UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

HUG
Hôpitaux Universitaires de Genève

Traitement du mélanome : enfin des bonnes nouvelles !

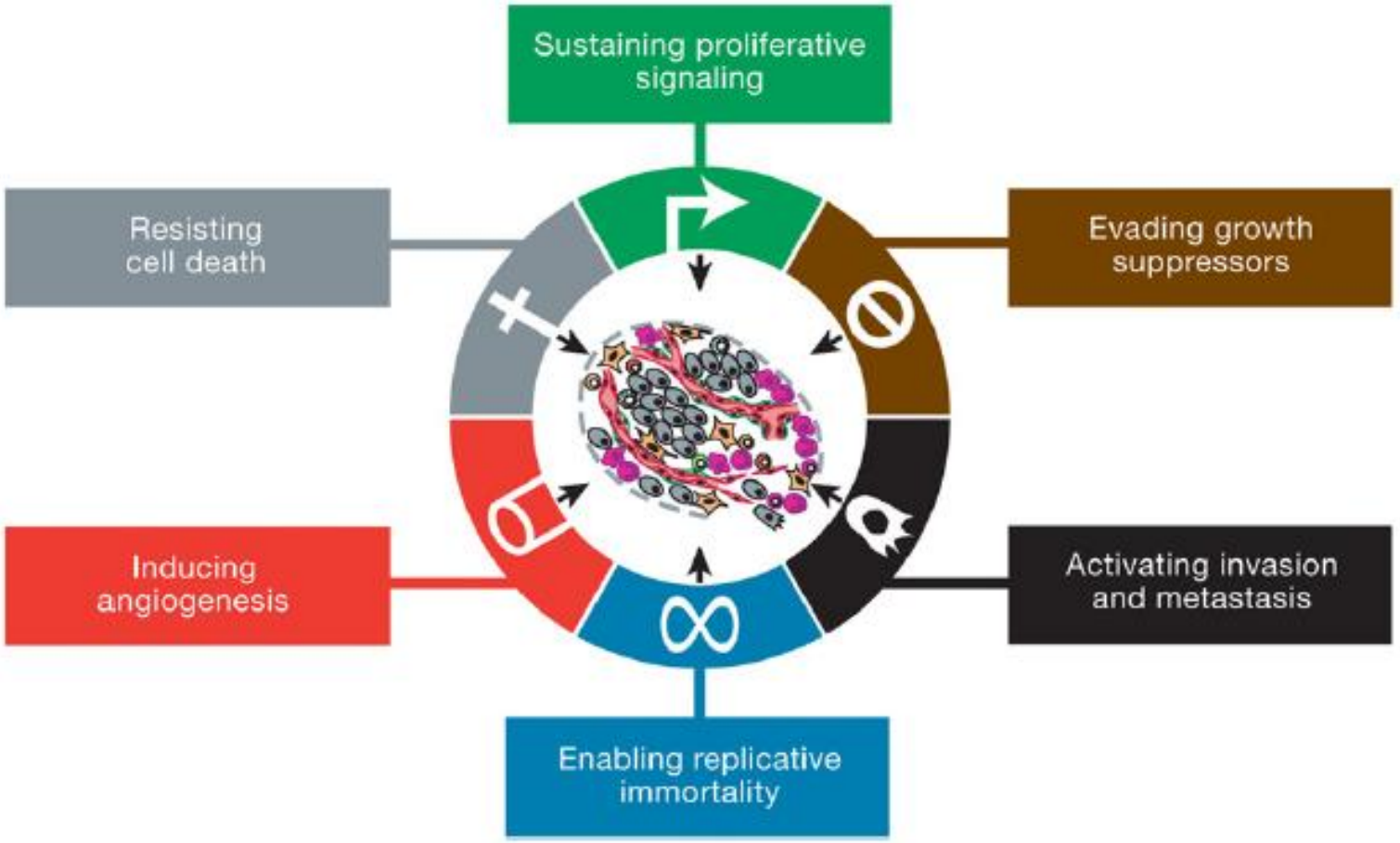
Genève, oct 2014

PY Dietrich

From new biological concepts

to new treatment opportunities

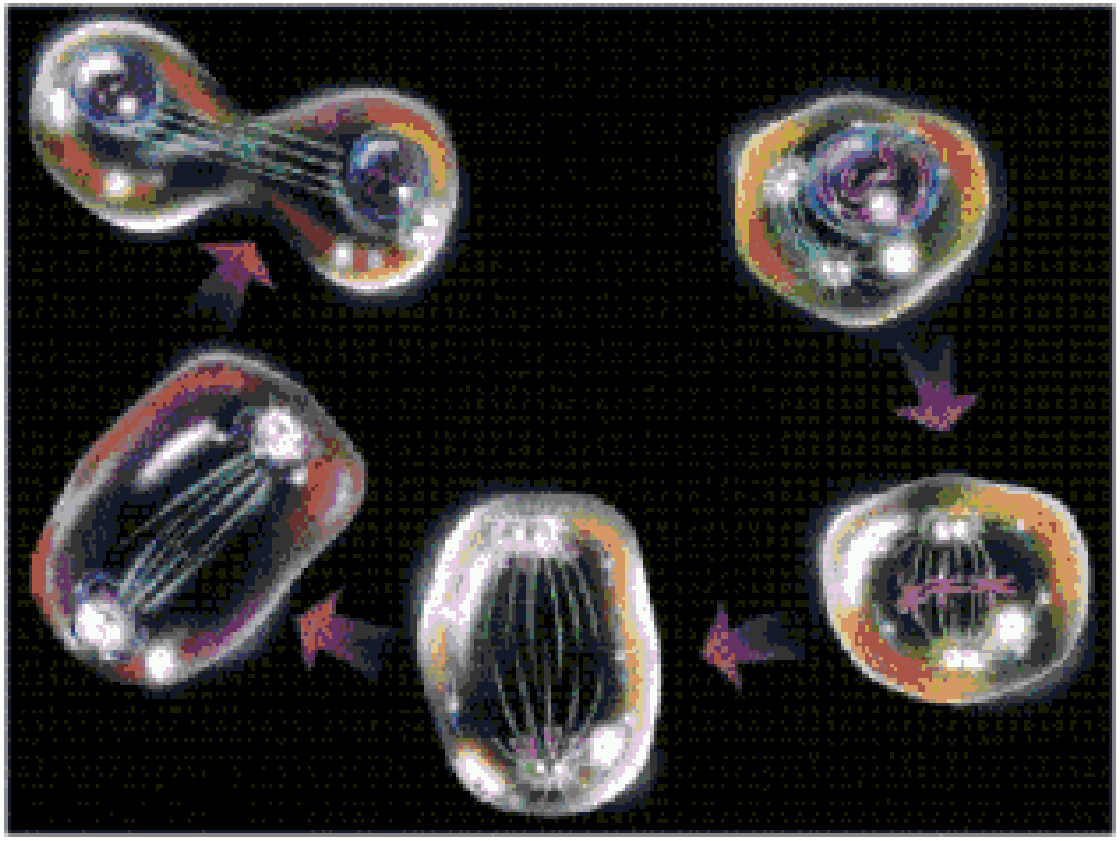
Cancer = cell autonomous disease



Hallmarks of Cancer: Cell 2001

Douglas Hanahan , Robert A. Weinberg

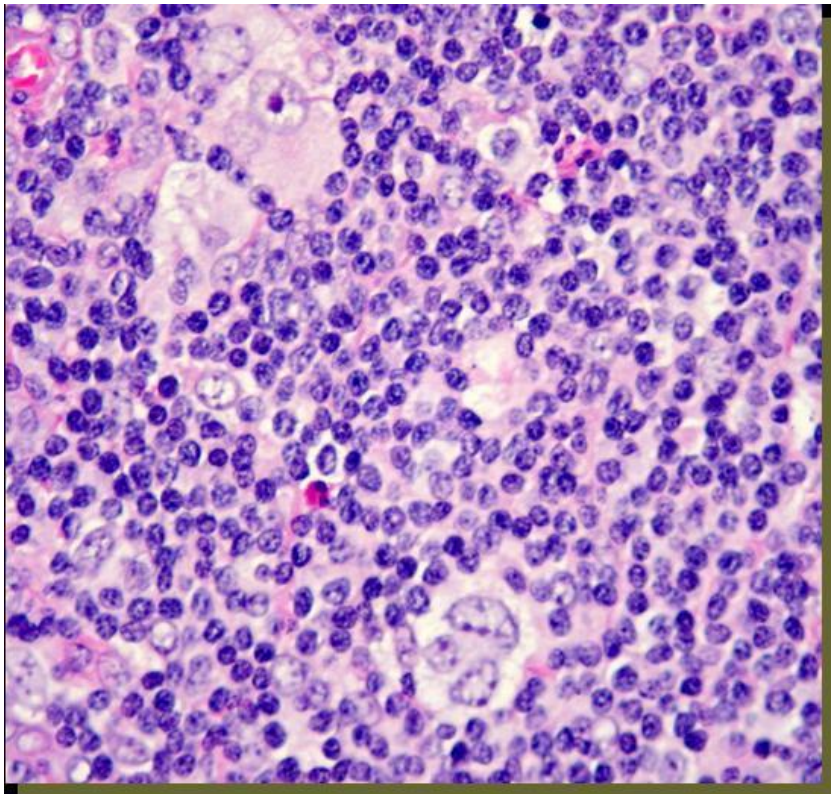
Conventional chemotherapy targeting dividing cells



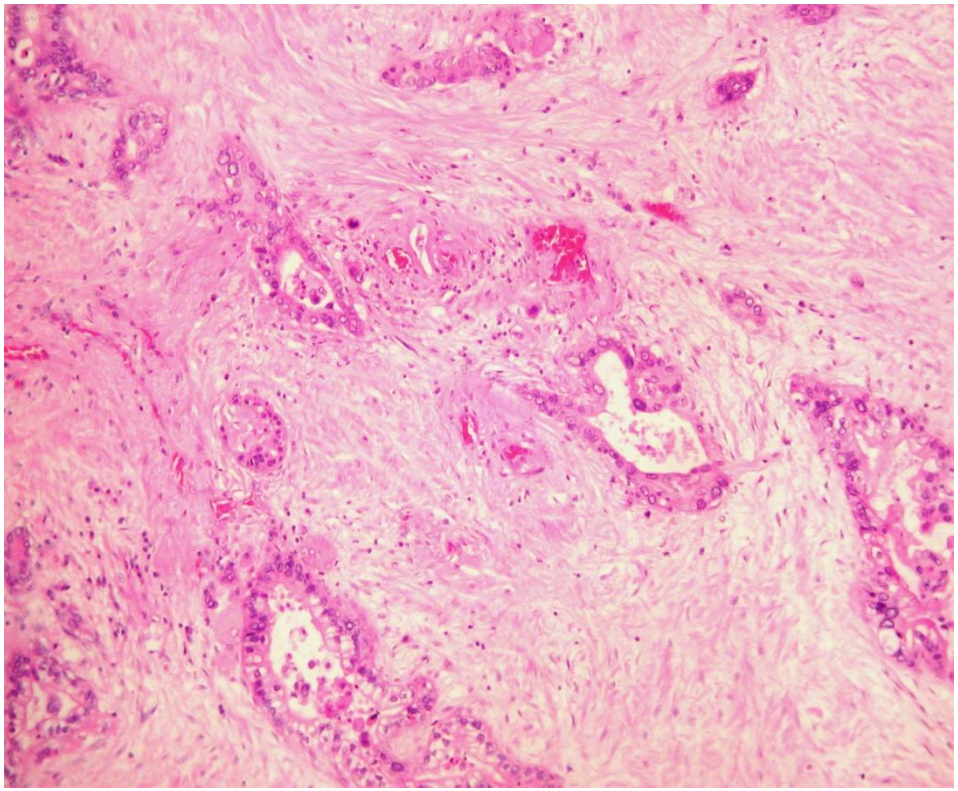
But normal cells also divide → severe side effects

The role of the tumor microenvironment

Hodgkin's lymphoma

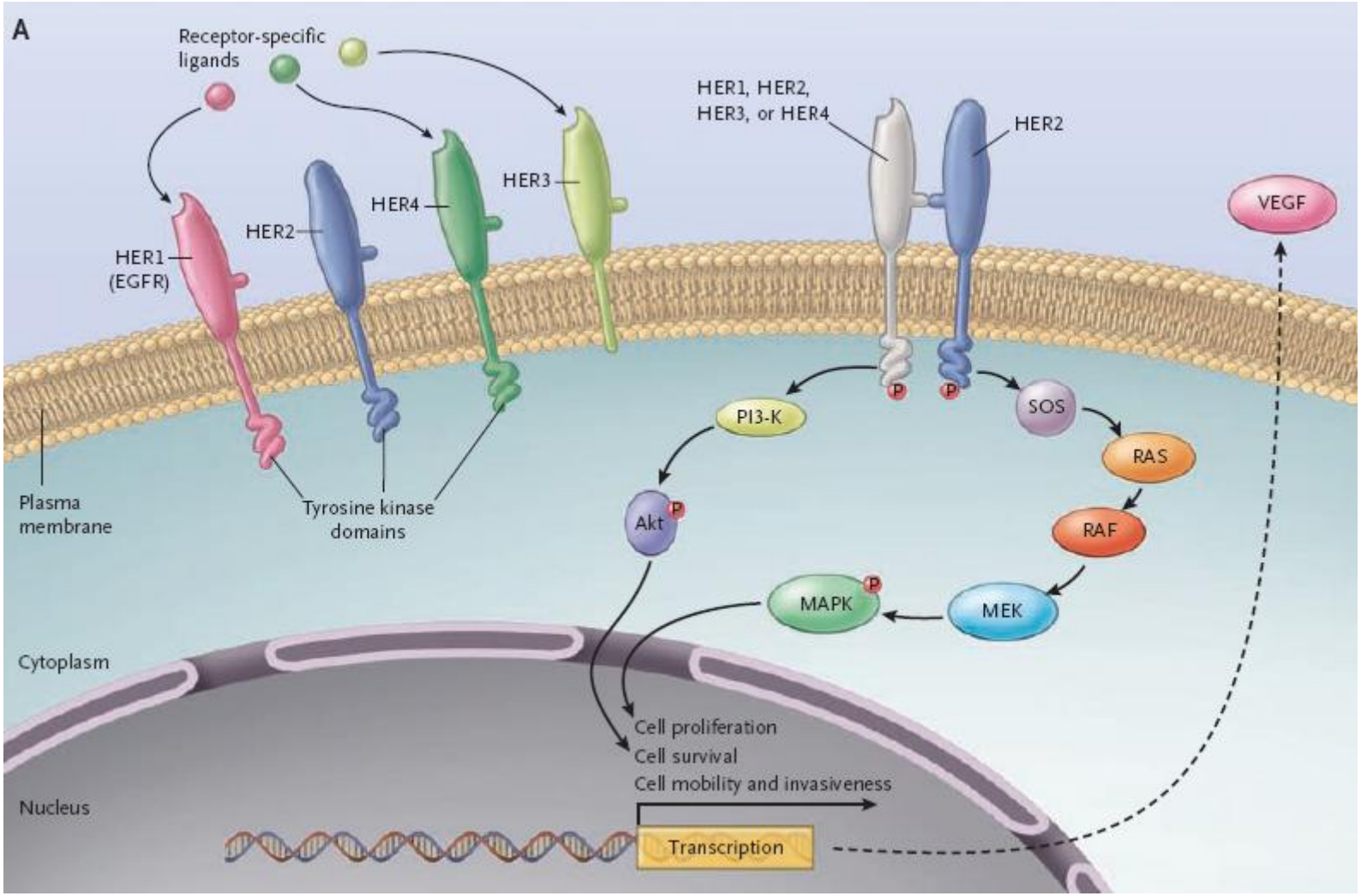


Pancreatic cancer



Courtesy Dr T Mckee and M Genevay

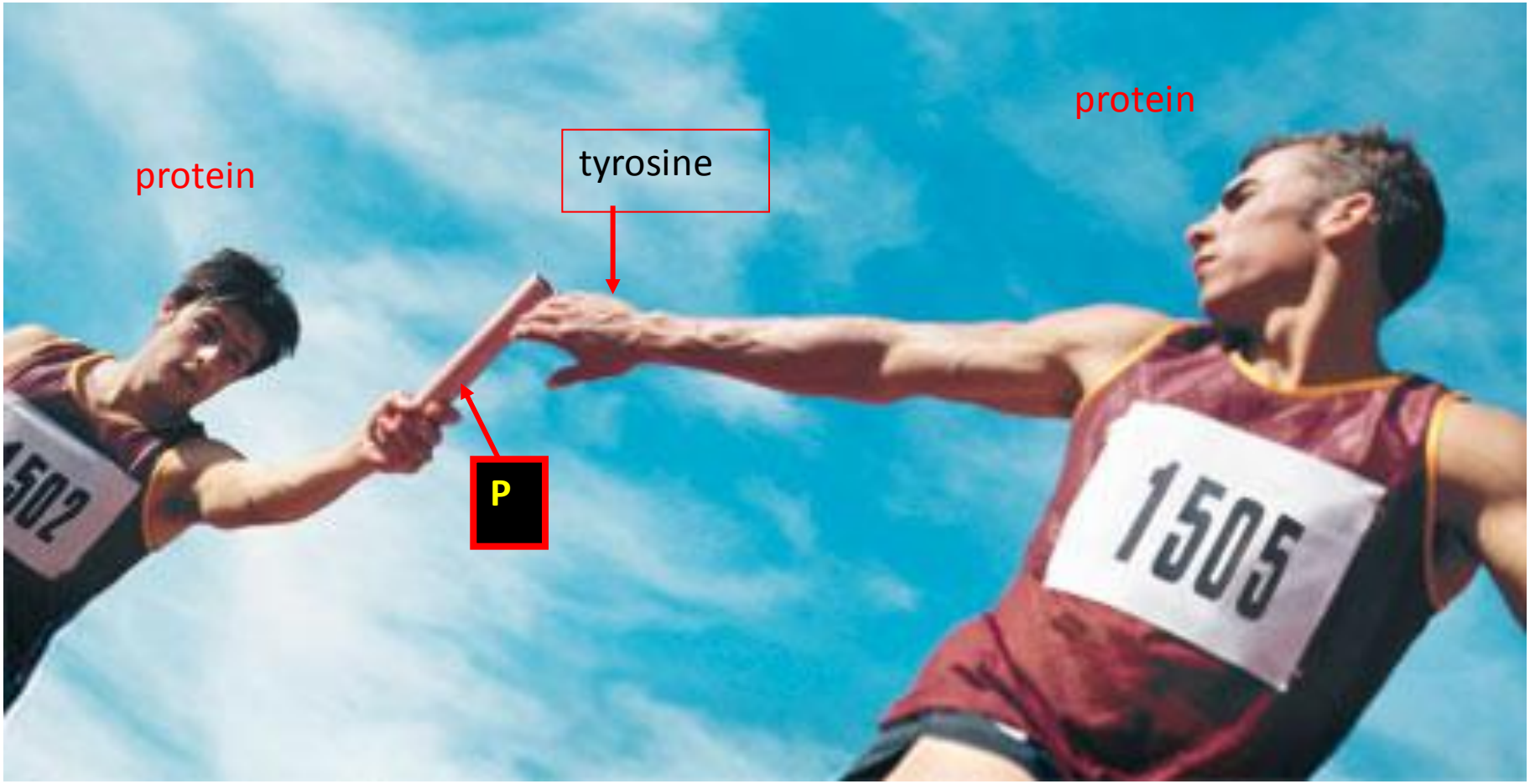
The tumor micro-environnement



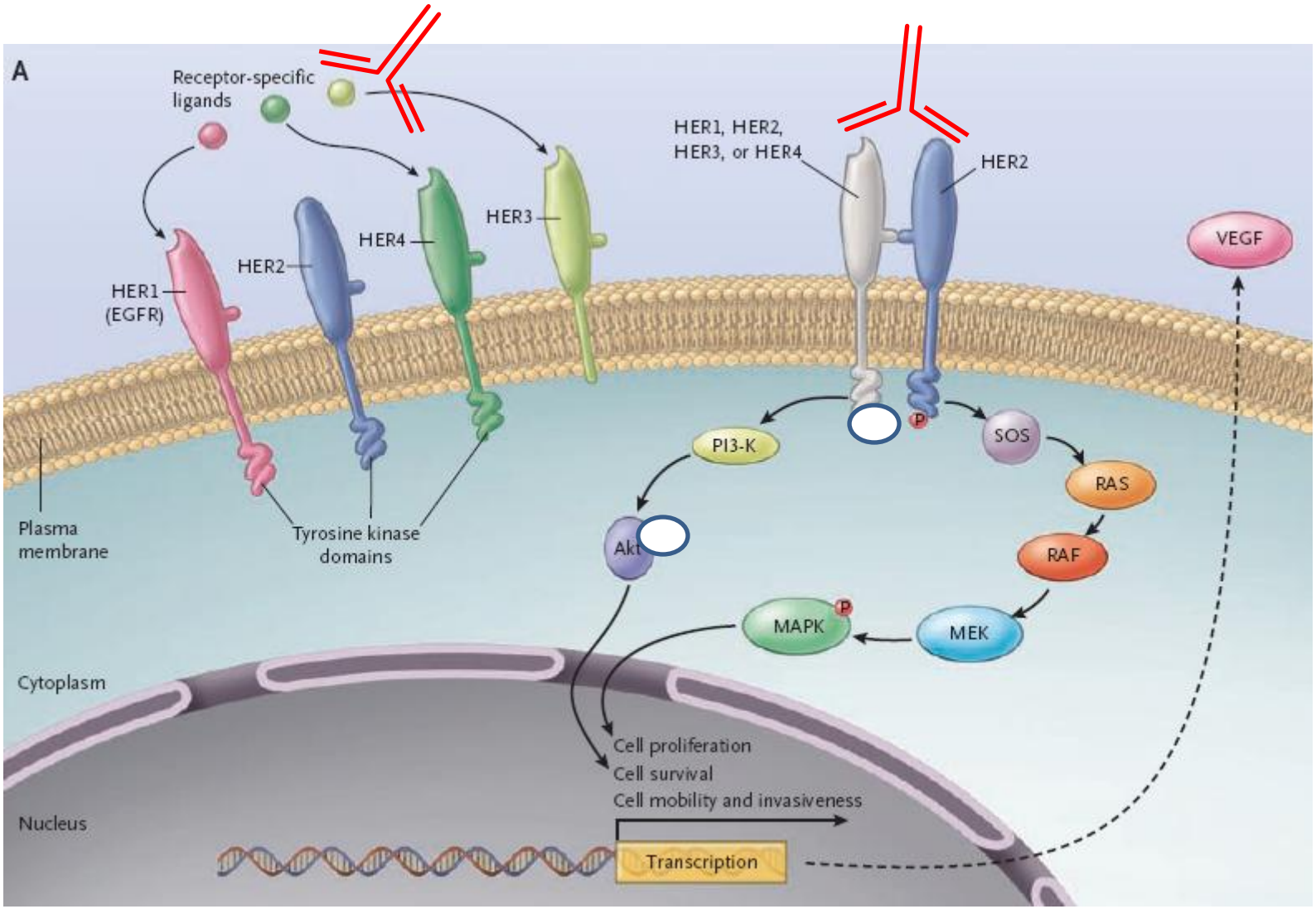
The intracellular signaling pathways

NEJ Med 2007;357: 39

Signal transduction via Tyrosine or serine/threonine kinases



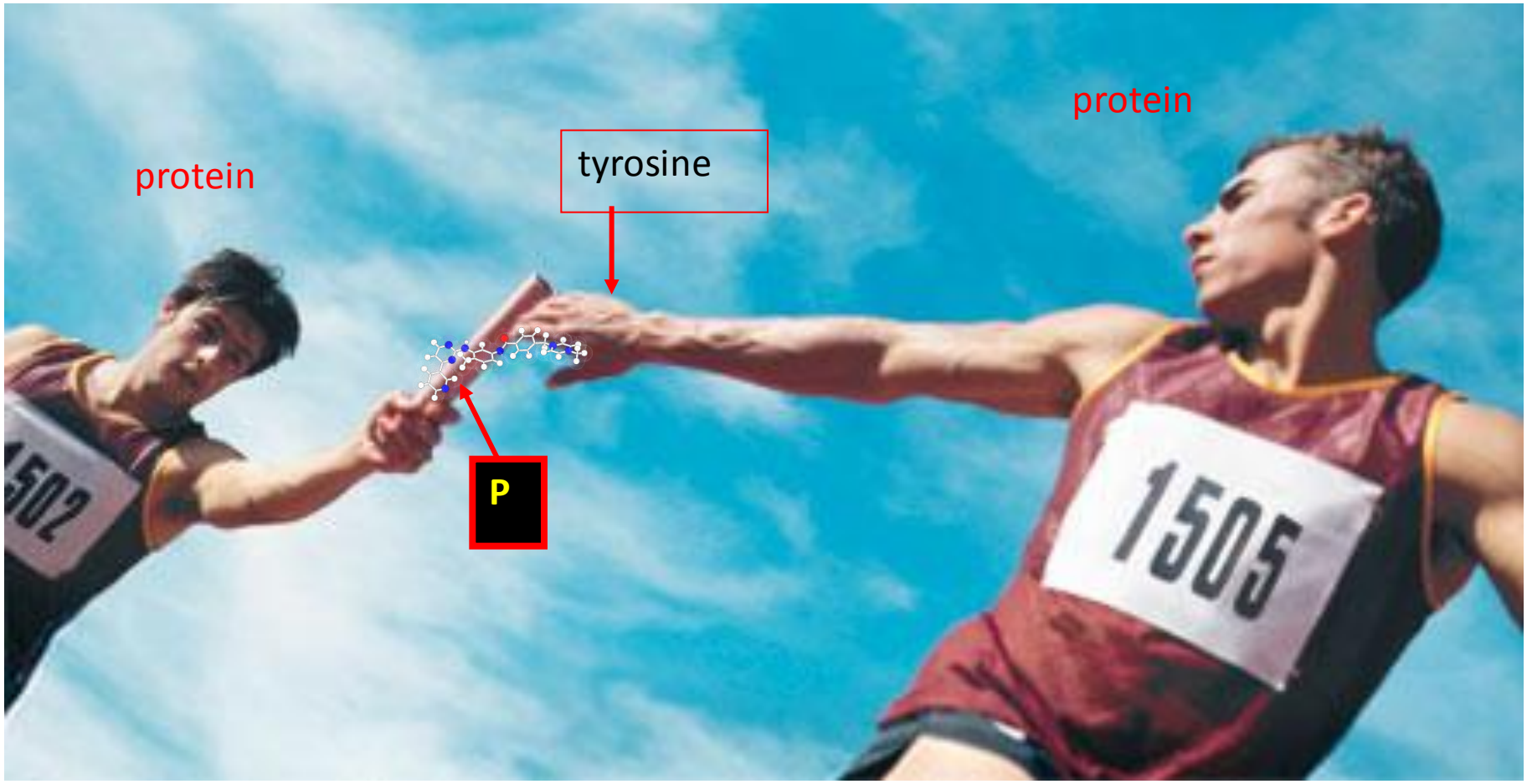
Outside : mAbs



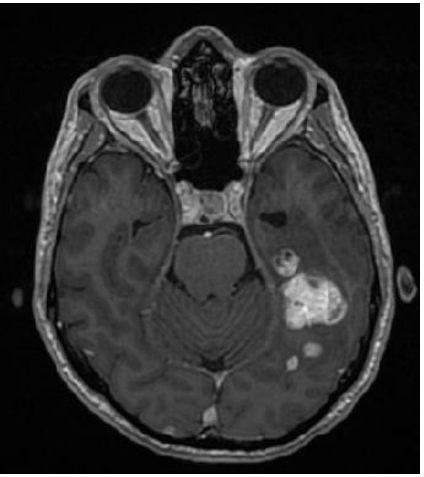
Inside : Tyrosine or serine threonine kinase inhibitors

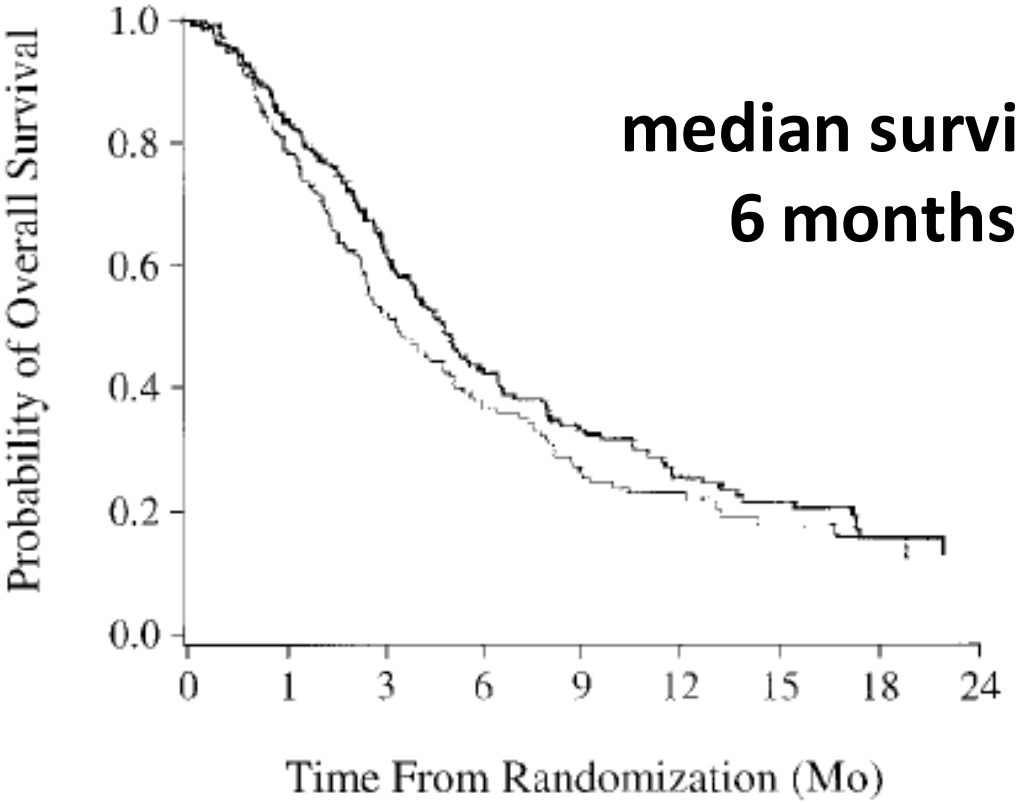
NEJ Med 2007;357: 39

Tyrosine and serine/threonine kinase inhibitors

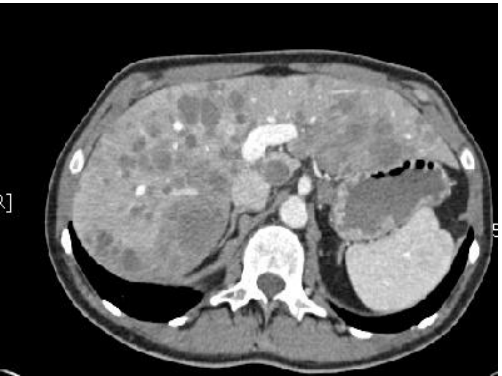


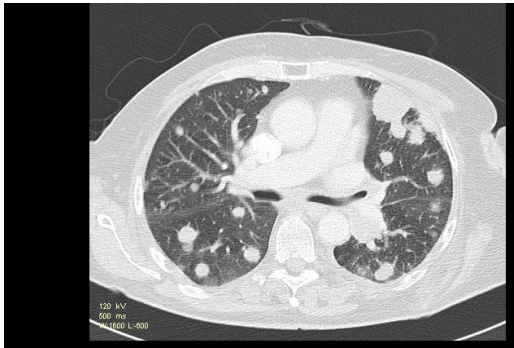
Metastatic melanoma in 2010



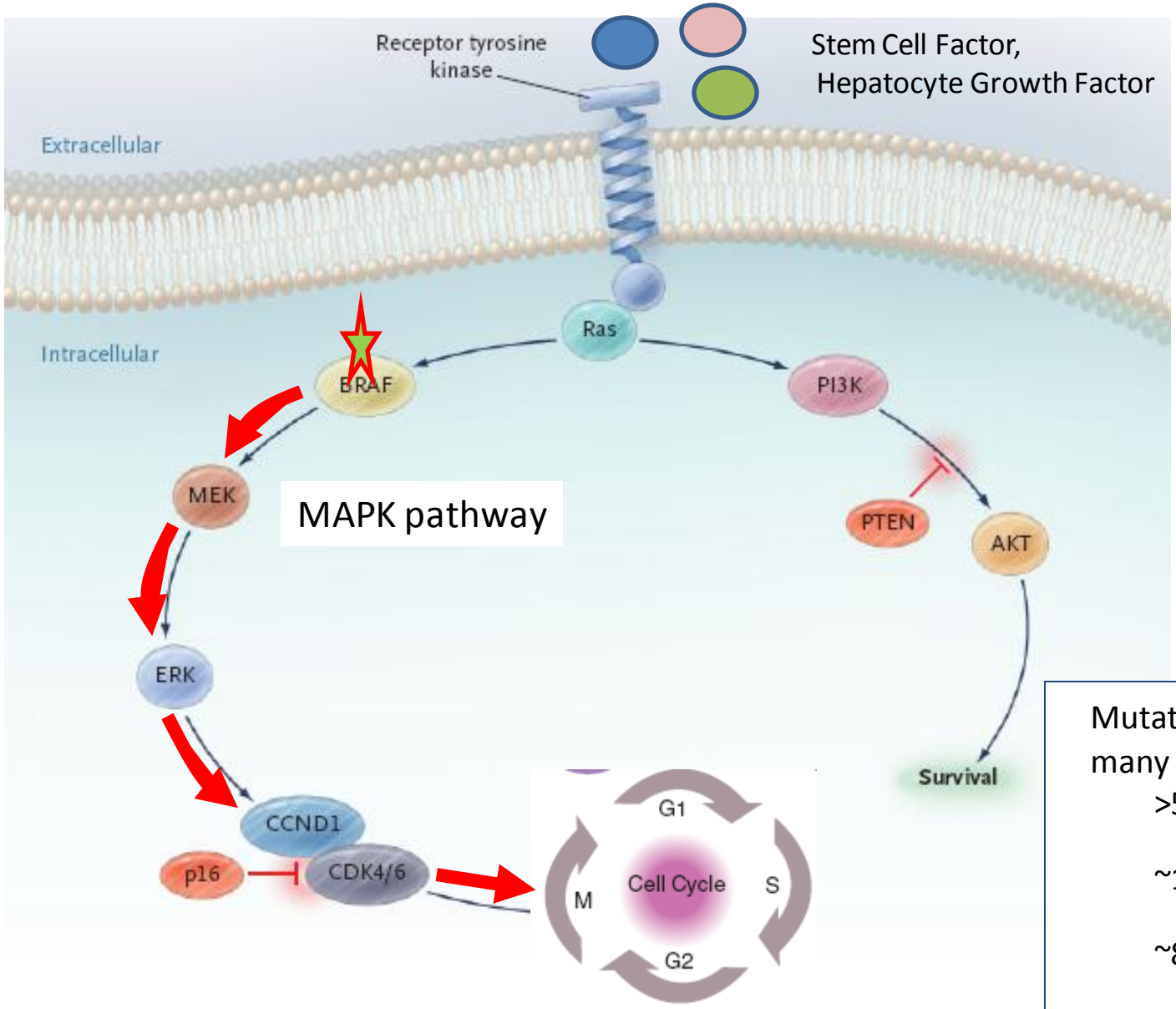


median survival
6 months





For melanoma ?

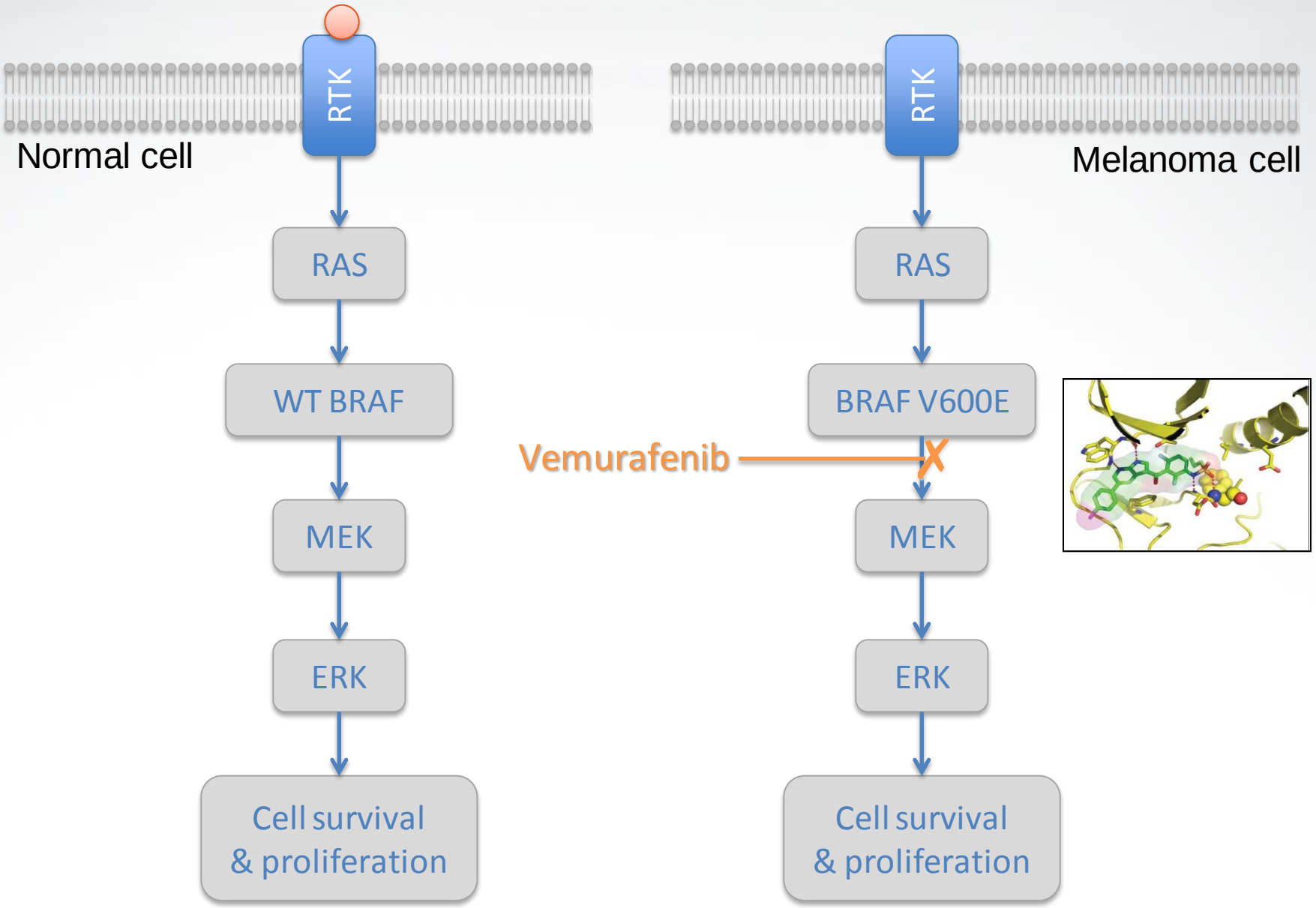


Mutated BRAF is present in many cancers:

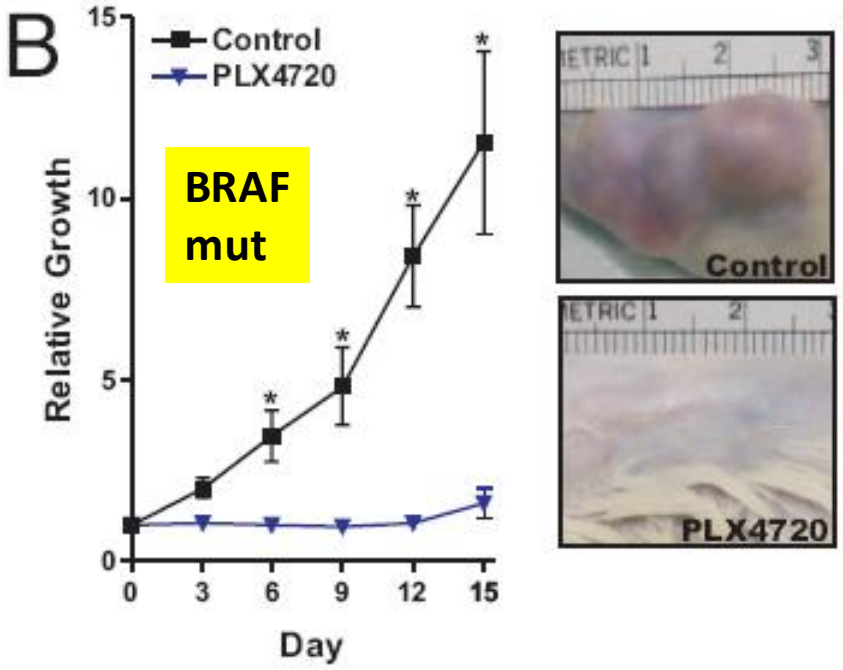
- >50% melanomas
- ~10% colorectal
- ~8% all solid tumors

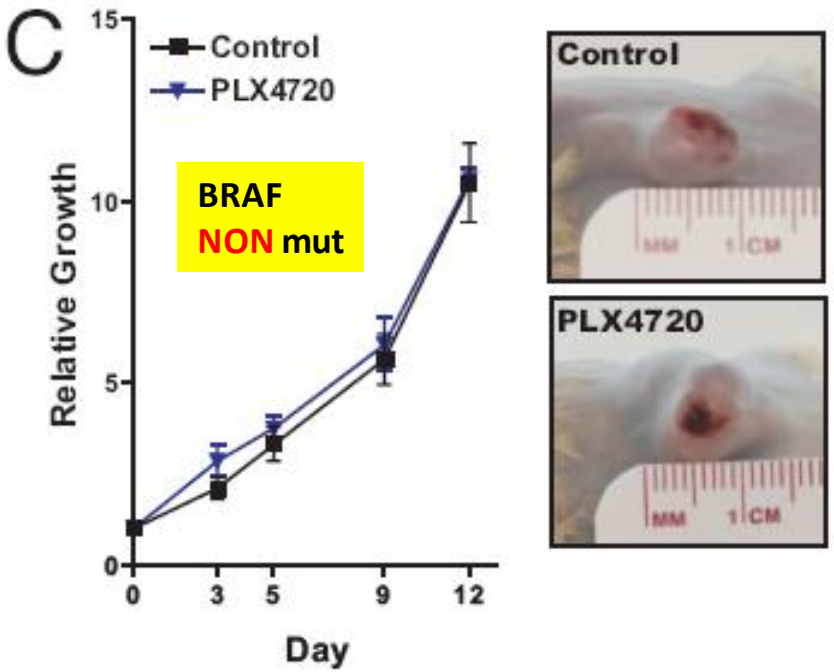
Adapted from JID 2010; 130: 28 and NEJMed 2005; 353: 2135

WT and V600E BRAF signaling:



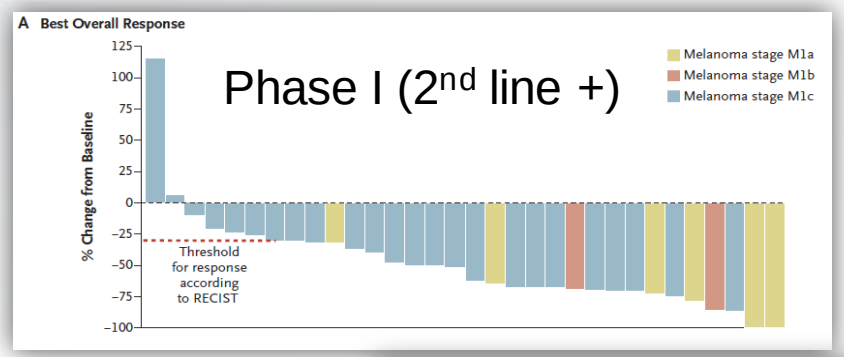
Selective anti-tumor effect : BRAF V600E

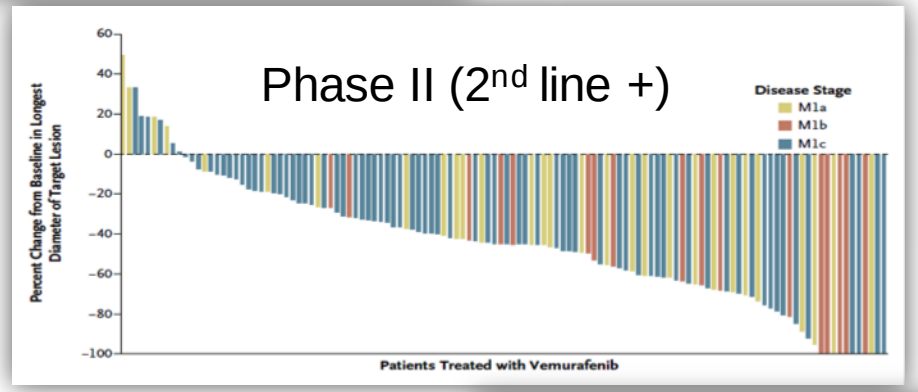


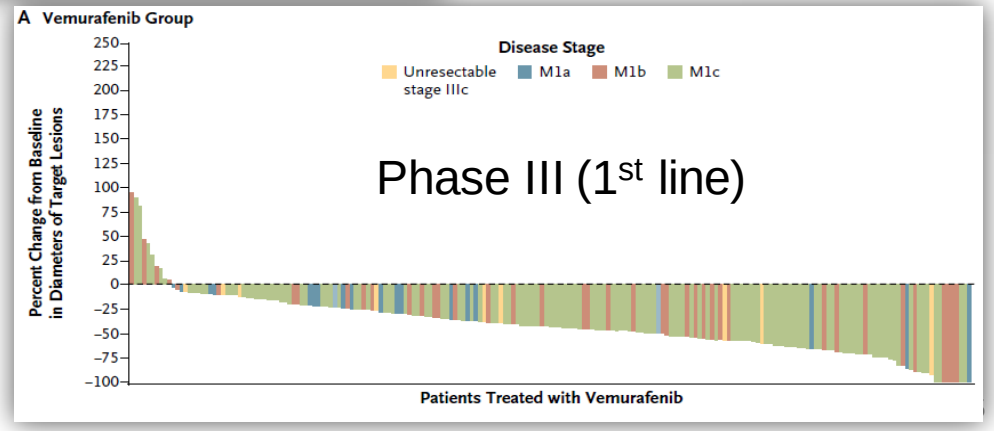


Tsai J et al. PNAS 2008 105 3041

Role of Vemurafenib: Phase I-III Waterfall Plots



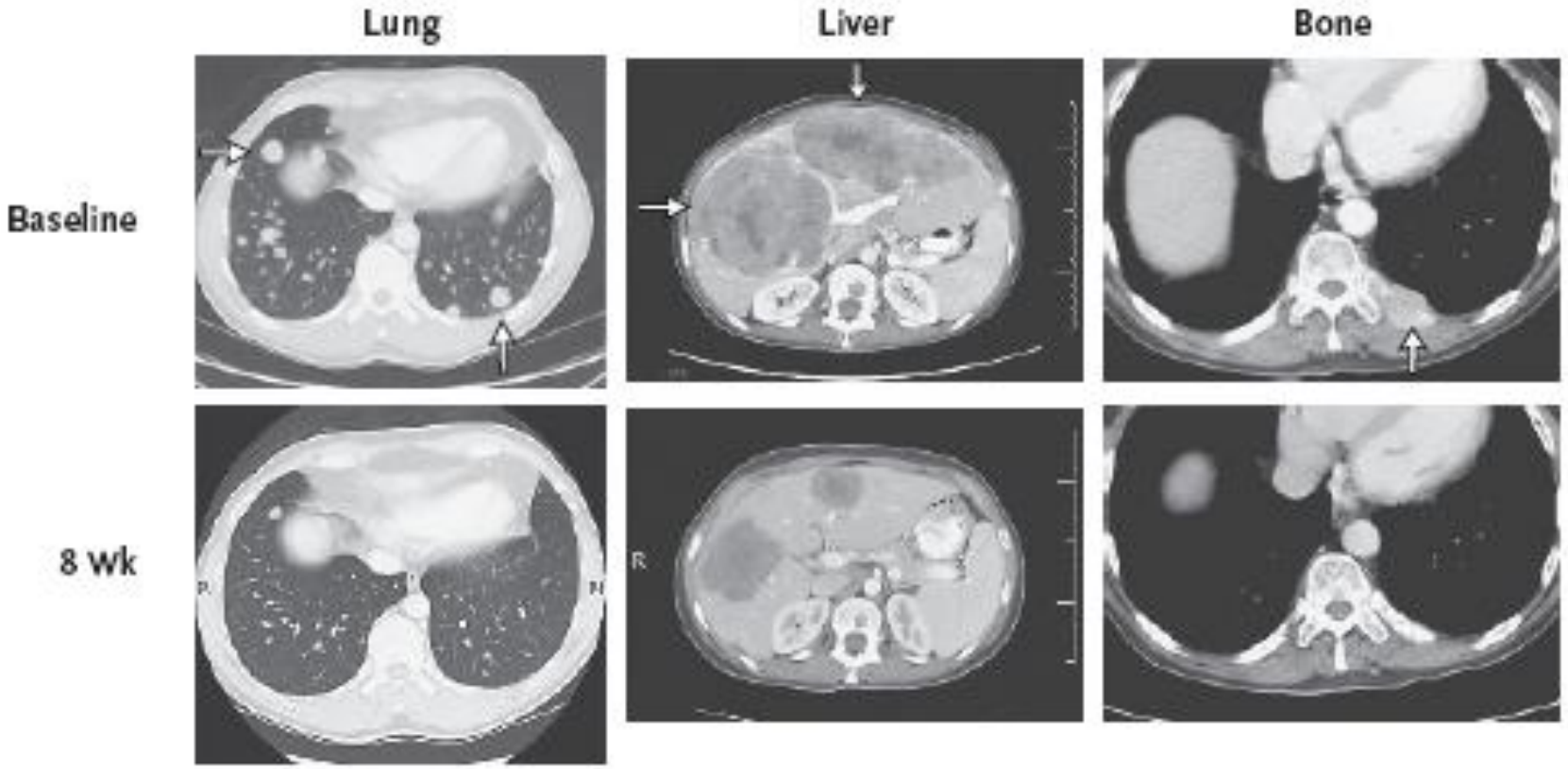




Sosman et al.: 2012, N Engl J Med; 366:707-14
Chapman et al.: 2011, N Engl J Med; 364:2507-16
Flaherty et al.: 2010, N Engl J Med; 363:809-819

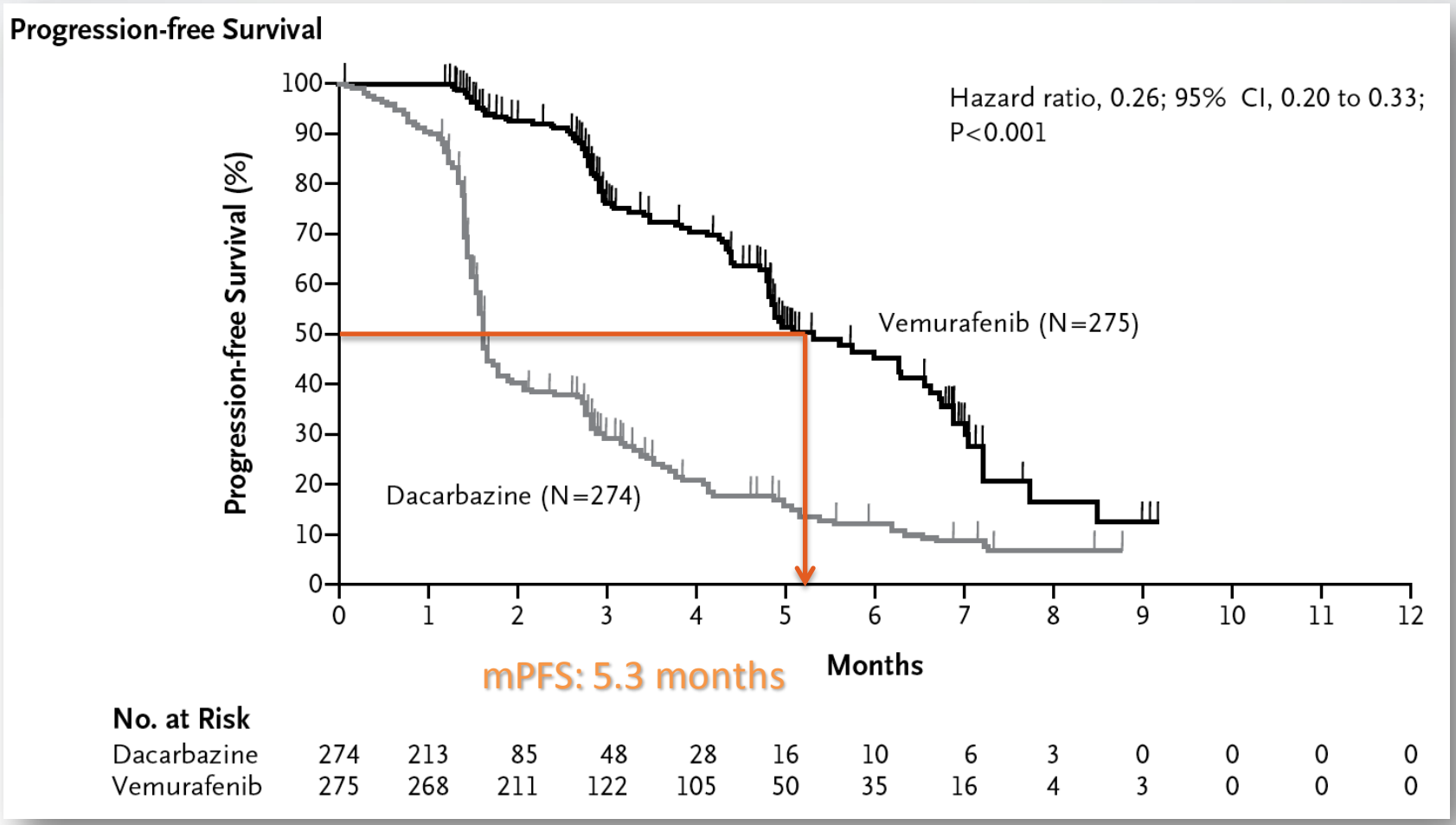
Anti-tumor effects are

- rapid
- in all metastatic sites



NEJMed 2010; 363: 809

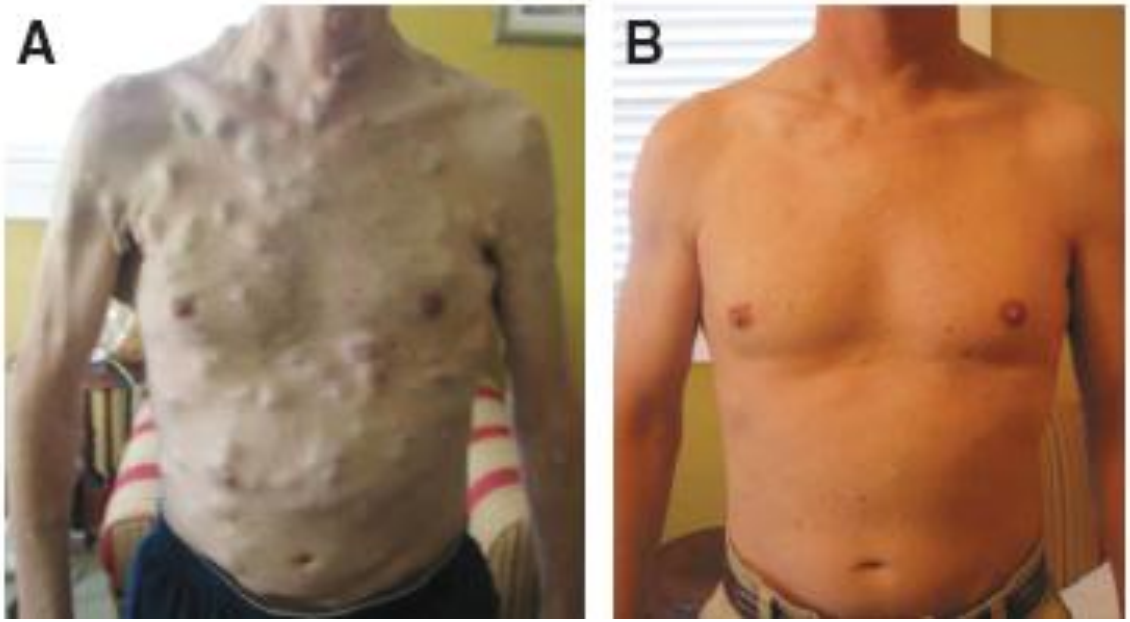
BRIM-3: PFS



Chapman & al, NEJM, 2011

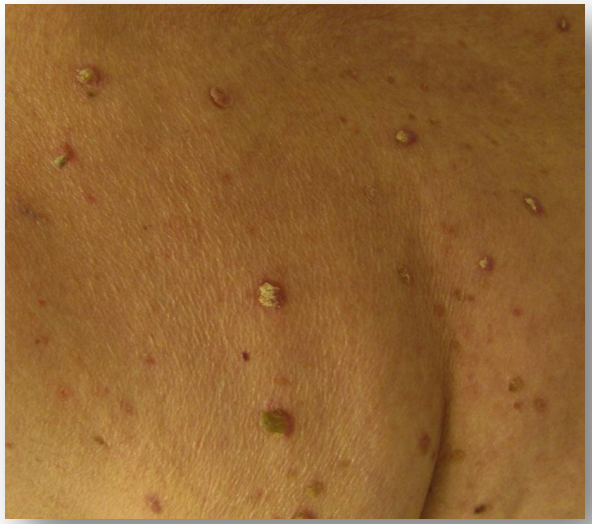
Acquired resistance to BRAF inhibition

Week15

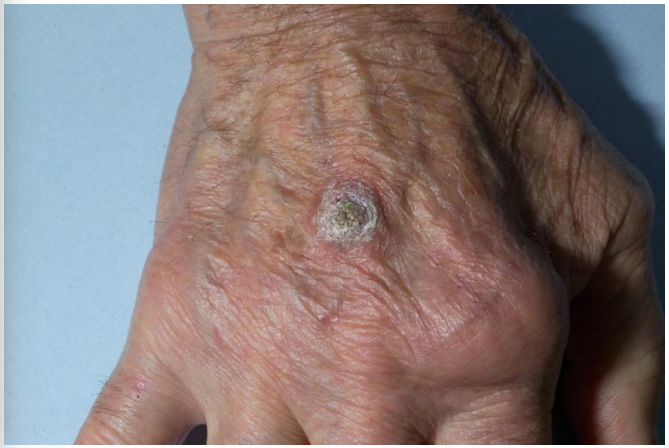


JCO 2011 , N Wagle

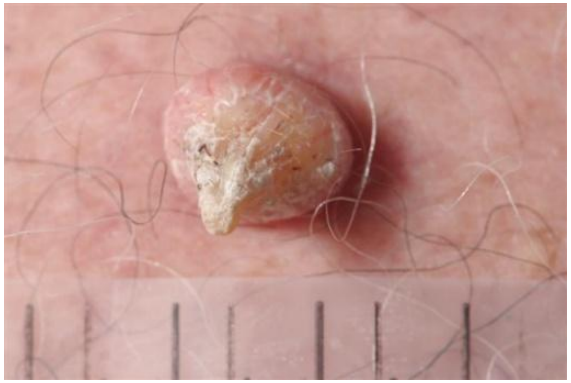
Secondary skin tumors



Acanthopapilloma



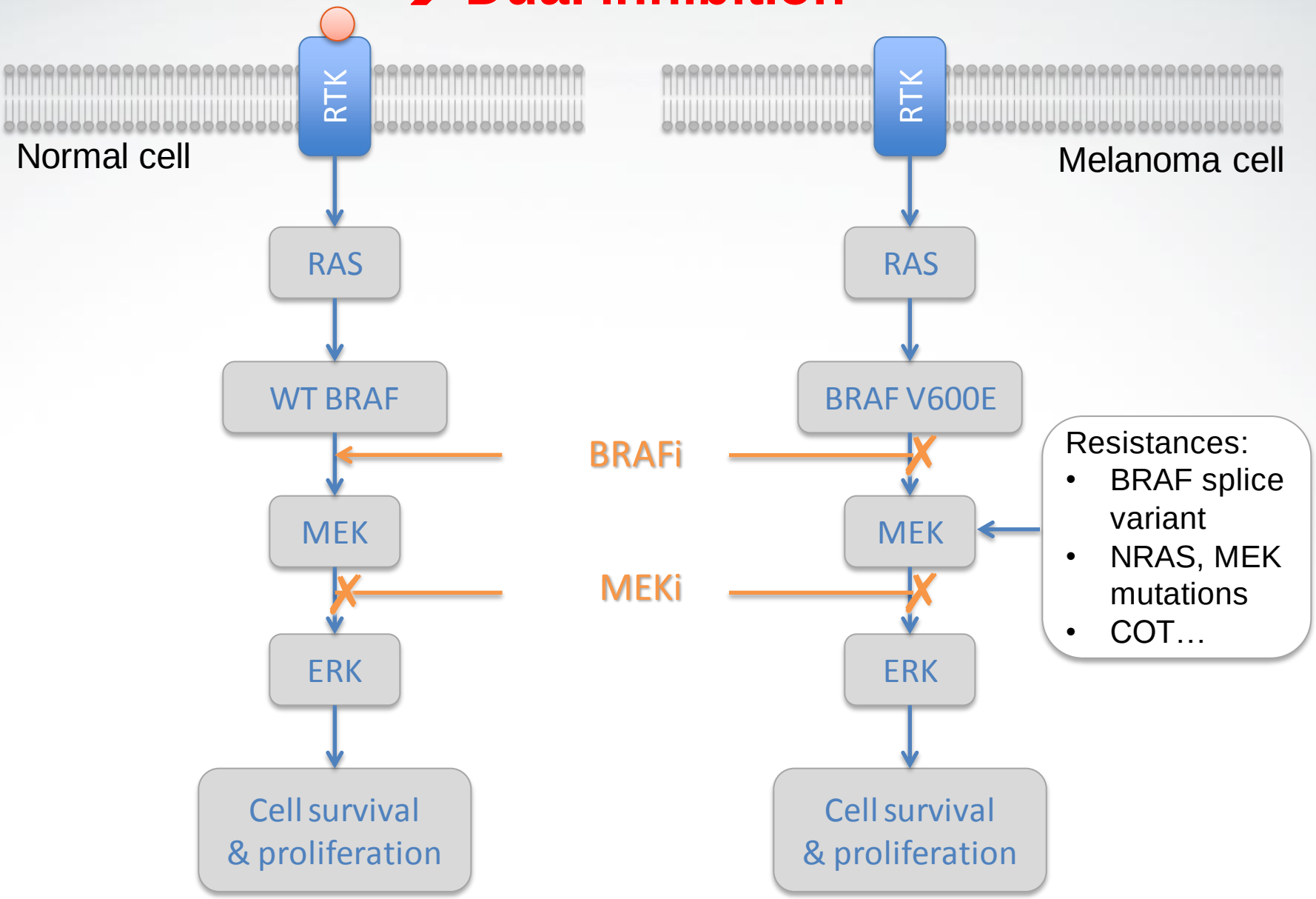
Kerato-acanthoma



SCC

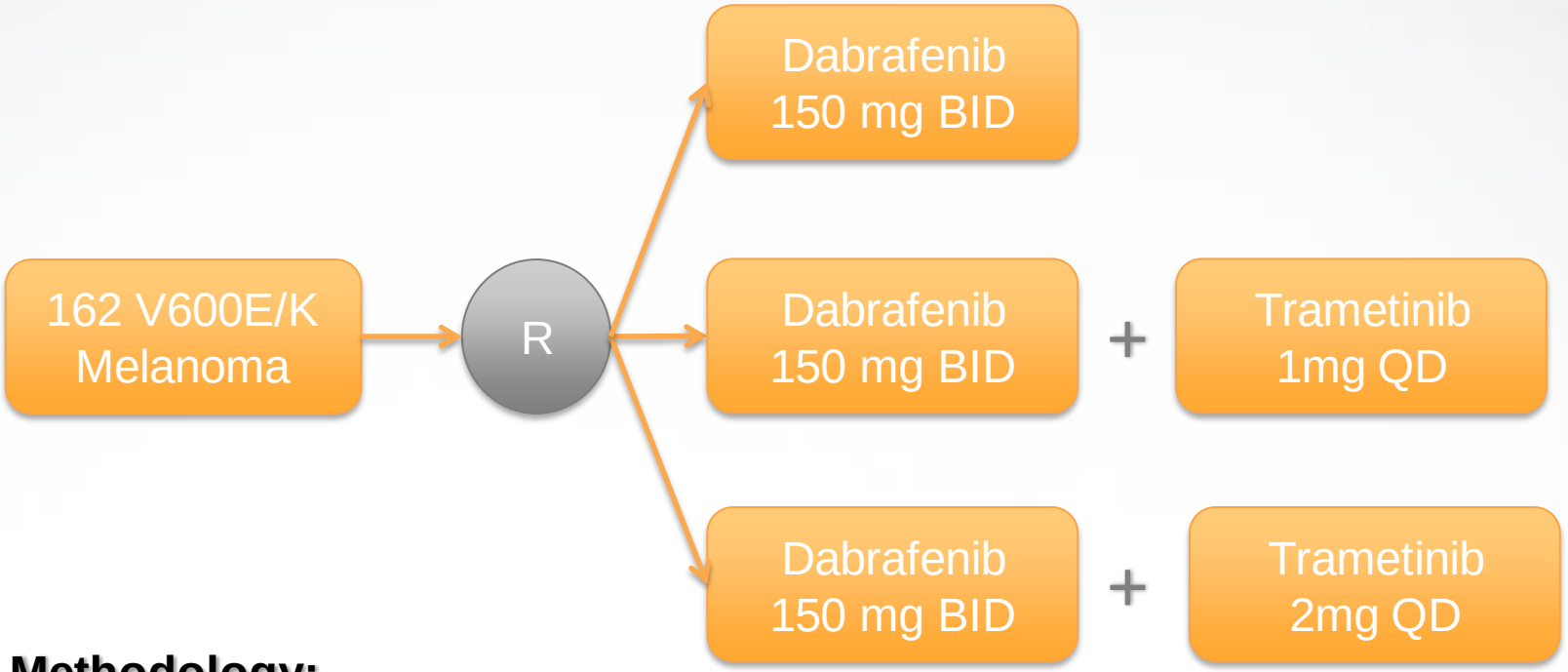
a single solution for two problems ?

➔ Dual inhibition



Adapted from O Michielin

Dabrafenib & trametinib combination phase I-II: first line stage IV melanoma



Methodology:

Primary endpoint:

- incidence of cuSCC, PFS, and RR

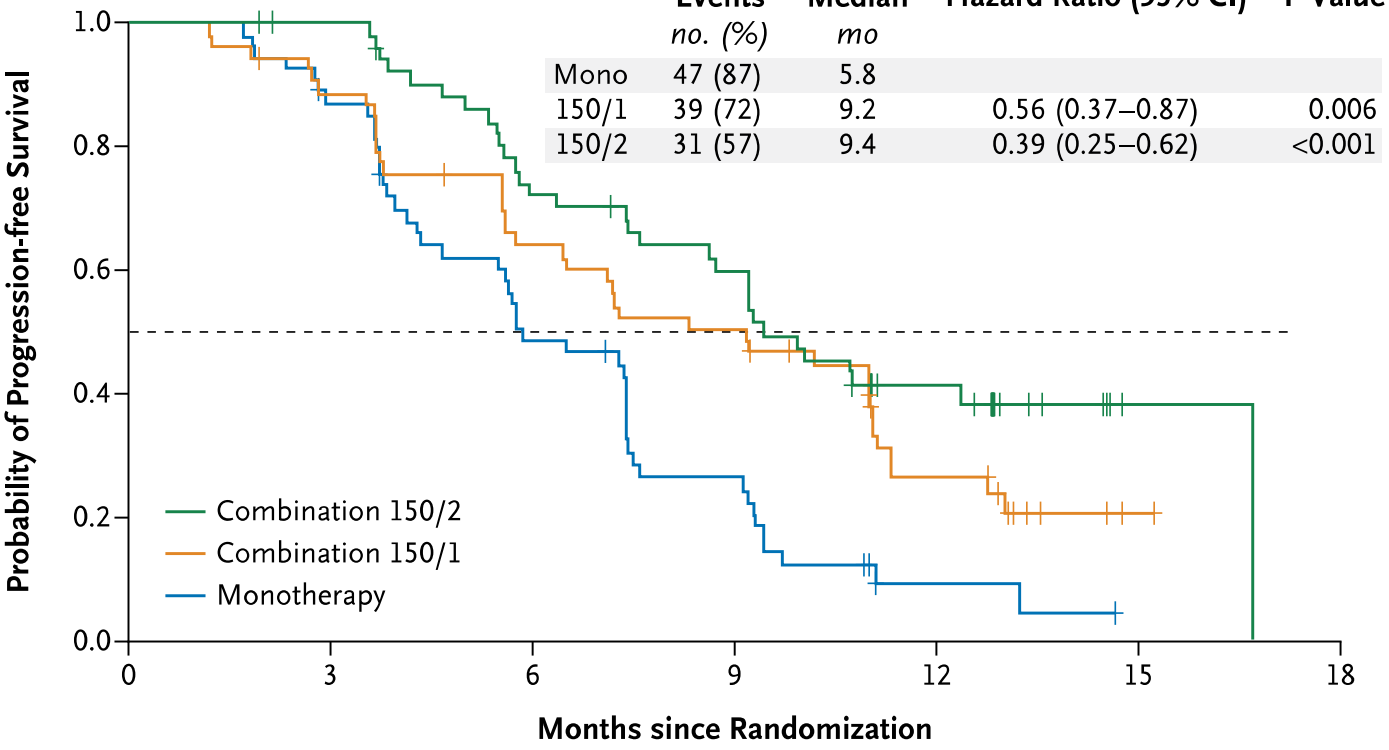
Secondary endpoint:

- Overall survival, response rate and pharmacokinetic activity

Flaherty & al. *NEJM* 2012

Dabrafenib & trametinib combination: PFS (very short FU)

A Progression-free Survival



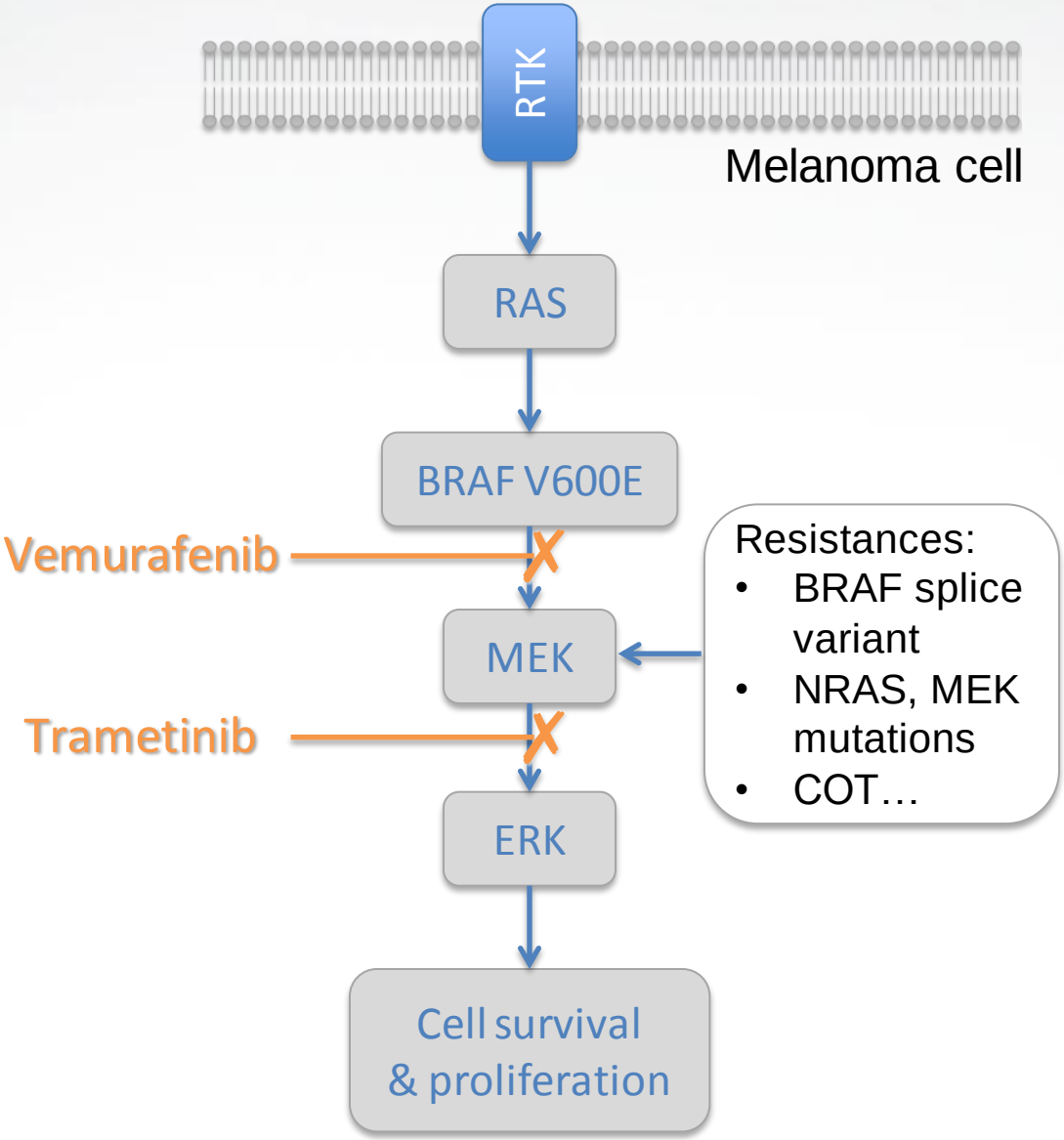
	Events *no. (%)*	Median *mo*	Hazard Ratio (95% CI)	P Value
Mono	47 (87)	5.8		
150/1	39 (72)	9.2	0.56 (0.37–0.87)	0.006
150/2	31 (57)	9.4	0.39 (0.25–0.62)	<0.001

No. at Risk

Monotherapy	54	46	25	13	2	0
Combination 150/1	54	47	33	26	11	1
Combination 150/2	54	52	36	29	15	1

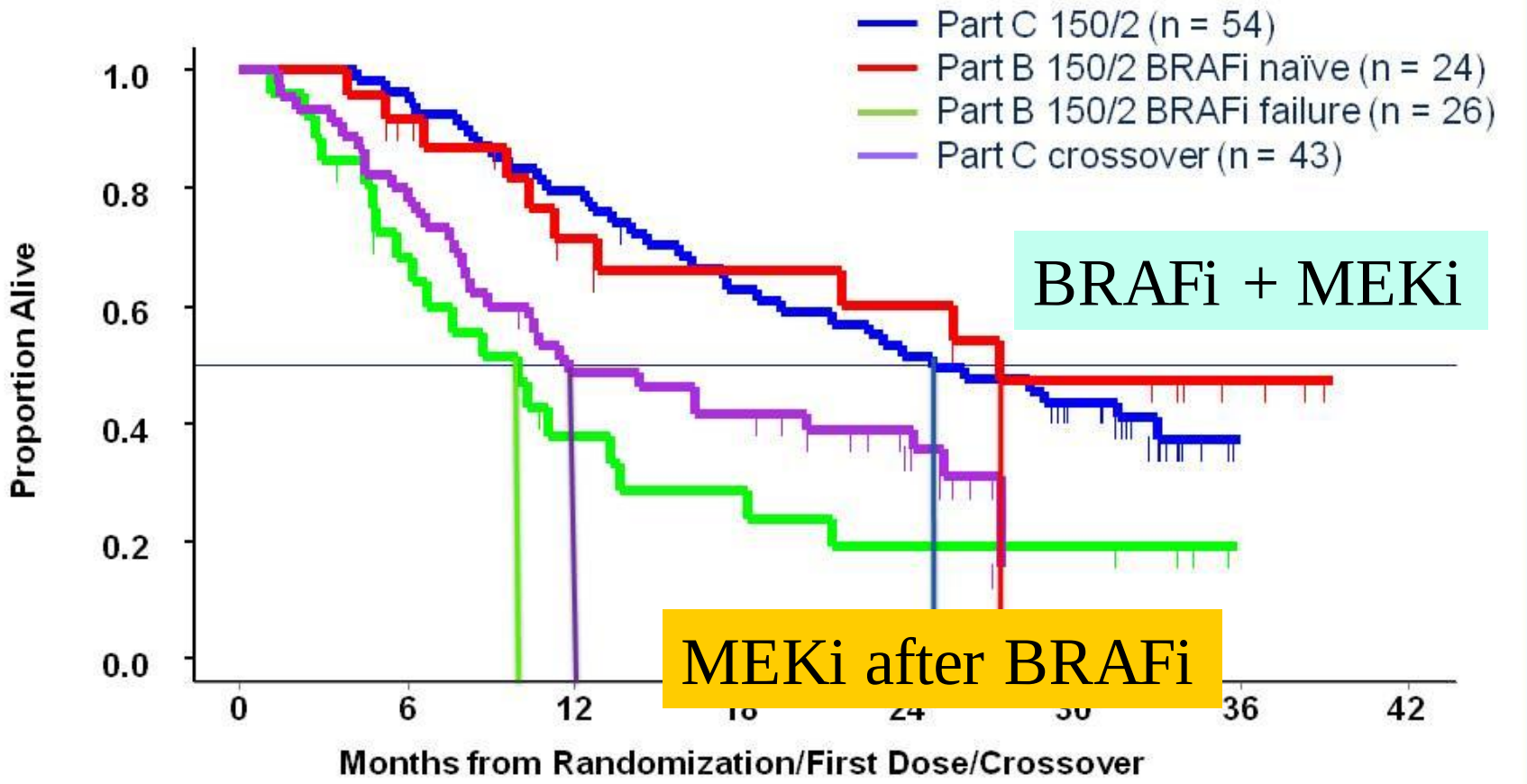
Flaherty & al. *NEJM* 2012

Acquired resistance : ➔ Dual inhibition



Overall survival by study arm: Part B and C

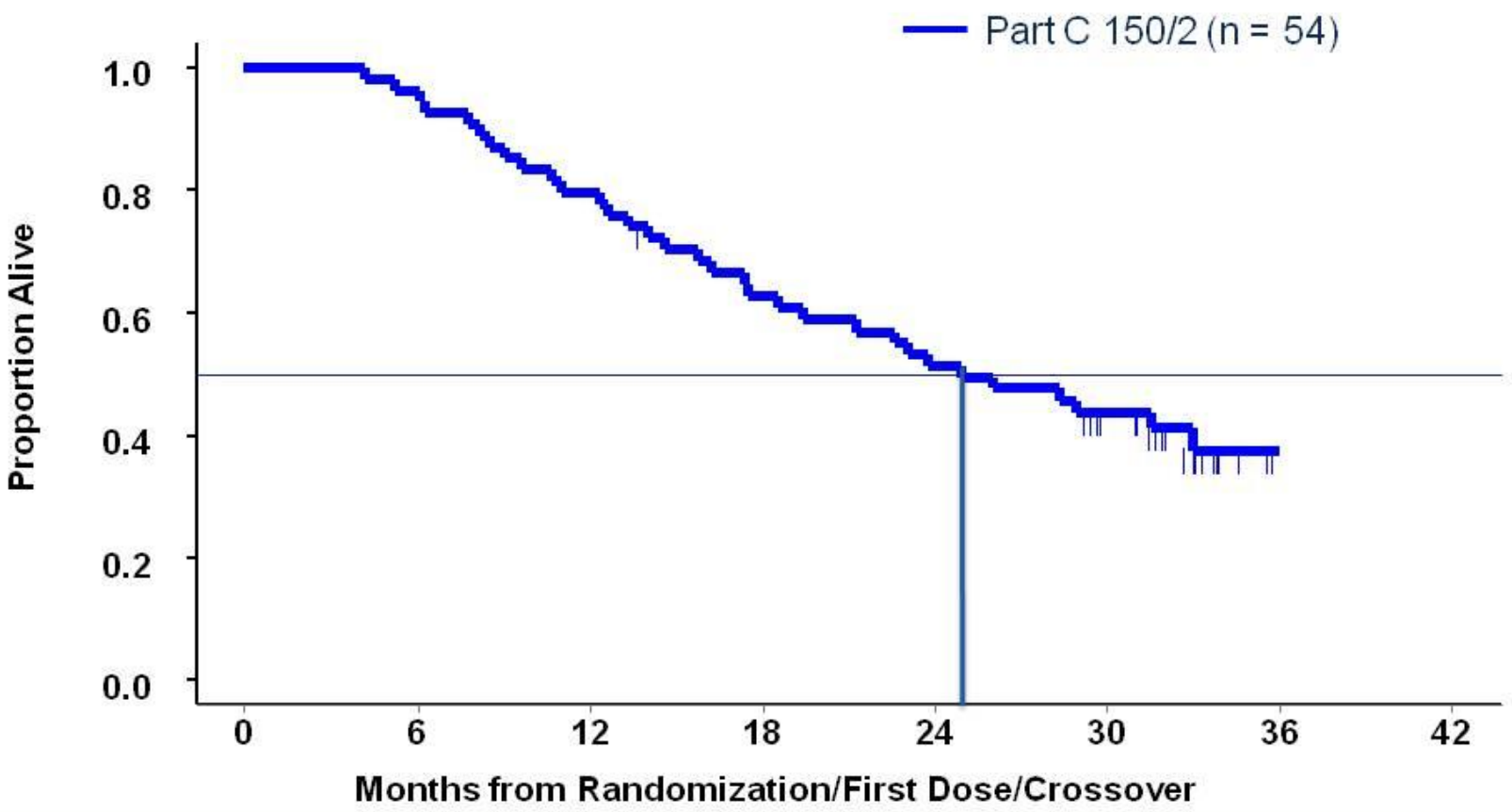
Data as of 15JAN2014. CI = 95%



PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Overall survival by study arm: Part B and C

Data as of 15JAN2014. CI = 95%



PRESENTED AT:

ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

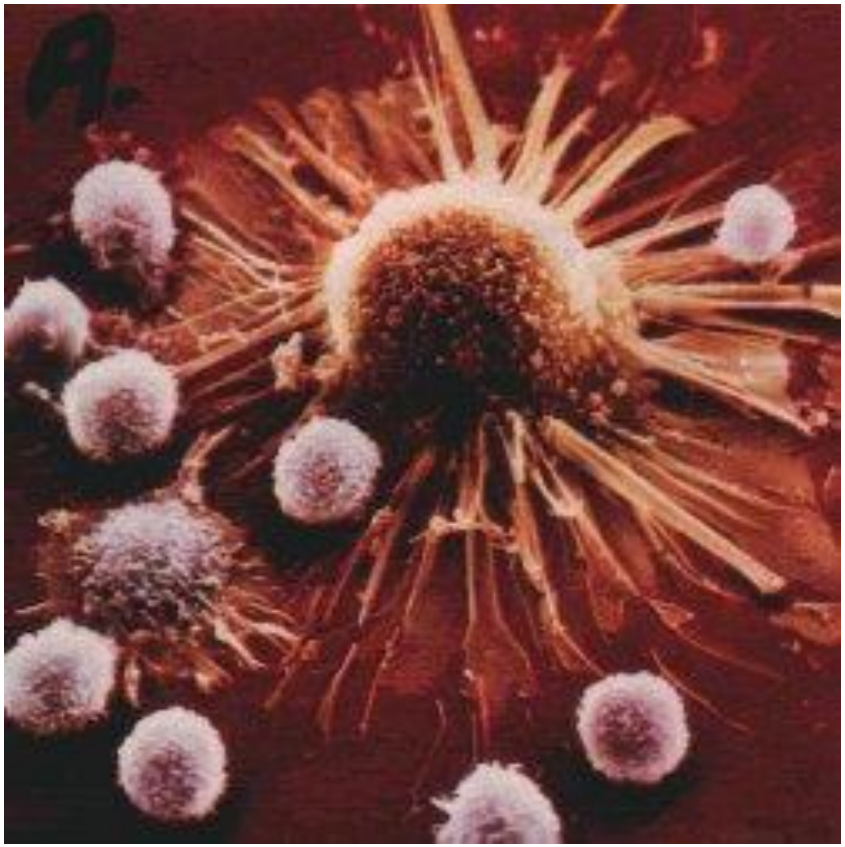
Immunotherapy

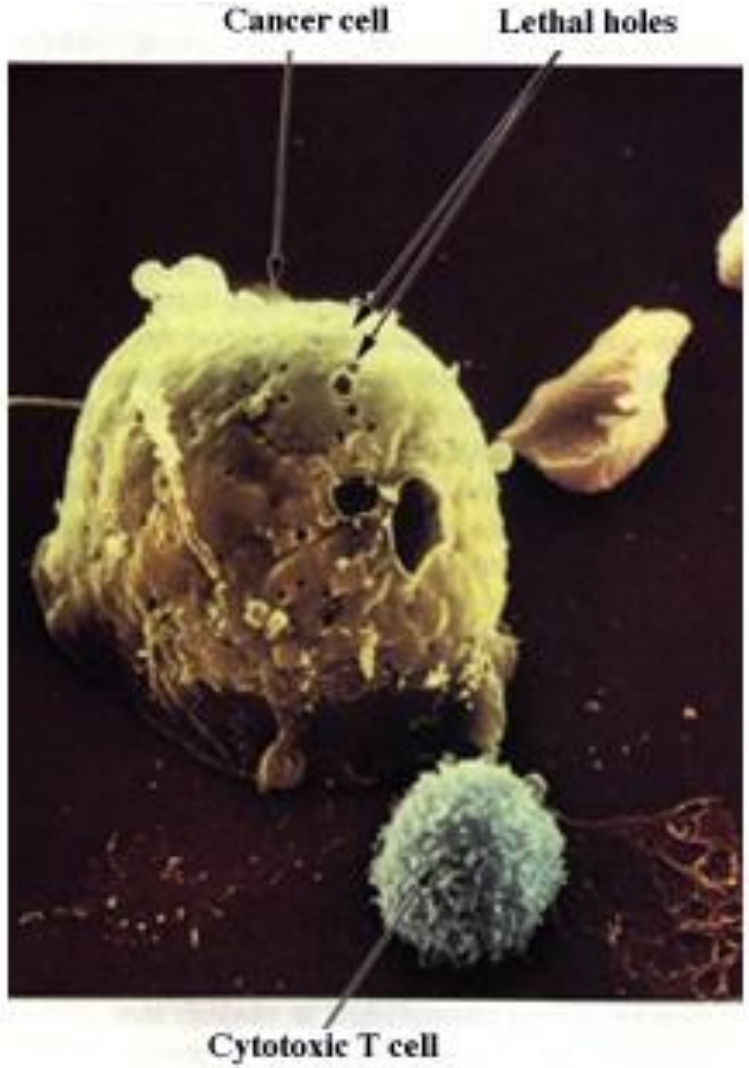
Immune checkpoints

Anti-tumor Immune surveillance

- Incidence of cancers is increased
  - Souris Rag-/- et STAT-1 -/-
  - Constitutive Immunodeficiencies
  - HIV
  - Immunosuppressive treatments
    - transplantation

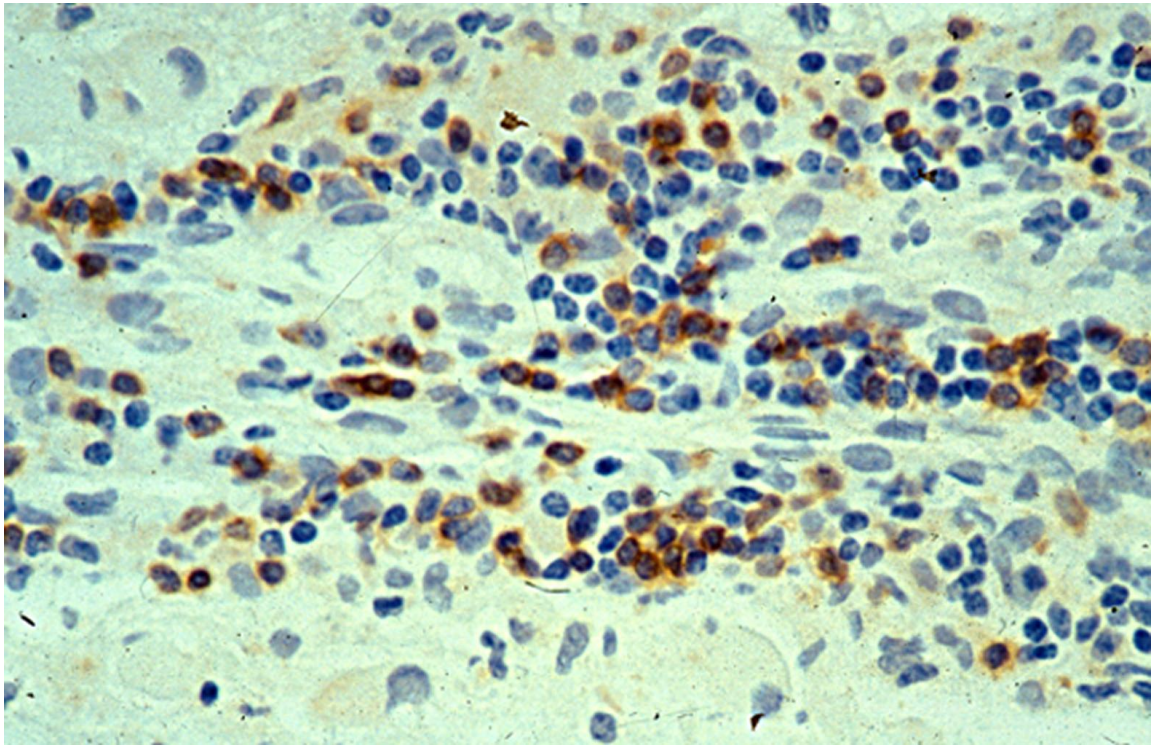
T lymphocytes are killer cells





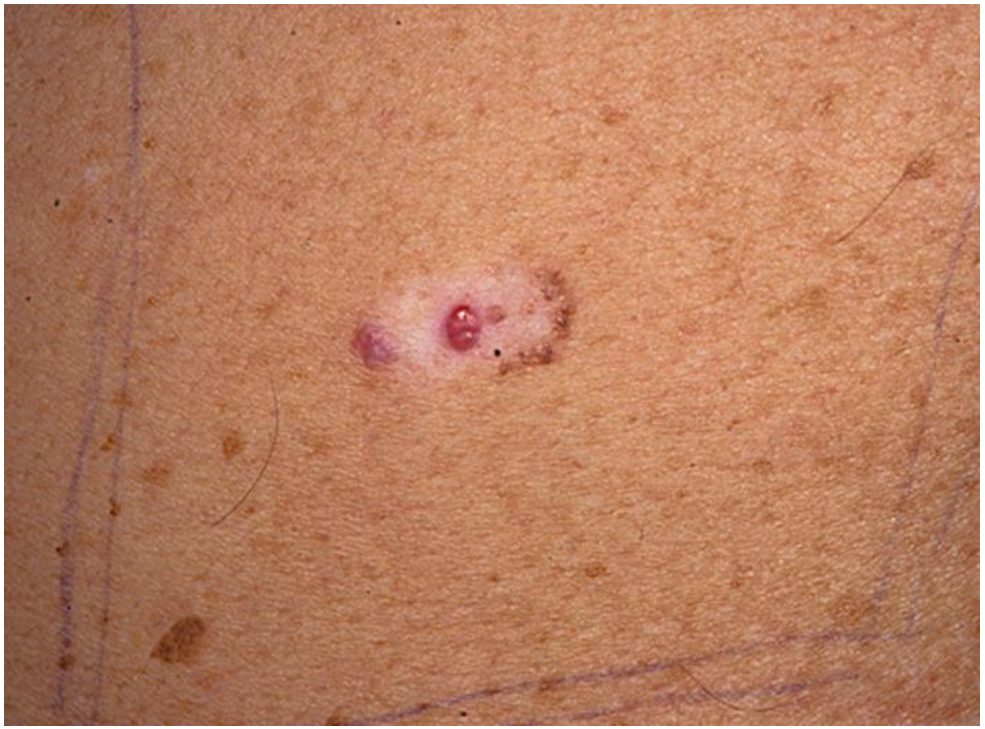
wellesley.edu

T cells invade tumors



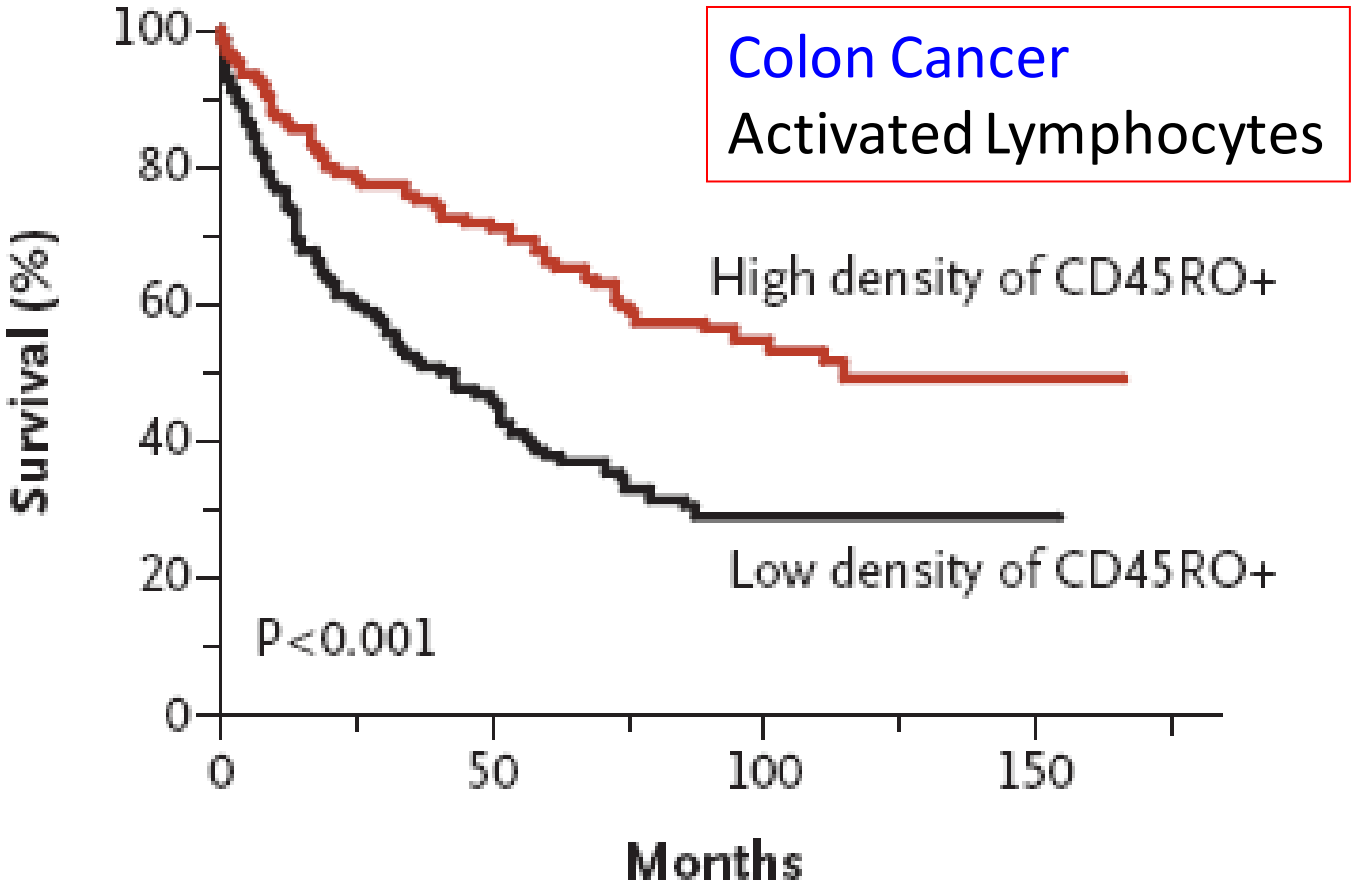
Lymphocytes T

➔ spontaneous regression



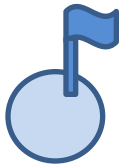
Regressive Melanoma

Intratumoral T cells:
Good prognosis factor

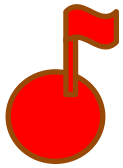


Pages F, N Engl J Med 2005; 353: 2654

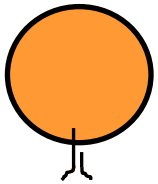
surveillance patrol ?



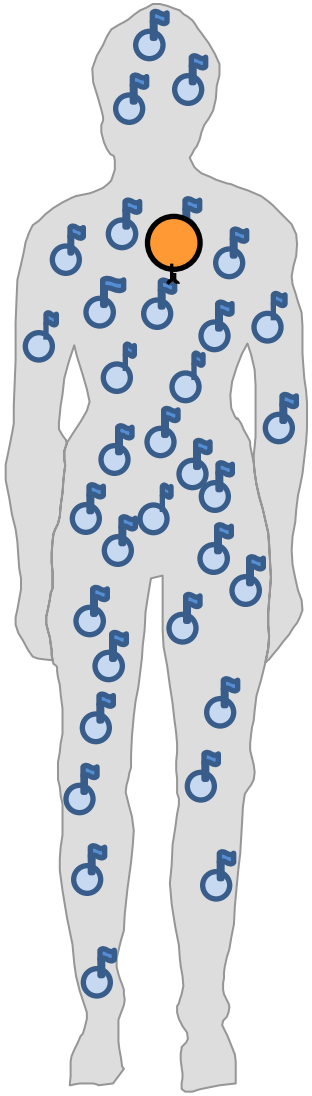
Normal cell

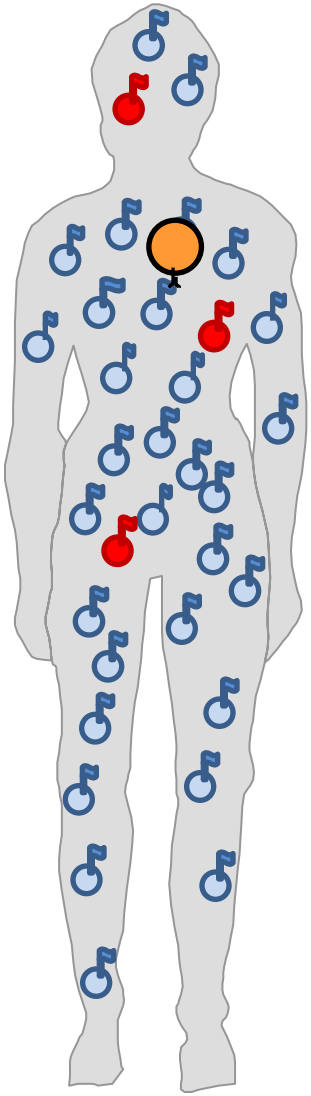


Cancer cell

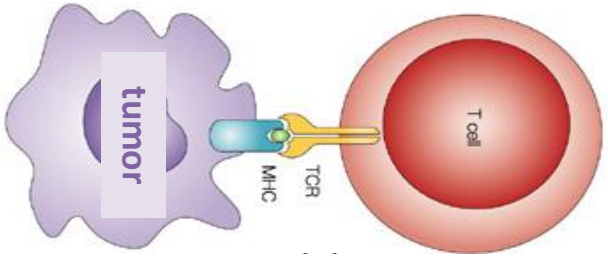


lymphocyte

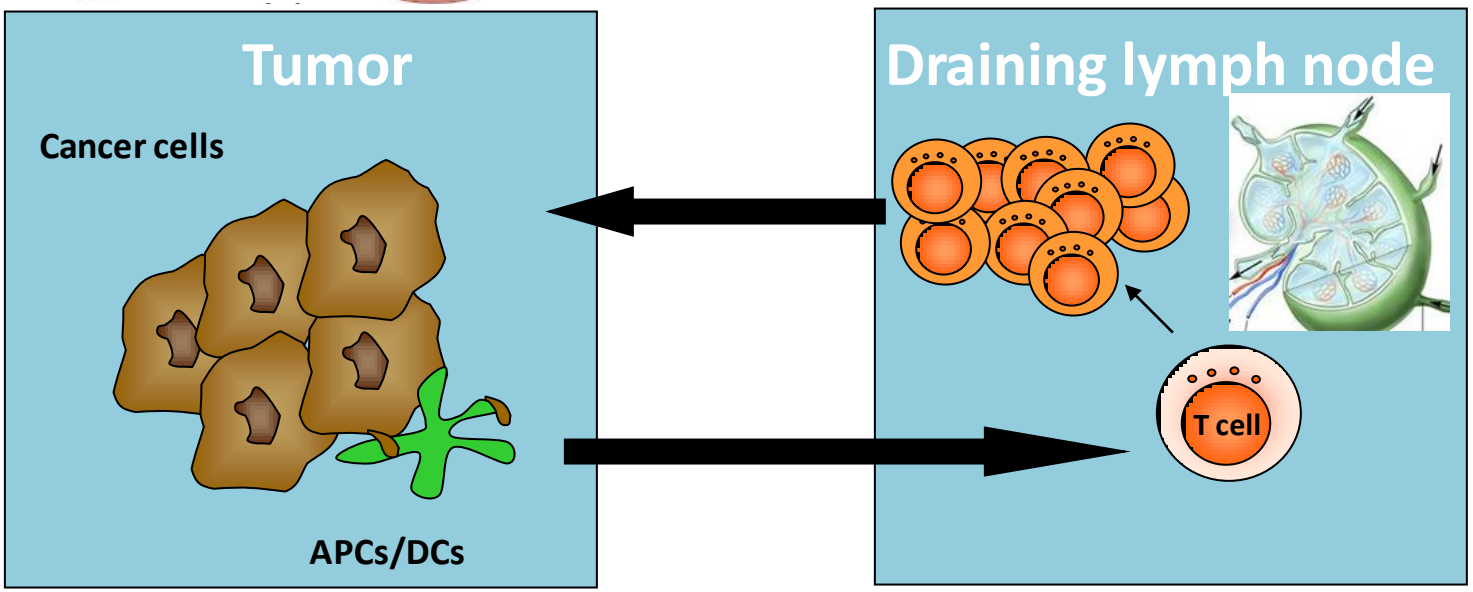




Tumor immunity : how does it work ?

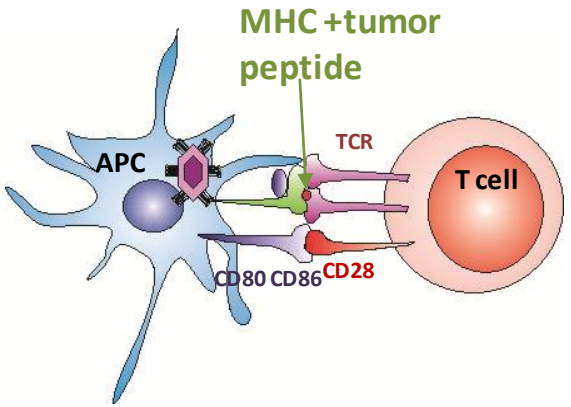


2) T cell killing function

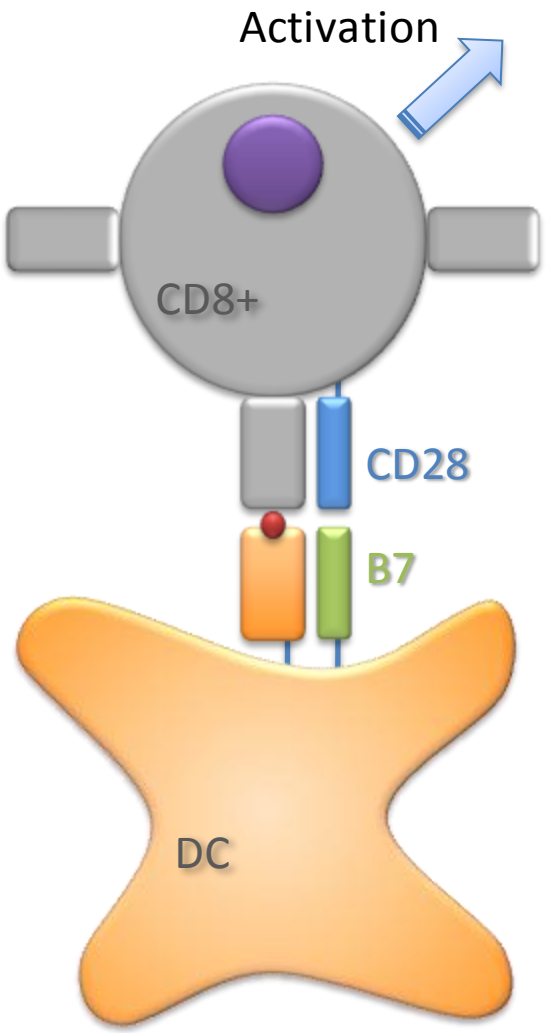


Could we re-inforce ?

1) T cell activation



Co-stimulation "positive"



Adapted from O Michielin

L'interaction entre un APC professionnel et lymphocyte T naïf

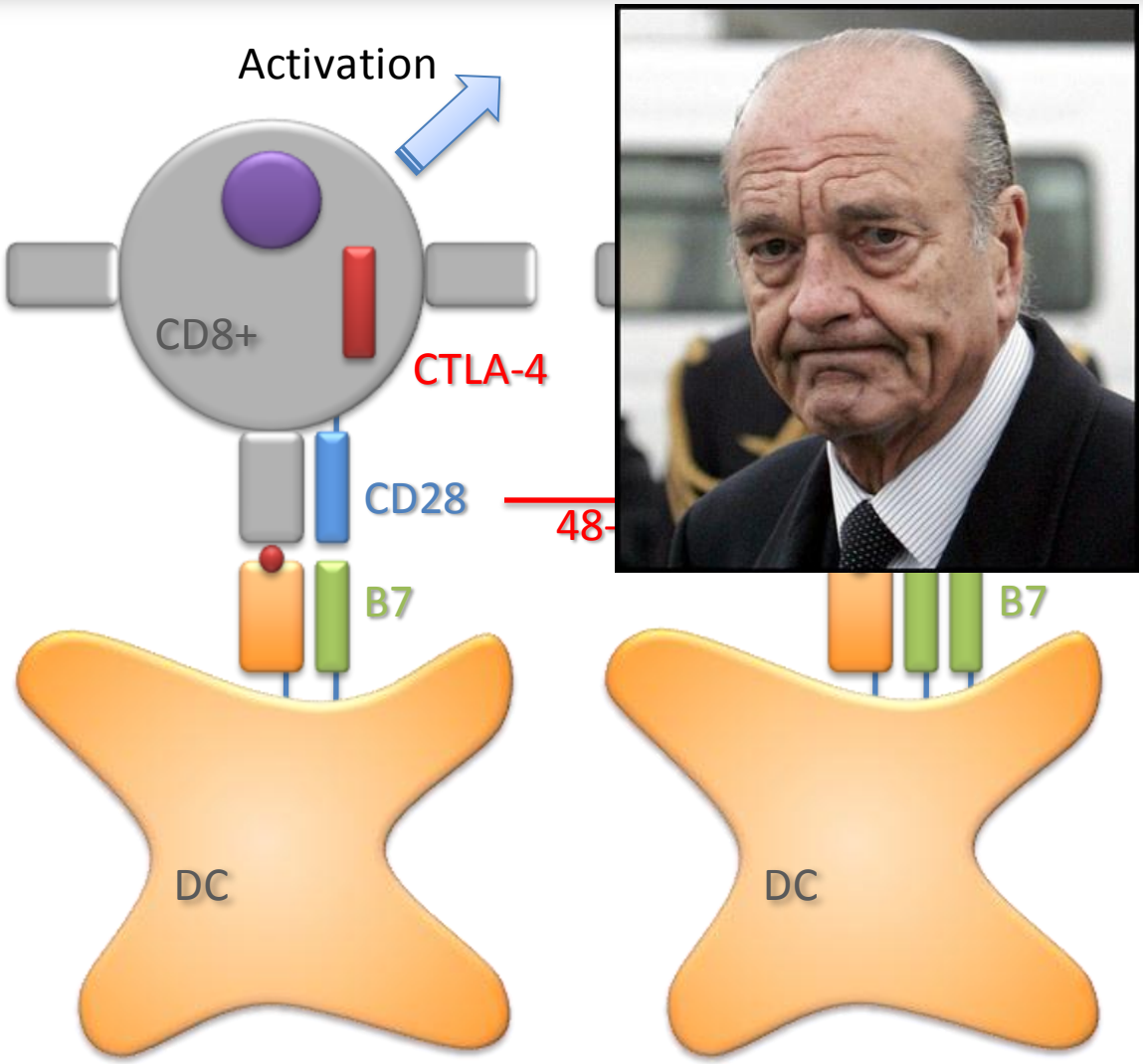
Co-stimulation

- Regard
- Parole
- Pieds (?)

co-stimulation " positive "

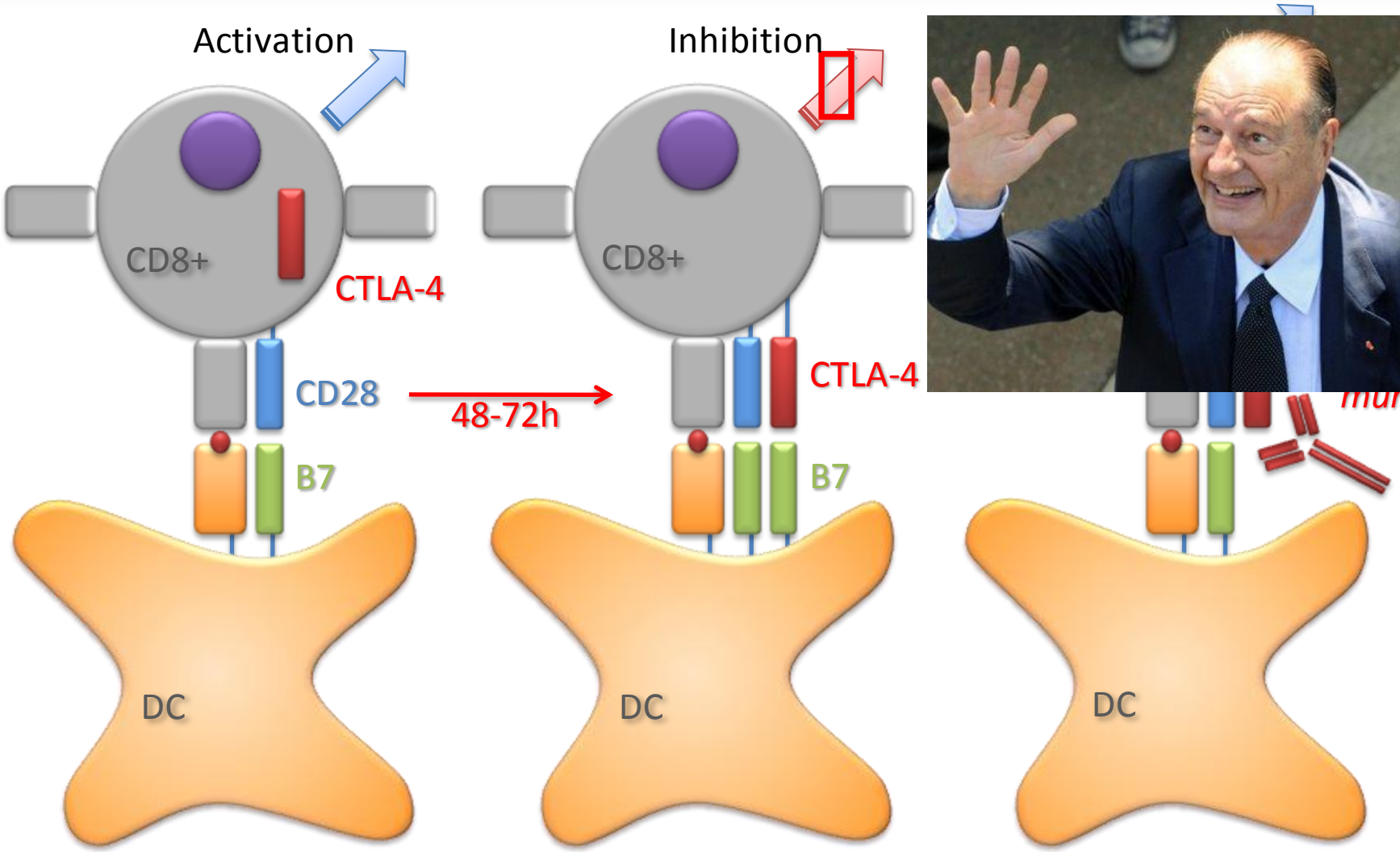
Adapted from O Michielin

Tolérance par co-stimulation inhibitrice



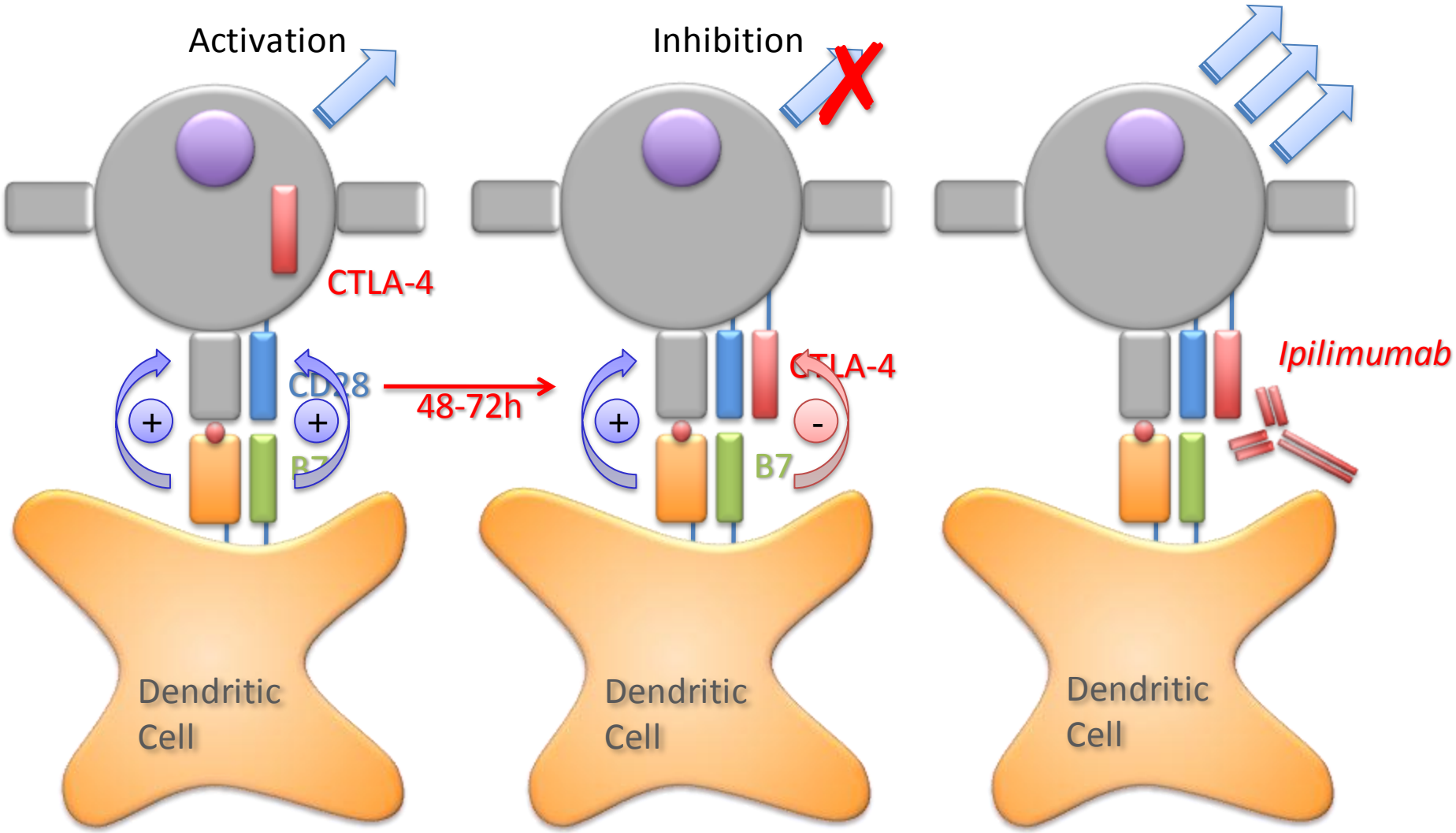
Adapted from O Michielin

Activation T par blocage du frein (immune checkpoint) l'ex de l'ipilimumab



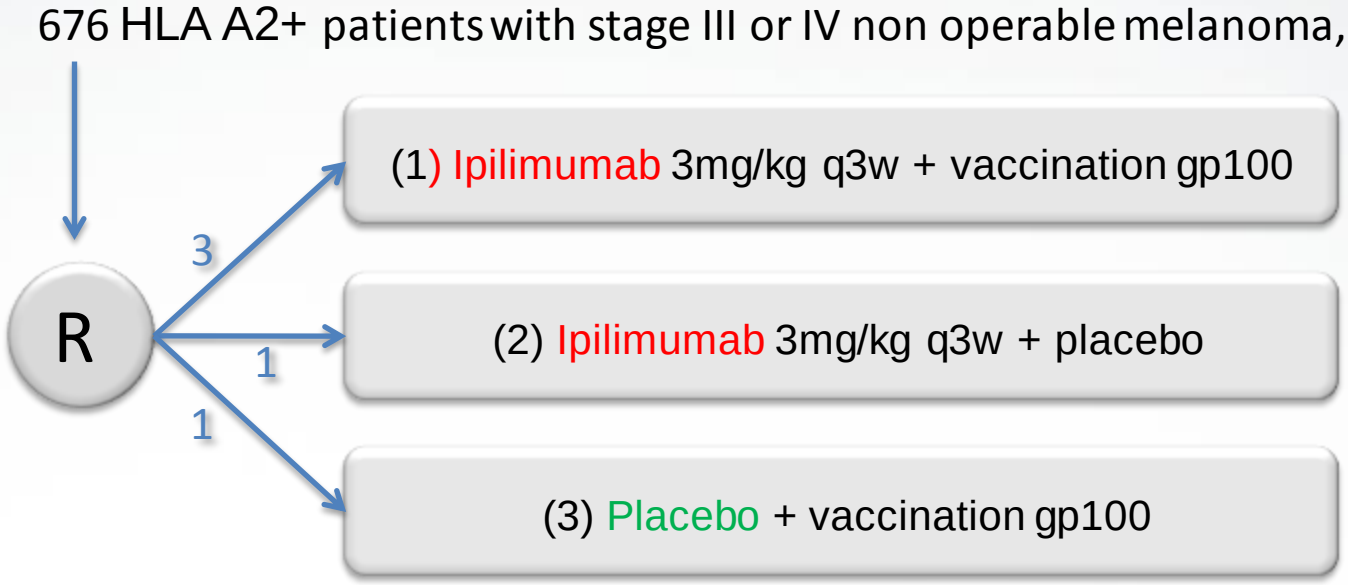
Adapted from O Michielin, Thank you !

Positive and negative co-stimulation



Courtesy O Michielin

Randomized phase III study: 020 trial



Methodology:

Primary endpoint: Overall survival (OS)

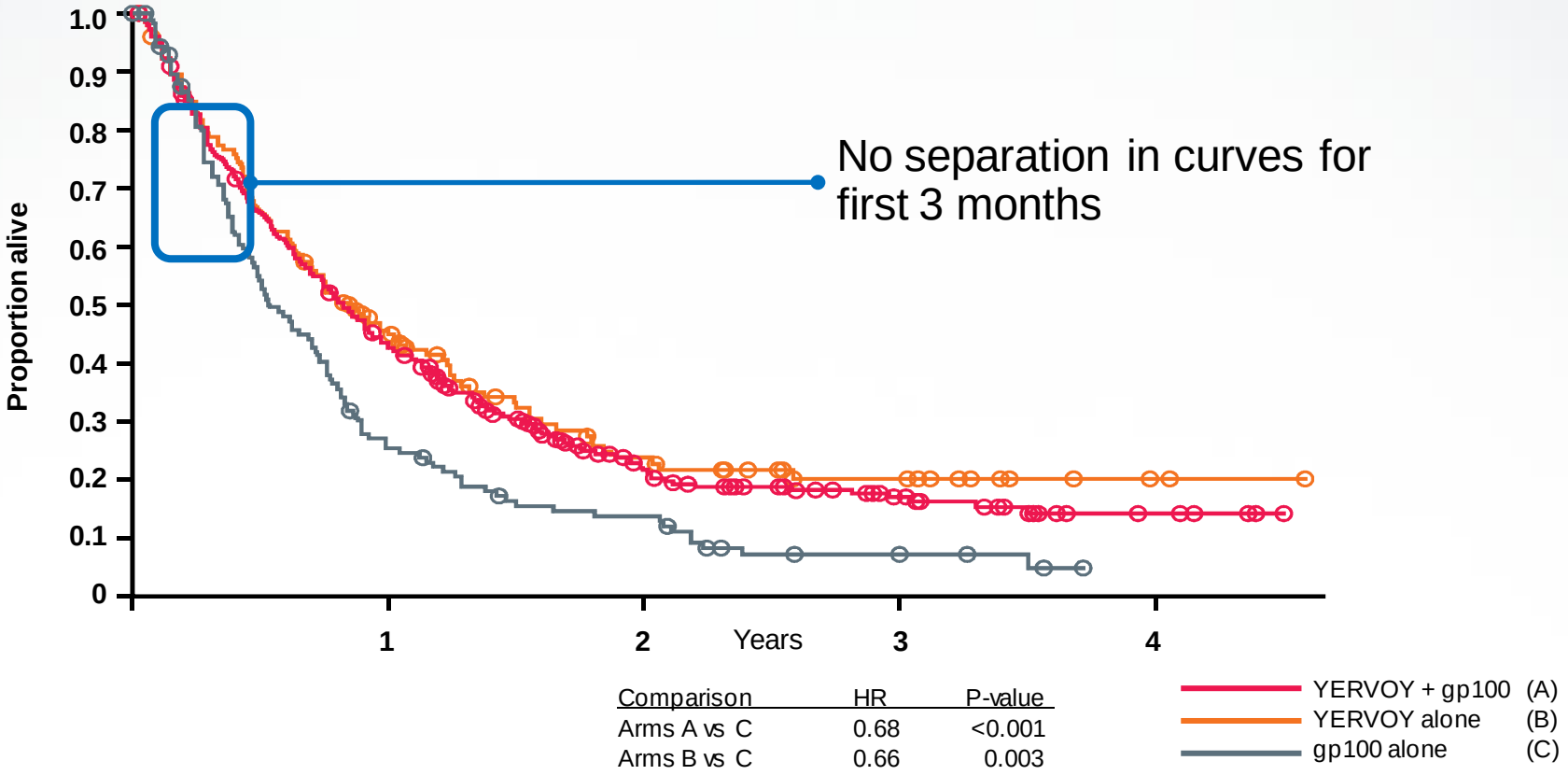
Secondary endpoint: PFS, response rate

Results:

Comparison gp100 + ipi vs. gp100 alone (arm 1 vs. 3):
Median OS 10.0 vs. 6.4 m, *p*=0.0004, HR 0.68 (CI 0.55 – 0.85)
Comparison ipi alone vs. gp100 alone (arm 2 vs. 3):
Median OS 10.1 vs. 6.4 m, *p*=0.0026, HR 0.66 (CI 0.51 – 0.87)
Comparison of the 2 ipi arms: no significant differences

Hodi & al, NEJM, 2010

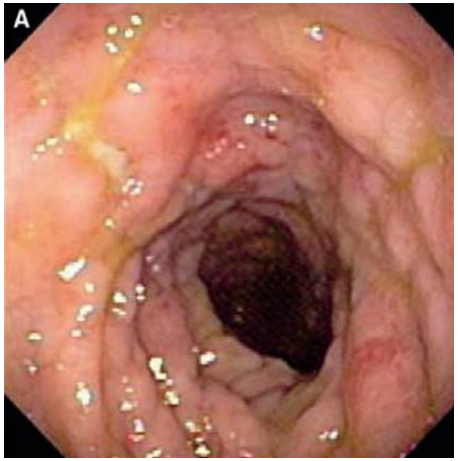
Improved Survival with Ipilimumab (> 4.5 Years of Follow-Up)

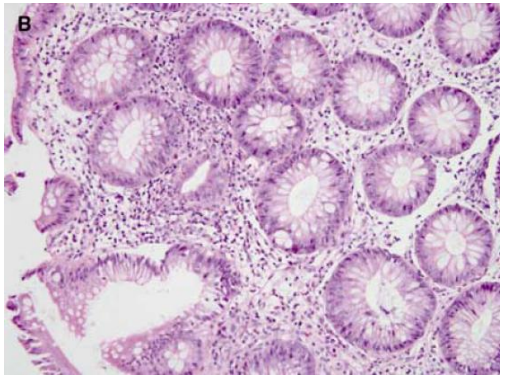


Hodi, FS, et al. *N Engl J Med* 2010;363:711–723

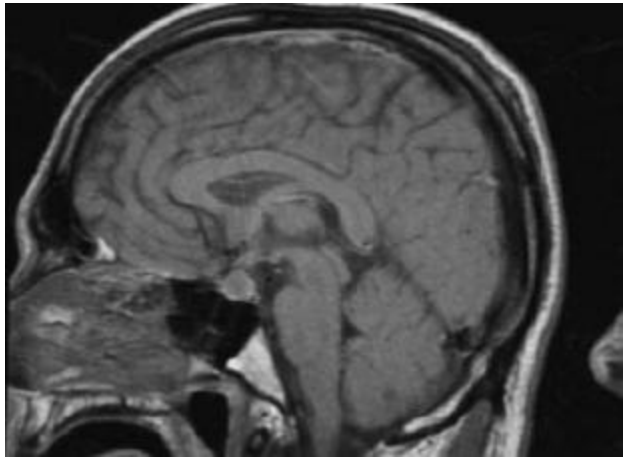
Immune side effects → proof of concept

- Skin erythema
- Colitis



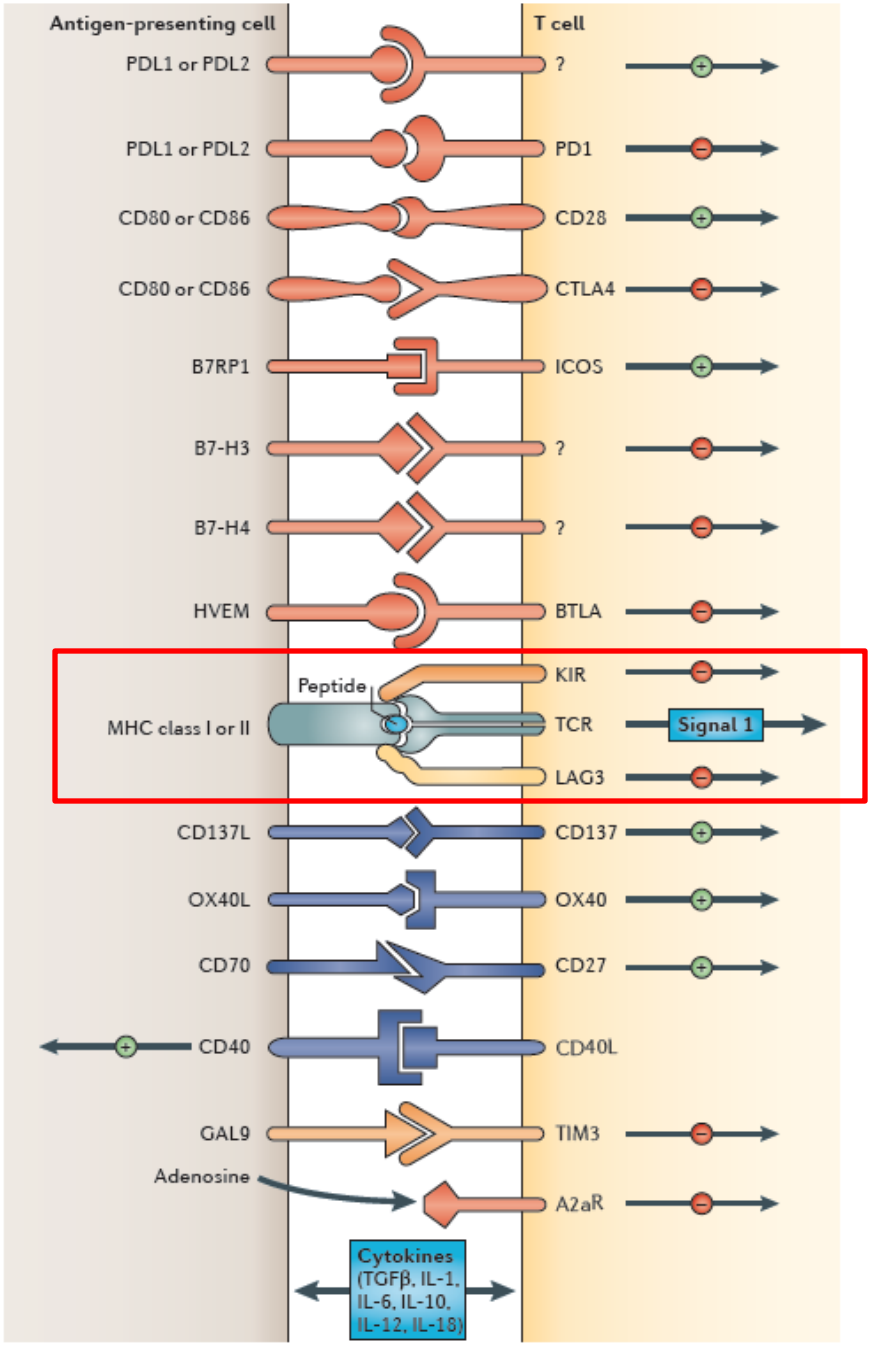


- hepatitis
- hypophysitis



Ann Surg Oncol 2005;12:1005-16.

J Immunother 2005;28(6):593-8.

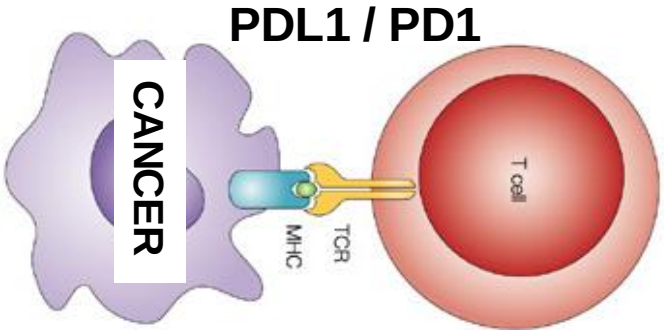


PD1 PD-L1

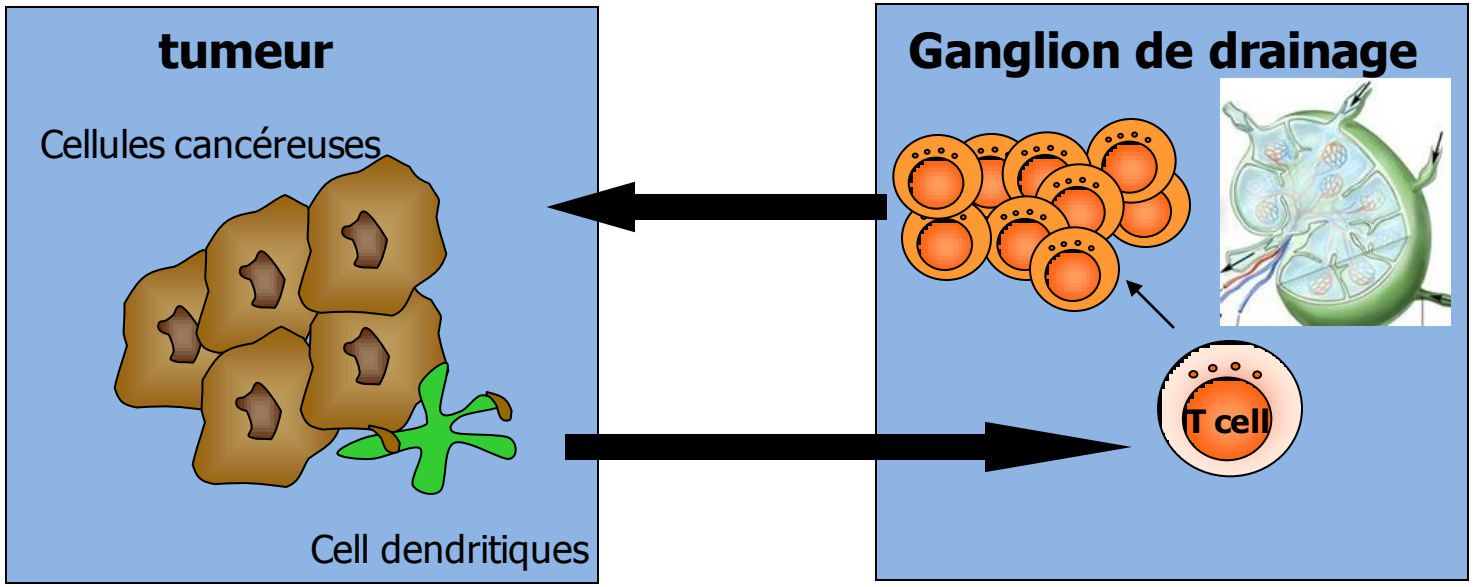
Immune checkpoints

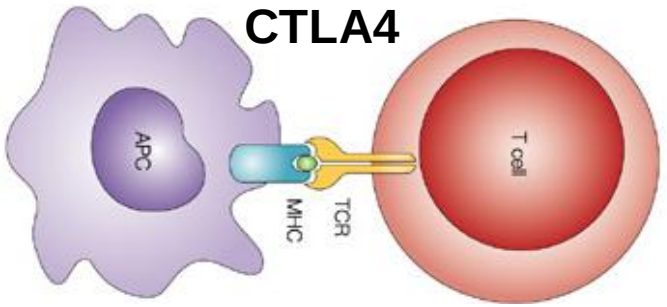
Nat Rev cancer 2012, 12 :252

Other checkpoints as targets ?



Less toxic ?





The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 28, 2012 VOL. 366 NO. 26

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

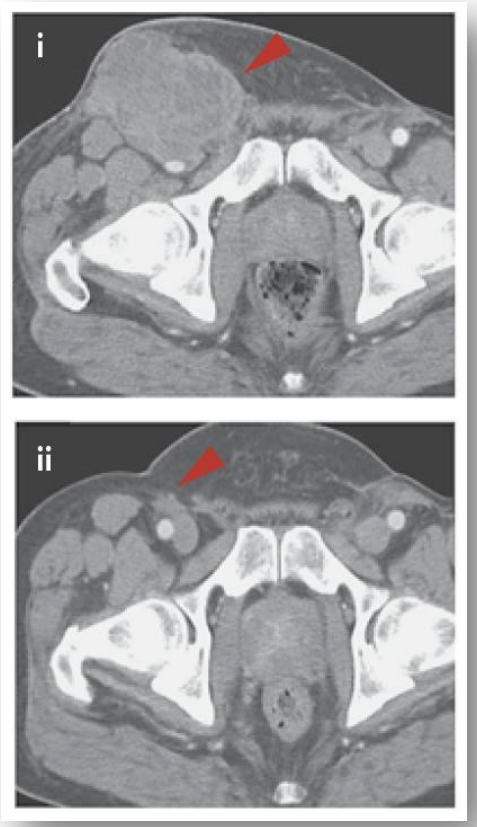
Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgia D. Kollia, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Sznol, M.D.

Advanced melanoma, NSCLC, CRPC, RCC, colorectal cancer

N = **296 patients**

Results and toxicity

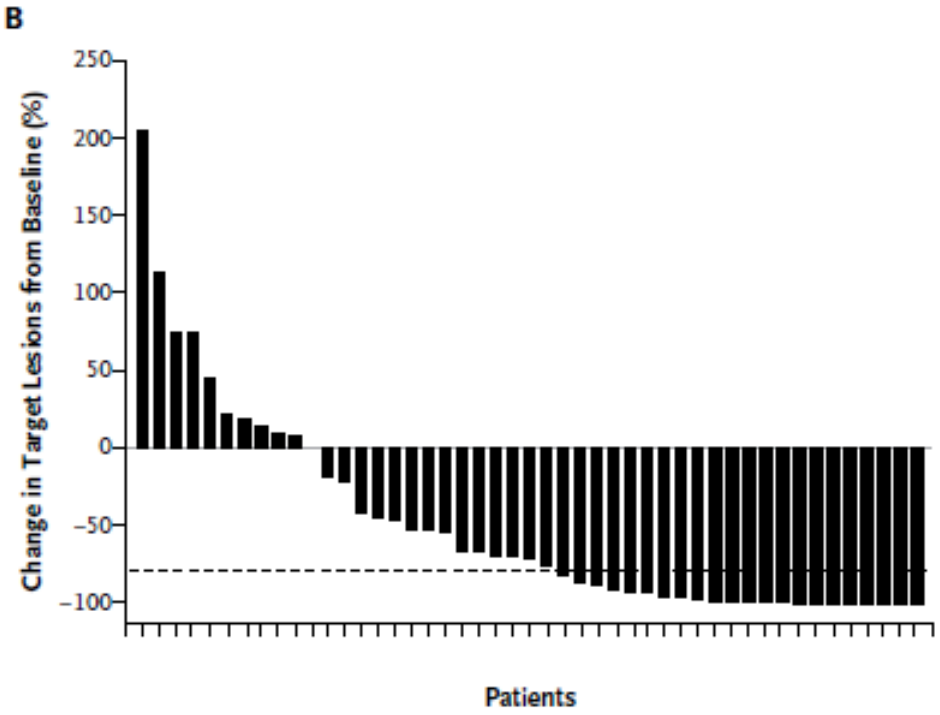
- Much less side effects than anti-CTLA4
- Objective responses (this is new !) in
  - melanoma,
  - renal-cell cancer
  - NSCLC
- and in various sites of metastasis
  - liver, lung, lymph nodes, and bone



ORIGINAL ARTICLE

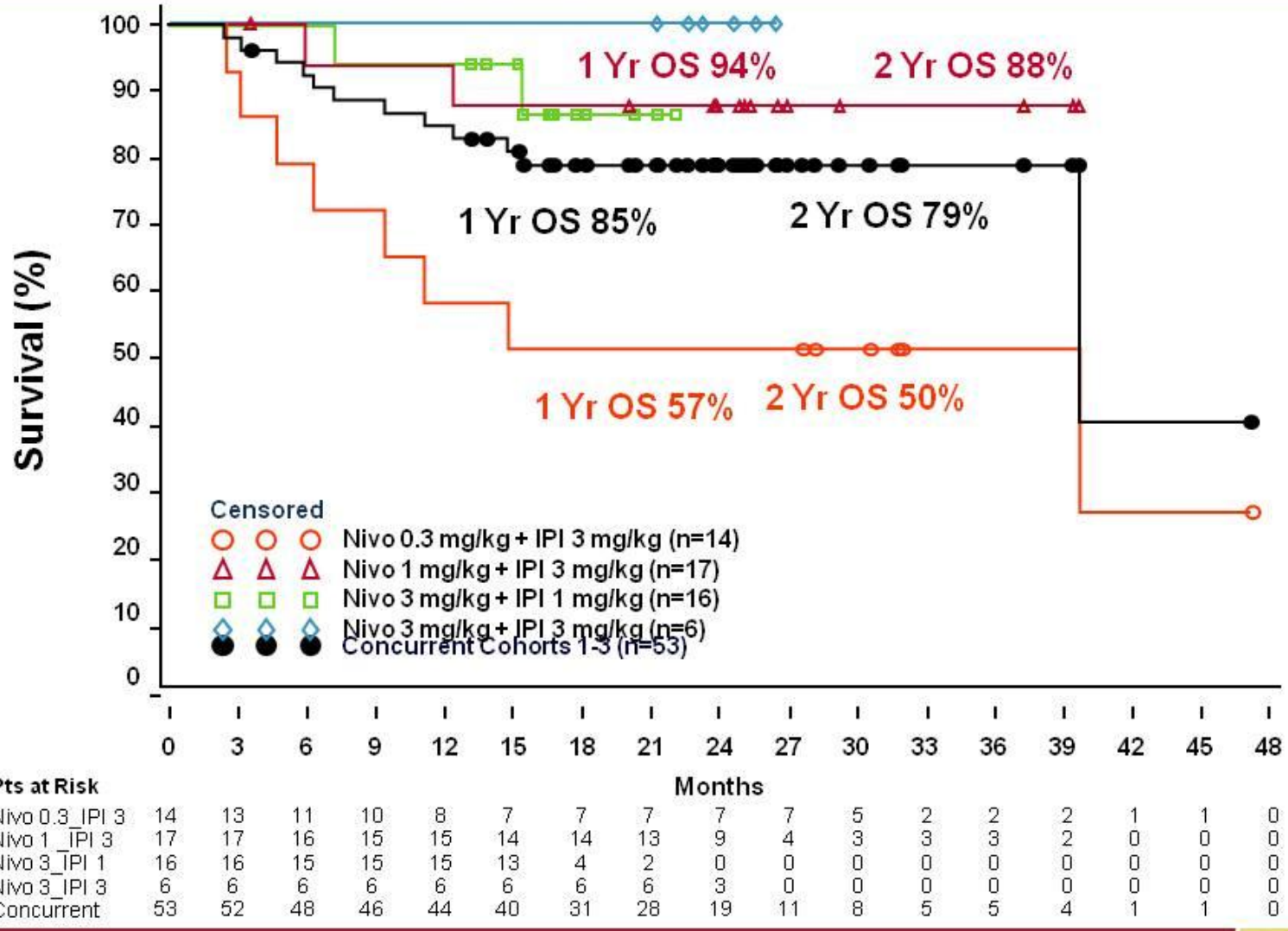
Nivolumab plus Ipilimumab in Advanced Melanoma

Jedd D. Wolchok, M.D., Ph.D., Harriet Kluger, M.D., Margaret K. Callahan, M.D., Ph.D.,



53 % grade ¾ side effects

Both mAb targeting CTLA4 and PD1



Presented by:

PRESENTED AT: 50th ANNUAL MEETING SCIENCE & SOCIETY

Presented By Mario Sznol at 2014 ASCO Annual Meeting

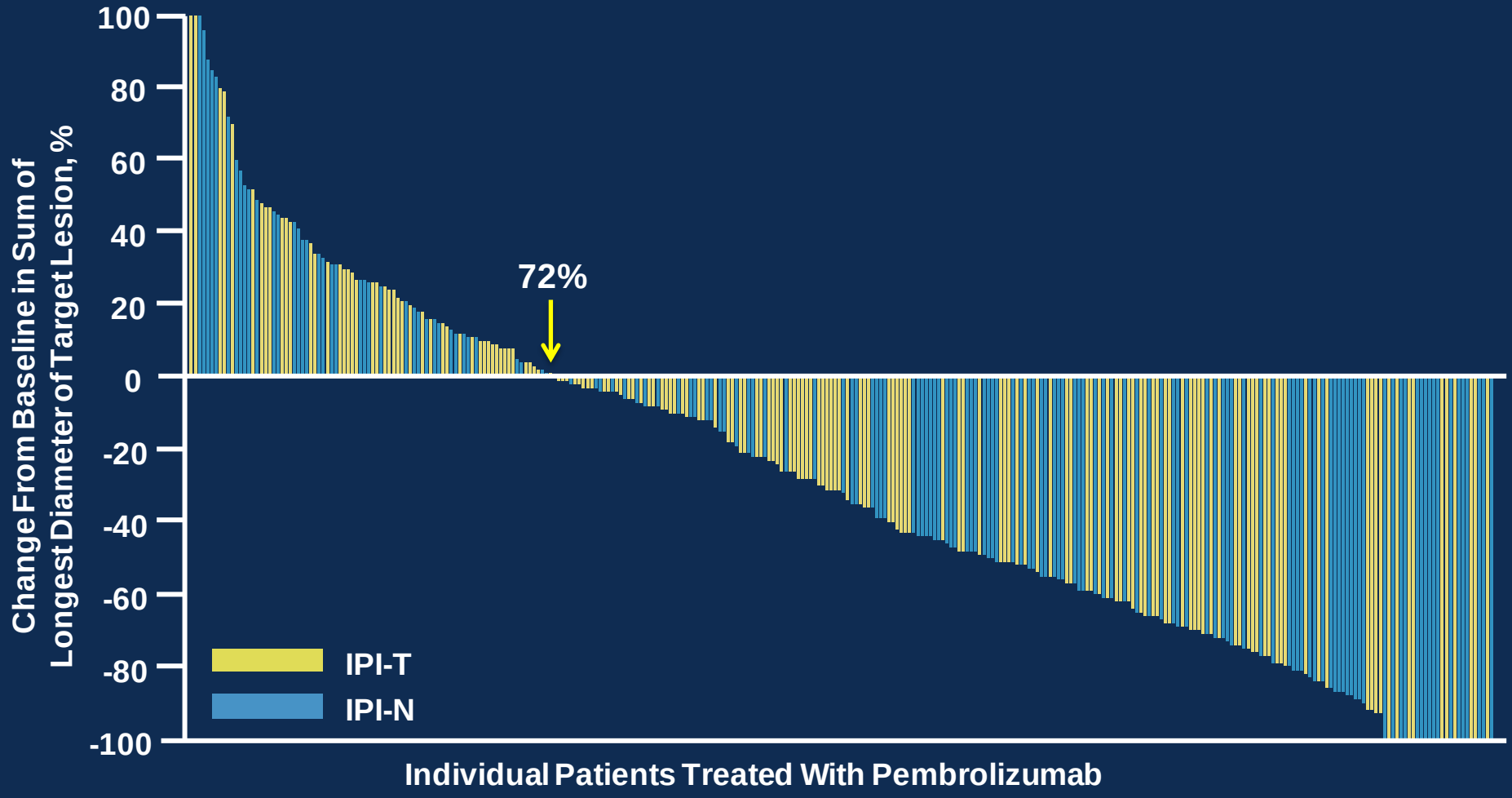
Efficacy and Safety of the Anti-PD-1 Monoclonal Antibody Pembrolizumab (MK-3475) in 411 Patients With Melanoma

Antoni Ribas,[1] F. Stephen Hodi,[2] Richard Kefford,[3,4] Omid Hamid,[5] Adil Daud,[6] Jedd D. Wolchok,[7] Wen-Jen Hwu,[8] Tara C. Gangadhar,[9] Amita Patnaik,[10] Anthony M. Joshua,[11] Peter Hersey,[4] Jeffrey Weber,[12] Roxana Dronca,[13] Hassane Zarour,[14] Kevin Gergich,[15] Xiaoyun (Nicole) Li,[15] Robert Iannone,[15] S. Peter Kang,[15] Scot Ebbinghaus,[15] Caroline Robert[16]

[1]University of California, Los Angeles, CA; [2]Dana-Farber Cancer Institute, Boston, MA; [3]Crown Princess Mary Cancer Centre, Westmead Hospital and Melanoma Institute Australia, Sydney, Australia; [4]University of Sydney, Sydney, Australia; [5]The Angeles Clinic and Research Institute, Los Angeles, CA; [6]University of California, San Francisco, CA; [7]Memorial Sloan-Kettering Cancer Center, New York, NY; [8]MD Anderson Cancer Center, Houston, TX; [9]Abramson Cancer Center at the University of Pennsylvania, Philadelphia, PA; [10]South Texas Accelerated Research Therapeutics, San Antonio, TX; [11]Princess Margaret Hospital, Toronto, Ontario; [12]H. Lee Moffitt Cancer Center, Tampa, FL; [13]Mayo Clinic, Rochester, MN; [14]University of Pittsburgh, Pittsburgh, PA; [15]Merck & Co., Inc., Whitehouse Station, NJ; [16]Institut Gustave-Roussy, Villejuif, France

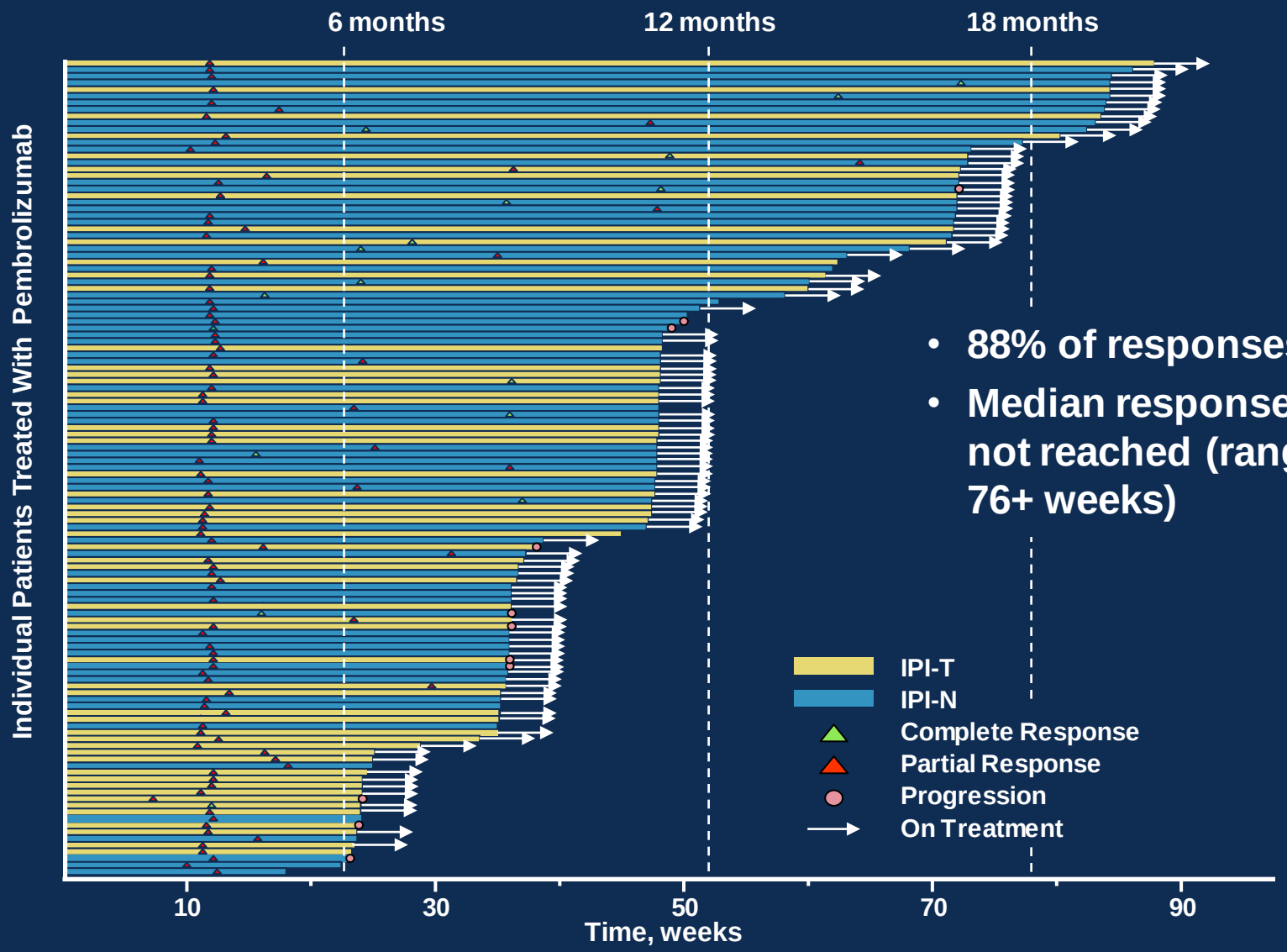
ASCO 50 ANNUAL MEETING SCIENCE & SOCIETY

Maximum Percent Change from Baseline in Tumor Size[a] (Central Review, RECIST v1.1)



[a]In patients with measurable disease at baseline by RECIST v1.1 by central review and ≥1 postbaseline assessment (n = 317).
Percentage changes >100% were truncated at 100%.
Analysis cut-off date: October 18, 2013.

Time to and Durability of Response (Central Review, RECIST v1.1)

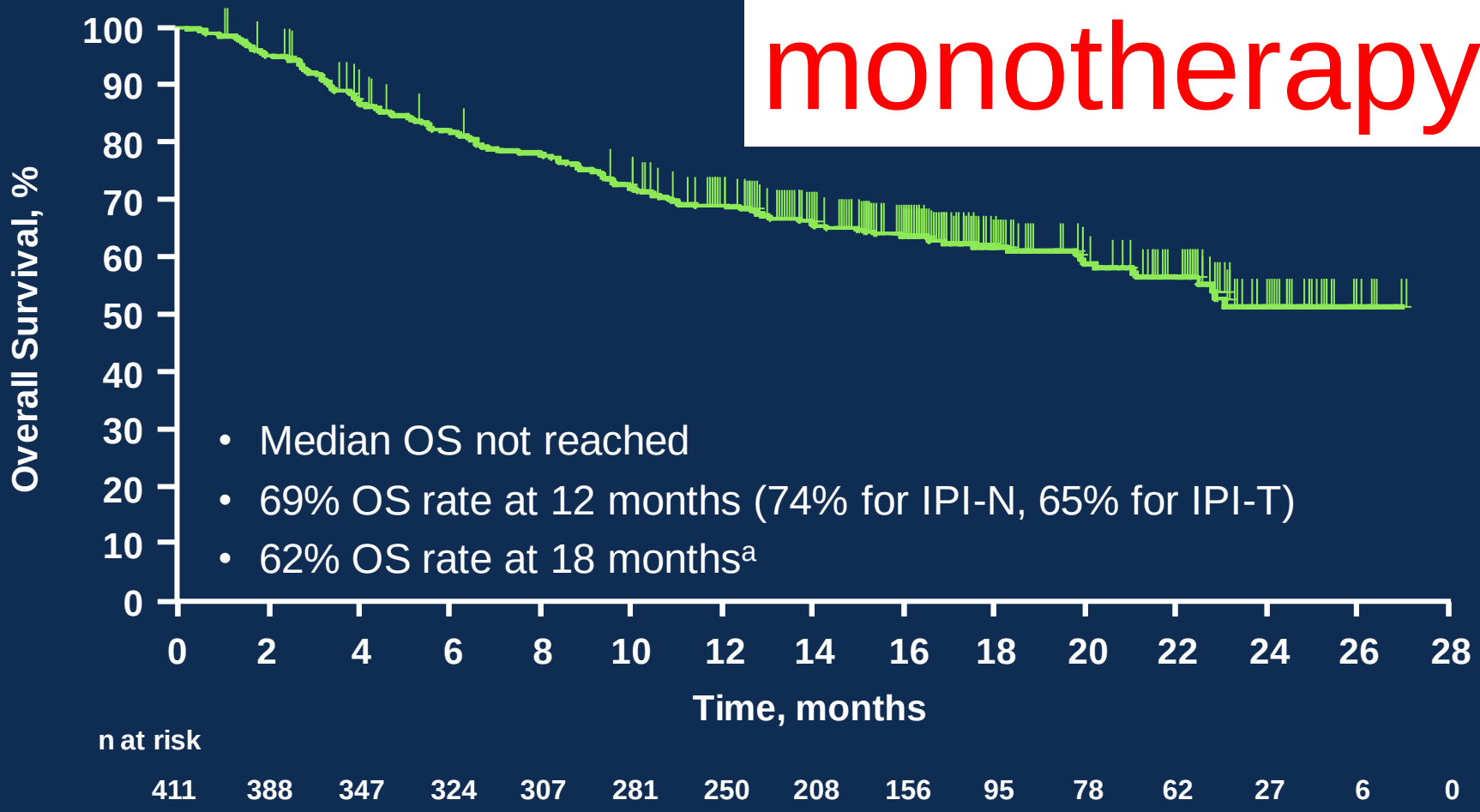


- 88% of responses ongoing[a]
- Median response duration not reached (range, 6+ to 76+ weeks)

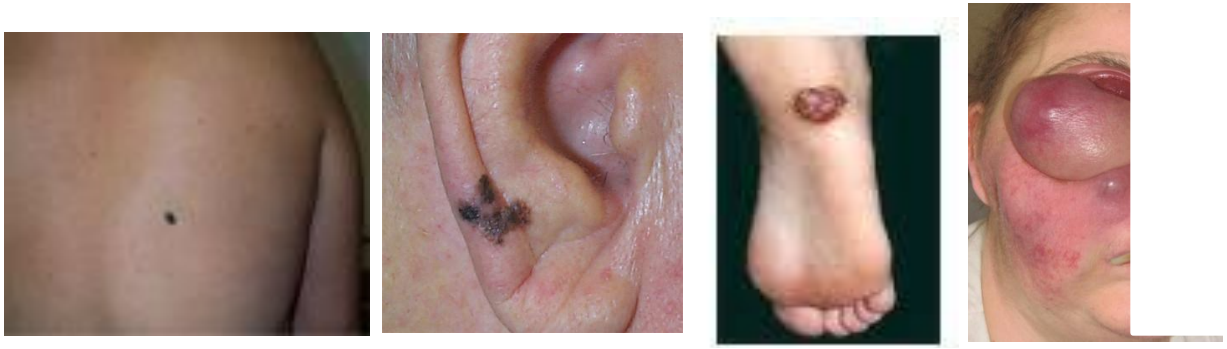
[a]Ongoing response defined as alive, progression free, and without new anticancer therapy.
Analysis cut-off date: October 18, 2013.

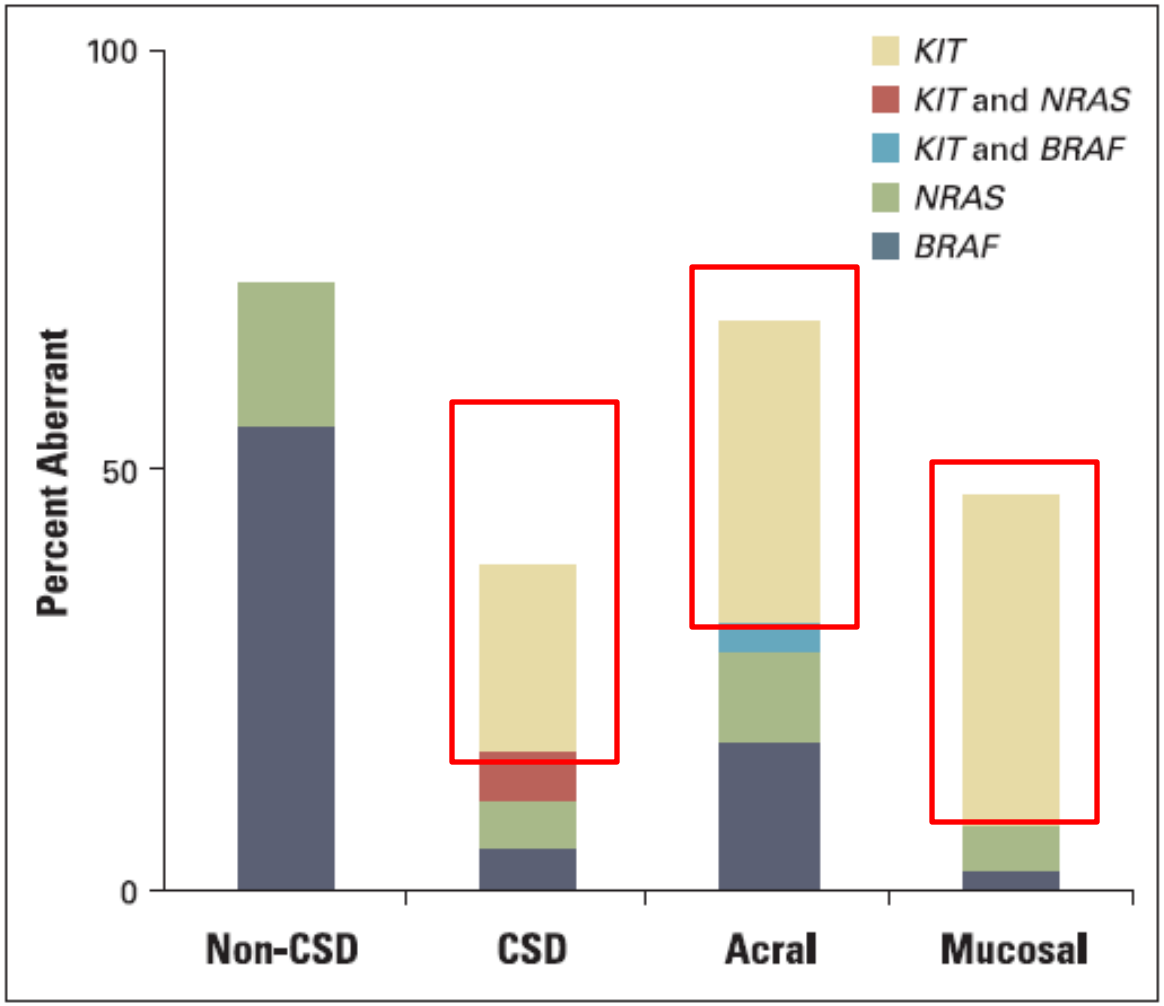
Kaplan-Meier Estimate of Overall Survival

monotherapy

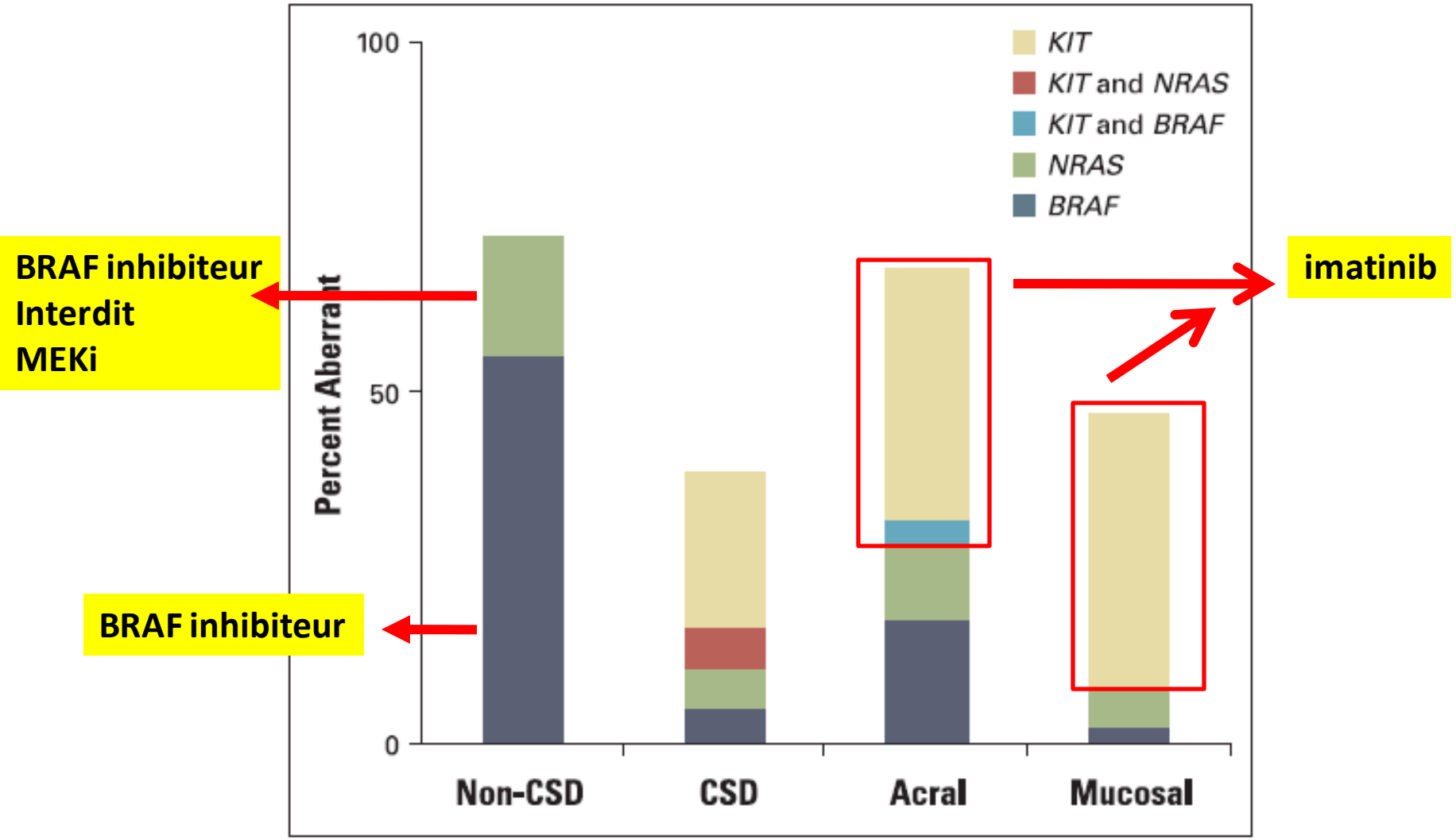


[a]OS rate at 18 months is driven by the 135 patients enrolled in the nonrandomized cohorts because they have the longest follow-up duration.
Analysis cut-off date: May 2014.




100
50
0
Percent Aberrant
KIT
KIT and NRAS
KIT and BRAF
NRAS
BRAF
Non-CSD
CSD
Acral
Mucosal

Vers un diagnostic moléculaire



JCO 2006; 24: 4340

Time to digest !

Targeted therapies

BRAFi
MEKi

Immune checkpoint

CTLA-4
PD1/PD-L1

A new player : T-VEC : oncolytic virus