

Session Immunité et Cancer

Immunomodulateurs concept et voies d'avenir

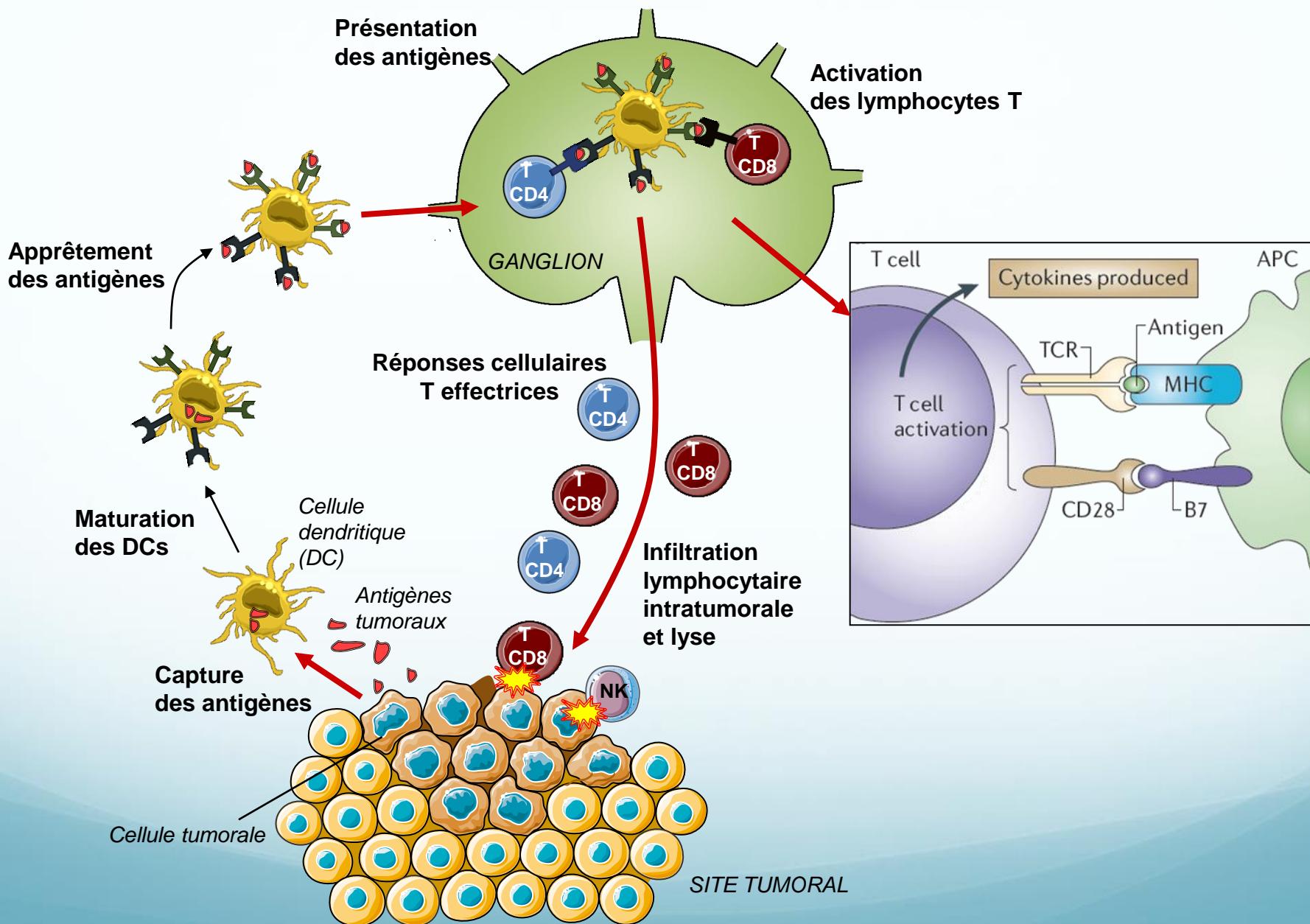
Mercredi 03 Février 2016

Dr Laura MANSI
Hôpital J Minjoz, Besançon

Conflits d'intérêts

- **Board:** Novartis, Roche
- **Lab meeting:** BMS, Novartis

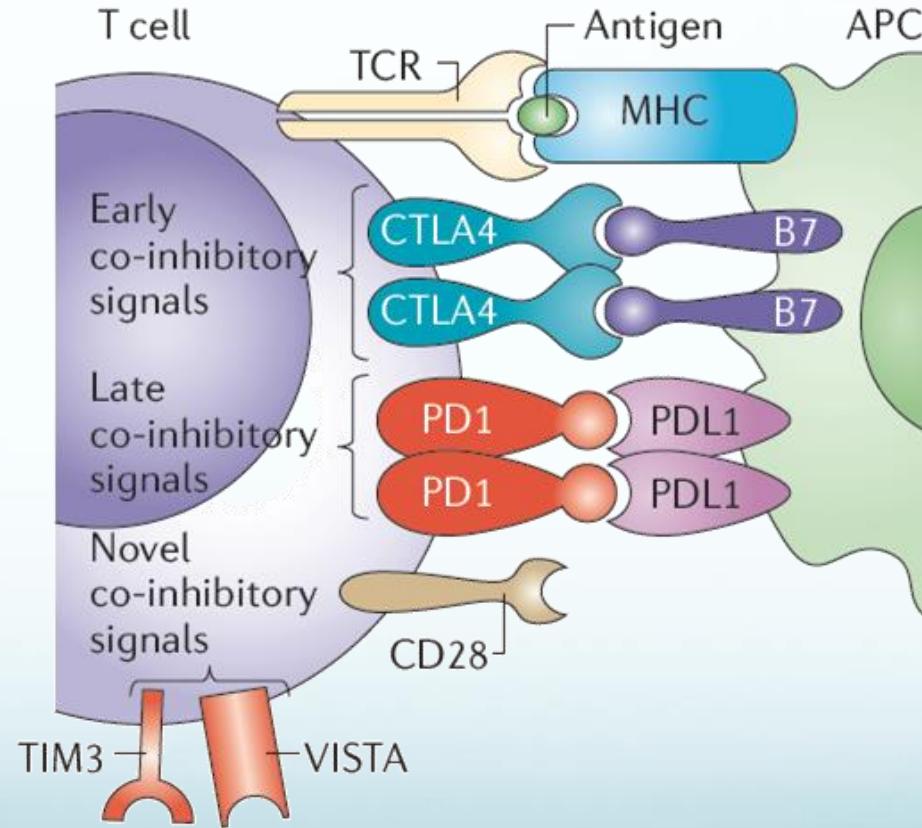
Le réponse immunitaire T anti-tumorale



Les checkpoints inhibiteurs

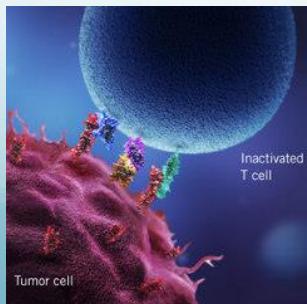
Check points immunologiques : qu'est ce que c'est?

Inhibition des lymphocytes T



La vrai question... le vrai problème.. L'enjeu scientifique

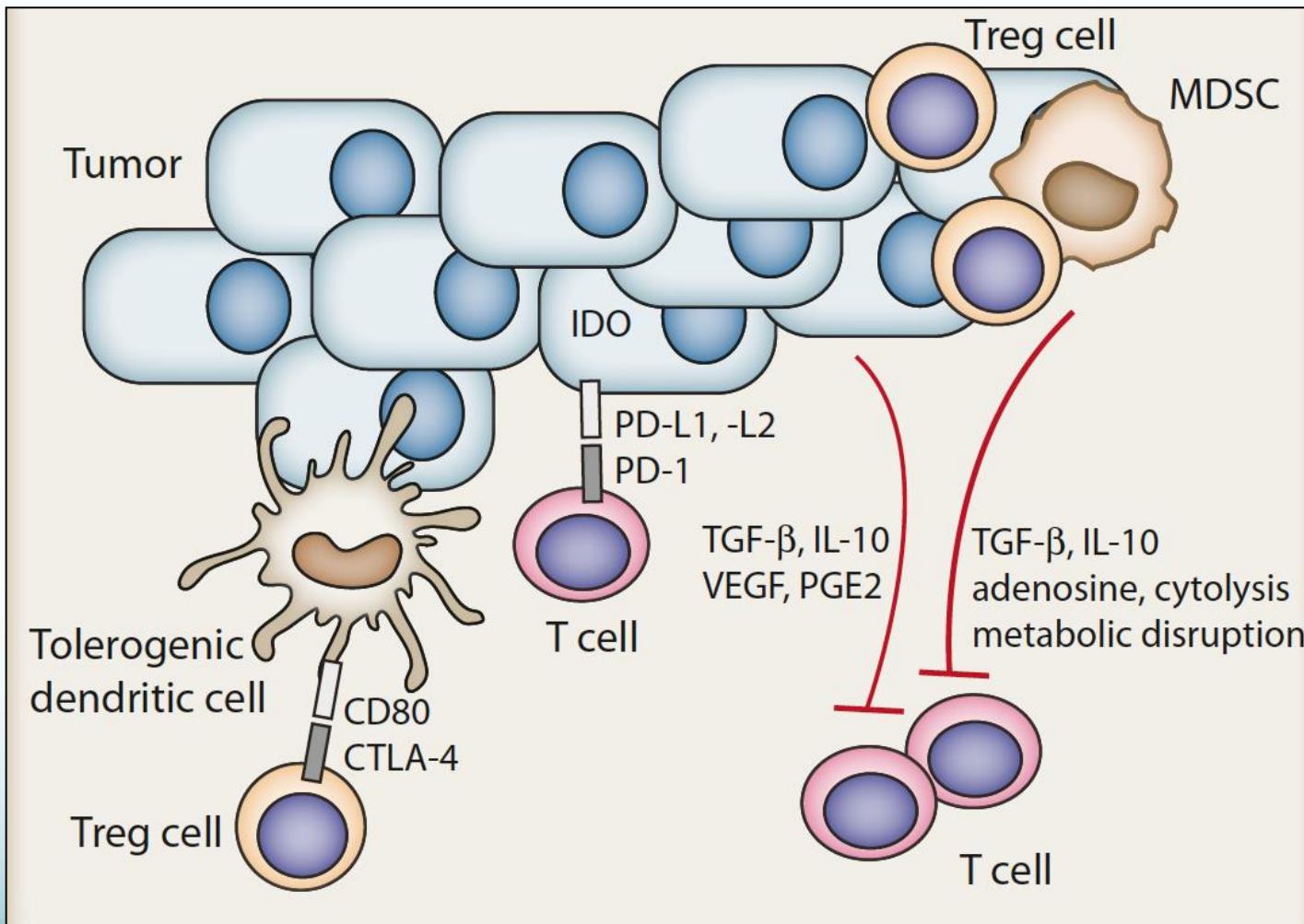
**COMMENT EVITER QUE LES
TUMEURS RENDENT LE SYSTEME
IMMUNITAIRE TOLERANT ?**



« L'avancée scientifique »
selon Science 2013...

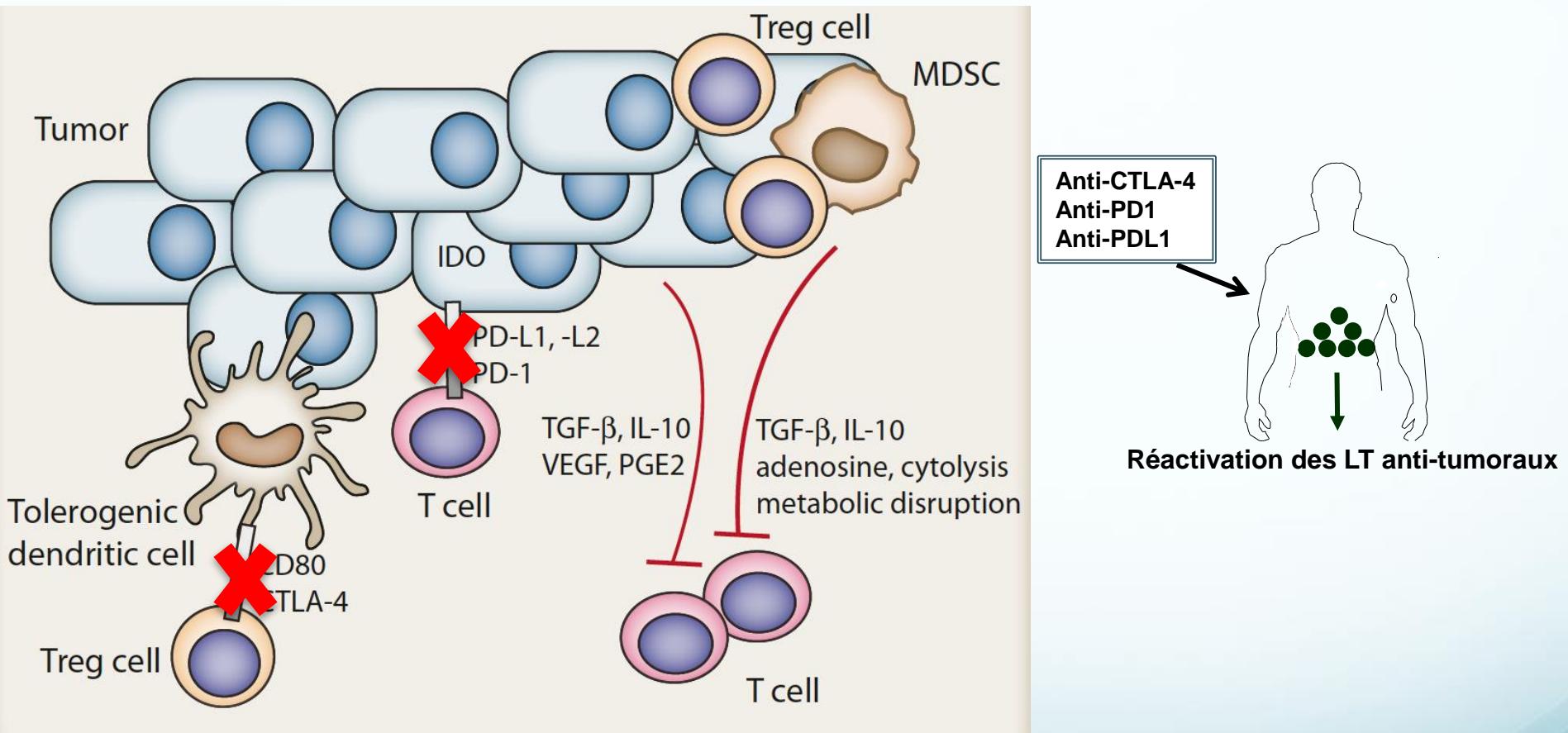


Les tumeurs développent des moyens d'échappement au SI

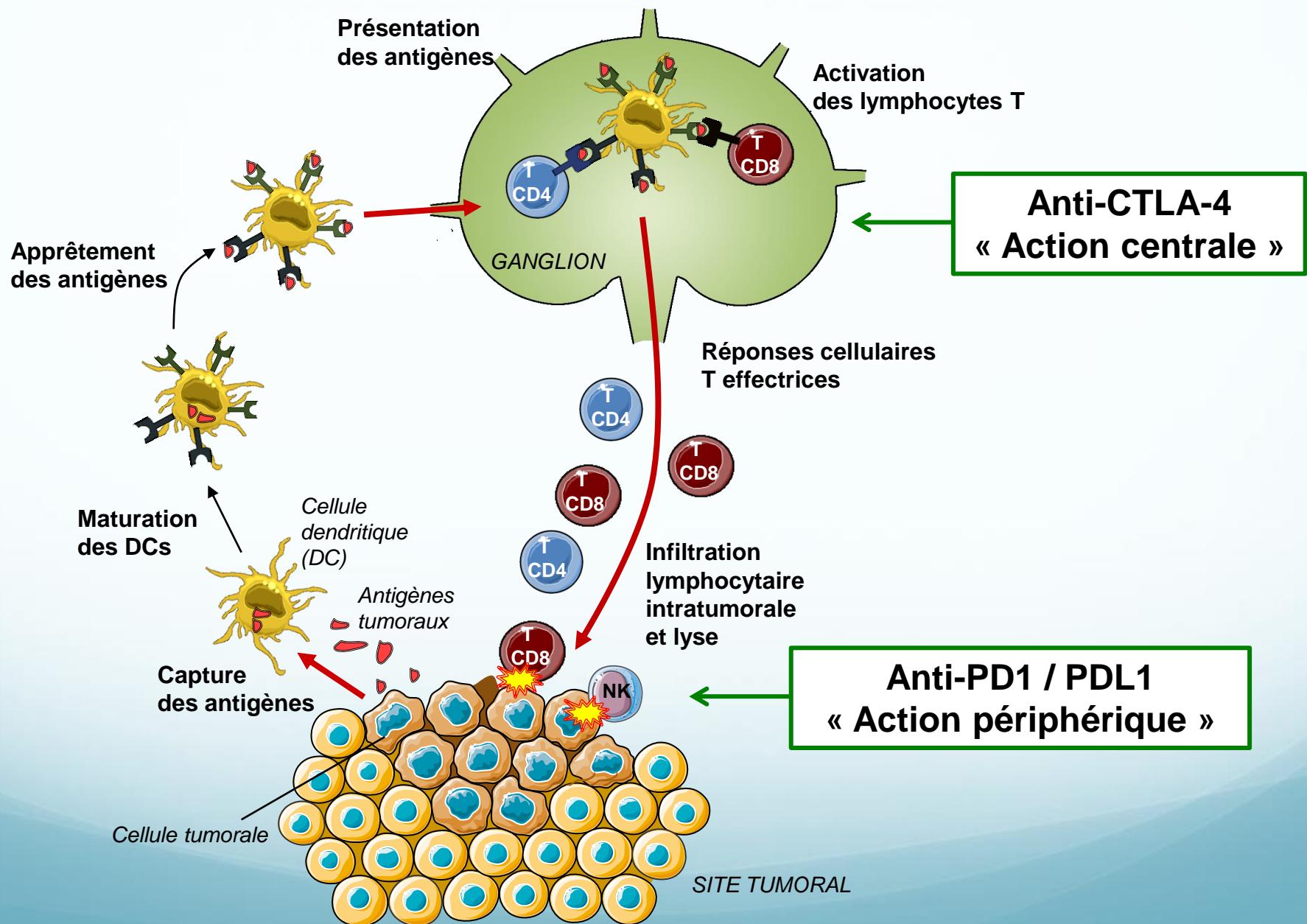


Les checkpoints inhibiteurs

✓ Principe = Bloquer les inhibiteurs des lymphocytes T antitumoraux



Les checkpoints inhibiteurs



Les checkpoints inhibiteurs: blocage de CTLA-4

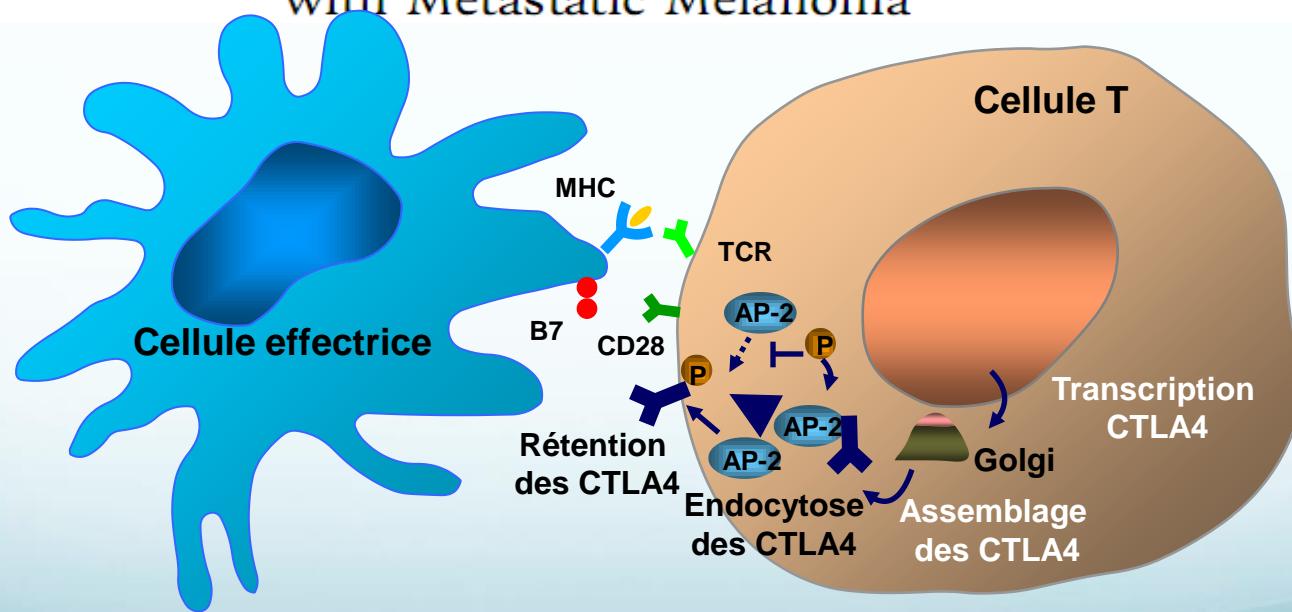
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

AUGUST 19, 2010

VOL. 363 NO. 8

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma



Efficacité oui et dans le mélanome !!

Les checkpoints inhibiteurs: blocage de CTLA-4

The NEW ENGLAND
JOURNAL of MEDICINE

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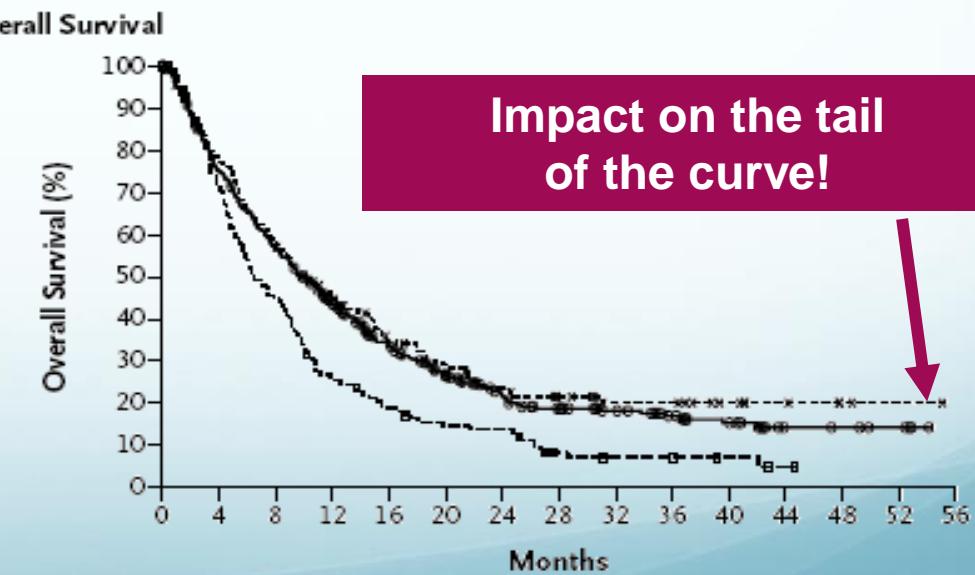
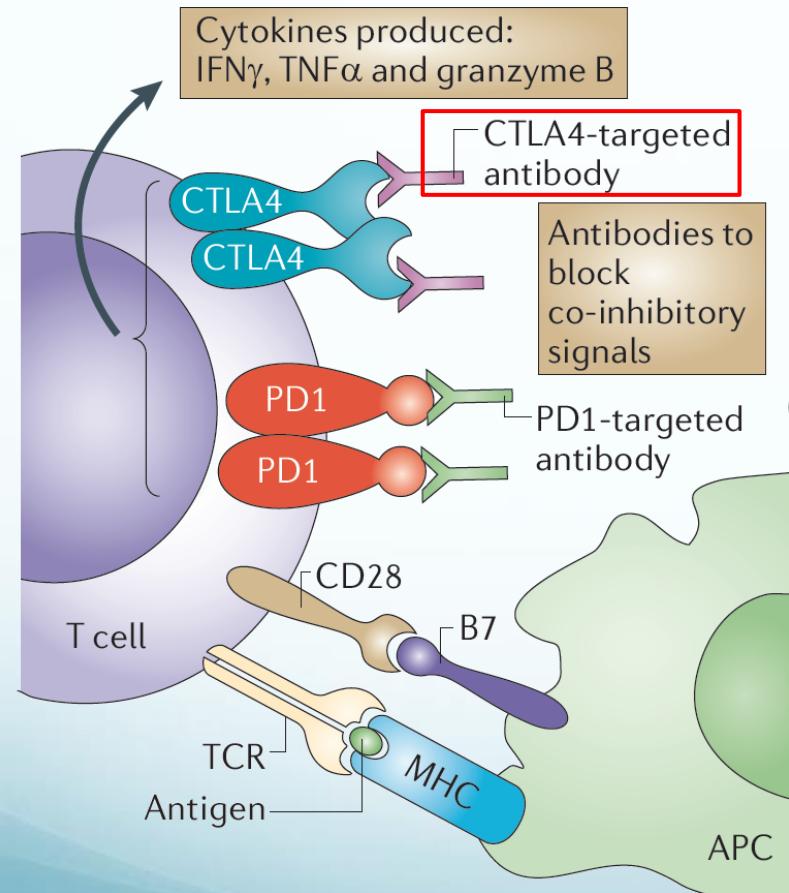
AUGUST 19, 2010

VOL. 363 NO. 8

Improved Survival with Ipilimumab in Patients
with Metastatic Melanoma

Ipilimumab:
The major benefit is in durable
tumor regressions

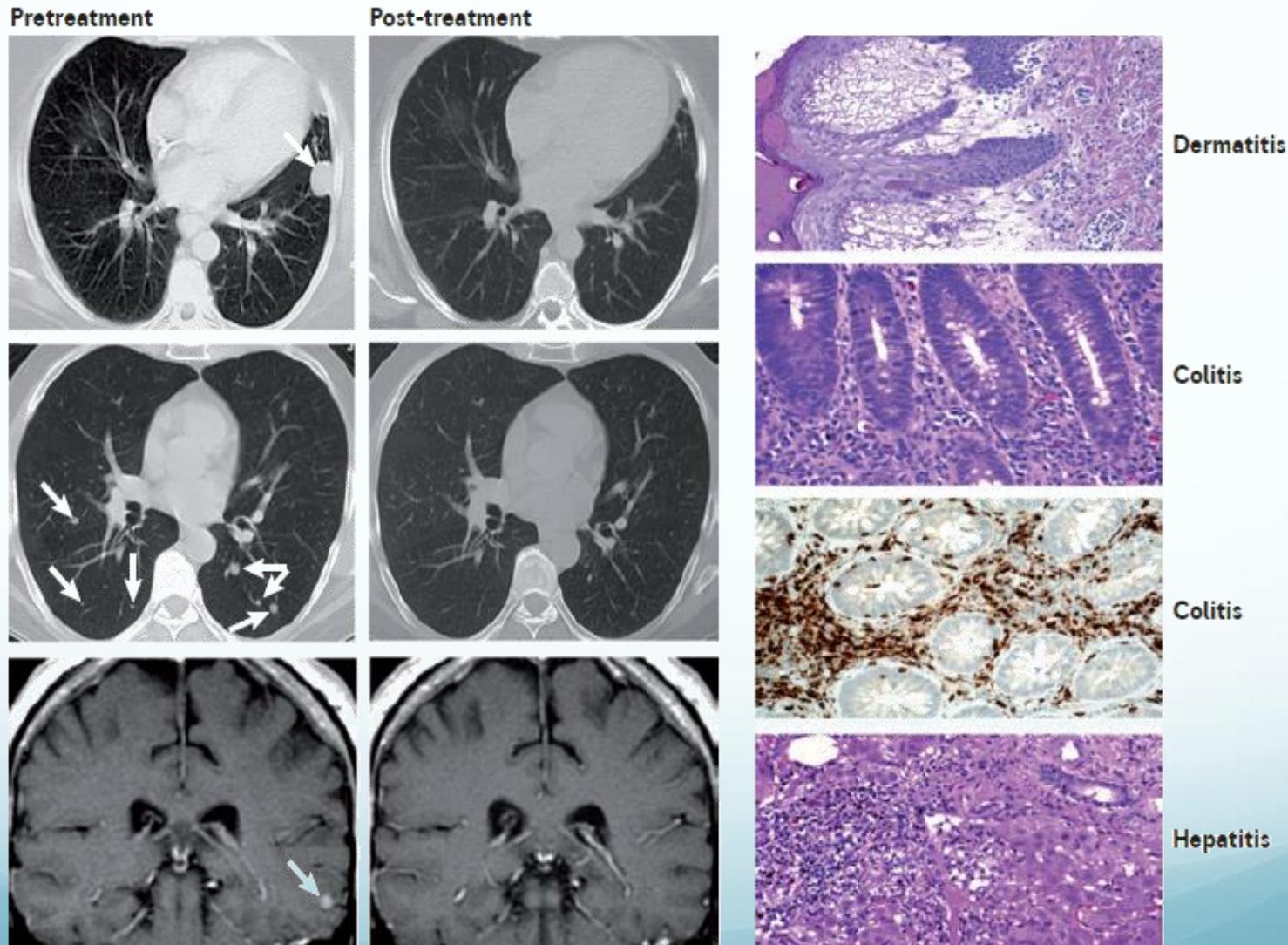
Impact on the tail
of the curve!



10.1056/NEJMoa1003466 NEJM.ORG

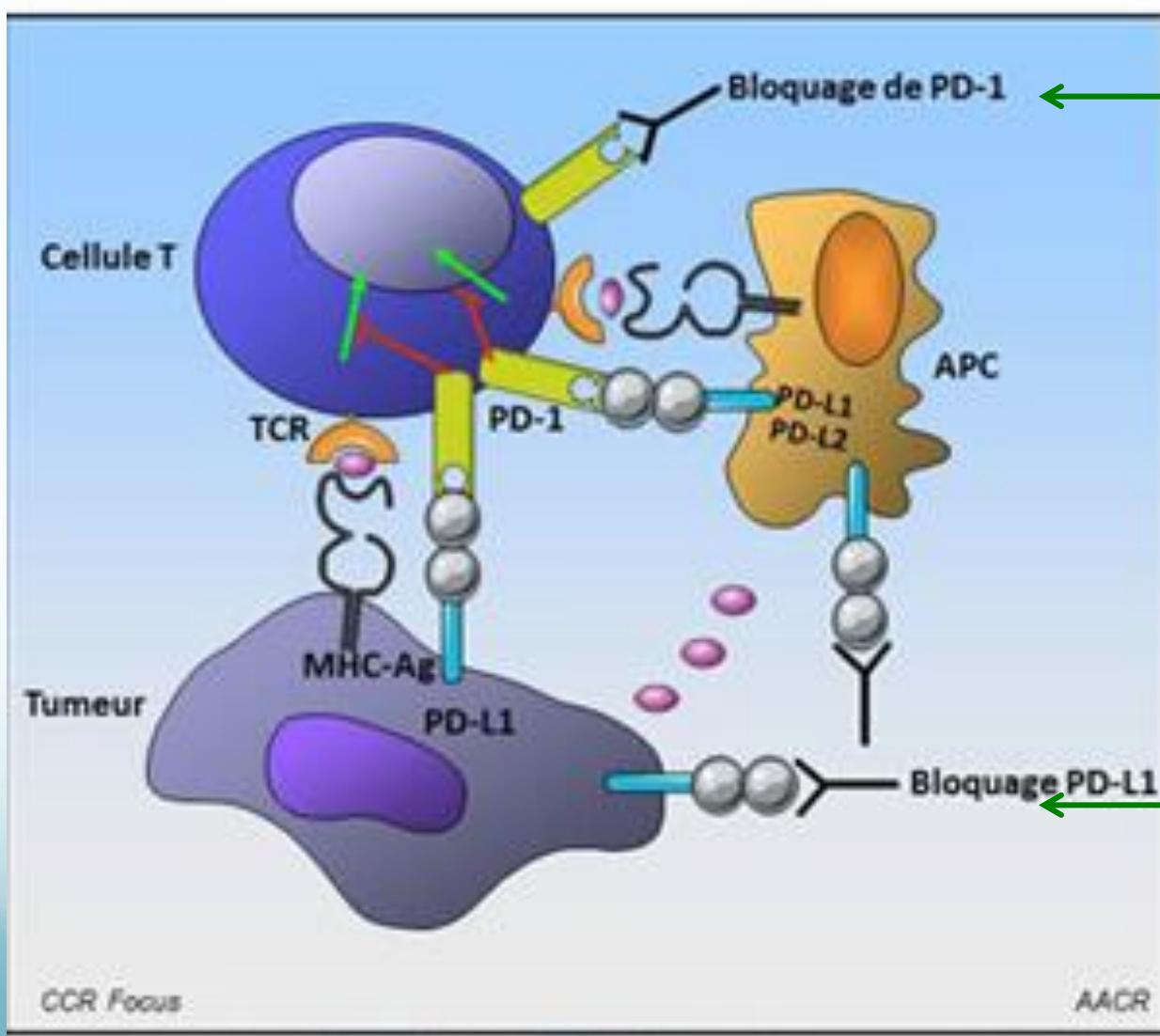
Les checkpoints inhibiteurs: blocage de CTLA-4

Anti-CTLA4 : activité anti-tumorale et toxicité



Les checkpoints inhibiteurs: anti PD-1 / PDL1

Efficacité dans de nombreux cancers



Anti-PD-1
Nivolumab,
Pembrolizumab,
Pidilizumab

Anti-PDL1
MPDL328017
BMS-936559

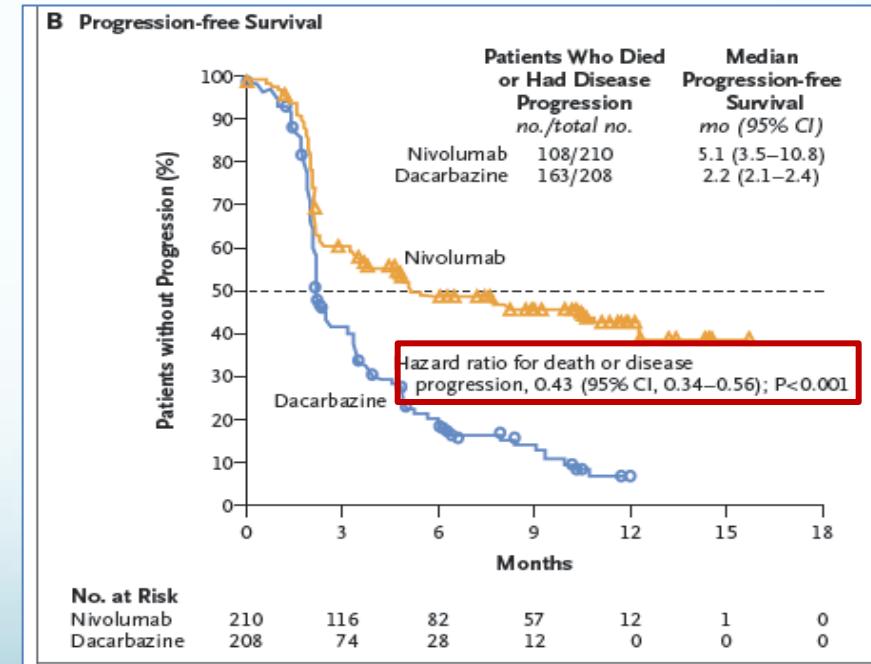
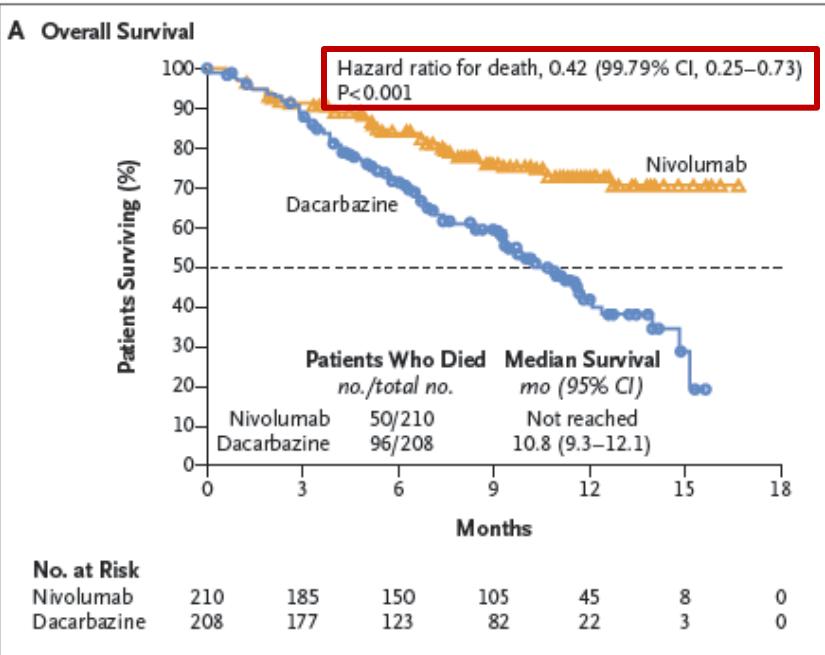
Les checkpoints inhibiteurs: anti PD-1

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab in Previously Untreated Melanoma without BRAF Mutation

Caroline Robert, M.D., Ph.D., Georgina V. Long, M.D., Ph.D., Benjamin Brady, M.D.,



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

JUNE 28, 2012

VOL. 366 NO. 26

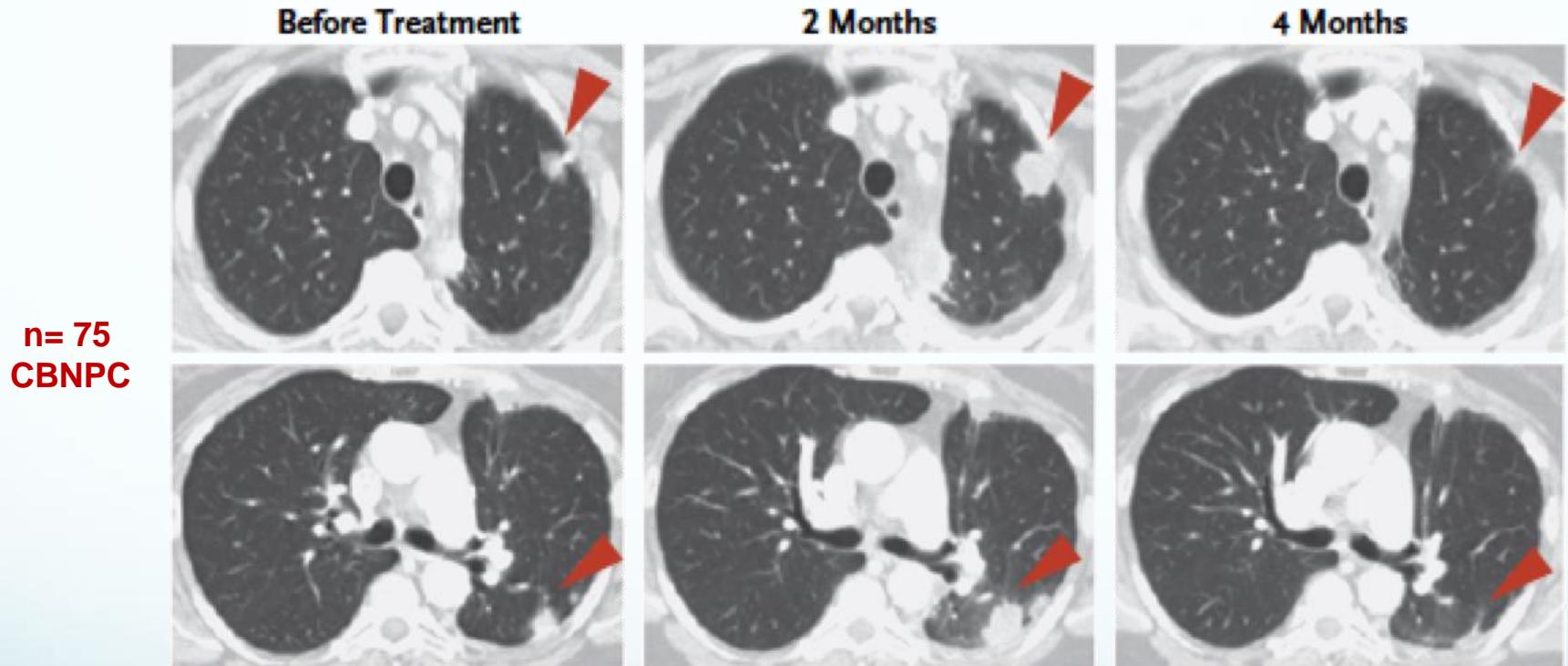
Safety, Activity, and Immune Correlates of Anti-PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D.,
David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D.,
Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D.,
Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D.,
Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D.,
Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D.,
Daniel McDonald, M.B.A., Georgia D. Kollia, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D.,
and Mario Sznol, M.D.

Les checkpoints inhibiteurs: anti PD-1

Réponses objectives dans le CBNPC

Patient with Non-Small-Cell Lung Cancer



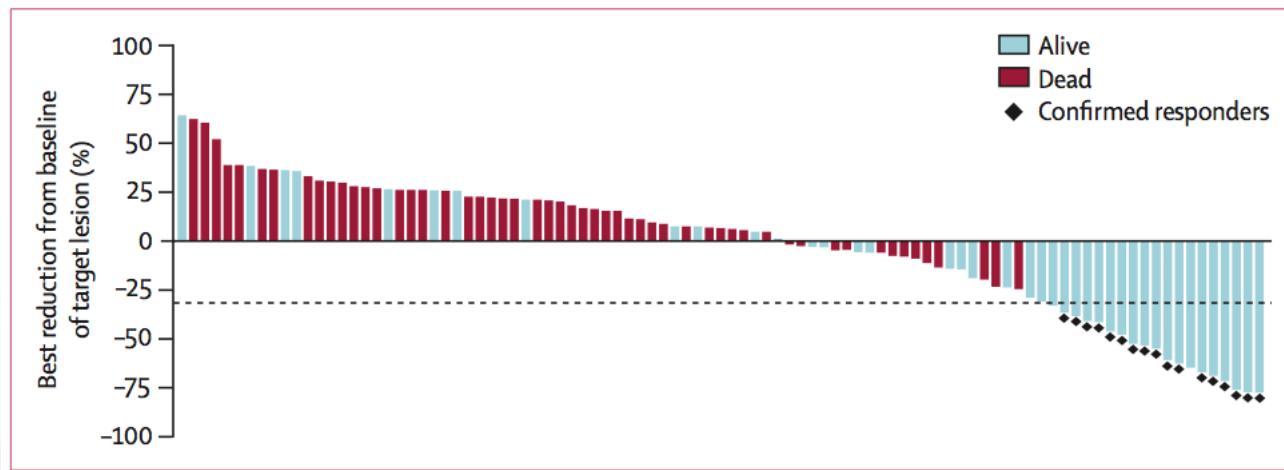
20/31 réponses ont duré ≥ 1 an chez des patients suivi au-delà de 1 an réponse DURABLE

Les checkpoints inhibiteurs: anti PD-1

Réponses objectives dans le CBNPC

Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial

n= 117



15% ORR dont 60 % > 6 mois

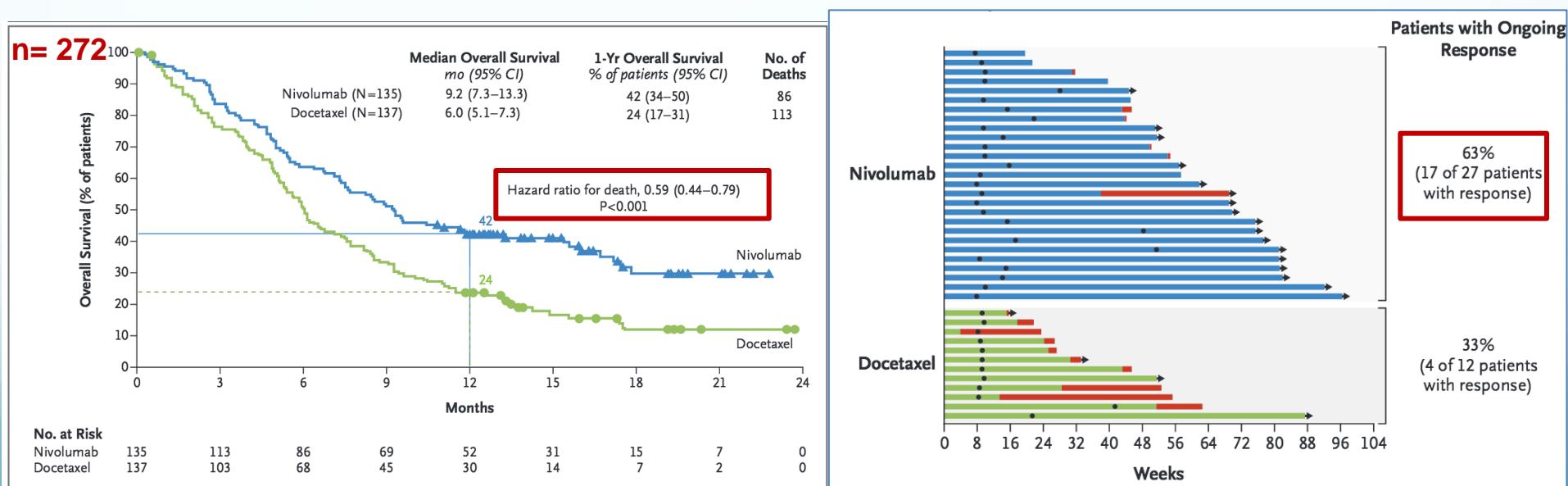
Les checkpoints inhibiteurs: anti PD-1

CHECKMATE 017 : Arrêt prématûré

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer



Les checkpoints inhibiteurs: anti PD-1

Efficacité dans le cancer du rein

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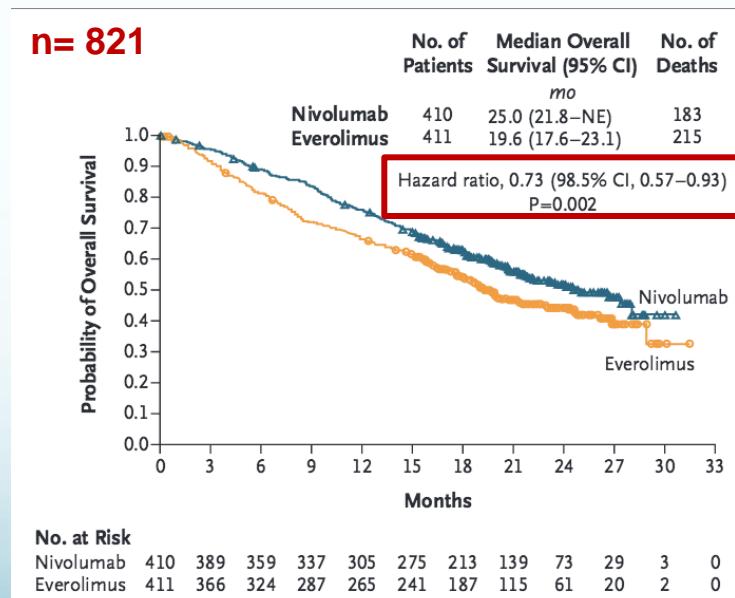
ESTABLISHED IN 1812

NOVEMBER 5, 2015

VOL. 373 NO. 19

Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma

R.J. Motzer, B. Escudier, D.F. McDermott, S. George, H.J. Hammers, S. Srinivas, S.S. Tykodi, J.A. Sosman,



Les checkpoints inhibiteurs: anti PD-1

Efficacité dans le cancer du sein triple négatif

Les immuno-modulateurs débarquent dans le cancer du sein triple-négatif

Les premiers résultats d'essais de phase précoce évaluant les régulateurs du checkpoint immunologique dans des populations de cancers du sein triple-négatif lourdement pré-traités sont rapportés et sont encourageants !

A phase Ib study of pembrolizumab (MK-3475) in patients with advanced triple-negative breast cancer

Phase Ib (KEYNOTE-012) : cohorte TNBC

TBNC
PS 0/1
PD-L1 positif IHC
Pas de méta cérébrales actives
Pas de maladie AI



Pembrolizumab
10 mg/kg/2 sem.
Administré jusqu'à progression ou intolérance (possible arrêt si RC)

→ Evaluation toutes les 8 semaines (RECIST 1.1)

*PD-L1+ = \geq 1% des cellules (tumorales ou stromales) sur tissu archivé
58% des patientes screenées étaient PD-L1 positives

Les checkpoints inhibiteurs: anti PD-1

Phase Ib (KEYNOTE-012) : cohorte TNBC

■ Activité antitumorale (RECIST 1.1)

Patients évaluables pour la réponse	n= 27
Réponse objective <ul style="list-style-type: none">● Réponse complète● Réponse partielle	5 (18,5%) 1 (3,7%) 4 (14,8%)
Maladie stable	7 (25,9%)
Maladie progressive	12 (44,4%)
Pas d'évaluation	3 (11,1%)

■ Tolérance

Effets indésirables reliés au traitement	n= 32
Tous grades <ul style="list-style-type: none">● Grade 3● Grade 4● Sévères● Fatal (CIVD)	18 (56,3%) 4 (12,5%) 1 (3,1%) 3 (9,4%) 1 (3,1%)

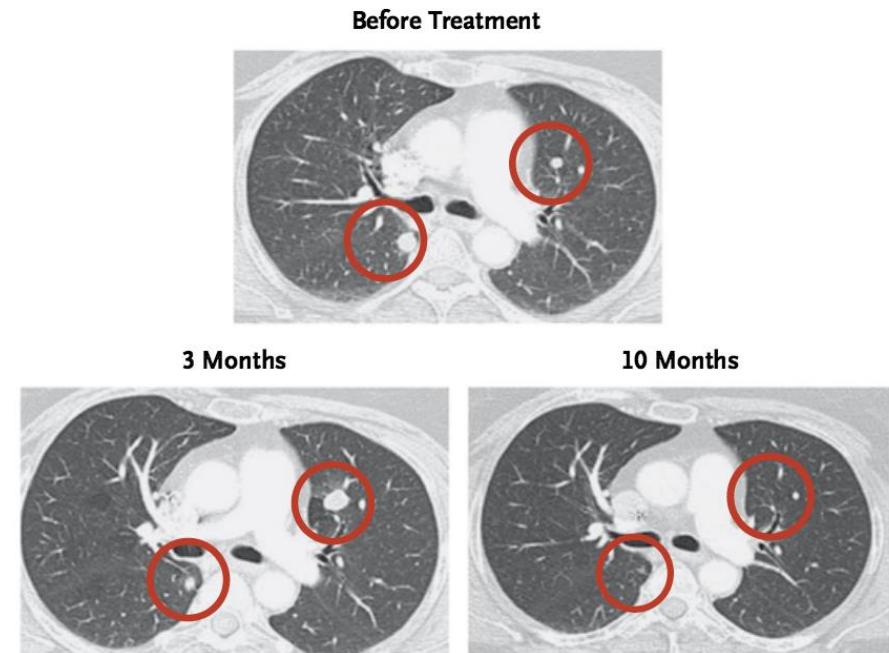
Les checkpoints inhibiteurs: anti PD-L1

ORIGINAL ARTICLE

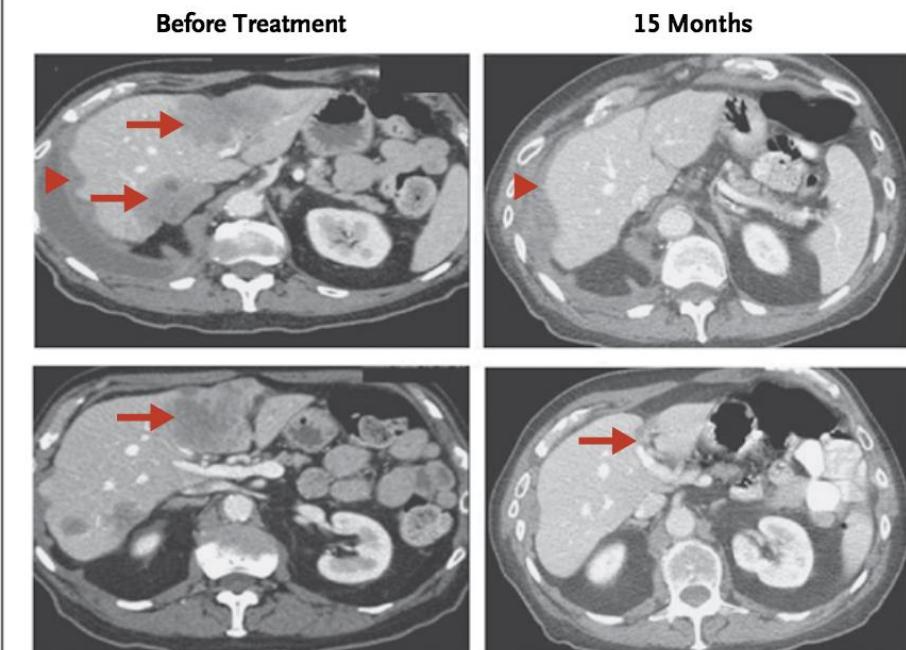
Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer

Julie R. Brahmer, M.D., Scott S. Tykodi, M.D., Ph.D., Laura Q.M. Chow, M.D.,

A Melanoma

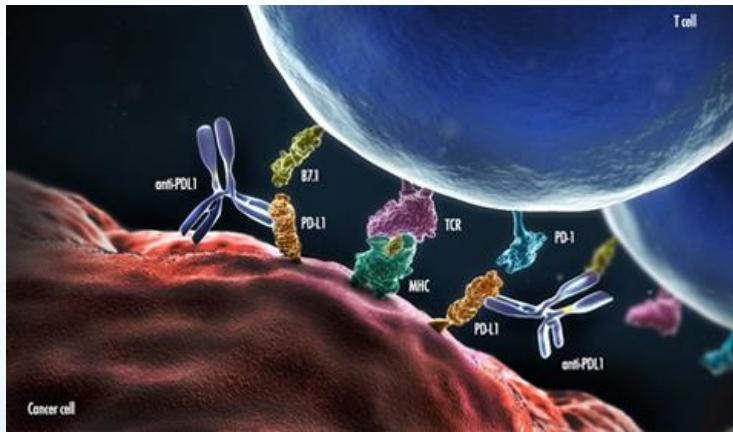


B Non-Small-Cell Lung Cancer



Les checkpoints inhibiteurs: anti PD-L1

Inhibition de PD-L1 (MPDL3280A): activité clinique dans les cancers du sein triple négatif

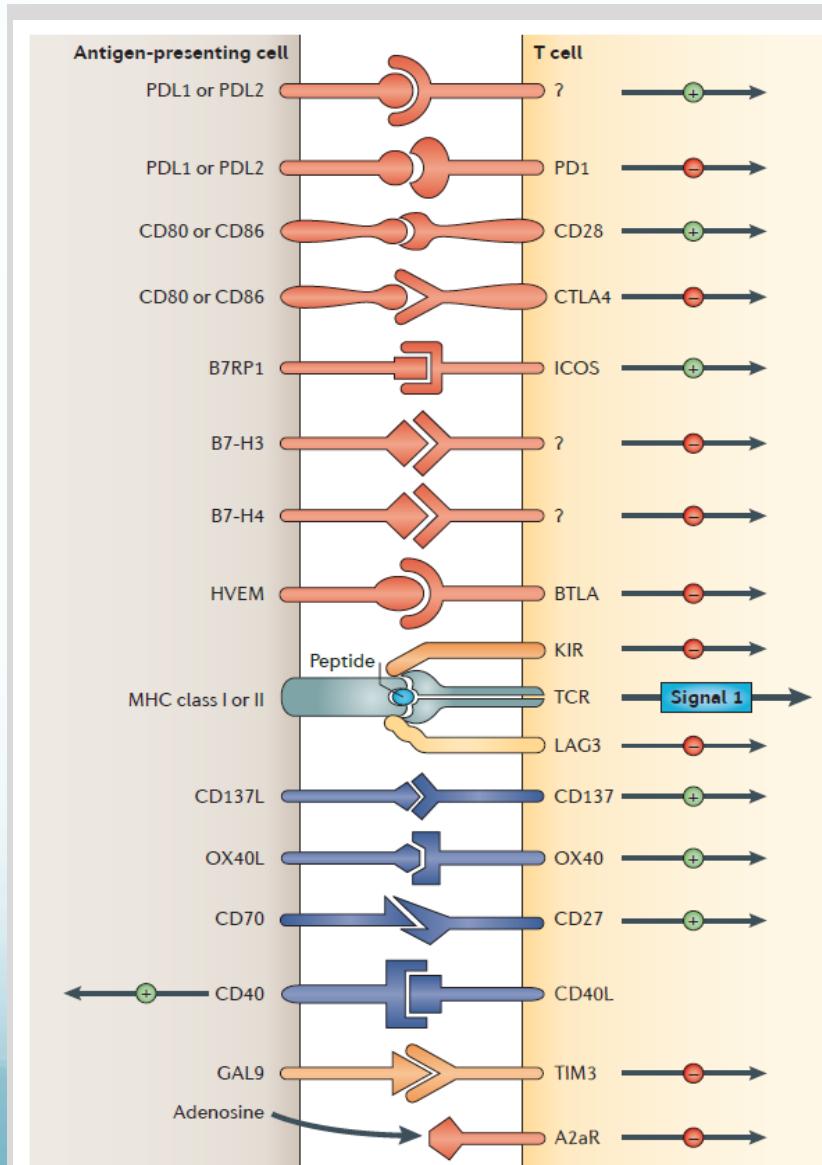


n= 9 patientes évaluables pour la réponse

- 3 réponses objectives (33% ; 1 RC et 2 RP)
- Obtenue dans les 6 semaines pour les 3 patientes

Les checkpoints inhibiteurs: voies d'avenir

Check points immunologiques, il en existe d'autres !!!



Pardoll et al. Nat Rev Cancer 2012

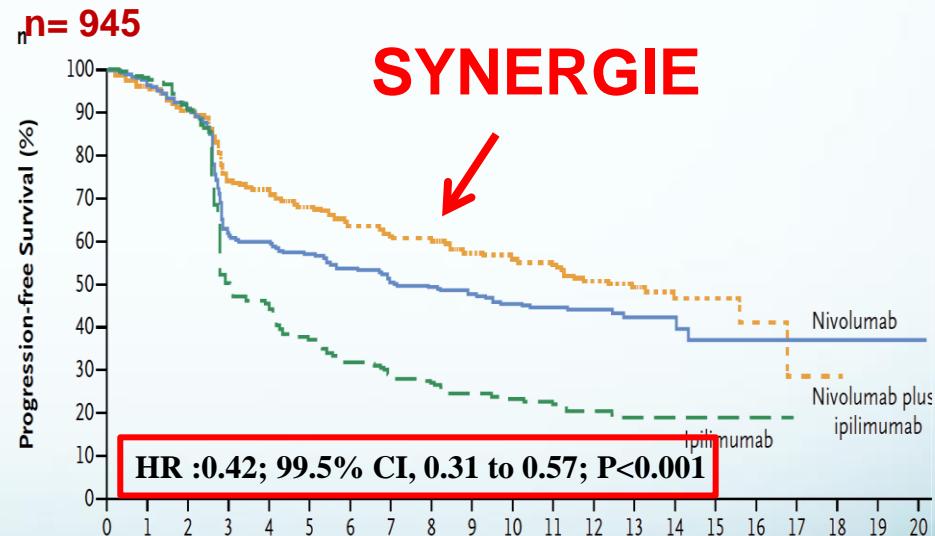
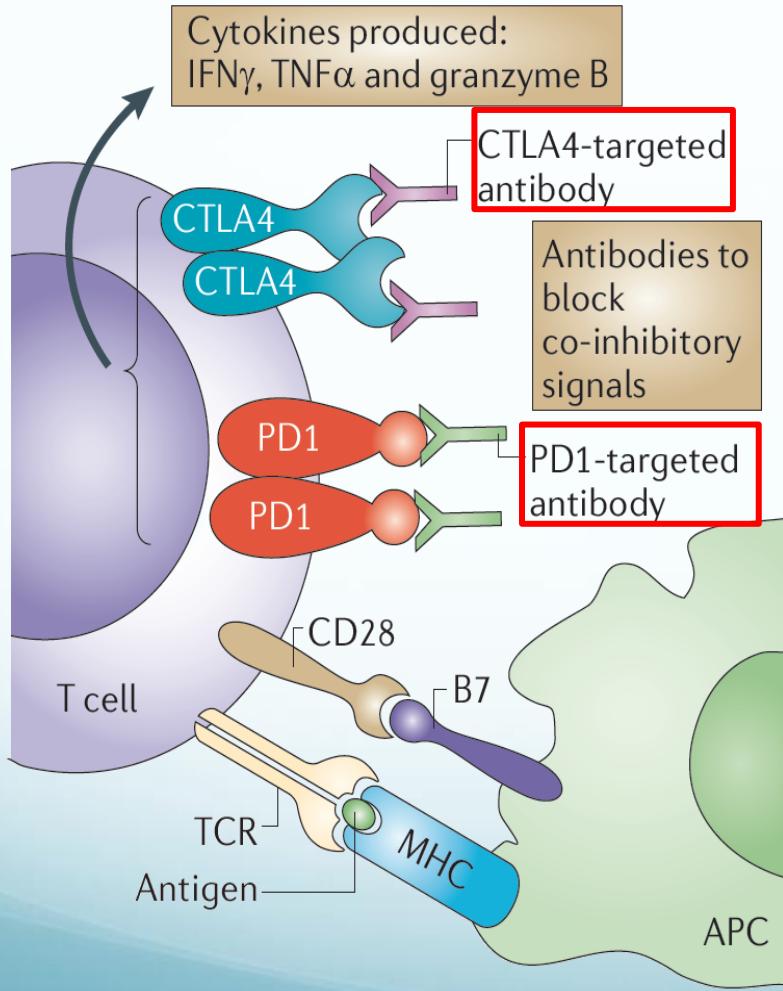
Les checkpoints inhibiteurs: voies d'avenir

Anti-CTLA4 + Anti-PD-1 Combo

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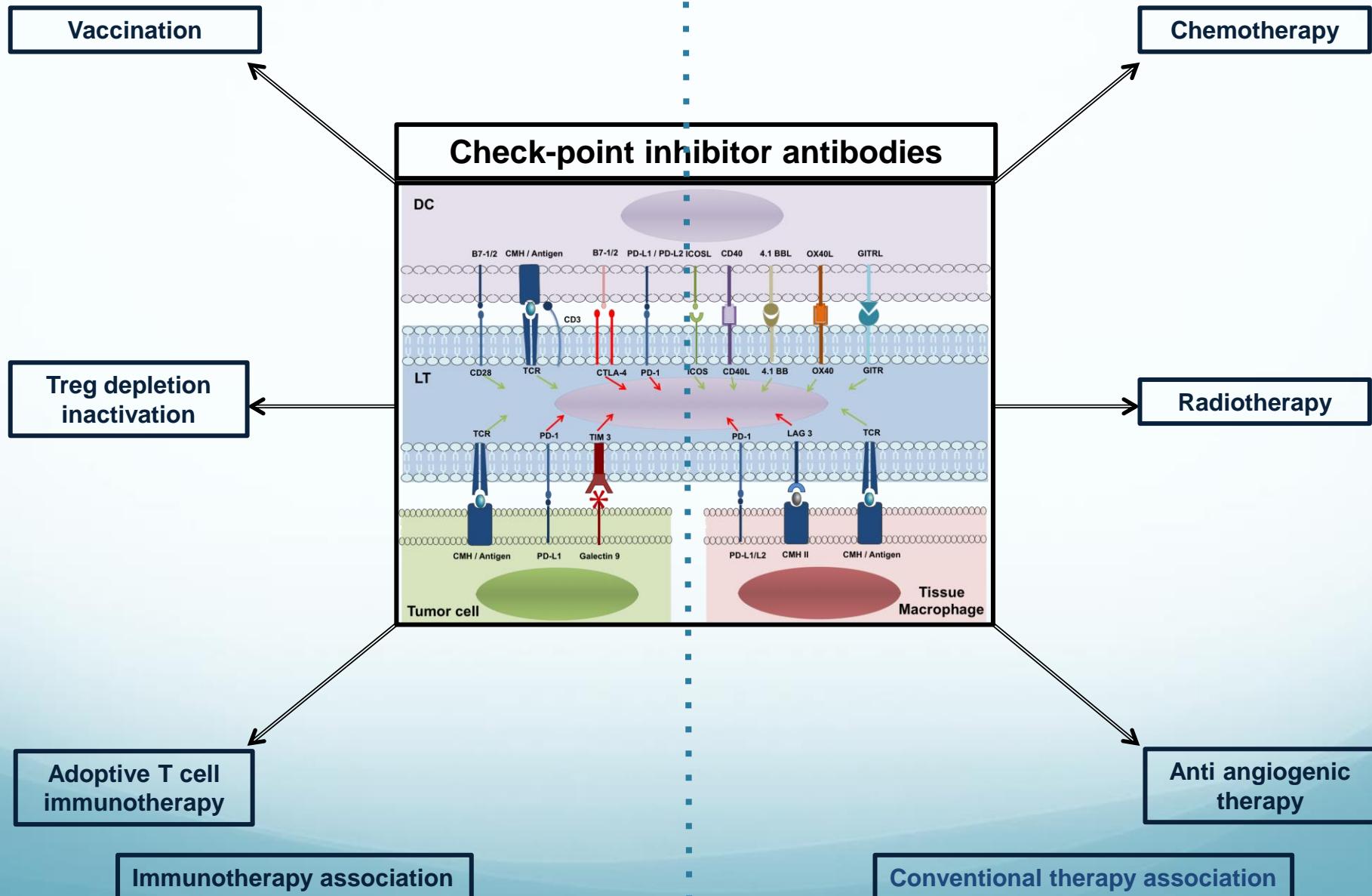
ORIGINAL ARTICLE

Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma



Immunostimulatory mAb	Company	Status	NCT #	Completion	Tumors
Anti-KIR					
lirilumab (IPH2102)	Innate Pharma / BMS	Phase 2	NCT01687387	Jun 2016	Acute Myeloid Leukemia
lirilumab + ipilimumab		Phase 1	NCT01750580	Oct 2016	Cancer NOS
lirilumab + nivolumab		Phase 1	NCT01714739	Sep 2017	Cancer NOS
elotuzumab + lirilumab or + urelumab		R-Phase 1	NCT02252263	Apr 2017	Multiple Myeloma
Anti-CD137					
urelumab (BMS-663513)	BMS	Phase 1	NCT01471210	Mar 2019	Solid Tumors / B-Cell NHL
urelumab + cetuximab		Phase 1	NCT02110082	Jan 2017	CRC, HNSCC
urelumab + nivolumab		Phase 1	NCT02253992	Dec 2018	Solid Tumors / B-cell NHL
urelumab + rituximab		Phase 1	NCT01775631	Feby 2017	B-Cell Malignancies
Anti-OX40					
aOX40 + Stereotactic Body Radiation	Providence Health&Service	Phase 1/2	NCT01862900	Feb 2023	M+ Breast K; M+ Lung; M+ Liver
aOX40 + cyclophosphamide +RT		Phase 1/2	NCT01303705	Oct 2015	Prostate Cancer
MEDI6383	MedImmune/AZ	Phase 1	NCT02221960	Aug 2018	Bladder, CRC, NSCLC, HNSCC
RG7888 (anti-OX40, MOXR0916)	Roche/Gene	Phase I	NCT02219724	Aug 2018	Solid Cancers
Anti-LAG3					
BMS-986016	BMS	Phase 1	NCT02061761	Jun 2018	Hematologic Neoplasms
BMS-986016 +/- nivolumab		Phase 1	NCT01968109	May 2018	Solid Cancers
Anti-CD40					
BMS-986090	BMS	R-Phase 1	NCT02079480	Apr 2015	Healthy Volunteers (R vs Placebo)
Anti-CD27					
Varlilumab (CDX-1127)	Celldex	Phase 1	NCT01460134	Mar 2015	B&T-cellLymphomas, Solid Tumors
Anti-B7H3					
MGA271	MacroGenics	Phase 1	NCT01918930	Mar 2014	Melanoma
Anti-GITR					
TRX518	GITR, Inc.CRI	Phase 1	NCT012391 34	Dec 2014	Stage III/IV Melanoma; Solid Tumors

Les checkpoints inhibiteurs: voies d'avenir



MERCI de votre attention



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Lise Queiroz



Plateforme de monitoring-CIC
C Laheurte
Ph Saas

