# Innate Core and Adaptive Shell

**3:15-4:15pm 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

# Cytokines (1728) and Bispecific (216) Clinical Trials for Cancer clinicaltrials.gov

Showing: 1-100 of **216** studies 100 ▾ studies per page

Show/Hide Columns

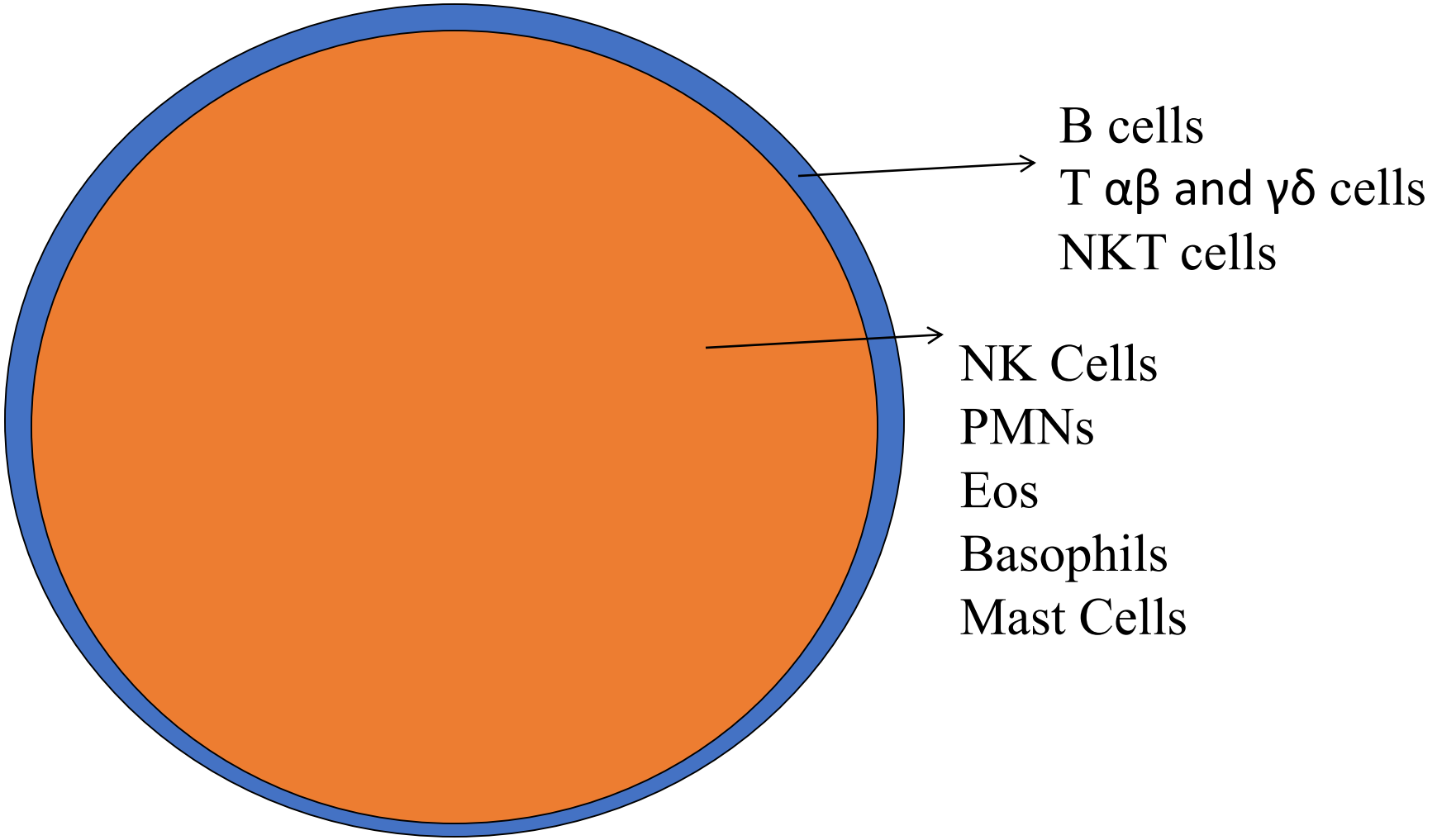
| Row | Saved | Status | Study Title | Conditions | Interventions | Locations |
|---|---|---|---|---|---|---|
| 1 | ☐ | Recruiting | Study of Activated Cytokine-induced Killer Armed With **Bispecific** Antibody for Advanced Liver **Cancer** | • Advanced Liver **Cancer** | • Biological: Activated CIK and CD3-MUC1 **Bispecific** Antibody in Treating Liver Cancer<br>• Procedure: cryotherapy | • Biological treatment center in Fuda cancer hospital Guangzhou, Guangdong, China<br>• Institutional Review Board of Guangzhou Fuda Cancer Hospital Guangzhou, Guangdong, China |
| 2 | ☐ | Recruiting | Study of Activated Cytokine-induced Killer Armed With **Bispecific** Antibody for Advanced Breast **Cancer** | • Advanced Breast **Cancer** | • Biological: Activated CIK and | • Institutional Review Board of Guangzhou |

Showing: 1-100 of **1,728** studies 100 ▾ studies per page

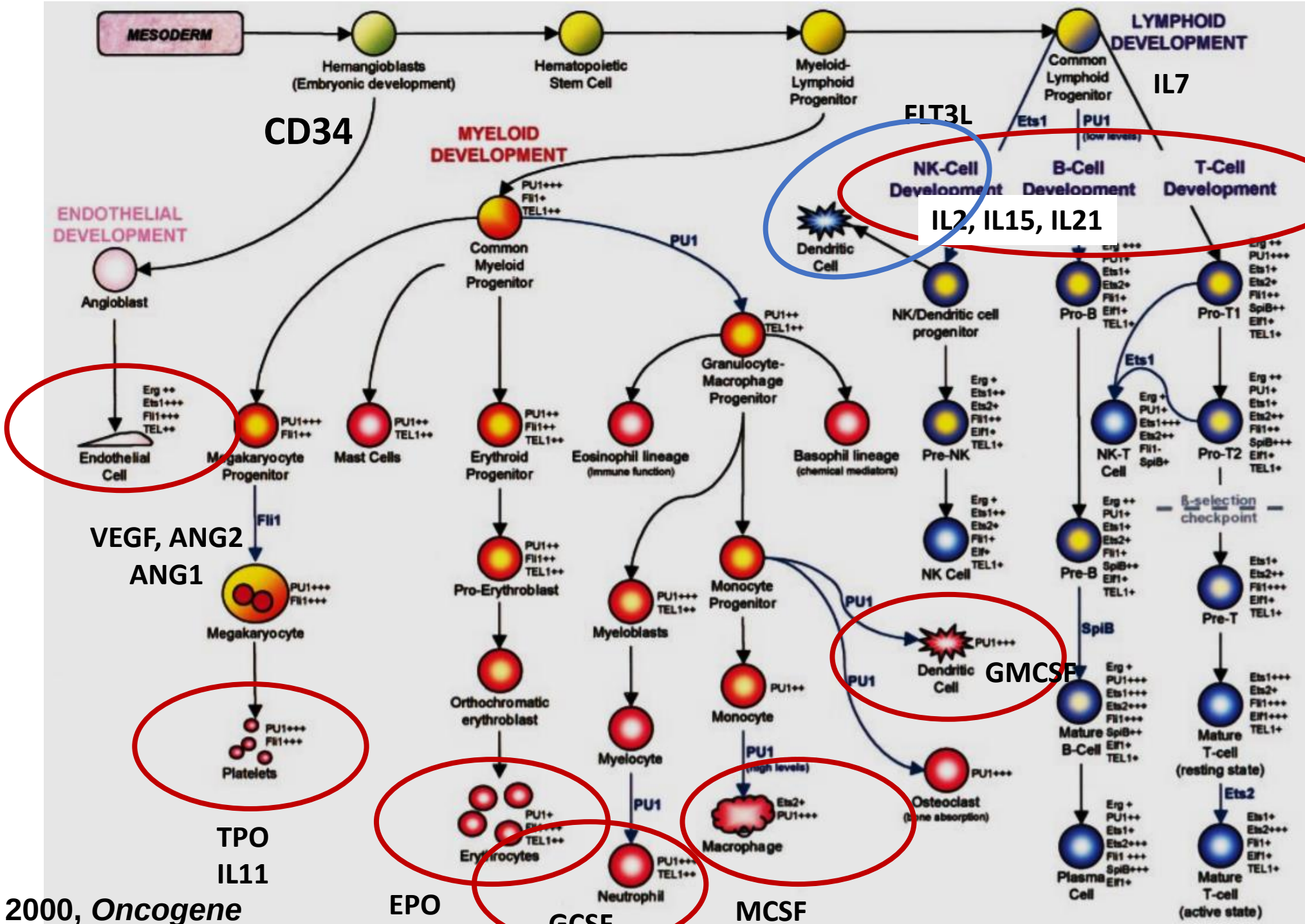
Show/Hide Columns

| Row | Saved | Status | Study Title | Conditions | Interventions | Locations |
|---|---|---|---|---|---|---|
| 1 | ☐ | Completed | Radiofrquency Ablation Combined With **Cytokine-**induced Killer Cells for Colorectal **Cancer** Liver Metastases | • Colorectal **Cancer** | • Procedure: Radiofrequency ablation<br>• Biological: **Cytokine-**induced killer cells | • The First People's Hospital of Changzhou Changzhou, Jiangsu, China |
| 2 | ☐ | Active, not recruiting | ELR+CXCL **Cytokines** in Metastatic Kidney **Cancers**: Predictive Markers of Resistance to Sunitinib | • Metastatic Kidney **Cancers** | • Diagnostic Test: ELR+CXCL **cytokines** levels are of sunitinib response | • Centre Antoine LACASSAGNE Nice, France |

# Innate Core and Adaptive Shell

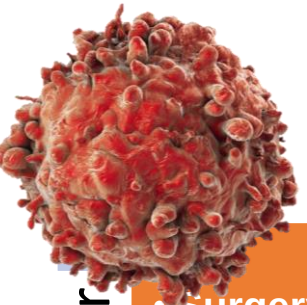


# Endothelial Myeloid, Lymphoid Cell Develop-ment




Maroulakou & Bowe © 2000, *Oncogene*

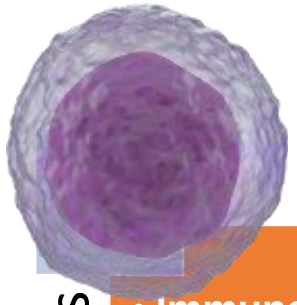
# Foundations of Cancer Therapy (WuXing Again)



Tumor

- Surgery
- Chemotherapy
- Radiation

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

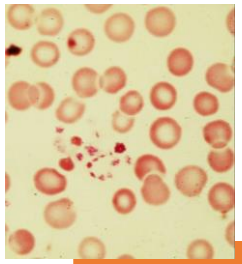


T Cells

- 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<br>BTCT4465A<br>RO7082859 | I |
| | | CD123 × CD3 | MGD006<br>JNJ-63709178<br>Xmab14045 | I |
| | | BCMA × CD3 | JNJ-64007957<br>BI 836909 | I |
| | | B7H3 × CD3 | MGD009 | I |
| | | CEA × CD3 | RO6958688<br>MT111 | I |
| | | PSMA × CD3 | Pasotuximab<br>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 |

# Classes Of Bispecific Antibodies In Cancer Immunotherapy

Based on the types of biological targets and modes of action, bispecific immunotherapies can be divided into three main categories:

(1) Cytotoxic effector cell redirectors, including

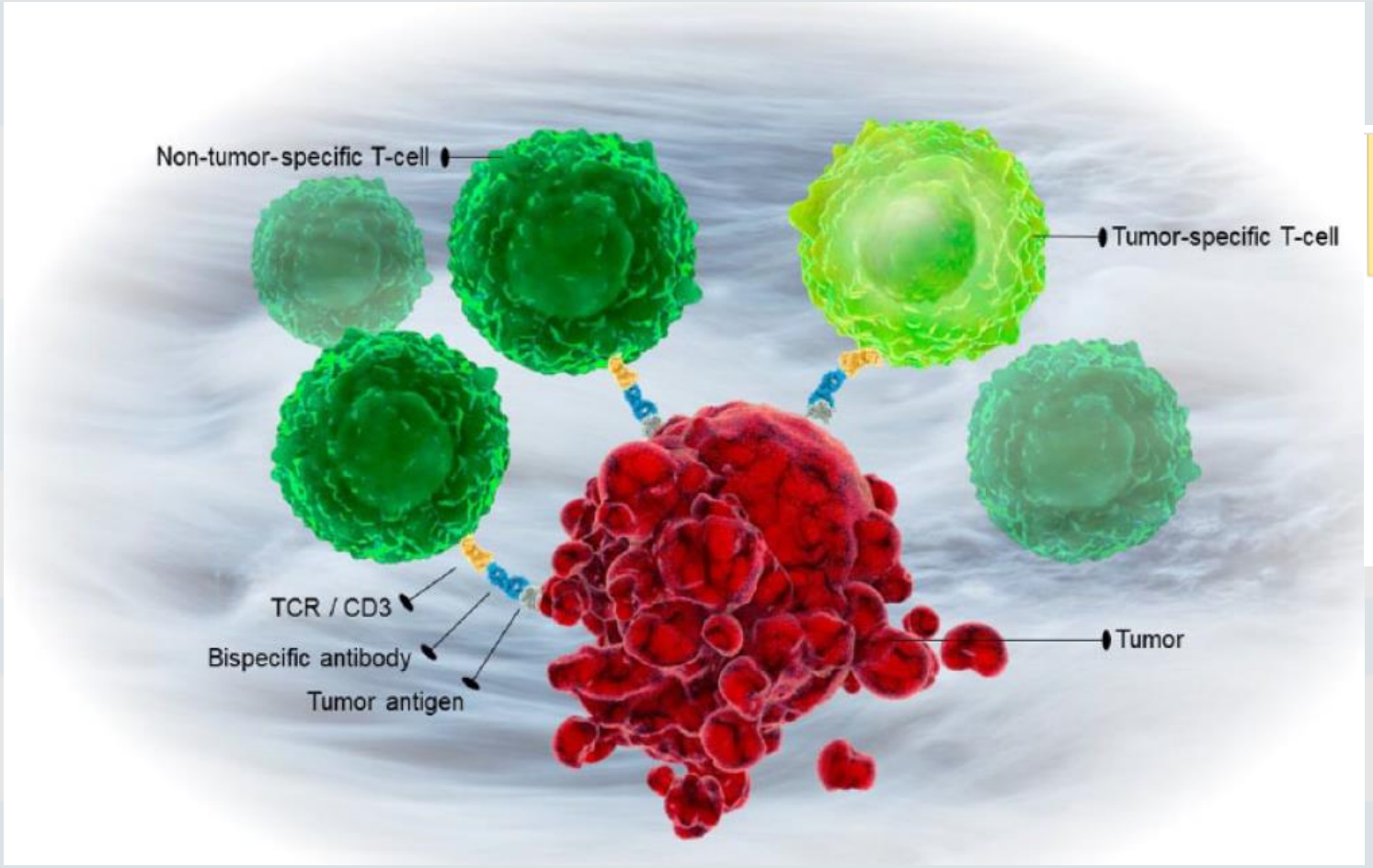
- (a) T-cell redirectors
- (b) NK-cell redirectors

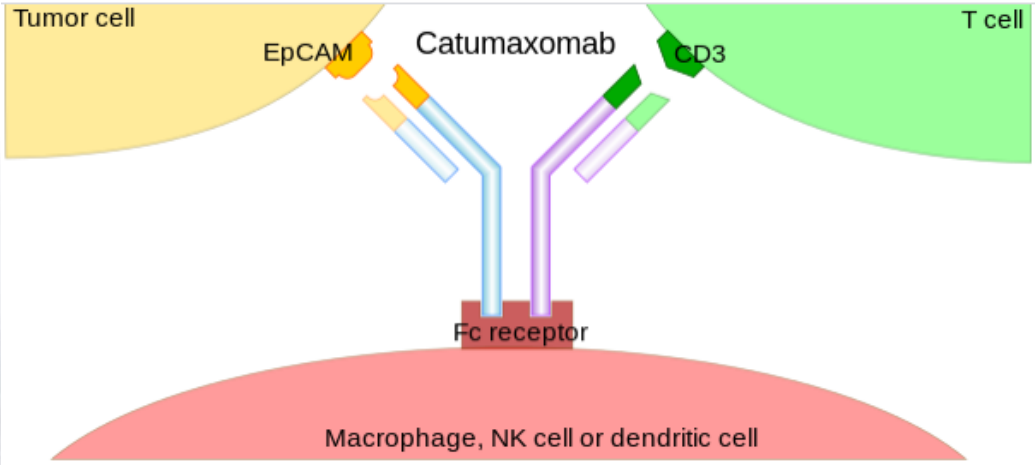
(2) Tumor-targeted immunomodulators

(3) Dual immunomodulators.

# Cytotoxic Effector Cell Redirectors

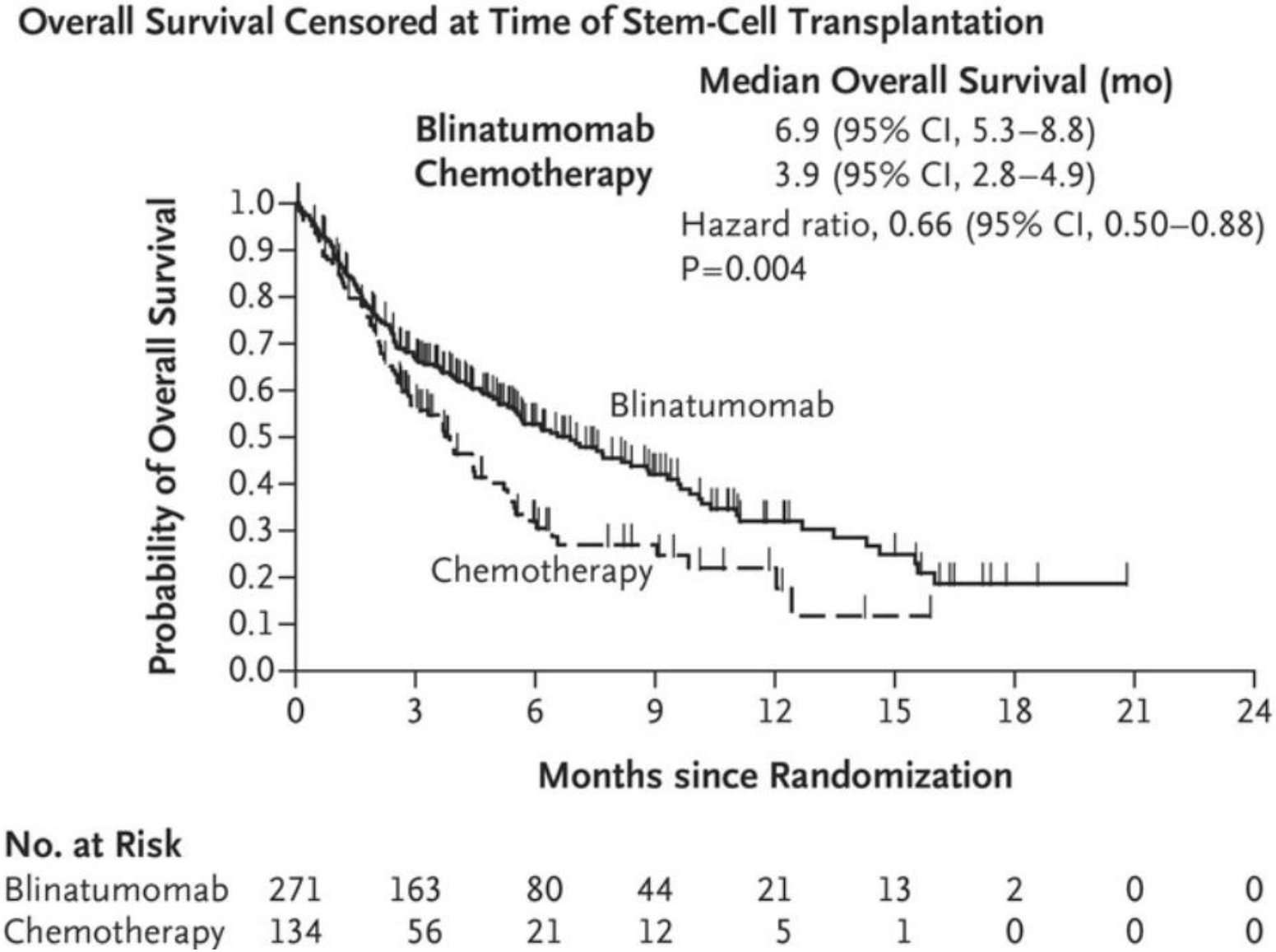
| Class | Description | Targets | Examples | Stage* |
|---|---|---|---|---|
| T-cell redirectors | Redirects T cells to malignant cells by targeting a tumor antigen and CD3 | CD19 × CD3 | Blinatumomab | Market |
| | | EpCAM × CD3 | Catumaxomab | Marketed (withdrawn) |
| | | B7H3 × CD3 | MGD009 | I |
| | | CEA × CD3 | RO6958688<br>MT111 | I |
| | | PSMA × CD3 | Pasotuximab<br>ES414/MOR209 | I |



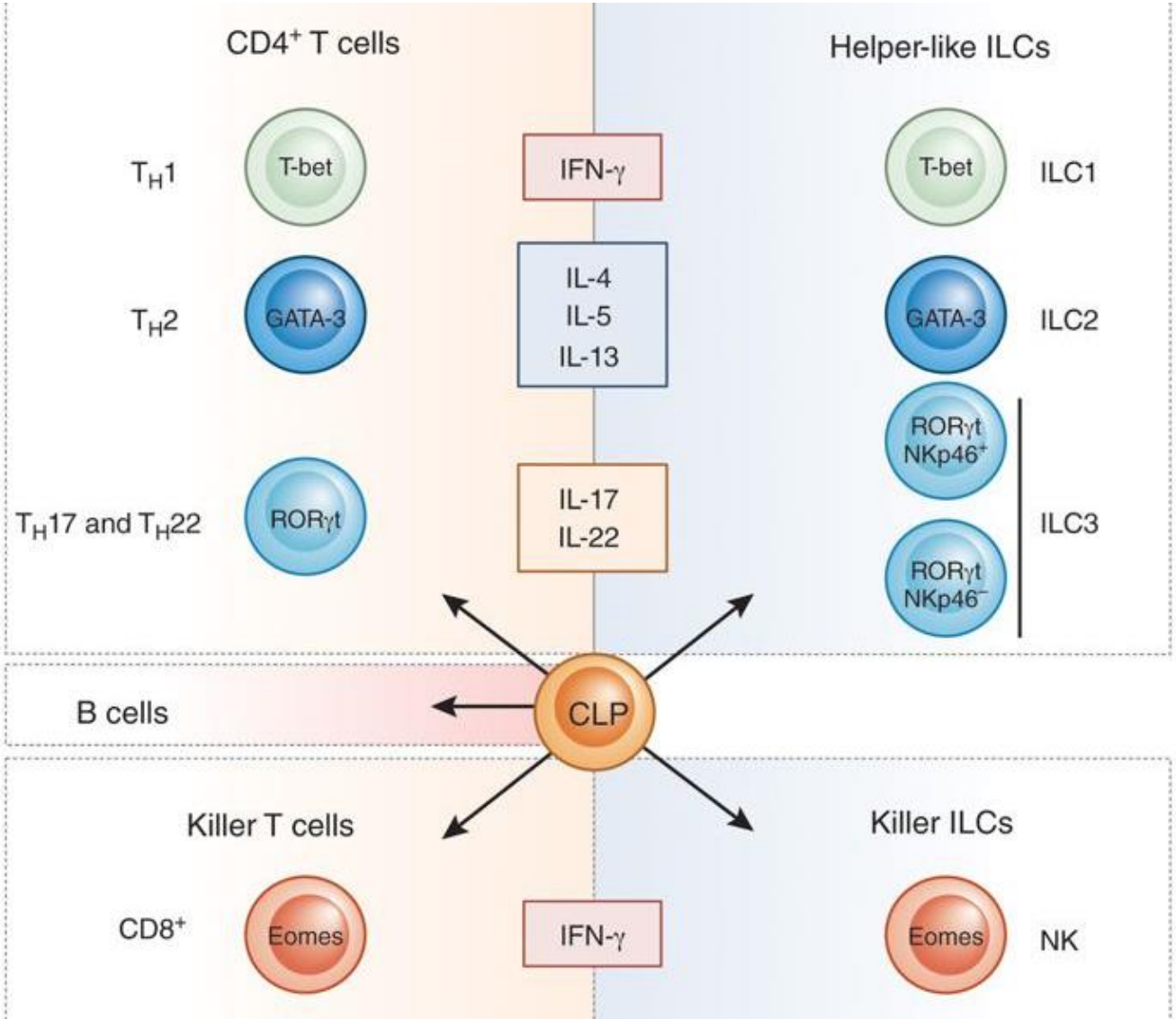
# Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia

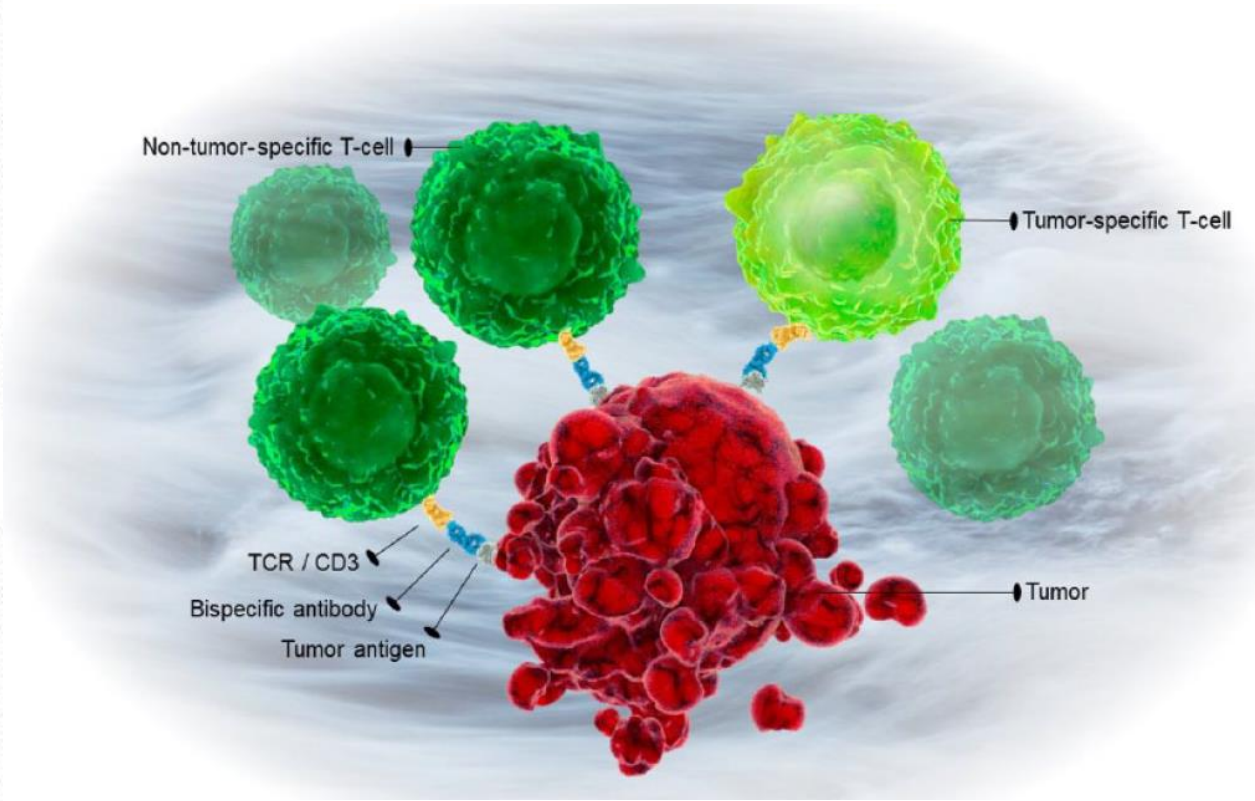
March 2, 2017 N Engl J Med 2017; 376:836-847
DOI: 10.1056/NEJMoa1609783 Chinese 中文翻译



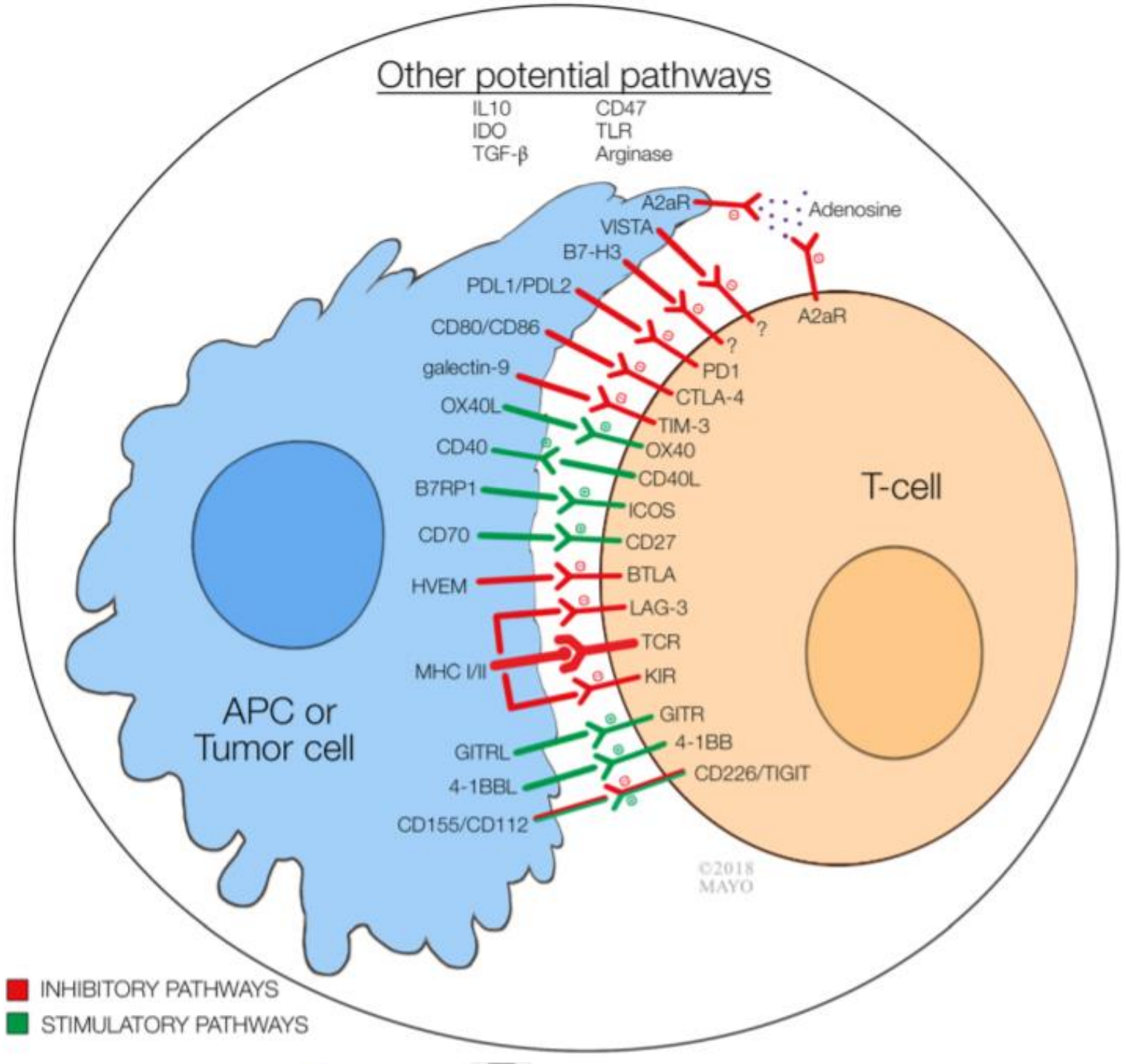
# Cytotoxic Effector Cell Redirectors-NK

| Class | Description | Targets | Examples | Stage* |
|---|---|---|---|---|
| s by targeting | | CD30 × CD16A | AFM13 | II |
| | | EGFR × CD16A | AFM24 | PC |
| | | BCMA × CD16A | AFM26 | PC |

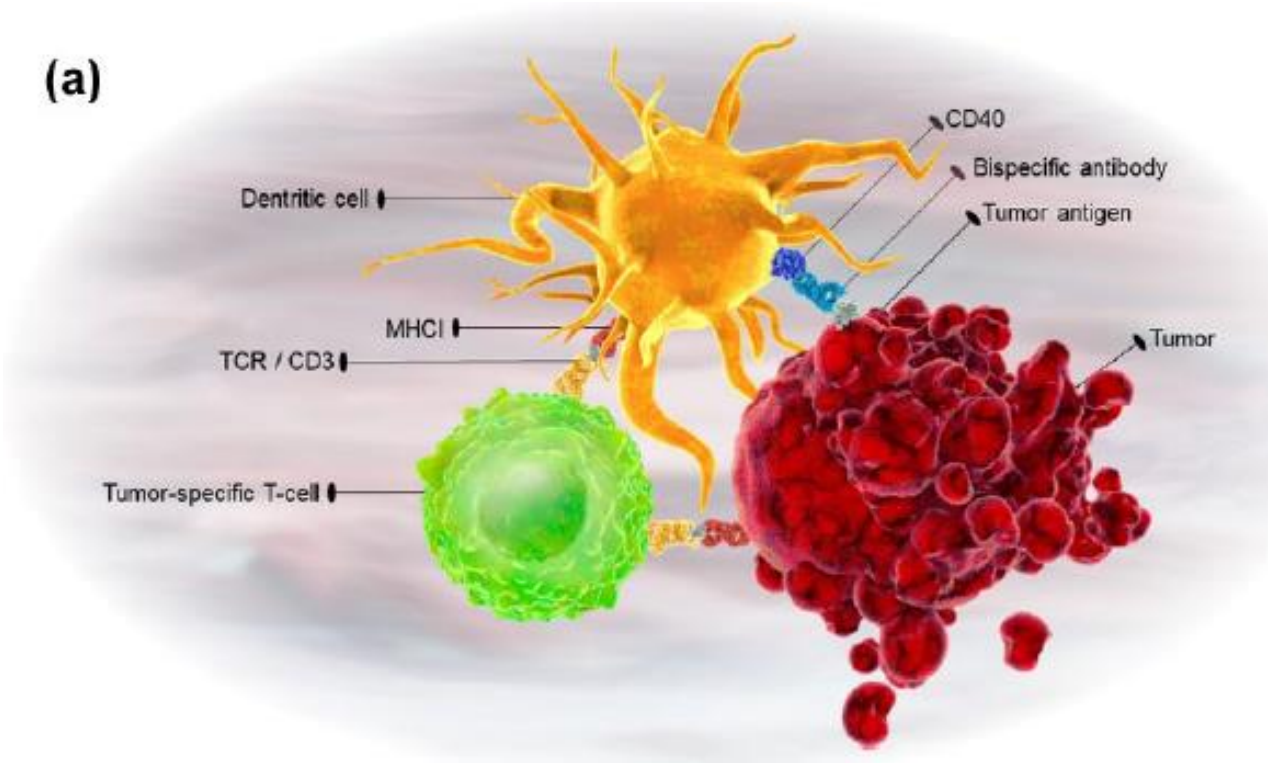


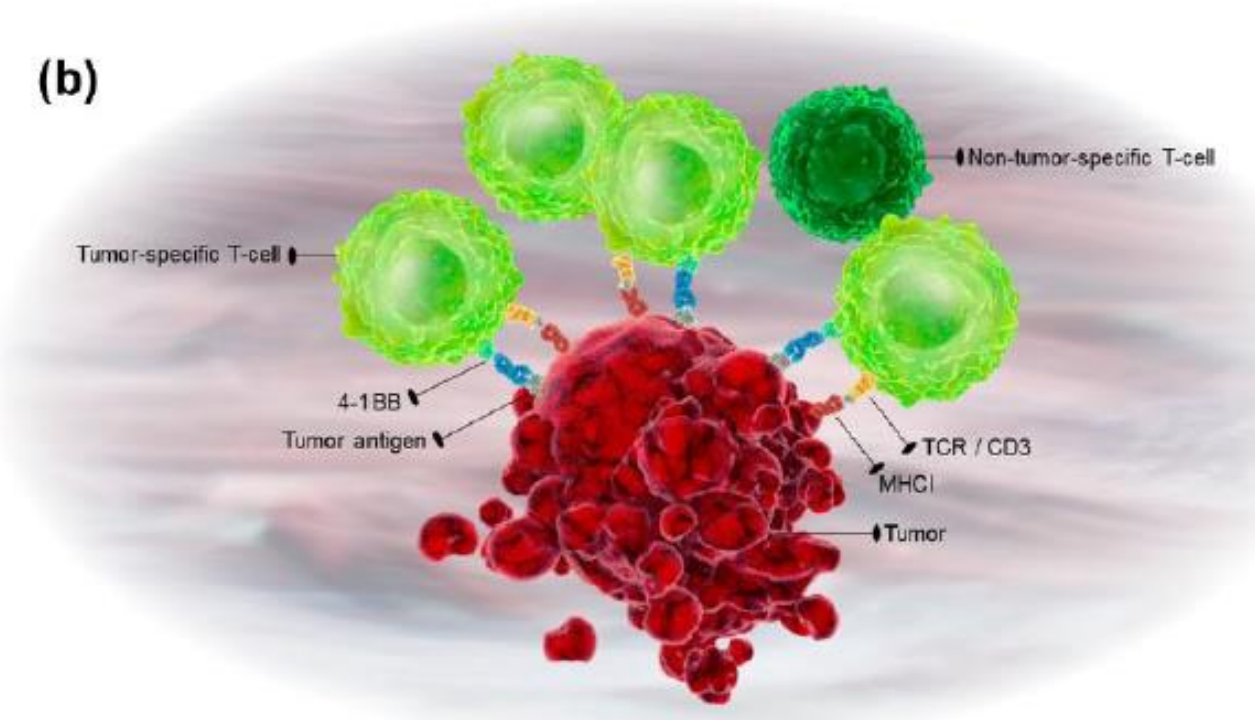



| Class | es | Stage* |
|---|---|---|
| Tumor-targeted immunomodulators | 428 | I |
| | 3 | I |
| | agonist | PC |
| | PV-527 | PC |
| Dual immunomodulators | | I |
| | 13 | I |
| | | PC |
| | 134 | PC |
| | 20717 | PC |
| | 1015 | PC |

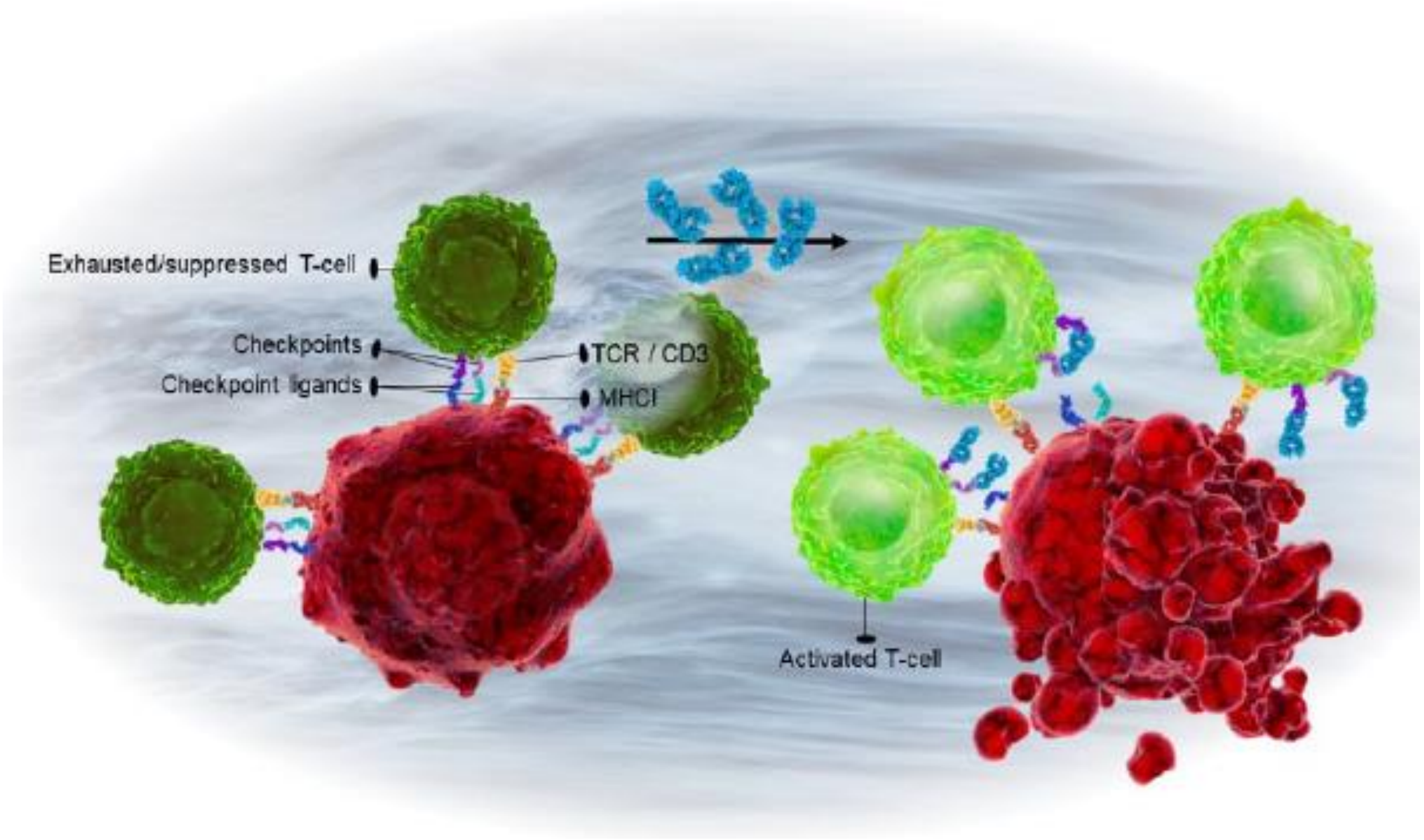


# Tumor Targeted Immunomodulators



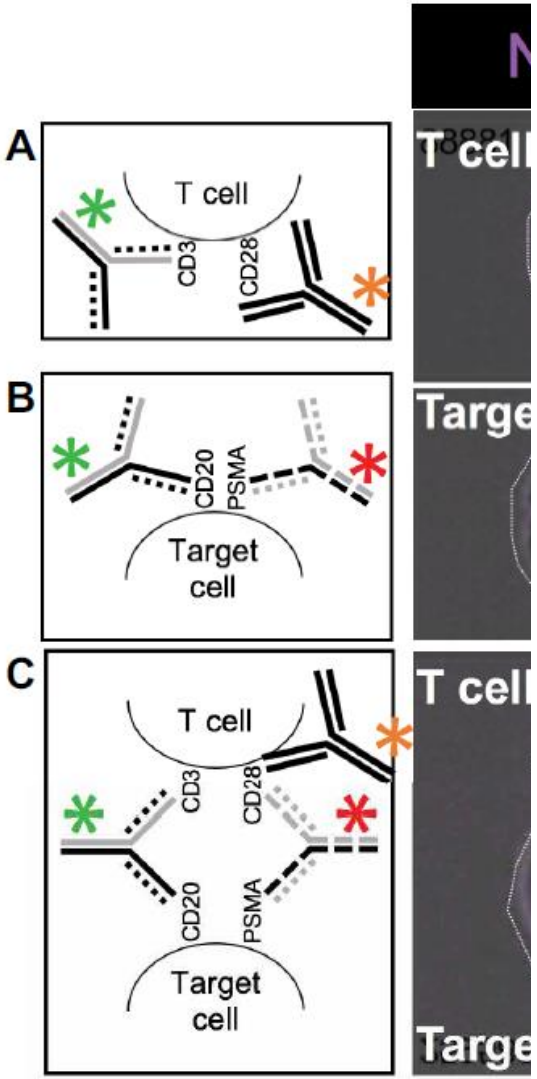
# Dual Tumor Targeted Immunomodulators

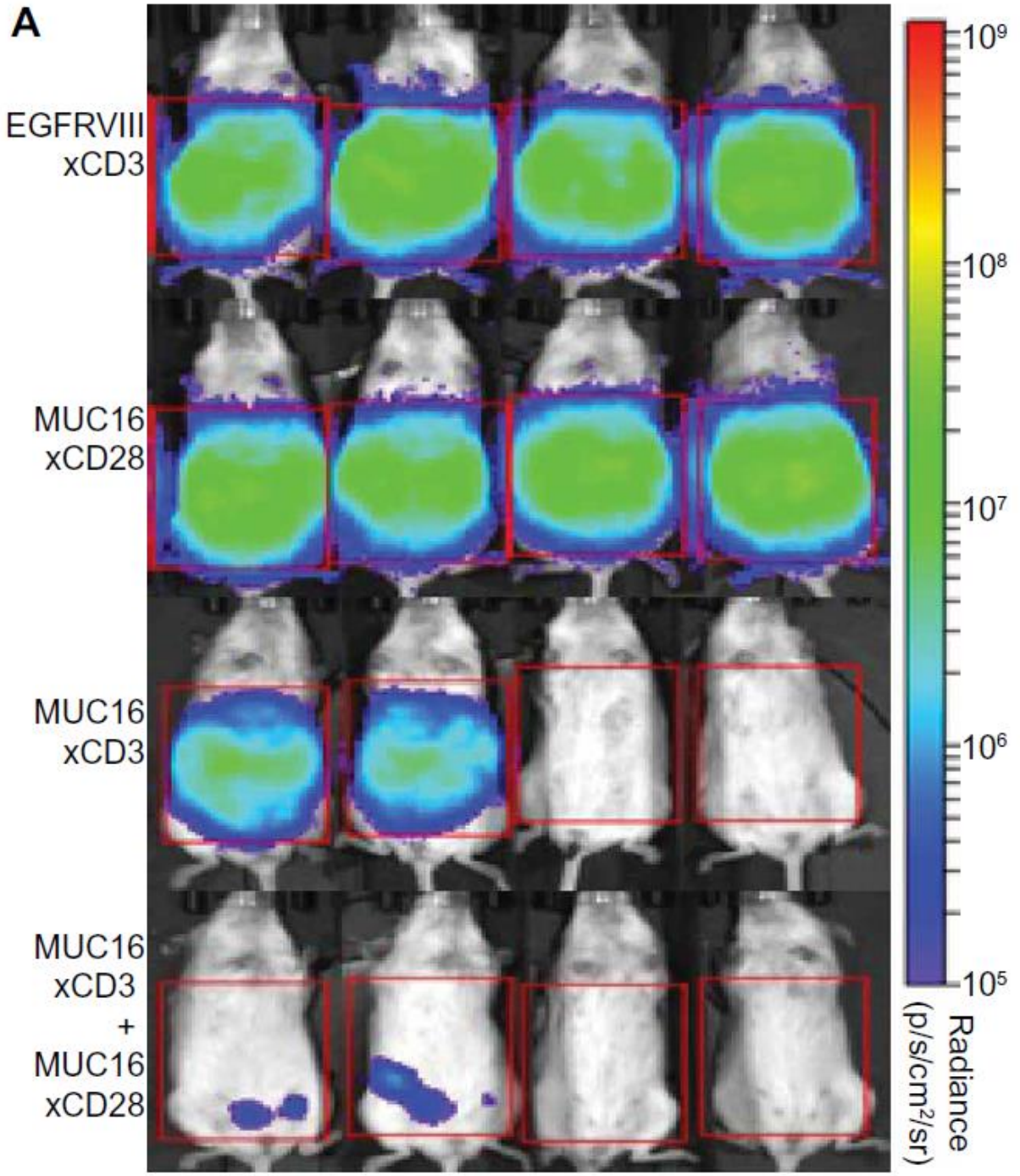


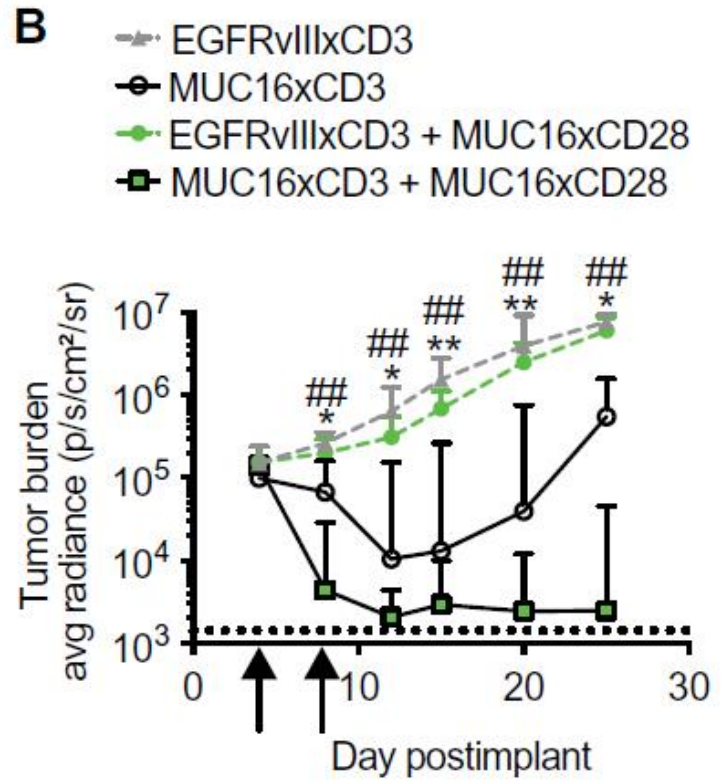
ALLIGATOR bioscience

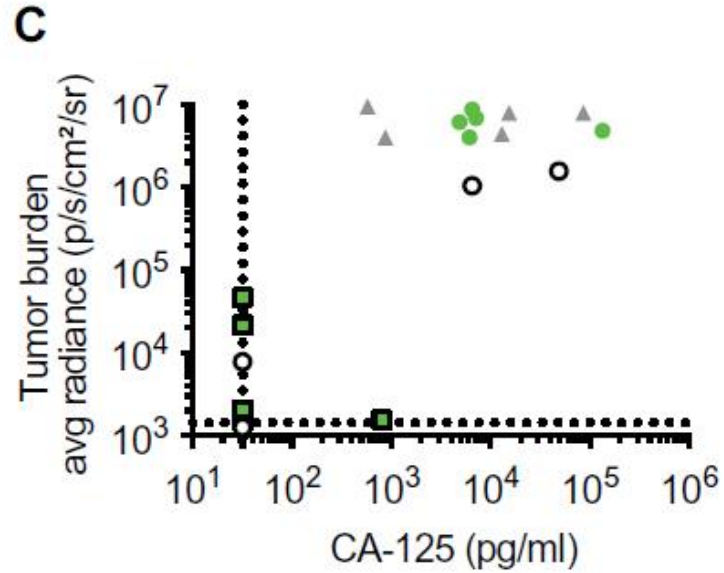
| PROJECT | ANTIBODY | TARGET | DISCOVERY | PRECLINICAL | CLINICAL PHASE I | CLINICAL PHASE II |
|---|---|---|---|---|---|---|
| **MITAZALIMAB** (ADC-1013) |  | ● CD40 | | | | |
| **ATOR-1015** |  | ● CTLA-4<br>● OX40 | | | | |
| **ATOR-1017** |  | ● 4-1BB | | | | |
| **ALG.APV-527** |  | ● 4-1BB<br>● 5T4 | | | | *Co-developed with* Aptevo Therapeutics |
| **ATOR-1144** |  | ● CTLA-4<br>● GITR | | | | |
| **AC101 (HLX22)** | | ○ HER2 | | | | *Partnered with AbClon/Henlius.* |

SCIENCE TRANS




Skokos *et al.*, S

# Macrophages (WuXi Again)

Science
AAAS

## 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.

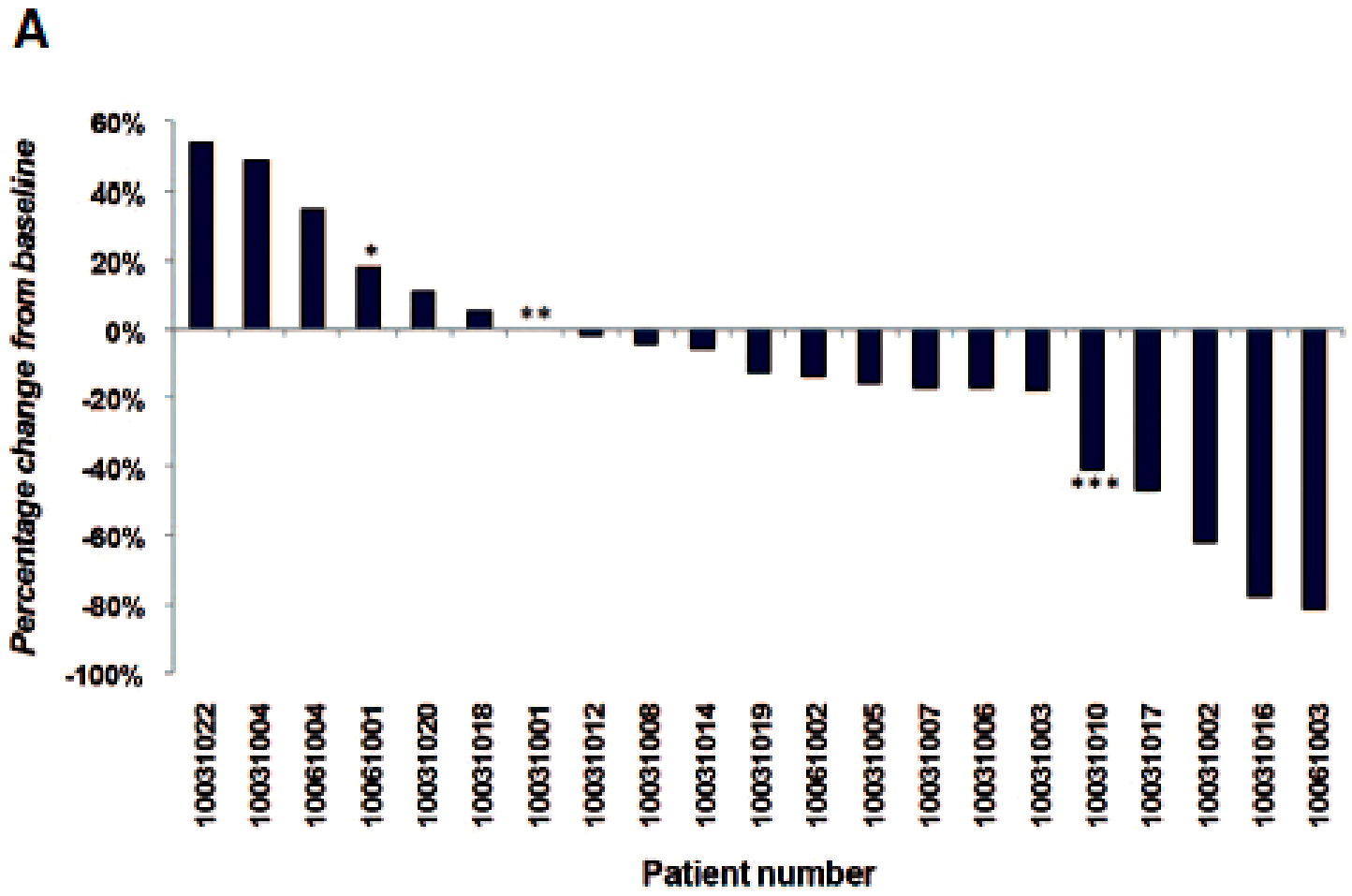
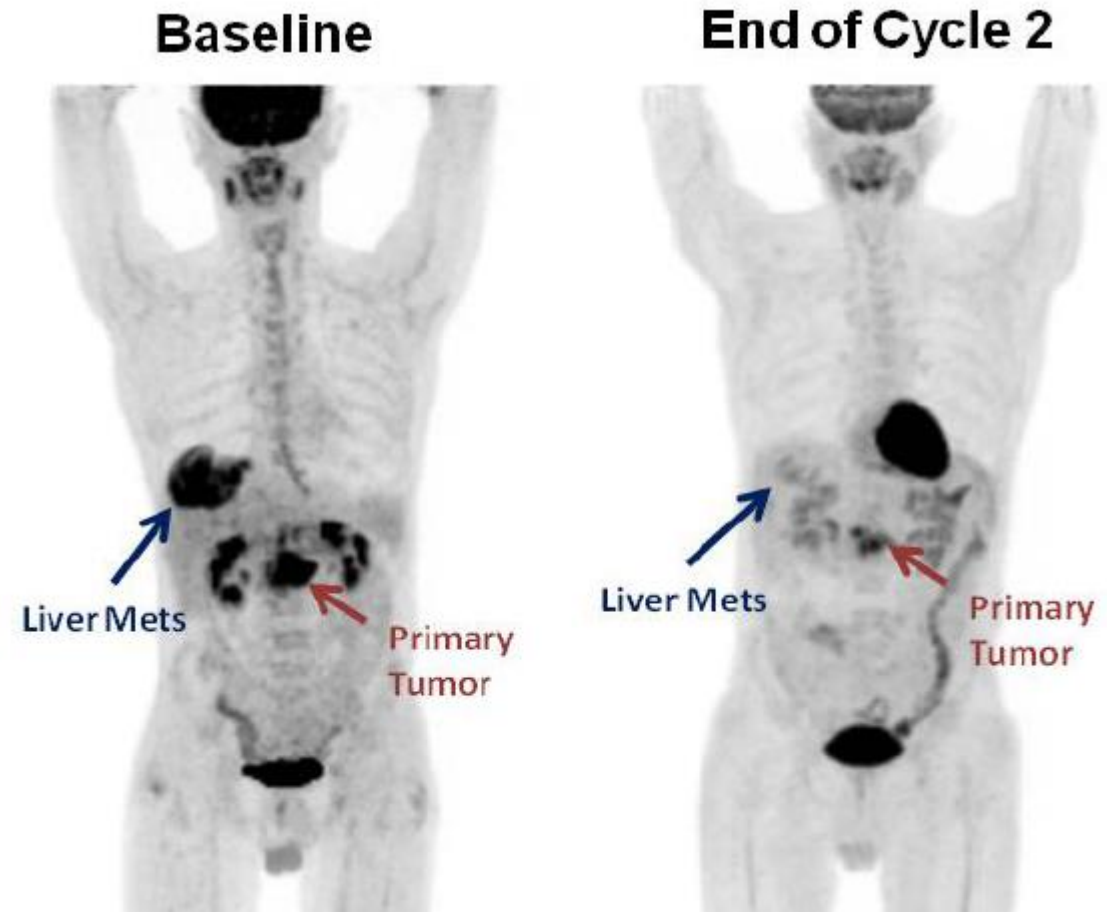
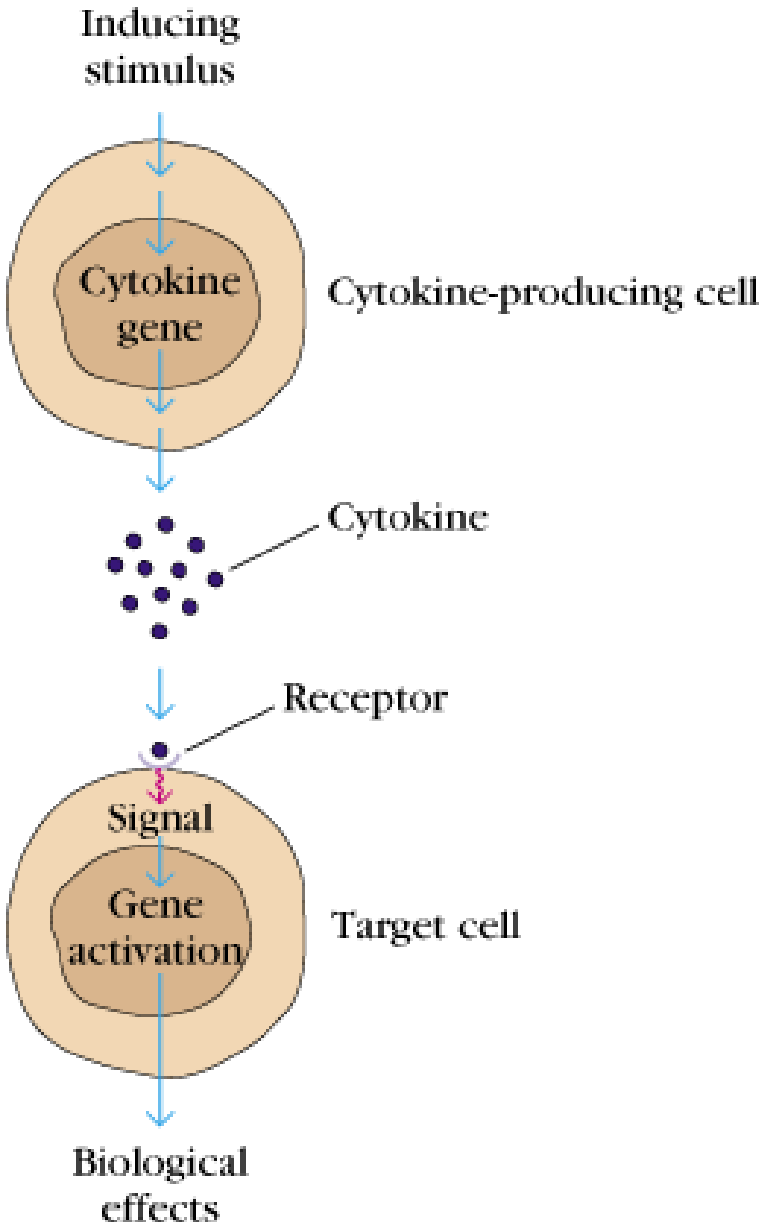


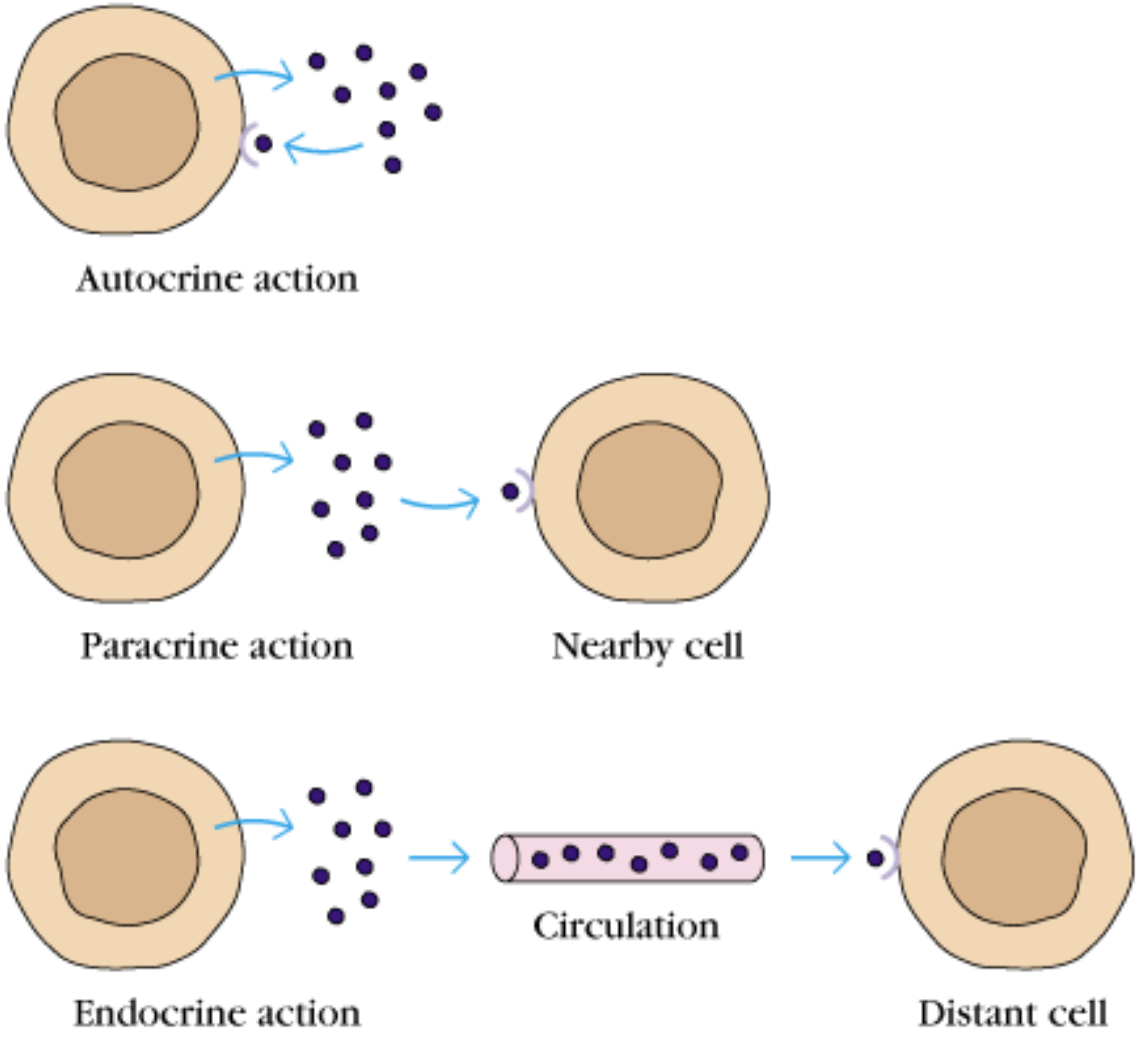
**Figure S3.** Metabolic tumor response to treatment



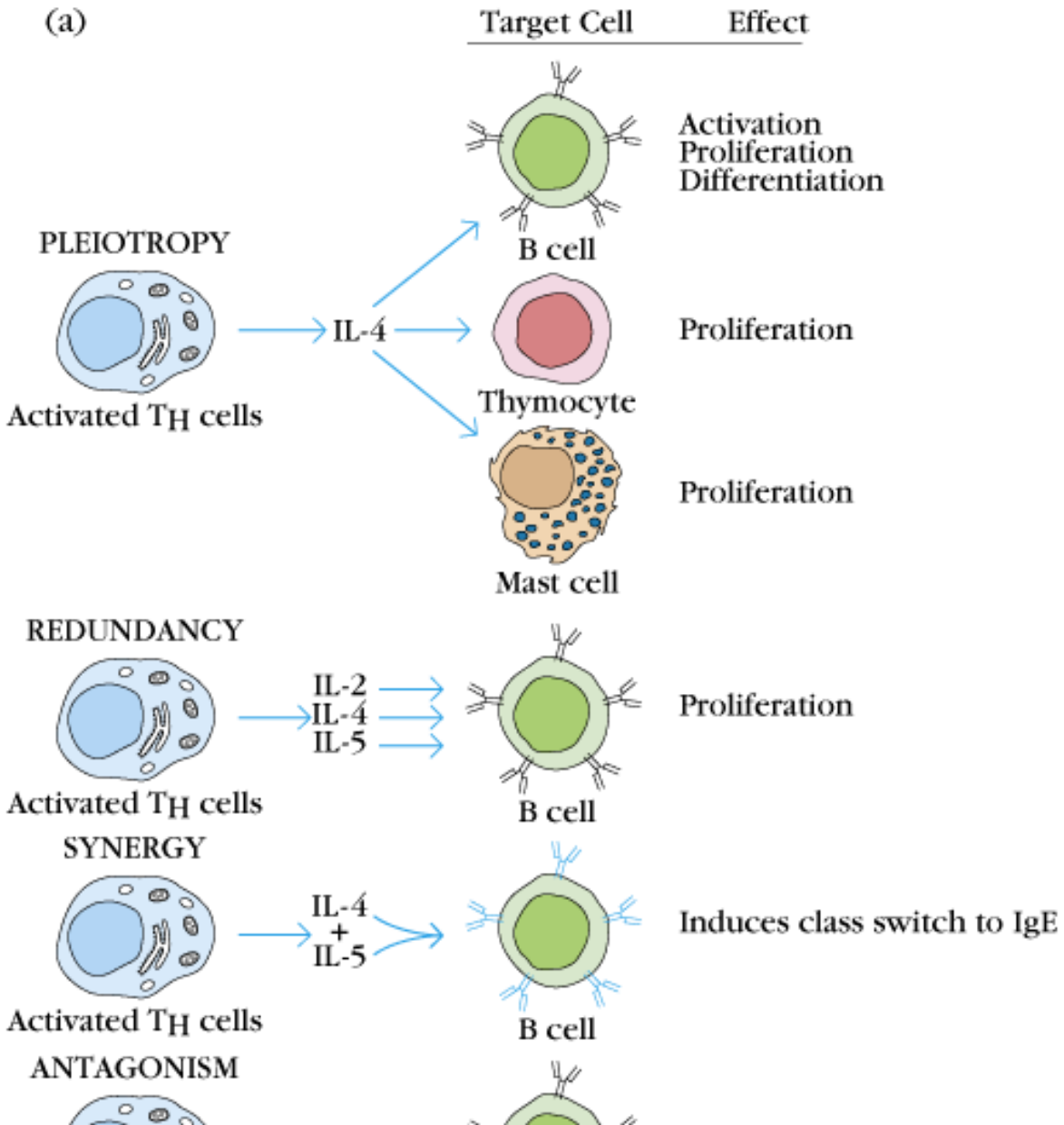
# General properties of cytokines



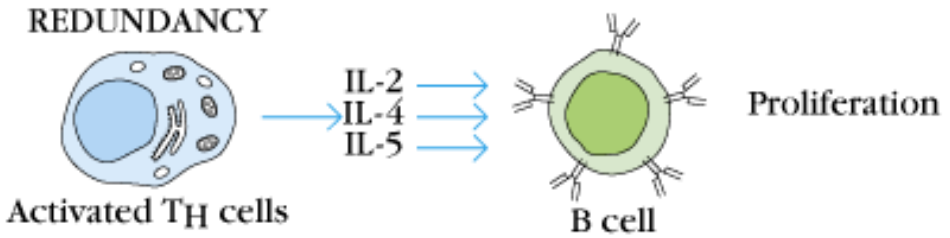
# General properties of cytokines



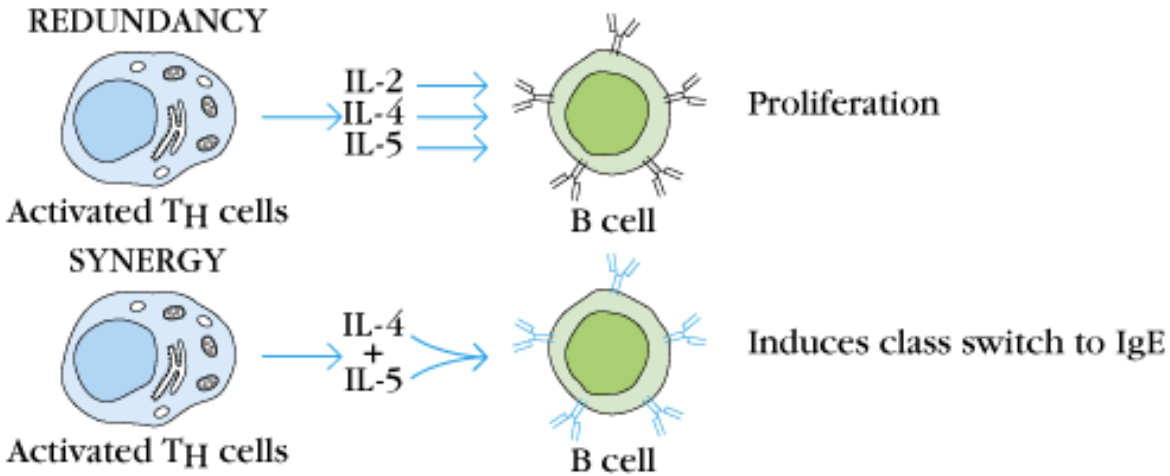
# General Properties Of Cytokines



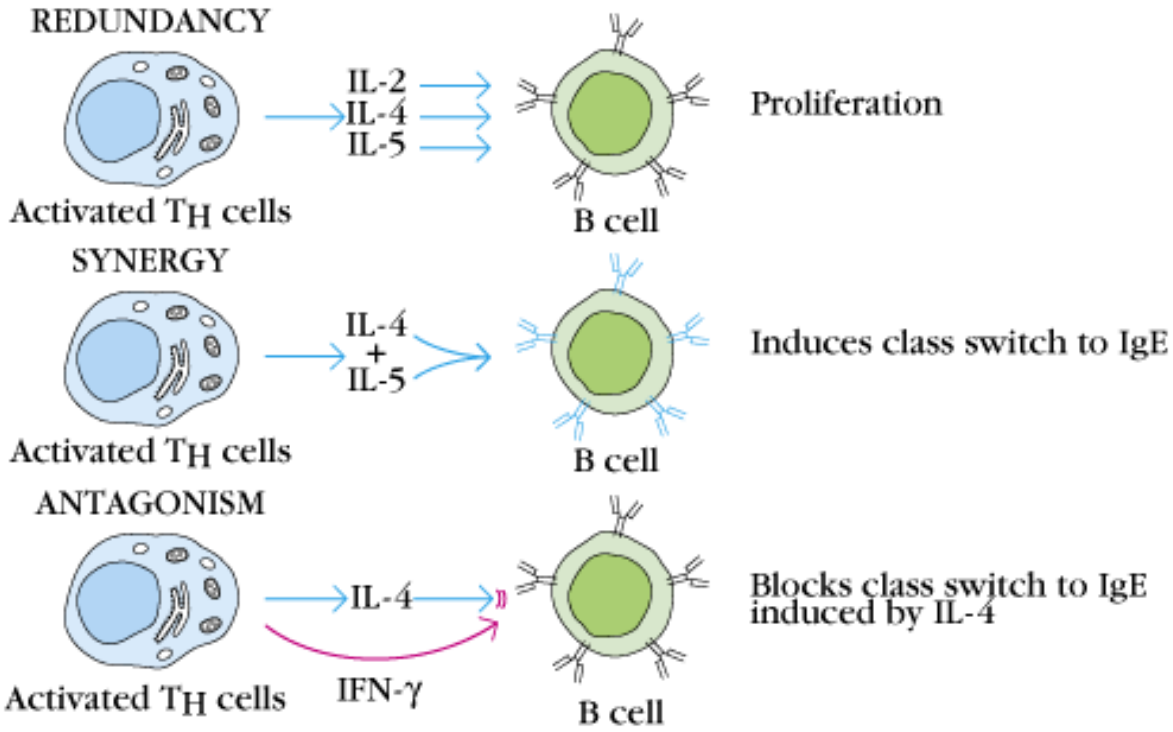
# General Properties Of Cytokines



# General properties of cytokines



# General Properties Of Cytokines



# 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

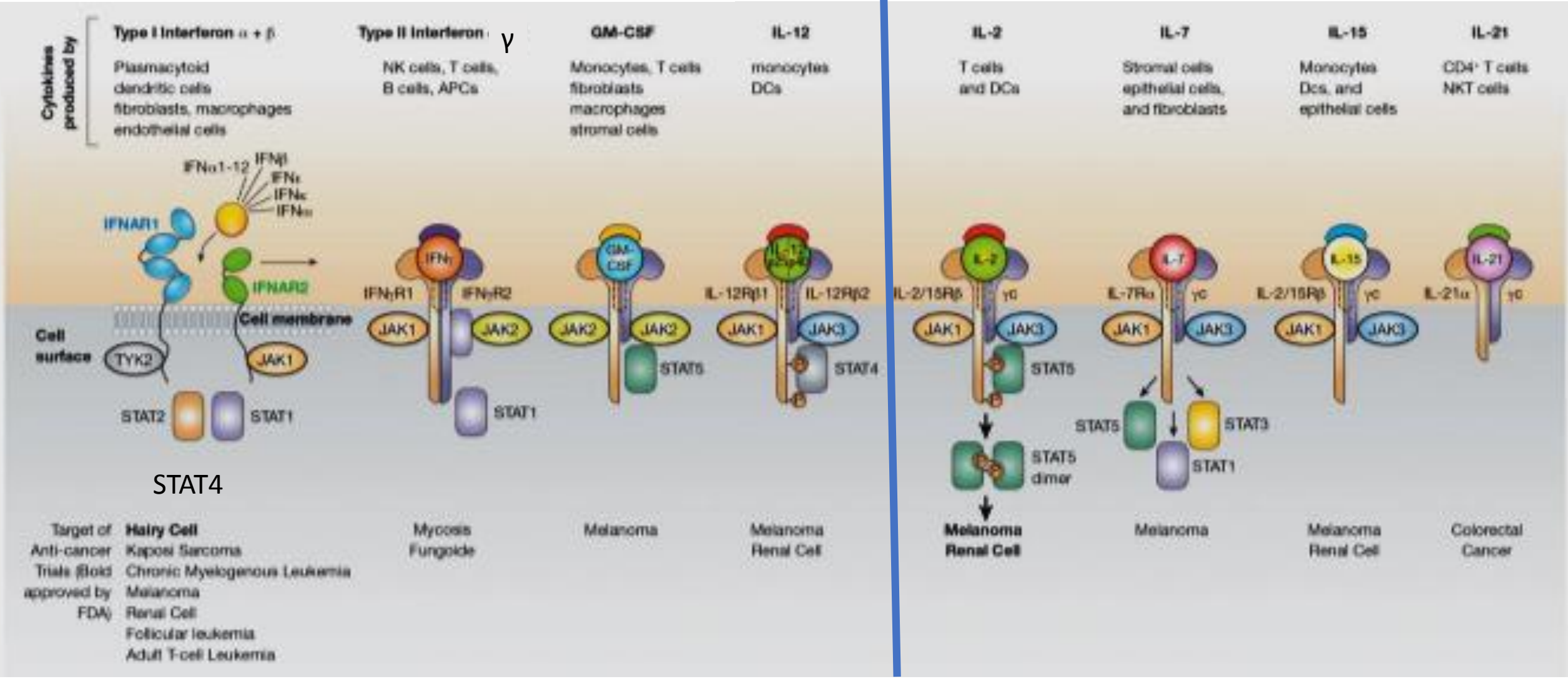


# Cytokines in the Treatment of Cancer

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

IL23
IL27
IL35

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




STAT4

# Cytokines are medically relevant endogenous small (~15kDa) proteins

Cytokine-based therapies in human disease

| Cytokine | Brand name | Status | Indication | Year of 1st FDA Approval |
|---|---|---|---|---|
| IL-2 | Proleukin | Approved | Cancer | 1992 |
| IL-11 | Neumega | Approved | Thrombocytopenia | 1994 |
| EPO | Epogen | Approved | Anemia | 1989 |
| GCSF | Neupogen | Approved | Myelosuppression from chemo | 1991 |
| GM-CSF | Leukine | Approved | Myelosuppression from chemo | 1991 |
| IFN-α | Intron-A | Approved | Hepatitis, Cancer | 1991 |
| IFN-β | Betaseron | Approved | Multiple sclerosis | 1993 |
| IFN-γ | Actimmune | Approved | Granulomatosis | 1990 |
| IL-7 | | Clin dev | Cancer, anti-viral | |
| IL-10 | | Clin Dev | Cancer, anti-inflammatory | |
| IL-12 | | Clin dev | Cancer, anti-viral | |
| IL-15 | | Clin dev | Cancer | |
| IL-21 | | Clin dev | Cancer | |

Baldo, 2018 Drug Safety

doi:10.1038/nature04808

nature

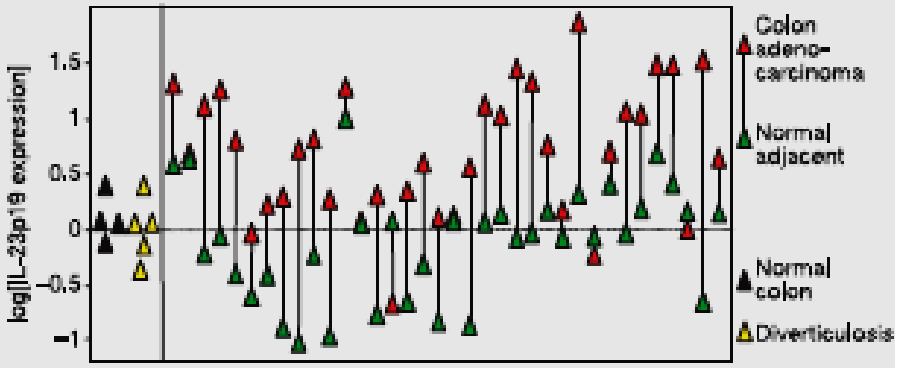
May 2006

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 |

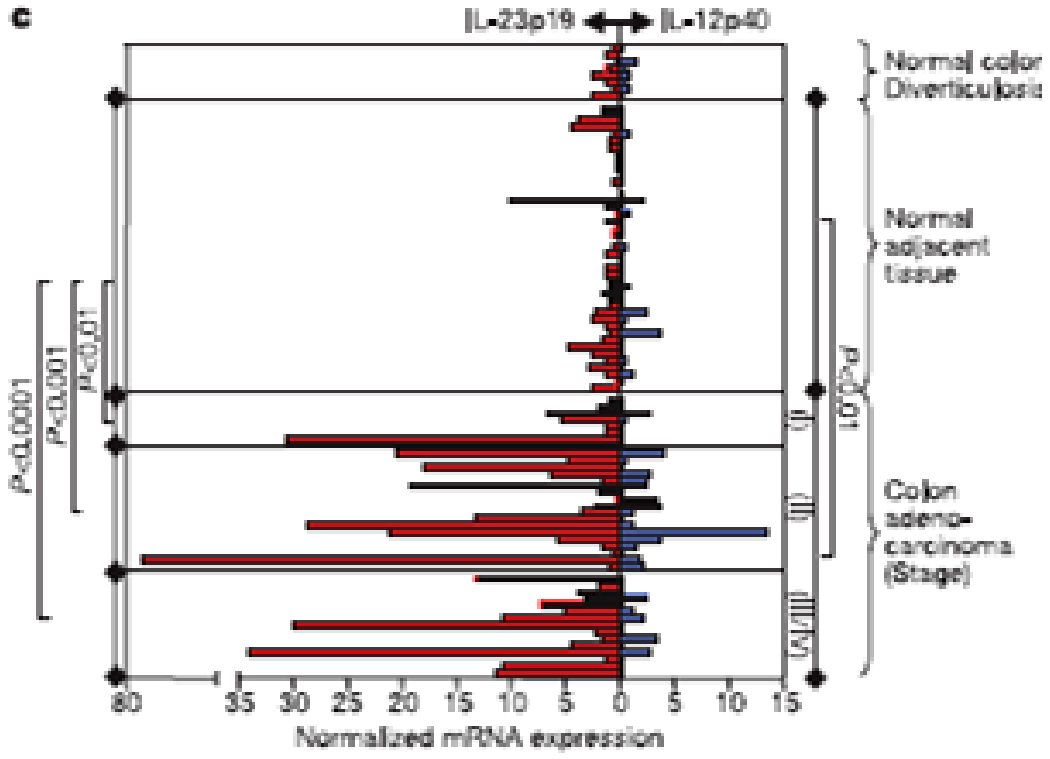
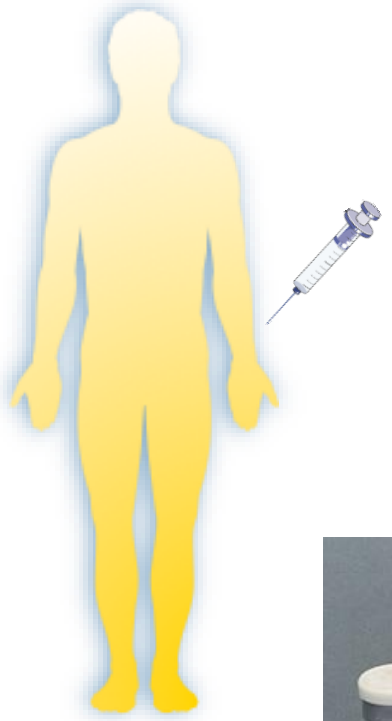
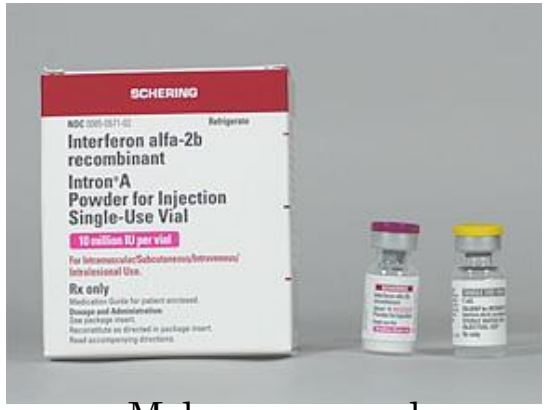



**Figure 1 | Overexpression of IL-23 but not of IL-12 in human cancer.**

# Systemic Injection Of Cytokines For Tumor Therapy

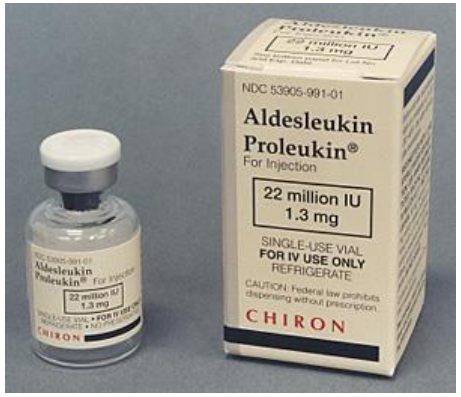

Melanoma






Melanoma, renal cancer


Bone marrow recovery




Kidney cancer

# 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 (BRAF mutant; purine analogues)

# 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

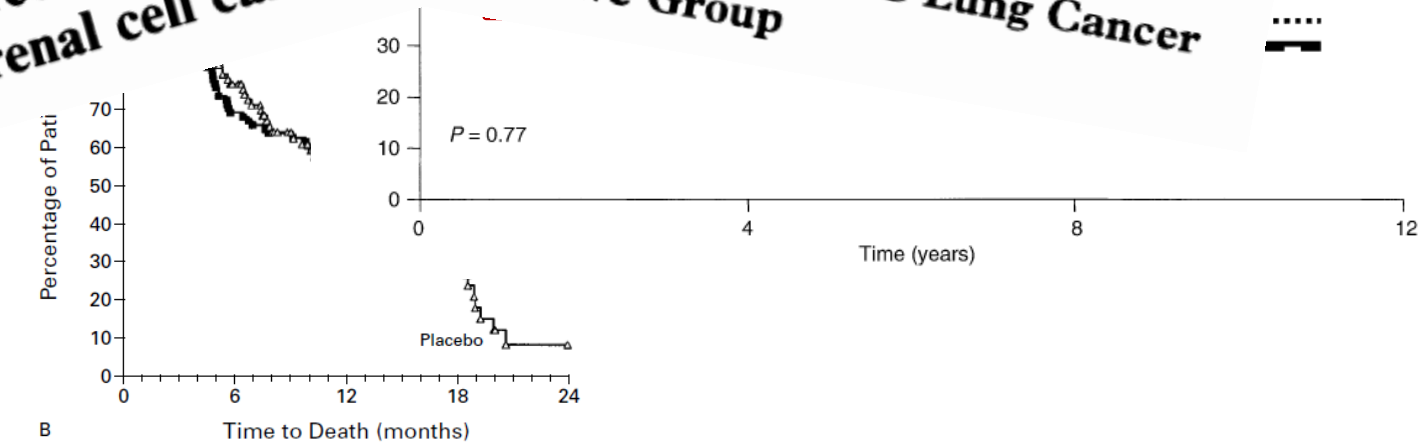
advanced renal cell carcinoma

Maintenance in

ell Lung Cancer. A

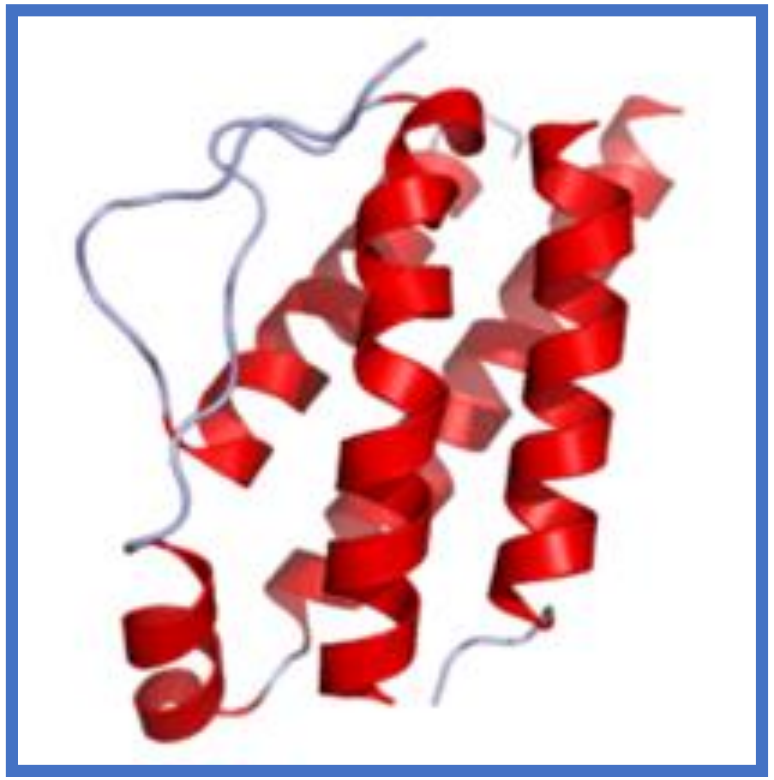
the EORTC Lung Cancer

ative Group



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

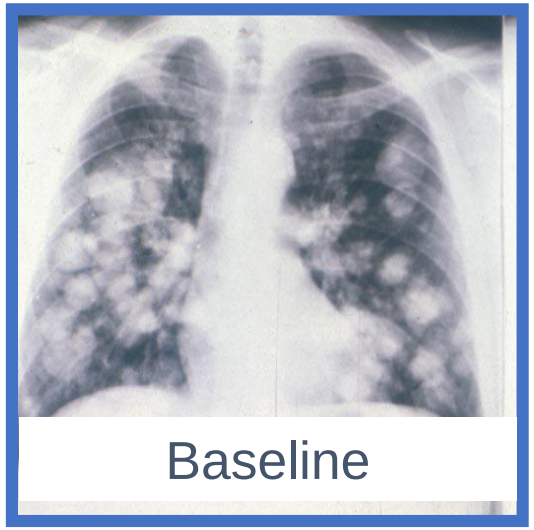
- IL-2 Discovered in 1976 and described as a protein that stimulated growth of T cells[1]
- Jurkat IL-2 in 1983 [Lotze]
- Recombinant IL-2 first cloned in 1983[1]
- First phase I studies of rIL-2 in malignant disease in 1984[2]
- Phase II clinical trials began in 1985[3]




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

# 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.



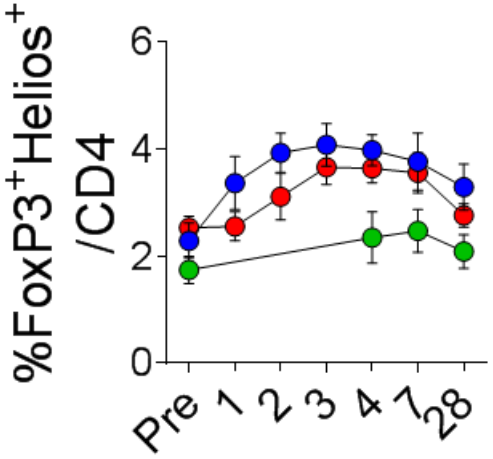


*AR. Chavez, X Liang, MT Lotze.*
*Ann. N.Y.Acad.Sci.1182:14-27 (2009)*

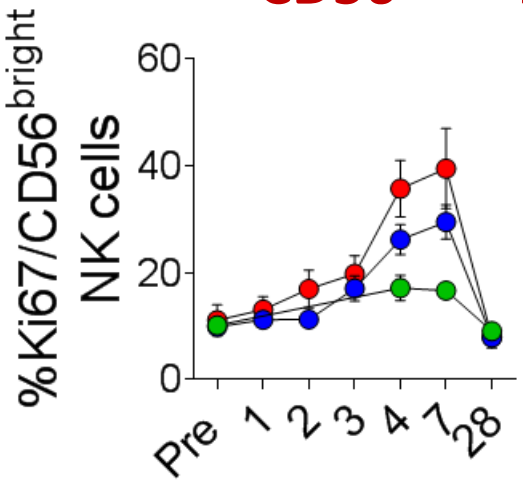

Dupont 1983
Taniguchi, N
Roche 9/84
Cetus-PEG
Chiron
Novartis
Prometheus
Nestle
Clinigen

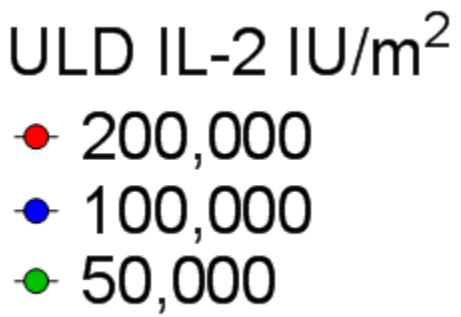
# Ultra-low dose IL-2 expands regulatory T cells and NK cells in healthy donors

## $T_{regs}$ expansion

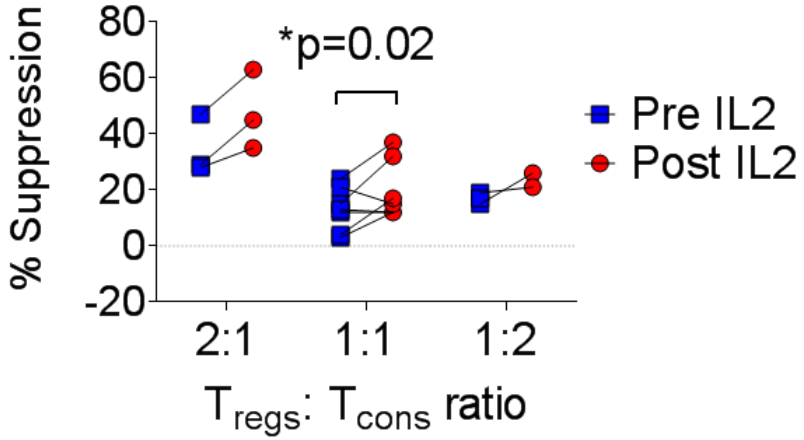



## $CD56^{bright}$ NK expansion

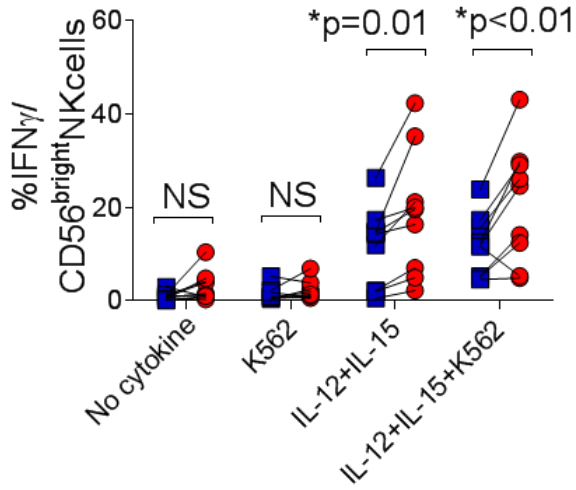



## Increased $T_{reg}$ suppression




## Enhanced IFNγ production in NK




*Ito S, Bollard C et al. Mol Ther. 2014; 22: 1388*

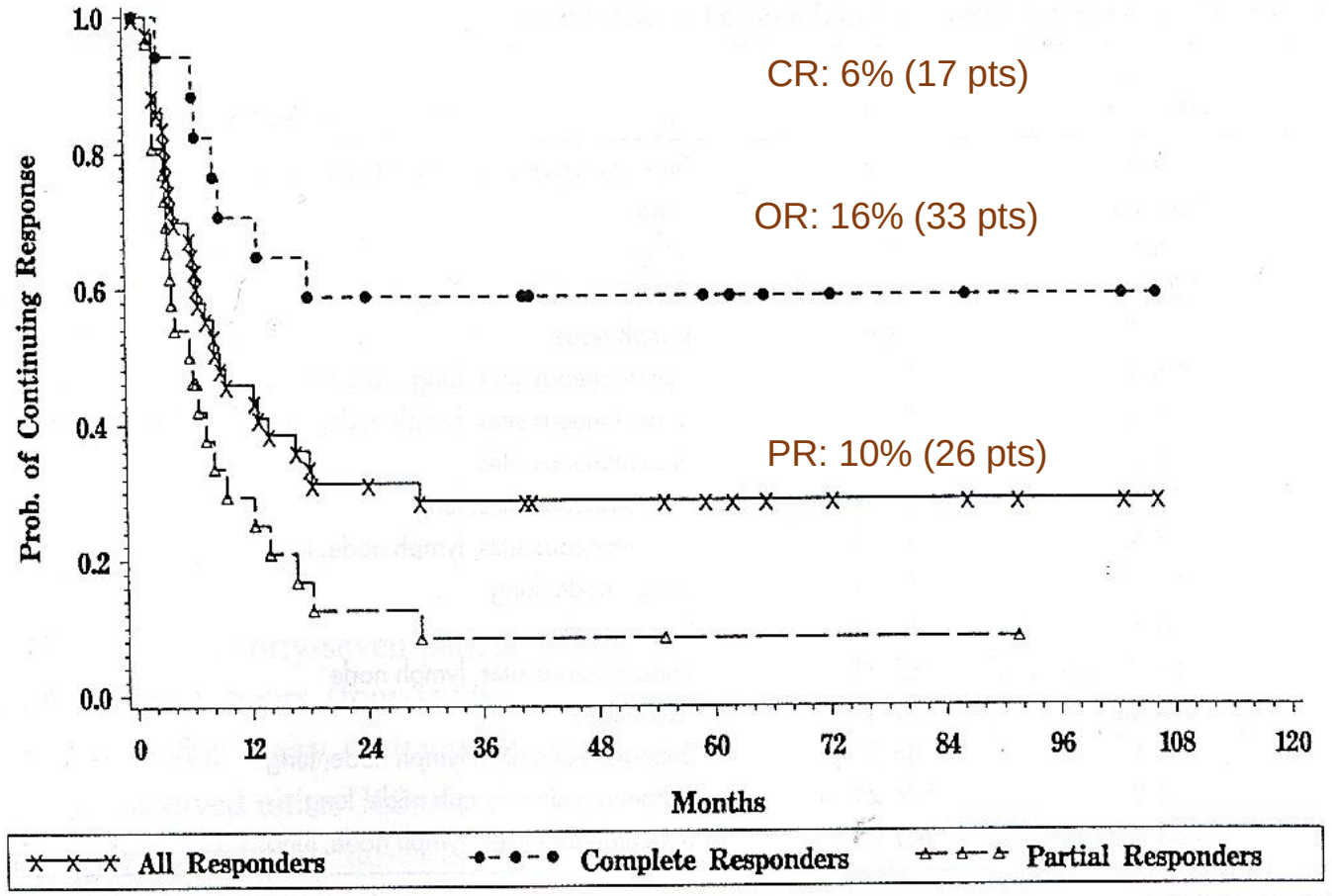
# ULD IL-2 for GVHD prophylaxis: rationale

- **Ultra low dose IL-2**
  - **Expands $T_{regs}$ and NK cells**
  - **Effective for steroid refractory GVHD**
  - **Has been used for GVHD prophylaxis in matched donor SCT**

- **Quality and quantity of regulatory $T_{reg}$ and NK cells impact haplo-SCT outcomes**

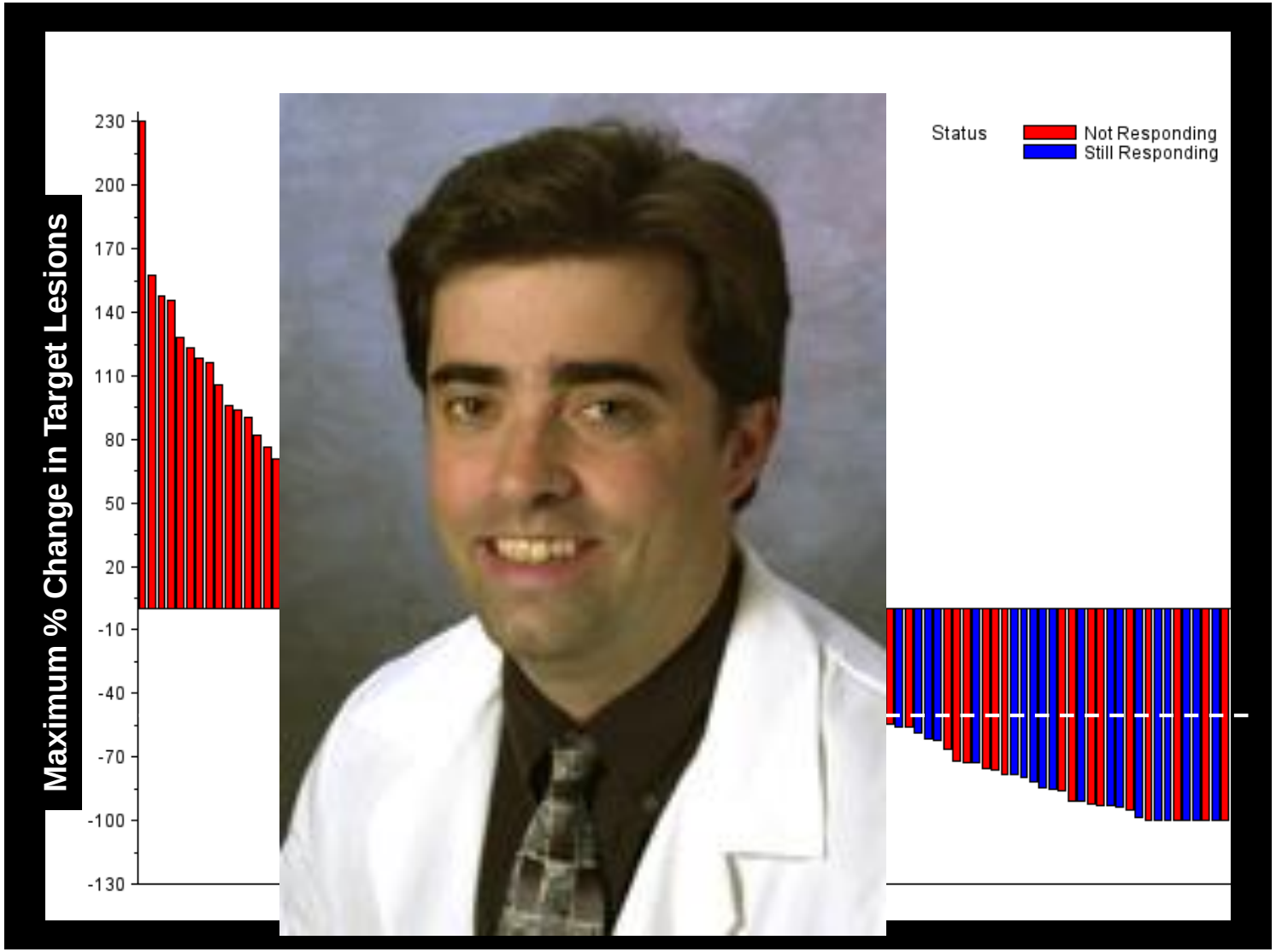
*Koreth et al. N Engl J Med 2011; 365: 2055, Koreth et al. Blood 2016; 128: 130*
*Kennedy-Nasser, Ito S et al. Clin Cancer Res 2014; 20: 2215*

# 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

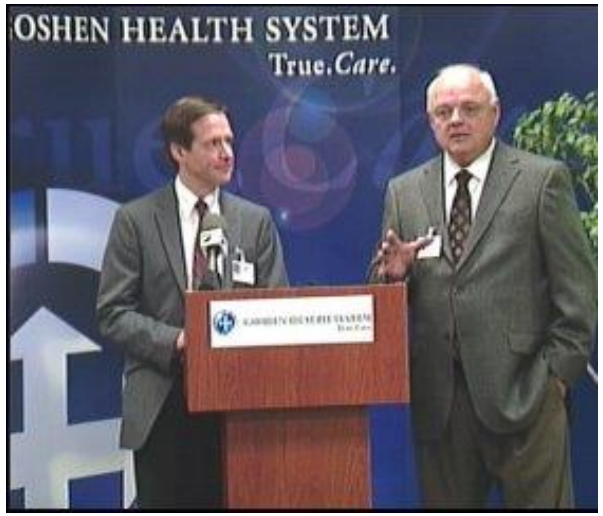
# N Engl J Med 2011; June 2; 364:2119-27

The NEW ENGLAND JOURNAL of MEDICINE

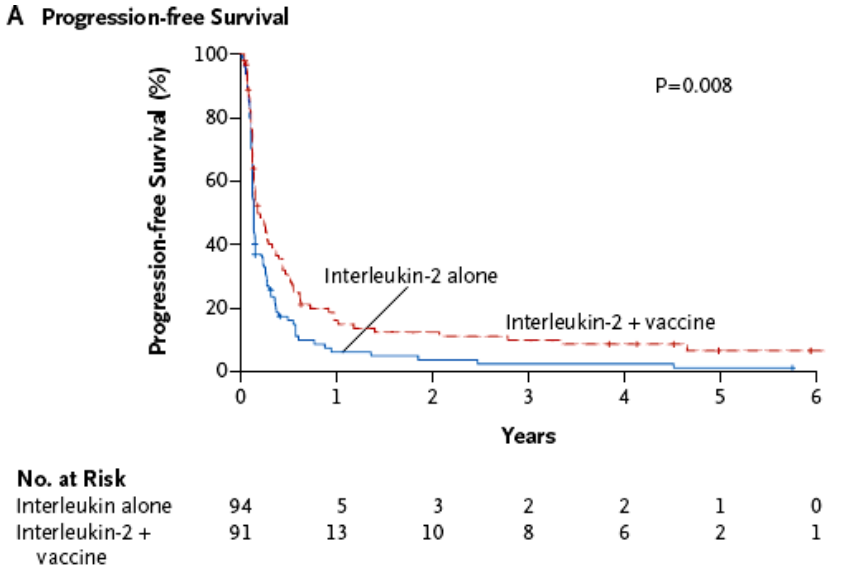
ORIGINAL ARTICLE

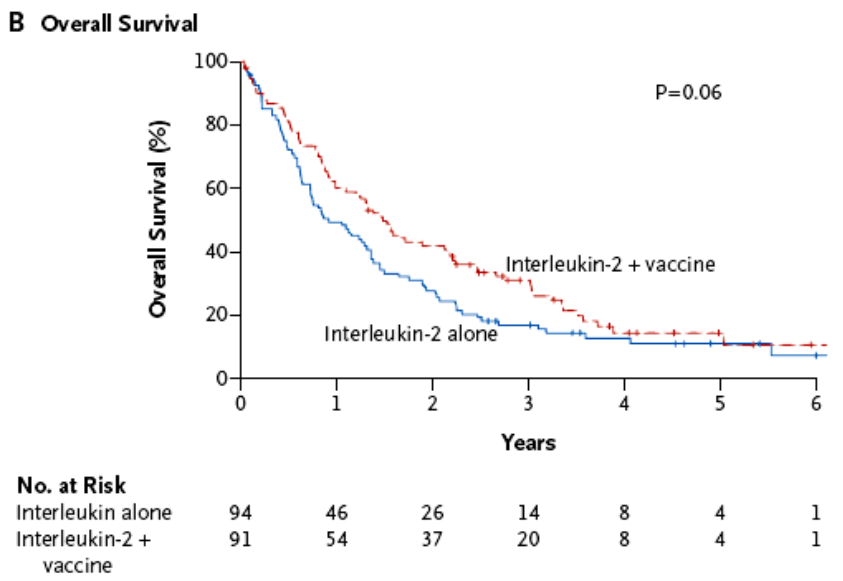
## gp100 Peptide Vaccine and Interleukin-2 in Patients with Advanced Melanoma

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





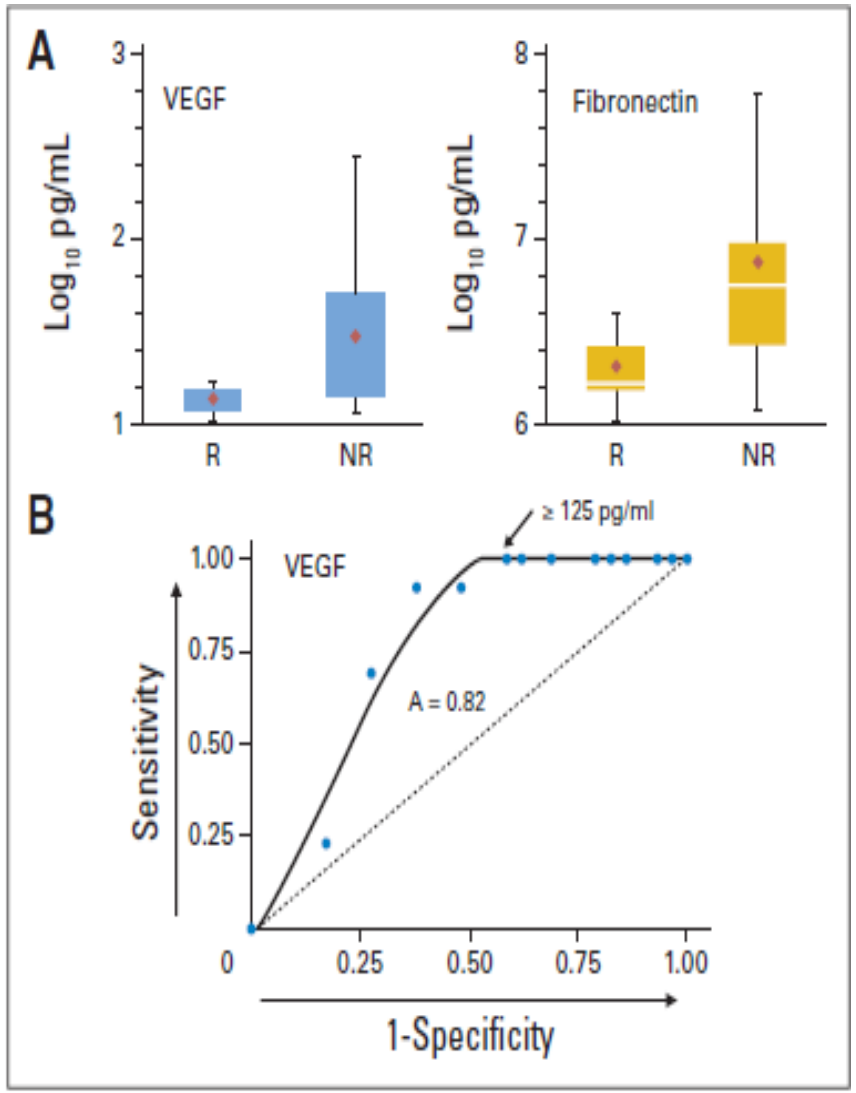


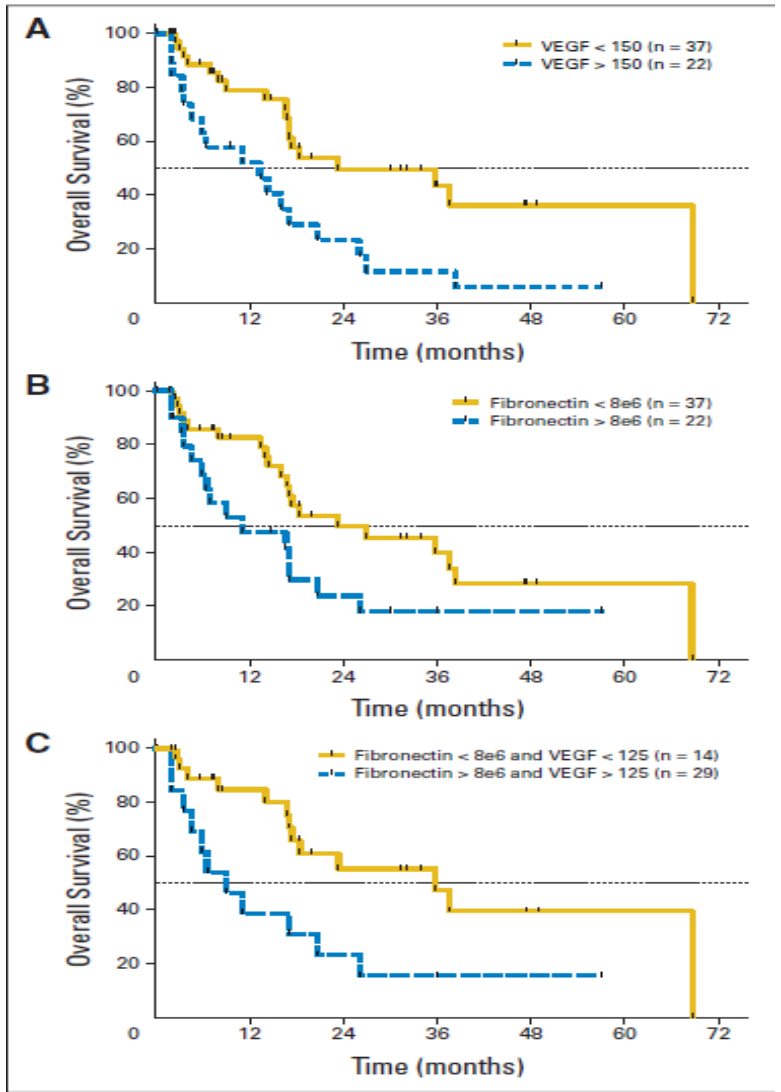



VOLUME 27 · NUMBER 16 · JUNE 1 2009
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

# 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*



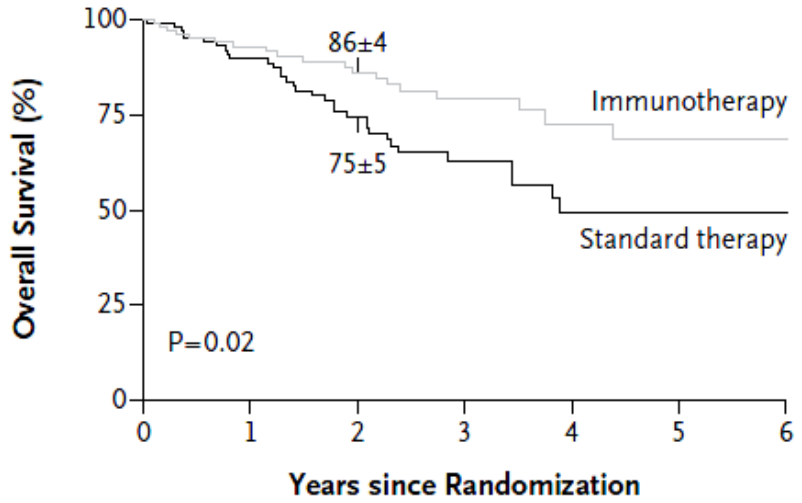



The NEW ENGLAND JOURNAL of MEDICINE

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:

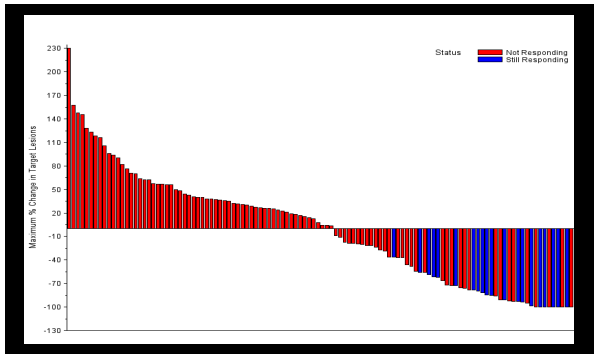
1. high expression of immune checkpoints in the absence of fully functional mature DC→↑ risk of disease progression.
2. low expression of immune checkpoints and localization of mature DC in peritumoral immune

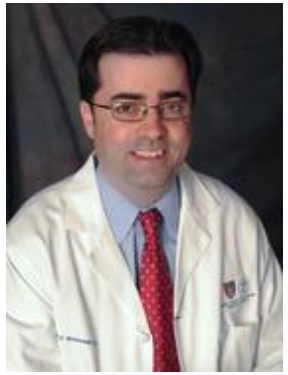
# Inhibiting the Systemic Autophagic Syndrome – A Phase I/II Study of Hydroxychloroquine and Aldesleukin in Renal Cell Carcinoma Patients (RCC) – 30 Patients

A Cytokine Working Group (CWG) Study

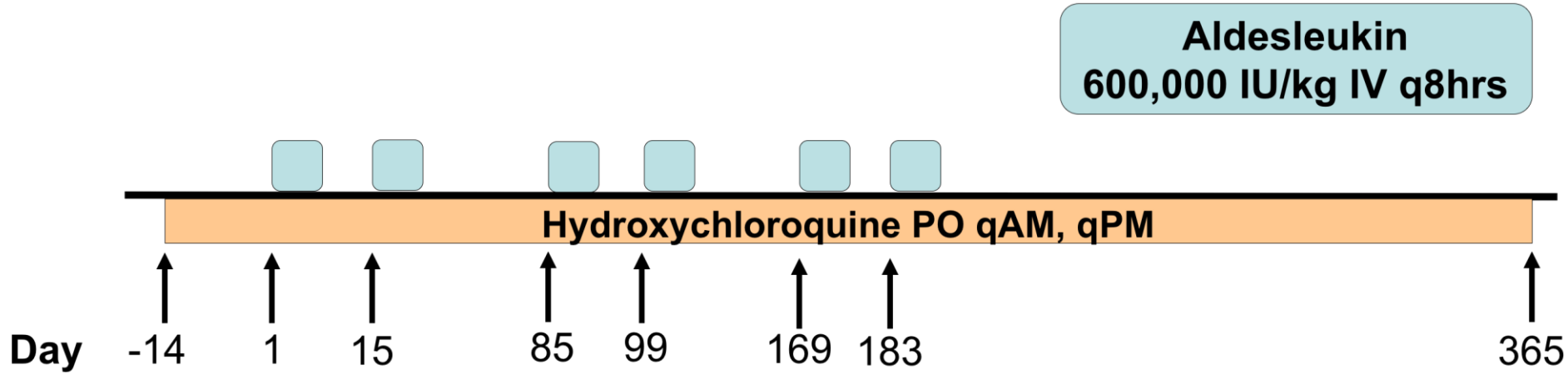
Principal Investigator: Michael T. Lotze, MD,
Len Appleman, MD, PhD
Prometheus/Nestle

Dartmouth
Harvard
Indiana
Oregon
Pittsburgh
Portland



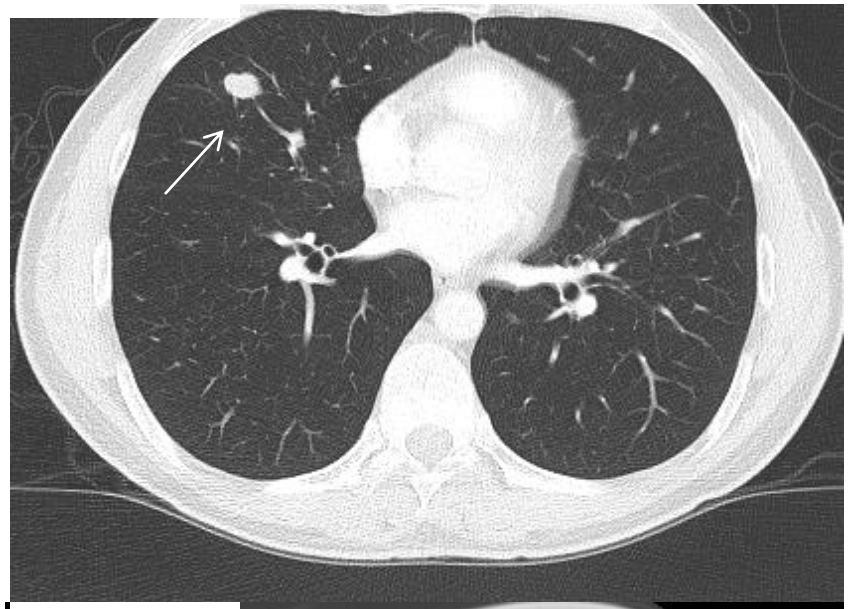
# STUDY DESIGN

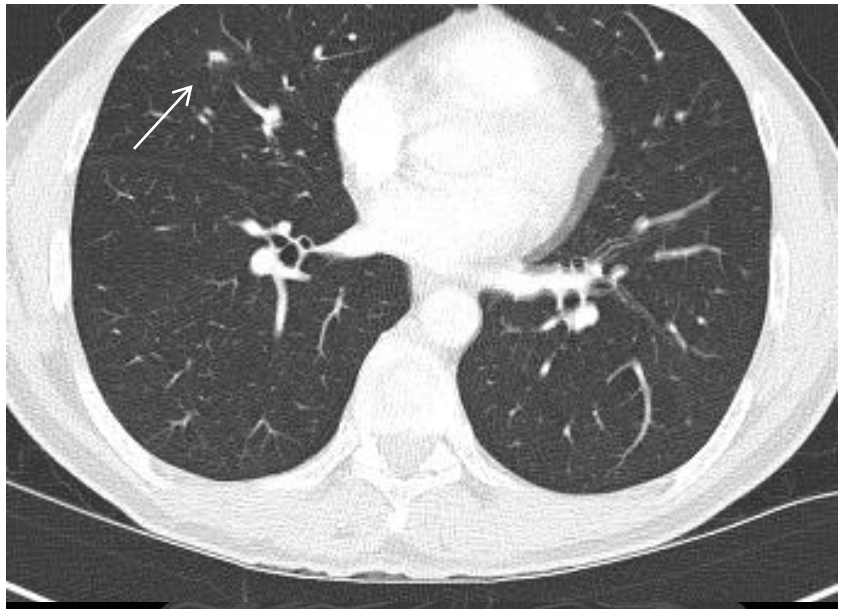


Patient 3

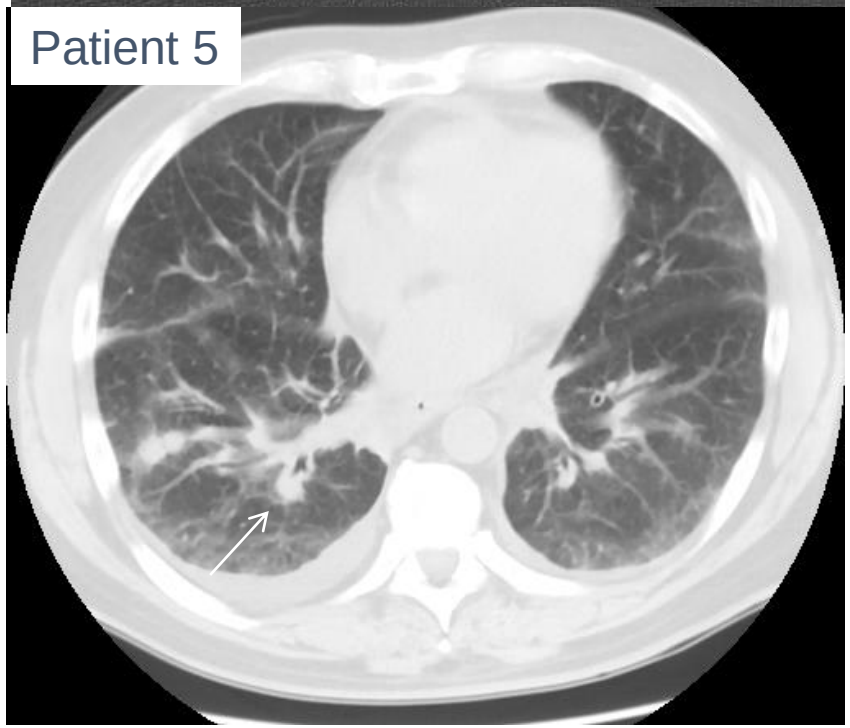
Pre-Therapy

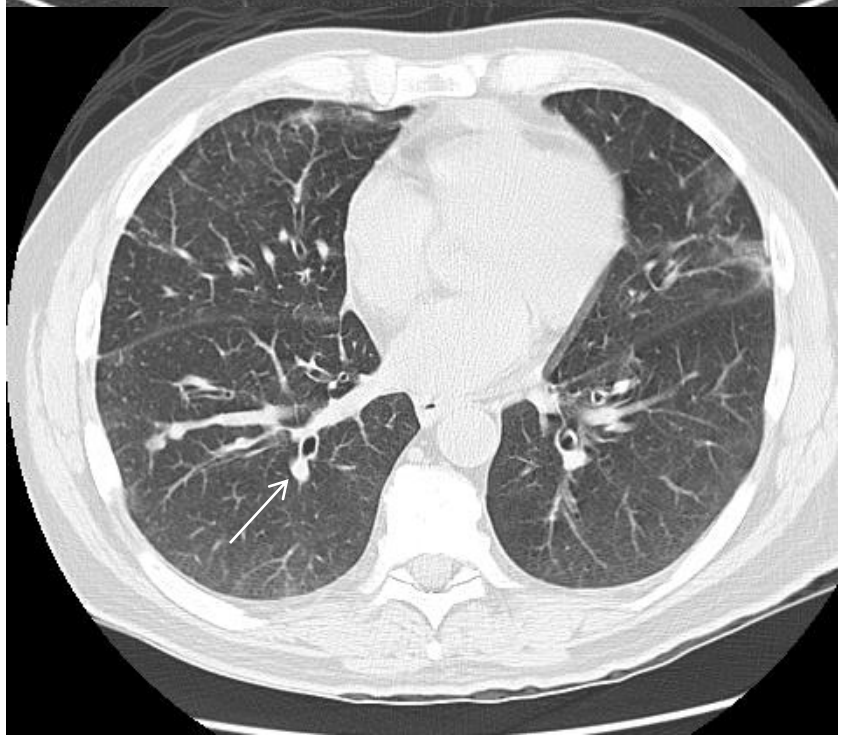
Post-therapy



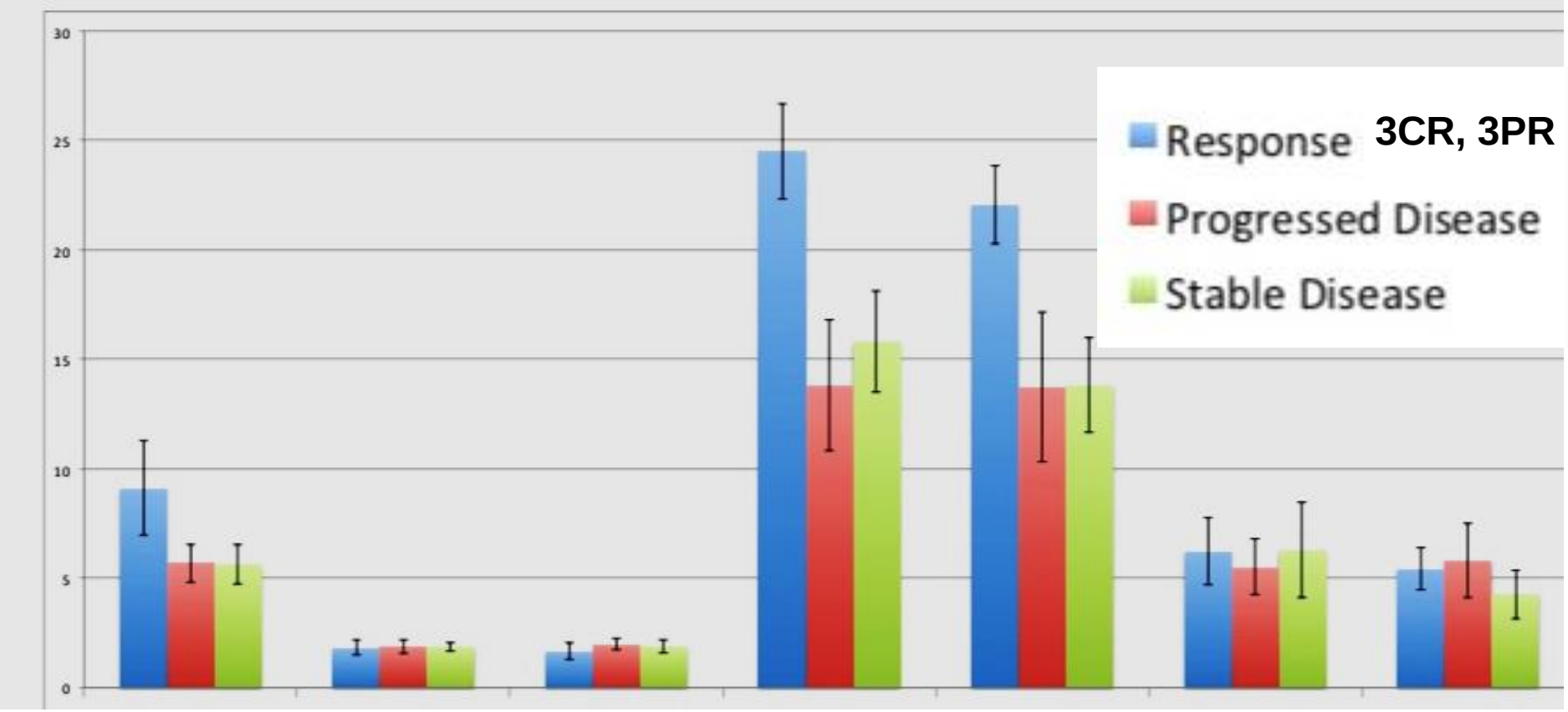


Patient 5



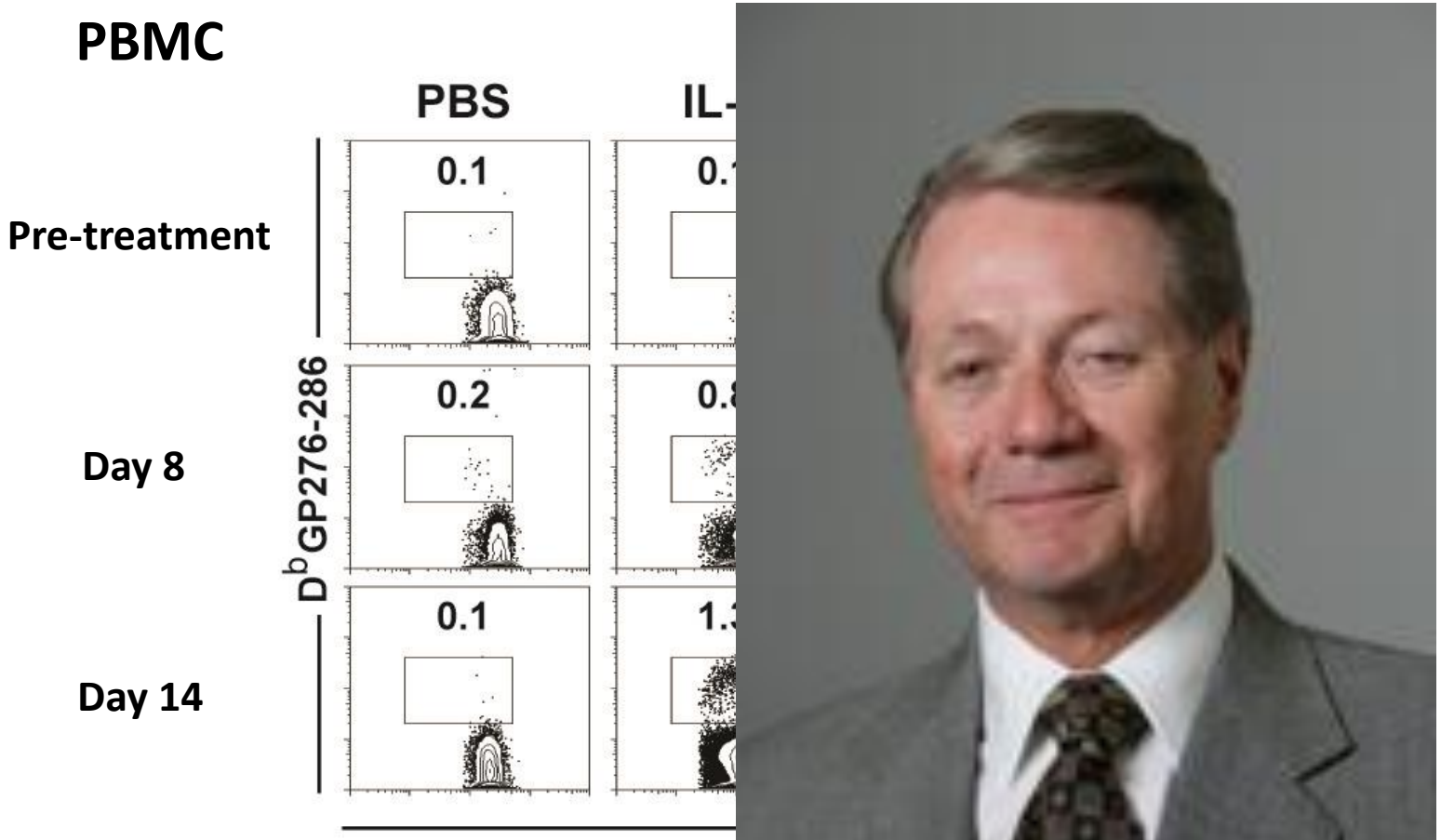


# D50 in 29 Advanced Renal Cancer Patients Treated with High Dose Interleukin 2 (IL-2) and Hydroxychloroquine Associated with Clinical Response




IgH κ λ α β δ γ

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




Gated on CD8⁺ cells

y 3 days
nents

e daily

Kendall Smith, Rafi Ahmed

# 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]

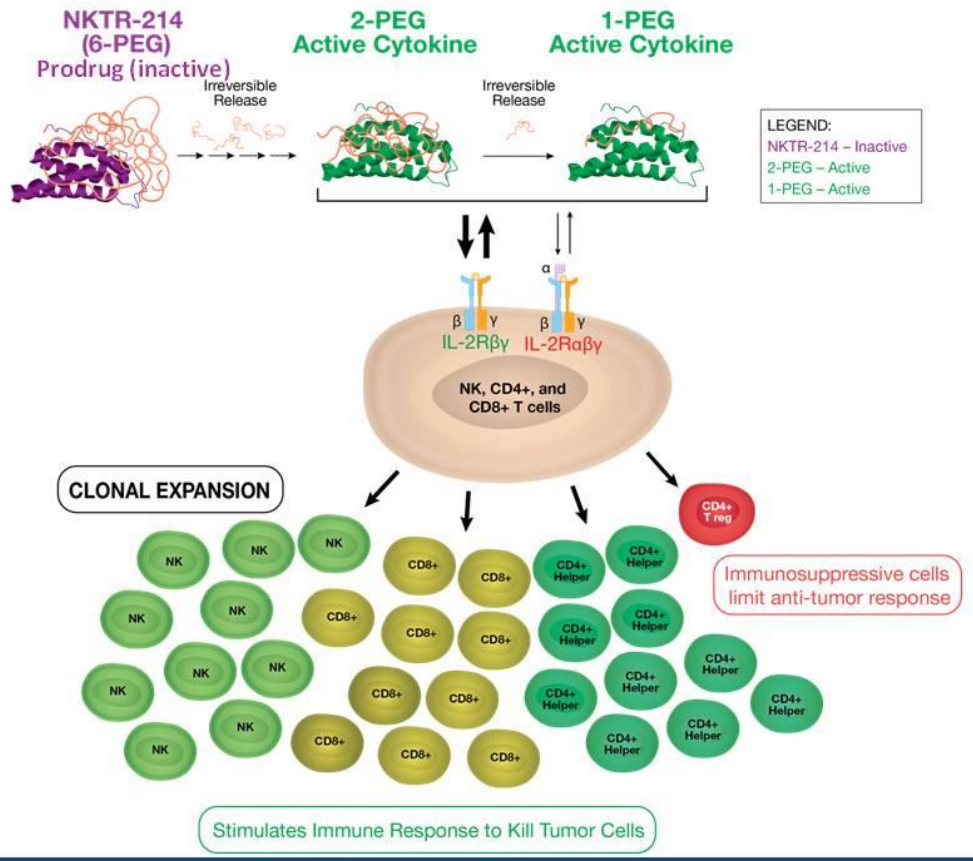
[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Yale School of Medicine, New Haven, CT, USA, [3]NYU Medical Oncology Associates, New York, NY, USA; [4]Providence Cancer Center and Earle A. Chiles Research Institute, Portland, OR, USA; [5]University of Washington and Fred Hutchinson 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

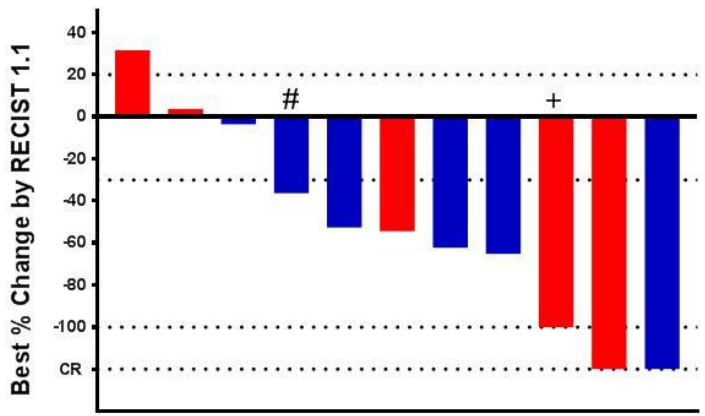
Dose Limiting Toxicities (N=2)

RP2D, recommended Phase 2 dosing

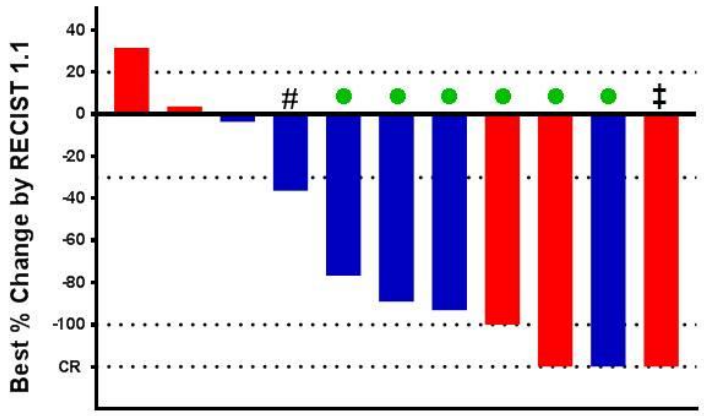
# Stage IV IO-Naïve 1L Melanoma Dose Escalation Cohort (N=11)
# Deepening of Responses Over Time

**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%)

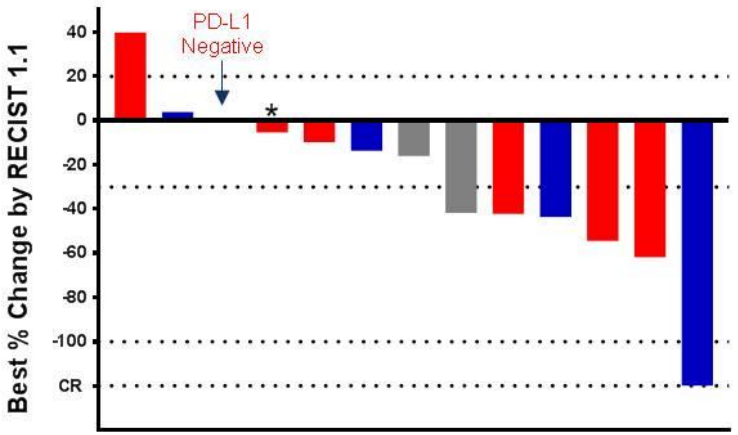



Horizontal dotted lines indicate the thresholds for PD, PR and CR response according to RECIST (version 1.1) criteria. CR: Complete response, all target and non-target lesions cleared.# Best Overall Response is SD (PR for target lesions, PD per new lesion on confirmatory scan) + Best overall response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

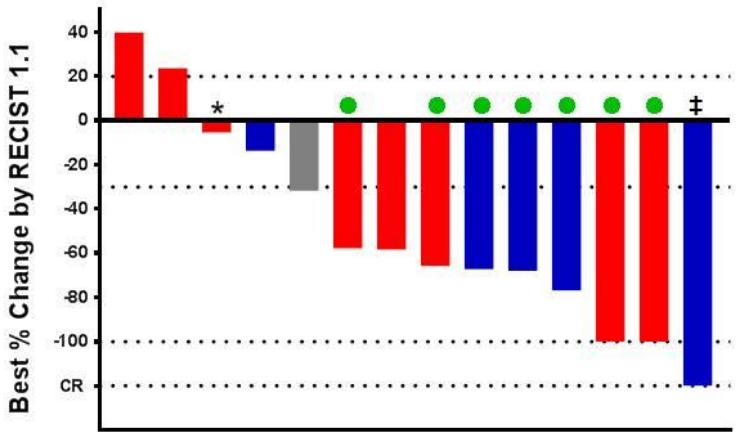
# Stage IV IO-Naïve 1L RCC Dose Escalation Cohort (N=14)
# Deepening of Responses Over Time

**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**

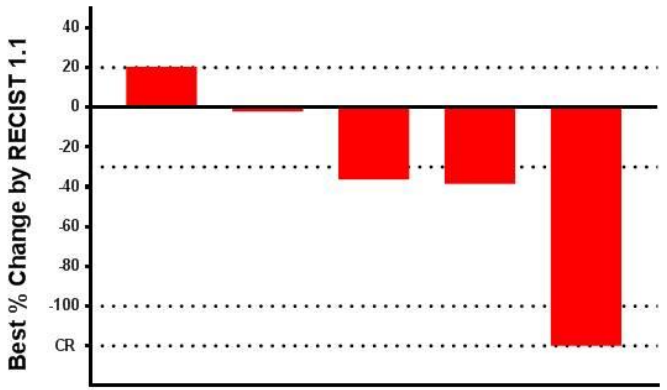



Horizontal dotted lines indicate the thresholds for PD, PR and CR response according to RECIST (version 1.1) criteria. *Best overall response is PD (SD for target lesions, PD per non-target lesions). "u": Unconfirmed.

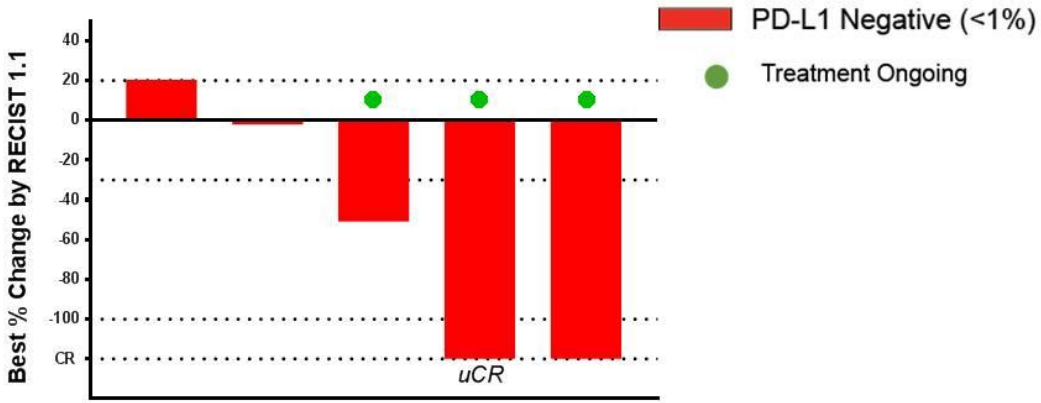
# Stage IV IO-Naïve 1-2L NSCLC Dose Escalation Cohort (N=5)
# Deepening of Responses Over Time in PD-L1 Negative Patients

**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)

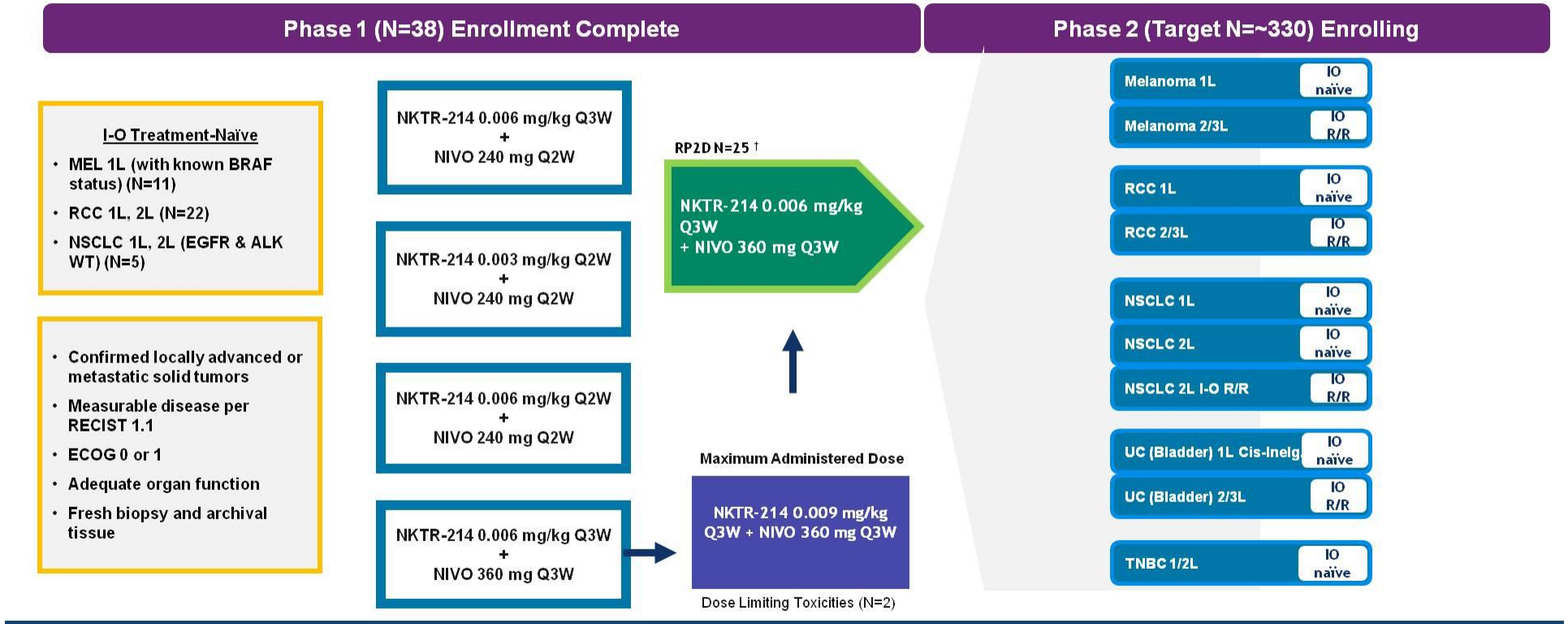






PDL1 positivity for this analysis was 1% or greater. Horizontal dotted lines indicate the thresholds for PD, PR and CR response according to RECIST (version 1.1) criteria., CR: Complete response, all target and non-target lesions cleared,. "u": Unconfirmed

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







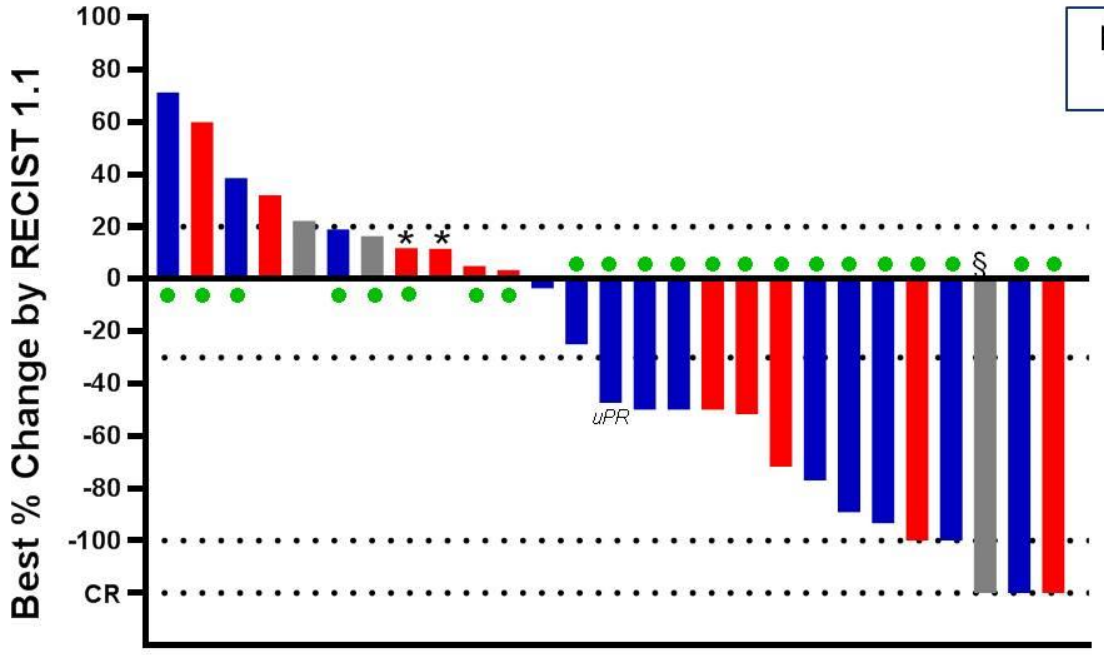

†7 patients from 1L melanoma dose escalation cohort, 11 patients from 1L RCC dose escalation cohort included in RP2D expansion cohorts
RP2D: recommended Phase 2 dosing



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%)

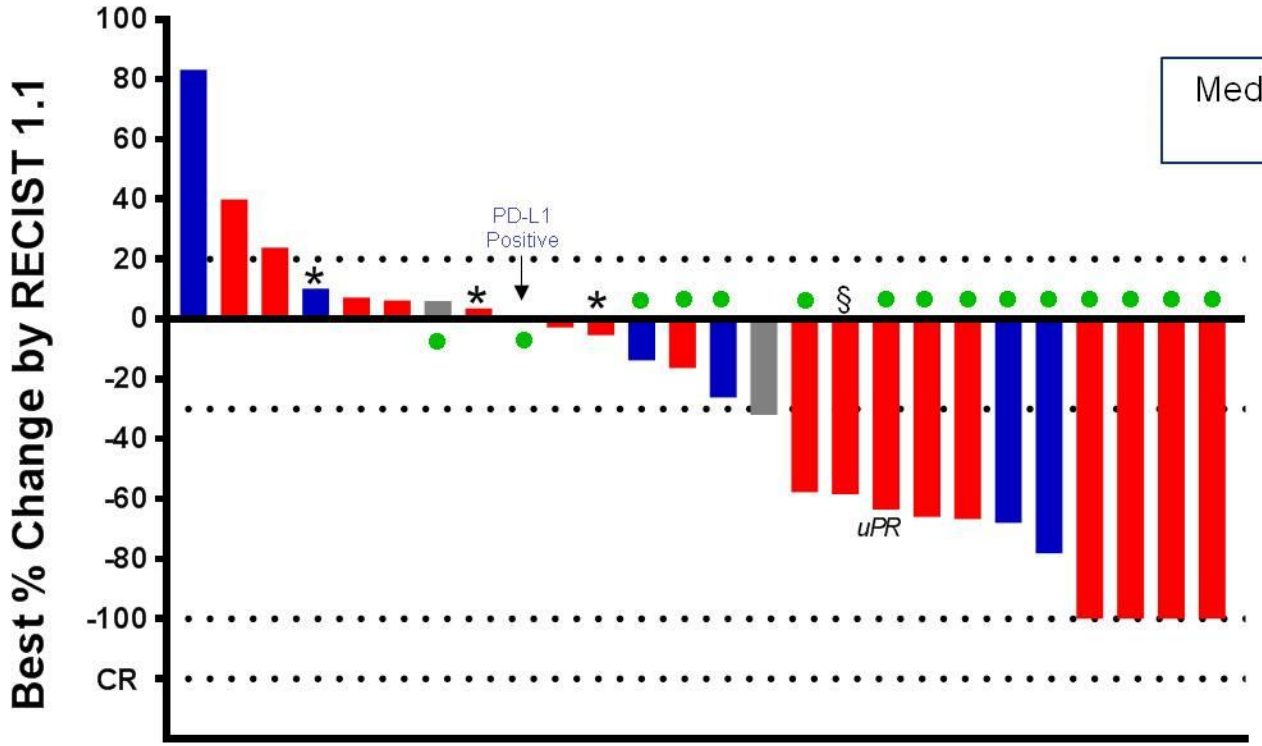
Data cut: May 29, 2018




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%)

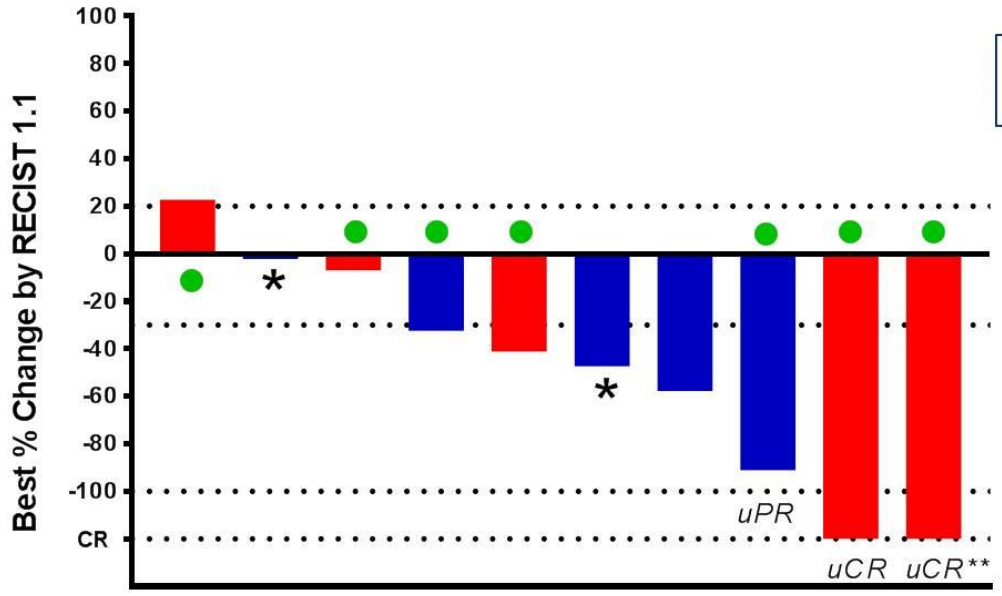
Data cut: May 29, 2018




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

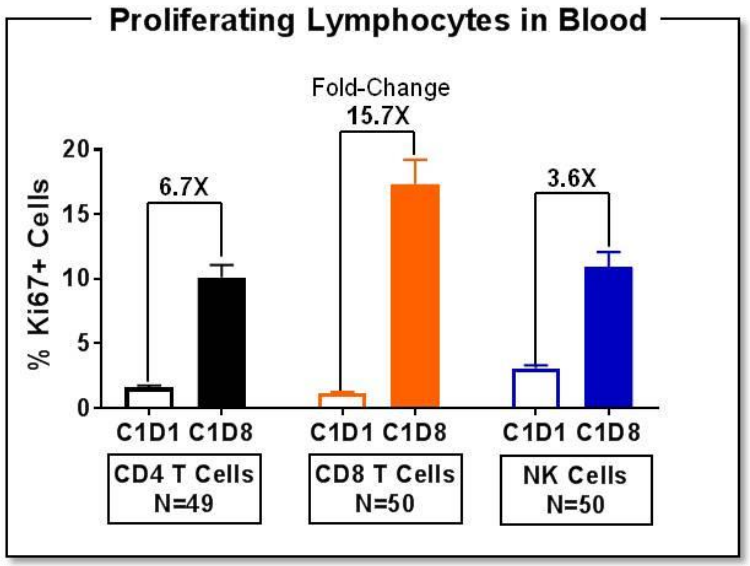
ORR PD-L1(-) 3/5 (60%)
ORR PD-L1(+) 3/5 (60%)

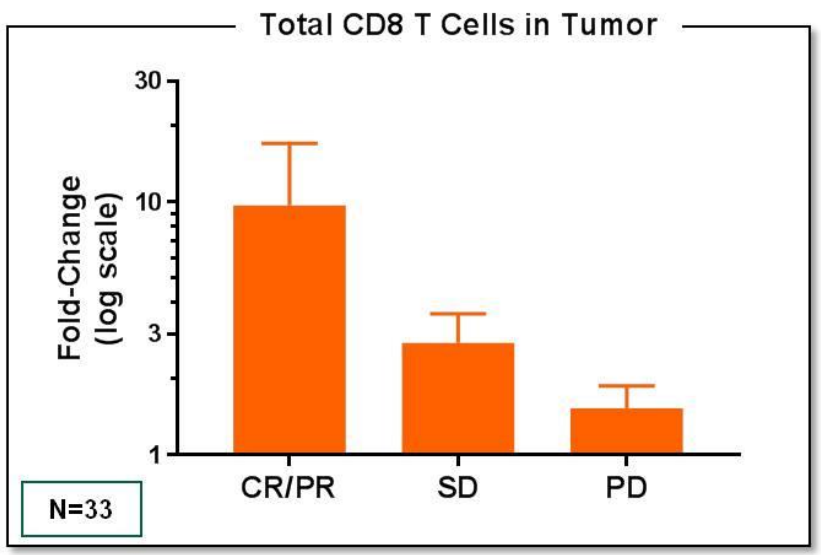
Data cut: May 29, 2018




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).

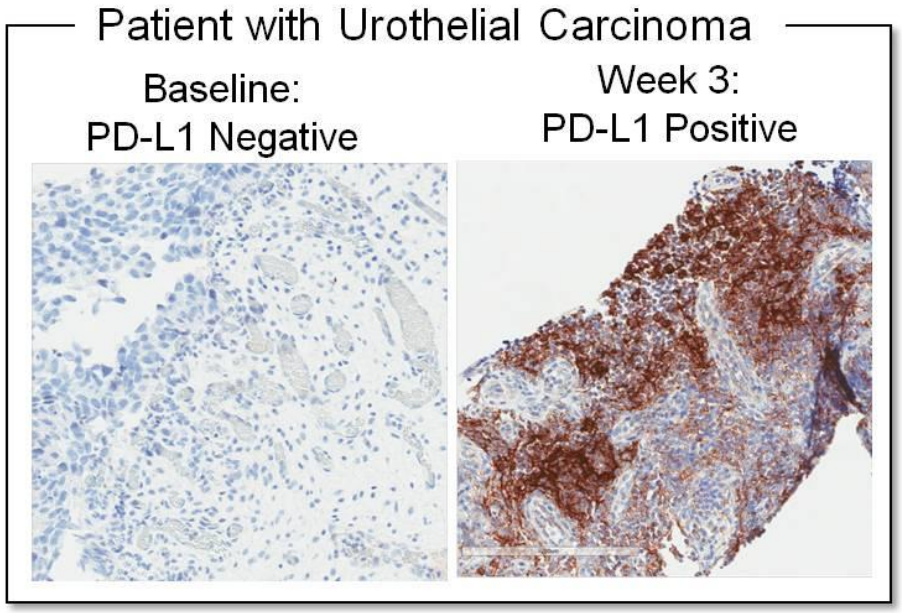
# NKTR-214 + Nivolumab Increased Lymphocyte Proliferation in Blood and CD8 T Cells in Tumor

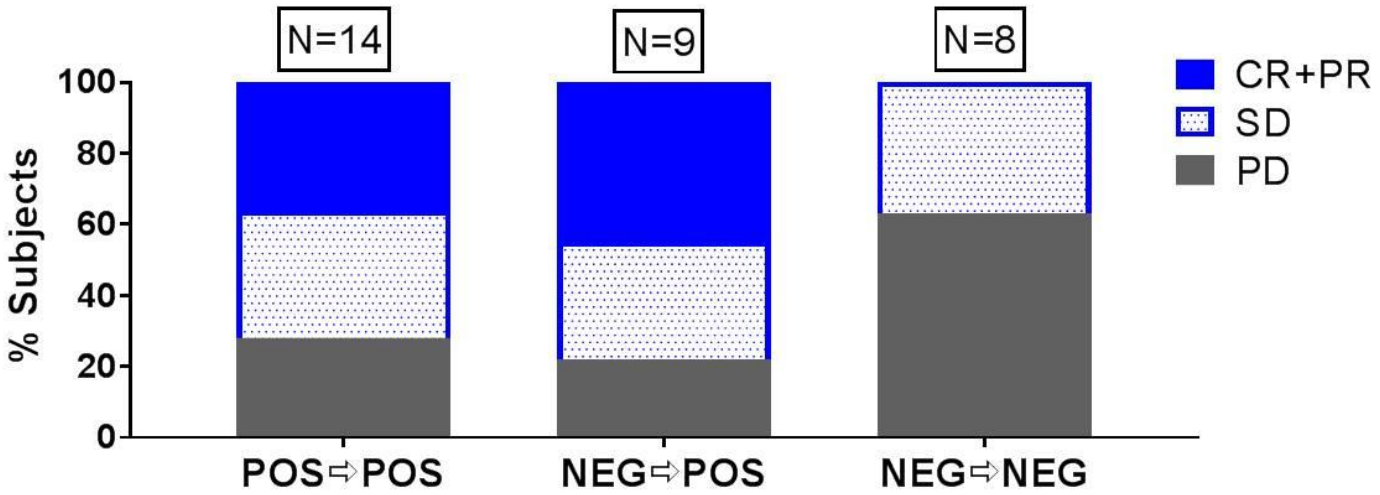



"Proliferating Lymphocytes in Blood" were measured using flow cytometry of fresh whole blood for all patients that the met inclusion criteria and had matched Cycle 1 Day 1 (C1D1) and Cycle 1 Day 8 (C1D8) blood collections. Data presented as mean ± standard error. Fold-change calculated for C1D8/C1D1. 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.

Cancer Immunology at the Crossroads

# Treg Fragility: A Prerequisite for Effective Antitumor Immunity?

Abigail E. Overacre-Delgoffe and Dario A.A. Vignali

**DOI:** 10.1158/2326-6066.CIR-18-0066 Published August 2018



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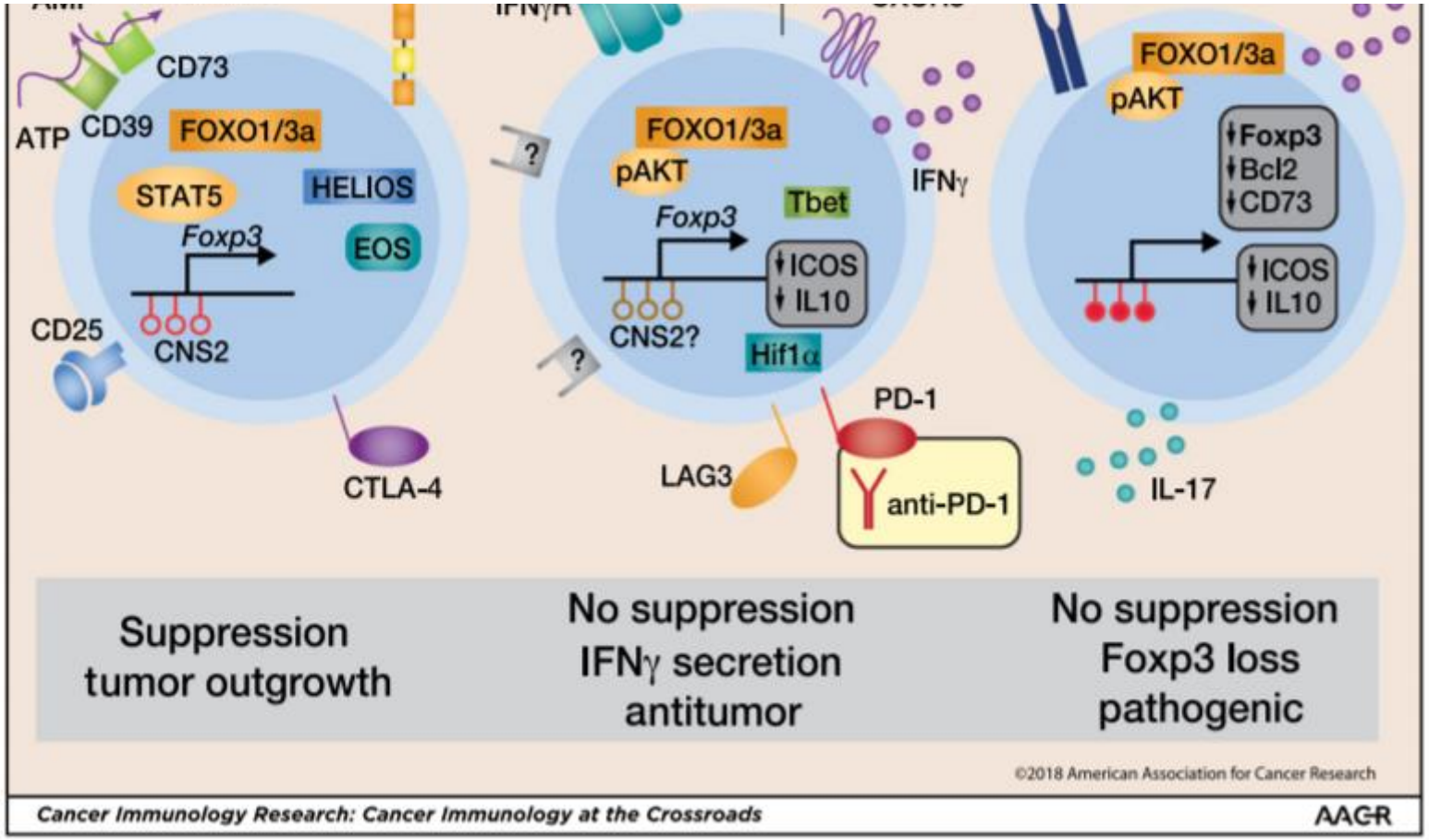


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# Interleukin 7 (IL-7)

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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.*

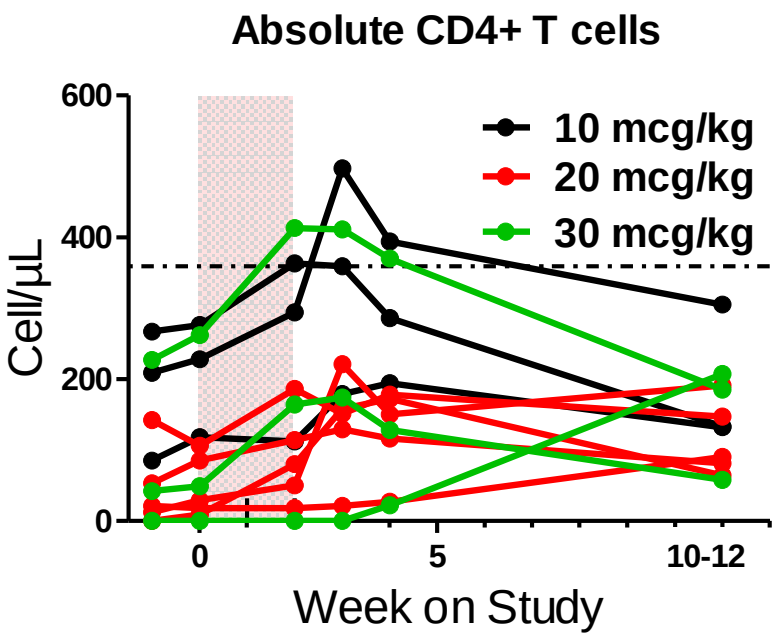
# IL-7 – Initial Clinical Trials with CYT99 007

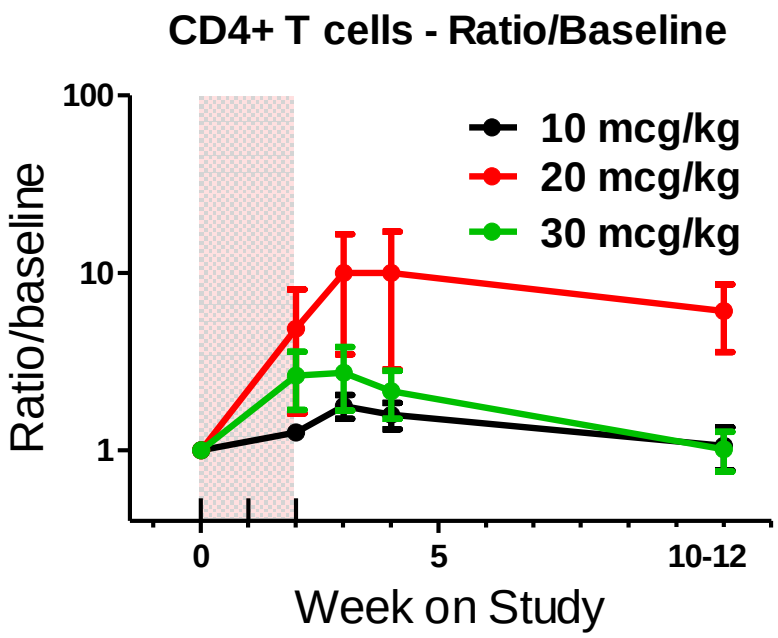
**Table - 62 patients treated on 5 clinical trials with CYT 99 007**

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



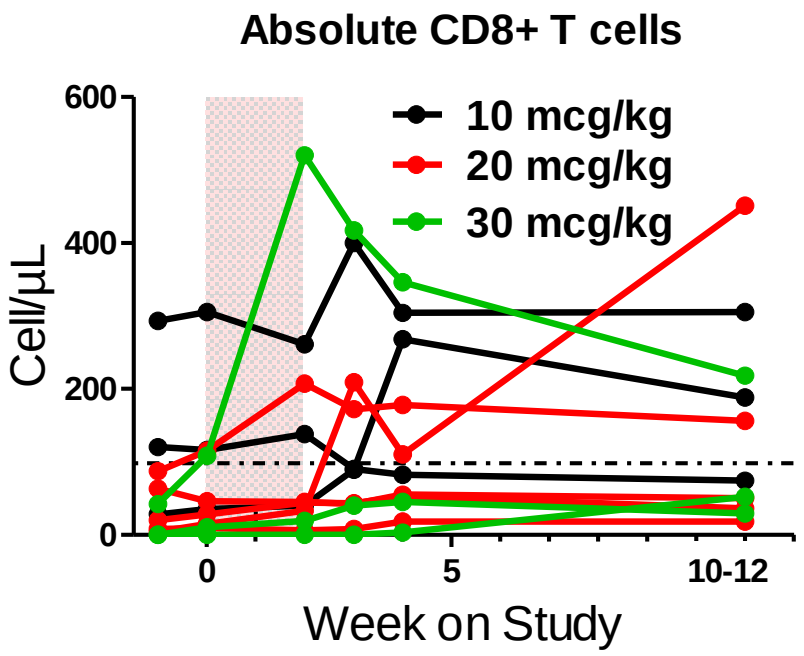



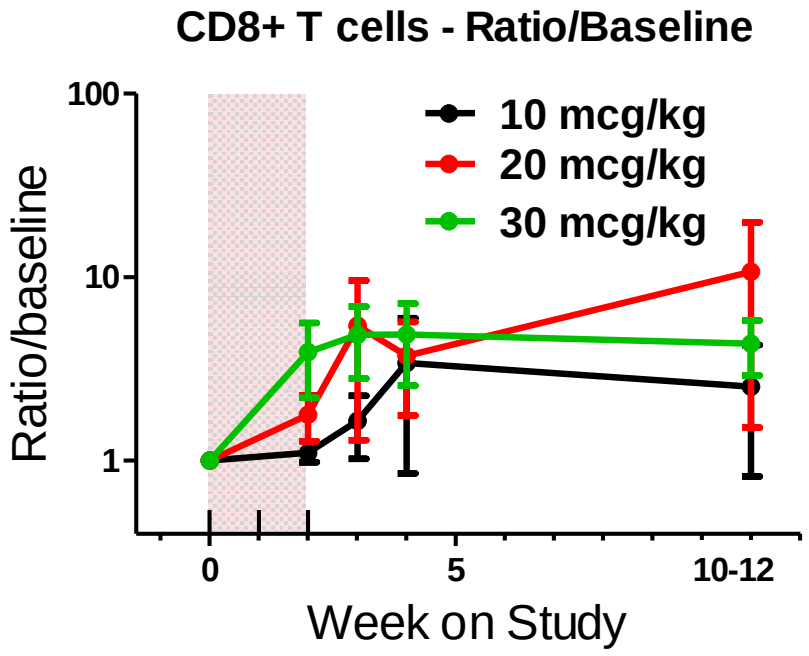

**107.4/mm³ average increase at day 21, p=0.002**
(range 0 to 35-fold increase)

*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



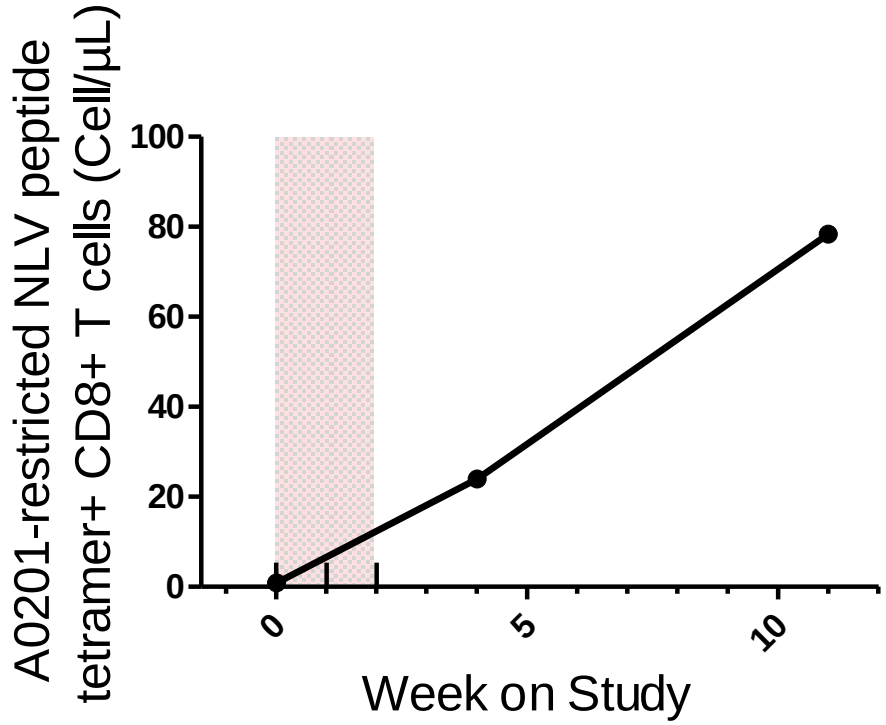




**66.9/mm³ average increase at day 28, p=0.05**
**(range 0 to 11-fold increase)**

*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

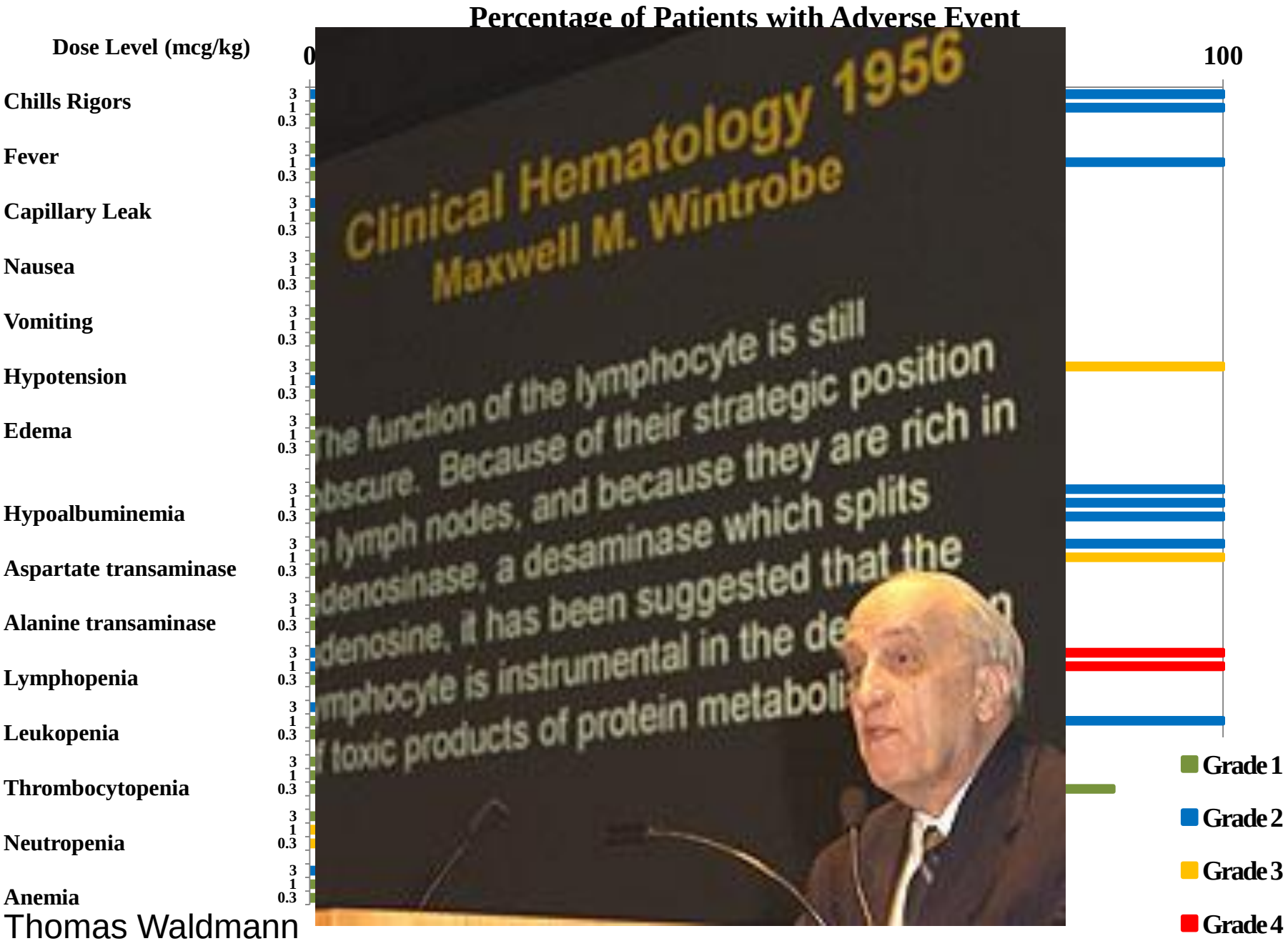



CMV responses were also detected after rhIL-7 injection in 2 other CMV-seropositive patients

*Perales, CITN Investigator Meeting – Nov 2013*

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

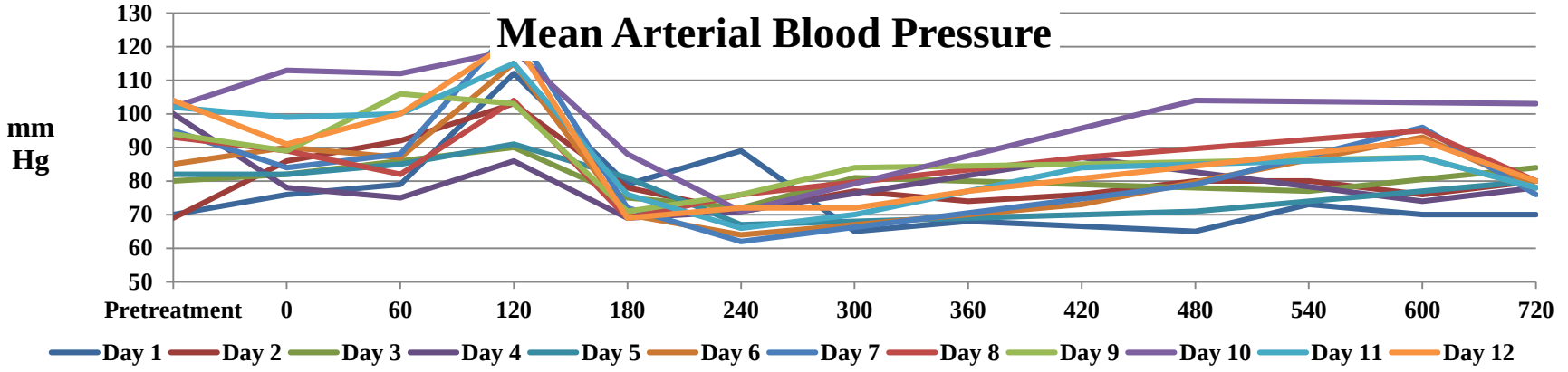
# Interleukin 15 Adverse Event Summary

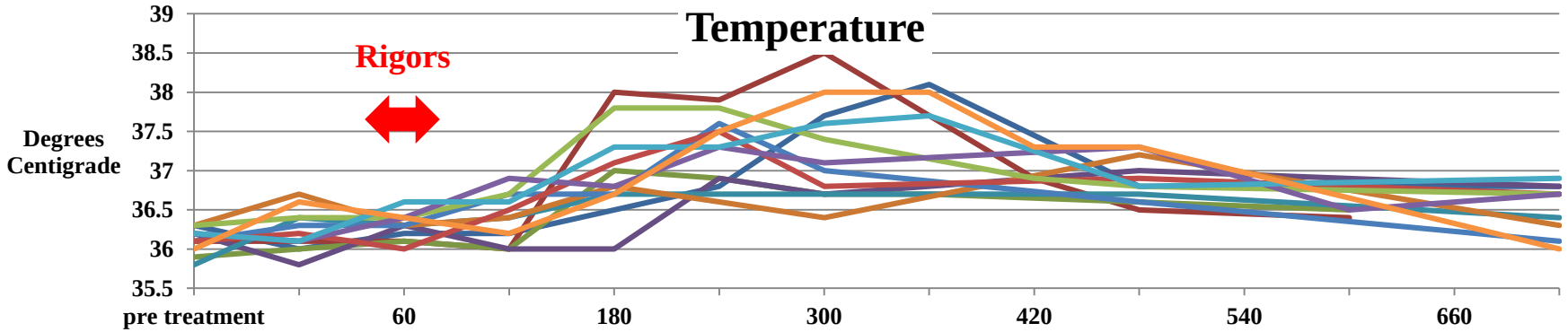


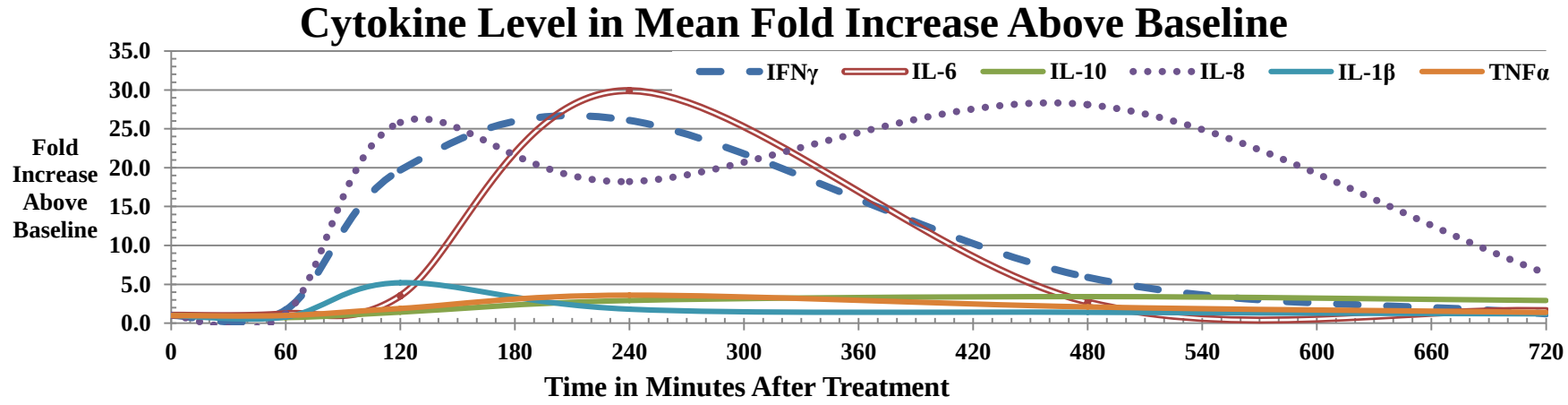



Thomas Waldmann

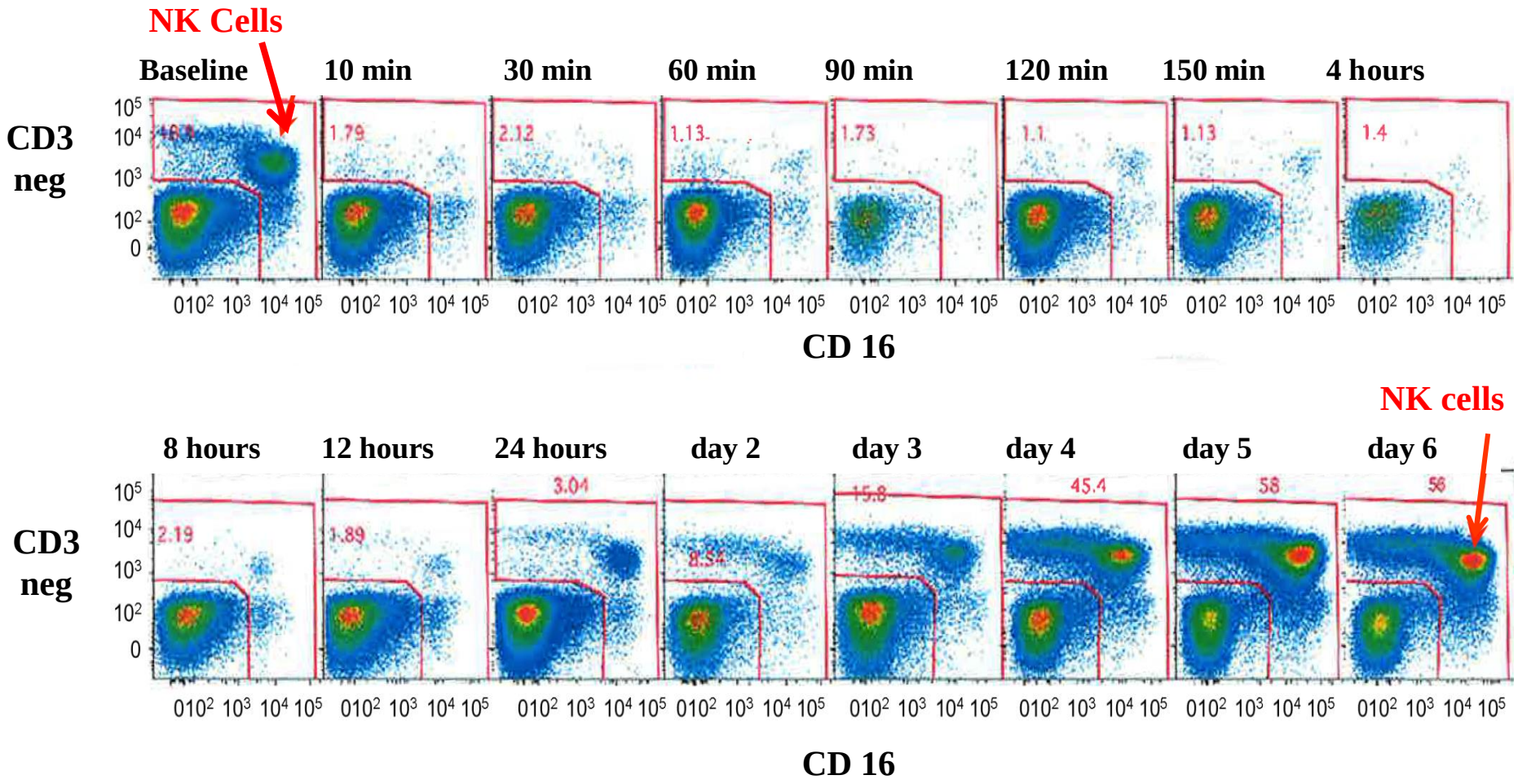
# Cytokine Release and Adverse Events 3 mcg patients



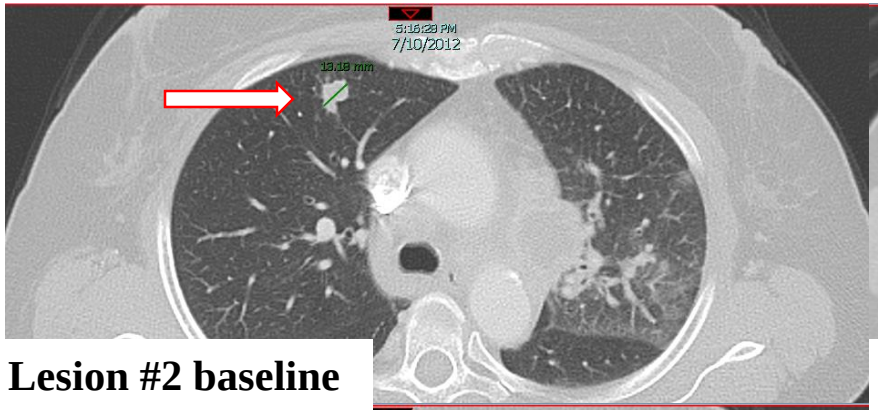



# Rapid Disappearance Of NK Cells rhIL-15 Treatment

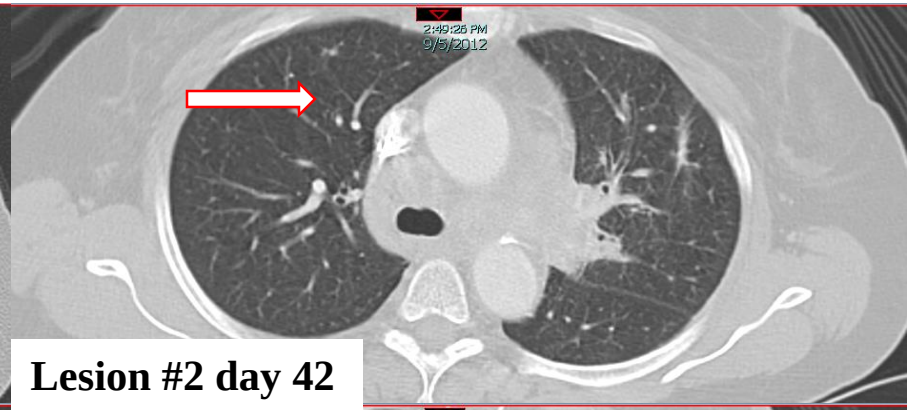


# Clinical Activity

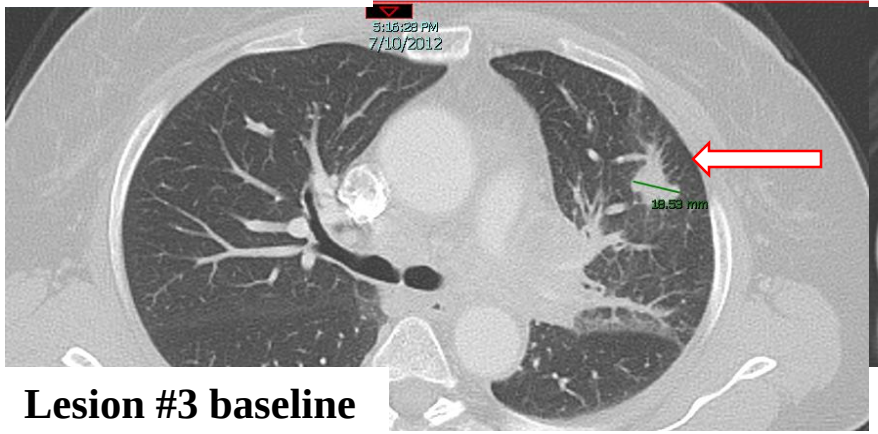
## Patient #16 Unconfirmed PR at day 42 restaging



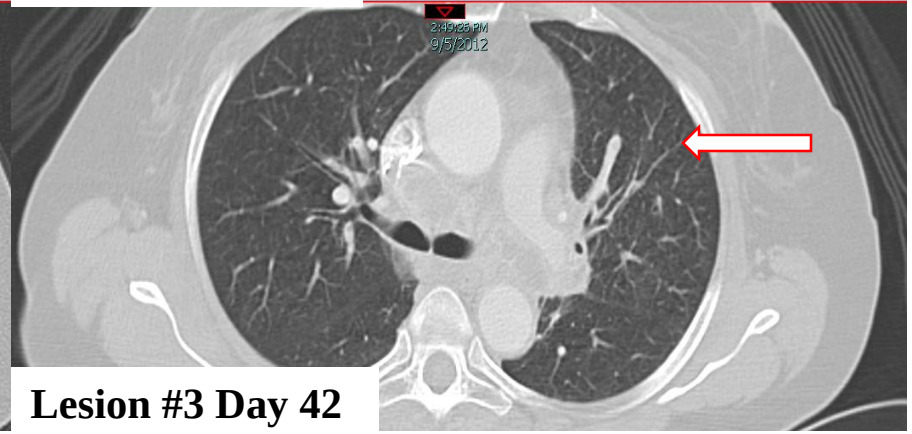

Lesion #2 baseline




Lesion #2 day 42

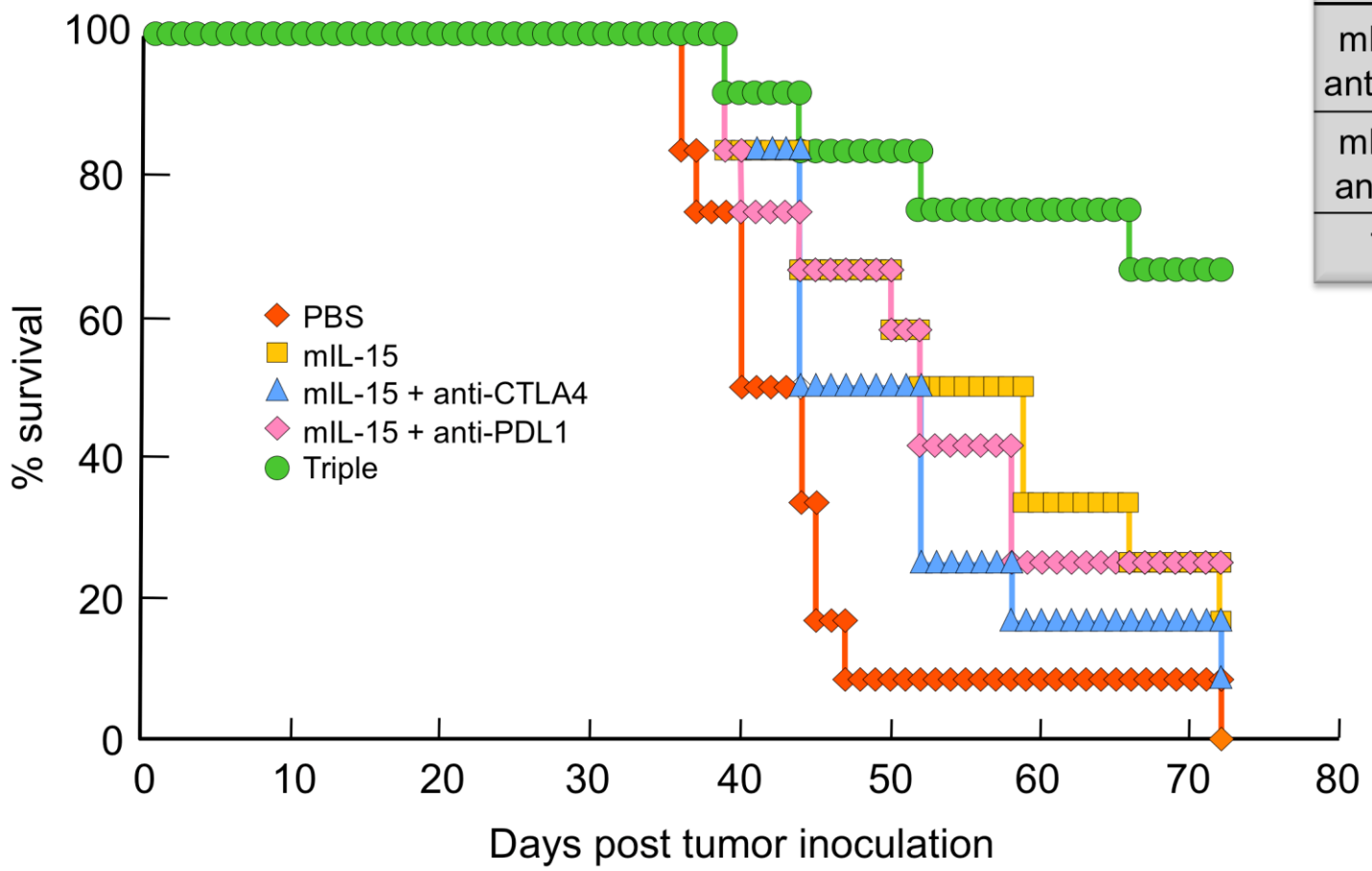



Lesion #3 baseline




Lesion #3 Day 42

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

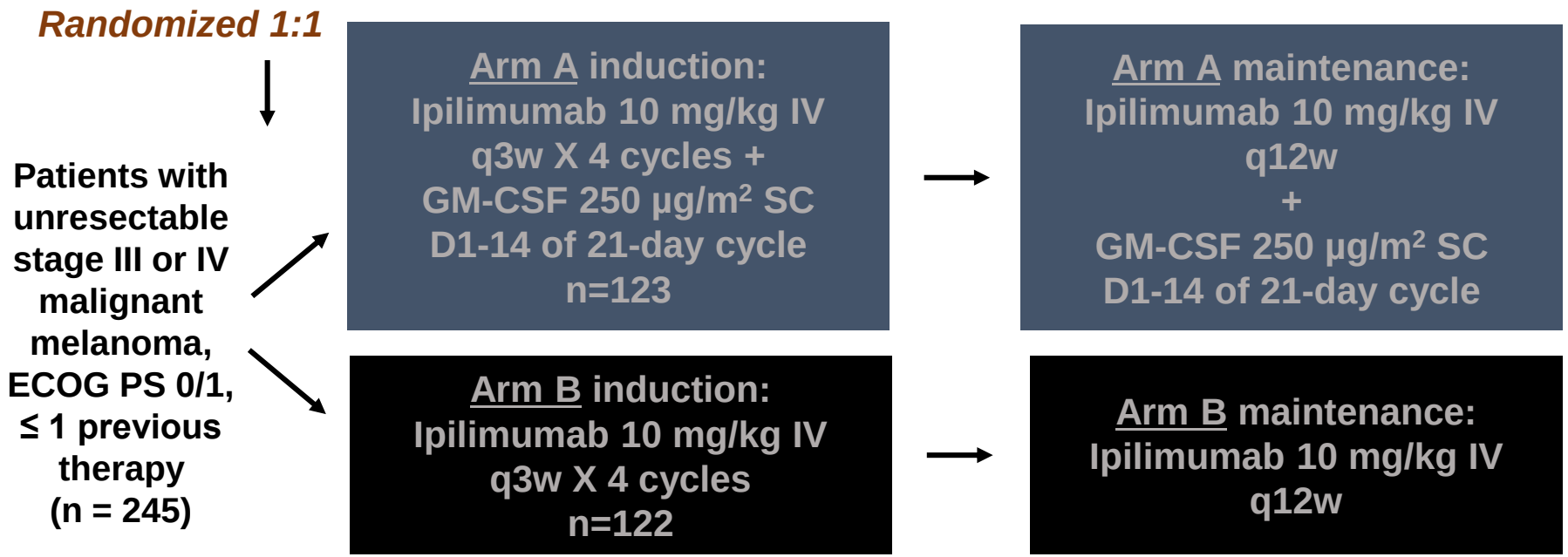



| Compare to mIL-15 | p value |
|---|---|
| mIL-15 + anti-CTLA4 | 0.4197 |
| mIL-15 + anti-PDL1 | 0.7729 |
| Triple | 0.0405 |

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.

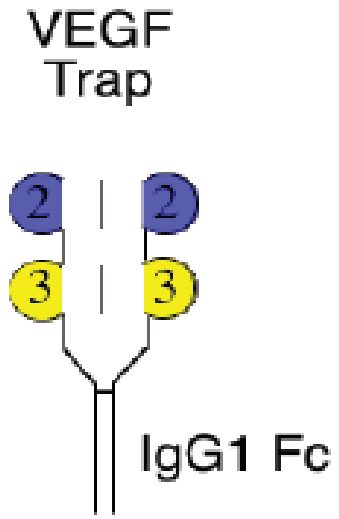
# Randomized Phase II Study of GM-CSF + Ipilimumab

| 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.

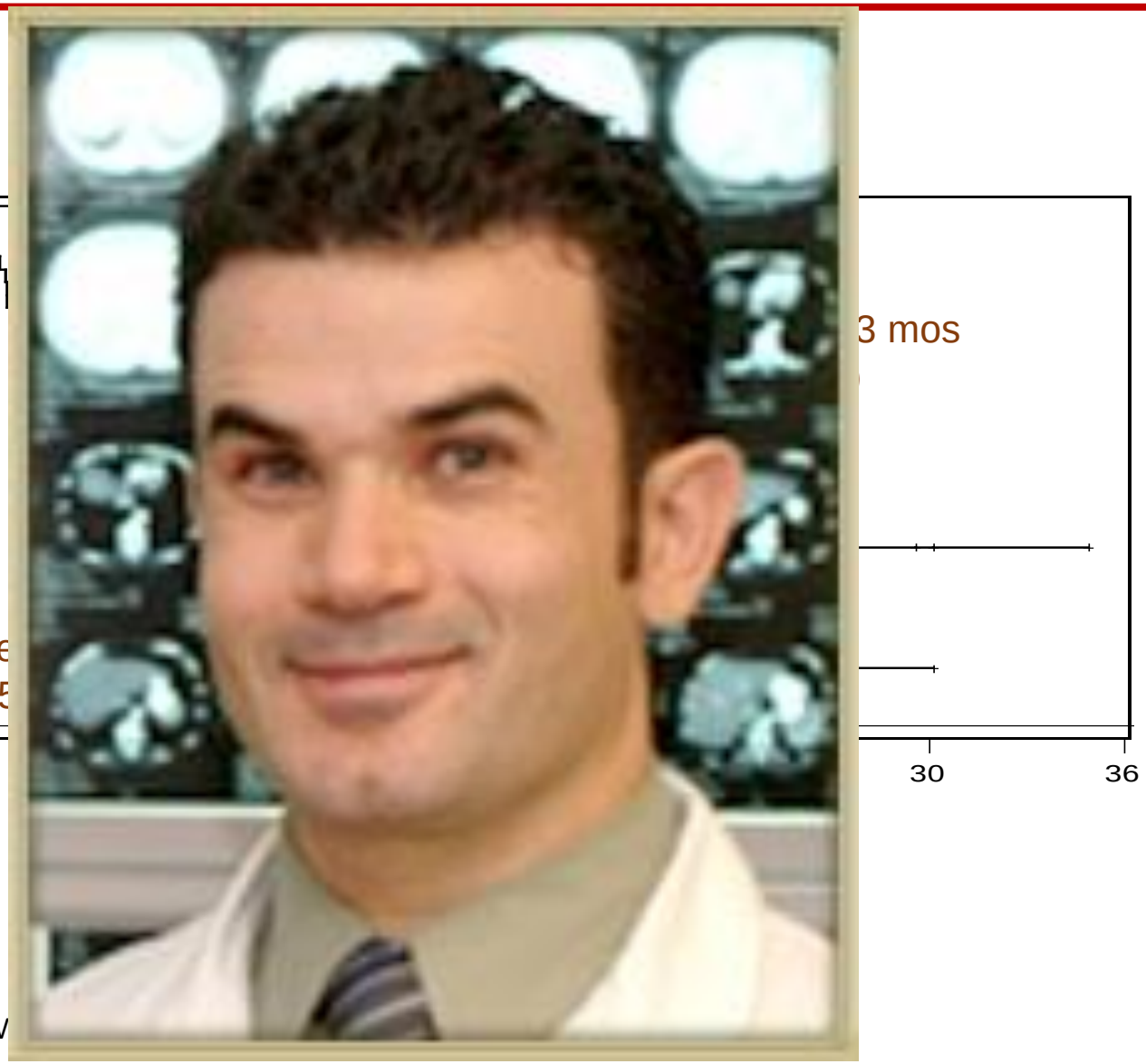
# VEGF Trap

- 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

# Why Women Live Longer Than Men