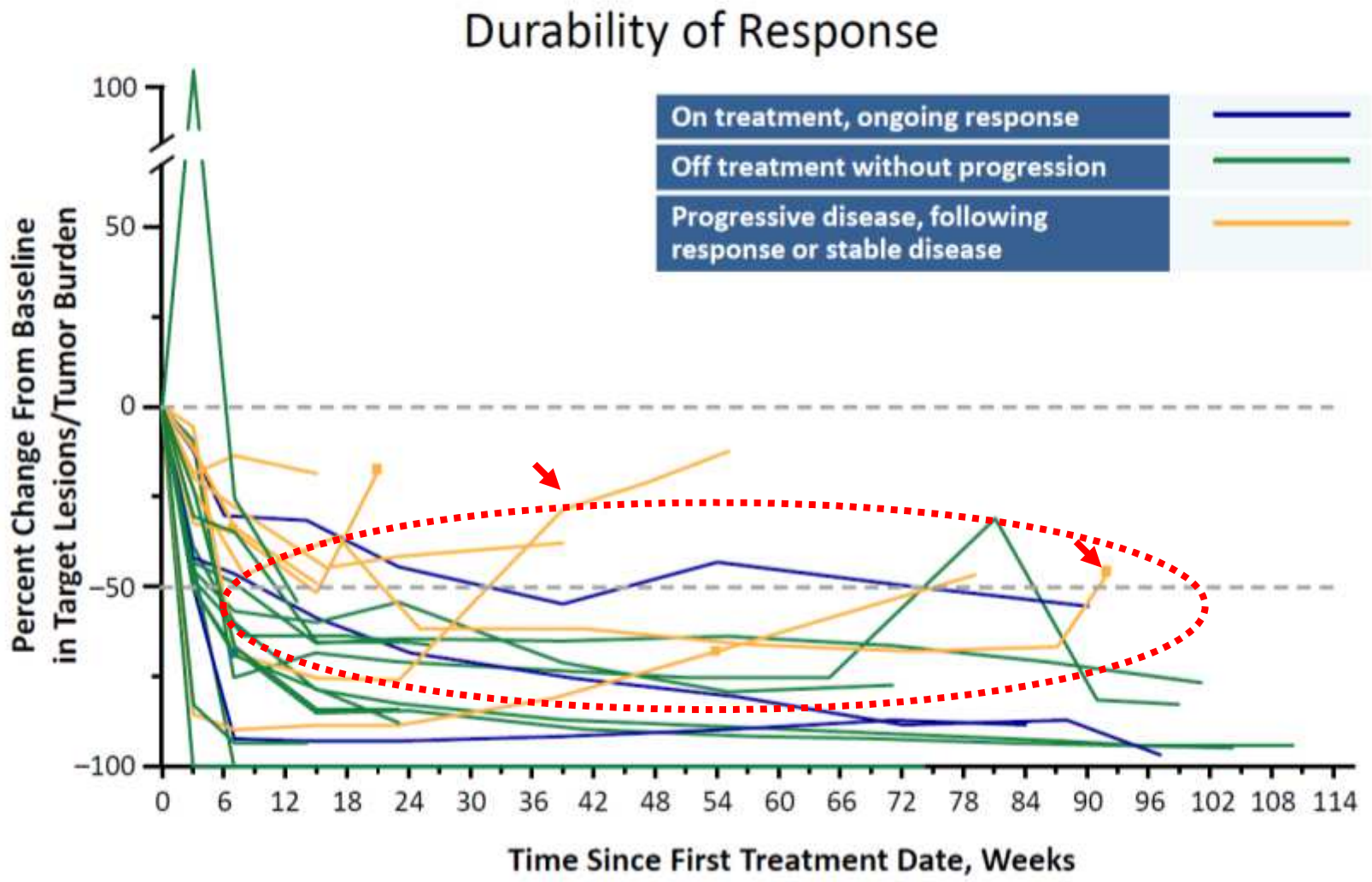
PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma

Partial responder

Response in Lymphoma

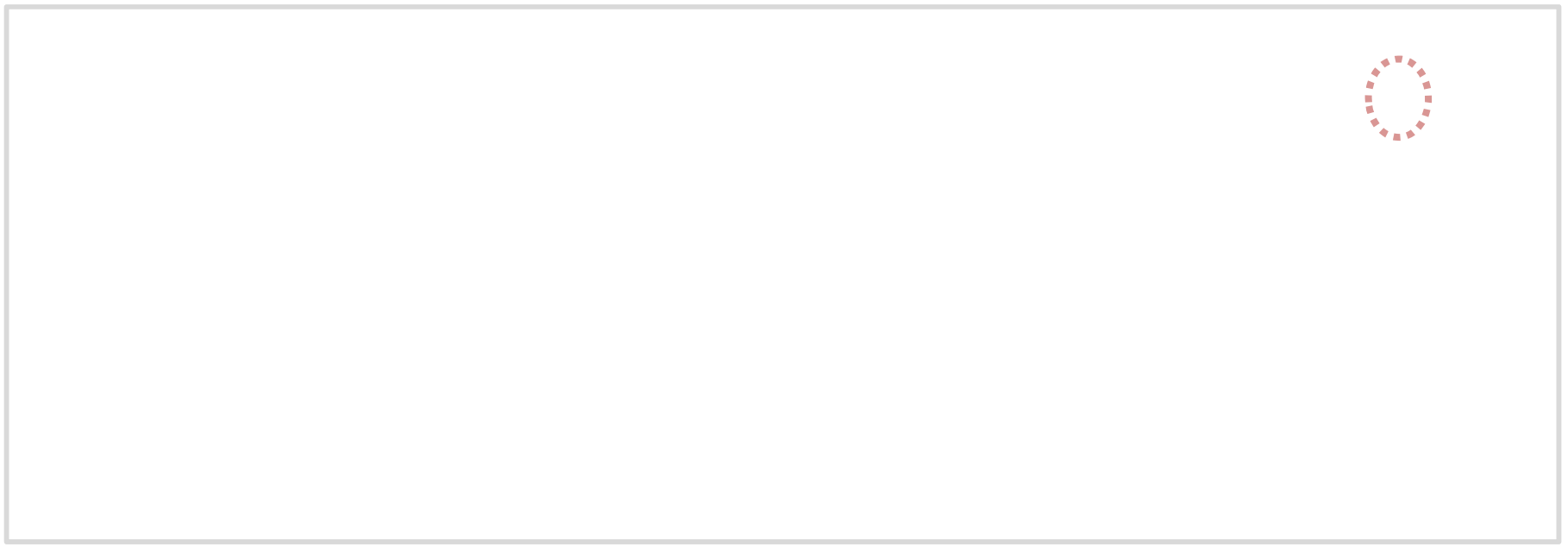


Ansell et al ASH 2015



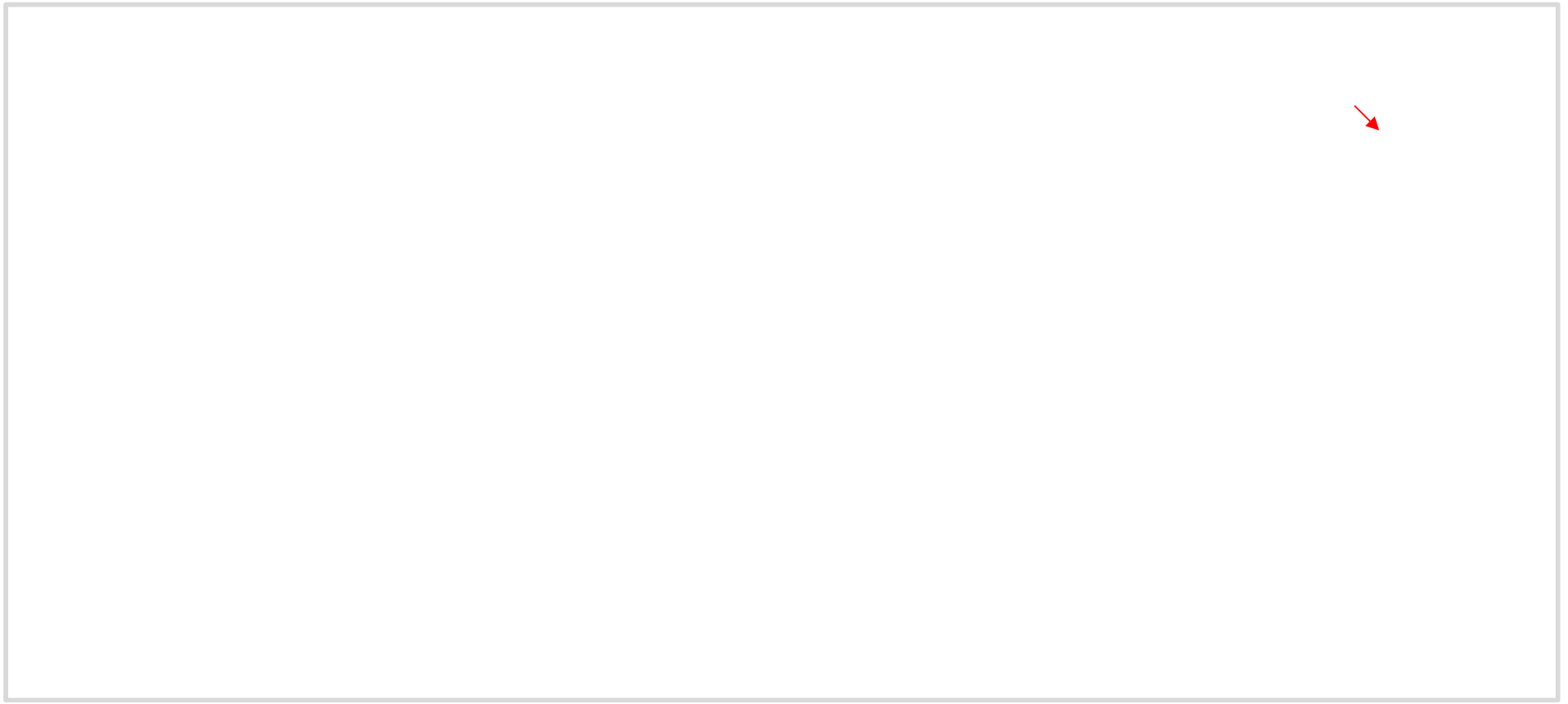
Ansell et al ASH 2015

PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma



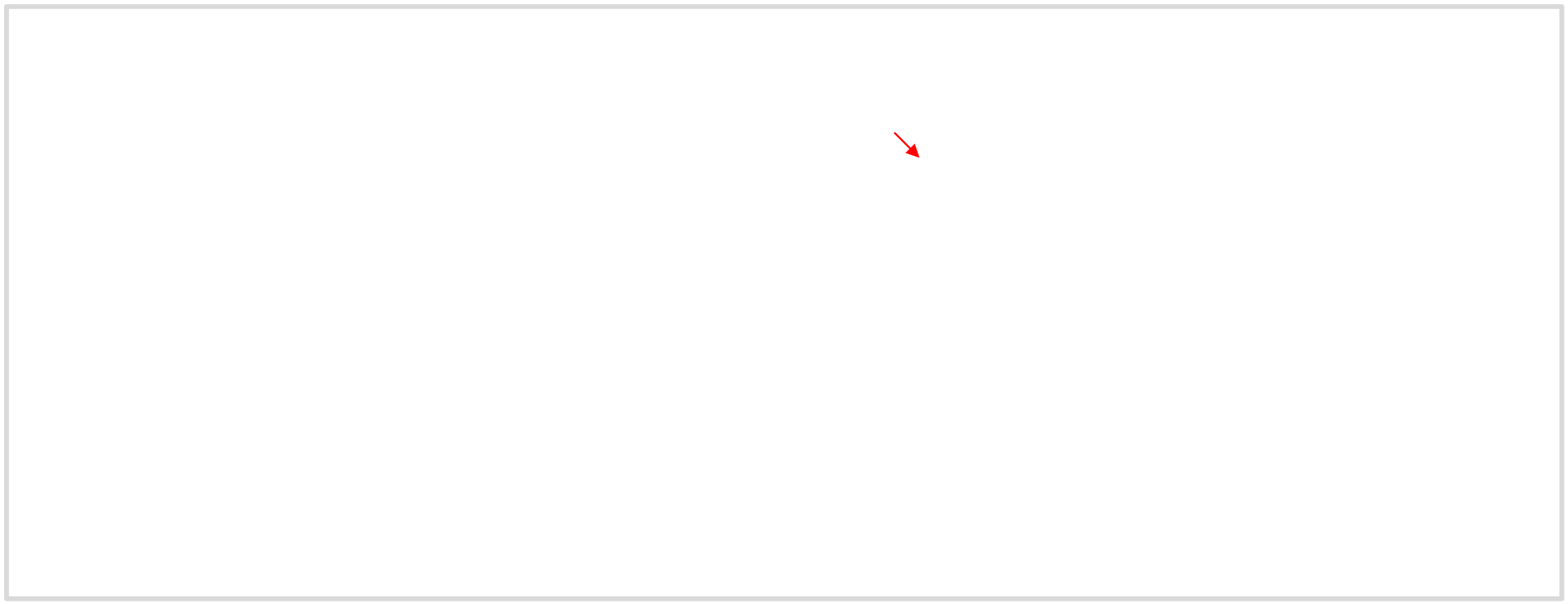
Progressive responder

PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma

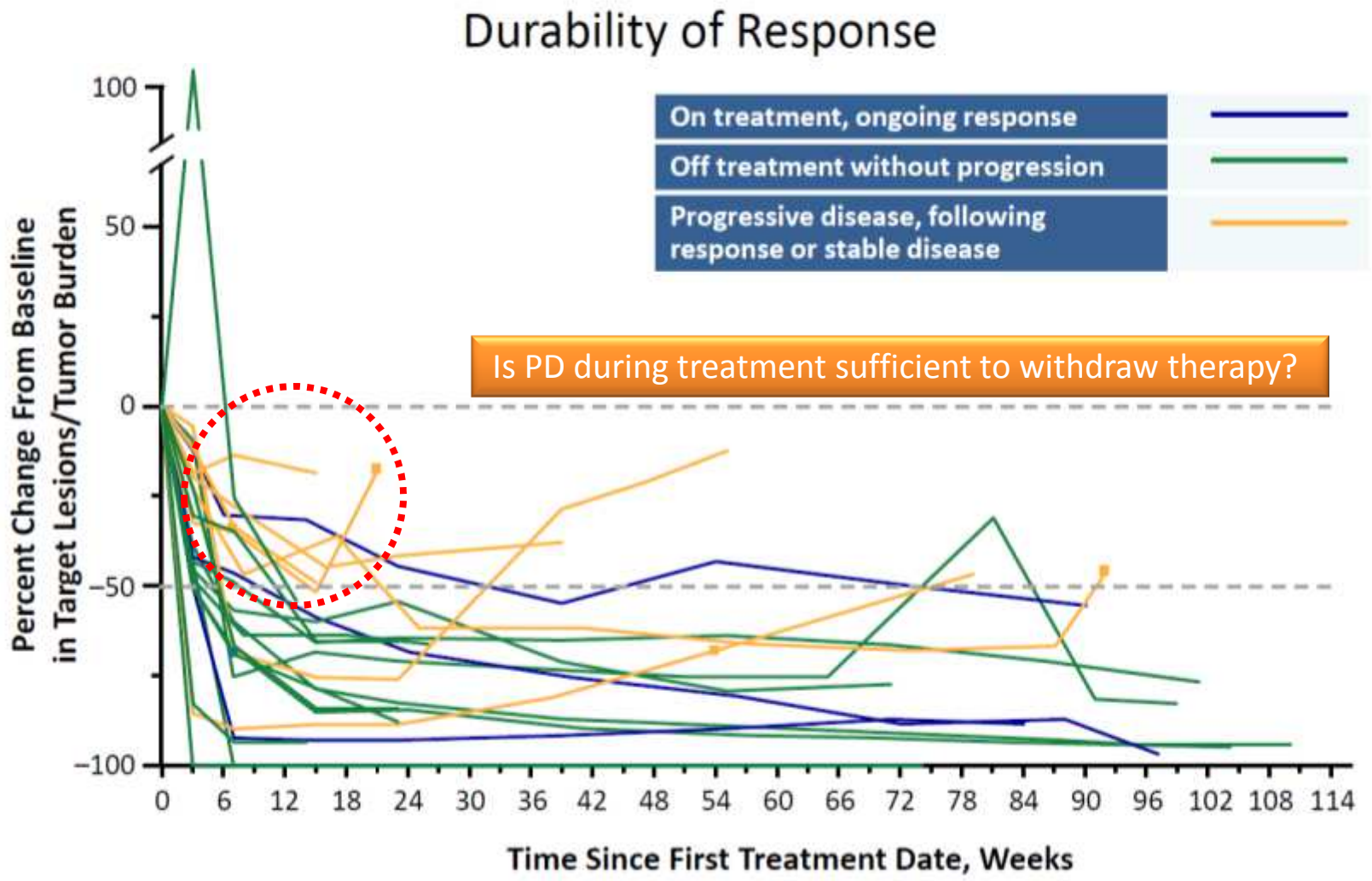


Early response than Progression or Pseudoprogression?

PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma



Progression or Pseudoprogression?

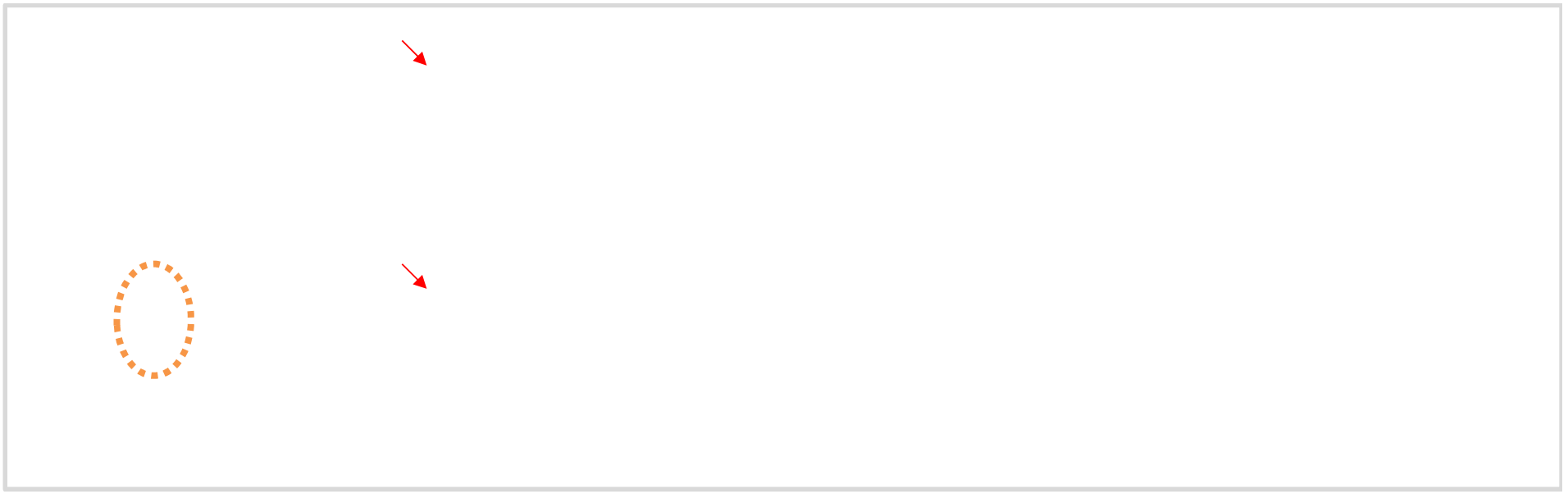


Ansell et al ASH 2015

PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma

Alternating responder

PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma



Partial responder? Early progression?

a
- Response paradigm is different for immunotherapy?

b
- Tumor burden more important than single lesion progression?

c
- Clinics play a more important role in treatment change?

Refinement of the Lugano classification response criteria for lymphoma in the era of immunomodulatory therapy

Bruce D. Cheson, Stephen Ansell, Larry Schwartz, Leo I. Gordon, Ranjana Advani, Heather A. Jacene, Axel Hoos, Sally F. Barrington and Philippe Armand

Criteria	CR	PR	PD
Lugano	PET-CT, score 1, 2, or 3* with or without a residual mass on 5PS† OR on CT, target nodes /nodal masses must regress to ≤ 1.5 cm in LDi	PET-CT Score 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size. OR On CT ≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites	PET-CT score 4 or 5 with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment. OR On CT, an individual node /lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly. New or clear progression of preexisiting nonmeasured lesions. Regrowth of previously resolved lesions. A new node > 1.5 cm in any axis or a new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma
LYRIC	Same as Lugano	Same as Lugano	As with Lugano with the following exceptions: Indeterminate response (IR) IR1: >50% increase in SPD in first 12 wks IR2: <50% increase in SPD with a. New lesion(s), or b. >50% increase in PPD of a lesion or set of lesions at any time during treatment IR(3): Increase in FDG uptake without a concomitant increase in lesion size meeting criteria for PD

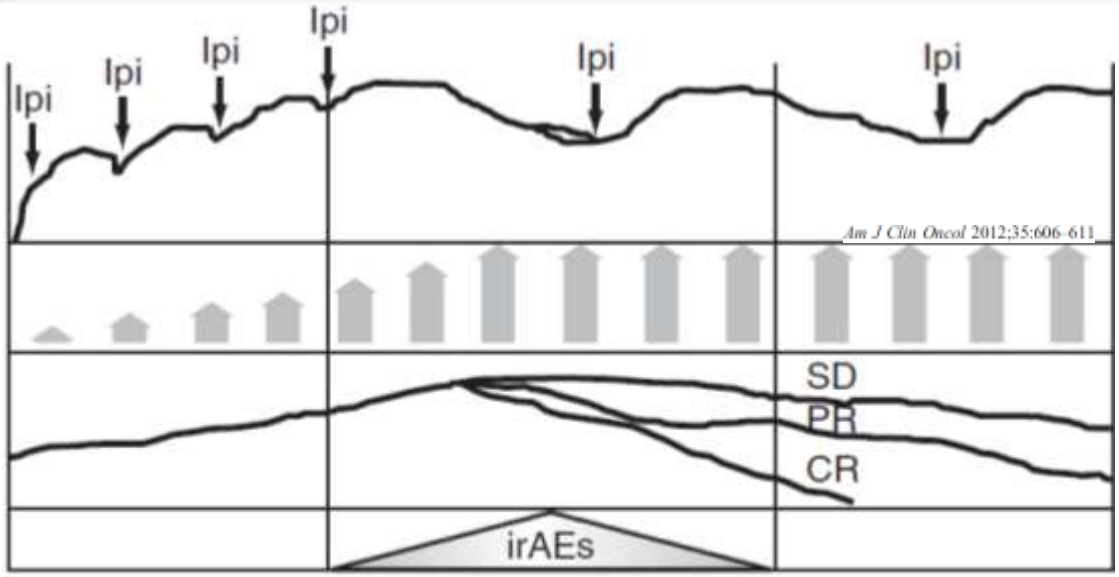
Indeterminate Response (IR)

Prepublished online August 29, 2016; doi:10.1182/blood-2016-05-718528

blood

PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma

Immunotherapy Related Advanced Events



Event	No. of Patients	Clinically Evident Adverse Event	Median Duration of Therapy (mo)	Median Interval Between Start of Treatment and Adverse Event (mo)	Response (No. of Patients)	
					Controlled Disease	Progressive Disease
Colitis	6 (5.0)	Yes	9 (3–35)	3 (2–26)	2	4
Hypophysitis	2 (1.7)	Yes	7 (4–9)	2 (2)	1	1
Arthritis	4 (3.4)	Yes	18 (4–36)	9 (2–14)	3	1
Thyroiditis	1 (0.8)	Yes	9	8	1	0
Lymphadenopathy	8 (6.7)	No	37 (2–118)	5 (1–13)	5	3
Myositis	2 (1.7)	No	37 (36–37)	5(3–6)	2	0
Retroperitoneal fat opacities	2 (1.7)	No	20 (4–36)	9 (2–16)	2	0

Note—Values in parentheses are percentages or range.

Radiologic Manifestations of Immune-Related Adverse Events in Patients With Metastatic Melanoma Undergoing Anti–CTLA-4 Antibody Therapy

AJR 2011; 197:W992–W1000

PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma

Table 2. Drug-Related Adverse Events in the 23 Patients.*

Event	Any Grade	Grade 3
	no. of patients (%)	
Any adverse event	18 (78)	5 (22)
Drug-related adverse events reported in ≥5% of patients		
Rash	5 (22)	0
Decreased platelet count	4 (17)	0
Fatigue	3 (13)	0
Pyrexia	3 (13)	0
Diarrhea	3 (13)	0
Nausea	3 (13)	0
Pruritus	3 (13)	0
Cough	2 (9)	0
Hypothyroidism	2 (9)	0
Decreased lymphocyte count	2 (9)	1 (4)
Hypophosphatemia	2 (9)	0
Hypercalcemia	2 (9)	0
Increased lipase level	2 (9)	1 (4)
Stomatitis	2 (9)	1 (4)
Drug-related serious adverse events		
Myelodysplastic syndrome	1 (4)	1 (4)
Lymph-node pain	1 (4)	0
Pancreatitis	1 (4)	1 (4)

Related Adverse Events	Grade
Pancreatitis	3
Pneumonitis	3
Gastrointestinal inflammation	3
Stomatitis	3
Colitis	3
Unrelated Adverse Events	**Grade**
Bacteremia	4
Enchephalitis	3
Graft versus host disease	5
Infection	3
Pneumonia mycoplasma	3
Skin infection	3
Small intestinal infection	3

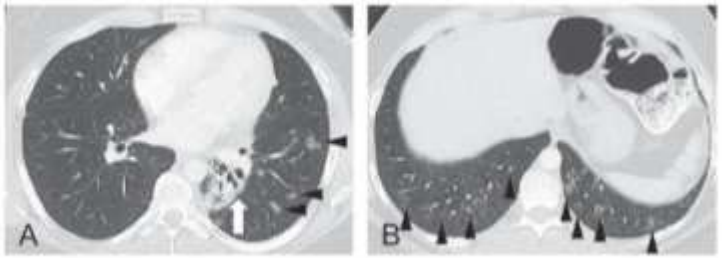
N Engl J Med 2015;372:311-9

Abstract 3053

PD-1 inhibitor-related pneumonitis in advanced cancer patients

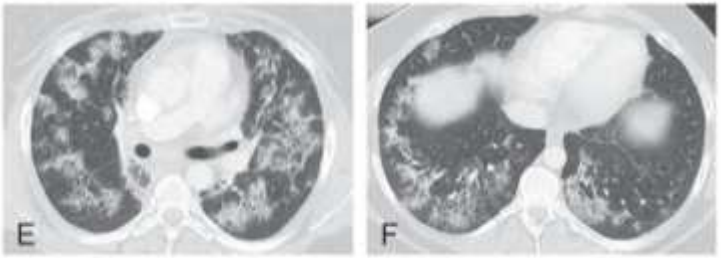
Mizuki Nishino, MD, MPH, Nikhil H. Ramaiya, MD, Mark M. Awad, MD, PhD, Lynette M. Sholl, MD, Jennifer A. Maattala, Myriam Taibi, Hiroto Hatabu, MD, PhD, Patrick A. Ott, MD, PhD, Philippe F. Armand, MD, PhD, F. Stephen Hodi, MD

Nivolumab & ipilimumab



A, B. At 1.4 months of therapy

Nivolumab & ipilimumab, then nivolumab alone

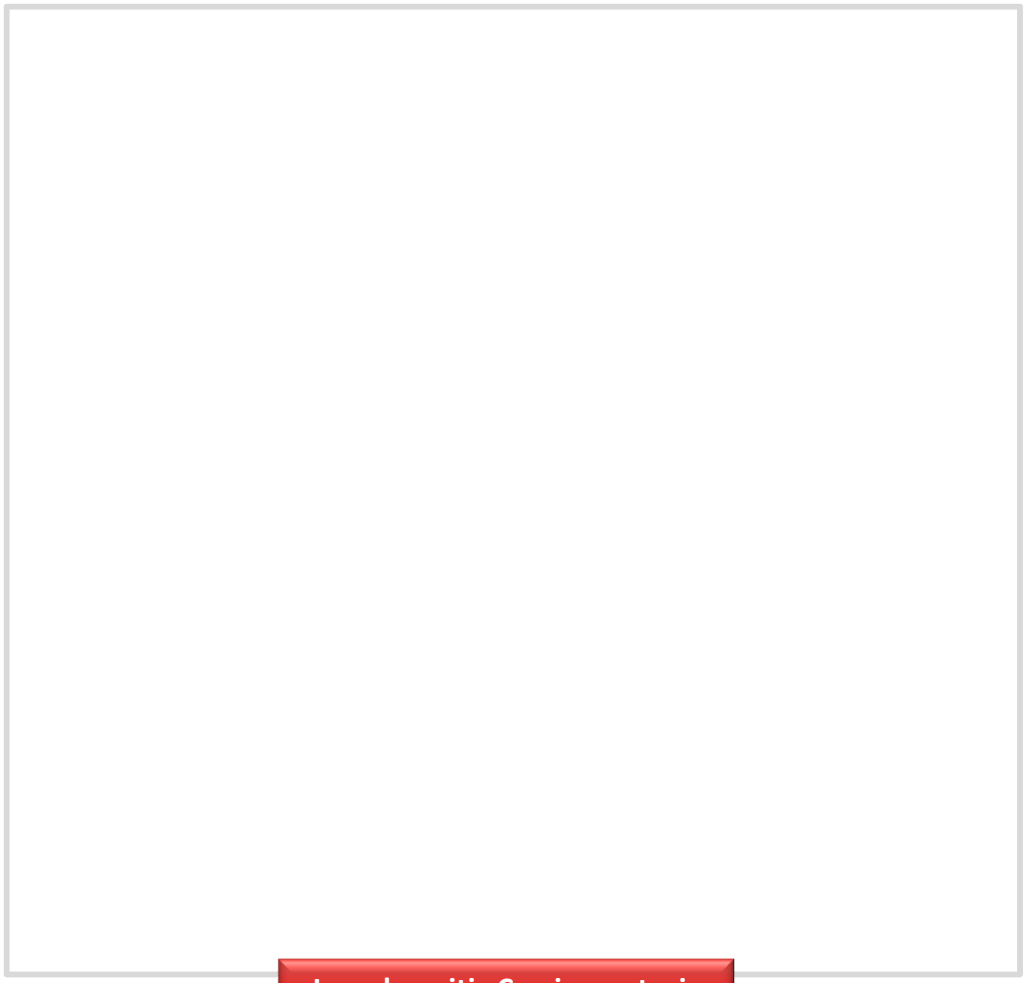


E, F. 2 months after restarting therapy

- Among 170 patients treated on 10 different trials of nivolumab, either alone or in combination with other immune checkpoint inhibitors, 20 patients (11.8%) developed pneumonitis
- 7 (35%) were male and 13 (65%) were female, with a median age of 52 (range 28-71)
- 5 patients received nivolumab monotherapy and 15 patients received combination therapy (with ipilimumab in 12 and with anti-KIR antibody lirilumab in 3 patients)
- Ten patients had melanoma, 6 had lymphoma, and 4 had lung cancer (3 non-small-cell and one small-cell lung cancer)
- Severity of pneumonitis was Grade 1 in 5 (25%), Grade 2 in 10 (50%), and Grade 3 in 5 patients (25%)
- Median time from therapy initiation to pneumonitis was 2.6 months (range: 0.5-11.5)
- Time to pneumonitis was shorter in 4 lung cancer patients compared to 16 patients with melanoma and lymphoma (media time to pneumonitis: 1.1 vs. 3.1 months; p=0.008)

Dana-Farber Cancer Institute and Brigham and Women's Hospital, Harvard Medical School, Boston, MA
E-mail: mizuki_nishino@dfci.harvard.edu

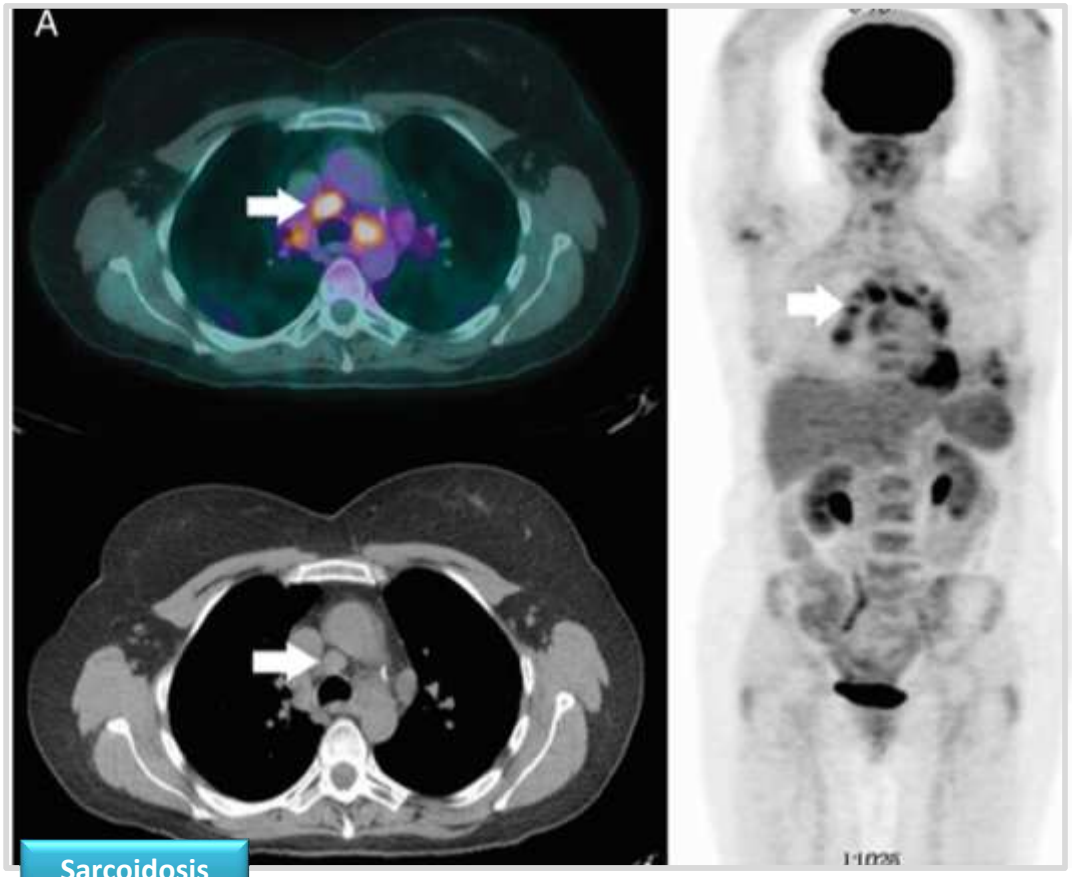
Immunotherapy Related Advanced Events



Lymphangitic Carcinomatosis

Disease or inflammation?

Immunotherapy Related Advanced Events

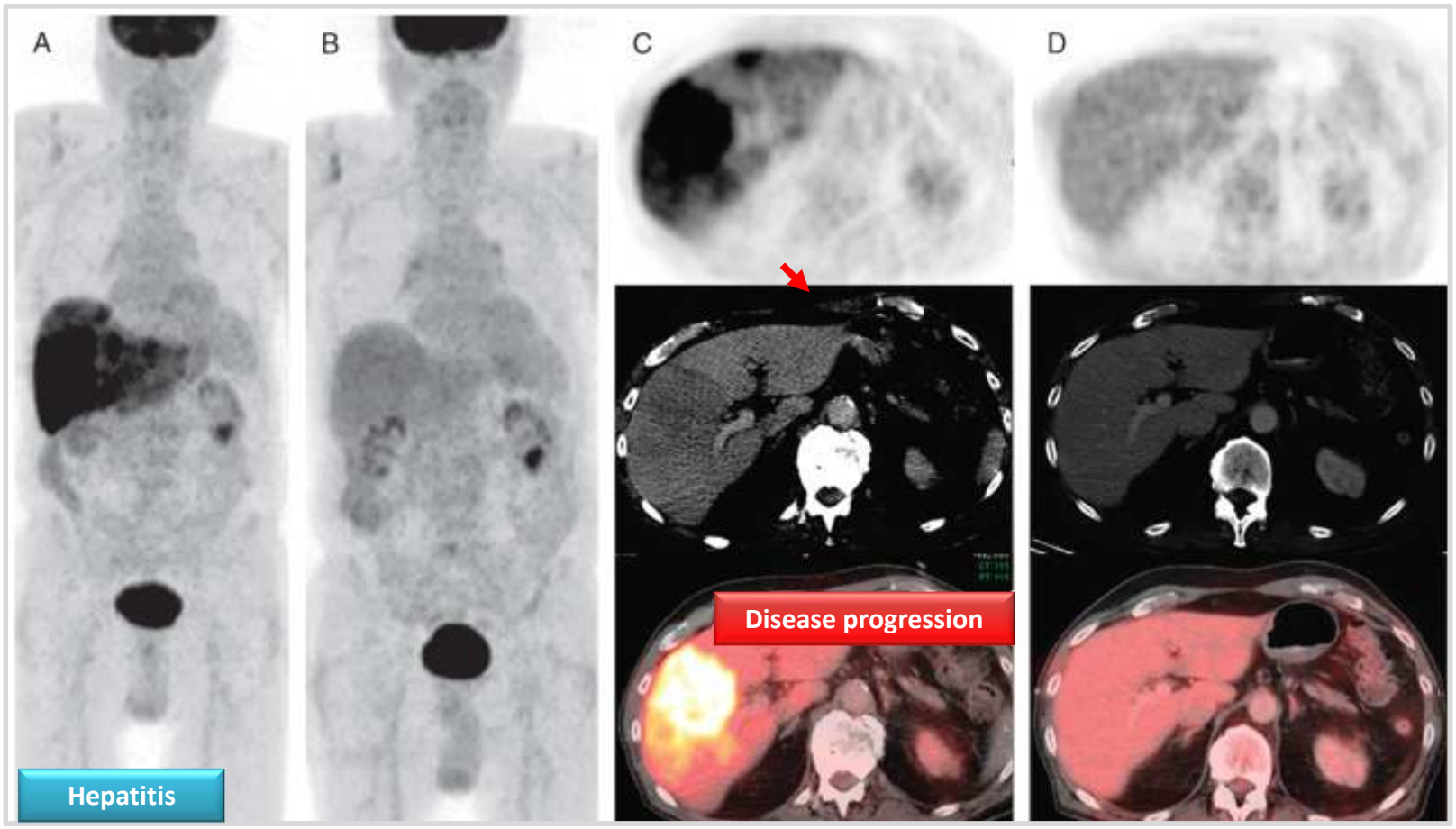


Sarcoidosis

Clin Nucl Med 2014;39: e93–e96

Granulomatosis? Disease?

Immunotherapy Related Advanced Events



Clinical situation

Clin Nucl Med 2015;40: 258–259

Immunotherapy Related Advanced Events

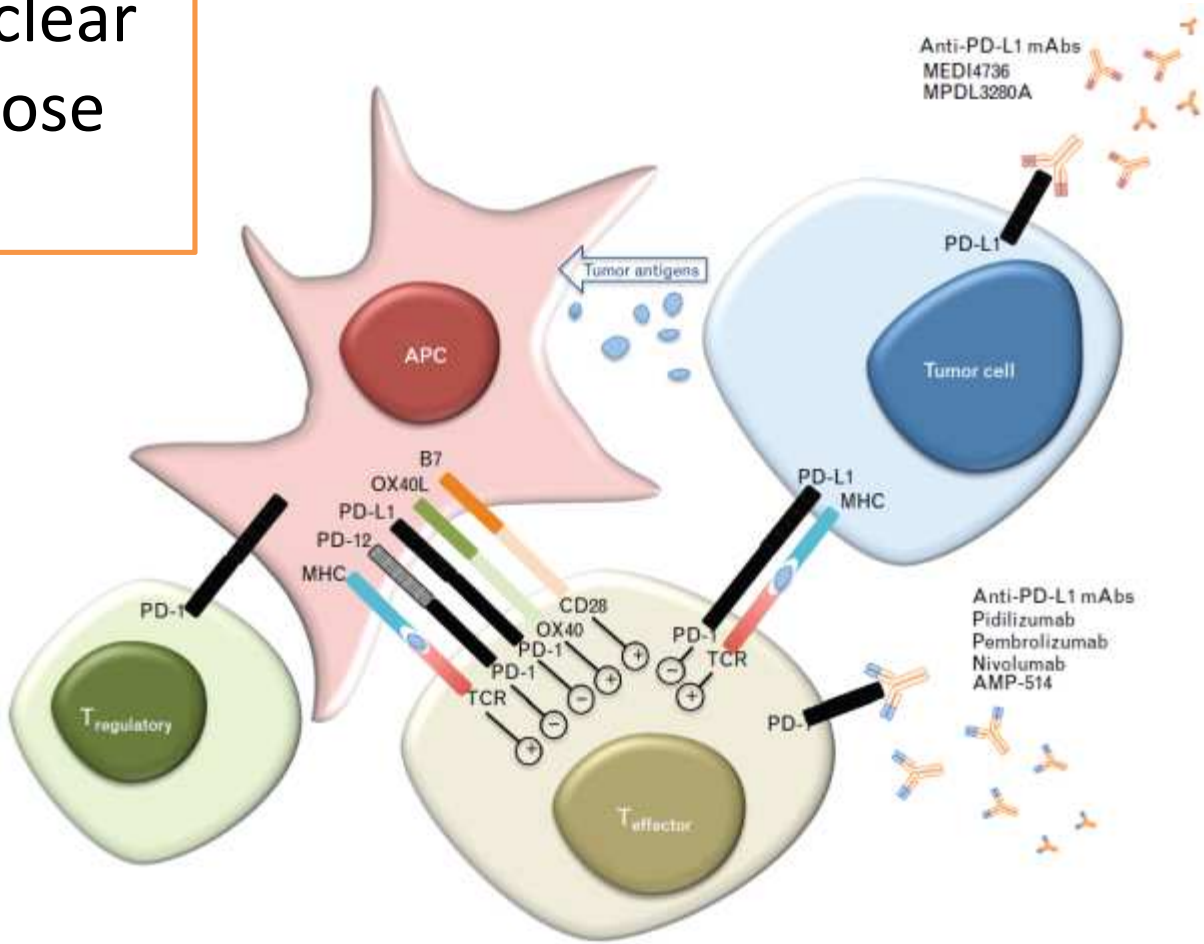
a
- IrAE affect a vast majority of immunotherapy patients

b
- IrAE can lead to misinterpretation and drop-offs

C
- Clinics play an important role in their recognition

D
- Biopsy or confirmation with subsequent scan

Can we come to a clear conclusion on respose in lymphoma?



Curr Opin Oncol 2015, 27:384–391

Prospective clinical trials for response in lymphoma patients candidate to immunotherapy

Acknkowledgments:

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Prof Carmelo Carlo-Stella

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