Melanoma Immunotherapy

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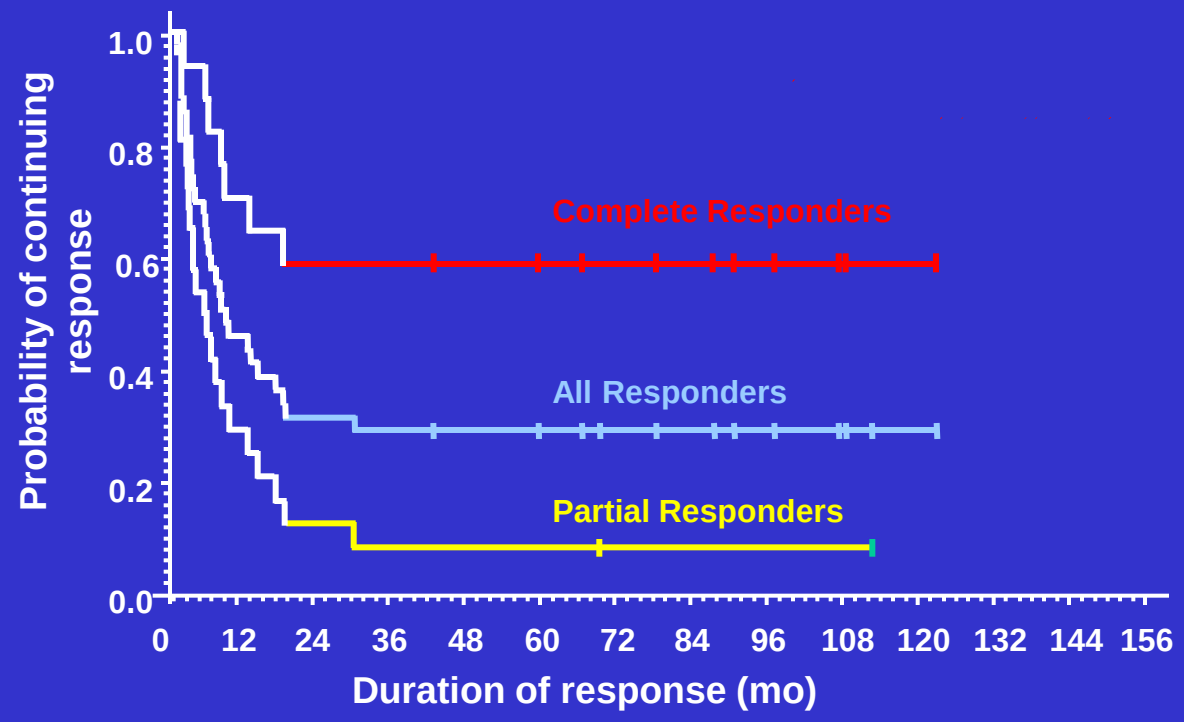
Immunotherapy of Melanoma

1901	Leyden	autologous oncolysate
1968	Symes	allogenic spleen cells
1973	Falk	Bacille Calmette-Guerin
mid 1980th	Morton	whole cell vaccines
1987	Rosenberg	Interleukin-2
1996	Boon	MAGE; peptide vaccines
1998	Schuler, Steinman	dendritic cells
2002	Rosenberg	anti-CTLA-4

Long duration of tumour responses with IL-2

- 270 patients in multi-institutional phase II clinical trials



Hallmarks of Melanoma in Immunotherapy

- Melanoma immunotherapy has a ceiling of response in the order of 10-20% of patients
- Responses may take a long time to declare
- Once there is a response, it tends to be durable and some patients are seemingly cured
- Clinical features associated with increased responses:
  - Skin, in-transit and nodal metastasis
  - Low LDH
  - Pre-existing or induced autoimmune phenomenon

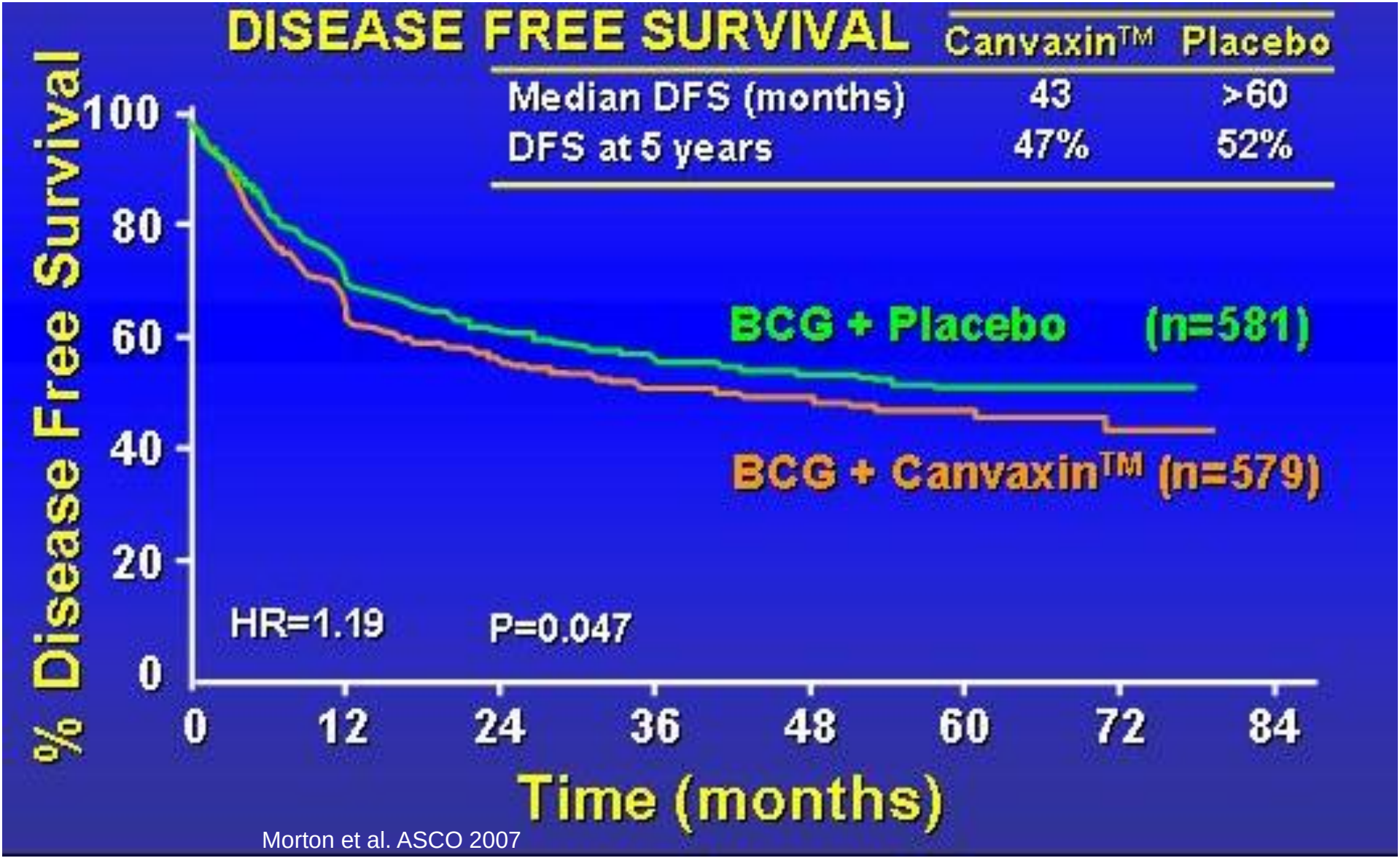
State-of-the-Art of Melanoma

Immunotherapy

- Several immunotherapy approaches can lead to long term remission of metastatic melanoma:
  - Spontaneous remission
  - HD IL-2
  - Dendritic cell vaccines
  - Immune modulating antibodies: anti-CTLA4
  - Adoptive transfer cell therapy

- Some melanoma tumor vaccines shorten patients' PFS or OS:
  - Cancervax
  - GMK

Cancervaxin versus Placebo in Stage IV NED



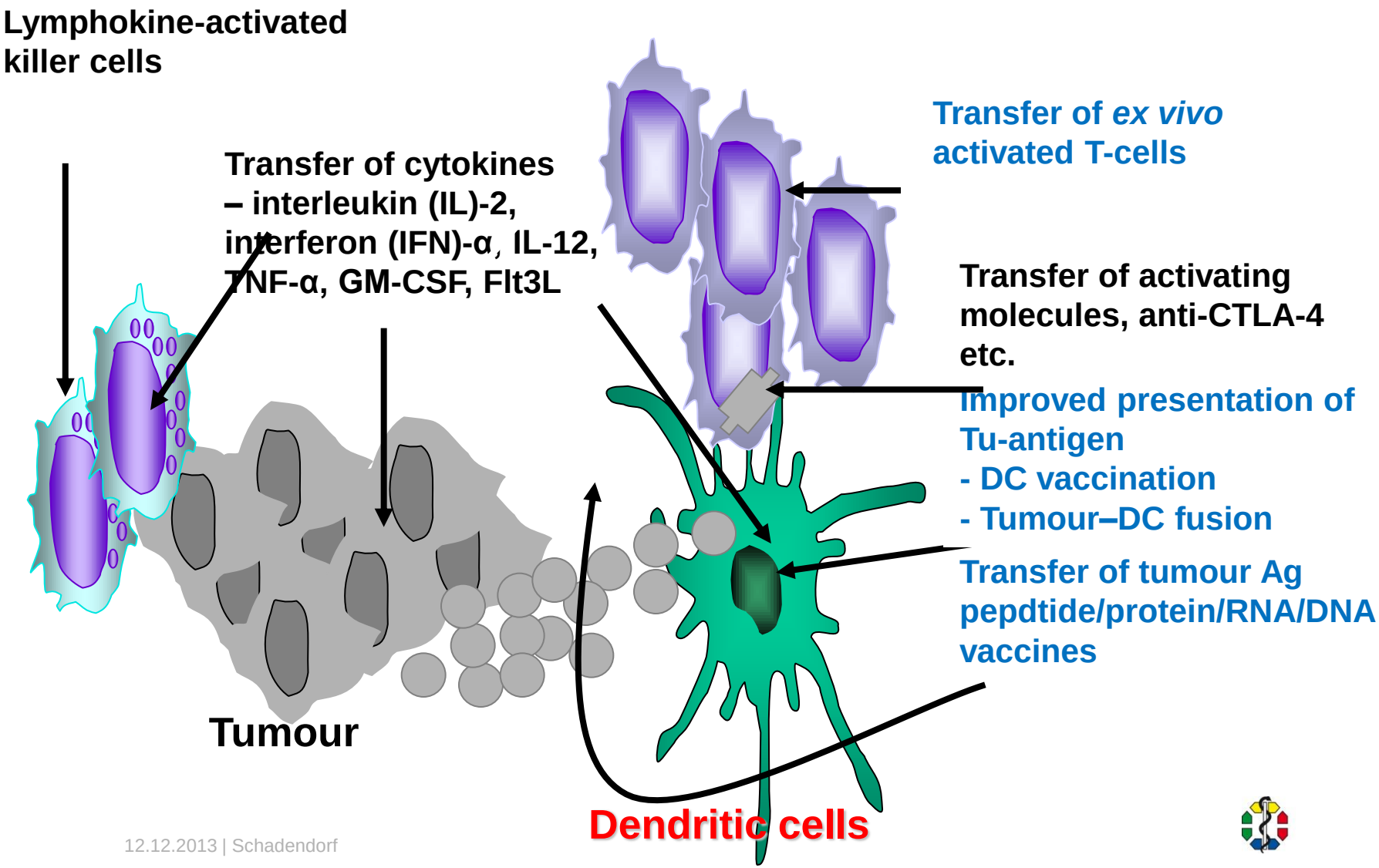
Morton et al. ASCO 2007

- Specific Immunization
- Unspecific immunostimulation

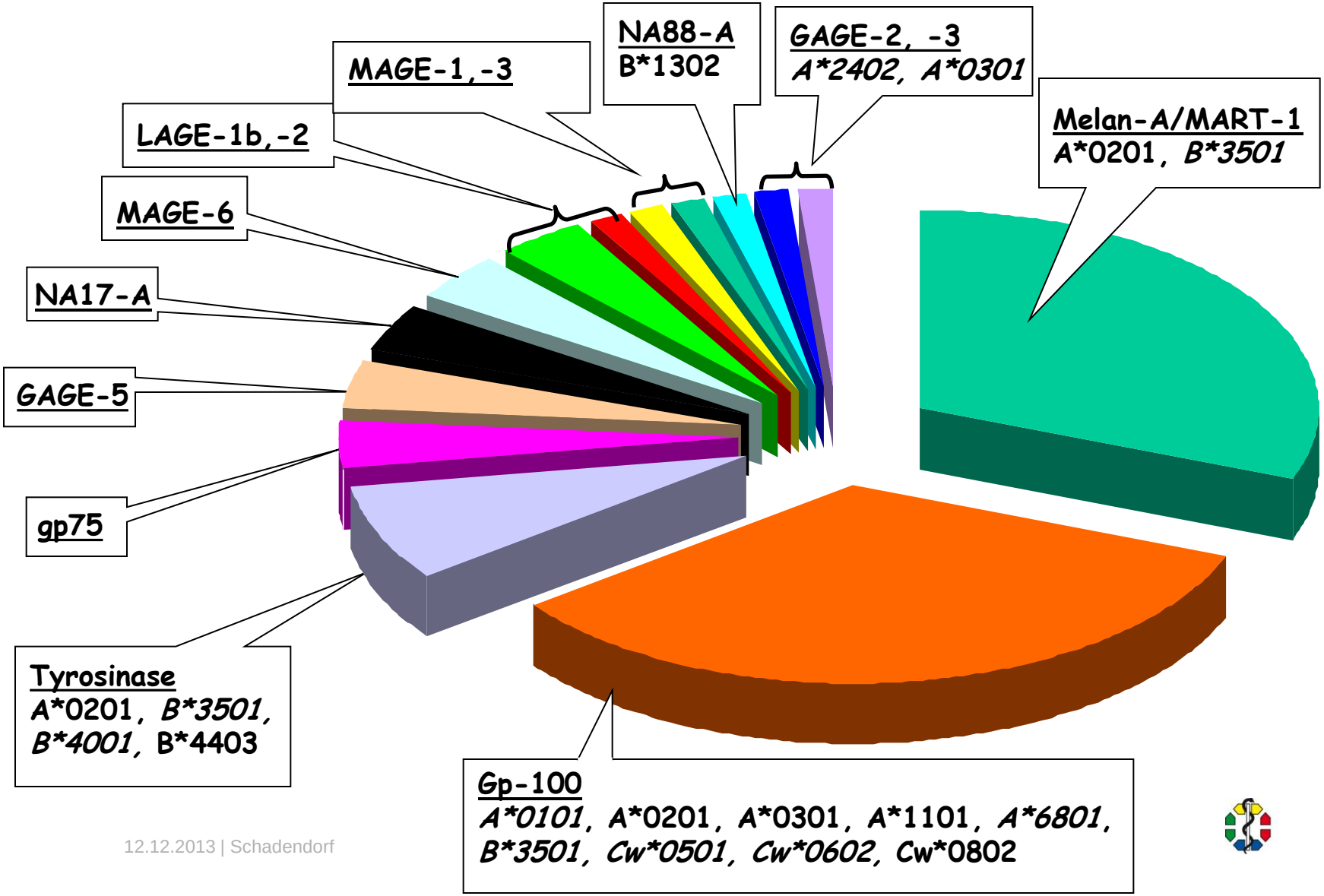
- Specific Immunization

- Unspecific immunostimulation

Immunotherapeutic strategies



Frequency of in vitro/ex vivo T-cell recognition of different self MAA in metastatic melanoma patients



Vaccination of melanoma patients with peptide- or tumor lysate-pulsed dendritic cells

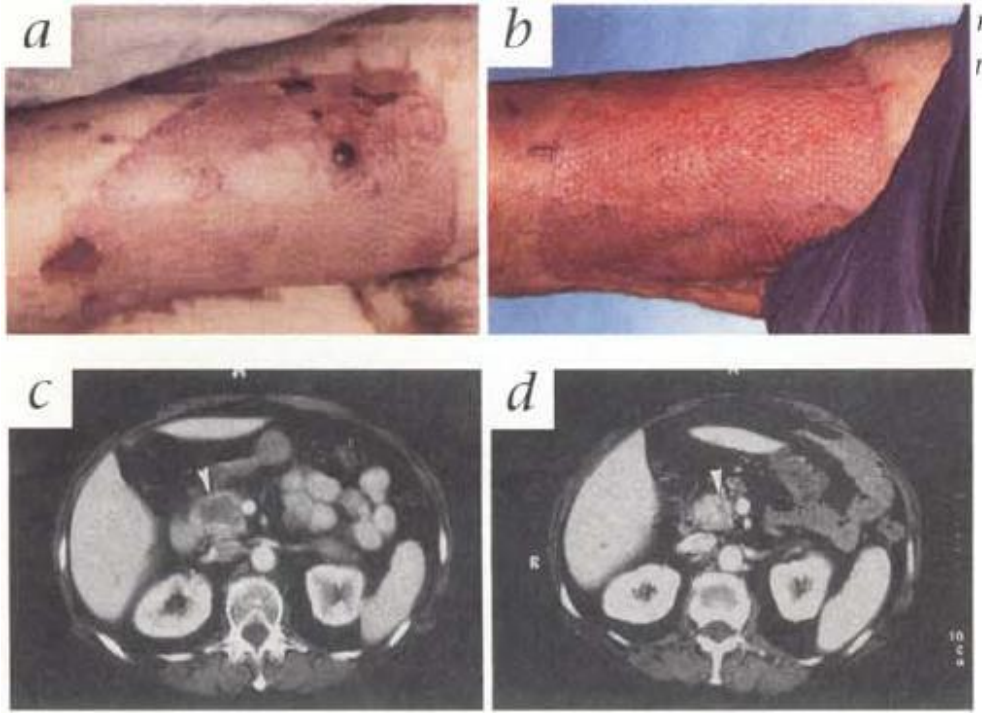
FRANK O. NESTLE[1], SELMA ALIJAGIC[2], MICHEL GILLIET[1], YUANSHENG SUN[2], STEPHAN GRABBE[3], REINHARD DUMMER[1], GÜNTER BURG[1] & DIRK SCHADENDORF[2]

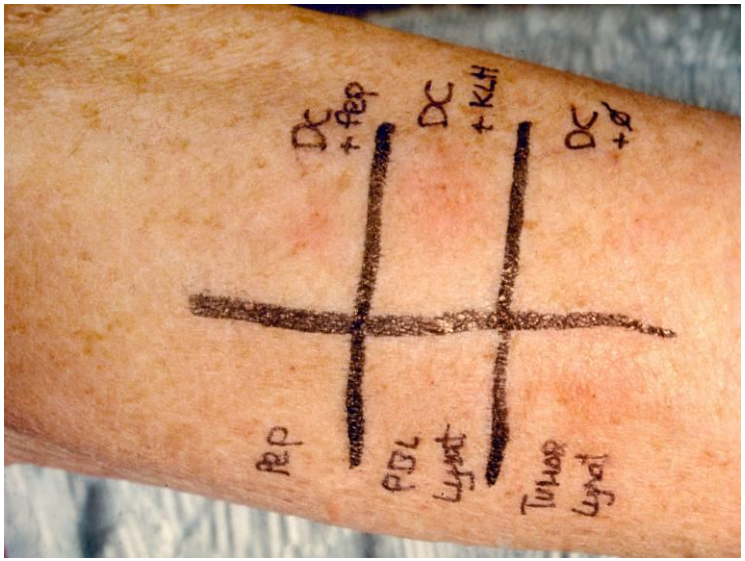
[1]*Department of Dermatology, University of Zurich Medical School, Gloriastrasse 31, 8091 Zurich, Switzerland*

[2]*Clinical Cooperation Unit for Dermatooncology (DKFZ) at the Klinikum Mannheim, University of Heidelberg, Theodor Kutzer Ufer 1, 68135 Mannheim, Germany*

marck Str. 56, 48149 Münster, Germany

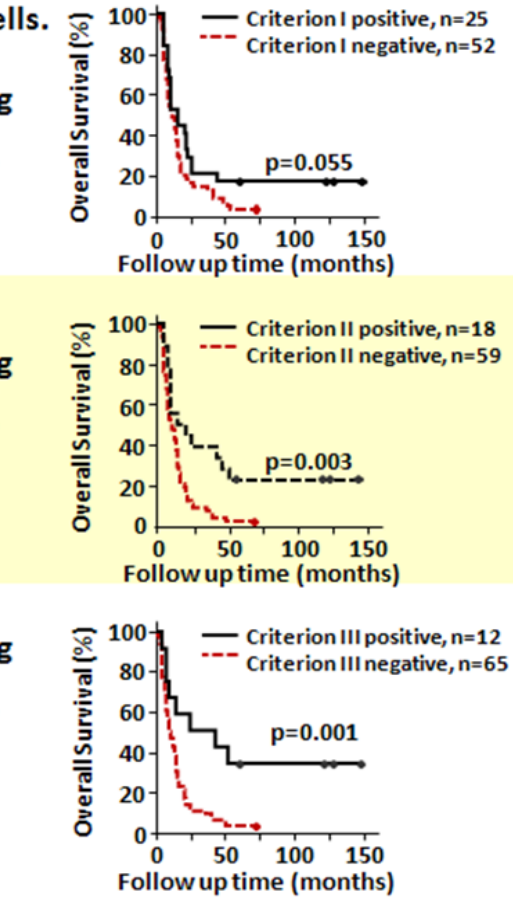
ressed to D.S.





NATURE MEDICINE • VOLUME 4 • NUMBER 3 • MARCH 1998

Skin-test infiltrating lymphocytes predict clinical outcome of dendritic cell based vaccination in metastatic melanoma



Kaplan-Meier survival curves

K. Bol et al. Cancer Res (2012) accepted

- Test #1 (n=77pts) : **Tetramer binding** (3 TAA); 25 pts +
- Test #2 (n=25pts) : **peptide recognition**; 18 pts +
- Test #3 (18=pts) : **natural TAA processing**; 12 pts +

Search for Biomarkers

- « Gene profiling » as optional, explorative research approach
- Tumor biopsies taken BEFORE MAGE-A3 immunisation

- MAGE-A3 screening
- Predictive signature to MAGE-A3 ASCI

Predictive gene signature
regarding MAGE-A3 vaccination:
immunological microenvironment critical

Louahed, ASCO 2008

Immune Resistance orchestrated by the Tumor Microenvironment,

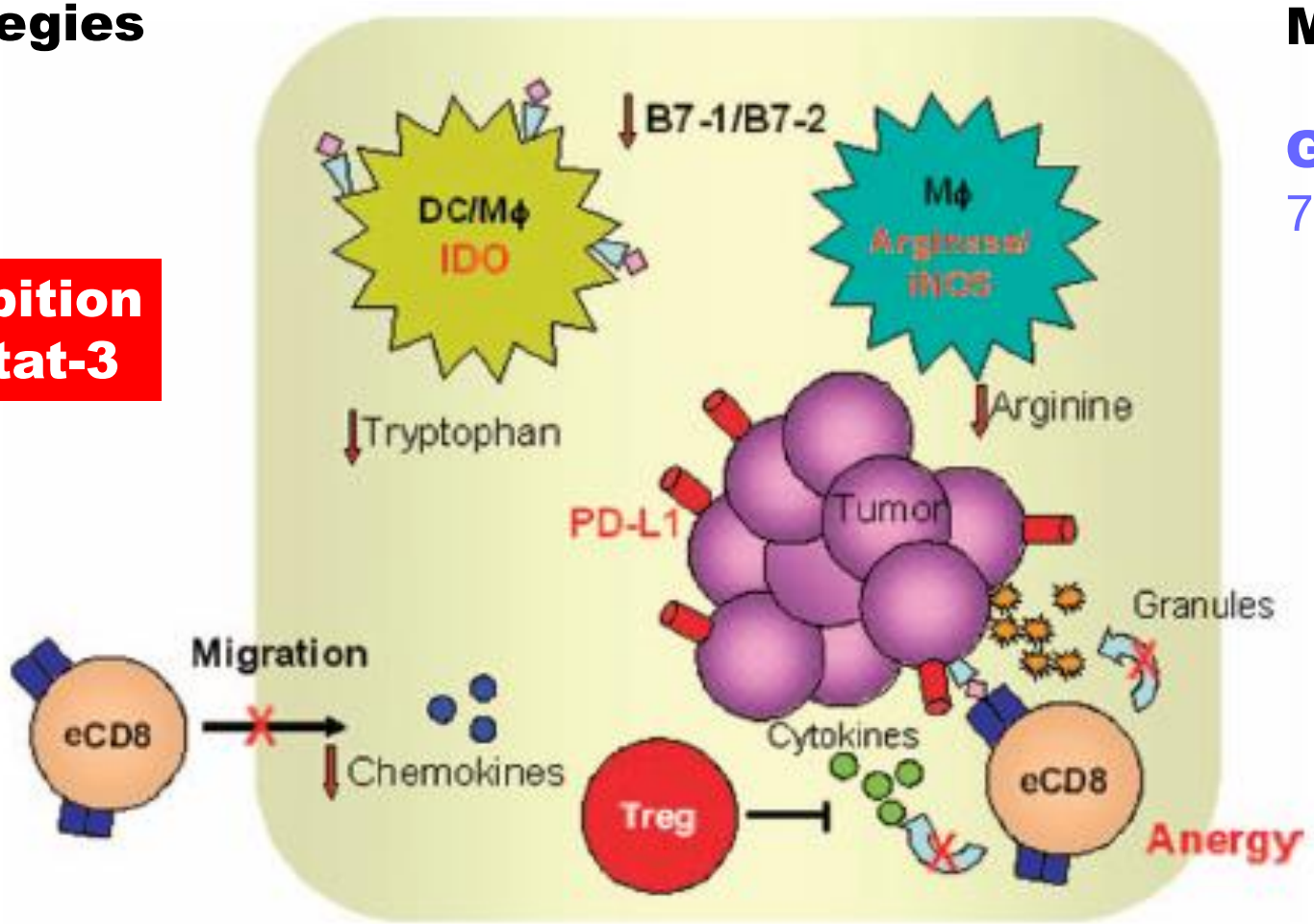
T.Gajewski, Immunol. Rev. 2006

Therapeutic Strategies

Inhibition of Stat-3

Predictive Markers

Genomics
7 Genes



US National Library of Medicine
National Institutes of Health

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Cancer J. 2010 Jul-Aug;16(4):399-403.

Gene signature in melanoma associated with clinical activity: a potential clue to unlock cancer immunotherapy.

Gajewski TF, Louahed J, Brichard VG.
University of Chicago, 5841 S. Maryland Ave., MC2115, Chicago, IL 60637, USA. tgajewsk@medicine.bsd.uchicago.edu

Abstract

Immunotherapeutic approaches for melanoma and other cancers can impart profound clinical benefit but only for a subset of patients. Interpatient heterogeneity could, in principle, be due to somatic differences in the tumor between individuals
Analysis of
microenviro
identified o
suggest that such profiling might be useful as a predictive biomarker for clinical benefit from vaccines and other immunotherapy approaches, and analysis of specific gene products has begun to suggest new therapeutic interventions to overcome mechanisms of tumor resistance.

Host environment critical for immune responsiveness ?

PMID: 20693853 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms, Substances

LinkOut - more resources

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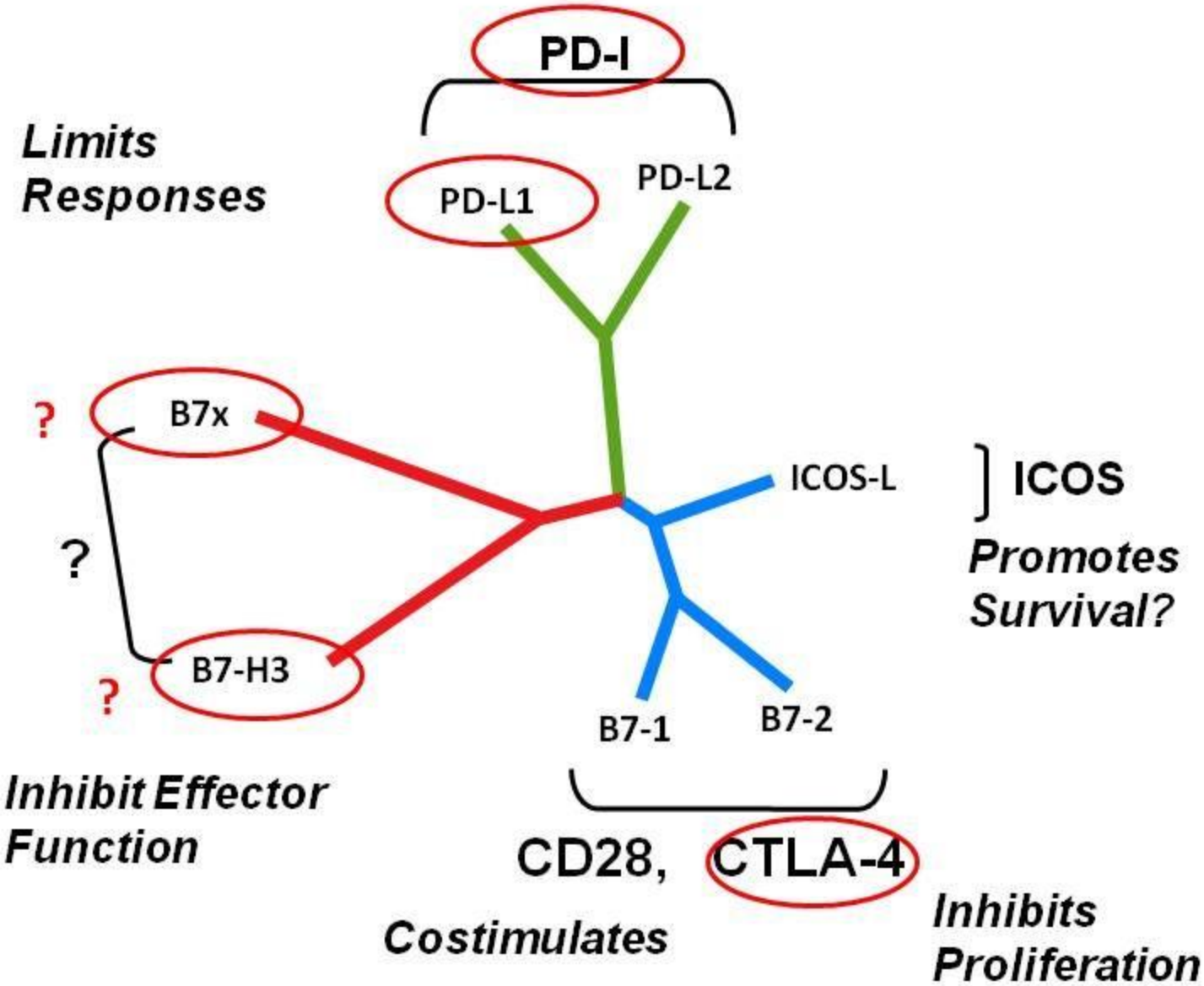
- Specific Immunization

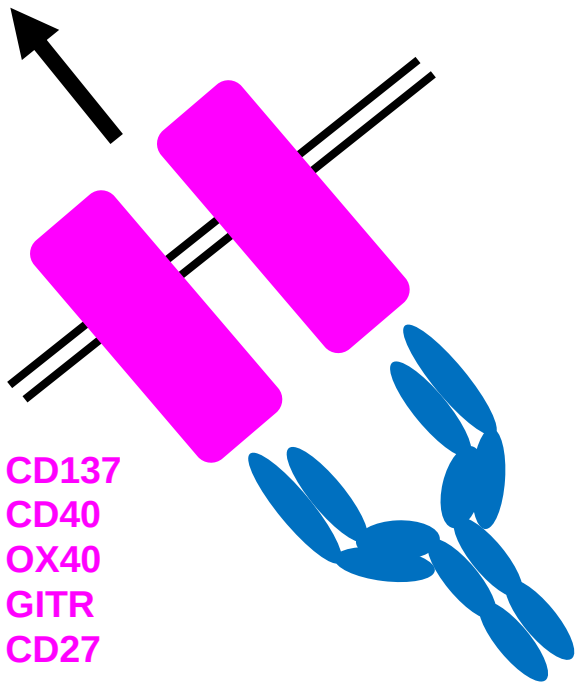
- Unspecific immunostimulation

Extended CD28/B7 Family

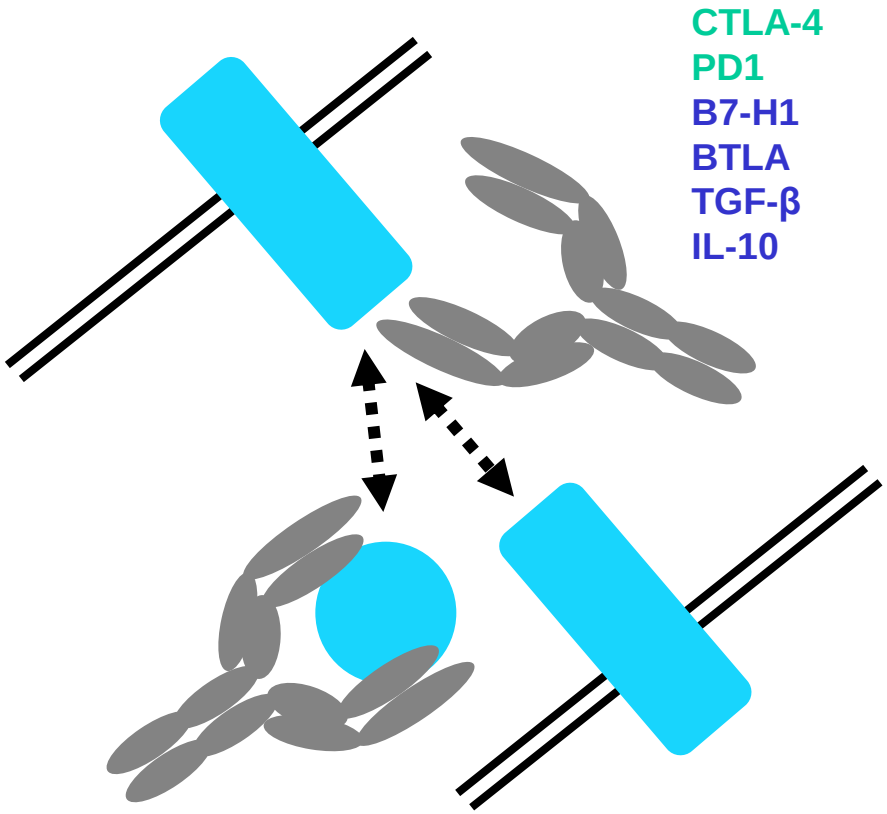


Immunomodulating Antibodies

+ Receptor agonist

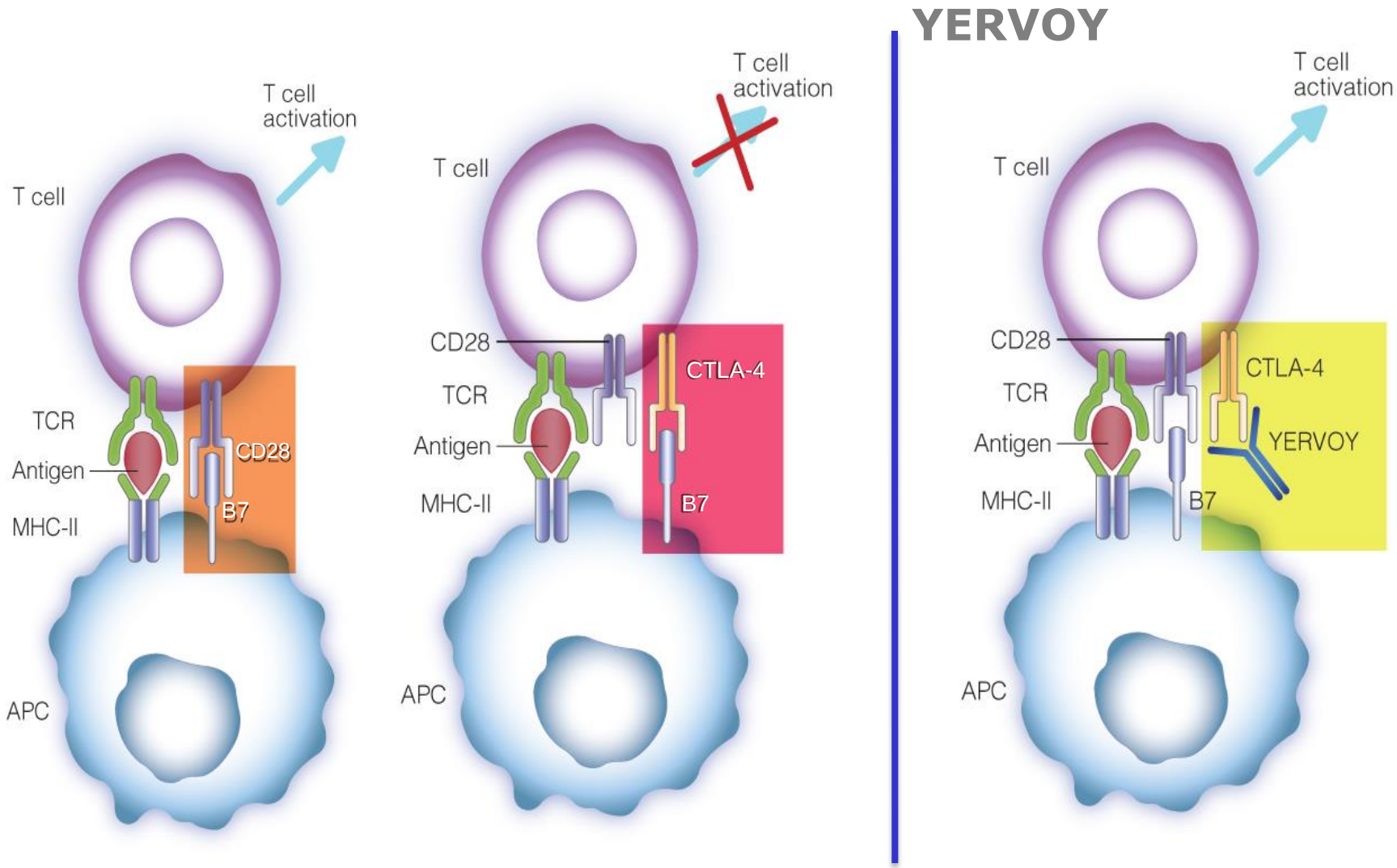


- Receptor antagonist

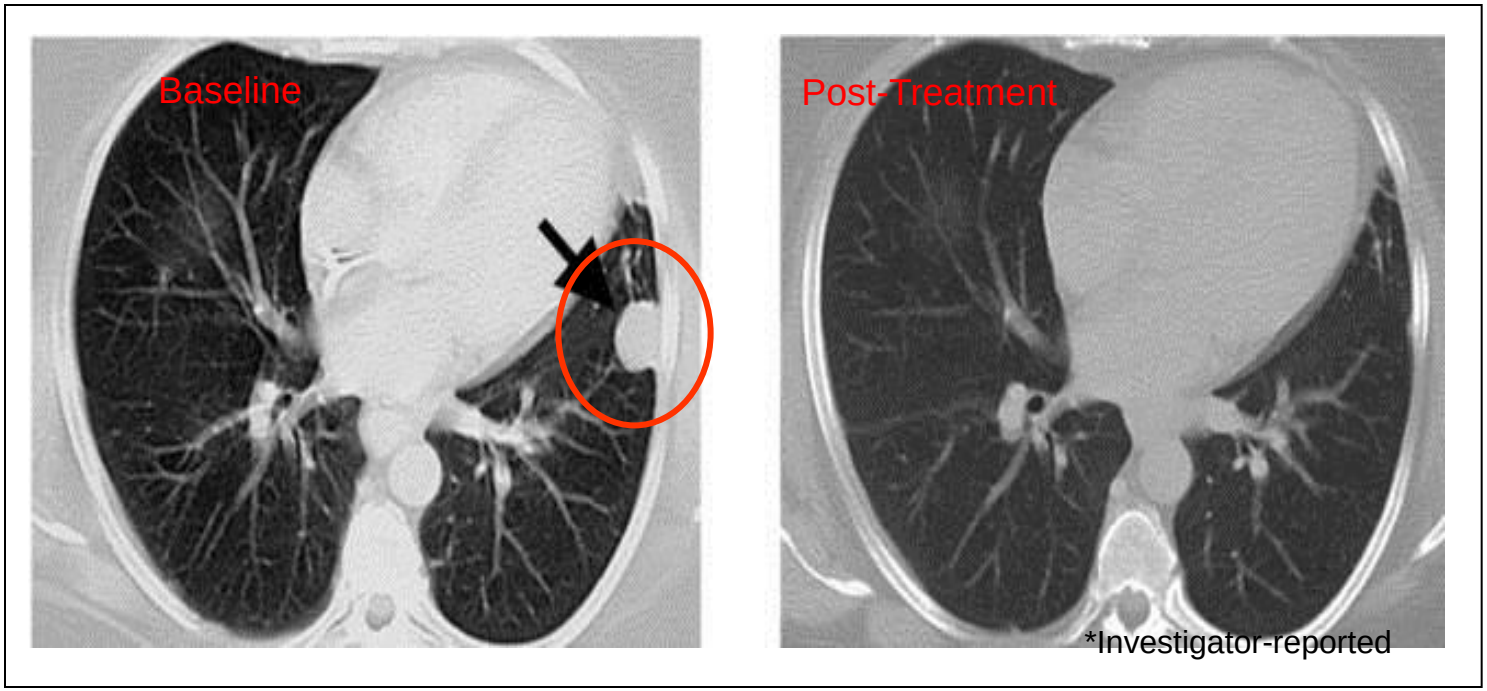


Peggs KS, et al. Clin Exp Immunol 2009;157(1):9–19

CTLA-4 and the immune response



Ipilimumab plus Peptid-Vakzine bei Patienten mit fortgeschrittenem malignen Melanom (NCI)



Complete Response

Patient 13 experienced complete resolution of abdominal subcutaneous nodule and lung lesion. Patient previously failed chemotherapy, immunotherapy, and surgery.

Phan GQ, et al. *Proc. Natl. Acad. Sci*. 2003;100:8372-8377.

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CTLA-4-Antikörper

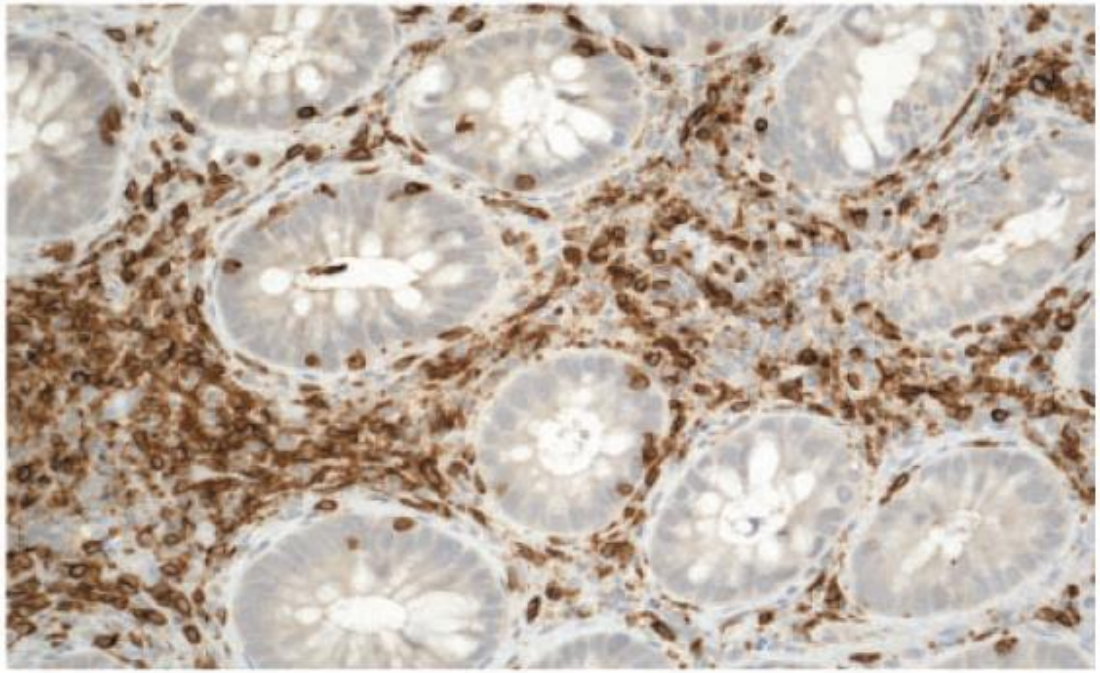
PNAS

Cancer regression and autoimmunity induced by cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma

Giao Q. Phan[†], James C. Yang[†], Richard M. Sherry[†], Patrick Hwu[†], Suzanne L. Topalian[†], Douglas J. Schwartzentruber[†], Nicholas P. Restifo[†], Leah R. Haworth[†], Claudia A. Seipp[†], Linda J. Freezer[†], Kathleen E. Morton[†], Sharon A. Mavroukakis[†], Paul H. Duray[‡], Seth M. Steinberg[§], James P. Allison[¶], Thomas A. Davis[‖], and Steven A. Rosenberg[†,††]

[†]Surgery Branch, [‡]Laboratory of Pathology, and [§]Biostatistics and Data Management Section, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892; [¶]Howard Hughes Medical Institute, Department of Molecular and Cell Biology, University of California, Berkeley, CA 94720; and [‖]Medarex, Inc., Princeton, NJ 08540

Contributed by James P. Allison, May 27, 2003



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

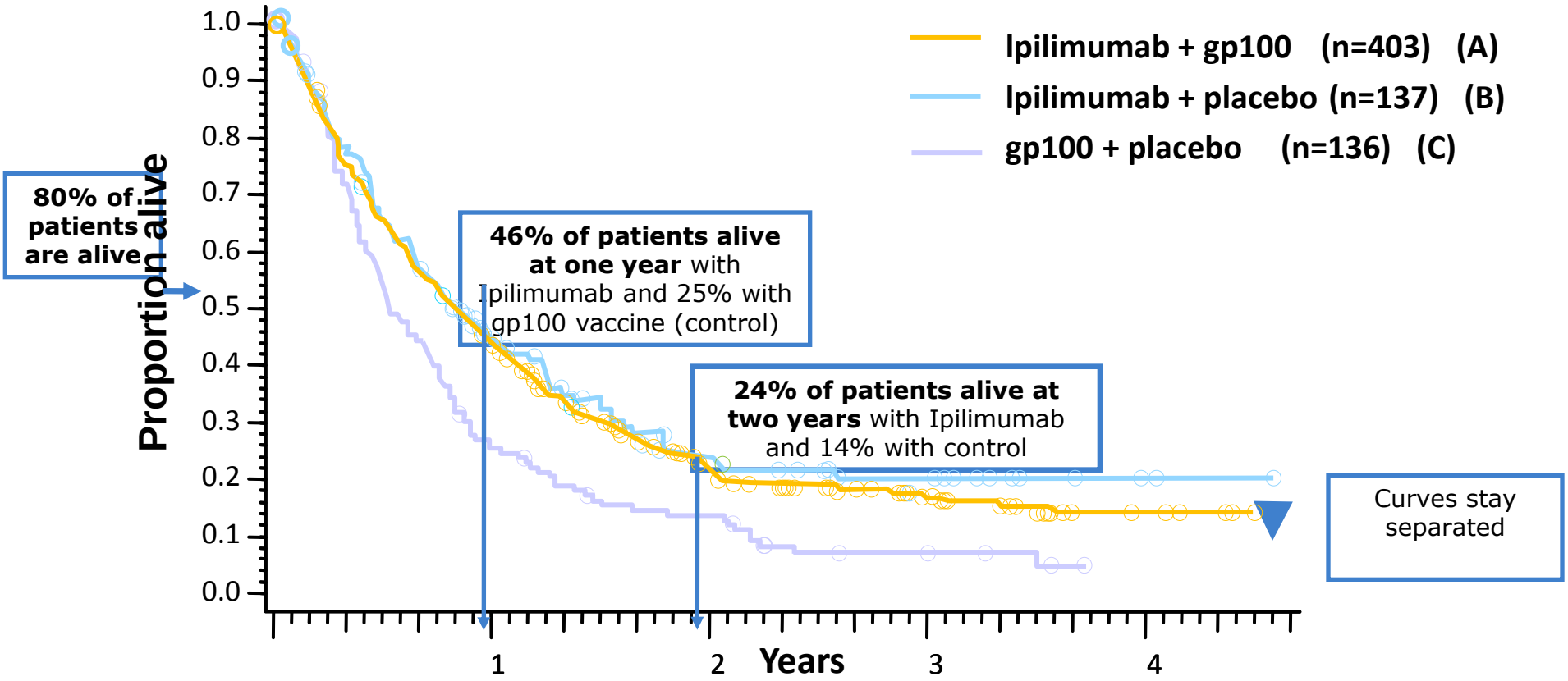
Survival benefit: 3 Mo in both Ipi arms

Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian Quirt, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.D., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.

This article (10.1056/NEJMoa1003466) was published on June 5, 2010, at NEJM.org.

N Engl J Med 2010.

Phase III study in pre-treated patients: prolonged survival at 1 and 2 years



Hodi FS et al. New Engl J Med 2010;363:711-23

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma

Caroline Robert, M.D., Ph.D., Luc Thomas, M.D., Ph.D., Igor Bondarenko, M.D., Ph.D., Steven O'Day, M.D., Jeffrey Weber M.D., Ph.D., Claus Garbe, M.D., Celeste Lebbe, M.D., Ph.D., Jean-François Baurain, M.D., Ph.D., Alessandro Testori, M.D., Jean-Jacques Grob, M.D., Neville Davidson, M.D., Jon Richards, M.D., Ph.D., Michele Maio, M.D., Ph.D., Axel Hauschild, M.D., Wilson H. Miller, Jr., M.D., Ph.D., Pere Gascon, M.D., Ph.D., Michal Lotem, M.D., Kaan Harmankaya, M.D., Ramy Ibrahim, M.D., Stephen Francis, M.Sc., Tai-Tsang Chen, Ph.D., Rachel Humphrey, M.D., Axel Hoos, M.D., Ph.D., and Jedd D. Wolchok, M.D., Ph.D.

This article (10.1056/NEJMoa1104621) was published on June 5, 2011, at NEJM.org.

Design

Screening	INDUCTION	MAINTENANCE *

Previously Untreated Metastatic Melanom (N=502

R

Ipilimumab 10 mg/kg Q3W X4

Dacarbazine 850 mg/m^2 Q3W x8

Ipilimumab 10 mg/kg Q12W

Survival Benefit: 2 Mo in Ipi+DTICArm
Despite higher dosage & maintainance

Q3W X4

Q12W

Dacarbazine 850 mg/m^2 Q3W x8

R = blinded randomization (1:1)

* in absence of progression or dose-limiting toxicity

Week 1 | Week 12 | Week 24

Baseline Tumor Assessment

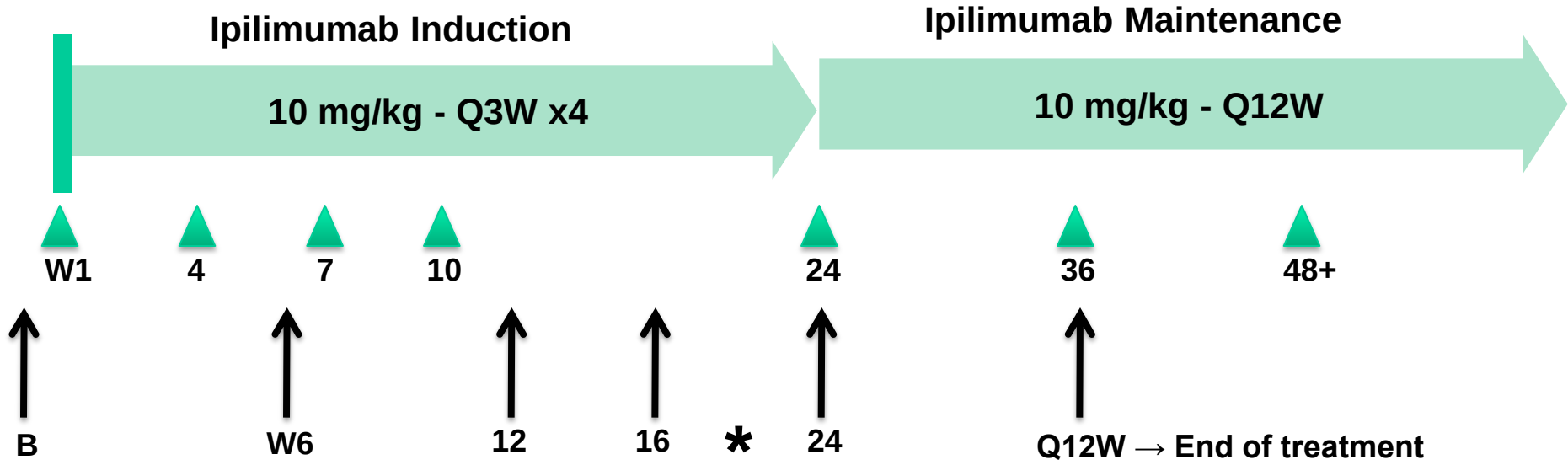
First Scheduled Tumor Assessment

STATISTICAL DESIGN: primary endpoint changed to OS

Ipilimumab in Brainmetastases of Melanoma Patients

Lancet Oncol. 2012 May;13(5):459-65. Epub 2012 Mar 27.

Methods: treatment and assessment



Single arm trial

- Cohort A (n=51): patients not requiring steroids
- Cohort B (n=21): patients requiring steroids

Efficacy endpoints

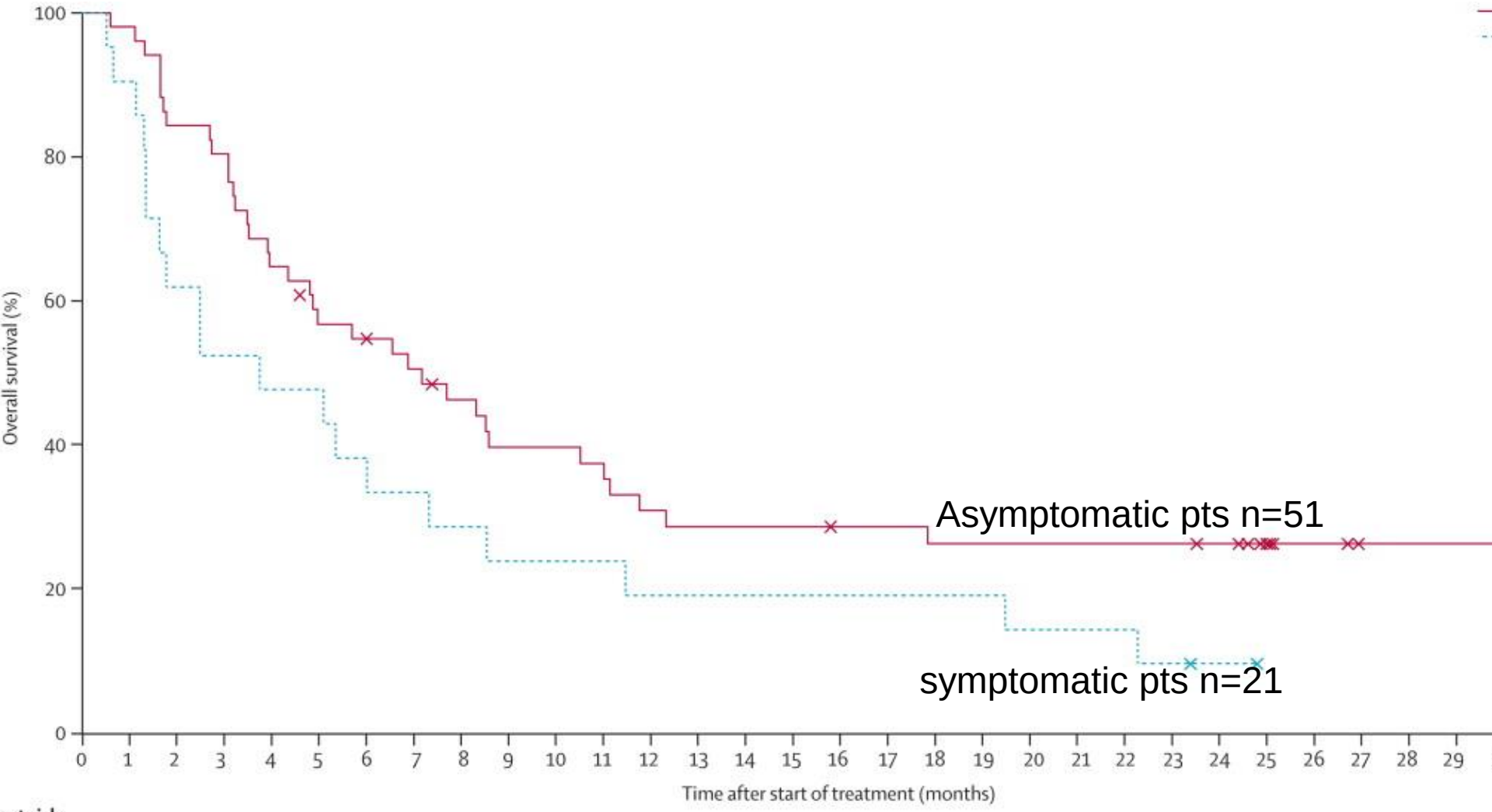
- Best overall response rate
- Survival

* An additional W 20 brain assessment was required in CA184-042

B = baseline ▲ = ipilimumab dosing ↑ = tumour assessment (brain, extracranial)

Ipilimumab in Brainmetastases of Melanoma Patients

Lancet Oncol. 2012 May;13(5):459-65. Epub 2012 Mar 27.



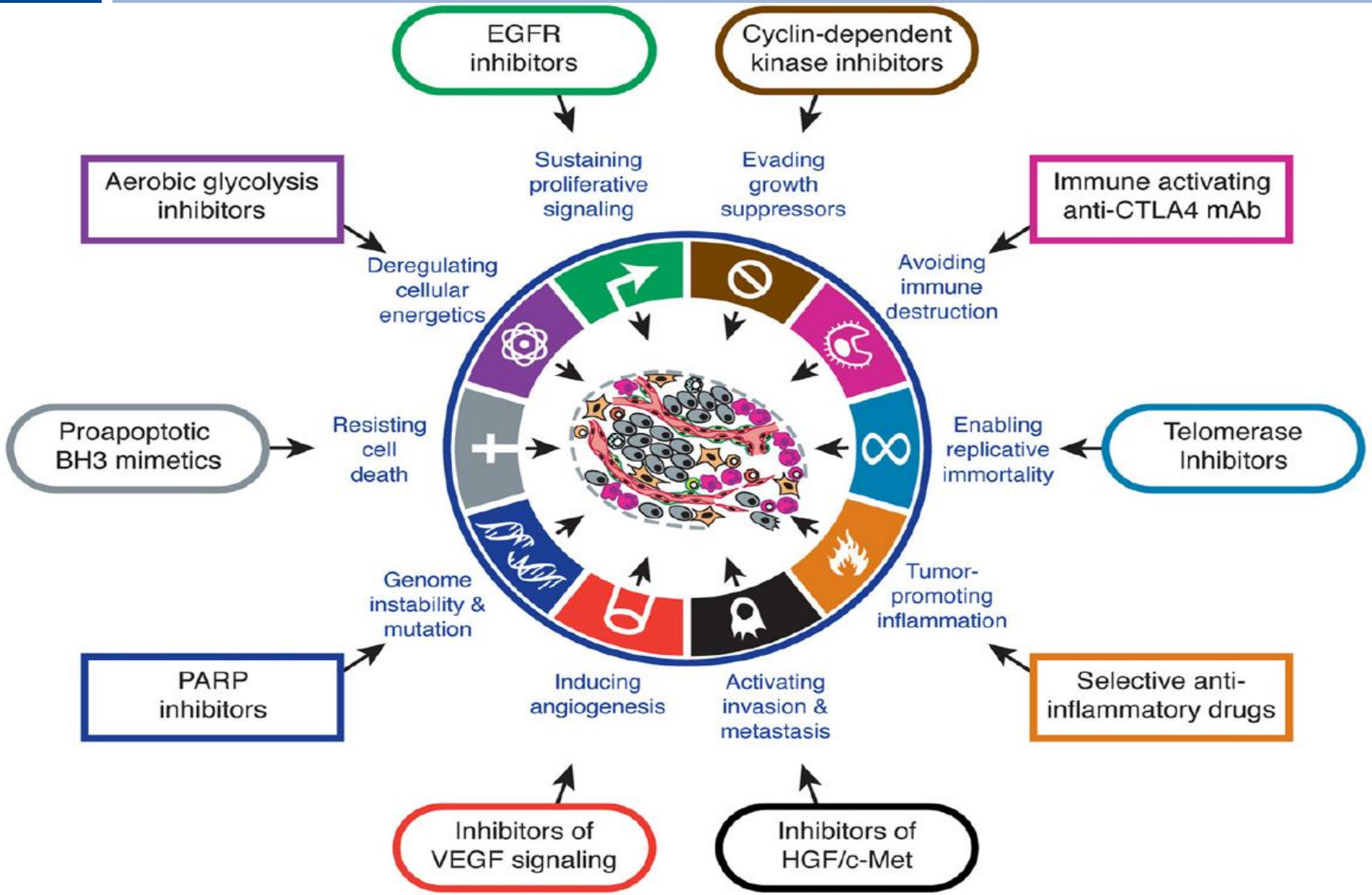
r at risk

ohort A	51	49	43	38	33	28	27	23	21	18	18	15	14	13	13	13	12	12	11	11	11	11	11	11	10	7	4	2	2	2
ohort B	21	19	13	11	10	10	8	7	6	5	5	5	4	4	4	4	4	4	4	4	3	3	3	2	1	0	0	0	0	0

Conclusions

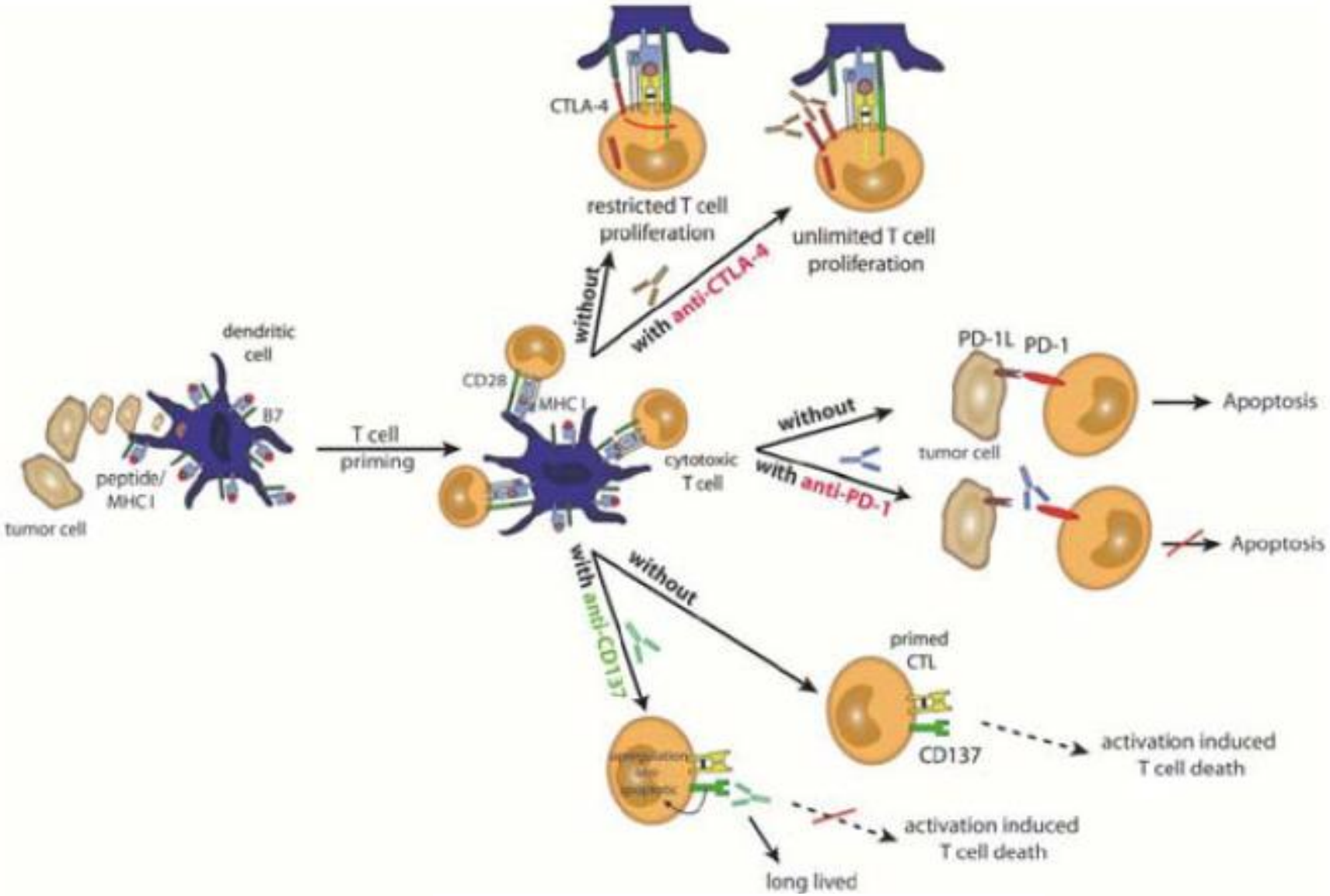
- **Clinical activity of ipilimumab (10mg/kg)**
  - Nearly doubles 1- and 2-year survival rates vs the comparator
  - Prolonged survival: 26% alive at 2 years
  - Clinical activity is evident in patients with metastatic melanoma and brain metastases
  - Response rate in CNS of **13.0 %**
- **Safety**
  - Similar safety profile as in patients without brain metastases
  - No unique toxicities or increase in CNS toxicities

Overview: Therapeutic Approches



Douglas Hanahan and Robert A. Weinberg, Cell 2011; DOI 10.1016/j.cell.2011.02.013 March 4: 646-674

Modulation of Cellular Immune Response



Schrama & Becker, Nat Rev Drug Discov. 2006 Feb;5(2):147-59

VOLUME 28 · NUMBER 19 · JULY 1 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase I Study of Single-Agent Anti–Programmed Death-1 (MDX-1106) in Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates

Julie R. Brahmer, Charles G. Drake, Ira Wollner, John D. Powderly, Joel Picus, William H. Sharfman, Elizabeth Stankevich, Alice Pons, Theresa M. Salay, Tracee L. McMiller, Marta M. Gilson, Changyu Wang, Mark Selby, Janis M. Taube, Robert Anders, Lieping Chen, Alan J. Korman, Drew M. Pardoll, Israel Lowy, and Suzanne L. Topalian

Merck	MK-3475 (SCH 900475)	PD-1 blockade	Phase I
Bristol-Myers Squibb	BMS-936559 (MDX-1105-01)	PD-L1 (B7-H1) blockade	Phase I
Tolerx	TRX518	GITR activation	Phase I on temporary hold
Pfizer	CP-870893	CD40 activation	Phase I in pancreatic cancer and melanoma
Portland Providence Medical Center	Agonist anti-OX40	OX40 activation	Phase Ib in prostate cancer

Garber JNCI Vol. 103, Issue 14 | July 20, 2011

Anti – PD-1 (BMS-936558)

Suzanne Topalian

This article (10.1056/NEJMoa1200690) was published on June 2, 2012, at NEJM.org.

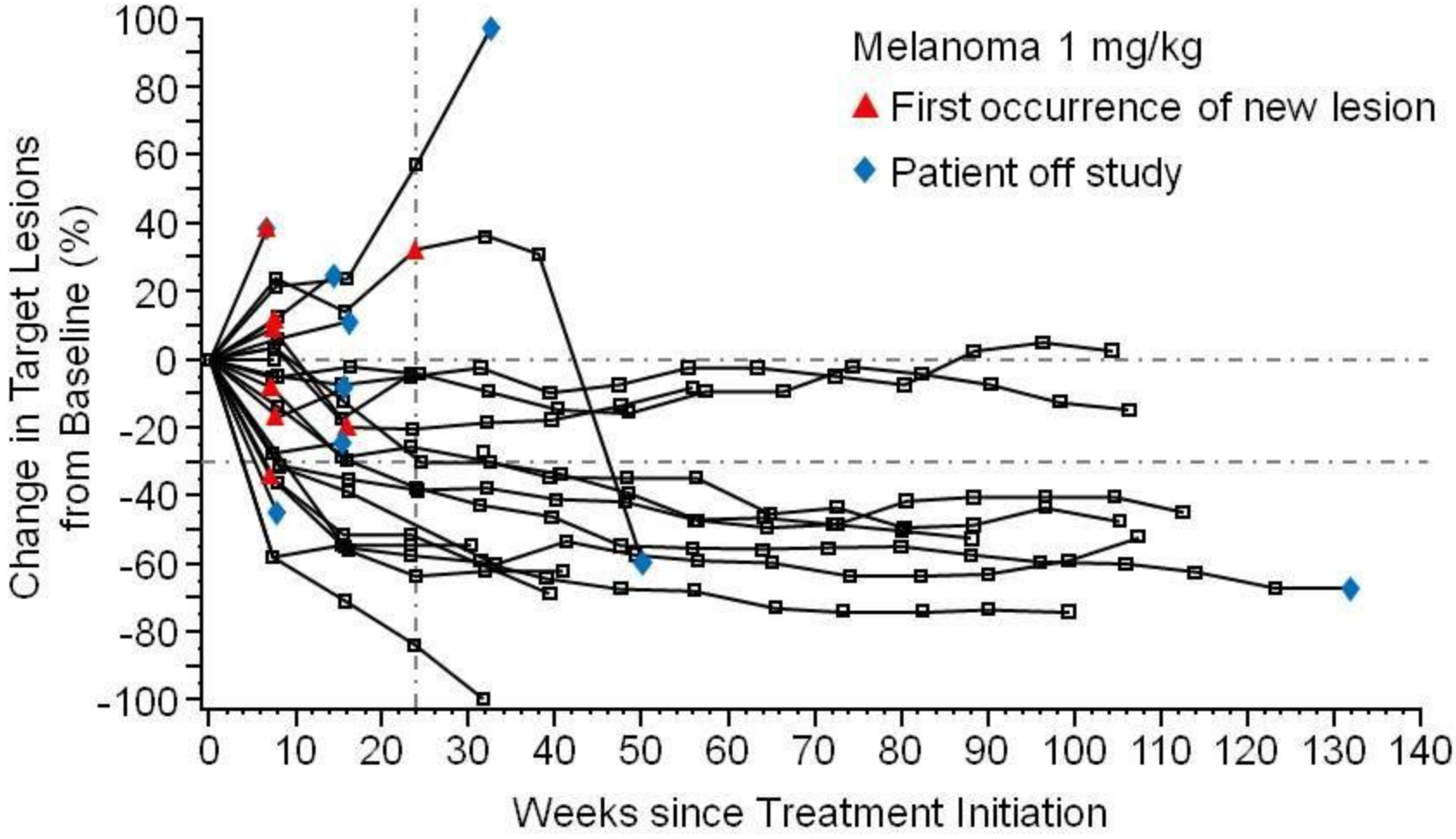
296 Patients with Metastatic Cancer
1, 3, 10 mg/kg, MTD not reached

Safety: Adverse events similar to Ipilimumab, but 4% pneuomonitis (3 deaths)

Clinical Activity:

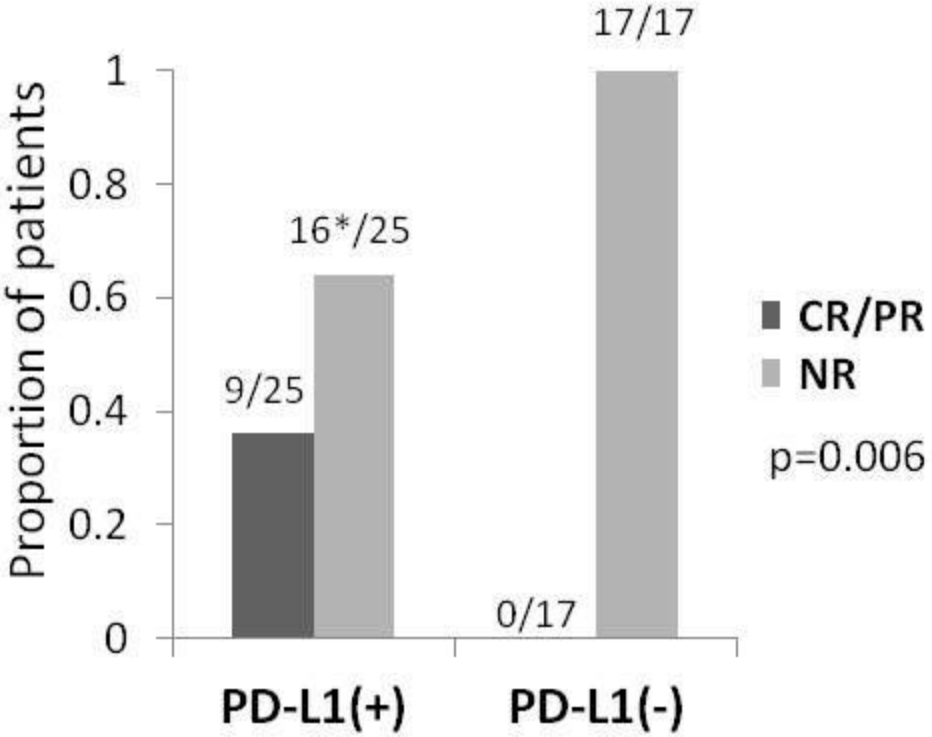
- Melamona (n= 94): 28% CR/PR, 6% SD
- NSCLC (n=76): 18% CR/PR, 7% SD
- RCC (n= 33): 27% CR/PR, 27% SD
- CRC (n=19), CRPC (n=13): No responses

Response kinetics in patients treated with BMS-936558



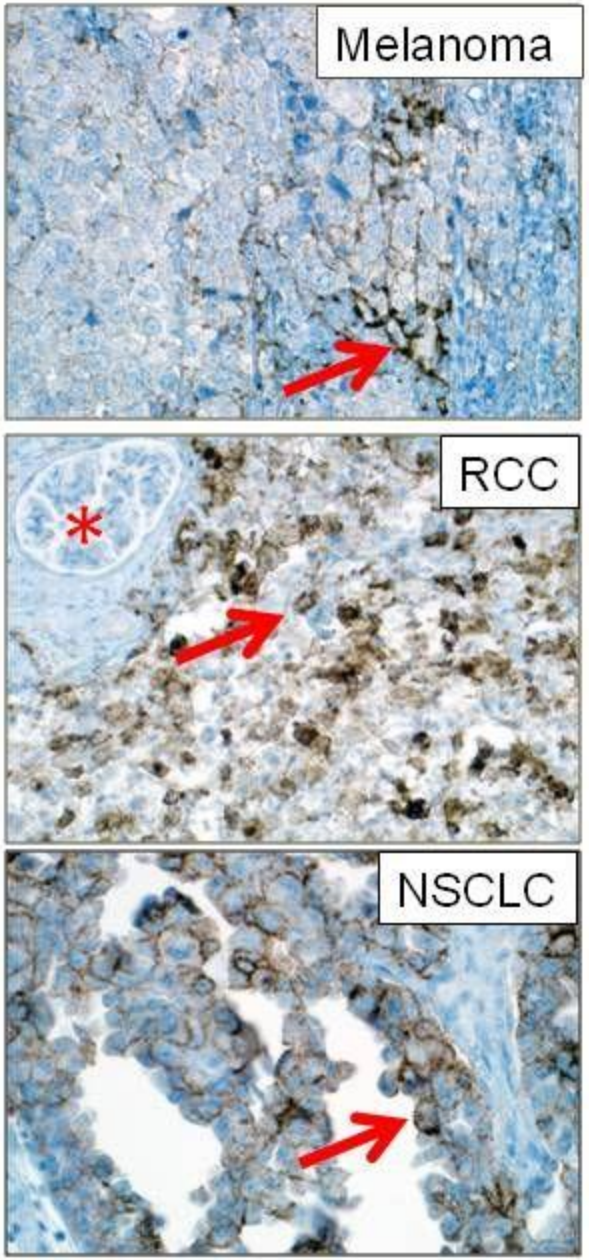
This article (10.1056/NEJMoa1200690) was published on June 2, 2012, at NEJM.org.

Correlation of PD-L1 expression in pretreatment tumor biopsies with clinical outcomes



42 pts include 18 MEL, 10 NSCLC, 7 CRC, 5 RCC, and 2 CRPC.

**2 pts still under evaluation*



This article (10.1056/NEJMoa1200690) was published on June 2, 2012, at NEJM.org.

Anti – PD-1 (MK3475)

Amita Patnaik

17 Patients with Metastatic Cancer
1, 3, 10 mg/kg

Safety: No grade 3 or 4 AE

Clinical Activity:

Melamona (n=3): 2 PR, 1 SD
NSCLC (n=2): 1 SD

Anti – PD-L1 (BMS-936559)

Scott Tykodi

Metastatic Cancer
1, 3, 10 mg/kg

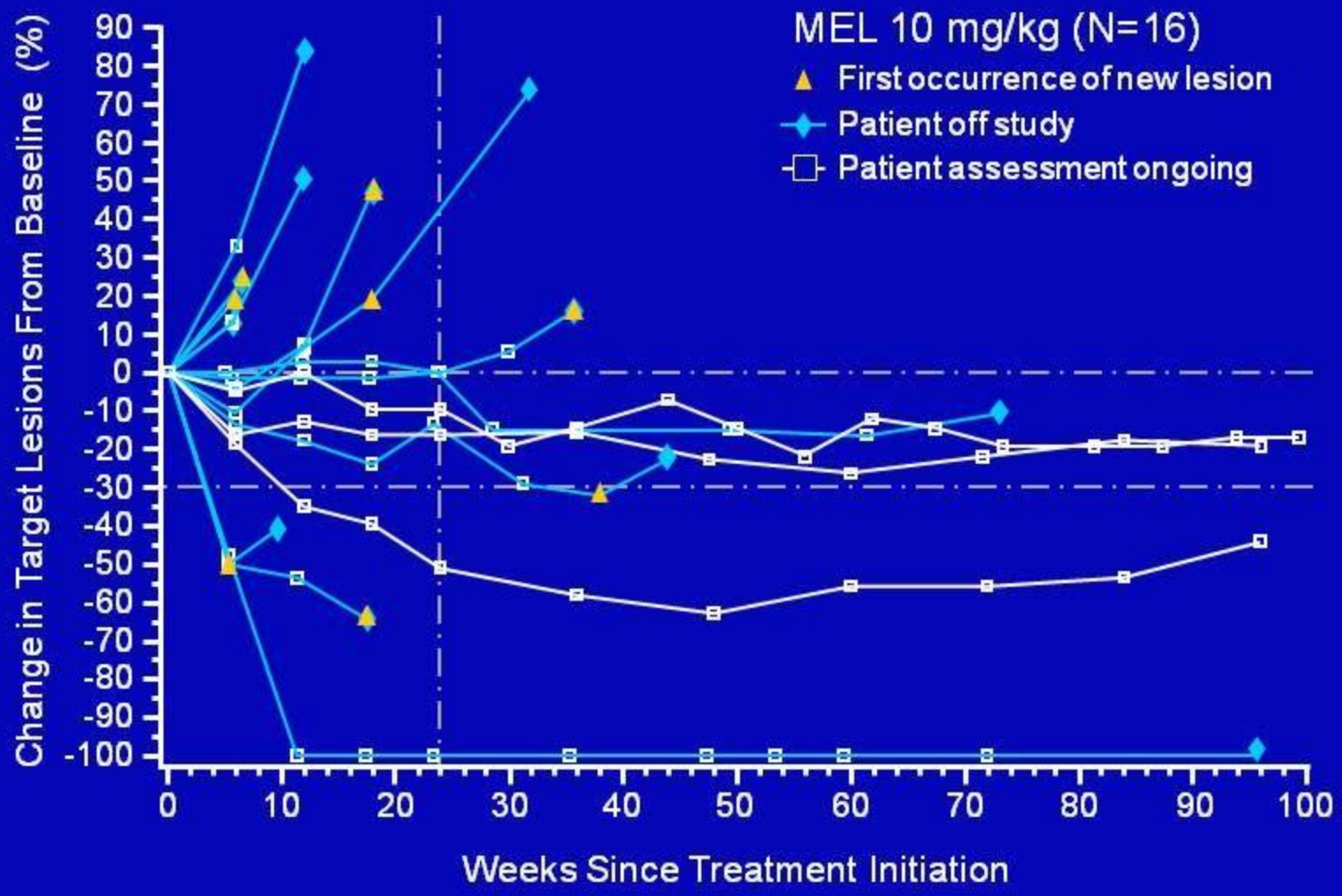
Safety (n=207): 9% Grade 3/4, No deaths

Clinical Activity (n=160):

- Melamona (n=52): 17% OR
- RCC (n=17): 12% OR
- NSCLC (n=49): 10% OR
- Ovarian (N=17): 6%

This article (10.1056/NEJMoa1200694) was published on June 2, 2012, at NEJM.org.

Change in Target Lesions Over Time for Melanoma Patients



PD-1/PD-L1 Experience to Date

- Effective in many advanced cancers
- Spectrum of responsive tumors may be different from anti-CTLA-4
- Well tolerated

- Questions:
  - Is efficacy restricted to tumors expressing PD-L1?
  - How durable are responses?
  - What combinations can be used to increase efficacy?

Combinations to Increase Efficacy of Immune Checkpoint Blockade

- Vaccines
- Blockade of Additional Immune Checkpoints
- Conventional Therapies
- Targeted Therapies
- Stimulation of Additional Costimulatory Pathways

CD137 (41BB), OX40, ICOS

Adjusted Goals of Cancer Treatment

Adult Solid Tumors

- Cancer Containment versus Cancer Eradication
- Focus on novel immuno-modulation through critical targets for immune-directed cancer therapy
  - Immune checkpoint blockade
- Immunotherapy Outcomes
  - Lower traditional response rates
  - High quality of responses
  - Disproportional greater effect on OS
  - Long Term OS > Median OS

Today We Should Aim for Improving Long-term Survival in Advanced Melanoma

- Treatment goals in advanced melanoma
  - What are we trying to do?

- "Clinical cure" but not necessarily a "biological cure"
  - The role of cancer cell directed therapy?
  - The role of immune directed cancer therapy?
  - Cancer containment versus cancer eradication?
  - What is long-term survival?
  - How do we get there?

Summary & Conclusion

- Conclusions can only be drawn from clinical phase III studies!

  - Whole tumor cell vaccines should be considered with care

  - Ganglioside vaccine seems to be disadventageous

- No results of phase III available for peptide and protein vaccines
- **Induce more and better T cells by exploiting DC biology, adjuvants etc**

- **Check point control** mediates OS benefit and clinical responses

- **Biomarkers** to identify responsive patients

- **Block escape and suppressive mechanisms** (combination therapy)

Thank you for your attention

DKG KREBSGESELLSCHAFT | Zertifiziertes Hautkrebszentrum

TÜV SÜD ISO 9001

Hauttumorzentrum Essen