Melanoma's Road to Personlalized Therapy In the ERA of Immuno-Oncology

Omid Hamid MD

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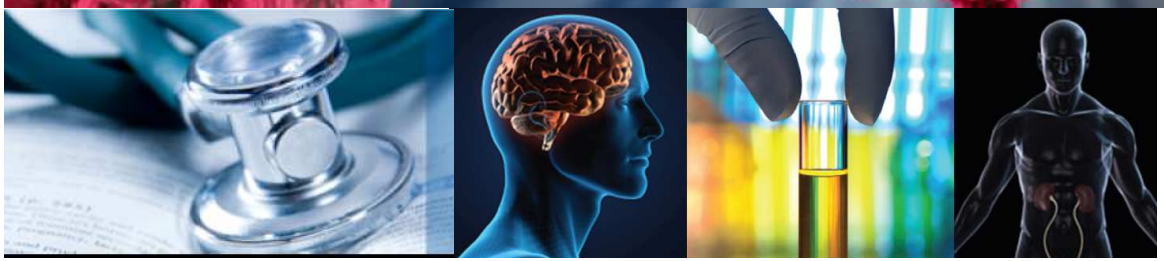


The Angeles Clinic and Research Institute

Disclosures

The more conflicts of interest for the speaker, the more balanced the talk . . . . . Hauschild 2015

- Pfizer
- Rinat
- Genentech
- Roche
- BMS
- Merck
- Merck Serano
- Immunocore
- Medimmune
- Astra Zeneca
- Novartis
- Celldex
- Incyte
- Esai

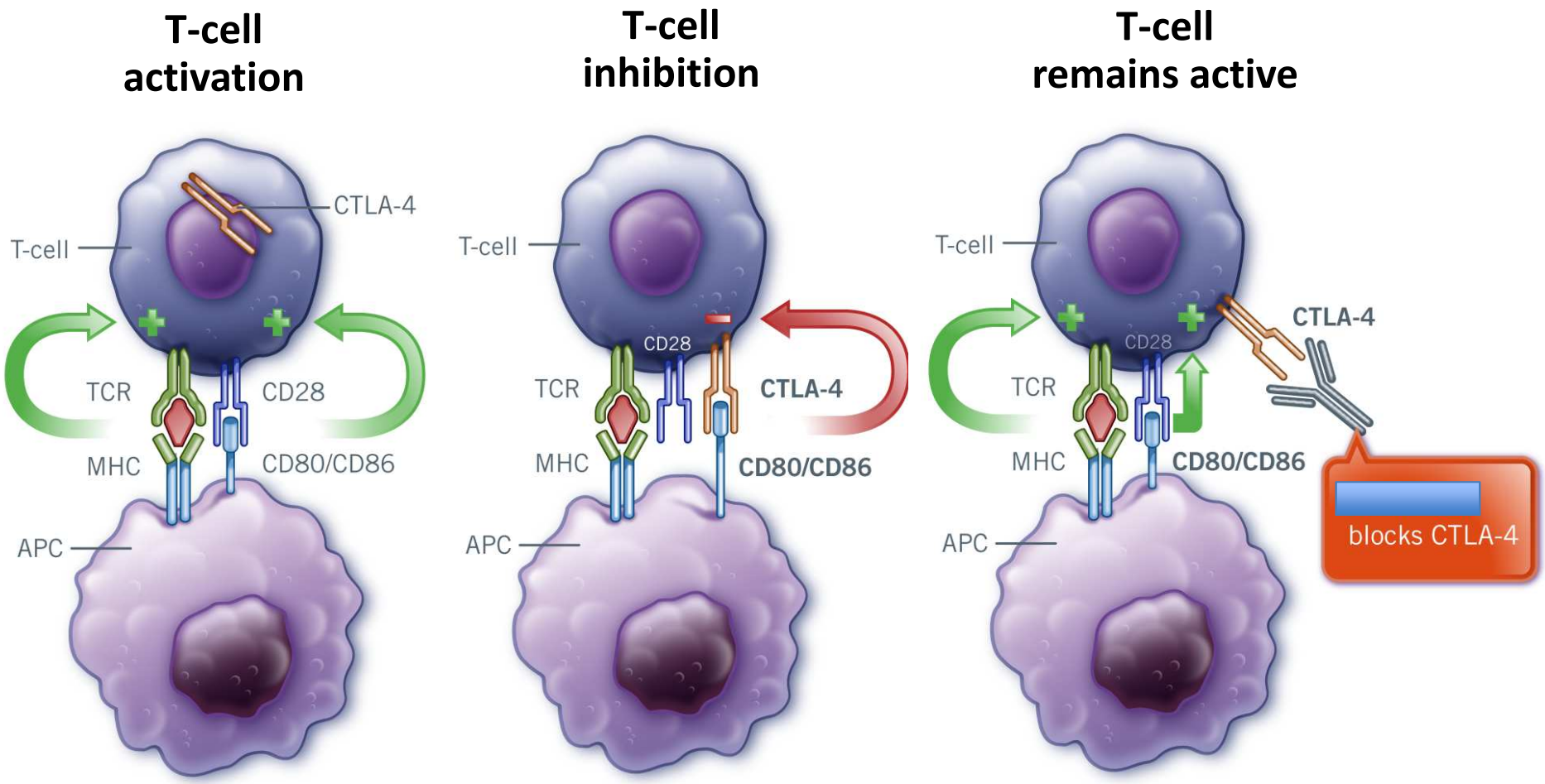

CHEMICAL & ENGIN
Behind the scenes of consecutive papers P.39
CANCER, MEET YOUR MATCH
Reprogrammed T cells are ready

Self-Tolerance Blockade Drugs in Development

- Anti-CTLA-4
  - Ipilimumab (Fully human IgG1) FDA Approved 2011
  - Tremelimumab (Fully human IgG2) Phase III
- Anti-PD-1
  - MDX-1106, Nivolumab, (Fully human IgG4) Phase III
  - CT-011 Pidilizumab (Humanized IgG1) Phase II
  - MK3475 Pembrolizumab (formerly Lambrolizumab) (Humanized IgG4) FDA Approved 2014
  - AMP-224 (B7-DC/IgG1fusion protein) Phase I-II
  - MEDI0680, AMP514 Phase I
- Anti-PD-L1
  - MDX-1105, (Fully human IgG4) Phase I
  - MPDL3280A, RG7446 Phase II
  - MEDI4736 Phase III
  - MSB0010718C Phase I

How does this work ?

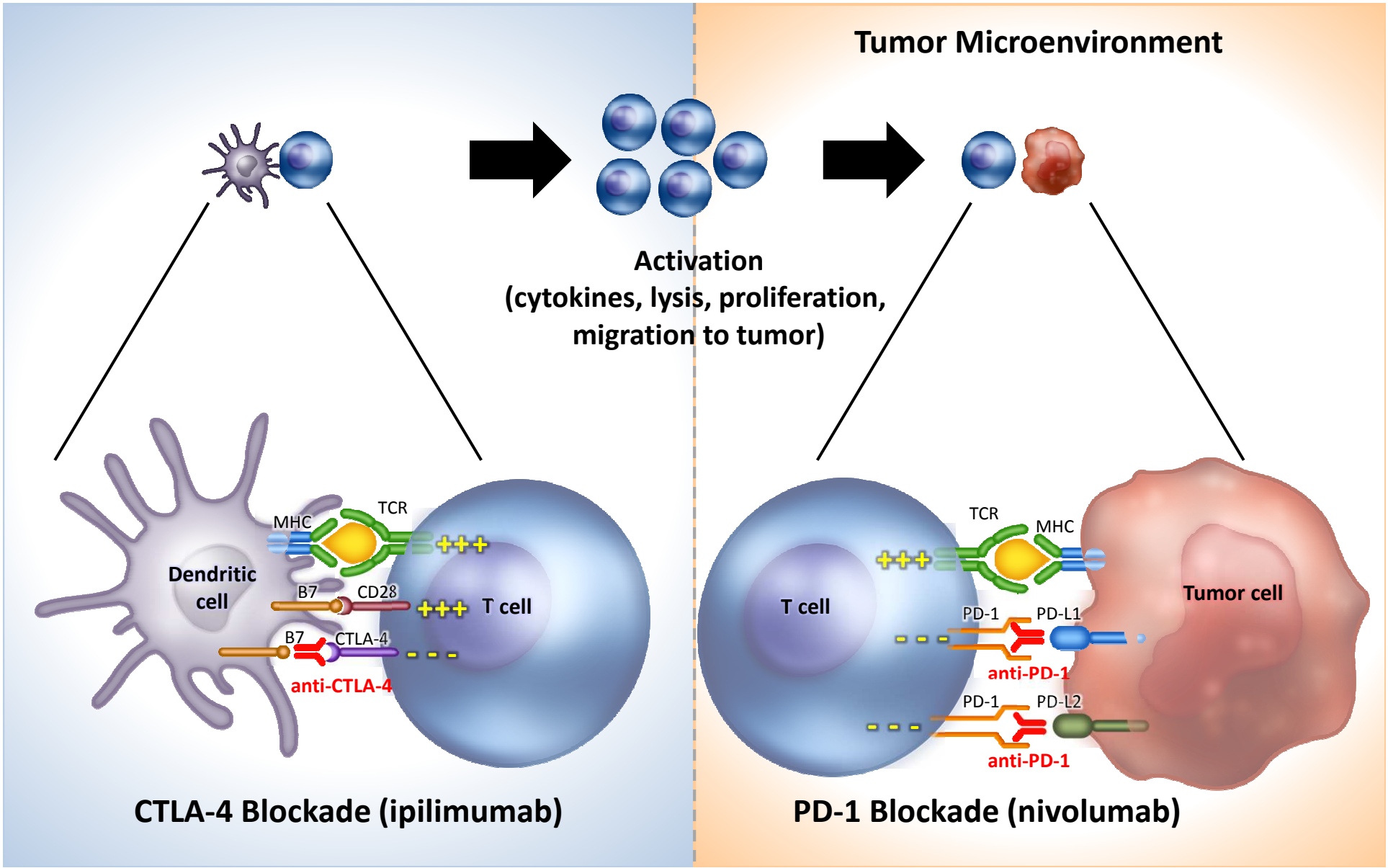
Ipilimumab: An Anti-CTLA-4 Therapy That Augments T-Cell Activation and Proliferation



APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte antigen-4; MHC, major histocompatibility complex; TCR, T-cell receptor.

Adapted from. Plenary session presentation, abstract #4, ASCO 2010.

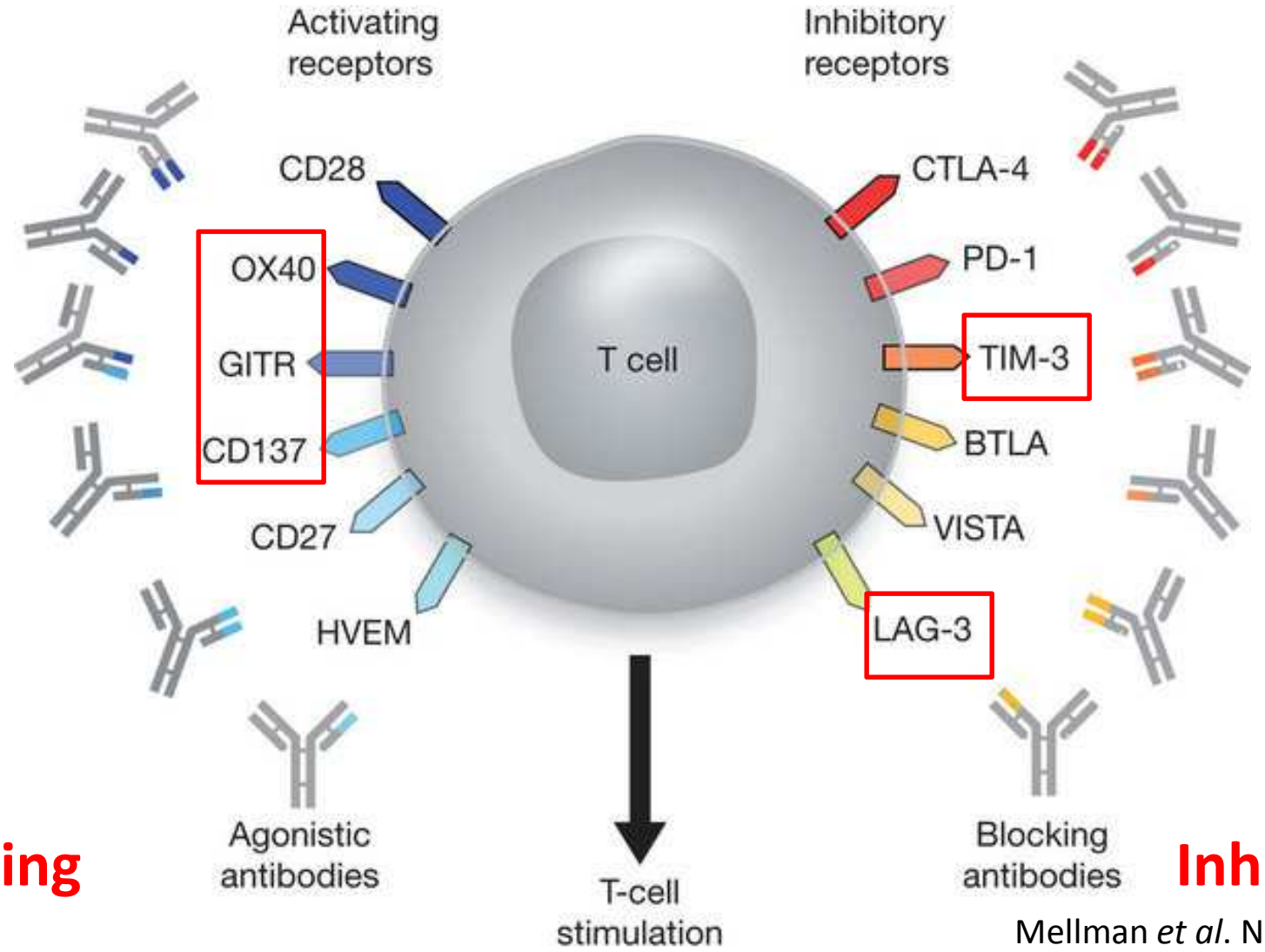
Blocking CTLA-4 and PD-1



Immune Modulatory Receptors

Turning up The Activating

Blocking the Inhibiting



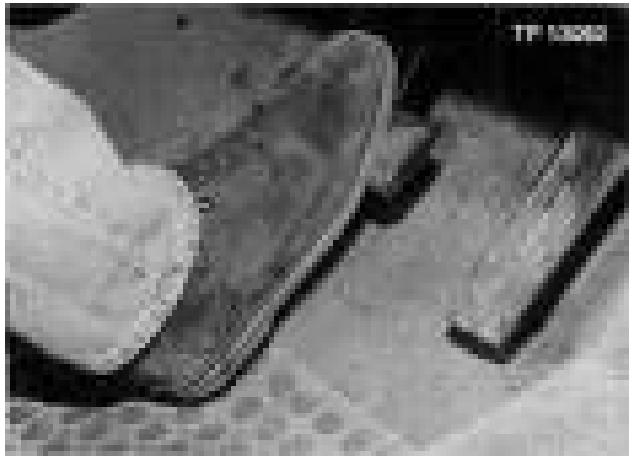
Activating **Inhibiting**

Mellman *et al*. Nature, 2011

CTLA-4: The Brake on T cell Activation

T-cell receptor: Antigen-MHC

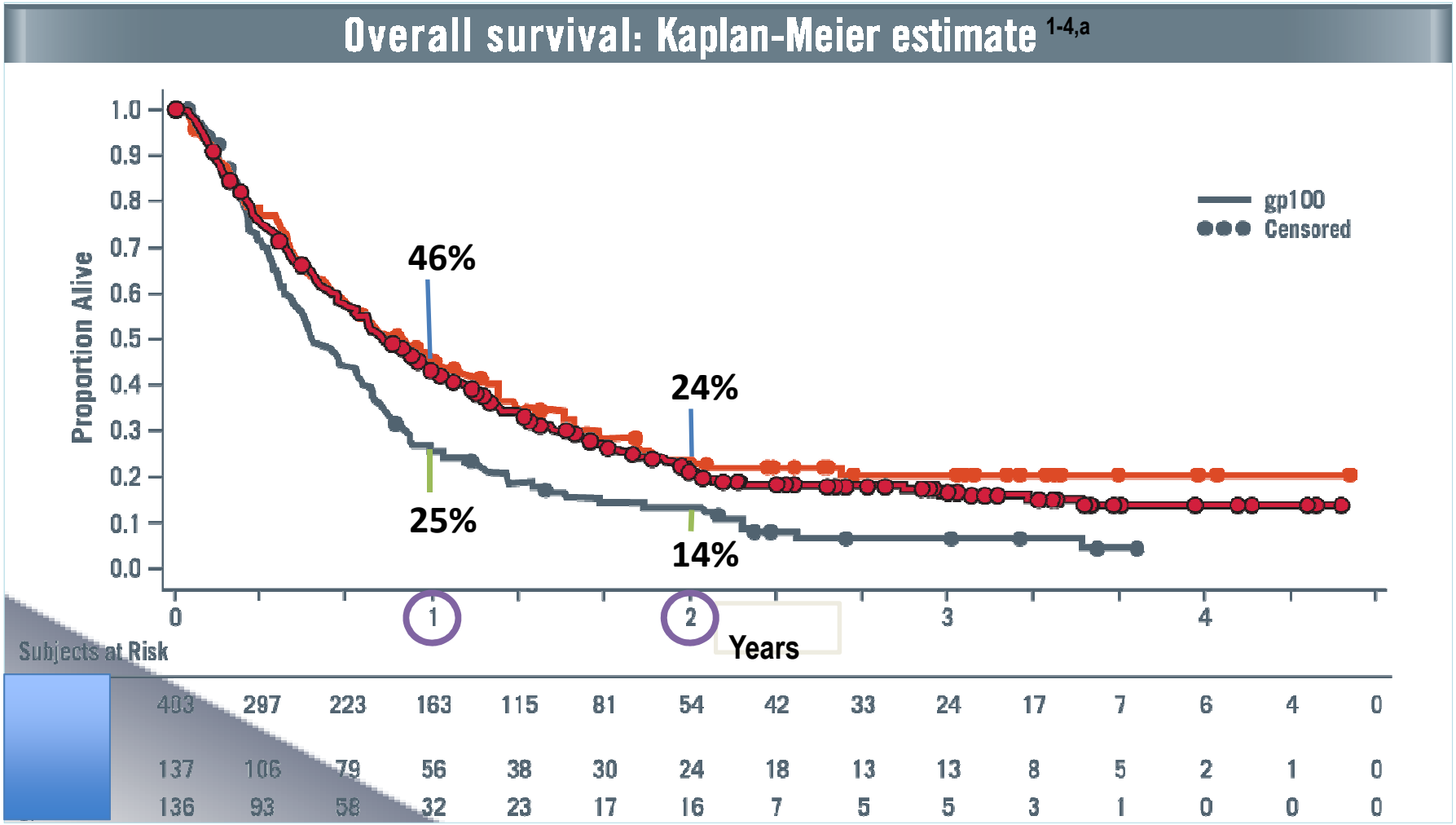
CD28: B7



CTLA-4: B7

Vaccine?

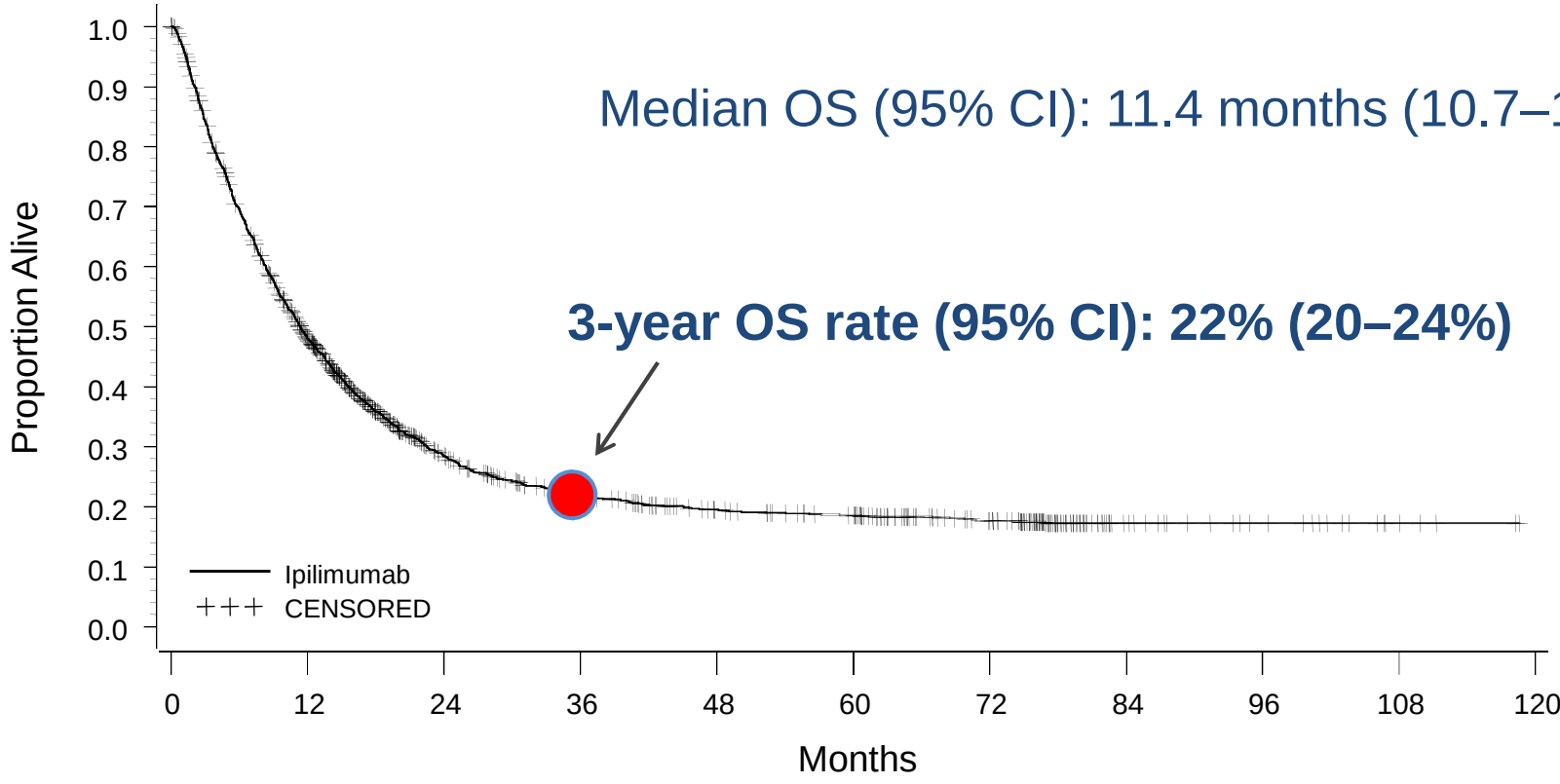
Ipilimumab Experience



[a]Estimated overall survival rates as in the pivotal phase 3 study publication.[2]

1. package insert. Princeton, NJ: Bristol-Myers Squibb; 2011.
2. FS et al. *N Engl J Med*. 2010;363:711-723.
3. Wolchuk JD et al. *Cancer Immun*. 2010;10:9.
4. Data on file. YERV 008.

Primary Analysis of Pooled OS Data on Ipilimumab in 1861 Patients



Median OS (95% CI): 11.4 months (10.7–12.1)

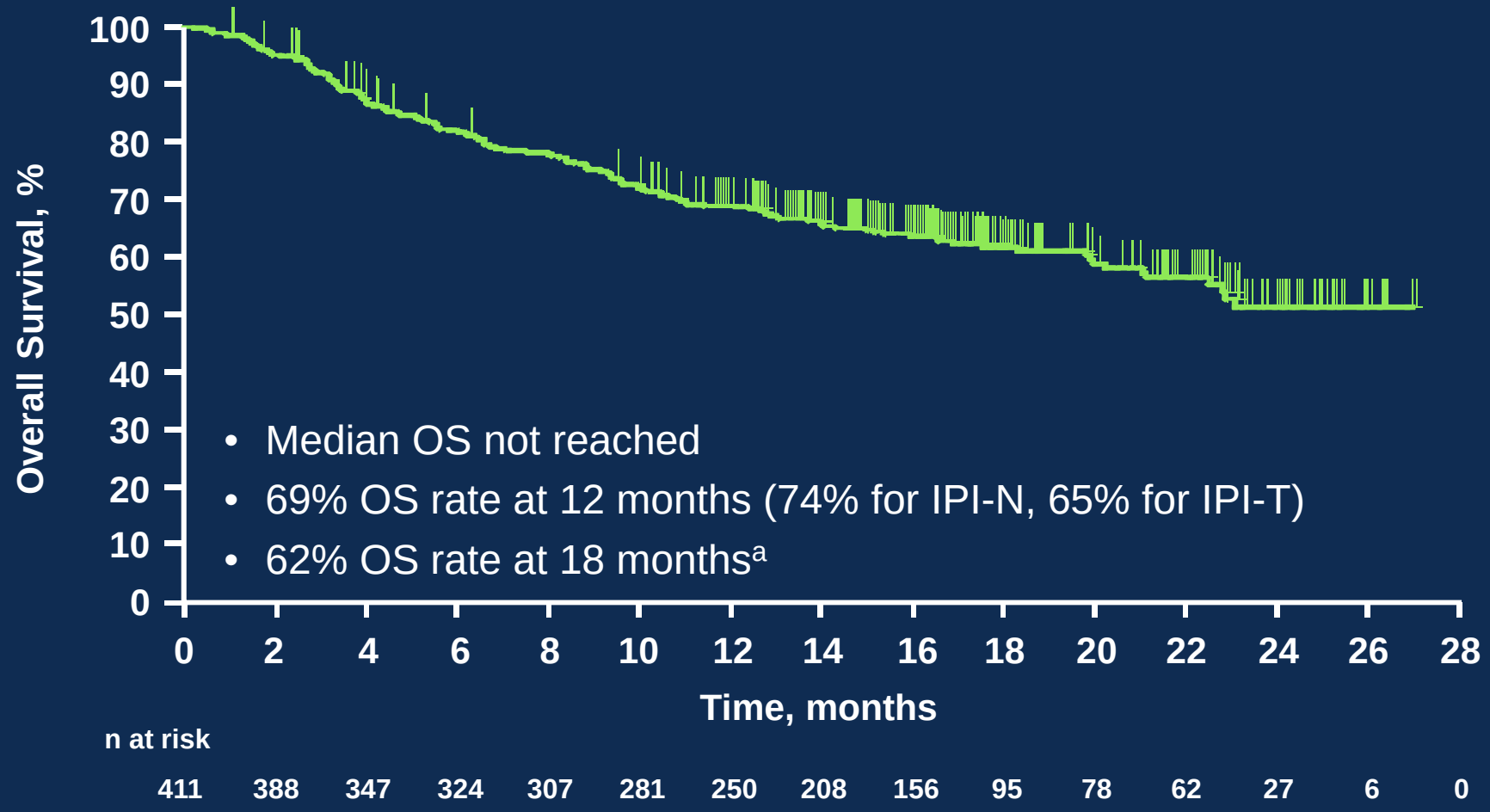
3-year OS rate (95% CI): 22% (20–24%)

Patients at Risk

Ipilimumab	1861	839	370	254	192	170	120	26	15	5	0

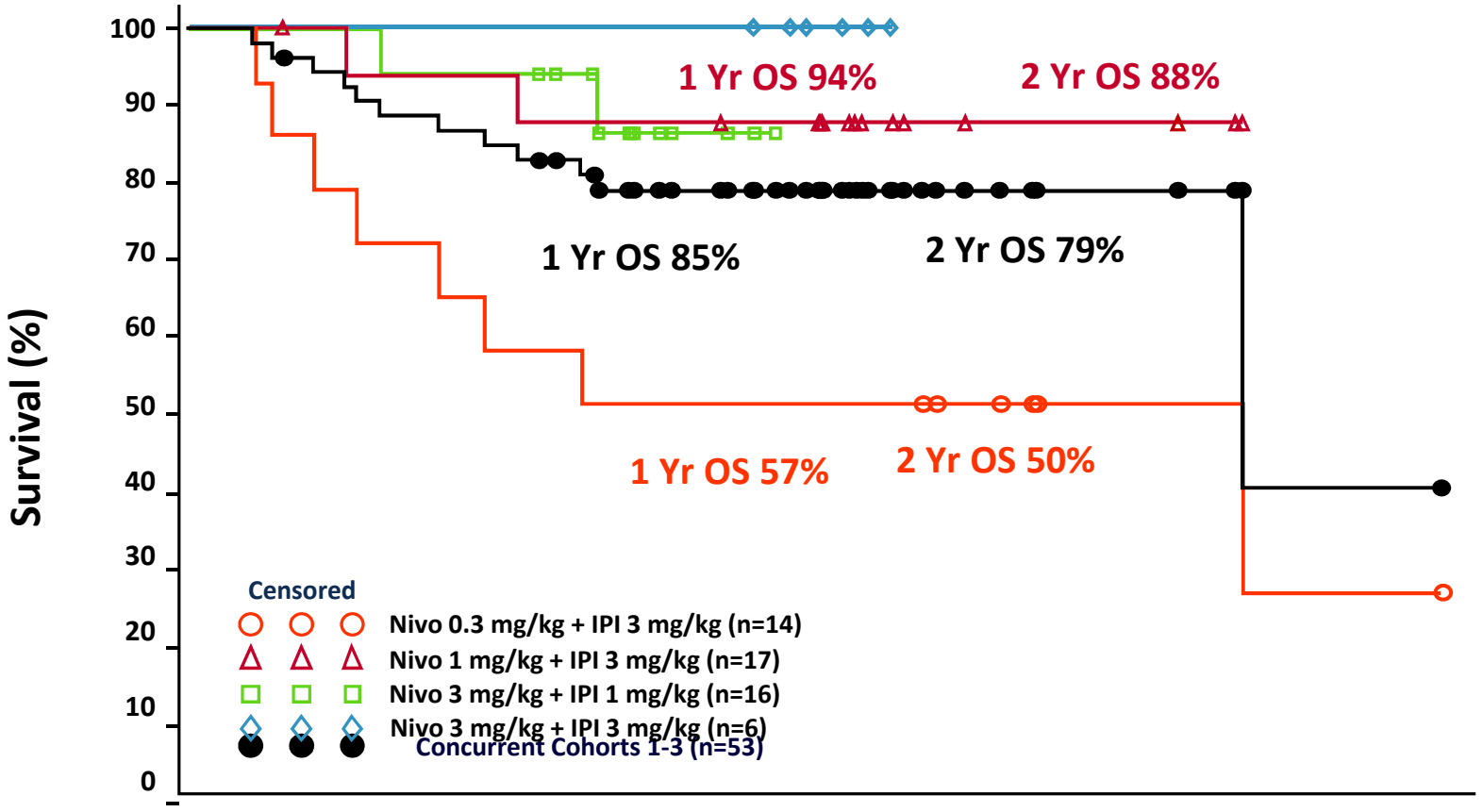
Schadendorf et al, ESMO 2013

Kaplan-Meier Estimate of Overall Survival



[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.

Overall Survival for Concurrent Therapy by Dose Cohort

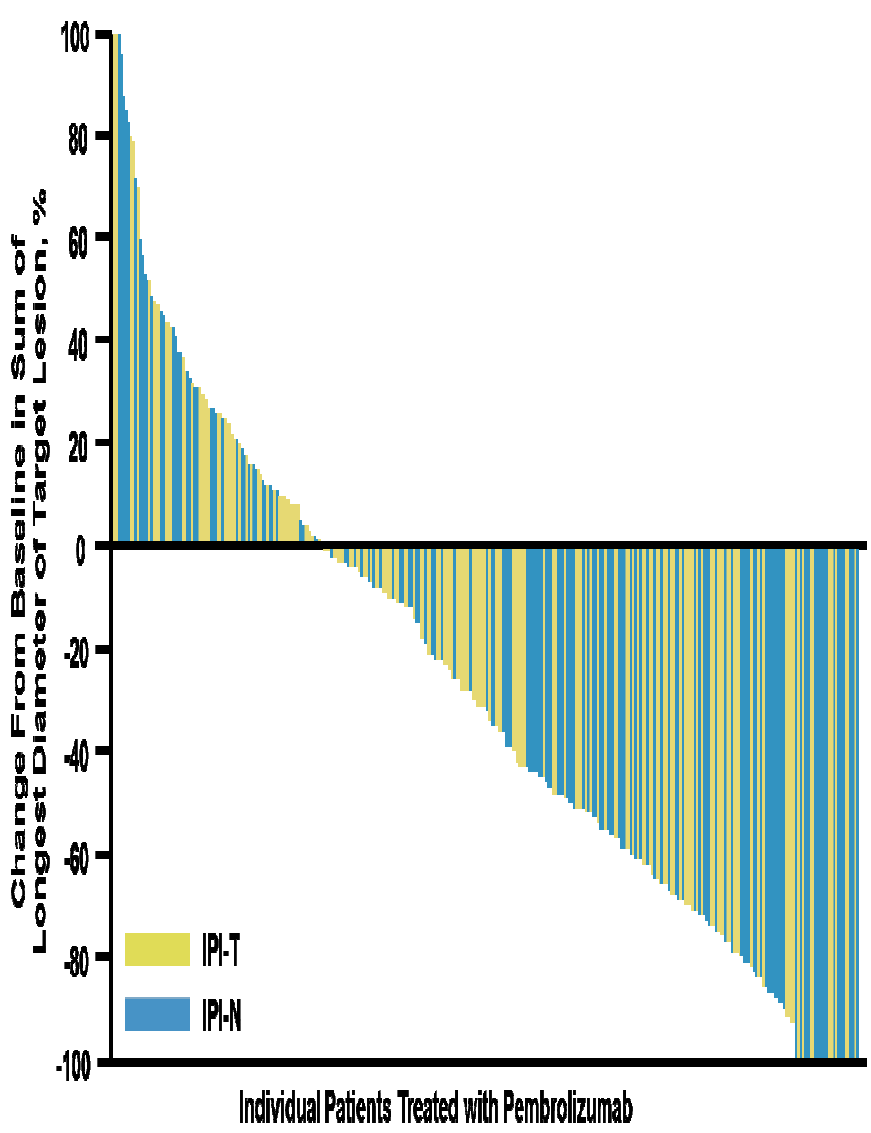


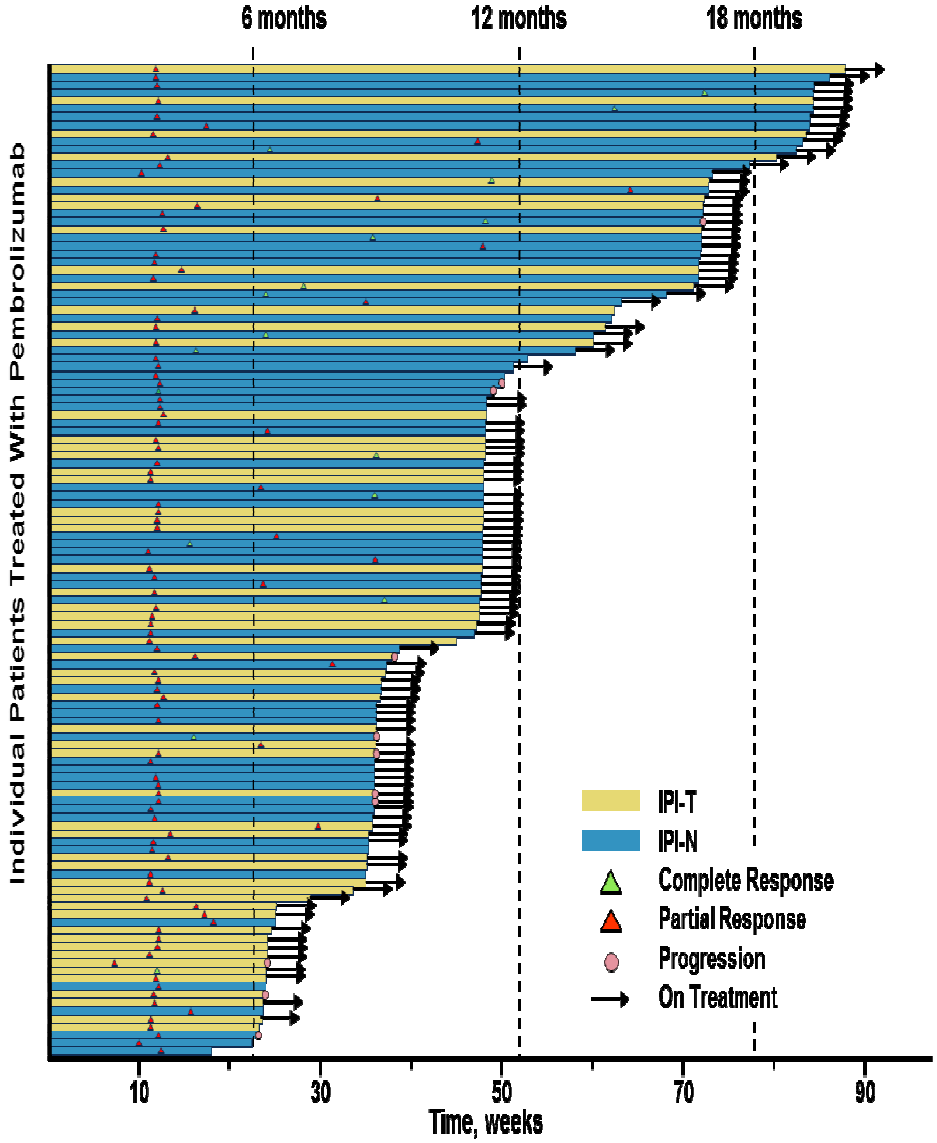
Pts at Risk																	
Nivo 0.3_IPI 3	14	13	11	10	8	7	7	7	7	7	5	2	2	2	1	1	0
Nivo 1 _IPI 3	17	17	16	15	15	14	14	13	9	4	3	3	3	2	0	0	0
Nivo 3_IPI 1	16	16	15	15	15	13	4	2	0	0	0	0	0	0	0	0	0
Nivo 3_IPI 3	6	6	6	6	6	6	6	6	3	0	0	0	0	0	0	0	0
Concurrent	53	52	48	46	44	40	31	28	19	11	8	5	5	4	1	1	0

Presented by:

ML2

Pembrolizumab Efficacy in KEYNOTE-001



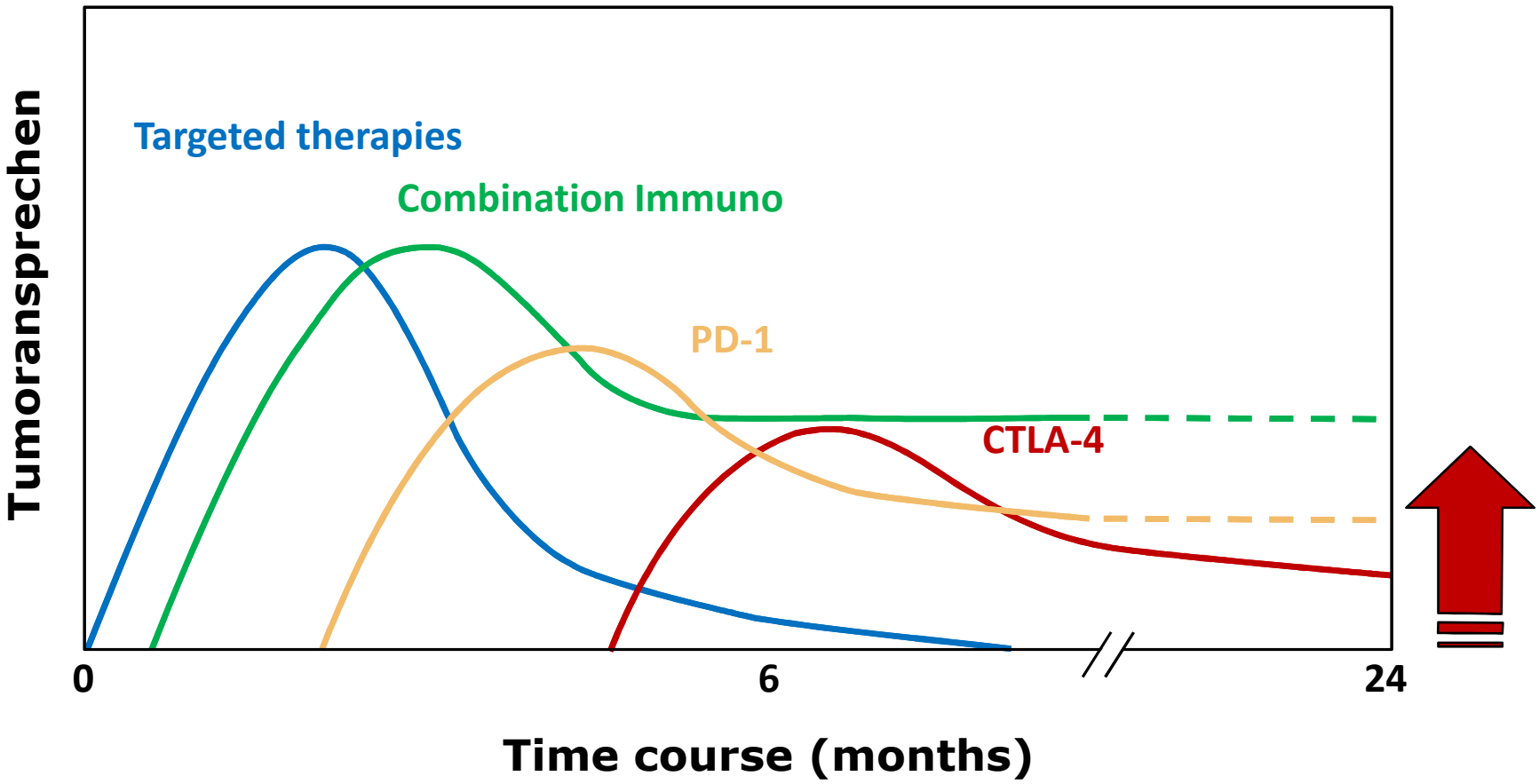


3. Daud A et al. Presented at: Society for Melanoma Research 2014 Annual Meeting; November 13-16, 2014; Zurich, Switzerland.

Slide 14

ML2 We will work on the formatting of the graphs and their arrangement on the slide.
Melanie Leiby, 4/1/2015

Antitumoral response: Targeted therapies vs. Immunotherapies

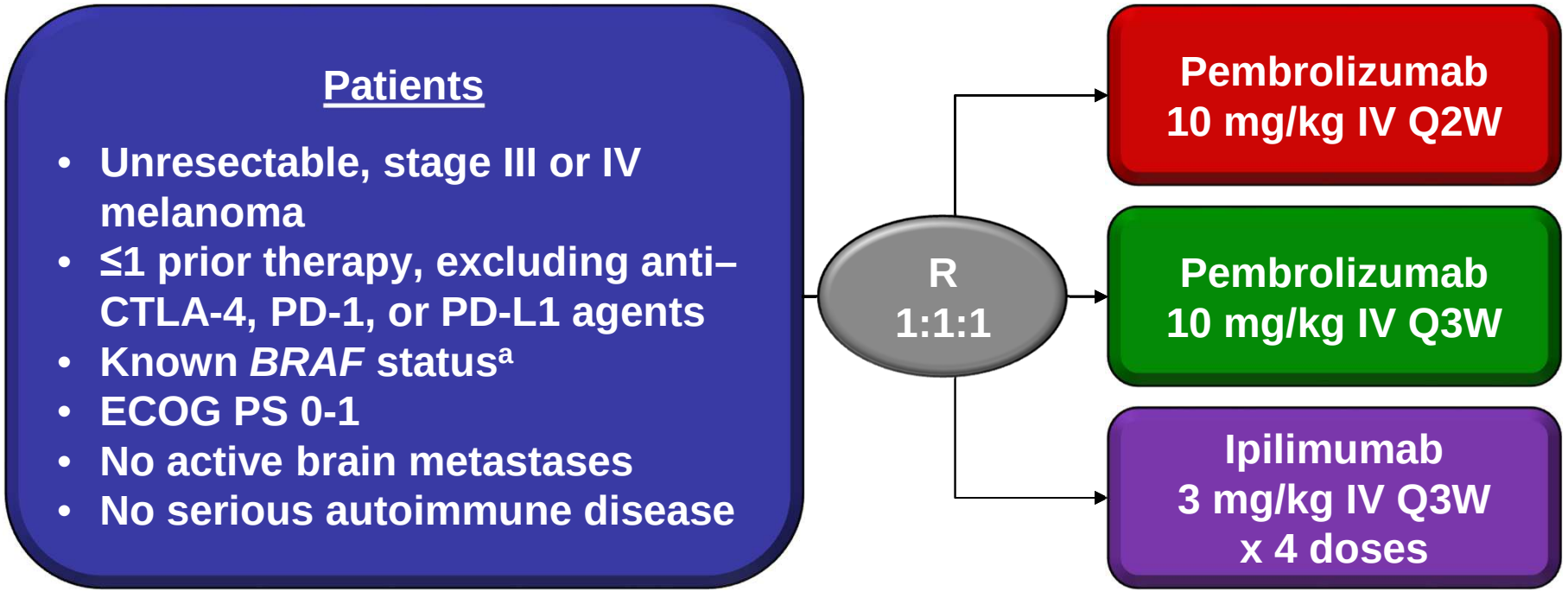


KEYNOTE-006: Phase III Study of Pembrolizumab (MK-3475) versus Ipilimumab in Patients With Ipilimumab-Naive Advanced Melanoma

Antoni Ribas,[1] Jacob Schachter,[2] Georgina V. Long,[3] Ana Arance,[4] Jean Jacques Grob,[5] Laurent Mortier,[6] Adil Daud,[7] Matteo S. Carlino,[8] Catriona McNeil,[9] Michal Lotem,[10] James Larkin,[11] Paul Lorigan,[12] Bart Neyns,[13] Christian U. Blank,[14] Omid Hamid,[15] Michele Kosh,[16] Honghong Zhou,[16] Nageatte Ibrahim,[16] Scot Ebbinghaus,[16] Caroline Robert[17]

[1]University of California, Los Angeles, Los Angeles, CA; [2]Ella Lemelbaum Institute for Melanoma, Sheba Medical Center, Tel Hashomer, Israel; [3]Melanoma Institute Australia and The University of Sydney, Sydney, Australia; [4]Department of Medical Oncology, Hospital Clinic and Translational Genomics and Targeted Therapeutics in Solid Tumors (IDIBAPS), Barcelona, Spain; [5]Hôpital de la Timone, Marseille, France; [6]Université Lille, CHRU LILLE, Lille, France; [7]University of California, San Francisco, San Francisco, CA; [8]Westmead and Blacktown Hospitals, The University of Sydney, and Melanoma Institute Australia, Sydney, Australia; [9]Chris O'Brien Lifehouse, Royal Prince Alfred Hospital, and Melanoma Institute Australia, Camperdown, Australia; [10]Sharett Institute of Oncology, Hadassah Hebrew University Medical Center, Jerusalem, Israel; [11]The Royal Marsden Hospital, London, UK; [12]University of Manchester and The Christie NHS Foundation Trust, Manchester, UK; [13]Universitair Ziekenhuis Brussel, Brussels, Belgium; [14]The Netherlands Cancer Institute, Amsterdam, The Netherlands; [15]The Angeles Clinic and Research Institute, Los Angeles, CA; [16]Merck & Co., Inc., Kenilworth, NJ; [17]Gustave Roussy Département de Médecine Oncologique, Service de Dermatologie, F-94805, Villejuif France and Université Paris-Sud, Faculté de Médecine, F-94270 Le Kremlin–Bicetre Paris-Sud, France

KEYNOTE-006 (NCT01866319): International, Randomized, Phase III Study



Stratification factors:
- ECOG PS (0 vs 1)
- Line of therapy (first vs second)
- PD-L1 status (positive[b] vs negative)

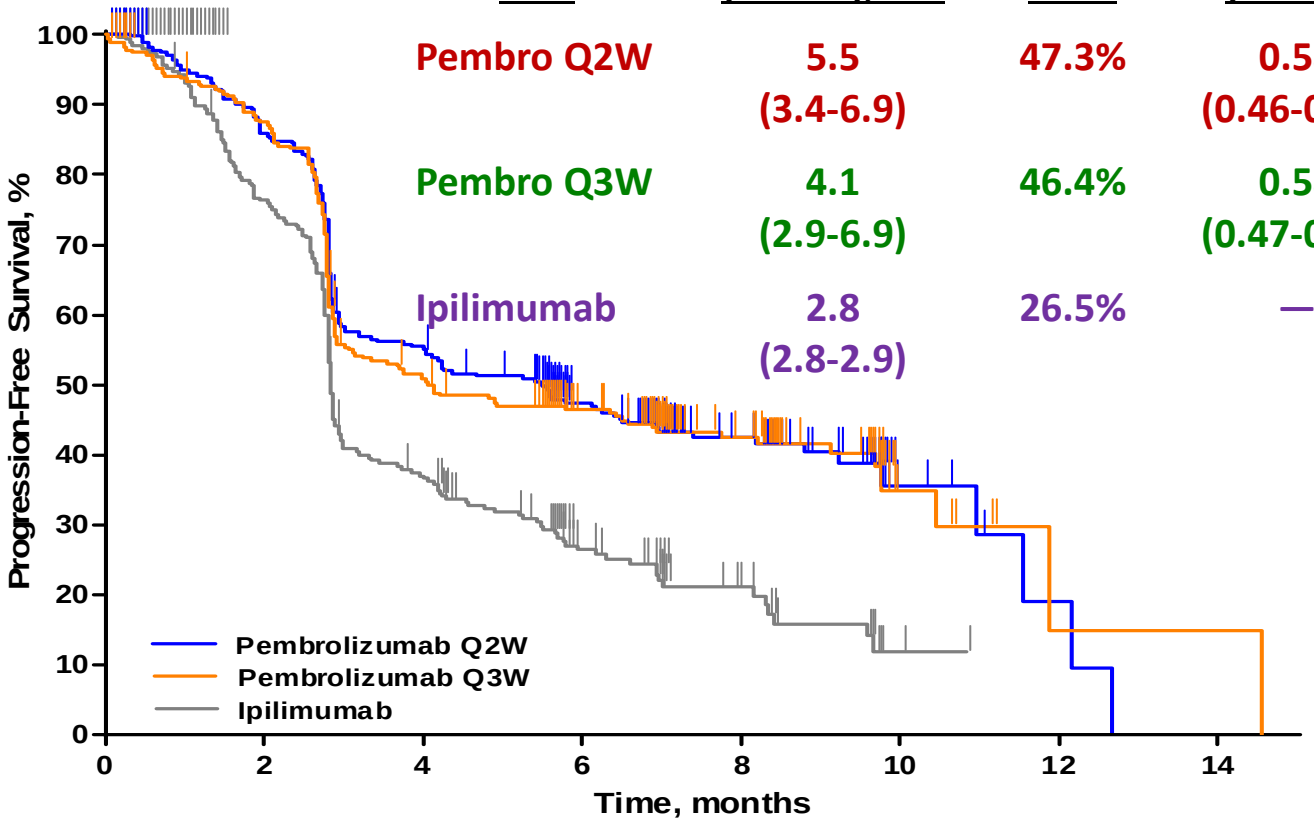
- **Primary end points: PFS and OS**
- **Secondary end points: ORR, duration of response, safety**

[a]Prior anti-BRAF targeted therapy was not required for patients with normal LDH levels and no clinically significant tumor-related symptoms or evidence of rapidly progressing disease.
[b]Defined as membranous PD-L1 expression in ≥1% of tumor cells as assessed by IHC using the 22C3 antibody.

ML4

First Interim Analysis: PFS

Arm	Median (95% CI), mo	Rate at 6 mo	HR (95% CI)	*P*
Pembro Q2W	5.5 (3.4-6.9)	47.3%	0.58 (0.46-0.72)	<0.0001
Pembro Q3W	4.1 (2.9-6.9)	46.4%	0.58 (0.47-0.72)	<0.0001
Ipilimumab	2.8 (2.8-2.9)	26.5%	—	—



No. at risk								
Pembrolizumab Q2W	279	231	147	98	49	7	2	0
Pembrolizumab Q3W	277	235	133	95	53	7	1	1
Ipilimumab	278	186	88	42	18	2	0	0

Analysis cut-off date: September 3, 2014.

Slide 18

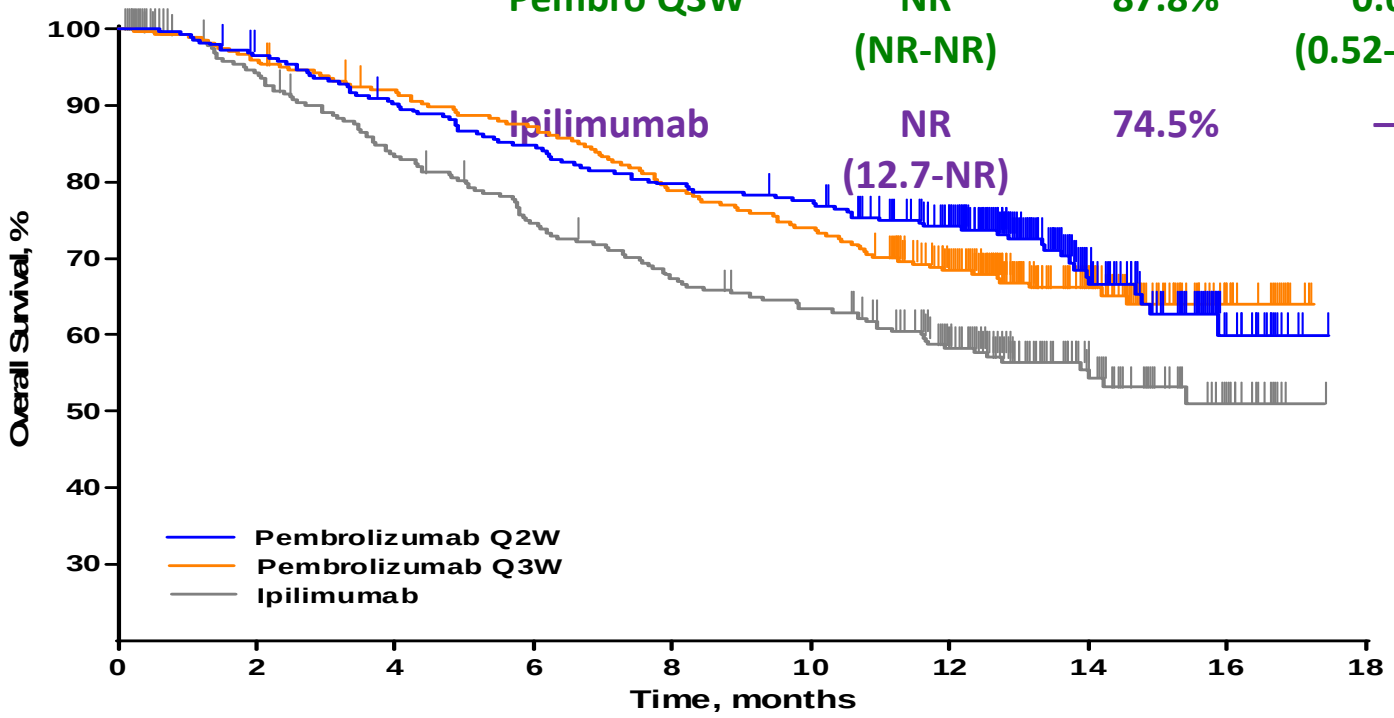
ML4 The figure is from the manuscript - our graphics team is formatting for a slide presentation, which will include matching the color scheme. We'll also do a full format of the slides after that.

Melanie Leiby, 3/29/2015

ML5

Second Interim Analysis: OS

Arm	Median (95% CI), mo	Rate at 12 mo	HR (95% CI)	*P*
Pembro Q2W	NR (NR-NR)	84.8%	0.63 (0.47-0.83)	0.00052
Pembro Q3W	NR (NR-NR)	87.8%	0.69 (0.52-0.90)	0.00358
Ipilimumab	NR (12.7-NR)	74.5%	—	—



sk									
ılizumab Q2W	279	266	248	233	219	212	177	67	19	0
ılizumab Q3W	277	266	251	238	215	202	158	71	18	0
nab	278	242	212	188	169	157	117	51	17	0

Analysis cut-off date: March 3, 2015.

Slide 19

ML5 The figure is from the manuscript - our graphics team is formatting for a slide presentation, which will include matching the color scheme. We'll also do a full format of the slides after that.

Melanie Leiby, 3/29/2015

Conclusions

- Superioriority for pembrolizumab over ipilimumab demonstrated for OS ($P \leq 0.00358$), PFS ($P < 0.00001$), and ORR ($P \leq 0.00013$)
  - Risk of death reduced by 37% to 31%
  - ~1.8-fold increase in 6-month PFS rates
  - ~2.8-fold increase in ORR
- Favorable safety profile for pembrolizumab versus ipilimumab
- Similar efficacy and tolerability for both pembrolizumab schedules
- Results support the use of pembrolizumab in patients with melanoma, regardless of whether they have received prior ipilimumab

Multicenter, Randomized Phase II Trial of GM-CSF (GM) plus Ipilimumab (Ipi) vs. Ipi Alone in Metastatic Melanoma: E1608

FS Hodi, S Lee, DF McDermott, UN Rao, LH Butterfield, AA Tarhini, P Leming, I Puzanov, JM Kirkwood

Dana-Farber Cancer Institute, Boston, MA; Beth Israel-Deaconess Medical Center, Boston ,MA; University of Pittsburgh Cancer Institute, Pittsburgh, PA; The Christ Hospital, Cincinnati, OH, Vanderbilt University, Nashville, TN

Randomized Phase II Trial of Ipilimumab plus GM-CSF versus Ipilimumab Alone
E1608

Randomization

- AJCC stage (Unresectable stage III, M1a/M1b, M1c)
- Prior therapy (none, IFN/IL-2/GM-CSF, One investigational therapy)

Arm A

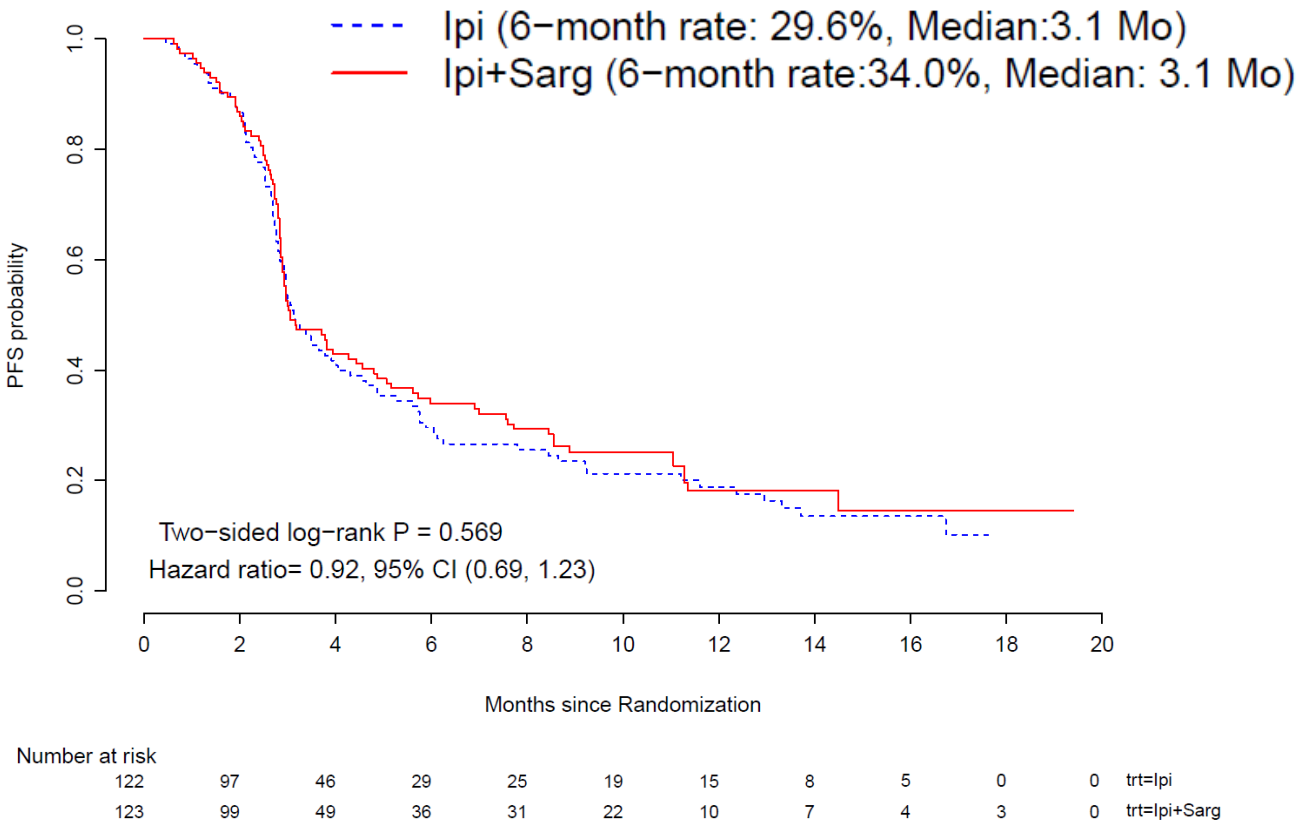
Induction - Ipilimumab 10 mg/kg IV, Day 1 x 4 cycles
Maintenance - Ipilimumab 10 mg/kg IV, Day 1 every 4th cycle

Sargramostim (GM-CSF) 250 mcg SQ Q Day, Days 1-14 of 21 day cycle

Arm B

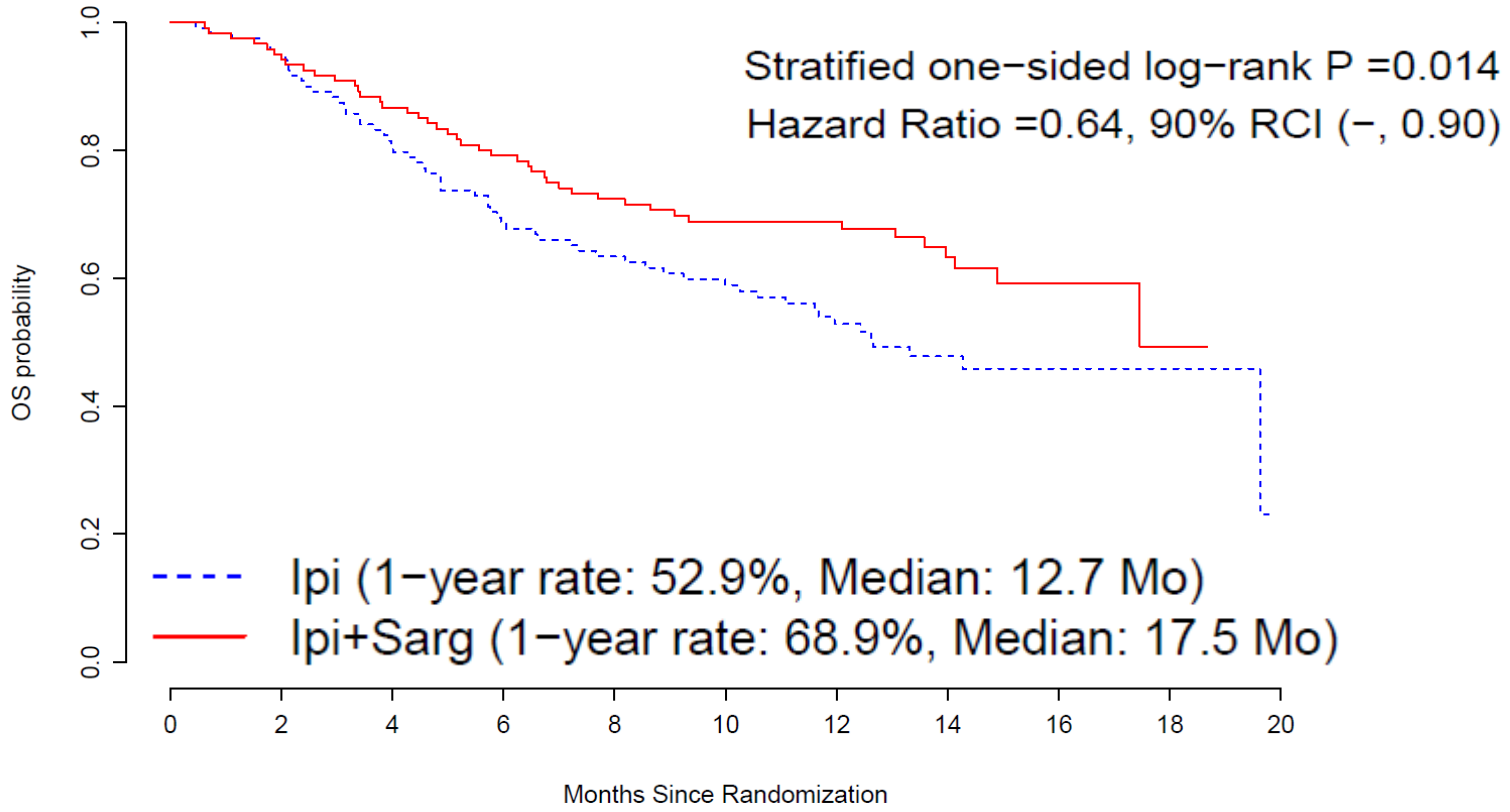
Induction - Ipilimumab 10 mg/kg IV, Day 1 x 4 cycles
Maintenance - Ipilimumab 10 mg/kg IV, Day 1 every 4th cycle

Progression-Free Survival



	Arm A: Ipi+Sarg (n=123)	Arm B: Ipi (n=122)	Comparisons
Progression-Free Survival (PFS)			
-Median, (95%CI)	3.1 mo (2.9, 4.6)	3.1 mo (2.9, 4.0)	P_2=0.569 (Log rank test)
- 6-mo PFS rate (95% CI)	34.0% (25.3,42.8)	29.6% (21.1,38.1)	
-HR (95% CI)	0.92 (0.69,1.23)	Reference	P_2= 0.571 (Cox model)

Overall Survival



Number at risk

122	114	94	80	72	64	49	28	14	6	0	trt=Ipi
123	115	104	94	84	75	63	39	11	2	0	trt=Ipi+Sarg

	Arm A: Ipi+Sarg (n=123)	Arm B: Ipi (n=122)	Comparisons
Overall Survival (OS)			
- Median , (95% CI)	17.5 mo (14.9, NR)	12.7 mo (10.0, NR)	P1*=0.014 (Stratified Logrank test)
- 1-Year OS rate, (95% CI)	68.9% (60.6, 85.5)	52.9% (43.6, 62.2)	
- HR 90% RCI for HR	0.64 (-, 0.90)	Reference	P1* =0.014 (Stratified Cox model)

Tolerability and Safety

- The addition of sargramostim to ipilimumab decreased the incidence of high grade adverse events

- The addition of sargramostim to ipilimumab specifically improved pulmonary and gastrointestinal high grade events

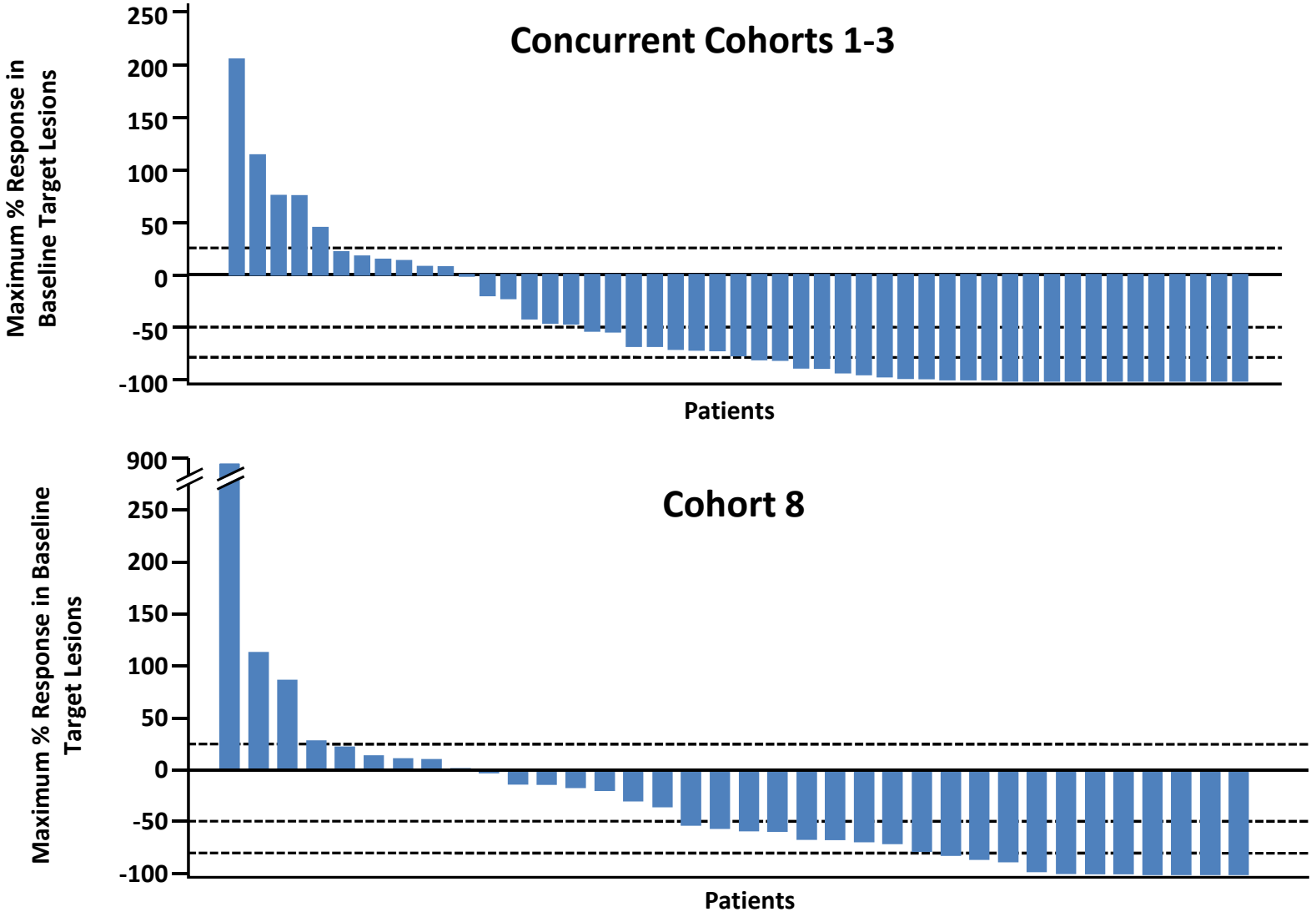
Survival, response duration, and activity by BRAF mutation (MT) status of nivolumab (NIVO, anti-PD-1, BMS-936558, ONO-4538) and ipilimumab (IPI) concurrent therapy in advanced melanoma (MEL)

Mario Sznol,[1] Harriet Kluger,[1] Margaret K. Callahan,[2] Michael A. Postow,[2] RuthAnn Gordon,[2] Neil H. Segal,[2] Naiyer A. Rizvi, [2]Alexander M. Lesokhin,[2] Michael B. Atkins,[3] John M. Kirkwood,[4] Matthew M. Burke,[1] Amanda Ralabate,[1] Angel Rivera,[1] Stephanie A. Kronenberg,[2] Blessing U. Agunwamba,[2] William Feely,[5] Quan Hong,[5] Suba Krishnan,[5] Jedd D. Wolchok[2]

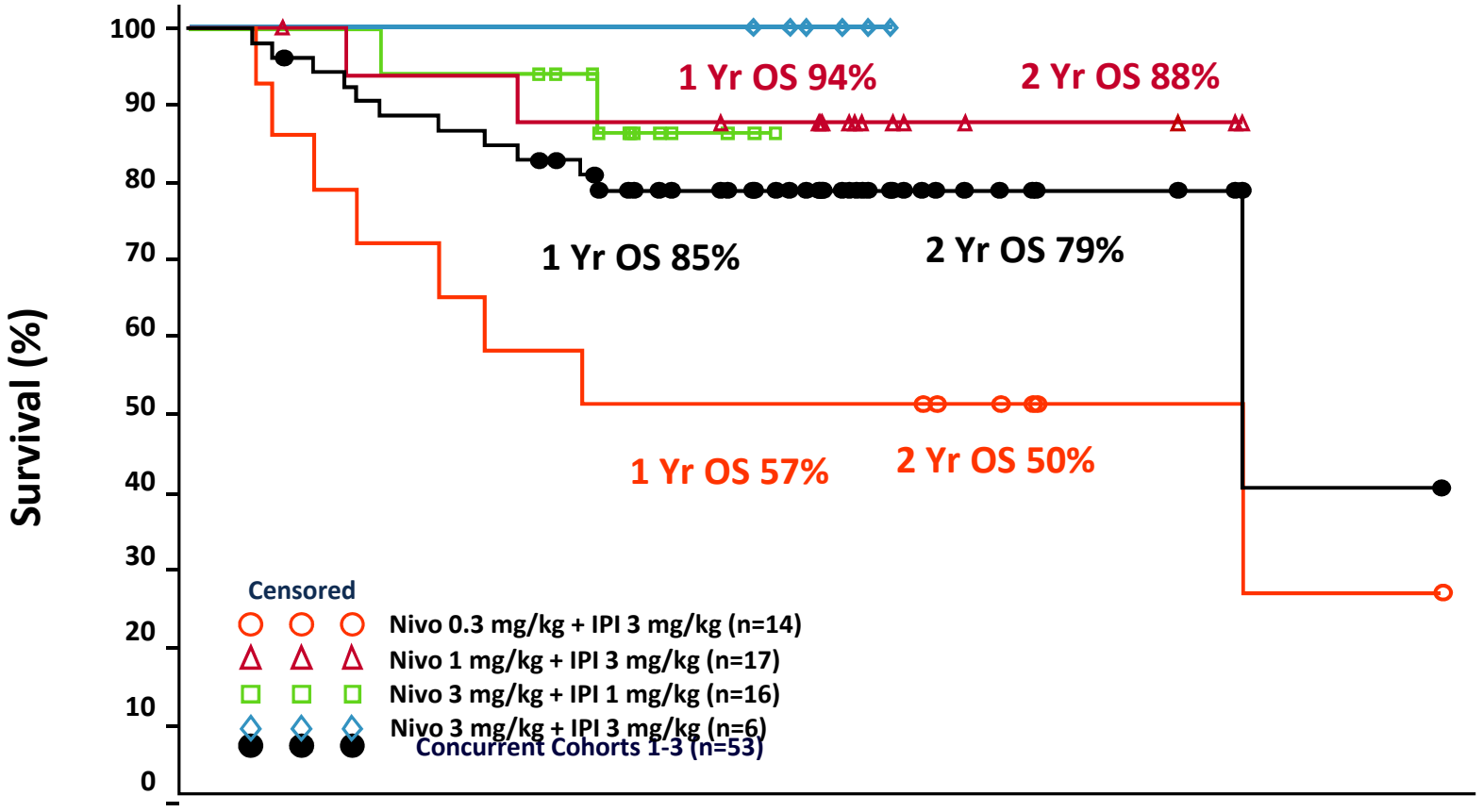
[1]Yale University School of Medicine and Yale Cancer Center, New Haven, CT, USA; [2]Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [3]Georgetown-Lombardi Comprehensive Cancer Center, Washington, DC, USA; [4]University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [5]Bristol-Myers Squibb, Princeton, NJ, USA

ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Response in Target Lesions



Overall Survival for Concurrent Therapy by Dose Cohort

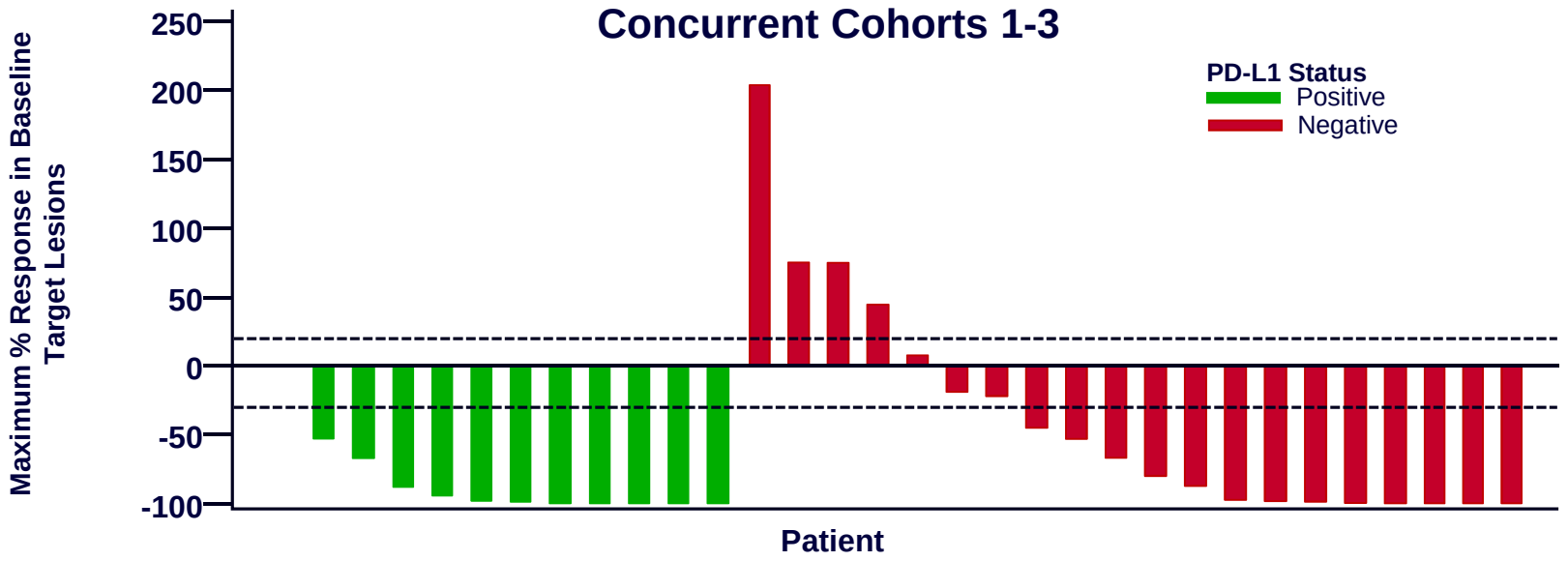


Pts at Risk																	
Nivo 0.3_IPI 3	14	13	11	10	8	7	7	7	7	7	5	2	2	2	1	1	0
Nivo 1 _IPI 3	17	17	16	15	15	14	14	13	9	4	3	3	3	2	0	0	0
Nivo 3_IPI 1	16	16	15	15	15	13	4	2	0	0	0	0	0	0	0	0	0
Nivo 3_IPI 3	6	6	6	6	6	6	6	6	3	0	0	0	0	0	0	0	0
Concurrent	53	52	48	46	44	40	31	28	19	11	8	5	5	4	1	1	0

Presented by:

ORR by PD-L1 Status (5% cutoff)

Cohort [n]	Evaluable Samples	ORR, n (%)	
PD-L1 Status		PD-L1+	PD-L1-
Concurrent Cohorts 1-3 [53]	36	8/14 (57)	9/22 (35)
Cohort 8 [41; Nivo1 + IPI3]	20	0/0	8/20 (40)
Sequenced [33]	23	5/8 (63)	3/15 (20)



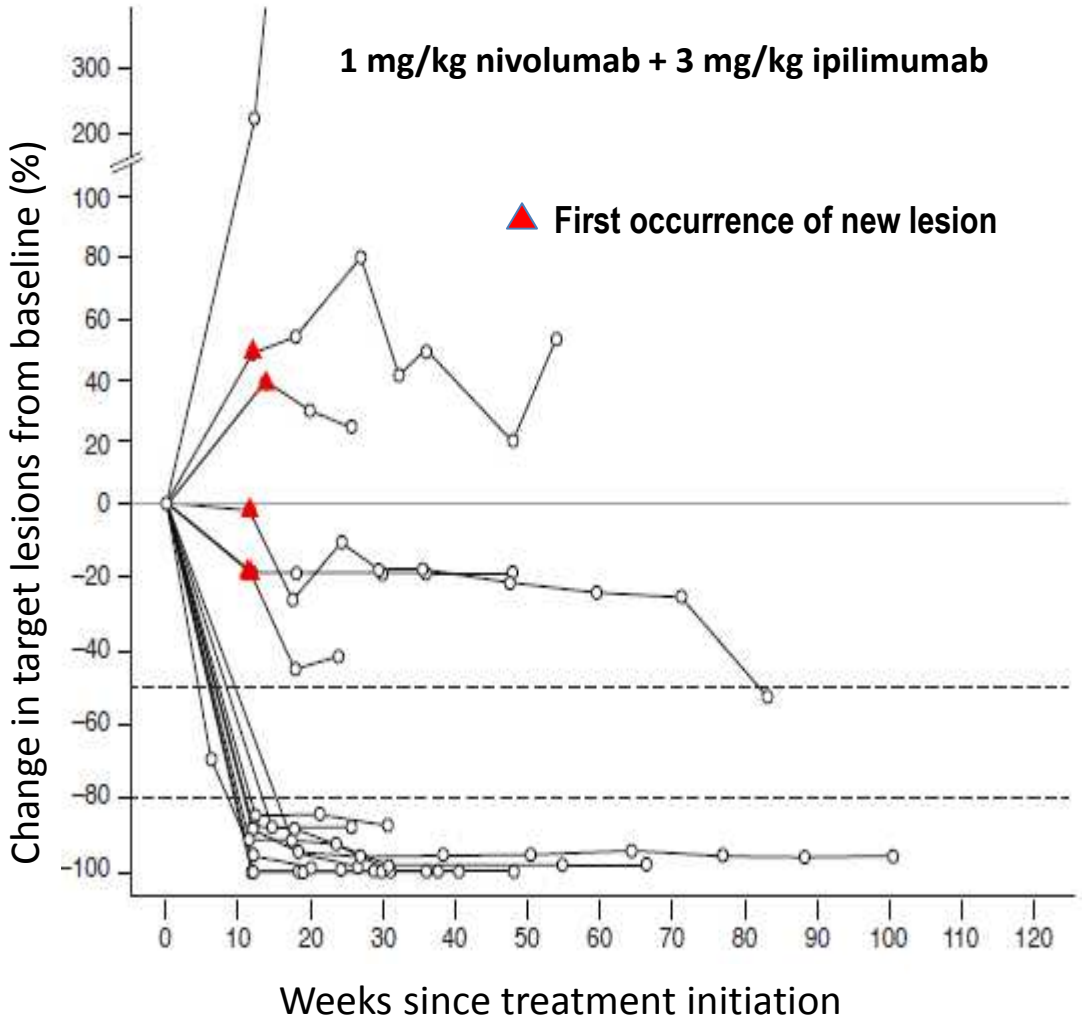
Activity Summary: Concurrent and Sequenced Cohorts from 004

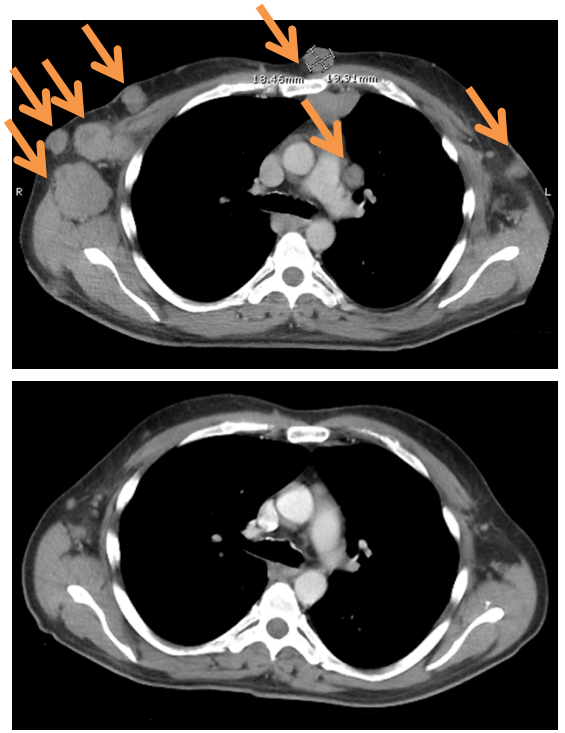
Nivolumab (mg/kg) + IPI (mg/kg)	N	ORR[a], %	CR, %	Aggregate Clinical Activity Rate	≥80% tumor burden reduction at 36 wks[b], %
Concurrent Cohorts 1-3	53	42	17	70	42
0.3 + 3	14	21	14	57	36
1 + 3	17	53	18	65	53
3 + 1	16	44	25	81	31
3 + 3	6	50	0	83	50
1 + 3 [Cohort 8][c]	40	43	10[d]	53	28
Sequenced	33	31	3	44	31

[a]per RECIST, [CR+PR]/N x 100; [b] Best overall response; [c]Cohort 8: Phase 2/3 trial; last patient, first dose Nov 2013. [d]2 confirmed and 2 unconfirmed responses

n: no. response-evaluable pts.

Rapid and Durable Changes in Target Lesions





Pre-treatment

12 weeks

- A 52-year-old patient presented with extensive nodal and visceral disease
- Baseline LDH was elevated (2.3 x ULN); symptoms included nausea and vomiting
- Within 4 wk, LDH normalized and symptoms resolved
- At 12 wk, there was marked reduction in all areas of disease as shown

Primary Analysis of a Phase 1b Multicenter Trial to Evaluate Safety and Efficacy of Talimogene Laherparepvec (T-VEC) and Ipilimumab in Previously Untreated, Unresected Stage IIIB–IV Melanoma

Igor Puzanov,1 Mohammed Milhem,2 Robert H. I. Andtbacka,3 David Minor,4 Omid Hamid,5 Ai Li,6 Michael Chastain,7 Kevin Gorski,6 Abraham Anderson,6 Ari VanderWalde,6 Jeffrey Chou,6 Howard Kaufman8,9

1Vanderbilt University, Nashville, TN; 2University of Iowa, Iowa City, IA; 3Huntsman Cancer Institute, Salt Lake City, UT; 4California Pacific Center, San Francisco, CA; 5The Angeles Clinic and Research Institute, Los Angeles, CA; 6Amgen Inc., Thousand Oaks, CA; 7Amgen Inc., Seattle, WA; 8Rush University Medical Center, Chicago, IL; 9Currently at Rutgers Cancer Institute of New Jersey, New Brunswick, NJ

PRESENTED AT THE 2014 ASCO ANNUAL MEETING. PRESENTED DATA IS THE PROPERTY OF THE AUTHOR.

Efficacy and Safety Results From a Phase III Trial of Nivolumab Alone or Combined With Ipilimumab vs. Ipilimumab Alone in Treatment-naïve Patients With Advanced Melanoma (CheckMate 067)

Jedd D. Wolchok,[1] Vanna Chiarion-Sileni,[2] Rene Gonzalez,[3] Piotr Rutkowski,[4] Jean-Jacques Grob,[5] C. Lance Cowey,[6] Christopher D. Lao,[7] Dirk Schadendorf,[8] Pier Francesco Ferrucci,[9] Michael Smylie,[10] Reinhard Dummer,[11] Andrew Hill,[12] John Haanen,[13] Michele Maio,[14] Grant McArthur,[15] Arvin Yang,[16] Linda Rollin,[17] Christine Horak,[16] James Larkin,[18,*] F. Stephen Hodi[19,*]

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*Equal contributors.

Abstract #LBA1

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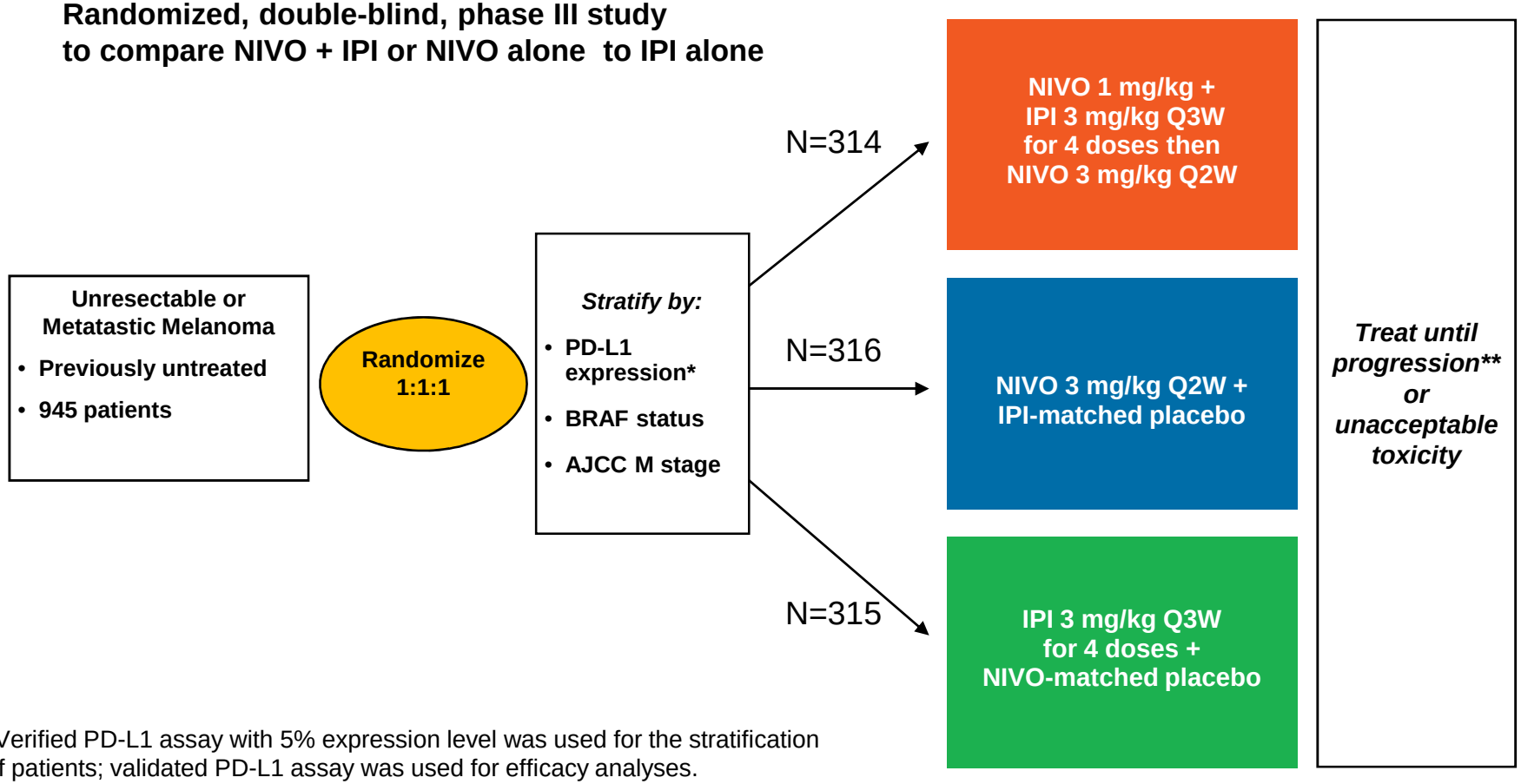
CA209-067: Study Design

Randomized, double-blind, phase III study to compare NIVO + IPI or NIVO alone to IPI alone



*Verified PD-L1 assay with 5% expression level was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses.

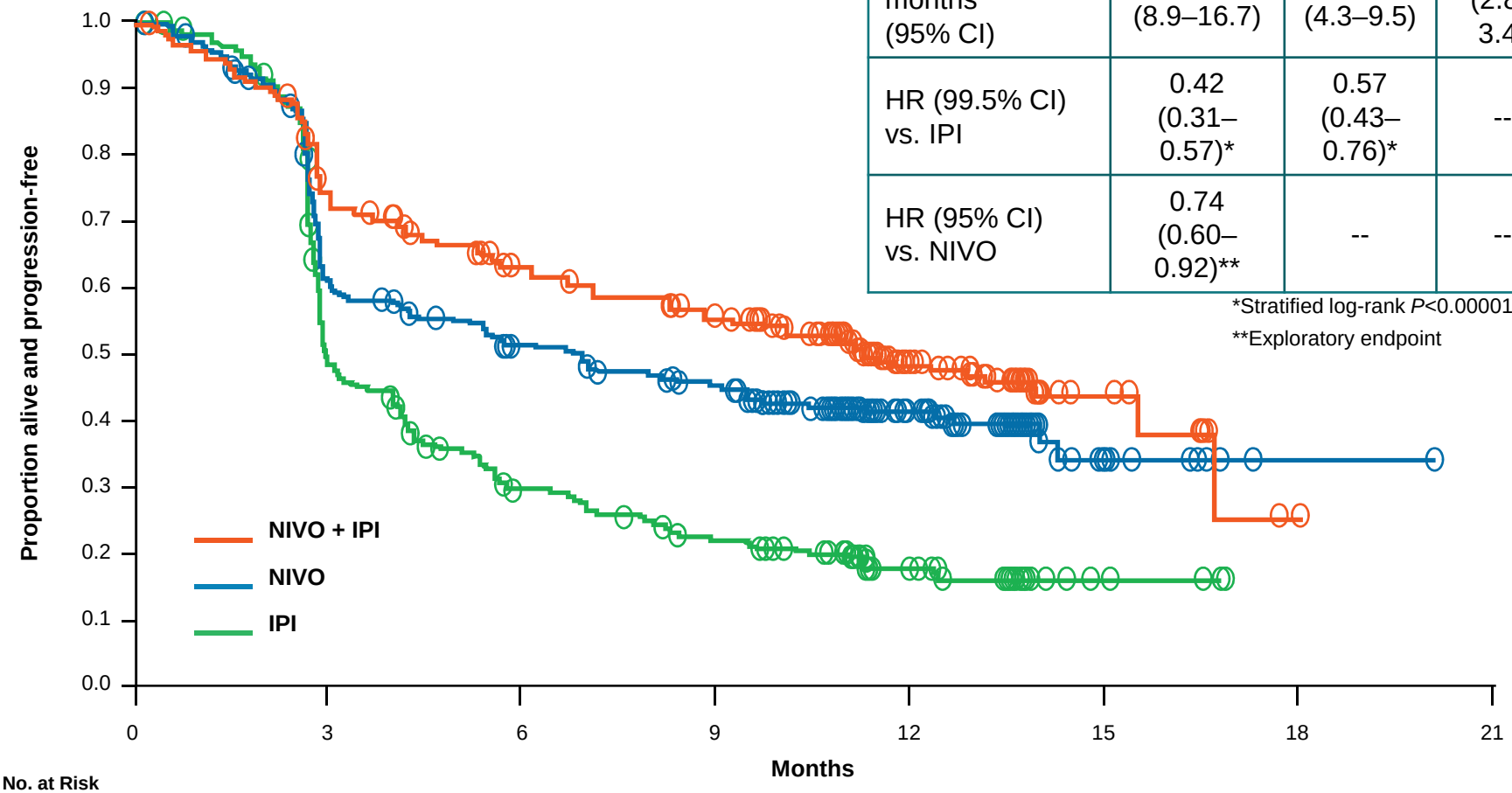
**Patients could have been treated beyond progression under protocol-defined circumstances.

PFS (Intent-to-Treat)

	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

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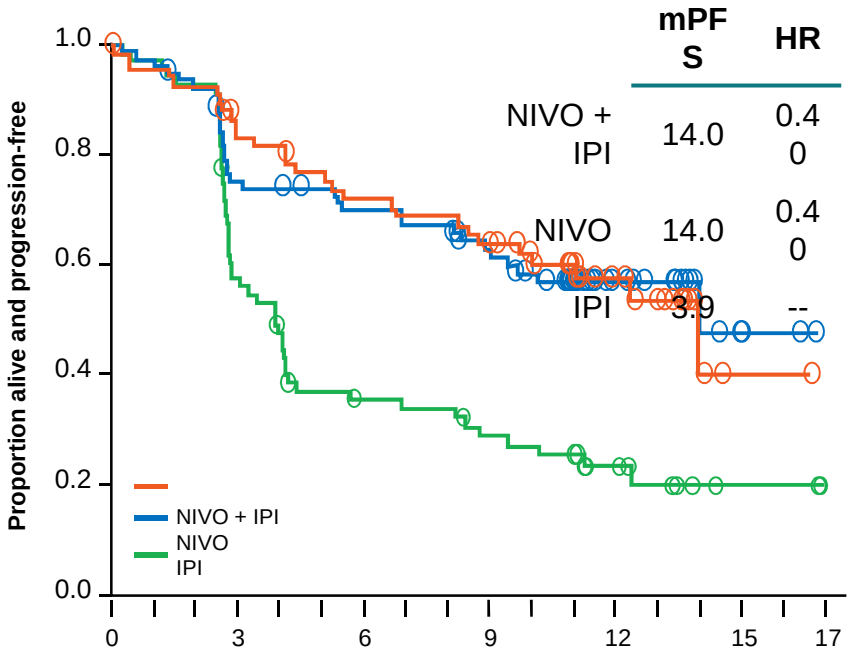
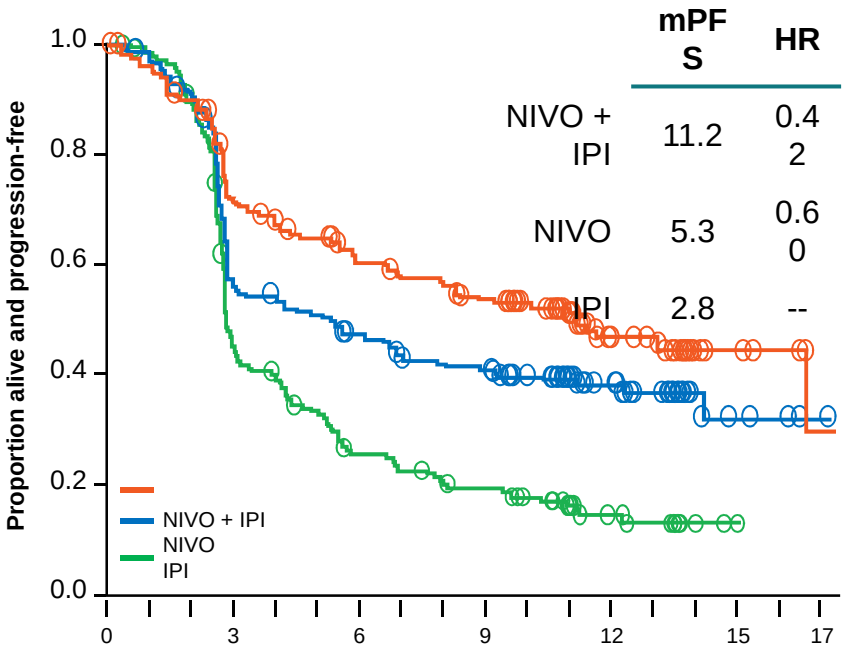
PFS by PD-L1 Expression Level (5%)

PD-L1 ≥5%*



No. at Risk							
NIVO + IPI	68	53	44	39	16	1	0
NIVO	80	57	51	43	16	4	0
IPI	75	40	22	17	9	2	0

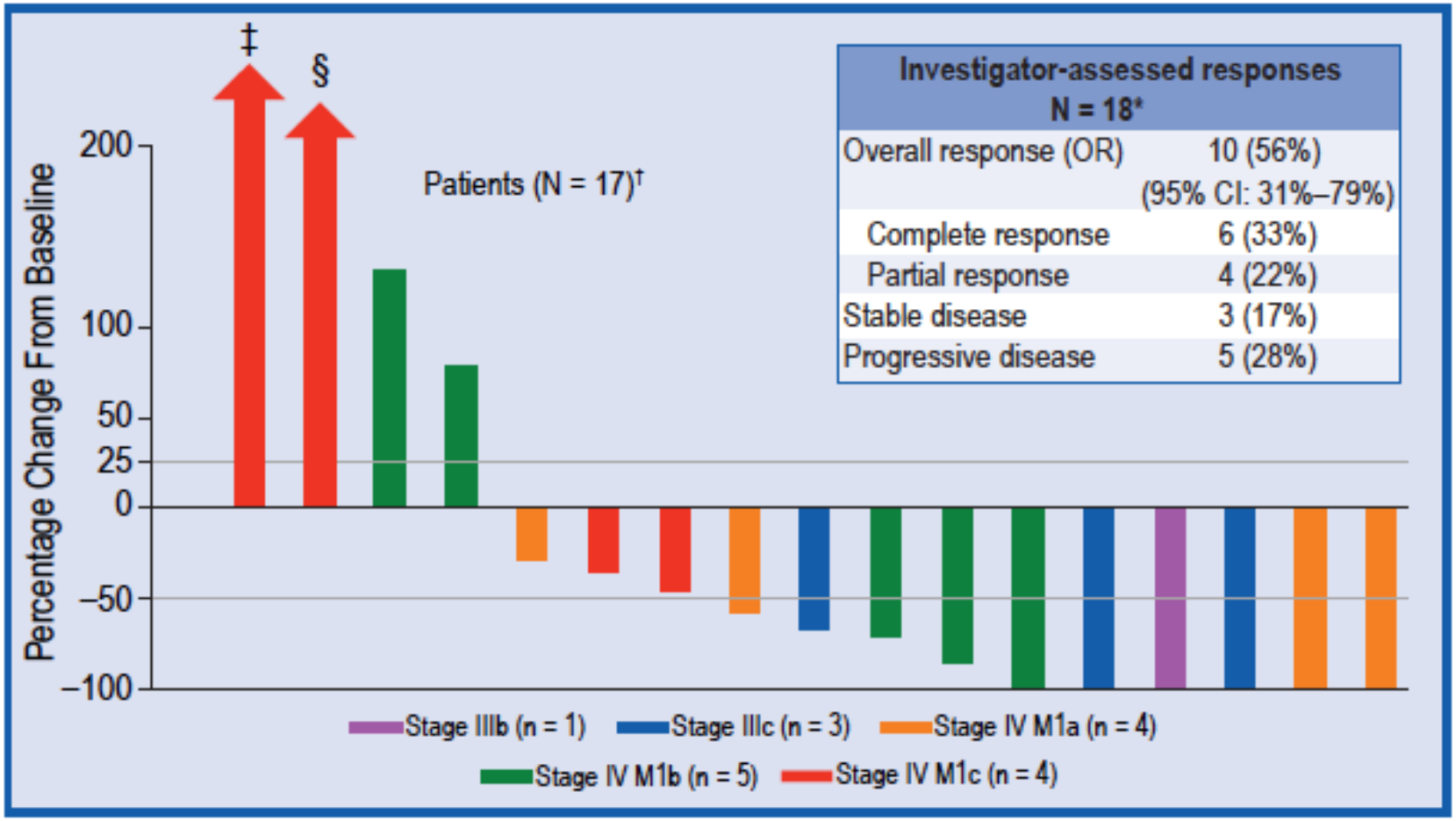
PD-L1 <5%*



No. at Risk							
NIVO + IPI	210	142	112	96	42	9	2
NIVO	208	108	88	74	31	5	2
IPI	202	82	44	31	12	1	–

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

Maximal Change in Tumor Burden

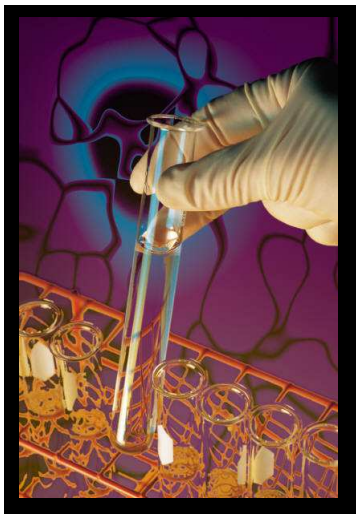


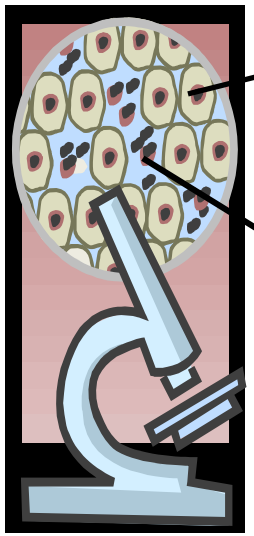
Investigator-assessed responses N = 18*	
Overall response (OR)	10 (56%) (95% CI: 31%–79%)
Complete response	6 (33%)
Partial response	4 (22%)
Stable disease	3 (17%)
Progressive disease	5 (28%)

Adoptive Cell Therapy (ACT) with Antigen Specific T-cells

Surgical Removal of Cancer Nodule

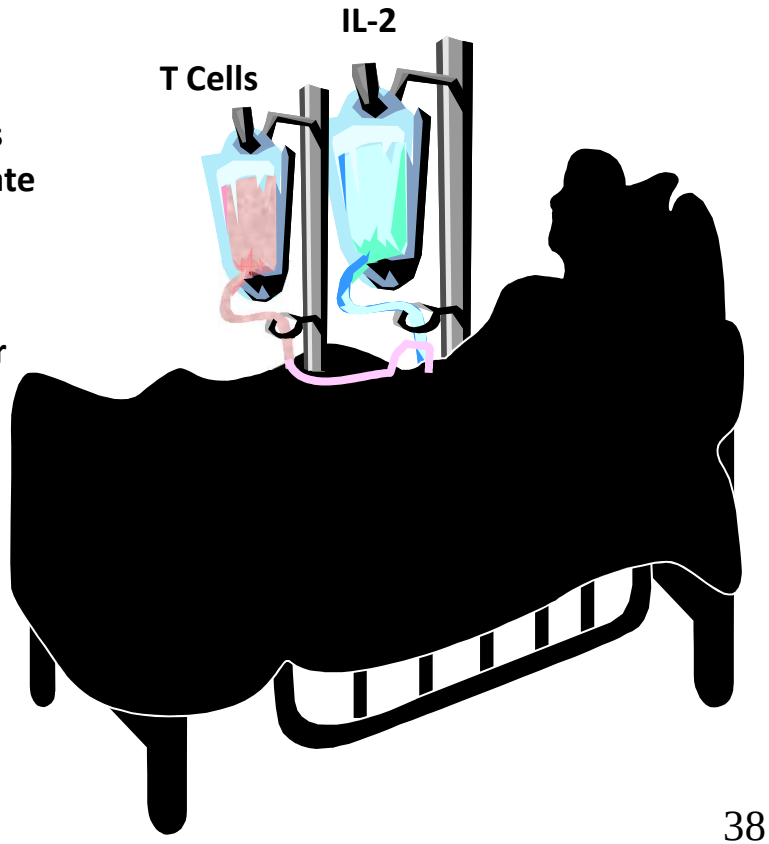
Single Cell Suspension Incubated with IL-2





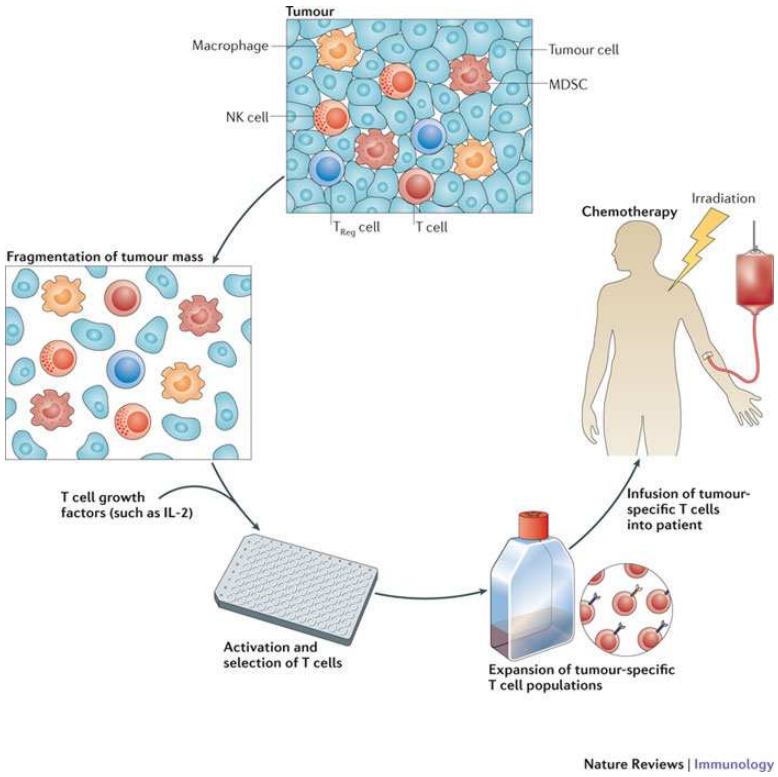
T Cells Proliferate

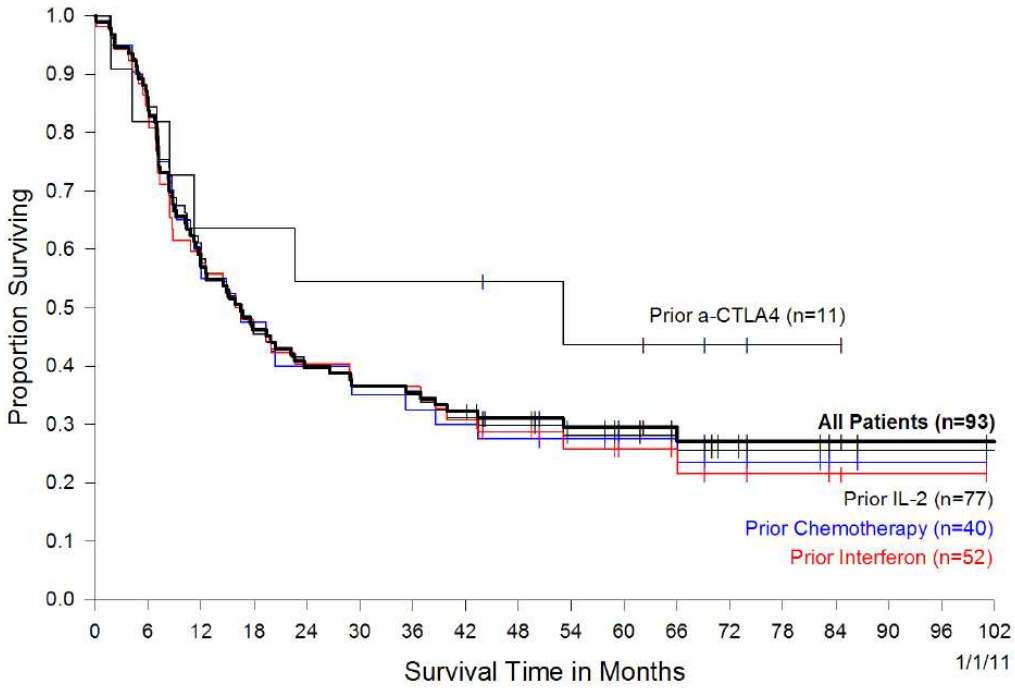
Cancer Cells Die



TIL Therapy

Durable Remission Rates Regardless of Use of Other Therapies





Adoptive immunotherapy for cancer: harnessing the T cell response
Nicholas P. Restifo, Mark E. Dudley & Steven A. Rosenberg
Nature Reviews Immunology **12**, 269-281 (April 2012)

Source: Steven A. Rosenberg, James C. Yang, Richard M. Sherry et al. Clin Cancer Res, 17(13):4550-7, Jul 2011

Atypical Patterns of Response in Patients With Metastatic Melanoma Treated With Pembrolizumab in KEYNOTE-001

Jedd Wolchok,[1] Omid Hamid,[2] Antoni Ribas,[3] Caroline Robert,[4] Richard Kefford,[5,6] Wen-Jen Hwu,[7] Jeffrey Weber,[8] Anthony M. Joshua,[9] Tara C. Gangadhar,[10] Roxana Dronca,[11] Adil Daud,[12] Amita Patnaik,[13] Richard W. Joseph,[14] Hassane Zarour,[15] Xiaoyun (Nicole) Li,[16] Darcy Hille,[16] Dahai Xue,[16] Scot W. Ebbinghaus,[16] S. Peter Kang,[16] Andrea Perrone,[16] F. Stephen Hodi[17]

[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]The Angeles Clinic and Research Institute, Los Angeles, CA; [3]University of California, Los Angeles, CA; [4]Institut Gustave-Roussy, Villejuif, France; [5]Crown Princess Mary Cancer Centre, Westmead Hospital and Melanoma Institute Australia, Sydney, Australia; [6]Macquarie University, Sydney, Australia; [7]MD Anderson Cancer Center, Houston, TX; [8]H. Lee Moffitt Cancer Center, Tampa, FL; [9]Princess Margaret Hospital, Toronto, ON; [10]Abramson Cancer Center at the University of Pennsylvania, Philadelphia, PA; [11]Mayo Clinic, Rochester, MN; [12]University of California, San Francisco, CA; [13]South Texas Accelerated Research Therapeutics, San Antonio, TX; [14]Mayo Clinic, Jacksonville, FL; [15]University of Pittsburgh, Pittsburgh, PA; [16]Merck & Co., Inc., Kenilworth, NJ; [17]Dana-Farber Cancer Institute, Boston, MA

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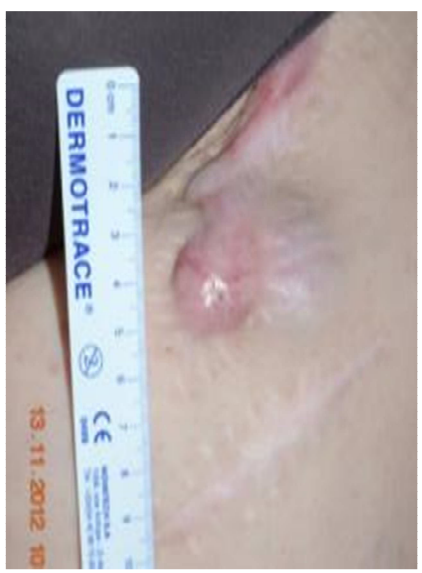
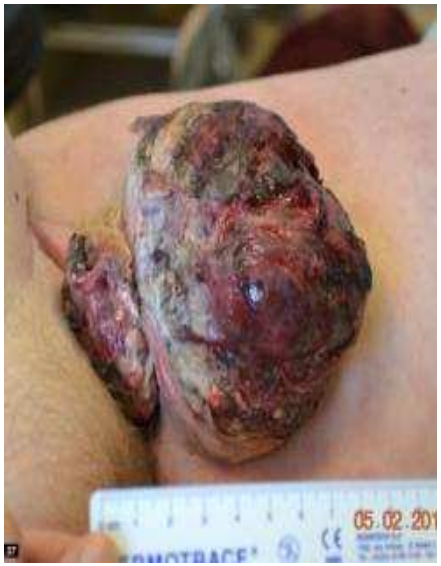
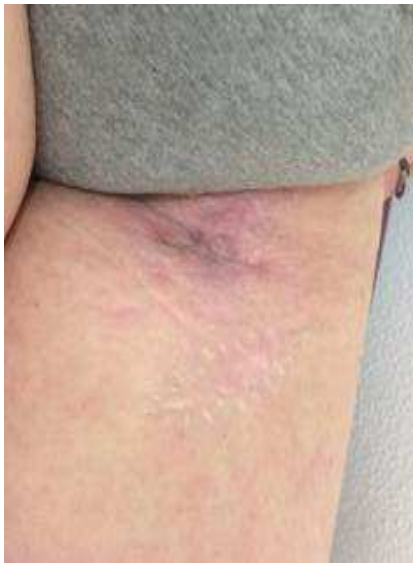
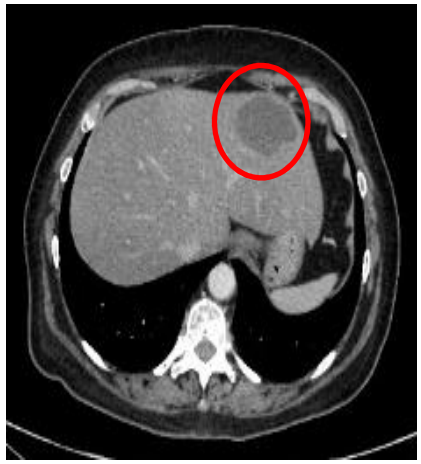
Patient With Melanoma Treated in KEYNOTE-001

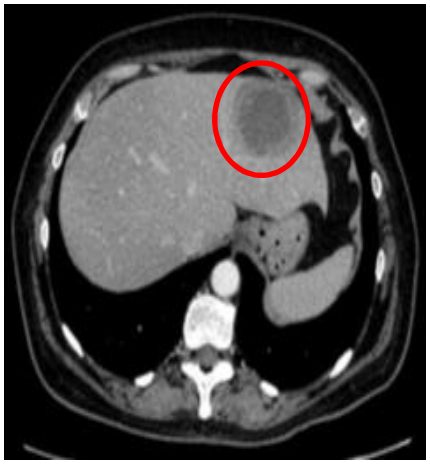


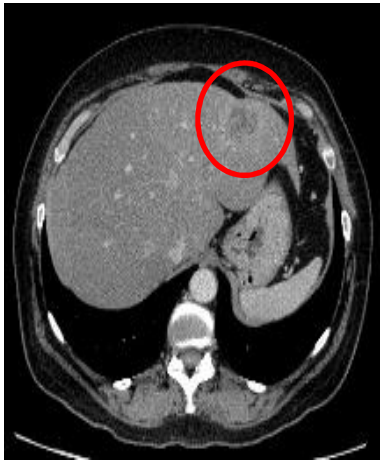


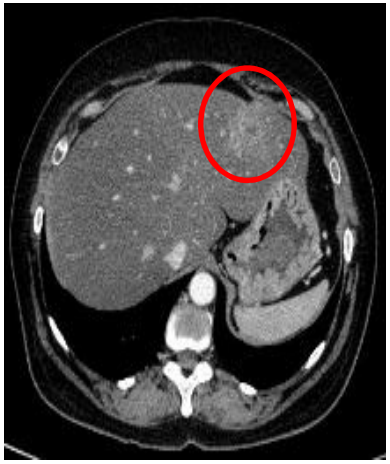


Baseline **Week 12** **Week 24** **Week 52**



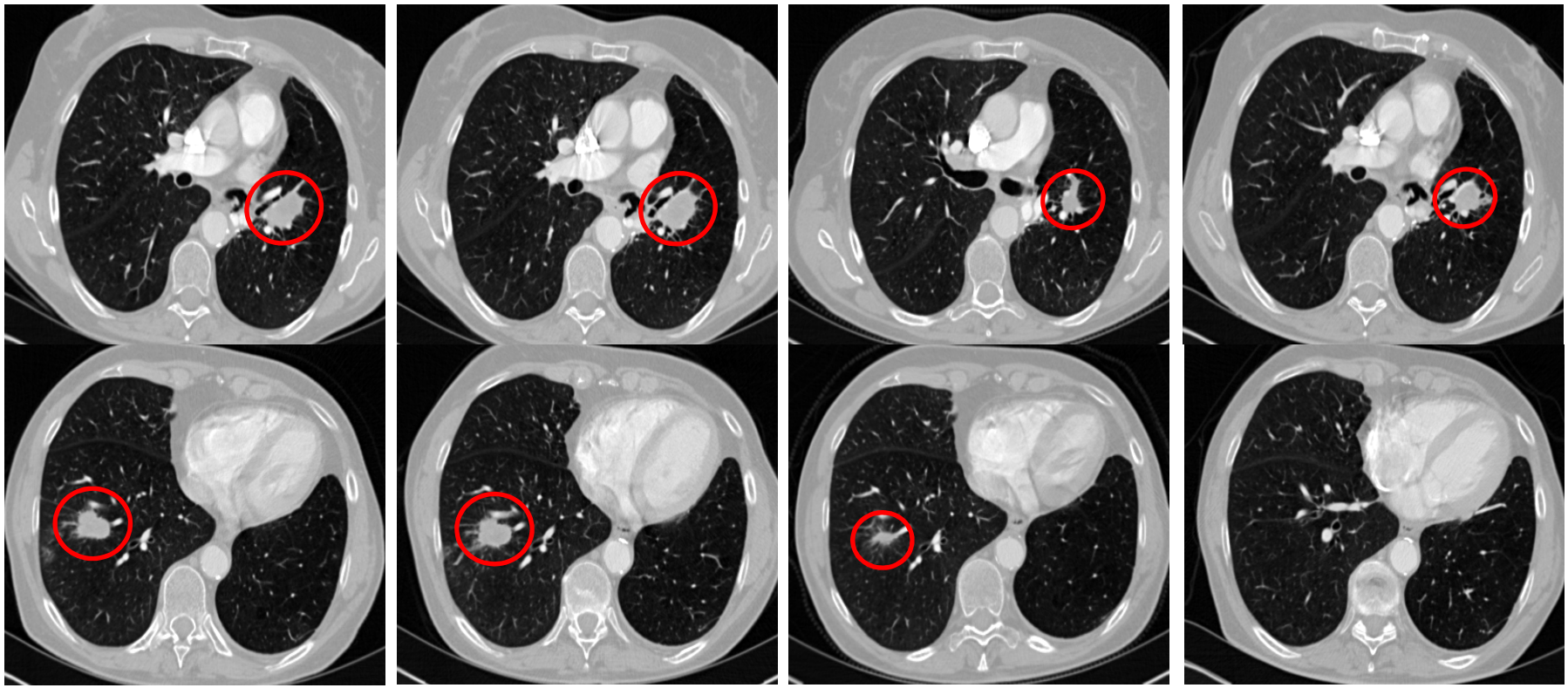






Case courtesy of C. Robert, Gustave Roussy, Villejuif, France.

Patient With NSCLC Treated in KEYNOTE-001



Baseline

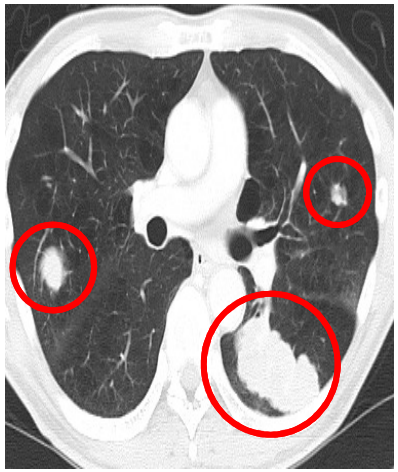
Week 9
- SLD increased 3.1%
  - SD by RECIST v1.1
- SPD increased 38%
  - PD by irRC

Week 18
- SLD decreased 34%
  - PR by RECIST v1.1
- SPD decreased 63%
  - PR by irRC

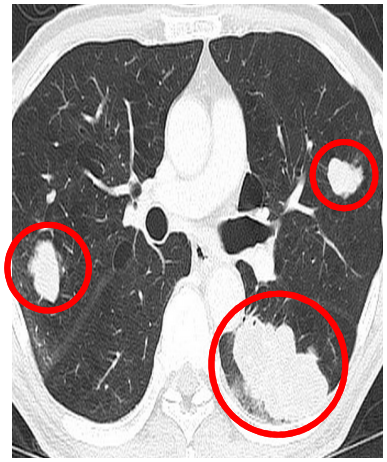
Week 27
- SLD decreased 47%
  - PR by RECIST v1.1
- SPD decreased 64%
  - PR by irRC

SLD, sum of the longest diameters.
SPD, sum of the longest diameter x perpendicular diameters.

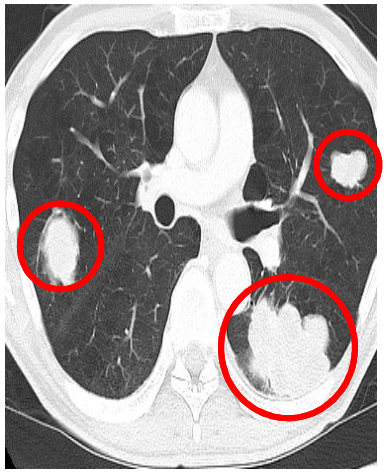
Patient With Gastric Cancer Treated In KEYNOTE-012



Baseline

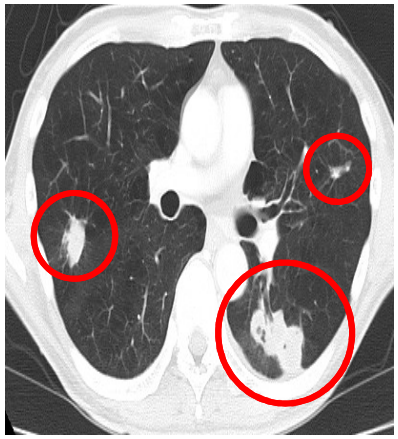


Week 8 SD

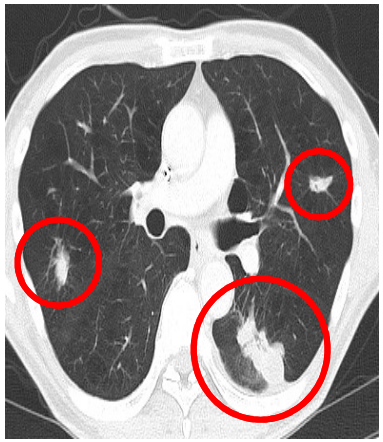


Week 16 PD due to non target progression

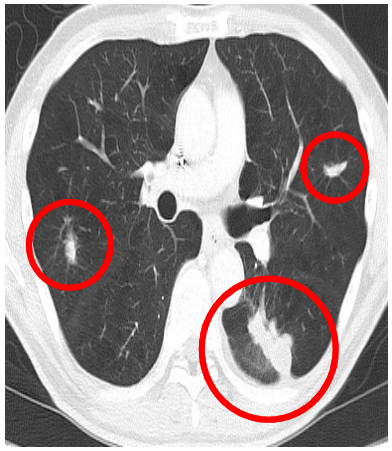
- PD by central review per RECIST 1.1 at week 16



Week 24
Tumor Burden ↓ 29.3%



Week 28
Tumor Burden↓ 37.3%

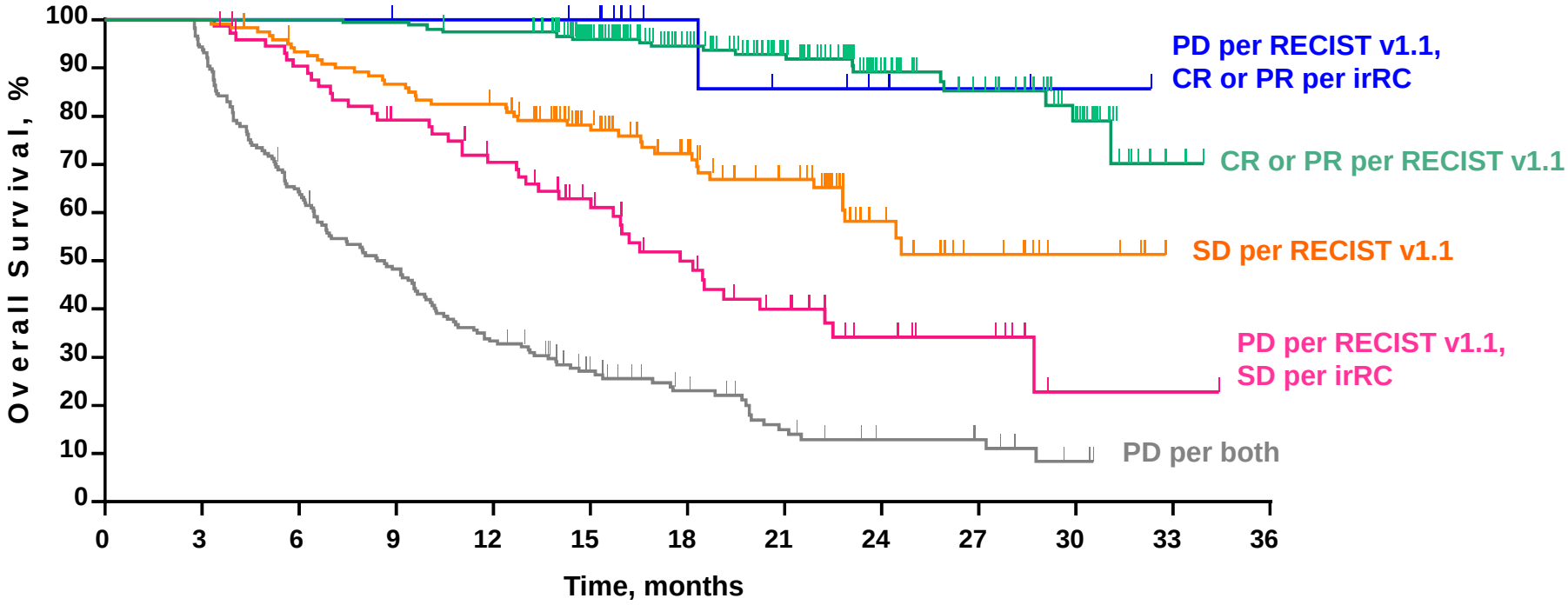


Week 32
Tumor Burden↓ 37.3%

- PR has been achieved at week 28 and confirmed at week 32 per *tumor burden and improved non-target disease* but cannot be captured per RECIST 1.1

Case presented by K Muro at 2015 Gastrointestinal Cancer Symposium (abstract 03).

Association of Overall Survival With Tumor Response (n = 594)



205	205	205	204	199	159	118	93	53	40	21	2	0
122	122	112	104	98	73	55	43	18	10	4	0	0
15	15	15	14	14	13	7	5	3	2	1	0	0
75	75	65	55	47	36	26	18	10	7	1	1	0
177	167	113	84	58	37	25	15	9	7	2	0	0

Analysis cutoff: October 2014

Phase 1 study combining anti-PD-L1 (MEDI4736) with BRAF (dabrafenib) and/or MEK (trametinib) inhibitors in advanced melanoma

Antoni Ribas,[1] Marcus Butler,[2] Jose Lutzky,[3] Donald Lawrence,[4] Caroline Robert,[5] Wilson Miller Jr,[6] Gerald Linette,[7] Paolo A. Ascierto,[8] Timothy M. Kuzel,[9] Alain Algazi,[10] Michael Postow,[11] Paul Nathan,[12] Brendan Curti,[13] Paul B. Robbins,[14] Xiaobai Li,[14] John A. Blake-Haskins,[14] Michael Gordon[15]

[1]University of California, Los Angeles, CA, USA; [2]Princess Margaret Cancer Centre, Toronto, ON, Canada; [3]Mount Sinai Medical Center, Miami Beach, FL, USA; [4]Massachusetts General Hospital, Boston, MA, USA; [5]Gustave Roussy Cancer Campus and Paris-Sud University, Villejuif, France; [6]Segal Cancer Center, Jewish General Hospital, McGill University, Montreal, QC, Canada; [7]Washington University, St. Louis, MO, USA; [8]Istituto Nazionale Tumori Fondazione Pascale, Naples, Italy; [9]Feinberg School of Medicine, Northwestern University, Chicago, IL, USA; [10]USCF Medical Center, San Francisco, CA, USA; [11]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [12]Mount Vernon Hospital, Middlesex, UK; [13]Earle A. Chiles Research Institute, Providence Cancer Center, Portland, OR, USA; [14]MedImmune, Gaithersburg, MD, USA; [15]Pinnacle Oncology Hematology, Scottsdale, AZ, USA.

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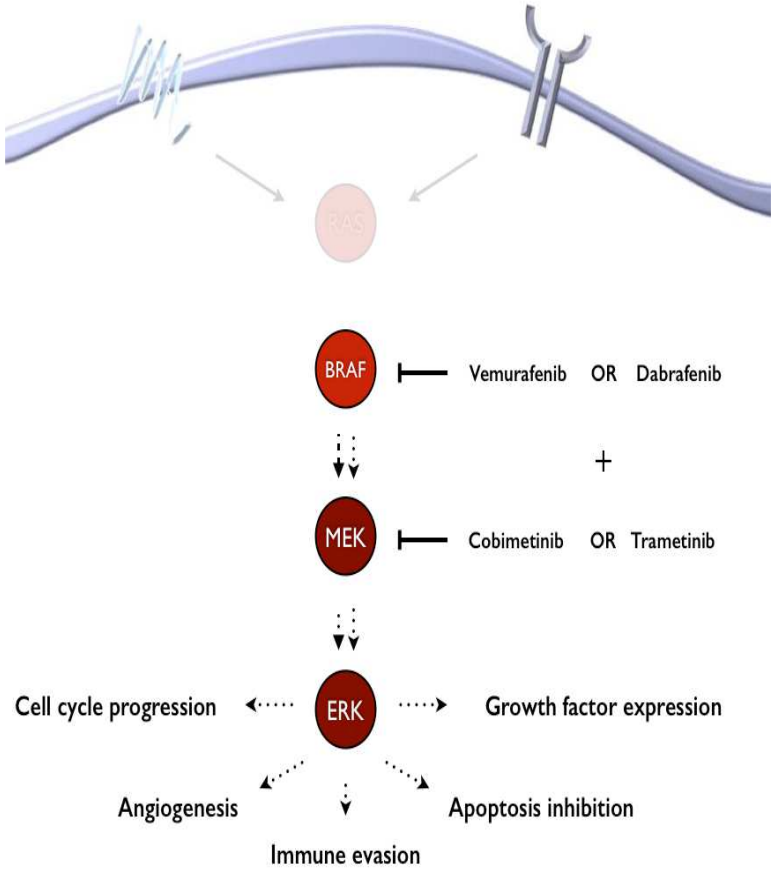
Oncogenic BRAF Mutations in Melanoma

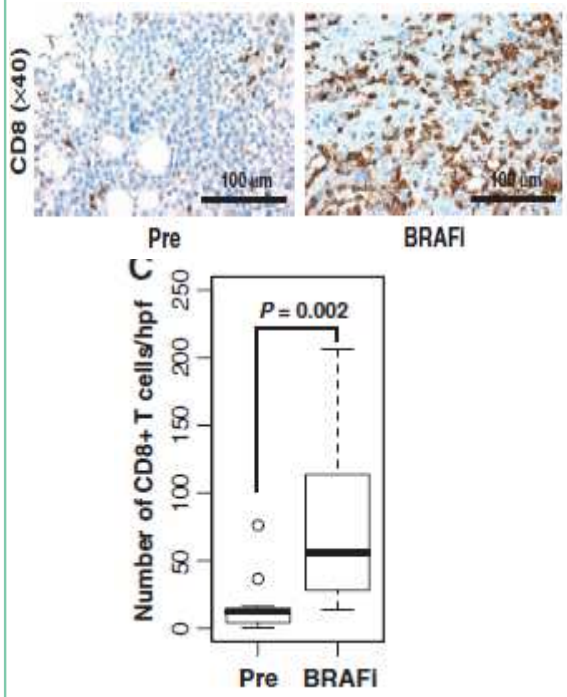
- BRAF V600 mutations present in 40–50% of patients
- Single-agent small-molecule inhibition of BRAF and MEK improves survival compared with chemotherapy[1–3]
- Combined BRAF and MEK inhibition improves survival compared with single-agent BRAF inhibitors[4–6]



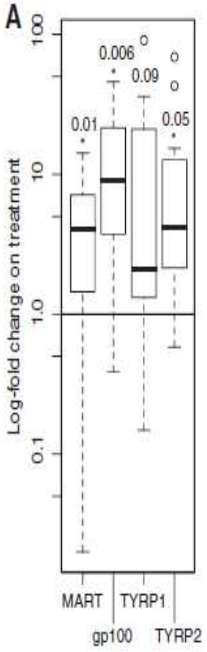
1. Chapman PB *et al. N Engl J Med* 2011;364:2507–2516; 2. Hauschild A *et al. Lancet* 2012;380:358–365; 3. Flaherty KT *et al. N Engl J Med* 2012;367:107–114;
4. Long GV *et al. N Engl J Med* 2014;371:1877–1888; 5. Larkin J *et al. N Engl J Med* 2014;371:1867–1876; 6. Robert C *et al. N Engl J Med* 2015;372:30–39.

BRAF/MEK inhibition modulates the immune microenvironment

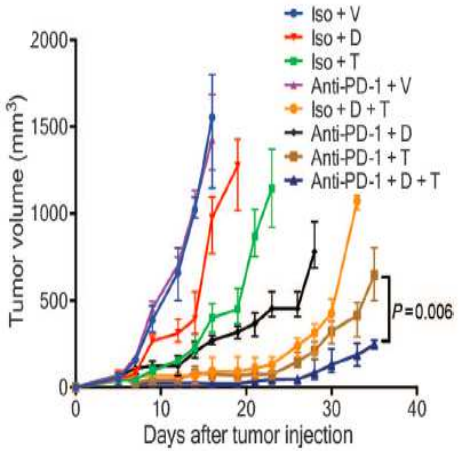
↑ CD8+ TILs[1,2]

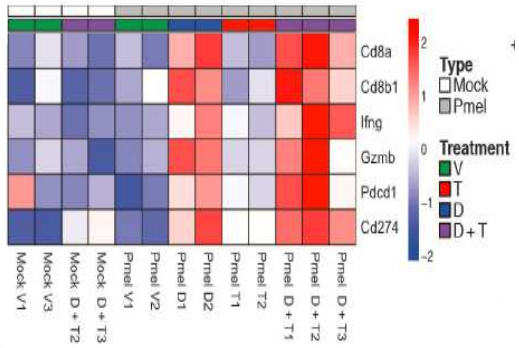


↑ Melanoma antigen expression[1]

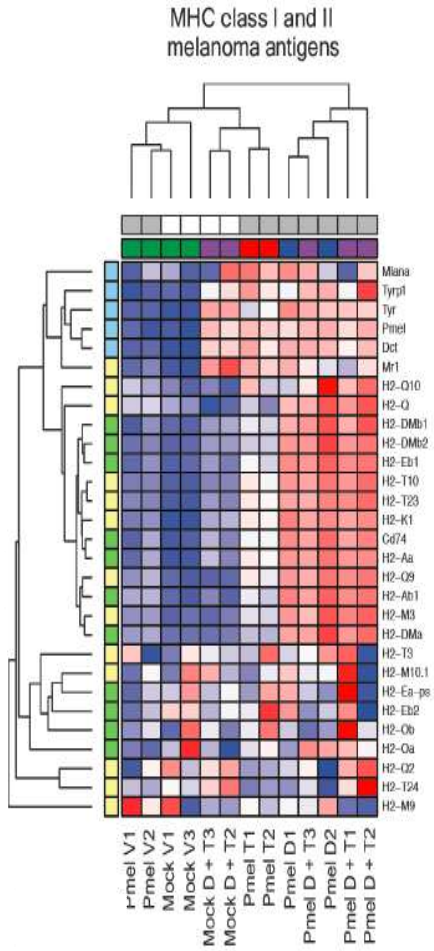


Antitumor activity of combined BRAFi+MEKi plus anti-PD-1[3]





↑ MHC and melanoma antigen expression[3]



1. Frederick DT, et al. Clin Cancer Res. 2013. 19 (5): 1225-31
2. Wilmott JS, et al. Clin Cancer Res. 2011. 18 (5): 1386-94

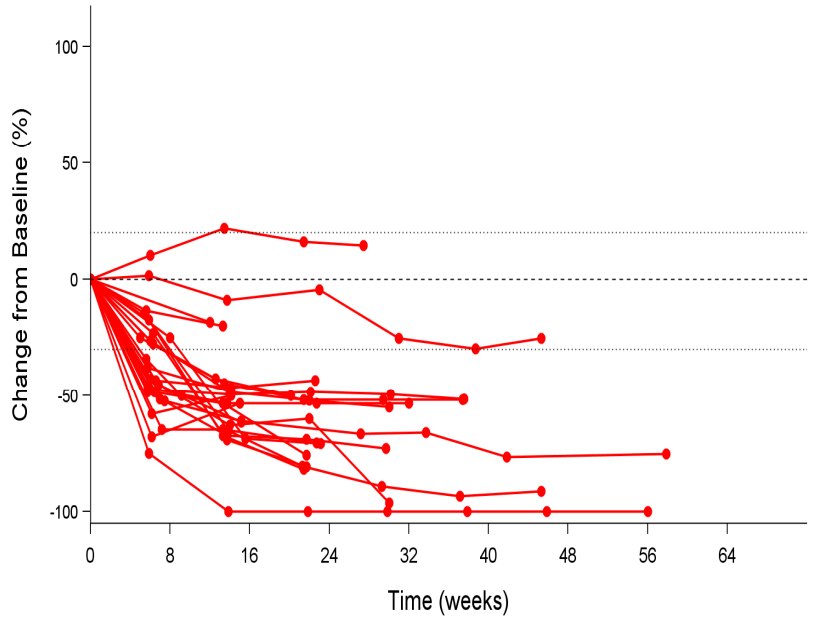
3. Hu-Lieskovan et al. Sci Transl Med 2015. 7 (279): 279ra41

MCH, melanin-concentrating hormone; PD-1, programmed cell death-1; TIL, tumor infiltrating lymphocyte

Tumor size change and time to response: Cohort A

Cohort A (D+T+M)

Tumor size change from baseline



Cohort A (D+T+M)

Time to response and duration of response

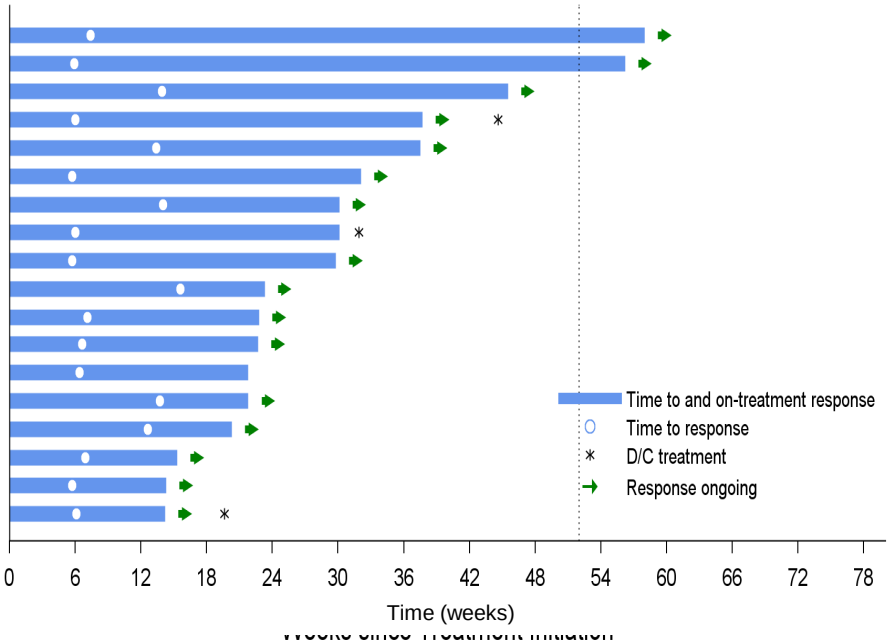
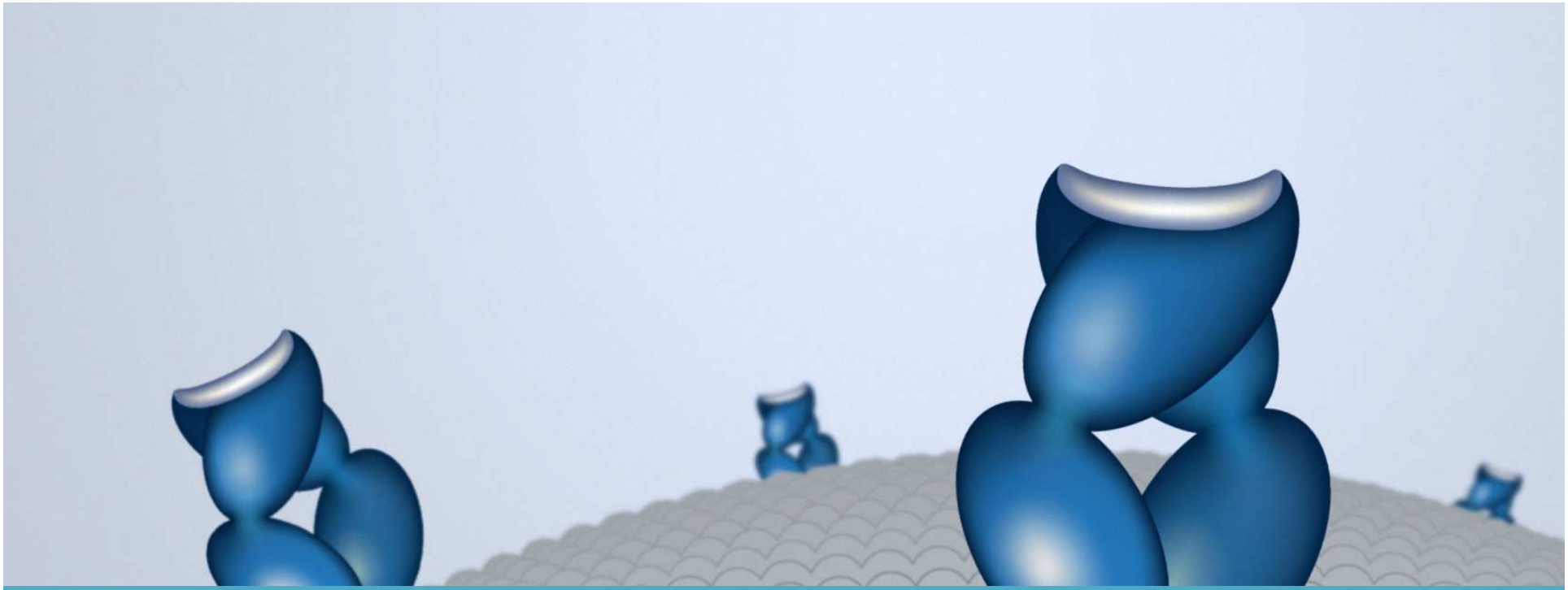


Figure includes subjects with confirmed response in response evaluable population;
D/C treatment=Discontinuation of the regimen

As-treated population. Data cut-off: 7 May 2015

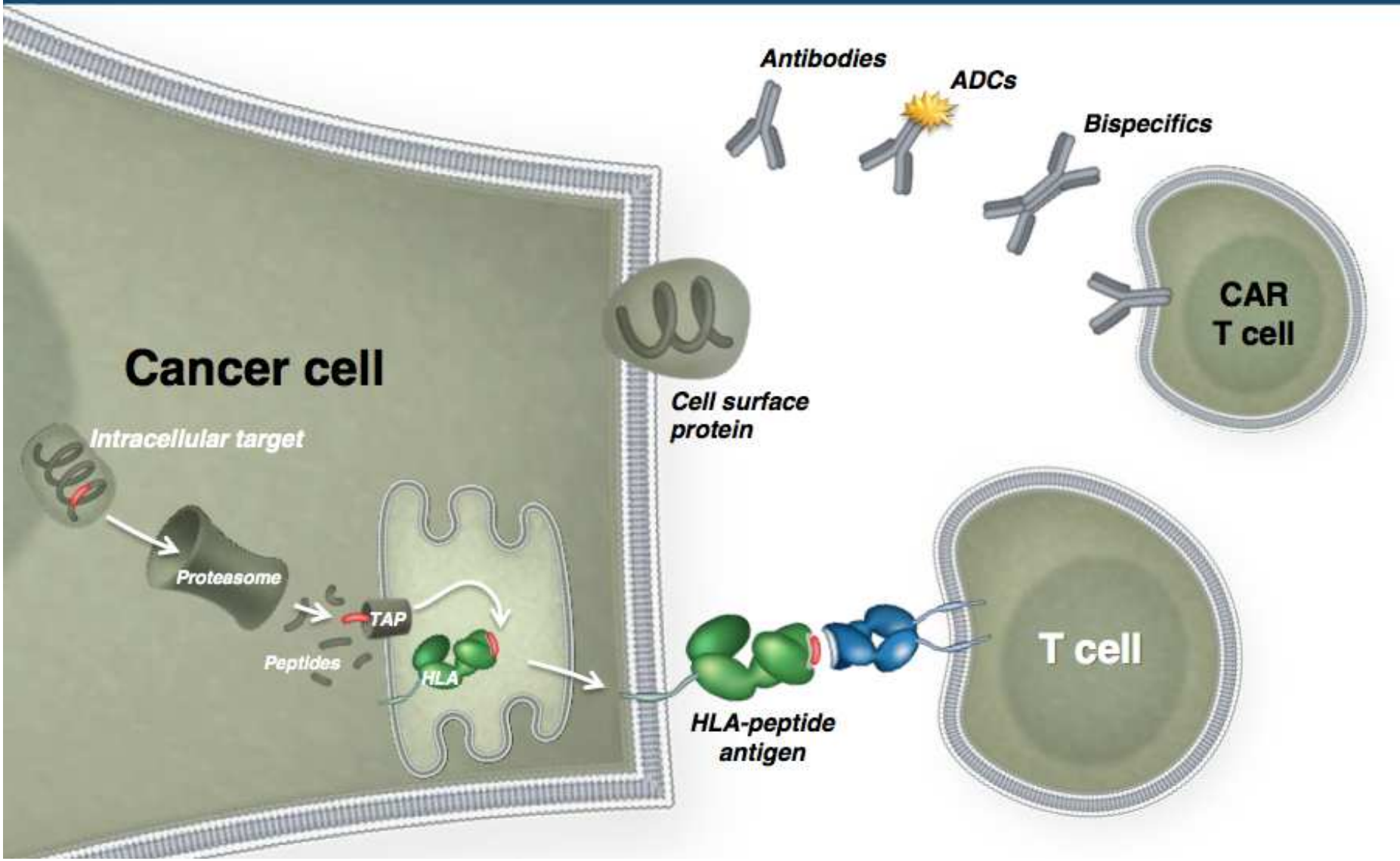


IMCgp100 – A novel immunotherapy for melanoma

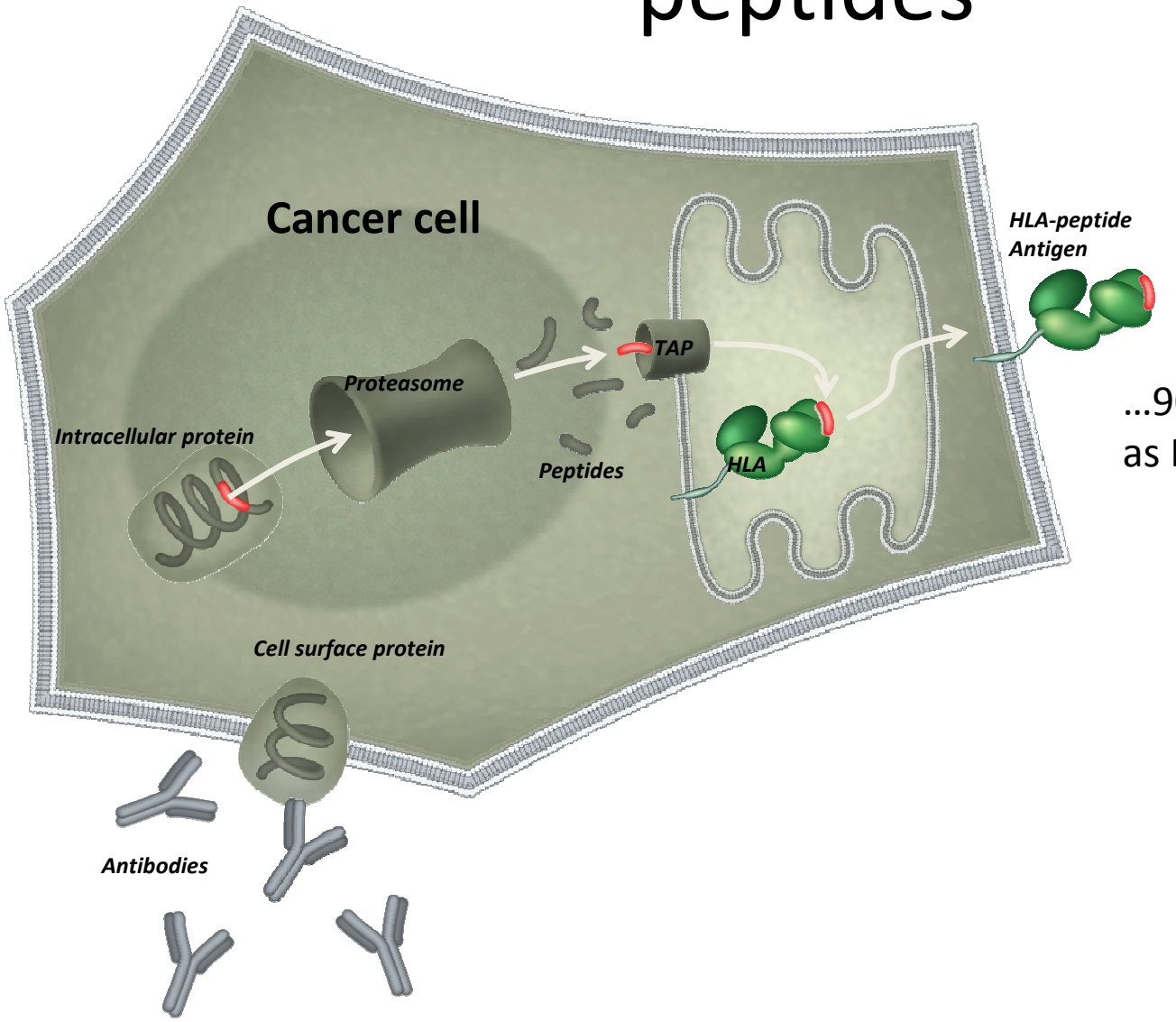
CONFIDENTIAL

IMMUNOCORE
targeting T cell receptors

Antibodies target cell surface proteins whilst TCRs access both cell surface and intracellular proteins

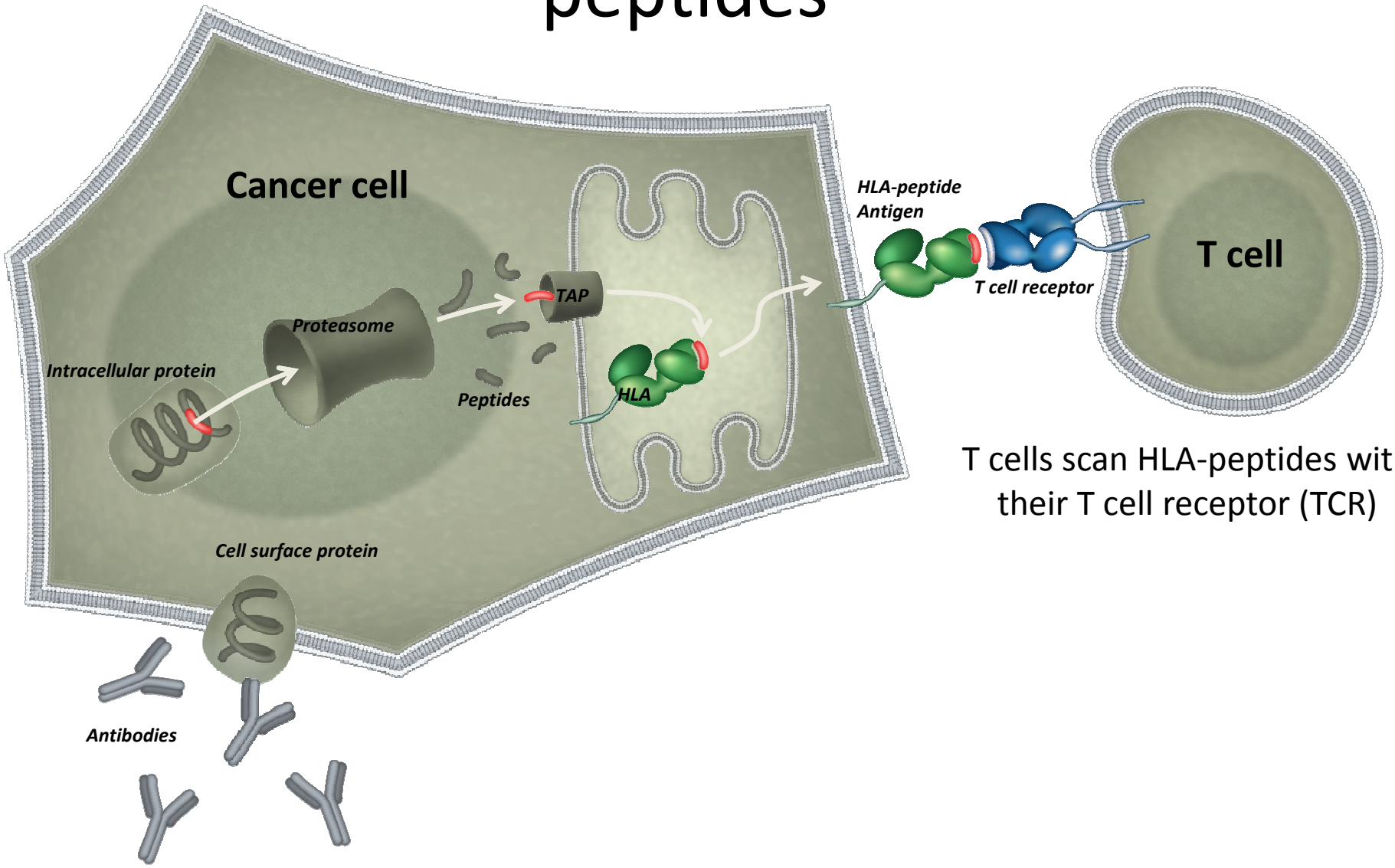


T cell receptors target HLA presented peptides



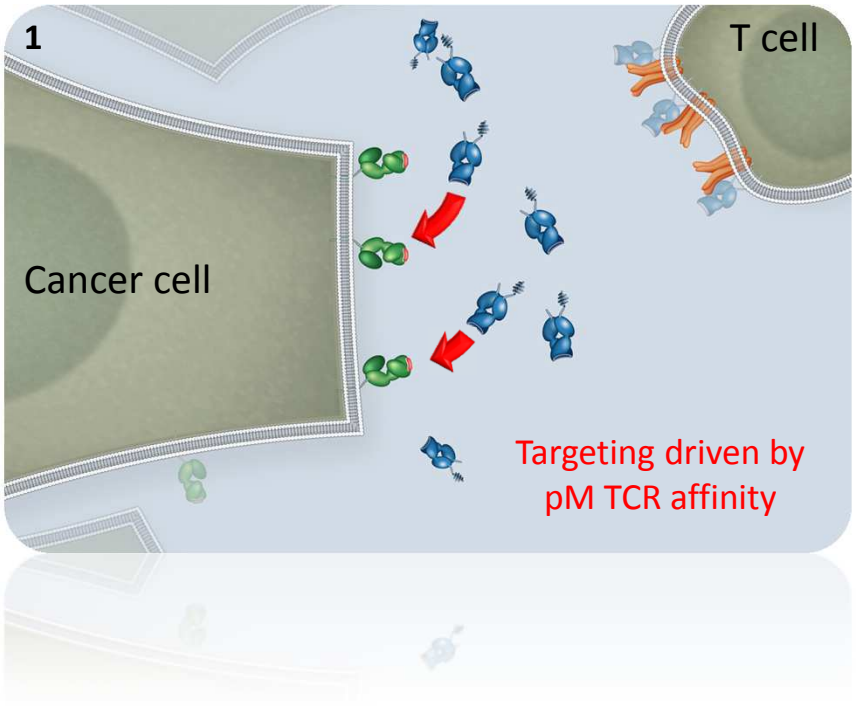
…90% of targets are available as HLA-peptides

T cell receptors target HLA presented peptides

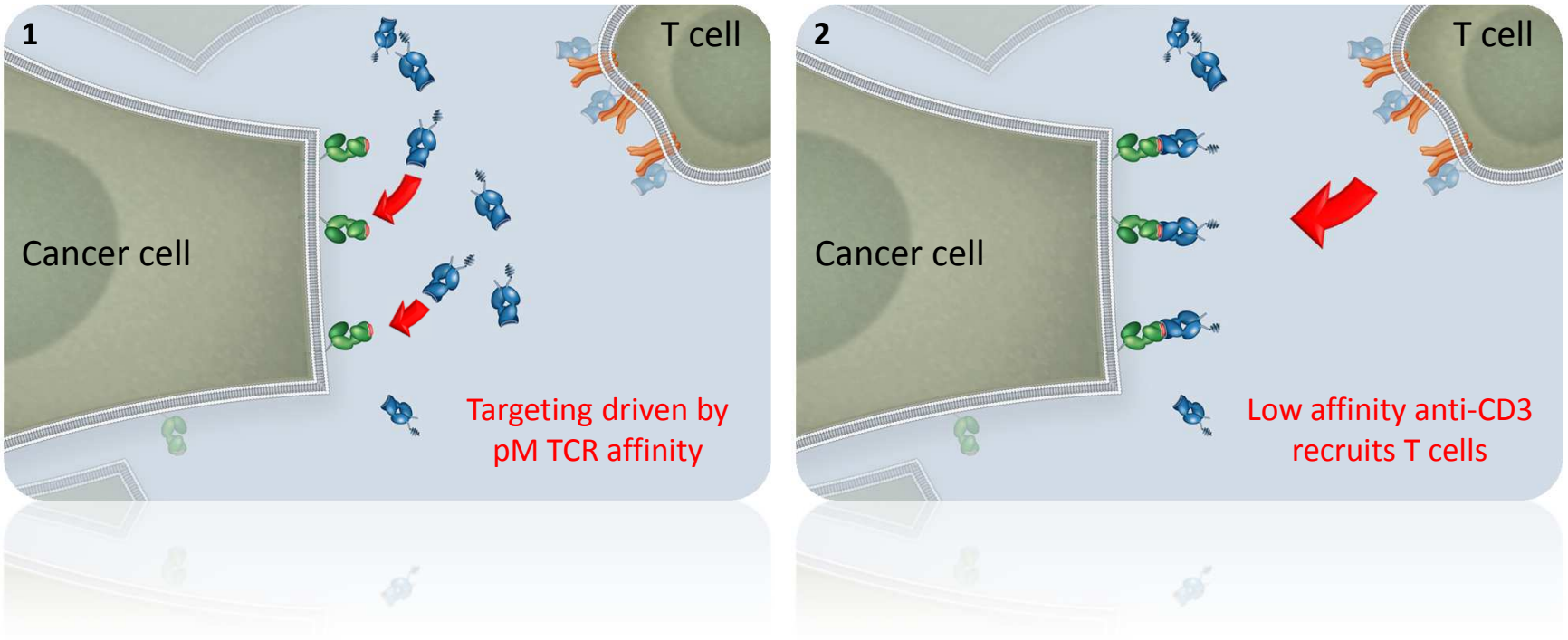


T cells scan HLA-peptides with their T cell receptor (TCR)

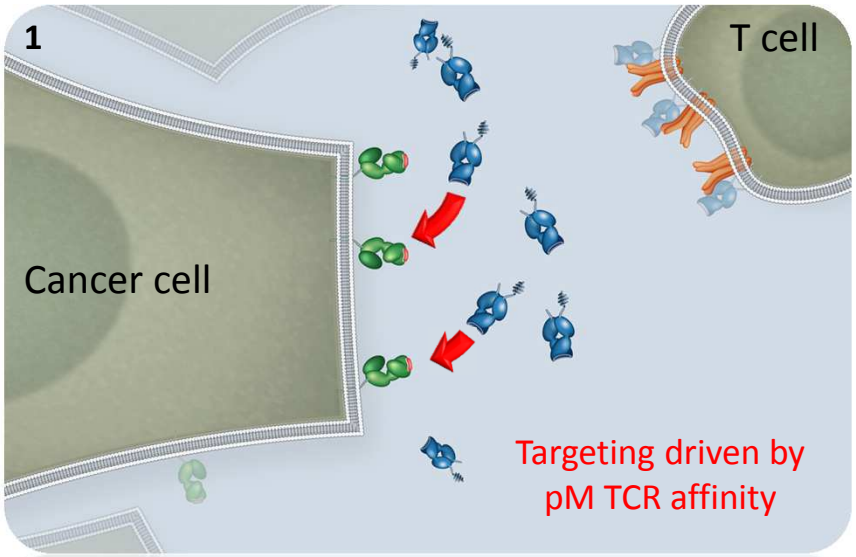
ImmTAC mechanism of action – T cell redirection

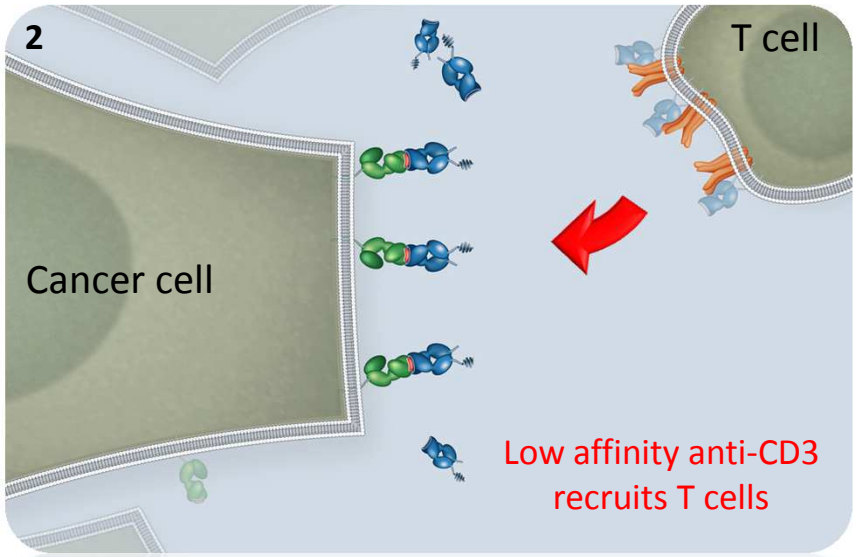


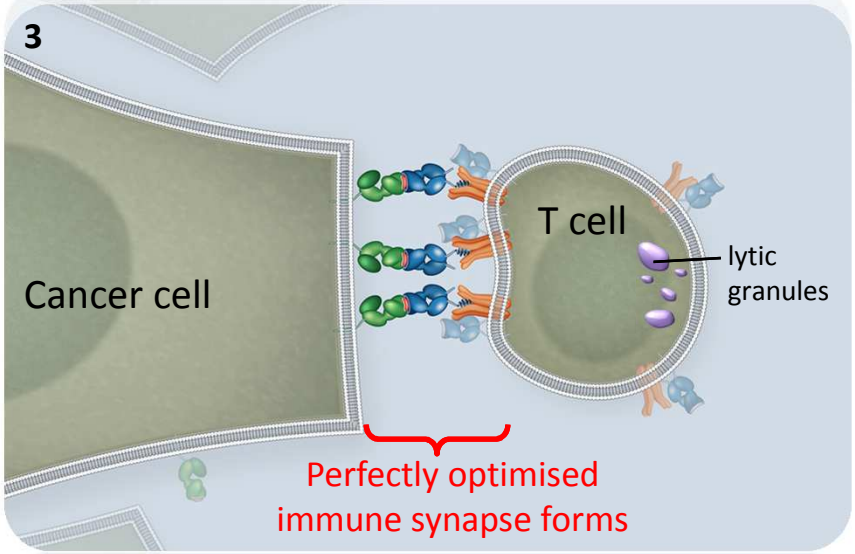
ImmTAC mechanism of action – T cell redirection



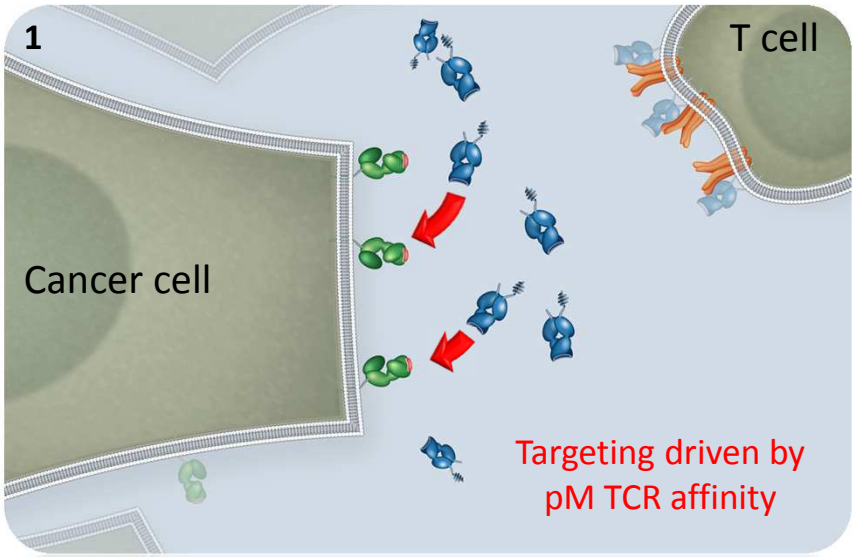
ImmTAC mechanism of action – T cell redirection

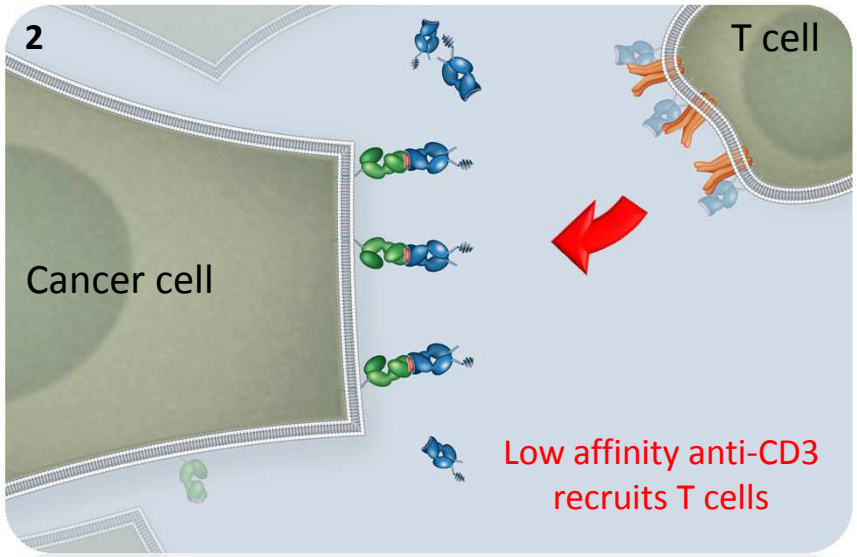


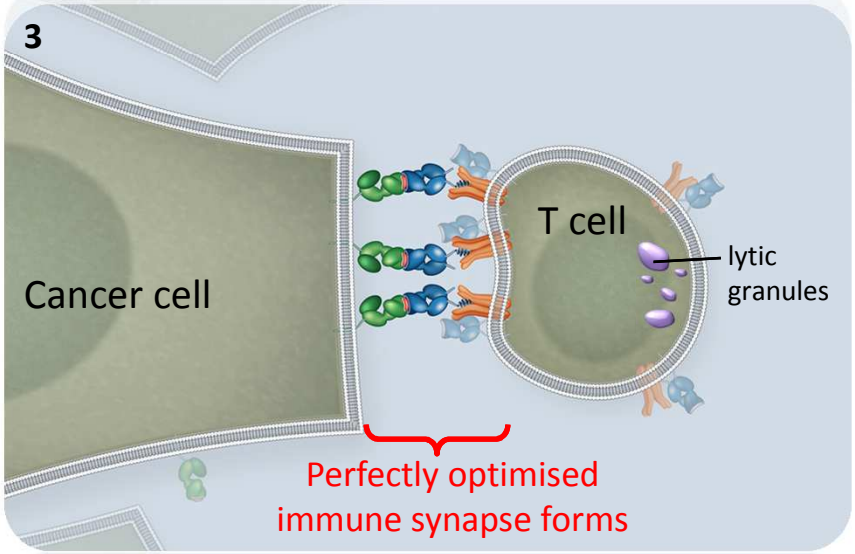


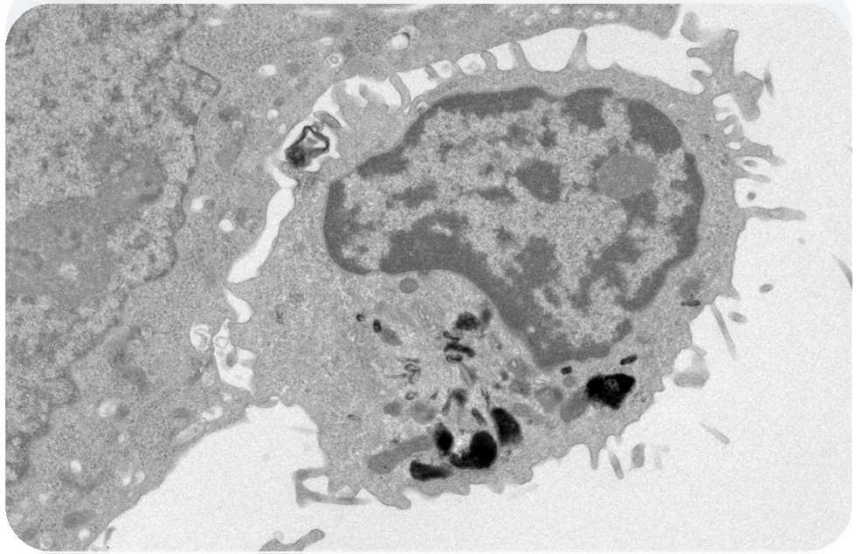


ImmTAC mechanism of action – T cell redirection

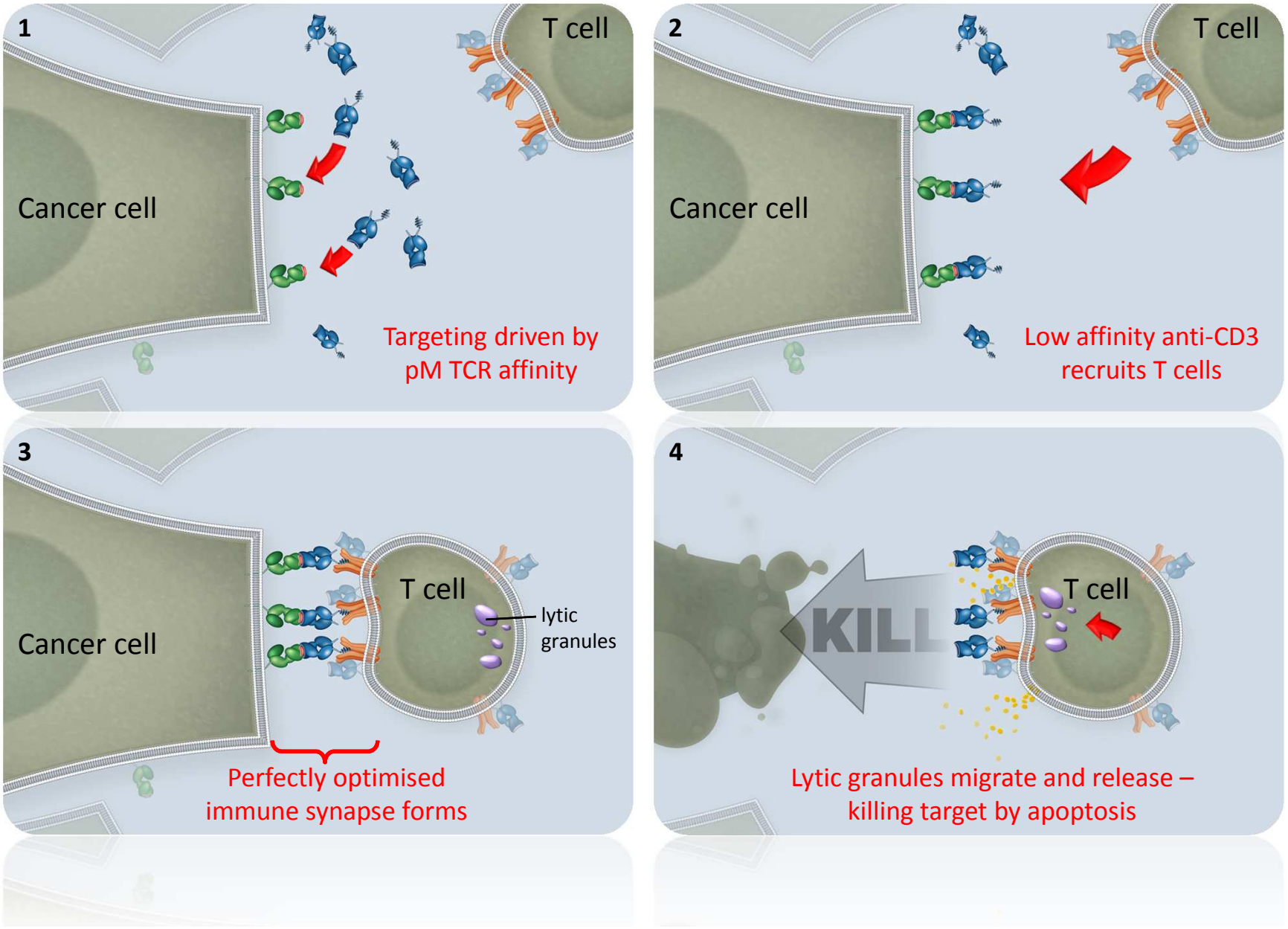




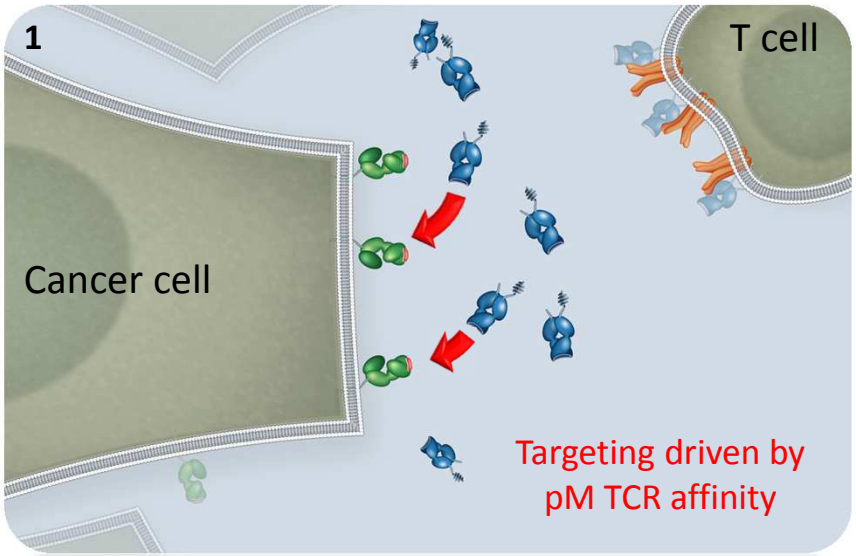


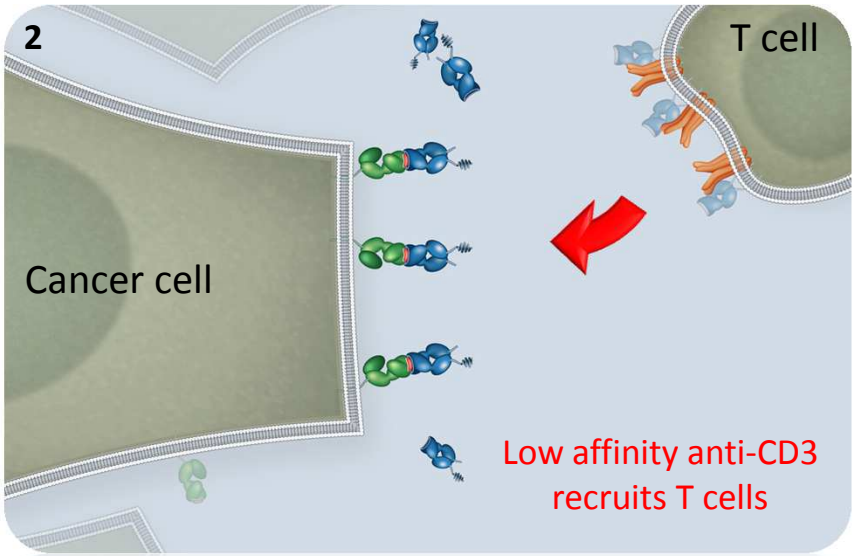


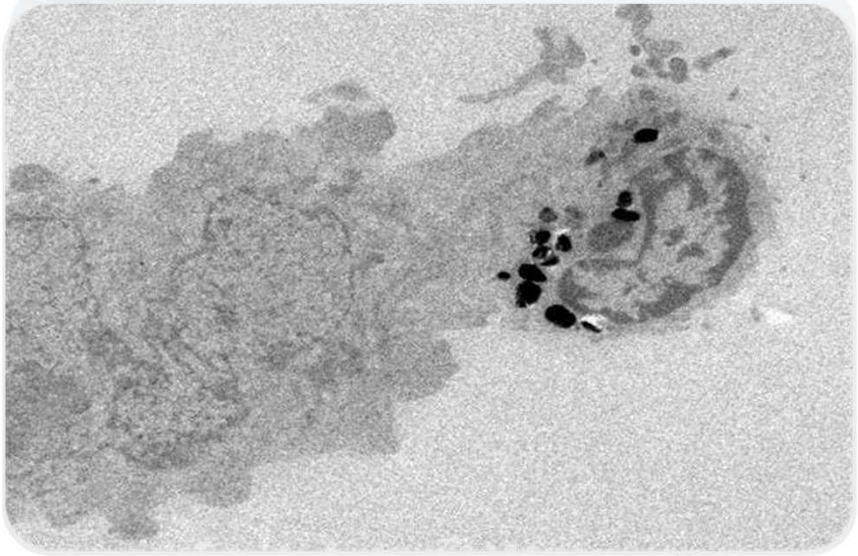
ImmTAC mechanism of action – T cell redirection

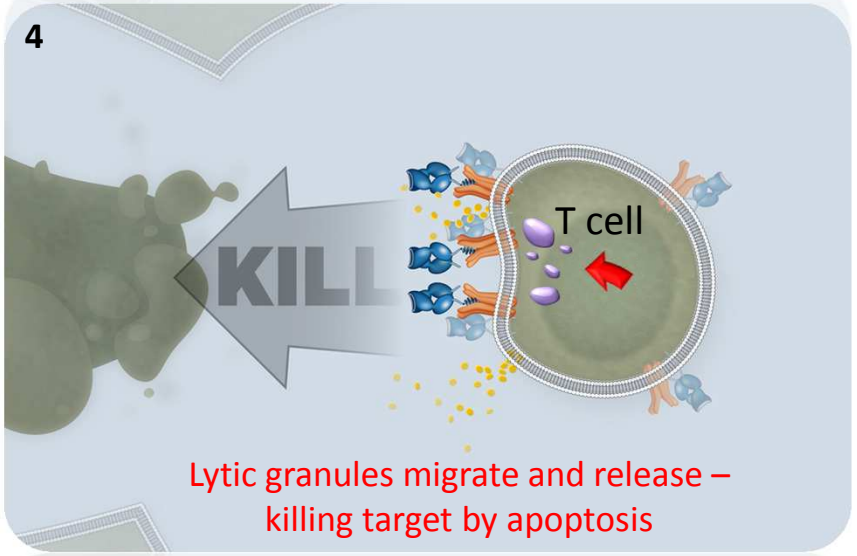


ImmTAC mechanism of action – T cell redirection

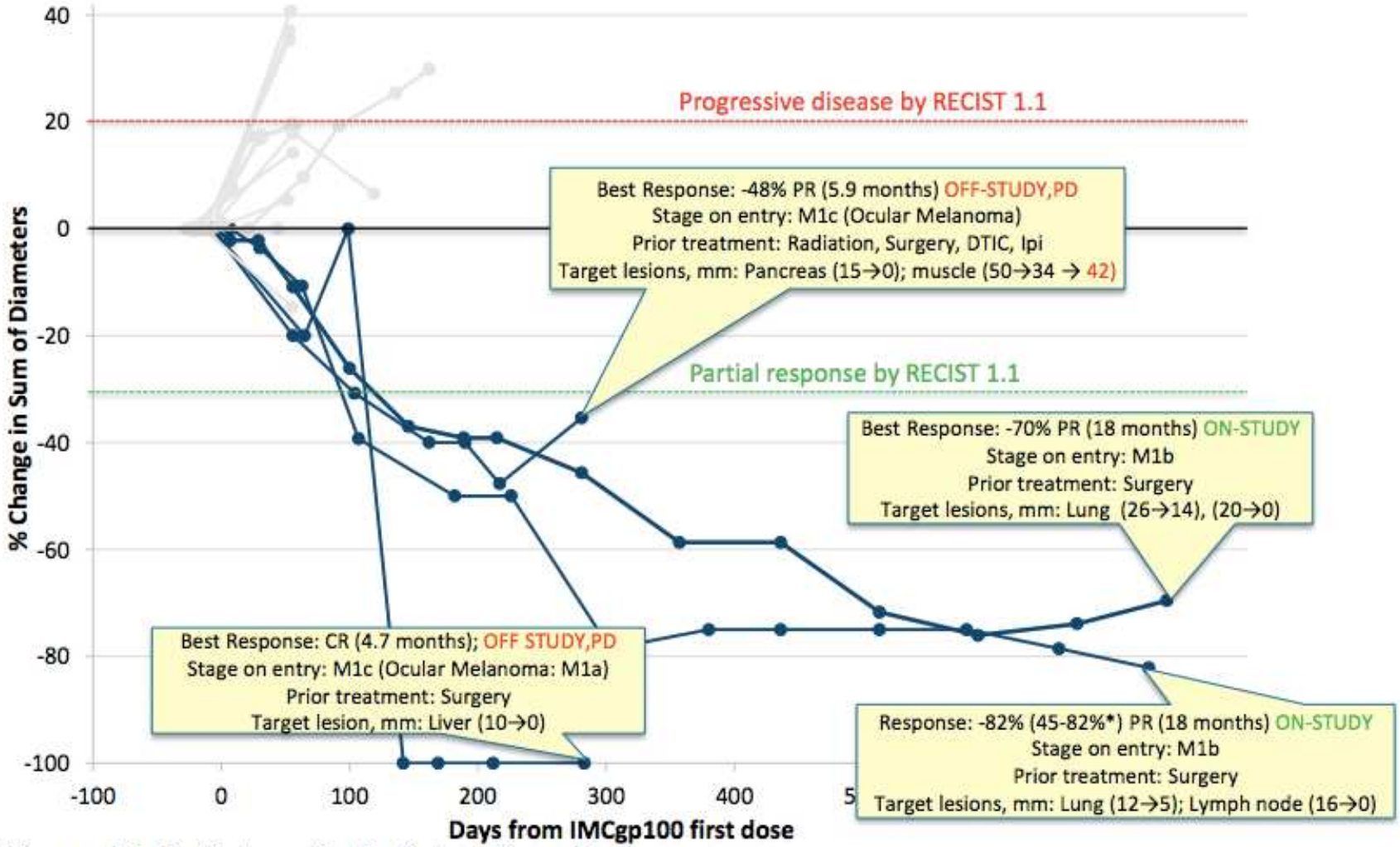








Spider plot of patients treated weekly, repeatedly at MTD (n=17)
Objective responses highlighted



gp100 IHC biopsy analysis: 3 patients negative; 8 patients positive and 6 unknown
Patients included where CT data available as of March 2015
Target lesions: (baseline → current SLD)

* PR could be - 45-75% as one of the target lesions is a lymph node; <10mm assessment is complex and requires further CT scan interpretation

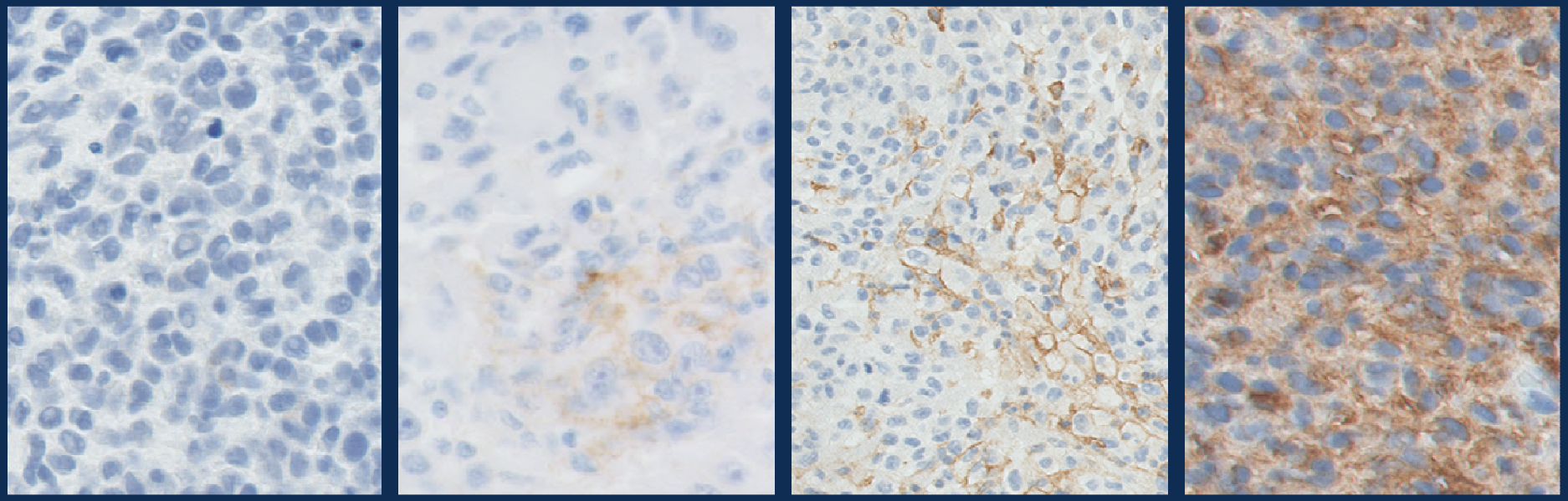
- IMCgp100 is the first in a new class of protein therapeutics capable of inducing redirected T cell responses against tumour antigens
- Administration at biologically effective doses is tolerated well and a dose and regimen identified for further study
- Durable partial responses have been observed in two melanoma patient groups: (1) checkpoint naïve as well as (2) patients refractory to ipilimumab and pembrolizumab
- Partial and complete responses have been observed in patients with ocular melanoma
- Further study of IMCgp100 will include combination studies with checkpoint inhibitors MEDI 4736 (anti-PDL1) and/or Tremelimumab (anti-CTLA-4) with evidence gained from pharmacodynamic assessments in this study

What predicts Response ?

I want your blood …..

I want your blood …..
and your tissue !!!

Examples of Baseline PD-L1 Melanoma Sample Immunohistochemical Staining[1]



PD-L1Negative **PD-L1Positive**

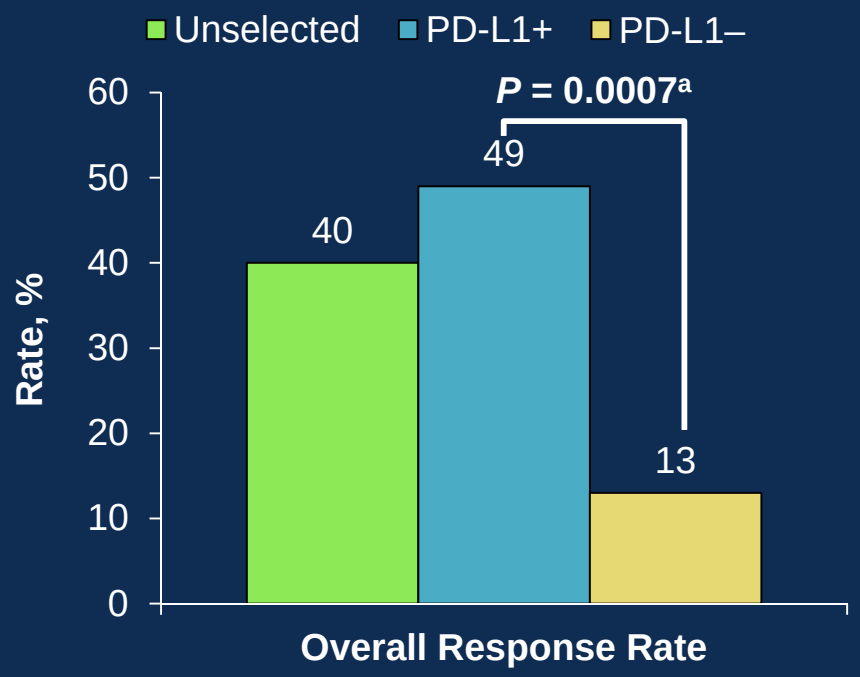
- PD-L1 positivity in pre-treatment biopsies defined as partial or complete membrane staining in ≥1% of tumor cells (brown chromogen) using the 22C3 antibody[1,2]
  - This threshold chosen from training set based on association with high response rate and high negative predictive value (87%)
  - Inflammatory cells within tumor nests also scored

Analysis cut-off date: 18 October 2013.

1. Daud A et al. Presented at: 2014 Annual AACR Meeting; April 5-9, 2014; San Diego, CA.
2. Garon, E.B. Clin Cancer Res 2014;20(2Suppl):Abstract nr A20

ORR Based on Tumor PD-L1 Expression (Central Review, RECIST v1.1)[1]

ORR by PD-L1 Positivity Across Doses/Schedules n=113



ORR by PD-L1 Positivity By Dose/Schedule

	10 mg/kg Q2W n = 35	10 mg/kg Q3W n = 47	2 mg/kg Q3W n = 31
Proportion PD-L1+	86%	77%	55%
Overall response rate to Pembro:			
Unselected	51%	32%	39%
PD-L1+	57%	39%	59%
PD-L1–	20%	9%	14%

- Differences in PD-L1 positivity may partly explain ORR differences between dosing cohorts

[a]1-sided *P* values calculated by logistic regression, adjusting for dose/schedule.
PD-L1 positivity defined as staining in ≥1% of tumor cells.
Analysis cut-off date: 18 October 2013.

1. Daud A et al. Presented at: 2014 Annual AACR Meeting; April 5-9, 2014; San Diego, CA.

PD-L1 Status Summary

Author	Population	Agent	Target	PD-L1 Ab	Cutoff	PD-L1+ ORR	PD-L1- ORR
[1]Petrylak	mUC	Atezolizumab	PD-L1	SP142	5%IC	50%	17%
[17]Herbst	mSolid Tumors	Atezolizumab	PD-L1	SP142	5%IC	34%	16%
[18]McDermott	mRCC	Atezolizumab	PD-L1	SP142	1%IC	20%	10%
[19]Horn	mNSCLC	Atezolizumab	PD-L1	SP142	10%IC or TC	45%	14%
[2]Plimack	mUC	Pembrolizumab	PD-1	22C3	1%TC	33%	9%
[20]Daud	mMel	Pembrolizumab	PD-1	22C3	1%TC	53%	6%
[21]Garon	mNSCLC	Pembrolizumab	PD-1	22C3	50%TC+IC	45%	17%
[3,22]Choueiri	mRCC	Nivolumab	PD-1	28-8	5%TC	22%	8%
[23]Brahmer	mNSCLC	Nivolumab	PD-1	28-8	5%TC	15%	14%
[24]Callahan	mMel	Nivolumab + Ipilimumab	PD-1/CTLA-4	28-8	5%TC	41%	46%
[25]Hammers	mRCC	Nivolumab + Ipilimumab	PD-1/CTLA-4	28-8	1%TC	50%	55%
[26]Larkin	mMel	Nivolumab + Ipilimumab	PD-1/CTLA-4	28-8	5%TC	72%	58%
[27]Grasso	mMel	Nivolumab	PD-1	28-8	5%TC	44%	17%
[28]Topalian	mSolid Tumors	Nivolumab	PD-1	5H1	5%TC	36%	0%

UC = Urothelial Cancer; RCC = Renal Cell Carcinoma; NSCLC = Non-small cell lung cancer; Mel = Melanoma; IC = Immune Cells, TC = Tumor Cells

[1]ASCO 2015;abst 4501 / [17]Nature 2014;515(7528):563-67 / [2]ASCO2015;abst 4502 / [3]ASCO 2015;abst 4500 / [18]ESMO 2014;abst 8090 / [19]ASCO2015;abst 8029 / [20]AACR 2014;abst / [21]NEJM 2015;372(21):2018-28 / [22]ASCO 2014;abst 5012 / [23]ASCO 2014;abst 8112 / [24]J Immuno Ther Cancer 2013;1(Suppl 1):O6 / [25]ASCO 2014;abst 4504 / [26]NEJM 2015;515:in-press/ [27]ASCO 2013;abst 3016 / [28]NEJM 2012;366(26):2443-54.

PD-L1 Antibody Conclusions

- The antibody matters
- PD-L1+ cut points should be consistent for a given antibody
- The disease may matter
- PD-L1+ patients have higher response rates
- Patient Enrichment in Clinical Trials
  - Dynamic marker, recent tissue better
  - Consider only if stable antibody with consistent cut points
  - Much more important in earlier stage trials (i.e. adjuvant)
  - Potentially not needed in combination trials

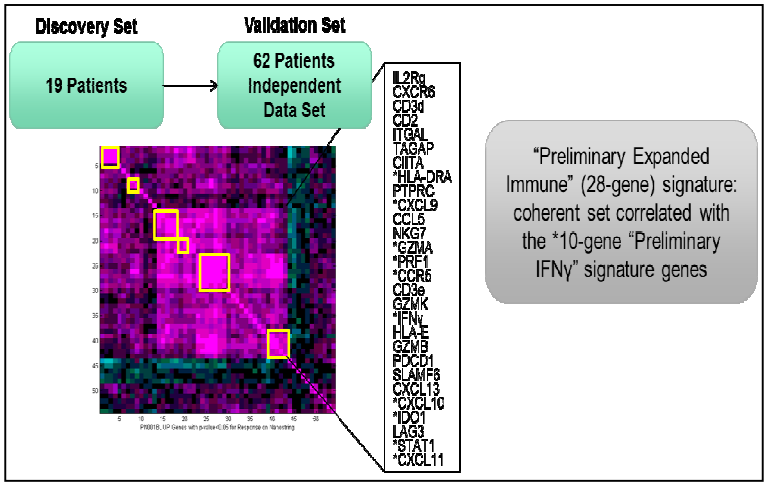
The Role of the Microenvironment in Response Prediction

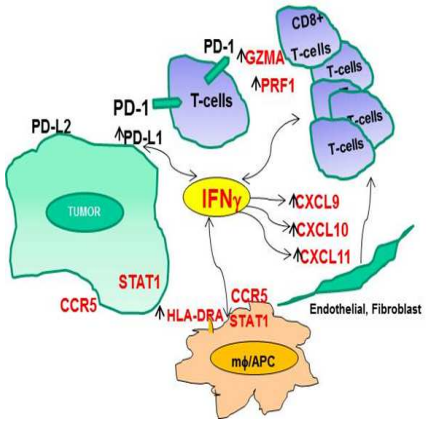
Jonathan Cebon
Olivia Newton-John Cancer & Wellness Centre
Melbourne, Australia

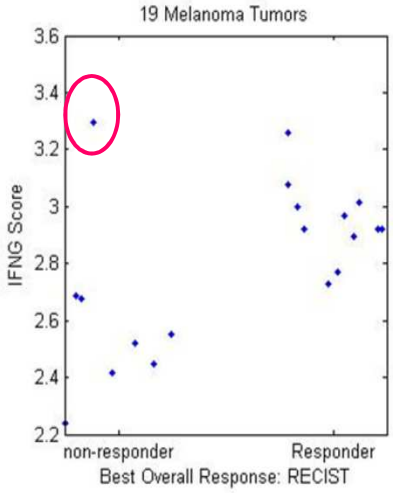
Olivia Newton-John
Cancer Research Institute

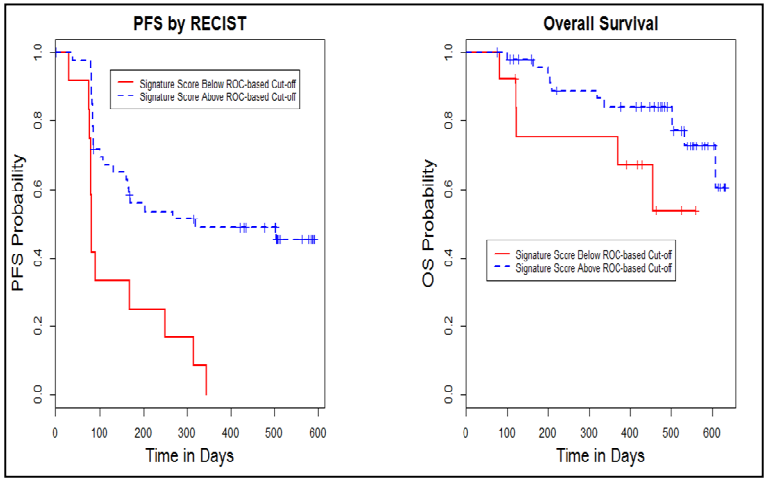
PRESENTED AT: ASCO Annual '15 Meeting

Antoni Ribas: Association of response to programmed death receptor 1 (PD-1) blockade with pembrolizumab (MK-3475) with an interferon-inflammatory immune gene signature.







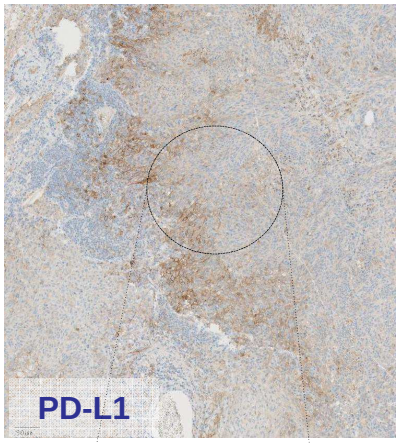


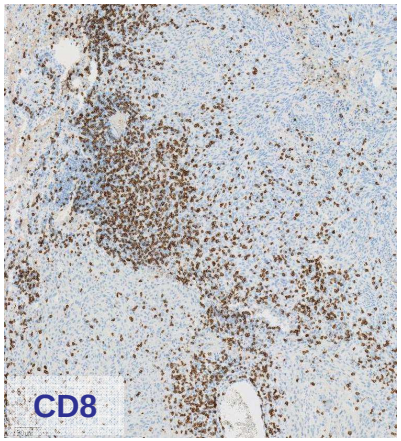
Gene signature with NanoString on FFPE tissue

- IFNγ signature predicts response to PD-1 blockade
- Not just melanoma: gastric, H&N
- Biomarker for improved selection
- Necessary but not sufficient?

Adaptive Regulation of Tumor PD-L1 Expression May Be an Indicator of Local TILs Attacking Tumor

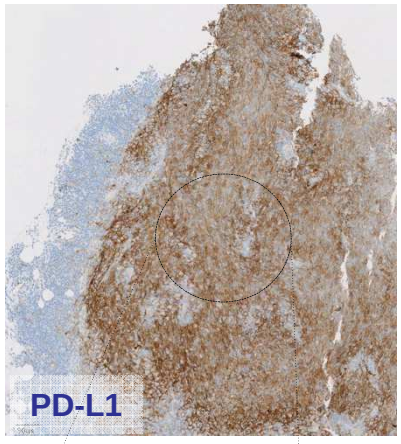
Baseline

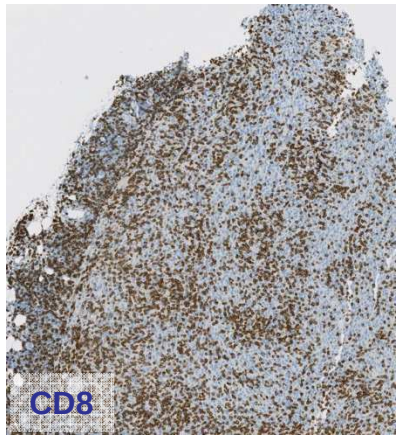


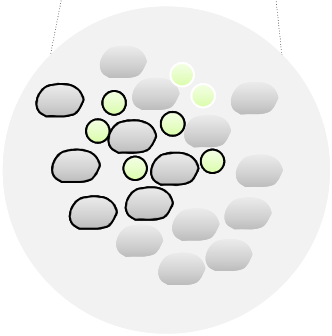


Anti-PD-L1

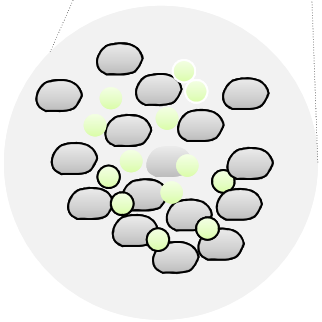
On-Tx







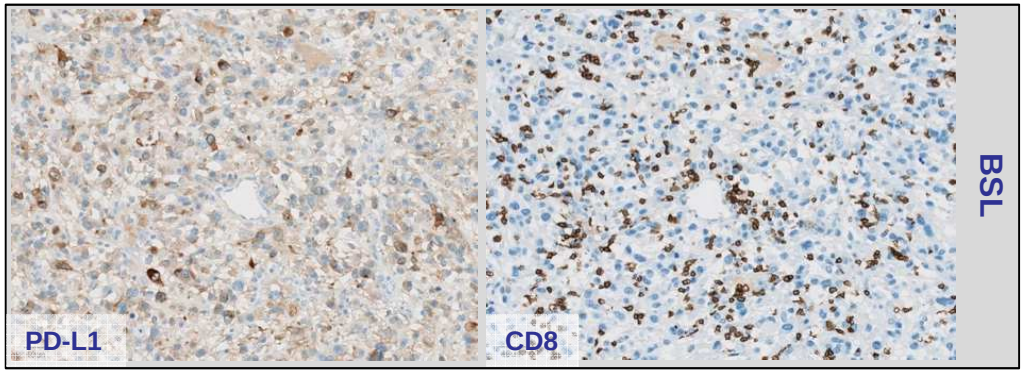
- T-cells and PD-L1+ tumor cells co-localize
- Focal PD-L1 expression may represent interface between cancer cells and immune cells (anti-tumor T-cell attack may be controlled by tumor PD-L1 or immune cell expression)



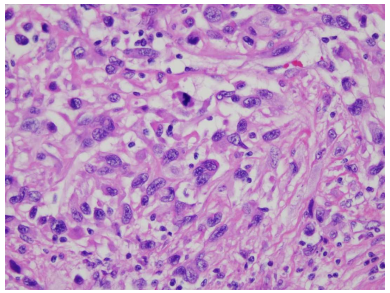
- T-cell mediated killing of tumor cells leads to T-cell proliferation and activation
- Activated T-cells release IFNγ and may induce PD-L1 expression in neighboring tumor cells

Tumor cells
PD-L1 expressing tumor cells
TIL/Immune cells

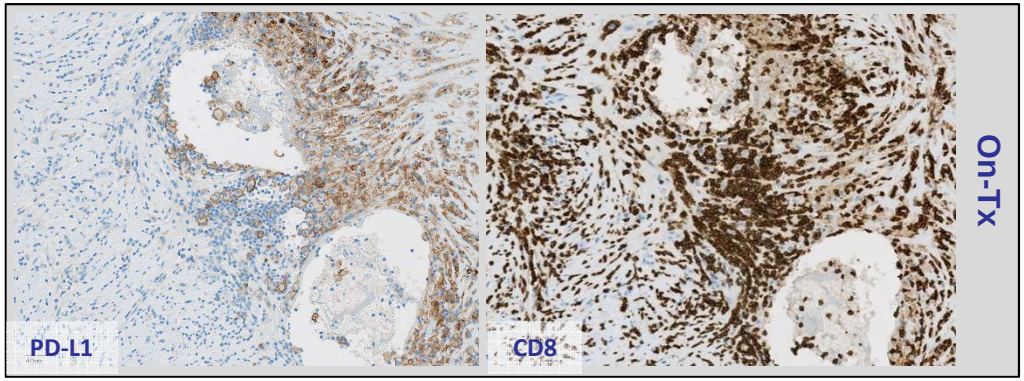
Serial biopsy in a PD-L1+ RCC patient with a rapid response to MPDL3280A:



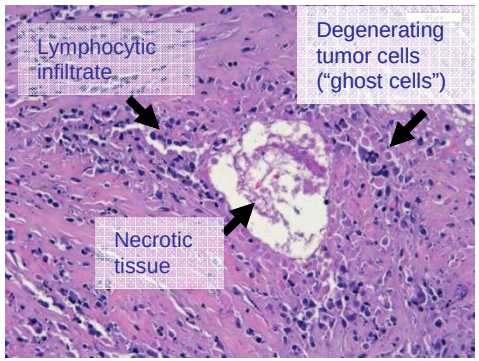
Biomarkers at baseline:
PD-L1+
Frequent CD8+ T-cells



Baseline H&E: RCC

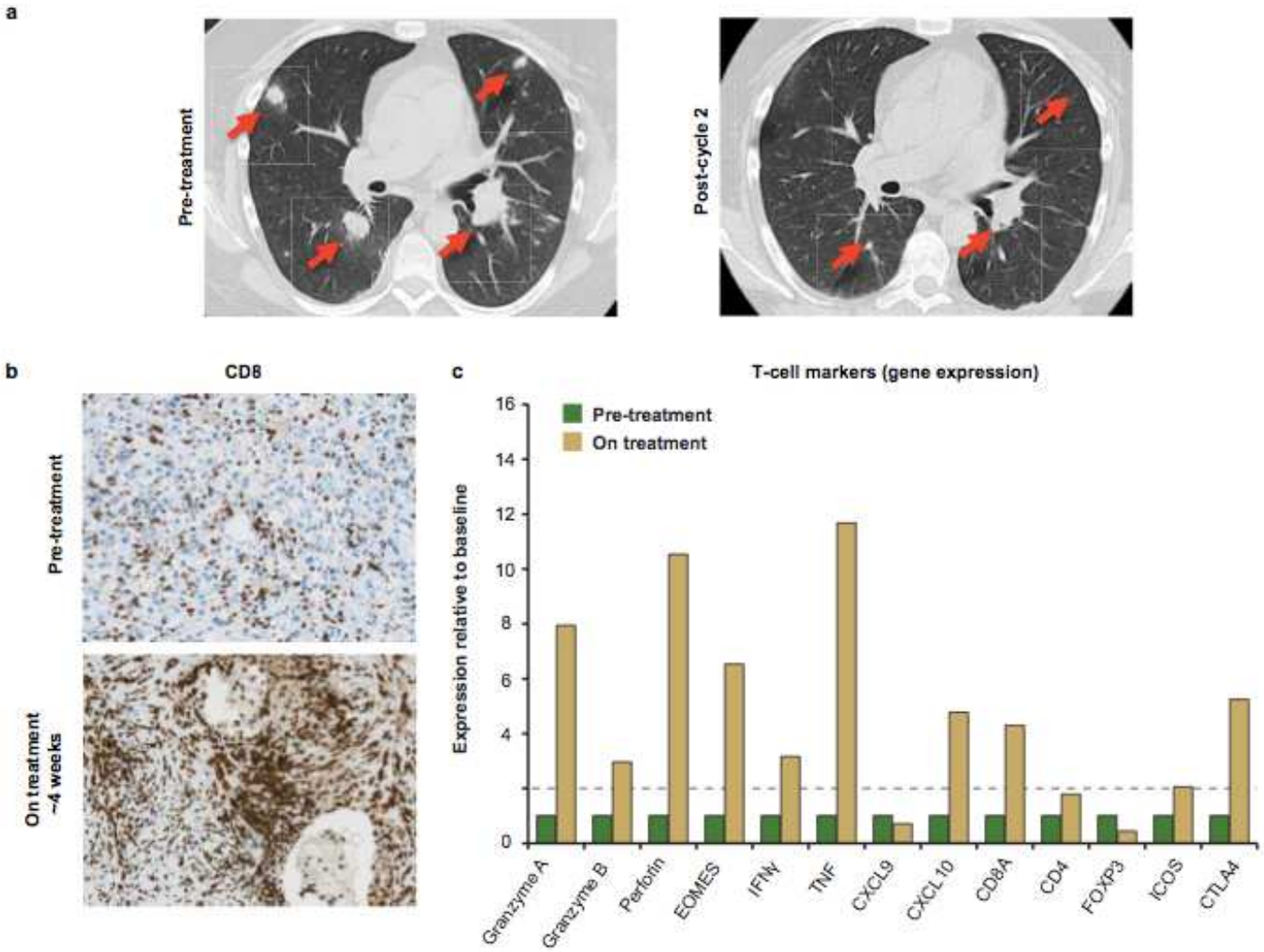


Biomarkers at week 4:
PD-L1+
Dense CD8+ T-cell infiltrate

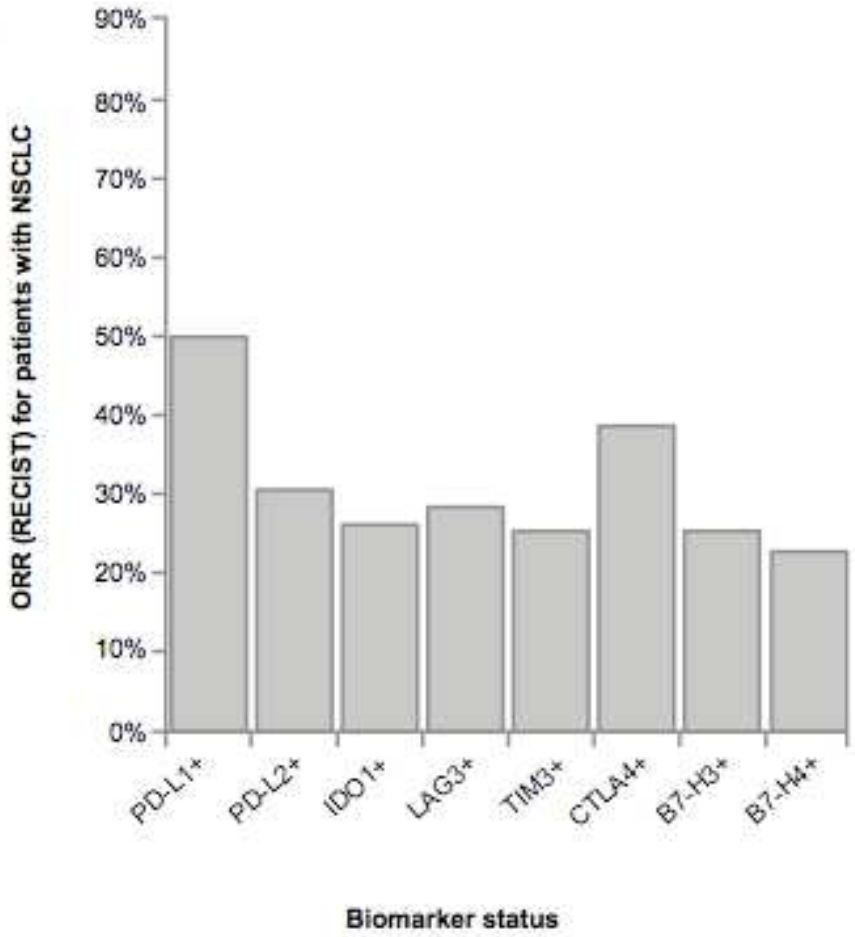


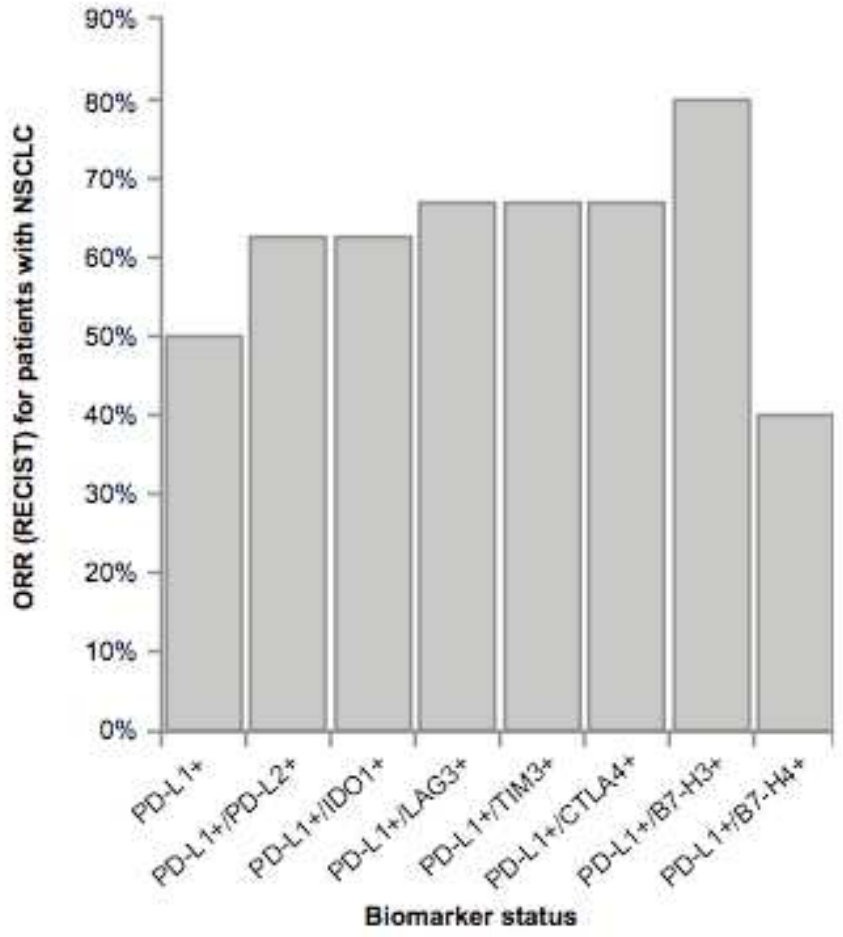
On-treatment H&E: dense lymphocytic infiltrate and *no viable* tumor cells seen

Became this…


a
Pre-treatment
Post-cycle 2
b
CD8
Pre-treatment
On treatment
~4 weeks
c
T-cell markers (gene expression)
Pre-treatment
On treatment
Expression relative to baseline
16
14
12
10
8
6
4
0
Granzyme A
Granzyme B
Perforin
EOMES
IFN
TNF
CXCL9
CXCL10
CD8A
CD4
FOXP3
ICOS
CTLA4

a


ORR (RECIST) for patients with NSCLC
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
PD-L1+
PD-L2+
IDO1+
LAG3+
TIM3+
CTLA4+
B7-H3+
B7-H4+
Biomarker status


ORR (RECIST) for patients with NSCLC
90%
80%
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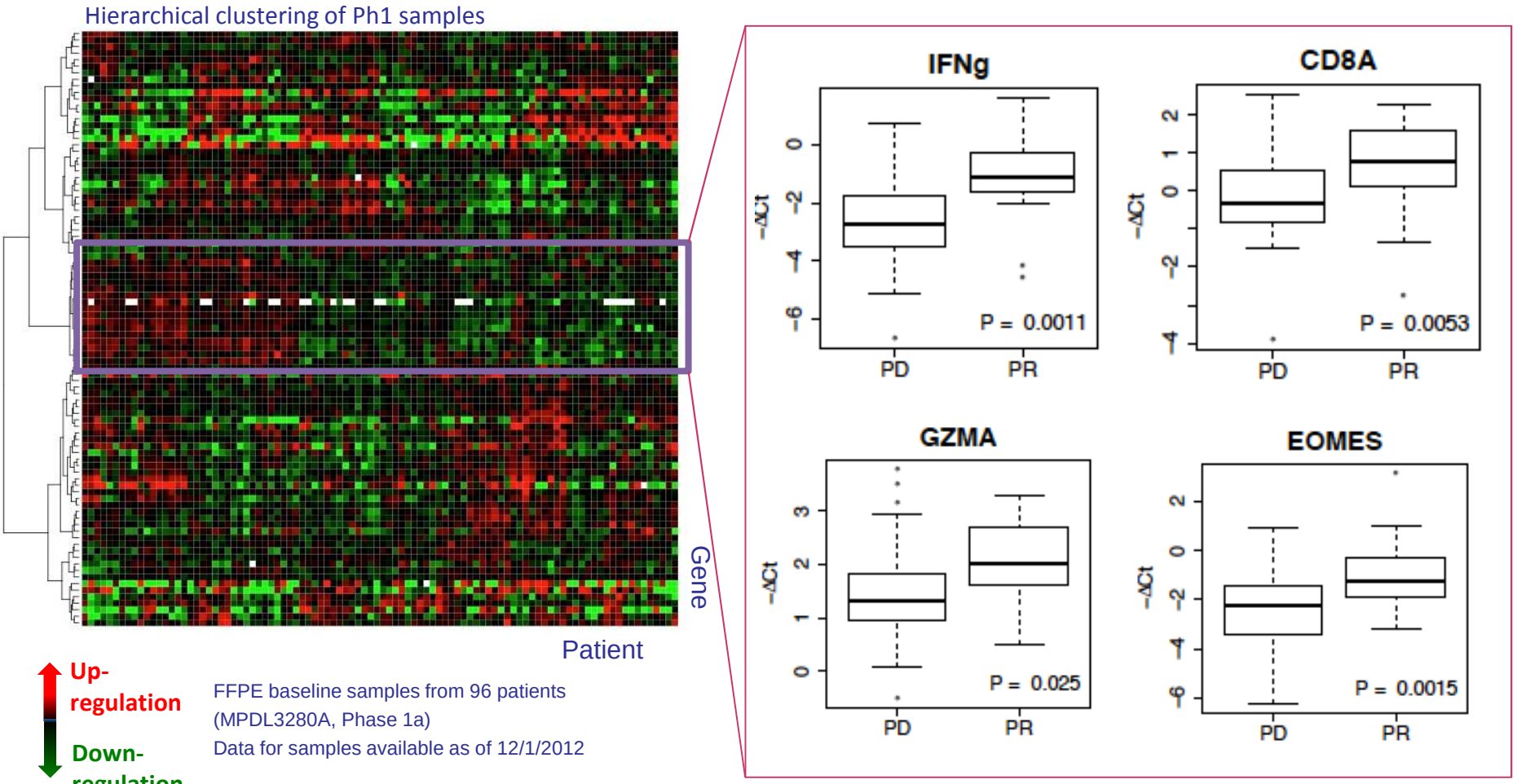
30%
20%
10%
0%
PD-L1+
PD-L1+/PD-L2+
PD-L1+/IDO1+
PD-L1+/LAG3+
PD-L1+/TIM3+
PD-L1+/CTLA4+
PD-L1+/B7-H3+
PD-L1+/B7-H4+
Biomarker status

Anti-tumor response to MPDL3280A is associated with Th1 T cell gene signature



Higher expression of cytotoxic Th1 T-cell markers in tumor tissue is associated with MPDL3280A activity

MK 34-75:

Baseline Tumor Size Is an Independent Prognostic Factor for Overall Survival Joseph et al ASCO 2014

Table 2. Antitumor Activity According to RECIST v1.1

Best Overall Response	Overall n = 365	Baseline Tumor Size		P
		Below Median n = 182	Above Median n = 183	
CR	5%	8%	2%	0.013
ORR	34%	42%	25%	0.001
DCR	54%	63%	45%	<0.001

CI = confidence interval; DCR = disease control rate.

Table 3. Analysis of Independent Predictors of OS

Factors	Hazard Ratio	P	Independent (BIC)
Baseline tumor size ≥ median	2.35	<0.001	Yes
Elevated LDH	1.70	0.002	Yes
ECOG PS	1.52	0.20	Yes
BRAF mutant	1.56	0.021	No
M1c	1.08	0.68	No
IPI naive	0.89	0.50	No

BIC = Bayesian information criterion; IPI = ipilimumab; LDH = lactate dehydrogenase.
Univariate factors with P < 0.10 were included in the analysis of potential prognostic factors.

Table 4. Analysis of Independent Predictors of ORR by RECIST v1.1

Factors	Odds Ratio	P	Independent (BIC)
Baseline tumor size above median	1.14	0.014	Yes
≥1 previous treatment	1.11	0.16	No
Elevated LDH	1.04	0.45	No
M1c	1.03	0.58	No
10 mg/kg Q3W treatment	1.00	0.96	No
IPI naive	0.98	0.72	No
10 mg/kg Q2W treatment	0.86	<0.05	No

IPI = ipilimumab; LDH = lactate dehydrogenase.

Figure 2. Kaplan-Meier estimates of OS by tumor size at baseline.

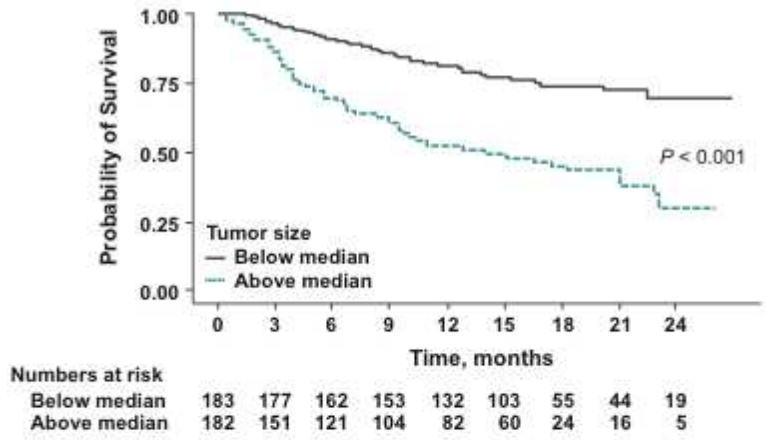
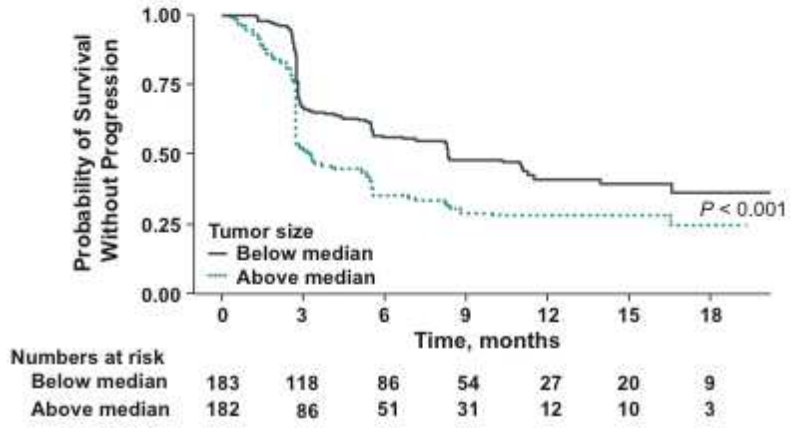


Figure 3. Kaplan-Meier estimates of PFS by tumor size at baseline.

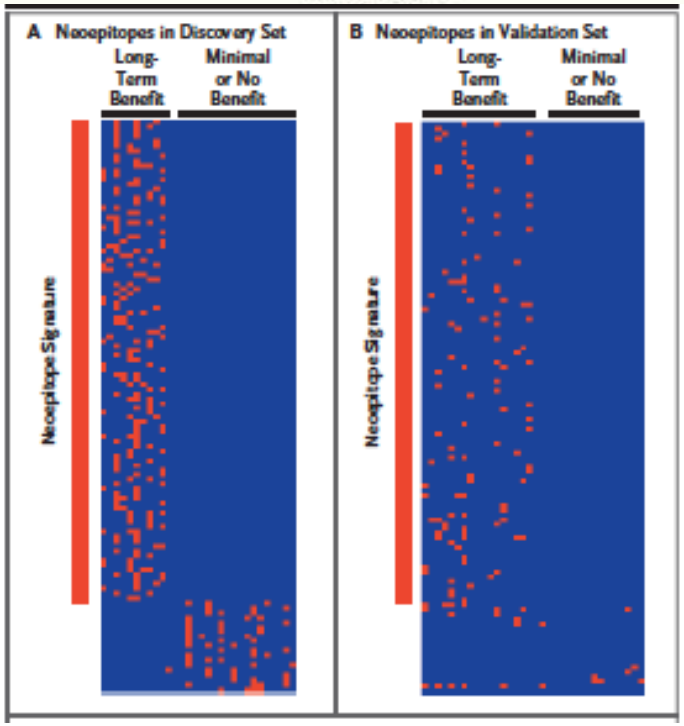


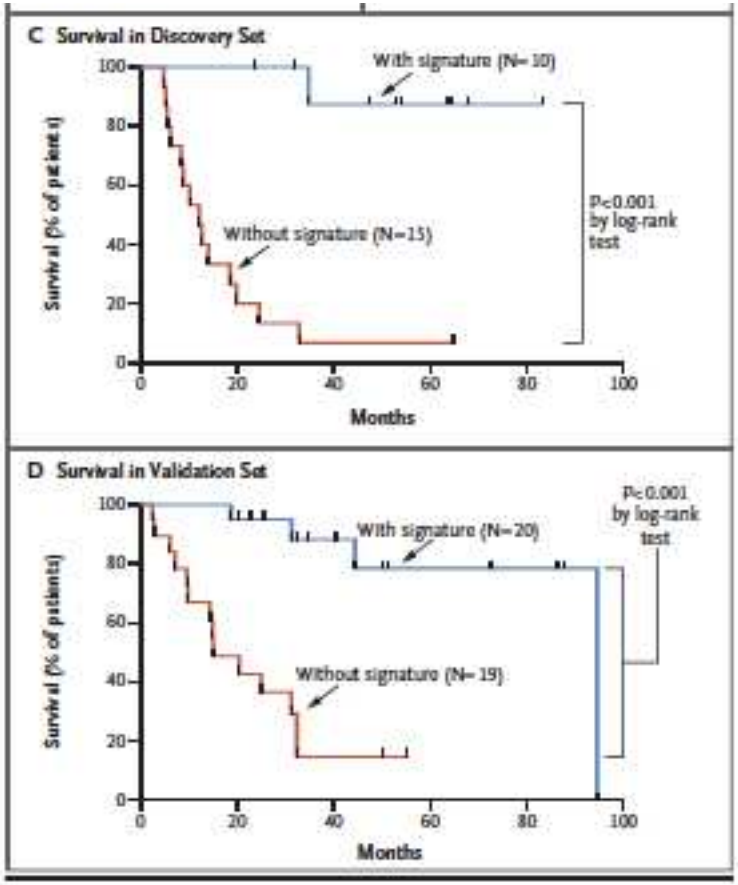
The NEW ENGLAND JOURNAL of MEDICINE

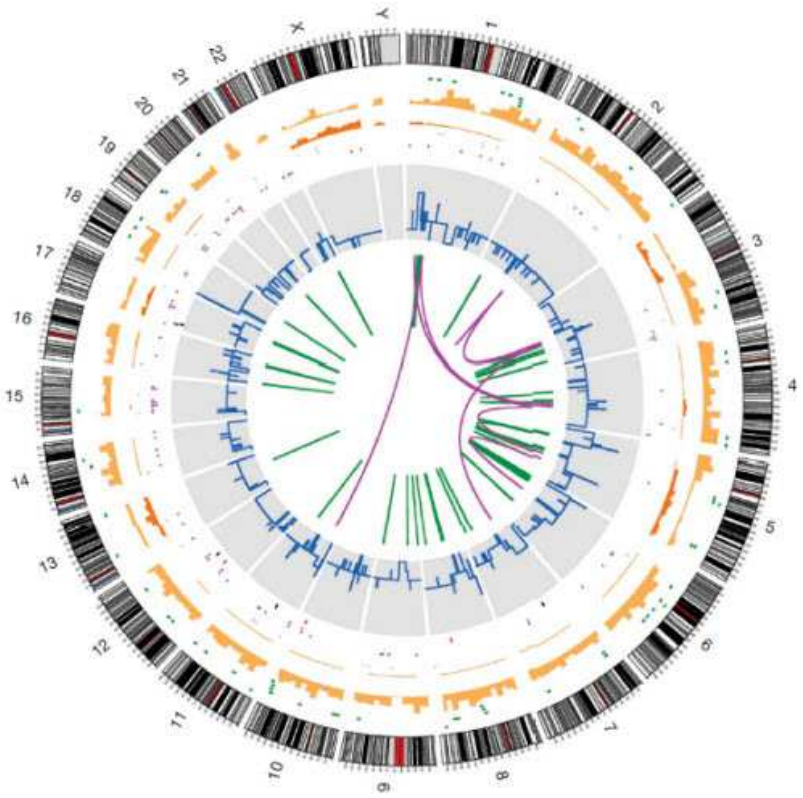
ORIGINAL ARTICLE

Genetic Basis for Clinical Response to CTLA-4 Blockade in Melanoma

Alexandra Snyder, M.D., Vladimir Makarov, M.D., Taha Merghoub, Ph.D., Jianda Yuan, M.D., Ph.D., Jesse M. Zaretsky, B.S., Alexis Desrichard, Ph.D., Logan A. Walsh, Ph.D., Michael A. Postow, M.D., Phillip Wong, Ph.D., Teresa S. Ho, B.S., Travis J. Hollmann, M.D., Ph.D., Cameron Bruggeman, M.A., Kasthuri Kannan, Ph.D., Yanyun Li, M.D., Ph.D., Ceyhan Elipenahli, B.S., Cailian Liu, M.D., Christopher T. Harbison, Ph.D., Lisu Wang, M.D., Antoni Ribas, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., and Timothy A. Chan, M.D., Ph.D.






X
Y
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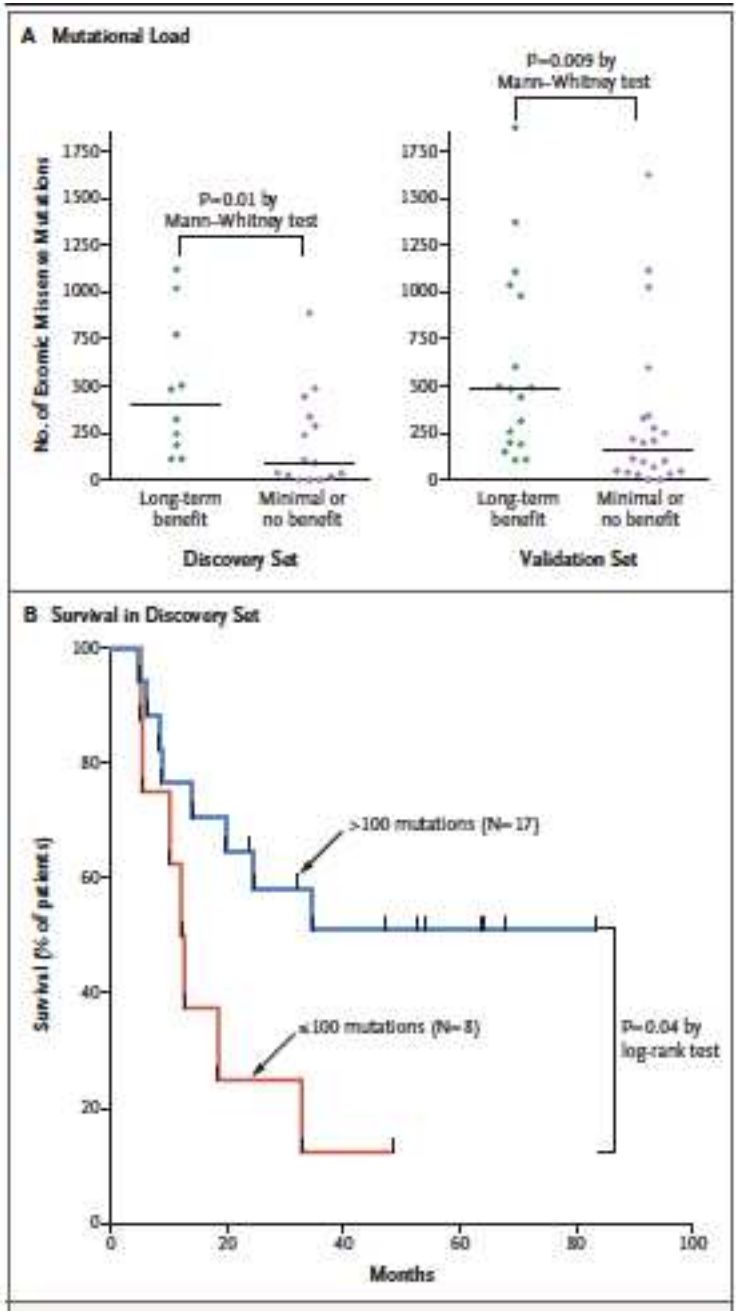
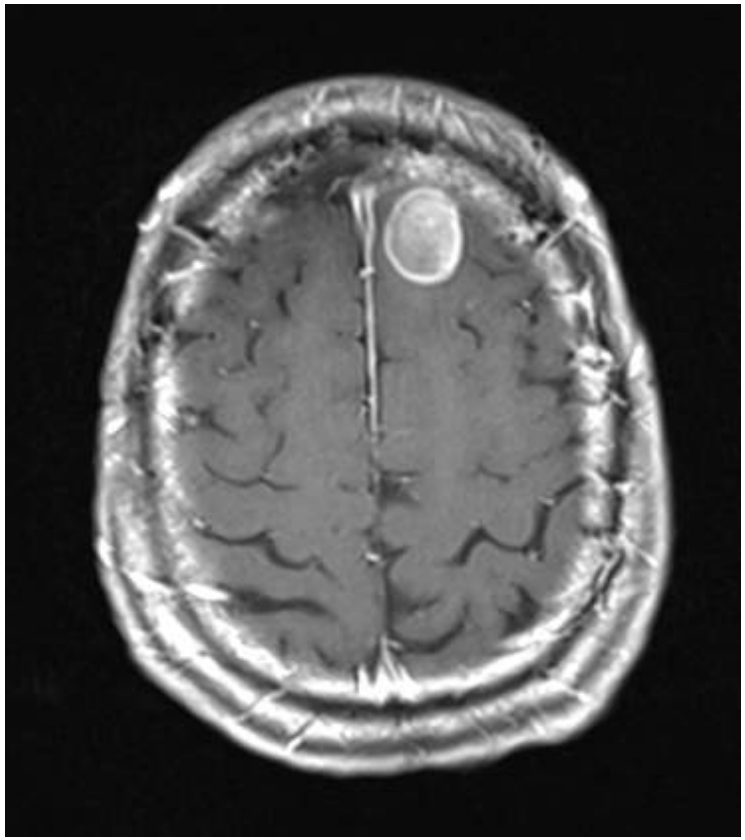
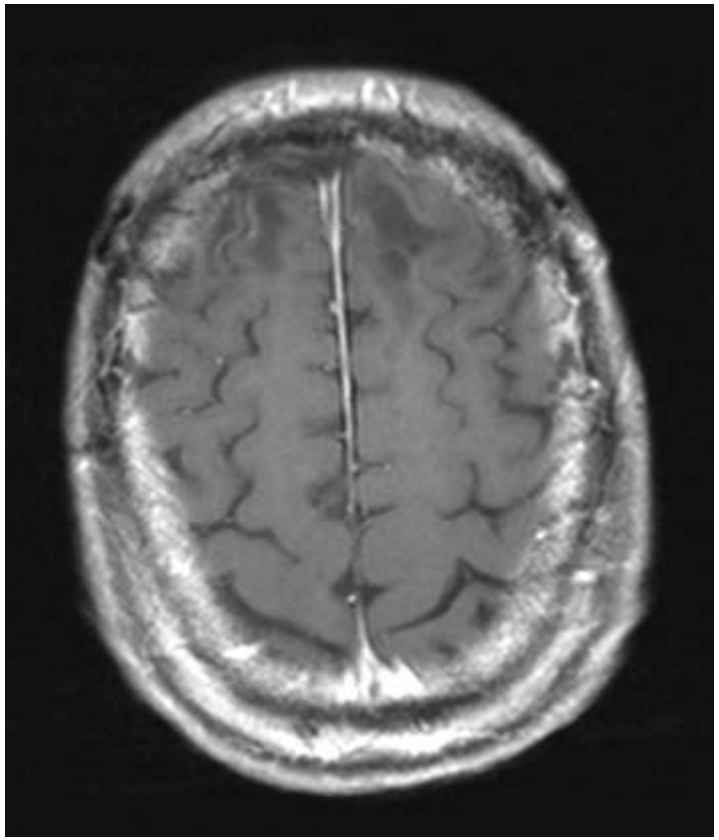

A Mutational Load
No. of Exomic Missense Mutations
P=0.01 by Mann–Whitney test
P=0.009 by Mann–Whitney test
1750
1500
1250
1000
750
500
250
0
Long-term benefit
Minimal or no benefit
Discovery Set
Validation Set
B Survival in Discovery Set
Survival (% of patients)
>100 mutations (N=17)
≤100 mutations (N=8)
P=0.04 by log-rank test
100
80
60
40
20
0
0
20
40
60
80
100
Months

Brain metastases
The final frontier……

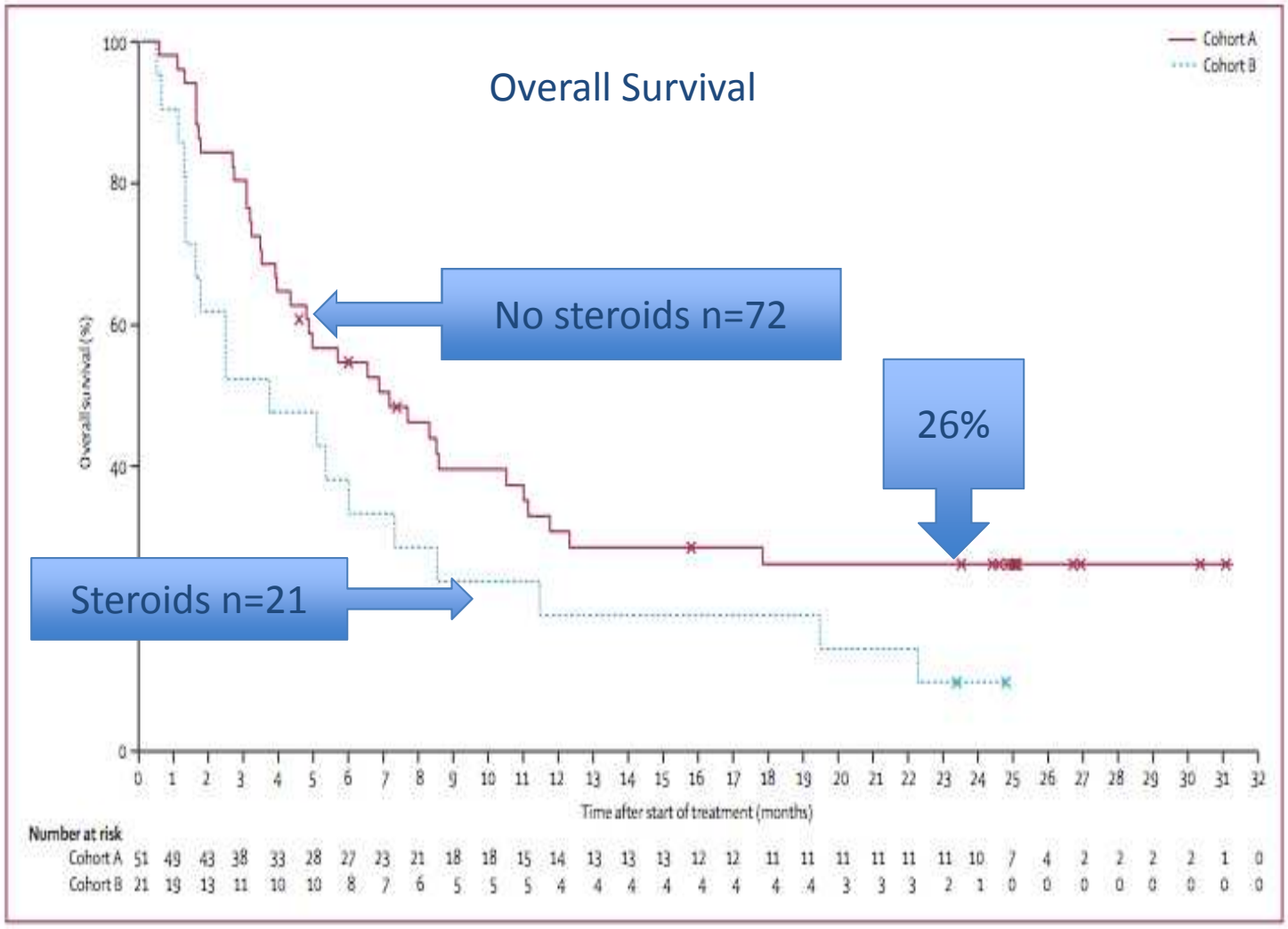
Durable brain responses in two patients

A: Partial response (PR) in brain and PR in total tumor burden, duration 11+ months



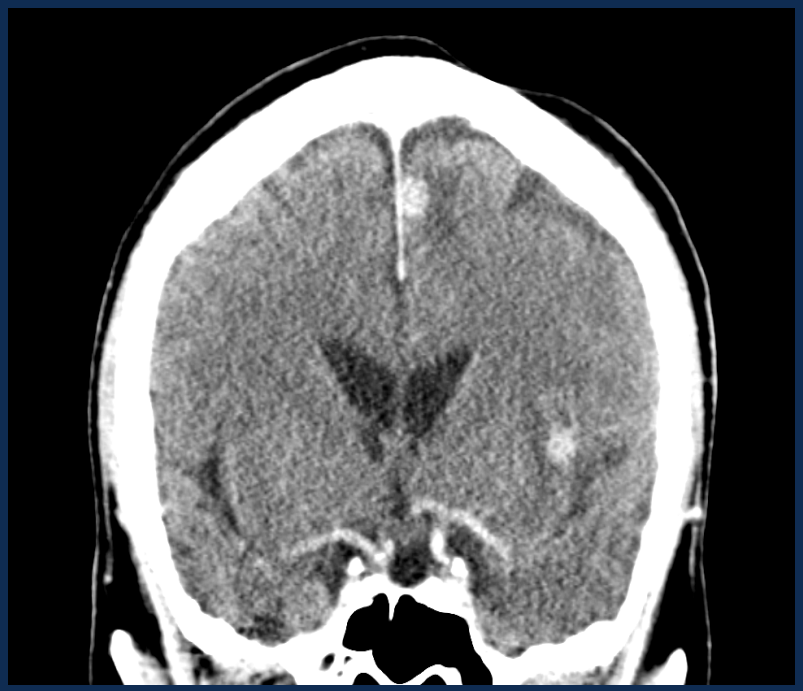


Ipilimumab Ph 2: Melanoma brain metastases

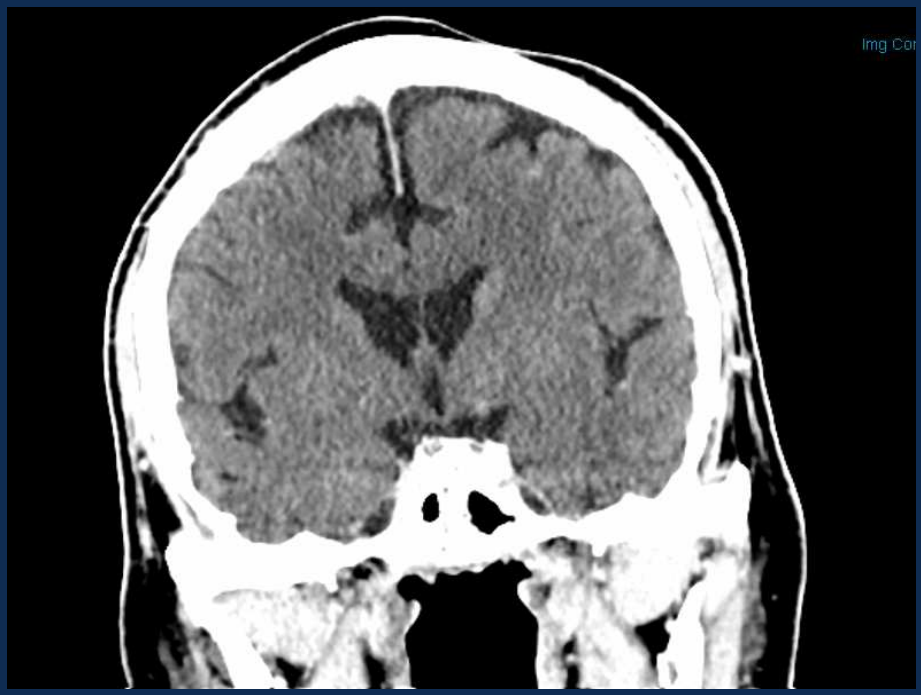


Margolin K et al Lancet Oncol 13,459 2012

72-year-old Male
Failed Ipilimumab, WBRT. PDL1+



Baseline



Cycle 5 Pembro 2 mg/kg Q3/52

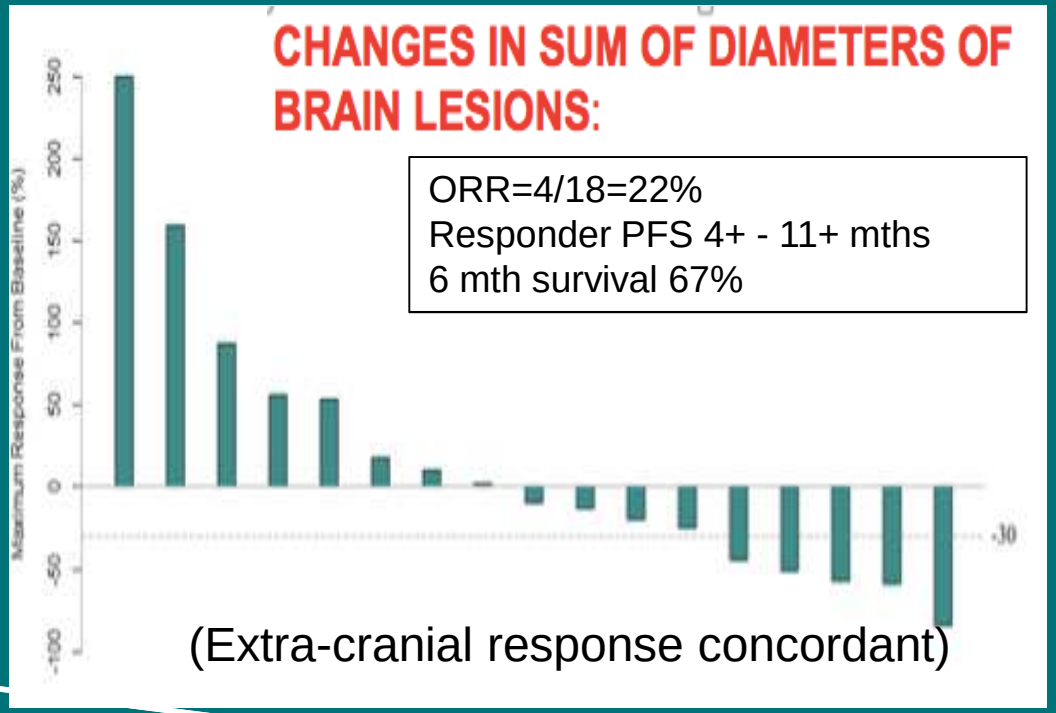
At 30 months:

- CR in brain and lung
- Almost CR in adrenal

Harriet Kluger et al Abstract ID: 9009 Phase 2 pembrolizumab (NCT02085070)

Prospective Ph 2: 18 pts

- Asympt
- ECOG 0-2
- ≥1 met ≥ 5-20 mm
- Brain tissue available
- No steroids
- Pembro 10mg/kg q 2/52
- 16 prior ipi, 4 prior BRAFi



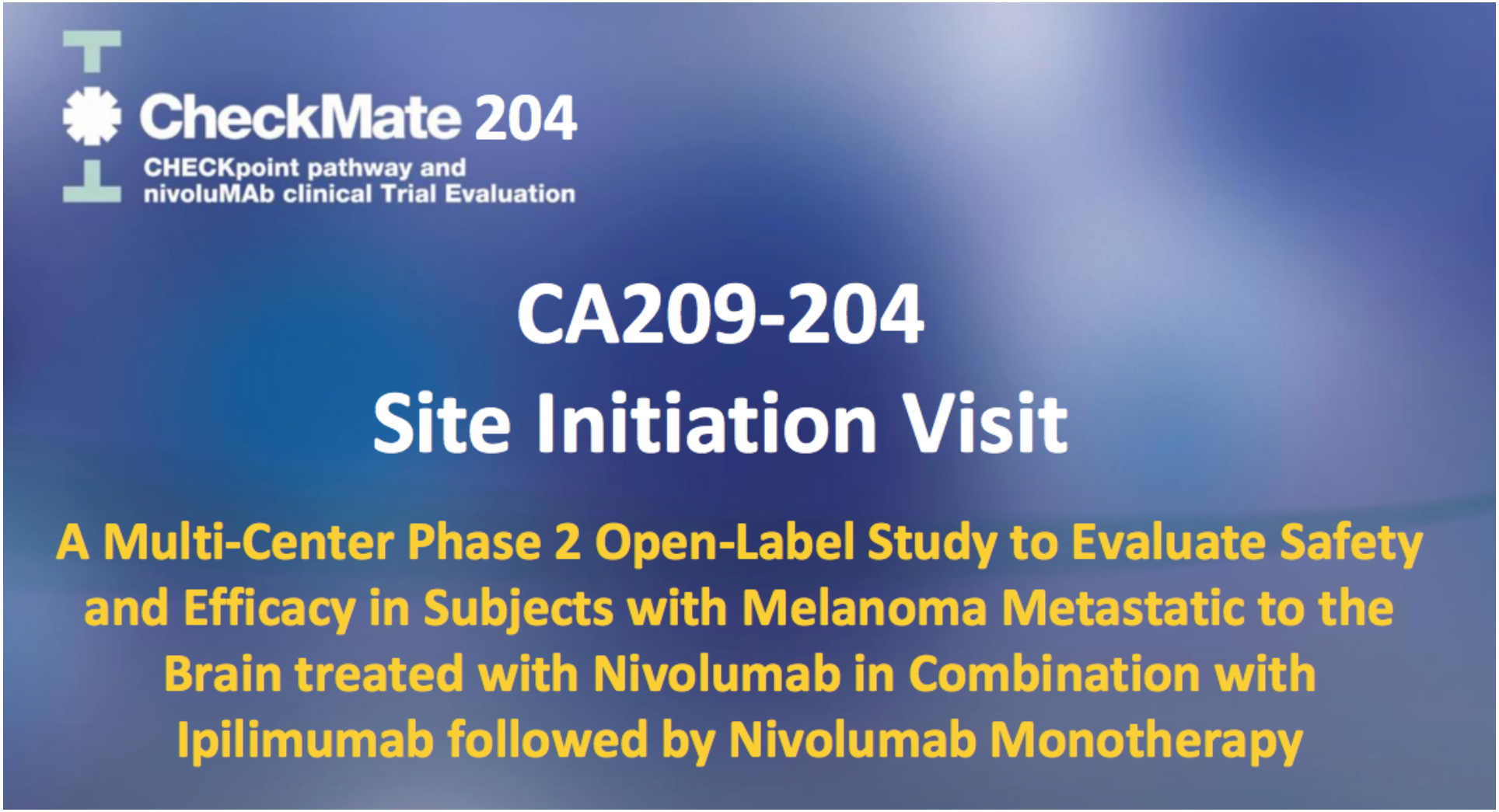
4
Unevaluable
- 3 rapid PD (extra-cranial)
- 1 hemorrhage

4 PR
(brain)
(All at 8 wk scan)

3 SD
(brain)

7 PD
(brain)
(1 pseudo-prog)

Shameless plug….



Earlier ? Adjuvant ??

Ipilimumab Versus Placebo After Complete Resection of Stage III Melanoma: Initial Efficacy and Safety Results from the EORTC 18071 Phase III Trial

Eggermont AM,[1] Chiarion-Sileni V,[2] Grob JJ,[3] Dummer R,[4] Wolchok JD,[5] Schmidt H,[6] Hamid O,[7] Robert C,[1] Ascierto PA,[8] Richards JM,[9] Lebbé C,[10] Ferraresi V,[11] Smylie M,[12] Weber JS,[13] Maio M,[14] Konto C,[15] Karra Gurunath R,[16] de Pril V,[17] Suciu S,[16] Testori A[18]

[1]Gustave Roussy Cancer Campus Grand Paris, Villejuif, France; [2]IOV-IRCCS, Melanoma Oncology Unit, Padova, Italy; [3]Hôpital de la Timone, Marseille, France; [4]University of Zürich Hospital, Zürich, Switzerland; [5]Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [6]Aarhus University Hospital, Aarhus, Denmark; [7]The Angeles Clinic and Research Institute, Los Angeles, CA, USA; [8]Istituto Nazionale Tumori Fondazione "G. Pascale", Naples, Italy; [9]Oncology Specialists S.C., Park Ridge, IL, USA; [10]Hôpital Saint-Louis, Paris, France; [11]Istituti Fisioterapici Ospitalieri, Rome, Italy; [12]Cross Cancer Institute, Edmonton, Alberta, Canada; [13]H Lee Moffitt Cancer Center, Tampa, FL, USA; [14]University Hospital of Siena, Istituto Toscano Tumori, Siena, Italy; [15]Bristol-Myers Squibb, Wallingford, CT, USA; [16]EORTC Headquarters, Brussels, Belgium; [17]Bristol-Myers Squibb, Braine-l'Alleud, Belgium; [18]European Institute of Oncology, Milan, Italy.

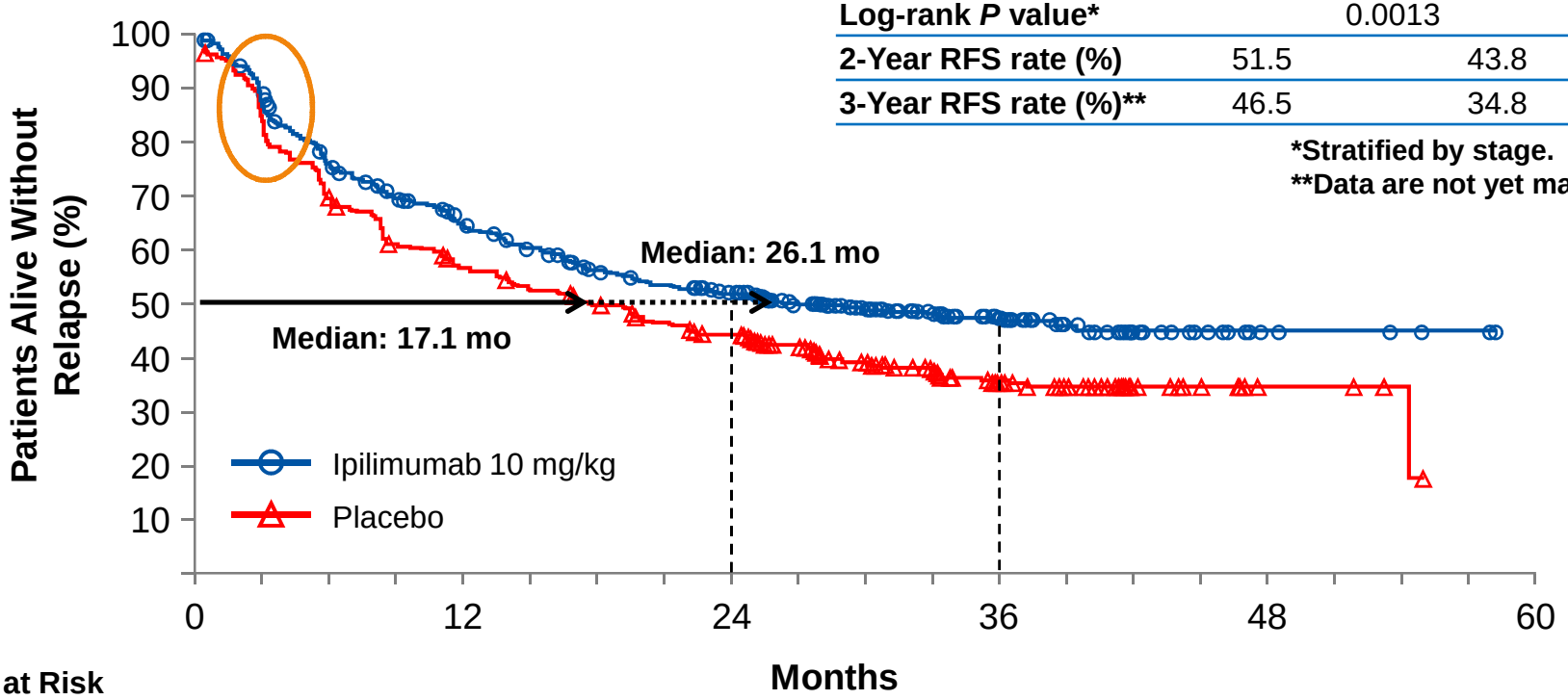
Abstract Number LBA9008

ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Primary Endpoint: Recurrence-free Survival (IRC)

	Ipilimumab	Placebo
Events/patients	234/475	294/476
HR (95% CI)*	0.75 (0.64–0.90)	
Log-rank *P* value*	0.0013	
2-Year RFS rate (%)	51.5	43.8
3-Year RFS rate (%)**	46.5	34.8

***Stratified by stage.**
****Data are not yet mature.**



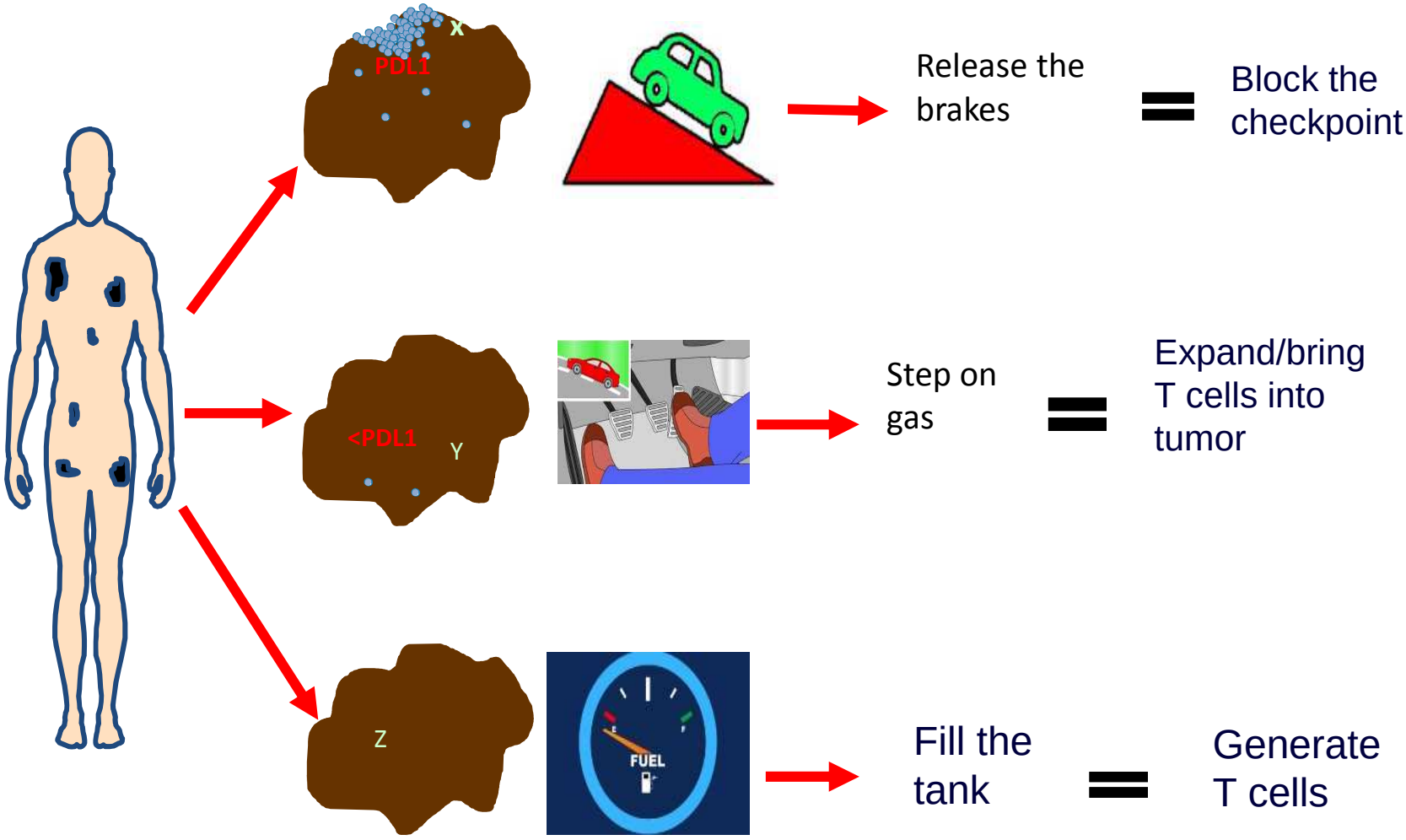
Patients at Risk

	O	N					
Ipilimumab	234	475	276	205	67	5	0
Placebo	294	476	260	193	62	4	0

PD-1 in the adjuvant

- Less toxic ?
- More response ?
- Combination ?

Tumor-guided PD-1 blockade treatment selection



Adapted from Ribas et al ASCO 2015 CPO

Melanoma Therapy: 2 Yet Another Breakthrough

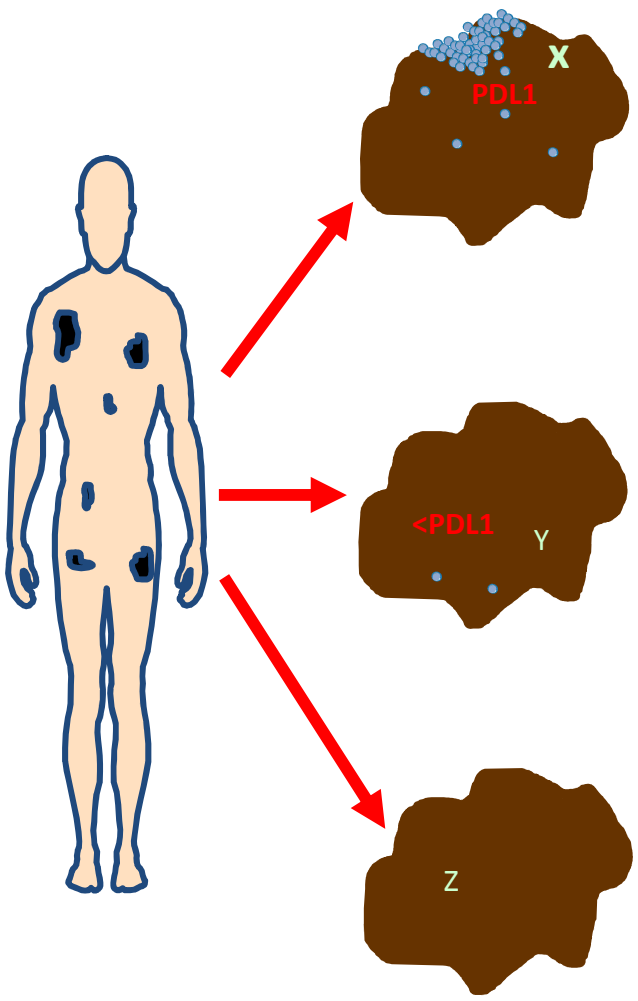
Michael B. Atkins, M.D.
Deputy Director
Lombardi Comprehensive Cancer Center
Professor of Medicine and Oncology
Georgetown University Medical Center
Washington, DC

PRESENTED AT: ASCO Annual '15 Meeting

2 Melanoma Therapy: A New Way to Skin the Cat

Louis Weiner, 5/22/2015

Tumor-guided PD-1 blockade treatment selection



Release the brakes

- Anti-PD1
- Anti-PDL1

Expand/bring T cells into tumors

- + anti-CTLA4
- + immune activating antibodies or cytokines
- + TLR agonists or oncolytic viruses
- + macrophage or IDO inhibitors
- + targeted therapies

Generate T cells

- Vaccines
- TCR engineered ACT
- CAR engineered ACT
- SRS
- Chemo

EORTC

The future of cancer therapy

Acknowledgments

THE PATIENTS AND THEIR FAMILIES!

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