PLENIERE

BILAN DES CARACTÉRISTIQUES MOLÉCULAIRES DANS L'IMMUNOTHÉRAPIE

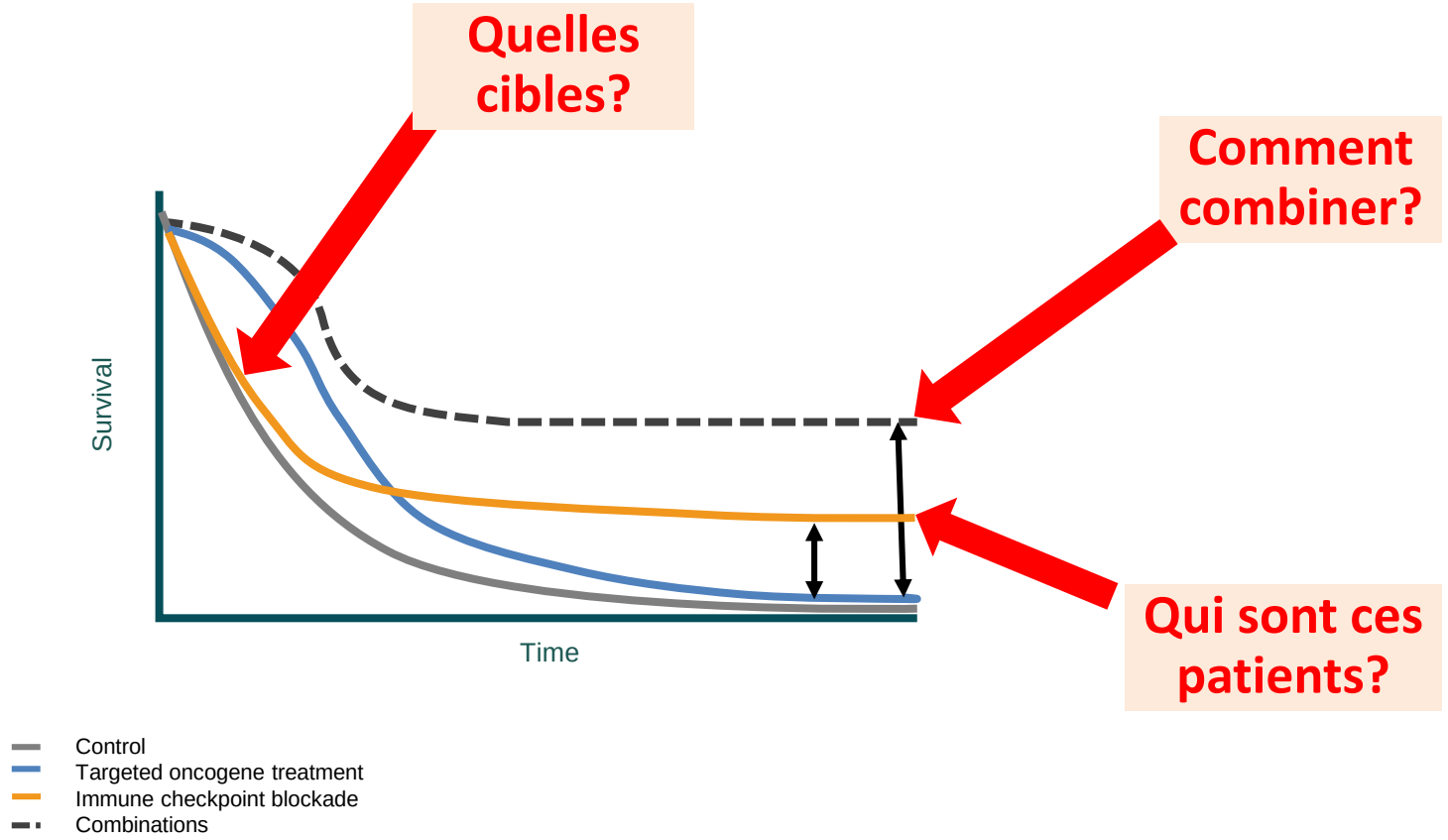
Jean-Yves Blay, Centre Léon Bérard, Lyon

Avec le soutien du

GFCO Groupe Francophone de Cytogénomique Oncologique

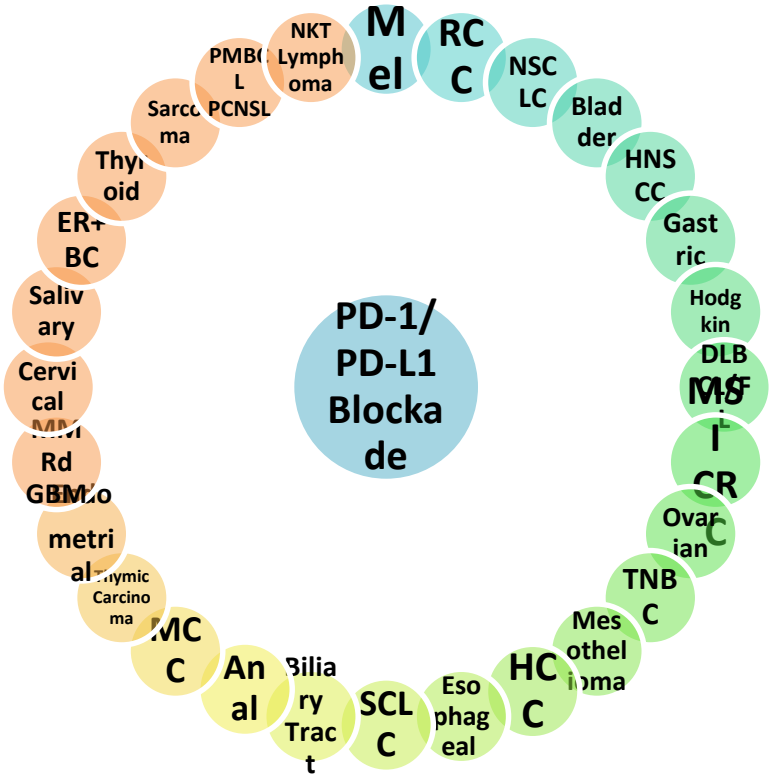
AstraZeneca

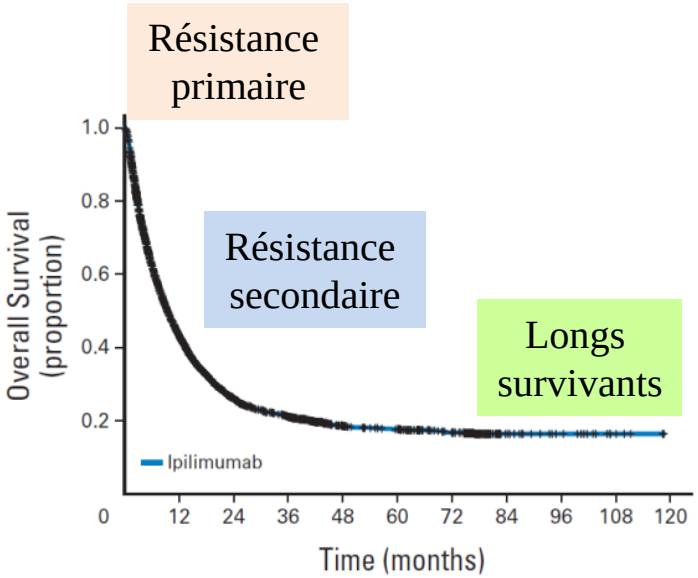
Liens d’intérêt



1. Adapted from Ribas A, presented WCM 2013. 2. Ribas A, et al. Clin Cancer Res 2012;18:336–41. 3. Drake CG. Ann Oncol 2012;23(suppl 8):viii41–viii46.

Immunothérapie pour tous les cancers en 2018?



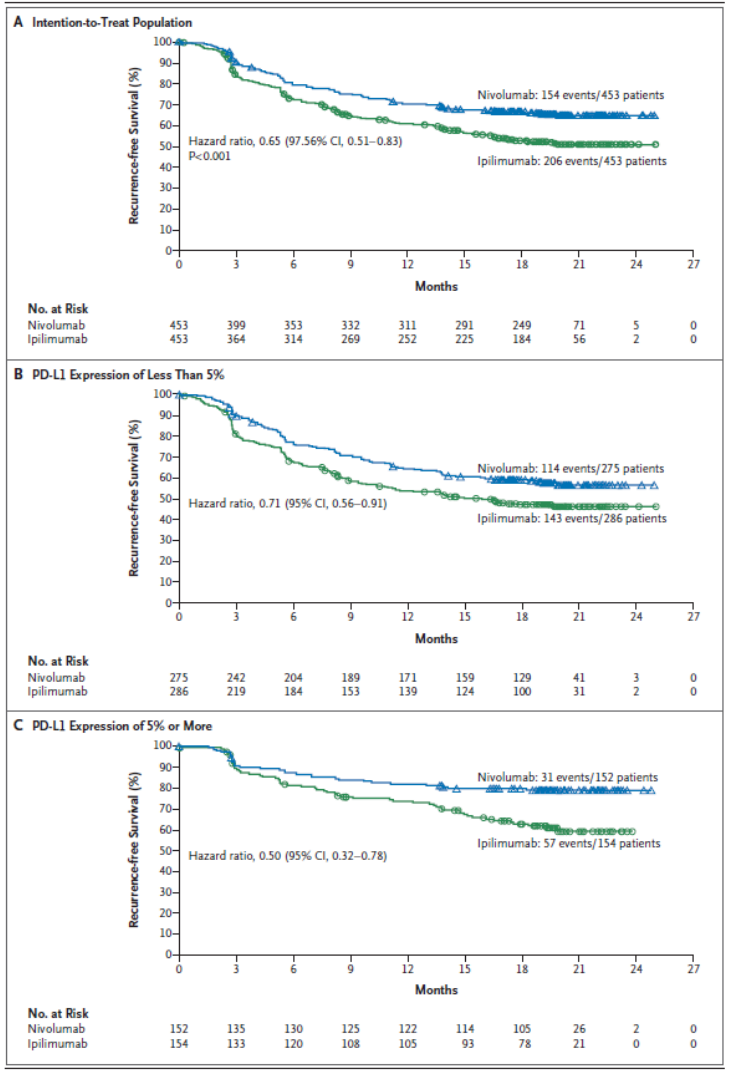


Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma

J. Weber, M. Mandala, M. Del Vecchio, H.J. Gogas, A.M. Arance, C.L. Cowey, S. Dalle, M. Schenker, V. Chiarion-Sileni, I. Marquez-Rodas, J.-J. Grob, M.O. Butler, M.R. Middleton, M. Maio, V. Atkinson, P. Queirolo, R. Gonzalez, R.R. Kudchadkar, M. Smylie, N. Meyer, L. Mortier, M.B. Atkins, G.V. Long, S. Bhatia, C. Lebbé, P. Rutkowski, K. Yokota, N. Yamazaki, T.M. Kim, V. de Pril, J. Sabater, A. Qureshi, J. Larkin, and P.A. Ascierto, for the CheckMate 238 Collaborators*

This article was published on September 10, 2017, at NEJM.org.

N Engl J Med 2017;377:1824-35.
DOI: 10.1056/NEJMoa1709030



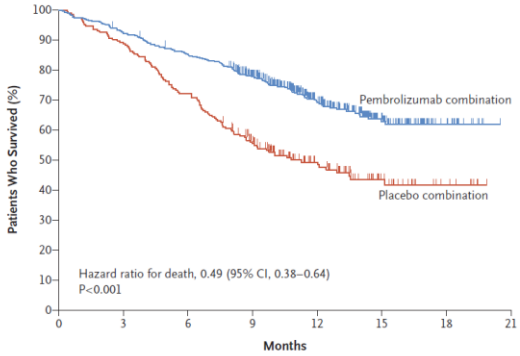
Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer

L. Gandhi, D. Rodríguez-Abreu, S. Gadgeel, E. Esteban, E. Felip, F. De Angelis, M. Domine, P. Clingan, M.J. Hochmair, S.F. Powell, S.Y.-S. Cheng, H.G. Bischoff, N. Peled, F. Grossi, R.R. Jennens, M. Reck, R. Hui, E.B. Garon, M. Boyer, B. Rubio-Viqueira, S. Novello, T. Kurata, J.E. Gray, J. Vida, Z. Wei, J. Yang, H. Raftopoulos, M.C. Pietanza, and M.C. Garassino, for the KEYNOTE-189 Investigators*

This article was published on April 16, 2018, at NEJM.org.

DOI: 10.1056/NEJMoa1801005

A Overall Survival



No. at Risk								
Pembrolizumab combination	410	377	347	278	163	71	18	0
Placebo combination	206	183	149	104	59	25	8	0

B Subgroup Analysis of Overall Survival

Subgroup	No. of Events/ No. of Patients	Hazard Ratio for Death (95% CI)
Overall	235/616	0.49 (0.38–0.64)
Age		
<65 yr	133/312	0.43 (0.31–0.61)
≥65 yr	102/304	0.64 (0.43–0.95)
Sex		
Male	143/363	0.70 (0.50–0.99)
Female	92/253	0.29 (0.19–0.44)
ECOG performance-status score		
0	74/266	0.44 (0.28–0.71)
1	159/346	0.53 (0.39–0.73)
Smoking status		
Current or former	211/543	0.54 (0.41–0.71)
Never	24/73	0.23 (0.10–0.54)
Brain metastases at baseline		
Yes	51/108	0.36 (0.20–0.62)
No	184/508	0.53 (0.39–0.71)
PD-L1 tumor proportion score		
<1%	84/190	0.59 (0.38–0.92)
≥1%	135/388	0.47 (0.34–0.66)
1–49%	65/186	0.55 (0.34–0.90)
≥50%	70/202	0.42 (0.26–0.68)
Platinum-based drug		
Carboplatin	176/445	0.52 (0.39–0.71)
Cisplatin	59/171	0.41 (0.24–0.69)

Quels gains en survie?

Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair–Deficient/Microsatellite Instability–High Metastatic Colorectal Cancer

Michael J. Overman, Sara Lonardi, Ka Yeung Mark Wong, Heinz-Josef Lenz, Fabio Gelsomino, Massimo Aglietta, Michael A. Morse, Eric Van Cutsem, Ray McDermott, Andrew Hill, Michael B. Sawyer, Alain Hendlisz, Bart Neyns, Magali Svrcek, Rebecca A. Moss, Jean-Marie Ledeine, Z. Alexander Cao, Shital Kamble, Scott Kopetz, and Thierry André

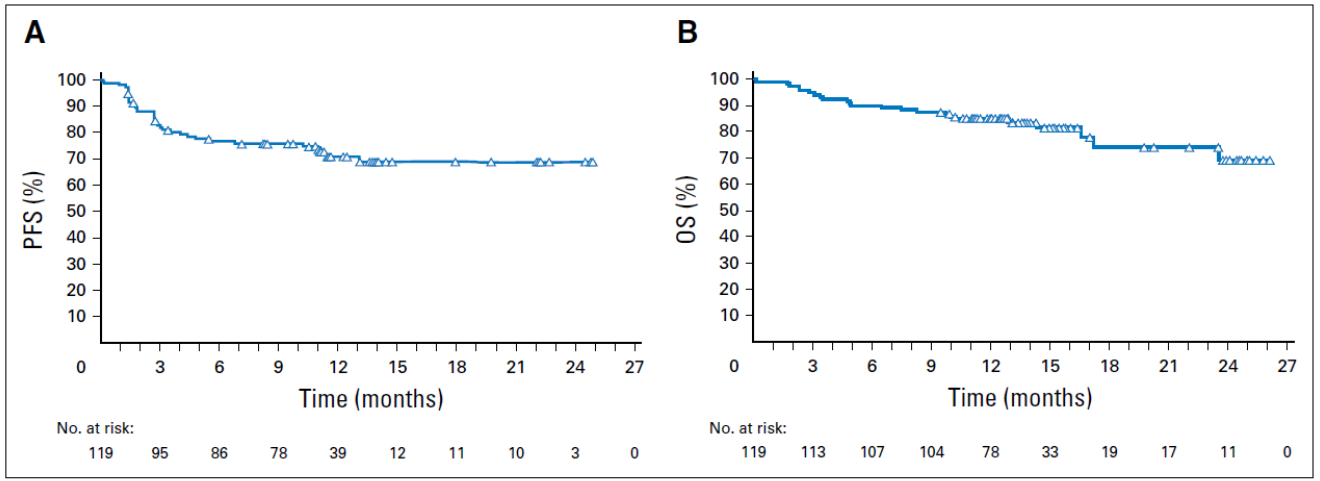


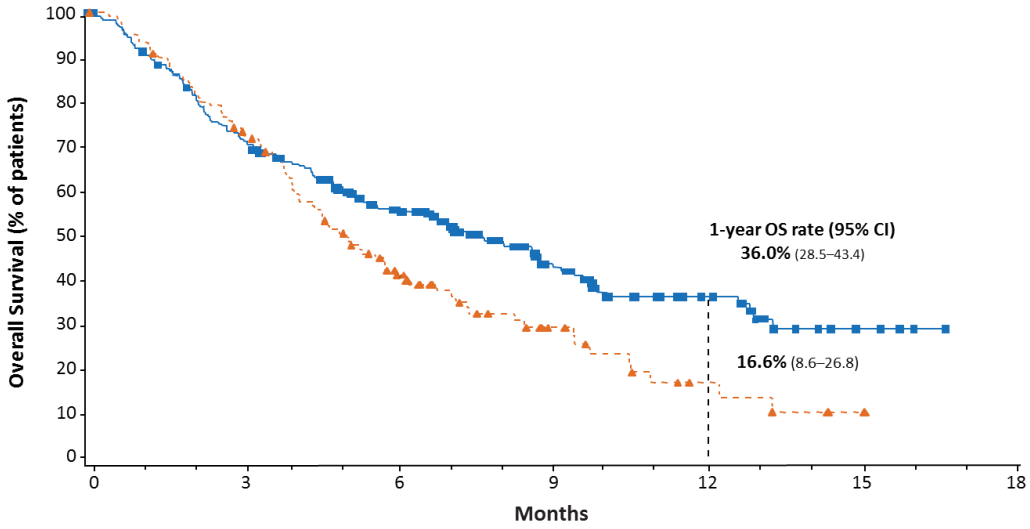
Fig 2. Kaplan-Meier plots of (A) progression-free survival (PFS) per investigator assessment and (B) overall survival (OS) in all patients.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck

R.L. Ferris, G. Blumenschein, Jr., J. Fayette, J. Guigay, A.D. Colevas, L. Licitra, K. Harrington, S. Kasper, E.E. Vokes, C. Even, F. Worden, N.F. Saba, L.C. Iglesias Docampo, R. Haddad, T. Rordorf, N. Kiyota, M. Tahara, M. Monga, M. Lynch, W.J. Geese, J. Kopit, J.W. Shaw, and M.L. Gillison



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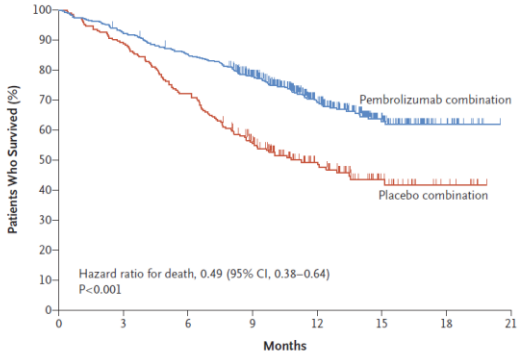

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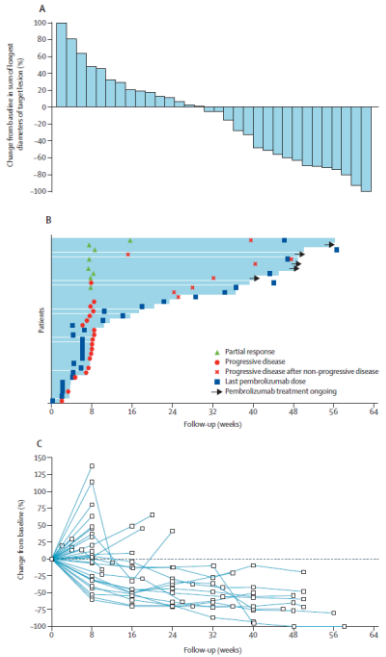
Carboplatin	176/445	0.52 (0.39–0.71)
Cisplatin	59/171	0.41 (0.24–0.69)

Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial

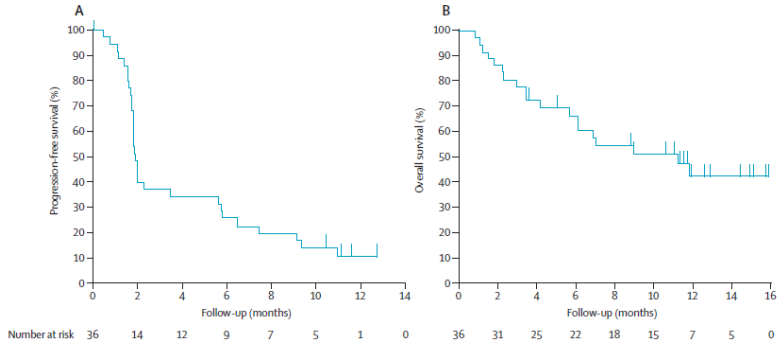
Kei Muro, Hyun Cheol Chung, Veena Shankaran, Ravit Geva, Daniel Catenacci, Shilpa Gupta, Joseph Paul Eder, Talia Golan, Dung T Le, Barbara Burtness, Autumn J McRee, Chia-Chi Lin, Kumudu Pathiraja, Jared Lunceford, Kenneth Emancipator, Jonathan Juco, Minori Koshiji, Yung-Jue Bang**

Tumour response



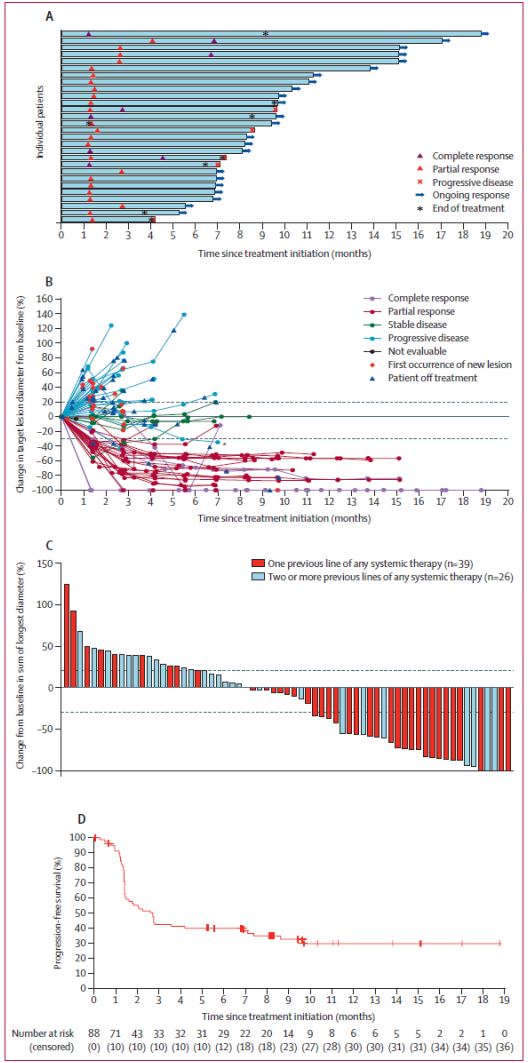
Patient survival

Kaplan-Meier estimates of centrally assessed progression-free survival (A) & overall survival (B)



Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial

Howard L Kaufman, Jeffery Russell, Omid Hamid, Shailender Bhatia, Patrick Terheyden, Sandra P D'Angelo, Kent C Shih, Céleste Lebbé, Gerald P Linette, Michele Milella, Isaac Brownell, Karl D Lewis, Jochen H Lorch, Kevin Chin, Lisa Mahnke, Anja von Heydebreck, Jean-Marie Cuillerot, Paul Nghiem

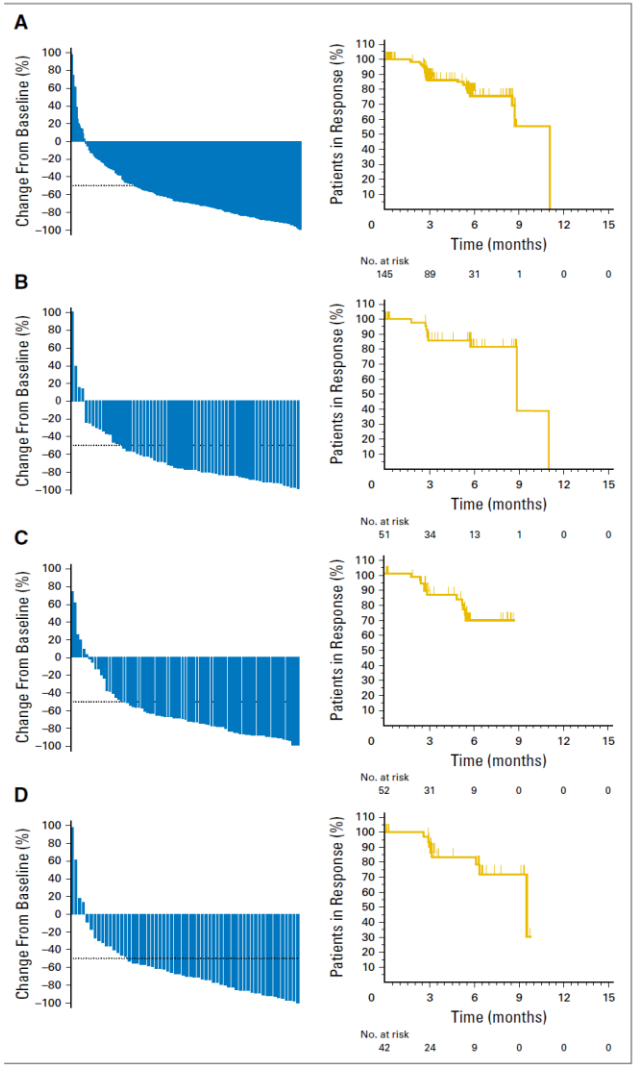


Phase II Study of the Efficacy and Safety of Pembrolizumab for Relapsed/Refractory Classic Hodgkin Lymphoma

Robert Chen, Pier Luigi Zinzani, Michelle A. Fanale, Philippe Armand, Nathalie A. Johnson, Pauline Brice, John Radford, Vincent Ribrag, Daniel Molin, Theodoros P. Vassilakopoulos, Akihiro Tomita, Bastian von Tresckow, Margaret A. Shipp, Yinghua Zhang, Alejandro D. Ricart, Arun Balakumaran, Craig H. Moskowitz, for the KEYNOTE-087 Investigators

VOLUME 35 · NUMBER 19 · JULY 1, 2017

JOURNAL OF CLINICAL ONCOLOGY



PD-1 blockade with nivolumab in relapsed/refractory primary central nervous system and testicular lymphoma

Lakshmi Nayak,[1,2] Fabio M. Iwamoto,[3] Ann LaCasce,[1,2] Srinivasan Mukundan,[1,2] Margaretha G. M. Roemer,[1] Bjoern Chapuy,[1] Philippe Armand,[1,2] Scott J. Rodig,[1,2] and Margaret A. Shipp[1,2]

[1]Dana-Farber Cancer Institute, Boston, MA; [2]Brigham and Women's Hospital, Boston, MA; and [3]New York Presbyterian Hospital, New York, NY

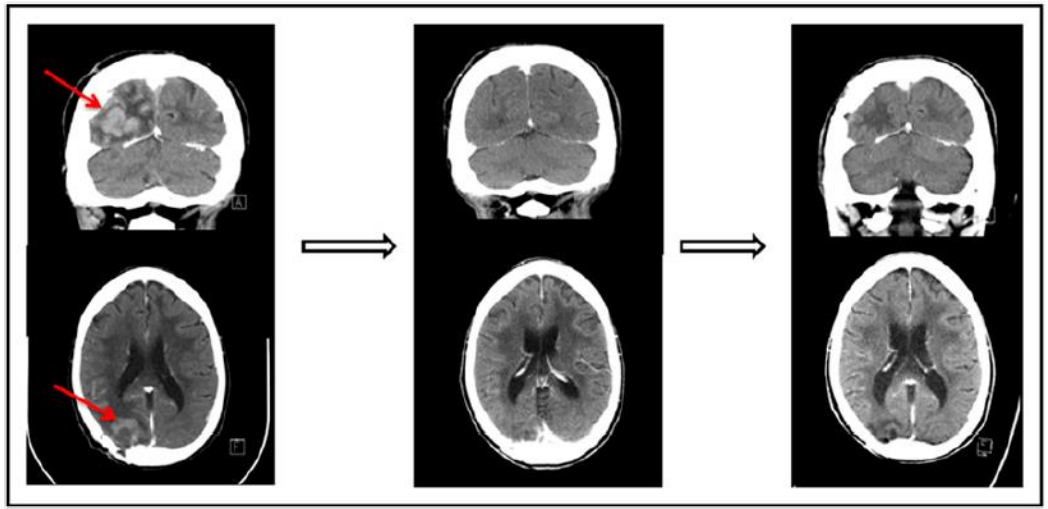
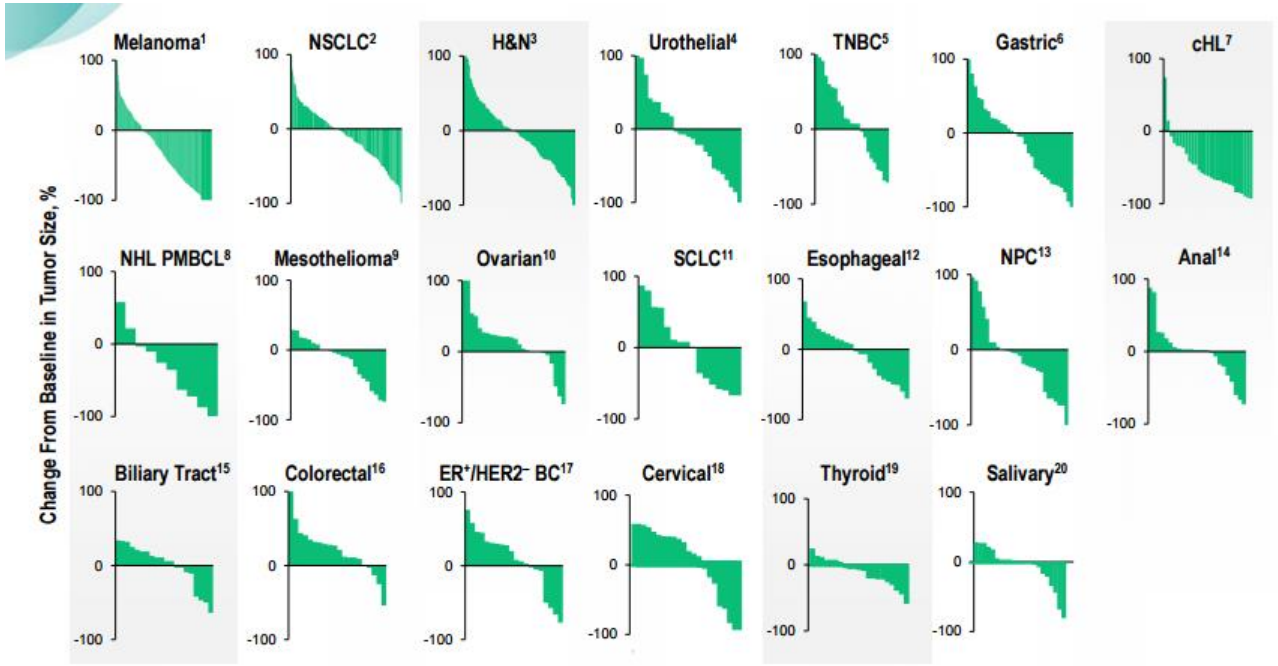


Figure 1. Pre- and posttreatment head CTs with contrast in a patient with primary refractory PCNSL. (Left) The contrast-enhancing lesion before treatment with nivolumab. (Middle) Complete response following 2 months therapy with nivolumab. (Right) Continued complete response 13 months following initiation of therapy.

Variable Sensitivity to Immunotherapy



1. Daud A et al. 2014 SMR; 2. Garon EB et al. ESMO 2014; 3. Chow LQ et al. ESMO 2014; 4. O'Donnell P et al. 2015 Genitourinary Cancers Symposium; 5. Muro K et al. 2015 Gastrointestinal Cancers Symposium; 6. Nanda R et al. SABCS 2014; 7. Moskowitz C et al. 2014 ASH Annual Meeting; 8. Alley EA et al. 2015 AACR.

Immunothérapie pour tous les cancers en 2018?

- Oui, mais

Pour des sous-groupes immunologiques…

de sous-groupes moléculaires…

de sous-types histologiques…

Pour certains>80%, d’autres 5%

Les questions saillantes en 2018

- **Quels patients?**
- Quelles cibles?
- Quelles combinaisons?
  - Immunothérapies
  - Chimiothérapies cytotoxiques
  - Radiothérapie
  - Thérapies ciblées
- Quelles modalités d’administration?
- Comment développer ces traitements?

Predictive immune markers

Predictive immune markers

PDL1 expression

Immune infiltrates

Mutation load

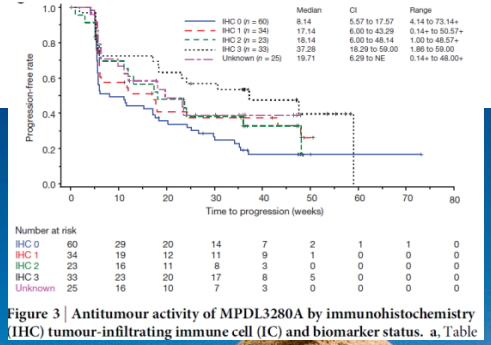


Figure 3 | Antitumour activity of MPDL3280A by immunohistochemistry (IHC) tumour-infiltrating immune cell (IC) and biomarker status. a, Table

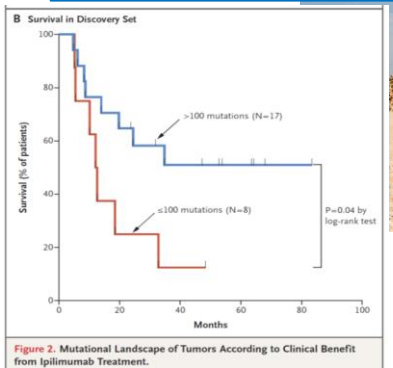
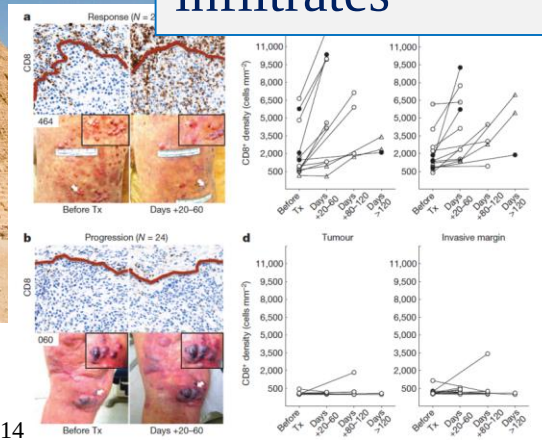
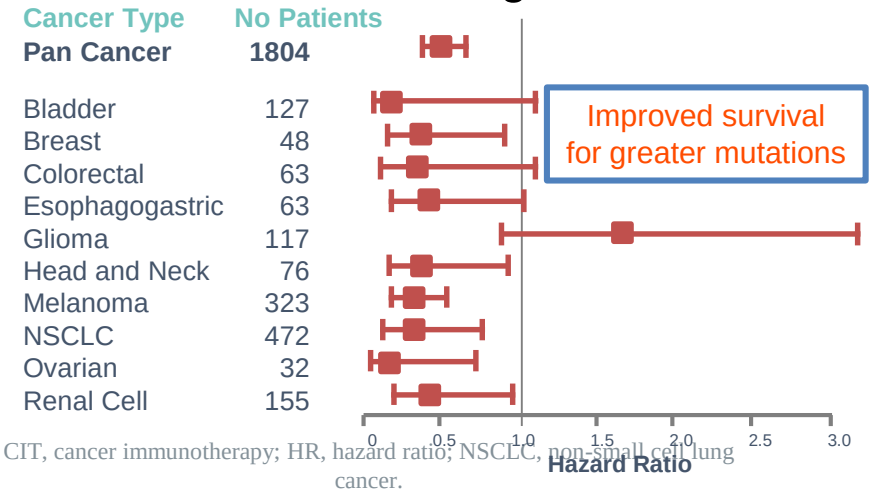


Figure 2. Mutational Landscape of Tumors According to Clinical Benefit from Ipilimumab Treatment.



Herbst Nature 2014, Tumeh Nature 2014, Snyder NEJM 2014

Tumor mutational burden predicts CIT response:
is this the next tissue-agnostic biomarker?

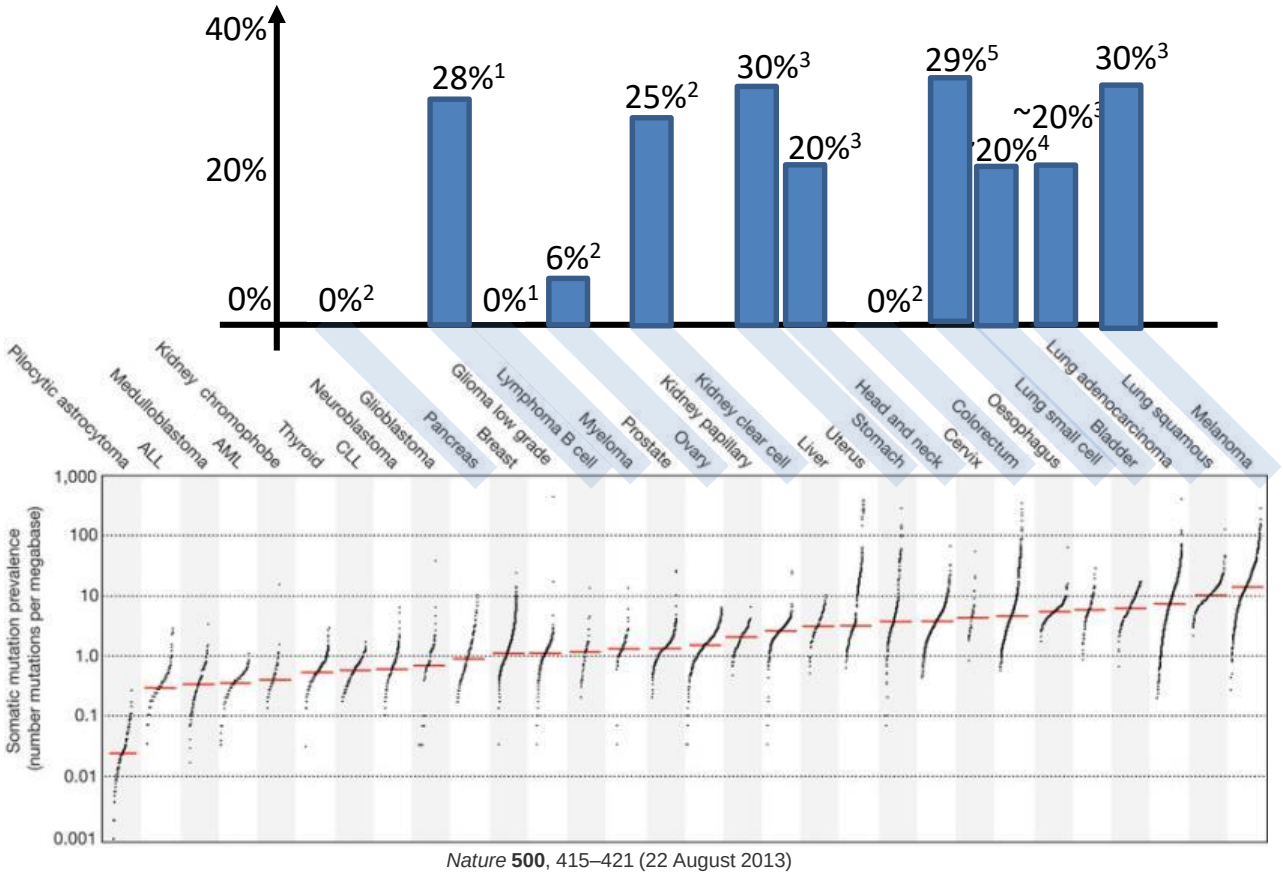


CIT, cancer immunotherapy; HR, hazard ratio; NSCLC, non-small cell lung cancer.

IMPACT Platform, MSKCC.

Chan, N. (2016) *ASCO Clinical Immuno-Oncology Symposium.*

Impact of Mutational Load on PD-1/PD-L1 Blockade ORR

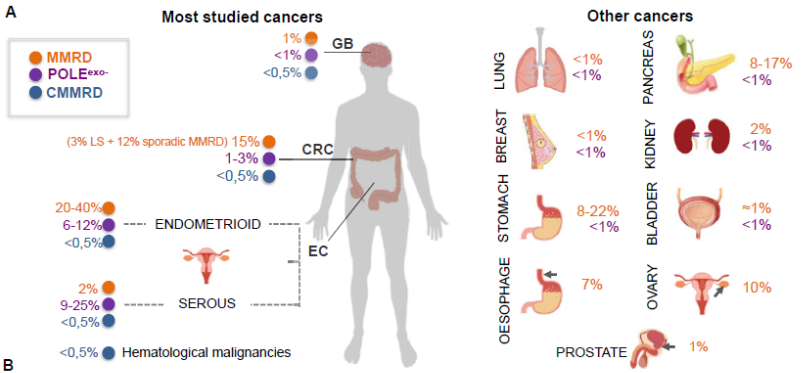


Nature **500**, 415–421 (22 August 2013)

1: nivolumab, ASH 2014; 2:nivolumab, NEJM 2015; 3: pembrolizumab, ESMO 2014; 4: MPDL3280A, Nature 2014; [5] Ott, pembrolizumab WCLC2015

Hypermutated tumours in the era of immunotherapy: The paradigm of personalised medicine

Laetitia Nebot-Bral [a,b,c,1], David Brandao [b,c,d,1], Loic Verlingue [b,e], Etienne Rouleau [b,f], Olivier Caron [b,g], Emmanuelle Despras [a,b,c], Yolla El-Dakdouki [b,e], Stéphane Champiat [b,e,h], Said Aoufouchi [a,b,c], Alexandra Leary [b,c,g,h], Aurélien Marabelle [b,c,e,i], David Malka [b,c,g], Nathalie Chaput [a,b,j,k], Patricia L. Kannouche [a,b,c,*]



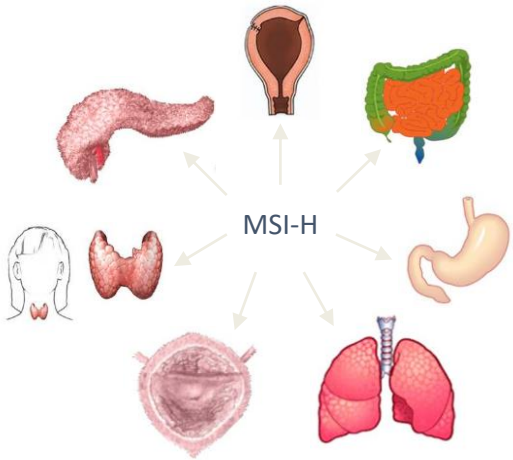
B

Cancer type	Risk		Mean age		
	general population	LS	general population	LS	CMMRD
Colon	4,3%	52-82%	65-74 years	44-61 years	8-35 years
Endometrium	2,8%	25-60%	55-64 years	48-62 years	23-31 years
Stomach	0,8%	6-13%	65-74 years	56 years	Not reported
Ovary	1,3%	4-12%	55-64 years	42,5 years	
Small bowel	0,3%	3-6%	65-74 years	49 years	
Brain/central nervous system	0,6%	1-3%	55-64 years	≈ 50 years	2-35 years

Fig. 1. Frequencies and risks of various cancers harbouring MMR deficiency (MMRD), *POLE* mutation or CMMRD syndrome. (A) Frequencies of cancers harbouring MMRD, *POLE* mutation or CMMRD syndrome. (B) Comparison of cancer risks between general population, Lynch Syndrome and CMMRD syndrome. CMMRD, constitutive mismatch repair deficiency; CRC, colorectal cancer; EC, endometrial cancer; MMRD, mismatch repair deficiency; *POLE*, mutation in the exonuclease domain of the catalytic subunit of the polymerase epsilon; GB, glioblastoma [39–43,51,55,58,65,69,77,78,117,118–136].

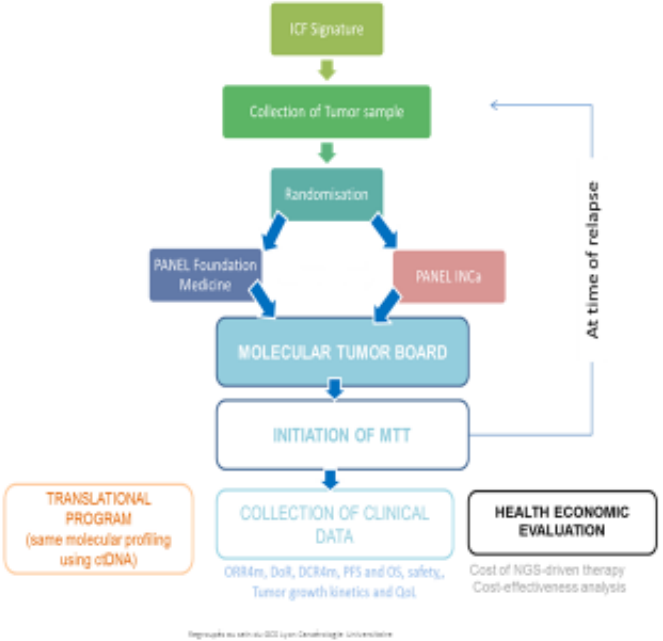
Pembrolizumab, a drug based on tumor biomarkers, recently received FDA approval

- Traditionally in oncology **approvals were based on a tumor type or a biomarker within a tumor type**
- For the first time, the FDA has **'approved a drug based on a tumor's biomarker without regard to the tumor's original location'**
- Pembrolizumab is indicated for the treatment of patients with unresectable or metastatic solid tumors possessing a **microsatellite instability-high (MSI-H) biomarker**
- **This represents a seismic shift in the global view of cancer**



FDA news release retrieved from:
https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm560167.htm [Accessed September 2017].
Image adapted from presentation by Steven Lemery at 2017 ASCO Annual Meeting.

PROFILER2 STUDY



Appel d'offre France Médecine Génomique 2025

Paris le 17 juillet 2017, Matignon

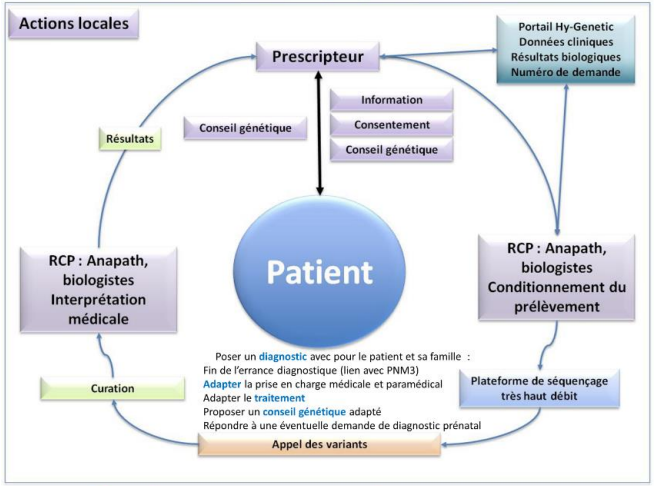
AURAGEN

AUvergne **R**hône-**A**lpes **GEN**omique

Cancer

Maladies rares

Notre projet



Information / discussion avec le **patient**

Production industrielle : qualité des données, productivité

Compétences en bio-informatique

Répondre à une demande **nationale**

Réunion de **C**oncertation **P**luridisciplinaire

Enseignement : augmentation des compétences

Evaluation médico-économique

Médecine Personnalisée

Le futur?

- Le traitement des tumeurs hypermutées en monothérapies ou en combo
- Sélectionnées (aussi) sur la base des mutations des gènes de réparation
- Génomique

Expression et infiltrats: baseline & en cours de traitement?

a Activity of MPDL3280A in NSCLC IHC (IC)

Diagnostic population	ORR (RECIST) (*n* (%))	SD (best response) (*n* (%))	SD ≥24 weeks (*n* (%))	PD (best response) (*n* (%))	24-week PFS (%)	Median PFS (weeks) (95% CI)
IHC 3 (*n* = 6)	5 (83)	0	0	1 (17)	83.3	NE (5,NE)
IHC 2 (*n* = 7)	1 (14)	3 (43)	0	2 (29)	14.3	11 (1,17)
IHC 1 (*n* = 13)	2 (15)	3 (23)	1 (8)	7 (54)	25.6	6 (5,43)
IHC 0 (*n* = 20)	4 (20)	7 (35)	4 (20)	9 (45)	45.0	13 (6,37)
Unknowns (*n* = 7)	0	5 (71)	4 (57)	2 (29)	71.4	NE (6,NE)
All patients (*n* = 53)	12 (23)	18 (34)	9 (17)	21 (40)	44.7	15 (6,43)

b Activity of MPDL3280A in all tumour types IHC (IC)

Diagnostic population	ORR (RECIST) (*n* (%))	SD (best response) (*n* (%))	SD ≥24 weeks (*n* (%))	PD (best response) (*n* (%))	24-week PFS (%)	Median PFS (weeks) (95% CI)
IHC 3 (*n* = 33)	15 (46)	9 (27)	4 (12)	8 (24)	60.0	37 (18,59)
IHC 2 (*n* = 23)	4 (17)	12 (52)	6 (26)	6 (26)	43.0	18 (6,48)
IHC 1 (*n* = 34)	7 (21)	11 (32)	6 (18)	14 (41)	40.9	17 (6,43)
IHC 0 (*n* = 60)	8 (13)	22 (37)	11 (18)	29 (48)	33.9	8 (6,18)
Unknowns (*n* = 25)	2 (8)	14 (56)	6 (24)	8 (32)	38.9	20 (6,NE)
All patients (*n* = 175)	36 (21)	68 (39)	33 (19)	65 (37)	42.2	18 (12,24)

c

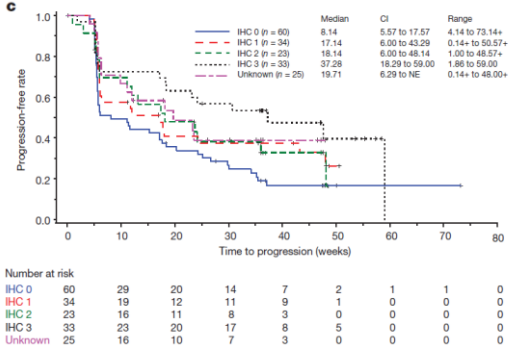


Figure 3 | Antitumour activity of MPDL3280A by immunohistochemistry (IHC) tumour-infiltrating immune cell (IC) and biomarker status. a, Table

LETTER

doi:10.1038/nature14011

Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients

Roy S. Herbst[1], Jean-Charles Soria[2], Marcin Kowanetz[3], Gregg D. Fine[3], Omid Hamid[4], Michael S. Gordon[5], Jeffery A. Sosman[6], David F. McDermott[7], John D. Powderly[8], Scott N. Gettinger[1], Holbrook E. K. Kohrt[9], Leora Horn[10], Donald P. Lawrence[11], Sandra Rost[3], Maya Leabman[3], Yuanyuan Xiao[3], Ahmad Mokatrin[3], Hartmut Koeppen[3], Priti S. Hegde[3], Ira Mellman[3], Daniel S. Chen[3] & F. Stephen Hodi[12]

a Summary of responses to MPDL3280A in paired biopsies

	Increase in PD-L1 (TC) (no. (%))	Increase in PD-L1 (IC) (no. (%))
Maximum SLD decrease		
>30% reduction	3/6 (50)	5/6 (83)
0%–30% reduction	3/8 (37)	2/8 (25)
0%–20% increase	2/9 (22)	1/9 (11)
>20% increase	0/3 (0)	1/3 (33)
Unevaluable SLD	1/1 (100)	1/1 (100)
Objective response per RECIST v1.1		
Best response of PR	3/5 (60)	4/5 (80)
Best response of SD	5/12 (42)	2/12 (17)
Best response of PD	1/11 (9)	4/11 (36)

b

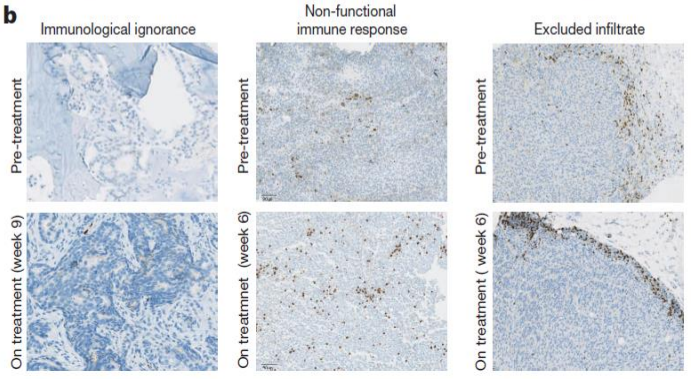
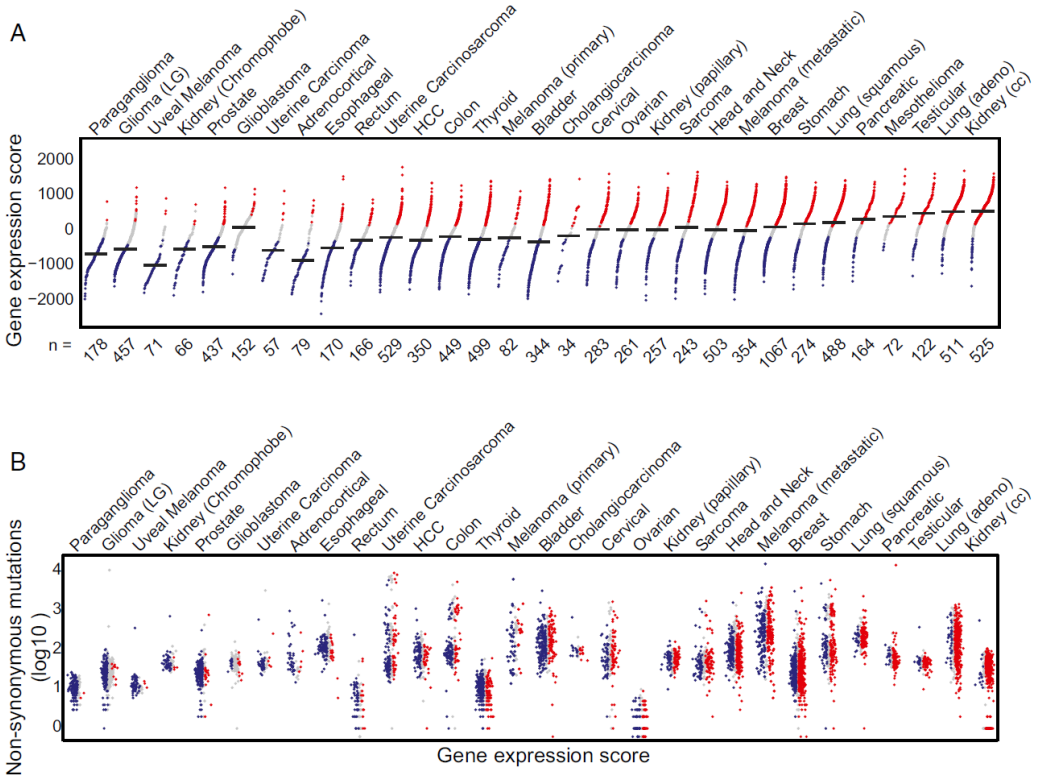


Figure 4 | Biomarker status and response to MPDL3280A. a, Table

Density of immunogenic antigens does not explain the presence or absence of the T-cell–inflamed tumor microenvironment in melanoma

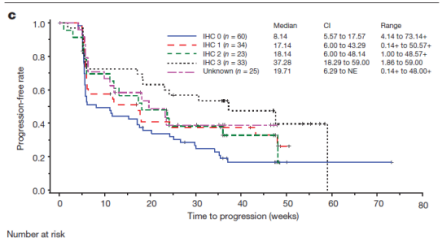
Stefani Spranger[a,1], Jason J. Luke[b,1], Riyue Bao[c], Yuanyuan Zha[d], Kyle M. Hernandez[c], Yan Li[c], Alexander P. Gajewski[c], Jorge Andrade[c], and Thomas F. Gajewski[a,b,d,2]



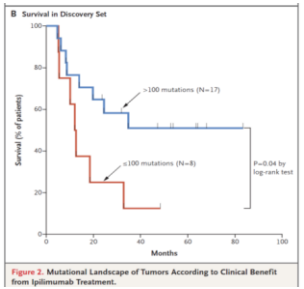
Spranger S, et al. PNAS; 2016;113:E7759–68.

Predictive immune markers

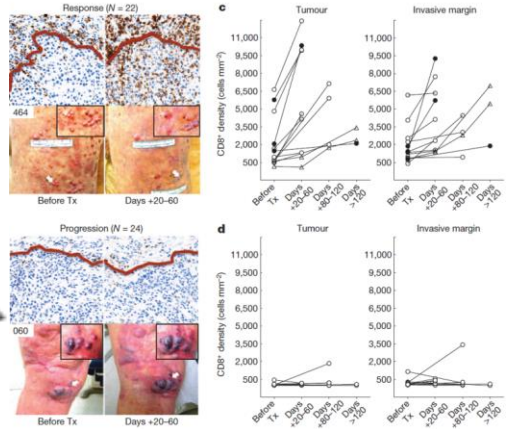
PDL1 expression



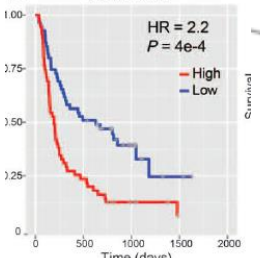
Mutation load



Immune infiltrates



Aneuploidy



Tumor aneuploidy correlates with markers of immune evasion and with reduced response to immunotherapy

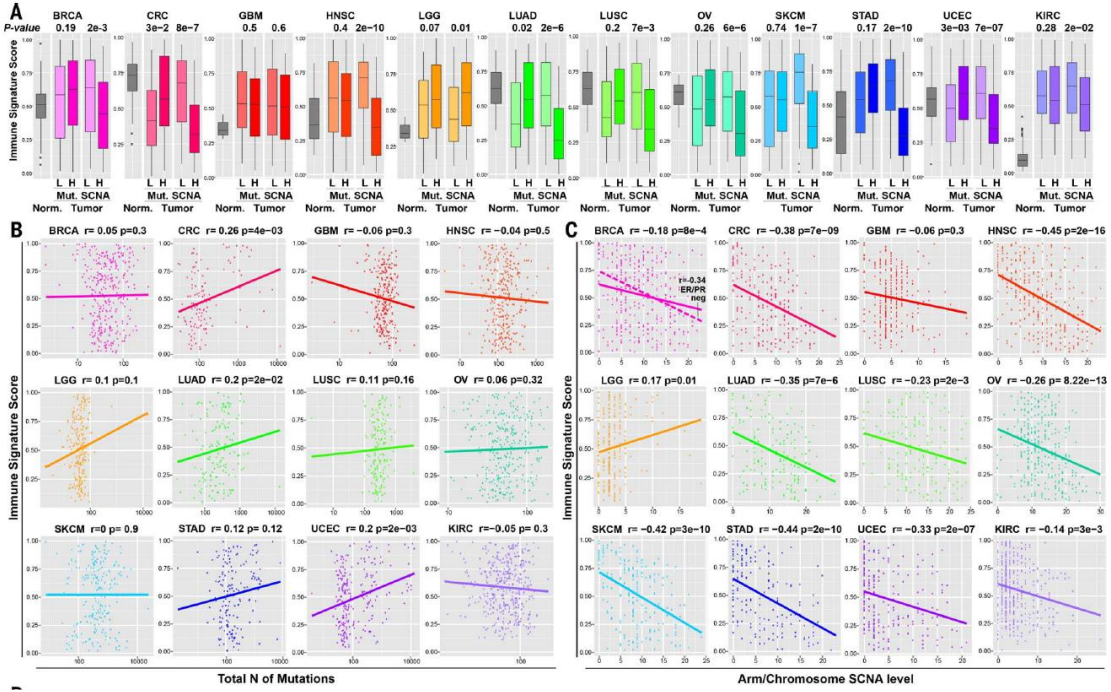
Teresa Davoli,[1] Hajime Uno,[2] Eric C. Wooten,[1] Stephen J. Elledge[1]*

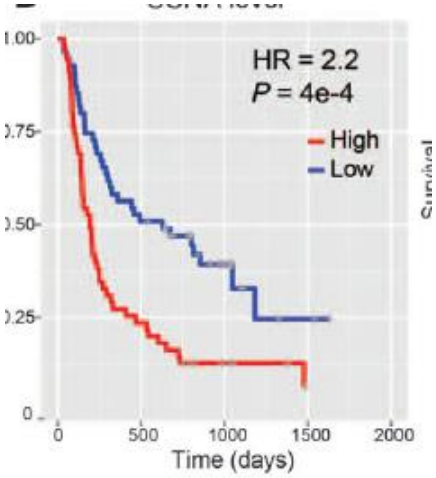
Herbst Nature 2014, Tumeh Nature 2014, Snyder NEJM 2014, Davoli et al, Sciance 2017

Tumor aneuploidy correlates with markers of immune evasion and with reduced response to immunotherapy

Teresa Davoli,[1] Hajime Uno,[2] Eric C. Wooten,[1] Stephen J. Elledge[1]*

Read the full article at http://dx.doi.org/10.1126/science.aaf8399





Le futur

- Intégration des profils d’altérations génomiques, CNV et mutations activatrices/inactivatrices comme biomarqueurs des immunothérapies

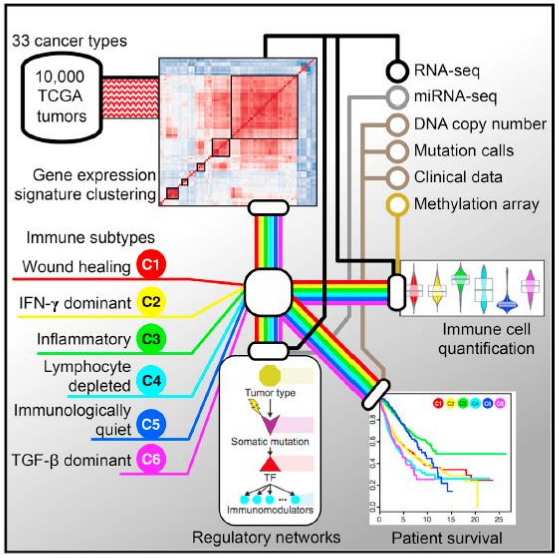
- Génomique

- Epigénétique et variation des niveau d’expression sur l’ensemble du génome

Immunity

The Immune Landscape of Cancer

Graphical Abstract



Highlights

- Six identified immune subtypes span cancer tissue types and molecular subtypes
- Immune subtypes differ by somatic aberrations, microenvironment, and survival
- Multiple control modalities of molecular networks affect tumor-immune interactions
- These analyses serve as a resource for exploring immunogenicity across cancer types

Authors

Vésteinn Thorsson, David L. Gibbs, Scott D. Brown, ..., Mary L. Disis, Benjamin G. Vincent, Ilya Shmulevich

Correspondence

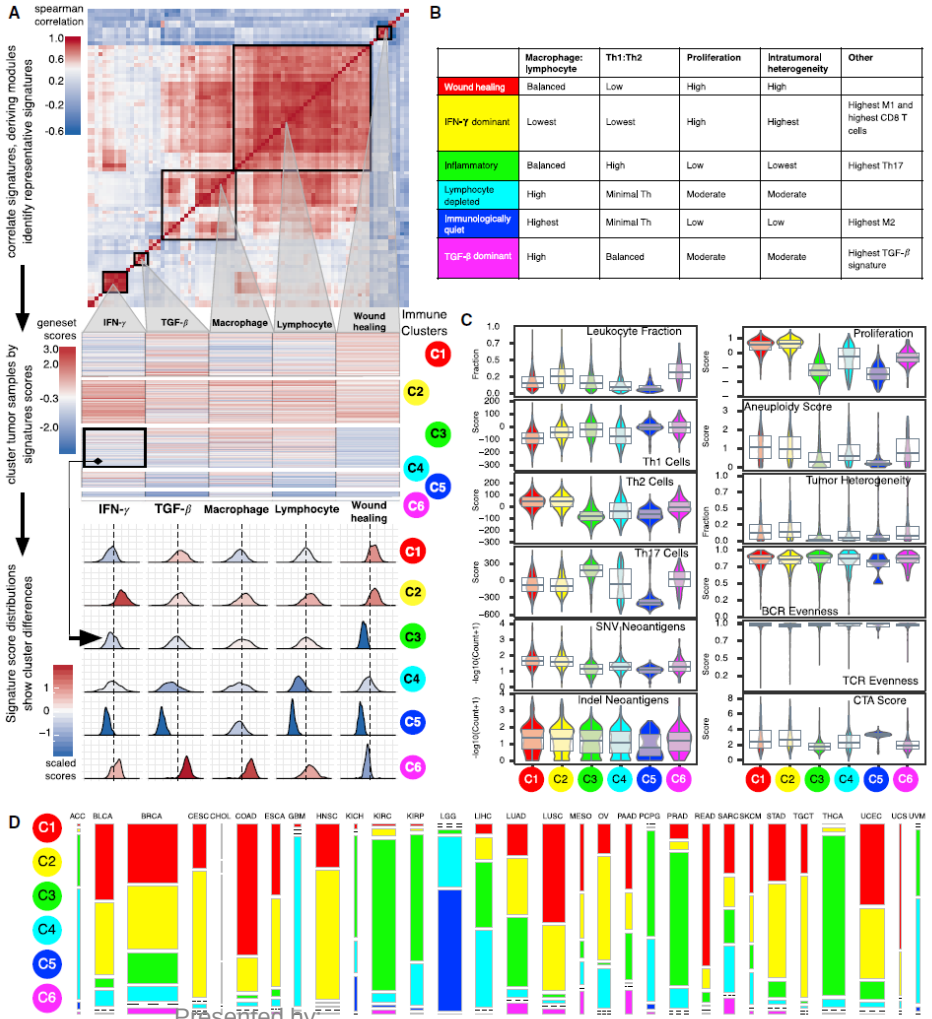
vesteinn.thorsson@systemsbiology.org (V.T.), benjamin.vincent@unchealth.unc.edu (B.G.V.), ilya.shmulevich@systemsbiology.org (I.S.)

In Brief

Thorsson et al. present immunogenomics analyses of more than 10,000 tumors, identifying six immune subtypes that encompass multiple cancer types and are hypothesized to define immune response patterns impacting prognosis. This work provides a resource for understanding tumor-immune interactions, with implications for identifying ways to advance research on immunotherapy.

The Immune Landscape of Cancer

Immunity *48*, 812–830, April 17, 2018

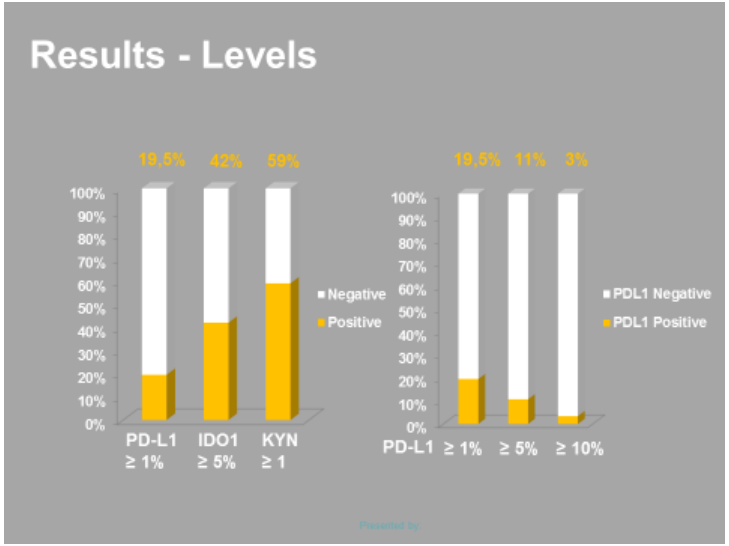


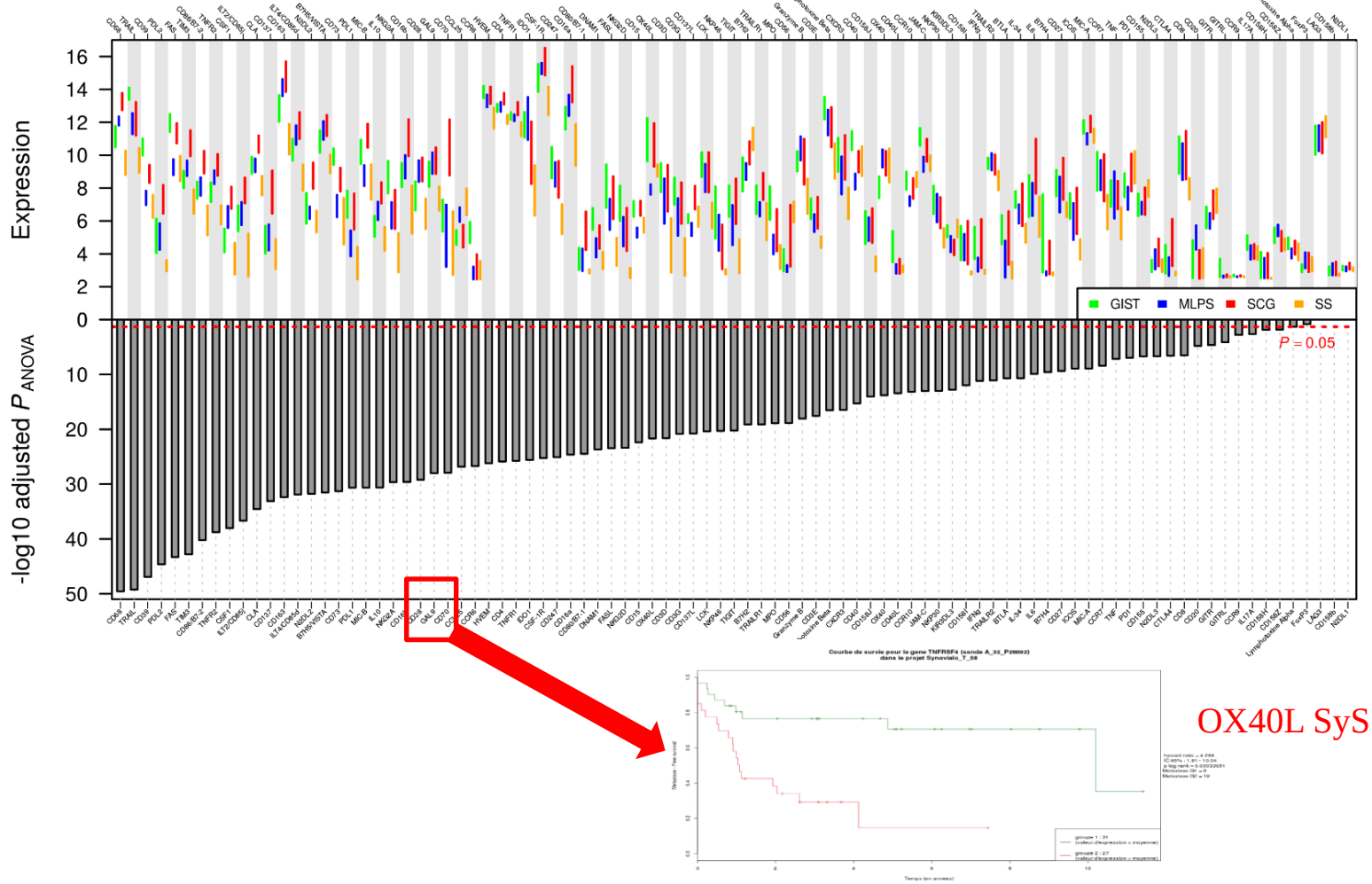
	Macrophage: lymphocyte	Th1:Th2	Proliferation	Intratumoral heterogeneity	Other
Wound healing	Balanced	Low	High	High	
IFN-γ dominant	Lowest	Lowest	High	Highest	Highest M1 and highest CD8 T cells
Inflammatory	Balanced	High	Low	Lowest	Highest Th17
Lymphocyte depleted	High	Minimal Th	Moderate	Moderate	
Immunologically quiet	Highest	Minimal Th	Low	Low	Highest M2
TGF-β dominant	High	Balanced	Moderate	Moderate	Highest TGF-β signature

Figure 1. Immune Subtypes in Cancer

Use of PD-1 Targeting, Macrophage Infiltration, and IDO Pathway Activation in Sarcomas: A Phase 2 Clinical Trial, Toulmonde et al [JAMA Oncol.](#) 2017 Jun 29. doi: 10.1001/jamaoncol.2017.1617.

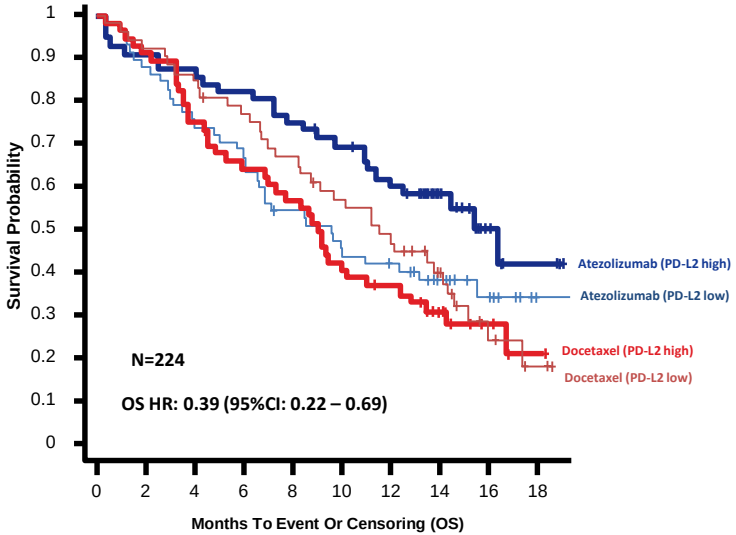
- 57 patients: n=1 PR.
- The 6-month nonprogression rates were 0%, 0%, 14.3% for LMS, UPS, and others, respectively, and 11.1% for GIST.
- Strong infiltration by macrophage expressing the inhibitory enzyme indoleamine 2,3-dioxygenase 1 (IDO1)
- Significant increase in the kynurenine to tryptophan ratio was observed in patient plasma samples during the study treatment.




Expression
-log10 adjusted P_{ANOVA}
GIST
MLPS
SCG
SS
$P = 0.05$
Courbe de survie pour le gene TNFRSF4 (sonde A_32_P28092)
dans le projet Synovialo_T_58
OX40L SyS

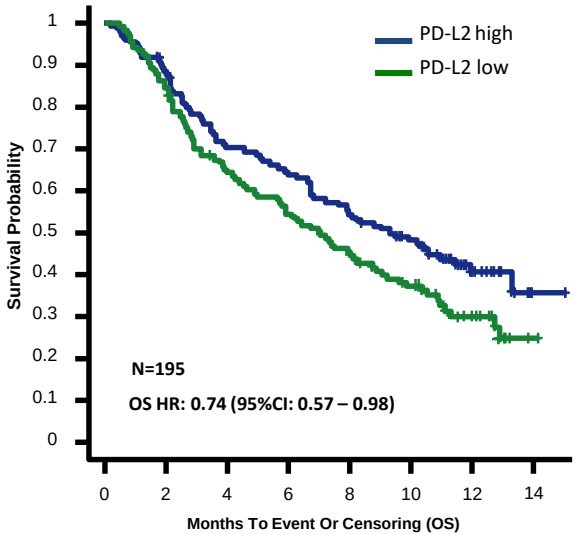
Markers of immune escape likely not as simple as alternate checkpoints

Data from randomized Phase II study POPLAR in NSCLC (atezolizumab vs docetaxel)



OS HR is for atezolizumab vs docetaxel.
PD-L2 'high' defined as ≥ median expression; PD-L2 'low' defined as < median expression.

Data from single arm Phase II mUBC study IMvigor 210



OS HR is for atezolizumab PD-L2 hi vs PD-L2 Low.
PD-L2 'high' defined as ≥ median expression; PD-L2 'low' defined as < median expression.

Atezolizumab improves overall survival benefit in tumor PD-L2 high patients

Hegde PS, AACR, New Orleans 2016

Gut microbiome influences efficacy of PD-1 based-immunotherapy against epithelial tumors
Science, publication advanced online,
http://science.sciencemag.org/lookup/doi/10.1126/science.aan3706

Bertrand Routy[1,2,3], Emmanuelle Le Chatelier[4], Lisa Derosa[1,2,3], Connie P. M. Duong[1,2,5], Maryam Tidjani Alou[1,2,3], Romain Daillère[1,2,3], Aurélie Fluckiger[1,2,5], Meriem Messaoudene[1,2], Conrad Rauber[1,2,3], Maria P. Roberti[1,2,5], Marine Fidelle[1,3,5], Caroline Flament[1,2,5], Vichnou Poirier-Colame[1,2,5], Paule Opolon[6], Christophe Klein[7], Kristina Iribarren[8,9,10,11,12], Laura Mondragón[8,9,10,11,12], Nicolas Jacquelot[1,2,3], Bo Qu[1,2,3], Gladys Ferrere[1,2,3], Céline Clémenson[1,13], Laura Mezquita[1,14], Jordi Remon Masip[1,14], Charles Naltet[15], Solenn Brosseau[15], Coureche Kaderbhai[16], Corentin Richard[16], Hira Rizvi[17], Florence Levenez[4], Nathalie Galleron[4], Benoit Quinquis[4], Nicolas Pons[4], Bernhard Ryffel[18], Véronique Minard-Colin[1,19], Patrick Gonin[1,20], Jean-Charles Soria[1,14], Eric Deutsch[1,13], Yohann Loriot[1,3,14], François Ghiringhelli[16], Gérard Zalcman[15], François Goldwasser[9,21,22], Bernard Escudier[1,14,23], Matthew D. Hellmann[24,25], Alexander Eggermont[1,2,14], Didier Raoult[26], Laurence Albiges[1,3,14], Guido Kroemer[8-12,27,28]*, and Laurence Zitvogel[1,2,3,5]*.

: Routy B, Le Chatelier E, Derosa L, Duong CPM, Alou MT, Daillère R, Fluckiger A, Messaoudene M, Rauber C, Roberti MP, Fidelle M, Flament C, Poirier-Colame V, Opolon P, Klein C, Iribarren K, Mondragón L, Jacquelot N, Qu B, Ferrere G, Clémenson C, Mezquita L, Masip JR, Naltet C, Brosseau S, Kaderbhai C, Richard C, Rizvi H, Levenez F, Galleron N, Quinquis B, Pons N, Ryffel B, Minard-Colin V, Gonin P, Soria JC, Deutsch E, Loriot Y, Ghiringhelli F, Zalcman G, Goldwasser F, Escudier B, Hellmann MD, Eggermont A, Raoult D, Albiges L, Kroemer G, Zitvogel L.Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial
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2: Gopalakrishnan V, Spencer CN, Nezi L, Reuben A, Andrews MC, Karpinets TV, Prieto PA, Vicente D, Hoffman K, Wei SC, Cogdill AP, Zhao L, Hudgens CW, Hutchinson DS, Manzo T, Petaccia de Macedo M, Cotechini T, Kumar T, Chen WS, Reddy SM, Sloane RS, Galloway-Pena J, Jiang H, Chen PL, Shpall EJ, Rezvani K, Alousi AM, Chemaly RF, Shelburne S, Vence LM, Okhuysen PC, Jensen VB, Swennes AG, McAllister F, Sanchez EMR, Zhang Y, Le Chatelier E, Zitvogel L, Pons N, Austin-Breneman JL, Haydu LE, Burton EM, Gardner JM, Sirmans E, Hu J, Lazar AJ, Tsujikawa T, Diab A, Tawbi H, Glitza IC, Hwu WJ, Patel SP, Woodman SE, Amaria RN, Davies MA, Gershenwald JE, Hwu P, Lee JE, Zhang J, Coussens LM, Cooper ZA, Futreal PA, Daniel CR, Ajami NJ, Petrosino JF, Tetzlaff MT, Sharma P, Allison JP, Jenq RR, Wargo JA. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science. 2017 Nov 2. pii: eaan4236. doi: 10.1126/science.aan4236. [Epub ahead of print] PubMed PMID: 29097493.

Gut microbiome influences efficacy of PD-1 based-immunotherapy against epithelial tumors

Science, publication advanced online,
http://science.sciencemag.org/lookup/doi/10.1126/science.aan3706

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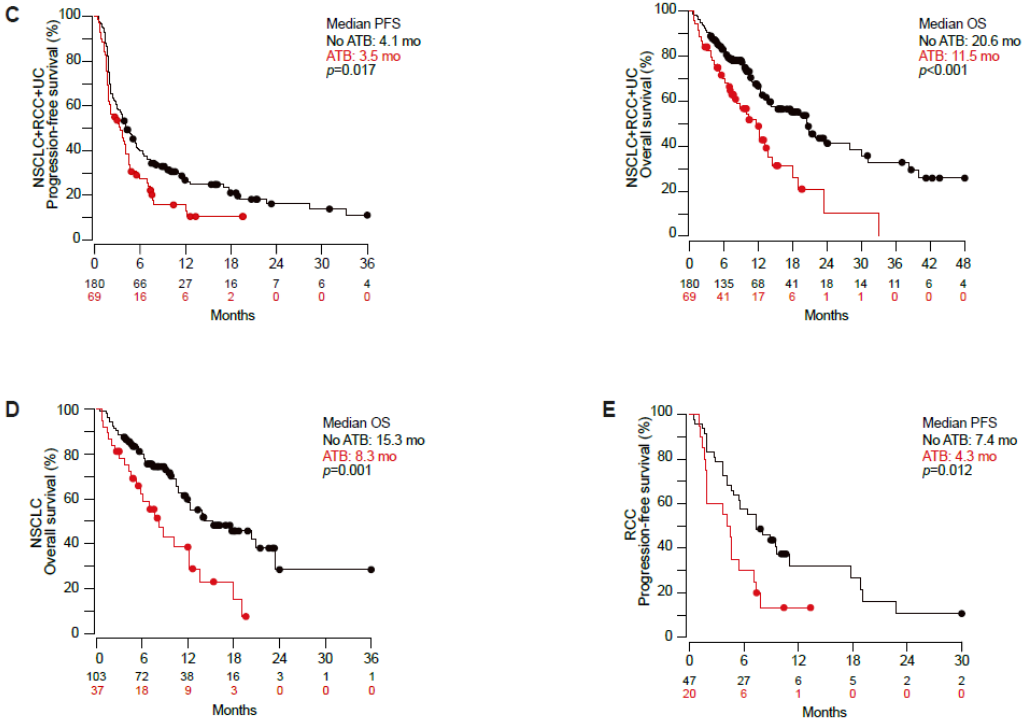


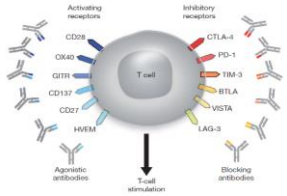
Donc…

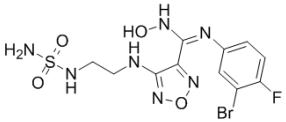
- Charge en néoantigènes
- PDL1 (Kc, infiltrats, PBL)
- Infiltrats (CD4,CD8,M2,Treg…)
- Aneuploidie
- PDL2
- Profils predictifs
- Mutations JAK, B2M..
- Microbiote
- …

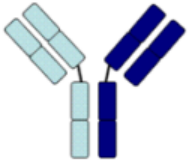
Les questions saillantes en 2018

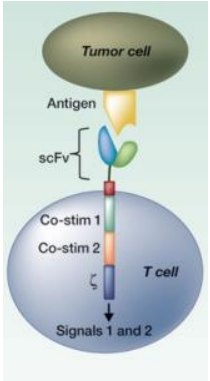
- Quels patients?
- **Quelles cibles?**
- Quelles combinaisons?
  - Immunothérapies
  - Chimiothérapies cytotoxiques
  - Radiothérapie
  - Thérapies ciblées
- Quelles modalités d’administration?
- Comment développer ces traitements?

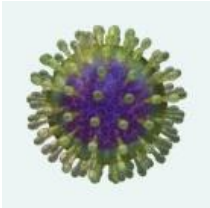
New (or not so new) immunotherapy strategies











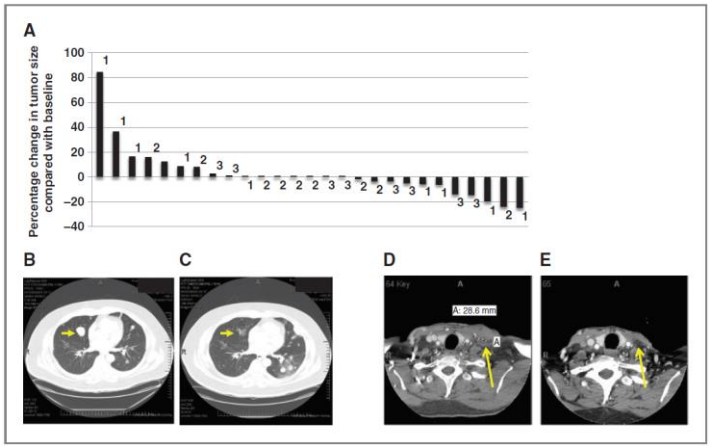
ICP inhibitors	IDO inhibitors	BiSpe Ab	CAR T-cells	Cytokines	Oncolytic Virus

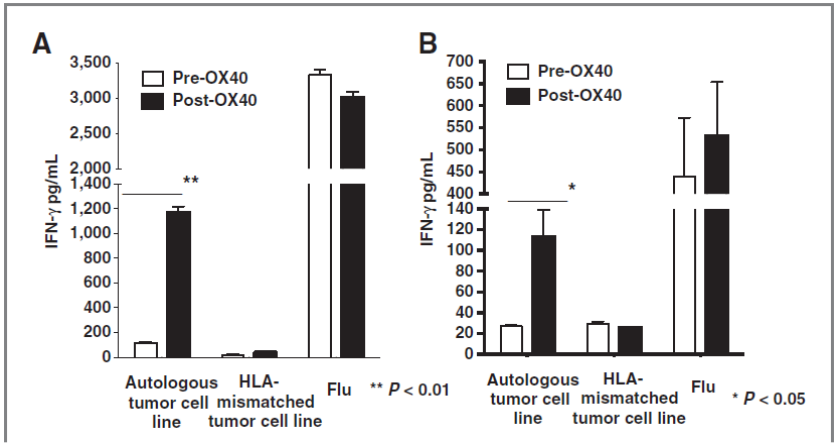
Cancer Research

Cancer Res; 73(24); 7189–98.

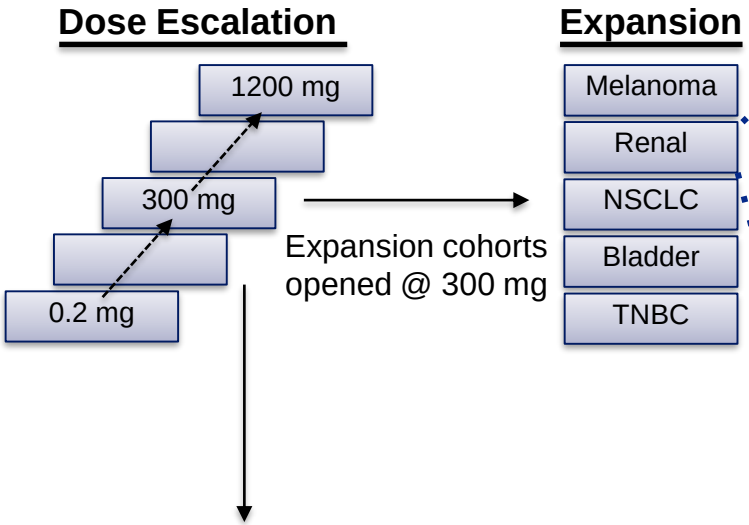
OX40 Is a Potent Immune-Stimulating Target in Late-Stage Cancer Patients

Brendan D. Curti[1], Magdalena Kovacsovics-Bankowski[1], Nicholas Morris[1], Edwin Walker[1], Lana Chisholm[1], Kevin Floyd[1], Joshua Walker[2], Iliana Gonzalez[1], Tanisha Meeuwsen[1], Bernard A. Fox[1], Tarsem Moudgil[1], William Miller[1], Daniel Haley[1], Todd Coffey[1], Brenda Fisher[1], Laurie Delanty-Miller[1], Nicole Rymarchyk[1], Tracy Kelly[1], Todd Crocenzi[1], Eric Bernstein[1], Rachel Sanborn[1], Walter J. Urba[1], and Andrew D. Weinberg[1]



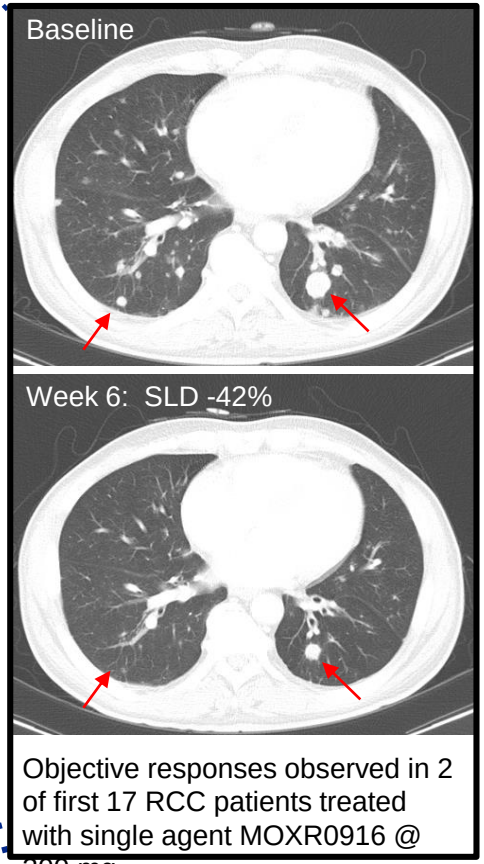


Anti-OX40 (MOXR0916) Phase I Genentech AACR 2016



Phase Ib to evaluate MOXR0916 in combination with atezolizumab (anti-PD-L1) is underway

Clinicaltrials.gov: NCT02410512



Objective responses observed in 2 of first 17 RCC patients treated with single agent MOXR0916 @ 300 mg

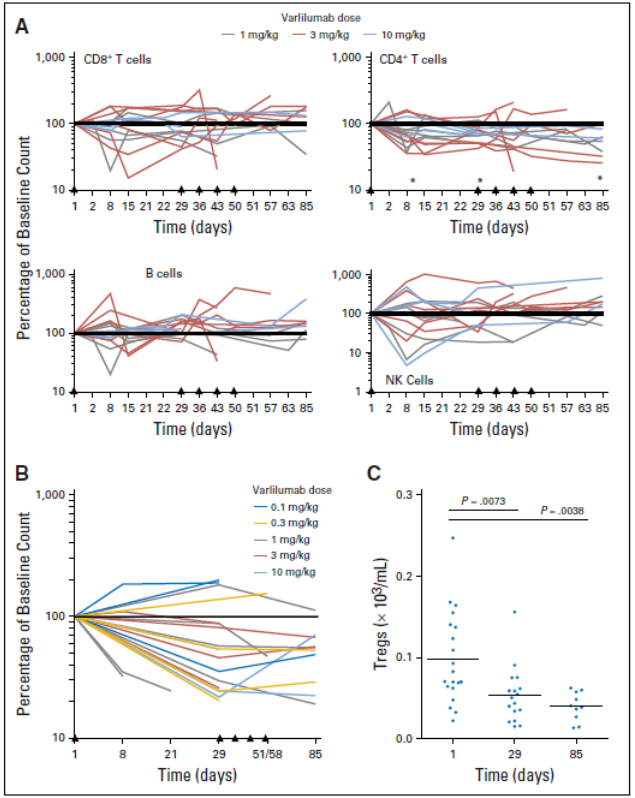
Safety and Activity of Varlilumab, a Novel and First-in-Class Agonist Anti-CD27 Antibody, in Patients With Advanced Solid Tumors

Howard A. Burris, Jeffrey R. Infante, Stephen M. Ansell, John J. Nemunaitis, Geoffrey R. Weiss, Victor M. Villalobos, Branimir I. Sikic, Matthew H. Taylor, Donald W. Northfelt, William E. Carson III, Thomas R. Hawthorne, Thomas A. Davis, Michael J. Yellin, Tibor Keler, and Timothy Bullock

VOLUME 35 · NUMBER 18 · JUNE 20, 2017

JOURNAL OF CLINICAL ONCOLOGY

N=31pts, MM, RCC
1 PR, 8 SD



Cancer Therapy: Clinical

Clinical Cancer Research

Results from an Integrated Safety Analysis of Urelumab, an Agonist Anti-CD137 Monoclonal Antibody

Neil H. Segal[1], Theodore F. Logan[2], F. Stephen Hodi[3], David McDermott[4], Ignacio Melero[5], Omid Hamid[6], Henrik Schmidt[7], Caroline Robert[8], Vanna Chiarion-Sileni[9], Paolo A. Ascierto[10], Michele Maio[11], Walter J. Urba[12], Tara C. Gangadhar[13], Satyendra Suryawanshi[14], Jaclyn Neely[14], Maria Jure-Kunkel[14], Suba Krishnan[14], Holbrook Kohrt[15,†], Mario Sznol[16], and Ronald Levy[15]

The clinical evaluation of urelumab is ongoing at 0.1 mg/kg every 3 weeks as monotherapy and in combination with targeted mAbs, cetuximab, rituximab, or elotuzumab (NCT01775631, NCT02110082, and NCT02252263). This approach is based on evaluate urelumab in combination with nivolumab, an anti-PD-1 immune checkpoint inhibitor, in patients with advanced solid tumors and B-cell non-Hodgkin lymphoma (NCT02253992).

Targeting Tumor-Associated Macrophages with Anti-CSF-1R Antibody Reveals a Strategy for Cancer Therapy

Carola H. Ries,[1,13,*] Michael A. Cannarile,[1,13] Sabine Hoves,[1] Jörg Benz,[2] Katharina Wartha,[1] Valeria Runza,[1] Flora Rey-Giraud,[1] Leon P. Pradel,[1] Friedrich Feuerhake,[3] Irina Klaman,[1] Tobin Jones,[1] Ute Jucknischke,[1] Stefan Scheiblich,[1] Klaus Kaluza,[1] Ingo H. Gorr,[1] Antje Walz,[2] Keelara Abiraj,[4] Philippe A. Cassier,[5] Antonio Sica,[6,7] Carlos Gomez-Roca,[8] Karin E. de Visser,[9] Antoine Italiano,[10] Christophe Le Tourneau,[11] Jean-Pierre Delord,[7] Hyam Levitsky,[12] Jean-Yves Blay,[5] and Dominik Rüttinger[1]

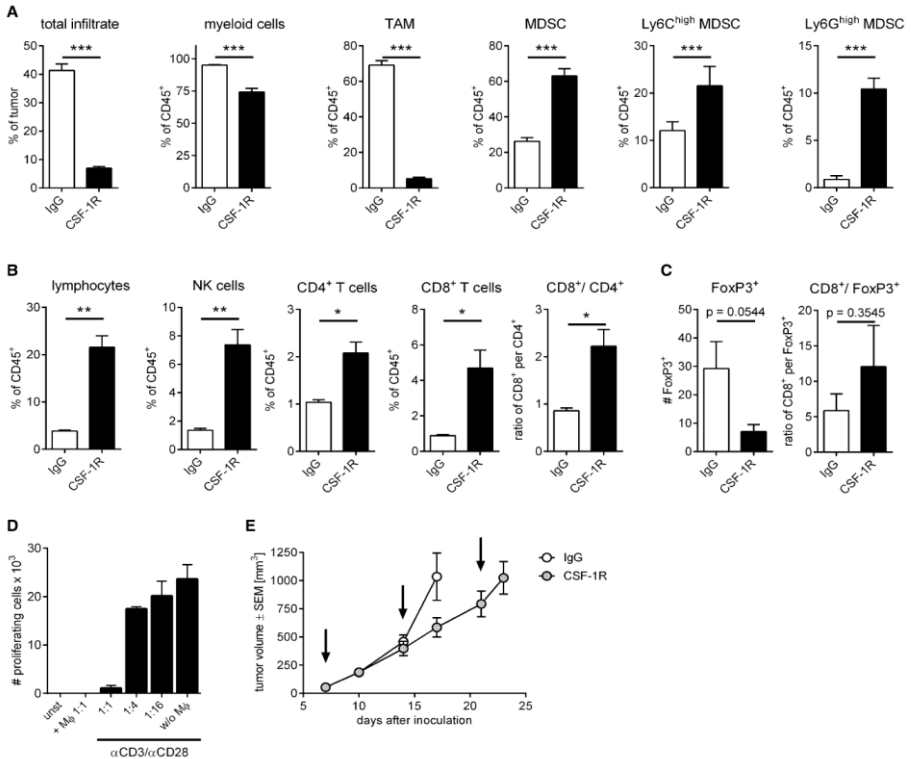


Figure 4. CSF-1R Inhibition Depletes TAMs and Increases Lymphocyte Infiltration into MC38 Colon Carcinomas

A phase I study of indoximod in patients with advanced malignancies

Hatem H. Soliman[1], Susan E. Minton[1], Hyo Sook Han[1], Roohi Ismail-Khan[1], Anthony Neuger[1], Fatema Khambati[1], David Noyes[1], Richard Lush[1], Alberto A. Chiappori[1], John D. Roberts[2], Charles Link[3], Nicholas N. Vahanian[3], Mario Mautino[3], Howard Streicher[4], Daniel M. Sullivan[1] and Scott J. Antonia[1]

agent antitumor activity of indoximod was modest

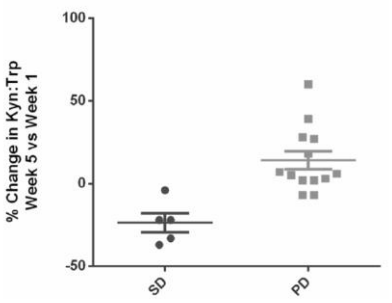


Figure 3: Comparison of percent change in kynurenine-to-tryptophan ratios over 5 weeks on treatment between patients with stable disease versus progressive disease. There appears to be a trend toward either no increase or a slight decrease in patients who had prolonged stable disease for over 6 months.

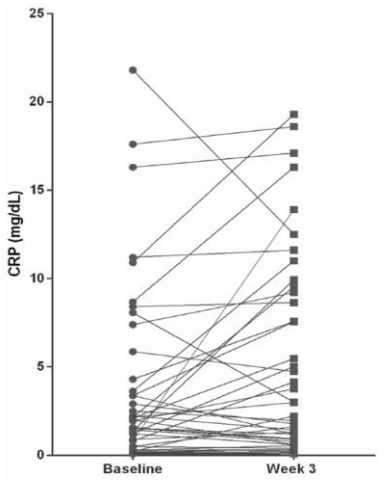


Figure 4: Scatter plot showing the relative changes (in percent) in C-reactive protein at week 3 when compared to baseline. The difference between the means (from 3.81 mg/dL at baseline to 5.13 mg/dL at week 3) was

First-in-Human Phase I Study of the Oral Inhibitor of Indoleamine 2,3-Dioxygenase-1 Epacadostat (INCB024360) in Patients with Advanced Solid Malignancies

Gregory L. Beatty[1,2], Peter J. O'Dwyer[1,2], Jason Clark[3], Jack G. Shi[3], Kevin J. Bowman[3], Peggy A. Scherle[3], Robert C. Newton[3], Richard Schaub[3], Janet Maleski[3], Lance Leopold[3] and Thomas F. Gajewski[4]

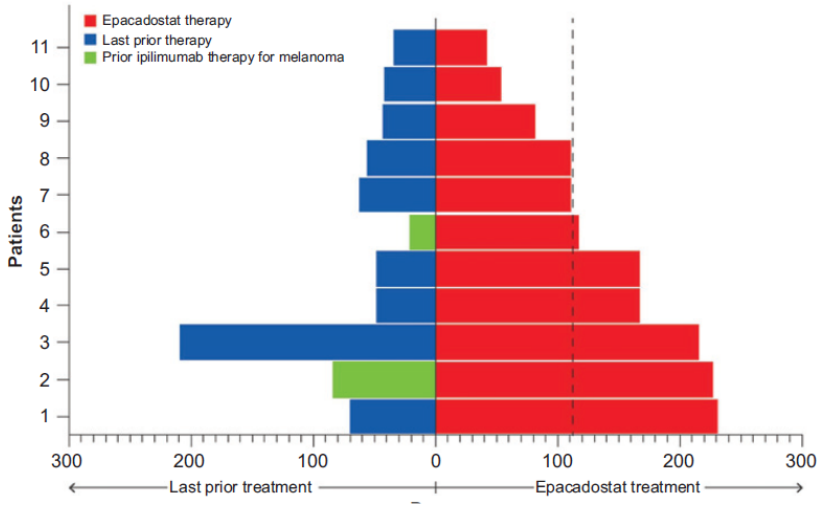


Figure 2.
Prolonged stable disease compared with last prior therapy was achieved in a subset of patients ($n = 11$). Two patients with melanoma refractory to ipilimumab achieved stable disease with epacadostat. The dashed line represents at least 16 weeks (112 days) on epacadostat therapy.

A randomised, open-label, phase 2 study of the IDO1 inhibitor epacadostat (INCB024360) versus tamoxifen as therapy for biochemically recurrent (CA-125 relapse)–only epithelial ovarian cancer, primary peritoneal carcinoma, or fallopian tube cancer

Rebecca Kristeleit [a,*], Irina Davidenko [b], Vadim Shirinkin [c], Fatima El-Khouly [a], Igor Bondarenko [d], Michael J. Goodheart [e], Vera Gorbunova [f], Carol A. Penning [g], Jack G. Shi [g], Xiangdong Liu [g], Robert C. Newton [g], Yufan Zhao [g], Janet Maleski [g], Lance Leopold [g], Russell J. Schilder [h]

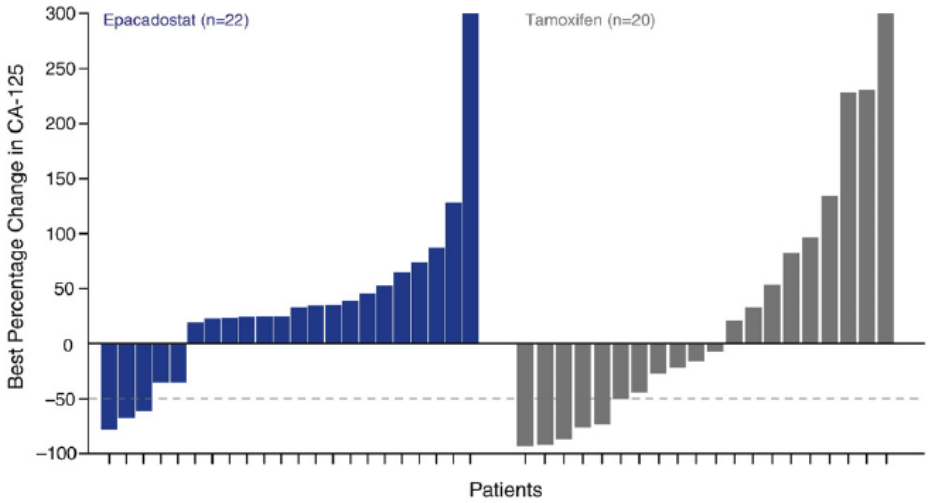


Fig. 2. Best percentage change from baseline in CA-125 (modified intent-to-treat population).

Targeting Tumor-Associated Macrophages with Anti-CSF-1R Antibody Reveals a Strategy for Cancer Therapy

Carola H. Ries,[1,13,*] Michael A. Cannarile,[1,13] Sabine Hoves,[1] Jörg Benz,[2] Katharina Wartha,[1] Valeria Runza,[1] Flora Rey-Giraud,[1] Leon P. Pradel,[1] Friedrich Feuerhake,[3] Irina Klaman,[1] Tobin Jones,[1] Ute Jucknischke,[1] Stefan Scheiblich,[1] Klaus Kaluza,[1] Ingo H. Gorr,[1] Antje Walz,[2] Keelara Abiraj,[4] Philippe A. Cassier,[5] Antonio Sica,[6,7] Carlos Gomez-Roca,[8] Karin E. de Visser,[9] Antoine Italiano,[10] Christophe Le Tourneau,[11] Jean-Pierre Delord,[7] Hyam Levitsky,[12] Jean-Yves Blay,[5] and Dominik Rüttinger[1]

Microenvironment and Immunology

Cancer Research

OX40 Is a Potent Immune-Stimulating Target in Late-Stage Cancer Patients

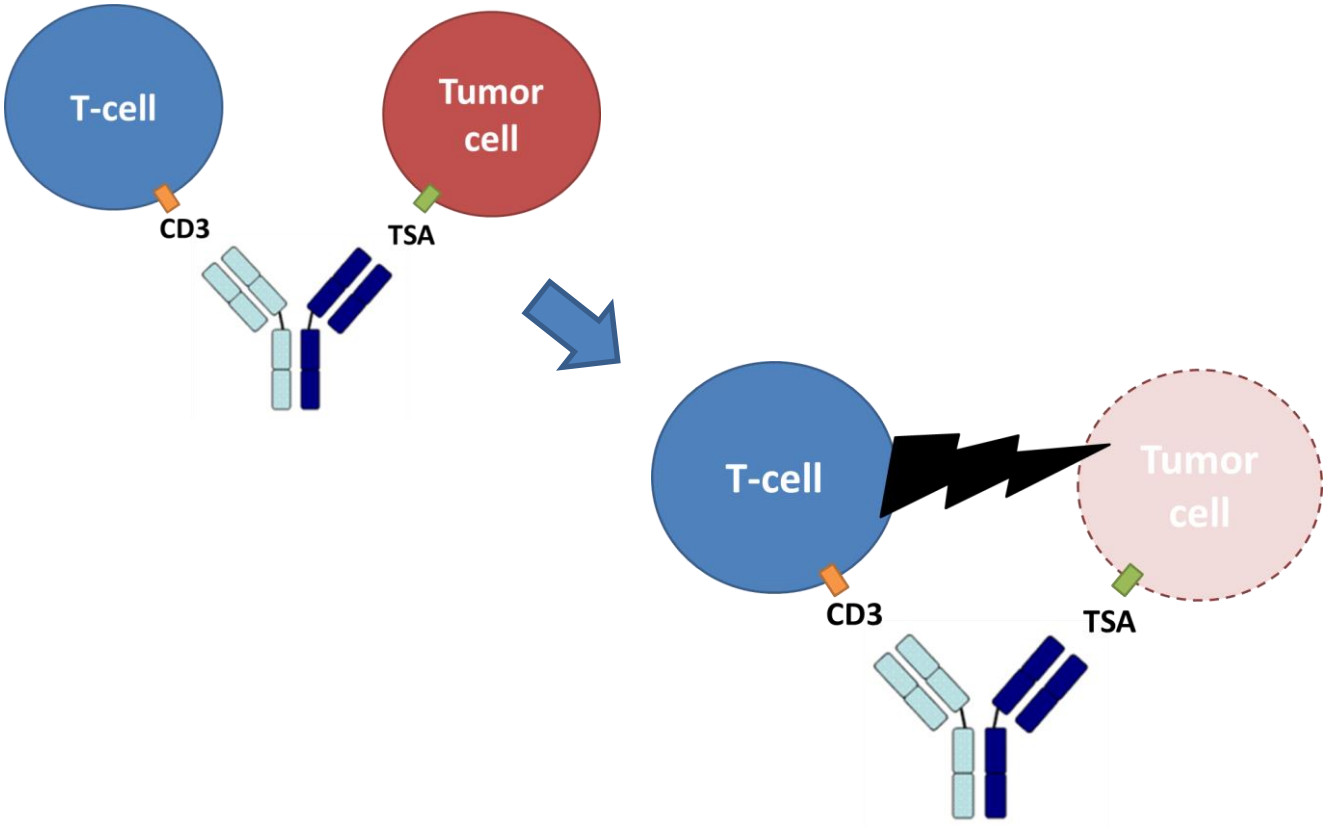
Brendan D. Curti[1], Magdalena Kovacsovics-Bankowski[1], Nicholas Morris[1], Edwin Walker[1], Lana Chisholm[1], Kevin Floyd[1], Joshua Walker[2], Iliana Gonzalez[1], Tanisha Meeuwsen[1], Bernard A. Fox[1], Tarsem Moudgil[1], William Miller[1], Daniel Haley[1], Todd Coffey[1], Brenda Fisher[1], Laurie Delanty-Miller[1], Nicole Rymarchyk[1], Tracy Kelly[1], Todd Crocenzi[1], Eric Bernstein[1], Rachel Sanborn[1], Walter J. Urba[1], and Andrew D. Weinberg[1]

Pas d'autres monothérapies très actives ?

Safety and Activity of Varlilumab, a Novel and First-in-Class Agonist Anti-CD27 Antibody, in Patients With Advanced Solid Tumors

Howard A. Burris, Jeffrey R. Infante, Stephen M. Ansell, John J. Nemunaitis, Geoffrey R. Weiss, Victor M. Villalobos, Branimir I. Sikic, Matthew H. Taylor, Donald W. Northfelt, William E. Carson III, Thomas R. Hawthorne, Thomas A. Davis, Michael J. Yellin, Tibor Keler, and Timothy Bullock

Bispecific T-cell Engaging mAbs

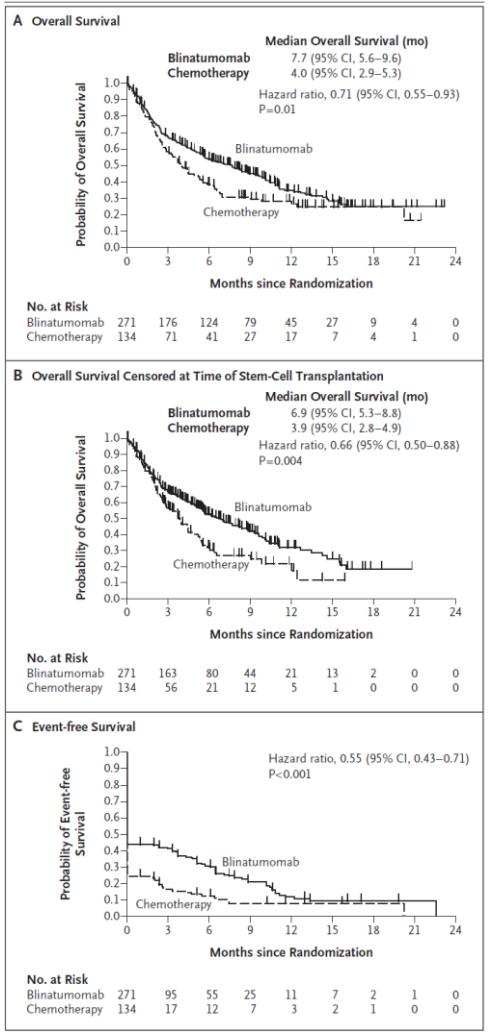


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia

Hagop Kantarjian, M.D., Anthony Stein, M.D., Nicola Gökbuget, M.D., Adele K. Fielding, M.B., B.S., Ph.D., Andre C. Schuh, M.D., Josep-Maria Ribera, M.D., Ph.D., Andrew Wei, M.B., B.S., Ph.D., Hervé Dombret, M.D., Robin Foà, M.D., Renato Bassan, M.D., Önder Arslan, M.D., Miguel A. Sanz, M.D., Ph.D., Julie Bergeron, M.D., Fatih Demirkan, M.D., Ewa Lech-Maranda, M.D., Ph.D., Alessandro Rambaldi, M.D., Xavier Thomas, M.D., Ph.D., Heinz-August Horst, M.D., Ph.D., Monika Brüggemann, M.D., Wolfram Klapper, M.D., Ph.D., Brent L. Wood, M.D., Ph.D., Alex Fleishman, M.S., Dirk Nagorsen, M.D., Ph.D., Christopher Holland, M.S., Zachary Zimmerman, M.D., Ph.D., and Max S. Topp, M.D.



Bispecific T-Cell Engager (BiTE) Antibody Construct Blinatumomab for the Treatment of Patients With Relapsed/Refractory Non-Hodgkin Lymphoma: Final Results From a Phase I Study

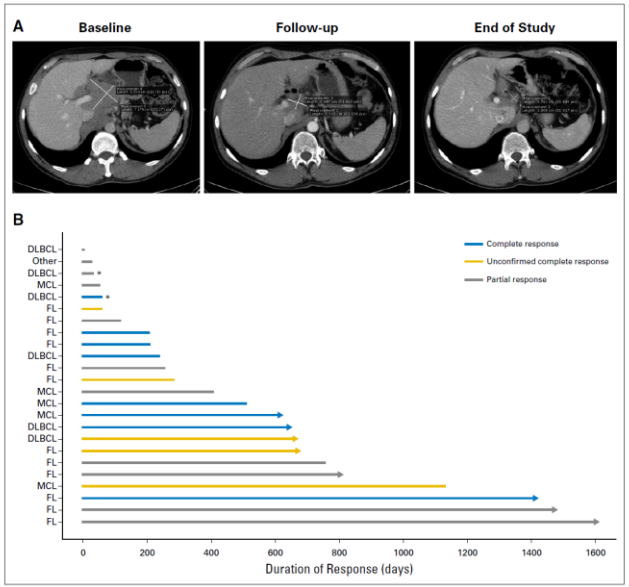
Maria-Elisabeth Goebeler, Stefan Knop, Andreas Viardot, Peter Kufer, Max S. Topp, Hermann Einsele, Richard Noppeney, Georg Hess, Stefan Kallert, Andreas Mackensen, Kathrin Rupertus, Lothar Kanz, Martin Libicher, Dirk Nagorsen, Gerhard Zugmaier, Matthias Klinger, Andreas Wolf, Brigitte Dorsch, Beate D. Quednau, Margit Schmidt, Jürgen Scheele, Patrick A. Baeuerle, Eugen Leo, and Ralf C. Bargou

VOLUME 34 · NUMBER 10 · APRIL 1, 2016

JOURNAL OF CLINICAL ONCOLOGY

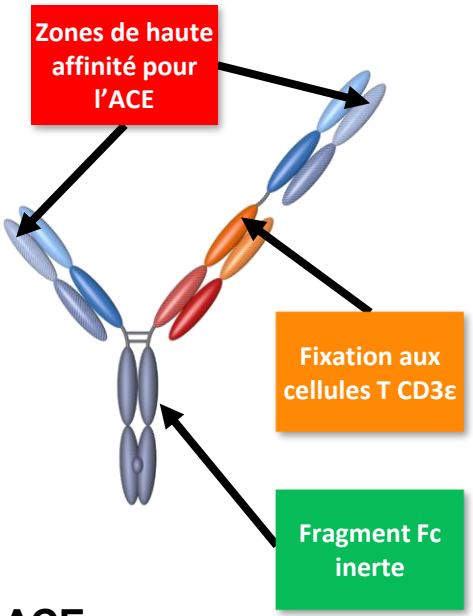
Table 5. Clinical Response

	Dose ($\mu g/m^2$/day)	No. of Patients	No. of Responses: CR	CRu	CR/CRu	PR	ORR CR + CRu + PR, n (%)	SD	PD
Response at highest actual dose received*	0.5, 1.5	9	0	0		0	0 (0)	4	5
	5	7†	0	0		0	0 (0)	4	2
	15	15†	1	0		2	3 (20)	7	4
	30	6†	1	0		0	1 (17)	2	2
	60	35†	8	5		11	24 (69)	5	5
	90	4†	1	0		1	2 (50)	1	0
Response at target dose*									
By histology									
FL	60	15			6	6	12 (80)		
MCL	60	7			3	2	5 (71)		
DLBCL‡	60§	11			4	2	6 (55)		
Other	60	2			0	1	1 (50)		
By early relapse status‖									
Early relapse	60	19			5	5	10 (53)		
No early relapse	60	16			8	6	14 (88)		



CEA-TCB : anticorps bispécifique CD3-ACE

- Fixation à la tumeur (exprimant l'ACE) et aux cellules T
- Activation des cellules T
- Augmentation de l'infiltrat immunitaire
- Indépendamment du CMH
- Lyse des cellules tumorales par les cellules T
- Synergie avec atézolizumab in vivo



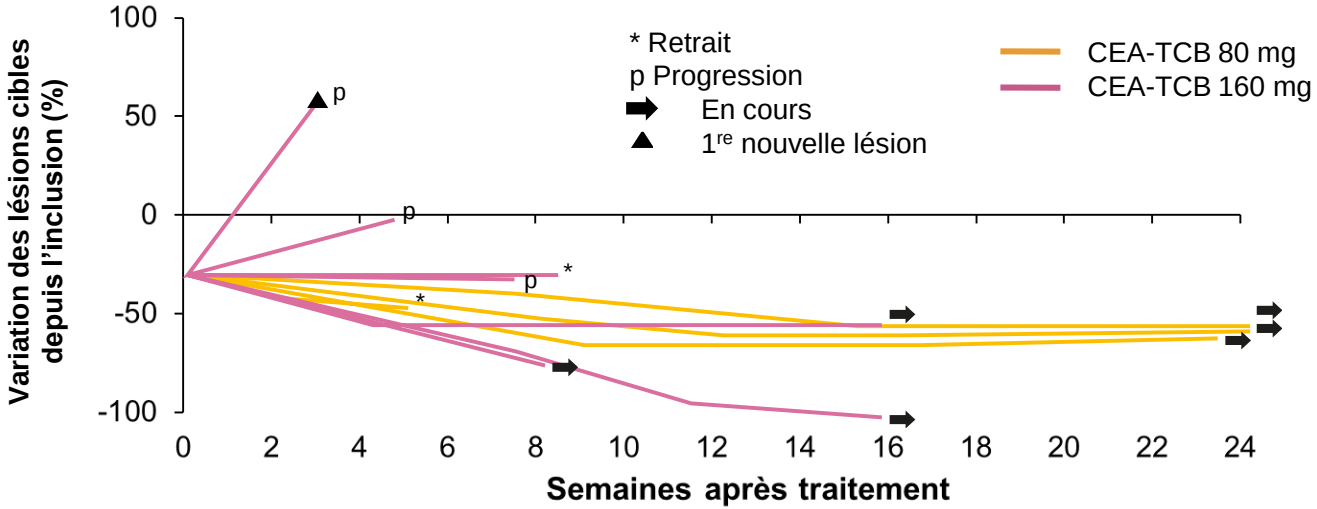
➔ **Anticorps bispécifique dirigé contre l'ACE**

➔ **Bases rationelles pour les CCR**

ASCO 2017 - Tabernero J et al., abstr. 3002

CEA-TCB : anticorps bispécifique CD3-ACE

NCT02650713 trial: CEA TCB + atezolizumab (anti-PD-L1)

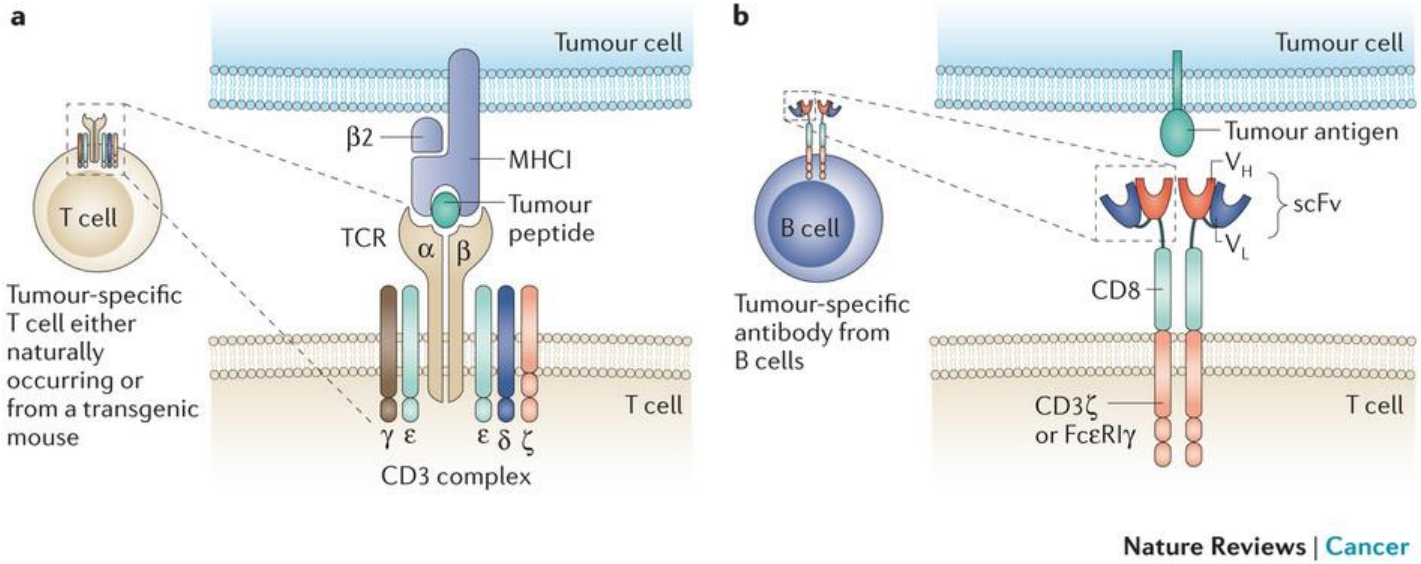


➔ **Activité dans les CCR, développement dans d'autres cancers ACE+**

ASCO 2017 - Tabernero J et al., abstr. 3002

Thérapies cellulaire adoptive T

T-CELL **CAR T-CELL**



Nature Reviews Cancer, **13**, 525–541 (2013)

Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia

Shannon L. Maude, M.D., Ph.D., Noelle Frey, M.D., Pamela A. Shaw, Ph.D., Richard Aplenc, M.D., Ph.D., David M. Barrett, M.D., Ph.D., Nancy J. Bunin, M.D., Anne Chew, Ph.D., Vanessa E. Gonzalez, M.B.A., Zhaohui Zheng, M.S., Simon F. Lacey, Ph.D., Yolanda D. Mahnke, Ph.D., Jan J. Melenhorst, Ph.D., Susan R. Rheingold, M.D., Angela Shen, M.D., David T. Teachey, M.D., Bruce L. Levine, Ph.D., Carl H. June, M.D., David L. Porter, M.D., and Stephan A. Grupp, M.D., Ph.D.

N ENGL J MED 371;16 NEJM.ORG OCTOBER 16, 2014

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Pediatric Cohort (N=25)	Adult Cohort (N=5)	Total (N=30)
Sex — no. (%)			
Female	11 (44)	1 (20)	12 (40)
Male	14 (56)	4 (80)	18 (60)
Age at infusion — yr			
Median	11	47	14
Range	5–22	26–60	5–60
Allogeneic transplantation — no. (%)	18 (72)	0	18 (60)
Primary refractory disease — no. (%)	0	3 (60)	3 (10)
Relapse — no. (%)			
1	3 (12)	2 (40)	5 (17)
≥2	22 (88)		22 (73)
Baseline burden of acute lymphoblastic leukemia — no. (%)			
Presence of detectable disease†	20 (80)	4 (80)	24 (80)
Morphologic remission‡		1 (20)	1 (3)
Absence of minimal residual disease	5 (20)		5 (17)
High-risk cytogenetic factors — no.			
BCR–ABL1	2		
IKZF1 deletion	2		
iAMP21	1		
MLL translocation	1		
Hypodiploidy	2		
CNS status — no.§			
CNS-1	23		
CNS-2	2		

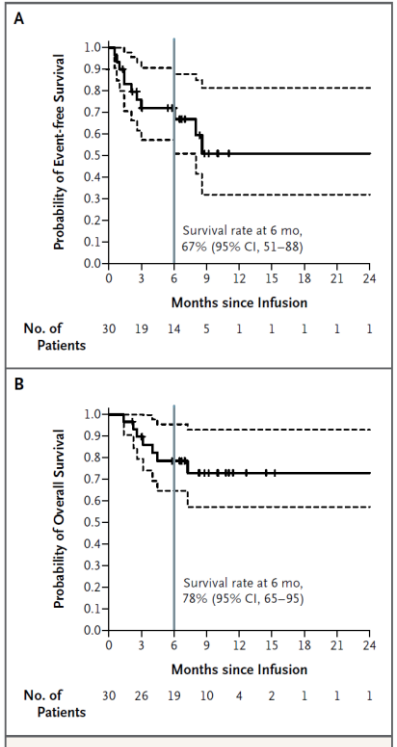
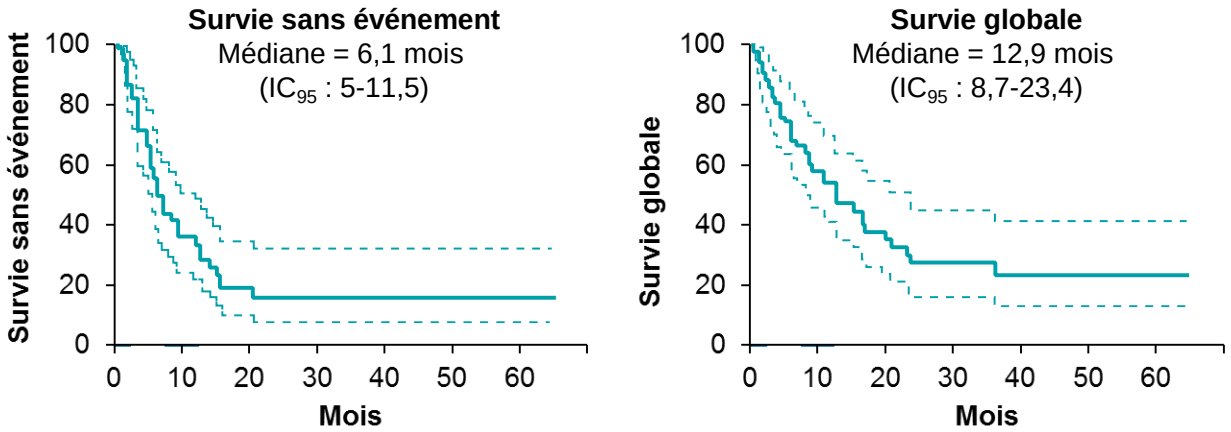


Figure 1. Probability of Event-free and Overall Survival at 6 Months.

Cellules T à récepteur chimérique (CAR-T cells) anti-CD19

Résultats à long terme dans la leucémie aiguë lymphoblastique de l'adulte en rechute

Suivi médian de 29 mois (1-65)



➔ **RC avec maladie résiduelle indétectable : 32/48**

➔ **Tolérance et efficacité meilleures si blastose médullaire < 5 %**

ASCO 2017 - Park JH et al., abstr. 7008

Molecular Therapy
Original Article

Phase 1 Results of ZUMA-1: A Multicenter Study of KTE-C19 Anti-CD19 CAR T Cell Therapy in Refractory Aggressive Lymphoma

Frederick L. Locke,[1,8] Sattva S. Neelapu,[2,8] Nancy L. Bartlett,[3] Tanya Siddiqi,[4] Julio C. Chavez,[5] Chitra M. Hosing,[6] Armin Ghobadi,[3] Lihua E. Budde,[4] Adrian Bot,[7] John M. Rossi,[7] Yizhou Jiang,[7] Allen X. Xue,[7] Meg Elias,[7]

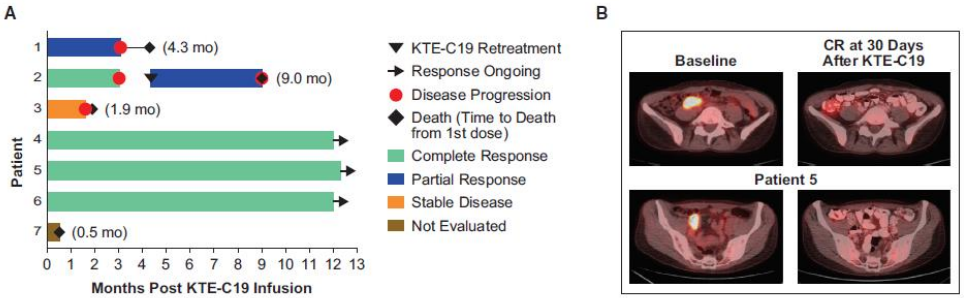
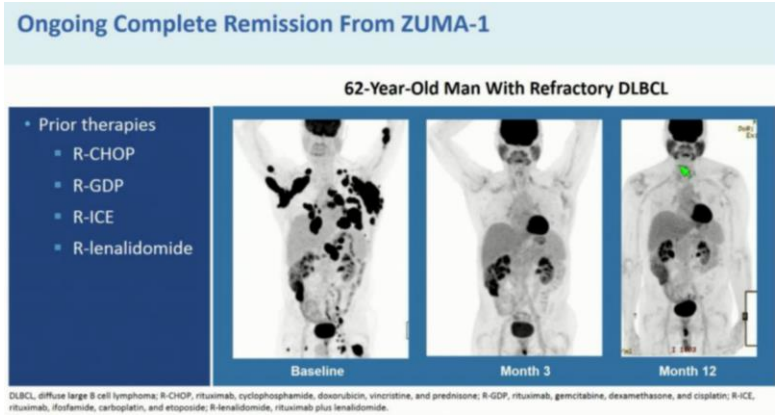


Figure 1. Clinical Efficacy after KTE-C19 Infusion

(A) Duration of response and survival post-infusion with KTE-C19. (B) CR at 30 days post KTE-C19 infusion in patient 5. Representative PET-CT scans at baseline and 30 days post KTE-C19 infusion in a patient with DLBCL relapsing after prior therapy with R-CHOP, R-ICE, and ASCT with Rituximab-gemcitabine-busulfan-melphalan+azacitidine-vorinostat.



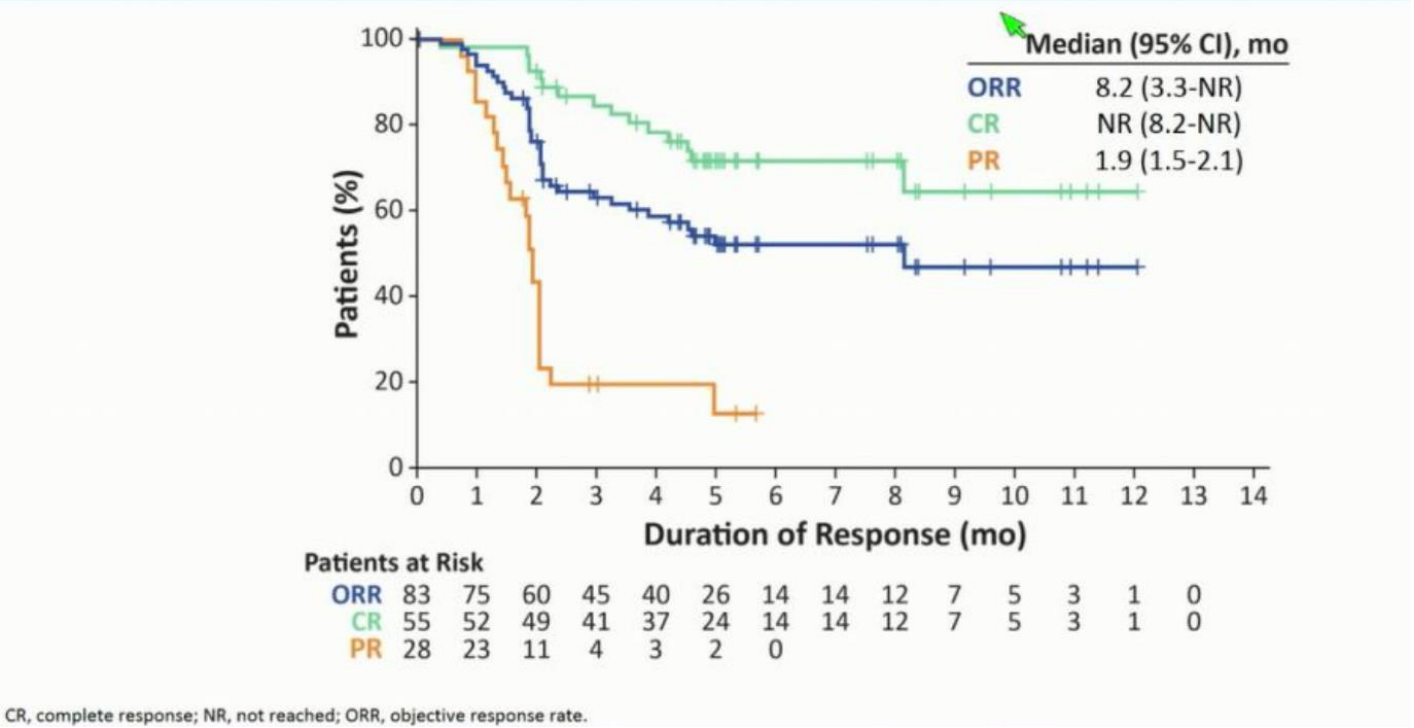
ZUMA-1: Met Primary Endpoint ORR ($P < .0001$)[a] in Combined Group

Best Response	ZUMA-1 Phase 2					
	DLBCL		TFL/PMBCL		Combined	
	ORR (%)	CR (%)	ORR (%)	CR (%)	ORR (%)	CR (%)
mITT[b]	n = 77		n = 24		n = 101	
	82	49	83	71	82	54

[a] Inferential testing when 92 axi-cel–dosed patients had 6 mo of follow-up. ORR 82%, $P<0.0001$. [b] mITT (modified intention-to-treat) set of all patients dosed with axi-cel. CR, complete response; DLBCL, diffuse large B cell lymphoma; ORR; objective response rate; PMBCL; primary mediastinal B-cell lymphoma; TFL, transformed follicular lymphoma.

Locke et al. AACR 2017

Duration of Responses At a Median Follow-Up of 8.7 Months



CR, complete response; NR, not reached; ORR, objective response rate.

Locke et al. AACR 2017

Targeting the T cell receptor β-chain constant region for immunotherapy of T cell malignancies

Paul M Maciocia[1], Patrycja A Wawrzyniecka[1], Brian Philip[1], Ida Ricciardelli[2], Ayse U Akarca[1], Shimobi C Onuoha[3], Mateusz Legut[4], David K Cole[4], Andrew K Sewell[4], Giuseppe Gritti[5], Joan Somja[6], Miguel A Piris[7], Karl S Peggs[1], David C Linch[1], Teresa Marafioti[1] & Martin A Pule[1,3]

nature medicine

CD22-targeted CAR T cells induce remission in B-ALL that is naive or resistant to CD19-targeted CAR immunotherapy

Terry J Fry[1], Nirali N Shah[1], Rimas J Orentas[1,8], Maryalice Stetler-Stevenson[2], Constance M Yuan[2], Sneha Ramakrishna[1], Pamela Wolters[1], Staci Martin[1], Cindy Delbrook[1], Bonnie Yates[1], Haneen Shalabi[1], Thomas J Fountaine[1], Jack F Shern[1], Robbie G Majzner[3], David F Stroncek[4], Marianna Sabatino[4], Yang Feng[5], Dimiter S Dimitrov[5], Ling Zhang[1], Sang Nguyen[1], Haiying Qin[1], Boro Dropulic[6,8], Daniel W Lee[1,8] & Crystal L Mackall[7]

CR 17/21, 5/5 CD19-

The activated conformation of integrin β_7 is a novel multiple myeloma–specific target for CAR T cell therapy

Naoki Hosen[1–3], Yukiko Matsunaga[4,20,21], Kana Hasegawa[1,21], Hiroshi Matsuno[5], Yuki Nakamura[1], Mio Makita[1], Kouki Watanabe[1], Mikako Yoshida[1], Kei Satoh[1], Soyoko Morimoto[6], Fumihiro Fujiki[7], Hiroko Nakajima[7], Jun Nakata[6], Sumiyuki Nishida[2], Akihiro Tsuboi[6], Yoshihiro Oka[1–3], Masahiro Manabe[8], Hiroyoshi Ichihara[9], Yasutaka Aoyama[9], Atsuko Mugitani[9], Takafumi Nakao[10], Masayuki Hino[11], Ryosuke Uchibori[12], Keiya Ozawa[12,13], Yoshihiro Baba[14], Seitaro Terakura[15], Naoki Wada[16], Eiichi Morii[16], Junichi Nishimura[5], Kiyoshi Takeda[3,17,18], Yusuke Oji[19], Haruo Sugiyama[7], Junichi Takagi[4] & Atsushi Kumanogoh[2,3,18]

Donor CD19 CAR T cells exert potent graft-versus-lymphoma activity with diminished graft-versus-host activity

Arnab Ghosh[1,7], Melody Smith[1,7], Scott E James[1,2,7], Marco L Davila[2,6,7], Enrico Velardi[1], Kimon V Argyropoulos[1], Gertrude Gunset[2], Fabiana Perna[2], Fabiana M Kreines[1], Emily R Levy[1], Sophie Lieberman[1], Hillary V Jay[1], Andrea Z Tuckett[1], Johannes L Zakrzewski[3], Lisa Tan[1], Lauren F Young[1], Kate Takvorian[1], Jarrod A Dudakov[1,6], Robert R Jenq[1], Alan M Hanash[1], Ana Carolina F Motta[4,6], George F Murphy[4], Chen Liu[5], Andrea Schietinger[1], Michel Sadelain[1,2,7] & Marcel R M van den Brink[1,2,7]

Solid tumors?

1: Migliorini D, Dietrich PY, Stupp R, Linette GP, Posey AD, June CH. CAR-T cell Therapies in Glioblastoma: a first look. Clin Cancer Res. 2017 Nov 20. pii: clincanres.2871.2017. doi: 10.1158/1078-0432.CCR-17-2871. [Epub ahead of print] PubMed PMID: 29158268.

2: Kiesgen S, Chicaybam L, Chintala NK, Adusumilli PS. Chimeric antigen receptor (CAR) T-cell therapy for thoracic malignancies. J Thorac Oncol. 2017 Oct 26. pii: S1556-0864(17)32787-9. doi: 10.1016/j.jtho.2017.10.001. [Epub ahead of print] Review. PubMed PMID: 29107016.

3: Brown CE, Aguilar B, Starr R, Yang X, Chang WC, Weng L, Chang B, Sarkissian A, Brito A, Sanchez JF, Ostberg JR, D'Apuzzo M, Badie B, Barish ME, Forman SJ. Optimization of IL13Rα2-Targeted Chimeric Antigen Receptor T Cells for Improved Anti-tumor Efficacy against Glioblastoma. Mol Ther. 2017 Oct 5. pii: S1525-0016(17)30467-7. doi: 10.1016/j.ymthe.2017.10.002. [Epub ahead of print] PubMed PMID: 29103912.

4: Varghese AM. Chimeric antigen receptor (CAR) T and other T cell strategies for pancreas adenocarcinoma. Chin Clin Oncol. 2017 Oct 24. pii: cco.2017.09.04. doi: 10.21037/cco.2017.09.04. [Epub ahead of print] PubMed PMID: 29156888.

HER2,
EGFRviii
CEA
PMSA
IGFR1
ROR2
IL-13R2
…

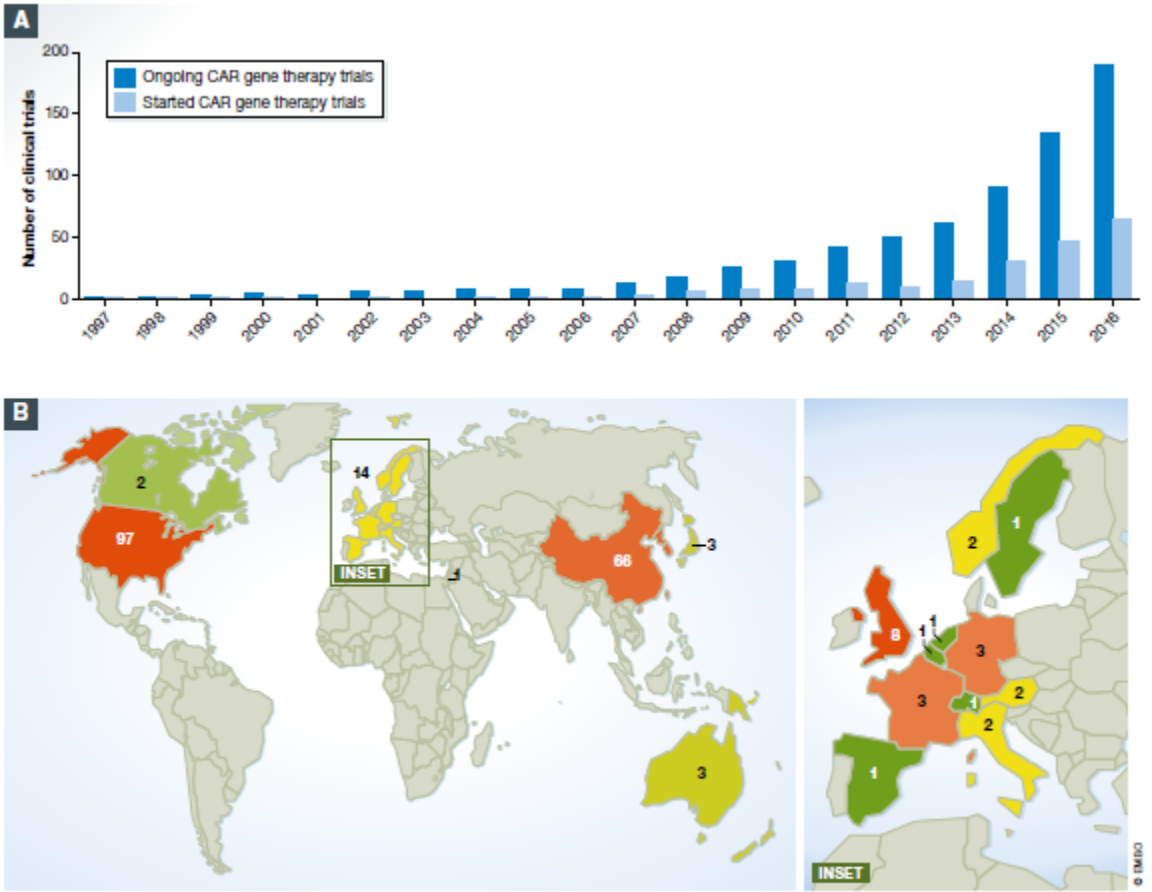
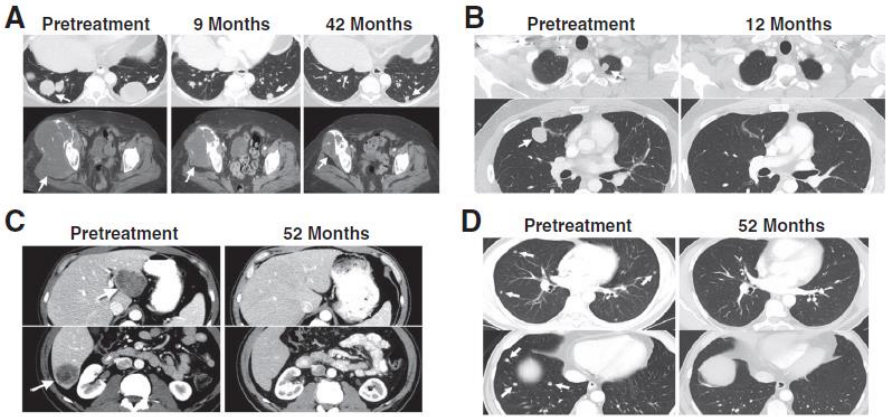


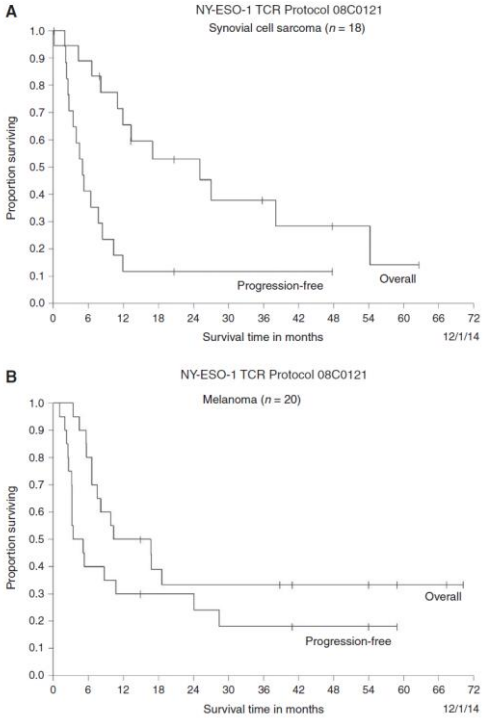
Figure 2. CAR T cell trials over time and geographical distribution.

(A) Timeline of cancer CAR T cell trials as listed in Datasets EV1 and EV2 distinguishing between ongoing number (dark blue bars) and newly initiated trials in the indicated year (light blue bars). (B) Geographical distribution of worldwide ongoing CAR T cells clinical trials (left) and distribution of trial sites of the ongoing European studies (right). Five studies are multi-centric, of which four are multi-country trials in Europe (Dataset EV5). Long-term follow-up studies are not included. Color code indicates the prevalence of trials from low (green) to high (red).

A Pilot Trial Using Lymphocytes Genetically Engineered with an NY-ESO-1–Reactive T-cell Receptor: Long-term Follow-up and Correlates with Response

Paul F. Robbins[1], Sadik H. Kassim[1], Thai L.N. Tran[2], Jessica S. Crystal[1], Richard A. Morgan[1], Steven A. Feldman[1], James C. Yang[1], Mark E. Dudley[1], John R. Wunderlich[1], Richard M. Sherry[1], Udai S. Kammula[1], Marybeth S. Hughes[1], Nicholas P. Restifo[1], Mark Raffeld[3], Chyi-Chia R. Lee[3], Yong F. Li[1], Mona El-Gamil[1], and Steven A. Rosenberg[1]





IL-7 to treat lymphopenia

Lymphopenia

Toxicity of chemotherapy

1- FN
(Blay et al JCO 1996)
- CT HR
- Lymphopenia d5 or d1

2 - Grade 4 Anemia
(Ray-Coquard et al JCO 1999)
- Hb < 12
- Lymphopenia
- PS > 1

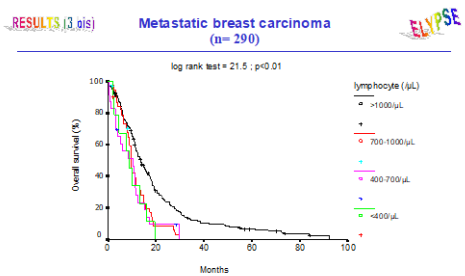
3 - Grade 4 thrombopenia
(Ray-Coquard et al Blood 1998)
- Plt < 150
- CT HR
- PS > 1
- Lymphopenia

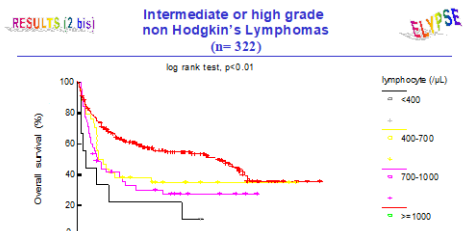
Toxic death

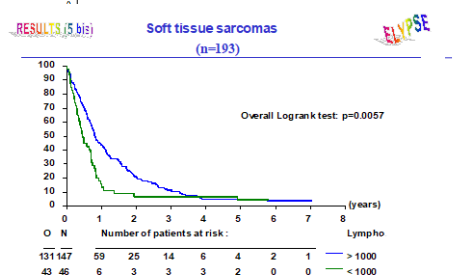
Death at 31 d
(Ray et al Br J Cancer 2001)
- Lymphopenia
- PS > 1

N=1997 pts
Deaths:
- 20% at 31 d
- 48% at 3 mos

Survival







ELYPSE-7: a randomized placebo-controlled phase IIa trial with CYT107 exploring the restoration of CD4⁺ lymphocyte count in lymphopenic metastatic breast cancer patients

O. Trédan[1,2,3,4,†], C. Ménétrier-Caux[2,3,4,5,6,†], I. Ray-Coquard[1,2,3,4,†*], G. Garin[7], C. Cropet[7], E. Verronèse[8], T. Bachelot[1], P. Rebattu[1], P. E. Heudel[1], P. Cassier[1], S. Chabaud[2], T. Croughs[9], P. Dupont[7], A. C. Cadore[7], G. Clapisson[9], A. Dalgado[9], C. Bardin-dit-Couragoet[9], C. Rigal[9], A. N'Kodia[9], L. Gilles-Afchain[10], M. Morre[11], D. Perol[2], J. Y. Blay[1,2,3,4,6,†] & C. Caux[2,3,4,5,6,†]

Low CD4 count and to restore CD4 counts

Available at www.sciencedirect.com

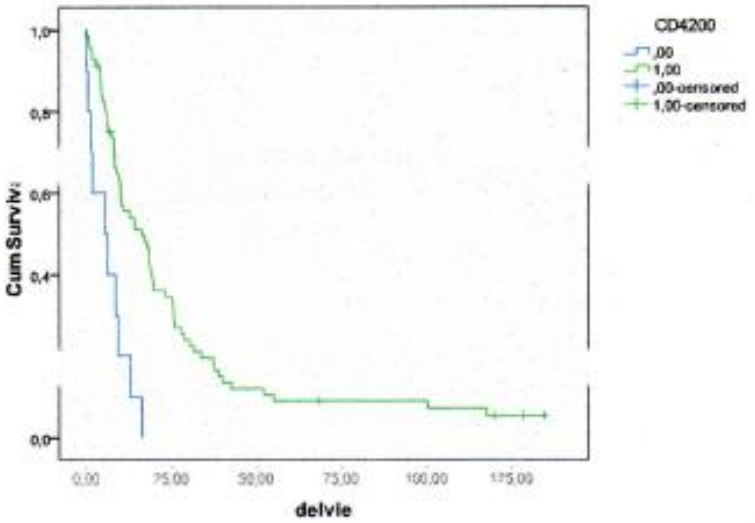
SciVerse ScienceDirect

journal homepage: www.ejcancer.info

CD4 lymphopenia to identify end-of-life metastatic cancer patients

Julien Péron [a,b,c,d], Claire Cropet [e], Olivier Tredan [d], Thomas Bachelot [d], Isabelle Ray-Coquard [d], Gilles Clapisson [d], Sylvie Chabaud [e], Irene Philip [d], Christophe Borg [f], Philippe Cassier [d], Inthidar Labidi Galy [d], Catherine Sebban [d], David Perol [e], Pierre Biron [d], Christophe Caux [g], Christine Menetrier-Caux [g], Jean-Yves Blay [d,*]

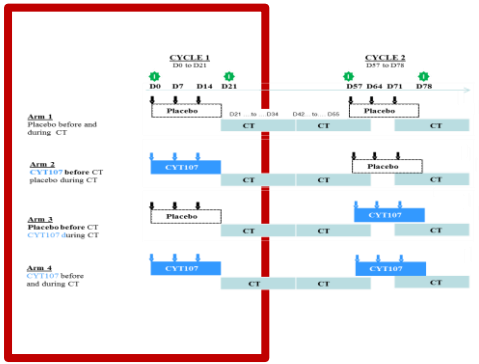
[a] Université de Lyon, F-69000 Lyon, France
[b] Université Lyon 1, F-69100 Villeurbanne, France
[c] CNRS UMR 5558, Laboratoire de Biométrie et Biologie Evolutive, Equipe Biostatistique-Santé, Villeurbanne, France
[d] Department of Medical Oncology, Centre Léon BERARD, 28, rue Laënnec, 69008 Lyon, France
[e] Department of Statistics, Centre Léon BERARD, 28, rue Laënnec, 69008 Lyon, France
[f] Department of Medical Oncology, CHU Besançon, 2, Place Saint-Jacques 25030 Besançon cedex, France
[g] Equipe 11, Cancer Research Center of Lyon, Centre Léon BERARD, 28, rue Laënnec, 69008 Lyon, France

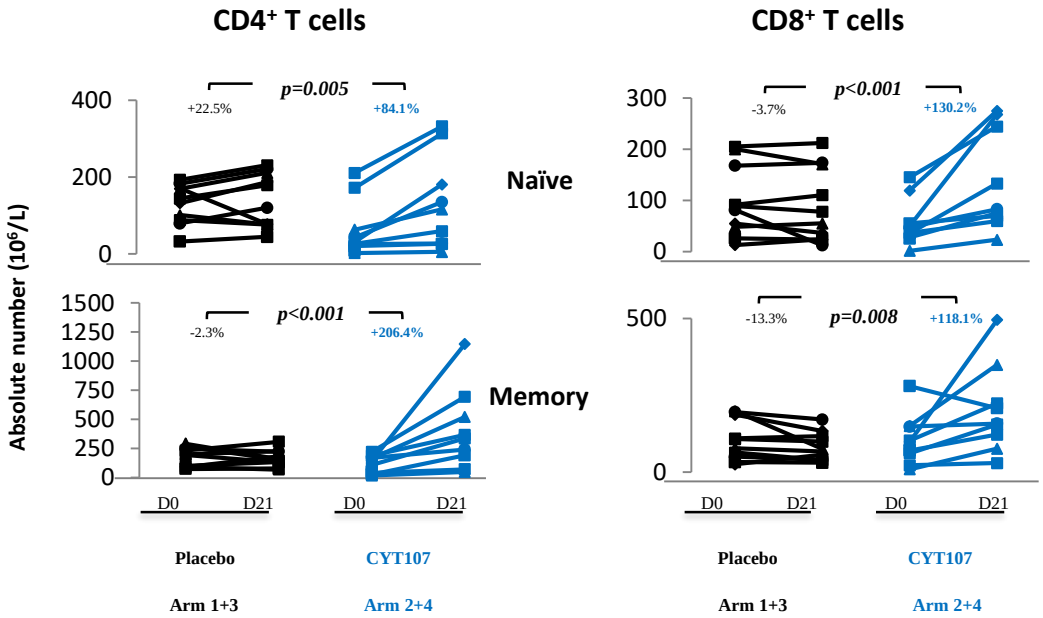


ELYPSE-7: a randomized placebo-controlled phase IIa trial with CYT107 exploring the restoration of CD4+ lymphocyte count in lymphopenic metastatic breast cancer patients

Annals of Oncology 26: 1353–1362, 2015
doi:10.1093/annonc/mdv173
Published online 7 April 2015

O. Trédan[1,2,3,4,†], C. Ménétrier-Caux[2,3,4,5,6,†], I. Ray-Coquard[1,2,3,4,†*], G. Garin[7], C. Cropet[7], E. Verronèse[5], T. Bachelot[1], P. Rebattu[1], P. E. Heudel[1], P. Cassier[1], S. Chabaud[7], T. Croughs[8], P. Dupont[7], A. C. Cadore[7], G. Clapisson[9], A. Delgado[5], C. Bardin-dit-Courageot[5], C. Rigal[5], A. N'Kodia[5], L. Gilles-Afchain[10], M. Morre[11], D. Pérol[7], J. Y. Blay[1,2,3,4,6,†] & C. Caux[2,3,4,5,6,†]





Less G3 hematological toxicity in IL-7 treated patients

Safety, Antitumor Activity, and Immune Activation of Pegylated Recombinant Human Interleukin-10 (AM0010) in Patients With Advanced Solid Tumors

Aung Naing, Kyriakos P. Papadopoulos, Karen A. Autio, Patrick A. Ott, Manish R. Patel, Deborah J. Wong, Gerald S. Falchook, Shubham Pant, Melinda Whiteside, Drew R. Rasco, John B. Mumm, Ivan H. Chan, Johanna C. Bendell, Todd M. Bauer, Rivka R. Colen, David S. Hong, Peter Van Vlasselaer, Nizar M. Tannir, Martin Oft, and Jeffrey R. Infante

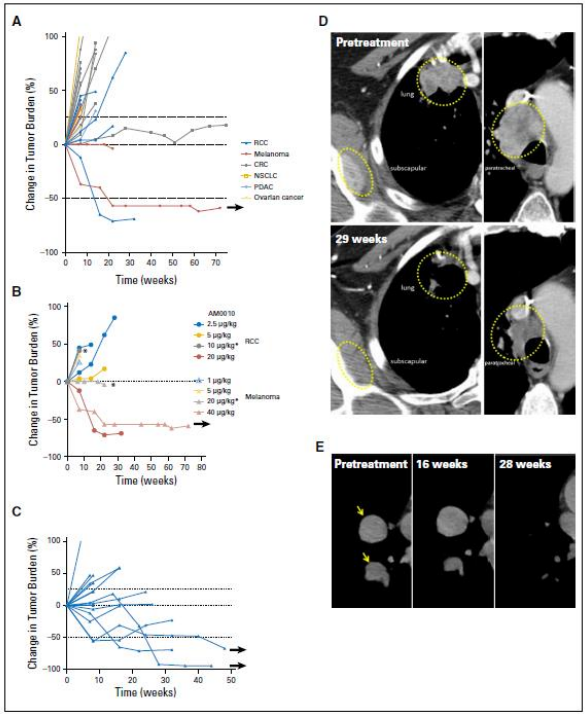
VOLUME 34 · NUMBER 29 · OCTOBER 10, 2016

JOURNAL OF CLINICAL ONCOLOGY

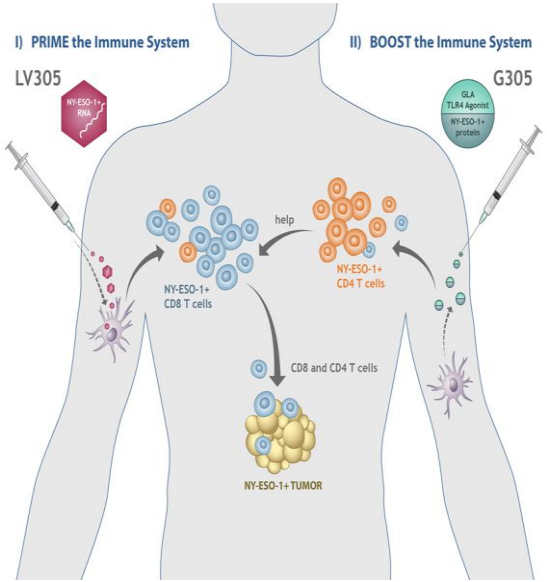
Table 3. Clinical Response

Variable	No. of Evaluable Patients (total)	Best Response (duration in months)
Dose escalation, μg/kg		
1	2 (4)	1 SD (2)
2.5	5 (6)	1 MXR (2)
5	5 (6)	2 SDs (20 and 6)
10	5 (6)	2 MXRs (2 and 2)
20	5 (6)	1 PR (4), 2 MXRs (6 and 2), 1 SD (4)
40	5 (5)	1 PR (19+)
All patients (1 to 40 μg/kg)	27 (33)	2 PRs, 5 MXRs, 1 SD (20)
Tumor histology (escalation cohort)		
CRC	14 (16)	1 SD (20), 2 MXRs (2 and 2)
Melanoma	4 (4)	1 PR (19+), 1 MXR (6)
Prostate cancer	0 (1)	
NSCLC	1 (1)	
RCC	5 (6)	1 PR (4), 2 MXRs (2 and 2) 1 SD (6)
Pancreatic cancer	2 (4)	1 SD (4)
Ovarian cancer	1 (1)	1 SD (2)
All patients with RCC at RP2D (20 μg/kg)	15 (19)	4 PRs (2, 4, 4+, and 4+), 6 SDs (8, 6, 4, 4, 2, and 2)

ORR	OR (No.)	RR (%)
All escalation cohorts (1 to 40 μg/kg)	2 (27)	7
All patients at active dose (20 to 40 μg/kg)	5 (24)	21
Patients with RCC at active dose (20 μg/kg)	4 (15)	27



CMB305: Prime-Boost Immunotherapy Targeting NY-ESO-1



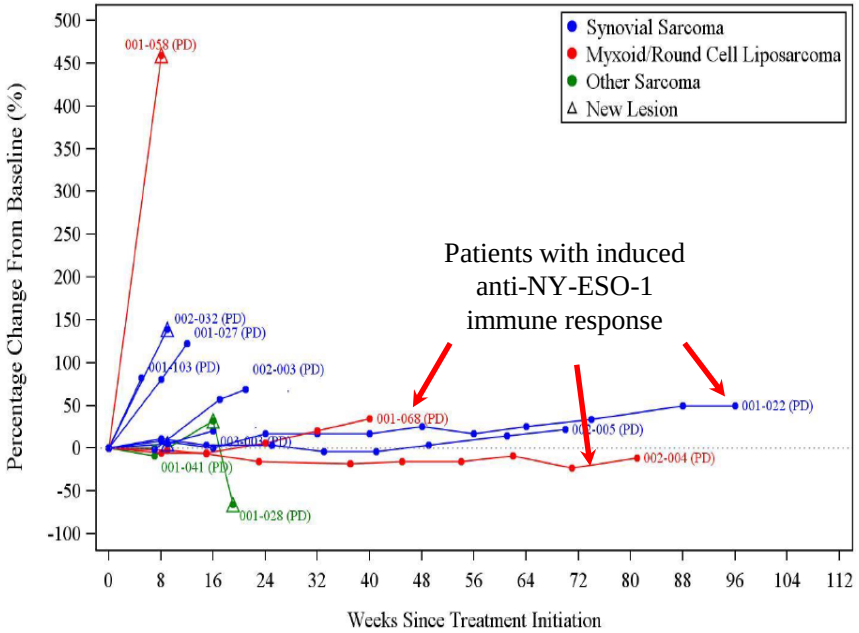
- No ex vivo manipulation or HLA matching
- Sequential administration of LV305 and G305 (3 months) followed by monthly G305
- LV305 Priming:
  - Dendritic cell (DC) targeting NY-ESO-1 lentiviral vector encoding full length NY-ESO-1
  - Integration deficient, replication incompetent
  - Induces and expands NY-ESO-1 specific CD8 and CD4 T Cells
- G305 boosting:
  - Potent TLR-4 agonist co-formulated with NY-ESO-1 full length protein
  - Enhances LV305 immunogenicity and triggers anti-NY-ESO-1 antibodies

C131 Study: Disease Control in STS Patients

STS Patients n=25	
ORR, pt (%)	0
SD, pt (%)	16 (64)
DCR, pt (%)	16 (64)
Median PFS, mos	4.7
95% CI	2.1 – 7.8
6 mos PFS Rate, %	36.4

STS patients with disease progression at entry:

Experienced durable tumor growth arrest



Nouvelles cibles

- ICP (s)
- Bispecifiques
- CAR T
- Cytokines
- Vaccins
- …

Les questions saillantes en 2017

- Quels patients?
- Quelles cibles?
- Quelles combinaisons?
  - Immunothérapies
  - Chimiothérapies cytotoxiques
  - Radiothérapie
  - Thérapies ciblées
- Quelles modalités d'administration?
- Comment développer ces traitements?

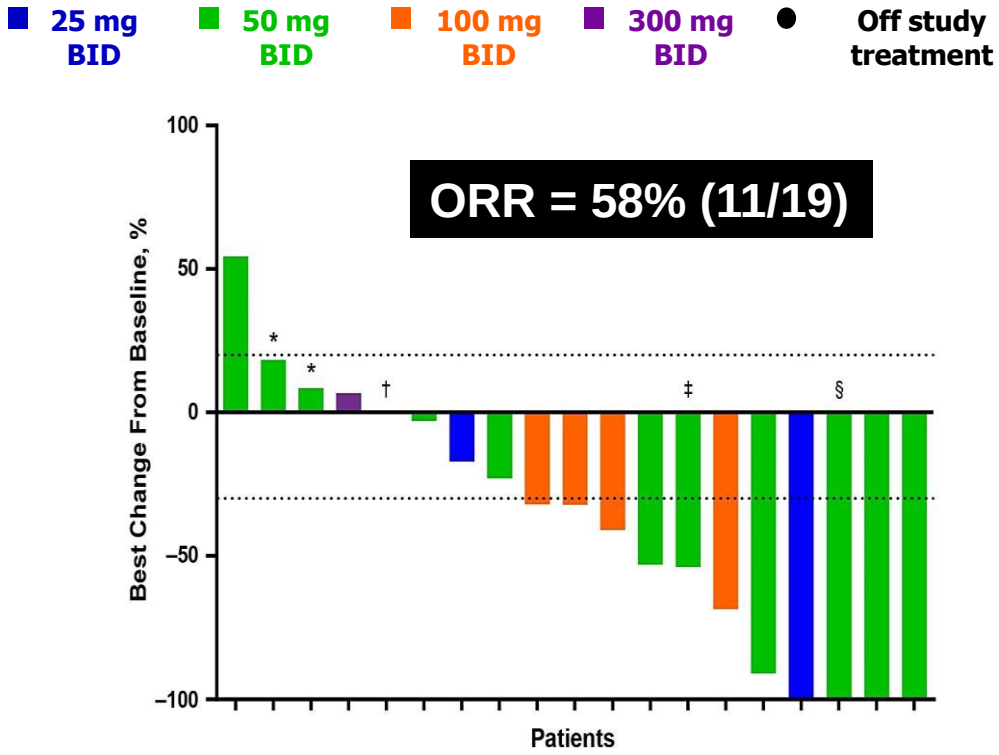
Essais cliniques Ab LAG3

TABLE 1 (Continued)

ClinicalTrials.gov ID/ Sponsor (year opened)	Trial	Patient Population Phase (estimated enrollment) Primary endpoint	Description	Status/outcomes
NCT02614833 Immutep S.A. (2015)	IMP321 as adjunctive to standard chemotherapy paclitaxel metastatic breast carcinoma	• **Hormone receptor-positive metastatic breast cancer** • Phase IIb, 1:1randomization; 2-stage design (n=211) • Assessment of PFS	• Paclitaxel + **IMP321** (experimental) vs paclitaxel + placebo • 6 cycles of 4 wks: weekly paclitaxel D1, D8, D15, and **IMP321** D2 and D16	• Currently recruiting participants • Estimated completion, Jun 2019
NCT02676869 Prima BioMed Ltd (2016)	Phase I study of IMP321 adjuvant to anti-PD-1 therapy in unresectable or metastatic melanoma	• **Stage III/IV unresectable or metastatic melanoma** (n=24) • Phase I dose-escalation study • Number of patients with treatment emergent AEs, serious AEs and DLTs	• 3 dose cohorts: **IMP321** administered as SC injection of 1, 6, or 30 mg every 2 wks • Pembrolizumab per approved label	Currently recruiting participants Estimated completion, Mar 2018
BMS-986016 (Bristol-Myers Squibb)				
NCT01968109 Bristol-Myers Squibb (2013)	Safety study of anti-LAG-3 with and without anti-PD-1 in the treatment of solid tumors	• Advanced solid tumors: **cervical, ovarian, bladder, CRC, H&N, gastric, HCC, RCC, NSCLC, melanoma** • Phase I/IIa, dose-escalation, and cohort expansion study (n=360) • Safety: rate of AEs	**BMS-986016** ± Nivolumab	• Currently recruiting participants • Estimated completion, May 2018
NCT02061761 Bristol-Myers Squibb (2014)	Safety study of anti-LAG-3 in relapsed or refractory haematologic malignancies	• **Relapsed or refractory B-cell malignancy** – CLL, HL, NHL, MM (n=132) • Phase I/IIa dose-escalation and cohort expansion study • Safety – AEs, serious AEs and laboratory abnormalities	**BMS-986016** ± Nivolumab	• Currently recruiting participants • Estimated completion, Jan 2020 • Immunogenicity as measured by ADA for **BMS-986016**
NCT02750514 Bristol-Myers Squibb (2016)	A study to test combination treatment in people with advanced non-small cell lung cancer	• **Advanced NSCLC** • Phase II (n=504) • ORR, Duration of response, and PFS rate • Safety/tolerability	Nivolumab monotherapy vs Nivolumab + Dasatinib vs Nivolumab + **BMS-986016**	• Currently recruiting participants • Estimated completion, Apr 2021
NCT02658981 Sidney Kimmel Comprehensive Cancer Center (2016)	Anti-LAG-3 or urelumab alone and in combination with Nivolumab in treating patients with glioblastoma	• **Recurrent GBM or gliosarcoma**, following RT + temozolomide (n=68) • Phase I; MTD of **BMS-986016** ± anti-PD1 OR anti-CD137 ± anti-PD1	**BMS-986016** IV on D1 and 15, even 28 days×24 courses unless POD or unacceptable toxicity	• Currently recruiting participants • Estimated completion, Dec 2019
NCT02935634 Bristol-Myers Squibb (2016)	A study to test combination treatments in people with advanced gastric cancer (FRACTION-GC)	• **Advanced gastric cancer** • Phase II • ORR, duration of response, and PFS rate • Safety/tolerability	Nivolumab+Ipilimumab vs Nivolumab+**BMS-986016**	• Currently recruiting participants • Estimated completion, Nov 2021
ClinicalTrials.gov ID/ Sponsor (year opened)	**Trial**	**Patient Population Phase (estimated enrollment) Primary endpoint**	**Description**	**Status/outcomes**
LAG525 (Novartis)				
NCT02460224 Novartis Pharmaceuticals (2015)	Safety and efficacy of LAG525 single agent and in combination with PDR001 in patients with advanced malignancies	• Phase I/II (n=416): **advanced NSCLC, advanced melanoma, mRCC** • Phase I: incidence of DLTs for **LAG525** as single agent and in combination with PDR001 • Phase II: ORR, per RECIST v1.1	3 arms: (A) single-agent **LAG525**; (B) **LAG525**+PDR001; (C) **LAG525** in Japanese patients	• Immunological readout: correlate PD-L1, LAG-3 expression, IFNɣ-related gene mRNA profiling, emergence of anti-LAG525/PDR001 antibodies • Currently recruiting participants • Estimated completion, Oct 2018
MK-4280-001 (Merck)				
NCT02720068 Merck Sharp & Dohme Corp. (2016)	Study of MK-4280 as monotherapy and in combination with Pembrolizumab (MK-3475) in adults with advanced solid tumors (MK-4280-001)	• **Metastatic solid tumors** • Phase I (n=70) • Number of participants with DLT, AEs, and discontinuation due to AE	Non-randomized, dose-escalation safety study Five dose levels (A-E) of **MK-4280-001**±MK-2475	• Currently recruiting participants • Estimated completion, Aug 2020

Epacadostat + pembrolizumab in Metastatic Melanoma

(Incyte, NCT02178722)



Gangadhar et al. SITC 2015. Abstract #07

Les questions saillantes en 2018

- Quels patients?
- Quelles cibles?
- Quelles combinaisons?
  - Immunothérapies
  - Chimiothérapies cytotoxiques
  - Radiothérapie
  - Thérapies ciblées
- Quelles modalités d’administration?
- Comment développer ces traitements?

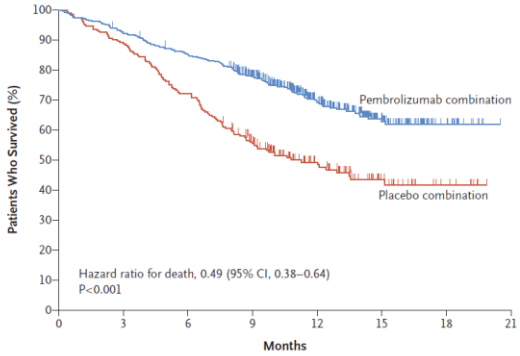
Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer

L. Gandhi, D. Rodríguez-Abreu, S. Gadgeel, E. Esteban, E. Felip, F. De Angelis, M. Domine, P. Clingan, M.J. Hochmair, S.F. Powell, S.Y.-S. Cheng, H.G. Bischoff, N. Peled, F. Grossi, R.R. Jennens, M. Reck, R. Hui, E.B. Garon, M. Boyer, B. Rubio-Viqueira, S. Novello, T. Kurata, J.E. Gray, J. Vida, Z. Wei, J. Yang, H. Raftopoulos, M.C. Pietanza, and M.C. Garassino, for the KEYNOTE-189 Investigators*

This article was published on April 16, 2018, at NEJM.org.

DOI: 10.1056/NEJMoa1801005

A Overall Survival



No. at Risk								
Pembrolizumab combination	410	377	347	278	163	71	18	0
Placebo combination	206	183	149	104	59	25	8	0

B Subgroup Analysis of Overall Survival

Subgroup	No. of Events/ No. of Patients	Hazard Ratio for Death (95% CI)
Overall	235/616	0.49 (0.38–0.64)
Age		
<65 yr	133/312	0.43 (0.31–0.61)
≥65 yr	102/304	0.64 (0.43–0.95)
Sex		
Male	143/363	0.70 (0.50–0.99)
Female	92/253	0.29 (0.19–0.44)
ECOG performance-status score		
0	74/266	0.44 (0.28–0.71)
1	159/346	0.53 (0.39–0.73)
Smoking status		
Current or former	211/543	0.54 (0.41–0.71)
Never	24/73	0.23 (0.10–0.54)
Brain metastases at baseline		
Yes	51/108	0.36 (0.20–0.62)
No	184/508	0.53 (0.39–0.71)
PD-L1 tumor proportion score		
<1%	84/190	0.59 (0.38–0.92)
≥1%	135/388	0.47 (0.34–0.66)
1–49%	65/186	0.55 (0.34–0.90)
≥50%	70/202	0.42 (0.26–0.68)
Platinum-based drug		
Carboplatin	176/445	0.52 (0.39–0.71)
Cisplatin	59/171	0.41 (0.24–0.69)

Les questions saillantes en 2018

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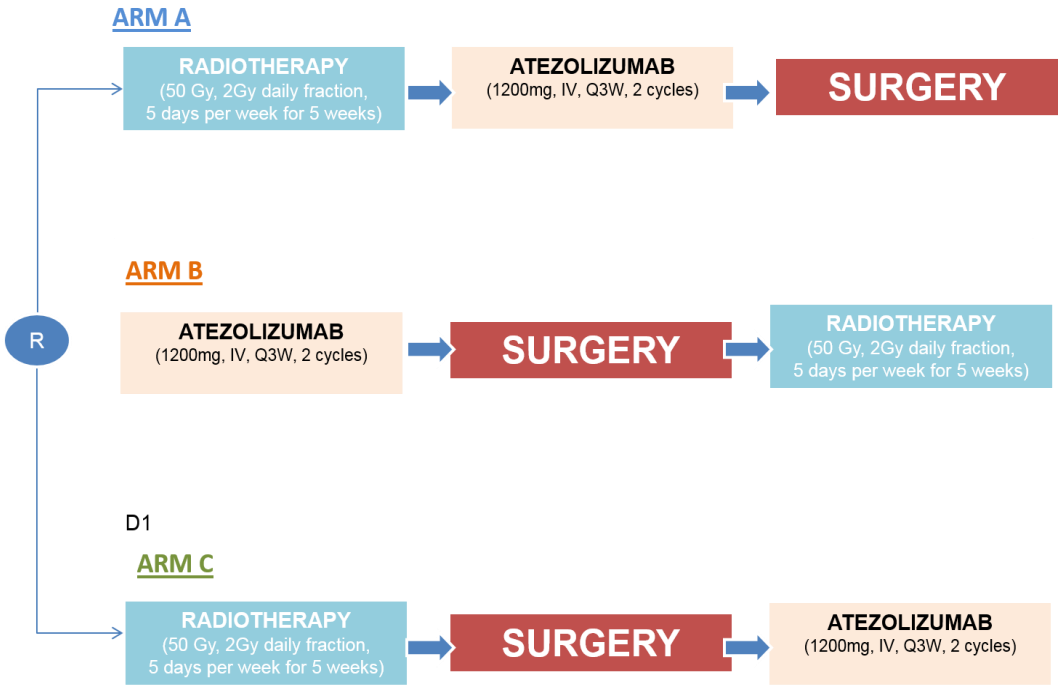
Combining RT and ICP Ab : a PoC



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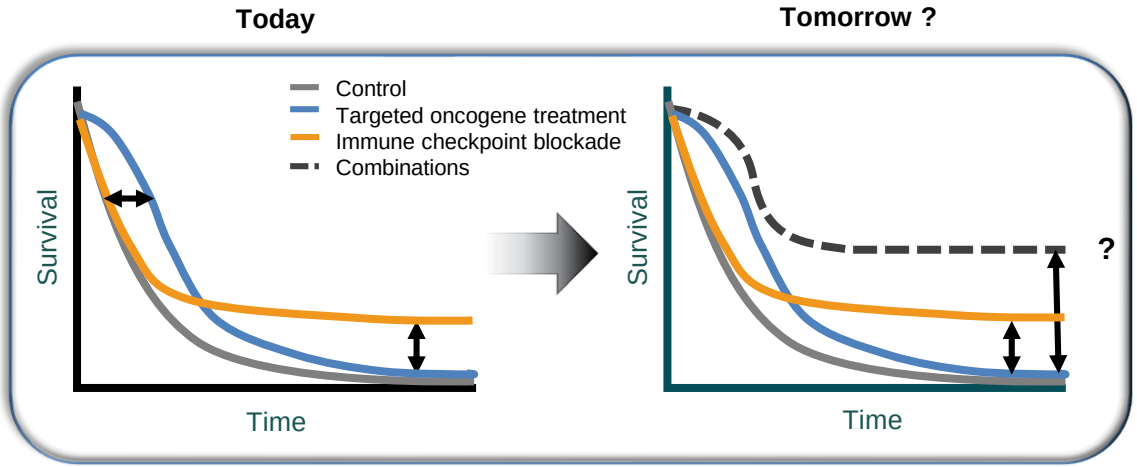
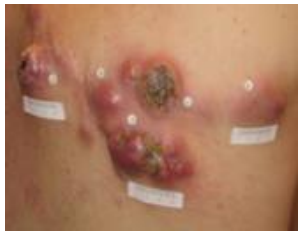
Immunotherapies vs targeted oncogene therapies



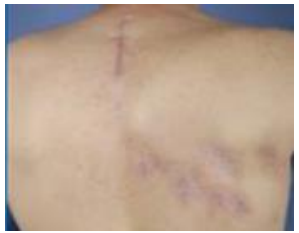
1. Adapted from Ribas A, presented WCM 2013. 2. Ribas A, et al. Clin Cancer Res 2012;18:336–41. 3. Drake CG. Ann Oncol 2012;23(suppl 8):viii41–viii46.

Immune vs oncogene targeted therapy

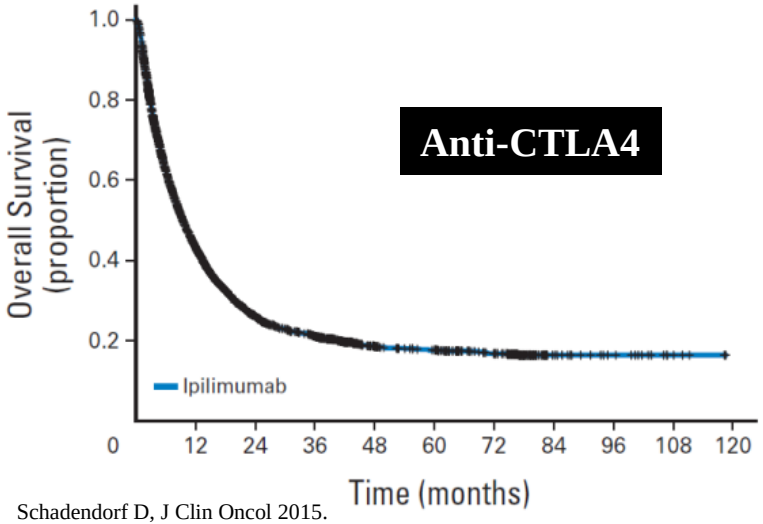
Screening



Week 72



Hodi et al. Abstract #3008 ASCO 2008



Anti-CTLA4

Schadendorf D, J Clin Oncol 2015.

Ten-Year Progression-Free and Overall Survival in Patients With Unresectable or Metastatic GI Stromal Tumors: Long-Term Analysis of the European Organisation for Research and Treatment of Cancer, Italian Sarcoma Group, and Australasian Gastrointestinal Trials Group Intergroup Phase III Randomized Trial on Imatinib at Two Dose Levels

Paolo G. Casali, John Zalcberg, Axel Le Cesne, Peter Reichardt, Jean-Yves Blay, Lars H. Lindner, Ian R. Judson, Patrick Schöffski, Serge Leyvraz, Antoine Italiano, Viktor Grünwald, Antonio Lopez Pousa, Dusan Kotasek, Stefan Sleijfer, Jan M. Kerst, Piotr Rutkowski, Elena Fumagalli, Pancras Hogendoorn, Saskia Litière, Sandrine Marreaud, Winette van der Graaf, Alessandro Gronchi, and Jaap Verweij on behalf of the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group, Italian Sarcoma Group, and Australasian Gastrointestinal Trials Group

VOLUME 35 · NUMBER 15 · MAY 20, 2017

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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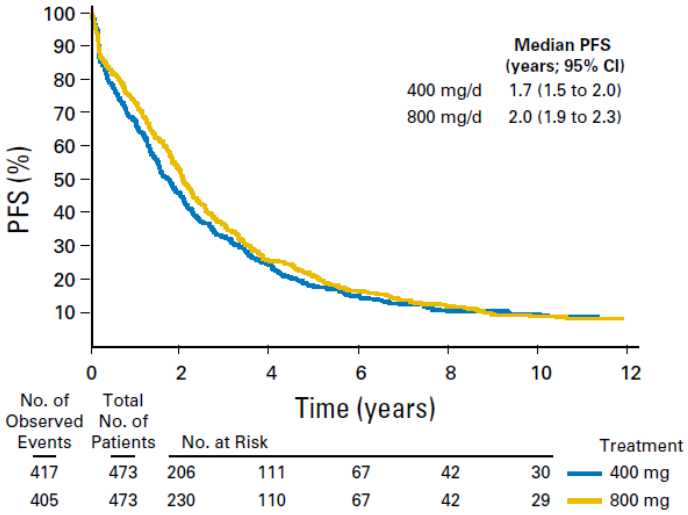
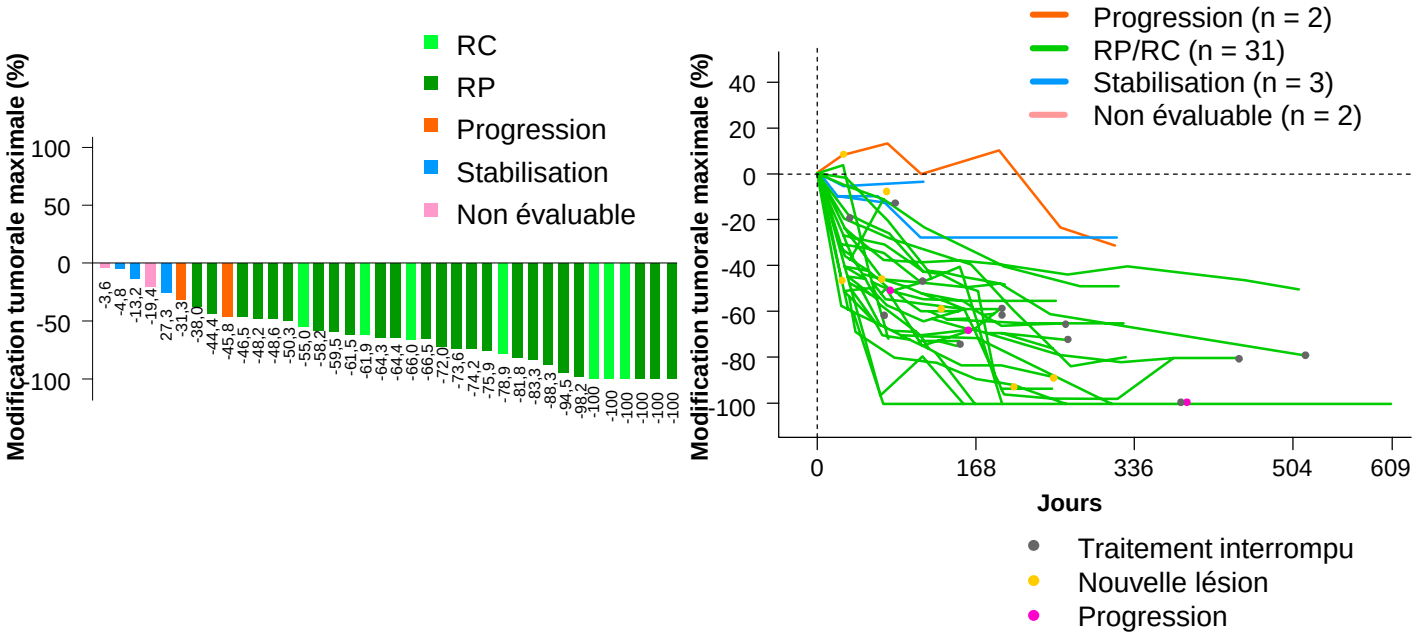


Étude de phase I atézolizumab + vémurafénib + cobimétinib (mélanomes BRAF V600 muté)



ASCO 2017 - Sullivan RJ et al., abstr. 3063

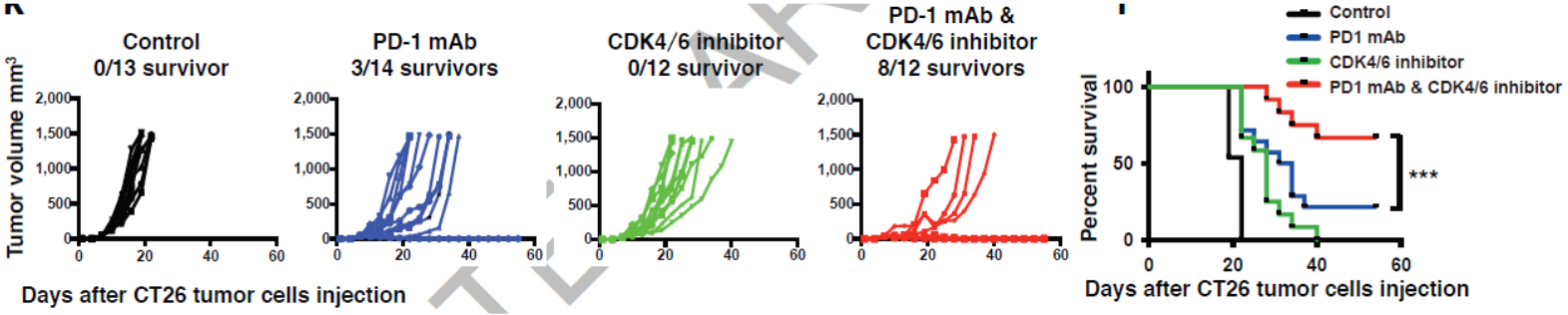
nature Accelerated Article Preview

LETTER

doi:10.1038/nature25015

Cyclin D–CDK4 kinase destabilizes PD-L1 via Cul3^{SPOP} to control cancer immune surveillance

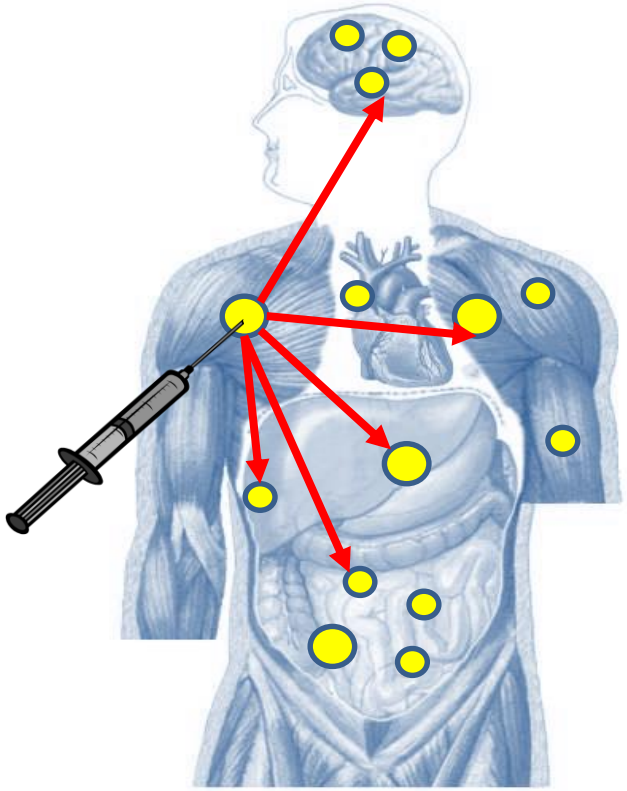
Jinfang Zhang, Xia Bu, Haizhen Wang, Yasheng Zhu, Yan Geng, Naoe Taira Nihira, Yuyong Tan, Yanpeng Ci, Fei Wu, Xiangpeng Dai, Jianping Guo, Yu-Han Huang, Caoqi Fan, Shancheng Ren, Yinghao Sun, Gordon J. Freeman, Piotr Sicinski and Wenyi Wei



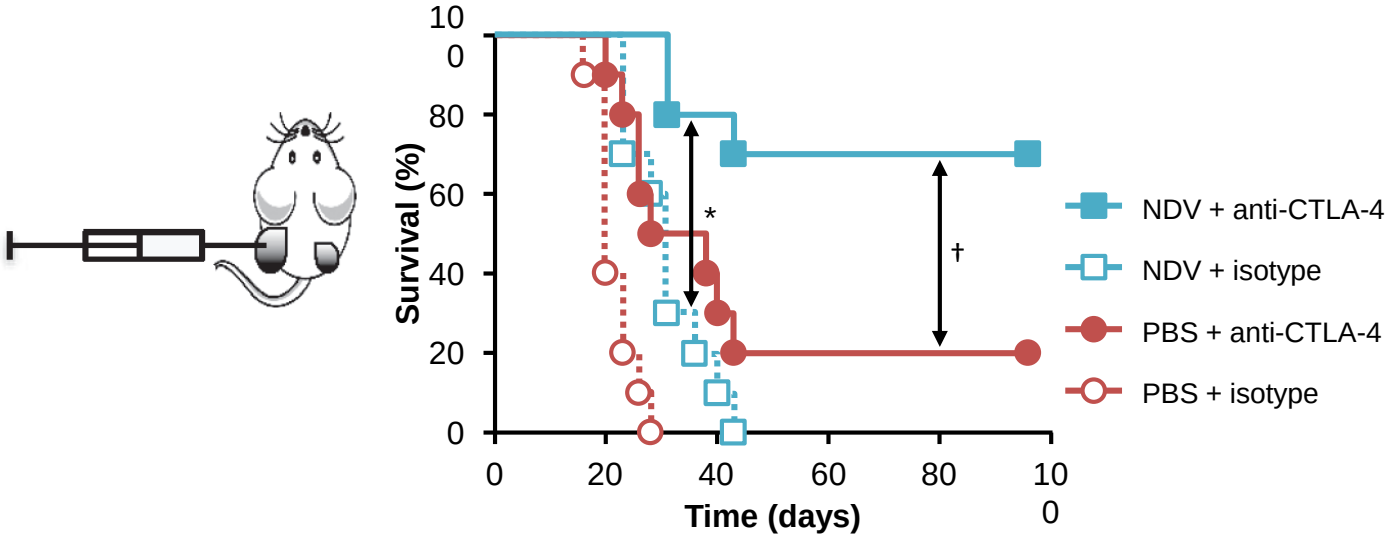
Les questions saillantes en 2018

- Quelles cibles?
- Quels patients?
- **Quelles combinaisons?**
  - Immunothérapies
  - Chimiothérapies cytotoxiques
  - Radiothérapie
  - Thérapies ciblées
- **Quelles modalités d’administration?**
- Quand appliquer?

in situ immunization



Localised oncolytic virotherapy can overcome systemic tumour resistance to immune checkpoint blockade therapy



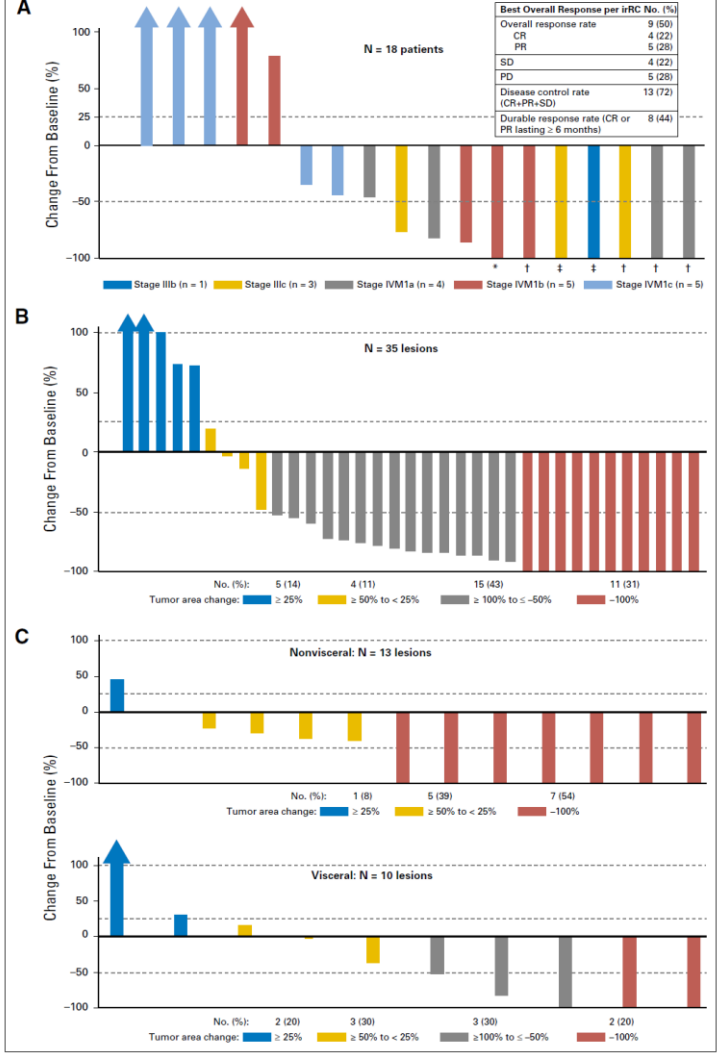
Zamarin D, et al. Sci Transl Med 2014;6,:226ra32.

Localized oncolytic therapy+ICP

- T-VEC + ipilimumab
- T –VEC+ pembrolizumab
- Cocksackie A21+ipilimumab

Talimogene Laherparepvec in Combination With Ipilimumab in Previously Untreated, Unresectable Stage IIIB-IV Melanoma

Igor Puzanov, Mohammed M. Milhem, David Minor, Omid Hamid, Ai Li, Lisa Chen, Michael Chastain, Kevin S. Gorski, Abraham Anderson, Jeffrey Chou, Howard L. Kaufman, and Robert H.I. Andtbacka



Les questions saillantes en 2018

- Quelles cibles?
- Quels patients?
- Quelles combinaisons?
  - Immunothérapies
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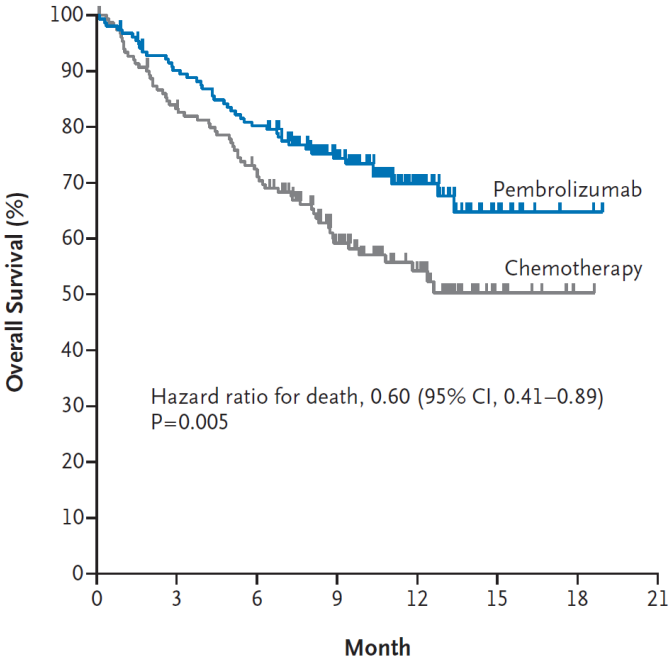
  - Radiothérapie
  - Thérapies ciblées
- Quelles modalités d'administration?
- **Comment et quand développer ces traitements?**

Anti-PD-1 1st line in PD-L1^{high} NSCLC



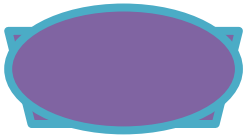
No. at Risk

Pembrolizumab	154	136	121	82	39	11	2	0
Chemotherapy	151	123	106	64	34	7	1	0

Reck M, et al. Pembrolizumab versus Chemotherapy for PD-L1–Positive NSCLC. N Engl J Med; 2016

Therapeutic clinical trial design is evolving

Basket
One gene: Different histologies



Umbrella
One histology: Different genes

Octopus
One study: Multiple arms

AcSé
Pembrolizumab

ACCÈS SÉCURISÉ AU PEMBROLIZUMAB POUR DES PATIENTS ADULTES PORTEURS DE CERTAINS TYPES DE CANCERS RARES

Sponsor N° : UC-0105/1612
EudraCT N° : 2016-002260-14

Médecin Coordonnateur :
Dr Christophe Massard – Gustave Roussy – Villejuif
Statisticien :
Pr Sylvie Chevret – Paris Diderot - Paris 7 – PARIS CEDEX 10

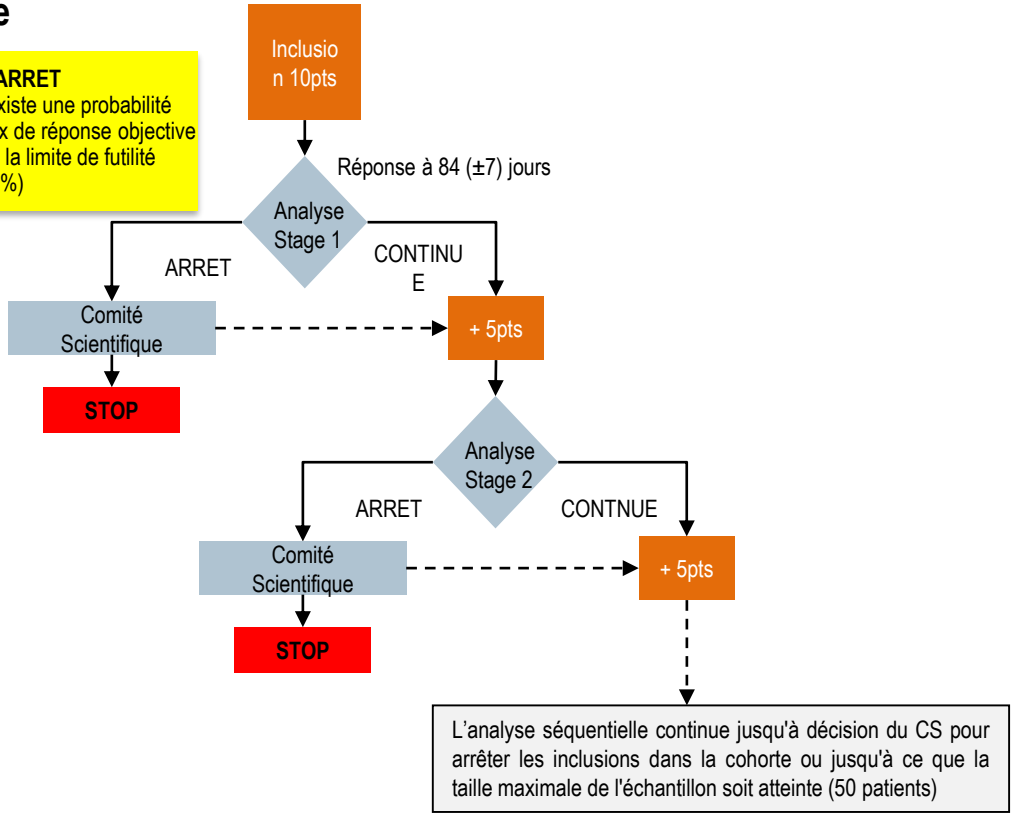
Cohortes

- Sarcome Rare **Pr Jean-Yves BLAY** NETSARC
- Cancer rare des ovaires **Pr Isabelle RAY-COQUARD** TMRO
- Lymphome primitif du système nerveux central **Pr Khê HOANG-XUAN** LOC
- Cancer rare de la thyroïde **Dr Martin SCHLUMBERGER** TUTHYREF
- Cancer neuroendocrinien rare **Pr Patricia NICCOLI** RENATEN
- Cancer des cellules germinales **Dr Christophe MASSARD**
- Lymphome des cellules T/Natural Killer (NK) **Dr Arnaud JACCARD**

Design statistique

- Essai adaptatif - approche Bayésienne en 2 étapes
- Par cohorte

REGLE D'ARRET
arrêt recommandé s'il existe une probabilité élevée (≥ 85 %) que le taux de réponse objective soit inférieur ou égal à la limite de futilité (p0=10%)



Les questions saillantes en 2018

- Quelles cibles?
- Quels patients?
- Quelles combinaisons?
- Quelles modalités d’administration?
- Comment évaluer?
- Quand appliquer?
- **Peut on les offrir en routine aux patients?**

Médicaments accessibles?

Pembrolizumab ligne 1 dans les cancers bronchiques non a petite cellules
Ipilimumab nivolumab pour les melanome pdl1 0 ou les meta cerebrales de melanome
Pembrolizumab dans les cancers MSI (5% des cancers)
Nivolumab, pembrolizumab dans les maladies de Hodgkin
Mifamurtide dans les osteosarcomes non métastatique en premiere ligne

Cyramza dans les cancers oesogastriques et dans les cancers coliques et bronchiques en deuxième ligne
Daratumumab dans le myélome multiple
Bevacizumab dans les cancers du cols de l'utérus
NAB paclitaxel dans le cancer du pancreas avancé

Carfilzomib , dans le myélome multiple en seconde ou troisième ligne avec la dexamethasone
Nintedanib dans les adénocarcinomes pulmonaires en seconde ligne en combinaison avec le docetaxel (AMM européenne)
Caelyx dans les maladies de Hodgkin
223R pour les cancers de prostate métastatiques osseux
Trabectedine : sarcomes

Conclusions

- Facteurs prédictifs
  - Génomiques, immunologiques, microbiote,…
- Nouvelles cibles
  - Monothérapies?
- Combinaisons
  - Quelle stratégie pour chosir les combo et les patients
- Quels essais cliniques?
- Accès

DISCUSSION

Avec le soutien du

GFCO Groupe Francophone de Cytogénomique Oncologique

AstraZeneca