Melanoma
Immune Checkpoints & Combination Therapies

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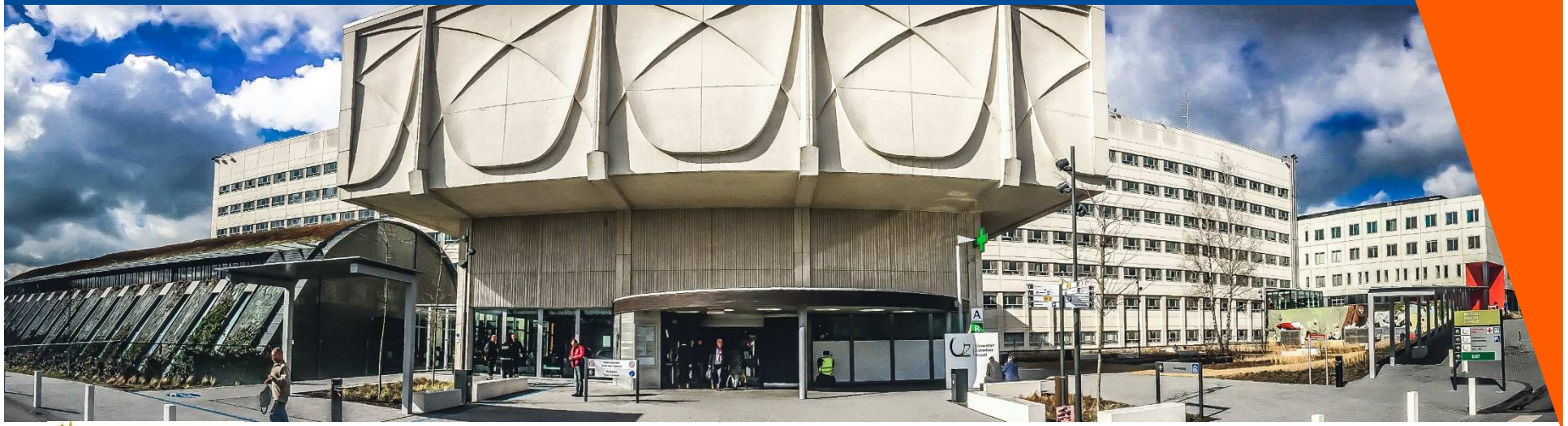

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DISCLOSURES

- Personal financial compensation from Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, AstraZeneca, EtheRNA, CryoStorage for public speaking, consultancy and participation in advisory board meetings
- My institution (UZ Brussel) received research funding related to research projects conducted by my team from Pfizer, Novartis, Roche, Merck-Serono

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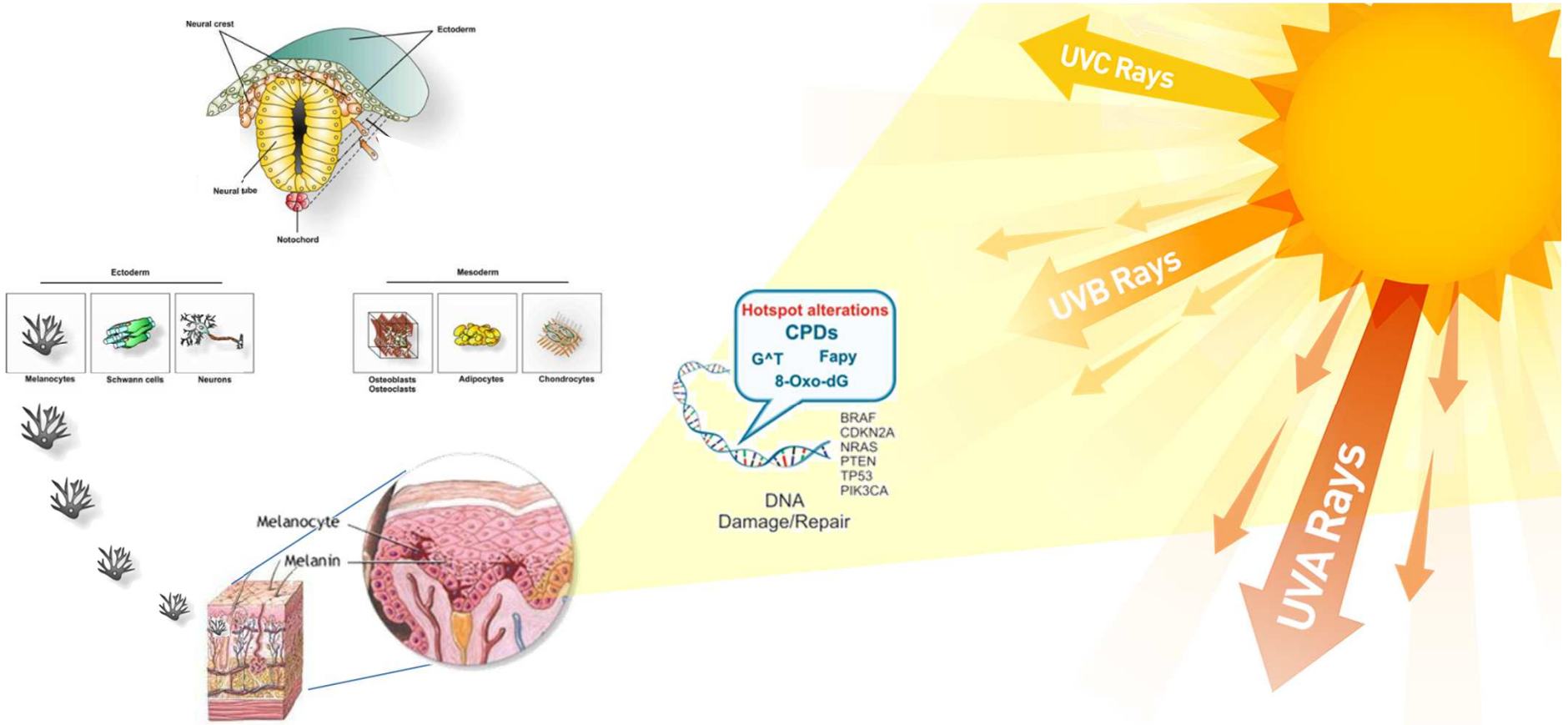
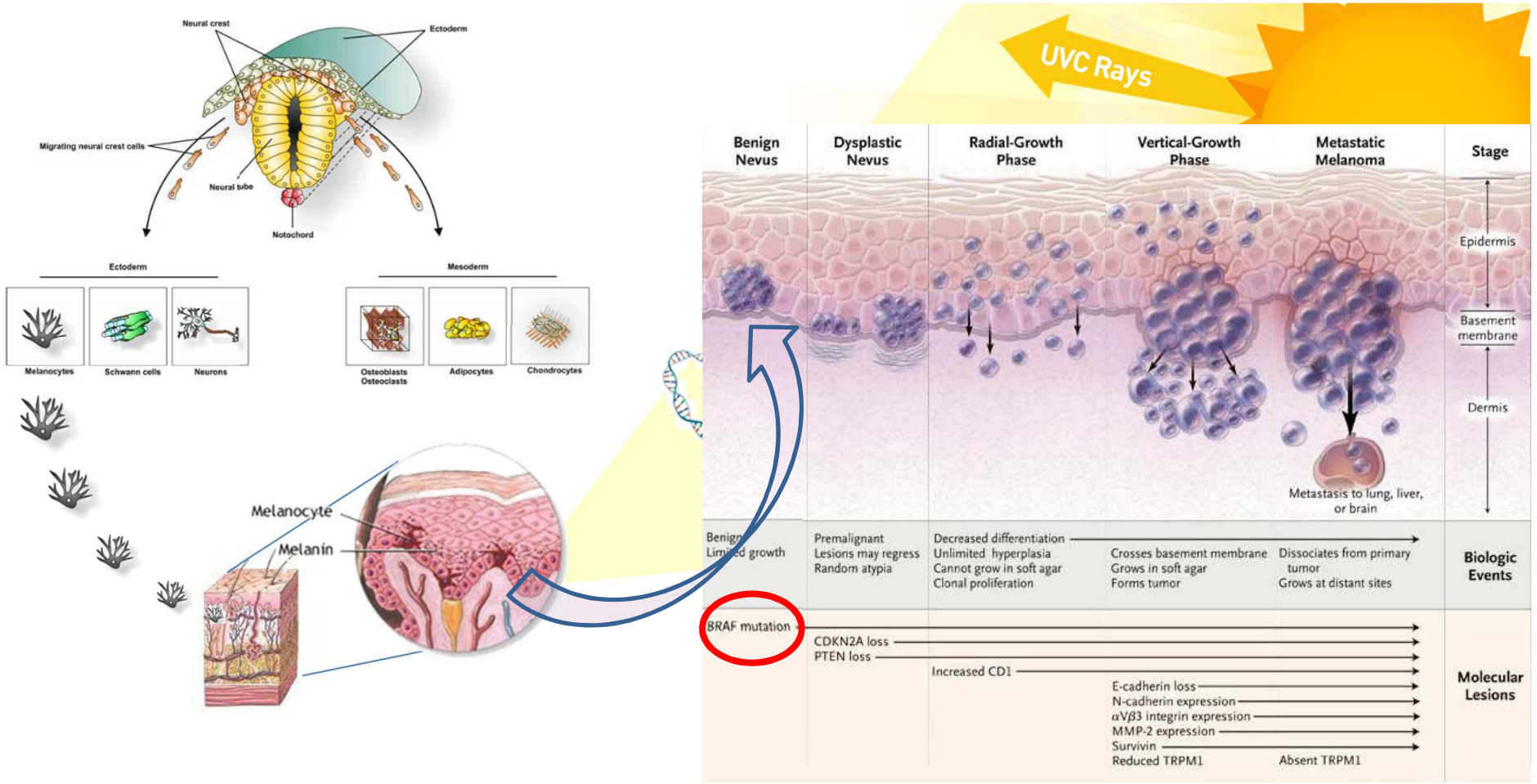
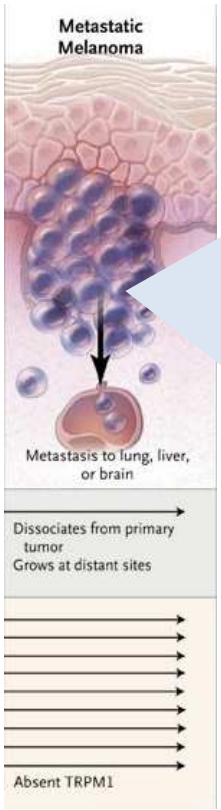


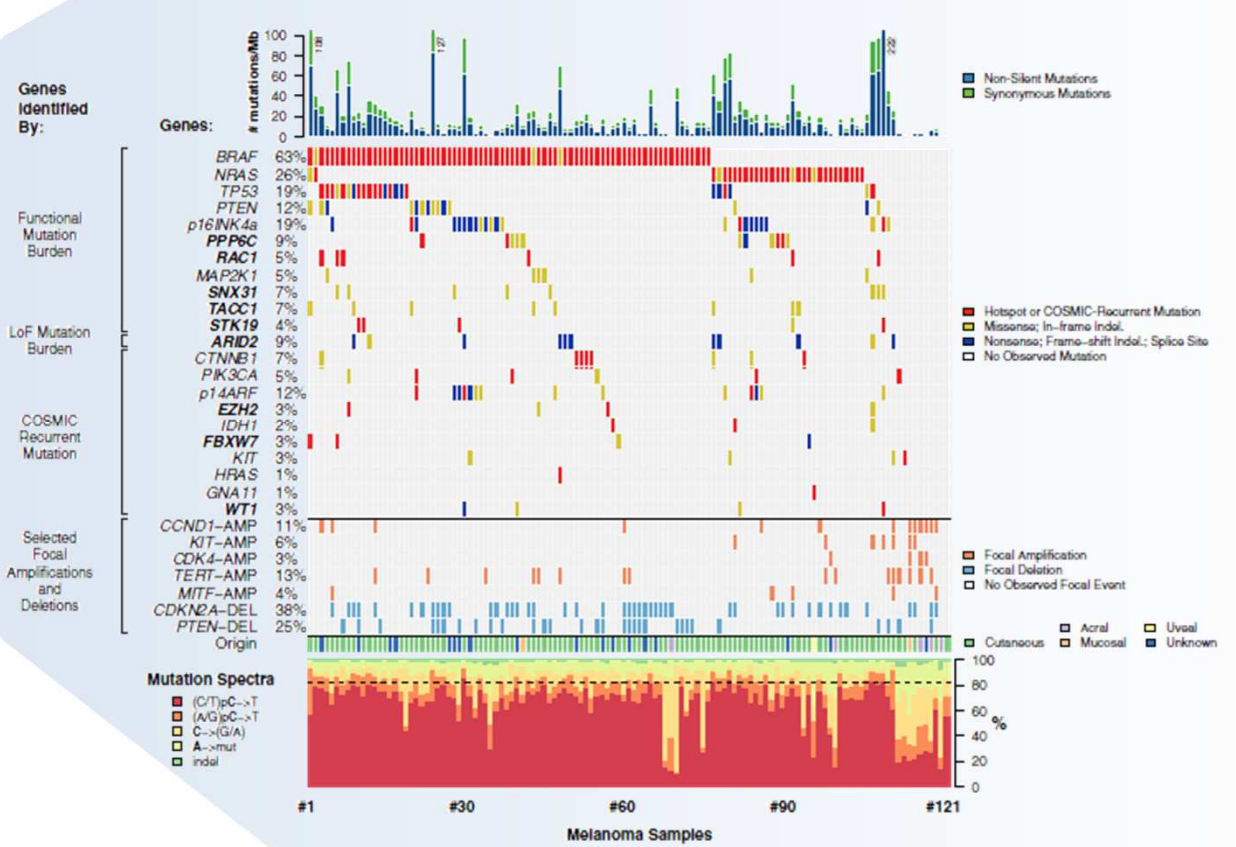
Adapted from Miller AJ, Mihm MC Jr. N Engl J Med 2006;355:51-65



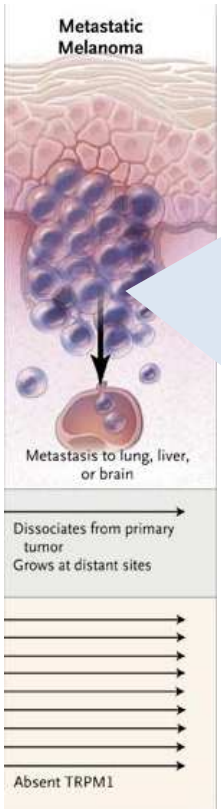
Adapted from Miller AJ, Mihm MC Jr. N Engl J Med 2006;355:51-65

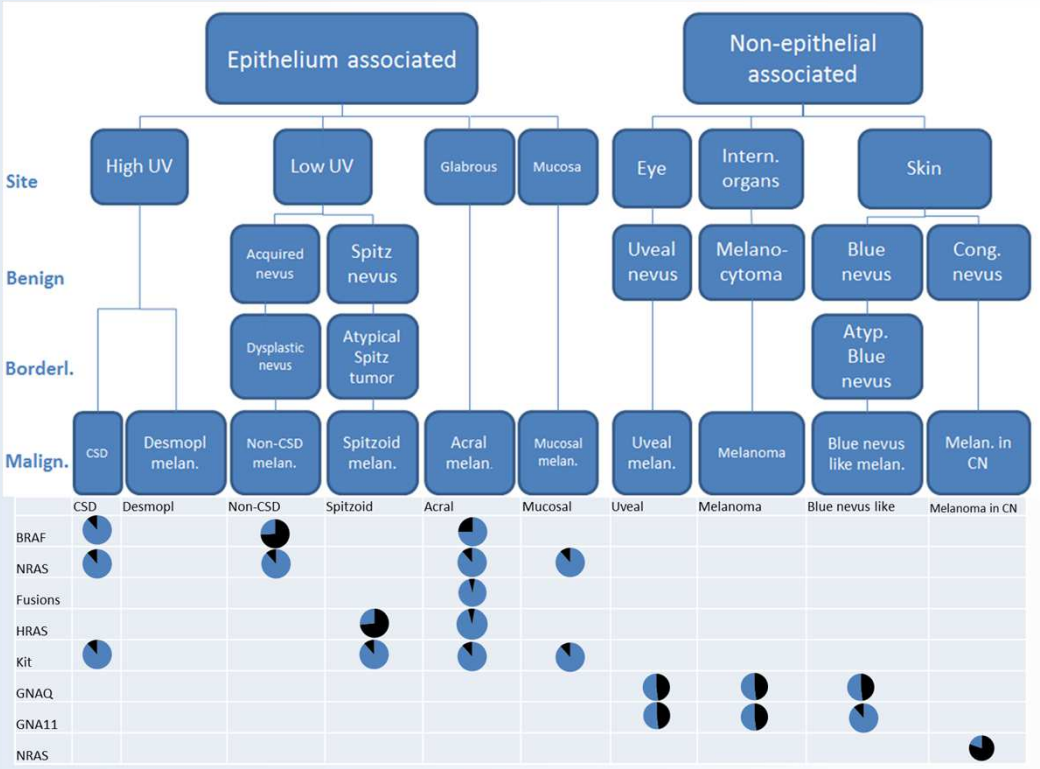
BRAF V600- vs. *RAS-* vs. *NF1-mut, vs. triple-WT vs cKIT- or GNA11-/GNAQ mut* subsets (significant heterogeneity within subsets)





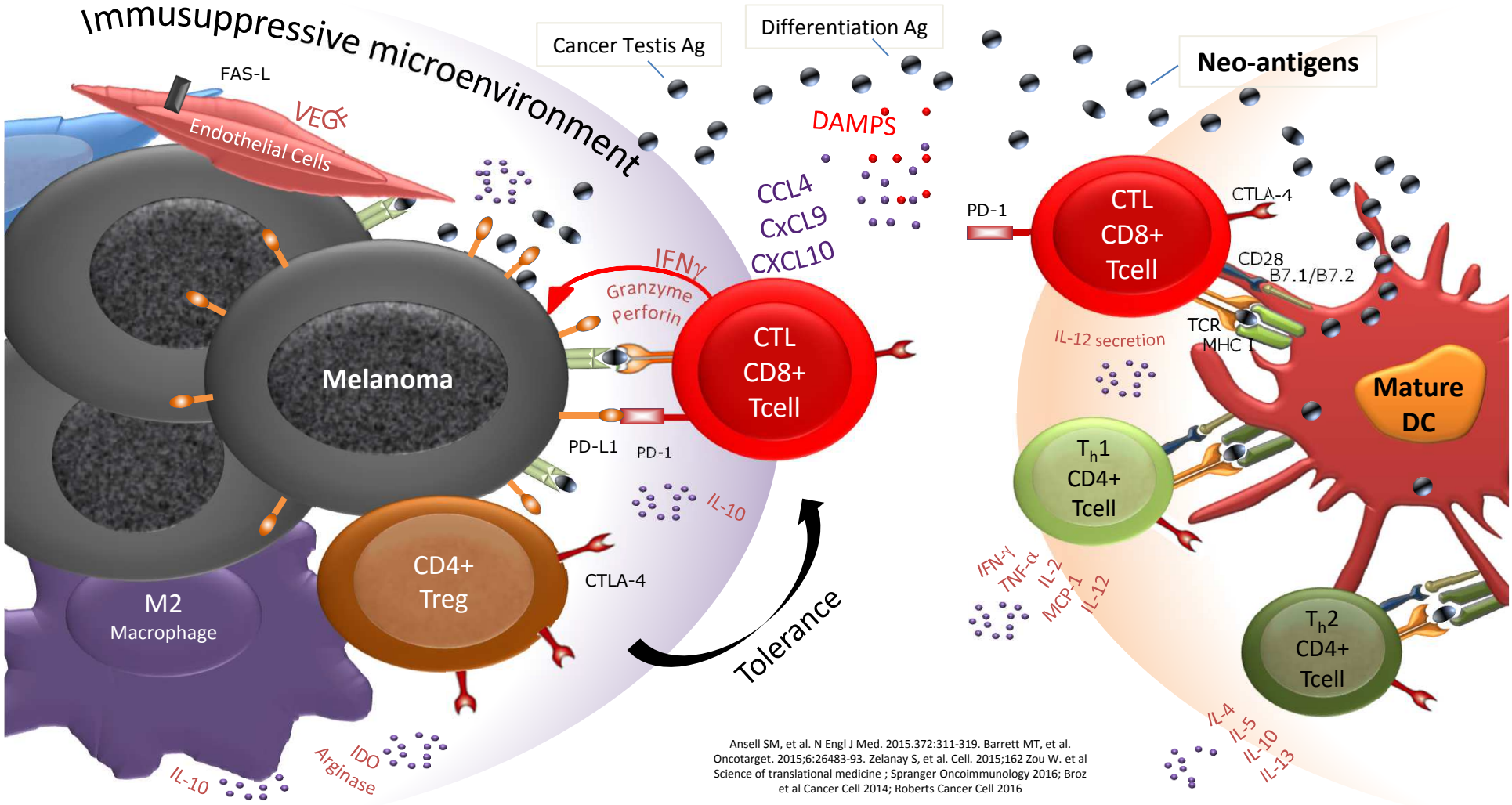
Hodis E et al. Cell 150, 251-263, July 20, 2012; Akbani R, et al. Cell 2015;161:1681–1696



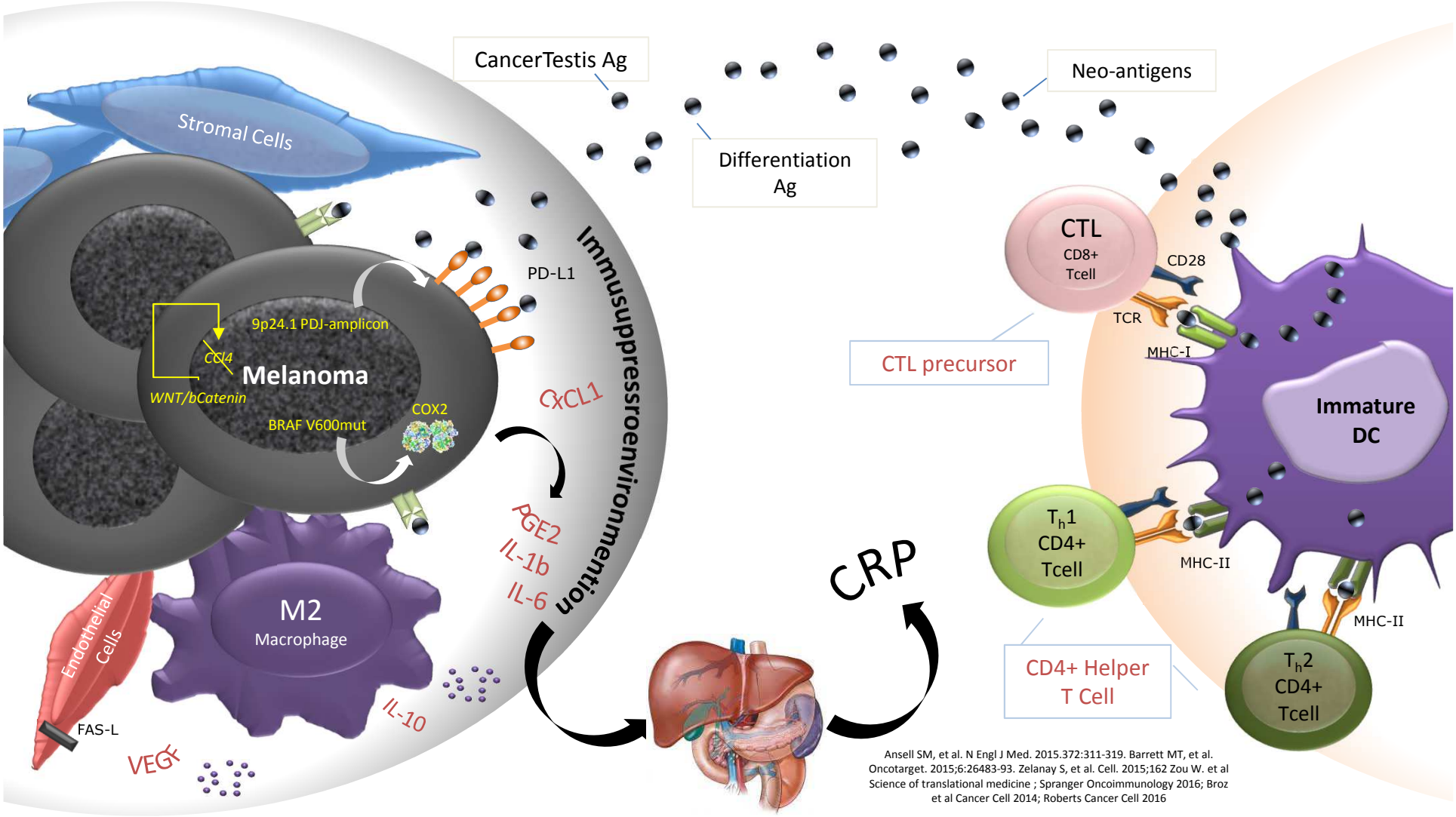


An integrated taxonomy of melanocytic neoplasia

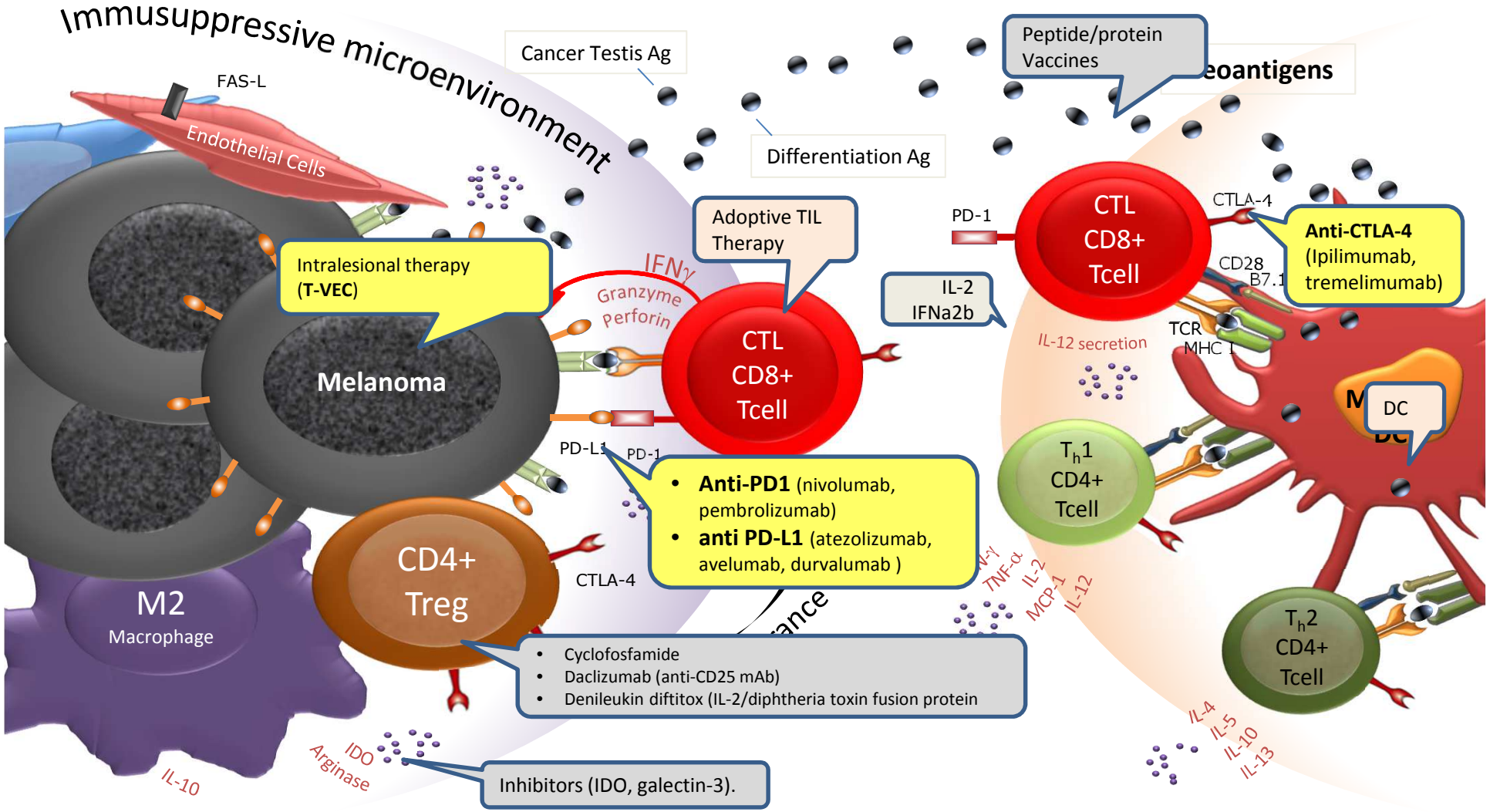
Hodis E et al. Cell 150, 251-263, July 20, 2012; Boris BC, Annu Rev Pathol 2014;9:239-71



Ansell SM, et al. N Engl J Med. 2015.372:311-319. Barrett MT, et al. Oncotarget. 2015;6:26483-93. Zelanay S, et al. Cell. 2015;162 Zou W. et al Science of translational medicine ; Spranger Oncoimmunology 2016; Broz et al Cancer Cell 2014; Roberts Cancer Cell 2016

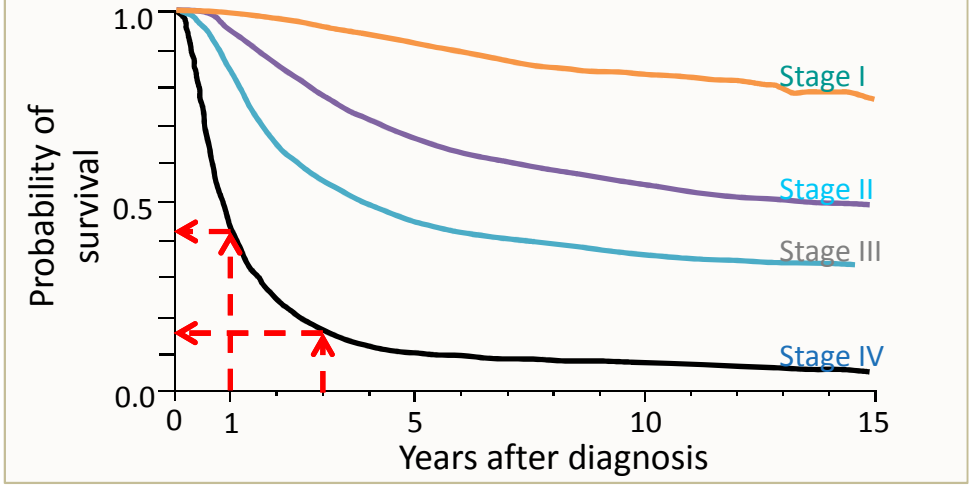


Ansell SM, et al. N Engl J Med. 2015.372:311-319. Barrett MT, et al. Oncotarget. 2015;6:26483-93. Zelanay S, et al. Cell. 2015;162 Zou W. et al Science of translational medicine ; Spranger Oncoimmunology 2016; Broz et al Cancer Cell 2014; Roberts Cancer Cell 2016


Immusuppressive microenvironment
FAS-L
Endothelial Cells
Cancer Testis Ag
Differentiation Ag
Peptide/protein Vaccines
eoantigens
Intralesional therapy (T-VEC)
Melanoma
Adoptive TIL Therapy
IFNγ
Granzyme
perforin
CTL CD8+ Tcell
PD-1
CTLA-4
Anti-CTLA-4 (Ipilimumab, tremelimumab)
CD28
B7.1
IL-2 IFNa2b
IL-12 secretion
TCR
MHC 1
DC
PD-L1
PD-1
• Anti-PD1 (nivolumab, pembrolizumab)
• anti PD-L1 (atezolizumab, avelumab, durvalumab)
Th1 CD4+ Tcell
CD4+ Treg
CTLA-4
M2 Macrophage
IFN-γ
TNF-α
IL-2
MCP-1
IL-12
Th2 CD4+ Tcell
IL-4
IL-5
IL-10
IL-13
• Cyclofosfamide
• Daclizumab (anti-CD25 mAb)
• Denileukin diftitox (IL-2/diphtheria toxin fusion protein
IDO
Arginase
IL-10
Inhibitors (IDO, galectin-3).

Prognosis of Melanoma following Surgery

- **Early disease[1]**
  - High proportion cured by surgery
- **Advanced disease[1]**
  - No systemic treatment (cytotoxic chemotherapy, IFNa2b, IL2) improved median survival for non-resectable stage IIIC–IV melanoma in a randomized trial before 2010
  - AJCC Stage IV
    - 1y OS <50%
    - 3y OS <20%

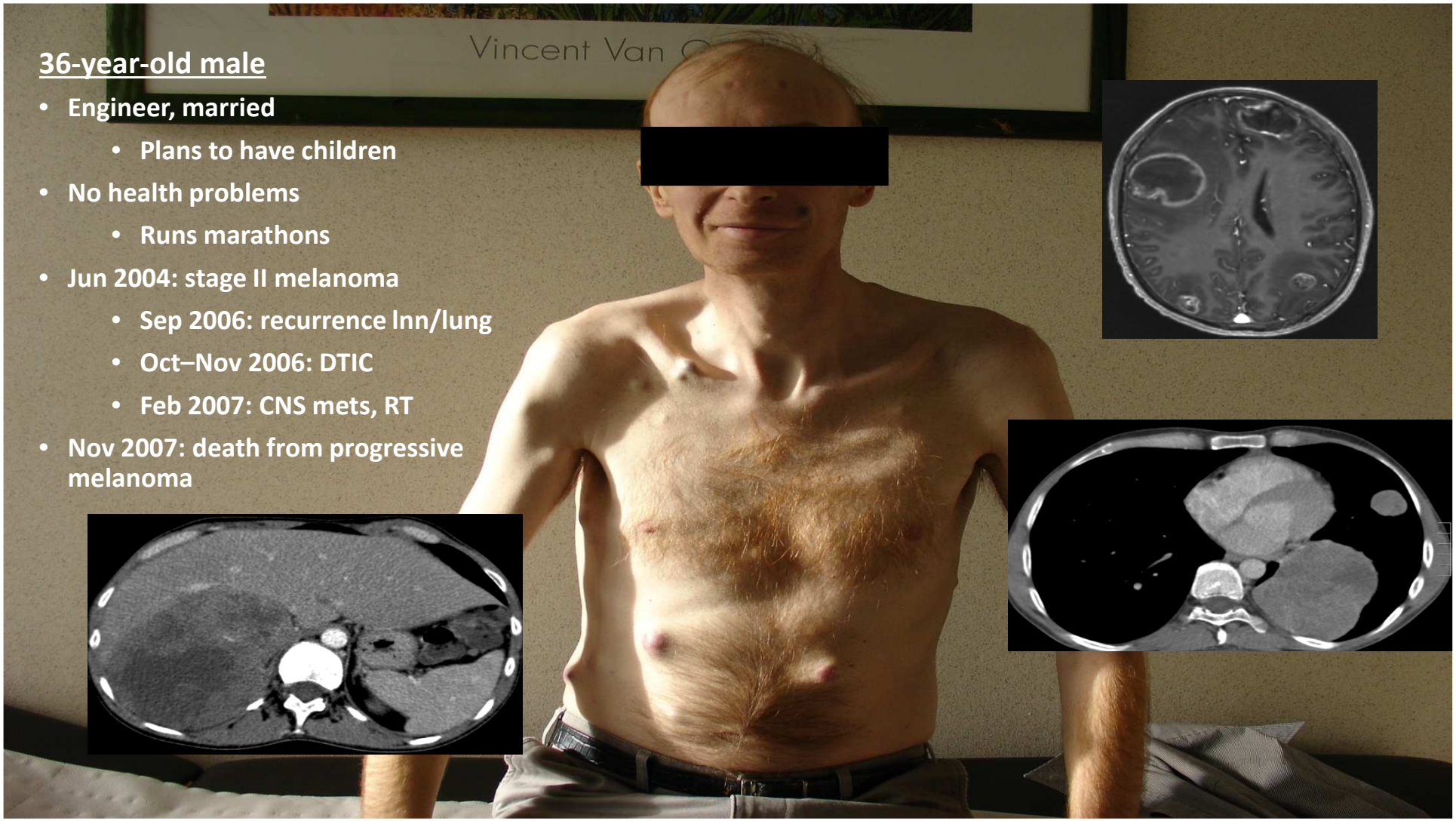


Relationship between the stage of melanoma and survival[2]
Kaplan–Meier survival curves are adapted from the American Joint Committee on Cancer.

1. Cancer Research UK. Available at http://www.cancerresearchuk.org/about-cancer/type/melanoma/. Accessed Nov 2014;
2. Adapted from Tsao H *et al. N Engl J Med* 2004; 351:998–1012.

36-year-old male

- Engineer, married
  - Plans to have children
- No health problems
  - Runs marathons
- Jun 2004: stage II melanoma
  - Sep 2006: recurrence lnn/lung
  - Oct–Nov 2006: DTIC
  - Feb 2007: CNS mets, RT
- Nov 2007: death from progressive melanoma

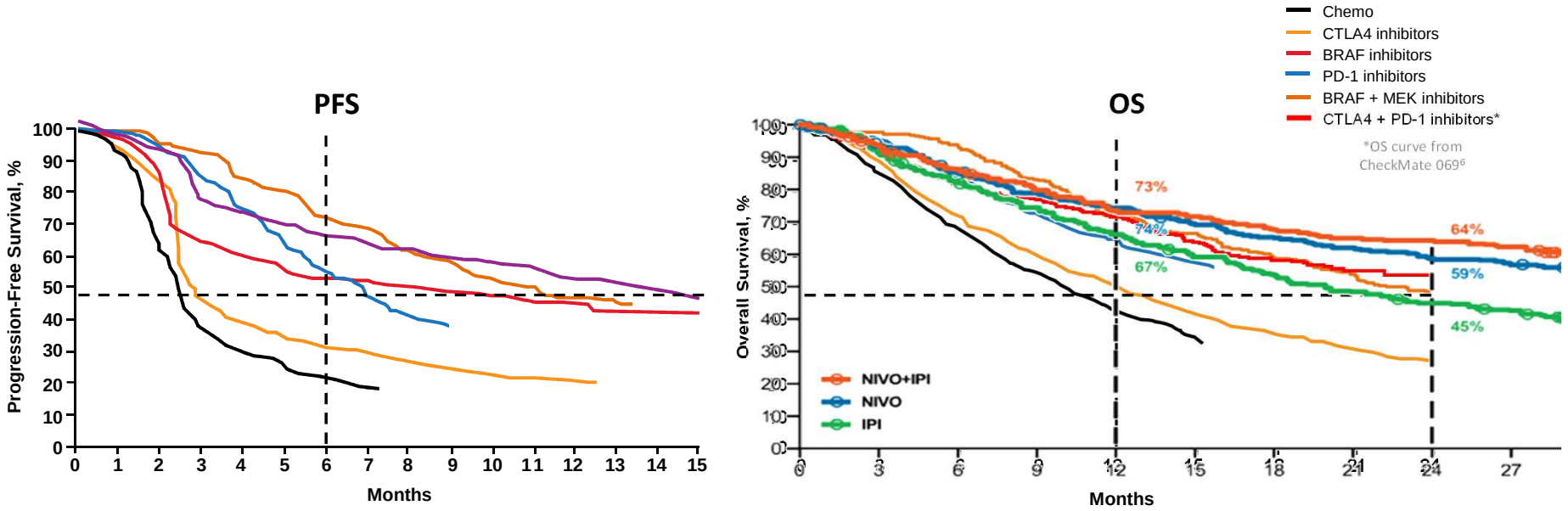


Results from Pivotal Phase III Clinical Trials Shaping the Therapeutic Landscape for Patients with Advanced Melanoma

	Cytotoxic Chemo-therapy	Immune Checkpoint Blockade				BRAF V600mut	Stage IIIC/IV-M1A
		CTLA-4 [2,4,5]	PD-1 blockade		PD-1+CTLA-4	BRAF/MEK-Inhibition [1,6,8,12]	Oncolytic Immunotherapy
	DTIC [3,7,8]	Ipilimumab	Pembrolizumab [4,11,13] (2 mg/kg q3w)	Nivolumab [9,14] (3 mg/kg q2w)	Nivolumab +ipilimumab [5,10]	Dabrafenib/Trametinib Vemurafenib/Cobi-metinib	T-VEC
ORR%	9.5%	11-19%	42%	44%	58%	64-68%	26%
mPFS (mths)	2.2	2.8-3.3	8.3	6.9	11.5	12.6	NR
mOS (mths)	10.8	13.5-16	32.3	36.9	*Not reached*	25.6	23.3
1y OS	42%	58%	68-74%	74%	73%	73%	74%
2y OS	17%	30%	55%	59%	64%	52-53%	50%
3y OS	12%	26%	50%	52%	58%	44-45%	39%
Gr 3-4 AE	17%	19-27%	17%	11-20%	54-58%	48-62%	11%

1. Larkin et al. NEJM 2015; 2. Robert et al NEJM 2015; 3. Robert et al NEJM 2014; 4.Schachter Lancet 2017; 5. Larkin NEJM 2014; 6. Long NEJM 2014;; 8. Maio et al JCO 2014; Ascierto et al MB 2015; 9. Long GV, et al. Oral presentation at: SMR 2015.; 10. Wolchok et al NEJM 2017; Schachter ASCO 2016; 12 Flaherty ASCO 2016; 13. C Robert ASCO 2016; 14. Hodi S Lancet Oncol 2018; Andtbacka,et al JCO

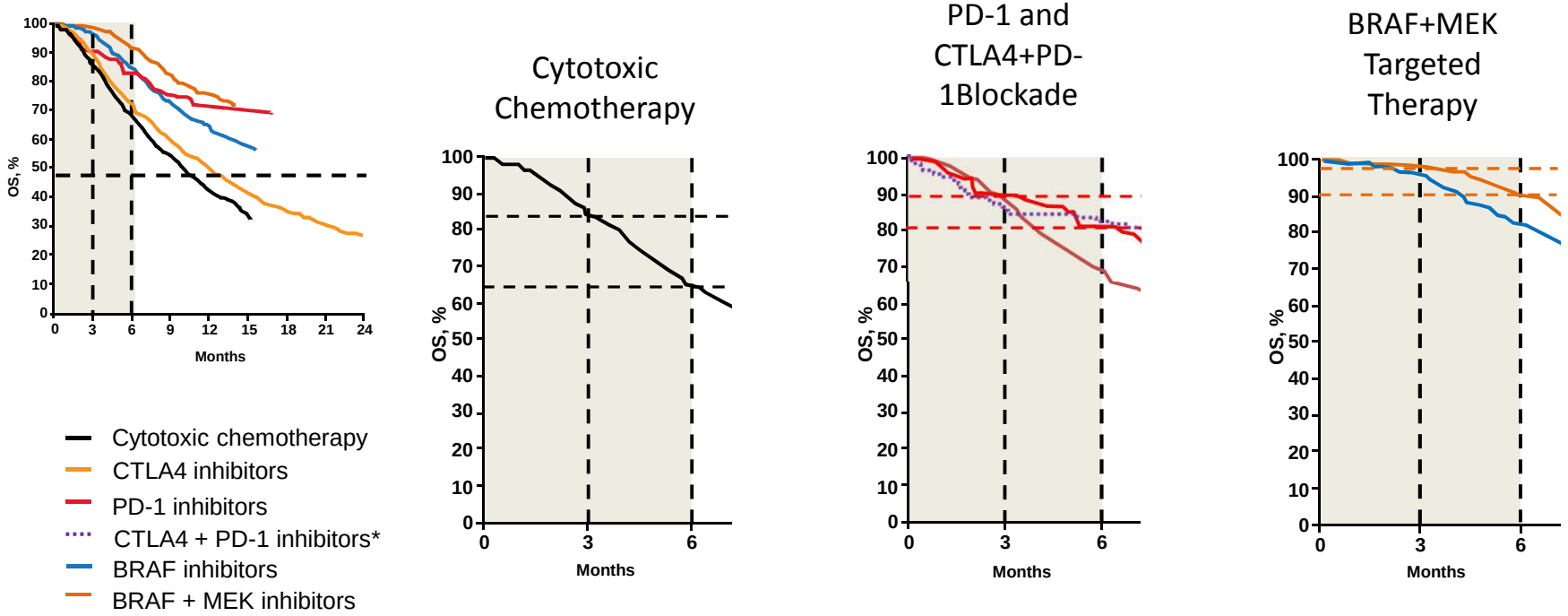
Survival Outcome for Patients With Advanced Melanoma According to Therapy



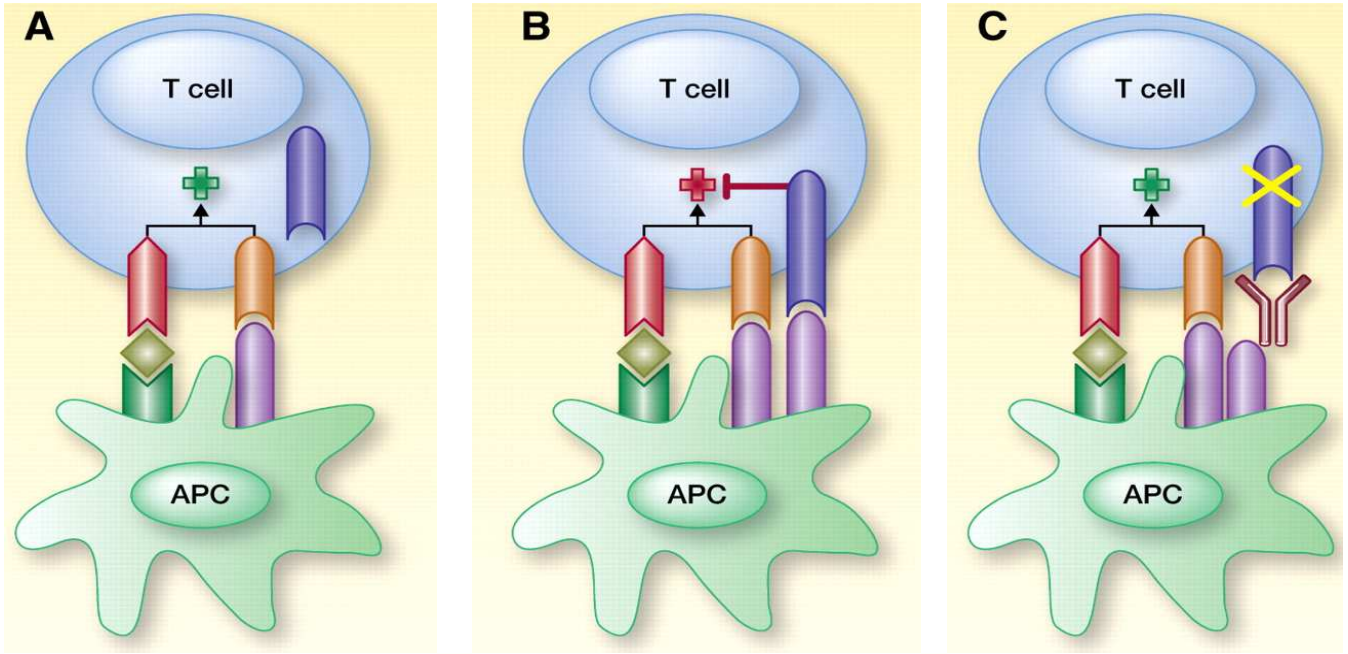
	Chemotherapy	CTLA4 Inhibitors	BRAF Inhibitors	PD-1 Inhibitors	BRAF + MEK Inhibitors	CTLA4 + PD-1 Inhibitors
6-mo PFS (95% CI), %[1]	22.1 (19.1-25.0)	31.0 (27.0-35.1)	56.0 (53.3-58.8)	51.0 (46.4-55.6)	71.6 (68.2-75.0)	63.8 (58.7-68.9)
1-y OS (95% CI), %[1]	42.2 (37.2-47.2)	50.1 (45.4-54.8)	64.4 (58.1-70.7)	71.9 (60.7-83.0)	74.5 (70.7-78.4)	ND
First approval[2-5]	Pre-1960s	2011	2011	2014	2014	2015

ND, not determined; OS, overall survival; PFS, progression-free survival. 1. Ugurel S, et al. *Eur J Cancer*. 2016;53:125-134. 2. http://www.cancerprogress.net/timeline/melanoma. Accessed October 4, 2016.
3. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm412802.htm. Accessed October 4, 2016. 4. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm381159.htm. Accessed October 4, 2016.
5. http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm465274.htm. Accessed October 4, 2016; 6. Hodi FS, et al. *Lancet Oncol*. 2016 Sept 9. [Epub ahead of print]

Six-months Overall Survival on Approved First-line Treatment Options



Adapted from Ugurel S, et al. *Eur J Cancer*. 2016;53:125-134.; *OS curve from CheckMate 069 Hodi FS, et al. *Lancet Oncol*. 2016 Sept 9.



Adapted from Postow M A et al. Clin Cancer Res 2012

Best objective tumor response following induction therapy

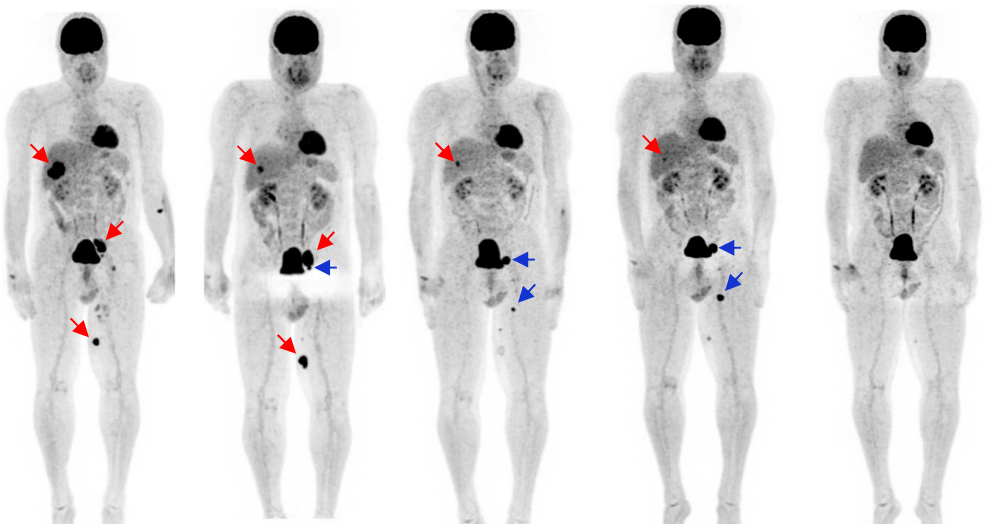
	EAP UZ Brussel N=50		Hodi et al. N=137	Wolchok et al. N=72
	mWHO % (No.)	irRC % (No.)	mWHO %	mWHO %
CR	**2** (1)	**2** (1)	**1,5**	**0**
PR	**8** (4)	**12** (6)	**9,5**	**4,2**
SD	**6** (3)	**6** (3)	**17,5**	**22,2**
BORR	***10***	***14***	***11***	***4,2***
DCR	***16***	***20***	***28,5***	***26,4***

*** Tumor response assessment by total body 18FDG-PET/CT**

Wilgenhof S et al. J Immunother. 2013 Apr;36(3):215-22

Case Illustration 2 – complete response by irRC

61y M acral ulcerated cKIT-wt melanoma on the third toe of his left foot in Jan 2009 (pT4bN1Mx)
April 2010: stage IV-M1c disease with liver, lymph node and subcutaneous metastases
PD following 2x DTIC



Baseline	12 weeks	24 weeks	43 weeks (pre re-induction)	56 weeks (post re-induction)
20/08/2010	17/11/2010	15/02/2011	28/06/2011	27/09//2011

Wilgenhof S. et al. Cancer Invest. 2012 Dec 7; 30(10): 712–720.

Case Illustration 2 – Early PD followed by regression

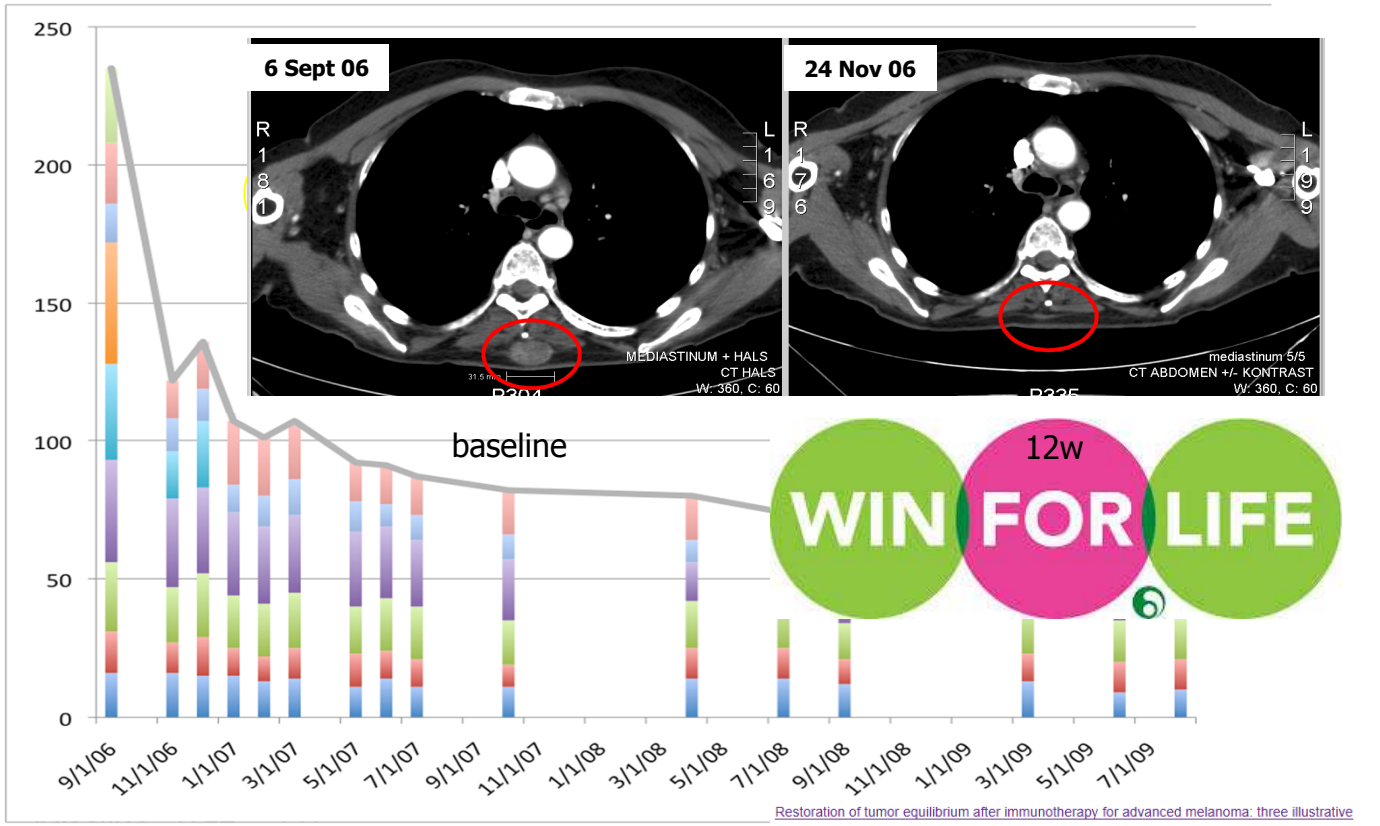
Pre-treatment

During treatment
(3 weeks)

1 year
Post-treatment

Wilgenhof S. et al. Cancer Invest. 2012 Dec 7; 30(10): 712–720.

Durable Disease Control on Ipilimumab

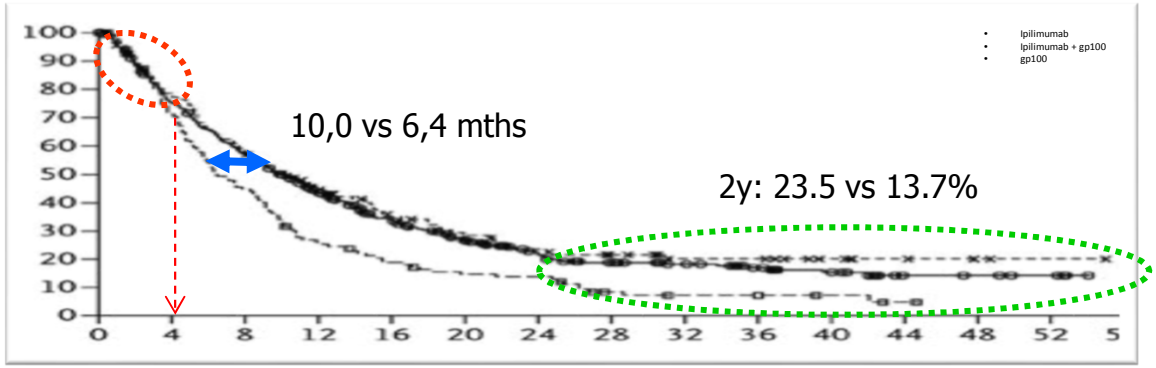


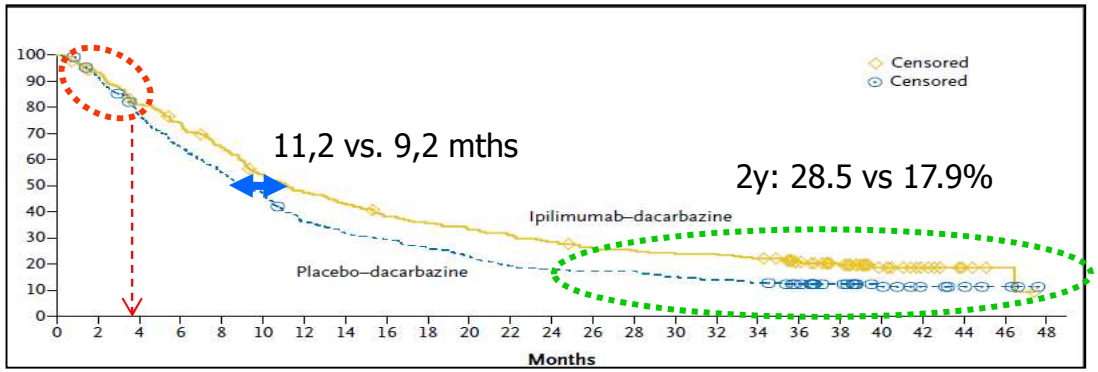
Restoration of tumor equilibrium after immunotherapy for advanced melanoma: three illustrative cases.

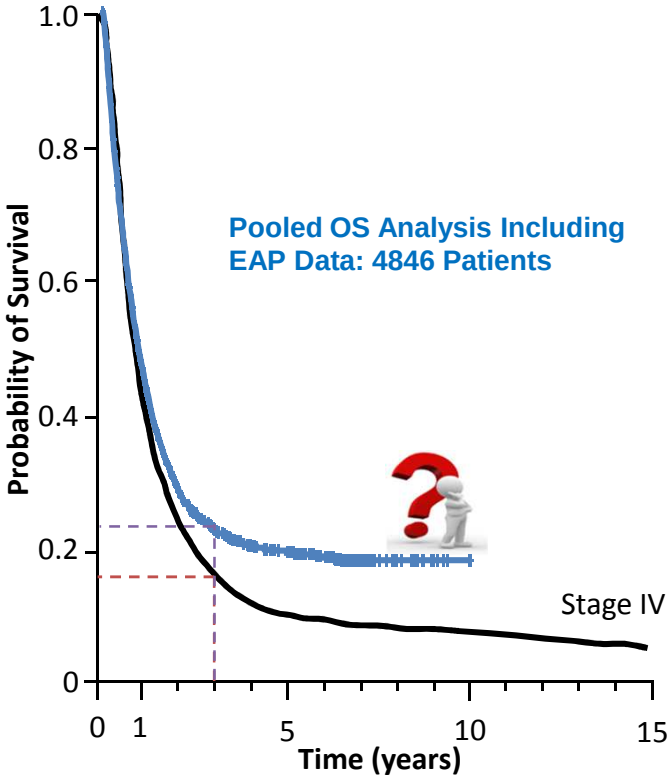
Wilgenhof S, **Pierret** L, Corthals J, Van Nuffel AM, Heirman C, Roelandt T, De Coninck A, Verfaillie G, Vandenbroucke F, Van Riet I, Bonehill A, Thielemans K, **Neyns** B.

Melanoma Res. 2011 Apr;21(2):152-9. doi: 10.1097/CMR.0b013e328343ece0.

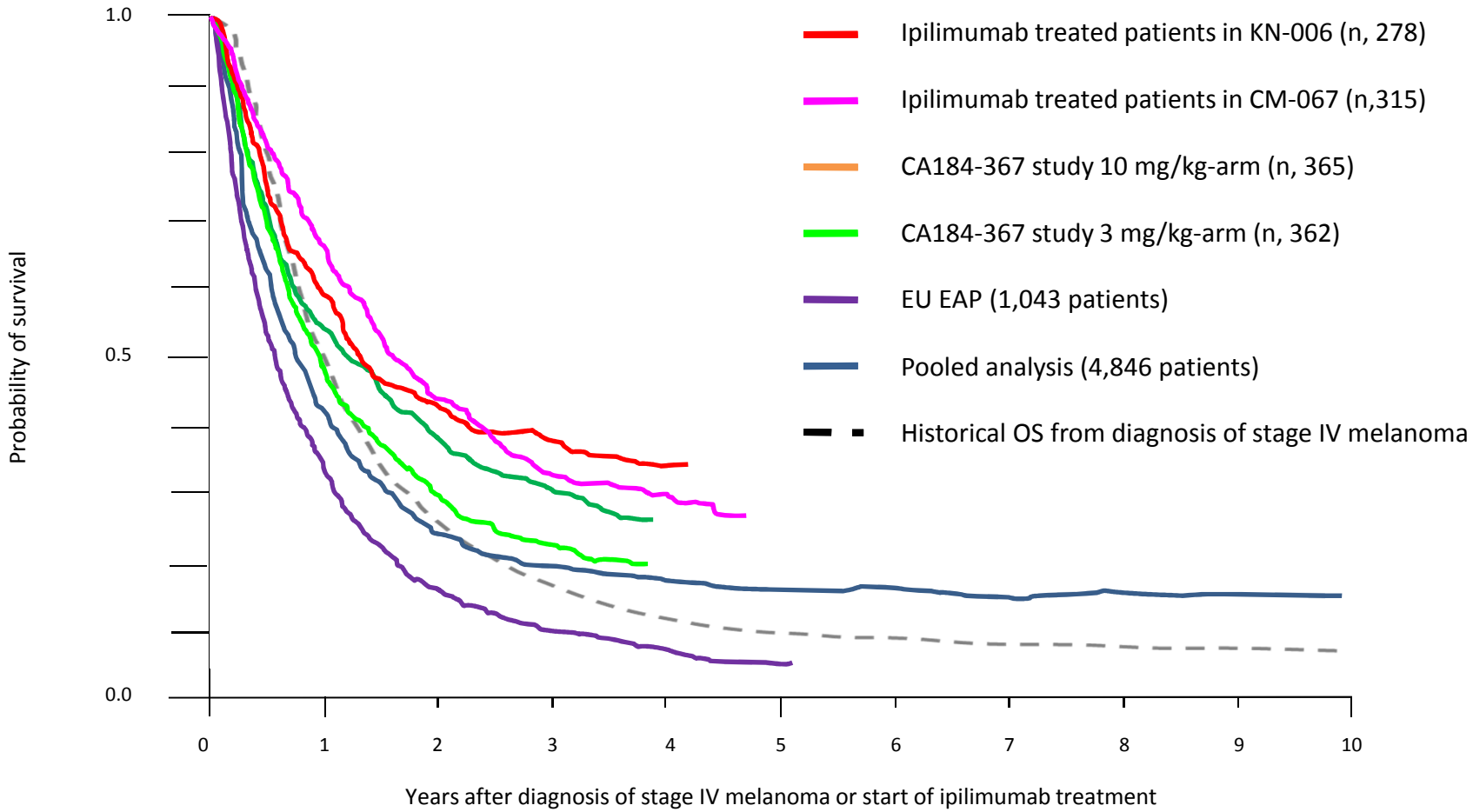
Long-term survival benefit from ipilimumab

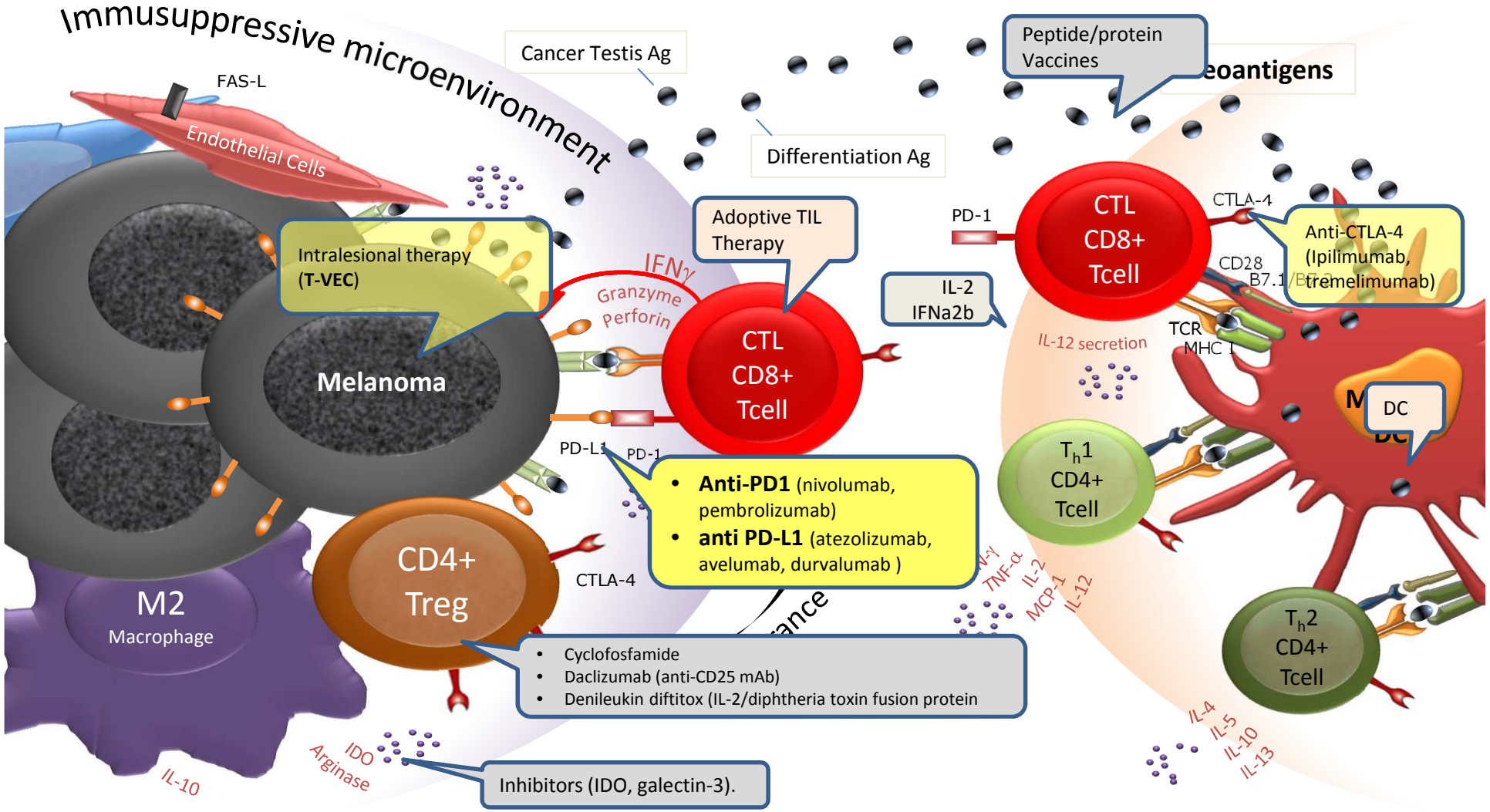






Robert et al. NEJM, 2011; Hodi et al. NEJM, 2010; Hodi S. et al ECC 2013; Schadendorf JCO 2014; . Adapted from Tsao H et al. N Engl J Med 2004


1.0
0.5
0.0
Probability of survival
0
1
2
3
4
5
6
7
8
9
10
Years after diagnosis of stage IV melanoma or start of ipilimumab treatment
Ipilimumab treated patients in KN-006 (n, 278)
Ipilimumab treated patients in CM-067 (n,315)
CA184-367 study 10 mg/kg-arm (n, 365)
CA184-367 study 3 mg/kg-arm (n, 362)
EU EAP (1,043 patients)
Pooled analysis (4,846 patients)
Historical OS from diagnosis of stage IV melanoma


Immusuppressive microenvironment
FAS-L
Endothelial Cells
Cancer Testis Ag
Differentiation Ag
Peptide/protein Vaccines
eoantigens
Intralesional therapy (T-VEC)
Melanoma
Adoptive TIL Therapy
IFNγ
Granzyme
perforin
CTL CD8+ Tcell
PD-1
CTL CD8+ Tcell
CTLA-4
Anti-CTLA-4 (Ipilimumab, tremelimumab)
CD28
B7.1/B7.2
IL-2 IFNa2b
IL-12 secretion
TCR
MHC 1
DC
PD-L1
PD-1
• Anti-PD1 (nivolumab, pembrolizumab)
• anti PD-L1 (atezolizumab, avelumab, durvalumab)
Th1 CD4+ Tcell
CD4+ Treg
CTLA-4
M2 Macrophage
IFN-γ
TNF-α
IL-2
MCP-1
IL-12
Th2 CD4+ Tcell
• Cyclofosfamide
• Daclizumab (anti-CD25 mAb)
• Denileukin diftitox (IL-2/diphtheria toxin fusion protein
IL-4
IL-5
IL-10
IL-13
IL-10
IDO
Arginase
Inhibitors (IDO, galectin-3).

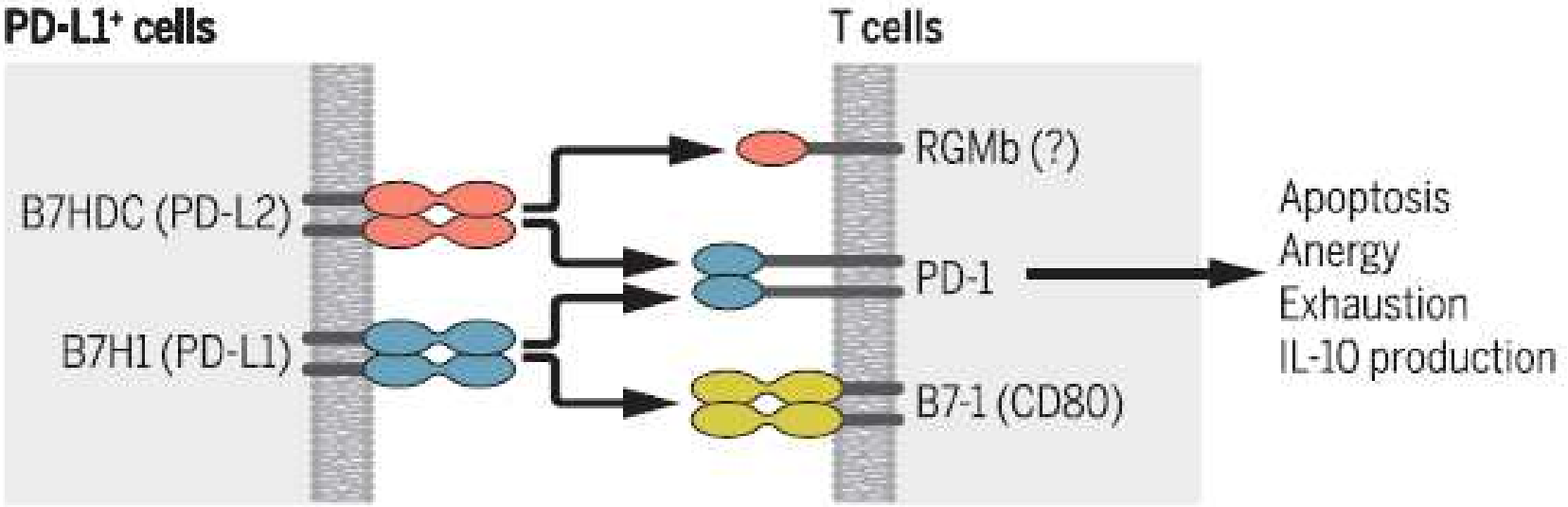


Fig. 1. Mechanisms of action of the PD-L1 and PD-1 pathway. Cells that express high levels of PD-L1 may include tumor cells, APCs (DCs, macrophages, MDSCs, and B cells), T lymphocytes, epithelial cells, fibroblasts, and others. Engagement of PD-L1 by PD-L1$^+$ cells induces T cell apoptosis, anergy, functional exhaustion, or IL-10 production.

Response (irRC, investigator review)

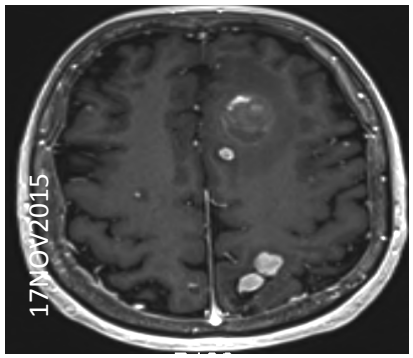
	All Patients		Treatment Naive	
	Pembrolizumab n = 556	**Ipilimumab n = 278**	**Pembrolizumab n = 368**	**Ipilimumab n = 181**
	n (%)	n (%)	n (%)	n (%)
ORR	236 (42)	46 (17)	171 (47)	31 (17)
CR	76 (14)	9 (3)	61 (17)	6 (3)
PR	160 (29)	37 (13)	110 (30)	25 (14)
SD	116 (21)	70 (25)	69 (19)	45 (25)
PD	163 (29)	107 (39)	97 (26)	75 (41)

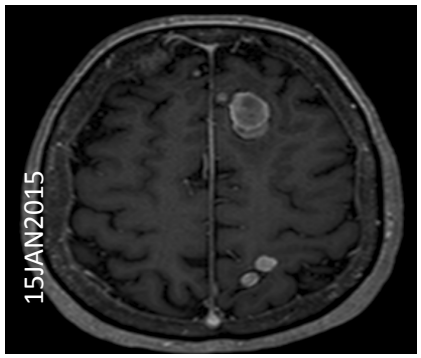
- Median follow-up: 45.9 (range, 0.3-50.0) months

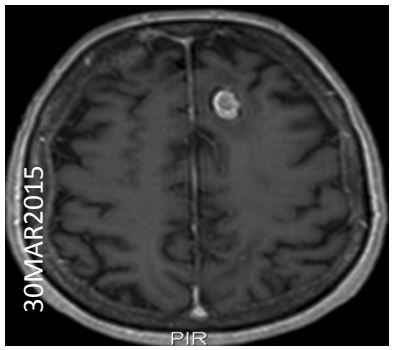
Data cutoff: Dec 4, 2017.

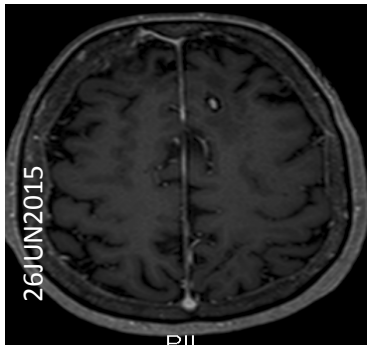
Response to anti-PD-1 (pemrolizumab MNP) in a patient with melanoma brain metastases and high tumor burden

72y F, stage IV-M1c
BRAF V600E, failed Vemurafenib, WBRT
Baseline CRP 6 mg/dl, LDH 836 mg/dl





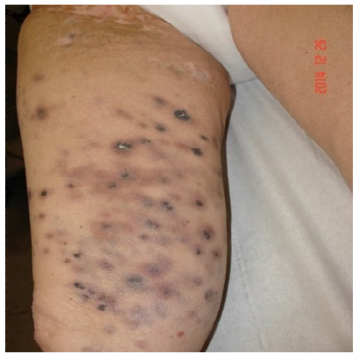




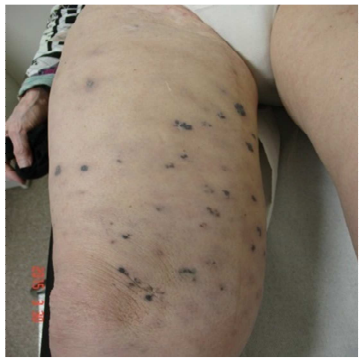
17NOV2014

2 administrations of pembrolizumab

9DEC2014



26DEC2014



30MAR2015

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

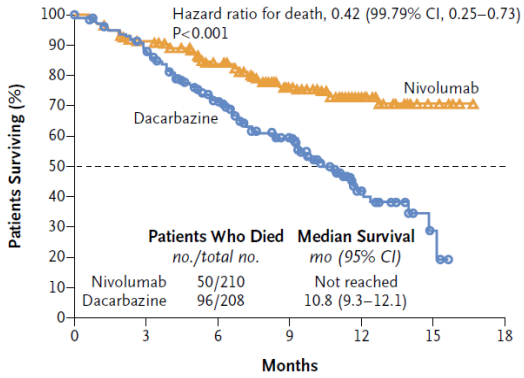
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab in Previously Untreated Melanoma without *BRAF* Mutation

Caroline Robert, M.D., Ph.D., Georgina V. Long, M.D., Ph.D., Benjamin Brady, M.D., Caroline Dutriaux, M.D., Michele Maio, M.D., Laurent Mortier, M.D., Jessica C. Hassel, M.D., Piotr Rutkowski, M.D., Ph.D., Catriona McNeil, M.D., Ph.D., Ewa Kalinka-Warzocha, M.D., Ph.D., Kerry J. Savage, M.D.,

A Overall Survival



No. at Risk

Nivolumab	210	185	150	105	45	8	0
Dacarbazine	208	177	123	82	22	3	0

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

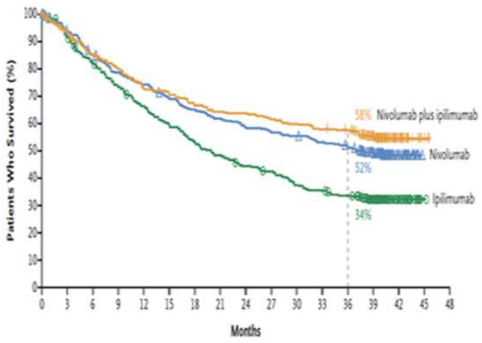
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma

J.D. Wolchok, V. Chiarion-Sileni, R. Gonzalez, P. Rutkowski, J.-J. Grob, C.L. Cowey, C.D. Lao, J. Wagstaff, D. Schadendorf, P.F. Ferrucci, M. Smylie, R. Dummer, A. Hill, D. Hogg, J. Haanen, M.S. Carlino, O. Bechter, M. Maio, I. Marquez-Rodas, M. Guidoboni, G. McArthur, C. Lebbé, P.A. Ascierto, G.V. Long, J. Cebon, J. Sosman, M.A. Postow, M.K. Callahan, D. Walker, L. Rollin, R. Bhore, F.S. Hodi, and J. Larkin

B Overall Survival



No. at Risk

Nivolumab plus ipilimumab	314	292	265	247	226	221	209	200	198	192	186	180	177	131	27	3	0						
Nivolumab	316	292	265	244	230	213	201	191	181	175	171	163	156	120	28	0	0						
Ipilimumab	315	285	253	227	203	181	163	148	135	128	117	107	100	68	20	2	0						

This article was published on September 11, 2017, at NEJM.org.

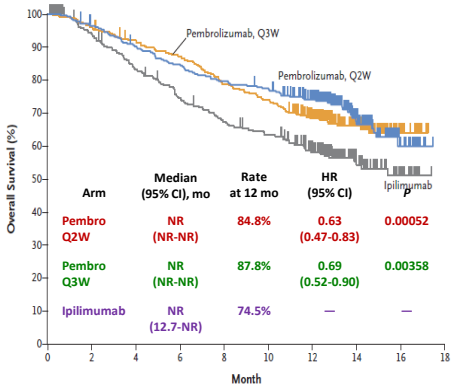
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab versus Ipilimumab in Advanced Melanoma

Caroline Robert, M.D., Ph.D., Jacob Schachter, M.D., Georgina V. Long, M.D., Ph.D., Ana Arance, M.D., Ph.D., Jean Jacques Grob, M.D., Ph.D., Laurent Mortier, M.D., Ph.D., Adil Daud, M.D., Matteo S. Carlino, M.B., B.S., Catriona McNeil, M.D., Ph.D.,

B Overall Survival

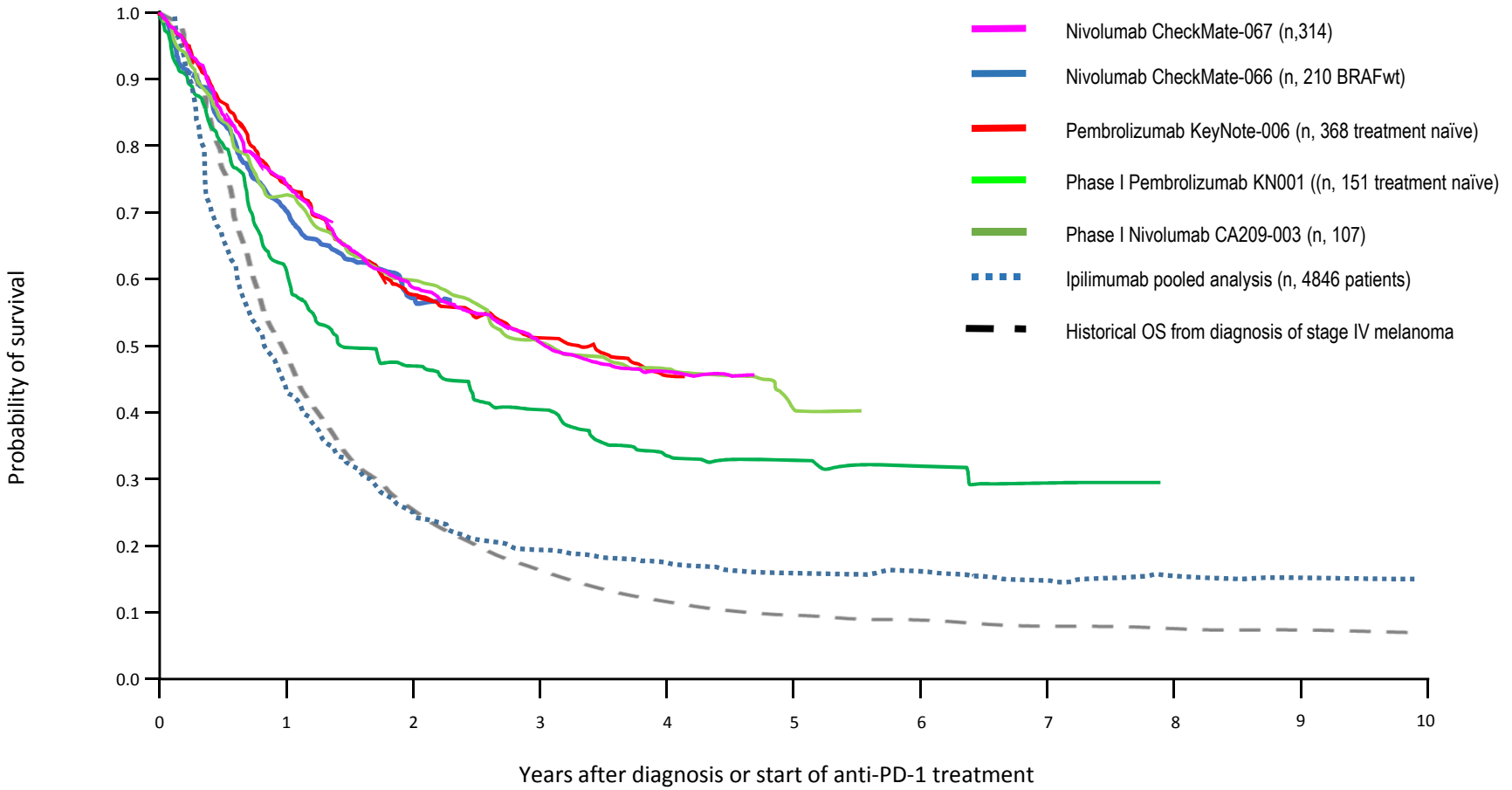


Arm	Median (95% CI), mo	Rate at 12 mo	HR (95% CI)	P
Pembro Q2W	NR (NR-NR)	84.8%	0.63 (0.47-0.83)	0.00052
Pembro Q3W	NR (NR-NR)	87.8%	0.69 (0.52-0.90)	0.00358
Ipilimumab	NR (12.7-NR)	74.5%	—	—

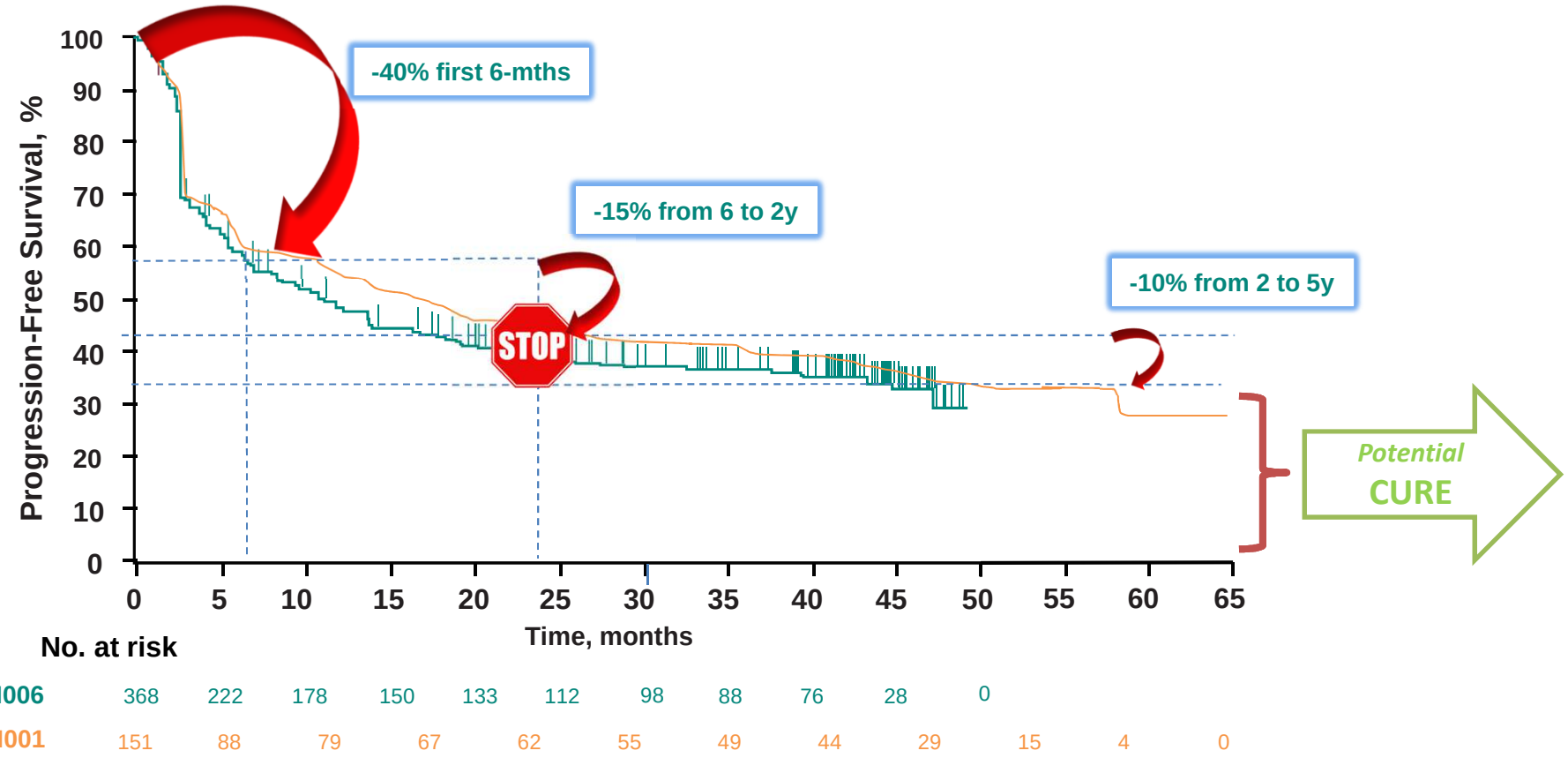
No. at Risk

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

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


Probability of survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
1
2
3
4
5
6
7
8
9
10
Years after diagnosis or start of anti-PD-1 treatment
Nivolumab CheckMate-067 (n,314)
Nivolumab CheckMate-066 (n, 210 BRAFwt)
Pembrolizumab KeyNote-006 (n, 368 treatment naïve)
Phase I Pembrolizumab KN001 ((n, 151 treatment naïve)
Phase I Nivolumab CA209-003 (n, 107)
Ipilimumab pooled analysis (n, 4846 patients)
Historical OS from diagnosis of stage IV melanoma

Overlay Progression-Free Survival of Treatment-Naive Patients in KN001 and KN006



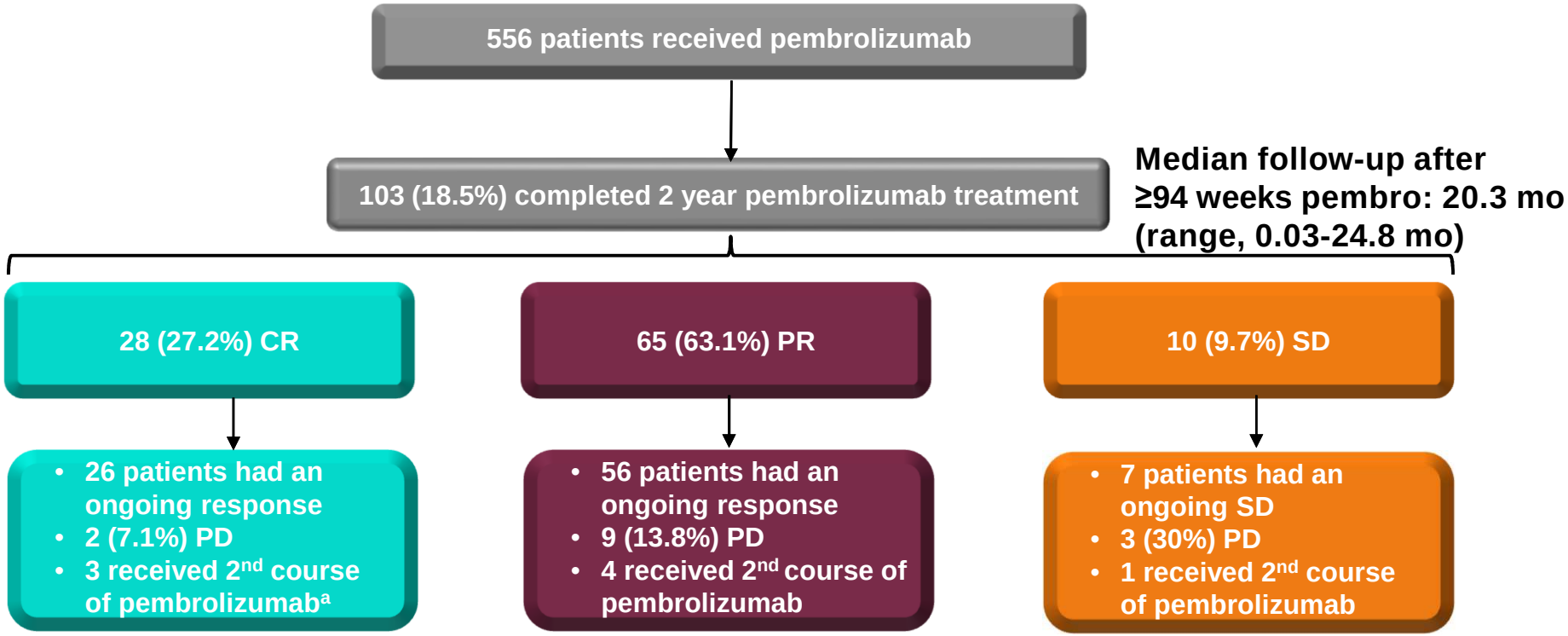
[a]Per immune-related response criteria by investigator review. [b]Based on Cox regression model with treatment as covariate stratified by line of therapy (1st vs 2nd), PD-L1 status (positive vs negative), and ECOG (0 vs 1); if no patients are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum was excluded from treatment comparison. [c]Derived by the product-limit (Kaplan-Meier) method for censored data. Data cutoff: Dec 4, 2017.

Outcome of advanced melanoma patients stopping treatment in the absence of disease progression

	Study	Patient #	Reason for stopping therapy	FU post treatments stop (months)	PFS%
PD-1 inhibitor	Phase I Nivolumab[6]	17	Other than PD during response	≥ 4	71%
	Phase I Pembrolizumab (Keynote-001)[1]	67	CR	10	97%
	Phase III Pembrolizumab (Keynote-006)[2]	104	After 2 years of therapy (protocol defined)	9.7	91%
	Pembrolizumab-Real World[3]	189	Other than PD or AE	12	97%
BRAF-/MEK-inhibitors	Cohort-study[4]	12	Other than PD	6.6	50%
	Cohort-study[5]	12	Other than PD	3	50%

[1] Robert, JCO 2017; [2] Robert, ASCO 2017, Abstract 9504; [3] Jansen, SMR 2017;
[4] Carlino, *Br J Cancer* 2016; [5] Tolk, *Mel Res* 2015; [6] Topalian et al JCO 2014

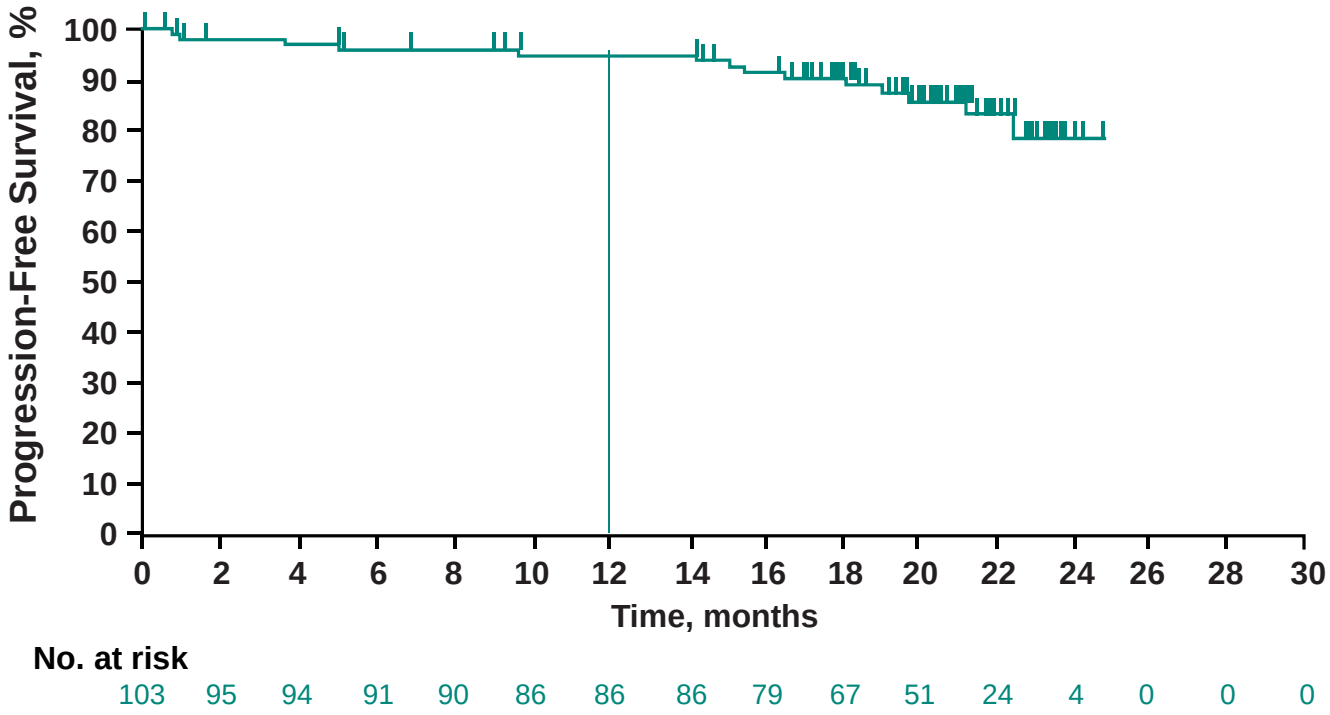
Disposition of Patients Completing ≥94 Weeks of Pembrolizumab Treatment



[a]Includes 1 patient who discontinued early with CR and then progressed. Data cutoff: Dec 4, 2017.

Long G. et al ASCO AM 2018

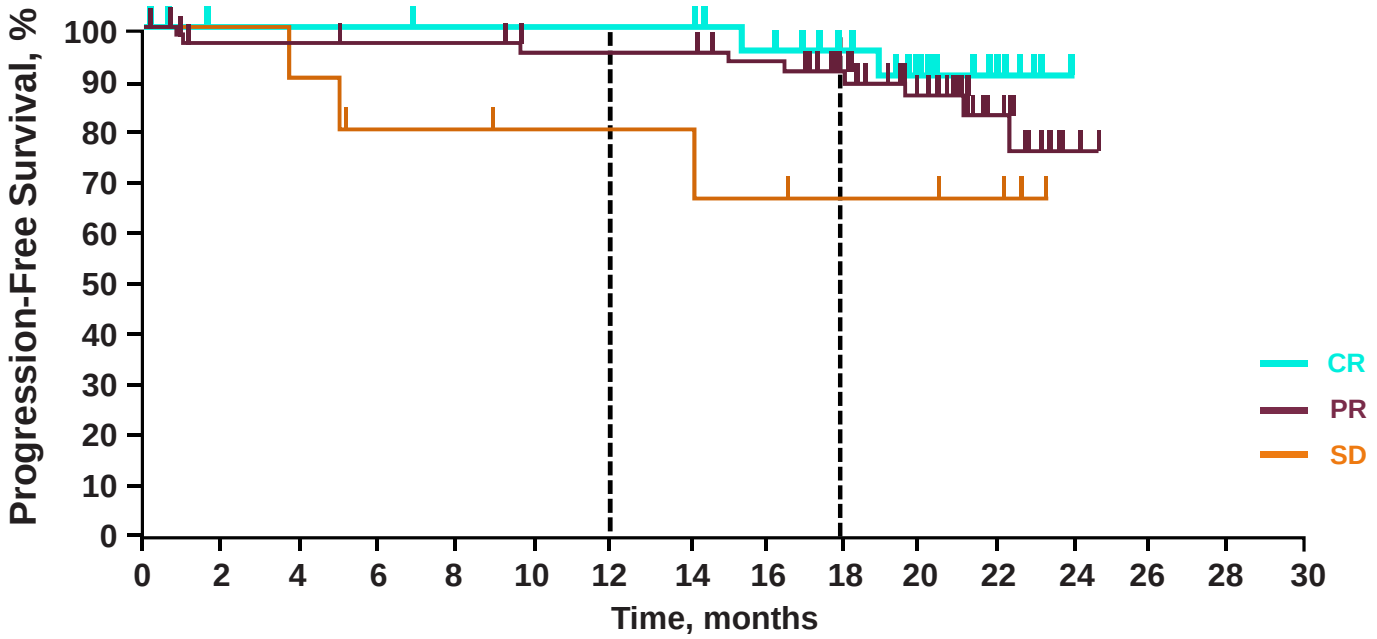
PFS[a] in Patients Who Completed the 2y Protocol-Specified Time on Pembrolizumab (n = 103)



[a]Per immune-related response criteria by investigator review. Data cutoff: Dec 4, 2017.

Long G. et al ASCO AM 2018

PFS[a] in Patients Who Completed Protocol-Specified Time on Pembrolizumab (n = 103)



No. at risk

CR	28	27	27	27	26	26	26	26	23	19	15	6	1	0	0	0
PR	65	58	58	57	57	54	51	54	51	44	32	15	3	0	0	0
SD	10	10	9	7	7	6	6	6	5	4	4	3	0	0	0	0

[a]Per immune-related response criteria by investigator review. Data cutoff: Dec 4, 2017.

Long G. et al ASCO AM 2018

Utility of 1-year FDG-PET (PET) to determine outcomes from anti-PD-1 (PD1) based therapy in patients (pts) with metastatic melanoma (MM)

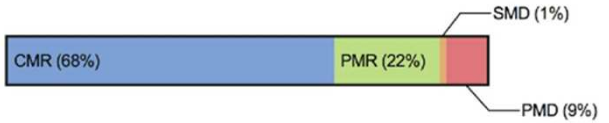
Aaron C. Tan[1,2], Louise Emmett[1,3,4], Serigne Lo[1], Victor Liu[3], Alexander D. Guminski[1,2,5], Georgina V. Long[1,2,5], Alexander M. Menzies[1,2,5]
[1]Melanoma Institute Australia and The University of Sydney; [2]Royal North Shore Hospital; [3]St Vincent's Hospital; [4]The University of New South Wales; [5]Mater Hospital

- Retrospective analysis of metastatic melanoma patients treated with anti-PD-1 with baseline and 1-year 18F-FDG PET and CT imaging at Melanoma Institute Australia
- 1-year response was determined using RECIST for CT and EORTC criteria for PET
- 104 patients were evaluated with median follow-up 30.1 months and 98% remain alive
- Most received anti-PD-1 as monotherapy (67%) or combined with ipilimumab (31%)
- At 1-year, 28% had CR, 66% had PR and 6% had SD on CT, while 75% had CMR, 16% PMR and 9% SMD/PMD on PET
- CMR was observed in 68% of patients with PR on CT

Table 2. Correlation of CT and PET response at 1 year

		No. of pts (%)			
		CT response at 1 year			
		CR	PR	SD	Total
PET response at 1 year	CMR	27 (26)	47 (45)	2 (2)	76 (73)
	PMR	2 (2)	15 (14)	2 (2)	19 (18)
	SMD	0 (0)	1 (1)	0 (0)	1 (1)
	PMD	0 (0)	6 (6)	2 (2)	8 (8)
	Total	29 (28)	69 (66)	6 (6)	

Figure 1. PET response in pts with PR on CT



Tan et al. ASCO AM 2018; Tan et al. *Annals of Oncology 2018*

Melanoma Institute Australia

Utility of 1-year FDG-PET (PET) to determine outcomes from anti-PD-1 (PD1) based therapy in patients (pts) with metastatic melanoma (MM)

Aaron C. Tan[1,2], Louise Emmett[1,3,4], Serigne Lo[1], Victor Liu[3], Alexander D. Guminski[1,2,5], Georgina V. Long[1,2,5], Alexander M. Menzies[1,2,5]
[1]Melanoma Institute Australia and The University of Sydney; [2]Royal North Shore Hospital; [3]St Vincent's Hospital; [4]The University of New South Wales; [5]Mater Hospital

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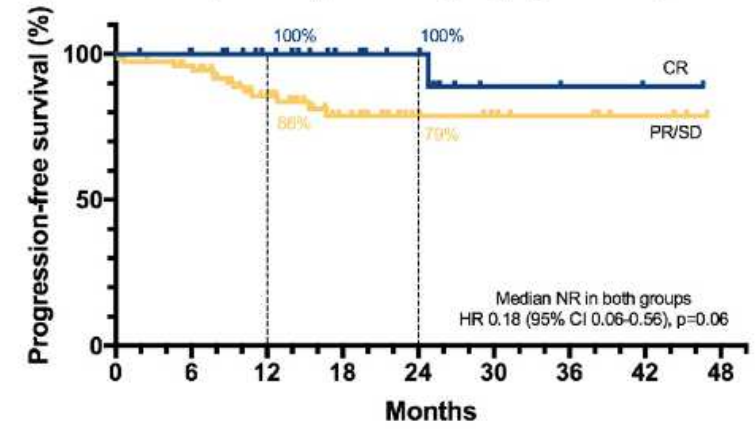
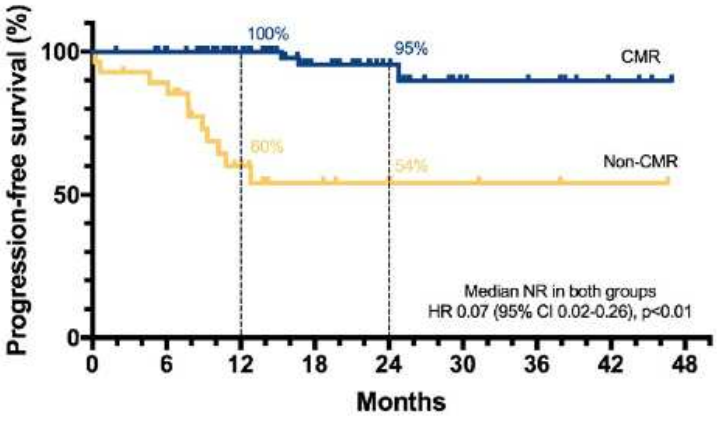
- RECIST PFS post 1-year landmark was similar in patients with CR vs PR/SD, but improved in patients with CMR vs non-CMR (median not reached [NR] vs 12.8 mths; HR 0.06 [95% CI 0.02-0.23]; p<0.01)
- In the 78 CMR patients, 78% had discontinued treatment and 96% had ongoing response.

Figure 2. PFS post 1-year imaging by CT response



No. at risk								
CR	29	27	21	15	11	4	3	2
PR/SD	75	70	51	30	13	10	8	4

Figure 3. PFS post 1-year imaging by PET response



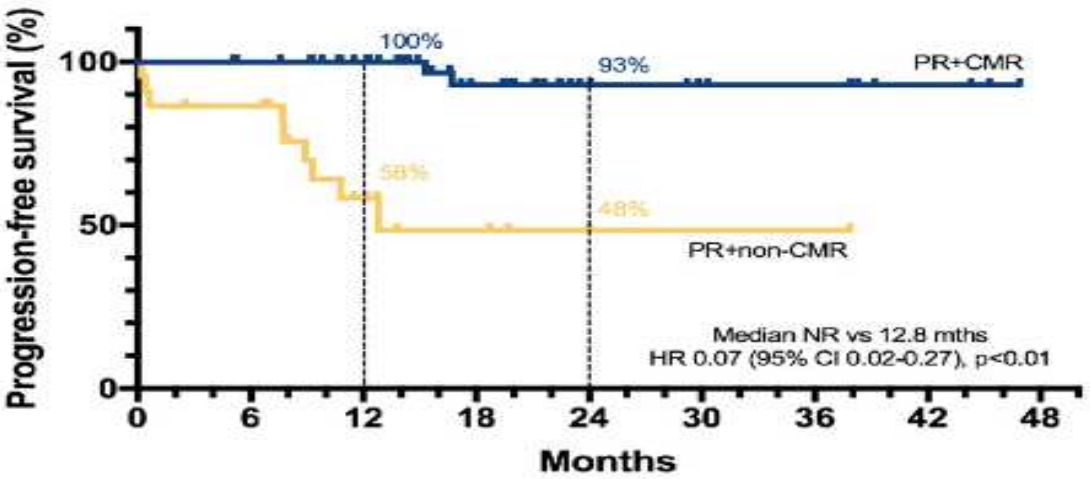
No. at risk								
CMR	76	72	58	37	19	9	8	4
Non-CMR	28	26	13	8	5	4	3	2

Tan et al. ASCO AM 2018; Tan et al. *Annals of Oncology 2018*

Aaron C. Tan[1,2], Louise Emmett[1,3,4], Serigne Lo[1], Victor Liu[3], Alexander D. Guminski[1,2,5], Georgina V. Long[1,2,5], Alexander M. Menzies[1,2,5]
[1]Melanoma Institute Australia and The University of Sydney; [2]Royal North Shore Hospital; [3]St Vincent's Hospital; [4]The University of New South Wales; [5]Mater Hospital

In patients with PR on CT, PFS was improved in patients with PR+CMR vs PR+non-CMR (median NR vs 12.8 months; HR 0.07 [95% CI 0.02-0.27]; p<0.01).

Figure 4. PFS post 1-year imaging in pts with PR on CT



No. at risk								
PR+CMR	47	46	39	24	11	8	7	4
PR+non-CMR	22	19	9	5	2	2	2	1

Tan et al. ASCO AM 2018; Tan et al. *Annals of Oncology 2018*

Real life outcome of advanced melanoma patients who discontinue pembrolizumab in the absence of disease progression

Yanina Jansen, Elisa A. Rozeman, Marnix Geukes Foppen, Lars Bastholt, Henrik Schmidt, Johannes v. Van Thienen, John B. A. G. Haanen, Leena Tiainen, Inge Marie Svane, Siru Päivikki Mäkelä, Ana Arance, Lise Hoejberg, Marta Nyakas, Oddbjorn Straume, Christian U. Blank, Bart Neyns

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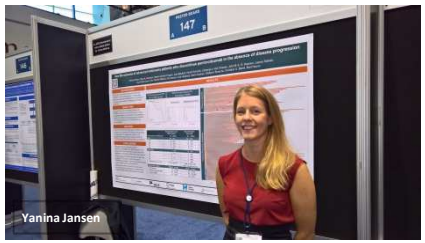
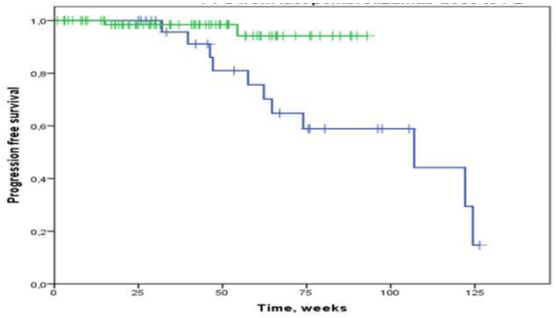
- 509 pts with advanced melanoma treated with PEMBRO outside of an interventional clinical trial at 9 European hospitals
- 40 pts (8%) PEMBRO ongoing
- 343 pts (67%) stopped @PD
- 108 pts (21%) stopped in absence of PD
  - 81 (16%) Pt/MD decision
  - 29 (6%)@AE

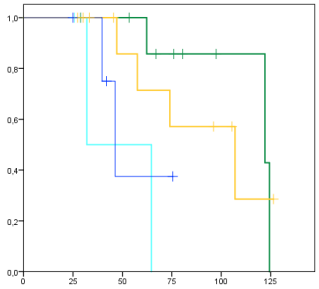


PFS from last dose to PD: AE vs Pt/MD decision



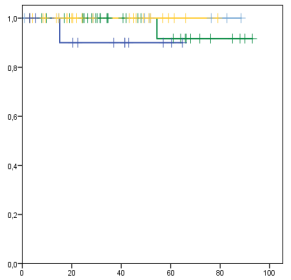
PFS from last dose to PD: according to BORR

Adverse event



Time, weeks

Patient/physician choice



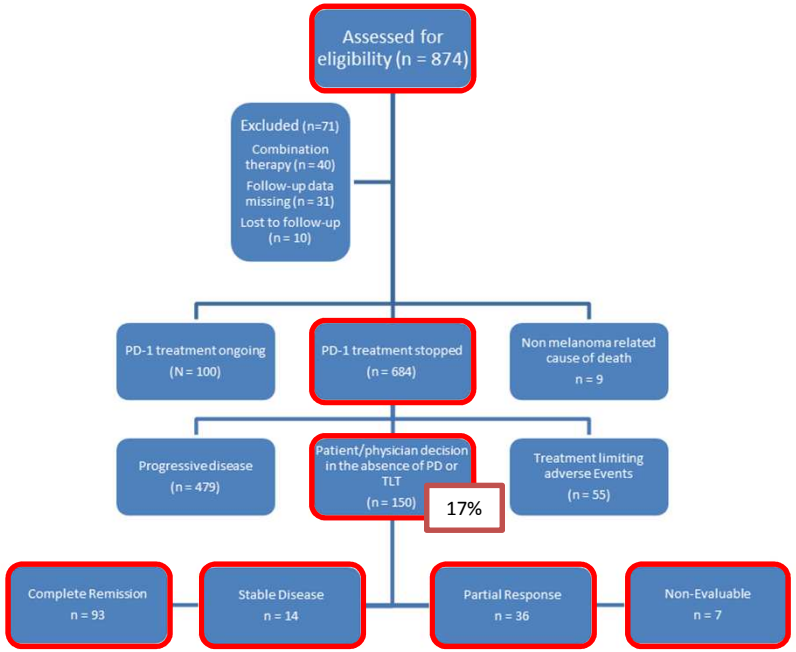
Time, weeks

Total number of patients	Stopping upon PT/MD decision 81 (100%)		Discontinuation due to AE 29 (100%)	
ORR	**Total**	**%**	**Total**	**%**
CR	34	43	8	28
PR	31	39	13	45
SD	15	19	5	17
NE	0	0	2	7
RELAPSES	2	2,5	9	31
CR	1*	3	2	25
PR			6*	46
SD	1	7	2	25
NE			1	50
* Reintroduction of PD-1	1 CR → new CR		3 PR → 1CR, 1 PR and 1 not yet evaluated	
MEDIAN TIME	**Weeks**	**Range**	**Weeks**	**Range**
On treatment	54	9-122	27	0-103
Follow up after last dose	42	0-93	60	25-126
Time to relapse	12	9-15	23	7-48

Oslo University Hospital · HELSE BERGEN Haukeland University Hospital · HUS · Herlev Hospital · Aarhus University Hospital · OUH Odense University Hospital · CLÍNIC Barcelona Hospital Universitari · Netherlands Cancer Institute · Universitair Ziekenhuis Brussel

CLINICAL OUTCOME OF ADVANCED MELANOMA PATIENTS AFTER DISCONTINUATION OF AN ANTI-PD-1 ANTIBODY IN THE ABSENCE OF DISEASE PROGRESSION OR TREATMENT LIMITING TOXICITY

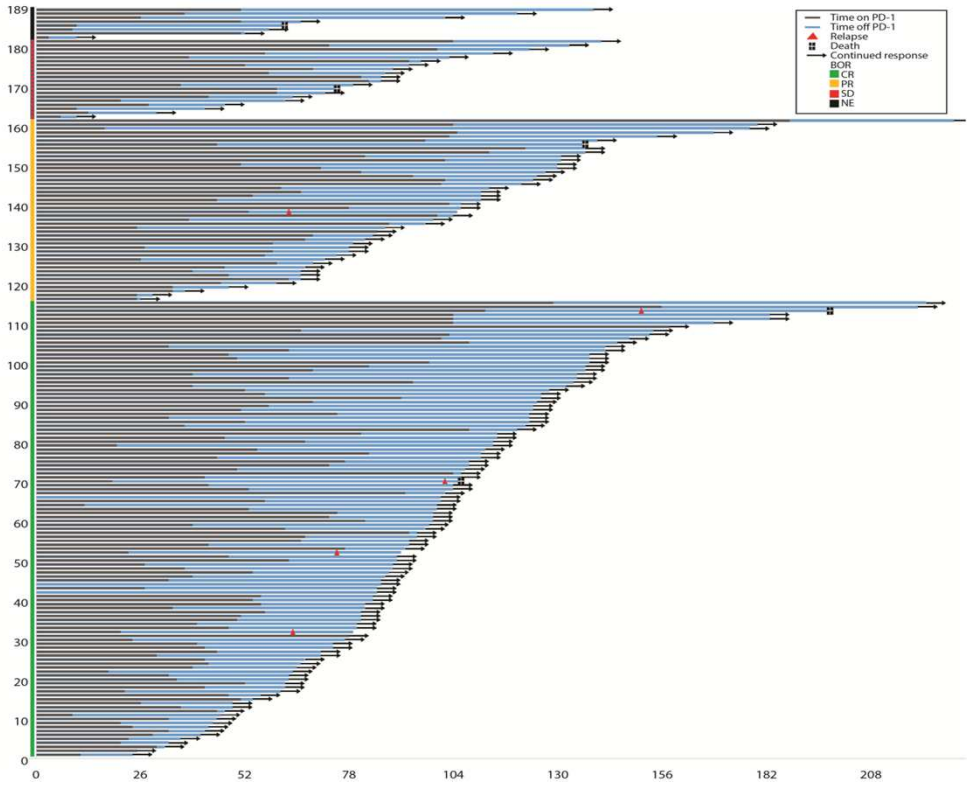
Yanina Jansen, MD[*1]; Elisa A. Rozeman, MD[*2]; Robert Mason, MD[3,4]; Simone Goldinger, MD[5,6]; Marnix H. Geukes Foppen, MD[2]; Lise Hoejberg, MD, PhD[7]; Henrik Schmidt, MD[8]; Johannes V. Van Thienen, MD, PhD[2]; John B. A. G. Haanen, MD, PhD[2]; Leena Tiainen, MD[9]; Inge Marie Svane, MD, PhD[10,11]; Siru Päivikki Mäkelä, MD[12]; Teofila Seremet, MD, PhD[1, 13]; Ana Arance, MD, PhD[14]; Reinhard Dummer, MD[5],;Lars Bastholt, MD[7]; Marta Nyakas, MD[15]; Oddbjorn Straume, MD, PhD[16]; Alexander M. Menzies, BSc, MBBS, PhD, [6,17]; Georgina V. Long, BSc, MBBS, PhD[6,17]; Victoria Atkinson, MD[3,4,18]; Christian U. Blank, MD, PhD[o,2]; Bart Neyns, MD, PhD[o,1]



Jansen Y et al. Under Review

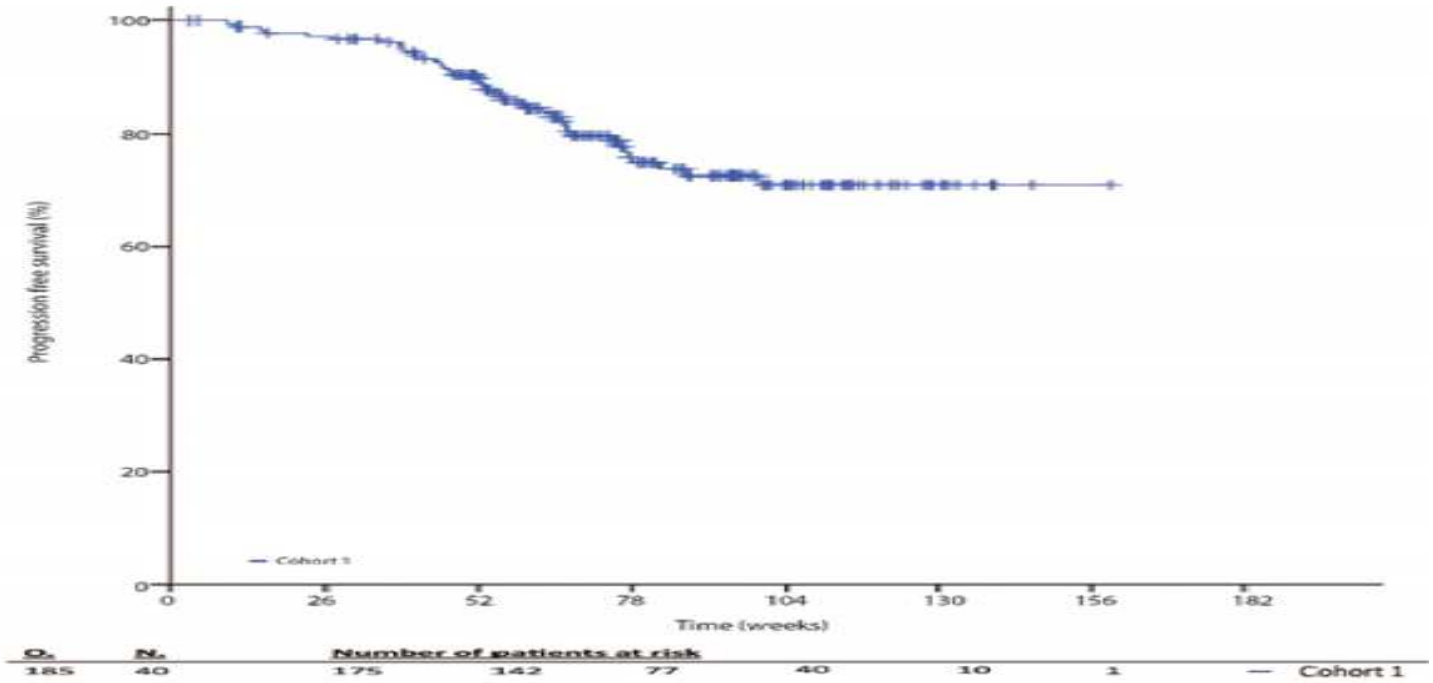
CLINICAL OUTCOME OF ADVANCED MELANOMA PATIENTS AFTER DISCONTINUATION OF AN ANTI-PD-1 ANTIBODY IN THE ABSENCE OF DISEASE PROGRESSION OR TREATMENT LIMITING TOXICITY

- 185 pts stopped aPD1 in the absence of PD or TLT
- Median time on treatment: 52 weeks (range, 3 to 188 weeks)
- BOR tumor response at the time of treatment discontinuation was
  - CR in 117 (63%) patients
  - PR in 44 (24%) patients
  - SD in 16 (9%) patients
  - 8 (4%) patients had no evaluable disease
- After a median follow-up of 80 weeks (range, 3 to 210 weeks) following discontinuation, 78 % of patients remained free of progression
- Median time to progression was 53 weeks (range, 9 to 100 weeks).
- The risk for progression after stopping therapy was lower in patients with a CR, but did not correlate with treatment duration



Jansen Y et al. Under Review

CLINICAL OUTCOME OF ADVANCED MELANOMA PATIENTS AFTER DISCONTINUATION OF AN ANTI-PD-1 ANTIBODY IN THE ABSENCE OF DISEASE PROGRESSION OR TREATMENT LIMITING TOXICITY



Progression-free survival after discontinuation of anti-PD-1

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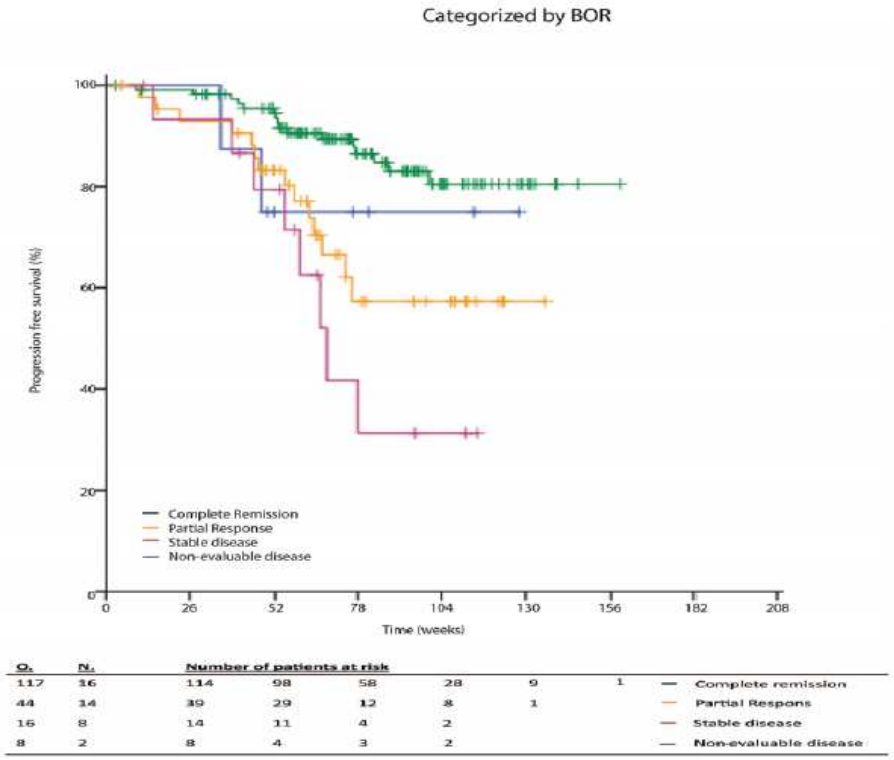
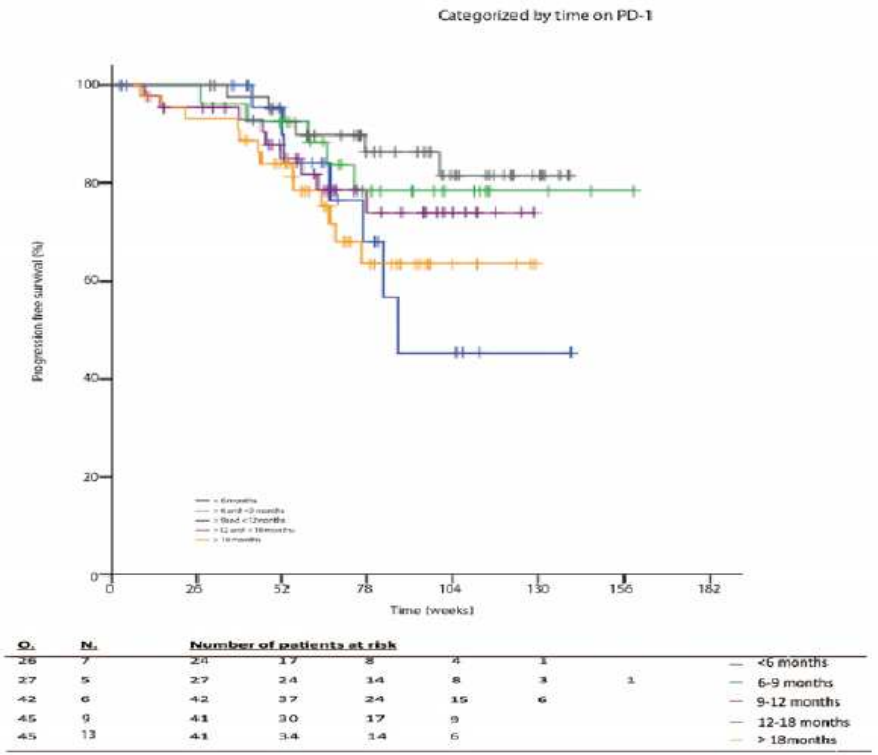
CLINICAL OUTCOME OF ADVANCED MELANOMA PATIENTS AFTER DISCONTINUATION OF AN ANTI-PD-1 ANTIBODY IN THE ABSENCE OF DISEASE PROGRESSION OR TREATMENT LIMITING TOXICITY





Jansen Y et al. Under Review

CLINICAL OUTCOME OF ADVANCED MELANOMA PATIENTS AFTER DISCONTINUATION OF AN ANTI-PD-1 ANTIBODY IN THE ABSENCE OF DISEASE PROGRESSION OR TREATMENT LIMITING TOXICITY

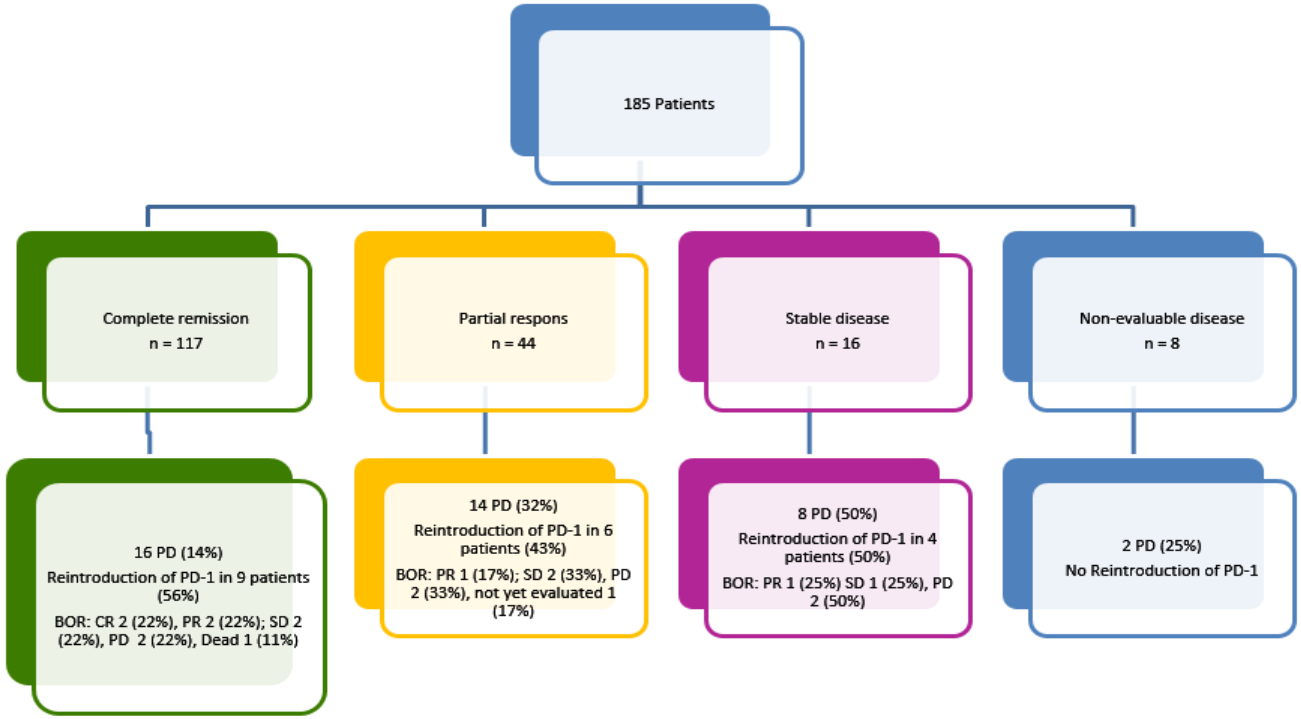
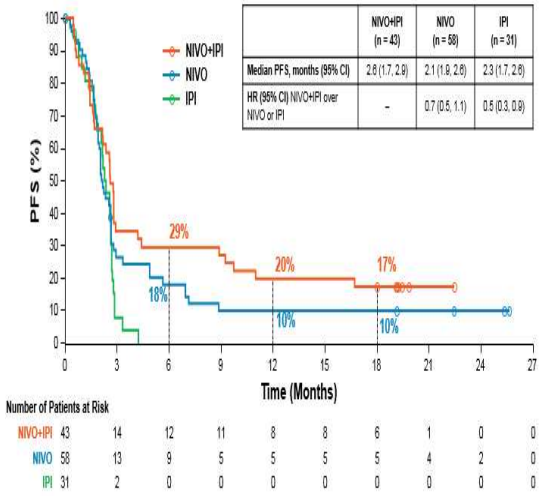
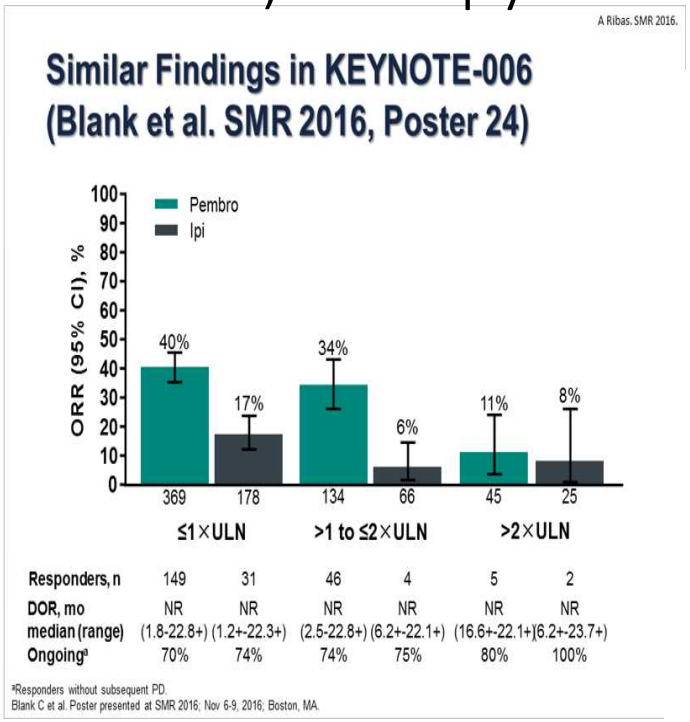
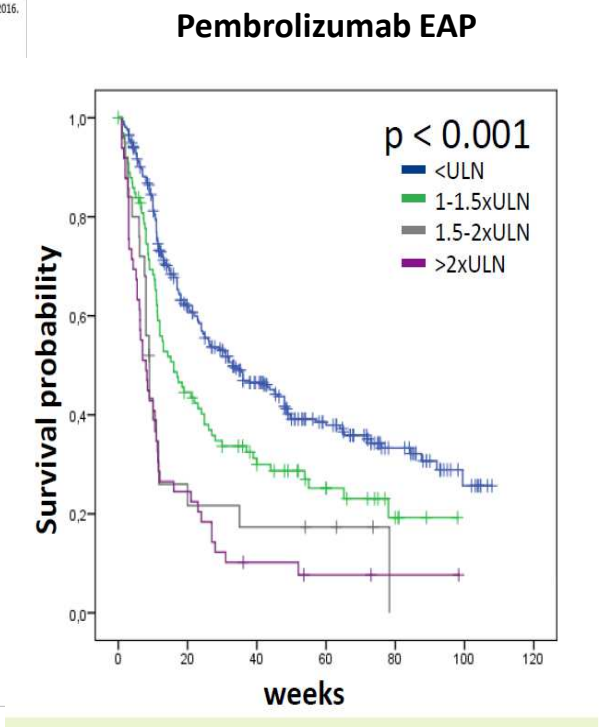


Figure 3 Reintroduction of PD-1 after relapse. Of the 185 patients who discontinued PD-1, 40patients experienced a relapse. A PD-1 inhibitor was re-introduced in 19 patients leading to 6 renewed objective responses (32%, 2 patients with a CR (11%) and 4 patients with a PR (21%)). CR: complete Remission, PR: partial response, SD: stable disease, NE: non-evaluable disease, PD: progressive disease, BOR: Best objective response

Baseline LDH as a predictive biomarker for anti-PD-1 (+/- anti-CTLA-4) therapy







Larkin et al SMR 2016; Ribas et al SMR 2016; Jansen et al ESMO AM 2016

1127P
Presented at the European Society of Medical Oncology (ESMO) Congress
7-11 October 2016
Copenhagen, Denmark

Correlation between baseline characteristics and clinical outcome of patients with advanced melanoma treated with pembrolizumab (PEMBRO)

Yanina Jansen[a], Elisa A. Rozeman[b], Lise Hoejberg[c], Marnix H. Geukes Foppen[b], Max Schreuer[a], Johannes V. van Thienen[b], Lars Bastholt[c], Henrik Schmidt[d], John B.A.G. Haanen[b], Inge M. Svane[e], Anna M. Arance[f], Christian U. Blank[b], Bart Neyns[a]
The following people provided data to the project but are not represented in the author list: Siru Mäkelä[g], Marta Nyakas[h], Oddbjørn Straume[i]

Introduction

The PD-1 blocking monoclonal antibody PEMBRO is approved for the treatment of patients with advanced melanoma. Correlation between baseline characteristics and outcome of patients treated outside of a prospective clinical trial has not yet been established.

Methods

The correlation between baseline characteristics and progression free survival (PFS) and overall survival (OS) were explored using Kaplan-Meier analysis and compared using a log-rank test. Hazard ratios and 95% confidence intervals were estimated by Cox regression.

Results

A total of 500 patients were included out of 9 centers from Belgium, the Netherlands, Denmark, Norway, Spain and Finland.
Median follow-up at time of database lock (1-9-2016) was 40 weeks.
The median PFS of the total cohort was 23 weeks (95% CI 19-27).
The median OS of the total cohort was 68 week (95% CI 58-78).
Number of events: tumor progression: 328/499, death: 266/500.

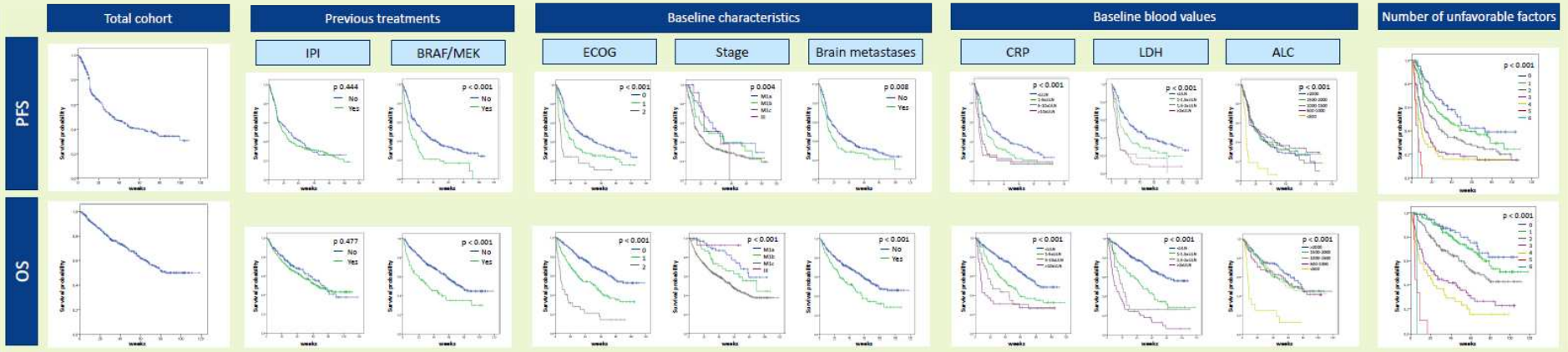
Previous treatment with BRAF inhibitors, ECOG 0, brain metastases, stage IV M1c, CRP > 10xULN, LDH > 2xULN, and ALC < 500x10^6/mm^3 are unfavorable prognostic factors for PFS and OS. Previous treatment with IPI did not significantly influence PFS and OS.

Multivariate analysis: Independent unfavorable prognostic factors

	PFS	OS
LDH > 2xULN	2.27 (1.57-3.33)	3.06(4.54-2.06)
Stage IV M1c	1.30 (1.01-1.83)	1.56 (1.02-2.40)
ECOG 1-2	1.41 (1.10-1.82)	1.72 (1.26-2.35)
ALC < 500 x10^6/mm^3	1.87 (1.06-3.30)	2.36 (1.28-4.37)
Previous BRAF	2.05 (1.58-2.66)	1.71 (1.25-2.34)
CRP > 10 ULN	Not independent	1.74 (1.07-2.82)
Brain metastases	Not independent	1.40 (1.00-1.95)

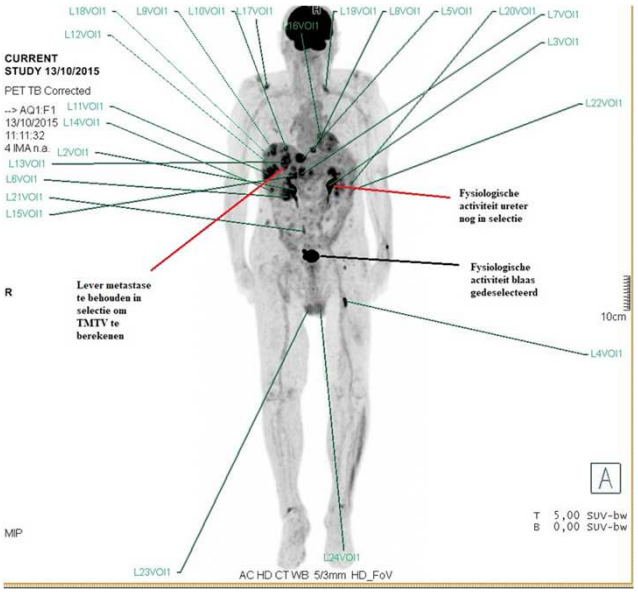
Conclusions

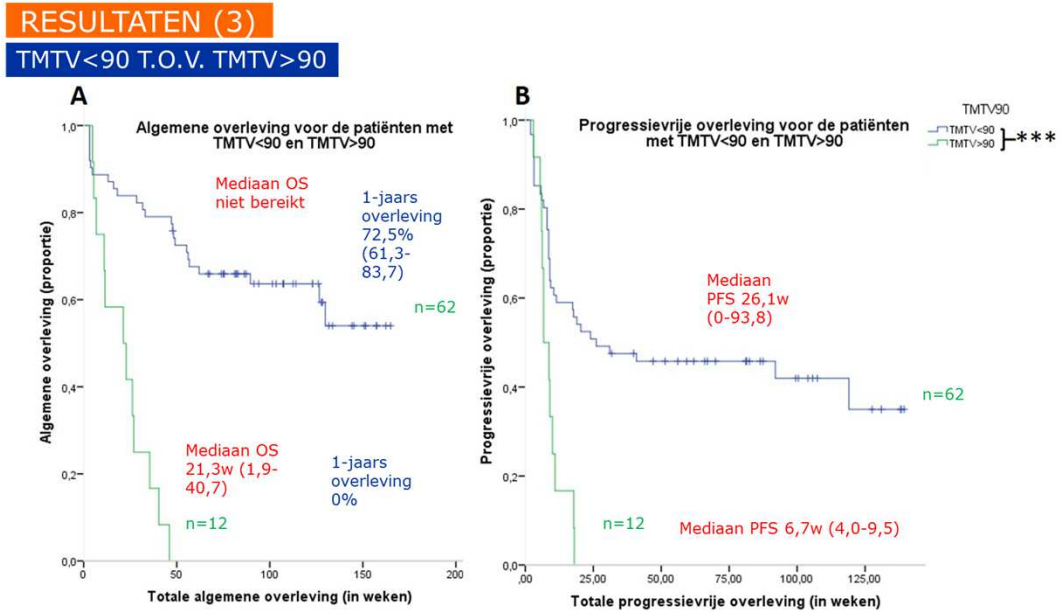
- The PFS and OS in this large real life cohort of patients with metastatic melanoma treated with PEMBRO are comparable to that of randomized clinical trials.
- There is a strong correlation between the number of unfavorable prognostic factors and PFS and OS. Patients with ≥5 unfavorable factors had a PFS and OS of less than 20 weeks.
- The assessment of these baseline predictive factors could be easily integrated into daily clinical practice and help to guide the optimal treatment per patient.

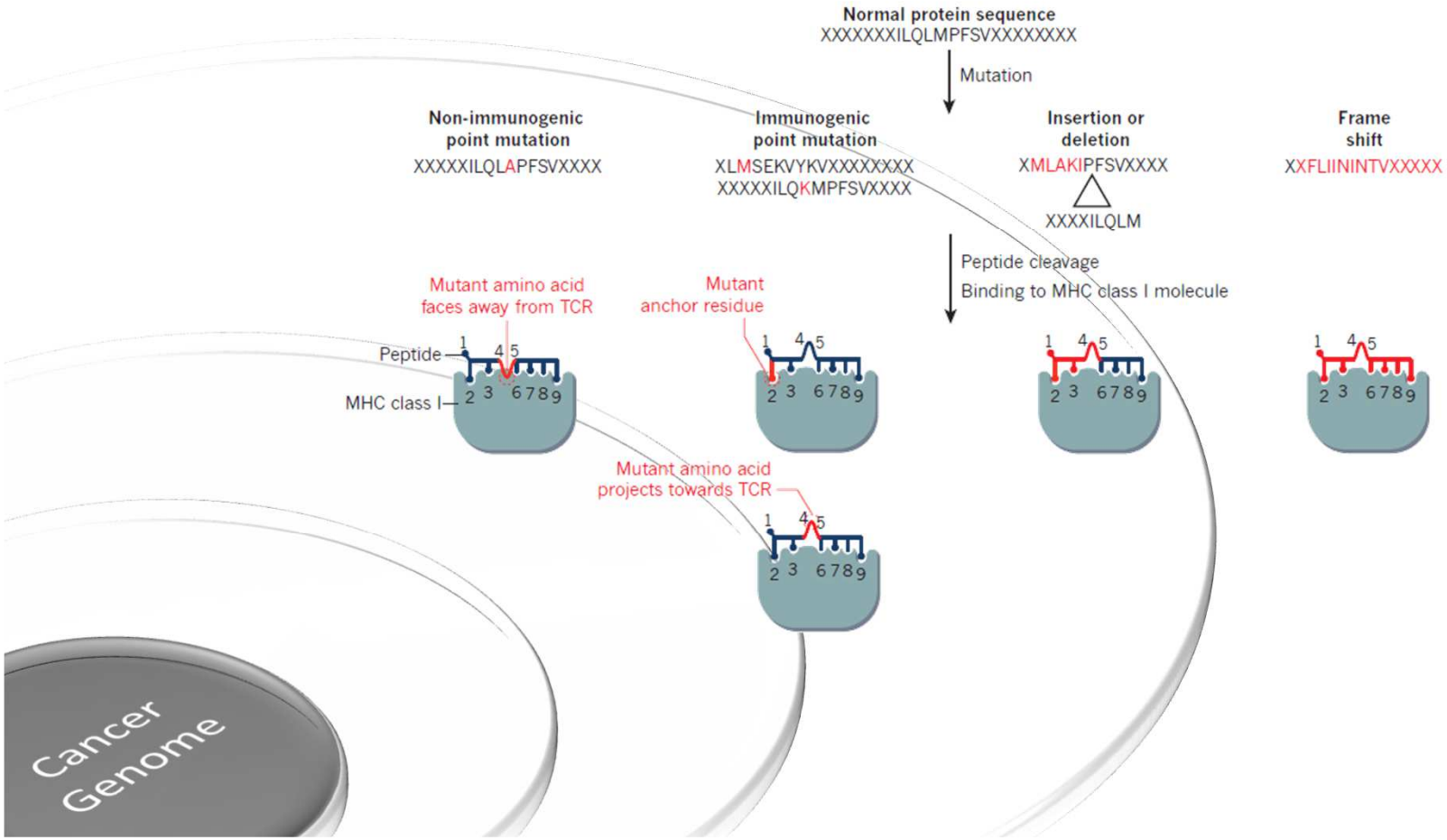


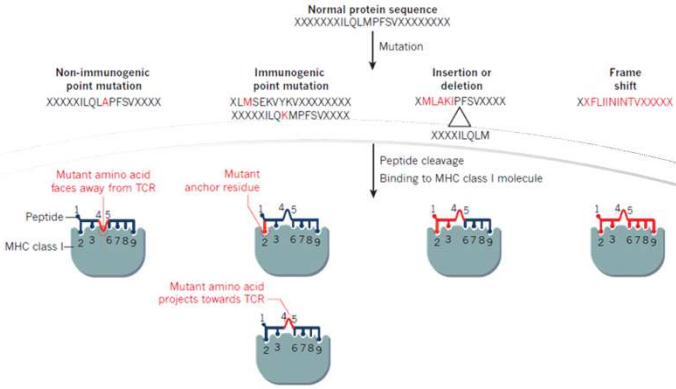
[a]UZ Brussel, Brussels, Belgium; [b]Netherlands Cancer Institute, Amsterdam, the Netherlands; [c]Odense University Hospital, Odense, Denmark; [d]Aarhus University Hospital, Aarhus, Denmark; [e]Herlev Hospital, Herlev, Denmark; [f]Hospital Clínic Barcelona, Barcelona, Spain; [g]Comprehensive Cancer Center, Helsinki, Finland [h]Oslo University Hospital, Oslo, Norway; [i]Haukeland University Hospital, Bergen, Norway.

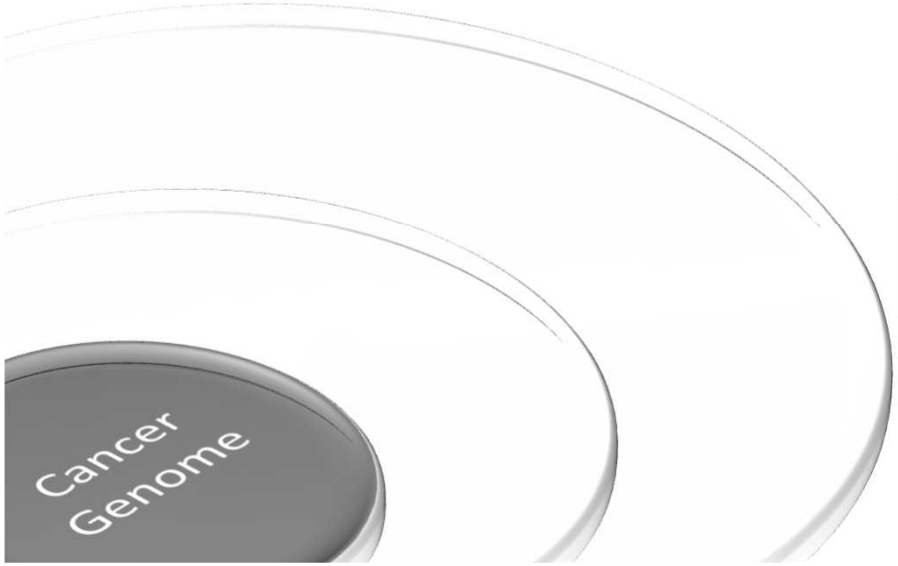
Baseline TMTV as a predictive imaging biomarker for activity of anti-PD1 therapy






Normal protein sequence
XXXXXXXILQLMPFSVXXXXXXXX
Mutation
Non-immunogenic point mutation
XXXXXILQLAPFSVXXXX
Immunogenic point mutation
XLMSEKVYKVXXXXXXX
XXXXXILQKMPFSVXXXX
Insertion or deletion
XMLAKIPFSVXXXX
XXXXILQLM
Frame shift
XXFLIININTVXXXXX
Peptide cleavage
Binding to MHC class I molecule
Mutant amino acid faces away from TCR
Mutant anchor residue
Peptide
MHC class I
Mutant amino acid projects towards TCR
Cancer Genome



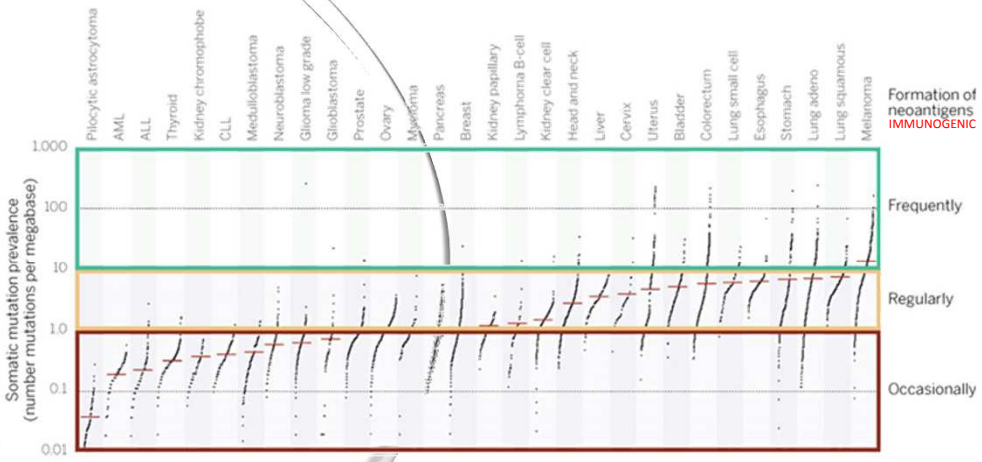


REVIEW

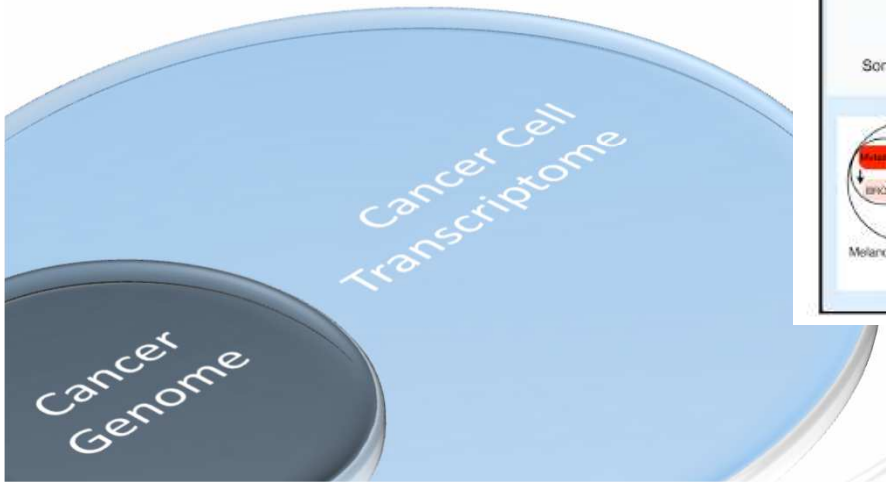
Neoantigens in cancer immunotherapy

Ton N. Schumacher[1,*], Robert D. Schreiber[2,*]
+ See all authors and affiliations

Science 03 Apr 2015:
Vol. 348, Issue 6230, pp. 69-74
DOI: 10.1126/science.aaa4971



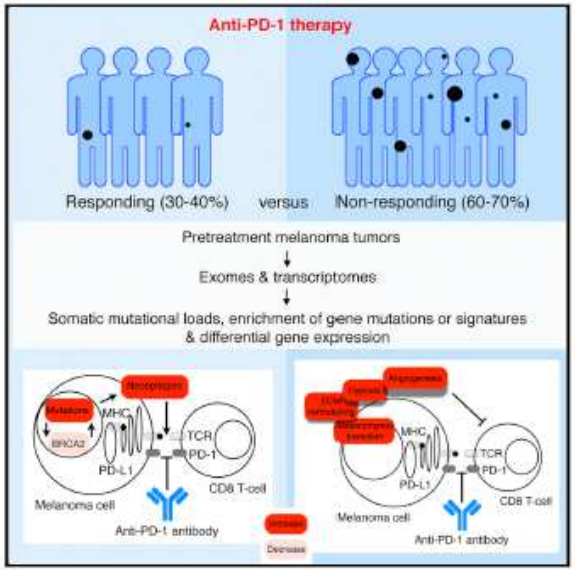
Ton N. Schumacher, and Robert D. Schreiber Science 2015;348:69-74



Cell

Genomic and Transcriptomic Features of Response to Anti-PD-1 Therapy in Metastatic Melanoma

Graphical Abstract



Authors

Willy Hugo, Jesse M. Zaretsky, Lu Sun, ..., Douglas B. Johnson, Antoni Ribas, Roger S. Lo

Correspondence

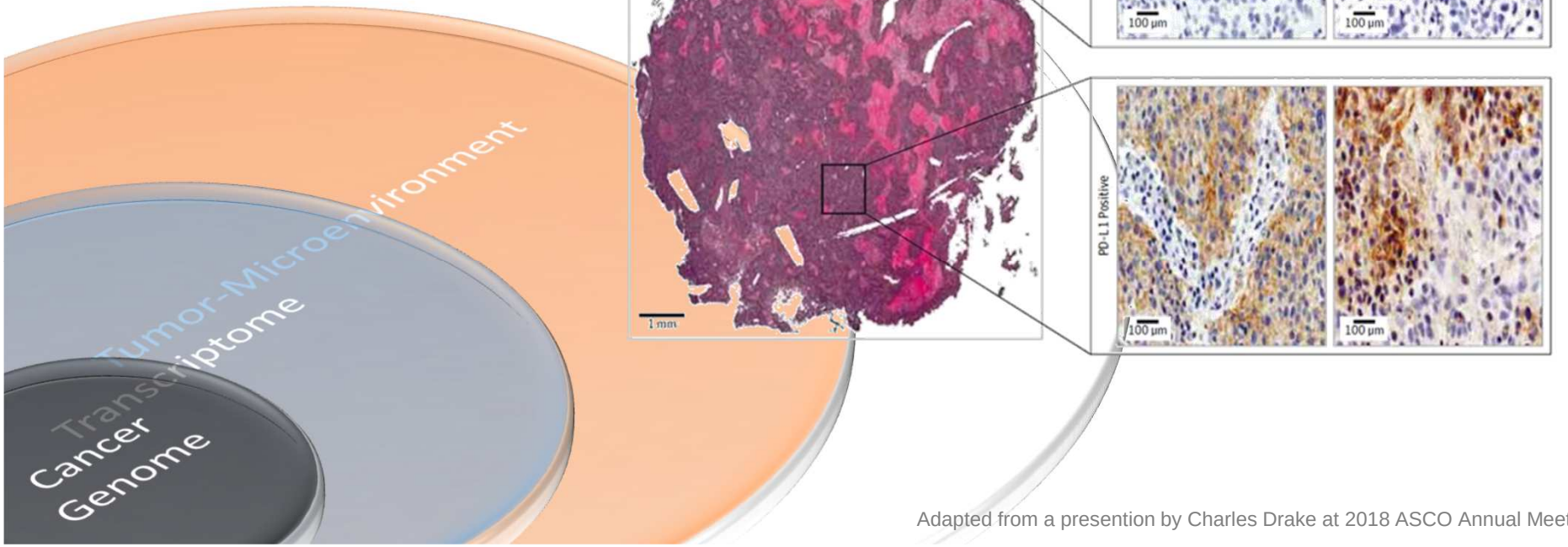
rlo@mednet.ucla.edu

In Brief

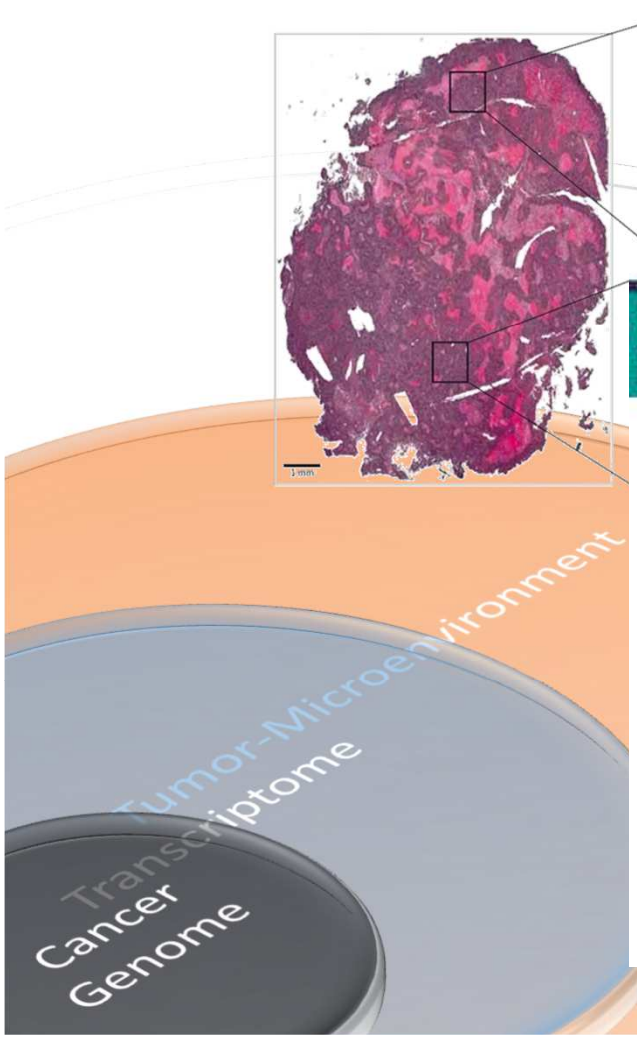
High mutational loads are associated with improved survival in melanoma patients but are not predictive of response to anti-PD-1 therapy, suggesting that other genomic and non-genomic features also contribute to response patterns on PD-1 checkpoint blockade therapy.

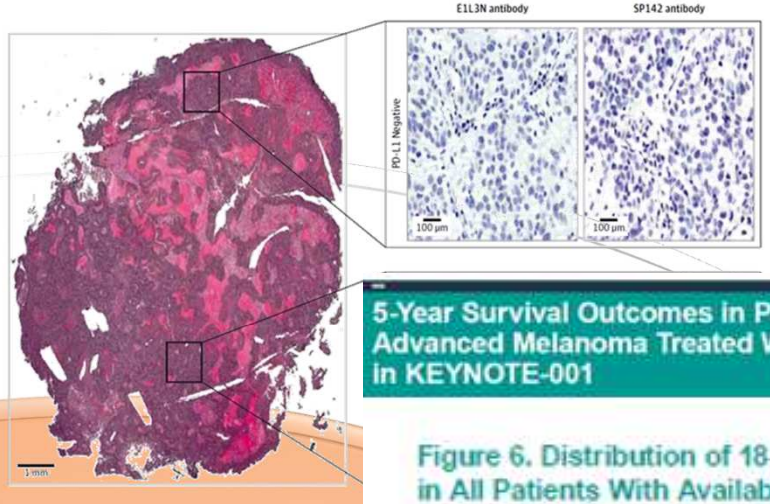
PD-L1 IHC

- ✓ *Heterogeneous within metastases*
- ✓ *Heterogeneous between metastases*
- ✓ *Dynamic biomarker*
- ✓ *Discrepancy between assay's*



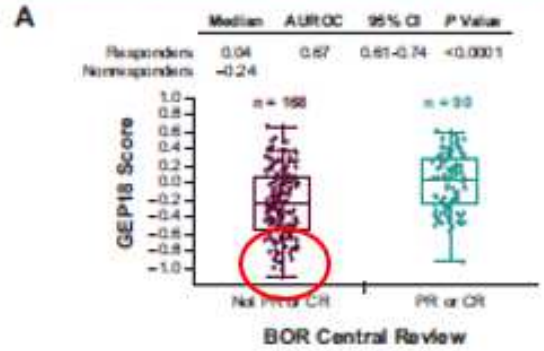
Adapted from a presention by Charles Drake at 2018 ASCO Annual Meeting





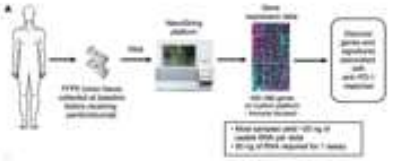
5-Year Survival Outcomes in Patients With Advanced Melanoma Treated With Pembrolizumab in KEYNOTE-001

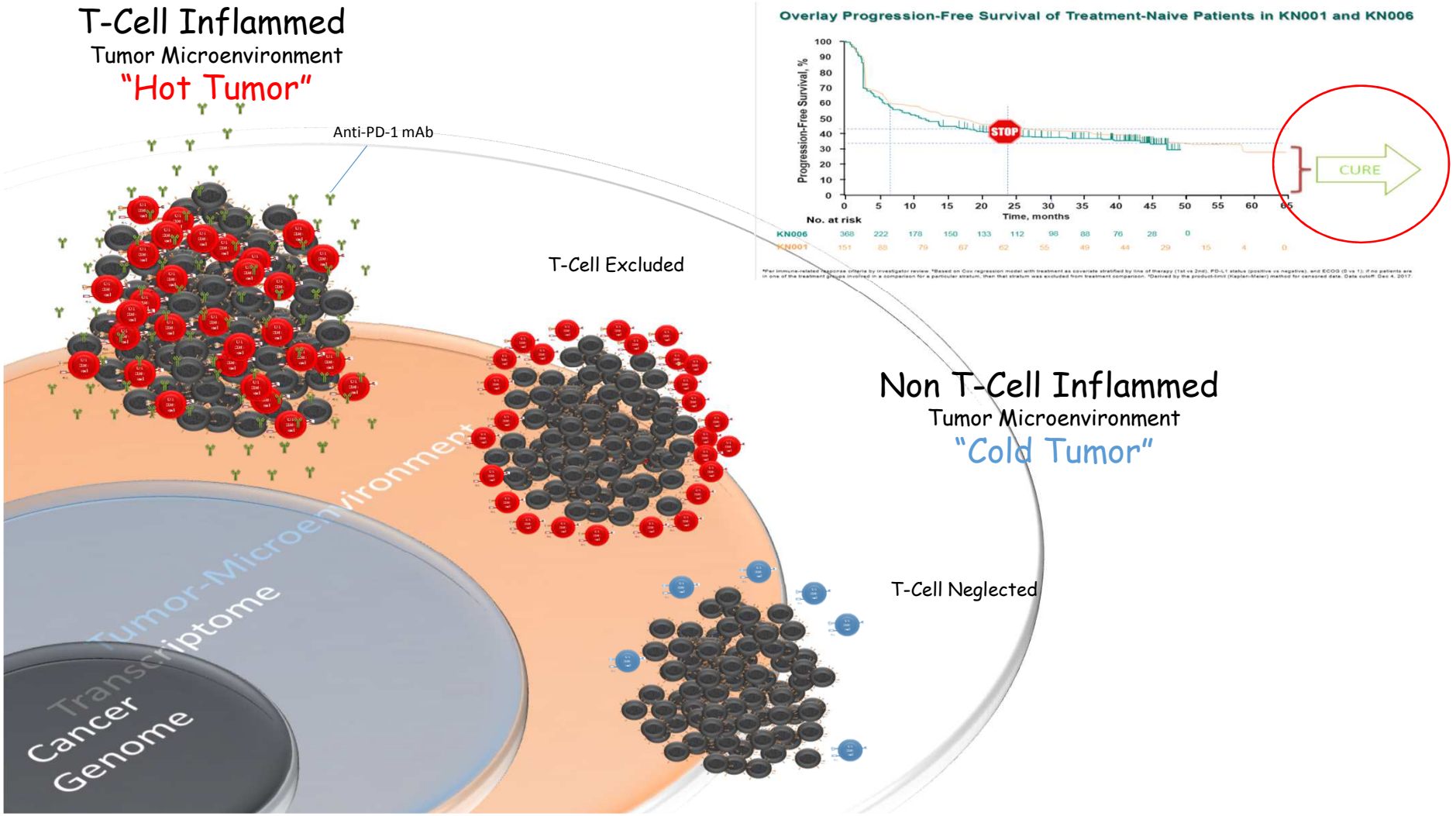
Figure 6. Distribution of 18-Gene GEP in Responders Versus Nonresponders in All Patients With Available GEP Data (A), Treatment-Naive Versus Treatment-Exposed Subgroups (B), and Ipilimumab-Naive Versus Ipilimumab-Refractory/Exposed Subgroups (C)

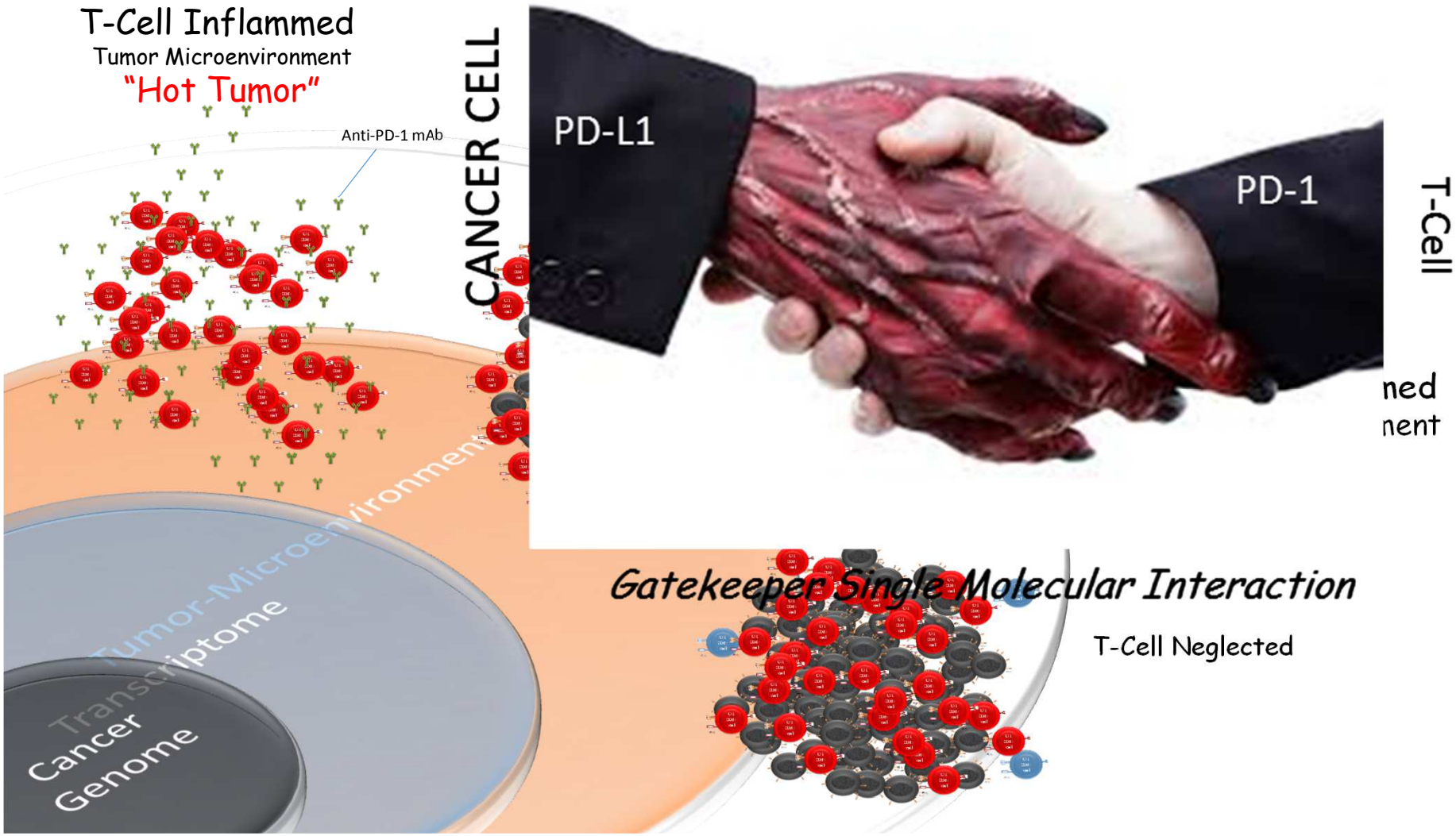


Biomarker Expression

- RNA was isolated from formalin-fixed, paraffin-embedded tumor tissue samples obtained at baseline in patients treated with pembrolizumab
- GEP related to interferon gamma signaling and activated T-cell biology was assessed in tumor samples as previously described[9] and consisted of genes related to antigen presentation, chemokine expression, cytolytic activity, and adaptive immune resistance
  - Genes: *CCL5, CD27, CD274 (PD-L1), CD276 (B7-H3), CD8A, CMKLR1, CXCL9, CXCR6, HLA-DQA1, HLA-DRB1, HLA-E, IDO1, LAG3, NKG7, PDCD1LG2 (PD-L2), PSMB10, STAT1, TIGIT*
  - The GEP score was computed by taking a weighted sum of the housekeeping normalized values of the 18 genes on the GEP18 signature
- 1-sided *P* values were based on logistic regression analysis adjusted for ECOG performance status




T-Cell Inflammed
Tumor Microenvironment
"Hot Tumor"
Anti-PD-1 mAb
T-Cell Excluded
Non T-Cell Inflammed
Tumor Microenvironment
"Cold Tumor"
T-Cell Neglected
Tumor-Microenvironment
Transcriptome
Cancer Genome
Overlay Progression-Free Survival of Treatment-Naive Patients in KN001 and KN006
Progression-Free Survival, %
Time, months
No. at risk
KN006
KN001
STOP
CURE


T-Cell Inflammed
Tumor Microenvironment
"Hot Tumor"
Anti-PD-1 mAb
CANCER CELL
PD-L1
PD-1
T-Cell
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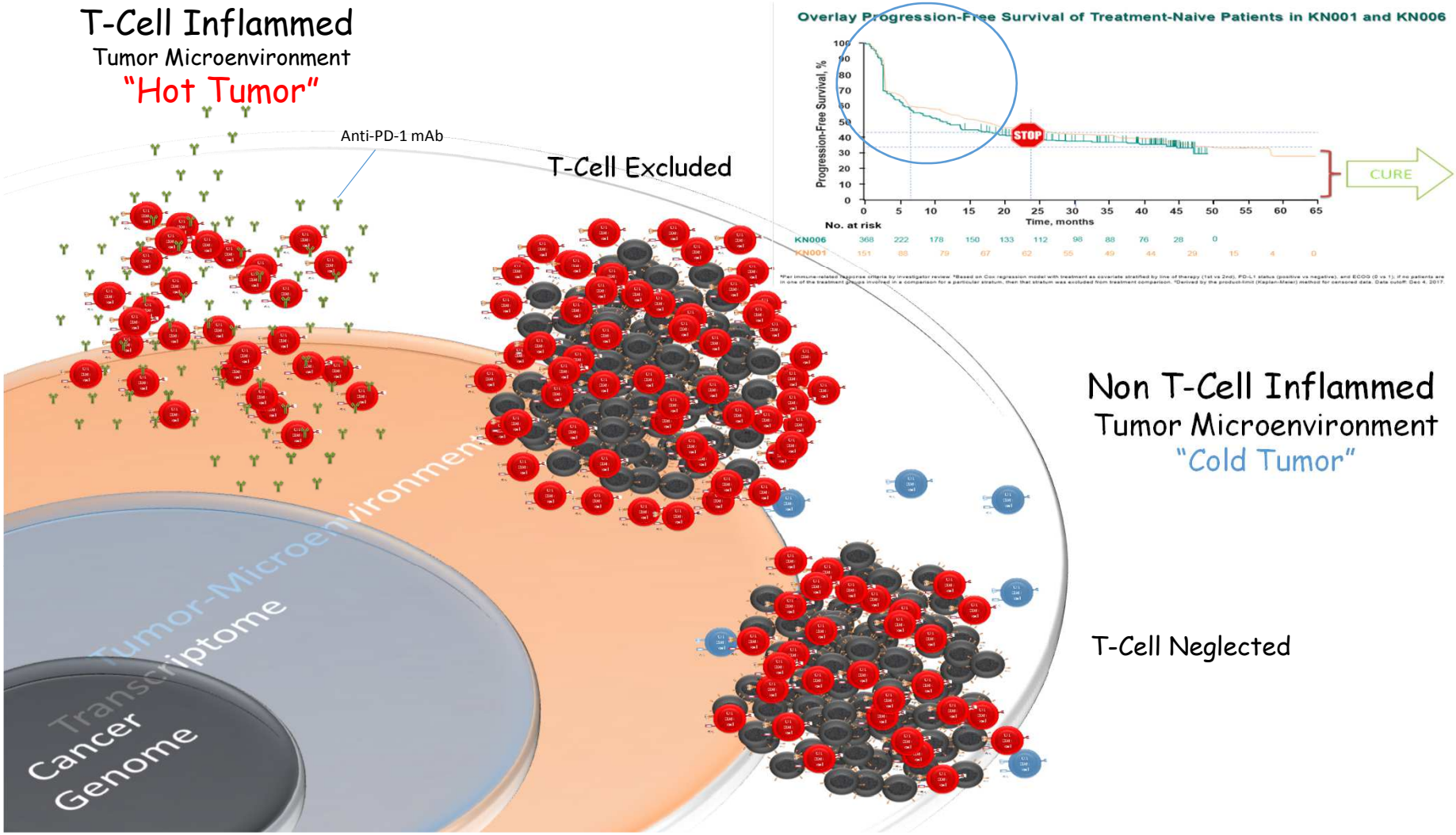
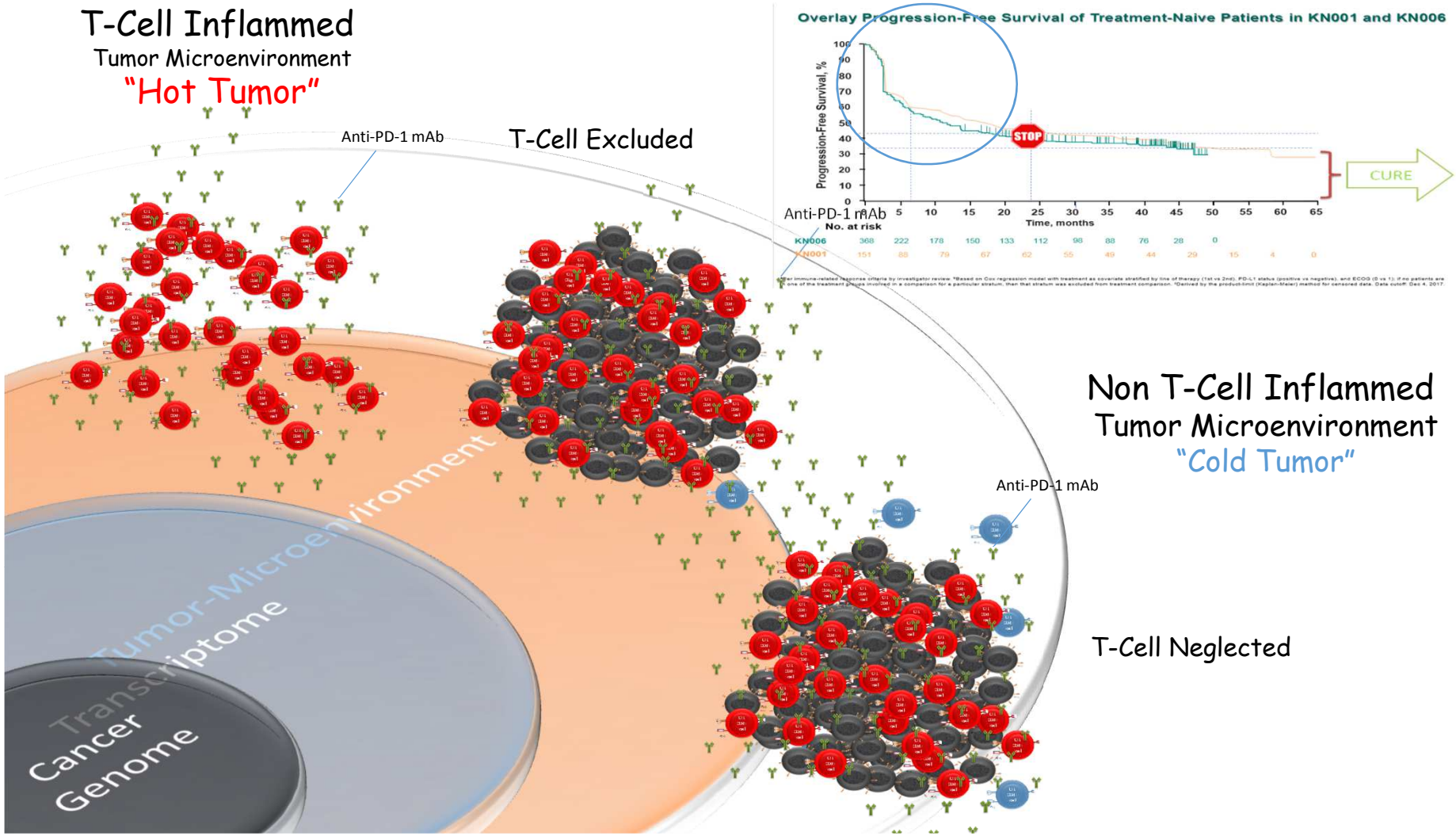
nent
Tumor-Microenvironment
Transcriptome
Cancer
Genome
Gatekeeper Single Molecular Interaction
T-Cell Neglected


T-Cell Inflammed
Tumor Microenvironment
"Hot Tumor"
Anti-PD-1 mAb
T-Cell Excluded
Tumor-Microenvironment
Transcriptome
Cancer Genome
Overlay Progression-Free Survival of Treatment-Naive Patients in KN001 and KN006
Progression-Free Survival, %
STOP
CURE
Time, months
No. at risk
KN006 368 222 178 150 133 112 98 88 76 28 0
KN001 151 88 79 67 62 55 49 44 29 15 4 0
Non T-Cell Inflammed
Tumor Microenvironment
"Cold Tumor"
T-Cell Neglected


T-Cell Inflammed
Tumor Microenvironment
"Hot Tumor"
Anti-PD-1 mAb
T-Cell Excluded
Overlay Progression-Free Survival of Treatment-Naive Patients in KN001 and KN006
Progression-Free Survival, %
STOP
CURE
Anti-PD-1 mAb
Time, months
No. at risk
KN006 368 222 178 150 133 112 98 88 76 28 0
KN001 151 88 79 67 62 55 49 44 29 15 4 0
Non T-Cell Inflammed
Tumor Microenvironment
"Cold Tumor"
Anti-PD-1 mAb
T-Cell Neglected
Tumor-Microenvironment
Transcriptome
Cancer
Genome

REPORT

Patient HLA class I genotype influences cancer response to checkpoint blockade immunotherapy

Diego Chowell[1,2], Luc G.T. Morris[2,3,*], Claud M. Grigg[4,*], Jeffrey K. Weber[5], Robert M. Samstein[1,2], Vladimir Makarov[1,2], Fen...
+ See all authors and affiliations

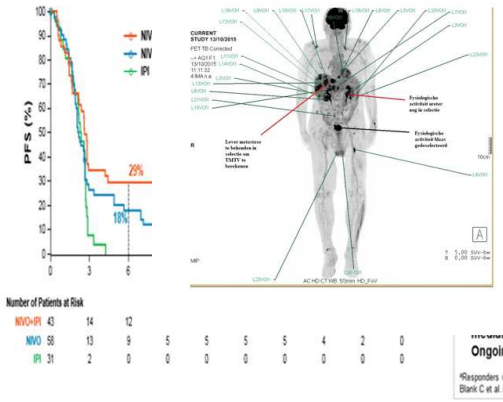
Science 07 Dec 2017:
eaao4572
DOI: 10.1126/science.aao4572

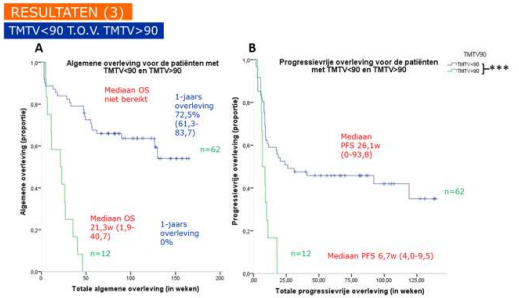
Baseline LDH as a predictive biomarker for anti-PD-1 (+/- anti-CTLA-4) therapy

PFS in Pat...

A Ribas. SMR 2016.

Baseline TMTV as a predictive imaging biomarker for activity of anti-PD1 therapy





Ongoing[a]	70%	74%	74%	75%	80%	100%

[a]Responders without subsequent PD.
Blank C et al. Poster presented at SMR 2016; Nov 6-9, 2016; Boston, MA.

Larkin et al SMR 2016; Ribas et al SMR 2016

REPORT

Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients

V. Gopalakrishnan[1,2,*], C. N. Spencer[2,3,*], L. Nezi[3,*], A. Reuben[1], M. C. Andrews[1], T. V. Karpinets[3], P. A. Prieto[1,†], D. Vicente[1]...
+ See all authors and affiliations

Science 02 Nov 2017:
eaan4236
DOI: 10.1126/science.aan4236

Combinatorial Immunotherapies Involving Immune-Checkpoint Inhibitors

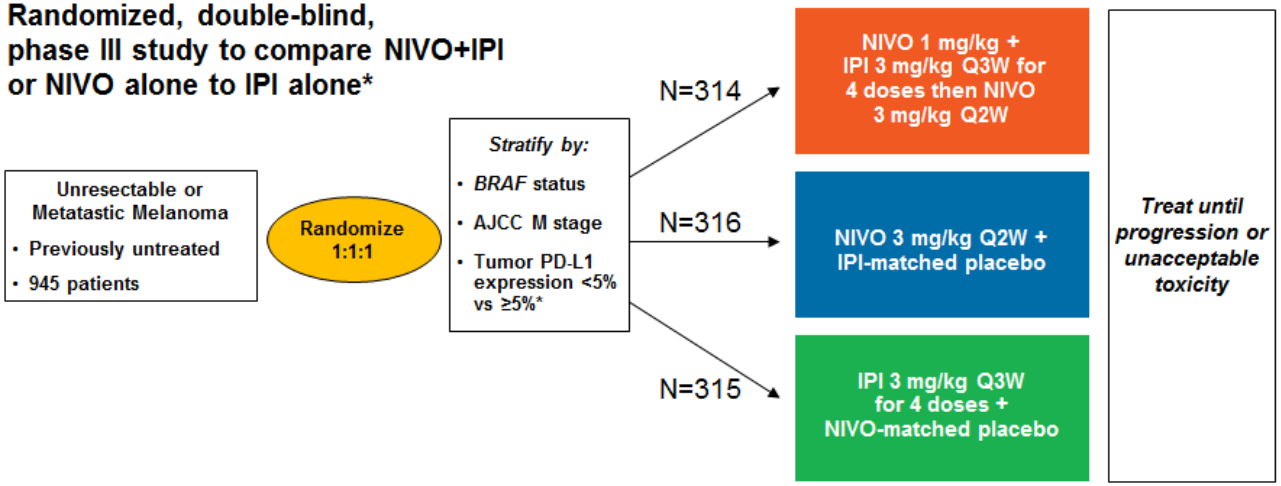
- **CTLA-4 plus PD-1 blockade**
  - Nivolumab/Ipilimumab; Durvalumab/Tremelimumab; Pembrolizumab/Ipilimumab
- **PD-1/-L1 inhibition plus BRAFi + /- MEKi**
  - Ipilimumab + Vemurafenib [3]; Pembrolizumab + Dabrafenib + Trametinib; MEDI4736+ Dabrafenib + Trametinib [5]; atezolizumab + vemurafenib[6]
- **IDO1-inhibitor**
  - Epacadostat plus pembrolizumab (phase III recruited)
- **Oncolytic viruses + anti-PD-1 mAb**
  - T-VEC plus pemrolizumab (phase III ongoing)
- **Anti-VEGF(R)**
  - Bevacizumab [2]; Sunitinib, pazopanib, axitinib
- **mAb against additional immune checkpoint receptors**
  - LAG3, CD137, CD40, …
- **NK activation (e.g. lirilumab)**
  - Killer-cell Ig-like receptors (KIR) on NK cells directed mAb
- **Cell therapy**
  - DC therapy (TriMixDC-MEL [4]), adoptive TIL therapy, CAR-Tcell therapy

1. Hodi et al JAMA 2014; 2. Hodi et al Cancer Immunol Res; 3. Ribas A. et al NEJM 2013; 4. Neyns et al ASCO AM 2014; 5.Ribas et al. ASCO AM 2015; 6. Hamid O SMR 2015

Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial

Frank Stephen Hodi, Vanna Chiarion-Sileni, Rene Gonzalez, Jean-Jacques Grob, Piotr Rutkowski, Charles Lance Cowey, Christopher D Lao, Dirk Schadendorf, John Wagstaff, Reinhard Dummer, Pier Francesco Ferrucci, Michael Smylie, Andrew Hill, David Hogg, Ivan Marquez-Rodas, Joel Jiang, Jasmine Rizzo, James Larkin*, Jedd D Wolchok*

CheckMate 067: Study Design



Database lock: Sept 13, 2016 (median follow-up ~30 months in both NIVO-containing arms)

**The study was not powered for a comparison between NIVO and NIVO+IPI*

Lancet Oncol 2018
Published Online
October 22, 2018
http://dx.doi.org/10.1016/S1470-2045(18)30700-9

Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial

Frank Stephen Hodi, Vanna Chiarion-Sileni, Rene Gonzalez, Jean-Jacques Grob, Piotr Rutkowski, Charles Lance Cowey, Christopher D Lao, Dirk Schadendorf, John Wagstaff, Reinhard Dummer, Pier Francesco Ferrucci, Michael Smylie, Andrew Hill, David Hogg, Ivan Marquez-Rodas, Joel Jiang, Jasmine Rizzo, James Larkin*, Jedd D Wolchok*

Response to Treatment

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
ORR, % (95% CI)	58.3 (52.6, 63.8)	44.6 (39.1, 50.3)	19.0 (14.9, 23.8)
Best overall response, %			
Complete response	21.3	17.7	5.1
Partial response	36.9	26.9	14.0
Stable disease	12.1	9.5	21.6
Progressive disease	23.6	38.3	50.5
Unknown	6.1	7.6	8.9
Median duration of response, months (95% CI)	50.1 (44.0, NR)	NR (45.7, NR)	14.4 (8.3, NR)

Lancet Oncol 2018
Published Online
October 22, 2018
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Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial

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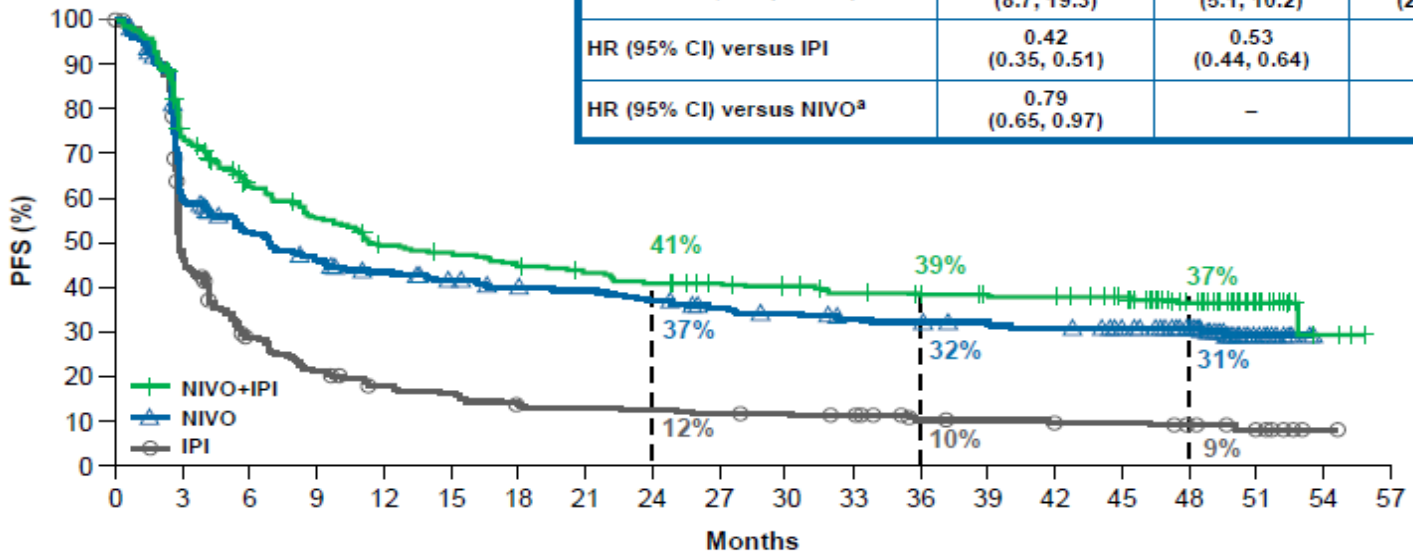
	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median PFS, mo (95% CI)	11.5 (8.7, 19.3)	6.9 (5.1, 10.2)	2.9 (2.8, 3.2)
HR (95% CI) versus IPI	0.42 (0.35, 0.51)	0.53 (0.44, 0.64)	–
HR (95% CI) versus NIVO[a]	0.79 (0.65, 0.97)	–	–



Patients at risk:

NIVO+IPI	314	218	175	155	136	131	124	117	110	104	101	95	93	89	88	81	53	19	3	0
NIVO	316	177	151	132	120	112	106	103	97	88	84	79	77	75	72	66	50	18	0	0
IPI	315	136	78	58	46	42	34	32	31	29	28	26	19	18	16	16	11	7	1	0

[a]Descriptive analysis

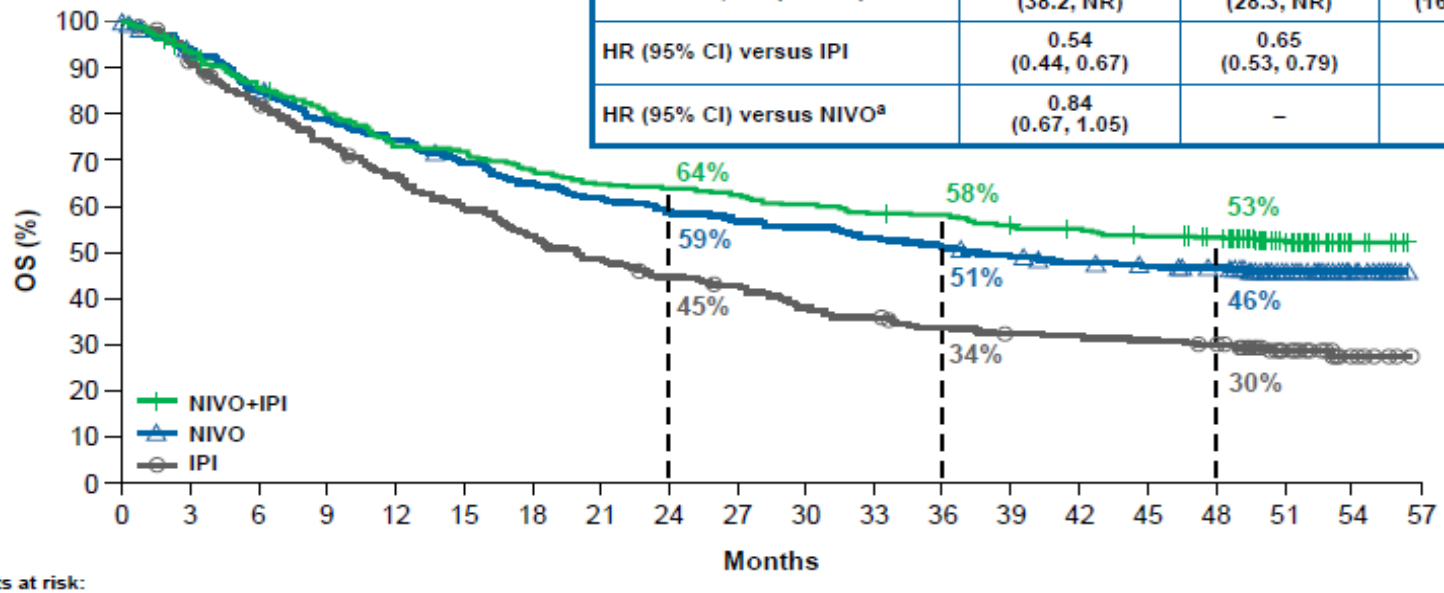
Lancet Oncol 2018

Published Online October 22, 2018 http://dx.doi.org/10.1016/S1470-2045(18)30700-9

Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial

Frank Stephen Hodi, Vanna Chiarion-Sileni, Rene Gonzalez, Jean-Jacques Grob, Piotr Rutkowski, Charles Lance Cowey, Christopher D Lao, Dirk Schadendorf, John Wagstaff, Reinhard Dummer, Pier Francesco Ferrucci, Michael Smylie, Andrew Hill, David Hogg, Ivan Marquez-Rodas, Joel Jiang, Jasmine Rizzo, James Larkin, Jedd D Wolchok**

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2, NR)	36.9 (28.3, NR)	19.9 (16.9, 24.6)
HR (95% CI) versus IPI	0.54 (0.44, 0.67)	0.65 (0.53, 0.79)	–
HR (95% CI) versus NIVO[a]	0.84 (0.67, 1.05)	–	–



Patients at risk:

NIVO+IPI	314	292	265	247	226	221	209	200	198	192	186	180	178	171	166	160	154	96	13	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	144	140	135	85	18	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	99	94	93	90	86	50	11	0

[a]Descriptive analysis

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Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial

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Subsequent Therapies: All Randomized Patients

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Any subsequent therapy, n (%)[a]	**135 (43)**	**182 (58)**	**236 (75)**
Subsequent systemic therapy	104 (33)	150 (48)	206 (65)
Subsequent immunotherapy	53 (17)	103 (33)	148 (47)
Anti-PD-1 agents[b]	36 (12)	47 (15)	143 (45)
Anti-CTLA-4 agents[b]	19 (6)	91 (29)	17 (5)
Other immunotherapy	7 (2)	12 (4)	11 (4)
BRAF inhibitor[c]	42 (13)	60 (19)	72 (23)
MEK inhibitor[c]	32 (10)	43 (14)	42 (13)
Other investigational agent	8 (3)	9 (3)	15 (5)
Other	45 (14)	63 (20)	75 (24)
Subsequent radiotherapy	61 (19)	92 (29)	123 (39)
Subsequent surgery	60 (19)	69 (22)	95 (30)
Median time from randomization to subsequent systemic therapy, mo (95% CI)[d]	**NR**	**25.2 (16.0, 43.2)**	**8.1 (6.5, 8.7)**

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[a]Patients may have received more than 1 subsequent therapy (eg, radiation, surgery, and systemic therapies). [b]May include patients treated with PD-1+CTLA-4 combination. [c]May include patients treated with BRAF+MEK combination. [d]Excluding patients who died and never received subsequent therapy

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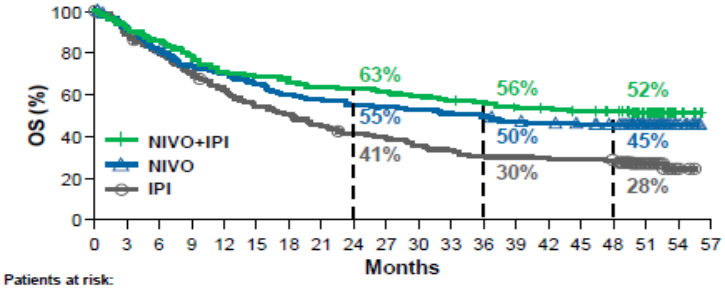
OS by Tumor PD-L1 Expression, 5% Cutoff

PD-L1 Expression Level <5%

	NIVO+IPI	NIVO	IPI
Median, mo (95% CI)	NR (32.7, NR)	35.9 (23.1, NR)	18.4 (13.7, 22.5)
HR (95% CI) versus IPI	0.54 (0.42, 0.69)	0.64 (0.50, 0.82)	–
HR (95% CI) versus NIVO[a]	0.83 (0.64, 1.09)	–	–



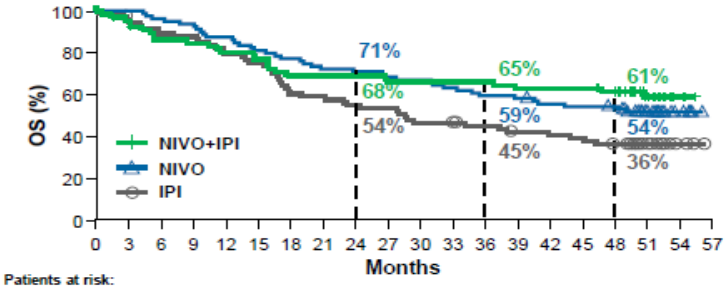
Patients at risk:

NIVO+IPI	210	194	178	163	146	144	139	131	130	127	123	118	116	111	107	103	100	62	9	0
NIVO	208	189	169	151	144	133	123	118	112	110	108	104	102	95	92	89	86	56	10	0
IPI	202	179	158	140	124	107	99	89	80	77	69	64	59	58	57	56	55	31	6	0

[a]Descriptive analysis

PD-L1 Expression Level ≥5%

	NIVO+IPI	NIVO	IPI
Median, mo (95% CI)	NR (39.1, NR)	NR (33.6, NR)	28.9 (18.1, 44.2)
HR (95% CI) versus IPI	0.56 (0.35, 0.90)	0.65 (0.42, 0.99)	–
HR (95% CI) versus NIVO[a]	0.86 (0.53, 1.41)	–	–



Patients at risk:

NIVO+IPI	68	63	56	55	52	50	45	45	45	44	43	43	43	42	41	41	38	24	3	0
NIVO	80	79	76	74	69	64	61	58	57	54	53	50	47	46	43	42	41	24	6	0
IPI	75	72	66	64	60	55	46	43	40	39	34	34	31	28	28	26	24	13	3	0

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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 AE, %	95.8	59.1	86.3	22.4	86.2	27.7
Treatment-related AE leading to discontinuation, %	40.3	30.4	12.5	8.0	15.1	13.5
Treatment-related death, n (%)	2 (0.6)		1 (0.3)		1 (0.3)	

- No new safety signals were observed with the additional follow-up
- No additional deaths due to study drug toxicity were reported since the prior analysis
  - Previously reported treatment-related deaths were cardiomyopathy and liver necrosis for NIVO+IPI (n = 1 each and both occurred >100 days after last treatment), neutropenia for NIVO (n = 1), and colonic perforation for IPI (n = 1)
- Patients who discontinued NIVO+IPI during induction due to a treatment-related AE had similar 4-year PFS (35%) and OS (54%) to patients in the overall population (37% and 53%, respectively)

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	Nivolumab plus ipilimumab group (n=313)			Nivolumab group (n=313)			Ipilimumab group (n=311)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any treatment-related adverse event	115 (37%)	151 (48%)	34 (11%)	200 (64%)	54 (17%)	16 (5%)	181 (58%)	74 (24%)	12 (4%)
Diarrhoea	112 (36%)	29 (9%)	1 (<1%)	60 (19%)	9 (3%)	0	87 (28%)	18 (6%)	0
Fatigue	107 (34%)	13 (4%)	0	111 (36%)	3 (1%)	0	86 (28%)	3 (1%)	0
Pruritus	106 (34%)	6 (2%)	0	68 (22%)	1 (<1%)	0	112 (36%)	1 (<1%)	0
Rash	83 (27%)	10 (3%)	0	73 (23%)	1 (<1%)	0	64 (21%)	5 (2%)	0
Nausea	81 (26%)	7 (2%)	0	41 (13%)	0	0	49 (16%)	2 (1%)	0
Pyrexia	58 (19%)	1 (<1%)	1 (<1%)	21 (7%)	0	0	20 (6%)	1 (<1%)	0
Decreased appetite	56 (18%)	4 (1%)	0	35 (11%)	0	0	40 (13%)	1 (<1%)	0
Hypothyroidism	53 (17%)	1 (<1%)	0	32 (10%)	0	0	14 (5%)	0	0
Vomiting	41 (13%)	7 (2%)	0	21 (7%)	1 (<1%)	0	23 (7%)	1 (<1%)	0
Arthralgia	41 (13%)	2 (1%)	0	31 (10%)	1 (<1%)	0	22 (7%)	0	0
Headache	33 (11%)	2 (1%)	0	24 (8%)	0	0	25 (8%)	1 (<1%)	0
Increased aspartate aminotransferase	33 (11%)	18 (6%)	1 (<1%)	11 (4%)	3 (1%)	0	10 (3%)	2 (1%)	0
Increased alanine aminotransferase	33 (11%)	25 (8%)	2 (1%)	9 (3%)	3 (1%)	1 (<1%)	7 (2%)	4 (1%)	1 (<1%)
Dyspnoea	33 (11%)	3 (1%)	0	18 (6%)	1 (<1%)	0	12 (4%)	0	0
Maculopapular rash	32 (10%)	6 (2%)	0	14 (5%)	2 (1%)	0	37 (12%)	1 (<1%)	0
Hyperthyroidism	32 (10%)	3 (1%)	0	14 (5%)	0 (0%)	0	3 (1%)	0	0
Vitiligo	28 (9%)	0	0	30 (10%)	1 (<1%)	0	16 (5%)	0	0
Hypophysitis	19 (6%)	5 (2%)	0	1 (<1%)	1 (<1%)	0	7 (2%)	5 (2%)	0
Increased amylase	17 (5%)	9 (3%)	0	14 (5%)	7 (2%)	0	11 (4%)	3 (1%)	1 (<1%)
Colitis	14 (5%)	25 (8%)	1 (<1%)	5 (2%)	3 (1%)	0	11 (4%)	23 (7%)	1 (<1%)
Increased lipase	11 (4%)	19 (6%)	15 (5%)	13 (4%)	6 (2%)	10 (3%)	6 (2%)	8 (3%)	4 (1%)
Dehydration	9 (3%)	5 (2%)	0	1 (<1%)	0	0	3 (1%)	2 (1%)	0
Adrenal insufficiency	5 (2%)	5 (2%)	1 (<1%)	2 (1%)	2 (1%)	0	3 (1%)	1 (<1%)	0
Increased transaminases	2 (1%)	9 (3%)	1 (<1%)	1 (<1%)	1 (<1%)	0	3 (1%)	0	0
Hepatotoxicity	2 (1%)	8 (3%)	0	0	1 (<1%)	0	1 (<1%)	0	0
Hepatitis	2 (1%)	5 (2%)	0	0	0	0	0	0	0

Data are n (%). The table shows grade 1–2 adverse events occurring in at least 10% of patients in any treatment group and all grade 3 and 4 adverse events occurring in at least 2% of patients in any treatment group. A complete table of adverse events showing grade 1–2 events occurring in at least 5% of patients in any group and all grade 3 and 4 events is in the appendix (pp 5–8).

Table 2: **Treatment-related adverse events**

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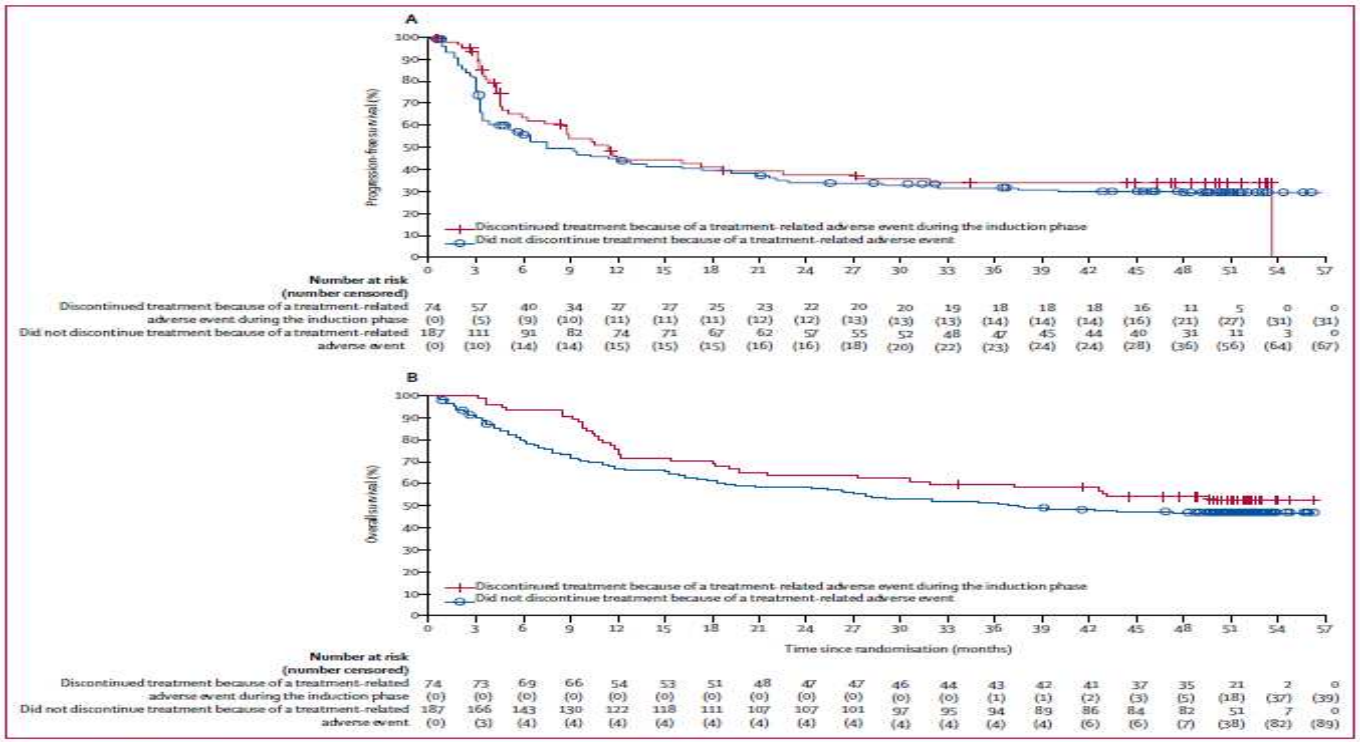

Figure 4: **Post-hoc Kaplan-Meier estimates of (A) progression-free survival and (B) overall survival in patients treated with combination therapy who discontinued treatment because of a treatment-related adverse event during the induction phase and those who did not discontinue treatment because of a treatment-related adverse event**

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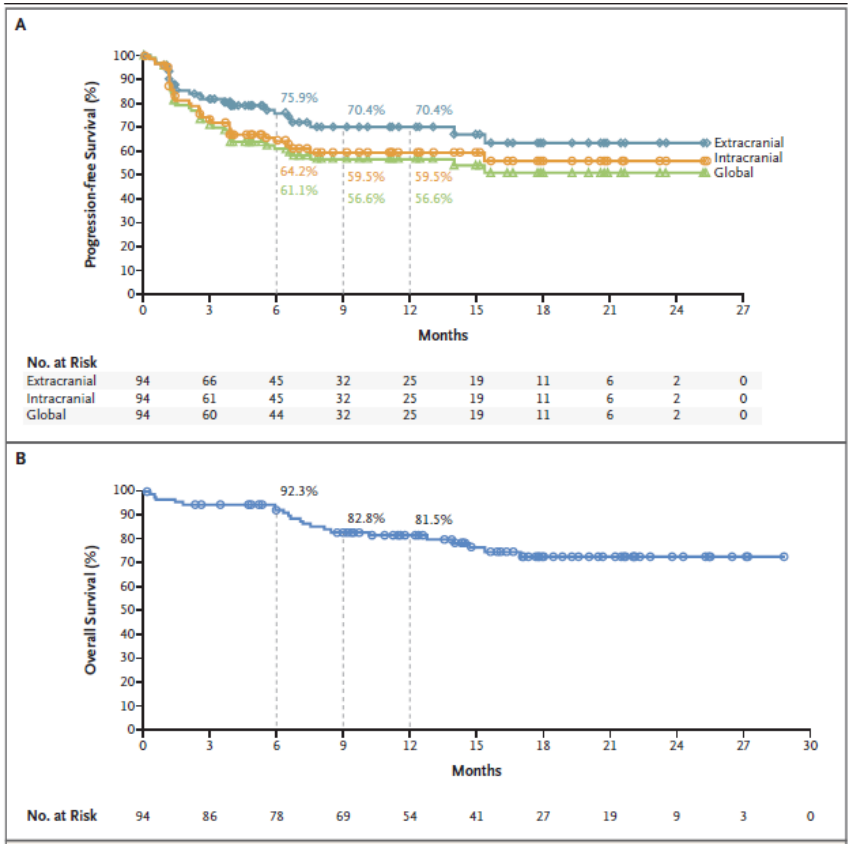
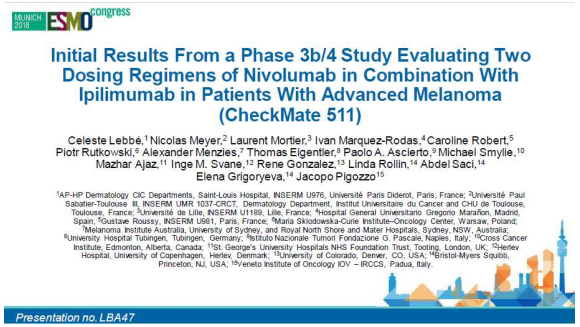
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain

Hussein A. Tawbi, M.D., Ph.D., Peter A. Forsyth, M.D., Alain Algazi, M.D., Omid Hamid, M.D., F. Stephen Hodi, M.D., Stergios J. Moschos, M.D., Nikhil I. Khushalani, M.D., Karl Lewis, M.D., Christopher D. Lao, M.D., M.P.H., Michael A. Postow, M.D., Michael B. Atkins, M.D., Marc S. Ernstoff, M.D., David A. Reardon, M.D., Igor Puzanov, M.D., Ragini R. Kudchadkar, M.D., Reena P. Thomas, M.D., Ph.D., Ahmad Tarhini, M.D., Ph.D., Anna C. Pavlick, D.O., Joel Jiang, Ph.D., Alexandre Avila, M.D., Ph.D., Sheena Demelo, M.D., and Kim Margolin, M.D.





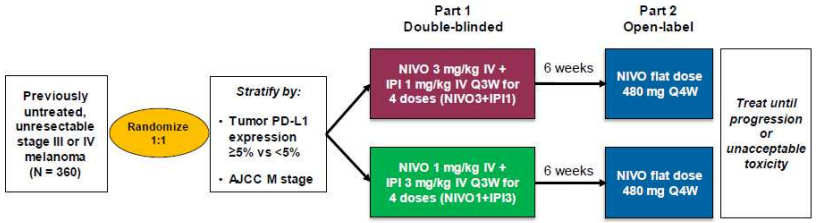


Table 2. Safety summary[a]

	NIVO3+IPI1 (n = 180)	NIVO1+IPI3 (n = 178)
Rate of treatment-related grade 3-5 AEs, % (n/N) (95% CI)	**33.9%** (61/180) (27.0–41.3)	**48.3%** (86/178) (40.8–55.9)
Difference between treatment-related grade 3-5 AE rates (95% CI)	**-14.4%** (-24.5 to -4.3)	
***P* value**	**0.0059**	
Treatment-related AEs, %	85.6	93.8
Grade 3–4	33.3	48.3
Grade 5	0.6	0
All cause serious AEs, %	47.8	63.5
Grade 3–4	33.9	47.8
Grade 5	3.3	1.7
Treatment-related AEs leading to discontinuation, %	23.9	33.1
Grade 3–4	16.7	27.5
Grade 5	0.6	0

[a]Includes events reported between the first dose and 30 days after the last dose of study therapy

Table 3. Treatment-related AEs

Treatment-related AEs of any grade ≥10%	NIVO3+IPI1 (n = 180)		NIVO1+IPI3 (n = 178)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Any AE, %	85.6	33.3	93.8	48.3
Diarrhea	26.1	2.8	30.9	6.2
Fatigue	24.4	0.6	21.9	0.6
Pruritus	23.9	0.6	26.4	0
Rash	17.2	0	26.4	0.6
Asthenia	16.1	0	23.6	1.7
Hypothyroidism	13.9	0	20.2	0
Nausea	12.2	0	18.5	2.8
Hyperthyroidism	10.6	0	17.4	1.7
Decreased appetite	10.6	0	10.7	1.7
Vitiligo	10.6	0	6.2	0
Alanine aminotransferase increased	8.9	1.7	18.0	4.5
Aspartate aminotransferase increased	7.8	0.6	15.2	2.8
Pyrexia	7.8	0	19.7	1.1
Headache	7.2	0	14.0	0
Dry mouth	6.1	0.6	11.8	0.6
Vomiting	5.0	0.6	12.4	1.7

MUNICH 2018 ESMO congress

Initial Results From a Phase 3b/4 Study Evaluating Two Dosing Regimens of Nivolumab in Combination With Ipilimumab in Patients With Advanced Melanoma (CheckMate 511)

Celeste Lebbé,[1] Nicolas Meyer,[2] Laurent Mortier,[3] Ivan Marquez-Rodas,[4] Caroline Robert,[5] Piotr Rutkowski,[6] Alexander Menzies,[7] Thomas Eigentler,[8] Paolo A. Ascierto,[9] Michael Smylie,[10] Mazhar Ajaz,[11] Inge M. Svane,[12] Rene Gonzalez,[13] Linda Rollin,[14] Abdel Saci,[14] Elena Grigoryeva,[14] Jacopo Pigozzo[15]

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Presentation no. LBA47

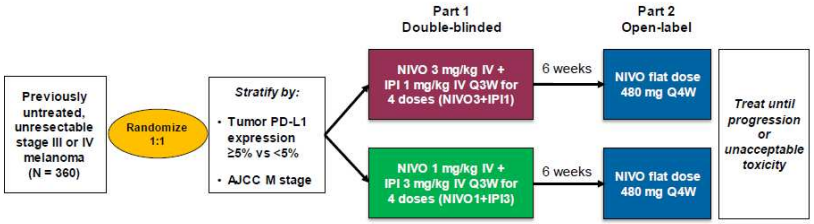
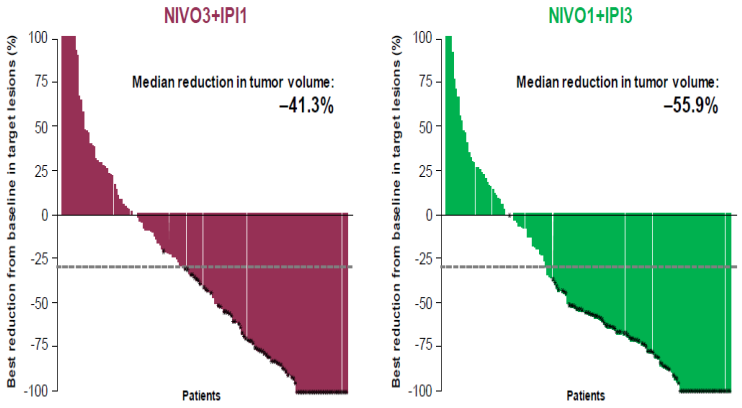


Table 4. Response per investigator assessment

	NIVO3+IPI1 (n = 180)	NIVO1+IPI3 (n = 178)
Best overall response, %		
Complete response	15.0	13.5
Partial response	30.6	37.1
Stable disease	11.7	11.8
Progressive disease	34.4	26.4
Unknown	8.3	11.2
ORR, % (95% CI)	**45.6% (38.1–53.1)**	**50.6% (43.0–58.1)**
Median time to response, months	2.83	2.79
Ongoing responses, %	76.8	75.6
Median duration of response, months	NR	NR

NR, not reached

Figure 2. Tumor burden change from baseline in target lesions[a]



[a]Based on investigator-assessed responses

MUNICH 2018 ESMO congress

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Celeste Lebbé,[1] Nicolas Meyer,[2] Laurent Mortier,[3] Ivan Marquez-Rodas,[4] Caroline Robert,[5] Piotr Rutkowski,[6] Alexander Menzies,[7] Thomas Eigentler,[8] Paolo A. Ascierto,[9] Michael Smylie,[10] Mazhar Ajaz,[11] Inge M. Svane,[12] Rene Gonzalez,[13] Linda Rollin,[14] Abdel Saci,[14] Elena Grigoryeva,[14] Jacopo Pigozzo[15]

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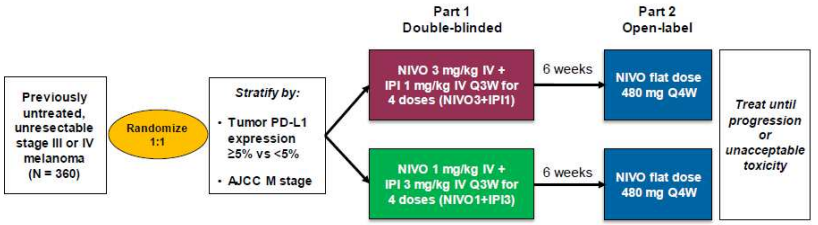
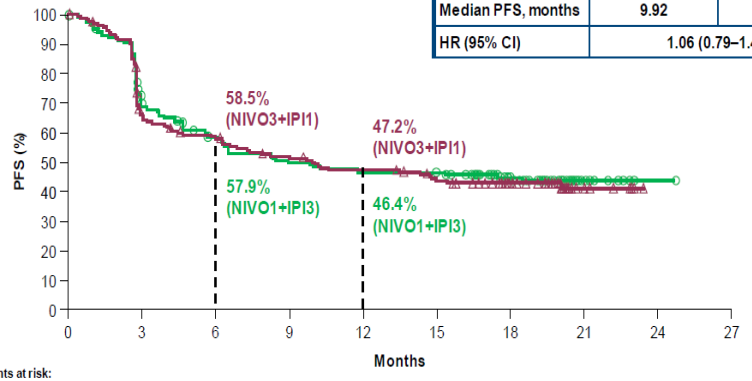


A. Progression-free survival

	NIVO3+IPI1 (n = 180)	NIVO1+IPI3 (n = 178)
Median PFS, months	9.92	8.94
HR (95% CI)	1.06 (0.79–1.42)	

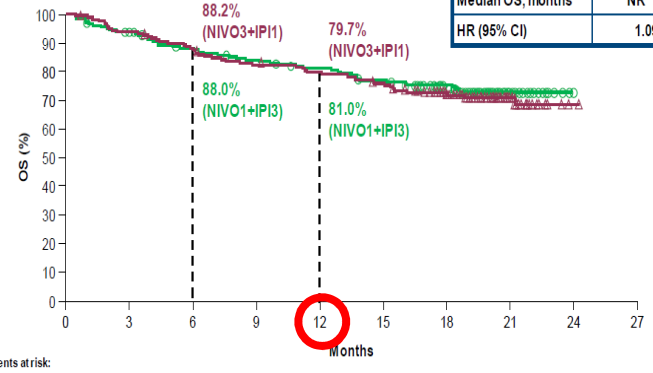


Patients at risk:

NIVO3+IPI1	180	105	90	78	70	62	37	5	0	0
NIVO1+IPI3	178	110	86	74	69	67	44	9	1	0

B. Overall survival

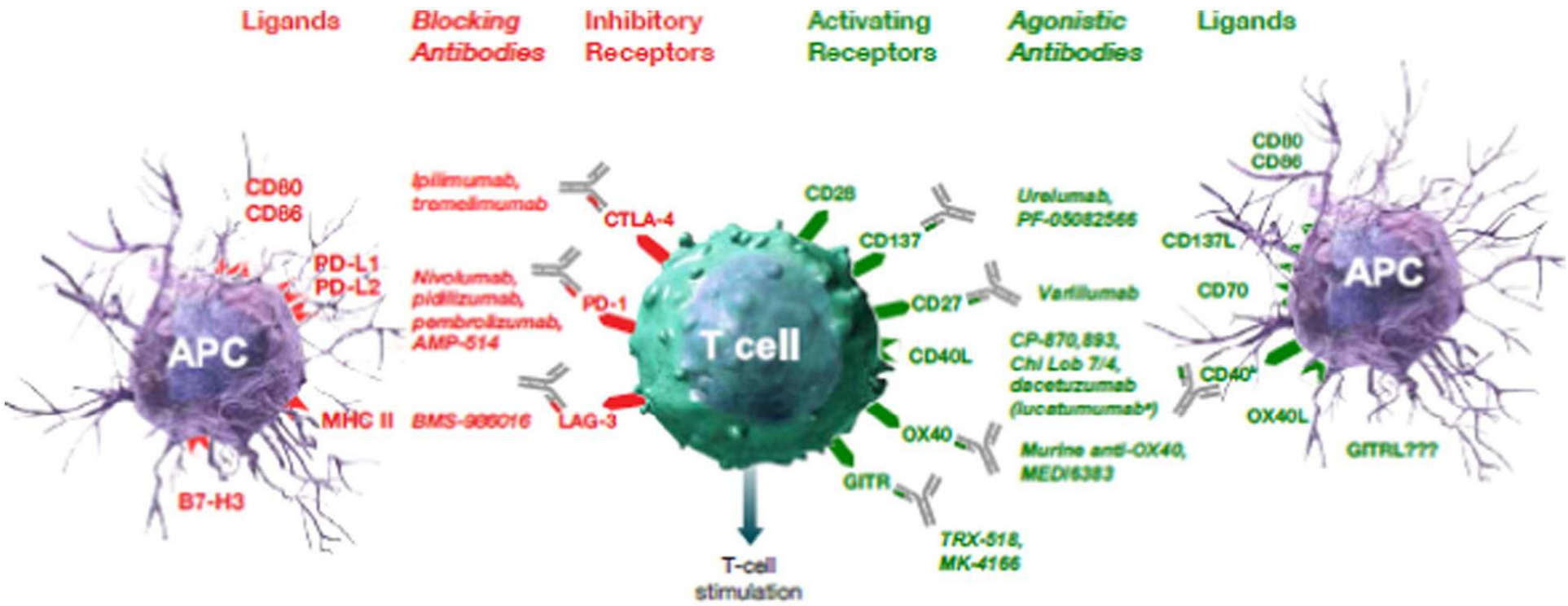
	NIVO3+IPI1 (n = 180)	NIVO1+IPI3 (n = 178)
Median OS, months	NR	NR
HR (95% CI)	1.09 (0.73–1.62)	



Patients at risk:

NIVO3+IPI1	180	168	157	146	140	132	106	39	1	0
NIVO1+IPI3	178	164	151	143	136	128	104	28	0	0

NR, not reached



Ligand - directed Antibodies

Anti-PD-L1: BMS-936559
MPDL3280A
MSB0010718C
MEDI4736

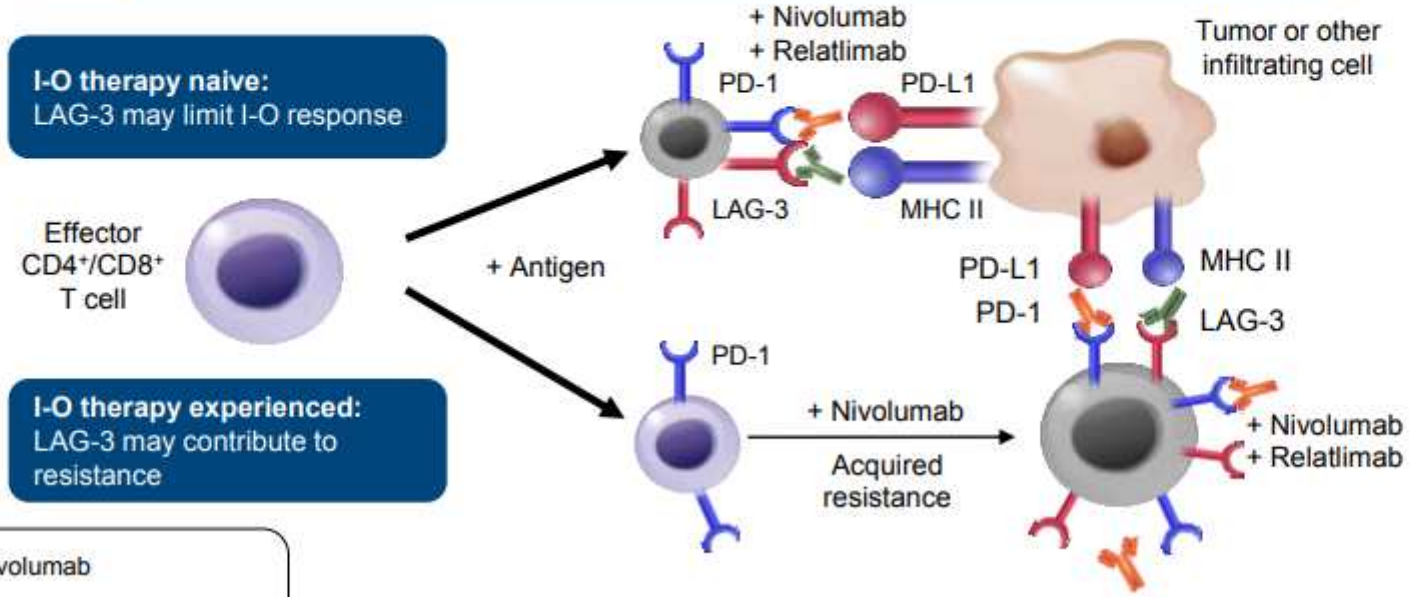
Anti-B7-H3: MGA271

Ligand - directed Antibodies

Anti-CD70: BMS-936561
ARGX-110

Potential Role of LAG-3 in T-Cell Exhaustion and Anti–PD-1 Resistance

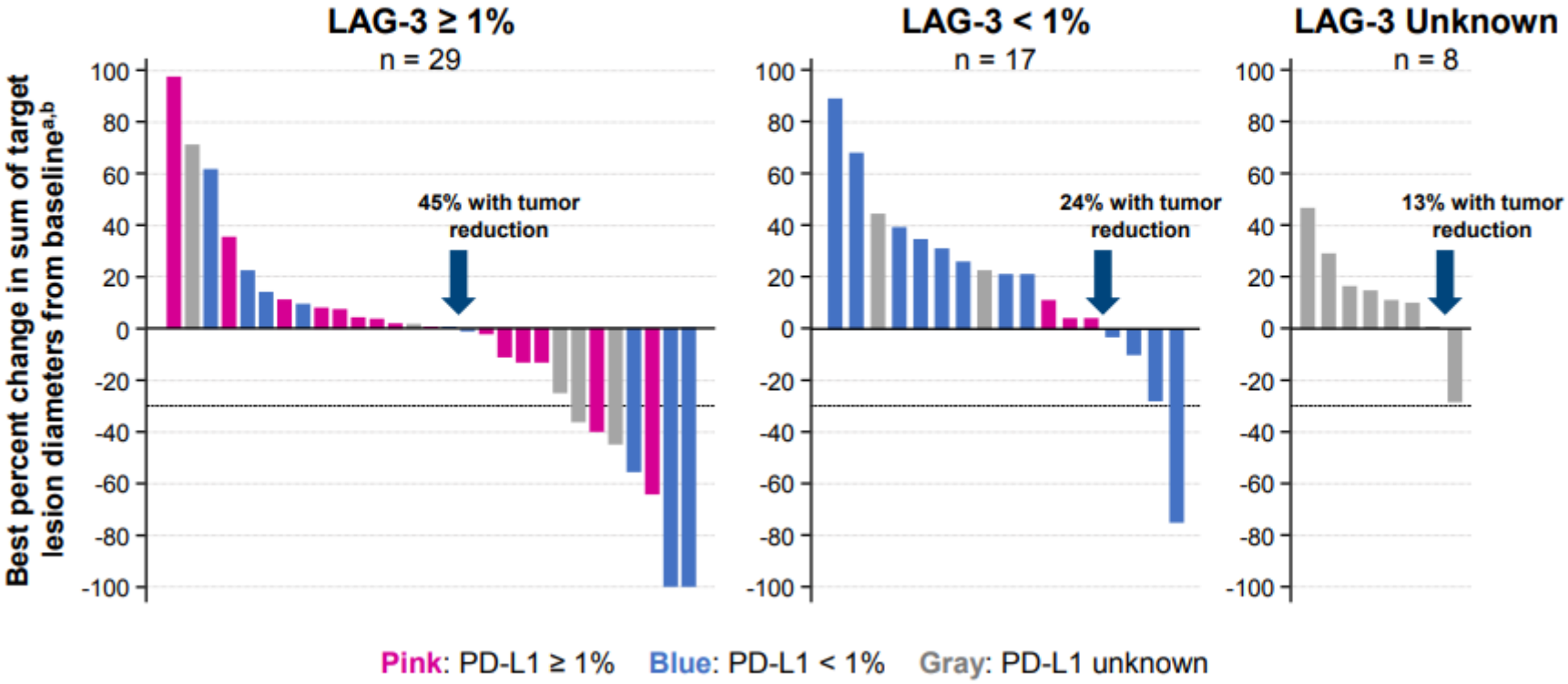
- **LAG-3 regulates a checkpoint pathway that limits the activity of T cells[1]**
- **LAG-3 and PD-1 receptors are overexpressed and/or co-expressed on tumor-infiltrating lymphocytes in melanoma[2,3]**



I-O, immuno-oncology; MHC II, major histocompatibility complex class II; PD-1, programmed death-1; PD-L1, programmed death ligand 1.

1. Grosso JF et al. *J Clin Invest*. 2007;117:3383–3392. 2. Goding SR et al. *J Immunol*. 2013;190:4899–4909. 3. Taube JM et al. *Clin Cancer Res*. 2015;21:3969–3976.

Best Change in Target Lesion Size by LAG-3 and PD-L1 Expression

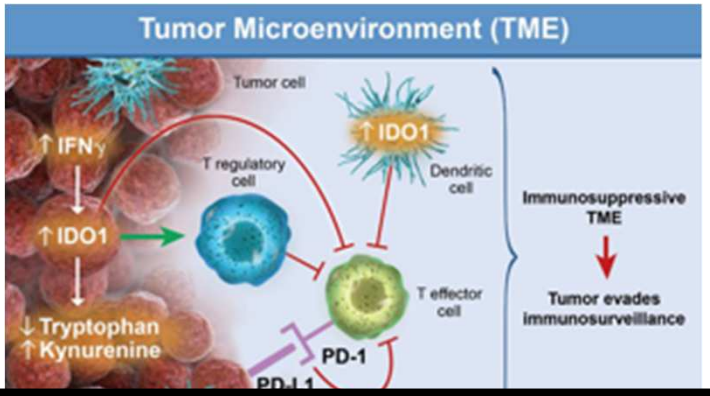


[a]Six patients with clinical progression prior to their first scan and 1 with PD due to a new symptomatic brain metastasis prior to getting full scans were not included.
[b]One patient with best change from baseline > 30% had a best response of SD.

Epacadostat Plus Pembrolizumab Versus Pembrolizumab Alone in Patients With Unresectable or Metastatic Melanoma: Results of the Phase 3 ECHO-301/KEYNOTE-252 Study

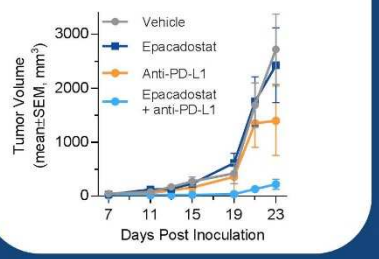
Georgina V. Long,[1] Reinhard Dummer,[2] Omid Hamid,[3] Thomas Gajewski,[4] Christian Caglevic,[5] Stephane Dalle,[6] Ana Arance,[7] Matteo S. Carlino,[8] Jean-Jacques Grob,[9] Tae Min Kim,[10] Lev Demidov,[11] Caroline Robert,[12] James Larkin,[13] James R. Anderson,[14] Janet Maleski,[15] Mark Jones,[15] Scott J. Diede,[14] Tara C. Mitchell[16]

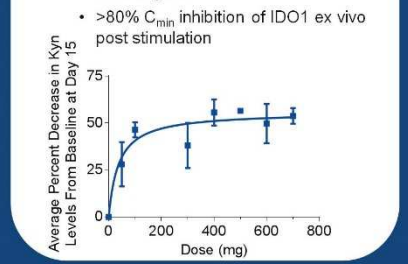
[1]Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals, Sydney, Australia; [2]University Hospital Zürich, Zurich, Switzerland; [3]The Angeles Clinic and Research Institute, Los Angeles, CA, USA; [4]University of Chicago Medical Center, Chicago, IL, USA; [5]Fundacion Arturo Lopez Perez, Santiago, Chile; [6]Hospices Civils De Lyon, Cancer Research Center of Lyon, Claude Bernard University Lyon, Pierre Benite, France; [7]Hospital Clinic de Barcelona, Barcelona, Spain; [8]Westmead and Blacktown Hospitals, Melanoma Institute Australia, The University of Sydney, Sydney, Australia; [9]Aix-Marseille University, Marseille, France; [10]Seoul National University Hospital, Seoul, South Korea; [11]N.N. Blokhin Russian Cancer Research Center, Moscow, Russia; [12]Gustave Roussy Comprehensive Cancer Center, Villejuif, France; [13]The Royal Marsden NHS Foundation Trust, London, United Kingdom; [14]Merck & Co., Inc., Kenilworth, NJ, USA; [15]Incyte Corporation, Wilmington, DE, USA; [16]Abramson Cancer Center of the University of Philadelphia, Philadelphia, PA, USA



? = No MTD determined
? = No target inhibition demonstrated in human tumor biopsies
? = 95% CI ORR may overlap with KNOO6 ORR
? = Median and landmark 6-mths and 1y PFS

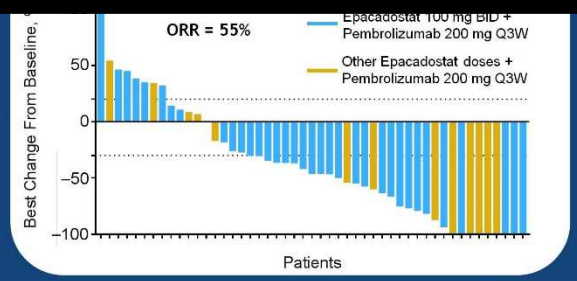
Back





BID, twice daily; IDO1, indoleamine 2,3 dioxygenase 1; Kyn, kynurenine; mAb; monoclonal antibody; PD-L1, programmed death ligand-1.
1. WIPO #WO/2014/056834 https://patentscope.wipo.int/ Accessed August 2, 2017. 2. Spranger S, et al. *J Immunother Cancer*. 2014;2:3. 3. Beatty GL, et al. *Clin Cancer Res*. 2017;23:3269-3276, with permission from AACR.

sing



- , 100, or 300 mg PO BID + Pembrolizumab 200 mg IV Q3W
- MTD of epacadostat not reached
- Phase 2: Epacadostat 100 mg PO BID
- Phase 1/2 efficacy in treatment-naive melanoma:
  - ORR = 55%
  - Median PFS = 22.8 mo (12.4 mo all melanoma)

BID, twice daily; MTD, maximally tolerated dose; PD-L1, programmed death ligand-1; Q3W, every 3 weeks.
Hamid O, et al. *Ann Oncol*. 2017;28(suppl 5):1214O.

Study Design: Phase III Randomized Controlled Trial

Key Eligibility Criteria

- Unresectable stage III or IV melanoma, advanced/metastatic disease
  - Patients with *BRAF* mutation could have received prior BRAF/MEK therapy
  - Prior anti-CTLA-4 or interferon in adjuvant setting permitted
- ECOG performance status 0–1
- No active CNS metastases

N=706
R 1:1

Epacadostat 100 mg PO BID
+
Pembrolizumab 200 mg IV Q3W
n=354

Placebo
+
Pembrolizumab 200 mg IV Q3W
n=352

Stratification

- PD-L1 status (positive[a] vs negative)
- *BRAF* mutation status
  - Wild type
  - Mutant with prior *BRAF*-directed therapy
  - Mutant without prior *BRAF*-directed therapy

- **Primary endpoints:** PFS (RECIST v1.1) and OS
- **Secondary endpoints:** ORR (RECIST v1.1), DOR, safety

BID, twice daily; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria In Solid Tumors.
[a]≥1% staining in tumor and adjacent immune cells as assessed by IHC (22C3 antibody).

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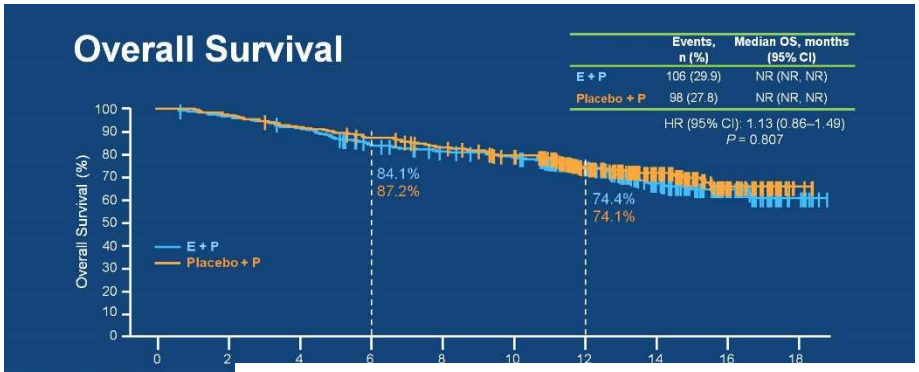
Overall Survival



	Events, n (%)	Median OS, months (95% CI)
E + P	106 (29.9)	NR (NR, NR)
Placebo + P	98 (27.8)	NR (NR, NR)

HR (95% CI): 1.13 (0.86–1.49)
P = 0.807

Number at risk

E + P	354	340
Placebo + P	352	342

CI, confidence interval; E, epacadostat; HR, hazard ratio

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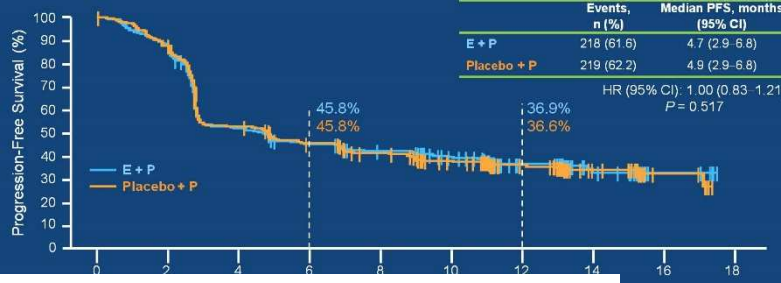
Progression-Free Survival (RECIST v1.1, BICR)



	Events, n (%)	Median PFS, months (95% CI)
E + P	218 (61.6)	4.7 (2.9–6.8)
Placebo + P	219 (62.2)	4.9 (2.9–6.8)

HR (95% CI): 1.00 (0.83–1.21)
P = 0.517

	5	0
	7	0

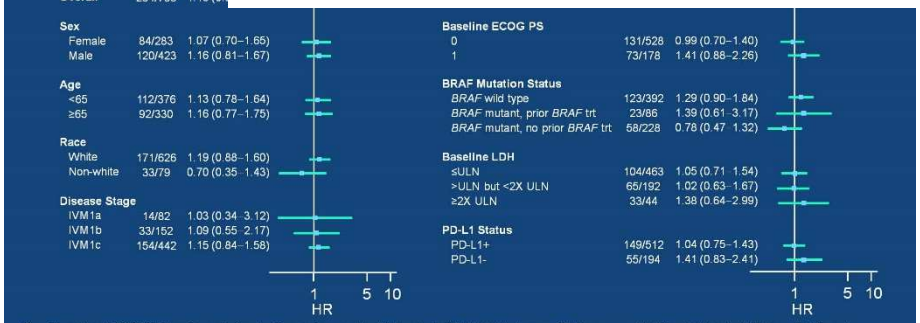
valuation Criteria In Solid Tumors.

10

Incyte's shares plunged 23% on the news, wiping out more than $3.5 billion in market cap. The implications for other IDO1 drugs also damaged other companies in the field, including NewLink $NLNK, down 44%, as well as Bristol-Myers Squibb $BMY down 2.6%.

Overall S

	# Events/N	HR (9
Overall	204/706	1.13 (0.8
Sex		
Female	84/283	1.07 (0.70–1.65)
Male	120/423	1.16 (0.81–1.67)
Age		
<65	112/376	1.13 (0.78–1.64)
≥65	92/330	1.16 (0.77–1.75)
Race		
White	171/626	1.19 (0.88–1.60)
Non-white	33/79	0.70 (0.35–1.43)
Disease Stage		
IVM1a	14/82	1.03 (0.34–3.12)
IVM1b	33/152	1.09 (0.55–2.17)
IVM1c	154/442	1.15 (0.84–1.58)
Baseline ECOG PS		
0	131/528	0.99 (0.70–1.40)
1	73/178	1.41 (0.88–2.26)
BRAF Mutation Status		
BRAF wild type	123/392	1.29 (0.90–1.84)
BRAF mutant, prior *BRAF* trt	23/86	1.39 (0.61–3.17)
BRAF mutant, no prior *BRAF* trt	58/228	0.78 (0.47–1.32)
Baseline LDH		
≤ULN	104/463	1.05 (0.71–1.54)
>ULN but <2X ULN	65/192	1.02 (0.63–1.67)
≥2X ULN	33/44	1.38 (0.64–2.99)
PD-L1 Status		
PD-L1+	149/512	1.04 (0.75–1.43)
PD-L1-	55/194	1.41 (0.83–2.41)



CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; LDH, lactate dehydrogenase; PD-L1, programmed death ligand 1; trt, treatment; ULN, upper limit of normal.

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PRESENTED BY: Georgina V. Long

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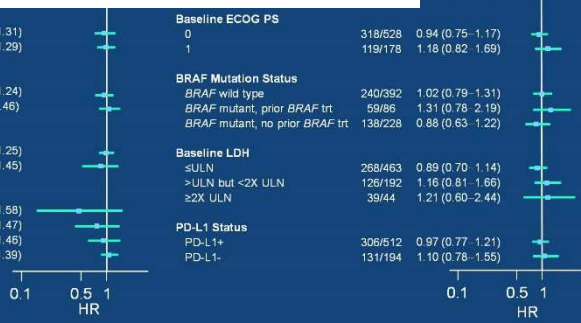
roups

		HR (95% CI)
		00 (0.83–1.21)
Sex		
Female	182/283	0.97 (0.73–1.31)
Male	255/423	1.01 (0.79–1.29)
Age		
<65	240/376	0.96 (0.74–1.24)
≥65	197/330	1.1 (0.83–1.46)
Race		
White	372/626	1.02 (0.83–1.25)
Non-white	65/79	0.87 (0.52–1.45)
Disease Stage		
III	18/26	0.47 (0.14–1.58)
IVM1a	44/82	0.79 (0.42–1.47)
IVM1b	82/152	0.94 (0.60–1.46)
IVM1c	291/442	1.11 (0.88–1.39)
Baseline ECOG PS		
0	318/528	0.94 (0.75–1.17)
1	119/178	1.18 (0.82–1.69)
BRAF Mutation Status		
BRAF wild type	240/392	1.02 (0.79–1.31)
BRAF mutant, prior *BRAF* trt	59/86	1.31 (0.78–2.19)
BRAF mutant, no prior *BRAF* trt	138/228	0.88 (0.63–1.22)
Baseline LDH		
≤ULN	268/463	0.89 (0.70–1.14)
>ULN but <2X ULN	126/192	1.16 (0.81–1.66)
≥2X ULN	39/44	1.21 (0.60–2.44)
PD-L1 Status		
PD-L1+	306/512	0.97 (0.77–1.21)
PD-L1-	131/194	1.10 (0.78–1.55)



CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; LDH, lactate dehydrogenase; PD-L1, programmed death ligand 1; trt, treatment; ULN, upper limit of normal.

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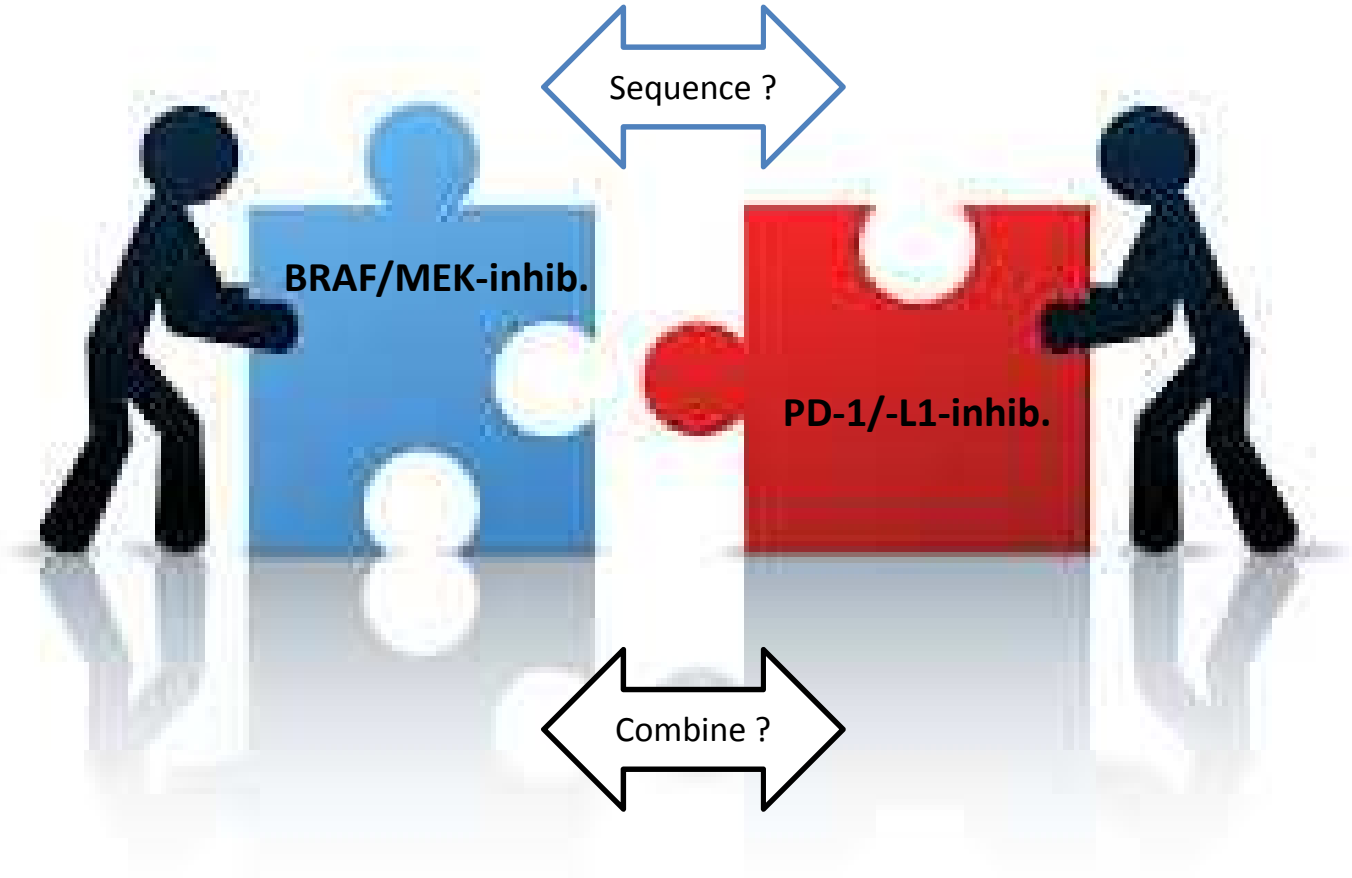
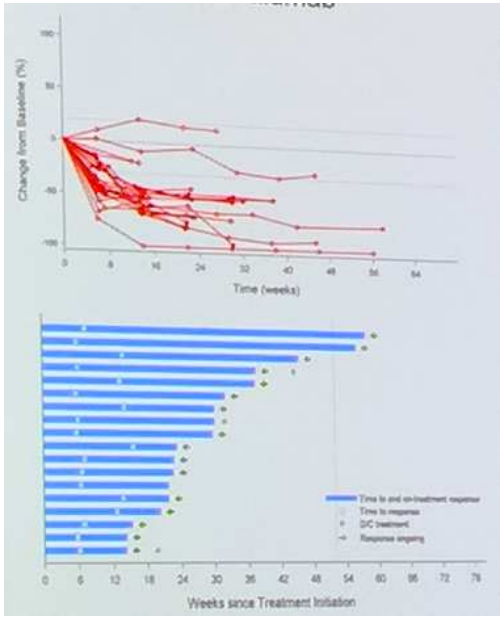
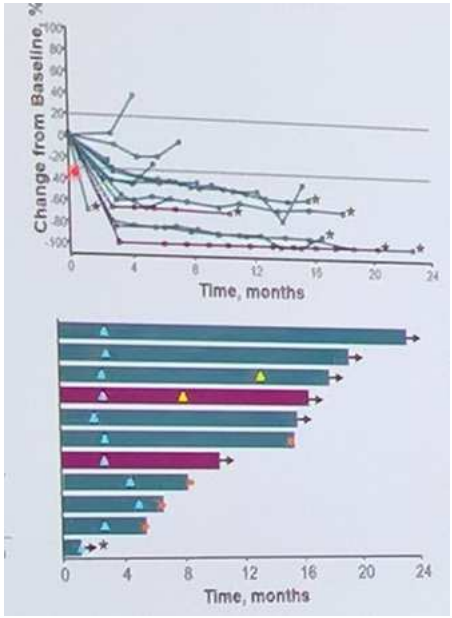
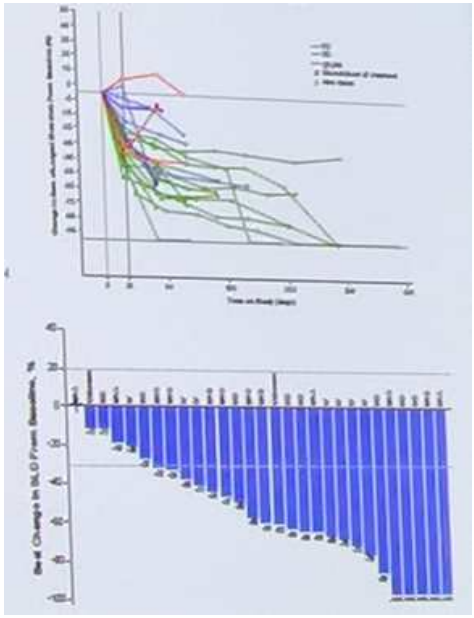

Sequence ?
BRAF/MEK-inhib.
PD-1/-L1-inhib.
Combine ?

Phase I clinical trials on BRAF/MEK-inhibitors + anti-PD-1/-L1 mAb

Dabrafenib/Trametinib Durvalumab	Dabrafenib/Trametinib Pembrolizumab	Vemurafenib/Cobimetinib Atezolizumab
		
Ribas*et al.* ASCO AM 2015	Ribas *et al*. ESMO 2017	Hwu et al. ESMO 2016

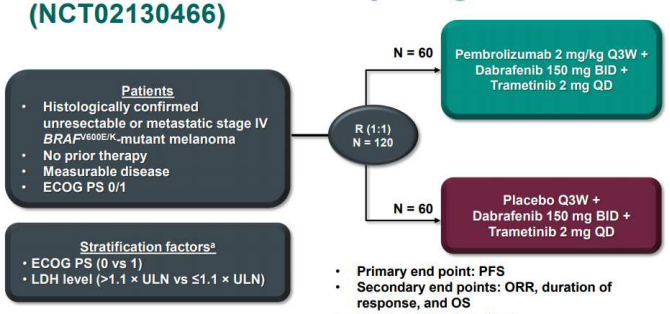
KEYNOTE-022 Part 3: Phase 2 Randomized Study of First-Line Dabrafenib and Trametinib Plus Pembrolizumab or Placebo for *BRAF*-Mutant Advanced Melanoma

P. A. Ascierto,[1,a] P. F. Ferrucci,[2,a] R. Fisher,[3] M. Del Vecchio,[4] V. Atkinson,[5] H. Schmidt,[6] J. Schachter,[7] P. Queirolo,[8] G. V. Long,[9] A. M. Di Giacomo,[10] I.M. Svane,[11] M. Lotem,[12] G. Bar-Sela,[13] F. Couture,[14] B. Mookerjee,[15] R. Ghori,[16] N. Ibrahim,[16] B. Homet Moreno,[16] A. Ribas[17]

[a]Both authors contributed equally

[1]Istituto Nazionale Tumori Fondazione G. Pascale, Napoli, Italy; [2]European Institute of Oncology, IRCCS, Milan, Italy; [3]Auckland City Hospital, Auckland, New Zealand; [4]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [5]Gallipoli Medical Research Foundation, Greenslopes Private Hospital, Brisbane, QLD, Australia; [6]Aarhus University Hospital, Aarhus, Denmark; [7]Ella Lemelbaum Institute for Melanoma, The Chaim Sheba Medical Center at Tel HaShomer, Cancer Center (Oncology Institute), Ra mat Gan, Israel; [8]IRCCS San Martino-IST, Genova, Italy; [9]Melanoma Institute Australia and the University of Sydney, Sydney, NSW, Australia; [10]Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy; [11]Herlev Hospital, University of Copenhagen, Herlev, Denmark; [12]Sharett Institute of Oncology, Hadassah Hebrew Medical Center, Jerusalem, Israel; [13]Rambam Health Care Campus, Haifa, Israel; [14]Centre Hospitalier Universitaire de Québec Research Center, Laval University, Québec, QC, Canada; [15]Novartis, East Hanover, NJ, USA; [16]Merck & Co., Inc., Kenilworth, NJ, USA; [17]Ronald Reagan UCLA Medical Center, Los Angeles, CA, USA

KEYNOTE-022 Part 3 Study Design (NCT02130466)

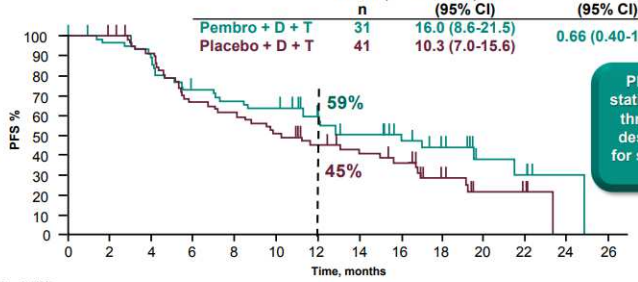


- Primary end point: PFS
- Secondary end points: ORR, duration of response, and OS
- Data cutoff: Feb 15, 2018

[a]Owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.

Progression-Free Survival

	Events, n	Median,[a] mo (95% CI)	HR[b] (95% CI)[b]	*P* Value[c]
Pembro + D + T	31	16.0 (8.6-21.5)	0.66 (0.40-1.07)	0.04287
Placebo + D + T	41	10.3 (7.0-15.6)		



PFS did not reach statistical significance threshold per study design (required HR for significance ≤0.62, $P \leq 0.025$)

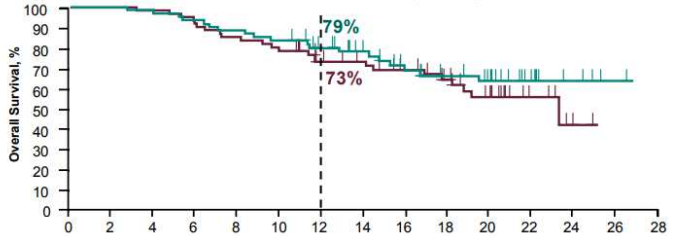
No. at risk

Pembro + D + T	60	55	49	39	36	34	27	21	17	12	5	4	1	0
Placebo + D + T	60	59	52	38	35	29	23	20	16	9	4	3	0	0

[a]Based on Kaplan-Meier estimate of PFS, per investigator assessment.
[b]Based on Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs 1) and LDH (LDH >1.1 × ULN vs =1.1 × ULN); owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.
[c]One-sided *P* value based on stratified log-rank test.
Data cutoff: Feb 15, 2018.

Overall Survival

	Events, n	Median[a] (95% CI), mo	HR[b] (95% CI)[b]	*P* Value[c]
Pembro + D + T	19	NR (19.6-NR)	0.76 (0.41-1.39)	0.18467
Placebo + D + T	24	23.4 (17.8-NR)		



No. at risk

Pembro + D + T	60	60	59	56	53	50	43	35	29	23	18	9	4	1	0
Placebo + D + T	60	60	59	55	51	47	39	36	31	25	18	7	2	0	0

[a]Based on Kaplan-Meier estimate of overall survival.
[b]Based on Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs 1) and LDH (>1.1 × ULN vs ≤1.1 × ULN; owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.
[c]*P* values are provided for descriptive purposes only, no multiplicity adjustment is made. One-sided *P* value based on stratified log-rank test.
Data cutoff: Feb 15, 2018.

Ongoing randomized clinical trials on BRAF/MEK-inhibitors + anti-PD-1/-L1

Clinical trial	Agents			Primary Endpoint	Phase & Patient No.	Recruitment Status	Expected Reporting Date
NCT02130466 (MK-3475-022/KEYNOTE-022 Part 3, MSD)	Dabrafenib Trametinib + Pembrolizumab	Vs.	Dabrafenib Trametinib + Placebo	PFS	Phase II No.: 120	Completed (APR 2017)	Q2 2018
NCT02908672 (Trilogy, Roche)	Vemurafenib CoBimetinib + Atezolizumab	Vs.	Vemurafenib/Cobimetinib Placebo	PFS	Phase III No.: 500	Ongoing	Q4 2019
NCT02967692 (Combi-I, Novartis)	Dabrafenib Trametinib + PDR001	Vs.	Dabrafenib Trametinib + Placebo	PFS	Phase III No.: 500	Ongoing	Q4 2020

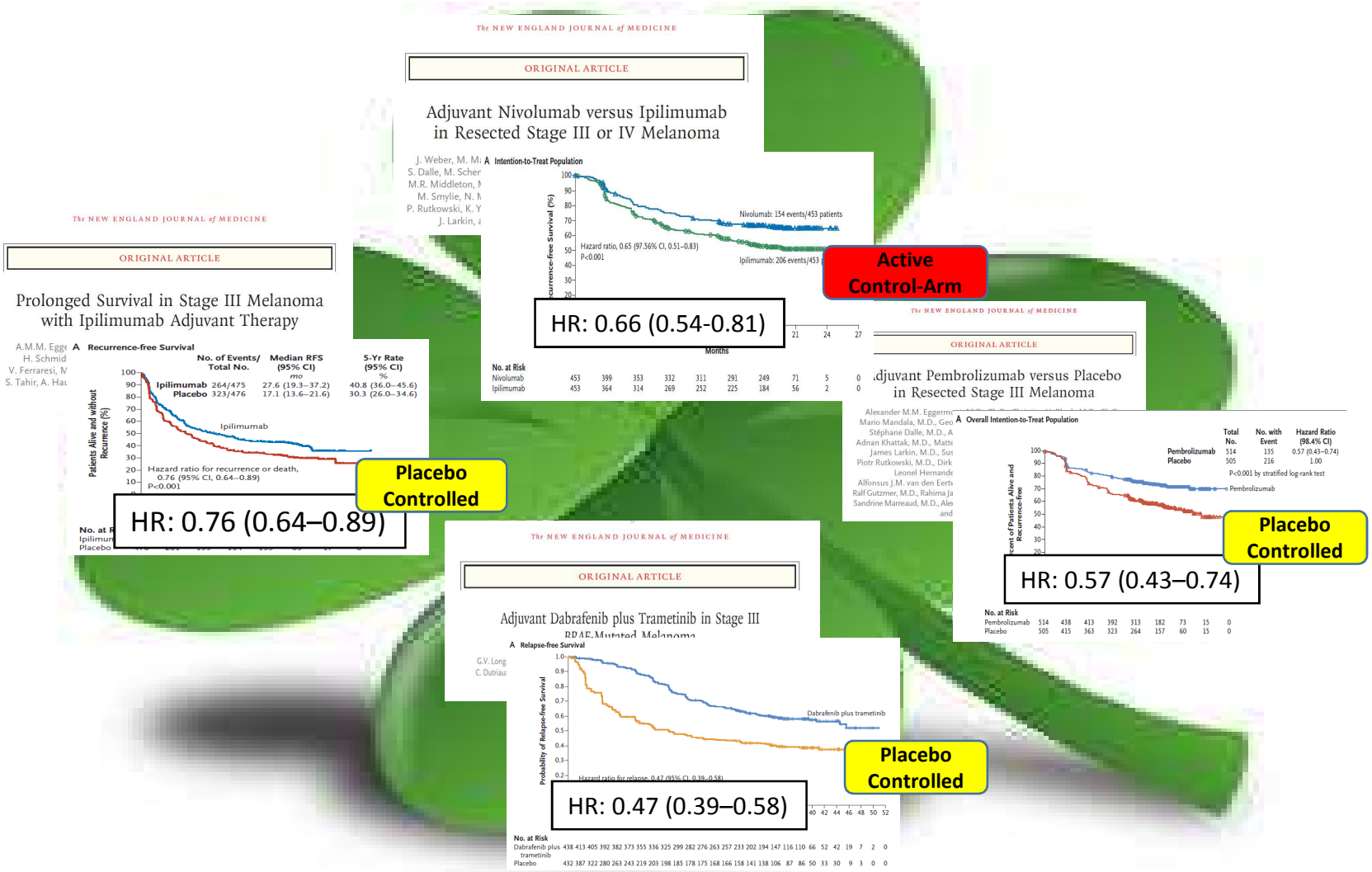
The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE
Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma
J. Weber, M. Mandala, M. Del Vecchio, H.J. Gogas, A.M. Arance, C.L. Cowey, S. Dalle, M. Schenker, V. Chiarion-Sileni, I. Marquez-Rodas, J.-J. Grob, M.O. Butler, M.R. Middleton, M. Maio, V. Atkinson, P. Queirolo, R. Gonzalez, R.R. Kudchadkar, M. Smylie, N. Meyer, L. Mortier, M.B. Atkins, G.V. Long, S. Bhatia, C. Lebbé, P. Rutkowski, K. Yokota, N. Yamazaki, T.M. Kim, V. de Pril, J. Sabater, A. Qureshi, J. Larkin, and P.A. Ascierto, for the CheckMate 238 Collaborators*
The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE
Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy
A.M.M. Eggermont, V. Chiarion-Sileni, J.-J. Grob, R. Dummer, J.D. Wolchok, H. Schmidt, O. Hamid, C. Robert, P.A. Ascierto, J.M. Richards, C. Lebbé, V. Ferraresi, M. Smylie, J.S. Weber, M. Maio, L. Bastholt, L. Mortier, L. Thomas, S. Tahir, A. Hauschild, J.C. Hassel, F.S. Hodi, C. Taitt, V. de Pril, G. de Schaetzen, S. Suciu, and A. Testori
The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE
Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma
Alexander M.M. Eggermont, M.D., Ph.D., Christian U. Blank, M.D., Ph.D., Mario Mandala, M.D., Georgina V. Long, M.D., P.D., Victoria Atkinson, M.D., Stéphane Dalle, M.D., Andrew Haydon, M.D., Mikhail Lichinitser, M.D., Adnan Khattak, M.D., Matteo S. Carlino, M.D., Ph.D., Shahneen Sandhu, M.D., James Larkin, M.D., Susana Puig, M.D., Ph.D., Paolo A. Ascierto, M.D., Piotr Rutkowski, M.D., Dirk Schadendorf, M.D., Ph.D., Rutger Koornstra, M.D., Leonel Hernandez-Aya, M.D., Michele Maio, M.D., Ph.D., Alfonsus J.M. van den Eertwegh, M.D., Ph.D., Jean-Jacques Grob, M.D., Ph.D., Ralf Gutzmer, M.D., Rahima Jamal, M.D., Paul Lorigan, M.D., Nageatte Ibrahim, M.D., Sandrine Marreaud, M.D., Alexander C.J. van Akkooi, M.D., Ph.D., Stefan Suciu, Ph.D., and Caroline Robert, M.D., Ph.D.
The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE
Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma
G.V. Long, A. Hauschild, M. Santinami, V. Atkinson, M. Mandalà, V. Chiarion-Sileni, J. Larkin, M. Nyakas, C. Dutriaux, A. Haydon, C. Robert, L. Mortier, J. Schachter, D. Schadendorf, T. Lesimple, R. Plummer, R. Ji, P. Zhang, B. Mookerjee, J. Legos, R. Kefford, R. Dummer, and J.M. Kirkwood

- **Stage IIIB, IIIC, or IV melanoma**
- **CLND or metastasectomy required <12 weeks before randomization**

- **Stage IIIA (N1a with micrometastasis >1 mm), stage IIIB or IIIC with no in-transit metastases**
- **CLND required <12w before randomization**

- **Stage IIIA (N1a with micrometastasis >1 mm), stage IIIB or IIIC with no in-transit metastases**
- **CLND required <12w before randomization**

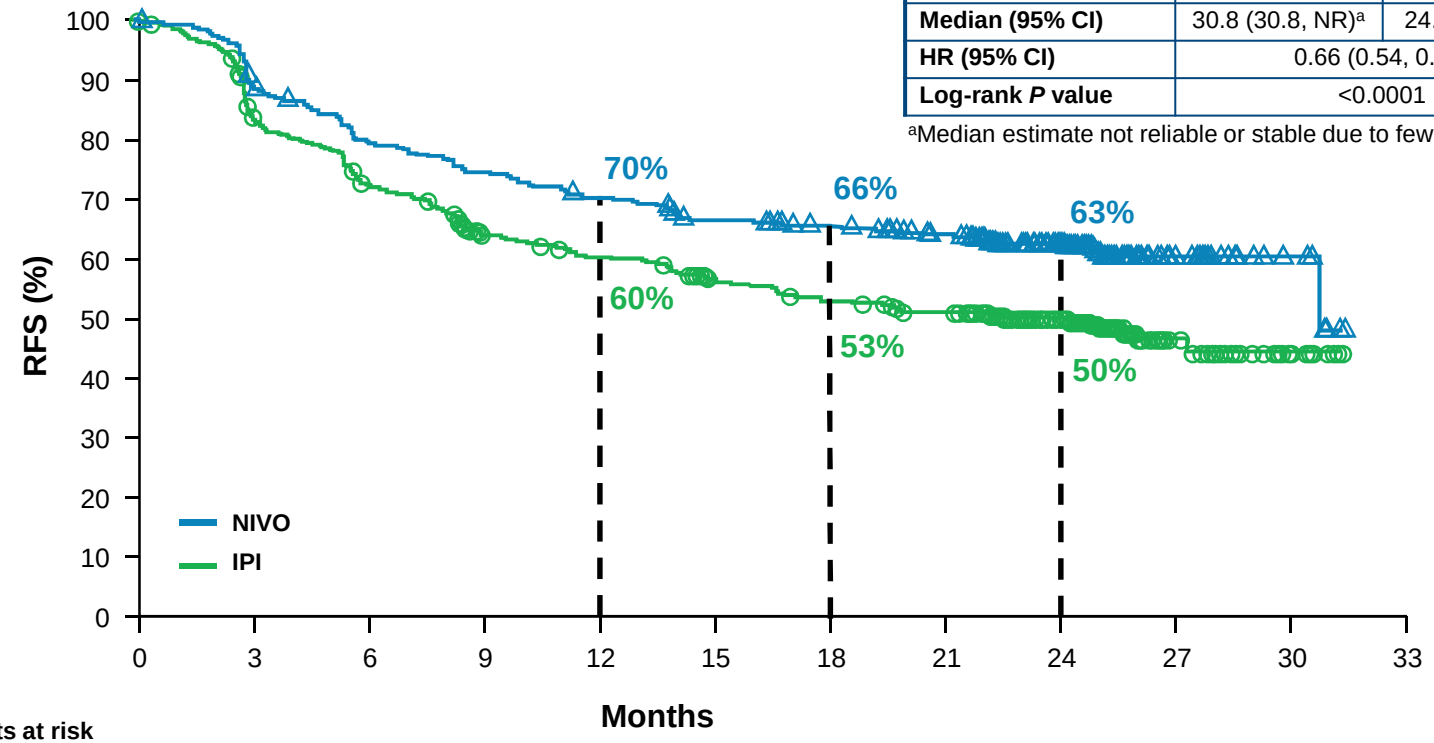
- **Stage IIIA (N1a with micrometastasis >1 mm), IIIB or IIIC with no in-transit metastases**
- **BRAF V600E or V600K mutations**
- **CLND required <12w before randomization**


The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE
Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma
A Intention-to-Treat Population
Nivolumab: 154 events/453 patients
Ipilimumab: 206 events/453
Hazard ratio, 0.65 (97.56% CI, 0.51–0.83)
P<0.001
Active Control-Arm
HR: 0.66 (0.54-0.81)
The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE
Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy
A Recurrence-free Survival
Ipilimumab 264/475 27.6 (19.3–37.2) 40.8 (36.0–45.6)
Placebo 323/476 17.1 (13.6–21.6) 30.3 (26.0–34.6)
Hazard ratio for recurrence or death, 0.76 (95% CI, 0.64–0.89)
P<0.001
Placebo Controlled
HR: 0.76 (0.64–0.89)
The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE
djuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma
A Overall Intention-to-Treat Population
Pembrolizumab 514 135 0.57 (0.43–0.74)
Placebo 505 216 1.00
P<0.001 by stratified log-rank test
Placebo Controlled
HR: 0.57 (0.43–0.74)
The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE
Adjuvant Dabrafenib plus Trametinib in Stage III
A Relapse-free Survival
Dabrafenib plus trametinib
Placebo Controlled
HR: 0.47 (0.39–0.58)

Primary Endpoint: RFS in All Patients

	NIVO	IPI
Events/patients	171/453	221/453
Median (95% CI)	30.8 (30.8, NR)[a]	24.1 (16.6, NR)
HR (95% CI)	0.66 (0.54, 0.81)	
Log-rank *P* value	<0.0001	

[a]Median estimate not reliable or stable due to few patients at risk.



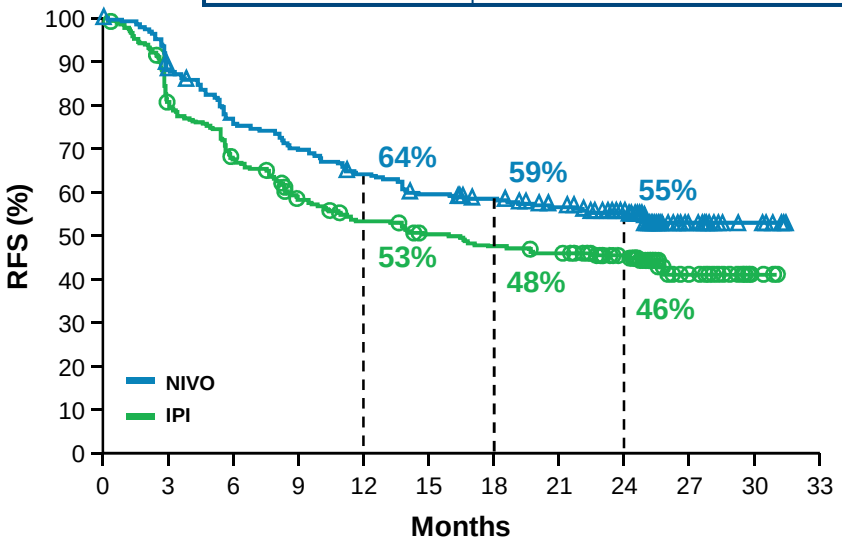
Number of patients at risk

NIVO	453	394	353	331	311	291	280	264	205	28	7	0
IPI	453	363	314	270	251	230	216	204	149	23	5	0

Subgroup Analysis of RFS: 5% PD-L1 Expression Level

PD-L1 <5%

	NIVO	IPI
Events/patients	123/275	151/286
Median (95% CI)	NR (21.7, NR)	15.9 (10.3, 25.5)
HR (95% CI)	0.73 (0.57, 0.92)	



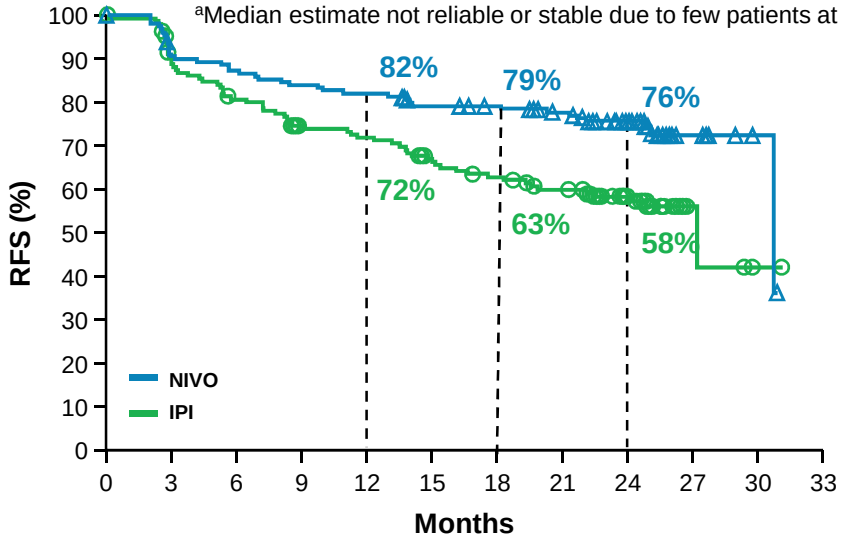
Number of patients at risk

NIVO	275	238	204	188	171	158	151	141	108	17	5	0
IPI	286	218	184	154	139	128	121	116	83	17	3	0

PD-L1 ≥5%

	NIVO	IPI
Events/patients	39/152	64/154
Median (95% CI)	30.8 (30.8, NR)[a]	27.2 (22.4, NR)[a]
HR (95% CI)	0.54 (0.36, 0.81)	

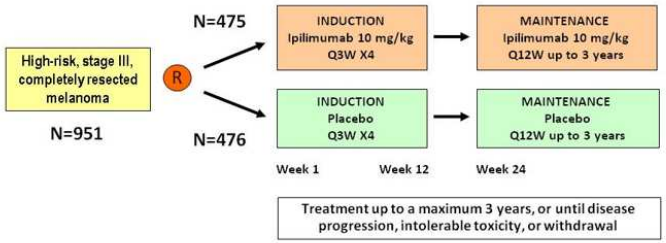
[a]Median estimate not reliable or stable due to few patients at risk.



Number of patients at risk

NIVO	152	135	130	125	122	115	112	106	87	10	2	0
IPI	154	133	120	108	104	94	88	81	61	4	1	0

EORTC 18071/CA184-029: Study Design

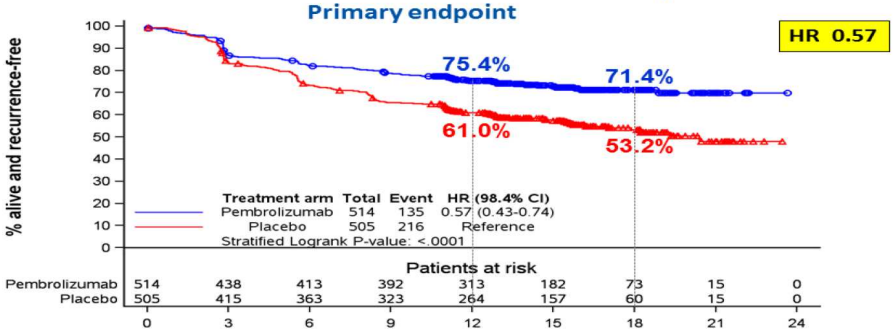


Stratification factors:

- Stage (IIIA vs IIIB vs IIIC 1-3 positive lymph nodes vs IIIC ≥4 positive lymph nodes)
- Regions (North America, European countries and Australia)

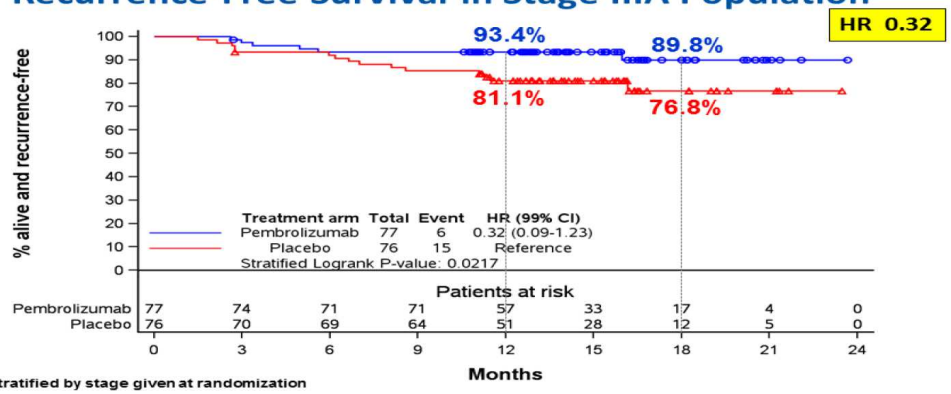
Recurrence-Free Survival in the ITT Population

Primary endpoint



*Stratified by stage given at randomization

Recurrence-Free Survival in Stage IIIA Population



*Stratified by stage given at randomization

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Parque Na
Thibaut
10 août 2017
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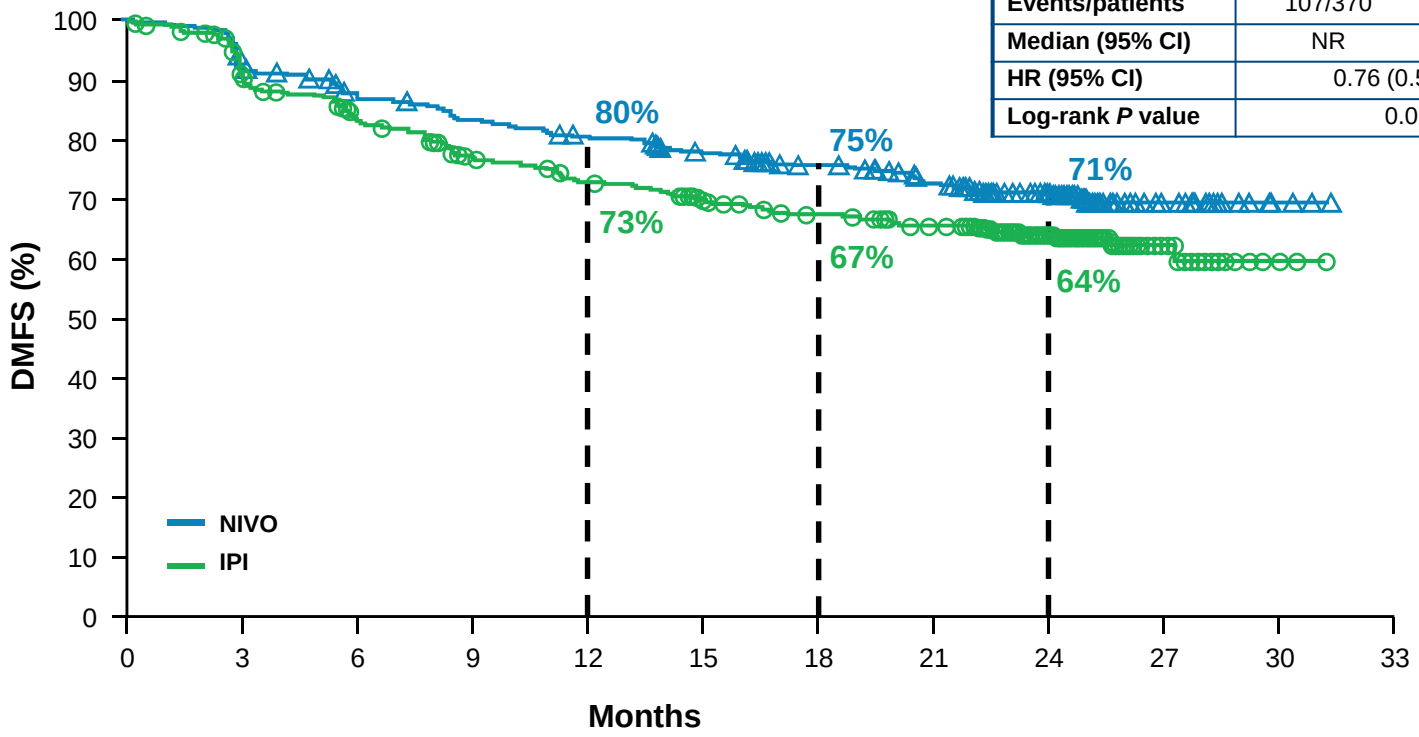
papa Lorenz
meter
Alice
peter
Florian
2,4 kg
47 cm
ROBIN
Luca
Adriaens
ROLF
Joseph
Adriaens
meter
Charlotte
peter
Florian
22.01.2018
2,9 kg
50 cm
2018

Exploratory Endpoint: DMFS for Stage III Patients

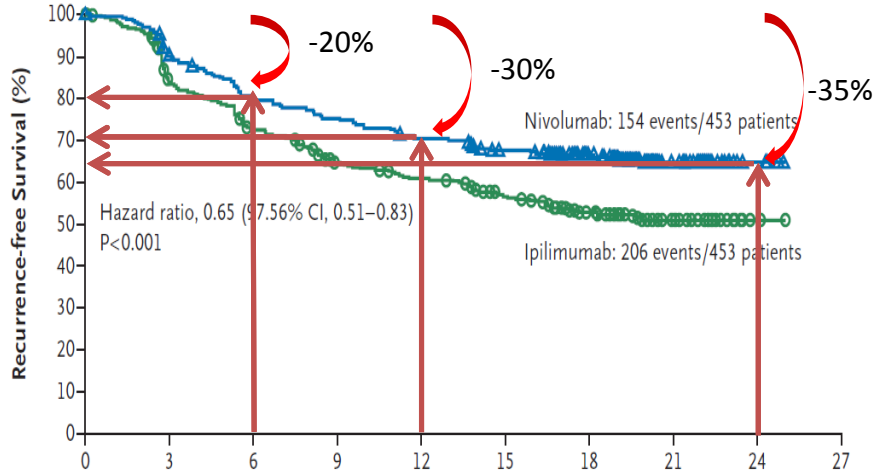
	NIVO	IPI
Events/patients	107/370	126/366
Median (95% CI)	NR	NR
HR (95% CI)	0.76 (0.59, 0.98)	
Log-rank *P* value	0.0340	



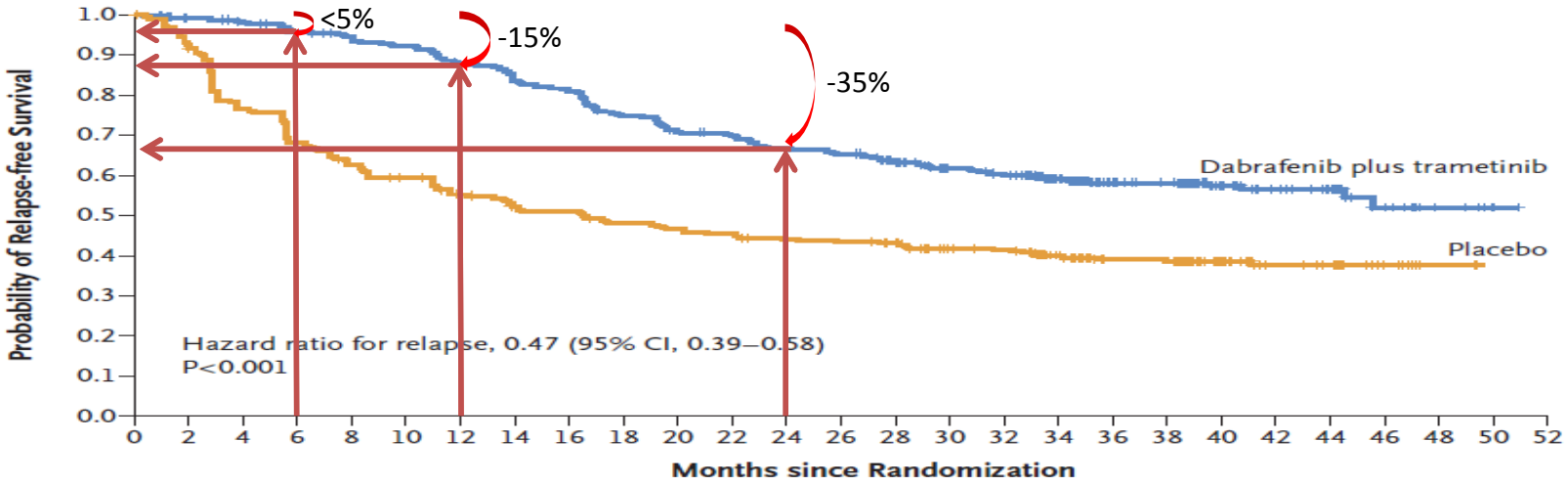
Number of patients at risk

NIVO	370	334	312	295	283	269	249	231	175	24	4	0
IPI	366	313	286	254	239	223	210	197	141	22	3	0

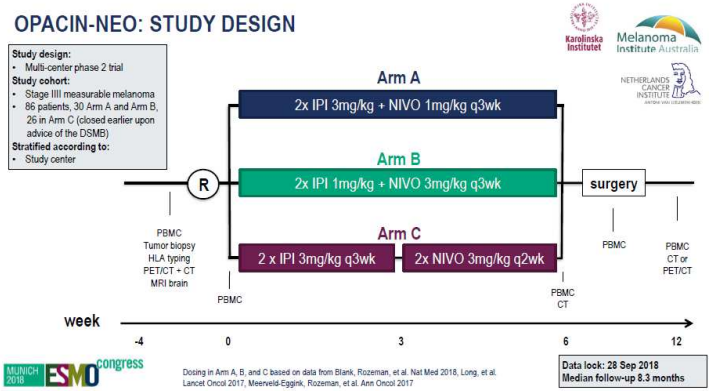
Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma



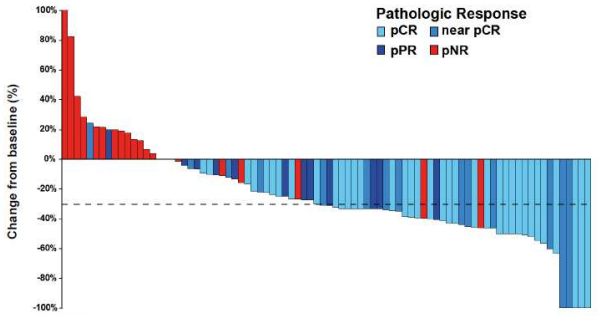
Adjuvant Dabrafenib plus Trametinib in Stage III *BRAF*-Mutated Melanoma



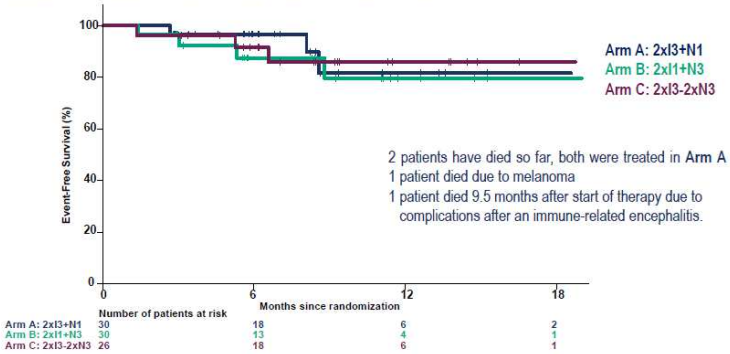
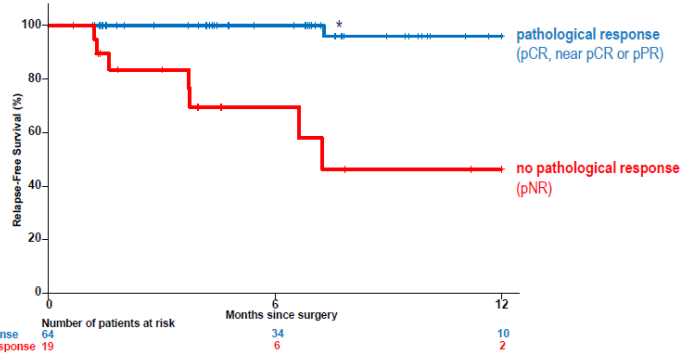
OPACIN-NEO: STUDY DESIGN



CORRELATION RADIOLOGIC/PATHOLOGIC RESPONSE



EVENT-FREE SURVIVAL PER TREATMENT ARM



RELAPSE FREE SURVIVAL ACCORDING TO PATHOLOGIC RESPONSE