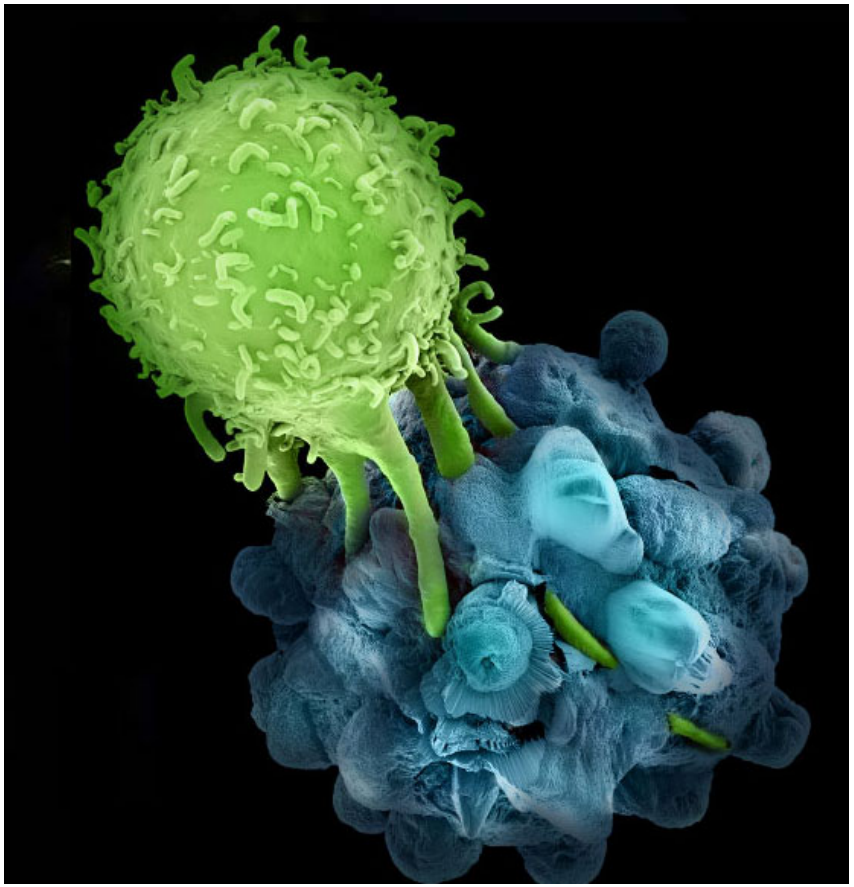
Advances in Cancer Immunotherapy

“Prediction: Cancer Immunotherapy in 10 Years”

SITC: December 14th 2013

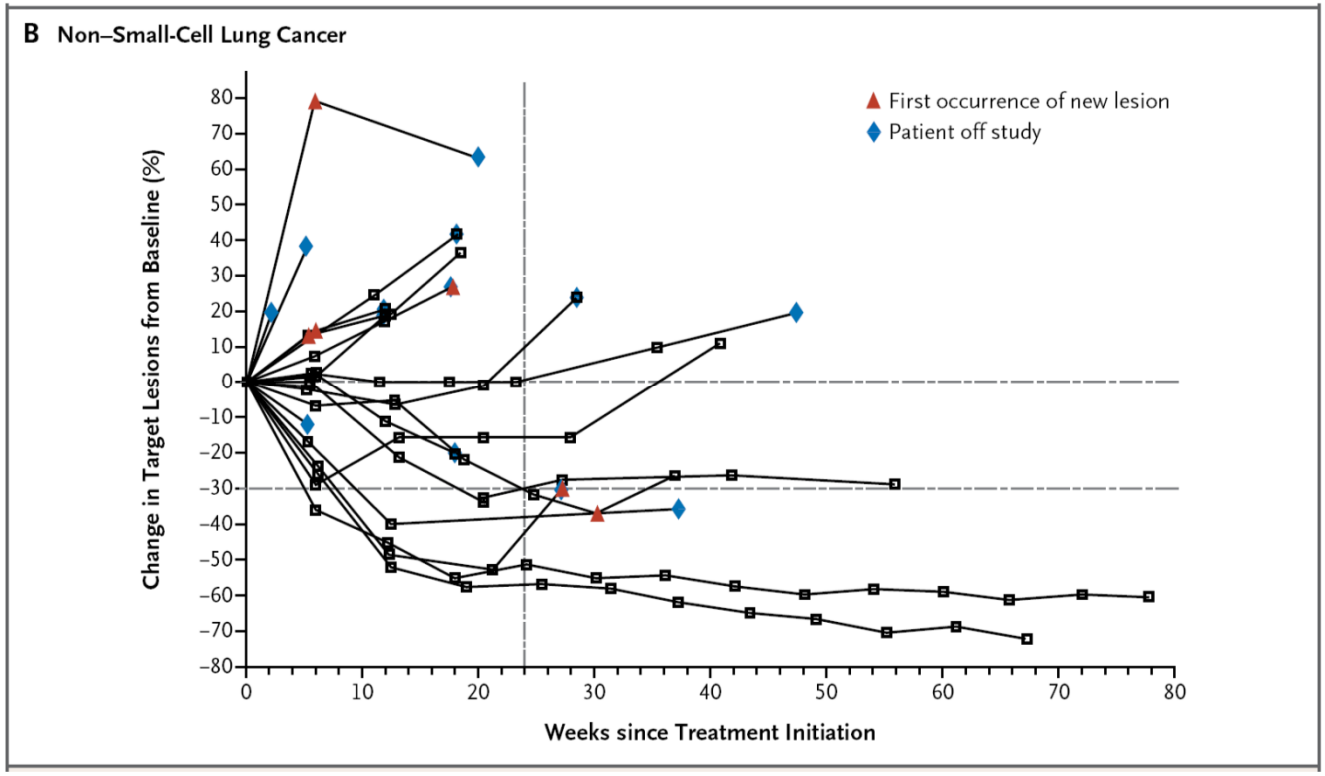


Martin A “Mac” Cheever MD
PI: Cancer Immunotherapy Trials Network
Member: Fred Hutchinson Cancer Research Center
mcheever@fhrc.org

cancer immunotherapy trials network

"Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer" [NSCLC: Partial Responses in 5 of 49]

[Brahmer and Tykodi et al (with Chow, Bhatia, Martins, Eaton) NEJM June 4 2012]



Anti-PD1

NSCLC: PR 14 of 76 (18%)

All patients: Objective Responses:

9 of 25 (36%) with PD-L1–positive tumors (P = 0.006)

0 of 17 (0%) with PD-L1–negative tumors

[Topalian et al NEJM June 4 2012]

Seven Companies with Inhibitors of PD-L1 or PD-1 in Development &/or Pivotal Trials

Table 2. Inhibitors of PD-L1 or PD-1 Currently Being Developed in Oncology

Therapeutic	Lead Company	Antibody Type	Affinity/K_d	Interaction Inhibited	Development
Anti-PD-L1					
MPDL3280A Herbst et al., 2013.	Genentech/Roche	Engineered IgG1 (no ADCC)	0.4 nM	PD-L1:PD-1 PD-L1:B7.1	Broad (lung pivotal)
MEDI-4736 Stewart et al., 2011.	AstraZeneca	Modified IgG1 (no ADCC)	Not available	PD-L1:PD-1 PD-L1:B7.1	Phase I
Anti-PD-1					
Nivolumab Brahmer et al., 2010.	Bristol-Myers Squibb	IgG4	2.6 nM	PD-L1:PD-1 PD-L2:PD-1	Broad (lung, melanoma, RCC pivotal)
Lambrolizumab Patnaik et al., 2012.	Merck & Co	IgG4 (humanized)	29 pM	PD-L1:PD-1 PD-L2:PD-1	Broad (melanoma pivotal)
Pidilizumab Rotem-Yehudar et al., 2009; Westin et al., 2012.	CureTech	IgG1 (humanized)	Not available		Broad
AMP-224 Smothers et al., 2013.	GlaxoSmithKline	PD-L2 IgG1 Fc fusion	Not available	PD-L1:PD-1 PD-L2:PD-1	Phase I
MSB0010718C	EMD Sorono (Merck KGa)	IgG mAb		PD-L1	Phase I

[Chen & Mellman Immunity 39, July 25, 2013]

Immunotherapy – The Beginning of the End for Cancer: Transforming Cancer into Chronic Disease

- **"Immunotherapies…**will likely become the treatment backbone in up to 60% of cancers over the next 10 years compared with <3% today"**.**
  - **Potential/likely $35B potential/ annum market**

- The current explosion in all ongoing approaches (including checkpoint agents, vaccines and cell therapy) to utilise the immune system to seek and destroy cancer cells marks a watershed, analogous to the impact of HIV drugs transforming life expectancy in HIV, in our view.

[From Citi Research / Division of Citigroup Global Markets Inc.
Andrew Baum (May 2013)]

Phase I Trial: Roche anti-PD-L1

- Overall objective response (ORR)
  - All pts = 21%
  - NSCLC =23%
  - Responses were stable over 24 weeks in responders
- Response rate in patients with high expression of PD-L1 = 83%
  - Surrogate for T cell infiltration
- Response rate in former smokers = 26% vs never smokers = 10%
  - Surrogate for T cell infiltration

[Jean-Charles Soria, European Cancer Congress 2013 (Abstract 3408)]

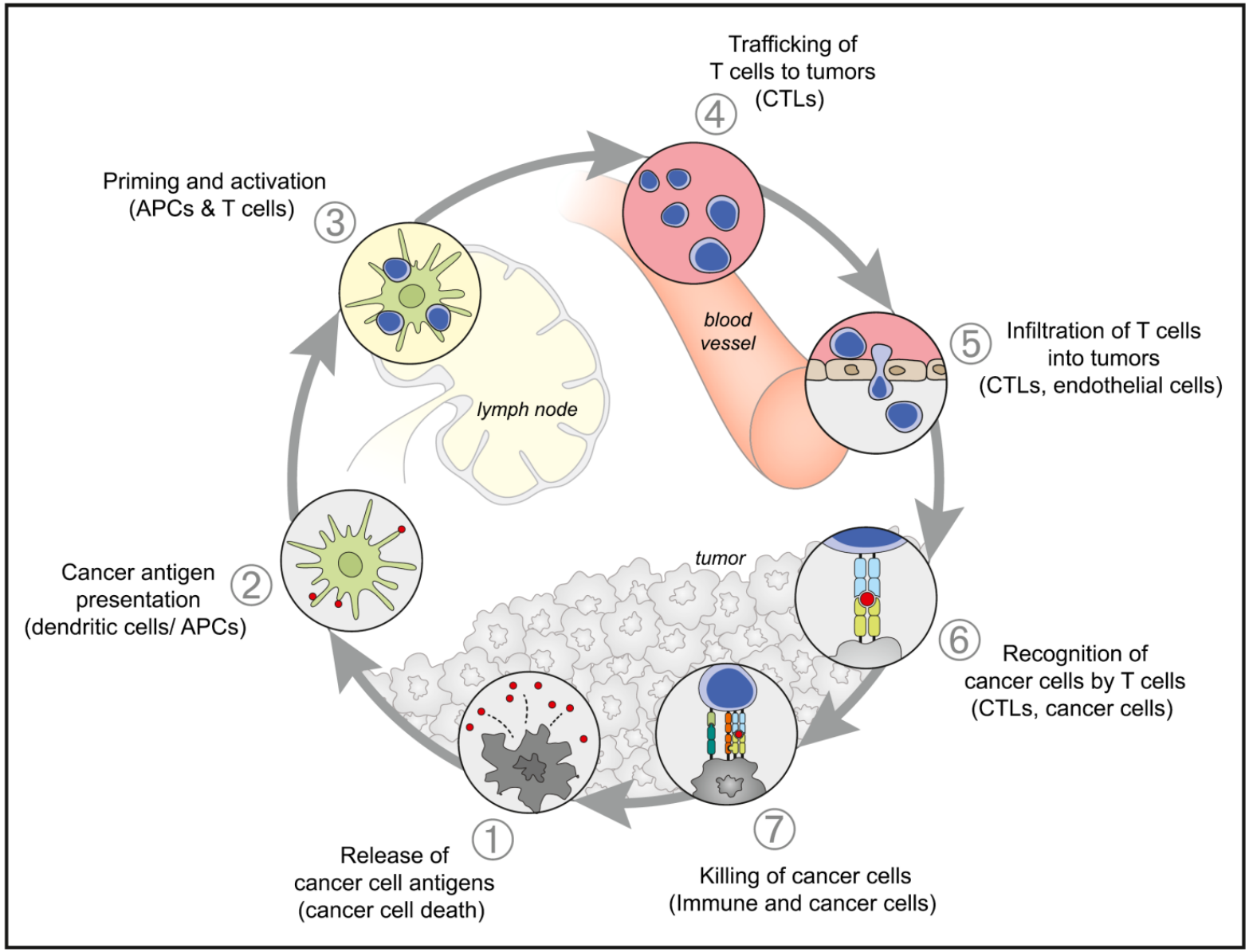
The **MAJOR** Goal for Immunotherapy (& Likely 60% of Cancer Therapy)

- Converting check-point inhibitor non-responders into check-point inhibitor responders
  - i.e., Converting T-cell poor tumors into T-cell inflamed tumors

Agents to convert T cell poor tumors into T cell inflamed tumors are available

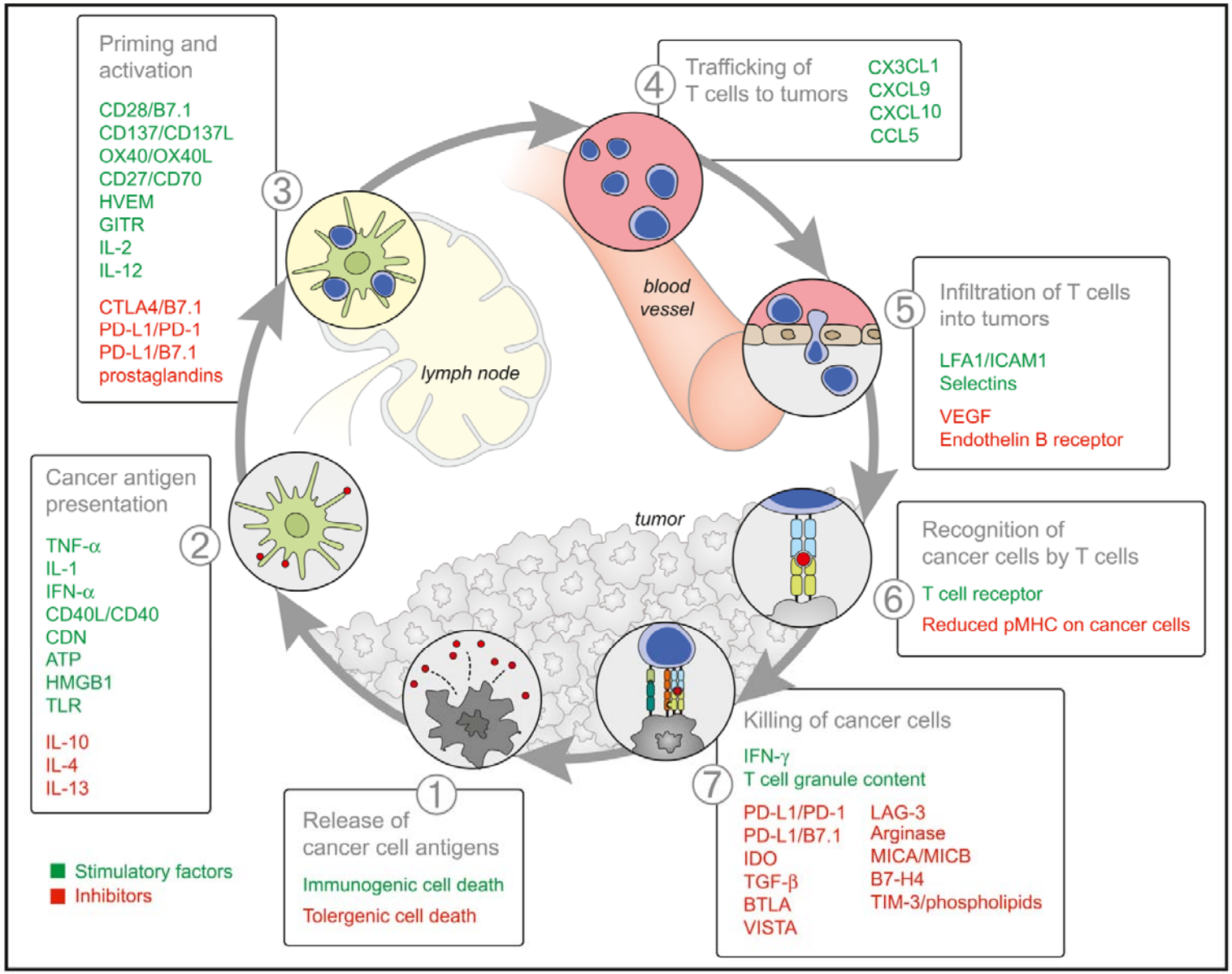
- Standard therapy: Radiation, chemotherapy, targeted therapy
- Immunotherapy
  - Dendritic cell activators
  - Dendritic cell growth factors
  - Vaccines
  - Vaccine adjuvants
  - T-cell stimulators
  - T-cell growth factors
  - Genetically modified T cells
  - Immune checkpoint inhibitors
  - Agents to neutralize or inhibit suppressive cells, cytokines and enzymes

Cancer Immunity Cycle



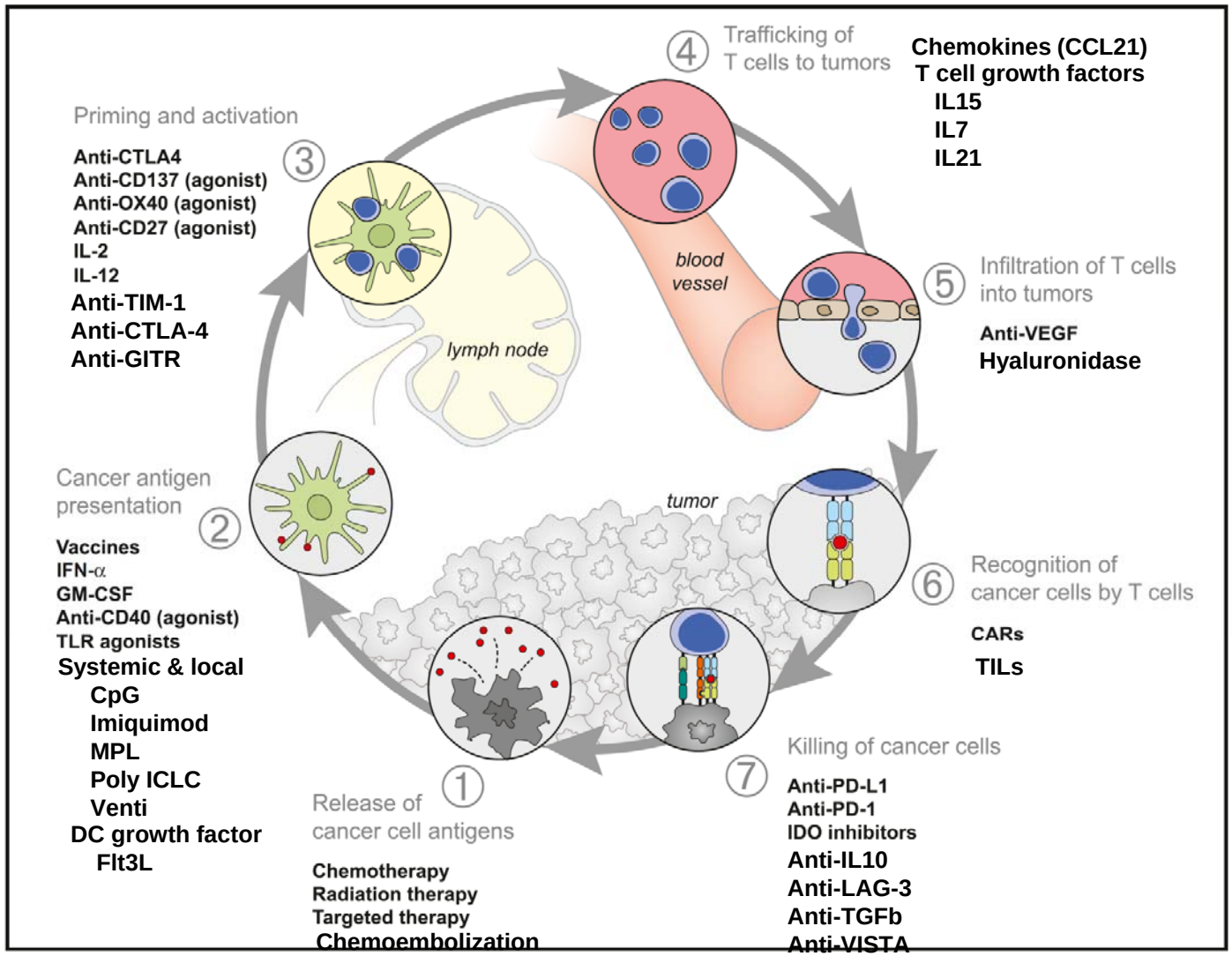
[Chen & Mellman Immunity 39, July 25, 2013]

Stimulatory and Inhibitory Factors in the Cancer-Immunity Cycle



[Chen & Mellman Immunity 39, July 25, 2013]

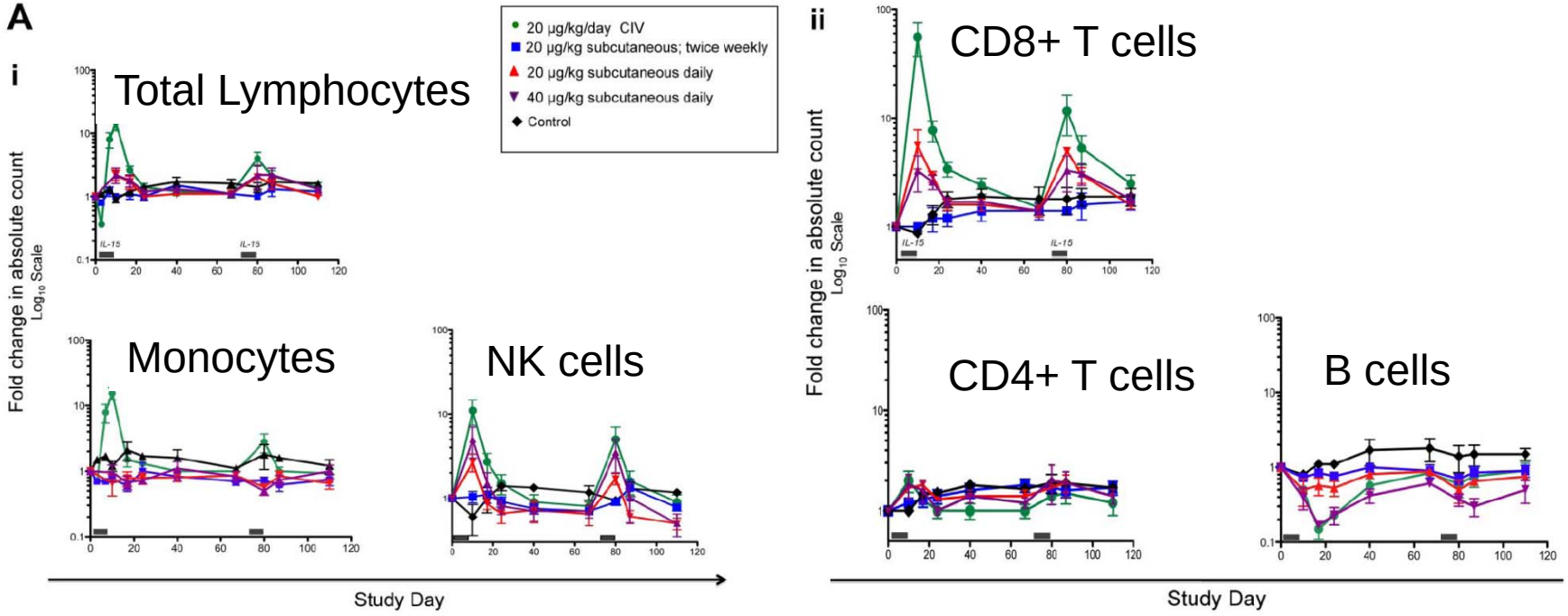
Agents to convert T cell poor tumors into T cell inflamed tumors



[Revised from: Chen & Mellman Immunity 39, July 25, 2013]

(Example 1) IL15 – Growth Factor for CTL & NK Cells

"IL-15 administered by continuous infusion to rhesus macaques induces massive expansion of CD8 T effector memory population in peripheral blood"



Continuous intravenous infusion for 10 days resulted in a massive (70-fold) expansion of CD8 TEM cells in the peripheral blood

[Sneller et al BLOOD, DEC 2011 VOLUME 118, NUMBER 26]

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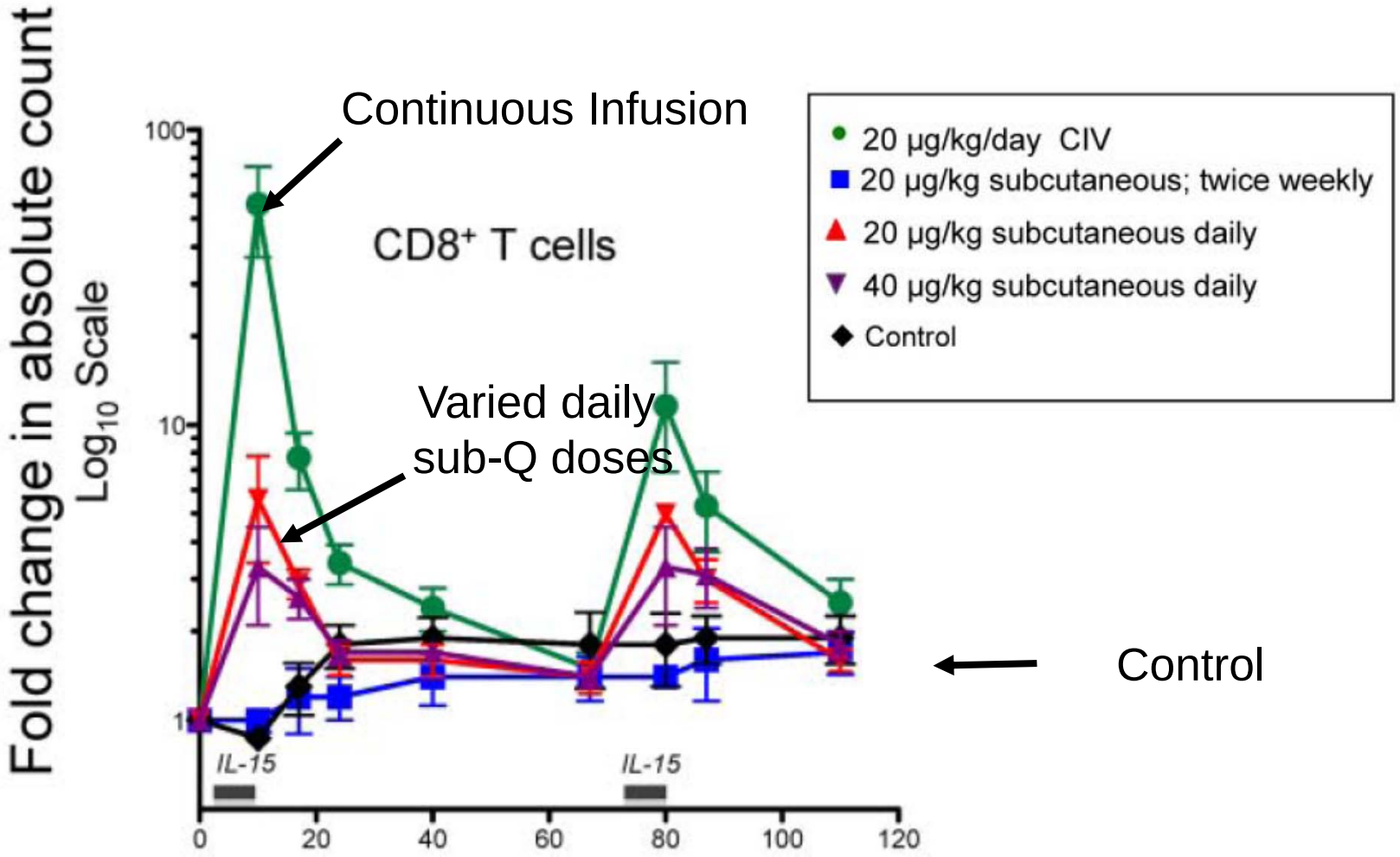


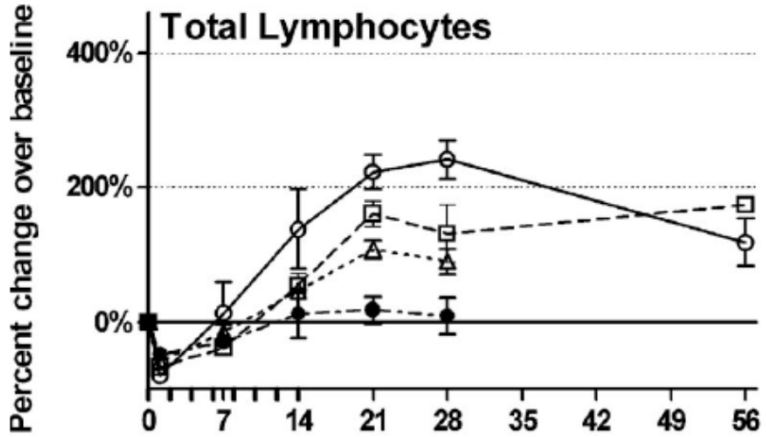
Sneller et al BLOOD, DEC 2011 VOLUME 118, NUMBER 26

(Example 2) IL-7: Homeostatic T cell Growth Factor

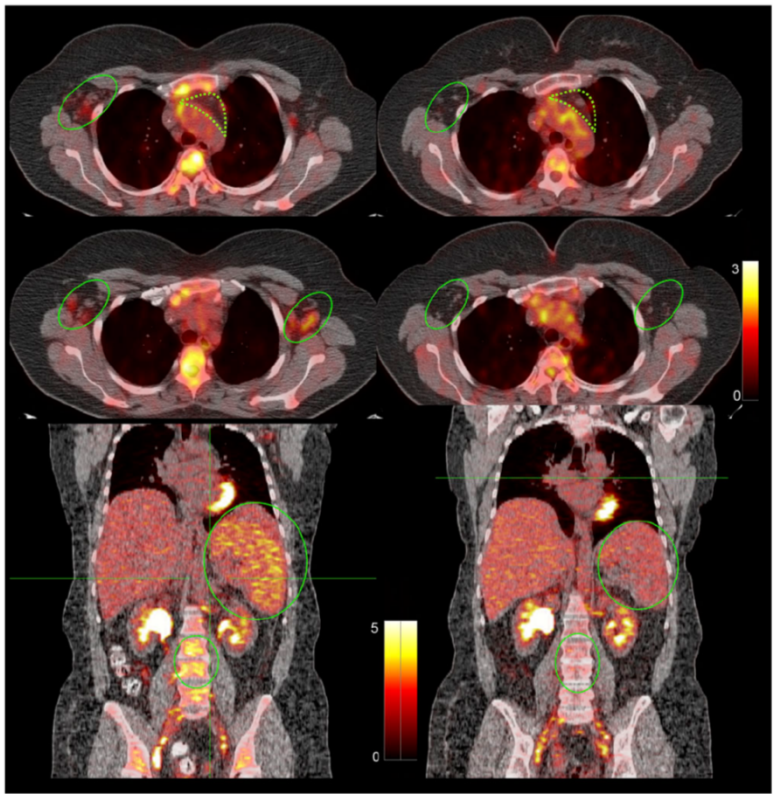
"Administration of rhIL-7 in humans increases in vivo TCR repertoire diversity by preferential expansion of naive T cell subsets"

IL-7 administered every other day (days 1 – 14) at 4 dose levels

IL-7 therapy increases circulating T cells



PET-CT imaging of lymphoid organs & increased metabolic activity after rhIL-7

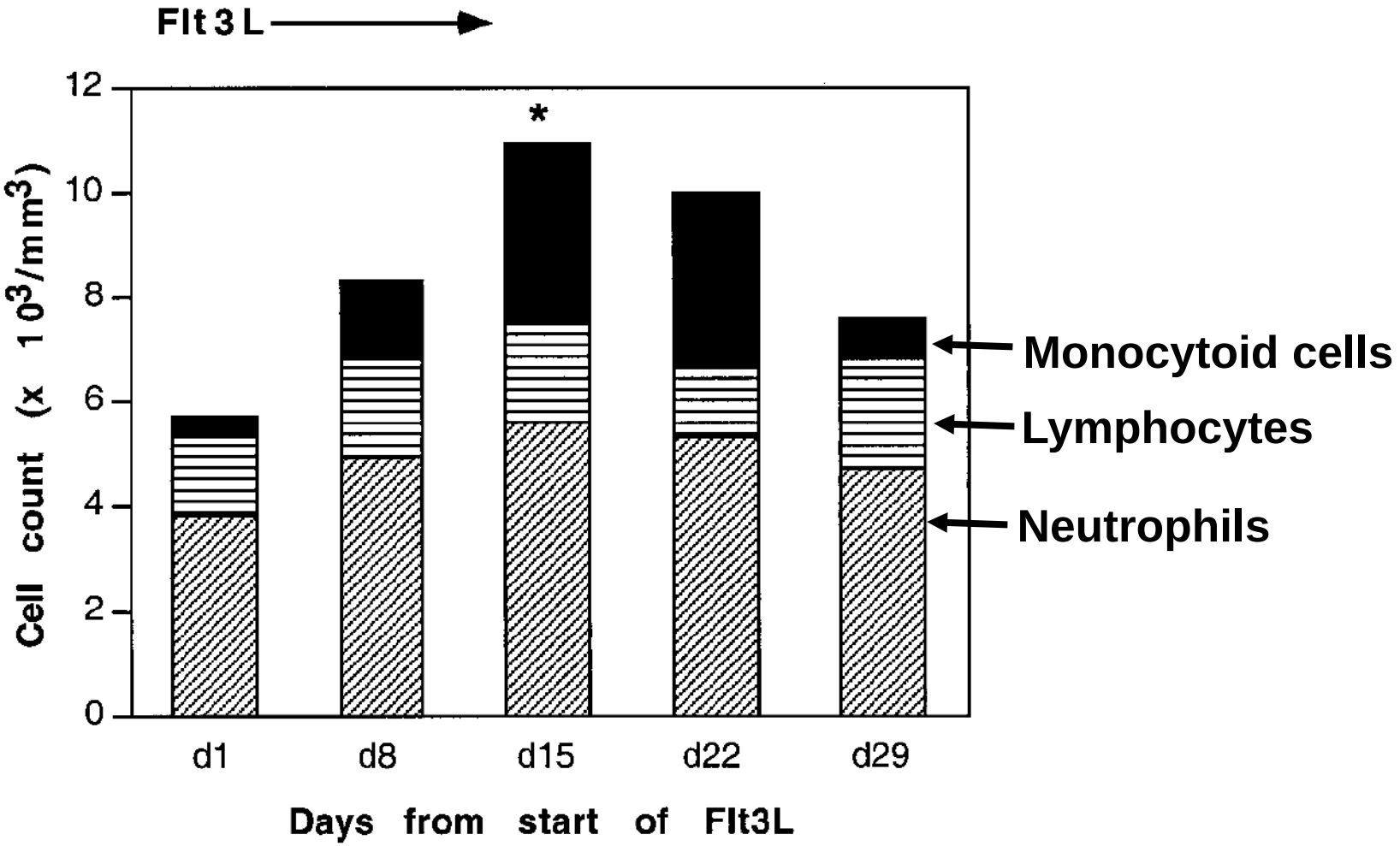


Increased metabolic activity = pink →
Maximal = yellow

[Sportès (Mackall) et al JEM 1681:2007]

(Example 3) Flt3-L : Dendritic Cell Growth Factor

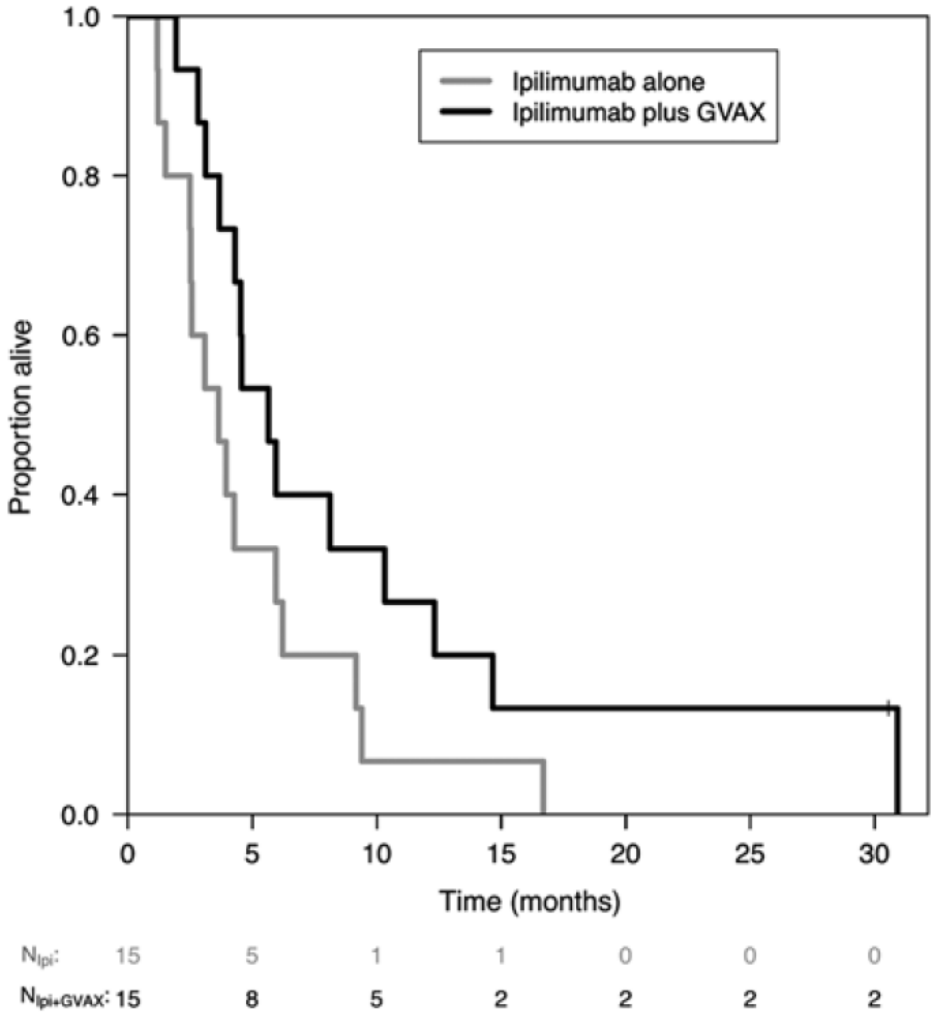
Peripheral Blood Counts during Flt3-L Administration



[Morse et al. JCO 18:3883-3893, 2000]

(Example 4) Vaccine + Check Point Inhibitor

"Evaluation of Ipilimumab in Combination With Allogeneic Pancreatic Tumor Cells Transfected With a GM-CSF Gene in Previously Treated Pancreatic Cancer"

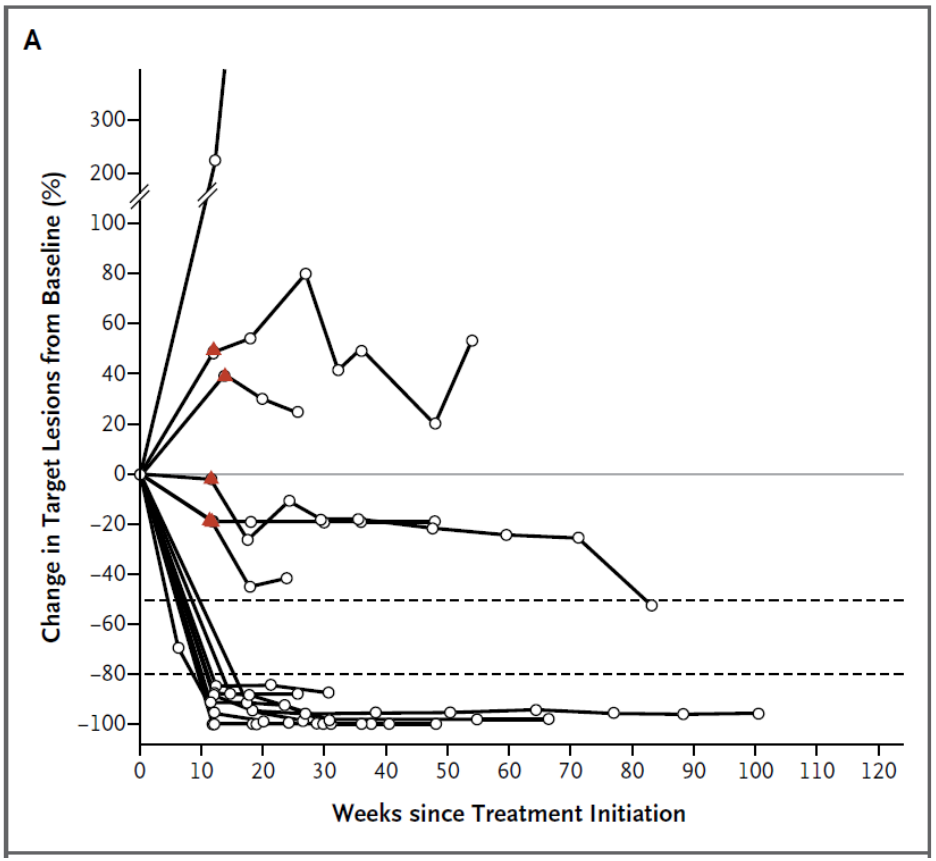


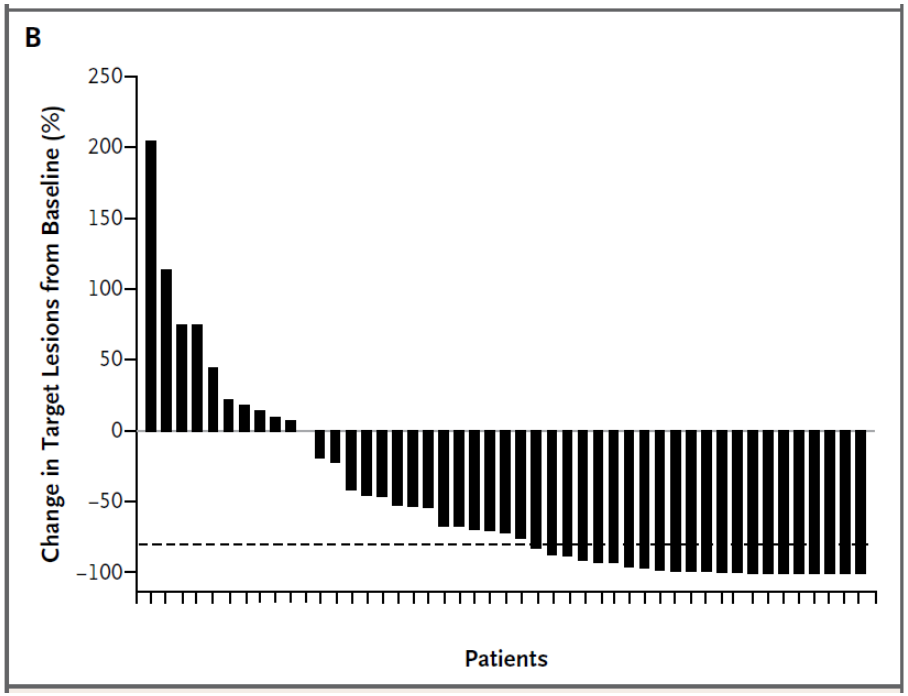
The Kaplan-Meier overall survival curve as of January 27, 2013. One patient in arm 2 (ipi + GVAX) is still alive.

[Le et al J Immunother 36 (7) September 2013]

(Example 5) Two Check Point Inhibitors

Nivolumab (anti-PD1) plus ipilimumab in advanced melanoma.





[Wolchok et al NEJM 2013 Jul 11;369(2):122-33]

Foreseeable Future: Realistic Assessment

- Majority of NSCLC patients in US will be treated with anti-PD-1/ anti-PD-L1 (or next generation check point inhibitors)
  - 25% will respond
    - Therapeutic interventions to increase depth of response
  - 75% of lung cancers will not respond
    - Therapeutic interventions to convert to responsive
- Majority of NSCLC patients will be assessed for possible response to anti-PD1/ anti-PD-L1
  - IHC for T cells and PD-L1; Gene signature for immune responsiveness)
- Small subsets of most cancers will respond
  - Therapeutic interventions to increase depth of response
- Most will be predicted to not respond
  - Therapeutic interventions to convert to responsive