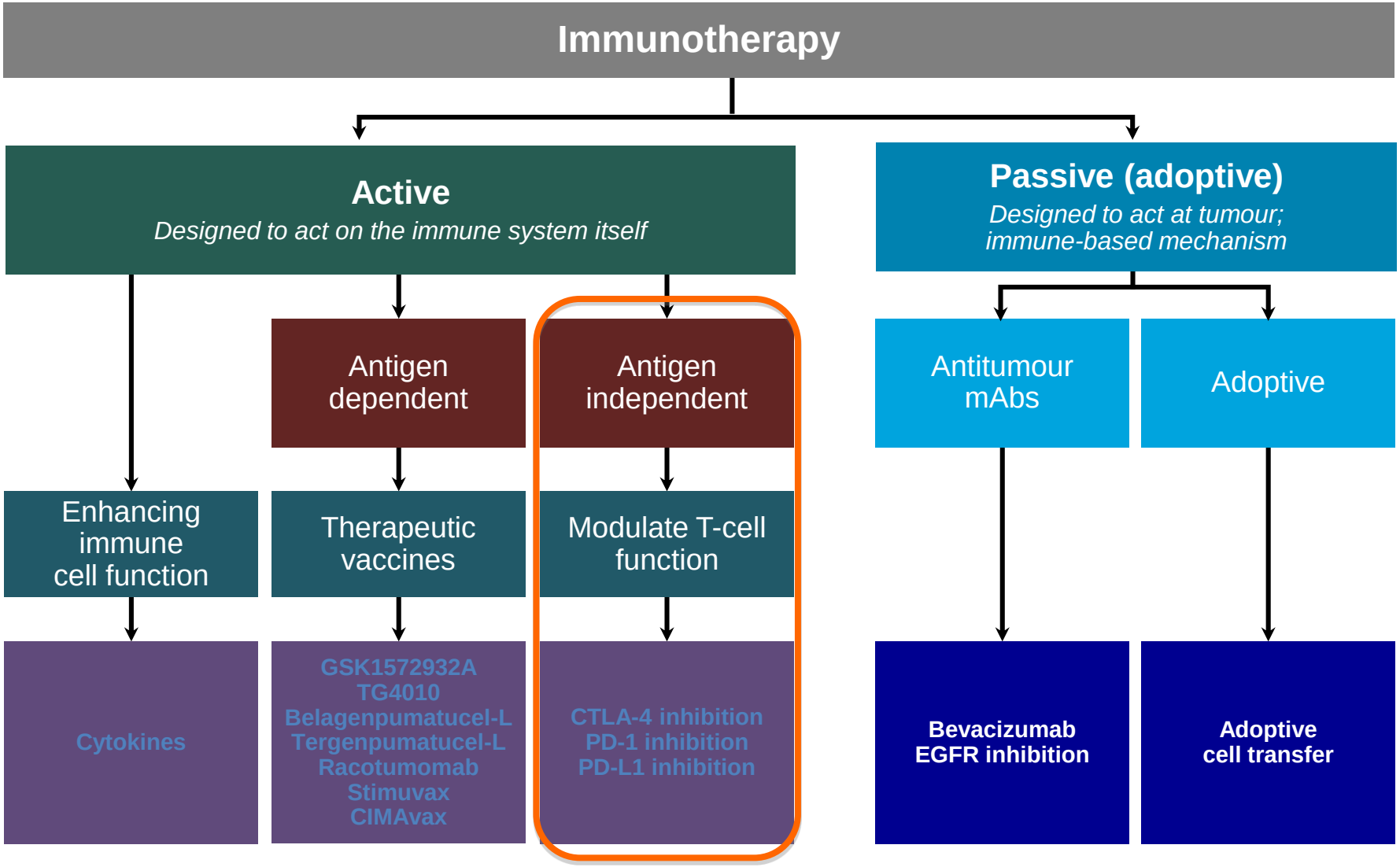
Journées Francophones de Médecine Nucléaire

15h20 – 16h00 Evaluation thérapeutique : thérapie ciblées et immunothérapie
Pr Frédéric COURBON - Toulouse

UNIVERSITÉ TOULOUSE III PAUL SABATIER Université de Toulouse

INSTITUT UNIVERSITAIRE DU CANCER DE TOULOUSE Oncopole

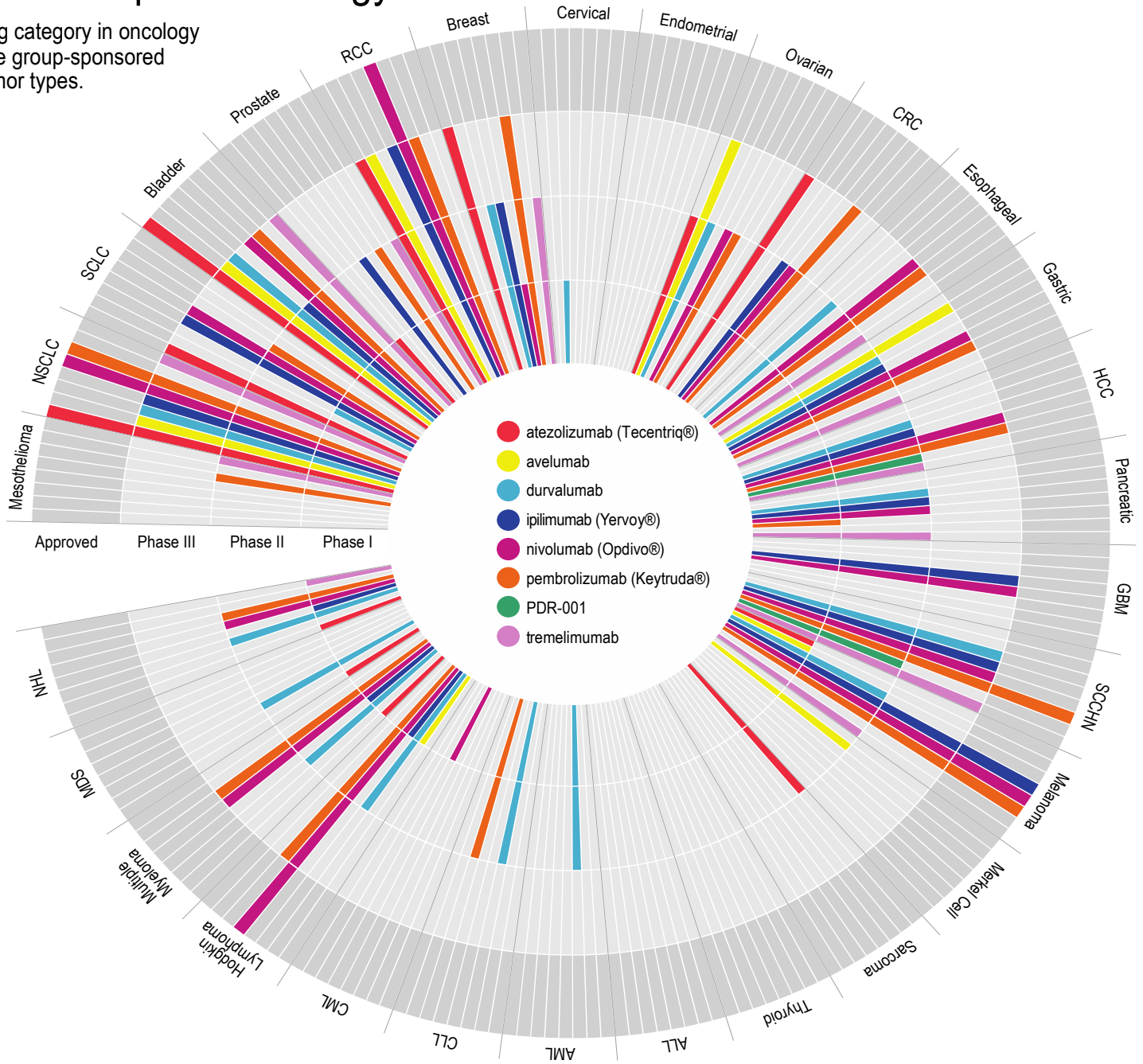

Immunotherapy
Active
Designed to act on the immune system itself
Passive (adoptive)
Designed to act at tumour; immune-based mechanism
Antigen dependent
Antigen independent
Antitumour mAbs
Adoptive
Enhancing immune cell function
Therapeutic vaccines
Modulate T-cell function
Cytokines
GSK1572932A
TG4010
Belagenpumatucel-L
Tergenpumatucel-L
Racotumomab
Stimuvax
CIMAvax
CTLA-4 inhibition
PD-1 inhibition
PD-L1 inhibition
Bevacizumab
EGFR inhibition
Adoptive cell transfer

Les molécules actuelles etc….

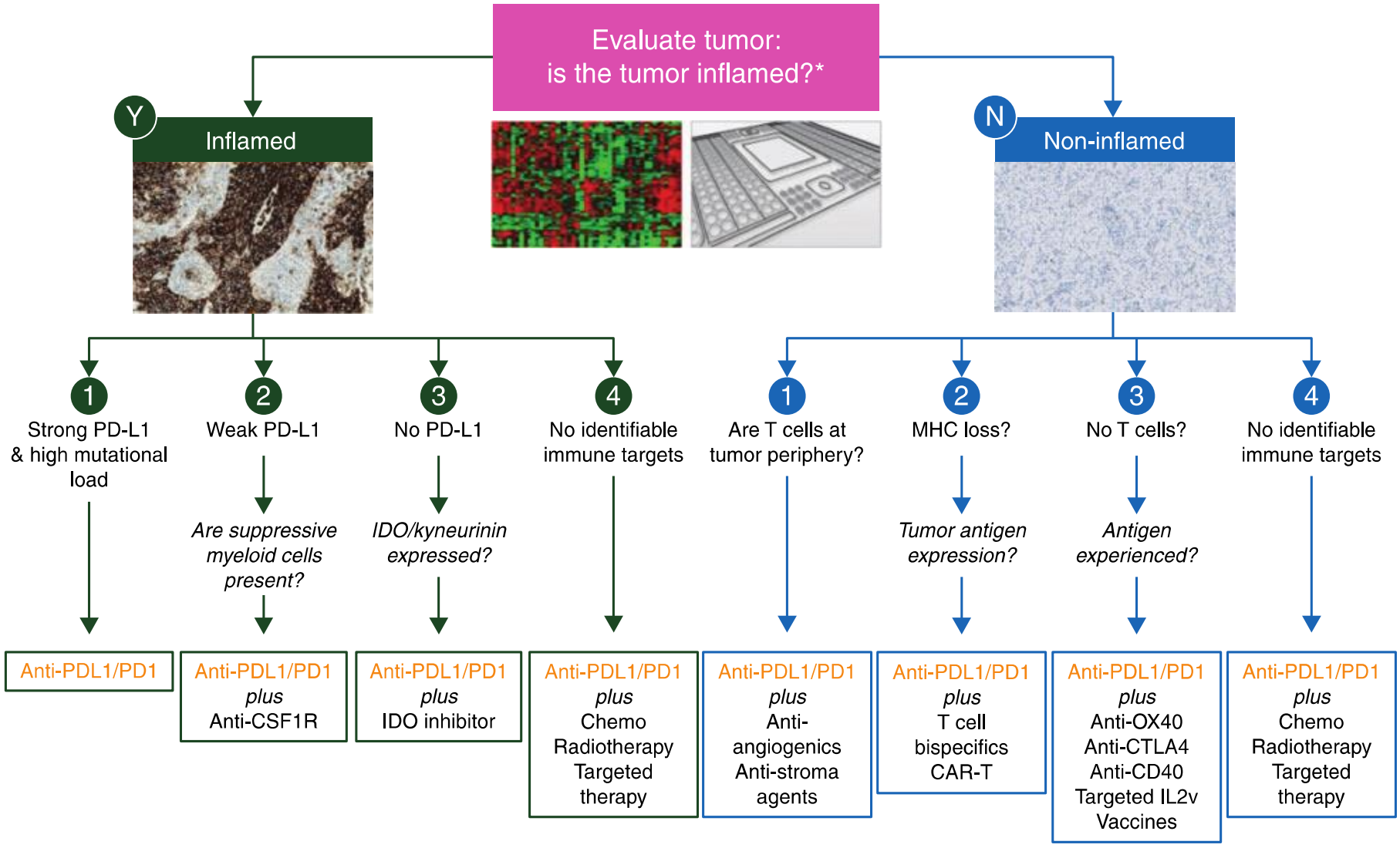
Type	Nom	Laboratoire	Indications
Anti-CTLA4	Ipilimumab (YERVOY)	BMS	AMM mélanome
	Tremelimumab	MedImmune, Astra-Zeneca	Phase 3
Anti-PD1	Nivolumab (OPDIVO)	BMS	AMM mélanome, poumon, rein, hodgkin
	Pembrolizumab (KEYTRUDA)	MSD	AMM mélanome, poumon
	Avelumab	Merck KGaA, Pfizer	Phase 3
Anti-PDL1	Durvalumab	MedImmune, Astra-Zeneca	Phase 3
	Atezolizumab (TECENTRIQ)	Genentech-Roche	ATU vessie

The Immunotherapy Landscape in Oncology

Immunotherapy continues to be a growing category in oncology treatment, and company- and cooperative group-sponsored trials are being conducted in all major tumor types.

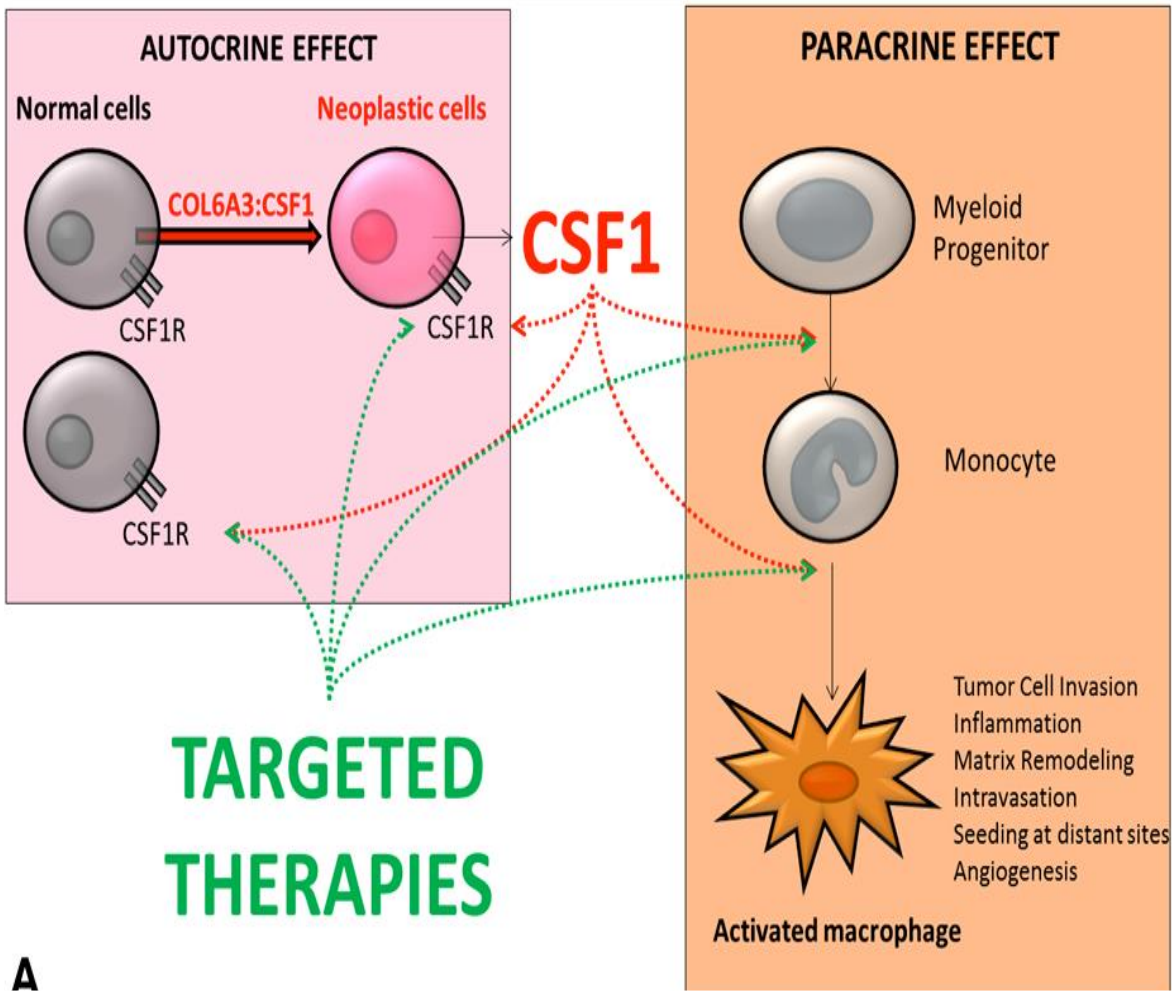


le médicament c'est nous !



une autre cible : les macrophages !

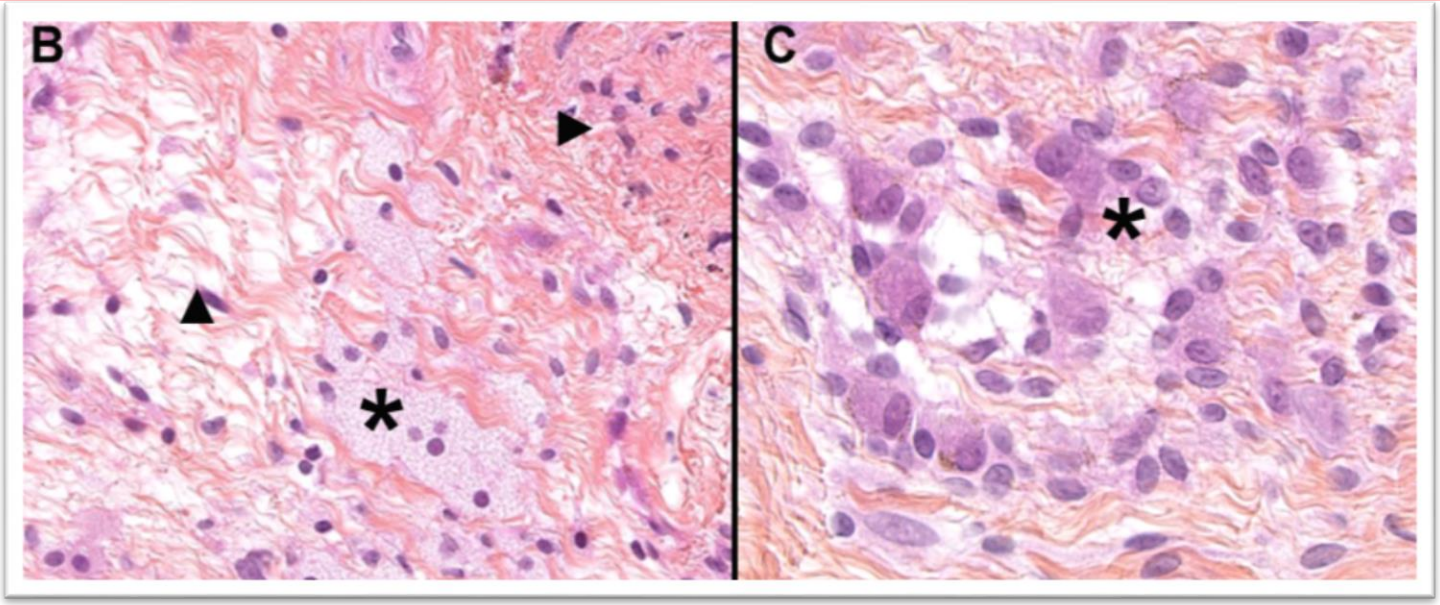
- Infiltration of the **fibrous stroma with a deposition of siderin**
- Chromosomic translocation **t(1:2)(p13;q37) :** Fusion of CSF1 and the collagene promotor type VIa3 (COL6A3)
- **Over-expression of CSF-1**
  - Autocrine effect : CSF1R
  - Paracrine effect: CD163 and CSF1R/ monocytes and macrophages



TUMORAL HETEROGENEITY

2-16% of tumoral cells / 80 % macrophages

- MRI : **Hemosiderin deposition** (low T2 enhancement and blooming artifact with gradient-echo sequences)
- PET: **GLUT-1 up-regulation**



► intra and extra-cellular hemosiderin deposition

▲ synoviocyte and fibrous stroma

* Mononuclear and giant cells

Evaluation de la réponse en imagerie

1° Des fragilités méthodologiques qui demeurent!

43 % des PD* sont fausses (*OMS due to interobserver measurement variability)

Erasmus J et al.. J Clin Oncol. 2003;21:2574–82

Plus les lesions sont petites plus l'incertitude sur la mesure a un impact sur la réponse en %
Oxnard GR,et al. J Clin Oncol. 2011;29:3114–9

2° Des fragilités méthodologiques nouvelles !

COMMENTARY Open Access

CrossMark

Immune-related response evaluations during immune-checkpoint inhibitor therapy: establishing a "common language" for the new arena of cancer treatment

Mizuki Nishino

Evaluation thérapeutique des modulateurs des λT : Les données du pb !

- La réponse peut être **différée, voir tardive**
- La réponse peut apparaitre après une **pseudo progression** ;
- L'arrêt immédiat du traitement après progression peut être inapproprié (il faut confirmation à 4s),
- La réponse clinique dissociée ne doit pas être considérée comme un échec
- Une stabilisation durable peut être l'effet de l'immunothérapie
- on peut avoir un bénéfice sur la Survie Globale **mais sans** amélioration de la Survie sans Progression …. (à quoi sert la PFS et donc à quoi sert l'imagerie?)

Borghaei H, et al . N. Engl. J. Med. 2015; 373(17):1627–1639.
Larkin J, et al N. Engl. J. Med. 2015; 373(1):23–34.
Motzer RJ, et al. N. Engl. J. Med. 2015; 373(19):1803–1813.

Immunothérapie : le médicament c'est nous !

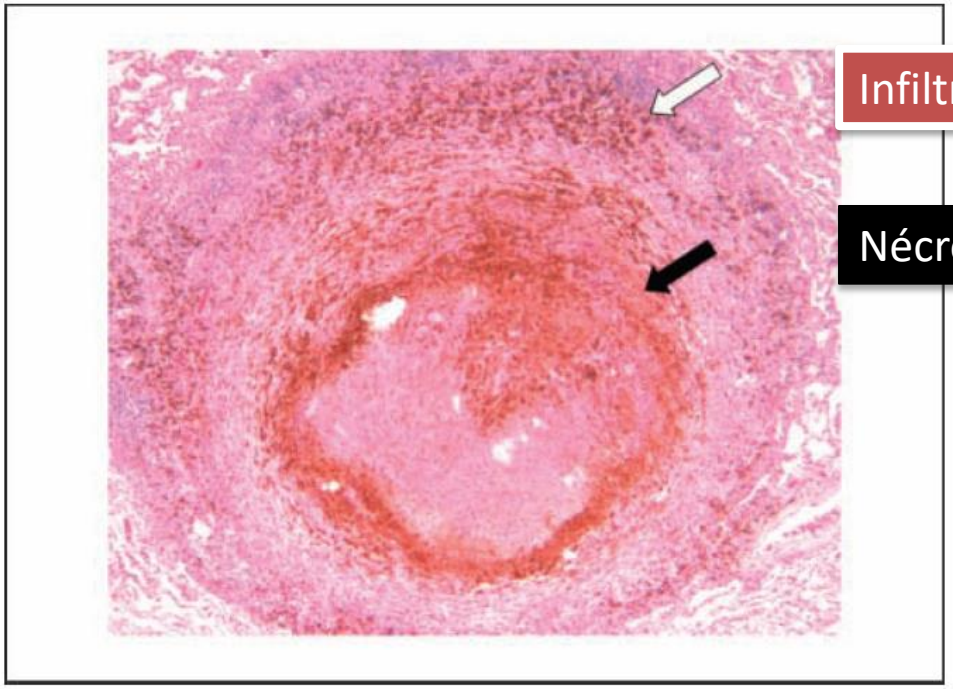


Fig. 4. Resected metastatic melanoma tumor nodule of the lung. This case is a 53-y-old male, diagnosed with melanoma of the scalp, who underwent resection and adjuvant biochemotherapy. After two cycles, imaging confirmed multiple new lung nodules consistent with recurrent disease (stage M1b). Eight months after starting ipilimumab, the dominant lung lesion was resected along with two small nodules (3 mm each). From a biopsy of one of the small nodules, note the T-cell infiltrate (*white arrow*) and extensive necrosis (*black arrow*) with no residual tumor cells. Section was stained with H&E.

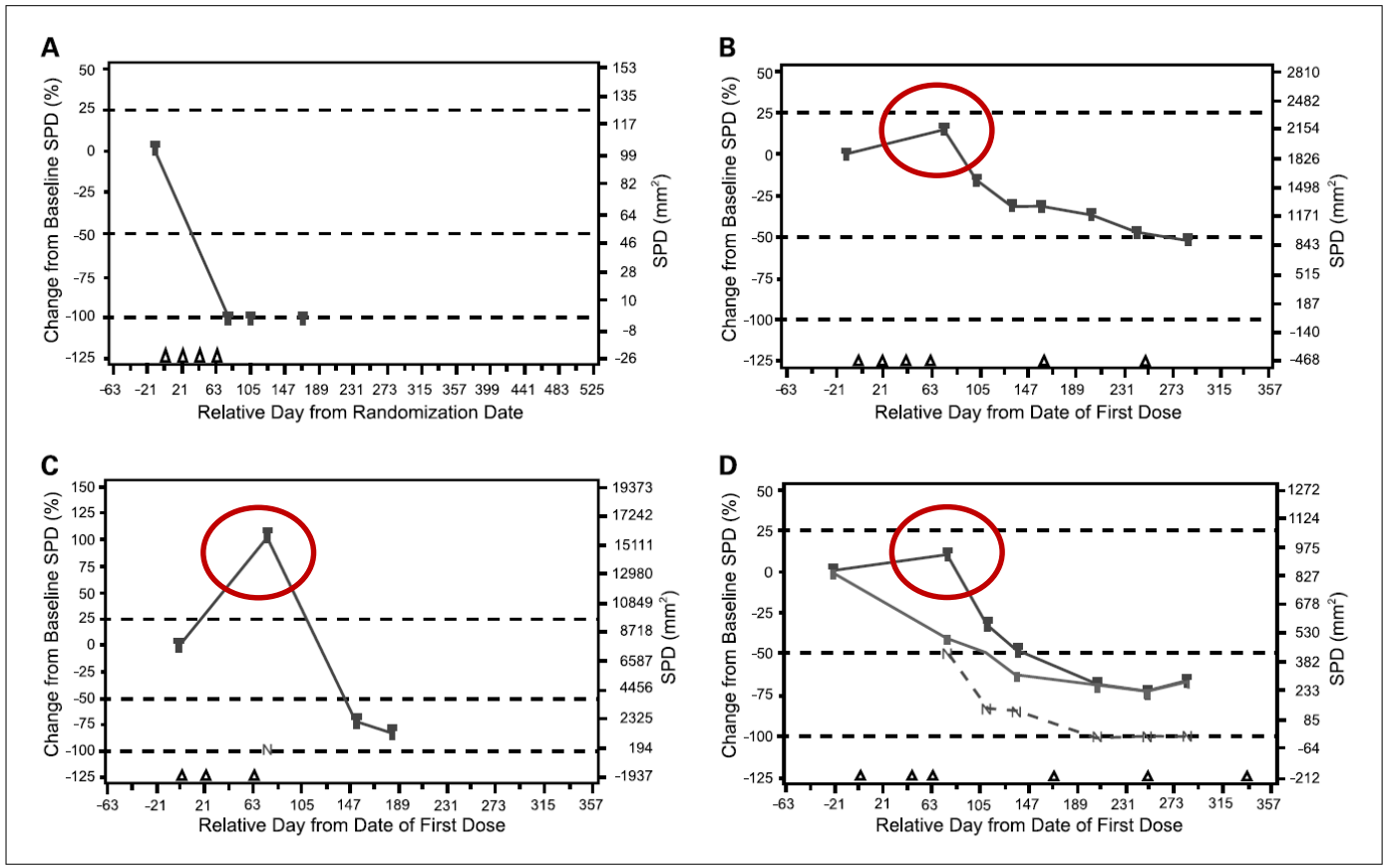
30% CR PR SD à S 12

4 TYPES DE REPONSES

- ✓ Σ L x l
- ✓ Lésions les plus larges
- ✓ 5 lésions/ organes
- ✓ Max 10 lésions (+ lésions cibles cutanée)

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

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



Apport de l'imagerie moléculaire?

Fig. 1. Patterns of response to ipilimumab observed in advanced melanoma. Shown are the four response patterns observed in advanced melanoma patients treated with ipilimumab at 10 mg/kg in the CA184-008 and CA184-022 studies. *A*, response in baseline lesions; *B*, "stable disease" with slow, steady decline in total tumor volume; *C*, response after initial increase in total tumor volume; *D*, reduction in total tumor burden after the appearance of new lesions. SPD, sum of the product of perpendicular diameters. N, tumor burden of new lesions (*C* and *D*). *D*, top line, total tumor burden; middle line, tumor burden of baseline lesions; bottom line, tumor burden of new lesions. Triangles, ipilimumab dosing time points; dashed lines, thresholds for response or PD/irPD.

Table 1. Comparison between WHO criteria and the irRC

	WHO	irRC
New, measurable lesions (i.e., ≥5 × 5 mm)	Always represent PD	Incorporated into tumor burden
New, nonmeasurable lesions (i.e., <5 × 5 mm)	Always represent PD	Do not define progression (but preclude irCR)
Non-index lesions	Changes contribute to defining BOR of CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions in two consecutive observations not less than 4 wk apart	Disappearance of all lesions in two consecutive observations not less than 4 wk apart
PR	≥50% decrease in SPD of all index lesions compared with baseline in two observations at least 4 wk apart, in absence of new lesions or unequivocal progression of non-index lesions	≥50% decrease in tumor burden compared with baseline in two observations at least 4 wk apart
SD	50% decrease in SPD compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir
PD	At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 wk apart

NB seuil 5mm

Du boulot pour la radio!!!

Table 1. Comparison of Key Differences in RECIST v1.1 and irRC

Category	RECIST v1.1	irRC
Measurement of tumor burden	Unidimensional	Bidimensional
Target lesions	Maximum, 5*	Maximum, 15 index lesions
New lesion	Results in progressive disease at first appearance	Up to 10 new visceral lesions and 5 cutaneous lesions may be added to the sum of the products of the two largest perpendicular diameters of all index lesions at any time point
Complete response	Disappearance of all target and nontarget lesions Nodes must regress to < 10 mm short axis No new lesions Confirmation required	
Partial response	≥ 30% decrease in tumor burden compared with baseline Confirmation required	≥ 50% decrease in tumor burden compared with baseline† Confirmation required
Progressive disease	≥ 20% + 5-mm absolute increase in tumor burden compared with nadir Appearance of new lesions or progression of nontarget lesions	≥ 25% increase in tumor burden compared with baseline, nadir, or reset baseline† New lesions added to tumor burden Confirmation required
Stable disease	Neither partial response nor progressive disease	

Abbreviations: irRC, immune-related response criteria; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1.
*For the present analyses, the maximum number of target lesions was 10.
†If an increase in tumor burden is observed at the first scheduled assessment, the baseline is reset to the value observed at the first assessment.

Evaluation of Immune-Related Response Criteria and RECIST v1.1 in Patients With Advanced Melanoma Treated With Pembrolizumab

JCO 2016

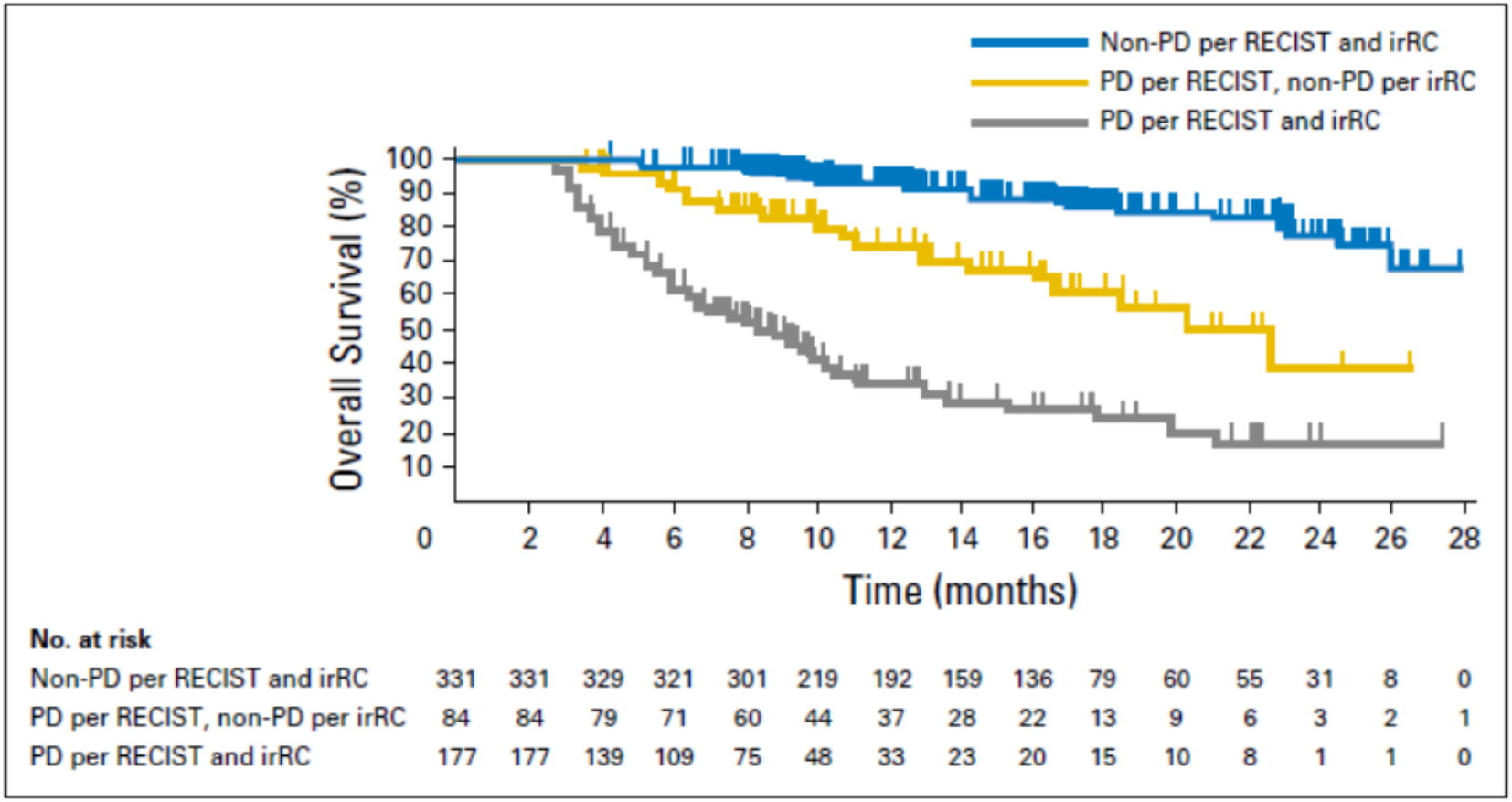
F. Stephen Hodi, Wen-Jen Hwu, Richard Kefford, Jeffrey S. Weber, Adil Daud, Omid Hamid, Amita Patnaik, Antoni Ribas, Caroline Robert, Tara C. Gangadhar, Anthony M. Joshua, Peter Hersey, Roxana Dronca, Richard Joseph, Darcy Hille, Dahai Xue, Xiaoyun Nicole Li, S. Peter Kang, Scot Ebbinghaus, Andrea Perrone, and Jedd D. Wolchok

KEYNOTE-001 (clinical trial information: NCT01295827) was as international, multicenter, open-label, phase Ib study of **pembrolizumab** for patients with advanced solid tumors, which included multiple melanoma expansion cohorts.

655 mélanomes,
327pts CT @ semaine 28.
24/327 réponses atypiques
15 pseudoprogressions précoces
9 pseudoprogressions retardées

592 survivants @ semaines 12
331 (56%) non progressif
177 (30%) **progression RECISTS 1,1 et irRC**
84 (14%) **progression RECISTS 1,1 mais pas irRC**

<u>Survie globale 2 ans</u>
77.6% si **non** progressif RECIST iRRC (n = 331),
37.5% si progressif r RECIST v1.1 mais non progressifs irRC (n= 84)
17.3% si progressif RECIST et iRRC (n = 177).

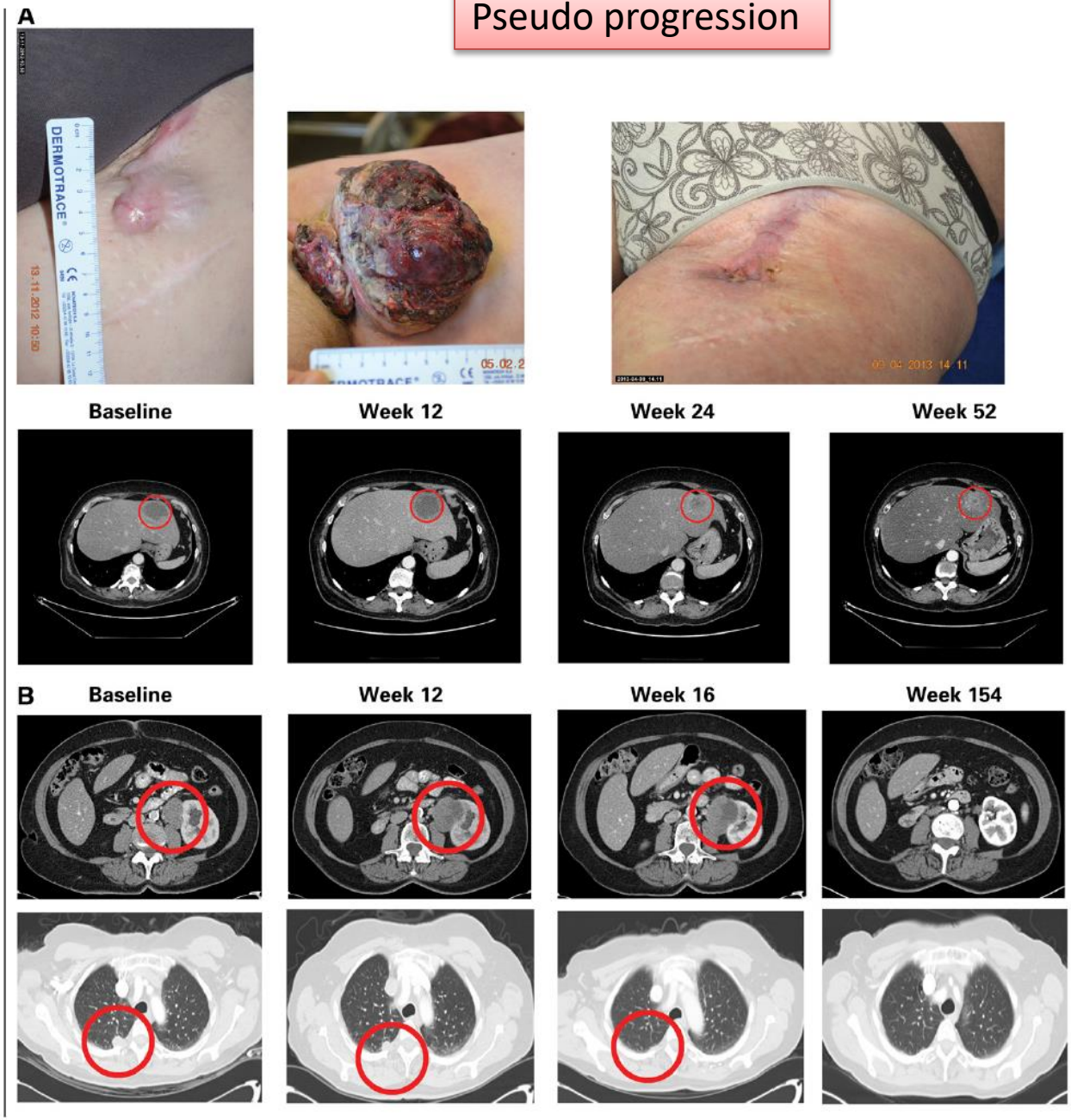


No. at risk

Non-PD per RECIST and irRC	331	331	329	321	301	219	192	159	136	79	60	55	31	8	0
PD per RECIST, non-PD per irRC	84	84	79	71	60	44	37	28	22	13	9	6	3	2	1
PD per RECIST and irRC	177	177	139	109	75	48	33	23	20	15	10	8	1	1	0

Fig 5. Kaplan-Meier estimates of overall survival on the basis of best overall response per RECIST v1.1 and irRC in patients who survived ≥ 12 weeks (n = 592). irRC, immune-related response criteria; non-PD, non-progressive disease; PD, progressive disease; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1.

Pseudo progression

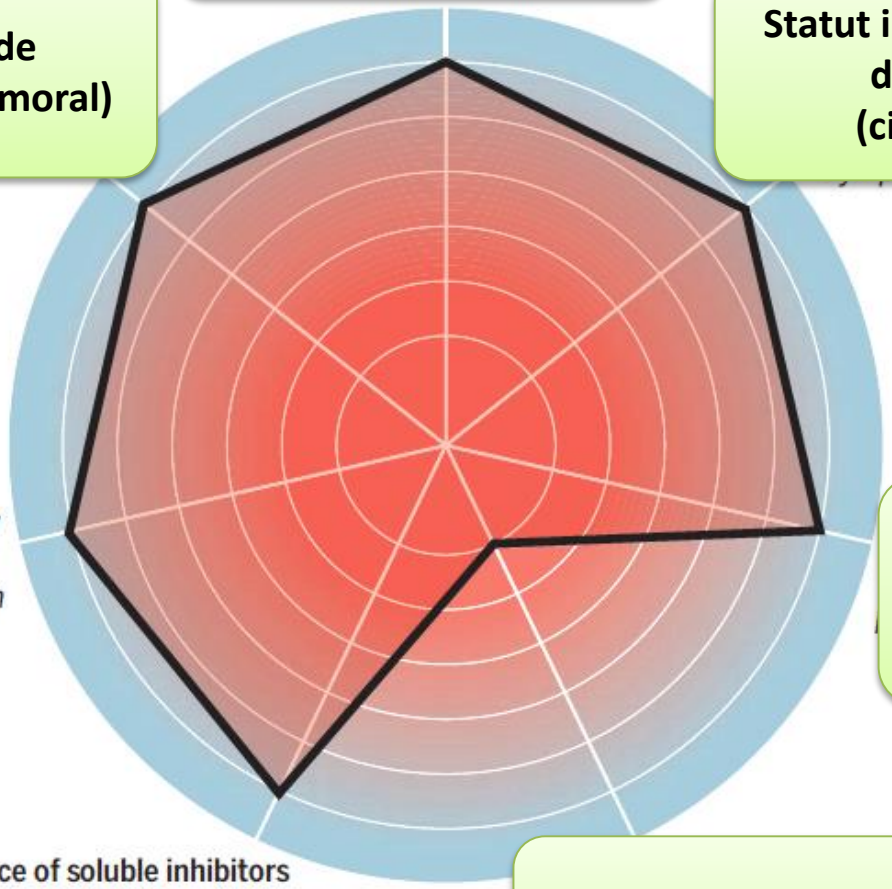


Les biomarqueurs en immunothérapie

Charge antigénique tumorale

Mécanismes de résistance (site tumoral)

Statut immunologique du patient (circulation)



TEP ?

Absence of inhibitory tumor metabolism
LDH, glucose utilization

TEP ?

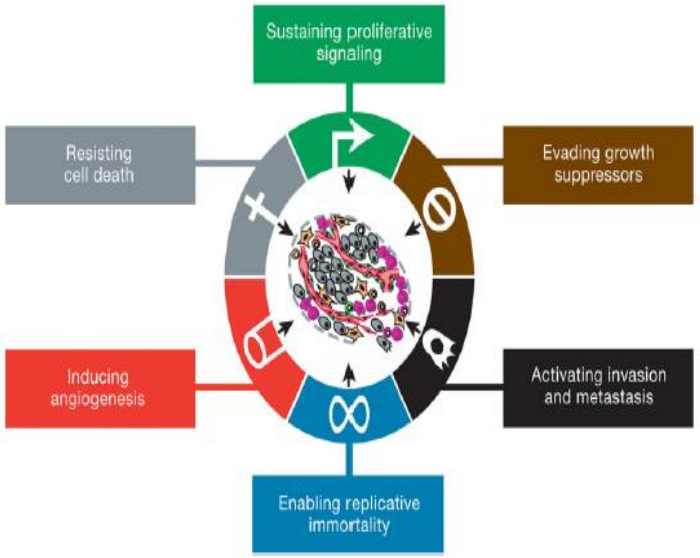
Immunité intratumorale (L-T infiltrat)

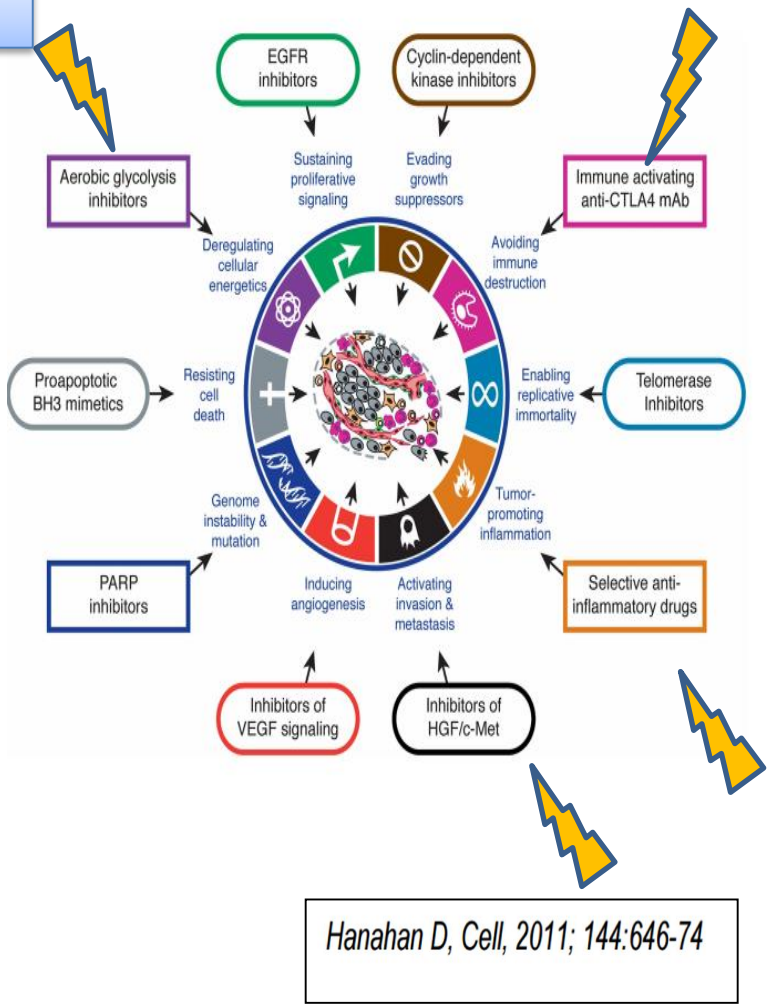
Absence of soluble inhibitors
IL-6, CRP

Expression de checkpoint (site tumoral)

Métabolisme tumoral

Années 2000





Hanahan D, Cell, 2011; 144:646-74

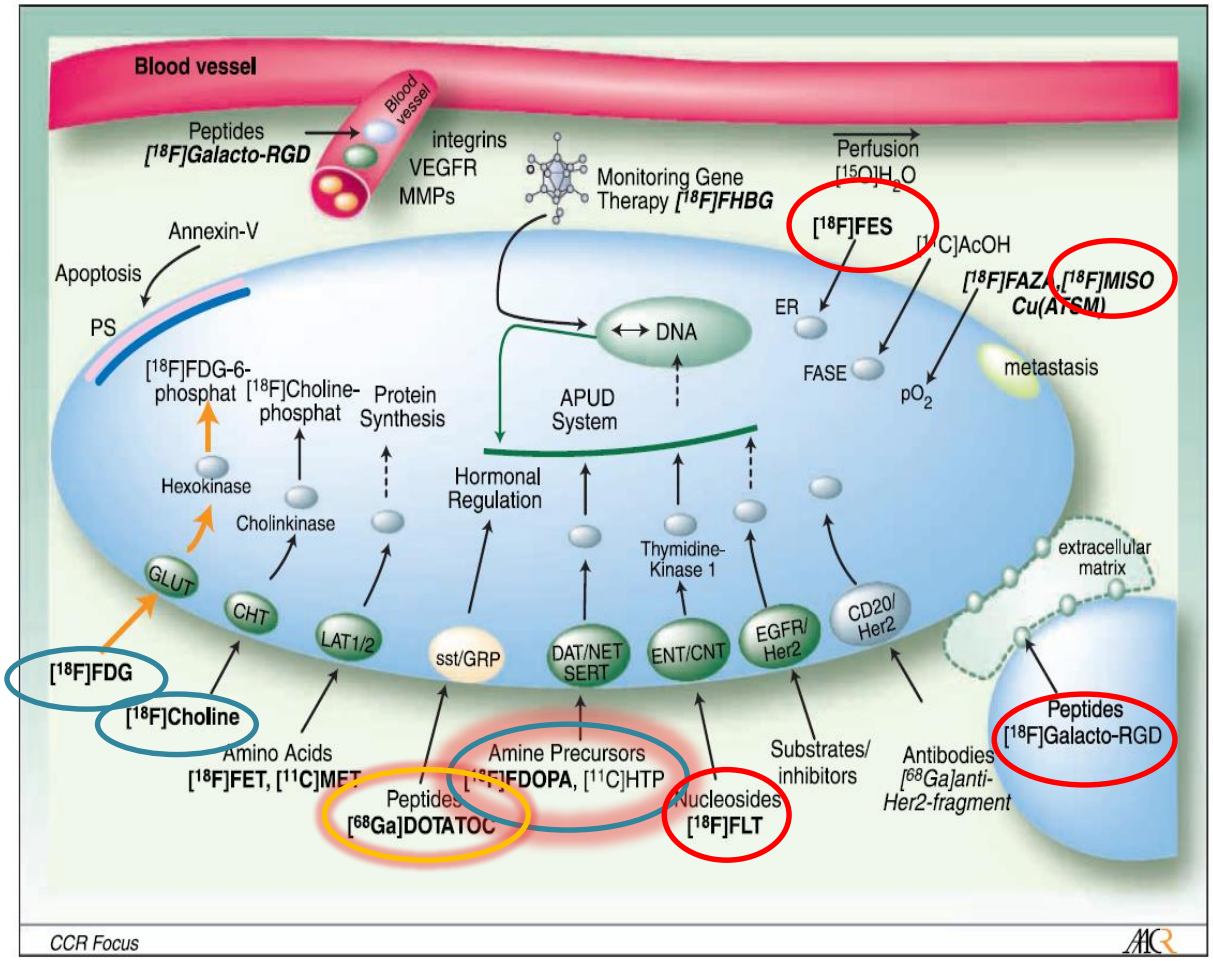


Fig. 2. Selected targets and corresponding nuclear imaging probes already established for nuclear molecular imaging in the clinic (*bold*) or currently under assessment in clinical studies (*italic*).

Prediction of Response to Immune Checkpoint Inhibitor Therapy Using Early Time-Point FDG-PET/CT Imaging in Patients with Advanced Melanoma

Whal et al JNM 2017

20 pts Mélanome M+ : ipilimumab ou nivolumab

FDG PET/CT
@ Baseline (SCAN-1),
@ days 21-28 (SCAN-2),
@ 4 months (SCAN-3).

RECIST 1.1 / irRC / PERSIST / EORTC vs Best Overall Reponse BOR

Bénéfice clinique 5/ 20 !

CR et PR

CT-based criteria			PET-based criteria		
	RECIST 1.1	**irRC**		**PERCIST 1.0**	**EORTC**
Complete Response	Disappearance of all target and non-target lesions; all lymph nodes <10 mm short axis	Resolution of all lesions (whether measurable or not) and no new lesions	Complete Metabolic Response	Complete resolution of FDG uptake within measurable target lesion and disappearance of all other lesions to background blood-pool levels	Complete resolution of FDG uptake within the tumor volume so that it is indistinguishable from surrounding normal tissue
Partial Response	≥ 30% decrease in sum of diameters of target lesions; non-target lesions may persist but not unequivocally progress	Decrease in tumor burden ≥50%, measured as the sum of the products of the two largest perpendicular diameters of all index lesions, relative to baseline	Partial Metabolic Response	>30% relative decrease and >0.8 absolute decrease in SULpeak of the hottest lesion	Reduction of 15-25% in tumor SUV after 1 cycle of therapy, and >25% after more than 1 treatment cycle

SD et PD

CT-based criteria			PET-based criteria		
	RECIST 1.1	irRC		PERCIST 1.0	EORTC
Stable Disease	Neither sufficient tumor regression nor growth to qualify for PR or PD	Not meeting criteria for irCR or irPR, in absence of irPD	Stable Metabolic Disease	Not meeting criteria for CMR, PMR, or PMD	Increase in tumor SUV of <25% or decrease of <15% and no visible increase in extent of FDG tumor uptake (20% in the longest dimension)
Progressive Disease	≥ 20% increase in sum of diameters of target lesions or unequivocal progression of non- target lesion or appearance of new lesion	Increase in tumor burden ≥25% relative to nadir, measured as the sum of the products of the two largest perpendicular diameters of all index lesions	Progressive Metabolic Disease	>30% relative increase and >0.8 absolute increase in SULpeak of the hottest lesion or unequivocal progression of FDG-avid non-target lesion or appearance of new FDG–avid lesion	Increase from baseline in tumor SUV of >25% within the tumor region, visible increase in the extent of FDG tumor uptake (20% in the longest dimension), or appearance of new FDG uptake in metastatic lesions

SCAN-2 / SCAN-3

Kappa coef : Bon agrément intra modalité
RECIST1.1 vs. irRC(CT-based), 0.9;
PERCIST vs. EORTC (PET-based), 0.886

SCAN - 2

RECIST 1,1 valeur prédictive de Best Over all Response @ 4 mois = 75%

SCAN-1 / SCAN-2

RECIST **VPP = 85%**
PERCIST ou EORTC **=15%** ↗ FDG compatible avec bénéfice Clinique
Mélange RECIST / PERCIST = PECRIT : **90%**

TABLE 3

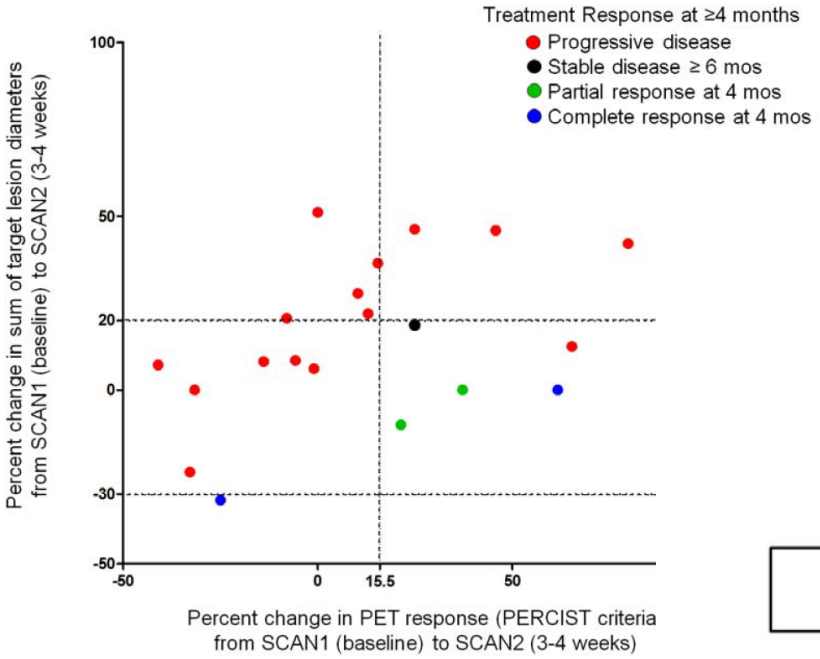
Performance of Four Radiologic Evaluation Criteria Applied to Early (3-4 weeks) PET/CT Scans in Predicting Best Overall Response (RECIST 1.1) to Immune Checkpoint Inhibitor Therapy at ≥4 Months.

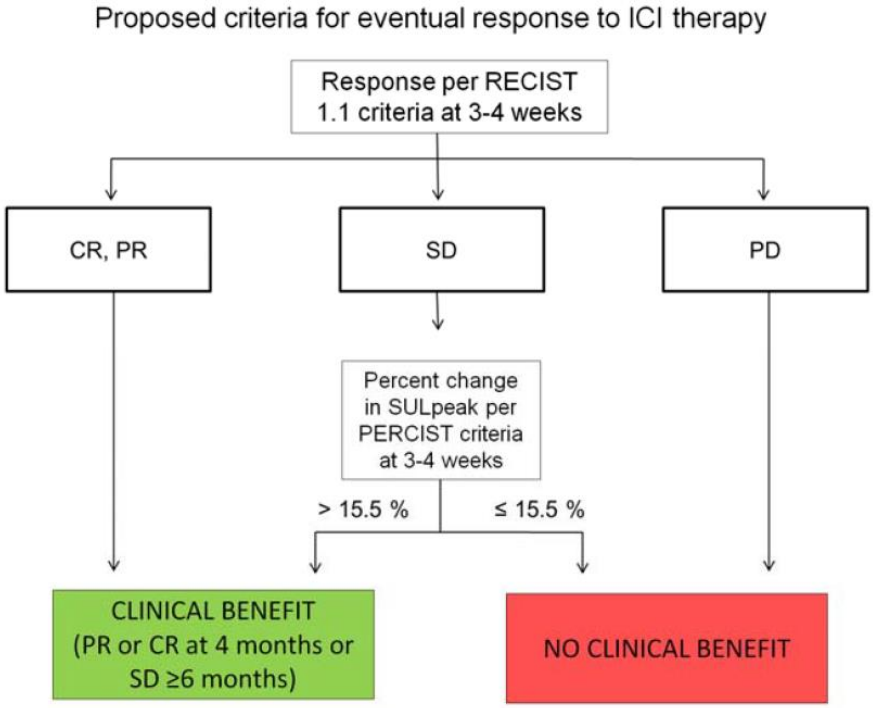
	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	Accuracy (%)
RECIST1.1	100.0 (48.0-100.0)	66.7 (38.4-88.1)	50.0 (18.9-81.1)	100.0 (69.0-100.0)	75.0
irRC	80.0 (28.8-96.7)	66.7 (38.4-88.1)	44.4 (14.0-78.6)	90.9 (58.7-98.5)	70.0
PERCIST	60.0 (15.4-93.5)	73.3 (44.9-92.0)	42.9 (10.4-81.2)	84.6 (54.5-97.6)	70.0
EORTC	40.0 (6.5-84.6)	73.3 (44.9-92.0)	33.3 (5.3-77.3)	78.6 (49.2-95.1)	65.0

TABLE 4

Performance Characteristics of Four Methods of Early Tumor Response Evaluation in Predicting Response (RECIST 1.1) to Immune Checkpoint Inhibitor Therapy at 4 Months.

Method number	Tumor response evaluation method description	SCAN-1 to SCAN-2 optimal percent change cutoff	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	Accuracy (%)
1	Change in sum of RECIST 1.1-based target lesion diameters	≤ 0	80.0 (28.8-96.7)	86.7 (59.5-98.0)	66.7 (22.7 - 94.7)	92.9 (66.1 - 98.8)	85.0
2	Change in sum of the products of the two largest perpendicular diameters of irRC-based index lesions	≤ -14.7	60.0 (15.4 - 93.5)	93.3 (68.0 - 98.9)	75.0 (20.3 - 95.9)	87.5 (61.6 - 98.1)	85.0
3	Change in SULpeak of the hottest lesion	> 15.5	80.0 (28.8 - 96.7)	73.3 (44.9 - 92.0)	50.0 (16.0 - 84.0)	91.7 (61.5 - 98.6)	75.0
4	Change in sum of SUVmax of all FDG-avid metastatic lesions	> 14.7	80.0 (28.8 - 96.7)	66.7 (38.4 - 88.1)	44.4 (14.0 - 78.6)	90.9 (58.7 - 98.5)	70.0
	Methods 1 and 3, above, combined (PECRIT)		100.0 (48.0-100)	93.3 (68.0-98.9)	83.3 (36.1-97.2)	100.0 (76.7-100.0)	95.0





Proposer TEP si SD (ou pseudo PD)

20 PATIENTS !

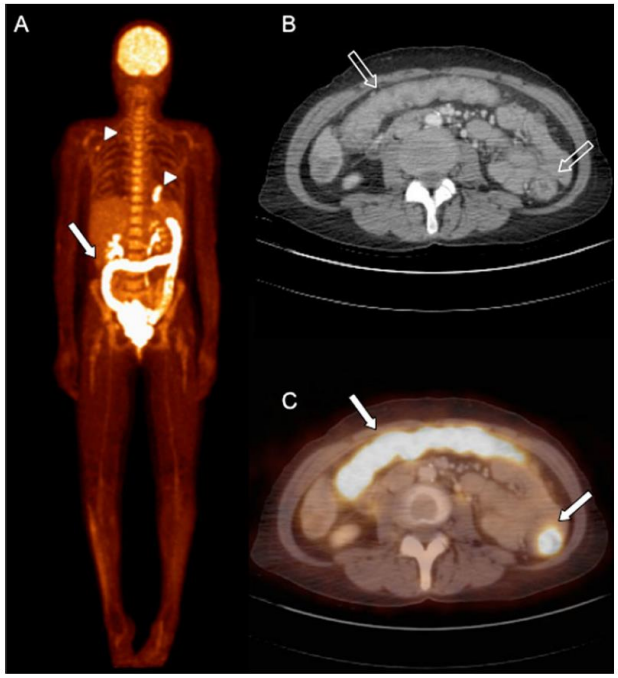
Pas de données sur la compliance thérapeutique

Le challenger c'est la biologie : ADN tumoral circulant

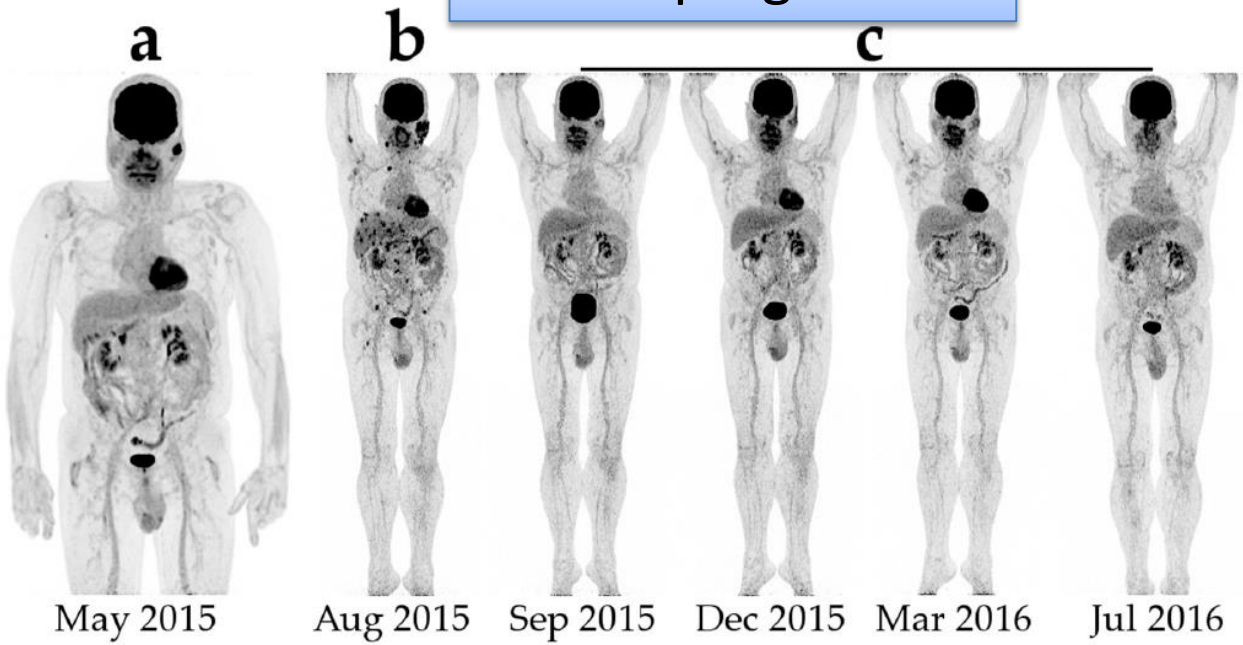
Considérations pratiques

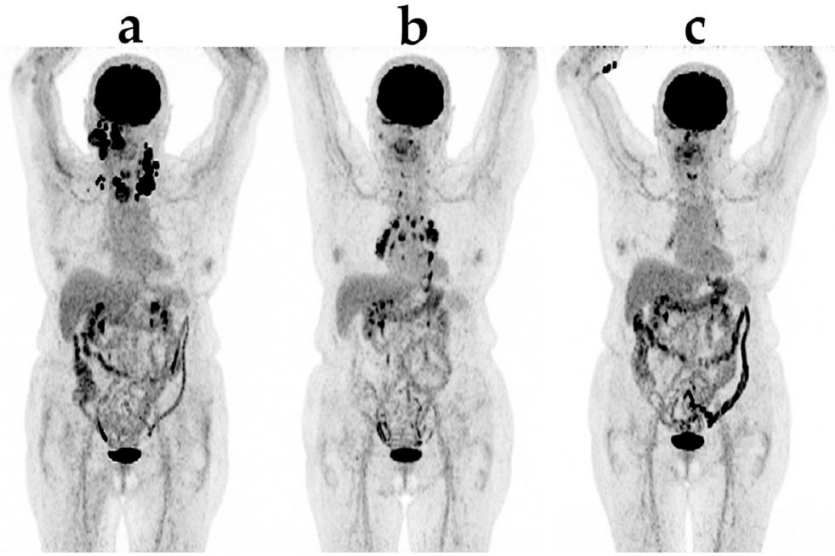
Faux positif du FDG

Goethals L, et al 18F-FDG PET/CT imaging of an anti-CTLA-4 antibody-associated autoimmune pancolitis. *Eur J Nucl Med Mol Imaging* 2011;
Koo PJ, et al Anti-CTLA4 antibody therapy related complications on FDG PET/CT. *Clin Nucl Med* 2014; **39**:



Pseudo progression





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

AJR 2011

119 pts Anti CTLA-4

Signes radiologiques de réactions immunologiques **20%**

- Symptomatiques colites, thyroïdites, hypophysite, arthrites
- Asymptomatiques, adénomégalie, myosites, faciites, infiltration rétropéritoine
- Associés à la réponse clinique

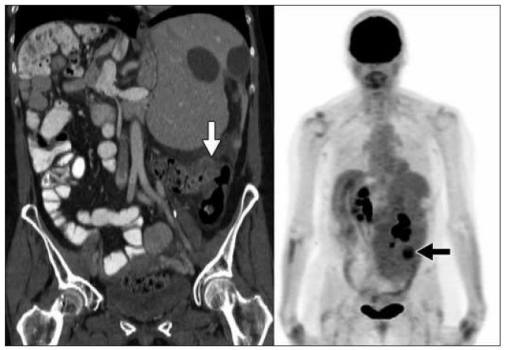


Fig. 2—62-year-old woman with asymptomatic melanoma. Contrast-enhanced CT scan (*left*) shows focal edema of colonic wall of transverse colon and pericolic fat (*arrow*) associated with increased FDG uptake on PET scan (*right*). Findings suggest focal colitis.

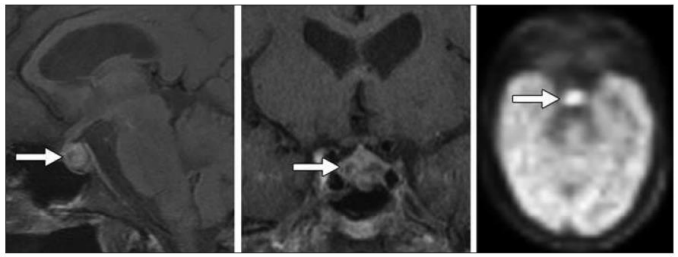


Fig. 3—67-year-old man with melanoma, intractable headaches, and laboratory evidence of panhypopituitarism. Gadolinium-enhanced T1-weighted MR images (*left* and *center*) show diffusely enlarged hypophysis with ill-defined small hypoenhancing areas (*arrows*). PET image (*right*) shows FDG-avid hypophysis (*arrow*).

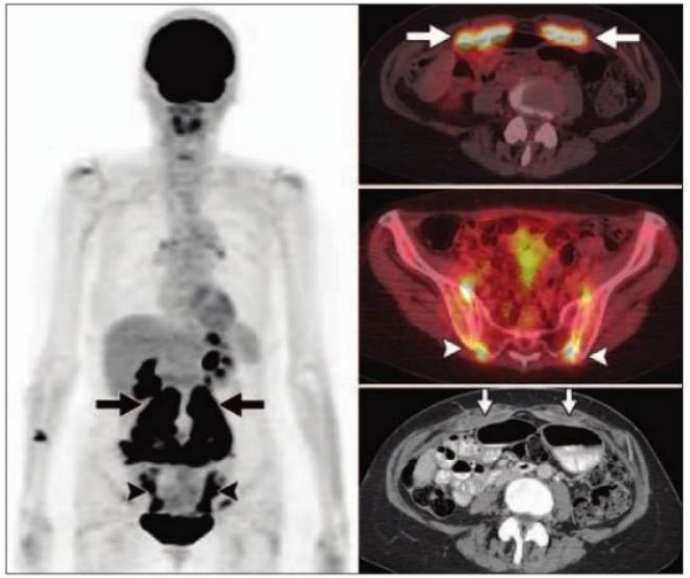


Fig. 4—74-year-old woman with melanoma and abdominal pain after 14 months of anti–CTLA-4 treatment. PET images (*left*; *top* and *center right*) show intensely FDG-avid abdominal fascia (*arrows*) and FDG-avid bilateral sacroiliac joints (*arrowheads*). Contrast-enhanced CT scan (*bottom right*) shows diffuse thickening and hyperenhancement of fascia (*arrows*). Anti–CTLA-4 treatment was suspended for 1 month and resumed. Manifestations spontaneously resolved 3 months later.

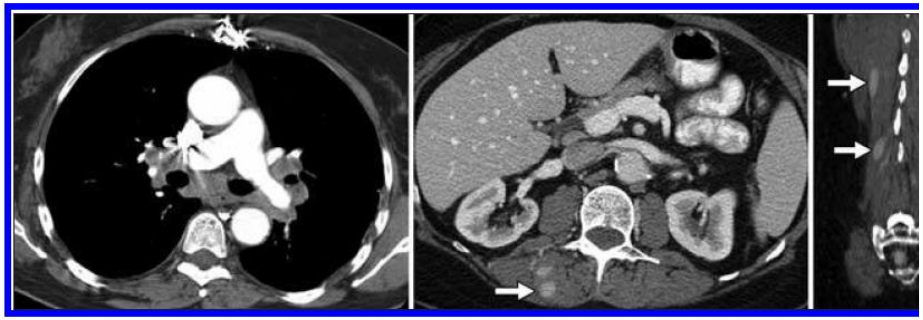


Fig. 5—71-year-old woman with melanoma. Contrast-enhanced CT scan (*left*) shows diffuse symmetric mediastinal and bilateral hilar lymphadenopathy, presumably benign reactive process. PET/CT images (and *right*) obtained at same time show new elongated hyperenhancing foci in paraspinal muscles (*arrov* which resolved spontaneously 4 months later.

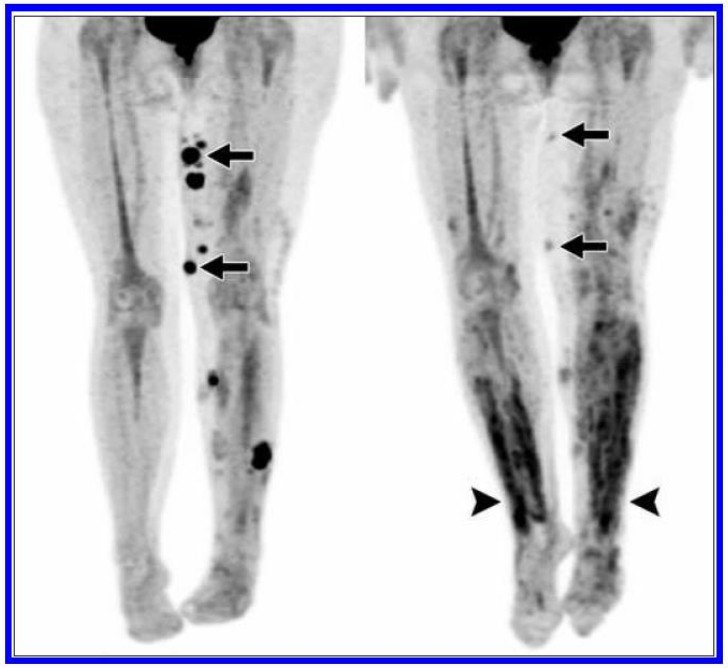
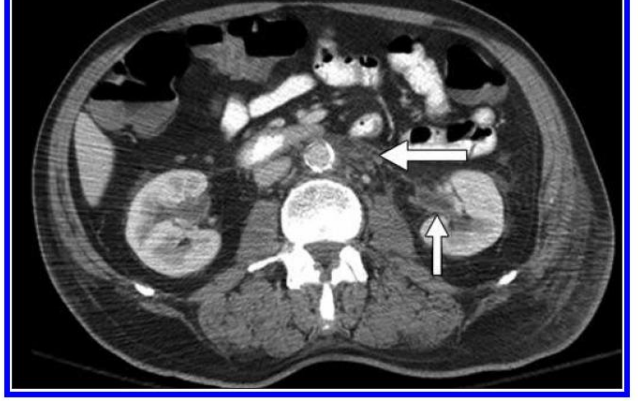
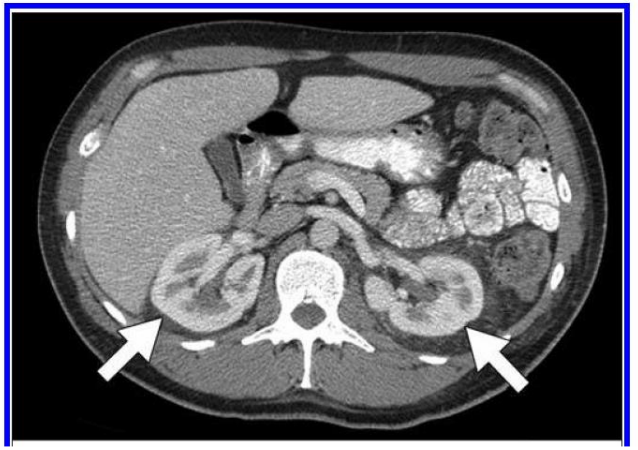


Fig. 6—69-year-old woman with unresectable in-trans melanoma metastasis PET image (*left*) show multiple FDG-avid metastatic lesions (*arrows*) in left leg. PE image (*right*) obtained after 3 months of anti–CTLA-4 treatmer shows metastatic lesions (*arrows*) are smaller and less FDG avid, but new diffuse areas of intramuscula hypermetabolism (*arrowheads*) are pres in both calves.



Contrast-enhanced CT scan shows diffuse opacity of retroperitoneal fat (*large arrow*) and thickening (*small arrow*) of walls of renal pelvis after 2 months of anti–CTLA-4 therapy. Nearly complete resolution was found after 3 months of steroid treatment.



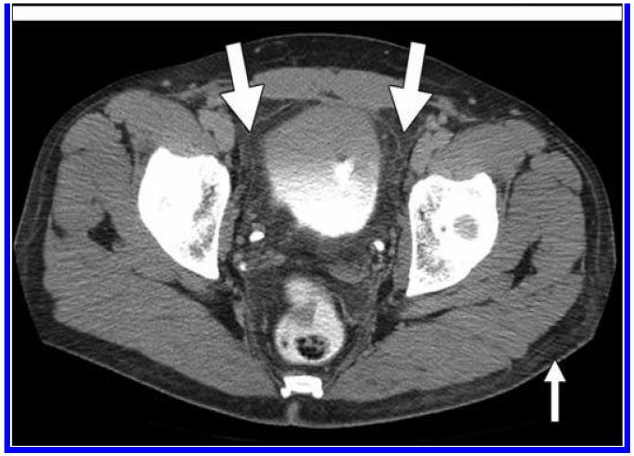


Fig. 8—37-year-old man with melanoma. Contrast-enhanced CT scans show diffuse opacity of abdominal retroperitoneal fat (*arrows, top*) and pelvic fat (*large arrows, bottom*) and patchy haziness of subcutaneous fat (*small arrow, bottom*) after 16 months of anti–CTLA-4 treatment. Opacities progressed for 5 months and spontaneously regressed within 1 year with no steroid therapy.

PVNS : CSF1 inhib PET vs IRM Dercle et al 2015

Staging in PET/CT subgroup (n=7)

- Se (MRI) = Se (PET) for the detection of lesions and to assess the extend
- SUV mean = 8.8 (4-16)

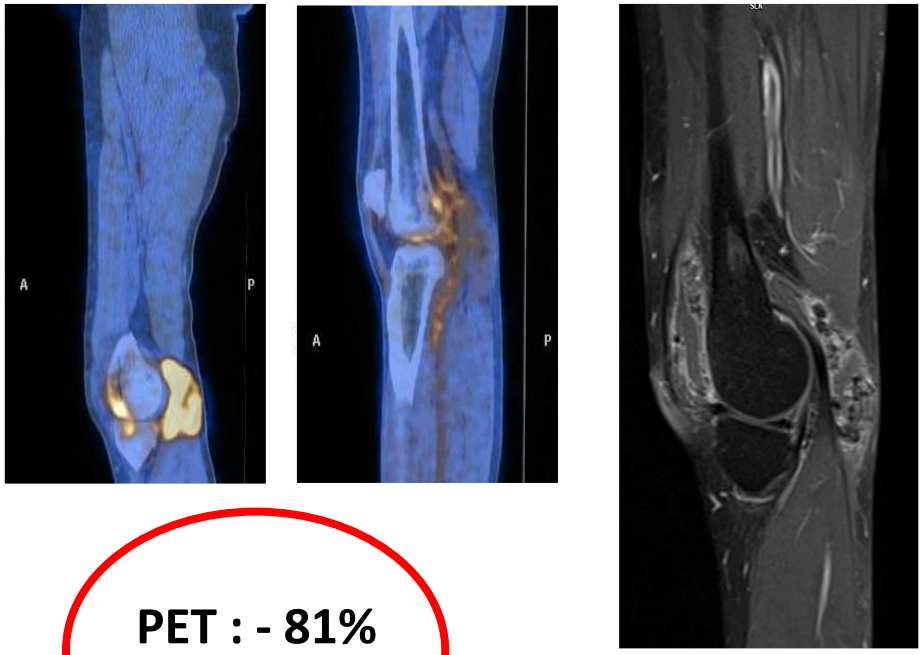
Follow-up in the Targeted Therapy group (n=4/7 PET/CT)

- Responses: PERCIST = 3, RECIST = 1, late symptomatic assessment : 3
- Agreement with the late symptomatic evolution : K = 1 with PERCIST and 0.2 with RECIST

Review of the litterature concerning the Targeted Therapies

- Bad agreement between PERCIST/RECIST (kappa = 0.3)
- Response rates:
  - Late symptomatic improvement : 65%
  - PERCIST : 77%
  - RECIST : 26%

BEFORE AFTER TREATMENT : PR



PET : - 81%
MRI : - 24%

MRI : stable tumoral size

diagnostics

MDPI

Review

Nuclear Molecular Imaging Strategies in Immune Checkpoint Inhibitor Therapy

Table 1. FDG PET/CT [1] for response monitoring in immunotherapies.

Study	No. of Patients	Method of Response Assesment	Results
Sachpekidis et al. [32]	22	FDG PET/CT at baseline, after two cycles of ipilimumab and post-treatment. EORTC [2] criteria used for response classification	Early scan predictive of post-treatment response in 18 of 22 patients
Kong et al. [33]	27	FDG PET/CT after at least 12 months of treatment with pembrolizumab or nivolumab categorized as positive or negative for presence of metabolically active disease compared to response on CT at the time of the PET/CT scan	43% of patients with residual disease on CT had negative PET scans
Breki et al. [34]	31	FDG PET/CT at baseline, after two cycles of ipilimumab and post-treatment. Fractal and multifractal analysis compared to visual image assesment by nuclear medicine physicians. Seven patients excluded in comparison because of hypermetabolic lesions not related to melanoma (such as irAEs [3])	Fractal analysis results match treatment outcome in 20 out of 24 cases
Zheng et al. (Abstract) [35]	28	Retrospective study. FDG PET/CT at baseline and after 2–4 cycles of ipilimumab treatment. Response assessed according to PERCIST [4]	Two-year survival rate 31% with PMD [5] and 73% with non-PMD
Fredrickson et al. (Abstract) [36]	103	Retrospective study. FDG PET/CT at baseline and after six weeks of atezolizumab treatment evaluated according to EORTC	Metabolic responders had higher overall response rate than non-responders (73.9% vs. 6.3%)

[1] Positron Emission Tomography/Computer Tomography with ^{18}F-Fluorodeoxyglucose; [2] European Organisation for Research and Treatment of Cancer; [3] Immune-related adverse events; [4] PET Response Criteria In Solid Tumors; [5] Progressive Metabolic Disease.

Nouveaux traceurs

PD-L1 : Souris

FLT : une étude sur le mélanome ; non conclusive Ribas et al JNM 2010

λT

: anti CD8 pb fixation physiologique++ (rate ganglion)

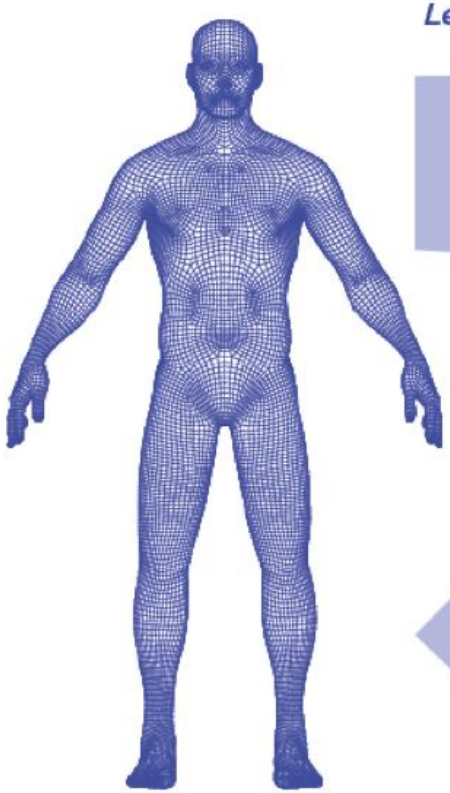
: IL2

: CD3

Perspectives

- Évolution du paradigme
- Compétiteurs

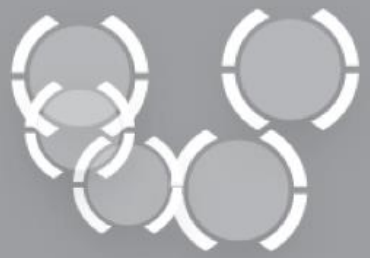
Validated Targets | Engineered TCRs | Safety Testing | Robust Manufacturing



Leukapheresis

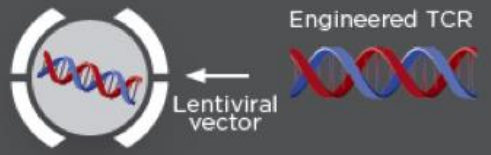
Collection

Natural T-cells isolated from patients



Vein to vein in 17 to 24 days

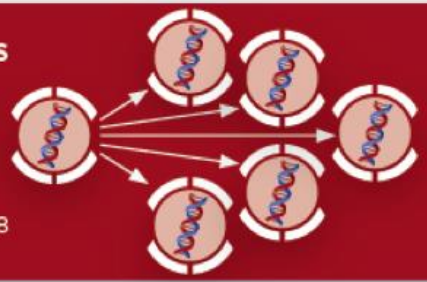
Genes encoding enhanced TCR delivered to patient's natural T-cells



Frozen, tested for release

Infusion

Enhanced T-cells expanded



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Prepare patient with lymphodepletion

Immunomonitoring

Site de suivi

Circulation (sérum+cellules)

Populations immunitaires principales :
- Myéloïdes et lymphocytaires
- Etat de différenciation et d'activation
- Sous-populations lymphocytaires (Treg, effecteurs types 1, 2, 3/17, 22 etc…)
- Cytométrie en flux (15 couleurs)

Sérum :
- Cytokines

Réponse immunitaire spécifique de l'antigène :
- Lymphocytes T CD4 et CD8 : tetramères, production spécifique de cytokines
- Réponse anticorps : ELISA

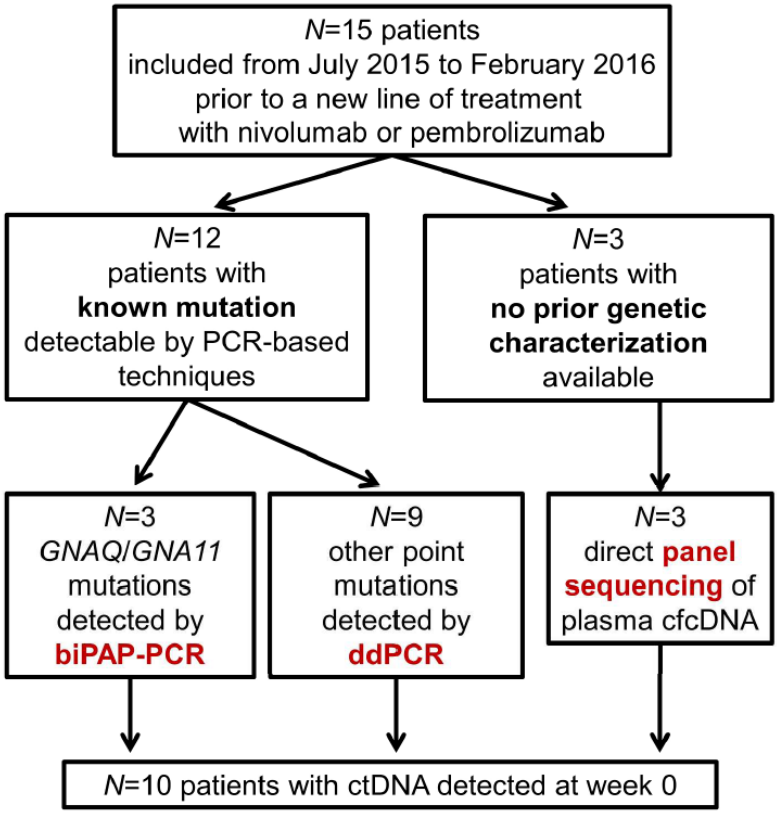
Tumeur (tissu frais, FFPE, congelé)

Populations immunitaires principales :
- Cytométrie en flux (15 couleurs)
- IHC

Signatures moléculaires :
- Immunitaire, inflammatoire, stromale, épithéliale/mésenchymateuse…

Réponse immunitaire spécifique de l'antigène :
- Lymphocytes T CD4 et CD8 : tetramères, production spécifique de cytokines
- Réponse anticorps : ELISA

Circulating tumor DNA changes for early monitoring of anti-PD1 immunotherapy: a proof-of-concept study. Cabel L et al Ann Oncol. 2017

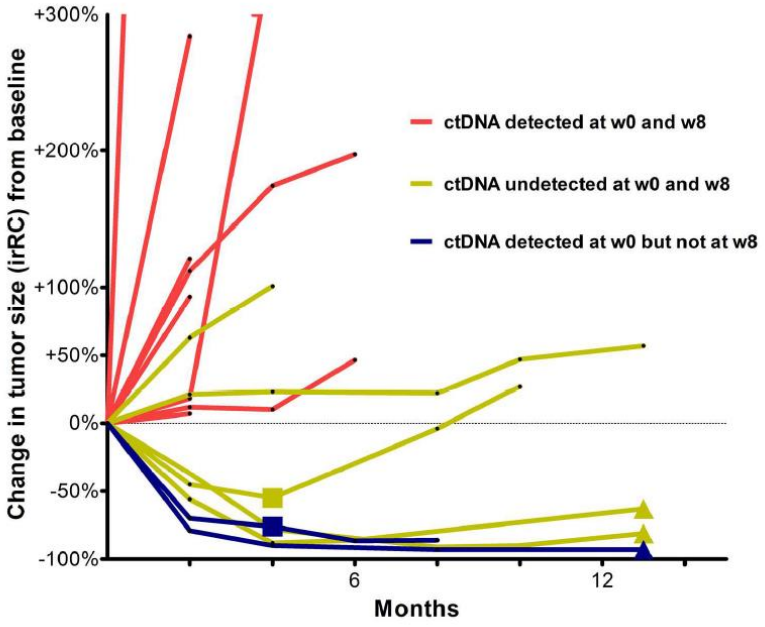


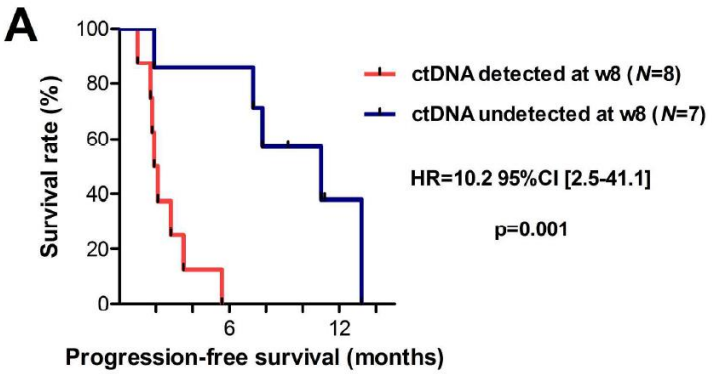
15 pts
radiological evaluation @baseline and 8 weeks

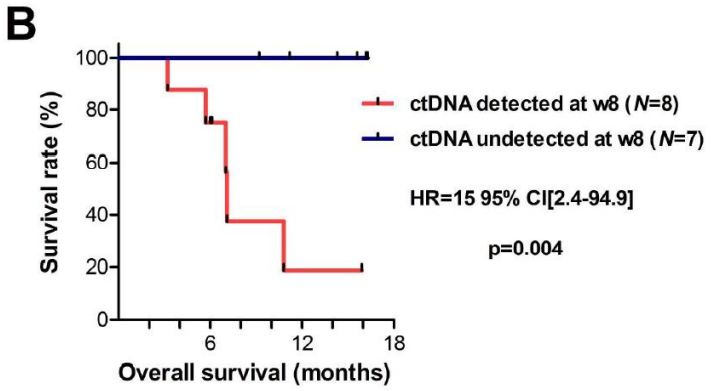
2 pts en RC ct DNA sont en RC radiologique @ s8
8 pts en RP ou SD ct DNA sont en SD ou PD radiologique @ s8

La guerre des clones

Un patient en réponse complete ctDNA avec PD en iRC sauf une lesion en RC







Conclusions

- Développements explosifs de l'immunothérapie;
- iRC = référence, mais avec des limites
- Place de l'imagerie TEP FDG qui reste à définir
- Attention aux Fx + du FDG
- On a besoin d'un marqueur spécifique des λT