Biomarcatori e Tecniche di Diagnostica per Immagini nella Valutazione dell'Infiammazione in Oncologia

Il ruolo dell'imaging molecolare nell'era della immunoterapia

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Issues

1. Background
2. Needs and priorities
3. Evidences
    1. Literature
    2. Clinical impact
4. Comparative data (vs. standards)
5. Practical aspects
    1. Patient preparation
    2. Interpretation of the images

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Immunotherapy

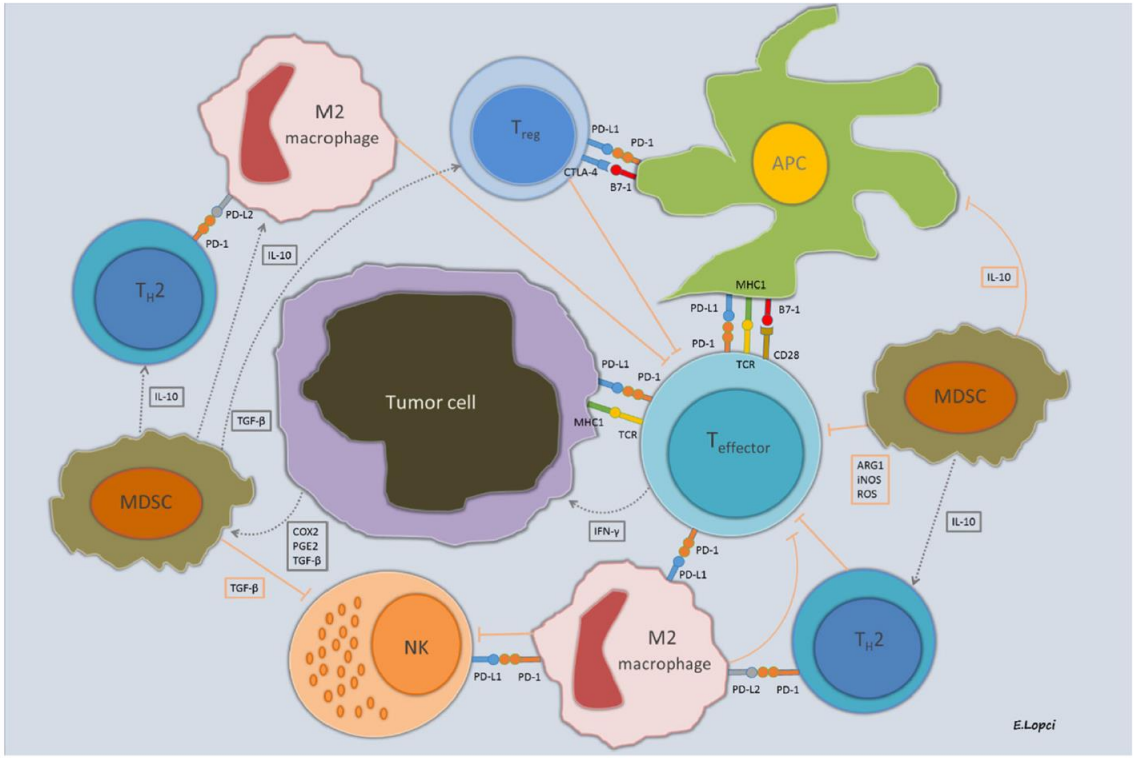


Fig. 1 Immune suppressive mechanisms in the tumor microenvironment. The impact of immune checkpoints and the mutual interactions of the principal components of the immune system plays a crucial pro-tumorigenic role. APC Antigen-presenting cell; MDSC Myeloid-derived suppressor cells; NK Natural Killer; T_H2 T-helper; T_{reg} T-regulatory; TCR T-cell receptor; MHC1 major histocompatibility complex 1; PD-1 programmed cell death 1; PD-L1 programmed cell death ligand 1; PD-L2 programmed cell death ligand 2; CTLA-4 cytotoxic T-lymphocyte antigen 4; IL-10 interleukin 10; IFN-γ interferon gamma; TGF-β transforming growth factor beta; COX2 Cyclooxygenase 2; PGE2 Prostaglandin E2; ARG1 arginase 1; iNOS Inducible nitric oxide synthase; ROS reactive oxygen species

Eur J Nucl Med Mol Imaging. 2017; 44:2310–2325

Patterns or response to immunotherapeutic agents differ from those to other targeted therapies.

1. Early and delayed response
2. Pseudoprogression (15% of cases)
3. Hyperprogression (<5%)

Eur J Nucl Med Mol Imaging. 2019;46:238-250

PET-positron emission tomography

Accurate staging → Correct therapeutic choice

Accurate staging → Correct prognosis definition (DFS, OS)

The response → **Interim PET** → **Change of therapy?**

The response → **End of treatment** → **More therapy?**

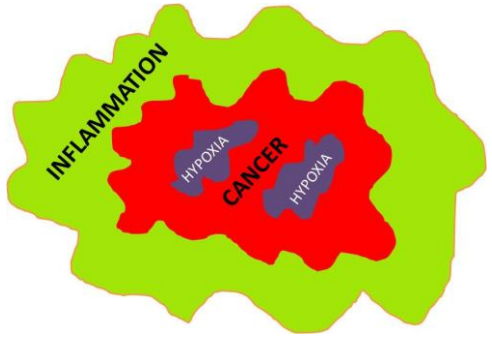
The response → **End of treatment** → **Prognosis (DFS, OS)**

RT planning → Accurate staging

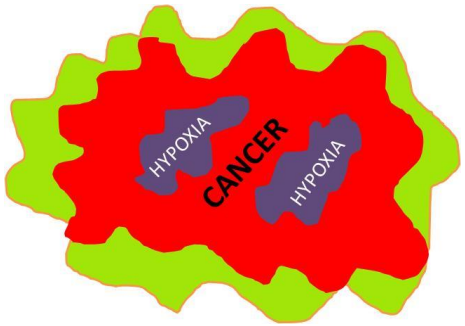
RT planning → Definition of target volume

RT planning → Response to therapy

Evolution of cancer

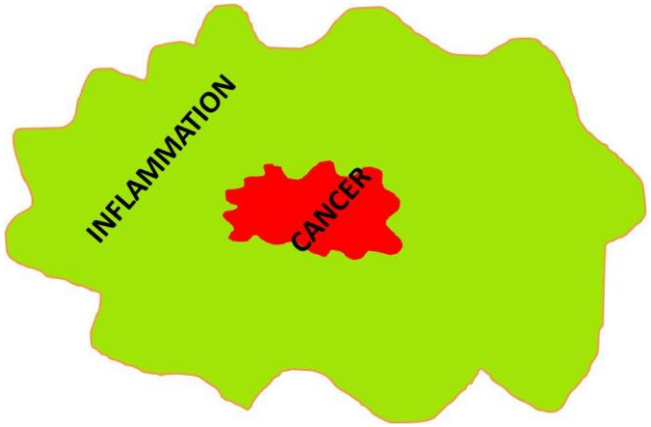


INTERIM EFFECT



EFFECT OF CORTICOSTEROIDS

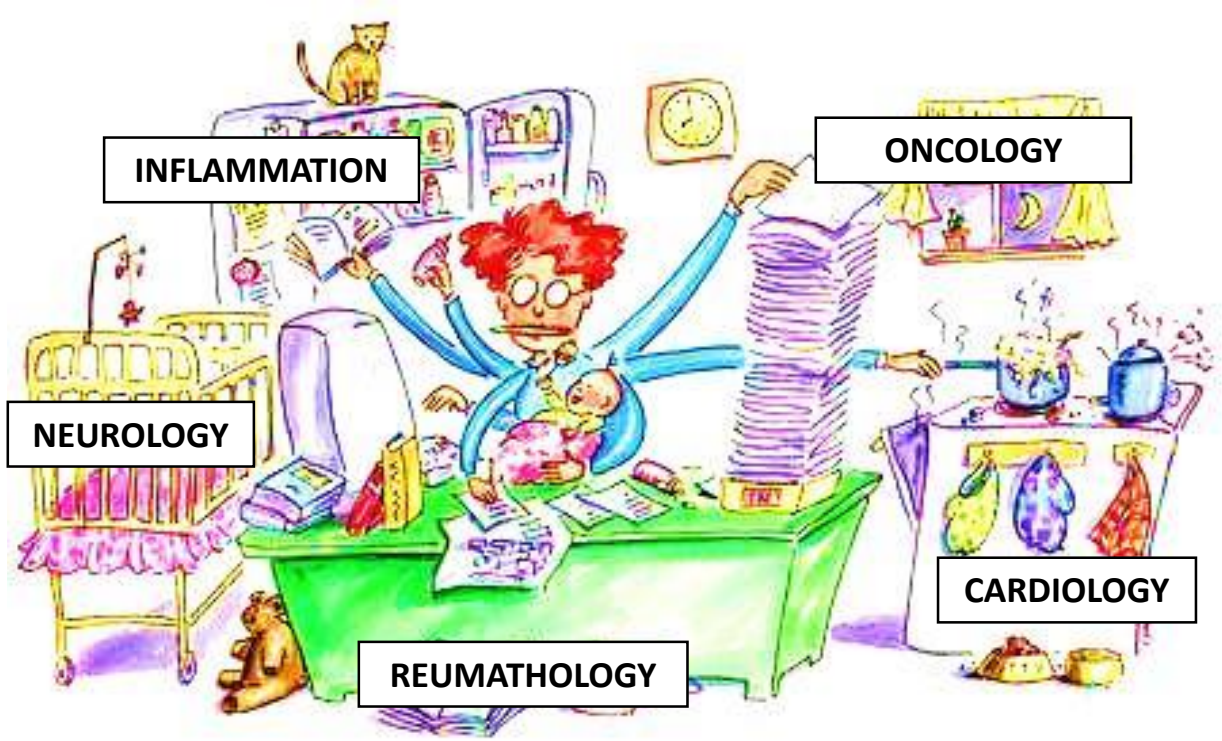
EFFECT OF CYTOTOXIC AGENTS



EFFECT OF CHECKPOINT-INHIBITORS

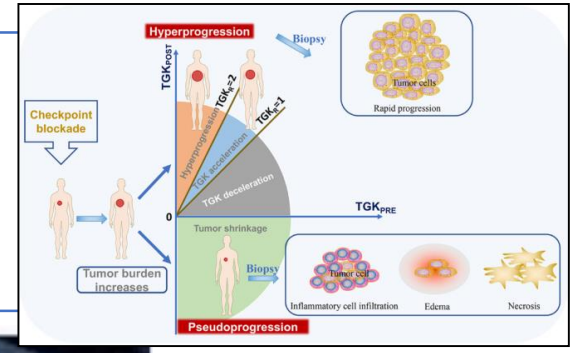
Courtesy by Cristina Nanni

What about FDG PET/CT?

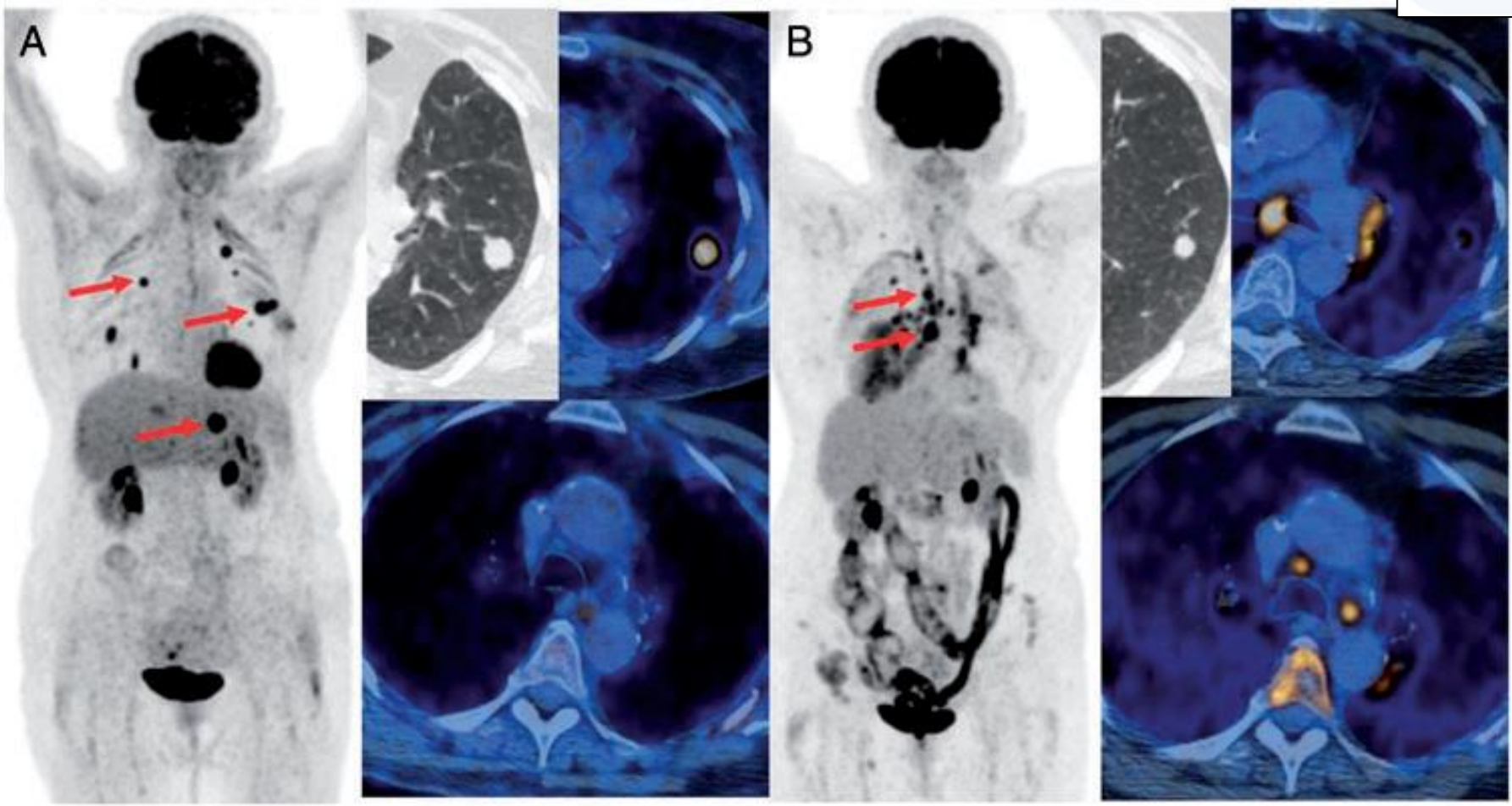


- FDG is trapped in tissues with high glicolytic activity
- FDG is not specific
- Low specificity
- High false positive findings
- Time between therapy and imaging is essential!

Pseudoprogression at FDG PET/CT



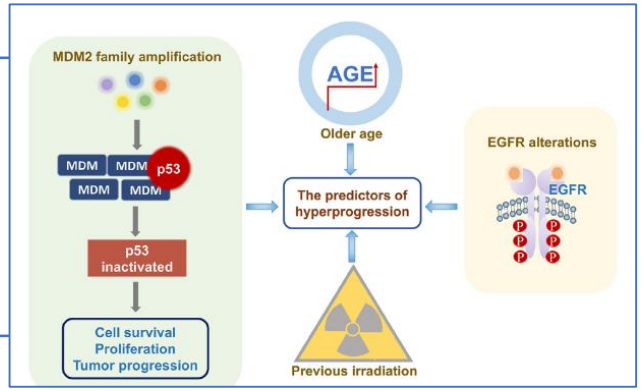
Curioni-Fontecedro et al. Annals of Oncology Vol 28|Issue 8|2017



A: before Th.
B: 6-weeks after Th.

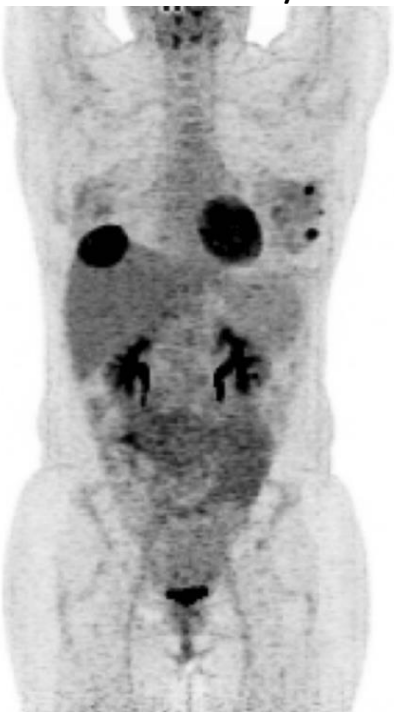
Diffuse pseudoprogression after Nivolumab in a NSCLC patient

Hyperprogression at FDG PET

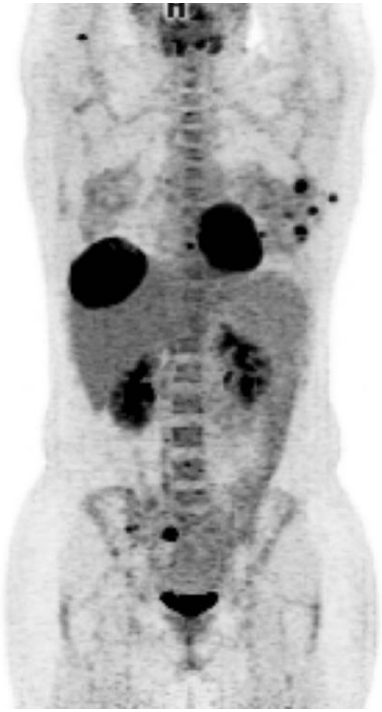


Eur J Nucl Med Mol Imaging. 2019;46:238-250

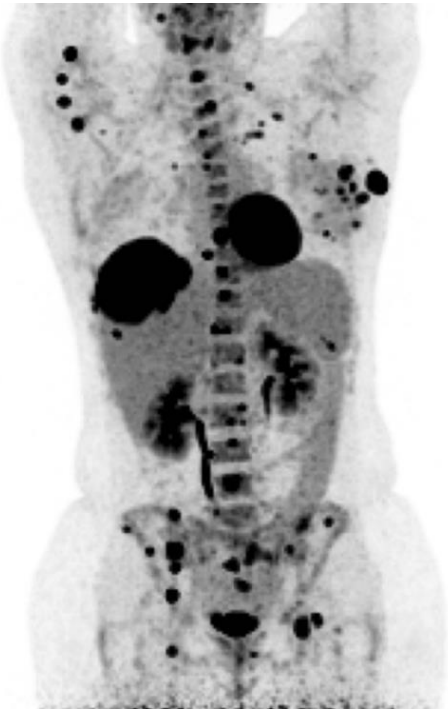
Baseline PET/CT



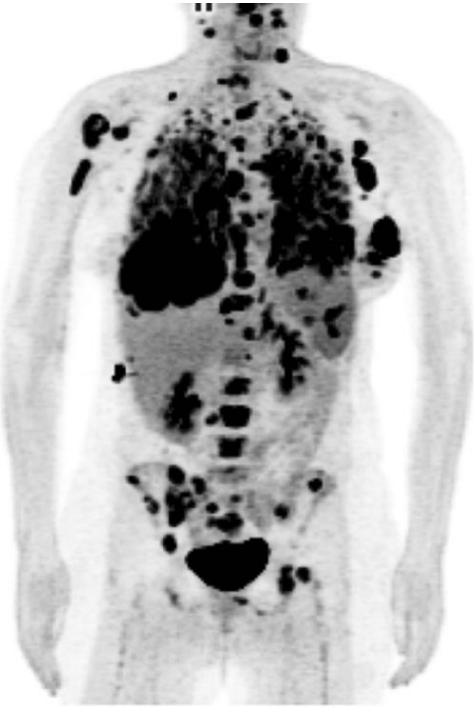
2-cycles later



6-cycles later



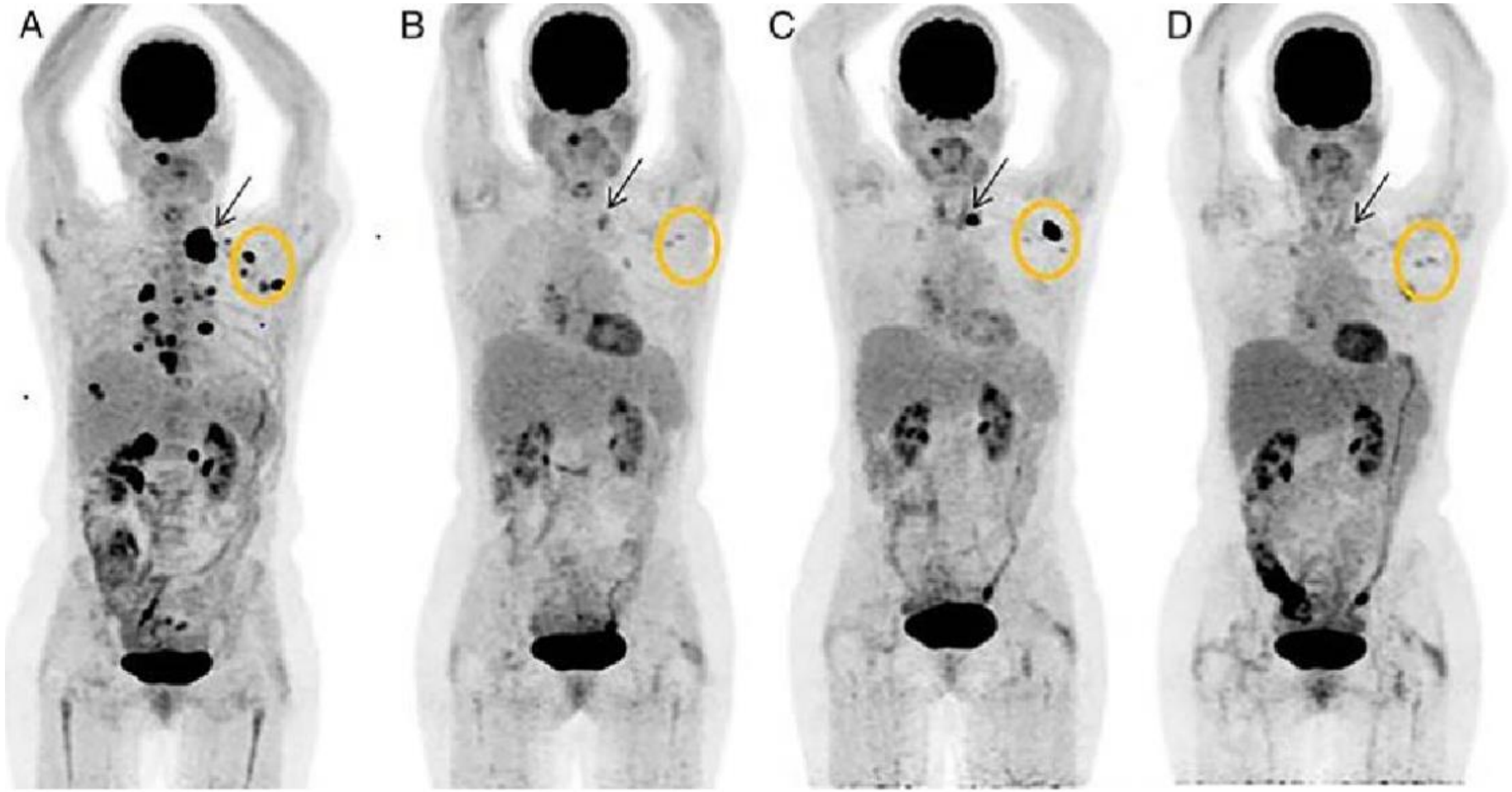
Follow-up PET/CT



Diffuse iperprogression after Nivolumab in a melanoma patient

Dynamic adaption

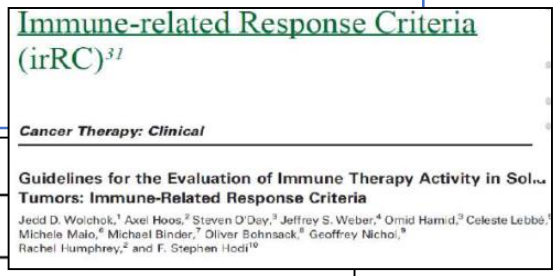
In patients with late progression of disease, one should consider continuing immunotherapy, because **the immune system may adapt again control the tumor**



baseline | 7-weeks | 15-weeks | 20-weeks

Clin Nucl Med 2018; 43:118

PET criteria for the definition of response to therapy


Immune-related Response Criteria (irRC)[31]

Cancer Therapy: Clinical

Guidelines for the Evaluation of Immune Therapy Activity in Sol... Tumors: Immune-Related Response Criteria

Jedd D. Wolchok,[1] Axel Hoos,[2] Steven O'Day,[3] Jeffrey S. Weber,[4] Omid Hamid,[5] Celeste Lebbé,[6] Michele Malo,[6] Michael Binder,[7] Oliver Bohnsack,[8] Geoffrey Nichol,[9] Rachel Humphrey,[2] and F. Stephen Hodi[10]

Table 2 Summary of the principal morphological and functional response criteria in solid tumors

Category	Metabolic response		Morphological response		
	EORTC 1999	PERCIST	RECIST 1.1	irRC	irRECIST
Measurable lesions	the most FDG uptake lesions by SUVs normalized by body surface area	minimum tumor SUL 1.5 times the mean SUL of the liver	10 mm at CT (longest diameter, except in lymph nodes)	5 mm × 5 mm	not change from RECIST 1.1
New lesions	as progressive disease	as progressive disease	as progressive disease	Does not constitute progressive disease in itself	Does not constitute progressive disease in itself
Number of lesions	not specified	changes in the sum of up to 5 lesions as secondary measure to assess response	up to 5, maximum 2 per organ	up to 5 cutaneous lesions and 10 visceral lesions (no more than 5 per organ)	not change from RECIST 1.1
Complete response	complete resolution of [18F]-FDG uptake	disappearance of all metabolically active tumors	disappearance of all target lesions reduction in short axis of target lymph nodes to <10 mm no new lesions		total remission of all target, nontarget, and new lesions for two consecutive evaluations at least 4 weeks apart
Partial Response	reduction of a minimum of 15% ± 25% in tumor SUV after 1 cycle of chemotherapy, and >25% after more than one treatment cycle	0.8-unit (>30%) decline in SUL peak between the most intense lesion before treatment and the most intense lesion after treatment	decrease in target lesion diameter sum >30%	decrease of at least 50% of the tumor burden compared to the baseline (confirmed by a consecutive scan after no less than 4 weeks)	
Stable disease	increase in SUV of less than 25% or a decrease of less than 15%	does not meet other criteria	does not meet other criteria		an increase less than 25% from smallest recorded tumor burden (nadir) or a decrease less than 50% from baseline
Progression disease	increase in tumor FDG uptake >25%, increase of the maximum tumor >20%, new metastases	increase (>30%) in SUL peak or the appearance of a new metabolically active lesion	increase in target lesion diameter sum >20% and at least 5 mm or new lesions	At least 25% increase in tumor burden compared with nadir in two consecutive observations at least 4 weeks apart	

Notes: EORTC = European Organization for Research and Treatment of Cancer; PERCIST = PET) Response Criteria in Solid Tumors; RECIST = Response Evaluation Criteria In Solid Tumors; irRC = Immune-Related Response Criteria; irRECIST = Immune-Related RECIST

Eur J Nucl Med Mol Imaging (2017) 44:2310–2325

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Needs

- Is there any response to immunotherapy?
- How can differentiate between pseudoprogression and hyperprogression?
- May I predict the response to immunotherapy, by selecting appropriate patients?
- May I anticipate the development of immune related side effects?

Priorities

- Selection of patients who may benefit from immunotherapy
- An early prediction of response to immunotherapy (indirect on costs)
- Data about follow-up after stopping immunotherapy
- D.D. between pseudoprogression and hyperprogression

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Clinical Evidences

Reference	Study type	Number of patients	Tumour	Treatment	Response criteria	Results
[20]	Prospective	22	Melanoma	Ipilimumab	EORTC after two cycles of treatment (early) and at the end of treatment after four cycles (late)	Early response evaluation after (two cycles) is predictive of final treatment outcome in patients with PMD and SMD
[26]	Prospective	27	Melanoma	20 pembrolizumab, 7 nivolumab	Visual analysis (qualitative visual inspection, positive when FDG uptake greater than background activity or hepatic uptake; Deauville score)	43% of patients who had residual disease by CT criteria, either PR or SD, were FDG-negative
[36]	Prospective	31	Melanoma	Ipilimumab	Fractal and multifractal analysis before and after two and after four cycles of treatment	Operator-independent method with a correct classification rate of 83.3%
[23]	Prospective	20	Melanoma	16 Ipilimumab, 1 nivolumab, 3 BMS-936559	RECIST 1.1 and PERCIST at early (4 weeks) and late assessment (4 months)	Combined anatomical and functional data at 21–28 days (PECRIT) criteria predicted response with 100% sensitivity, 93% specificity and 95% accuracy. Introduction of clinical benefit in response criteria
[22]	Prospective	24	NSCLC	Nivolumab	RECIST 1.1 versus PERCIST; additional semiquantitative analyses (SUVmax, MTV, TLG)	Metabolic response on PET (especially TLG) associated with therapeutic response and survival at 1 month after nivolumab
[28]	Prospective	27	NSCLC	23 nivolumab, 4 pembrolizumab	Baseline semiquantitative analysis	SUVmax ≤17.1 (sensitivity 88.9%) or a SUVmean ≤8.3 (sensitivity 100%) identified fast progression after 8 weeks of therapy
[24]	Prospective enrolment, retrospective PET analysis	41	Melanoma	Ipilimumab	RECIST and appearance of new FDG-avid lesions (PERCIMT); patients were dichotomized into those with and those without clinical benefit	A cut-off of four newly emerged FDG-avid lesions on posttreatment PET/CT gave reliable indication of treatment failure
[25]	Prospective	41	Melanoma	Ipilimumab	EORTC and PERCIMT after two cycles of immunotherapy	PERCIMT to interim PET/CT provides a more sensitive predictor of final response than EORTC criteria

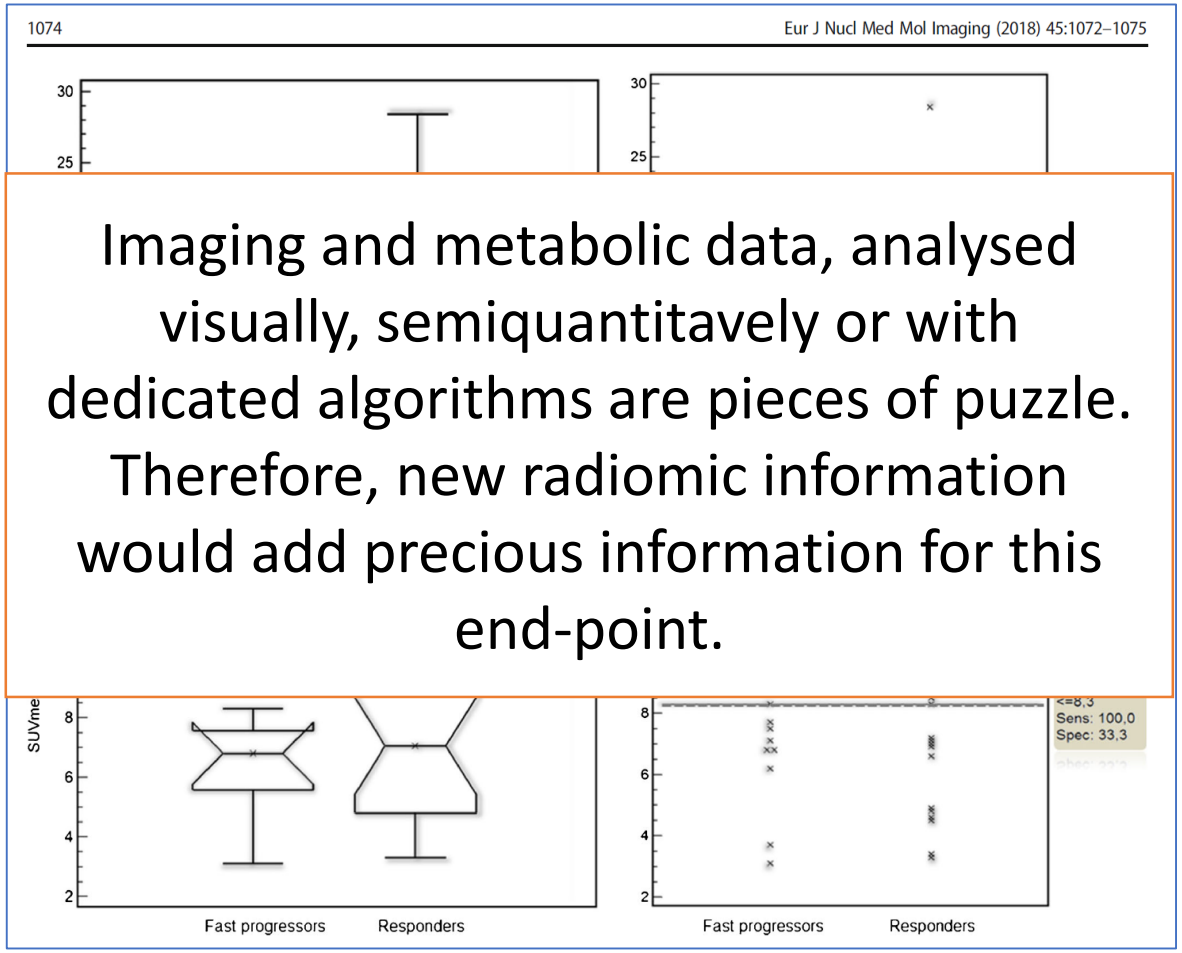
182 patients with melanoma

51 patients with NSCLC

- EORTC in 2 studies
- Visual and semiquantitative analysis in 2 studies
- PERCIST and new in 3 studies

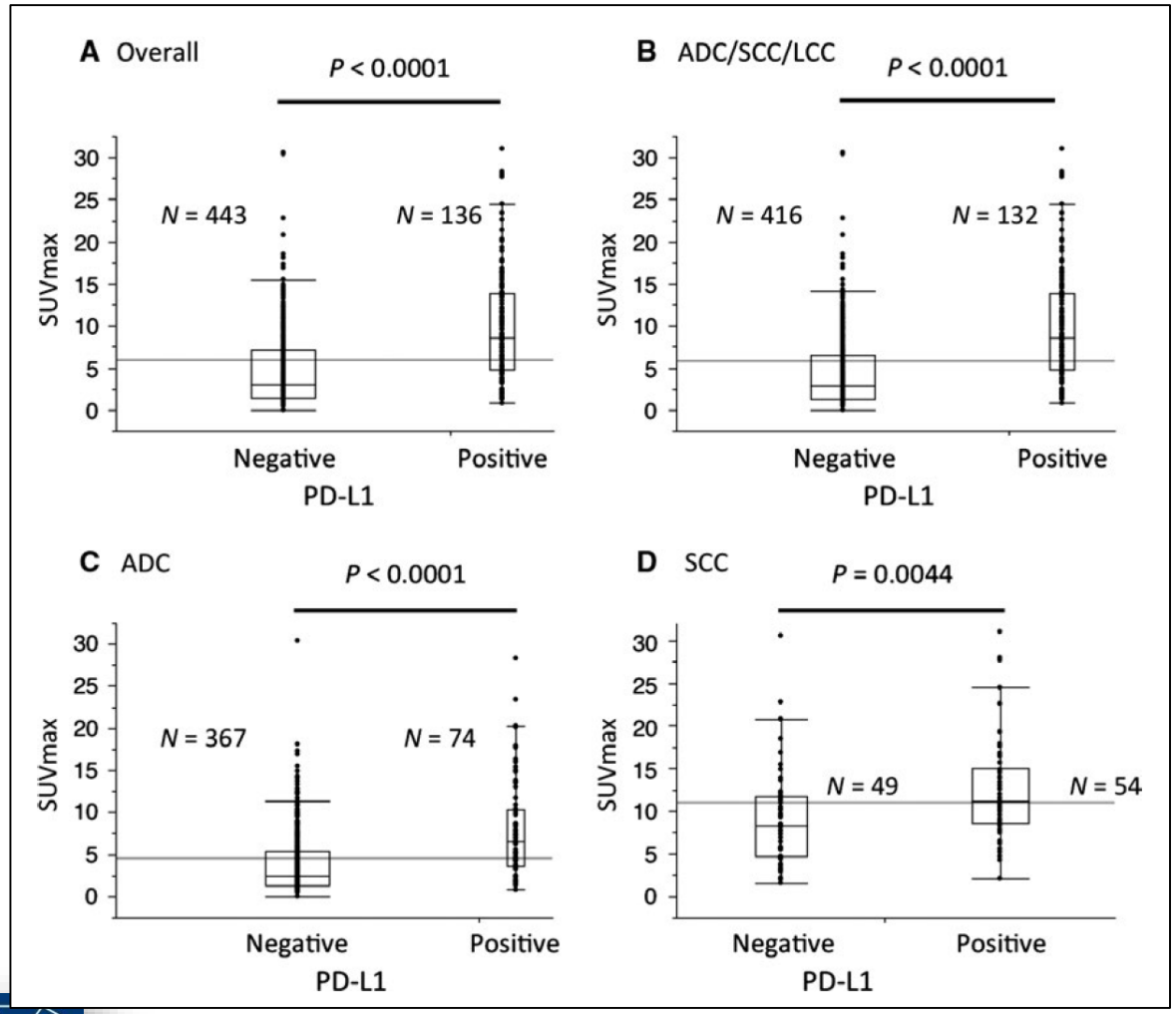
Prediction of response/selection of patients 1

Radiomics



Imaging and metabolic data, analysed visually, semiquantitavely or with dedicated algorithms are pieces of puzzle. Therefore, new radiomic information would add precious information for this end-point.

PD-L1 expression and FDG PET

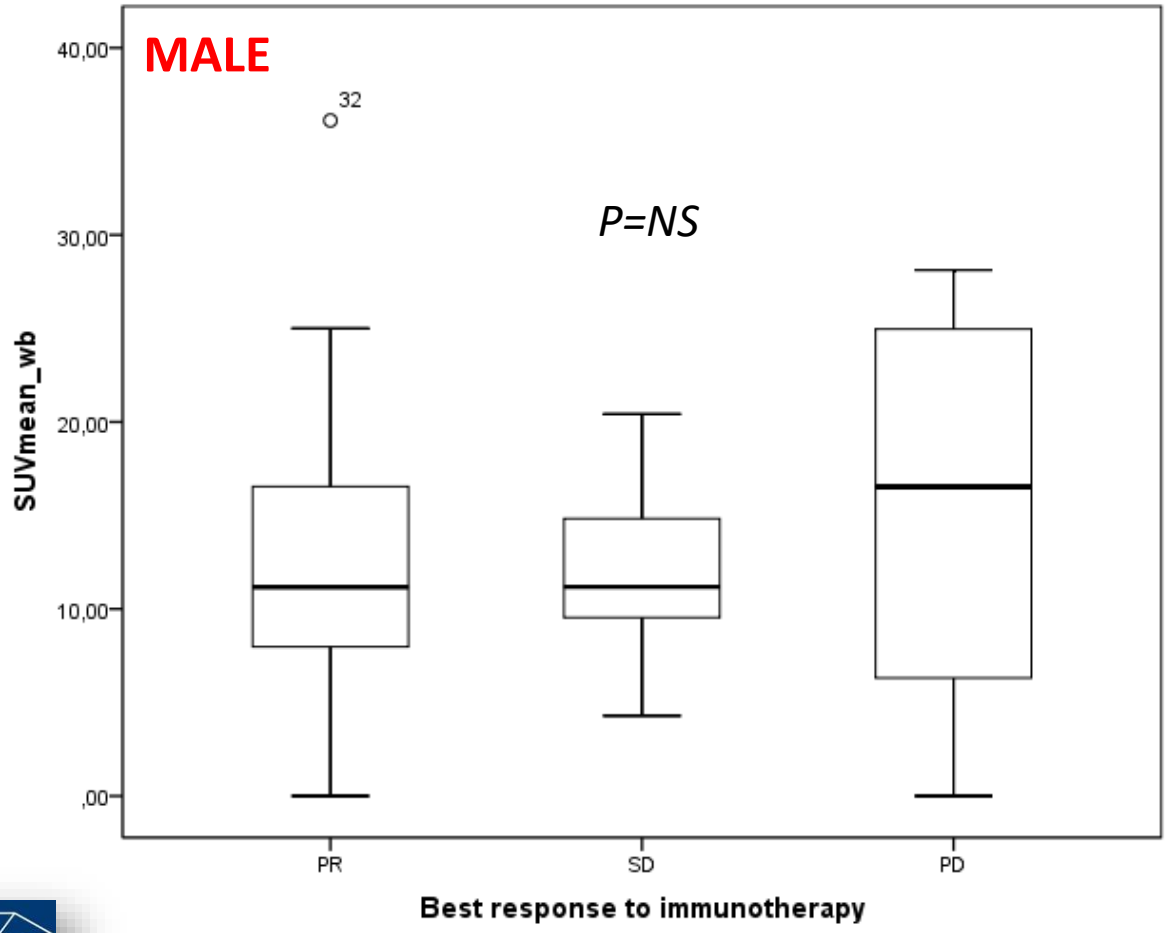


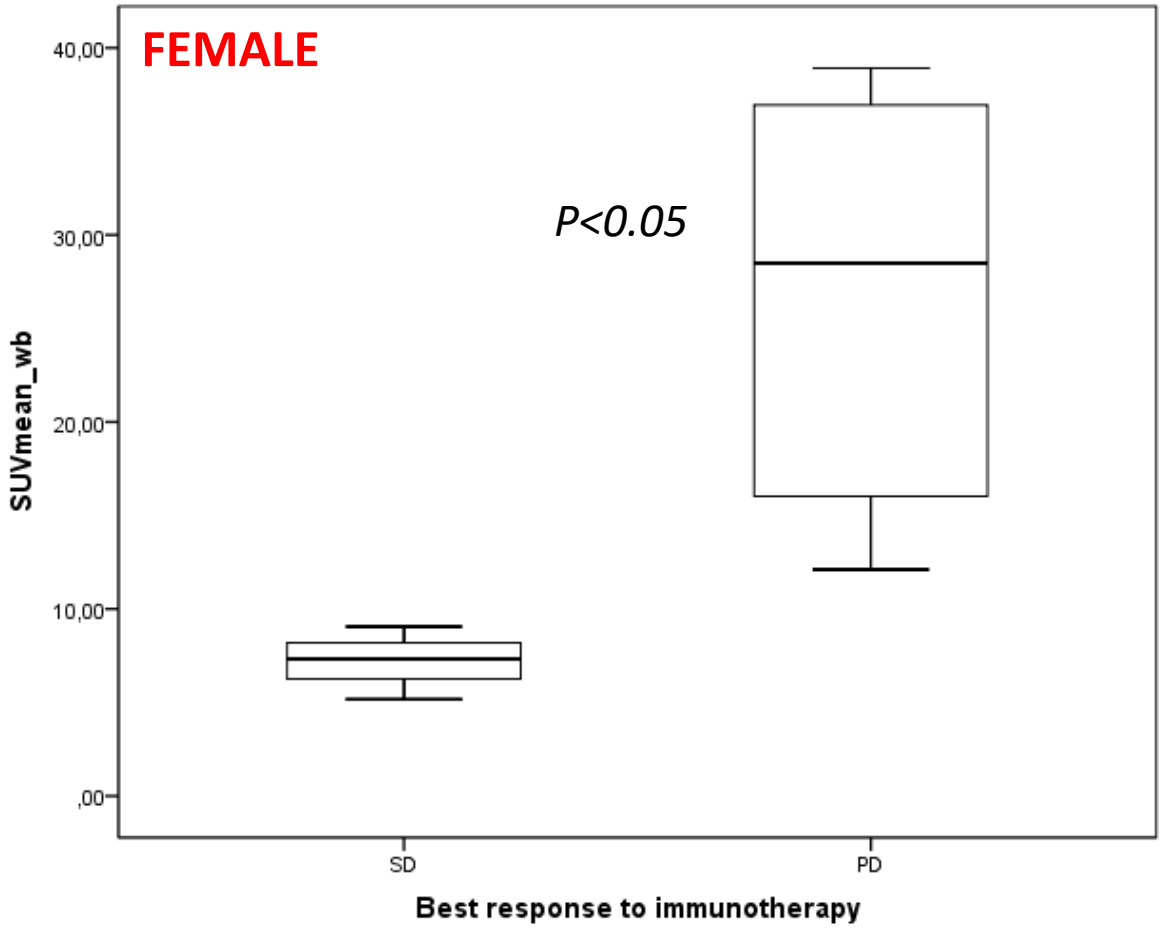
Histology	*N*	SUVmax according to PD-L1 expression, mean value (range)		
		Negative	Positive	*P* value
Overall[1]	579	4.69 (0–30.6)	9.89 (0.8–31.05)	<0.0001
ADC	441	3.84 (0–30.4)	7.81 (0.8–28.3)	<0.0001
SCC	103	9.18 (1.5–30.6)	12.60 (2.1–31.05)	0.0044
LCC	4	-	12.76 (4.81–21.4)	-
SCLC	16	7.40 (2.42–14.7)	3.4	0.3225
LCNEC	15	8.88 (2.8–14.57)	10.91 (6.1–14.54)	0.4491

- **Glucose metabolism was generally higher in patients with PD-L1 protein expression** than those without PD-L1.
- Smoking, the presence of pleural invasion, and **high SUVmax** in PET/CT were **predictors of PD-L1 protein expression** in patients with lung cancer, especially NSCLC.

Cancer Medicine 2017; 6:2552

Prediction of response/selection of patients 2



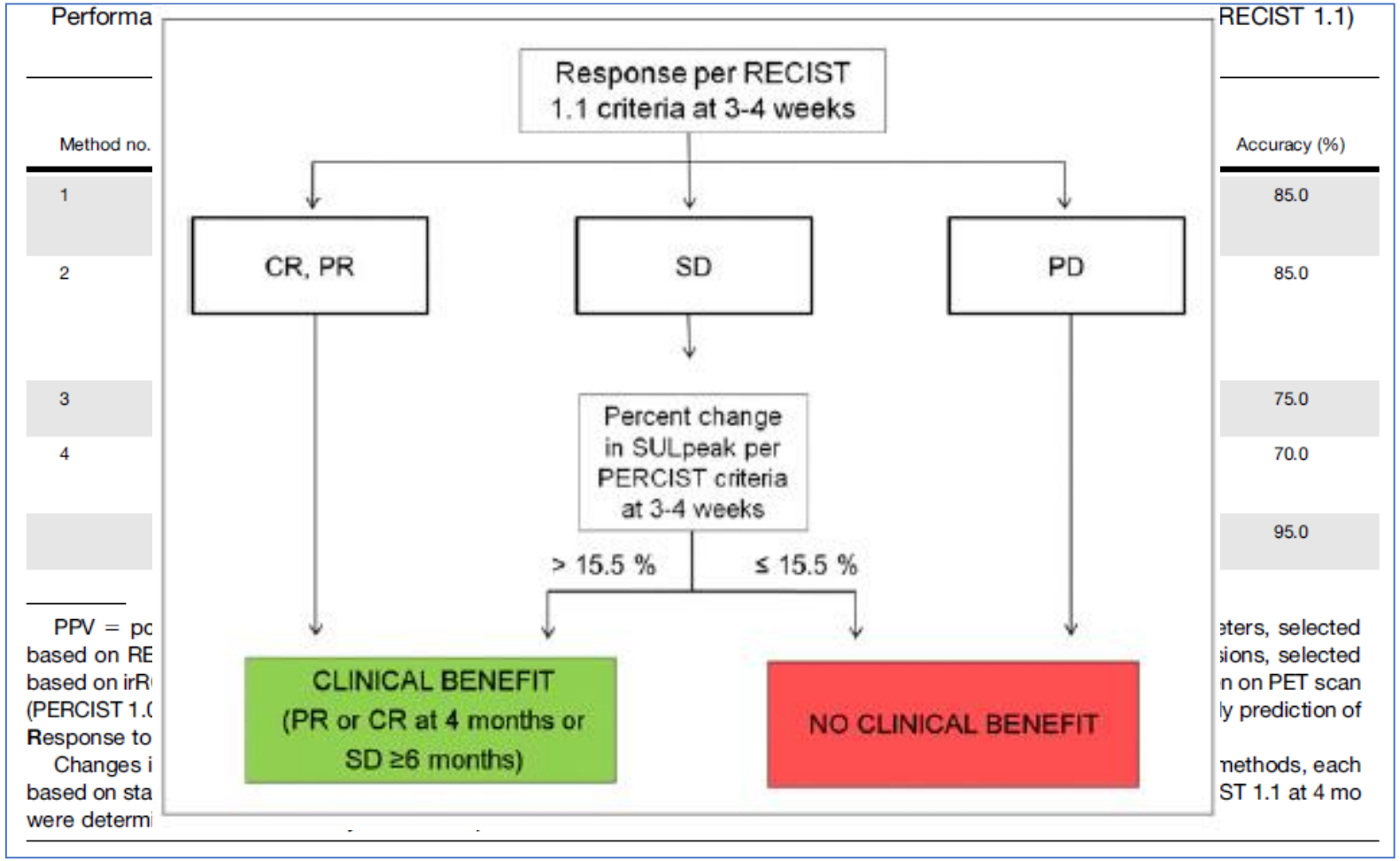


Istituto Oncologico Veneto

Evangelista et al. Submitted to Nucl Med Comm

Evaluation of response to immunotherapy

- 20 patients with melanoma
- Ipilumab or nivolumab
- Scan intervals: before (SCAN-1), days 21–28 (SCAN-2), 4 mo (SCAN-3)



J Nucl Med 2017; 58:1421–1428

The response to therapy: old *vs* immuno-criteria

Eur J Nucl Med Mol Imaging. 2019;46:238-250

Response	EORTC[a]	PERCIST[b]	PECRIT[c]			PERCIMT[d]	
Complete response (CR)	Complete resolution of FDG uptake	Disappearance of all metabolically	RECIST 1.1 (disappearance of all target lesions;		Clinical benefit	Complete resolution of all preexisting ^{18}F-FDG-avid	Clinical benefit
Stable disease (SD)	increase in SUV of less than 25% or a decrease of less than 15%	Does not meet other criteria	Does not meet other criteria	Change in SUL peak of the hottest lesion of >15%	Clinical benefit	Neither PD nor PR/CR	Clinical benefit
				Change in SUL peak of the hottest lesion of ≤15%	No clinical benefit		
Progressive disease (PD)	Increase in tumour FDG uptake of >25%; increase in maximum tumour of >20%; new metastases	Increase in SULpeak of >30% or the appearance of a new metabolically active lesion	RECIST 1.1 (increase in target lesion diameter sum of >20% and at least 5 mm or new lesions)		No clinical benefit	Four or more new lesions of <1 cm in functional diameter or three or more new lesions of >1.0 cm in functional diameter or two or more new lesions of more than 1.5 cm in functional diameter	No clinical benefit

LYmphoma Response to Immunomodulatory Therapy Criteria (Agosto 2016)

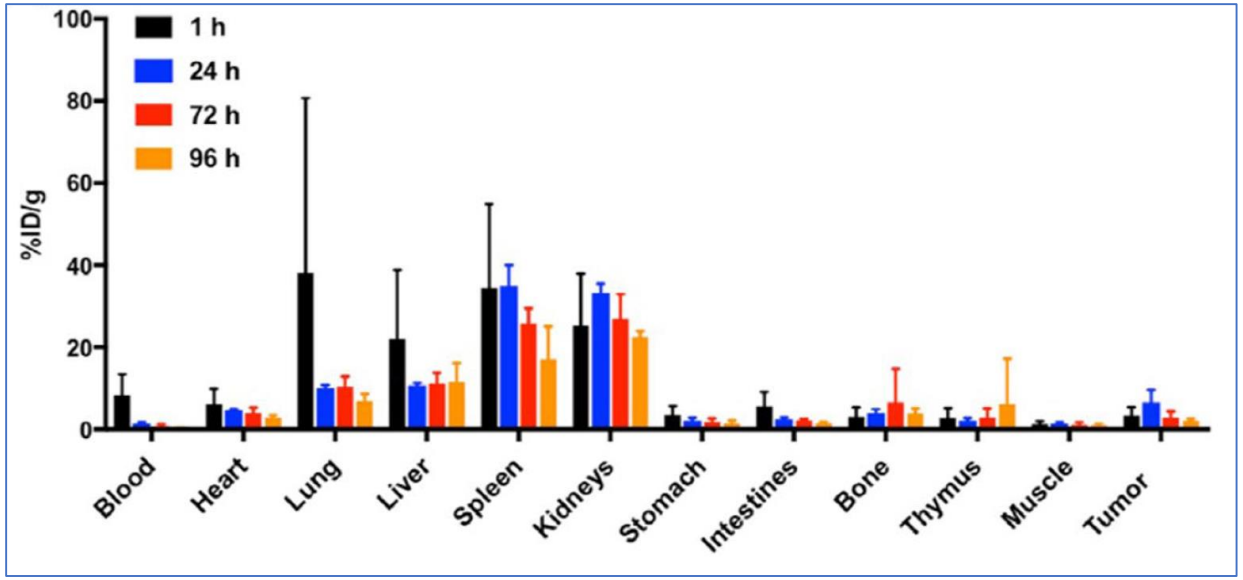
Adattamento dei criteri di Lugano, con l'introduzione di una nuova categoria di risposta alla terapia, chiamata **"RISPOSTA INDETERMINATA" (IR), in cui rientrano tutti i casi di pseudoprogressione** [nelle prime 12 sett in assenza di deterioramento clinico].

Other than FDG -alternative tracers

preclinical evidence

Clin Transl Imaging 2018; 6:429-39

Author	Year	Anti-PD-L1	Radion.	Modality
Chatterjee et al	2016	MPDL3280A	111In	SPECT/CT
Heskamp et al	2015	Anti-PD-L1	111In	SPECT/CT
Josefsson et al	2016	N/A	111In	SPECT
Nedrow et al	2017	Anti-PD-L1	111In	SPECT
Lesniak et al	2016	MPDL3280A	64Cu	PET/CT
Hettich et al	2016	N/A	64Cu	PET/CT
Mayer et al	2017	HACA/HAC	64Cu	PET/CT
Maute et al	2015	HAC	64Cu	PET/CT
Chatterjee et al	2017	WL12	64Cu	PET/CT
Trotter et al	2017	ZPD L1_1	18F	PET
Donnelly et al	2018	ADX5322A02	18F	PET/CT



Other than FDG -alternative tracers

clinical evidence

J Nucl Med 2019; in press

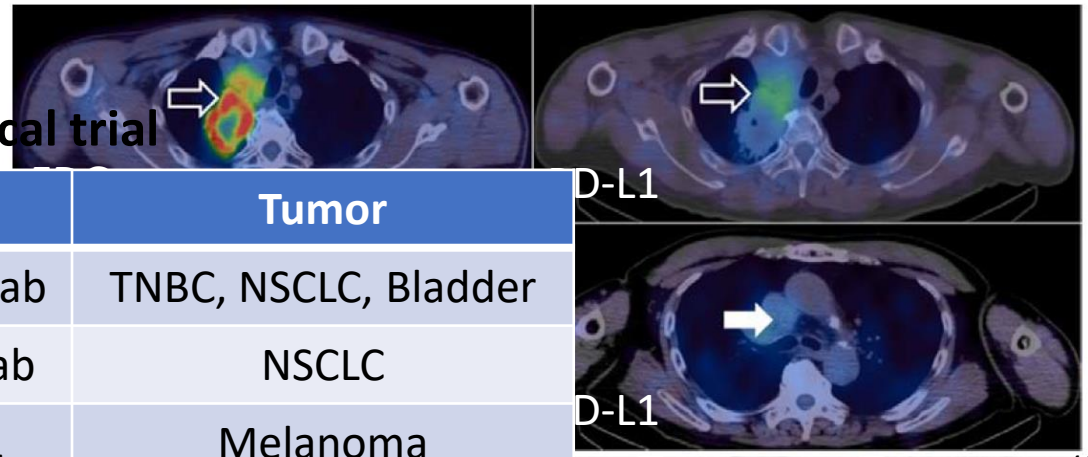
Table 1: Patient Characteristics

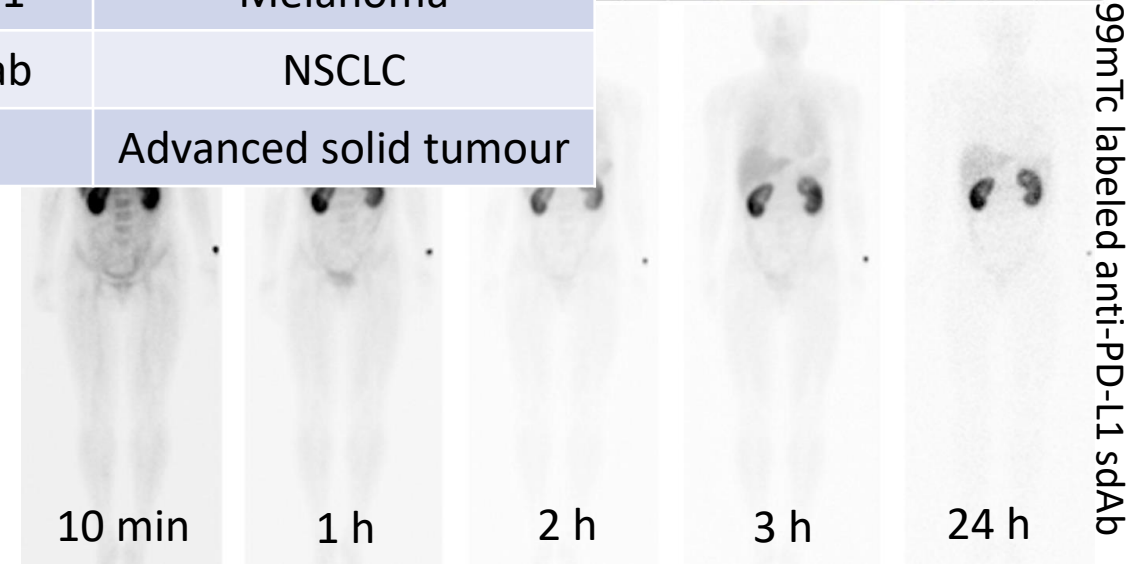
Dose Group	Patient No.	Age	Gender	Tumor Type	Tumor Size (CT axial dimensions)	PD-L1 IHC (%)	ECOG Score
100 µg Group 1 3.8-8.4 MBq/kg- 1.2-2.1 µg/kg	1	49	Male	Adenocarcinoma	37*27mm	NA	1
	2	75	Male	Squamous Cell Carcinoma	44*48mm	20	
	3	75	Male				
400 µg Group 2 9.1-10.4 MBq/kg- 5.6-6.1 µg/kg	4	65	Male				
	5	57	Male				
	6	65	Male				
100 µg Group 1 3.8-8.4 MBq/kg- 1.2-2.1 µg/kg	7	75	Fema				
	8	52	Fema				
	9	36	Female	Adenocarcinoma	45*35mm	1	1
	10	46	Female	Adenocarcinoma	42*35mm	50	0
	11	51	Male	Squamous Cell Carcinoma	47*35mm	2	0
	12	72	Male	Adenocarcinoma	46*53mm	NA	1
	13	55	Male	Squamous Cell Carcinoma	71*78mm	85	0
	14	69	Male	Squamous Cell Carcinoma	20*28mm	10	0
	15	71	Female	Squamous Cell Carcinoma	78*95mm	NA	1
	16	60	Male	Adenocarcinoma	93*75mm	2	0

*NA= not available

Ongoing clinical trial

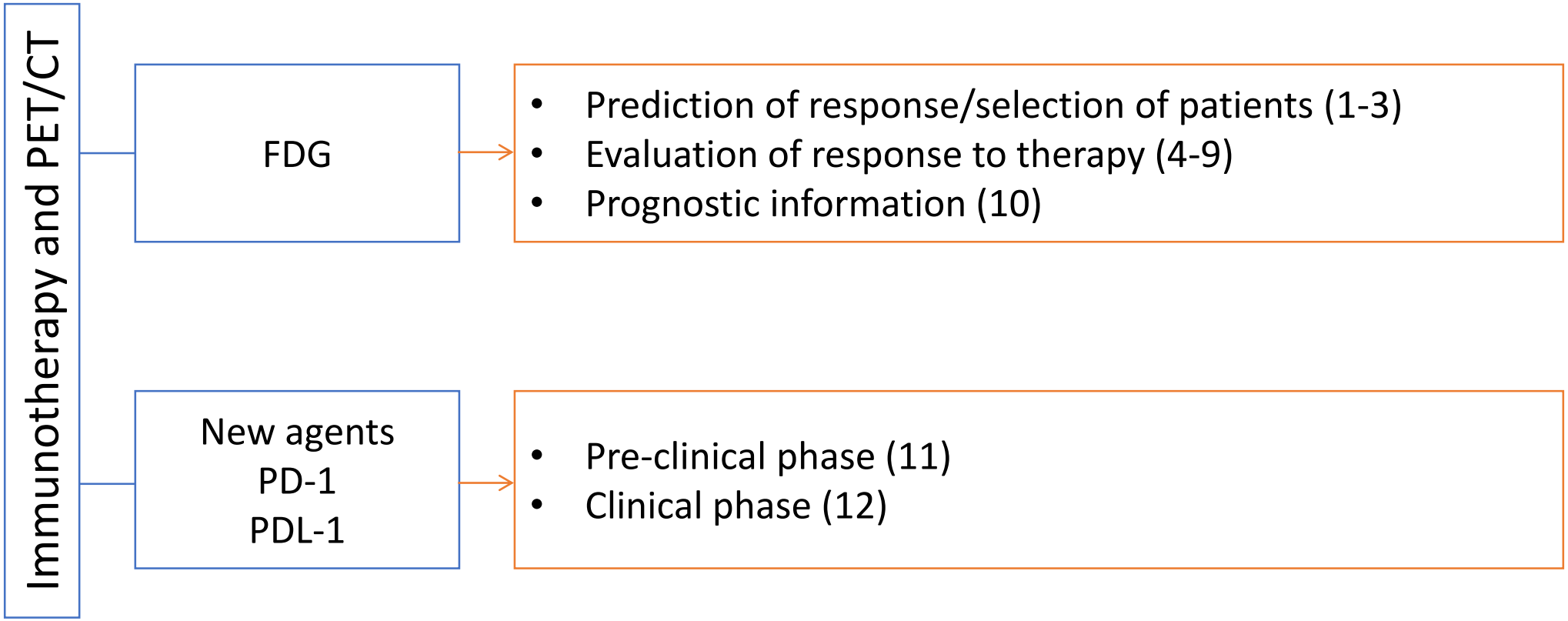
Number	RF	Tumor
NCT02453984	89Zr-Atezolizumab	TNBC, NSCLC, Bladder
2015-005765-23	89Zr-Durvalumab	NSCLC
NCT03520634	18F-anti-PD-l1	Melanoma
NCT03514719	89Zr-avelumab	NSCLC
NCT03638804	89Zr-KN035	Advanced solid tumour





99mTc labeled anti-PD-L1 sdAb

Clinical evidences-summary



References.(1) Eshghi N, 2018; (2) Grizzi F, 2018; (3) Evangelista L, 2019; (4) Sachpekidis C, 2015; (5) Kong BY, 2016; (6) Breki CM, 2016; (7) Cho SY, 2017; (8) Anwar H, 2018; (9) Sachpekidis C, 2018; (10) Kaira K, 2018; (11) Vaz SC, 2018; (12) Xing Y, 2019.

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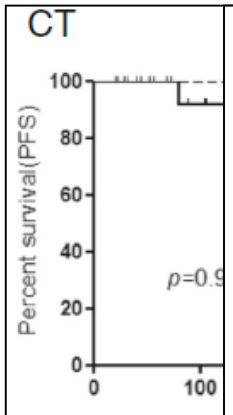
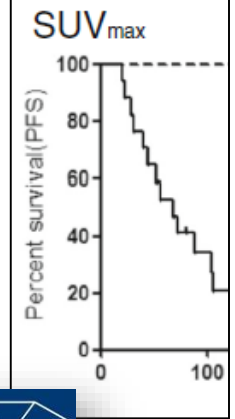
Comparison between GS and PET/CT

24 pts; FDG PET/CT before and 1 month after nivolumab

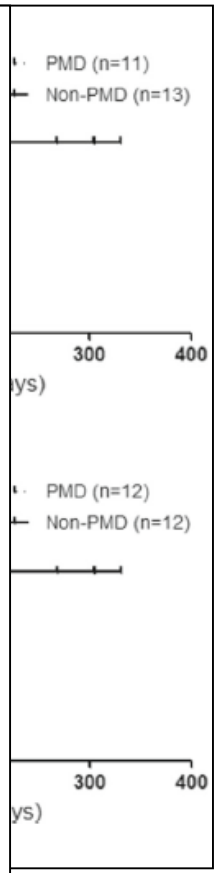
RECIST1.1 *vs* PERCIST





		Univariate analysis		Multivariate analysis		
		MST (months)	*p*-value	HR	95%CI	*p*-value
Overall survival (OS)						
Gender	Male/Female	17.0 / 7.7	0.002	1.692	0.886–3.402	0.109
PS	0 or 1 / 2	17.0 / 5.1	0.348			
Stage	III / IV	10.6 /17.0	0.266	1.269	0.319–6.247	0.741
Histology	Adeno / SQC	12.1 / NR	0.105			
TLG	PMR/non-PMR	NR / 10.6	0.006	2.461	0.269–7.192	0.012
Progression-free survival (PFS)						
Gender	Male/Female	6.7 / 1.7	0.006	1.640	0.896–3.002	0.106
PS	0 or 1 / 2	3.5 / 3.1	0.228			
Stage	III / IV	3.5 / 3.5	0.717	2.859	0.856–11.48	0.089
Histology	Adeno / SQC	2.7 / NR	0.069			
TLG	PMR/non-PMR	NR / 2.1	<0.001	3.624	1.728–9.557	<0.001

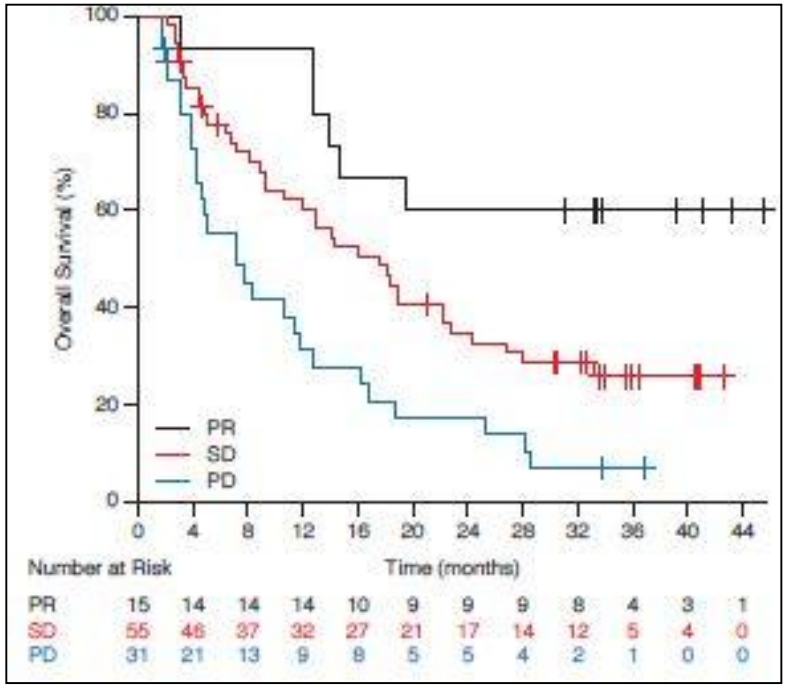
PS, performance status; *Adeno*, adenocarcinoma; *SQC*, squamous cell carcinoma; *TLG*, total lesion glycolysis; *PMR*, partial metabolic response; *MST*, median survival time; *HR*, hazard ratio; *95%CI*, 95% confidential interval; *NR*, not reached



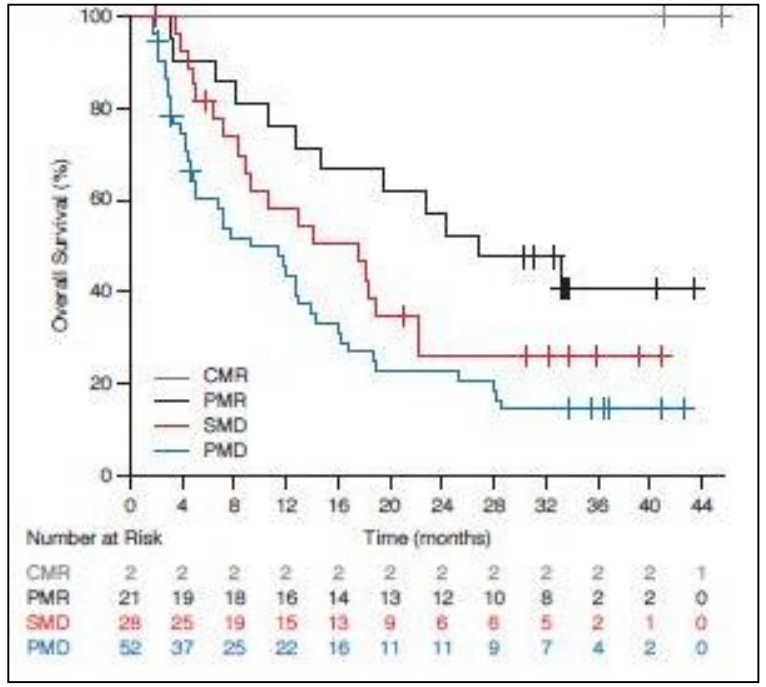
Eur J Nucl Med Mol Imaging (2018) 45:56–66

Comparison between GS and PET/CT-The FIR trial

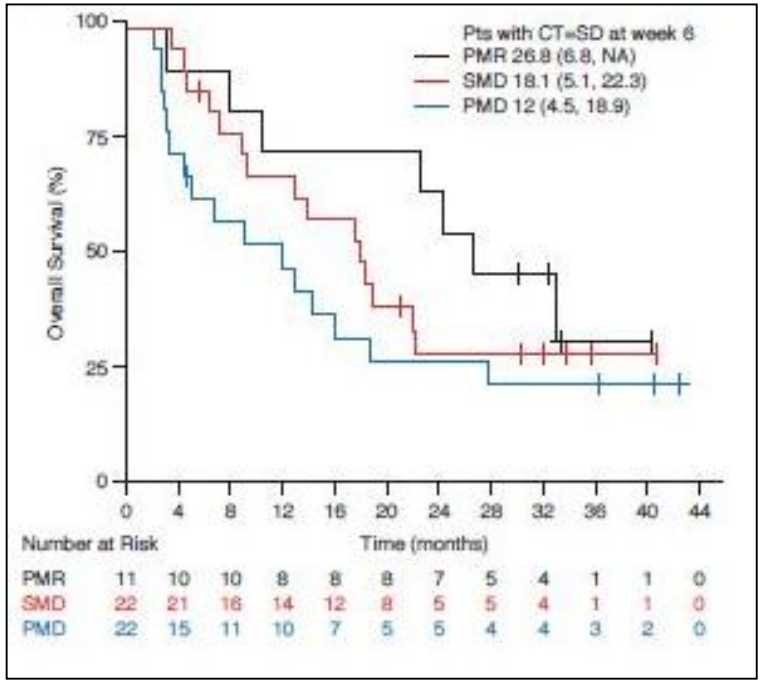
CT RECIST



FDG-PET response based on EORTC criteria



PET and CT



More patients demonstrated progressive disease (52 versus 31) by early PET with correspondingly fewer having stable disease (28 versus 55) compared with CT RECIST.

In patients with stable disease by CT-based RECIST v1.1 at Week 6, metabolic response further informs outcome.

Journal of Thoracic Oncology 2018; 13: 1733-1742

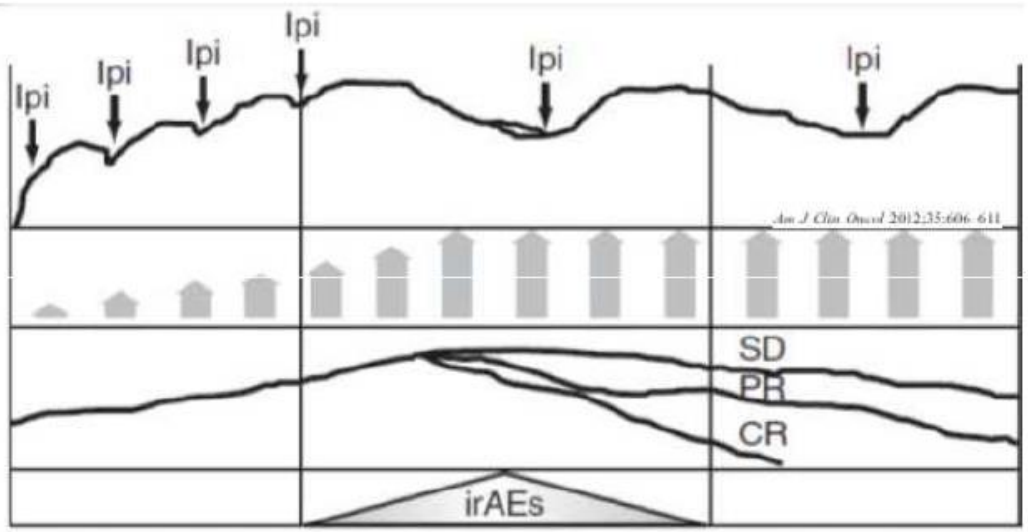
Issues

1. Background
2. Needs and priorities
3. Evidences
    1. Literature
    2. Clinical impact
4. Comparative data (vs. standards)
5. Practical aspects
    1. Patient preparation
    2. Interpretation of the images

Patient preparation-patient medical examination

- Type of immune modulator received (anti-CTLA or anti-PD1 or association in the clinical trials).
- Number of cycles received and the date of the last injection.
- Clinical symptoms associated with immune related side effects*.
- For diabetic patients, check whether drugs likely to mimic colities have been withdrawn or not.

*Immune related side effects



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.

Related adverse events
Pancreatitis
Pneumonitis
Gastrointestinal inflammation
Stomatitis
Colitis
Unrelated adverse events
Bacteremia
Enchephalitis
GVHD
Infection
Pneumonia mycoplasma
Skin infection
Small intestine infection

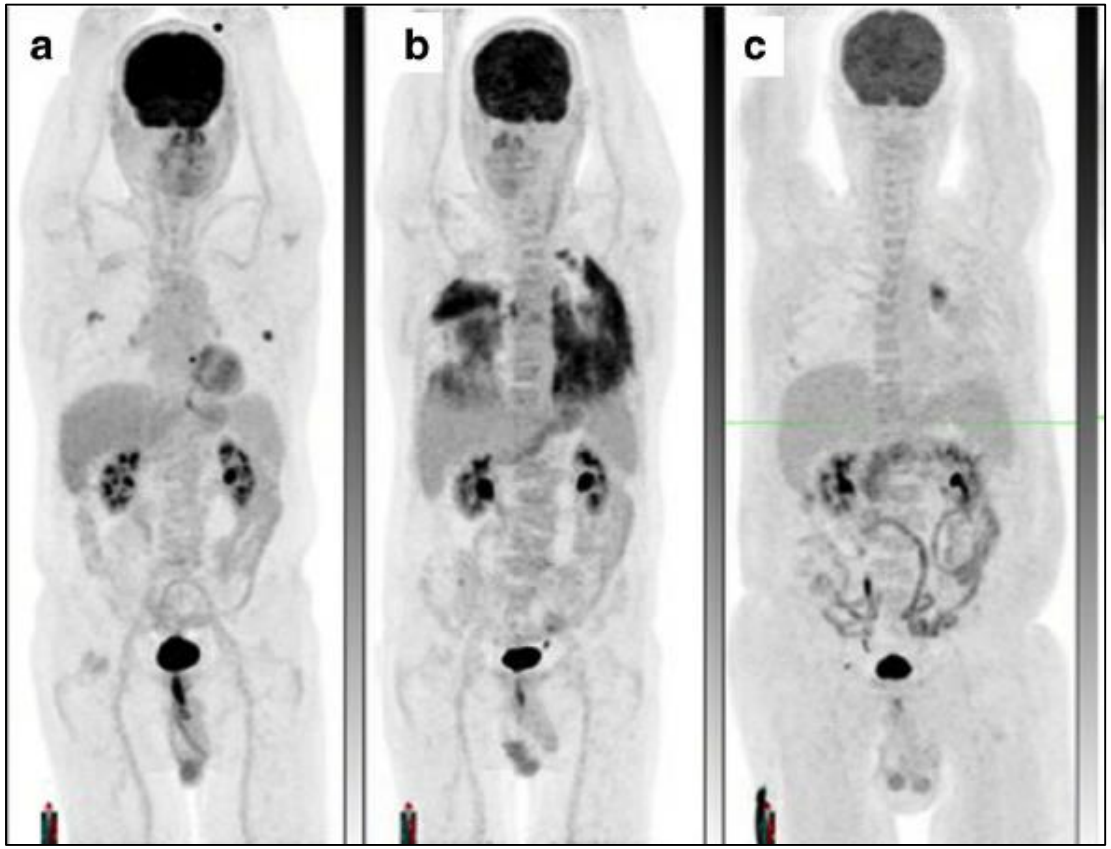
N Engl Med 2015; 372: 311-9

Interpretation of images

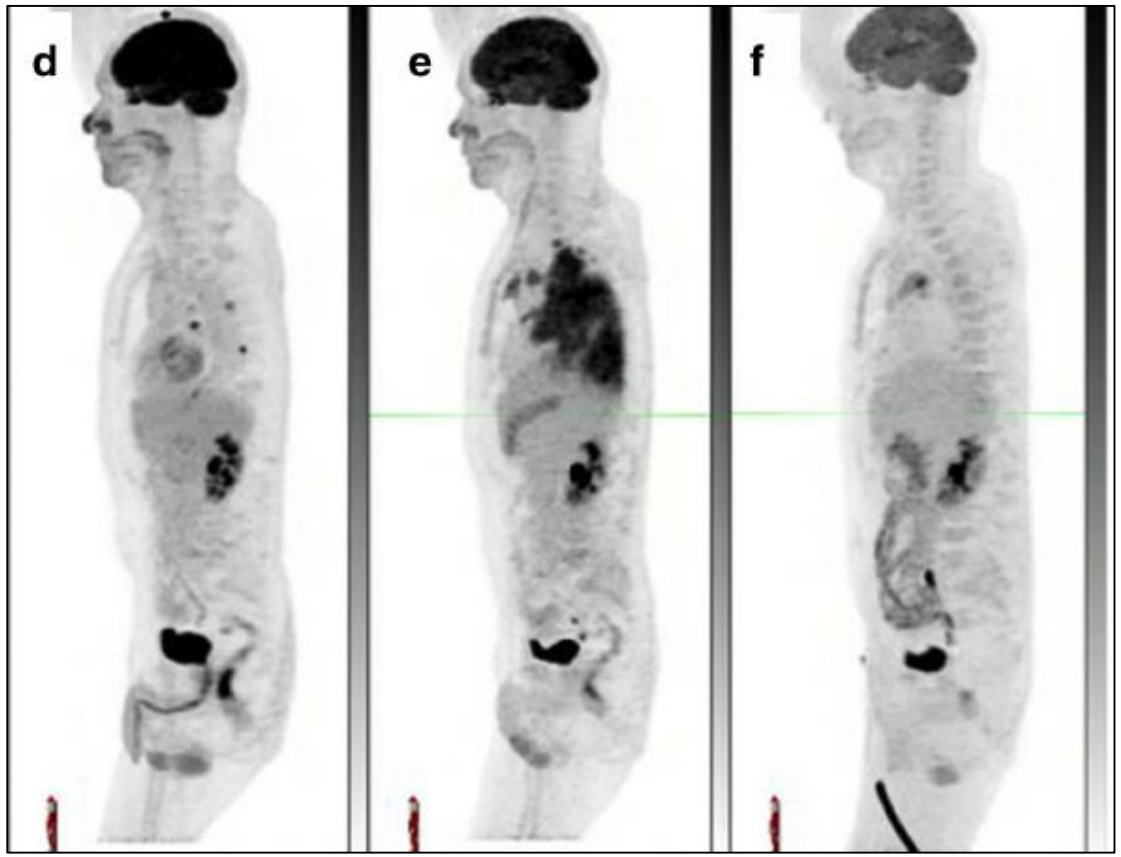
- To evaluate the response in the target lesion(s)
- To compute (if possibile) and report MATV and TLG
- In case of new lesions:
  - Evaluate the site of appearance
  - Check whether new lesions may be related to immune-related side effects (before to classify the patient as a PMD)

Pneumonitis

CT images are necessary



Baseline 8-weeks 14-weeks

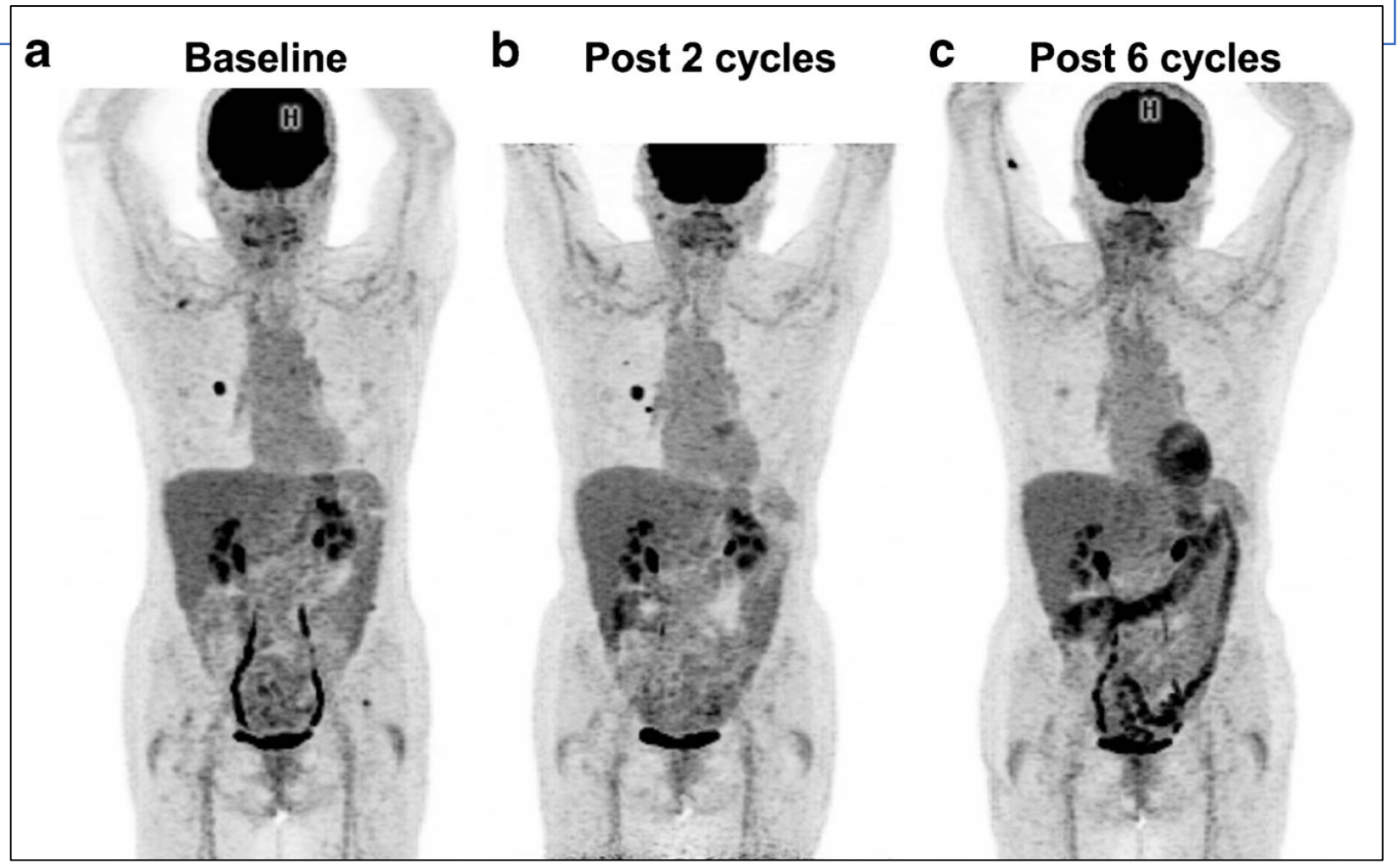


Baseline 8-weeks 14-weeks

Eur J Nucl Med Mol Imaging. 2019;46:238-250

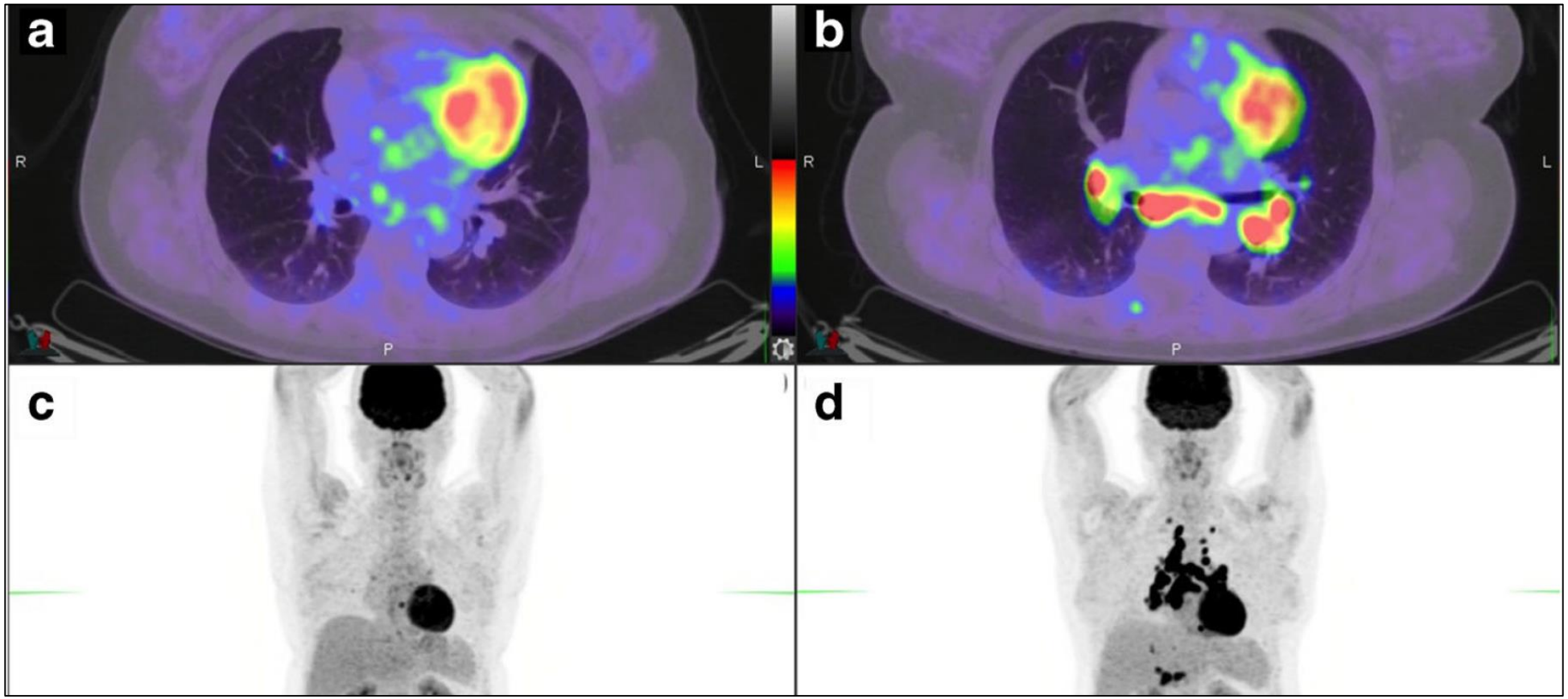
Colitis

The appearance of diffuse colonic uptake reported as possible colitis (no digestive symptoms).
The progression seen after two cycles was considered to represent pseudoprogression



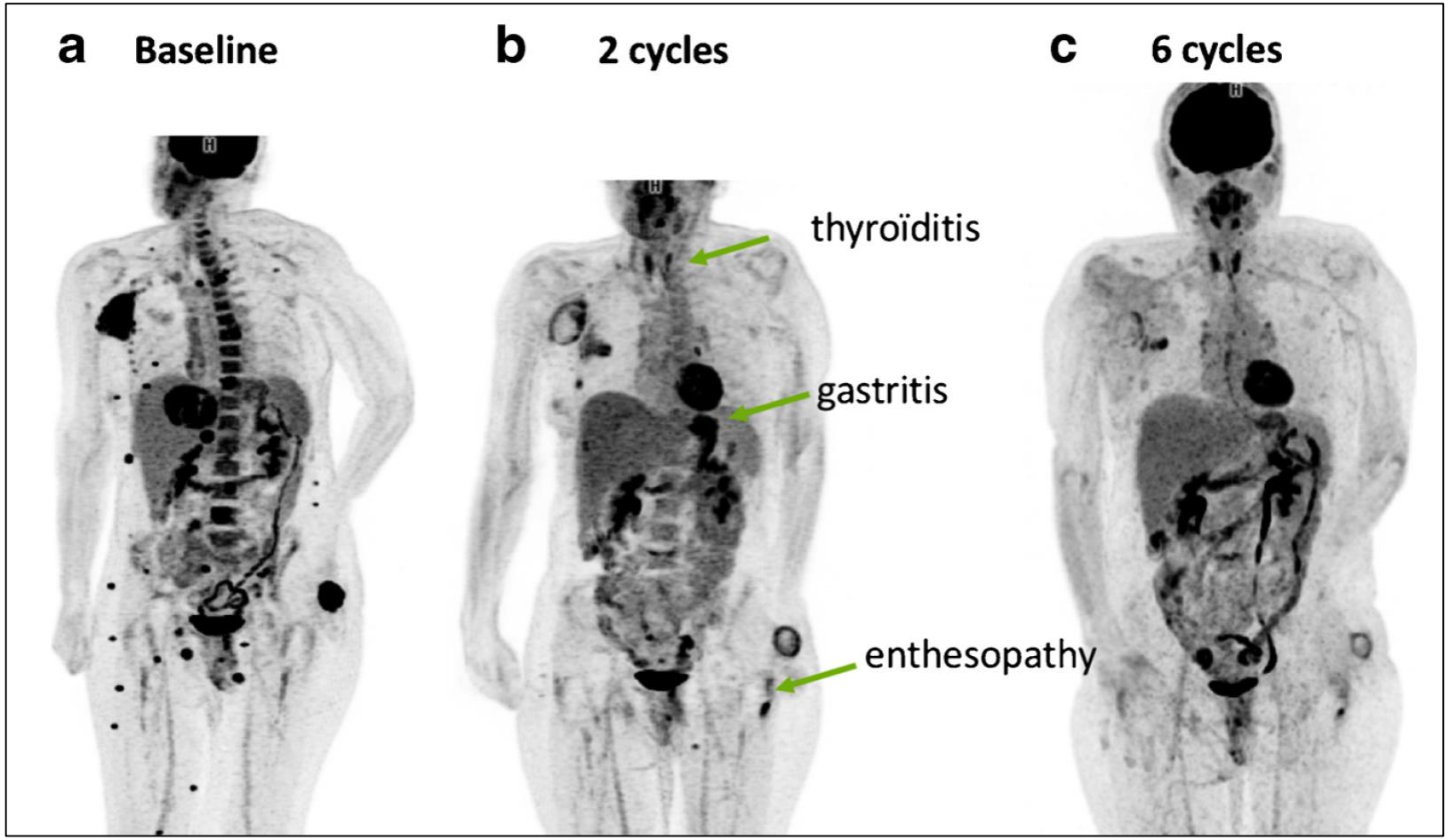
Eur J Nucl Med Mol Imaging. 2019;46:238-250

Sarcoidosis



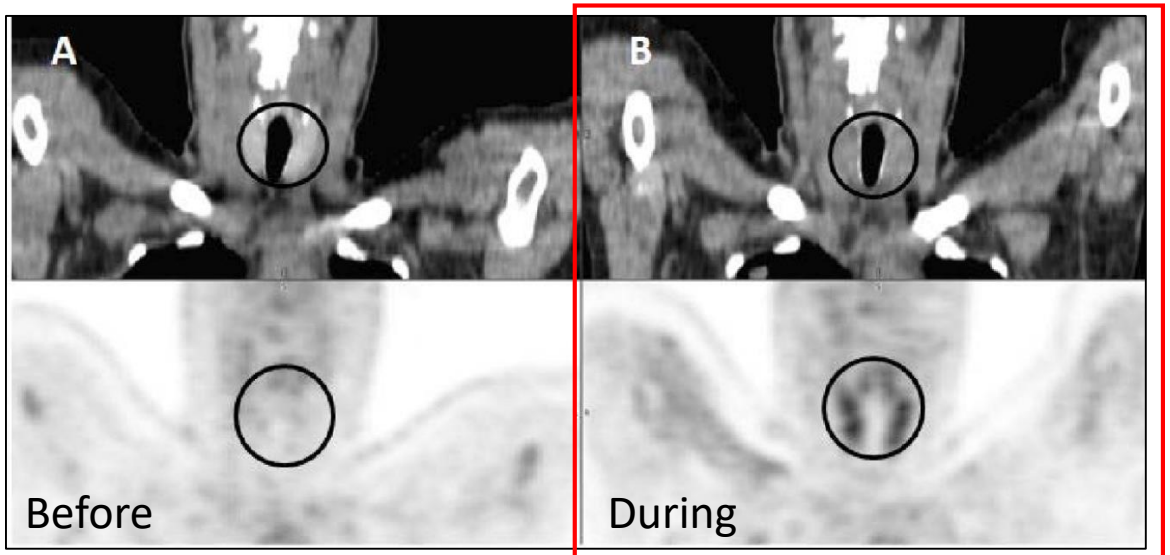
Eur J Nucl Med Mol Imaging. 2019;46:238-250

Multiple immune-related side effects



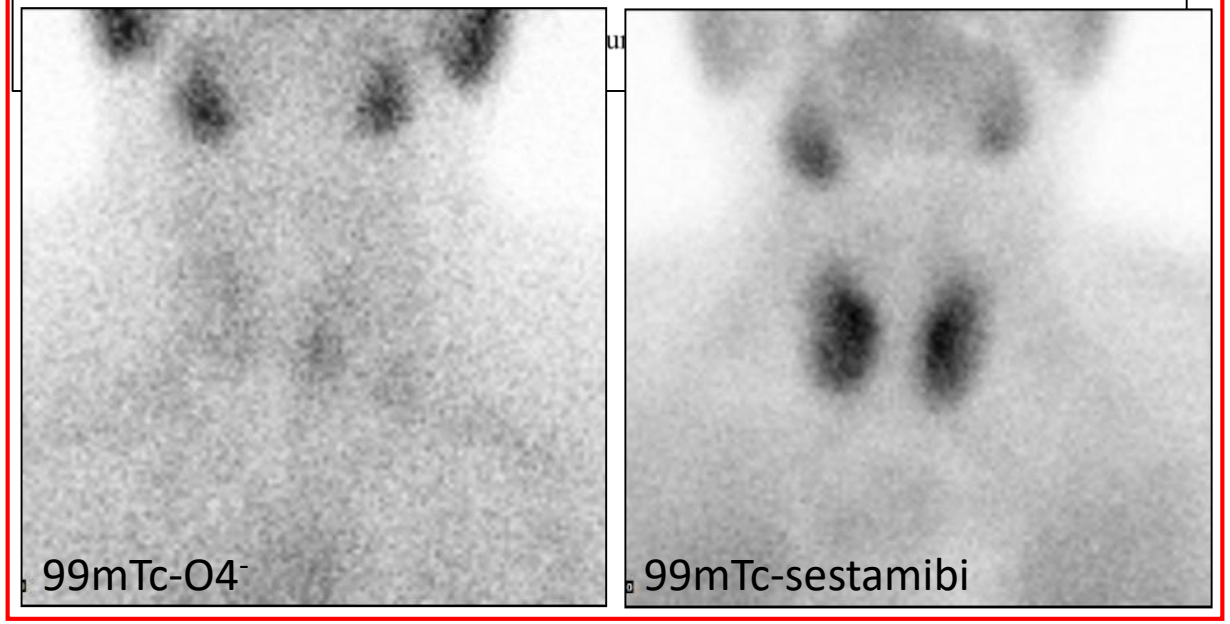
Eur J Nucl Med Mol Imaging. 2019;46:238-250

18F-FDG PET/CT Can Predict Development of Thyroiditis due to Immunotherapy for Lung Cancer



Since lung cancer patients treated with immunotherapy are staged and followed with ^{18}F-FDG PET/CT, standard of care use of this imaging could predict the development of the irAE thyroiditis before laboratory testing. Thus, oncologists and patients can be more vigilant for signs or symptoms of early hypothyroidism and initiate thyroid hormone replacement optimally. Further work is required to establish more strongly the predictive power of finding increased ^{18}F-

	Thyroid irAE (n=6)	No Thyroid irAE (n=12)	
	Mean (SD)	Mean (SD)	Difference (P-Value)
SUV $_{mean}$	2.41 (1.04)	1.64 (0.44)	0.77 (0.04)
SUV $_{max}$	2.96 (1.28)	2.00 (0.5)	0.96 (0.038)
TLG	1.96 (1.05)	1.00 (0.47)	0.96 (0.016)



J Nucl Med 2018; in press

Conclusions

- More clinical trials are necessary in order to identify the role of FDG PET/CT in patients candidates to or undergoing immunotherapy
- Need for standardization of criteria and definition of optimal time of realization of the images (during and after immunotherapy)
- Potential benefit of PD1 / PD-L1 theranostic imaging for selecting patients (waiting for the humans studies)

Thanks

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