The emerging role of immunology in sarcoma

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Topics

- **Immunotherapy of cancers**
- Immune status and immunotherapy of sarcomas

Immunotherapy of cancers
A brief summary

- Coley's toxin(1890-1930)
- BCG therapy (1960-1970)
- Allogeneic stem cell transplantation
- Local BCG therapy (superficial bladder cancer) (1980+)
- Interferon alpha (1980)
- Interleukin 2 (1980-1990)
- TNF alpha (1990+)
- Interferon gamma, IL-4, IL-12… (1990)
- Imiquimod local (2000+)
- Passive immunotherapy (ADCC), anti CD20, HER1, HER2 (2000+)
- Immune checkpoint (2011+)
- CAR T cells (2012+)

William Coley

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES.

MAY, 1893.

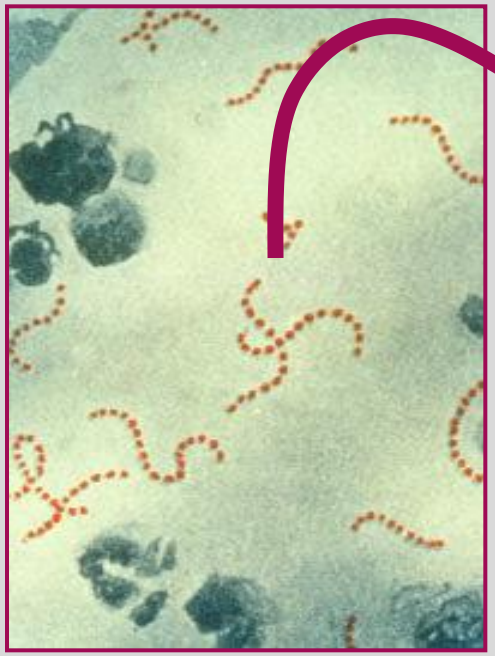
THE TREATMENT OF MALIGNANT TUMORS BY REPEATED INOCULATIONS OF ERYSIPELAS: WITH A REPORT OF TEN ORIGINAL CASES.[1]

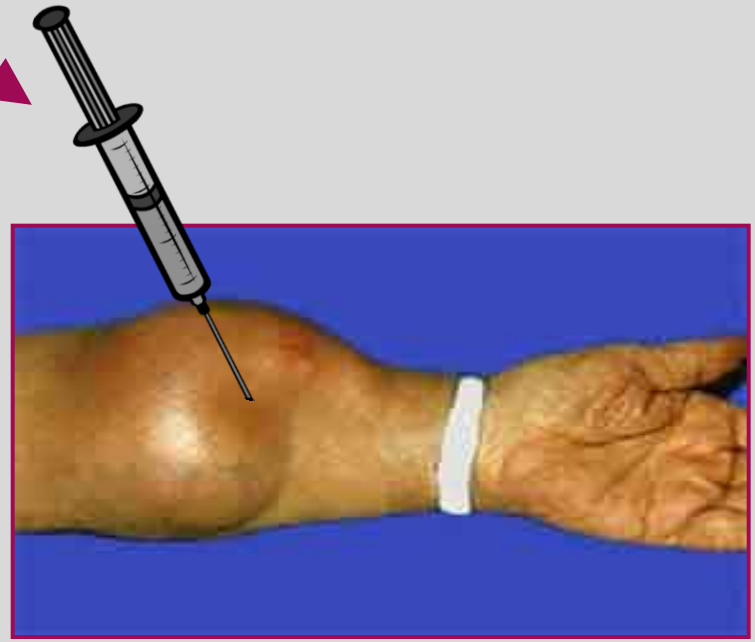
By William B. Coley, M.D.,

Assistant Surgeon to the Hospital for Ruptured and Crippled; Instructor in Surgery in the Post-Graduate Medical School, New York.

"… on May 2, 1891, i inoculated a case of sarcoma"

"At the end of two weeks, the tumor had disappeared"





Streptococcus pyogenes

Immunosurveillance of cancer ?

Cancer in HIV+	HR
Kaposi	310
NHL	112
Anal cancer	32
Hodgkin	7.6
Other sarcomas	7.2 (1993); 3,3 (2001)
Epidermoïd Ca any site	6.8
Cervix	2.9
Lung adenocarcinoma	2.5
Non AIDS defining cancers	1.9
Breast Ca	<1
Colorectal Ca	<1

Frisch et al JAMA 285, 1736 ; Boshoff C, et al. Nat Rev Cancer 2002

Cytokines for cancer immunotherapy

- Interleukin 2 & Interferon alpha
  - Few responses
  - Impact on median PFS/OS vs BSC unclear
  - 3-5% very long term responders (cure?)

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

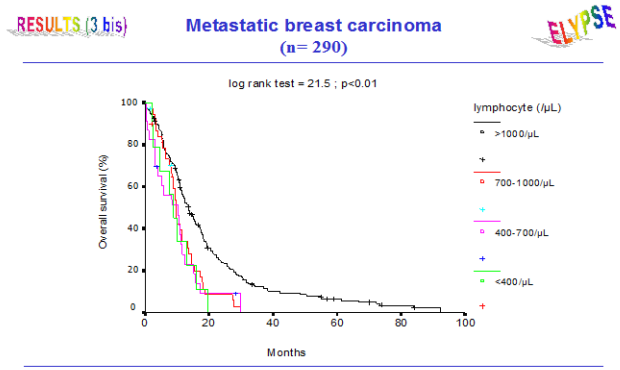
3 - Grade 4 thrombopenia
(Ray-Coquard et al Blood 1998)
- Plt < 150
- CT HR
- PS > 1
- Lymphopenia

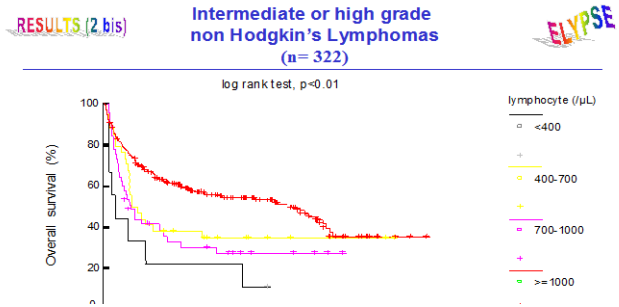
Toxic death

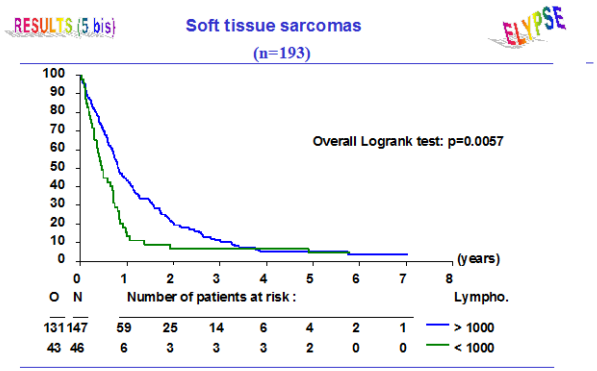
Death at 31 d
(Ray et al Br J Cancer 2001)
- Lymphopenia
- PS > 1

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

Survival







Immune cell infiltrates and prognosis

Meta-analysis of 124 published articles

Tumor	CD8+ CD45RO+ LT	LT TH1
Melanoma	Favorable	
HN	Favorable	
Breast	Favorable	Favorable
Bladded	Favorable	
Ovarian	Favorable	Favorable
Oesophagus	Favorable	Favorable
Colorectal	Favorable	Favorable
Renal	Favorable Poor	Favorable
Prostate	Favorable	
Lung	Favorable	
Pancreas	Favorable	
Cervix		Favorable
Anal Carcinoma		
C		
Carcinome hépatocellulaire	Favorable Poor	Favorable
Gastric		Favorable
Medulloblastome		Favorable
Merkel	Favorable	
Urothelial Ca	Favorable	
Follicular and Hodgkins lymphoma	Favorable	

Fridman W, et al. Nature Reviews Cancer 2012;12:298-306.

Tumor escape

Operated by many mechanisms

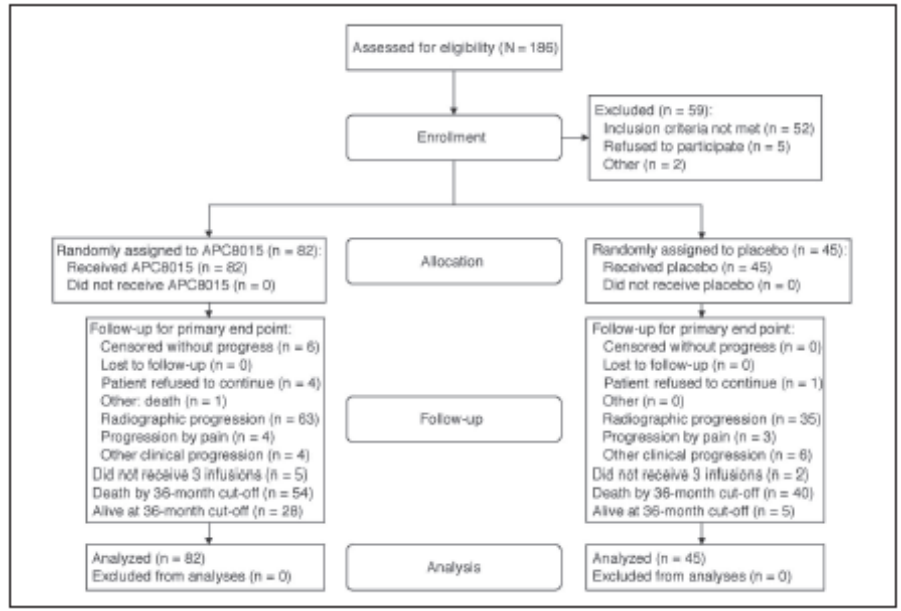
- Cells
  - T reg cells ($CD4^{+}CD25^{+}FoxP3^{+}$), MDSCs, M2 macrophages, tolerogenicDCs
- Cytokines and mediators
  - TGFb, VEGF, MCSF, IL-6, PGE2, Arginase, IDO, Adenosine
- Immune checkpoints
  - PD1, CTLA-4, TIM-3, LAG-3, KIR, FAS,

Immunotherapy of cancers

- Vaccinations
- Immune check point inhibitors
- M2 macrophages
- Lymphopenia
- CARs

Placebo-Controlled Phase III Trial of Immunologic Therapy with Sipuleucel-T (APC8015) in Patients with Metastatic, Asymptomatic Hormone Refractory Prostate Cancer

Eric J. Small, Paul F. Schellhammer, Celestia S. Higano, Charles H. Redfern, John J. Nemunaitis, Frank H. Valone, Suleman S. Verjee, Lori A. Jones, and Robert M. Hershberg



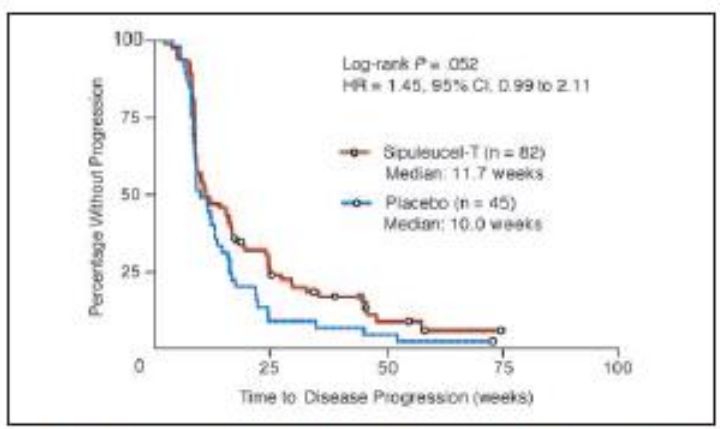


Fig 2. Primary end point, time to disease progression (intent-to-treat population). HR, hazard ratio.

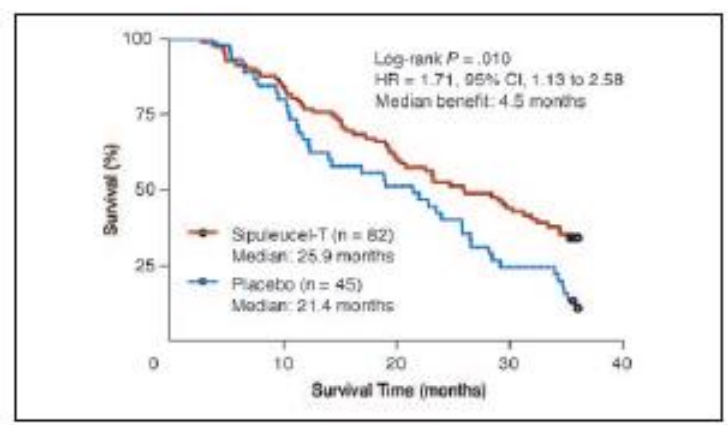
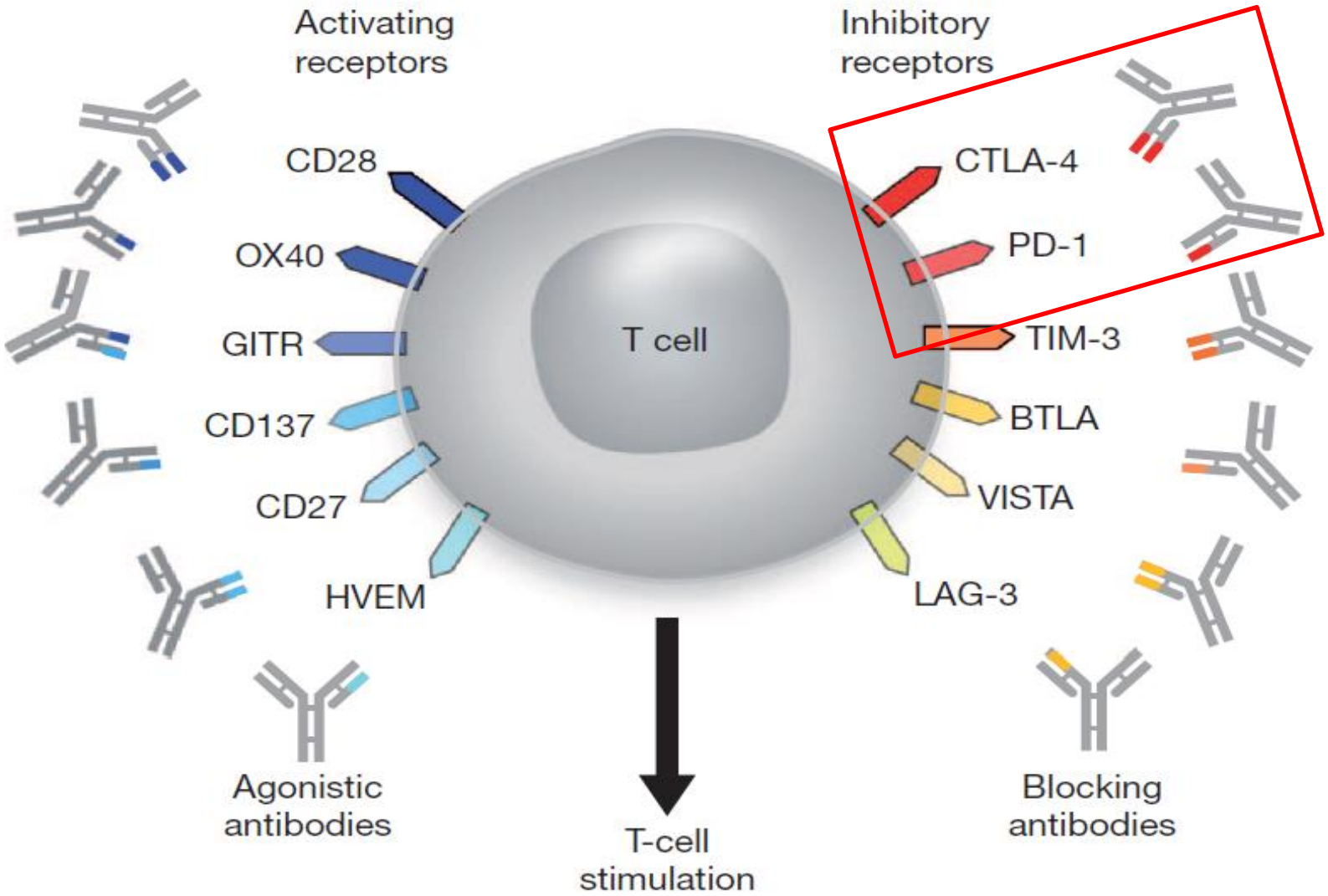


Fig 3. Final overall survival (intent-to-treat population). HR, hazard ratio.

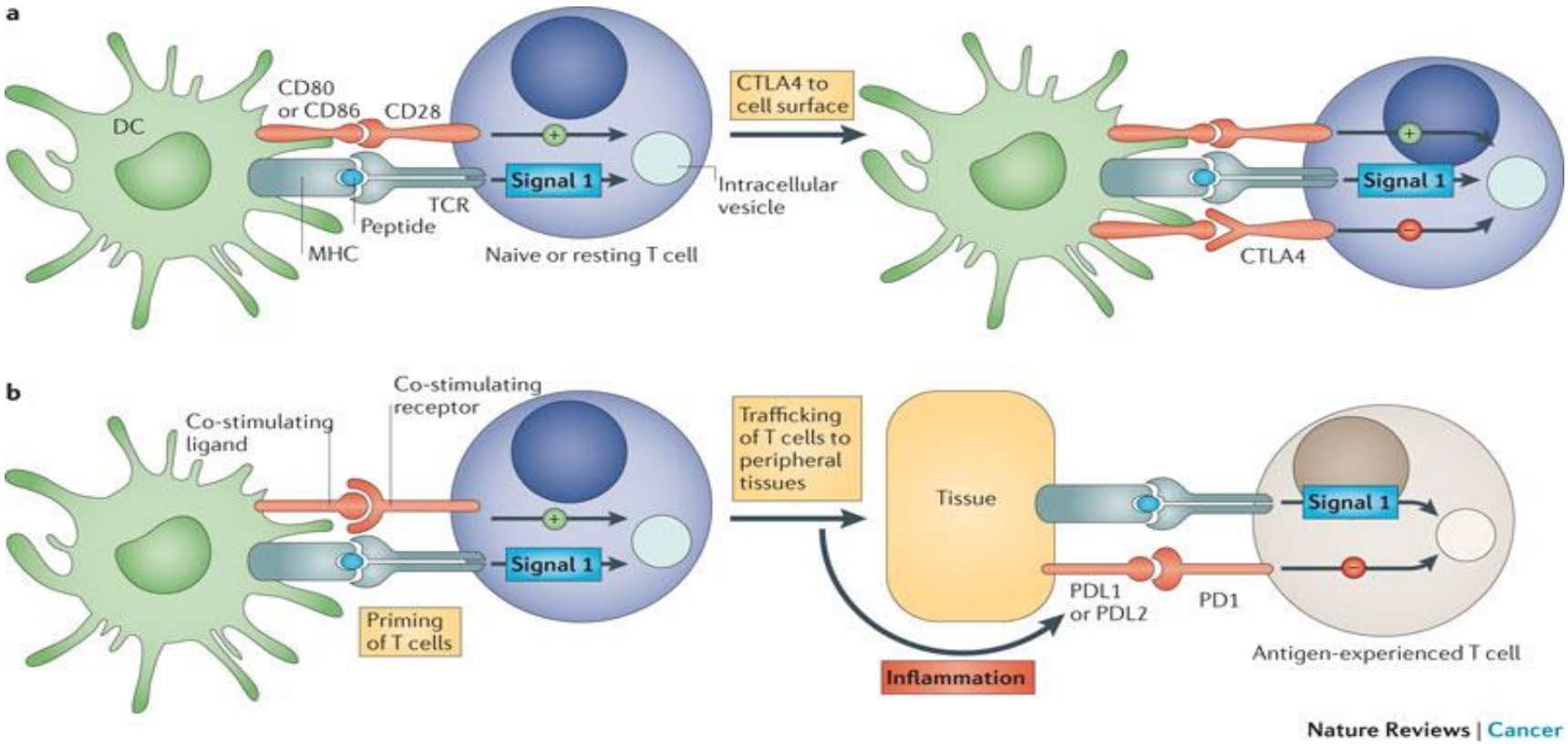
Immune checkpoints and Ab



Immune checkpoints (negative regulators of T cells)

- CTLA4/B7.1-B7.2 pathway
- PD1/PDL1 pathway

⇒Clinical trials with anti-CTLA4 antibodies (Ipilimumab)
⇒Clinical trials with anti-PD1/PDL1 antibodies



Pardoll D, Nat Rev Cancer 2012

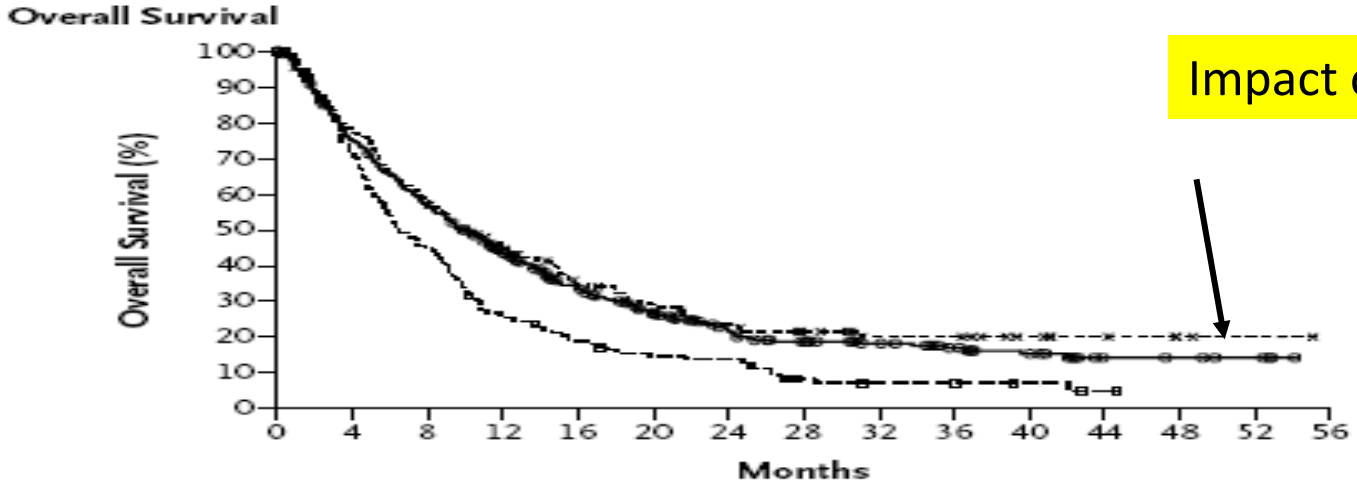
Ipilimumab (anti-CTLA4): The major benefit is in durable tumor regressions

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian Quirt, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.D., Axel Hoos, M.D., Ph.D., and Wal r J. Urba, M.D., Ph.D.

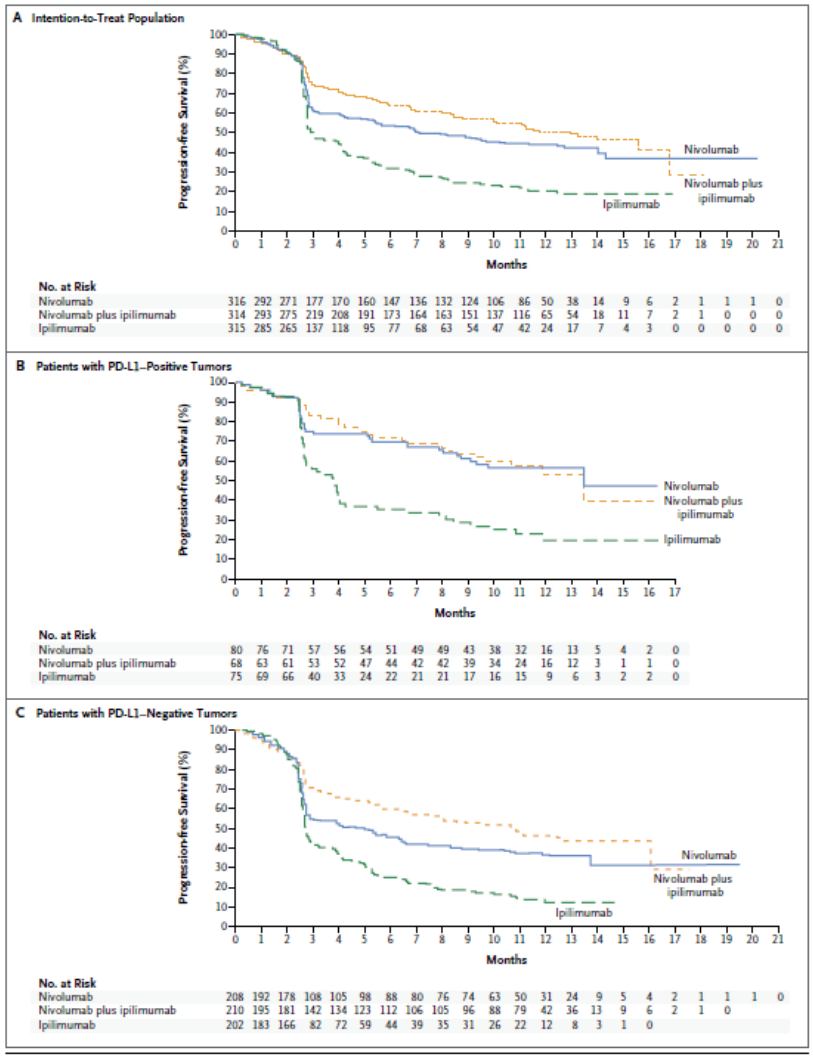


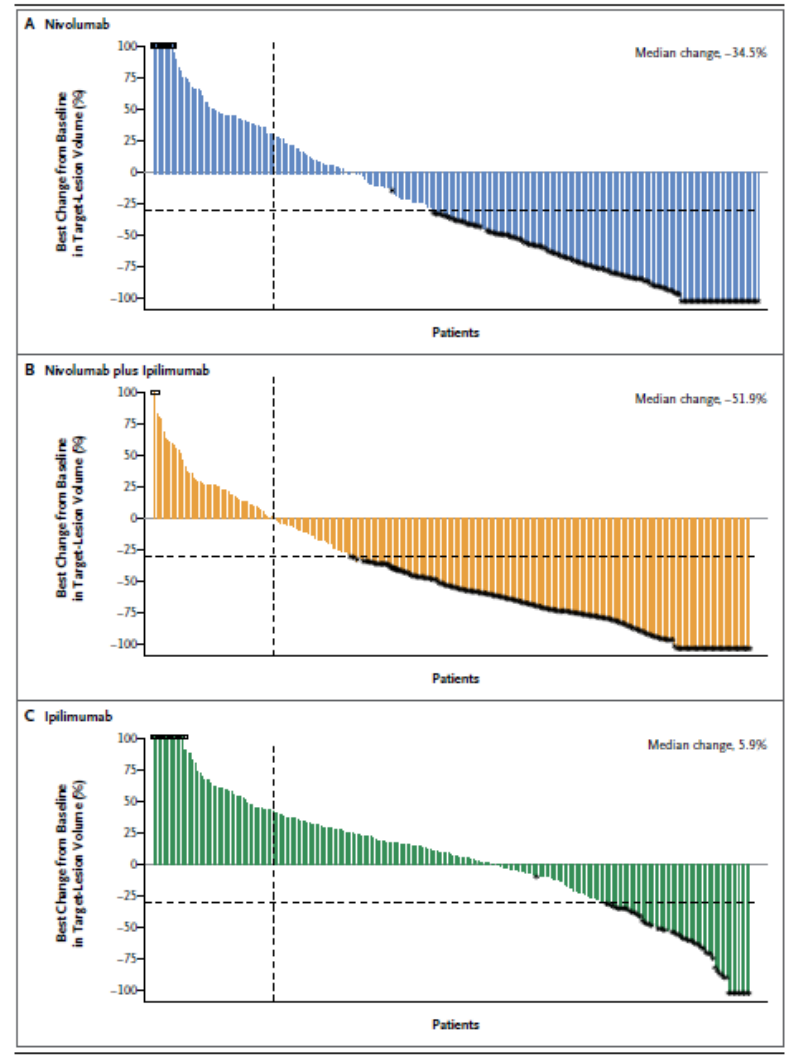
Impact on the tail of the curve!

10.1056/NEJMoa1003466 NEJM.ORG

Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.J. Grob, C.L. Cowey, C.D. Lao, D. Schadendorf, R. Dummer, M. Smylie, P. Rutkowski, P.F. Ferrucci, A. Hill, J. Wagstaff, M.S. Carlino, J.B. Haanen, M. Maio, I. Marquez-Rodas, G.A. McArthur, P.A. Ascierto, G.V. Long, M.K. Callahan, M.A. Postow, K. Grossmann, M. Sznol, B. Dreno, L. Bastholt, A. Yang, L.M. Rollin, C. Horak, F.S. Hodi, and J.D. Wolchok





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

Julie Brahmer, M.D., Karen L. Reckamp, M.D., Paul Baas, M.D., Lucio Crinò, M.D., Wilfried E.E. Eberhardt, M.D., Elena Poddubskaya, M.D., Scott Antonia, M.D., Ph.D., Adam Pluzanski, M.D., Ph.D., Everett E. Vokes, M.D., Esther Holgado, M.D., Ph.D., David Waterhouse, M.D., Neal Ready, M.D., Justin Gainor, M.D., Osvaldo Arén Frontera, M.D., Libor Havel, M.D., Martin Steins, M.D., Marina C. Garassino, M.D., Joachim G. Aerts, M.D., Manuel Domine, M.D., Luis Paz-Ares, M.D., Martin Reck, M.D., Christine Baudelet, Ph.D., Christopher T. Harbison, Ph.D., Brian Lestini, M.D., Ph.D., and David R. Spigel, M.D.

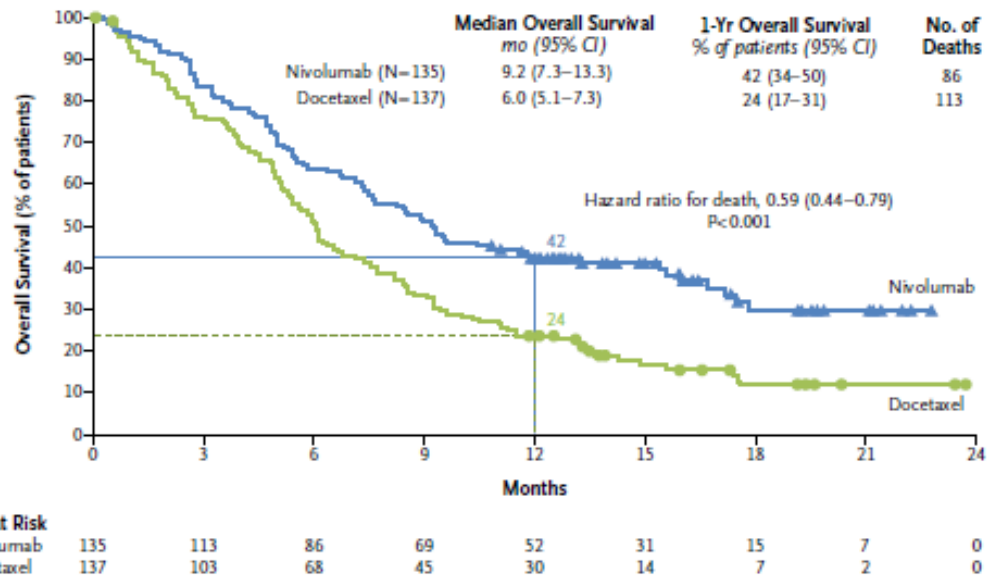
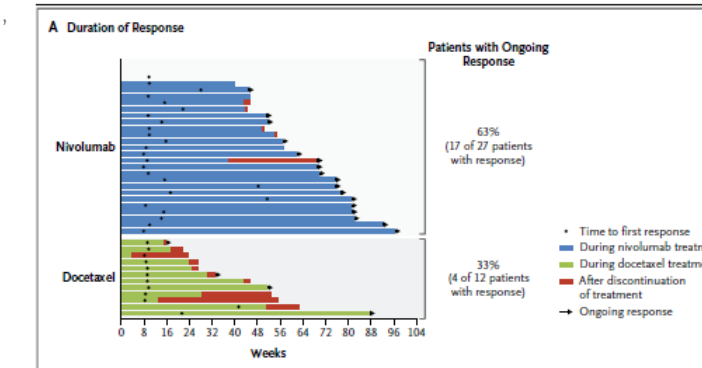
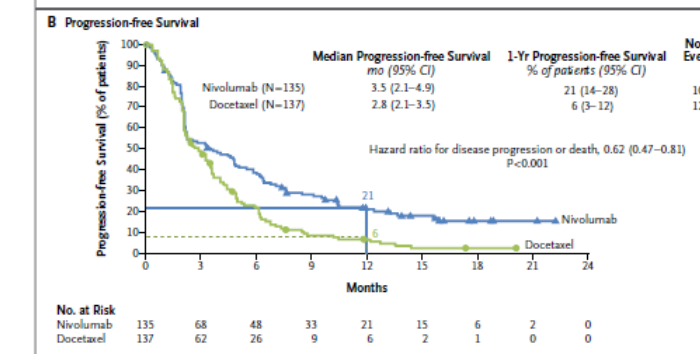
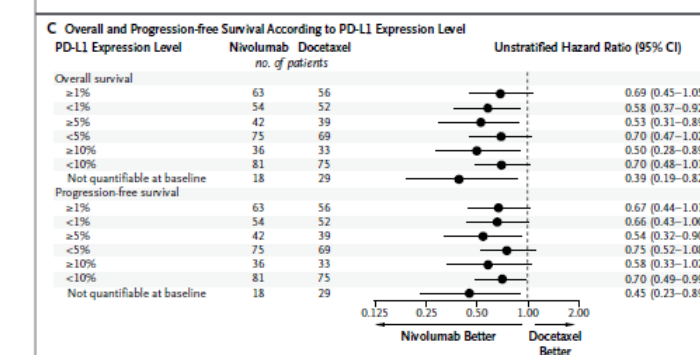


Figure 1. Kaplan–Meier Curves for Overall Survival.

The analysis included all the patients who underwent randomization. Symbols indicate censored observations, and horizontal lines the rates of overall survival at 1 year.

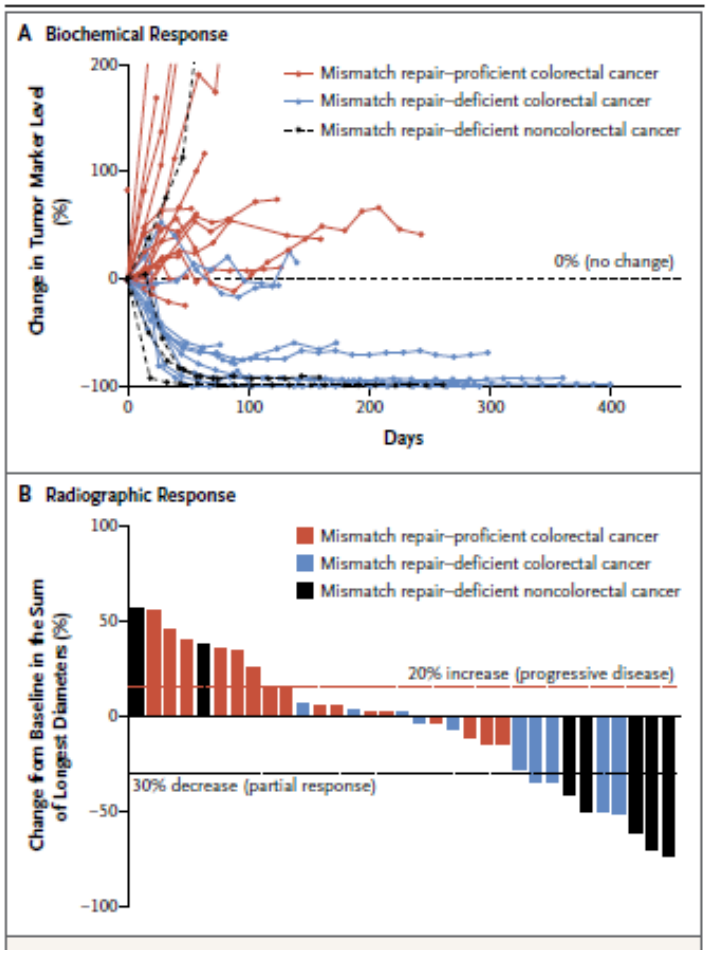


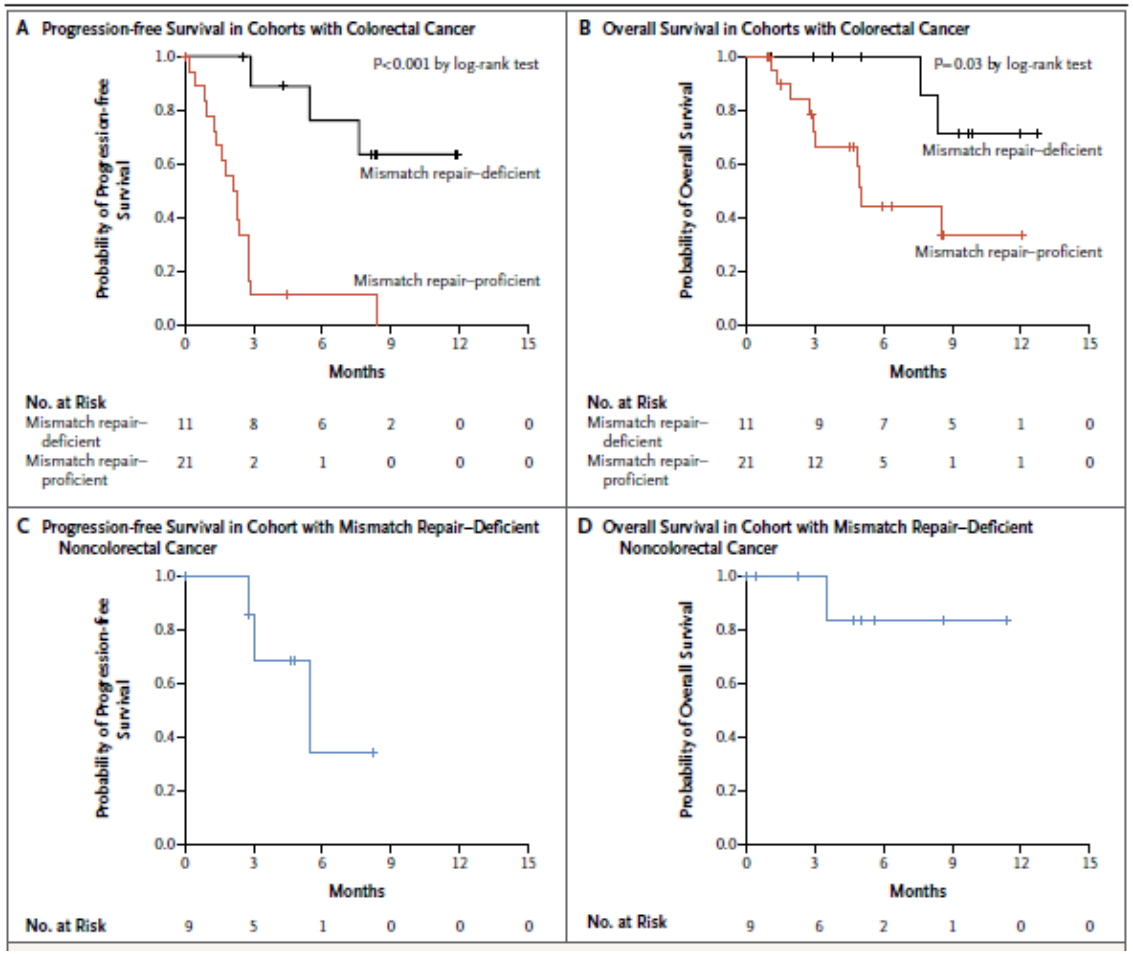




PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.





doi:10.1038/nature13904

MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer

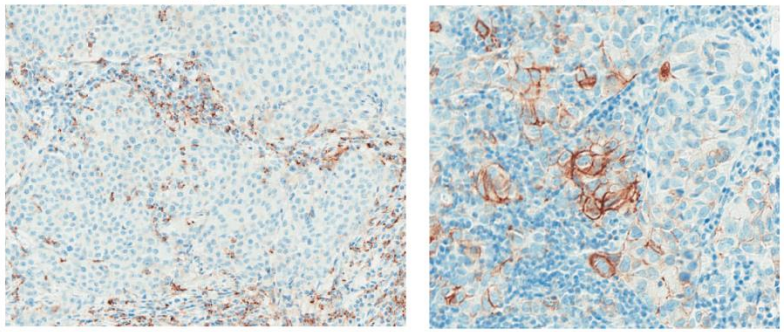
Thomas Powles[1], Joseph Paul Eder[2], Gregg D. Fine[3], Fadi S. Braiteh[4], Yohann Loriot[5], Cristina Cruz[6], Joaquim Bellmunt[7], Howard A. Burris[8], Daniel P. Petrylak[2], Siew-leng Teng[3], Xiaodong Shen[3], Zachary Boyd[3], Priti S. Hegde[3], Daniel S. Chen[3] & Nicholas J. Vogelzang[9]

a

PD-L1 prevalence in UBC tumours by IHC

n = 205	PD-L1-positive tumour-infiltrating immune cells (no. of specimens (%))	PD-L1-positive tumour cells (no. of specimens (%))
IHC 3	18 (9)	14 (7)
IHC 2	37 (18)	8 (4)
IHC 1	89 (43)	37 (18)
IHC 0	61 (30)	146 (71)

b



Tumour-infiltrating immune cells Tumour cells

c

Tumour-infiltrating immune cells and objective response rates

	Objective response rate n (%)	Stable disease n (%)	Progressive disease n (%)
IHC 2/3 (n = 30)	13 (43.3) (95% CI: 25.5–62.6)	8 (26.7)	8 (26.7)
IHC 3 (n = 10)	5 (50.0) (95% CI: 22.2–77.8)	2 (20.0)	3 (30.0)
IHC 2 (n = 20)	8 (40.0) (95% CI: 20.9–63.9)	6 (30.0)	5 (25.0)
IHC 0/1 (n = 35)	4 (11.4) (95% CI: 4.0–26.3)	13 (37.1)	13 (37.1)
IHC 1 (n = 23)	3 (13.0) (95% CI: 3.7–31.7)	8 (34.8)	8 (34.8)
IHC 0 (n = 12)	1 (8.3) (95% CI: 0.4–34.9)	5 (41.7)	5 (41.7)

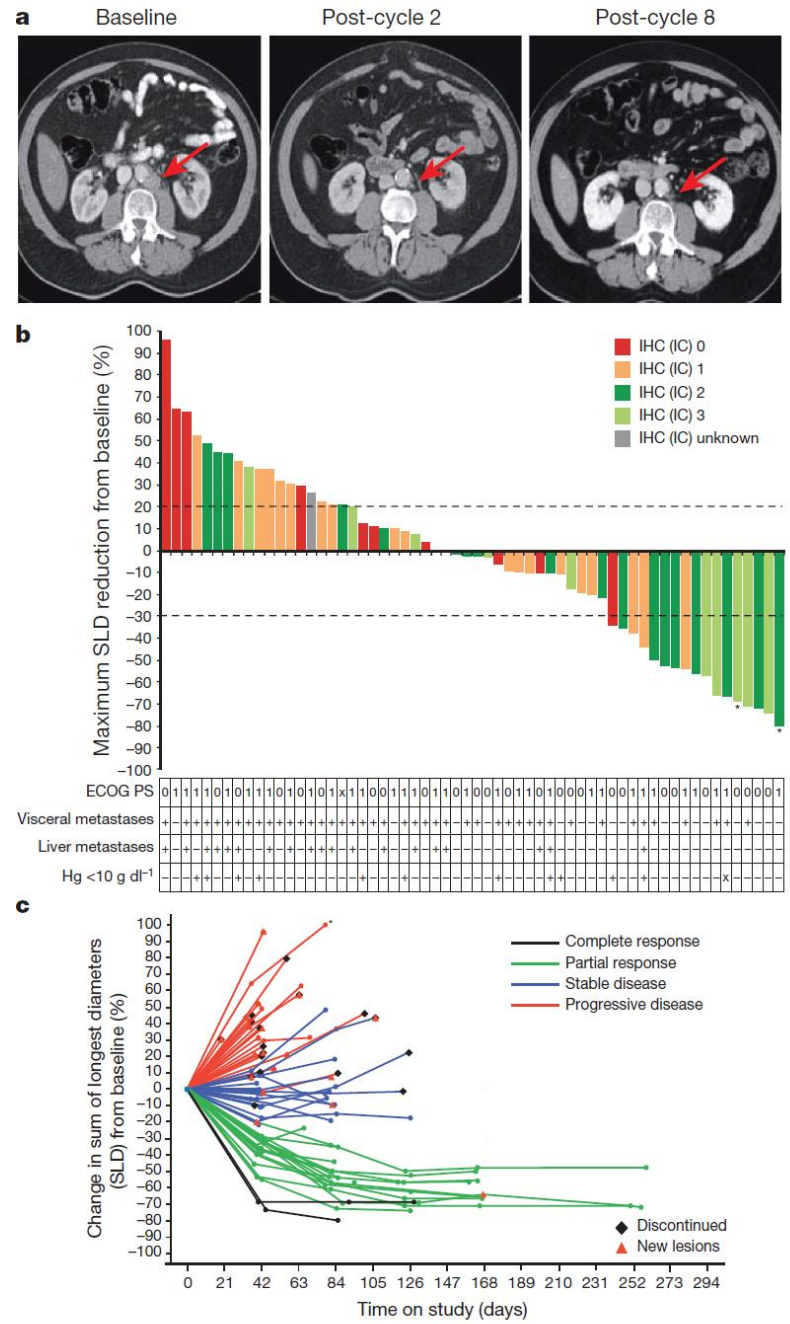


Figure 2 | MPDL3280A anti-tumour activity in patients with UBC.

Response rates PD-1 / PD-L1

	anti-PD-1			anti-PD-L1		
	Nivolumab BMS–936558	Pembrolizumab MK 34-75	Pidilizumab CT-011	BMS-936559 MDX-1105	MEDI 4736	MPDL 3280 A
Melanoma	**32%** (34/107)	**34 %** (124/365)	**6%** (5/85)	**17 %** (9/52)		**29%** (11/38)
NSCLC	**17%** (22/129)	**20%** (39/194)		**16%** (9/56)	**16 %** (9/58)	**23%** (12/53)
RCC	**21%** (35/168)			**10%** (5/49)		**13%** (6/47)
Urothelial						**26%** (17/65)
HN		**20%** (11/56)			**14%** (3/22)	
Ovarian	**17%** (3/18)			**6%** (1/17)		
	Hodi ASCO 2014 Brahmer ASCO 2014 Motzer ASCO 2014 Hamanishi ASCO 2014	Ribas ASCO 2014 Rivzi ASCO 2014 Seiwert ASCO 2014	Atkins ASCO 2014	Brahmer et al. 2012	Brahmer ASCO 2014 Segal ASCO 2014	Hamid, Soria, Cho et al.2013, Powles ASCO 2014

Biomarkers of response

- PD1/ PDL1 expression on tumor and/or infiltrating cells
- PD1/ PDL1 expression before and/or after treatment
- CD8 Ly in tumors, on invasion front and close to tumor cells.
- Antigen tumor load

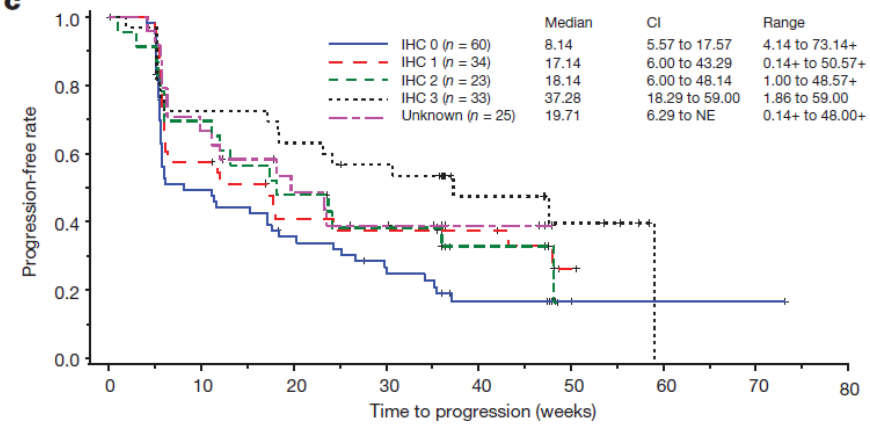
a Activity of MPDL3280A in NSCLC IHC (IC)

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



Number at risk

IHC 0	60	29	20	14	7	2	1	1	0
IHC 1	34	19	12	11	9	1	0	0	0
IHC 2	23	16	11	8	3	0	0	0	0
IHC 3	33	23	20	17	8	5	0	0	0
Unknown	25	16	10	7	3	0	0	0	0

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	3/12 (42)	2/12 (17)
Best response of PD	1/11 (9)	4/11 (36)

b

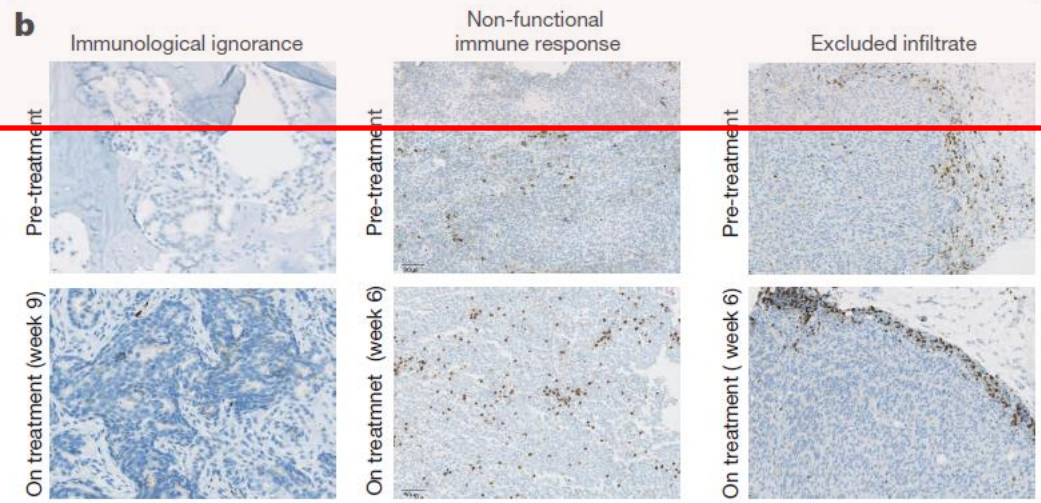
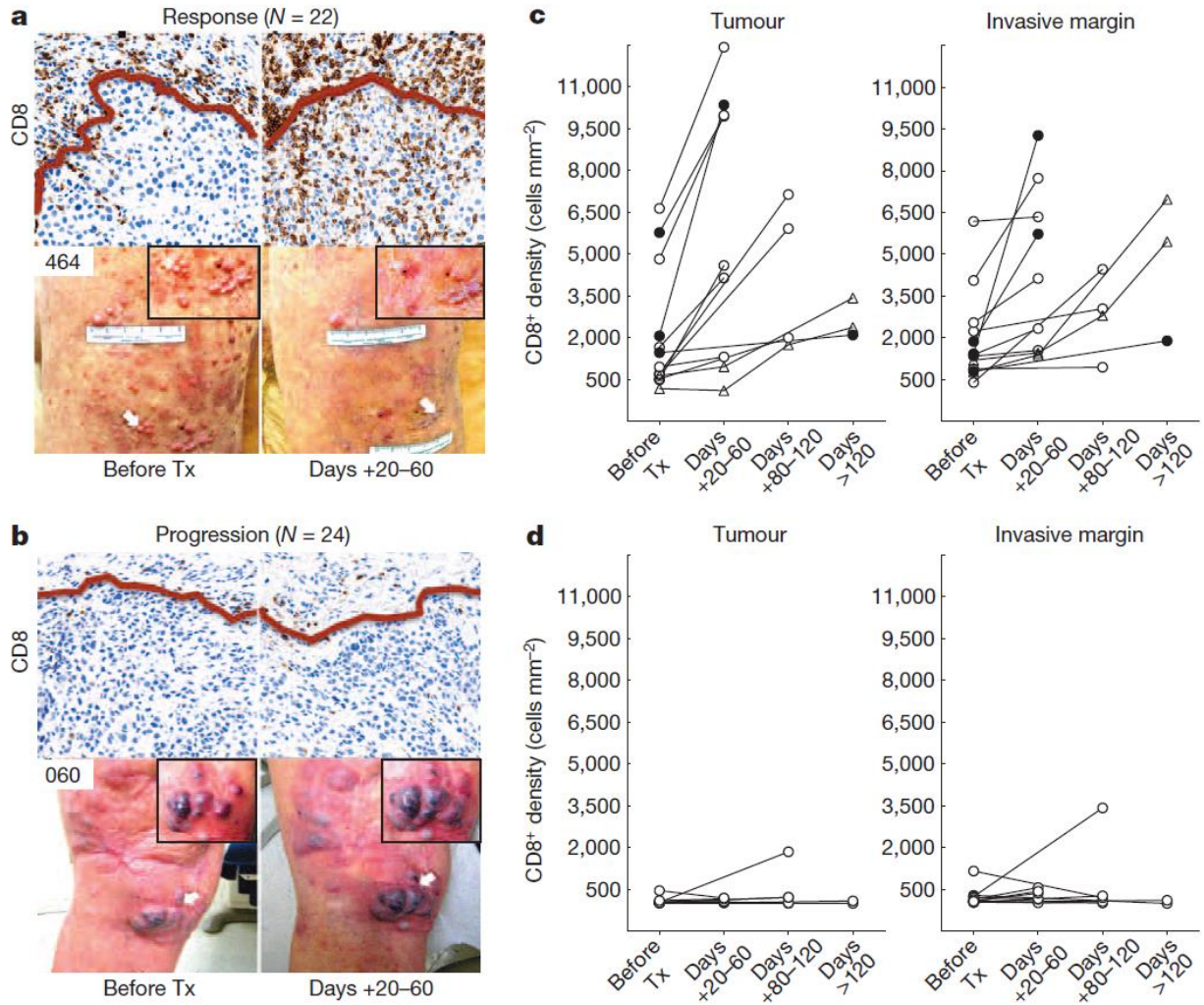


Figure 4 | Biomarker status and response to MPDL3280A. a, Table

doi:10.1038/nature13954

PD-1 blockade induces responses by inhibiting adaptive immune resistance

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

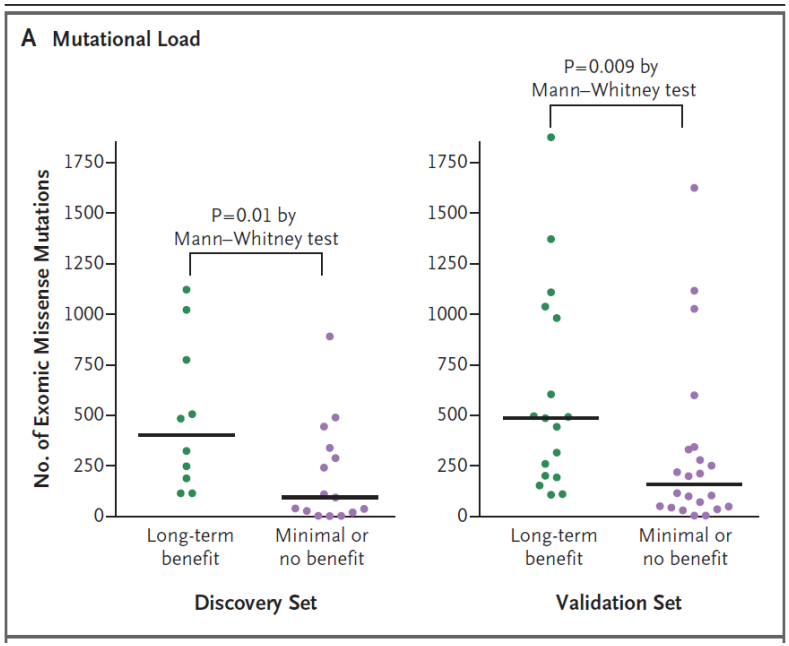


Neoantigen load and response to CTLA-4 Ab

ORIGINAL ARTICLE

Genetic Basis for Clinical Response to CTLA-4 Blockade in Melanoma

Alexandra Snyder, M.D., Vladimir Makarov, M.D., Taha Merghoub, Ph.D., Jianda Yuan, M.D., Ph.D., Jesse M. Zaretsky, B.S., Alexis Desrichard, Ph.D., Logan A. Walsh, Ph.D., Michael A. Postow, M.D., Phillip Wong, Ph.D., Teresa S. Ho, B.S., Travis J. Hollmann, M.D., Ph.D., Cameron Bruggeman, M.A., Kasthuri Kannan, Ph.D., Yanyun Li, M.D., Ph.D., Ceyhan Elipenahli, B.S., Cailian Liu, M.D., Christopher T. Harbison, Ph.D., Lisu Wang, M.D., Antoni Ribas, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., and Timothy A. Chan, M.D., Ph.D.



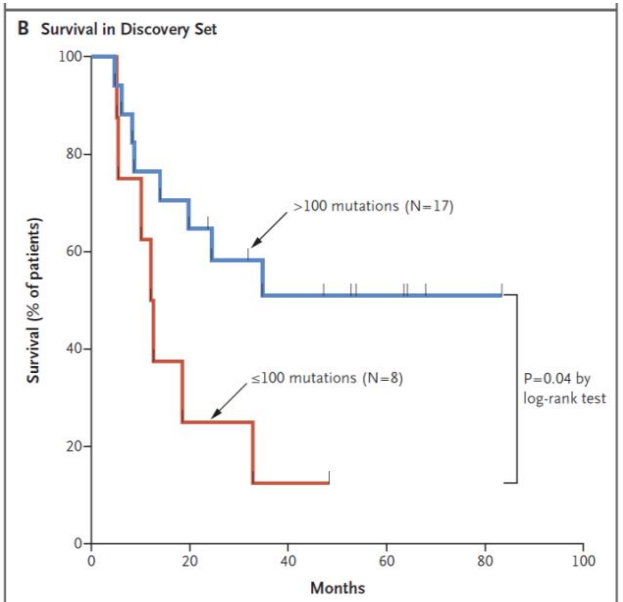
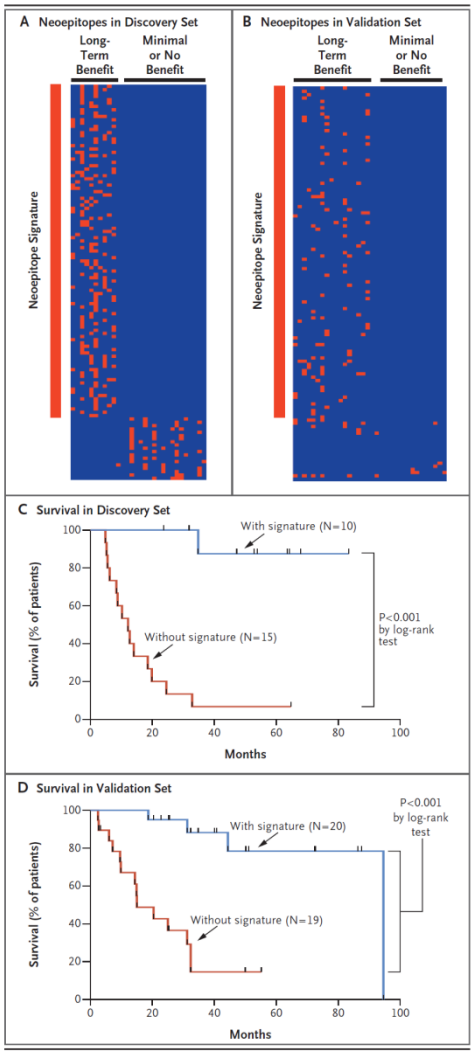
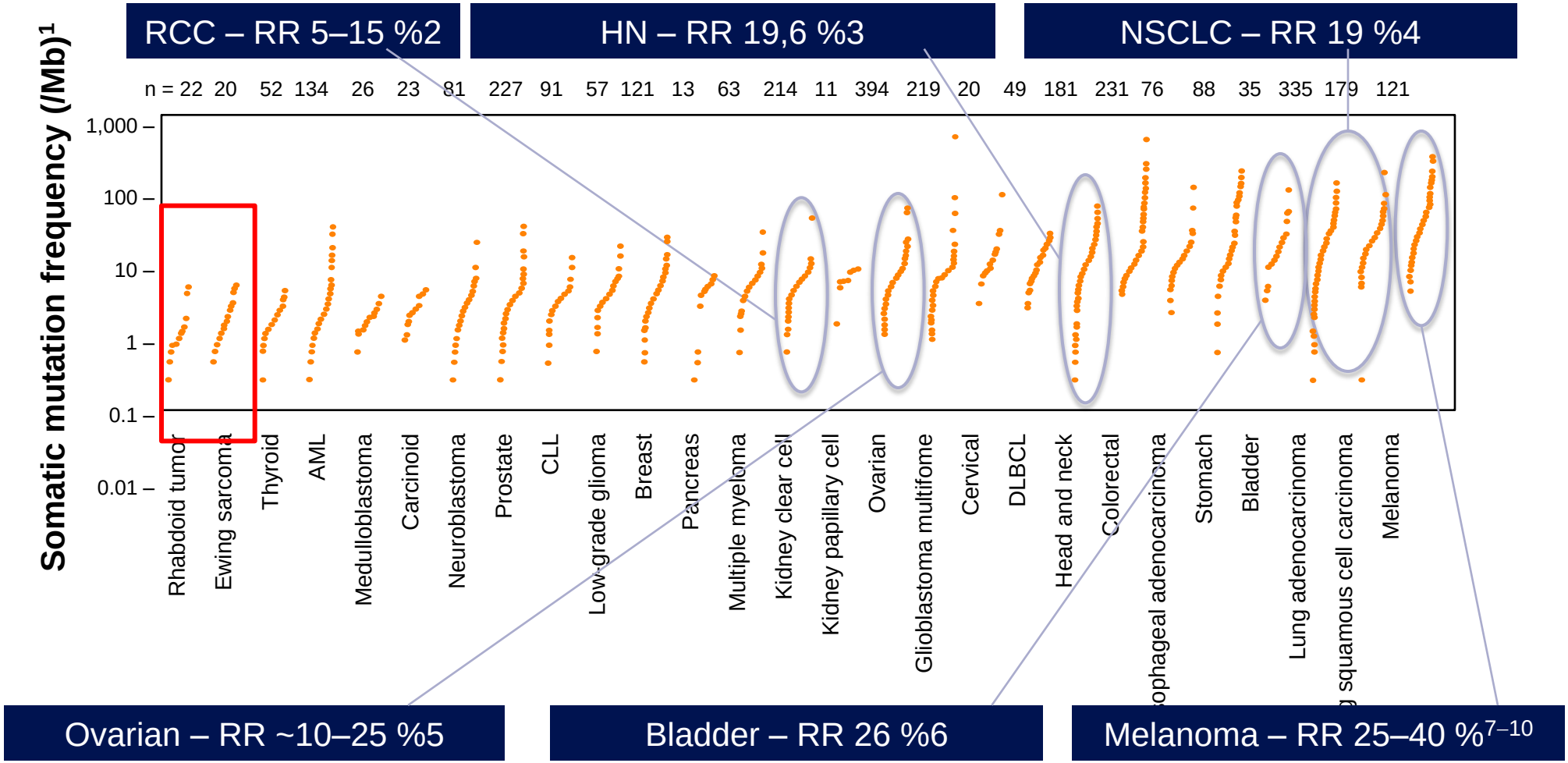


Figure 2. Mutational Landscape of Tumors According to Clinical Benefit from Ipilimumab Treatment.



Mutations load and reponse to immunotherapy



•1. Lawrence MS, et al. *Nature* 2013;499:214–218; 2. Fosså SD, et al. *Cancer* 2004;101:533–40[a]; 3. Siewert TY, et al. Oral presentation at ASCO 2014 (abstr. 6011)[b]; 4. Schiller JH, et al. *N Engl J Med.* 2002;346: 92-98[c]; 5. Vargas-Hernández VM, et al. *Gland Surgery*, 2013 (published ahead of print) [c]; 6. De Santis M, et al. *J Clin Oncol.* 2009;27:5634-5639[d]; 7. Jang S, Atkins MB. *Clin Pharmacol Ther*. 2014;95:24-31; 8. Hamid O, et al. *N Engl J Med* 2013; 369:134-144[e]; 9. Topalian SL, et al. *N Engl J Med*. 2012;366:2443–2454[f]; 10. Hamid O, et al. *J Clin Oncol* 2013; 31(suppl; abstr 9010)[g].

M2 macrophage infiltration and prognosis of cancer

- In breast and pancreatic cancer,infiltrating CD68+ or CD163+ tumor-associated macrophages (TAMs) correlate with poor outcome

- The tumor-promoting function of TAMs is based on:
  - secretion of proangiogenic and growth factors,
  - to potently suppress T cell effector function
  - by releasing immunosuppressive cytokines

- Macrophages exerting these protumorigenic functions are also termed M2-type macrophages, in contrast to the antitumorigenic M1 subtype

- Phenotype: CD163+, and expressing MCSFR , CD115

References: DeNardo et al., 2011; Kurahara et al., 2011; Shabo et al., 2008; (Wynn et al., 2013; Biswas and Mantovani 2010; Gordon and Martinez 2010; Hoves et al.,2006; Mantovani et al., 2002.

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]

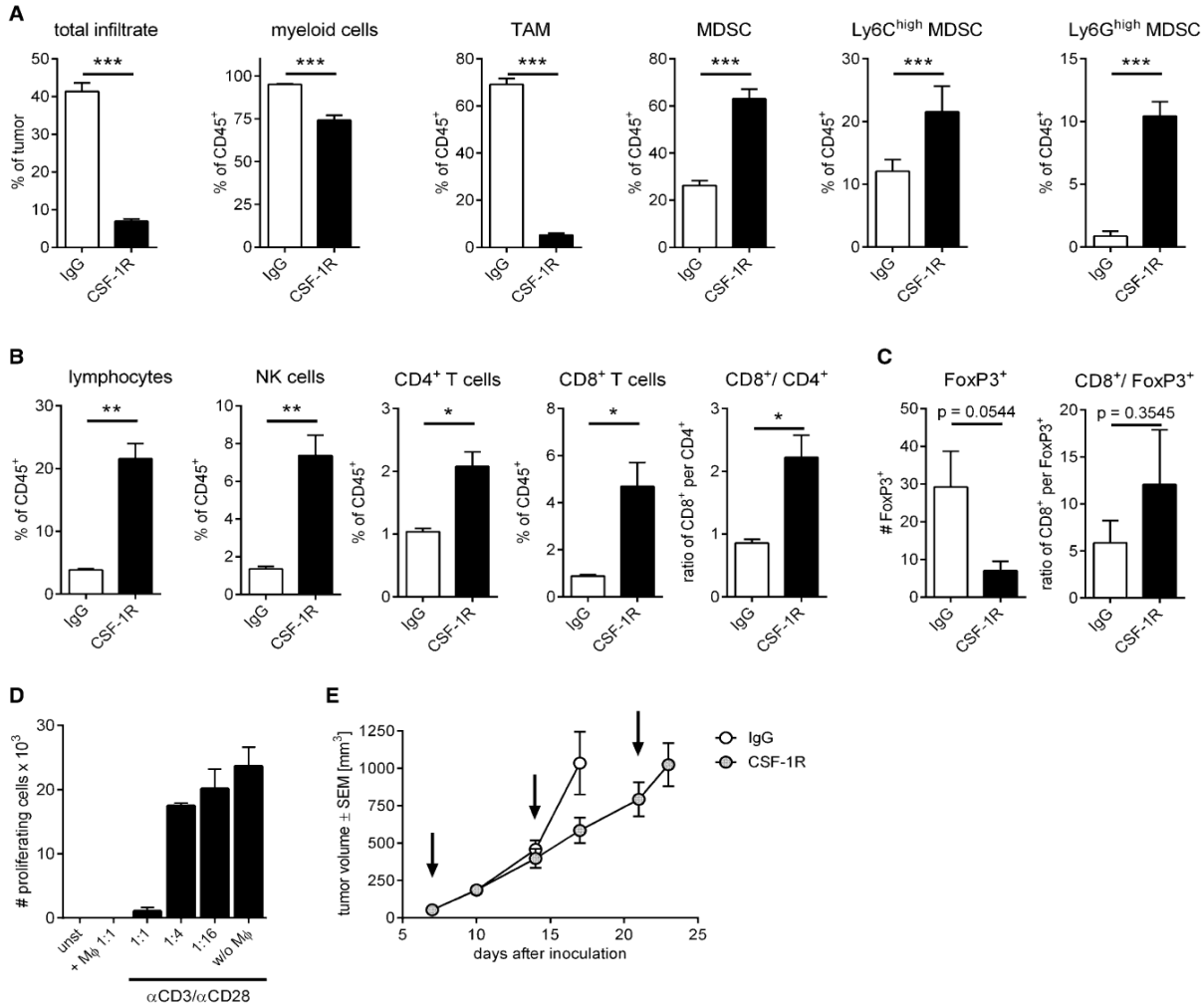


Figure 4. CSF-1R Inhibition Depletes TAMs and Increases Lymphocyte Infiltration into MC38 Colon Carcinomas

LOW CD4 COUNT AND TO RESTORE CD4 COUNTS

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journal homepage: www.ejcancer.info

EJC

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,*]

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[b] Université Lyon 1, F-69100 Villeurbanne, France
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[d] Department of Medical Oncology, Centre Léon BERARD, 28, rue Laënnec, 69008 Lyon, France
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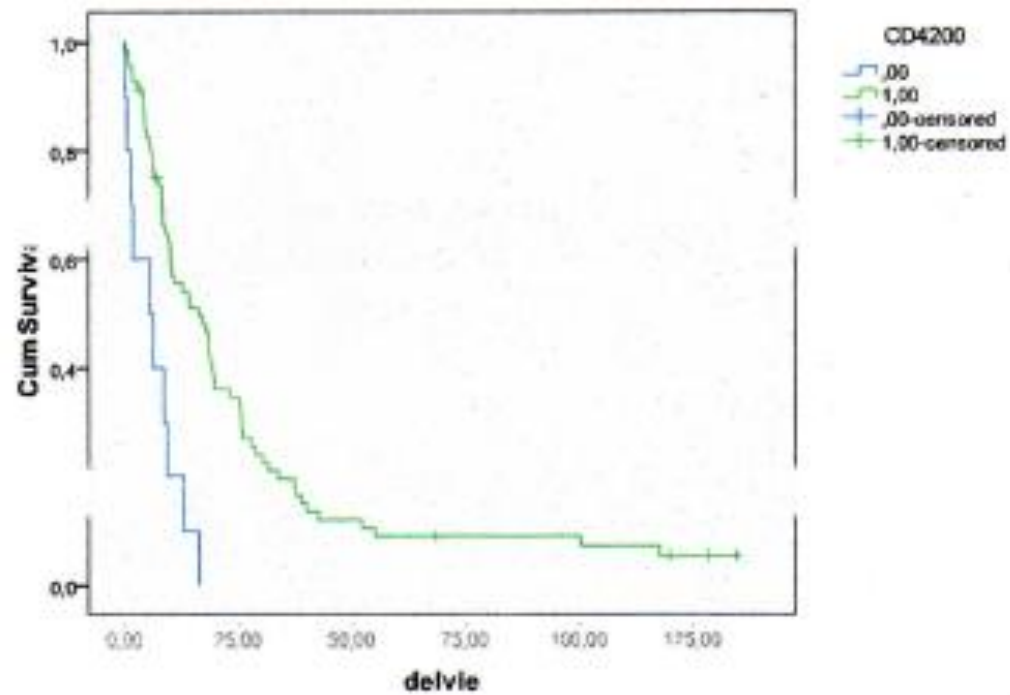
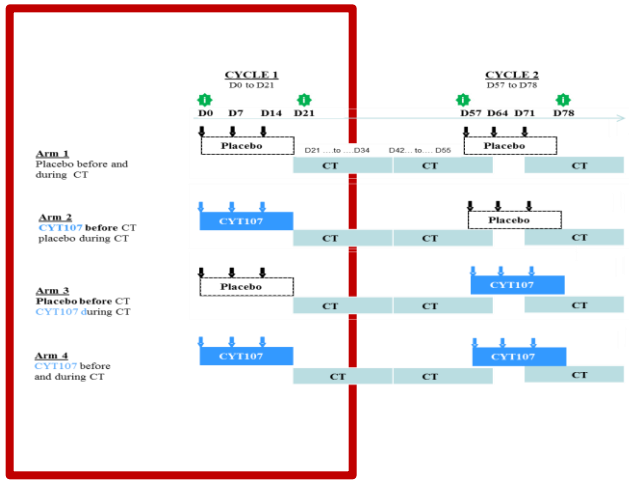
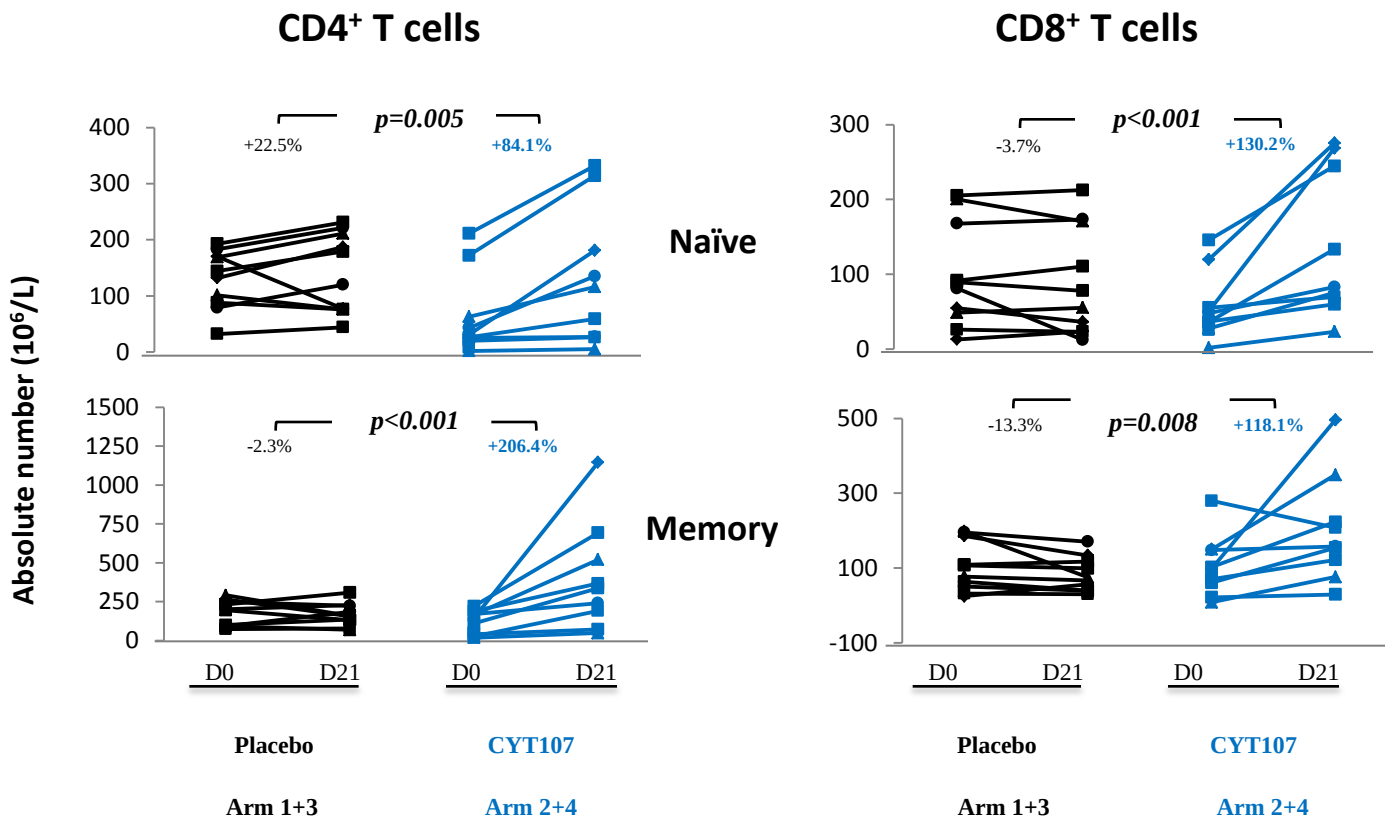
[g] Equipe 11, Cancer Research Center of Lyon, Centre Léon BERARD, 28, rue Laënnec, 69008 Lyon, France



ELYPSE 7: A RANDOMIZED STUDY OF IL-7 TO RESTORE CD4 COUNTS





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		

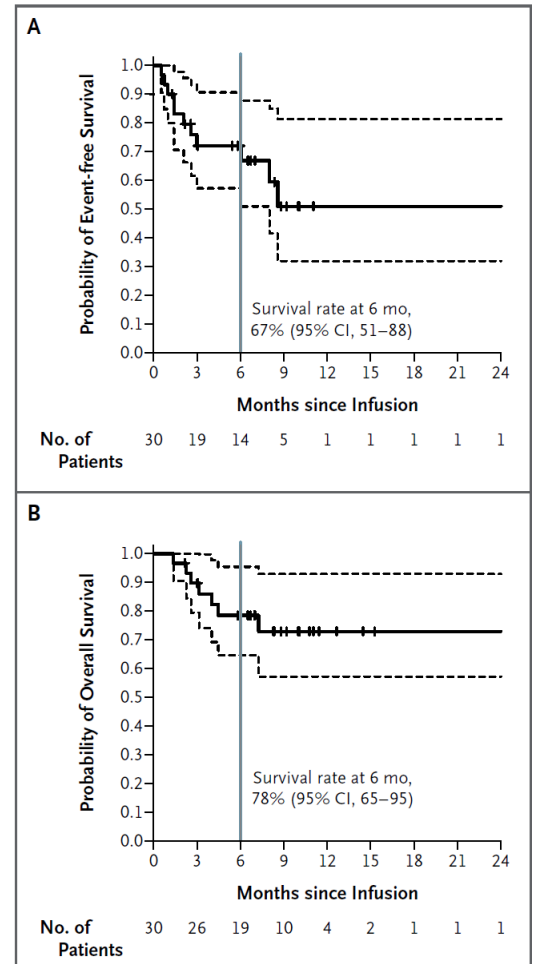
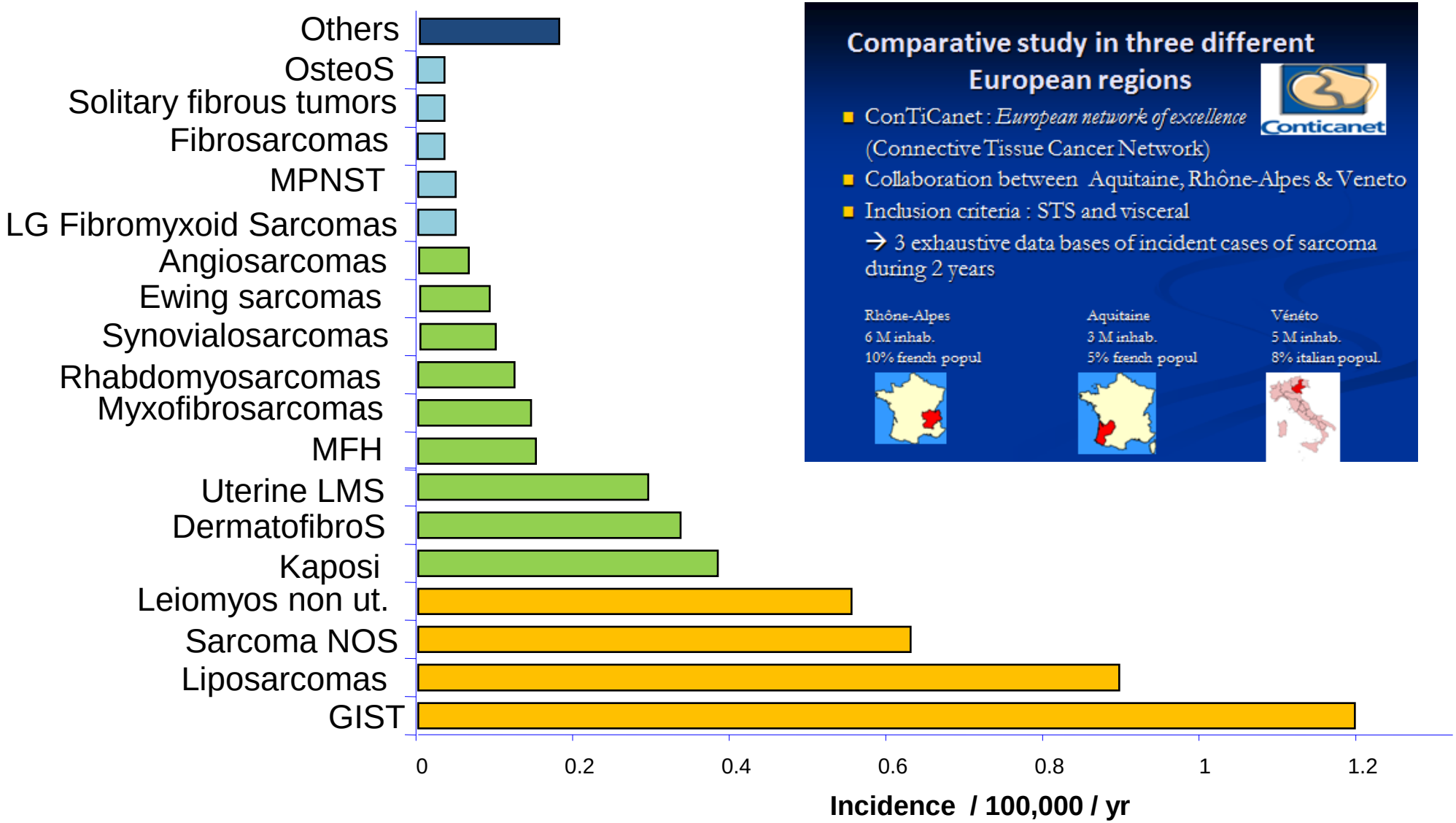


Figure 1. Probability of Event-free and Overall Survival at 6 Months.

Topics

- Immunotherapy of cancers
- **Immune status and immunotherapy of sarcomas**

Over 80 histotypes of sarcomas…

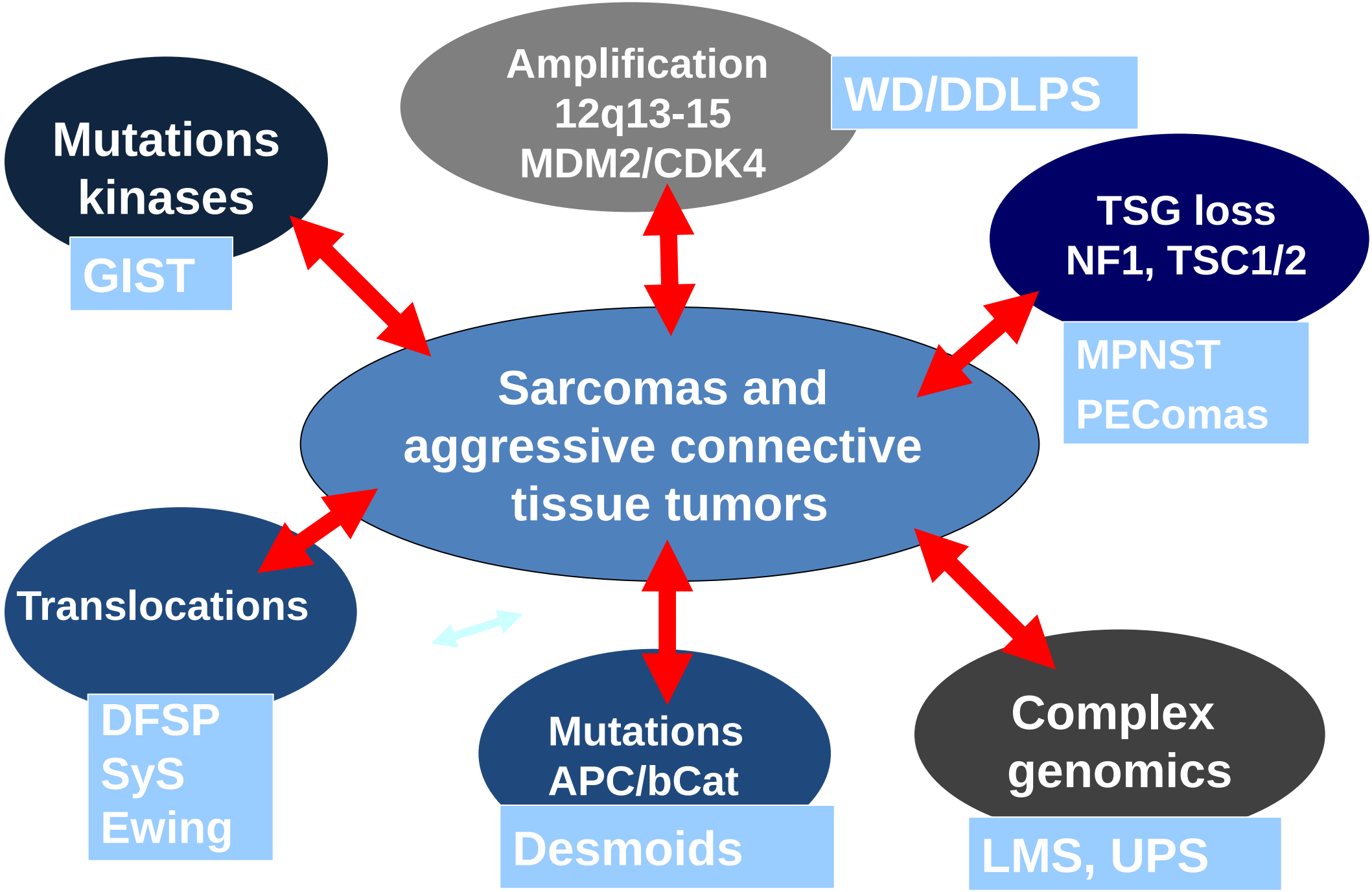


Comparative study in three different European regions

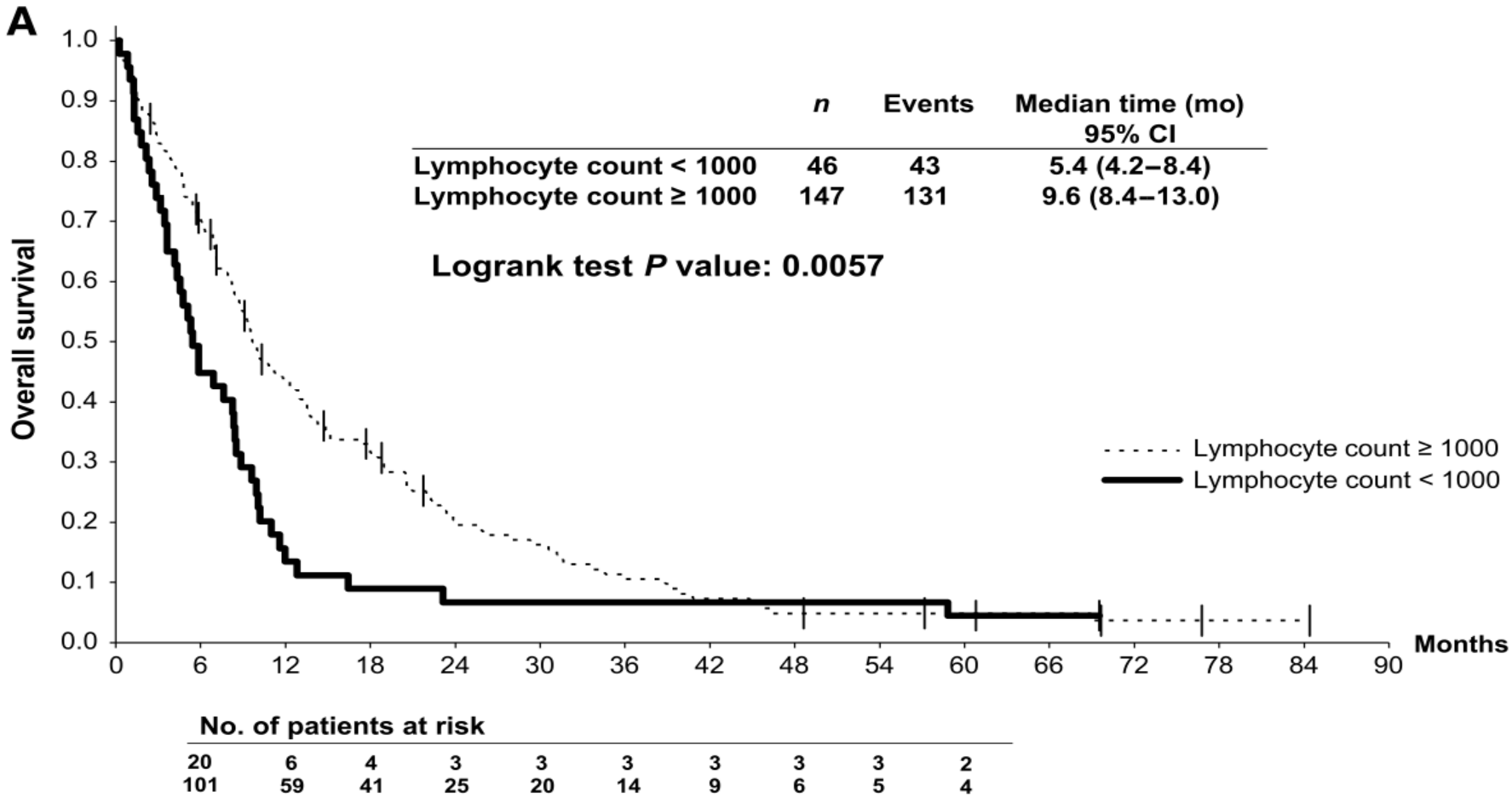
- ConTiCanet : *European network of excellence* (Connective Tissue Cancer Network)
- Collaboration between Aquitaine, Rhône-Alpes & Veneto
- Inclusion criteria : STS and visceral

→ 3 exhaustive data bases of incident cases of sarcoma during 2 years

Rhône-Alpes	Aquitaine	Vénéto
6 M inhab.	3 M inhab.	5 M inhab.
10% french popul	5% french popul	8% italian popul.


Mutations
kinases
GIST
Amplification
12q13-15
MDM2/CDK4
WD/DDLPS
TSG loss
NF1, TSC1/2
MPNST
PEComas
Sarcomas and
aggressive connective
tissue tumors
Translocations
DFSP
SyS
Ewing
Mutations
APC/bCat
Desmoids
Complex
genomics
LMS, UPS

Overall survival of advanced soft tissue sarcoma patients according to baseline lymphocyte counts

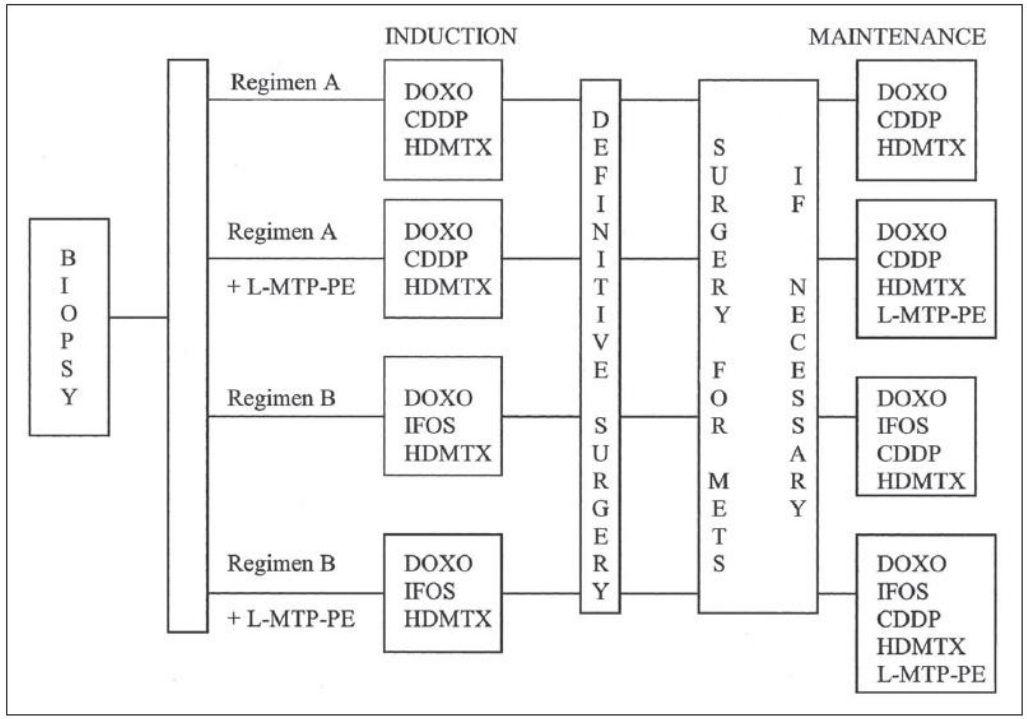


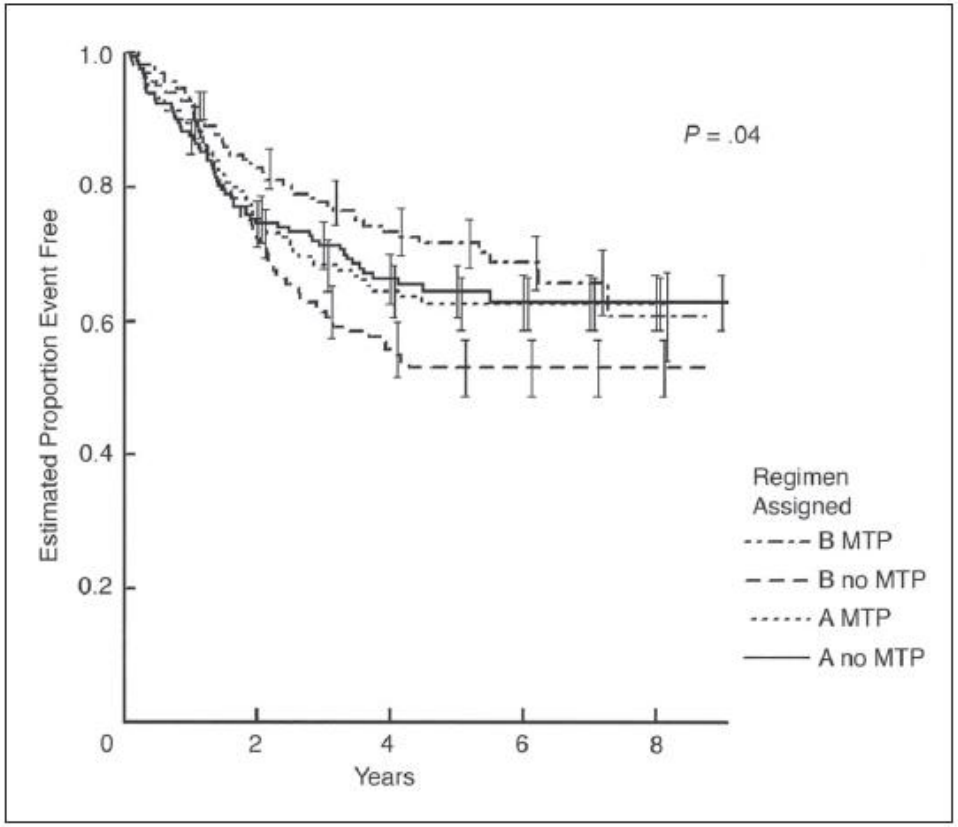
Statistically significant even in multivariate analysis

Isabelle Ray-Coquard et al, on behalf of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. Cancer Res 2009;69(13):5383

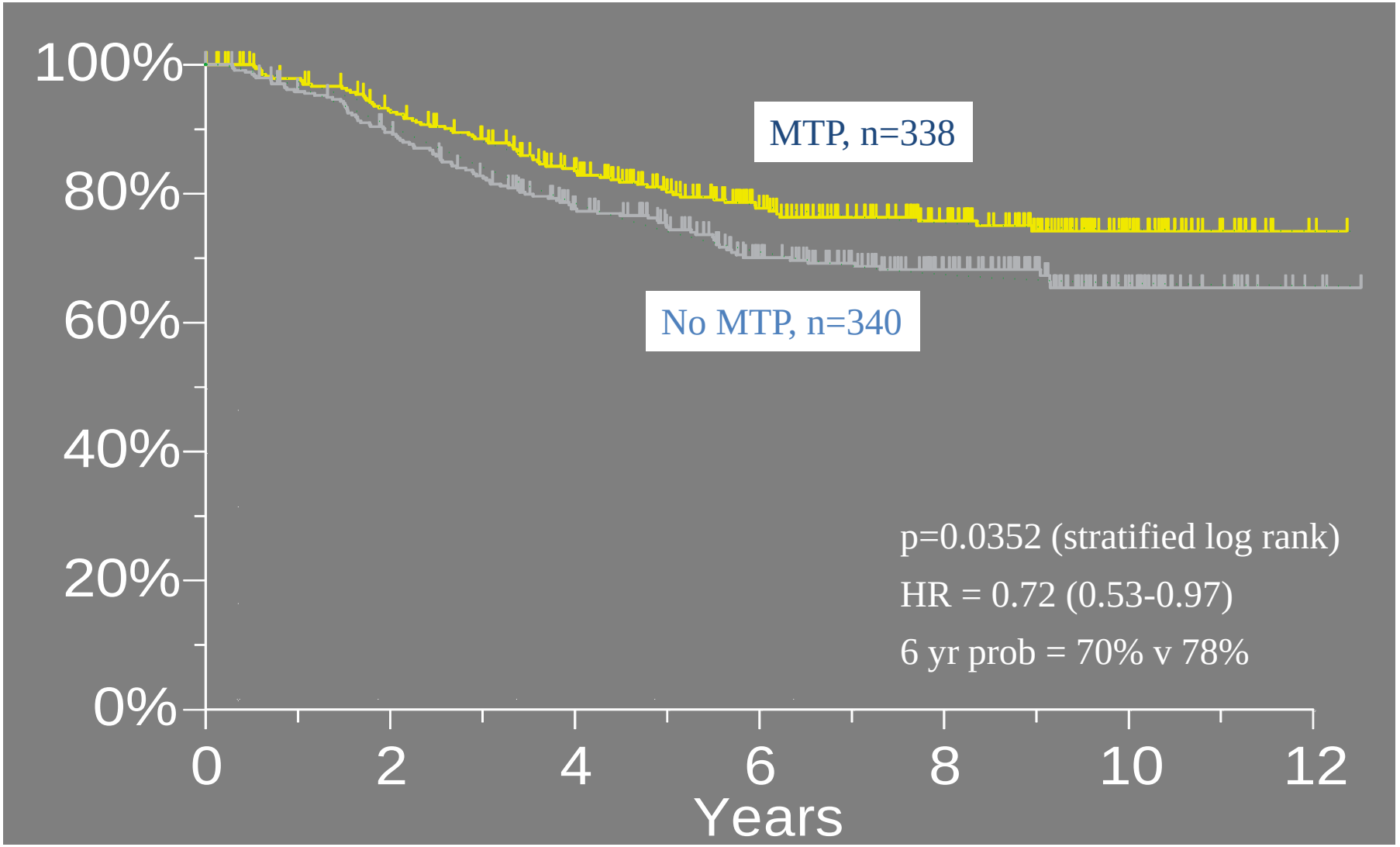
Osteosarcoma: A Randomized, Prospective Trial of the Addition of Ifosfamide and/or Muramyl Tripeptide to Cisplatin, Doxorubicin, and High-Dose Methotrexate

Paul A. Meyers, Cindy L. Schwartz, Mark Krailo, Eugenie S. Kleinerman, Donna Betcher, Mark L. Bernstein, Ernest Conrad, William Ferguson, Mark Gebhardt, Allen M. Goorin, Michael B. Harris, John Healey, Andrew Huvos, Michael Link, Joseph Montebello, Helen Nadel, Michael Nieder, Judith Sato, Gene Siegal, Michael Weiner, Robert Wells, Lester Wold, Richard Womer, and Holcombe Grier



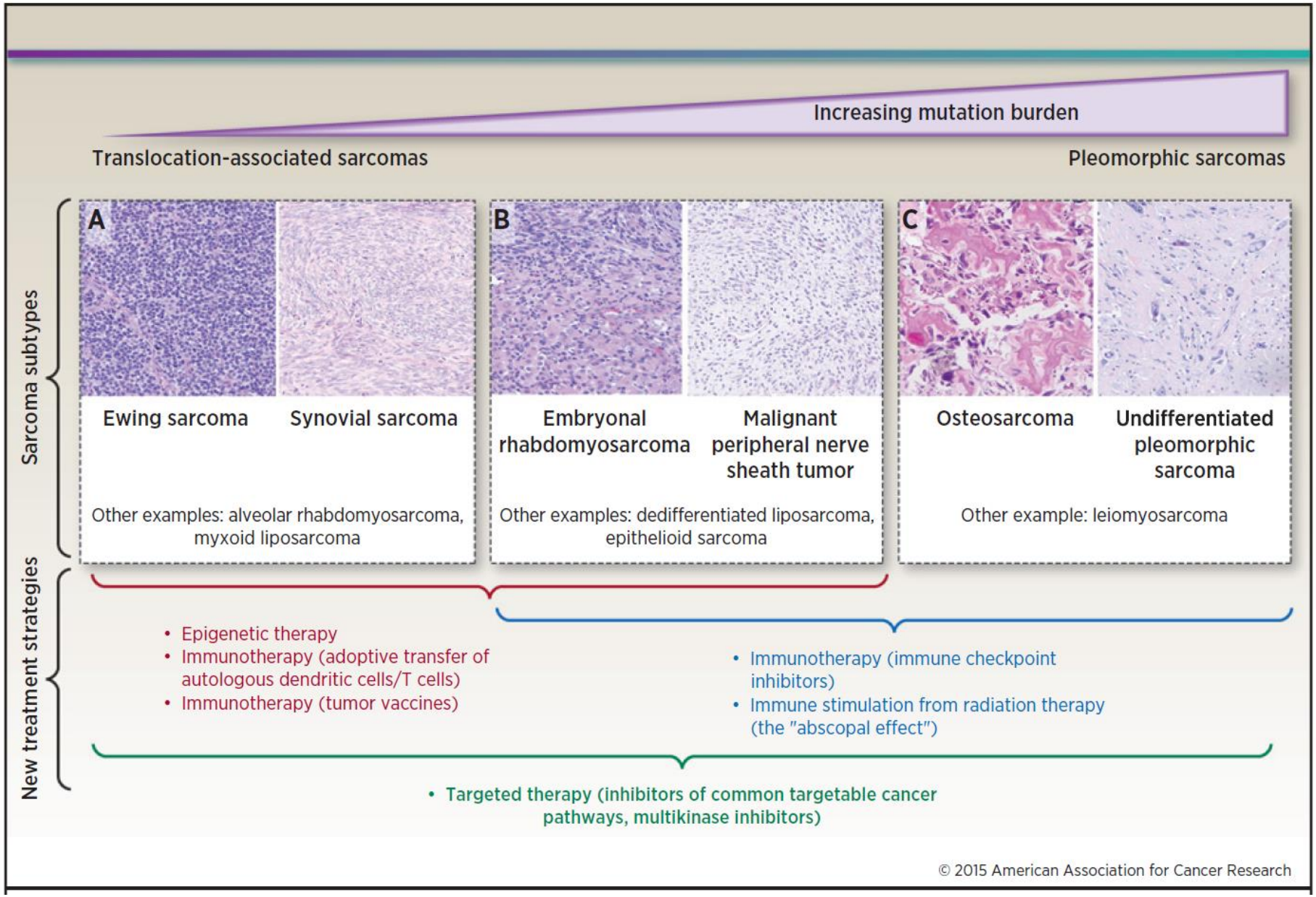


Impact on survival



Immunology of sarcoma

- Antigen load
- PD1/PDL1 expression
- M2 macrophages
- GIST
- CARs



Lim et al 2015

Lymphocytes infiltration and PDL1 expression in sarcomas

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Tumor Infiltrating PD1-Positive Lymphocytes and the Expression of PD-L1 Predict Poor Prognosis of Soft Tissue Sarcomas

Jung Ryul Kim[1], Young Jae Moon[1], Keun Sang Kwon[2], Jun Sang Bae[3], Sajeev Wagle[3], Kyoung Min Kim[3], Ho Sung Park[3], Ho Lee[4], Woo Sung Moon[3], Myoung Ja Chung[3], Myoung Jae Kang[3], Kyu Yun Jang[3*]

Multi-platform profiling of over 2000 sarcomas: Identification of biomarkers and novel therapeutic targets

Sujana Movva[1,*], Wenhsiang Wen[2,*], Wangjuh Chen[2], Sherri Z. Millis[2], Zoran Gatalica[2], Sandeep Reddy[2], Margaret von Mehren[1], Brian A. Van Tine[3]

Prevalence of tumor-infiltrating lymphocytes and PD-L1 expression in the soft tissue sarcoma microenvironment☆,☆☆

Sandra P. D'Angelo MD[a,b,*], Alexander N. Shoushtari MD[a], Narasimhan P. Agaram MD[c], Deborah Kuk[d], Li-Xuan Qin PhD[d], Richard D. Carvajal MD[b,e], Mark A. Dickson MD[a,b], Mrinal Gounder MD[a,b], Mary Louise Keohan MD[a,b], Gary K. Schwartz MD[f], William D. Tap MD[a,b]

Programmed Cell Death Ligand 1 Expression in Osteosarcoma

Jacson K. Shen[1], Gregory M. Cote[2], Edwin Choy[2], Pei Yang[1], David Harmon[2], Joseph Schwab[1], G. Petur Nielsen[3], Ivan Chebib[3], Soldano Ferrone[4], Xinhui Wang[4], Yangyang Wang[4], Henry Mankin[1], Francis J. Hornicek[1], and Zhenfeng Duan[1]

www.impactjournals.com/oncotarget/ Oncotarget, Vol. 6, No. 13

Expression of programmed cell death ligand 1 (PD-L1) and prevalence of tumor-infiltrating lymphocytes (TILs) in chordoma

Yong Feng[1,2], Jacson Shen[1], Yan Gao[1], Yunfei Liao[1,3], Gregory Cote[4], Edwin Choy[4], Ivan Chebib[5], Henry Mankin[1], Francis Hornicek[1] and Zhenfeng Duan[1]

Analysis of the Intratumoral Adaptive Immune Response in Well Differentiated and Dedifferentiated Retroperitoneal Liposarcoma

William W. Tseng,[1,2] Shruti Malu,[3] Minying Zhang,[3] Jieqing Chen,[3] Geok Choo Sim,[3] Wei Wei,[4] Davis Ingram,[5] Neeta Somaiah,[6] Dina C. Lev,[5] Raphael E. Pollock,[7] Gregory Lizée,[3] Laszlo Radvanyi,[8,9] and Patrick Hwu[3,6]

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Tumor Infiltrating PD1-Positive Lymphocytes and the Expression of PD-L1 Predict Poor Prognosis of Soft Tissue Sarcomas

Jung Ryul Kim[1], Young Jae Moon[1], Keun Sang Kwon[2], Jun Sang Bae[3], Sajeev Wagle[3], Kyoung Min Kim[3], Ho Sung Park[3], Ho Lee[4], Woo Sung Moon[3], Myoung Ja Chung[3], Myoung Jae Kang[3], Kyu Yun Jang[3*]

Table 1. The expression status of PD1 and PD-L1 according to the histological type of soft-tissue sarcomas.

Histological type	*N*	PD1	PD-L1		PD1/PD-L1	
		positive	positive	-/-	-/+ or +/-	+/+
Leiomyosarcoma	20	9 (45%)	14 (70%)	3 (15%)	11 (55%)	6 (30%)
Synovial sarcoma	16	10 (63%)	12 (75%)	2 (13%)	6 (38%)	8 (50%)
Undifferentiated sarcoma	11	11 (100%)	9 (82%)	0 (0%)	2 (18%)	9 (82%)
Myxoid liposarcoma	10	1 (10%)	3 (30%)	6 (60%)	4 (40%)	0 (0%)
Well differentiated liposarcoma	4	1 (25%)	2 (50%)	1 (25%)	3 (75%)	0 (0%)
Dedifferentiated liposarcoma	3	2 (67%)	2 (67%)	0 (0%)	2 (67%)	1 (33%)
Ewing sarcoma	6	4 (67%)	4 (67%)	0 (0%)	4 (67%)	2 (33%)
Malignant peripheral nerve sheath tumor	6	3 (50%)	3 (50%)	2 (33%)	2 (33%)	2 (33%)
Adult fibrosarcoma	5	3 (60%)	3 (60%)	1 (20%)	2 (40%)	2 (40%)
Angiosarcoma	5	4 (80%)	4 (80%)	1 (20%)	0 (0%)	4 (80%)
Myxofibrosarcoma	4	1 (25%)	1 (25%)	3 (75%)	0 (0%)	1 (25%)
Epithelioid sarcoma	4	4 (100%)	3 (75%)	0 (0%)	1 (25%)	3 (75%)
Alveolar rhabdomyosarcoma	4	3 (75%)	4 (100%)	0 (0%)	1 (25%)	3 (75%)
Embryonal rhabdomyosarcoma	2	1 (50%)	1 (50%)	0 (0%)	2 (100%)	0 (0%)
Pleomorphic rhabdomyosarcoma	2	2 (100%)	2 (100%)	0 (0%)	0 (0%)	2 (100%)
Low grade myofibroblastic sarcoma	2	1 (50%)	0 (0%)	1 (50%)	1 (50%)	0 (0%)
Clear cell sarcoma	1	1 (100%)	1 (100%)	0 (0%)	0 (0%)	1 (100%)

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Tumor Infiltrating PD1-Positive Lymphocytes and the Expression of PD-L1 Predict Poor Prognosis of Soft Tissue Sarcomas

Jung Ryul Kim[1], Young Jae Moon[1], Keun Sang Kwon[2], Jun Sang Bae[3], Sajeev Wagle[3], Kyoung Min Kim[3], Ho Sung Park[3], Ho Lee[4], Woo Sung Moon[3], Myoung Ja Chung[3], Myoung Jae Kang[3], Kyu Yun Jang[3*]

Table 4. Multivariate Cox regression analysis for overall survival and event-free survival of soft-tissue sarcoma patients.

Characteristics	OS		EFS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Model 1*				
Stage, III/IV (*vs* I/II)	2.635 (1.419-4.890)	0.002	2.387 (1.403-4.060)	0.001
PD1, positive (*vs* negative)	4.501 (2.132-9.502)	< 0.001	3.174 (1.761-5.720)	< 0.001
PD-L1, positive (*vs* negative)	4.827 (2.093-11.131)	< 0.001	2.629 (1.407-4.911)	0.002
Model 2**				
Stage, III/IV (*vs* I/II)	2.642 (1.422-4.910)	0.002	2.388 (1.403-4.064)	0.001
PD1/PD-L1, -/-	1.000 (Ref)	< 0.001	1.000 (Ref)	< 0.001
-/+ or +/-	3.627 (0.798-16.480)	0.095	2.596 (0.879-7.667)	0.084
+/+	17.898 (3.850-83.208)	< 0.001	7.854 (2.684-22.976)	< 0.001

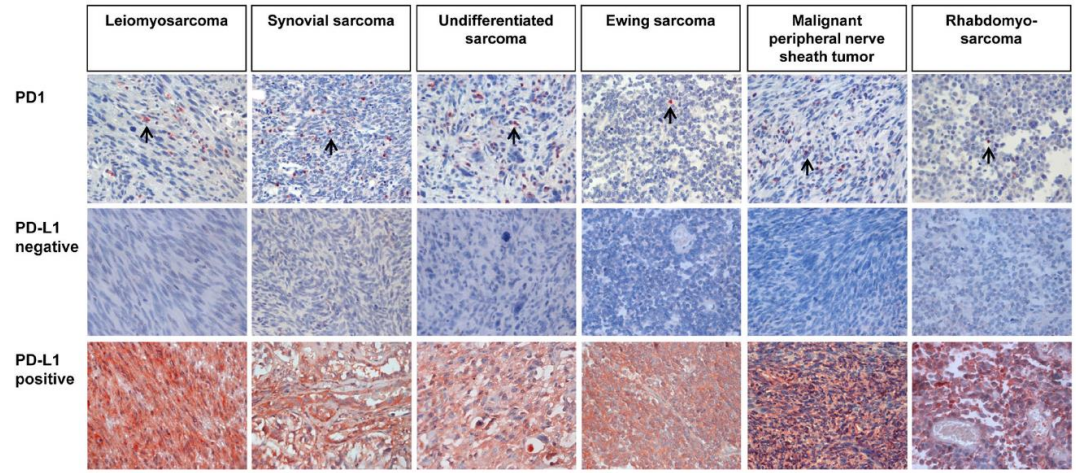


Figure 1. Immunohistochemical expression of PD1 and PD-L1 in various soft-tissue sarcomas. Arrows indicate PD1 positive lymphocytes. Original magnification, x400.

doi: 10.1371/journal.pone.0082870.g001

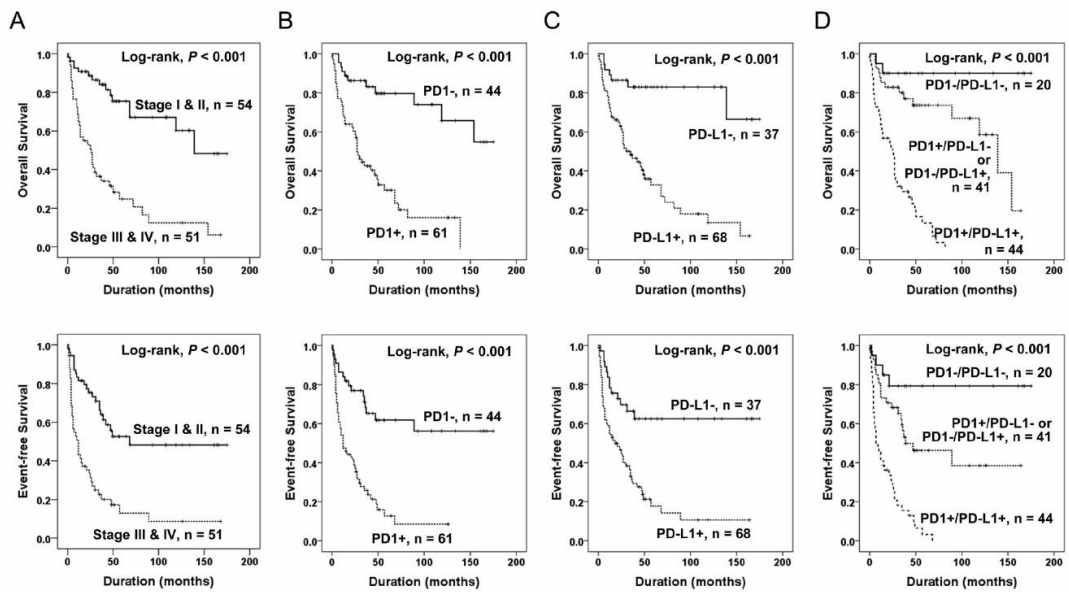
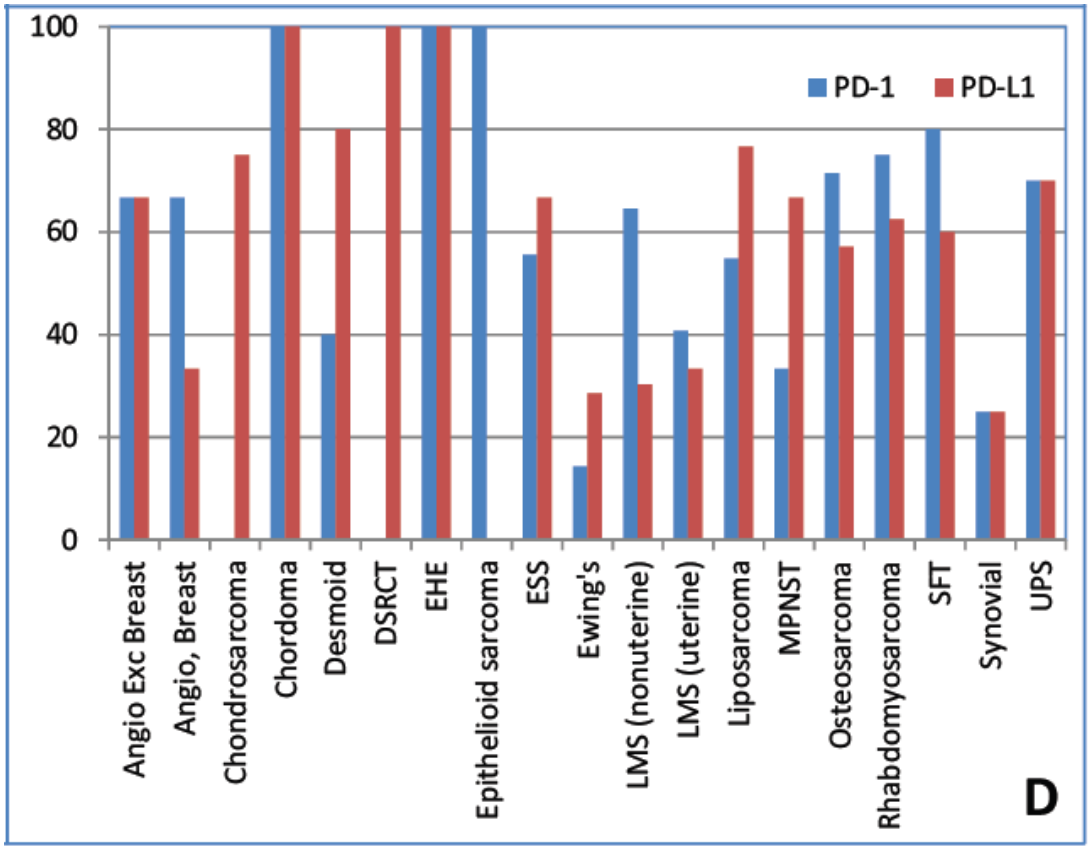


Figure 2. Kaplan-Meier survival analysis in soft-tissue sarcomas. Overall survival and event-free survival according to tumor stage (A), intra-tumoral infiltration of PD1-positive lymphocytes (B), expression of PD-L1 (C), and the combined expression pattern of PD1 and PD-L1 (PD1/PD-L1) (D).

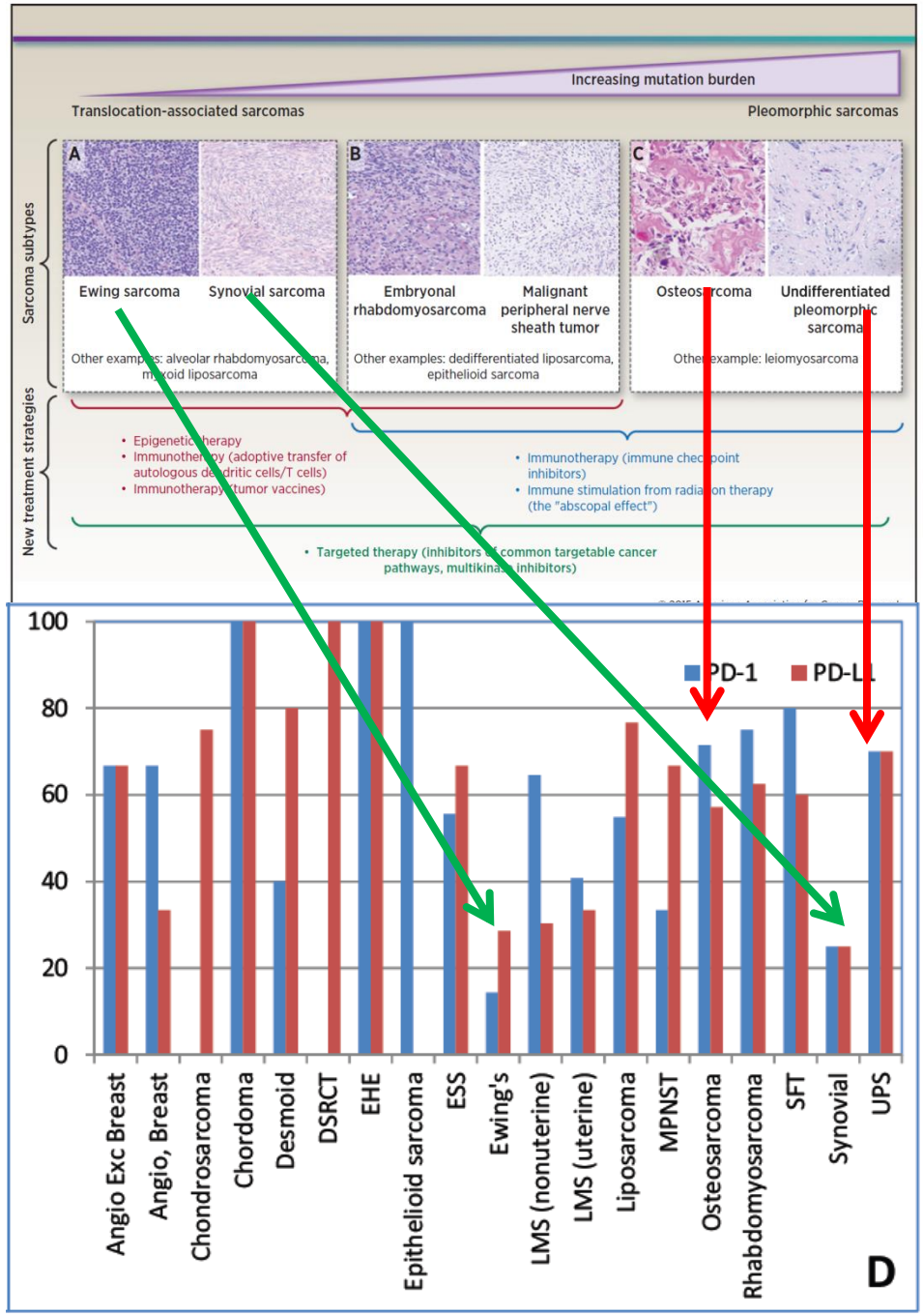
doi: 10.1371/journal.pone.0082870.g002

Multi-platform profiling of over 2000 sarcomas: Identification of biomarkers and novel therapeutic targets

Sujana Movva[1,*], Wenhsiang Wen[2,*], Wangjuh Chen[2], Sherri Z. Millis[2], Zoran Gatalica[2], Sandeep Reddy[2], Margaret von Mehren[1], Brian A. Van Tine[3]



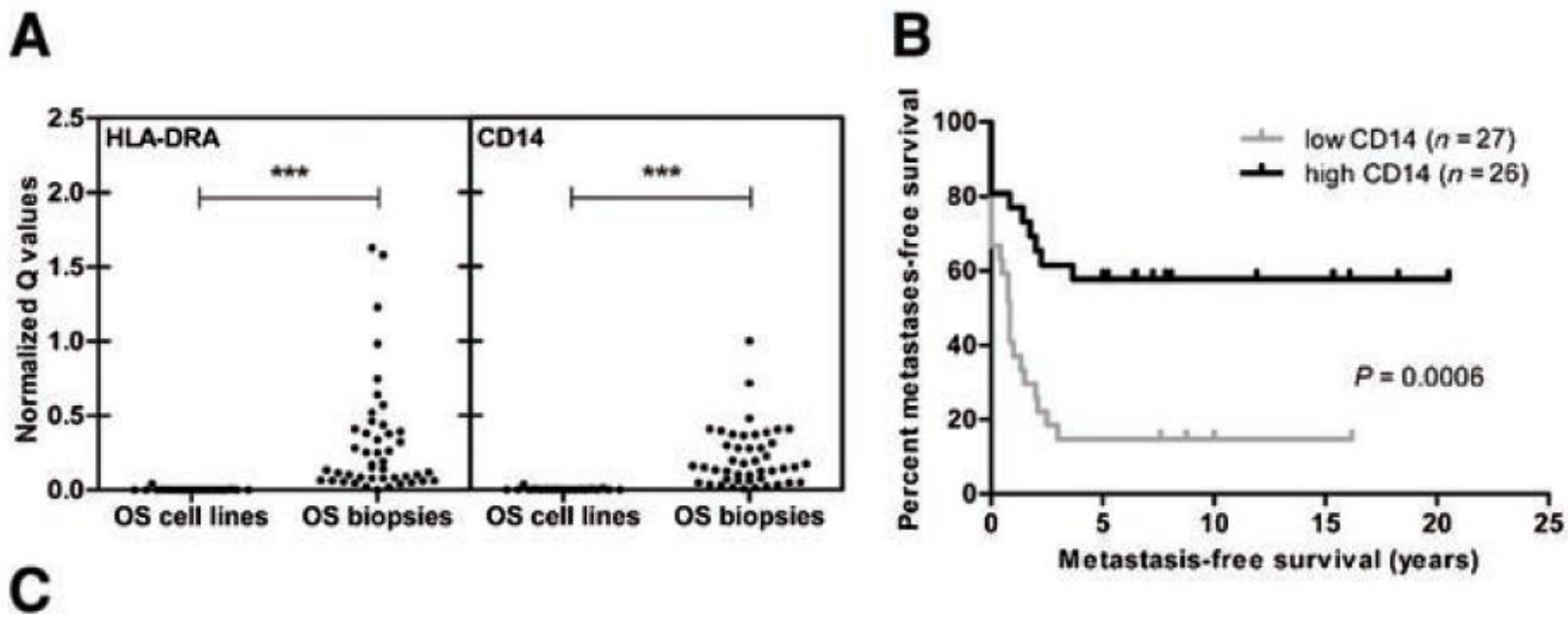
Overall, approximately 50% of the sarcomas expressed PD-L1 by IHC and presented with PD-1+ TILs, similar to other series [22]. Sarcomas with sufficient number of cases and overexpression of these proteins included LMS, chondrosarcoma, liposarcoma and UPS. Only 4 cases of synovial sarcoma were available for testing, 1 of which had simultaneous overexpression of PD-L1 and presence of PD-1+ TILs (Figure 1d and Supplementary Table 2). This rate is lower than published literature [22].


Increasing mutation burden
Translocation-associated sarcomas
Pleomorphic sarcomas
Sarcoma subtypes
A
B
C
Ewing sarcoma
Synovial sarcoma
Embryonal rhabdomyosarcoma
Malignant peripheral nerve sheath tumor
Osteosarcoma
Undifferentiated pleomorphic sarcoma
Other examples: alveolar rhabdomyosarcoma, myxoid liposarcoma
Other examples: dedifferentiated liposarcoma, epithelioid sarcoma
Other example: leiomyosarcoma
New treatment strategies
• Epigenetic therapy
• Immunotherapy (adoptive transfer of autologous dendritic cells/T cells)
• Immunotherapy (tumor vaccines)
• Immunotherapy (immune checkpoint inhibitors)
• Immune stimulation from radiation therapy (the "abscopal effect")
• Targeted therapy (inhibitors of common targetable cancer pathways, multikinase inhibitors)
PD-1
PD-L1
100
80
60
40
20
0
Angio Exc Breast
Angio, Breast
Chondrosarcoma
Chordoma
Desmoid
DSRCT
EHE
Epithelioid sarcoma
ESS
Ewing's
LMS (nonuterine)
LMS (uterine)
Liposarcoma
MPNST
Osteosarcoma
Rhabdomyosarcoma
SFT
Synovial
UPS
D

Tumor-Infiltrating Macrophages Are Associated with Metastasis Suppression in High-Grade Osteosarcoma: A Rationale for Treatment with Macrophage Activating Agents

Emilie P. Buddingh[1], Marieke L. Kuijjer[2], Ronald A.J. Duim[2], Horst Bürger[3], Konstantin Agelopoulos[4], Ola Myklebost[5], Massimo Serra[6], Fredrik Mertens[7], Pancras C.W. Hogendoorn[2], Arjan C. Lankester[1], and Anne-Marie Cleton-Jansen[2]

Clin Cancer Res; 17(8) April 15, 2011



Macrophage infiltration in sarcomas

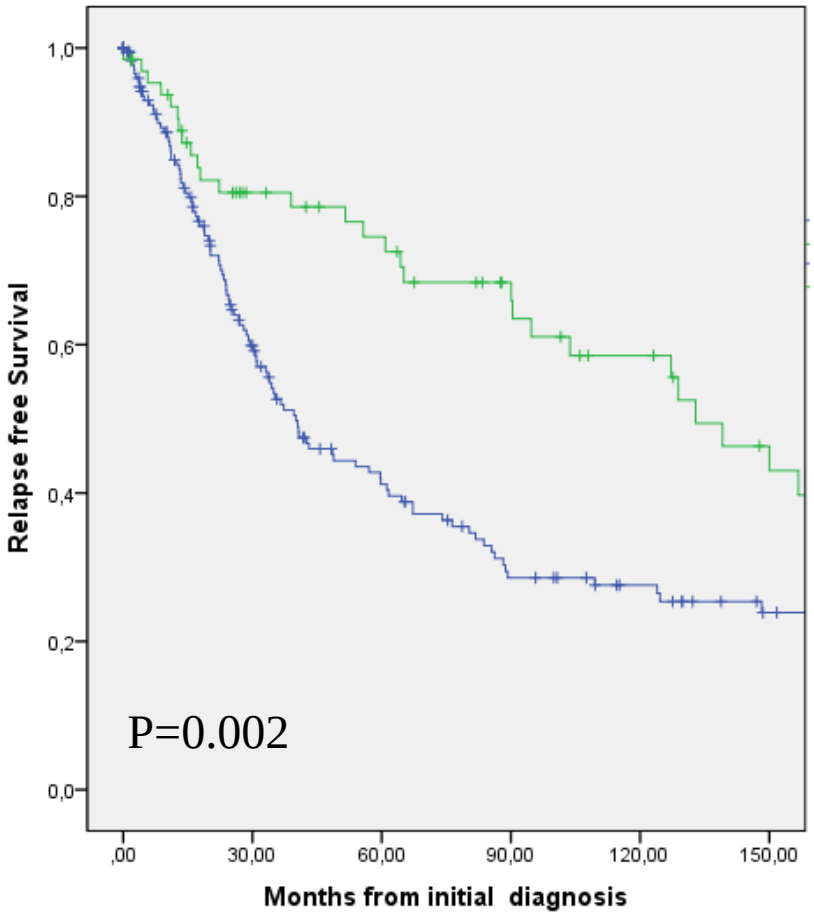
Table 3A- Series 1: Expression of markers on the different histotypes

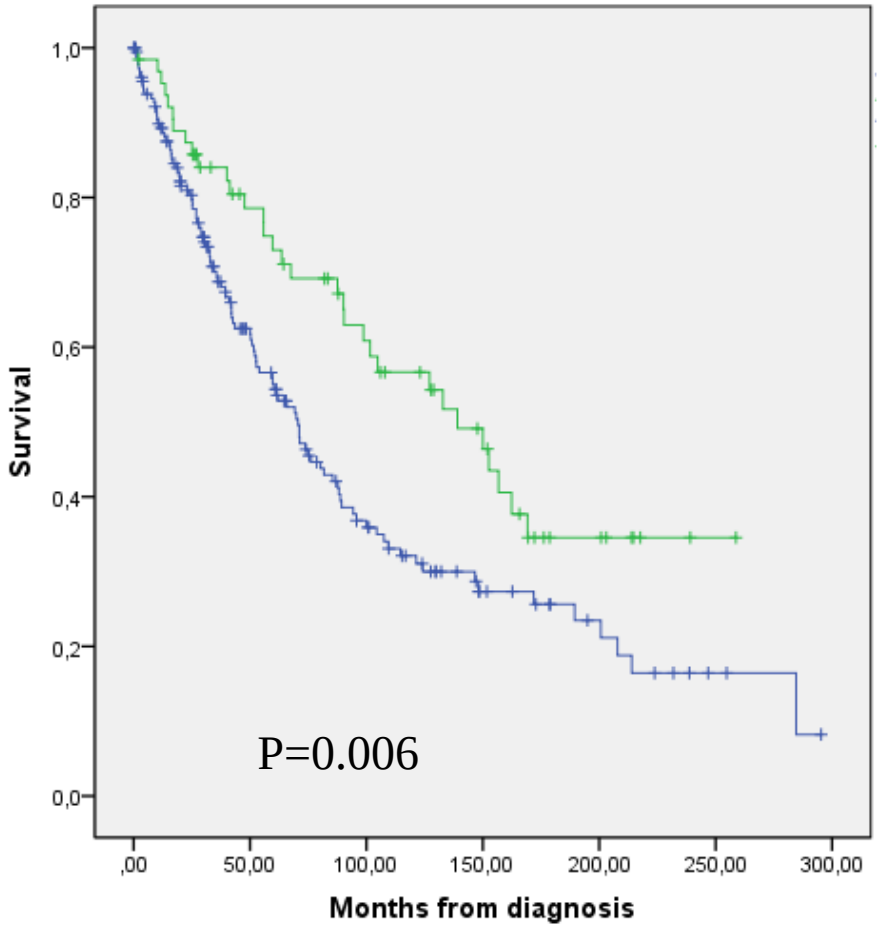
	CD68$^+$ MNC				chi2	CD163$^+$MNC				chi2
	0	+	++	+++		0	+	++	+++	
Histotypes										
DDLPS	0	10	6	4		1	5	9	5	
LMS	2	16	4	0		2	16	4	1	
UPS	0	0	12	6		0	8	8	8	
					.001					.02
Grade										
1	0	6	1	0		1	4	3	0	
2	2	12	3	2		2	12	2	3	
3	0	14	15	9		0	13	15	10	
					.037					.046

Table 3A- Series 2: Expression of markers on the different histotypes

	CD68$^+$ MNC				chi2	CD163$^+$MNC				chi2
	0	+	++	+++		0	+	++	+++	
Histotypes										
DDLPS	0	12	15	10		0	14	13	10	
LMS	9	30	7	11		4	27	16	10	
UPS	1	5	4	6		1	3	5	7	
MFH	6	10	19	12		0	8	18	21	
MFS	4	1	2	1		0	3	3	2	
NOS	1	6	2	1		0	5	2	3	
GIST	0	3	0	0		0	2	1	0	
					.000					.03
Grade										
1	1	4	4	0		0	5	3	1	
2	9	33	21	15		3	35	21	19	
3	11	30	19	20		2	23	29	26	
					.62					.31

Survival according to CD163 infiltrates





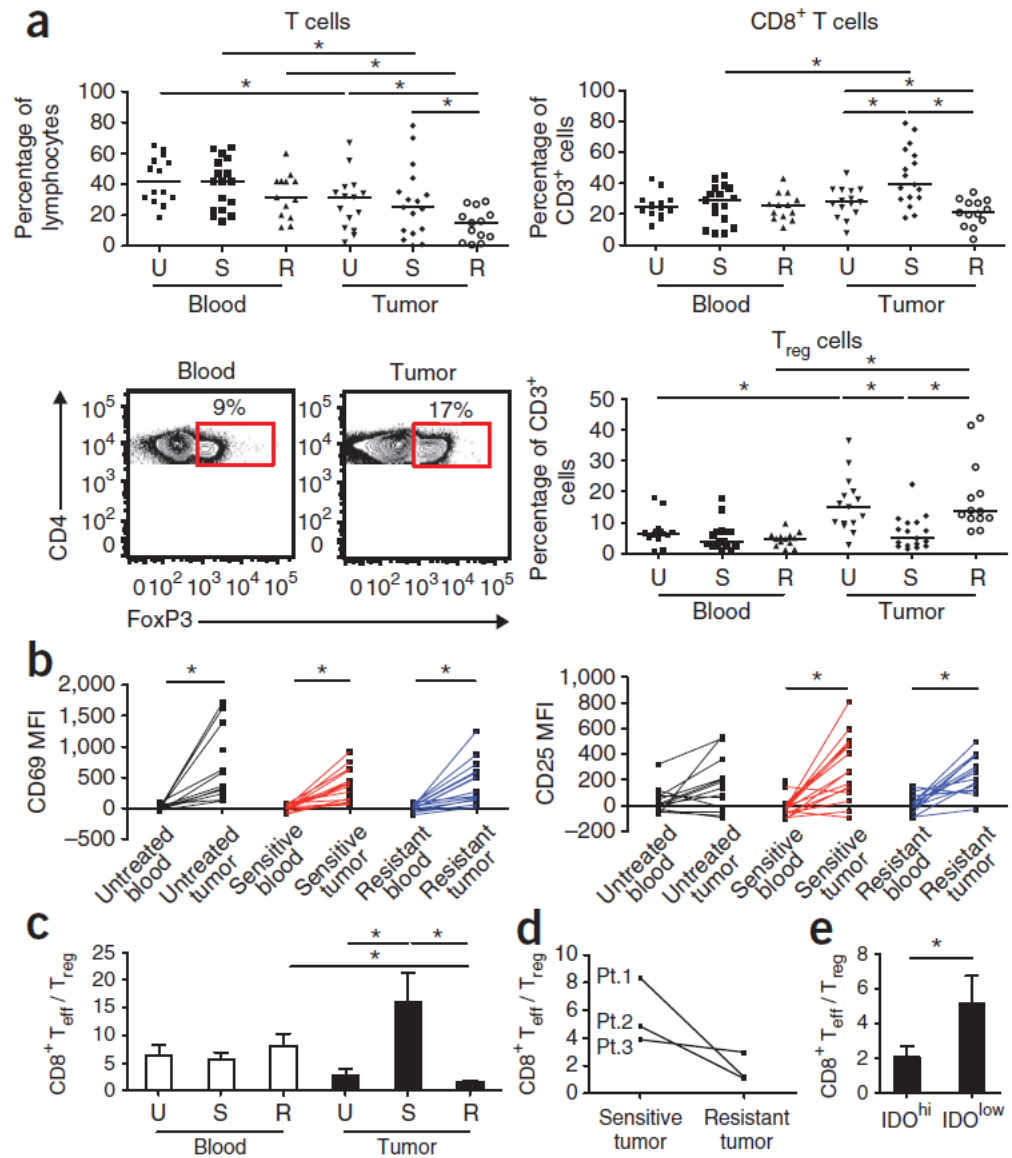
Green: CD163 high (n=64), Blue CD163 low (n=183)

Ms in preparation

Imatinib potentiates antitumor T cell responses in gastrointestinal stromal tumor through the inhibition of Ido

Vinod P Balachandran[1], Michael J Cavnar[1], Shan Zeng[1], Zubin M Bamboat[1], Lee M Ocuin[1], Hebroon Obaid[1], Eric C Sorenson[1], Rachel Popow[1], Charlotte Ariyan[1], Ferdinand Rossi[2], Peter Besmer[2], Tianhua Guo[3], Cristina R Antonescu[3], Takahiro Taguchi[4], Jianda Yuan[5], Jedd D Wolchok[5,6], James P Allison[5,7] & Ronald P DeMatteo[1]

- Preclinical model and human
- IM activates CD8 and block T regs
- IM blocks IDO expression
- CD8/Treg Ratio correlates with response to IM in GIST patients



KIT oncogene inhibition drives intratumoral macrophage M2 polarization

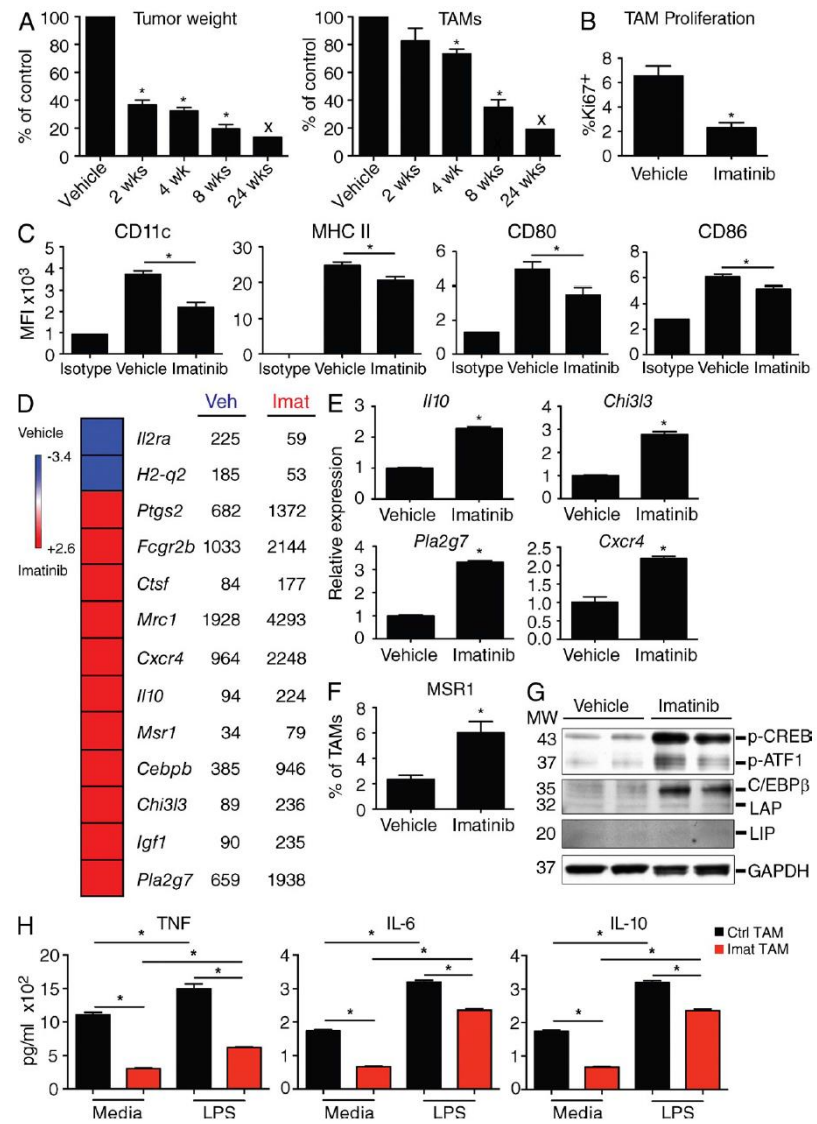
Michael J. Cavnar,[1] Shan Zeng,[1] Teresa S. Kim,[1] Eric C. Sorenson,[1]
Lee M. Ocuin,[1] Vinod P. Balachandran,[1] Adrian M. Seifert,[1]
Jonathan B. Greer,[1] Rachel Popow,[1] Megan H. Crawley,[1]
Noah A. Cohen,[1] Benjamin L. Green,[1] Ferdinand Rossi,[2]
Peter Besmer,[2] Cristina R. Antonescu,[3] and Ronald P. DeMatteo[1]

M1 TAM have anti-tumor activities

CSF1 dependent

Shift to M2 in pts responding to IM

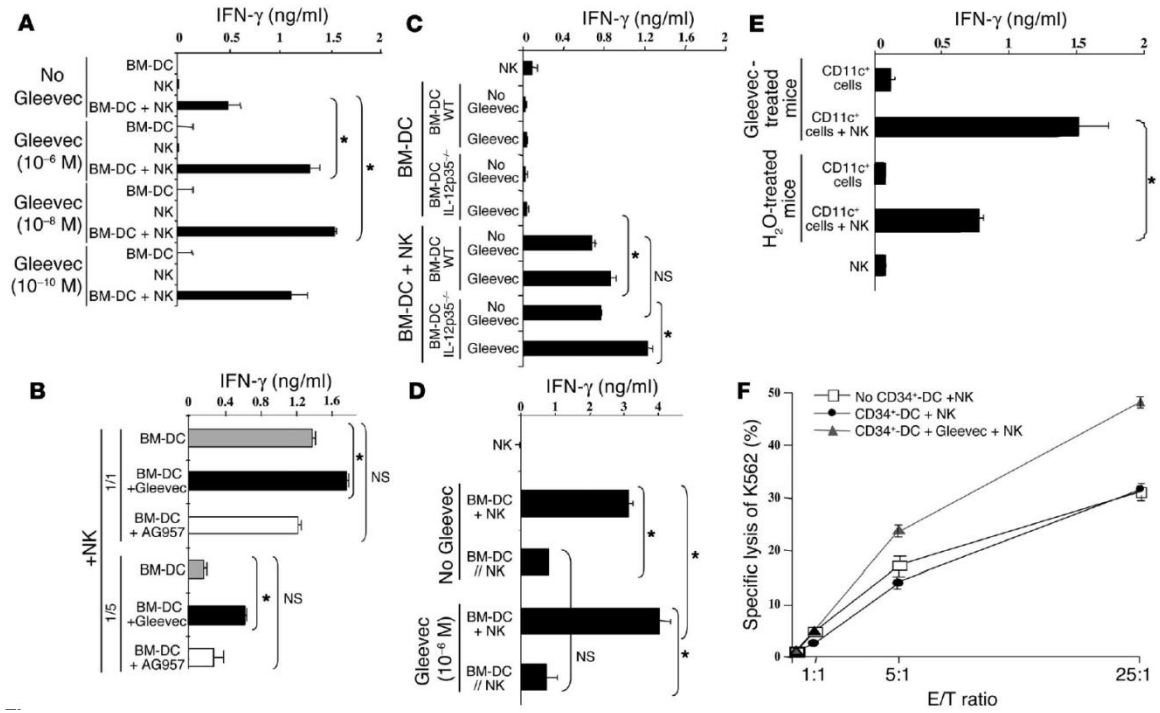
Switch back to M1 in progressive pts

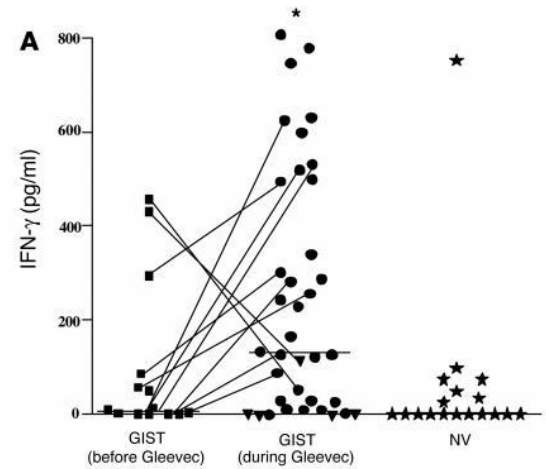


J. Exp. Med. 2013 Vol. 210 No. 13 2873-2886

Novel mode of action of c-kit tyrosine kinase inhibitors leading to NK cell–dependent antitumor effects

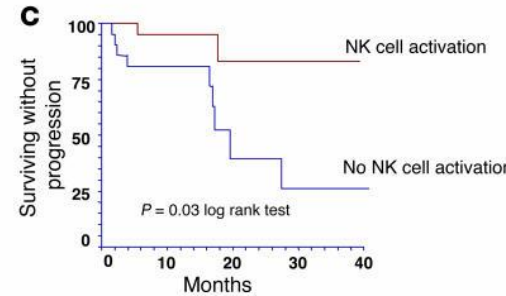
Christophe Borg,[1] Magali Terme,[1] Julien Taïeb,[1] Cédric Ménard,[1] Caroline Flament,[1]
Caroline Robert,[1] Koji Maruyama,[1,2] Hiro Wakasugi,[2] Eric Angevin,[1] Kris Thielemans,[3]
Axel Le Cesne,[4] Véronique Chung-Scott,[1] Vladimir Lazar,[1] Isabelle Tchou,[1] Florent Crépineau,[1]
François Lemoine,[5] Jacky Bernard,[6] Jonhantan A. Fletcher,[7] Ali Turhan,[8] Jean-Yves Blay,[9]
Alain Spatz,[10] Jean-François Emile,[11] Michael C. Heinrich,[12] Salah Mécheri,[13]
Thomas Tursz,[1] and Laurence Zitvogel[1]





B Correlation between clinical and immunological status of Gleevec-treated patients

Enhanced NK cell functions	Progressive disease: Yes	Progressive disease: No
Yes	0	24
No	10**	15



JCI 2004

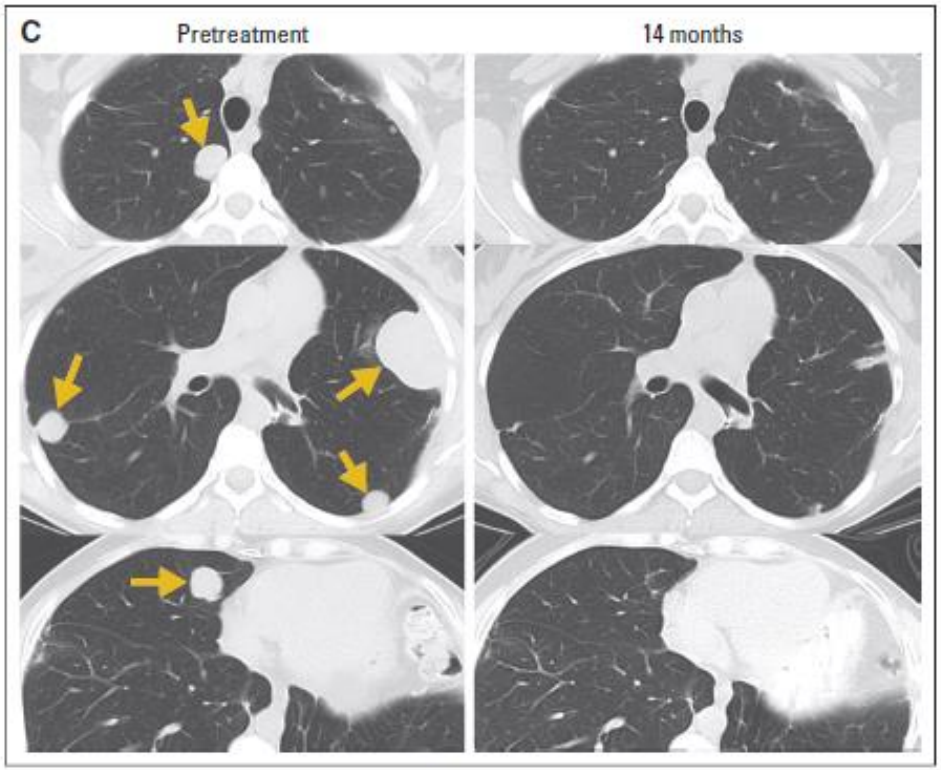
Tumor Regression in Patients With Metastatic Synovial Cell Sarcoma and Melanoma Using Genetically Engineered Lymphocytes Reactive With NY-ESO-1

Paul F. Robbins, Richard A. Morgan, Steven A. Feldman, James C. Yang, Richard M. Sherry, Mark E. Dudley, John R. Wunderlich, Azam V. Nahvi, Lee J. Helman, Crystal L. Mackall, Udai S. Kammula, Marybeth S. Hughes, Nicholas P. Restifo, Mark Raffeld, Chyi-Chia Richard Lee, Catherine L. Levy, Yong F. Li, Mona El-Gamil, Susan L. Schwarz, Carolyn Laurencot, and Steven A. Rosenberg

CAR T cells TCR anti NY-ESO-1

N=11 melanoma, N=6 SynovialS

4 PR, duration (6 to 10 months)



Human Epidermal Growth Factor Receptor 2 (HER2) –Specific Chimeric Antigen Receptor–Modified T Cells for the Immunotherapy of HER2-Positive Sarcoma

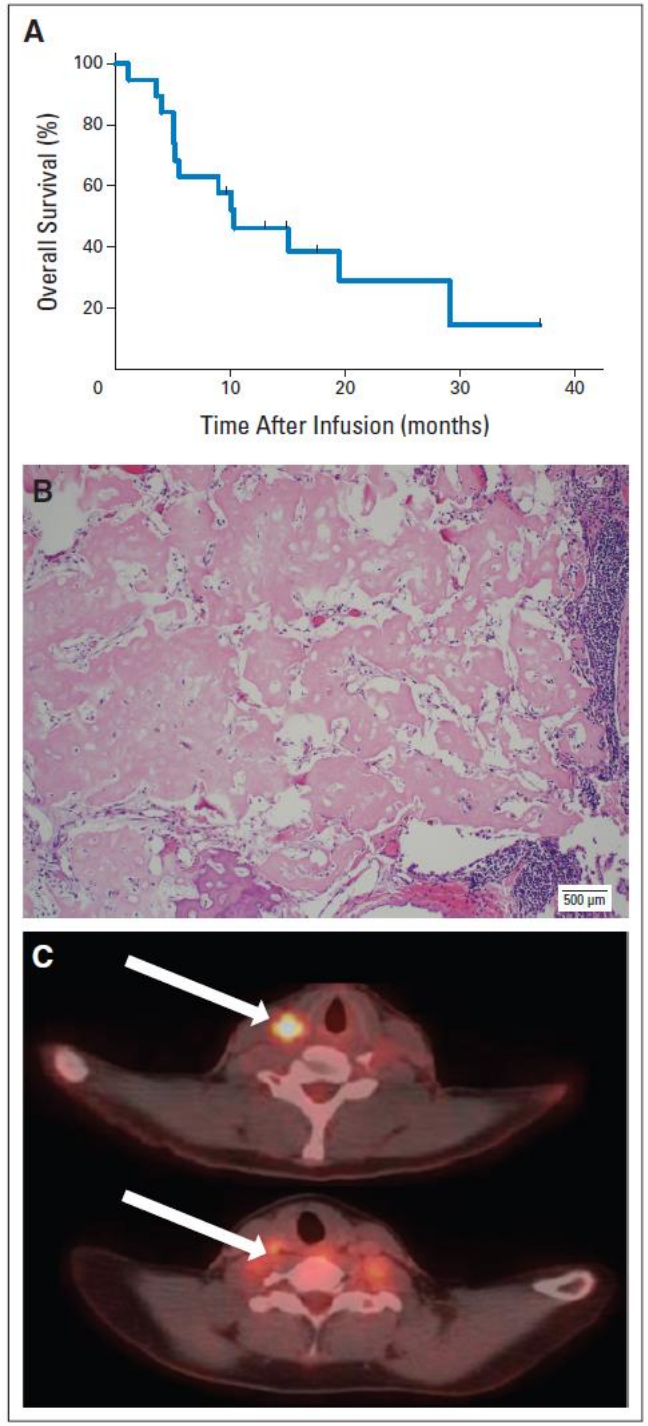
Nabil Ahmed, Vita S. Brawley, Meenakshi Hegde, Catherine Robertson, Alexia Ghazi, Claudia Gerken, Enli Liu, Olga Dakhova, Aidin Ashoori, Amanda Corder, Tara Gray, Meng-Fen Wu, Hao Liu, John Hicks, Nino Rainusso, Gianpietro Dotti, Zhuyong Mei, Bambi Grilley, Adrian Gee, Cliona M. Rooney, Malcolm K. Brenner, Helen E. Heslop, Winfried S. Wels, Lisa L. Wang, Peter Anderson, and Stephen Gottschalk

N=19 pediatric patients

Osteosarcoma and Ewing

Detection of CAR T cells in PB and in the tumor

4 SD, 3 to 14months



Ag expression and vaccine studies in sarcomas

Table 2: Vaccine studies in sarcoma.

Vaccine	Sarcoma histology	Number of patients	Immune response	Results
Irradiated autologous tumor cells [69]	Various pediatric	16	Not reported	16.6 m versus 8.2 m survival (skin test responders)
Dendritic cell pulsed with autologous tumor lysate [70]	Various pediatric	10	Not reported	One response in patient with fibrosarcoma
Dendritic cell pulsed with peptides from tumor specific translocation breakpoints and E7 [71]	Metastatic Ewing's family of tumors or alveolar rhabdomyosarcoma	30/52 initiated vaccine after standard therapy	39% with immune response to translocation breakpoint 25% with E7-specific response	5-year OS: 31% for all patients versus 43% for patients initiating immunotherapy
105AD7 (CD55 target) [72]	Osteosarcoma	28 patients within 1–6 months of chemotherapy	20/28 (71%) showed T cell proliferation response in vitro to 105AD7 9/28 (32%) weak antibody response to CD55	2 patients with possible clinical responses, alive and disease free 5.8 and 6.5 years from time of diagnosis
Dendritic vaccine pulsed with synthetic tumor specific peptide [73]	Posttransplant, residual tumor (synovial, Ewing's)	5	DTH response against tumor lysate in 1 patient	1 patient complete response, 77 months
Peptide encompassing SYT-SSX [74]	Synovial	6	Peptide specific CTLs generated in 4 patients	Suppression of tumor progression 1 patient
SYT-SSX derived peptide [75]	Synovial	20	9 showed twofold increase in CTLs in tetramer analysis	1/9 stable disease (received vaccine with peptide alone) 6/12 stable disease (received vaccine with incomplete Freund's adjuvant)

Table 3: Cancer testis antigens expressed in sarcoma.

Antigen	Sarcoma type	Total expression
NY-ESO [110, 111, 113]	Synovial	80%
	Myxoid round cell liposarcoma	100%
	Uterine leiomyosarcoma	50% (3/6)
	Osteosarcoma	89% (8/9)
LAGE [109, 112]	Myxoid round cell liposarcoma	70%
	Nonmyxoid liposarcoma	60%
	Osteosarcoma	89% (8/9)
PRAME [112]	Synovial sarcoma	100% (4/4)
	Nonmyxoid liposarcoma	100% (4/4)
	Myxoid liposarcoma	14% (1/7)
MAGE-A3 [109]	Uterine leiomyosarcoma	67% (4/6)
	Nonuterine leiomyosarcoma	14% (1/7)

D'Angelo et al 2015

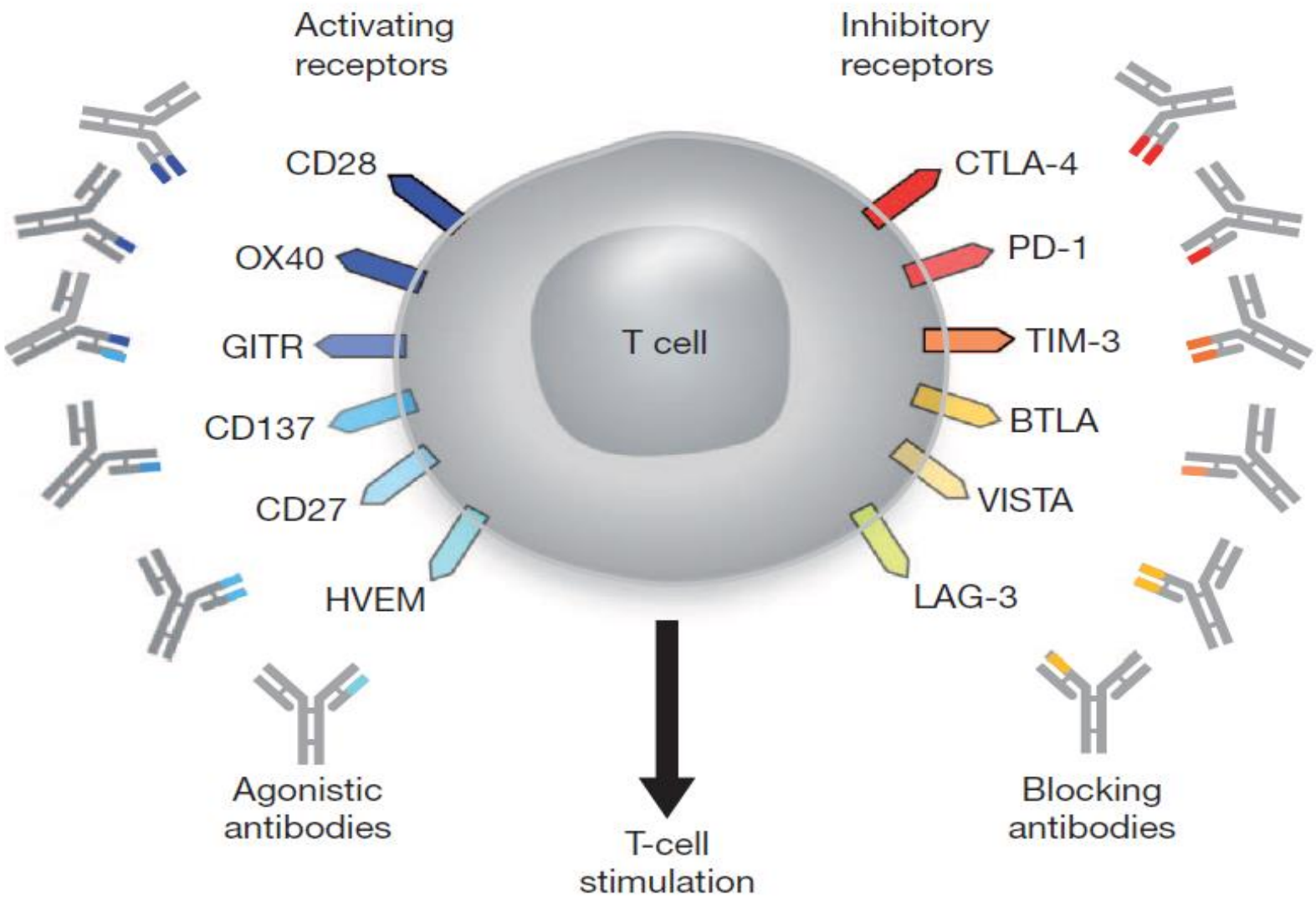
Immunotherapy trials in sarcomas

Table 1. Survey of epigenetic drug trials in cancer and immunotherapy trials in sarcoma

NCT number	Agent	Other agent	Inclusion	Phase	Start	End	Enrollment
EZH2 inhibitor trials							
NCT02082977	GSK2816126		Diffuse large B-cell lymphoma	I	2014	2017	100
NCT01897571	E7438		Diffuse large B-cell lymphoma	I/II	2013	2015	154
NCT02395601	CPI-1205		B-cell lymphoma	I	2015	2016	41
Bromodomain inhibitor trials							
NCT02259114	OTX015		Advanced solid tumors	I	2014	2016	98
NCT02296476	OTX015		Glioblastoma multiforme	I/II	2014	2016	51
NCT02303782	OTX015	Azacitidine	Acute myeloid leukemia	I/II	2015	2016	88
NCT01949883	CPI-0610		Progressive lymphoma	I	2013	2015	33
NCT02157636	CPI-0610		Multiple myeloma	I	2014	2015	36
NCT02158858	CPI-0610		Leukemias	I	2014	2015	36
NCT02419417	BSM-986158	Paclitaxel	Advanced solid tumors	I/II	2015	2020	185
NCT01587703	GSK525762		NUT midline carcinoma	I	2012	2018	90
NCT02391480	ABBV-075		Advanced cancer	I	2015	2017	78
NCT02308761	TEN-010		AML and myelodysplastic syndrome	I	2014	2017	68
NCT01987362	TEN-010		Advanced solid tumors	I	2013	2016	66
NCT02369029	BAY1238097		Neoplasms	I	2015	2017	140
Immunotherapy trials in sarcoma							
NCT01643278	Ipilimumab	Dasatinib	GIST, advanced sarcoma	I	2012	2015	39
NCT02210104	Ipilimumab	Cyclophosphamide, CD4 T cells	NY-ESO–expressing, advanced sarcoma	I	2015	2018	12
NCT02406781	Pembrolizumab	Cyclophosphamide (metronomic)	Advanced sarcoma	II	2015	2017	163
NCT02304458	Nivolumab	(±) Ipilimumab	Recurrent childhood sarcomas	I/II	2015	2016	204
NCT02428192	Nivolumab		Advanced uterine LMS	II	2015	2016	37
NCT02301039	Pembrolizumab		Advanced sarcomas	II	2015	2018	80
NCT01241162	Decitabine	Dendritic cell (lysate pulsed)	Relapsed pediatric sarcoma, neuroblastoma	I	2010	2015	15
NCT01522820	DEC-205/NY-ESO-1 fusion	Sirolimus	Advanced, NY-ESO-1–expressing	I	2012	2016	18
NCT02387125	LV305 (viral NY-ESO-1 expression)	NY-ESO-1 vaccine	Synovial sarcoma, myxoid liposarcoma	IB	2015	2017	33
NCT01291420	Dendritic cells (transfected)		Recurrent sarcoma (limited disease)	I/II	2011	2014	10
NCT01343043	NY-ESO-1 T cells		Synovial sarcoma	I	2011	2016	10
NCT02319824	NY-ESO-1 T cells	Radiation therapy	NY-ESO-1–expressing sarcomas	I	2015	2016	12
NCT02059850	NY-ESO-1 T cells	Cyclophosphamide	Synovial sarcoma, myxoid liposarcoma	I	2014	2016	12
NCT02387125	CMB305		Metastatic, NY-ESO-1–expressing	I	2015	2017	33
NCT02457650	NY-ESO-1 T cells	Cyclophosphamide; fludarabine	NY-ESO-1–expressing cancers	I	2015	2019	36
NCT02122861	ID-LV305		Advanced, NY-ESO-1–expressing	I	2014	2016	42
NCT01883518	Dendritic cell vaccine (cancer-testis antigens)		Sarcoma	I/II	2013	2015	48

Abbreviations: AML, acute myeloid leukemia; GIST, gastrointestinal stromal tumors; LMS, leiomyosarcoma.

Immunostimulatory mAbs: What's Next ?



22/29 DECEMBER 2011 | VOL 480 | NATURE | 485

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	NCT01239134	Dec 2014	Stage III/IV Melanoma; Solid Tumors

Now this is not the end.
It is not even the beginning of the end.
But it is, perhaps, the end of the beginning.

Conclusions

The emerging role of immunology in sarcoma

- Molecular heterogeneity
- Sarcoma incidence in immunosuppressed patients
- Immune cell infiltrates in sarcomas
- PDL1 expression in sarcoma and on immune cells
- M1/M2 macrophage infiltration
- Heterogeneity across sarcomas
- Lymphopenia
- CAR T cells, PD1 Ab PDL1 Ab trials ongoing

OncoImmunology 3, e28694; April 2014; © 2014 Landes Bioscience

Trial Watch

Oncolytic viruses for cancer therapy

Jonathan Pol[1,2,3,4,†], Norma Bloy[1,2,3,4,†], Florine Obrist[1,2,3,4], Alexander Eggermont[1], Jérôme Galon[5,6,7,8], Isabelle Cremer[5,6,7,9], Philippe Erbs[10], Jean-Marc Limacher[10], Xavier Preville[10], Laurence Zitvogel[1,11], Guido Kroemer[2,3,5,12,13,‡,*], and Lorenzo Galluzzi[1,3,5,‡,*]

Table 1. Clinical trials recently launched to evaluate the safety and efficacy of oncolytic virotherapy in cancer patients*

Virus	Indication(s)	Phase	Status	Route	Notes	Ref.
CG0070	Bladder carcinoma	I	n.a.	Intravesical	As a single agent	NCT00109655
ColoAd1	Colorectal carcinoma	I	Recruiting	i.t. or i.v.	As a single agent	NCT02053220
	Ovarian carcinoma	I/II	Not yet recruiting	i.p.	As a single agent	NCT02028117
	Solid tumors	I/II	Recruiting	i.v.	As a single agent	NCT02028442
CVA21	Solid tumors	I	Not yet recruiting	i.v.	As a single agent	NCT02043665
DNX2401	Glioblastoma	I	Recruiting	i.t.	Combined with temozolomide and/or surgery	NCT01956734
HSV-1716	Glioma	I	Recruiting	Into the tumor resection cavity	Combined with dexamethasone and surgery	NCT02031965
ICOVIR-5	Melanoma	I	Recruiting	i.v.	As a single agent	NCT01864759
	Solid tumors	I/II	Recruiting	i.p. (via MSCs)	As a single agent	NCT01844661
MV-NIS	HNSCC	I	Recruiting	i.t.	As a single agent	NCT01846091
	Ovarian carcinoma	I/II	Not yet recruiting	i.p. (via MSCs)	As a single agent	NCT02068794
Pexa-Vec	Ovarian carcinoma	II	Not recruiting	i.v.	As a single agent	NCT02017678
T-vec	Melanoma	II	Not yet recruiting	i.t.	As a single agent	NCT02014441
Toca 511	Brain tumors	I	Recruiting	i.v.	Combined with 5-FC	NCT01985256
VCN-01	Pancreatic cancer	I	Recruiting	i.t.	Combined with gemcitabine	NCT02045589
	Solid tumors	I	Recruiting	i.v.	Combined with gemcitabine	NCT02045602

Abbreviations: 5-FC, 5-fluorocytosine; CVA21, coxsackievirus A21; i.a., intra arteriam; i.p., intra peritoneum; i.t., intra tumorem; i.v., intra venam; HNSCC, head and neck squamous cell carcinoma; MSC, mesenchymal stem cell; n.a., not available; T-vec, talimogene laherparepvec. *Between 2013, March 1st and the date of submission.

REVIEW

OncoImmunology 2:12, e26621; December 2013; © 2013 Landes Bioscience

Trial Watch

Peptide vaccines in cancer therapy

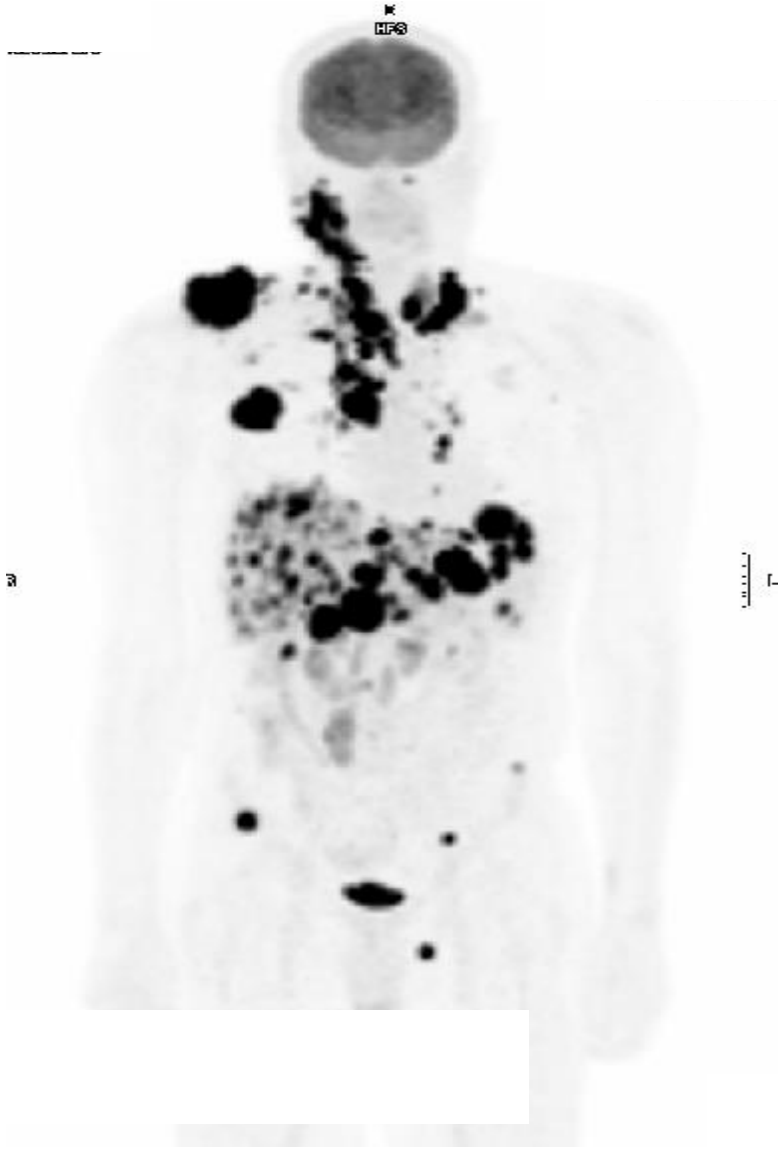
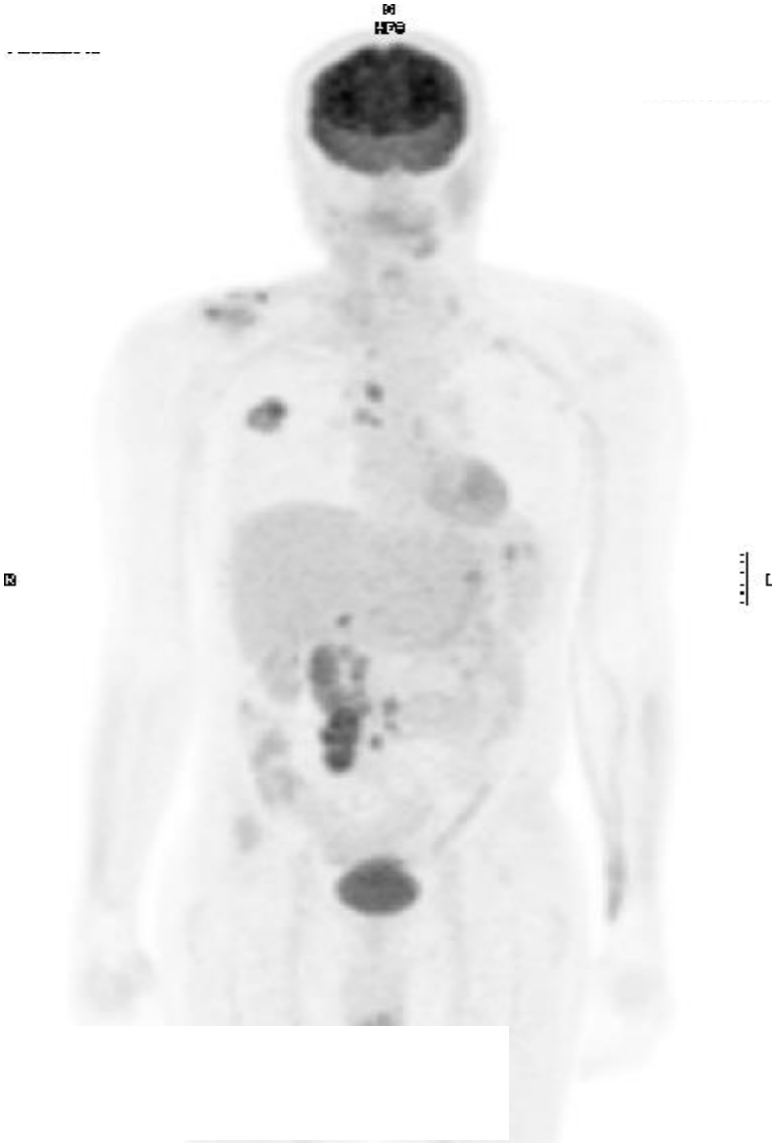
Fernando Aranda[1,2,3,4,†], Erika Vacchelli[1,2,3,4,†], Alexander Eggermont[1], Jerome Galon[5,6,7,8], Catherine Sautès-Fridman[6,7,9], Eric Tartour[10,11], Laurence Zitvogel[1,12], Guido Kroemer[2,4,5,10,13,‡,*], and Lorenzo Galluzzi[1,4,5,‡,*]

Indications	Phase	Status	Type	TAAs	Notes	Ref.
AML CML CMML MDS	I	Recruiting	Fusion proteins	NY-ESO-1	As Hiltonol®-adjuvanted intervention, combined with decitabine	NCT01834248
	I/II	Recruiting	Fusion proteins	MAGEA10 WT1	As AS01B-adjuvanted intervention, following HSCT	NCT01819558
Breast carcinoma	I/II	Not yet recruiting	Peptides	ERBB2	Combined with trastuzumab ± PSK	NCT01922921
	II	Recruiting	Peptides	ERBB2	As standalone adjuvanted intervention	NCT01729884
CIN	I	Active, not recruiting	Fusion proteins	E7	As GPI-0100-adjuvanted intervention	NCT01880411
GBM	I	Not yet recruiting	Peptides	CMV-derived antigens	Combined with temozolomide	NCT01854099
	I/II	Recruiting	Peptides	Multiple	As Hiltonol®-adjuvanted intervention, combined with temozolomide	NCT01920191
	II	Recruiting	HSP-TAA complexes	Multiple	Combined with bevacizumab	NCT01814813
Melanoma	I	Recruiting	Full length TAAs Peptides	NY-ESO-1	As Hiltonol®- and Montanide ISA51-adjuvanted intervention, combined with ipilimumab	NCT01810016
	I	Recruiting	HSP-TAA complexes	gp100	As standalone adjuvanted intervention	NCT01744171
	I	Recruiting	Phosphopeptides	BCAR3 IRS2	As Hiltonol®-, Montanide ISA51- and tetanus peptide-adjuvanted intervention	NCT01846143
	I/II	Recruiting	Peptides	MAGEA3.A1 NA17.A2	Combined with GM-CT-01	NCT01723813
	n.a.	Recruiting	Peptides	MART-1	As resiquimod-and Montanide ISA51-adjuvanted intervention, alone or combined with $Gag_{267-274}$	NCT01748747
MPM	II	Recruiting	Peptides	WT1	As GM-CSF- and Montanide ISA51-adjuvanted intervention	NCT01890980
Multiple myeloma	I	Recruiting	Peptides	Multiple	As standalone adjuvanted intervention	NCT01718899
	n.a.	Recruiting	Peptides	WT1	As GM-CSF-adjuvanted intervention	NCT01827137
NSCLC	I	Withdrawn	Peptide-containing liposomes	MUC1	Combined with cyclophosphamide	NCT01731587
	I/II	Recruiting	Peptides	MUC1	As Hiltonol®-adjuvanted intervention	NCT01720836
	I/II	Recruiting	Peptides	TERT	As GM-CSF-adjuvanted intervention	NCT01789099
Prostate cancer	I/II	Recruiting	Peptides	TERT	As GM-CSF-adjuvanted intervention	NCT01784913

Abbreviations: AML, acute myeloid leukemia; CIN, cervical intraepithelial neoplasia; CML, chronic myeloid leukemia; CMML, chronic myelomonocytic leukemia; CMV, cytomegalovirus; GBM, glioblastoma multiforme; GM-CSF, granulocyte-macrophage colony-stimulating factor; HSCT, hematopoietic stem cell transplantation; HSP, heat-shock protein; MDS, myelodysplastic syndrome; MPM, malignant pleural mesothelioma; MTC; medullary thyroid carcinoma; n.a., not available; NSCLC, non-small cell lung carcinoma; PSK, polysaccharide K; TAA, tumor-associated antigen. *started after September, 1st 2012 (source http://www.clinicaltrials.gov).

Metastatic Melanoma Response to Ipilimumab (anti-CTLA4)

Before Ipilimumab
04/22/11



After Ipilimumab
08/05/11