Melanoma:
Beyond Checkpoint Inhibitors

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Overview

- Where we are now
- Where we are going

Where We Are Now

- Metastatic Melanoma
  - Current data with CPI
  - Choosing between CPI and targeted therapy
- Adjuvant Therapy
  - Current Options

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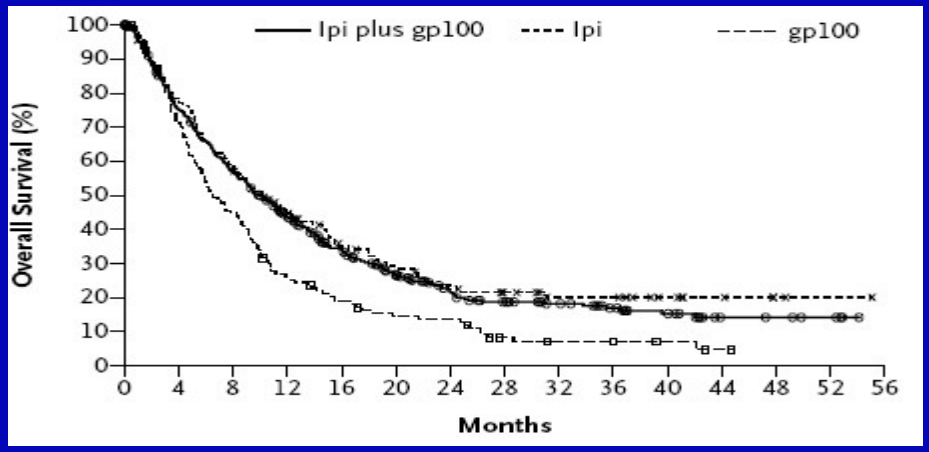
Check-Point Inhibitors
Approved for Metastatic Melanoma

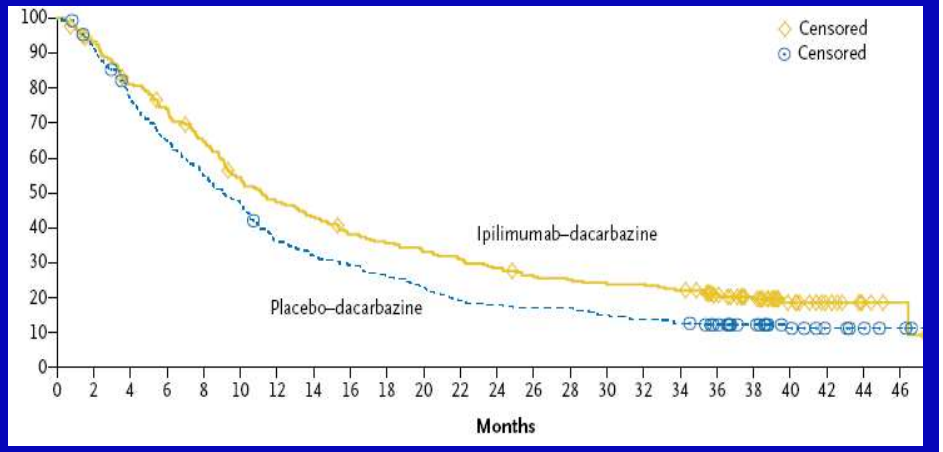
- Anti CTLA4 antibody: Ipilimumab
- Anti PD-1 inhibitors: pembrolizumab, nivolumab
- Combination anti CTLA-4 and anti-PD1 (ipilimumab and nivolumab)

Clinical Results with Ipilimumab (2nd and 1st line)
Ipilimumab vs vaccine and Ipi + DTIC vs DTIC



HR: 0.66 and 0.68
Pre-treated pts
Ipi 3 mg/kg +/- gp100

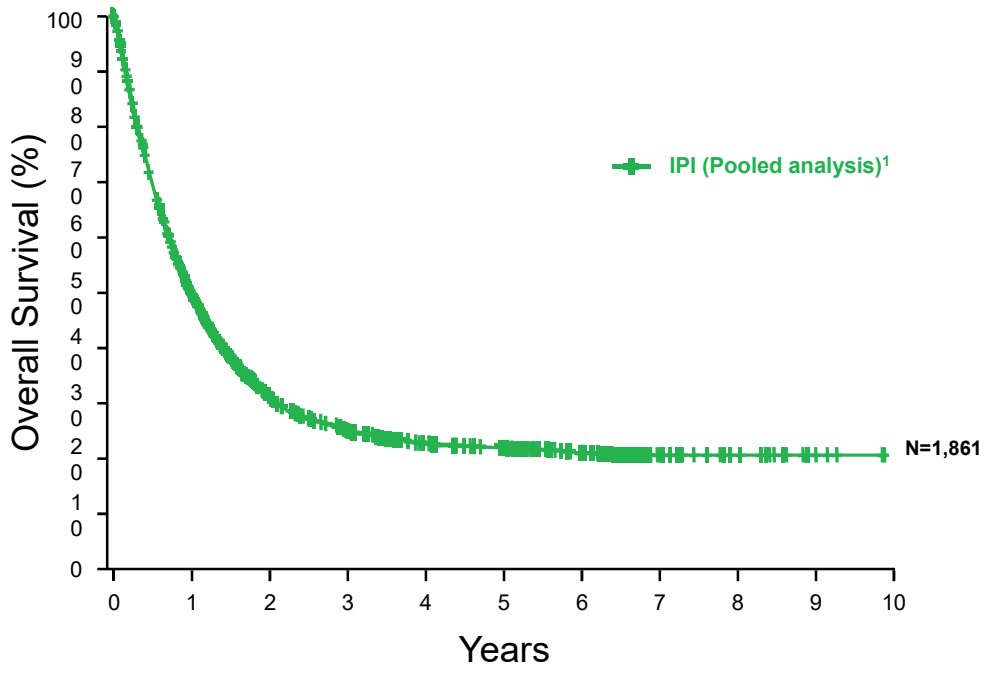
Hodi FS, et al. *N Engl J Med.* 2010;363:711-23.



HR: 0.72
First line
Ipi 10 mg/kg + DTIC

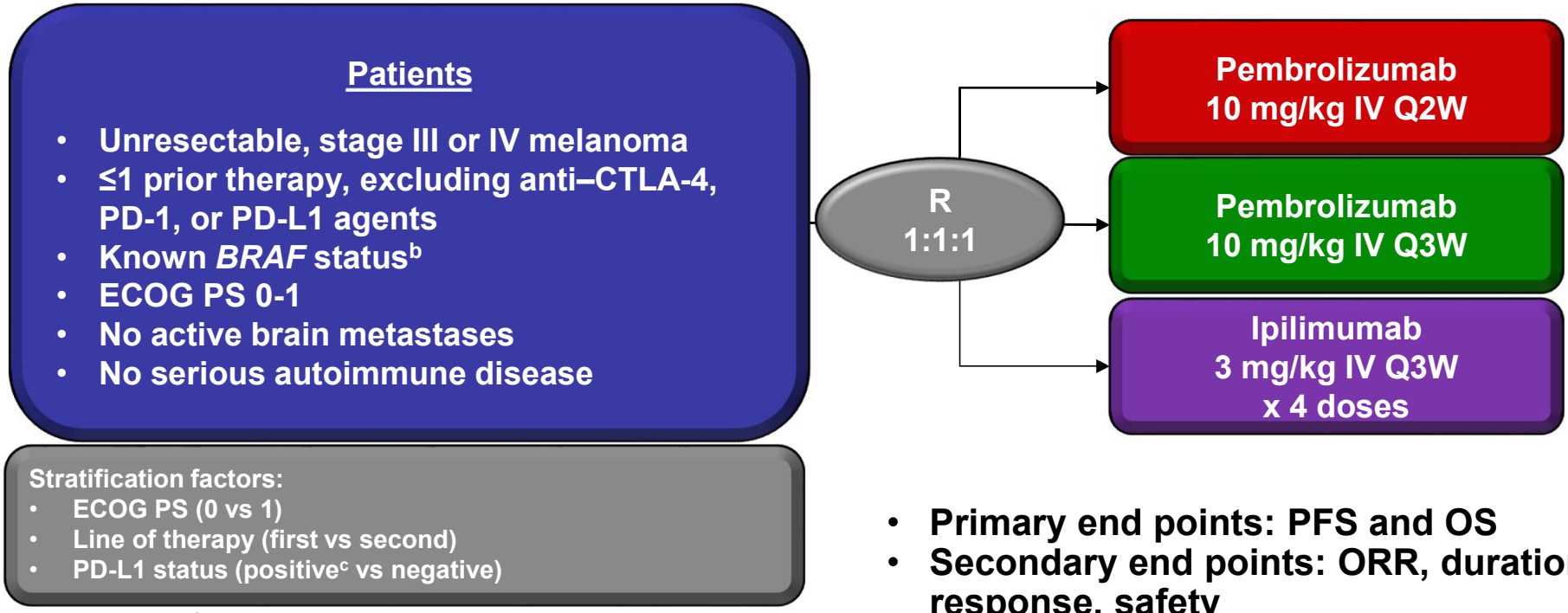
Robert C, et al. *N Engl J Med*. 2011;364:2517-26.

Immune Checkpoint Inhibitors Provide Durable Long-term Survival for Patients with Advanced Melanoma



1. Schadendorf et al. *J Clin Oncol* 2015;33:1889-1894; 2. Current analysis; 3. Poster presentation by Dr. Victoria Atkinson at SMR 2015 International Congress.

Keynote-006 Front-line Pembrolizumab vs Ipilimumab



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

[a]Patients enrolled from 83 sites in 16 countries.

[b]Prior anti-BRAF targeted therapy was not required for patients with normal LDH levels and no clinically significant tumor-related symptoms or evidence of rapidly progressing disease.

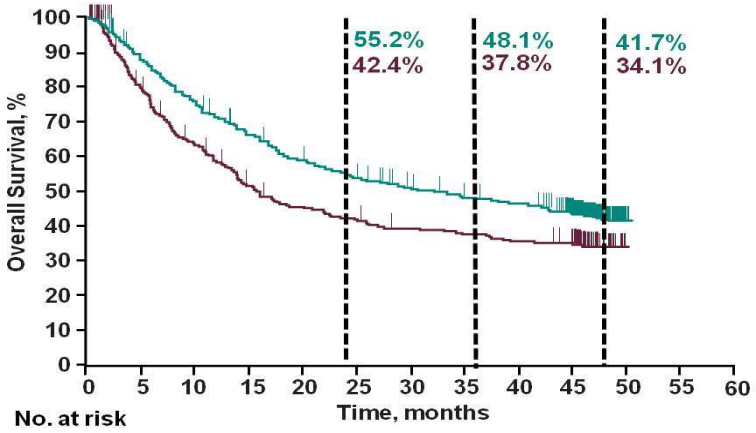
[c]Defined as membranous PD-L1 expression in ≥1% of tumor cells as assessed by IHC using the 22C3 antibody.

Overall Survival

Median Follow-Up 45.9 (0.3-50.0) Months

All Patients

	Events, n	HR[a] (95% CI)	Median,[b] mo (95% CI)
Pembro	309	0.73 (0.61-0.89)	32.7 (24.5-41.6)
Ipi	164	-	15.9 (13.3-22.0)

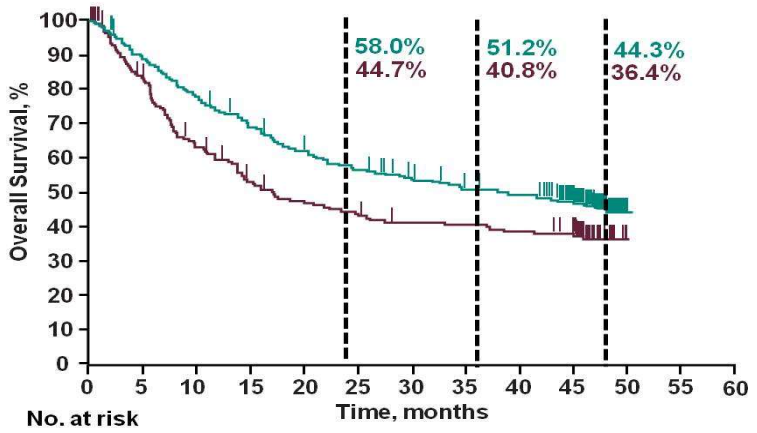


No. at risk

556	481	416	357	317	289	266	250	239	181	0	0	0
278	202	158	127	111	102	94	90	85	76	0	0	0

Treatment-Naive Patients

	Events, n	HR[a] (95% CI)	Median,[b] mo (95% CI)
Pembro	193	0.73 (0.57-0.93)	38.7 (27.3-NR)
Ipi	104	-	17.1 (13.8-26.2)

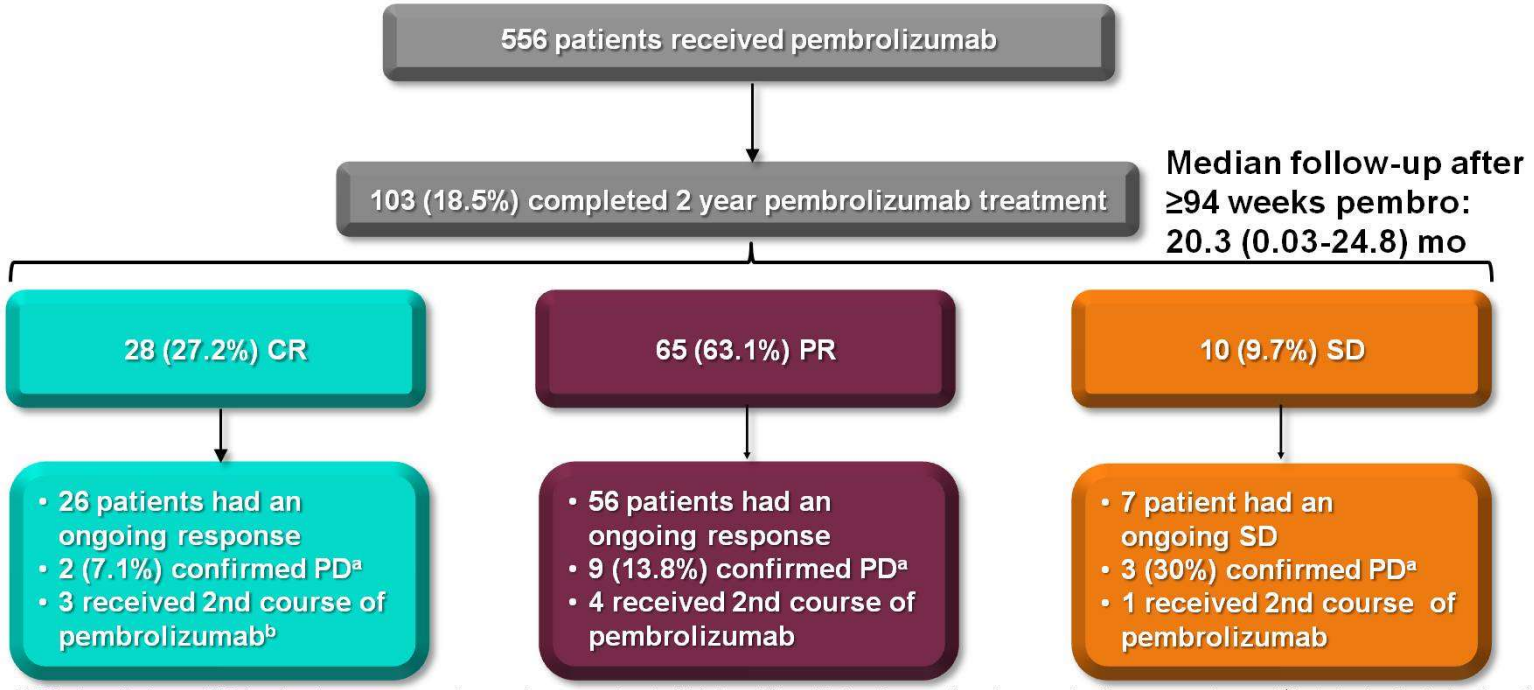


No. at risk

368	324	284	248	221	201	186	174	167	124	0	0	0
181	140	105	86	76	70	64	63	60	51	0	0	0

[a]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. [b]Derived by the product-limit (Kaplan-Meier) method for censored data. Data cutoff: Dec 4, 2017.

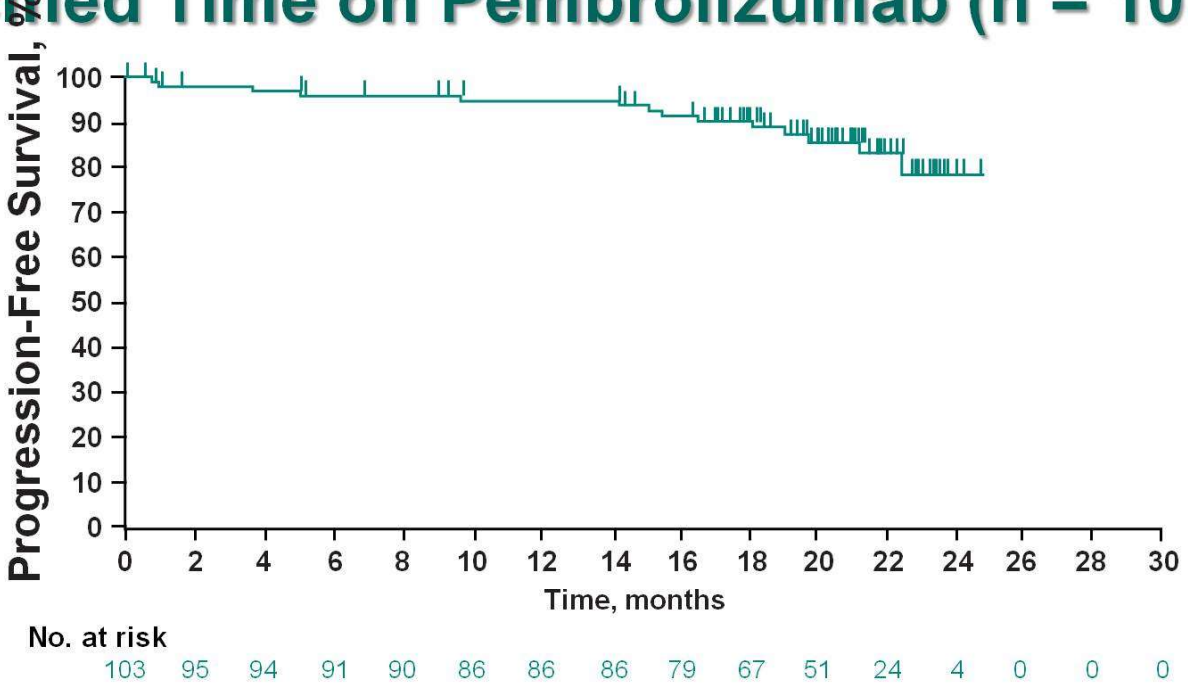
Disposition of Patients Completing ≥94 Weeks of Pembrolizumab Treatment



[a]Confirmed PD by investigator per irRC (confirmatory scan or no subsequent scan or not evaluable). An additional 5 pts with unconfirmed progressive disease were observed. [b]Includes 1 patient who discontinued early with CR and then progressed. Data cutoff: Dec 4, 2017.

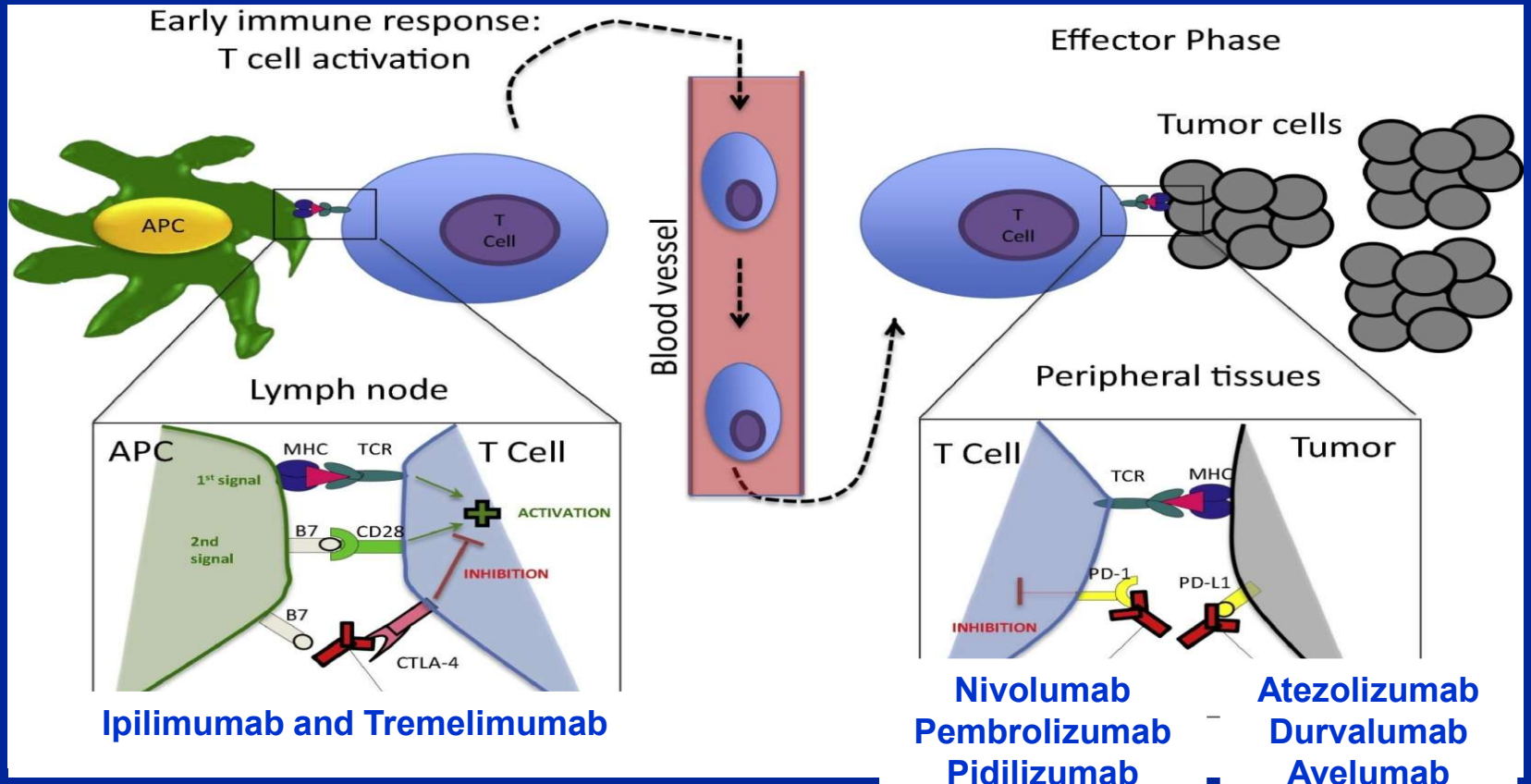
Abstract 9503, 2018 ASCO Annual Meeting

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



[a]Per immune-related response criteria by investigator review; time is measured from last dose of pembrolizumab. Data cutoff: Dec 4, 2017.

Blocking CTLA-4 and PD-1



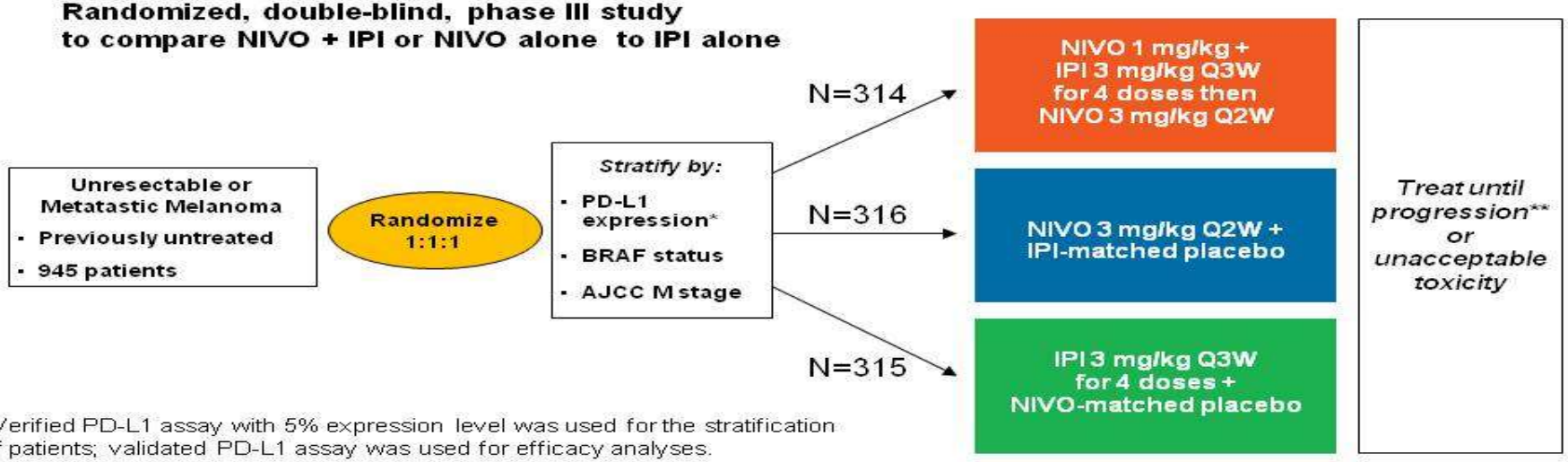
Ipilimumab and Tremelimumab

Nivolumab
Pembrolizumab
Pidilizumab

Atezolizumab
Durvalumab
Avelumab

CA209-067: Study Design

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



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

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

Presented By Jedd Wolchok at 2015 ASCO Annual Meeting

Updated Response To Treatment

	NIVO+IPI (N=314)	NIVO (N=316)	IPI (N=315)
ORR, % (95% CI)*	**58.9** (53.3–64.4)	**44.6** (39.1–50.3)	**19.0** (14.9–23.8)
Best overall response — %			
Complete response	17.2	14.9	4.4
Partial response	41.7	29.7	14.6
Stable disease	11.5	9.8	21.3
Progressive disease	23.6	38.6	51.1
Unknown	6.1	7.0	8.6
Median duration of response, months (95% CI)	**NR** (NR–NR)	**31.1** (31.1–NR)	**18.2** (8.3–NR)

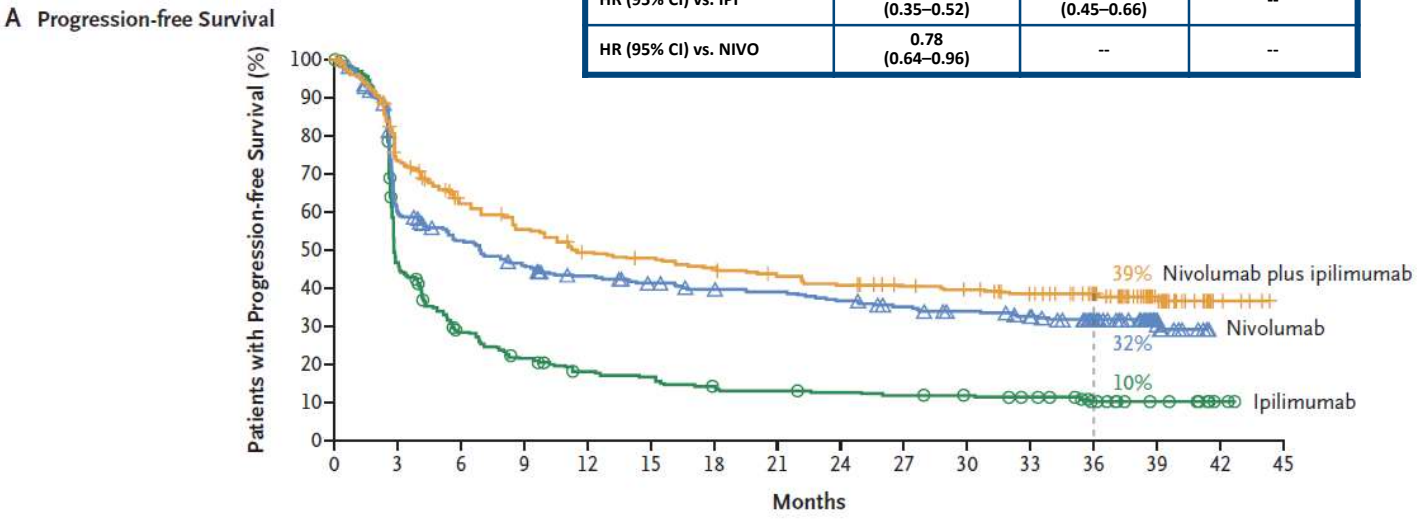
*By RECIST v1.1; NR = not reached.

- At the 18-month DBL, the CR rate for NIVO+IPI, NIVO and IPI was 12.1%, 9.8% and 2.2%, respectively

Database lock: Sept 13, 2016, minimum f/u of 28 months

CM-67 Progression-Free Survival

	NIVO+IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median PFS, mo (95% CI)	11.5 (8.7–19.3)	6.9 (5;1–9.7)	2.9 (2.8–3.2)
HR (95% CI) vs. IPI	0.43 (0.35–0.52)	0.55 (0.45–0.66)	--
HR (95% CI) vs. NIVO	0.78 (0.64–0.96)	--	--



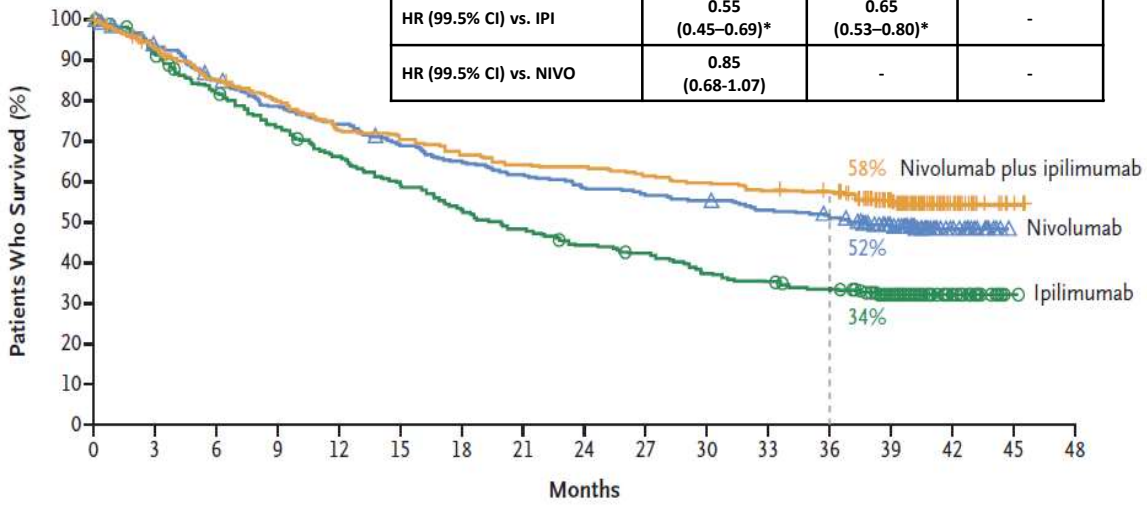
No. at Risk																
Nivolumab plus ipilimumab	314	218	175	155	136	131	124	117	110	104	100	92	75	29	5	0
Nivolumab	316	177	151	131	119	111	105	102	96	87	81	75	61	24	0	0
Ipilimumab	315	136	78	58	46	42	34	32	30	28	26	23	15	8	2	0

Database lock May 24, 2017

Wolchok, NEJM, 2017

CM-67 Overall Survival

	NIVO + IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median OS, months (95% CI)	38.2-NR	37.6 (29.1-NR)	19.9 (16.9-24.6)
HR (99.5% CI) vs. IPI	0.55 (0.45–0.69)*	0.65 (0.53–0.80)*	-
HR (99.5% CI) vs. NIVO	0.85 (0.68-1.07)	-	-

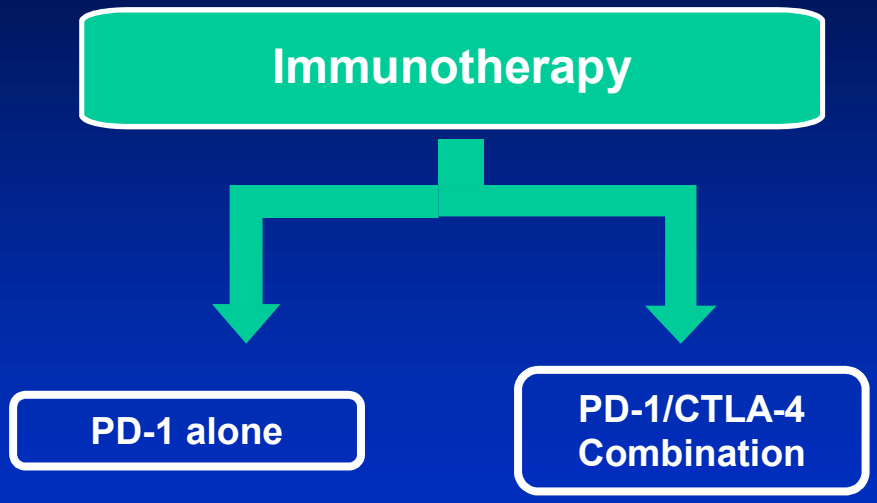


No. at Risk																	
Nivolumab plus ipilimumab	314	292	265	247	226	221	209	200	198	192	186	180	177	131	27	3	0
Nivolumab	316	292	265	244	230	213	201	191	181	175	171	163	156	120	28	0	0
Ipilimumab	315	285	253	227	203	181	163	148	135	128	117	107	100	68	20	2	0

Database lock May 24, 2017

Wolchok, NEJM, 2017

Decision Point….



Safety Summary

- With an additional 19 months of follow-up, safety was consistent with the initial report[1]

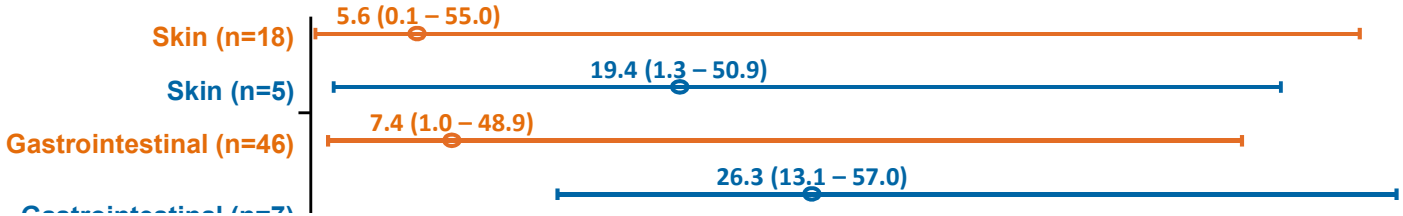
	NIVO+IPI (N=313)		NIVO (N=313)		IPI (N=311)	
Patients reporting event, %	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Treatment-related adverse event (AE)	95.8	58.5	86.3	20.8	86.2	27.7
Treatment-related AE leading to discontinuation	39.6	31.0	11.5	7.7	16.1	14.1
Treatment-related death, n (%)	2 (0.6)[a]		1 (0.3)[b]		1 (0.3)[b]	

- Most select AEs were managed and resolved within 3-4 weeks (85–100% across organ categories)
- ORR was 70.7% for pts who discontinued NIVO+IPI due to AEs, with median OS not reached

[a]Cardiomyopathy (NIVO+IPI, n=1); Liver necrosis (NIVO+IPI, n=1). Both deaths occurred >100 days after the last treatment.
[b]Neutropenia (NIVO, n=1); colon perforation (IPI, n=1).[1]

1. Larkin J, et al. *NEJM* 2015;373:23–34.

Checkmate 067: Safety
Onset Grade 3–4 Treatment-Related Select AEs



Toxicity Earlier

Longer Time to Resolution

Circles represent medians; bars signify ranges

Larkin J et al ECC 2015

Where We Are Now

- Metastatic Melanoma
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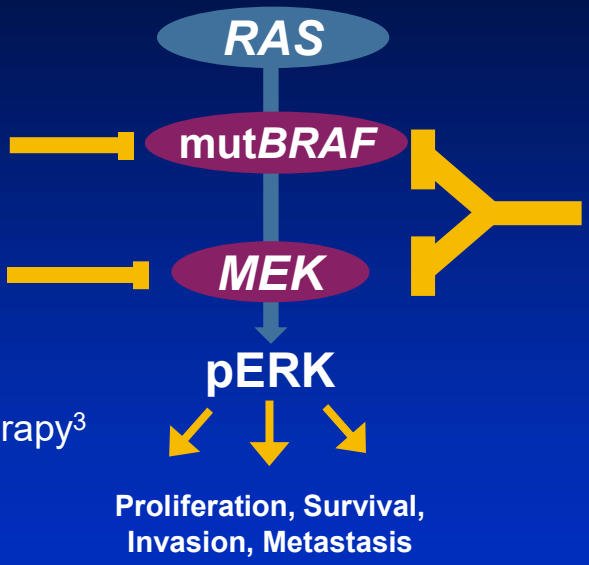
MAPK Pathway Targeted Therapy

BRAFi (dabrafenib)
PFS HR, 0.37 vs DTIC[1]
Hyperproliferative skin AEs

BRAFi (vemurafenib)
PFS HR, 0.38 vs DTIC[2]
Hyperproliferative skin AEs

MEKi (trametinib)
PFS HR, 0.45 vs chemotherapy[3]



BRAFi + MEKi ph III studies

Dabrafenib + trametinib (D + T)
PFS HR, 0.67 vs dabrafenib[4]
OS HR, 0.71 vs dabrafenib[4]

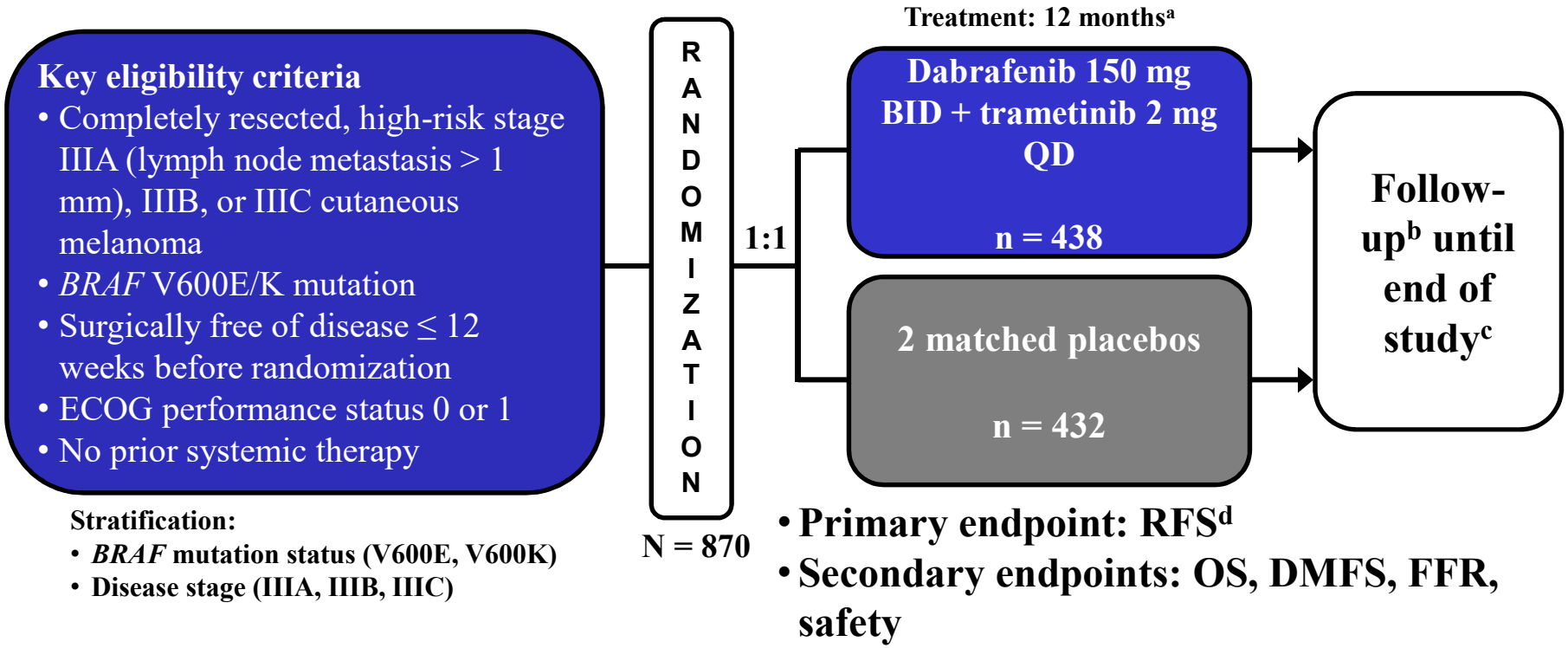
PFS HR, 0.56 vs vemurafenib[5]
OS HR, 0.69 vs vemurafenib[5]

Vemurafenib + cobimetinib
PFS HR, 0.58 vs vemurafenib[6]
OS HR, 0.70 vs vemurafenib[6]

Decreased hyperproliferative skin AEs[4,5,6]

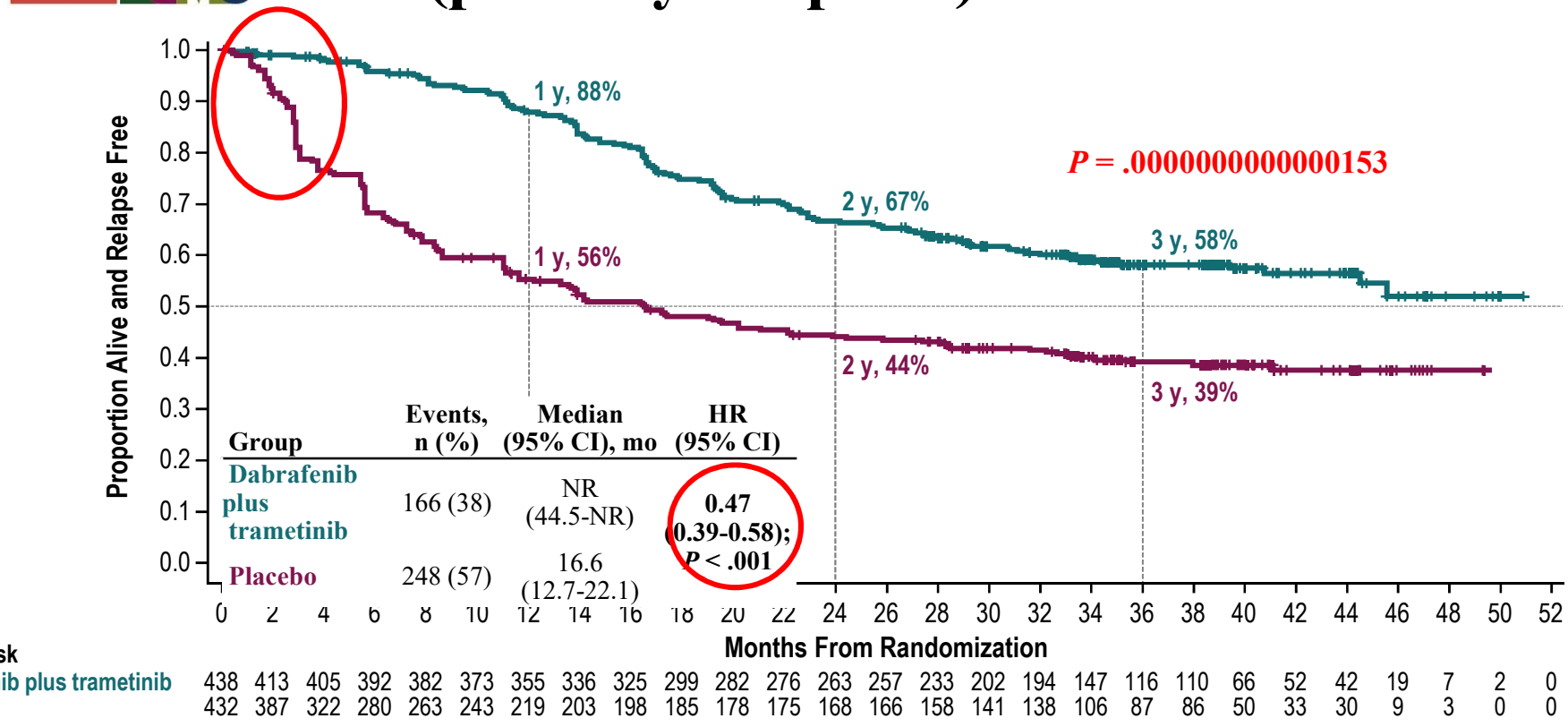
1. Hauschild A, et al. *Lancet.* 2012;380(9839):358-365.
2. McArthur GA, et al. *Lancet Oncol.* 2014;15(3):323-332.
3. Flaherty KT, et al. *N Engl J Med.* 2012;367(2):107-114.
4. Long GV, et al. *Lancet.* 2015;386(9992):444-451.
5. Robert C, et al. *N Engl J Med.* 2015;372(1):30-39.
6. Atkinson V, et al. Presented at:Society for Melanoma Research 2015 Congress.

Adjuvant BRAF/MEK Combi-AD



Hauschild A, et al. Oral presented at: ESMO 2017 [abstract LBA6PR].

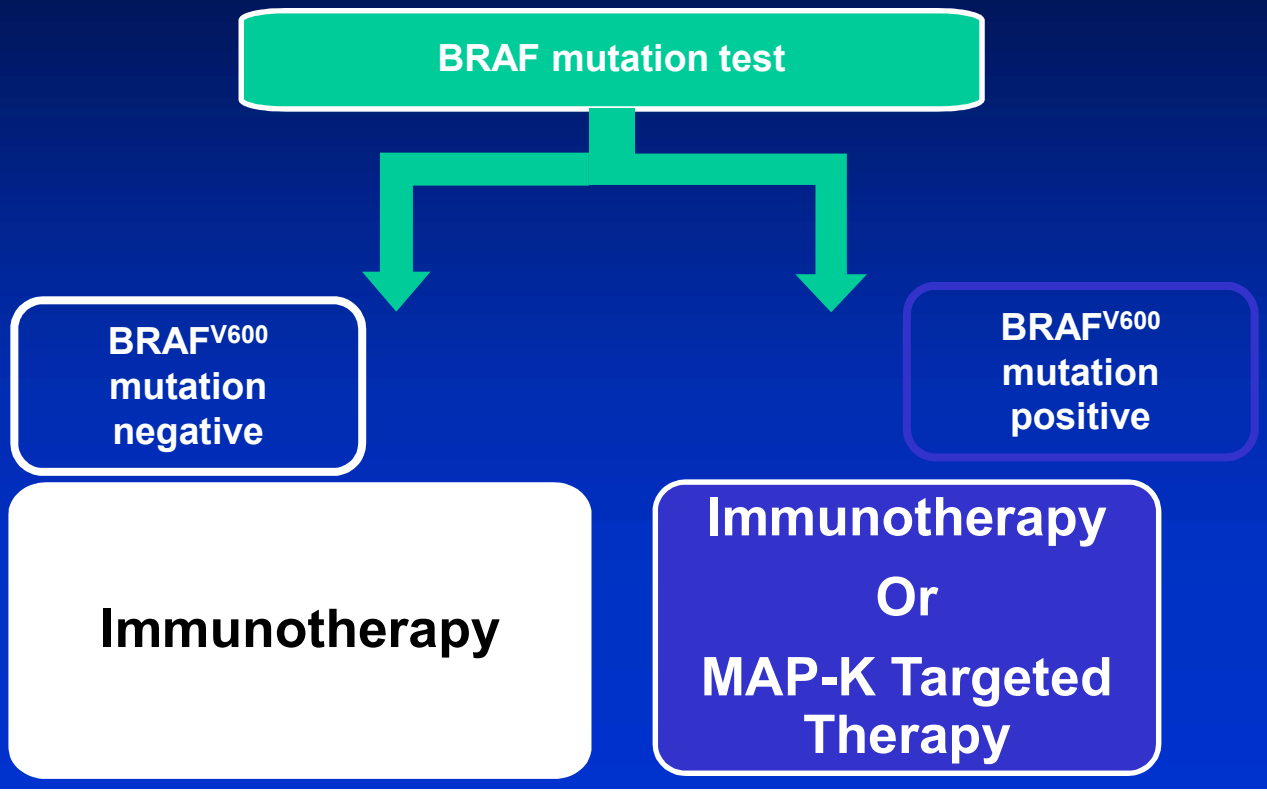
Relapse-free survival (primary endpoint)



NR, not reached.

Hauschild A, et al. Oral presented at: ESMO 2017 [abstract LBA6PR].

Decision Point….



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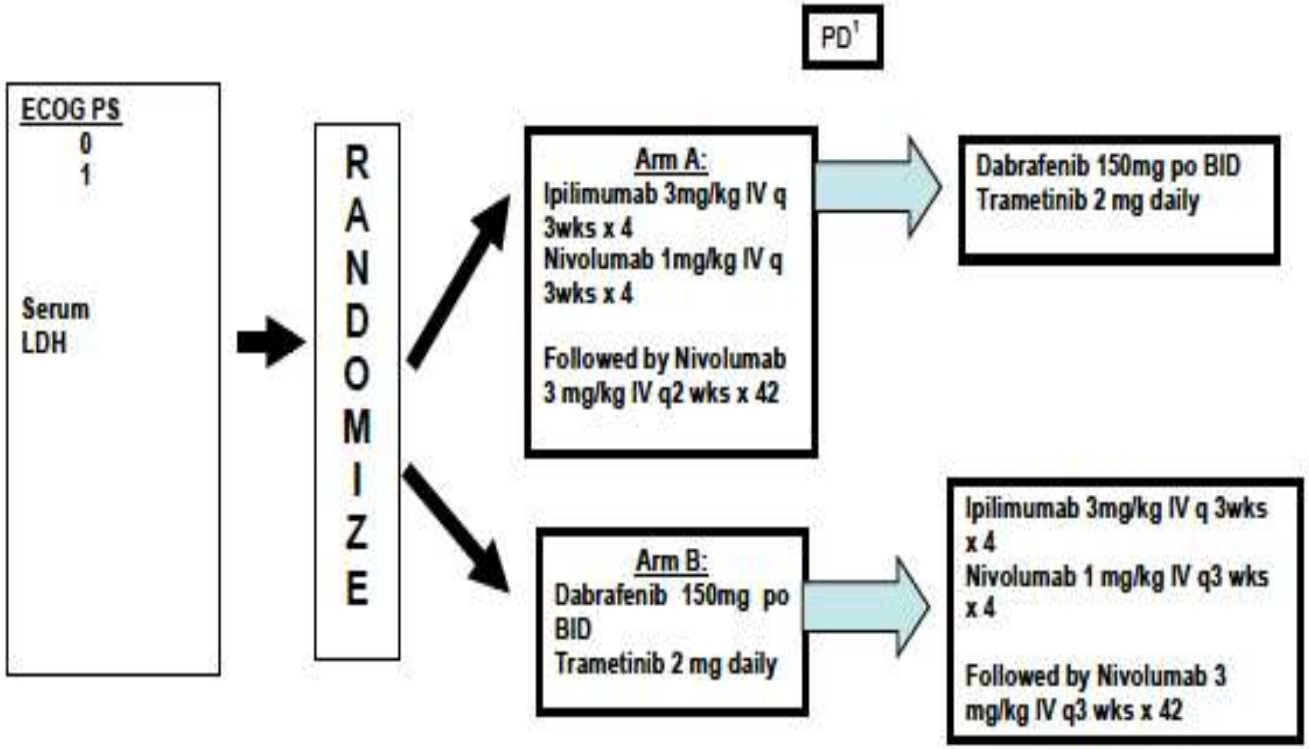
PD[1]
ECOG PS
0
1
Serum
LDH
RANDOMIZE
Arm A:
Ipilimumab 3mg/kg IV q 3wks x 4
Nivolumab 1mg/kg IV q 3wks x 4
Followed by Nivolumab 3 mg/kg IV q2 wks x 42
Dabrafenib 150mg po BID
Trametinib 2 mg daily
Arm B:
Dabrafenib 150mg po BID
Trametinib 2 mg daily
Ipilimumab 3mg/kg IV q 3wks x 4
Nivolumab 1 mg/kg IV q3 wks x 4
Followed by Nivolumab 3 mg/kg IV q3 wks x 42

Where We Are Now

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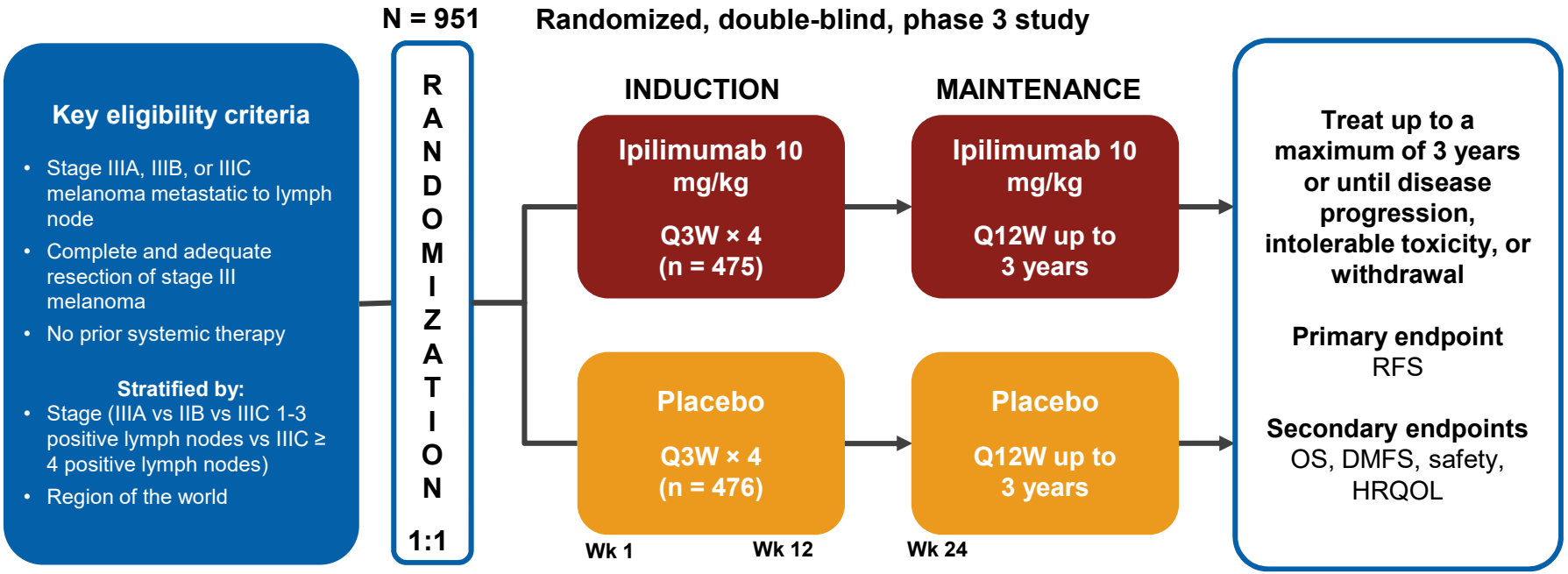
Available Options

- High-dose Interferon
- High-dose Ipilimumab
- Anti-PD1
  - Nivolumab
  - Pembrolizumab
- BRAF/MEK combination for BRAF+ patients

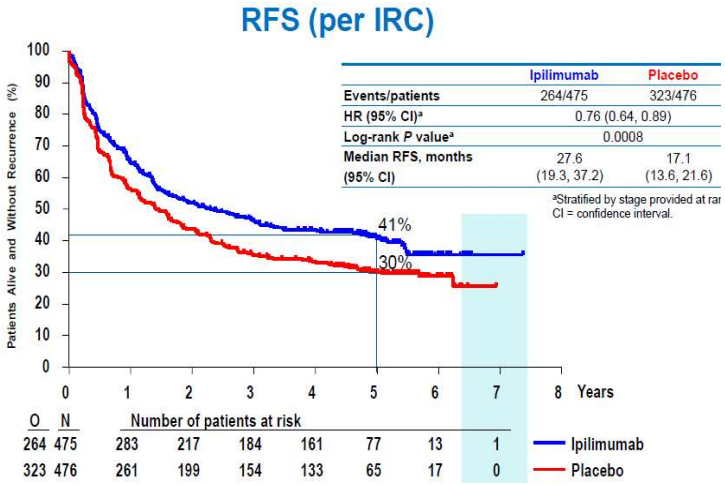
EORTC 18071: phase 3 study design[1,2]

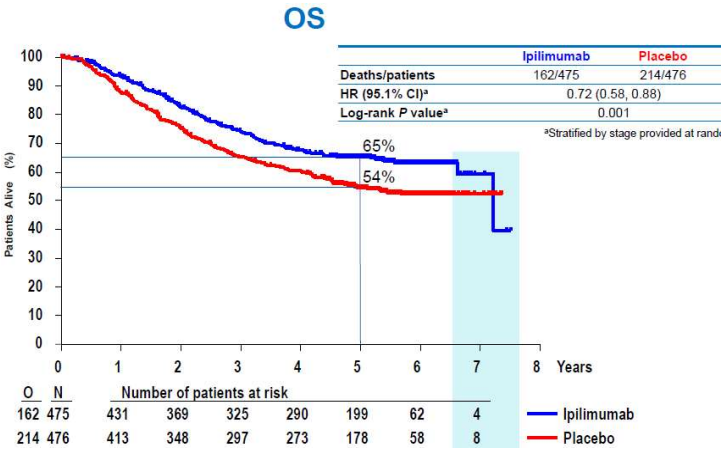


DMFS, distant metastasis-free survival; HRQOL, health-related quality of life; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; Q12W, every 12 weeks; RFS, relapse-free survival.

1. Eggermont AM, et al. *J Clin Oncol* 2014;32:5s(suppl; abstr LBA9008); 2. Eggermont A, et al. ESMO. 2016;[abstr LBA2_PR].

EORTC 18071
Ipilimumab vs Placebo





Safety Summary

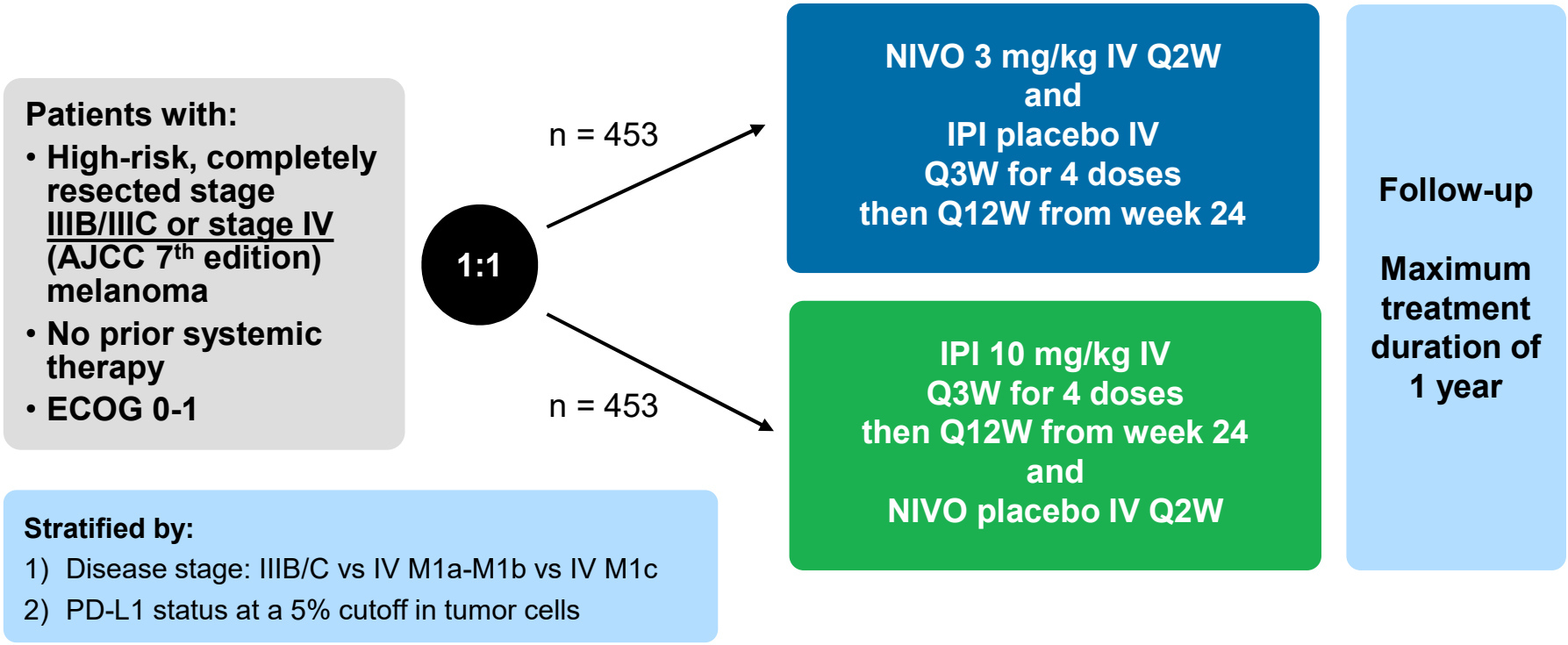
	Ipilimumab (n = 471)	
	Any Grade	Grade 3/4
Any AE, %	98.7	54.1
Treatment-related AE, %	94.1	45.4
Treatment-related AE leading to discontinuation, %	48.0	32.9
Any immune-related AE, %	90.4	41.6

Deaths due to drug-related AEs

- 5 patients (1.1%) in the ipilimumab group
  - 3 patients with colitis (2 with gastrointestinal perforations)
  - 1 patient with myocarditis
  - 1 patient had multiorgan failure with Guillain-Barré

Eggermont et al. NEJM 2016

CheckMate 238: Study Design



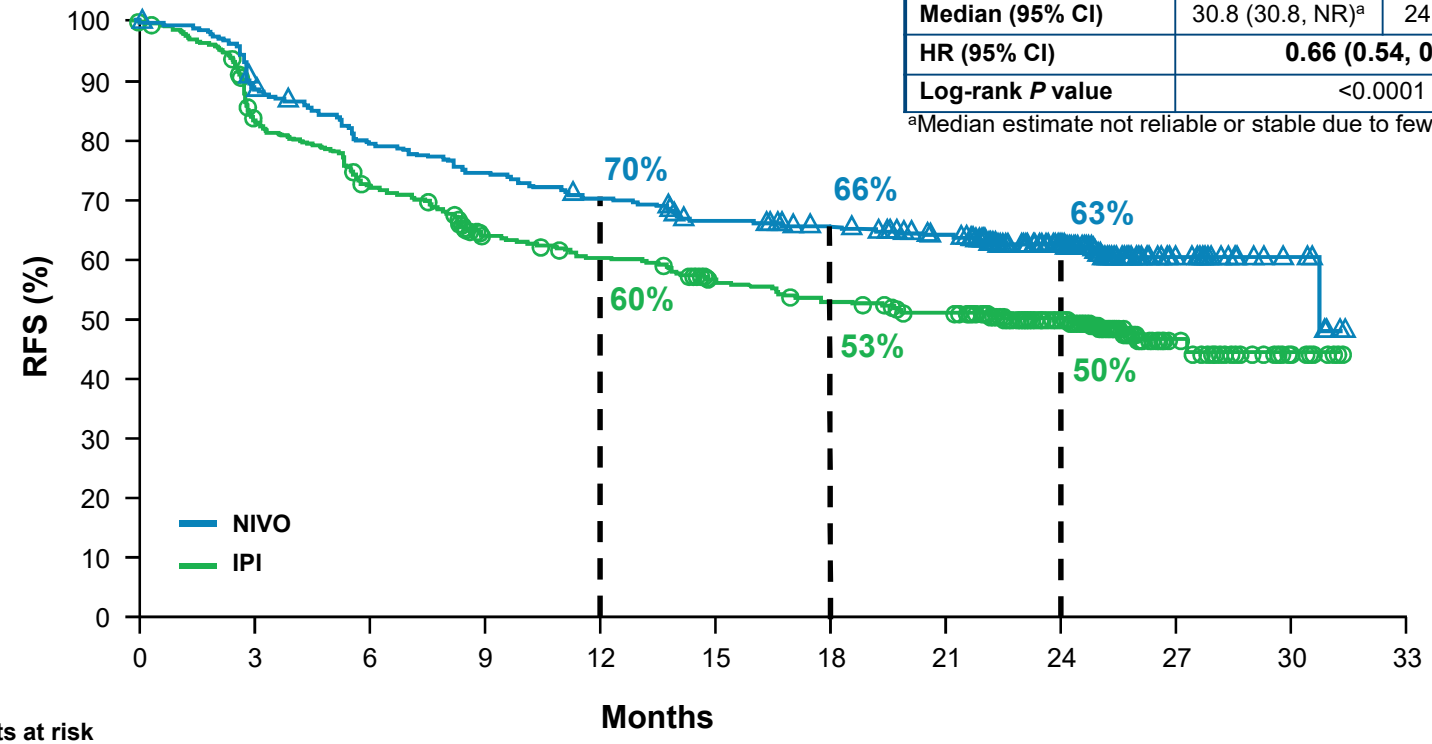
Enrollment period: March 30, 2015 to November 30, 2015

Jeffrey Weber, Oral Presentation ASCO 2018

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

Jeffrey Weber, Oral Presentation ASCO 2018

Safety Summary

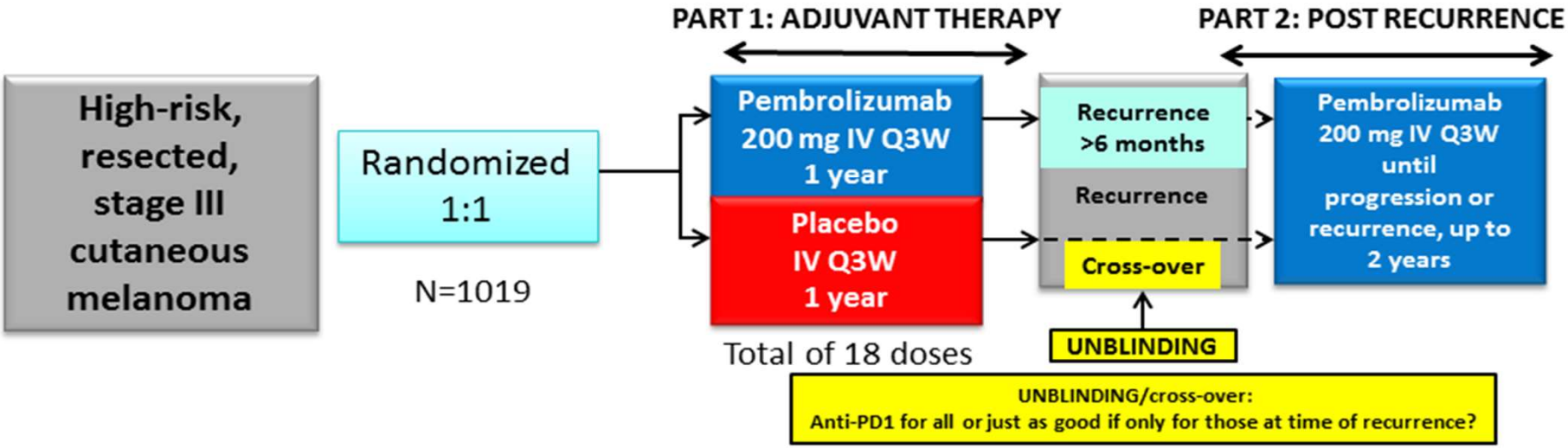
AE, n (%)	NIVO (n = 452)		IPI (n = 453)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any AE	438 (97)	115 (25)	446 (98)	250 (55)
Treatment-related AE	385 (85)	65 (14)	434 (96)	208 (46)
Any AE leading to discontinuation	44 (10)	21 (5)	193 (43)	140 (31)
Treatment-related AE leading to discontinuation	35 (8)	16 (4)	189 (42)	136 (30)

- There were no treatment-related deaths in the NIVO group
- There were 2 (0.4%) treatment-related deaths in the IPI group (marrow aplasia and colitis), both >100 days after the last dose

Weber, J et al ESMO 2017

L. Eggermont AACR 2018

EORTC 1325/KEYNOTE-54: Study Design



Stratification factors:

- ✓ **Stage**: IIIA (>1 mm metastasis) vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥4 positive lymph nodes
- ✓ **Region**: North America, European countries, Australia/New Zealand, other countries

Primary Endpoints:

- **RFS (per investigator) in overall population,** and **RFS in patients with PD-L1-positive tumors**

Secondary Endpoints:

- **DMFS and OS** in all patients, and in patients with PD-L1-positive tumors; **Safety, Health-related quality of life**

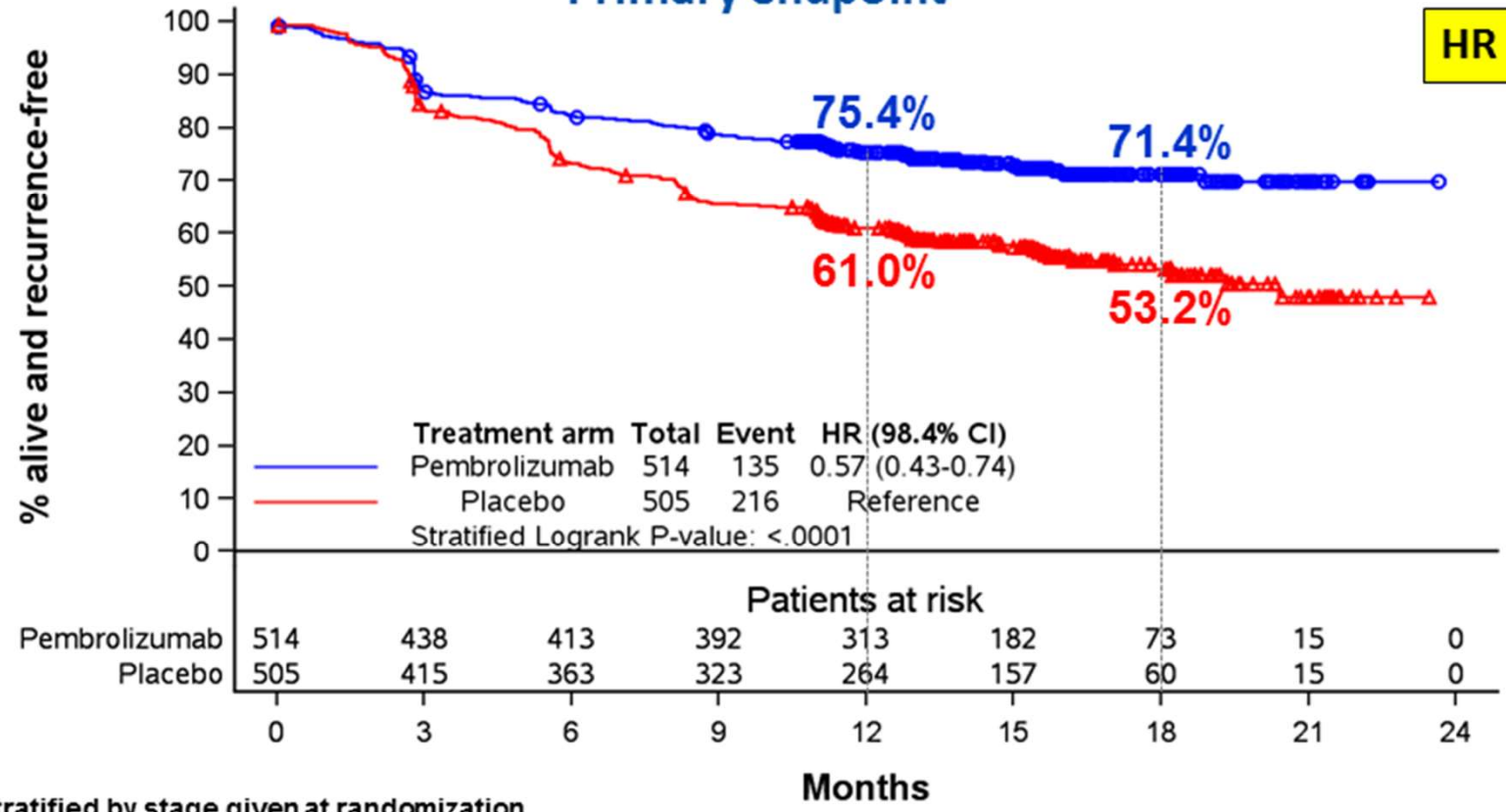
EORTC

The future of cancer therapy

L. Eggermont AACR 2018

Recurrence-Free Survival in the ITT Population

Primary endpoint

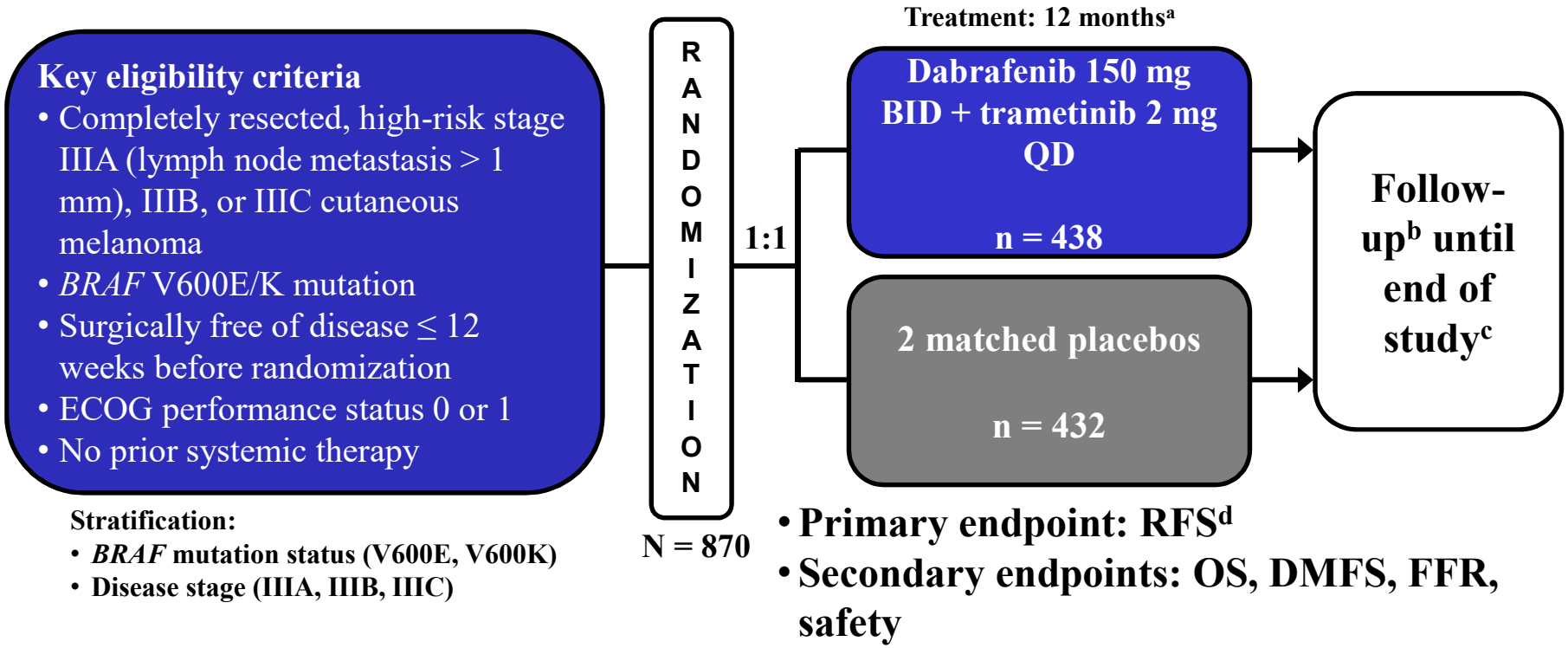


*Stratified by stage given at randomization

EORTC

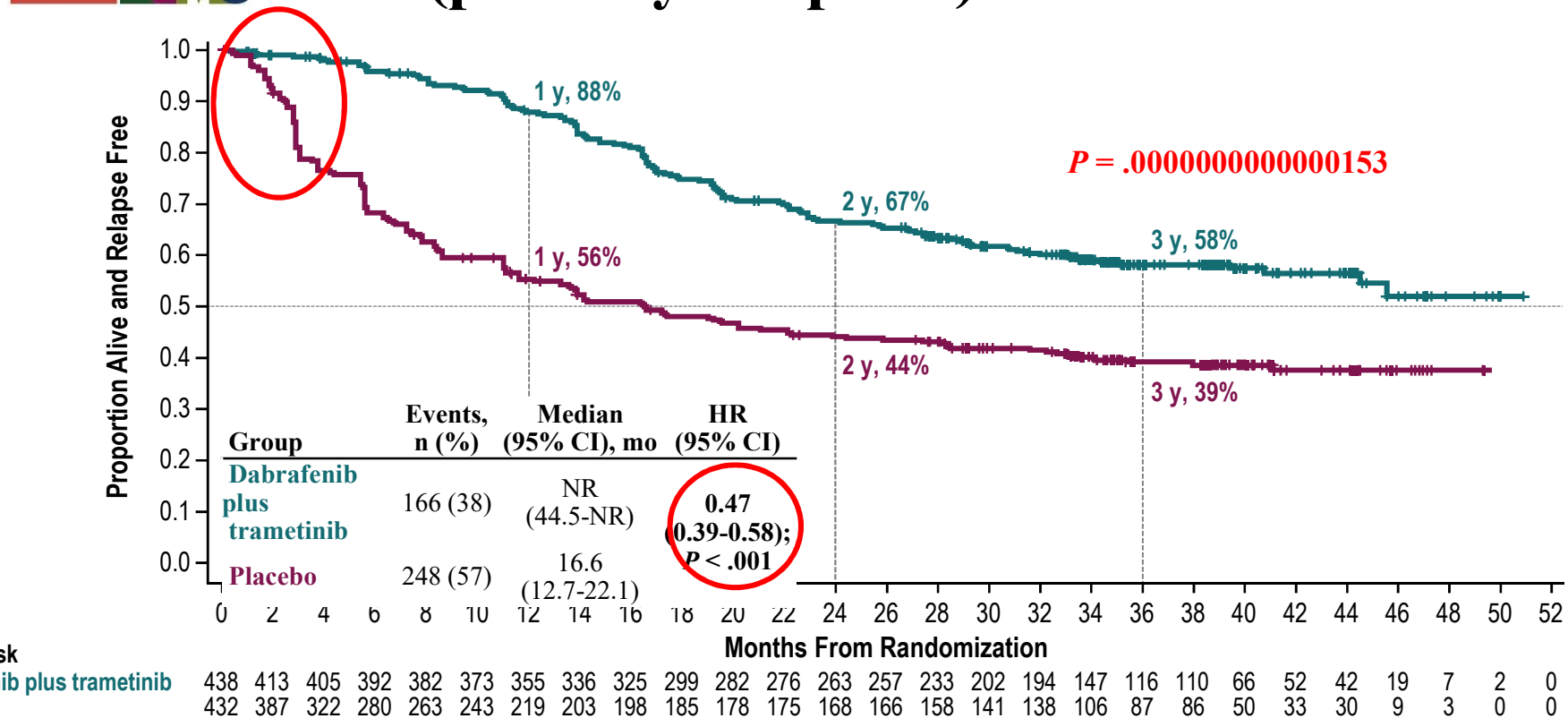
The future of cancer therapy

Adjuvant BRAF/MEK Combi-AD



Hauschild A, et al. Oral presented at: ESMO 2017 [abstract LBA6PR].

Relapse-free survival (primary endpoint)



NR, not reached.

Hauschild A, et al. Oral presented at: ESMO 2017 [abstract LBA6PR].

Interferon

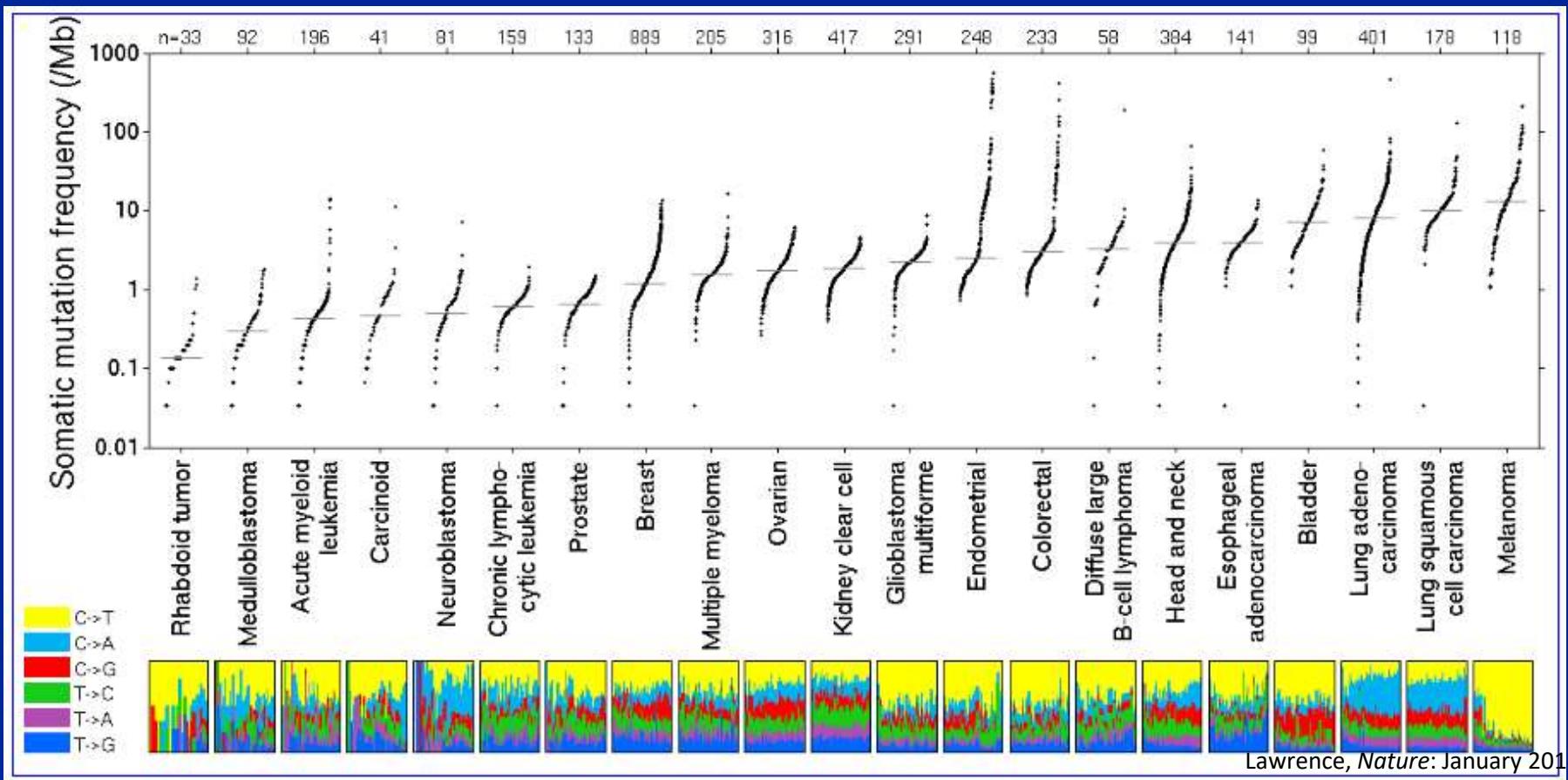
Overview

- Where we are now
- Where we are going

Where Are We Going?

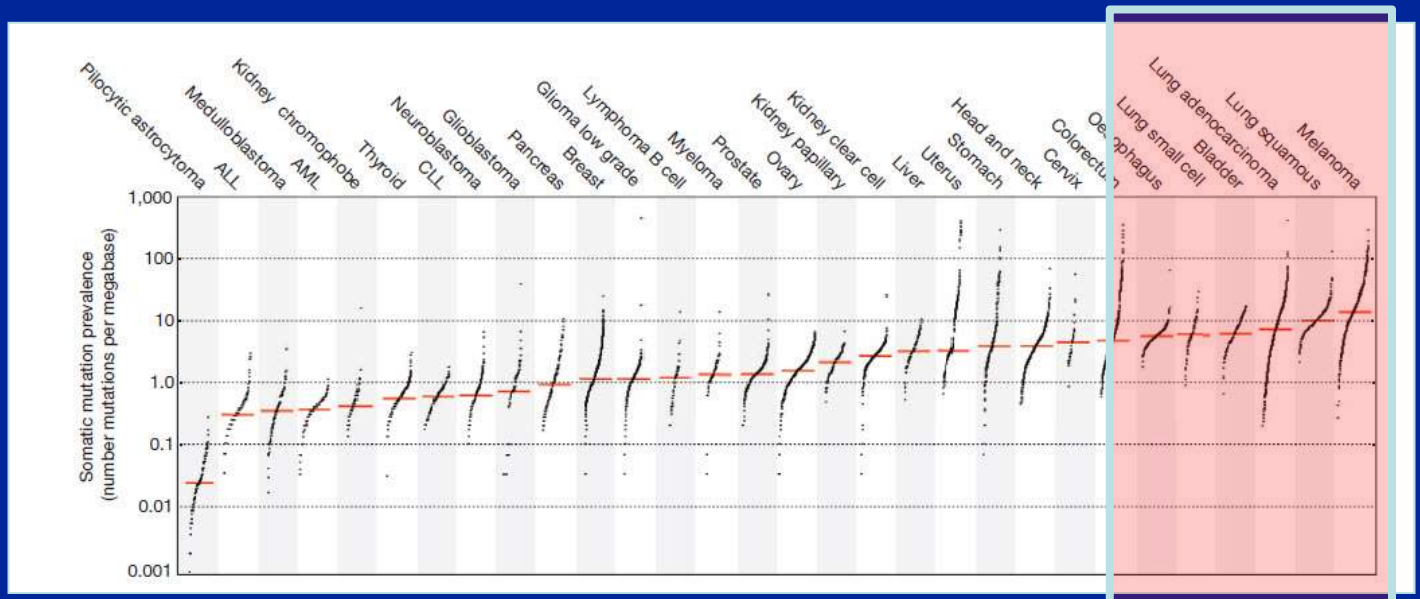
- Tumor biology vs tumor type
- Overcoming resistance
- A glimpse into the future

Somatic Mutation Load Immunogenicity

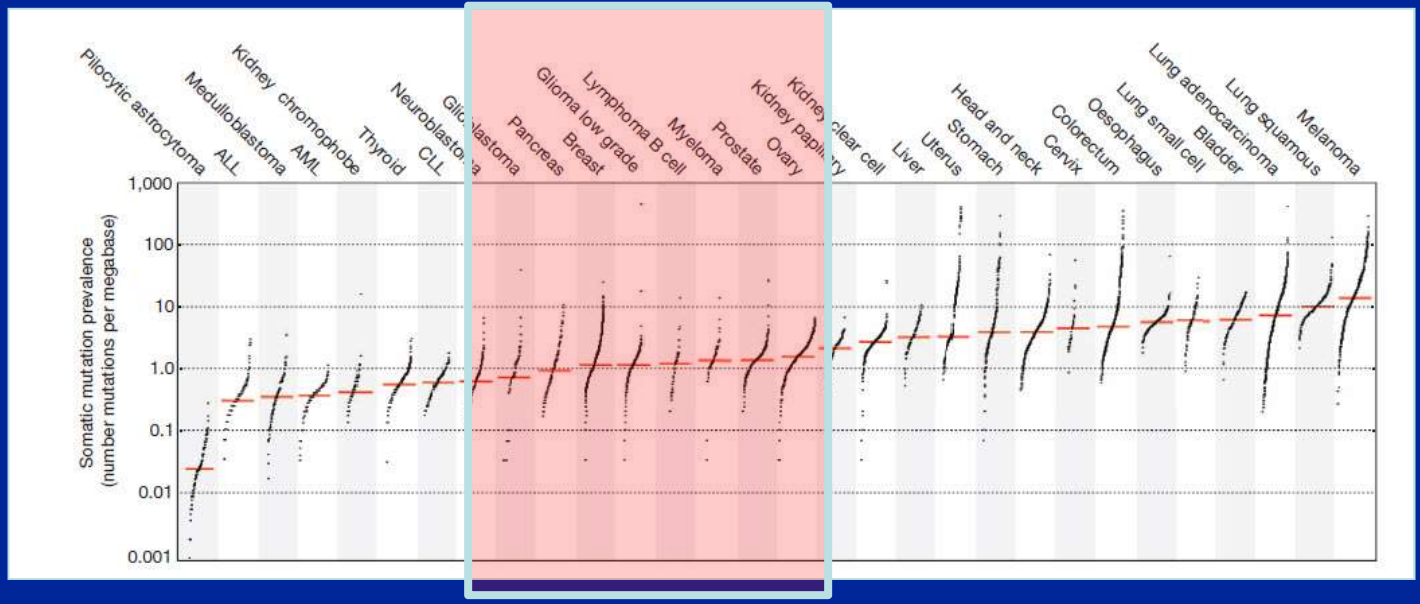


Lawrence, *Nature*: January 2014

Mutational Burden



Mutational Burden



D. Le. Presented May 30, 2015.

Mutations per tumor

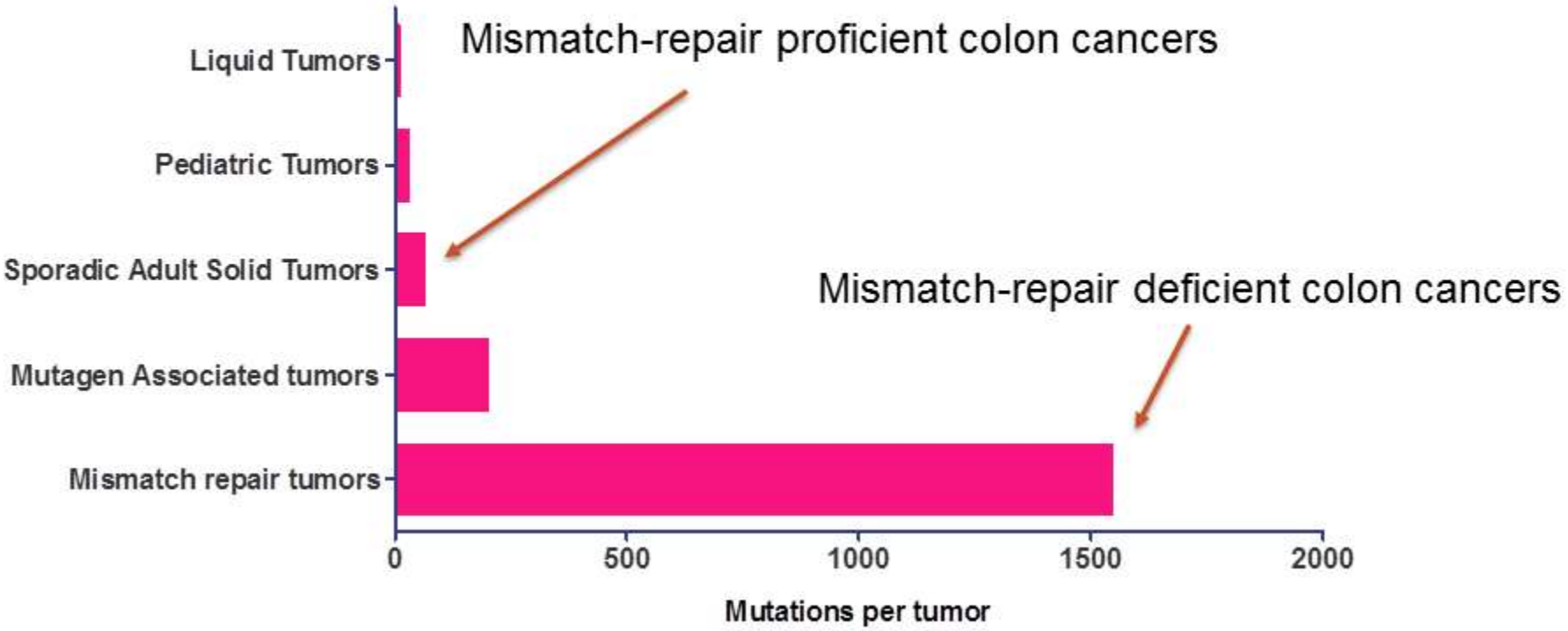
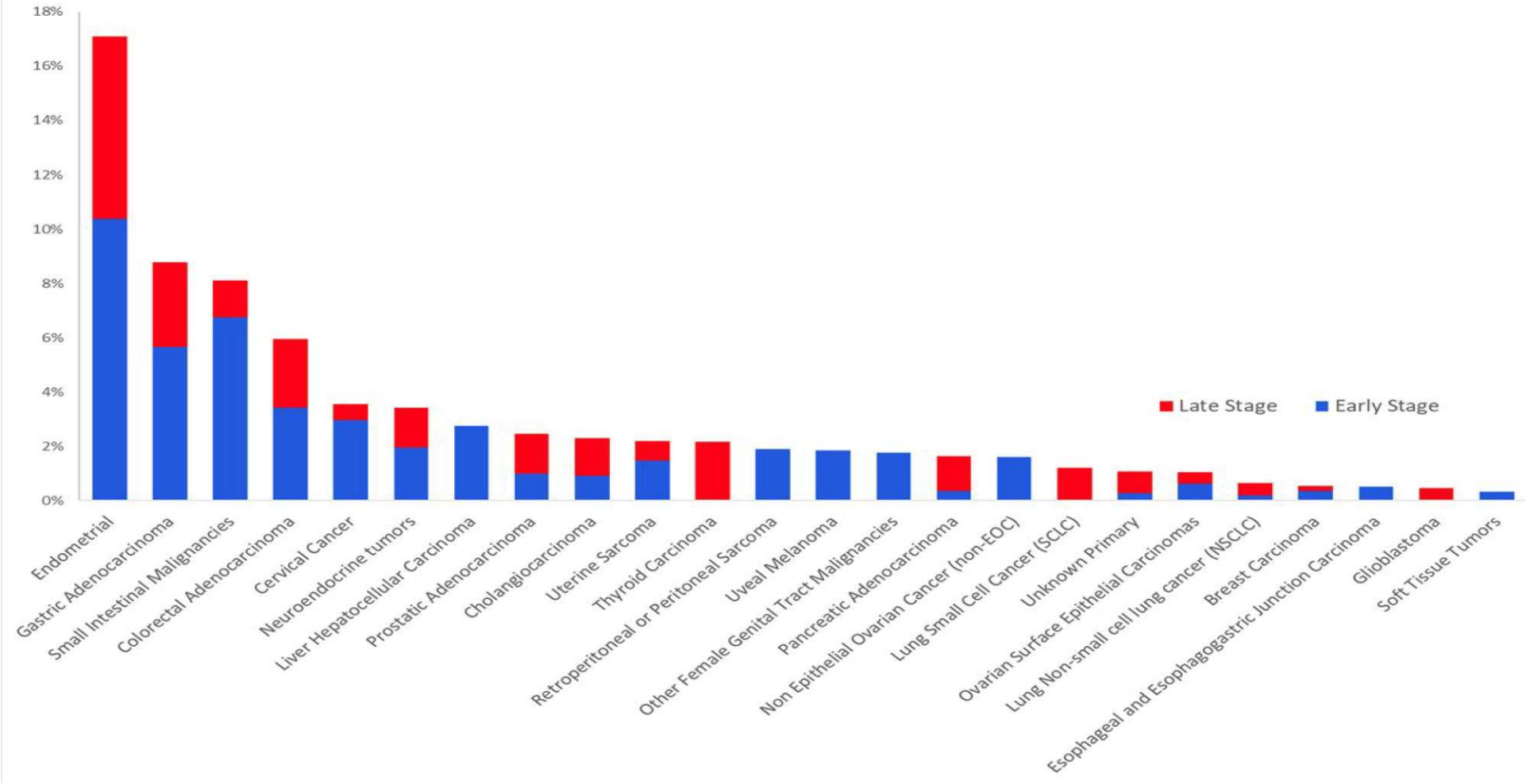


Fig. 3 Mismatch repair deficiency across 12,019 tumors.

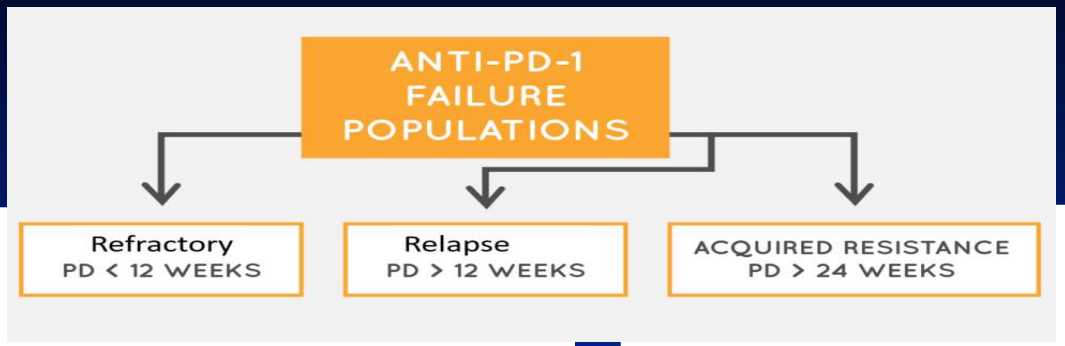


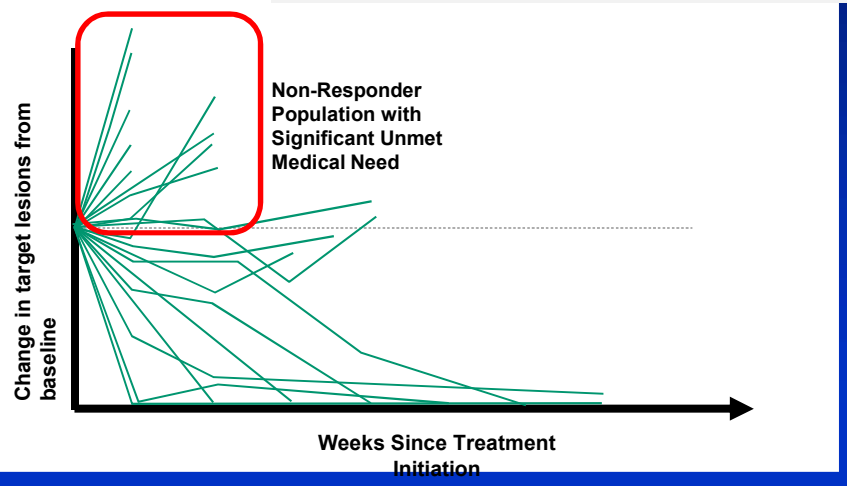
A New Paradigm in FDA Approval That is Agnostic to Histology and Primary Site: Pembrolizumab Approved for MSI-H or Mismatch Repair Deficient Tumors

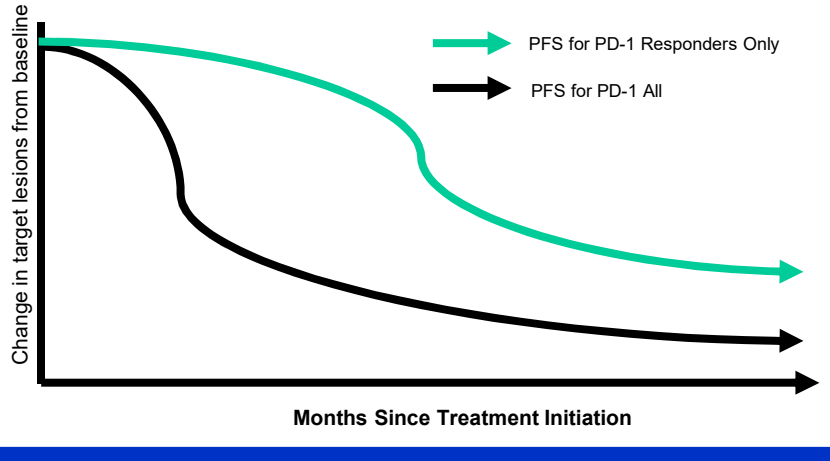
Where Are We Going?

- Tumor biology vs tumor type
- Overcoming resistance
- A glimpse into the future

Anatomy of Anti-PD-1 Failures in Melanoma

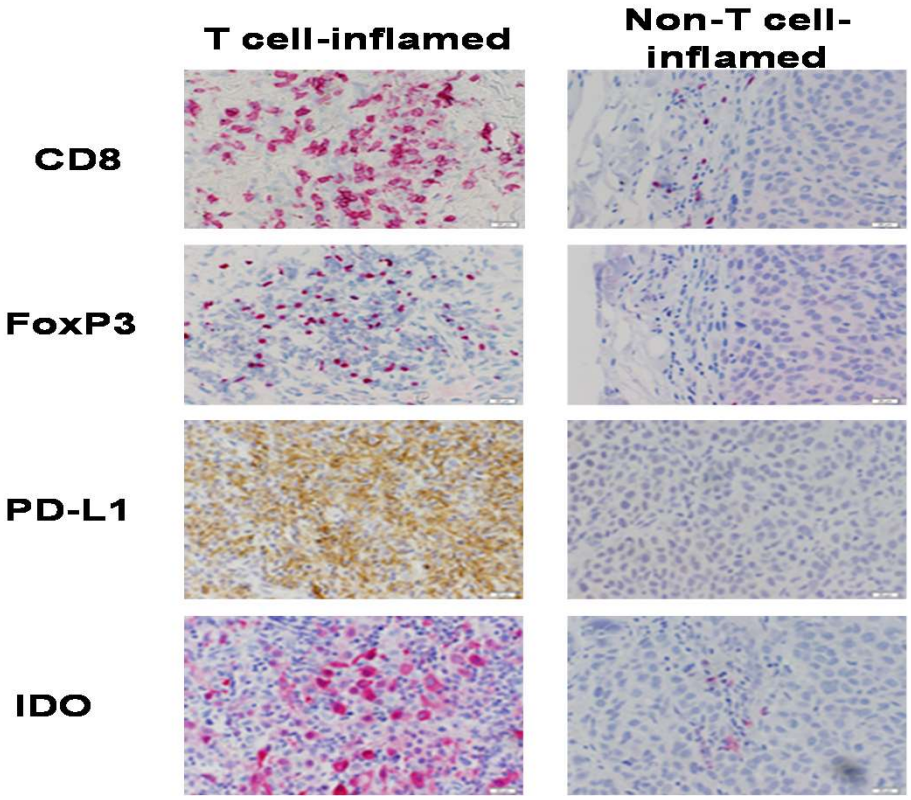


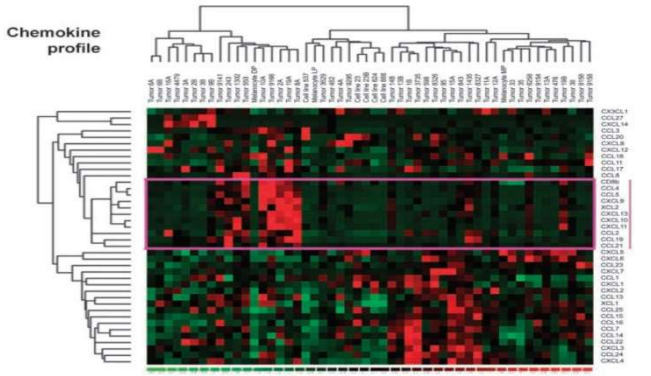




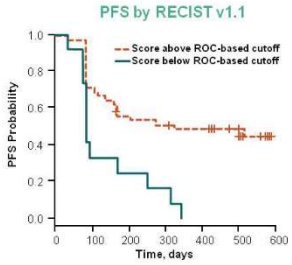
Figures adapted from Topalian et al.(April 2014), 32(10); 1020-1030

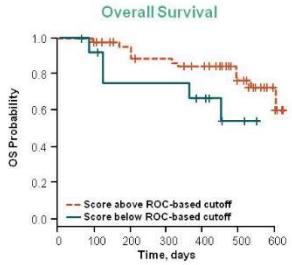
The T Cell-Inflamed Tumor Microenvironment is Characterized by Expression of Immune-Inhibitory Pathways and Predicts Outcomes to Immunotherapy





PFS and OS in Patients With Melanoma and IFNγ Signature Score Above and Below the Cutoff



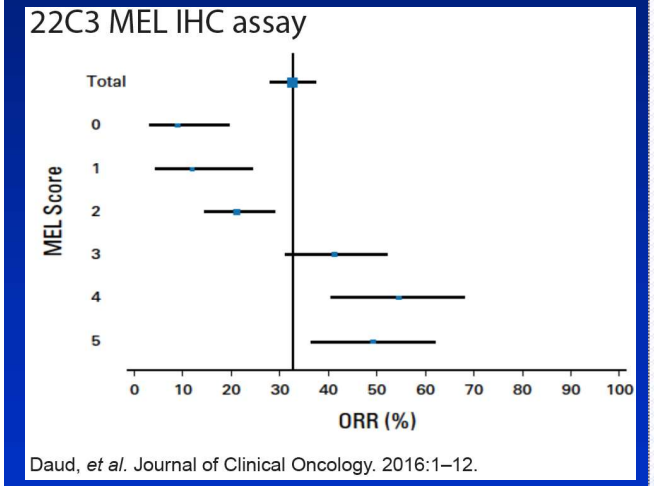


Spranger *et al.*, Science Trans. Med. 2013

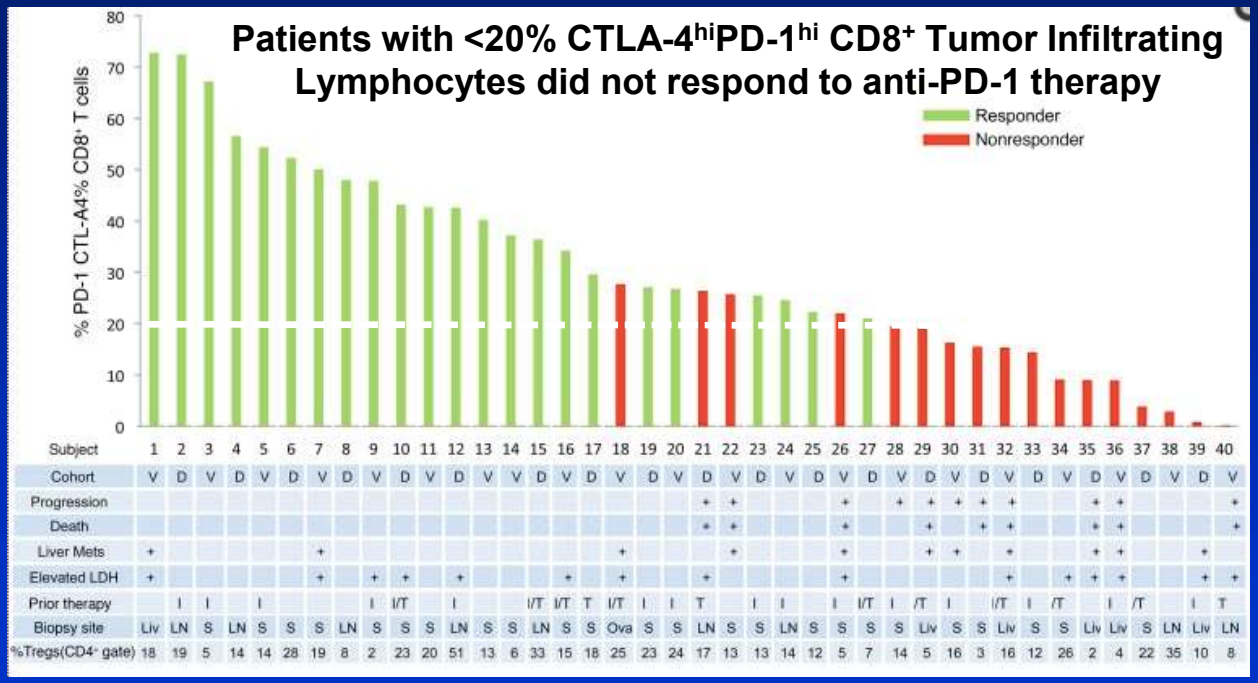
Harlin *et al*. Clin Can Res 2009

Ribas *et al*. J Clin Oncol 33, 2015 (suppl; abstr 3001)

Predicting Which Patients are Unlikely to Respond to PD-1 antibodies



Daud, *et al*. Journal of Clinical Oncology. 2016:1–12.

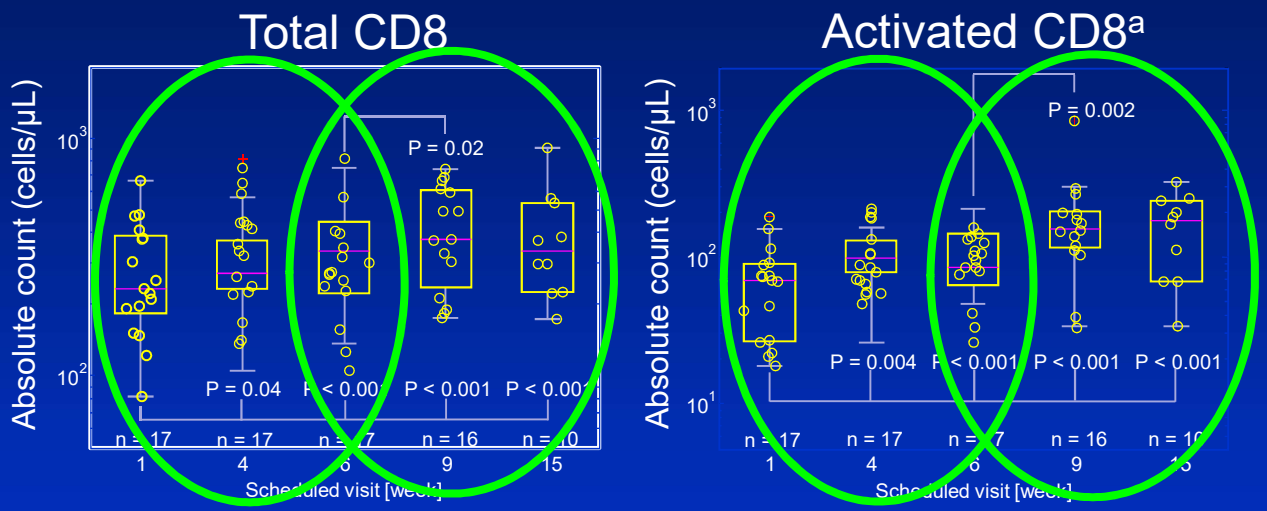


Daud AI et al. *J Clin Invest*. 2016;126(9):3447–3452

How Can We Overcome Resistance?

- Can we “Injure” the tumor to render it more vulnerable to systemic immune attack?
  - Oncolytic therapy
  - Radiation/Chemotherapy

Total and activated CD8 T-cells* increase after T-VEC and combination treatment



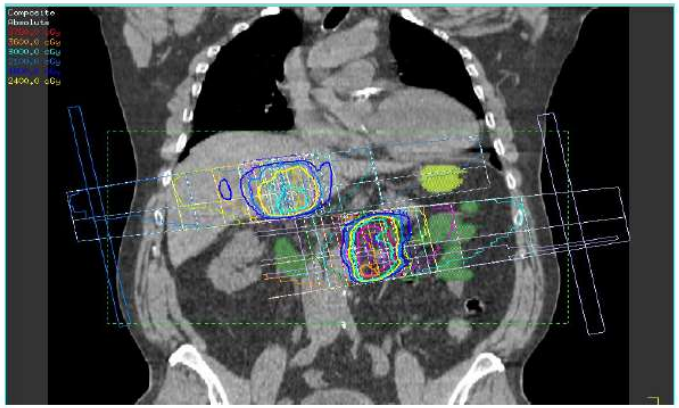
- Total and activated CD8 T cells in the peripheral blood increased from baseline after T-VEC administration at weeks 4 and 6 and further increased at weeks 9 and 15 after combination T-VEC and ipilimumab

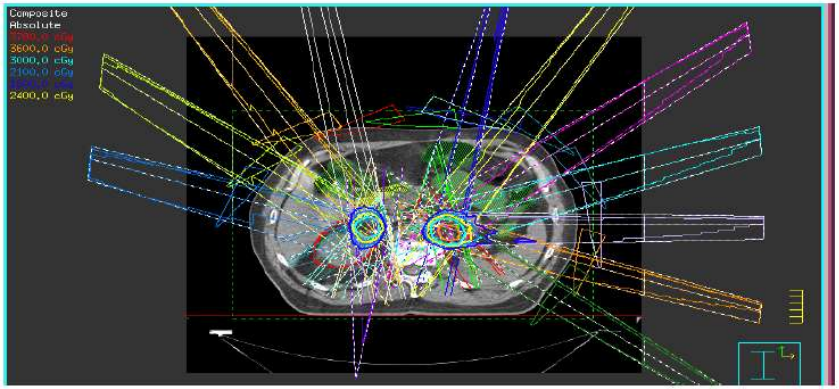
Data points are overlaid on the box plots. Each box plot shows the range between 25th percentile (q1) and 75th percentile (q3) as a yellow box, with a pink line showing the 50th percentile. The whiskers on each box are q3 ± 1.5* (q3 – q1). A red plus sign indicates outlier data within a subset. P-values below each post week 1 subset indicate significant changes from baseline level on week 1, and those above week 9 subset indicate significant changes from week 6 to week 9.

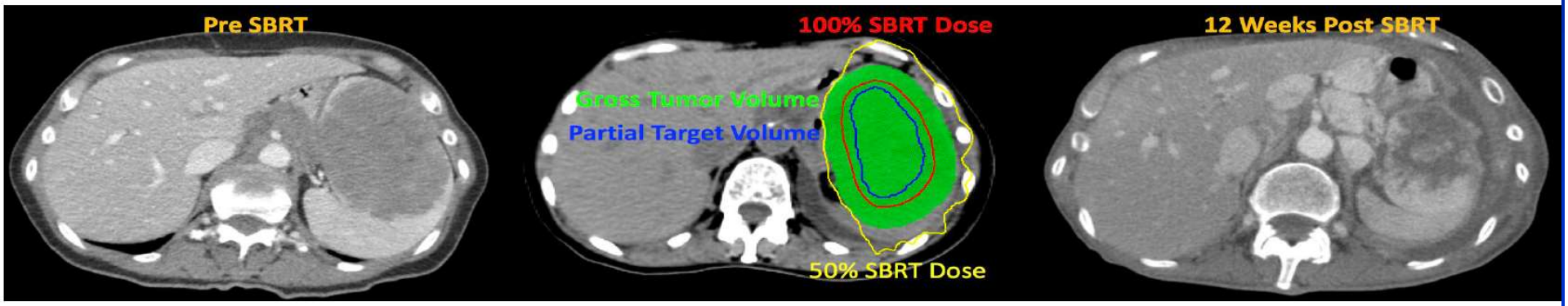
*Activated CD8 T cells are defined as HLA-DR+CD3+CD4- cells.

Puzanov I, et al J Clin Oncol. 2016 Aug 1;34(22):2619-26

Safety and activity of pembrolizumab and multi-site stereotactic body radiotherapy







Luke *et al. J Clin Oncol* 2018

Where Are We Going?

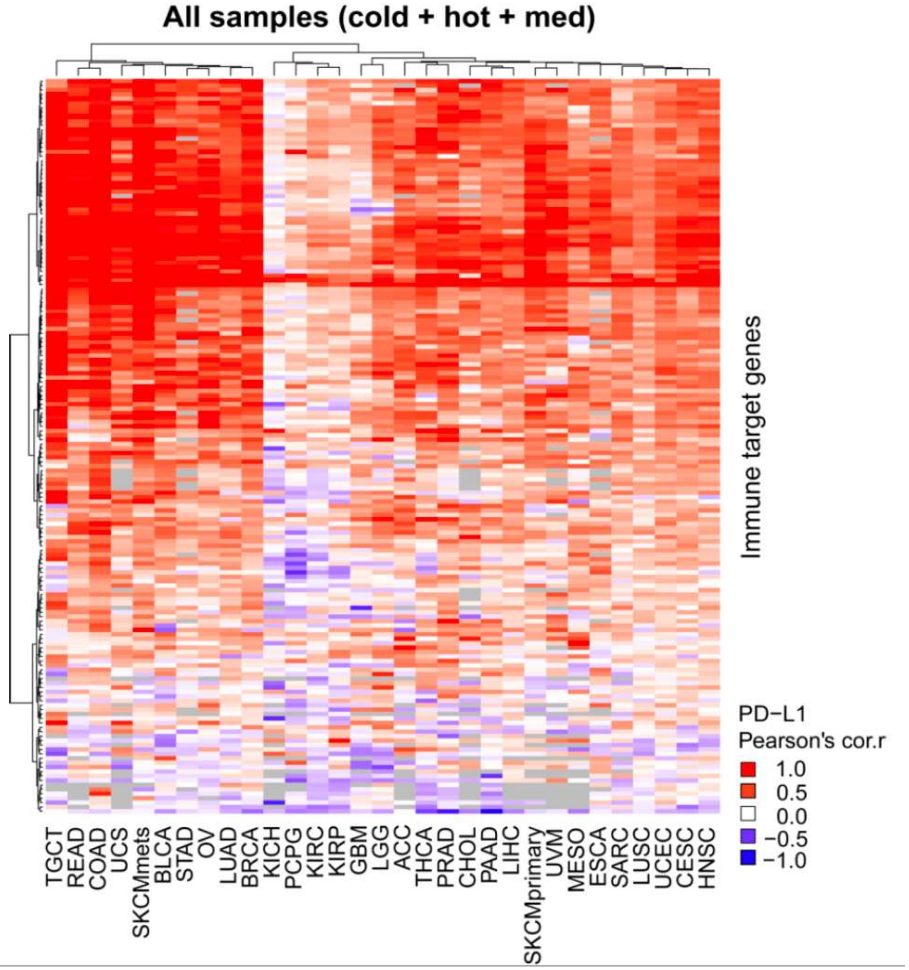
- Tumor biology vs tumor type
- Overcoming resistance
- A glimpse into the future

Future Directions

- Better application of biomarkers
- Making ”cold” tumors “hot”
- Gut microbiome
- New targets

Most Immune Targets Show Strong Correlation With PD-L1

A4GALT	CD70	HLA-DQA2	IL17A	KIR3DS1	STAT6
ADAM8	CD72	HLA-DQB1	IL17F	KLRK1	TBX21
ADORA2A	CD79A	HLA-DQB2	IL18	KRT20	TGFB1
ARG1	CD79B	HLA-DRA	IL1A	LAG3	TGFB2
ARG2	CD80	HLA-DRB1	IL1B	LAMP3	TGFB3
BATF3	CD86	HLA-DRB3	IL22	LAYN	TIGIT
BCL6	CD8A	HLA-DRB4	IL23A	LTA	TLR7
BTLA	CD93	HLA-DRB5	IL3RA	LY75	TLR9
CCL20	CEACAM8	HMGB1	IL4	MAGEH1	TMEM173
CCL5	CLEC4C	ICAM1	IL5	MB21D1	TNF
CCR1	CSF1R	ICOS	IL6	MICA	TNFRSF14
CCR6	CSF2RA	ICOSLG	IRF4	MICB	TNFRSF18
CCR8	CTLA4	IDO1	IRF9	MME	TNFRSF4
CD14	CX3CL1	IFNA1	ISG20	MST1R	TNFRSF9
CD160	CXCL10	IFNA10	ITGAL	NCAM1	TNFSF4
CD163	CXCL9	IFNA13	ITGAM	NCR1	TNFSF9
CD19	CXCR3	IFNA14	ITGAX	NDUFA2	TYK2
CD22	EDNRB	IFNA16	ITGB2	NT5E	VEGFA
CD24	ENTPD1	IFNA17	JAK1	PDCD1	VSIR
CD244	FCER2	IFNA2	JAK2	PDCD1LG2	VTCN1
CD247	FCGR3B	IFNA21	KIR2DL1	PRDM1	XBP1
CD27	FOXP3	IFNA4	KIR2DL2	PTGDR2	
CD274	GATA3	IFNA5	KIR2DL3	RORA	
CD276	HAVCR2	IFNA6	KIR2DL4	RORC	
CD28	HLA-A	IFNA7	KIR2DL5A	RSAD2	
CD33	HLA-B	IFNA8	KIR2DL5B	SIGLEC1	
CD3D	HLA-C	IFNB1	KIR2DS1	SIRPG	
CD3E	HLA-DMA	IFNG	KIR2DS2	SMAD3	
CD3G	HLA-DMB	IFNK	KIR2DS3	ST6GAL1	
CD4	HLA-DOA	IFNW1	KIR2DS4	STAT1	
CD40	HLA-DOB	IL10	KIR2DS5	STAT2	
CD40LG	HLA-DPA1	IL12A	KIR3DL1	STAT3	
CD68	HLA-DPB1	IL12B	KIR3DL2	STAT4	
CD69	HLA-DQA1	IL13	KIR3DL3	STAT5B	



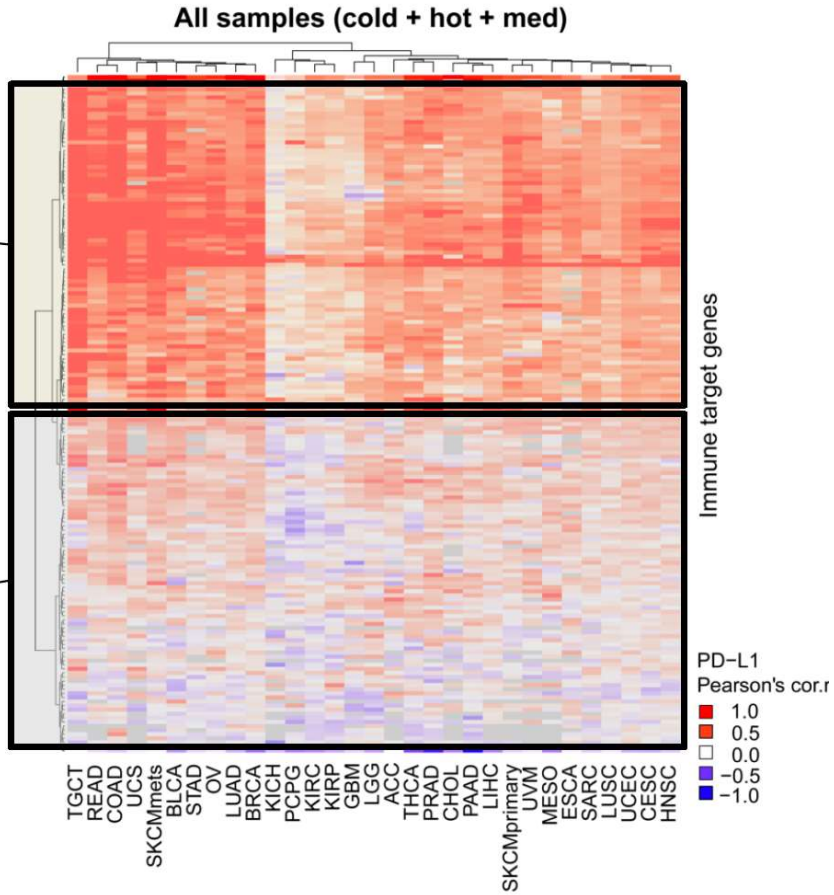
Genes Separate Into Those Strongly Correlated and Less Strongly Correlated to PDL1

Strongly correlated

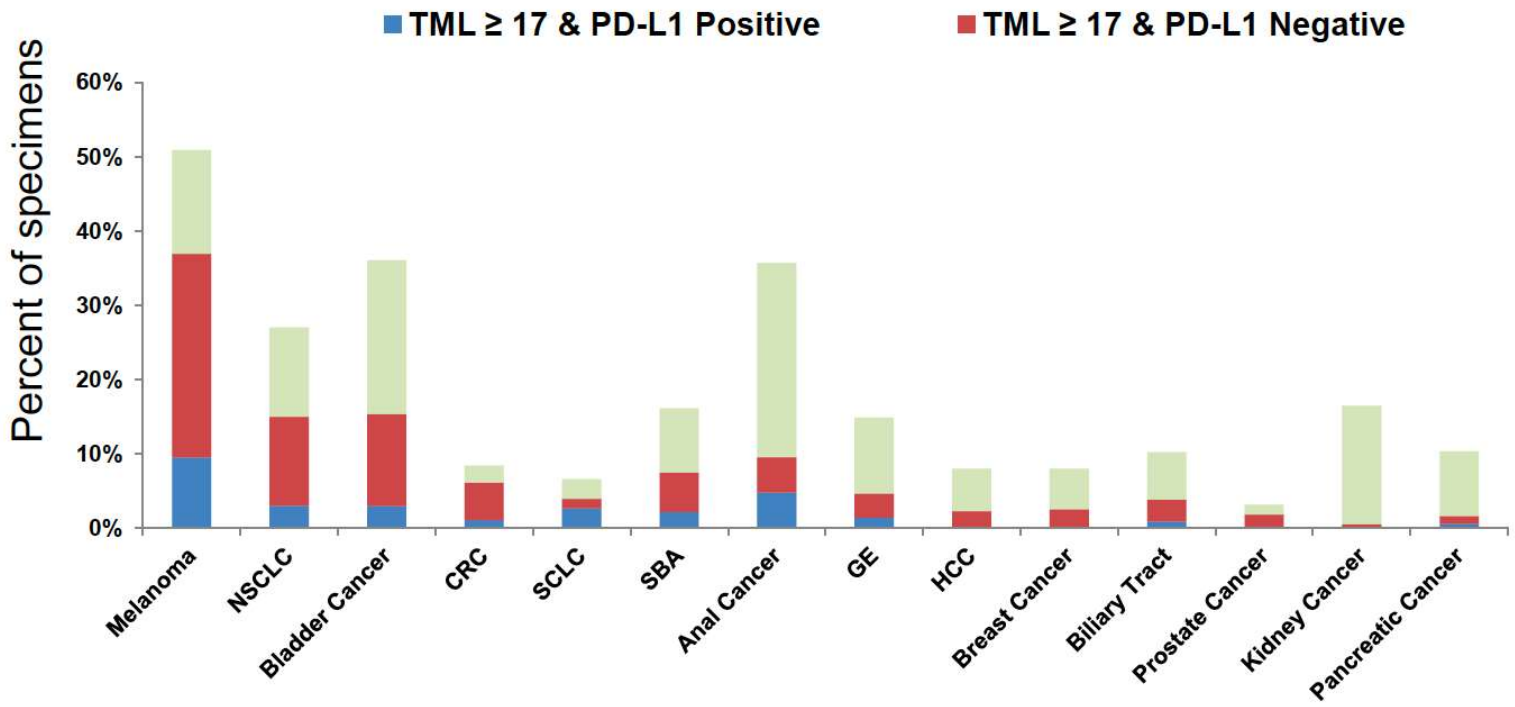
CD163, CCR8, PRDM1, SIGLEC1, CD28, **FOXP3, CSF1R**, CD33, CD4, TLR7, IL10, **HLA−DRA**, HLA−DPA1, HLA−DQA1, HLA−DOA, CD69, RSAD2, HLA−DMB, CD3E, CD3D, CCL5, CD247, **PDCD1**, **CD8A**, SIRPG, **CTLA4**, IFNG, TBX21, **LAG3**, KLRK1, LTA, **ICOS**, **TIGIT**, CD3G, ITGAL, CXCL10, CXCL9, CD80, CD86, **HAVCR2**, ITGB2, CCR1, TNFRSF9, **IDO1**, STAT1, JAK2, PDCD1LG2, HLA−DPB1, HLA−DRB1, HLA−DMA, HLA−DRB5, HLA−DQB1, KIR2DL4, HLA−DQA2, HLA−DOB, HLA−DQB2, BTLA, LAMP3, CD244, CSF2RA, CD14, IL1B, CD40LG, ITGAX, ITGAM, CD68, ICAM1, MICB, IRF4, STAT4, TNF, CD27, CD72, STAT2, CD40, HLA−B, HLA−C, HLA−A, CXCR3, JAK1, CCR6, LY75, CD79A

IL12B, IRF9, ADAM8, NCR1, TNFSF4, **KIR2DL3, KIR2DS4, KIR2DL1, KIR3DL2, KIR3DL1**, ISG20, **TNFRSF18**, IL18, CD93, TMEM173, IL1A, STAT3, FCGR3B, IL6, BATF3, CD70, ENTPD1, **TGFB1**, CD79B, IL3RA, TNFRSF4, ADORA2A, LAYN, A4GALT, CX3CL1, TNFSF9, IL23A, IL13, CD19, FCER2, TLR9, CLEC4C, CD22, CD160, RORA, BCL6, GATA3, NT5E, IL12A, MME, CCL20, ICOSLG, XBP1, STAT5B, MST1R, TGFB3, TGFB2, IL17A, CD276, STAT6, EDNRB, SMAD3, **VEGFA**, IFNB1, MICA, KIR3DL3, TYK2, TNFRSF14, ST6GAL1, RORC, CEACAM8, ARG2, KRT20, VTCN1, CD24, IFNK, NCAM1, MAGEH1, IL17F, IL5, HMGB1, IFNA1, IFNA13, IFNW1, IFNA21, ARG1, IL4, NDUFA2

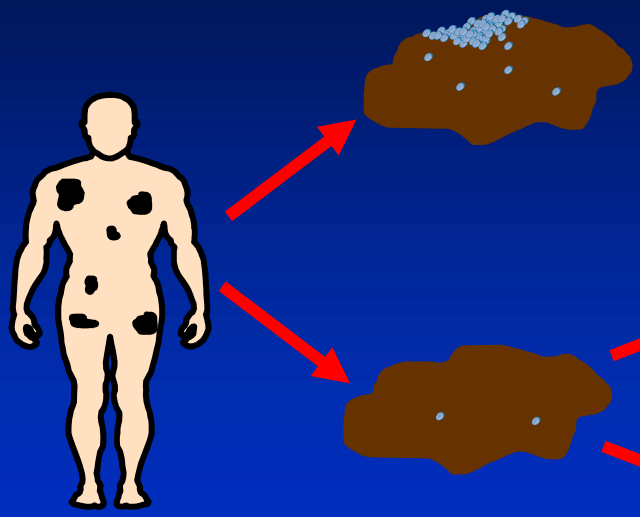
Less correlated



Combination of Tumor Mutational Load and PD-L1 expression



Making Tumors “Hot”



PD-1/PD-L1 Monotherapy

Bring T-cells into tumors:

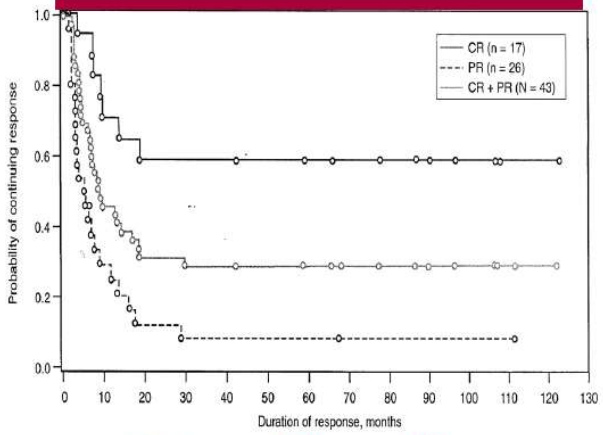
+ Anti–CTLA-4
+ Immune activating antibodies or cytokines
+ TLR agonists or oncolytic viruses
+ IDO or macrophage inhibitors
+ Targeted therapies

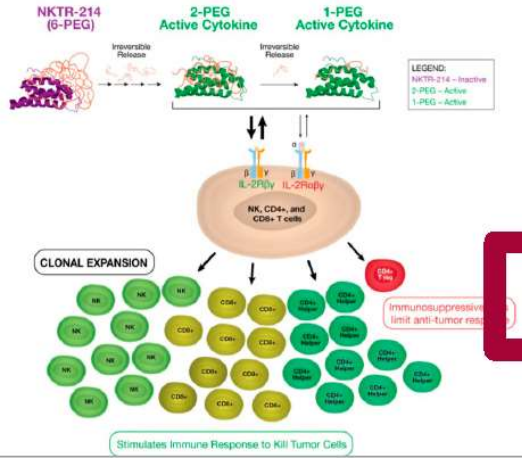
Generate T-cells:

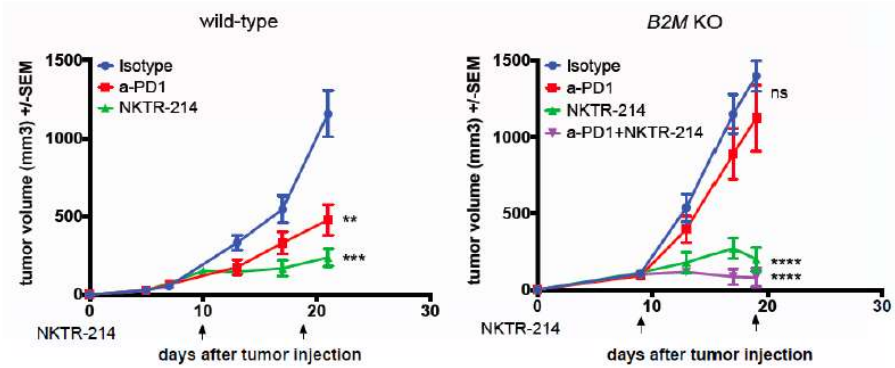
Vaccines
TCR engineered ACT
CAR engineered ACT

HD IL-2 or peg-CD122 agonist (NTRK-214) + PD1?

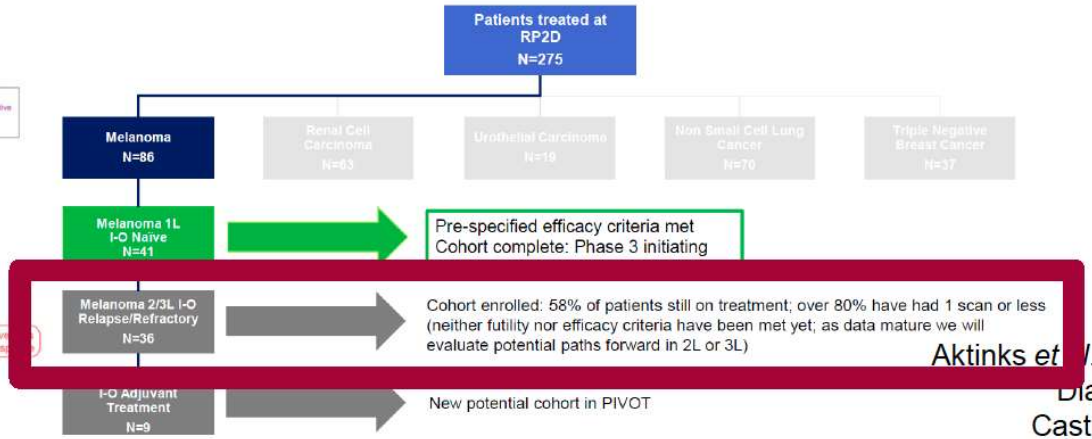
HD IL-2





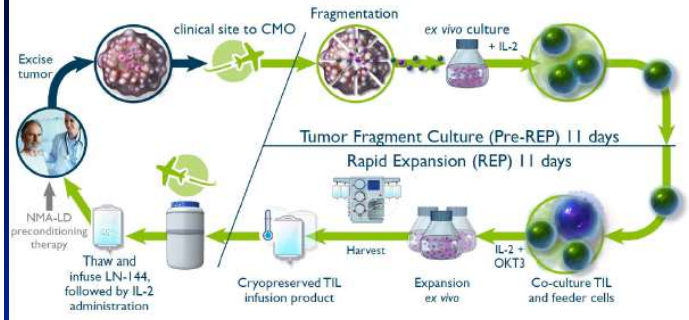


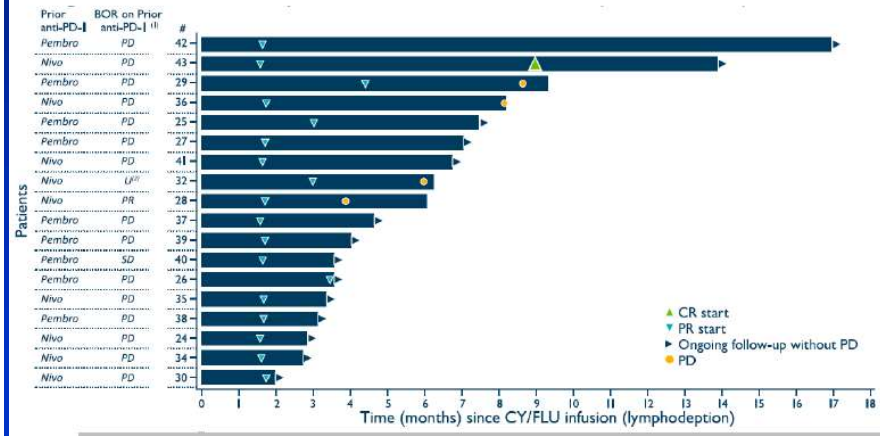
PIVOT-02 Melanoma Strategy: NKTR-214 + Nivolumab

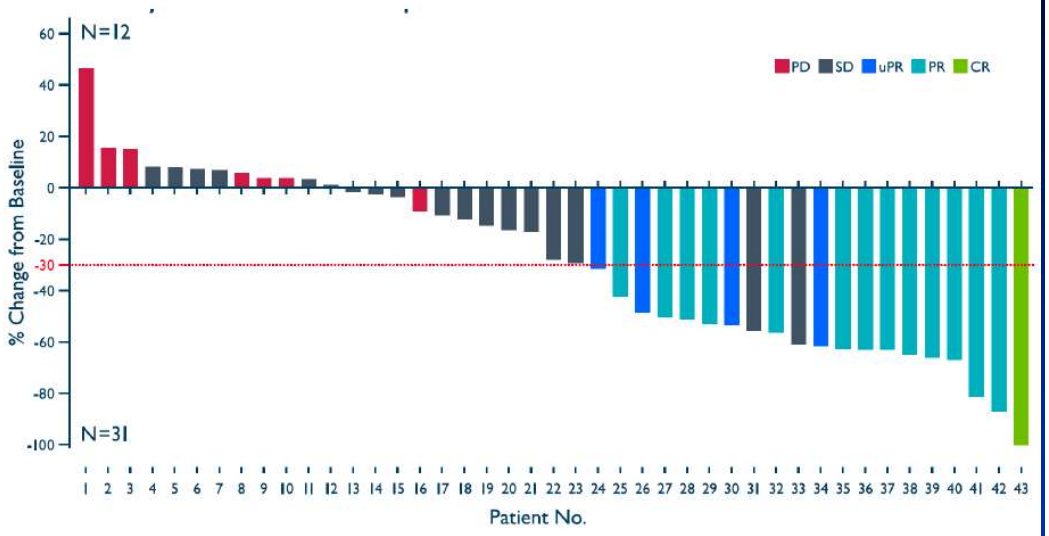


Aktinks *et al*. *J Clin Oncol* 1999
Diab *et al*. SITC 2018
Castro *et al*. SITC 2018
Nektar Investor Materials 2018

Adoptive Cell Transfer with Tumor Infiltrating Lymphocytes







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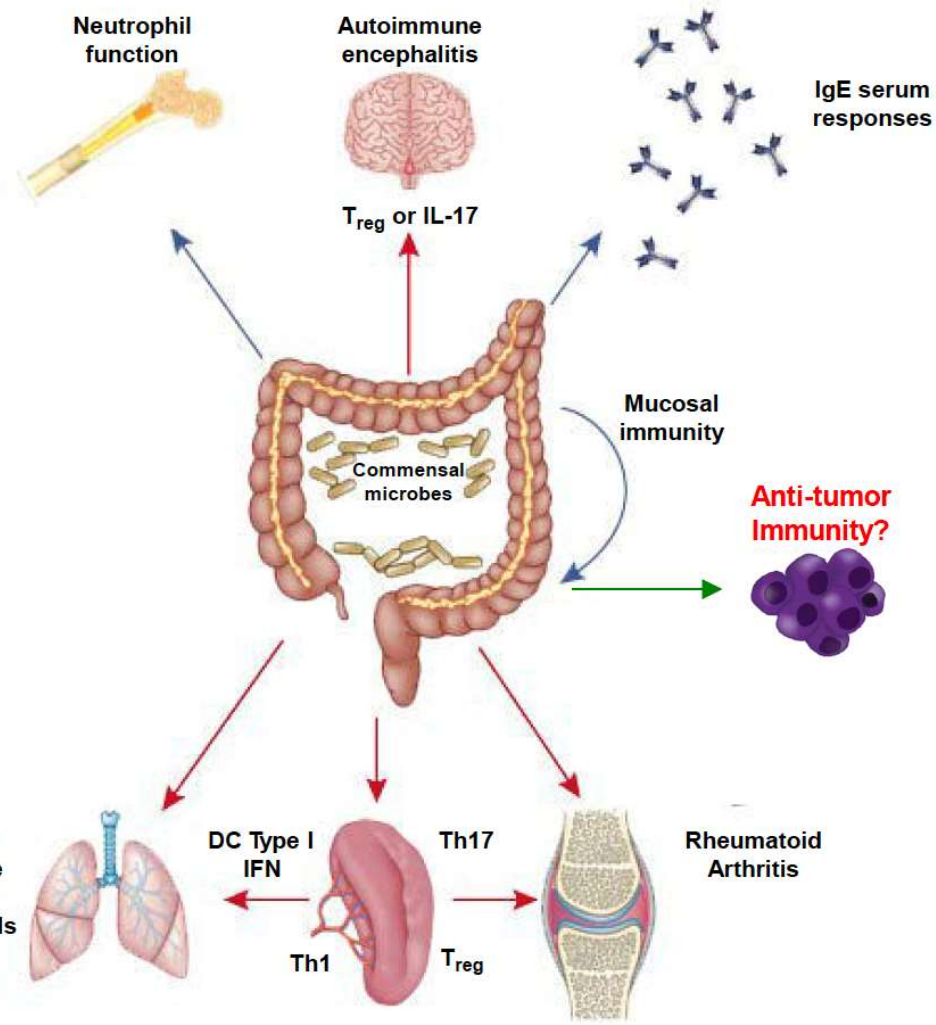
Sarniak *et al*. SITC 2018

Commensal bacteria shape systemic immunity



Adapted from Goldszmid RS & Trinchieri G, Nature Immunology 2012

Immune Cycle and Drug Targets

Recognize Tumor

Presence of antigen

APC present

Antigen processing & presentation occurs

Lack of inhibitors

Targeted Therapy
TVEC
Sting agonist
TLR9 agonist
Vaccines
RT

Activation of Immune Cells*

T cells

NK cells

T reg

Myeloid

Anti-CTLA-4
CD137 agonist
GITR agonist

OX40 agonist
CD40 agonist
IL2Rβγ agonist

Move to Target

Stroma – permissive (other immune cells, fibroblasts, angiogenesis)

Chemoattractants

CSF1R

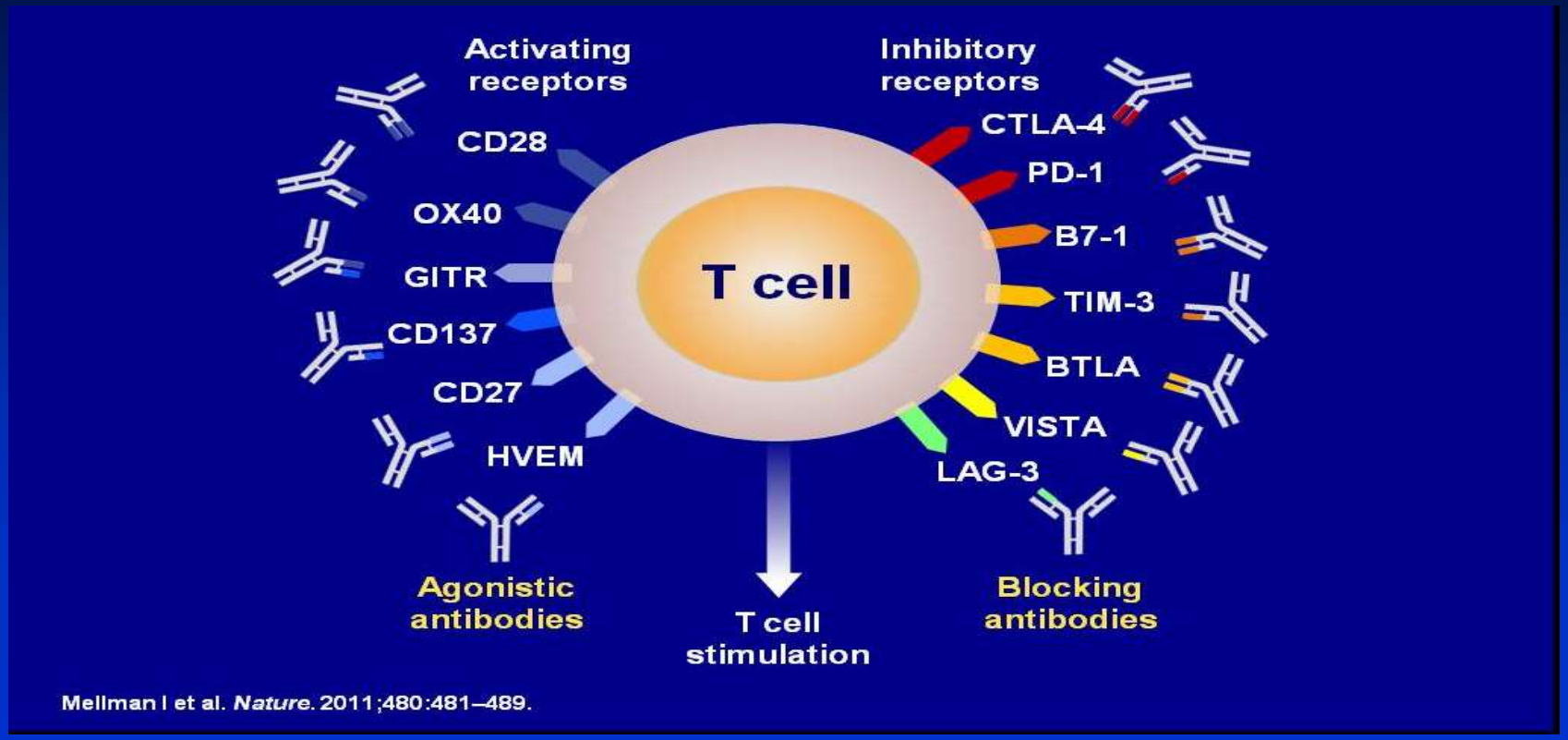
Kill Target

Lack of Inhibitors

- cellular (Treg, myeloid, tumor)
- chemical (cytokines, IDO, metabolites)

Anti-PD-1/PD-L1
LAG3 inhibitor
TIM3 inhibitor
GITR agonist
Adenosine 2A receptor inhibitor
TIGIT inhibitor
IDO inhibitor

T-Cell Immune Checkpoints



Mellman I et al. *Nature*. 2011;480:481–489.

Presented By Scott Gettinger at 2014 ASCO Annual Meeting

The Future