Immunotherapie voor Kanker

Ronde Tafel 2 Juli 2015

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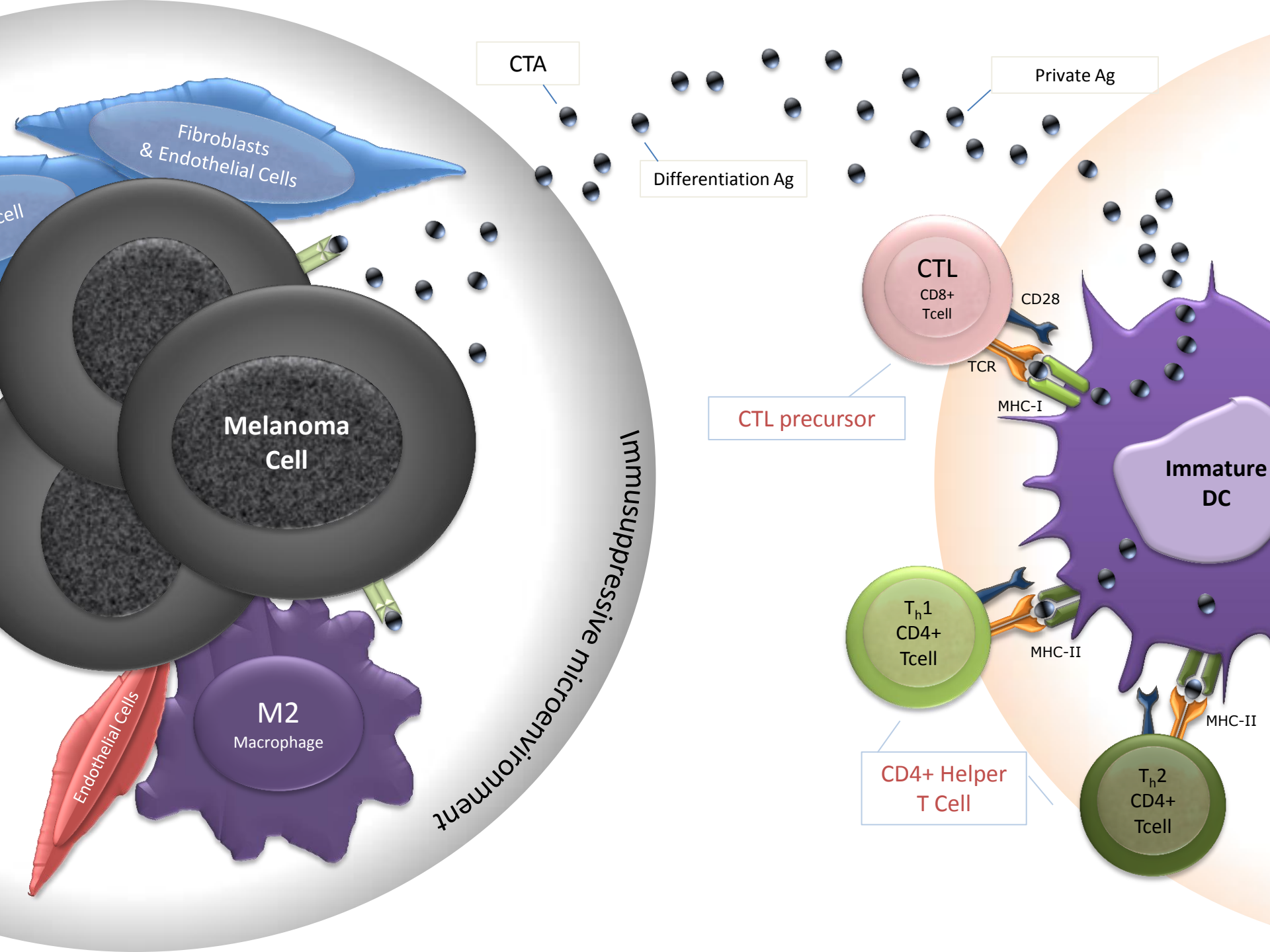
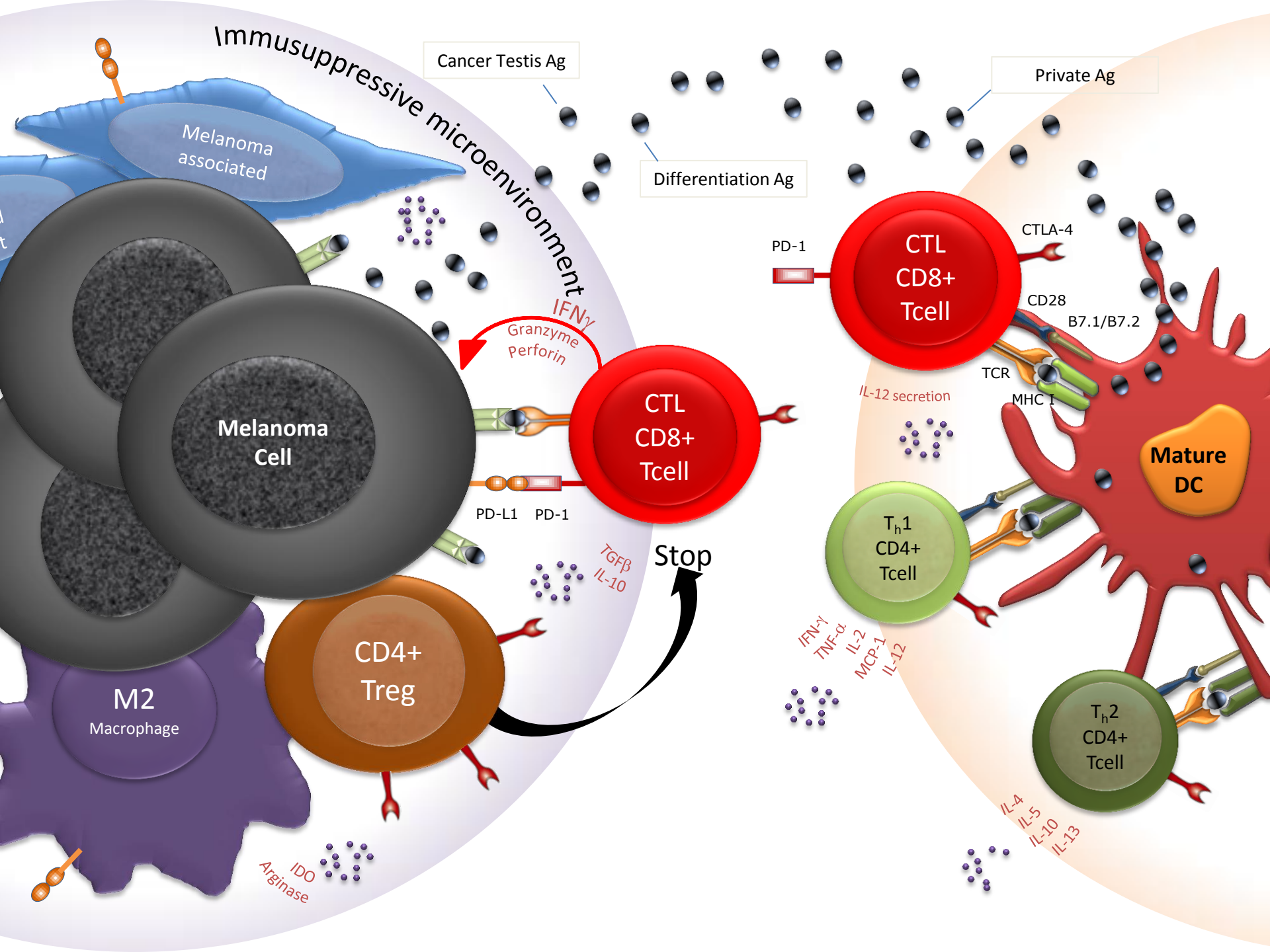
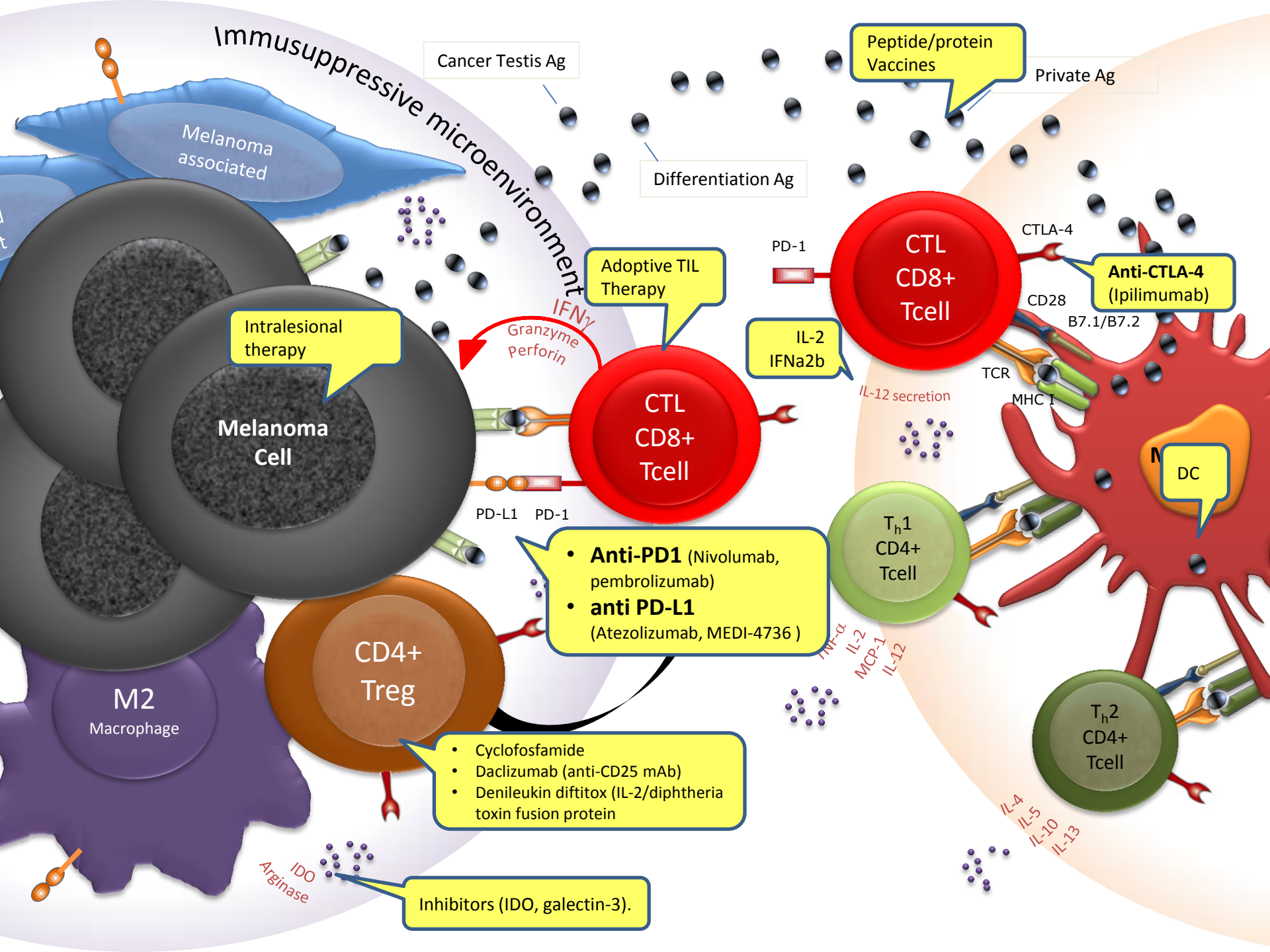

CTA
Private Ag
Differentiation Ag
Fibroblasts
& Endothelial Cells
Melanoma
Cell
M2
Macrophage
Endothelial Cells
Immunosuppressive microenvironment
CTL
CD8+
Tcell
CD28
TCR
MHC-I
CTL precursor
Immature
DC
T_h1
CD4+
Tcell
MHC-II
MHC-II
CD4+ Helper
T Cell
T_h2
CD4+
Tcell


Immusuppressive microenvironment
Cancer Testis Ag
Private Ag
Differentiation Ag
Melanoma associated
Melanoma Cell
M2 Macrophage
CD4+ Treg
IFNγ
Granzyme
Perforin
CTL CD8+ Tcell
PD-L1
PD-1
TGFβ
IL-10
Stop
IDO
Arginase
PD-1
CTL CD8+ Tcell
CTLA-4
CD28
B7.1/B7.2
TCR
MHC I
IL-12 secretion
Mature DC
Th1 CD4+ Tcell
IFN-γ
TNF-α
IL-2
MCP-1
IL-12
Th2 CD4+ Tcell
IL-4
IL-5
IL-10
IL-13

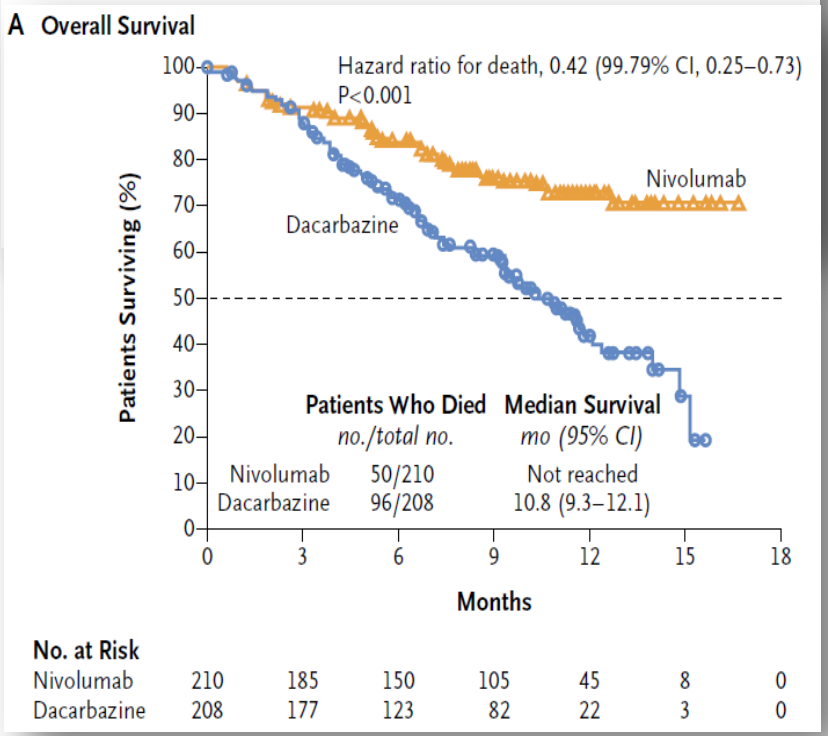

Immusuppressive microenvironment
Cancer Testis Ag
Peptide/protein Vaccines
Private Ag
Differentiation Ag
Melanoma associated
Adoptive TIL Therapy
Intralesional therapy
IFNγ
Granzyme
Perforin
Melanoma Cell
CTL CD8+ Tcell
PD-1
CTLA-4
Anti-CTLA-4 (Ipilimumab)
CD28
B7.1/B7.2
IL-2 IFNa2b
TCR
MHC I
IL-12 secretion
DC
PD-L1
PD-1
• Anti-PD1 (Nivolumab, pembrolizumab)
• anti PD-L1 (Atezolizumab, MEDI-4736)
Th1 CD4+ Tcell
TNF-α
IL-2
MCP-1
IL-12
M2 Macrophage
CD4+ Treg
• Cyclofosfamide
• Daclizumab (anti-CD25 mAb)
• Denileukin diftitox (IL-2/diphtheria toxin fusion protein
Th2 CD4+ Tcell
IL-4
IL-5
IL-10
IL-13
IDO
Arginase
Inhibitors (IDO, galectin-3).

Immunotherapy with anti-PD-1 monocloncal antiodies (pembrolizumab, nivolumab) improves the overall survival of patients with advanced melanoma

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab in Previously Untreated Melanoma without *BRAF* Mutation

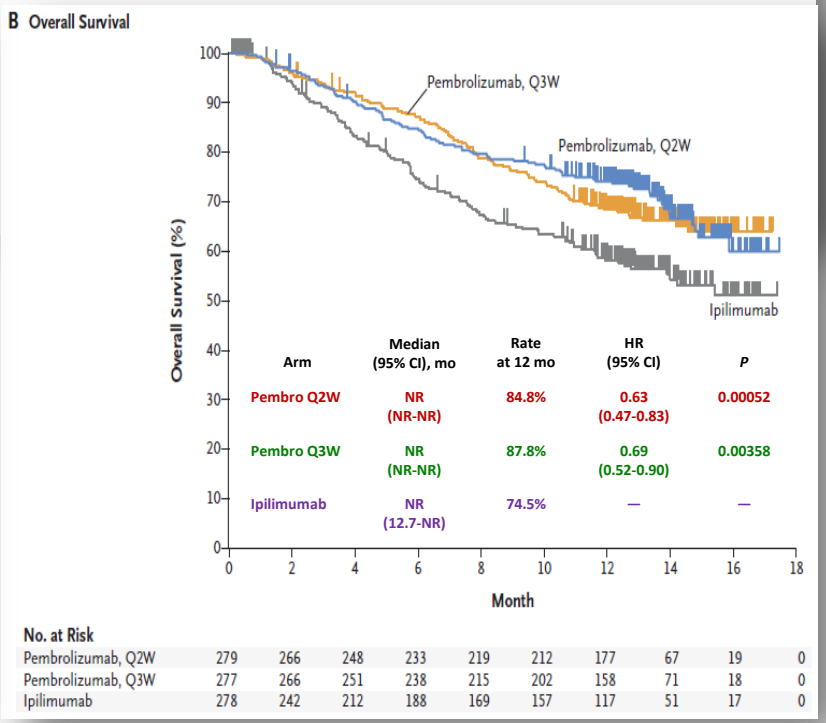


This article was published on November 16, 2014, at NEJM.org.

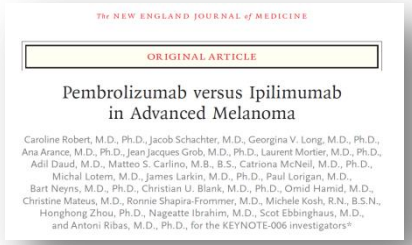
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

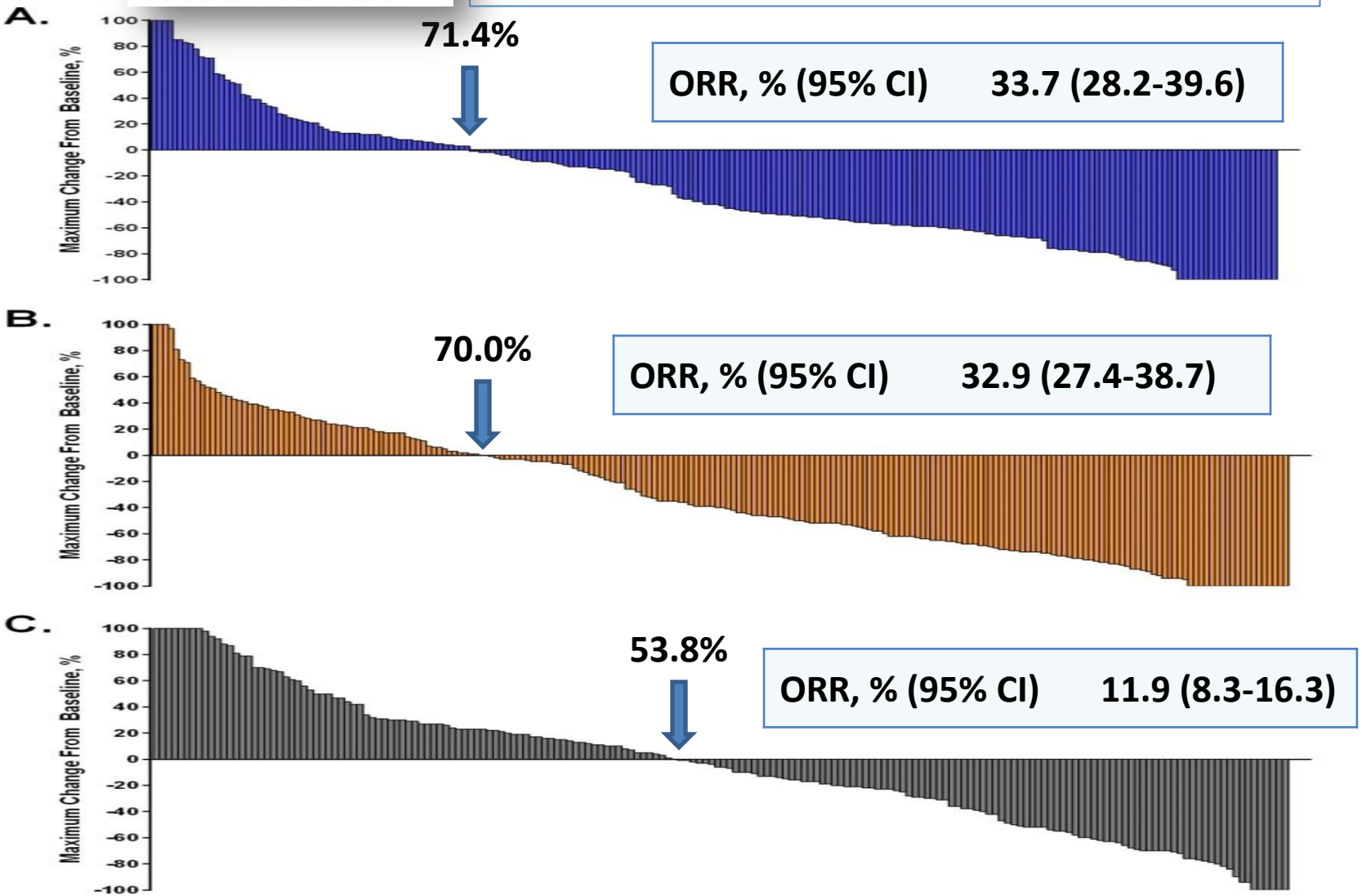
Pembrolizumab versus Ipilimumab in Advanced Melanoma



This article was published on April 19, 2015, at NEJM.org.



Best Percentage Change From Baseline in Target Lesions (RECIST v1.1, Central Review)



Analysis cut-off date: September 3, 2014.

Tumor response by irRC in ipilimumab pretreated melanoma patients treated at the UZ Brussel with pembrolizumab (Compassionate Use Program)

	No.	(%)		
Evaluable population	36			
irCR	4	(11)	ORR 25%°	DCR 53%
irPR	5	(14)		
irSD	10	(28)		
irPD	13	(36)		
Clinical PD*	4	(11)		
Under evaluation	7			

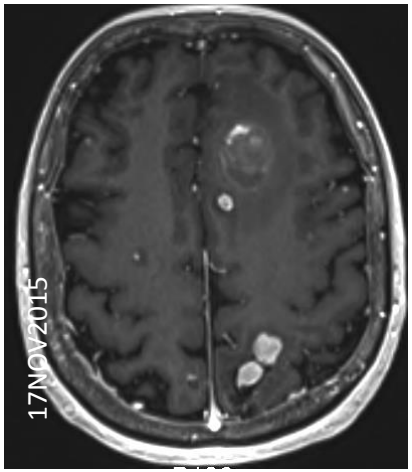
* No CT-based response assessment was obtained due to rapid disease progression and clinical deterioration

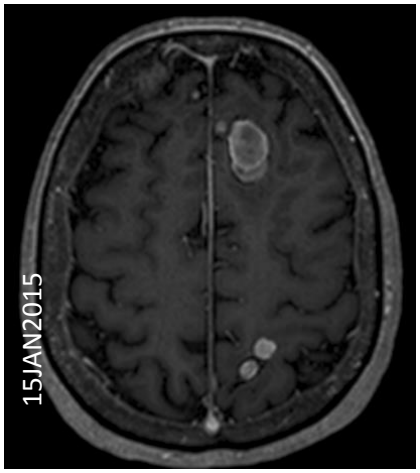
°ORR in non-uveal mealnoma = 28% (9/32)

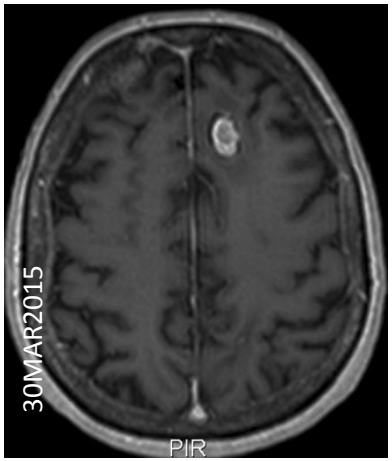
Abstract submitted for the SMR 2015 Meeting

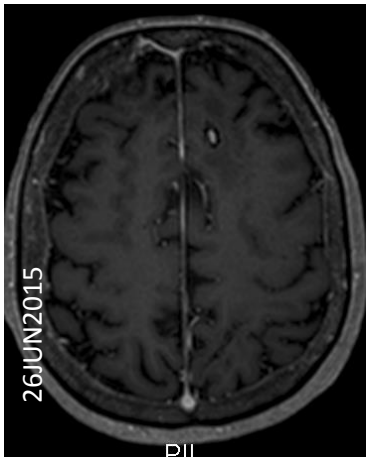
Case illustration

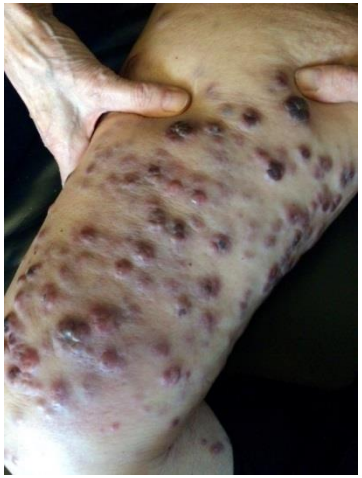
72y F, stage IV-M1c BRAF V600E





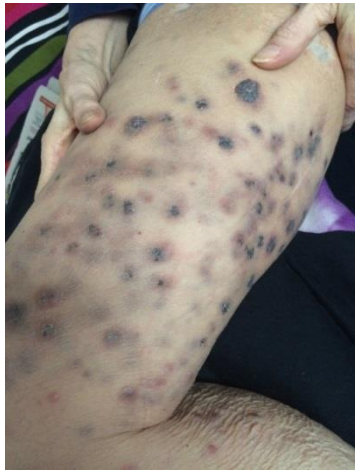




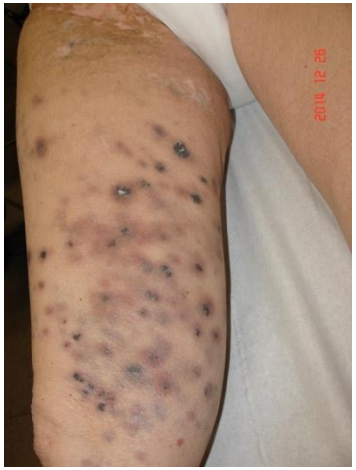


17NOV2014

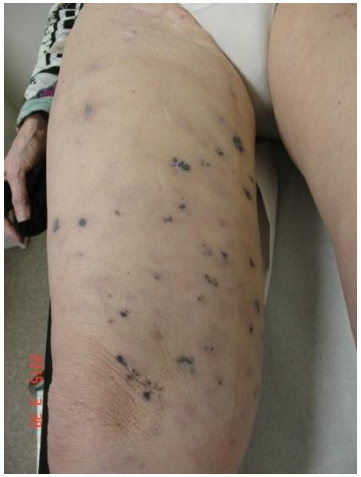
2 administrations of pembrolizumab



9DEC2014



26DEC2014



30MAR2015

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

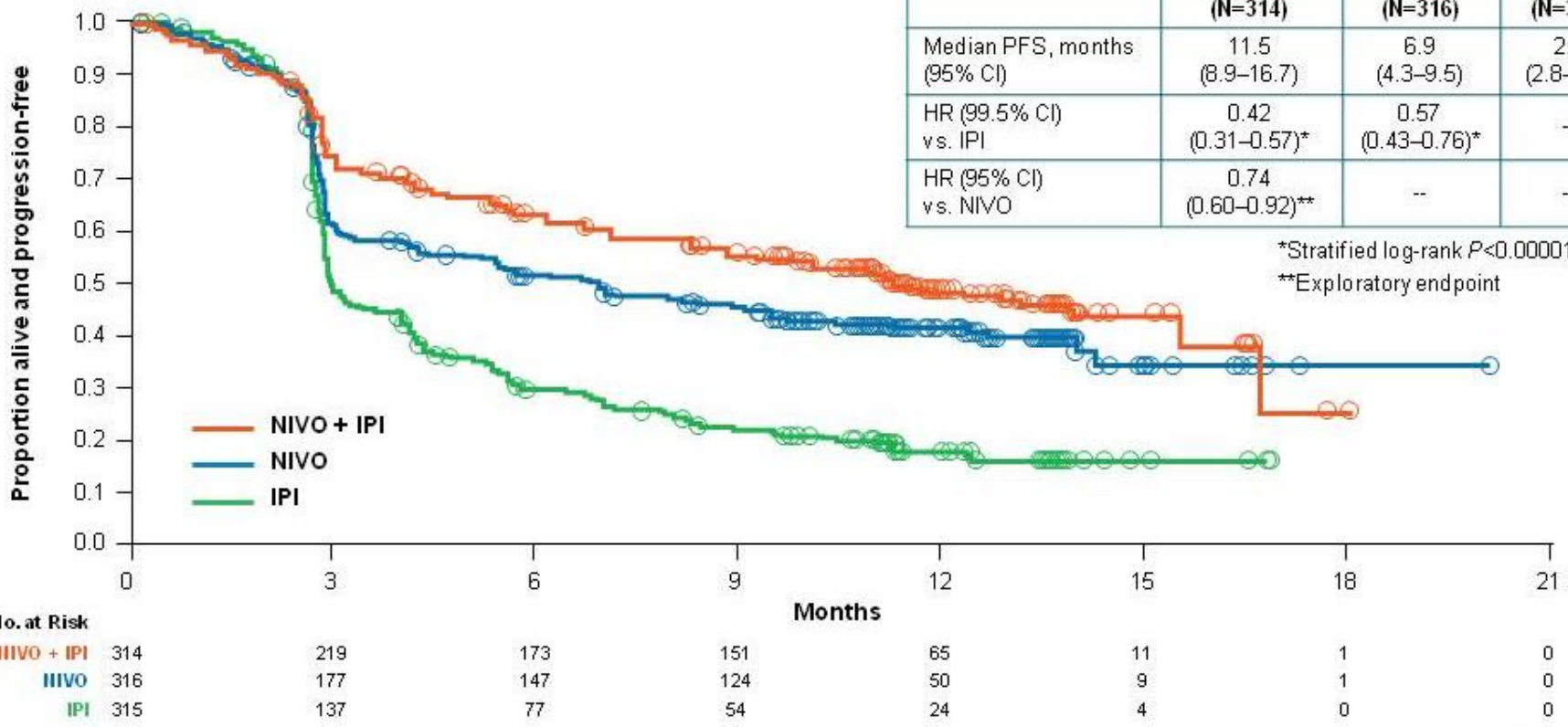
J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.J. Grob, C.L. Cowey, C.D. Lao, D. Schadendorf, R. Dummer, M. Smylie, P. Rutkowski, P.F. Ferrucci, A. Hill, J. Wagstaff, M.S. Carlino, J.B. Haanen, M. Maio, I. Marquez-Rodas, G.A. McArthur, P.A. Ascierto, G.V. Long, M.K. Callahan, M.A. Postow, K. Grossmann, M. Sznol, B. Dreno, L. Bastholt, A. Yang, L.M. Rollin, C. Horak, F.S. Hodi, and J.D. Wolchok

Progression-free survival

	NIVO + IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median PFS, months (95% CI)	11.5 (8.9–16.7)	6.9 (4.3–9.5)	2.9 (2.8–3.4)
HR (99.5% CI) vs. IPI	0.42 (0.31–0.57)*	0.57 (0.43–0.76)*	--
HR (95% CI) vs. NIVO	0.74 (0.60–0.92)**	--	--

*Stratified log-rank $P<0.00001$ vs. IPI

**Exploratory endpoint



No. at Risk								
NIVO + IPI	314	219	173	151	65	11	1	0
NIVO	316	177	147	124	50	9	1	0
IPI	315	137	77	54	24	4	0	0

PRESENTED AT: ASCO Annual '15 Meeting

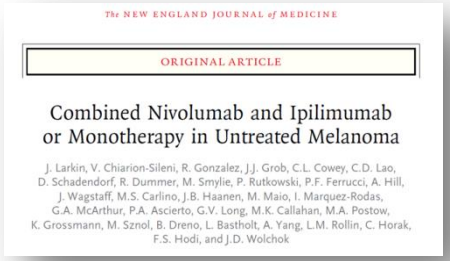
This article was published on May 31, 2015, at NEJM.org.

Safety Summary

Patients Reporting Event, %	NIVO + IPI (N=313)		NIVO (N=313)		IPI (N=311)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Treatment-related adverse event (AE)	95.5	55.0	82.1	16.3	86.2	27.3
Treatment-related AE leading to discontinuation	36.4	29.4	7.7	5.1	14.8	13.2
Treatment-related death*	0		0.3		0.3	

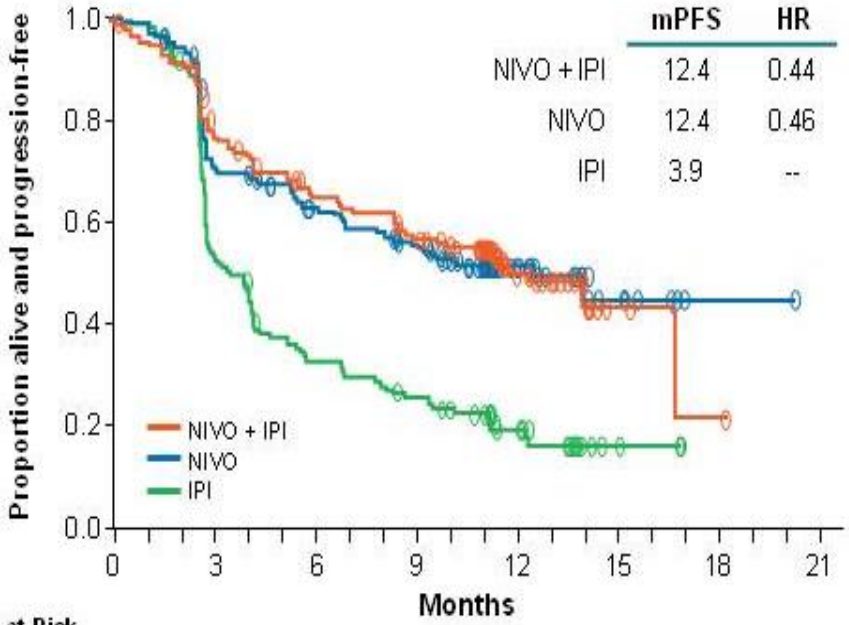
*One reported in the NIVO group (neutropenia) and one in the IPI group (cardiac arrest).

- 67.5% of patients (81/120) who discontinued the NIVO + IPI combination due to treatment-related AEs developed a response



PFS by PD-L1 Expression Level (1%)

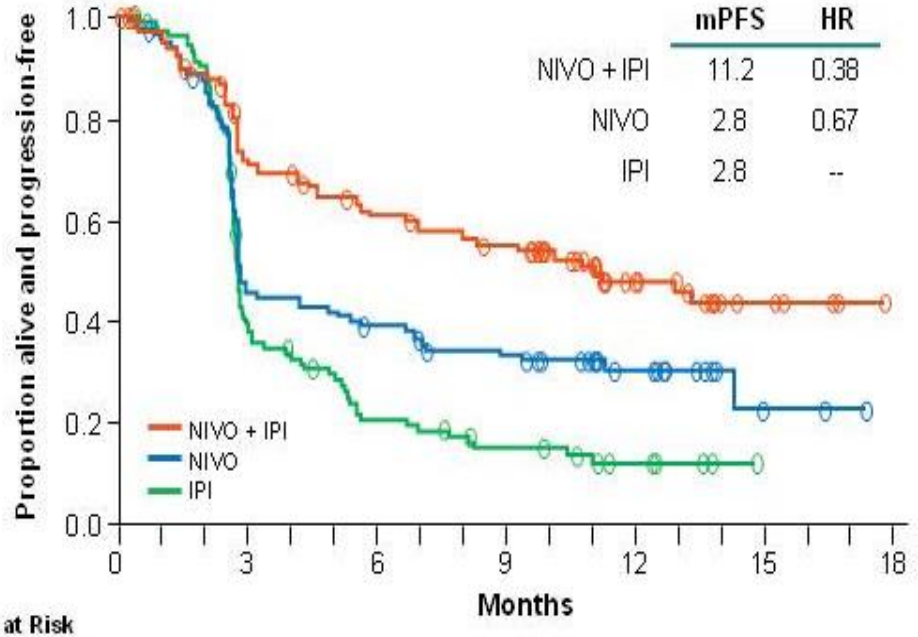
PD-L1 ≥1%*



No. at Risk

NIVO + IPI	155	113	91	78	32	4	1	
NIVO	171	115	97	83	34	7	1	0
IPI	164	83	47	36	16	3		

PD-L1 <1%*



No. at Risk

NIVO + IPI	123	82	65	57	26	6	0
NIVO	117	50	42	34	13	2	0
IPI	113	39	19	12	5	0	

*Per validated PD-L1 immunohistochemical assay based on PD-L1 staining of tumor cells in a section of at least 100 evaluable tumor cells.

This article was published on May 31, 2015, at NEJM.org.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer

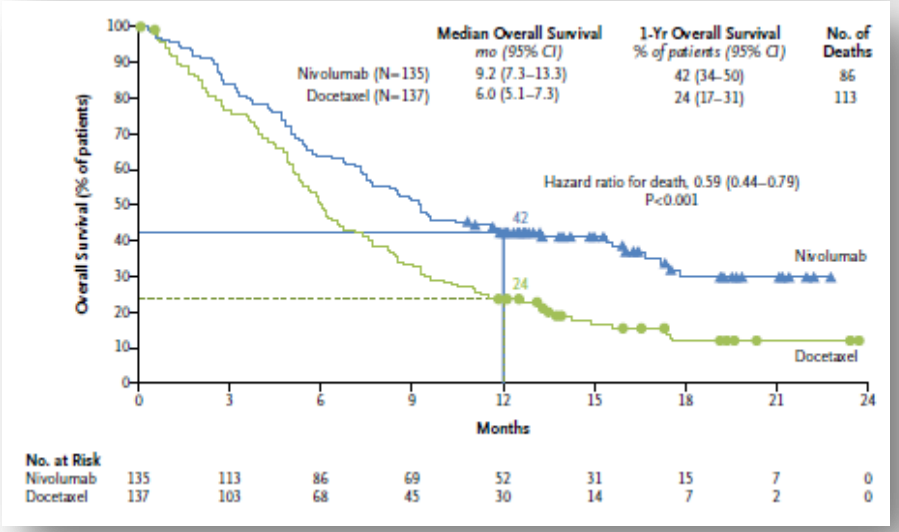
Julie Brahmer, M.D., Karen L. Reckamp, M.D., Paul Baas, M.D., Lucio Crinò, M.D., Wilfried E.E. Eberhardt, M.D., Elena Poddubskaya, M.D., Scott Antonia, M.D., Ph.D., Adam Pluzanski, M.D., Ph.D., Everett E. Vokes, M.D., Esther Holgado, M.D., Ph.D., David Waterhouse, M.D., Neal Ready, M.D., Justin Gainor, M.D., Osvaldo Arén Frontera, M.D., Libor Havel, M.D., Martin Steins, M.D., Marina C. Garassino, M.D., Joachim G. Aerts, M.D., Manuel Domine, M.D., Luis Paz-Ares, M.D., Martin Reck, M.D., Christine Baudelet, Ph.D., Christopher T. Harbison, Ph.D., Brian Lestini, M.D., Ph.D., and David R. Spigel, M.D.

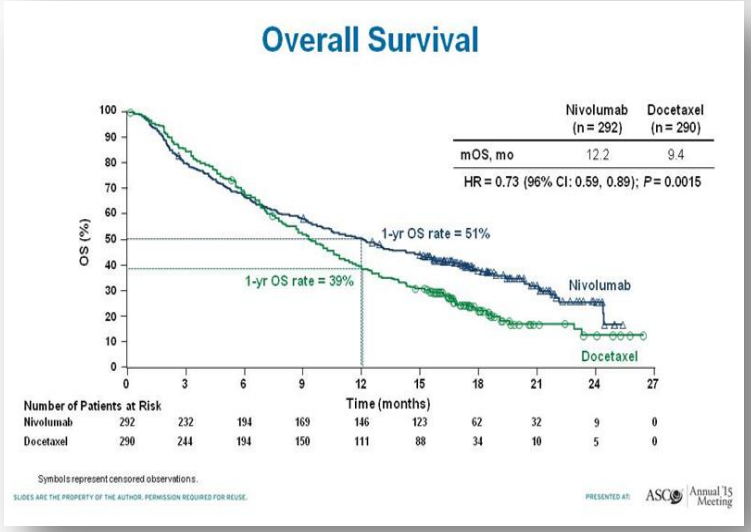
This article was published on May 31, 2015, and updated on June 17, 2015, at NEJM.org.

Phase III, Randomized Trial (CheckMate 057) of Nivolumab versus Docetaxel in Advanced Non-squamous (non-SQ) Cell Non-small Cell Lung Cancer (NSCLC)

Luis Paz-Ares,[1] Leora Horn,[2] Hossein Borghaei,[3] David R. Spigel,[4] Martin Steins,[5] Neal E. Ready,[6] Laura Q. Chow,[7] Everett E. Vokes,[8] Enriqueta Felip,[9] Esther Holgado,[10] Fabrice Barlesi,[11] Martin Kohlhäufl,[12] Oscar Arrieta,[13] Marco Angelo Burgio,[14] Jérôme Fayette,[15] Scott N. Gettinger,[16] Christopher T. Harbison,[17] Cécile Dorange,[17] Friedrich Graf Finckenstein,[17] Julie R. Brahmer[18]

[1]Hospital Universitario Virgen Del Rocio, Sevilla, Spain; [2]Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; [3]Fox Chase Cancer Center, Philadelphia, PA, USA; [4]Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN, USA; [5]Thoraxklinik, Heidelberg University Hospital, Heidelberg, Germany; [6]Duke University Medical Center, Durham, NC, USA; [7]University of Washington, Seattle, WA, USA; [8]University of Chicago Medicine & Biological Sciences, Chicago, IL, USA; [9]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [10]Hospital De Madrid, Norte Sanchinarro, Spain; [11]Aix Marseille University; Assistance Publique Hôpitaux de Marseille, Marseille, France; [12]Robert-Bosch-Krankenhaus, Gerlingen, Germany; [13]Instituto Nacional De Cancerologia, Mexico City, Mexico; [14]IRST IRCCS Meldola (Forlì - Cesena) Italy; [15]Centre Léon Bérard, Lyon, France; [16]Yale Comprehensive Cancer Center, New Haven, CT, USA; [17]Bristol-Myers Squibb, Princeton, NJ, USA; [18]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA





Presented By Luis Paz-Ares at 2015 ASCO Annual Meeting

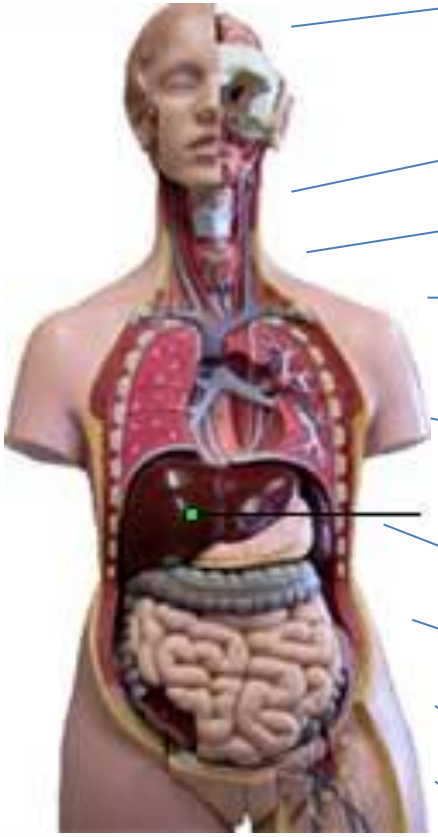
Immunotherapeutic activity of anti-PD-1 monoclonal antibodies

No established activity in frequent solid tumors

ER/PR + breast cancer

CIN colorectal carcinoma

Prostate carcinoma



Glioblastoom

Uveal melanoma

Head and neck SCC

Skin melanoma

Hodgkin's lymphoma

Triple negative breast cancer

Gastric cancer

Non-small cell lung cancer

Hepatocellular carcinoma

Renal cell carcinoma

MSI-High colorectal carcinoma

Uroepithelial carcinoma

Epithelial ovarian cancer

(Wolchok, Kluger et al. 2013; Robert, Ribas et al. 2014; Ansell, Lesokhin et al. 2015; Bajorin, Plimack et al. 2015; Bellmunt, Sonpavde et al. 2015; Brahmer, Reckamp et al. 2015; Burgess, Crowley et al. 2015; Cohen, Machiels et al. 2015; El-Khoueiry, Melero et al. 2015; Fuchs, Denker et al. 2015; Gettinger, Horn et al. 2015; Hamanishi, Mandai et al. 2015; Larkin, Chiarion-Sileni et al. 2015; McDermott, Drake et al. 2015; Motzer, Rini et al. 2015; Plimack, Bellmunt et al. 2015; Postow, Callahan et al. 2015; Postow, Chesney et al. 2015; Powell, Liu et al. 2015; Seiwert, Haddad et al. 2015; Seiwert, Haddad et al. 2015)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

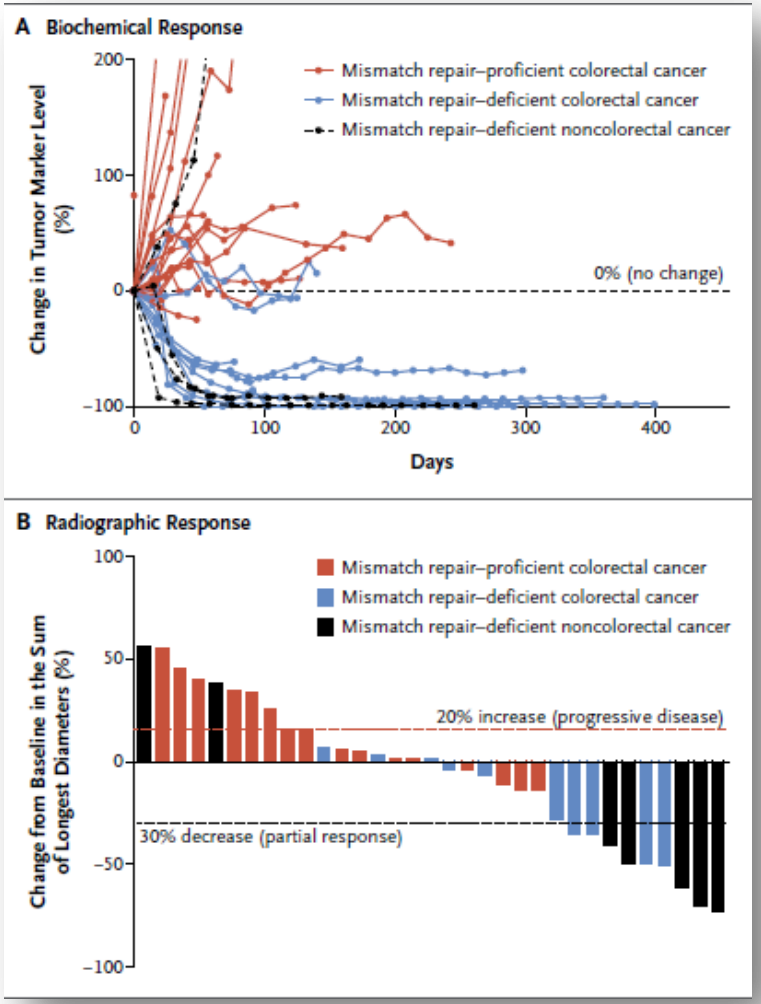
PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.

Table 2. Objective Responses According to RECIST Criteria.

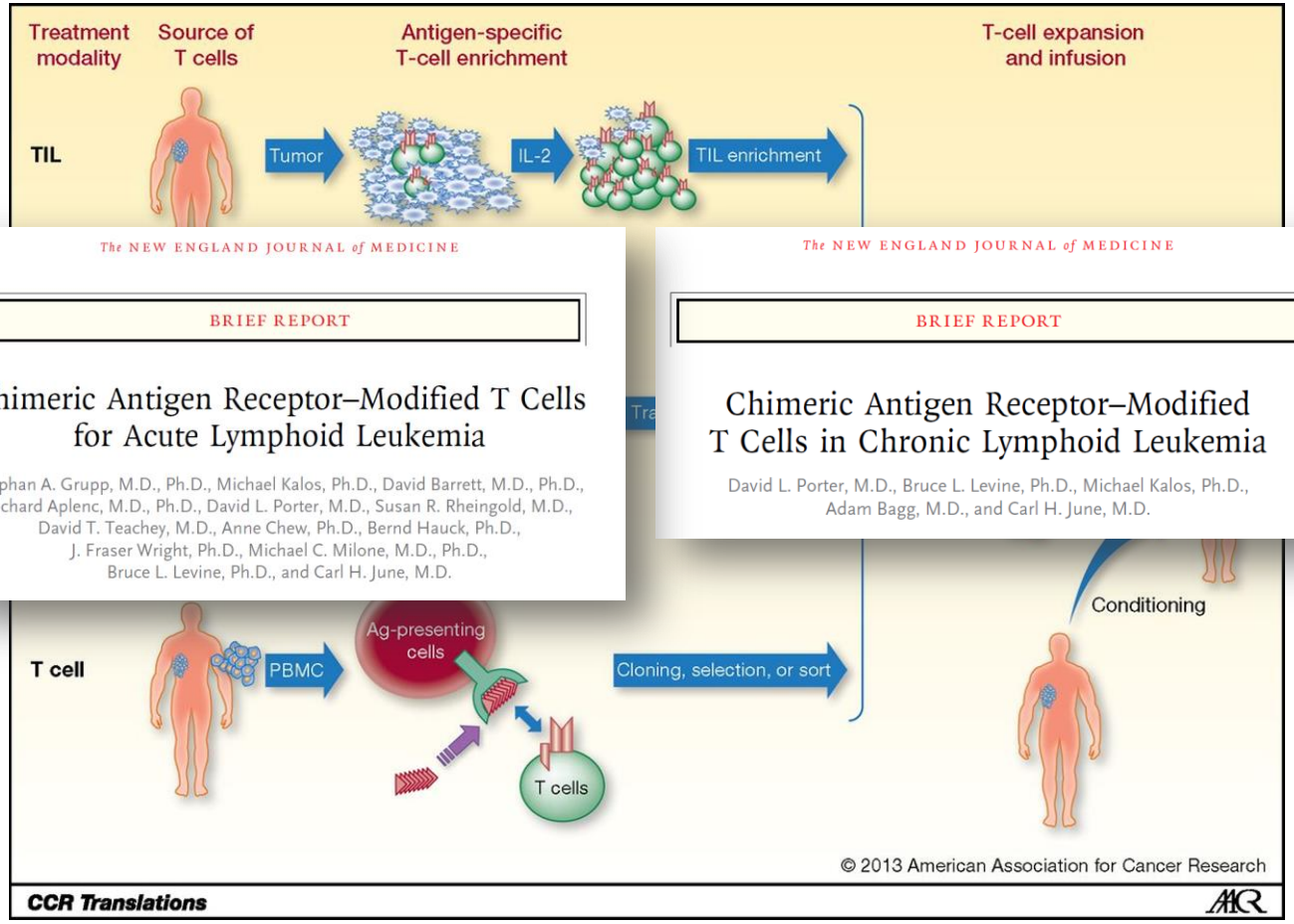
Type of Response	Mismatch Repair–Deficient Colorectal Cancer (N=10)	Mismatch Repair–Proficient Colorectal Cancer (N=18)	Mismatch Repair–Deficient Noncolorectal Cancer (N=7)
Complete response — no. (%)	0	0	1 (14)*
Partial response — no. (%)	4 (40)	0	4 (57)†
Stable disease at week 12 — no. (%)	5 (50)	2 (11)	0
Progressive disease — no. (%)	1 (10)	11 (61)	2 (29)
Could not be evaluated — no. (%)‡	0	5 (28)	0
Objective response rate (95% CI) — %	40 (12–74)	0 (0–19)	71 (29–96)
Disease control rate (95% CI) — %§	90 (55–100)	11 (1–35)	71 (29–96)
Median duration of response — wk	Not reached	NA¶	Not reached
Median time to response (range) — wk	28 (13–35)	NA¶	12 (10–13)

* The patient had a partial response at 12 weeks, which then became a complete response at 20 weeks.
† One patient had a partial response at 12 weeks.
‡ Patients could not be evaluated if they did not undergo a scan at 12 weeks because of clinical progression.
§ The rate of disease control was defined as the percentage of patients who had a complete response, partial response, or stable disease for 12 weeks or more.
¶ The median time to response was not applicable (NA) because no responses were observed among patients with mismatch repair–proficient colorectal cancer.



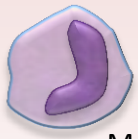
This article was published on May 30, 2015, at NEJM.org.

Adoptive T-cell Therapies



Yee C
Clin Cancer Res
2013;19:4550-4552

Leukapheresis
15L blood

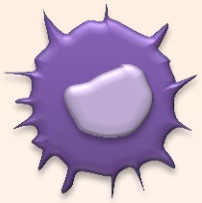


Monocyte

Enrichment of monocytes by plastic adherence in Cell Factories

6 day culture in GM-CSF/IL4 supplemented medium

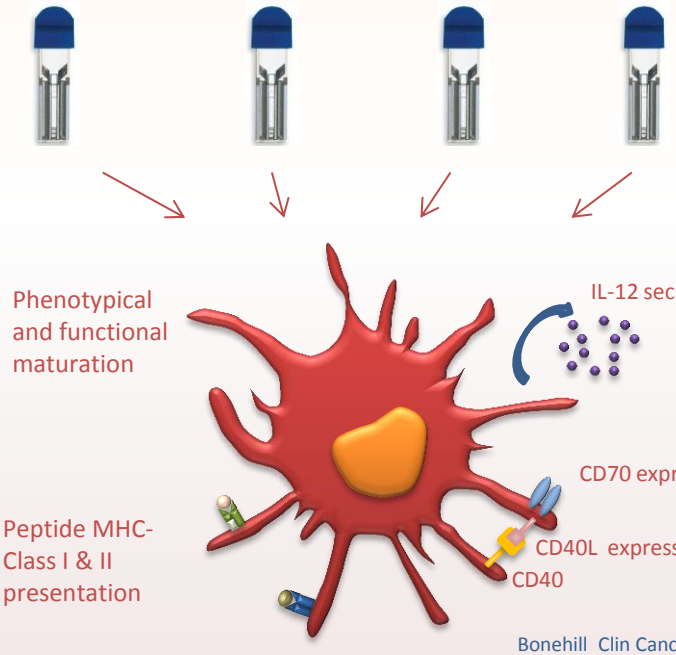
Electroporation of synthetic messenger RNA



Immature DC

TriMix mRNA
[caTLR4 + CD70+ CD40L]
+

MAGE.A3 DC.LAMP	MAGE.C2 DC.LAMP	Tyrosinase DC.LAMP	gp100 DC.LAMP



Bonehill Clin Cancer Res 2009

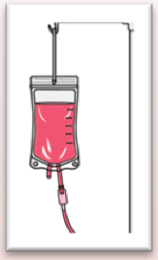
Quality control
Cryopreservation

Sterility
CD14 ≤ 20%
CD40 ≥ 30%
CD80 ≥ 40%
CD83 ≥ 40%
CCR7 ≥ 20%
CD70 ≥ 50%
≥ 70% viable cells

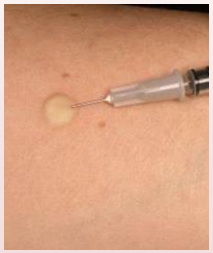
Release for clinical use

TriMixDC-MEL

Administration
24.10^6 viable DC



iv

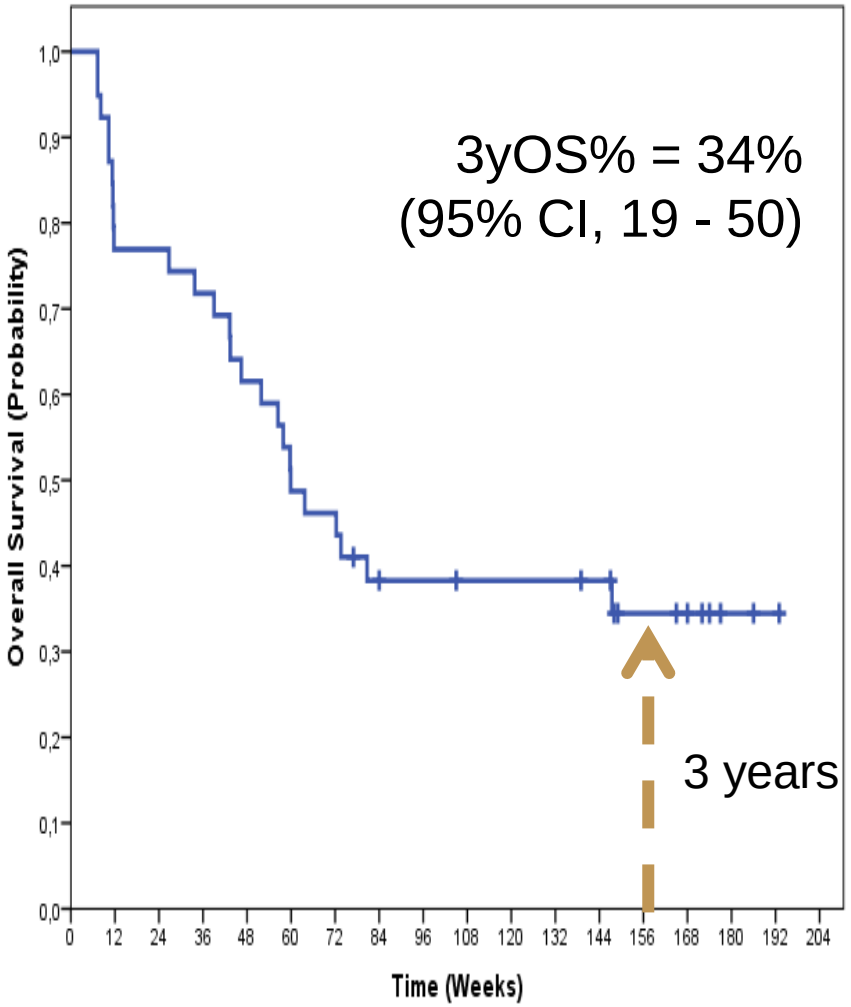


id

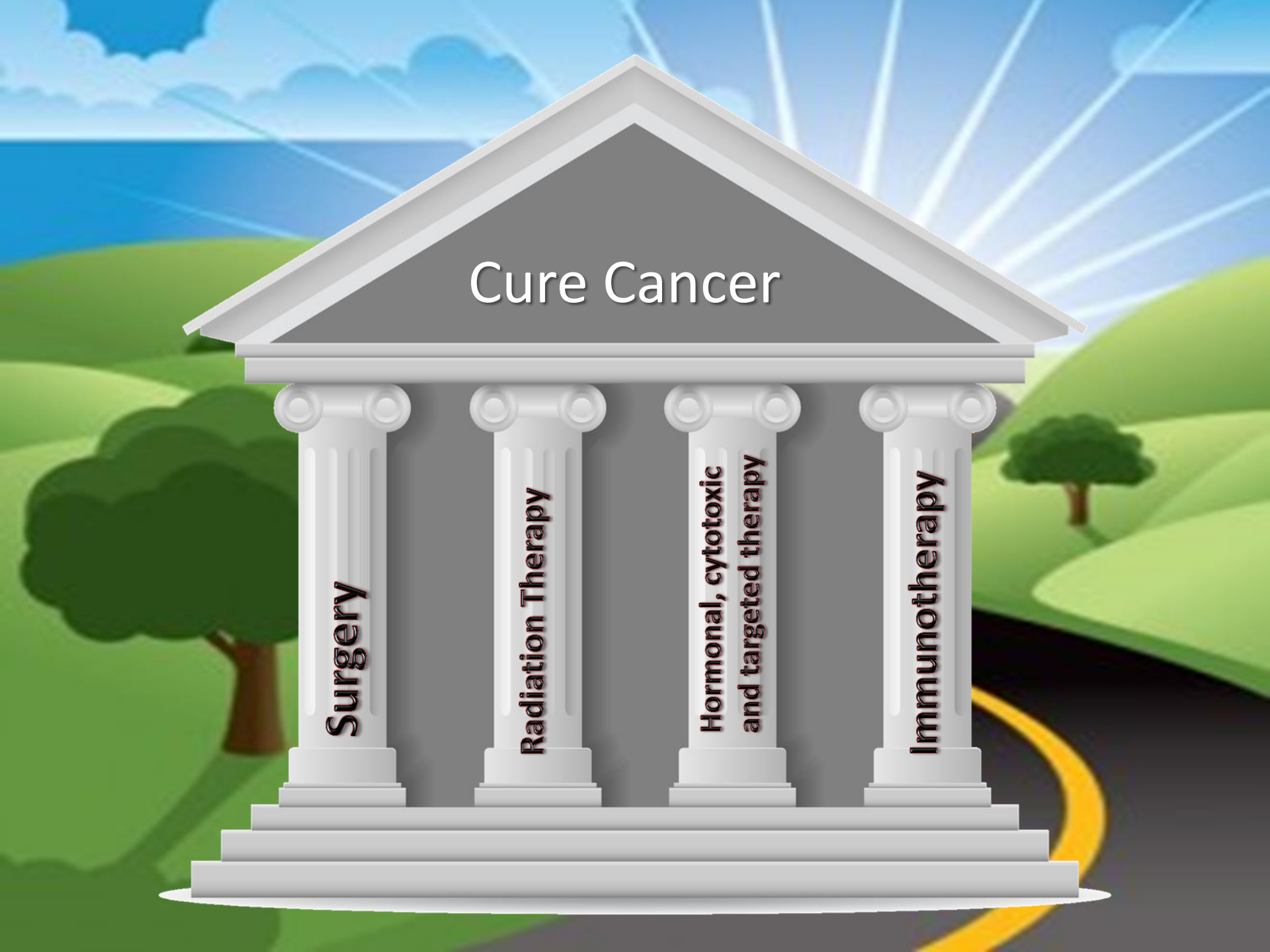
Tumor response and overall survival with TriMixDC plus ipilimumab in pretreated melanoma patients

Best objective tumor response by irRC			
CR	8	BORR 38%	DCR 53%
PR	7		
SD	6		
PD	18		
Tot. patient No.	39		

BORR: best overall response rate;
DCR: disease control rate



Surgery
Radiation Therapy
Hormonal, cytotoxic and targeted therapy
Immunotherapy


Cure Cancer
Surgery
Radiation Therapy
Hormonal, cytotoxic and targeted therapy
Immunotherapy