Combination Immunotherapy: Can 1 + 1 = 4?

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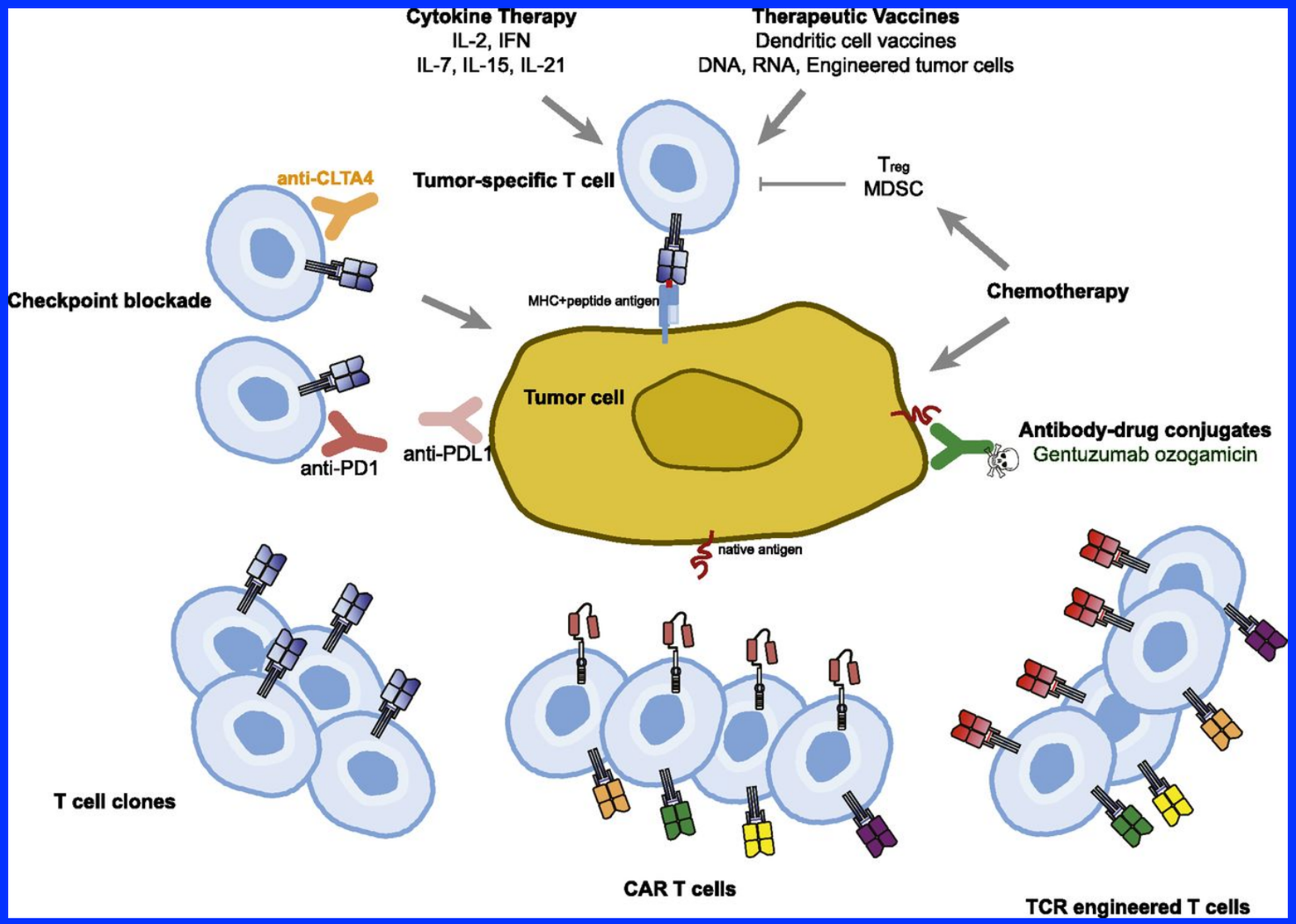
Disclosures

- I have the following relationships with industry:
  - Alkermes Scientific Advisory Board
  - Amgen Scientific Advisory Board, Clinical Trial Funding
  - BMS Clinical Trial Funding
  - EMD Serono Scientific Advisory Board (non-compensated), Clinical trial Funding
  - Merck Scientific Advisory Board
  - Prometheus Scientific Advisory Board, Clinical Trial funding

- I will be discussing the following off-label products:
  - Nivolumab
  - MK-3475
  - Talimogene laherparepvec
  - Adoptive T cell therapy

Cancer Immunotherapy

Therapeutic approaches to overcome immune tolerance to tumors



Maus M V et al. Blood 2014

Treatment of Advanced Melanoma

Chemotherapy

· DTIC
·Temozolomide
·Combinations

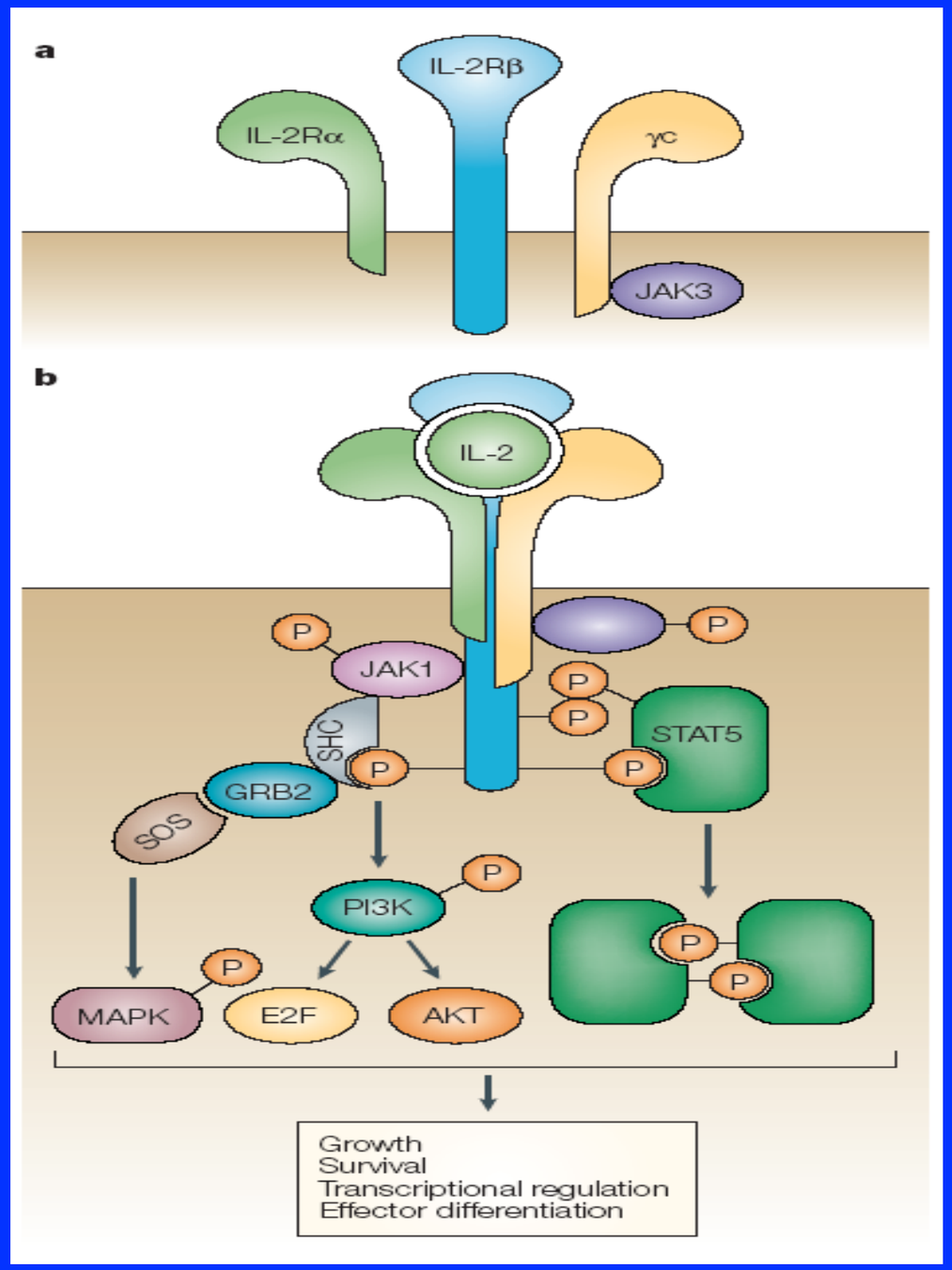
Targeted Therapy

·BRAF
·MEK
C-KIT
·AKT
PI3K

Immunotherapy

·Interferon-α
·Interleukin-2
·α-CTLA-4 (Ipilimumab)
·α-PD1 (Nivolumab, MK 3475)
α-PD-L1
T-VEC (Talimogene laherparepvec)
Adoptive T cell therapy

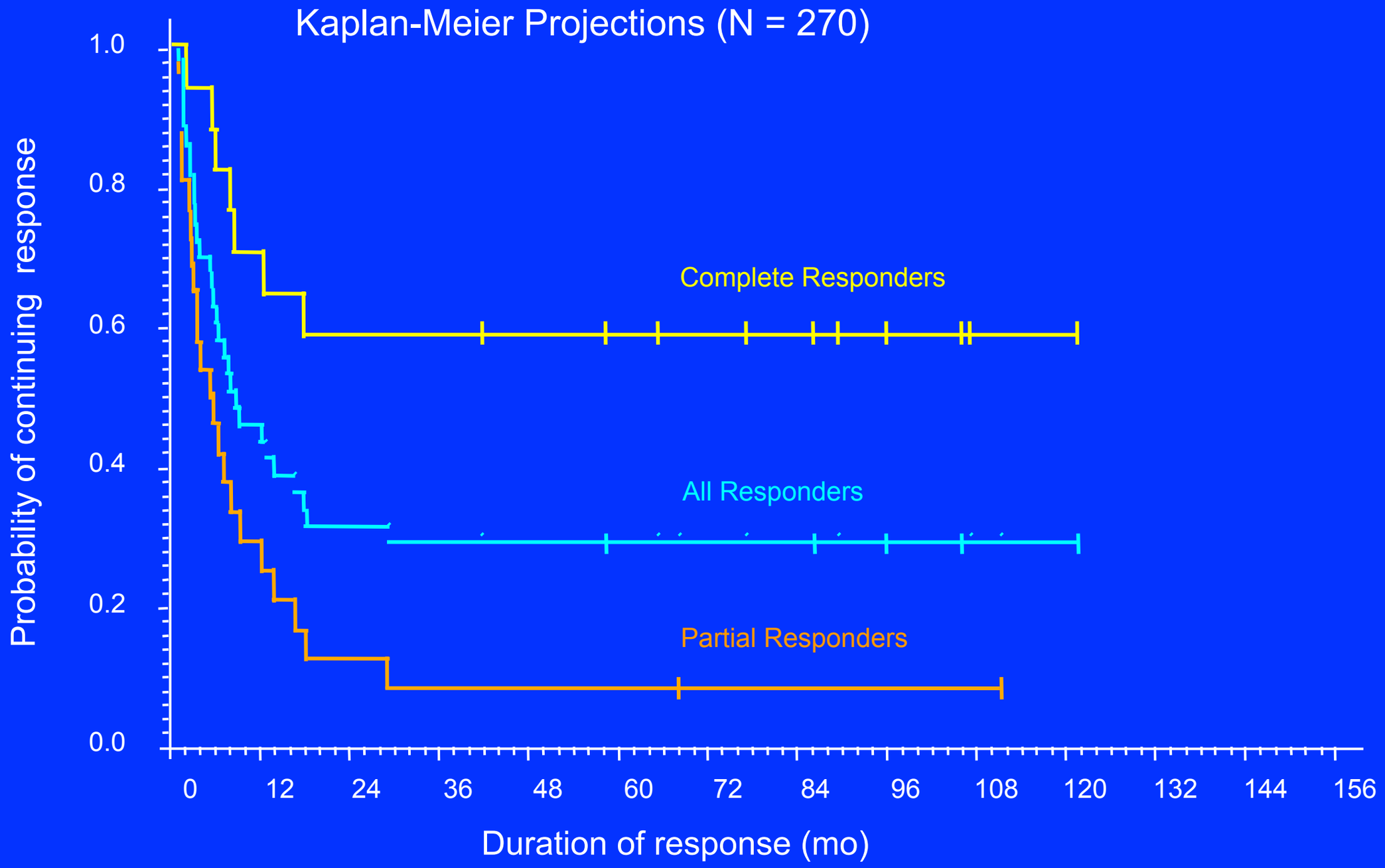
IL-2 Receptor



- Il-2 binds α chain
- Forms heterotrimeric complex
- Signals through β and γc chains
- Induces T cell growth and promotes survival
- Results in clonal expansion of T cells

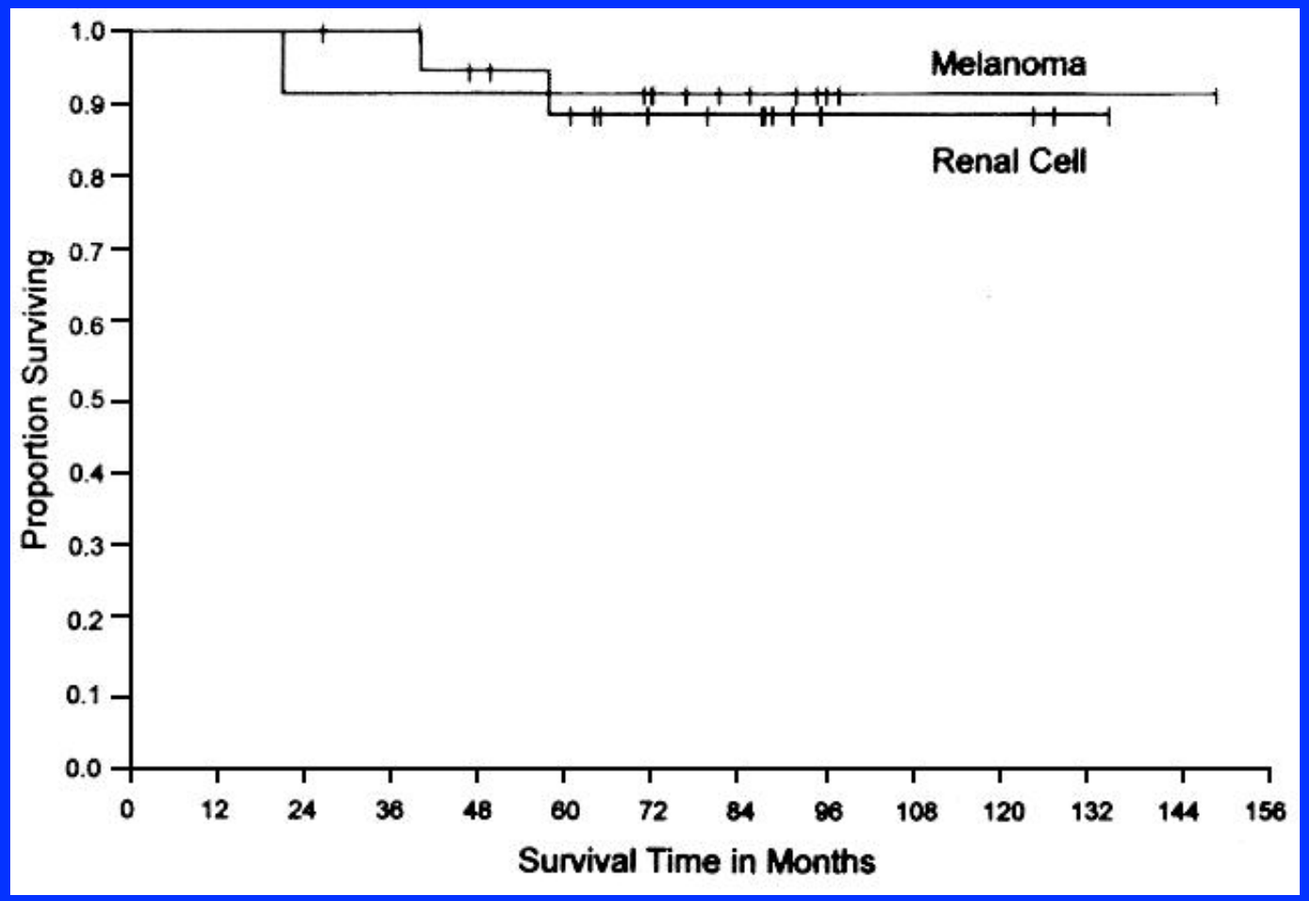
Malek and Bayer, Nature Immunol Rev, 2004

High-dose IL-2 induces durable objective clinical responses in 15-20%



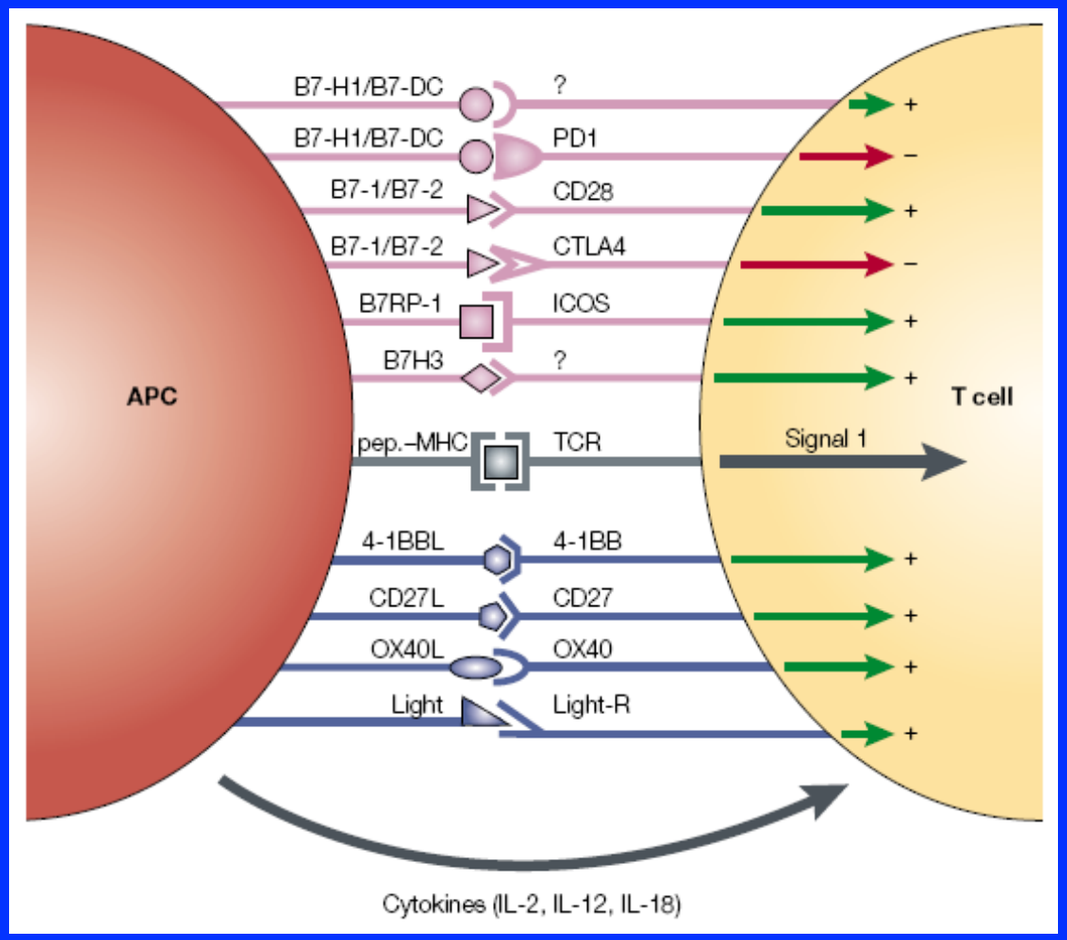
Atkins et al. J Clin Oncol 1999

High-dose IL-2 promotes durable disease free survival in responders



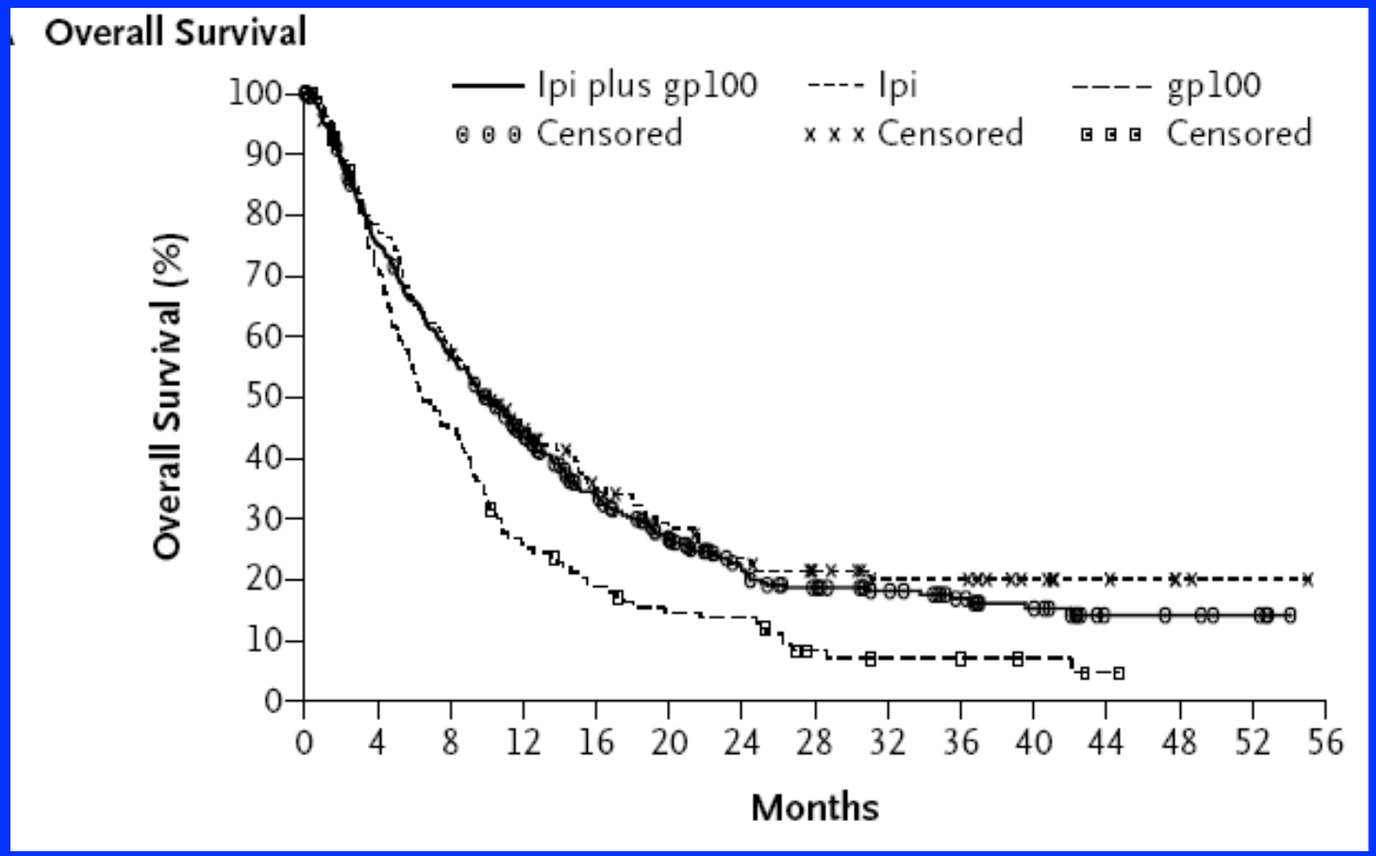
Rosenberg et al. Ann Surg 1998

T cell Checkpoint Inhibitors



Pardoll Nature Immunol Rev 2002

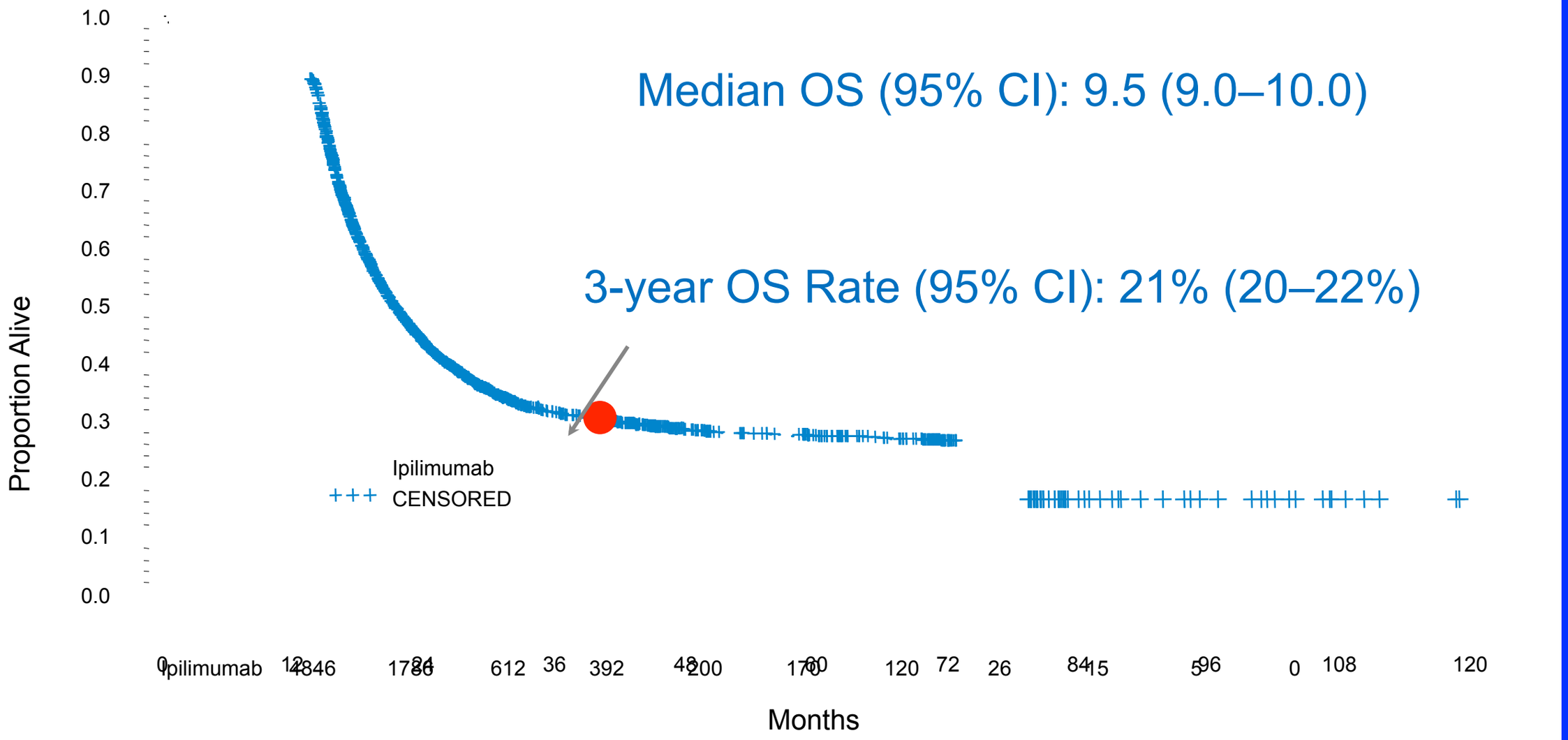
Ipilumumab improves overall survival in melanoma



HR 0.68
P<0.001

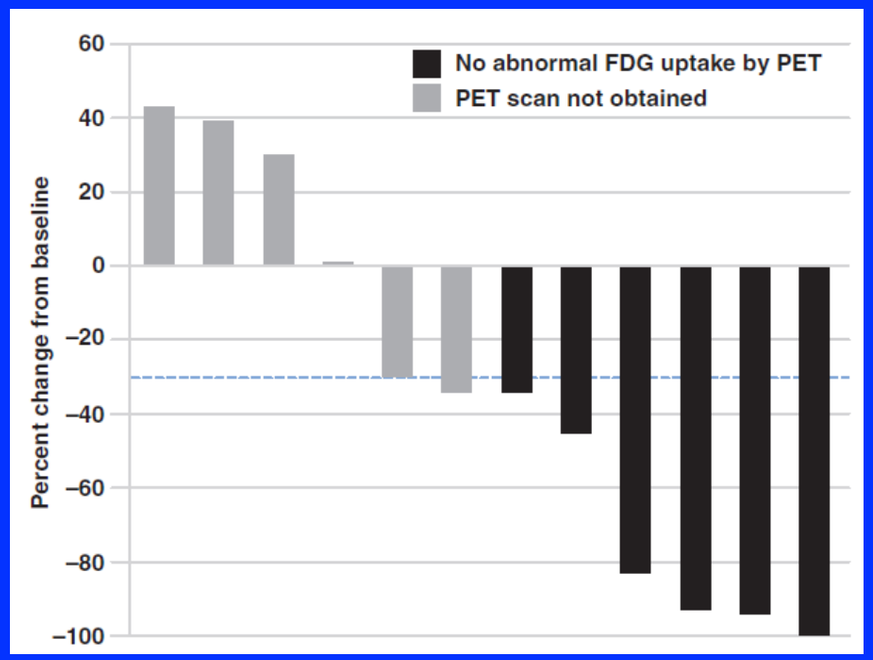
Hodi et al. NEJM 2010

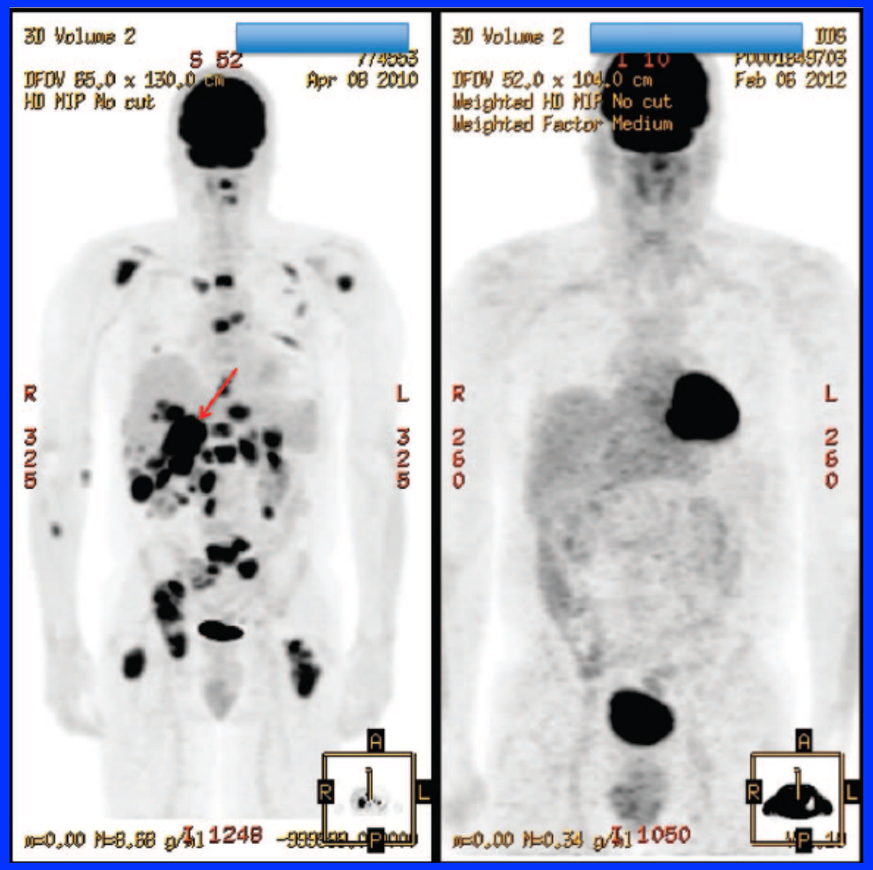
Ipilimumab pooled survival of 4846 melanoma patients



Hodi et al., ESMO, 2013

IL-2 and radiation therapy: The abscopal effect

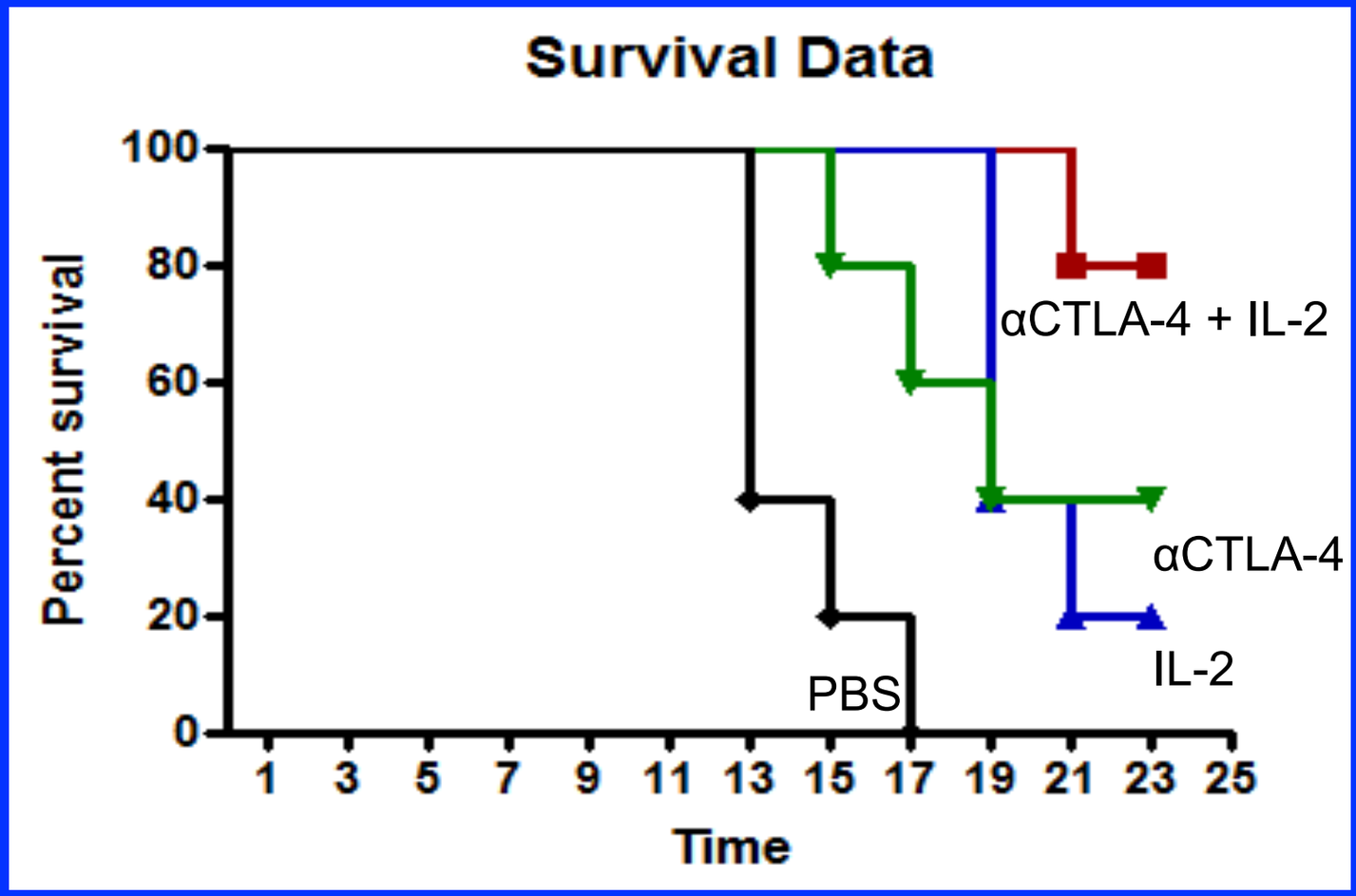




66% objective response rate

Seung et al. Sci Transl Med 2012

αCTLA4 + IL-2 combination immunotherapy is associated with improved 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

Phase I/II Trial of IL-2 and Ipilumimab

TABLE 1. *Patient characteristics, clinical response, and autoimmune toxicity*

Patient no.	Age (y)	Sex	Disease sites	Prior therapy	Dose (mg/kg)	No. cycles received	Response (mo)[a]	Autoimmune toxicity (grade III/IV)
1	45	M	Adrenal, ALN, kidney, lung hilum, mesenteric, RP, SQ, pleura	S	1	3	NR	
2	61	M	Brain, SQ	S, I	1	3	NR	
3	42	M	SQ	S, C, I	1	3	NR	
4	43	M	Mediastinum	S	3	9	PR (19+)	
5	58	F	Iliac LN	S, C, I	3	3	NR	
6	54	M	Lung, SQ, spleen	S, I	3	6	NR	
7	31	M	Liver, lung, mediastinum, mesentery, SQ	R, S, C, I	1	3	NR	
8	51	M	ALN, intramuscular	R, S, C	1	6[b]	PR (7)	Colitis
9	33	M	ALN, intraperitoneal, liver, mediastinum, spleen	S	1	3	NR	
10	49	F	ALN, liver, SQ	S, I	2	3	NR	
11	60	F	SQ	S, I	2	3	NR	Gastritis, enterocolitis, colitis
12	60	M	Lung	S	2	7	CR (16+)	
13	48	M	Liver, lung	S	3	3	NR	
14	44	M	Subclavicular LN, submandibular	R, S, C, I	3	9[+]	PR (11)	
15	47	M	Abdominal wall, SQ	R, S	3	9	PR (14+)	
16	42	F	ALN, SQ	S, I	3	3	NR	
17	45	F	Lung	S, I	3	3	NR	
18	50	F	Adrenal, brain, lung RP, SQ	S, I	3	3	NR	
19	50	M	Inguinal LN, lung, mesentery, pulmonary hila, SQ	S, I	3	3	CR (13+)	Colitis
20	67	F	Inguinal LN, SQ	S, I	3	2	CR (13+)	
21	45	M	Liver, lung	S, I	3	1	NR	
22	57	M	Bone, liver, spleen	S, I	3	2	NR	
23	39	F	Lung	S, I	3	5	NR	
24	28	F	Iliac LN, liver, lung	S, C, I	3	3	NR	
25	48	M	Liver, parotid	S	3	6	NR	
26	21	M	Lung	S, I	3	6	NR	
27	58	M	ALN submandibular, skin, SQ	R, S, I	3	3	NR	
28	51	F	Lung, mediastinum, SQ	S	3	9	PR (11+)	
29	40	M	ALN, lung	S, I	3	3	NR	Colitis
30	48	F	Lung, SQ	S, I	3	3	NR	
31	25	M	Abdominopelvic, adrenal, ALN, heart, mediastinum, spleen, SQ	S	3	3	NR	
32	49	F	Iliac LN, inguinal LN, SQ	R, S, C, I	3	3	NR	Arthritis, uveitis
33	56	M	ALN, cervical LN, iliac LN, SQ, lung	R, S, C, I	3	2	NR	
34	44	M	Lung, lung hilum	S, I	3	2	NR	
35	52	F	Bone, cervical LN, SQ, liver, lung, spleen	S	3	2	NR	
36	58	F	Adrenal, liver, lung, spleen	S	3	3	NR	

- 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

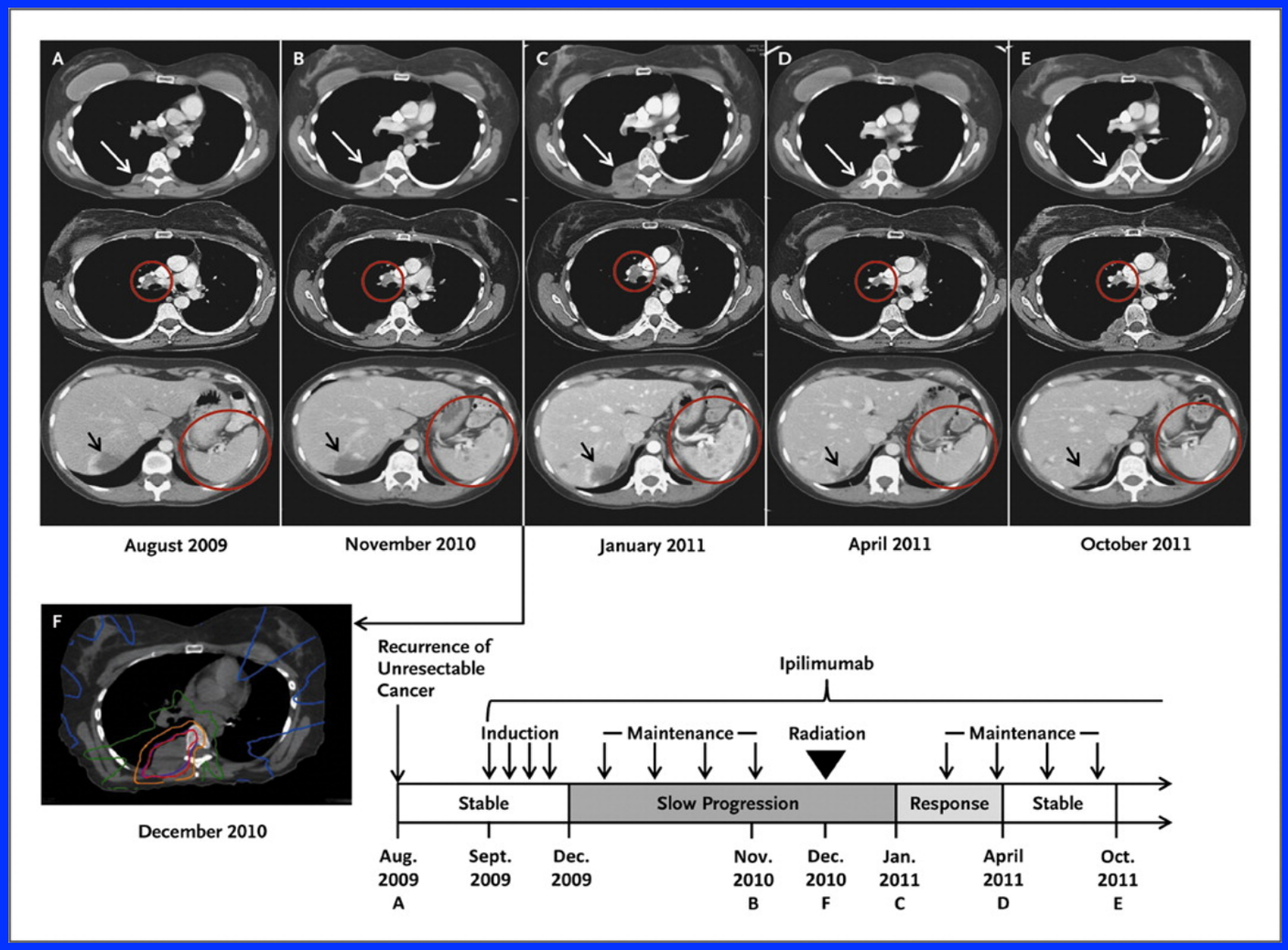
- At median follow-up of 71 months
- 25% objective response rate
- 17% complete response
- Median survival of 16 months

Prieto et al. ASCO Abstract 8544 2010

Planned IL-2 and Ipilimumab Trials

- BMS/CWG Phase II single arm trial of high-dose IL-2 and ipilimumab
- Prometheus Phase II randomized trial of sequential high-dose IL-2 and ipilimumab

Ipilimumab and radiation therapy: The abscopal effect



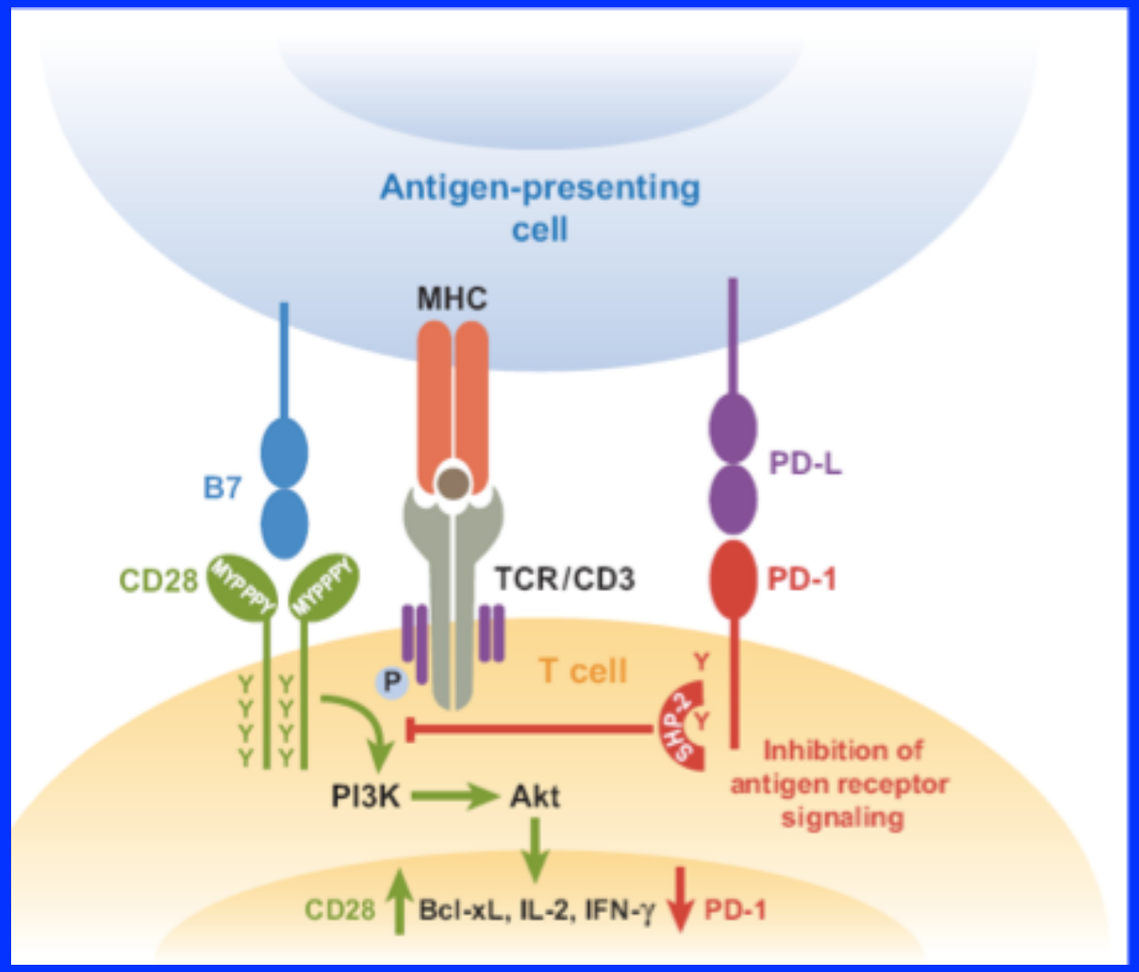
Postow MA et al. N Engl J Med 2012

E1608: Ipilimumab and GM-CSF

- Ipilimumab (10 mg/kg) + GM-CSF (250 ug) vs. Ipilimumab alone (10 mg/kg)
- 245 Stage IV melanoma patients
- 13.3 months follow-up
- Combination RR 11.3 % vs. 14.7% (ns)
- Combination PFS 3 vs. 3.2 m (ns)
- Combination Median OS nr vs. 12.6
- 1-year survival 67.9% vs. 51.2% (p1=0.016)
- Grade 3-5 AE 45% vs 57.7% (p=0.078)

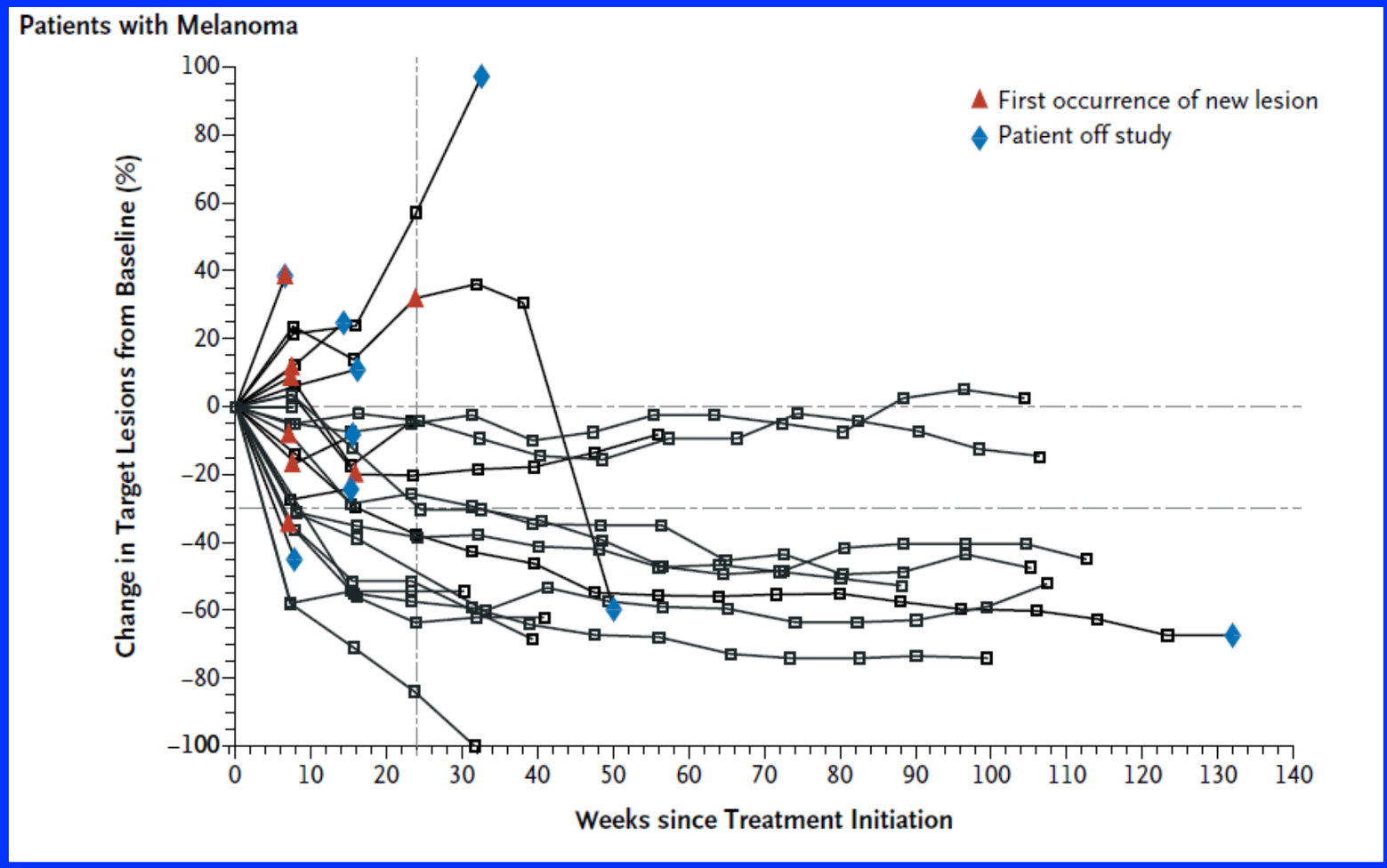
Hodi et al. ASCO 2013

PD1-PD-L1 is another negative T cell checkpoint pathway



Keir et al. Annu Rev Immunol 2008

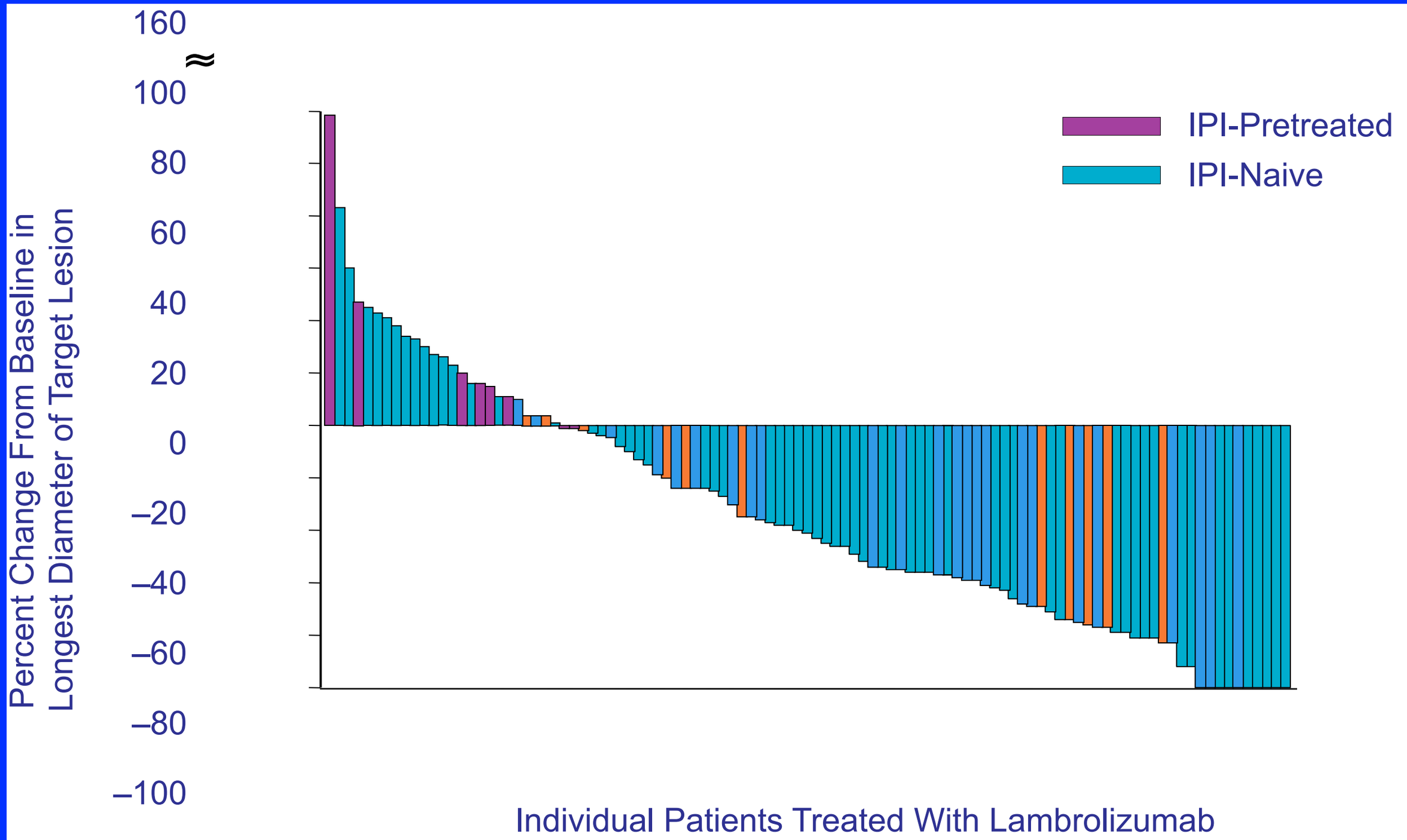
Melanoma responses to anti-PD1 MoAb treatment



Topalian et al. NEJM 2012

MK-3475 induces clinical responses in melanoma

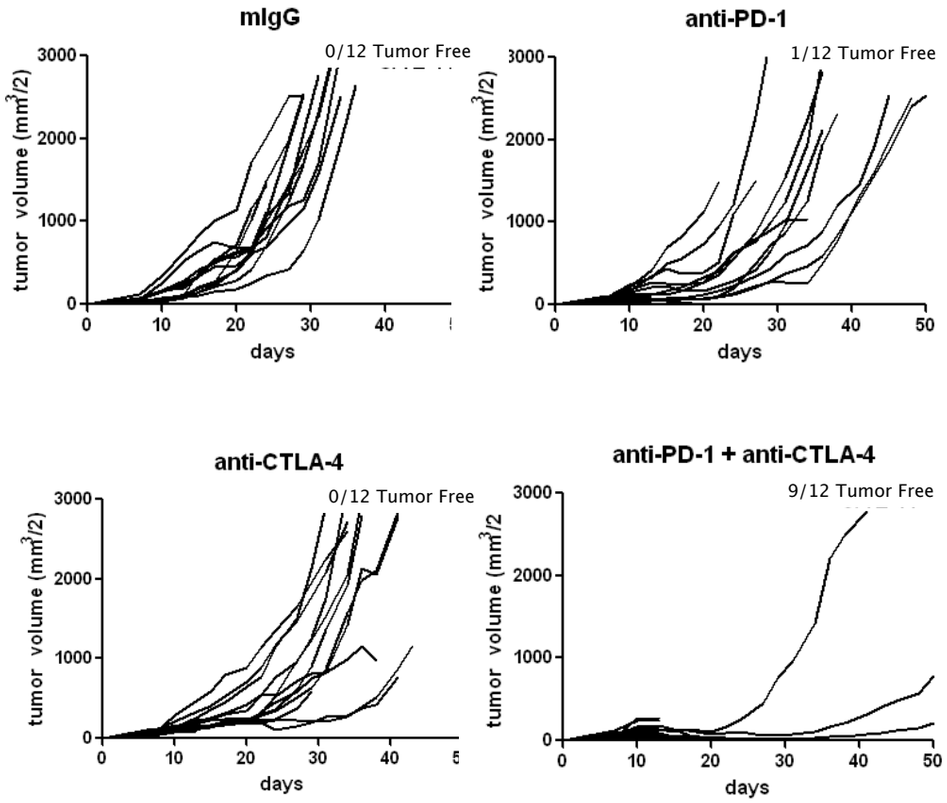
(Independent Central Review per RECIST 1.1)



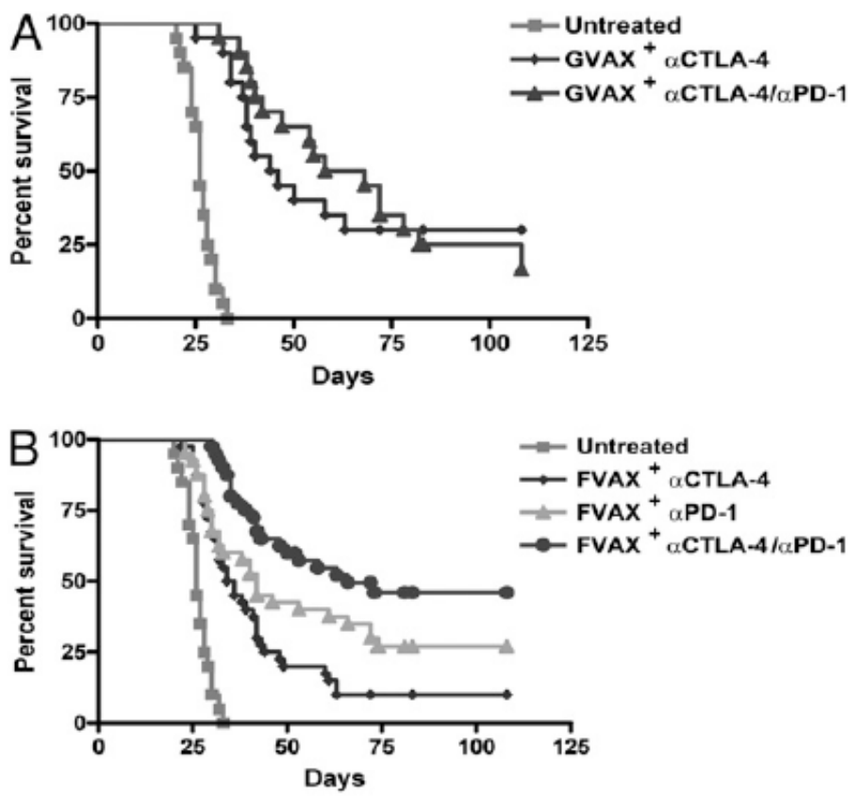
Hamid et al. NEJM 2013

Antitumor Activity of Anti–CTLA-4 and Anti–PD-1 Antibodies in Murine Tumor Models

MC38 Colon Cancer
Antibody Rx Only [1, 2]



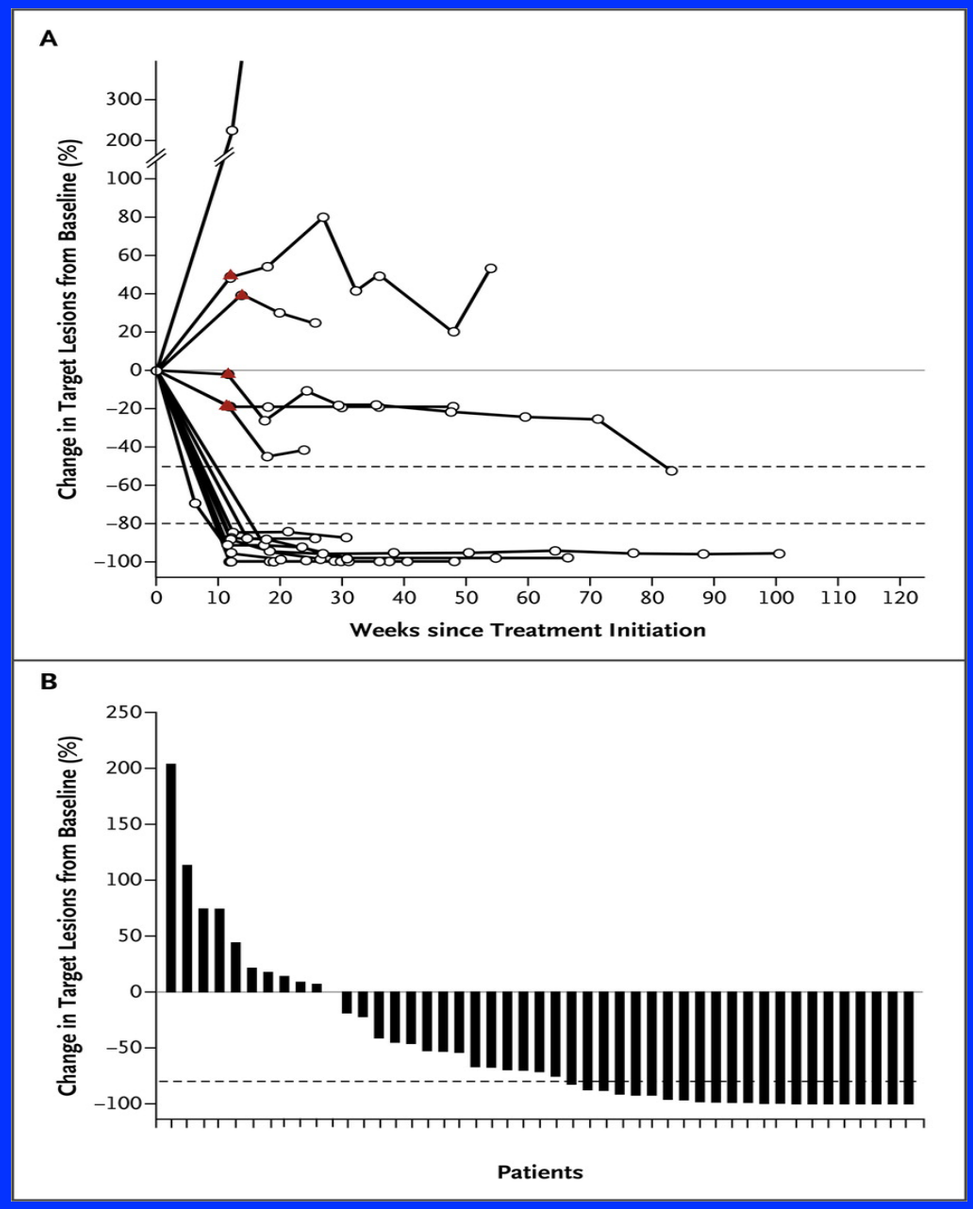
B16BL6 Melanoma
Antibody Rx + Cellular Vaccine[3]



[1]Korman et al. J Immunol. 2007;178:48.37. [2]Selby et al. ASCO 2013, abs 3061. [3]Curran et al. Proc Natl Acad Sci. 2010;107:4275.

Nivolumab and Ipilimumab in melanoma

- Nivolumab and ipilimumab every 3 weeks for 4 doses, followed by nivolumab alone every 3 weeks for 4 doses (concurrent regimen)
- The combined treatment was subsequently administered every 12 weeks for up to 8 doses.
- In a sequenced regimen, patients previously treated with ipilimumab received nivolumab every 2 weeks for up to 48 doses.
- 53 patients received concurrent therapy and 33 received sequenced treatment.
- The objective-response rate (modified WHO) for the concurrent-regimen group was 40%.

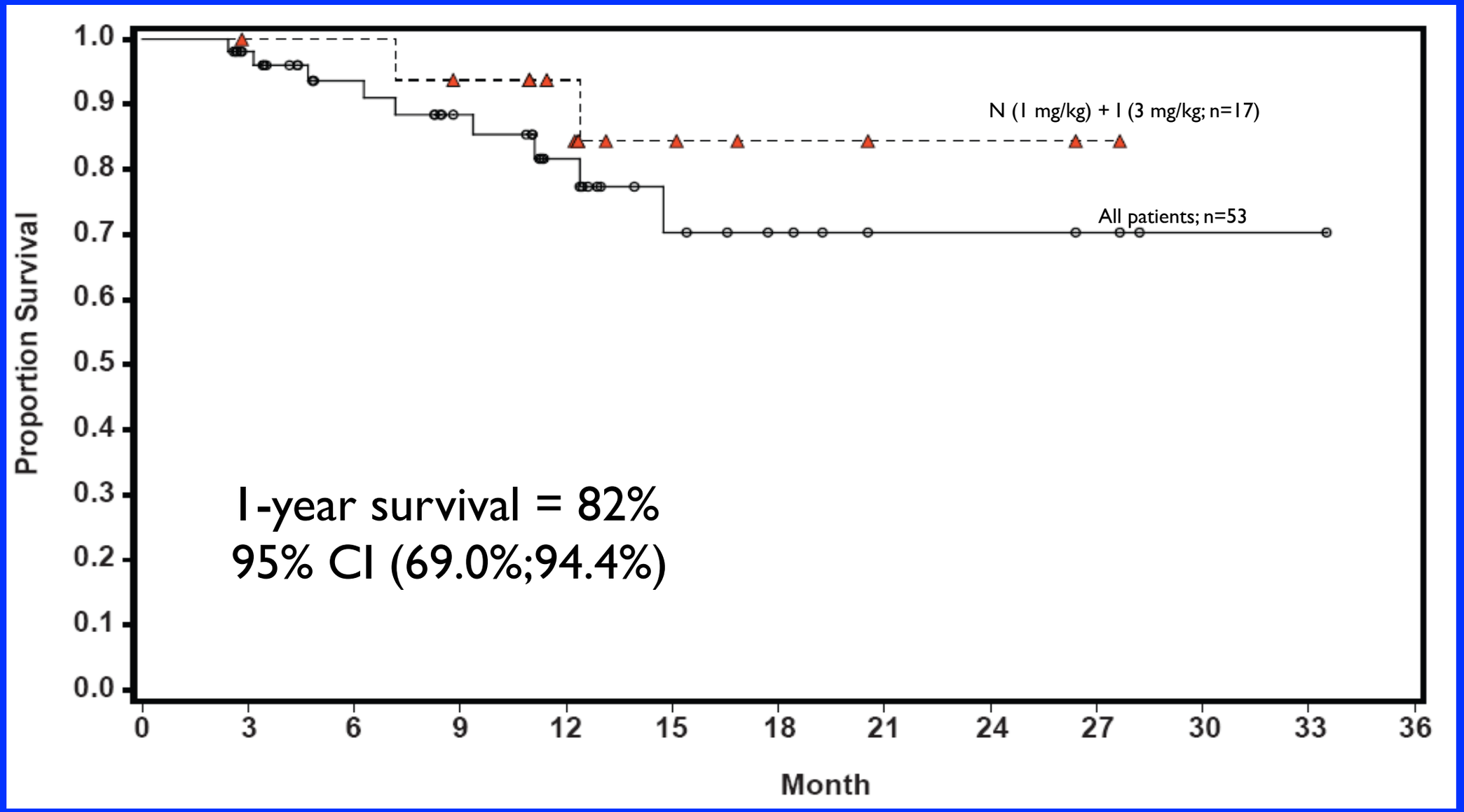


Clinical Activity: Concurrent Regimen

Dose (mg/kg)		Response Evaluable Patients n	CR n	PR n	Objective Response Rate % [95% CI]	Aggregate Clinical Activity Rate % [95% CI]	≥80% Tumor Reduction at 12 wk n (%)
Nivolumab	Ipilimumab						
0.3	3	14	1	2	21 [5–51]	50 [23–77]	4 (29)
1	3	17	3	6	53 [28–77]	65 [38–86]	7 (41)
3	1	15	1	5	40 [16–68]	73 [45–92]	5 (33)
3	3	6	0	3	50 [12–88]	83 [36–100]	0
Concurrent		52	5	16	40 [27–55]	65 [51–78]	16 (31)

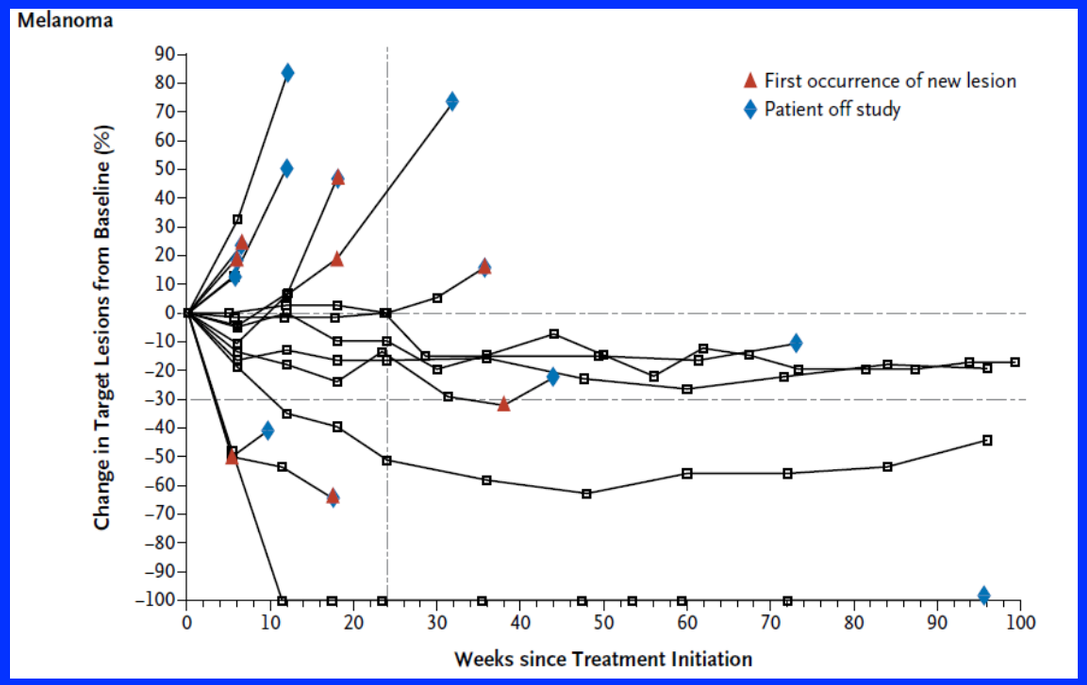
- With 1 mg/kg nivolumab + 3 mg/kb ipilimumab, 53% of patients had confirmed objective responses (3 CRs and 6 PRs)
- All 9 of these had ≥80% tumor reduction, 7 at 12 weeks and 2 at their first assessment, which was after week 12
- ≥80% tumor reductions appear infrequently (<10%) in the nivolumab and ipilimumab monotherapy experiences

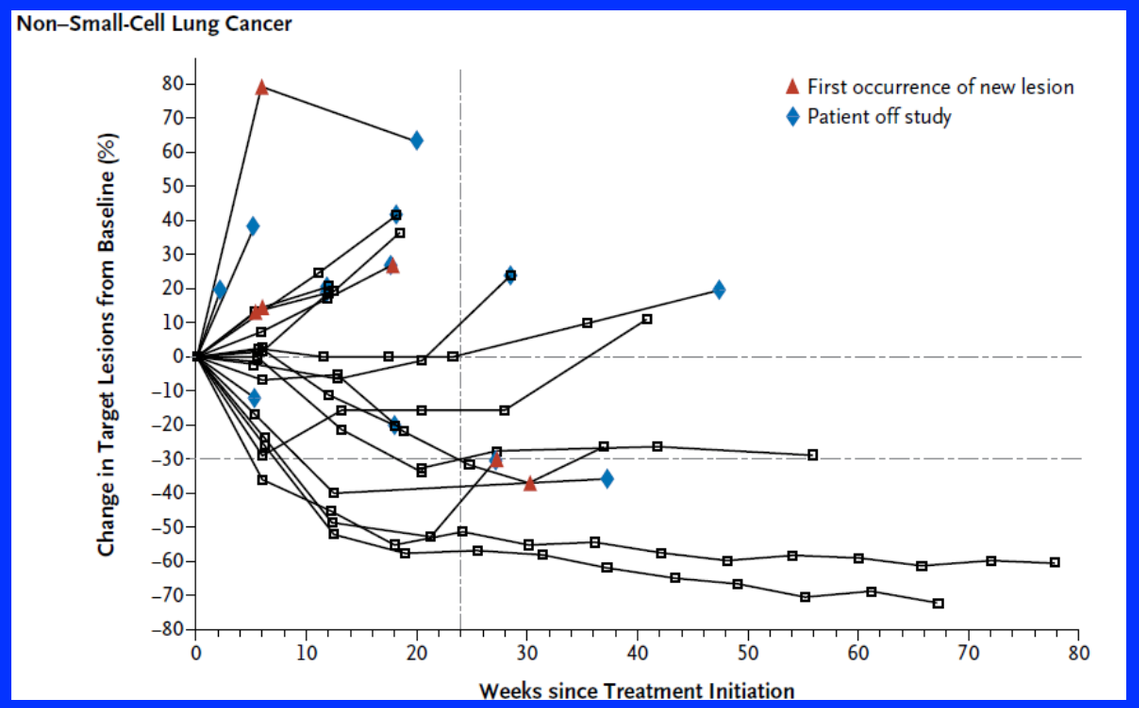
Preliminary survival with concurrent nivolumab and ipilimumab



Courtesy Dr. J. Wolchok 2014

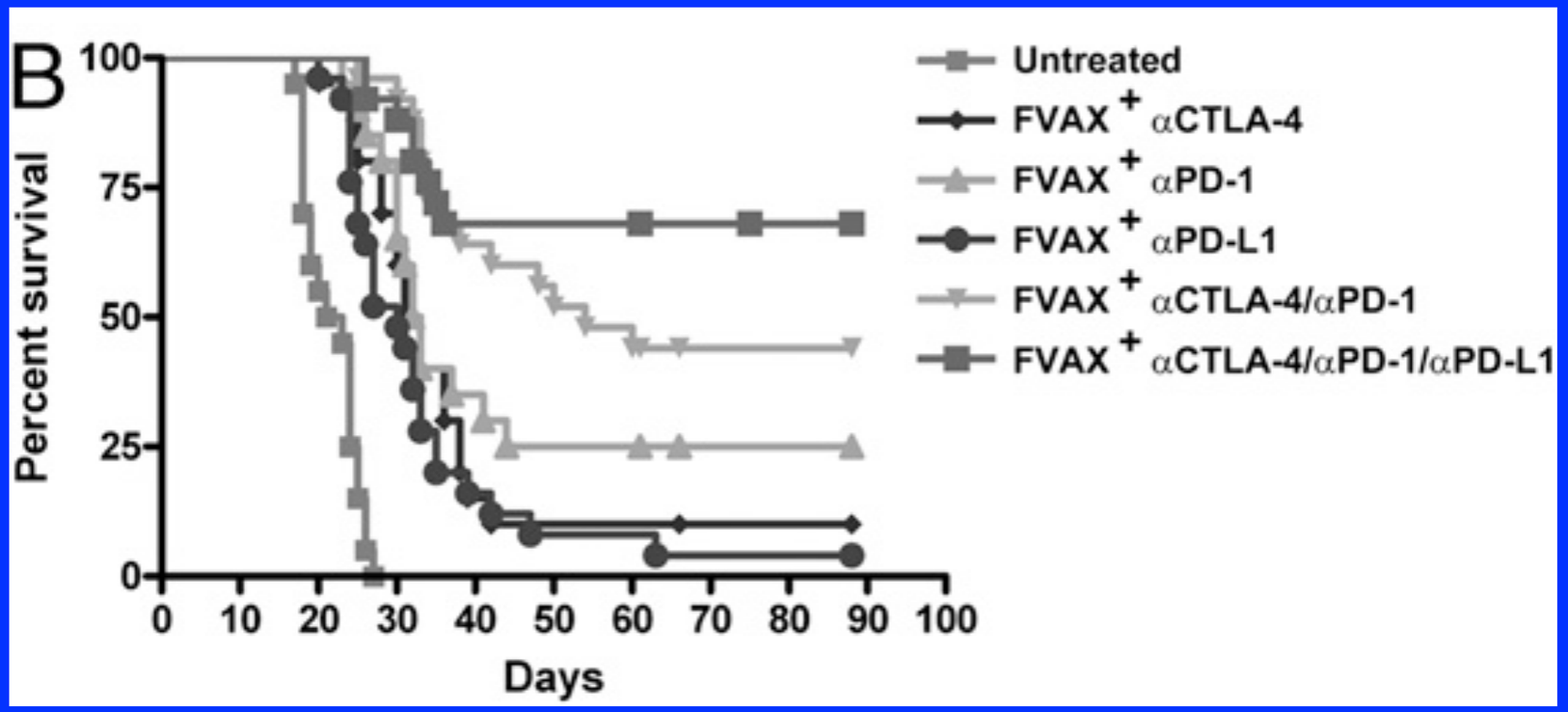
Anti-PDL1 Mo AB has anti-tumor activity in melanoma and lung cancer





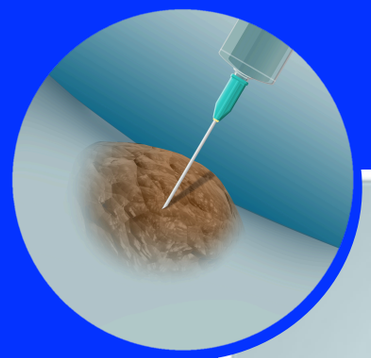
Brahmer et al. NEJM 2012

Blockade of multiple T cell checkpoints results in synergistic therapeutic activity

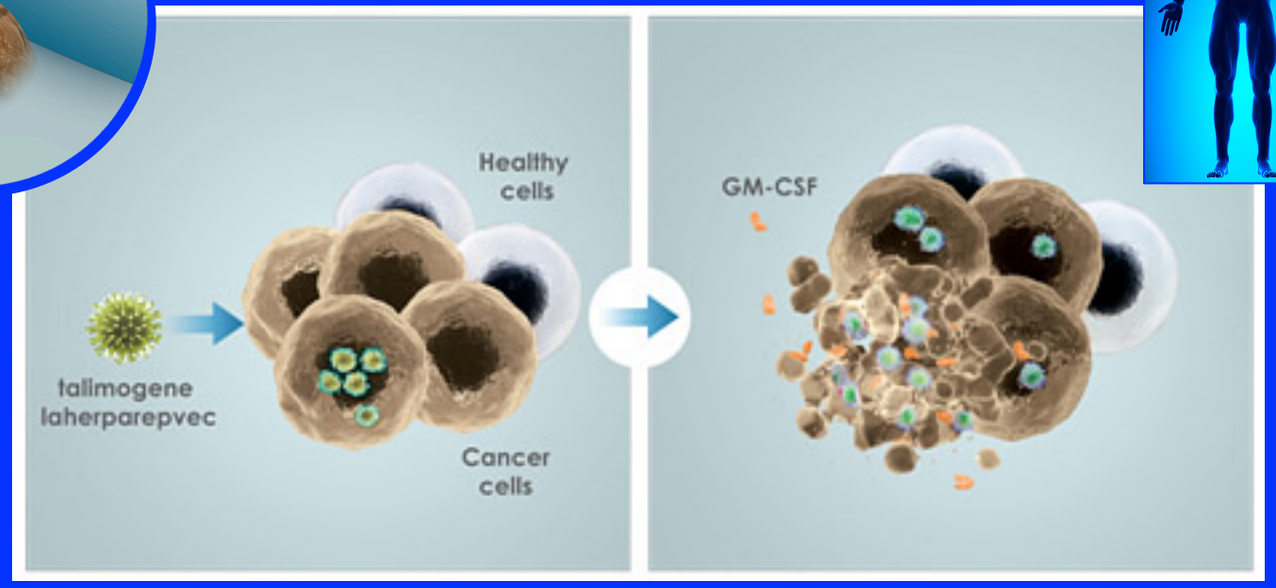


Curran et al. PNAS 2010

T-VEC: An HSV-1 Oncolytic Immunotherapy Designed to Produce Both Local and Systemic Effects



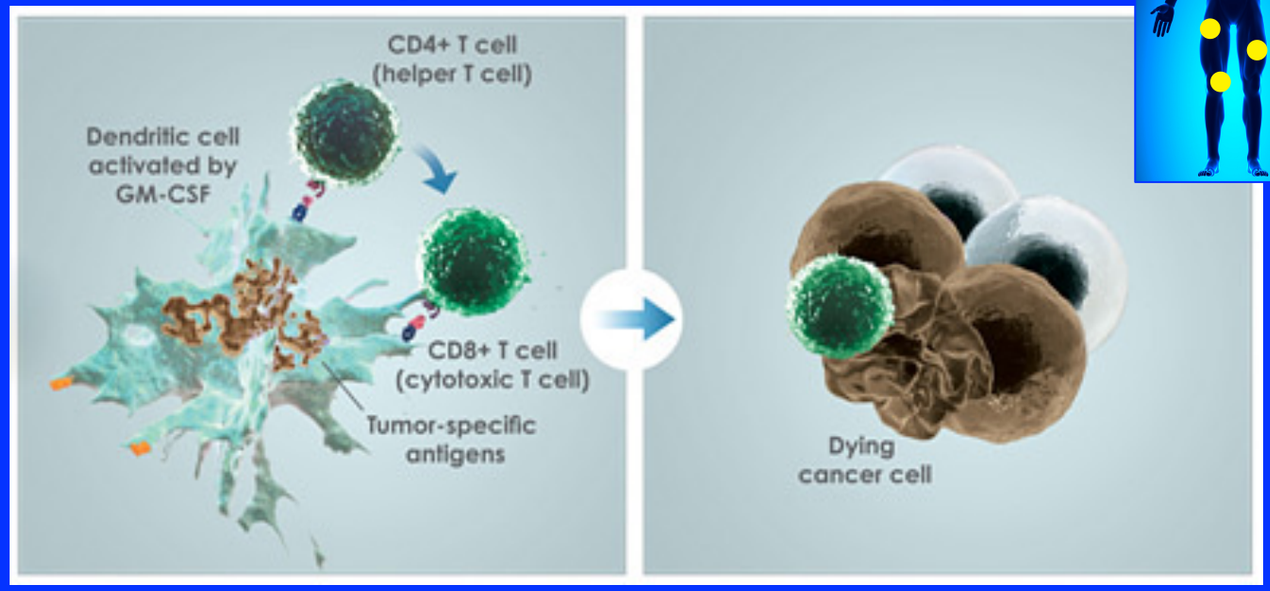
Local Effect: Virally-Induced Tumor Cell Lysis



1. Selective viral replication in tumor tissue

2. Tumor cells rupture for an oncolytic effect

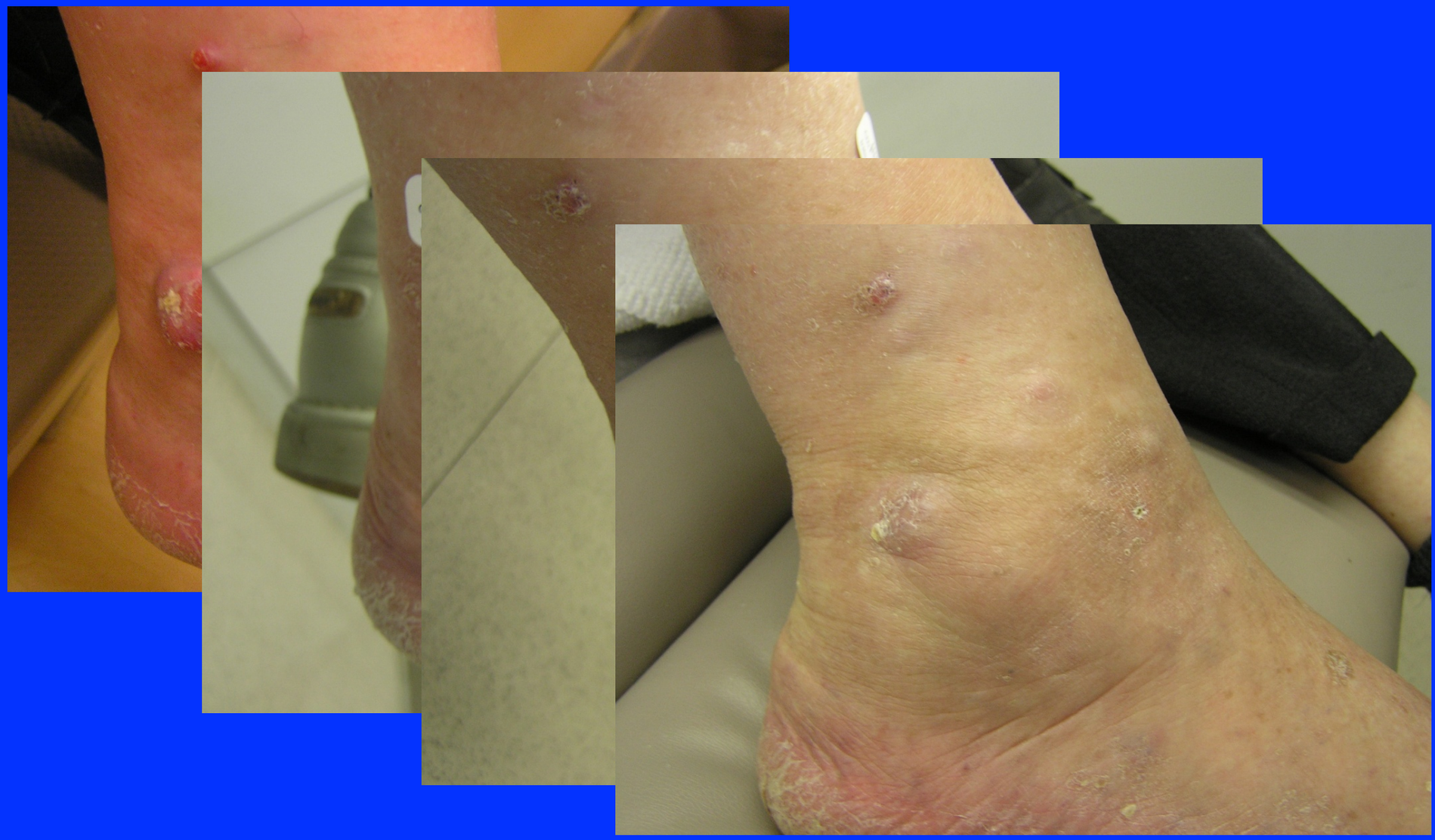
Systemic Effect: Tumor-Specific Immune Response



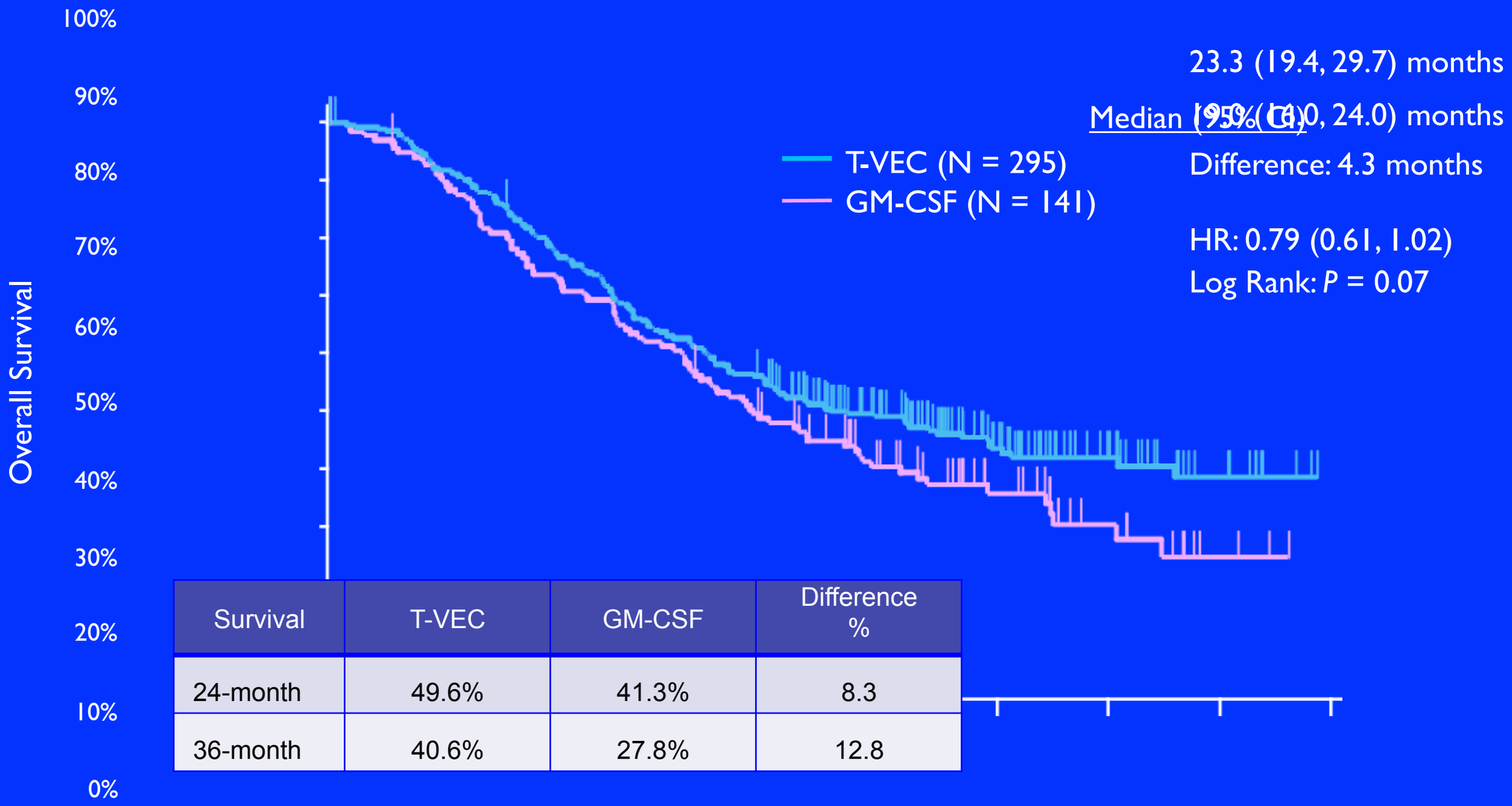
3. Systemic tumor-specific immune response

4. Death of distant cancer cells

Complete regression of soft tissue melanoma after Oncovex$^{GM\text{-}CSF}$



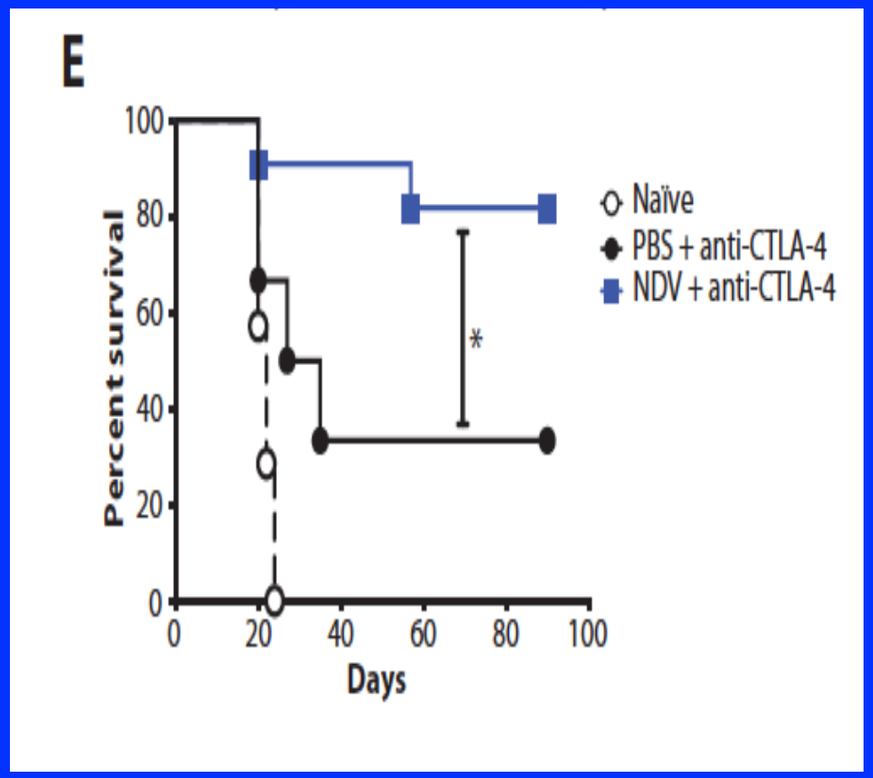
T-VEC Interim Overall Survival



Survival	T-VEC	GM-CSF	Difference %
24-month	49.6%	41.3%	8.3
36-month	40.6%	27.8%	12.8

Combination oncolytic viruses and anti-CTLA-4

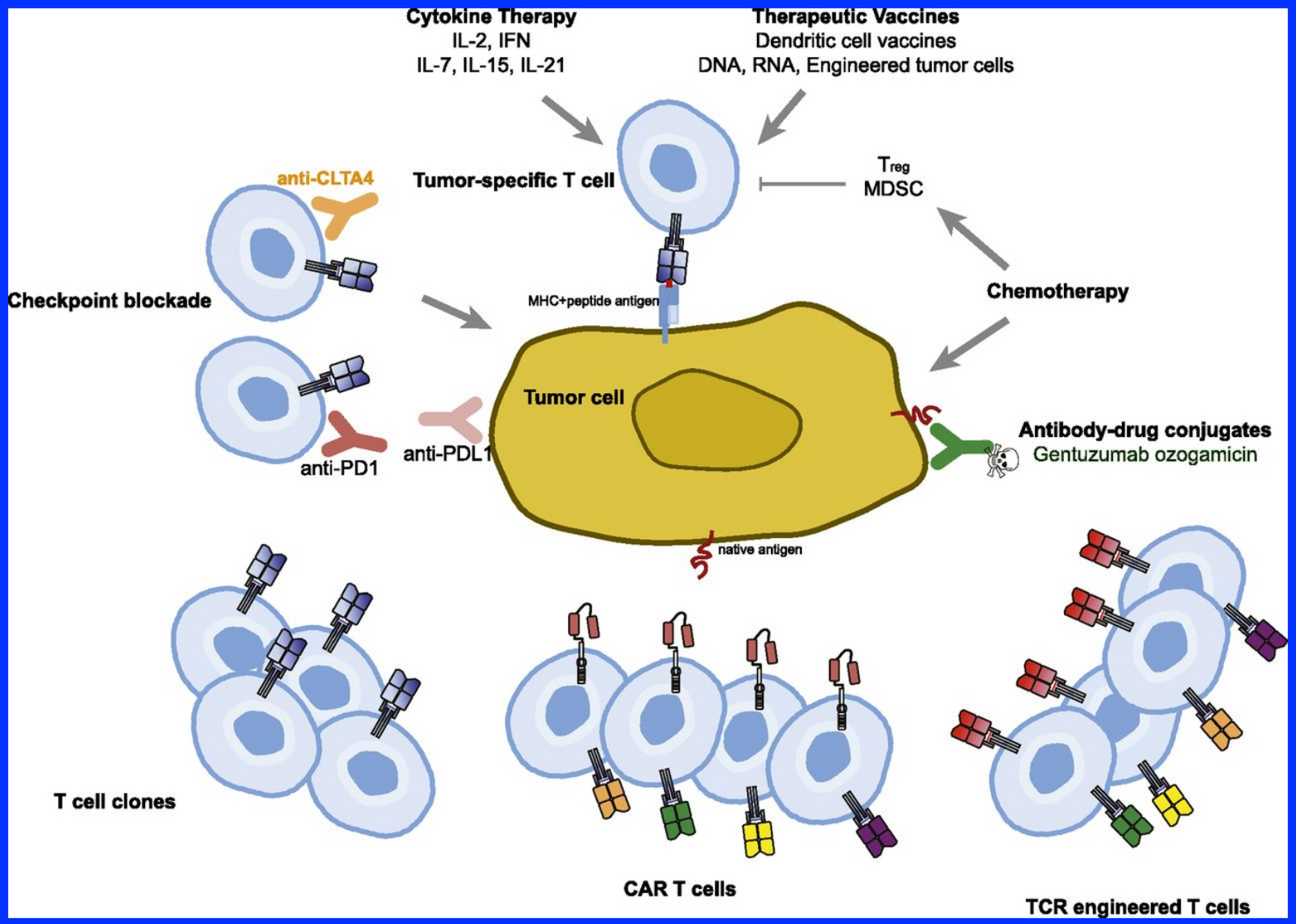
- NDV and anti-CTLA-4



Zamain et al. Science Transl Med 2014

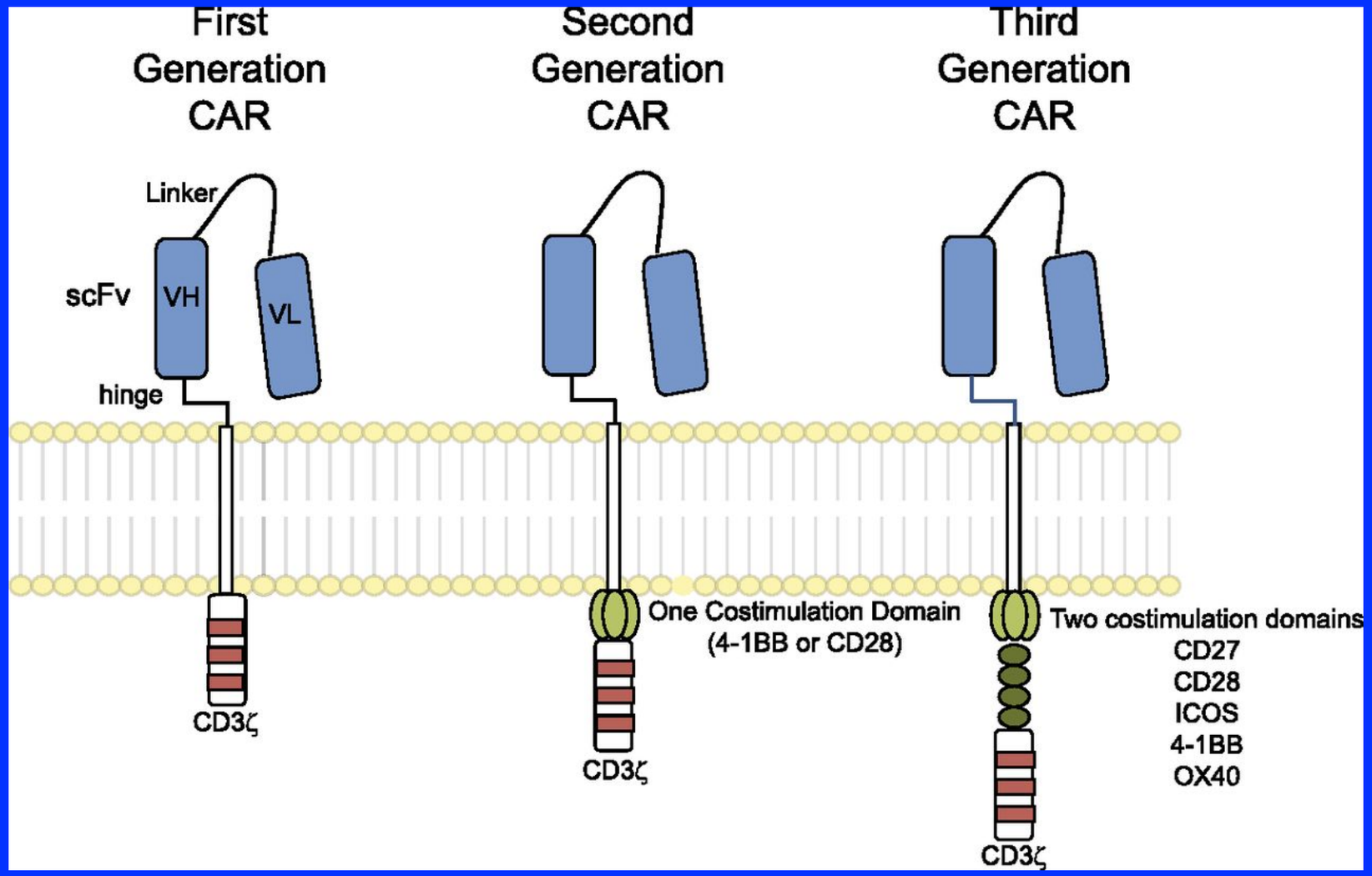
- T-VEC and anti-CTLA-4
- ASCO abstract 20110264
- Primary analysis of a Phase 1b multicenter trial to evaluate safety and efficacy of talimogene laherparepvec (T-VEC) and ipilimumab (ipi) in previously untreated, unresected, stage IIIB-IV melanoma
- Igor Puzanov, Mohammed Milhem,Robert H. I. Andtbacka, David Minor, Omid Hamid, Ai Li, Michael Chastain, Ari VanderWalde, Jeffrey Chou, Howard Kaufman

Therapeutic approaches to overcome immune tolerance to tumors



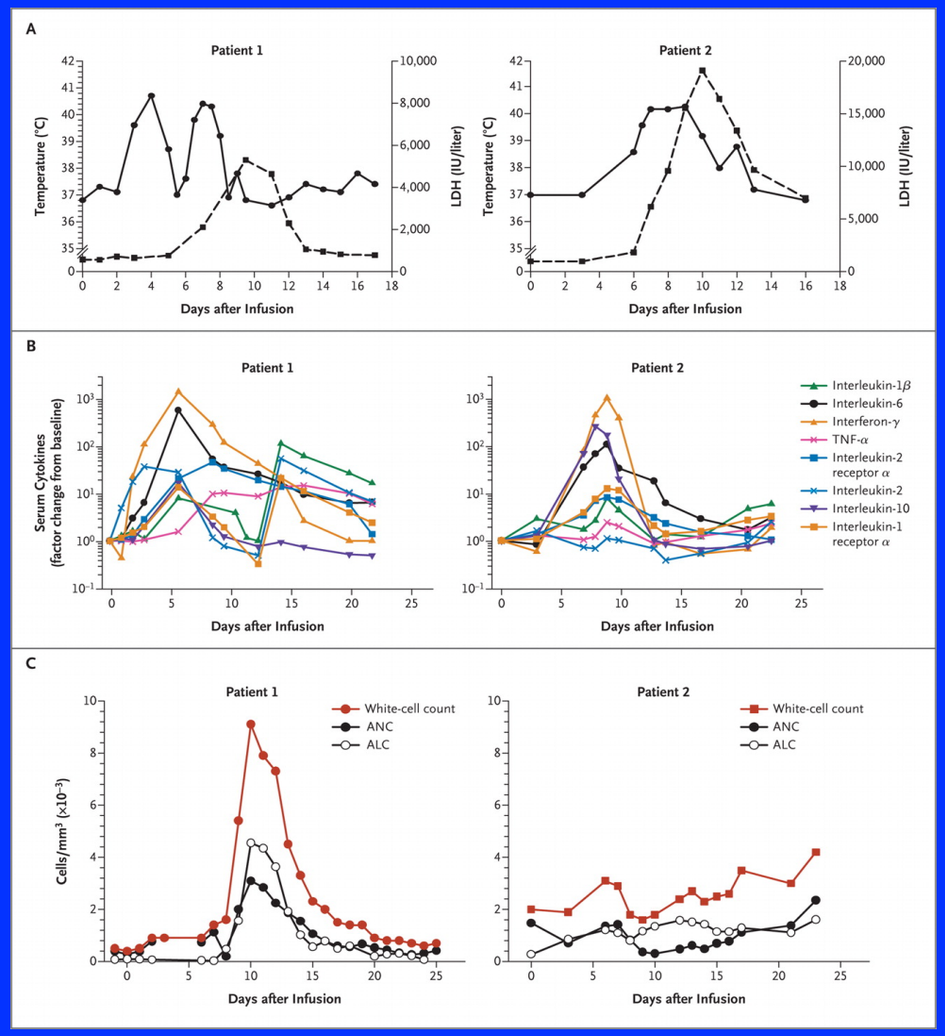
Maus M V et al. Blood 2014

Chimeric antigen receptors



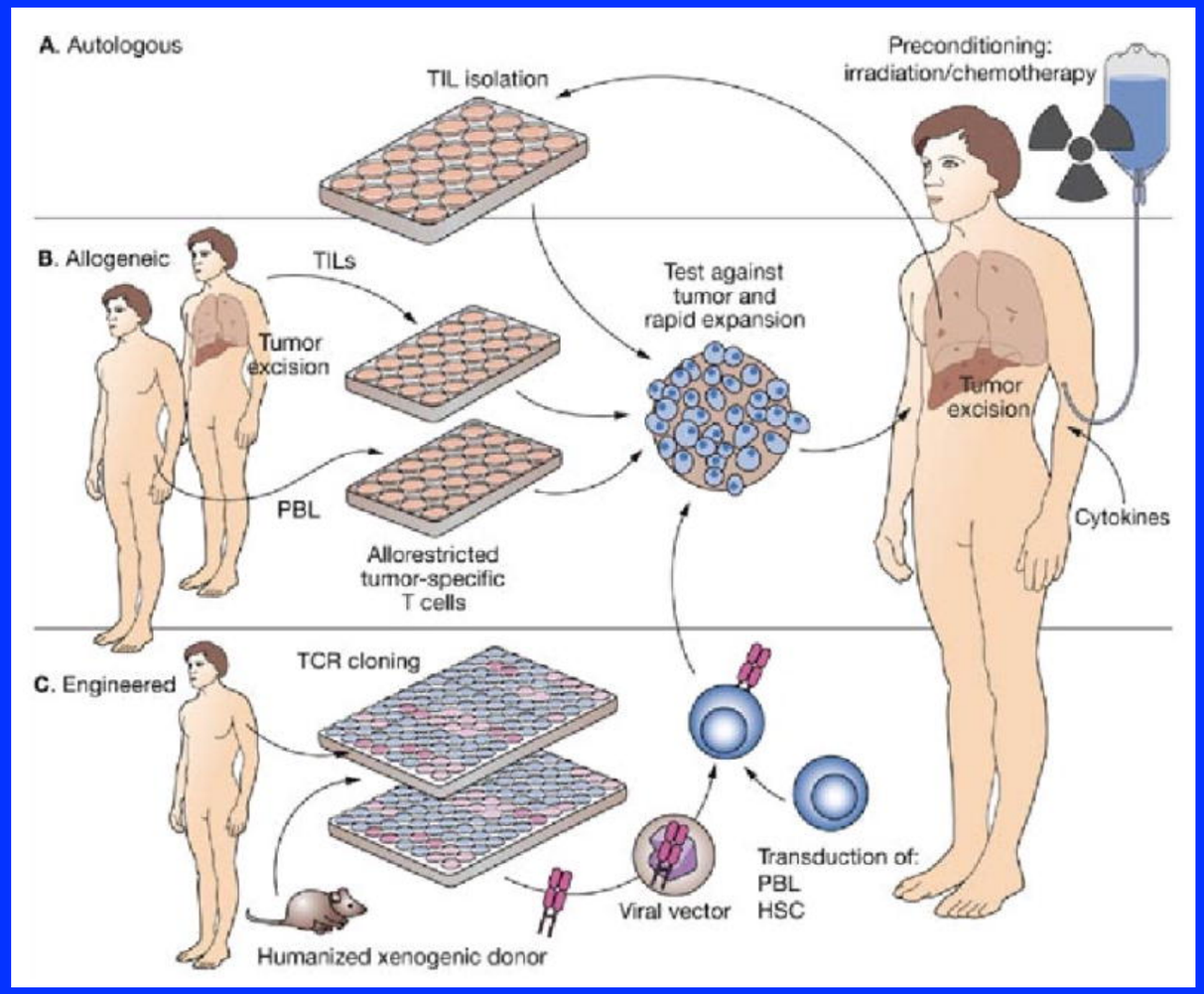
Maus M V et al. Blood 2014

Clinical responses to CTL019 CAR infusion in 2 children with relapsed and refractory acute lymphoblastic leukemia (ALL)



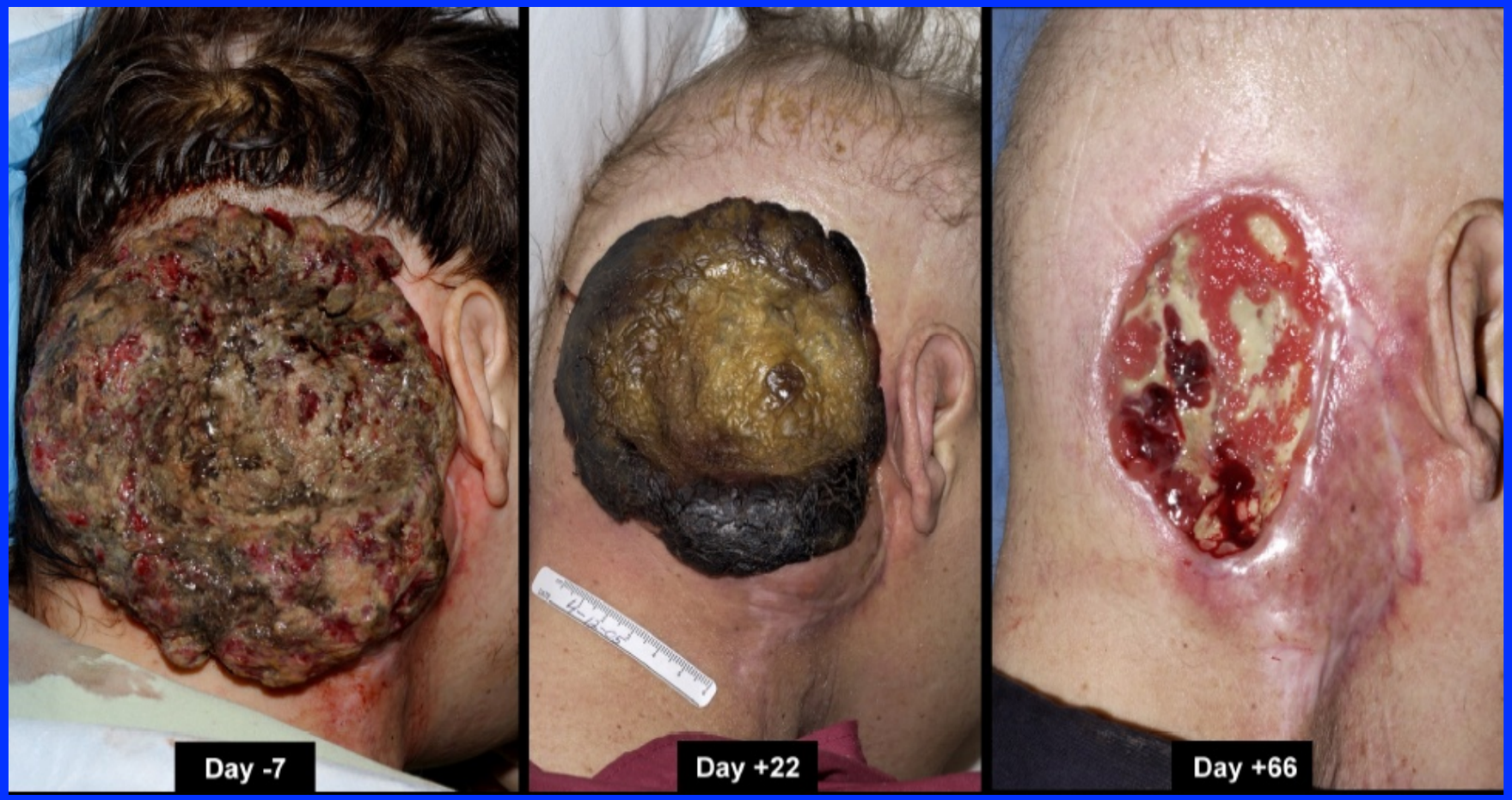
Grupp SA et al. N Engl J Med 2013

Strategies for Adoptive T cell Transfer in Melanoma

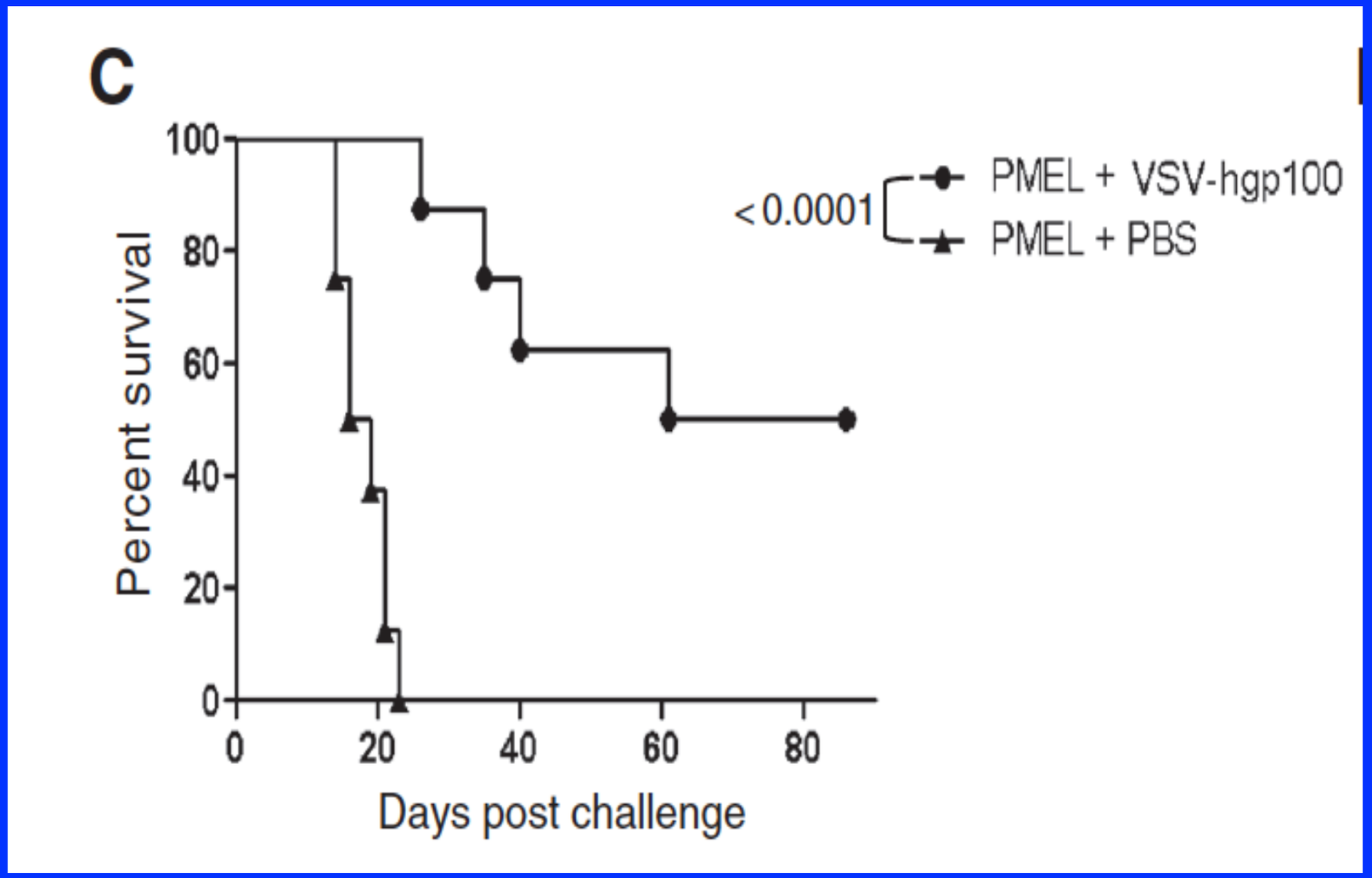


Maranski et al. Nature Clin Pract Oncol 2006

Clinical response to adoptive T cell transfer

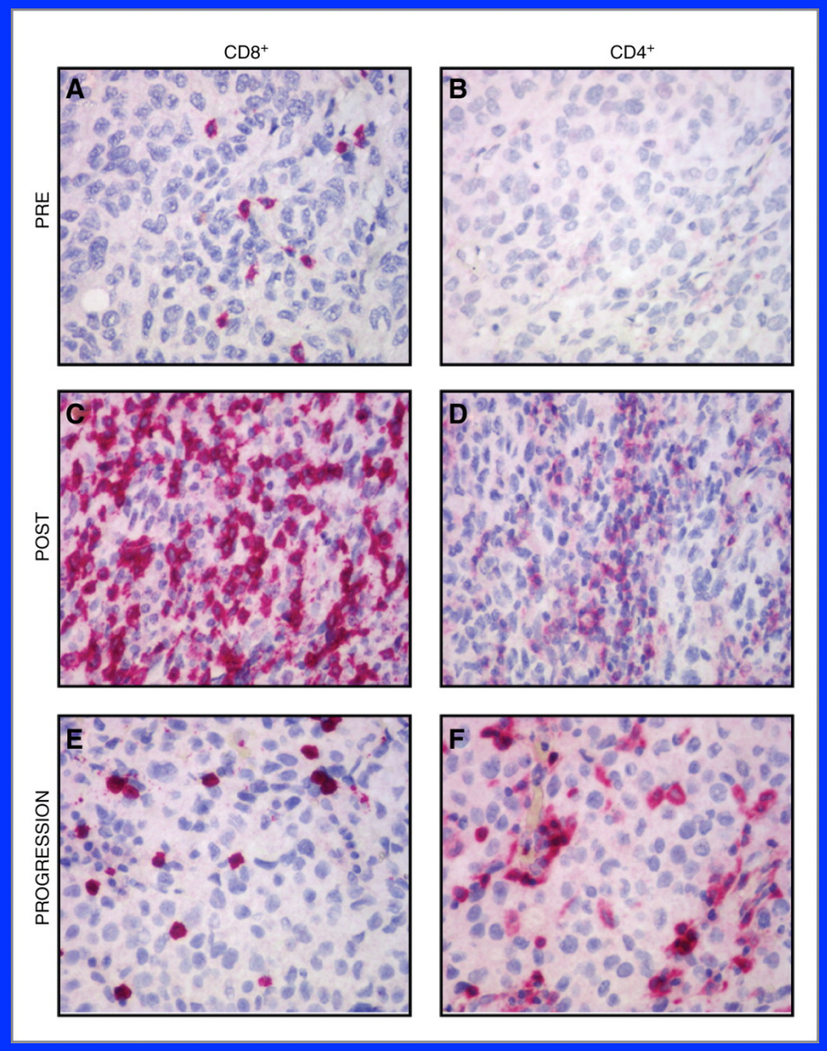


Combination oncolytic virus and adoptive T cell therapy



Rommelfanger et al. Cancer Res 2012

Vemurafenib induces T cell infiltrates into the melanoma tumor microenvironment



Wilmott J S et al. Clin Cancer Res 2012

General Conclusions

- Many promising new agents in development for immunotherapy
  - Cytokines (IL-2 and IL-2-related cytokines)
  - T cell checkpoint inhibitors (ipilimumab, anti-PD1, anti-PD-L1)
  - Oncolytic virus immunotherapy (T-VEC)
  - CAR and adoptive T cell therapy
- Pre-clinical data supports improved therapeutic effectiveness with combined immunotherapy agents
- Clinical data suggests combined ipilimumab and nivolumab has superior clinical activity in melanoma
- Combined immunotherapy and standard therapeutic approaches may also have synergistic therapeutic activity
- Predictive biomarkers have become a major priority for the field

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