

SITC workshop 2:50 pm - 3:10 pm

Clinical Trials: Provoking Immunity in the Tumor Microenvironment

Antoni Ribas, M.D., Ph.D.
Professor of Medicine
Professor of Surgery
Professor of Molecular and Medical Pharmacology
Director, Tumor Immunology Program,
Jonsson Comprehensive Cancer Center (JCCC)
University of California Los Angeles (UCLA)

Disclosure Information

Antoni Ribas

I have the following financial relationships to disclose:

- Consultant for: Kite Pharma
- Speaker's Bureau for: None
- Grant/Research support from: None
- Stockholder in: Kite Pharma
- Honoraria from: Amgen, Celgene, Genentech-Roche, GSK, Millennium, Novartis, Prometheus
- Employee of: None

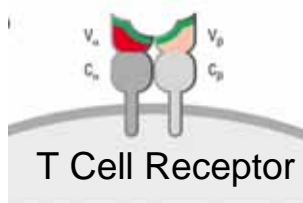
-and -

- I will discuss the following off label use and/or investigational use in my presentation: tremelimumab, nivolumab

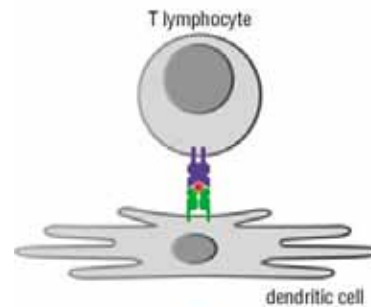
Monitoring Tumor Immunotherapy

In vitro

Molecules



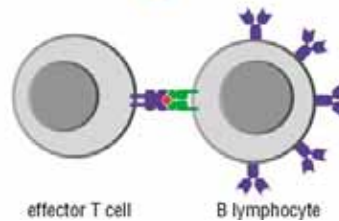
Cells



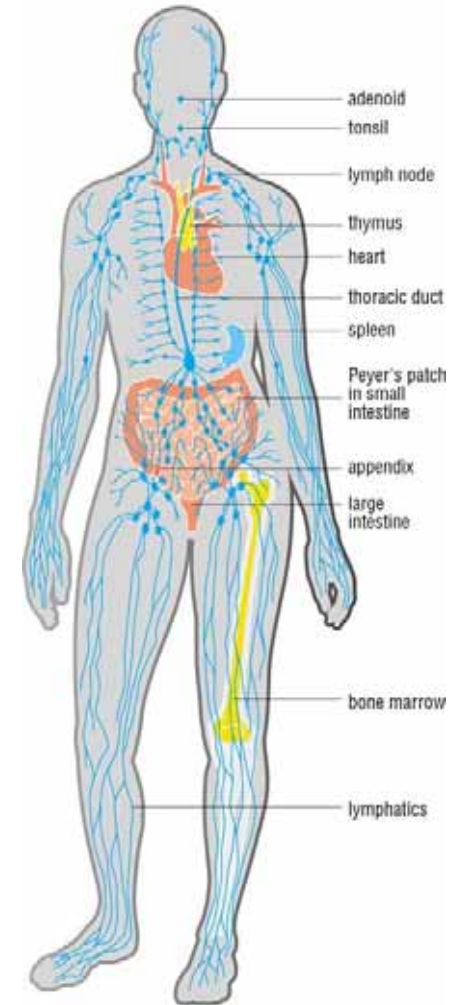
proliferation



differentiation



In vivo



Whole-body imaging

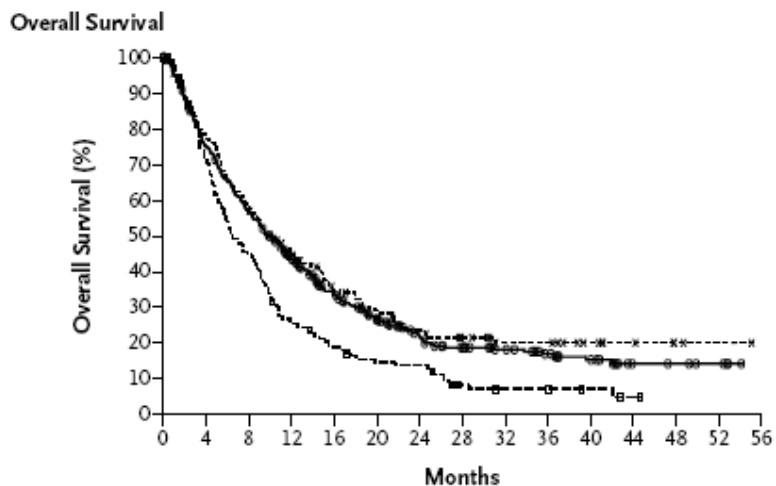
Durable responses with anti-CTLA4 in approximately 10-15% of patients

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 Walter J. Urba, M.D., Ph.D.

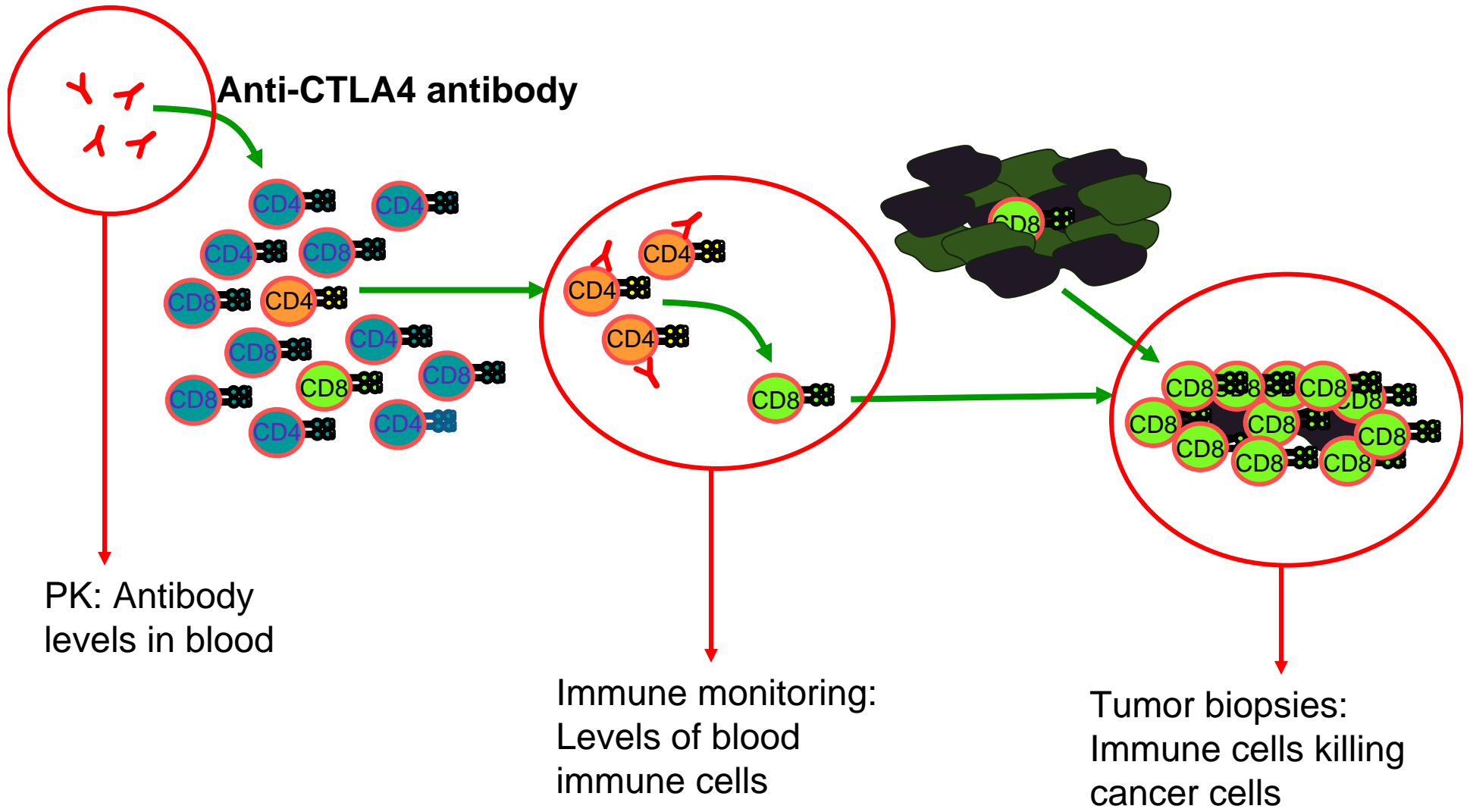


CTLA4 response since 2004



CTLA4 response since 2003

How can CTLA4 blockade therapy be studied in humans?



Cancer regression and autoimmunity induced by cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma

Giao Q. Phan¹, James C. Yang¹, Richard M. Sherry¹, Patrick Hwu¹, Suzanna L. Topalian¹, Douglas J. Schwartzentruber¹, Nicholas P. Restifo¹, Leah R. Haworth¹, Claudia A. Selpp¹, Linda J. Frezza¹, Kathleen E. Morton¹, Sharon A. Mavroukakis¹, Paul H. Duray¹, Seth M. Steinberg¹, James P. Allison¹, Thomas A. Davis¹, and Steven A. Rosenberg^{1,†}

VOLUME 23 • NUMBER 25 • SEPTEMBER 1, 2005

JOURNAL OF CLINICAL ONCOLOGY

Autoimmunity Correlates With Tumor Regression in Patients With Metastatic Melanoma Treated With Anti-Cytotoxic T-Lymphocyte Antigen-4

Peter Aulic, Giao Q. Phan, Ajay V. Maker, Michael R. Robinson, Marsha M. Quazzio, James C. Yang, Richard M. Sherry, Suzanna L. Topalian, Linda J. Frezza, Kathleen E. Morton, Nicholas P. Restifo, Leah R. Haworth, Catherine Levy, Sharon A. Mavroukakis, Geoff Nichol, Michael J. Yellin, and Steven A. Rosenberg

Analysis of the Cellular Mechanism of Antitumor Responses and Autoimmunity in Patients Treated with CTLA-4 Blockade

Ajay V. Maker, Peter Attia, and Steven A. Rosenberg[†]

The Journal of Immunology

CTLA-4 blockade enhances polyfunctional NY-ESO-1 specific T cell responses in metastatic melanoma patients with clinical benefit

Jianda Yuan¹, Sacha Gnjatic¹, Hao Li¹, Sarah Powell¹, Humildad F. Gallardo¹, Erika Ritter¹, Geoffroy Y. Ku¹, Achim A. Jungbluth¹, Neil H. Segal¹, Teresa S. Rasalan¹, Gregor Manukian¹, Yinyan Xu¹, Ruth-Ann Roman¹, Stephanie L. Terzilli¹, Melanie Hoywood¹, Evelina Pogoriler¹, Gord Ritter¹, Lloyd J. Old¹, James P. Allison^{1,2,3,4}, and Jedd D. Wolchok^{1,2,3,4}

Integrated NY-ESO-1 antibody and CD8⁺ T-cell responses correlate with clinical benefit in advanced melanoma patients treated with ipilimumab

Jianda Yuan¹, Matthew Admon¹, Brian A. Ginsberg¹, Teresa S. Rasalan¹, Erika Ritter¹, Humildad F. Gallardo¹, Yinyan Xu¹, Evelina Pogoriler¹, Stephanie L. Terzilli¹, Deborah Kuk¹, Katherine S. Panagess¹, Gord Ritter¹, Mario Sznol¹, Ruth Halaban¹, Achim A. Jungbluth¹, James P. Allison^{1,2,3,4}, Lloyd J. Old^{1,2}, and Jedd D. Wolchok^{1,2,3,4}

Cancer Immunol Immunother (2011) 60:1137–1146

DOI 10.1007/s00262-011-1011-0

FOCUSSED RESEARCH REVIEW

CTLA-4 blockade increases antigen-specific CD8⁺ T cells in prevacinated patients with melanoma: three cases

Jianda Yuan • Brian Ginsberg • David Page • Yanyun Li • Teresa Rasalan • Humildad F. Gallardo • Yinyan Xu • Sylvia Adams • Nina Bhardwaj • Klaus Busam • Lloyd J. Old • James P. Allison • Achim Jungbluth • Jedd D. Wolchok

Immunologic and clinical effects of antibody blockade of cytotoxic T lymphocyte-associated antigen 4 in previously vaccinated cancer patients

F. Stephen Hodt^{1,2}, Marcus Butler¹, Darryl A. Oblo¹, Michael V. Solder^{1,2}, Frank G. Haluska¹, Andrea Kruse¹, Suzanne MacRae¹, Marybeth Nelson¹, Christine Canning¹, Israel Lowy¹, Alan Korman¹, David Lautz¹, Sara Russell¹, Michael T. Jaklitsch¹, Nikhil Ramaley¹, Teresa C. Chen¹, Donna Neuberg¹, James P. Allison^{1,2}, Martin C. Mihm¹, and Glenn Dranoff¹

blood

CTLA4 blockade expands FoxP3⁺ regulatory and activated effector CD4⁺ T cells in a dose-dependent fashion

Brian Kavanagh^{1,2}, Shaun O'Brien^{1,2}, David Lee^{1,2}, Yalei Hou^{1,2}, Vivian Weinberg¹, Brian Rini¹, James P. Allison¹, Eric J. Small¹, and Lawrence Fong^{1,2}

Potentiating Endogenous Antitumor Immunity to Prostate Cancer through Combination Immunotherapy with CTLA4 Blockade and GM-CSF

Lawrence Fong^{1,2}, Serena S. Kwek^{1,3}, Shaun O'Brien^{1,2}, Brian Kavanagh^{1,2}, Douglas G. McNeil¹, Vivian Weinberg¹, Amy M. Liu¹, Jonathan Rosenberg¹, Charles J. Ryan¹, Brian I. Rini¹, and Eric J. Small¹

Cancer Res 2009; 69: (2). January 15, 2009

Definition of an Immunologic Response Using the Major Histocompatibility Complex Tetramer and Enzyme-Linked Immunospot Assays

Begoña Comin-Anduix¹, Antonio Gualberto¹, John A. Glaspy^{2,3}, Elisabeth Seja², Maribel Ontiveros², Deborah L. Reardon⁴, Roberto Renteria⁵, Brigitte Englaffner⁴, James S. Economou^{1,3}, Jesus Gomez-Navarro⁴, and Antoni Ribas^{1,2,3}

Clin Cancer Res 2006;12(1) January 1, 2006

Journal of Translational Medicine

Research

Open Access

Detailed analysis of immunologic effects of the cytotoxic T lymphocyte-associated antigen 4-blocking monoclonal antibody tremelimumab in peripheral blood of patients with melanoma
Begoña Comin-Anduix¹, Yohan Lee¹, Jason Jali¹, Alain Algazi¹, Pilar de la Rocha¹, Luis H Camacho¹, Viviana A Bozon¹, Cecile A Bulanagui¹, Elisabeth Seja¹, Arturo Villanueva¹, Bradley R Straatman¹, Antonio Gualberto¹, James S Economou^{1,2,3}, John A Glaspy^{1,3,4}, Jesus Gomez-Navarro¹ and Antoni Ribas^{1,1,3,4}

Intratumoral Immune Cell Infiltrates, FoxP3, and Indoleamine 2,3-Dioxygenase in Patients with Melanoma Undergoing CTLA4 Blockade

Antoni Ribas^{1,2,3}, Begoña Comin-Anduix², James S. Economou^{2,3,4}, Timothy B. Donahue⁵, Pilar de la Rocha², Lihai F. Momo², Jason Jali², Vivian B. Dissette², Itzushi Peter Shintaku⁶, John A. Glaspy^{1,3}, Jesus Gomez-Navarro¹, and Alistair J. Cochran^{2,3,6}

Clin Cancer Res 2009;15(1) January 1, 2009

Dendritic Cell Vaccination Combined with CTLA4 Blockade in Patients with Metastatic Melanoma

Antoni Ribas^{1,2,3}, Begoña Comin-Anduix², Bartosz Chmielowski¹, Jason Jali², Pilar de la Rocha², Tara A. McCannell⁴, Maria Teresa Ochoa⁵, Elisabeth Seja¹, Arturo Villanueva¹, Denise K. Oseguera¹, Bradley R. Straatman¹, Alistair J. Cochran^{2,3,6}, John A. Glaspy^{1,3}, Liu Hui², Francesco M. Marincola¹, Ena Wang⁷, James S. Economou^{2,3} and Jesus Gomez-Navarro¹

Clin Cancer Res 2009;15(19) October 1, 2009

VOLUME 23 • NUMBER 4 • FEBRUARY 1, 2005

JOURNAL OF CLINICAL ONCOLOGY

Autoimmunity in a Phase I Trial of a Fully Human Anti-Cytotoxic T-Lymphocyte Antigen-4 Monoclonal Antibody With Multiple Melanoma Peptides and Montanide ISA 51 for Patients With Resected Stages III and IV Melanoma

Kristin Sanderson, Ronald Savadoni, Peter Lee, Dongxin Liu, Susan Grisham, Joie Stohry, Shirley Stan, Geoffrey Nichol, Thomas Davis, Tibor Keler, Michael Yellin, and Jeffrey Weber

CTLA-4 Blockade Confers Lymphocyte Resistance to Regulatory T-Cells in Advanced Melanoma: Surrogate Marker of Efficacy of Tremelimumab?

Cédric Miranville^{1,2}, François Ghiringhelli^{1,2,3}, Stephen Roux^{1,2}, Nathalie Chaput^{1,2}, Christine Matusz¹, Ursula Grohmann¹, Soohie Caillaud-Zucman¹, Laurence Zitvoan^{1,2}, and Caroline Robert^{1,3}

Clin Cancer Res 2008;14(16) August 15, 2008

Melan-A-specific Cytotoxic T Cells Are Associated with Tumor Regression and Autoimmunity Following Treatment with Anti-CTLA-4

Oliver Klein¹, Lisa M. Ebert¹, Theo Ntcholas¹, Judy Brownings¹, Sarah E. Russell¹, Marina Zuber¹, Heather M. Jackson¹, Nektaria Demopoulou¹, Bee Shin Tan¹, Axel Hoos², Immanuel F. Luescher¹, Jan D. Davis¹, Weisan Chen¹, and Jonathan Ceballos¹

Clin Cancer Res 2009;15(7) April 1, 2009

Anti-CTLA-4 therapy results in higher CD4⁺ICOS^{hi} T cell frequency and IFN- γ levels in both nonmalignant and malignant prostate tissues

Hong Chan¹, Chrysoula I. Laskou¹, Ashish Kamat¹, Curtis Pettaway¹, John F. Ward¹, Derek Ng Tang¹, Jingling Sun¹, Achim A. Jungbluth¹, Patricia Troncoso¹, Christopher Logothetis¹, and Padmanee Sharma^{1,†}

Departments of ¹Gastrointestinal Medical Oncology, ²Urology, ³Pathology, and ⁴Immunology, The University of Texas M. D. Anderson Cancer Center, Houston, TX 77030; and ⁵Cedars-Sinai Cancer Research, New York Branch, Memorial Sloan-Kettering Cancer Center, New York, NY 10025

CTLA-4 blockade increases IFN γ -producing CD4⁺ICOS^{hi} cells to shift the ratio of effector to regulatory T cells in cancer patients

Chrysoula I. Laskou¹, Ashish Kamat¹, Derek Ng Tang¹, Hong Chan¹, Jingling Sun¹, Patricia Troncoso¹, Christopher Logothetis¹, and Padmanee Sharma^{1,†}

Departments of ¹Gastrointestinal Medical Oncology, ²Urology, ³Pathology, and ⁴Immunology, M.D. Anderson Cancer Center, University of Texas, Houston, TX 77030

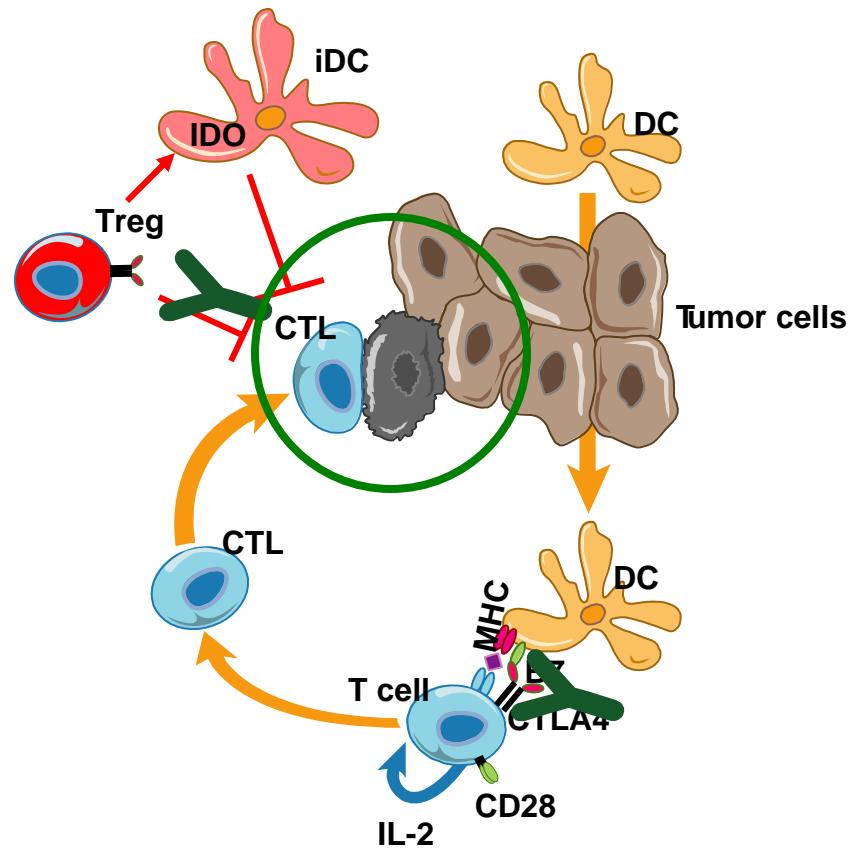
Cancer Therapy: Clinical

Preoperative CTLA-4 Blockade: Tolerability and Immune Monitoring in the Setting of a Presurgical Clinical Trial

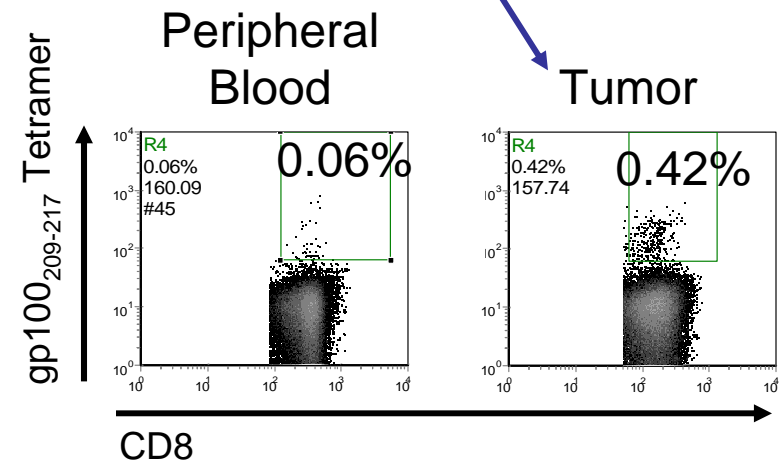
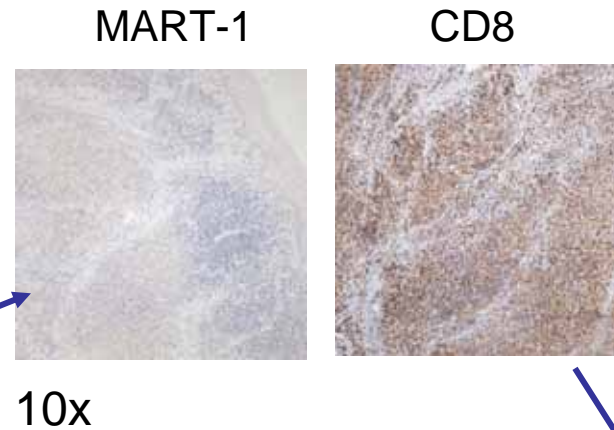
Bradley C. Carlton¹, Jedd D. Wolchok^{1,2}, Jianda Yuan¹, Ashish Kamat¹, Derek S. Ng Tang¹, Jingling Sun¹, Geoffroy Ku¹, Patricia Troncoso¹, Christopher J. Logothetis¹, James P. Allison^{1,2}, and Padmanee Sharma^{1,2,4}

Clinical
Cancer
Research

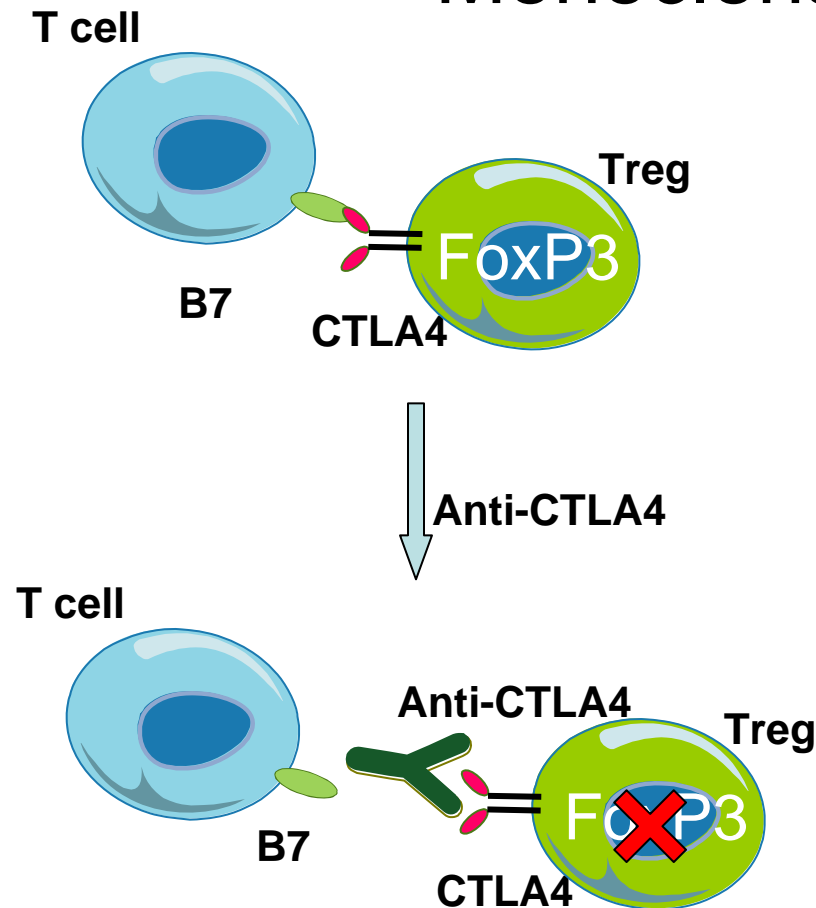
Studying where it counts: The Tumor



Anti-CTLA4 Antibodies Induce Dense Intratumoral Infiltrated by CD8+ CTLs in Regressing Tumors



Treg Depletion with CTLA4 Blocking Monoclonal Antibodies



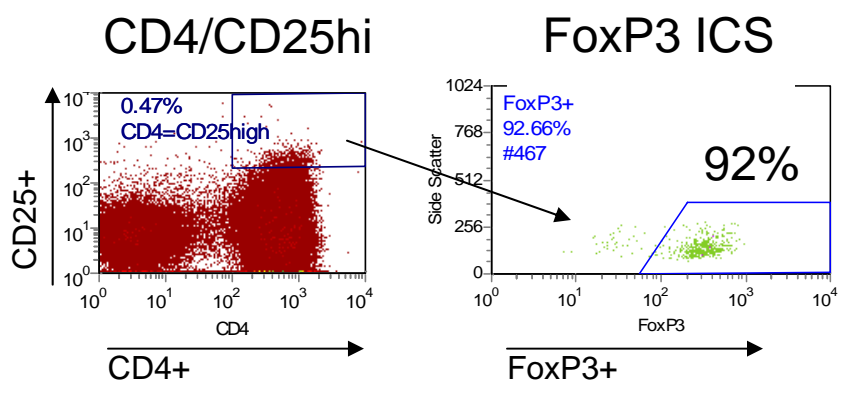
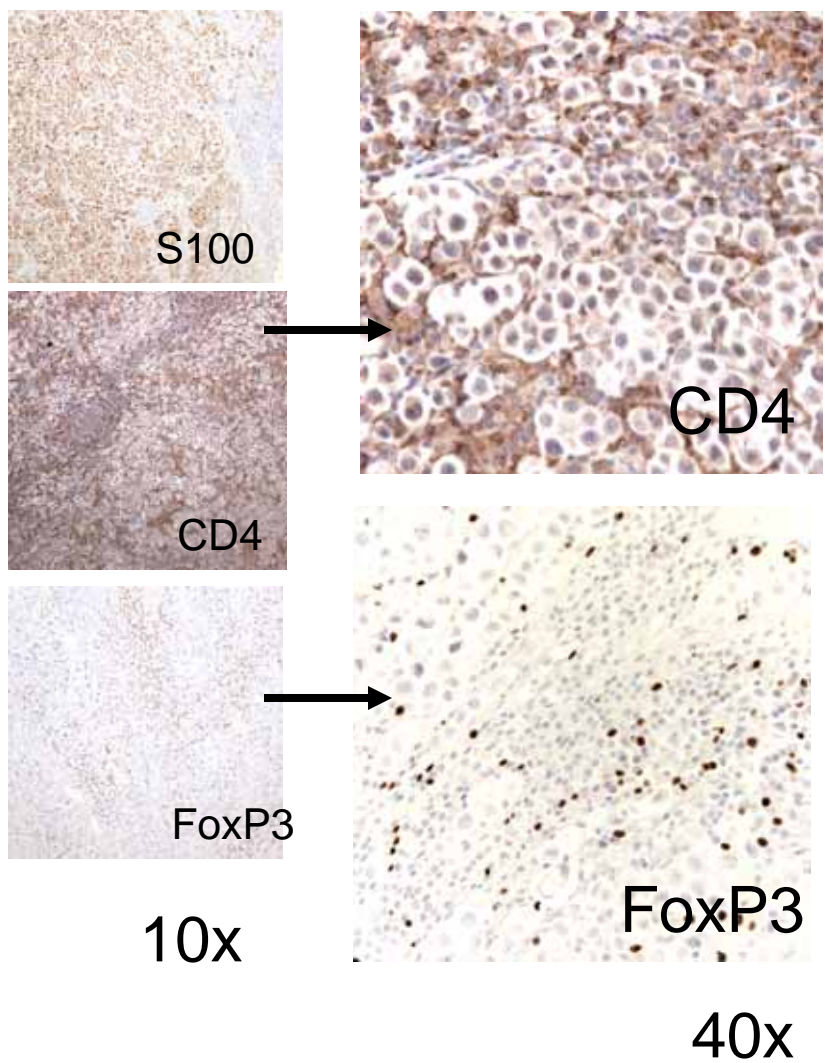
- Treg depletion in peripheral blood with anti-CTLA4 mAb:
 - Reuben *et al.* Cancer 2006
- No Treg depletion in peripheral blood with anti-CTLA4 mAb:
 - Maker *et al.* J Immunol 2005
 - Comin-Anduix *et al.* iSBTc 2006

Patient PD: FoxP3 by IHC or ICS in TIL

Post

FoxP3 in TIL by IHC

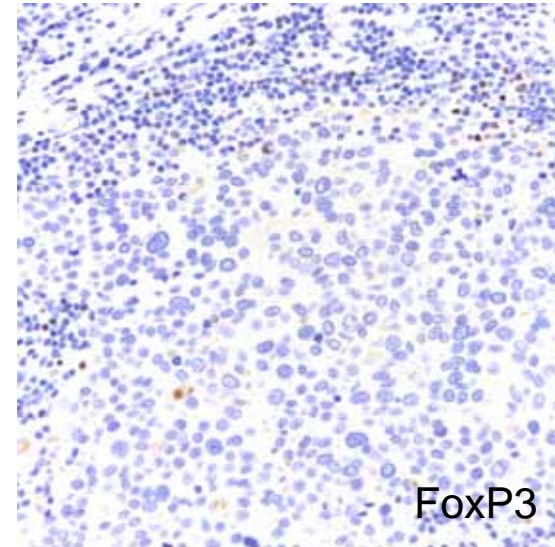
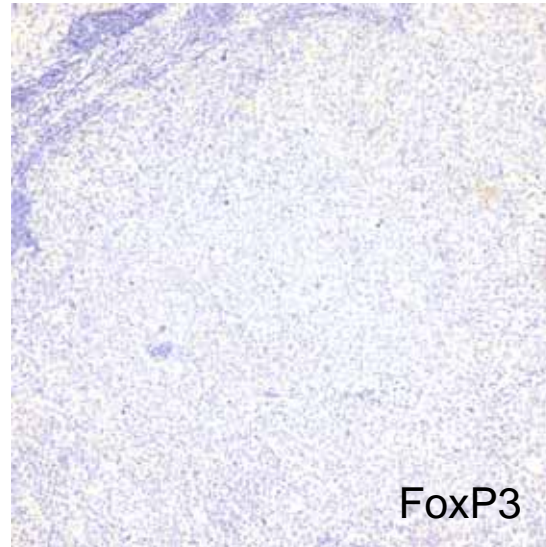
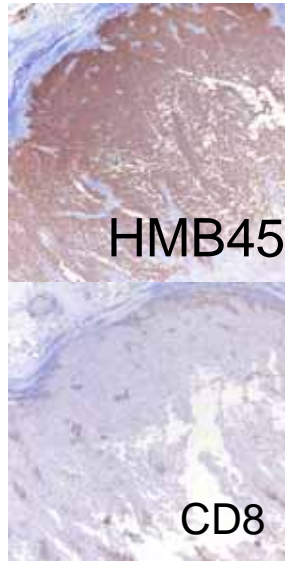
FoxP3 in TIL by ICS



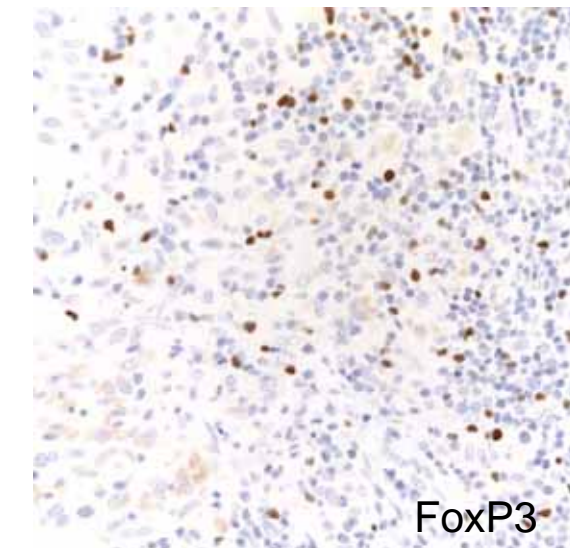
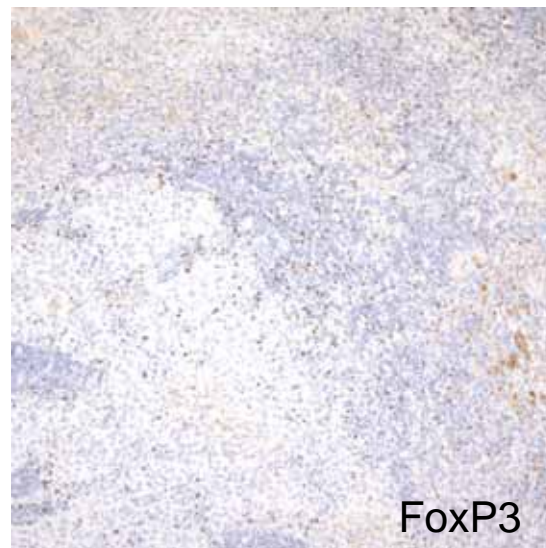
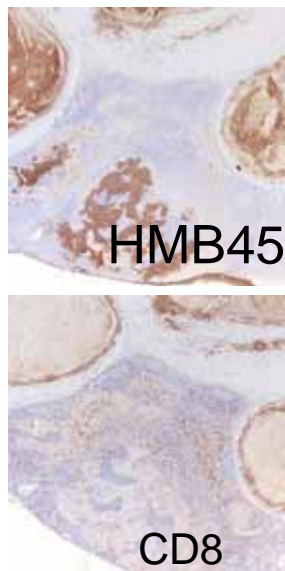
Begonya Comin-Anduix, PhD
Alistair Cochran, MD

pPR: FoxP3 Pre and Post CP-675,206

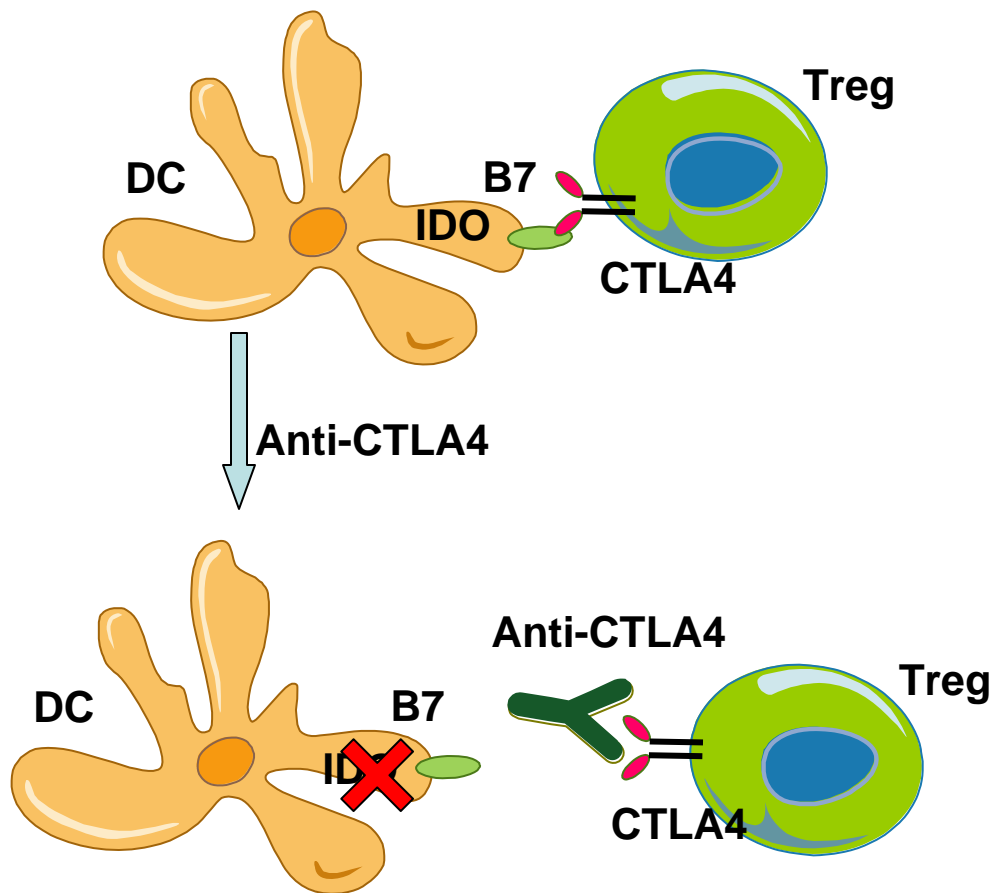
Pre



Post



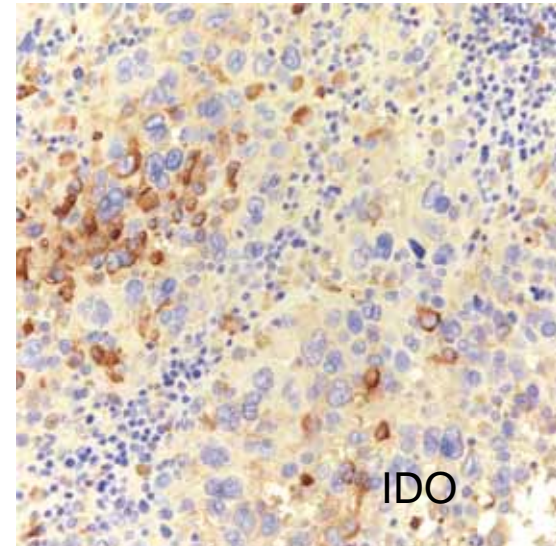
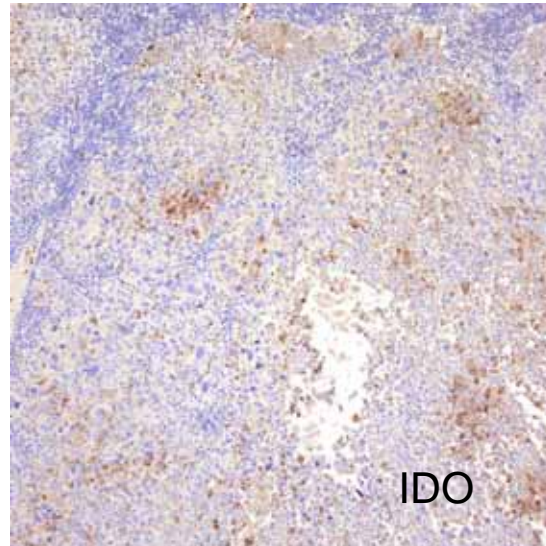
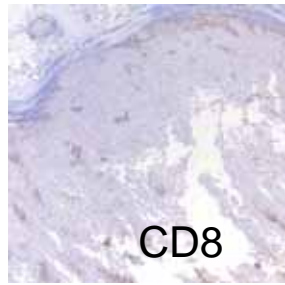
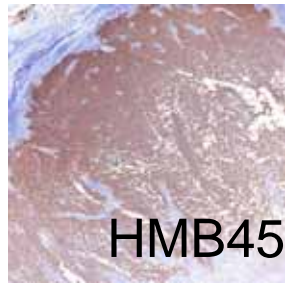
Inhibition of IDO by CTLA4 Blocking Monoclonal Antibodies



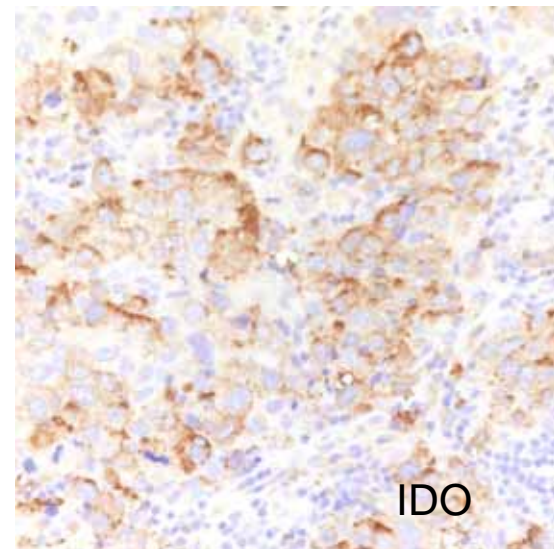
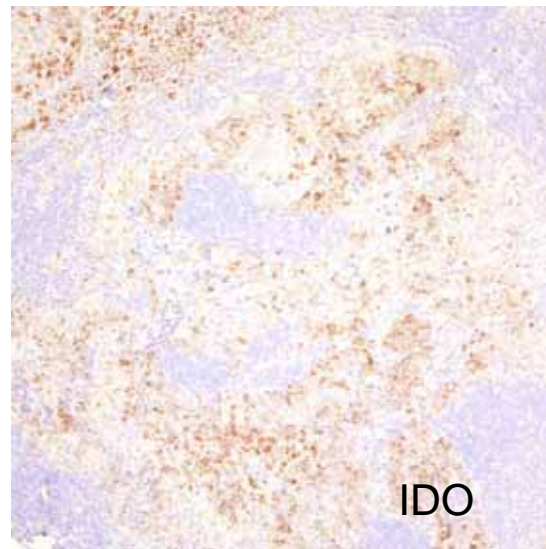
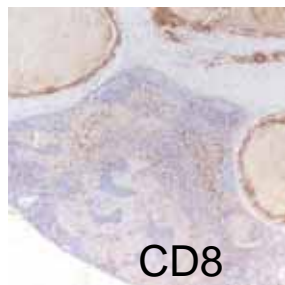
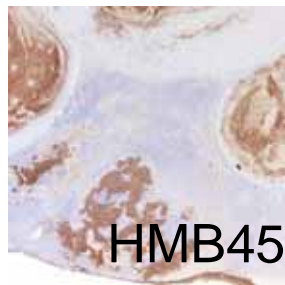
- Grohmann, Fallarino *et al.* Nat Immunol. 3, 1097 (2002)
- Grohmann, Fallarino *et al.* Nat Immunol. 4, 1206 (2003)
- Munn, Mellor *et al.* J Clin Invest. 114, 280 (2004)
- Munn, Mellor *et al.* Int Immunol. 16, 1391 (2004)

pPR: IDO Pre and Post CP-675,206

Pre



Post



4x

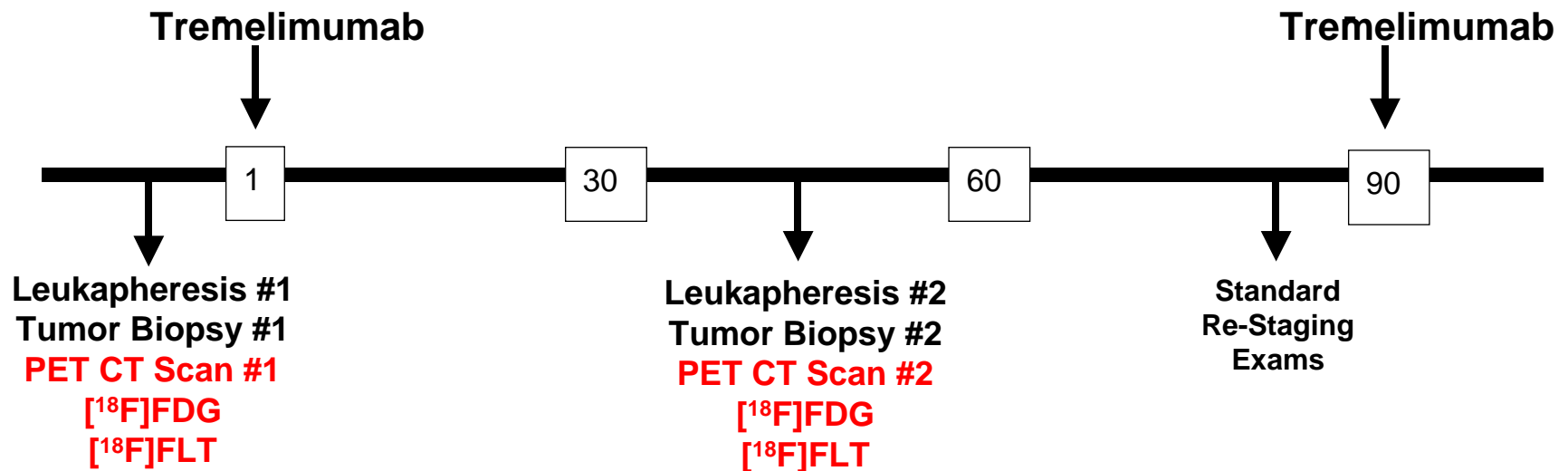
10x

40x

Intratumoral FoxP3+ and IDO+ Cells

Pt No.	Response	Timing of Biopsy	FoxP3	FoxP3 Change	IDO	IDO Change
1	PR	Pre	0		++ diffuse	
		Post (3 mo/3mo)	+ patchy	↑	+ patchy	↓
2	PR	Pre	0		+ patchy	
		Post (2 mo/1 mo)	+ patchy	↑	+ patchy	=
3	pPR	Pre	+ patchy		+ patchy	
		Post (9 mo/1 mo)	++ patchy	↑	+ patchy	=
4	Progr	Pre	+ patchy		-	
		Post (1 mo/1 mo)	+ patchy	=	-	=

Phase 2 to Study the Mechanism of Action of Tremelimumab in Patients Using Repeated Outpatient Tumor Biopsies



Modulation of Cell Signaling Networks after CTLA4 Blockade in Patients with Metastatic Melanoma

Begoña Comin-Anduix^{1,2*}, Hooman Sazegar³, Thinle Chodon³, Douglas Matsunaga³, Jason Jalil¹, Erika von Euw¹, Helena Escuin-Ordinas³, Robert Balderas⁴, Bartosz Chmielowski³, Jesus Gomez-Navarro^{5*}, Richard C. Koya¹, Antoni Ribas^{1,2,3*}

Journal of Translational Medicine 

Research

Open Access

CTLA4 blockade increases Th17 cells in patients with metastatic melanoma

Erika von Euw¹, Thinle Chodon², Narsis Attar², Jason Jalil¹, Richard C Koya¹, Begonya Comin-Anduix¹ and Antoni Ribas^{* 1,2,3}

Cancer Therapy: Clinical

Clinical
Cancer
Research

CTLA4 Blockade Induces Frequent Tumor Infiltration by Activated Lymphocytes Regardless of Clinical Responses in Humans

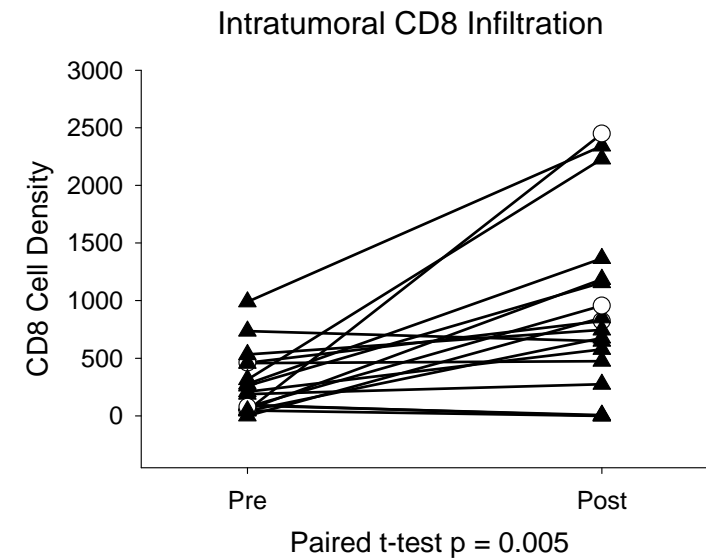
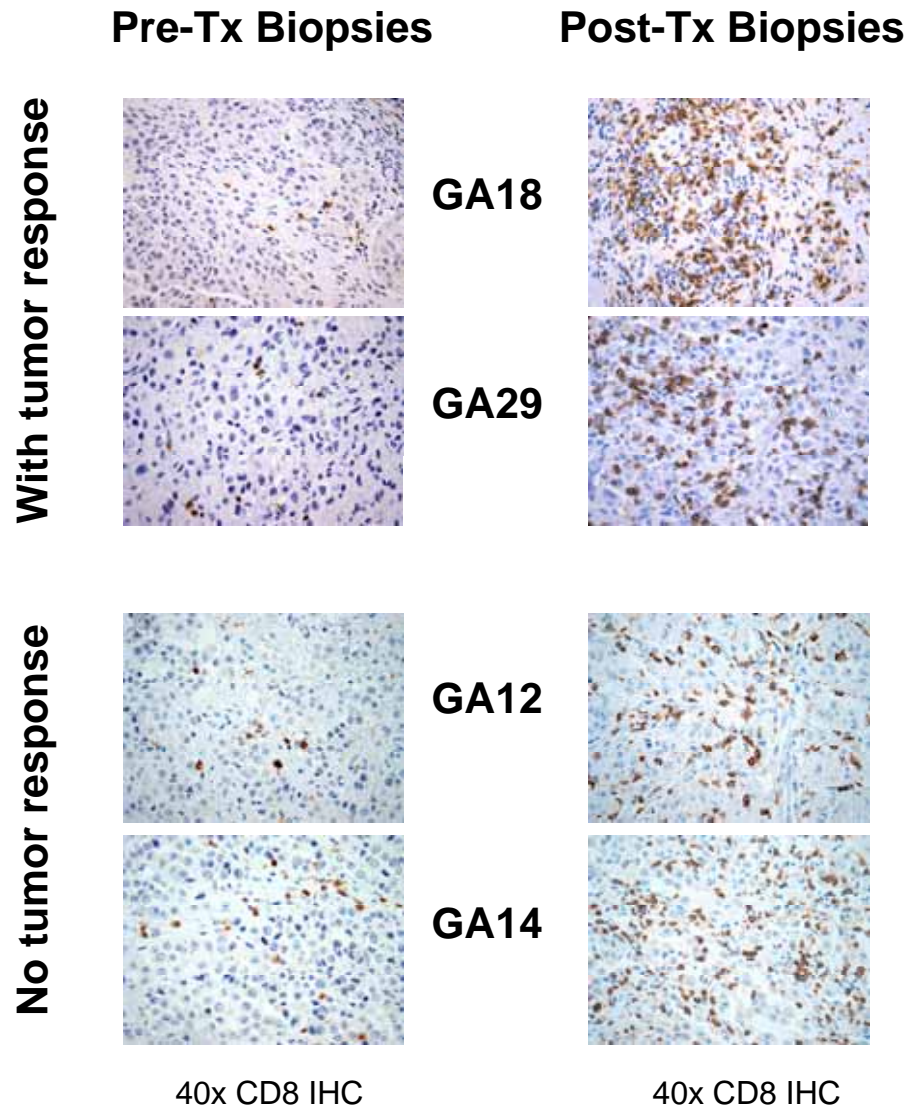
Rong Rong Huang¹, Jason Jalil², James S. Economou^{3,4}, Bartosz Chmielowski², Richard C. Koya³, Stephen Mok³, Hooman Sazegar², Elizabeth Seja², Arturo Villanueva², Jesus Gomez-Navarro⁵, John A. Glaspy^{2,4}, Alistair J. Cochran¹, and Antoni Ribas^{2,3,4}

Journal of Nuclear Medicine, published on February 11, 2010 as doi:10.2967/jnumed.109.070946

Imaging of CTLA4 Blockade-Induced Cell Replication with ¹⁸F-FLT PET in Patients with Advanced Melanoma Treated with Tremelimumab

Antoni Ribas¹⁻³, Matthias R. Benz⁴, Martin S. Allen-Auerbach⁴, Caius Radu²⁻⁴, Bartosz Chmielowski¹, Elizabeth Seja¹, John L. Williams⁴, Jesus Gomez-Navarro⁵, Timothy McCarthy⁵, and Johannes Czernin²⁻⁴

Increase in TIL in most patients regardless of tumor response



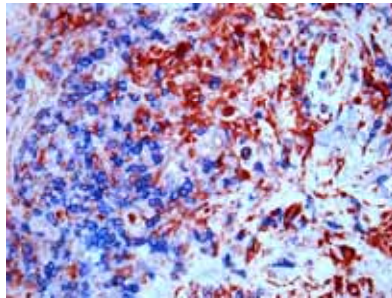
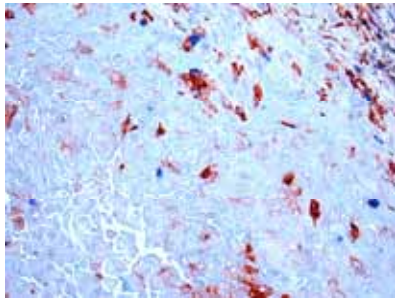
No difference in TIL activation or replication

HLA-DR+/CD45RO+ Activated T Cells

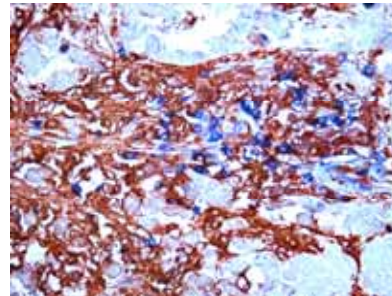
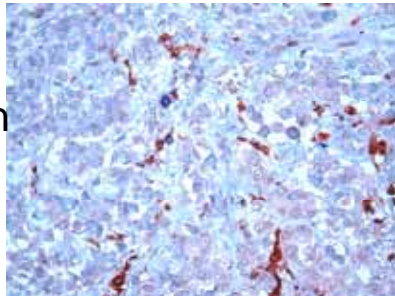
Pre-Tx

Post-Tx

Pt w
Response



Pt w
Progression

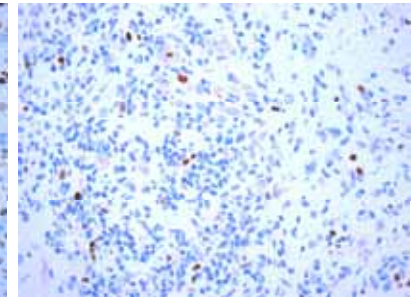
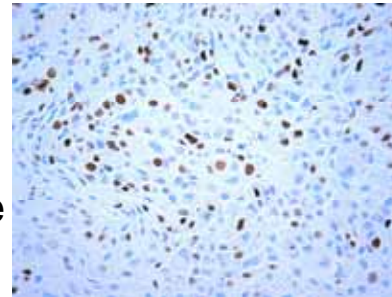


Ki-67+ Proliferating Cells

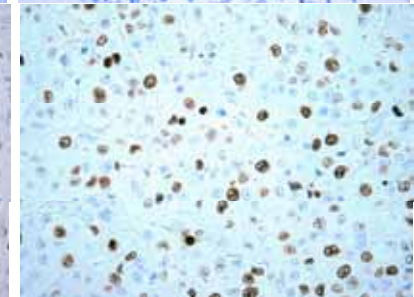
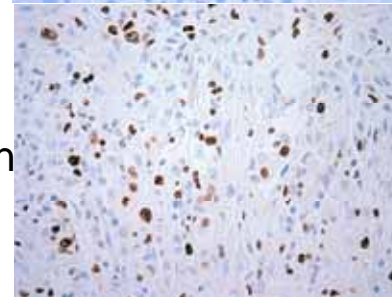
Pre-Tx

Post-Tx

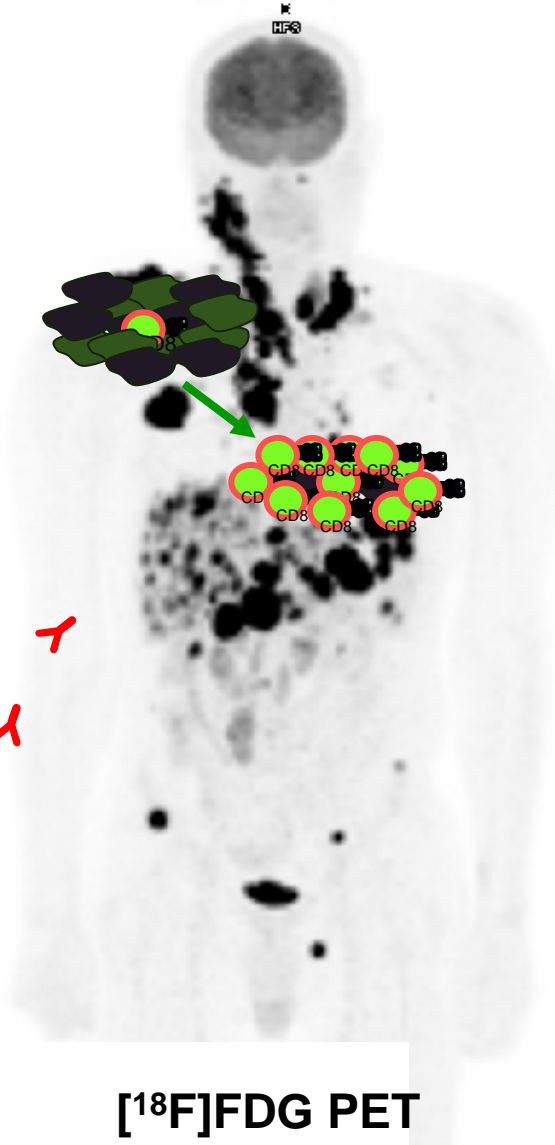
Pt w
Response



Pt w
Progression

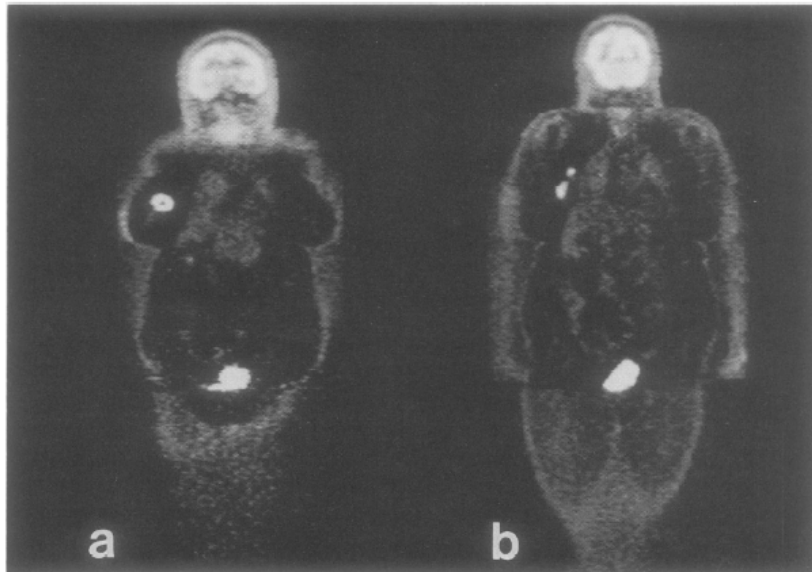


Where in the body is anti-CTLA4 working?



Where does lymphocyte replication happen?

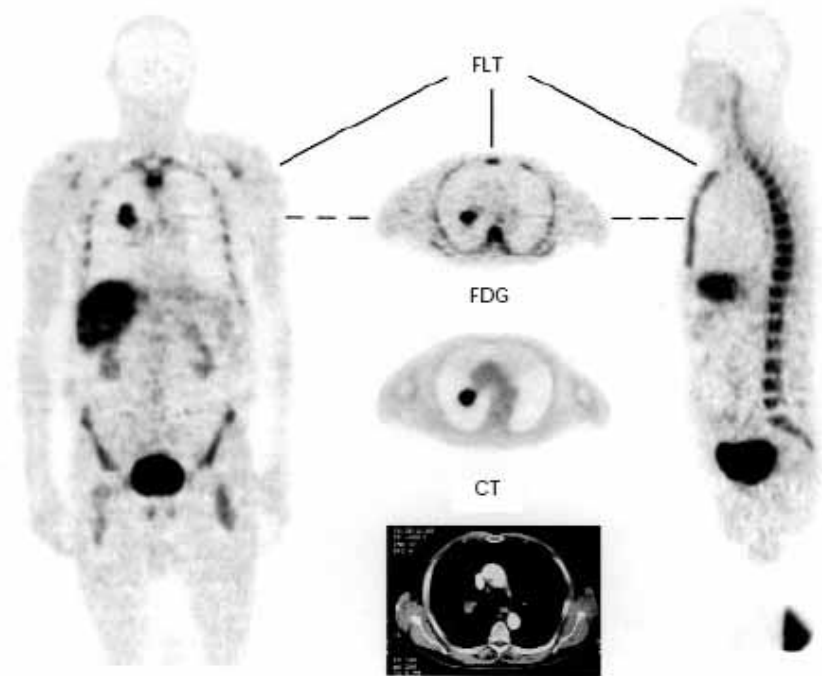
Whole Body Imaging with PET Probes: [¹⁸F]FDG and [¹⁸F]FLT



[¹⁸F]FDG:

- Positron emitting glucose analog
- Images glucose metabolism

Tse, ... Phelps, Glaspy *et al.* The application of positron emission tomographic imaging with fluorodeoxyglucose to the evaluation of breast disease. *Ann Surg* 1992

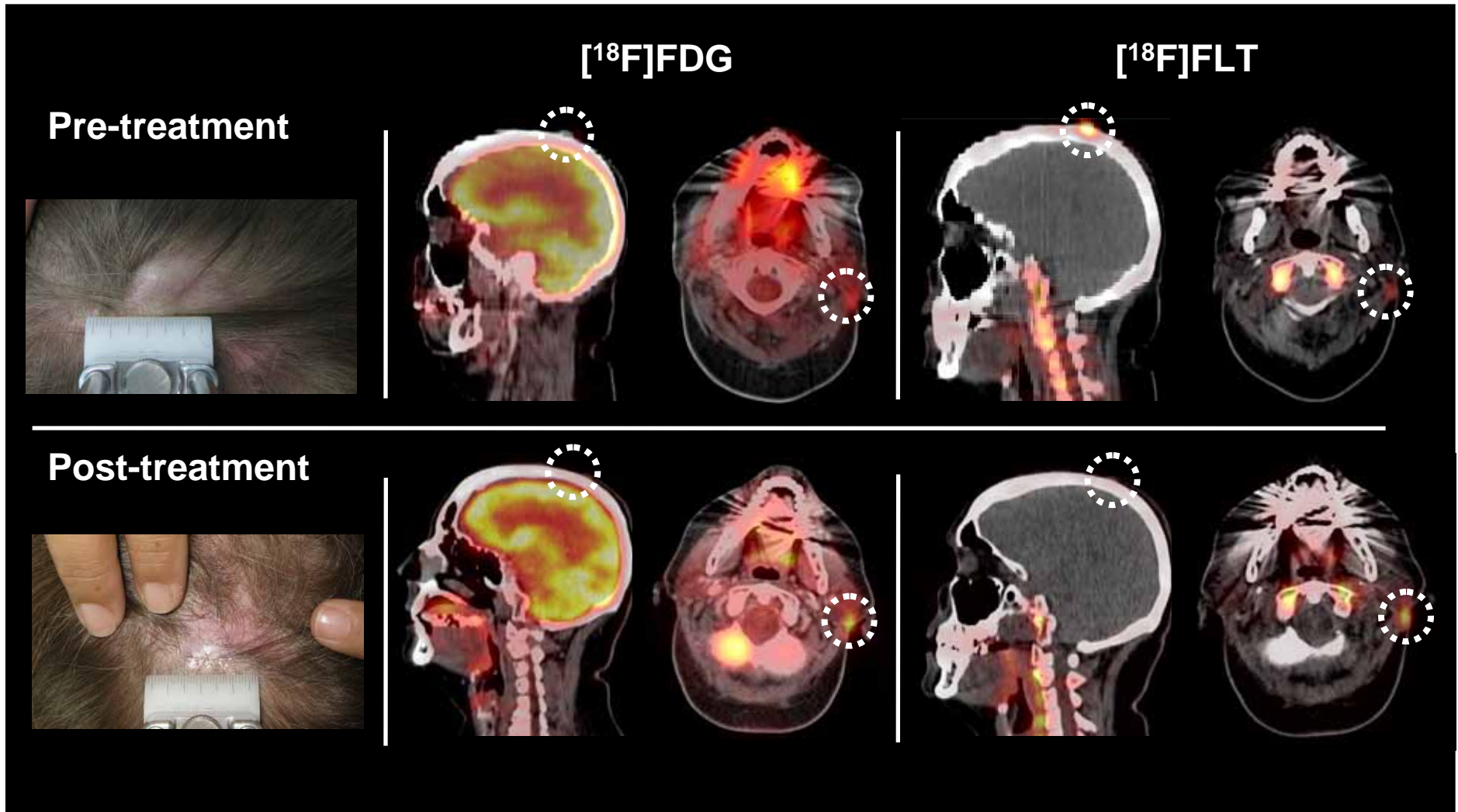


[¹⁸F]FLT:

- Positron emitting thymidine nucleoside analog
- Images cell replication

Shields *et al.* Imaging proliferation in vivo with [¹⁸F]FLT and positron emission tomography. *Nature Med* 1998

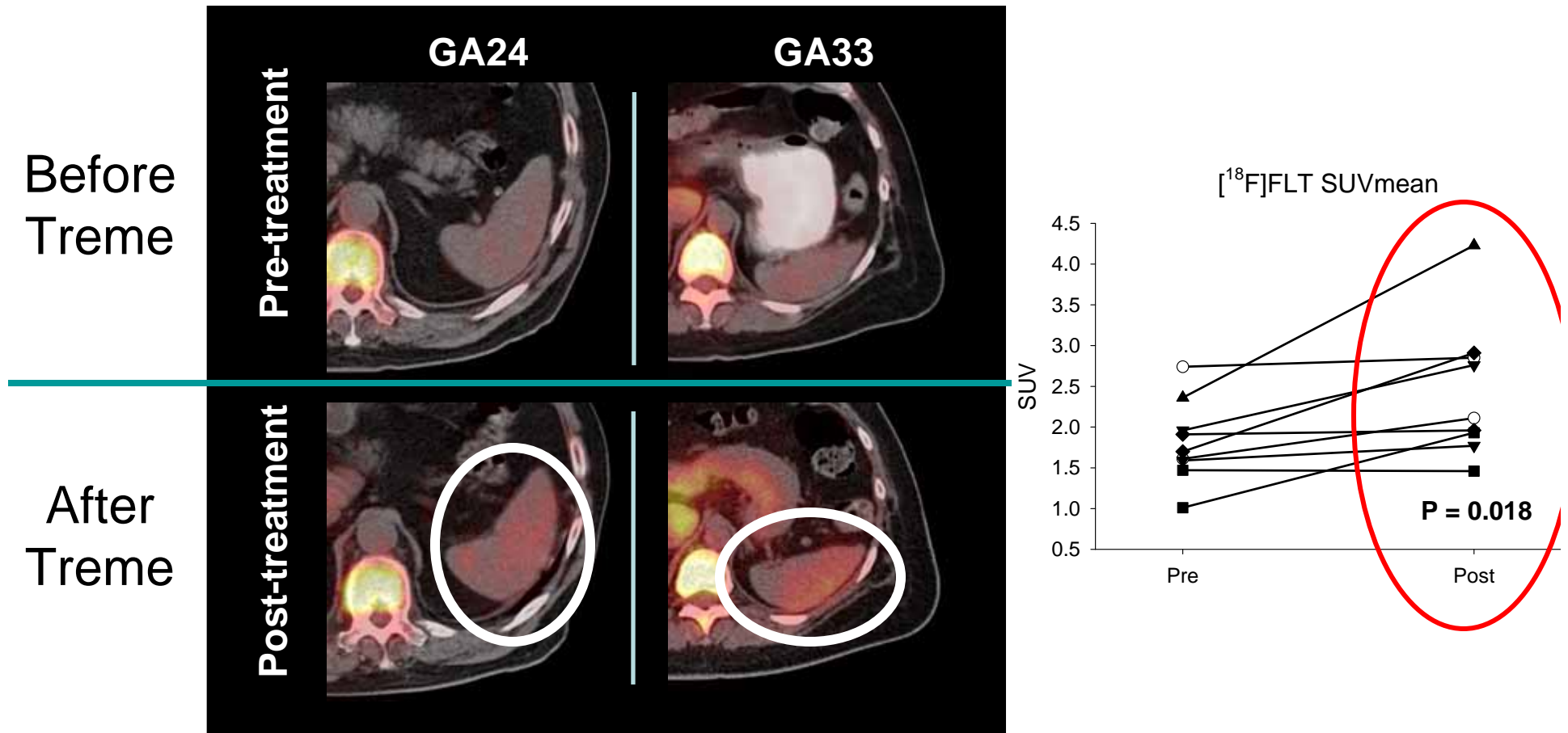
[¹⁸F]FDG and [¹⁸F]FLT PET in a Patient with Response to Tremelimumab



[¹⁸F]FDG:
- Positron emitting glucose analog
- Images glucose metabolism

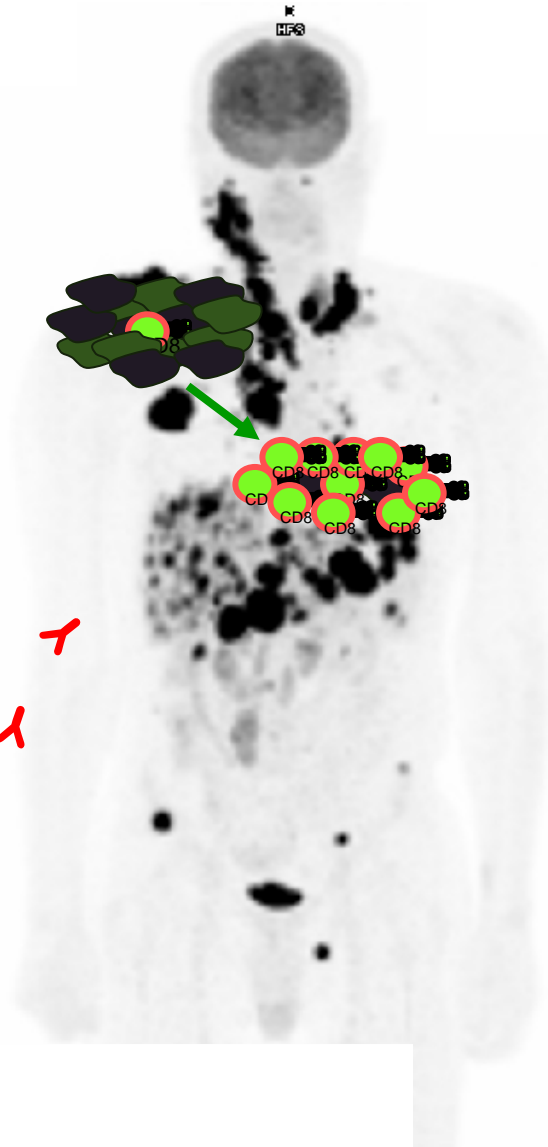
[¹⁸F]FLT:
- Positron emitting thymidine nucleoside analog
- Images cell replication

[¹⁸F]FLT PET Tracer Uptake in the Spleen Before and After Tremelimumab



Molecular imaging with the PET probe [¹⁸F]FLT (radiolabeled thymidine) allows mapping and non-invasive imaging of cell proliferation in spleen after CTLA4 blockade in patients with metastatic melanoma.

Where in the body is anti-CTLA4 working?



Where does lymphocyte replication happen? In lymphoid organs

ORIGINAL ARTICLE

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

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

ORIGINAL ARTICLE

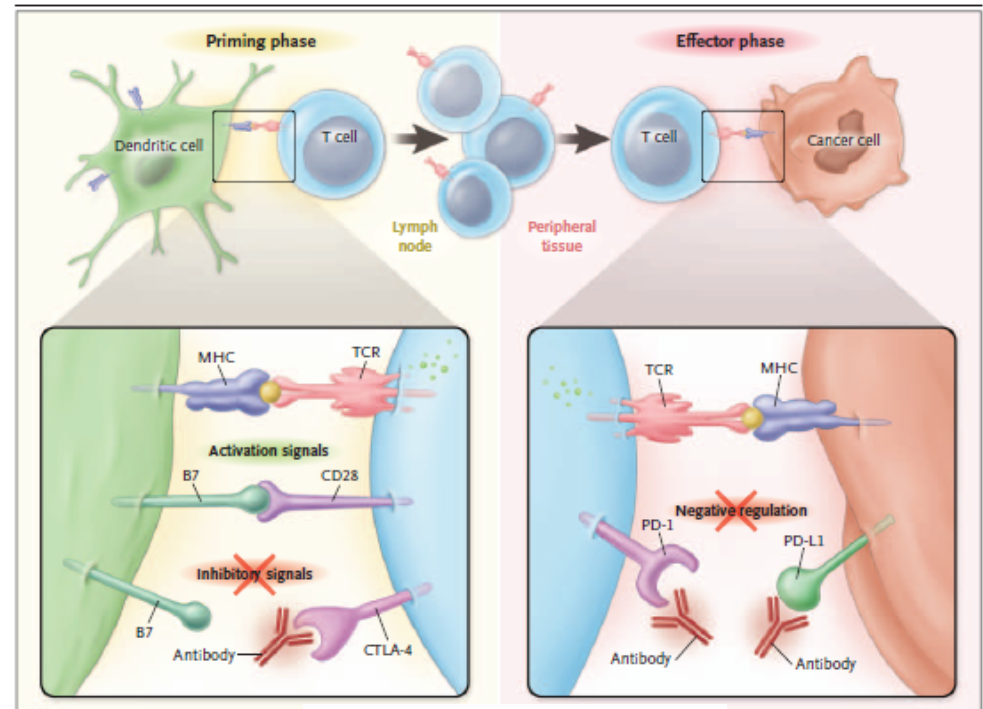
Safety and Activity of Anti-PD-L1 Antibody in Patients with Advanced Cancer

Julie R. Brahmer, M.D., Scott S. Tykodi, M.D., Ph.D., Laura Q.M. Chow, M.D., Wen-Jen Hwu, M.D., Ph.D., Suzanne L. Topalian, M.D., Patrick Hwu, M.D., Charles G. Drake, M.D., Ph.D., Luis H. Camacho, M.D., M.P.H., John Kauh, M.D., Kunle Odunsi, M.D., Ph.D., Henry C. Pitot, M.D., Omid Hamid, M.D., Shailender Bhatia, M.D., Renato Martins, M.D., M.P.H., Keith Eaton, M.D., Ph.D., Shuming Chen, Ph.D., Theresa M. Salay, M.S., Suresh Alaparthi, Ph.D., Joseph F. Grosso, Ph.D., Alan J. Korman, Ph.D., Susan M. Parker, Ph.D., Shruti Agrawal, Ph.D., Stacie M. Goldberg, M.D., Drew M. Pardoll, M.D., Ph.D., Ashok Gupta, M.D., Ph.D., and Jon M. Wigginton, M.D.



Tumor Immunotherapy Directed at PD-1

Antoni Ribas, M.D., Ph.D.

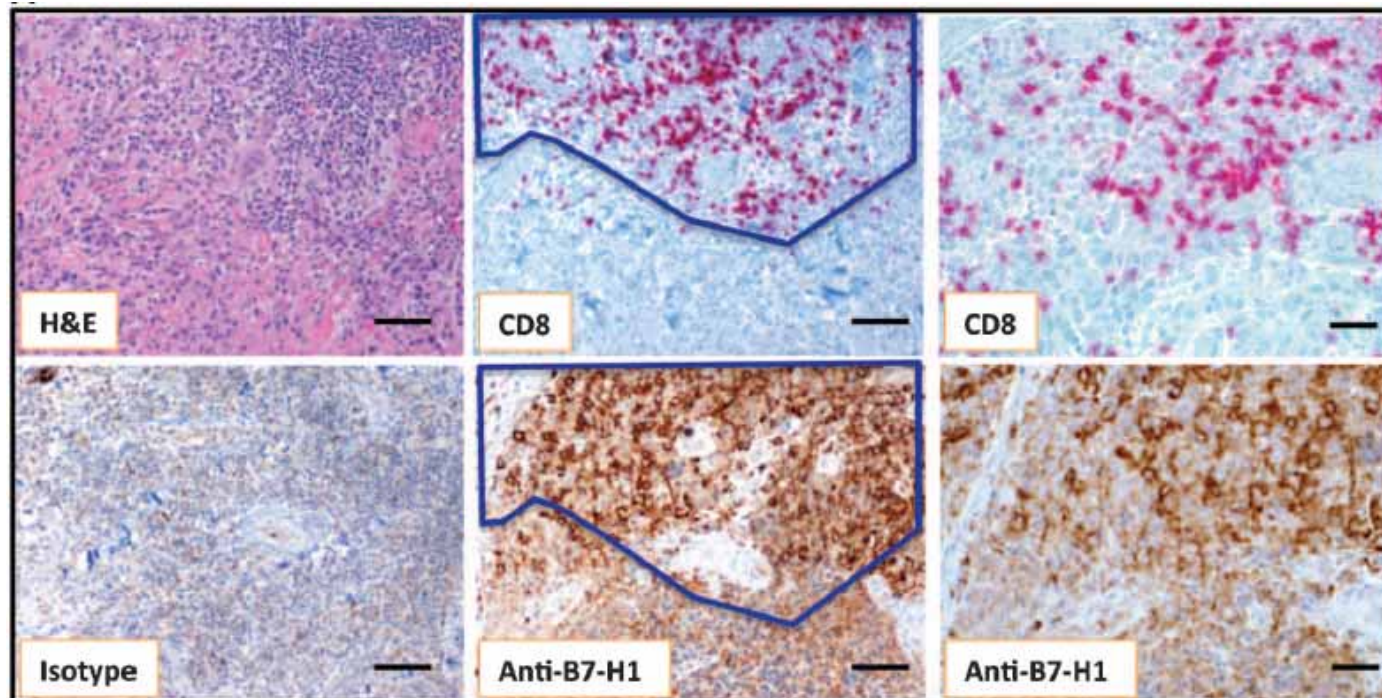


CANCER

Colocalization of Inflammatory Response with B7-H1 Expression in Human Melanocytic Lesions Supports an Adaptive Resistance Mechanism of Immune Escape

Janis M. Taube,^{1,2*} Robert A. Anders,² Geoffrey D. Young,^{3,4} Haiying Xu,¹ Rajni Sharma,² Tracee L. McMiller,⁴ Shuming Chen,⁴ Alison P. Klein,^{2,5} Drew M. Pardoll,⁵ Suzanne L. Topalian,^{4*} Lieping Chen^{1,5,6*}

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Conclusions

- The main goal of tumor immunotherapy is to bring activated T cells into tumors:
 - Vaccination with DC can occasionally achieve durable immune responses to cancer
 - CTLA4 blockade induces reproducible but low frequency durable tumor responses to cancer
- T cell infiltration is necessary but not sufficient to result in tumor responses
- FOXP3 and IDO expression in tumors does not seem to be associated with resistance to CTLA4 blockade
- T cell replication upon CTLA4 blockade happens in lymphoid organs and not in tumors



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