The Immuno-Oncology Revolution in Melanoma and the Development of Combination Therapies

Alexander EGGERMONT. MD, PhD , *Gustave Roussy Cancer Campus Grand Paris,*

IMMUNOGENIC CELL DEATH

and

involvement of immune system in any durable response

- **Chemotherapy**
- **Targeted therapy**
- **Radiotherapy**

IMMUNOGENIC CELL DEATH

Release of DAMPs → Induces Adaptive Immune Response

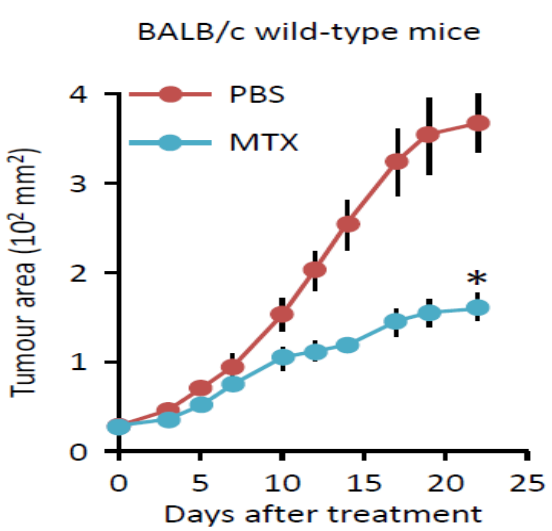
(Danger Associated Molecular Products)

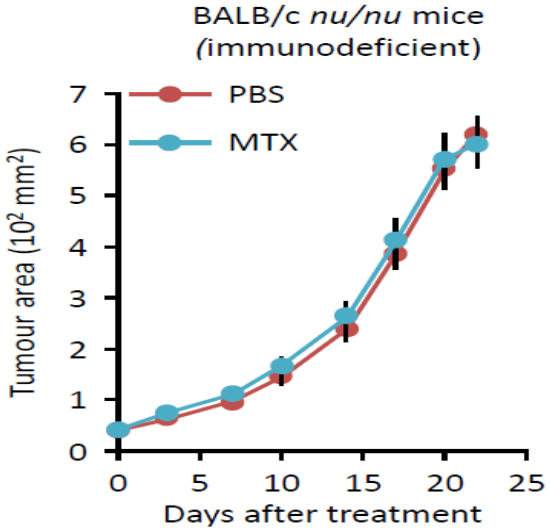
- Calreticulin
- HMGB1
- IL-1β
- ATP

Laurence Zitvogel & Guido Kroemer (Science 2011, Immunity 2016, Cell 2017)

IMMUNOGENIC CELL DEATH
Zitvogel & Kroemer

Chemotherapy Efficacy & the Immune System





*P < 0.05; n = 10 mice per group; means ± SEM are shown.
MTX, mitoxantrone; PBS, phosphate-buffered saline (control).

Michaud M, et al. Science 2011;334:1573–7.

FS MCA205

Cisplatin: NO
Doxorubicin: YES

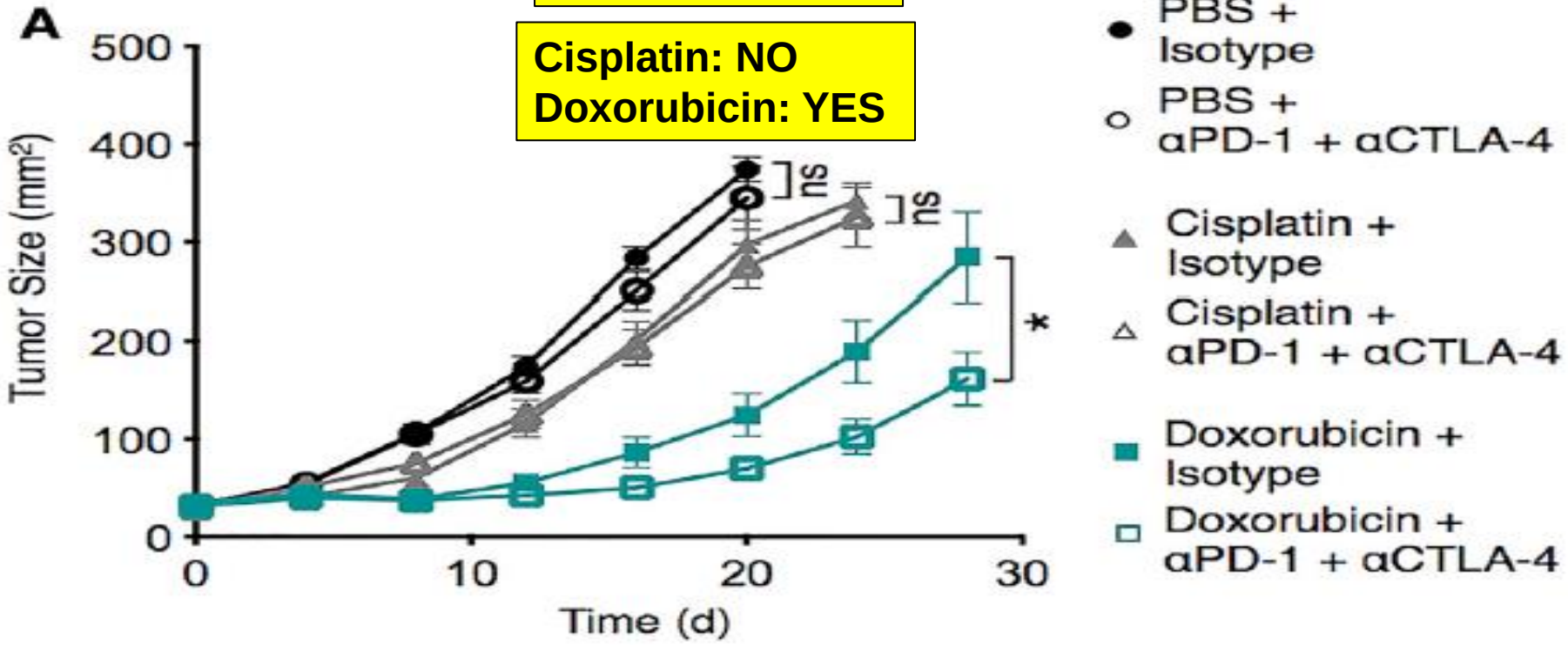
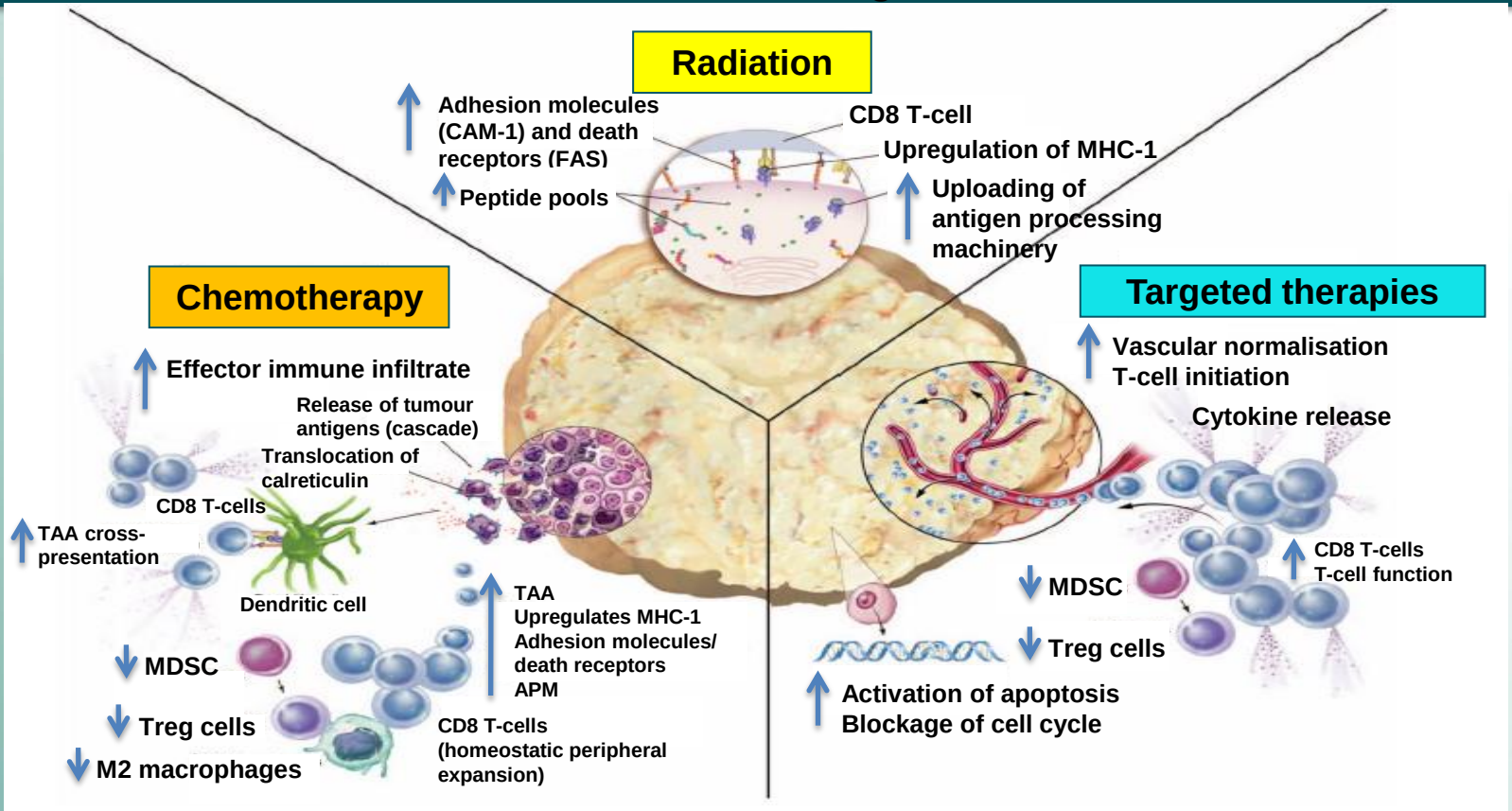


Figure 7. Immunogenic Chemotherapeutics Improve Immune Checkpoint Blockade Treatment against MCA205 Fibrosarcoma and CT26 Colon Carcinoma

Immunotherapy + Other Modalities
Guidance by Immunogenic Cell Death
Zitvogel & Kroemer



Adapted from Hodge JW. *Semin Oncol* 2012;39(3):323–339; Drake CG *Ann Oncol* 2012;23 Suppl 8:viii41-6; Ménard C, et al. *Cancer Immunol Immunother* 2008;57:1579-87; Hannani D, et al. *Cancer J* 2011;17:351-358; Ribas A at al. *Curr Opin Immunol* 2013:25:291-296.

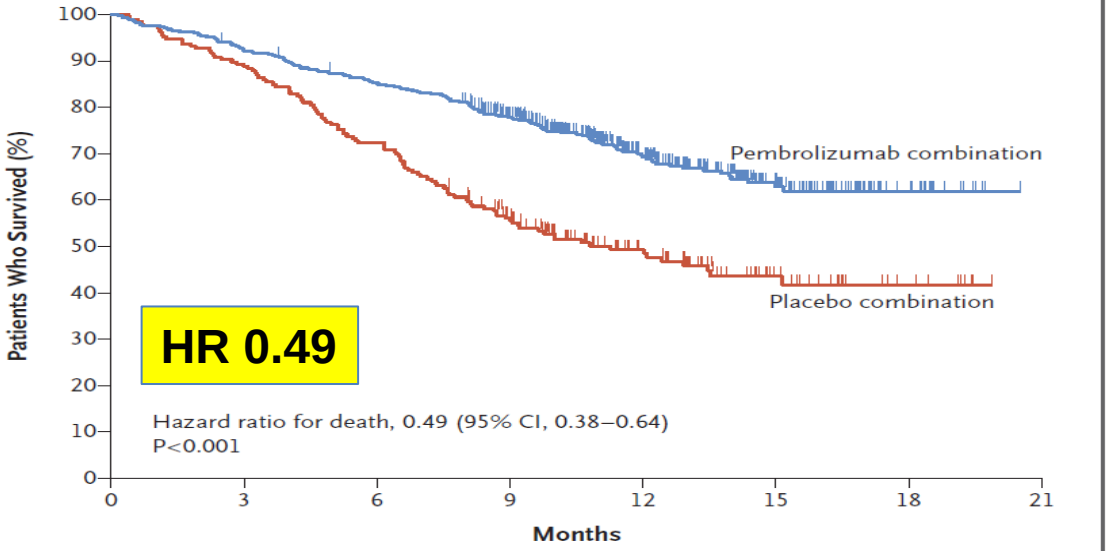
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer

L. Gandhi, D. Rodríguez-Abreu, S. Gadgeel, E. Esteban, E. Felip, F. De Angelis, M. Domine, P. Clingan, M.J. Hochmair, S.F. Powell, S.Y.-S. Cheng, H.G. Bischoff, N. Peled, F. Grossi, R.R. Jennens, M. Reck, R. Hui, E.B. Garon, M. Boyer, B. Rubio-Viqueira, S. Novello, T. Kurata, J.E. Gray, J. Vida, Z. Wei, J. Yang, H. Raftopoulos, M.C. Pietanza, and M.C. Garassino, for the KEYNOTE-189 Investigators*

A Overall Survival



No. at Risk								
Pembrolizumab combination	410	377	347	278	163	71	18	0
Placebo combination	206	183	149	104	59	25	8	0

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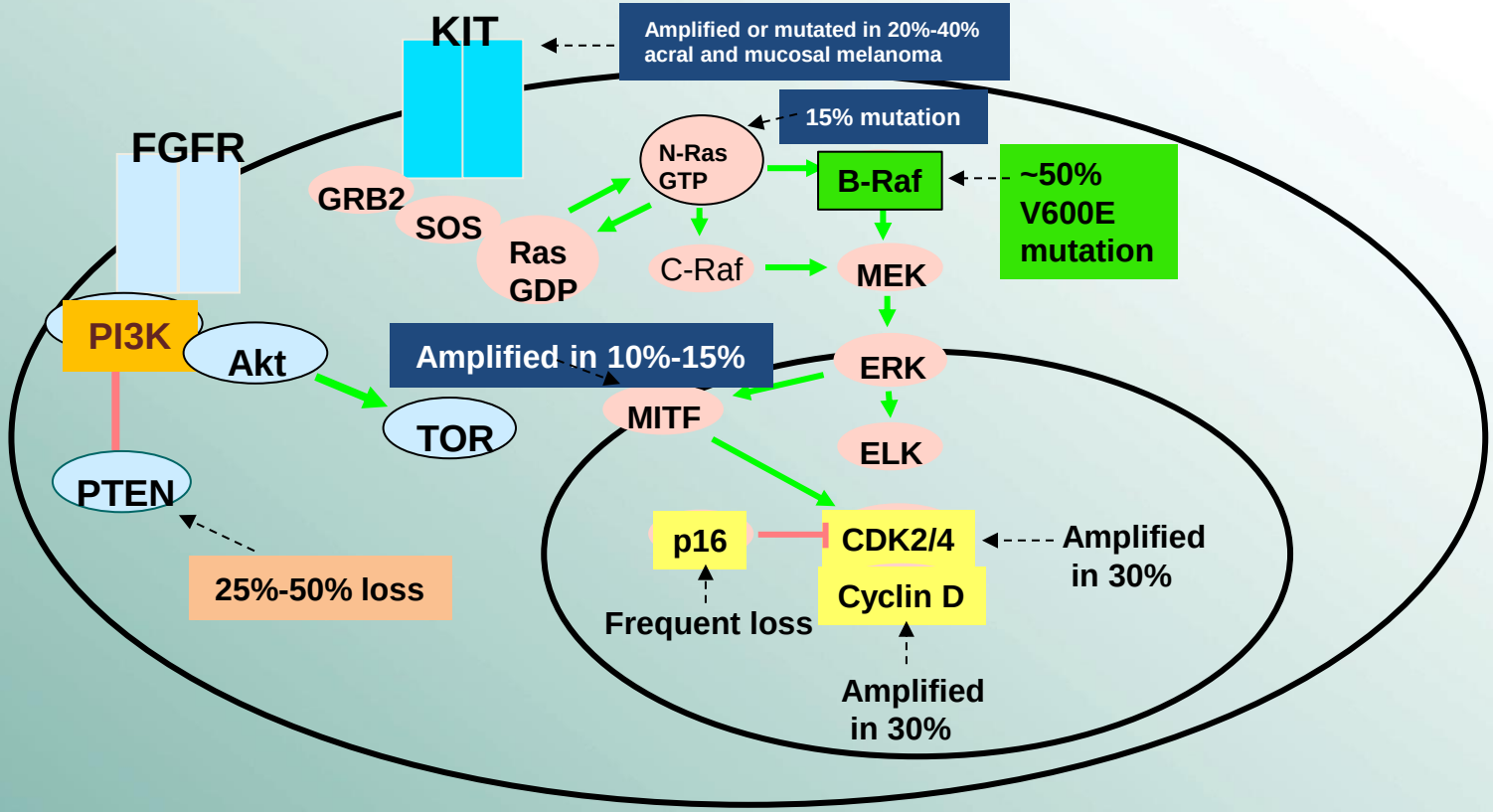
THE MELANOMA PARADIGM

MUTATION DRIVEN DRUG DEVELOPMENT

INNOVATIVE IMMUNOMODULATION

Molecular Alterations in Melanoma
BRAF inhibition



Adapted from Sosman, *Curr. Oncol. Rep*. 11, 405 (2009)

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GRAND PARIS

Safety and efficacy of vemurafenib in $BRAF^{V600E}$ and $BRAF^{V600K}$ mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open

www.thelancet.com/oncology Vol 15 March 2014

Grant A McArthur, Paul B Chapman, Caroline Robert, James Larkin, John B Haanen, Reinhard Dummer, Antoni Ribas, David Hogg, Omid Hamid, Paolo A Ascierto, Claus Garbe, Alessandro Testori, Michele Maio, Paul Lorigan, Celeste Lebbé, Thomas Jouary, Dirk Schadendorf, Stephen J O'Day, John M. Kirkwood, Alexander M Eggermont, Brigitte Dréno, Jeffrey A Sosman, Keith T Flaherty, Ming Yin, Ivor Caro,

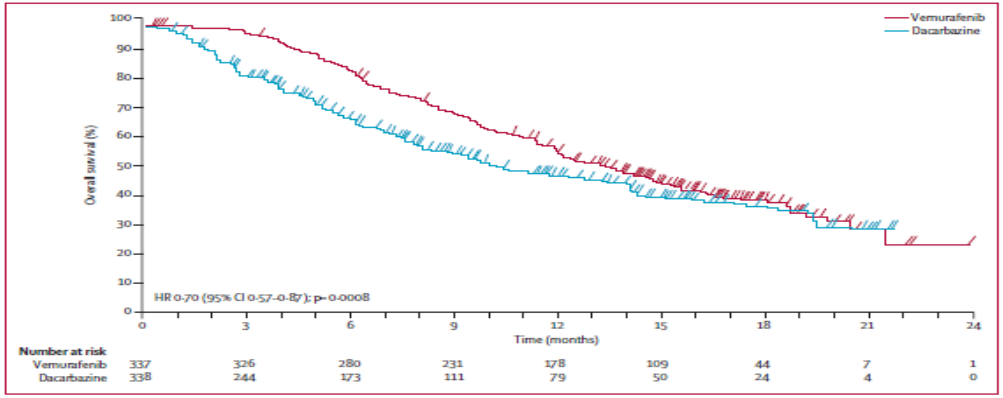


Figure 2: Overall survival (randomised population; censored at crossover) for patients randomly assigned to vemurafenib or to dacarbazine (cutoff Feb 1, 2012)

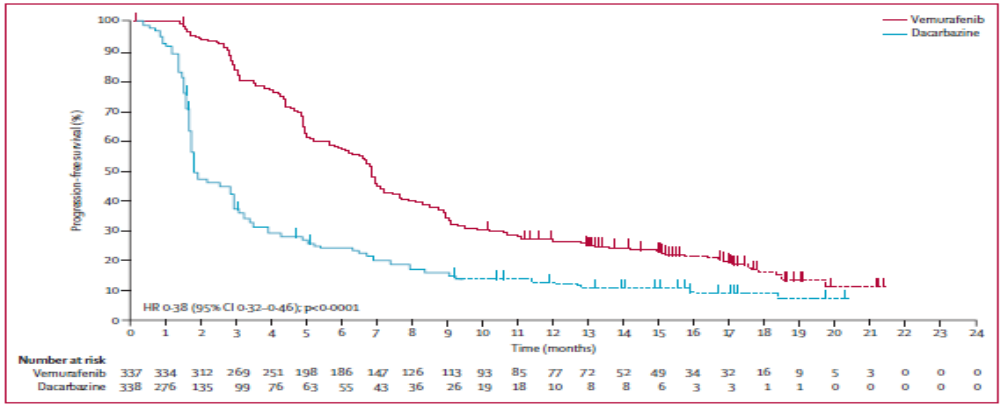
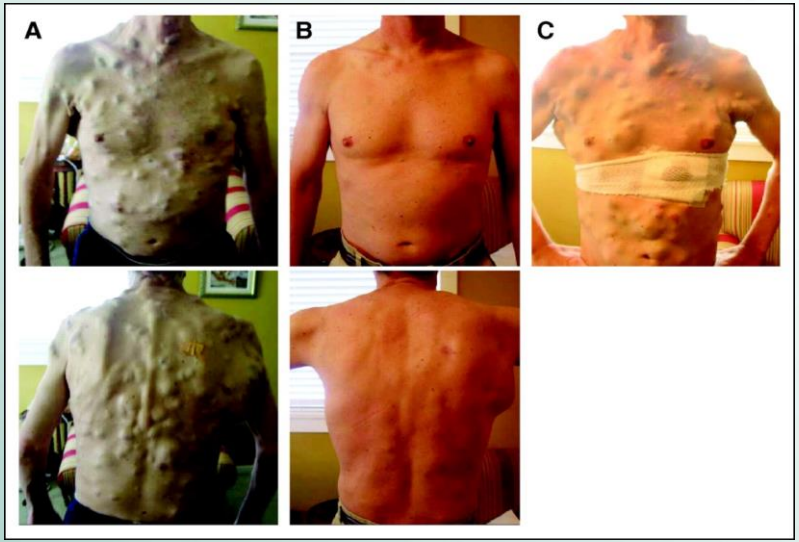
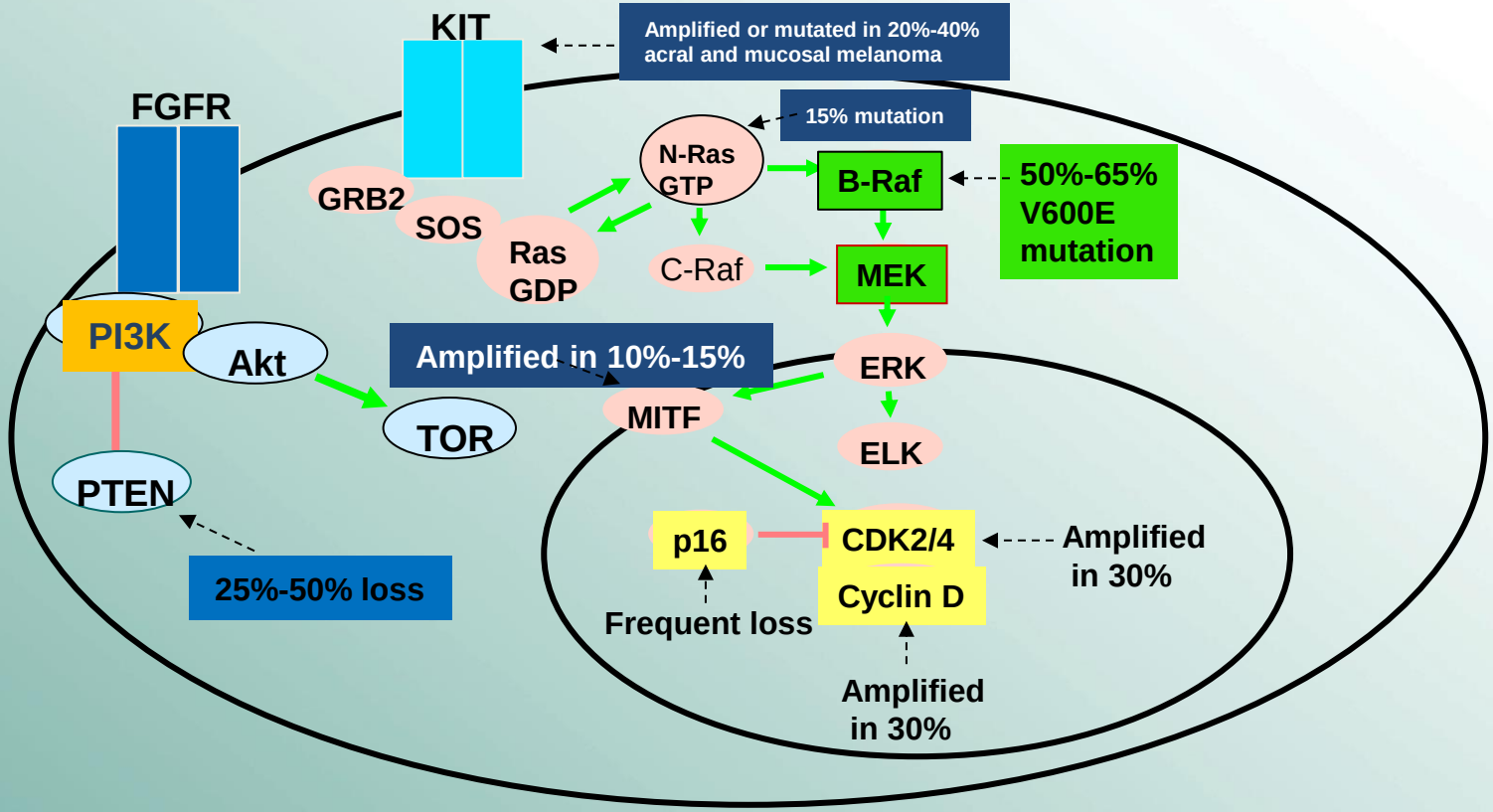


Figure 3: Progression-free survival (randomised population; censored at crossover) for patients randomly assigned to vemurafenib or to dacarbazine (cutoff Feb 1, 2012)

OS 9.7-13.6 mts
Gain: 3.9 mts
HR 0.70
BRAFi Monotherapy
SUCCESS and FAILURE

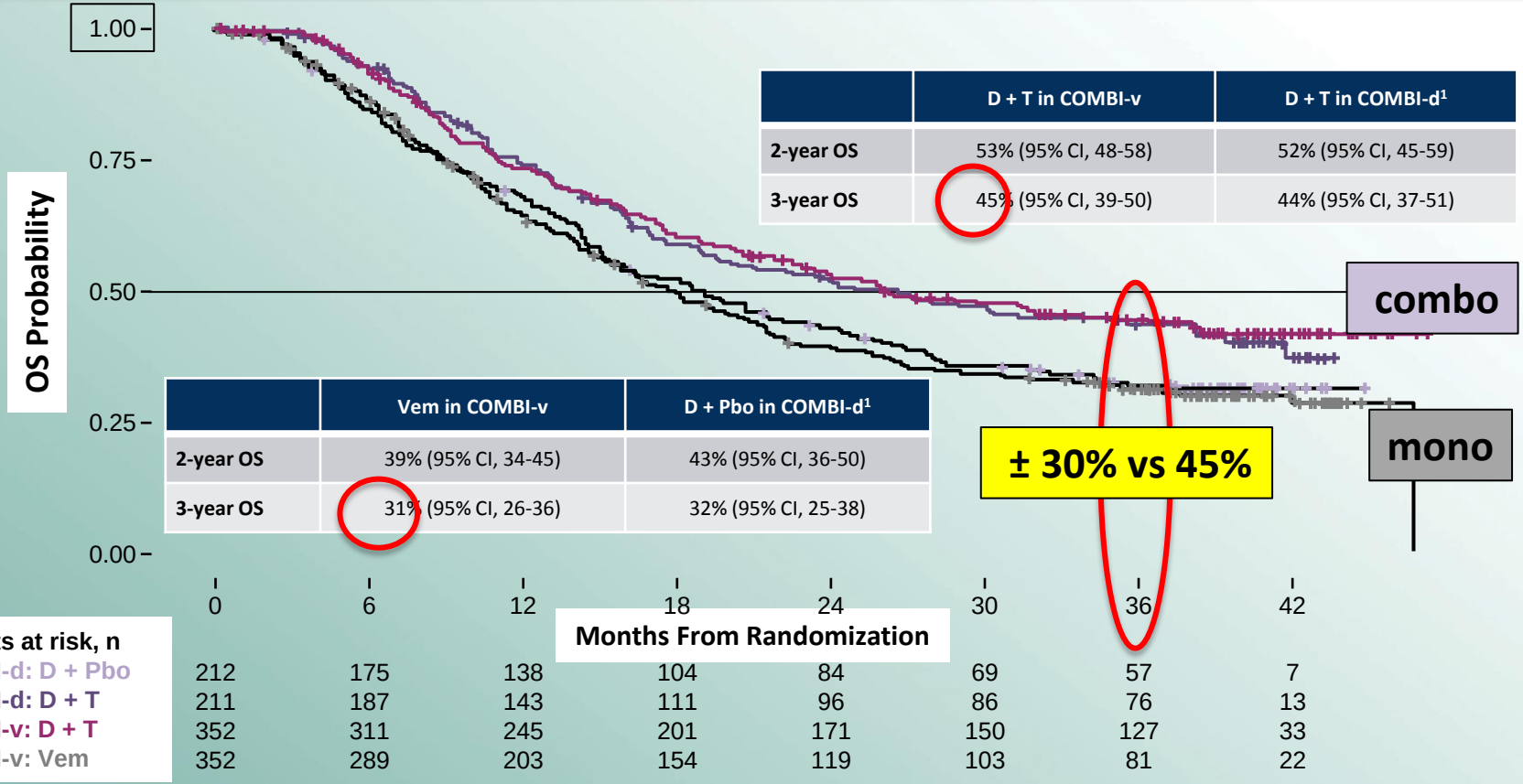


BRAF + MEK Inhibitors Combo



Adapted from Sosman, *Curr. Oncol. Rep*. 11, 405 (2009)

Dabrafenib (D) + Trametinib (T) vs monotherapy
Overall Survivall @ 3yrs : ± 30% vs 45%



	D + T in COMBI-v	D + T in COMBI-d[1]
2-year OS	53% (95% CI, 48-58)	52% (95% CI, 45-59)
3-year OS	45% (95% CI, 39-50)	44% (95% CI, 37-51)

	Vem in COMBI-v	D + Pbo in COMBI-d[1]
2-year OS	39% (95% CI, 34-45)	43% (95% CI, 36-50)
3-year OS	31% (95% CI, 26-36)	32% (95% CI, 25-38)

Patients at risk, n	0	6	12	18	24	30	36	42
COMBI-d: D + Pbo	212	175	138	104	84	69	57	7
COMBI-d: D + T	211	187	143	111	96	86	76	13
COMBI-v: D + T	352	311	245	201	171	150	127	33
COMBI-v: Vem	352	289	203	154	119	103	81	22

COPENHAGEN 2016 ESMO congress

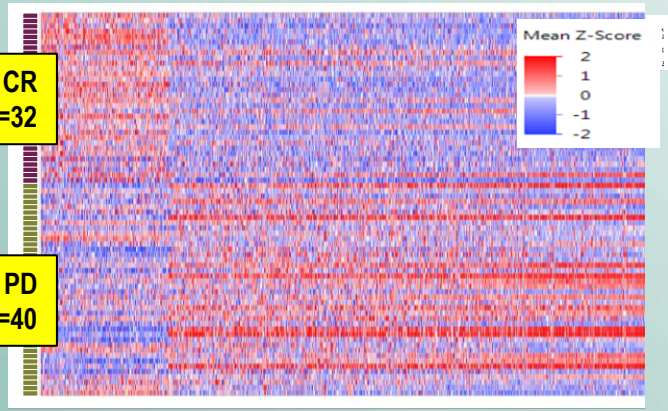
Genomic Features of Complete Responders versus Fast Progressors in Patients with *BRAF*^{V600}-Mutated Metastatic Melanoma Treated with Cobimetinib▼ Combined with Vemurafenib Or Vemurafenib Alone

Yibing Yan,[1] Caroline Robert,[2] James Larkin,[3] Paolo A. Ascierto,[4] Brigitte Dréno,[5] Michele Maio,[6] Claus Garbe,[7] Paul B. Chapman,[8] Jeffrey A. Sosman,[9] Matthew J. Wongchenko,[1] Jessie J. Hsu,[1] Ilsung Chang,[1] Ivor Caro,[1] Isabelle Rooney,[1] Grant A. McArthur,[10] Antoni Ribas[11]

[1]Genentech, Inc., South San Francisco, CA, USA; [2]Institut Gustave Roussy, Paris, France; [3]The Royal Marsden NHS Foundation Trust, London, UK; [4]Istituto Nazionale Tumori Fondazione Pascale, Naples, Italy; [5]Nantes University, Nantes, France; [6]University Hospital of Siena, Siena, Italy; [7]Universitätsklinikum Tübingen, Tübingen, Germany; [8]Memorial Sloan Kettering Cancer Center, New York, NY, USA;
[9]Vanderbilt University School of Medicine, Nashville, TN, USA; [10]Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia and University of Melbourne, Parkville, VIC, Australia; [11]Jonsson Comprehensive Cancer Center at the University of California, Los Angeles, Los Angeles, CA, USA

▼This medicinal product is subject to additional monitoring. This will allow for quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

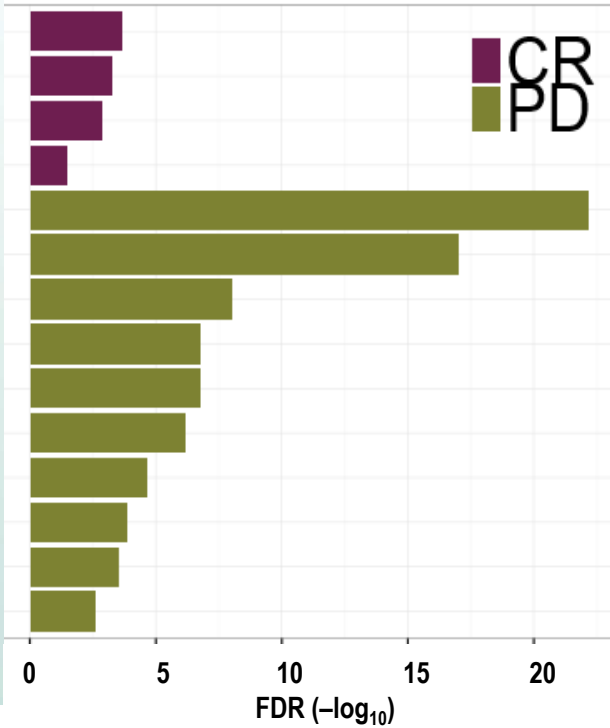
Differential Gene Expression by RNA-Seq Distinguishes Patients with CR vs PD



- The enriched gene expression was associated with:
  - Immune response processes in patients with CR
  - Keratinization in patients with PD

Adaptive immune response
Lymphocyte-mediated immunity
NK cell-mediated toxicity
Innate immune response

Keratinization
Peptide cross-linking
Xenobiotic glucuronidation
Neg. regulation of cellular glucuronidation
Negative regulation of GT activity
Flavonoid glucuronidation
Drug metabolic process
Flavonoid biosynthetic process
Neg. regulation of FA metabolic process
Flavone metabolic process



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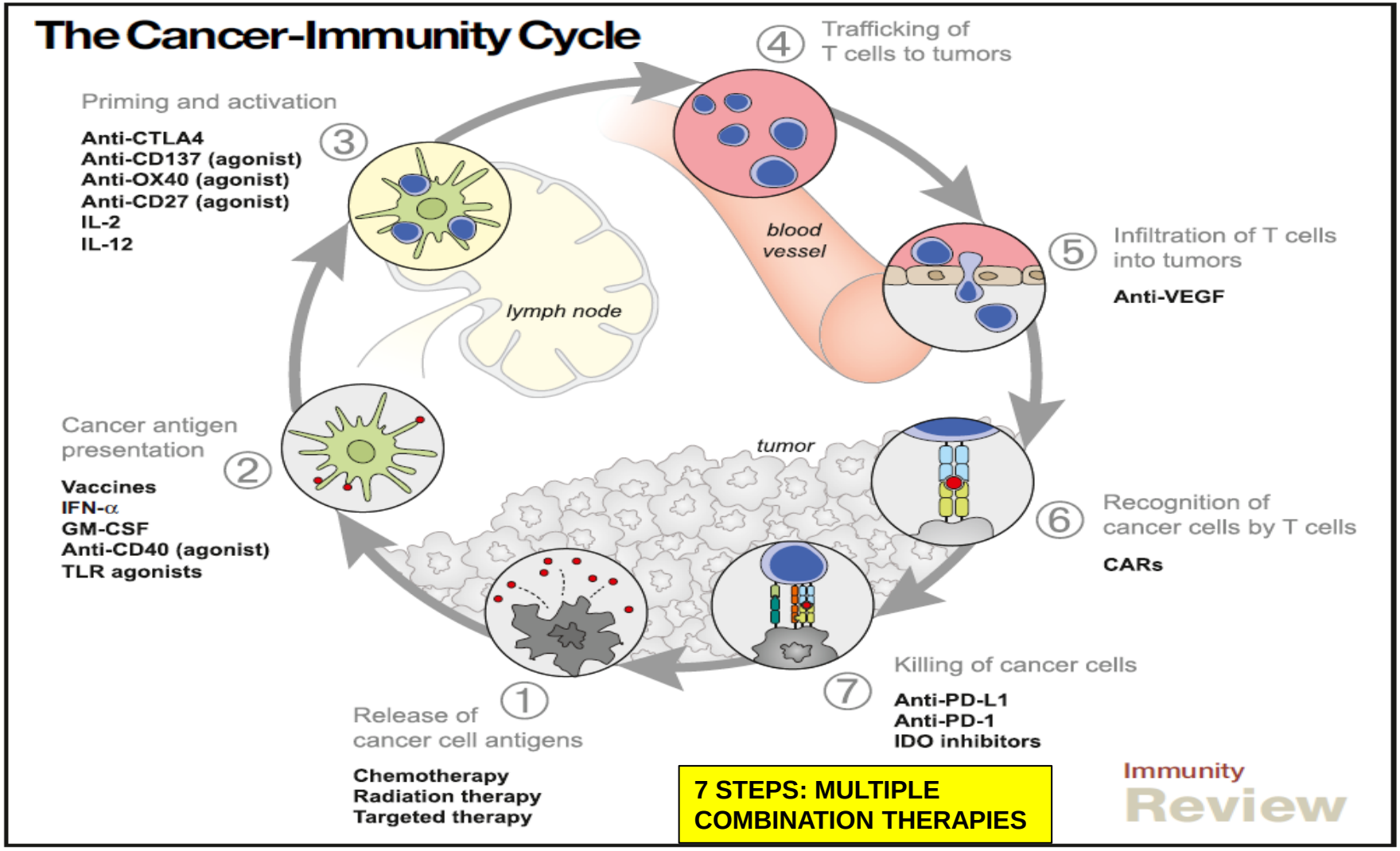
THE MELANOMA PARADIGM

MUTATION DRIVEN DRUG DEVELOPMENT

INNOVATIVE IMMUNOMODULATION


The Cancer-Immunity Cycle
4 Trafficking of T cells to tumors
Priming and activation
Anti-CTLA4
Anti-CD137 (agonist)
Anti-OX40 (agonist)
Anti-CD27 (agonist)
IL-2
IL-12
3
blood vessel
lymph node
5 Infiltration of T cells into tumors
Anti-VEGF
Cancer antigen presentation
2
Vaccines
IFN-α
GM-CSF
Anti-CD40 (agonist)
TLR agonists
tumor
6 Recognition of cancer cells by T cells
CARs
7 Killing of cancer cells
Anti-PD-L1
Anti-PD-1
IDO inhibitors
1 Release of cancer cell antigens
Chemotherapy
Radiation therapy
Targeted therapy
7 STEPS: MULTIPLE COMBINATION THERAPIES
Immunity
Review

IMMUNE SYSTEM BLOCKED AT MULTIPLE LEVELS

- 1) **CTL PROGRAMMING**
  - e.g. CTLA4 ……. **Unblock with anti-CTLA4**
- 2) **CTL execution function**
  - e.g. PD-1 / PDL-1…… **Unblock with anti-PD1/PDL1**
- 3) **CTL tumor infiltration**
  - e.g. M2 (macrophages) **Unblock: M2-M1 repolarization agents**
- 4) **Immune escape mechanims**
  - e.g.:
    - JAK1/2 mutations and loss Gamma-IFN pathways
    - B2M mutations
    - B-actenin pathway activation : immune exclusion

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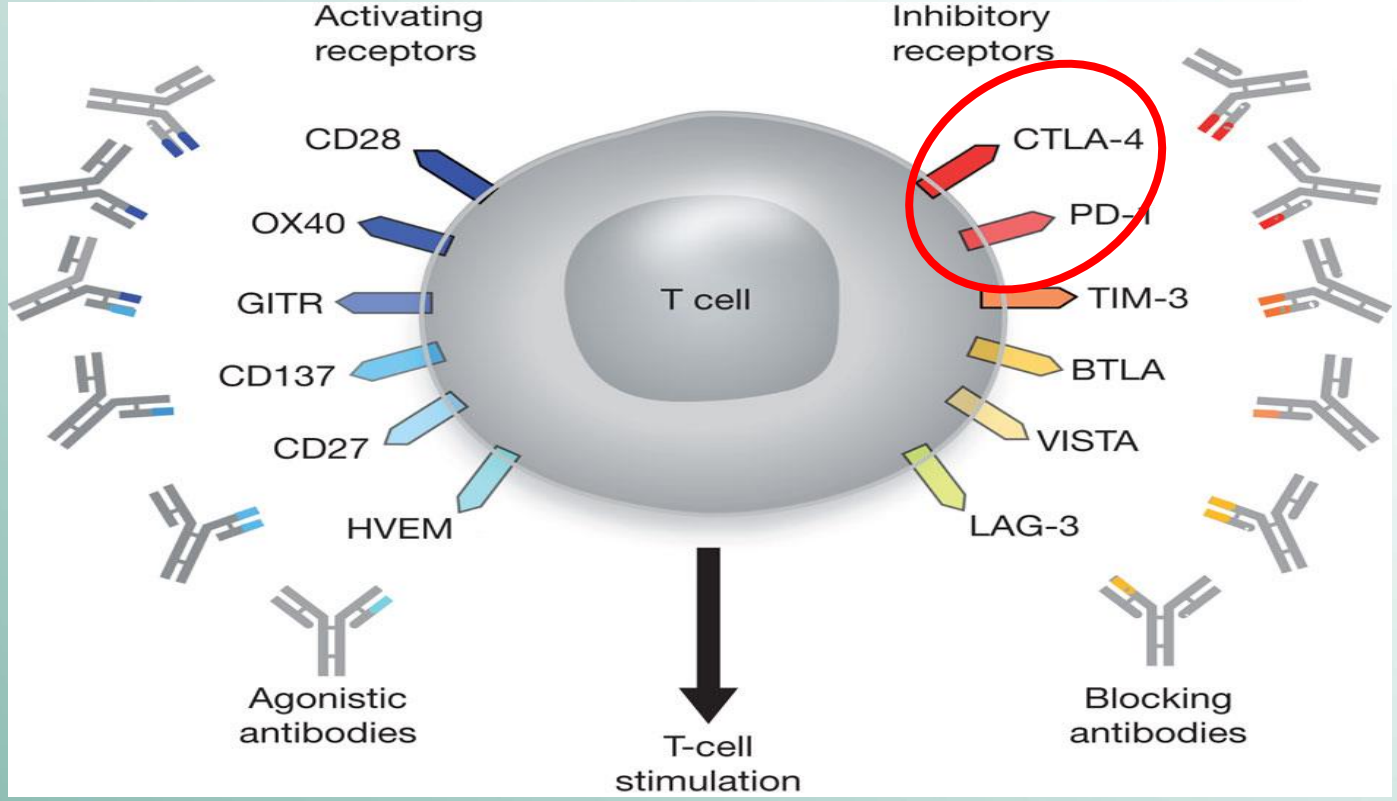
REVOLUTION IN IMMUNOTHERAPY

BREAKING TOLERANCE
Unblock a blocked Immune Response

INHIBIT THE INHIBITOR
vs
ACTIVATE THE ACTIVATOR

2 KEY Regulators



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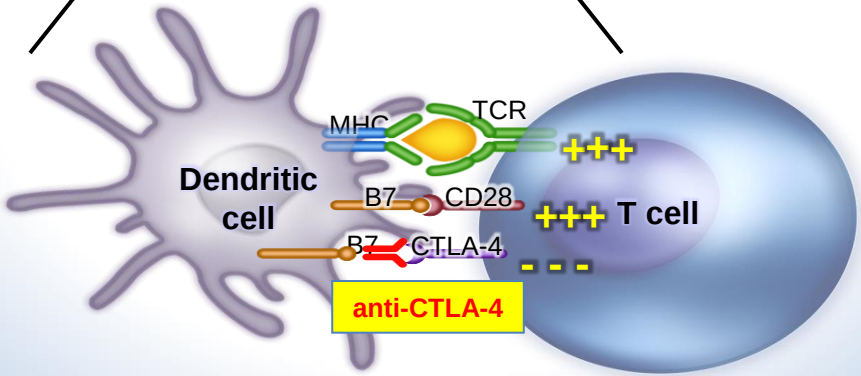
AVOID: CTLA4-B7

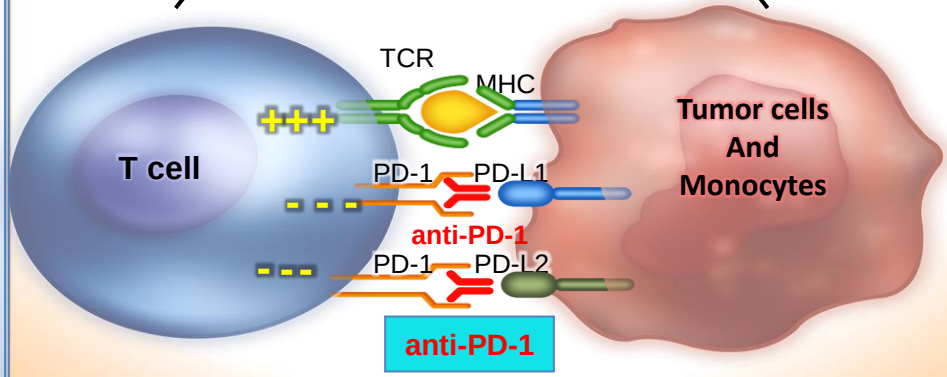
AVOID: PD1-PDL1

PRIMING CTL
Mostly CENTRAL in LNN

EXECUTING CTL
Mostly PERIPHERAL
Tumor Microenvironment

Activation
(cytokines, lysis, proliferation, migration to tumor)





CTLA-4 Blockade (ipilimumab tremelimumab)

PD-1 Blockade (nivolumab, pembrolizumab)

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ANTI-CTLA4
Ipilimumab
Tremelimumab

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma

Dirk Schadendorf, F. Stephen Hodi, Caroline Robert, Jeffrey S. Weber, Kim Margolin, Omid Hamid, Debra Patt, Tai-Tsang Chen, David M. Berman, and Jedd D. Wolchok

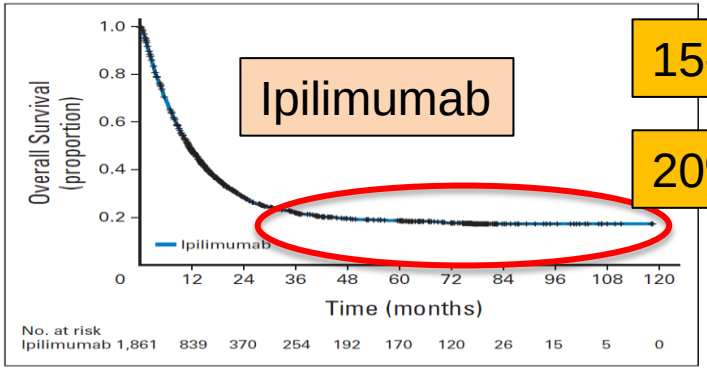
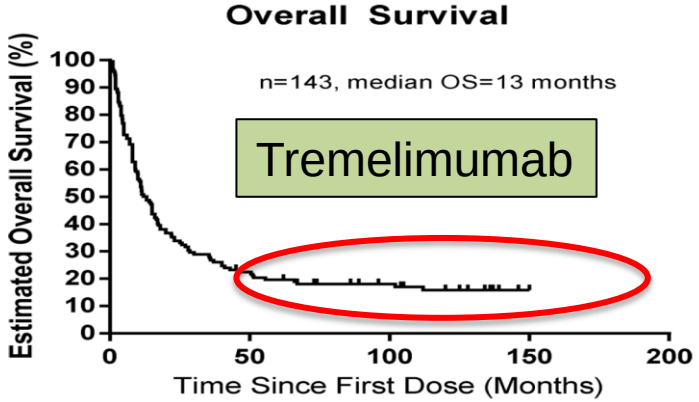


Fig 1. Primary analysis of pooled overall survival (OS) data. Individual patient data were pooled from 10 prospective trials and two retrospective, observational



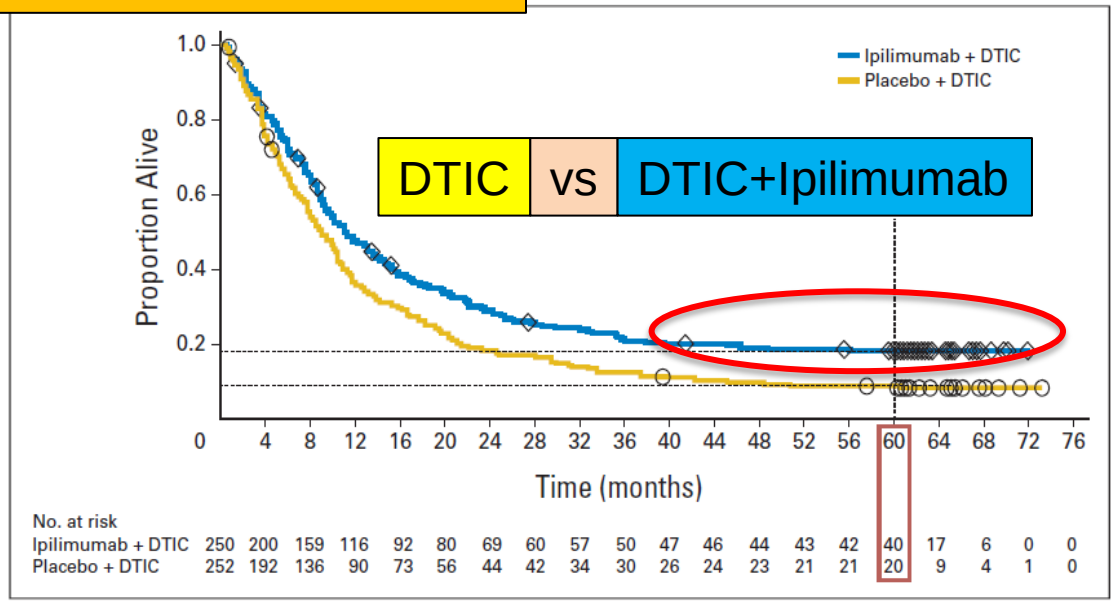
15-20% ORR

20% LONGTERM SURVIVAL

VOLUME 33 · NUMBER 10 · APRIL 1 2015
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Five-Year Survival Rates for Treatment-Naive Patients With Advanced Melanoma Who Received Ipilimumab Plus Dacarbazine in a Phase III Trial

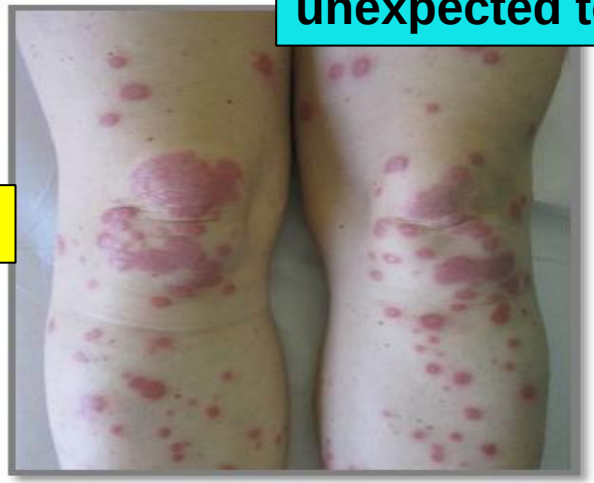
Michele Maio, Jean-Jacques Grob, Steinar Aamdal, Igor Bondarenko, Caroline Robert, Luc Thomas, Claus Garbe, Vanna Chiarion-Sileni, Alessandro Testori, Tai-Tsang Chen, Marina Tschaika, and Jedd D. Wolchok



New Types of Toxicities in Oncology

unexpected toxicities in combinations !!

DERMATITIS



PNEUMONITIS

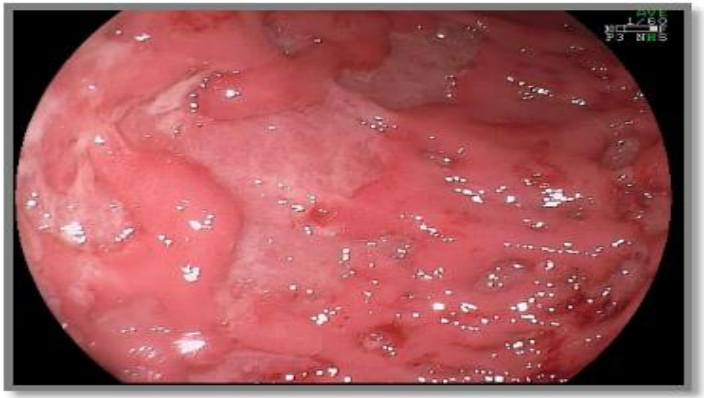
MYOCARDITIS

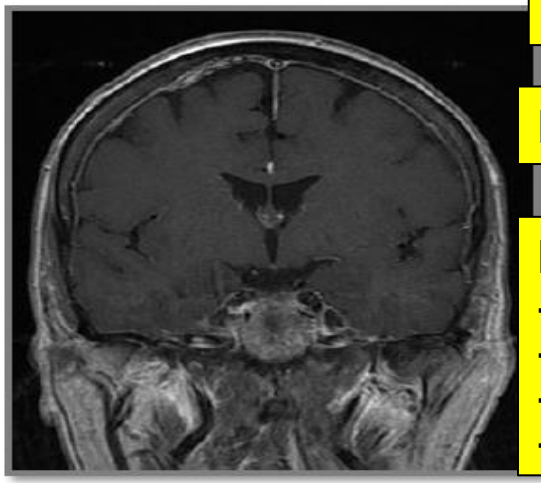
HEPATITIS

Pancreatitis

Nephritis

COLITIS

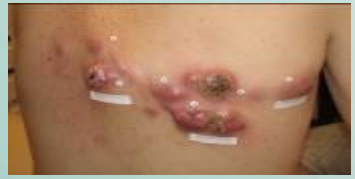
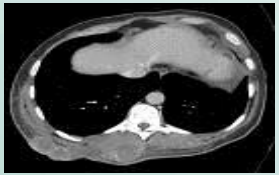




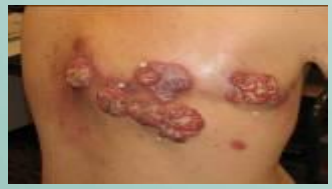
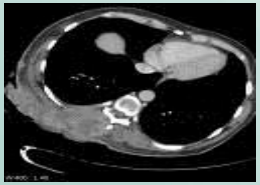
NEURITIS

ENDOCRINE
- thyroiditis
- hypophysitis
- adrenalitis
- diabetes

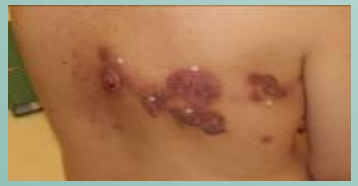
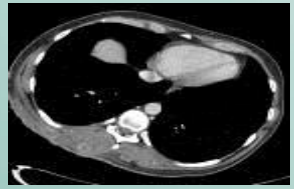
NEW TYPES OF RESPONSES: “pseudoprogression”

Screening

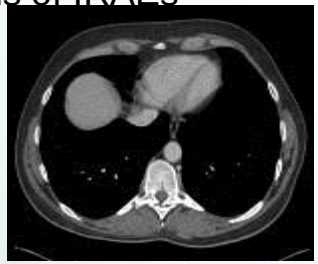



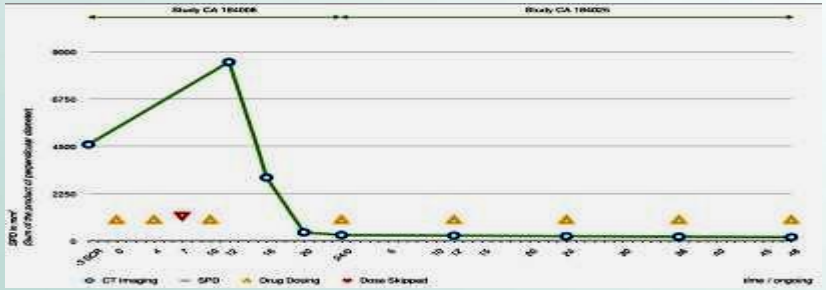
Week 12
Initial increase in total tumour burden (mWHO PD)

Week 16
Responding

Week 96
Durable & ongoing response without signs of IRAEs



Courtesy of K. Harmankaya, Vienna

Harmankaya et al. Presented at EADO 2009, Vienna, Austria

Combos with ipilimumab

But all have been replaced by Anti-PD(L)1

• Fotemustine	Some effect on brain mets?
• Carbotaxol	RR 27%
• IL2	(NCI) higher CR rate (17%)
• IFN-alpha	RR 32% but tox
• Bevacizumab	Improved DCR (67%)?
• Laherparvec (T-vec)	Marginal improvement RR
• Vemurafenib	Stopped for toxicity
• Dabrafenib + Trametenib	Stopped for toxicity

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AVOID: PD1-PDL1

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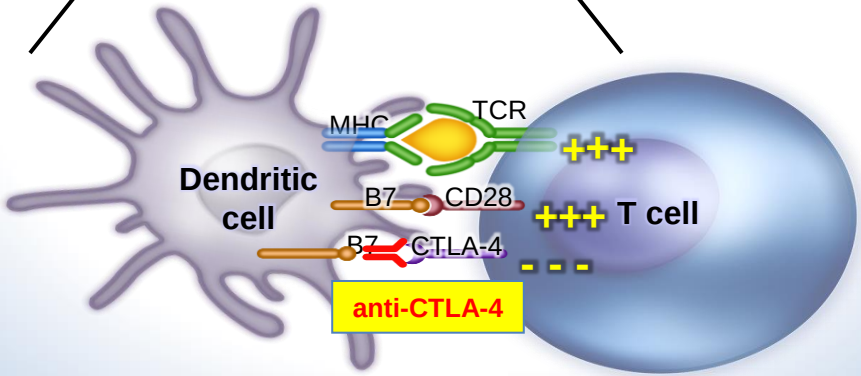

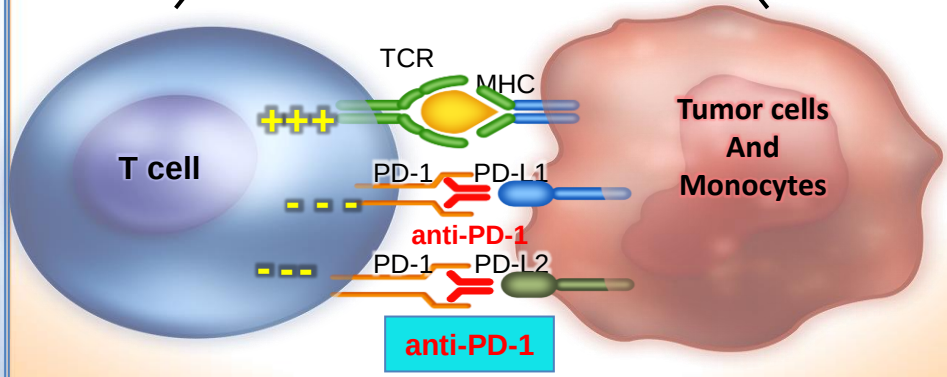

CTLA-4 Blockade (ipilimumab tremelimumab)

PD-1 Blockade (nivolumab, pembrolizumab)

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Anti-PD1
Nivolumab
Pembrolizumab
Data

Pembrolizumab Monotherapy in Advanced Melanoma

JAMA 2016;315:1600-1609

Research

Original Investigation

Association of Pembrolizumab With Tumor Response and Survival Among Patients With Advanced Melanoma

Antoni Ribas, MD, PhD; Omid Hamid, MD; Adil Daud, MD; F. Stephen Hodi, MD; Jedd D. Wolchok, MD, PhD; Richard Kefford, MD, PhD; Anthony M. Joshua, MBBS, PhD; Amita Patnaik, MD; Wen-Jen Hwu, MD, PhD; Jeffrey S. Weber, MD, PhD; Tara C. Gangadhar, MD; Peter Hersey, MD, PhD; Roxana Dronca, MD; Richard W. Joseph, MD; Hassane Zarour, MD; Bartosz Chmielowski, MD, PhD; Donald P. Lawrence, MD; Alain Algazi, MD; Naiyer A. Rizvi, MD; Brianna Hoffner, BA, RN, MSN; Christine Mateus, MD; Kevin Gergich, MA; Jill A. Lindia, MS; Maxine Giannotti, BS; Xiaoyun Nicole Li, PhD; Scot Ebbinghaus, MD; S. Peter Kang, MD; Caroline Robert, MD, PhD

40-50% ORR

Figure 4. Maximum Percentage of Change From Baseline in Sum of the Longest Diameter of Each Target Lesion in the Full Analysis Set

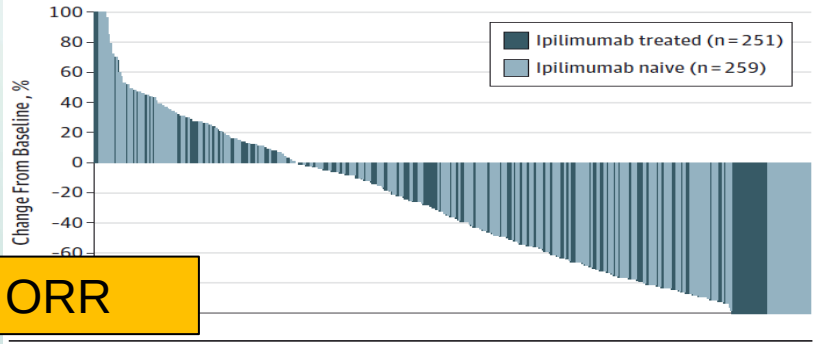
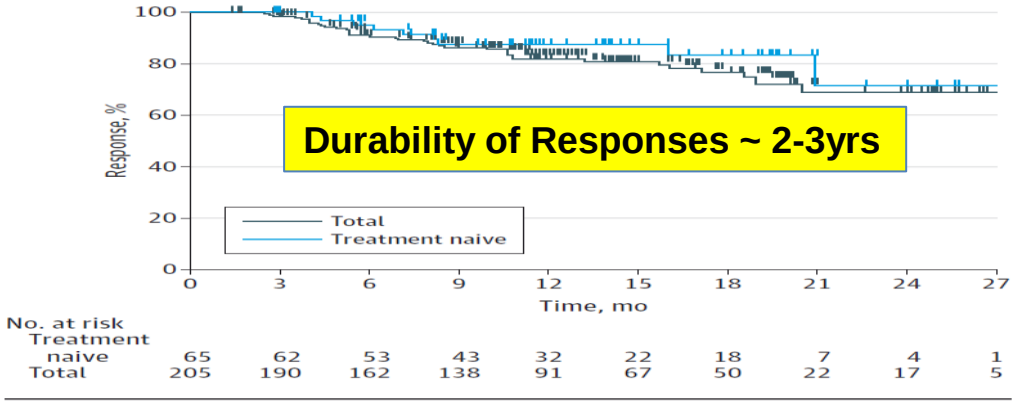
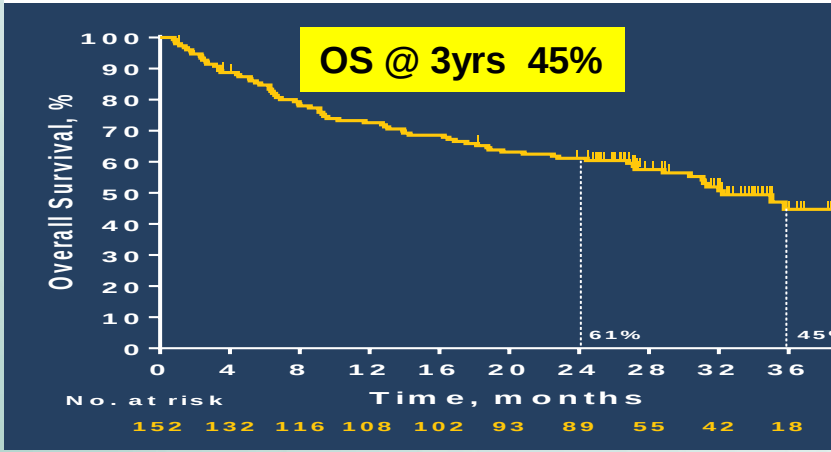


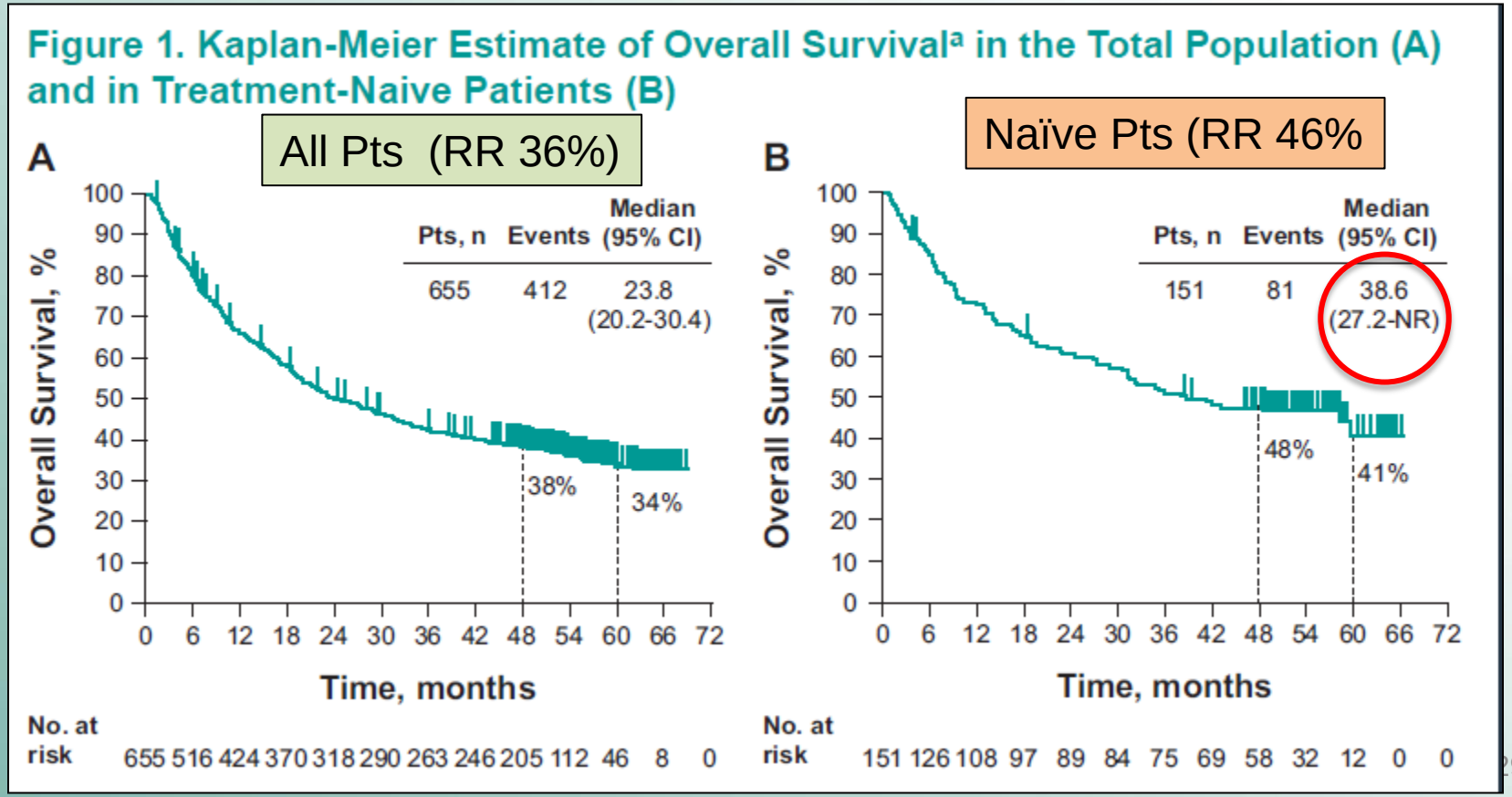
Figure 3. Duration of Response to Pembrolizumab Among Responders



Durability of Responses ~ 2-3yrs



Phase I Keynote-001 : 5 year survival Pembrolizumab in advanced melanoma (Hamid, ASCO 2018)



BRAFi monotherapy
Anti-PD1 Monotherapy

VEMURAFENIB
DACARBAZINE

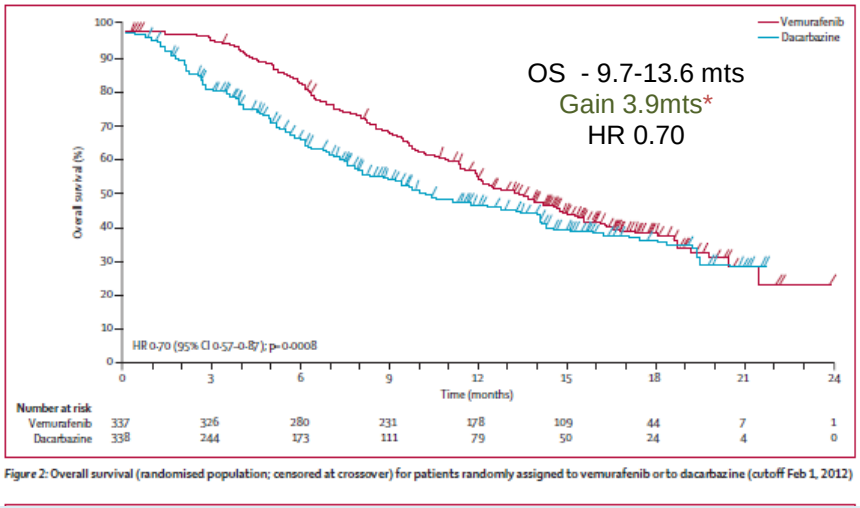
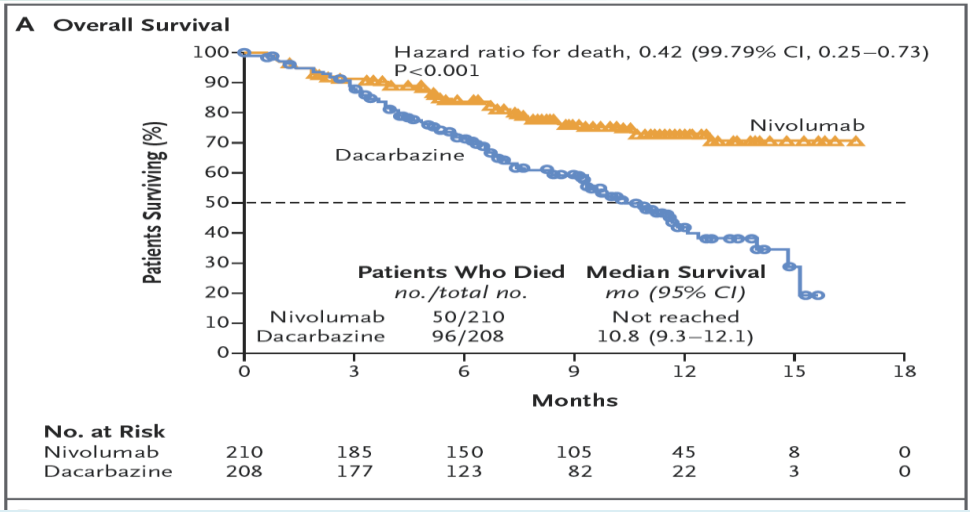


Figure 2: Overall survival (randomised population; censored at crossover) for patients randomly assigned to vemurafenib or to dacarbazine (cutoff Feb 1, 2012)

NIVOLUMAB
DACARBAZINE

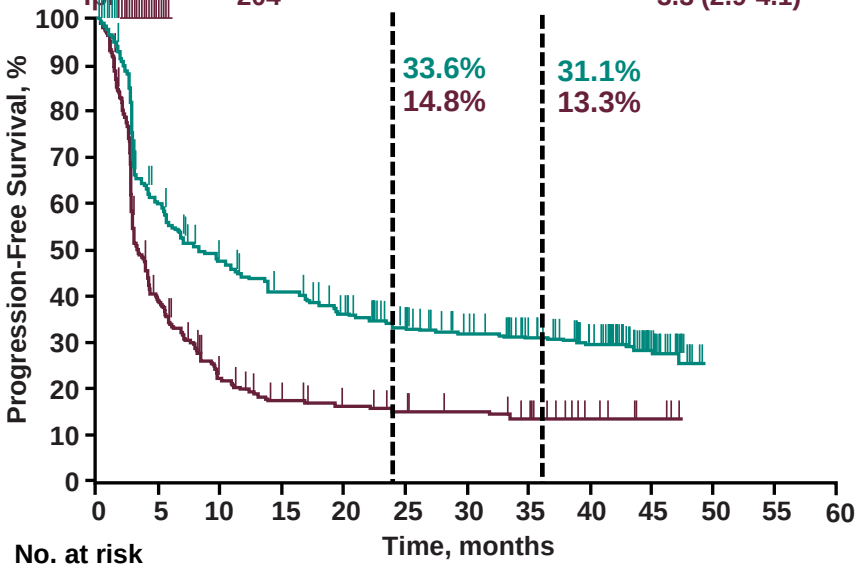


Progression-Free Survival[a] PEMBRO vs IPI

Median Follow-Up 45.9 (0.3-50.0) Months ASCO 2018

All Patients

	Events, n	HR[b] (95% CI)	Median,[c] mo (95% CI)
Pembro	378	0.56 (0.47-0.67)	8.3 (6.5-11.2)
Ipi	204	-	3.3 (2.9-4.1)

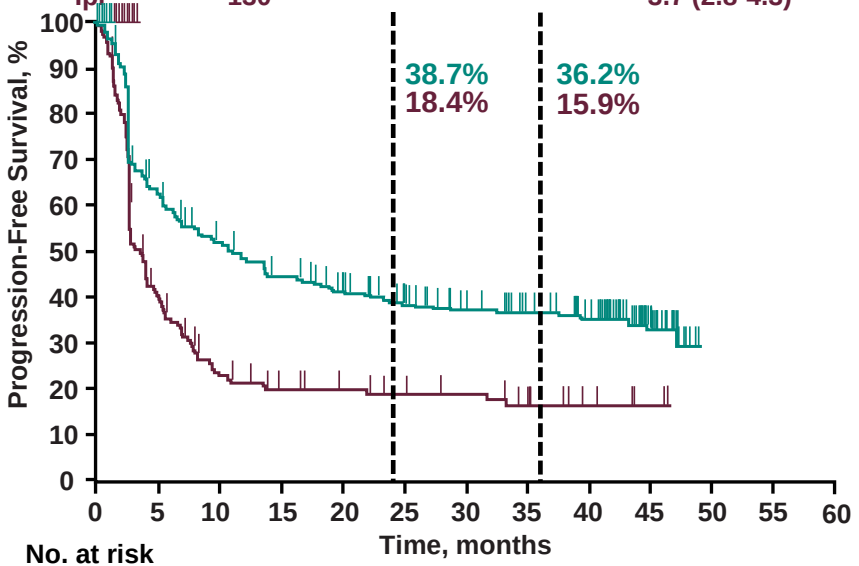


No. at risk

556	324	251	213	183	148	132	115	95	35	0	0	0
278	93	47	32	27	22	20	15	7	3	0	0	0

Treatment-Naive Patients

	Events, n	HR[b] (95% CI)	Median,[c] mo (95% CI)
Pembro	230	0.54 (0.43-0.67)	11.2 (7.1-13.9)
Ipi	130	-	3.7 (2.8-4.3)



No. at risk

368	222	178	150	133	112	98	88	76	28	0	0	0
181	64	32	23	20	17	15	10	5	2	0	0	0

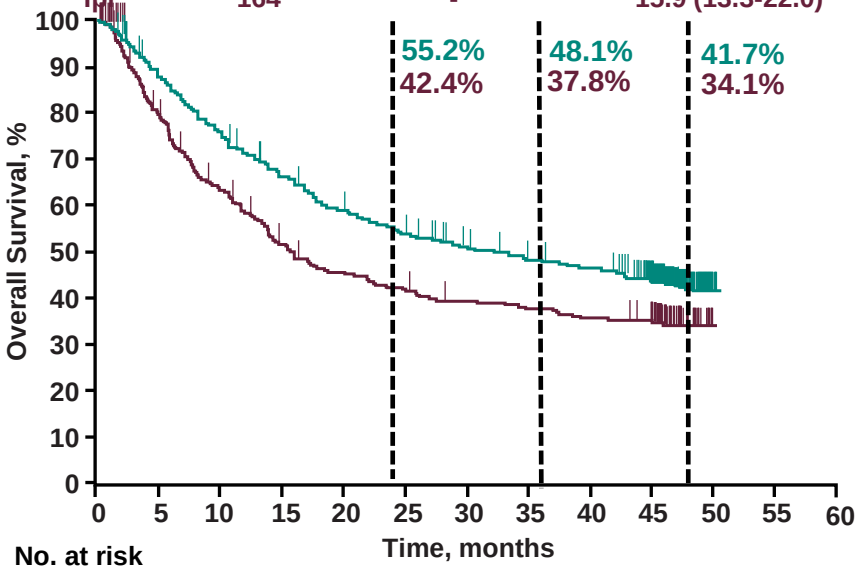
[a]Per immune-related response criteria by investigator review. [b]Based on Cox regression model with treatment as covariate stratified by line of therapy (1st vs 2nd), PD-L1 status (positive vs negative), and ECOG (0 vs 1); if no patients are in one of the treatment groups involved in a comparison for 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.

Overall Survival : Pembrolizumab vs Ipilimumab

Median Follow-Up 45.9 (0.3-50.0) Months ASCO 2018

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)

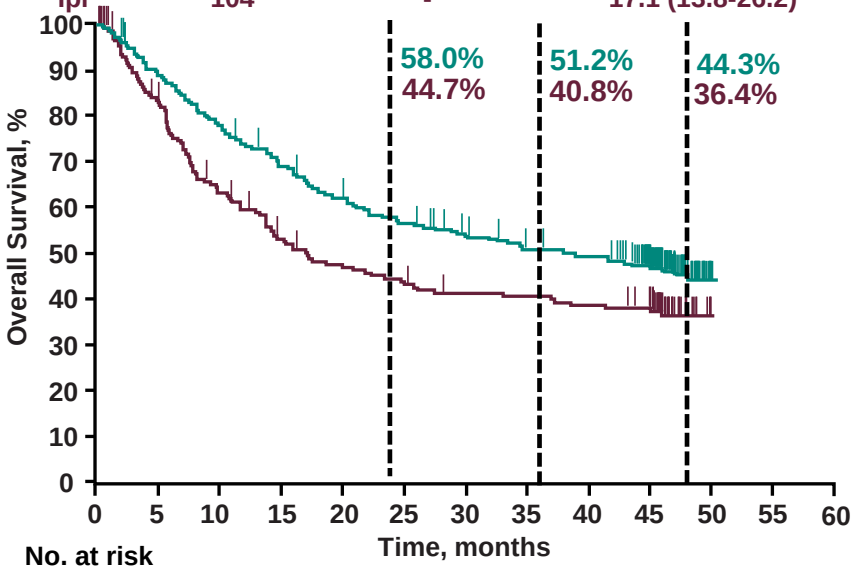


No. at risk

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.

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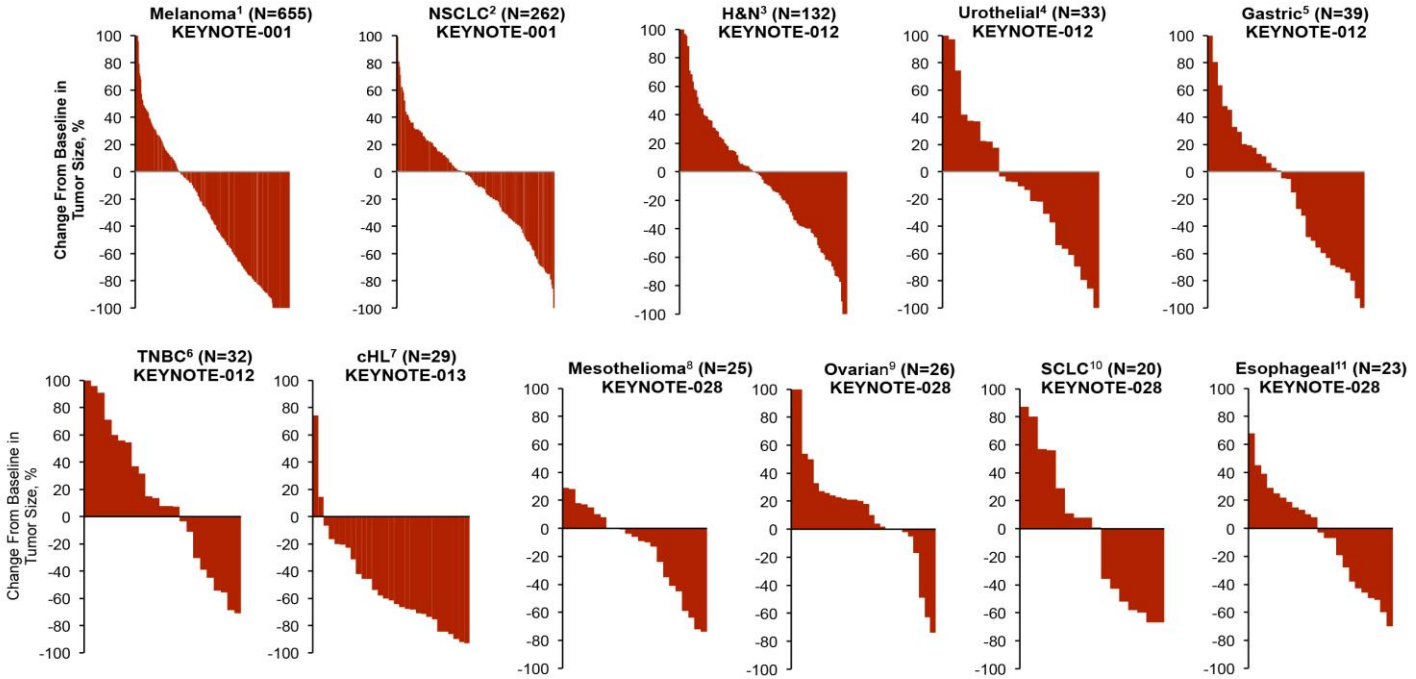
GRAND PARIS

Transversal Antitumor Effects

Anti-PD1
Nivolumab
Pembrolizumab

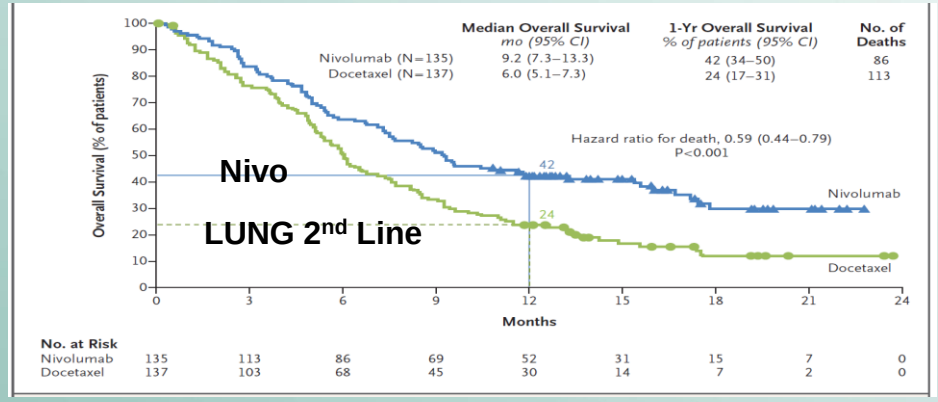
Anti-PDL1
Atezolizumab
Avelumab
Durvalumab

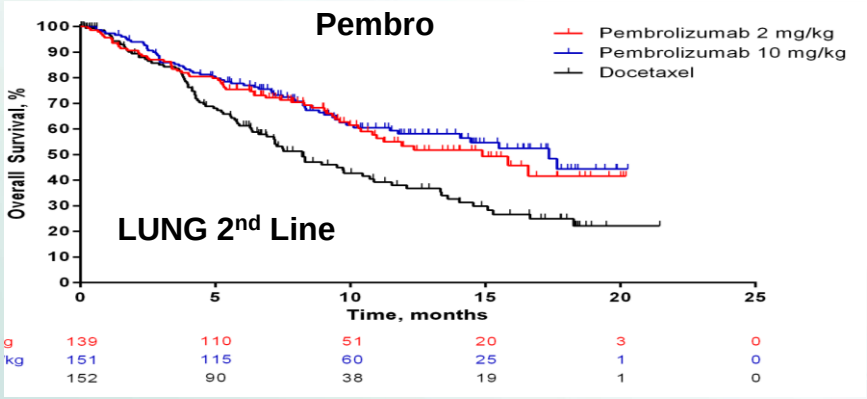
Pembrolizumab demonstrates broad antitumor activity

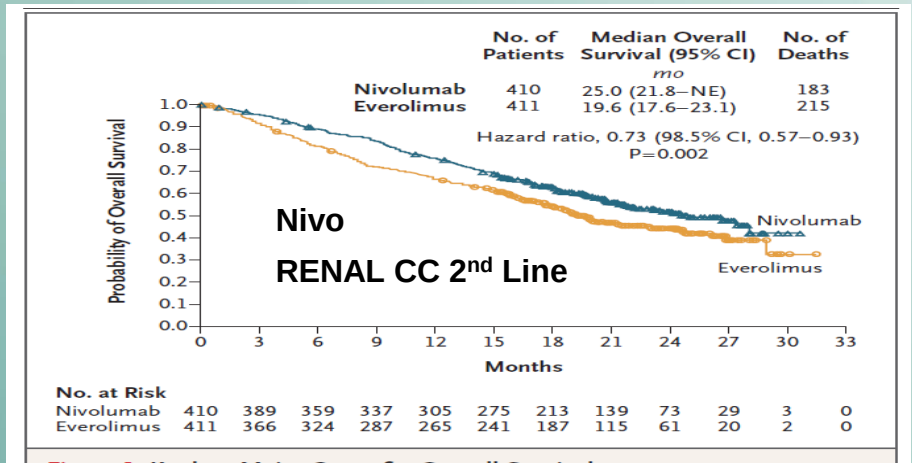


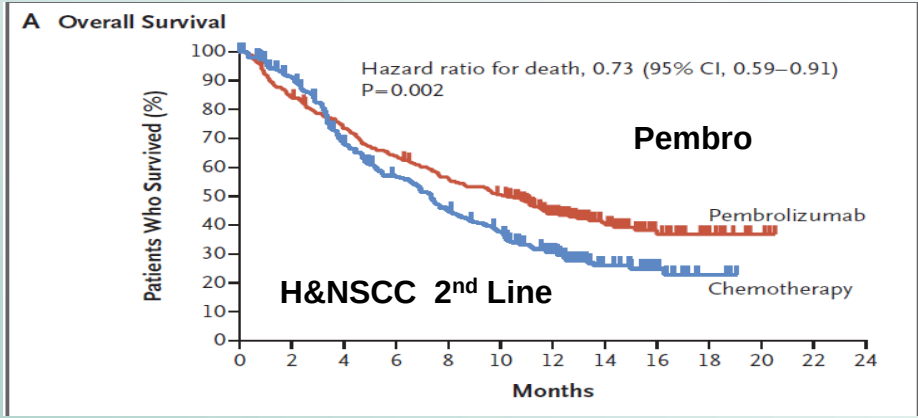
1. Daud A et al. ASCO 2015; 2. Garon EB et al. ESMO 2014; 3. Seiwert T et al. ASCO 2015; 4. Plimack E et al. ASCO 2015; 5. Bang YJ et al. ASCO 2015; 6. Nanda R et al. SABCS 2014; 7. Moskowitz C et al. ASH Annual Meeting 2014; 8. Alley EA et al. AACR 2015; 9. Varga A et al. ASCO 2015; 10. Ott PA et al. ASCO 2015; 11. Doi T et al. ASCO 2015.

LUNG, H&N, RENAL, BLADDER, GASTRIC, ESOPHAGEAL, HCC, MERKEL, SCC, ETC

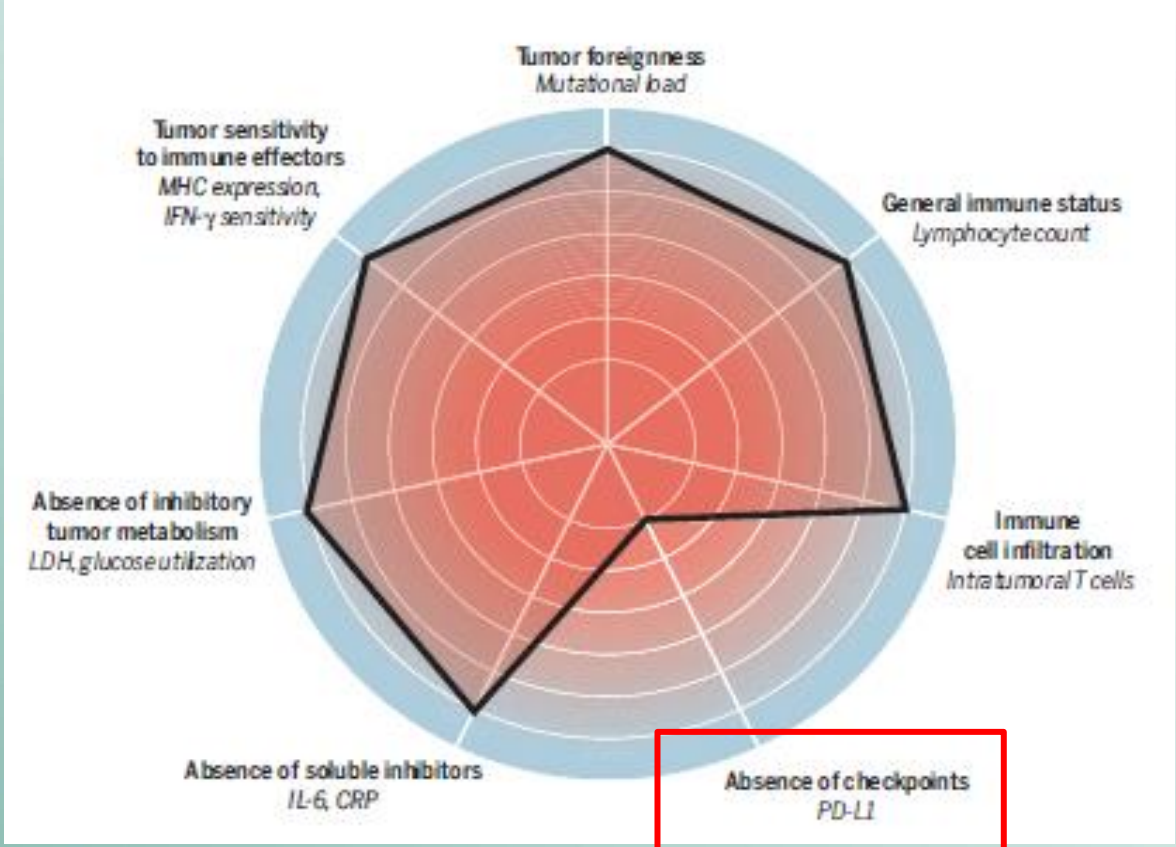






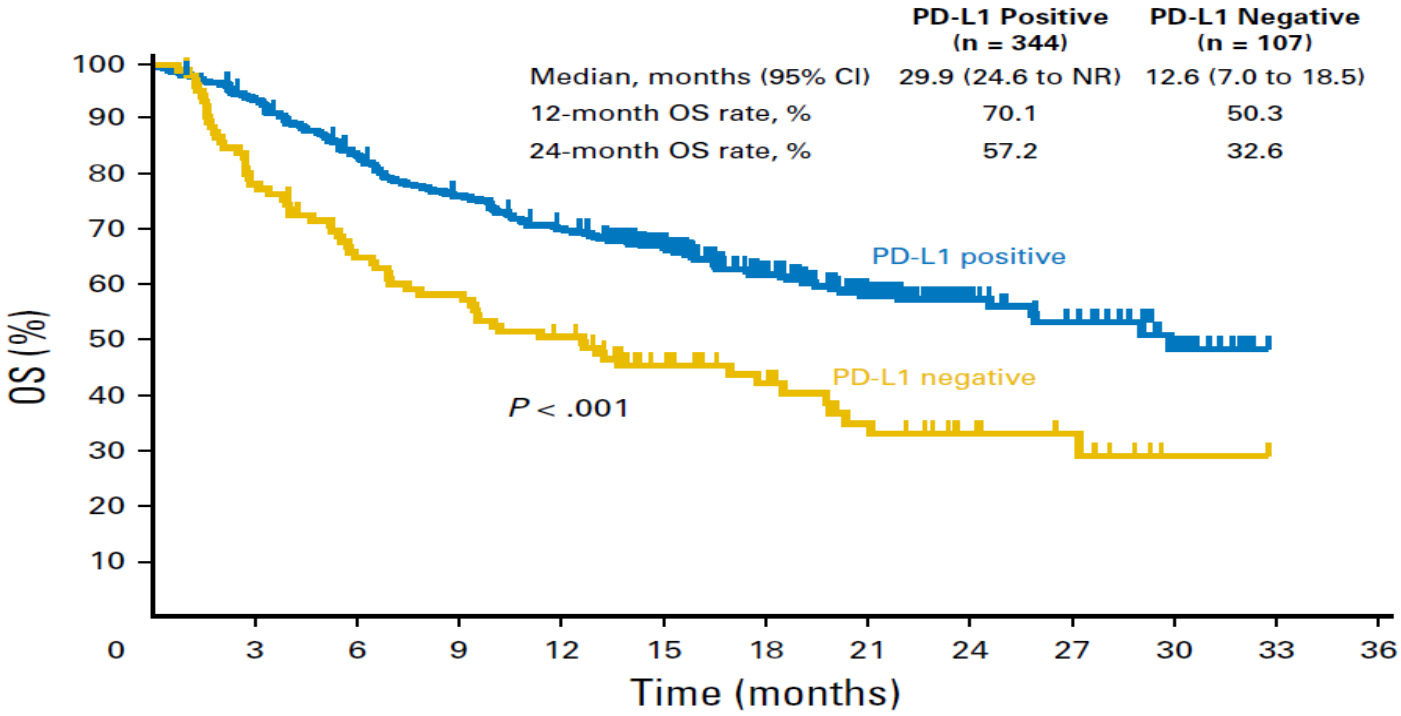


The “cancer immunogram”



Blank C et al Science 2016

PD-L1 expression and OS in advanced Melanoma



Prognostic Factors at Baseline

Good prognostic factors

LOW

- Low LDH, ECOG 0-1, Age, # Metastatic Sites,
- Low NLR: neutrophil/lymphocyte ratio
- Low CD4/CD8 ratio
- Low Tregs. Low MDSC in blood
- Low CRP

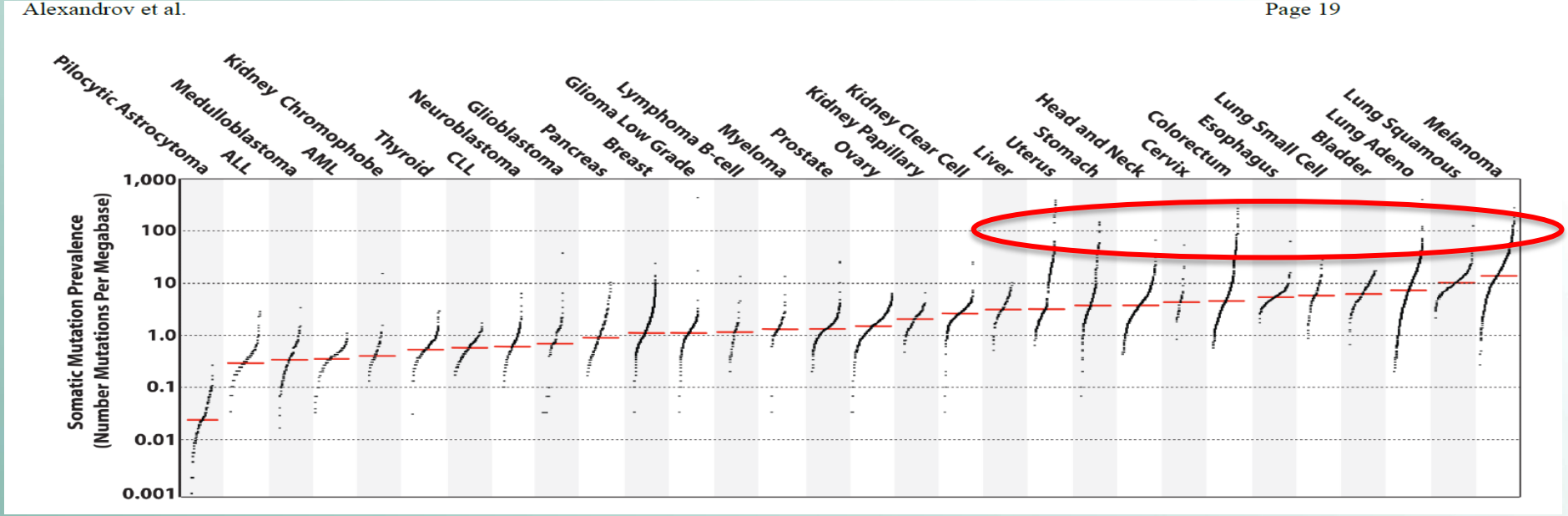
HIGH

- High ALC
- High eosinophiles

Likelihood of response to ICB

- **TILs** Tumor Infiltrating Lymphocytes
- **MTB** MutationalTumor Burden
- **NTB** Neoantigen Tumor Burden
- **TCR** T Cell Receptor:
  - clonal diversity and amplitude
- **MSI** Microsatellite Satellite Instability
- **IFNγ** Interferon- γ signature

Mutational Load - Sensitivity to anti-CTLA4/PD1



MSI tumors (CRC and others): > 60% response rate (ASCO 2015/16)

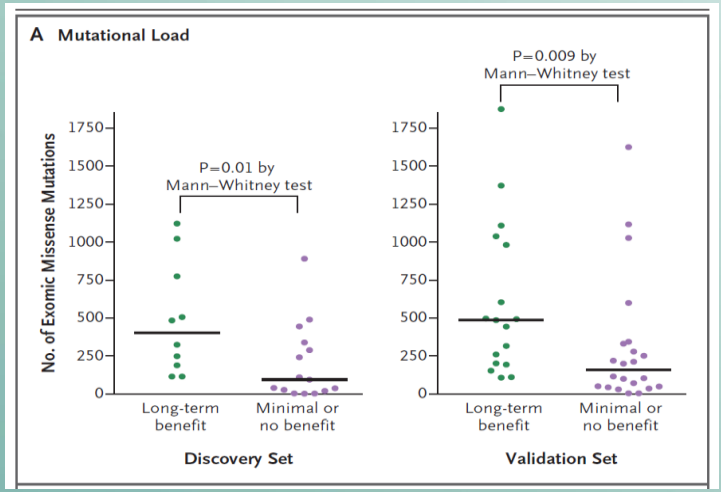
CRC MSI: RR 62% ; CRC RR 0%; Others MSI RR > 60% !!

Tumor neoantigens and response to Ab CTLA-4

ORIGINAL ARTICLE

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

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



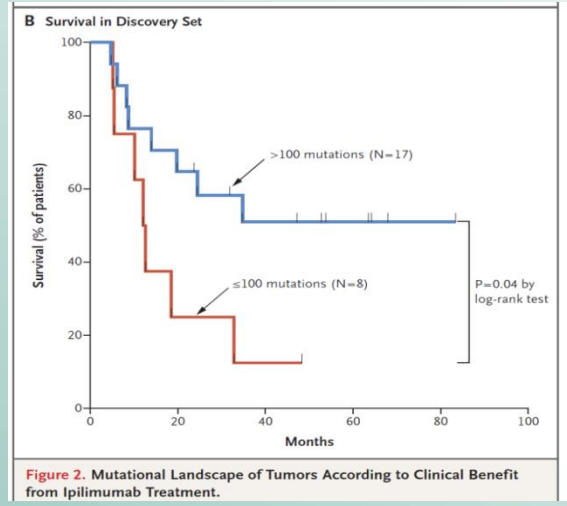
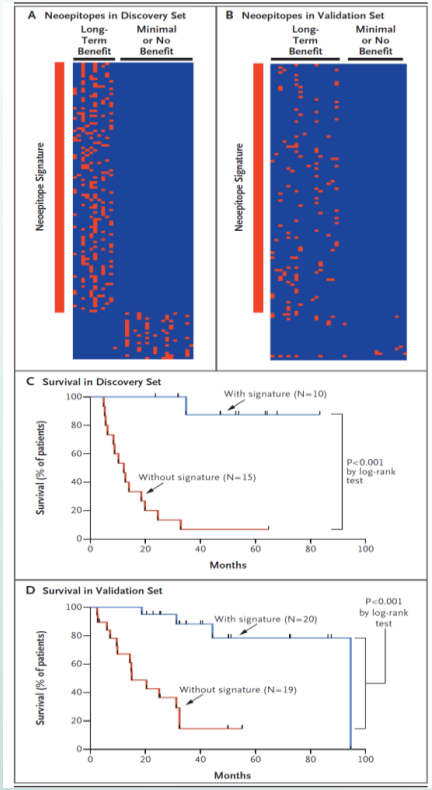


Figure 2. Mutational Landscape of Tumors According to Clinical Benefit from Ipilimumab Treatment.



Mutational landscape determines sensitivity to PD-1 blockade in non –small cell lung cancer

Naiyer A. Rizvi, Matthew D. Hellmann, Alexandra Snyder, Pia Kvistborg, Vladimir Makarov, Jonathan J. Havel, William Lee, Jianda Yuan, Phillip Wong, Teresa S. Ho, Martin L. Miller, Natasha Rekhtman, Andre L. Moreira, Fawzia Ibrahim, Cameron Bruggeman, Billel Gasmi, Roberta Zappasodi, Yuka Maeda, Chris Sander, Edward B. Garon, Taha Merghoub, Jedd D. Wolchok, Ton N. Schumacher and Timothy A. Chan (March 12, 2015)
Science **348** (6230), 124-128. [doi: 10.1126/science.aaa1348]
originally published online March 12, 2015

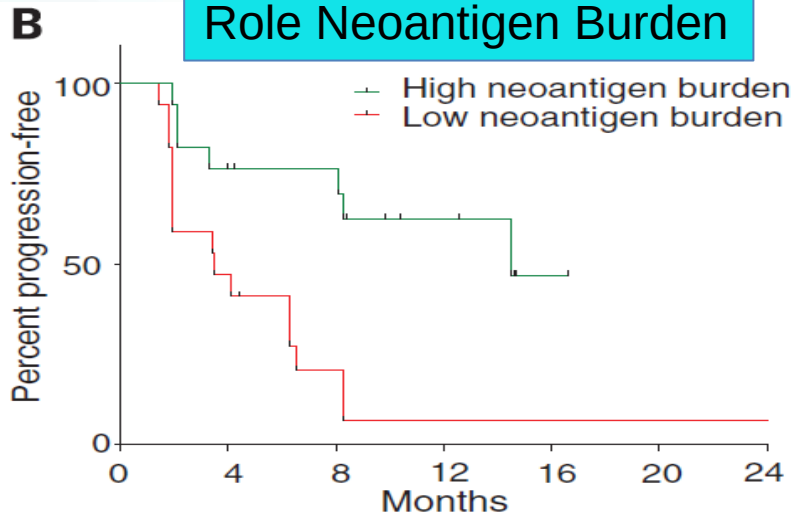
Editor's Summary

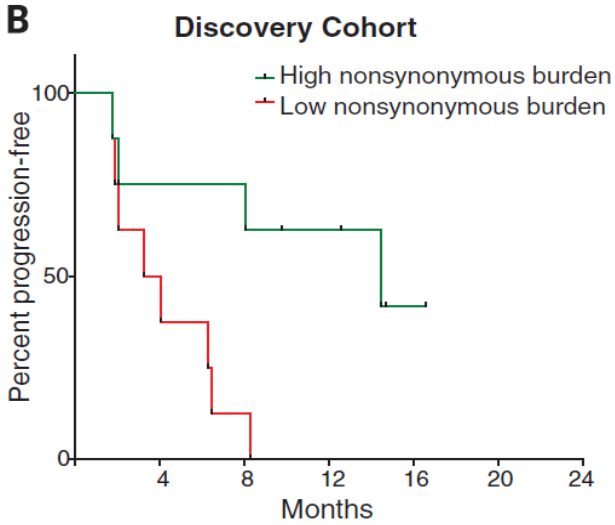
More mutations predict better efficacy

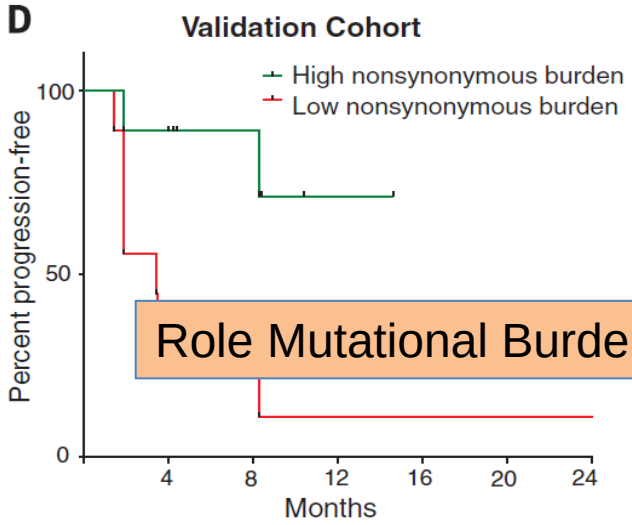
Despite the remarkable success of cancer immunotherapies, many patients do not respond to treatment. Rizvi *et al.* studied the tumors of patients with non–small-cell lung cancer undergoing immunotherapy. In two independent cohorts, treatment efficacy was associated with a higher number of mutations in the tumors. In one patient, a tumor-specific T cell response paralleled tumor regression.

Science, this issue p. 124

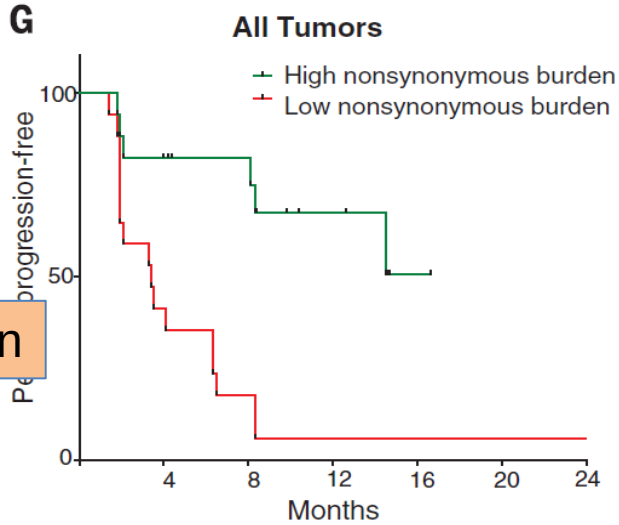
Role Neoantigen Burden





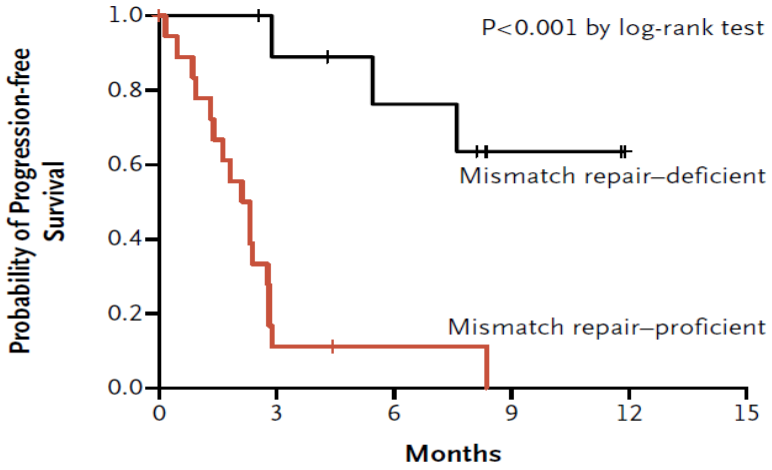


Role Mutational Burden



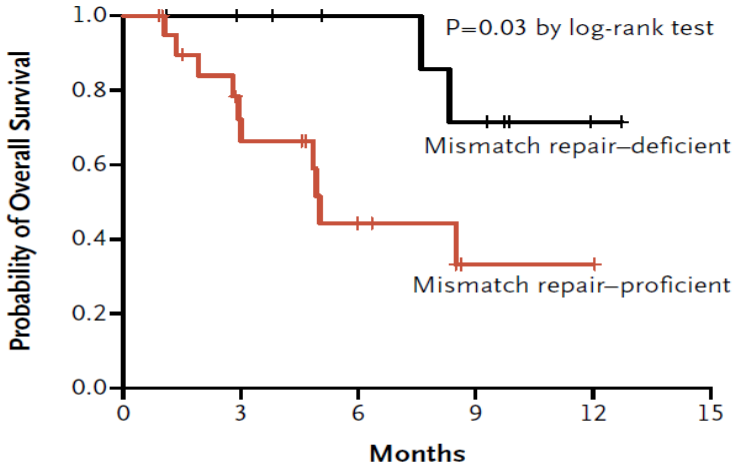
Pembrolizumab in Mismatched Repair Deficient Tumors

A Progression-free Survival in Cohorts with Colorectal Cancer



No. at Risk						
Mismatch repair–deficient	11	8	6	2	0	0
Mismatch repair–proficient	21	2	1	0	0	0

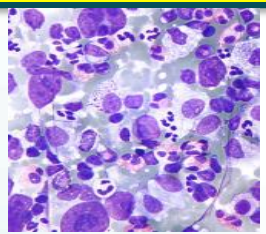
B Overall Survival in Cohorts with Colorectal Cancer



No. at Risk						
Mismatch repair–deficient	11	9	7	5	1	0
Mismatch repair–proficient	21	12	5	1	1	0

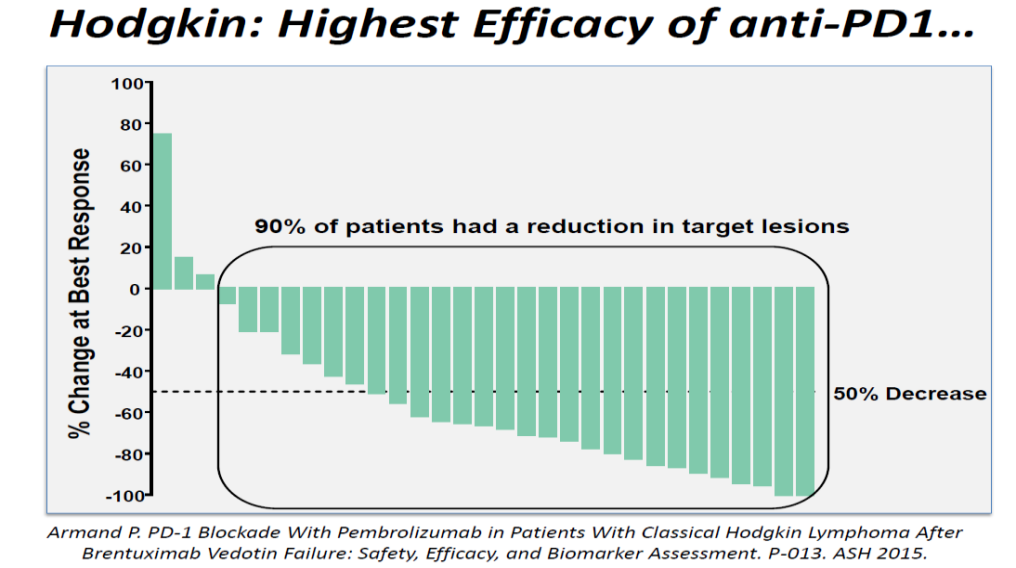
Pembrolizumab in Hodgkin Lymphoma

Hodgkin's lymphoma may represent a uniquely vulnerable target for PD-1 blockade.
Specifically, amplification of 9p24.1 is frequent in the disease and results in the overexpression of PD-L1 and PD-L2.



ORR	**86%**
CR	**21%**
PR	**45 %**
SD	**21%**

DURABILITY



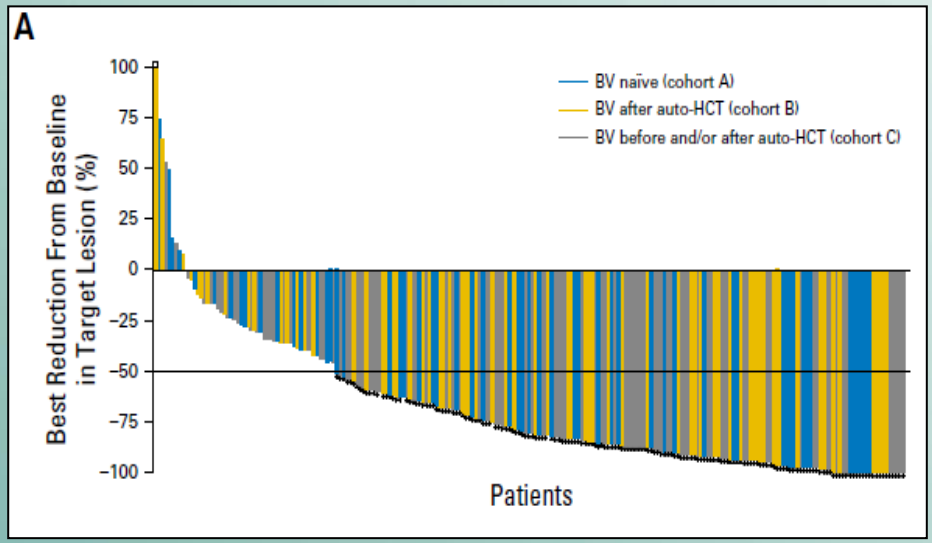
VOLUME 36 · NUMBER 14 · MAY 10, 2018

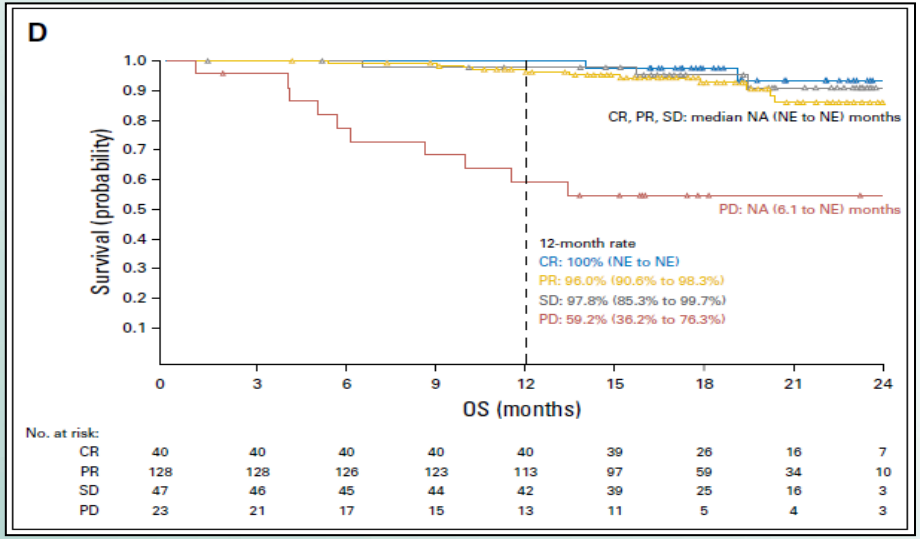
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Nivolumab for Relapsed/Refractory Classic Hodgkin Lymphoma After Failure of Autologous Hematopoietic Cell Transplantation: Extended Follow-Up of the Multicohort Single-Arm Phase II CheckMate 205 Trial

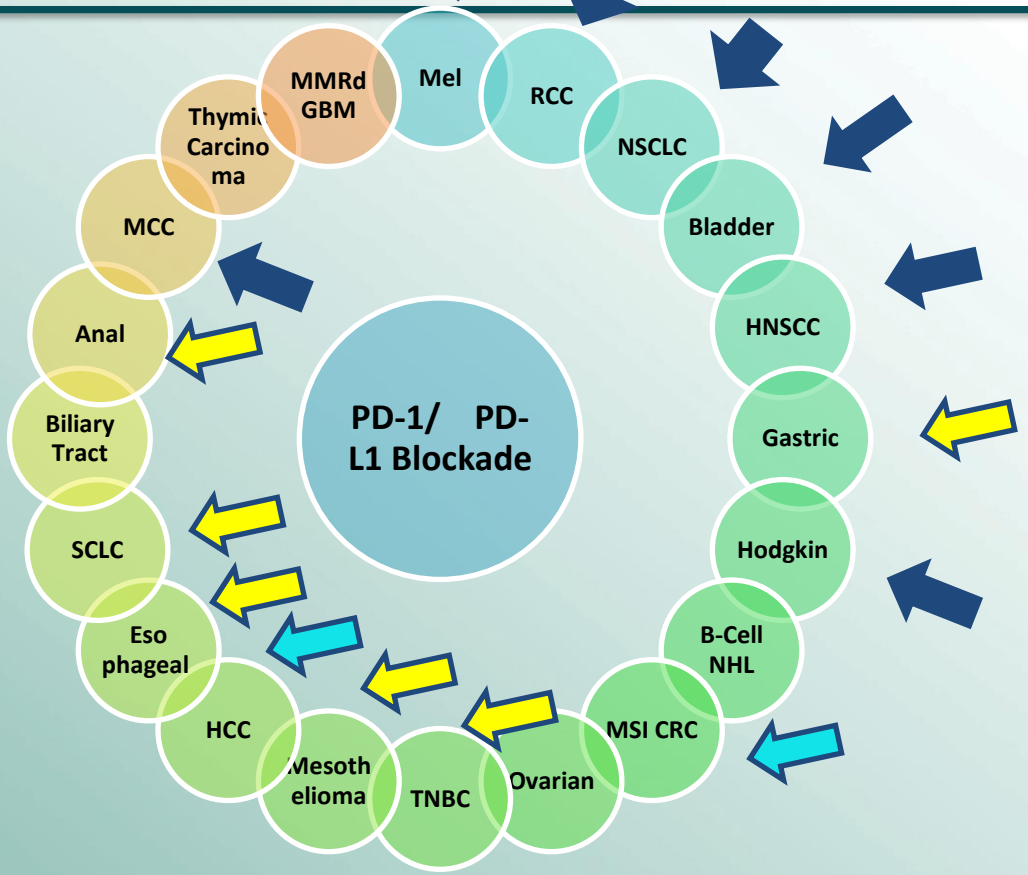
Philippe Armand, Andreas Engert, Anas Younes, Michelle Fanale, Armando Santoro, Pier Luigi Zinzani, John M. Timmerman, Graham P. Collins, Radhakrishnan Ramchandren, Jonathon B. Cohen, Jan Paul De Boer, John Kuruvilla, Kerry J. Savage, Marek Trneny, Margaret A. Shipp, Kazunobu Kato, Anne Sumbul, Benedetto Farsaci, and Stephen M. Ansell





FDA approvals 2014-16

2017-18



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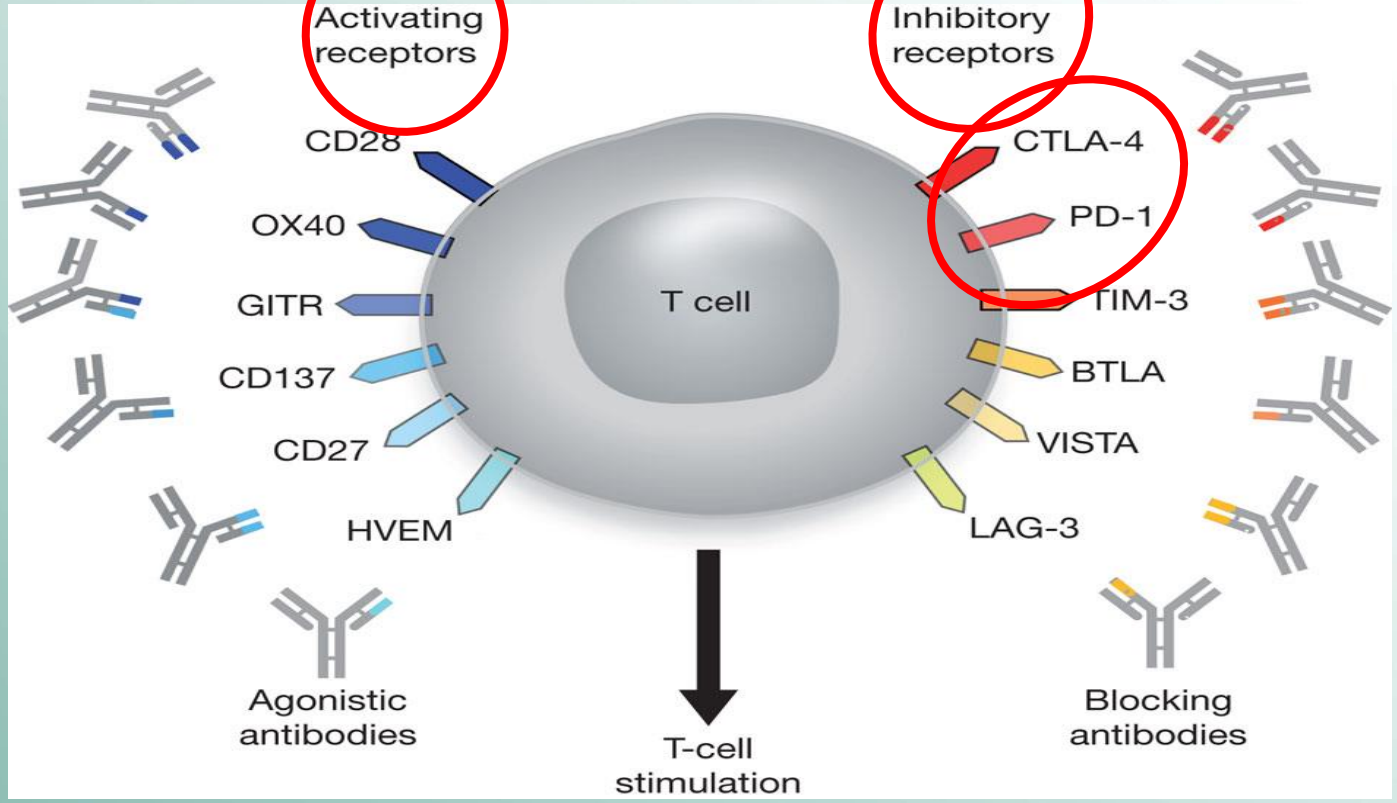
IMMUNO - COMBOS

2 KEY Regulators



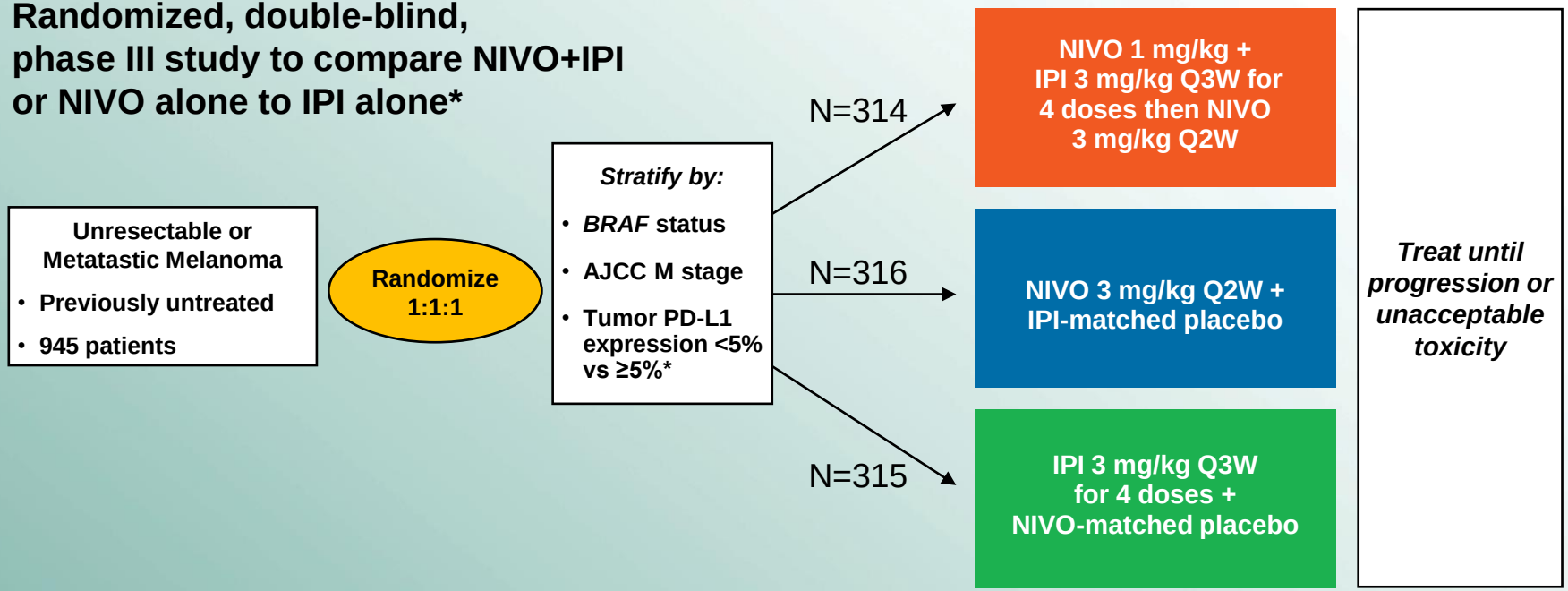
IMMUNO – COMBOS

INHIBITOR COMBOS

Anti-CTLA4 + Anti-PD1

CheckMate 067: Overall Survival

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



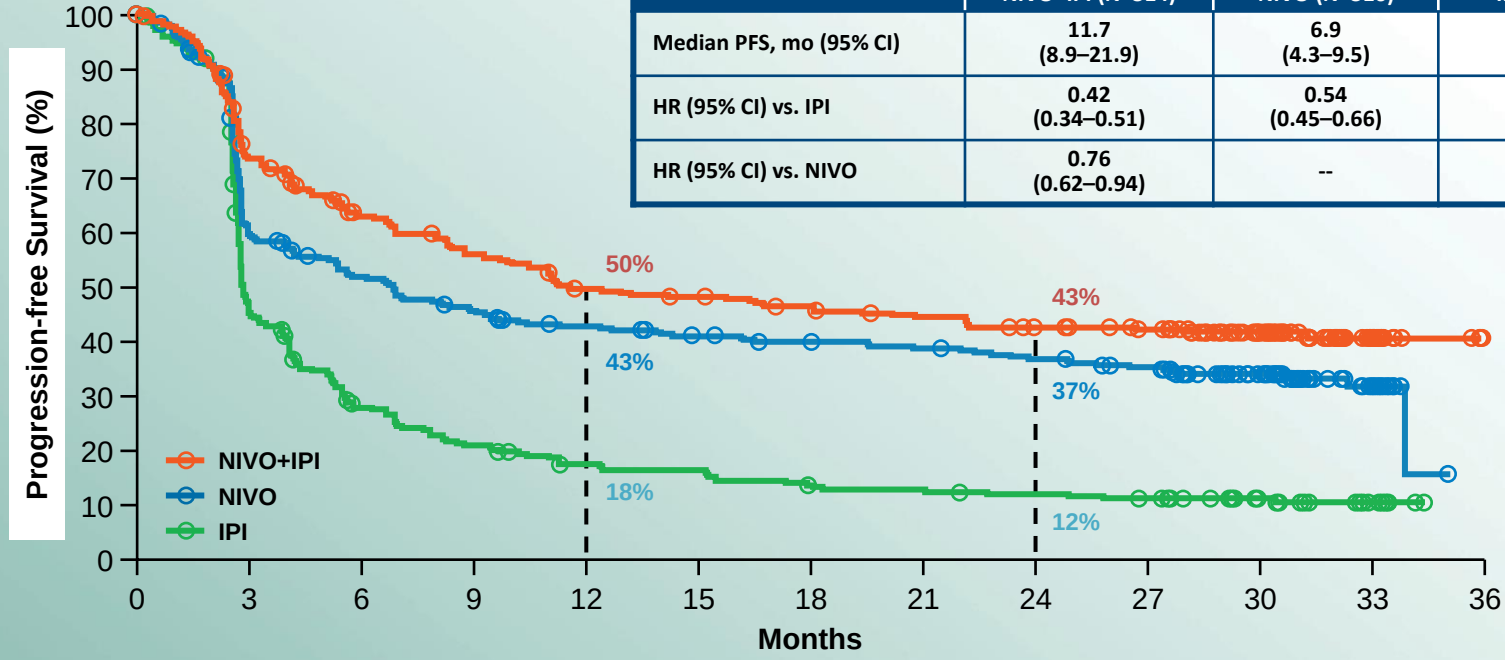
Database lock: Sept 13, 2016 (median follow-up ~30 months in both NIVO-containing arms)

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

J.Larkin et al. AACR 2017

Updated Progression-Free Survival

	NIVO+IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median PFS, mo (95% CI)	11.7 (8.9–21.9)	6.9 (4.3–9.5)	2.9 (2.8–3.2)
HR (95% CI) vs. IPI	0.42 (0.34–0.51)	0.54 (0.45–0.66)	--
HR (95% CI) vs. NIVO	0.76 (0.62–0.94)	--	--



Patients at risk:

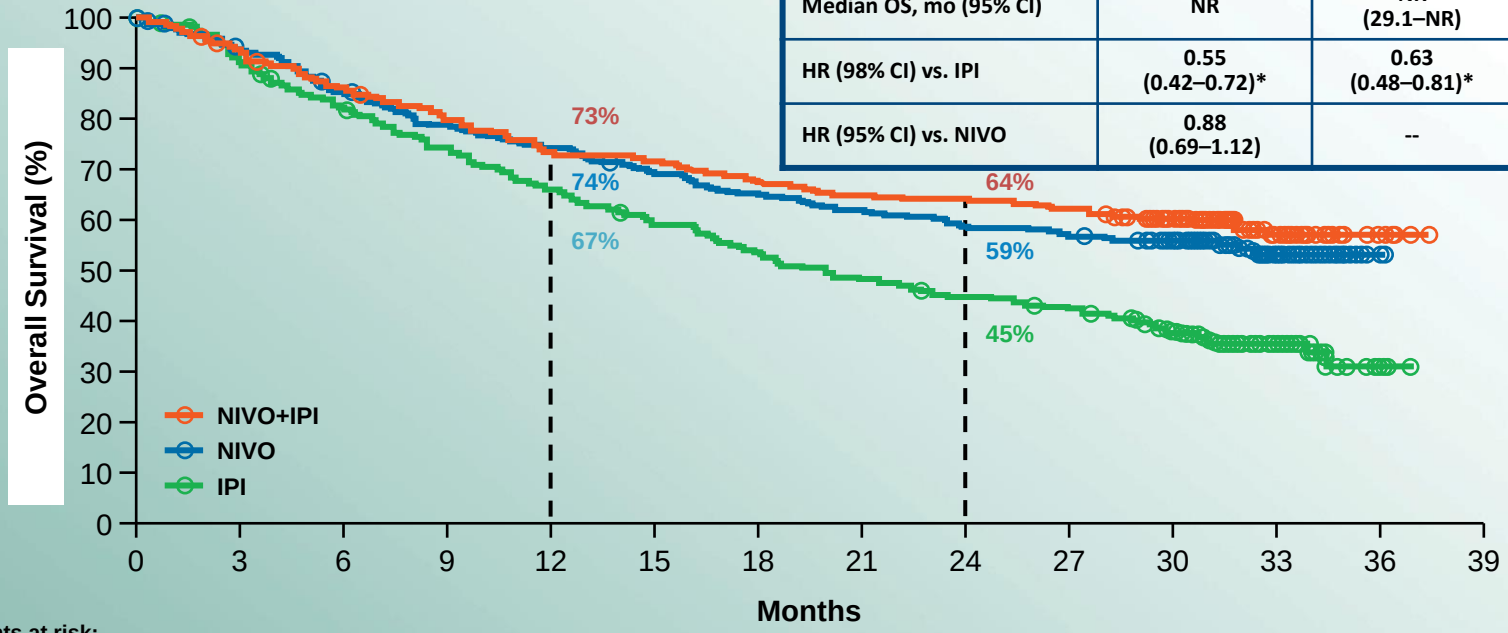
NIVO+ IPI	314	218	176	156	137	132	125	118	110	104	71	16	0
NIVO	316	178	151	132	120	112	107	103	97	88	62	16	0
IPI	315	136	77	58	46	43	35	33	30	27	16	5	0

J.Larkin et al. AACR 2017

Overall Survival

	NIVO+IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median OS, mo (95% CI)	NR	NR (29.1–NR)	20.0 (17.1–24.6)
HR (98% CI) vs. IPI	0.55 (0.42–0.72)*	0.63 (0.48–0.81)*	--
HR (95% CI) vs. NIVO	0.88 (0.69–1.12)	--	--

*P<0.0001



Patients at risk:

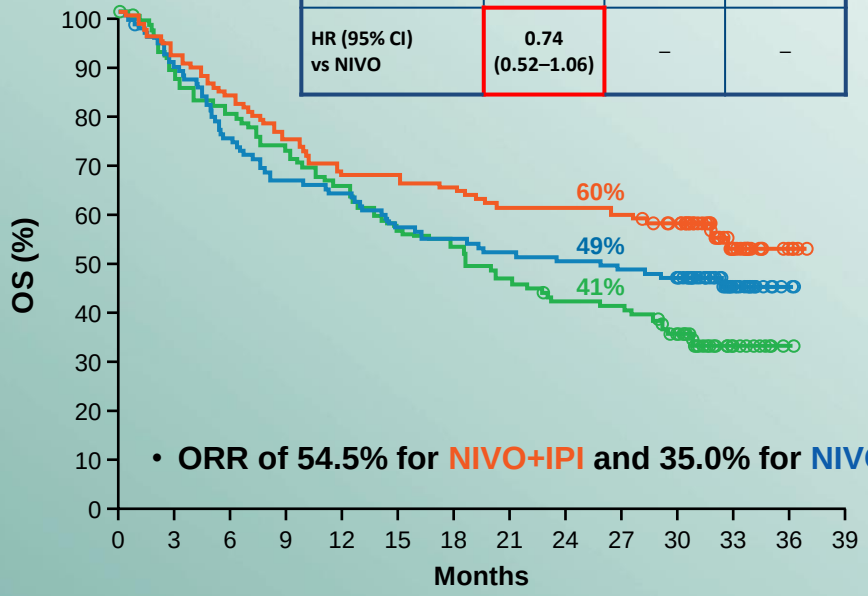
NIVO+IPI	314	292	265	247	226	221	209	200	198	192	170	49	7	0
NIVO	316	292	265	244	230	213	201	191	181	175	157	55	3	0
IPI	315	285	254	228	205	182	164	149	136	129	104	34	4	0

J.Larkin et al. AACR 2017

Similar Outcomes Were Observed at a ≥1% Cutoff

PD-L1 Expression Level <1%

<1% PD-L1	NIVO+IPI	NIVO	IPI
Median OS, mo (95% CI)	NR (26.5–NR)	23.5 (13.0–NR)	18.6 (13.7–23.2)
HR (95% CI) vs NIVO	0.74 (0.52–1.06)	–	–



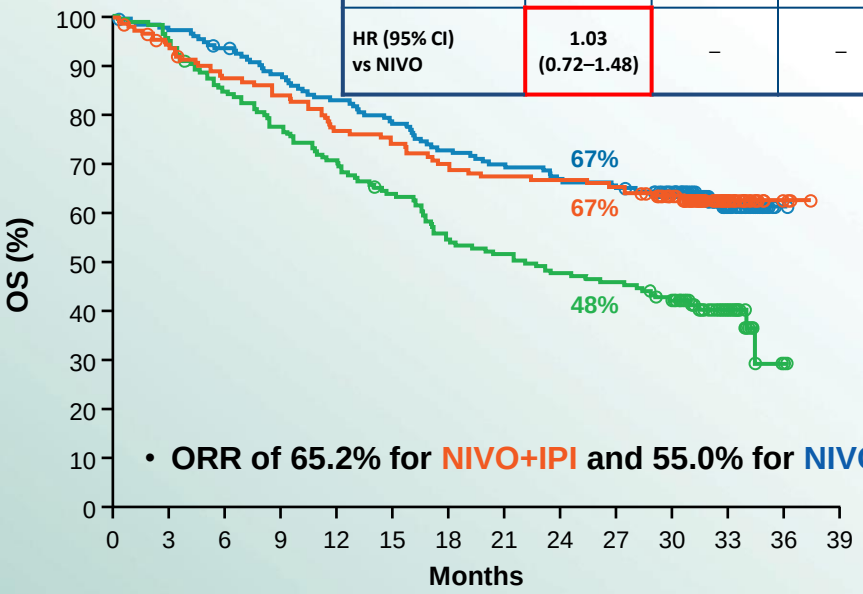
- ORR of 54.5% for NIVO+IPI and 35.0% for NIVO

Patients at risk:

NIVO+IPI	123	113	102	91	82	82	79	74	74	72	66	18	4	0
NIVO	117	103	86	76	73	65	62	59	57	55	50	16	2	0
IPI	113	96	87	79	71	61	57	50	44	43	32	10	1	0

PD-L1 Expression Level ≥1%

≥1% PD-L1	NIVO+IPI	NIVO	IPI
Median OS, mo (95% CI)	NR	NR	22.1 (17.1–29.7)
HR (95% CI) vs NIVO	1.03 (0.72–1.48)	–	–



- ORR of 65.2% for NIVO+IPI and 55.0% for NIVO

Patients at risk:

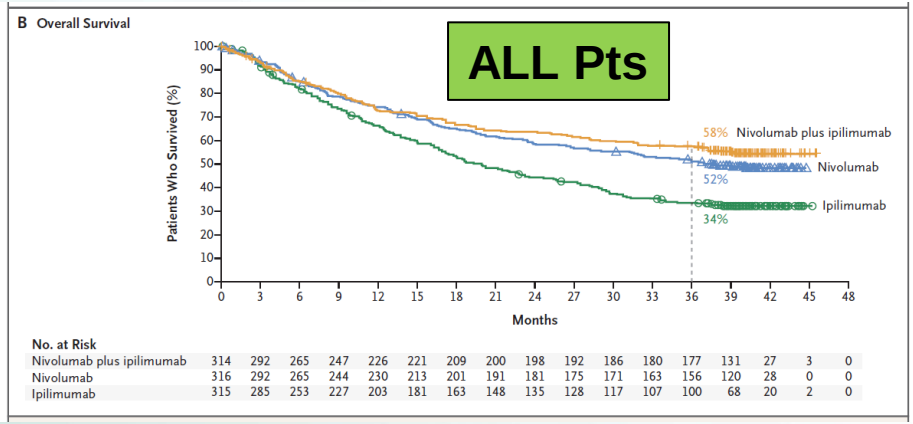
NIVO+IPI	155	144	132	127	116	112	105	102	101	99	85	27	3	0
NIVO	171	165	158	148	139	131	122	117	112	109	98	36	1	0
IPI	164	155	138	126	115	102	89	83	77	74	64	21	2	0

J.Larkin et al. AACR 2017

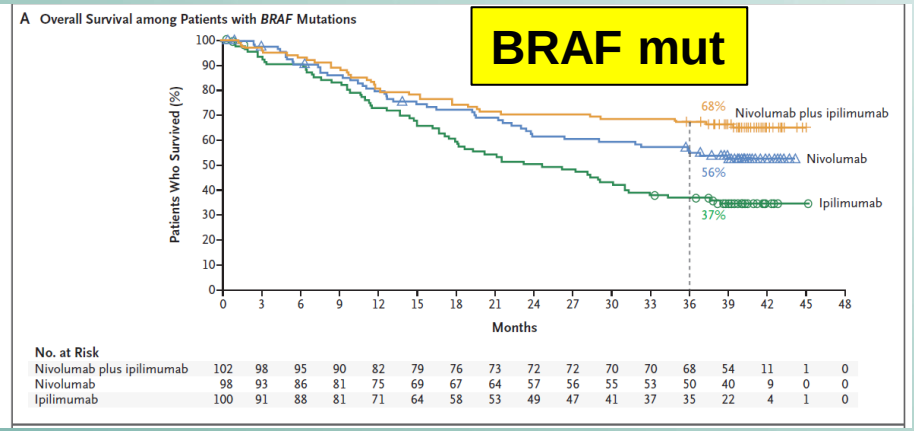
Nivo 1mg + Ipi 3mg
OS update NEJM 9/10/17
Wolchok J et al

IO-perspectives in BRAF mut population

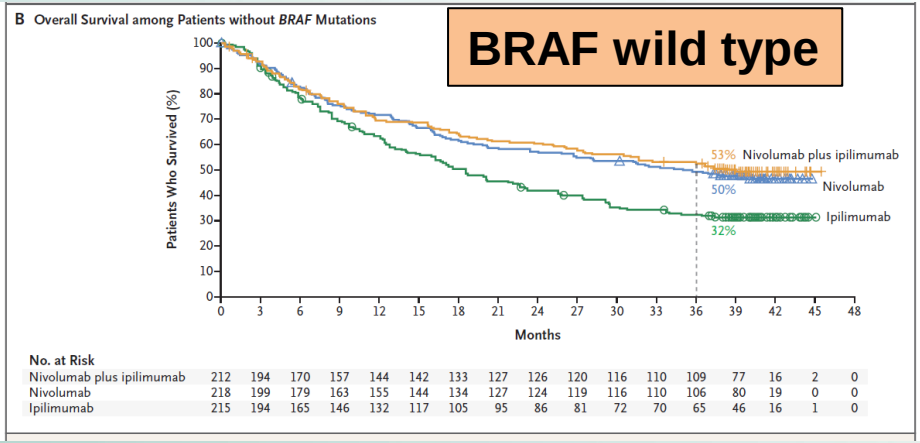
ALL Pts



BRAF mut



BRAF wild type



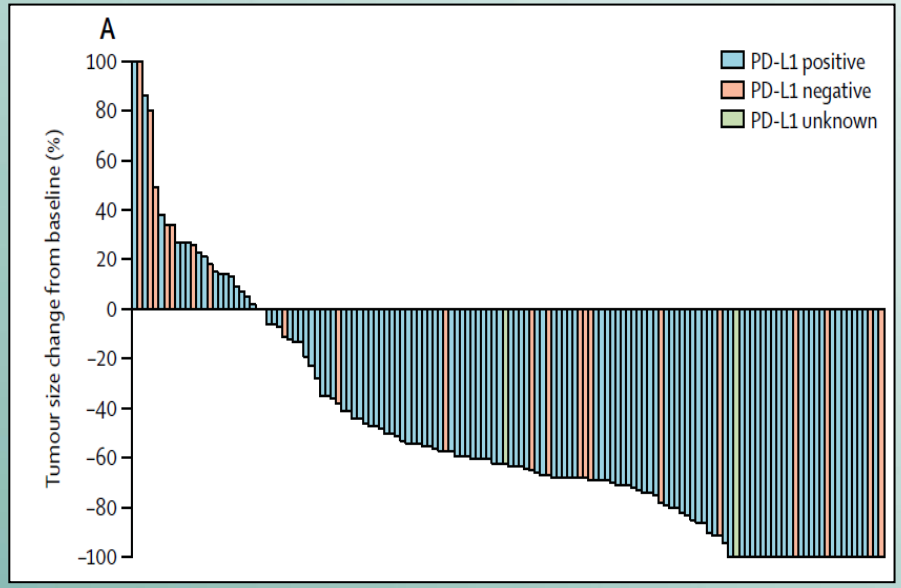
Standard-dose pembrolizumab in combination with reduced-dose ipilimumab for patients with advanced melanoma (KEYNOTE-029): an open-label, phase 1b trial

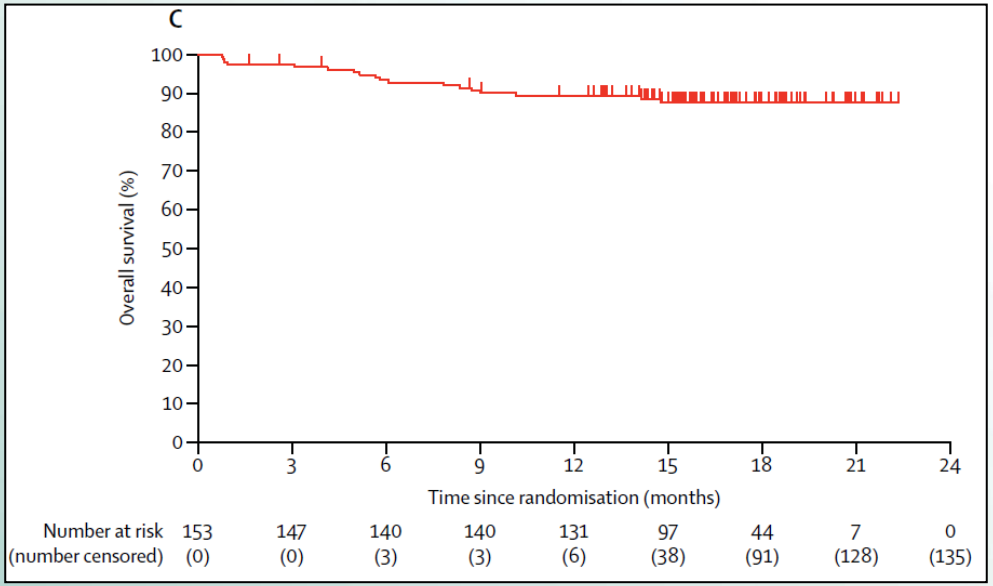
Georgina V Long, Victoria Atkinson, Jonathan S Cebon, Michael B Jameson, Bernie M Fitzharris, Catriona M McNeil, Andrew G Hill, Antoni Ribas, Michael B Atkins, John A Thompson, Wen-Jen Hwu, F Stephen Hodi, Alexander M Menzies, Alexander D Guminski, Richard Kefford, Benjamin Y Kong, Babak Tamjid, Archana Srivastava, Anna J Lomax, Mohammed Islam, Xinxin Shu, Scot Ebbinghaus, Nageatte Ibrahim, Matteo S Carlino

pembrolizumab 2mg/kg q3wk

ipilimumab 1mg/kg

prmbro maintenance 2 yrs



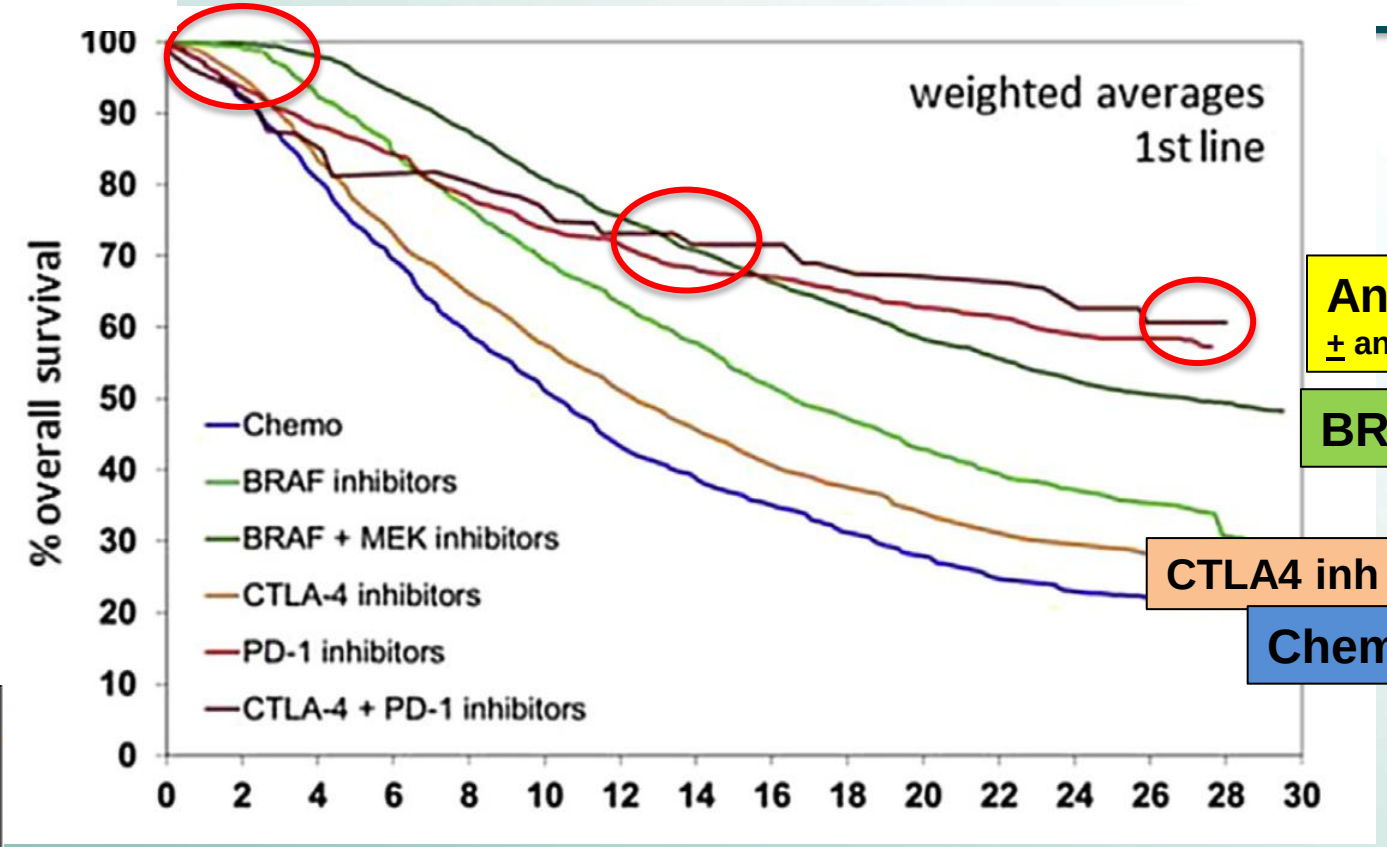


Translation Results in Advanced Disease

Into

ADJUVANT THERAPY

Effective Drugs in Advanced Melanoma



Anti-PD1
± anti CTLA4

BRAF+MEK

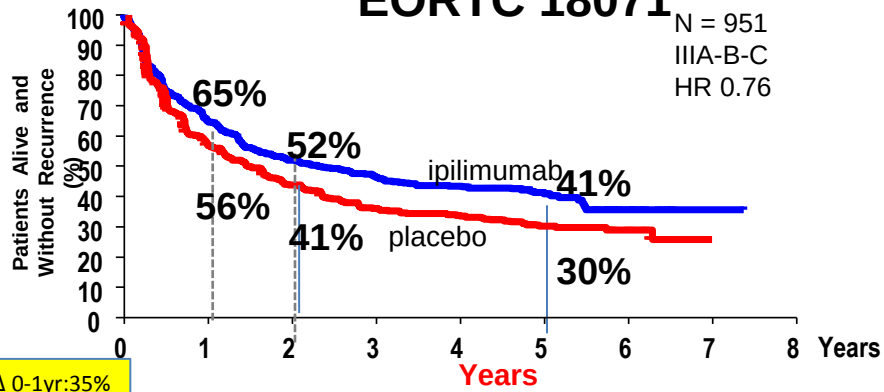
CTLA4 inh **BRAFinh**

Chemo

Ugurel S, et al. *Eur J Cancer* 2017;83:247-57.

Improvement in RFS in high risk melanoma

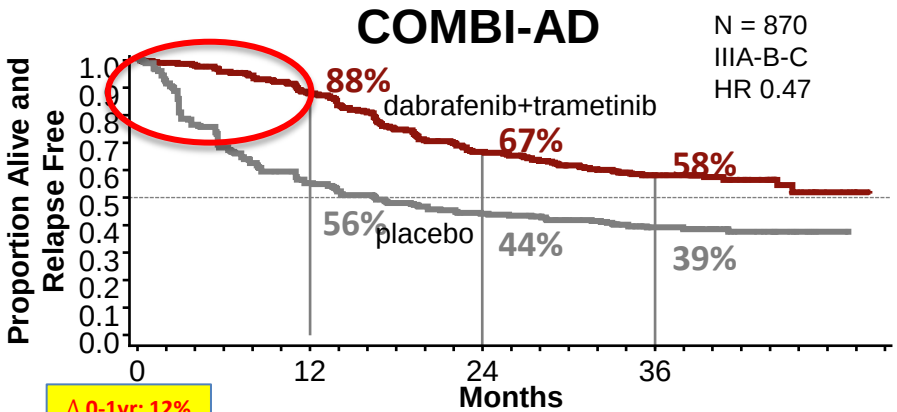
EORTC 18071



Δ 0-1yr:35%
Δ 1-2yr:13%

Eggermont *et al*. NEJM 2016

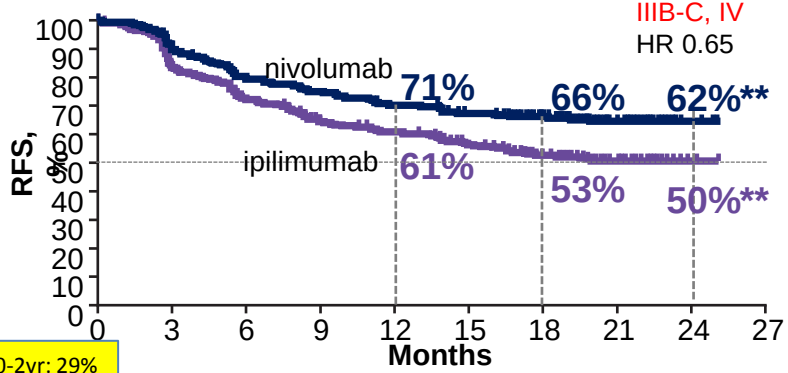
COMBI-AD



Δ 0-1yr: 12%
Δ 1-2yr: 21%

Long *et al*. NEJM 2017

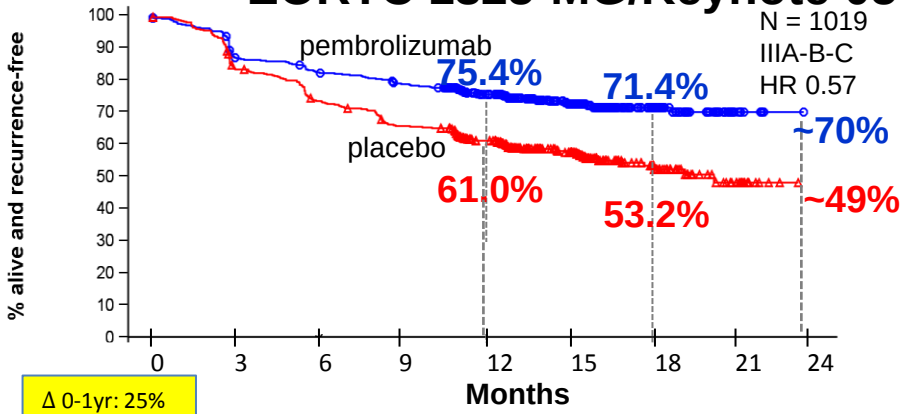
CheckMate-238



Δ 0-2yr: 29%
Δ 1-2yr: 9%

Weber *et al*. NEJM 2017

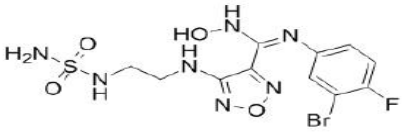
EORTC 1325-MG/Keynote 054

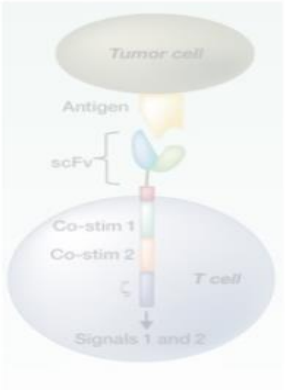


Δ 0-1yr: 25%
Δ 1-2yr: 6?

Eggermont *et al*. NEJM 2018

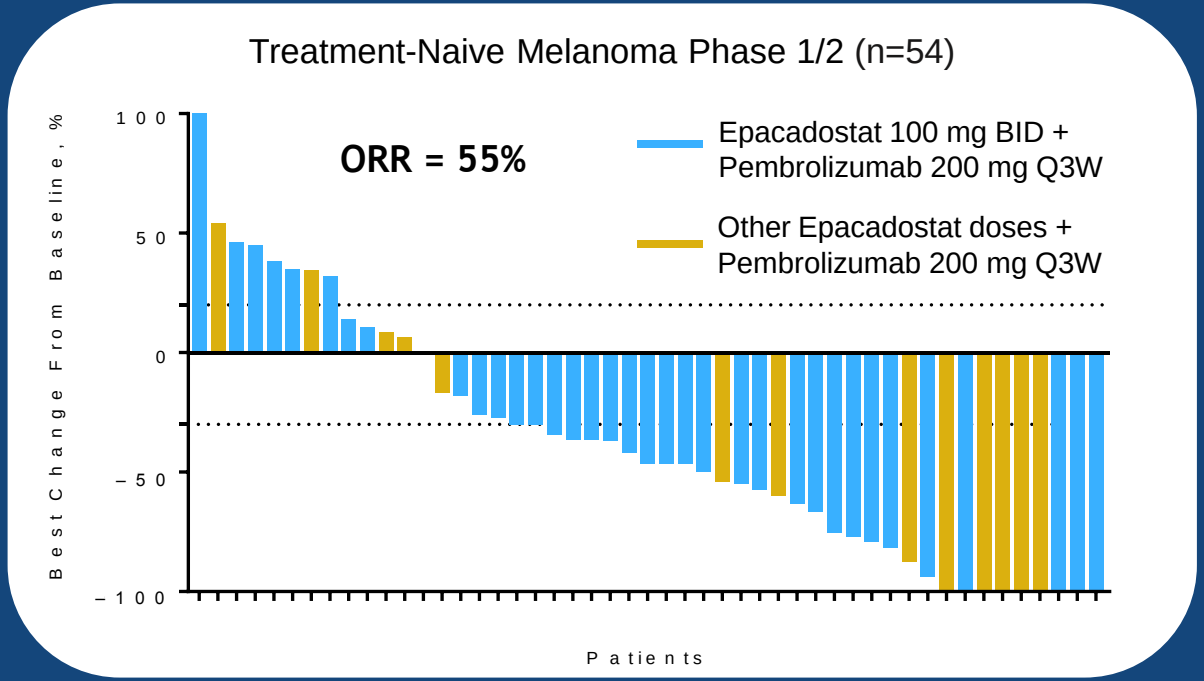
OTHER IMMUNOTHERAPIES





Oral Immuno Modulator	Oncolytic Virus	CAR T-cells	Bi Spe	Cytokines

Background: Rationale for Combination and Dosing

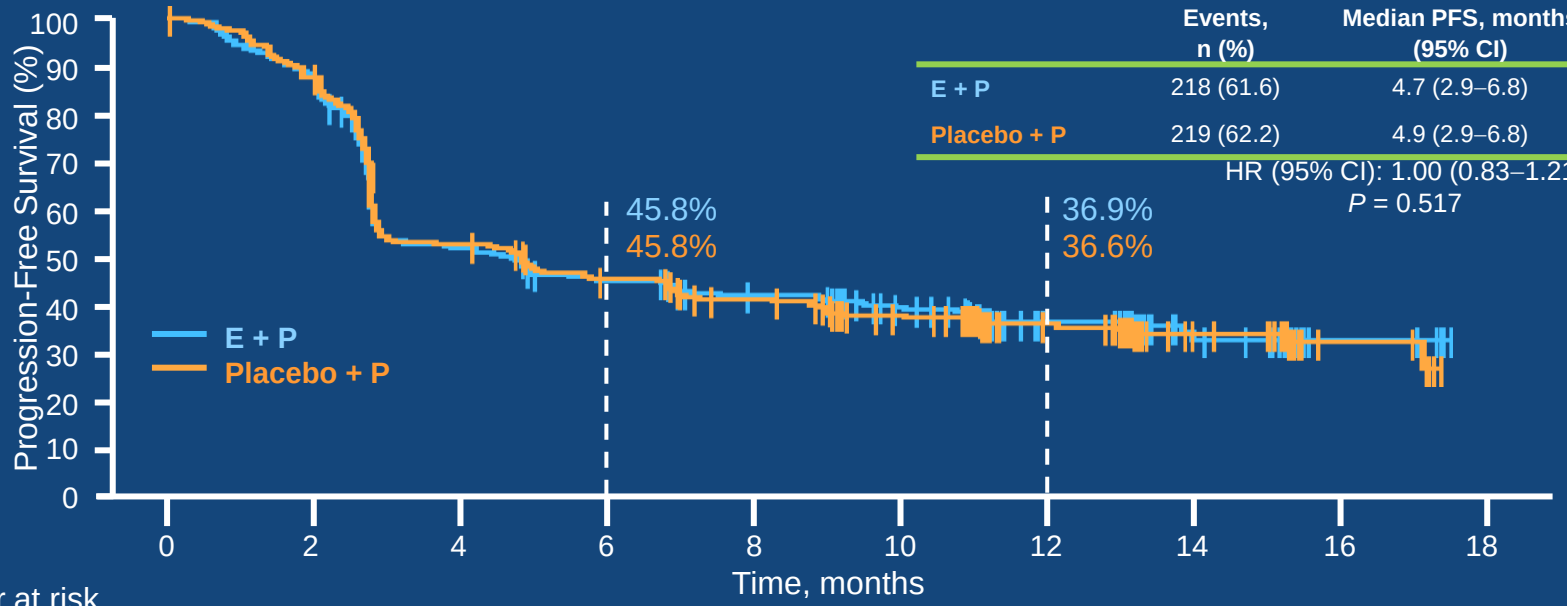


ECHO-202 / KEYNOTE-037

- Phase 1: Epacadostat 50, 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.

PFS: Pembro vs Pembro+Epacadostat



	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

Number at risk

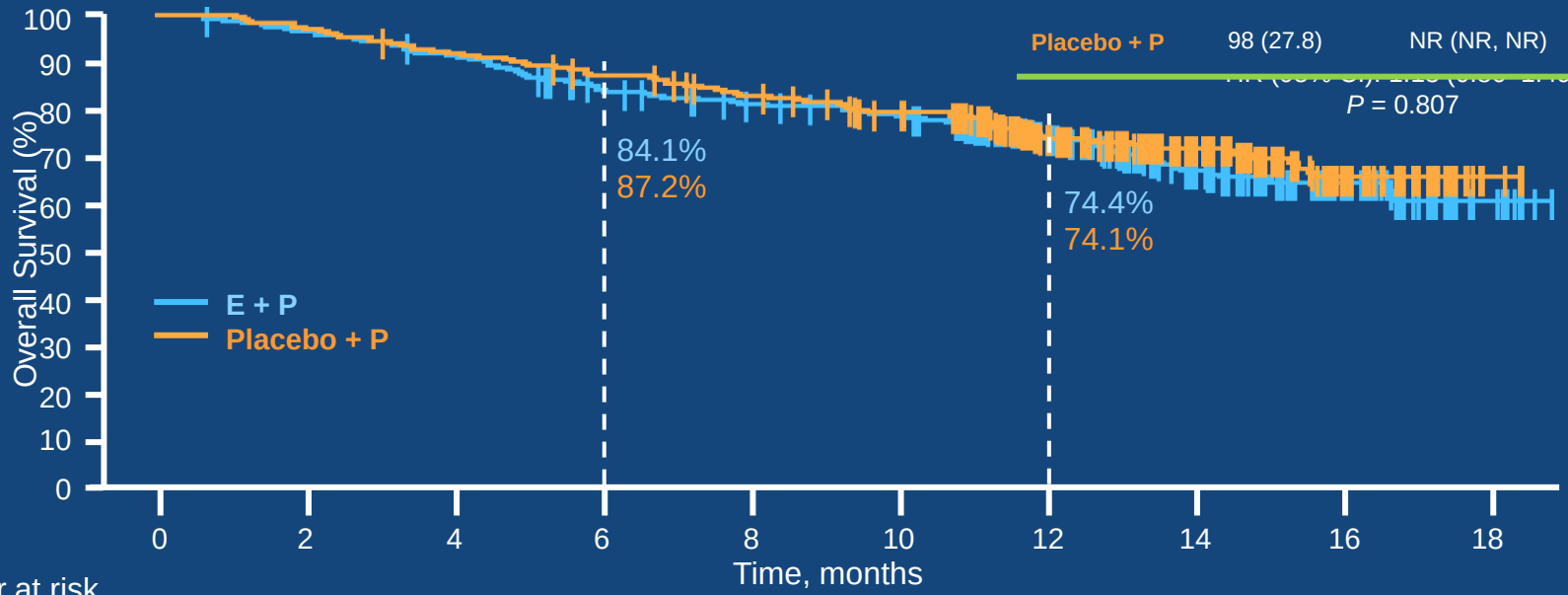
E + P	354	309	181	155	137	114	57	25	5	0
Placebo + P	352	304	181	151	132	109	65	28	7	0

BICR, blinded independent central review; CI, confidence interval; E, epacadostat; HR, hazard ratio; P, pembrolizumab; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors.
PFS defined as time from randomization to disease progression or death, whichever occurred first.

Overall Survival: P vs P+E

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

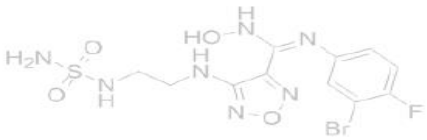
P = 0.807

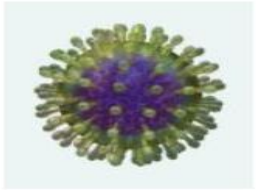


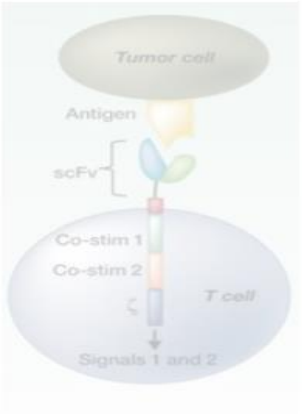
Number at risk

E + P	354	340	322	290	274	263	183	96	42	5
Placebo + P	352	342	323	304	285	263	186	115	43	2

CI, confidence interval; E, epacadostat; HR, hazard ratio; NR, not reached; OS, overall survival; P, pembrolizumab.







IDO inhibitors

Oncolytic Virus

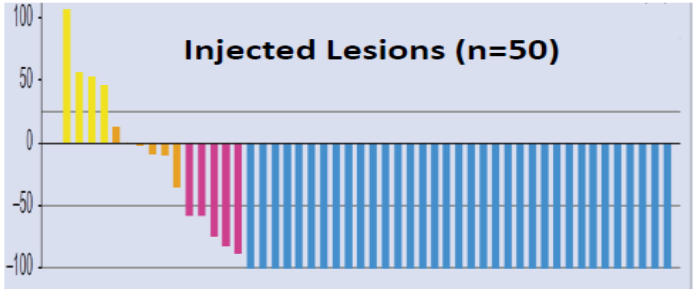
CAR T-cells

Bi Spe

Cytokines

T-VEC EMA approval Q4 2015

IT T-VEC + pembrolizumab in Melanoma



ORR = 57% (irRC)

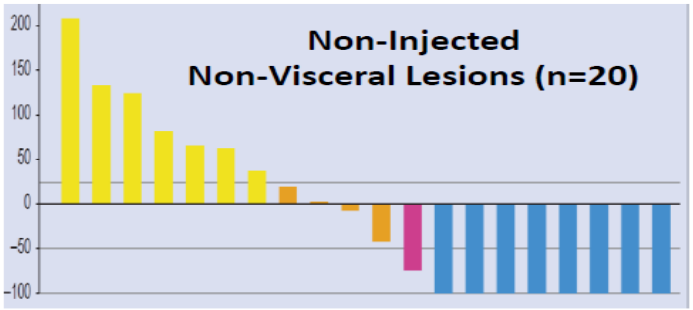
ORR pembro alone ~ 33%

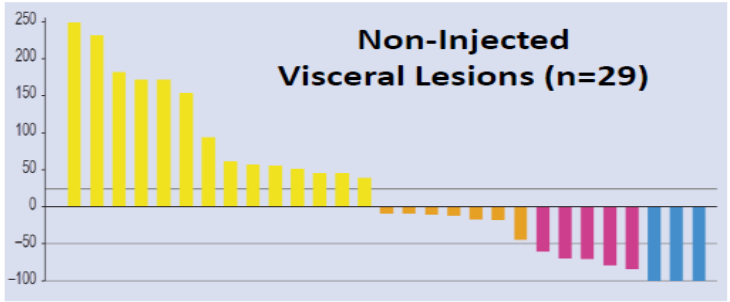
CR rate = 24% (irRC)

CR rate pembro alone ~ 6% (RECIST)

PFS at 9 month = 71%

PFS at 9 months pembro alone ~40%





G.Long, ASCO 2016

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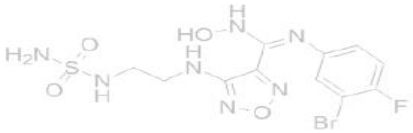
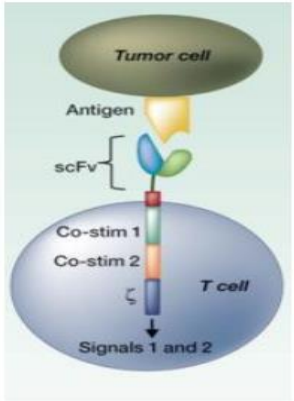
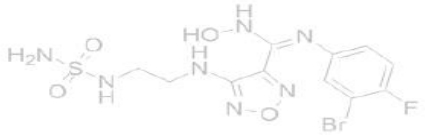
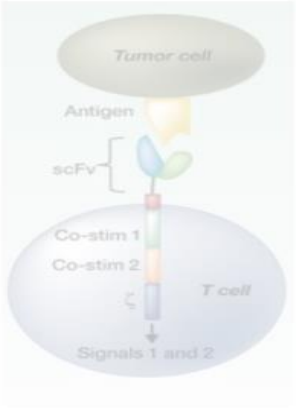
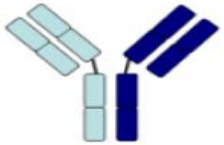




IDO inhibitors | Oncolytic Virus | **CAR T-cells** | Bi Spe | Cytokines







IDO inhibitors

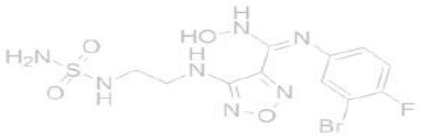
Oncolytic Virus

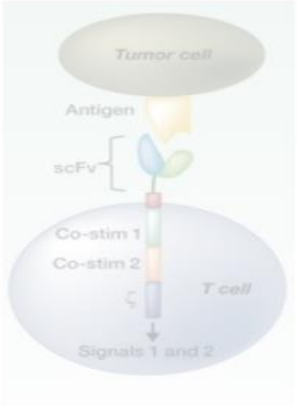
CAR T-cells

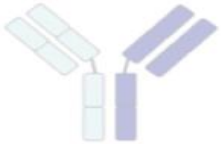
Bi Spe

Cytokines

Blinatumomab EMA approval Q4 2015







IDO inhibitors	Oncolytic Virus	CAR T-cells	Bi Spe	Cytokines

PREDICTIONS

IMMUNOTHERAPY REVOLUTION

- **Breaking Tolerance: Nobel Price**
- PD-1/PDL-1 antibodies **central** molecule in combination strategies
- **PD-1 ceiling** will be broken by SMART (**additional mechanism**) Combo's
  - M2-M1 repolarizing agents (e.g. CCR5, CXCR2/CXCR5)
  - Long peptides and personalized vaccines
  - Oncolytic vaccines
  - Chemokine modulators : CCR5, CCR2/5
  - IT TLR other IT approaches
  - Anti-TGFbeta?
  - CAR T cells / cellular therapies

- Hodgkin will approach 100 % cure rates
- Melanoma will be the new Hodgkin
- One by one others will follow

THANK YOU

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

COME VISIT GUSTAVE ROUSSY
Cancer Campus Grand Paris