Disclosures

I declare having the following relationship(s) with commercial interests.

RELATIONSHIP / NAME OF COMPANY:

Speaker (Genomic Health), Advisory Board Member (BMS, Merck, Genentech, Castle Biosciences, Oncology & Biotech News, Contemporary Oncology), Consultant (Intraop./Mobetron), Study Section Reviewer (DOD-CDMRP), Peer Reviewer for 28 journals, Associate Editor for the Ochsner Journal

RECEIVED: Honoraria, I have NO STOCK in any of the above companies

This presentation will not discuss the use of products for non-FDA approved indications.

Active Immunization Approaches

Adam I. Riker, M.D., F.A.C.S.

Professor and Chief

Section of Surgical Oncology

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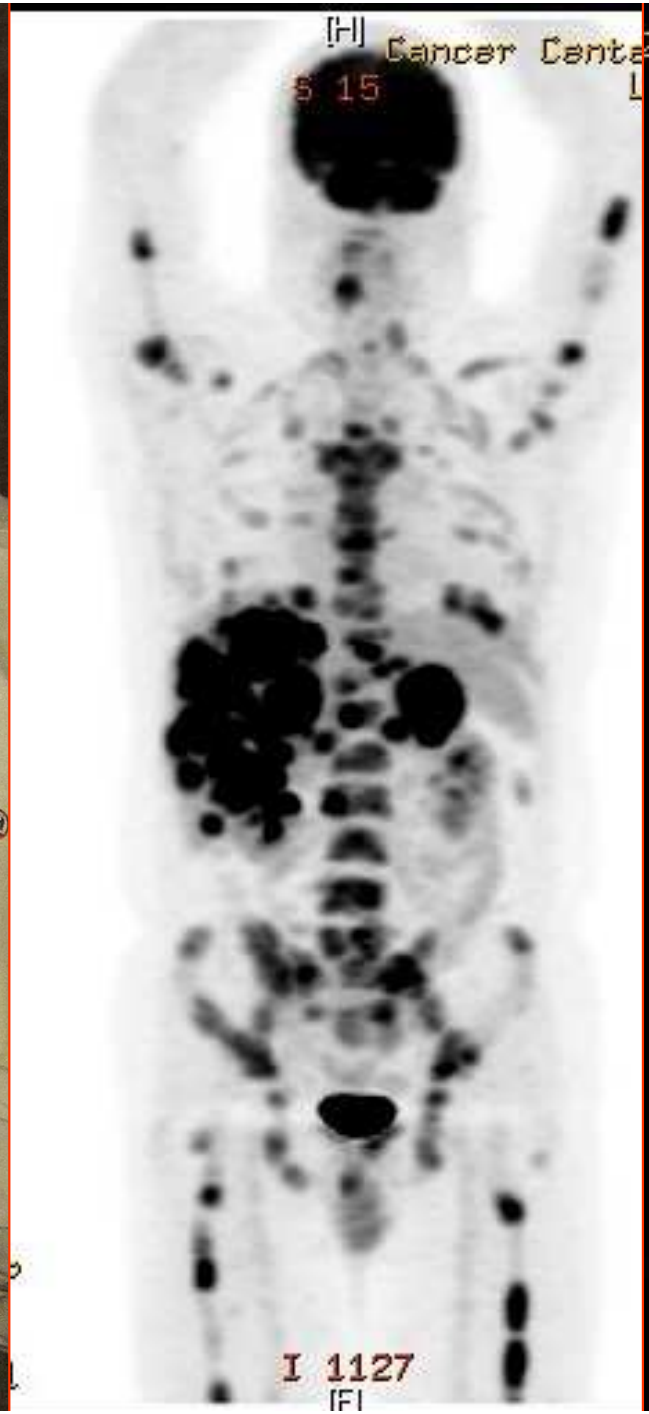
LCMC Health, New Orleans, Louisiana


2007 12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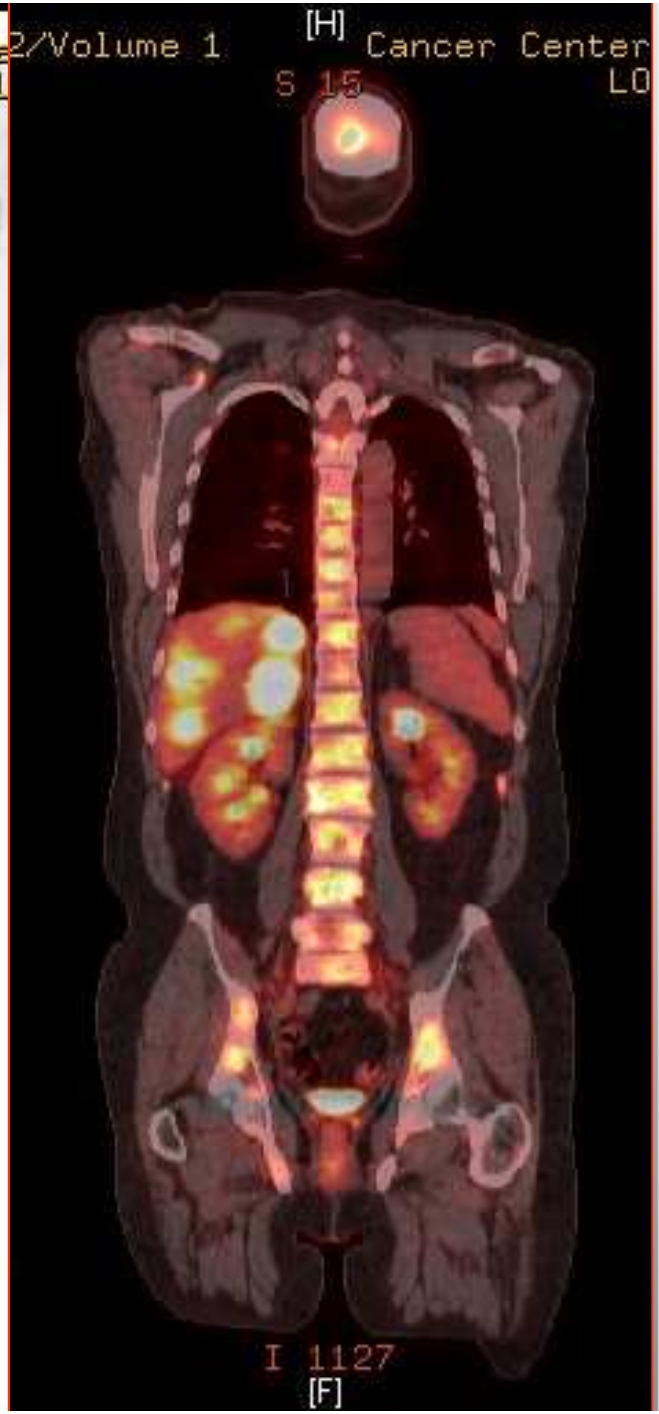
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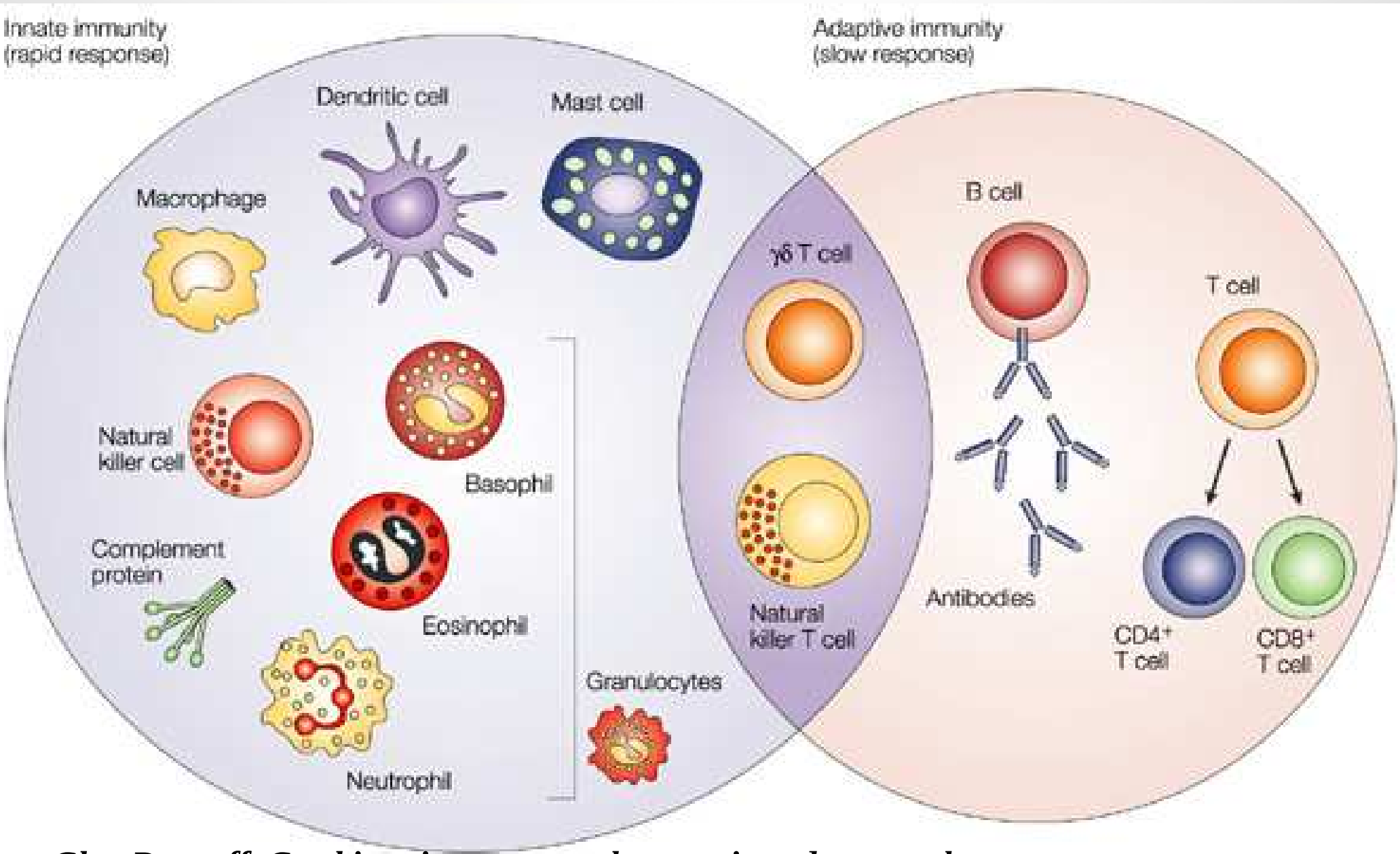
Human Immune System

Active Immunity

- Vaccine/infection
- Long-lasting protection
- Multiple immune cells and pathways affected
- It takes days/weeks to mount an immune response
- There is specificity
- There is memory

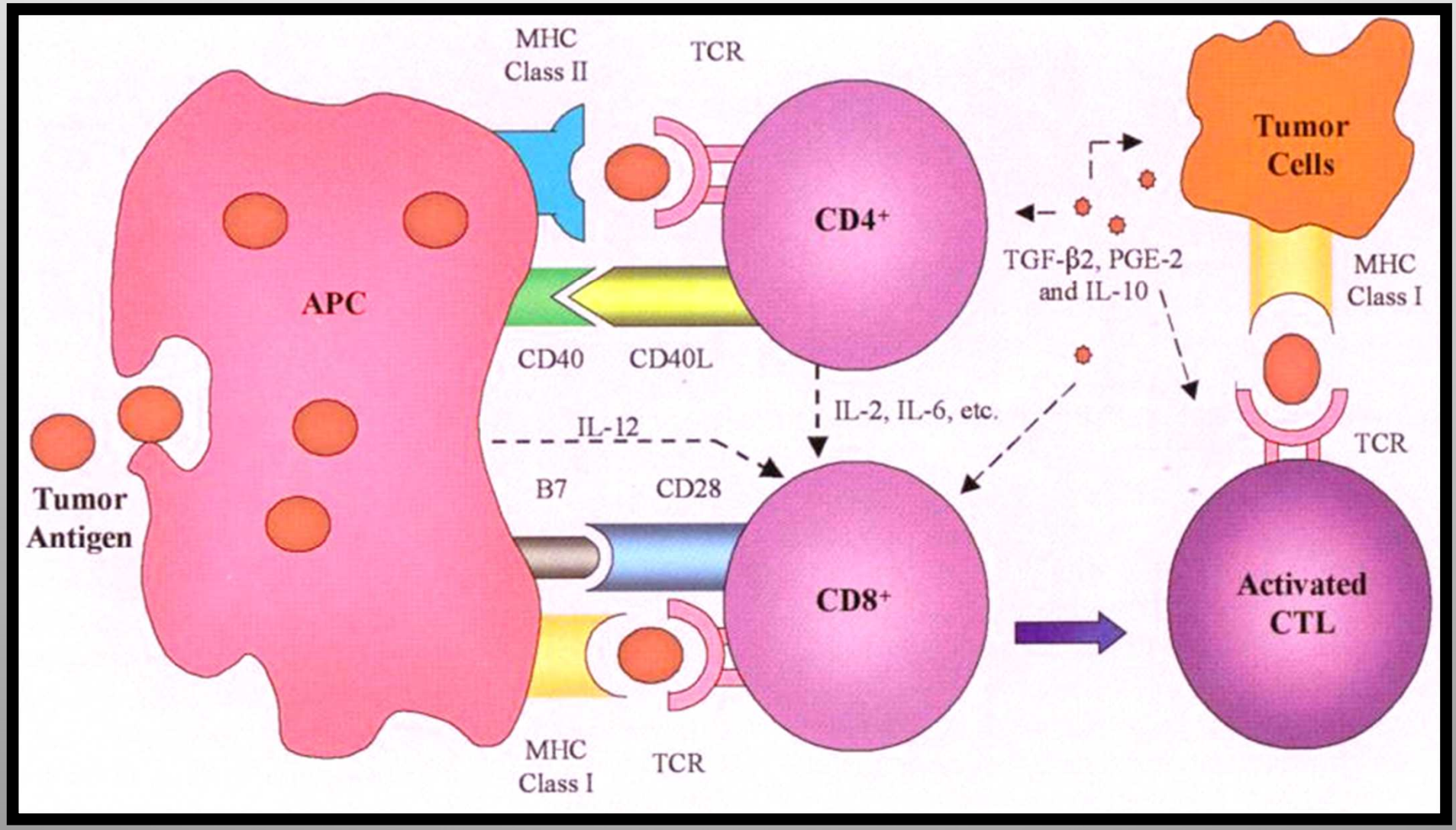
Passive Immunity

- Antibodies
- Rapid protection
- Short duration
- Antibody response
- There is specificity
- No memory immune response



Glen Dranoff, Cytokines in cancer pathogenesis and cancer therapy, Nature Reviews Cancer, 4, 11-22, 2004

Immunologic Response to Cancer



Slide courtesy of Steven A. Rosenberg, 1998

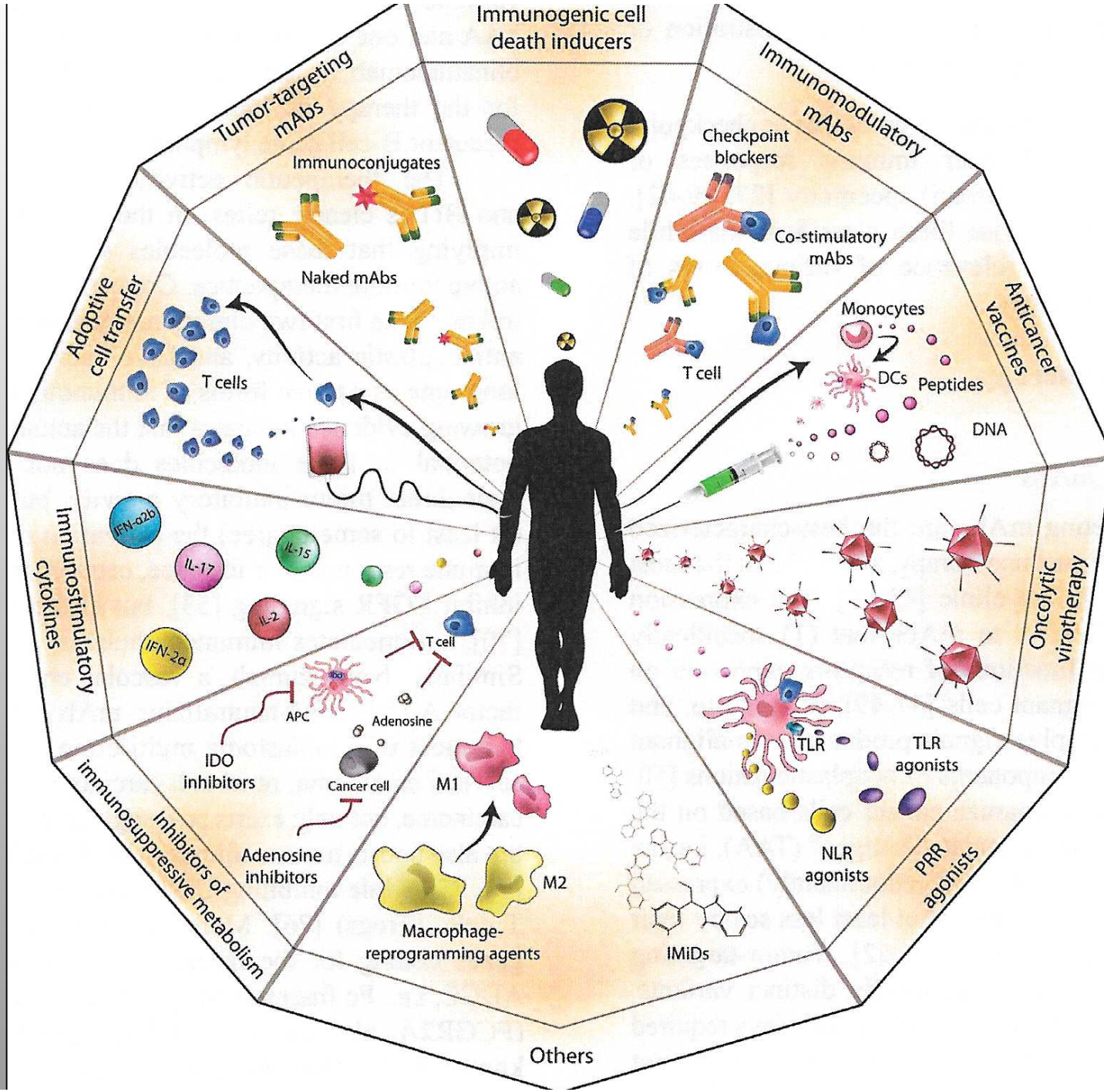
HISTORY OF CANCER TREATMENT MODALITIES

	SURGERY	RADIATION	CHEMO-THERAPY	TARGETED DRUGS	IMMUNO-THERAPY
APPROACH	Cut out accessible tumor cells to stop growth and prevent their spread	Use highly concentrated X-rays or radioactive isotopes to kill cancerous cells	Use cytotoxic drugs to kill or inhibit cancer cells	Interfere with a mechanism required for, or that supports tumor growth	Support the immune system's innate ability to recognize and eliminate tumor cells
SINCE	1800s	early 1900s	late 1940s	2000s	2010s
LIMITATIONS	Many inaccessible tumors ineligible; limited effectiveness if tumor has already begun to spread	Limited effectiveness if tumor has already begun to spread; potentially dangerous for tumors near vital organs	High toxicity and often does not destroy the whole tumor, leading to high rates of recurrence	Limited tumor types eligible; high efficiency but short durability driving high rates of recurrence	Applicable to all tumors at all stages of disease including metastatic tumors; responses are highly durable; potential for lower toxicity profiles; synergistic with other treatments

Cancer Research Institute, Website: www.cancerresearch.org

Classification of Current Anti-Cancer Immunotherapies

Oncotarget, Vol. 5, No. 24, 2015



Therapeutic Cancer Vaccines

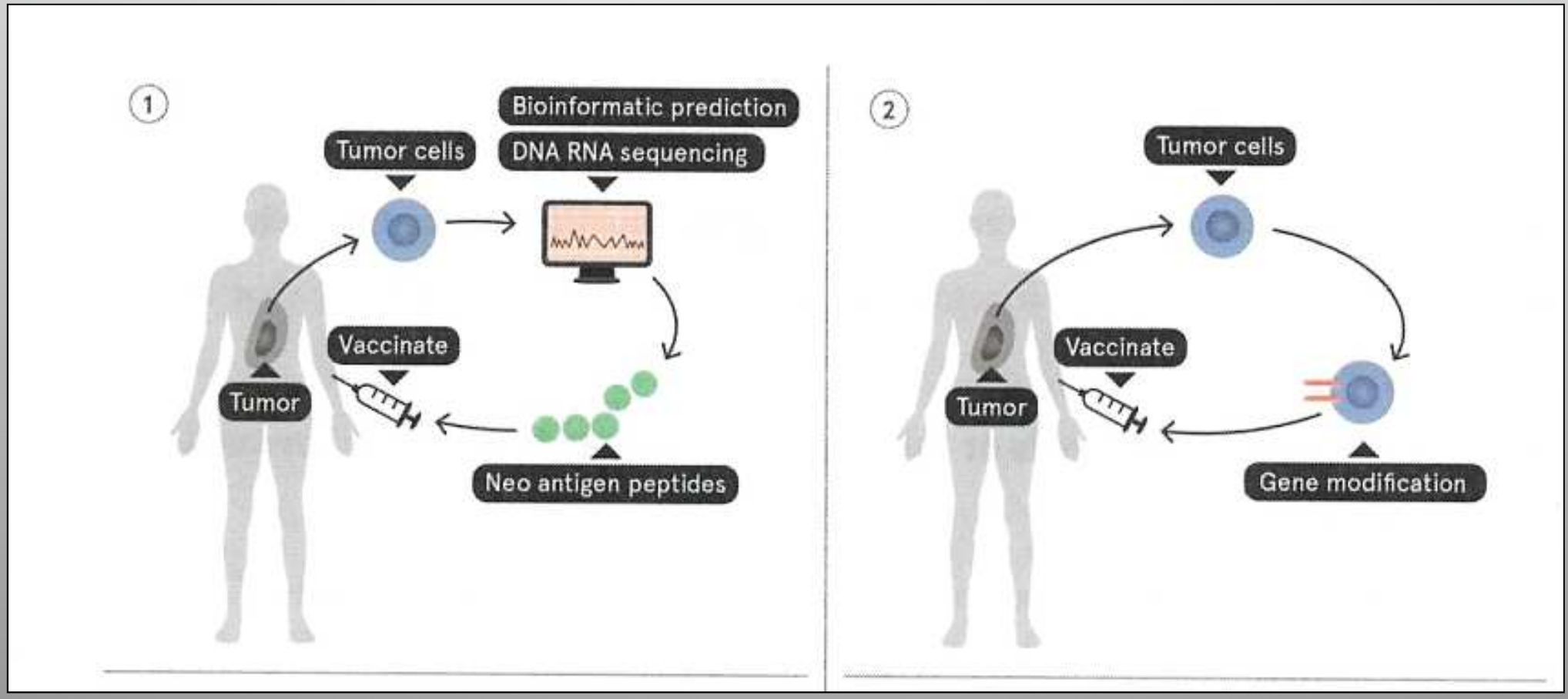
Approach to Immunization	Target	Subtype	Example	Comment
Active	Specific	Whole (irradiated) cell	GVAX prostate	Immunogen is irradiated autologous malignant pancreatic cells: also contains GM-CSF transfected gene and ipilimumab
		Component cell vaccine	Peptide, protein, tumor lysate and shed antigen vaccines have been developed	Non licensed as of May 2014
	Non-specific	Live, attenuated vaccine	BCG vaccine	Local tumor instillation (eg bladder cancer) enhances immune response
Passive	Specific	Antibody	trastuzumab	Blocks Human Epidermal Growth Receptor 2
		Antibody Drug Conjugate	brentuximab vedotin	Antibody targets malignant cell releasing the fused antineoplastic drug
		Autologous or allogeneic T cells	Tumor invading lymphocytes, CTLs, T_H and T regs cell vaccines developed	Termed adoptive T cell therapy – non licensed (May, 2014)
	Non-specific	Antibody	ipilimumab	CTLA4 blocking antibody
		Autologous or allogeneic T cells	Tumor invading lymphocytes, CTLs, T_H and T regs cell vaccines developed	Termed adoptive T cell therapy – non licensed (May 2014)

Table 1

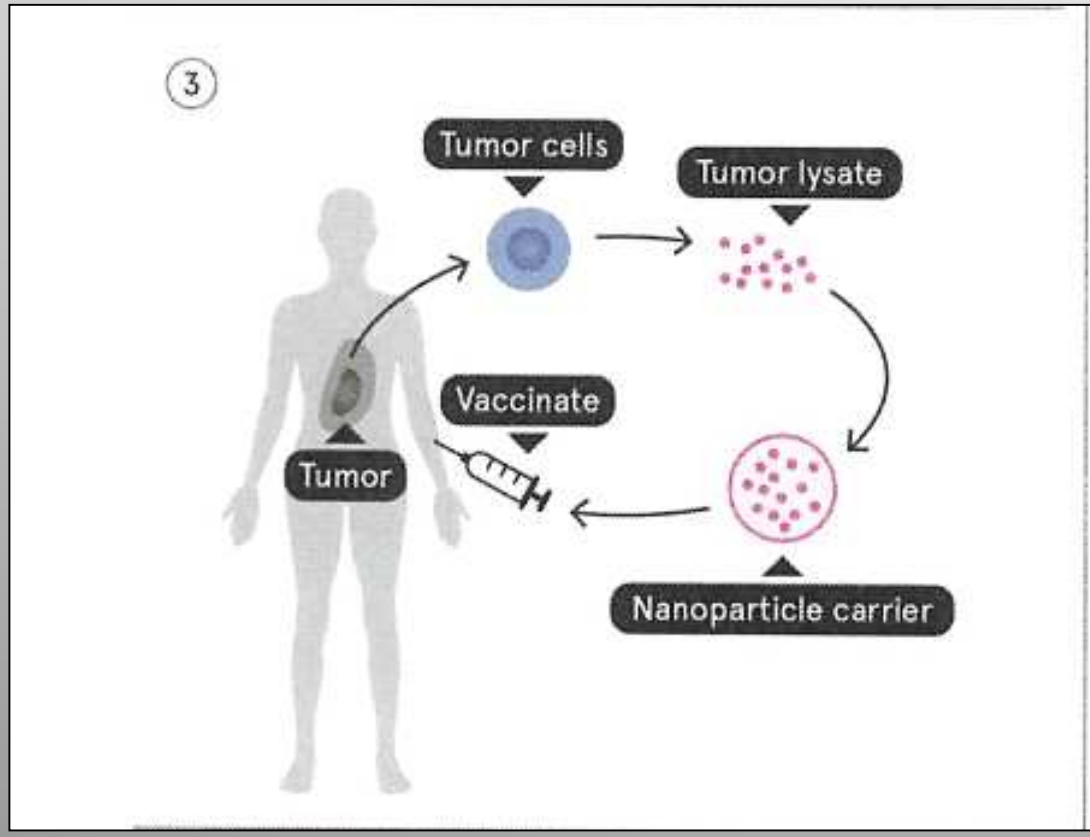
Overview of results from phase III vaccine trials and immune correlates to better patient outcomes

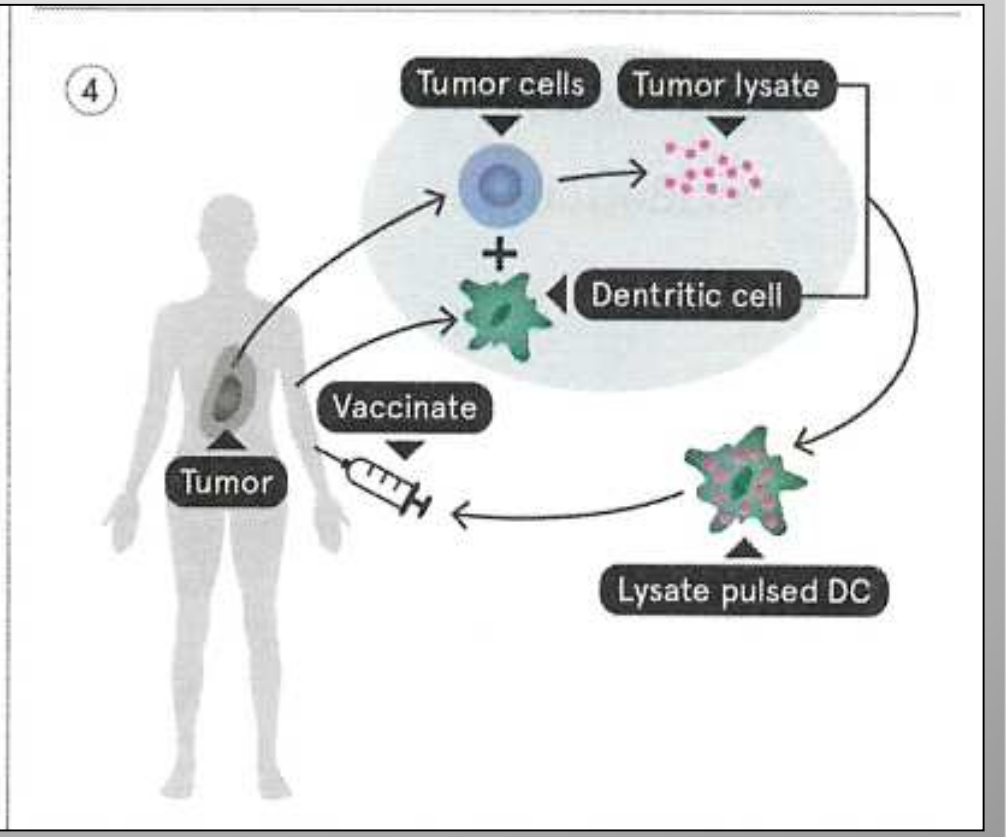
Trial/name	Cancer	Antigen	Adjuvant/delivery	Patients	Primary endpoint	Immune correlates to improved outcome	References
DERMA	Melanoma	MAGE-A3	AS15, AS02B	1351	Disease free survival — data pending	Gene signature (GS) suggesting active immune response within the tumor from Phase II data GS+ patients versus placebo, HR = 0.37, $p = 0.06$	[25**,28]
MAGRIT	Lung	MAGE-A3	AS15, AS02B	2278	Disease free survival, Terminated due to futility	Gene signature suggesting active immune response within the tumor GS+ patients versus placebo, HR = 0.42, $p = 0.06$	[23,24,25**]
Tecemotide/ SMART Trial	Lung	MUC1	Liposome	1239	Overall survival, 25.6 versus 22, $p = 0.12$	Concurrent Radiation + vaccine. Overall survival 30.8 versus 20.6, $p = 0.016$	[48]
IMA-901	Kidney	Multiple HLA-A2.1 peptides (10)	GM-CSF	68	Phase II, saftey and tolerability were met. Phase III trial is currently underway	Multiple eptiope response correlated with better disease controll, $p = 0.023$	[26]
Provenge/ IMPACT Study	Prostate	Prostatic Acid Phosphatase PAP	Autologous dendritic cells	512	Survival hazard ratio, 0.59, $p = 0.01$ Median overall survival 25.8 versus 21.7	Antibody titre >400, Increased overall survival $p = 0.001$, 28.5% of patients	[18–20]
gp100	Melanoma	gp100	Montanide/IL-2	185	Progression free survival, 2.2 versus 1.6, $p = 0.008$	No correlation with immune activity in Phase II or III trial	[21,30]
STn-KLH	Breast	Sialyl-Tn-KLH	KLH/Detox B	1022	Time to progression, 3.4 versus 3.0, $p = 0.305$ Overall survival, 23.1 vs. 22.3	Median or greater IgG response. Overall survival 39.6 versus 25.4, $p = 0.005$	[67,68]

Patient cells injected with tumor-specific mutations identified by high-throughput sequencing and bioinformatics, or whole tumor cells

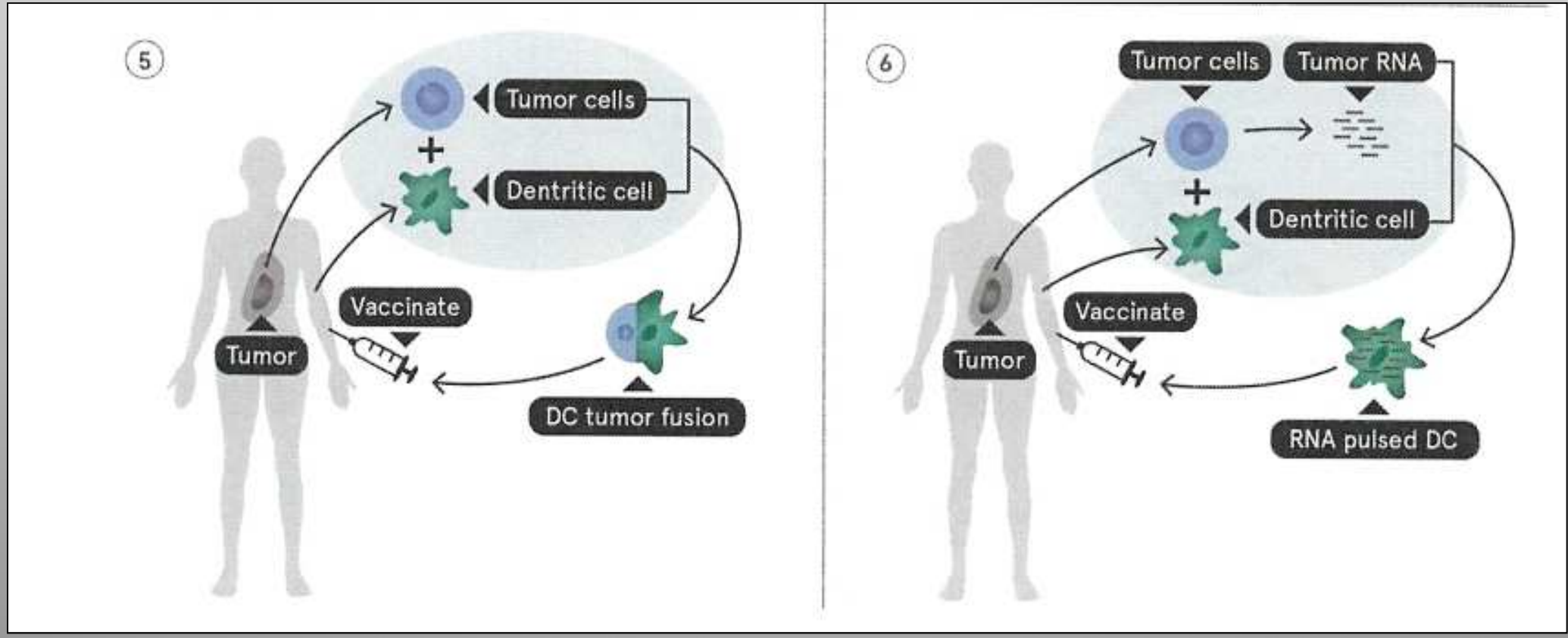


Autologous tumor lysate encapsulated into nanoparticle vehicles, delivered to DC's in vivo





Dendritic cells loaded ex-vivo with autologous tumor antigens via pulsing with either tumor RNA or lysate



Immune Dysfunction Inhibiting Vaccine Efficacy and Treatments to Overcome This

(a) Vaccine antigen specific T-cell pool is mostly exhausted

- Low proliferation in response to antigen
- No cytokine production
- High expression of PD1, LAG3, CTLA4

Treatments:

- Antibody treatments blocking PD1, LAG3 and CTLA4 can restore the function of exhausted CD8 cells

Current Opinions in Immunology

Immune Dysfunction Inhibiting Vaccine Efficacy and Treatments to Overcome This

(b) APCs are not optimally immunogenic

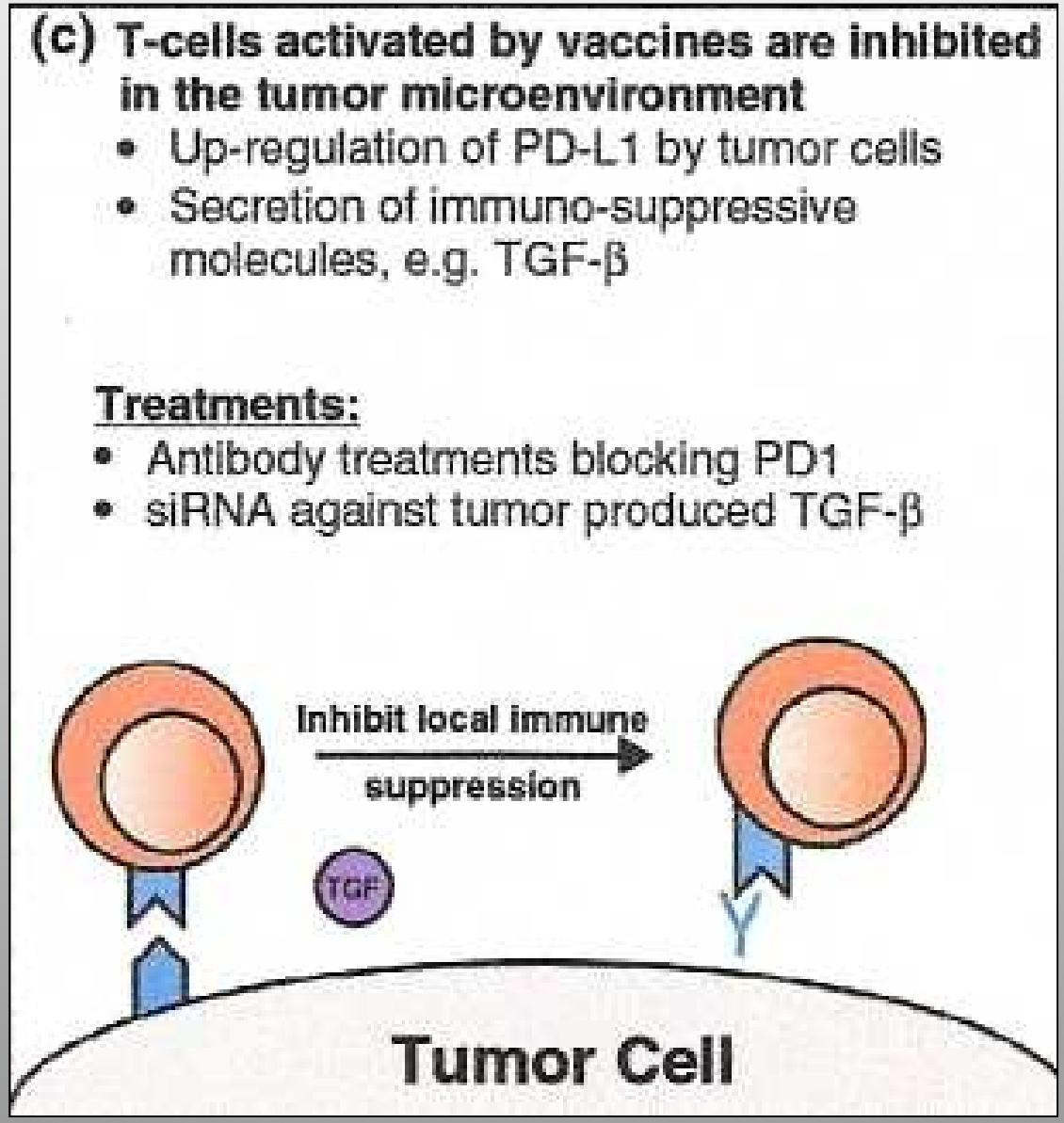
- Low co-stimulatory molecules
- Low MHC-I
- Poor cytokine production

Treatments:

- Vaccines using ex-vivo optimally activated dendritic cells to deliver antigen (Provenge)
- Co-treatment with radiation can improve antigen presentation
- Powerful adjuvants can improve vaccine antigen presentation (e.g. CpG)

Current Opinions in Immunology

Immune Dysfunction Inhibiting Vaccine Efficacy and Treatments to Overcome This



Current Opinions in Immunology

Preventing cancer:

True cancer vaccines

Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant

Cervical Cancer:

- Prevented 100% of HPV 16- and 18- related cervical pre-cancers and non-invasive cervical cancers
- Protects against 4 types of HPV in females ages 9 to 26
- Protects against 2 types of HPV that cause about 75% of cervical cancer cases, and 2 more types that cause 90% of genital warts.

Cervical Intraepithelial Neoplasia (CIN):

- Prevented 95% of low-grade cervical dysplasia and pre-cancers caused by HPV 6, 11, 16 or 18

Genital Warts:

- Prevented 99% of cases of genital warts caused by HPV 6 or 11
- Males ages 9 to 26, protect against 90% of genital warts

Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant

Vaginal cancer:

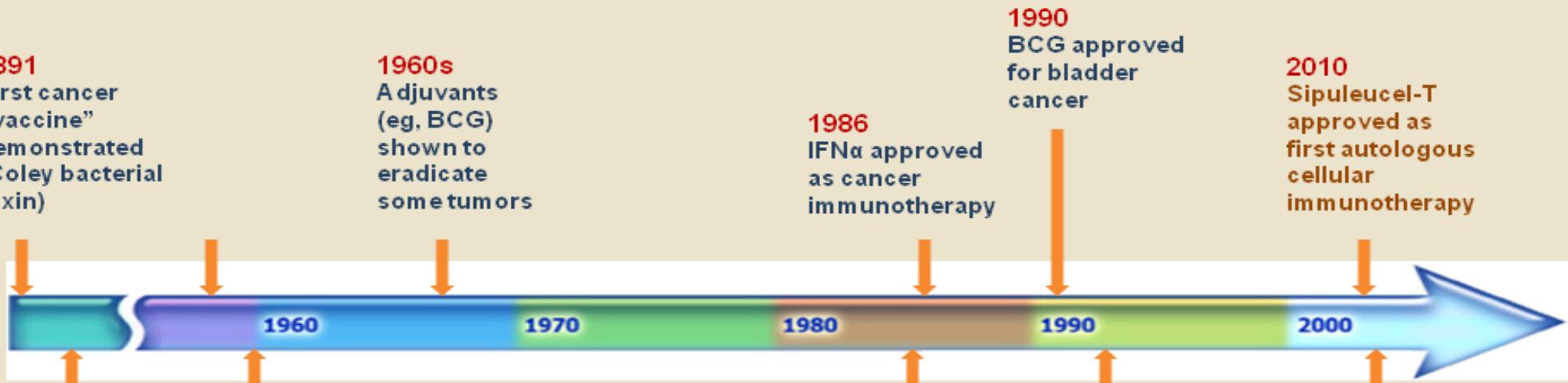
- **Helps protect females ages 9 to 26 against 70% of vaginal cancer cases and up to 50% of vulvar cancer cases.**

Head/Neck Cancer ???

- **HPV infections, especially HPV 16, contribute to some H/N cancers**
- **HPV is found in an estimated 26-35% of head and neck squamous cell carcinoma).**
- **In principle, HPV vaccines may help reduce incidence of such cancers caused by HPV, but this has not been demonstrated.**

- **Given as 3 injections over 6 months.**

Timeline of the Development of Immunotherapy

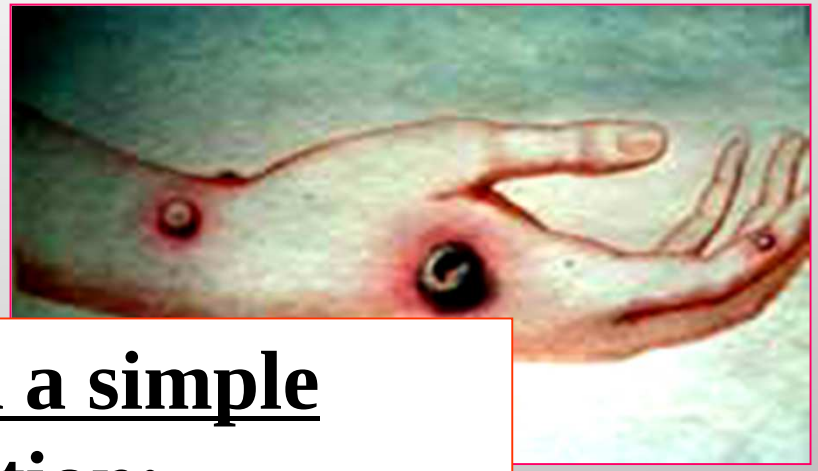


BCG = Bacille Calmette-Guérin
IFN = interferon
IL = interleukin
TIL = tumor-infiltrating lymphocyte

Coley WB. Ann Surg 1891;14:199–220
Kim CJ et al. *Cancer Control*. 2002;9:22-30.
Dudley ME et al. *Science*. 2002;298:850-854.
Nature Milestones Cancer 2006; S7-S23.
Cancer: Principles and Practice of Oncology. 9th ed. 2011.

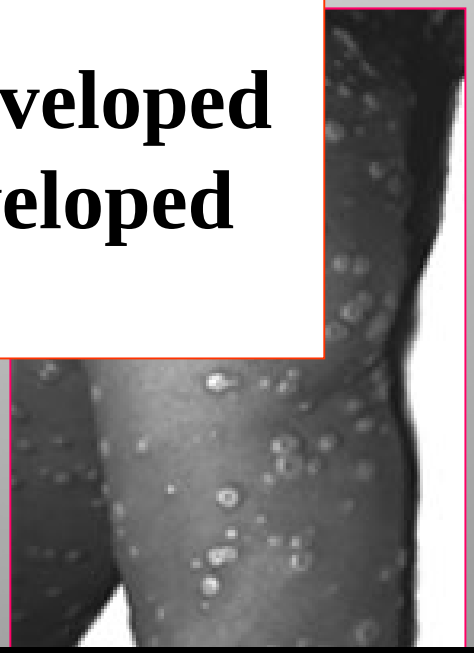
Edward Jenner

Milk maidens hand infected with cowpox virus



All based on a simple observation:

Milk maidens who developed cowpox NEVER developed smallpox



Smallpox

~ circa 1804

Bronze sculpture by Giulio Monteverde showing Edward Jenner inoculating his son with cowpox liquid as a prevention against smallpox

<u>Variolation:</u> Pricking into the skin with the fluid from a cowpox blister (vaccinia)

THE COW-POCKOR: THE WONDERFUL EFFECTS OF THE NEW INOCULATION [James Gilray, circa 1802]

The Cow-Pock — or — the Wonderful Effects of the New Inoculation! — Vide. the Publications of ye Anti-Vaccine Society.

William B. Coley

- **1891: Attending Surgeon to the NYC Cancer Hospital**
- **Utilized a combination of live bacterial cultures (Streptococcus pyogenes [erysipelas] and Bacillus prodigiosus)**
- **Injected around a cancerous tumor (sarcoma)**
- **Changed to filtered cultures due to high toxicity**
- **Coley's Toxin resulted in disappearance of large, bulky tumors in many patients, primarily with sarcoma**
- **Possibly led to discovery of tumor necrosis factor (TNF)**

William B. Coley

- **First patient: to receive Coley Fluid was a sixteen-year-old boy with a massive abdominal tumor.**
- **Every few days, Coley injected "Coley's fluid" directly into the tumor mass**
- **Produced the symptoms of an infectious disease, but did not produce the disease itself**
- **On each injection, there was a dramatic rise in body temperature and chills**
- **The tumor gradually diminished in size**
- **By May 1893, after four months of intensive treatment, the tumor was 1/5th its original size**
- **By August, the remains of the growth were barely perceptible**
- **The boy received no further anti-cancer treatment and remained in good health until he died of a heart attack 26 years later.**

1898.] INOPERABLE

THE TREATMENT OF INOPERABLE SARCOMA WITH THE MIXED TOXINS OF ERYSIPELAS AND BACILLUS PRODIGIOSUS.

IMMEDIATE AND FINAL RESULTS IN ONE HUNDRED AND FORTY CASES.

Presented to the Section on Surgery and Anatomy, at the Forty-ninth Annual Meeting of the American Medical Association, held at Denver, Colo., June 7–10, 1898.

BY WILLIAM B. COLEY, M.D.

ATTENDING SURGEON TO THE NEW YORK CANCER HOSPITAL; ASSISTANT SURGEON TO THE HOSPITAL FOR RUPTURED AND CR

NEW YORK, N. Y.

Annual Meeting of the AMA, June 7th, 1898

Memorial Sloan-Kettering Cancer Center

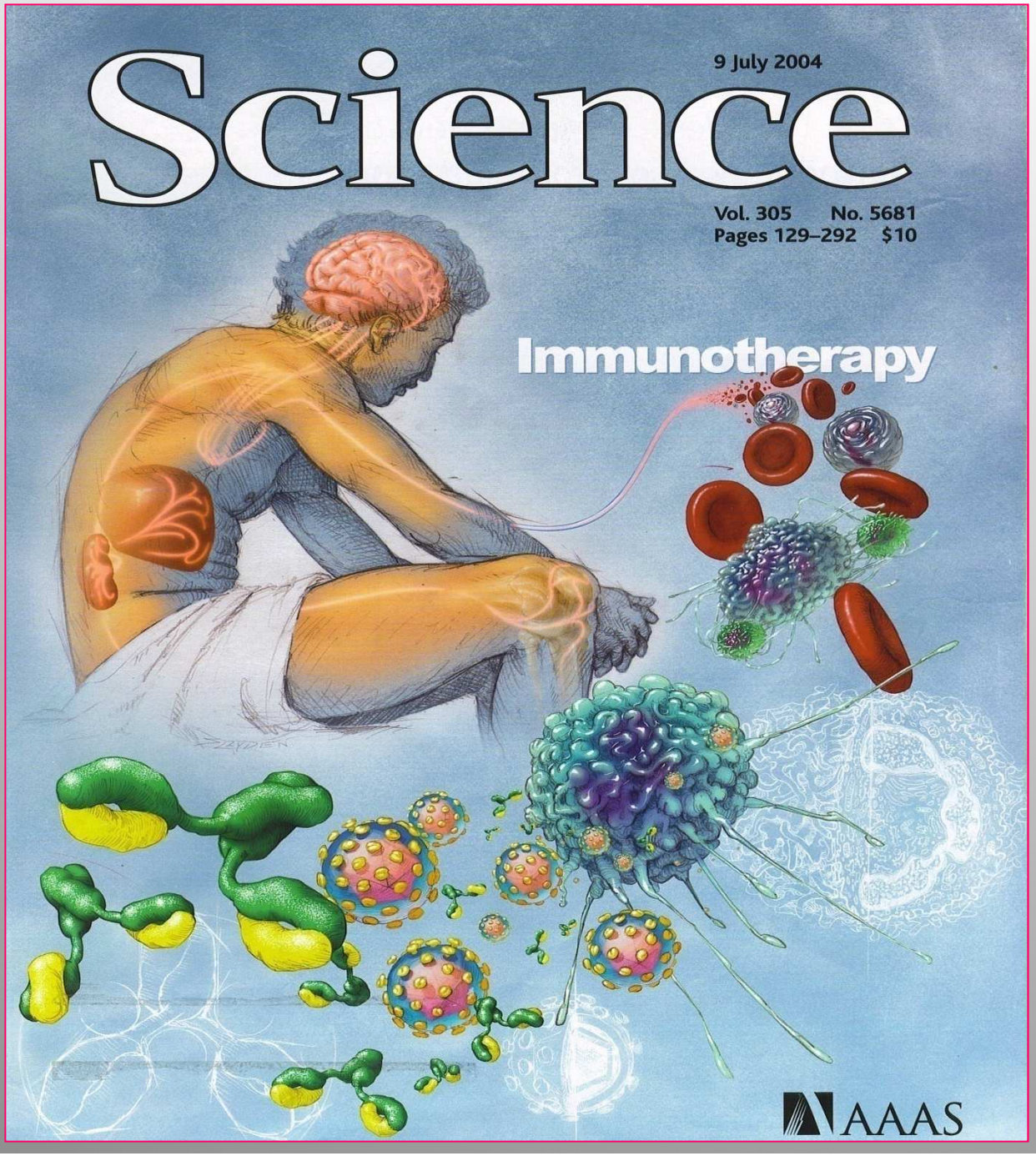
Table 2. *Summary of Patients Treated with Coley's Toxins before 1940*

Type of cancer	Total	A	B	C	D	E
Soft tissue sarcomas[1]	84	32	12	11	12	17
Lymphosarcomas (lymphomas)[2]	33	10	4	4	7	8
Osteosarcoma[3]	3	2	1	0	0	0
Ewing's tumor/reticulum cell sarcoma[4]	1	0	0	0	0	1
Ovarian carcinoma[5]	4	1	2	0	0	1
Cervical carcinoma[5]	2	0	1	0	0	1
Testicular[6]	14	5	3	3	2	1
Renal[7]	8	4	1	1	1	1
Multiple myeloma[8]	1	0	0	1	0	0
Colorectal carcinoma[9]	1	1	0	0	0	0
Breast carcinoma[10]	13	5	6	2	0	0
Melanoma[11]	6	2	3	0	1	0

Evaluation was restricted to those patients who were considered to be inoperable at the time of treatment, and who received no therapy other than the vaccine. Individual patient records are tabulated as follows: A, those making no beneficial response to the treatment; B, those making an initial response, but either known to relapse at any time or lost to follow-up in less than 5 years; C, those rendered free of disease, but lost to follow-up after at least 5, but less than 10, years; D, those rendered free of disease, but lost to follow-up after at least 10, but less than 20, years; E, those rendered free of any clinical evidence of disease for a period of time not less than 20 years. [1]Nauts, 1975c. [2]Nauts and Fowler, 1969. [3]Nauts, 1975b. [4]Nauts *et al.*, 1953. [5]Nauts, 1977. [6]Fowler, 1968. [7]Nauts, 1973. [8]Nauts, 1975a. [9]Fowler, 1969b. [10]Nauts, 1984. [11]Fowler, 1969a.

A complete response rate of 47.6% (40/84 pts. at 5 years)

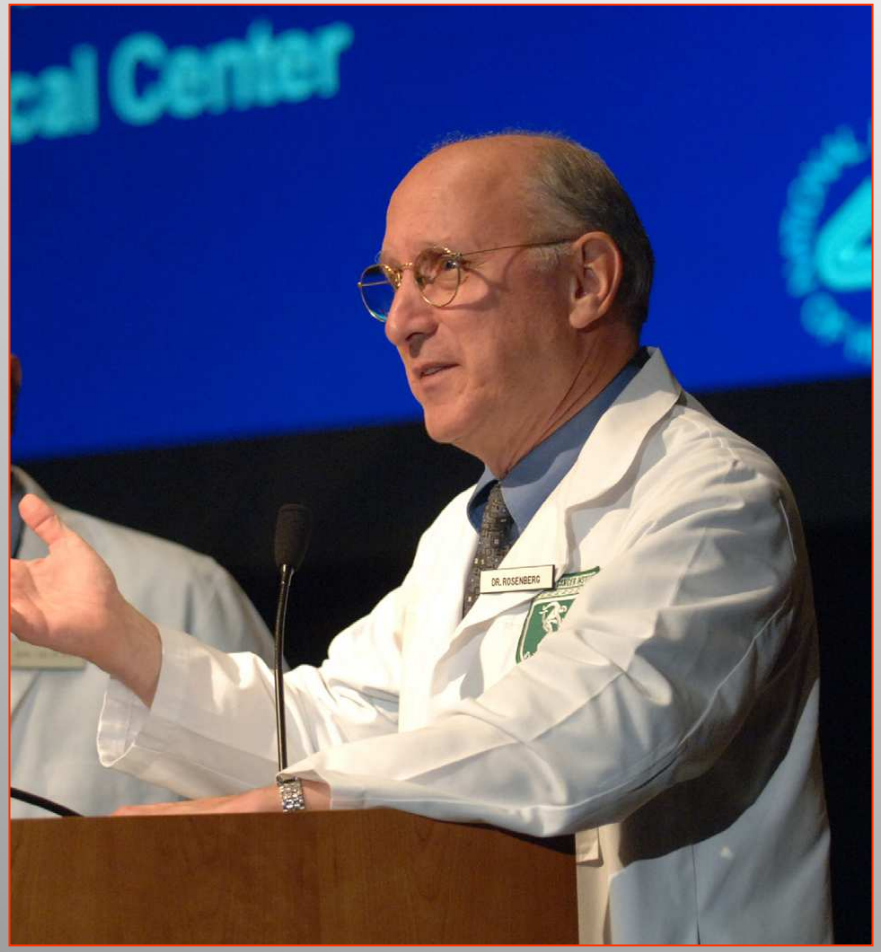
- **CR @ 5 yrs., but <10 yr (13%)**
- **CR @ >10 yrs., but <20 yr (13%)**
- **CR @ > 20 yr (20%)**



9July2004

IMMUNOTHERAPY OF CANCER: OFFERING THE PROMISE OF TREATING HUMAN DISEASES BY MOBILIZING OR INHIBITING MULTIPLE ARMS OF THE IMMUNE SYSTEM

Pioneers of cancer immunotherapy



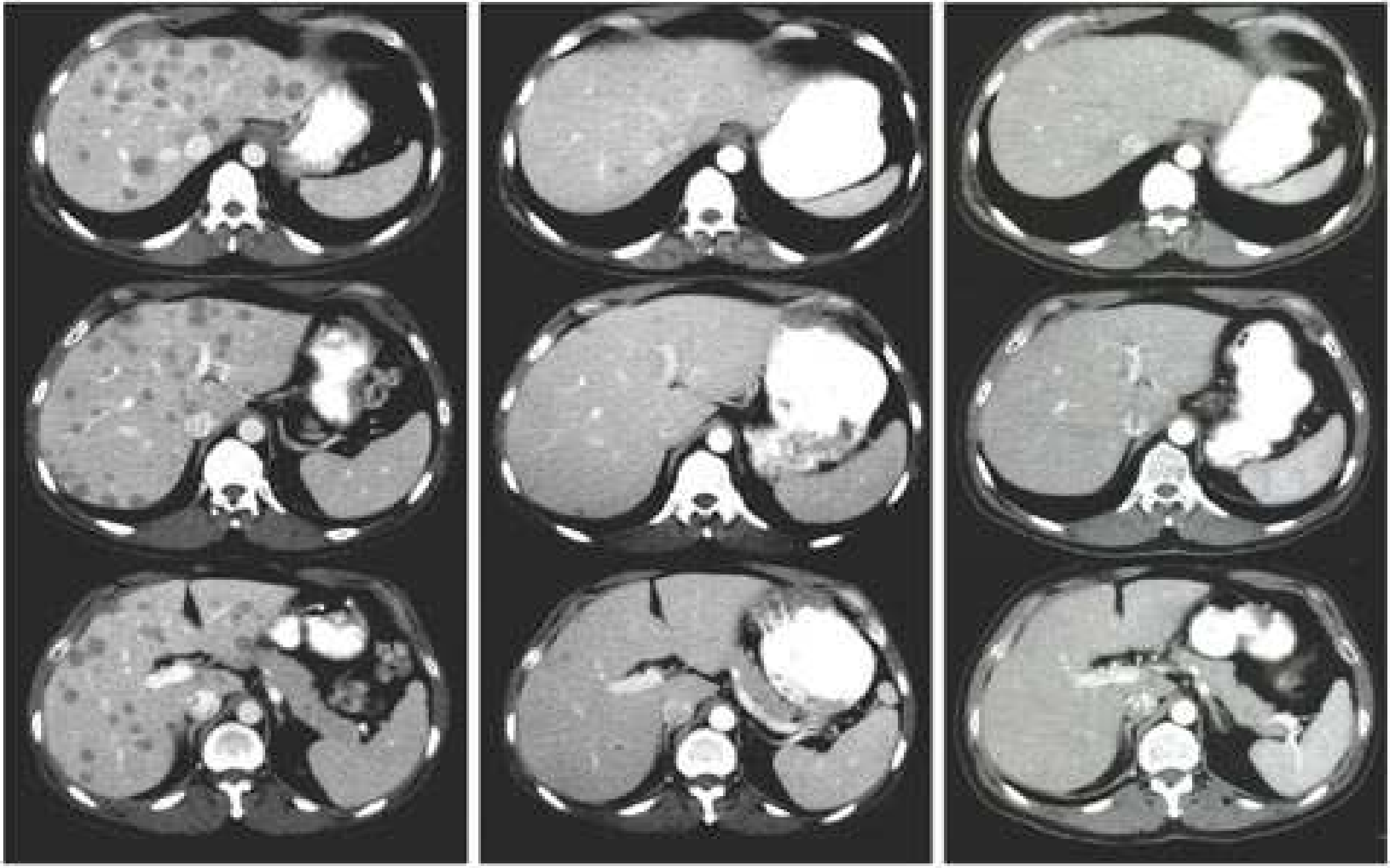
Steven A. Rosenberg

Donald Morton

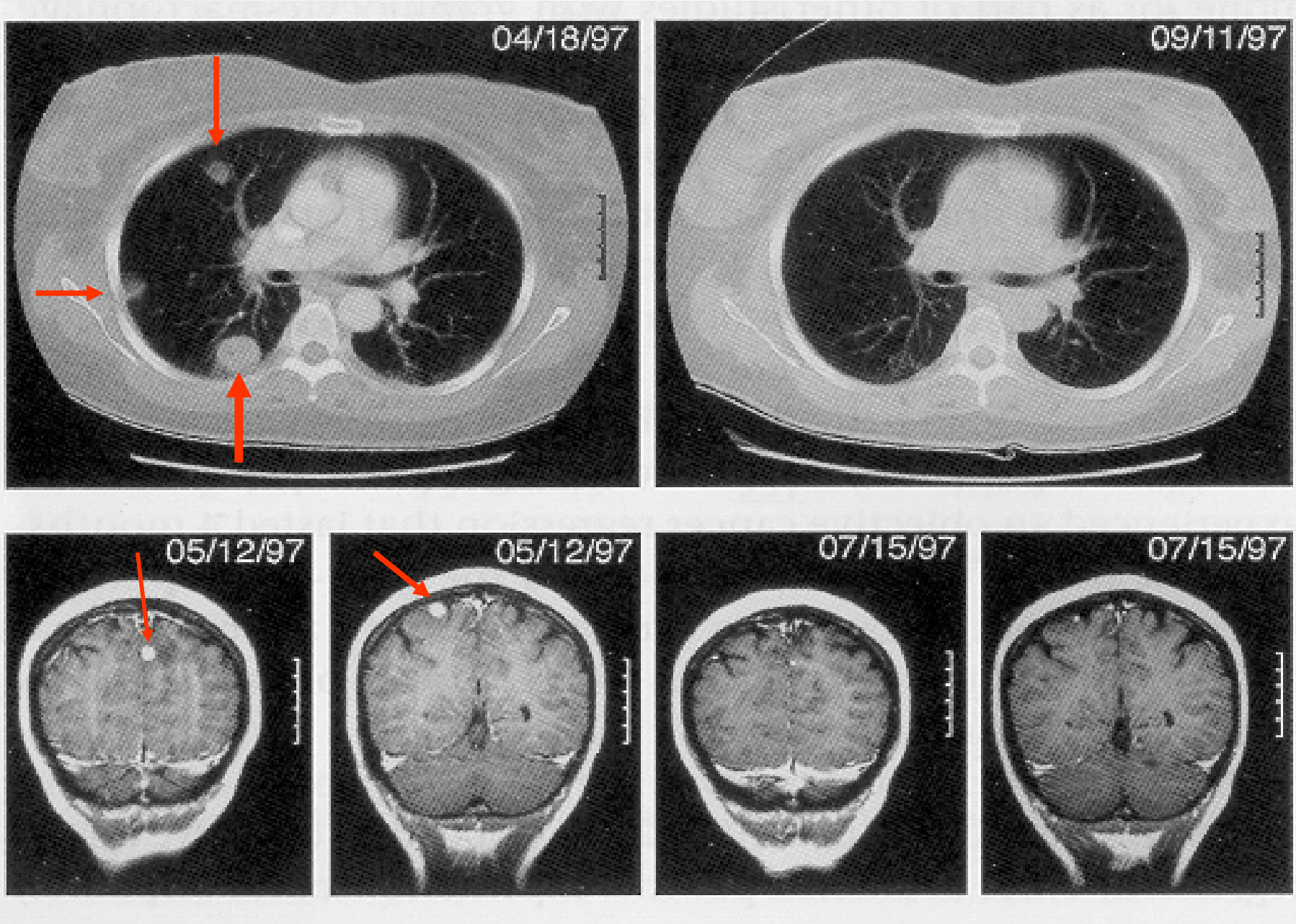
Clinical Studies with rIL-2 for the Treatment of Metastatic Melanoma

Investigator	Dosing//Schedule	Pts.	CR	PR	CR+PR	%
Hersh et al.	$12x10^6$ IU/m, day 1,3,5 every week		26	0	3	12%
Parkinson et al.	600,000 IU/kg, TID x 5 days, $q15^{th}$ d	46	2	8	22%	
Whitehead et al.	36-60 x 10^6 IU/m, day 1,3,5 q week		42	0	4	10%
Sparano et al.	6 x 10^6 U/m, TIDx 5 days, $q15^{th}$ d		44	0	2	5%
Demchak et al.	600,000 IU/kg, TID x 5 days, $q15^{th}$ d	27	0	4	26%	
Rosenberg et al.	720,000 IU/kg, TID x 5 days, $q15^{th}$		134	9	14	17%

CR = 7% **PR = 10%** **Total CR + PR = 17%**



Pretreatment 1 month 18 months



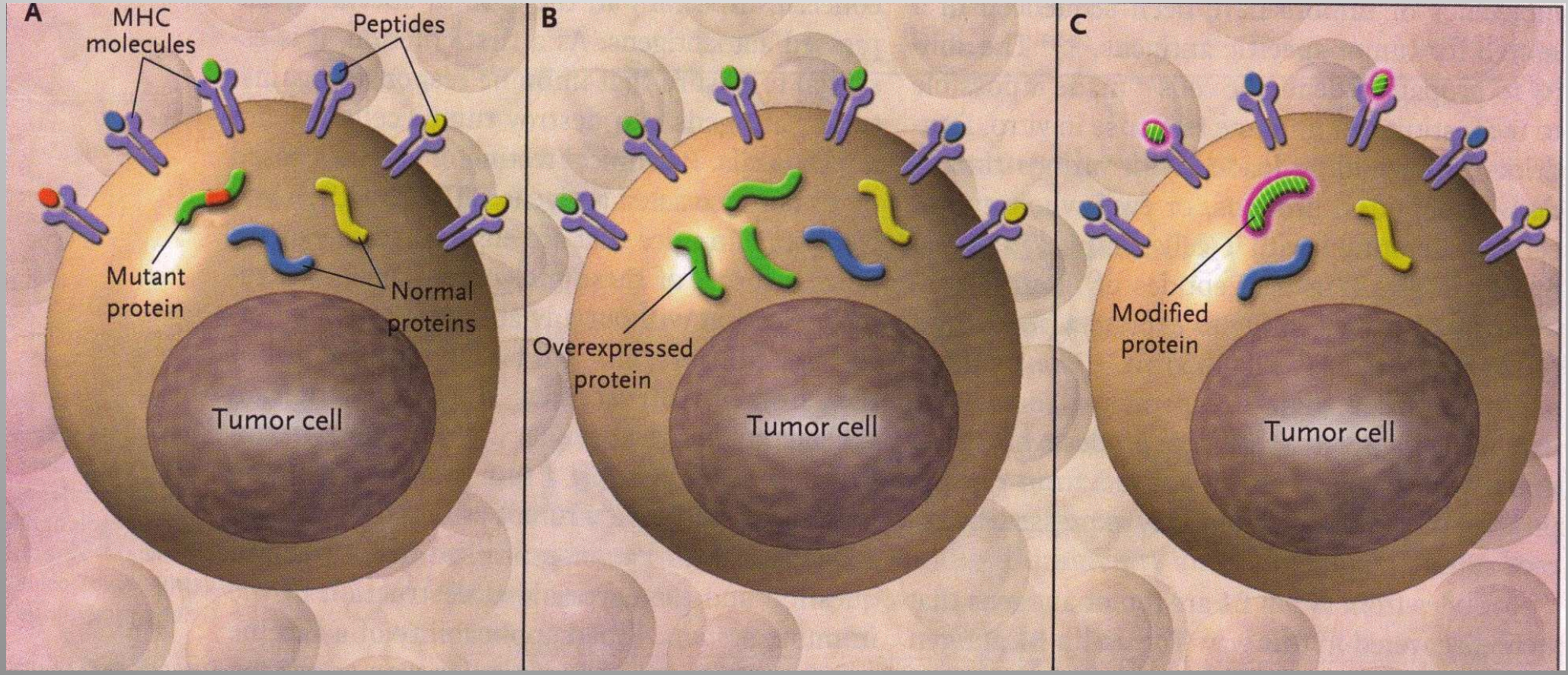
Rosenberg et al., Nature Med., 1998

Tumor Cell Recognition by the Host Immune System: Mechanisms for Self-Antigens to Become Tumor Antigens

Mutation

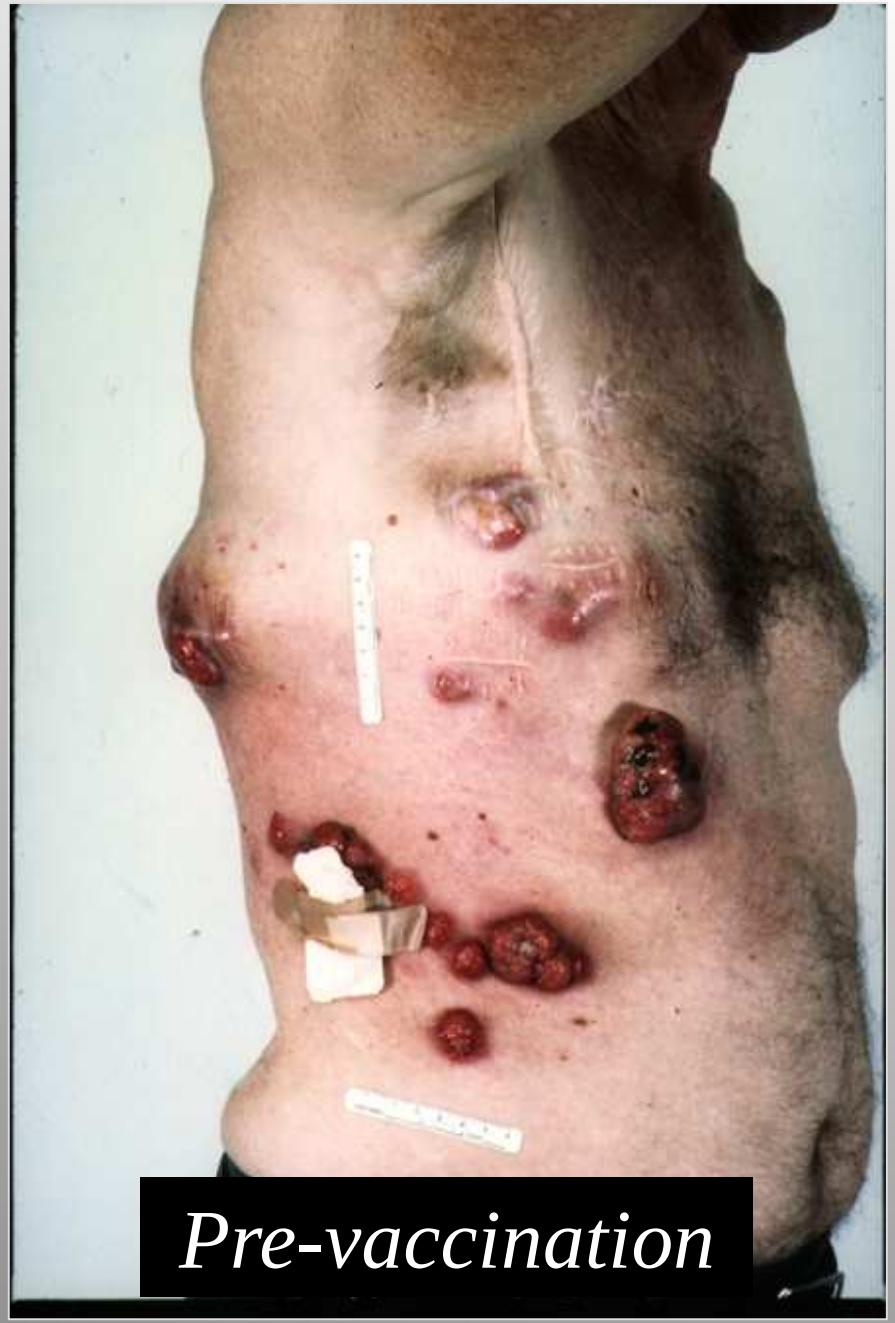
Over-expression

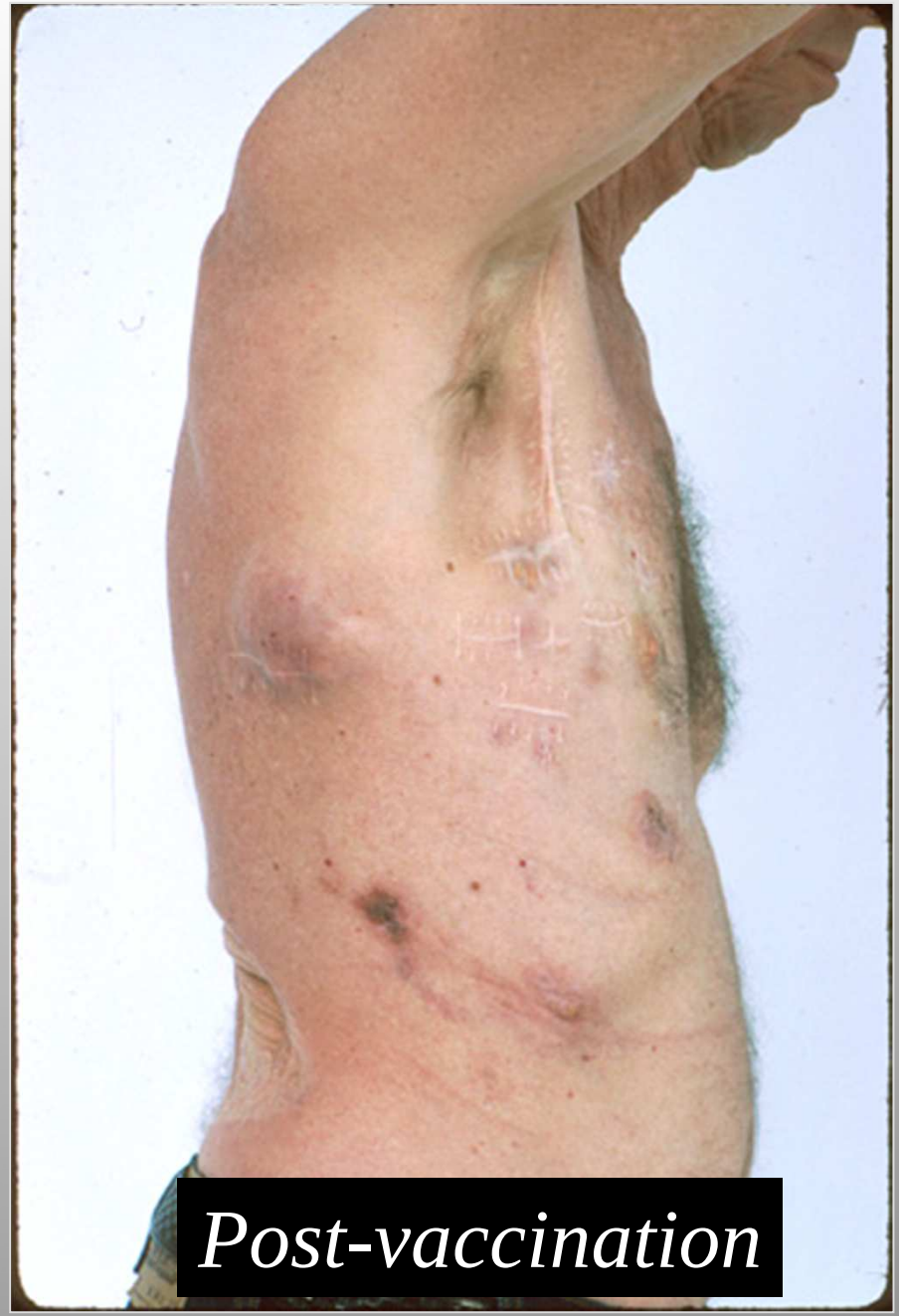
Post-Translational Modification

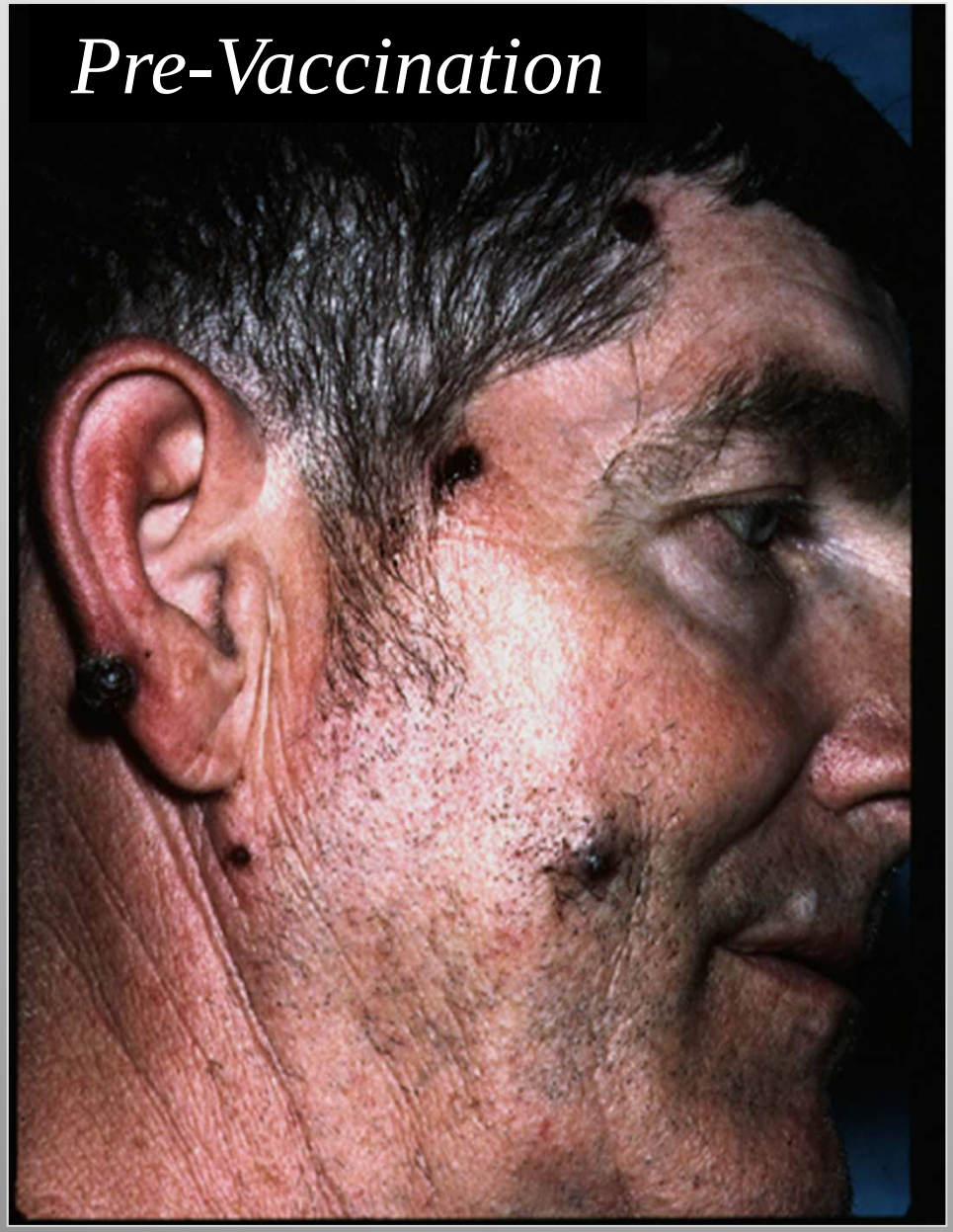


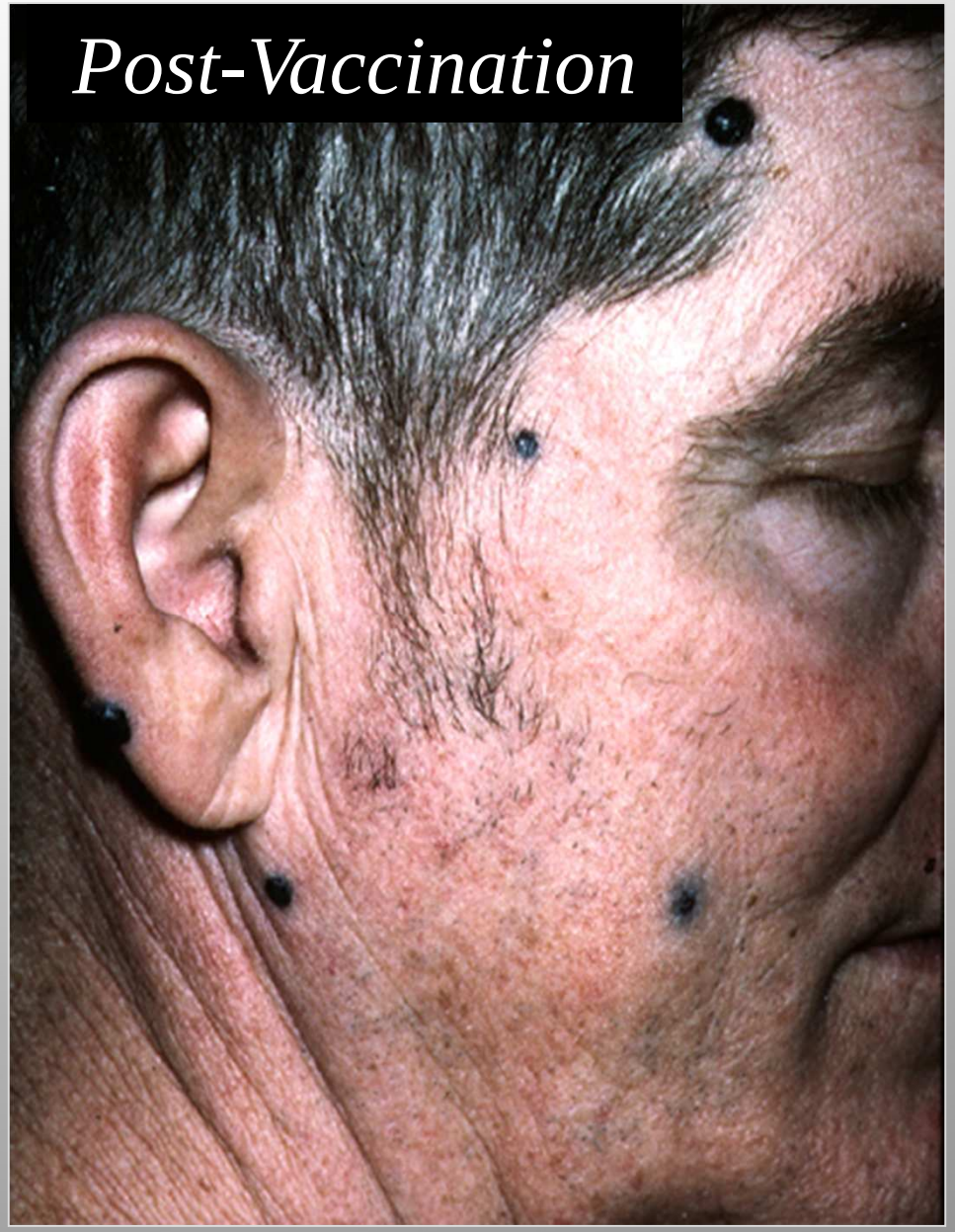
Immunologic and Therapeutic Evaluation of a Synthetic Peptide Vaccine for the Treatment of Patients with Metastatic Melanoma. Nature Medicine, March 1998. Rosenberg SA, Yang JC, Schwartzentruber DJ, Hwu P, Marincola FM, Topalian SL, Restifo NP, Dudley ME, Schwarz SL, Spiess PJ, Wunderlich JR, Parkhurst MR, Kawakami Y, Seipp CA, Einhorn JH, White DE.

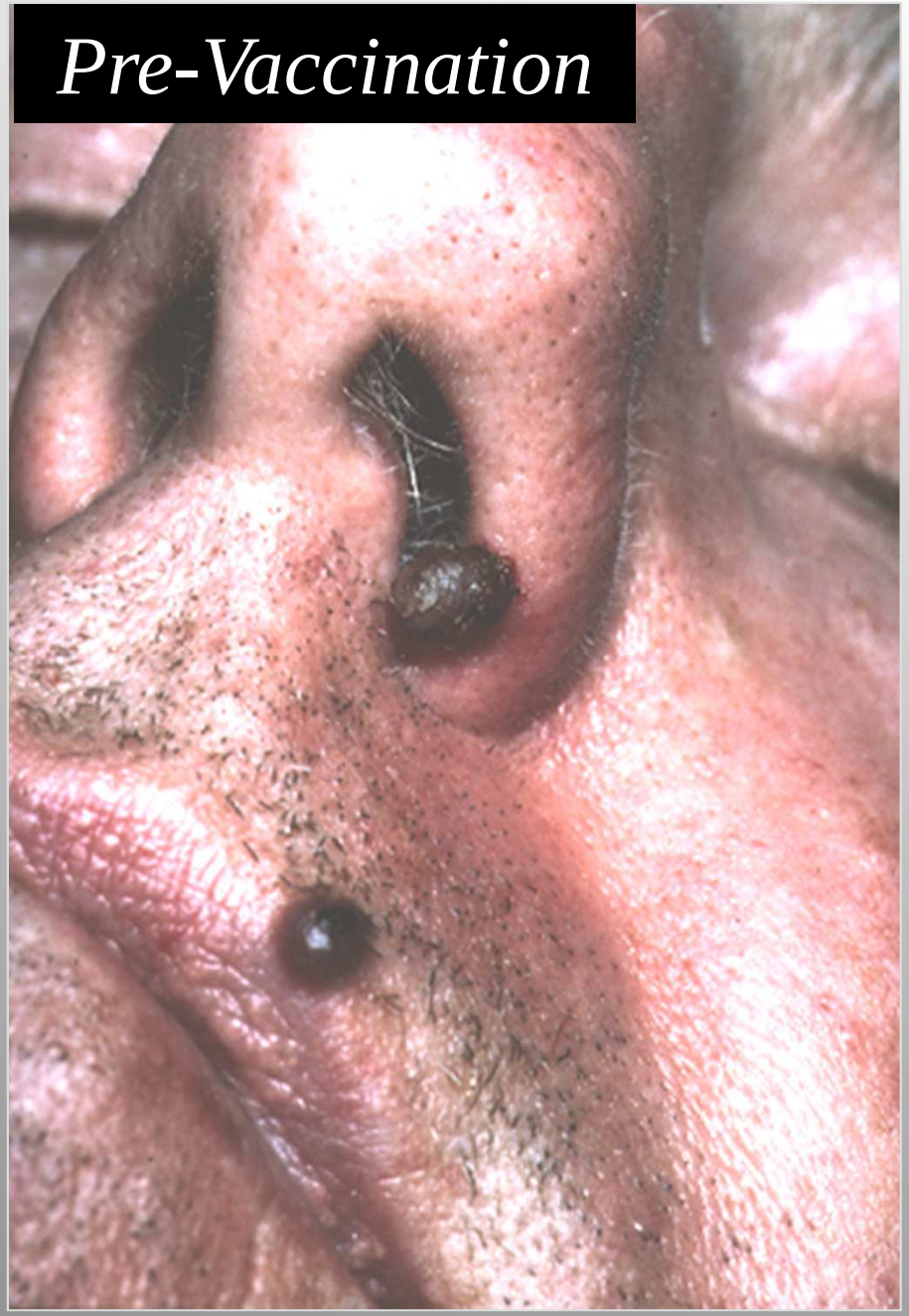
- **Immunodominant peptides from the gp100 melanoma-associated antigen were identified, and a synthetic peptide (gp209-2M), designed to increase binding to HLA-A2 molecules, was used as a cancer vaccine to treat patients with metastatic melanoma**
- **On the basis of immunologic assays, 91% of patients could be successfully immunized with this synthetic peptide**
- **13 of 31 patients (42%) receiving the peptide vaccine plus IL-2 had objective cancer responses**
- **Four additional patients had mixed or minor responses**
- **Proof-of-principle that synthetic peptide vaccines based on the genes encoding cancer antigens can be effective therapies for development of novel cancer immunotherapies**

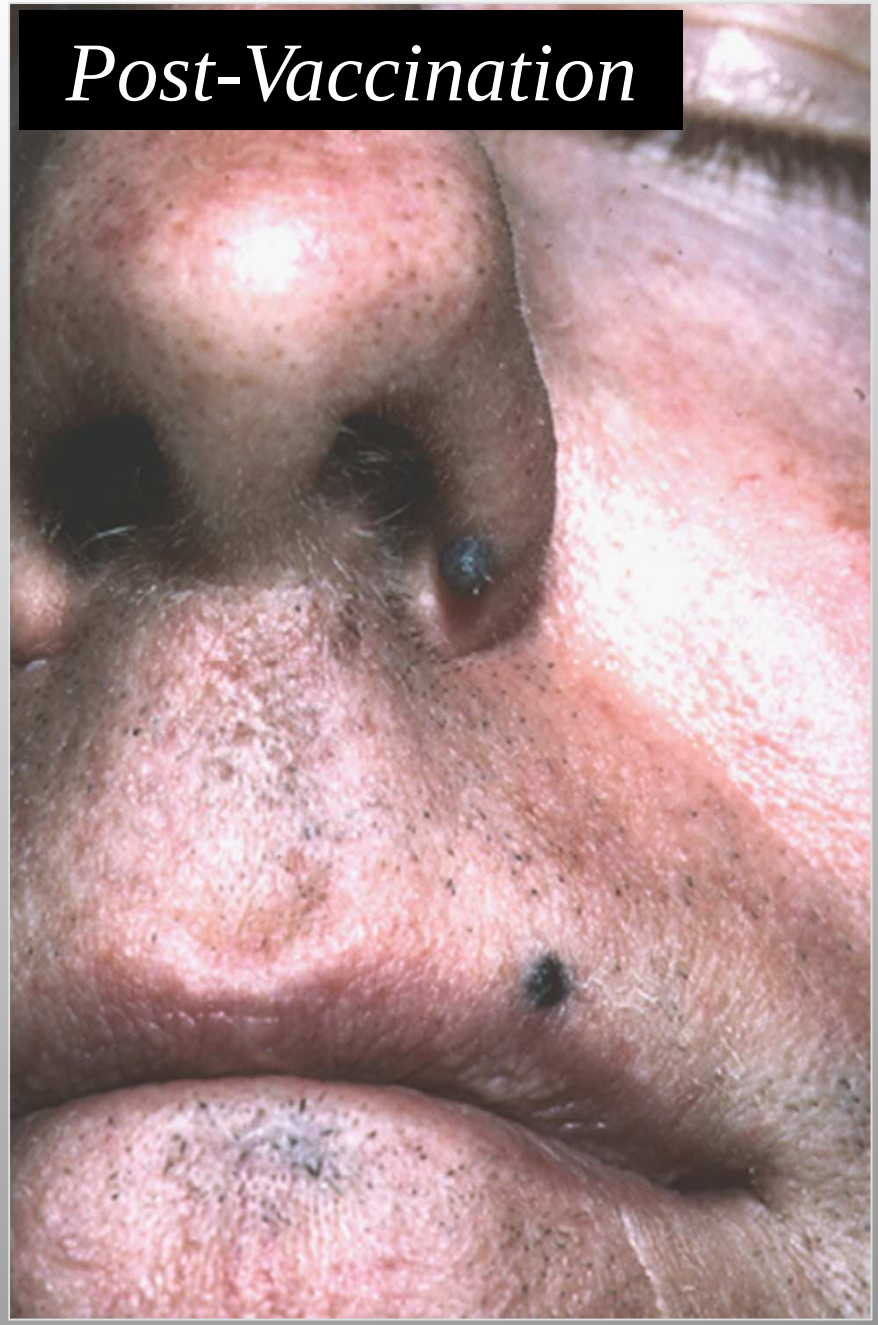

Pre-vaccination

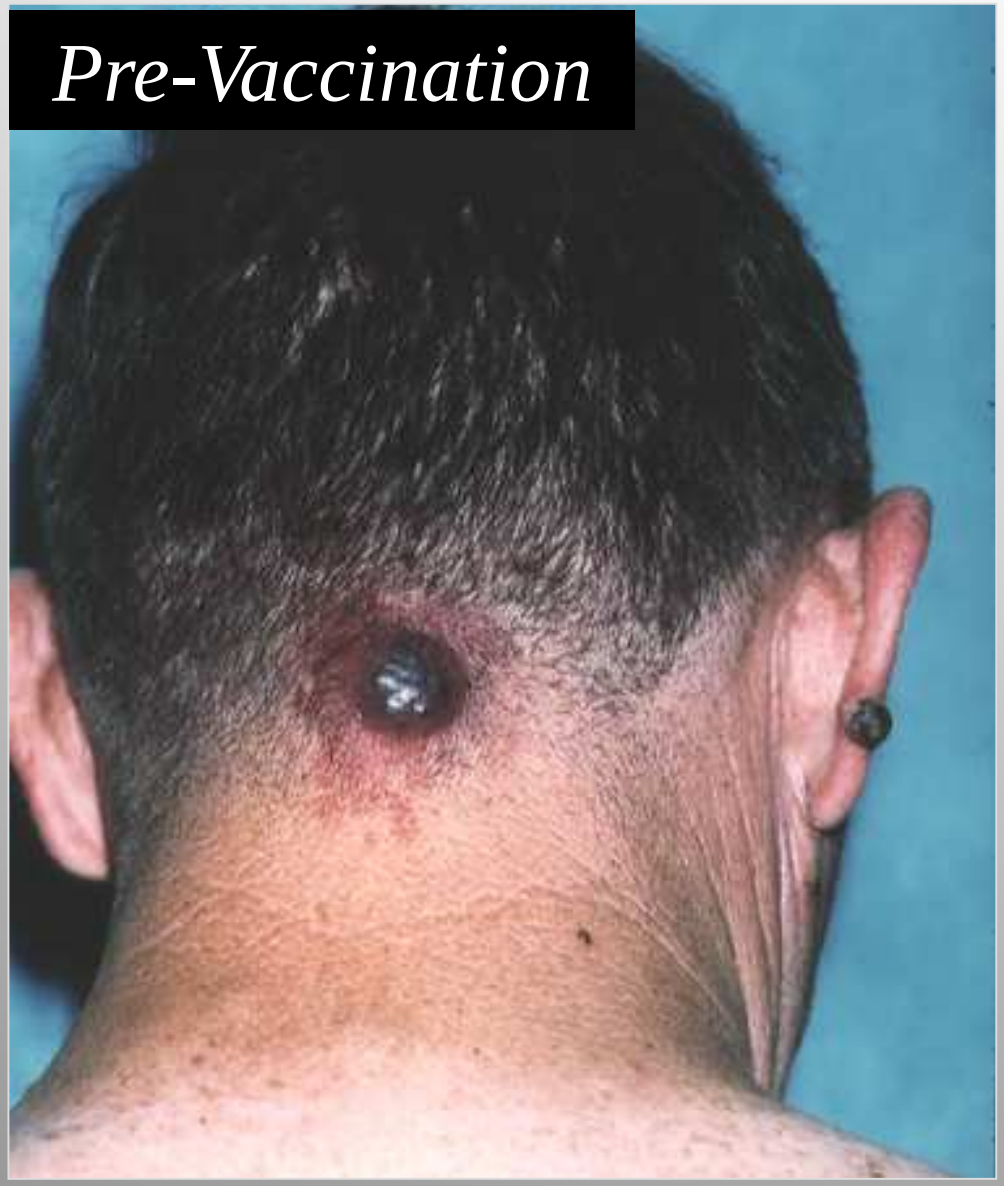

Post-vaccination


Pre-Vaccination


Post-Vaccination


Pre-Vaccination


Post-Vaccination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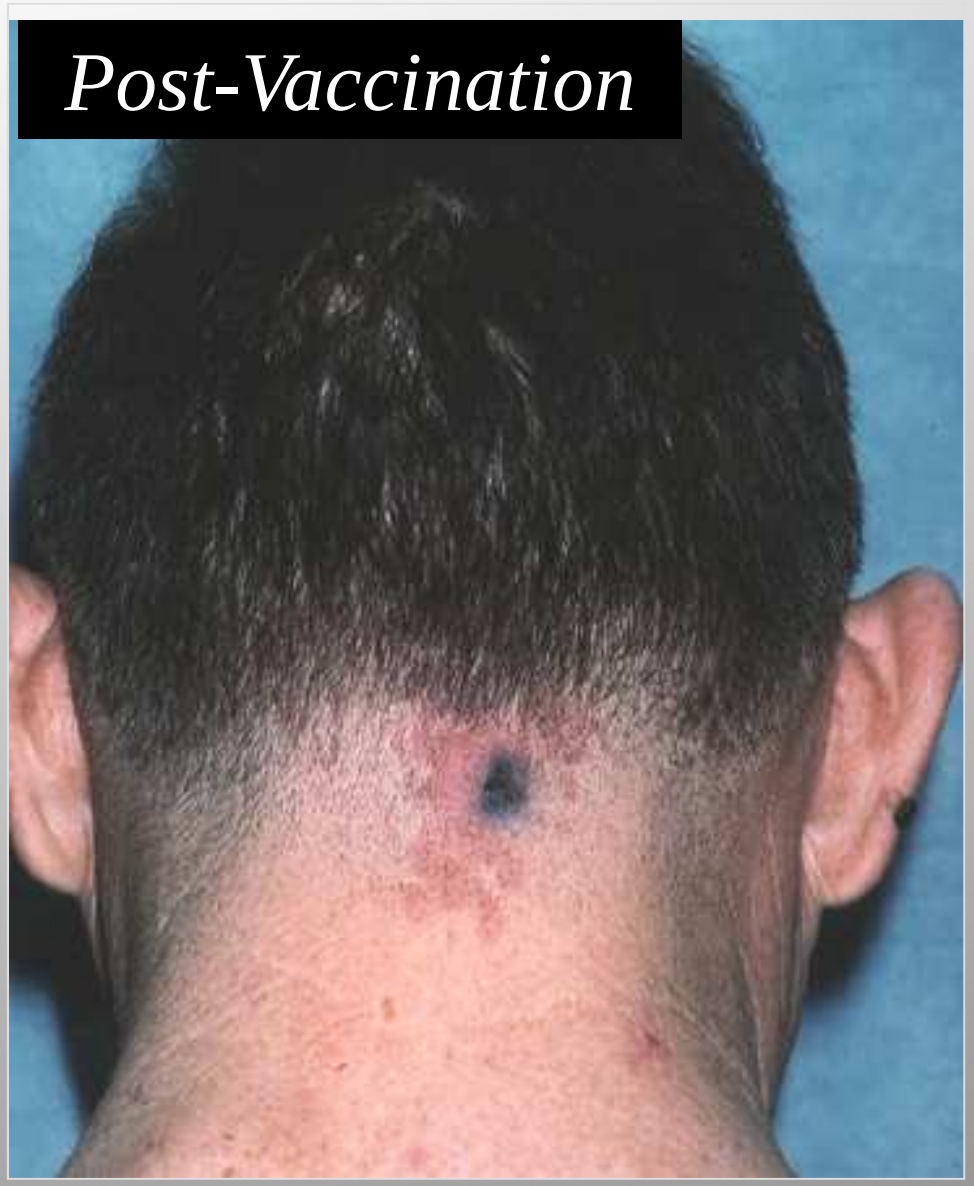
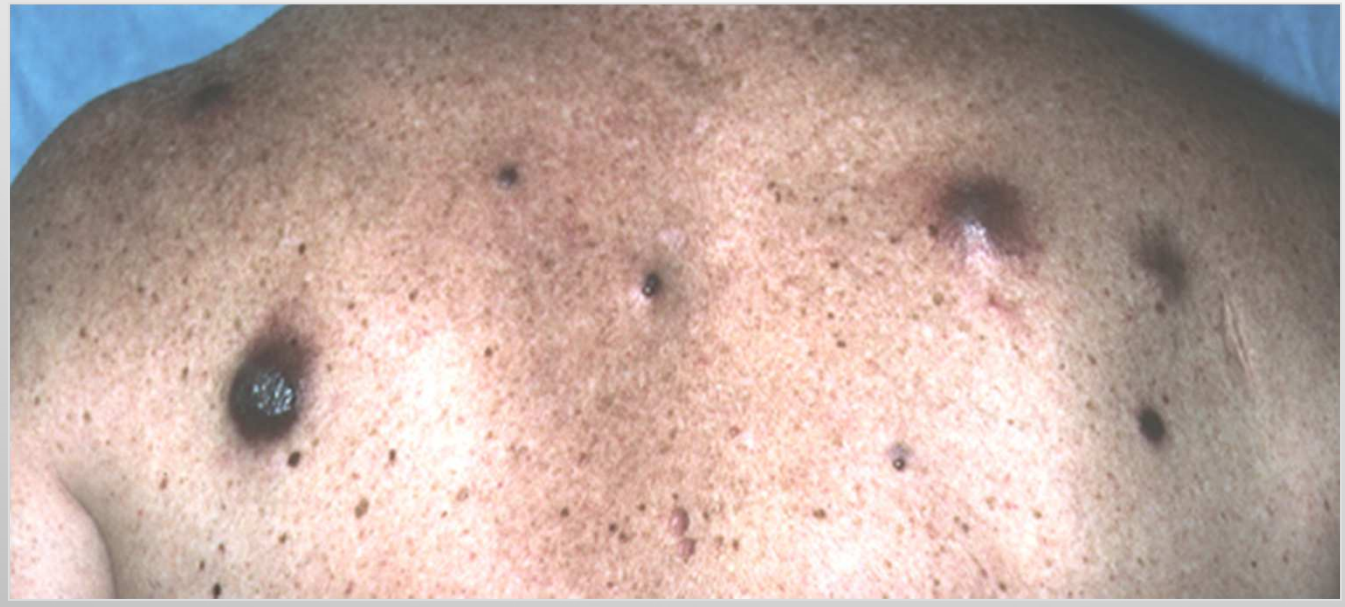
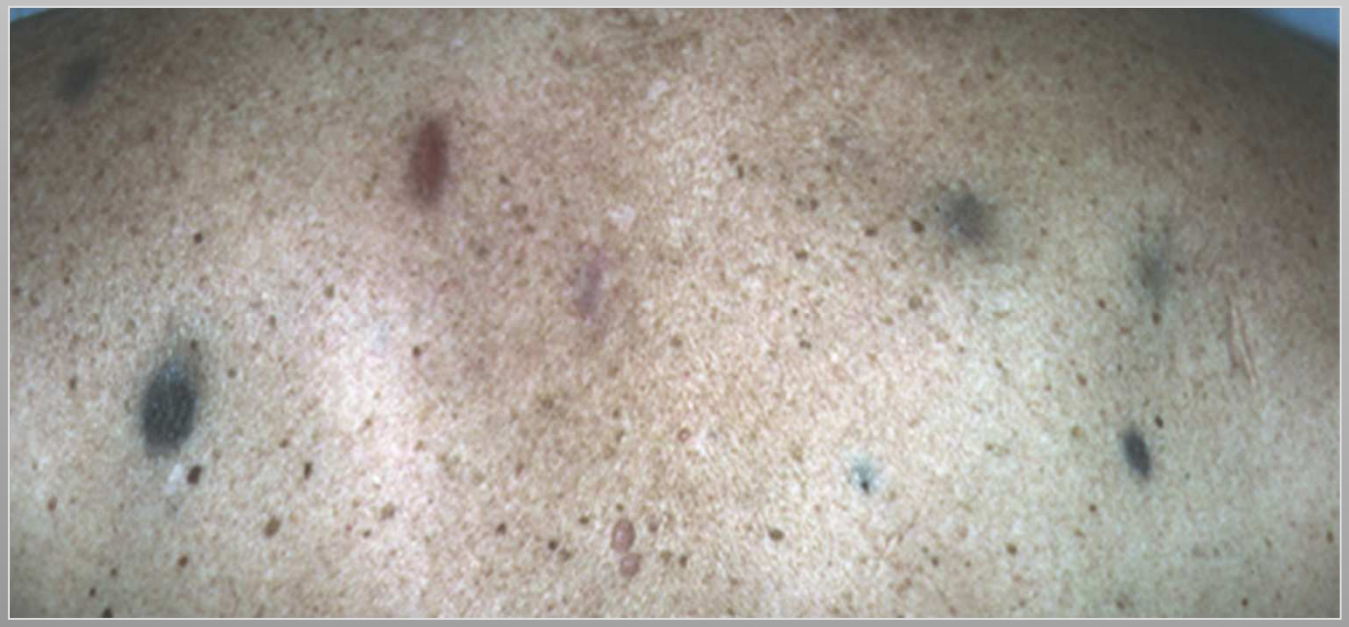
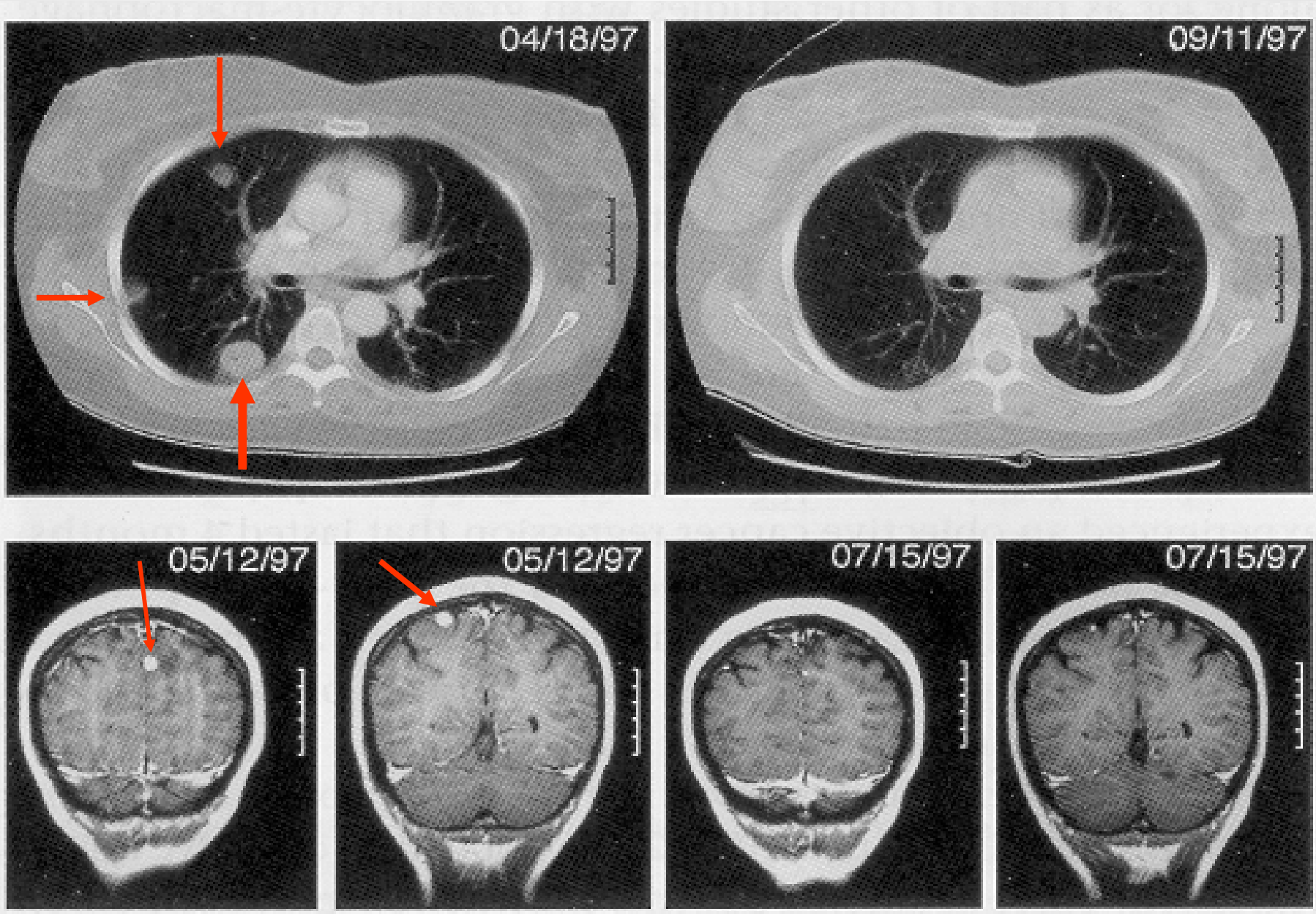

Post-Vaccination



Pre-Vaccination



Post-Vaccination



(Rosenberg et al., Nature Med., 1998)

PERSPECTIVE

nature medicine

NATURE MEDICINE, Volume 10(9), September 2004

Cancer immunotherapy: moving beyond current vaccines

Steven A Rosenberg, James C Yang & Nicholas P Restifo

Great progress has been made in the field of tumor immunology in the past decade, but optimism about the clinical application of currently available cancer vaccine approaches is based more on surrogate endpoints than on clinical tumor regression. In our cancer vaccine trials of 440 patients, the objective response rate was low (2.6%), and comparable to the results obtained by others. We consider here results in cancer vaccine trials and highlight alternate strategies that mediate cancer regression in preclinical and clinical models.

patients who achieved clinical responses, many cancer vaccine trials have been optimistically reported because surrogate or subjective endpoints were achieved. Sensitive techniques such as tetramer or ELISpot assays have been used to demonstrate the generation *in vivo* of antitumor T cells in vaccinated patients, but the scarcity of clinical responses in these patients has made it difficult to validate any of these assays as a useful surrogate of clinical response.

Analysis of trials using standard oncologic criteria

Standard oncologic criteria for evaluating and reporting objective clinical responses to treatment are well established in oncology and

In the year 2003, there were 216 ongoing vaccine trials in cancer patients. For DC-based vaccines alone, there are 98 published studies treating over 1,000 patients

Peptide	HLA restriction	Total patients	NR	PR	CR
MART-1_{27-35}	A2	23	22	1	0
MART-1_{27-35} + IL-12	A2	12	12	0	0
MART-1_{26-35}(27L)	A2	6	6	0	0
TRP-$2_{180-188}$	A2	20	19	1	0
$gp100_{209-217}$	A2	9	8	0	1
$gp100_{209-217}$(210M)[a]	A2	32	32	0	0
$gp100_{209-217}$(210M) + IL-12	A2	28	28	0	0
$gp100_{209-217}$(210M) + GM-CSF	A2	18	18	0	0
$gp100_{280-288}$	A2	9	9	0	0
$gp100_{280-288}$(2889V)[b]	A2	5	5	0	0
$gp100_{154-162}$	A2	10	0	0	0
gp100ES:$_{209-217}$(210)	A2	9	9	0	0
g209-2M + MART-27L	A2	23	23	0	0
g209-2M, g280-9V, MART-27L[c] + tyr3D[d]	A2	16	14	2	0
$gp100_{44-59}$	DR4	4	4	0	0
$gp100_{44-59}$ + g209-2M + MART-27L	A2/DR4	22	21	0	1
Tyrosinase$_{240-251}$	A1	16	15	1	0
$gp1001_{7-25}$	A3	12	12	0	0
Tyrosinase$_{206-214}$	A2	8	8	0	0
TRP-1 ORF1–9	A31	5	5	0	0
Combination peptides	Non-A2	15	15	0	0
MAGE-$12_{170-178}$	Cw7	9	8	1	0
NY-ESO-$1_{157-165}$(165V)	A2	19	19	0	0
NY-ESO-$1_{161-180}$	DP4	6	5	1	0
NY-ESO-$1_{161-180+157-165}$(165V)	A2/DP4	11	11	0	0
Her2/neu$_{369-378}$	A2	6	6	0	0
Telomerase$_{540-548}$	A2	13	13	0	0
Dendritic cells + g209-2M + MART-27L	A2	15	13	2	0
Total		381	370	9	2

<u>Peptide</u> Vaccine Immunization of Patients with Metastatic Cancer

Overall Response Rate = 2.9%

Virus	HLA restriction	Total patients	NR	PR	CR
Fowlpox MART-1	Any	12	12	0	0
Fowlpox gp100	Any	20	20	0	0
Fowlpox gp100(210M, 288V)	A2	15	14	1	0
Fowlpox gp100($ES_{209-271}$(210M))	A2	46	46	0	0
Vaccinia MART-1	Any	5	5	0	0
Vaccinia gp100	Any	16	16	0	0
Adenovirus MART-1	Any	17	16	0	1
Adenovirus gp100	Any	7	7	0	0
DNA gp100(210M, 288V)	A2	22	21	1	0
Total		160	157	2	1

<u>Viral</u> Vaccine Immunization of Patients with Metastatic Cancer

Overall Response Rate = 1.9%

Rosenberg SA, Yang JC, Restifo NP. *Cancer immunotherapy: moving beyond current vaccines*. Nature Medicine, 10(9), 909-915, 2004

- **440 patients with stage IV melanoma**
- **Treated with 541 different vaccines over a nine-year period [Surgery Branch, NCI]**
- **Vaccine strategies: synthetic peptides, naked DNA, dendritic cells (DC) and recombinant viruses**
- **Overall Objective Response Rate = 2.6%**
- **Comparison was made of 35 other vaccine trials from around the world: 765 patients receiving similar type vaccines**
- **Overall Objective Response Rate = 3.8%**
- **Combining the results: 1,306 vaccine treatments in over 1,200 patients:**

OVERALL RESPONSE RATE OF CANCER IMMUNOTHERAPY OF 3.3%

Adoptive Immunotherapy

- **Cancer "Vaccines"**
- **Dendritic Cell-Based Therapy**
- **Cell-Transfer Therapy**

Allogeneic Melanoma Vaccines

- **Polyvalent, allogeneic, antigen-enriched whole cell irradiated melanoma vaccine**
- **Developed at the JWCI in Santa Monica, CA. (Morton *et al*.)**
- **Composed of 3 melanoma cell lines**
- **HLA haplotype match in 95% of melanoma pts**
- **Grow separately, combine, XRAY (150 Gy), stored sterile**
- **Most extensively studied vaccine with the longest follow-up**

Common Tumor Antigens	Melanoma-Associated Antigens
(+) GM2, GM3, GD2, GD3	Tyrosinase
gp90	MART-1
gp70	gp75, gp100
MAGE 1	HMW antigen
MAGE 3	LP 180
Sialyl Lewis X, a	O-acetyl GD3

Vaccination Schedule

- ✓ **Induction Phase with SQ injections q 2weeks x 5 doses over 2 months**
- ✓ **BCG given with the first 2 vaccinations as a nonspecific immunostimulant**
- ✓ **Maintenance phase with SQ injections q 4 weeks x 1 year, then q 2 months x 1 year and then q 3 months for a total of 5 years**
- ✓ **Minimal toxicity noted (fever, local reactions, fatigue, and muscle weakness)**

Allogeneic Melanoma Vaccines are NOT Effective

Stage III Trial Results

Disease-free survival	5-year DF survival	Median DF survival
Placebo arm	52.1%	>60 months
Vaccine arm	47.2%	42.6 months

Overall survival	5-year survival	Median survival
Placebo arm	67.7%	>69 months
Vaccine arm	59.1%	>69 months

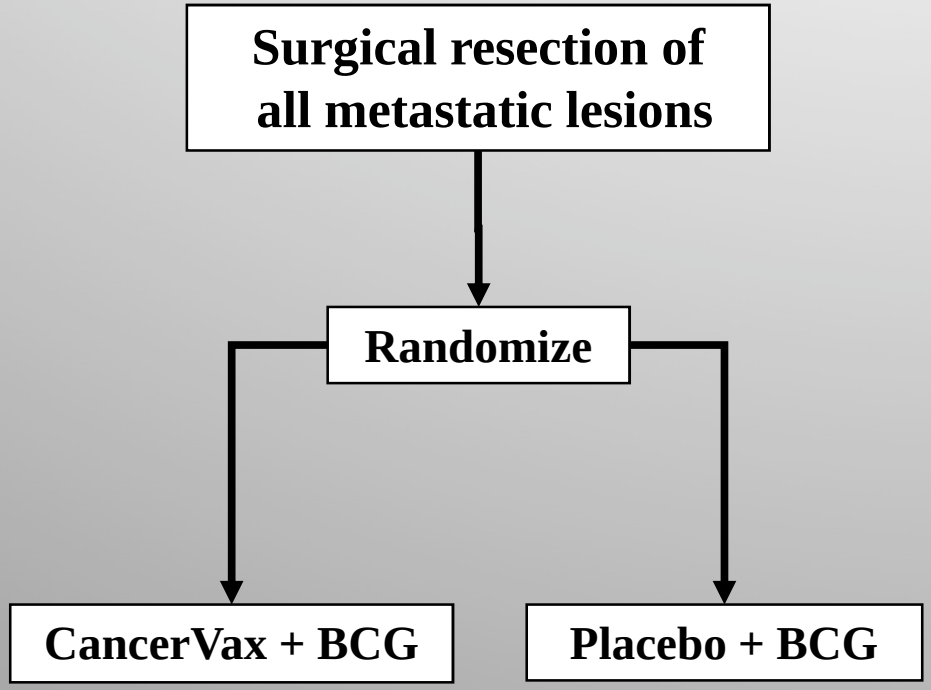
Stage IV Trial Results

Disease-free survival	5-year survival	Median survival
Placebo arm	20.9%	7.2 months
Vaccine arm	27.4%	8.3 months

Overall survival	5-year survival	Median survival
Placebo arm	44.9%	38.7 months
Vaccine arm	39.6%	31.5 months

Morton DL et al. SSO, San Diego 2006

Although the vaccine doesn't work: Up-Front Surgery May Help in Select Cases:



- **40% of all patients (in both arms) were alive at 5 years**
- **Prolonged survival not due to the vaccine**
- **Prolonged survival is likely due to complete surgical resection of metastatic disease**

Morton *et al.*, SSO 2006

Allogeneic Melanoma Lysates in Active Specific Immunotherapy

- **Composition: Two melanoma cell lines grown to confluence, expanded and mechanically disrupted**

- **Frozen lysates are thawed and mixed with Detox adjuvant (lipid A, mycobact. cell wall skeleton)and injected SQ in divided doses (0.5mL, 10-40 M tumor cell equivalents)**

1988 and 1990 (N=114):

Phase I and II trials with Melacine
20% Objective Response Rate
5% CR, 15% PR
8% (13/150) long-term survivors
Median duration of response of 21 months
Median survival time of 46 months

1993 (N=106)

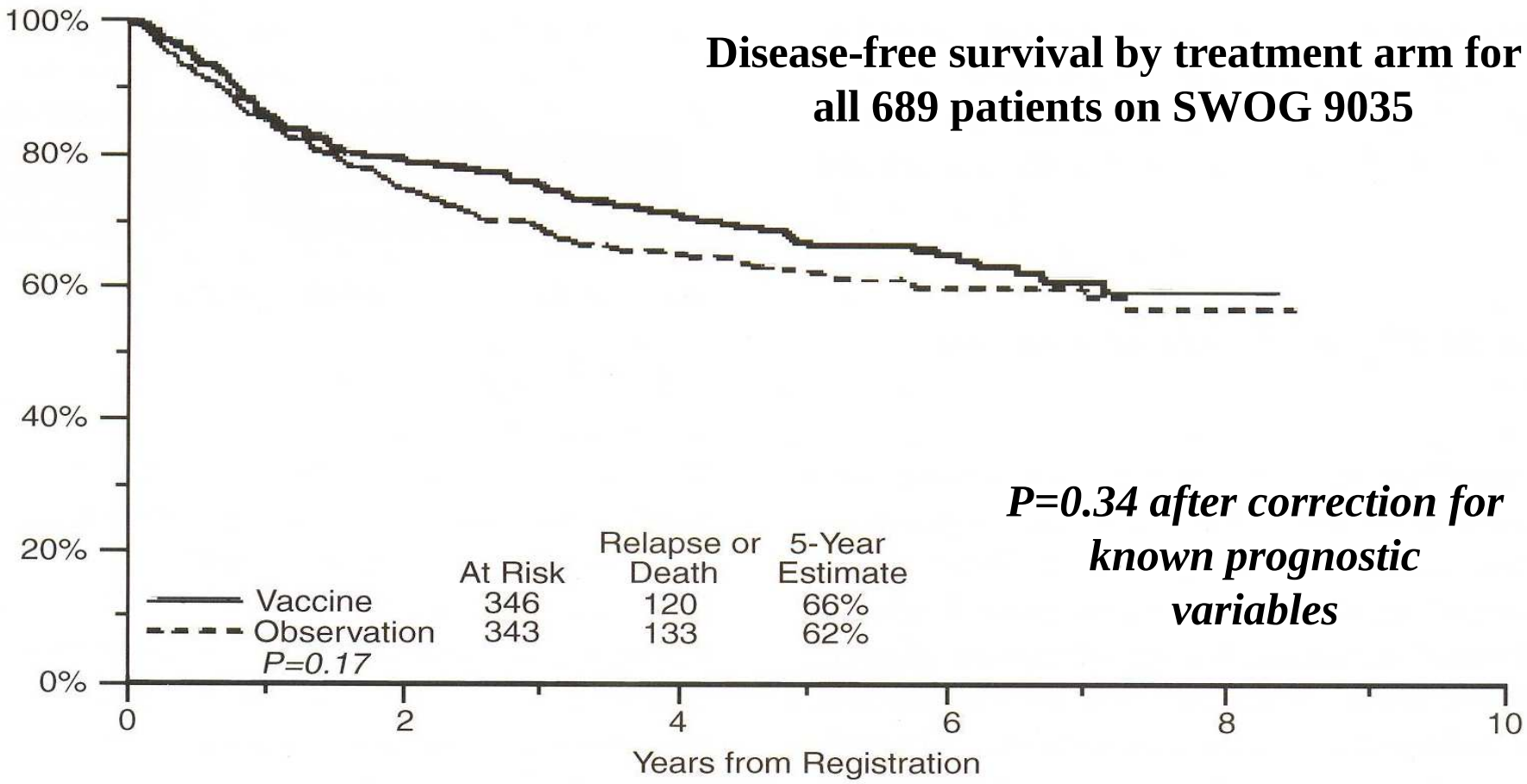
Multicenter Phase III Trial
Cyclophosphamide + Melacine vs.
DTIC+Cisplatin+Carmustine+Tamoxifen
Objective Response Rate=7%
10% chemo. with no diff. In OS (9.4 mo. vs. 12.3 mo., vs. chemo.)

Mitchell, M. et al. Active Immuntherapy of Melanoma. Phase I trial of allogeneic melanoma lysates and a novel adjuvant. Cancer Research 1988
Mitchell, M. et al. Active Specific Immuntherapy for Melanoma. J Clin Oncol 1990

SWOG 9035: Phase III observation-controlled trial of allogeneic melanoma vaccine in patients with intermediate thickness (1.5-4.0 mm Breslow's depth) melanoma and clinically negative regional lymph nodes (T3N0M0)

- **1:1 randomization of observation *vs.* 2 years of adjuvant vaccinations with four 6-month cycles composed of 10 treatments (2 injections/treatment or 20 injections/cycle)**
- **No clinical evidence of nodal or distant metastasis and surgical staging allowed, but not required**
- **Results reported after median follow-up of 5.6 years, RFS reported but OS endpoints not yet met**

***Sondak et al.*: Adjuvant Immunotherapy of Resected, Intermediate-Thickness Node-Negative Melanoma with an Allogeneic Tumor Vaccine. I. Overall Results of a Randomized Trial of the Southwest Oncology Group. J Clin Oncol 2002; 20: 2058-66**



Phase III, Randomized, Double-Blind, Placebo-Controlled Multicenter Vaccinia Melanoma Oncolysate Trial

Wallack, Balch, Sivanandham, Urist, Bland, Murray, Robinson, Flaherty, Richards, Bartolucci, Rosen. J Am Coll Surg 1998

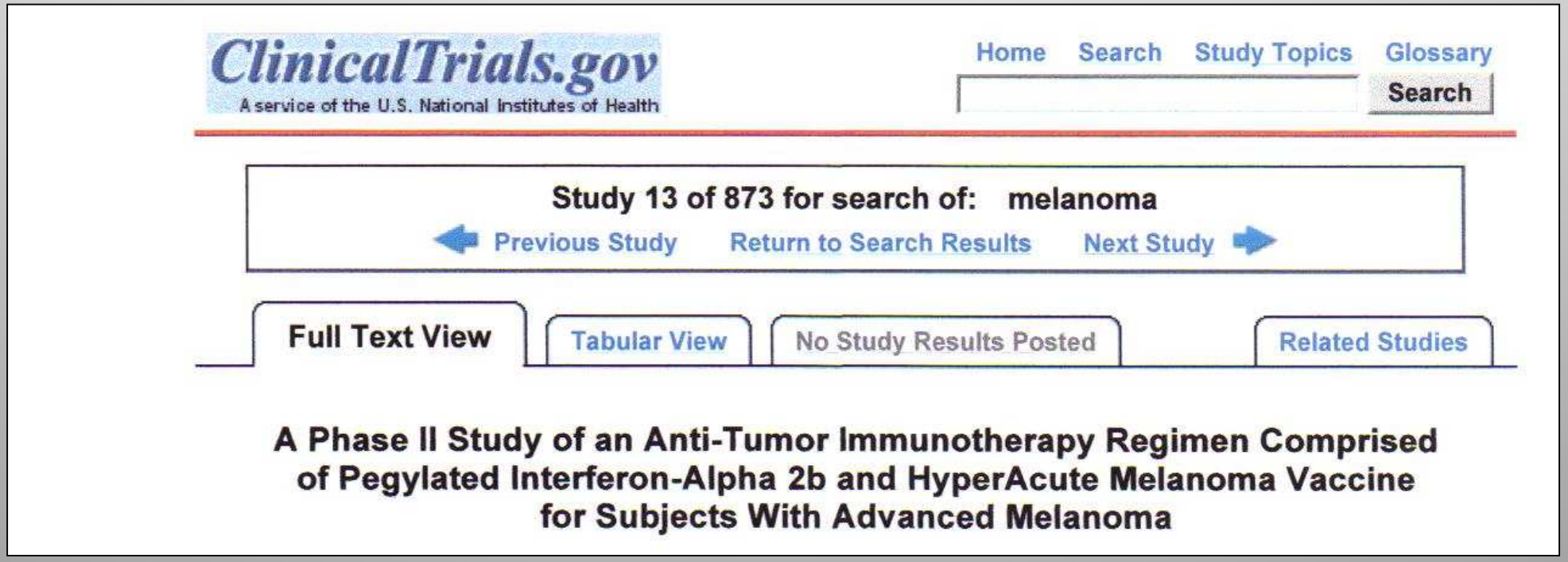
- ✓ **Polyvalent vaccina melanoma oncolysate developed from 4 cell lines and vaccinia virus**
- ✓ **Stage III patients randomized to VMO (n=104) vs. control virus (n=113)**

<u>Results:</u>

- ✓ **No difference in overall survival or disease-free survival in total group**
- ✓ **Retrospective subset analysis of pts. with 1-5 nodes (+), b/t the ages of 44-57, showed a survival advantage with VMO**

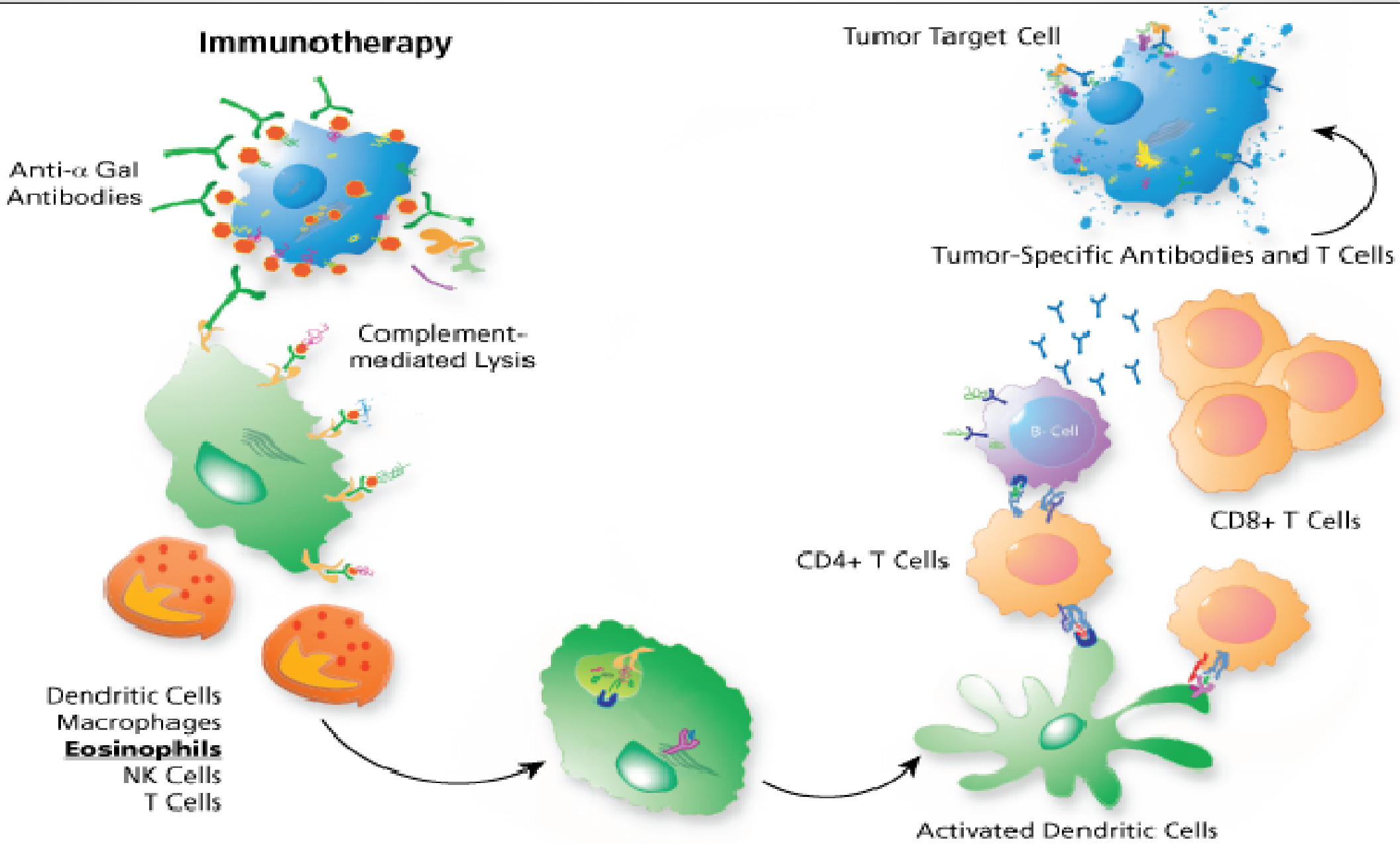
A Phase II Clinical Trial of an Anti-Tumor Immunotherapy Regimen Comprised of Pegylated Interferon-Alpha-2b and Dorgenmeltucel-L for Subjects with Advanced Melanoma.

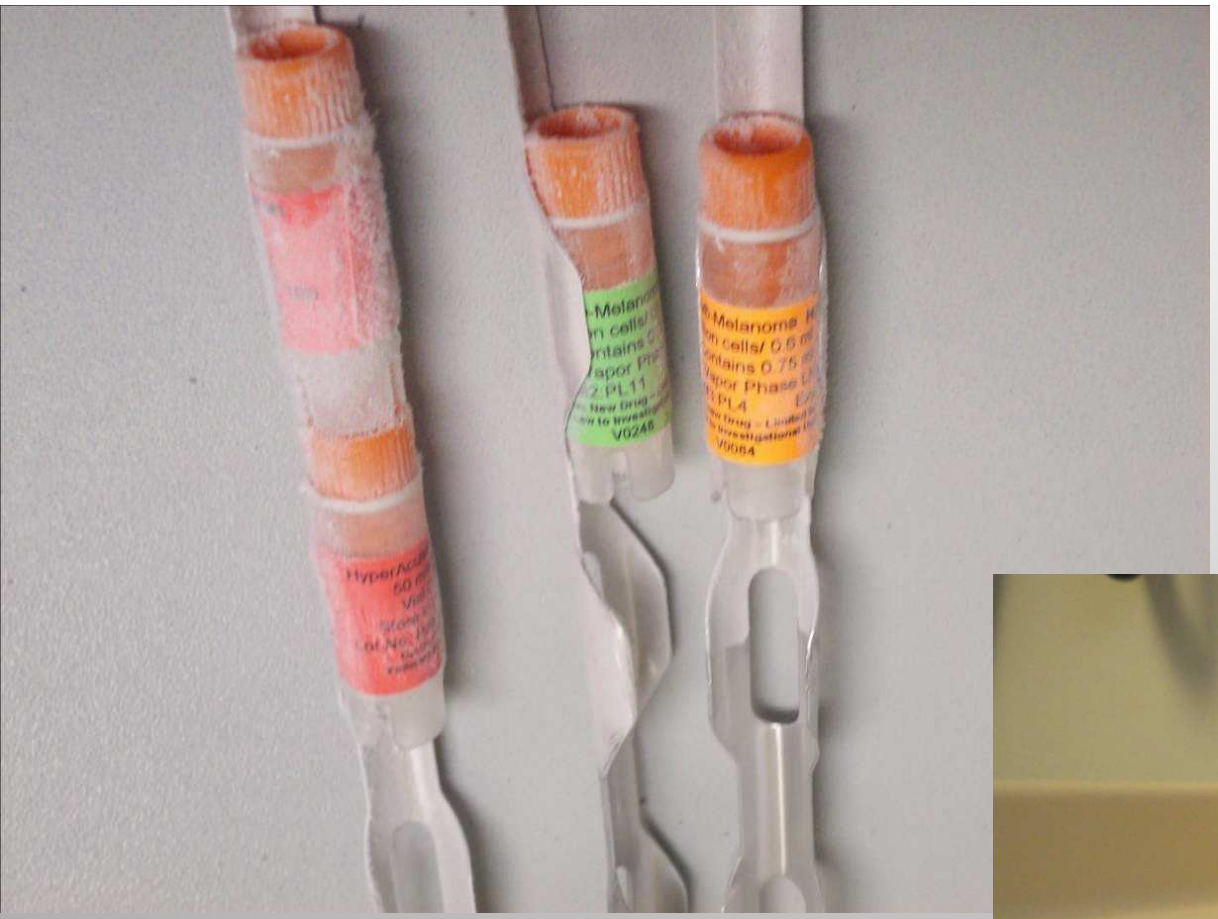
Riker et al. 2014, The Ochsner Journal



Dorgenmeltucel-L Vaccine Platform

- **Mixture of irradiated, allogeneic, whole cancer cells**
- **Genetically modified to add α-(1,3)-galactosyl transferase gene to cell surface antigens**
- **Based on mechanism of Hyperacute rejection in xeno-transplantation**
- **Designed to break tolerance and enable longer duration of anti-tumor effect**
- **Platform is broadly applicable to multiple cancers**
- **Simple to manufacture and QC**


Immunotherapy
Tumor Target Cell
Anti-α Gal Antibodies
Tumor-Specific Antibodies and T Cells
Complement-mediated Lysis
B- Cell
CD8+ T Cells
CD4+ T Cells
Dendritic Cells
Macrophages
Eosinophils
NK Cells
T Cells
Activated Dendritic Cells



Stored at -170^{0} C

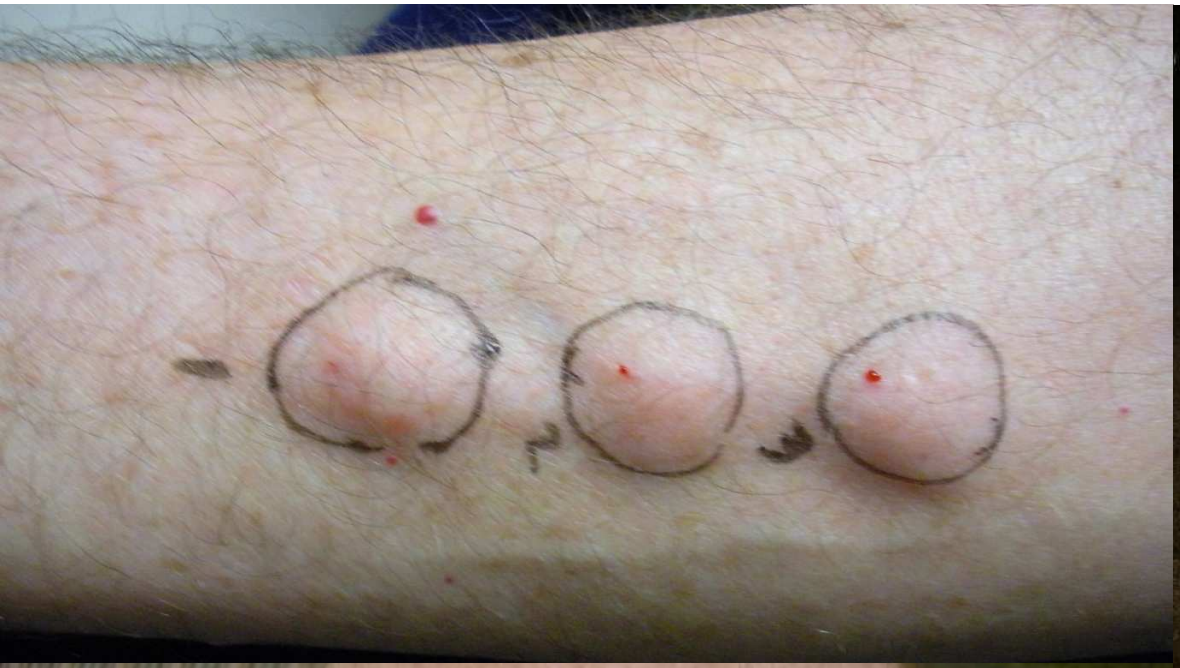
Thawed and injected (Intradermal) within 30 minutes

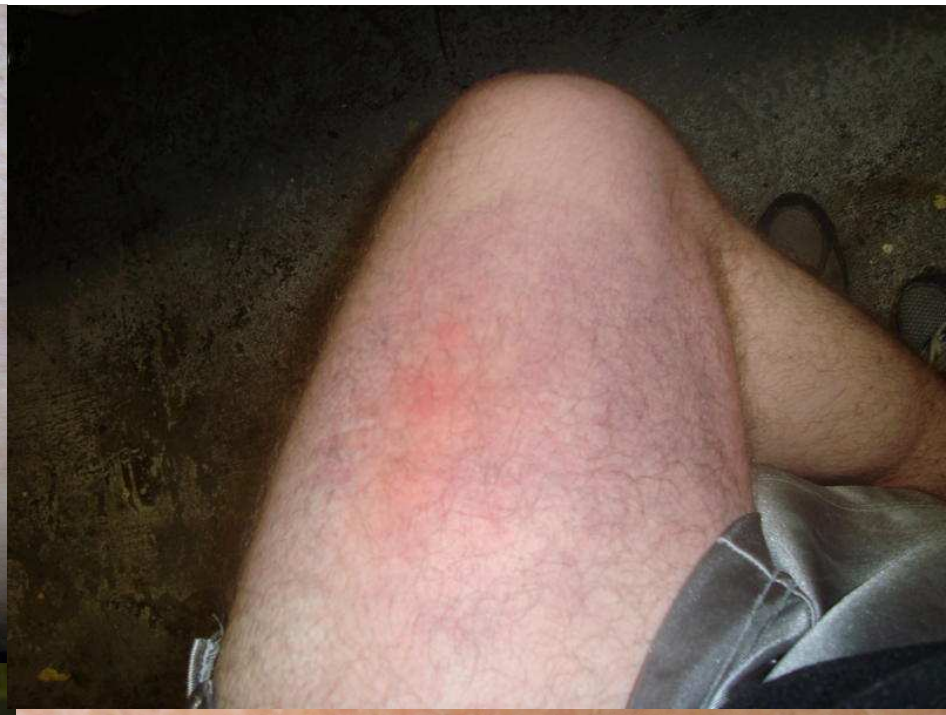
Combination Immunotherapy

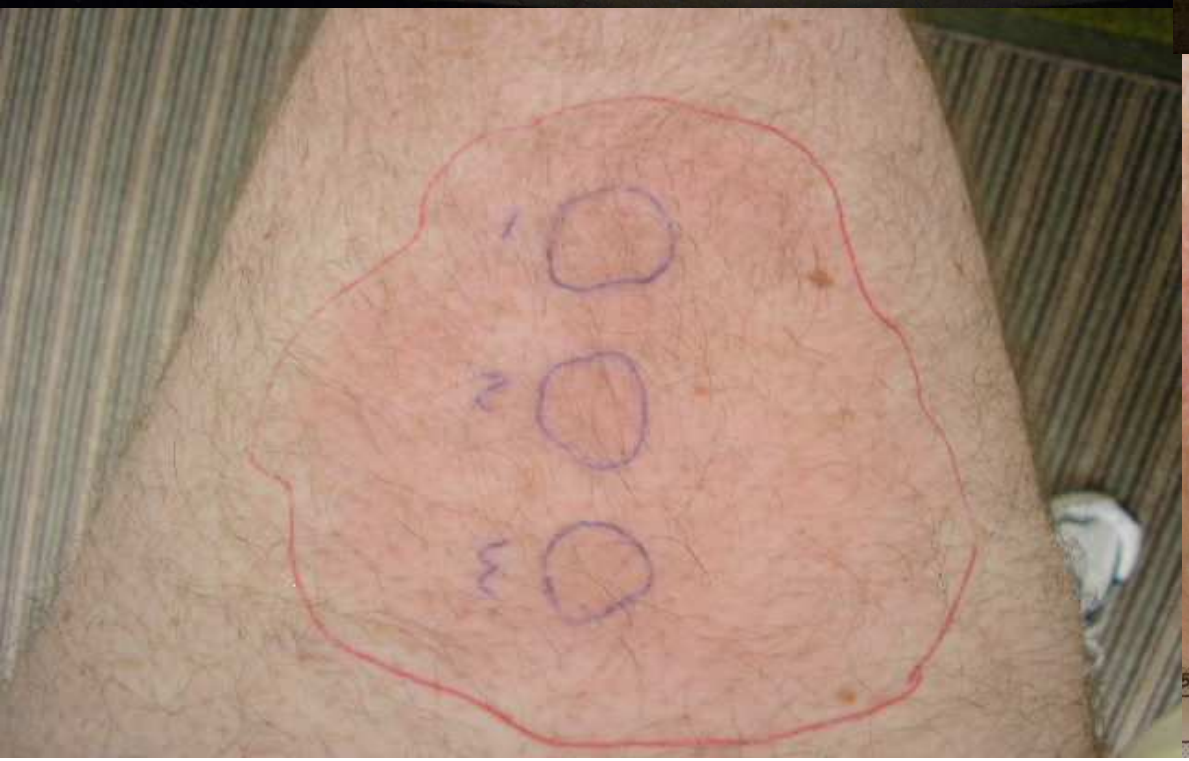
+

Pegylated Interferon [6 ug/kg]

Dorgenmeltucel-L



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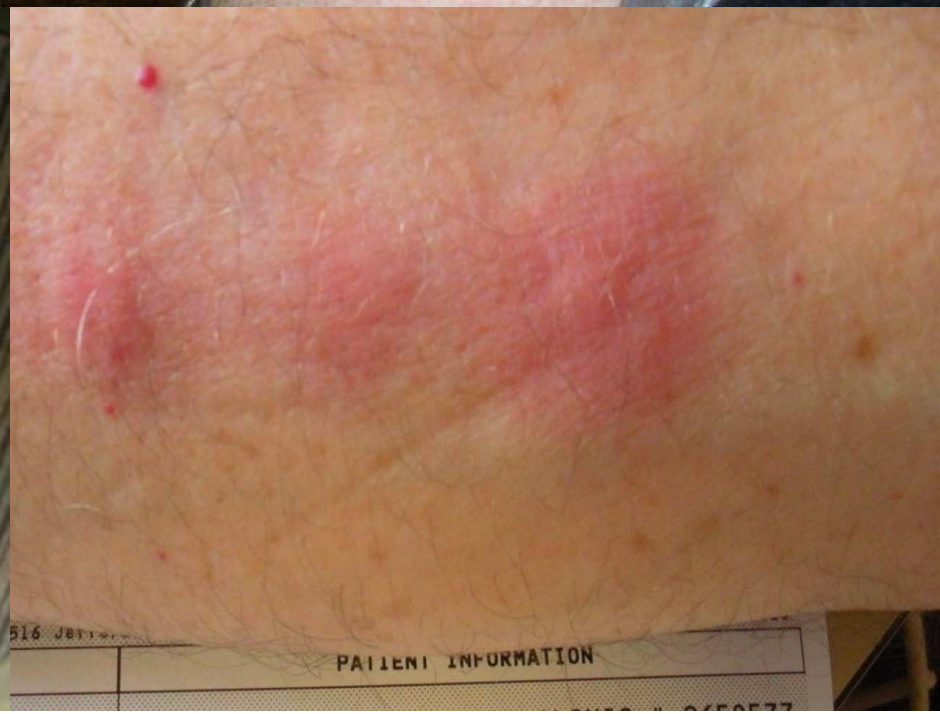
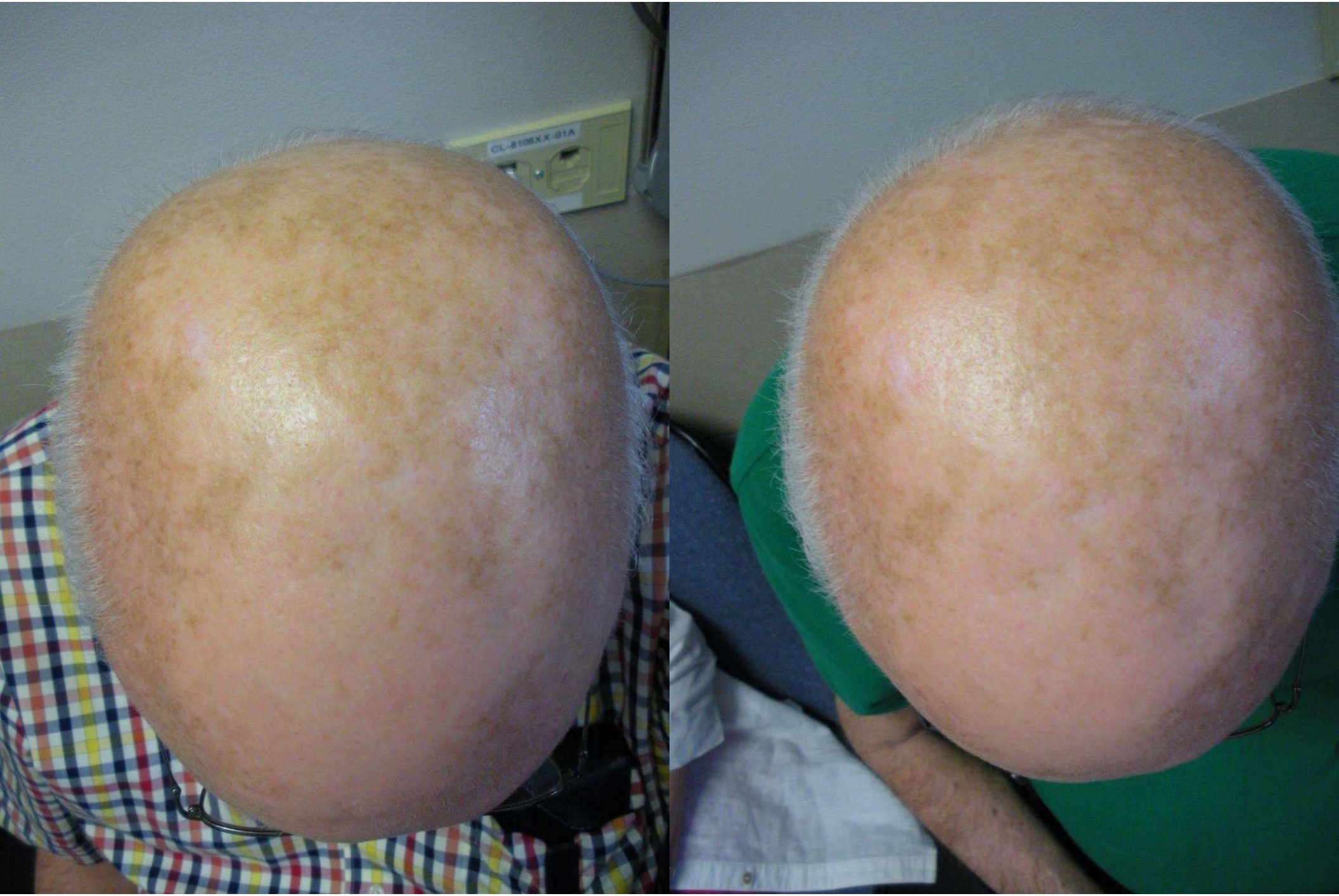
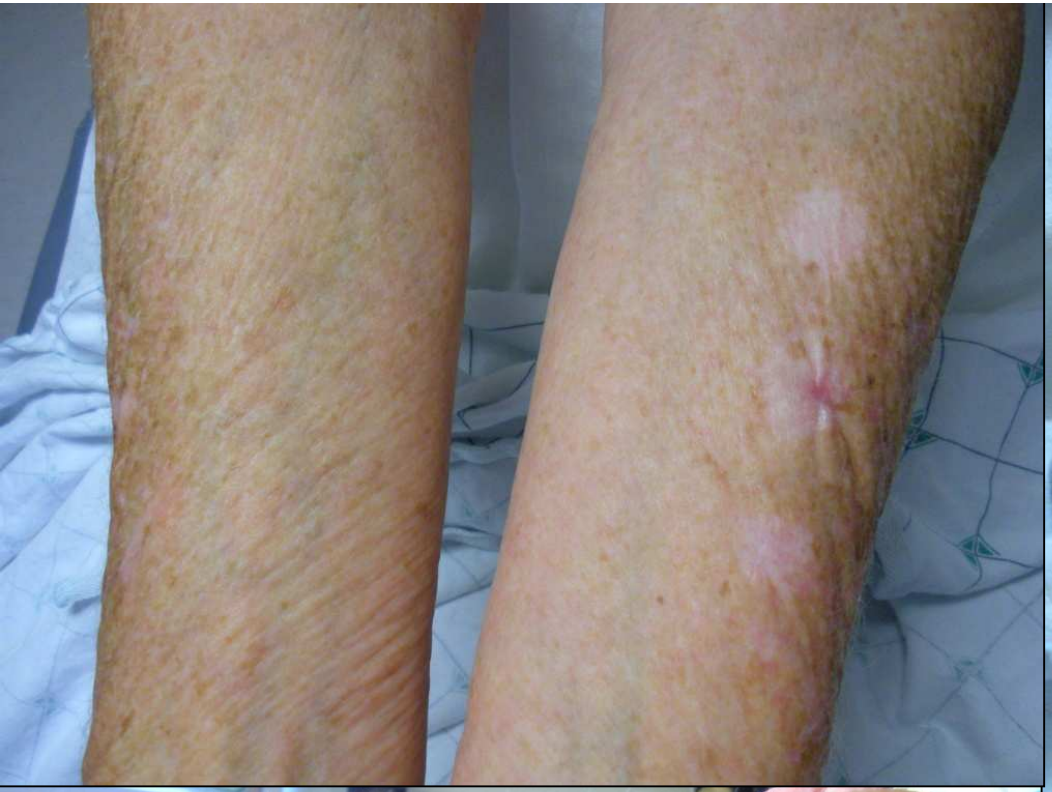
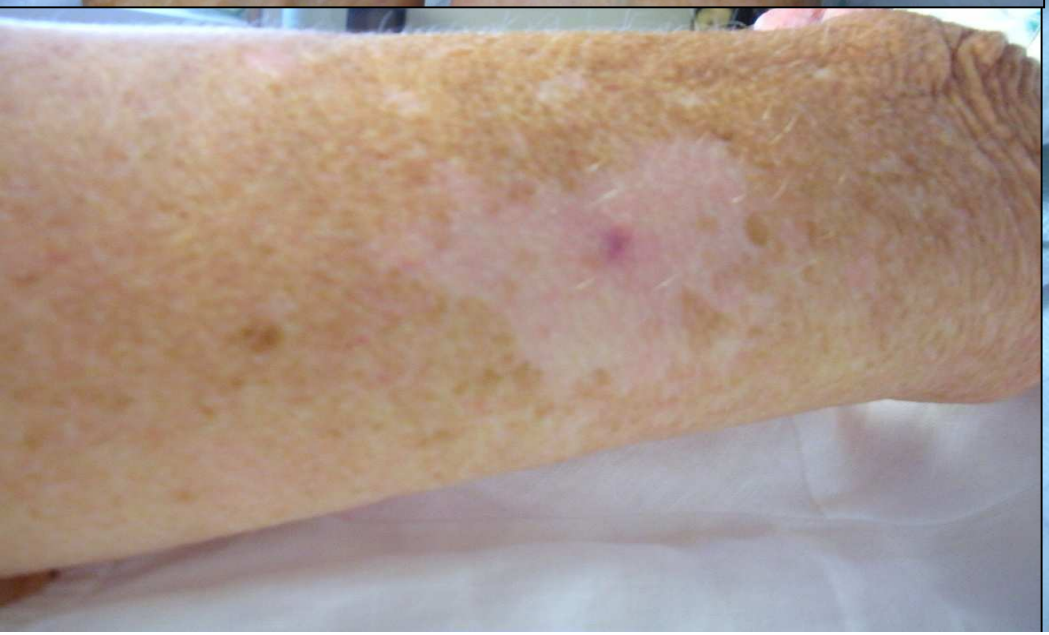
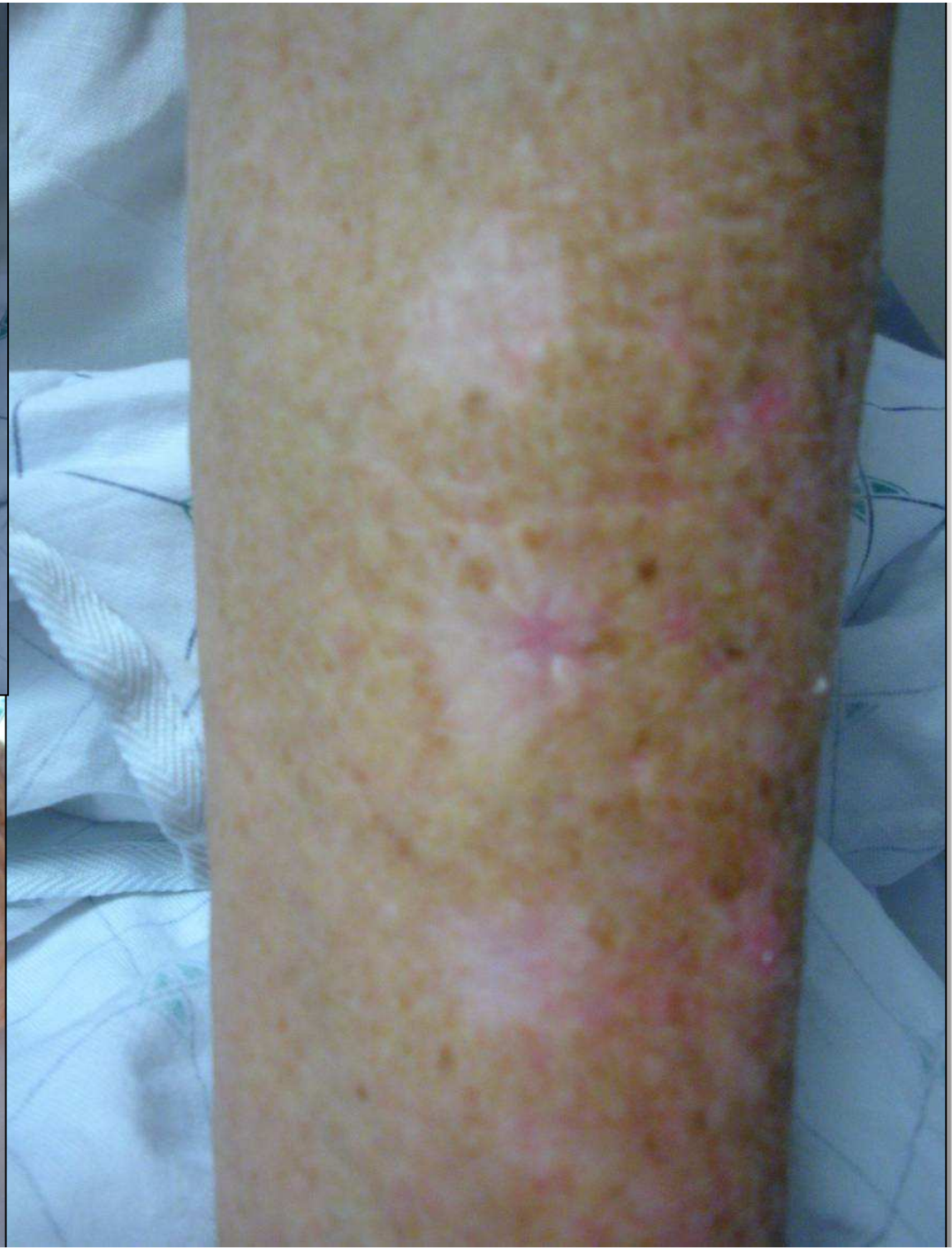
2
3

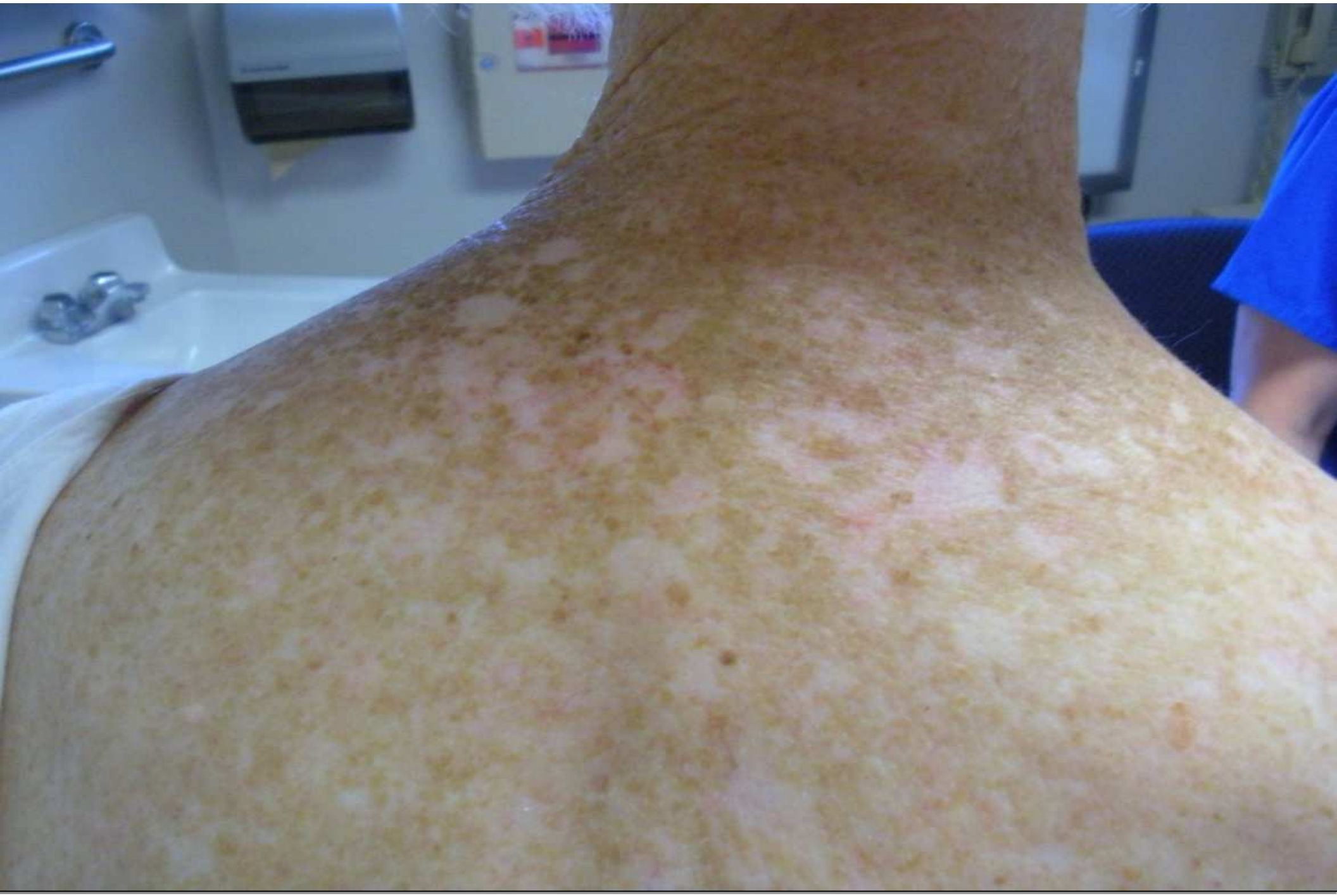

PATIENT INFORMATION


CL-8108XX-01A









Final results of a phase II immunotherapy trial for stage III and IV melanoma patients.

Meeting:
2012 ASCO Annual Meeting

Category:
Melanoma/Skin Cancers

Subcategory:
Melanoma

Session Type and Session Title:
This abstract will not be presented at the 2012 ASCO Annual Meeting but has been published in conjunction with the meeting.

Abstract Number:
e19008

Citation:
J Clin Oncol 30, 2012 (suppl; abstr e19008)

Author(s):
Adam Irwin Riker, Gabriela R. Rossi, Leonard C Alsfeld, Fiona Denham, Lucinda Tennant, William Jay Ramsey, Charles J. Link, Marilynn Harrison, Nicholas N. Vahanian; Advocate Christ Medical Center, Advocate Cancer Institute, Oak Lawn, IL; NewLink Genetics, Ames, IA; Louisiana State University Health Sciences Center, New Orleans, LA; Carilion Clinic, General Surgery Residency Program, Roanoke, VA; Ochsner Cancer Institute, New Orleans, LA

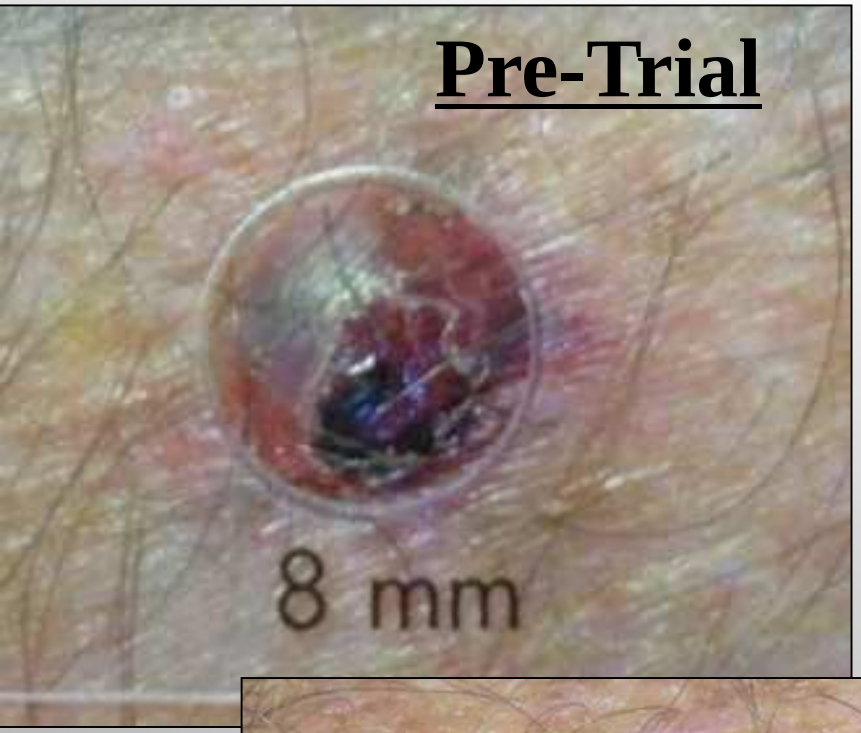
Table 3. Patient Responses

Patient	Stage at Enrollment in Trial	Clinical Response	Status	Duration of Survival, Months
1	4	CR	Alive	36
2	4	CR	Alive	28
3	4, NED	NED	Alive	26
4	4, NED	NED	Alive	21
5	4, NED	NED	Alive	21
6	4	NED	Alive	12
7	4	SD	Alive	21
8	4	PD	Alive	16
9	4	PD	DOD	9
10	4	PD	DOD	5
11	4	PD	DOD	2
12	4	PD	DOD	29
13	4	PD	DOD	10
14	4	PD	DOD	5
15	4	PD	DOD	16
16	4	PD	DOD	6
17	2C, NED	NED	Alive	30
18	3B, NED	NED	Alive	28
19	3B, NED	NED	Alive	28
20	3B, NED	NED	Alive	18
21	3B, NED	PD	DOD	9
22	3C, NED	PD	DOD	19
23	3B, NED	PD	DOD	11
24	3B, NED	PD	DOD	7
25	3C, NED	PD	DOD	2

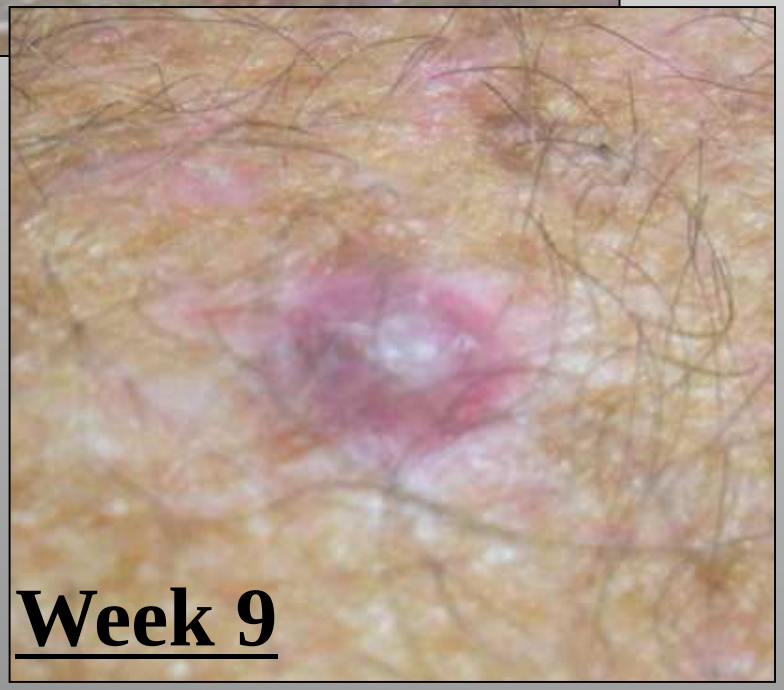
CR, complete response; DOD, dying as direct result of disease; NED, no evidence of disease; PD, progressive disease; SD, stable disease.

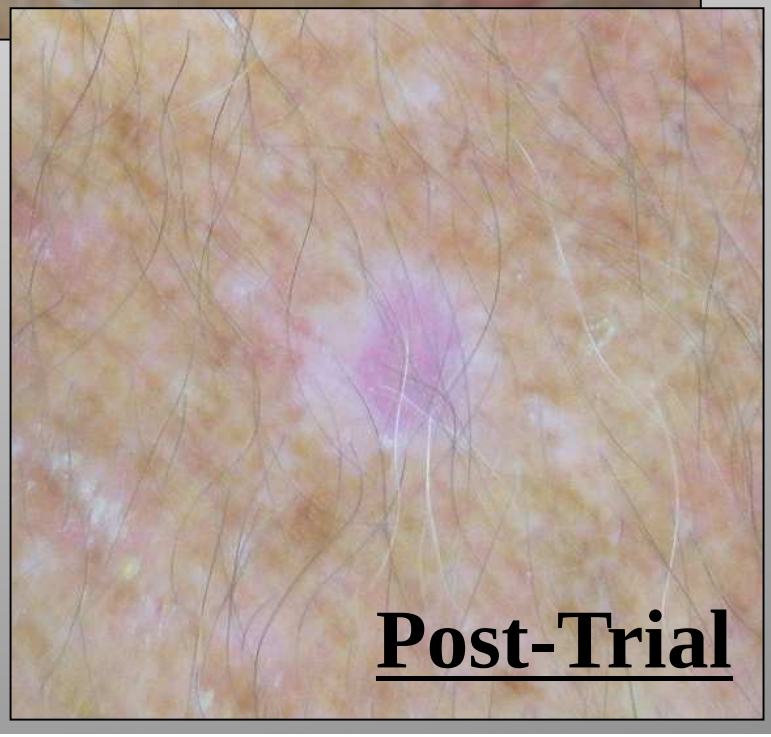
Table 4. Summary of Clinical Responses

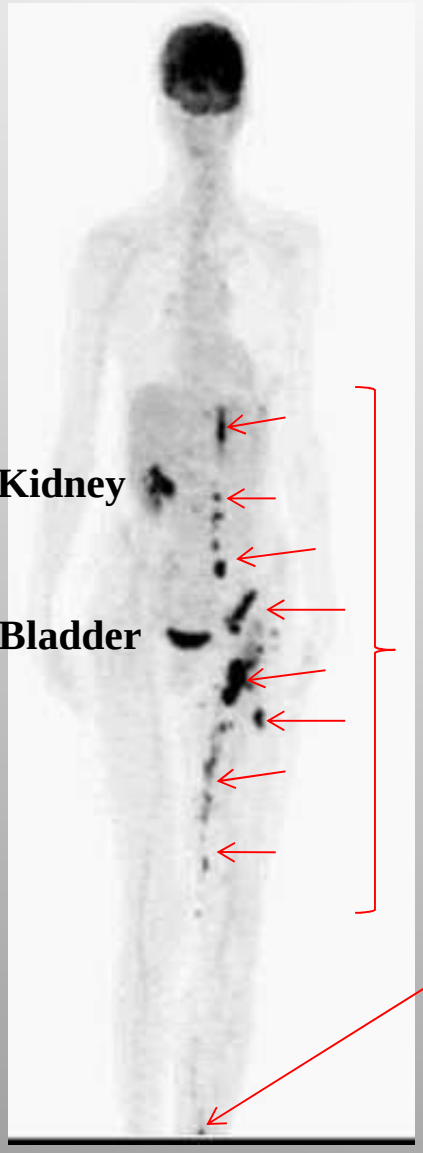
Response by Stage	Number of Patients (%)	Duration of Survival Range, Months
Stage 4		
Overall	**16**	
DOD	8 (50)	2-29
CR	2 (12.5)	28-36
NED	4 (25)	12-26
SD	1 (6.3)	21
PD (alive)	1 (6.3)	16
Stage 2/3		
Overall	**9**	
DOD	5 (55.5)	2-19
NED	3 (33.3)	18-28
PD[a]	1 (11.1)	30


Pre-Trial
8 mm


Week 6
1 mm

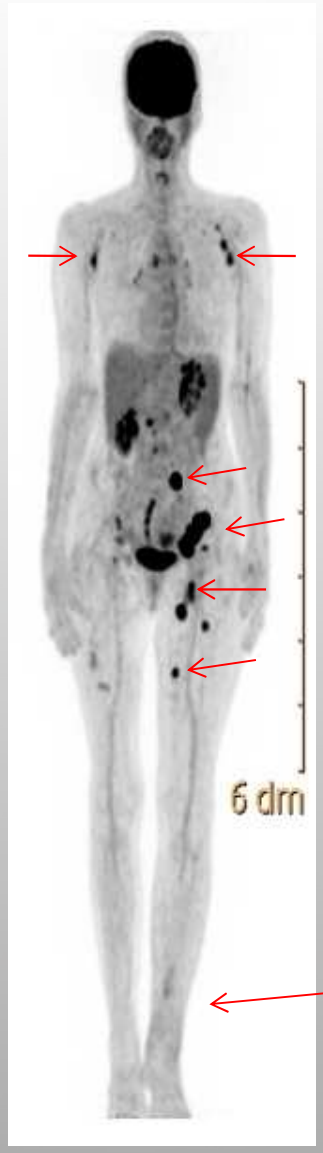

Week 9


Post-Trial



A

June 2008
Pre-treatment

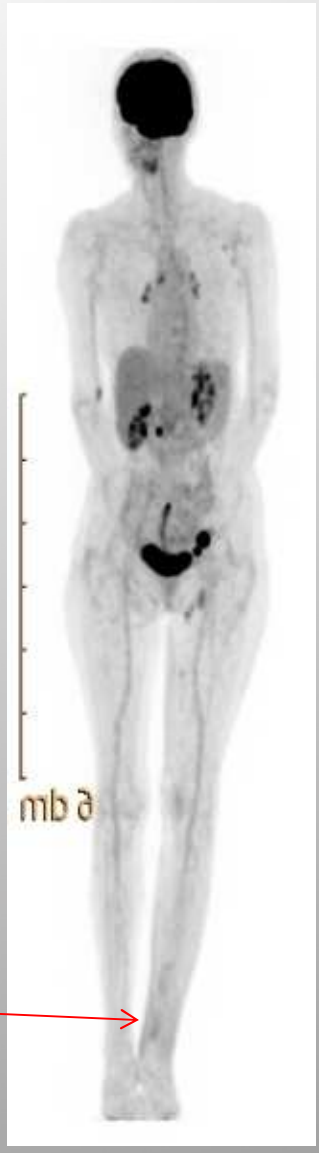


B

February 2009
Immediate Post-treatment

2 Residual Lesions

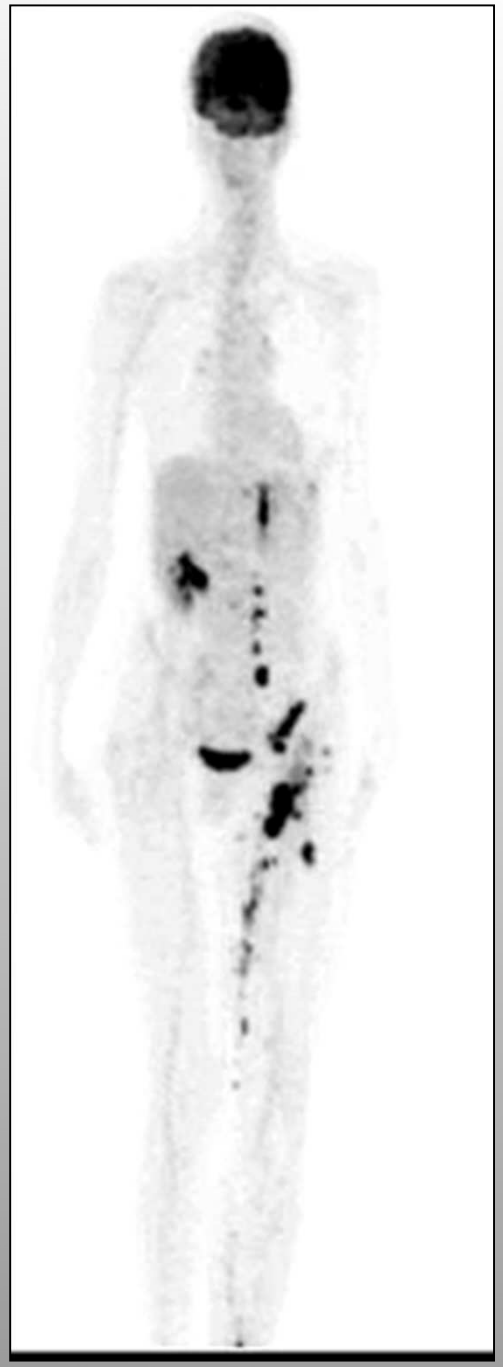
Primary Melanoma Regressed

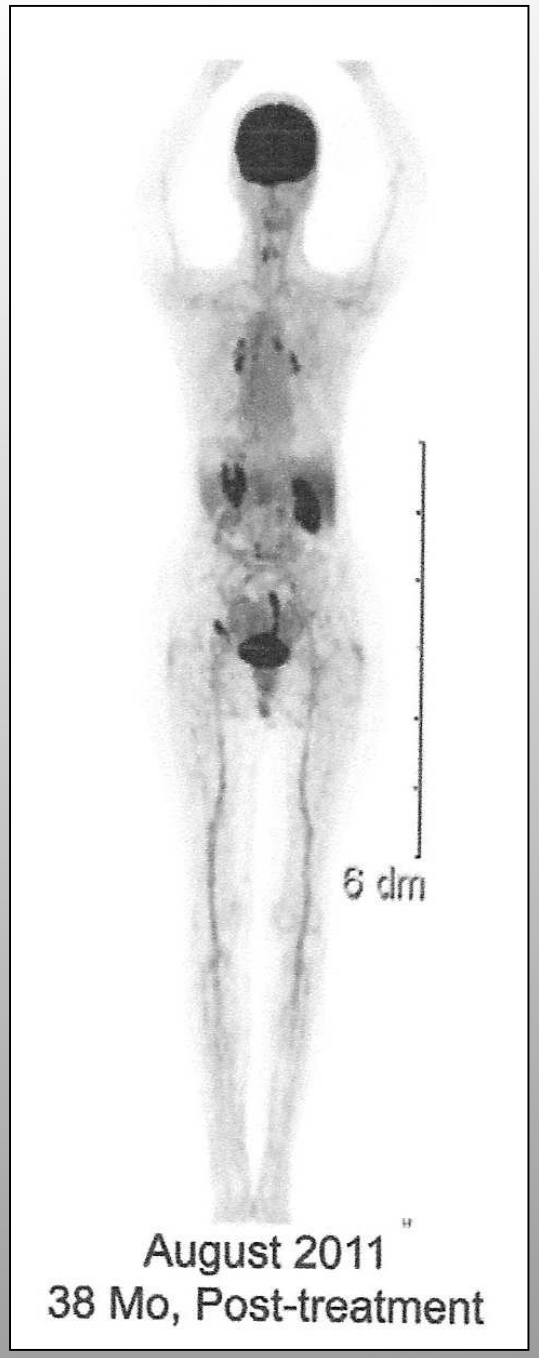


C

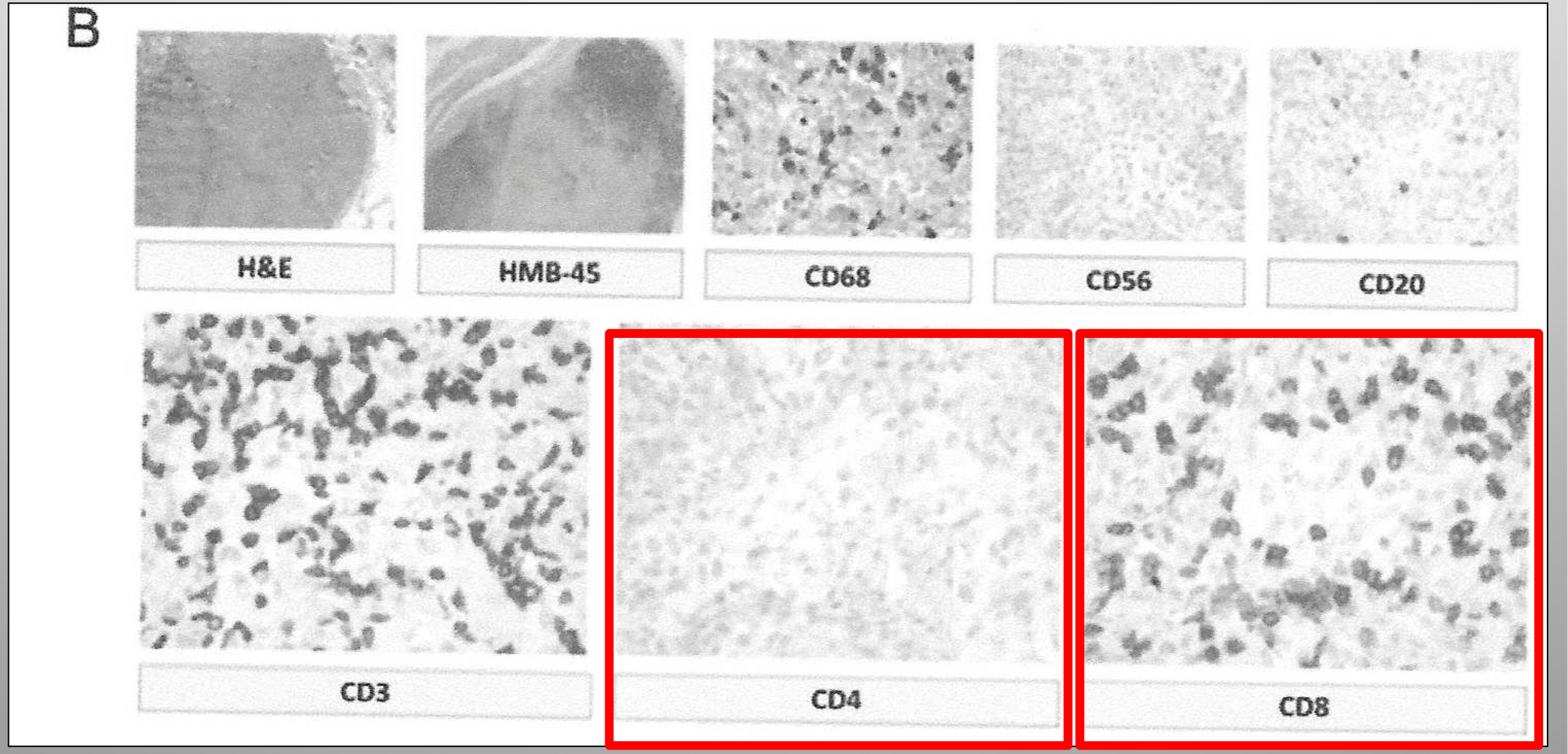
June 2009
5 months Post-treatment

June 2008 Pre-Treatment





August 2011, 38-months post-treatment


B
H&E
HMB-45
CD68
CD56
CD20
CD3
CD4
CD8

Published Ahead of Print on December 15, 2008 as 10.1200/JCO.2007.15.6794
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2007.15.6794

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase I Trial of Interleukin-12 Plasmid Electroporation in Patients With Metastatic Melanoma

Adil I. Daud, Ronald C. DeConti, Stephanie Andrews, Patricia Urbas, Adam I. Riker, Vernon K. Sondak, Pamela N. Munster, Daniel M. Sullivan, Kenneth E. Ugen, Jane L. Messina, and Richard Heller

From the Cutaneous Oncology and Experimental Therapeutics Programs, H. Lee Moffitt Cancer Center; and the Department of Molecular Medicine and Center For Molecular Delivery, College of Medicine, University of South Florida, Tampa, FL.

Submitted December 20, 2007; accepted July 25, 2008; published online ahead of print at www.jco.org on November 24, 2008.

Supported by the National Gene Vector Laboratory at the National Institutes of Health, the American Cancer Society (grant in aid to A.I.D) and Innovio Biomedical Corporation.

Presented in part at the 9th Annual Meeting of the American Society of Gene Therapy, May 31-June 4, 2006, Baltimore, MD, and at the AACR-NCI-EORTC Molecular Targets Meeting, November 7-10, 2006, Prague, Czech Republic.

Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

ABSTRACT

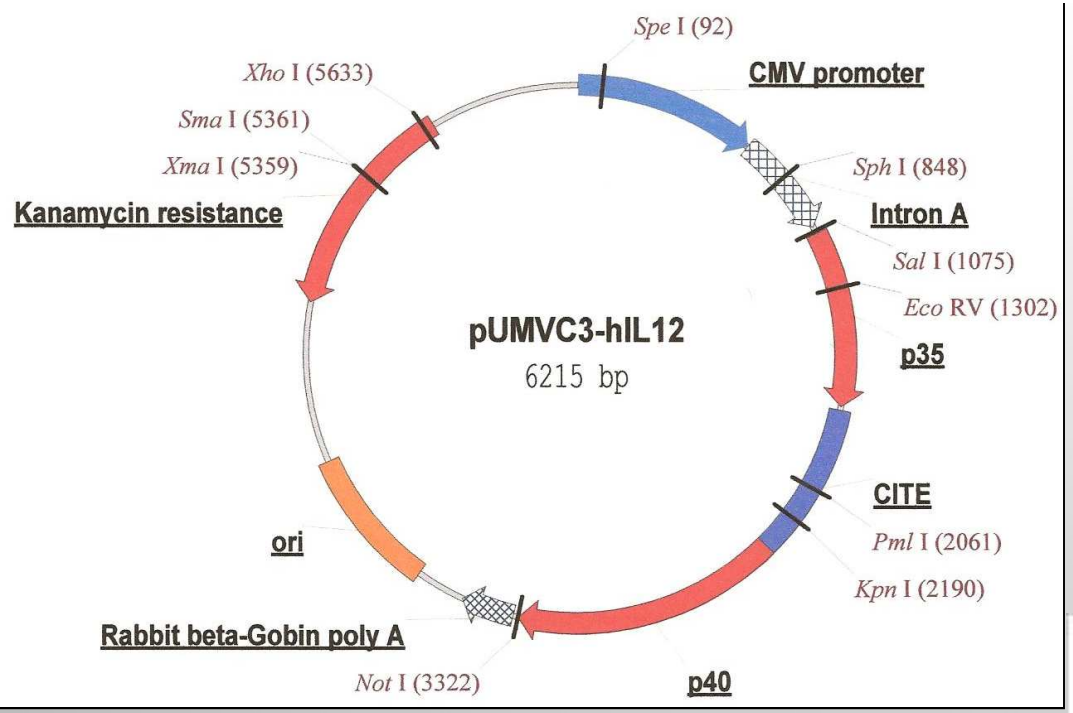
Purpose
Gene-based immunotherapy for cancer is limited by the lack of safe, efficient, reproducible, and titratable delivery methods. Direct injection of DNA into tissue, although safer than viral vectors, suffers from low gene transfer efficiency. In vivo electroporation, in preclinical models, significantly enhances gene transfer efficiency while retaining the safety advantages of plasmid DNA.

Patients and Methods
A phase I dose escalation trial of plasmid interleukin (IL)-12 electroporation was carried out in patients with metastatic melanoma. Patients received electroporation on days 1, 5, and 8 during a single 39-day cycle, into metastatic melanoma lesions with six 100-μs pulses at a 1,300-V/cm electric field through a penetrating six-electrode array immediately after DNA injection. Pre- and post-treatment biopsies were obtained at defined time points for detailed histologic evaluation and determination of IL-12 protein levels.

Results
Twenty-four patients were treated at seven dose levels, with minimal systemic toxicity. Transient pain after electroporation was the major adverse effect. Post-treatment biopsies showed plasmid dose proportional increases in IL-12 protein levels as well as marked tumor necrosis and lymphocytic infiltrate. Two (10%) of 19 patients with nonelectroporated distant lesions and no other systemic therapy showed complete regression of all metastases, whereas eight additional patients (42%) showed disease stabilization or partial response.

Conclusion
This report describes the first human trial, to our knowledge, of gene transfer utilizing in vivo DNA electroporation. The results indicated this modality to be safe, effective, reproducible, and titratable.

J Clin Oncol 26.



Intratumoral Electroporation Device

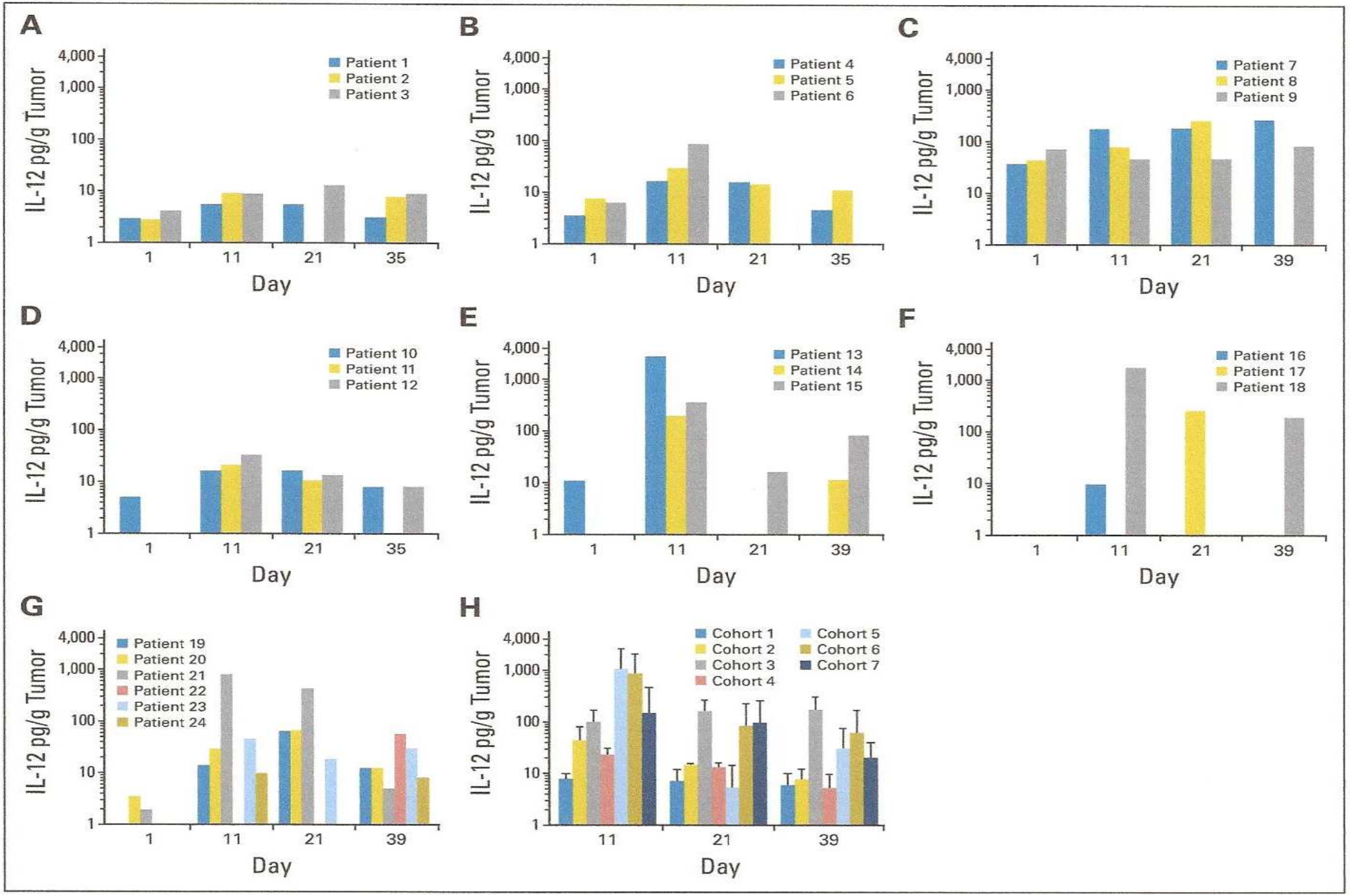
Plasmid Vector: Full-Length Human IL-12 Gene

Table 1. Patient Characteristics and Treatment Response

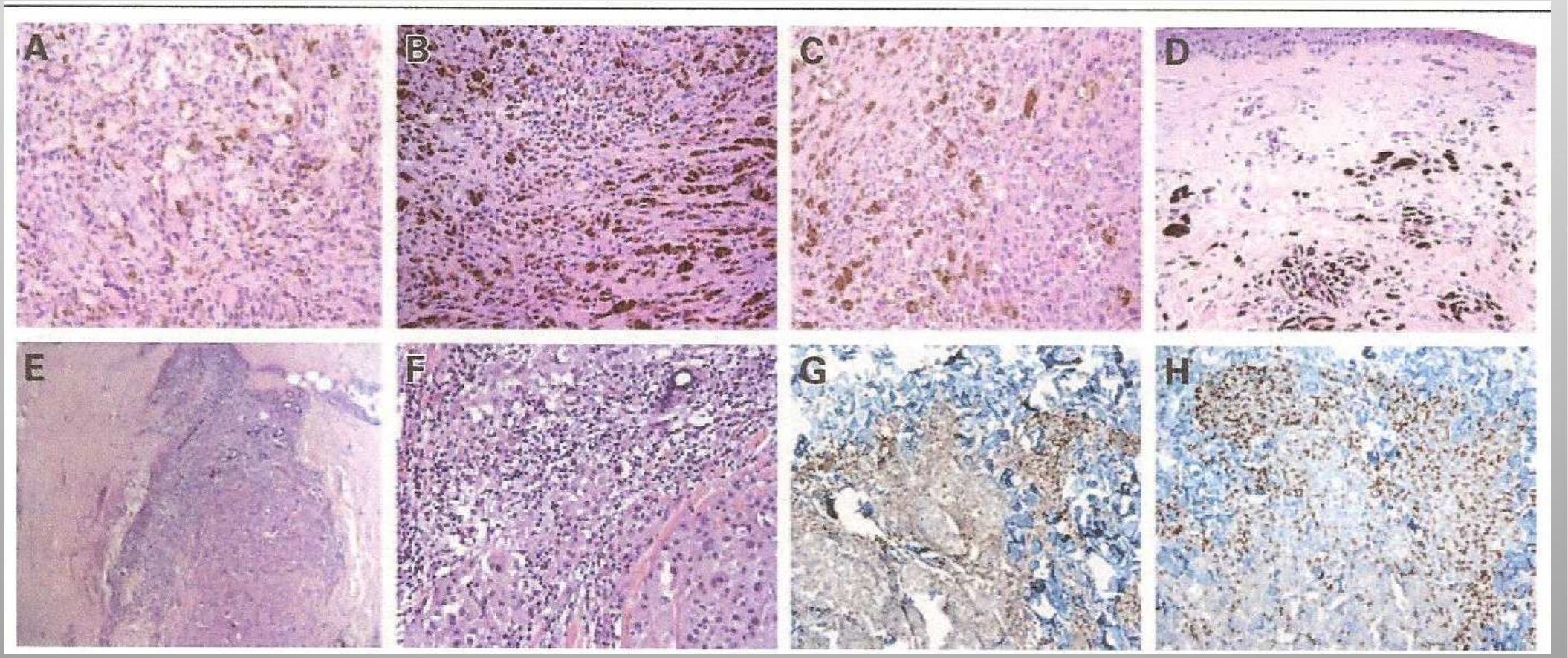
						IL-12 Plasmid		Electroporation			Objective Response	
Cohort	Patient	Age	Sex	AJCC Stage	LDH	Concentration (mg/mL)	Lesion Volume (mL)	No.	Site	Distant Disease Sites	Overall Response	Duration (months)
1	1	35	M	IVA	382	0.1	0.56	3	Leg	SQ, LN	PD	
	2	54	M	IVC	927	0.1	3.9	4	Trunk	SQ, LN	PD	
	3	69	M	IVC	923	0.1	4.4	2	Trunk	SQ	PD	
2	4	55	M	IVC	1,974	0.25	4.98	4	Trunk	Multiple sites	PD	
	5	66	M	IVB	368	0.25	4.03	3	Trunk	Multiple sites	SD	4
	6	43	M	IVA	483	0.25	2.98	2	Trunk, arm	SQ	PD	
3	7	50	M	IIIC	541	0.5	1.16	4	Trunk, arm	SQ	*	> 18
	8	61	M	IIIC	356	0.5	0.82	4	Leg	SQ	PD	
	9	80	M	IVA	449	0.5	0.13	4	Trunk, arm	SQ	CR	> 20
4	10	68	M	IVA	514	1	0.07	3	Trunk	SQ	SD	> 20
	11	64	F	IVC	908	1	1.2	3	Leg	SQ, LN	PD	
	12	70	M	IIIC	370	1	0.96	3	Trunk	—	PD	
5	13	61	M	IIIC	418	1.6	0.57	4	Arm	—	PD	
	14	76	F	IIIC	565	1.6	0.27	4	Leg	SQ	CR	> 16
	15	83	M	IIIC	465	1.6	0.04	4	Arm	SQ	PD	
6	16	56	M	IIIC	400	1.6	FV	4	Trunk	SQ	SD	4
	17	79	F	IIIB	470	1.6	FV	3	Leg	—	SD	> 4
	18	56	F	IIIC	584	1.6	FV	4	Leg	SQ	PD	
7	19	72	M	IIIC	507	1.6	FV	2	Leg	LN	PD	
	20	41	M	IIIB	433	1.6	FV	4	Leg	—	SD	4
	21	26	M	IVA	358	1.6	FV	4	Leg	SQ	SD	4
	22	62	M	IVA	480	1.6	FV	2	Trunk	SQ	PD	
	23	85	M	IVA	572	1.6	FV	4	Leg	SQ, LN	SD	> 6
	24	63	M	IVC	1,380	1.6	FV	3	Neck	Liver, lung	PD	

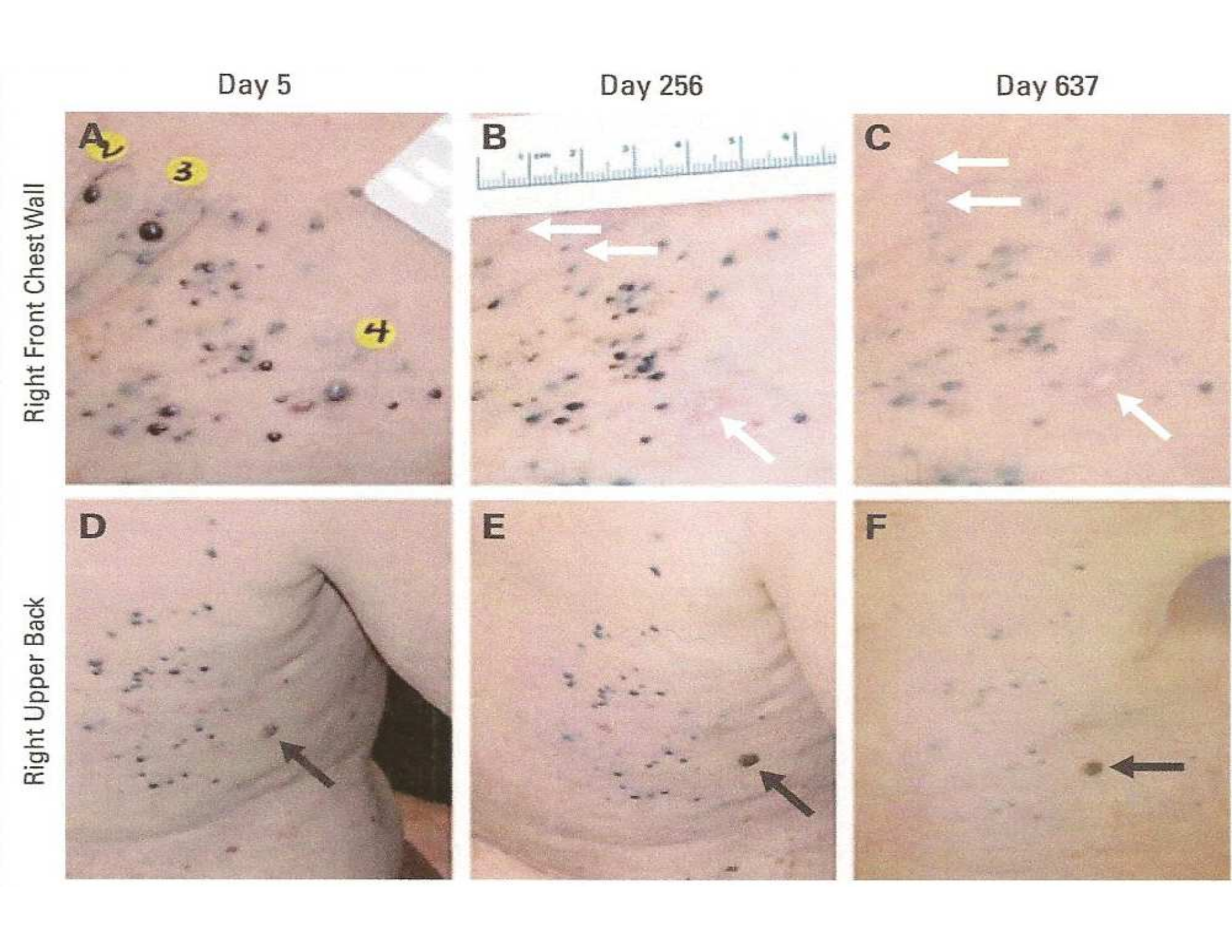
Abbreviations: AJCC, American Joint Committee on Cancer; LDH, lactate dehydrogenase; IL, interleukin; lesion volume, cumulative volume of lesions treated; M, male; SQ, subcutaneous; LN, lymph node; PD, progressive disease; F, female; SD, stable disease; CR, complete response; FV, fixed volume; em, no distant disease.

*Patient 7, overall response was a CR 5 after following treatment with plasmid IL-12 delivered with electroporation; however, the patient was treated with dacarbazine after completion of the IL-12 study and before the CR. Therefore, the response can not be definitively attributed to either therapy.


A
IL-12 pg/g Tumor
4,000
1,000
100
10
1
Patient 1
Patient 2
Patient 3
1
11
21
35
Day
B
IL-12 pg/g Tumor
4,000
1,000
100
10
1
Patient 4
Patient 5
Patient 6
1
11
21
35
Day
C
IL-12 pg/g Tumor
4,000
1,000
100
10
1
Patient 7
Patient 8
Patient 9
1
11
21
39
Day
D
IL-12 pg/g Tumor
4,000
1,000
100
10
1
Patient 10
Patient 11
Patient 12
1
11
21
35
Day
E
IL-12 pg/g Tumor
4,000
1,000
100
10
1
Patient 13
Patient 14
Patient 15
1
11
21
39
Day
F
IL-12 pg/g Tumor
4,000
1,000
100
10
1
Patient 16
Patient 17
Patient 18
1
11
21
39
Day
G
IL-12 pg/g Tumor
4,000
1,000
100
10
1
Patient 19
Patient 20
Patient 21
Patient 22
Patient 23
Patient 24
1
11
21
39
Day
H
IL-12 pg/g Tumor
4,000
1,000
100
10
1
Cohort 1
Cohort 2
Cohort 3
Cohort 4
Cohort 5
Cohort 6
Cohort 7
11
21
39
Day

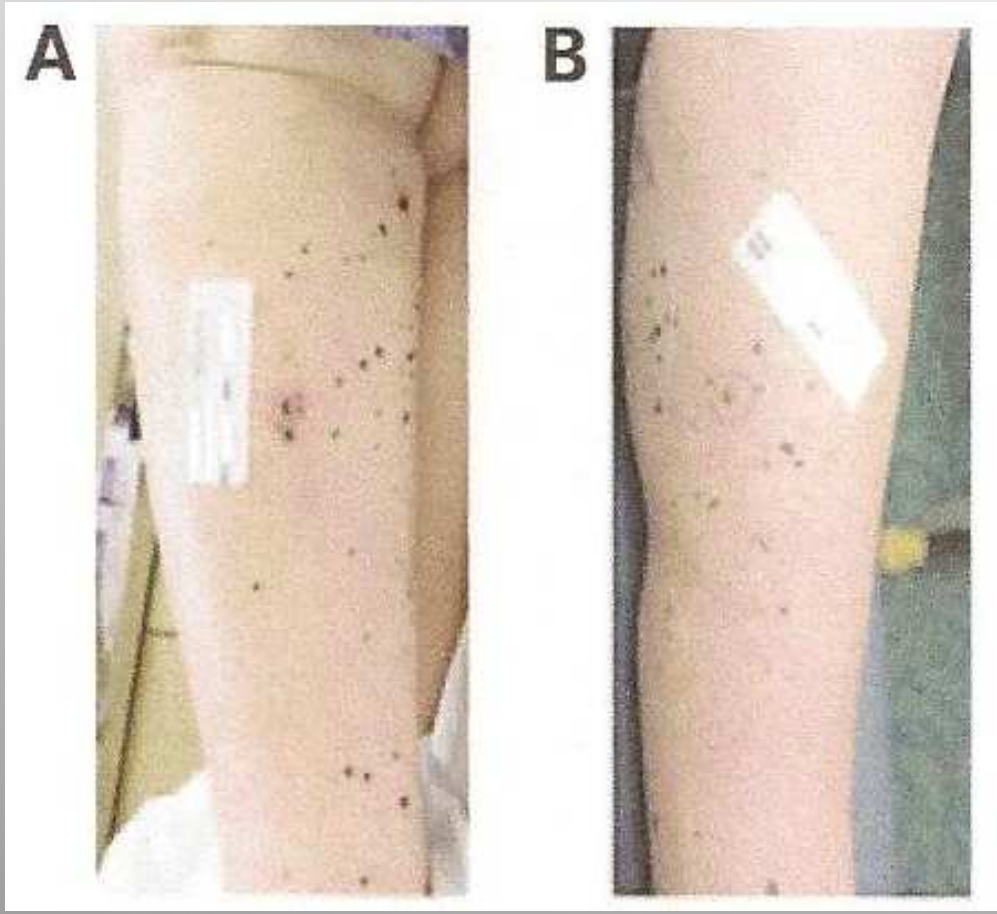
Histologic Appearance of Electroporated Lesions

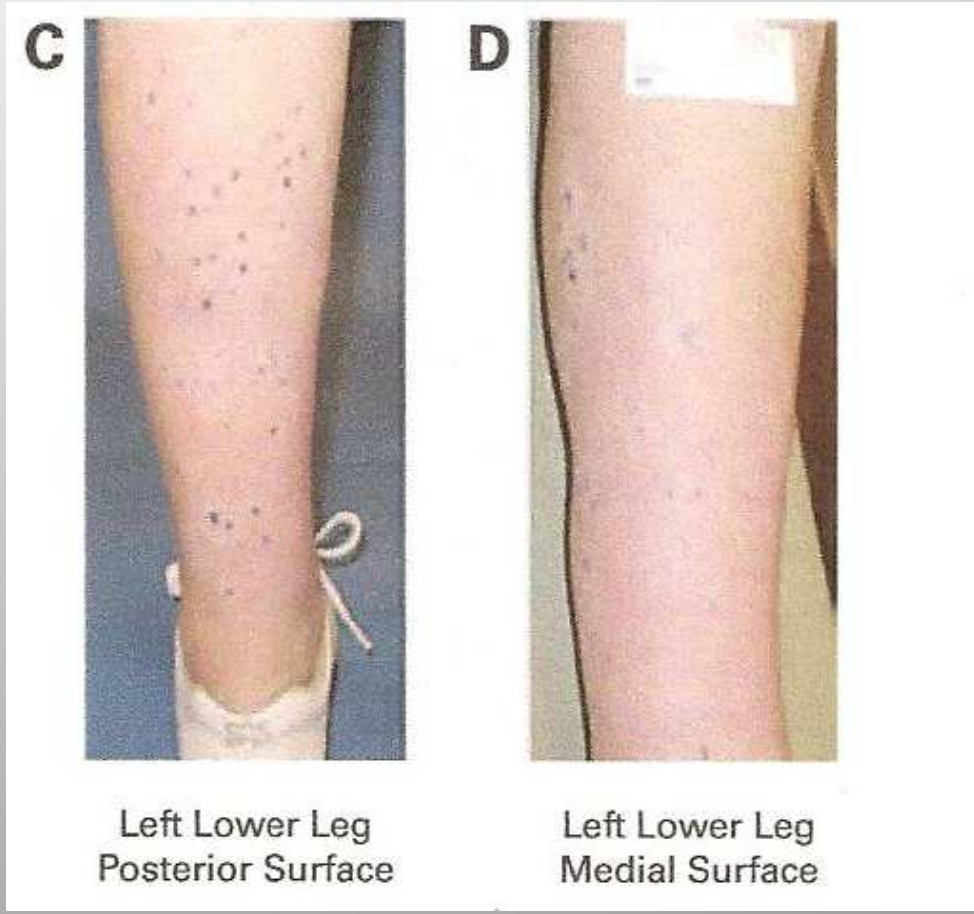



Day 5
Day 256
Day 637
Right Front Chest Wall
Right Upper Back
A
3
4
B
C
D
E
F

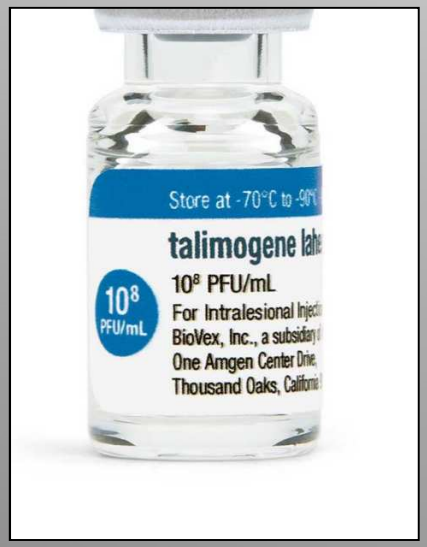
Day 5

Day 513


A
B

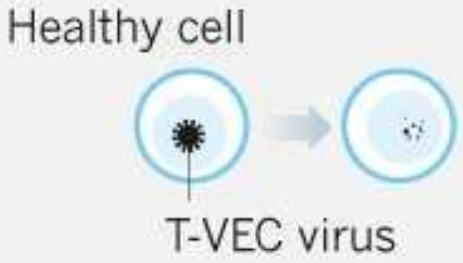

C
D
Left Lower Leg
Posterior Surface
Left Lower Leg
Medial Surface

Talimogene Laherparepvec

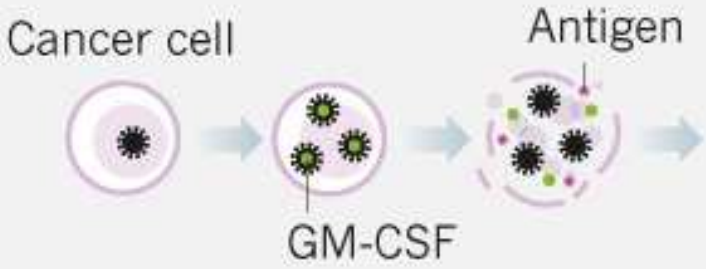


GOING VIRAL AGAINST CANCER

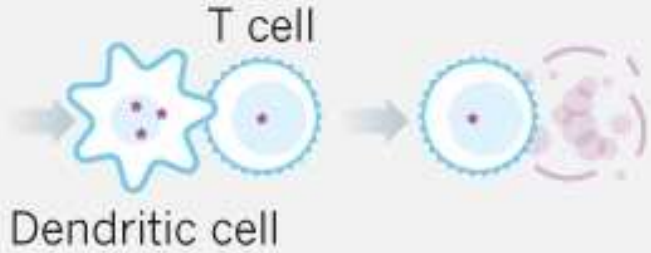
The virus-based cancer therapy T-VEC infects tumour cells and destroys them by stimulating the immune system to direct an attack against malignant cells in the body.



T-VEC enters but cannot replicate in normal cells.



T-VEC destroys malignant cells directly, releasing the protein GM-CSF and antigens that enable the immune system to target cancerous cells nearby and throughout the body.



GM-CSF attracts dendritic cells, which present tumour antigens to the immune system's T cells, programming them to destroy cancer cells throughout the body.

Overall Response Rate:

26.4% in T-VEC arm vs. 5.7% in the GM-CSF arm

Median Overall Survival

23.3 months in T-VEC vs. 18.9 months in the GM-CSF group

VOLUME 33 · NUMBER 25 · SEPTEMBER 1 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma

Robert H.I. Andtbacka, Howard L. Kaufman, Frances Collichio, Thomas Amatruda, Neil Senzer, Jason Chesney, Keith A. Delman, Lynn E. Spitler, Igor Puzanov, Sanjiv S. Agarwala, Mohammed Milhem, Lee Cranmer, Brendan Curti, Karl Lewis, Merrick Ross, Troy Guthrie, Gerald P. Linette, Gregory A. Daniels, Kevin Harrington, Mark R. Middleton, Wilson H. Miller Jr, Jonathan S. Zager, Yining Ye, Bin Yao, Ai Li, Susan Doleman, Ari VanderWalde, Jennifer Gansert, and Robert S. Coffin

See accompanying article on page 2812

Author affiliations appear at the end of this article.

Published online ahead of print at www.jco.org on June 22, 2015.

Written on behalf of the OPTiM investigators.

Supported by Amgen, which also funded medical writing assistance.

R.H.I.A. and H.L.K. contributed equally to this work.

Presented in part at the 49th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, May 31-June 4, 2013, and 50th ASCO Annual Meeting, Chicago, IL, May 30-June 3, 2014.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Clinical trial information: NCT00769704.

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0732-183X/15/3325w-2780w/$20.00

DOI: 10.1200/JCO.2014.58.3377

A B S T R A C T

Purpose
Talimogene laherparepvec (T-VEC) is a herpes simplex virus type 1–derived oncolytic immunotherapy designed to selectively replicate within tumors and produce granulocyte macrophage colony-stimulating factor (GM-CSF) to enhance systemic antitumor immune responses. T-VEC was compared with GM-CSF in patients with unresected stage IIIB to IV melanoma in a randomized open-label phase III trial.

Patients and Methods
Patients with injectable melanoma that was not surgically resectable were randomly assigned at a two-to-one ratio to intralesional T-VEC or subcutaneous GM-CSF. The primary end point was durable response rate (DRR; objective response lasting continuously ≥ 6 months) per independent assessment. Key secondary end points included overall survival (OS) and overall response rate.

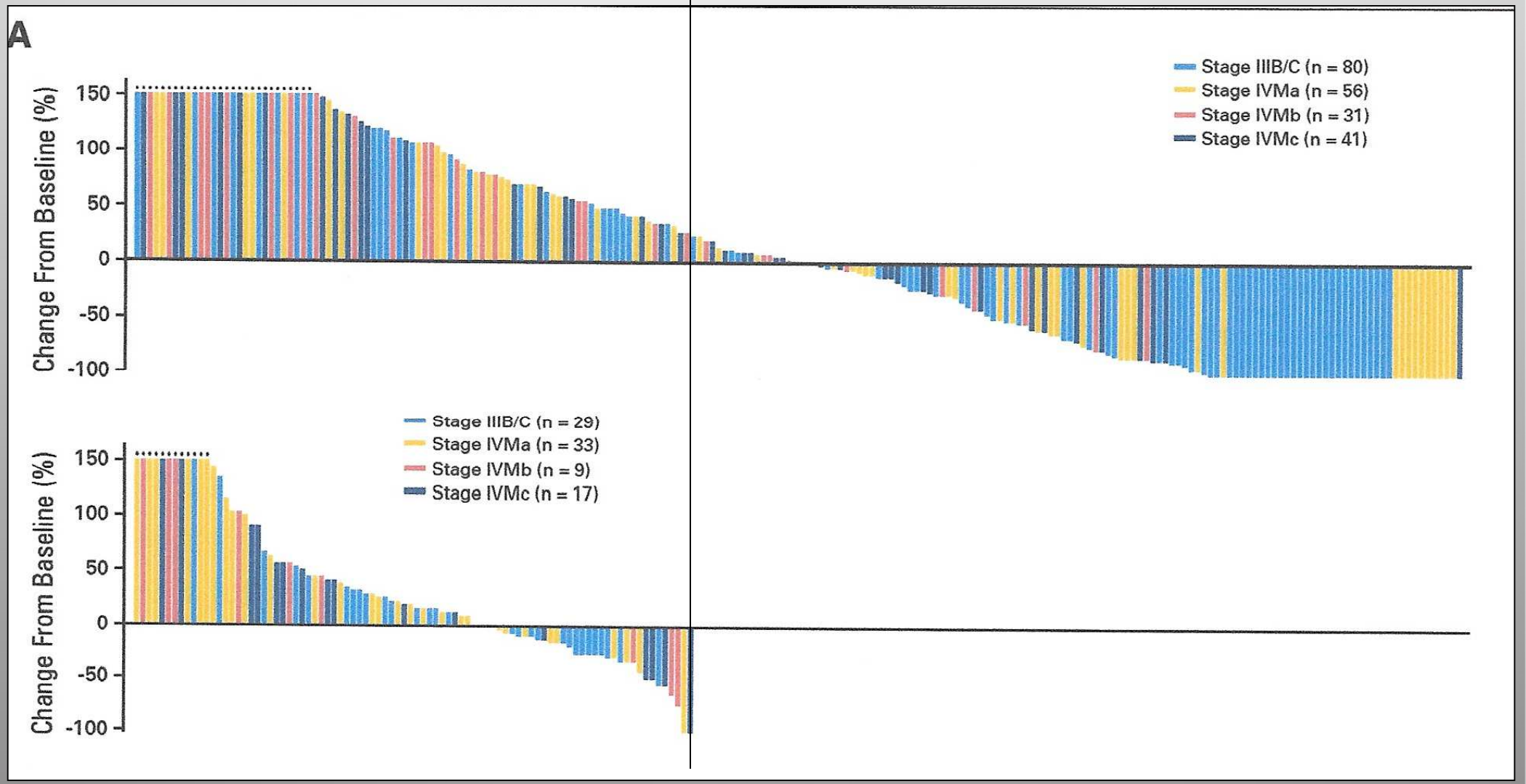
Results
Among 436 patients randomly assigned, DRR was significantly higher with T-VEC (16.3%; 95% CI, 12.1% to 20.5%) than GM-CSF (2.1%; 95% CI, 0% to 4.5%]; odds ratio, 8.9; $P < .001$). Overall response rate was also higher in the T-VEC arm (26.4%; 95% CI, 21.4% to 31.5% *v* 5.7%; 95% CI, 1.9% to 9.5%). Median OS was 23.3 months (95% CI, 19.5 to 29.6 months) with T-VEC and 18.9 months (95% CI, 16.0 to 23.7 months) with GM-CSF (hazard ratio, 0.79; 95% CI, 0.62 to 1.00; $P = .051$). T-VEC efficacy was most pronounced in patients with stage IIIB, IIIC, or IVM1a disease and in patients with treatment-naive disease. The most common adverse events (AEs) with T-VEC were fatigue, chills, and pyrexia. The only grade 3 or 4 AE occurring in ≥ 2% of T-VEC–treated patients was cellulitis (2.1%). No fatal treatment-related AEs occurred.

Conclusion
T-VEC is the first oncolytic immunotherapy to demonstrate therapeutic benefit against melanoma in a phase III clinical trial. T-VEC was well tolerated and resulted in a higher DRR ($P < .001$) and longer median OS ($P = .051$), particularly in untreated patients or those with stage IIIB, IIIC, or IVM1a disease. T-VEC represents a novel potential therapy for patients with metastatic melanoma.

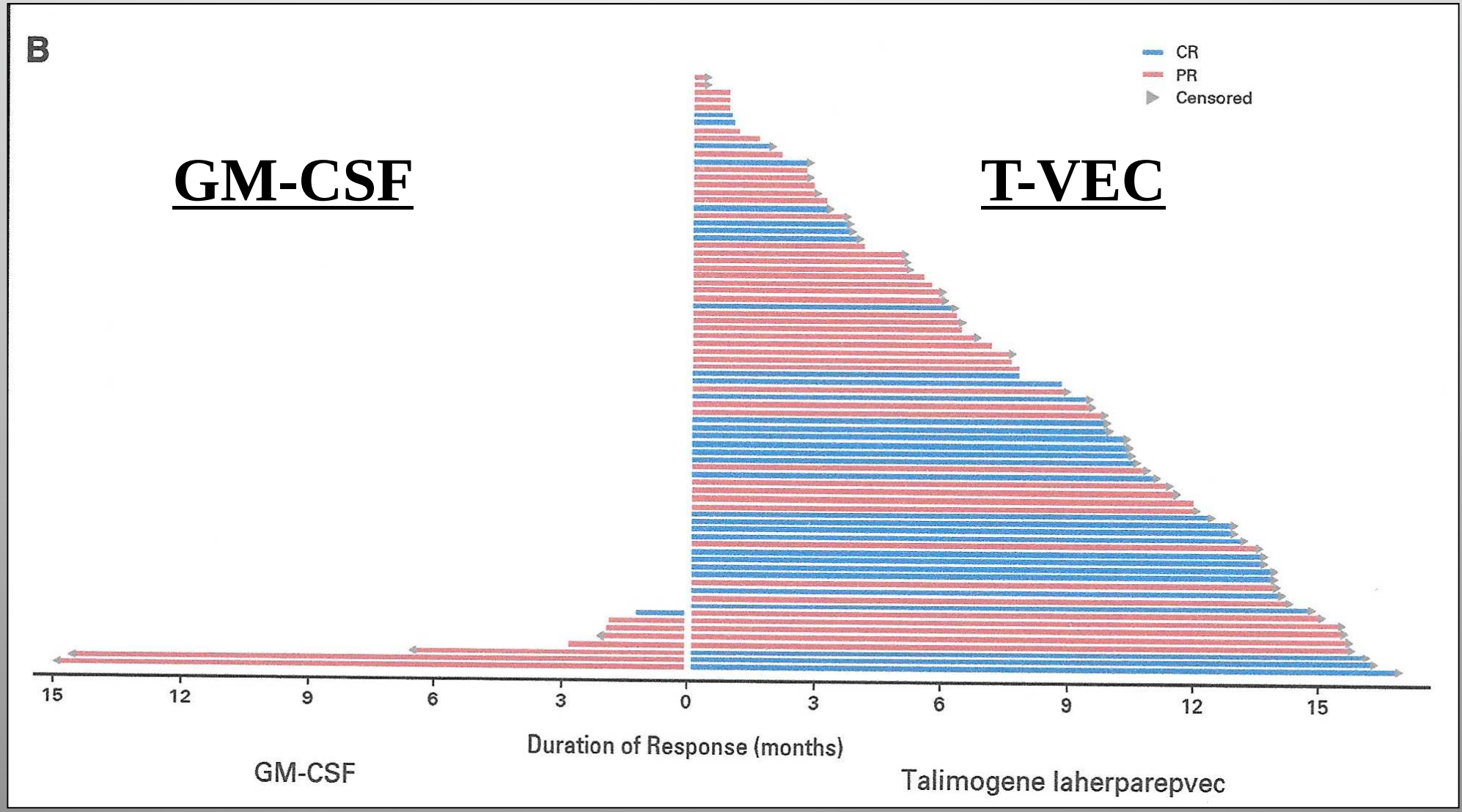
Change from Baseline

GM-CSF

T-VEC



Duration of Response [Months]



Median Overall Survival of 23.3 months in T-VEC vs. 18.9 months in the GM-CSF group

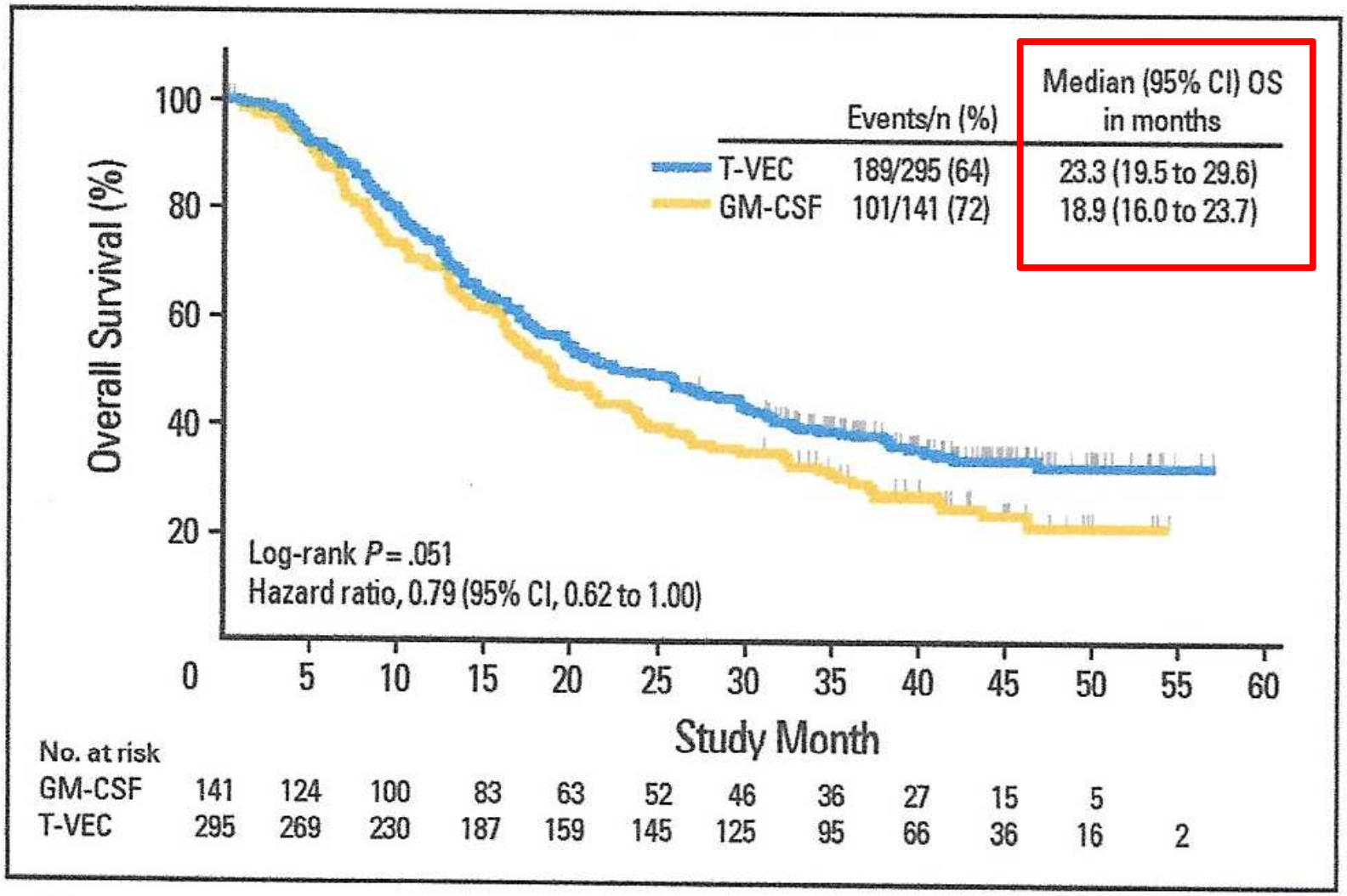
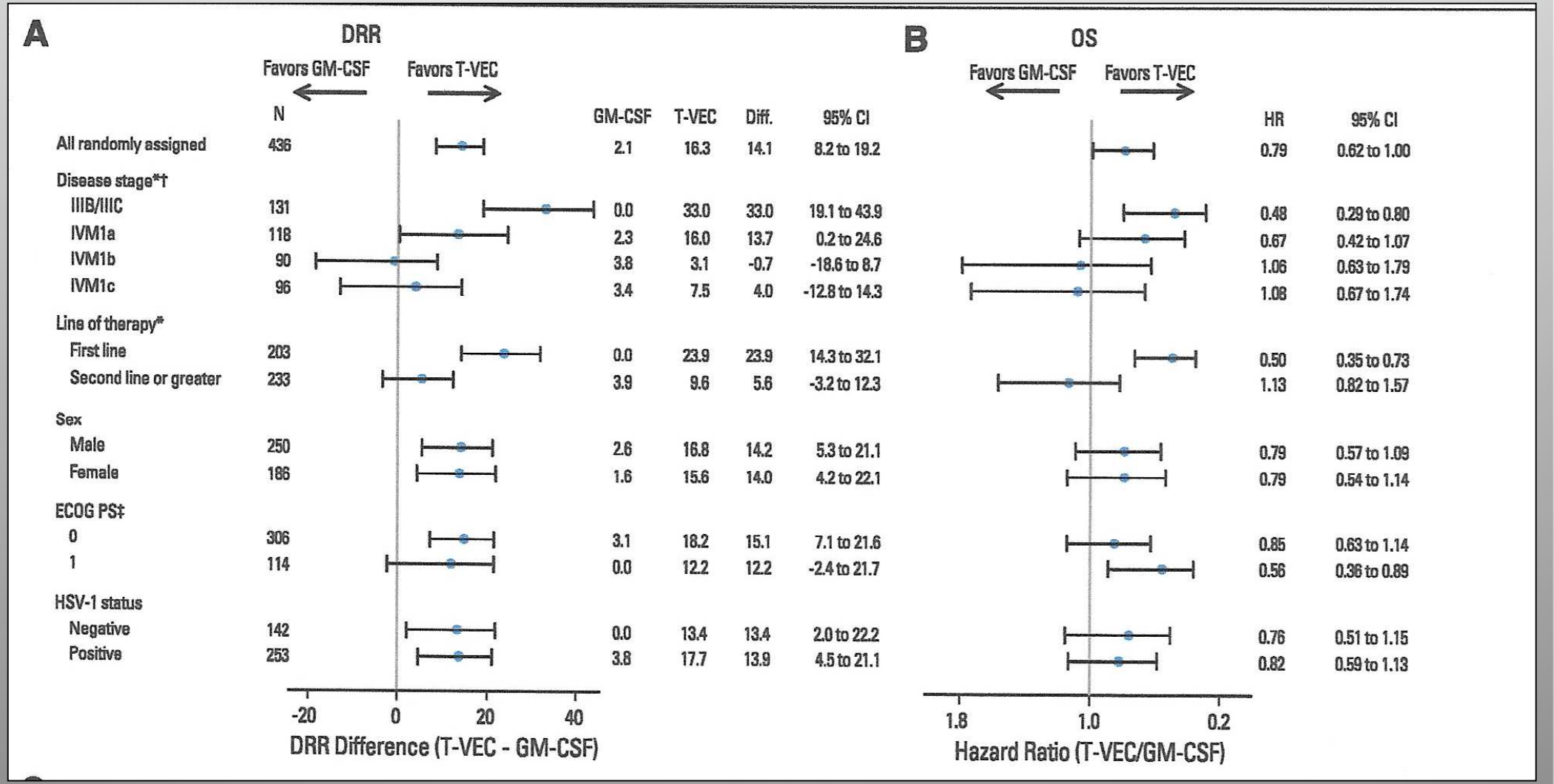
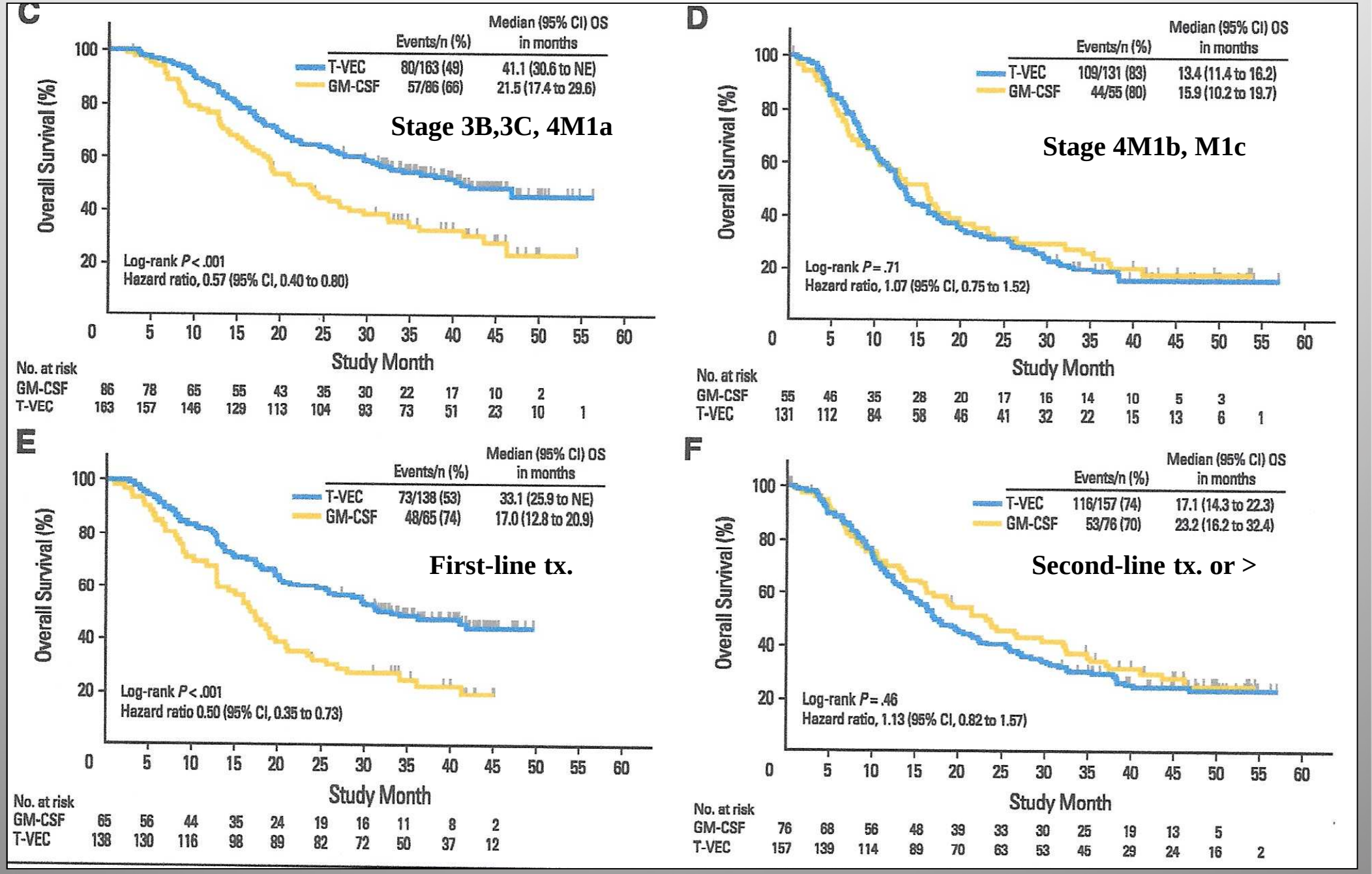


Fig 3. Primary analysis of overall survival (OS) in intent-to-treat population. GM-CSF, granulocyte macrophage colony-stimulating factor; T-VEC, talimogene laherparepvec.

Durable Response Rate

Overall Survival




C
Median (95% CI) OS
Events/n (%) in months
T-VEC 80/163 (49) 41.1 (30.6 to NE)
GM-CSF 57/86 (66) 21.5 (17.4 to 29.6)
Stage 3B,3C, 4M1a
Overall Survival (%)
Log-rank P < .001
Hazard ratio, 0.57 (95% CI, 0.40 to 0.80)
Study Month
No. at risk
GM-CSF 86 78 65 55 43 35 30 22 17 10 2
T-VEC 163 157 146 129 113 104 93 73 51 23 10 1
D
Median (95% CI) OS
Events/n (%) in months
T-VEC 109/131 (83) 13.4 (11.4 to 16.2)
GM-CSF 44/55 (80) 15.9 (10.2 to 19.7)
Stage 4M1b, M1c
Overall Survival (%)
Log-rank P = .71
Hazard ratio, 1.07 (95% CI, 0.75 to 1.52)
Study Month
No. at risk
GM-CSF 55 46 35 28 20 17 16 14 10 5 3
T-VEC 131 112 84 58 46 41 32 22 15 13 6 1
E
Median (95% CI) OS
Events/n (%) in months
T-VEC 73/138 (53) 33.1 (25.9 to NE)
GM-CSF 48/65 (74) 17.0 (12.8 to 20.9)
First-line tx.
Overall Survival (%)
Log-rank P < .001
Hazard ratio 0.50 (95% CI, 0.35 to 0.73)
Study Month
No. at risk
GM-CSF 65 56 44 35 24 19 16 11 8 2
T-VEC 138 130 116 98 89 82 72 50 37 12
F
Median (95% CI) OS
Events/n (%) in months
T-VEC 116/157 (74) 17.1 (14.3 to 22.3)
GM-CSF 53/76 (70) 23.2 (16.2 to 32.4)
Second-line tx. or >
Overall Survival (%)
Log-rank P = .46
Hazard ratio, 1.13 (95% CI, 0.82 to 1.57)
Study Month
No. at risk
GM-CSF 76 68 56 48 39 33 30 25 19 13 5
T-VEC 157 139 114 89 70 63 53 45 29 24 16 2

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Tuesday, October 27, 2015

Late-Breaking News

SITC RELEASE

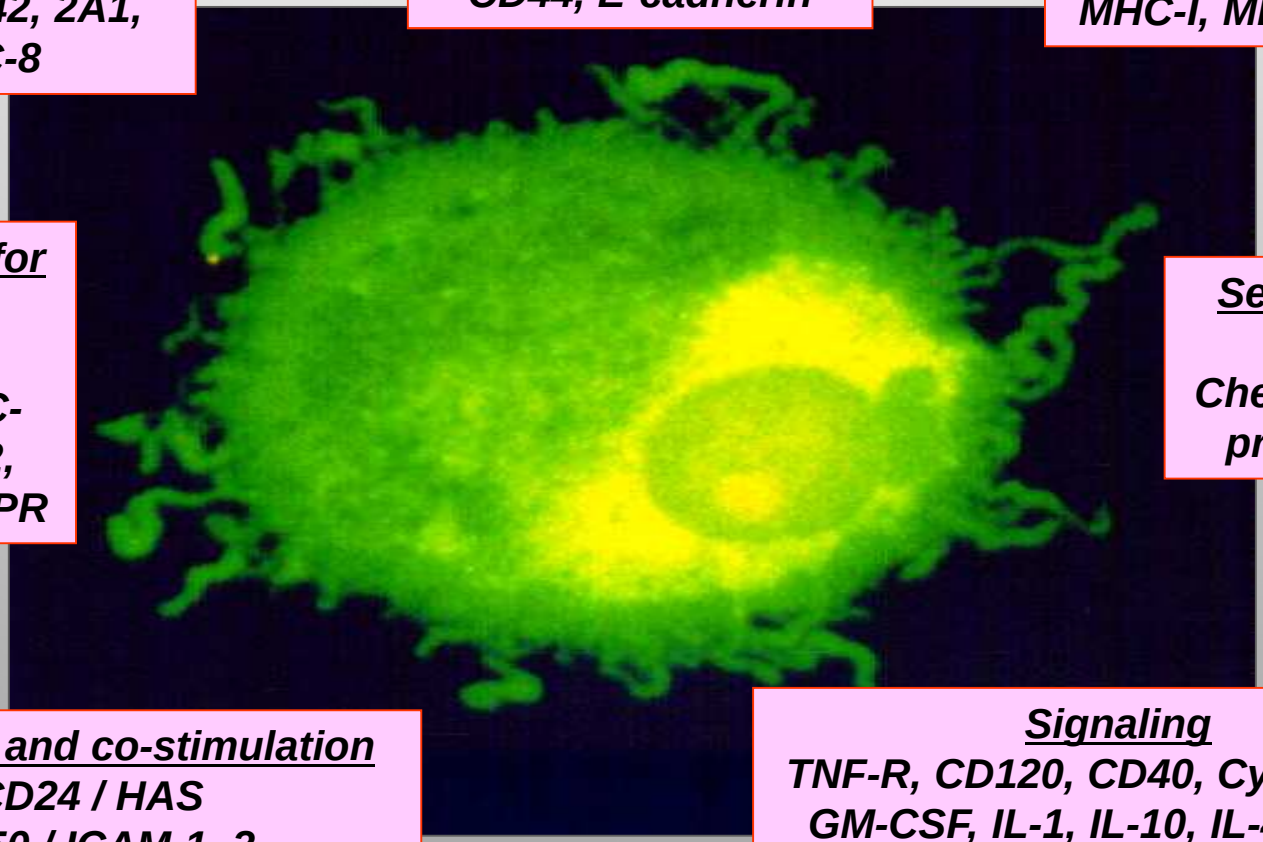
FDA Approves First-in-Class Oncolytic Virus Immunotherapy for the Treatment of Melanoma

The Ultimate Antigen Presenting Cell

Markers
S100, p55, CD83, OX62, M342, 2A1, MIDC-8

Homing
CD11A, B,C, CD49D, CD44, E-cadherin

High Level of Antigen Expression
MHC-I, MHC-II, CD1



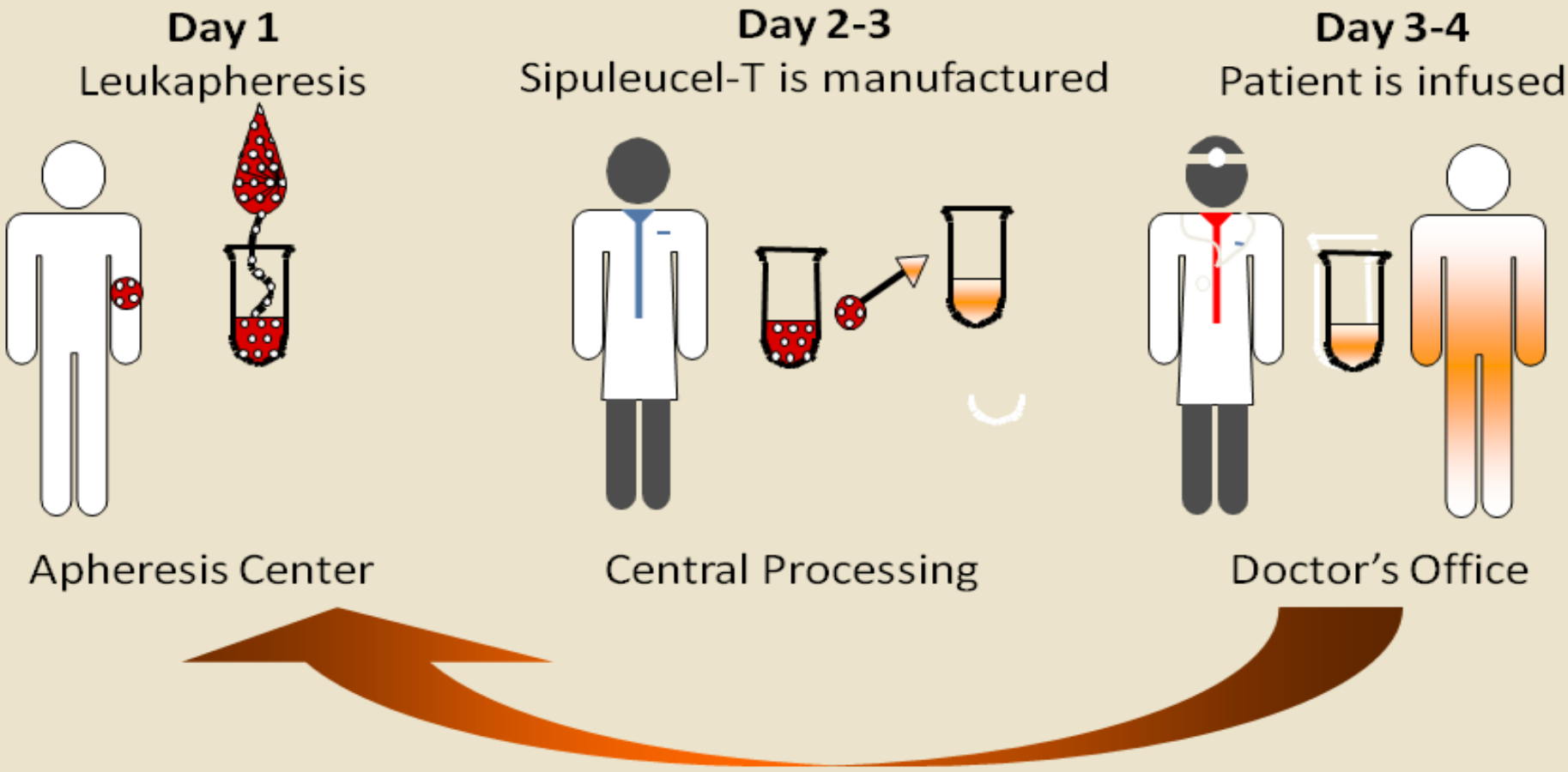
Receptors for antigen uptake
MMR, DEC-205, CD32, CD64, ASGPR

Secretions
IL-12, Chemokines, proteases

Adhesion and co-stimulation
CD24 / HAS
CD50 / ICAM-1, 3
CD58 / LFA-3
CD80, CD86 / B7-1, B7-2

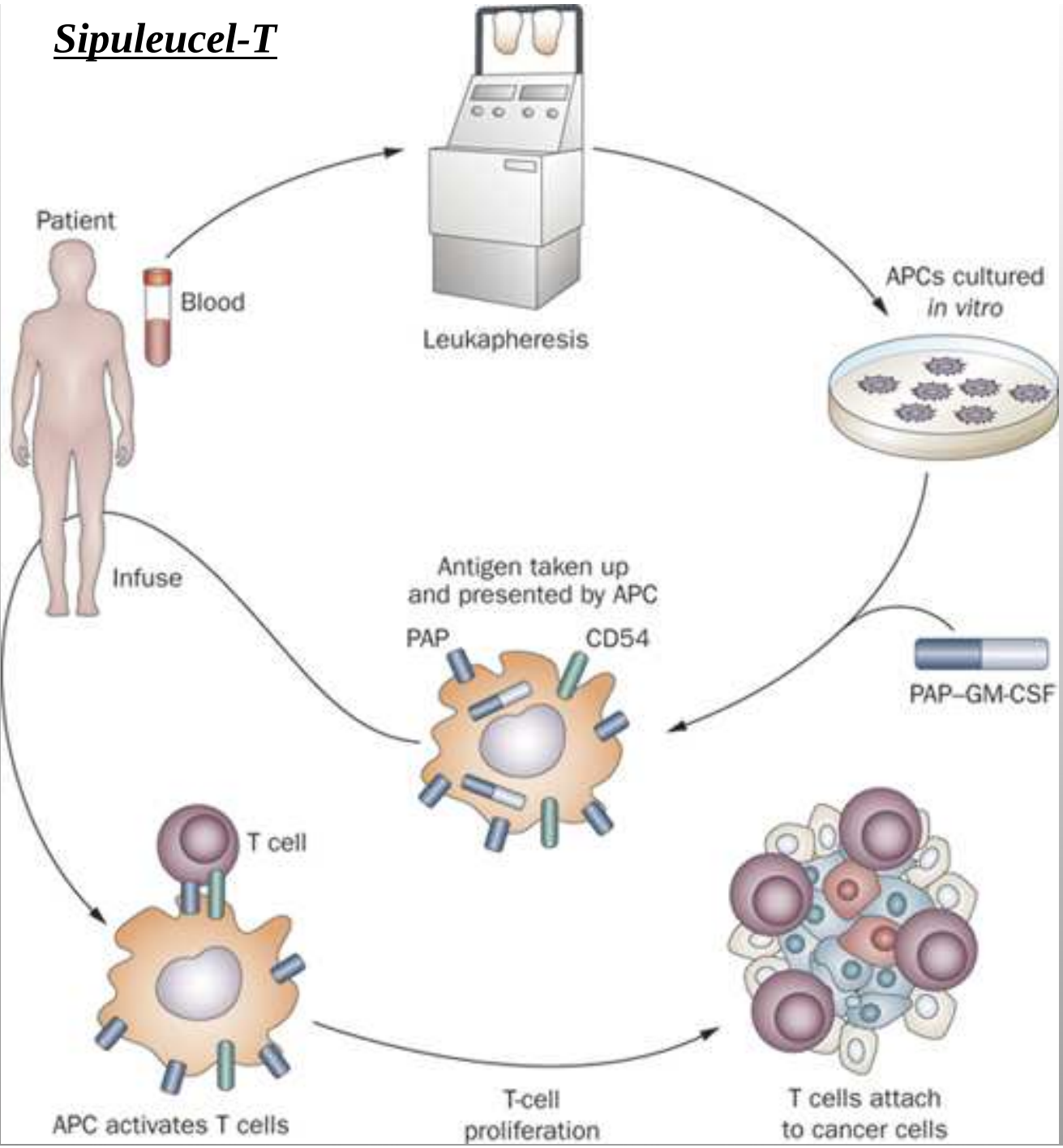
Signaling
TNF-R, CD120, CD40, Cytokine-R: GM-CSF, IL-1, IL-10, IL-4, TGF-β
7-TM-R: CCR5, CXCR4, CCR6, CD88, NFκB

Immune-based therapy: Sipuleucel-T



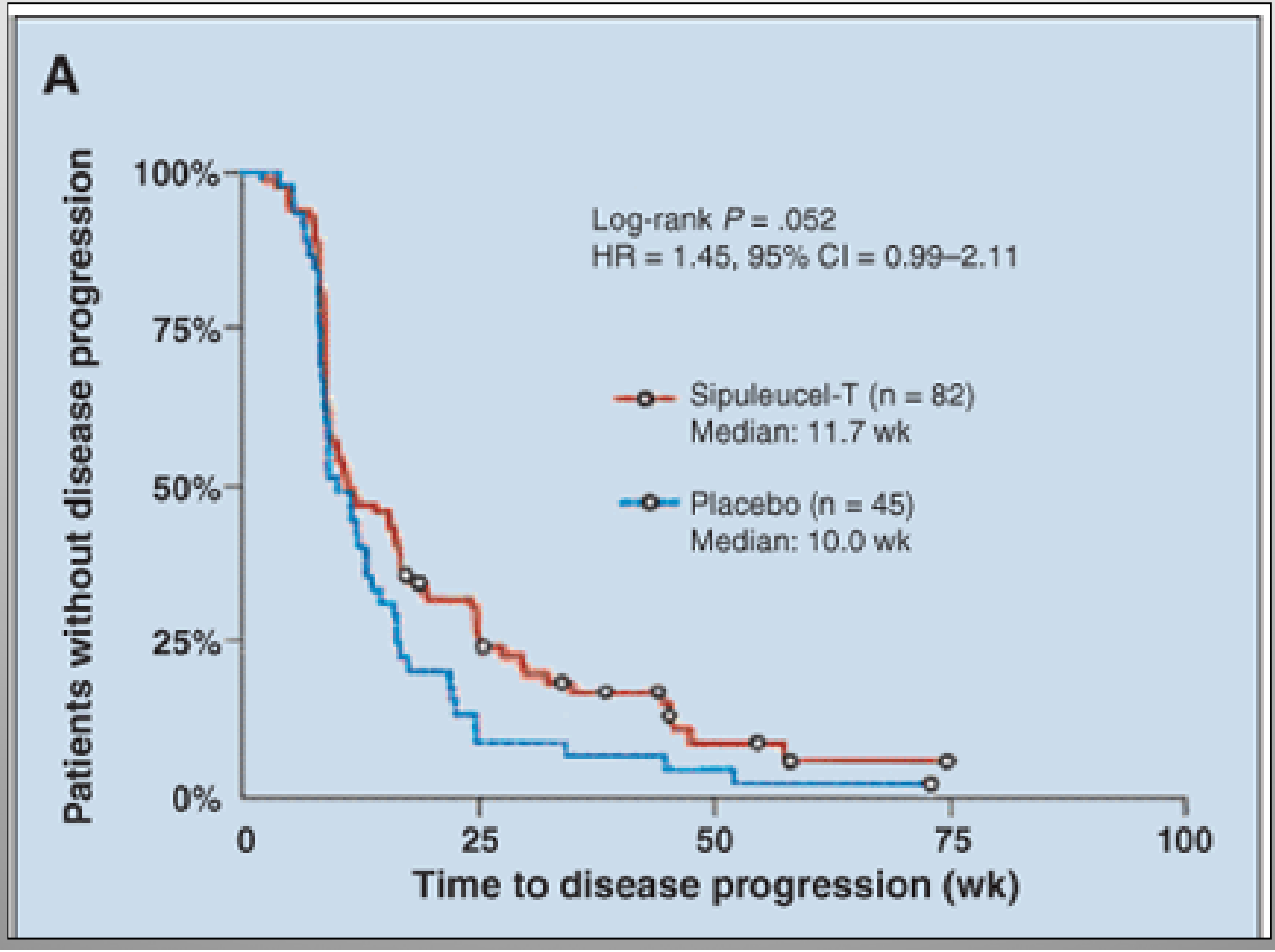
COMPLETE COURSE OF THERAPY:
Weeks 0, 2, 4

Sipuleucel-T

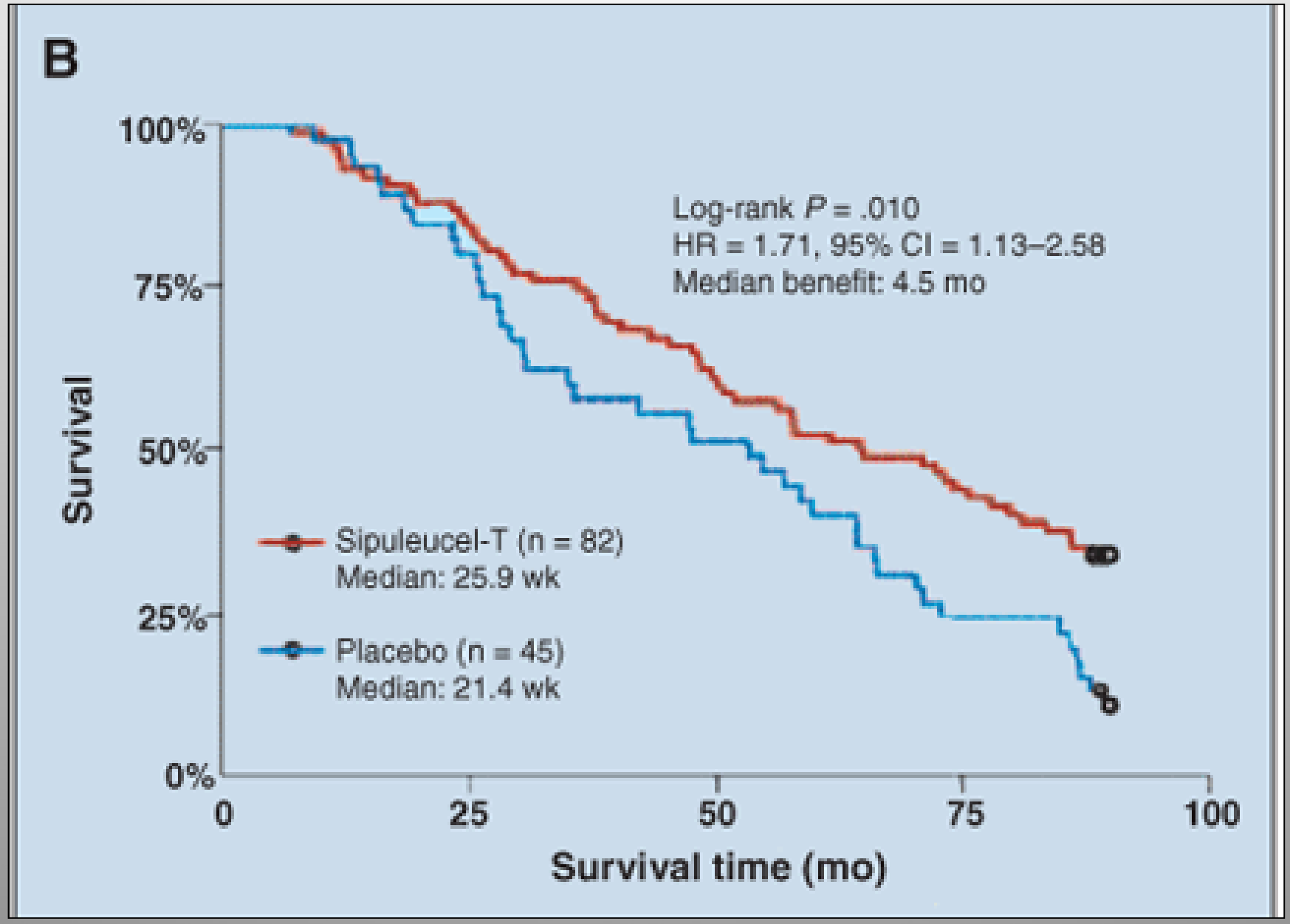


- ***Double-blind, placebo-controlled Phase 3 trial evaluating supuleucel-T in men with asymptomatic, metastatic androgen-independent prostate cancer.***
- ***Significantly improved survival compared to placebo.***
- ***Improvement of 4.5 months median survival and a greater than 3-fold increase in survival at 36 months when compared to placebo***
- ***Patients receiving placebo had a relative risk of dying 70% higher than those receiving sipuleucel-T***
- ***34% of patients receiving sipuleucel-T were alive at 36 months compared to 11% receiving placebo.***
- ***Survival benefit seen with sipuleucel-T was independent of Gleason's Score***

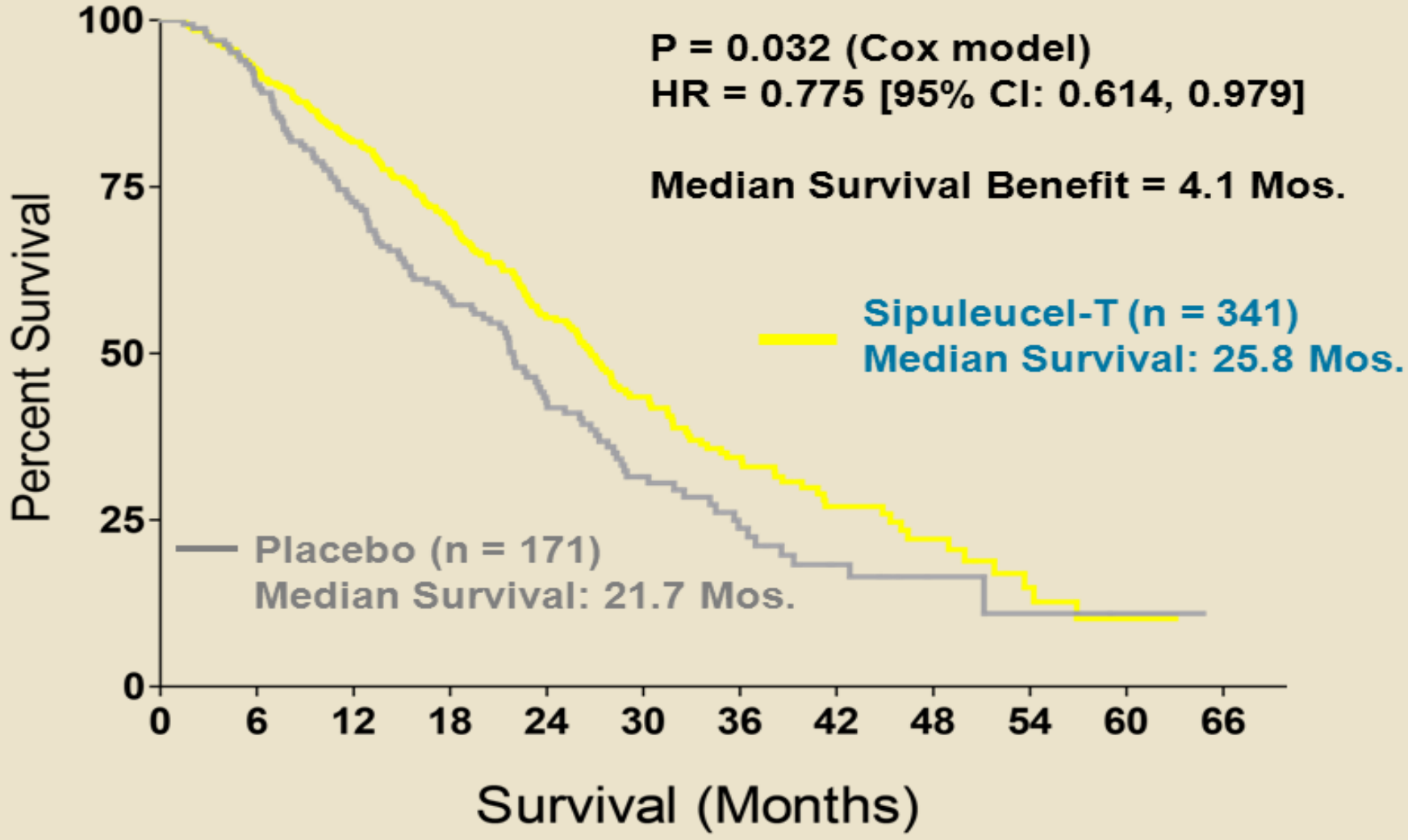
Disease-Free Progression with or without Sipuleucel-T



Overall Survival with or without Sipuleucel-T



Sipuleucel-T: Survival Benefit in Phase 3 Trial(s)



(For references, see text.)

Optimal Use of Sipuleucel-T

- Sipuleucel-T is approved for asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer and a rising PSA level.
- It should not be used in patients with a life expectancy of < 6 to 9 months, and after chemotherapy should be considered only in select patients.
- Consider the vaccine early in the course of advanced prostate cancer.

FDA Approval
April 29th, 2010

Dendritic Cell-Based Immunotherapy for Metastatic Melanoma

Schadendorf D, Nestle FO, Broecker EB, Enk A, Grabbe S, Ugurel S, Edler L, Schuler G, DeCOG-DC Study Group. Dacarbacine (DTIC) versus vaccination with autologous peptide-pulsed dendritic cells (DC) as first-line treatment of patients with metastatic melanoma: Results of a prospective-randomized phase III study Journal of Clinical Oncology, 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 22, No 14S (July 15 Supplement), 2004: 7508

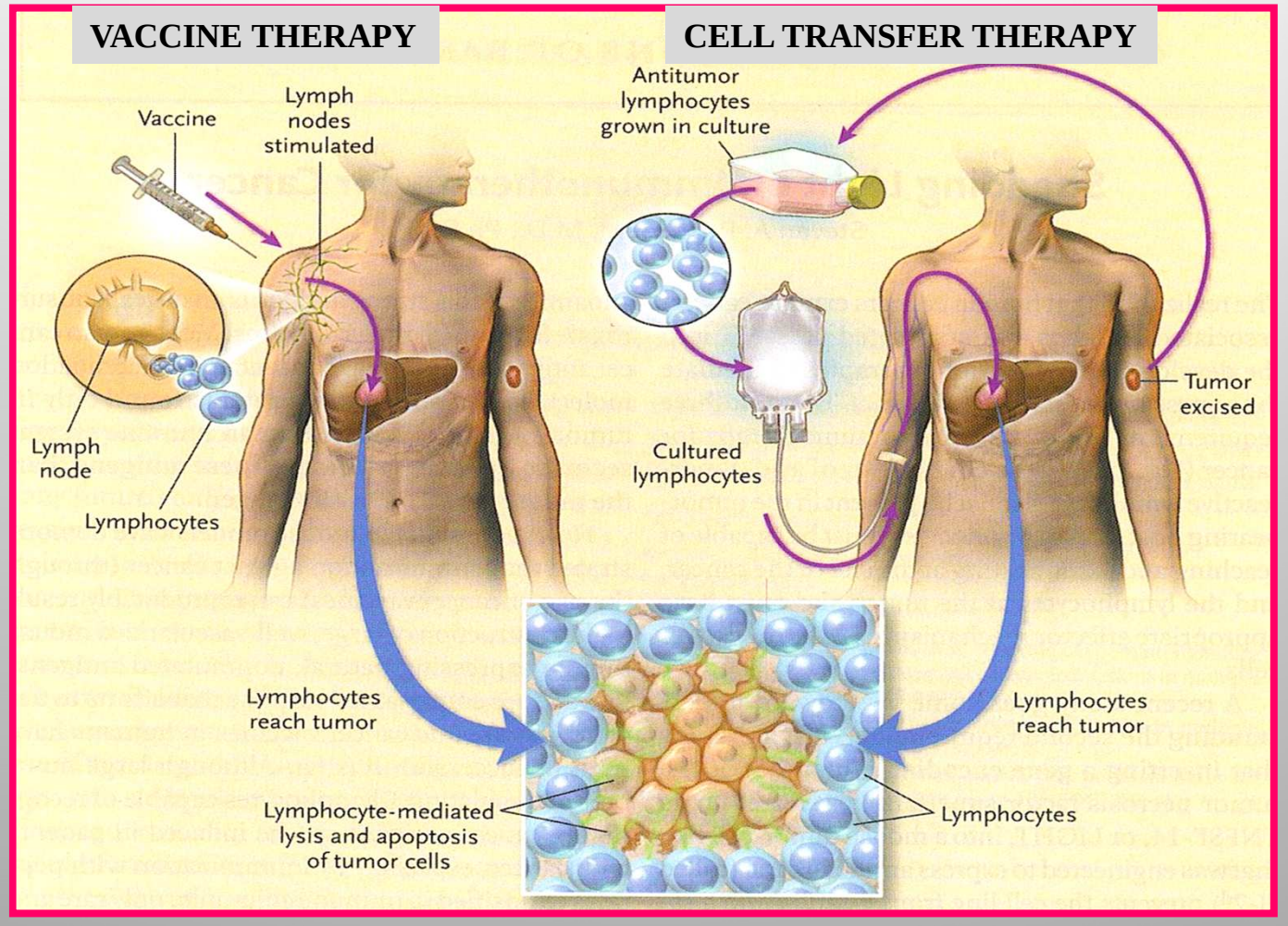
- **German Dendritic Cell Study Group: Prospective, randomized phase III clinical trial of autologous peptide-pulsed DC-based vaccine in patients with stage IV melanoma compared to standard chemotherapy with DTIC alone**

  Response Rates

  - **DC vaccine group = 3.8% TTP=2.8 OS=9 months**
  - **DTIC alone = 5.5% TTP=3.2 OS=11 months**

- **No statistically significant differences noted in response, toxicity, overall and progression-free survival between groups**

TWO MAIN APPROACHES TO TUMOR IMMUNOTHERAPY



THREE PRINCIPLES OF EFFECTIVE TREATMENT:

1. There must be a sufficient number of lymphocytes that recognize the tumor
2. These lymphocytes must reach the tumor
3. Once there, they must be able to destroy established tumor

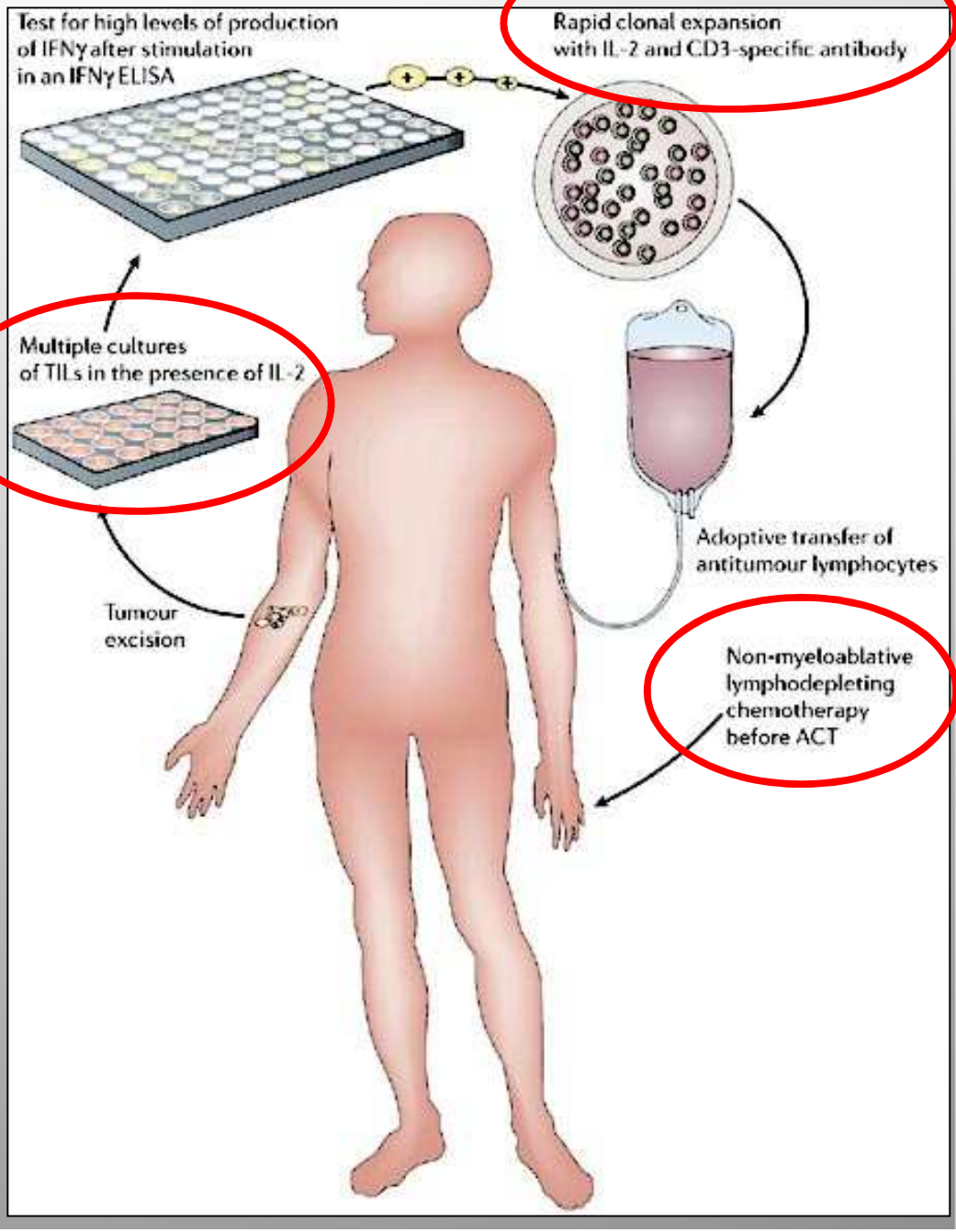
Concept of Adoptive Immunotherapy

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]*

We report here the adoptive transfer, to patients with metastatic melanoma, of highly selected tumor-reactive T cells directed against overexpressed self-derived differentiation antigens after a nonmyeloablative conditioning regimen. This approach resulted in the persistent clonal repopulation of T cells in those cancer patients, with the transferred cells proliferating in vivo, displaying functional activity, and trafficking to tumor sites. This led to regression of the patients' metastatic melanoma as well as to the onset of autoimmune melanocyte destruction. This approach presents new possibilities for the treatment of patients with cancer as well as patients with human immunodeficiency virus–related acquired immunodeficiency syndrome and other infectious diseases.

25 October 2002, Volume 298
SCIENCE



Patient	Age/sex	Treatment* Cells infused† ($x10^{-10}$)	CD4/CD8 phenotype‡ (%)	Antigen specificity§	IL-2 (doses)	Sites of evaluable metastases	Response duration‖ (months)	Auto-immunity
1	18/M	2.3	11/39	Other	9	lymph nodes (axillary, mesenteric, pelvic)	PR (21+)	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 (12+)	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 (8+)	Vitiligo
10	55/M	10.7	96/2	MART-1	12	lymph nodes, cutaneous, subcutaneous	CR (7+)	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

Cancer regression in patients with metastatic melanoma after the transfer of autologous anti-tumor lymphocytes. Rosenberg SA, Dudley ME, *Proc Natl Acad Sci., September 20th , 2004*

- **Autologous cell transfer after lymphodepleting chemotherapy**
- ***Eighteen of 35 patients (51.4%)* treated with tumor-reactive lymphocyte cultures with objective clinical response (>50% reduction in tumor)**
- **4 complete responders (11.4%)**
- **Tumor regression was accompanied by a large *in vivo* expansion of the administered anti-tumor lymphocytes (ATL)**
- **ATL persisted in peripheral blood at >70% of total lymphocytes for many months after transfer**
- **ATL consisted of heterogeneous lymphocyte populations with high avidity for tumor antigens, derived from tumor-infiltrating lymphocytes**

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

A

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

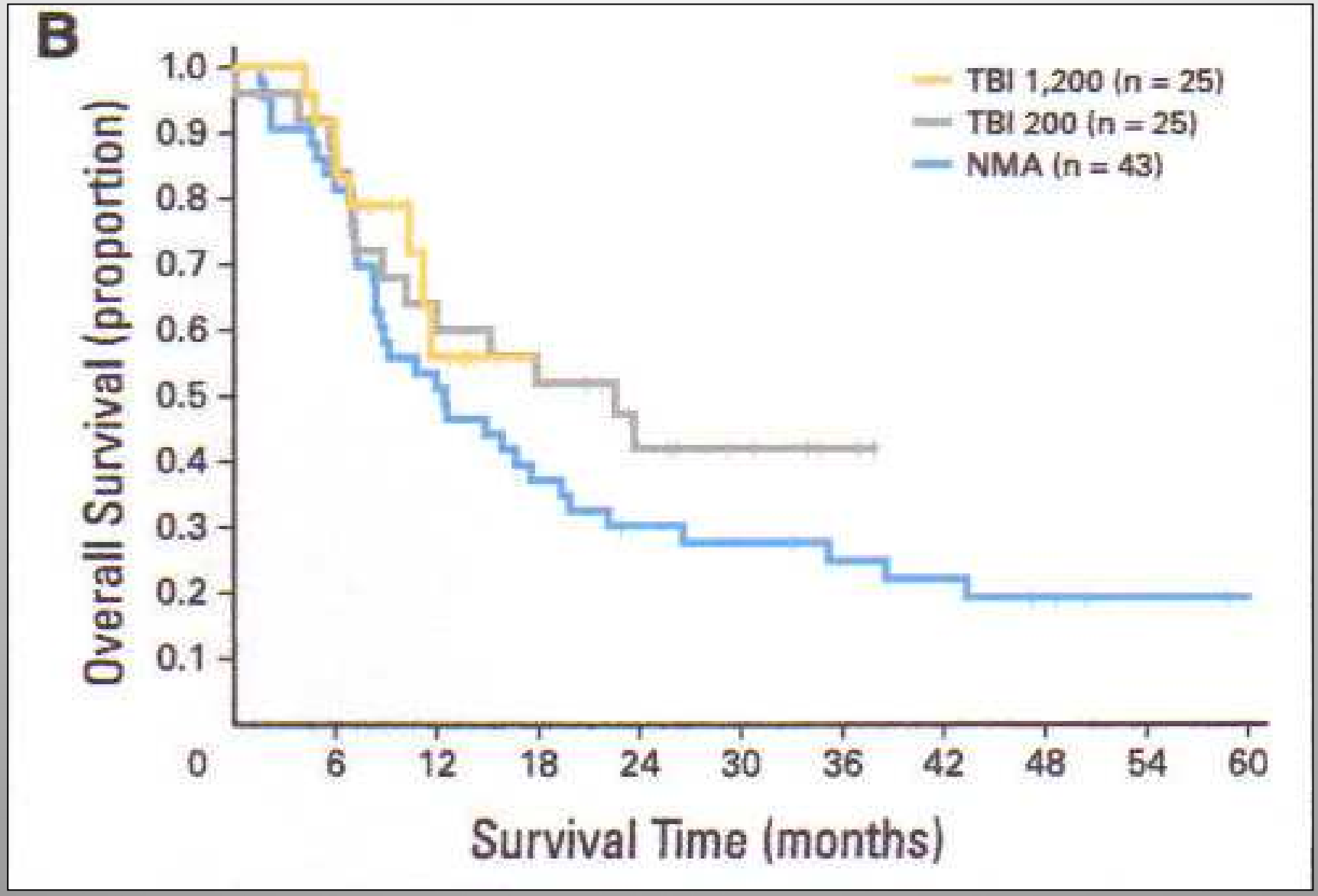
XRT

Overall Response Rate

49%

52%

72 %


B
Overall Survival (proportion)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
6
12
18
24
30
36
42
48
54
60
Survival Time (months)
TBI 1,200 (n = 25)
TBI 200 (n = 25)
NMA (n = 43)

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

NOTE. All patients received cyclophosphamide 60 mg/kg × 2 days + fludarabine 25 mg/m^2 × 5 day
Abbreviations: TBI, total-body irradiation; PR, partial response; CR, complete response; OR, objective

esponse; TIL, tumor-infiltrating lymphocytes.

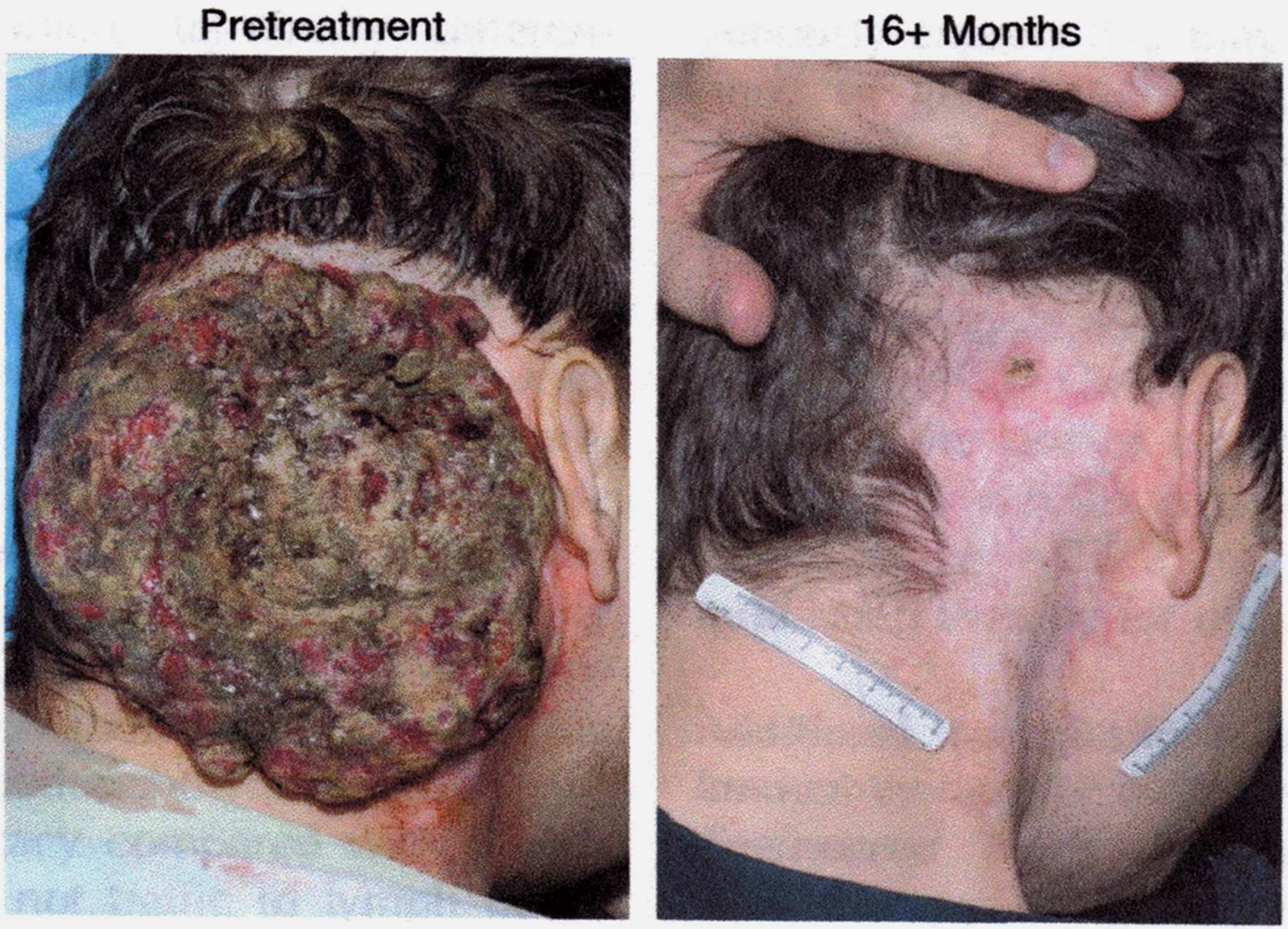


Figure 3. Response of a melanoma tumor to a lymphodepleting chemotherapy regimen combined with adoptive transfer of tumor-infiltrating T cells (Dudley *et al.*, 2002a). (photo courtesy of Dr Steven A. Rosenberg, Surgery Branch, NCI).

In Conclusion

- **The immunotherapy of cancer has dramatically changed the way we treat cancer patients today**
- **There is proof of principle that our own immune systems can become specifically activated to attack and destroy cancer cells**
- **The bodies immune system is powerful, against cancer, when properly activated**
- **There will certainly be more advances in the near future, with improved treatment options that are based upon activating our immune systems**


Thank you
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