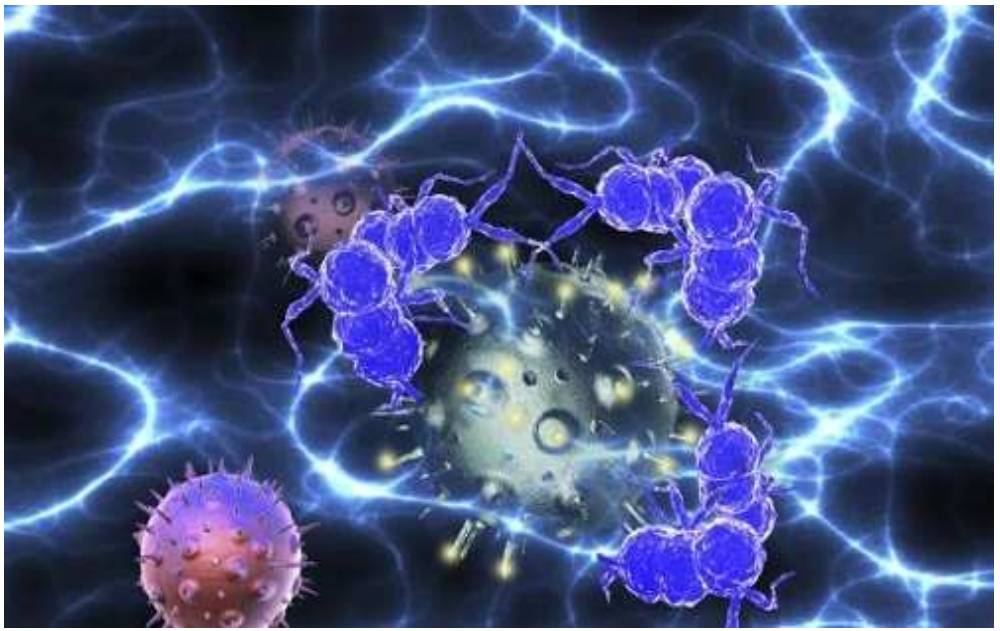
XXVI CORSO DI FORMAZIONE PER VOLONTARI ALL'ASSISTENZA DEL MALATO ONCOLOGICO



Nuove frontiere: la ricerca immunologica

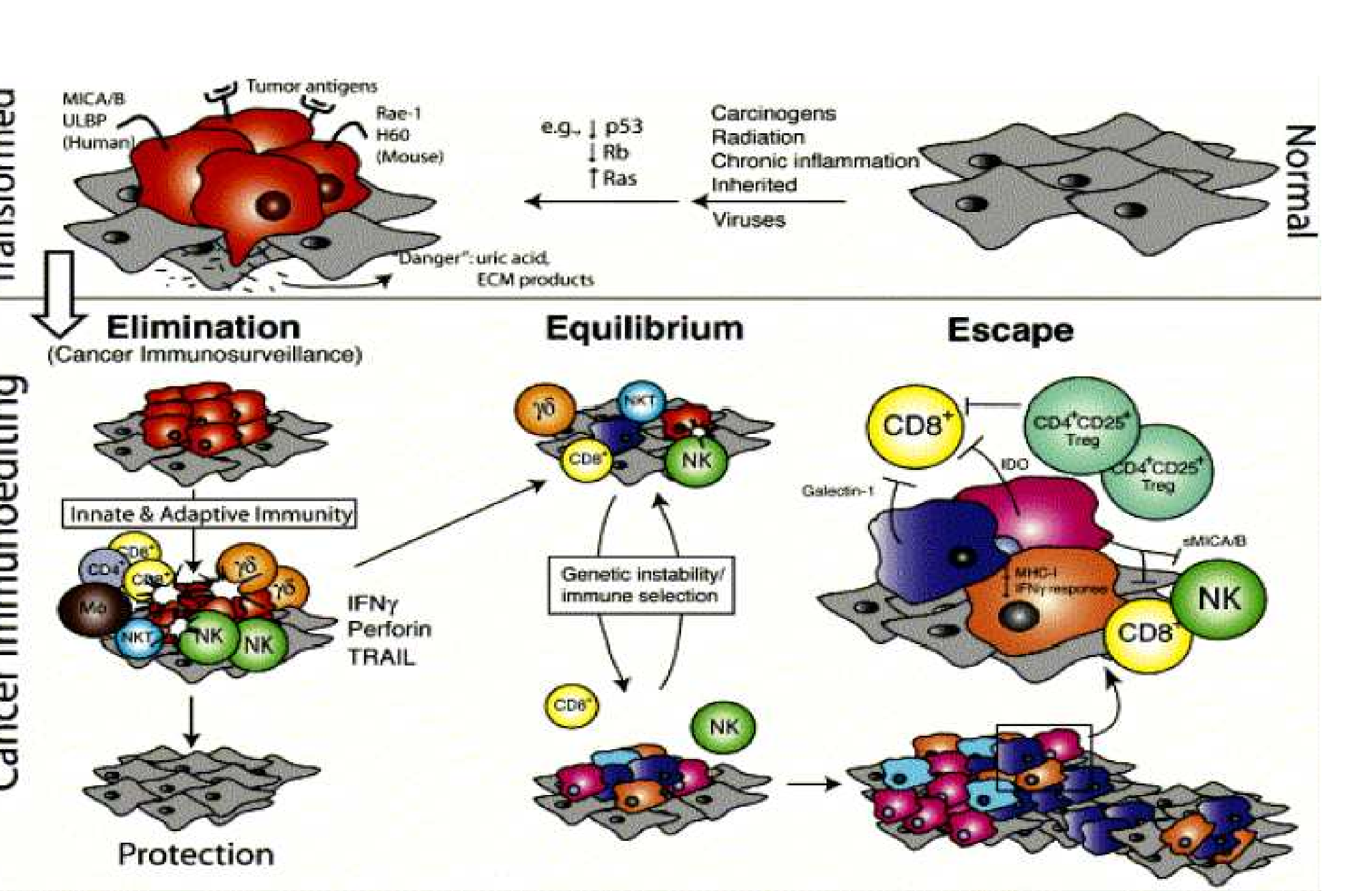
Vanna Chiarion Sileni
Vanna.chiarion@ioveneto.it

Current strategies to combat cancers

- **Mechanics** -- surgery, 1600BC
- **Physics** -- radiotherapy, 1896
- **Chemistry** -- chemotherapy, 1942
- **Biology** -- immunotherapy, 1976

Advantages of Immunotherapy for cancer

- Cancer cells are immunogenic
- Single cell kill
- Migrate to tissue
- Memory
- Specific
- Life-long protection


Transformed
MICA/B
ULBP
(Human)
Tumor antigens
Rae-1
H60
(Mouse)
"Danger": uric acid,
ECM products
e.g., ↓ p53
↓ Rb
↑ Ras
Carcinogens
Radiation
Chronic inflammation
Inherited
Viruses
Normal
Cancer immunoediting
Elimination
(Cancer Immunosurveillance)
Innate & Adaptive Immunity
IFNγ
Perforin
TRAIL
Protection
Equilibrium
Genetic instability/
immune selection
Escape
CD8+
CD4+CD25+
Treg
IDO
Galectin-1
sMICA/B
MHC-I
IFNγ response
NK
CD8-

Autoimmune Diseases

Brain
Multiple Sclerosis
Guillaun-Barre Syndrome
Autism

Thyroid
Thyroiditis
Hashimoto's Disease
Graves' Disease

Blood
Leukemia
Lupus Erythematosus
Hemolytic Dysglycemia

Bones
Rheumatoid Arthritis
Ankylosing Spondylitis
Polymyalgia Rheumatica

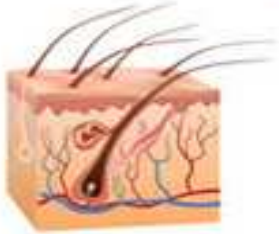
GI Tract
Celiac's Disease
Crohn's Disease
Ulceratic Colitis
Diabetes Type I

>100 Autoimmune Diseases

Muscles
Muscular Dystrophy
Fibromyalgia

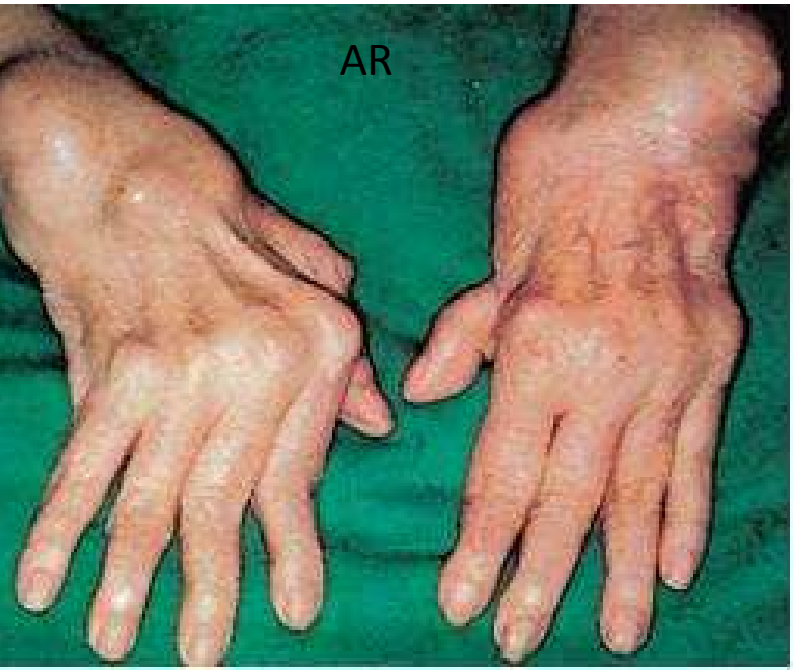
Nerves
Peripheral Neuropathy
Diabetic Neuropathy

Lung
Fibromyalgia
Wegener's Granulomatosis



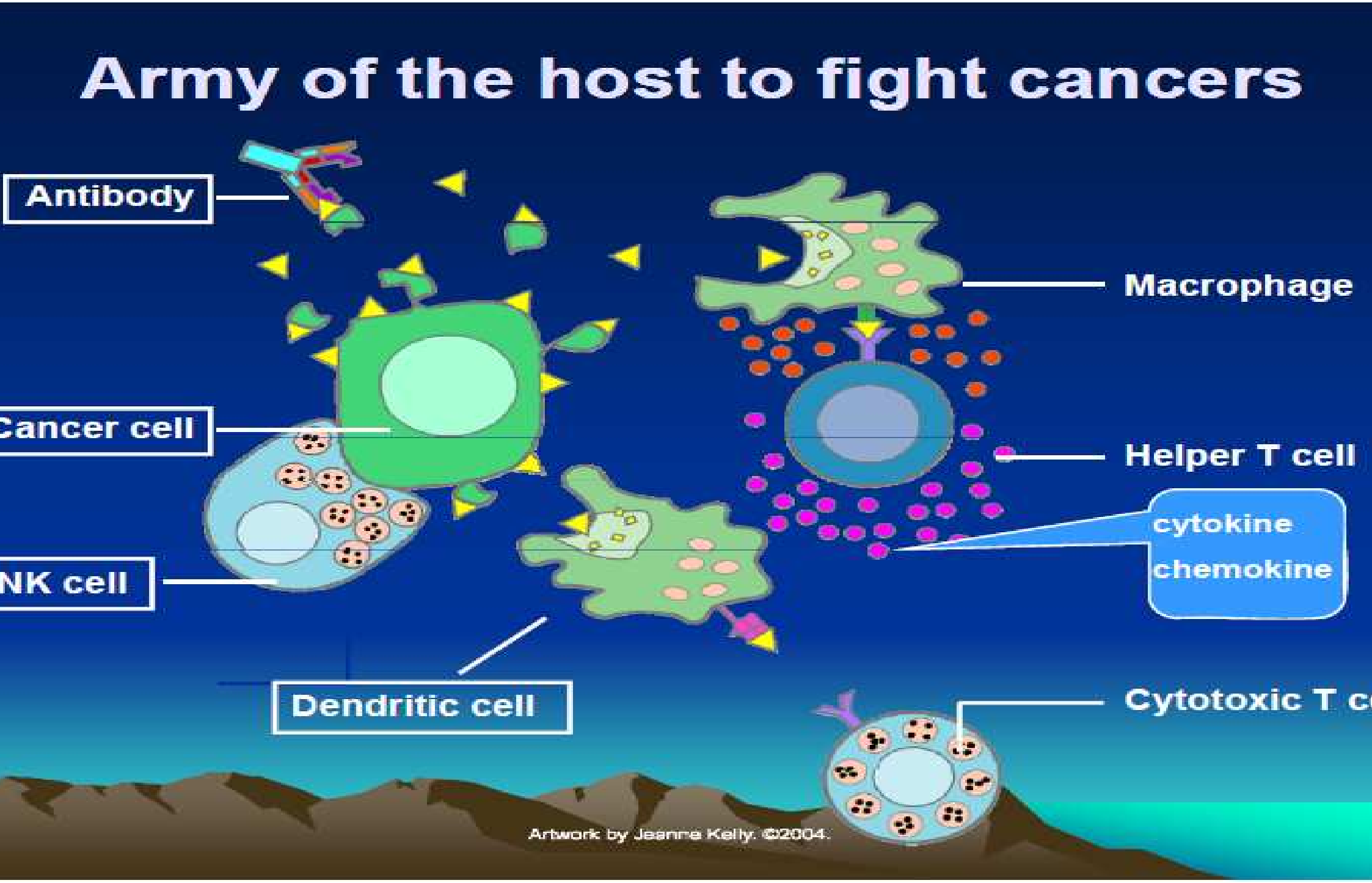
Skin
Psoriasis
Vitiligo
Eczema
Scleroderma


SEL

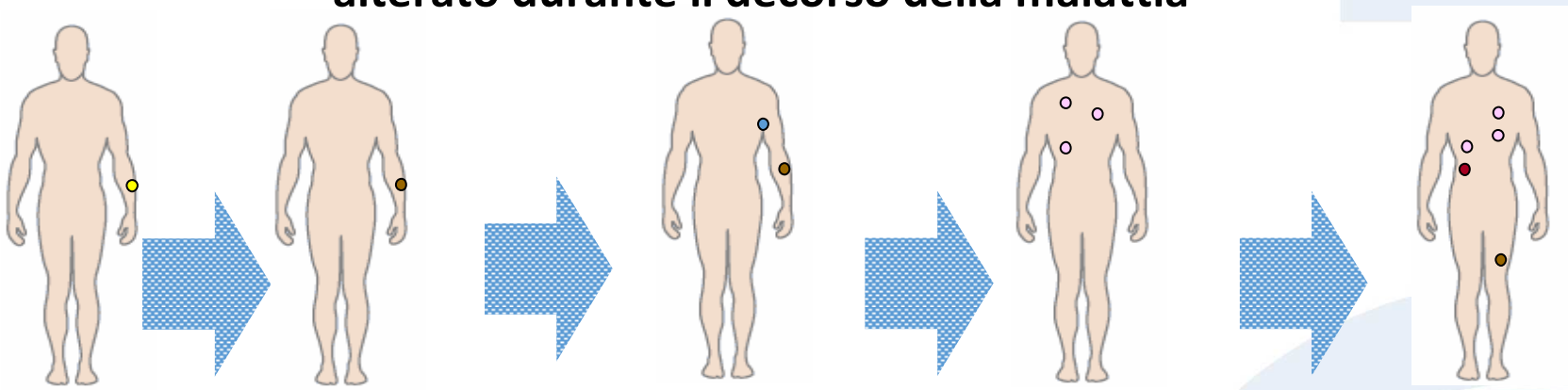

AR


psoriasis

Progressive vitiligo


Army of the host to fight cancers
Antibody
Macrophage
Cancer cell
Helper T cell
cytokine
chemokine
NK cell
Dendritic cell
Cytotoxic T c
Artwork by Jeanne Kelly. ©2004.

L'immunità anti-tumore è un fenomeno iniziale, che viene progressivamente alterato durante il decorso della malattia

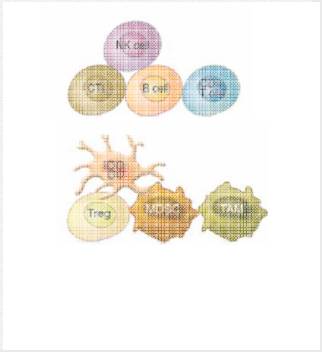


Stadio I
Malattia primitiva iniziale
Prognosi favorevole

Malattia non-clinicamente evidente

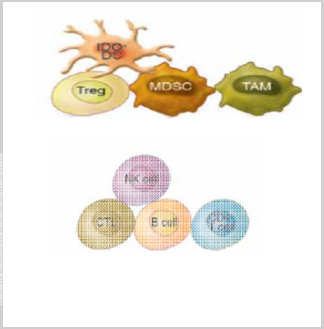
Risposte immunitarie efficaci

Stadio I-II
Malattia primitiva iniziale
Prognosi Sfavorevole



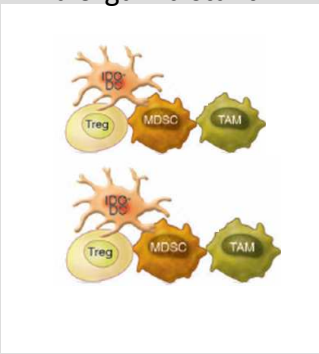
Limitata risposta immunitaria e iniziale immunosoppressione

Stadio III
Malattia nei linfonodi drenanti



Alterazioni strutturali e funzionali deil'immunità linfonodale

Stadio IV
Malattia metastatica a organi distanti

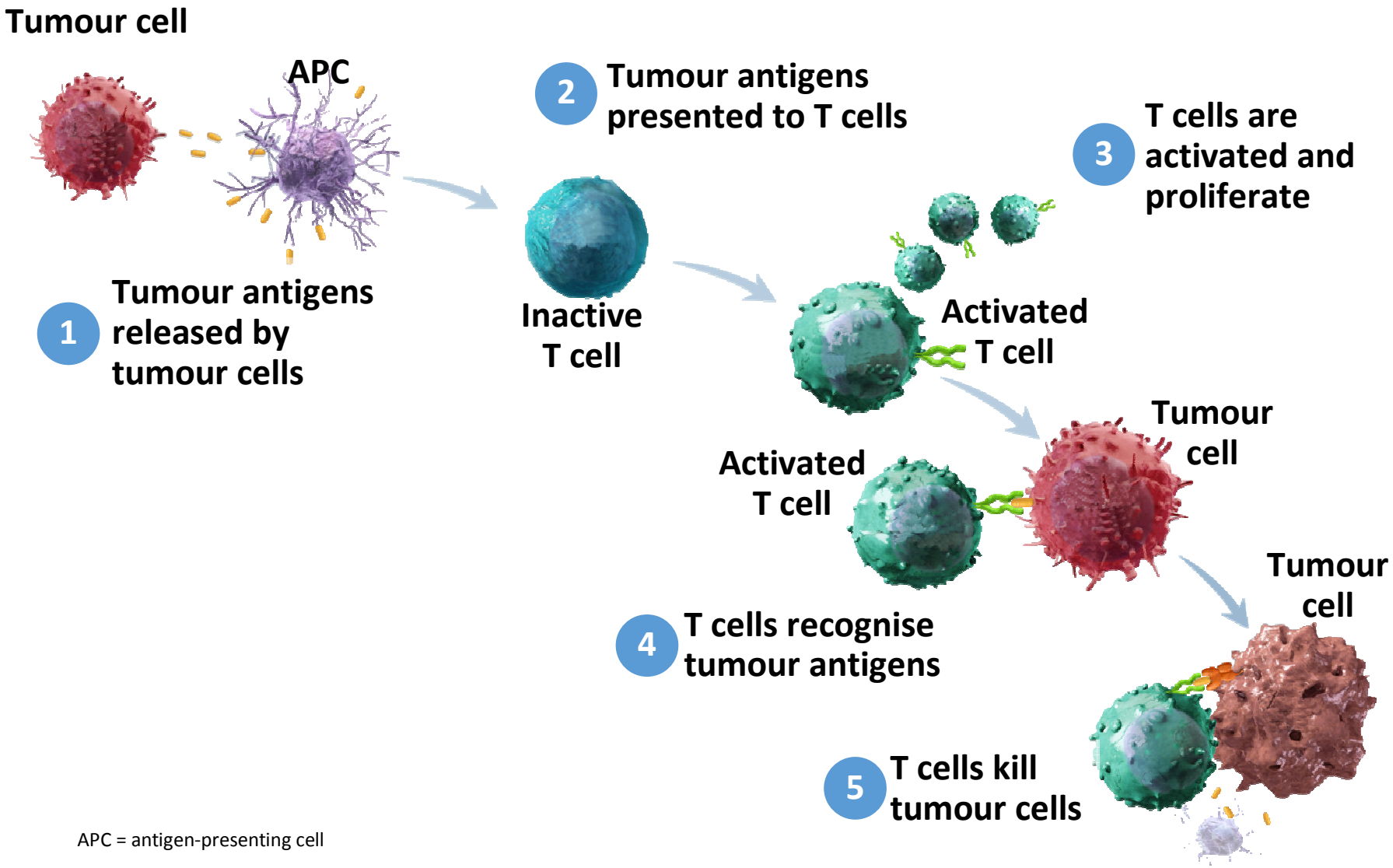


Accumulo di cellule disfunzionali e immunosoppressorie negli organi linfoidi e nel midollo

Stadio IV
Malattia metastatica avanzata

Soppressione dell'immunità anti-tumorale a livello sistemico

The T-cell Anti-Tumour Response

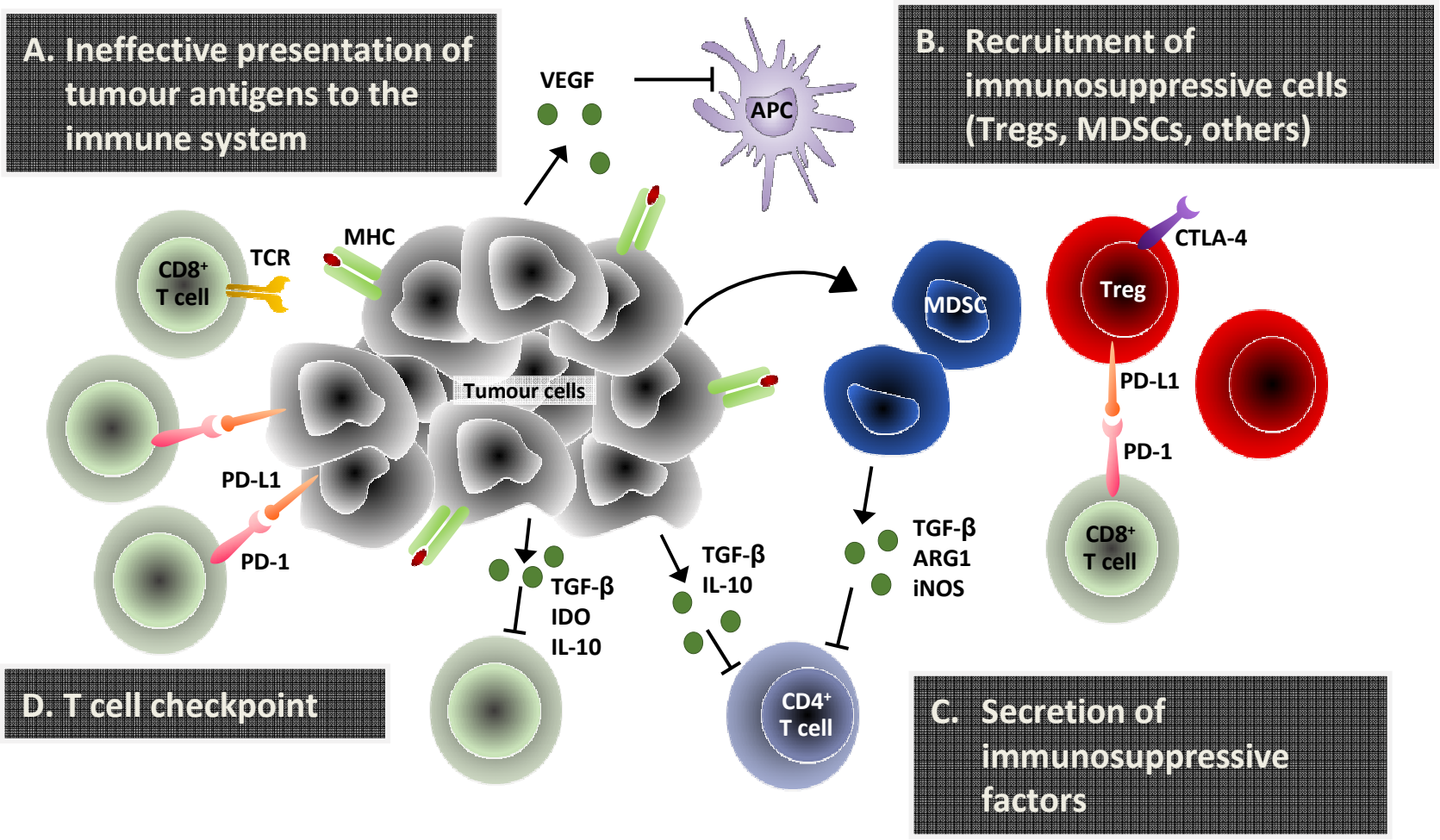


APC = antigen-presenting cell

Andersen MH, et al. J Invest Dermatol 2006;126:32–41; Pardoll DM. Nat Rev Cancer 2012;11:252–64; Mellman I, et al. Nature 2011;480:480–9; Heemskerk B, et al. EMBO J 2013;32:194–203; Boudreau JE, et
Mol Ther 2011;19:841–53; Janeway CA, et al. Immunobiology: The Immune System in Health and Disease. 6th ed. New York, NY: Garland Science; 20

Tumours Use Various Mechanisms to Escape the Immune System

Immune escape mechanisms are complex and frequently overlapping

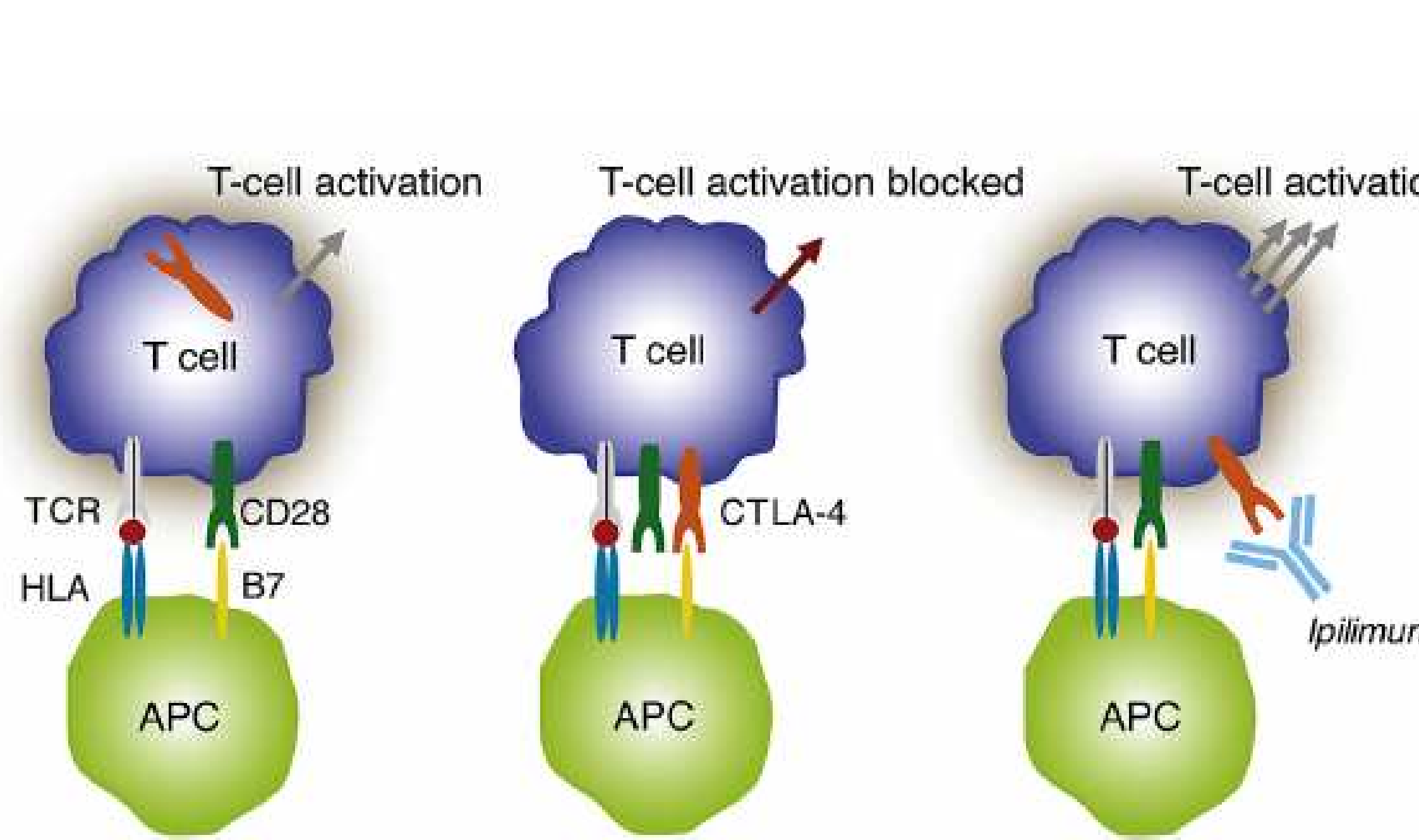


Vesely MD, et al. Ann Rev Immunol 2011;29:235-

Cancer is a chronic immunologic disease

- Cancer is recognized by immuno system
  (TAA, CTL)

- Tumors have multiple mechanisms to evade the immuno system
  - Expression of molecules that inhibit
    immune responses


T-cell activation
T cell
TCR
CD28
HLA
B7
APC
T-cell activation blocked
T cell
CTLA-4
APC
T-cell activatio
T cell
Ipilimur
APC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

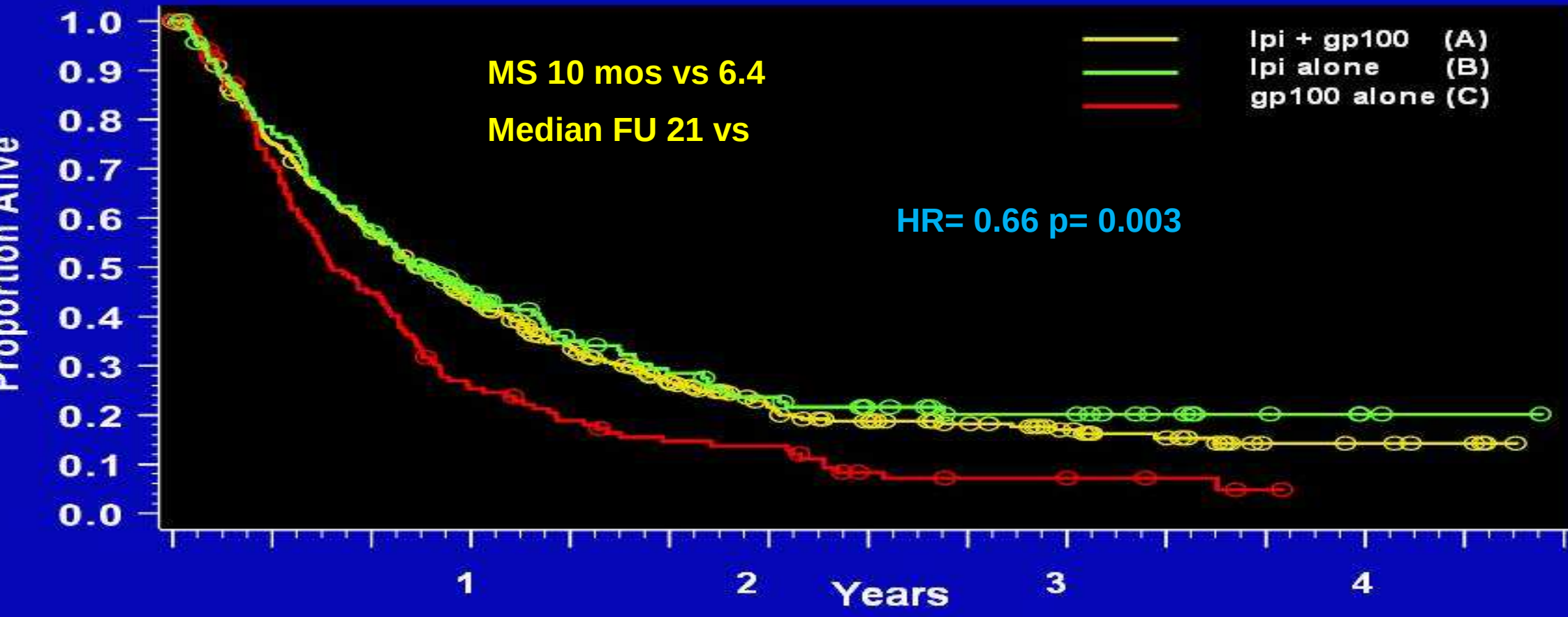
Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

Approval for any-line treatment of advanced melanoma by FDA in 2011

Approval for second-line treatment by EMA in 2012

Approval for any-line treatment since October 2013

Kaplan-Meier Analysis of Survival

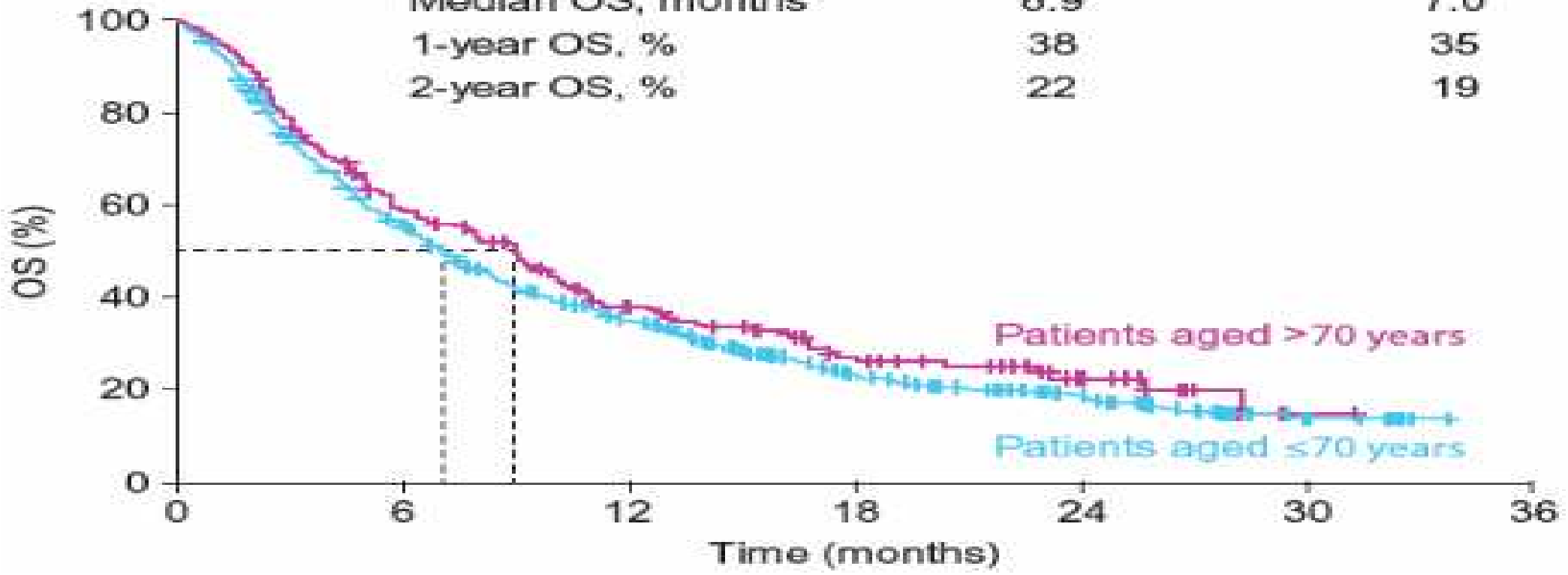


Survival Rate	Ipi + gp100 N=403	Ipi + pbo N=137	gp100 + pbo N=136
1 year	44%	46%	25%
2 year	22%	24%	14%

Efficacy and safety of ipilimumab in elderly patients with pretreated advanced melanoma treated at Italian centres through the expanded access programme

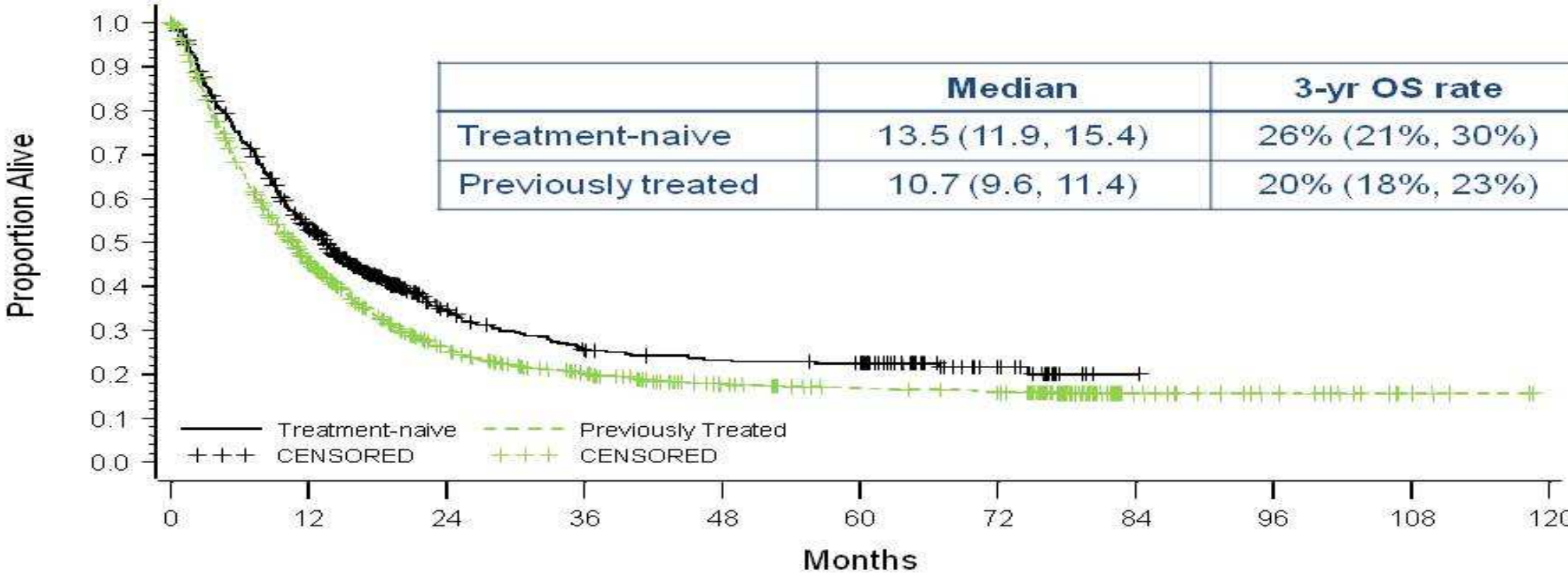
Anna Chiarion Sileni[1*], Jacopo Pigozzo[1], Paolo Antonio Ascierto[2], Antonio Maria Grimaldi[2], Michele Maio[3], Lorenza Di Guardo[4], Paolo Marchetti[5,6], Francesco de Rosa[7], Carmen Nuzzo[8], Alessandro Testori[9], Emilia Cocorocchio[10], Maria Grazia Bernengo[11], Michele Guida[12], Riccardo Marconcini[13], Barbara Merelli[14], Giorgio Parmiani[15], Gaetana Rinaldi[16], Massimo Aglietta[17,18], Marco Grosso[19] and Paola Queirolo[19]

	>70 years (n=193)	≤70 years (n=662)
Median OS, months	8.9	7.0
1-year OS, %	38	35
2-year OS, %	22	19



Journal of Experimental & Clinical Cancer Research 2014, 33:3

Subset Ipilimumab OS Analyses by Prior Therapy (N=1861)*



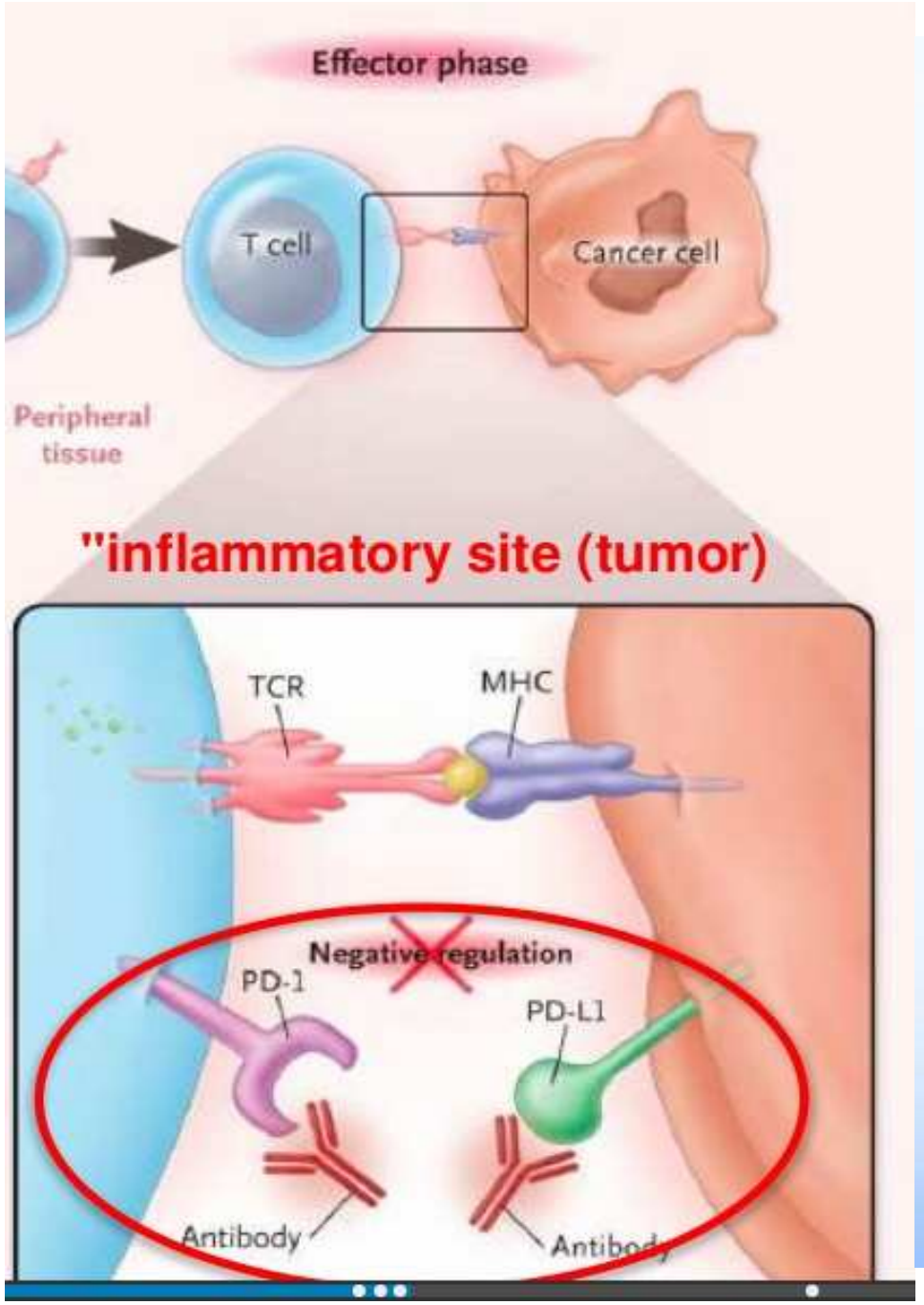
	Median	3-yr OS rate
Treatment-naive	13.5 (11.9, 15.4)	26% (21%, 30%)
Previously treated	10.7 (9.6, 11.4)	20% (18%, 23%)

ts at Risk

ent-naive	604	301	106	74	64	60	18	1	0	0	0
usly treated	1257	538	264	180	128	110	102	25	15	5	0

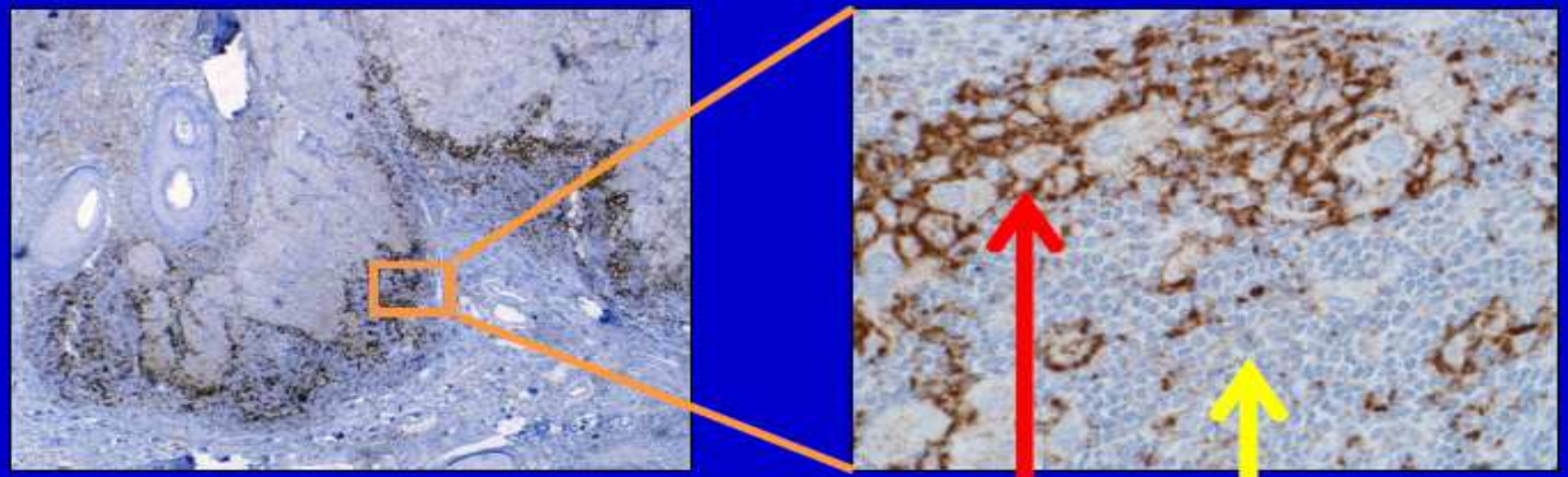
randomized subset analyses.

Presented By Axel Hauschild at 2014 ASCO Annual Meeting

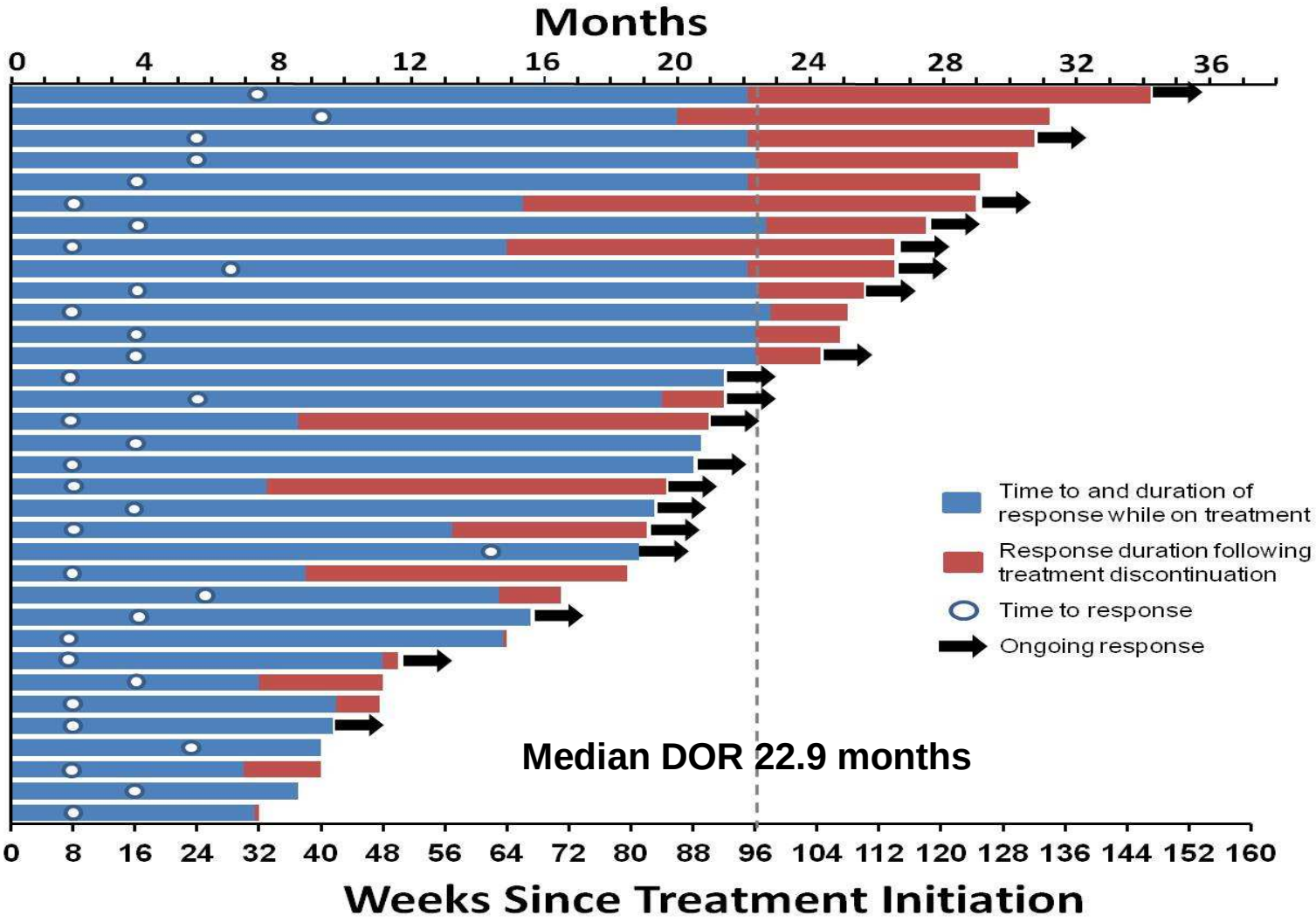


- anti-PD-1 mAbs
  - ✧ nivolumab, IgG4 (Opdivo^{tm}, BMS)
  - ✧ pembrolizumab, IgG4 (Keytruda^{tm},Merck)
- anti-PD-L1
  - ✧ MDPL3280A, IgG1 (Roche)
  - ✧ MEDI-4736, IgG1 (AZN)
- These agents block the interaction of PD-L1 (expressed on tumor cells and Tregs) with PD-1 expressed on T effector cells

Focal PD-L1 expression in melanoma: geographic co-localization with TILs creates a "shield" against immune attack

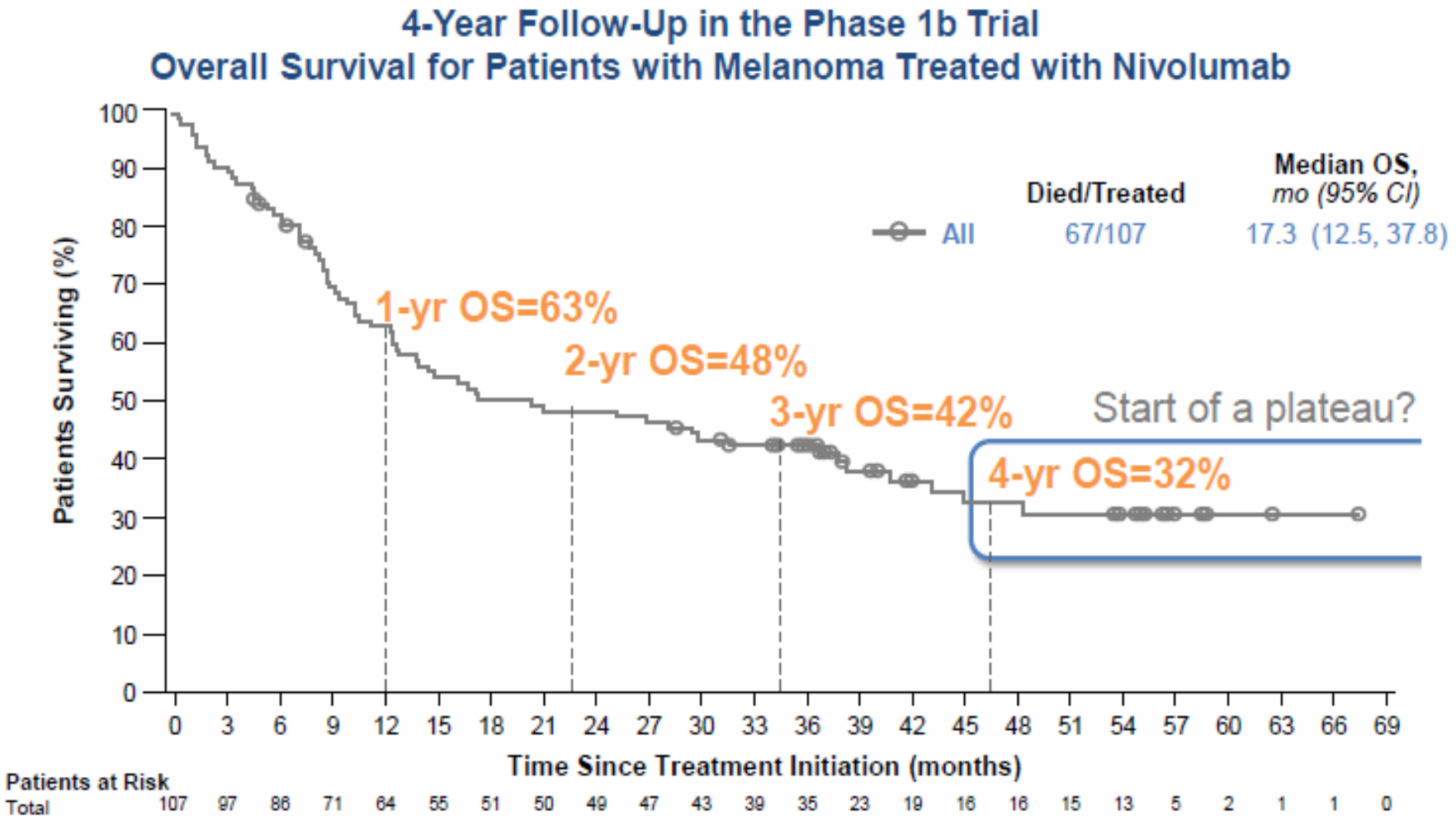


esponse Characteristics in Patients with Melanoma eceiving Nivolumab



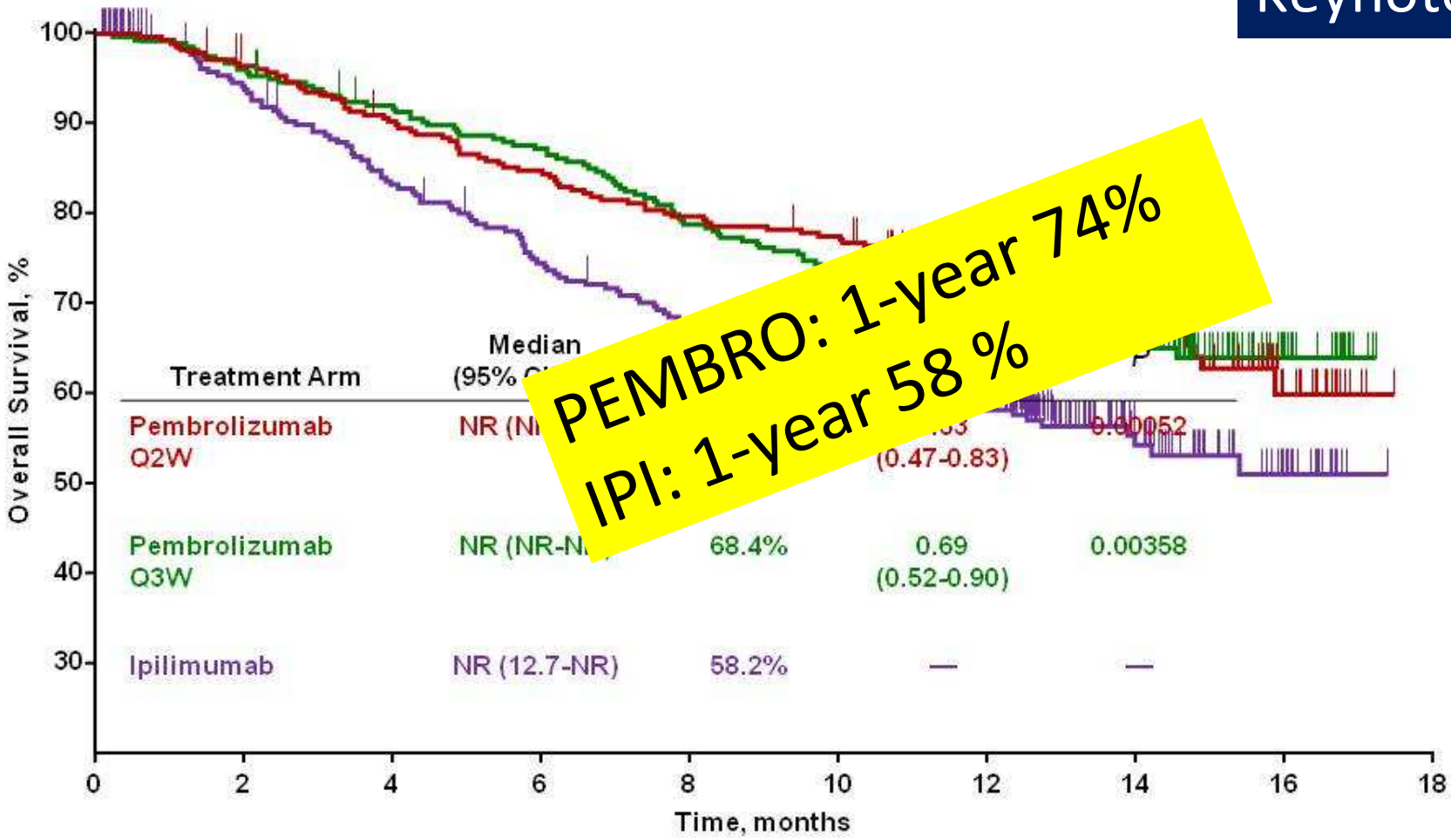
Presented by: F. Stephen Hodi, MD

Long-Term Survival in Checkmate-003



OS at the Second Interim Analysis

Keynote-006

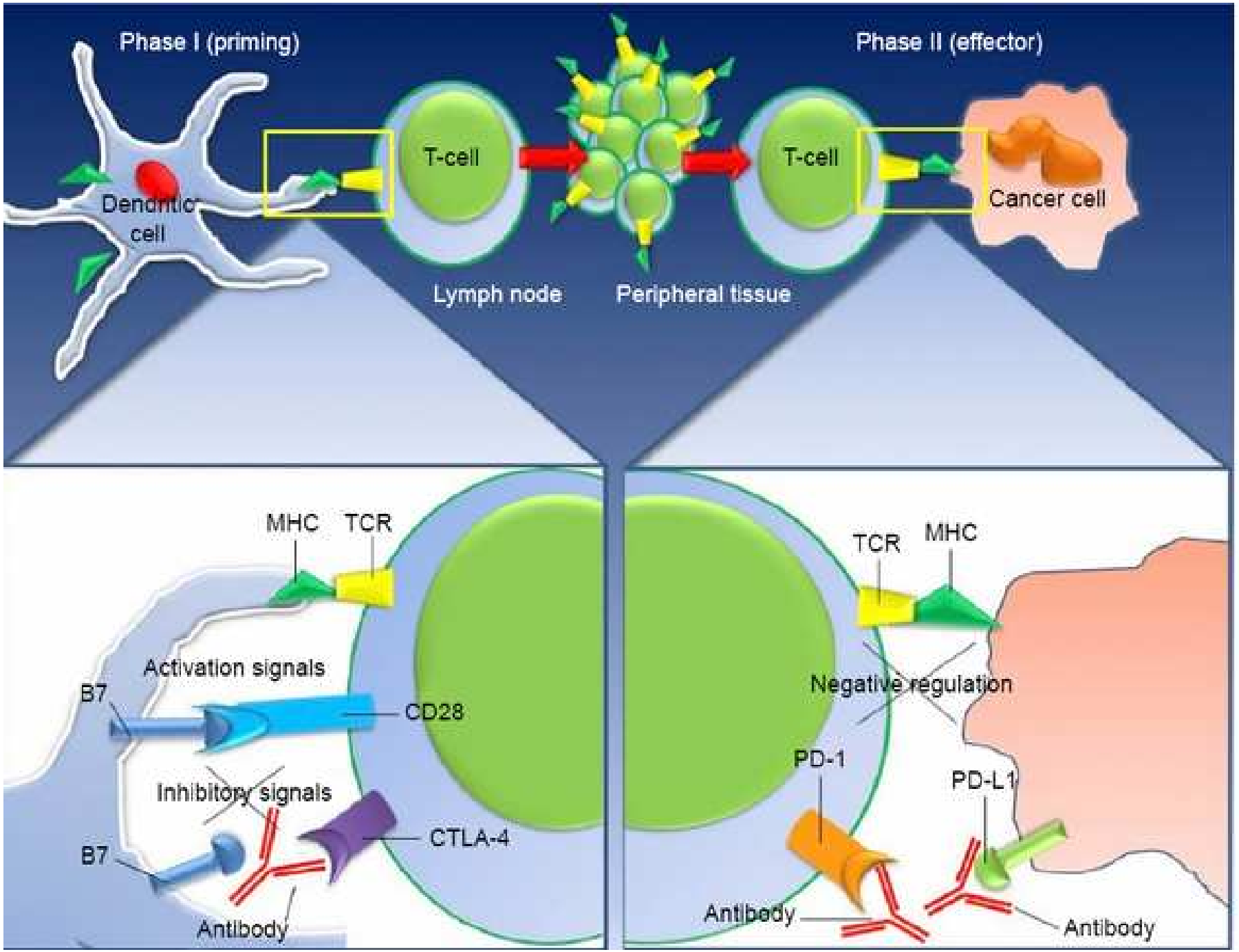


PEMBRO: 1-year 74%
IPI: 1-year 58 %

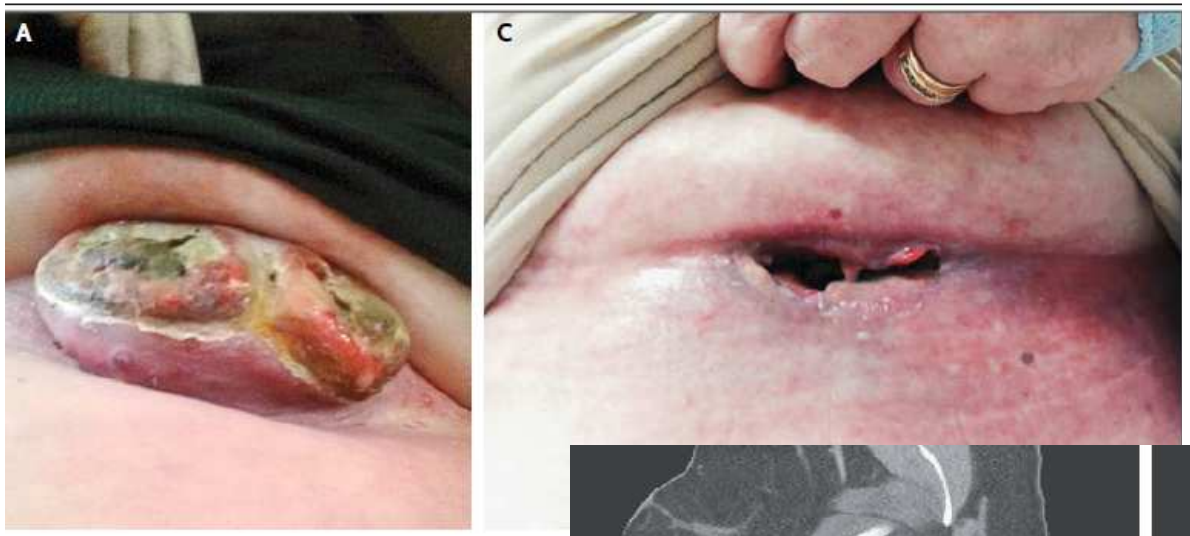
NEJM, Robert et al 2015

Analysis cut-off date: March 3, 2015.

Presented By Lynn Schuchter at 2015 ASCO Annual Meeting

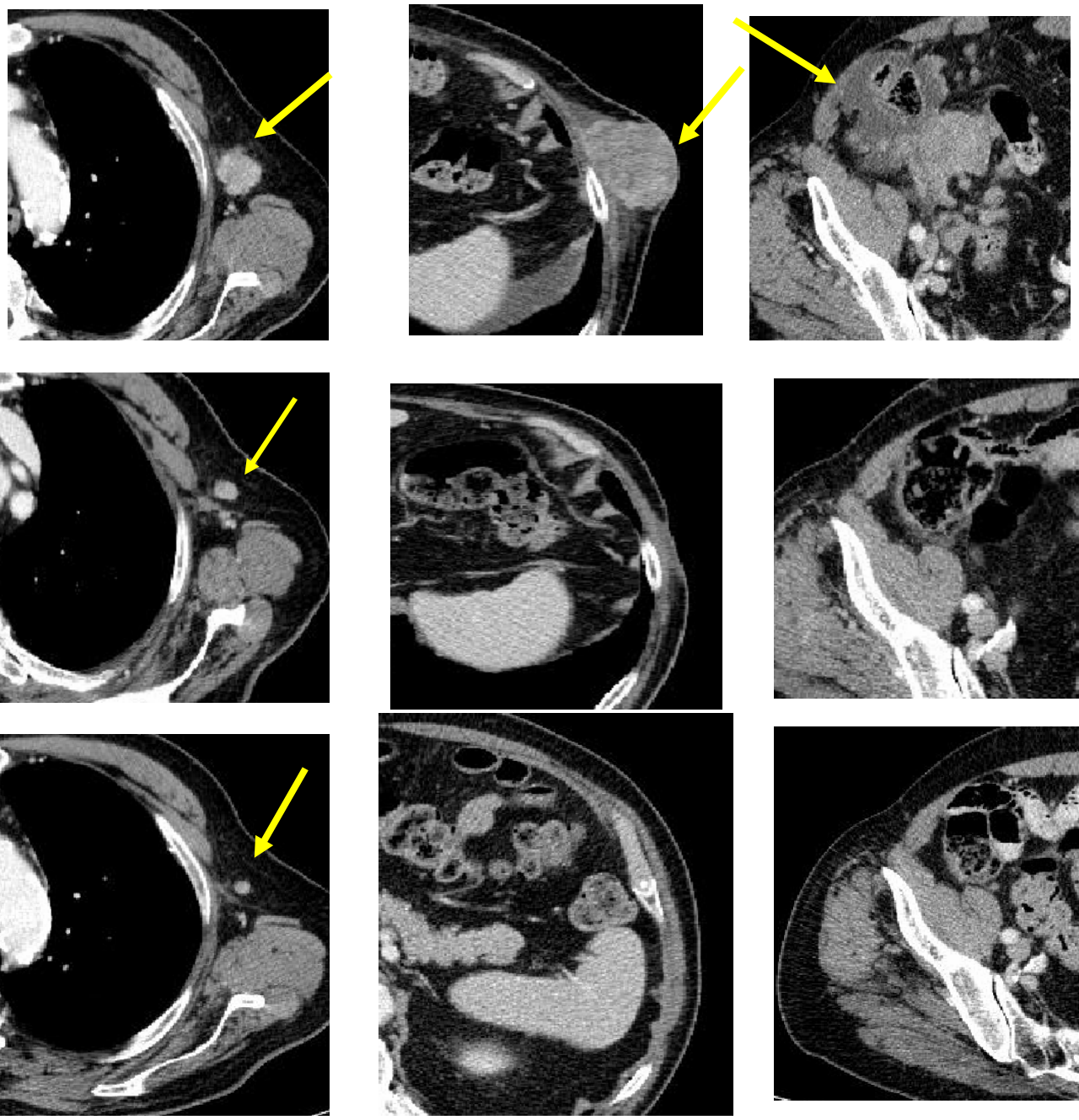

Phase I (priming)
Phase II (effector)
Dendritic cell
T-cell
T-cell
Cancer cell
Lymph node
Peripheral tissue
MHC
TCR
Activation signals
B7
CD28
Inhibitory signals
B7
CTLA-4
Antibody
TCR
MHC
Negative regulation
PD-1
PD-L1
Antibody
Antibody

Rapid Eradication of a Bulky Melanoma Mass with One Dose of Immunotherapy



Paul B. Chapman, M.D.
Sandra P. D'Angelo, M.D.
Jedd D. Wolchok, M.D., Ph.D.

IPI vs NIVO vs IPI+NIVO (M , 80-y, NRAS mut)

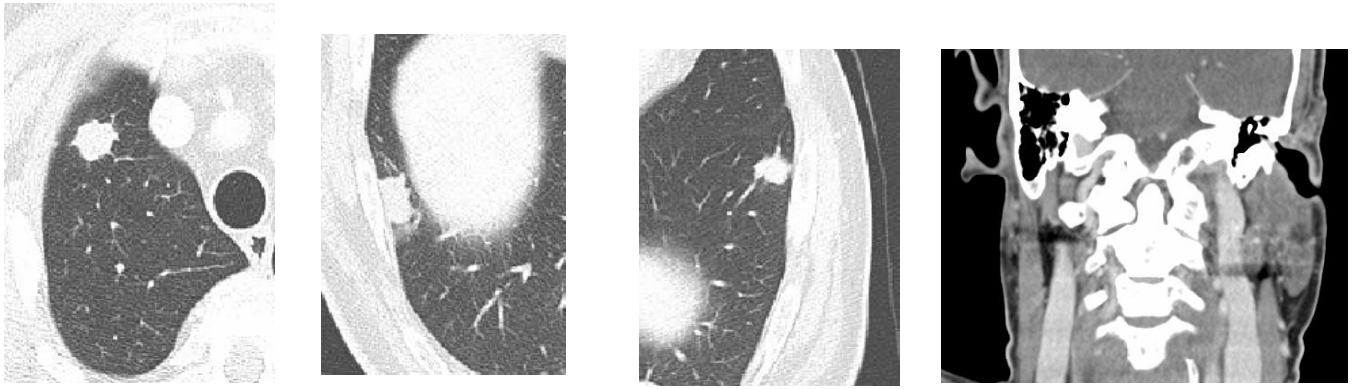


Nov 2013 baseline

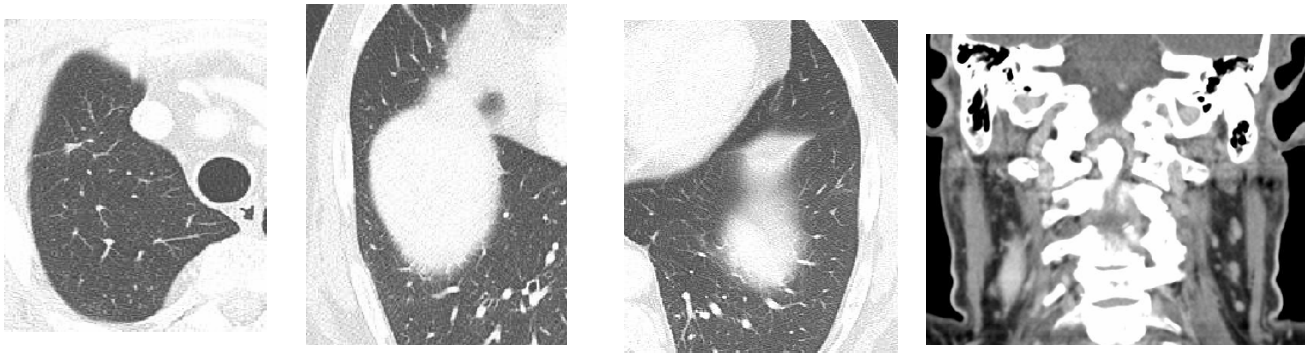
Feb 2014

Jan 2015

IPI vs NIVO vs IPI+NIVO (M,62-y, wt)



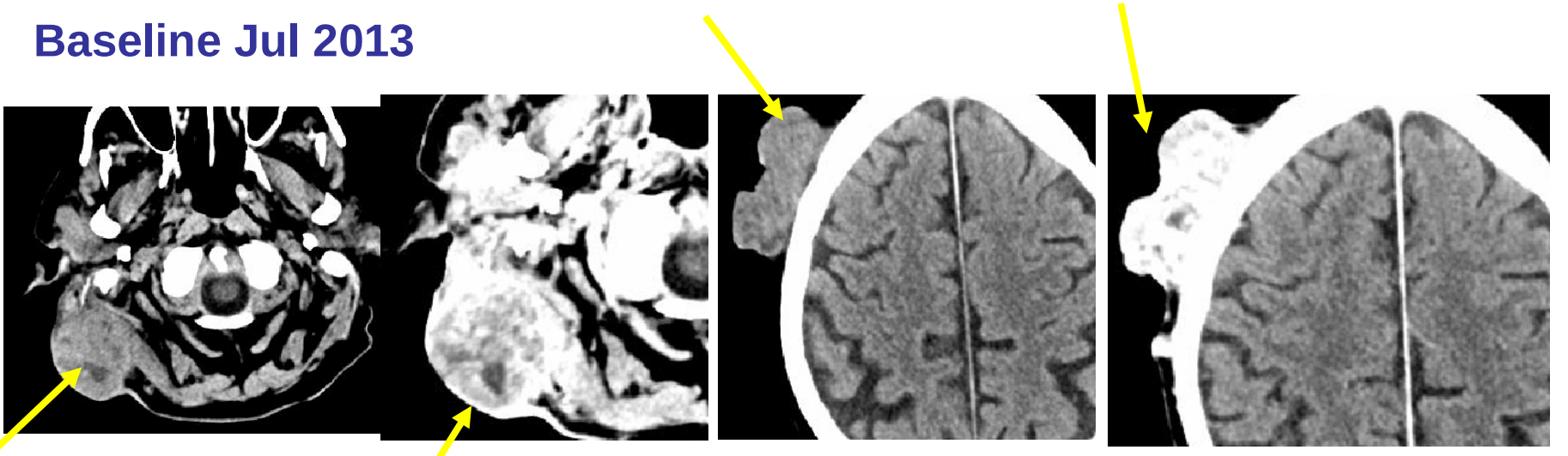
OCT 2013
baseline



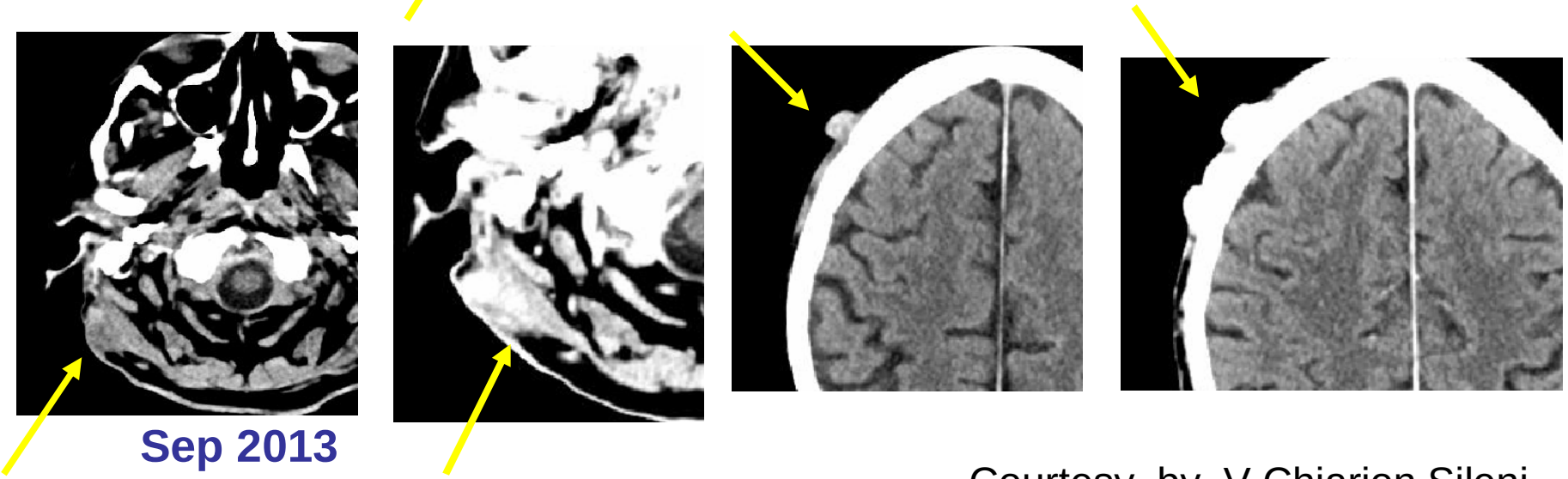
Jan 2014

262 BMS 066 Male 67-y old, pT4bN3M1b NRAS mut (c.182A>T=p.Q61L del)

Baseline Jul 2013

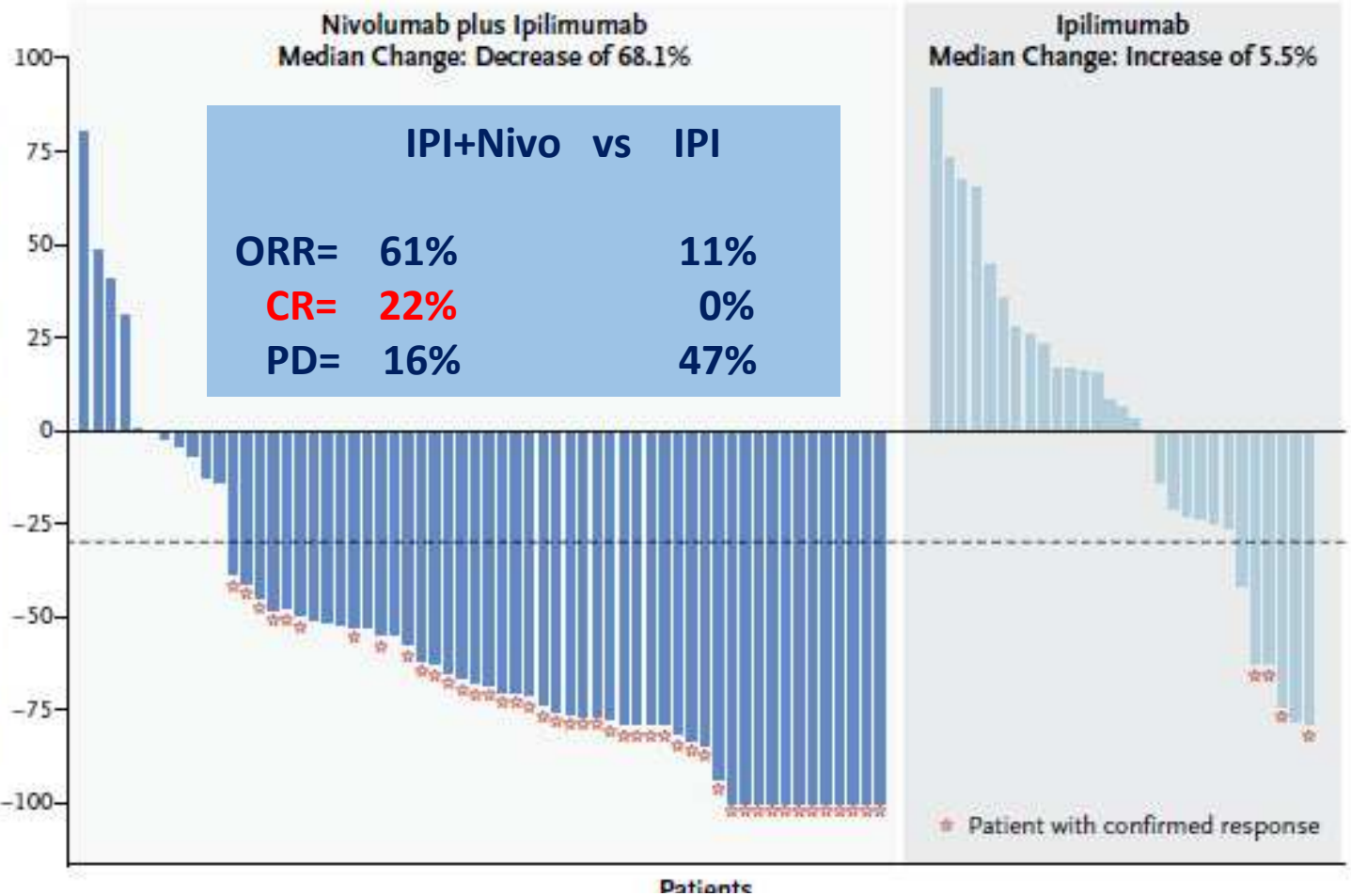


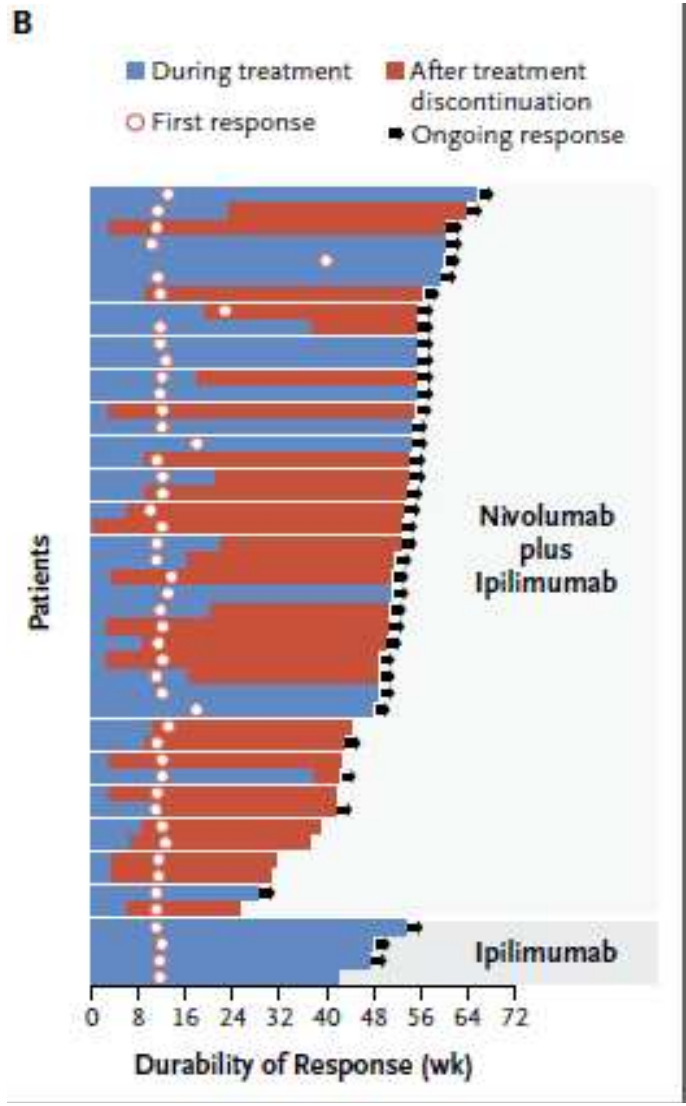
Sep 2013



Courtesy by V.Chiarion Sileni

Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma



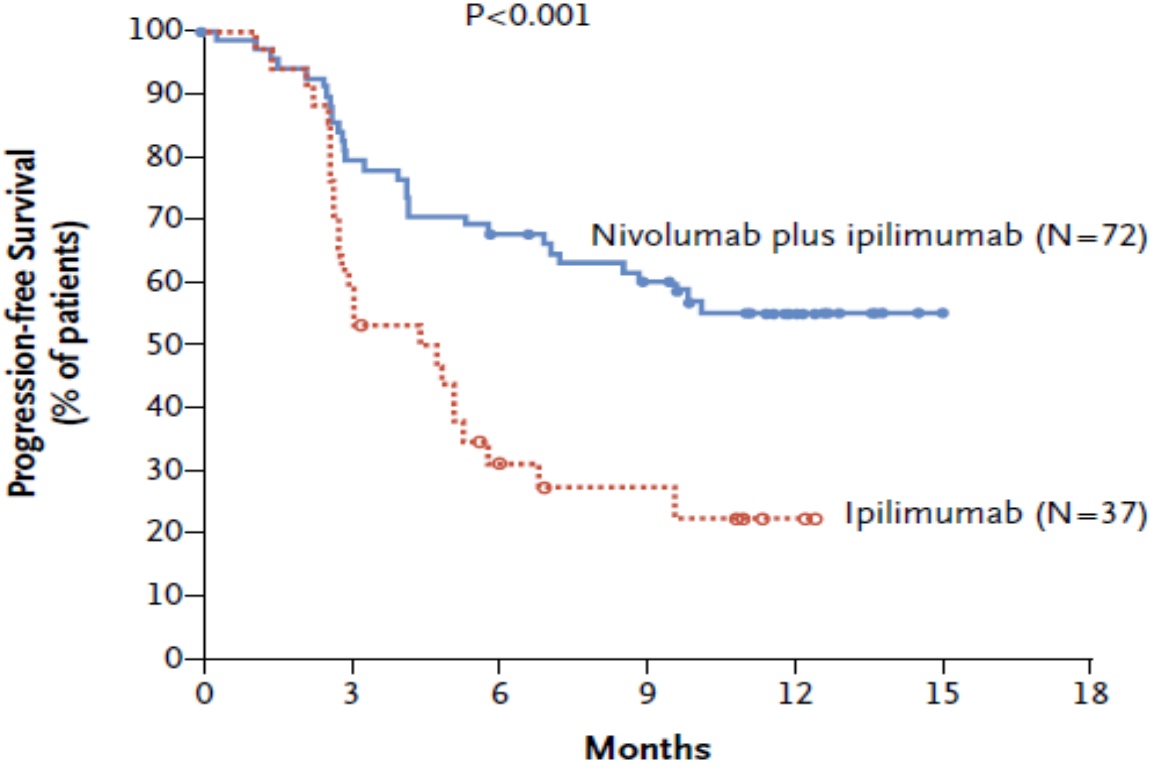


MA.Postow et al NEJM 2015

Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma

	Death or Disease Progression	Median Progression-free Survival
	no. of patients/total no.	*mo (95% CI)*
Nivolumab plus Ipilimumab	30/72	NR
Ipilimumab	25/37	4.4 (2.8–5.7)

Hazard ratio, 0.40 (95% CI, 0.23–0.68)
P<0.001

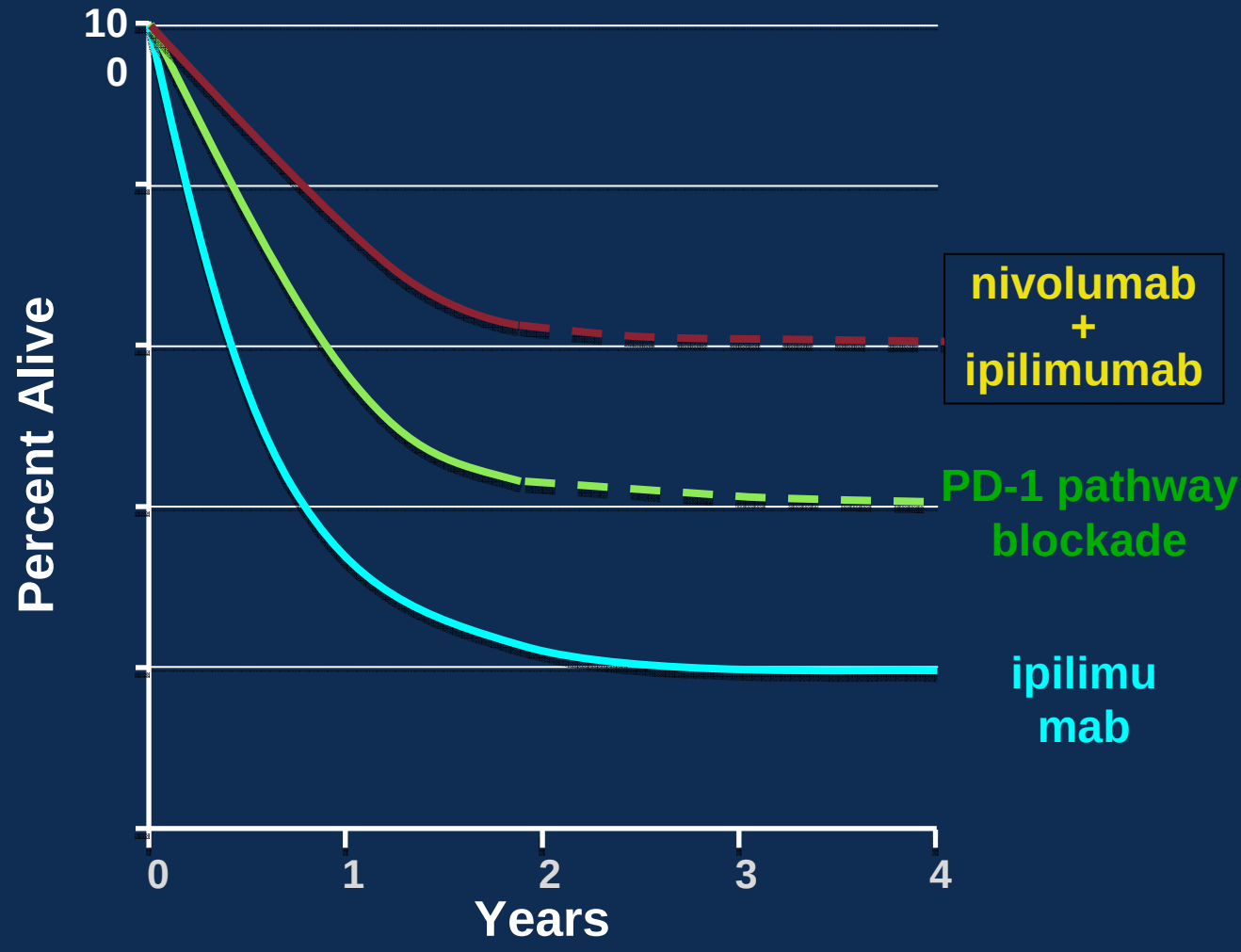


No. at Risk

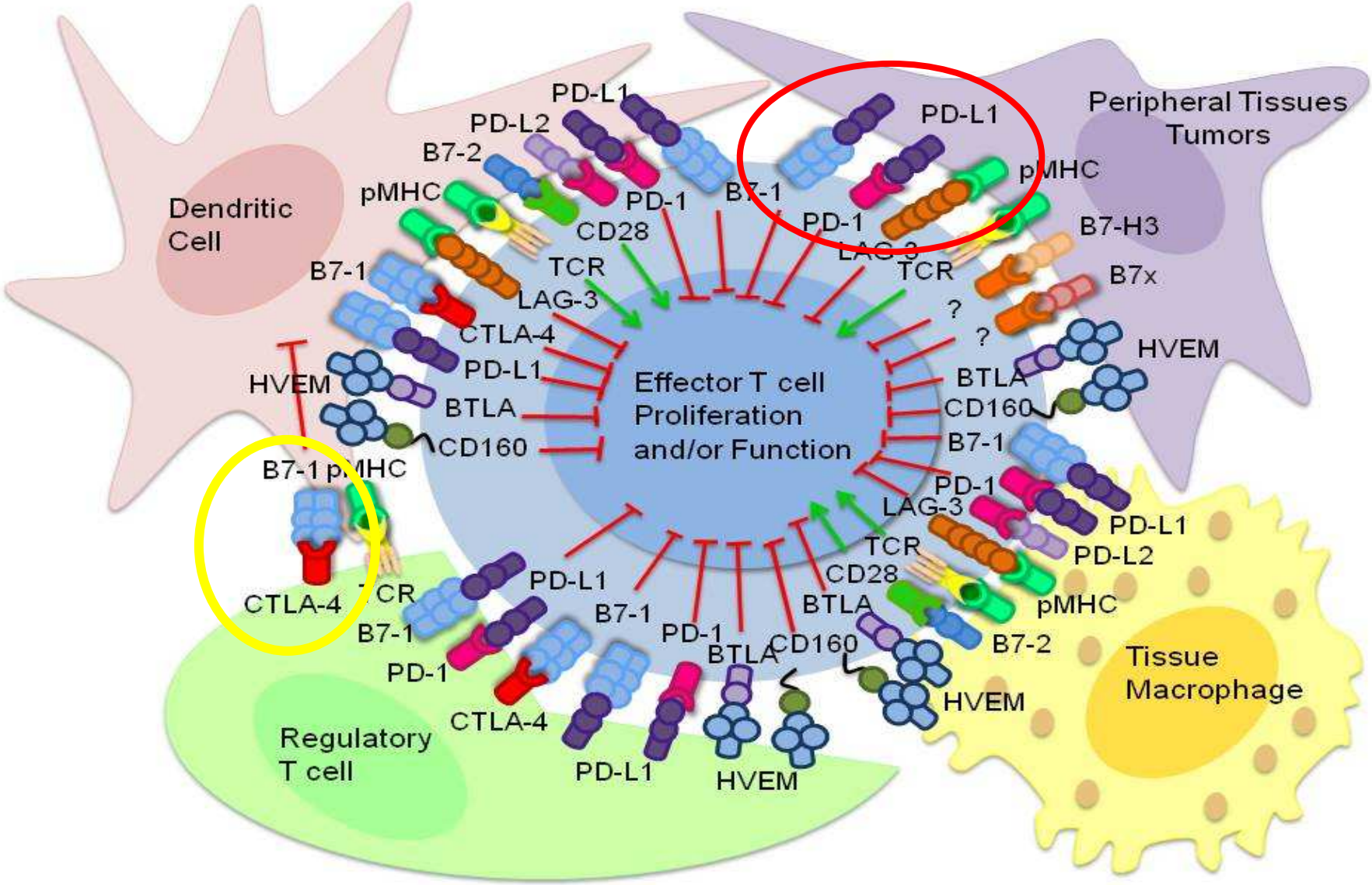
Nivolumab plus ipilimumab	72	54	45	38	20	1	0
Ipilimumab	37	20	9	6	2	0	0

MA.Postow et al NEJM 201

Overall survival after checkpoint blockade

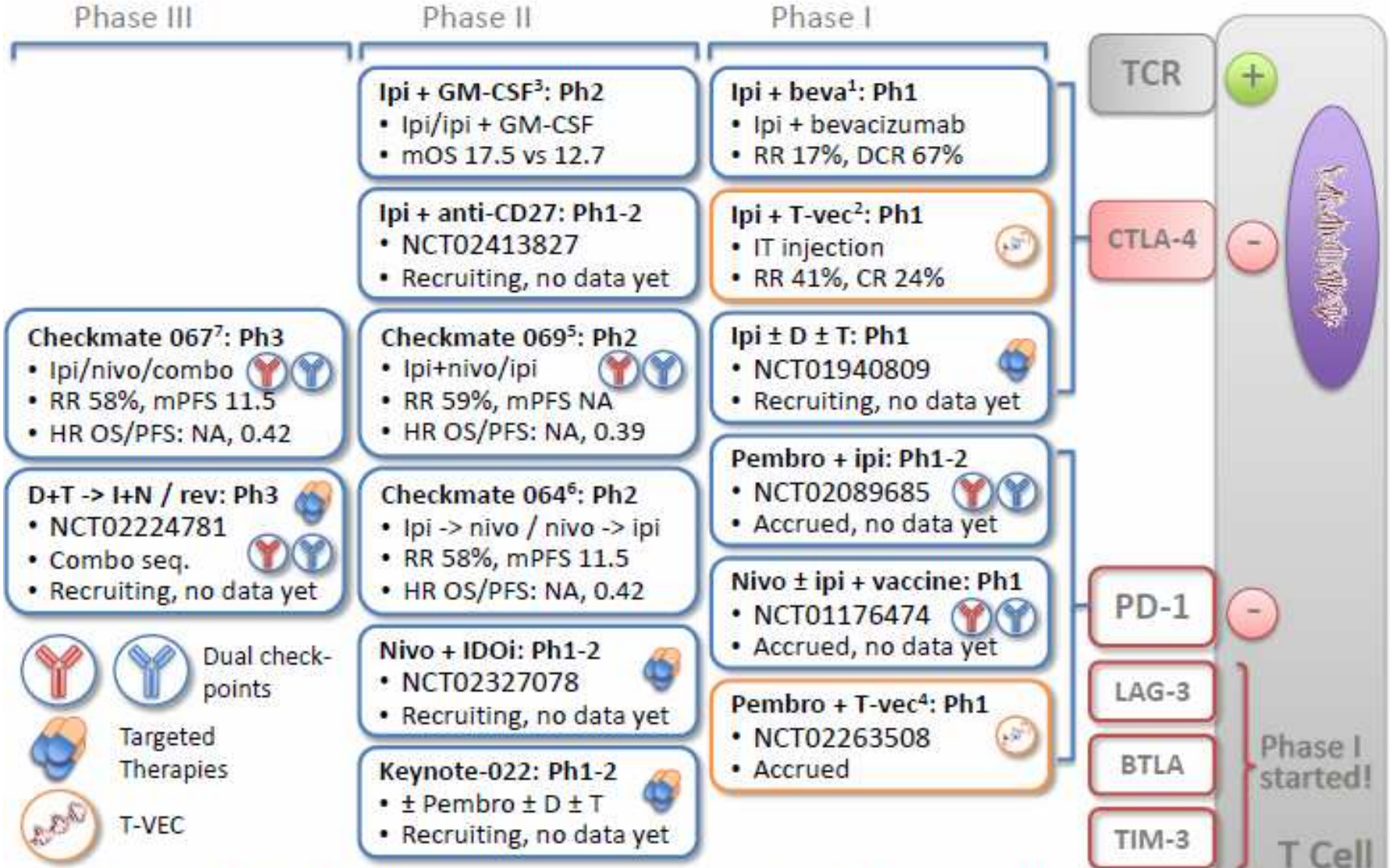


Mobilizing the Immune System to Treat Cancer: Immune Checkpoint Strategies



James Patrick Allison ASCO 2012

Overview of checkpoint combination trials



1 Hodi *Cancer Imm Res* 2014; 2 Puzanov, ASCO 2014; 3 Hodi, *JAMA* 2014; 4 Long, SMR 2015;
5 Hodi, *NEJM* 2015; 6 Hodi ECCO 2015; 7 Larkin, *NEJM* 2015; 14 (Time in months, NA: Not Available)

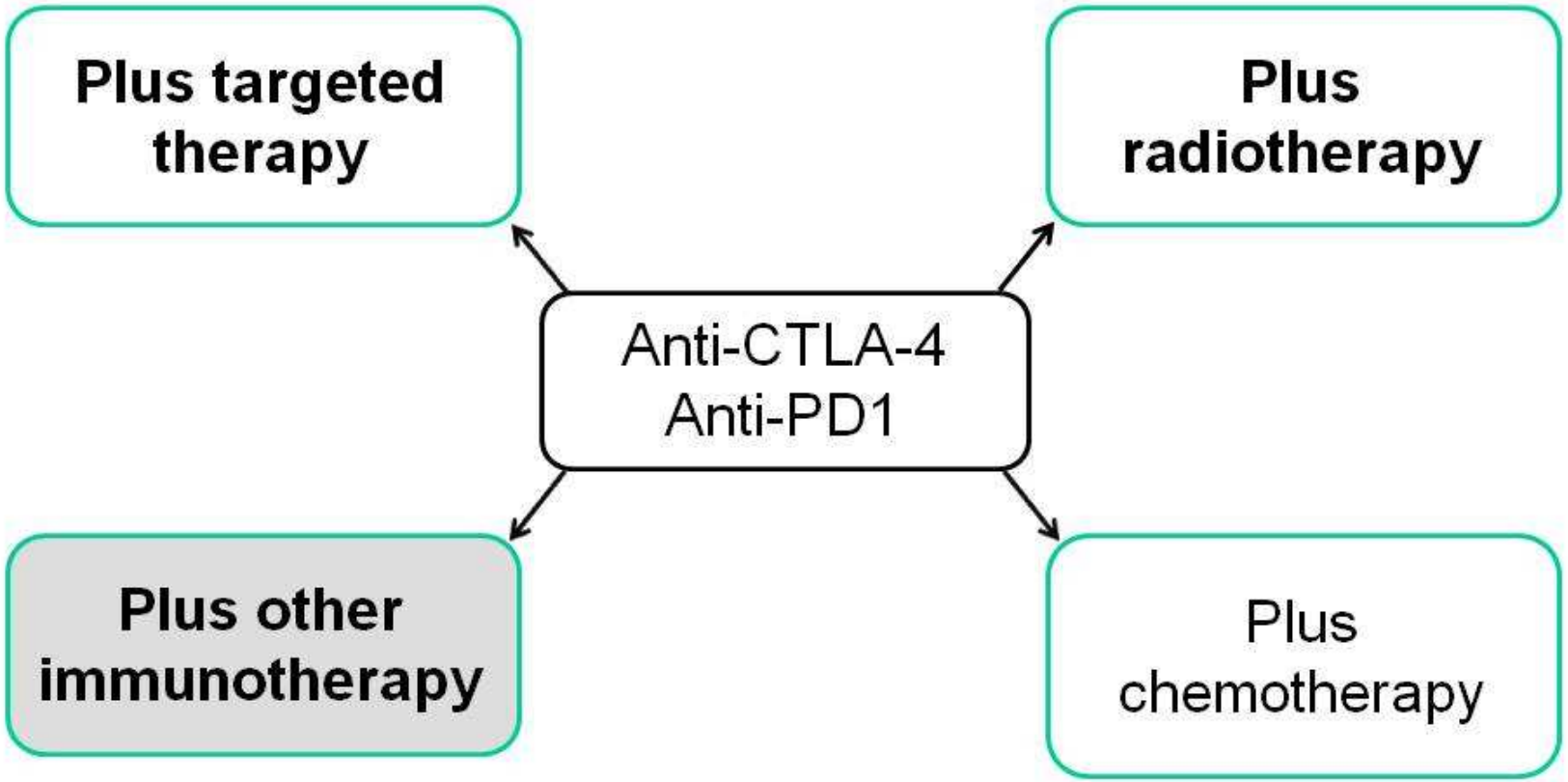
Table 6 Selected Trials for Other Tumor Types

Agents	Patient Population	N	Overall ORR	Other Efficacy Data	Study [Reference]
MEDI-4736	HNSCC	22	14%	ORR: 50% (2/4) in PD-L1–positive 6% (1/1) in PD-L1–negative	Segal et al[19]
Pembrolizumab	HNSCC, PD-L1 expression (≥ 1%)	60	19.6%	ORR: 20% in HPV-positive 19.4% HPV-negative PD-L1 positivity (≥ 1%) rate: 78% (PD-L1 expression appears to correlate with response)	Seiwert et al[48]
MPDL3280A	Metastatic urothelial bladder cancer	67	26%	ORR: 43% in PD-L1–positive (IHC 2/3) 11% in PD-L1–negative (IHC 1)	Powles et al[44]
Pembrolizumab	Metastatic urothelial bladder cancer	33	24%	10.3% complete response	Plimack et al[45]
Nivolumab	Metastatic ovarian cancer	20	17%	Unconventional response pattern observed: 1 mg/kg: 1 of 10 pts had a response 3 mg/kg: 2 of 8 pts had a response	Hamanishi et al[69]

HNSCC = head and neck squamous cell carcinoma; HPV = human papillomavirus; IHC = immunohistochemistry; ORR = objective response rate; PD-L1 = programmed death ligand 1.

Maximising clinical benefit: building on immunological approaches

Max



Ribas A, et al. *N Engl J Med* 2013;368:1365–6
Robert C, et al. *N Engl J Med* 2011;364:2517–26
Di Giacomo AM, et al. *Lancet Oncol* 2012;13:879–86
Patel S, et al. Presented at ESMO 2012:abstract 1126P
Knisely JPS, et al. *J Neurosurg* 2012;117:227–33

Bhatia S, et al. Presented at ASCO 2013:abstract TPS3109
Prieto PA, et al. *Clin Cancer Res* 2012;18:2039–47
Hodi FS, et al. Presented at ASCO 2013:abstract CRA9007
Kudchadkar RR, et al. Presented at ASCO 2013:abstract 9079
Chow LQ, et al. Presented at ASCO 2013:abstract TPS3112
Weber JS, et al. Presented at ASCO 2013:abstract 9011

Tumor Immunotherapy is an established reality in the treatment of melanoma