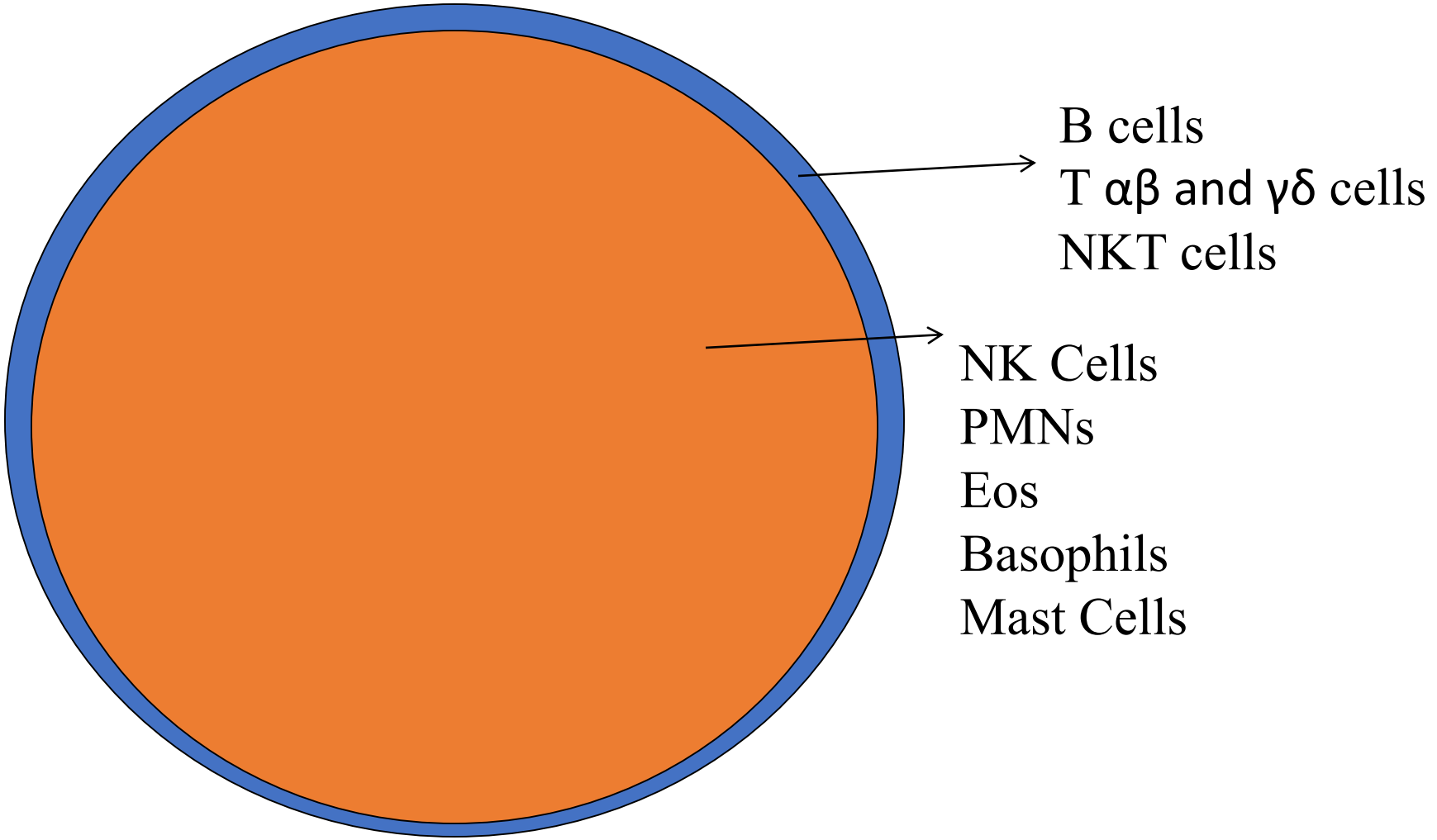
Innate Core and Adaptive Shell

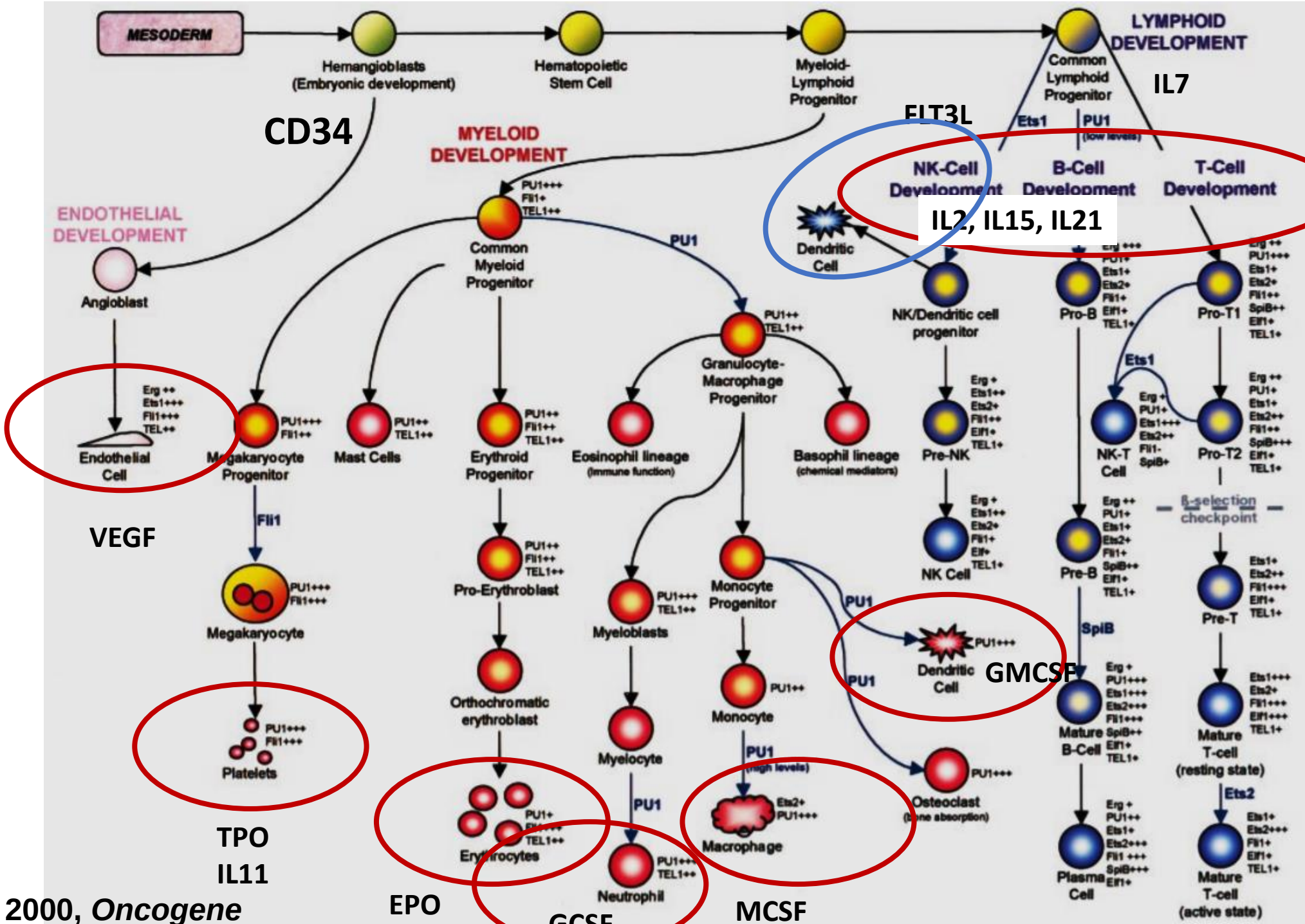
4:15-5:15pm Breakout Sessions 2
Topic D – Cytokine-based immunotherapies and other molecular bispecifics, other immunotherapies
Michael T. Lotze, MD—*University of Pittsburgh*

- TNF and IL-1/FGF Family Members (Leaderless cytokines)
- The Interferons, IL-10 Family
- IL-2 Family Members
- IL-12 Family Members
- Pegylated or Muteinized Cytokines
- Anti-cytokines (TNF, IL-17, etc.)
- Cytokine-antibody conjugates

Innate Core and Adaptive Shell

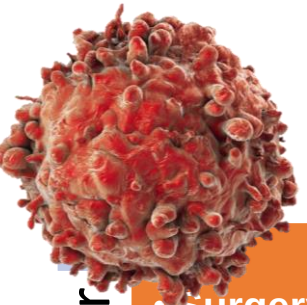


Endothelial Myeloid, Lymphoid Cell Develop-ment



Maroulakou & Bowe © 2000, *Oncogene*

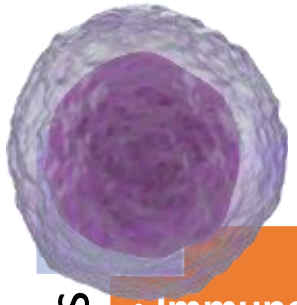
Foundations of Cancer Therapy (WuXing Again)



Tumor

- Surgery
- Chemotherapy
- Radiation

- Other Targets:
- Signal Transduction
- Autophagy
- Oncogenes
- Tumor Suppressor Genes

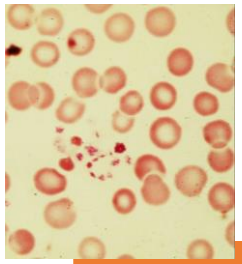


T Cells

- Immune Stimulants
- Checkpoint Inhibition
- Adoptive Cell Therapy (CARs, TIL)
- DC Vaccines
- Oncolytic Viruses

Endothelium

- Anti-VEGF
- Chloroquine
- Platelet Derived Growth Factor (PDGF)
- Fibroblast Growth Factor (FGF)
- TKI's (Sorafenib, Sunitinib, Axitinib, Pazopanib)



Platelets and RBC

- Erythropoietin
- Thrombopoietin
- Interleukin 11
- Red Cell Infusions

- Platelet Derived Growth Factor (PDGF)

Bispecific antibodies in cancer immunotherapy

Eva Dahlén, Niina Veitonmäki and Per Norlén

Therapeutic Advances in Vaccines and Immunotherapy

2018, Vol. 6(1) 3–17

DOI: 10.1177/2515135518763280

Class	Description	Targets	Examples	Stage*
T-cell redirectors	Redirects T cells to malignant cells by targeting a tumor antigen and CD3	CD19 × CD3	Blinatumomab	Market
		EpCAM × CD3	Catumaxomab	Marketed (withdrawn)
		CD20 × CD3	XmAb13676 BTCT4465A RO7082859	I
		CD123 × CD3	MGD006 JNJ-63709178 Xmab14045	I
		BCMA × CD3	JNJ-64007957 BI 836909	I
		B7H3 × CD3	MGD009	I
		CEA × CD3	RO6958688 MT111	I
		PSMA × CD3	Pasotuximab ES414/MOR209	I
NK-cell redirectors	Redirects NK cells to malignant cells by targeting a tumor antigen and CD16A	CD30 × CD16A	AFM13	II
		EGFR × CD16A	AFM24	PC
		BCMA × CD16A	AFM26	PC
Tumor-targeted immunomodulators	Directs potent costimulation to the tumor-infiltrating immune cells by targeting a tumor antigen and costimulatory molecules such as CD40 or 4-1BB	TA × CD40	ABBV-428	I
		HER2 × 4-1BB	PRS343	I
		FAP × 4-1BB	4-1BB agonist	PC
		5T4 × 4-1BB	ALG.APV-527	PC
Dual immunomodulators	Simultaneous targeting of two immunomodulating targets, resulting in blockade of inhibitory targets, depletion of suppressive cells or activation of effector cells	PD-L1 × TGF-β	M7824	I
		PD-1 × LAG-3	MGD013	I
			FS118	PC
		PD-1 × TIM-3	MCLA-134	PC
		PD-1 × CTLA-4	XmAb20717	PC
		CTLA-4 × OX40	ATOR-1015	PC

Macrophages

CD40 Agonists Alter Tumor Stroma and Show Efficacy Against Pancreatic Carcinoma in Mice and Humans

Gregory L. Beatty, *et al.*
Science **331**, 1612 (2011);
DOI: 10.1126/science.1198443

Gregory L. Beatty,[1,2,6] Elena G. Chiorean,[3] Matthew P. Fishman,[1] Babak Saboury,[5] Ursina R. Teitelbaum,[2,6] Weijing Sun,[2,6] Richard D. Huhn,[4] Wenru Song,[4] Dongguang Li,[4] Leslie L. Sharp,[4] Drew A. Torigian,[2,5] Peter J. O'Dwyer,[2,6] Robert H. Vonderheide[1,2,6]*

[1]Abramson Family Cancer Research Institute, University of Pennsylvania School of Medicine, 421 Curie Boulevard, Philadelphia, PA 19104, USA. [2]Abramson Cancer Center, University of Pennsylvania School of Medicine, Philadelphia, PA 19104, USA. [3]Division of Hematology/Oncology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN 46202, USA. [4]Pfizer Corporation, New London, CT 06320, USA. [5]Department of Radiology, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA 19104, USA. [6]Division of Hematology-Oncology, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA 19104, USA.

*To whom correspondence should be addressed. E-mail: rhv@exchange.upenn.edu

Fig. 1. Agonist CD40 mAb in combination with gemcitabine induces clinical responses in patients with surgically incurable PDA.

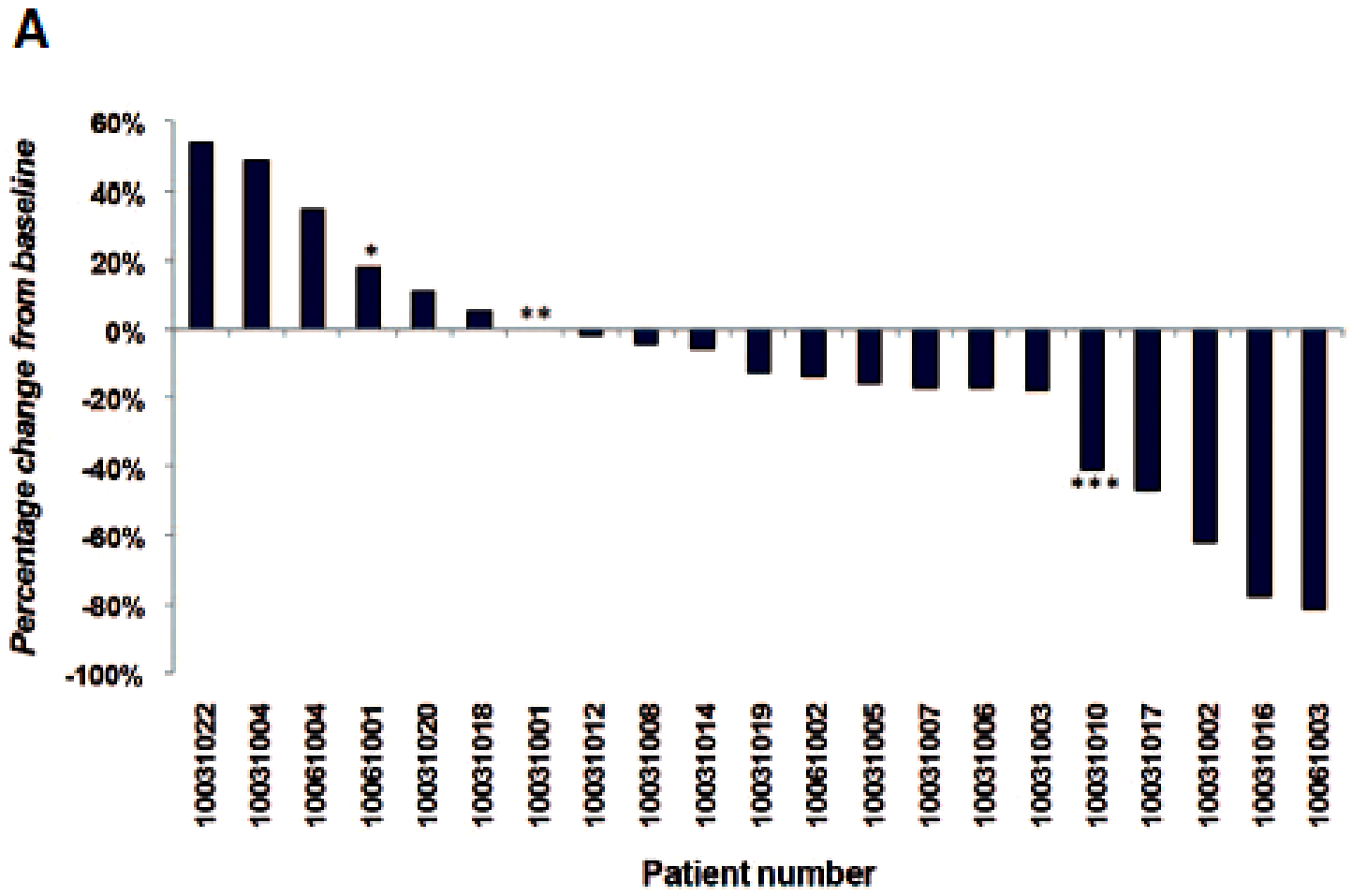
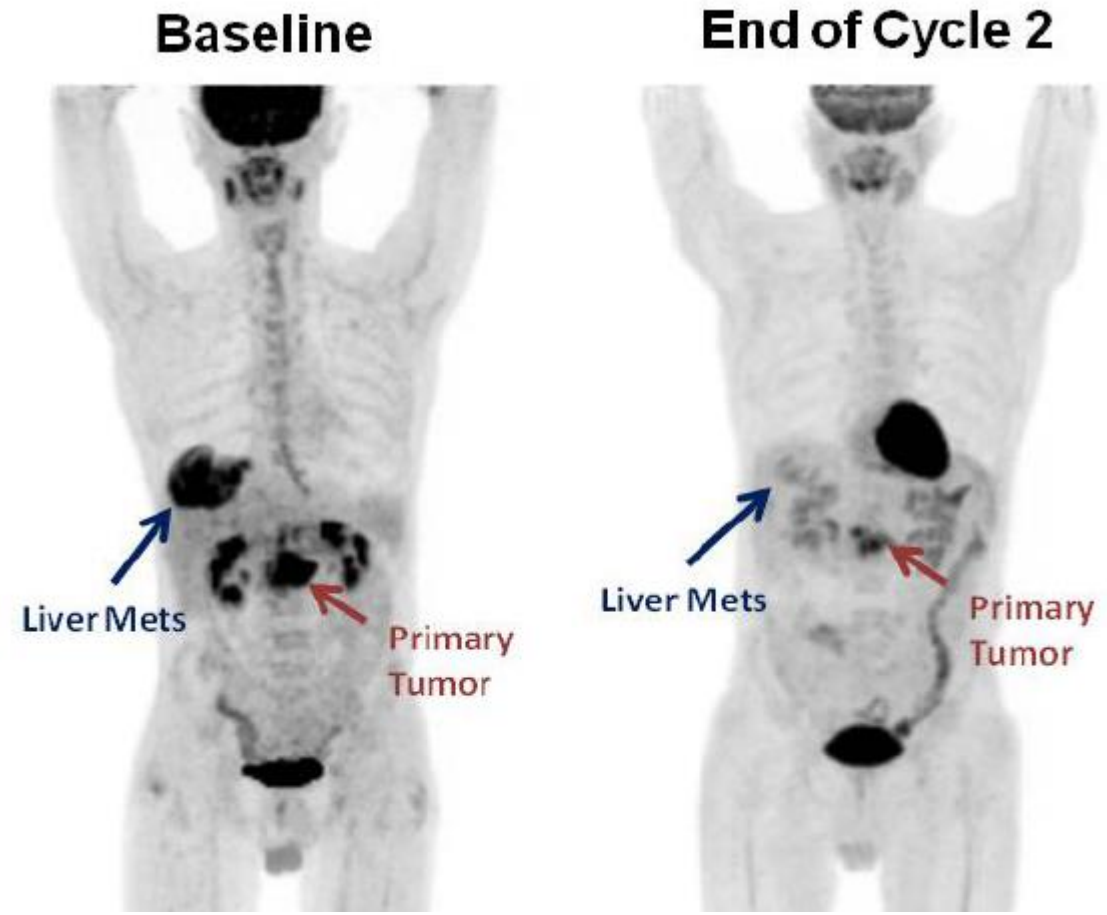


Figure S3. Metabolic tumor response to treatment



doi:10.1038/nature04808

nature

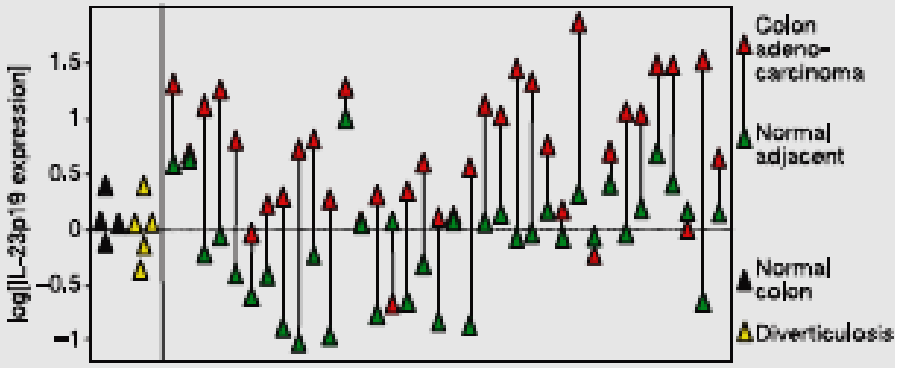
May 2006

IL23

LETTERS

IL-23 promotes tumour incidence and growth

John L. Langowski[1]*, Xueqing Zhang[1]*, Lingling Wu[1], Jeanine D. Mattson[1], Taiying Chen[1], Kathy Smith[1], Beth Basham[1], Terrill McClanahan[1], Robert A. Kastelein[1] & Martin Oft[1]



b

Cancer type	Number of paired (tumour and normal) samples	Fold increase in expression: Average	Number >5×	Number >10×	P
Colon	36	15,33	23	17	0,0001
Ovarian	32	9,45	12	4	0,0001
Head and neck	44	3,41	11	4	0,01
Lung	114	3,03	20	8	0,0001
Breast	78	2,86	16	6	0,0001
Stomach	64	2,13	9	3	0,001
Melanoma	89	1,47	5	0	0,0001

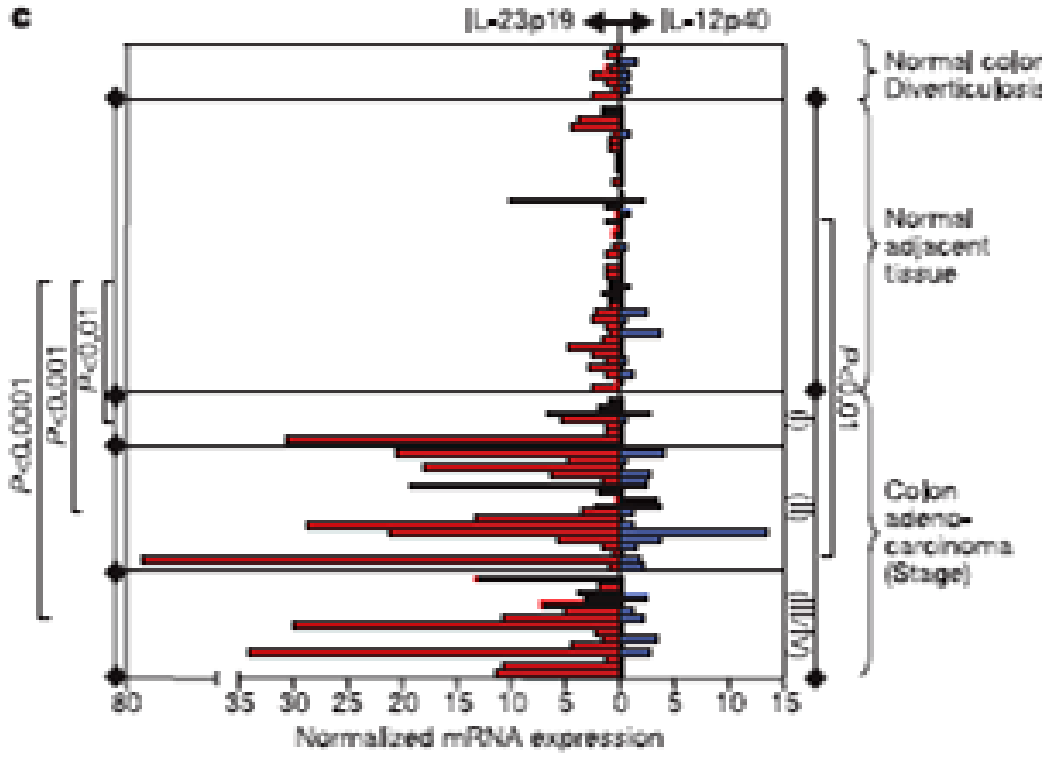


Figure 1 | Overexpression of IL-23 but not of IL-12 in human cancer.

Role of Cytokines in Promoting Cancer (Dranoff Review)

Cytokine	Cellular sources	Role in tumour formation
Il-1	Macrophages, dendritic cells, B cells, natural killer cells, keratinocytes	Required for tumour invasion and angiogenesis
Il-6	Macrophages, T cells, B cells, endothelial cells, fibroblasts	Required for chemically induced lymphoma
Il-12	Macrophages, dendritic cells, neutrophils	Inhibits chemical carcinogenesis
Il-15	Macrophages, dendritic cells	Promotes natural killer T cell leukaemias
Ifn-γ	Natural killer cells, natural killer T cells, T cells, B cells, macrophages, dendritic cells	Inhibits chemical carcinogenesis; inhibits lymphomas (especially with perforin); Stat1 and Rag2 inhibit carcinomas
M-csf	Macrophages, endothelial cells, fibroblasts, bone-marrow stroma	Promotes breast cancer invasion
Gm-csf	Respiratory epithelial cells, T cells, natural killer cells, natural killer T cells, macrophages, eosinophils, endothelial cells, fibroblasts	Inhibits lymphomas and carcinomas (with Ifn-γ and Il-3)
Tnf-α	Macrophages, natural killer cells, B cells, T cells, neutrophils, fibroblasts, keratinocytes	Required for chemically-induced skin cance
Mif	Macrophages, T cells, eosinophils, fibroblasts, keratinocytes, pituitary	Inhibits p53 tumour-suppressor functions
Tgf-β	T cells, B cells, macrophages, platelets, bone-marrow stroma, eye, testis	Inhibits colon carcinomas (with Rag2)
Fas–Fas ligand	B cells, T cells, hepatocytes, colon, ovary, respiratory epithelial cells	Inhibits lymphomagenesis

Clinical Administration of Cytokines (Dranoff)

Cytokine	Therapeutic actions	Clinical administration
IL-2	Enhances NK cell and $CD8^+$ T-cell function; increases vascular permeability	Systemic, local
IL-3	Enhances tumour antigen presentation	Systemic
IL-4	Enhances eosinophil function and T-cell activation	Systemic, local
IL-6	Enhances T-cell and B-cell function; inhibition of IL-6 reduces lymphoproliferation	Systemic, local
IL-7	Enhances T-cell function	Local
IL-10	Inhibits tumour antigen presentation	Pending
IL-12	Enhances T_H1 immunity and cytotoxicity; inhibits angiogenesis	Systemic, local
IL-13	Inhibits cytotoxicity against viral neoplasms	Pending
IL-15	Enhances cytotoxicity	Pending
IL-18	Enhances T_H1 immunity and cytotoxicity; inhibits angiogenesis	Pending
M-CSF	Enhances macrophage function	Systemic
GM-CSF	Enhances tumour antigen presentation	Systemic, local
IFN-α	Enhances tumour antigen presentation and cytotoxicity	Systemic
IFN-γ	Enhances tumour antigen presentation and cytotoxicity	Systemic, local
TNF-α	Induces tumour-cell apoptosis; activates endothelium and granulocytes	Systemic
TRAIL	Induces tumour-cell apoptosis	Pending
FLT3 ligand	Stimulates dendritic-cell and NK-cell function	Systemic
Lymphotactin	Enhances T-cell recruitment	Local
TGF-β	Inhibits T-cell effector function	Pending

JOURNAL OF INTERFERON & CYTOKINE RESEARCH
Volume 39, Number 1, 2019

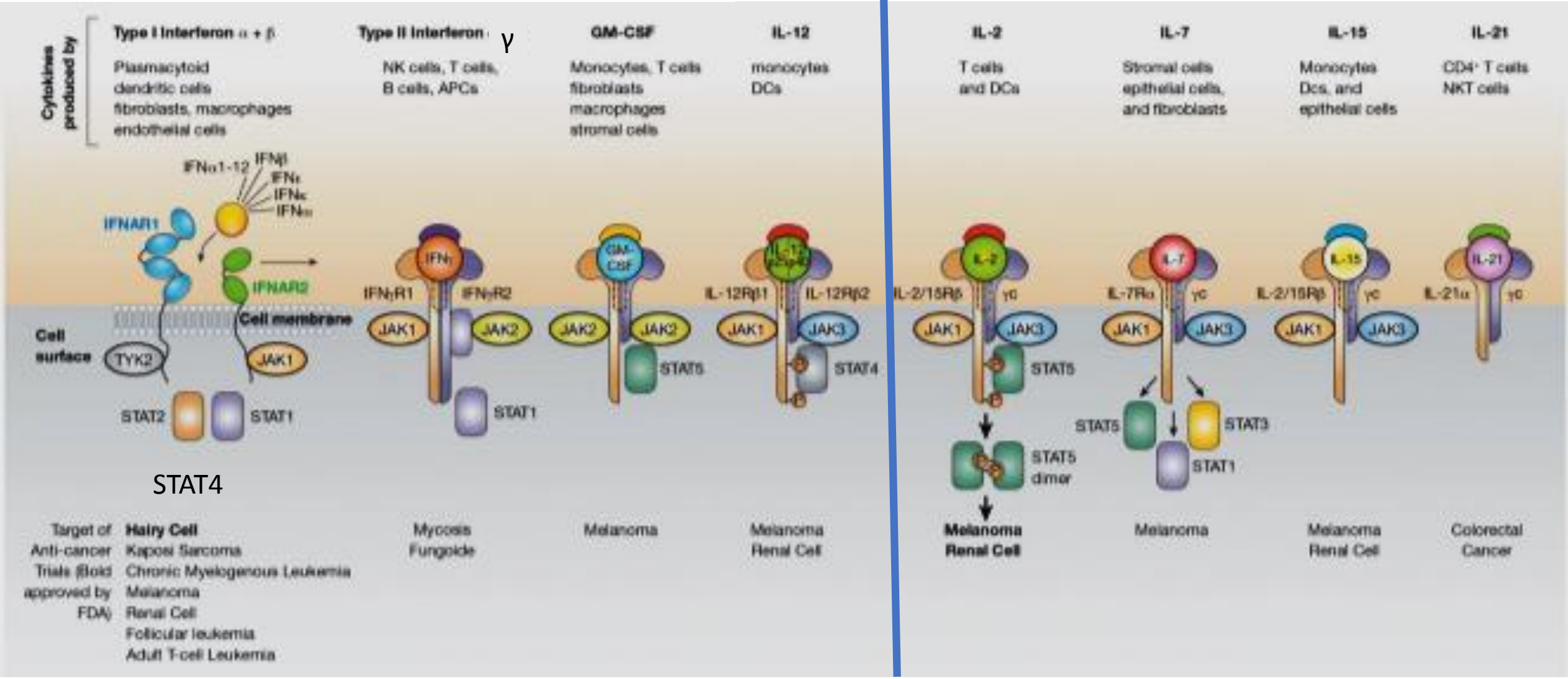
DOI: 10.1089/jir.2018.0019

Cytokines in the Treatment of Cancer

Kevin C. Conlon, Milos D. Miljkovic, and Thomas A. Waldmann

IL23
IL27
IL35

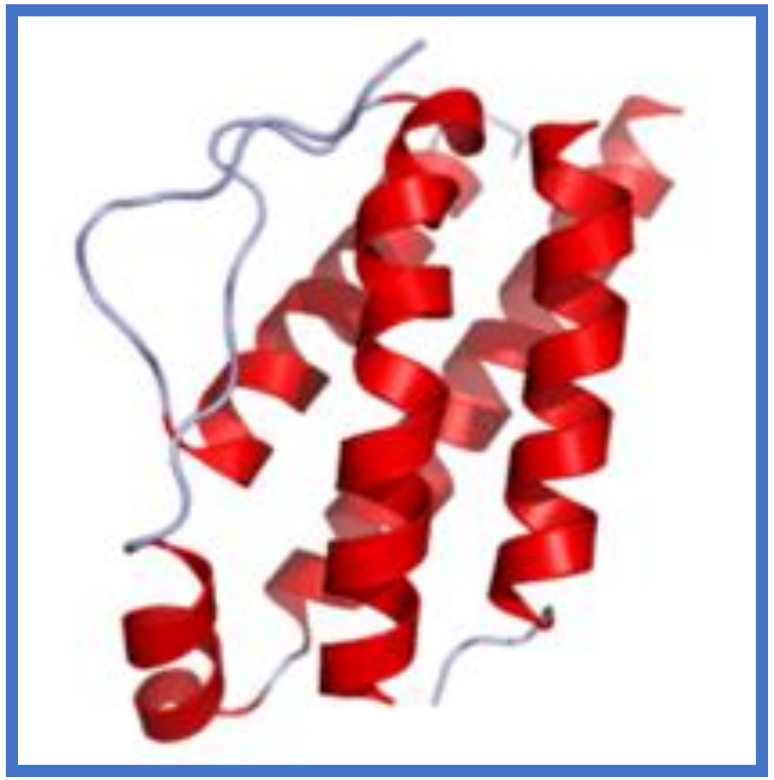
And IL-4 and IL-9 (mast cells)



STAT4

Cytokines IFNα, IL-1, IL-2, IL-4, IL-7, IL-10, IL-12, IL-15, IL-18, IL-21, IL-24….IL-41

- IL-2 Discovered in 1976 and described as a protein that stimulated growth of T cells[1]
- Jurkat IL-2 in 1983 [Lotze]
- Recombinant IL-2 first cloned in 1983[1]
- First phase I studies of rIL-2 in malignant disease in 1984[2]
- Phase II clinical trials began in 1985[3]



1. Atkins MB, Lotze MT et al. *J Clin Oncol*. 1999:17;2105-2116.
2. Lotze MT et al *J Immunol.* 1985;134:157-166
3. Atkins MB et al. *J Clin Oncol.* 1986;4:1380-1391

The Beginning of Molecular Therapeutics - 1978

PEOPLE.COM • ARCHIVE

Will Interferon Kill Cancer? Finnish Dr. Kari Cantell Is Helping the World Find Out

But Cantell and the Finnish Red Cross, now producing 250 billion units (5,285 quarts) a year, have provided the great bulk of pure interferon used for clinical studies on humans, including a $2 million batch bought last year by the American Cancer Society. “Production is the bottleneck,” says Cantell, who finds it “stupid and irritating” that until recently nobody else has tried to produce the substance in large-scale volume.

E1684, E1690, and E1694: Durable and significant Impact upon relapse-free * and

Meta-anal S impact

Kirkwood. *Clin Cancer Res*. 2004;10:1670; Wheatley, Ives et al., 2007, 2008

Interferon Alpha

- IFNa and Peginterferon alpha 2b are approved as adjuvant treatment for patients with completely resected stage III or IV high-risk melanoma
- Adjuvant in Melanoma (Kirkwood/ECOG); On February 15, 2019, the Food and Drug Administration approved pembrolizumab (KEYTRUDA, Merck) for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection.
- First-line treatment for patients with mRCC (alfa-2a, and alfa-2b in combination with bevacizumab),
- AIDS-related Kaposi's sarcoma (alfa-2b), follicular lymphoma (alfa-2b), HCL (alfa-2a, alfa-2b), chronic myelogenous leukemia (Philadelphia chromosome-positive alfa-2a),
- Condyloma acuminata (alfa-2b), and cervical intraperitoneal neoplasms (alfa-2b) (Gutterman and others 1980; Kirkwood and Ernstoff 1984; Windbichler and others 2000).
- Pegylated for Hepatitis
- Hairy cell leukemia

Interferon-gamma (IFN-γ)

- Only type II IFN
- Produced mainly by NK cells and T lymphocytes
- Works primarily as an immunomodulator
  - 100-10K x more active than Type I interferons
- Functions
  - Regulate MHC expression
  - Activates differentiation and function of phagocytes
  - Augments interactions between macrophages and T-cells
  - Key role in regulating T-cell subsets to determine the type of immune effector function during a specific immune response

Farrar, Schreiber. *Annu. Rev. Immunol*. 1993

INTERFERON GAMMA-1b

MARTIN E. GLEAVE,

Final results of the EORTC 18871/DKG 80-1 randomised phase III

observation after surgery in melanoma

LAURENCE H. KLOTZ,

FAILED!!!!!

Role of Recom

Phase Rand

EORTC (30885) randomised phase III study

alpha and recombinant interferon alpha and gamma in

advanced renal cell carcinoma

Maintenance in

ell Lung Cancer. A

the EORTC Lung Cancer

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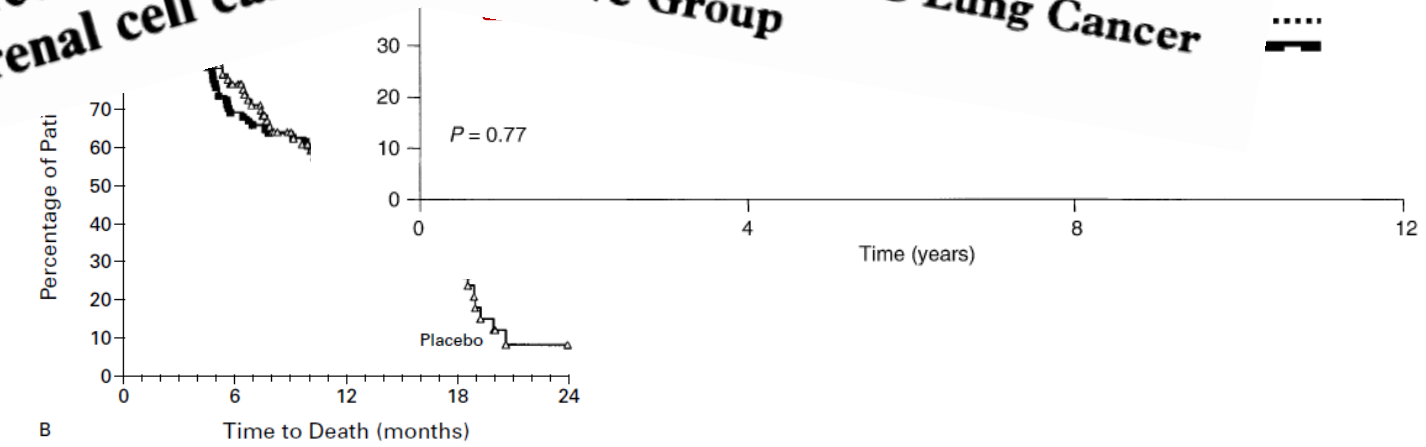
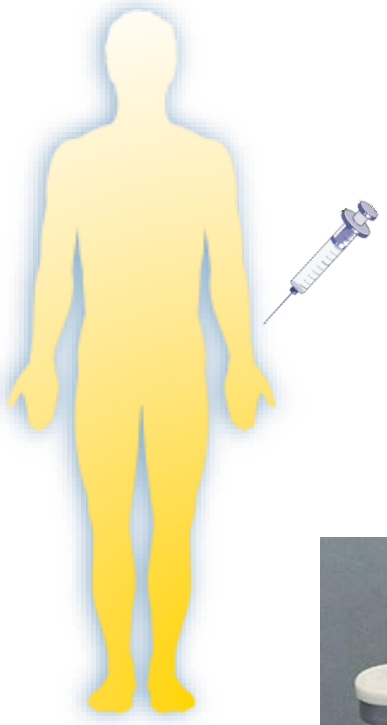
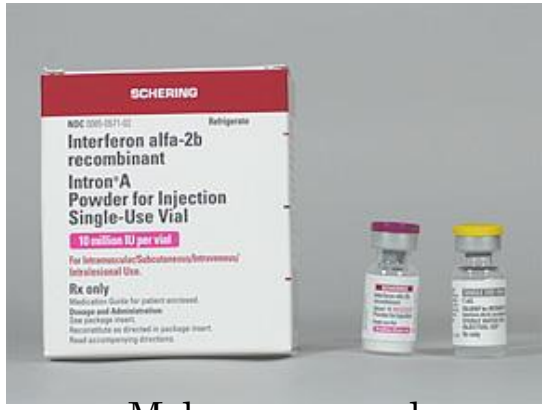


Systemic Injection Of Cytokines For Tumor Therapy

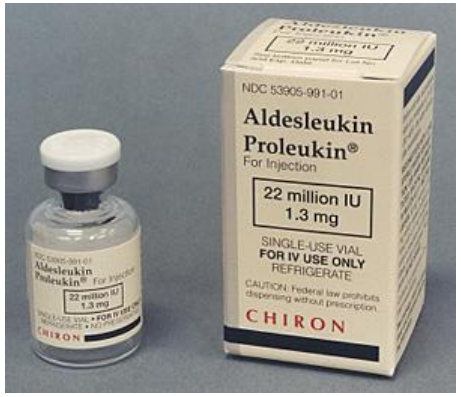
Melanoma





Melanoma, renal cancer

Bone marrow recovery



Kidney cancer

Classes of Molecules That Initiate The Innate Immune Response – Signal 0

Pathogen-associated Molecular Patterns (PAMPs):

Molecules expressed or released by invading microorganisms that are structurally unique to the pathogen.

Ruslan Medzhitov, 2000

Damage-associated Molecular Patterns (DAMPs):

Molecules expressed or released that are normally unavailable to the immune system but are released and recognized by immune cells following tissue injury [Danger].

Polly Matzinger, 1995

DAMPs -Chronic Tumor Lysis Syndrome

Cell Constituents:

HMGB1 – Cytochrome C

Heat shock proteins

Uric Acid, ATP, Adenosine; CpG DNA

s100 proteins

Hepatoma derived growth factor

LDH

DNA

Acute Tumor Lysis Syndrome

Secreted molecules:

Fibrinogen domain A

Surfactant protein A

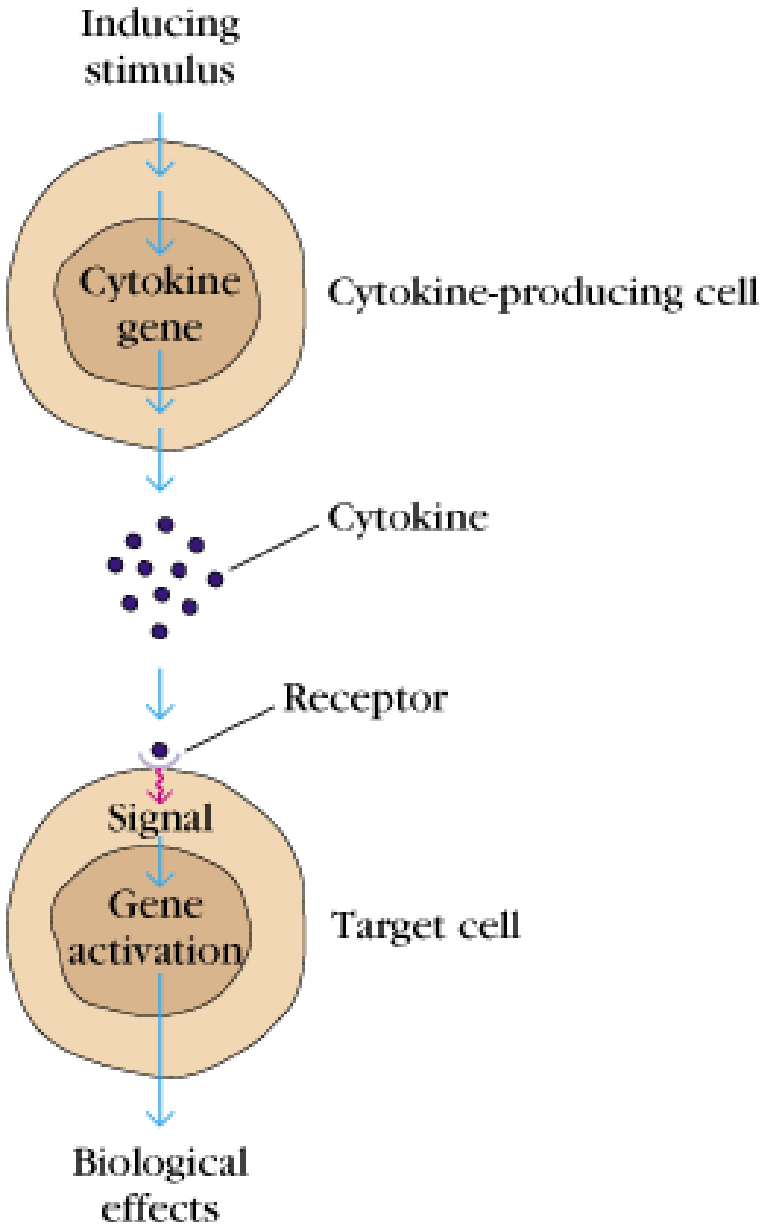
Matrix elements:

Heparan sulfate

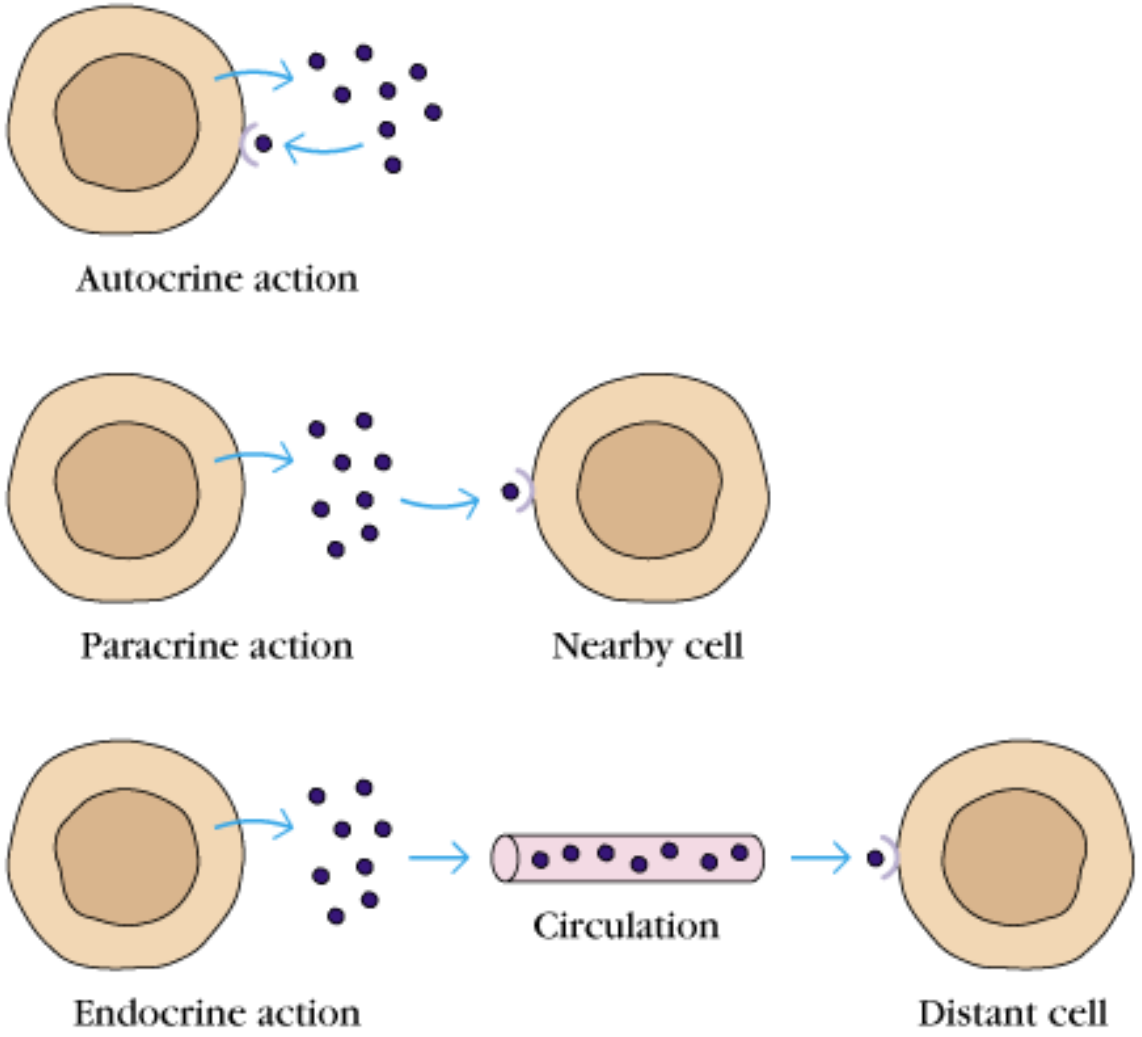
Soluble hyluranan

Fibronectin

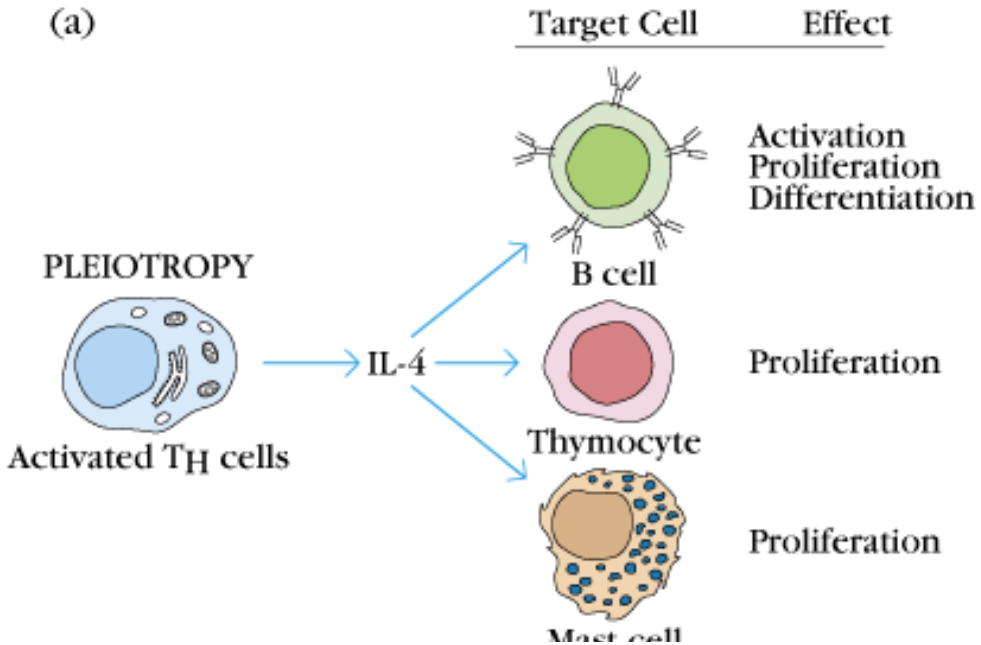
General properties of cytokines



General properties of cytokines



General Properties Of Cytokines



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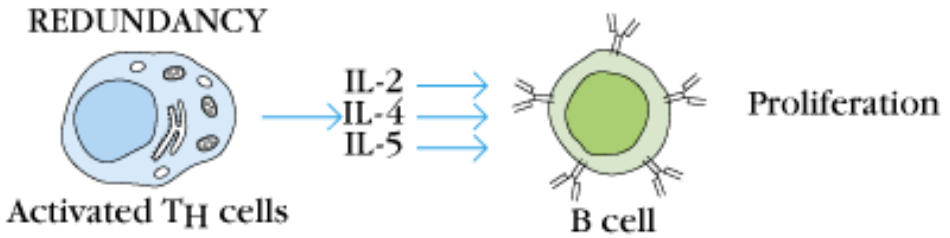
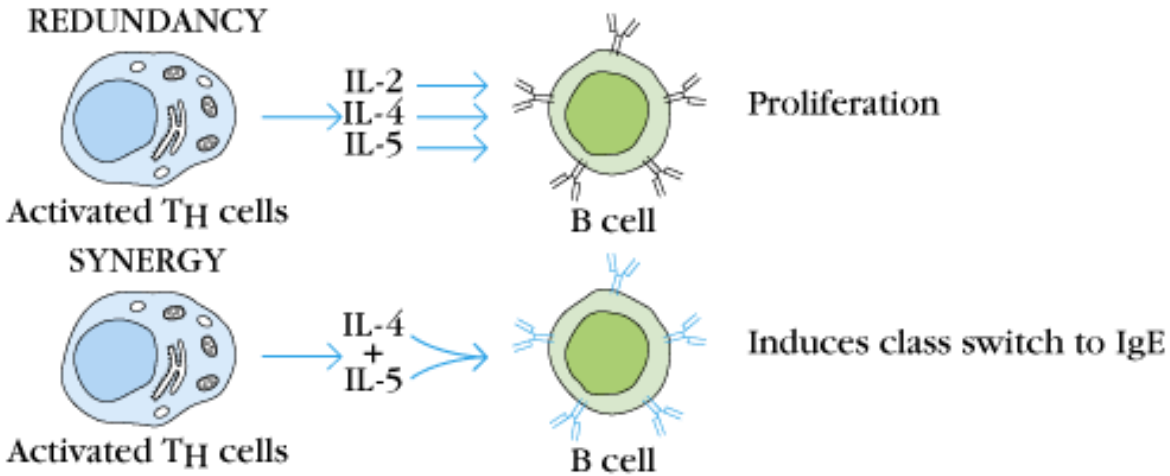
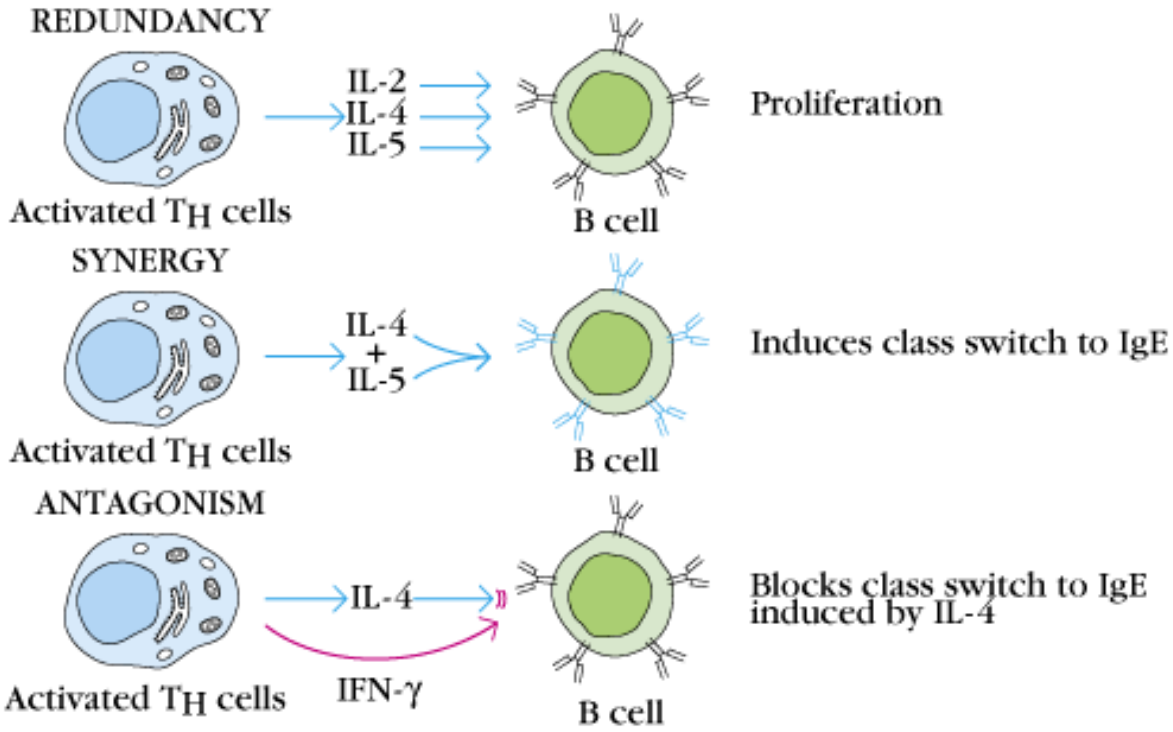


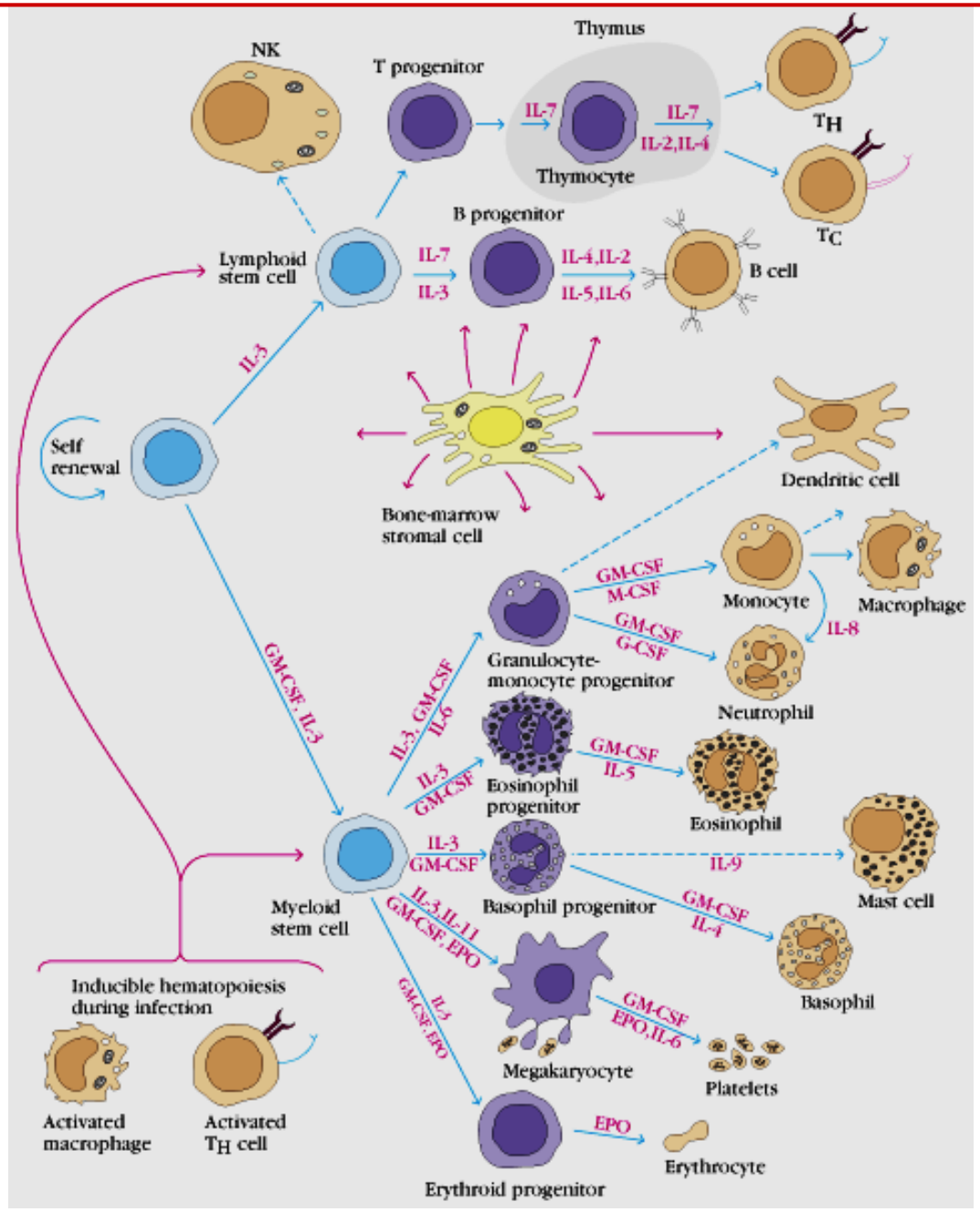
General properties of cytokines



General Properties Of Cytokines



Hematopoietic Cytokines



IL-3
IL-11
EPO
M-CSF
G-CSF
GM-CSF
IL-5
IL-9
IL-4
IL-12, IL-18
IL-24

Cytokines IFNα, IL-1, IL-2, IL-4, IL-7, IL-10, IL-12, IL-15, IL-18, IL-21, IL-24….IL-38

- IL-2 Discovered in 1976 and described as a protein that stimulated growth of T cells[1]
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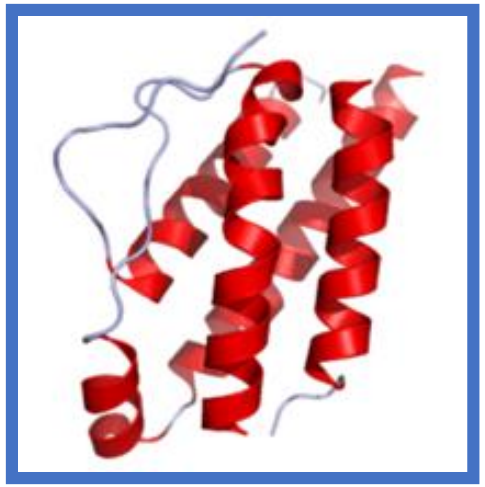

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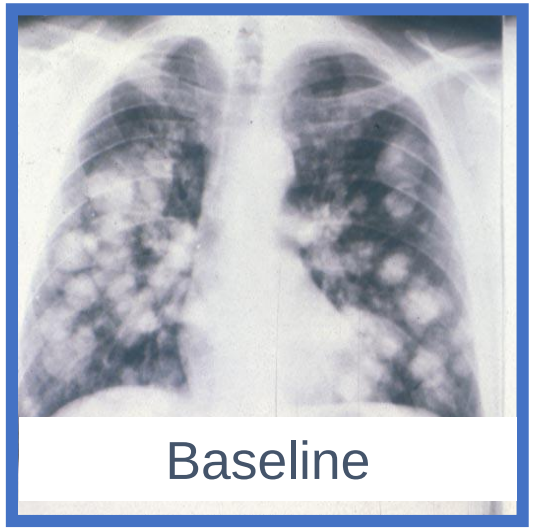
2. Lotze MT et al *J Immunol.* 1985;134:157-166
3. Atkins MB et al. *J Clin Oncol.* 1986;4:1380-1391

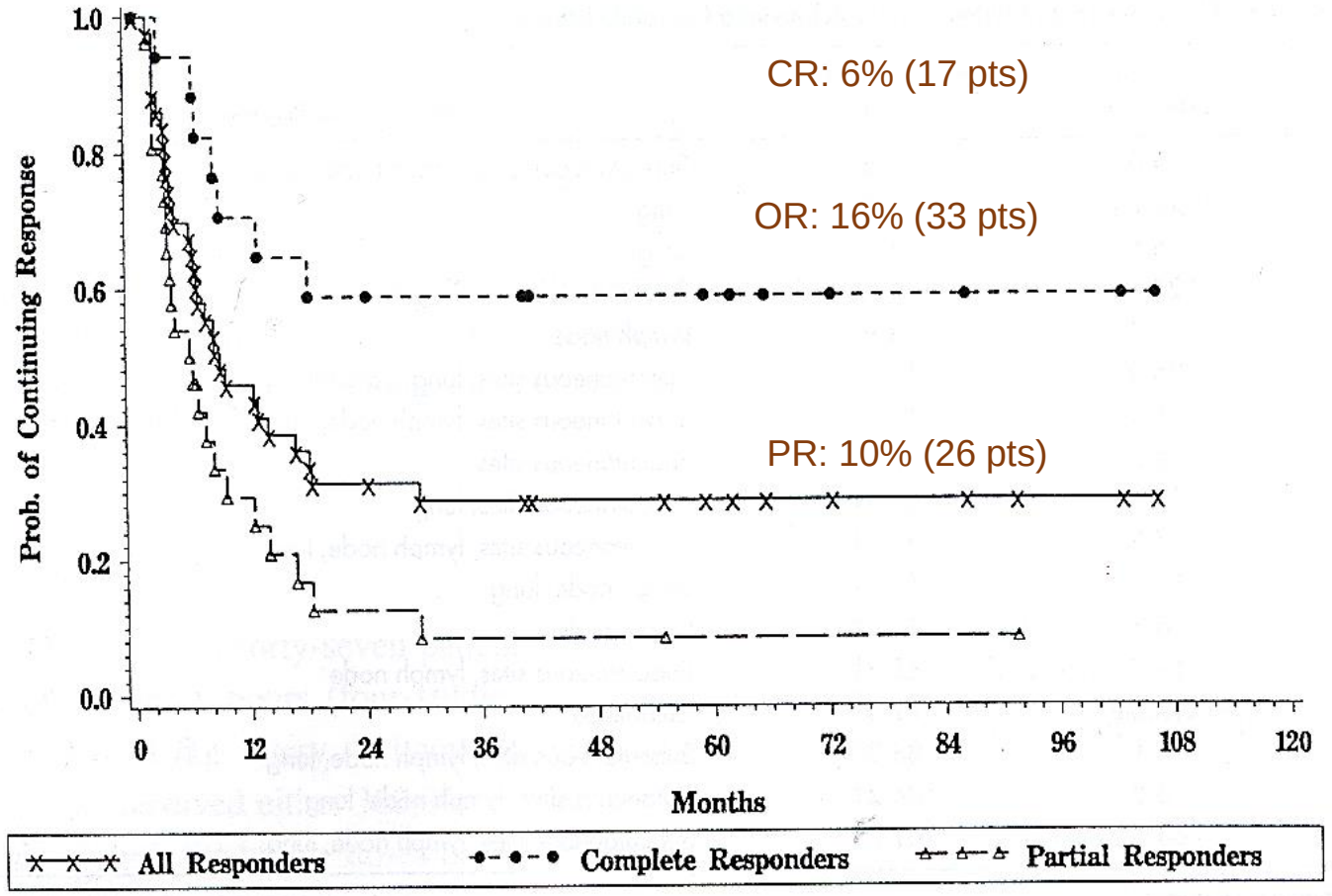
High Dose IL-2 Immunotherapy

- Approved in patients with melanoma and kidney cancer.
- Significant ‘toxicity’.
- Associated with ‘cytokine storm’.
- iNOS blockers, sTNF-R or IL-1Ra have yielded limited reduction in side effects.
- IL-2 treatment is associated with a ‘systemic autophagic syndrome’ and temporally limited tissue dysfunction.



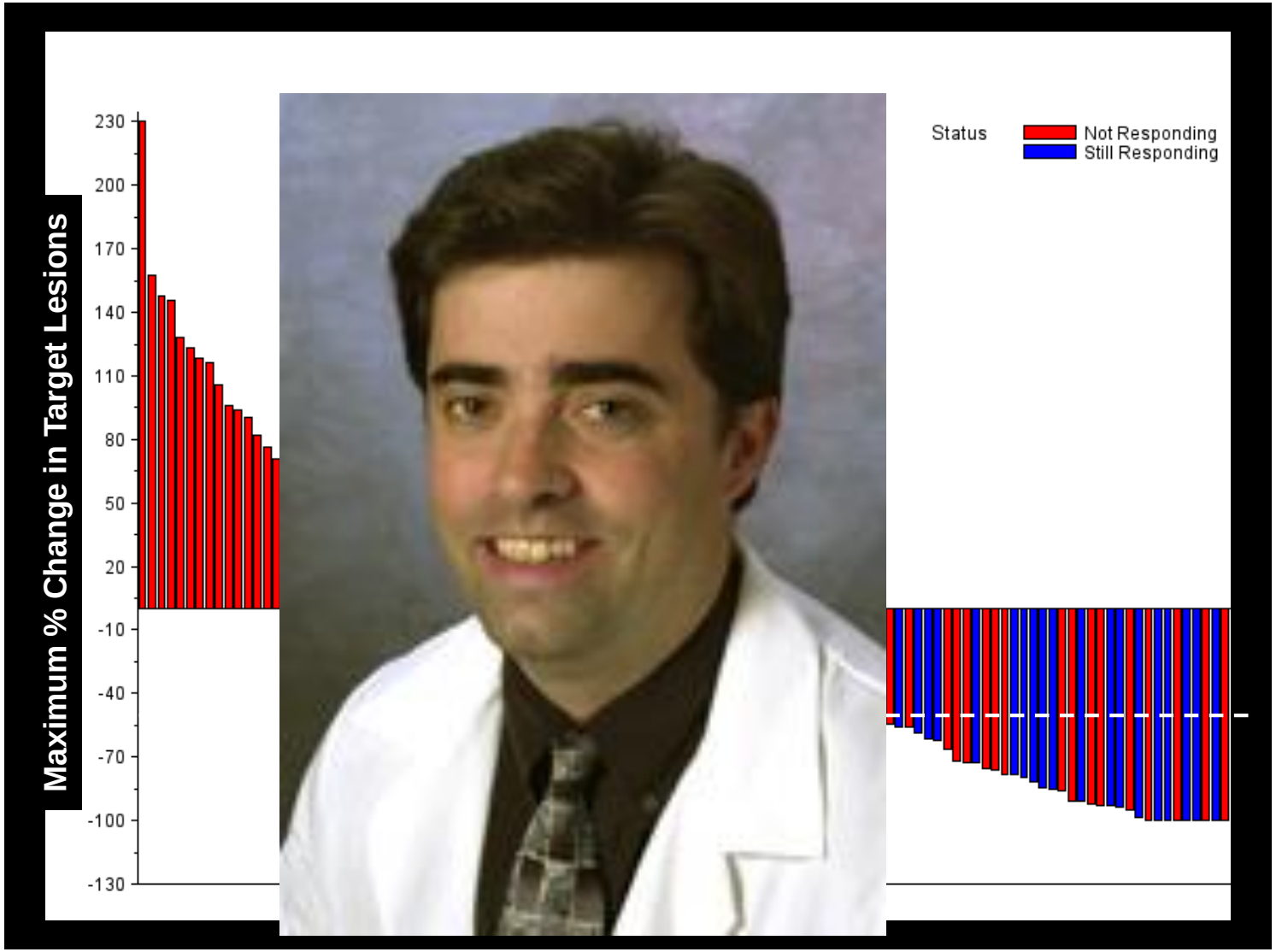
AR. Chavez, X Liang, MT Lotze.
Ann. N.Y.Acad.Sci.1182:14-27 (2009)

The Hallmark of IL-2 Therapy



Atkins MB, Lotze MT, et al. J Clin Oncol 1999

Renal Cancer Response Rate=25% (n=118)



May 27, 2010 — Two white-coated cancer researchers are among the luminaries picked for *TIME* magazine's 2010 list of the 100 most influential people in the world. Larry Kwak, MD, PhD, and Doug Schwartzentruber, MD, FACS, join Sarah Palin, James Cameron, Steve Jobs, & Lady Gaga on this year's "influentials" list.

Dr. Doug Schwartzentruber

Melanoma
gp100 2092M
+IL-2

BiovaxID
patient-specific
vaccine for
follicular
lymphoma

Dr. Larry Kwak

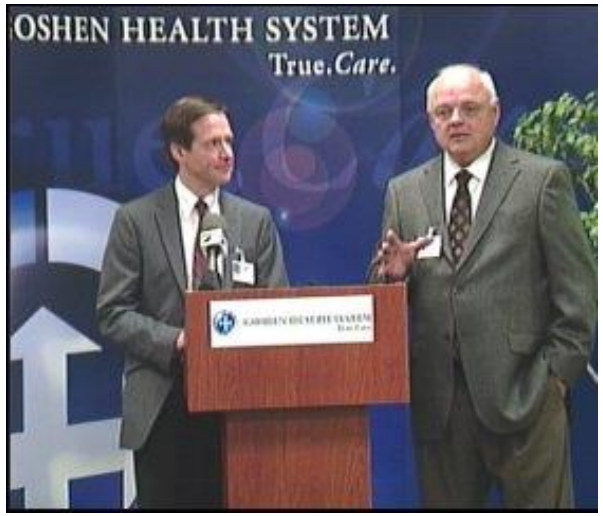
N Engl J Med 2011; June 2; 364:2119-27

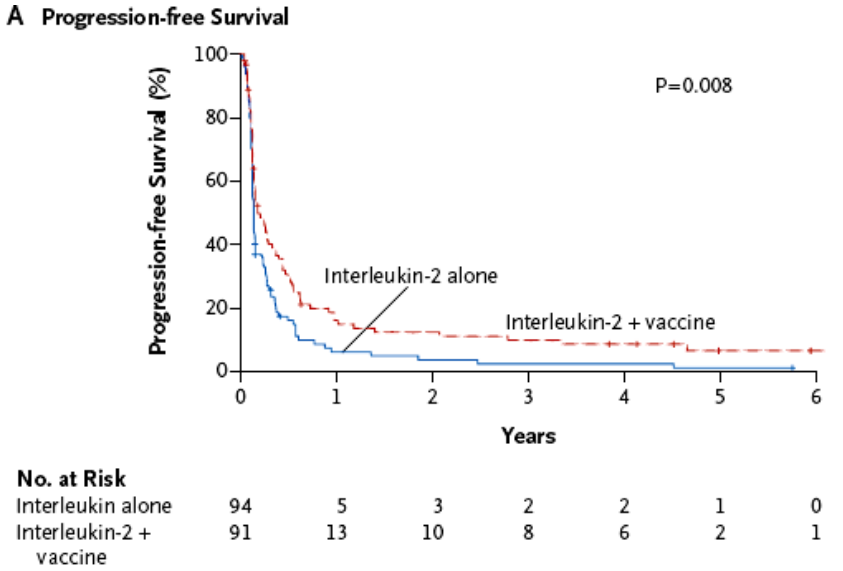
The NEW ENGLAND JOURNAL of MEDICINE

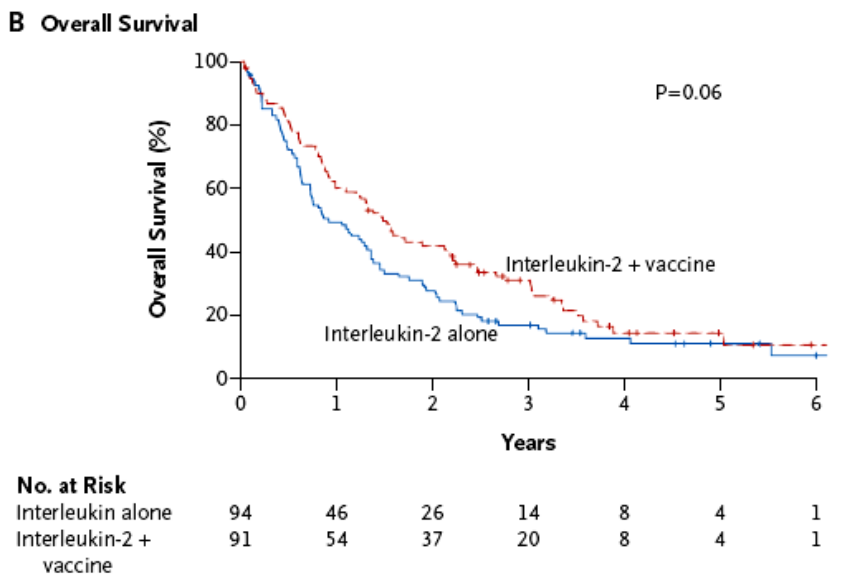
ORIGINAL ARTICLE

gp100 Peptide Vaccine and Interleukin-2 in Patients with Advanced Melanoma

Douglas J. Schwartzentruber, M.D., David H. Lawson, M.D.,



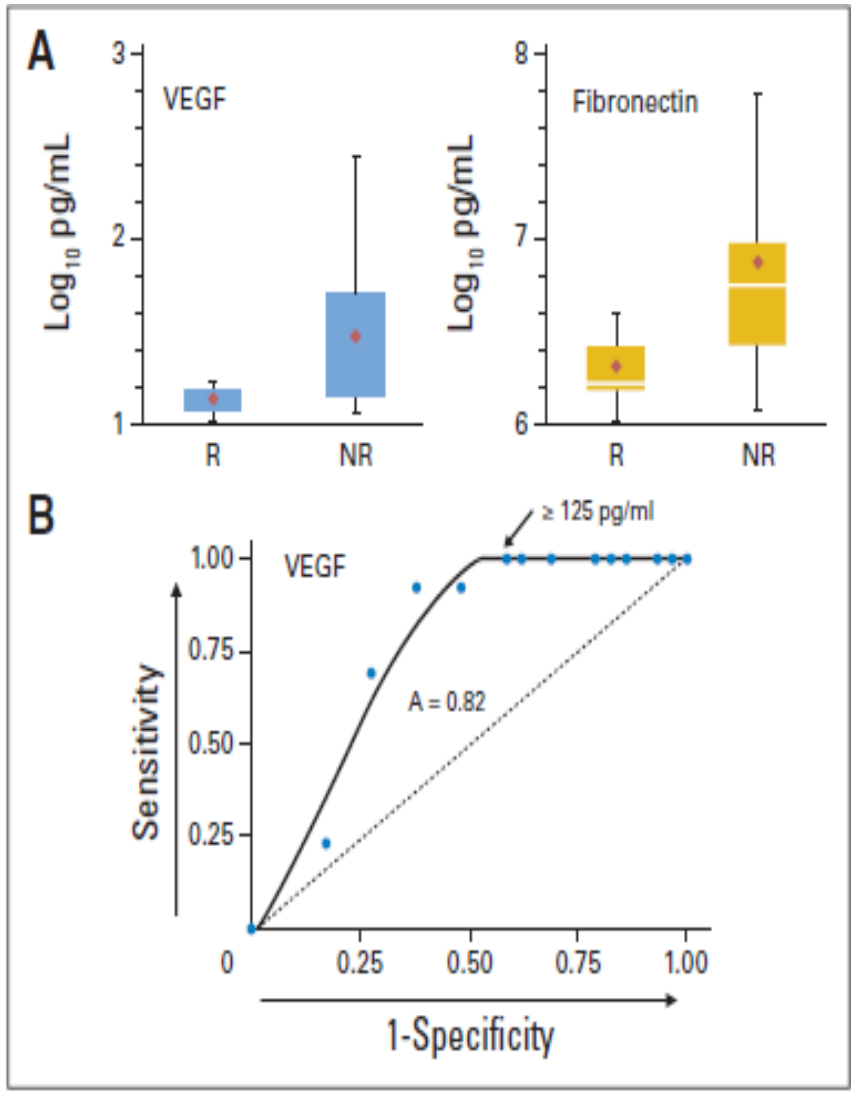


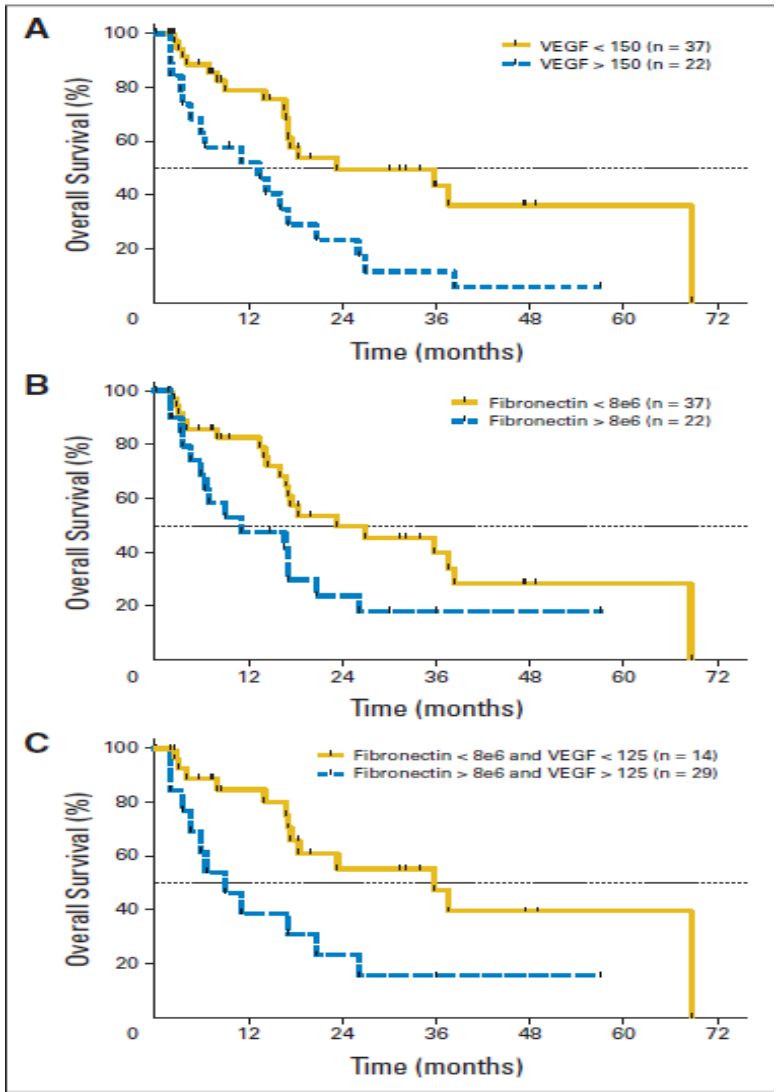


VOLUME 27 · NUMBER 16 · JUNE 1 2009
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Serum Vascular Endothelial Growth Factor and Fibronectin Predict Clinical Response to High-Dose Interleukin-2 Therapy

Marianna Sabatino, Seunghee Kim-Schulze, Monica C. Panelli, David Stroncek, Ena Wang, Bret Taback, Dae Won Kim, Gail DeRaffele, Zoltan Pos, Francesco M. Marincola, and Howard L. Kaufman



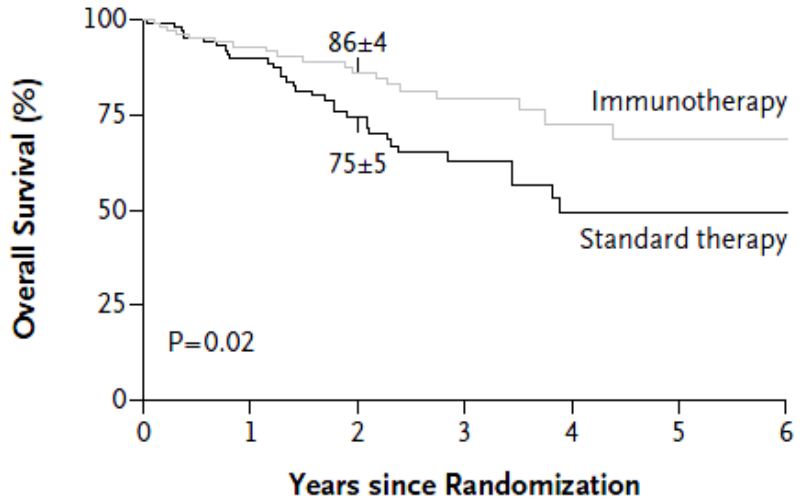


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Anti-GD2 Antibody with GM-CSF, Interleukin-2, and Isotretinoin for Neuroblastoma

Alice L. Yu, M.D., Ph.D., Andrew L. Gilman, M.D., M. Fevzi Ozkaynak, M.D., Wendy B. London, Ph.D., Susan G. Kreissman, M.D., Helen X. Chen, M.D., Malcolm Smith, M.D., Ph.D., Barry Anderson, M.D., Judith G. Villablanca, M.D., Katherine K. Matthay, M.D., Hiro Shimada, M.D., Stephan A. Grupp, M.D., Ph.D., Robert Seeger, M.D., C. Patrick Reynolds, M.D., Ph.D., Allen Buxton, M.S., Ralph A. Reisfeld, Ph.D., Steven D. Gillies, Ph.D., Susan L. Cohn, M.D., John M. Maris, M.D., and Paul M. Sondel, M.D., Ph.D., for the Children's Oncology Group



No. at Risk

Immunotherapy	113	77	59	37	20	10	3
Standard therapy	113	79	51	26	12	9	1

The Strange Immunobiology of RCC

RESPONSE	INTEFERON α	IL- 2	CTLA4 AB	PD-1 AB	TIL
MELANOMA	+	+++	++	++	++++
RCC	+	+++	++	++	-

1: **Lotze MT**, Maranchie J, Appleman L. Inhibiting autophagy: a novel approach for the treatment of renal cell carcinoma. Cancer J. 2013 Jul-Aug;19(4):341-7

2: Romo de Vivar Chavez A, de Vera ME, Liang X, **Lotze MT**. The biology of IL-2 efficacy in the treatment of patients with RCC. Med Oncol. 2009; 1:3-12.

3: Bernhard H, Maeurer MJ, Jäger E, Wölfel T, Schneider J, Karbach J, Seliger B, Huber C, Storkus WS, **Lotze MT**, Meyer zum Büschenfelde KH, Knuth A. Recognition of human RCC and melanoma by HLA-A2-restricted CTL is mediated by shared peptide epitopes and up-regulated by IFNg. Scand J Immunol. 1996;44:285-92.

4: Maeurer MJ, Martin DM, Castelli C, Elder E, Leder G, Storkus WJ, **Lotze MT**. Host immune response in RCC: IL-4 and IL-10 mRNA are frequently detected in freshly collected TIL. Cancer Immunol Immunother. 1995 Aug;41(2):111-21.

5: Spencer WF, Linehan WM, Walther MM, Haas GP, **Lotze MT**, Topalian SL, Yang JC, Merino MJ, Lange JR, Pockaj BA, et al. Immunotherapy with IL2 and IFNα in patients with metastatic RCC with *in situ* primary cancers. J Urol. 1992 147(1):24-30.

6: Rosenberg SA, **Lotze MT**, Muul LM, et al. Observations on the systemic administration of autologous lymphokine-activated killer cells and recombinant IL-2 to patients with metastatic cancer. N Engl J Med. 1985 Dec 5;313(23):1485-92.

Published OnlineFirst February 16, 2015; DOI: 10.1158/1078-0432.CCR-14-2926

Clinical Cancer Research

…two groups of tumors with extensive $CD8^+$T-cells:

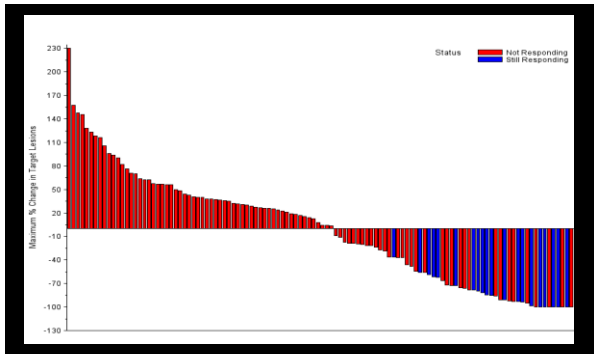
1. high expression of immune checkpoints in the absence of fully functional mature DC→↑ risk of disease progression.
2. low expression of immune checkpoints and localization of mature DC in peritumoral immune

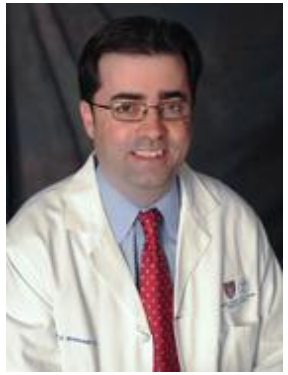
Inhibiting the Systemic Autophagic Syndrome – A Phase I/II Study of Hydroxychloroquine and Aldesleukin in Renal Cell Carcinoma Patients (RCC) – 30 Patients

A Cytokine Working Group (CWG) Study

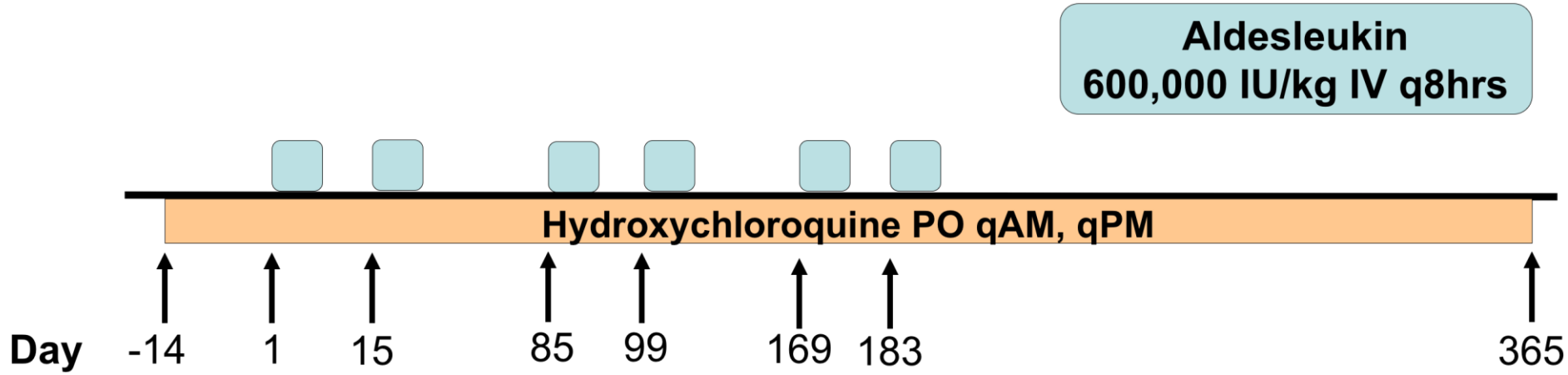
Principal Investigator: Michael T. Lotze, MD,
Len Appleman, MD, PhD
Prometheus/Nestle

Dartmouth
Harvard
Indiana
Oregon
Pittsburgh
Portland





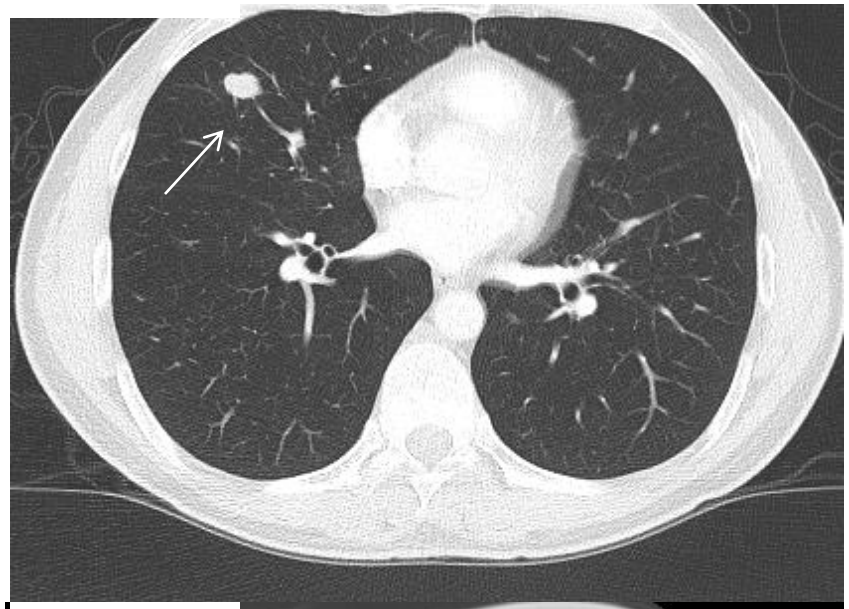
STUDY DESIGN

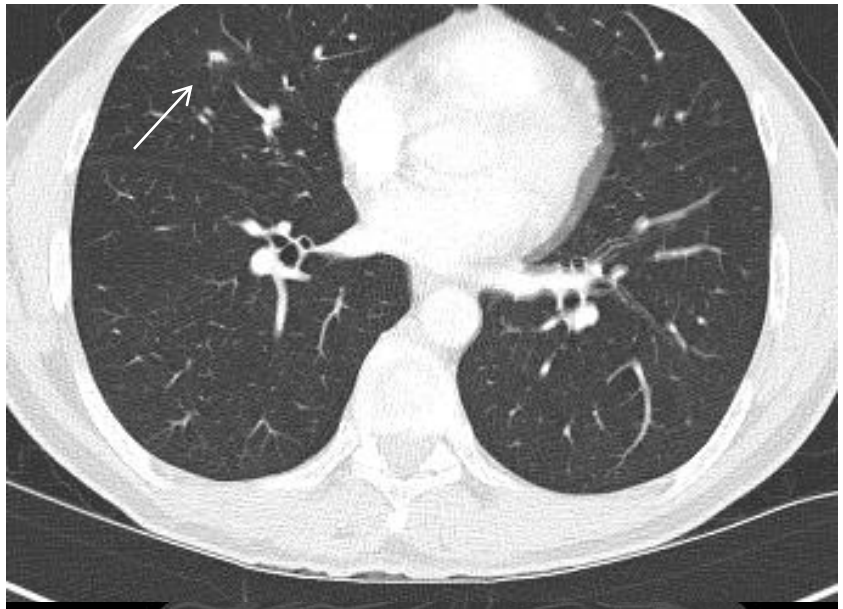


Patient 3

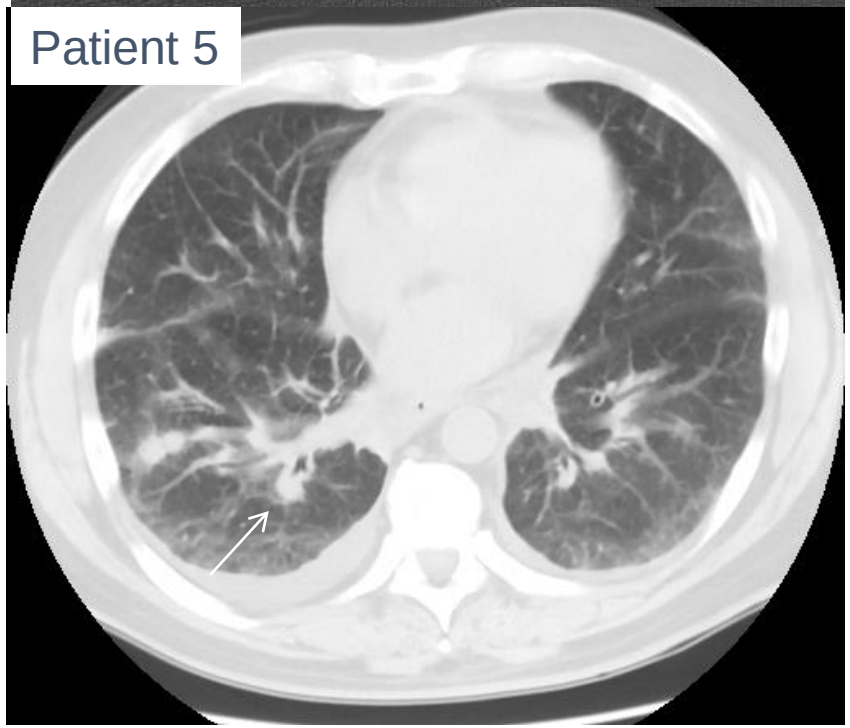
Pre-Therapy

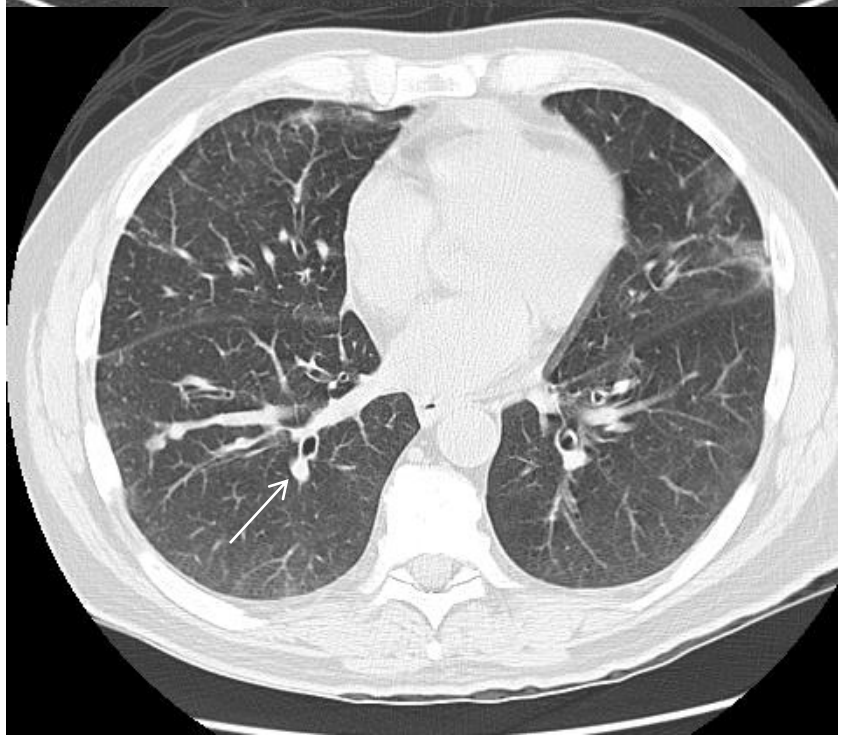
Post-therapy



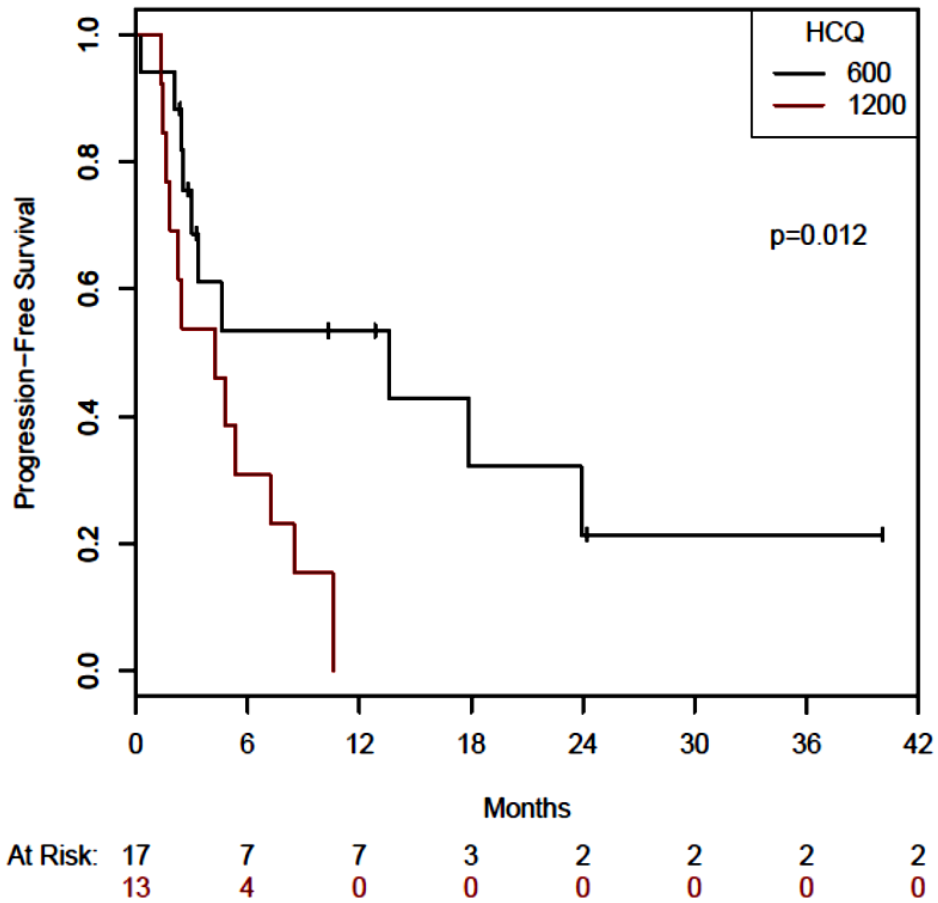


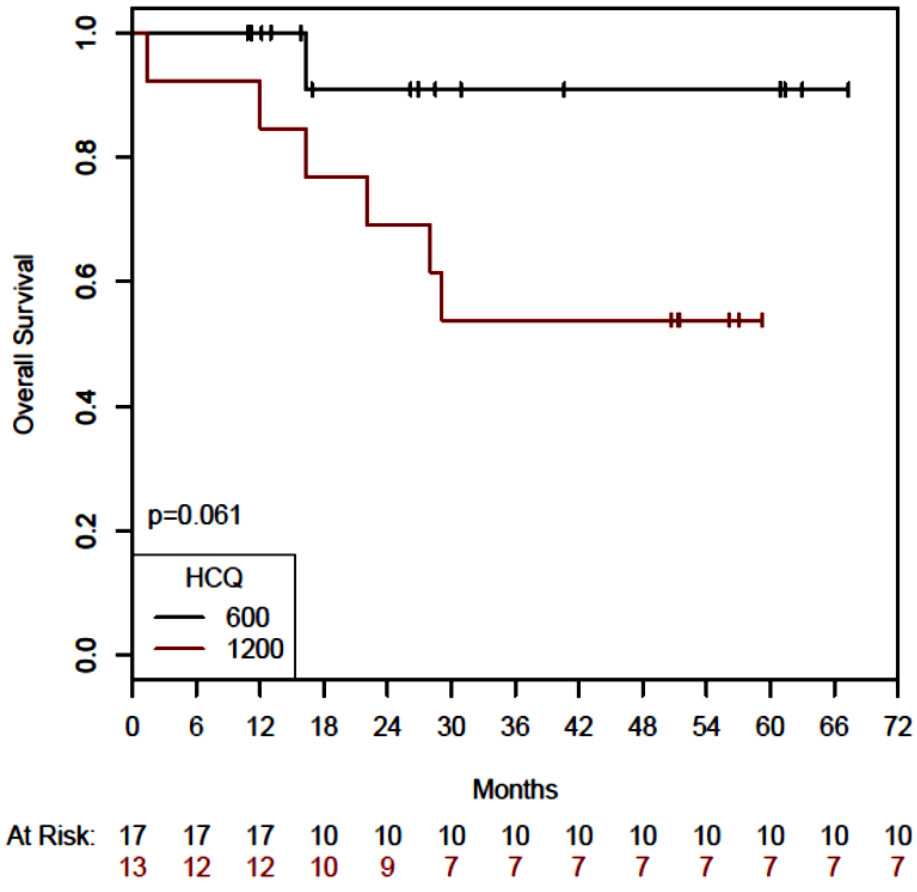
Patient 5



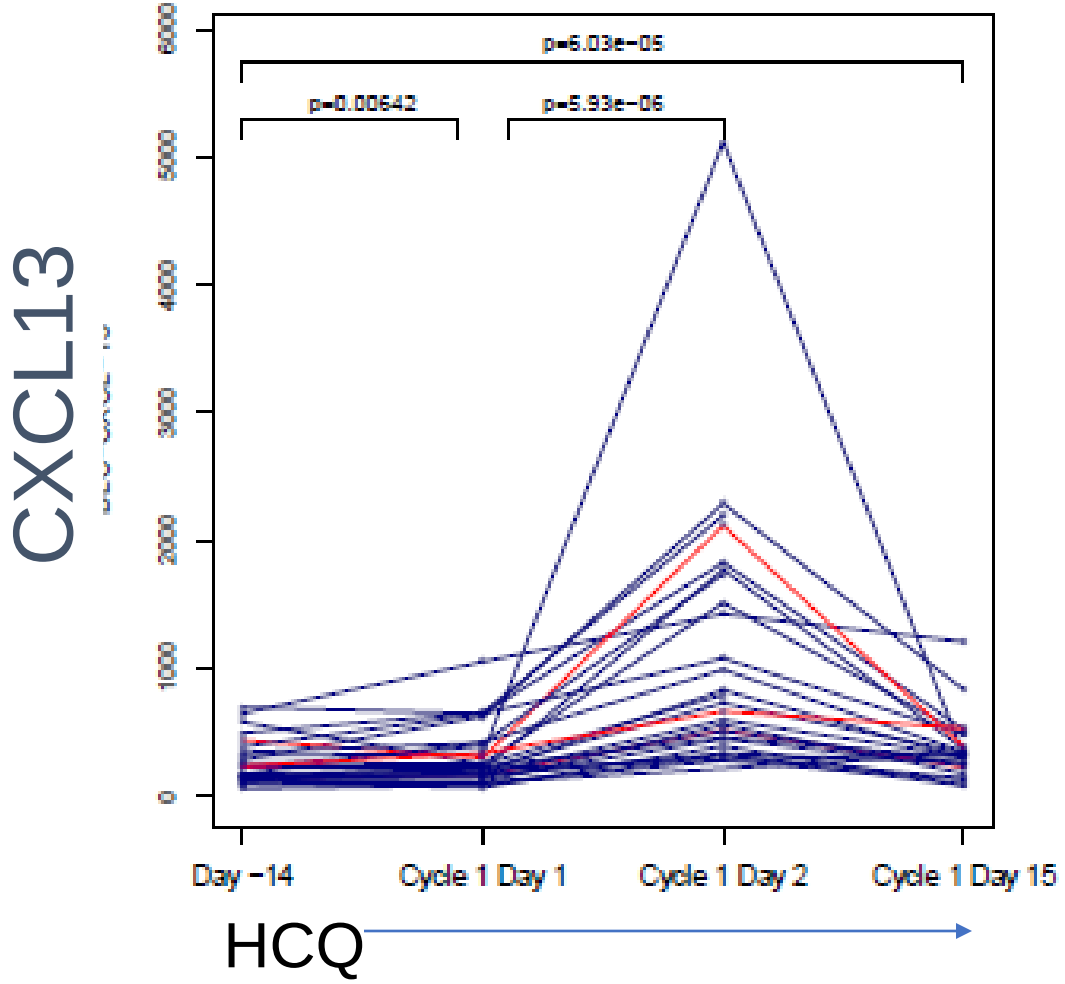


PFS AND OVERALL SURVIVAL





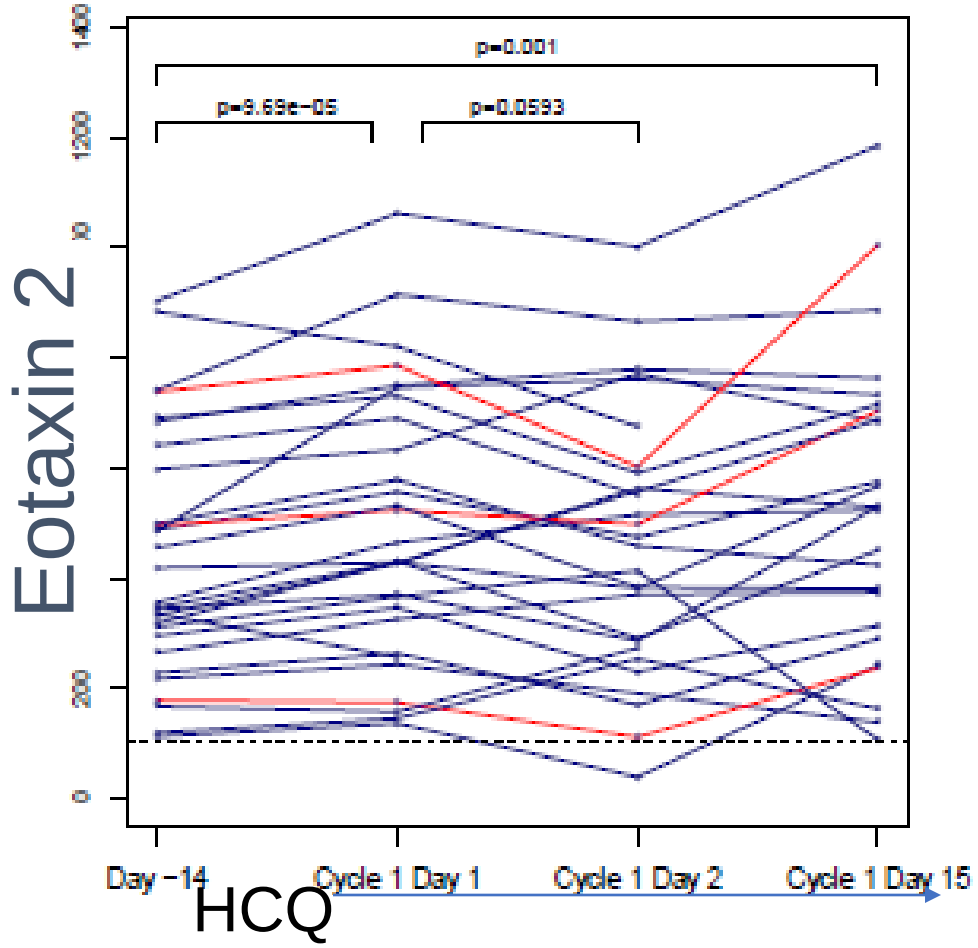
Dramatic Increases in CXCL13 (B cell Chemoattractant) on IL-2 and HCQ



Graphic: BLC-CXCL-13.pdf

Day	p10	p25	median	p75	p90
Day -14	111.5	136.2	165.5	308.8	503.2
Cycle 1 Day 1	103.8	164.5	221	377.5	643
Cycle 1 Day 2	326.6	482.5	791	1622	2146.4
Cycle 1 Day 15	134	229.8	314.5	390.2	524.5

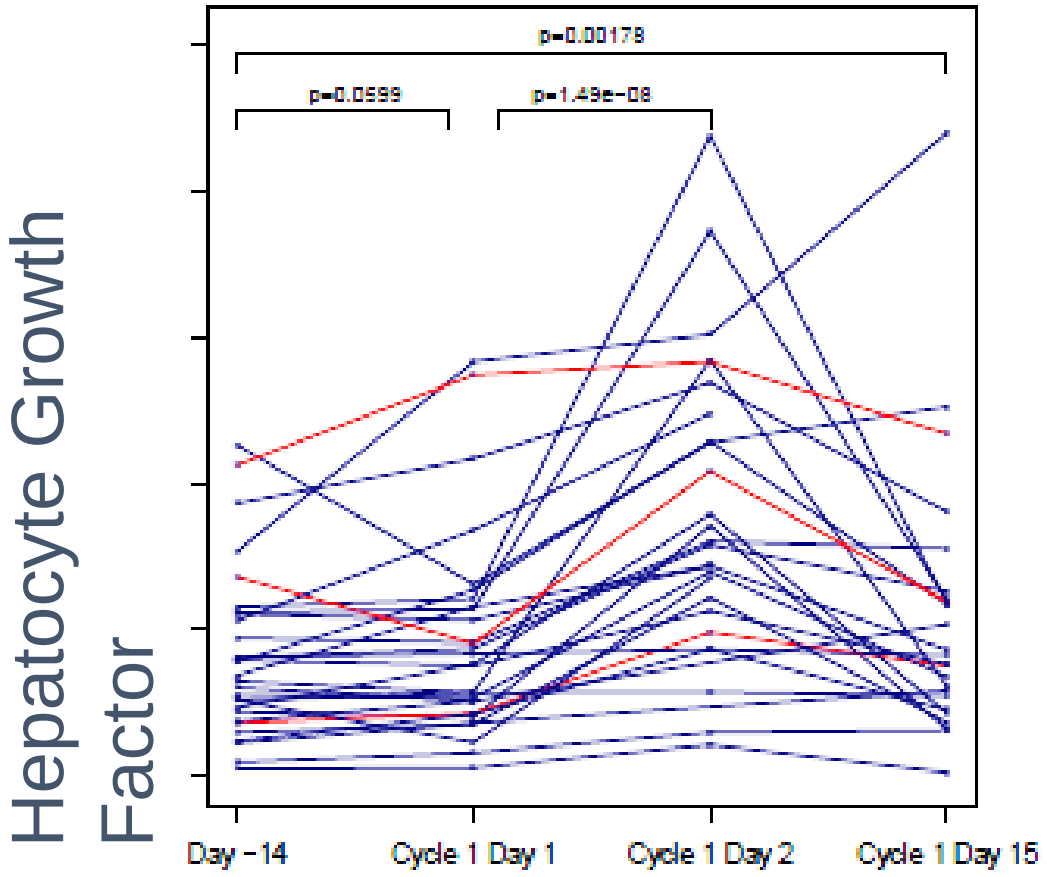
Increases in Eotaxin 2 on IL-2 and HCQ



Graphic: Exotaxin-2.pdf

Day	p10	p25	median	p75	p90
Day -14	176.9	299	387	573.2	738.3
Cycle 1 Day 1	172.3	330.2	447.5	675.8	789.4
Cycle 1 Day 2	206	298.5	474	630	774.2
Cycle 1 Day 15	200	328.2	526	699.8	824.5

Dramatic Increases Hepatocyte Growth Factor IL-2/HCQ

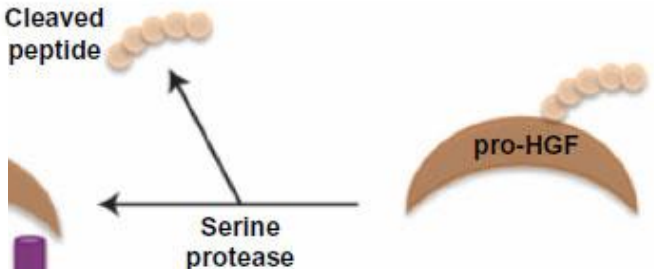


Graphic: HGF.pdf

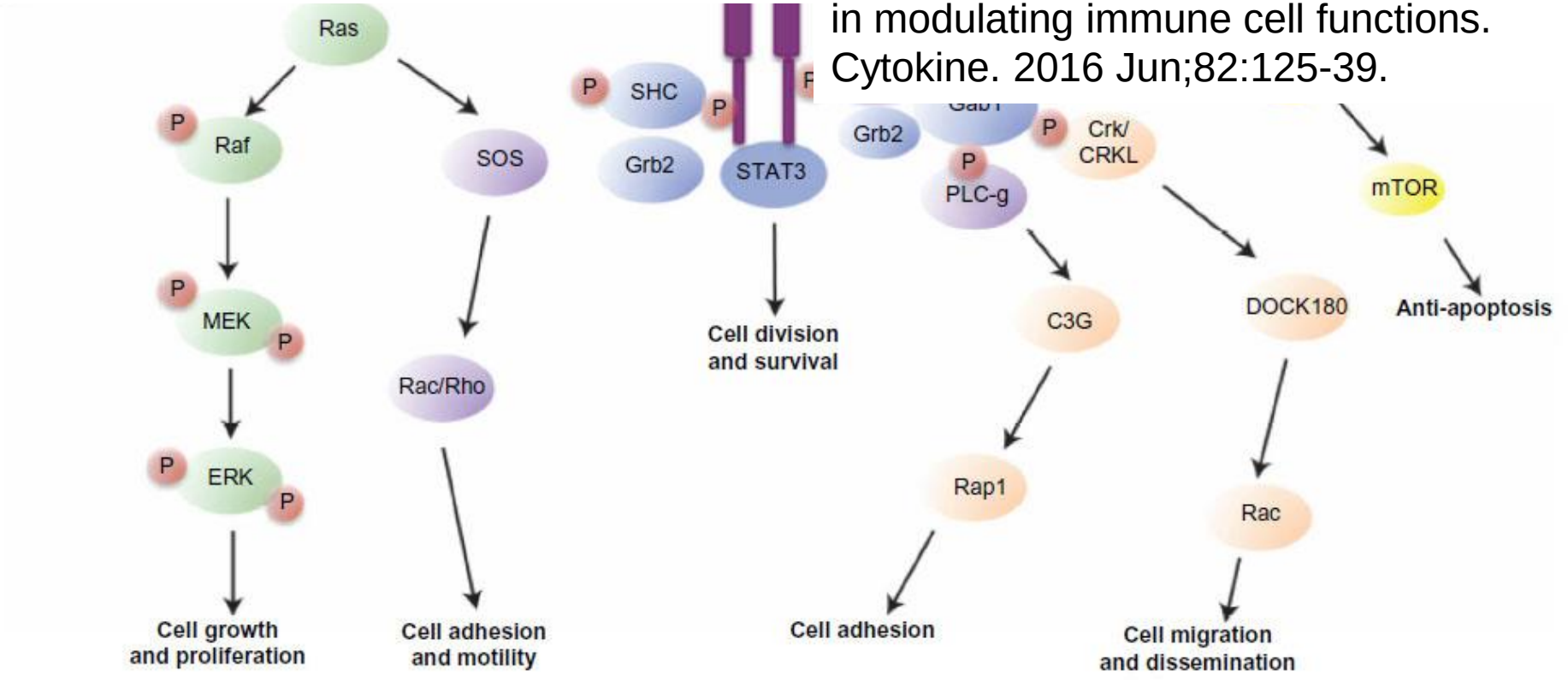
IL-2 Rest

Day	p10	p25	median	p75	p90
Day -14	46.7	98.5	133	218.8	313.6
Cycle 1 Day 1	67.5	89	151	230.2	345.8
Cycle 1 Day 2	149.4	234.5	316	477	583
Cycle 1 Day 15	67.5	110.8	158.5	239.5	414.5

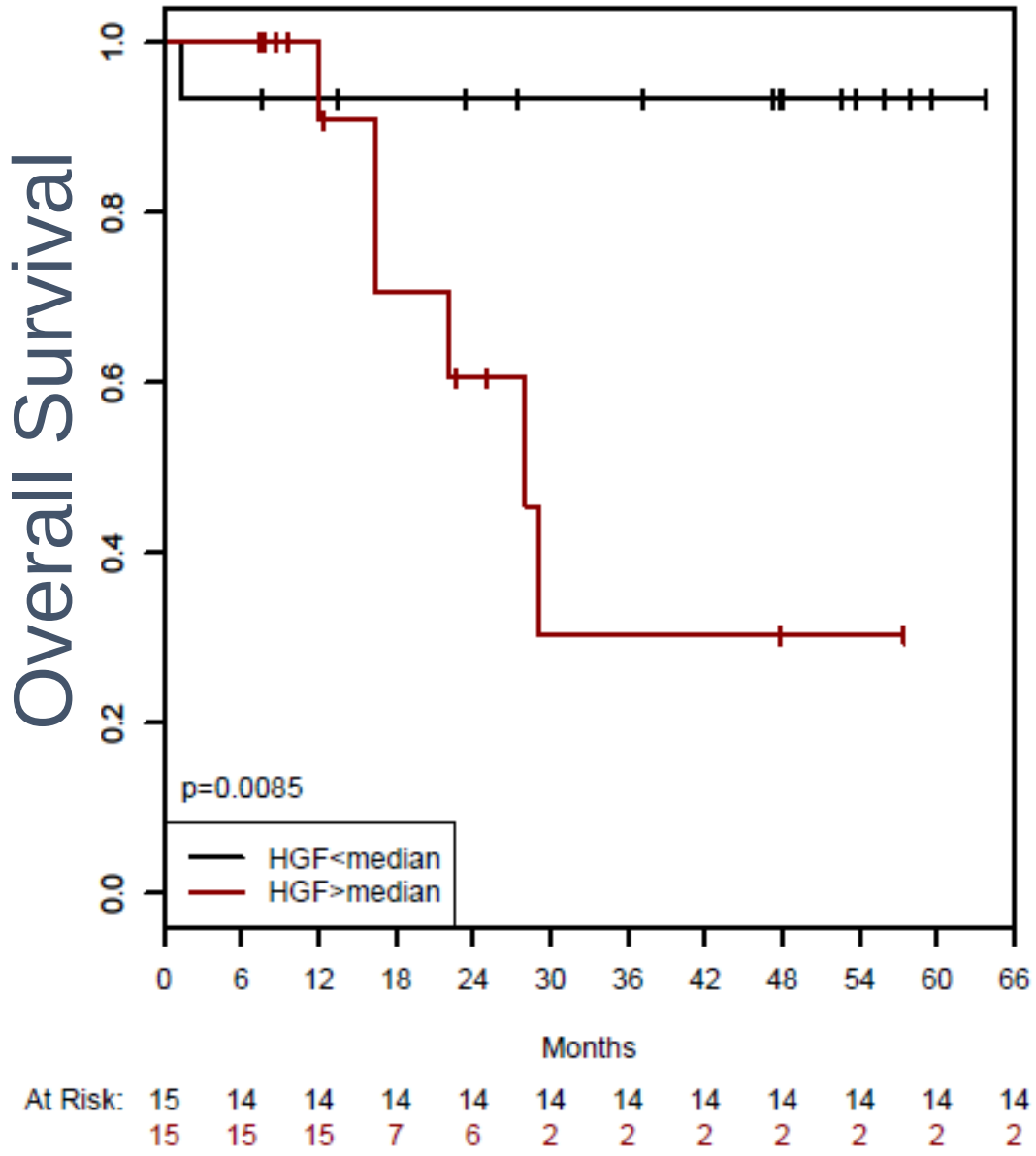
Vogel S, Börger V, Peters C, Förster M, Liebfried P, Metzger K, Meisel R, Däubener W, Trapp T, Fischer JC, Gawaz M, Sorg RV. Necrotic cell-derived high mobility group box 1 attracts antigen-presenting cells but inhibits hepatocyte growth factor-mediated tropism of mesenchymal stem cells for apoptotic cell death. Cell Death Differ. 2015 Jul;22(7):1219-30.



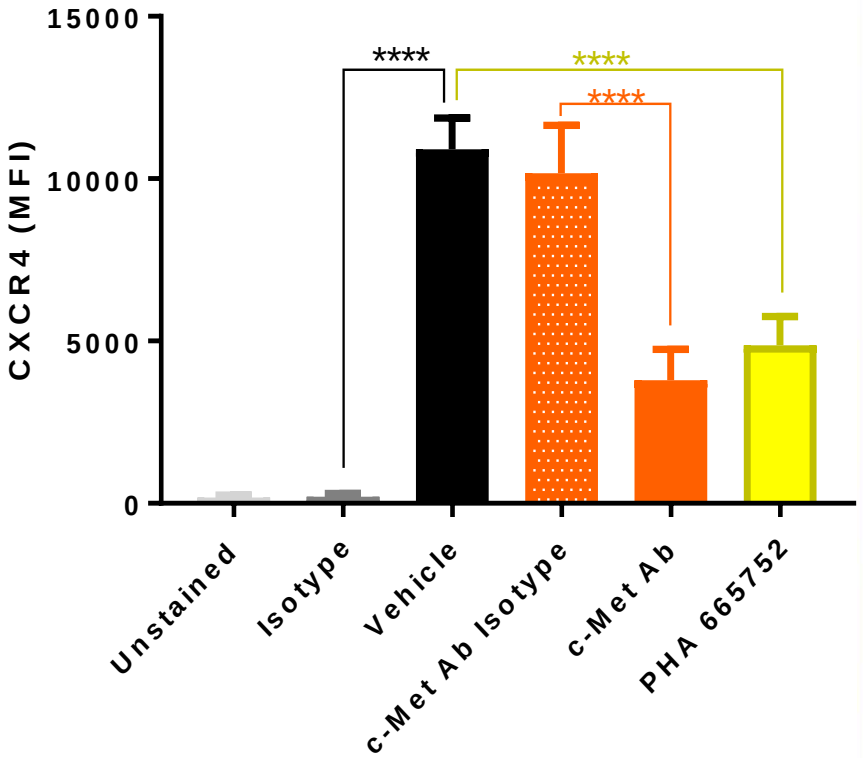
Ilangumaran S, Villalobos-Hernandez A, Bobbala D, Ramanathan S. The hepatocyte growth factor (HGF)-MET receptor tyrosine kinase signaling pathway: Diverse roles in modulating immune cell functions. Cytokine. 2016 Jun;82:125-39.

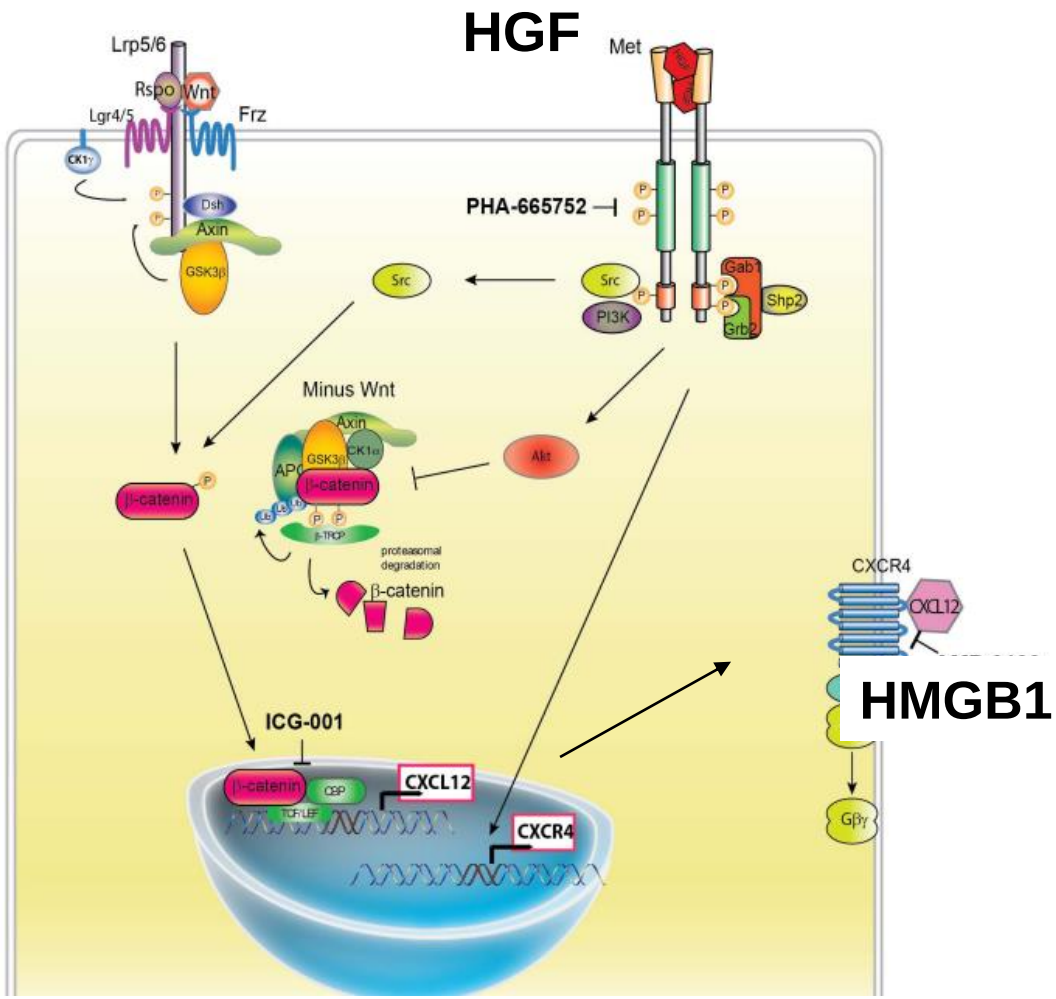


Decreased Survival in Individuals with High HGF Serum



Potential synergistic signaling pathways – HGFA and HMGB1

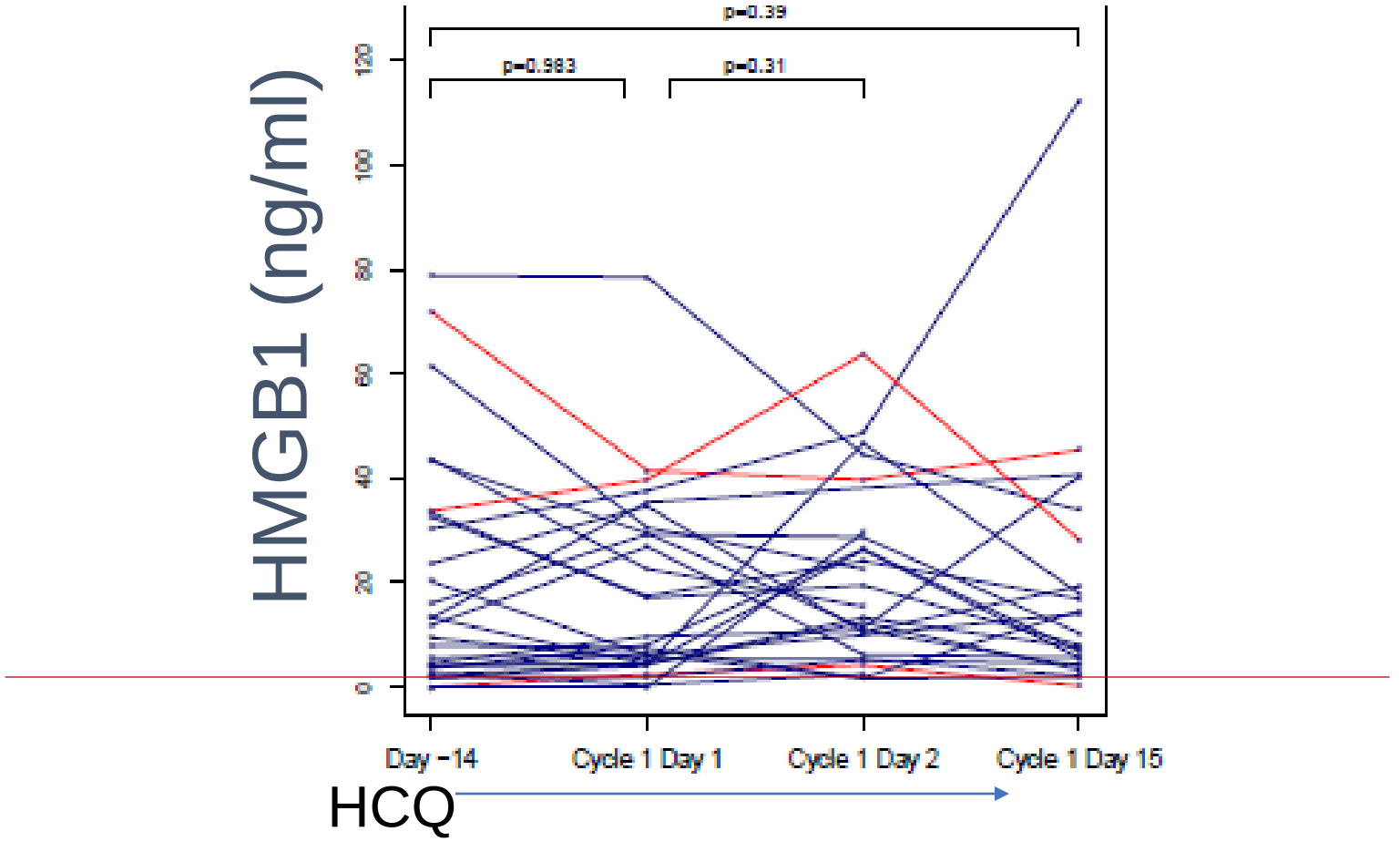




Jagdeep Nanchahal

Holland JD et al. Combined Wnt/β-catenin, Met, and CXCL12/CXCR4 signals characterize basal breast cancer and predict disease outcome. Cell Rep. 2013 Dec 12;5(5):1214-27.

No Relationship Between HMGB1 Levels and Response/Treatment



Graphic: HMGB1.pdf

Day	p10	p25	median	p75	p90
Day -14	1.9	3.9	11.8	32	45.5
Cycle 1 Day 1	2.4	4.4	8.9	30.1	37.9
Cycle 1 Day 2	3.5	8.1	15.4	29.1	45.4
Cycle 1 Day 15	2.5	5.4	12.2	25.4	40.7

Jack Butler
Tecan/IBL
Shinotest

CEA-IL2v (FAP-IL2v)

A CEA-targeted interleukin-2 variant

Clinical confirmation of tumor targeting and evidence of intra-tumoral immune activation

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Anti-GD2 Antibody with GM-CSF, Interleukin-2, and Isotretinoin for Neuroblastoma

Alice
Wen
Malcolr
Katherin
Robe
Ral
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D.,
M.D.,
Ph.D.,
S.,
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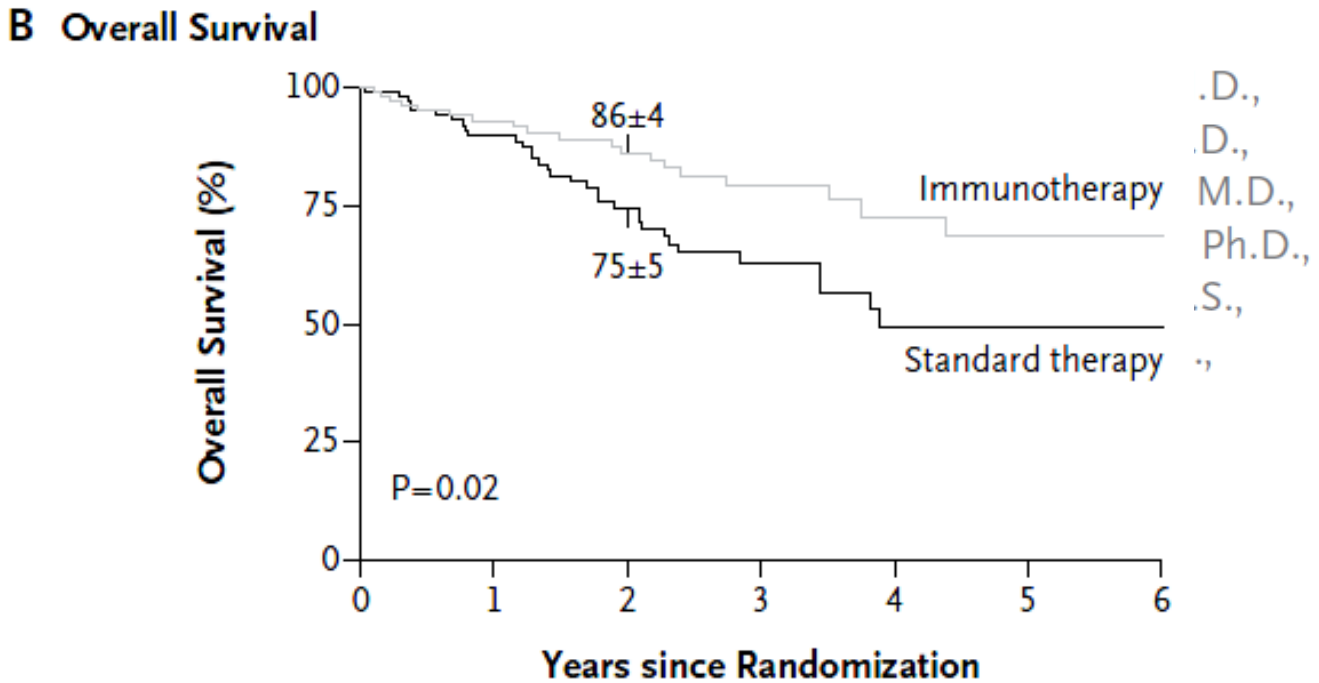
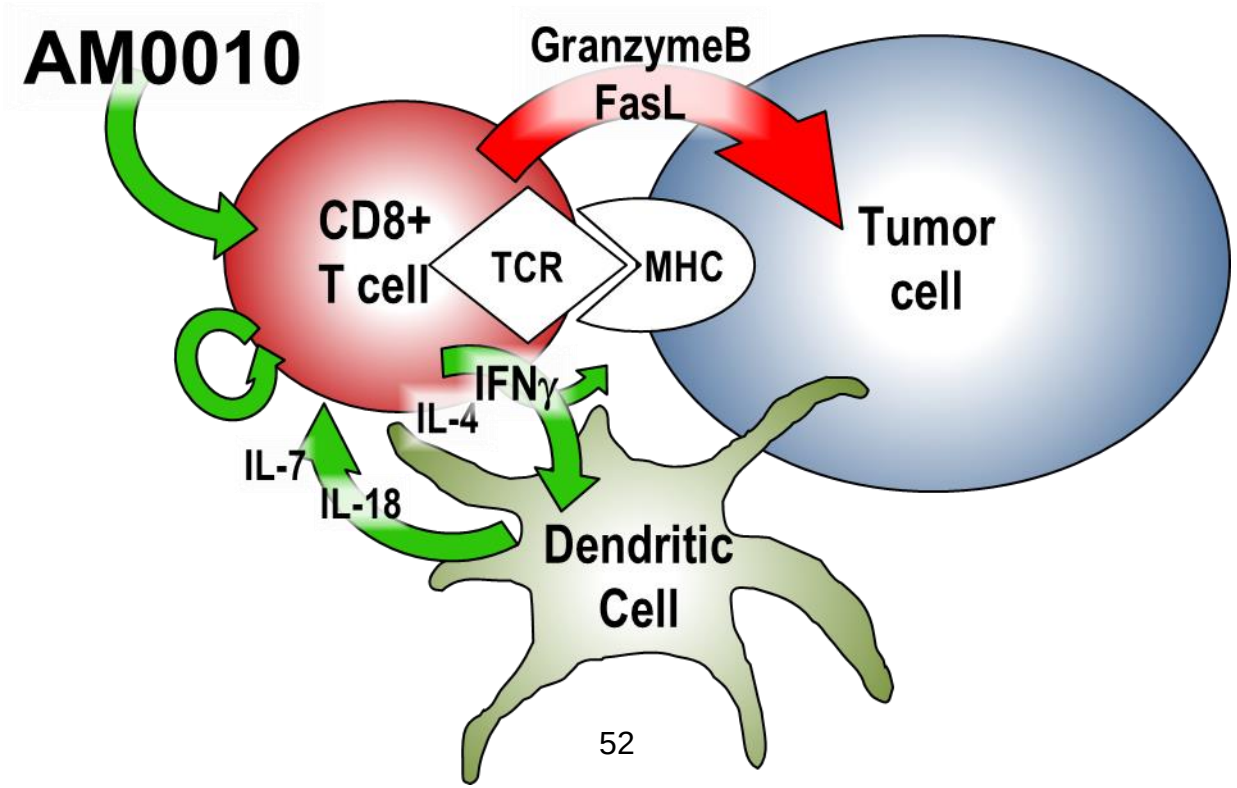


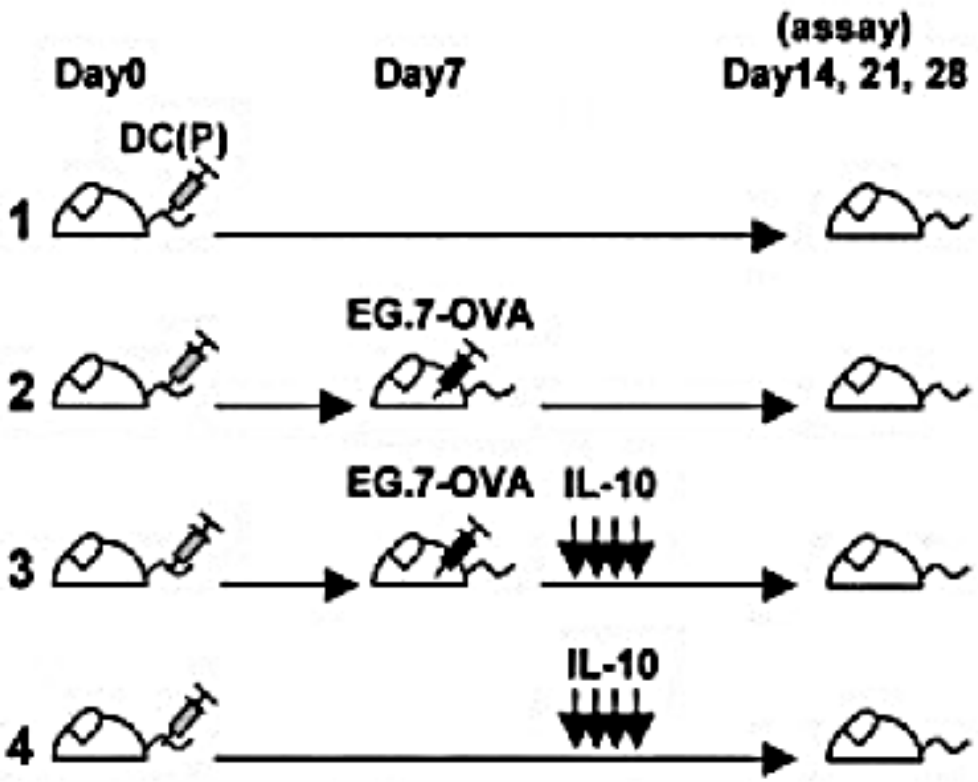
A first-in-human dose escalation study of PEGylated recombinant human IL-10 (AM0010) in advanced solid tumors

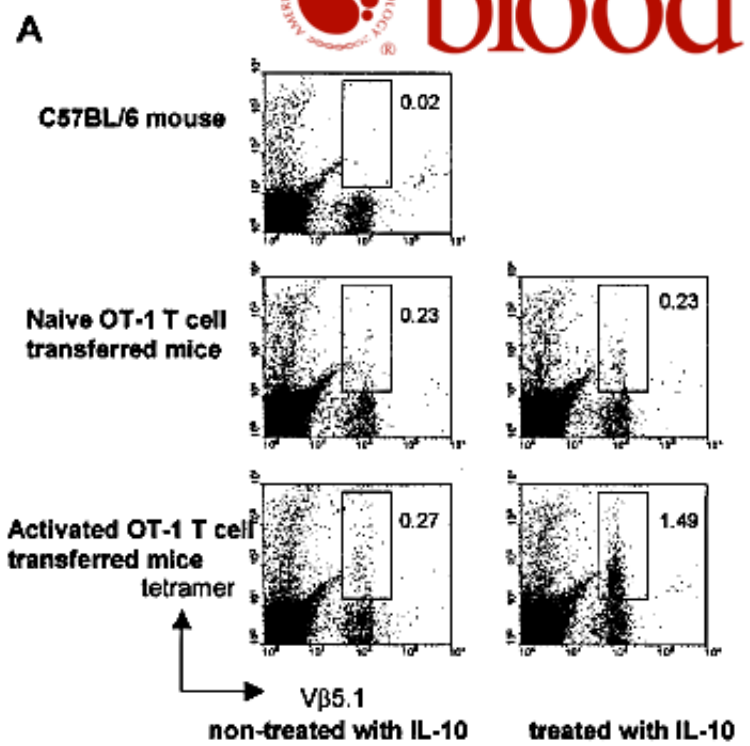
Jeffrey R. Infante[1], Aung Naing[2], Kyriakos P. Papadopoulos[3], Karen A. Autio[4], Patrick A. Ott[5], Deborah J. Wong[6], Gerald S. Falchook[7], Manish Patel[1,8], Shubham Pant[9], Melinda Whiteside[10], Johanna C. Bendell[1], Todd Bauer[1], Filip Janku[2], Milind Javle[2], David Hong[2], Martin Oft[10]

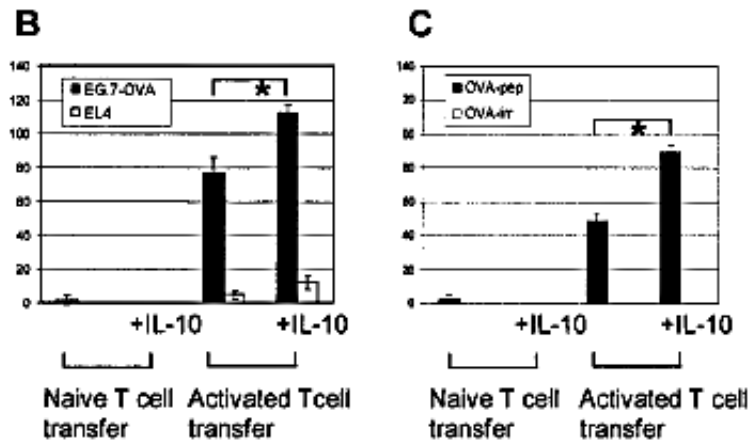


Interleukin-10 promotes the maintenance of antitumor CD8$^+$ T-cell effector function in situ

Shin-ichiro Fujii, Kanako Shimizu, Takashi Shimizu, and Michael T. Lotze







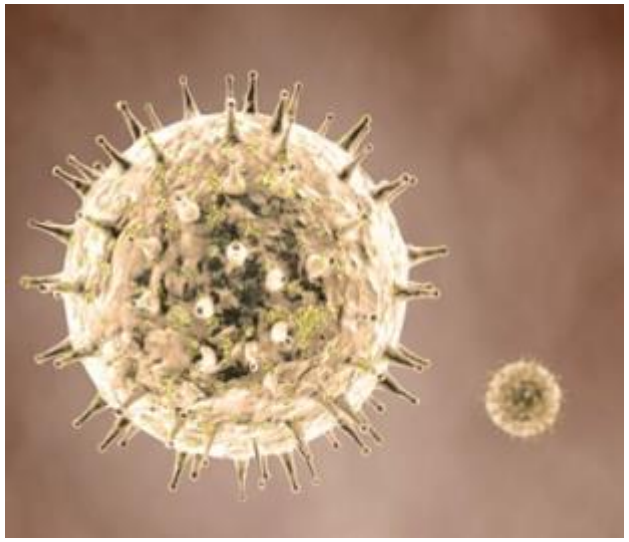
BLOOD, 1 OCTOBER 2001 VOLUME 98, NUMBER 7

IL-2+IL-10=IL-12

Immune Activation by AM0010 – PEG-IL-10

- AM0010 / Pegylated IL-10 induced a comprehensive immune signature
  - Th1 cytokines IFNγ , IL-18
  - Dendritic cell stimulation: GM-CSF, IL-4
  - Growth factor for memory CD8+ T cells IL-7
  - CD8+ T cell activity FasL
  - Inhibited immune suppression TGF-β
  - Immune activation signature is induced in all patients at RP2d
  - Combination with Chemotherapy, TKI and Immune checkpoint inhibition in progress
- Increase of PD-1+ CD8+ T cells in responding patients
- Increase of CD8+ T cells in tumor biopsies

Virotherapy with T-Vec: Melanoma Successfully Treated With Herpes-based Drug



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.

J Clin Oncol. 2015 May 26. pii: JCO.2014.58.3377. [Epub ahead of print] Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma. Andtbacka RH et al

Efficacy of Intratumoral B-Class CpG in NHL

VOLUME 28 · NUMBER 28 · OCTOBER 1 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

In Situ Vaccination With a TLR9 Agonist Induces Systemic Lymphoma Regression: A Phase I/II Study

Joshua D. Brody, Weiyun Z. Ai, Debra K. Czerwinski, James A. Torchia, Mia Levy, Ranjana H. Advani, Youn H. Kim, Richard T. Hoppe, Susan J. Knox, Lewis K. Shin, Irene Wapnir, Robert J. Tibshirani, and Ronald Levy

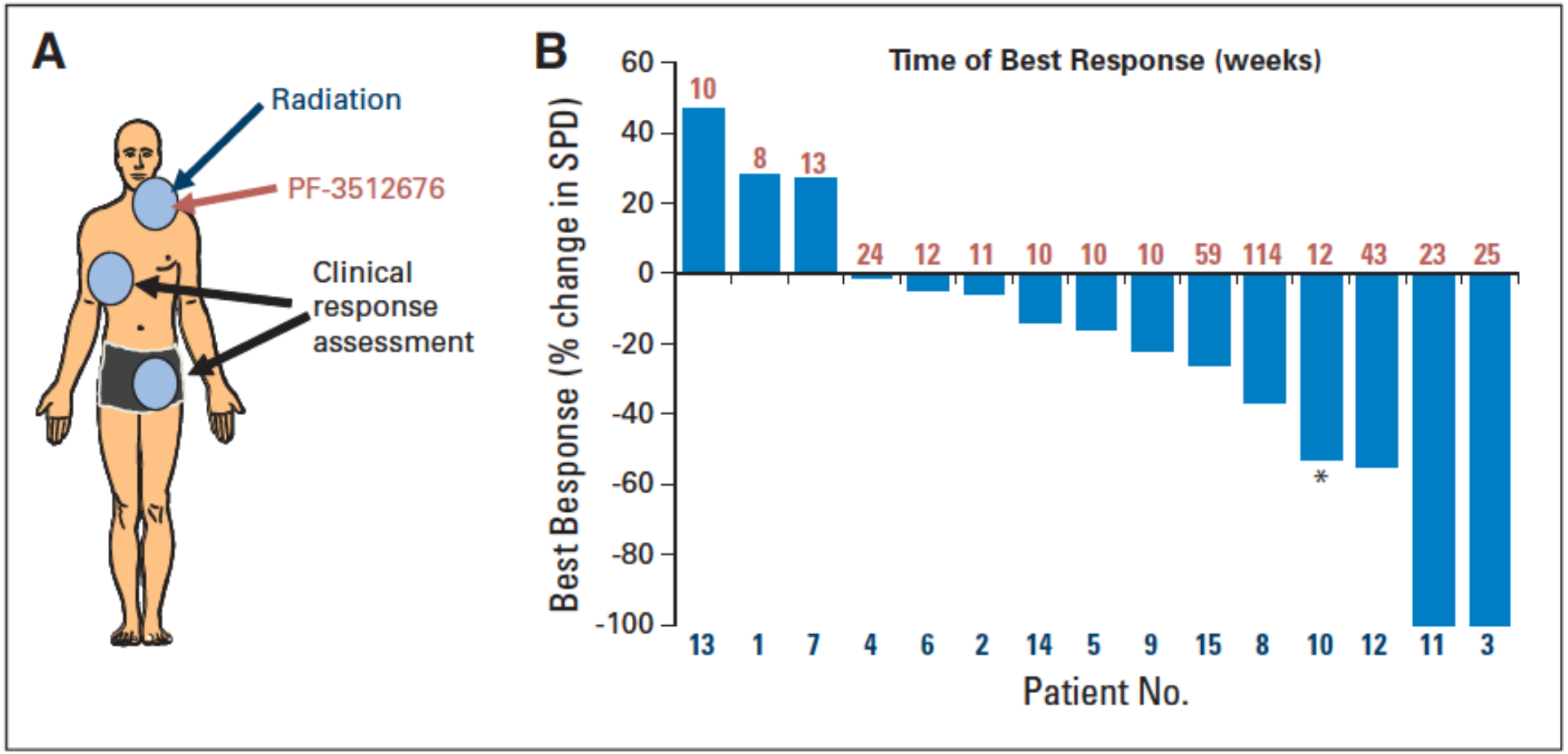
See accompanying editorial on page 4295

Efficacy of Intratumoral B-Class CpG in NHL

VOLUME 28 · NUMBER 28 · OCTOBER 1 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT



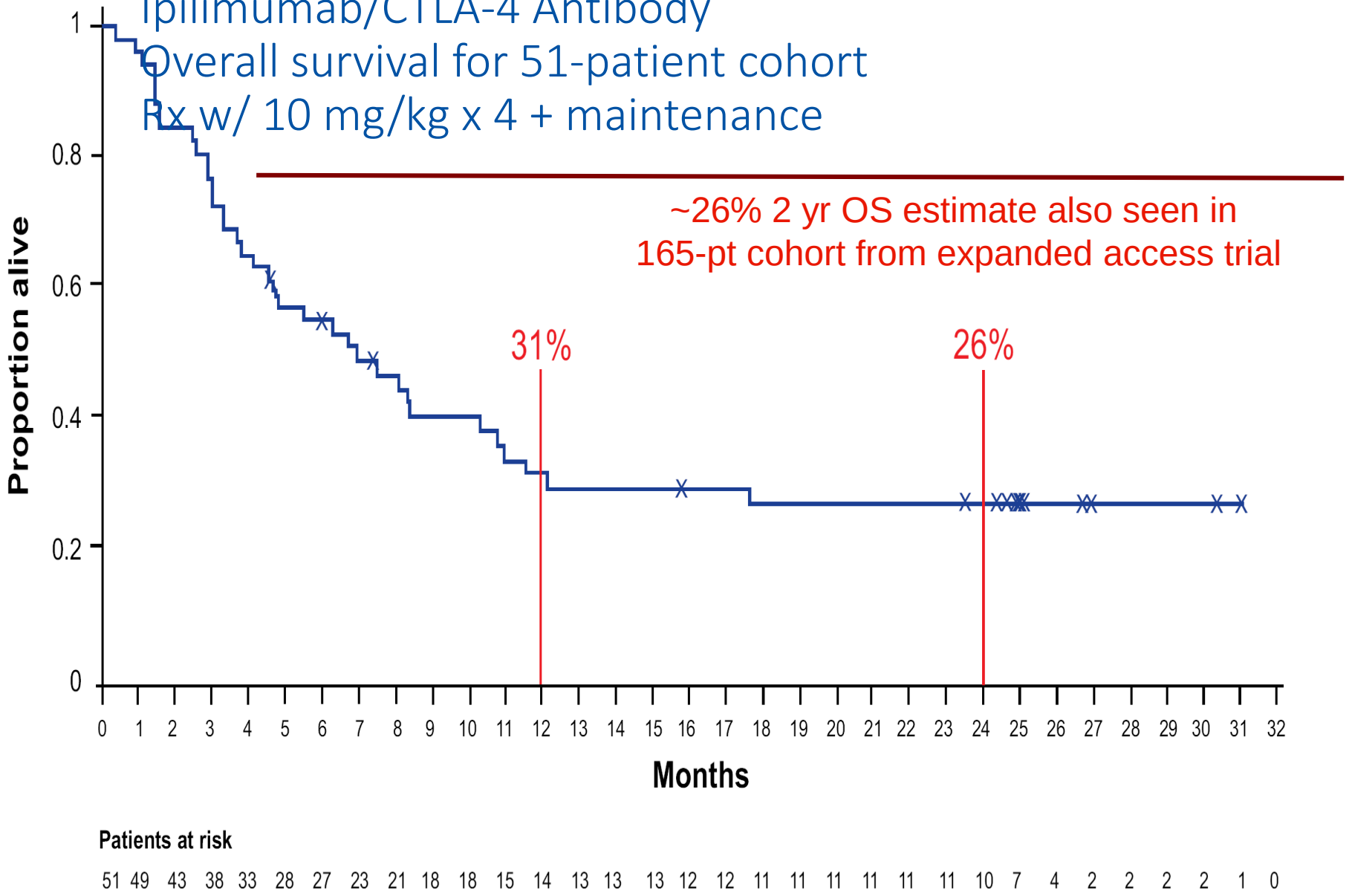
A phase I study of intratumoral injection of ipilimumab and interleukin-2 in patients with unresectable stage III-IV melanoma

R. C. Bowen[1], S. Meek, M. Williams[1], K. F. Grossmann[1], R. H. I. Andtbacka[1], T. L. Bowles[2], J. R. Hyngstrom[1], S. A. Leachman[3], D. Grossman[1], S. L. Holmen[1], M. W VanBrocklin[1], H. T. Khong[1]

3018

1. University of Utah-Huntsman Cancer Institute, Salt Lake City, UT; 2. Intermountain Medical Center, Murray, UT; 3. Oregon Health & Science University, Portland, OR

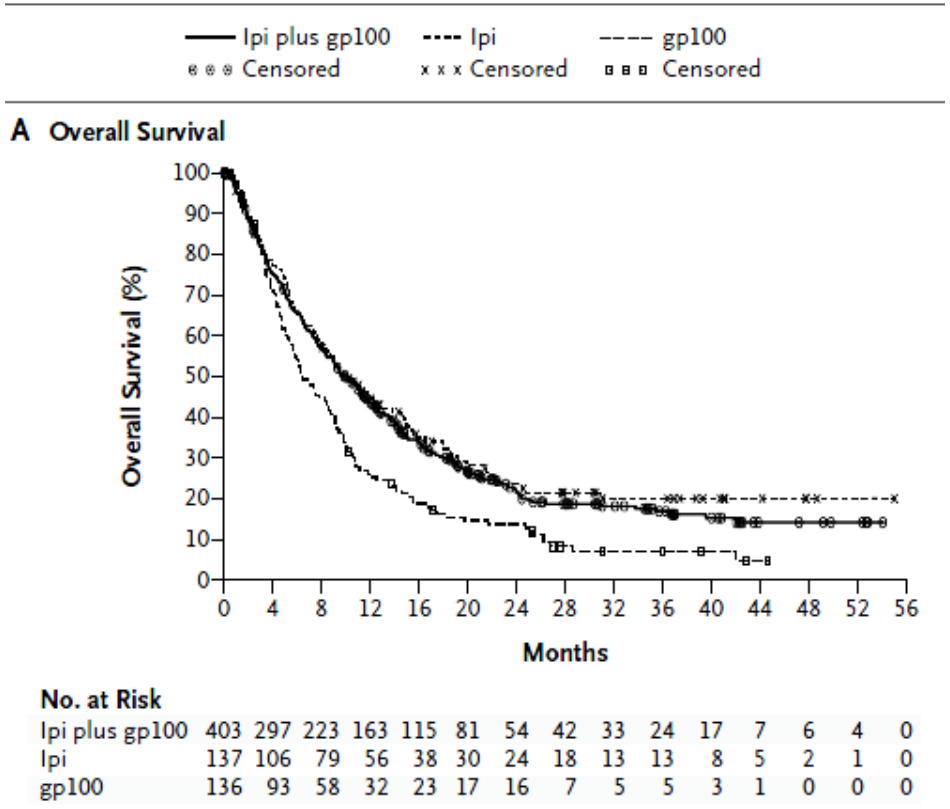
Ipilimumab/CTLA-4 Antibody
Overall survival for 51-patient cohort
Rx w/ 10 mg/kg x 4 + maintenance

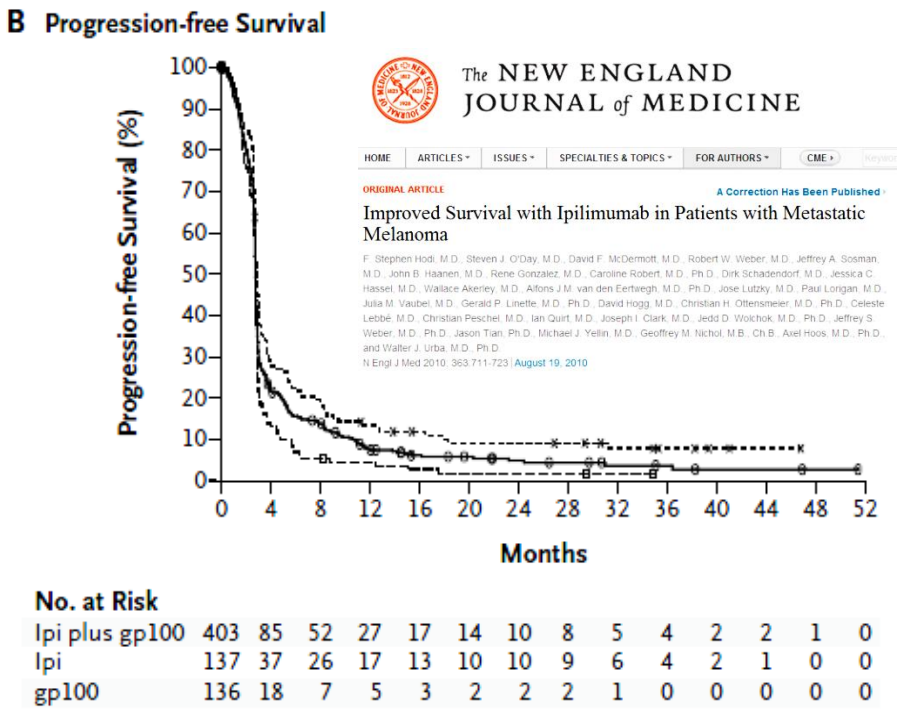


x = censored data

Kevin Heller, BMS—data presented in part at ESMO 2009, ASCO 2010, 2011 posters

Ipilimumab Treatment of Patients with Cancer

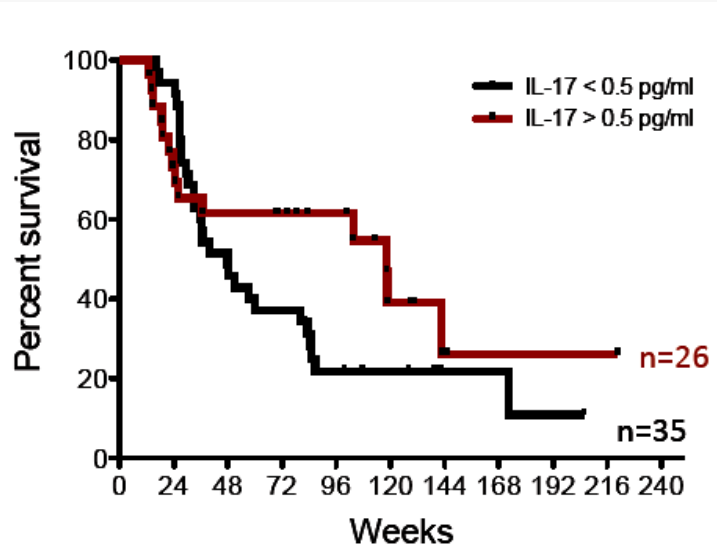




Evaluation of serum IL-17 levels during ipilimumab therapy: correlation with colitis.

Margaret Callahan, MD PhD

Memorial Sloan-Kettering Cancer Center



LUDWIG CENTER

Intratumoral Ipi and IL-2

Introduction

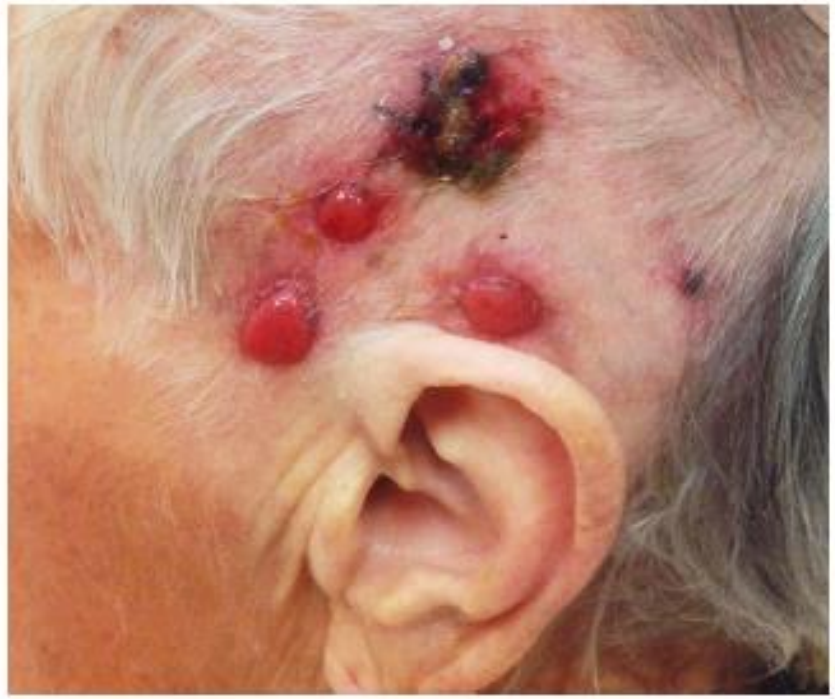
- We hypothesized that a combination of IT IL-2 and IT Ipi would effectively hyperactivate and expand TILs to engender systemic immunity with minimal toxicity.

Methods

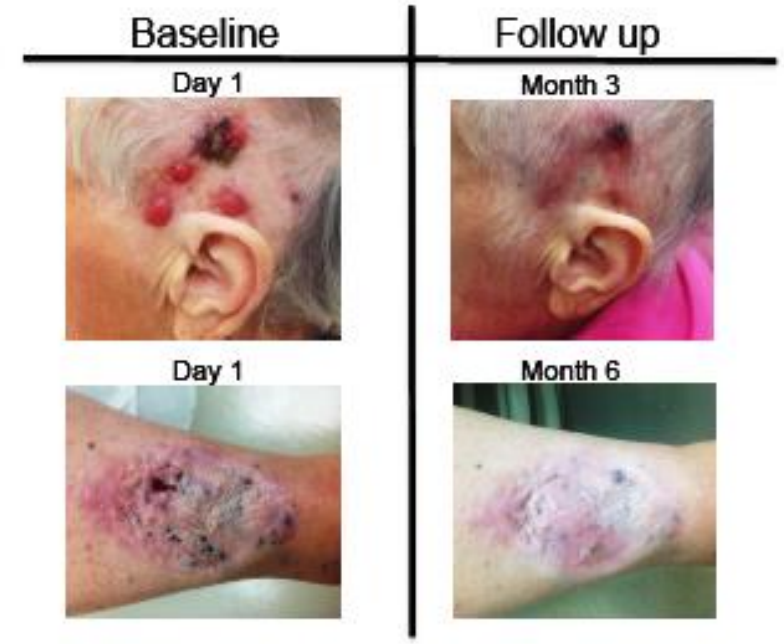
- Phase I dose escalation study for Ipi with fixed dose IL-2 in patients with unresectable stage III/IV melanoma and at least one injectable lesion.
- IL-2: (3 mIU) IT TIW x 2 weeks, then BIW x 6 weeks,
- Ipi: escalating doses of Ipi (0.5, 1, 2 mg) IT weekly x 8 wks.
- A minimum of 3 patients were enrolled at each dose level (total n=12).

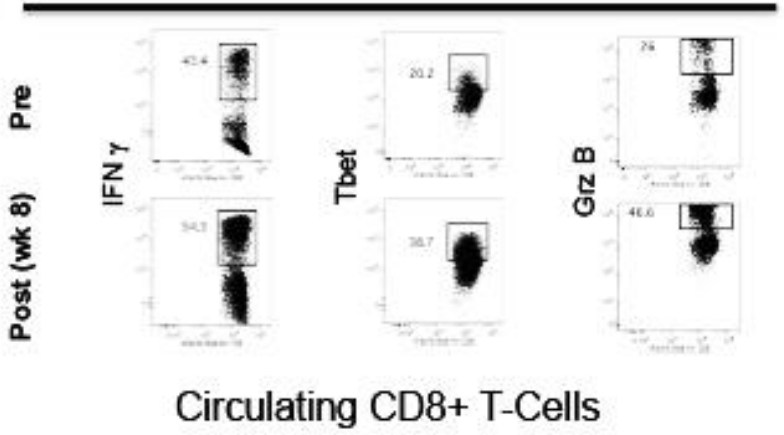
Toxicity of Local Injection

- Most toxicities were Grade 1 or 2 in nature (Fatigue, headache, pain, chills, rash, etc).
- Grade 3 adverse events (AEs) include hyponatremia, unrelated (n=1), injection site ulceration (n=4), lymphopenia (n=1), wound complication (n=1).
- The only related grade 3 toxicity observed was injection/tumor site ulceration/necrosis, not a DLT per protocol.

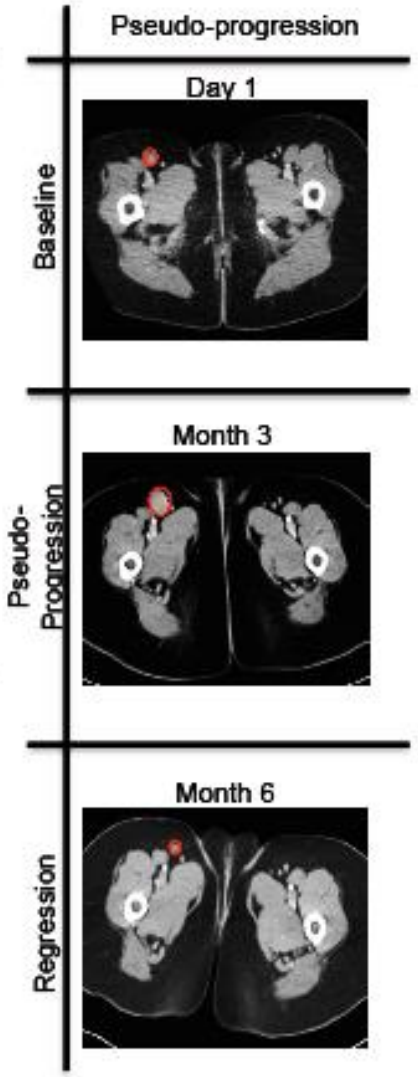


Results





Circulating CD8+ T-Cells



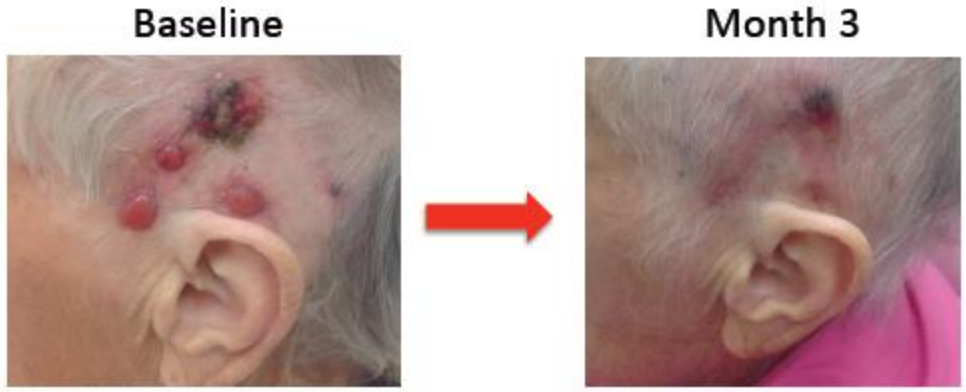
- An abscopal effect was seen in 9/12 patients (75%).
- 10 patients evaluable for response by immune-related response criteria: 4 PR (40%) and 6 PD.
- Circulating CD8+ T-Cells
  - IFN-γ in 6/8 abscopal responders.
  - Tbet+ cells in 4/5
  - Granzyme-B + 3/5

Conclusions

- IT injection with Ipi/IL-2 is well tolerated and generates a response in injected and non-injected lesions in most patients

Questions

- What about injection with systemic PD-1 inhibition?
- What about other local therapies including CpG's, cGAS/STING peptides, radiation therapy?
- What about direct injection of NK cells (allogeneic?) for low mutation load tumors?
- What about Radiation Therapy?



NKTR-214 (CD-122-biased agonist) plus nivolumab in patients with advanced solid tumors: Preliminary phase 1/2 results of PIVOT

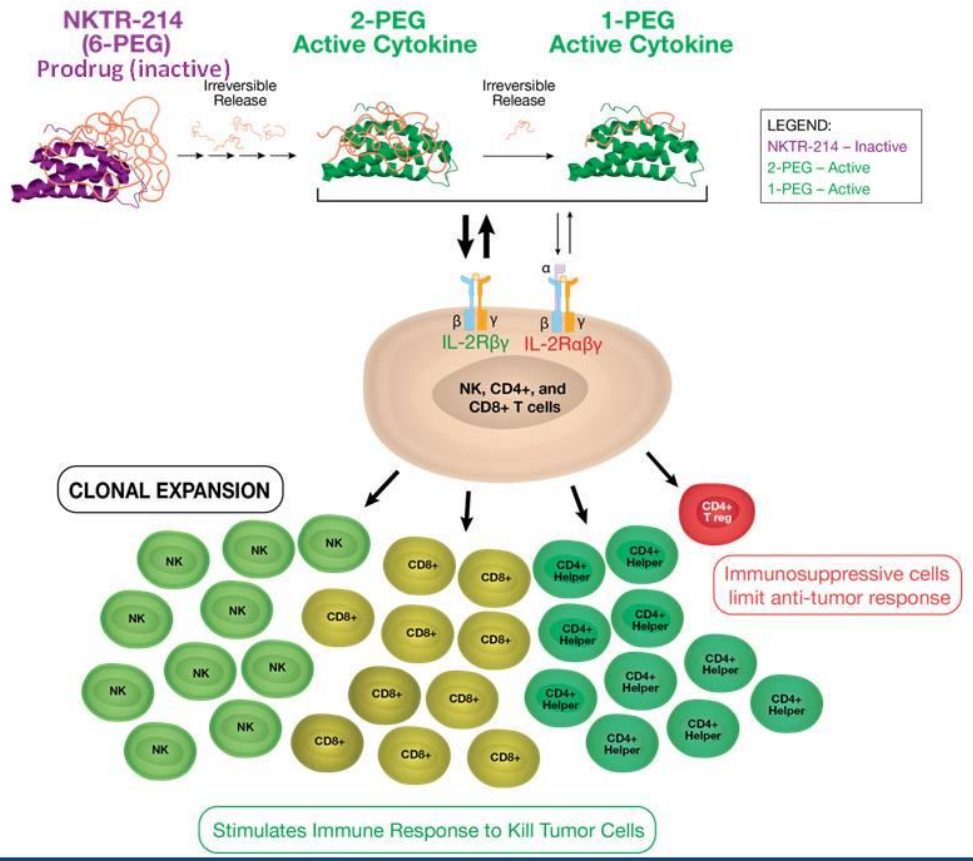
ClinicalTrials.gov Identifier: NCT02983045

Adi Diab[1], Michael Hurwitz[2], Daniel Cho[3], Vali Papadimitrakopoulou[1], Brendan Curti[4], Scott Tykodi[5], Igor Puzanov[6], Nuhad K. Ibrahim[1], Sara M. Tolaney[7], Debu Tripathy[1], Jianjun Gao[1], Arlene O. Siefker-Radtke[1], Wendy Clemens[8], Mary Tagliaferri[8], Scott N. Gettinger[2], Harriet Kluger[2], James M. G. Larkin[9], Giovanni Grignani[10], Mario Sznol[2], Nizar Tannir[1]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Yale School of Medicine, New Haven, CT, USA, [3]NYU Medical Oncology Associates, New York, NY, USA; [4]Providence Cancer Center and Earle A. Chiles Research Institute, Portland, OR, USA; [5]University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [6]Roswell Park Cancer Institute, Buffalo, NY, USA; [7]Dana Farber Cancer Institute, Boston, MA, USA; [8]Nektar Therapeutics, San Francisco, CA, USA; [9]Royal Marsden NHS Foundation Trust London, United Kingdom; [10]Candiolo Cancer Institute, Turin, Italy, Europe.

Presented By Adi Diab at 2018 ASCO Annual Meeting

NKTR-214 Background: Harnessing the IL-2 Pathway to Increase TILs



- NKTR-214 prodrug design with sustained signaling
- Mitigation of rapid immune stimulation to achieve safe, outpatient regimen administered every 3 week IV dosing
- Biased signaling preferentially activates and expands effector T cells and NK cells over Tregs in the tumor microenvironment
- NKTR-214 increases proliferation of TILs and PD-1 expression on the surface of CD8+ T cells providing a mechanistic rationale for combining with nivolumab

PIVOT-02 Study Dose-Escalation in I-O Treatment-Naïve Patients: Enrollment Complete

Phase 1 (N=38) Enrollment Compete

I-O Treatment-Naïve

- MEL 1L (with known BRAF status) (N=11)
- RCC 1L, 2L (N=22)
- NSCLC 1L, 2L (EGFR & ALK WT) (N=5)

- Confirmed locally advanced or metastatic solid tumors
- Measurable disease per RECIST 1.1
- ECOG 0 or 1
- Adequate organ function
- Fresh biopsy and archival tissue

NKTR-214 0.006 mg/kg Q3W + NIVO 240 mg Q2W

NKTR-214 0.003 mg/kg Q2W + NIVO 240 mg Q2W

NKTR-214 0.006 mg/kg Q2W + NIVO 240 mg Q2W

NKTR-214 0.006 mg/kg Q3W + NIVO 360 mg Q3W

RP2D N=25

NKTR-214 0.006 mg/kg Q3W + NIVO 360 mg Q3W

Maximum Administered Dose

NKTR-214 0.009 mg/kg Q3W + NIVO 360 mg Q3W

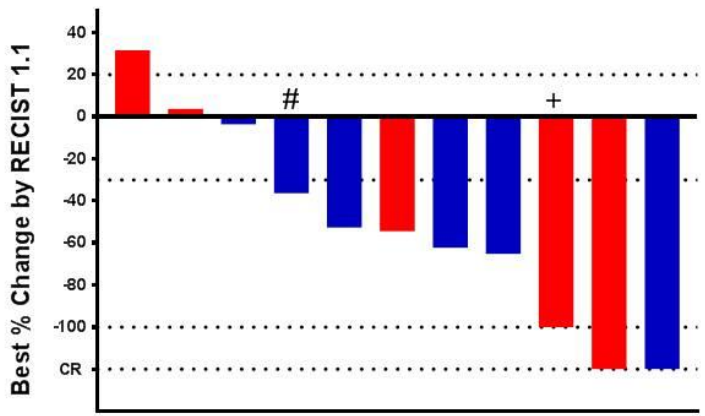
Dose Limiting Toxicities (N=2)

RP2D, recommended Phase 2 dosing

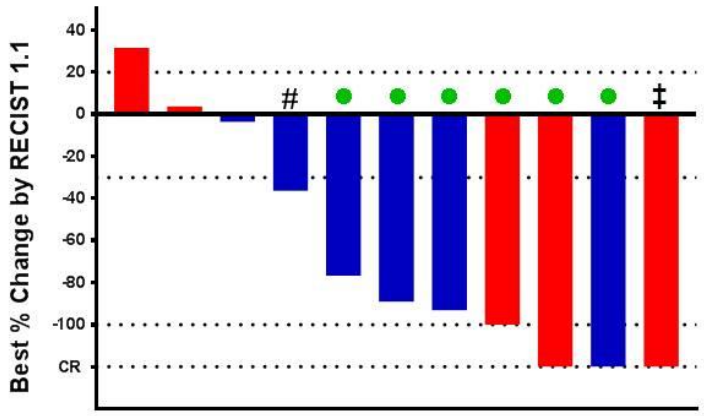
Stage IV IO-Naïve 1L Melanoma Dose Escalation Cohort (N=11)
Deepening of Responses Over Time

Best Overall Response by RECIST: ORR=7/11 (64%); DCR=10/11 (91%)

SITC 2017 (Data Cut: Nov 2, 2017)



ASCO 2018 (Data Cut: May 29, 2018)



PD-L1 Negative (<1%)
PD-L1 Positive (≥1%)
Treatment Ongoing
‡ Off Study Treatment (maximal clinical benefit achieved)

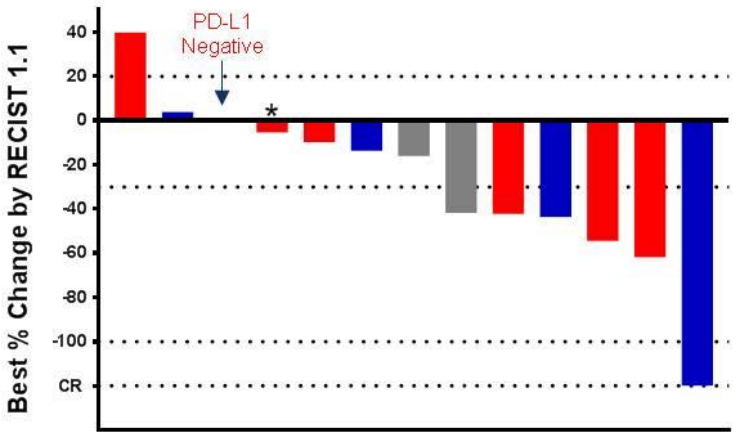
ORR PD-L1 (-) 3/5 (60%)
ORR PD-L1 (+) 4/6 (67%)

Horizontal dotted lines indicate the thresholds for PD, PR and CR response according to RECIST (version 1.1) criteria. CR: Complete response, all target and non-target lesions cleared.# Best Overall Response is SD (PR for target lesions, PD per new lesion on confirmatory scan) + Best overall response is PR to (CR for target lesions, non-target lesions still present).. -100% is PR (CR for target lesions, non-target lesions still present) "u": Unconfirmed.

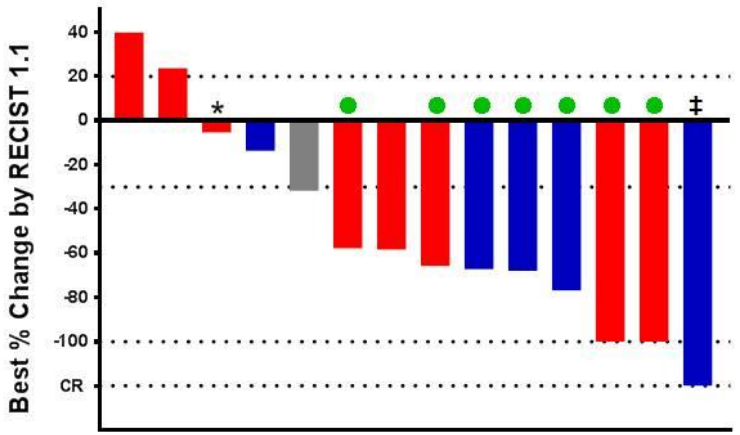
Stage IV IO-Naïve 1L RCC Dose Escalation Cohort (N=14)
Deepening of Responses Over Time

SITC 2017: ORR=6/13 (46%); DCR=11/13 (85%)
ASCO 2018: ORR=10/14 (71%); DCR=11/14 (79%)

SITC 2017 (Data Cut: Nov 2, 2017)



ASCO 2018 (Data Cut: May 29, 2018)



PD-L1 Negative (<1%)
PD-L1 Positive (≥1%)
Unknown
Treatment Ongoing
‡ Off Study Treatment (maximal clinical benefit achieved)

ORR PD-L1 (-) 5/8 (63%)
ORR PD-L1 (+) 4/5 (80%)
ORR PD-L1 Unknown 1/1

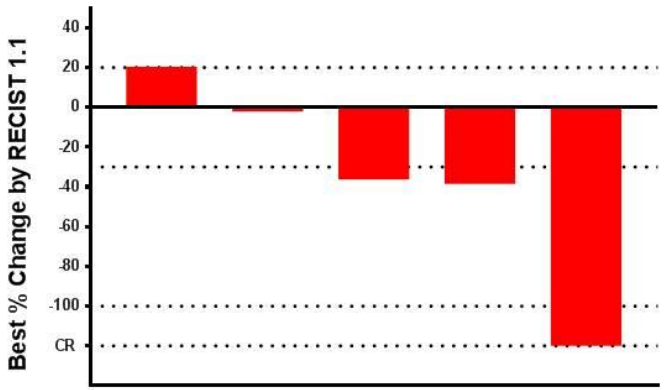
Increased ORR With Continued Treatment
Patients with Initial Stable Disease Convert to Responses Over Time

Horizontal dotted lines indicate the thresholds for PD, PR and CR response according to RECIST (version 1.1) criteria. *Best overall response is PD (SD for target lesions, PD per non-target lesions). "u": Unconfirmed.

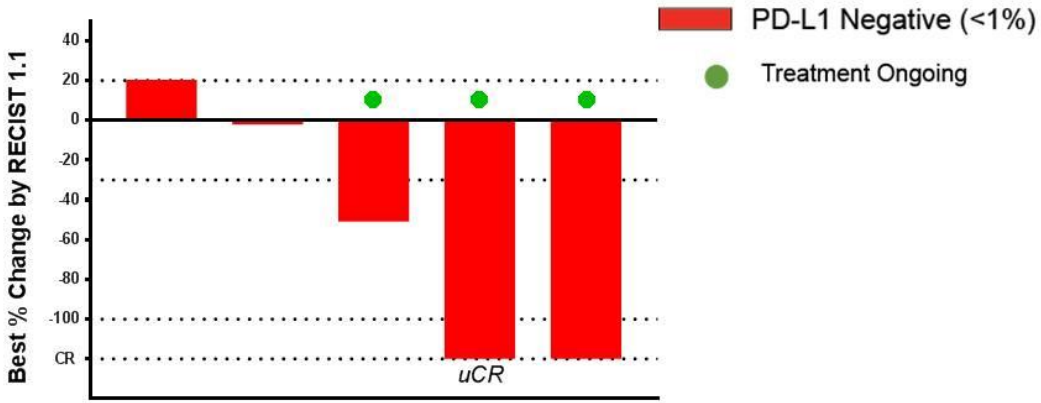
Stage IV IO-Naïve 1-2L NSCLC Dose Escalation Cohort (N=5)
Deepening of Responses Over Time in PD-L1 Negative Patients

Best Overall Response by RECIST (2L): ORR=3/4 (75%); DCR=3/4 (75%)
Best Overall Response by RECIST (1L and 2L): ORR=3/5 (60%); DCR=4/5 (80%)

SITC 2017 (Data Cut: Nov 2, 2017)

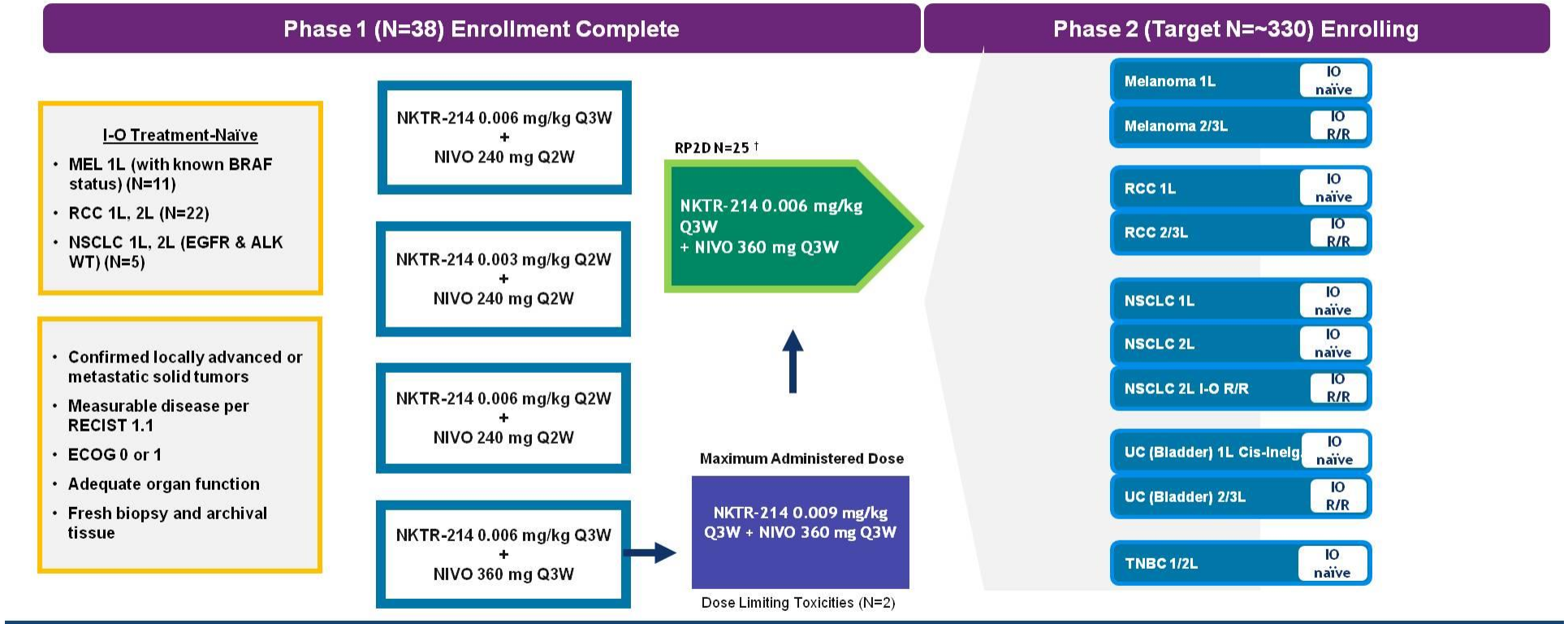


ASCO 2018 (Data Cut: May 29, 2018)



PDL1 positivity for this analysis was 1% or greater. Horizontal dotted lines indicate the thresholds for PD, PR and CR response according to RECIST (version 1.1) criteria., CR: Complete response, all target and non-target lesions cleared,. "u": Unconfirmed

PIVOT-02 RP2D Dose Expansion Cohorts in 5 Tumor Types: Enrollment Ongoing

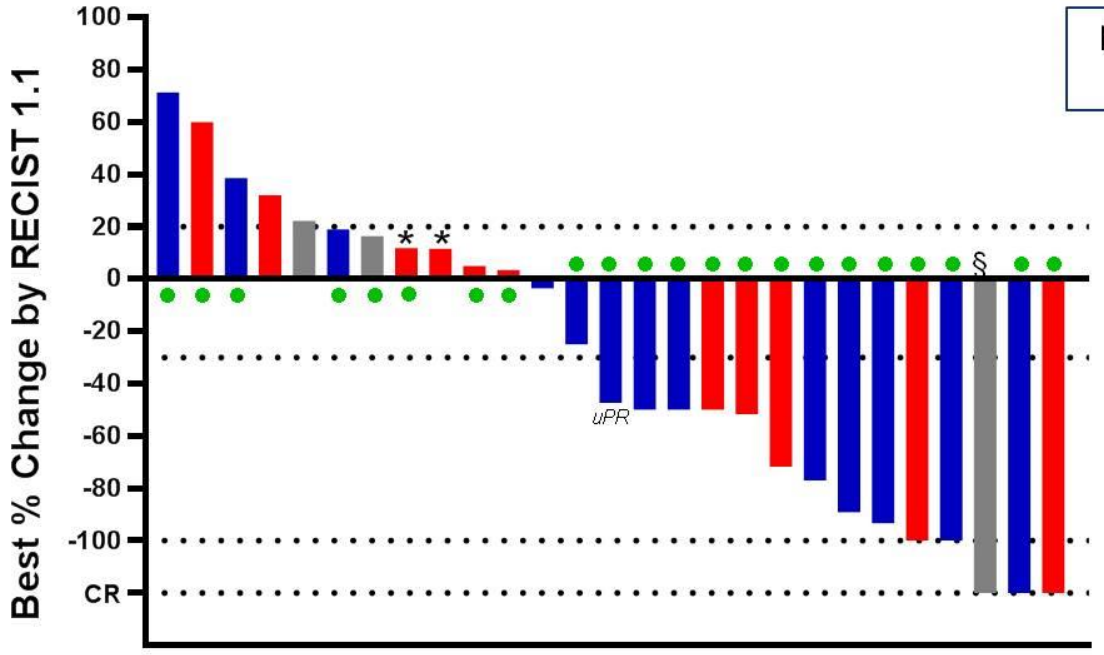


†7 patients from 1L melanoma dose escalation cohort, 11 patients from 1L RCC dose escalation cohort included in RP2D expansion cohorts
RP2D: recommended Phase 2 dosing

Presented By Adi Diab at 2018 ASCO Annual Meeting

Stage IV IO-Naïve 1L Melanoma Cohort at RP2D: Achieved Pre-Specified Efficacy Criteria

Stage 1: ORR 11/13 (85%)
Stage 2: Best Overall Response ORR=14/28 (50%); DCR=20/28 (71%)



Median Time on Study 4.6 Months (N=28)
As of May 29, 2018

PD-L1 Negative (<1%)
PD-L1 Positive (≥1%)
PD-L1 Unknown
Treatment Ongoing

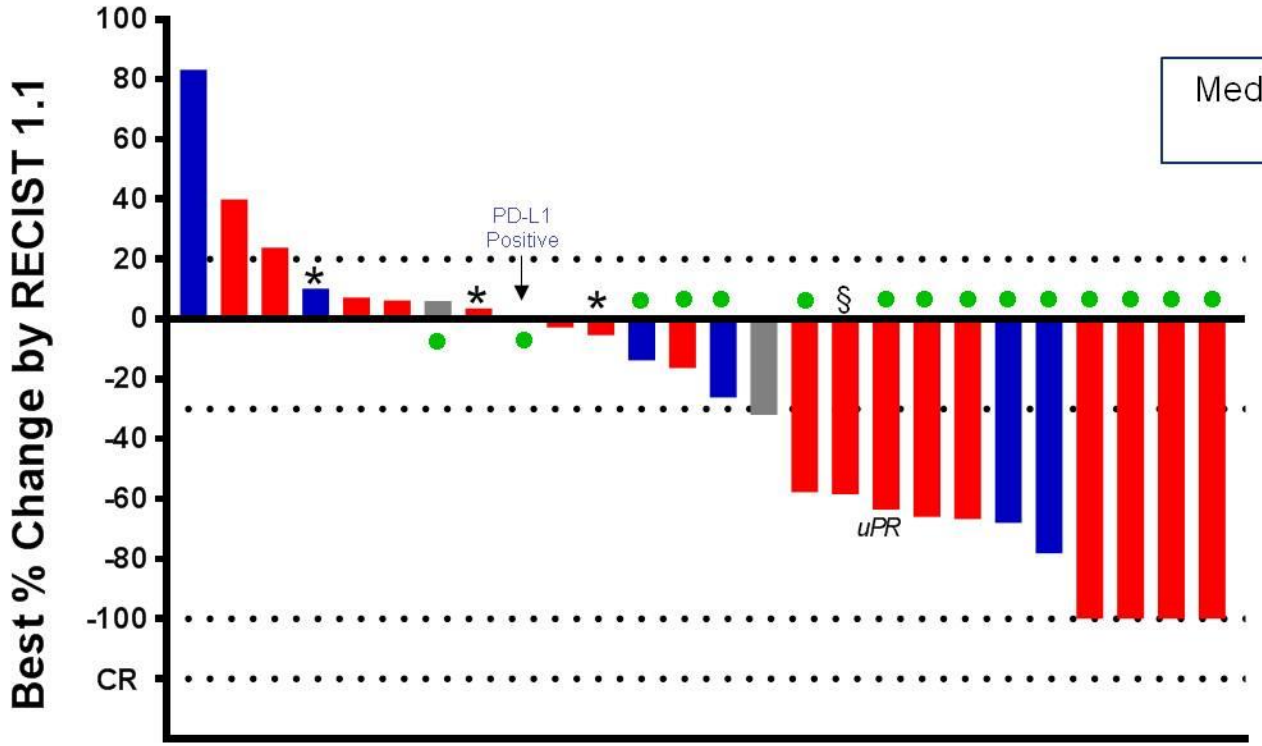
ORR PD-L1 (-) 5/12 (42%)
ORR PD-L1 (+) 8/13 (62%)
ORR PD-L1 Unknown 1/3 (33%)

Data cut: May 29, 2018

Horizontal dotted lines indicate the thresholds for PD, PR and CR response according to RECIST (version 1.1) criteria. -100% is PR for complete clearance of target lesions. CR is a complete response. "u": Unconfirmed. *Best overall response is PD; SD for target lesions but PD due to a new lesion. §Off study treatment with confirmed CR due to patient decision.
One PD-L1(-) patient had PD due to non-target lesions and target lesions were not assessed, therefore 27/28 patients included in waterfall plot..

Stage IV IO-Naïve 1L RCC Cohort Achieved Pre-Specified Efficacy Criteria

Stage 1: ORR 7/11 (64%)
Stage 2: Best Overall Response ORR=12/26 (46%); DCR=20/26 (77%)



Median Time on Study 5.6 Months (N=26)
As of May 29, 2018

PD-L1 Negative (<1%)
PD-L1 Positive (≥1%)
PD-L1 Unknown
Treatment Ongoing

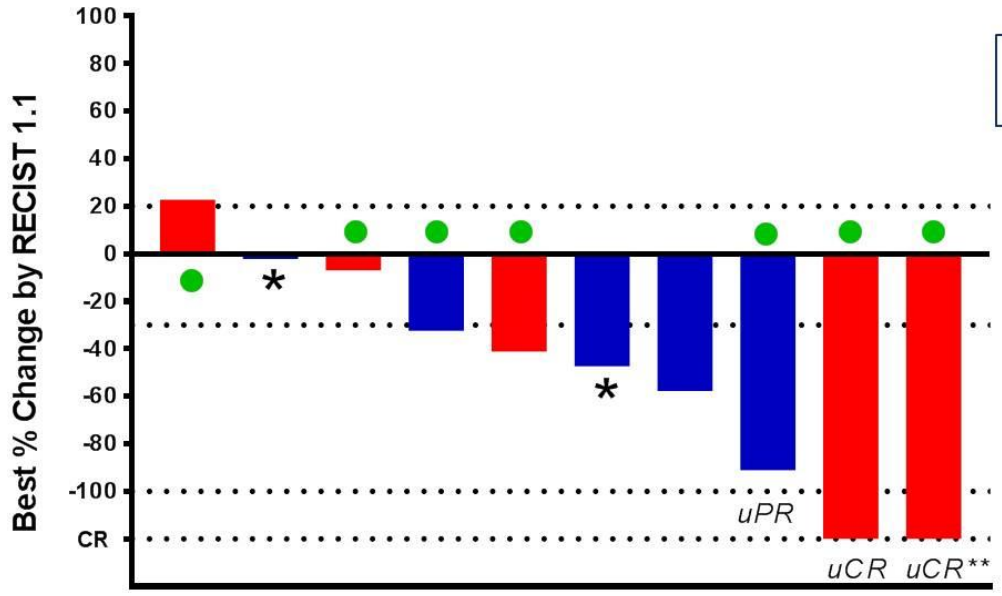
ORR PD-L1 (-) 9/17 (53%)
ORR PD-L1 (+) 2/7 (29%)
ORR PD-L1 Unknown 1/2 (50%)

Data cut: May 29, 2018

Horizontal dotted lines indicate the thresholds for PD, PR and CR response according to RECIST (version 1.1) criteria; -100% is PR for complete clearance of target lesions. CR is a complete response, "u": Unconfirmed. *Best overall response is PD (SD for target lesions, PD for non-target lesions). §Off study treatment with confirmed PR due to patient decision.

Stage IV IO-Naïve 1L Urothelial Cohort (Cisplatin-Ineligible) Achieved Pre-Specified Efficacy Criteria

Stage 1: Best Overall Response ORR=6/10 (60%); DCR=7/10 (70%)



Median Time on Study 3.9 Months (N=10)
As of May 29, 2018

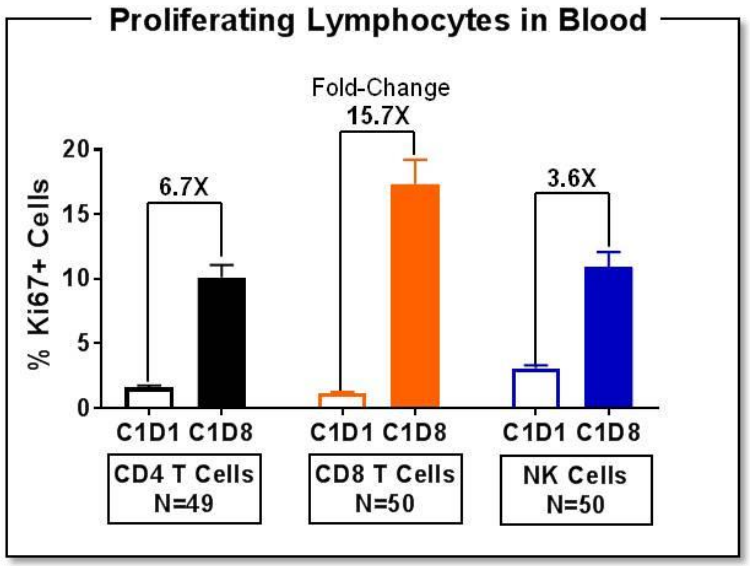
PD-L1 Negative (<1%)
PD-L1 Positive (≥1%)
Treatment Ongoing

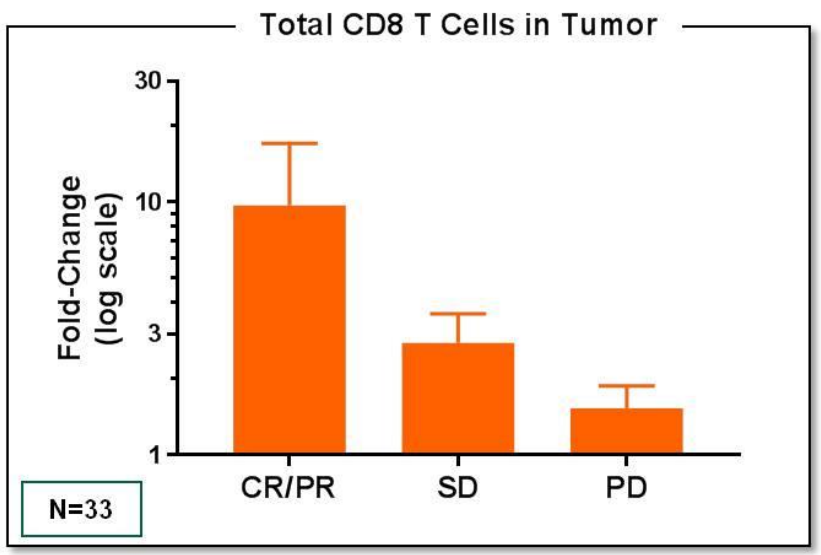
ORR PD-L1(-) 3/5 (60%)
ORR PD-L1(+) 3/5 (60%)

Data cut: May 29, 2018

Horizontal dotted lines indicate the thresholds for PD, PR and CR response according to RECIST (version 1.1) criteria.
"u": Unconfirmed. -100% is PR for complete clearance of target lesions. CR is a complete response. *Best overall response is PD due to new lesion or non-target lesion progression. **uCR (confirmed PR by prior scan).

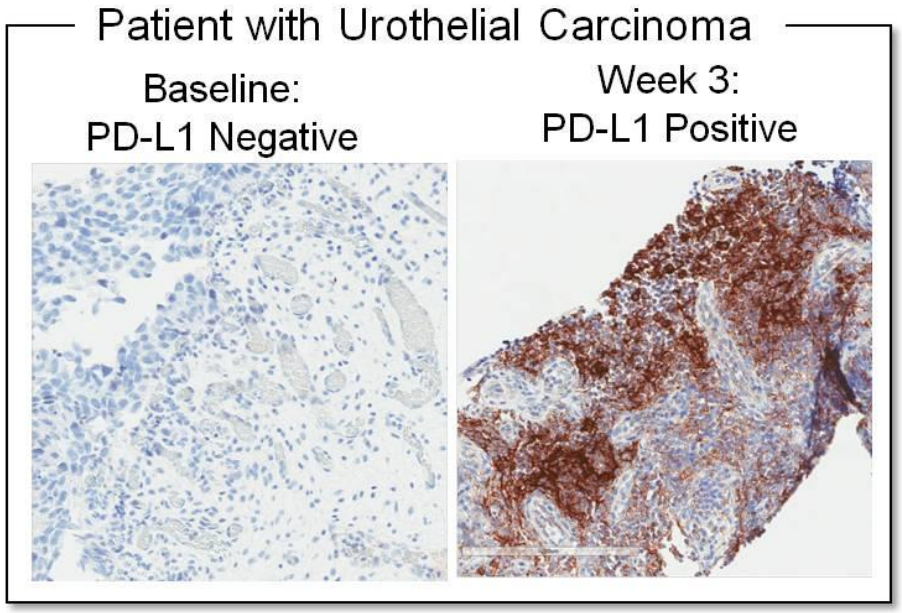
NKTR-214 + Nivolumab Increased Lymphocyte Proliferation in Blood and CD8 T Cells in Tumor

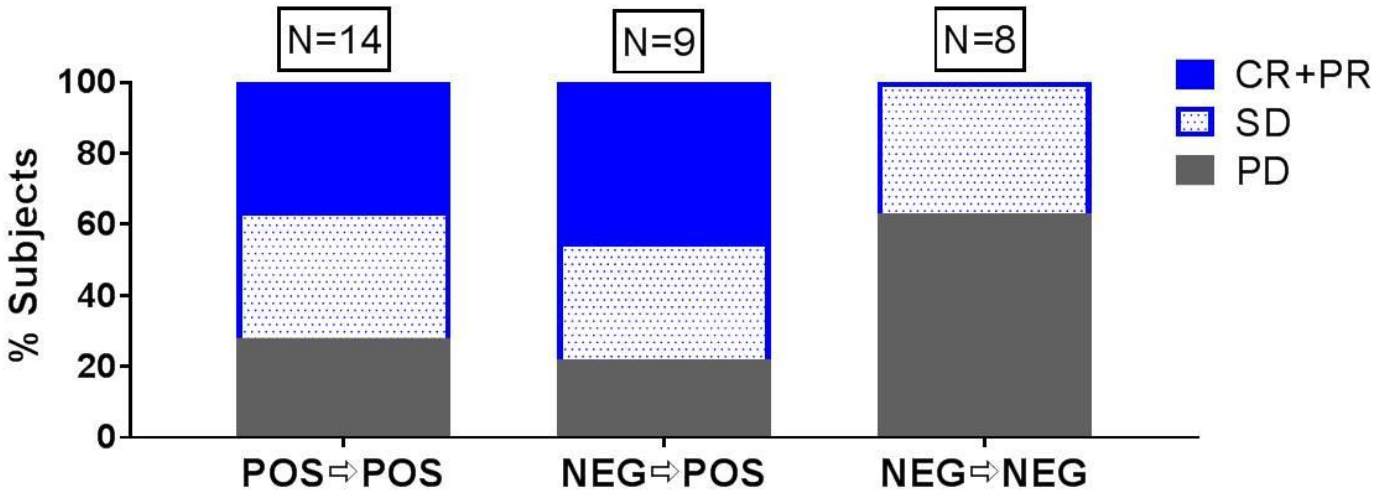




"Proliferating Lymphocytes in Blood" were measured using flow cytometry of fresh whole blood for all patients that the met inclusion criteria and had matched Cycle 1 Day 1 (C1D1) and Cycle 1 Day 8 (C1D8) blood collections. Data presented as mean ± standard error. Fold-change calculated for C1D8/C1D1. Ki67 is a marker of proliferation. "Total CD8 T Cells in Tumor" measured using immunohistochemistry using biopsy specimens collected at baseline and week 3. Cells/mm² were counted and fold-change calculated for week3/baseline, data presented as mean ± standard error.

Conversion of PD-L1(-) to PD-L1(+) in Tumor Biopsies from Baseline to Week 3 is Associated with Clinical Benefit



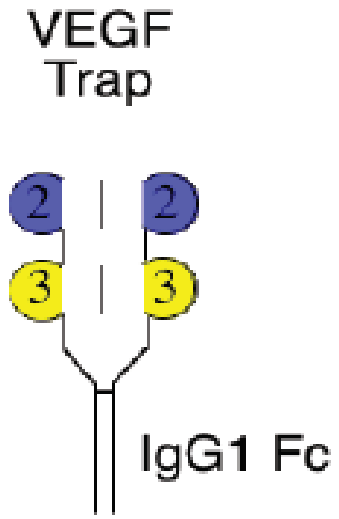


- NKTR-214 + nivolumab can convert PD-L1(-) tumors to PD-L1(+)
  - PD-L1 negative to positive conversion in 9/17 (53%) of patients
- Patients that were PD-L1(+) at baseline, or converted to PD-L1(+) after start of treatment showed greatest clinical benefit

31 patients were available with matched baseline and week 3 results for PD-L1 status. Of these, 17 were PD-L1 negative at baseline. PD-L1 was assessed on tumor cells using a validated 28-8 method. Example image shown for UC patient at baseline and week 3, 20x magnification.

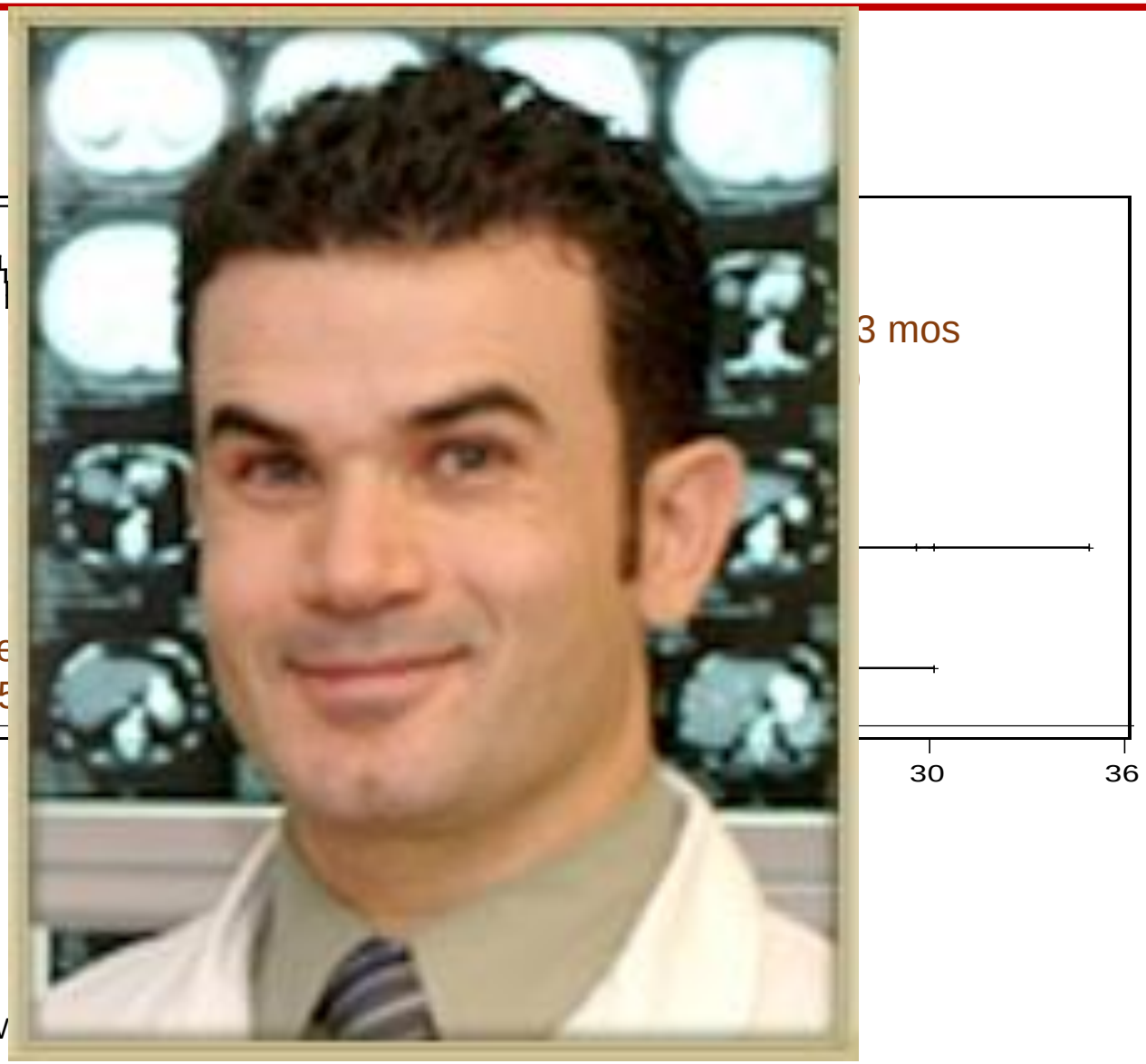
VEGF Trap

- Aflibercept (VEGF Trap) is a fusion protein combining the Fc portion of human IgG1 with the principal extracellular ligand-binding domains of human VEGFR1 & VEGFR2



- Acts as a high-affinity soluble decoy VEGF receptor and potent angiogenesis inhibitor
- Aflibercept has highest binding affinity for VEGF described to date. Dissociation constant 0.5 pM

Kaplan – Meier plots of the probability of OS and PFS (N=40)



Tarhini et. al. Clin Cancer Res 2011

IL-2 and Ipilimumab are FDA approved drugs for the treatment of melanoma

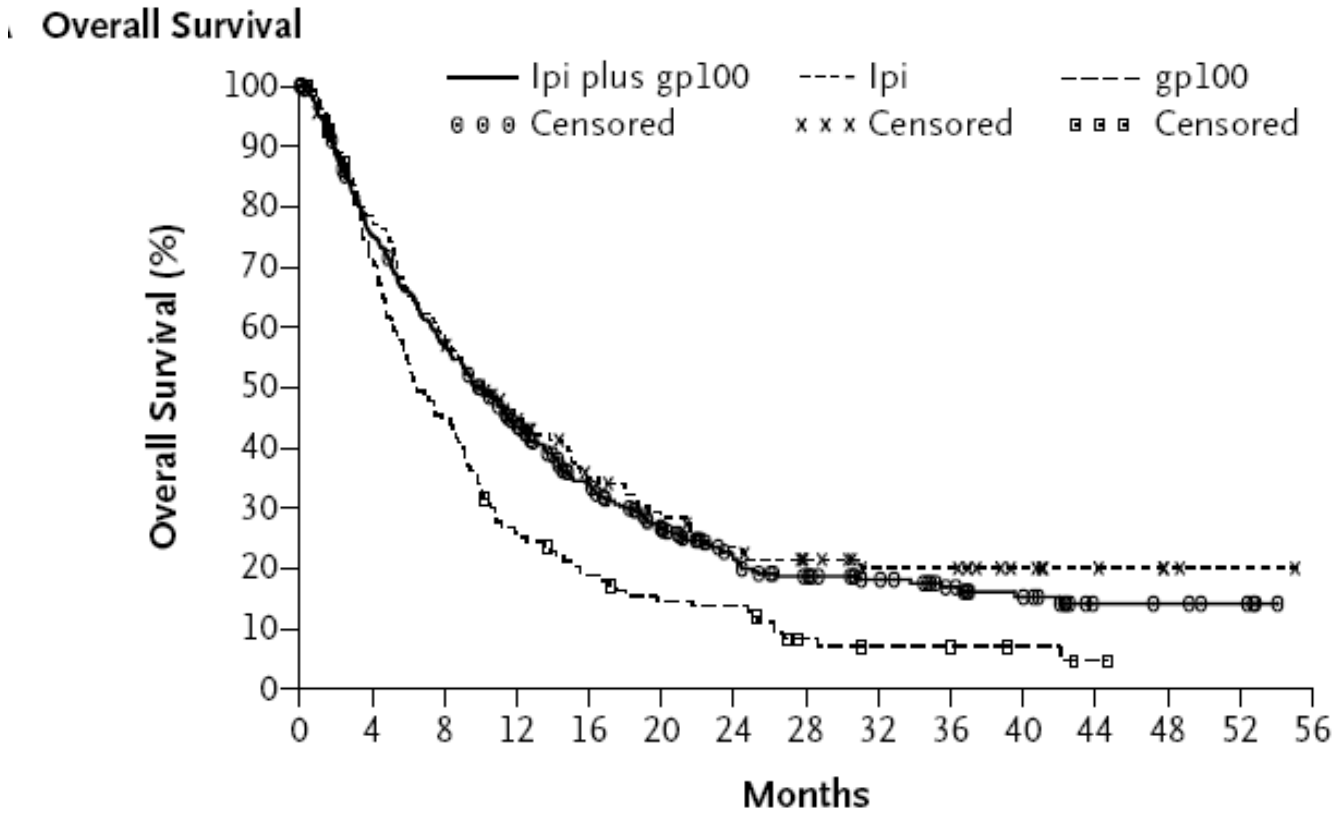
Proleukin (IL-2)

- Cytokine that promotes proliferation and cytotoxicity of T cells and NK cells
- Extensively evaluated in patients with cancer
- Results in durable objective responses in 16-17%
- FDA approved for metastatic melanoma in 1998

Ipilimimab (αCTLA-4)

- Monoclonal antibody that blocks CTLA-4 binding to B7
- Promotes anti-tumor activity through T cells
- Demonstrated improved overall survival in Phase III trial
- FDA approved for metastatic melanoma in 2011

Ipilumimab improves overall survival



Phase I/II Trial of IL-2 and Ipilumimab

- NCI Surgery Branch trial
- 36 patients with metastatic melanoma
- 3 patients treated with Ipilumab at 0.1, 0.3, 1.0 and 2.0 mg/kg every 3 weeks X 3
- 24 patients treated with Ipilumimab at 3.0 mg/kg every 3 weeks X 3
- All patients received IL-2 (720,000 IU/kg) after the 2nd and 3rd dose of Ipilumimab

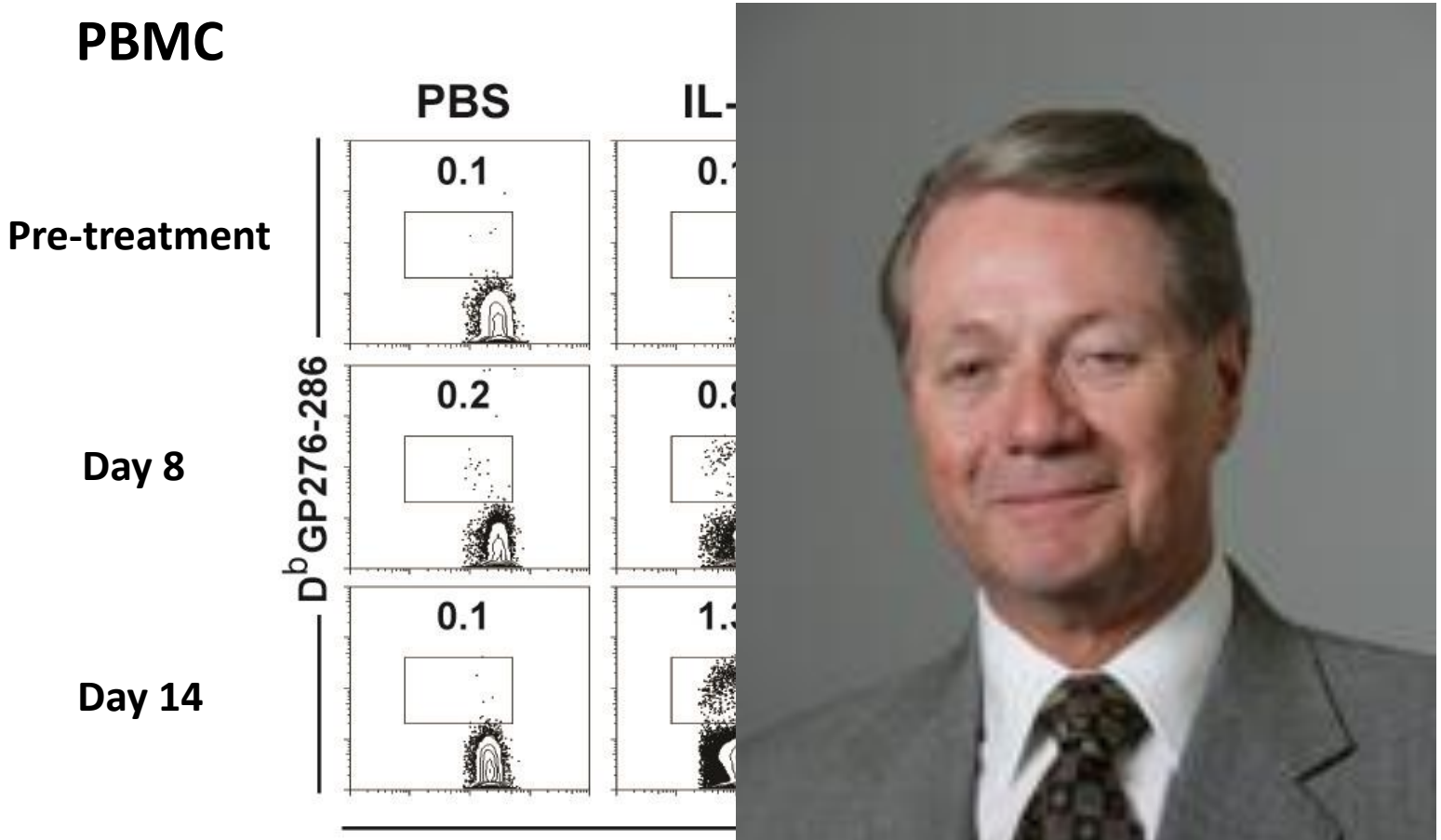
- 8/36 (22%) had an objective response
  - 3 CR
  - 5 PR
  - 6/8 ongoing >11-19 months
- 5/36 (14%) developed grade III/IV Ipi-related toxicities
- No correlation between Ipi dose and response or toxicity-all patients recovered

Study Update

- Median follow-up of 71 months

- 25% objective response rate
- 17% complete response
- Median survival of 16 months

IL-2 therapy synergizes with PD-1 blockade to rescue exhausted CD8 T cells chronic infection



Gated on CD8⁺ cells

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Kendall Smith, Rafi Ahmed

Interleukin 7 (IL-7)

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Alpdogan et al, Blood 2001;98:2256-226; Alpdogan et al, J. Clin. Invest. 2003; 112:1095–1107; Rosenberg et al, J Immunother 2006;29:313–319; Sportes et al, J Exp Med 2008; 205: 1710-1714; Levy et al, J. Clin. Invest. 2009; 119:997–1007; Sereti et al, Blood 2009: 113:6304-6314; Sportes et al, Clin Cancer Res 2010; 16: 727–735.

Administration of interleukin-7 after allogeneic bone marrow transplantation improves immune reconstitution without aggravating graft-versus-host disease

Onder Alpdogan, Cornelius Schmaltz, Stephanie J. Muriglan, Barry J. Kappel, Miguel-Angel Perales, Jimmy A. Rotolo, Jens A. Halm, Benjamin E. Rich, and Marcel R. M. van den Brink

Alpdogan et al, Blood 2001;98:2256-226

IL-7 enhances peripheral T cell reconstitution after allogeneic hematopoietic stem cell transplantation

Önder Alpdogan, Stephanie J. Muriglan, Jeffrey M. Eng, Lucy M. Willis, Andrew S. Greenberg, Barry J. Kappel, and Marcel R.M. van den Brink

Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York, USA

Alpdogan et al, J. Clin. Invest. 2003; 112:1095–1107.

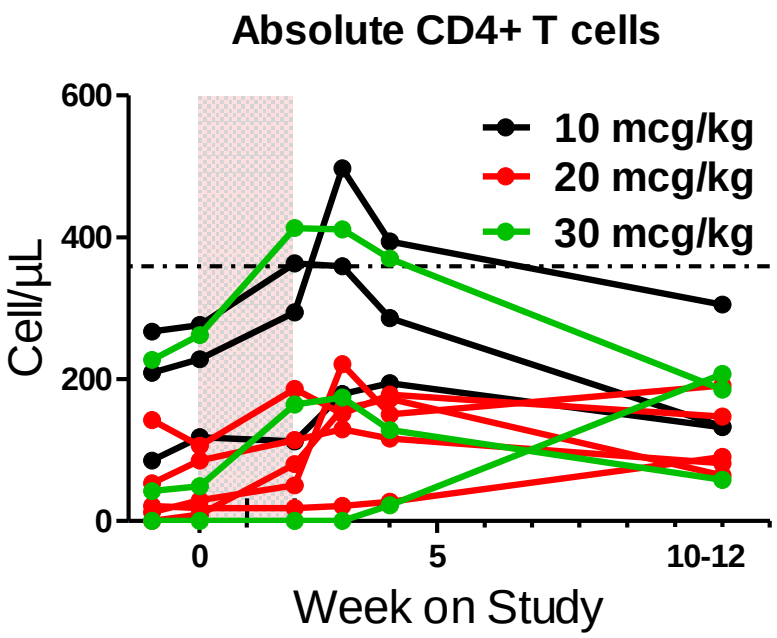
IL-7 – Initial Clinical Trials with CYT99 007

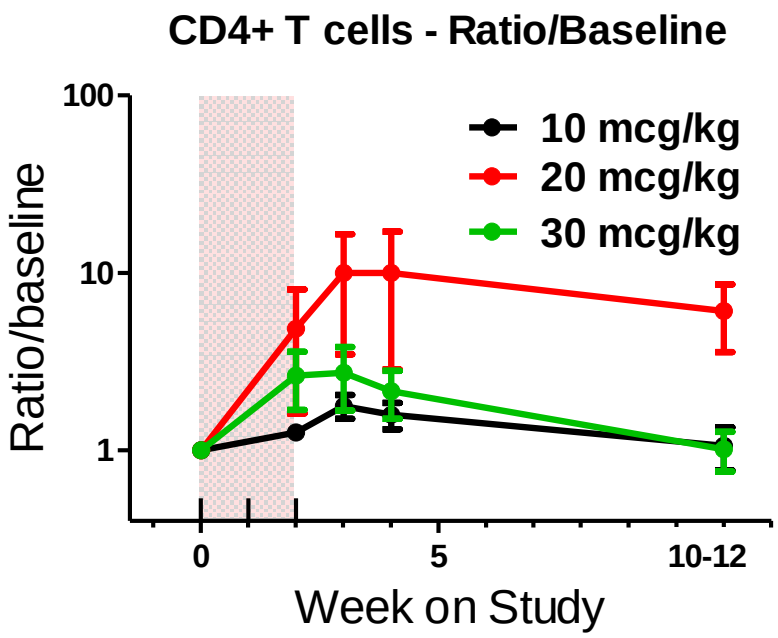
Table - 62 patients treated on 5 clinical trials with CYT 99 007

Study	Indication	N	IL-7 Dose	Outcome	*Ref*
1	Solid tumor	12	3 – 60 mcg/kg x8 + gp100 & MART1 pept vaccine	Rise in CD4 and CD8 T cells Decrease in Tregs	*1*
2	Solid tumor	16	3 – 60 mcg/kg x8	Rise in CD4 and CD8 T cells No objective tumor responses	*2,3*
3	HIV	19	3 – 30 mcg/kg x1	Rise in CD4 and CD8 T cells Transient rise in HIV RNA	*4*
4	HIV	14	3 – 10 mcg/kg x8	Rise in CD4 and CD8 T cells Transient rise in HIV RNA Rise in HIV-spec CD4 T cells	*5*
5					

[1]Rosenberg et al, J Immunother 2006;29:313–319; [2]Sportes et al, J Exp Med 2008; 205: 1710-1714; [3]Sportes et al, Clin Cancer Res 2010; 16: 727–735; [4]Sereti et al, Blood 2009: 113:6304-6314; [5]Levy et al, J. Clin. Invest. 2009; 119:997–1007; [6]Perales et al, unpublished.

rhIL-7 (CYT107) increases CD4+ T cell counts post TCD allo-HSCT



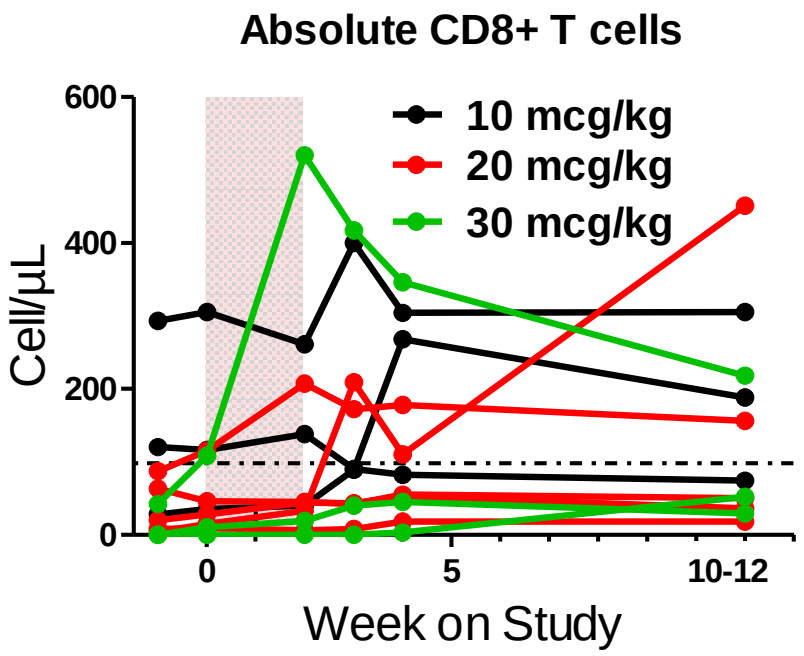


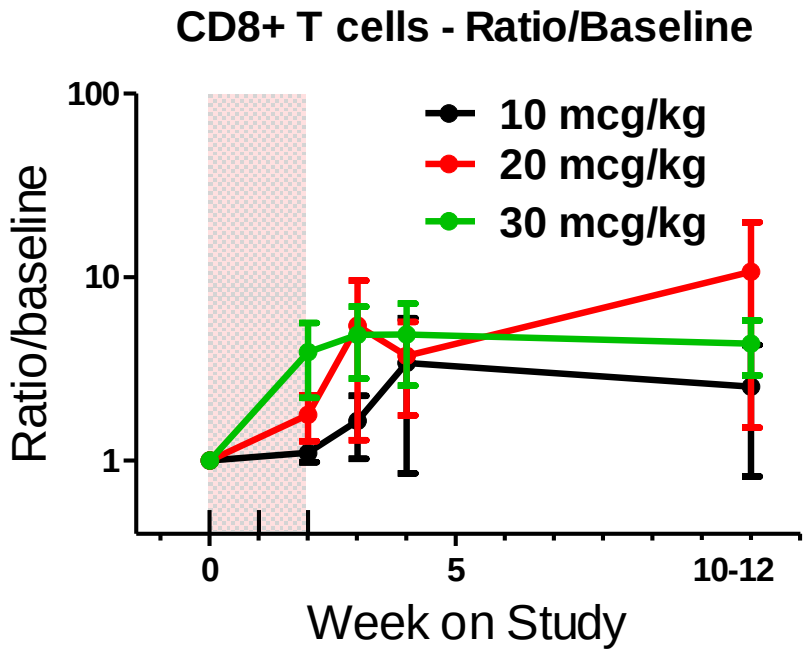
107.4/mm³ average increase at day 21, p=0.002
(range 0 to 35-fold increase)

Perales, CITN Investigator Meeting – Nov 2013

Perales, Blood. 2012 Dec 6;120(24):4882-91

rhIL-7 (CYT107) increases CD8+ T cell counts post TCD allo-HSCT



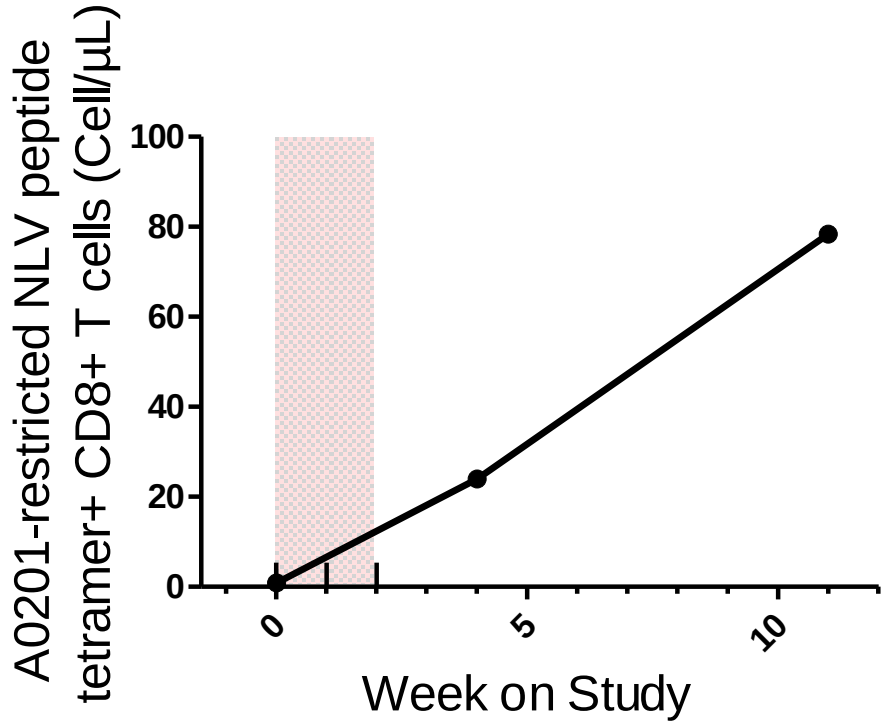


66.9/mm³ average increase at day 28, p=0.05
(range 0 to 11-fold increase)

Perales, CITN Investigator Meeting – Nov 2013

Perales, Blood. 2012 Dec 6;120(24):4882-91

CMV-specific responses were increased in a patient with a history of CMV viremia

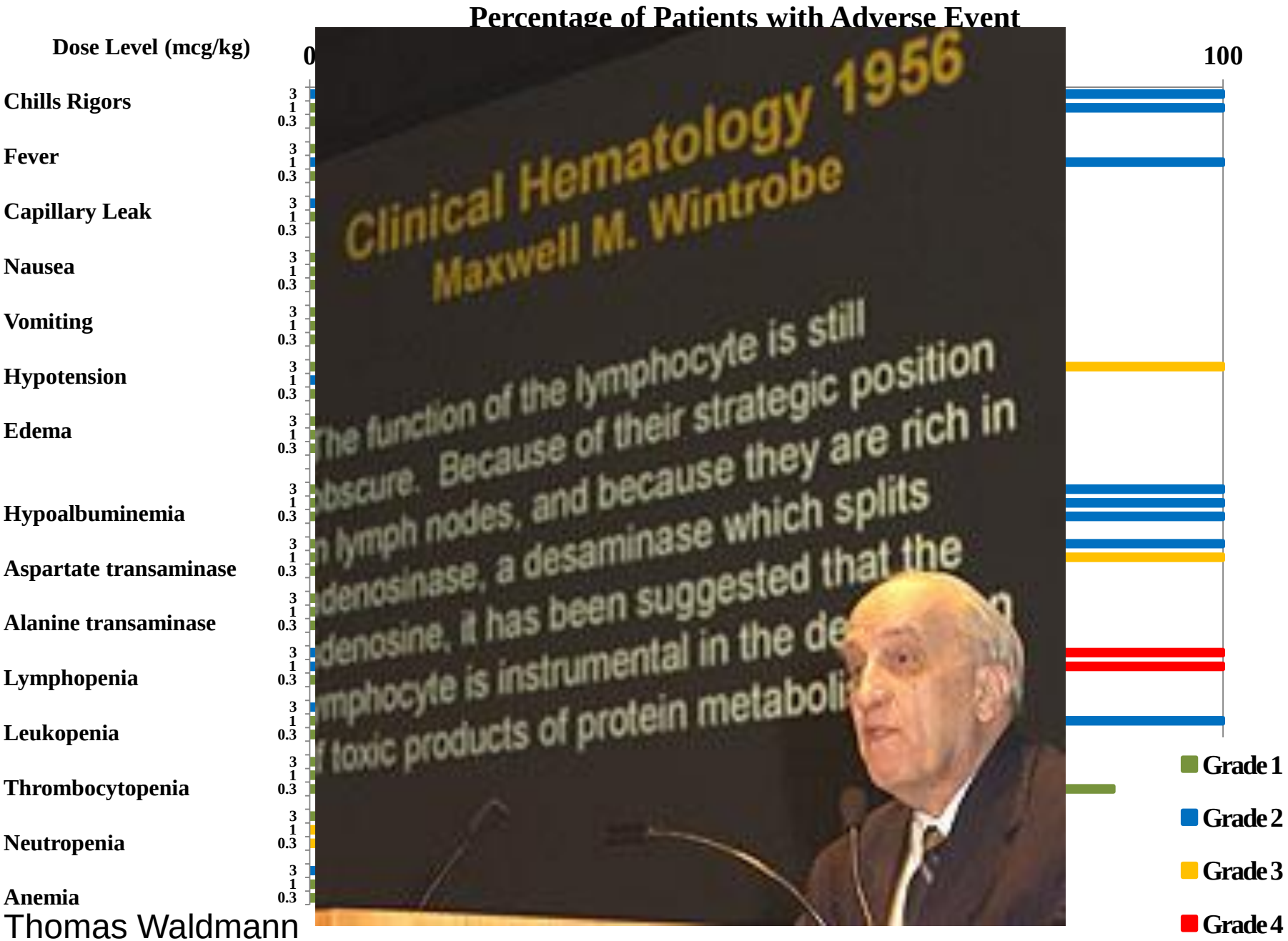


CMV responses were also detected after rhIL-7 injection in 2 other CMV-seropositive patients

Perales, CITN Investigator Meeting – Nov 2013

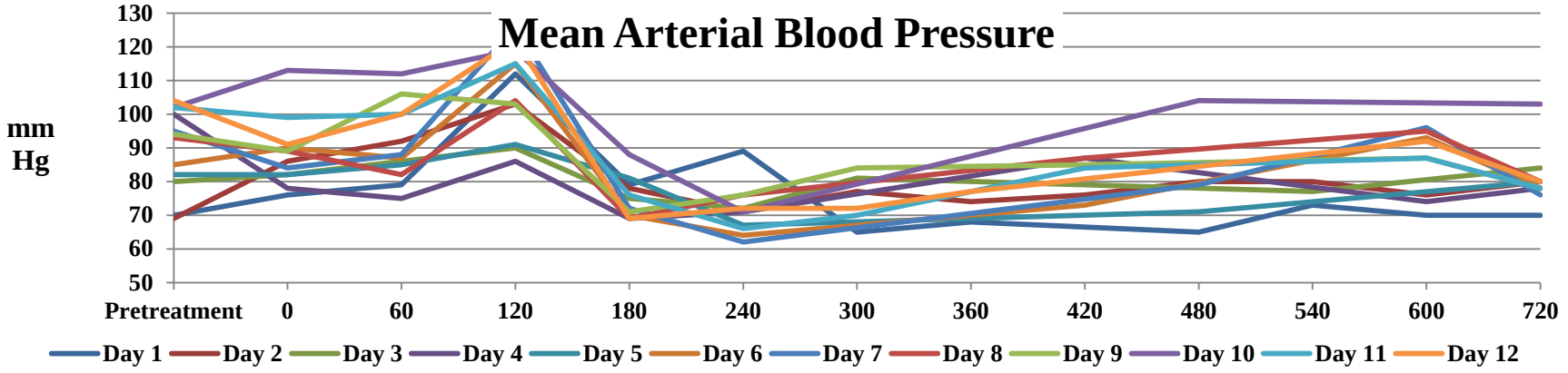
Perales, Blood. 2012 Dec 6;120(24):4882-91

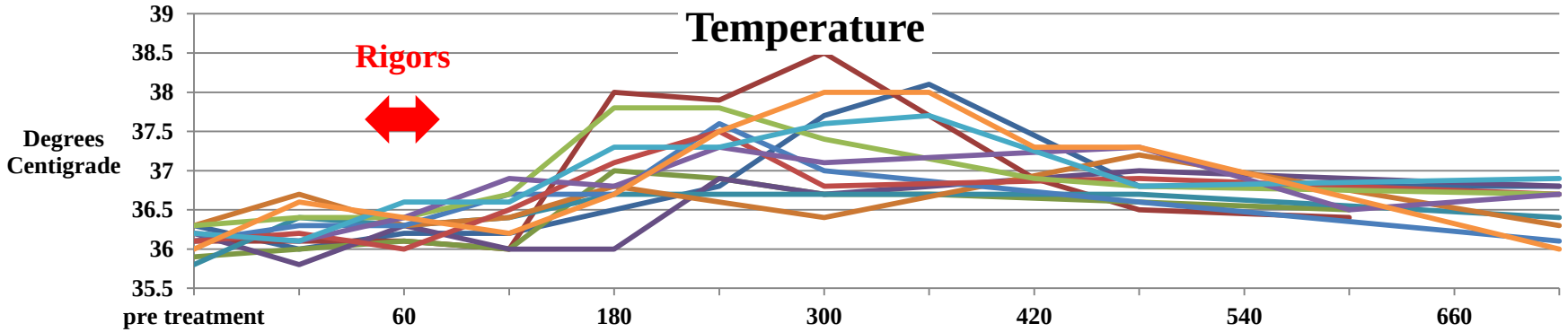
Interleukin 15 Adverse Event Summary

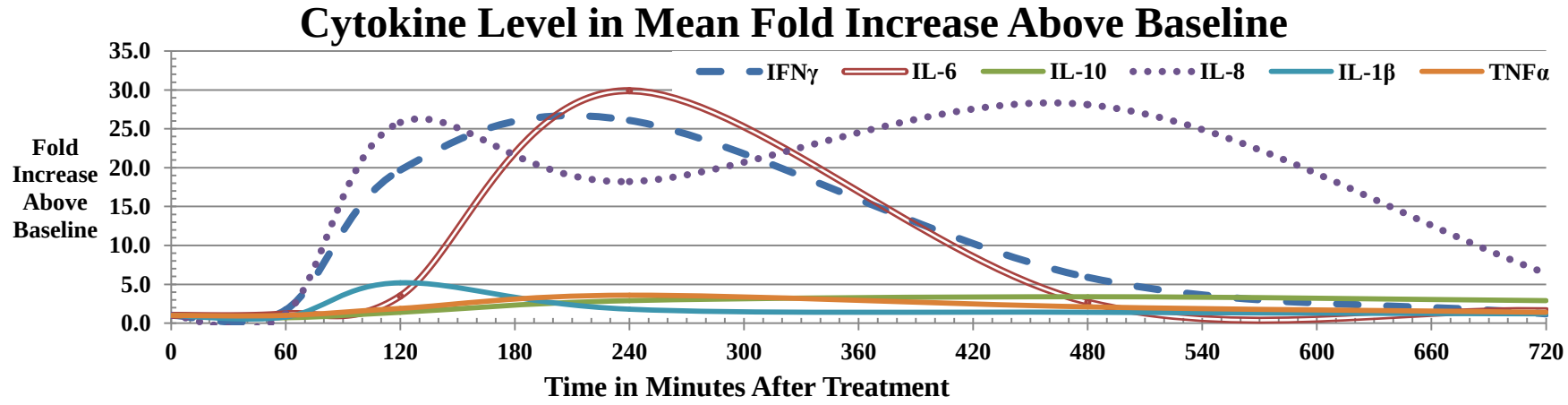


Thomas Waldmann

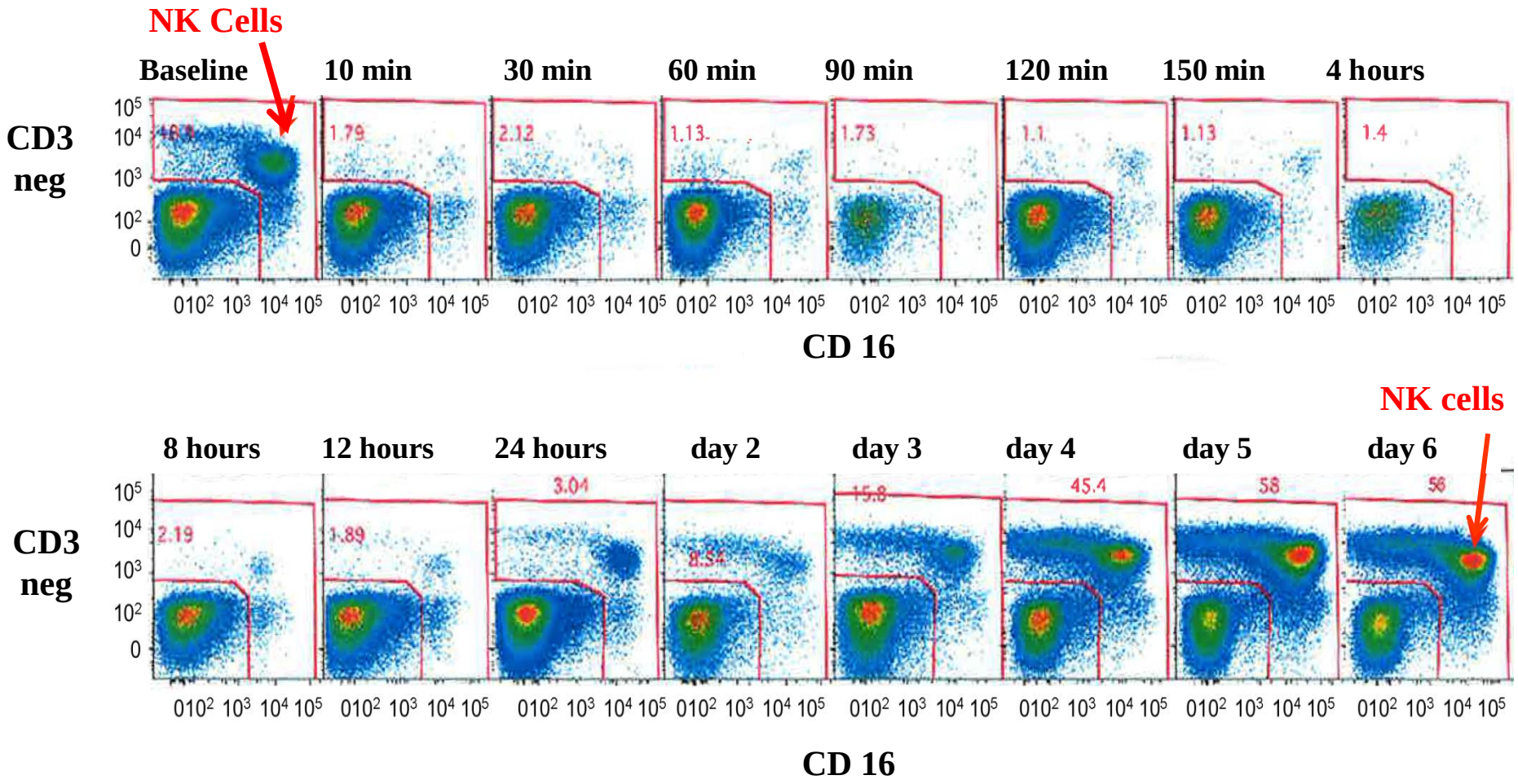
Cytokine Release and Adverse Events 3 mcg patients





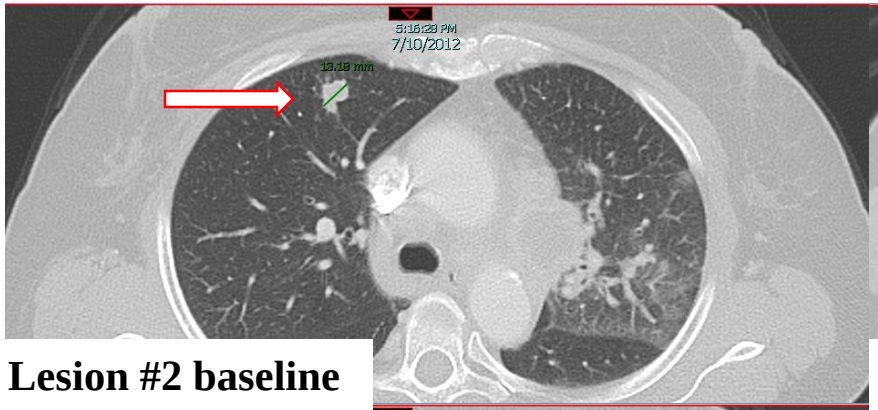


Rapid Disappearance Of NK Cells rhIL-15 Treatment

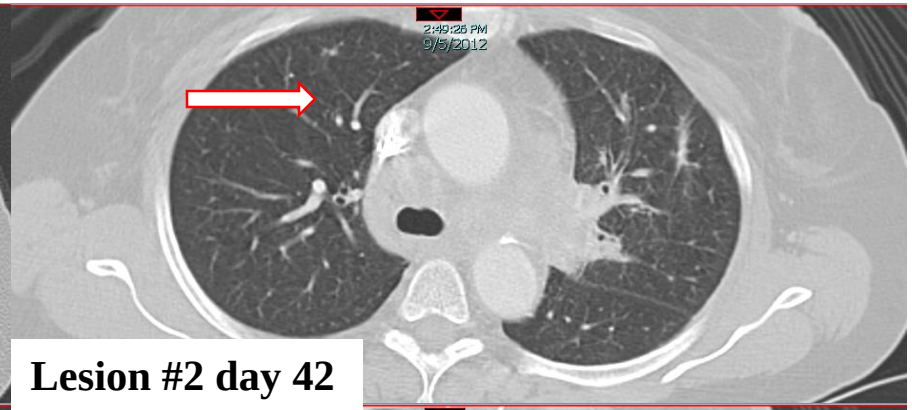


Clinical Activity

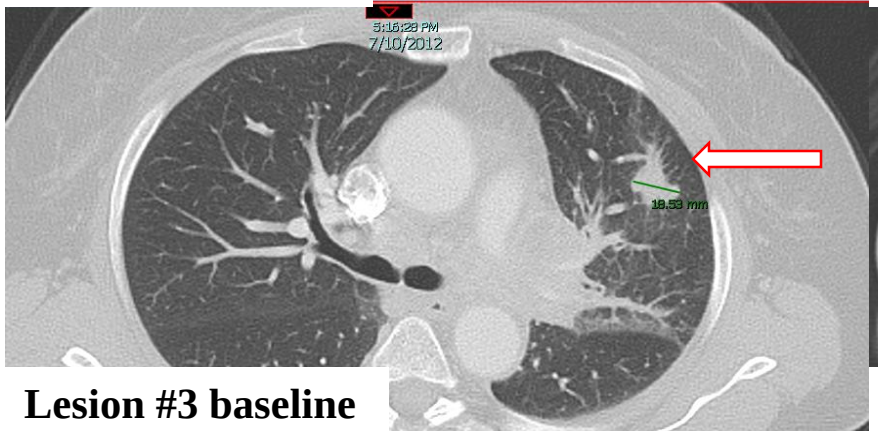
Patient #16 Unconfirmed PR at day 42 restaging



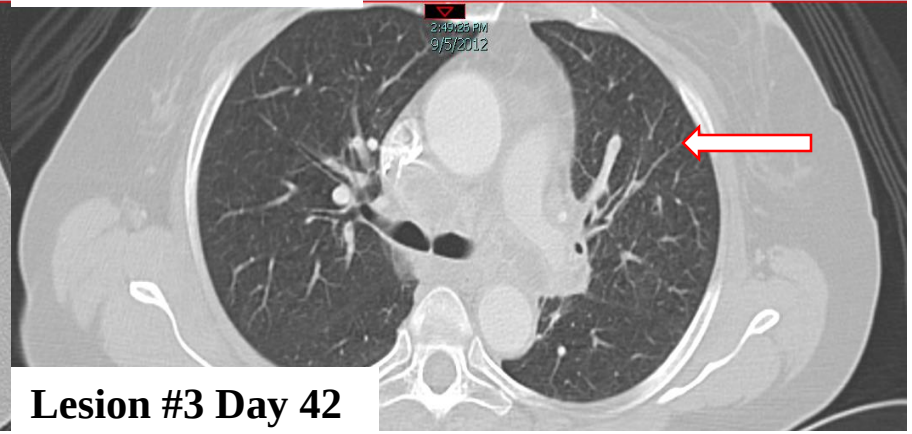
Lesion #2 baseline



Lesion #2 day 42

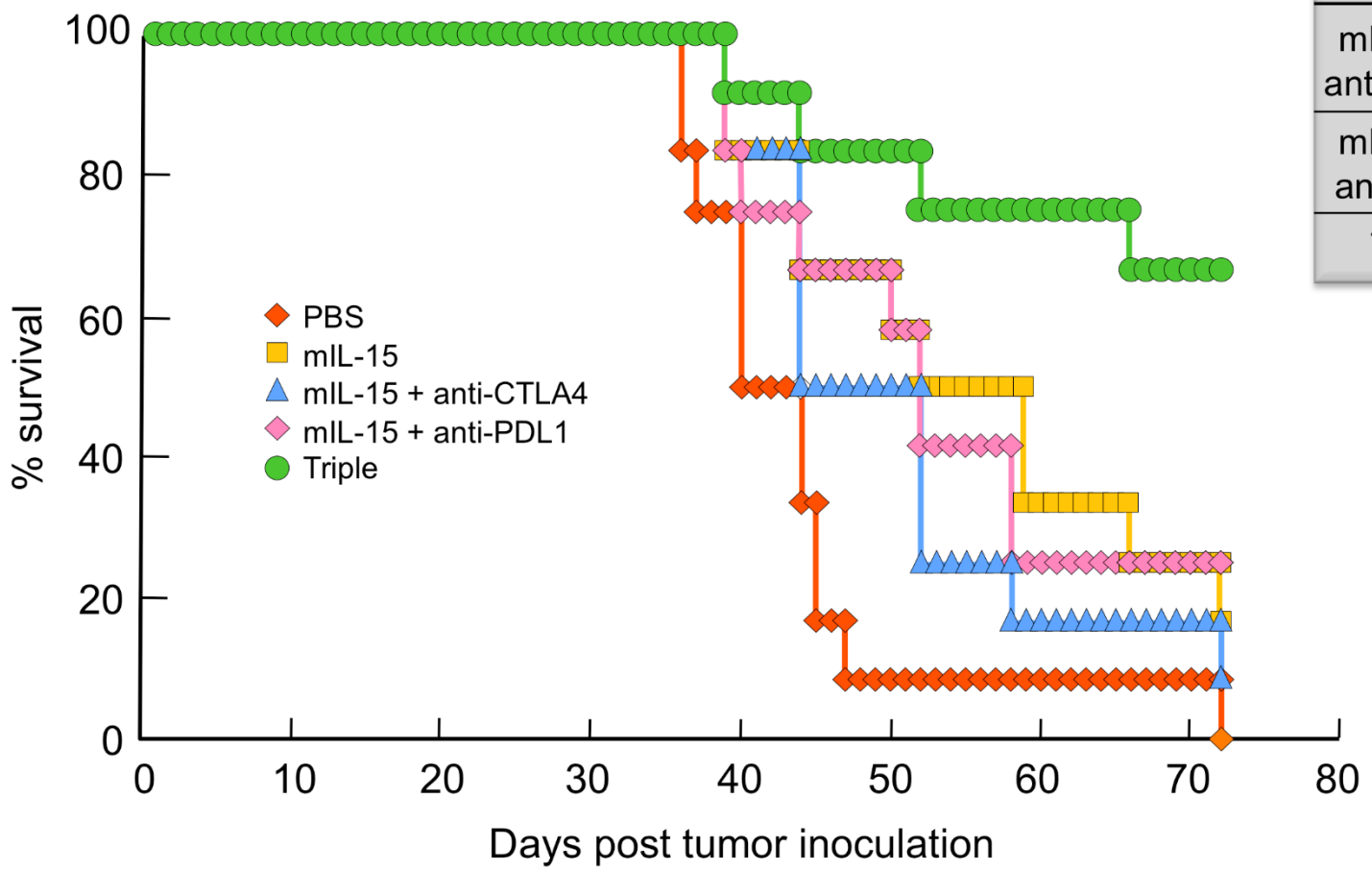


Lesion #3 baseline



Lesion #3 Day 42

The Combination of mIL-15, Anti-CTLA4 and Anti-PDL1 Enhances Survival of TRAMP-C2 Tumor Bearing Animals

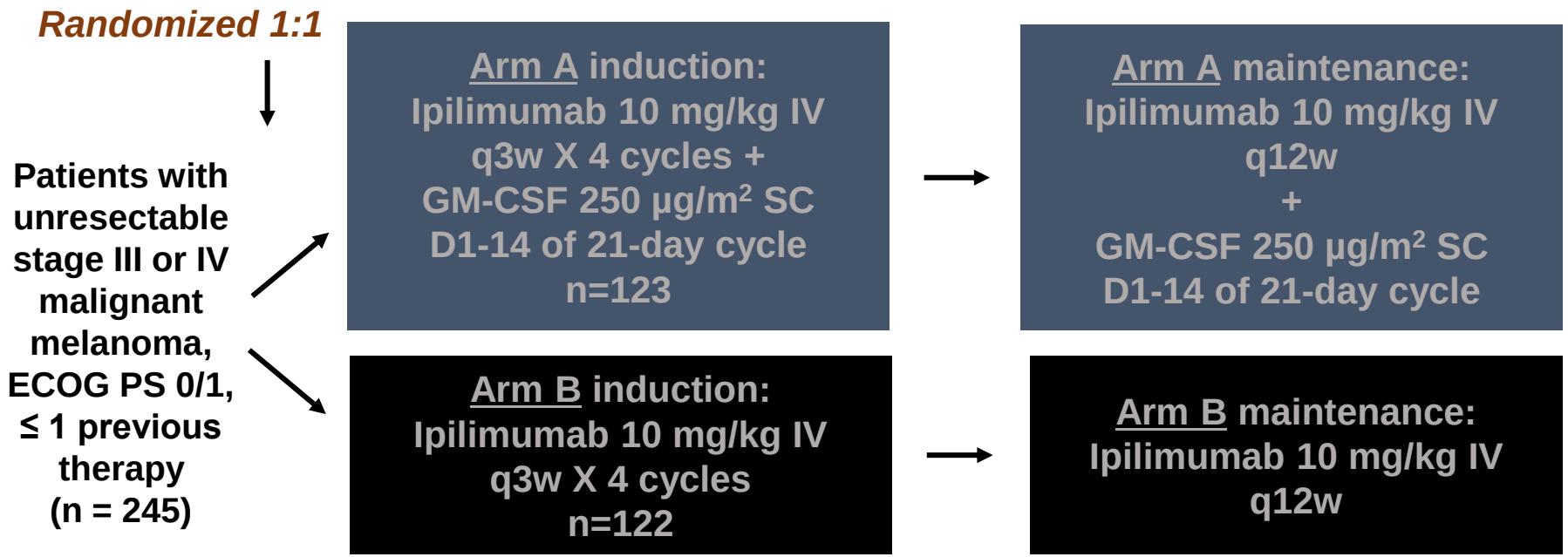


Compare to mIL-15	p value
mIL-15 + anti-CTLA4	0.4197
mIL-15 + anti-PDL1	0.7729
Triple	**0.0405**

10 mice/group

George Pavlakis, Thomas Waldmann; NIH

Randomized Phase II Study of GM-CSF + Ipilimumab vs. Ipilimumab



- Primary endpoint: OS
- Therapy continuation permitted with ≤ doubling of sum of target lesion diameter or ≤ 4 new lesions in absence of declining PS

Hodi FS, et al. ASCO 2013. CRA 9007.

Randomized Phase II Study of GM-CSF + Ipilimumab

Efficacy, n (%)	GM-CSF + Ipilimumab (n = 123)	Ipilimumab (n = 122)	HR	*P* Value
ORR	19 (15.5%)	18 (14.8%)	----	.880
CR	2 (1.6%)	0	----	NR
PR	17 (13.8%)	18 (14.8%)	----	NR
SD	26 (21.1%)	23 (18.9%)	----	NR
Median PFS	3.1 mos	3.1 mos	0.92	.569
Median OS	17.5 mos	12.7 mos	0.64	.014
1-year Survival Rate	68.9%	52.9%	NR	NR

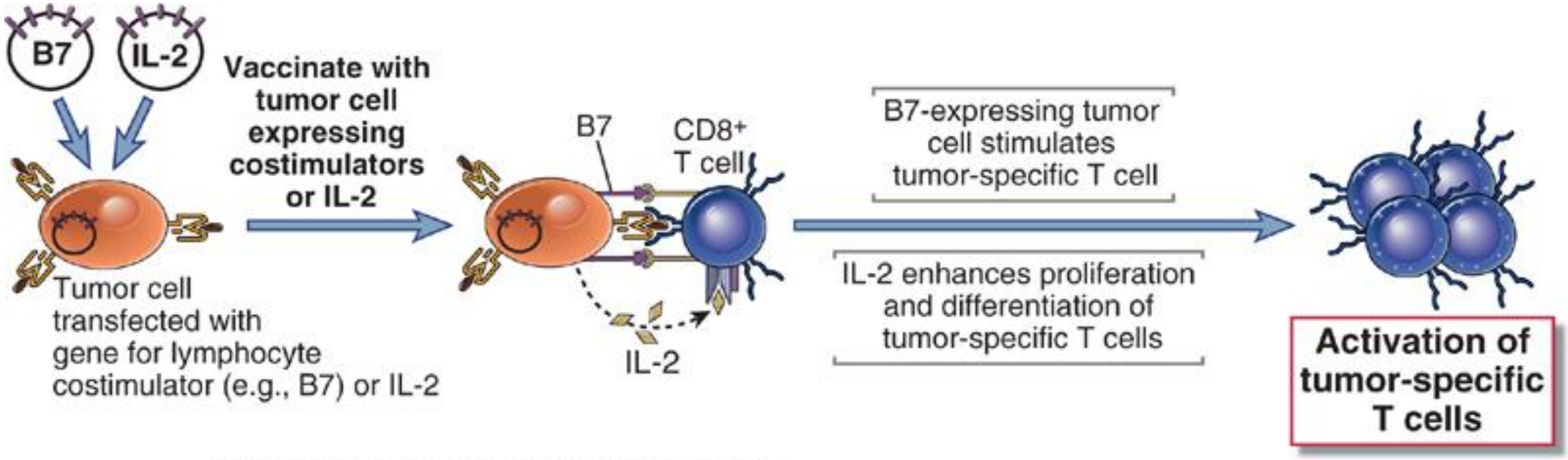
Hodi FS, et al. ASCO 2013. CRA 9007.

Why Women Live Longer Than Men

Conclusions

- Tumors release DAMPs which promote an immune response
- Cytokines are characterized by pleiotropy, redundancy, synergy, and antagonism
- IFNa and IL-2 remain our most effective cytokines for use in patients
- Novel combinations with GM-CSF and checkpoint inhibitors are on the horizon
- IL-15 appears promising in single agent studies and may be combined with antibodies and/or checkpoint inhibitors (CITN)

Enhancement Of Host Immunity With Costimulators And Cytokines



Normally, tumor cells do not have adequate co-stimulation and they downregulate antigen-presenting molecules.