Immunothérapies et évaluation thérapeutique

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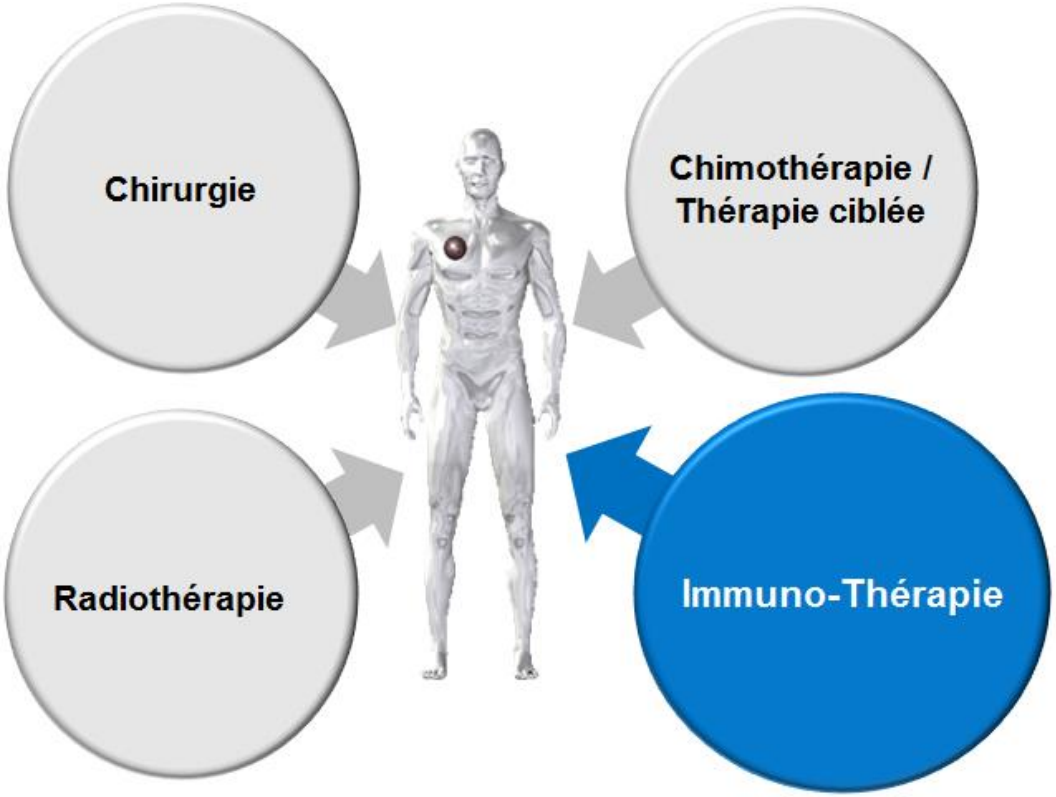
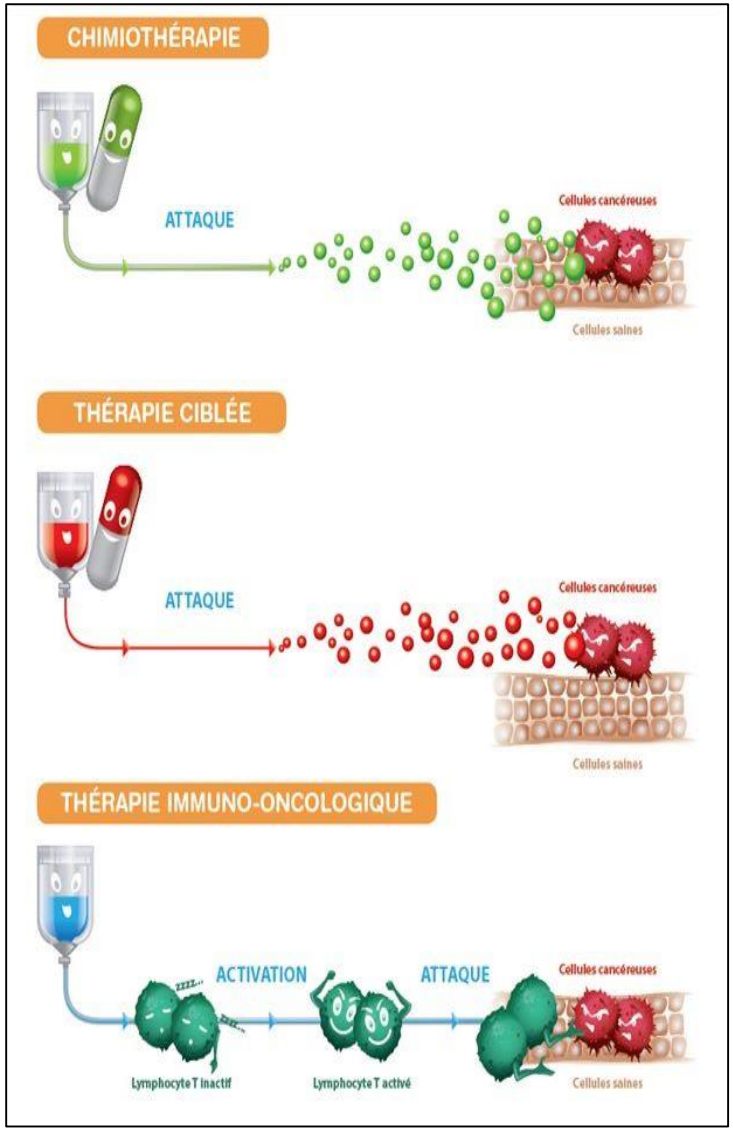
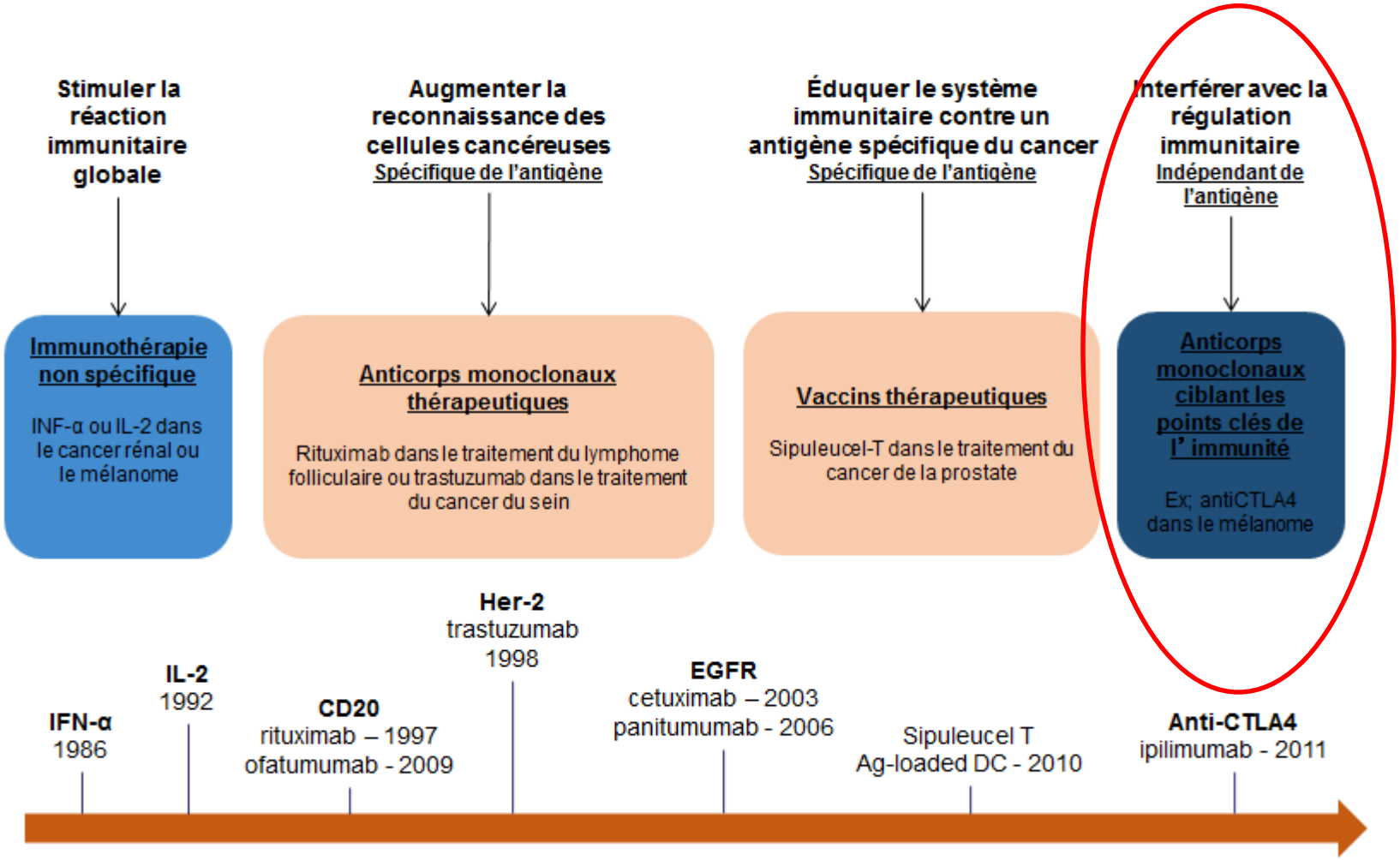
Cancer : Modalités thérapeutiques en 2017



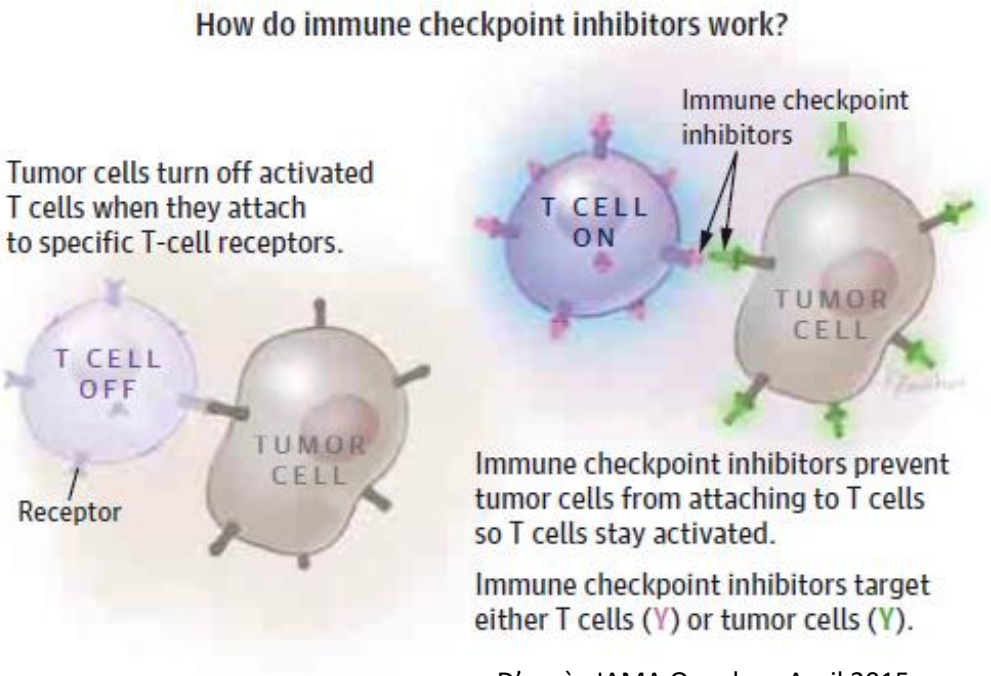


Histoire des immunothérapies

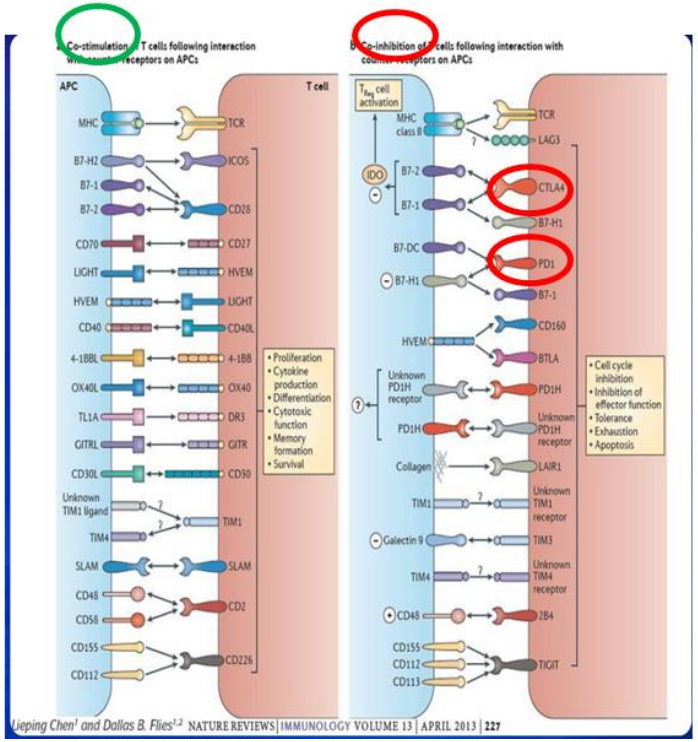


Diapositive empruntée au Dr Isabelle Lavrard – laboratoire BMS

Les check-point inhibiteurs



D'après JAMA Oncology April 2015



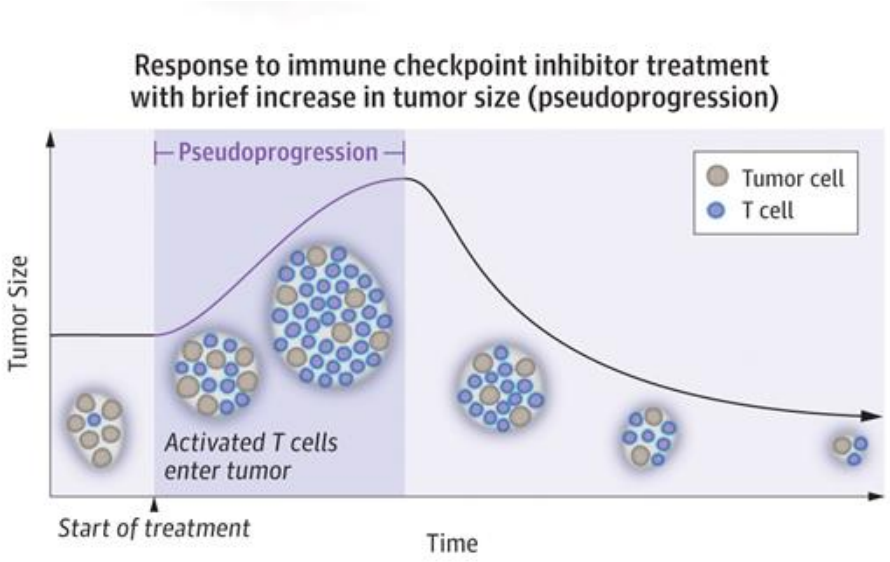
« Les + connus »

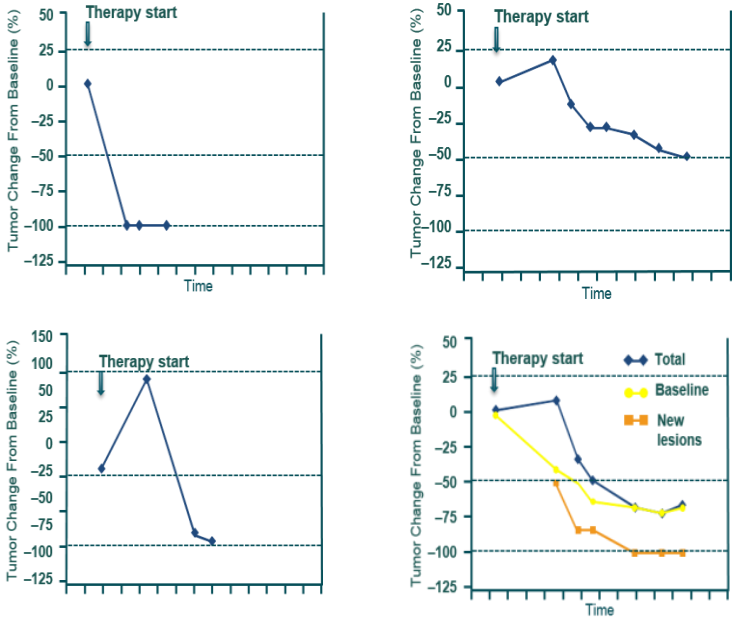
CTLA4 mAb: Ipilimumab

Anti-PD1 mAb: nivolumab, pembrolizumab, pidizulomab

Particularités de l'immuno-thérapie

- Réponses différentes par rapport aux réponses aux traitements conventionnels avec une efficacité parfois retardée et la notion de progression initiale avant régression
- Une MS durable peut être en rapport avec une efficacité antitumorale
- Nécessité de tolérance d'une progression minime infra-clinique



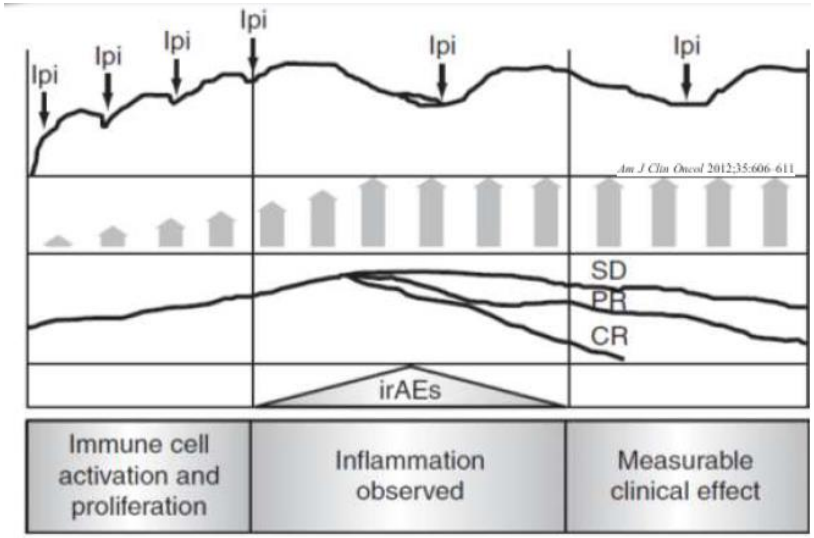


Adapted from Wolchok JD, et al. Clin Cancer Res. 2009;15:7412–7420;

Particularités de l'immuno-thérapie

- Tolérance: Notion d'irAEs « Immune reactive adverse effects »

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



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 (2–28)	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.

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

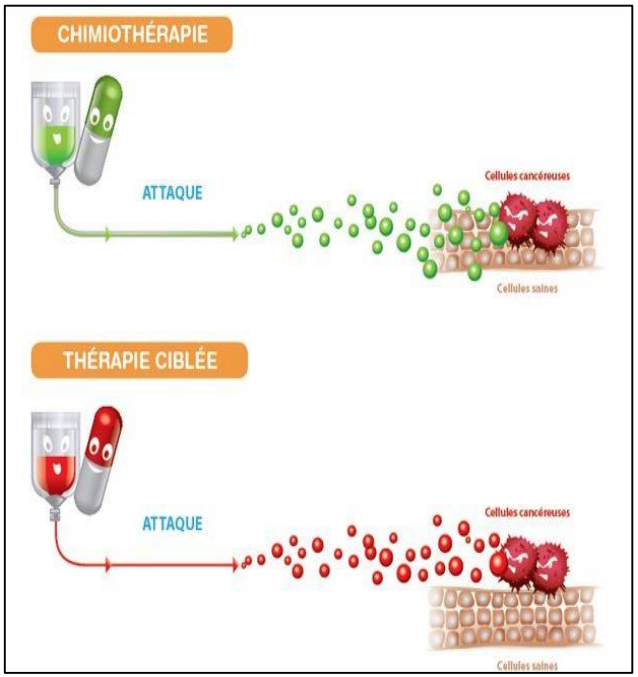
Table 2. Drug-Related Adverse Events in the 23 Patients.*

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

Tumeurs solides : Evaluation thérapeutique



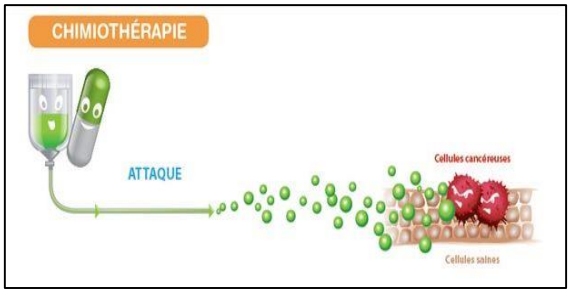
Critères morphologiques

	WHO	RECIST v1.1
Measurement of tumour burden	Bidimensional	Unidimensional
Maximum number of target lesions	10	5
Classification of new lesions	PD	PD
CR	Disappearance of all lesions	Disappearance of all lesions
PR	≥50% decrease in the tumour burden	≥30% decrease in the tumour burden
SD	Neither PR nor PD	Neither PR nor PD
PD	≥25% increase in tumour burden New lesions	≥20% increase and ≥5mm absolute increase in tumour burden New lesions

Critères métaboliques

PERCIST 2009
SUVpeak, normalized to lean body mass (SUL)
SUL increase by at least 30% and increase in by at least 0.8 SUL units of the target lesion – Or Development of at least one new lesion – Or – Increase in target lesion size by 30% – Or – Unequivocal progression of non-target lesions
Increase or decrease of SUL by less than 30%
Decrease of SUL by > = 30% and at least 0.8 SUL units difference – And- No new FDG-avid lesions, – And – No increase in size > 30% of the target lesion – And – No increase in SUL or size of non-target lesion
FDG uptake indistinguishable from surrounding background – And – SUL less than liver.

Lymphomes: Evaluation thérapeutique



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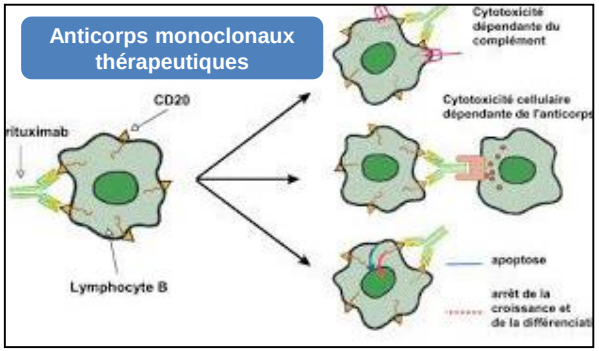


VOLUME 32 · NUMBER 27 · SEPTEMBER 20 2014

JOURNAL OF CLINICAL ONCOLOGY

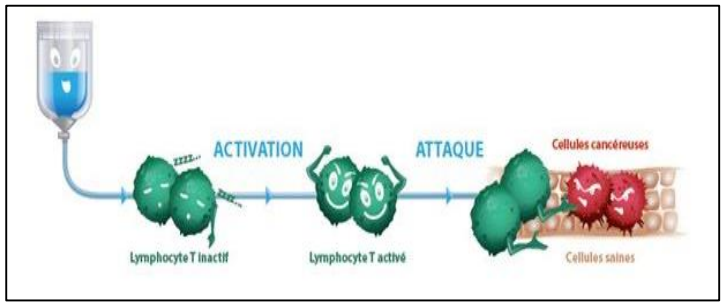
SPECIAL ARTICLE

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

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on EPS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	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
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

Tumeurs solides, Lymphomes : Evaluation thérapeutique de l'immunothérapie



irAEs

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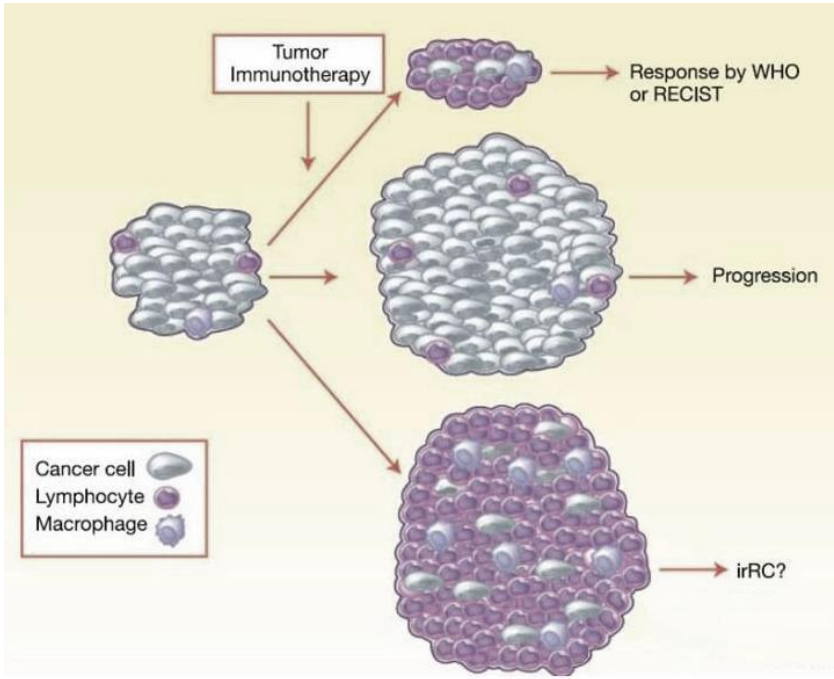
RECIST?

LUGANO?

PERCIST?



NOUVEAUX CRITERES?

Immune-related Response Criteria (irRC)[31]

- irCR, complete disappearance of all lesions (whether measurable or not, and no new lesions), and confirmation by a repeat consecutive assessment no less than 4 weeks from the date first documented
- irPR, decrease in tumor burden ≥50% relative to baseline confirmed by a consecutive assessment at least 4 weeks after first documentation
- irSD, not meeting the criteria for irCR or irPR, in absence of irPD
- irPD, increase in tumor burden ≥ 25% relative to nadir (minimum recorded tumor burden) and confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented

Cancer Therapy: Clinical

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]

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

31 - Wolchok JD, Hoos A, O'Day S, et al. **Guidelines for the evaluation of immune therapy activity in solid tumors: Immunerelated response criteria**. Clin Cancer Res 2009;15:7412-7420

VOLUME 34 · NUMBER 13 · MAY 1, 2016

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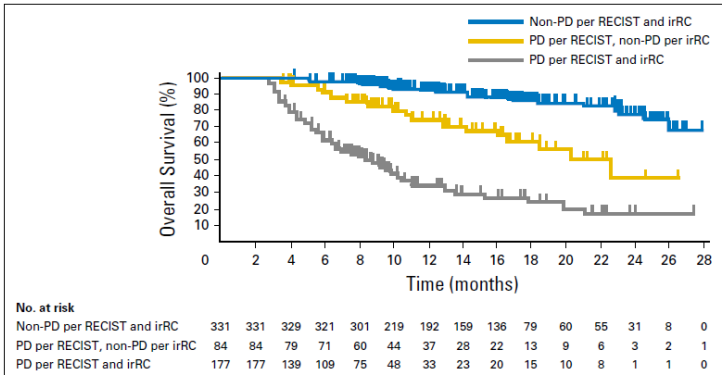
ORIGINAL REPORT



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

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

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	

D'après cette étude les critères RECIST sous-estiment la réponse chez 15% des patients

Hodi et al. JCO 2016

Vers Ir-RECIST?

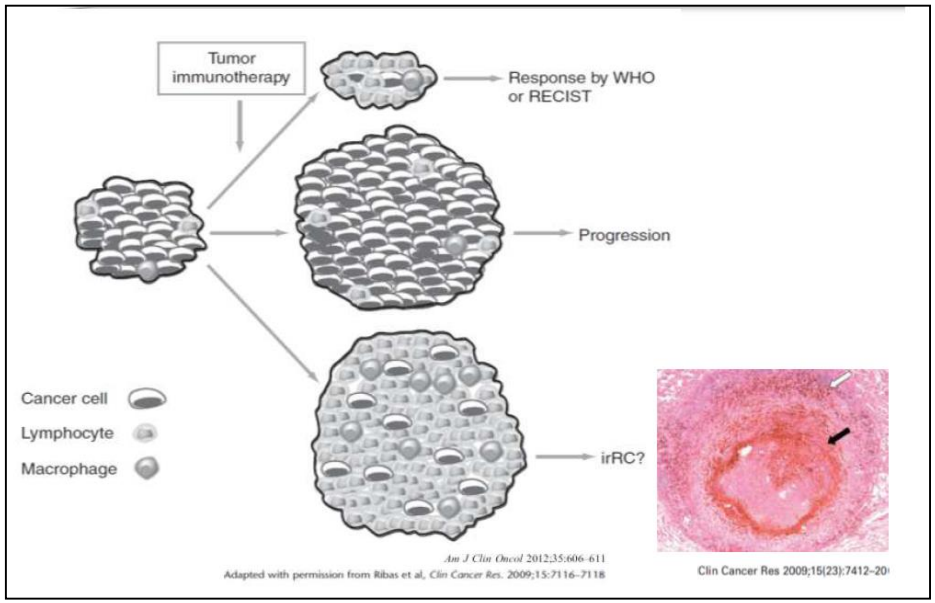
Table 1 Summary of the major differences between WHO, RECIST v1.1, irRC and IrRECIST classification

	WHO	RECIST v1.1	irRC	IrRECIST
Measurement of tumour burden	Bidimensional	Unidimensional	Bidimensional	Unidimensional
Maximum number of target lesions	10	5	10 visceral, 5 cutaneous	5
Classification of new lesions	PD	PD	Added to tumour burden	Added to tumour burden
CR	Disappearance of all lesions	Disappearance of all lesions	Disappearance of all lesions	Disappearance of all lesions
PR	≥50% decrease in the tumour burden	≥30% decrease in the tumour burden	≥50% decrease in tumour burden	≥30% decrease in the tumour burden
SD	Neither PR nor PD	Neither PR nor PD	Neither PR or PD	Neither PR or PD
PD	≥25% increase in tumour burden New lesions	≥20% increase and ≥5mm absolute increase in tumour burden New lesions	≥25% increase in tumour burden	≥20% increase and ≥5mm absolute increase in tumour burden

Abbreviations: *WHO*, World Health Organisation; *RECIST v1.1*, Response Evaluation Criteria In Solid Tumours version 1.1; *irRC*, Immune-related Response Criteria; *IrRECIST*, Immune-related Response Evaluation Criteria In Solid Tumours; *CR*, complete response; *PR*, partial response; *SD*, stable disease; *PD*, progressive disease

Wong, EJNM 2017

Quid de la TEP-FDG???



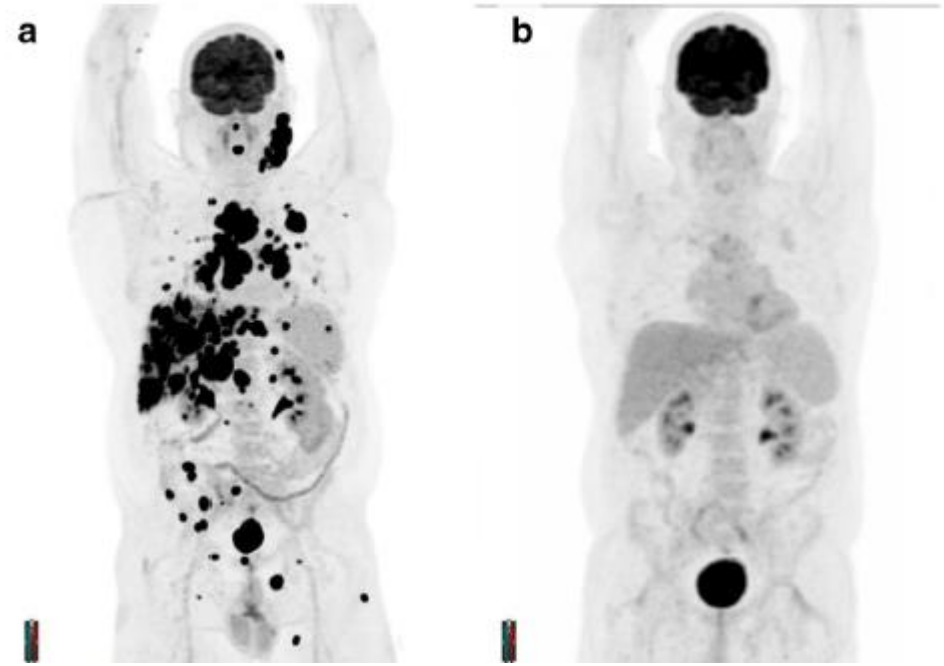
Augmentation de la SUV MAX:
Progression tumorale
ou
Réaction inflammatoire?

irAEs

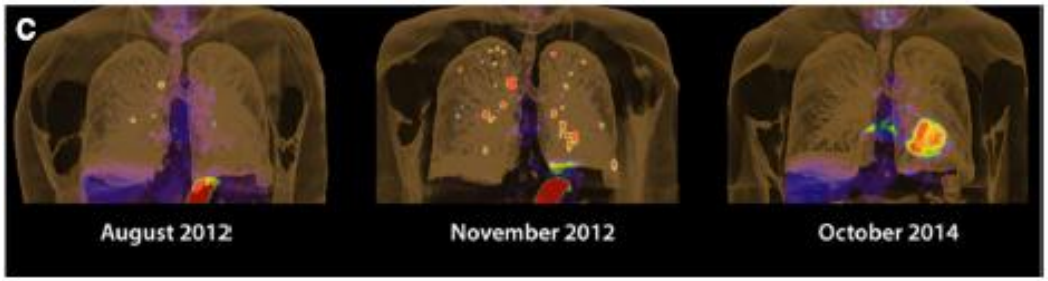
Related Adverse Events	Grade
Pancreatitis	3
Pneumonitis	3
Gastrointestinal inflammation	3
Stomatitis	3
Colitis	3

Apparition de nouvelles fixations:
Progression tumorale
ou
Manifestations immunes?

Thyroidite, sarcoidose, lésions spléniques, hépatiques…



RC 3 mois après le début de traitement par anti-PD1 d'un mélanome métastatique



Pseudo progression tumorale + « immune effect » suivi d'une RC métabolique à… 2 ans

Wong, EJNM 2017

Et le lymphome?

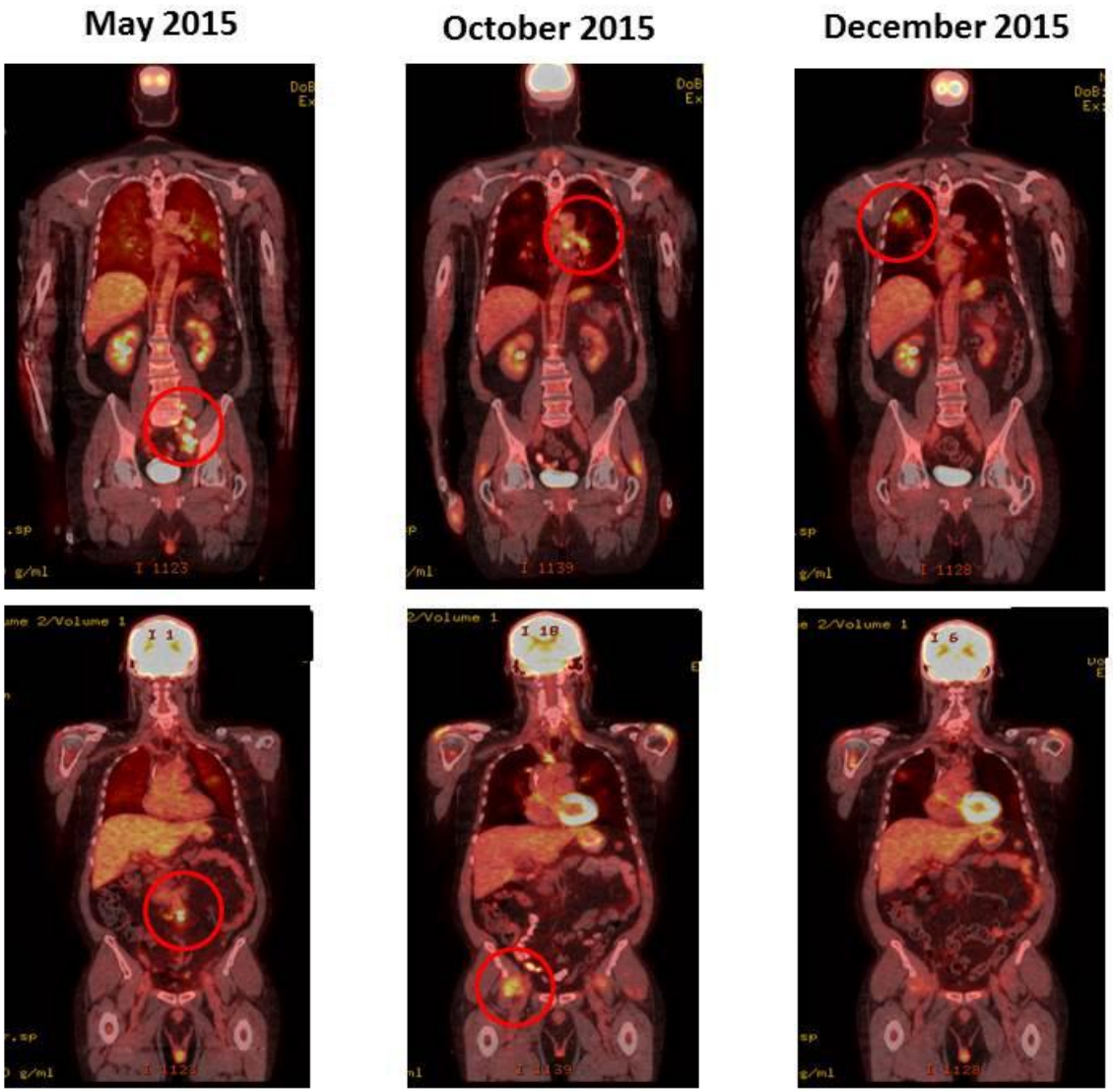
- Intérêt croissant des « checkpoints inhibiteurs » dans la maladie de Hodgkin

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

Stephen M. Ansell, M.D., Ph.D., Alexander M. Lesokhin, M.D., Ivan Borrello, M.D., Ahmad Halwani, M.D., Emma C. Scott, M.D., Martin Gutierrez, M.D., Stephen J. Schuster, M.D., Michael M. Millenson, M.D., Deepika Cattry, M.S., Gordon J. Freeman, Ph.D., Scott J. Rodig, M.D., Ph.D., Bjoern Chapuy, M.D., Ph.D., Azra H. Ligon, Ph.D., Lili Zhu, M.S., Joseph F. Grosso, Ph.D., Su Young Kim, M.D., Ph.D., John M. Timmerman, M.D., Margaret A. Shipp, M.D., and Philippe Armand, M.D., Ph.D.

NEJM 2015

- Comment évaluer la réponse?
  - Lugano? Mais quid de la pseudo-progression..
  - irRC: critères non adaptés et uniquement « morphologiques »



Cheson, Blood 2016

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

Cheson, Blood 2016

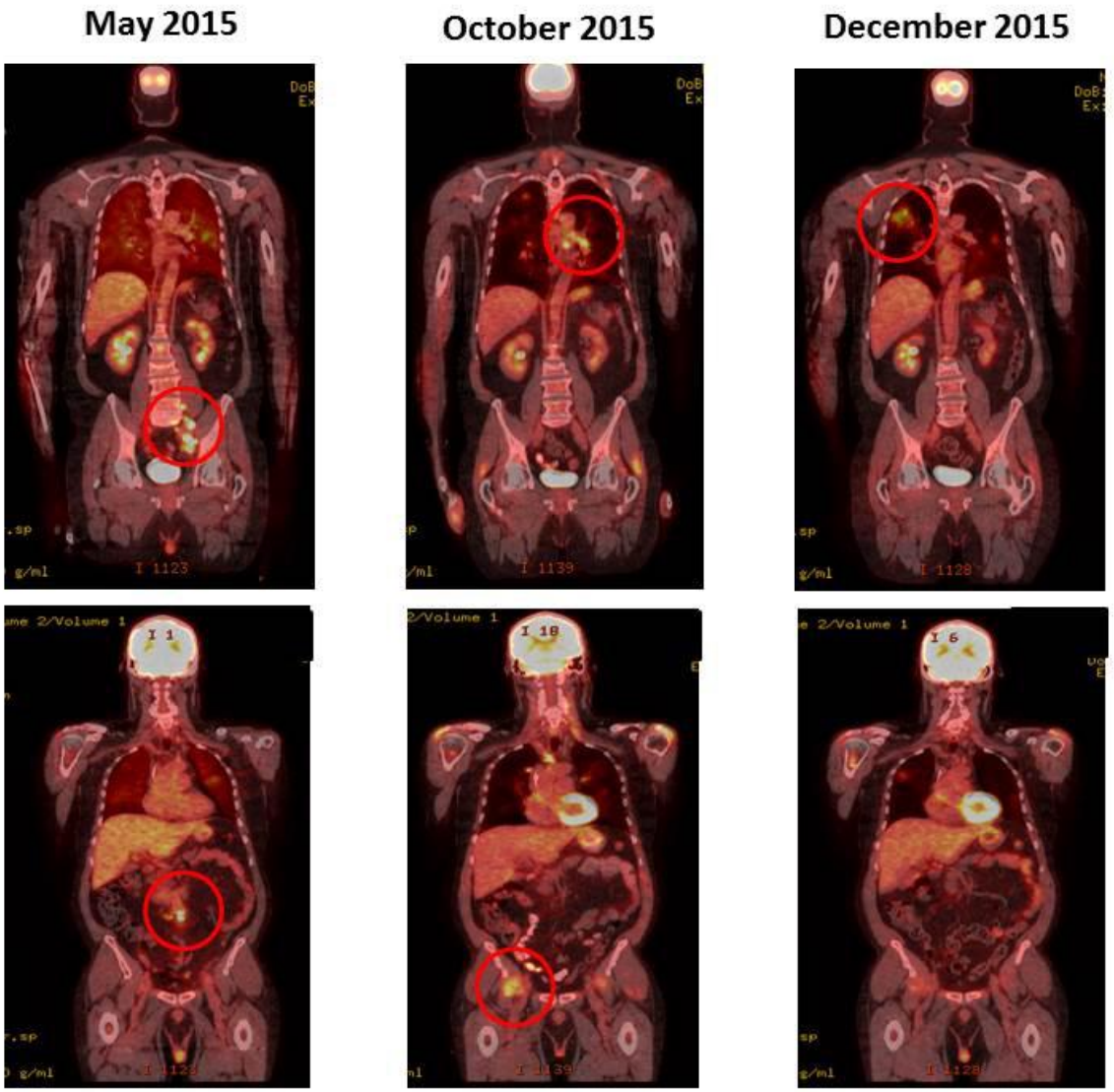
Indeterminate Response (IR)

IR1: Augmentation de la charge tumorale globale (évaluée par la somme du produit des diamètres [SPD]) de ≥50% de jusqu'à 6 lésions mesurables au cours des 12 premières semaines de traitement, **sans détérioration clinique**

IR2: Augmentation de la charge tumorale globale < 50% avec soit a) Apparition de nouvelles lésions ou b) croissance de ≥50% d'une ou plusieurs lésions existantes à tout moment pendant le traitement

IR3: Augmentation de la captation du FDG d'une ou de plusieurs lésions sans augmentation concomitante de la taille ou du nombre de lésions

Contrôle à 12 semaines (**ou avant si signes cliniques**) pour réévaluer la réponse



PET/CT demonstrating pseudo-progression in a patient on nivolumab for Hodgkin lymphoma. May 2015, pre-treatment, October and December 2015 shows transient flares in different nodal groups without overall progression in the original target lesions.

Cheson, Blood 2016

Conclusion

- Pour l'instant pas d'étude prospective évaluant la place de la TEP-FDG pour la réponse aux immunothérapies

- Beaucoup de question subsistent: Quel délai? Quels critères? PERCIST? Nécessité de définir des critères Ir-PERCIST? LYRIC?

- Nécessité d'études prospectives++++

Quelques recommandations:

- Attention aux faux-positifs liés aux effets immunitaires : colite, sarcoidose-like, adénopathie, pneumopathie/PID, hépatite, thyroïdite, pancréatite.

- Intérêt majeur de confronter les résultats aux données cliniques (traitement, contexte, symptômes).

- Attention aux pseudo-progressions tumorales par infiltration inflammatoire de la tumeur.

- Intérêt +++ d'un examen de confirmation quelques semaines plus tard (au moins 4 semaines?)

A propos des « Check-points inhibiteurs »

A. Ils agissent en inhibant l'action des lymphocytes T contre les cellules tumorales
B. Ils agissent en empêchant l'inactivation des lymphocytes T par les cellules tumorales
C. La réponse « optimale » au traitement est toujours observée dans les semaines qui suivent l'initiation du traitement
D. La réponse optimale au traitement peut être observée plusieurs mois après l'initiation du traitement
E. Des pseudo-progressions tumorales peuvent être observées avec ces traitements

A propos des Check-points inhibiteurs

A. Ils agissent en inhibant l'action des lymphocytes T contre les cellules tumorales
B. Ils agissent en empêchant l'inactivation des lymphocytes T par les cellules tumorales
C. La réponse « optimale » au traitement est toujours observée dans les semaines qui suivent l'initiation du traitement
D. La réponse optimale peut être observée plusieurs mois après l'initiation du traitement
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A propos de l'évaluation thérapeutique des « Check-points inhibiteurs »

A. Les critères « irRC » sont des critères basés sur l'évaluation morphologique.
B. Ces critères prennent en compte la notion de pseudo-progression tumorale
C. Ces critères sont adaptés pour l'évaluation des lymphomes
D. Les CPI ne sont pas efficaces dans les lymphopathies
E. Les critères LYRIC, critères basés sur les données morphologiques et métaboliques, sont proposés pour l'évaluation thérapeutique des hémopathies

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