Adoptive Cellular Immunotherapy

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Saint John's Health Center

PROVIDENCE Health & Services

Cell Therapy: Overview

- **Background: Lymphocytes and Cancer**
- **History of ACT**
- **Current Programs and Recent Discoveries**
- **Outstanding issues and questions**
  - **Challenges**
  - **Opportunities**

Tumor-Infiltrating Lymphocytes

- **Endogenous immune responses to cancer are described in numerous tumor types and are strongly related to outcomes**
- **New immune therapies that activate those cells in vivo (e.g. checkpoint blockade) have shown dramatic effects**
- **Adoptive Cell Transfer has demonstrated proof of concept in melanoma and other cancers**

Background

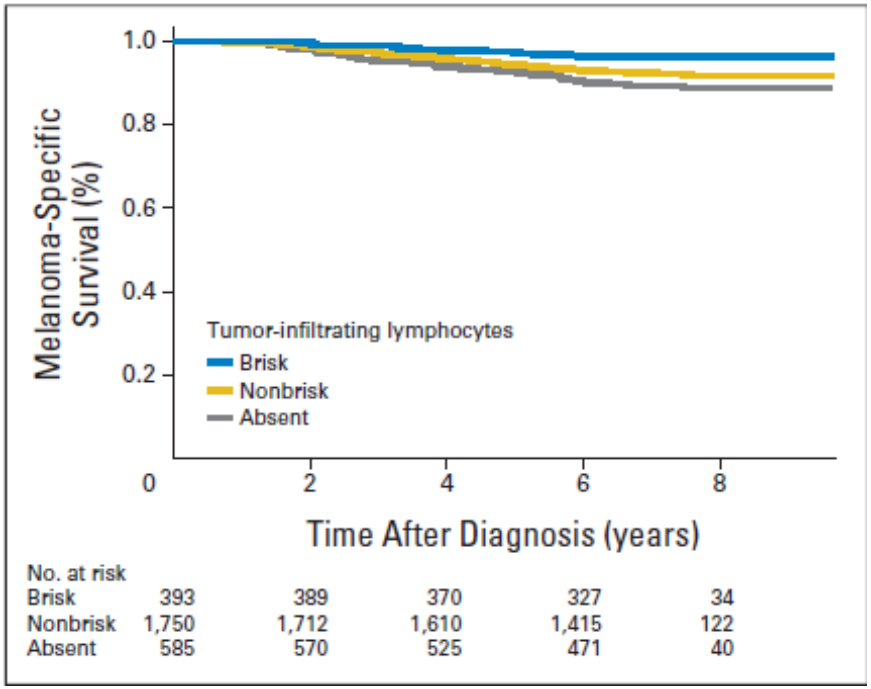
- **Natural immune recognition of melanoma is common**
- **In progressive metastatic melanoma, that response is (by definition) inadequate**
- **We can harness that natural immune activity.**

TIL in Melanoma

Tumor-Infiltrating Lymphocyte Grade in Primary Melanomas Is Independently Associated With Melanoma-Specific Survival in the Population-Based Genes, Environment and Melanoma Study

Nancy E. Thomas, Klaus J. Busam, Lynn From, Anne Kricker, Bruce K. Armstrong, Hoda Anton-Culver, Stephen B. Gruber, Richard P. Gallagher, Roberto Zanetti, Stefano Rosso, Terence Dwyer, Alison Venn, Peter A. Kanetsky, Pamela A. Groben, Honglin Hao, Irene Orlow, Anne S. Reiner, Li Luo, Susan Paine, David W. Ollila, Homer Wilcox, Colin B. Begg, and Marianne Berwick

JOURNAL OF CLINICAL ONCOLOGY NOVEMBER 20 2013

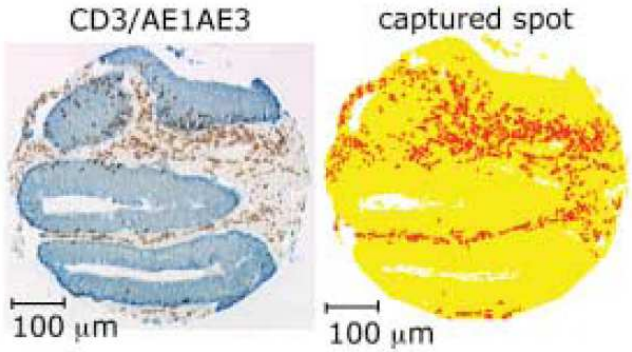


TIL in Colon: Immunoscore

Effector Memory T Cells, Early Metastasis, and Survival in Colorectal Cancer

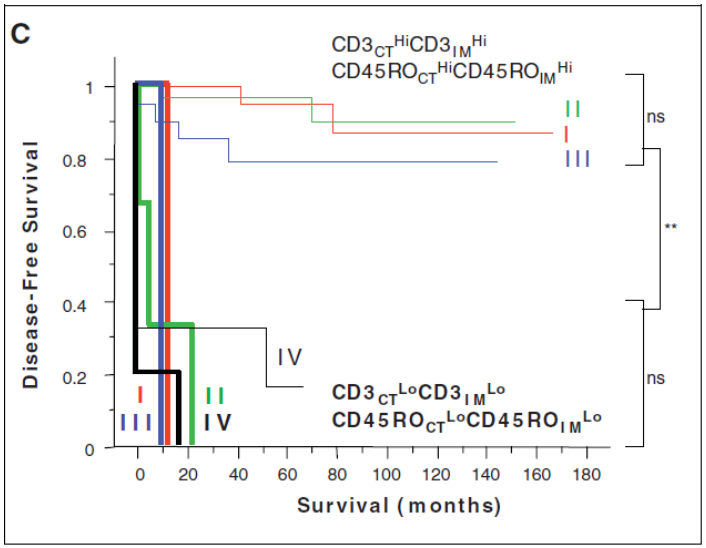
Franck Pagès, M.D., Ph.D., Anne Berger, M.D., Ph.D., Matthieu Camus, M.Sc., Fatima Sanchez-Cabo, Ph.D., Anne Costes, B.S., Robert Molidor, Ph.D., Bernhard Mlecnik, M.Sc., Amos Kirilovsky, M.Sc., Malin Nilsson, B.S., Diane Damotte, M.D., Ph.D., Tchao Meatchi, M.D., Patrick Bruneval, M.D., Ph.D., Paul-Henri Cugnenc, M.D., Ph.D., Zlatko Trajanoski, Ph.D., Wolf-Herman Fridman, M.D., Ph.D., and Jérôme Galon, Ph.D.

The NEW ENGLAND JOURNAL of MEDICINE DECEMBER 22, 2005



Type, Density, and Location of Immune Cells Within Human Colorectal Tumors Predict Clinical Outcome

Jérôme Galon *et al.*
Science **313**, 1960 (2006);

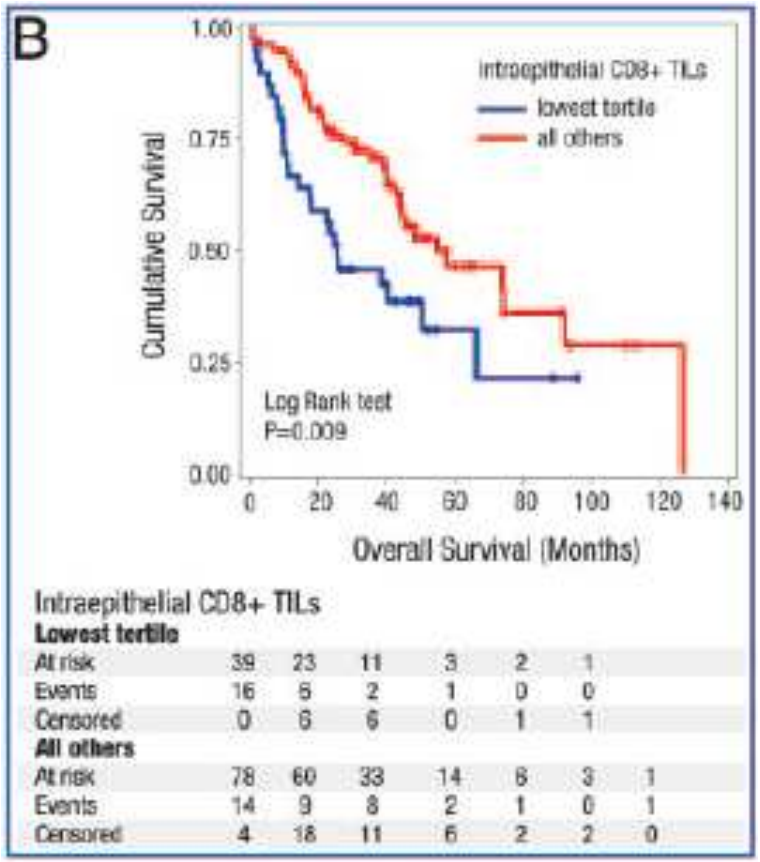


TIL in Ovarian

Intraepithelial CD8$^+$ tumor-infiltrating lymphocytes and a high CD8$^+$/regulatory T cell ratio are associated with favorable prognosis in ovarian cancer

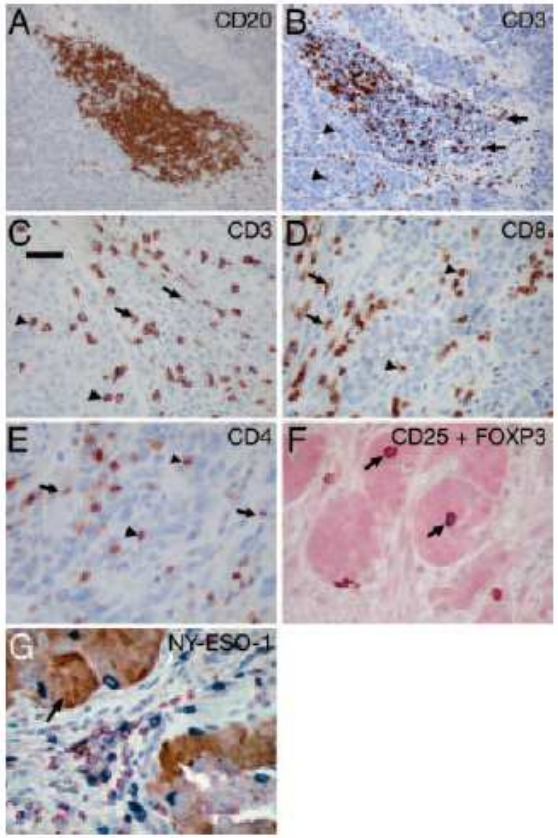
Eiichi Sato*†, Sara H. Olson‡, Jiyoung Ahn§¶, Brian Bundy‖, Hiroyoshi Nishikawa*, Feng Qian**††, Achim A. Jungbluth*, Denise Frosina*, Sacha Gnjatic*, Christine Ambrosone§, James Kepner‖, Tosin Odunsi¶, Gerd Ritter*, Shashikant Lele**, Yao-Tseng Chen‡‡, Haruo Ohtani§§, Lloyd J. Old*¶¶, and Kunle Odunsi**††‖‖

18538–18543 | PNAS | December 20, 2005 | vol. 102 | no. 51



Intraepithelial CD8+ TILs

Lowest tertile							
At risk	39	23	11	3	2	1	
Events	16	5	2	1	0	0	
Censored	0	6	6	0	1	1	
All others							
At risk	78	60	33	14	6	3	1
Events	14	9	8	2	1	0	1
Censored	4	18	11	6	2	2	0



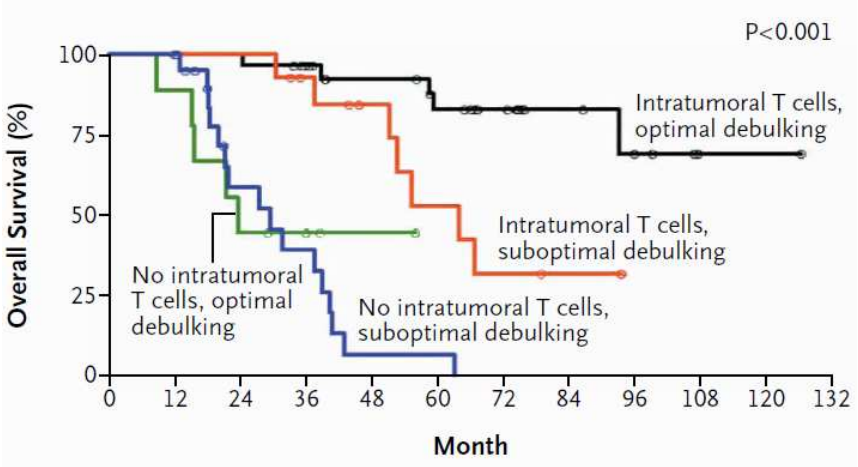
TIL in Ovarian

Intratumoral T Cells, Recurrence, and Survival in Epithelial Ovarian Cancer

Lin Zhang, M.D., Jose R. Conejo-Garcia, M.D., Ph.D., Dionyssios Katsaros, M.D., Ph.D., Phyllis A. Gimotty, Ph.D., Marco Massobrio, M.D., Giorgia Regnani, M.D., Antonis Makrigiannakis, M.D., Ph.D., Heidi Gray, M.D., Katia Schlienger, M.D., Ph.D., Michael N. Liebman, Ph.D., Stephen C. Rubin, M.D., and George Coukos, M.D., Ph.D.

The NEW ENGLAND JOURNAL of MEDICINE

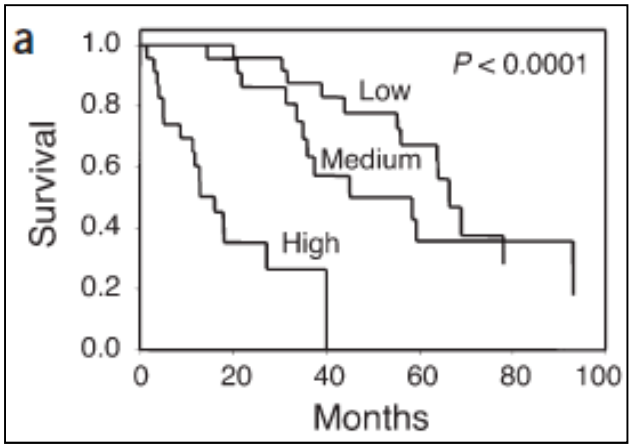
JANUARY 16, 2003



Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival

Tyler J Curiel[1], George Coukos[2], Linhua Zou[1], Xavier Alvarez[1], Pui Cheng[1], Peter Mottram[1], Melina Evdemon-Hogan[1], Jose R Conejo-Garcia[2], Lin Zhang[2], Matthew Burow[1], Yun Zhu[1], Shuang Wei[1], Ilona Kryczek[1], Ben Daniel[1], Alan Gordon[3], Leann Myers[1], Andrew Lackner[1], Mary L Disis[4], Keith L Knutson[4], Lieping Chen[5] & Weiping Zou[1]

VOLUME 10 | NUMBER 9 | SEPTEMBER 2004 NATURE MEDICINE

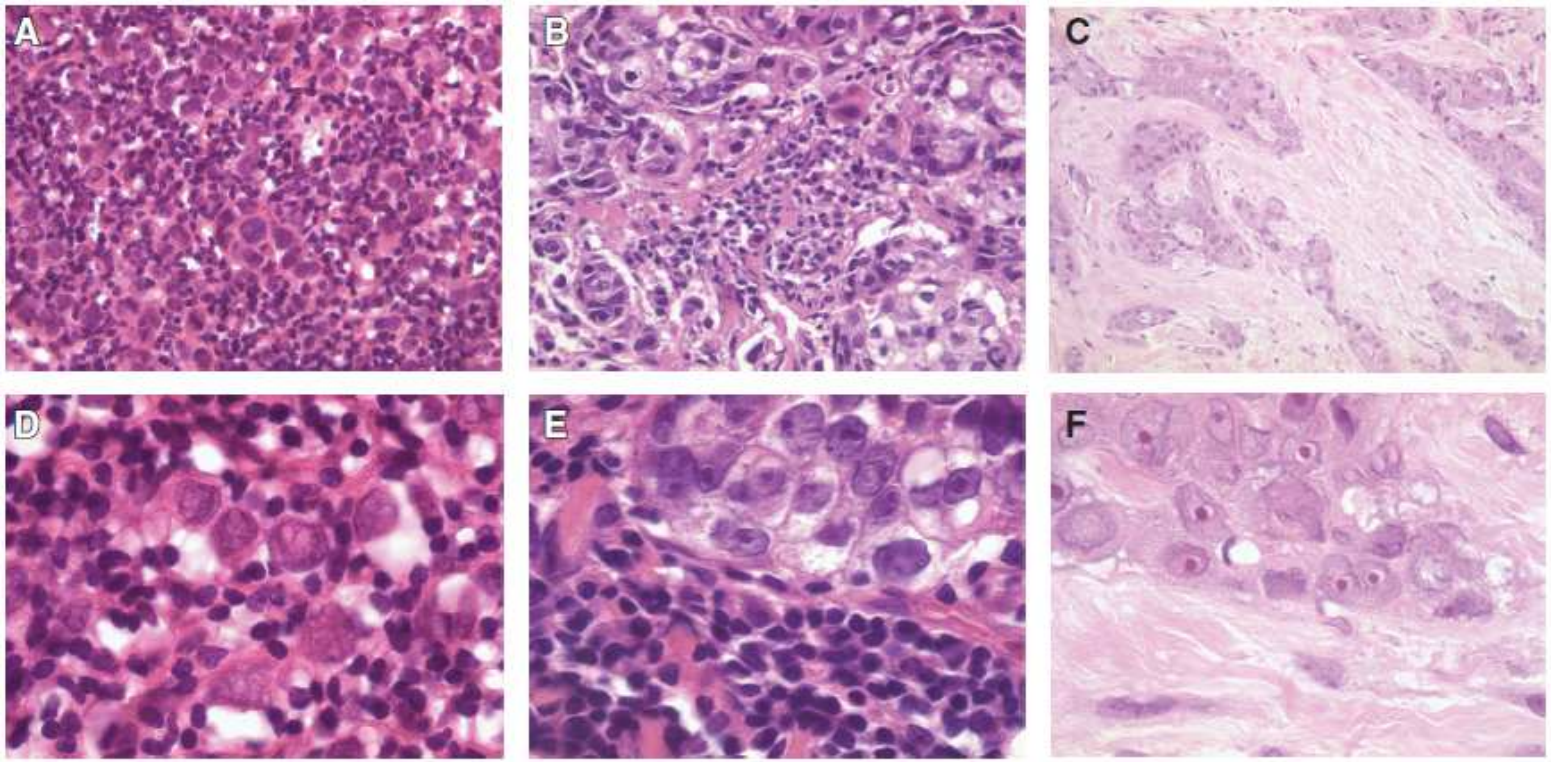


TIL in Breast Cancer

Tumor-Associated Lymphocytes As an Independent Predictor of Response to Neoadjuvant Chemotherapy in Breast Cancer

Carsten Denkert, Sibylle Loibl, Aurelia Noske, Marc Roller, Berit Maria Müller, Martina Komor, Jan Budczies, Silvia Darb-Esfahani, Ralf Kronenwett, Claus Hanusch, Christian von Törne, Wilko Weichert, Knut Engels, Christine Solbach, Iris Schrader, Manfred Dietel, and Gunter von Minckwitz

JANUARY 1 2010 *J Clin Oncol 28:105-113.*



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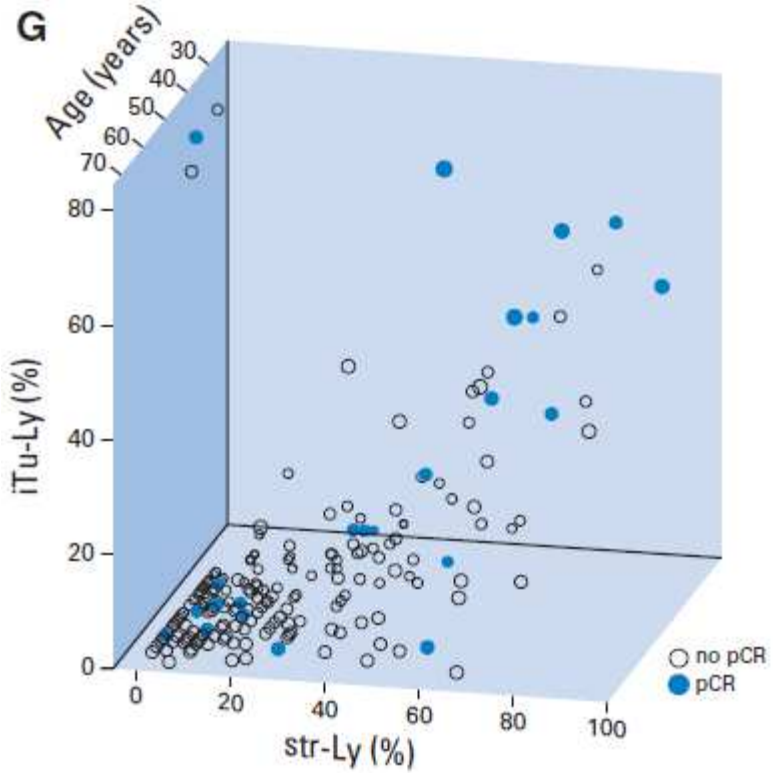

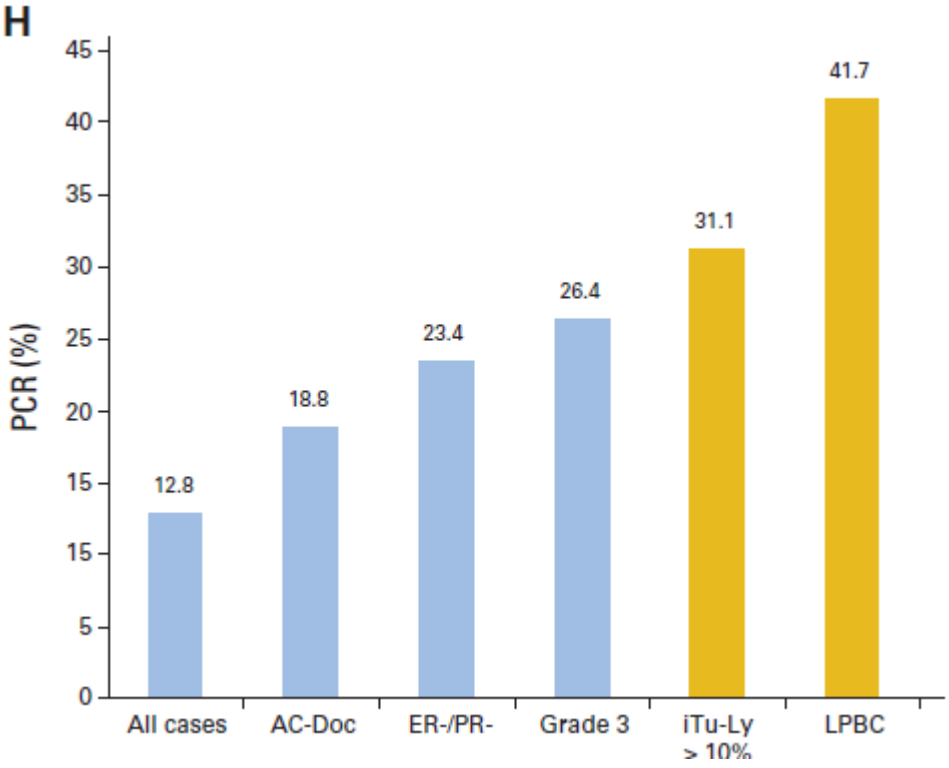

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JANUARY 1 2010 *J Clin Oncol 28:105-113.*

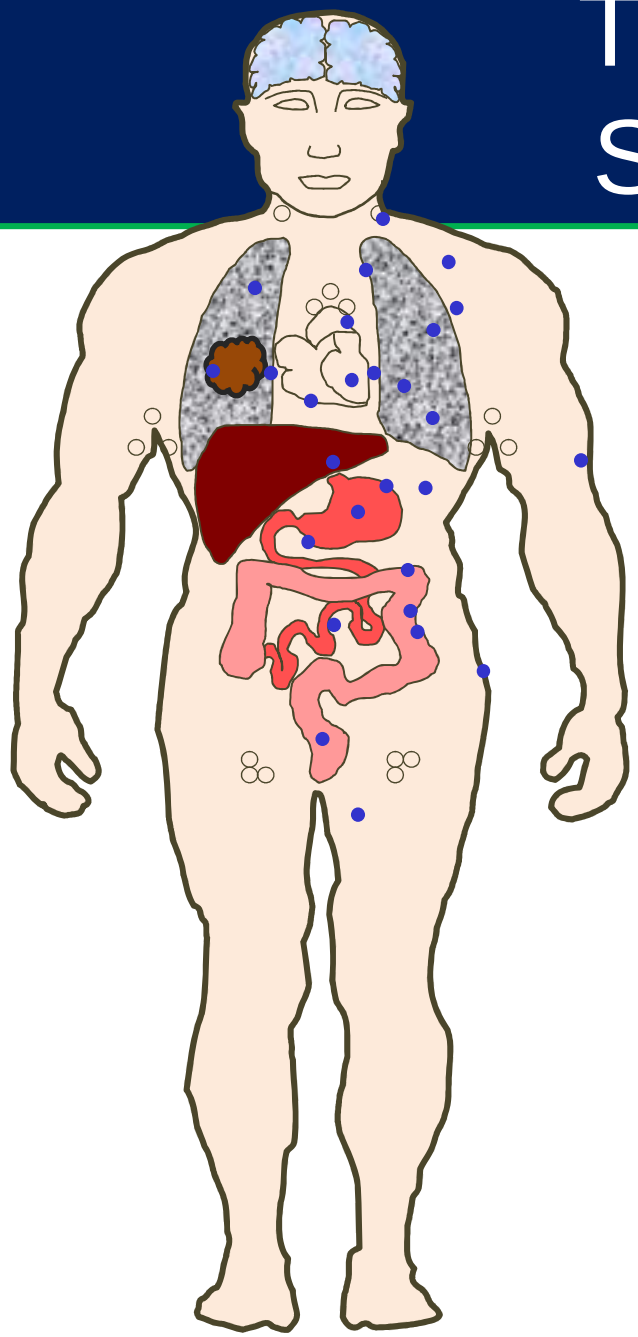
Table 2. Validation Cohort (GeparTrio): Factors Associated With a Pathologic Complete Response in the GeparTrio Cohort in Univariate and Multivariate Analysis

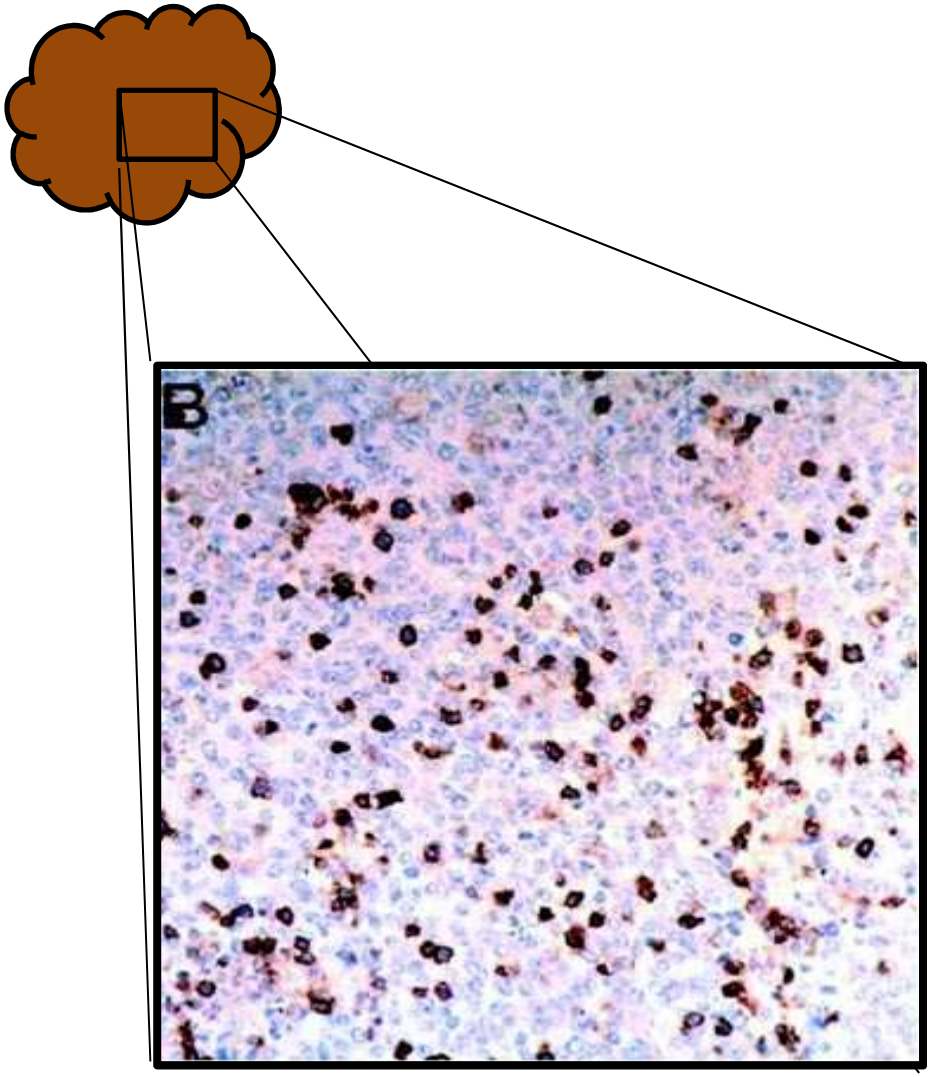
Variable	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
iTu-Ly (per 10%)	1.36	1.26 to 1.47	< .0005	1.21	1.08 to 1.35	.001
str-Ly (per 10%)	1.27	1.19 to 1.35	< .0005			
Age: < 50 *v* ≥ 50 years	1.50	1.04 to 2.15	.028	1.81	1.10 to 2.99	.02
Tumor type: ductal/other *v* lobular	2.40	1.22 to 4.71	.01	1.38	0.54 to 3.52	.51
Tumor grade: 3 *v* 1/2	2.91	1.94 to 4.35	< .0005	1.61	0.95 to 2.71	.076
ER/PR status: ER negative/PR negative *v* ER positive and/or PR positive	6.00	3.97 to 9.08	< .0005	4.13	2.42 to 7.04	< .0005
Tumor size: < 4 *v* ≥ 4 cm	1.09	0.75 to 1.57	.66	0.78	0.47 to 1.30	.34
Nodal status: cN0 *v* cN+	0.82	0.56 to 1.18	.28	0.84	0.50 to 1.40	.50
HER-2 status: negative *v* positive	0.86	0.57 to 1.27	.44	0.83	0.50 to 1.39	.47

NOTE. Results of univariate and multivariate logistic regression are shown. The parameter str-Ly is not included in multivariate analysis because it is correlated with iTu-Ly. In a separate multivariate analysis, the parameter str-Ly is significant as well (OR = 1.18; 95% CI, 1.08 to 1.29; $P < .0005$; data not shown).

Abbreviations: OR, odds ratio; iTu-Ly, intratumoral lymphocytes; str-Ly, stromal lymphocytes; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2.

TIL: Current Standard Procedure





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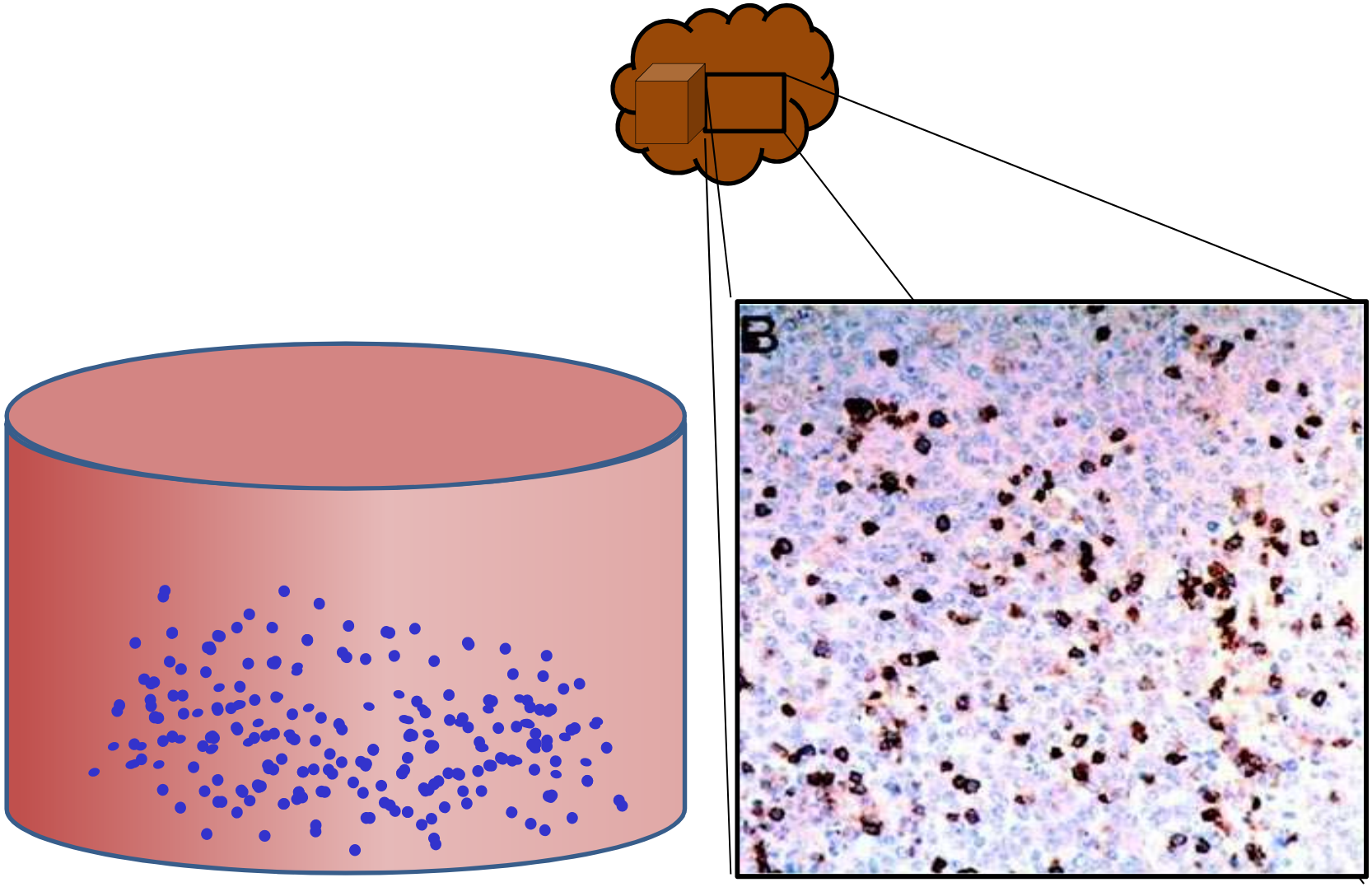

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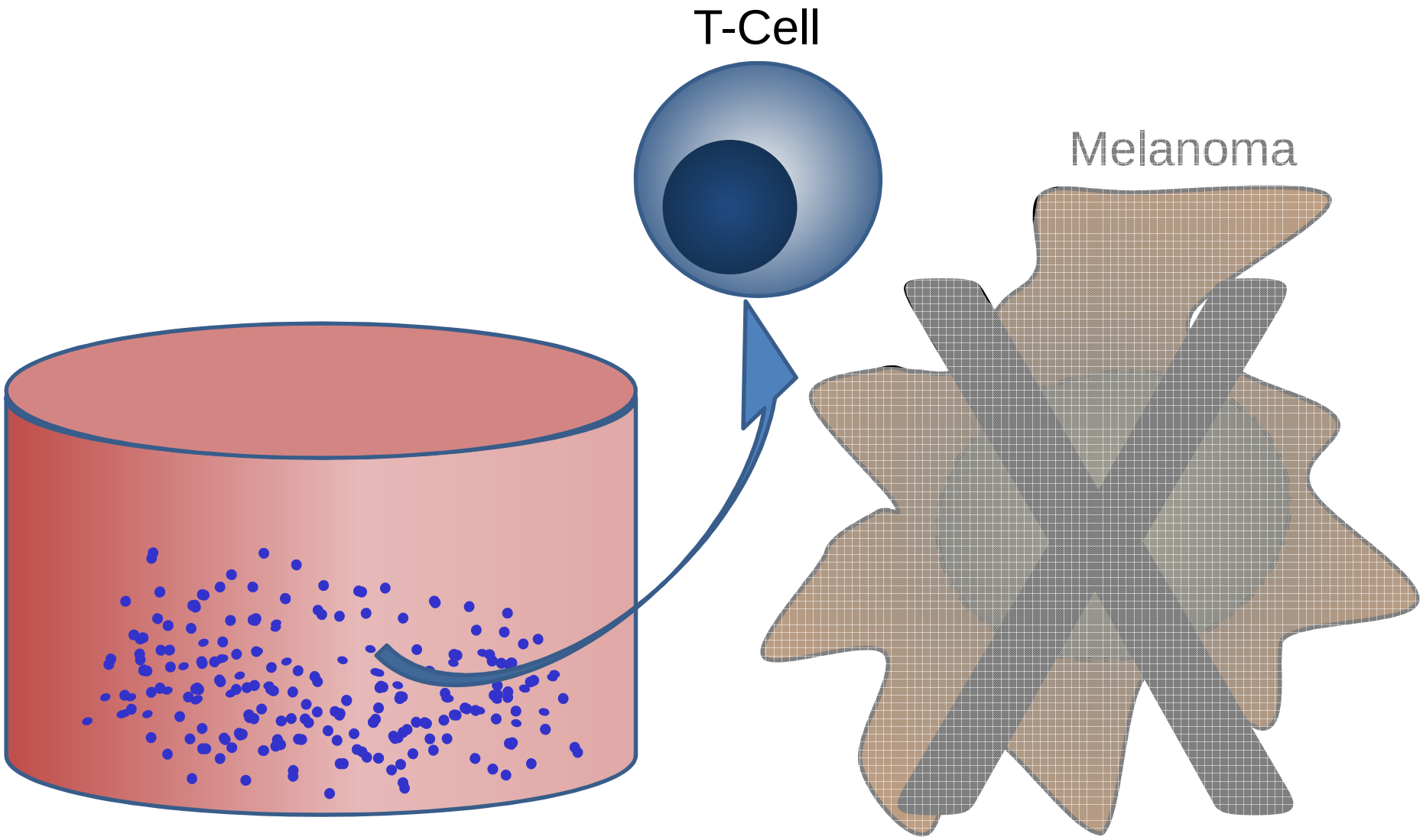
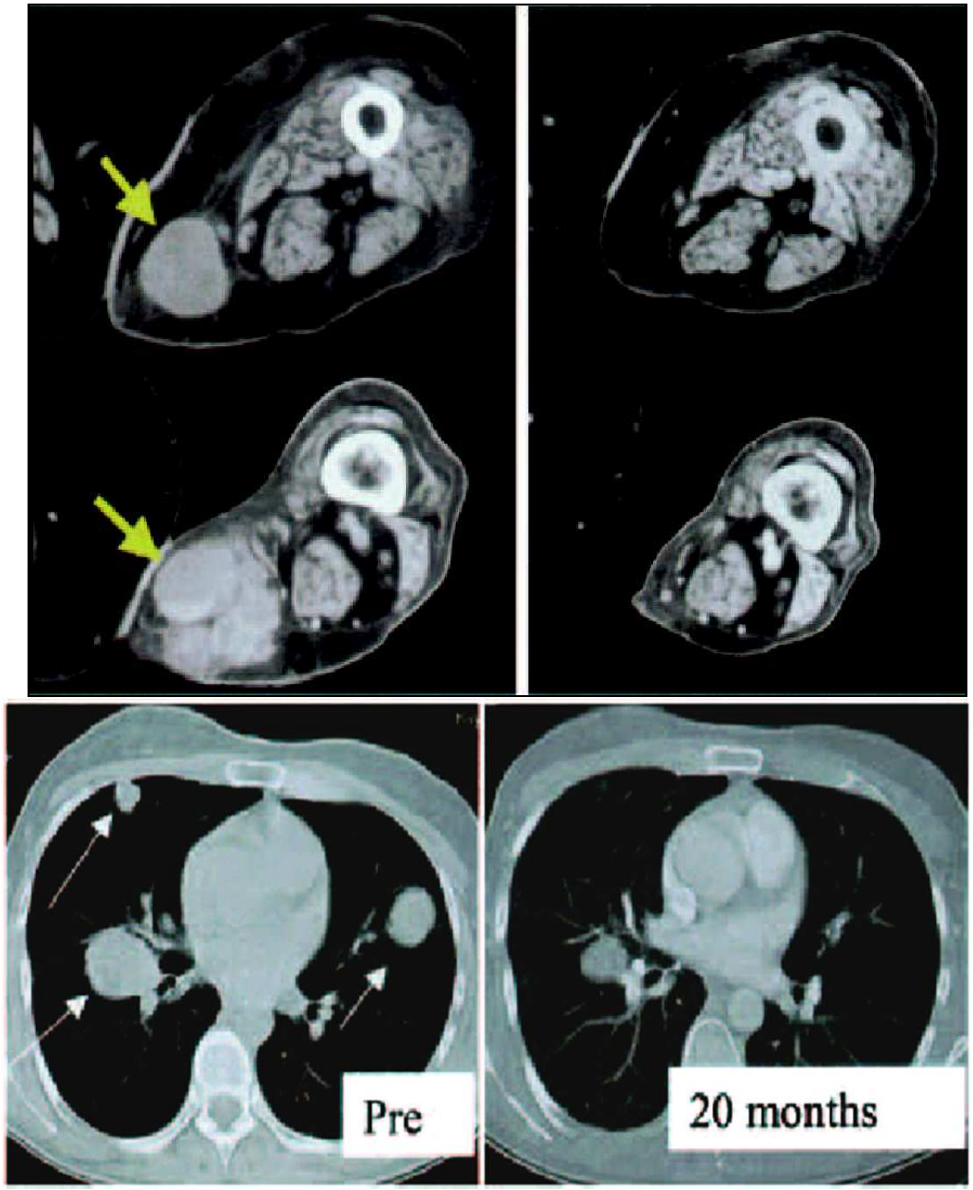


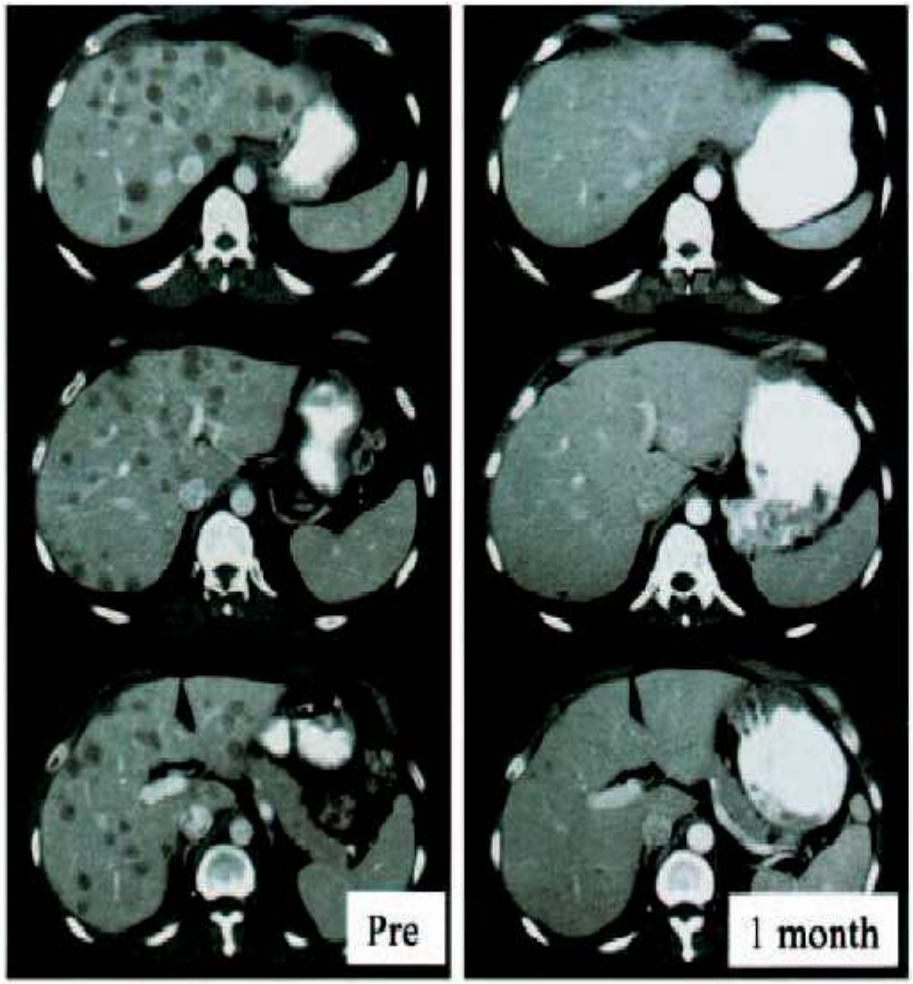
TIL: Current Standard Procedure

T-Cell

RAPID EXPANSION PROTOCOL

TIL: Clinical Responses





TIL: Early Clinical Data

Treatment of Patients With Metastatic Melanoma With Autologous Tumor-Infiltrating Lymphocytes and Interleukin 2

Journal of the National Cancer Institute,
, Vol. 86, No. 15, August 3, 1994

*Steven A. Rosenberg, John R. Yannelli, James C. Yang, Suzanne L. Topalian, Douglas J. Schwartzentruber, Jeffrey S. Weber, David R. Parkinson, Claudia A. Seipp, Jan H. Einhorn, Donald E. White**

Table 2. Number of patients responding to treatment with TILs plus IL-2 and duration of response*

	Response to treatment											
	No cyclophosphamide				Plus cyclophosphamide				Total			
	No. of patients				No. of patients				No. of patients			
	Total	CR	PR	% CR + PR	Total	CR	PR	% CR + PR	Total	CR	PR	% CR + PR
Prior IL-2	11	1	2	27	17	0	6	35	28	1	8	32
No prior IL-2	18	3	3	33	40	1	13	35	58	4	16	34
Total	29	4	5	31	57	1	19	35	86	5	24	34

	Duration of response, mo			
	No cyclophosphamide		Plus cyclophosphamide	
	CR	PR	CR	PR
Prior IL-2	23	4, 1	—	8, 7, 6, 5, 5, 1
No prior IL-2	46+, 38, 21+	7, 4, 2	20	53+, 9, 7, 7, 4, 4

*CR = complete response. PR = partial response.

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Journal of the National Cancer Institute, , Vol. 86, No. 15, August 3, 1994

Table 3. Treatment with TILs plus IL-2: characteristics of TILs associated with response and site of tumor harvest

Characteristics of TILs associated with response	Responder*	Nonresponder*	*P*
Time in culture, d	33 ± 1	43 ± 2	.0001
Doubling time, d	2.4 ± 0.2	3.5 ± 0.4	.03
% lysis (effector-to-target cell ratio of 40:1)			
Autologous tumor target	25 ± 4	10 ± 2	.0008
Daudi lymphoma target	11 ± 6	6 ± 2	.6
Phenotype, % of cells			
$CD3^+$	96 ± 1	95 ± 1	.9
$CD4^+$	24 ± 8	32 ± 5	.3
$CD8^+$	71 ± 8	62 ± 5	.3
$CD56^+$	9 ± 3	13 ± 2	.3

	No. of patients	
Site of tumor harvest	Responder	Nonresponder
Lymph node†	6	29
Subcutaneous tumor nodule†	18	19
Muscle	0	3
Lung	1	2
Intraperitoneal mass	0	2
Pleural effusion	0	1
Colon	1	0
Liver	1	0
Spleen	0	1
Ovary	1	0
Bone	1	0
Total	29	57

*Values = means ± SEM.
†Difference in response rates comparing lymph node and subcutaneous harvest sites, $P = .006$.

TIL: Early Clinical Data

Cancer Regression and Autoimmunity in Patients After Clonal Repopulation with Antitumor Lymphocytes

Mark E. Dudley,[1] John R. Wunderlich,[1] Paul F. Robbins,[1] James C. Yang,[1] Patrick Hwu,[1] Douglas J. Schwartzentruber,[1] Suzanne L. Topalian,[1] Richard Sherry,[1] Nicholas P. Restifo,[1] Amy M. Hubicki,[1] Michael R. Robinson,[2] Mark Raffeld,[3] Paul Duray,[3] Claudia A. Seipp,[1] Linda Rogers-Freezer,[1] Kathleen E. Morton,[1] Sharon A. Mavroukakis,[1] Donald E. White,[1] Steven A. Rosenberg[1]*

25 OCTOBER 2002 VOL 298 SCIENCE

Table 1. Patient demographics, treatments received, and clinical outcomes.

Patient	Age/sex	Treatment*				Sites of evaluable metastases	Response duration‖ (months)	Autoimmunity
		Cells infused† ($\times 10^{-10}$)	CD8/CD4 phenotype‡ (%)	Antigen specificity§	IL-2 (doses)			
1	18/M	2.3	11/39	Other	9	Lymph nodes (axillary, mesenteric, pelvic)	PR¶ (24+)	None
2	30/F	3.5	83/15	MART-1, gp100	8	Cutaneous, subcutaneous	PR (8)	Vitiligo
3	43/F	4.0	44/58	gp100	5	Brain, cutaneous, liver, lung	NR	None
4	57/F	3.4	56/52	gp100	9	Cutaneous, subcutaneous	PR (2)	None
5	53/M	3.0	16/85	Other	7	Brain, lung, lymph nodes	NR-mixed	None
6	37/F	9.2	65/35	Other	6	Lung, intraperitoneal, subcutaneous	PR (15+)	None
7	44/M	12.3	61/41	MART-1	7	Lymph nodes, subcutaneous	NR-mixed	Vitiligo
8	48/M	9.5	48/52	gp100	12	Subcutaneous	NR	None
9	57/M	9.6	84/13	MART-1	10	Cutaneous, subcutaneous	PR (10+)	Vitiligo
10	55/M	10.7	96/2	MART-1	12	Lymph nodes, cutaneous, subcutaneous	PR¶ (9+)	Uveitis
11	29/M	13.0	96/3	MART-1	12	Liver, pericardial, subcutaneous	NR-mixed	Vitiligo
12	37/F	13.7	72/24	MART-1	11	Liver, lung, gallbladder, lymph nodes	NR-mixed	None
13	41/F	7.7	92/8	MART-1	11	Subcutaneous	NR	None

TIL Clinical Effects

Cancer Regression and Autoimmunity in Patients After Clonal Repopulation with Antitumor Lymphocytes

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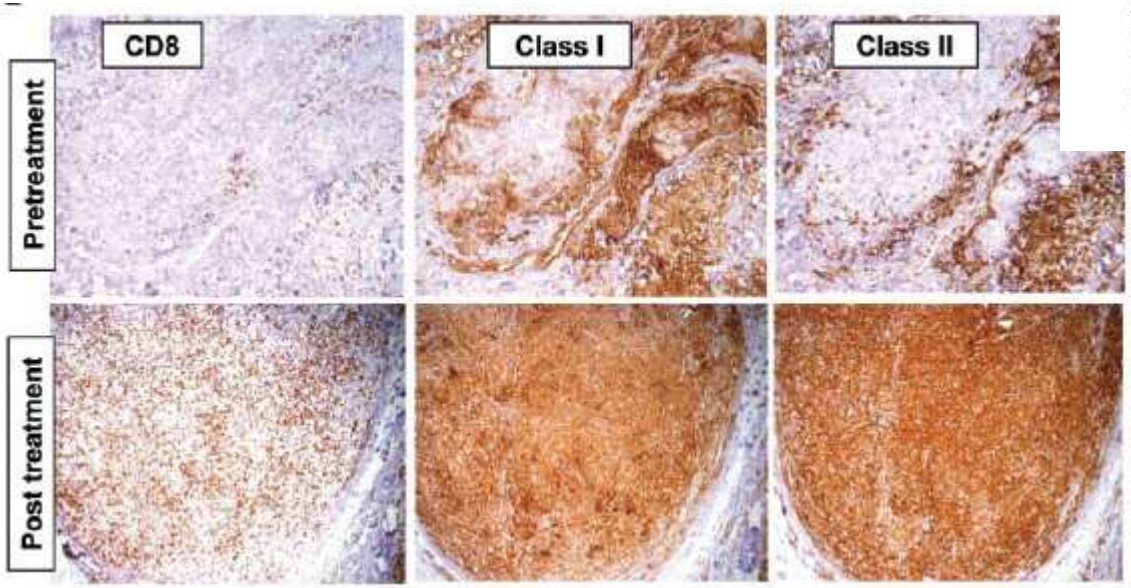
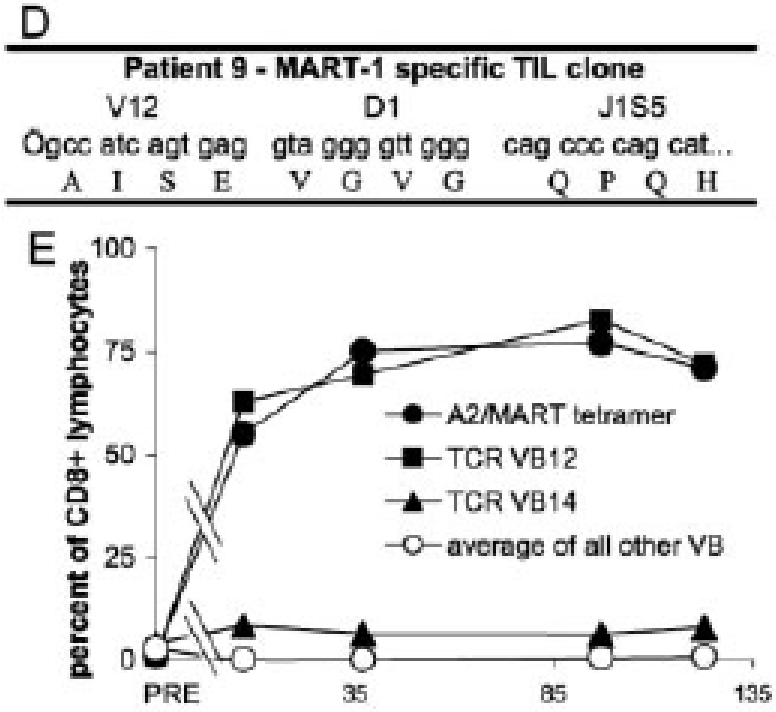




TIL: Early Clinical Data RCC

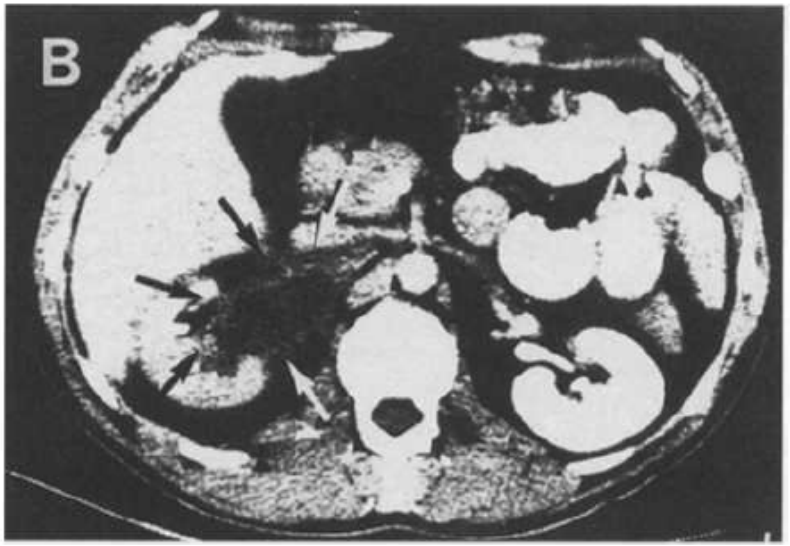
Adoptive Immunotherapy With Tumor-Infiltrating Lymphocytes and Interleukin-2 in Patients With Metastatic Malignant Melanoma and Renal Cell Carcinoma: A Pilot Study

By Peter S. Goedegebuure, Linda M. Douville, Hong Li, Glenn C. Richmond, Deric D. Schoof, Marybeth Scavone, and Timothy J. Eberlein

Journal of Clinical Oncology, Vol 13, No 8 (August), 1995: pp 1939-1949

Table 4. Clinical Responses to TIL and Low-Dose IL-2

	Melanoma		RCC		Total	
Response	No.	%	No.	%	No.	%
CR	3	19	0	0	4	20
MR	0	0	2	50	2	10
NR	9	56*	2	50	10	50
PD	4	25	0	0	4	20
Assessable	16	80	4	20	20	100

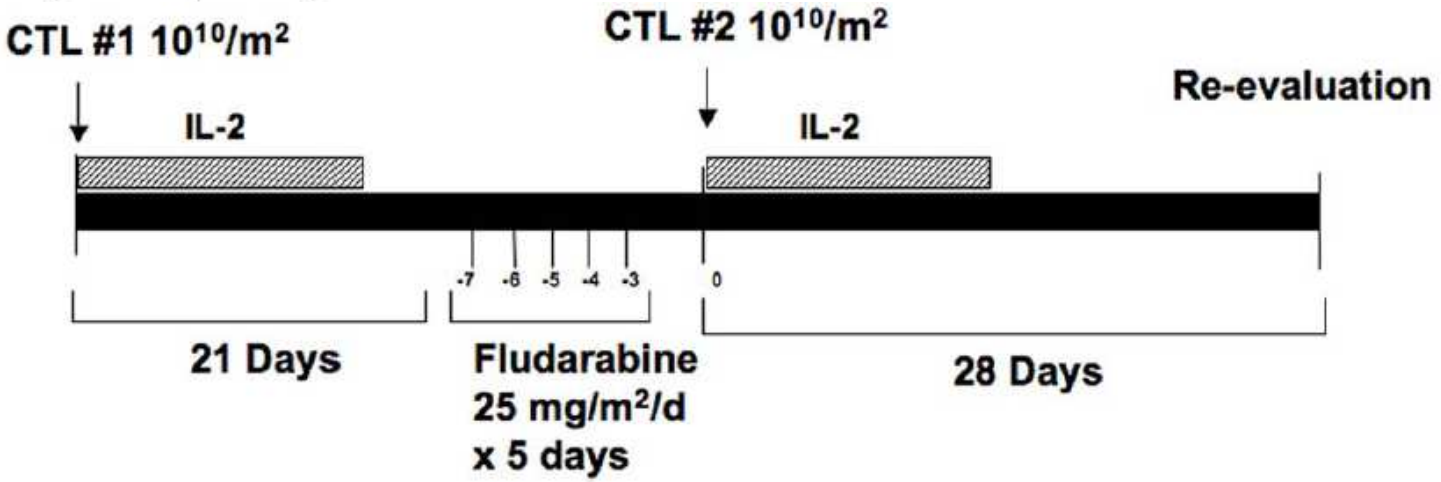


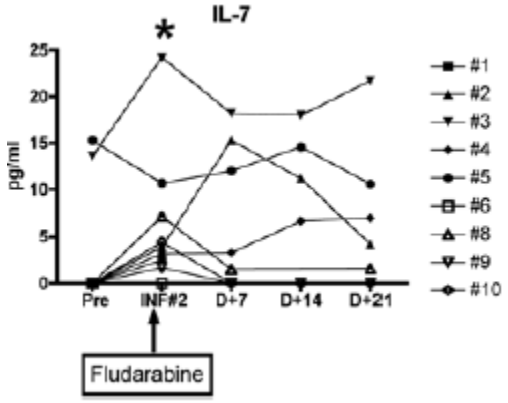
Lymphodepletion

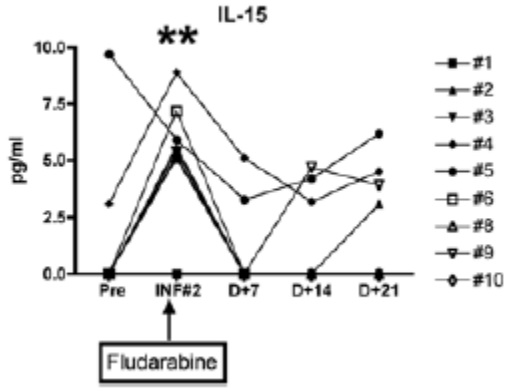
Fludarabine Modulates Immune Response and Extends *In Vivo* Survival of Adoptively Transferred CD8 T Cells in Patients with Metastatic Melanoma

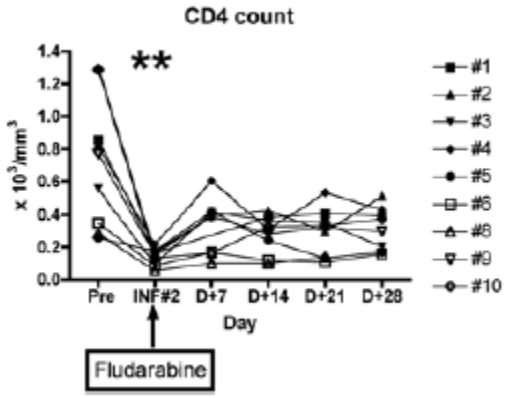
Herschel Wallen*, John A. Thompson, J. Zachary Reilly, Rebecca M. Rodmyre, Jianhong Cao, Cassian Yee

March 2009 | Volume 4 | Issue 3 | e4749









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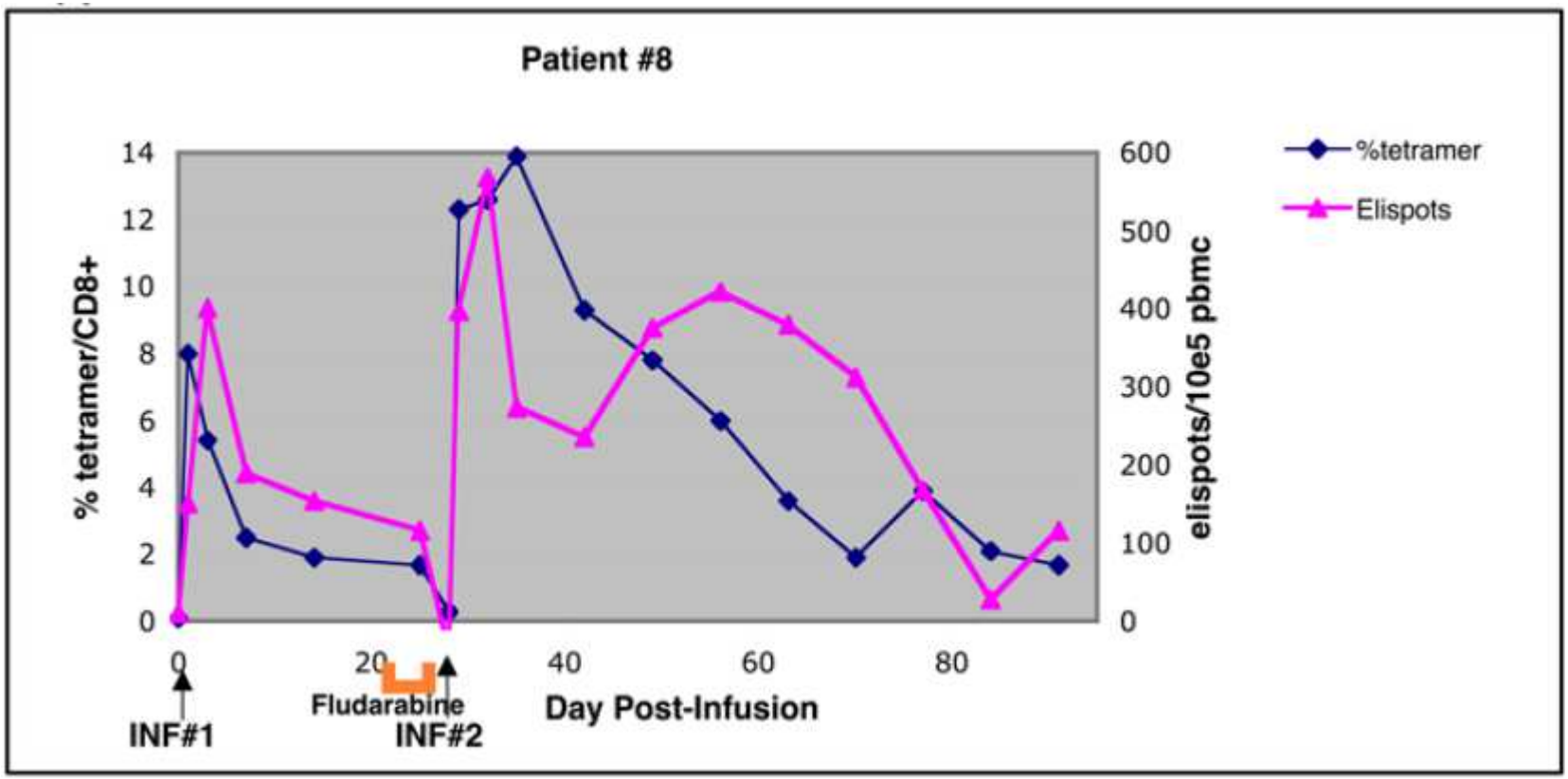

Lymphodepletion

Adoptive Cell Therapy for Patients With Metastatic Melanoma: Evaluation of Intensive Myeloablative Chemoradiation Preparative Regimens

Mark E. Dudley, James C. Yang, Richard Sherry, Marybeth S. Hughes, Richard Royal, Udai Kammula, Paul F. Robbins, JianPing Huang, Deborah E. Citrin, Susan F. Leitman, John Wunderlich, Nicholas P. Restifo, Armen Thomasian, Stephanie G. Downey, Franz O. Smith, Jacob Klapper, Kathleen Morton, Carolyn Laurencot, Donald E. White, and Steven A. Rosenberg

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VOLUME 26 · NUMBER 32 · NOVEMBER 10 2008

Day of treatment	-7	-6	-5	-4	-3	-2	-1	0	1	2	3
Non-myeloablative	Cy	Cy	Flu	Flu	Flu	Flu	Flu	TIL	IL-2	IL-2	IL-2
Ablative (200cGy)		Cy Flu	Cy Flu	Flu	Flu	Flu	TBI	TIL	IL-2	IL-2 CD34+	IL-2
Ablative (1,200cGy)	Cy Flu	Cy Flu	Flu	Flu	Flu TBI	TBI	TBI	TIL	IL-2 CD34+	IL-2	IL-2

Lymphodepletion

Adoptive Cell Therapy for Patients With Metastatic Melanoma: Evaluation of Intensive Myeloablative Chemoradiation Preparative Regimens

JOURNAL OF CLINICAL ONCOLOGY
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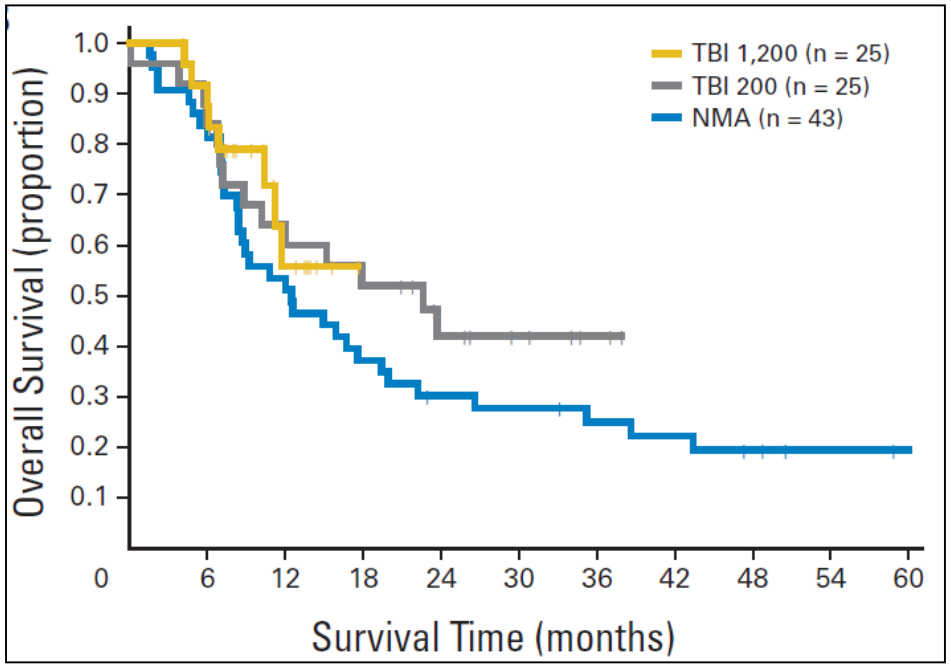
Table 2. Frequency and Duration of Objective Responses

TBI	Total No. of Patients	PR			CR			OR	
		No.	%	Duration (months)	No.	%	Duration (months)	No.	%
None*	43	17	39.5	64+, 32+, 20+, 29, 28, 14, 13, 11, 8, 8, 7, 4, 3, 3, 2, 2, 2	4	9.3	63+, 58+, 48+, 47+	21	48.8
2 Gy	25	11	44.0	33+, 29+, 23+, 14, 10, 6, 5, 5, 4, 3, 3	2	8.0	37+, 25+	13	52.0
12 Gy	25	14	56.0	14+, 13+, 10+, 7+, 7+, 7+, 6+, 6+, 4+, 7, 6, 6, 4, 3	4	16.0	17+, 15+, 13+, 8+	18	72.0



Lymphodepletion

Adoptive Cell Therapy for Patients With Metastatic Melanoma: Evaluation of Intensive Myeloablative Chemoradiation Preparative Regimens

Mark E. Dudley, James C. Yang, Richard Sherry, Marybeth S. Hughes, Richard Royal, Udai Kammula, Paul F. Robbins, JianPing Huang, Deborah E. Citrin, Susan F. Leitman, John Wunderlich, Nicholas P. Restifo, Armen Thomasian, Stephanie G. Downey, Franz O. Smith, Jacob Klapper, Kathleen Morton, Carolyn Laurencot, Donald E. White, and Steven A. Rosenberg

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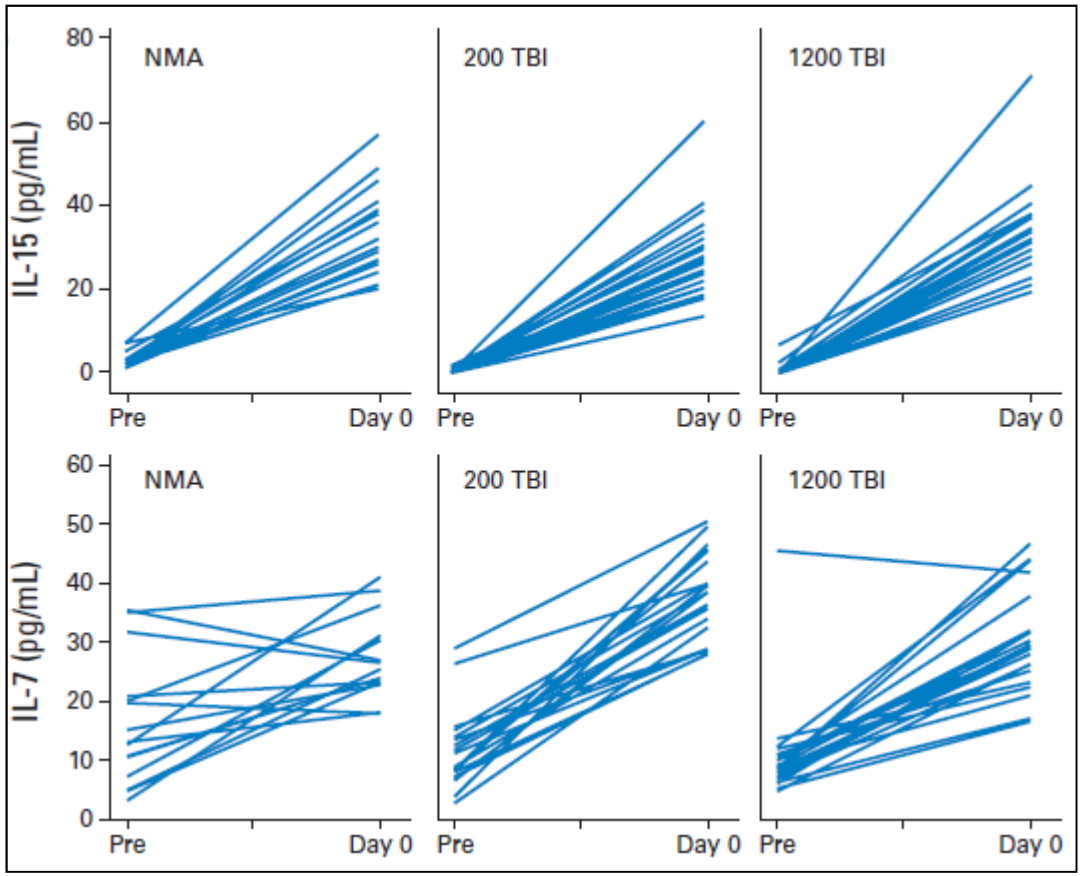

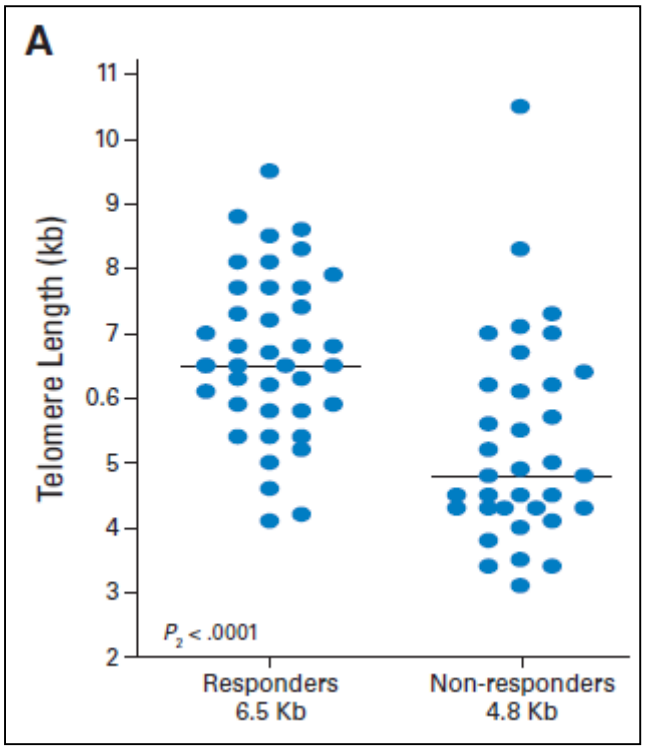

Young TIL

Randomized Selection Design Trial Evaluating CD8$^+$-Enriched Versus Unselected Tumor-Infiltrating Lymphocytes for Adoptive Cell Therapy for Patients With Melanoma

Mark E. Dudley, Colin A. Gross, Robert P.T. Somerville, Young Hong, Nicholas P. Schaub, Shannon F. Rosati, Donald E. White, Debbie Nathan, Nicholas P. Restifo, Seth M. Steinberg, John R. Wunderlich, Udai S. Kammula, Richard M. Sherry, James C. Yang, Giao Q. Phan, Marybeth S. Hughes, Carolyn M. Laurencot, and Steven A. Rosenberg

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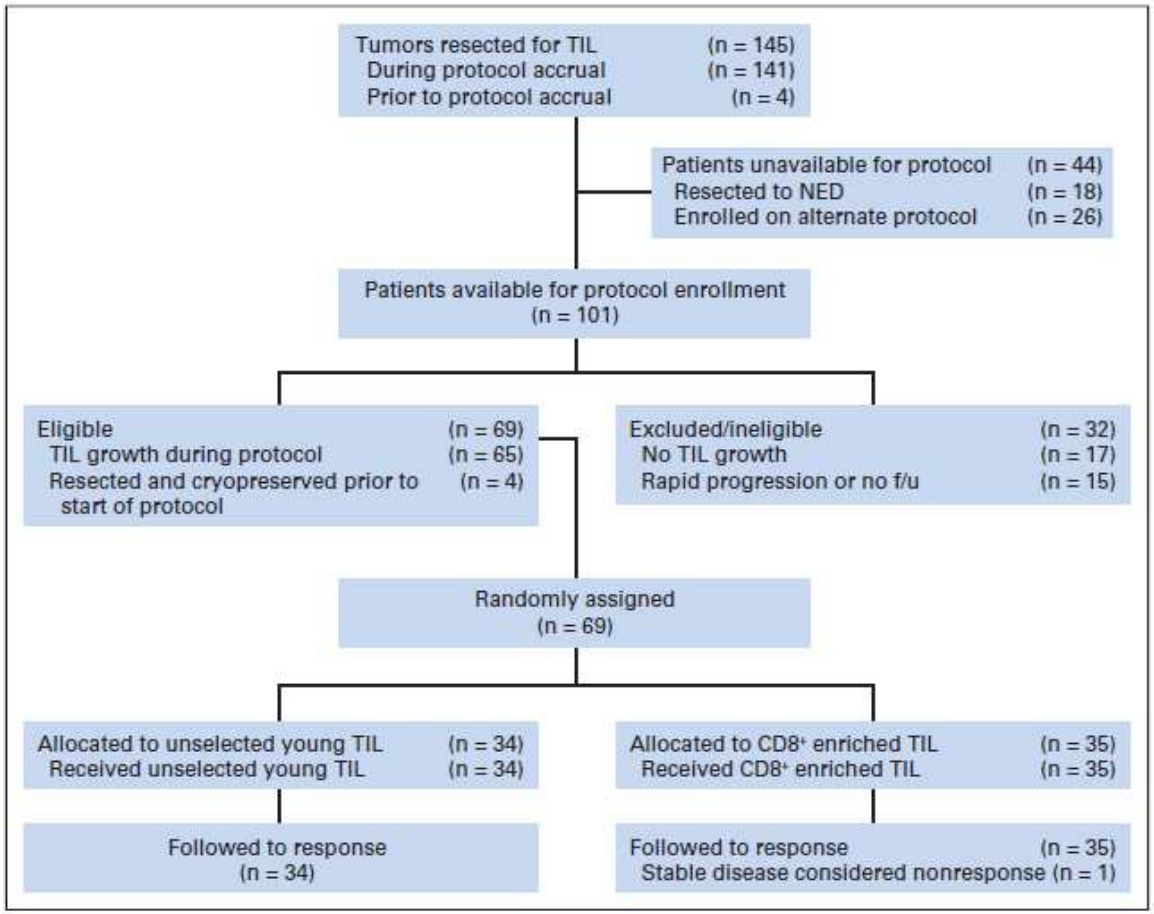

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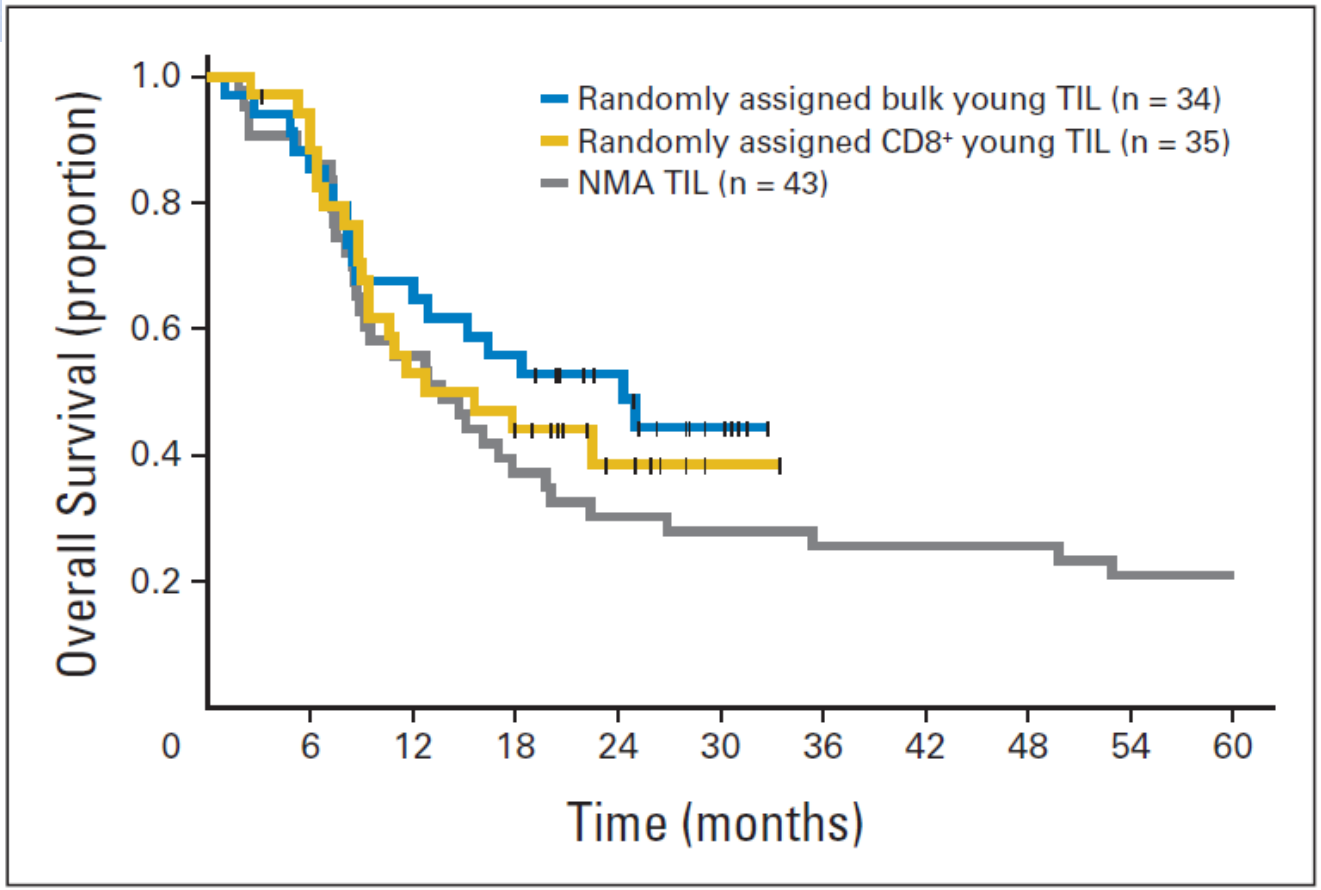
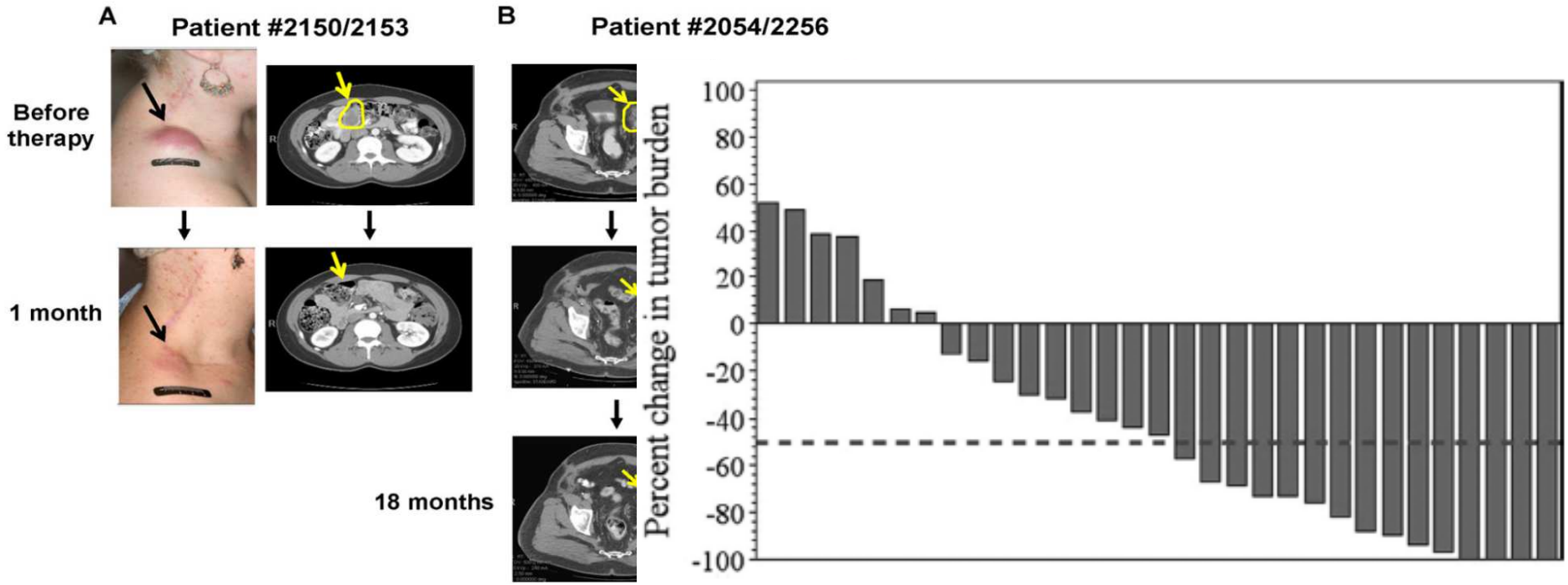


Predicting Response

Specific lymphocyte subsets predict response to adoptive cell therapy using expanded autologous tumor-infiltrating lymphocytes in metastatic melanoma patients

Laszlo G. Radvanyi[1,*], Chantale Bernatchez[1], Minying Zhang[1], Patricia S. Fox[2], Priscilla Miller[1], Jessica Chacon[1], Richard Wu[1], Gregory Lizee[1], Sandy Mahoney[1], Gladys Alvarado[1], Michelle Glass[1], Valen E. Johnson[2], John D. McMannis[3], Elizabeth Shpall[3], Victor Prieto[4], Nicholas Papadopoulos[1], Kevin Kim[1], Jade Homsi[1], Agop Bedikian[1], Wen-Jen Hwu[1], Sapna Patel[1], Merrick I. Ross[5], Jeffrey E. Lee[5], Jeffrey E. Gershenwald[5], Anthony Lucci[5], Richard Royal[5], Janice N. Cormier[5], Michael A. Davies[1], Rahmatu Mansaray[1,3], Orenthial J. Fulbright[1,3], Christopher Toth[1,3], Renjith Ramachandran[1,3], Seth Wardell[1,3], Audrey Gonzalez[1,3], and Patrick Hwu[1,*]

Clin Cancer Res. 2012 December 15; 18(24): 6758–6770.



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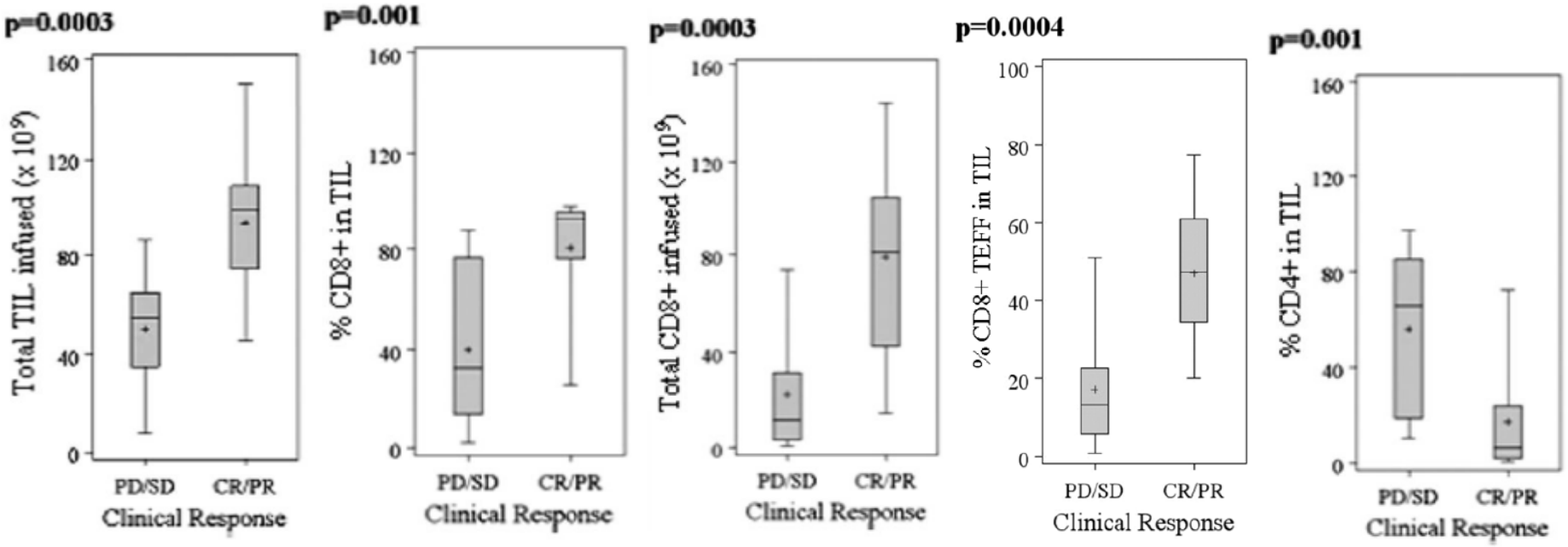

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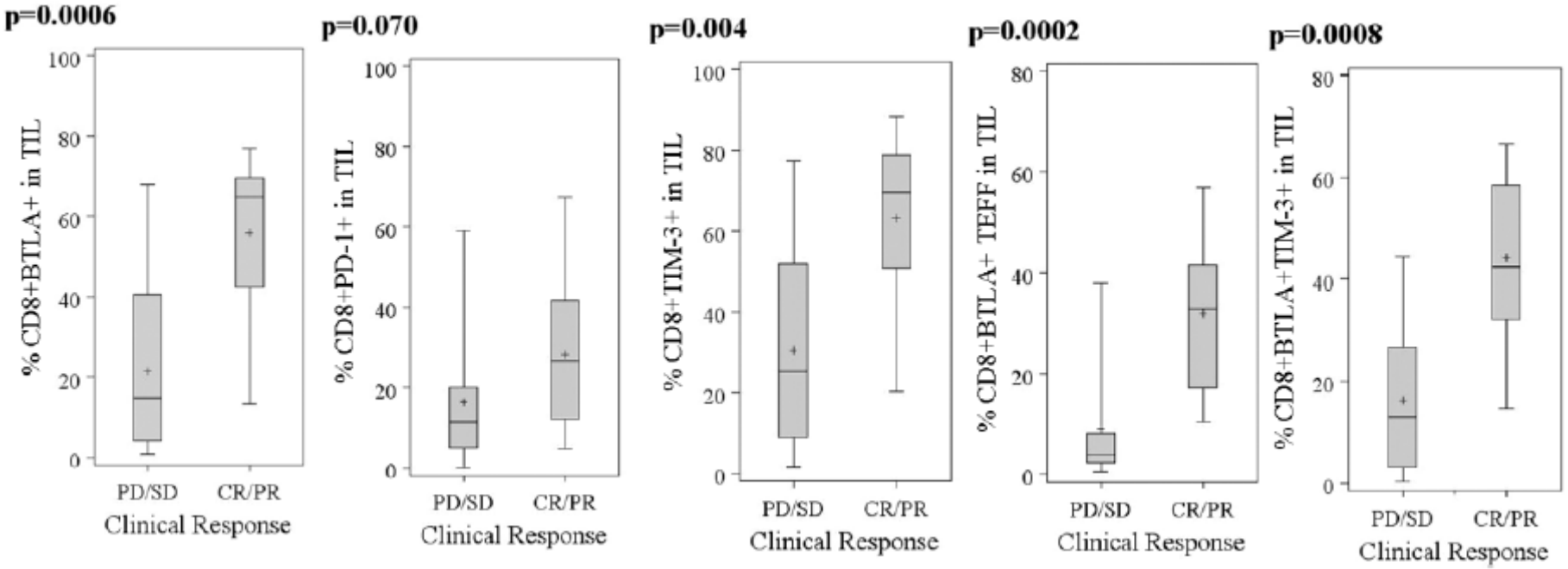
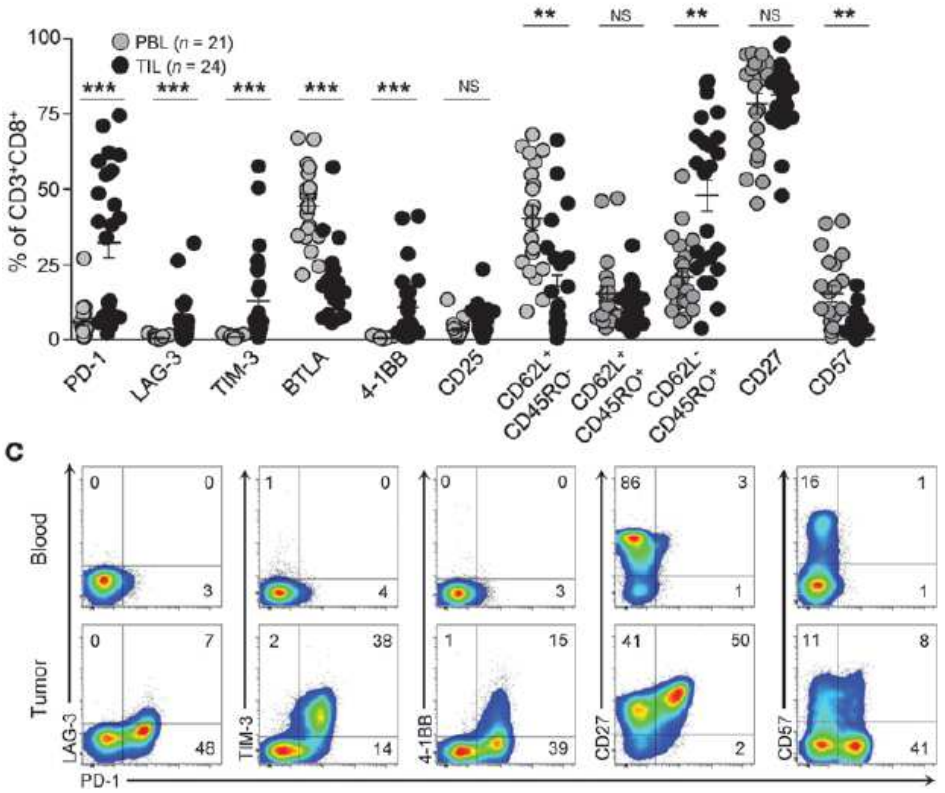


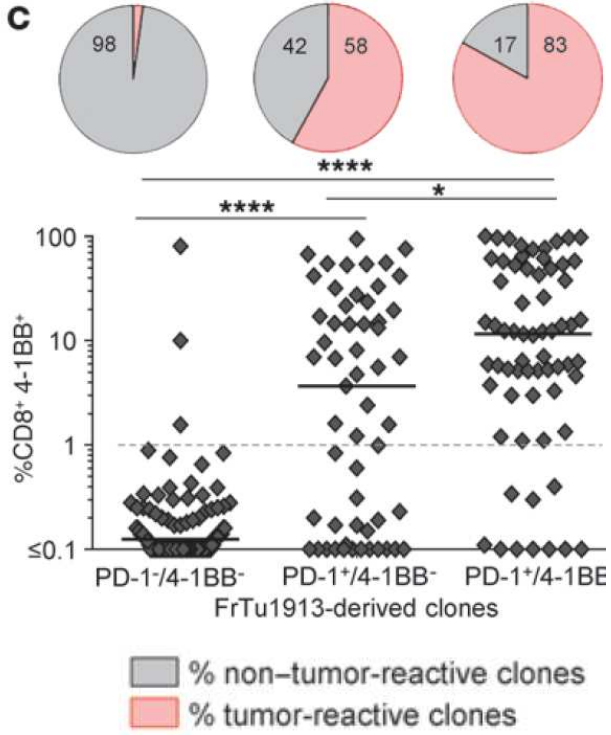
Predicting Response

PD-1 identifies the patient-specific CD8+ tumor-reactive repertoire infiltrating human tumors

Alena Gros,[1] Paul F. Robbins,[1] Xin Yao,[1] Yong F. Li,[1] Simon Turcotte,[1] Eric Tran,[1] John R. Wunderlich,[1] Arnold Mixon,[1] Shawn Farid,[1] Mark E. Dudley,[1] Ken-ichi Hanada,[1] Jorge R. Almeida,[2] Sam Darko,[2] Daniel C. Douek,[2] James C. Yang,[1] and Steven A. Rosenberg[1]

The Journal of Clinical Investigation
May 2014



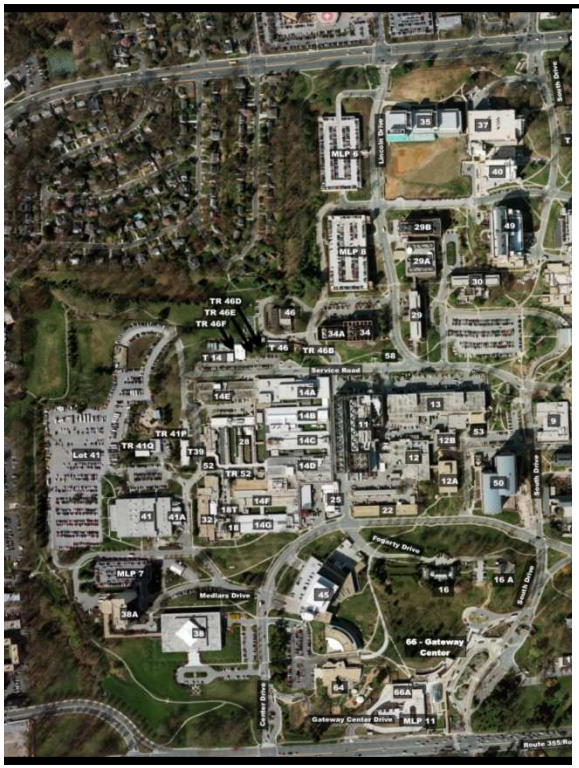


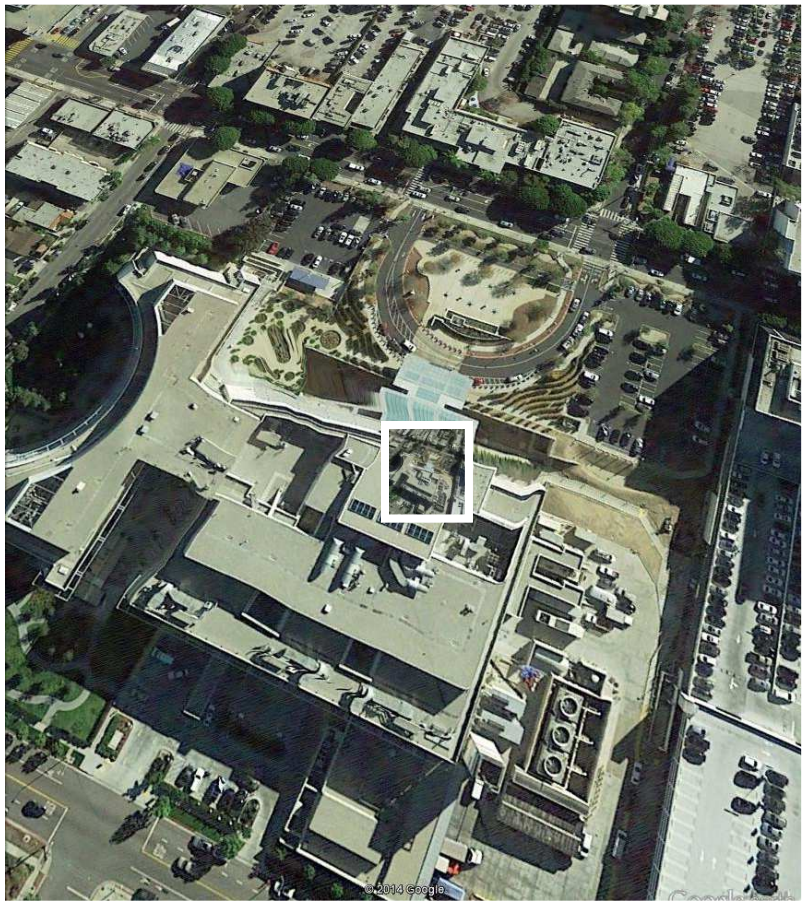
Tumor-Infiltrating Lymphocytes: Challenges

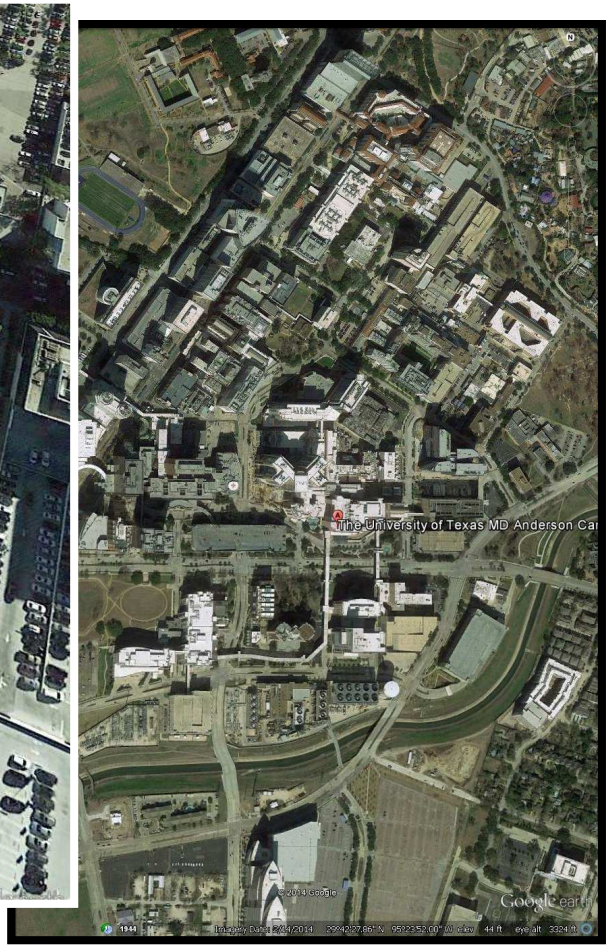
- **Technical challenges: (“GMP”)**
- **Timeline**
- **Tumor reactivity**
- **Interleukin-2**

Tumor-Infiltrating Lymphocytes: Challenges

- **Technical challenges: (“GMP”)**







Cell Production Facility

Cell Production Facility

Tumor-Infiltrating Lymphocytes: Challenges

- Technical challenges: (“GMP”)
- **Timeline**
- Tumor reactivity
- Interleukin-2

Tumor-Infiltrating Lymphocytes: Challenges

- Technical challenges: (“GMP”)

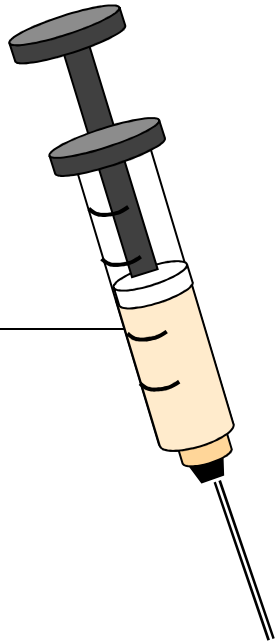
- **Timeline**

Tumor Removal

2-4 weeks

Testing

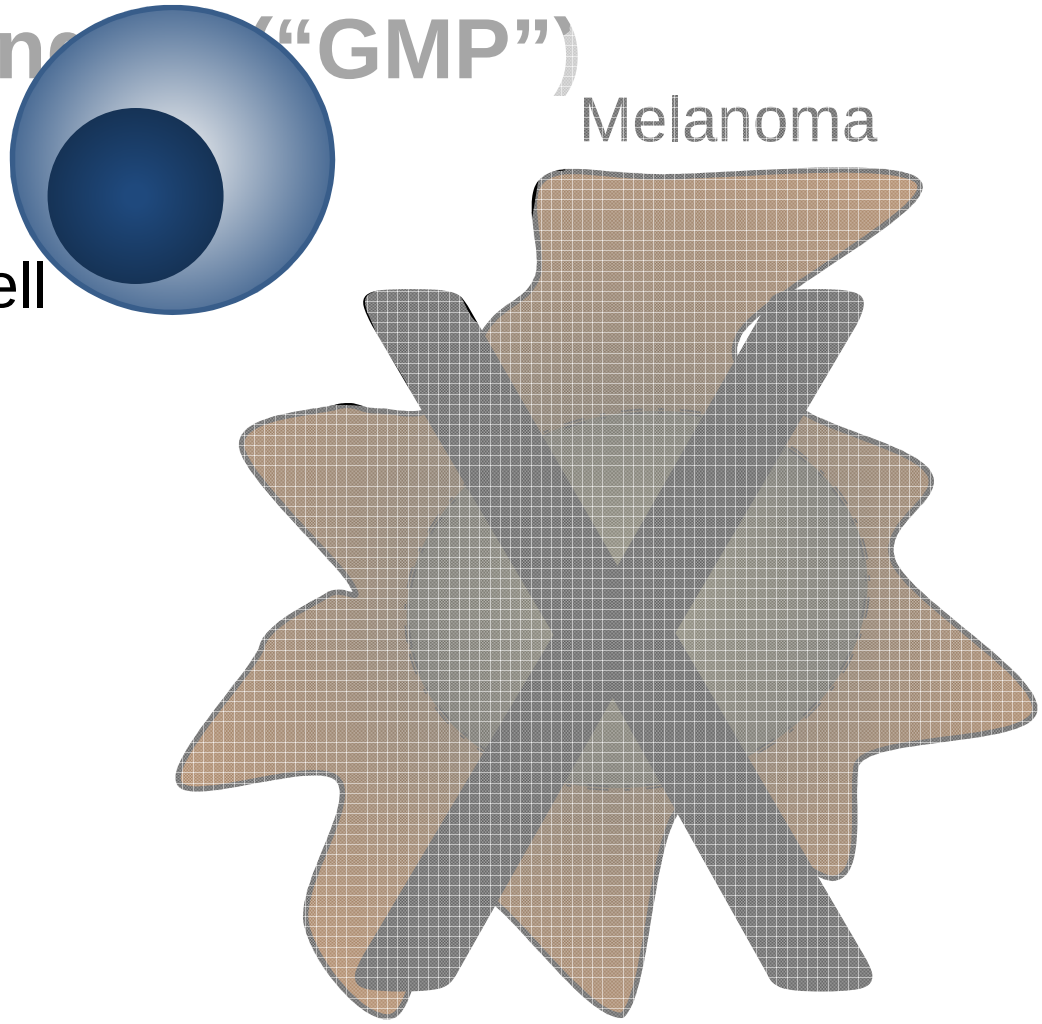
2 weeks



5-8 weeks

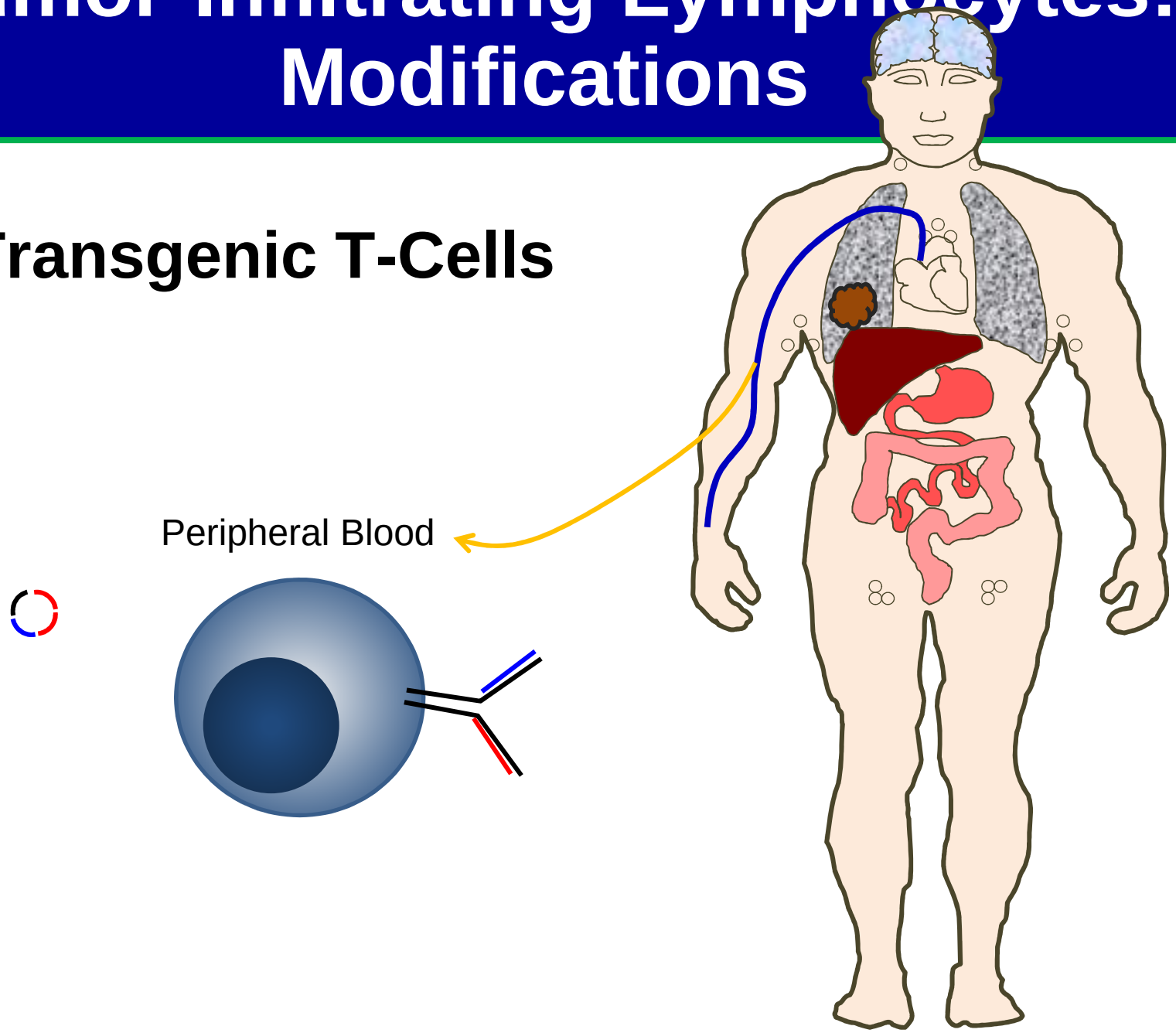
Tumor-Infiltrating Lymphocytes: Challenges

- Technical challenges (“GMP”)
- Timeline
- **Tumor reactivity**
- Interleukin-2



Tumor-Infiltrating Lymphocytes: Modifications

- **Transgenic T-Cells**

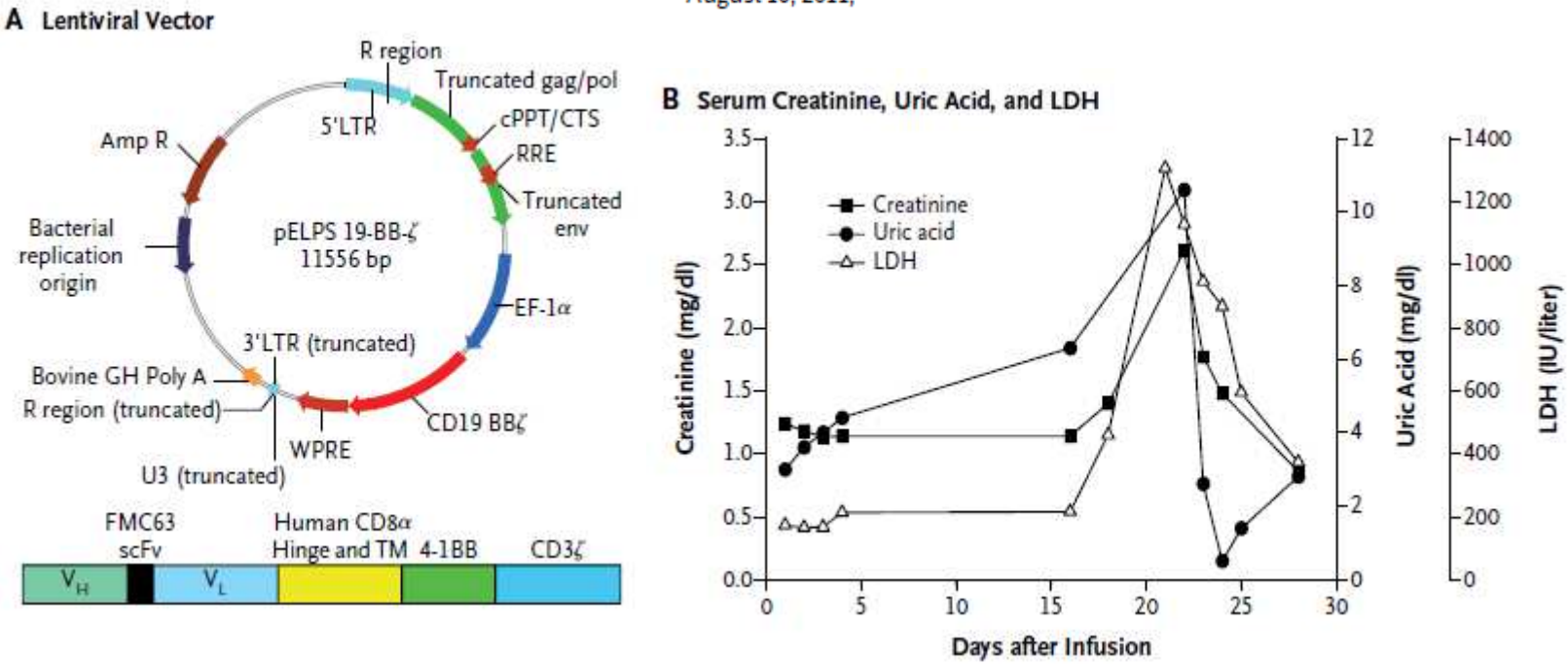


Engineered T Cells

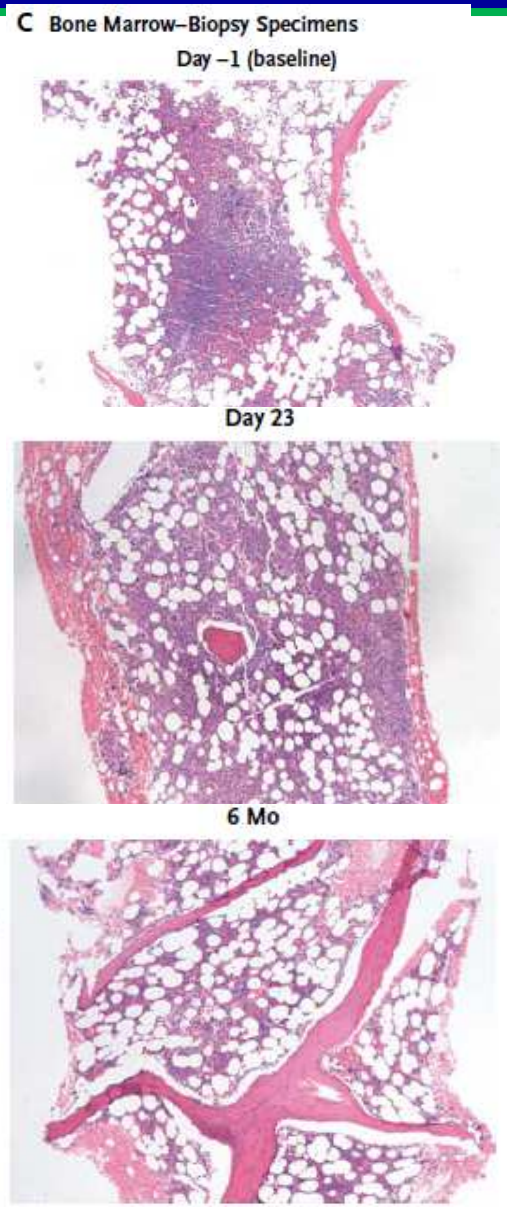
Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia

David L. Porter, M.D., Bruce L. Levine, Ph.D., Michael Kalos, Ph.D., Adam Bagg, M.D., and Carl H. June, M.D.

The NEW ENGLAND JOURNAL of MEDICINE
August 10, 2011,



Engineered T Cells



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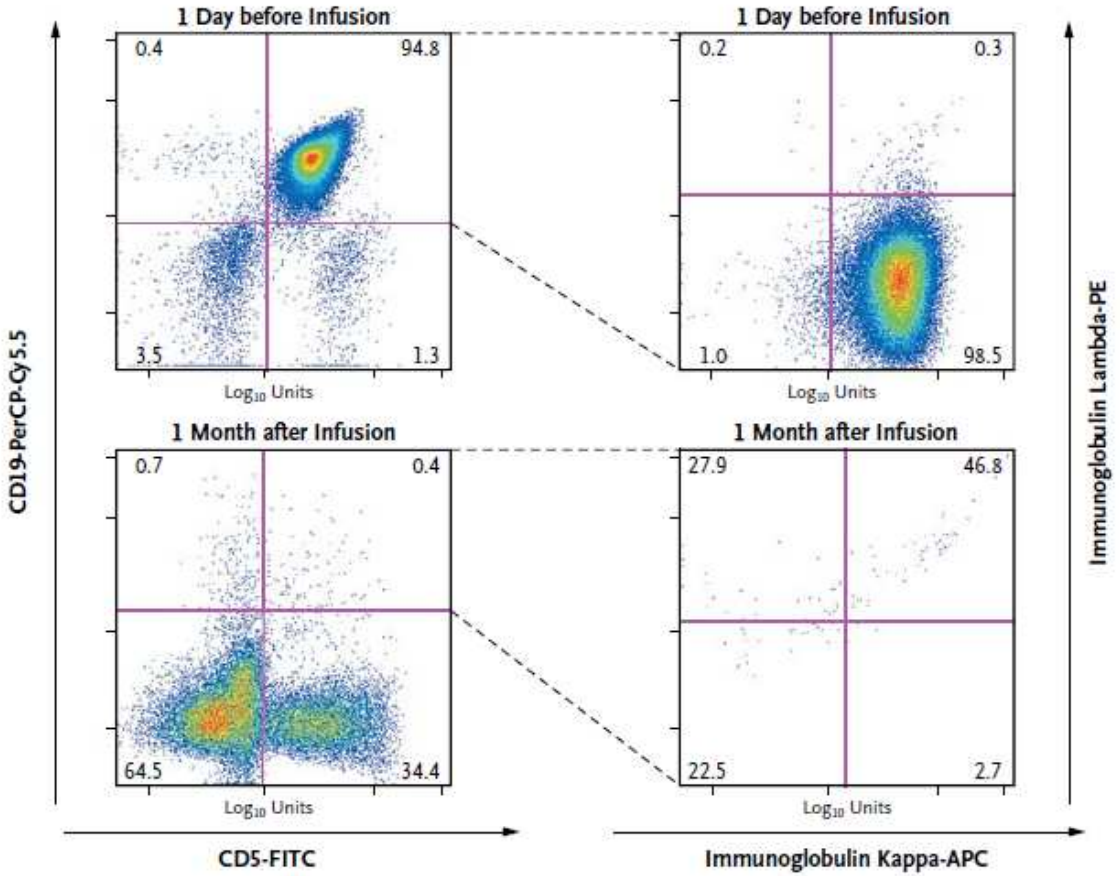

Tumor-Infiltrating Lymphocytes: Modifications

Science
AAAS

Cancer Immunotherapy Based on Mutation-Specific CD4+ T Cells in a Patient with Epithelial Cancer

Eric Tran, Simon Turcotte, Alena Gros, Paul F. Robbins, Yong-Chen Lu, Mark E. Dudley, John R. Wunderlich, Robert P. Somerville, Katherine Hogan, Christian S. Hinrichs, Maria R. Parkhurst, James C. Yang, Steven A. Rosenberg

Science 9 May 2014

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HEALTH | NYT NOW

Patient's Cells Deployed to Attack Aggressive Cancer

By DENISE GRADY MAY 8, 2014

Doctors have taken an important step toward a long-sought goal: harnessing a person's own immune system to fight cancer.

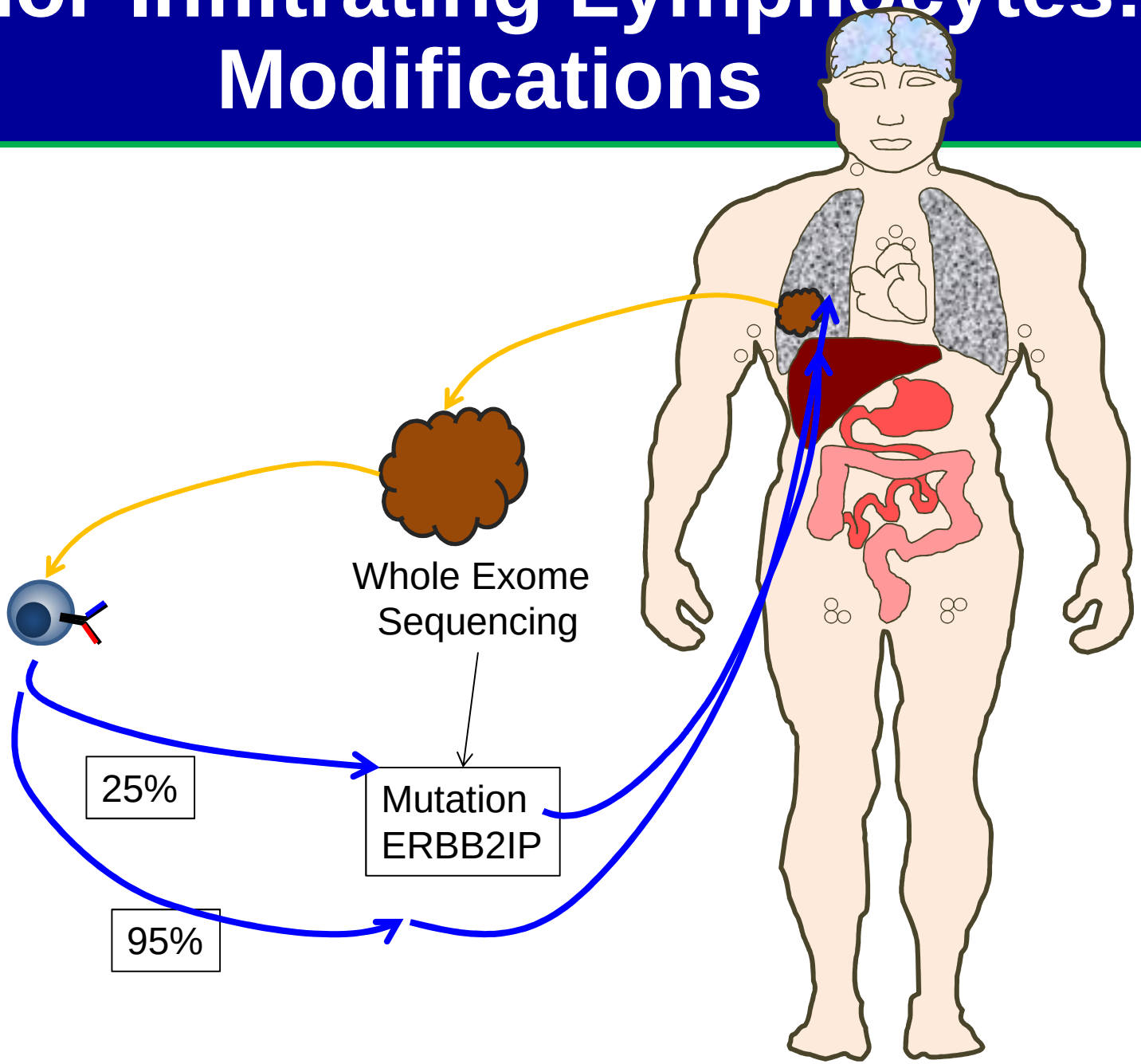
An article published Thursday in the journal Science describes the treatment of a 43-year-old woman with an advanced and deadly type of cancer that had spread from her bile duct to her liver and lungs, despite chemotherapy.

Researchers at the National Cancer Institute sequenced the genome of her cancer and identified cells from her immune system that attacked a specific mutation in the malignant cells. Then they grew those immune cells in the laboratory and infused billions of them back into her bloodstream.

The tumors began "melting away," said Dr. Steven A. Rosenberg, the senior author of the article and chief of the surgery branch at the cancer institute.

The woman is not cured: Her tumors are shrinking, but not gone. And an experiment on one patient cannot determine whether a new treatment works. But the report is noteworthy because it describes an approach that

Tumor-Infiltrating Lymphocytes: Modifications



TIL Opportunities: Combination

- **TIL Induction**
- **Enhanced Effectiveness**

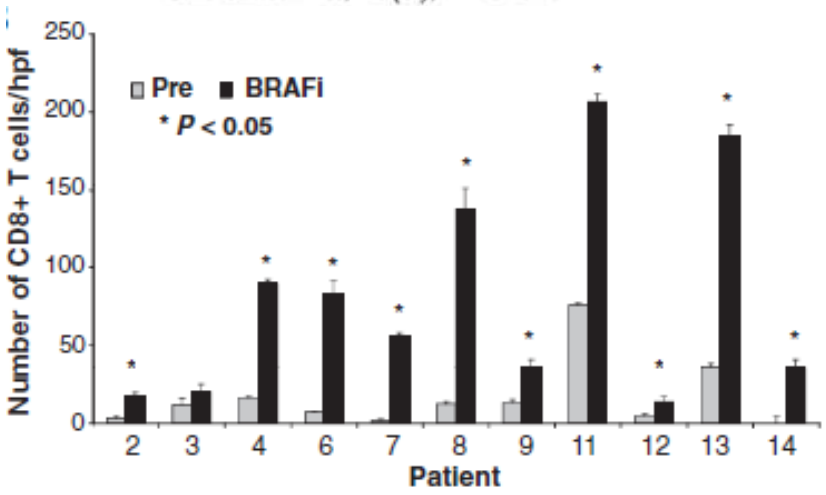
TIL Opportunities: Combination

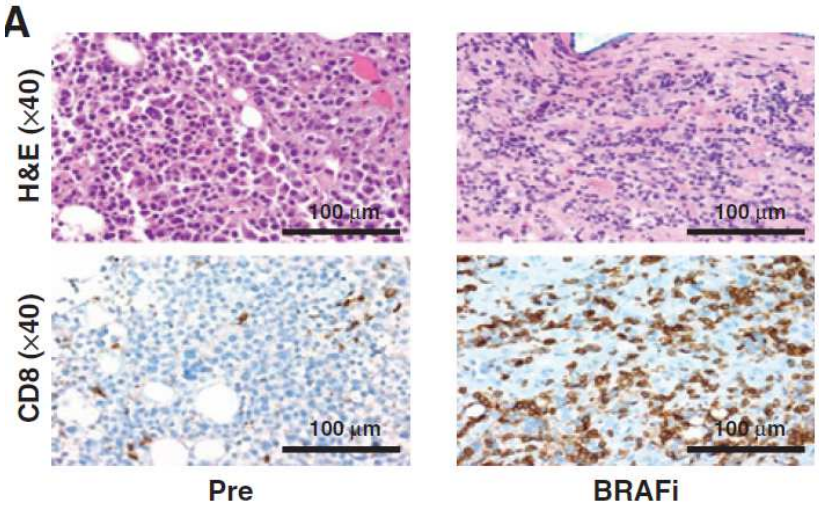
- **TIL Induction**
  - BRAFi
  - XRT
  - Vaccination

BRAF Inhibition Is Associated with Enhanced Melanoma Antigen Expression and a More Favorable Tumor Microenvironment in Patients with Metastatic Melanoma

Dennie T. Frederick[1], Adriano Piris[3], Alexandria P. Cogdill[1], Zachary A. Cooper[1], Cecilia Lezcano[6], Cristina R. Ferrone[1], Devarati Mitra[4], Andrea Boni[1], Lindsay P. Newton[1], Chengwen Liu[7], Weiyi Peng[7], Ryan J. Sullivan[2], Donald P. Lawrence[2], F. Stephen Hodi[5], Willem W. Overwijk[7], Gregory Lizée[7], George F. Murphy[6], Patrick Hwu[7], Keith T. Flaherty[2], David E. Fisher[4], and Jennifer A. Wargo[1]

Clin Cancer Res; 19(5); 1225–31. January 10, 2013;





TIL Opportunities: Combination

- **Enhanced Effectiveness of TIL**
  - **—Checkpoint Blockade**
  - **—Homeostatic Cytokines**