Les traitement d'immunothérapie dans le cancer du poumon

Nicolas Girard

Liens d’intérêt

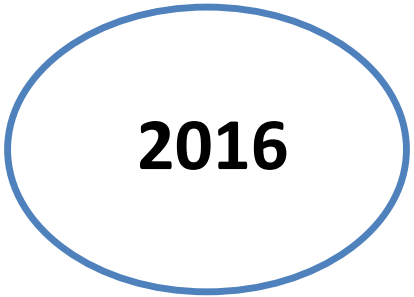
- Recherche clinique:
- MSD

- Symposia:
- Astra-Zeneca
- Hoffmann-La Roche
- BMS

- Réunions d’experts:
- Astra-Zeneca
- BMS
- Hoffman-La Roche

- Invitation à des congrès:
- Hoffman-La Roche

L’immunothérapie dans le cancer du poumon

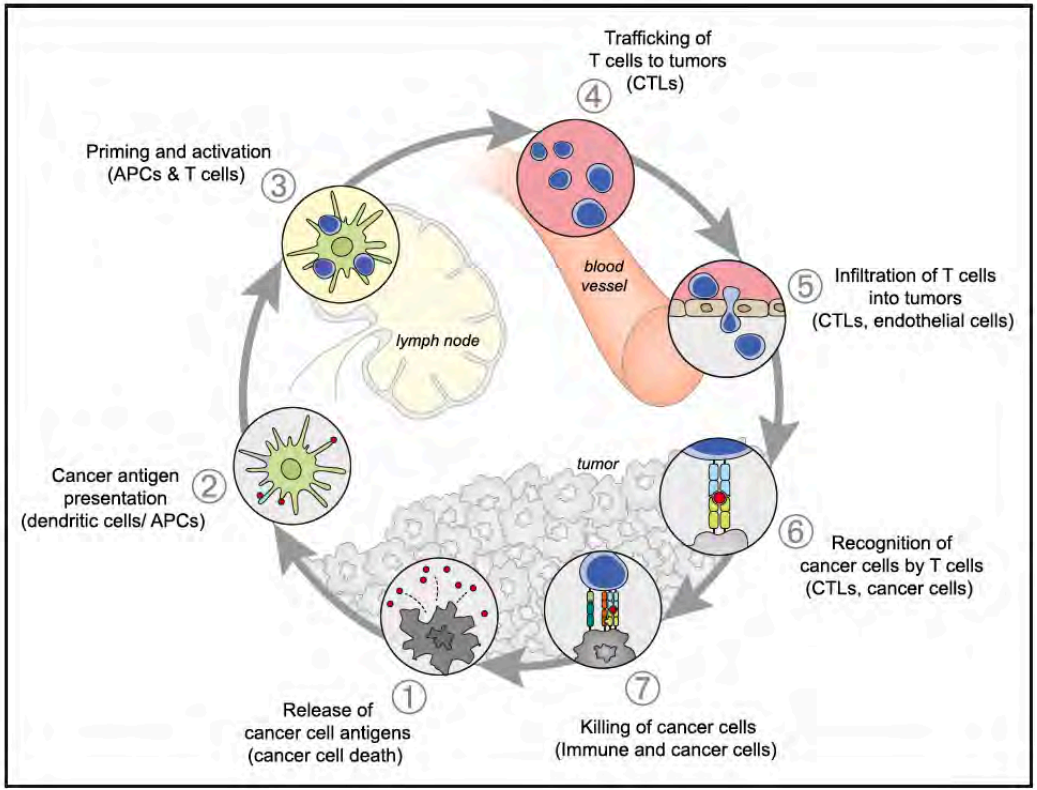


L’immunothérapie dans le cancer du poumon

Réponse immunitaire anti-tumorale

2016

La réponse immunitaire anti-tumorale



Chen et al. Immunity 2013;39:1

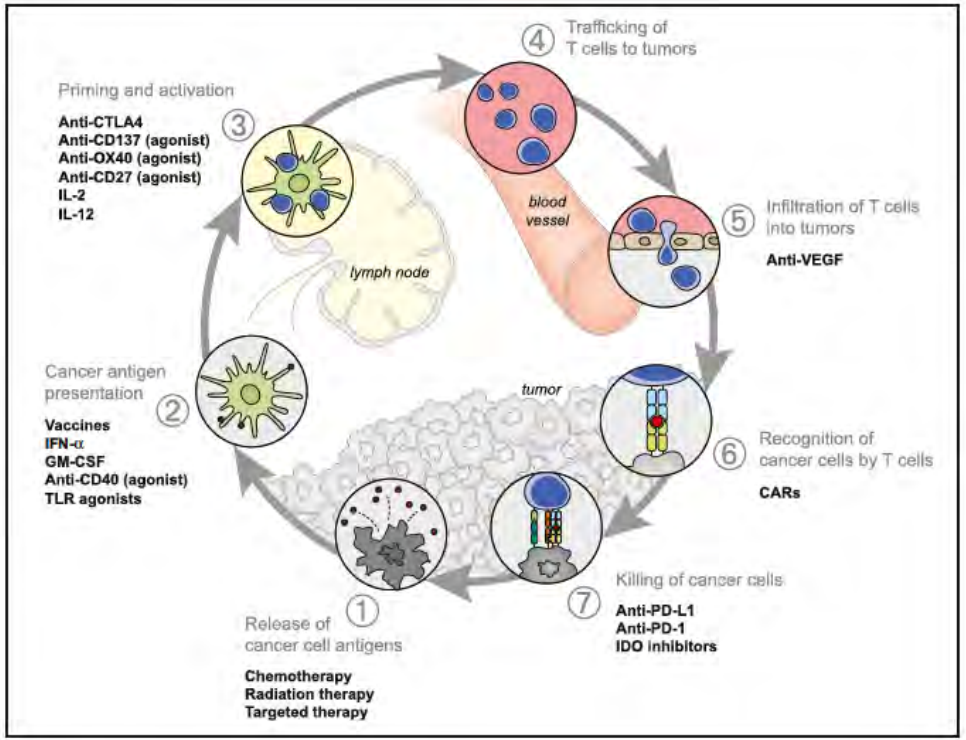
L’immunothérapie dans le cancer du poumon

Réponse immunitaire anti-tumorale

Stratégies d’immunothérapie

2016

Réactiver la réponse immunitaire anti-tumorale



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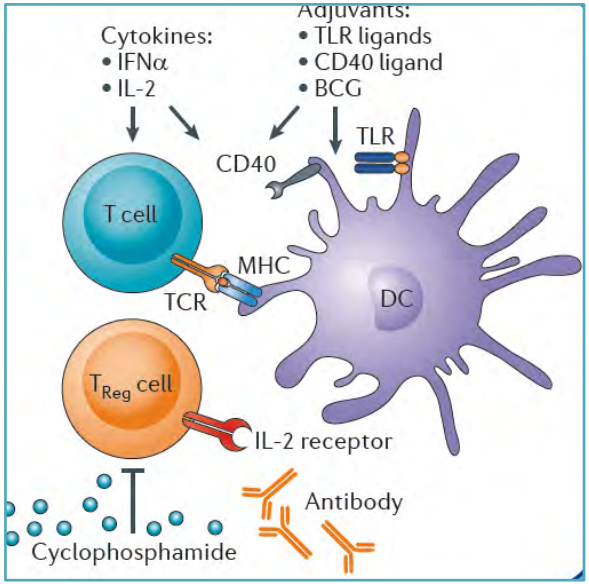
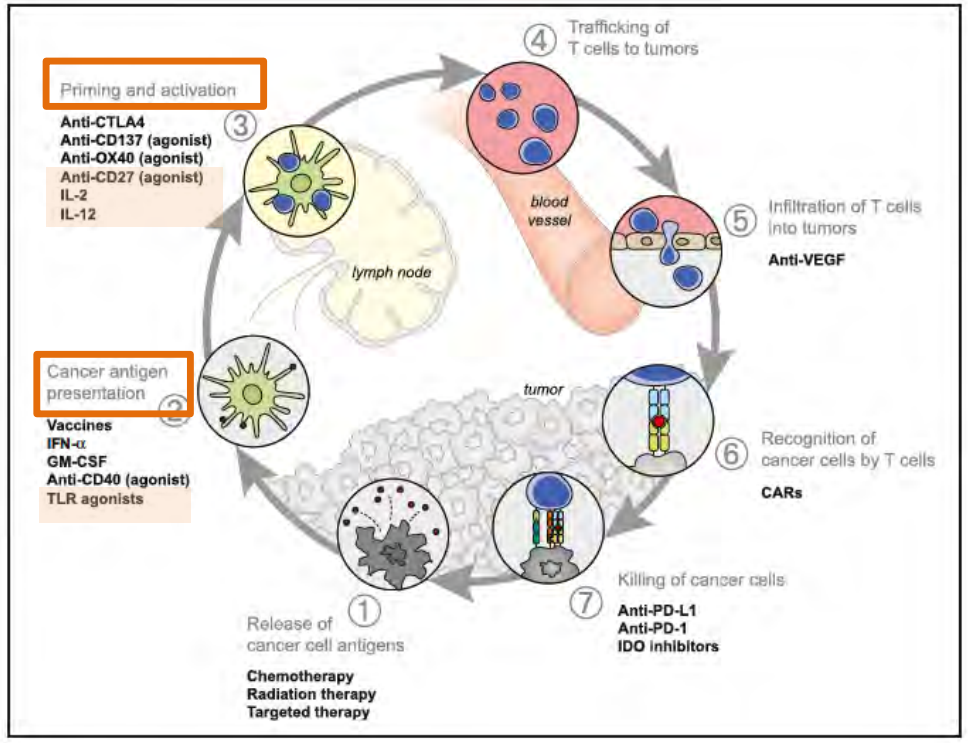
Lesterhuis et Punt. Nature Rev Cancer. Online poster

Réactiver la réponse immunitaire anti-tumorale

Stimulation globale de l'immunité innée

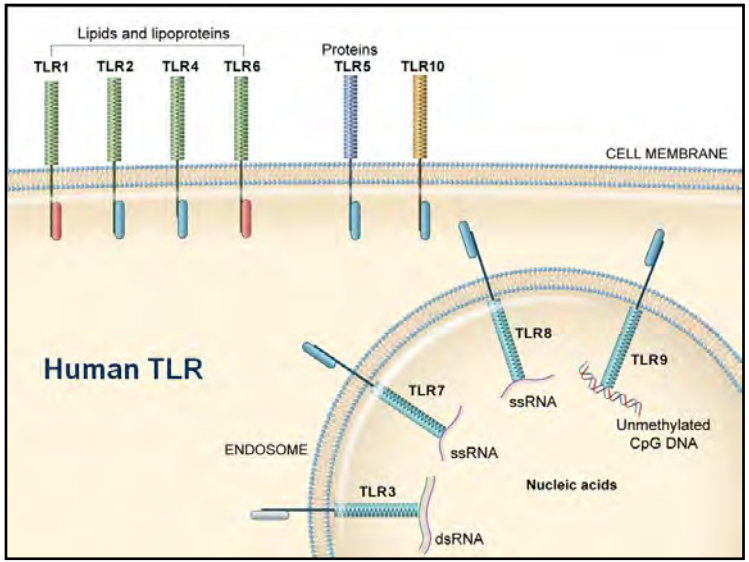




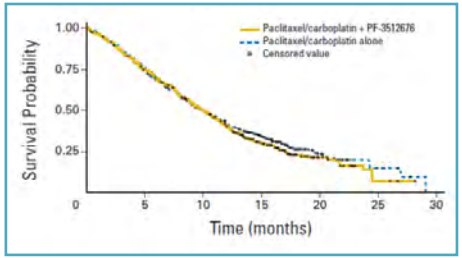
Chen et al. Immunity 2013;39:1
Lesterhuis et Punt. Nature Rev Cancer. Online poster

Stimulation gobale de l'immunité

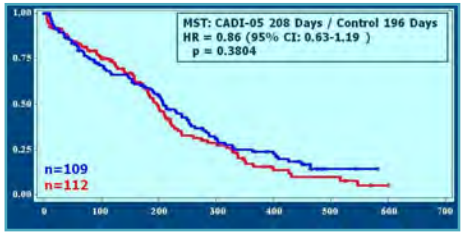
Agonistes des récepteurs Toll-like



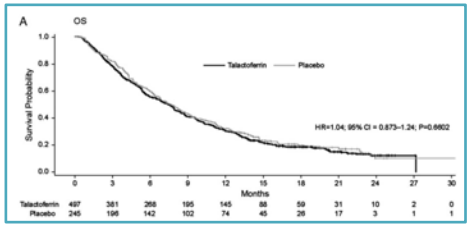
- **PF-3512676, agoniste TLR-9**
  - → Essai de phase III
  - → 828 patients
  - → Avec chimiothérapie, vs. placebo



- **Cadi-05, agoniste TLR-2**
  - → Essai de phase III
  - → 223 patients
  - → Avec chimiothérapie, vs. placebo

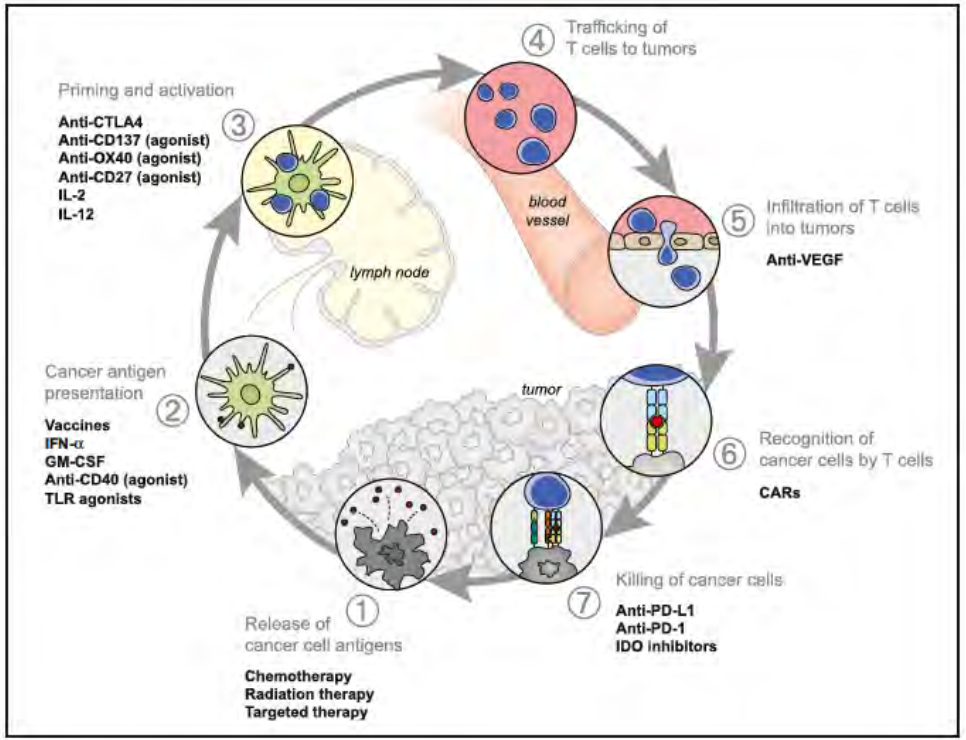


- **Talactoferrine**
  - → Essai de phase III FORTIS-M
  - → 742 patients
  - → Traitement exclusif, vs. placebo



Ramalingam et al. Ann Oncol 2013;24:2875; Hirsch et al. J Clin Oncol 2011; 29:2667; Belani et al. ASCO 2011; abstract 82145

Réactiver la réponse immunitaire anti-tumorale



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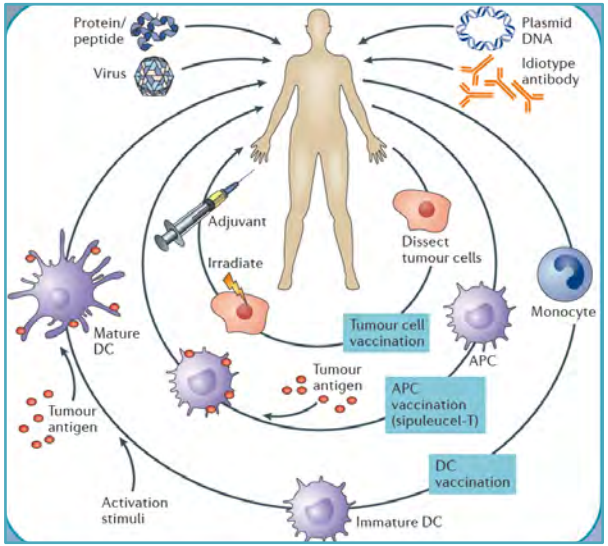
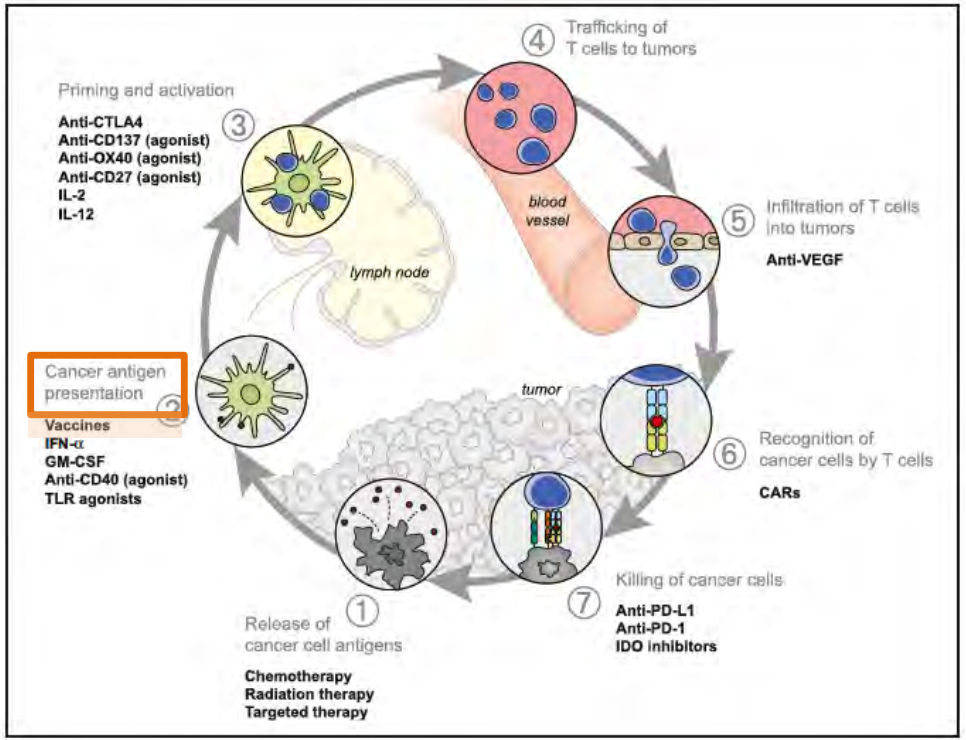
Réactiver la réponse immunitaire anti-tumorale

Vaccination contre un antigène tumoral





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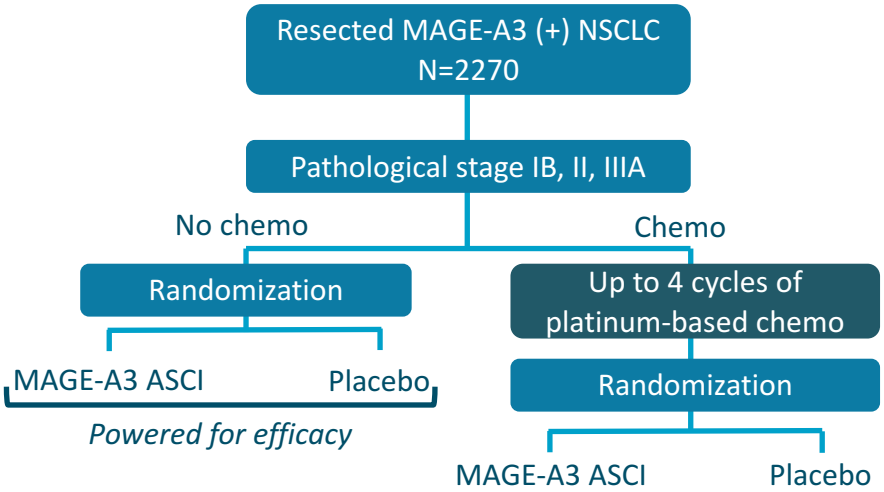
Lesterhuis et Punt. Nature Rev Cancer. Online poster

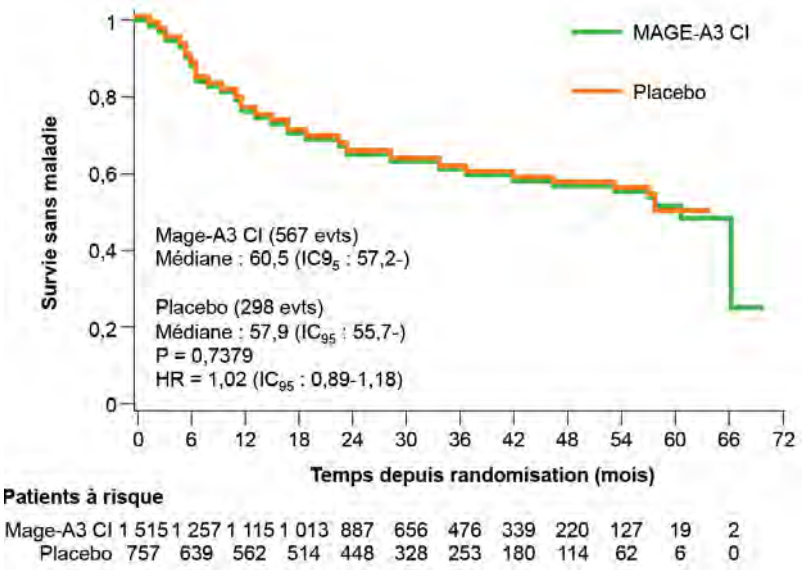
Vaccination anti-tumorale

Vaccination contre l'antigène MAGE-A3



Primary Endpoint: disease-free survival

Sélection IHC
Profil immun?



Vansteenkiste et al. ESMO 2014, abstract 1173O

Vaccination anti-tumorale

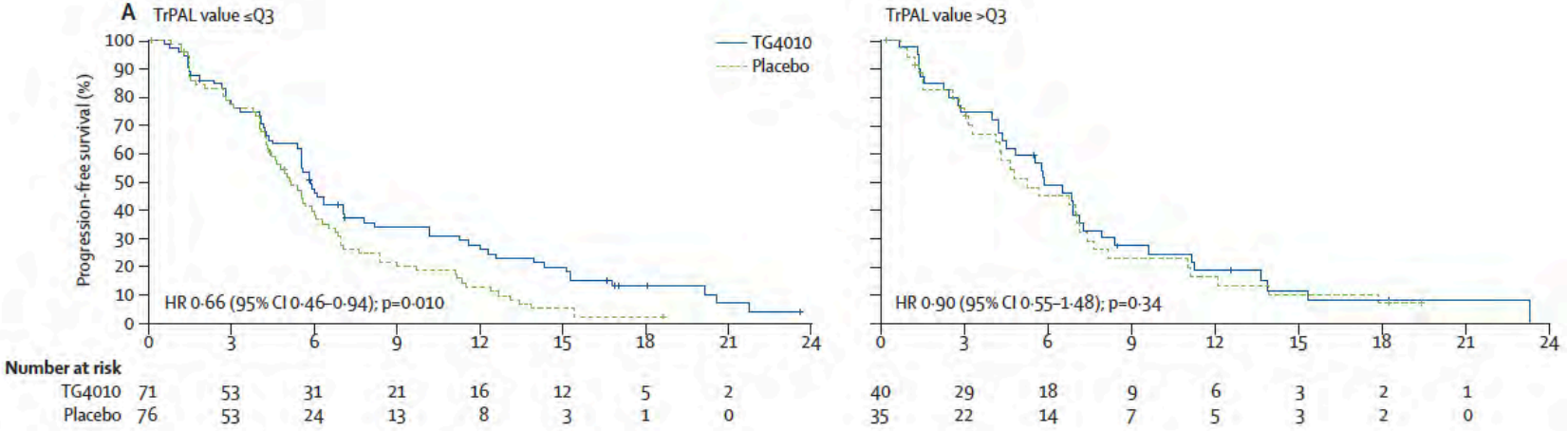
Vaccination contre l'antigène MUC-1

TG4010 immunotherapy and first-line chemotherapy for advanced non-small-cell lung cancer (TIME): results from the phase 2b part of a randomised, double-blind, placebo-controlled, phase 2b/3 trial

Elisabeth Quoix, Hervé Lena, Gyorgy Losonczy, Frédéric Forget, Christos Chouaid, Zsolt Papai, Radj Gervais, Christian Ottensmeier, Aleksandra Szczesna, Andrzej Kazarnowicz, Joseph T Beck, Virginie Westeel, Enriqueta Felip, Didier Debieuvre, Anne Madroszyk, Julien Adam, Gisèle Lacoste, An

MUC1 >50% of the tumor cells

CD16, CD56, CD69 triple-positive activated lymphocytes (TrPAL)



Lancet Oncol 2015; 10.1016/S1470-2045(15)00554-9

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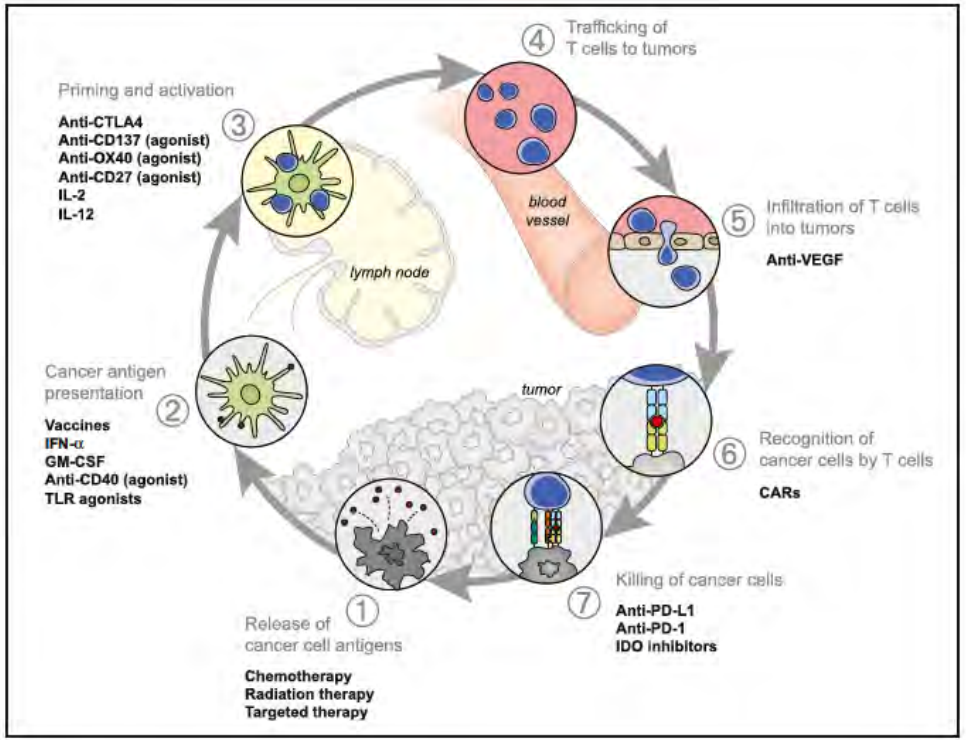

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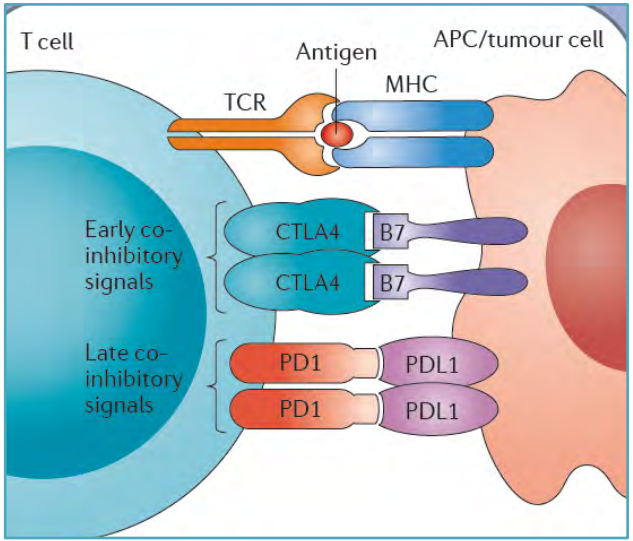
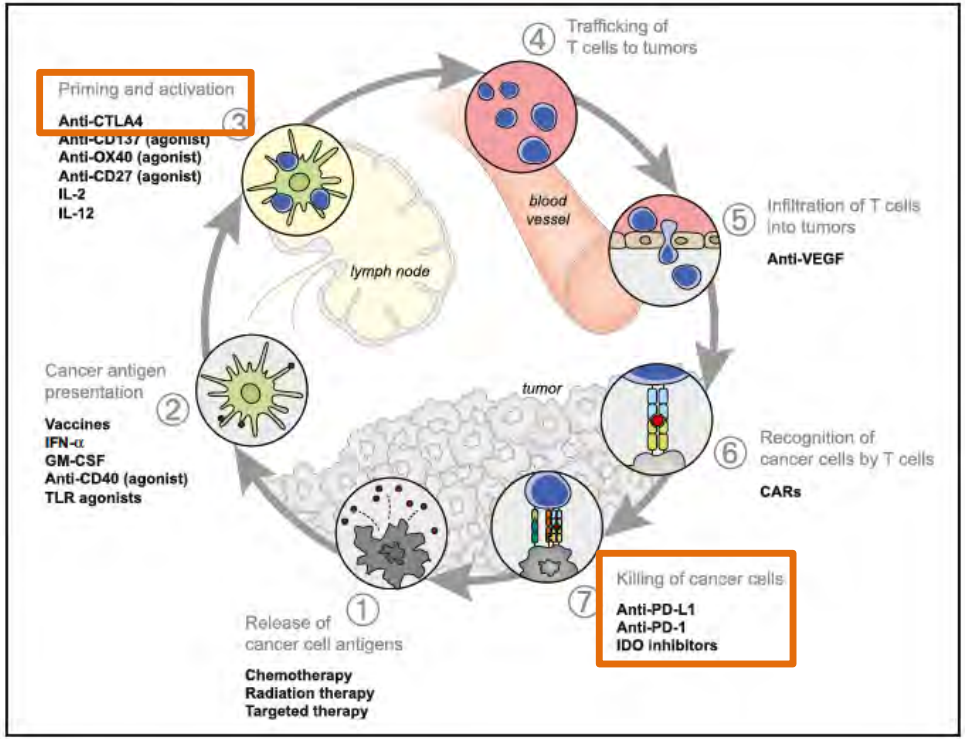
Inhibition des points de contrôle





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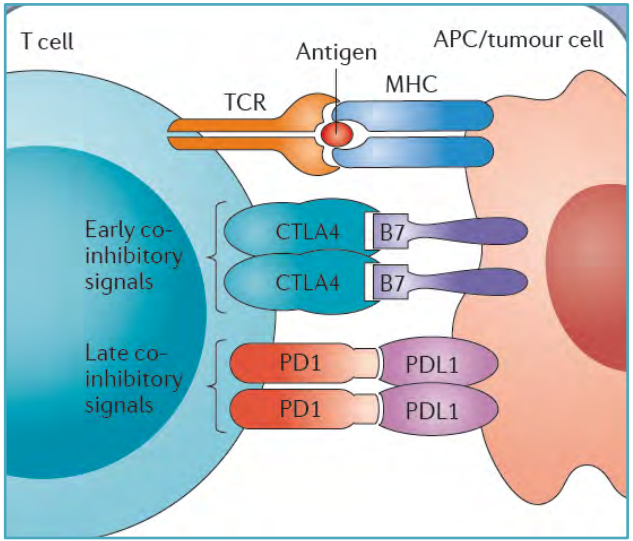

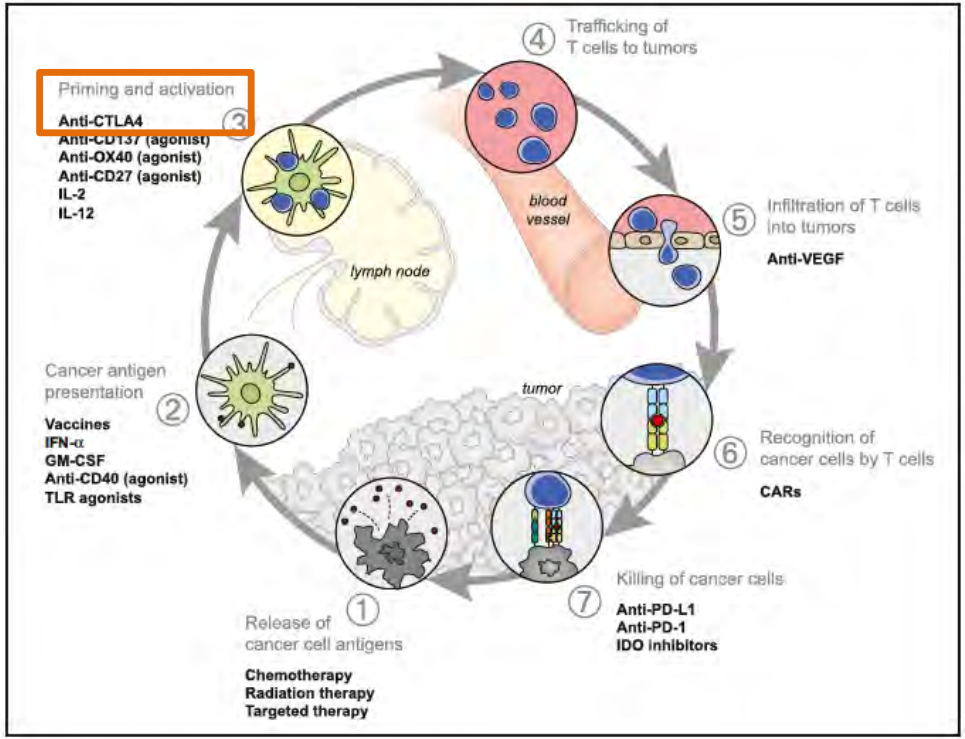

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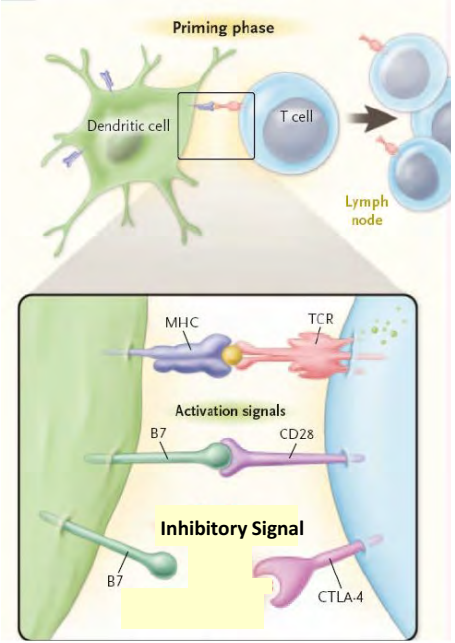
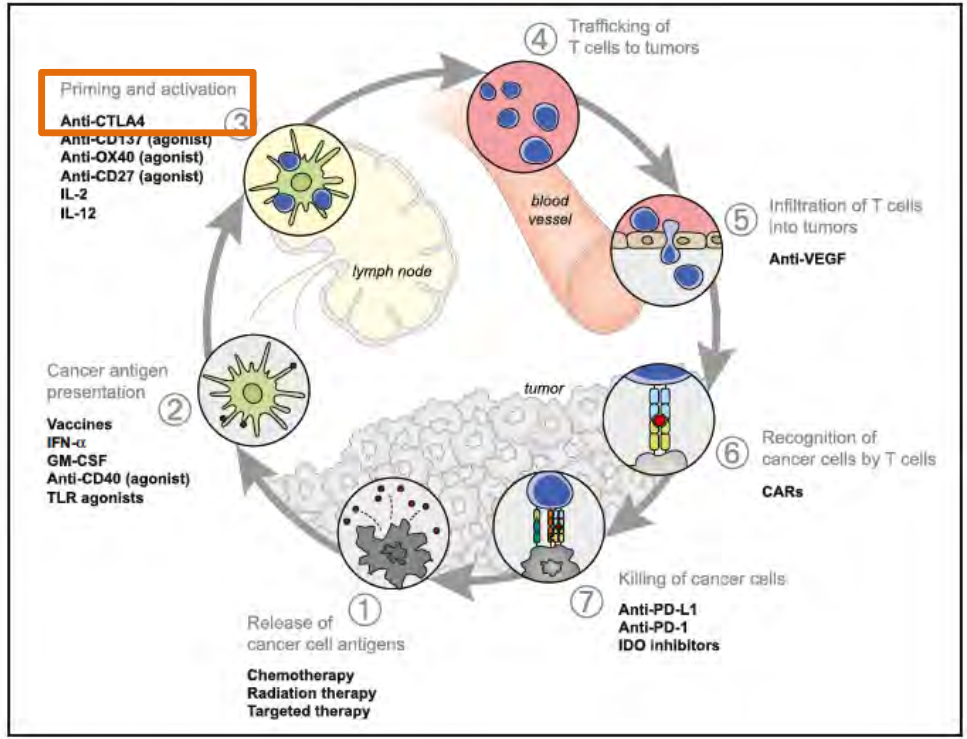
Inhibition des points de contrôle : CTLA-4





Chen et al. Immunity 2013;39:1
Ribas. N Engl J Med 2012; 366:2517

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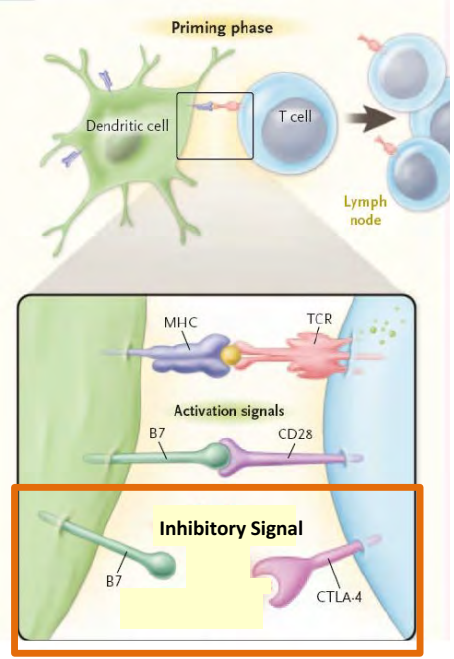

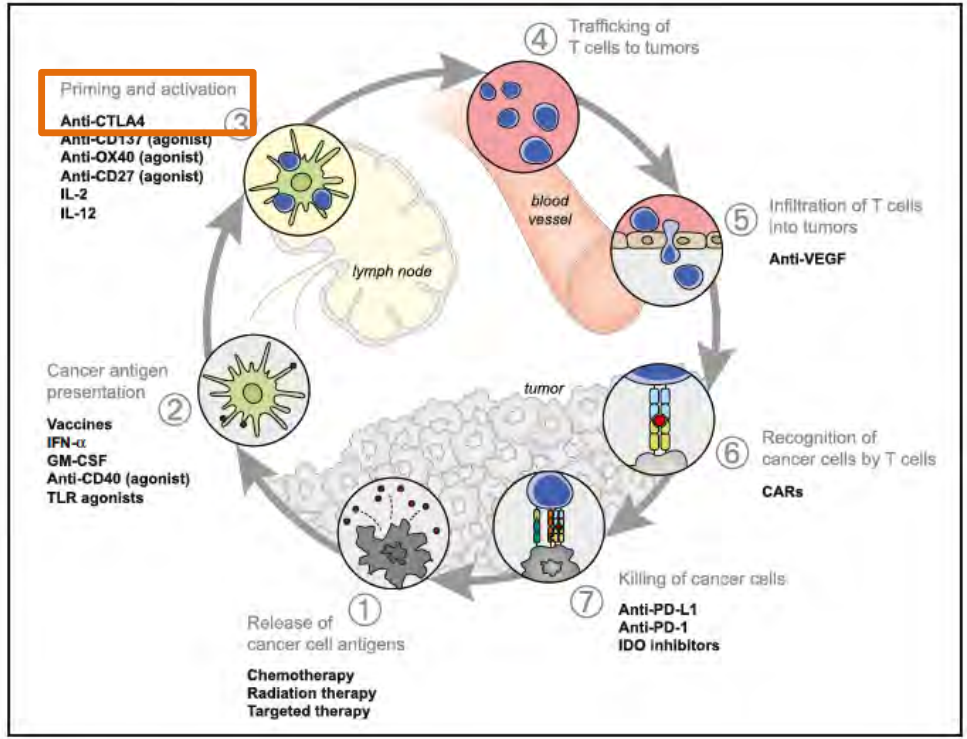

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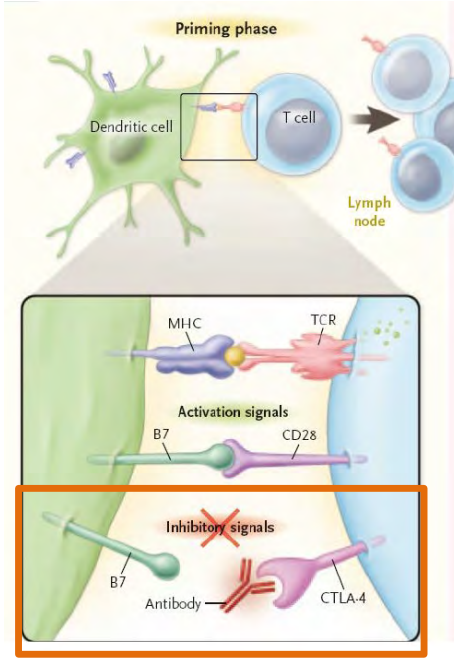

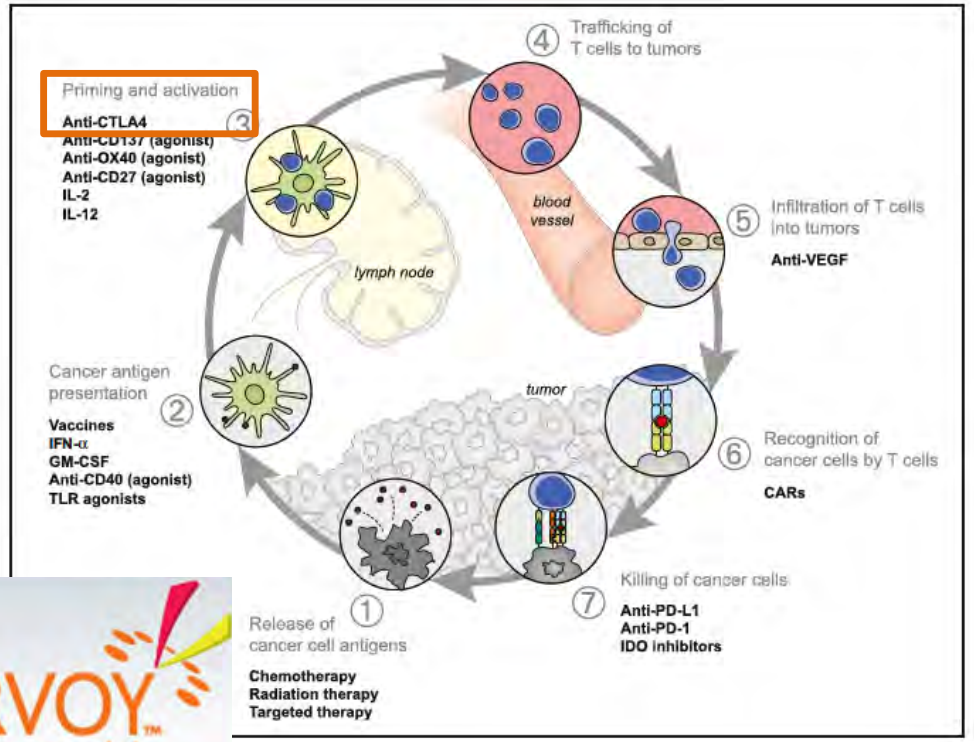

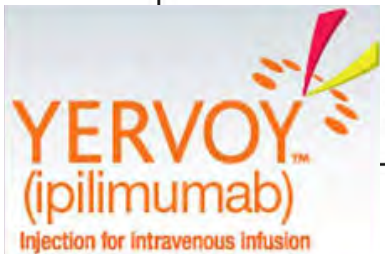

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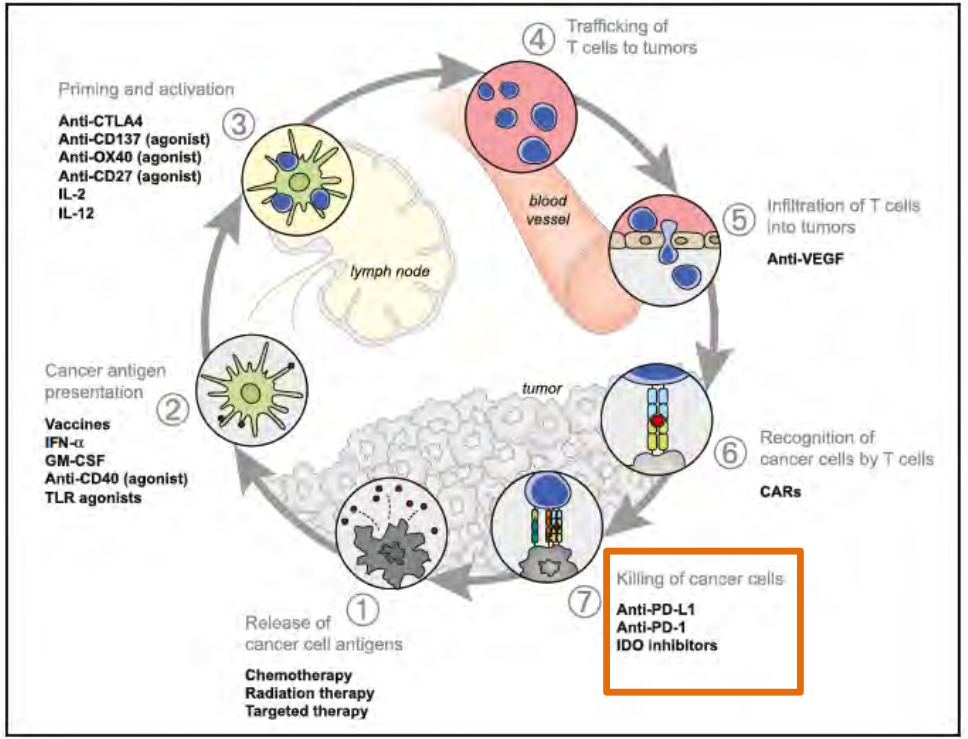
Inhibition des points de contrôle : PD-1 et PD-L1



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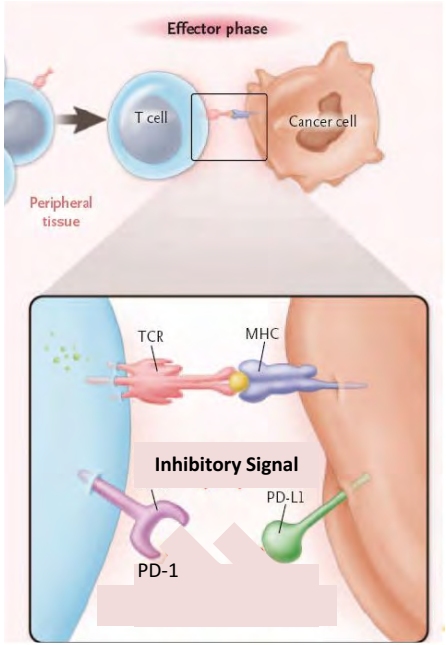

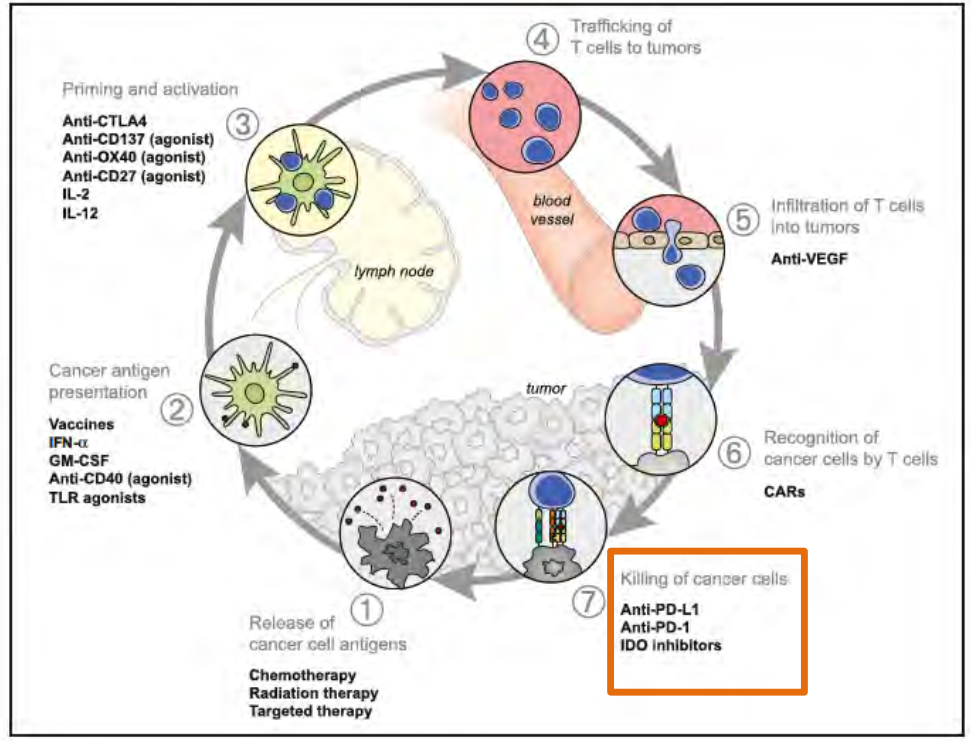

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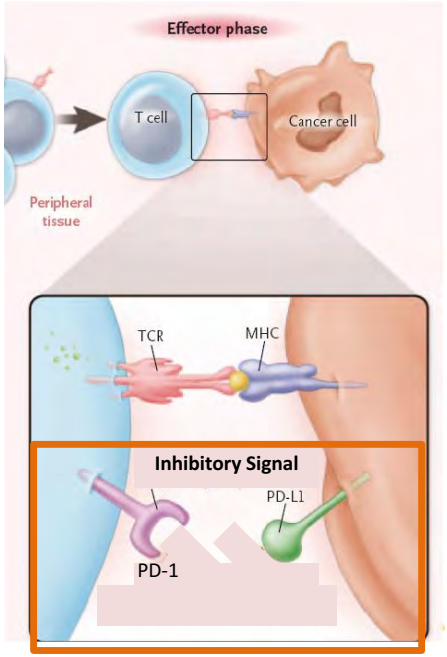

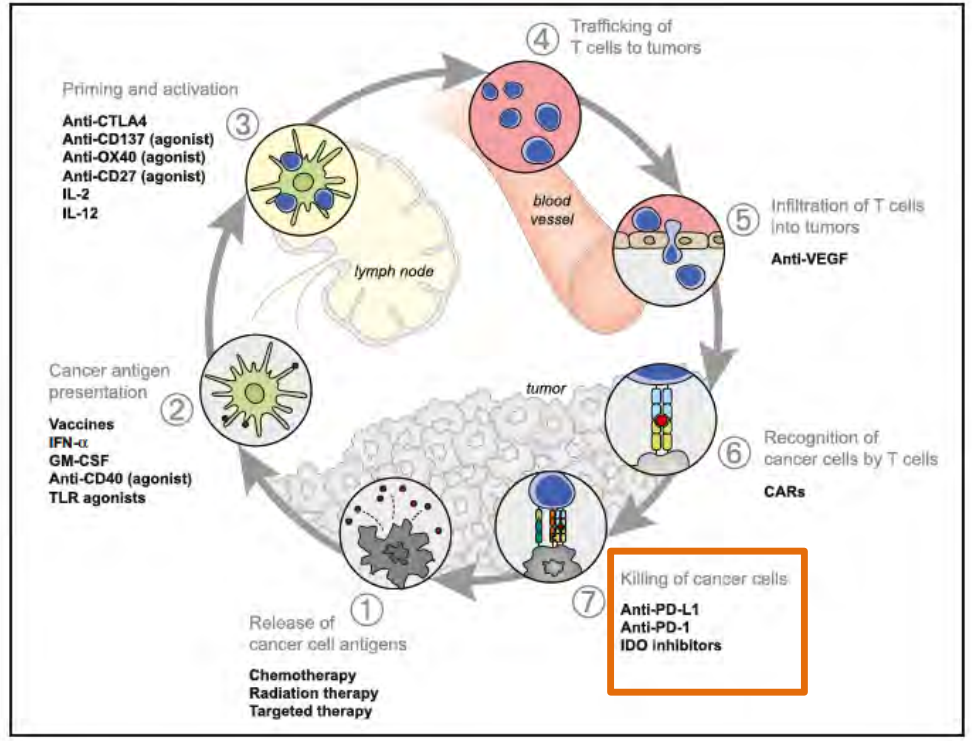

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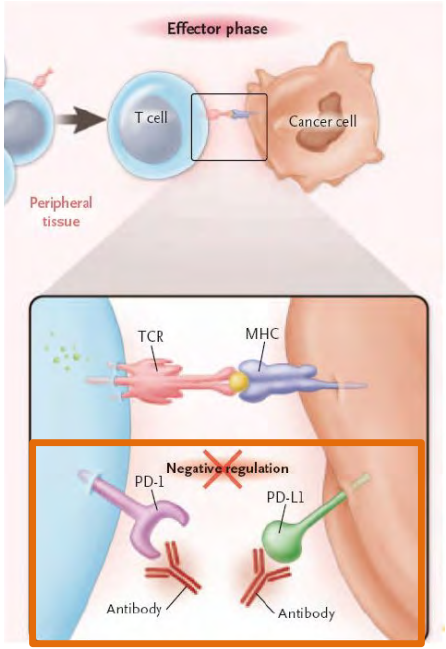

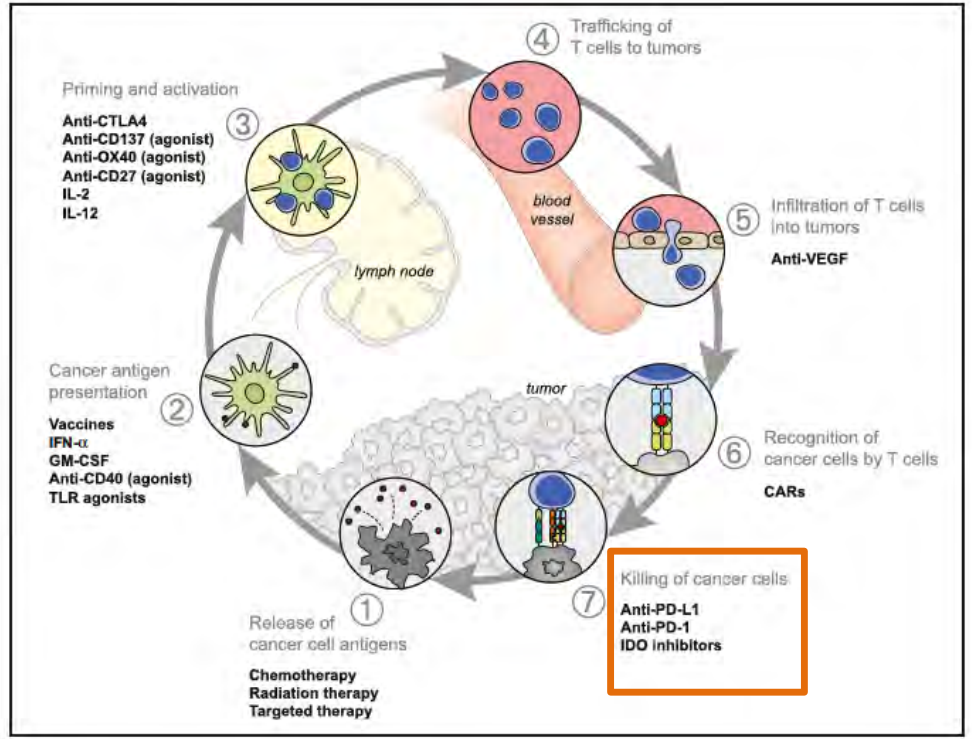

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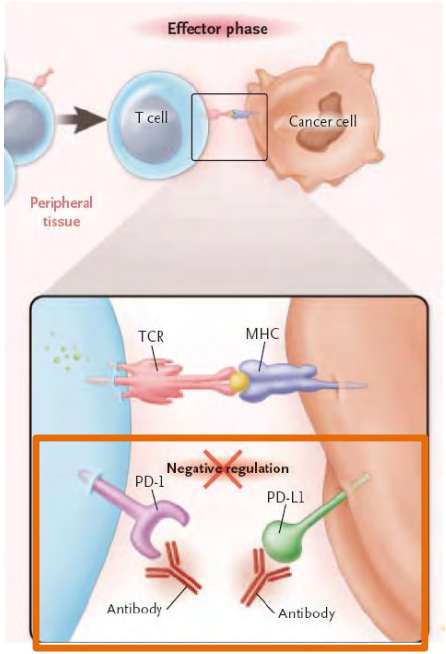

Cible	Anticorps	Type	Laboratoire
PD-1	Nivolumab	Humanisé IgG4	BMS
	Pembrolizumab	Humanisé IgG4	MSD
PD-L1	Durvalumab	IgG1	MedImmune/Astra-Zeneca
	Atezolizumab	IgG1	Genentech/Roche
	Avelumab	IgG1	Serono

Ribas. N Engl J Med 2012; 366:2517

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Inhibiteurs de PD-1
Profils d’efficacité

2016

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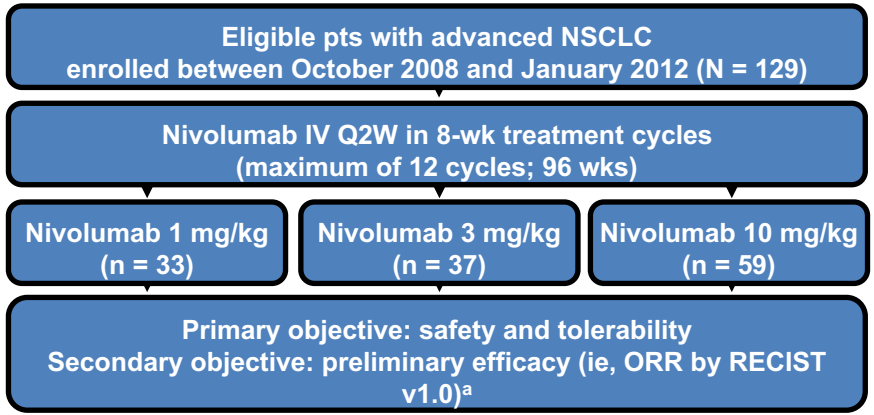
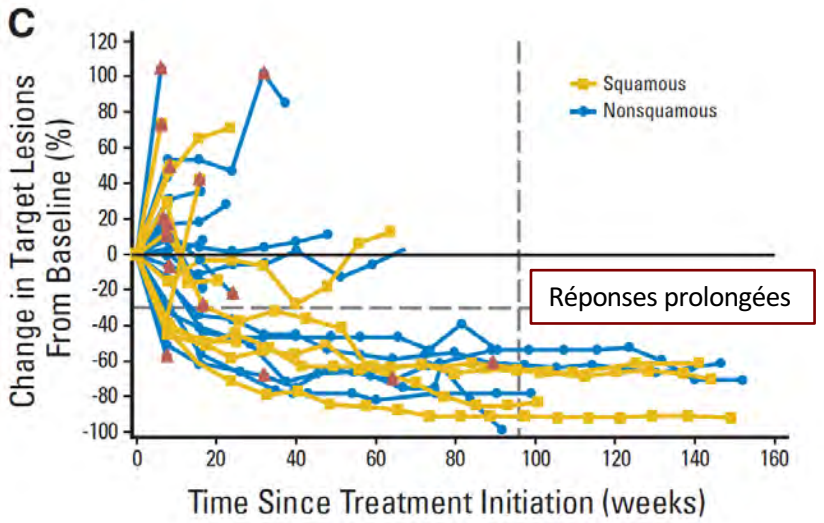
Nivolumab: essai de phase I, stades avancés réfractaires: CHECKMATE-003

Overall Survival and Long-Term Safety of Nivolumab (Anti–Programmed Death 1 Antibody, BMS-936558, ONO-4538) in Patients With Previously Treated Advanced Non–Small-Cell Lung Cancer

Scott N. Gettinger, Leora Horn, Leena Gandhi, David R. Spigel, Scott J. Antonia, Naiyer A. Rizvi, John D. Powderly, Rebecca S. Heist, Richard D. Carvajal, David M. Jackman, Lecia V. Sequist, David C. Smith, Philip Leming, David P. Carbone, Mary C. Pinder-Schenck, Suzanne L. Topalian, F. Stephen Hodi, Jeffrey A. Sosman, Mario Sznol, David F. McDermott, Drew M. Pardoll, Vindira Sankar, Christoph M. Ahlers, Mark Salvati, Jon M. Wigginton, Matthew D. Hellmann, Georgia D. Kollia, Ashok K. Gupta, and Julie R. Brahmer





J Clin Oncol 2016; in press

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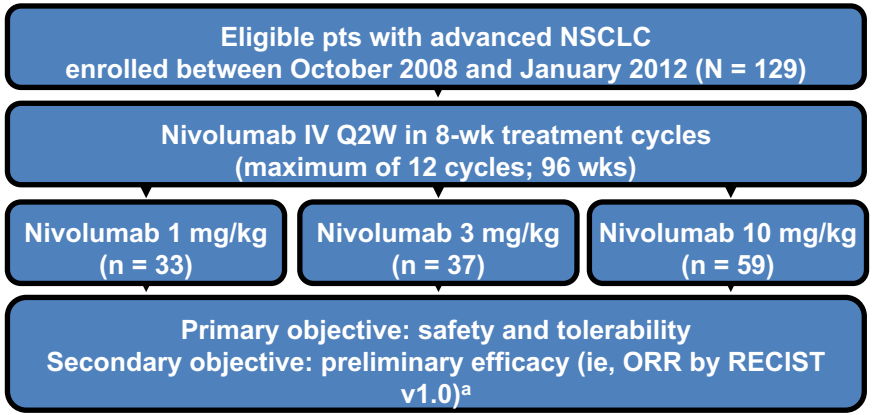

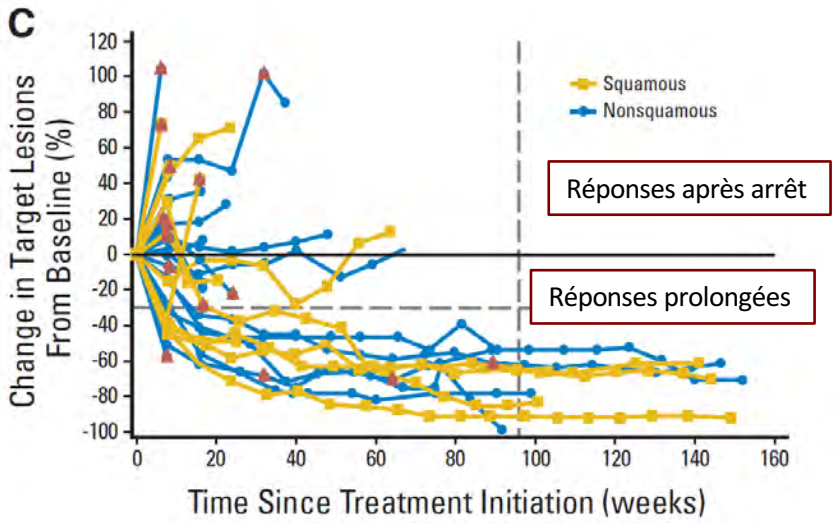

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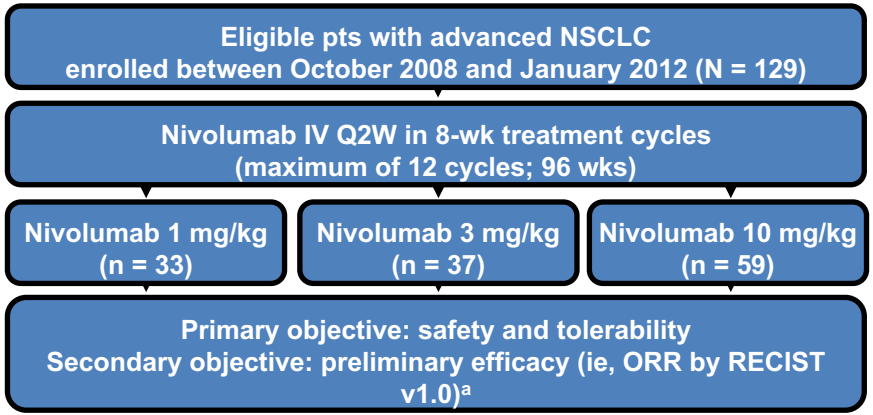

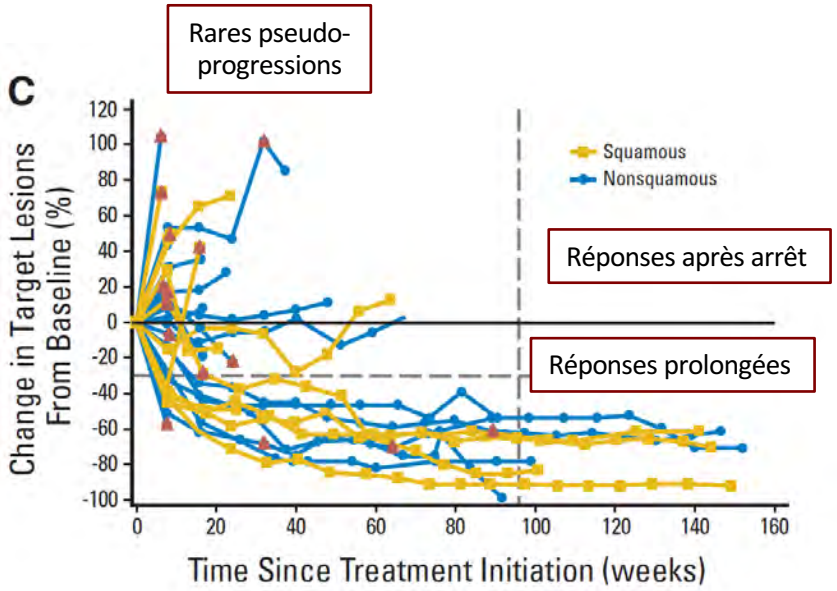

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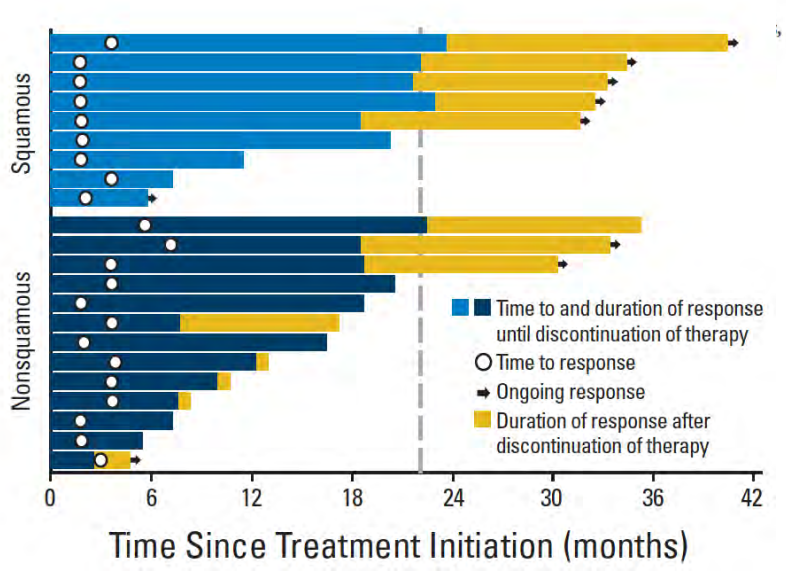

Taux de réponse: 17%
Répondeurs: durée de réponse: 17 mois

Durée de réponse prolongée après arrêt du traitement

Dose (mg/kg)	ORR† No. of Patients	ORR† %	ORR† 95% CI	Duration of Response (months)‡§ Median	Duration of Response (months)‡§ Range
NSCLC¶					
All doses	22 of 129	17.1	11.0 to 24.7	17.0	1.4+ to 36.8+
1	1 of 33	3.0	0.1 to 15.8	14.7	14.7 to 14.7
3	9 of 37	24.3	11.8 to 41.2	17.0	3.7+ to 32.6+
10	12 of 59	20.3	11.0 to 32.8	19.1	1.4+ to 36.8+

J Clin Oncol 2016; in press

Inhibition des points de contrôle : PD-1 et PD-L1

Nivolumab: essai de phase I, stades avancés réfractaires: CHECKMATE-003

Overall Survival and Long-Term Safety of Nivolumab (Anti–Programmed Death 1 Antibody, BMS-936558, ONO-4538) in Patients With Previously Treated Advanced Non–Small-Cell Lung Cancer

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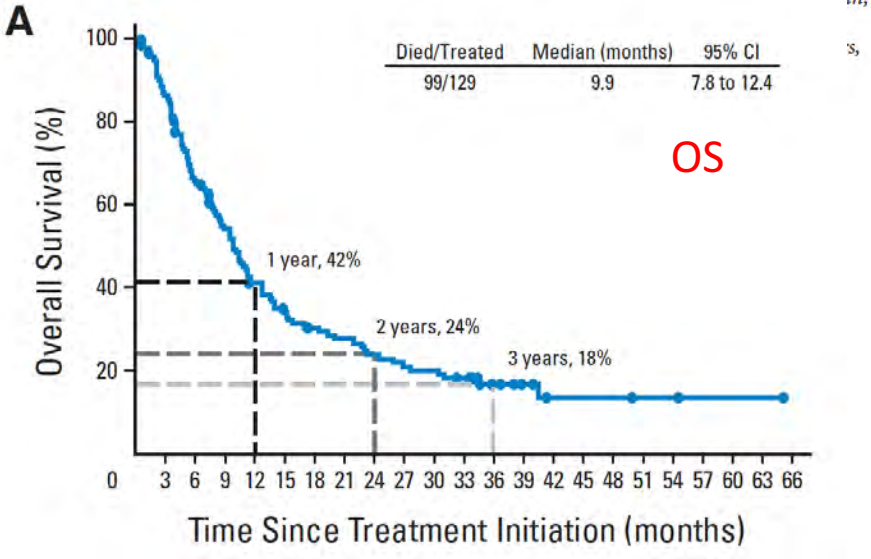
John D. [illegible] Philip L[illegible] Jeffrey A[illegible] Mark Sa[illegible] and Juli[illegible]



J Clin Oncol 2016; in press

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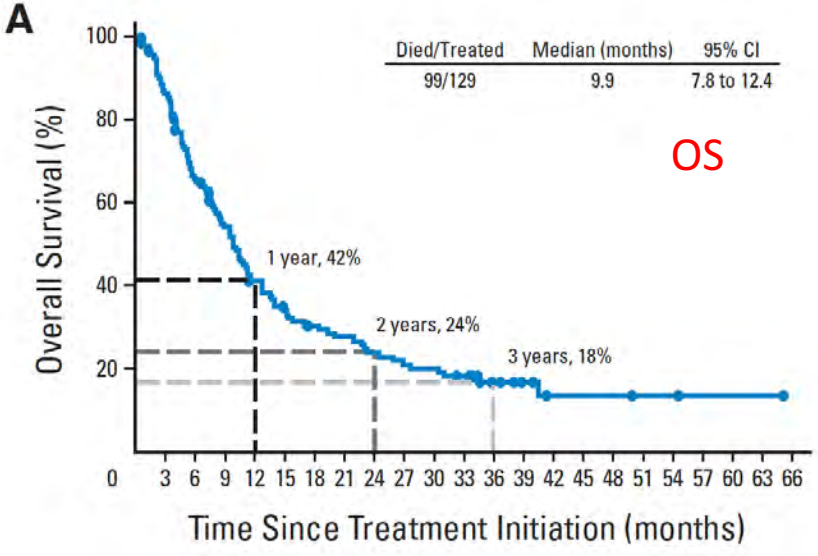

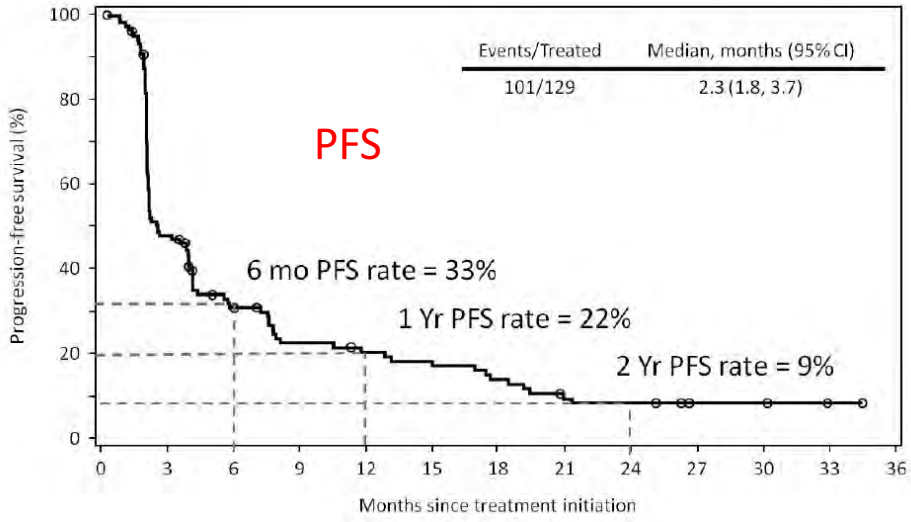

J Clin Oncol 2016; in press

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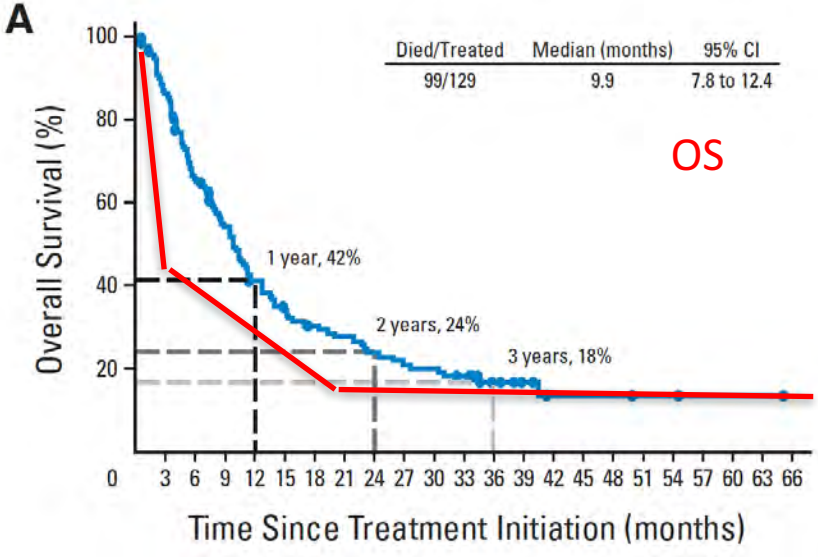
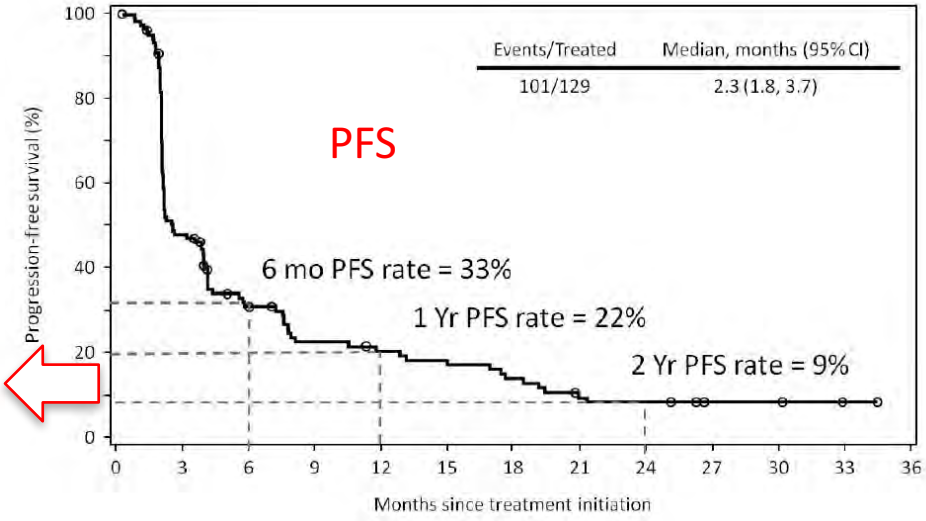




J Clin Oncol 2016; in press

L’immunothérapie dans le cancer du poumon

Réponse immunitaire anti-tumorale

Stratégies d’immunothérapie

Inhibiteurs de PD-1
Profils d’efficacité

Biomarqueur PD-L1

2016

Inhibition des points de contrôle : PD-1 et PD-L1

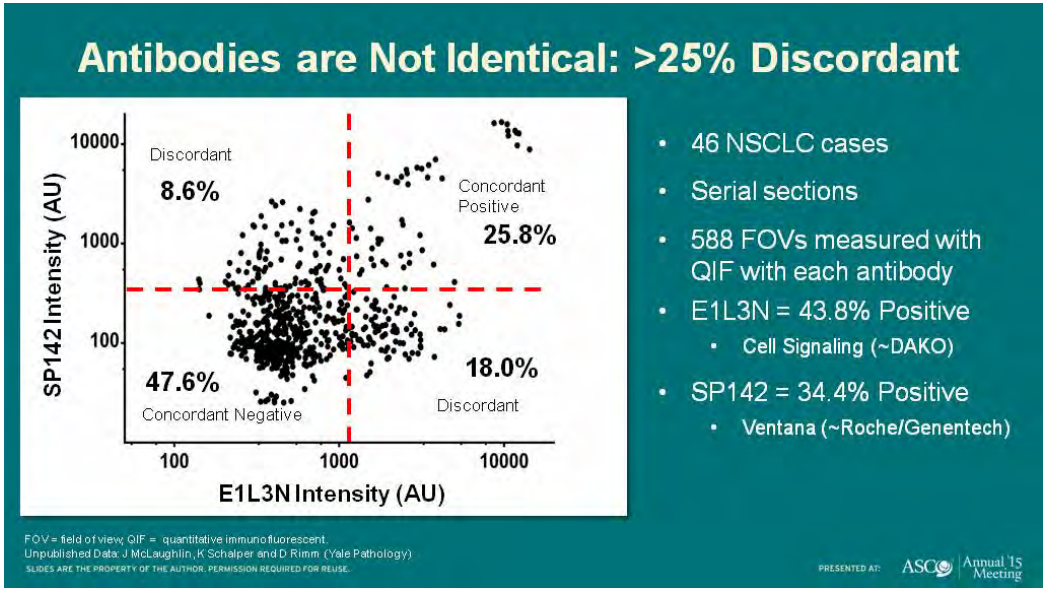
Expression de PD-L1

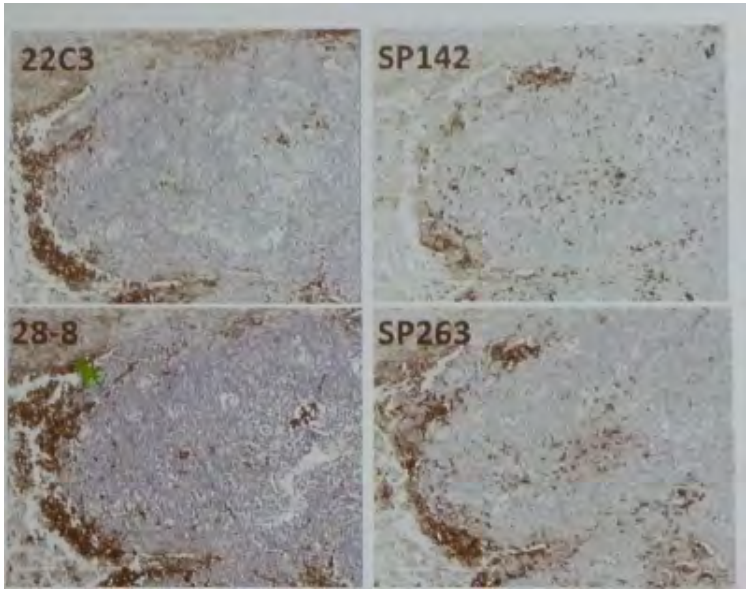
	Nivolumab	Pembrolizumab	MPDL3280A	MEDI4736
Type d'anticorps	Humanisé IgG4	Humanisé IgG4	IgG1	IgG1
Laboratoire	Bristol-Myers Squibb	MSD	Roche, Genentech	MedImmune, AstraZeneca
Évaluation de l'expression de PD-L1				
Clone	Dako AC 5H1/28-8	Dako AC 22C3	Genentech AC SP 142	Ventana SP263
Cellules	Tumorales	Tumorales et stromales	Immunitaires intratumorales	?
Seuil	1 % et 5 % sur 100 cellules	1-49 % : faible ; ≥ 50 % : fort	IHC+ : ≥ 1 % ; IHC++ : ≥ 5 % IHC+++ : ≥ 10 %	?
Proportion de PD-L1+	1 % : 56 %	1-49 % : 45-70 %	IHC+ : 75 %	48 %
	5 % : 49 %	≥ 50 % : 25 %	IHC++ : 14 % ; IHC+++ : 11 %	
Moment de la biopsie	Archive	Récente	Archive ou récente	Archive ou récente

Girard. La Lettre du Pneumologue 2016

Inhibition des points de contrôle : PD-1 et PD-L1

Expression de PD-L1

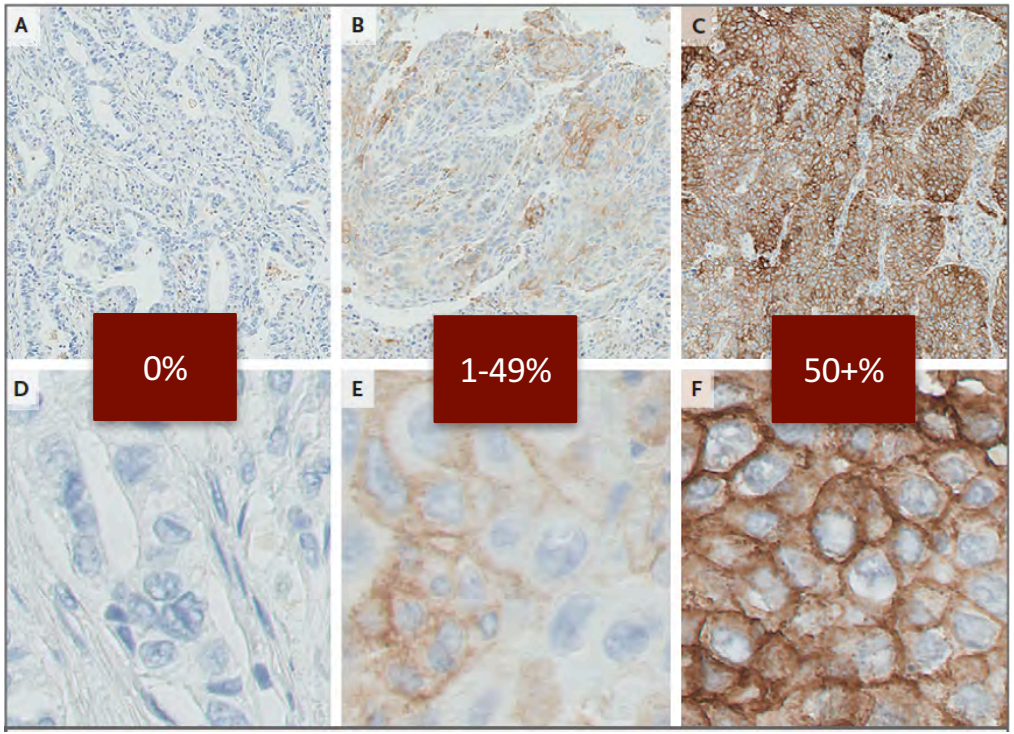




Presented By Roy Herbst at 2016 ASCO Annual Meeting
Presented by Fred Hirsch at 2016 ACCR annual meeting

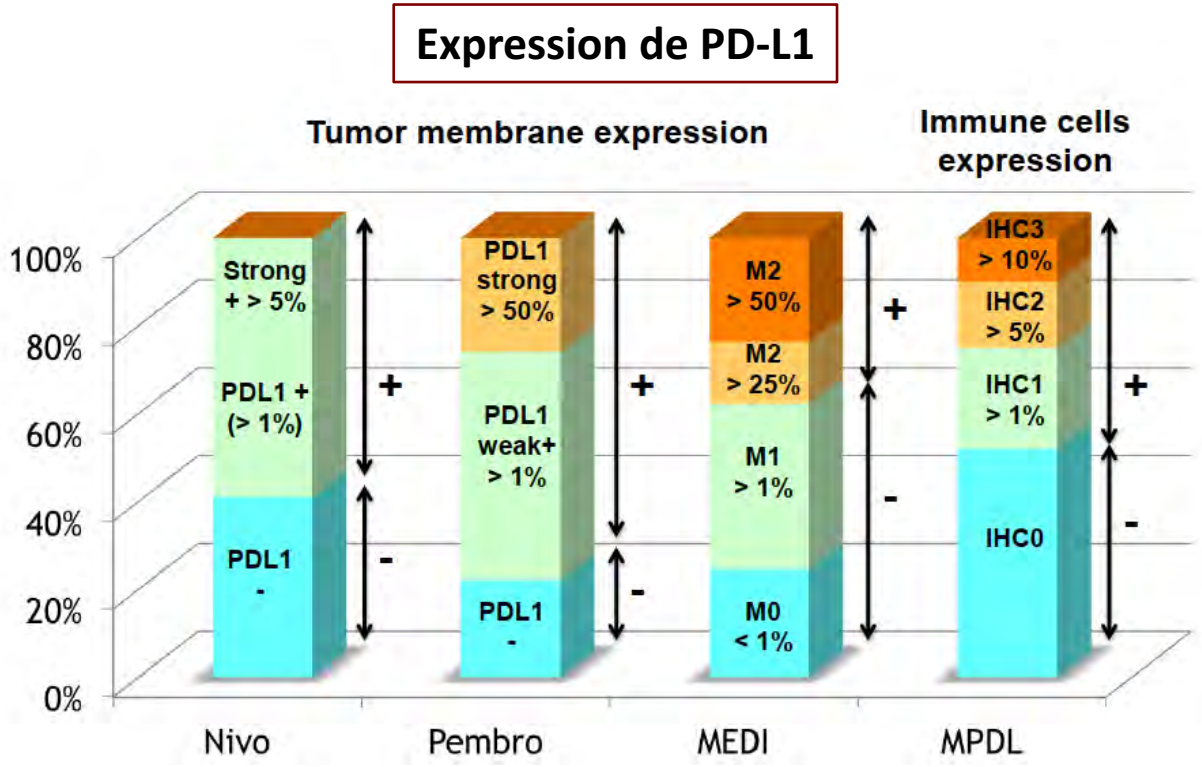
Expression de PD-L1: des méthodes variables

Dako 22C3 assay/Pembrolizumab trials



Garon et al. N Engl J Med 2016;372:2018

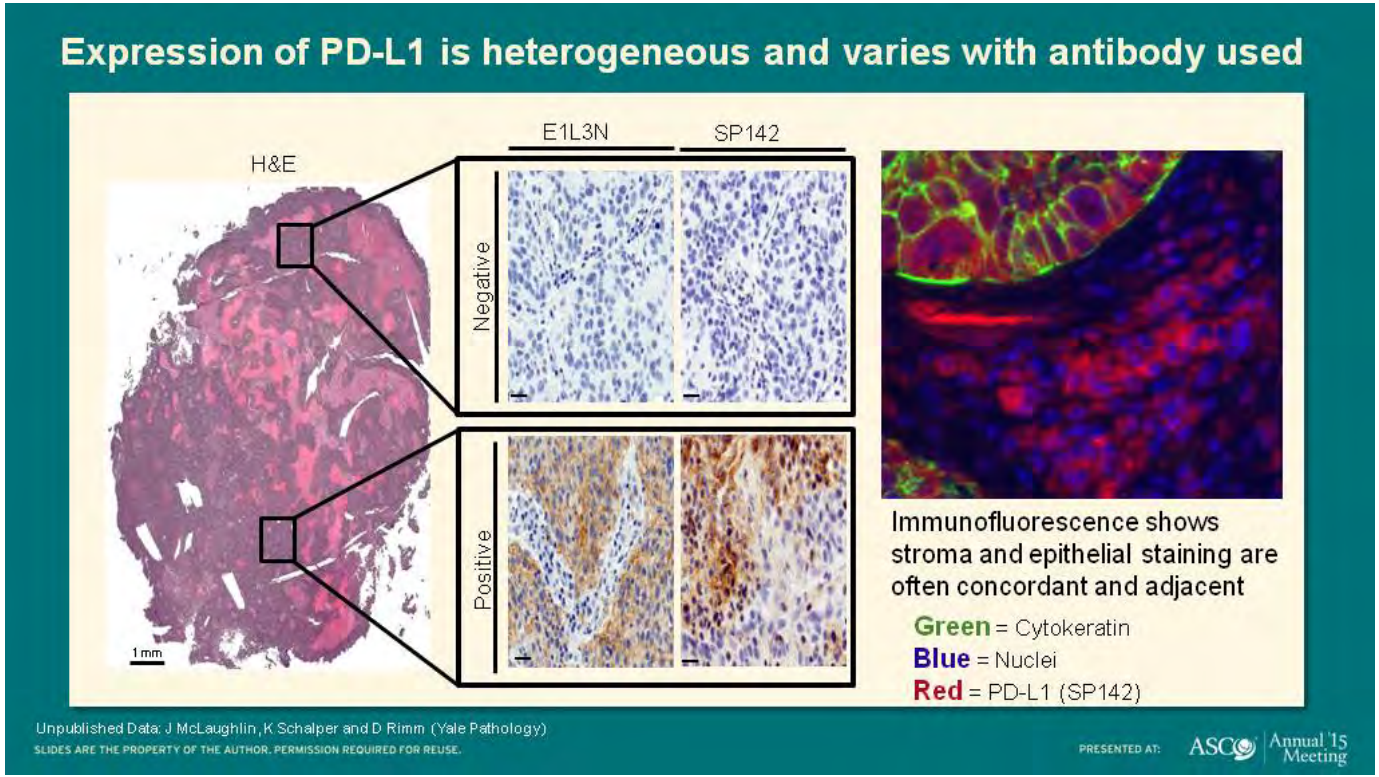
Des seuils différents selon les anticorps



Mazières et al. Ther Adv Respir Dis 2016; sous presse

Une hétérogénéité tumorale importante

Expression de PD-L1



Presented By Roy Herbst at 2016 ASCO Annual Meeting

Virchows Arch
DOI 10.1007/s00428-016-1910-4

REVIEW AND PERSPECTIVES

Assessment of the PD-L1 status by immunohistochemistry: challenges and perspectives for therapeutic strategies in lung cancer patients

Marius Ilie[1,2,3,4] · Véronique Hofman[1,2,3,4] · Manfred Dietel[5,6] · Jean-Charles Soria[7,8] · Paul Hofman[1,2,3,4]

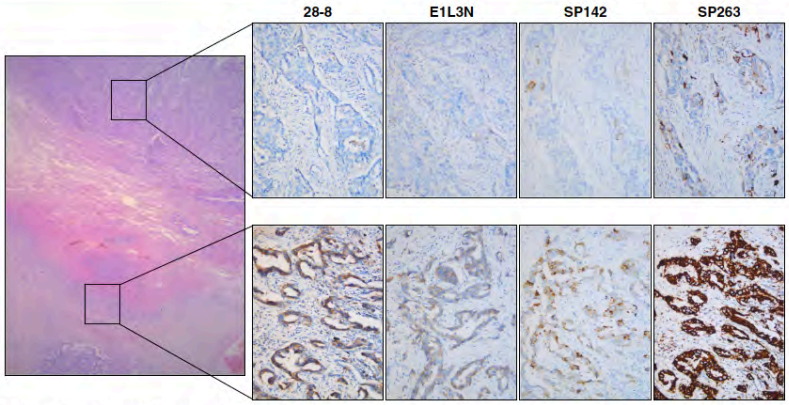
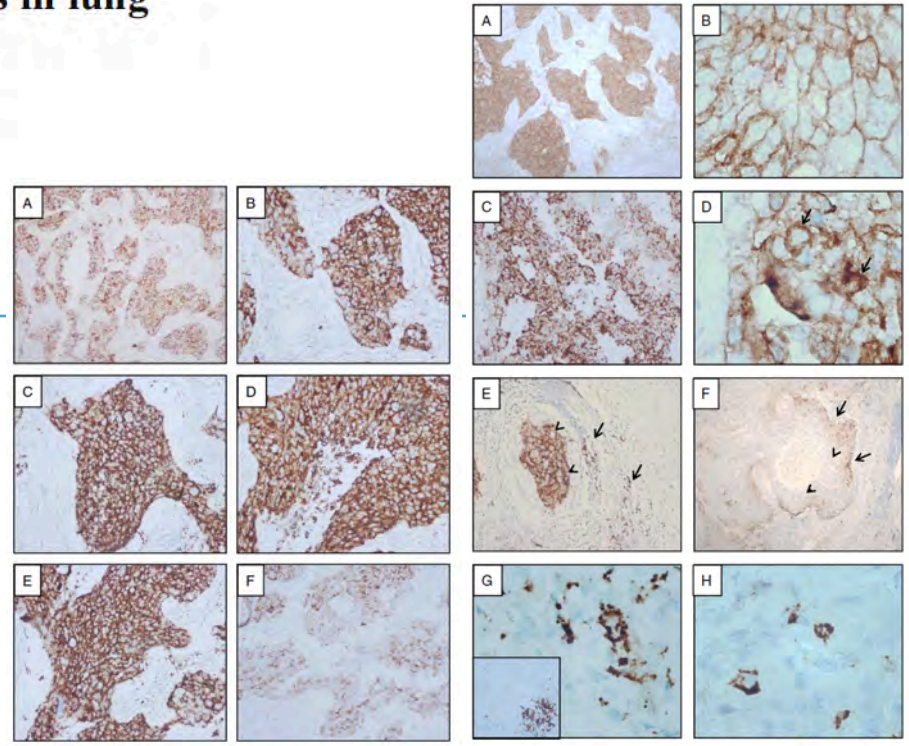


Fig. 2 PD-L1 protein intra-tumour heterogeneity and variability between different PD-L1 IHC assays. Representative cases are shown from different parts of the same tumour (*left large panel* showing haematoxylin eosin staining), with four antibodies (commercialised rabbit monoclonal 28-8 clone, Abcam; commercialised E1L3N clone, Cell Signaling Technology; SP142 clone, provided by Roche Tissue Diagnostics, France; SP263 clone, provided by Roche Tissue Diagnostics, France) using diaminobenzidine immune detection demonstrating positive staining in some regions of the tumour (*lower panels*) but absent or low expression in other regions (*upper panels*)



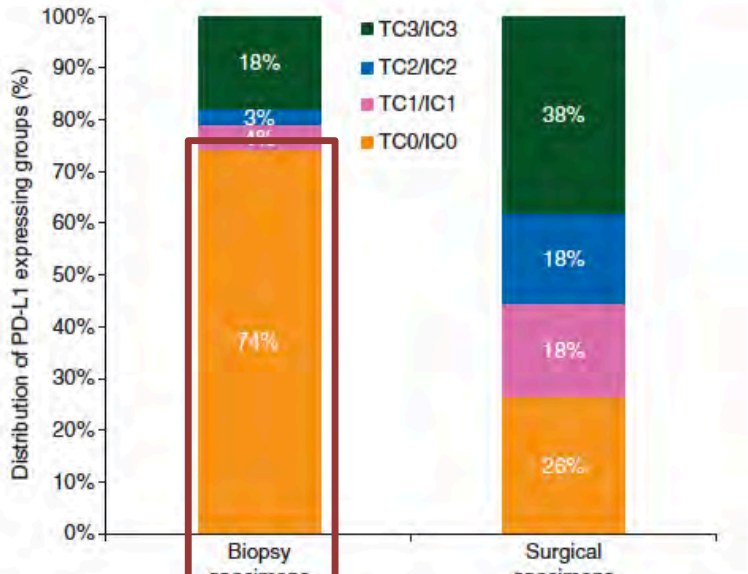
Expression de PD-L1: un risque de faux-négatif

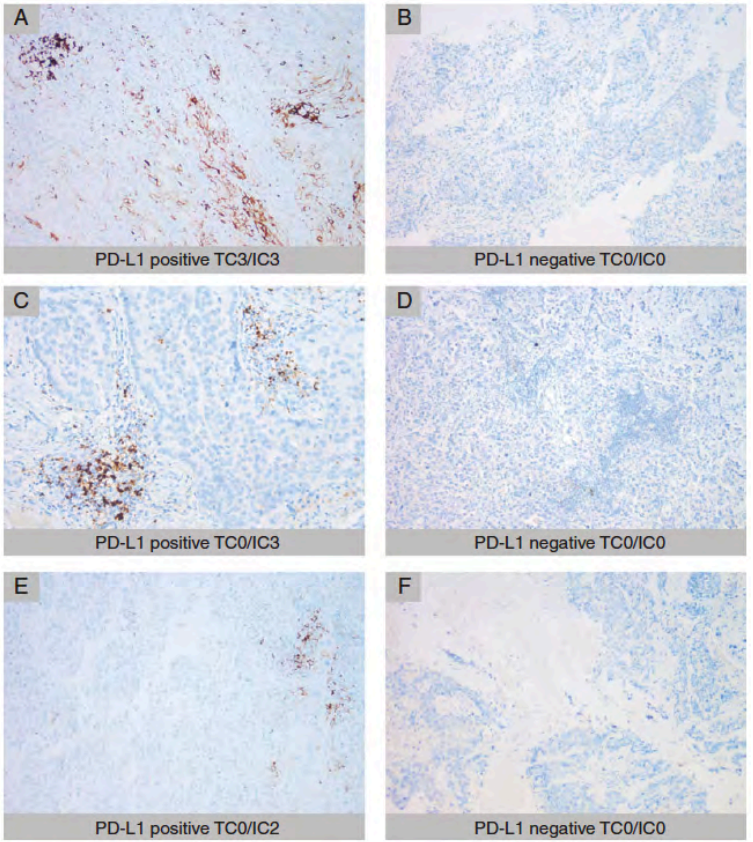
original article

Annals of Oncology 00: 1–7, 2015
doi:10.1093/annonc/mdv489

Comparative study of the PD-L1 status between surgically resected specimens and matched biopsies of NSCLC patients reveal major discordances: a potential issue for anti-PD-L1 therapeutic strategies

M. Ilie[1,2], E. Long-Mira[1,2], C. Bence[1], C. Butori[1], S. Lassalle[1,2], L. Bouhlel[2,3], L. Fazzalari[2], K. Zahaf[1], S. Lalvée[1], K. Wasl
C. H. Marquette[2,3]





Faut-il évaluer les cellules immunes?

Expression de PD-L1

	Nivolumab	Pembrolizumab	MPDL3280A	MEDI4736
Type d'anticorps	Humanisé IgG4	Humanisé IgG4	IgG1	IgG1
Laboratoire	Bristol-Myers Squibb	MSD	Roche, Genentech	MedImmune, AstraZeneca
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Moment de la biopsie	Archive	Récente	Archive ou récente	Archive ou récente

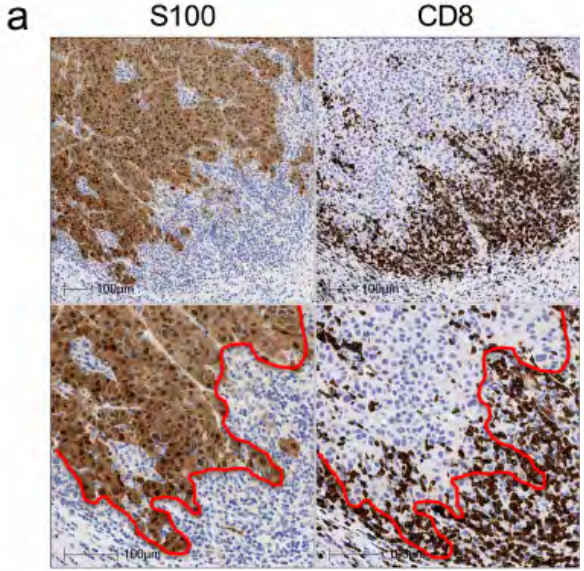
Girard. La Lettre du Pneumologue 2016

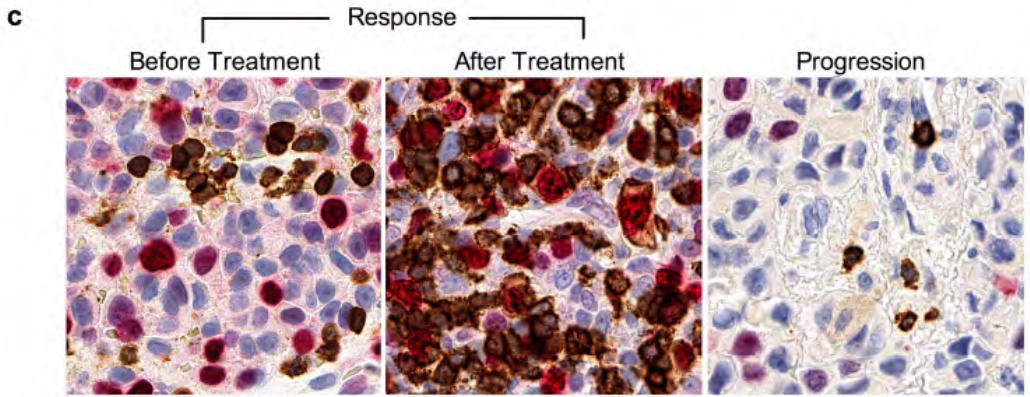
LETTER

doi:10.1038/nature13954

PD-1 blockade induces responses by inhibiting adaptive immune resistance

Paul C. Tumeh[1,2], Christina L. Harview[1], Jennifer H. Yearley[3], I. Peter Shintaku[1], Emma J. M. Taylor[1], Lidia Robert[1], Bartosz Chmielowski[1,2], Marko Spasic[1], Gina Henry[1], Voicu Ciobanu[1], Alisha N. West[1], Manuel Carmona[1], Christine Kivork[1], Elizabeth Seja[1], Grace Cherry[1], Antonio J. Gutierrez[1], Tristan R. Grogan[1], Christine Mateus[4], Gorana Tomasic[4], John A. Glaspy[1,2], Ryan O. Emerson[5], Harlan Robins[5,6], Robert H. Pierce[3], David A. Elashoff[1,2], Caroline Robert[4] & Antoni Ribas[1,2]





Nature 2014;515:568

A quel moment évaluer le statut PD-L1?

Expression de PD-L1

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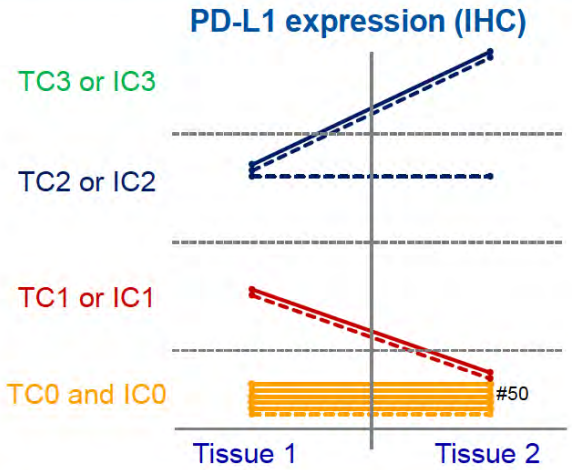
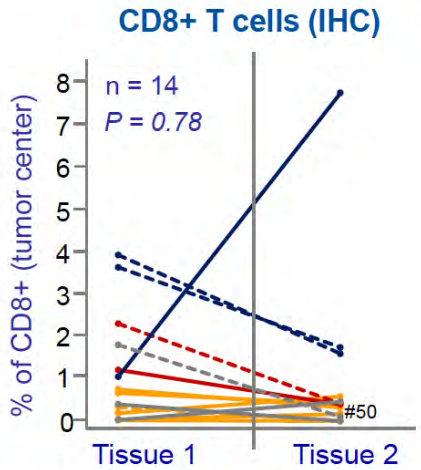
Girard. La Lettre du Pneumologue 2016

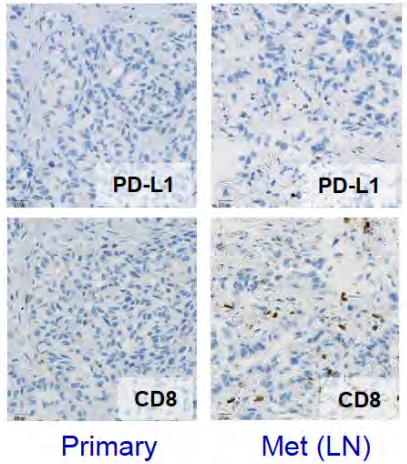
Expression de PD-L1: une variabilité temporelle

SOC Appears to Have a Minimal Impact on PD-L1 Expression and CD8+ T-cell Infiltration in Metachronous[a] Tumor Pairs

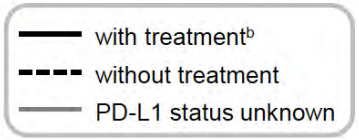




Median difference = -0.4%
(95% CI: -1.4%, 0.1%)



PD-L1 cut-off	# of paired metachronous biopsies with the same PD-L1 score, n/N (%)
TC3 or IC3	9/11 (82%)
TC2/3 or IC2/3	11/11 (100%)
TC1/2/3 or IC1/2/3	9/11 (82%)

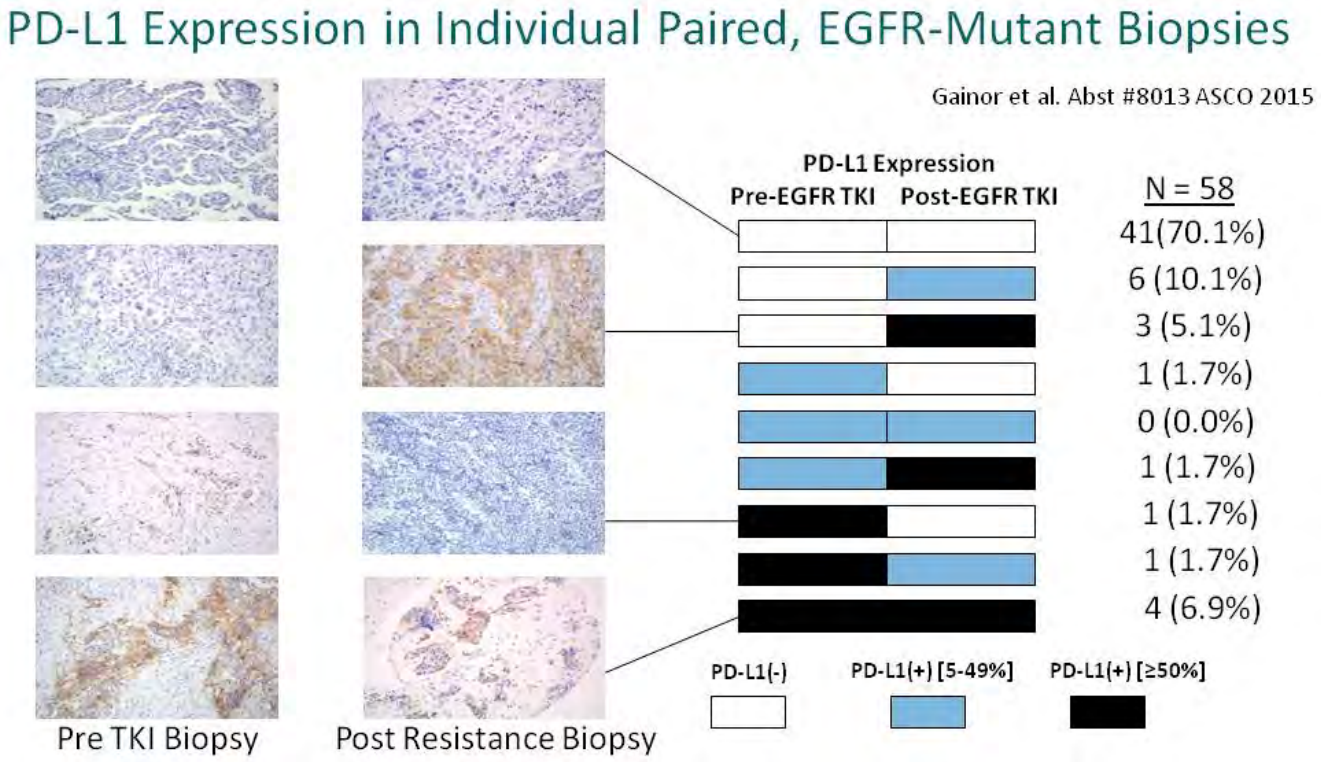


[a]Median time between the paired tissues with PD-L1 data available: 21.6 months.
[b]Chemotherapy, 7 patients; Chemotherapy/TKI, 2 patients.

Kowanetz et al., WCLC 2015

Inhibition des points de contrôle : PD-1 et PD-L1

Expression de PD-L1



L’immunothérapie dans le cancer du poumon

Réponse immunitaire anti-tumorale

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Biomarqueur
PD-L1

2016

Tolérance

Inhibition des points de contrôle : PD-1 et PD-L1

Profil de tolérance

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Table 4. Treatment-Related Select AEs Occurring in All Treated Patients in NSCLC Population*

	All Patients (N = 129)			
	Any Grade†		Grades 3 to 4	
Select AE	No.	%	No.	%
Any AE	53	41.1	6	4.7
Skin	20	15.5	0	0
GI	15	11.6	1	0.8
Pulmonary	9‡§	7.0§	3‡	2.3
Endocrinopathies	8	6.2	0	0
Hepatic	6	4.7	1	0.8
Infusion reaction	5	3.9	1	0.8
Renal	4	3.1	0	0

J Clin Oncol 2016; in press

Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer

Edward B. Garon, M.D., Naiyer A. Rizvi, M.D., Rina Hui, M.B., B.S., Natasha Leighl, M.D., Ani S. Balmanoukian, M.D., Joseph Paul Eder, M.D., Amita Patnaik, M.D., Charu Aggarwal, M.D., Matthew Gubens, M.D., Leora Horn, M… Enriqueta Felip, M… Omid Hamid, M.D., Marisa Dolled-Filt… Jared K. Lunceford, Ph… Charlot… and Leena Ga…

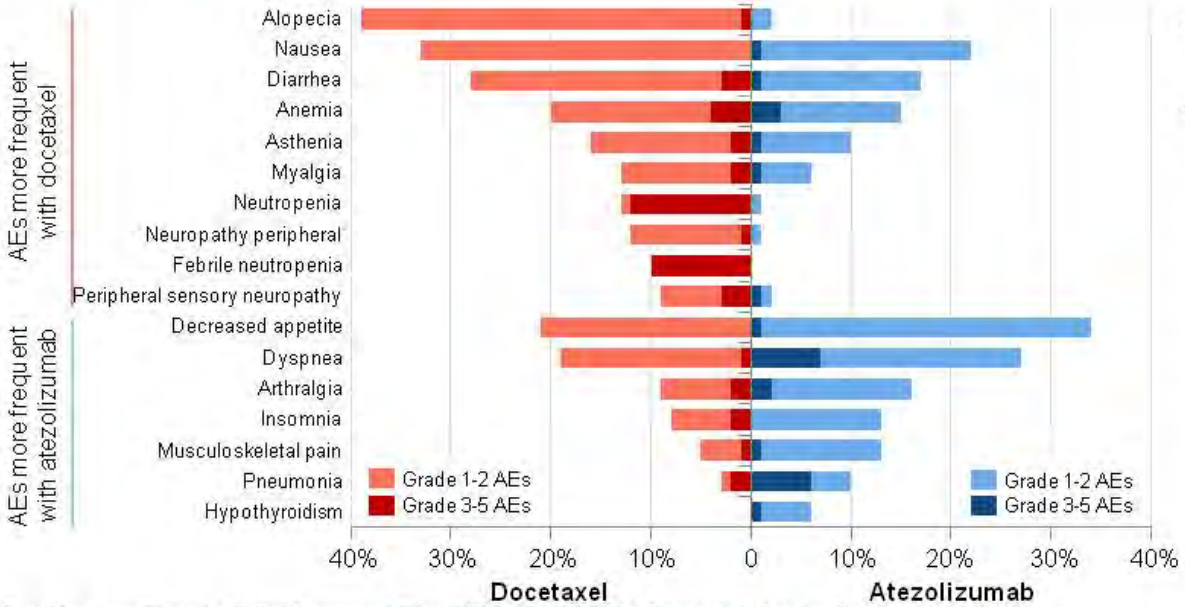
Table 1. Adverse Events in 495 Patients in the Treated Population.*

Adverse Event	Any Grade	Grade 3–5
	no. of patients (%)	
Fatigue	96 (19.4)	4 (0.8)
Pruritus	53 (10.7)	0
Decreased appetite	52 (10.5)	5 (1.0)
Rash	48 (9.7)	1 (0.2)
Arthralgia	45 (9.1)	2 (0.4)
Diarrhea	40 (8.1)	3 (0.6)
Nausea	37 (7.5)	4 (0.8)
Hypothyroidism	34 (6.9)	1 (0.2)
Asthenia	24 (4.8)	5 (1.0)
Anemia	21 (4.2)	0
Dyspnea	21 (4.2)	19 (3.8)
Pyrexia	21 (4.2)	3 (0.6)
Decreased weight	19 (3.8)	2 (0.4)
Dry skin	18 (3.6)	0
Pneumonitis†	18 (3.6)	9 (1.8)

New Engl J Med 2016;In press

Inhibiteurs de PD-1 et PD-L1
Toxicités

POPLAR: All-cause AEs (≥ 5% difference between arms)



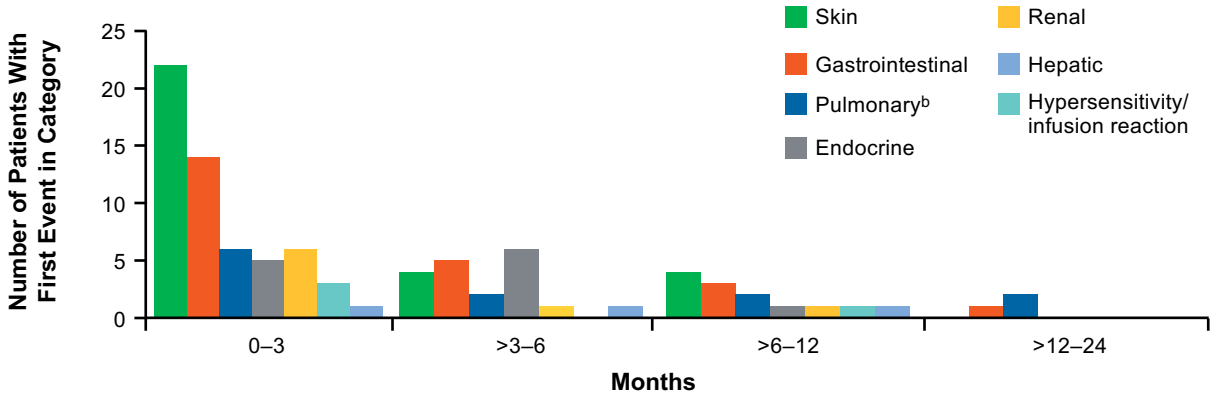
- AE profiles consistent with previous studies
- For atezolizumab, other immune-mediated AEs (any grade) included:
  - AST increased (4%)
  - ALT increased (4%)
  - Pneumonitis (2%)
  - Colitis (1%)
  - Hepatitis (1%)

Dry skin, stomatitis and nail disorder were additional AEs with ≥ 5% higher frequency in docetaxel.
Safety population includes patients who received any amount of either study treatment.
Data cut-off Jan 30, 2015.

Inhibition des points de contrôle : PD-1 et PD-L1

Profil de tolérance: Nivolumab

Time to onset of first treatment-related select AE by category (any grade)[a]



Pts still on study, n	248	206	153	84
Pts still on treatment, n	248	134	85	38
Total pts with a first event,[a] n	49	14	10	2

[a]Within each time interval, patients with ≥1 event were counted only once in each category but could be classified into more than one category.
[b]Does not include one event of grade 3 pneumonitis (CheckMate 017) updated to treatment-related after the database lock.

Gettinger et al. ECC 2016

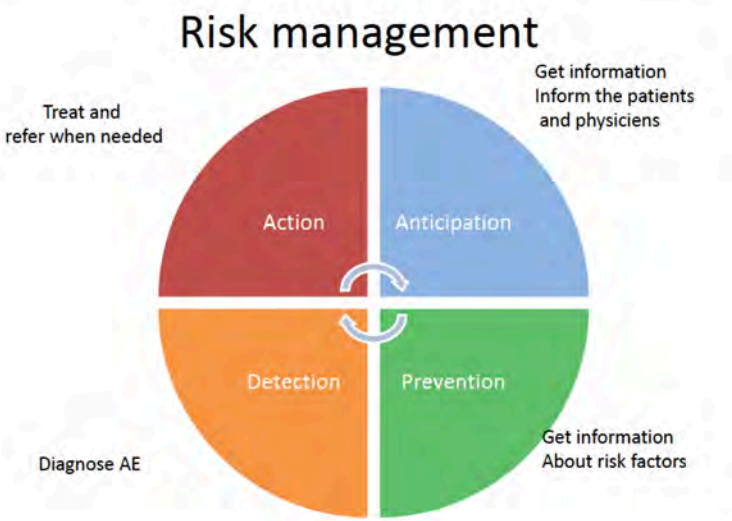
Inhibition des points de contrôle : PD-1 et PD-L1

Prévention et traitement des effets indésirables auto-immuns

KEYTRUDA Safety
irAEs Management Algorithms

Pneumonitis	Administer corticosteroids
	Withhold KEYTRUDA for moderate (Grade 2) pneumonitis
	Permanently discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) pneumonitis
Colitis	Administer corticosteroids
	Withhold KEYTRUDA for moderate (Grade 2) or severe (Grade 3) colitis
	Permanently discontinue KEYTRUDA for life-threatening (Grade 4) colitis
Hepatitis	Administer corticosteroids
	Based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA
Hyperthyroidism	Administer corticosteroids
	Withhold KEYTRUDA for severe (Grade 3) hyperthyroidism
	Permanently discontinue KEYTRUDA for life-threatening (Grade 4) hyperthyroidism
	Isolated hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids

KEYTRUDA (pembrolizumab)[package insert – United States]. Whitehouse Station, NJ: Merck & Co., Inc.; 2014.



Immunothérapies: Pneumopathies interstitielles

Patient Database

- MSKCC database: Anti-PD-1/PD-L1 protocols (+600 patients)
- 33 (~5%) pneumonitis cases
- 4 deaths (1= pneumonitis, 3=infection)

Patient Characteristics of Pneumonitis Patients (n=33)

Gender	
Female	13
Male	20
Smoking status	
Never	10
Former/Current	23
Primary Disease Site	
NSCLC	13
Melanoma	12
Hematologic Malignancy	4
Breast Carcinoma	1
Bladder Carcinoma	1
HNSCC	1
Pancreatic Carcinoma	1

Line of Treatment	
First-line	13
Second/Third-line	13
Fourth-line+	7
Type of Therapy	
Monotherapy	
Anti-PD-1	12
Anti-PD-L1	2
Combination	
Anti-PD-1	18
Anti-PD-L1	1
Prior Chest Radiation	
Yes	9
No	24

Naidoo et al. ECC 2016

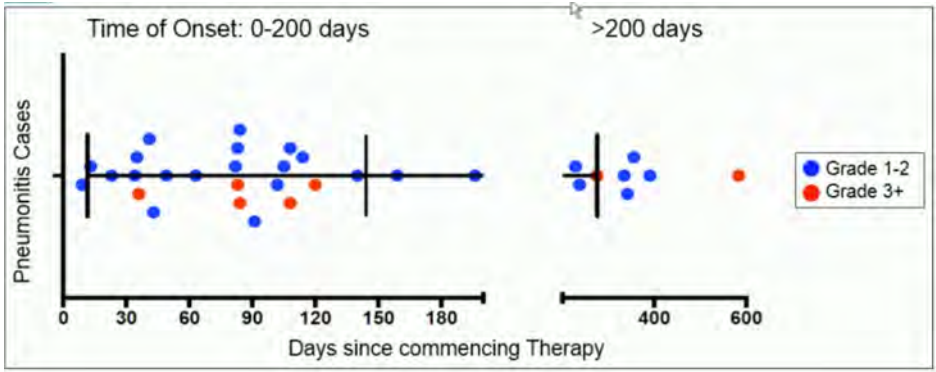
Immunothérapies: Pneumopathies interstitielles

Patient Database

- MSKCC database: Anti-PD-1/PD-L1 protocols (+600 patients)
- 33 (~5%) pneumonitis cases
- 4 deaths (1= pneumonitis, 3=infection)

Patient Characteristics of Pneumonitis Patients (n=33)

Gender		**Line of Treatment**	
Female	13	First-line	13
Male	20	Second/Third-line	13
Smoking status		Fourth-line+	7
Never	10	**Type of Therapy**	
Former/Current	23	Monotherapy	
Primary Disease Site		Anti-PD-1	12
NSCLC	13	Anti-PD-L1	2
Melanoma	12	Combination	
Hematologic Malignancy	4	Anti-PD-1	18
Breast Carcinoma	1	Anti-PD-L1	1
Bladder Carcinoma	1	**Prior Chest Radiation**	
HNSCC	1	Yes	9
Pancreatic Carcinoma	1	No	24



Naidoo et al. ECC 2016

Immunothérapies: Pneumopathies interstitielles

Patient Database

- MSKCC database: Anti-PD-1/PD-L1 protocols (+600 patients)
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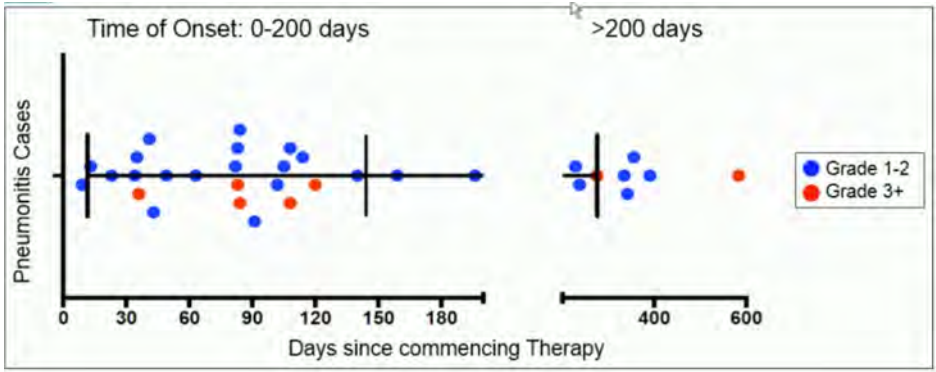
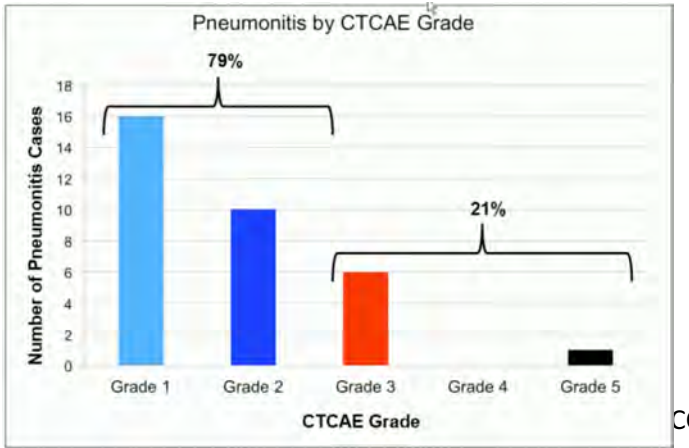
Patient Characteristics of Pneumonitis Patients (n=33)

Gender		**Line of Treatment**	
Female	13	First-line	13
Male	20	Second/Third-line	13
Smoking status		Fourth-line+	7
Never	10	**Type of Therapy**	
Former/Current	23	Monotherapy	
Primary Disease Site		Anti-PD-1	12
NSCLC	13	Anti-PD-L1	2
Melanoma	12	Combination	
Hematologic Malignancy	4	Anti-PD-1	18
Breast Carcinoma	1	Anti-PD-L1	1
Bladder Carcinoma	1	**Prior Chest Radiation**	
HNSCC	1	Yes	9
Pancreatic Carcinoma	1	No	24





CC 2016

Immunothérapies: Pneumopathies interstitielles

Radiologic Features

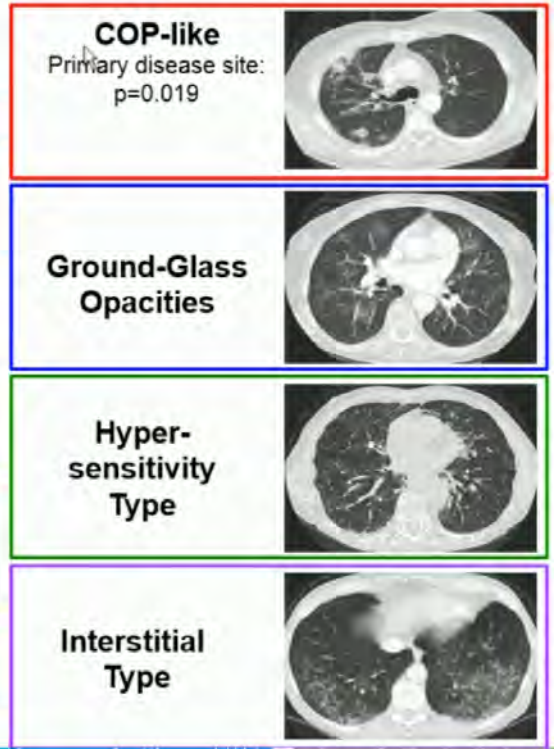
ECCO

- 5 subtypes of pneumonitis identified[1]

Subtype	Description
COP-like* (n=7)	• Discrete areas of consolidation • Peripheral distribution
Ground Glass Opacities (n=12)	• Discrete areas attenuation • Preserved bronchovascular markings
Hypersensitivity Type (n=6)	• 'Tree-in-bud' micronodularity • Centrilobular distribution
Interstitial Type (n=4)	• Interlobular septal thickening • Subpleural reticulations • Increased interstitial markings
Pneumonitis NOS (n=4)	• Does not clearly fit into other subtypes

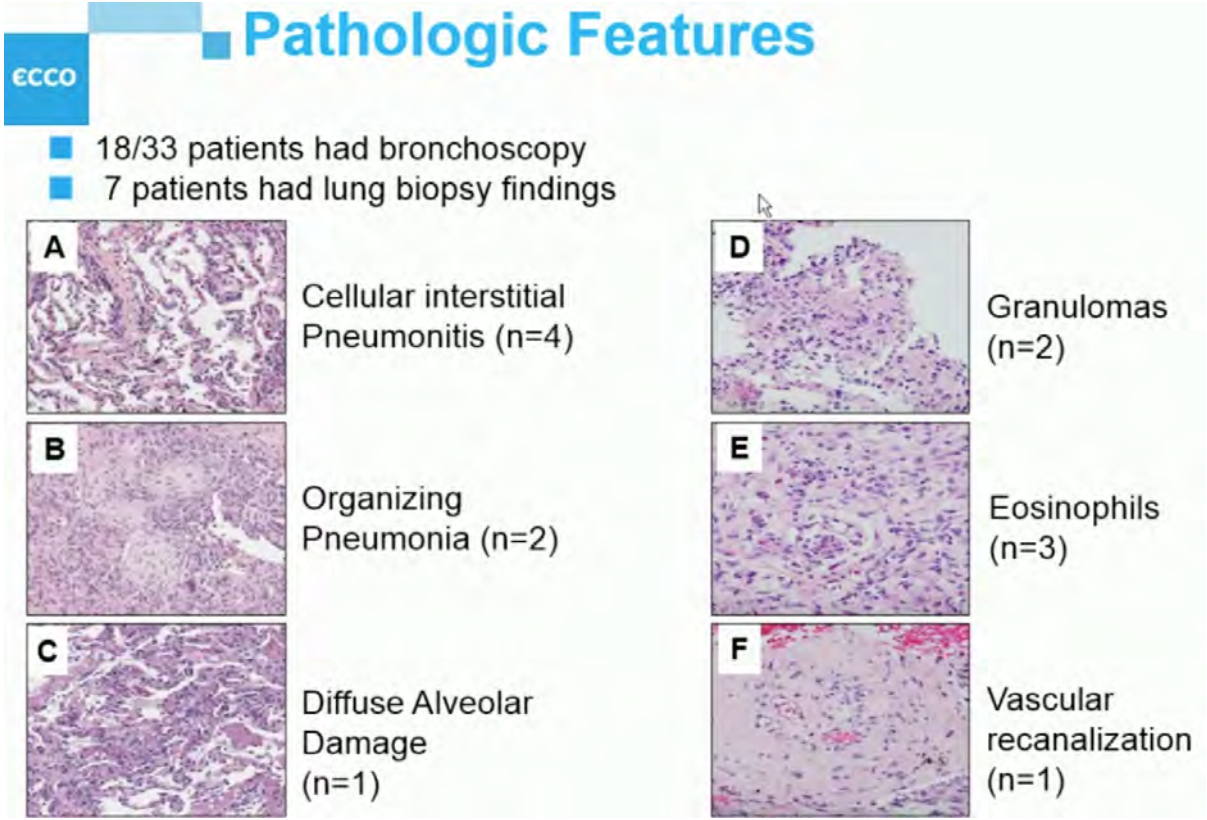
*Cryptogenic organizing pneumonia **Not otherwise specified

1. Johkoh et al. Eur J Radiol 2015



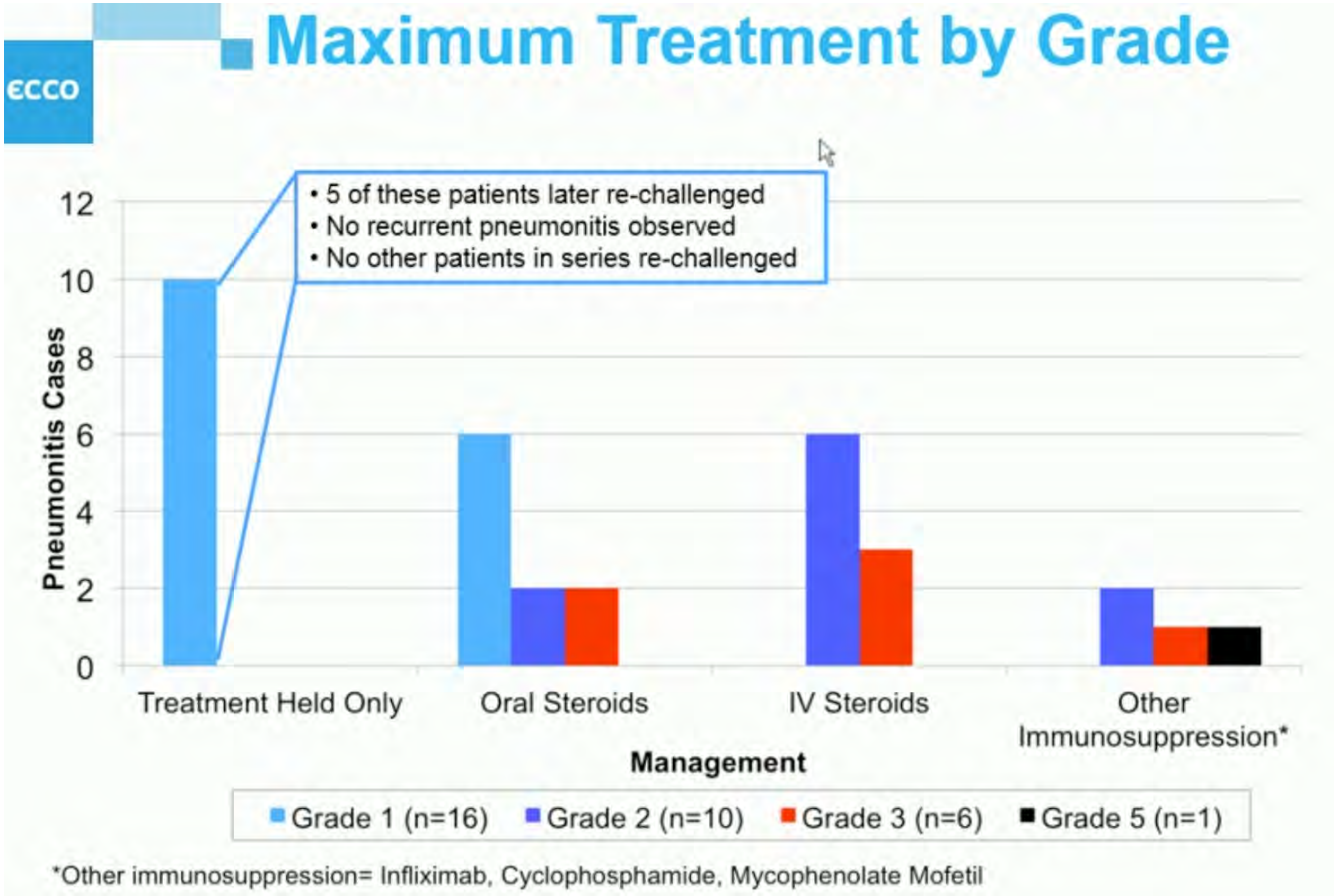
Naidoo et al. ECC 2016

Immunothérapies: Pneumopathies interstitielles



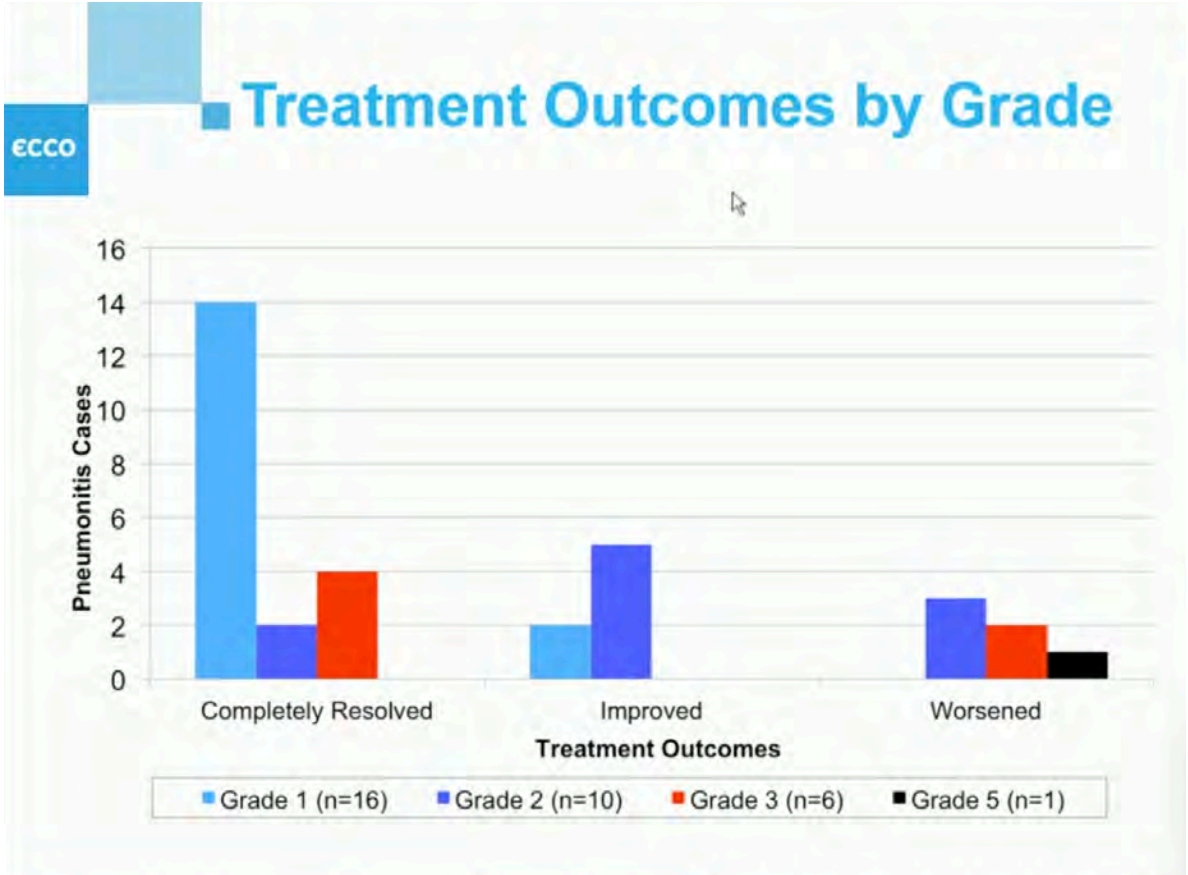
Naidoo et al. ECC 2016

Immunothérapies: Pneumopathies interstitielles



Naidoo et al. ECC 2016

Immunothérapies: Pneumopathies interstitielles



L’immunothérapie dans le cancer du poumon

Réponse immunitaire anti-tumorale

Stratégies d’immunothérapie

Inhibiteurs de PD-1
Profils d’efficacité

Biomarqueur
PD-L1

2016

Tolérance

Intégration en seconde ligne de traitement

L’immunothérapie dans le cancer du poumon

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Stratégies d’immunothérapie

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2016

Tolérance

Intégration en seconde ligne de traitement

Nivolumab

L'immunothérapie dans le cancer du poumon

Réponse immunitaire anti-tumorale

Stratégies d'immunothérapie

Inhibiteurs de PD-1
Profils d'efficacité

Biomarqueur
PD-L1

2016

Tolérance

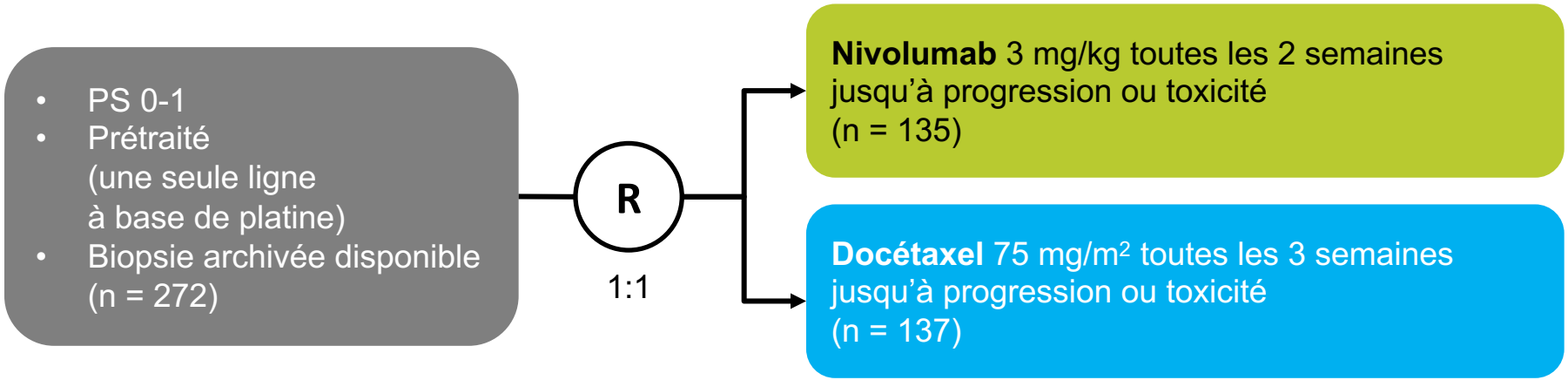
Intégration en seconde ligne de traitement

Nivolumab

- Carcinomes épidermoïdes

Seconde ligne
Nivolumab: carcinomes épidermoïdes

Essai CHECKMATE 017



Objectif principal : SG

- Objectifs secondaires
  - RO RECIST 1.1
  - SSP
  - Qualité de vie
  - Tolérance
  - Efficacité selon l'expression du PD-L1

N Engl J Med 2016;373:123

Seconde ligne
Nivolumab: carcinomes épidermoïdes

Essai CHECKMATE 017

Table 2. Clinical Activity of Nivolumab versus Docetaxel in Patients with Advanced Squamous-Cell Non–Small-Cell Lung Cancer.*

Variable	Nivolumab (N=135)	Docetaxel (N=137)
Objective response†		
No. of patients	27	12
% of patients (95% CI)	20 (14–28)	9 (5–15)
Estimated odds ratio (95% CI)	2.6 (1.3–5.5)	
P value	0.008	
Best overall response — no. (%)		
Complete response	1 (1)	0
Partial response	26 (19)	12 (9)
Stable disease	39 (29)	47 (34)
Progressive disease	56 (41)	48 (35)
Could not be determined	13 (10)	30 (22)
Time to response — mo‡§		
Median	2.2	2.1
Range	1.6–11.8	1.8–9.5
Duration of response — mo‡¶		
Median	NR	8.4
Range	2.9 to 20.5+	1.4+ to 15.2+

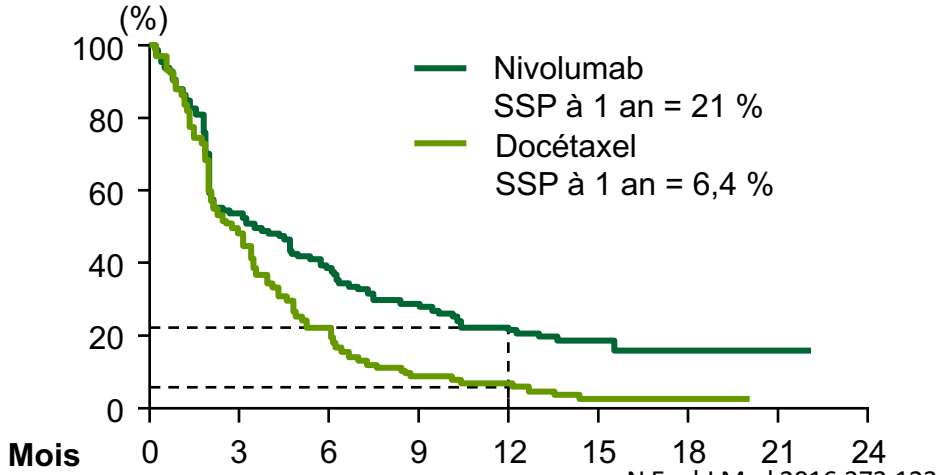
N Engl J Med 2016;373:123

Seconde ligne
Nivolumab: carcinomes épidermoïdes

Essai CHECKMATE 017

Survie sans progression

	Nivolumab (n = 292)	Docétaxel (n = 290)
Médiane, mois (IC_{95})	3,5 (2,1-4,9)	2,8 (2,1-3,5)
HR = 0,62 ; IC_{95} : 0,47-0,81 ; p = 0,0004		



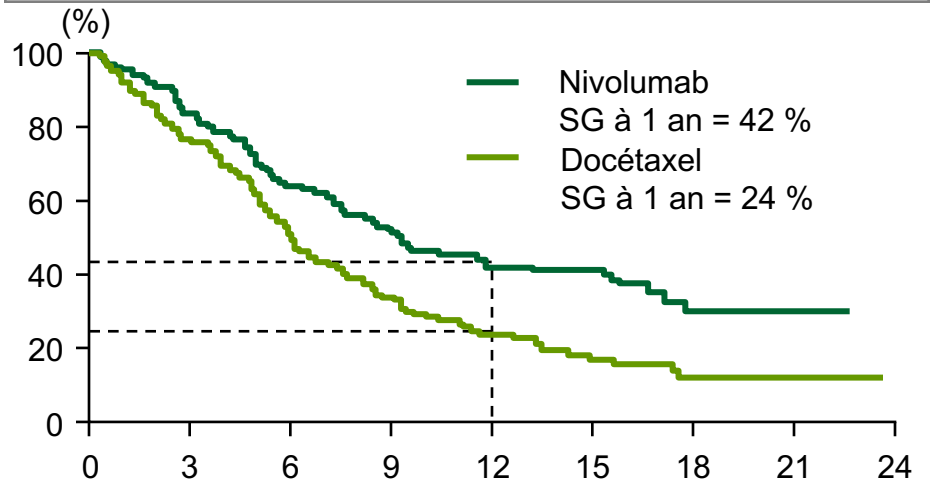
N Engl J Med 2016;373:123

Seconde ligne
Nivolumab: carcinomes épidermoïdes

Essai CHECKMATE 017

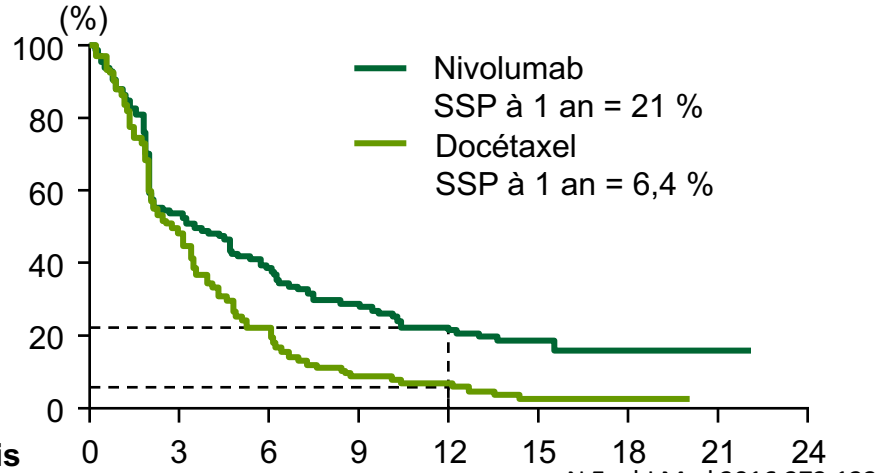
Survie globale

	Nivolumab (n = 135)	Docétaxel (n = 137)
Médiane, mois (IC_{95})	9,2 (7,3-13,3)	6,0 (5,1-7,3)
HR = 0,59 ; IC_{96} : 0,44-0,79 ; p = 0,00025		



Survie sans progression

	Nivolumab (n = 292)	Docétaxel (n = 290)
Médiane, mois (IC_{95})	3,5 (2,1-4,9)	2,8 (2,1-3,5)
HR = 0,62 ; IC_{95} : 0,47-0,81 ; p = 0,0004		



N Engl J Med 2016;373:123

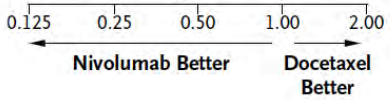
Seconde ligne
Nivolumab: carcinomes épidermoïdes

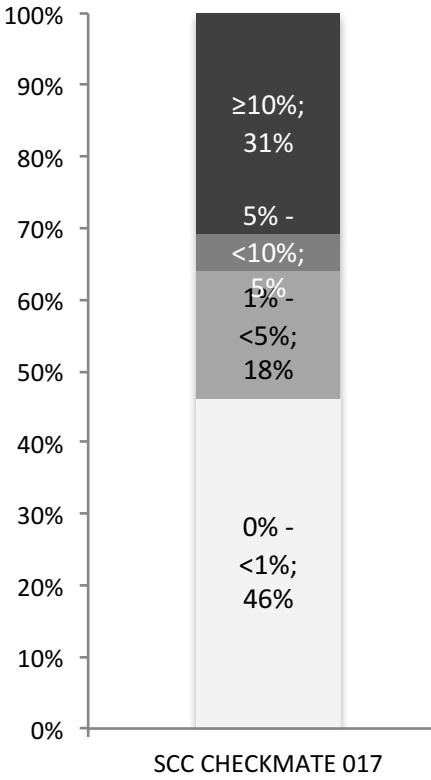
Essai CHECKMATE 017

	PD-L1 Expression Level						
	≥1%	<1%	≥5%	<5%	≥10%	<10%	Not quantifiable[a]
Nivolumab							
ORR,[b] % (n/N)	18 (11/63)	17 (9/54)	21 (9/42)	15 (11/75)	19 (7/36)	16 (13/81)	39 (7/18)
Docetaxel							
ORR,[b] % (n/N)	11 (6/56)	10 (5/52)	8 (3/39)	12 (8/69)	9 (3/33)	11 (8/75)	3 (1/29)
Interaction *P*-value	0.94		0.29		0.64		

C Overall and Progression-free Survival According to PD-L1 Expression Level

PD-L1 Expression Level	Nivolumab (no. of patients)	Docetaxel (no. of patients)	Unstratified Hazard Ratio (95% CI)
Overall survival			
≥1%	63	56	0.69 (0.45–1.05)
<1%	54	52	0.58 (0.37–0.92)
≥5%	42	39	0.53 (0.31–0.89)
<5%	75	69	0.70 (0.47–1.02)
≥10%	36	33	0.50 (0.28–0.89)
<10%	81	75	0.70 (0.48–1.01)
Not quantifiable at baseline	18	29	0.39 (0.19–0.82)
Progression-free survival			
≥1%	63	56	0.67 (0.44–1.01)
<1%	54	52	0.66 (0.43–1.00)
≥5%	42	39	0.54 (0.32–0.90)
<5%	75	69	0.75 (0.52–1.08)
≥10%	36	33	0.58 (0.33–1.02)
<10%	81	75	0.70 (0.49–0.99)
Not quantifiable at baseline	18	29	0.45 (0.23–0.89)





N Engl J Med 2016;373:123

L'immunothérapie dans le cancer du poumon

Réponse immunitaire anti-tumorale

Stratégies d'immunothérapie

Inhibiteurs de PD-1
Profils d'efficacité

Biomarqueur PD-L1

2016

Tolérance

Intégration en seconde ligne de traitement

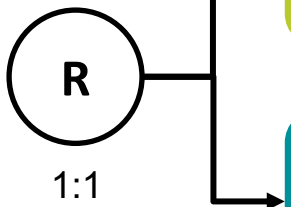
Nivolumab

- Carcinomes épidermoïdes
- Carcinomes non épidermoïdes

Seconde ligne
Nivolumab: carcinomes non épidermoïdes

Essai CHECKMATE 057

- Cancers non épidermoïdes
- Stades IIIB/IV
- ECOG PS 0-1
- Prétraités par un doublet à base de platine ± ITK



Nivolumab 3 mg/kg toutes les 2 semaines jusqu'à progression ou toxicité
(n = 292)

Docétaxel 75 mg/m^2 toutes les 3 semaines jusqu'à progression ou toxicité
(n = 290)

- Objectif principal : SG

- Objectifs secondaires
  - RO RECIST 1.1
  - SSP
  - Qualité de vie
  - Tolérance
  - Efficacité selon l'expression du PD-L1*

** IHC anti PD-L1 évaluée avec le système IHC Dako.*

Congrès américain d'oncologie 2016 - D'après Paz-Ares L et al., LBA109, actualisé

ORIGINAL ARTICLE

Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer

H. Borghaei, L. Paz-Ares, L. Horn, D.R. Spigel, M. Steins, N.E. Ready, L.Q. Chow, E.E. Vokes, E. Felip, E. Holgado, F. Barlesi, M. Kohlhäufl, O. Arrieta, M.A. Burgio, J. Fayette, H. Lena, E. Poddubskaya, D.E. Gerber, S.N. Gettinger, C.M. Rudin, N. Rizvi, L. Crinò, G.R. Blumenschein, Jr., S.J. Antonia, C. Dorange, C.T. Harbison, F. Graf Finckenstein, and J.R. Brahmer

Table 2. Tumor Response with Nivolumab versus Docetaxel in Patients with Advanced Nonsquamous Non–Small-Cell Lung Cancer.*

Variable	Nivolumab (N = 292)	Docetaxel (N = 290)
Objective response†		
No. of patients	56	36
% of patients (95% CI)	19 (15–24)	12 (9–17)
Estimated odds ratio (95% CI)	1.7 (1.1–2.6)	
P value	0.02	
Best overall response — no. (%)		
Complete response	4 (1)	1 (<1)
Partial response	52 (18)	35 (12)
Stable disease	74 (25)	122 (42)
Progressive disease	129 (44)	85 (29)
Could not be determined	33 (11)	47 (16)
Time to response — mo‡§		
Median	2.1	2.6
Range	1.2–8.6	1.4–6.3
Duration of response — mo‡¶		
Median	17.2	5.6
Range	1.8 to 22.6+	1.2+ to 15.2+

DOI: 10.1056/NEJMoa1507643

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Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer

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Variable	Nivolumab (N = 292)	Docetaxel (N = 290)
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% of patients (95% CI)	19 (15–24)	12 (9–17)
Estimated odds ratio (95% CI)	1.7 (1.1–2.6)	
P value	0.02	
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Complete response	4 (1)	1 (<1)
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Progressive disease	129 (44)	85 (29)
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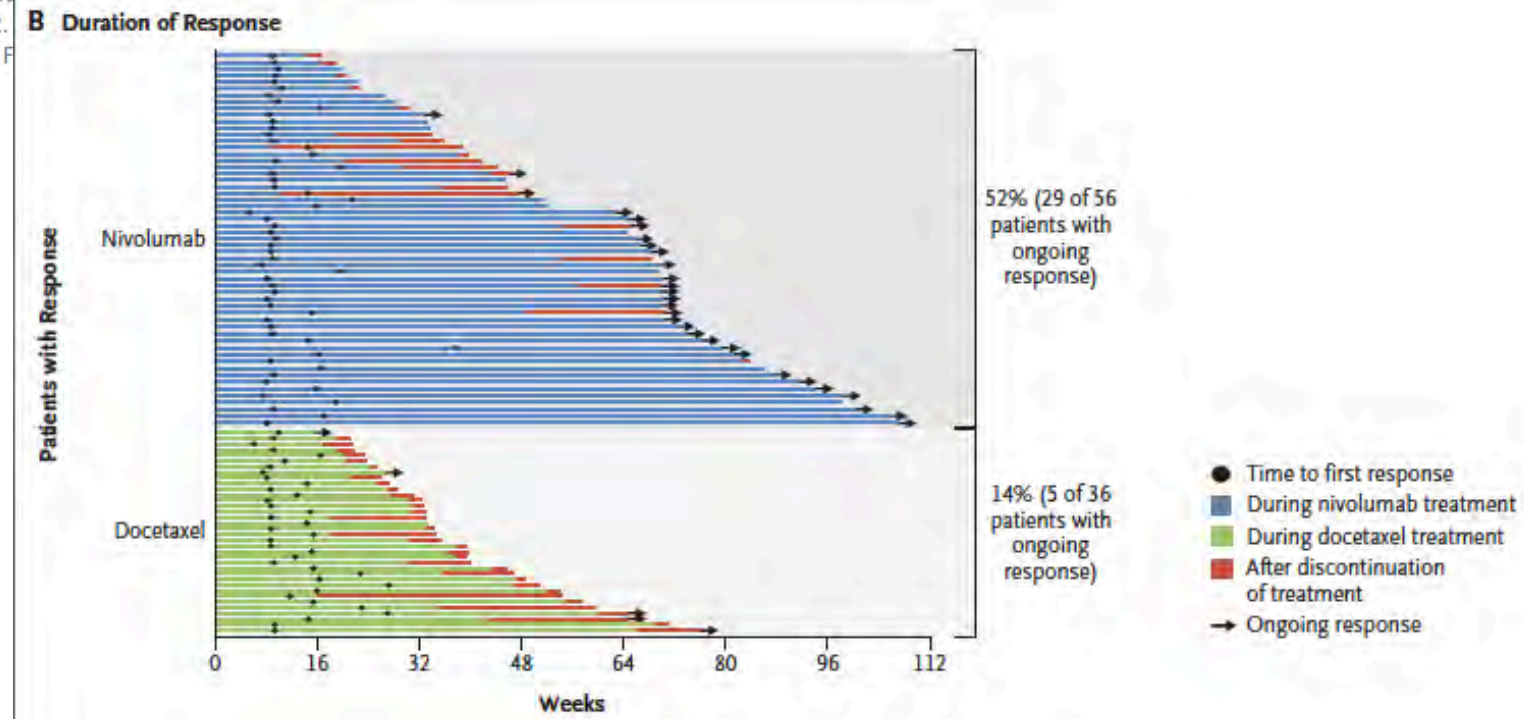

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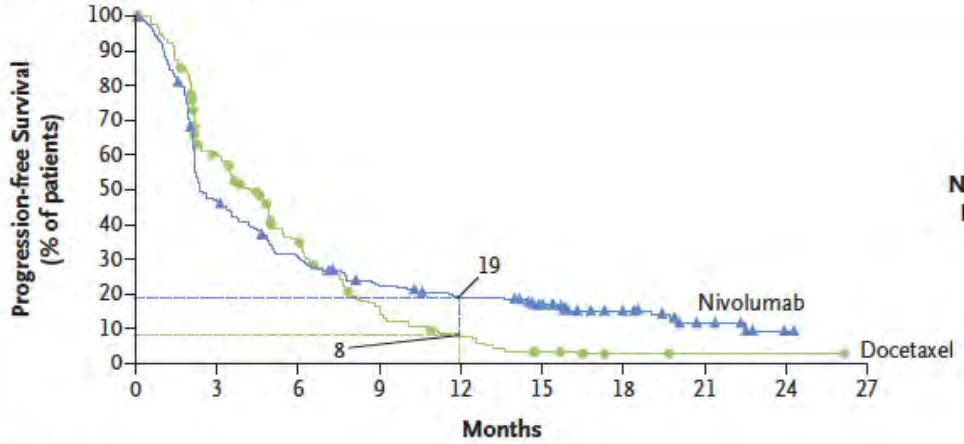
N. Rizvi, L.
C.T.

C Progression-free Survival



	No. of Events/ Total No. of Patients	Median Progression-free Survival (95% CI)	1-Yr Progression-free Survival Rate (95% CI)
		mo	%
Nivolumab	234/292	2.3 (2.2–3.3)	19 (14–23)
Docetaxel	245/290	4.2 (3.5–4.9)	8 (5–12)

Hazard ratio for disease progression or death, 0.92 (95% CI, 0.77–1.11); P=0.39

No. at Risk

Nivolumab	292	128	82	58	46	35	17	7	2	0
Docetaxel	290	156	87	38	18	6	2	1	1	0

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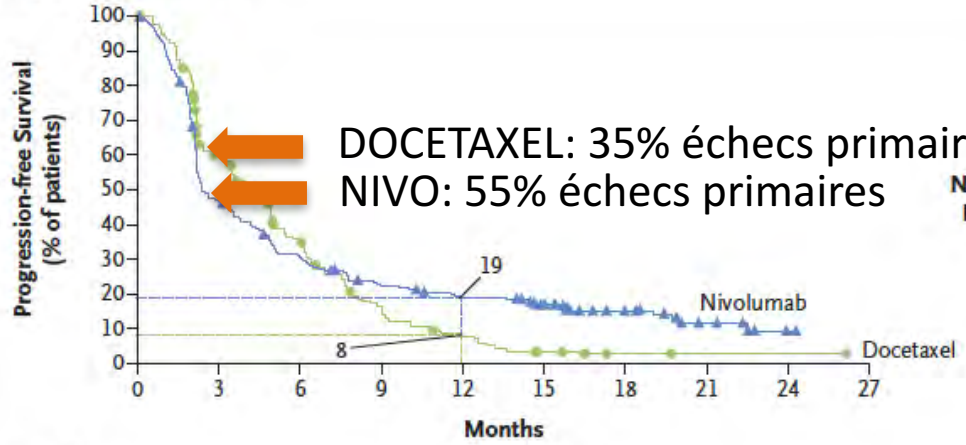
C.T.

C **Progression-free Survival**



DOCETAXEL: 35% échecs primaires
NIVO: 55% échecs primaires

	No. of Events/ Total No. of Patients	Median Progression-free Survival (95% CI)	1-Yr Progression-free Survival Rate (95% CI)
		mo	%
Nivolumab	234/292	2.3 (2.2–3.3)	19 (14–23)
Docetaxel	245/290	4.2 (3.5–4.9)	8 (5–12)

Hazard ratio for disease progression or death, 0.92 (95% CI, 0.77–1.11); P=0.39

No. at Risk

Nivolumab	292	128	82	58	46	35	17	7	2	0
Docetaxel	290	156	87	38	18	6	2	1	1	0

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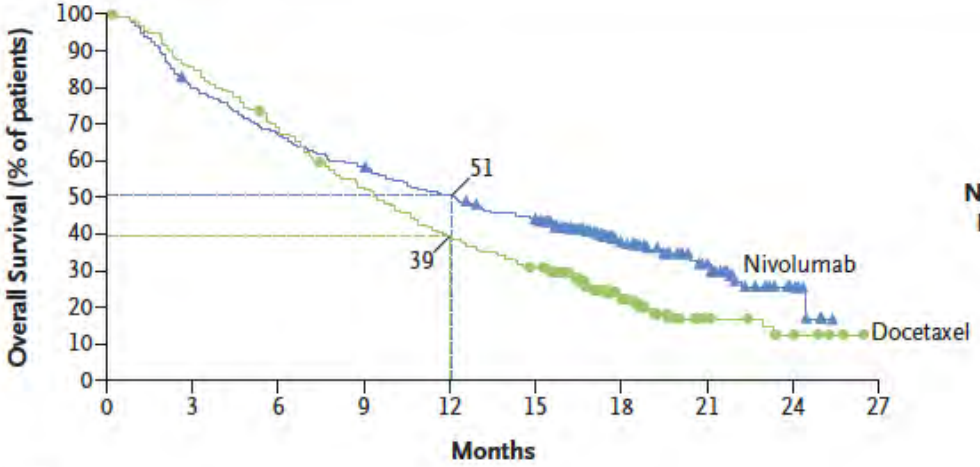
A Overall Survival



	No. of Deaths/ Total No. of Patients	Median Overall Survival (95% CI)	1-Yr Overall Survival Rate (95% CI)
		mo	%
Nivolumab	190/292	12.2 (9.7–15.0)	51 (45–56)
Docetaxel	223/290	9.4 (8.1–10.7)	39 (33–45)

Hazard ratio for death, 0.73 (96% CI, 0.59–0.89)
P=0.002

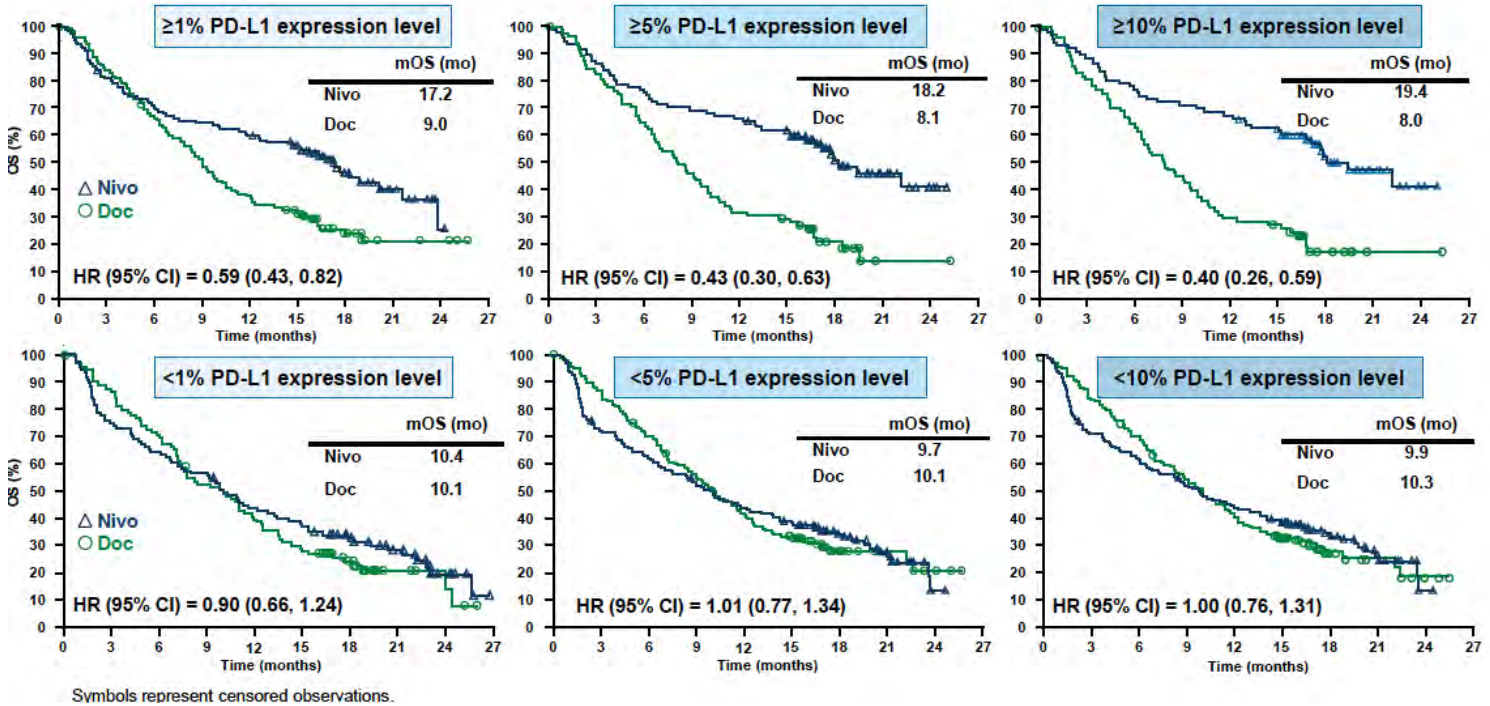
No. at Risk

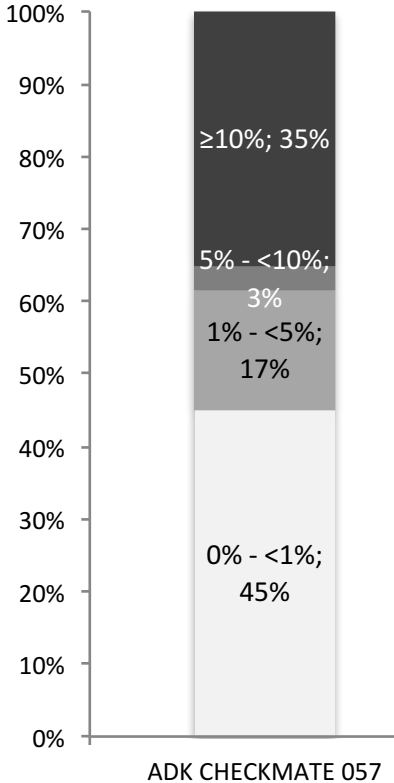
Nivolumab	292	232	194	169	146	123	62	32	9	0
Docetaxel	290	244	194	150	111	88	34	10	5	0

DOI: 10.1056/NEJMoa1507643

Seconde ligne
Nivolumab: carcinomes non épidermoïdes

Essai CHECKMATE 057

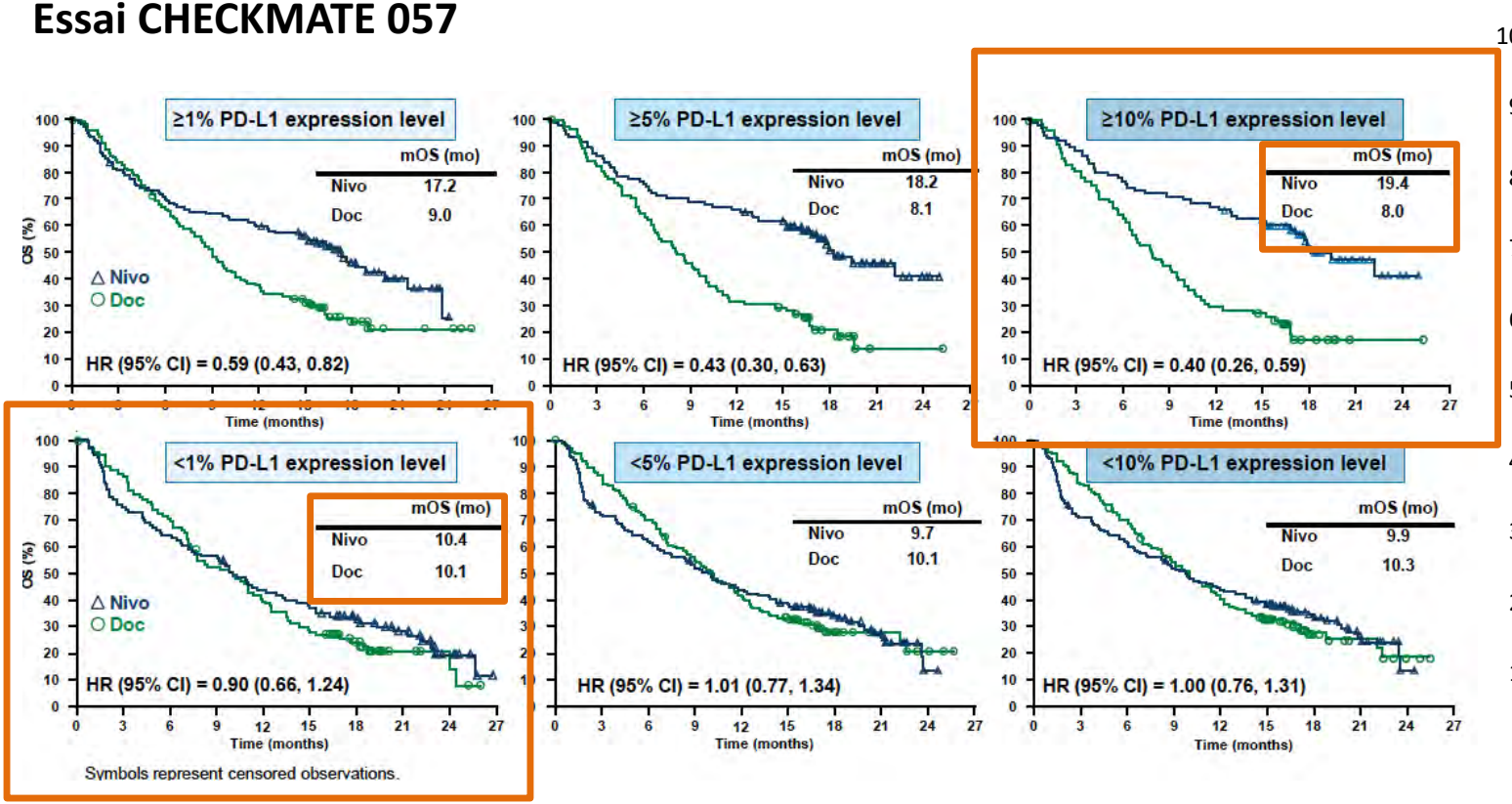


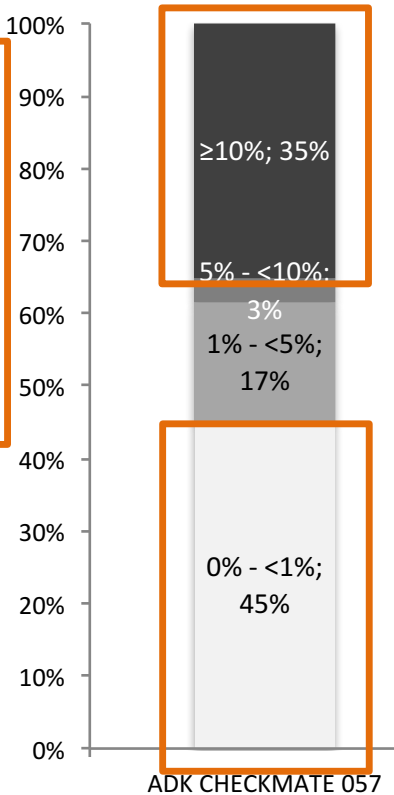


Congrès américain d'oncologie 2016 - D'après Paz-Ares L et al., LBA109, actualisé

Seconde ligne
Nivolumab: carcinomes non épidermoïdes

Essai CHECKMATE 057





Congrès américain d'oncologie 2016 - D'après Paz-Ares L et al., LBA109, actualisé

Essai Checkmate-057
Nivolumab: carcinomes non épidermoïdes

Essai CHECKMATE 057

Tableau 7 : ORR et SG selon l'expression tumorale de PD-L1 (CA209057)

Expression de PD-L1	nivolumab	docétaxel	
	ORR selon l'expression tumorale de PD-L1		
			Odds Ratio (IC 95%)
<1%	10/108 (9,3%) IC 95%: 4,5 ; 16,4	15/101 (14,9%) IC 95%: 8.6 ; 23,3	0,59 (0,22 ; 1,48)
≥1%	38/123 (30,9%) IC 95%: 22,9 ; 39,9	15/123 (12.2%) IC 95%: 7,0 ; 19 ,3	3,22 (1,60 ; 6,71)
≥1% à <10%[a]	6/37 (16,2%) IC 95%: 6,2 ; 32,0	5/44 (11,4%) IC 95%: 3,8 ; 24,6	1,51 (0,35 ; 6,85)
≥10% à <50%[a]	5/20 (25,0%) IC 95%: 8,7 ; 49,1	7/33 (21,2%) IC 95%: 9,0 ; 38,9	1,24 (0,26 ; 5,48)
≥50%[a]	27/66 (40,9%) IC 95%: 29,0 ; 53,7	3/46 (6,5%) IC 95%: 1.4 ; 17.9	9,92 (2,68 ; 54,09)
	SG selon l'expression tumorale de PD-L1		
	Nombre d'événements (nombre de patients)		**Hazard Ratio non stratifié (IC 95%)**
<1%	77 (108)	75 (101)	0,90 (0,66 ; 1,24)
≥1%	68 (123)	93 (123)	0,59 (0,43 ; 0,82)
≥1% à <10%[a]	27 (37)	30 (44)	1,33 (0,79 ; 2,24)
≥10% à <50%[a]	11 (20)	26 (33)	0,61 (0,30 ; 1,23)
≥50%[a]	30 (66)	37 (46)	0,32 (0,20 ; 0, 53)

Seconde ligne
Nivolumab: carcinomes non épidermoïdes

Essai CHECKMATE 057

ORR by PD-L1 Expression

PD-L1 expression level	ORR,[a] %		Odds Ratio (95% CI)	Interaction *P*-value	Median DOR, mo (95% CI)	
	Nivolumab	Docetaxel			Nivolumab	Docetaxel
≥1%	31	12	3.2 (1.6, 6.7)	0.0019	16.0 (8.4, NE)	5.6 (3.0, 5.7)
<1%	9	15	0.6 (1.6, 6.7)		18.3 (4.2, NE)	5.6 (4.2, 9.9)
≥5%	36	13	3.8 (1.7, 9.0)	0.0020	16.0 (8.4, NE)	5.6 (3.0, 7.0)
<5%	10	14	0.7 (0.3, 1.6)		18.3 (5.5, NE)	5.6 (4.2, 7.1)
≥10%	37	13	4.1 (1.8, 10)	0.0021	16.0 (6.9, NE)	5.6 (1.6, 6.2)
<10%	11	14	0.8 (0.4, 1.7)		18.3 (7.5, NE)	5.6 (4.2, 7.1)
Not quantifiable	13	9			7.3 (2.2, NE)	6.6 (2.8, 14.2)

[a]CR+PR as per RECIST v1.1 criteria. Confirmation of response required (investigator assessment)
NE = not evaluable

PRESENTED AT: ASCO Annual '15 Meeting

Congrès américain d´oncologie 2016 - D´après Paz-Ares L et al., LBA109, actualisé

Seconde ligne
Nivolumab: carcinomes non épidermoïdes

Essai CHECKMATE 057

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PRESENTED AT: ASCO Annual '15 Meeting

Congrès américain d´oncologie 2016 - D´après Paz-Ares L et al., LBA109, actualisé N Engl J Med 2016;373:123

Accès à des lignes ultérieures

Subsequent Cancer Therapy

	Nivolumab (n = 292)	Docetaxel (n = 290)
Patients with Any Subsequent Therapy,[a] %	52	60
Subsequent Systemic Therapy, %	42	50
Chemotherapy	38	34
Taxane	29	9
Antimetabolite	17	27
Platinum agents	8	8
EGFR/ALK Inhibitors, %	12	24
VEGF(R) Inhibitors, %	4	2
Immunotherapy, %	<1	2
Experimental Therapy,[b] %	6	4
Other, %	1	1

- Subsequent docetaxel was received by 23% of patients in the nivolumab arm and 5% of patients in the docetaxel arm

[a]Patients may have received more than one type of subsequent therapy; [b]Non-immunotherapy experimental agents.
Subsequent therapy was defined as therapy started on or after first dosing date (randomization date if patient never treated).

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 February 2016
EMA/CHMP/148121/2016
Committee for Medicinal Products for Human Use (CHMP)

Summary of opinion[1] (post authorisation)

Opdivo

nivolumab

On 25 February 2016, the Committee for Medicinal Products for Human Use (CHMP) adopted two positive opinions recommending changes to the terms of the marketing authorisation for the medicinal product Opdivo. The marketing authorisation holder for this medicinal product is Bristol-Myers Squibb Pharma EEIG.

The CHMP adopted a new indication as follows:

"Renal Cell Carcinoma (RCC)

Opdivo as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults."

In addition, the CHMP adopted an extension to an existing indication as follows[2]:

"Opdivo is indicated for the treatment of locally advanced or metastatic ~~squamous~~ non-small cell lung cancer (NSCLC) after prior chemotherapy in adults."

L'immunothérapie dans le cancer du poumon

Réponse immunitaire anti-tumorale

Stratégies d'immunothérapie

Inhibiteurs de PD-1
Profils d'efficacité

Biomarqueur
PD-L1

2016

Tolérance

Intégration en seconde ligne de traitement

Nivolumab

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2016

Tolérance

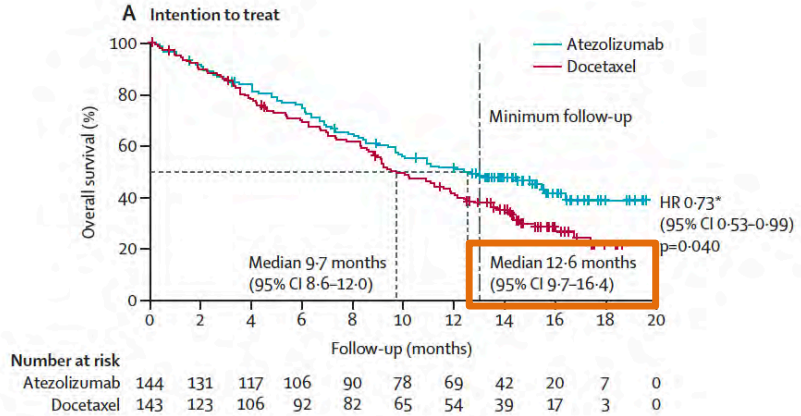
Intégration en seconde ligne de traitement

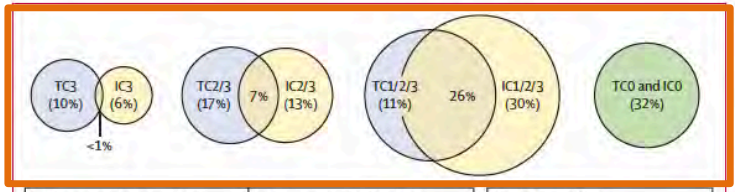
Nivolumab

Atezolizumab

Seconde ligne
Atezolizumab (MPDL3280A)

Essai POPLAR

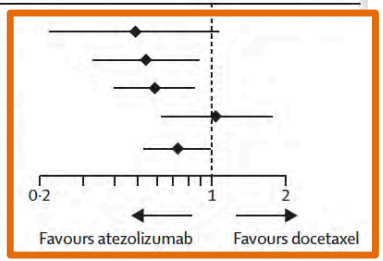




PD-L1 tumour cell scoring		PD-L1 tumour-infiltrating immune cell scoring		Overall prevalence	
Score	Percentage of PD-L1-expressing cells	Score	Percentage of PD-L1-expressing cells	Subgroup	Proportion
TC3	≥50%	IC3	≥10%	TC3 or IC3	16%
TC2	≥5% and <50%	IC2	≥5% and <10%	TC2/3 or IC2/3	37%
TC1	≥1% and <5%	IC1	≥1% and <5%	TC1/2/3 or IC1/2/3	68%
TC0	<1%	IC0	<1%	TC0 and IC0	32%

B

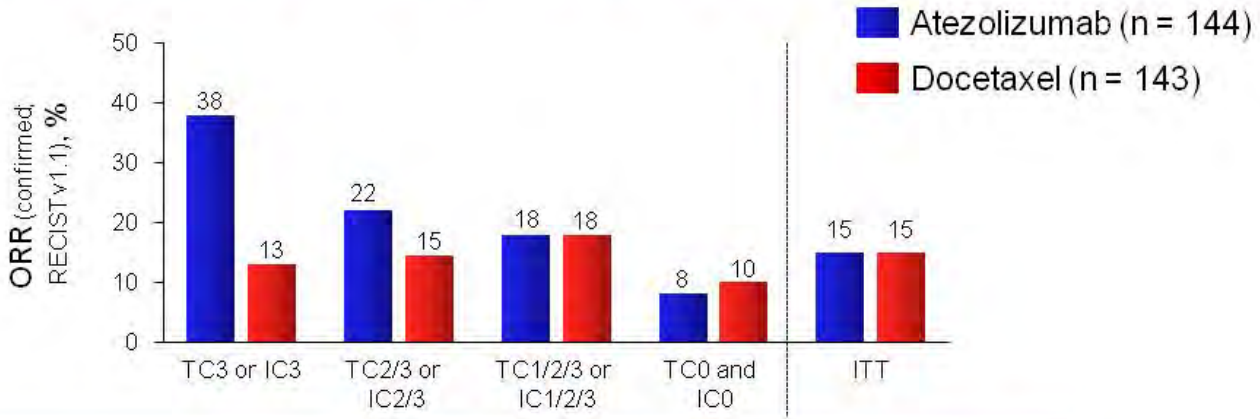
	n (%)	HR*	95% CI	p value	Median overall survival (months [95% CI])	
					Atezolizumab (n=144)	Docetaxel (n=143)
TC3 or IC3	47 (16%)	0·49	0·22–1·07	0·068	15·5 (9·8–NE)	11·1 (6·7–14·4)
TC2/3 or IC2/3	105 (37%)	0·54	0·33–0·89	0·014	15·1 (8·4–NE)	7·4 (6·0–12·5)
TC1/2/3 or IC1/2/3	195 (68%)	0·59	0·40–0·85	0·005	15·5 (11·0–NE)	9·2 (7·3–12·8)
TC0 and IC0	92 (32%)	1·04	0·62–1·75	0·871	9·7 (6·7–12·0)	9·7 (8·6–12·0)
Intention to treat	287	0·73	0·53–0·99	0·040	12·6 (9·7–16·4)	9·7 (8·6–12·0)



Seconde ligne
Atezolizumab (MPDL3280A)

Essai POPLAR

POPLAR: Confirmed Overall Response and Duration of Response



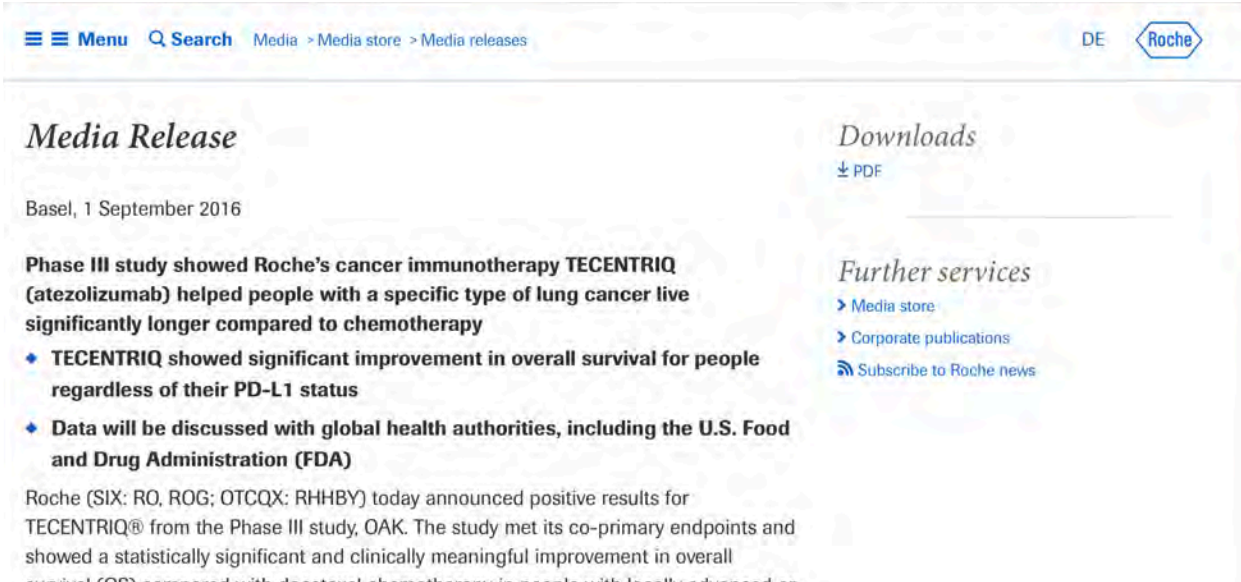
	Atezolizumab (n = 21)	Docetaxel (n = 22)
Median duration of response (95% CI), mo	Not reached	7.8 (5.8-12.9)
Responders with ongoing response[a], n (%)	16 (76%)	11 (50%)

[a]Ongoing without experiencing a PFS event.
Data cut-off Jan 30, 2015.

Congrès américain d'oncologie 2016 - D'après Spira AI et al., abstr. 8010, actualisé

Seconde ligne
Atezolizumab (MPDL3280A)

Essai OAK



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Media Release

Basel, 1 September 2016

Phase III study showed Roche's cancer immunotherapy TECENTRIQ (atezolizumab) helped people with a specific type of lung cancer live significantly longer compared to chemotherapy

- **TECENTRIQ showed significant improvement in overall survival for people regardless of their PD-L1 status**
- **Data will be discussed with global health authorities, including the U.S. Food and Drug Administration (FDA)**

Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced positive results for TECENTRIQ® from the Phase III study, OAK. The study met its co-primary endpoints and showed a statistically significant and clinically meaningful improvement in overall

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Tolérance

Intégration en seconde ligne de traitement

Nivolumab

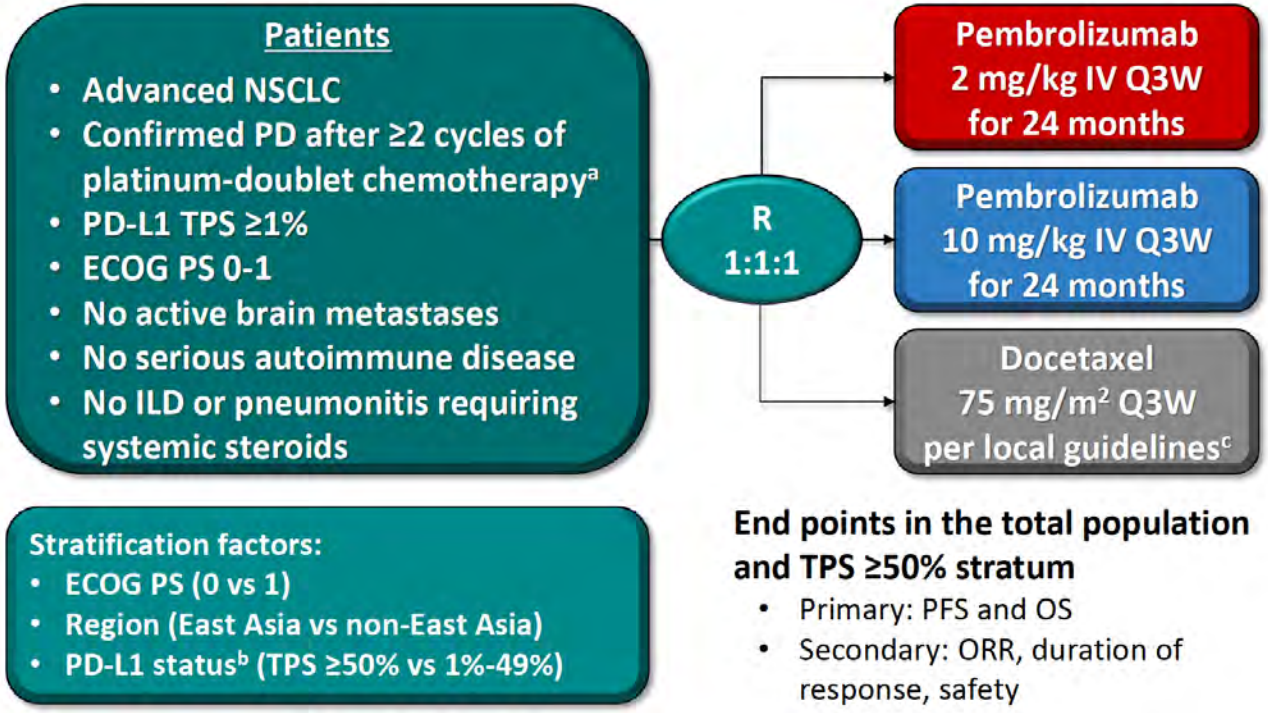
Atezolizumab

Pembrolizumab

Pembrolizumab: KEYNOTE-010

Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial

Roy S Herbst, Paul Baas, Dong-Wan Kim, Enriqueta Felip, José L Pérez-Gracia, Ji-Youn Han, Julian Molina, Joo-Hang Kim, Catherine Dubos Arvis, Myung-Ju Ahn, Margarita Majem, Mary J Fidler, Gilberto de Castro Jr, Marcelo Garrido, Gr Marisa Dolled-Filhart, Edward B Garon



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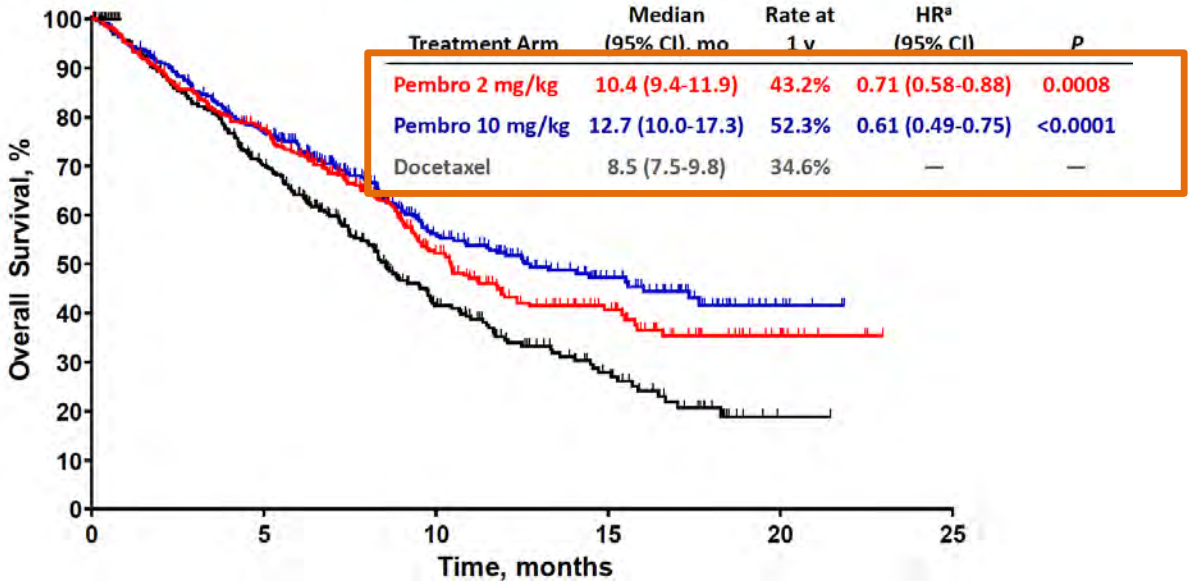
OS, PD-L1 TPS ≥1% (Total Population)



Treatment Arm	Median (95% CI), mo	Rate at 1 y	HR[a] (95% CI)	*P*
Pembro 2 mg/kg	10.4 (9.4-11.9)	43.2%	0.71 (0.58-0.88)	0.0008
Pembro 10 mg/kg	12.7 (10.0-17.3)	52.3%	0.61 (0.49-0.75)	<0.0001
Docetaxel	8.5 (7.5-9.8)	34.6%	—	—

Herbst et al. Lancet Oncol 2016; sous presse

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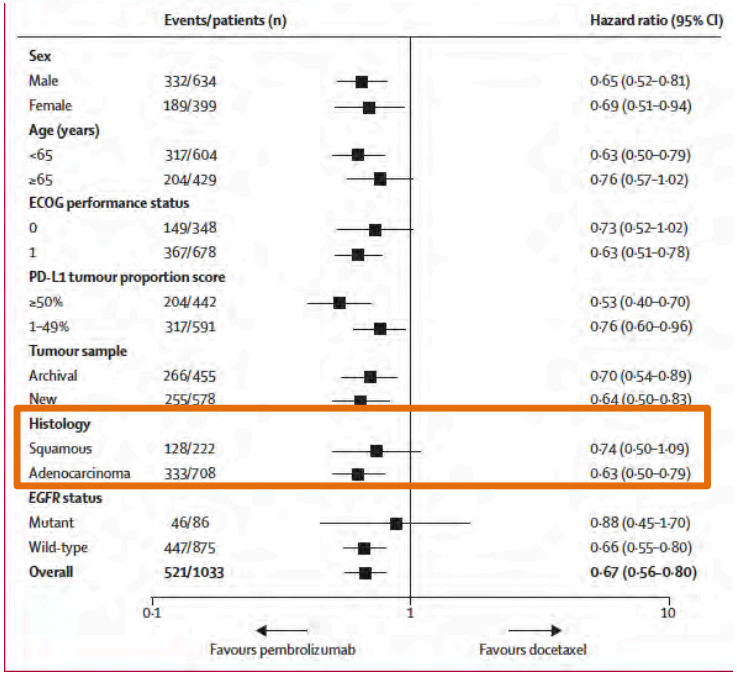

Herbst et al. Lancet Oncol 2016; sous presse

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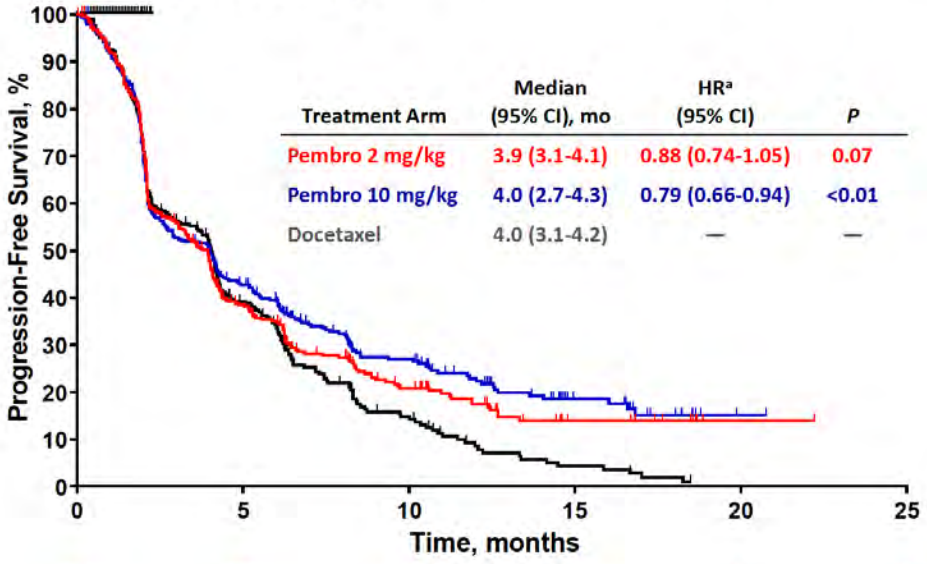
PFS (RECIST v1.1, Central Review), PD-L1 TPS ≥1%



Treatment Arm	Median (95% CI), mo	HR[a] (95% CI)	*P*
Pembro 2 mg/kg	3.9 (3.1-4.1)	0.88 (0.74-1.05)	0.07
Pembro 10 mg/kg	4.0 (2.7-4.3)	0.79 (0.66-0.94)	<0.01
Docetaxel	4.0 (3.1-4.2)	—	—

Herbst et al. Lancet Oncol 2016; sous presse

Accès à des lignes ultérieures

	Pembrolizumab 2 mg/kg (n=344)	Pembrolizumab 10 mg/kg (n=346)	Docetaxel (n=343)
Any, n (%)	138 (40·1)	133 (38·4)	151 (44·0)
Type of therapy,* n (%)			
Chemotherapy	119 (34·6)	100 (28·9)	93 (27·1)
Immunotherapy	2 (0·6)	6 (1·7)	45 (13·1)
EGFR-TKI	29 (8·4)	23 (6·6)	42 (12·2)
ALK inhibitor	2 (0·6)	5 (1·4)	4 (1·2)
Other	14 (4·1)	20 (5·8)	11 (3·2)

L'immunothérapie dans le cancer du poumon

Réponse immunitaire anti-tumorale

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Biomarqueur
PD-L1

2016

Tolérance

Intégration en seconde ligne de traitement

Nivolumab

Atezolizumab

Pembrolizumab

Intégration en première ligne de traitement

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Tolérance

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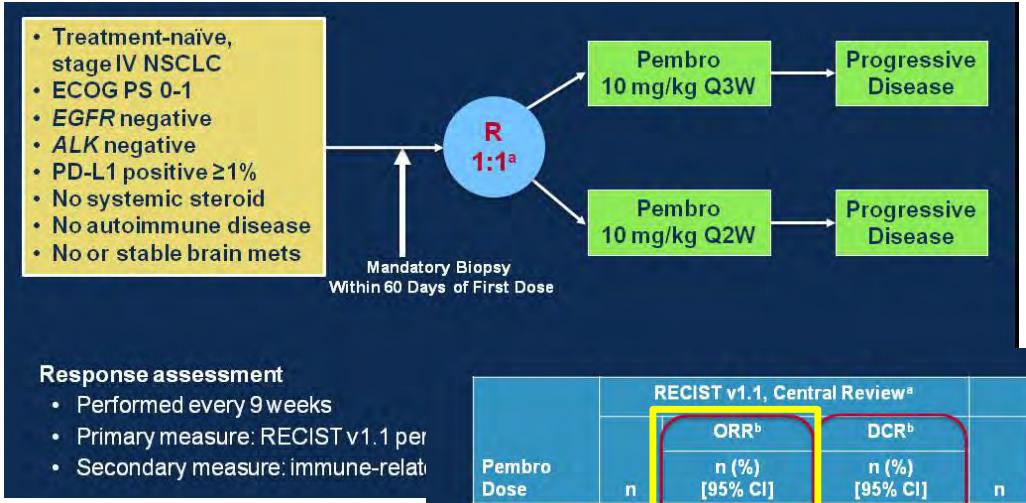
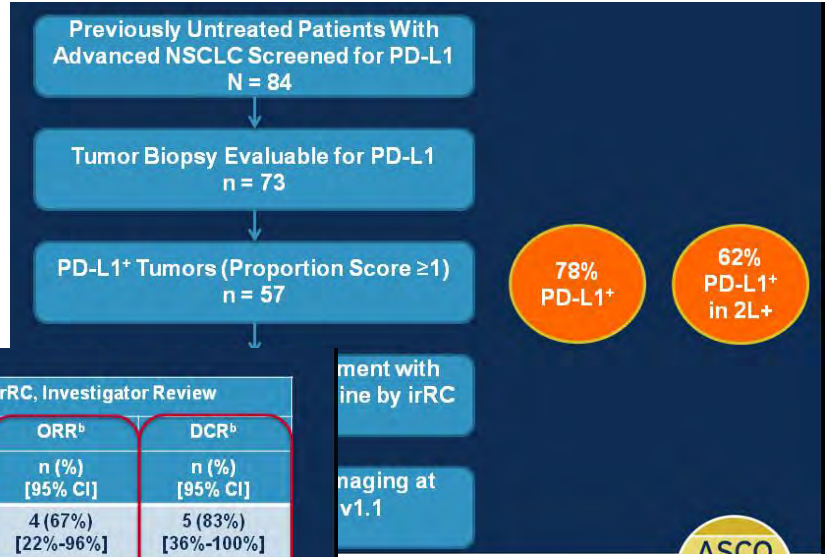
Pembrolizumab

Intégration en première ligne de traitement

Sélection sur positivité de PD-L1

Pembrolizumab: première ligne, monothérapie, PD-L1 +
Essai de phase II KEYNOTE-010





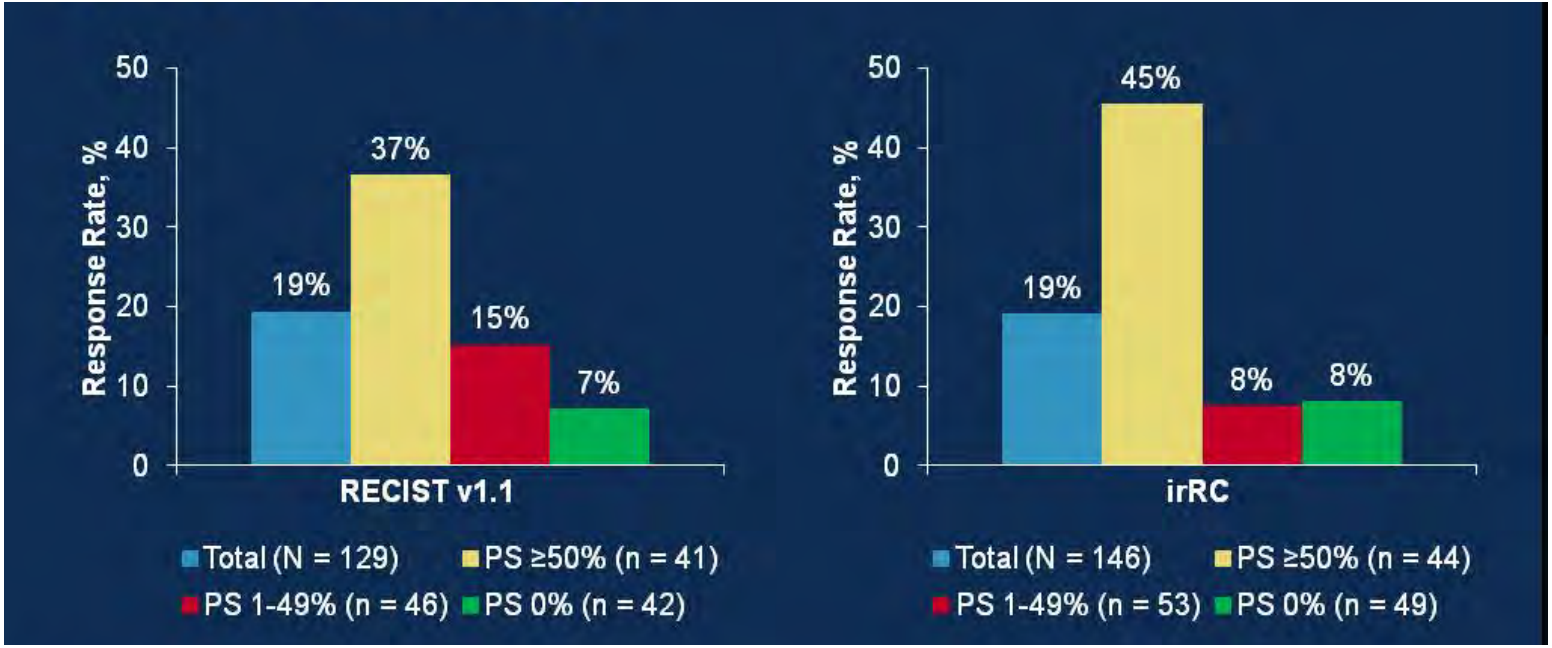
Pembro Dose	RECIST v1.1, Central Review[a] n	RECIST v1.1, Central Review[a] ORR[b] n (%) [95% CI]	RECIST v1.1, Central Review[a] DCR[b] n (%) [95% CI]	irRC, Investigator Review n	irRC, Investigator Review ORR[b] n (%) [95% CI]	irRC, Investigator Review DCR[b] n (%) [95% CI]
2 mg/kg Q3W	6	2 (33%) [4%-78%]	3 (50%) [12%-88%]	6	4 (67%) [22%-96%]	5 (83%) [36%-100%]
10 mg/kg Q3W	20	4 (20%) [6%-44%]	14 (70%) [46%-88%]	22	10 (46%) [24%-68%]	18 (82%) [60%-95%]
10 mg/kg Q2W	16	5 (31%) [11%-59%]	10 (63%) [35%-85%]	17	7 (41%) [18%-67%]	12 (71%) [44%-90%]
Total	42	11 (26%) [14%-42%]	27 (64%) [48%–78%]	45	21 (47%) [32%-62%]	35 (78%) [63%-89%]

• Interim median PFS[c]:

Rizvi et al. ASCO 2014

Intégration dans la stratégie actuelle: première ligne

Pembrolizumab: première ligne, monothérapie, PD-L1 +
Essai de phase II KEYNOTE-010

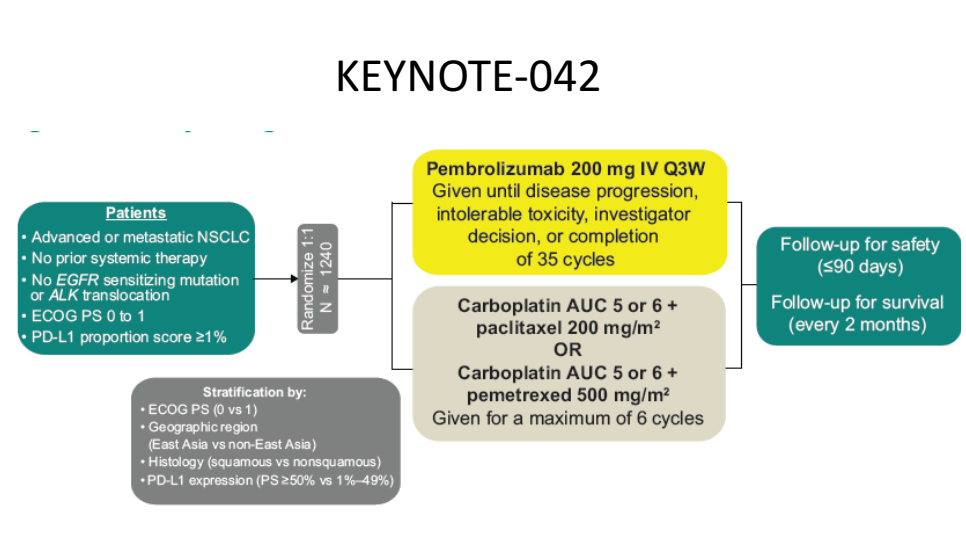


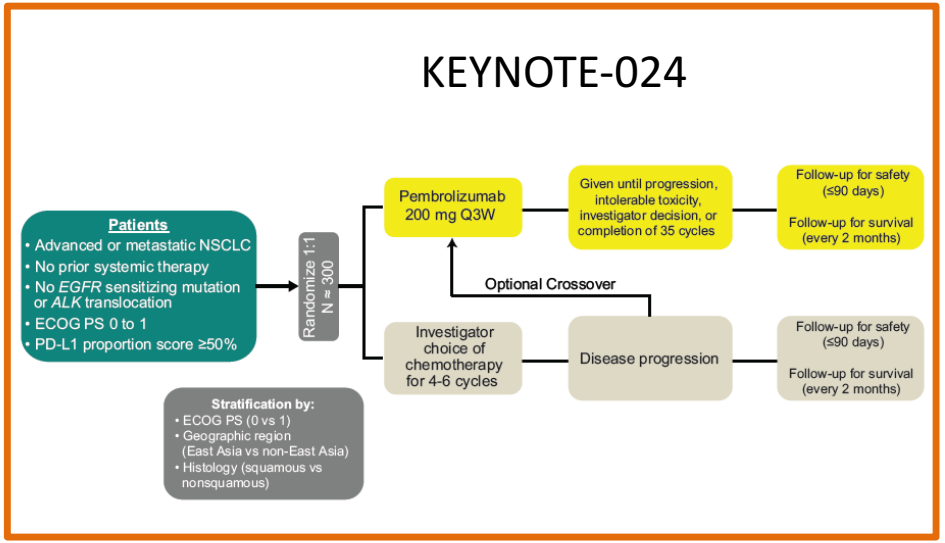
Rizvi et al. ASCO 2014

Intégration dans la stratégie actuelle: première ligne

Pembrolizumab: première ligne, monothérapie, PD-L1 +
Essais en cours

PD-L1 +++





ECOG PS = Eastern Cooperative Oncology Group performance status; IV = intravenous.

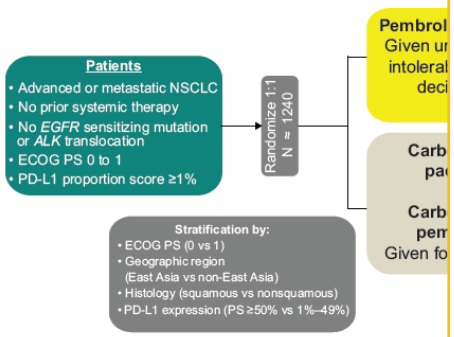
ASCO 2016

Monothérapies: première ligne

Pembrolizumab: première ligne, monothérapie, PD-L1 +
Essais en cours

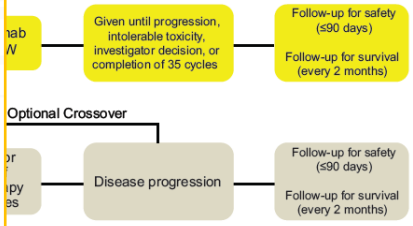
PD-L1 +++

KEYNOTE-04



ECOG PS = Eastern Cooperative Oncology Group performa

NOTE-024



MERCK

News Release

Media Contacts:	Pamela Eisele (267) 305-3558	Investor Contacts:	Teri Loxam (908) 740-1986
	Courtney Ronaldo (908) 236-1108		Justin Holko (908) 740-1879

Merck's KEYTRUDA® (pembrolizumab) Demonstrates Superior Progression-Free and Overall Survival Compared to Chemotherapy as First-Line Treatment in Patients with Advanced Non-Small Cell Lung Cancer

KEYNOTE-024 Studied Patients Whose Tumors Expressed High Levels of PD-L1

KENILWORTH, N.J., June 16, 2016 – Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced that the KEYNOTE-024 trial investigating the use of KEYTRUDA® (pembrolizumab), in patients with previously untreated advanced non-small cell lung cancer (NSCLC) whose tumors expressed high levels of PD-L1 (tumor proportion score of 50 percent or more), met its primary endpoint. In this trial, KEYTRUDA was superior compared to chemotherapy for both the primary endpoint of progression-free survival (PFS), and the

L’immunothérapie dans le cancer du poumon

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Biomarqueur
PD-L1

2016

Tolérance

Intégration en seconde ligne de traitement

Nivolumab

Atezolizumab

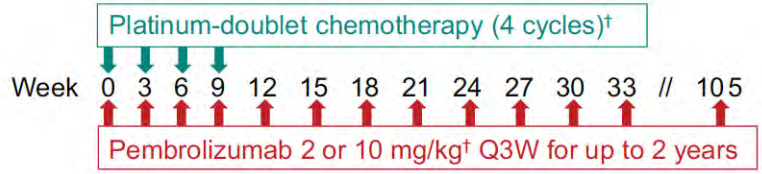
Pembrolizumab

Intégration en première ligne de traitement

Intégration dans la stratégie actuelle: première ligne

Pembrolizumab: première ligne, plus doublet, PD-L1 + KEYNOTE-021

PD-L1 +/-



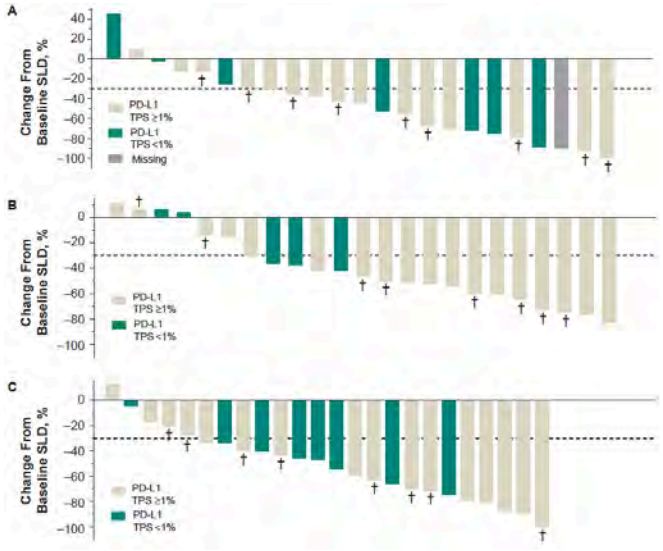
Pembrolizumab and platinum-doublet chemotherapy dosing

- Cohort A: pembrolizumab 2 or 10 mg/kg (randomized 1:1) plus carboplatin AUC 6 plus paclitaxel 200 mg/m² every 3 weeks (Q3W)
- Cohort B: pembrolizumab 2 or 10 mg/kg (randomized 1:1) plus carboplatin AUC 6 plus paclitaxel 200 mg/m² plus bevacizumab 15 mg/kg Q3W
- Cohort C: pembrolizumab 2 or 10 mg/kg (randomized 1:1) plus carboplatin AUC 5 plus pemetrexed 500 mg/m² Q3W

Carbo Taxol Pembro

Carbo Taxol Avastin Pembro

Carbo Peml Pembro



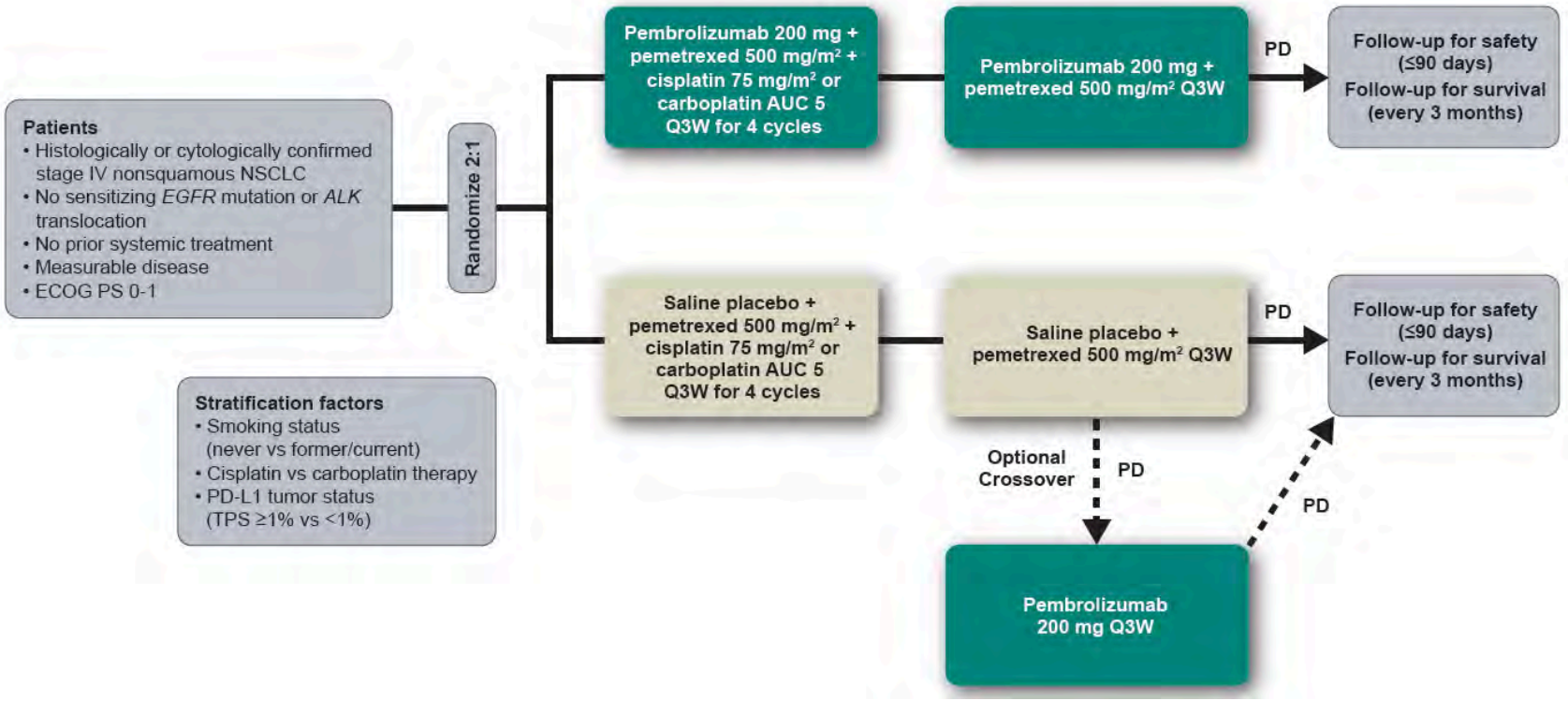
ORR (confirmed), n (%) [95% CI]	Carbo Taxol Pembro Cohort A N = 25	Carbo Taxol Avastin Pembro Cohort B N = 25	Carbo Peml Pembro Cohort C N = 24	All patients N = 74
Duration of follow-up, median, months (range)	13 (2-21)	9 (<1-17)	16 (4-21)	12 (<1-21)
Total population	13 (52) [31-72]	12 (48) [28-69]	17 (71) [49-87]	42 (57) [45-68]
CR, n (%)	0	0	1 (4)	1 (1)
PR, n (%)	13 (52)	12 (48)	16 (67)	41 (55)

ASCO 2016

Intégration dans la stratégie actuelle: première ligne

Pembrolizumab: première ligne, plus doublet, PD-L1 + ou -
KEYNOTE-189

PD-L1 +/-



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Nivolumab

Atezolizumab

Pembrolizumab

Intégration en première ligne de traitement

Monothérapies: première ligne

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

PD-L1 +/-

Nivolumab Monotherapy for First-Line Treatment of Advanced Non–Small-Cell Lung Cancer

Scott Gettinger, Naiyer A. Rizvi, Laura Q. Chow, Hossein Borghaei, Julie Brahmer, Neal Ready, David E. Gerber, Frances A. Shepherd, Scott Antonia, Jonathan W. Goldman, Rosalyn A. Juergens, Scott A. Laurie, Faith E. Nathan, Yun Shen, Christopher T. Harbison, and Matthew D. Hellmann

Table 3. Tumor Response in Patients With Advanced NSCLC Treated With Nivolumab Monotherapy[a]

Response/Survival	Squamous (n = 13)	Nonsquamous (n = 39)	All Patients (N = 52)
Confirmed ORR,[b] No. (%) [95% CI]	2 (15) [2 to 45]	10 (26) [13 to 42]	12 (23) [13 to 37]
Confirmed DCR,[c] No. (%) [95% CI]	8 (62) [32 to 86]	18 (46) [30 to 63]	26 (50) [36 to 64]
Ongoing responders,[d] No. (%)	1 (50)	7 (70)	8 (67)
BOR,[e] No. (%)			
Confirmed CR	1 (8)	3 (8)	4 (8)
Confirmed PR	1 (8)	7 (18)	8 (15)
SD	6 (46)	8 (21)	14 (27)
SD ≥ 21 weeks[f]	3 (23)	7 (18)	10 (19)
Progressive disease	5 (38)	15 (38)	20 (38)
Unable to determine	0	6 (15)[g]	6 (12)
Estimated DOR,[h] median (range), months	NR (16.5 to 23.3+)	NR (4.2 to 25.8+)	NR (4.2 to 25.8+)
PFS, median (range), months	3.5 (1.4 to 25.6+)	5.0 (< 0.1+ to 28.0+)	3.6 (< 0.1+ to 28.0+)
PFS at 24 weeks,[i] % (95% CI)	31 (9 to 55)	45 (28 to 60)	41 (27 to 54)
OS, median (range), months	16.8 (3.1 to 32.5+)	NR (0.2 to 35.8+)	19.4 (0.2 to 35.8+)
1-year OS, % (95% CI)	76 (43 to 92)	72 (55 to 83)	73 (59 to 83)
18-month OS, % (95% CI)	42 (16 to 67)	63 (45 to 76)	57 (42 to 70)

Monothérapies: première ligne

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

PD-L1 +/-

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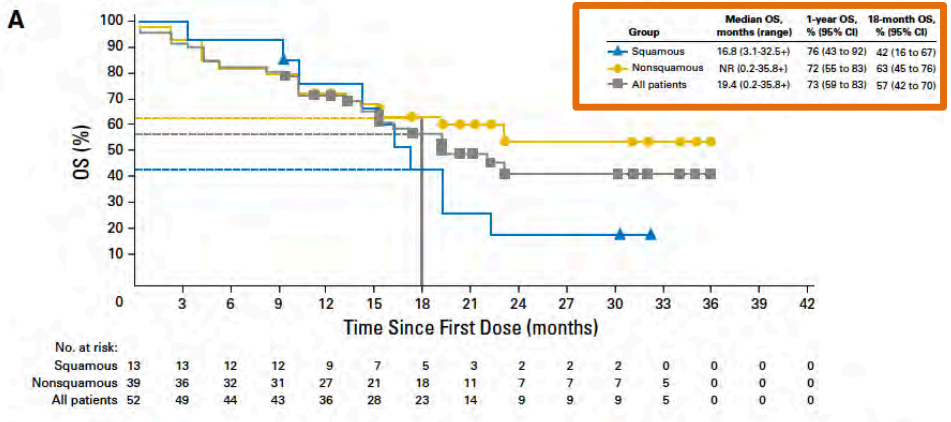
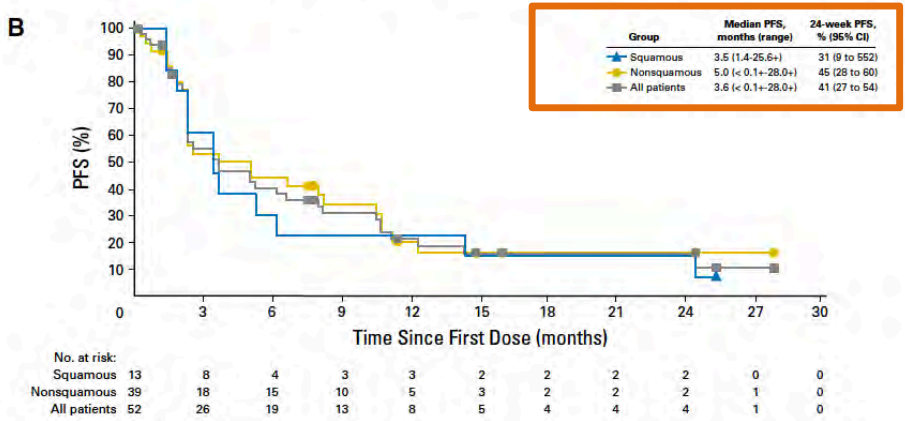
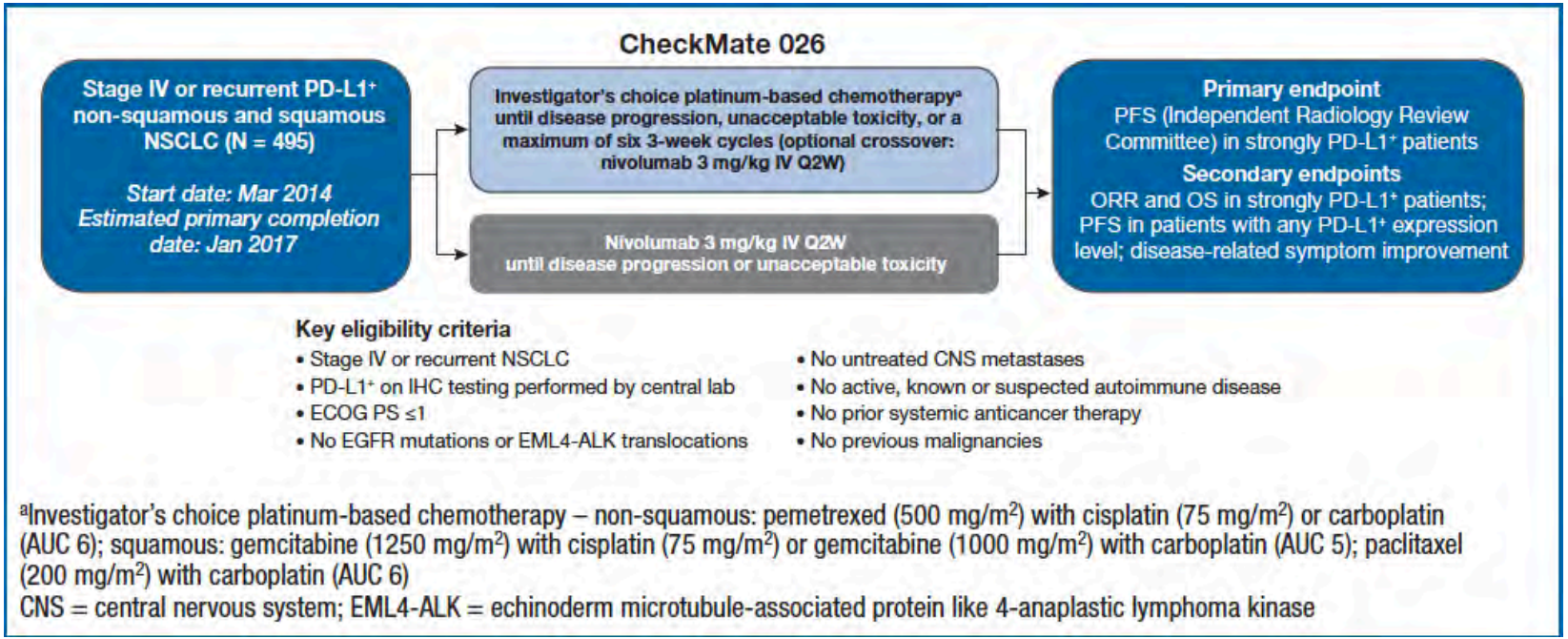




Monothérapies: première ligne

Nivolumab: première ligne, monothérapie, PD-L1 +
Essais en cours

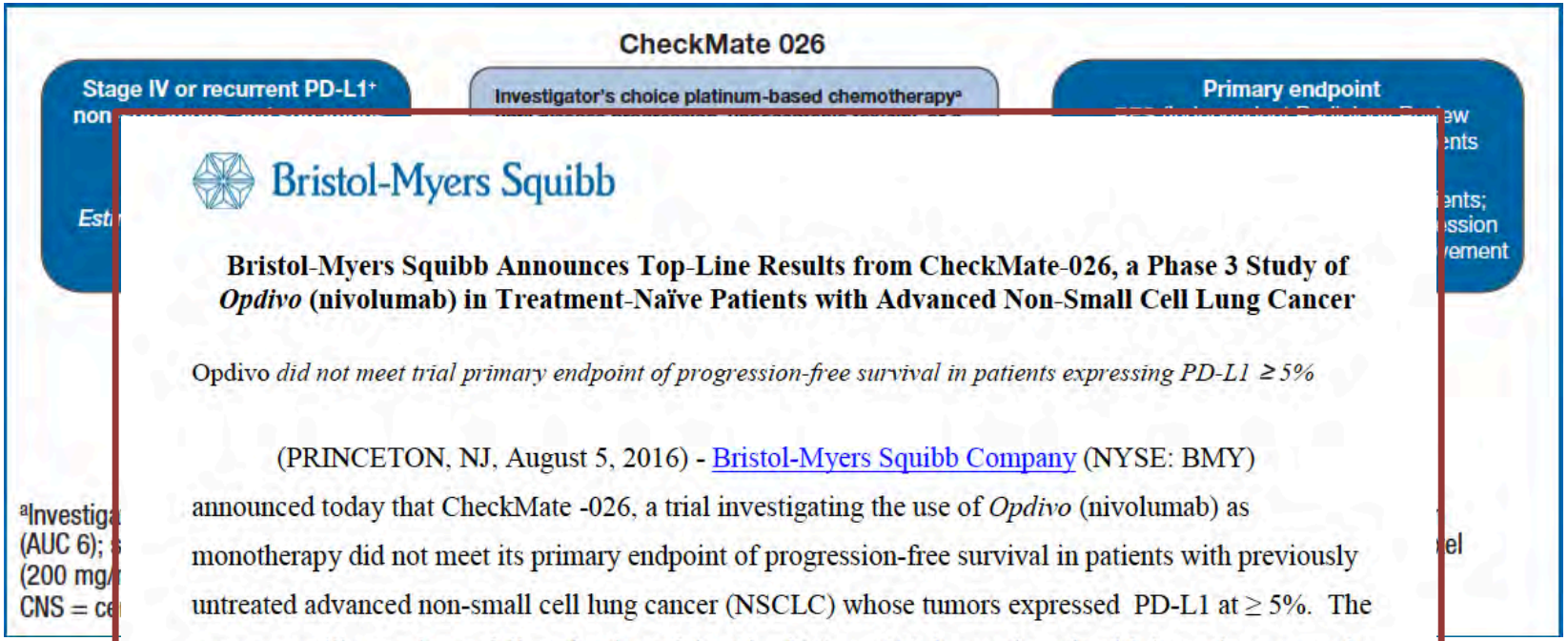
PD-L1 +



Monothérapies: première ligne

Nivolumab: première ligne, monothérapie, PD-L1 +
Essais en cours

PD-L1 +



Bristol-Myers Squibb

Bristol-Myers Squibb Announces Top-Line Results from CheckMate-026, a Phase 3 Study of *Opdivo* (nivolumab) in Treatment-Naïve Patients with Advanced Non-Small Cell Lung Cancer

Opdivo *did not meet trial primary endpoint of progression-free survival in patients expressing PD-L1 ≥ 5%*

(PRINCETON, NJ, August 5, 2016) - Bristol-Myers Squibb Company (NYSE: BMY) announced today that CheckMate -026, a trial investigating the use of *Opdivo* (nivolumab) as monotherapy did not meet its primary endpoint of progression-free survival in patients with previously untreated advanced non-small cell lung cancer (NSCLC) whose tumors expressed PD-L1 at ≥ 5%. The company will complete a full evaluation of the CheckMate -026 data and work with investigators on the future presentation of the results.

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PD-L1

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Nivolumab

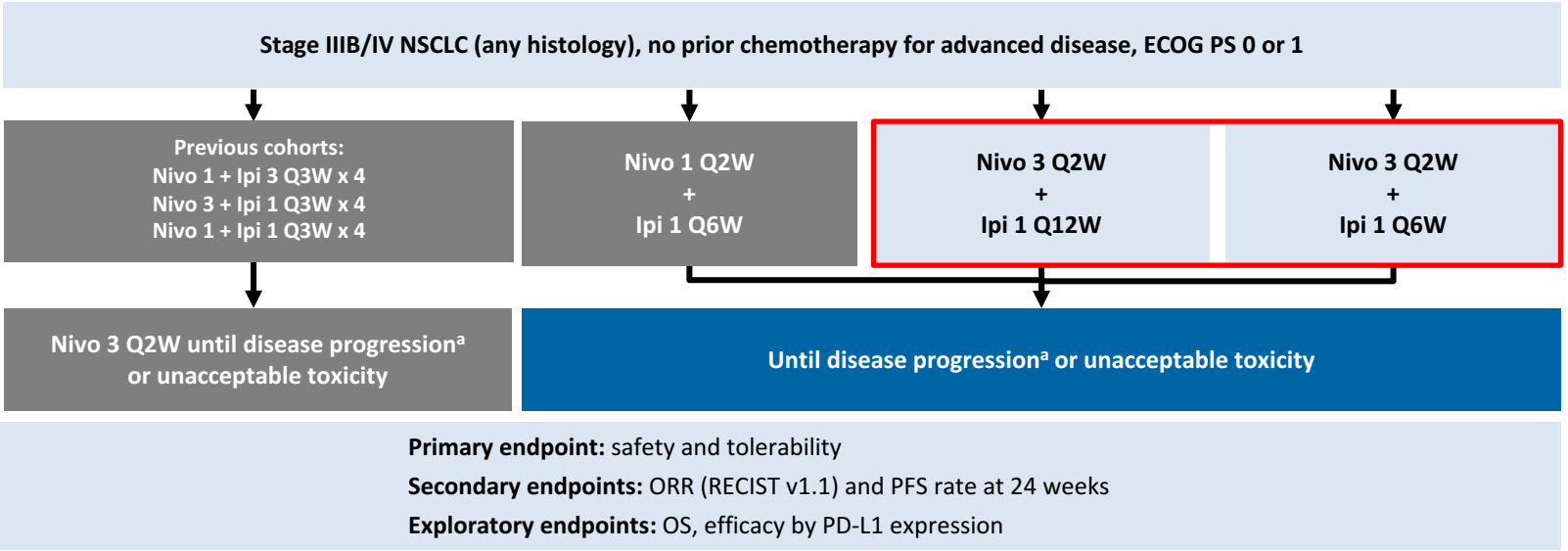
Atezolizumab

Pembrolizumab

Intégration en première ligne de traitement

Combinaisons d'immunothérapies: première ligne

Nivolumab: première ligne, monothérapie et combinaison
Essai de phase II CHECKMATE 012



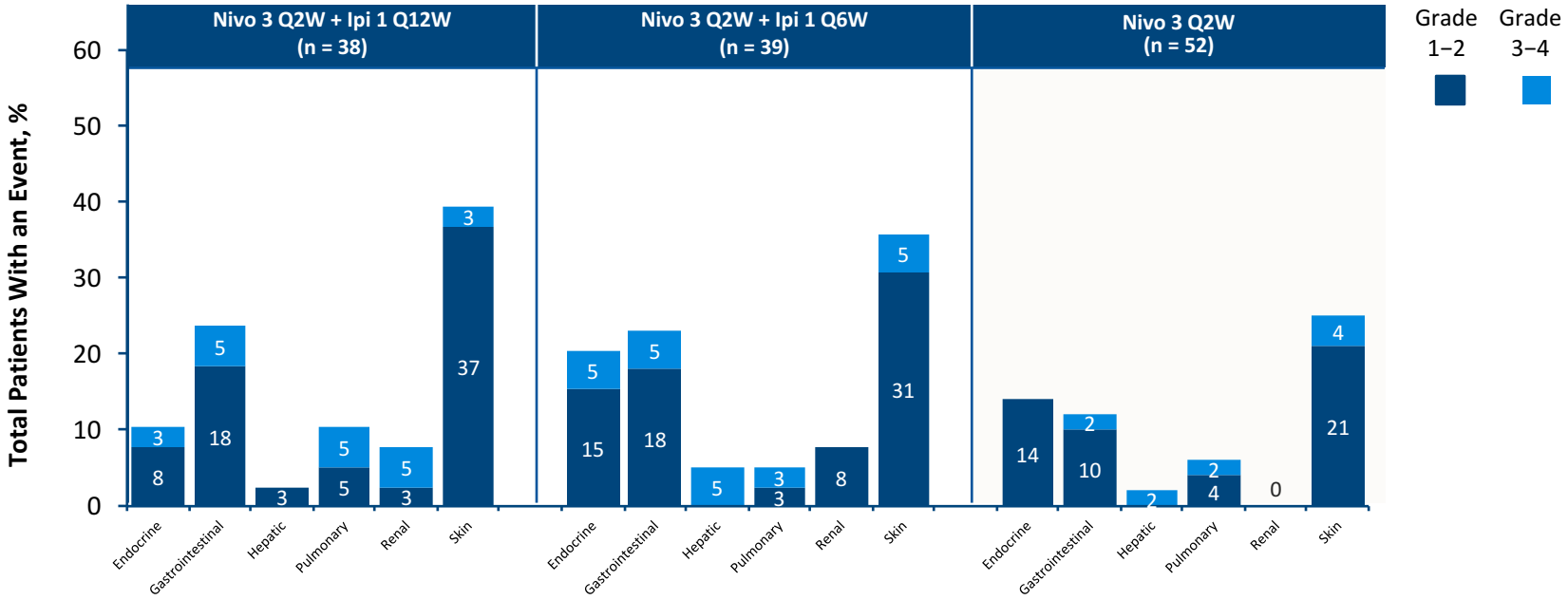
The safety and tolerability of the nivolumab–ipilimumab combination was improved with less frequent ipilimumab dosing[5]

Schedules with nivolumab 3 mg/kg also showed increased clinical efficacy in a previous analysis[5]

Here, we report longer follow-up on nivolumab 3 mg/kg plus ipilimumab schedules[b]

Combinaisons d'immunothérapies: première ligne

Nivolumab: première ligne, monothérapie et combinaison
Essai de phase II CHECKMATE 012

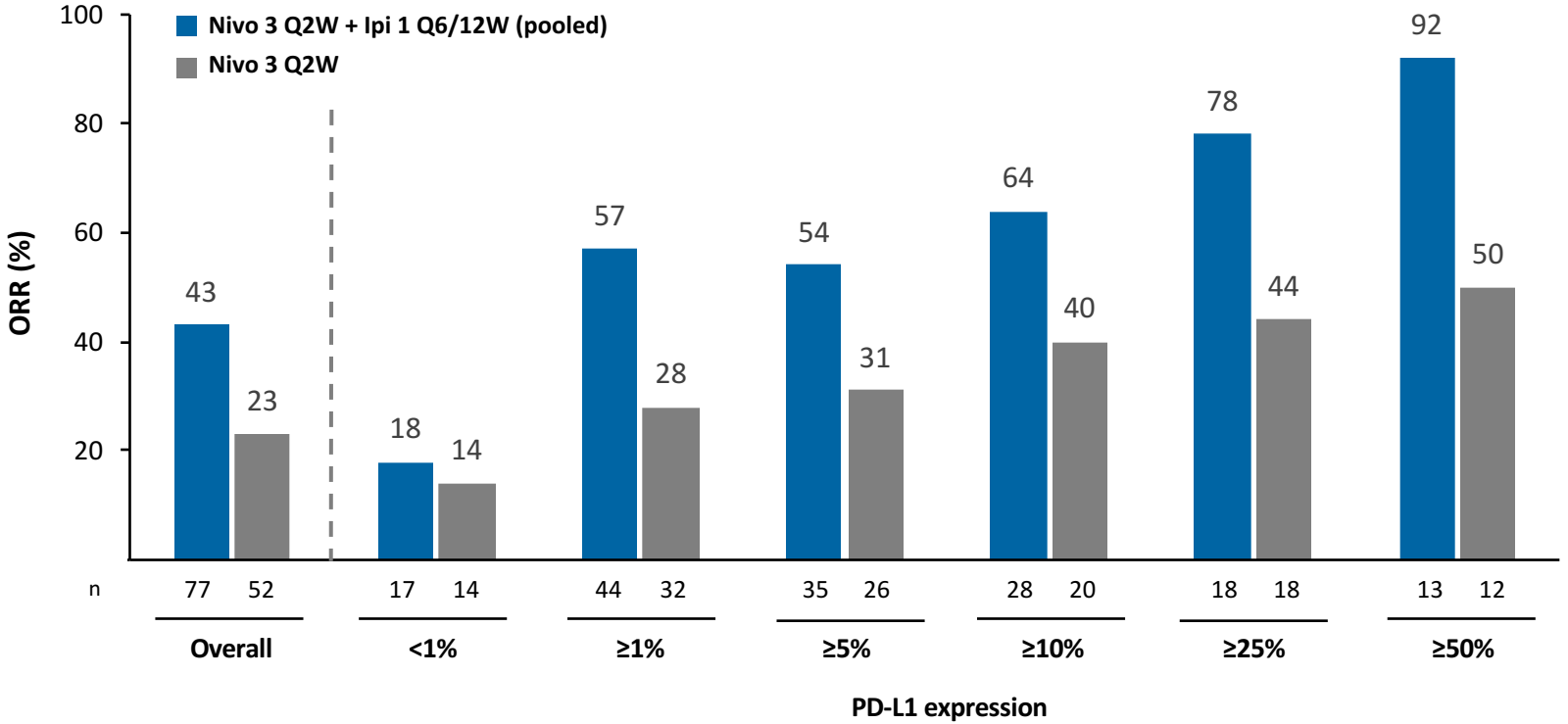


All treatment-related pulmonary events were pneumonitis

Grade 1–2 hypersensitivity/infusion reaction occurred in 5% and 6% of patients in the nivo 3 Q2W + ipi 1 Q12W and monotherapy groups, respectively

Combinaisons d'immunothérapies: première ligne

Nivolumab: première ligne, monothérapie et combinaison
Essai de phase II CHECKMATE 012



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PD-L1

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Atezolizumab

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Intégration en première ligne de traitement

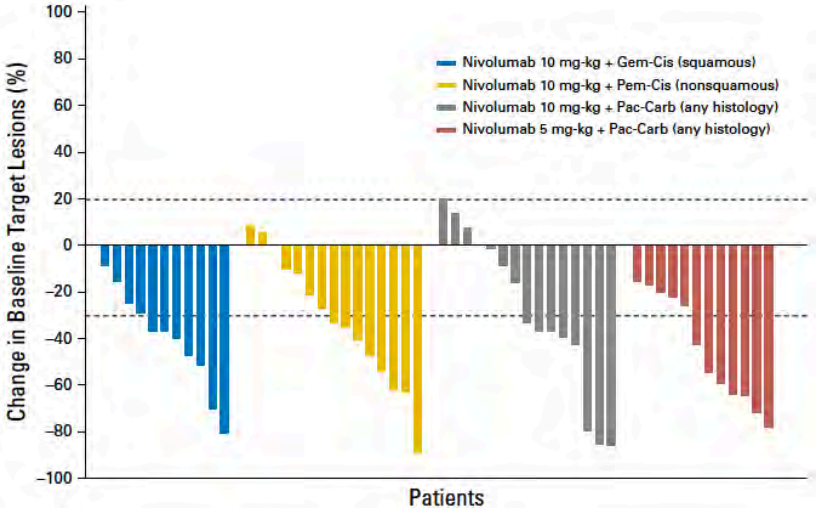
Intégration dans la stratégie actuelle: première ligne

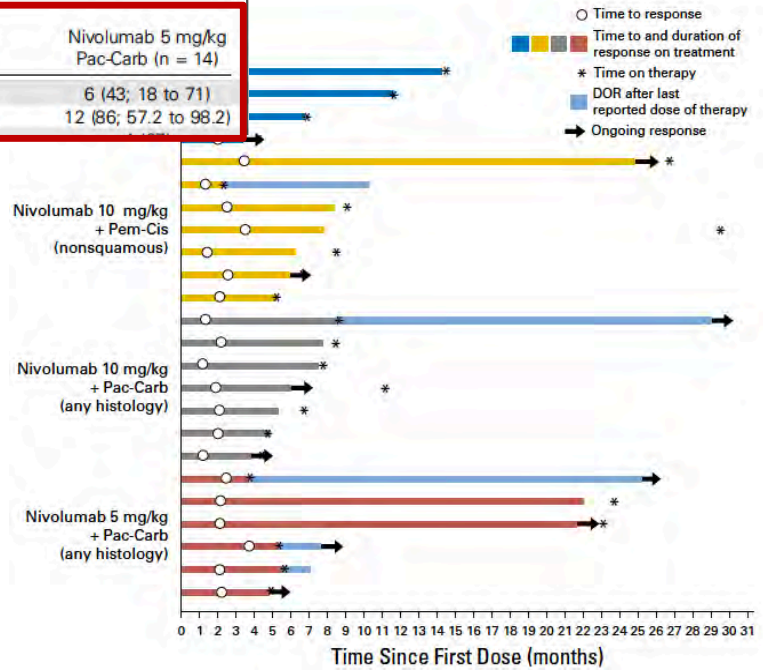
Nivolumab: première ligne, monothérapie et combinaison
Essai de phase II CHECKMATE 012

PD-L1 +/-

Table 4. Efficacy End Points in Patients With Advanced NSCLC Treated With Nivolumab Plus PT-DC

End Point	Nivolumab 10 mg/kg Gem-Cis (n = 12)	Nivolumab 10 mg/kg Pem-Cis (n = 15)	Nivolumab 10 mg/kg Pac-Carb (n = 15)	Nivolumab 5 mg/kg Pac-Carb (n = 14)
Confirmed ORR,* No. (%; 95% CI)	4 (33; 10 to 65)	7 (47; 21 to 73)	7 (47; 21 to 73)	6 (43; 18 to 71)
Confirmed DCR,† No. (%; 95% CI)	11 (92; 61.5 to 99.8)	14 (93; 68.1 to 99.8)	11 (73; 44.9 to 92.2)	12 (86; 57.2 to 98.2)





Rizvi et al. J Clin Oncol 2016; 10.1200/JCO.2016.66.9861

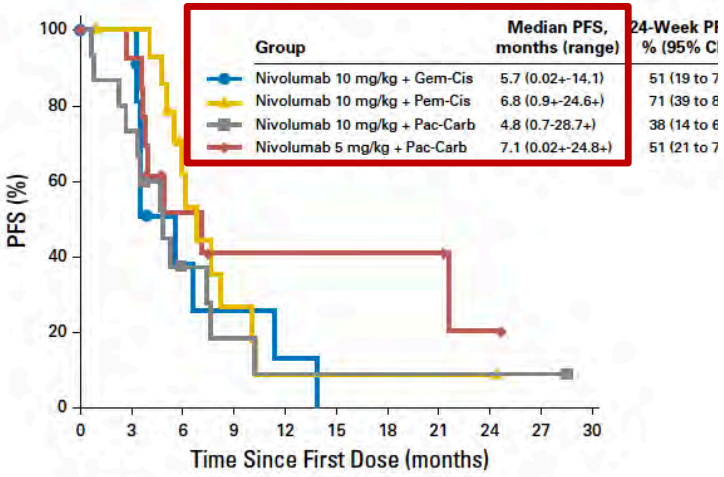
Intégration dans la stratégie actuelle: première ligne

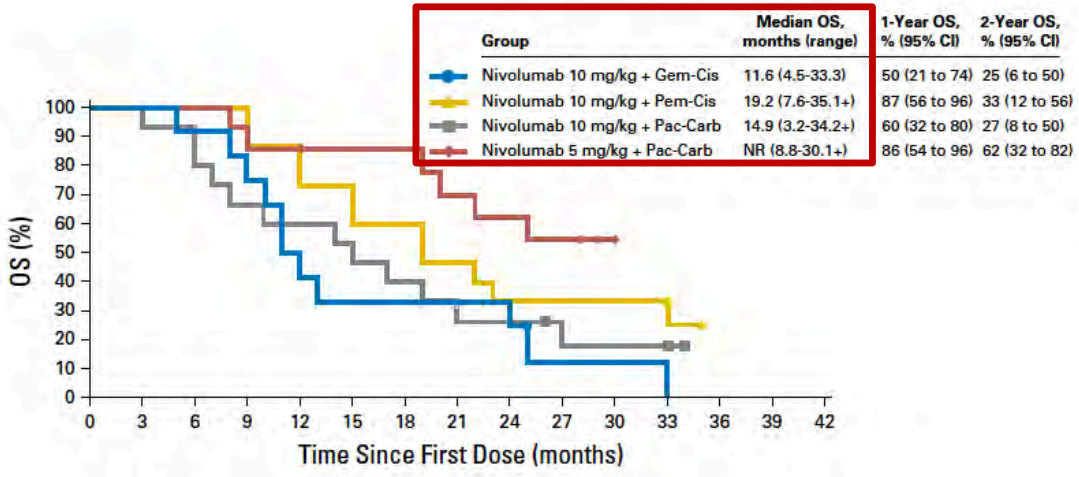
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

PD-L1 +/-

Nivolumab in Combination With Platinum-Based Doublet Chemotherapy for First-Line Treatment of Advanced Non–Small-Cell Lung Cancer

Naiyer A. Rizvi, Matthew D. Hellmann, Julie R. Brahmer, Rosalyn A. Juergens, Hossein Borghaei, Scott Gettinger, Laura Q. Chow, David E. Gerber, Scott A. Laurie, Jonathan W. Goldman, Frances A. Shepherd, Allen C. Chen,





Rizvi et al. J Clin Oncol 2016; 10.1200/JCO.2016.66.9861

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Biomarqueur
PD-L1

2016

Tolérance

Intégration en seconde ligne de traitement

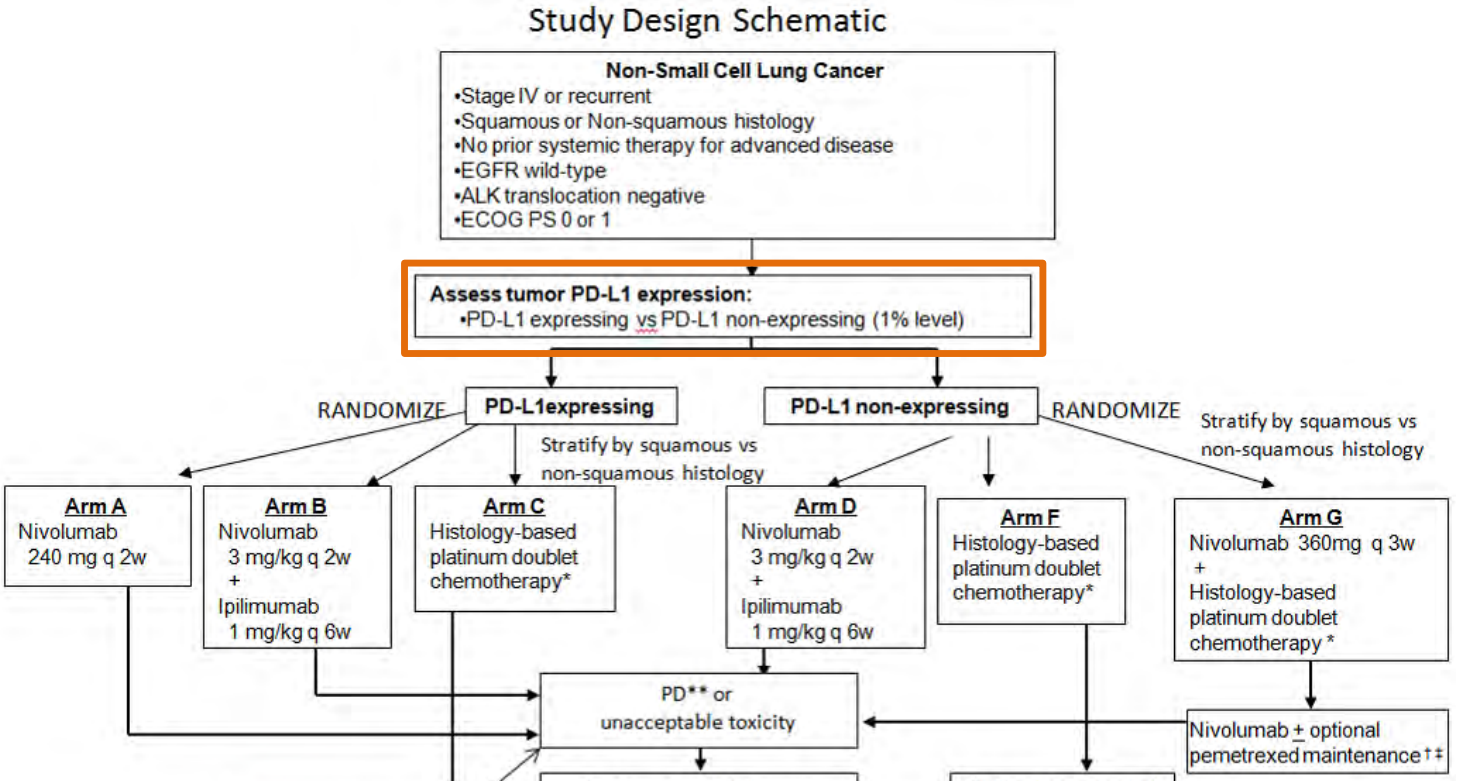
Nivolumab

Atezolizumab

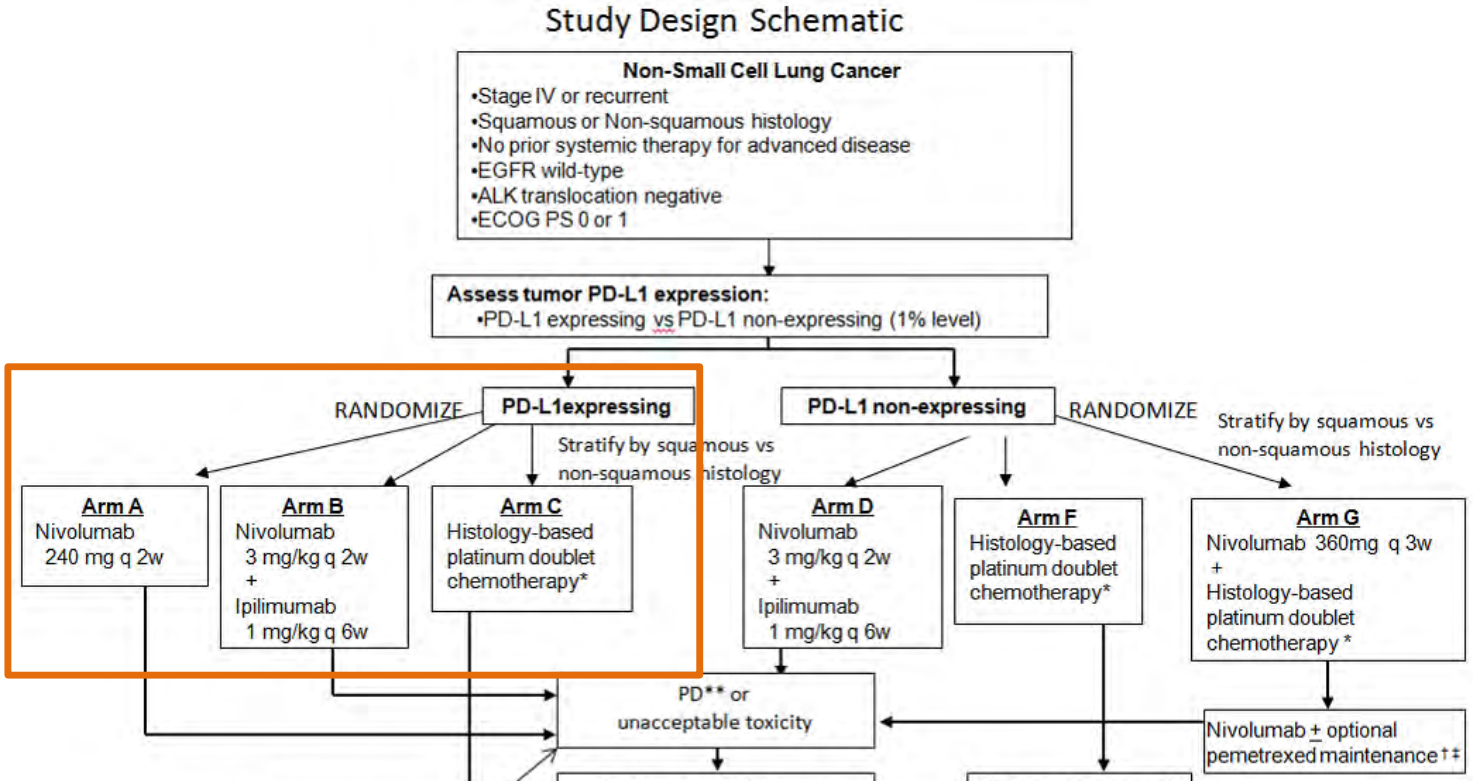
Pembrolizumab

Intégration en première ligne de traitement

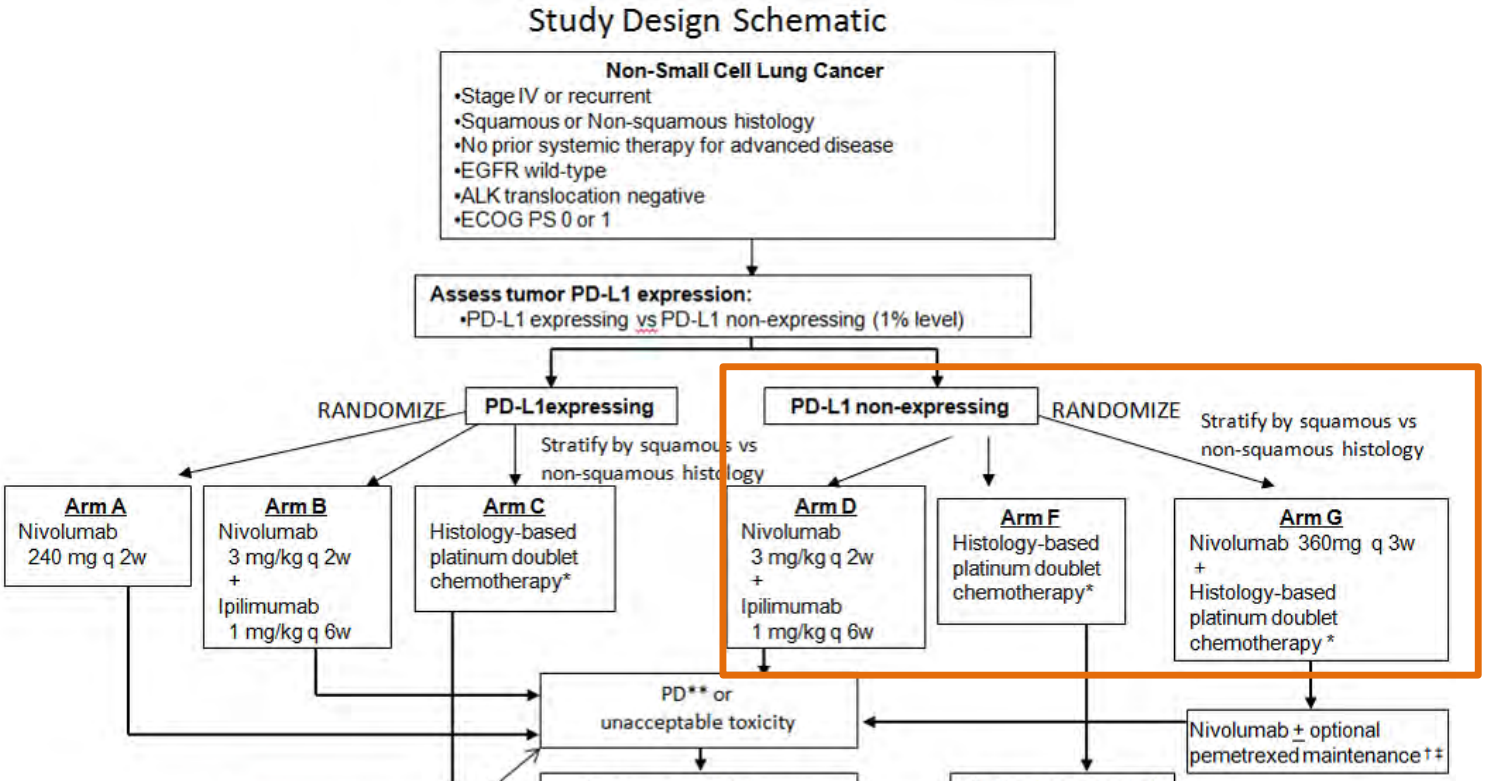
Essai Checkmate 227: première ligne nivolumab +/- ipilimumab +/- chimiothérapie



Essai Checkmate 227: première ligne nivolumab +/- ipilimumab +/- chimiothérapie



Essai Checkmate 227: première ligne nivolumab +/- ipilimumab +/- chimiothérapie



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2016

Tolérance

Intégration en seconde ligne de traitement

Nivolumab

Atezolizumab

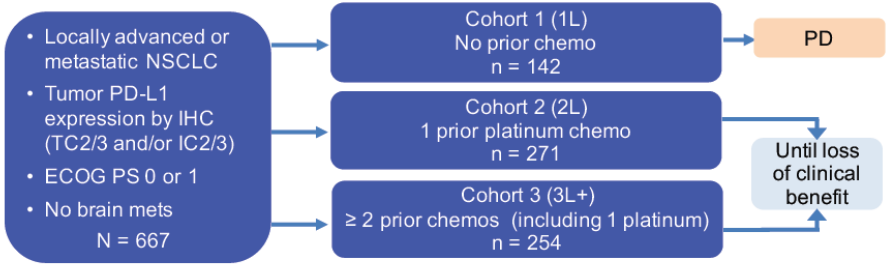
Pembrolizumab

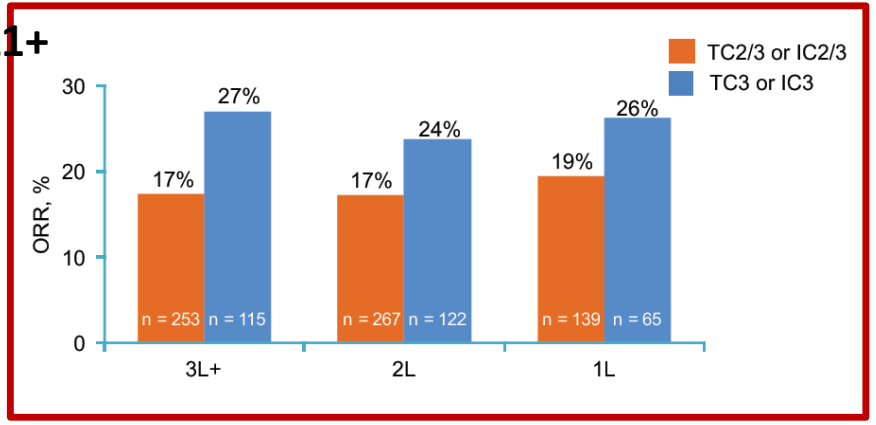
Intégration en première ligne de traitement

Monothérapies: première ligne

PD-L1 +

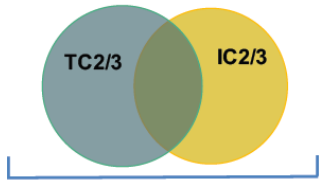
Atezolizumab: première ligne, monothérapie, PD-L1+



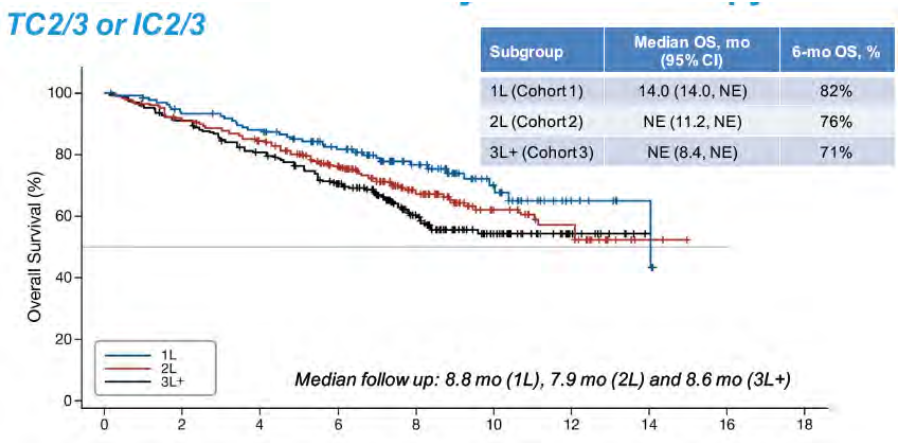


Atezolizumab dosed at 1200 mg IV q3w in all cohorts.

- Primary endpoint: Objective response rate assessed by Independent Review Facility (IRF-assessed ORR) per RECIST v1.1
- Secondary endpoints:
  - IRF-assessed progression-free survival (PFS), duration of response (DOR) per RECIST v1.1
  - INV-assessed ORR, PFS, DOR per RECIST v1.1 and modified RECIST
  - Overall survival (OS)
  - Safety



34% of screened patients between Jan. 2014 and Dec. 2014

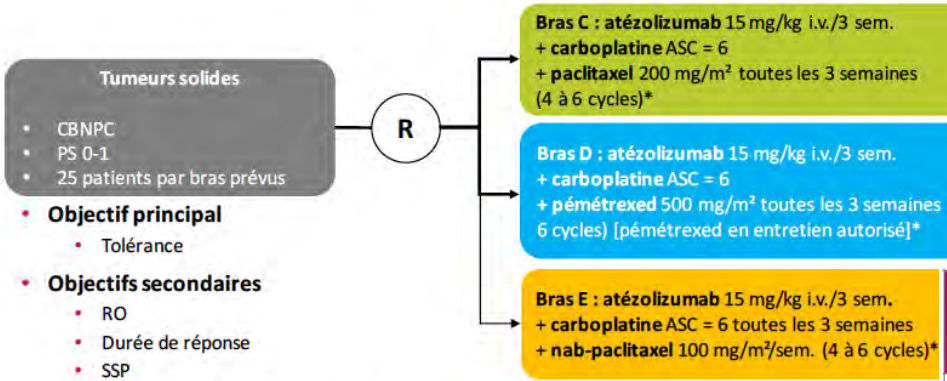


Besse et al. ECC 2016

Intégration dans la stratégie actuelle: première ligne

Atezolizumab: première ligne, plus doublet, PD-L1 +/- KEYNOTE-021

PD-L1 +/-



**Atézolizumab poursuivi jusqu'à perte du bénéfice clinique.*

	Bras C Carbo-paclitaxel (n = 14)	Bras D Carbo-pémétrexed (n = 24)	Bras E Carbo-nab-paclitaxel (n = 20)	Tous patients (n = 58)
Âge médian (ans)	66,5 (44-75)	64,5 (44-83)	66,0 (40-82)	65,0 (40-83)
Hommes (%)	71,4	37,5	75,0	58,6
ECOG PS 0/1 (%)	21,4/78,6	29,2/66,7	35,0/60,0	29,3/67,2
Épi./non-épi. (%)	28,6/71,4	0/95,8	35,0/65,0	19,0/79,3
EI, n (%)				
• Tous grades	14 (100)	24 (100)	19 (95,0)	57 (98,3)
• Grade 3-4	11 (78,6)	16 (66,7)	18 (90,0)	45 (77,6)
• Grade 5	0	1 (4,2)	0	1 (1,7)
	(n = 8)	**(n = 17)**	**(n = 16)**	**(n = 41)**
RO (%)	50,0	76,5	56,3	63,4
• RC (%)	0	0	25,0	9,8
• RP (%)	50,0	76,5	31,3	53,7
Stable (%)	50,0	5,9	25,0	22,0

Camidge et al. WCLC 2016

Intégration dans la stratégie actuelle: première ligne

Atezolizumab et chimiothérapie à base de platine
Programme IMpower

PD-L1 +/-

Figure 2A. IMpower130

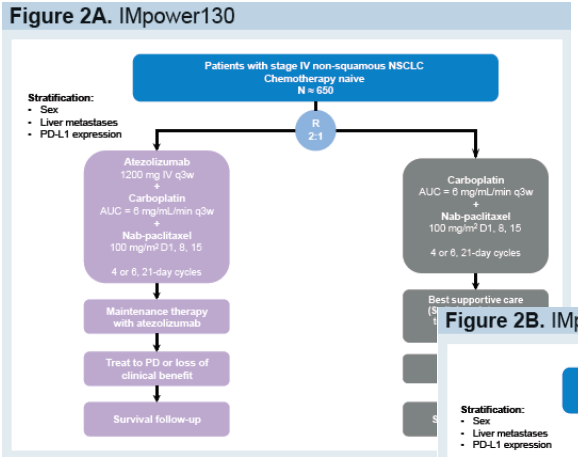


Figure 2B. IMpower131

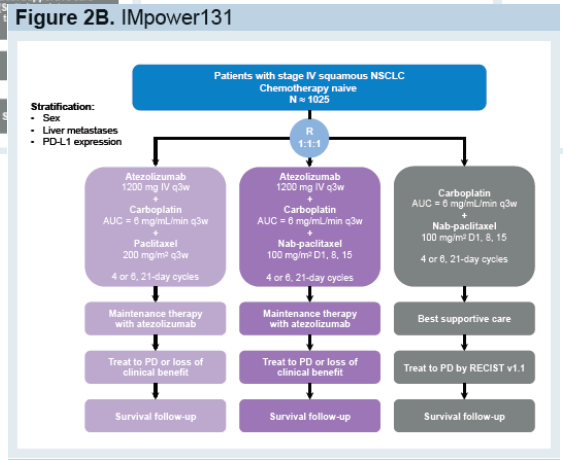


Figure 2C. IMpower132

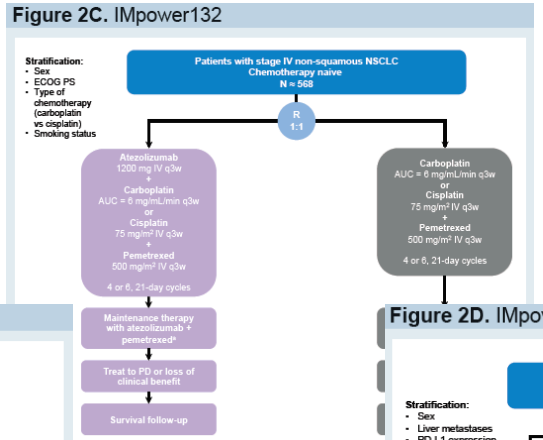
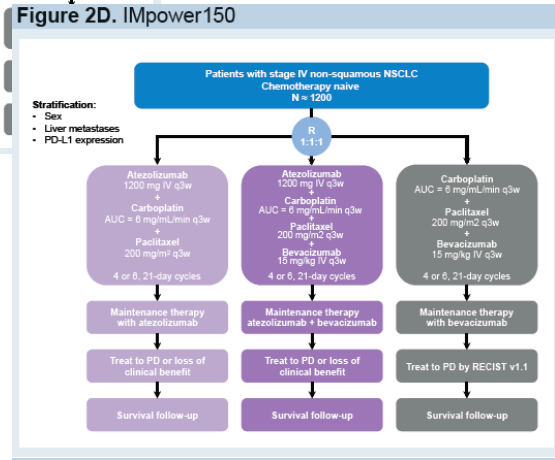


Figure 2D. IMpower150



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PD-L1

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Autres biomarqueurs?

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Atezolizumab

Pembrolizumab

Intégration en première ligne de traitement

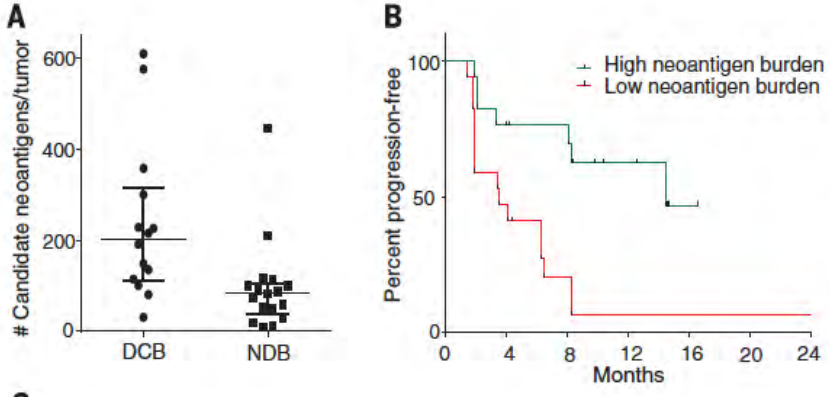
Nouveaux biomarqueurs

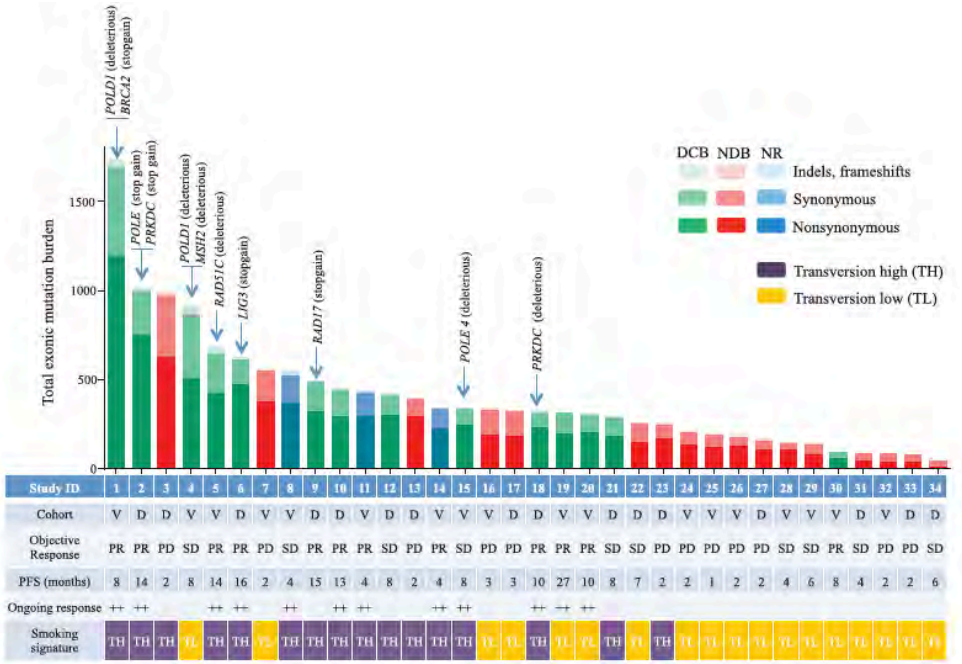
RESEARCH | *REPORTS*

CANCER IMMUNOLOGY

Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer

Naiyer A. Rizvi,[1,2*†] Matthew D. Hellmann,[1,2*] Alexandra Snyder,[1,2,3*] Pia Kvistborg,[4] Vladimir Makarov,[3] Jonathan J. Havel,[3] William Lee,[5] Jianda Yuan,[6] Phillip Wong,[6] Teresa S. Ho,[6] Martin L. Miller,[7] Natasha Rekhtman,[8] Andre L. Moreira,[8] Fawzia Ibrahim,[1] Cameron Bruggeman,[9] Billel Gasmi,[10] Roberta Zappasodi,[10] Yuka Maeda,[10] Chris Sander,[7] Edward B. Garon,[11] Taha Merghoub,[1,10] Jedd D. Wolchok,[1,2,10] Ton N. Schumacher,[4] Timothy A. Chan[2,3,5‡]

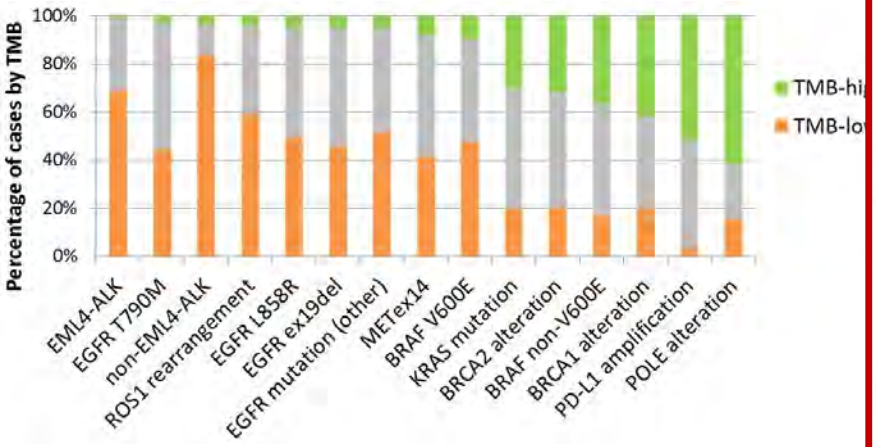




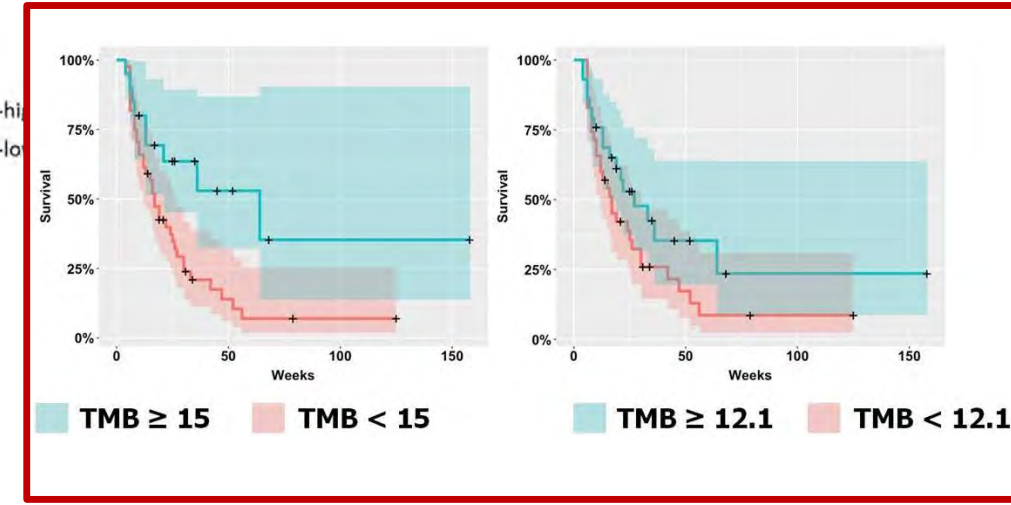
Rizvi et al. Science 2016; 348:124

Tumor Mutation Burden in NSCLC

Distribution of TMB across LC histologies				
	Adeno (n=7,925)	SCC (n=1,324)	NSCLC NOS (n=1,773)	SCLC (n=640)
Mean TMB	9.1	11.3	11.0	10.3
TMB > 10 (%)	2350 (30)	541 (41)	711 (40)	269 (42)
TMB > 20 (%)	760 (10)	113 (9)	233 (13)	42 (7)
TMB in top quartile (%)	1848 (23)	394 (30)	577 (33)	193 (30)



Spigel D, ASCO 2016: A9017.



Spigel D, ASCO 2016: A9017

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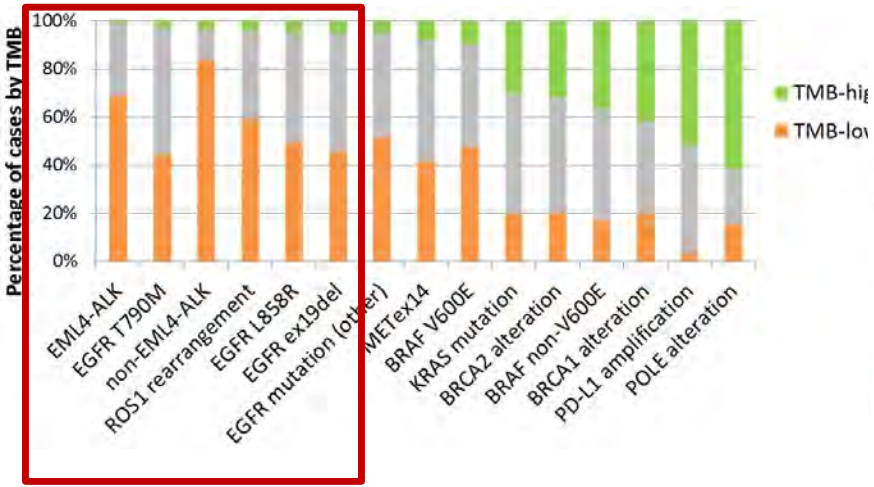
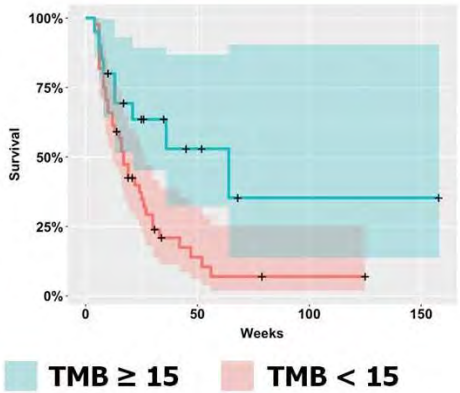
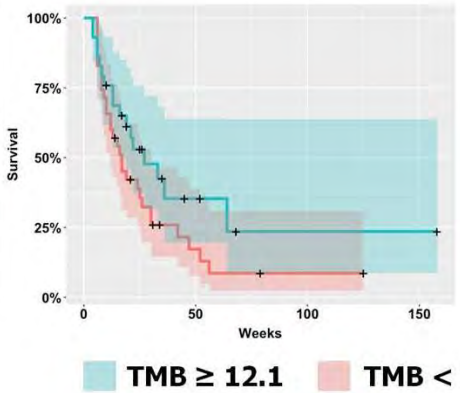
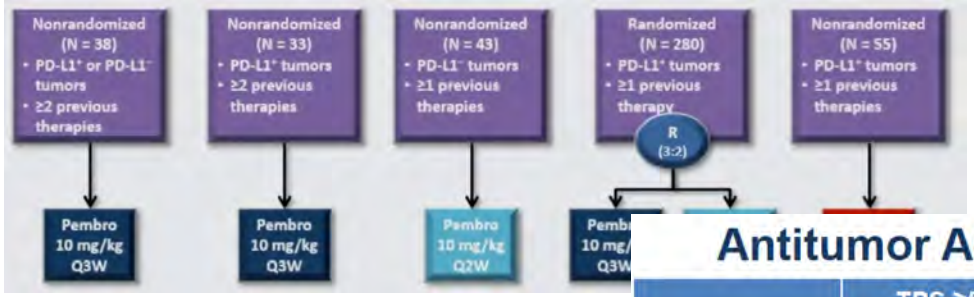






Spigel D, ASCO 2016: A9017

Mutations *EGFR*



Keynote-001

Antitumor Activity by *EGFR* and *KRAS* Status

	TPS ≥50%		TPS 1-49%		TPS <1%		Total[a]	
	n	ORR, % (95% CI)	n	ORR, % (95% CI)	n	ORR, % (95% CI)	N	ORR, % (95% CI)
Overall	144	38.2 (30.2-46.7)	185	11.9 (7.6-17.4)	80	10.0 (4.4-18.8)	550	20.2 (16.9-23.8)
EGFR wild type	113	39.8 (30.7-49.5)	156	12.2 (7.5-18.4)	63	12.7 (5.6-23.5)	450	21.6 (17.8-25.6)
EGFR mutant	20	20.0 (5.7-43.7)	23	8.7 (1.1-28.0)	14	0.0 (0.0-23.2)	77	7.8 (2.9-16.2)
KRAS wild type	51	29.4 (17.5-43.8)	85	12.9 (6.6-22.0)	40	7.5 (1.6-20.4)	238	16.4 (11.9-21.7)
KRAS mutant	26	30.8 (14.3-51.8)	24	0.0 (0.0-14.2)	11	18.2 (2.3-51.8)	87	17.2 (10.0-26.8)

[a]Includes patients for whom a PD-L1 TPS could not be assigned (n = 141). Data are not shown for patients with unknown *EGFR* (n = 23) or *KRAS* (n = 225) status.
Data cutoff date: January 23, 2015

3057 – Matthew D. Hellmann

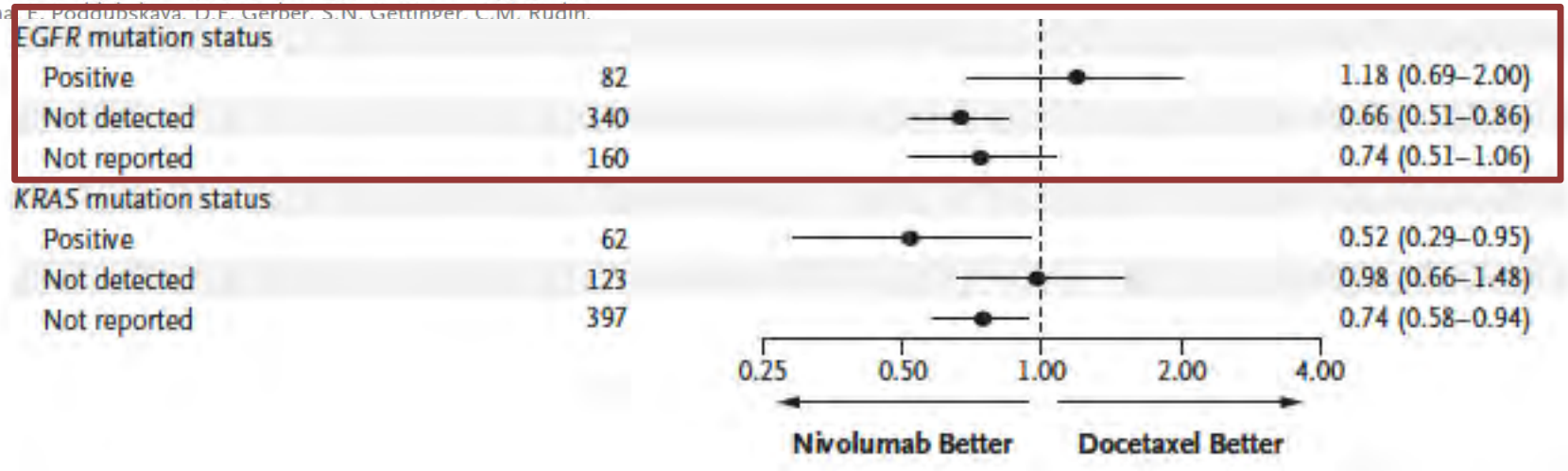
Hellmann et al. WCLC 2015

Mutations *EGFR*

ORIGINAL ARTICLE

Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer

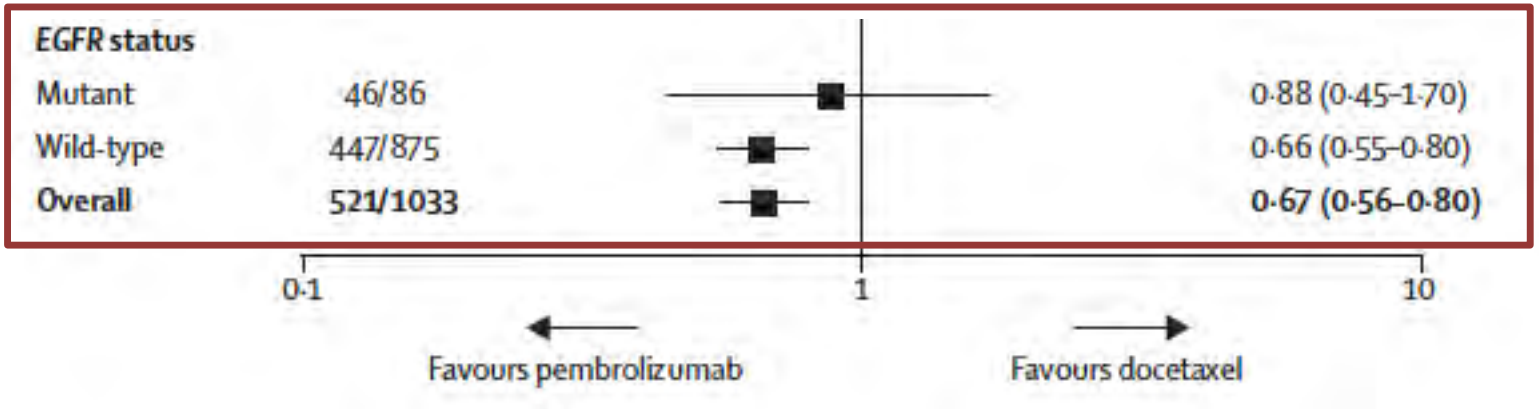
H. Borghaei, L. Paz-Ares, L. Horn, D.R. Spigel, M. Steins, N.E. Ready, L.Q. Chow, E.E. Vokes, E. Felip, E. Holgado, F. Barlesi, M. Kohlhäufl, O. Arrieta, M.A. Burgio, J. Fayette, H. Lena, E. Poddubskaya, D.E. Gerber, S.N. Gettinger, C.M. Rudin, N. Rizvi, L C.T



Mutations *EGFR*

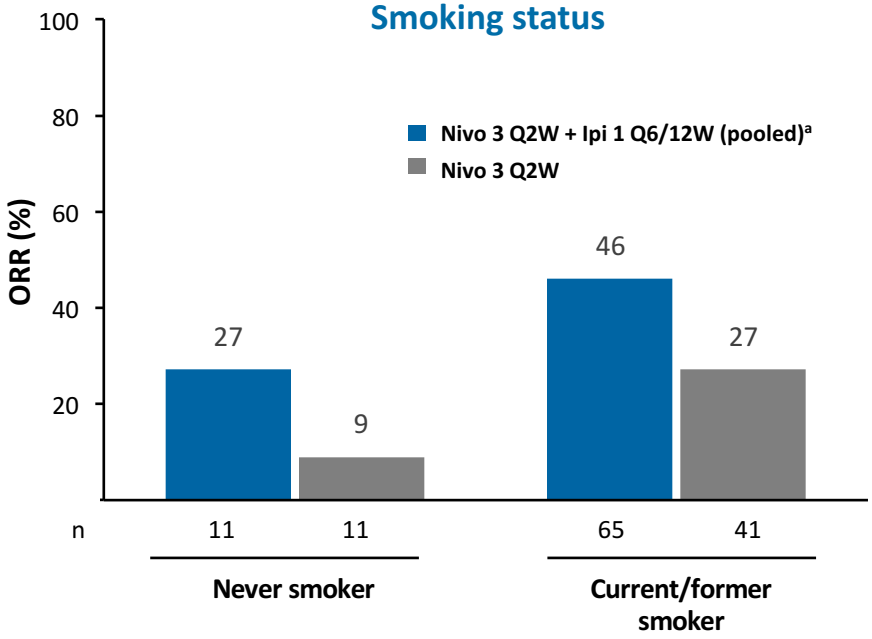
Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial

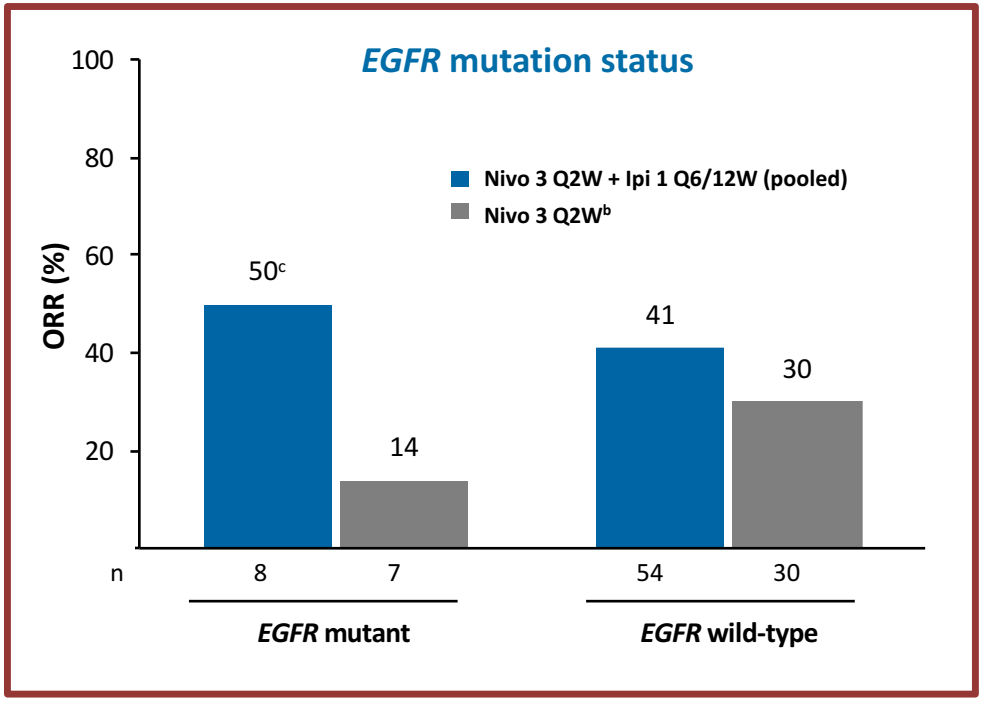
Roy S Herbst, Paul Baas, Dong-Wan Kim, Enriqueta Felip, José L Pérez-Gracia, Ji-Youn Han, Julian Molina, Joo-Hang Kim, Catherine Dubos Arvis, Myung-Ju Ahn, Margarita Majem, Mary J Fidler, Gilberto de Castro Jr, Marcelo Garrido, Gregory M Lubiniecki, Yue Shentu, Ellie Im, Marisa Dolled-Filhart, Edward B Garon



Combinaisons d'immunothérapies: première ligne

Nivolumab: première ligne, monothérapie et combinaison
Essai de phase II CHECKMATE 012





Combination data based on a February 2016 database lock; monotherapy data based on a March 2016 database lock

[a]Excludes 1 patient with unknown smoking status (nivo 3 Q2W + ipi 1 Q6W)

[b]In patients with non-squamous histology only

[c]Must be interpreted with caution: of these 4 responders, 1 did not have a classical exon 19 deletion or L858R *EGFR* activating mutations, 3 were former/current smokers, and 3 had high PD-L1 expression levels

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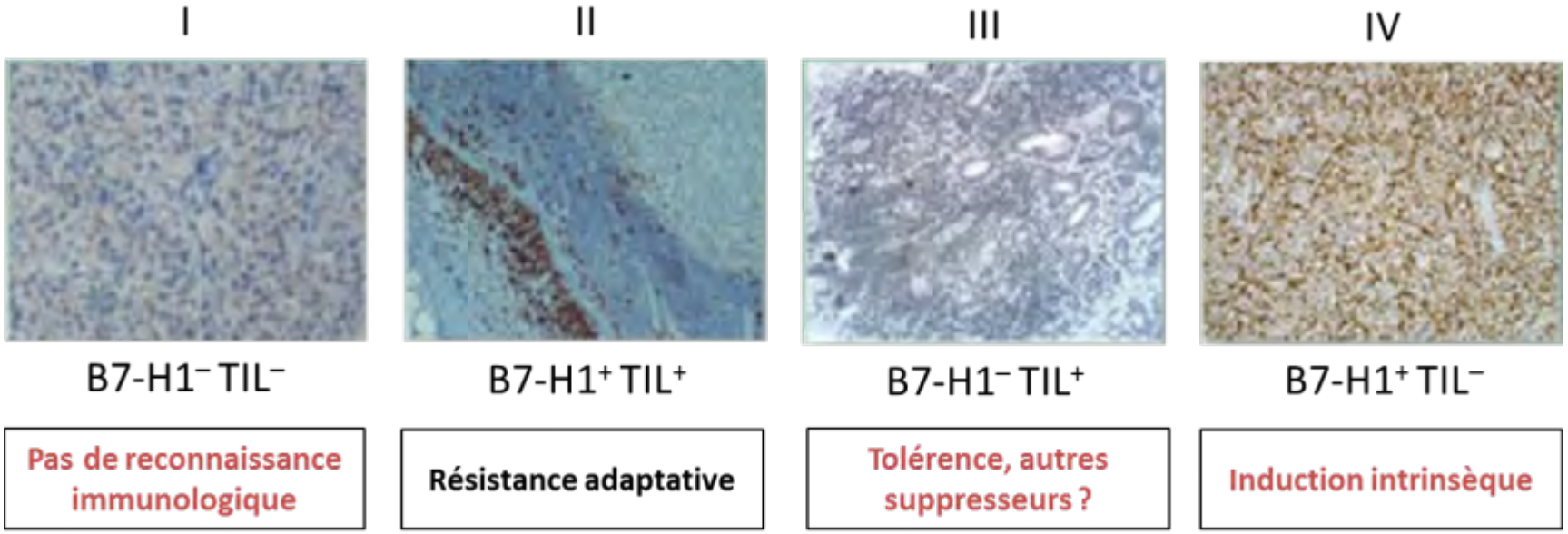
Infiltration par les lymphocytes

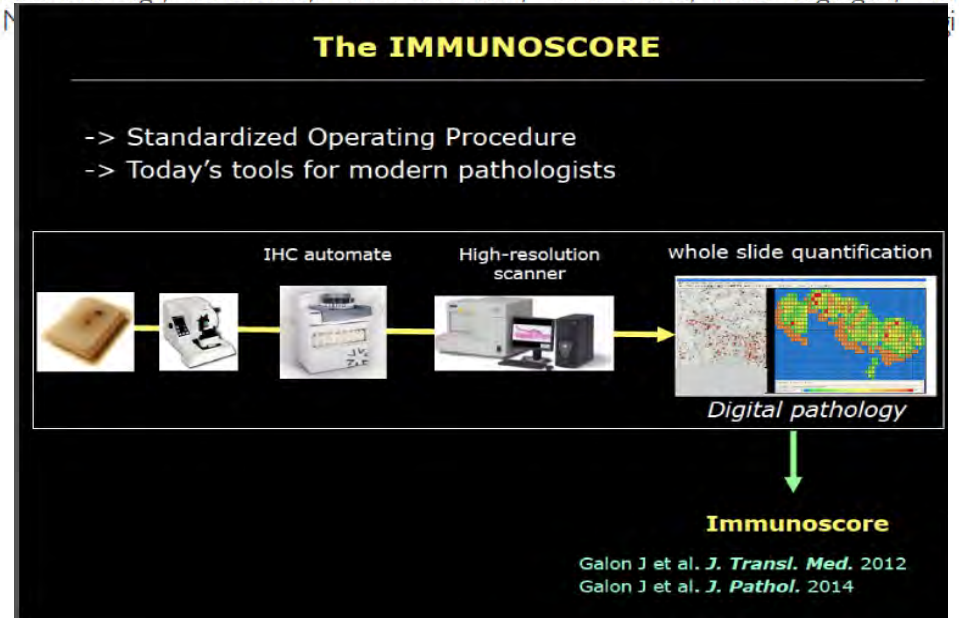


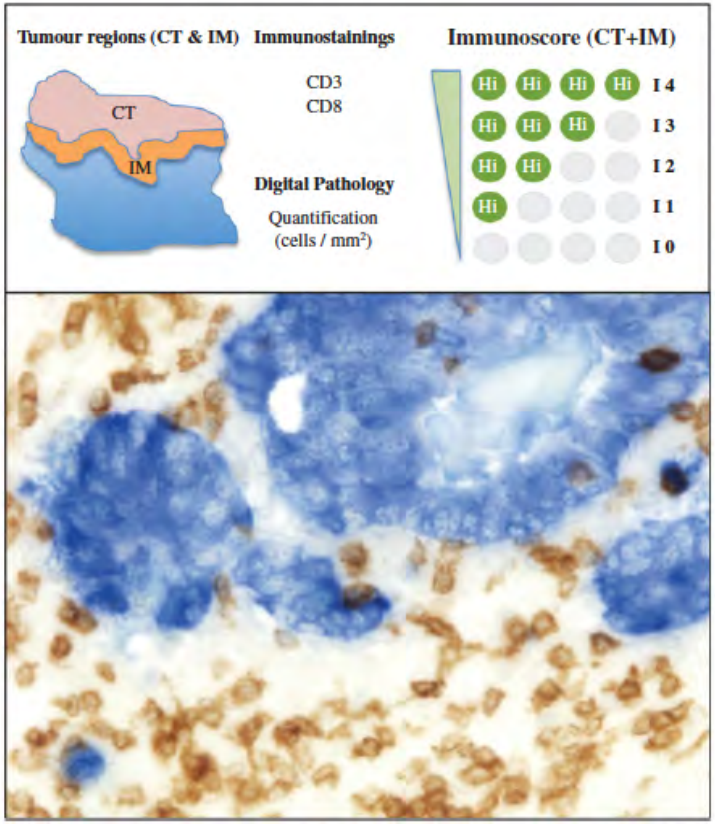
Sznol M, Chen L. Clin Cancer Res 2013;19:1021

Immunoscore?

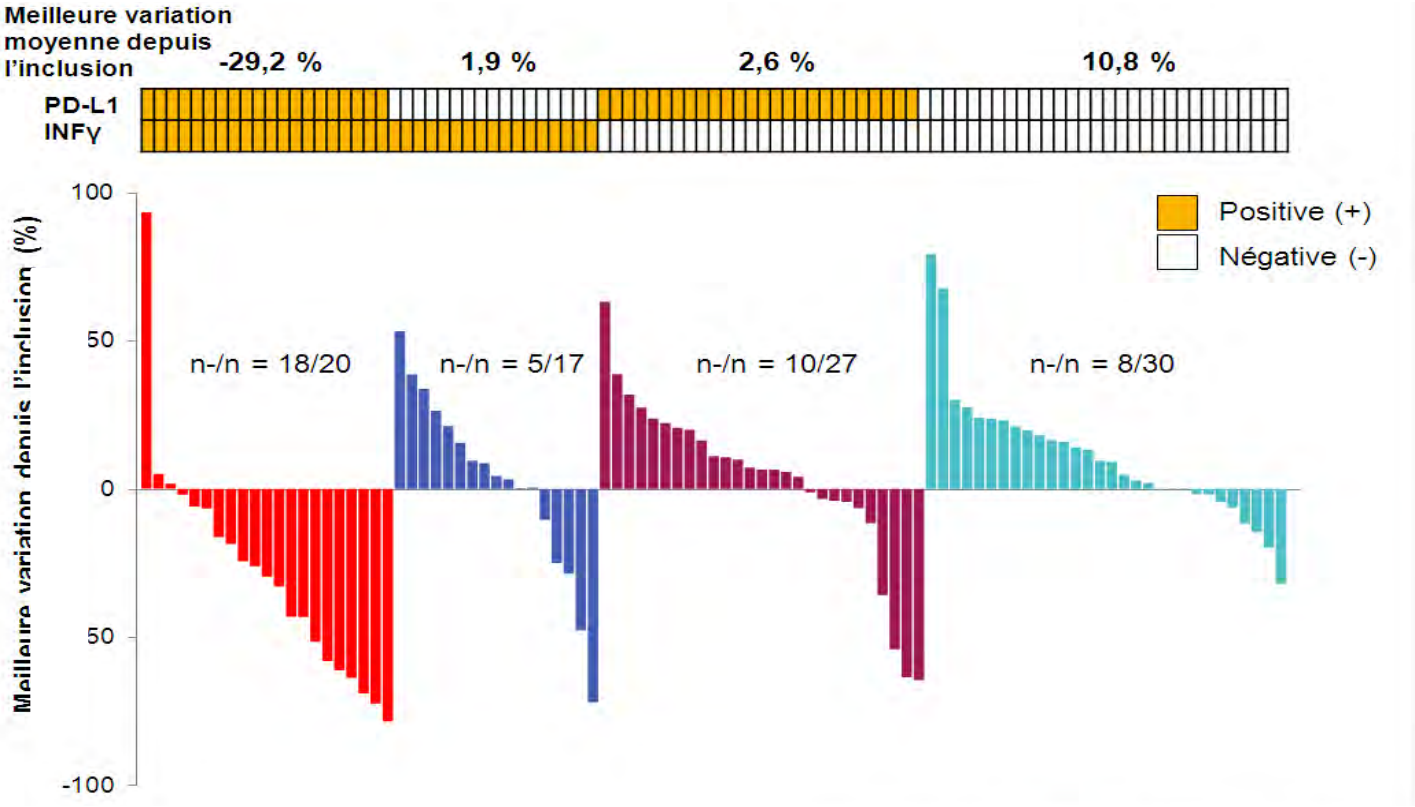
Towards the introduction of the 'Immunoscore' in the classification of malignant tumours

Jérôme Galon,[1,2,3]* Bernhard Mlecnik,[1,2,3] Gabriela Bindea,[1,2,3] Helen K Angell,[1,2,3] Anne Berger,[4] Ch
Alessandro Lugli,[6] Inti Zlobec,[6] Arndt Hartmann,[7] Carlo Bifulco,[8] Iris D Nagtegaal,[9] Richard Palm
V N ... i Laghi,[15] F





Interferon Gamma: Durvalumab



Higgs B et al., ECC 2016 : LBA15

Signature CYTOSCORE

Figure 8. Cytokines included in SQ- and non-SQ-cytoscores

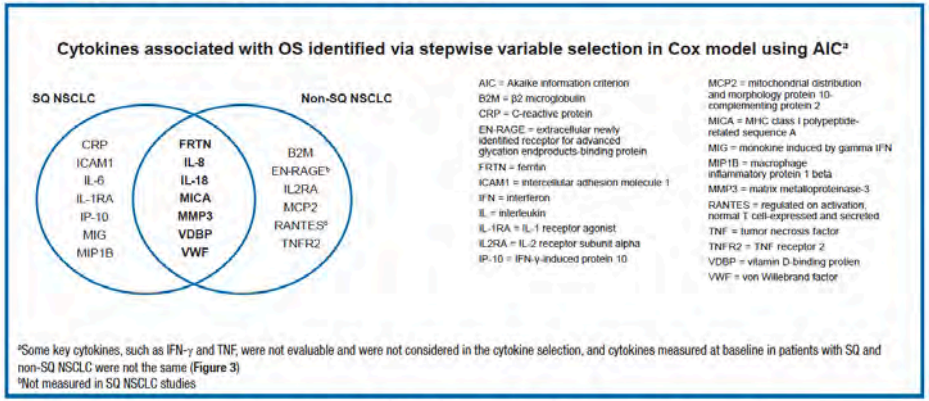


Figure 9. OS by SQ-cytoscore in patients with SQ NSCLC treated with nivolumab or docetaxel[6]

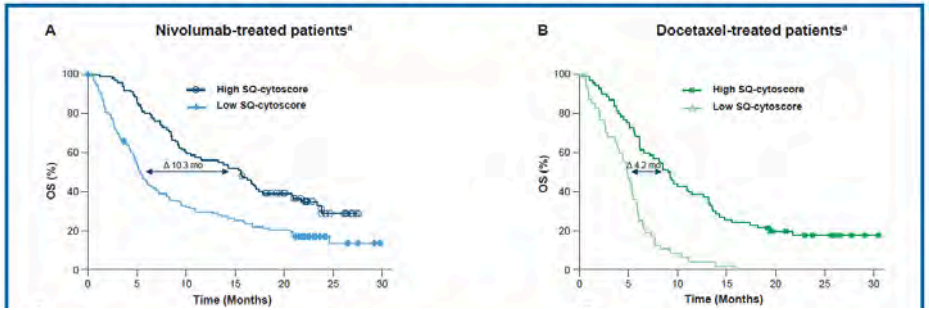
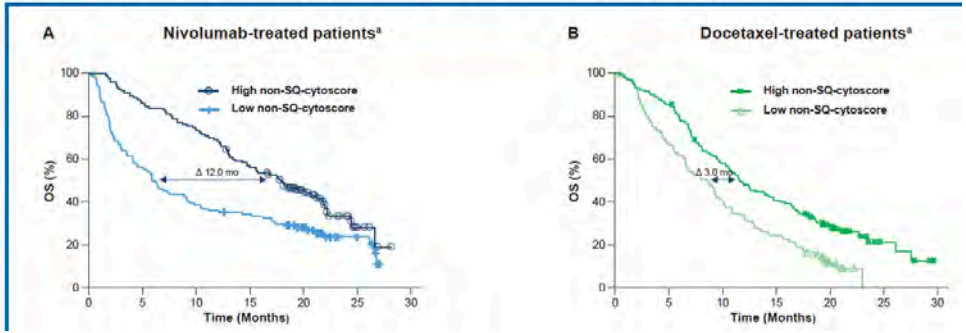
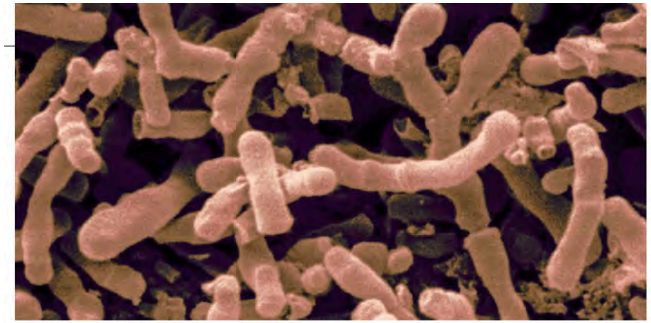


Figure 10. OS by non-SQ-cytoscore in patients with non-SQ NSCLC treated with nivolumab or docetaxel



Borghaiei et al. ASCO 2016

Microbiome?



Gut microbe. *Bifidobacterium* is found in the intestines of most mammals, including humans.

IMMUNOTHERAPY

Could microbial therapy boost cancer immun

Intestinal microbes affect in in mouse models of cancer

CANCER IMMUNOTHERAPY

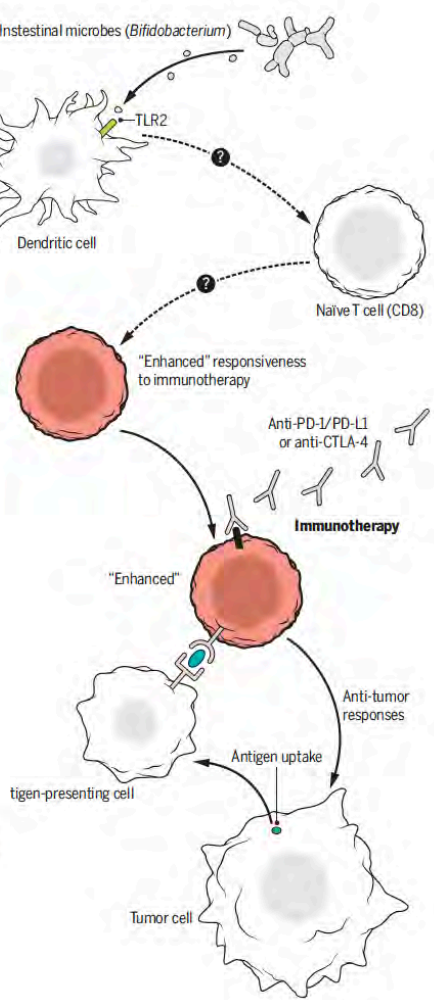
Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti–PD-L1 efficacy

Ayelet Sivan,[1*] Leticia Corrales,[1*] Nathani Keston Aquino-Michaels,[3] Zachary M. Ear Bana Jabri,[2] Maria-Luisa Alegre,[2] Eugene

CANCER IMMUNOTHERAPY

Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota

Marie Vétizou,[1,2,3] Jonathan M. Pitt,[1,2,3] Romain Daillère,[1,2,3] Patricia Lepage,[4] Nadine Waldschmitt,[5] Caroline Flament,[1,2,6] Sylvie Rusakiewicz,[1,2,6] Bertrand Routy,[1,2,3,6] Maria P. Roberti,[1,2,6] Connie P. M. Duong,[1,2,6]



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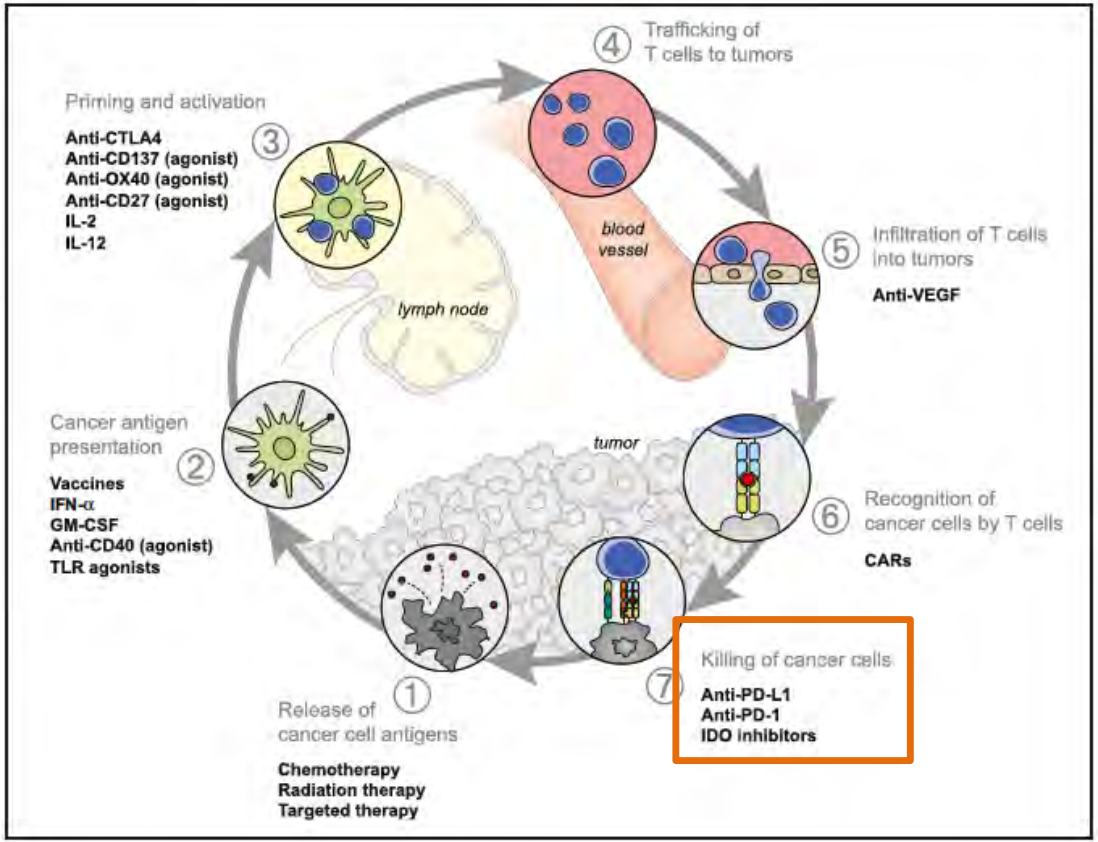
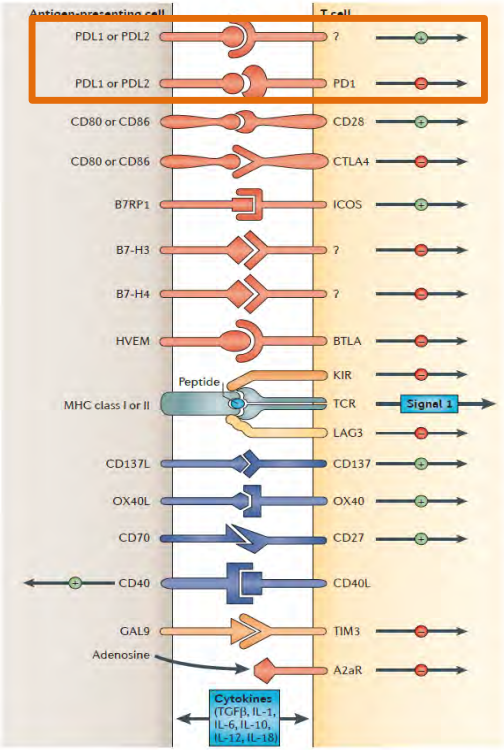
Multiples points de contrôle: l'immuno-oncologie en marche

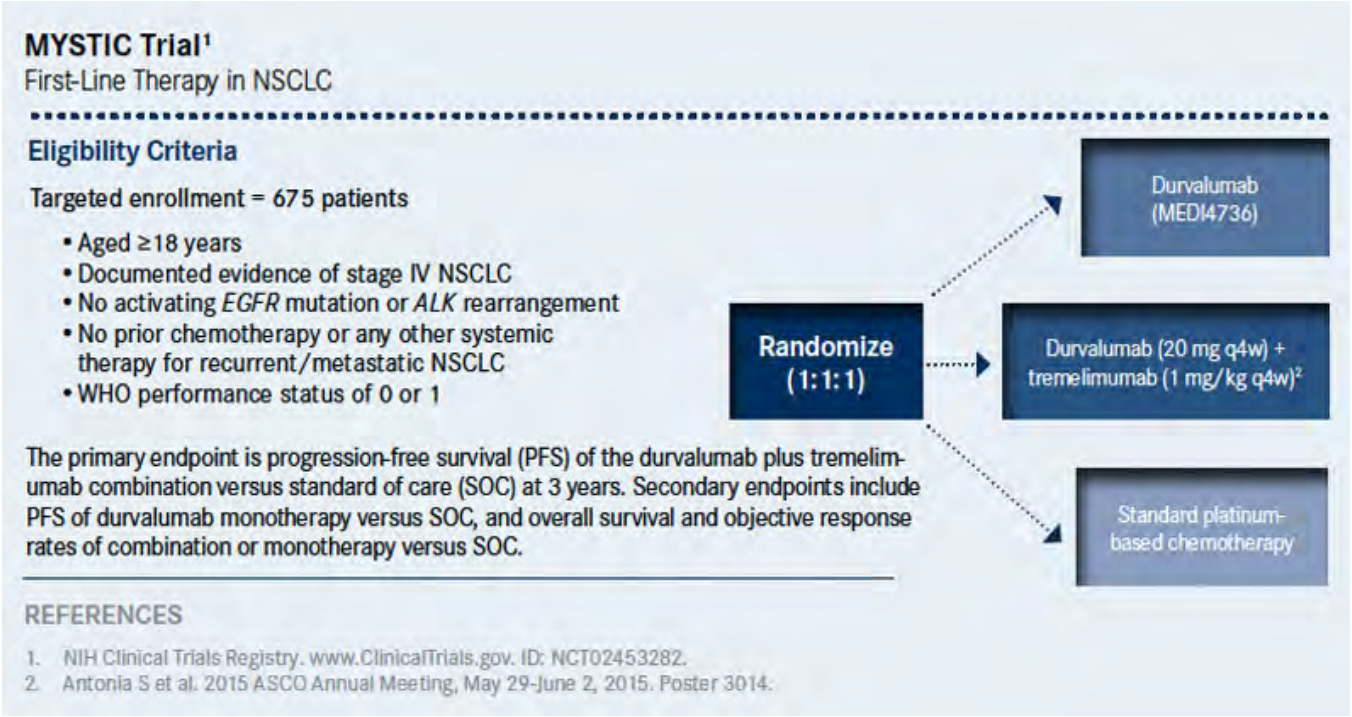




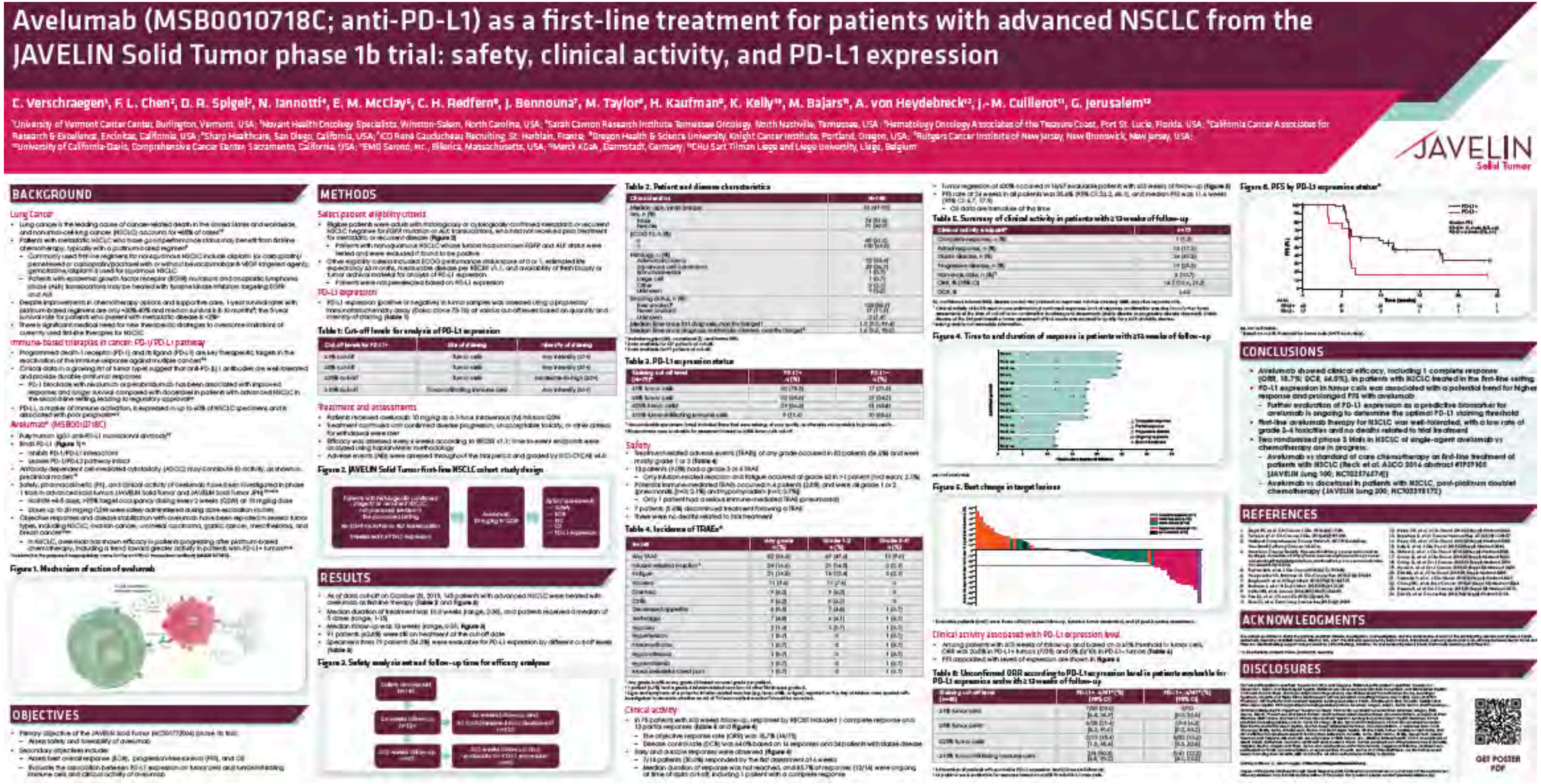
Chen et al. Immunity 2013;39:1
Pardoll et al. Nat Rev Cancer 2012;12:252

Durvalumab, Tremelimumab

Durvalumab: première ligne, plus tremelimumab
MYSTIC



Avelumab


Avelumab (MSB0010718C; anti-PD-L1) as a first-line treatment for patients with advanced NSCLC from the JAVELIN Solid Tumor phase 1b trial: safety, clinical activity, and PD-L1 expression
C. Verschraegen, F. L. Chen, D. R. Spigel, N. Iannotti, E. M. McClay, C. H. Redfern, J. Bennouna, M. Taylor, H. Kaufman, K. Kelly, M. Bajars, A. von Heydebreck, J.-M. Cuillerot, G. Jerusalem
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Solid Tumor
BACKGROUND
METHODS
RESULTS
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DISCLOSURES
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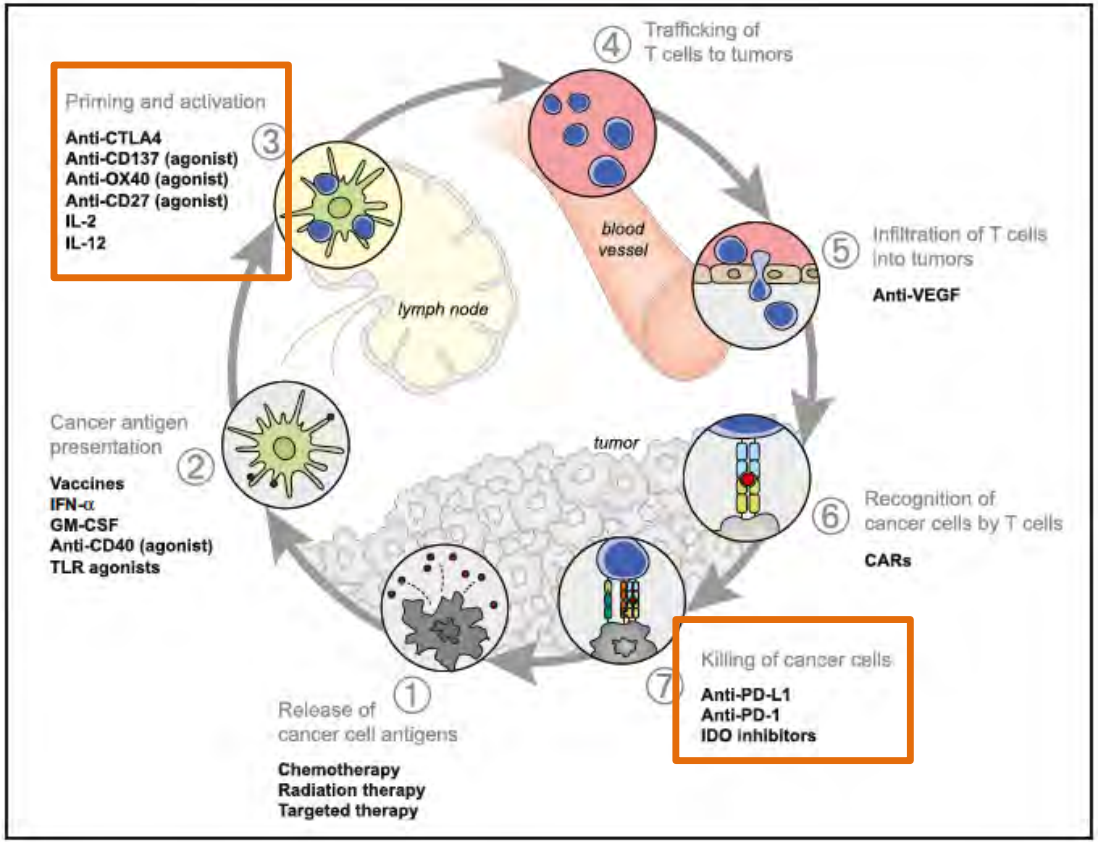
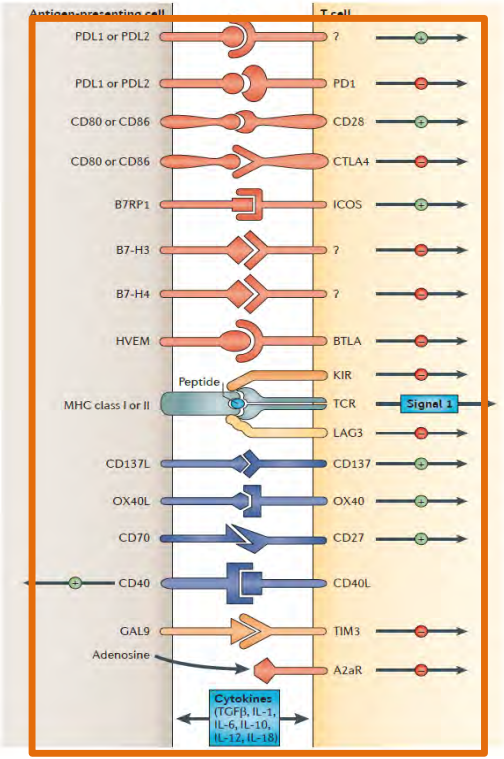
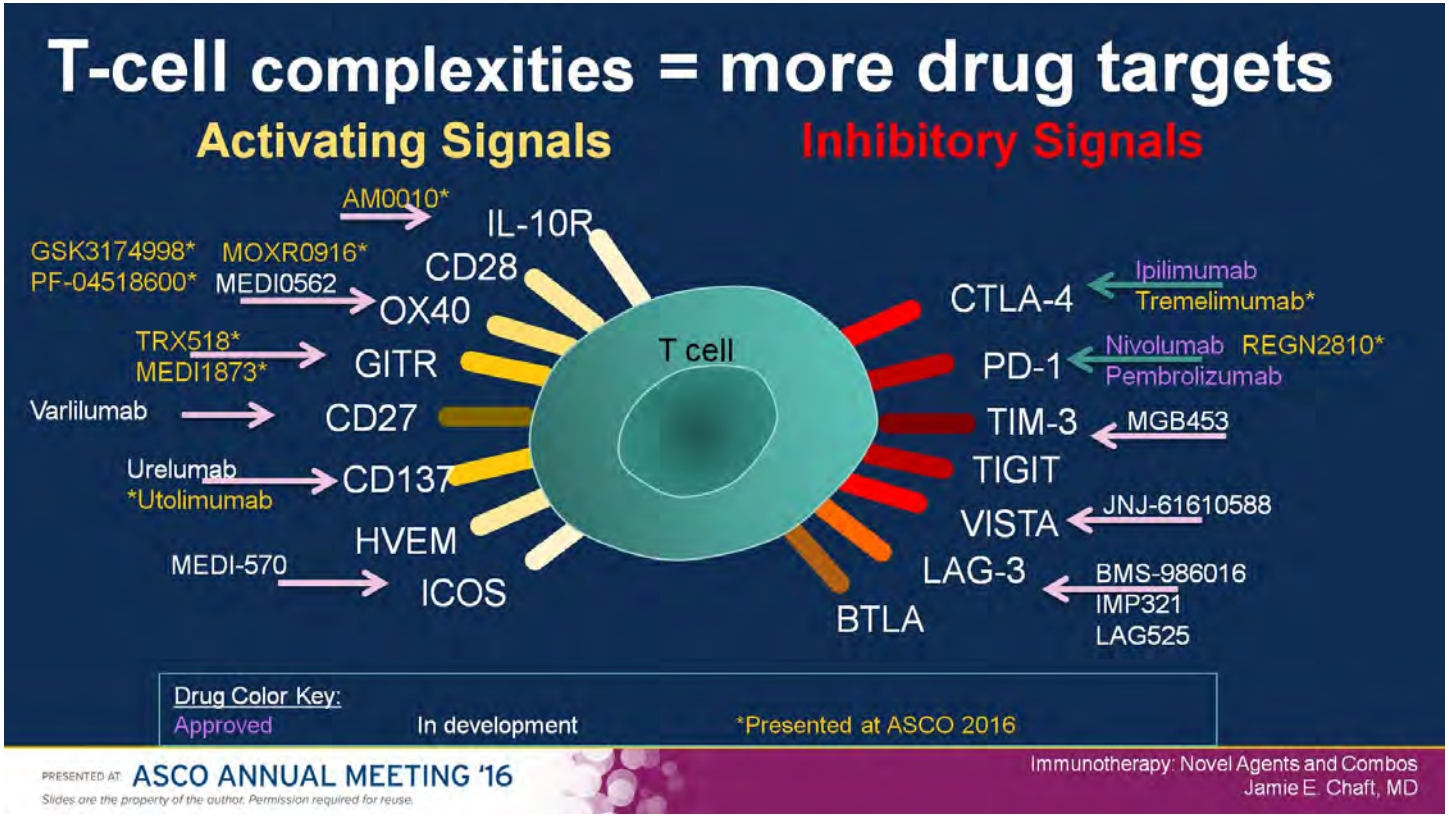
Multiples points de contrôle: l'immuno-oncologie en marche





Chen et al. Immunity 2013;39:1
Pardoll et al. Nat Rev Cancer 2012;12:252

Multiples points de contrôle: l'immuno-oncologie en marche



Presented By Jamie Chaft at 2016 ASCO Annual Meeting

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