ISTITUTO NAZIONALE TUMORI
RCCS – Fondazione Pascale

LESSONS LEARNT
Melanoma
Academic Perspective

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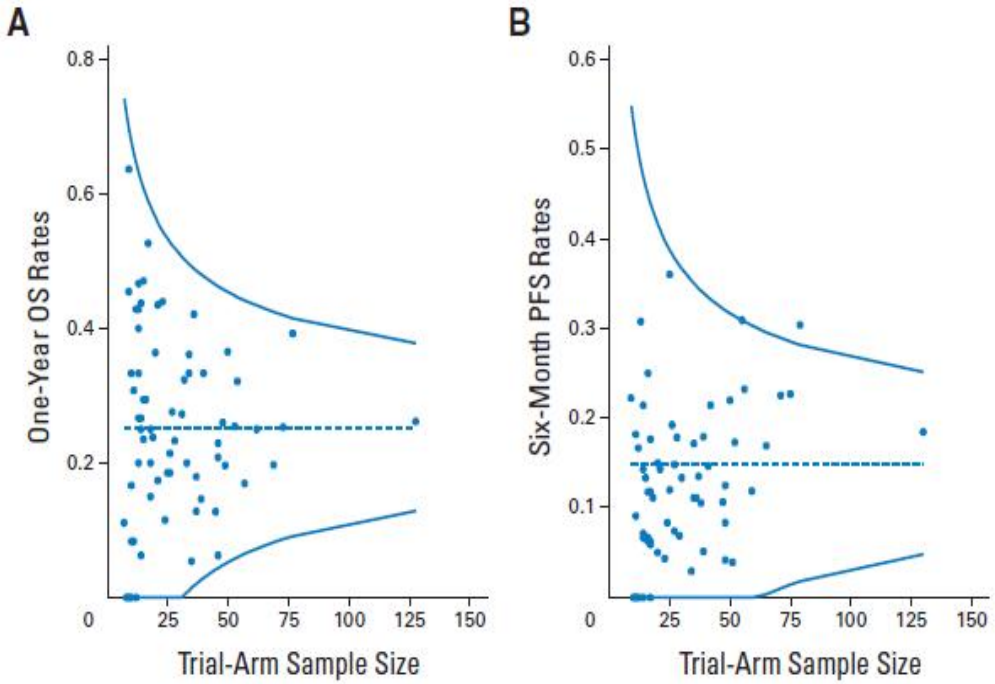
Disclosures

- **Employment or Leadership Position:** None
- **Consultant/Advisory Role:** Bristol-Meyers Squibb, Merck Sharp & Dohme, Roche-Genentech, Ventana, Novartis, Amgen, Array
- **Stock Ownership:** None
- **Honoraria:** None
- **Research Funding:** Bristol-Meyers Squibb, Roche-Genentech, Ventana
- **Expert Testimony:** None
- **Other Remuneration:** None

Meta-analysis of Phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future Phase II trials

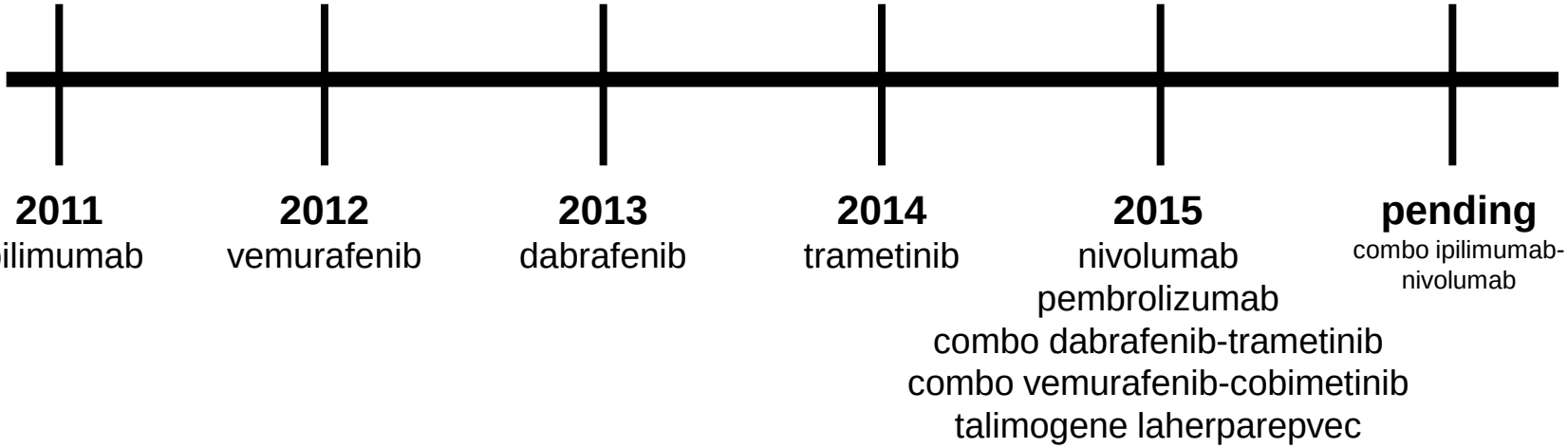
This metanalysis summarises the outcome of advanced melanoma patients before 2011



- Median survival time **6.2 months**
- Alive at 1 year **25.5%**
- Median PFS **1.7 months**
- Progression free at 6 months **14.5%**

Korn E , *et al*. J Clin Oncol 2008;26:527–34. Reprinted with permission

Treatment for advanced melanoma approved by EMA after 2011



Agent	Company	Indication
Nivolumab	BMS	Unresectable or metastatic melanoma
Ipilimumab	BMS	Unresectable or metastatic melanoma
Vemurafenib	Roche/Genentech	Unresectable or metastatic melanoma with BRAF V600E mutation
Dabrafenib	Novartis	Unresectable or metastatic melanoma with BRAF V600E mutation
Trametinib	Novartis	Unresectable or metastatic melanoma with BRAF V600E/K mutation
Talimogene laherparepvec	Amgen	Unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC, and IVM1a) with no bone, brain, lung, or other visceral disease.

Advanced melanoma: different approaches according to mutational status

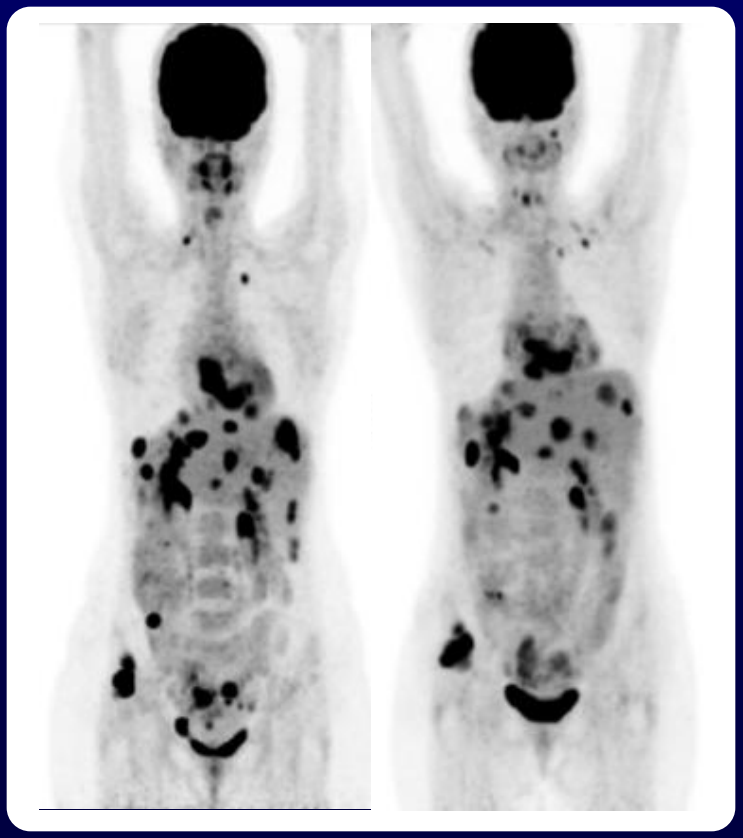
***BRAF*$^{V600E/K}$**
^{Q61}NRAS
c-KIT

***BRAF* wt**
***NRAS* wt**

Ascierto P, et al. J Transl Med. 2012 May 2;10(1):83

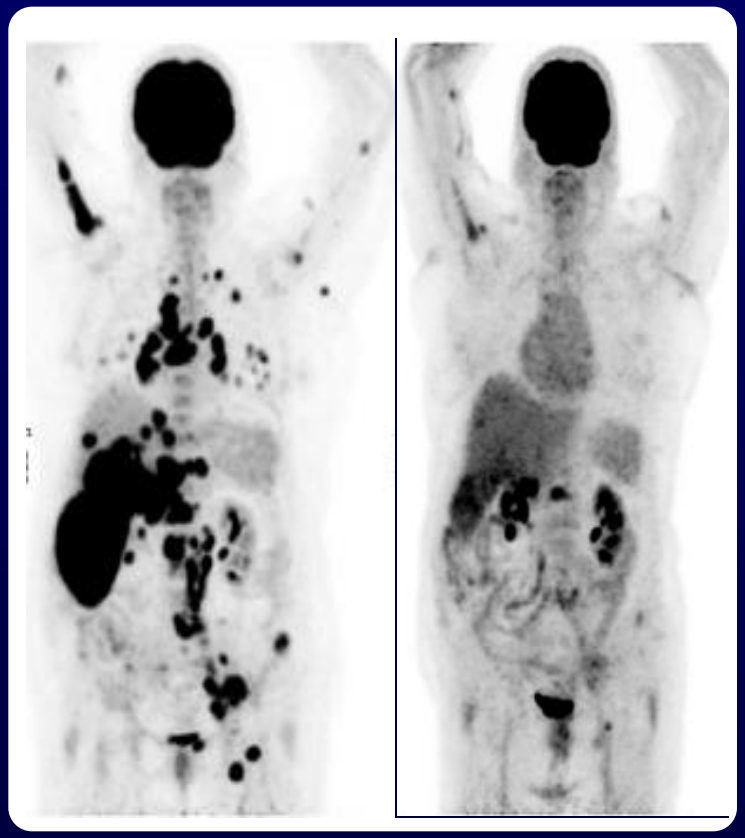
Two different drugs ...
Two different concepts

Ipilimumab
slow action, but it's able to make chronic the disease



Oct-2010 Jun-2011

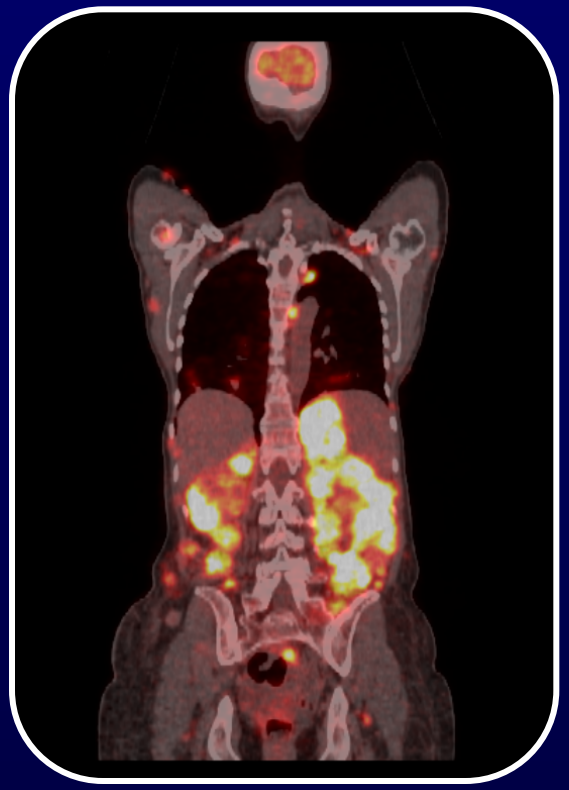
Vemurafenib
quick action, rapid metabolic shutdown, unfortunately resistance after a median of 6-8 months



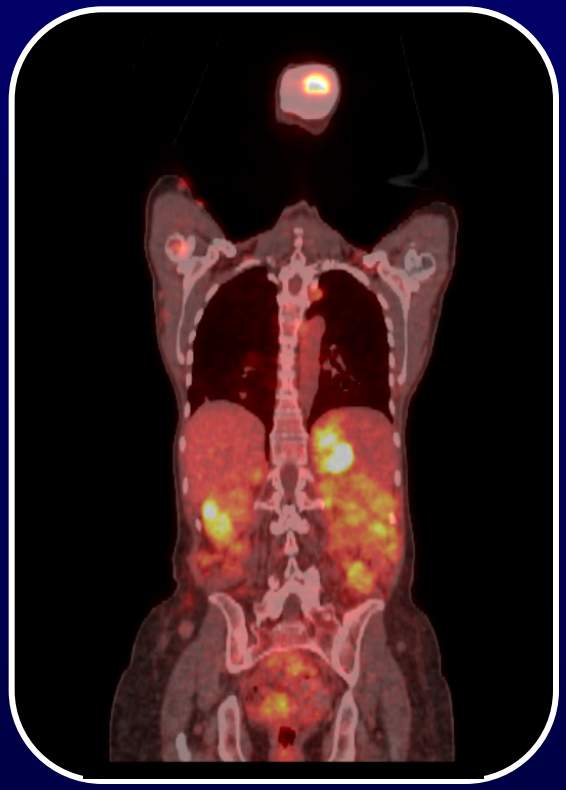
Day 0 Day 15

Target Therapy

VEMU-PET study
Patient # 18^{V600E}BRAF mutated



Day 0



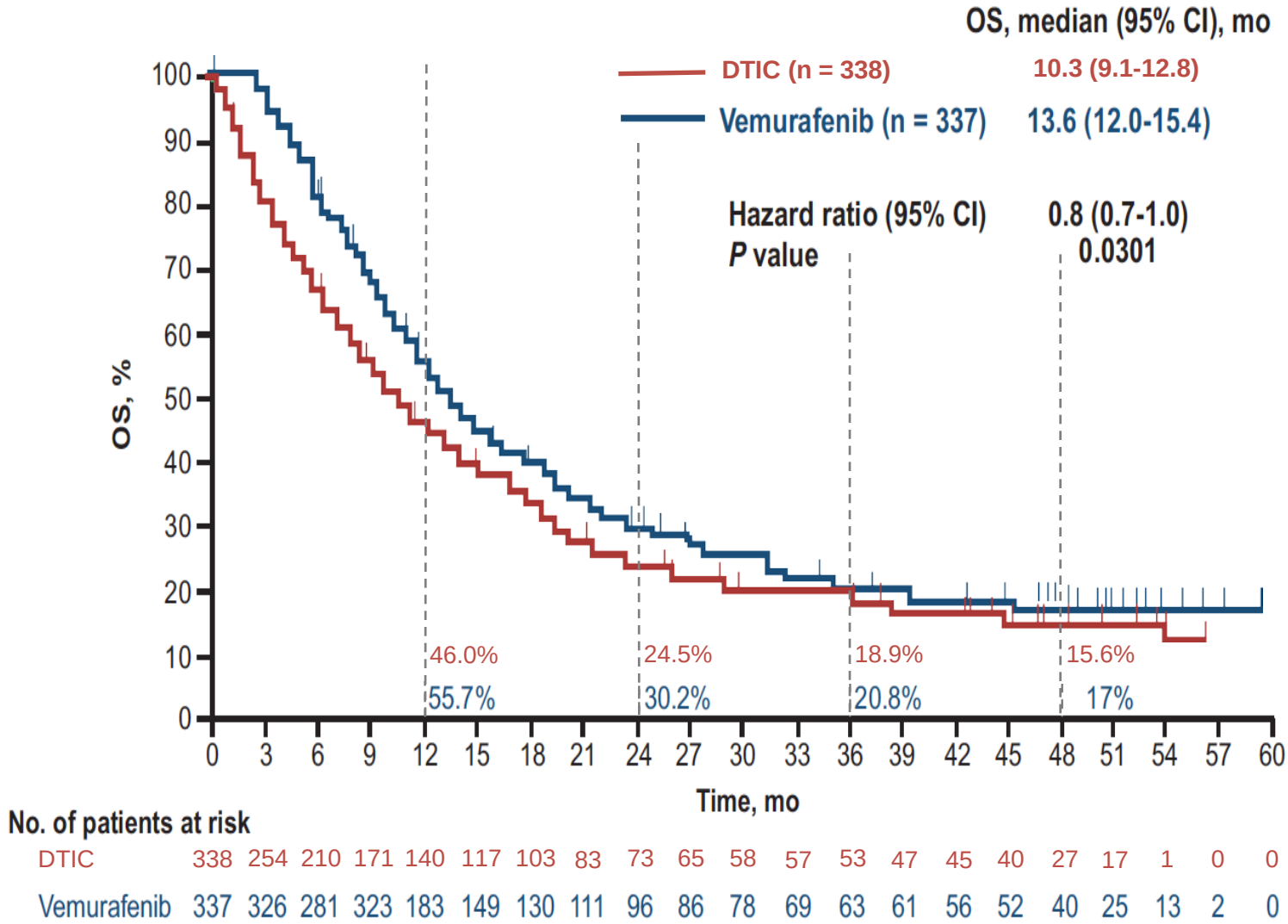
Day 7

Different evidences of rapid progression disease after BRAF inhibitors treatment

Experience	Patients sample (n)	% of patients with a rapid disease progression kinetics
BRIM-2	39	41%
BRIM-3	42	52%
Ascierto et al.	28	43%
Ackerman et al.	32	50%
Italian ipilimumab EAP	54	41%
Fisher et al.	42	38%

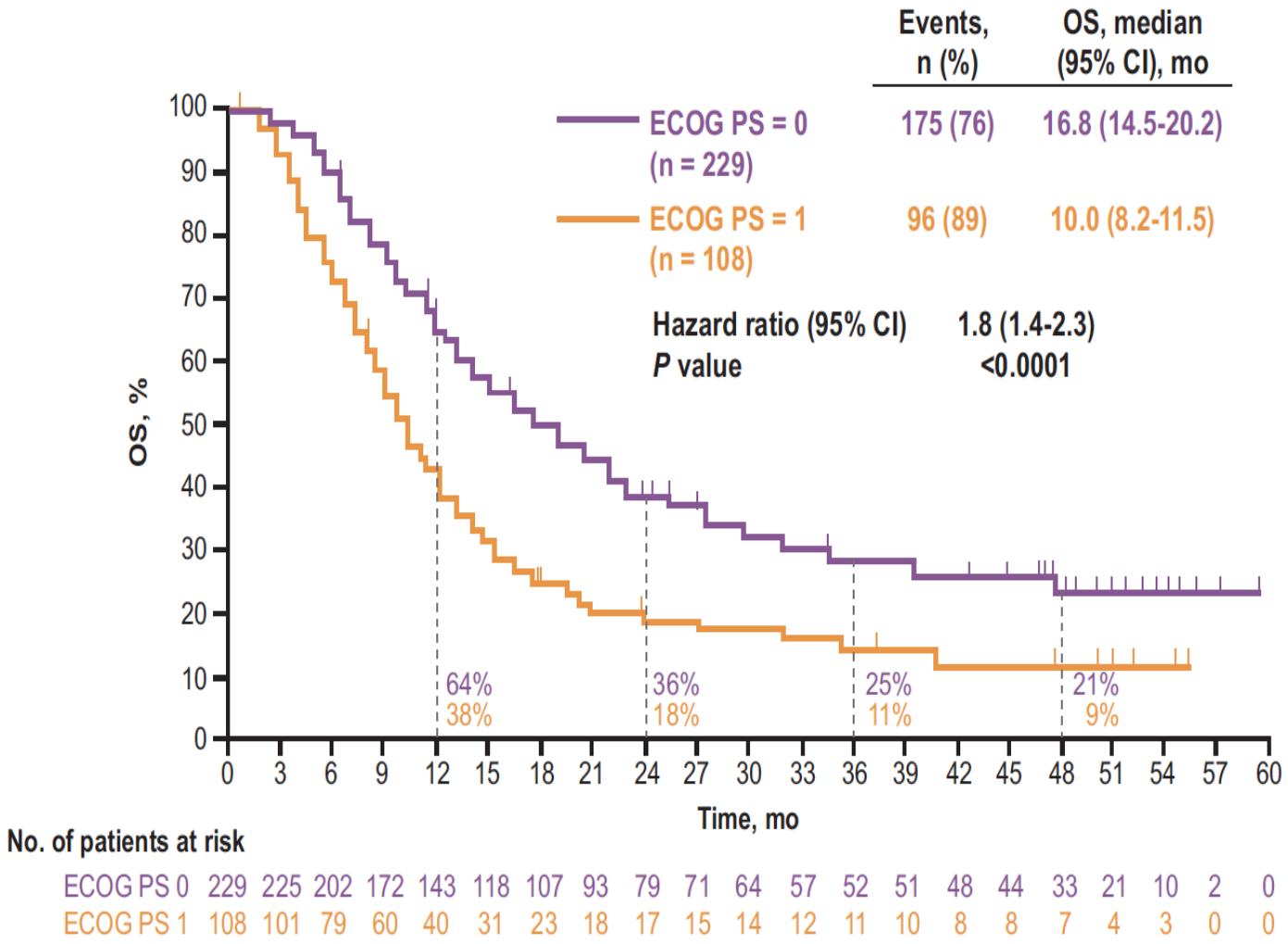
Ascierto et al. J Trans Med 2013

BRIM-3: OS Without Censoring at Crossover (ITT Population)



Data cutoff: August 14, 2015.
DTIC, dacarbazine; ITT, intention-to-treat.

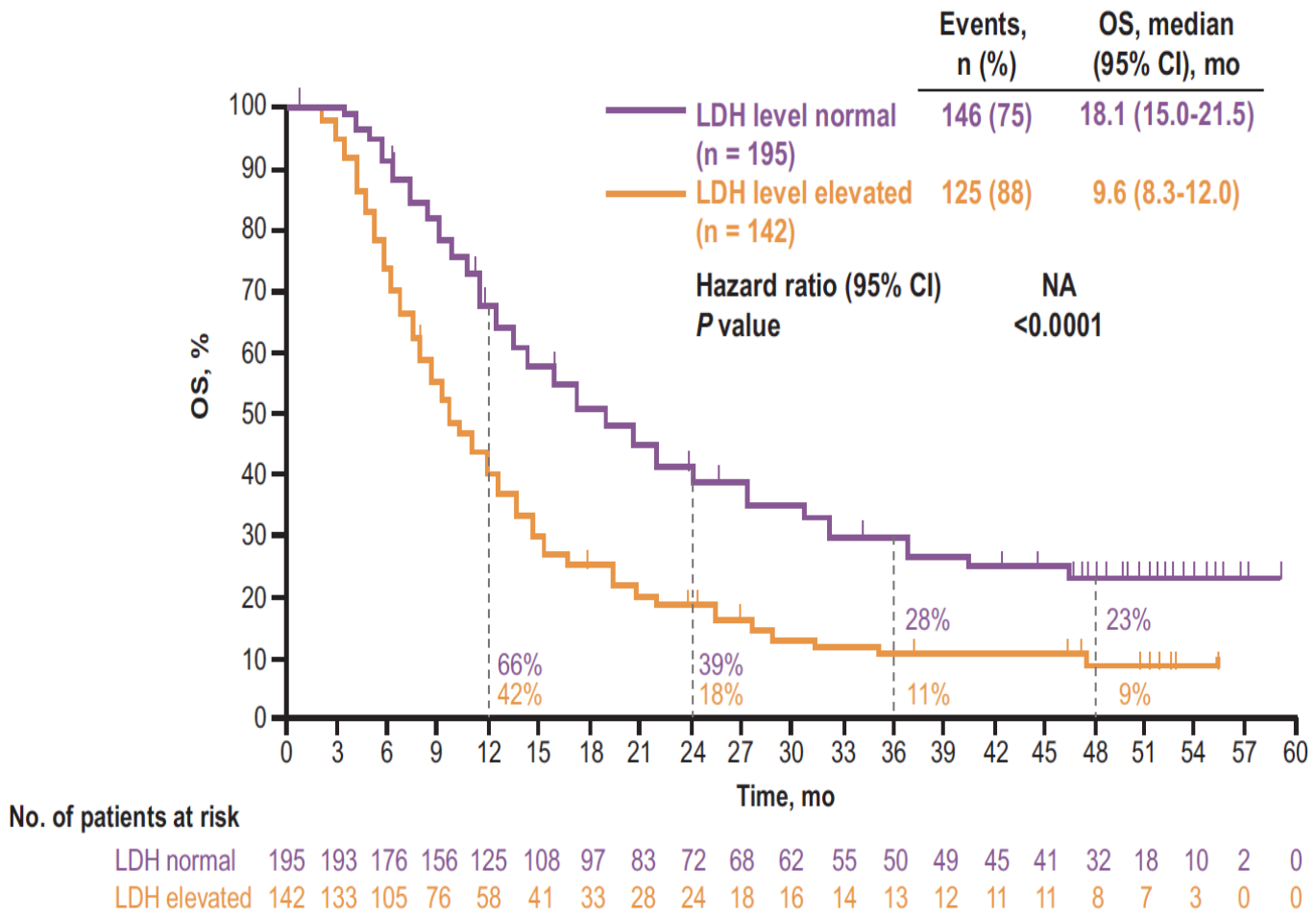
BRIM-3: OS Was Better for ECOG PS 0 in Vemurafenib Arm



Data cutoff: August 14, 2015.
ECOG PS, Eastern Cooperative Oncology Group performance status.

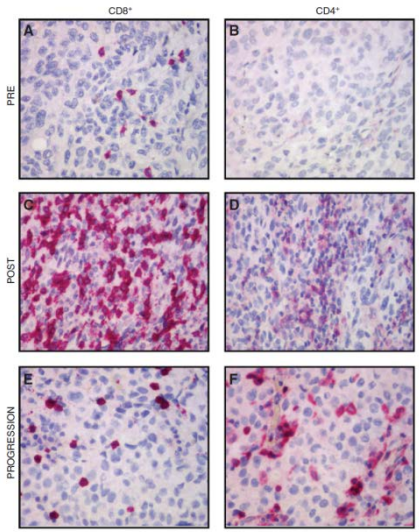
Ascierto P, *et al.* Bridge meeting 2015.

BRIM-3: OS Was Better for Normal Baseline LDH in Vemurafenib Arm

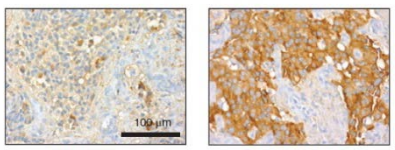


Data cutoff: August 14, 2015.
LDH, lactate dehydrogenase.

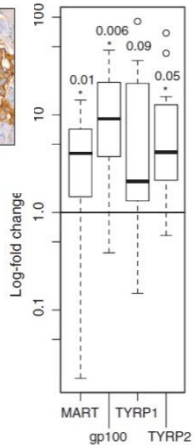
Effect of BRAF inhibitors on the immune system

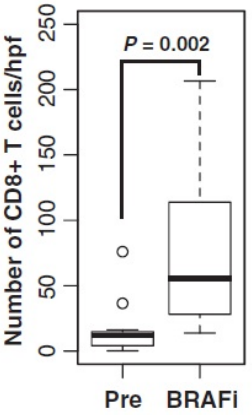


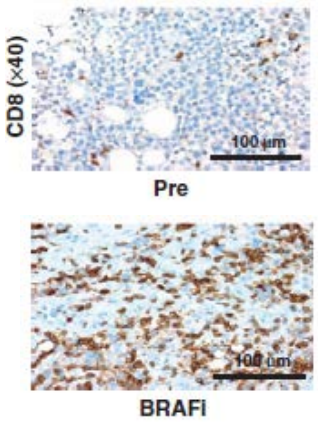
CD4+ and CD8+ increase in responder lesion and decrease in lesions which progressed



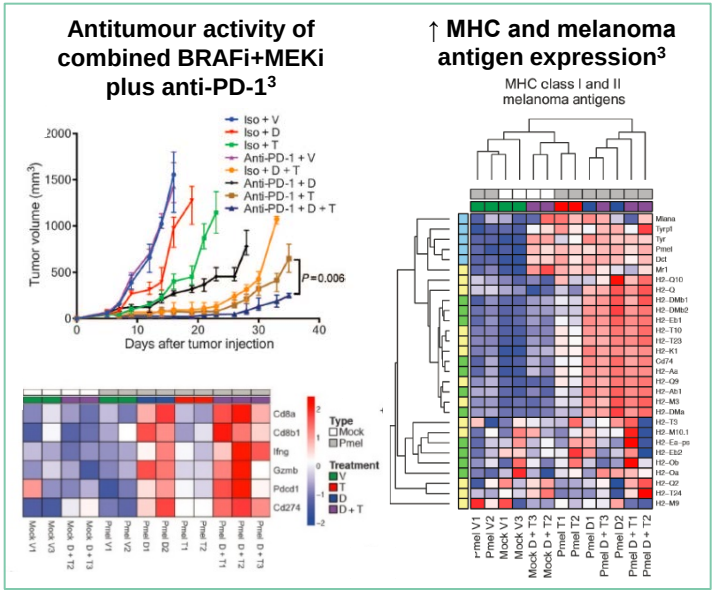
BRAF inhibition is associated with increased melanoma antigen expression in tumours of patients with metastatic melanoma







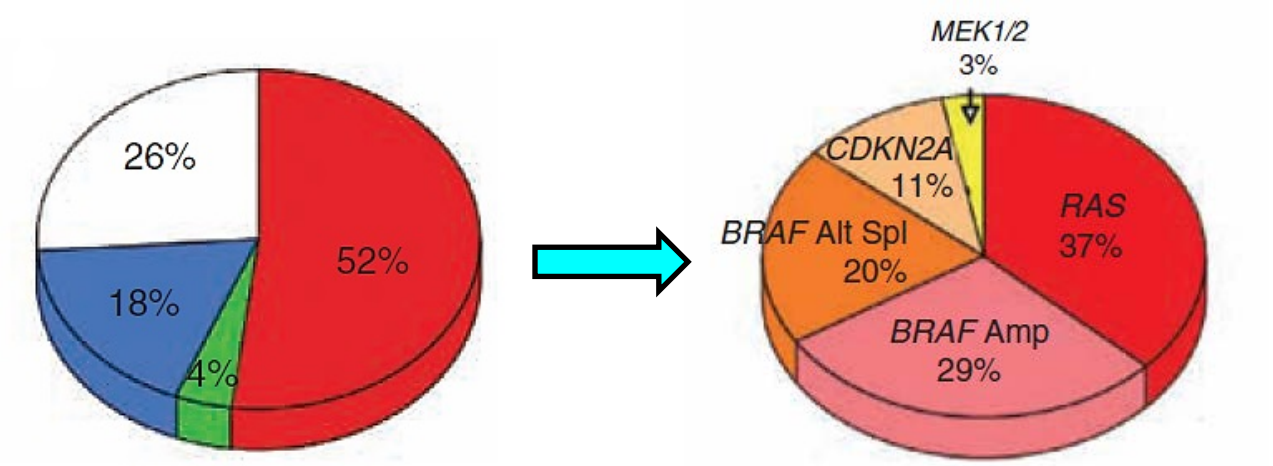
BRAF inhibition is associated with increased CD8+ T-cell infiltrate in tumours of patients with metastatic melanoma

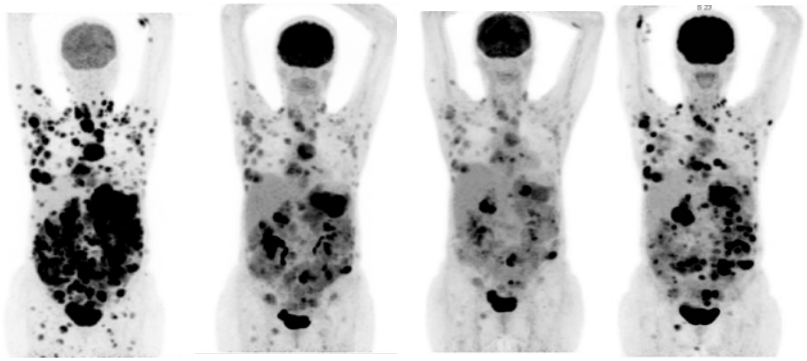


Wilmott JS, *et al*. Clin Cancer Res 2011;18:1386–94, Reprinted from Clinical Cancer Research 2012, with permission from AACR
Frederick DT, *et al*. Clin Cancer Res 2013;19:1225–31, Reprinted from Clinical Cancer Research 2013, with permission from AACR
3. From Hu-Lieskovan S *et al*. Sci Transl Med 2015;7:279ra41., Reprinted with permission from AAAS

Resistance

BRAF-mutant melanomas acquire BRAF inhibitor resistance via upregulation of both MAPK and PI3K–AKT pathways. However, MAPK reactivation is the major pathway of acquired BRAF inhibitor resistance in melanoma. Among MAPK-reactivating mechanisms associated with acquired BRAF inhibitor resistance the most frequents are NRAS mutations, mutant BRAF amplification and alternative splice variants, MAP2K1 and CDKN2A mutations



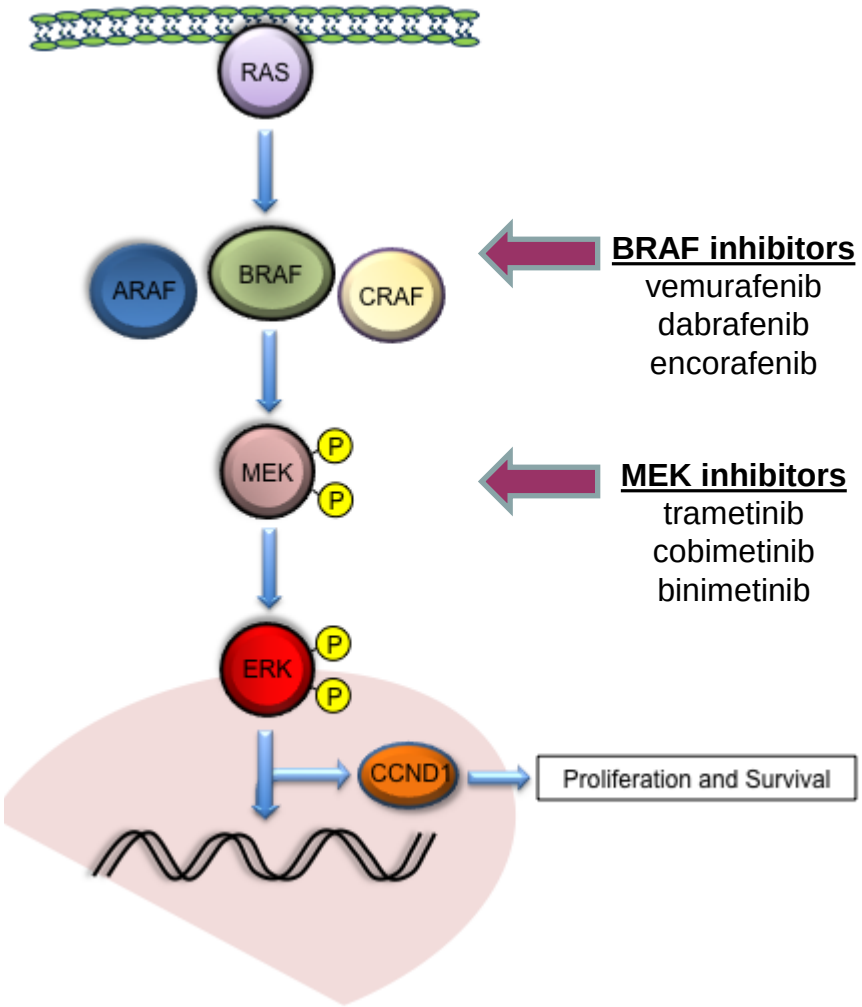


Shi H et al. Cancer Discovery 2014; 4:80-93

Rationale for the combination of BRAF and MEK inhibitors

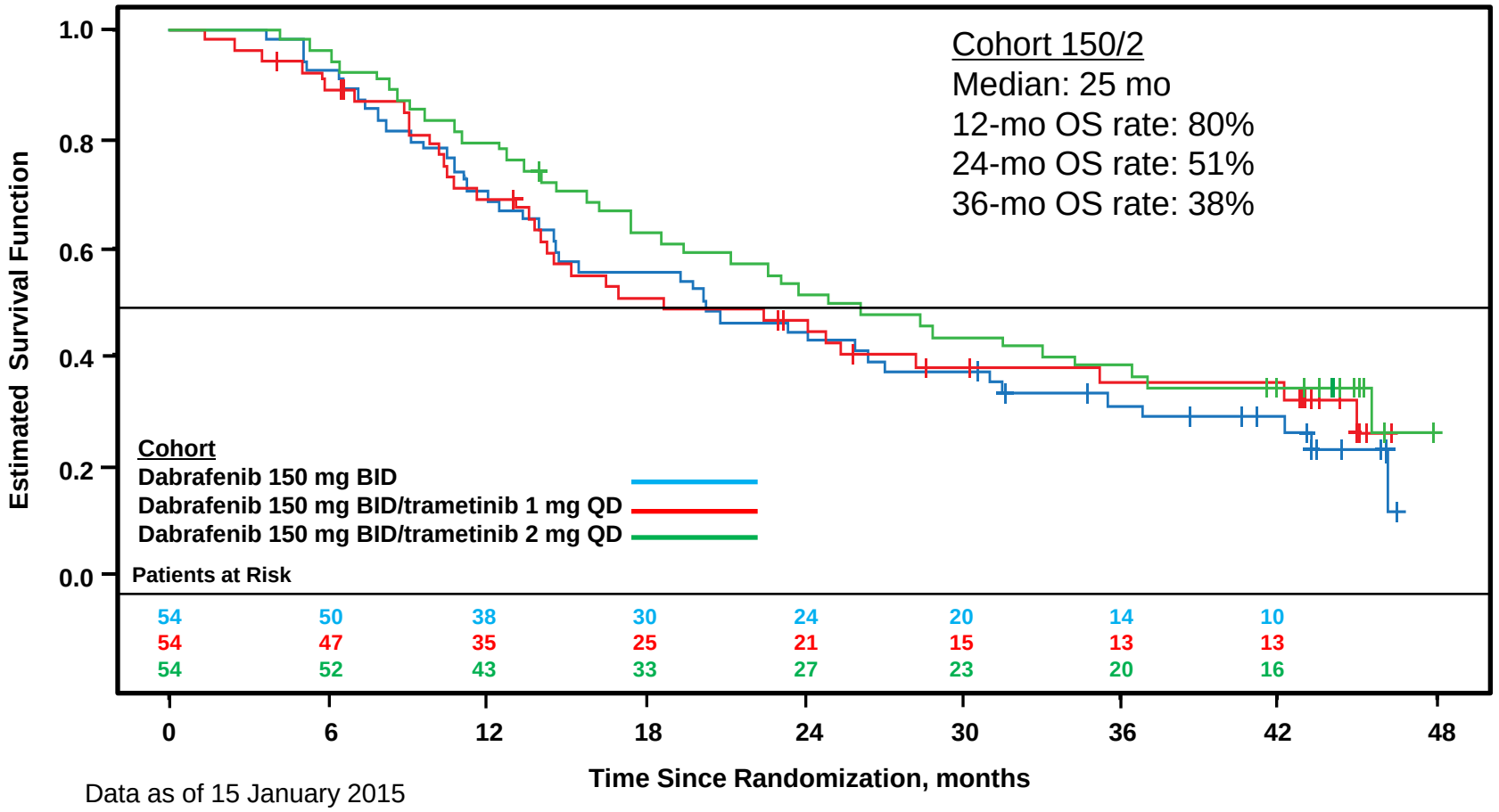
Rationale

- Most common mechanism of acquired resistance to vemurafenib is MAPK reactivation through MEK[1,2]
- MEK + BRAF inhibition prevents the development of acquired resistance in preclinical models[3]
- MEK + BRAF inhibition (dabrafenib + trametinib[4] phase 3 and vemurafenib + cobimetinib phase 1/2)[5] improved response rates and PFS in BRAF inhibitor–naive melanoma patients
- Reduced incidence of hyperproliferative lesions by blocking paradoxical activation of the MAPK pathway from RAF inhibition[6]



1. Shi H *et al*. Cancer Discov. 2014.
2. Trunzer K *et al.* J Clin Oncol. 2013
3. Paraiso K *et al*. Br J Cancer. 2010
4. Long GV *et al*. J Clin Oncol. 2014.
5. Ribas A *et al*. Lancet Oncol. 2014.
6. Su F *et al.* New Engl J Med 2012.

Results from the fase I/II dabrafenib/ trametinib

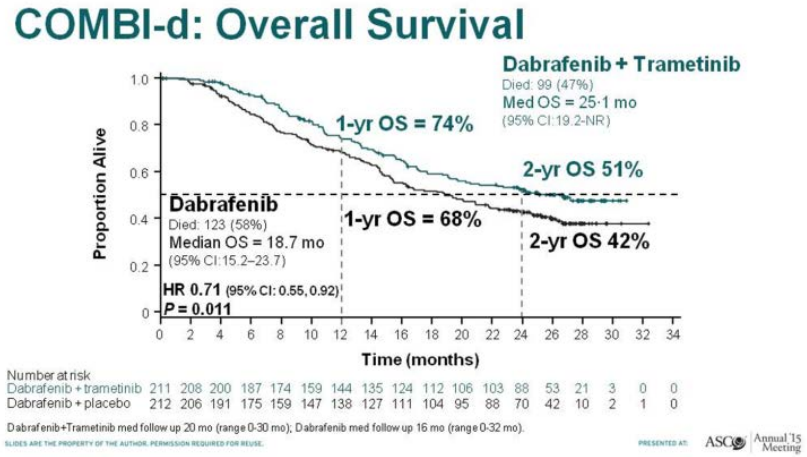


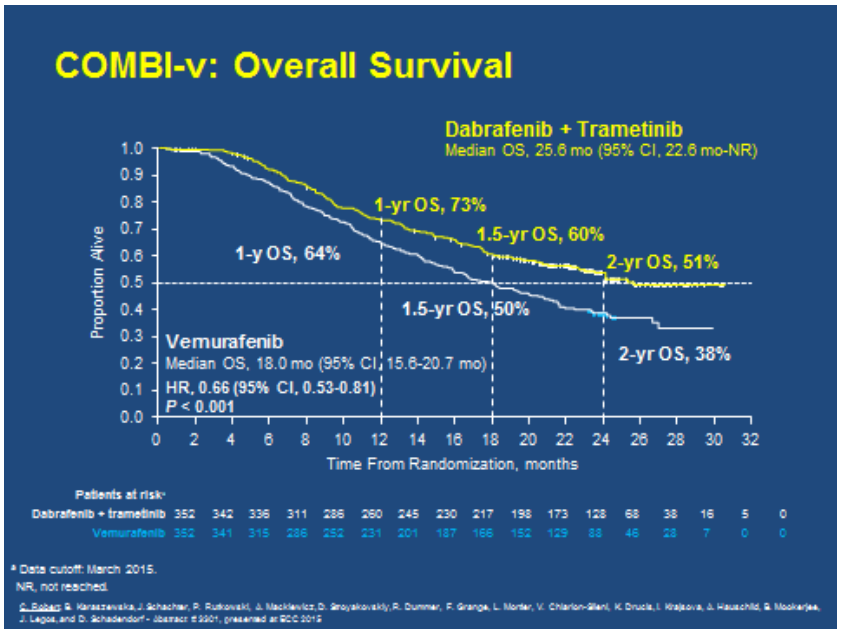
Data as of 15 January 2015

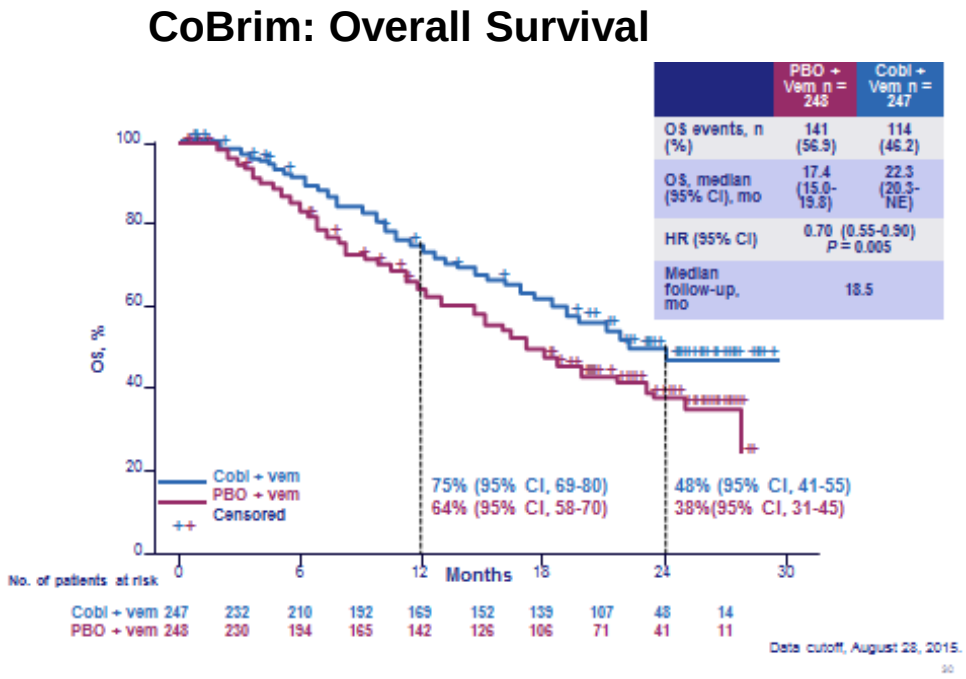
- Longer follow-up reveals median OS of 25 months for patients in the 150/2 cohort. Landmark OS results for the 150/2 cohort: 1 year, 80%; 2 year, 51%; 3 year, 38%. Normal LDH and fewer disease sites were associated with prolonged survival. Prior immunotherapy had no effect on OS. No new safety signal observed and no increase in cuSCC cases or treatment-emergent malignancies

Daud A, *et al.* ASCO 2015, J Clin Oncol 2015;33 (suppl; abstr 9036) Poster 279 (with permission of Daud A.)

BRAFì + MEKì: OS data from phase III clinical trial

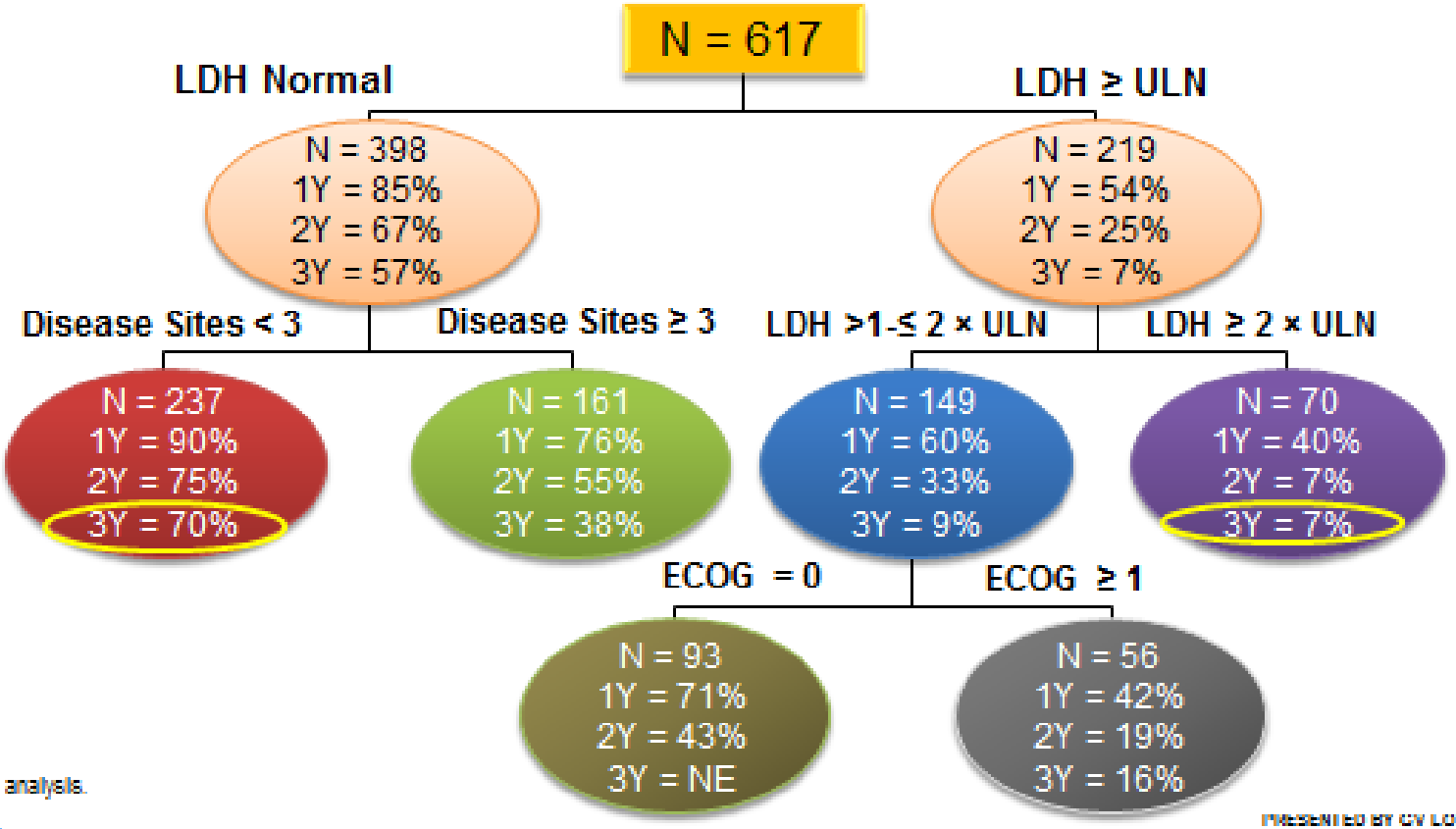






1. Long G *et al*. Lancet. 2015.
2. Robert C *et al*. ECC. 2015.
3. Atkinson V *et al.* SMR 2015.

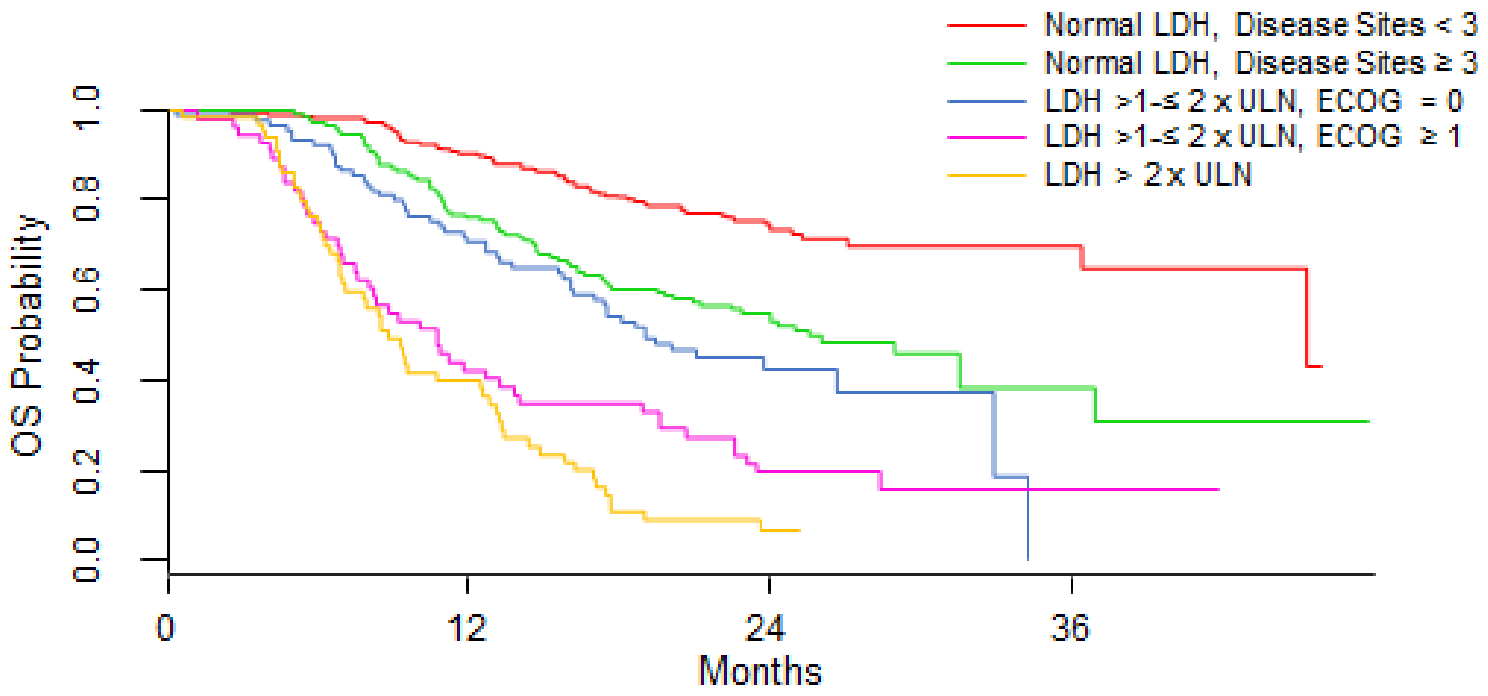
Five Baseline Factors Influenced OS[a]



[a] Regression tree analysis.

NE, not estimable.

OS by LDH, Number of Disease Sites, and ECOG[a]



No. at risk				
Normal LDH, Disease Sites < 3	237	206	103	14
Normal LDH, Disease Sites ≥ 3	161	119	58	5
LDH > 1 x ULN, ECOG = 0	93	61	15	0
LDH > 1 x ULN, ECOG ≥ 1	56	23	9	1
LDH > 2 x ULN	70	22	1	0

[a] Factors identified by the regression tree analysis.

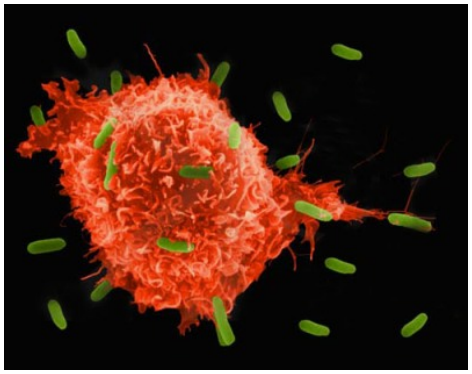
Immunotherapy

The potential of I-O therapies

- I-O therapies are being investigated for their potential to provide long-term survival in patients with various solid or haematologic malignancies[1–4]

1. Finn OJ. Ann Oncol 2012;23(suppl 8):viii6–viii9; 2. Eggermont AM. Ann Oncol 2012;23(suppl 8):viii53–viii57; 3. Hodi FS, et al. N Engl J Med 2010;363:711–723; 4. Kantoff PW, et al. N Engl J Med 2010;363:411–422; 5. Brahmer JR, et al. IASCL 15th WCLC 2013; Abs MO18.03
6. Hamid O, et al. N Eng J Med 2013;369:134–144

Anti-CTLA-4 and anti-PD-1/PD-L1 mechanism of action



Immune System

=

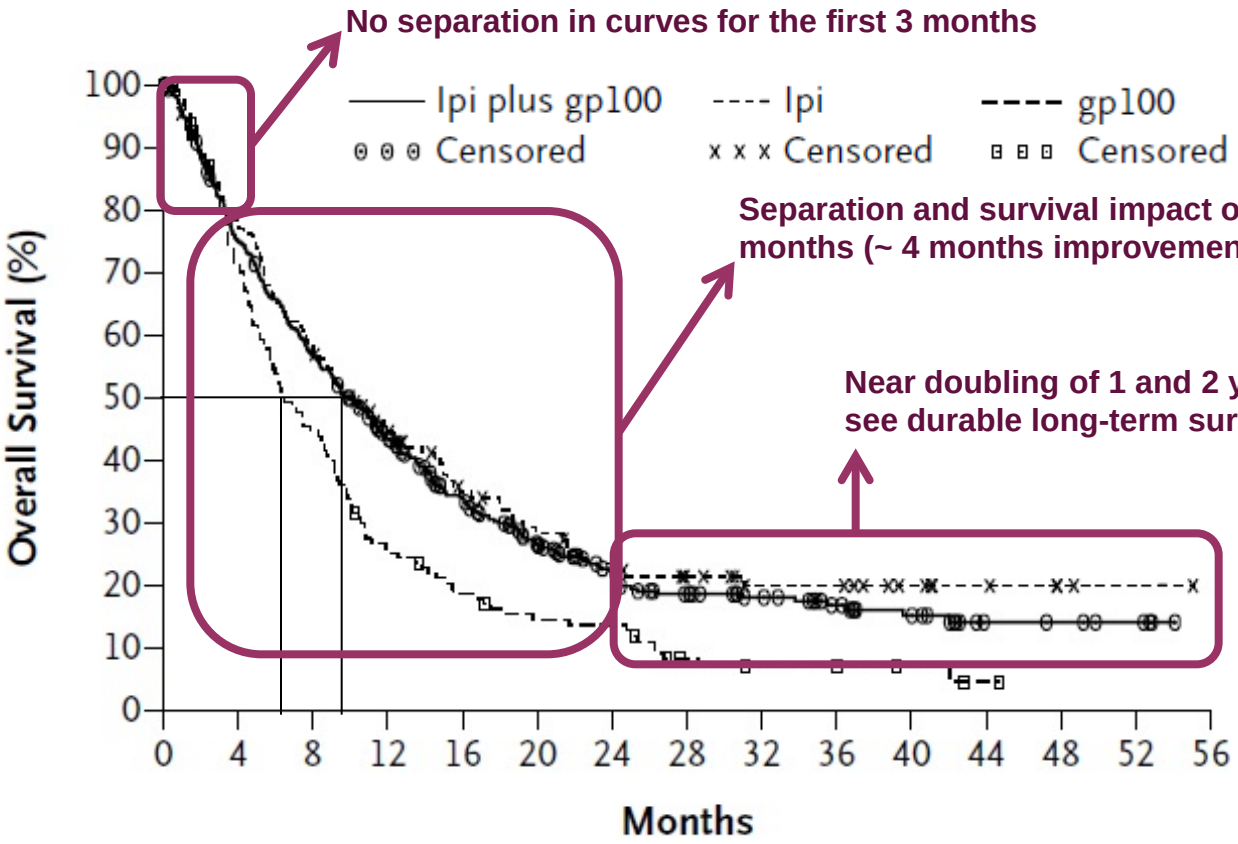
T-cell activation

Antigens

Regulatory molecules (CTLA-4, PD-1)

The MDX010-020 study: randomized phase III, double blinded, three arms study which compared ipilimumab + gp100 vs ipilimumab + placebo vs gp100 + placebo

N. 676 pretreated advanced melanoma patients were enrolled.
Randomization was 3:1:1 and the primary endpoint was OS

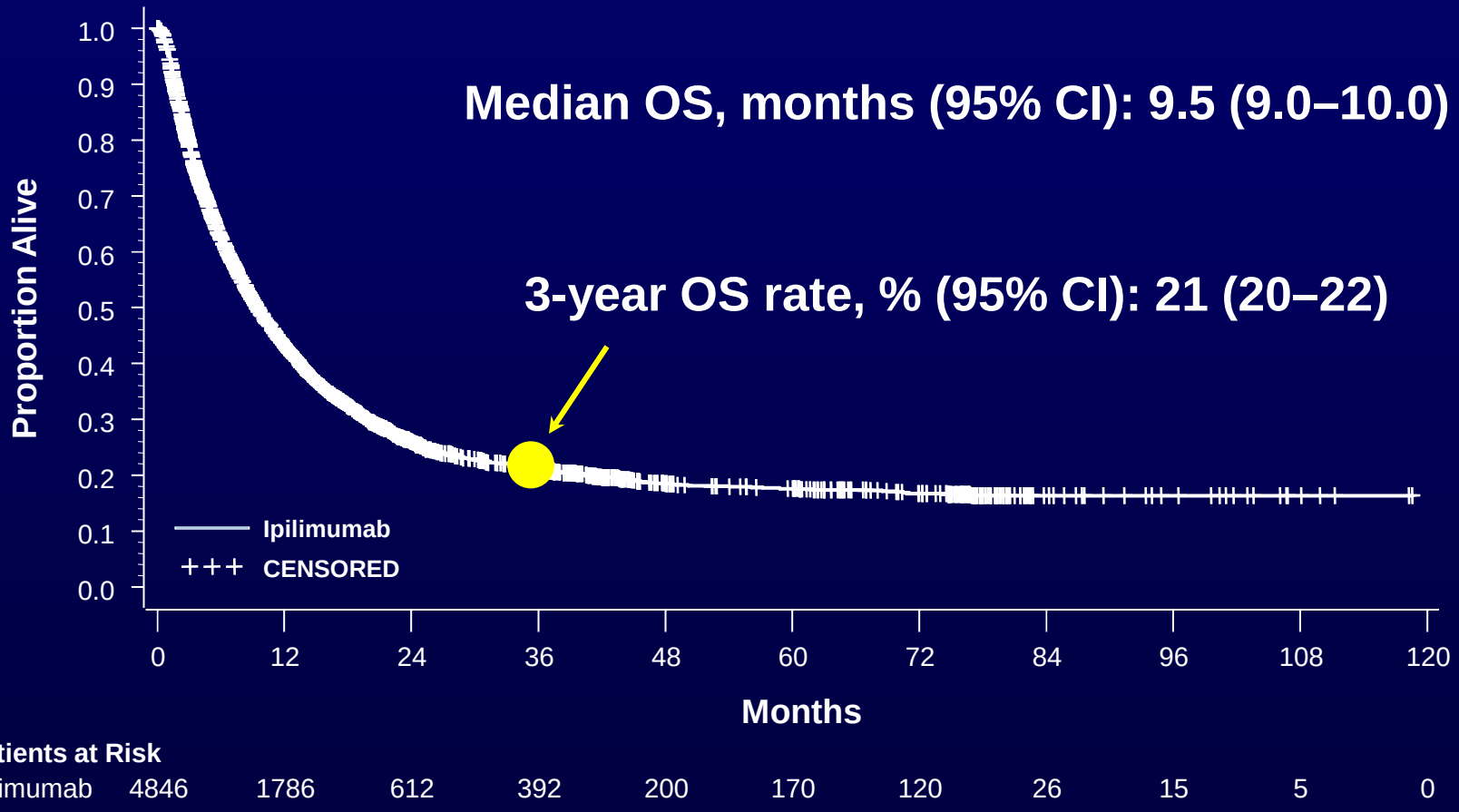


Median OS

ipi + gp100 = 10,0 mos
Ipi + placebo = 10,1 mos
gp100 + placebo = 6,4 mos

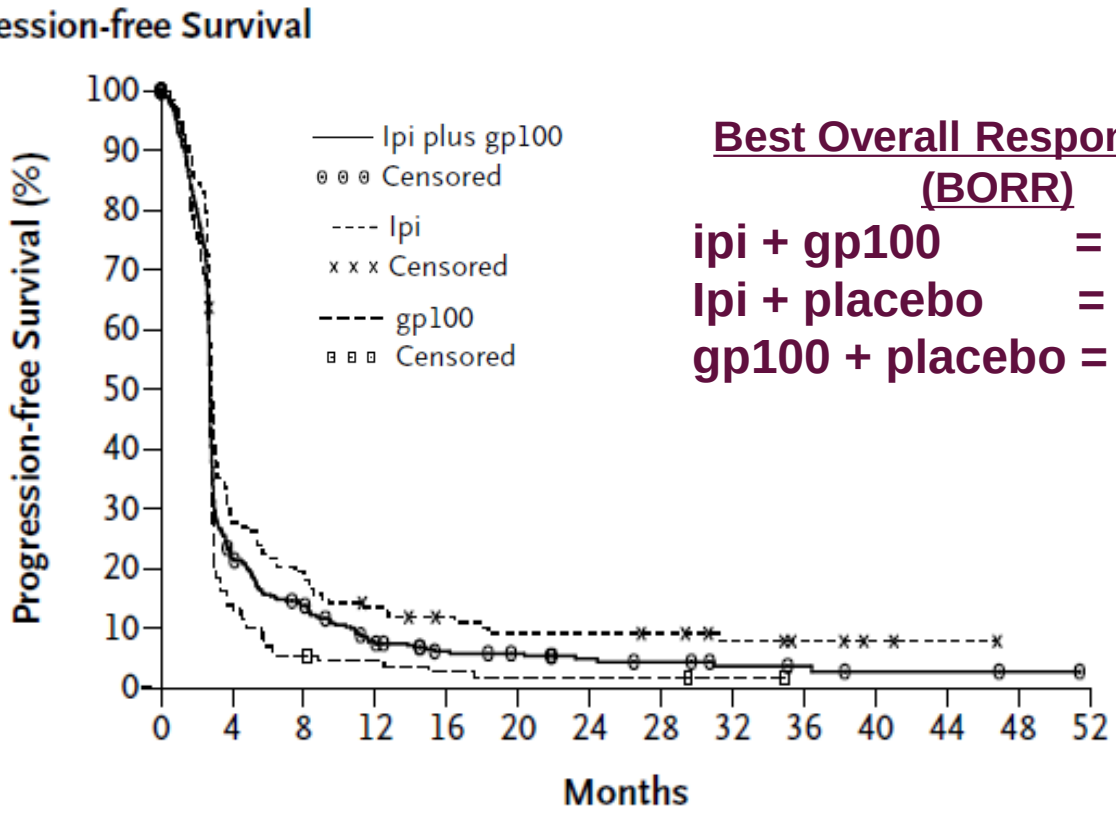
Hodi et al New Engl J Med 2010; 363:711-23

Pooled OS Analysis Including EAP Data: 4846 Patients



Schadendorf et al. JCO 2015

No effect in surrogate endpoints



Best Overall Response Rate (BORR)

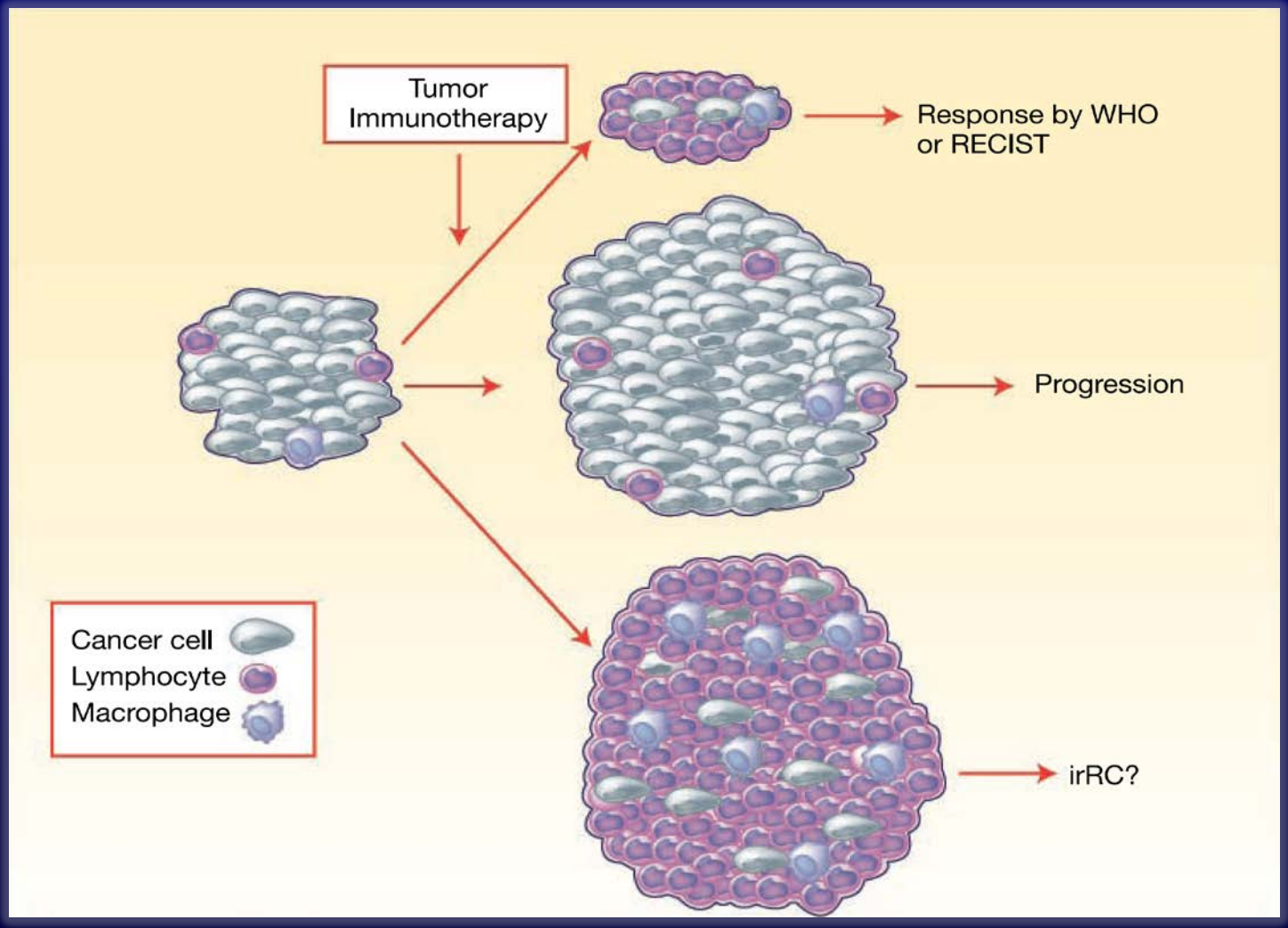
ipi + gp100 = 5,7 %
Ipi + placebo = 10,9 %
gp100 + placebo = 1,5 %

No. at Risk

Ipi plus gp100	403	85	52	27	17	14	10	8	5	4	2	2	1	0
Ipi	137	37	26	17	13	10	10	9	6	4	2	1	0	0
gp100	136	18	7	5	3	2	2	2	1	0	0	0	0	0

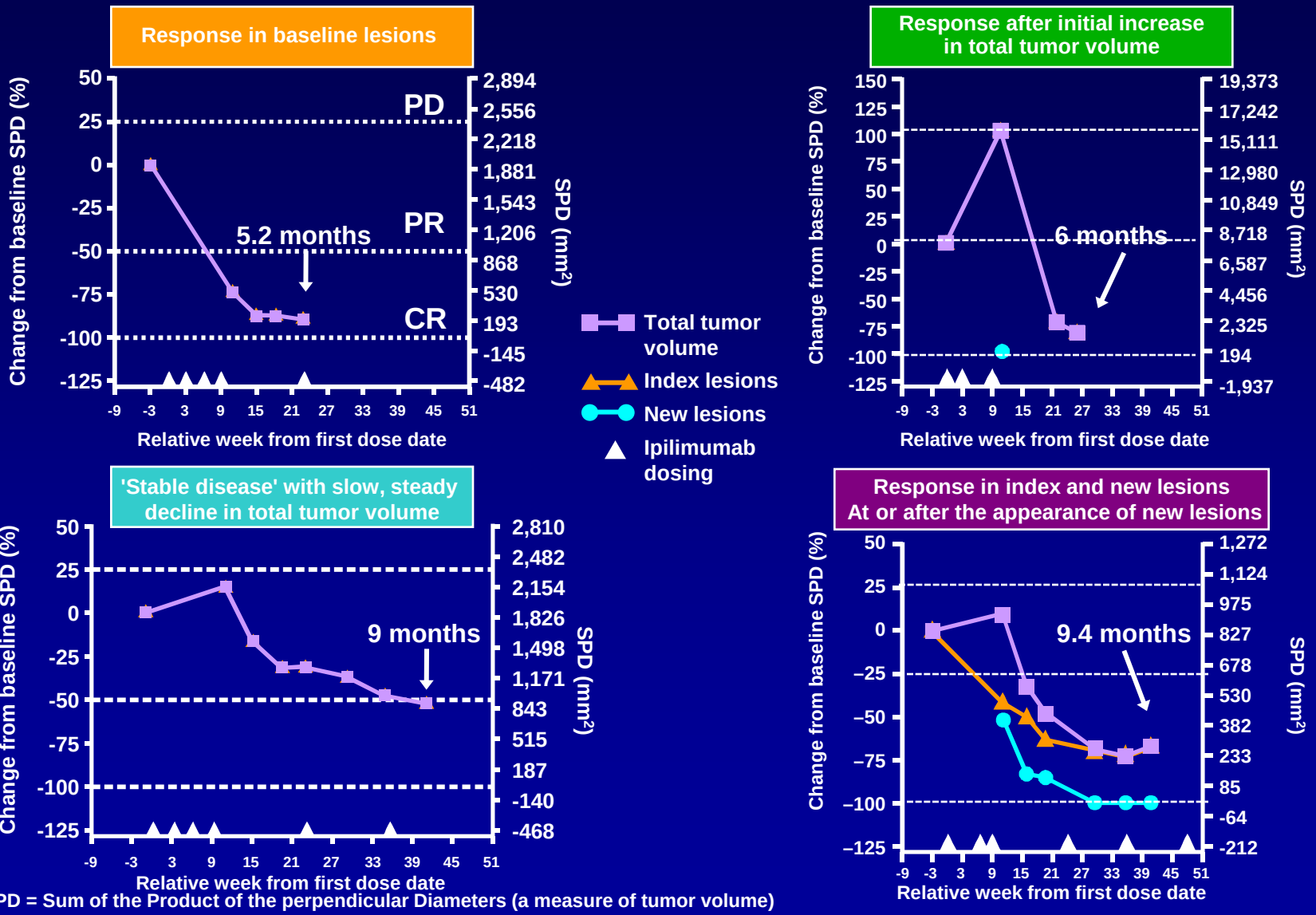
Hodi et al New Engl J Med 2010; 363:711-23

New response criteria about immunotherapy ?



Ribas A et al. Clin Cancer Res 2009;15(23):7116–8) 2009;15: 7116-8.

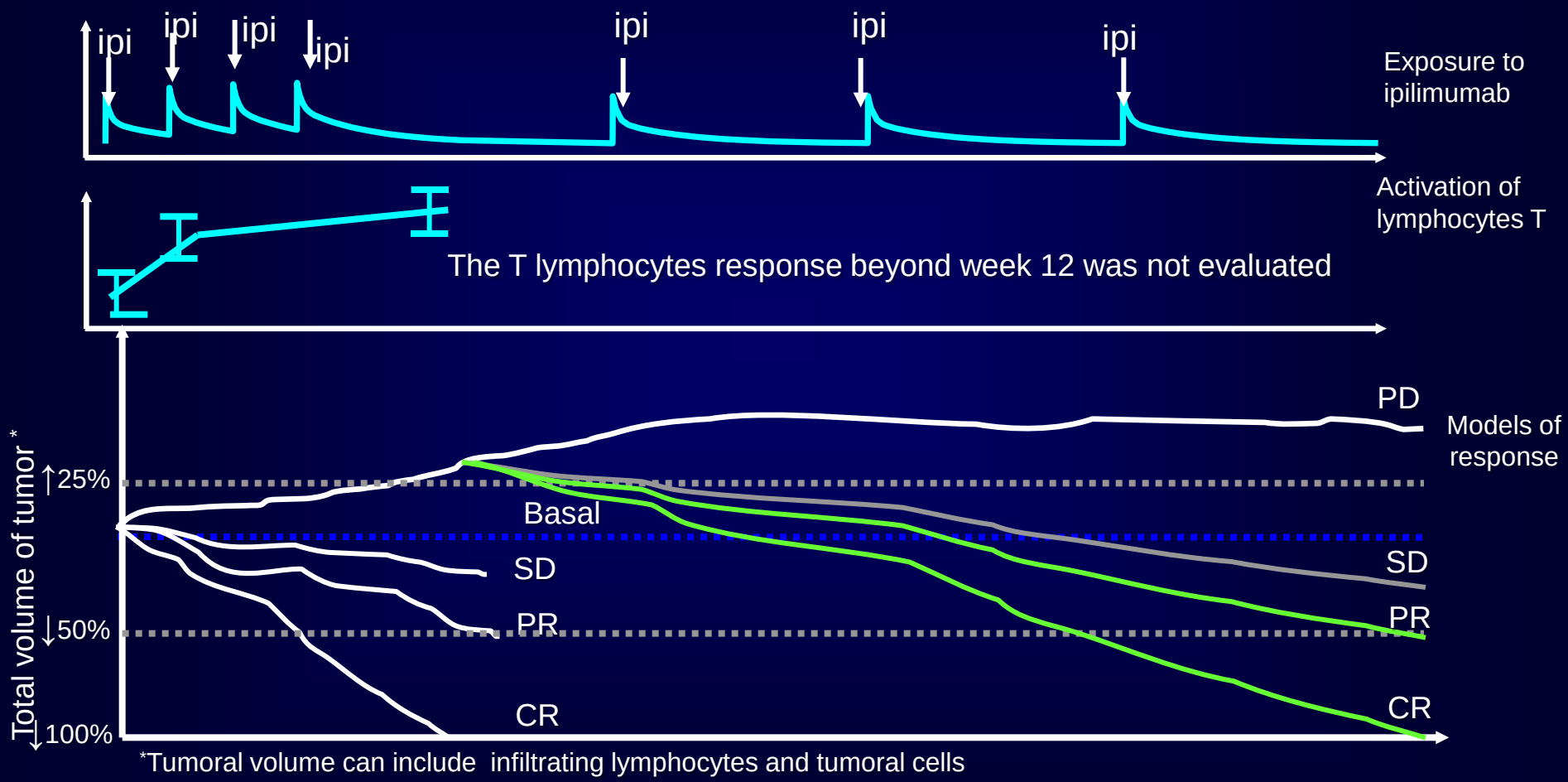
Example Response Patterns



SPD = Sum of the Product of the perpendicular Diameters (a measure of tumor volume)

Wolchok et al. Clin Cancer Res 2009;15(23):7412-20

Immunotherapy: evolution of the antitumoral effect



The activation and proliferation of the immune-system cells had early

The measurable clinical effect occurs in variable times

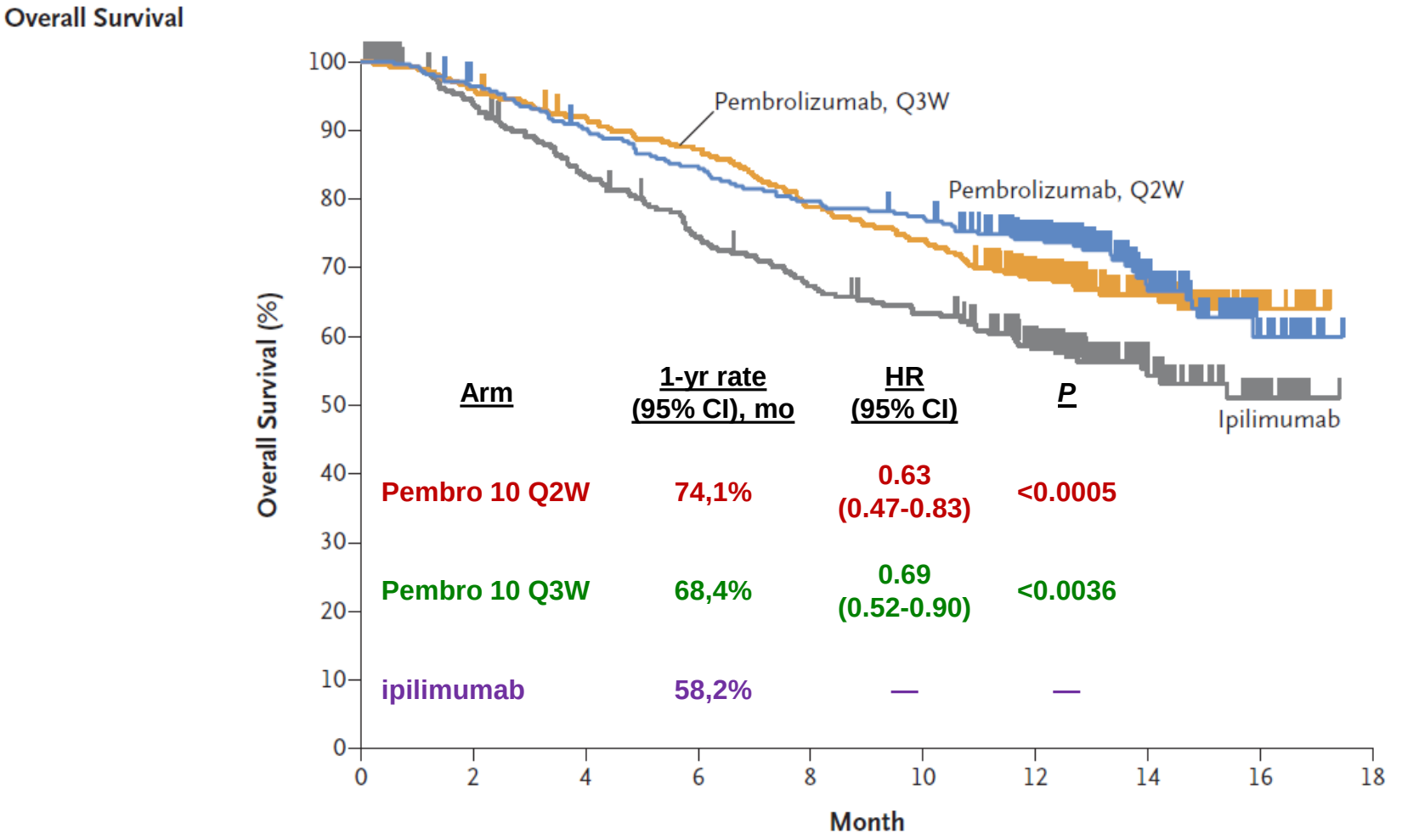
The NEW ENGLAND JOURNAL of MEDICINE

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., Michal Lotem, M.D., James Larkin, M.D., Ph.D., Paul Lorigan, M.D., Bart Neyns, M.D., Ph.D., Christian U. Blank, M.D., Ph.D., Omid Hamid, M.D., Christine Mateus, M.D., Ronnie Shapira-Frommer, M.D., Michele Kosh, R.N., B.S.N., Honghong Zhou, Ph.D., Nageatte Ibrahim, M.D., Scot Ebbinghaus, M.D., and Antoni Ribas, M.D., Ph.D., for the KEYNOTE-006 investigators*

Keynote 006: pembrolizumab vs ipilimumab OS



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

Robert et al. NEJM 2015

Results from CA209-003 and Ca209-037 studies

Unmet need in metastatic melanoma

- > 50% patients have BRAF wild-type tumor[1]
- Only ipilimumab has OS benefit in this group of patients[2,3]

Nivolumab

- A fully human anti-PD-1 monoclonal antibody[4] with clinical benefit[5–8]

Phase 1 Study 003[5,6]

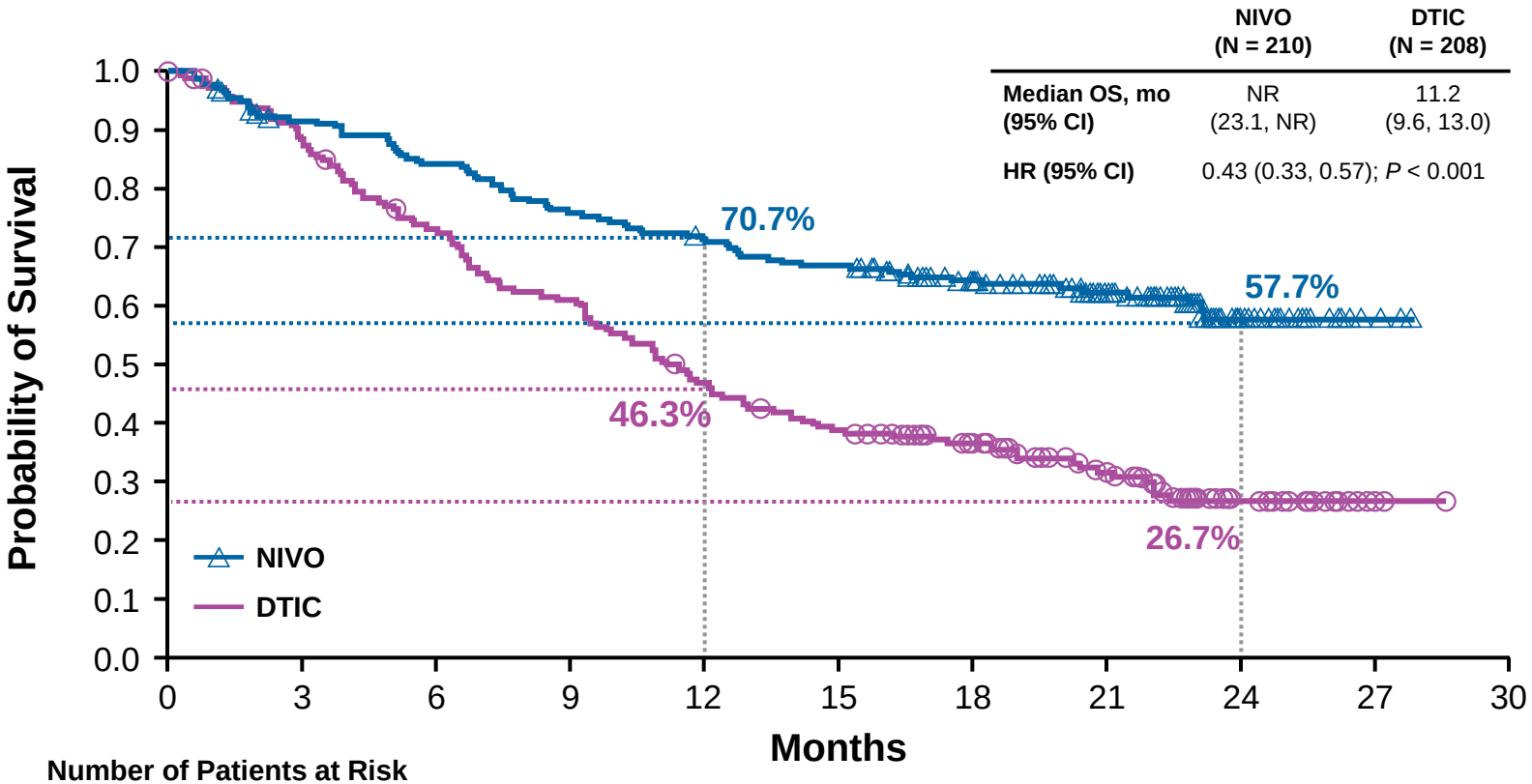
	1-Year	2-Year	3-Year	4-Year
OS	63%	48%	42%	32%

Phase 3 Study CheckMate-037[7,8]

	Nivolumab 3 mg/kg Q2W	Investigator's Choice of Chemotherapy
ORR	32%	11%

1. Long et al. *J Clin Oncol* 2011; 2. Hodi et al. *N Engl J Med* 2010; 3. Robert et al. *N Engl J Med* 2011; 4. Wang et al. *Cancer Immunol Res* 2014; 5. McDermott et al. ESMO 2014; 6. Hodi et al. SMR 2014; 7. Weber et al. ESMO 2014; 8. D'Angelo et al. SMR 2014.

Overall Survival – NIVO vs DTIC



Number of Patients at Risk

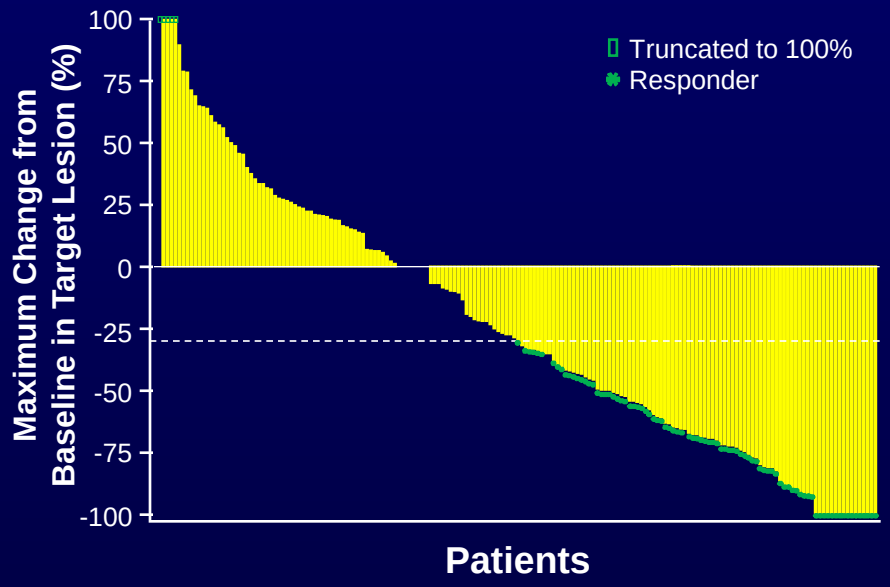
NIVO	210	186	171	154	143	135	111	81	30	4	0
DTIC	208	179	146	122	92	76	60	38	16	1	0

- Median follow-up was 18.5 months for NIVO and 10.9 months for DTIC
- Database lock was on July 15, 2015

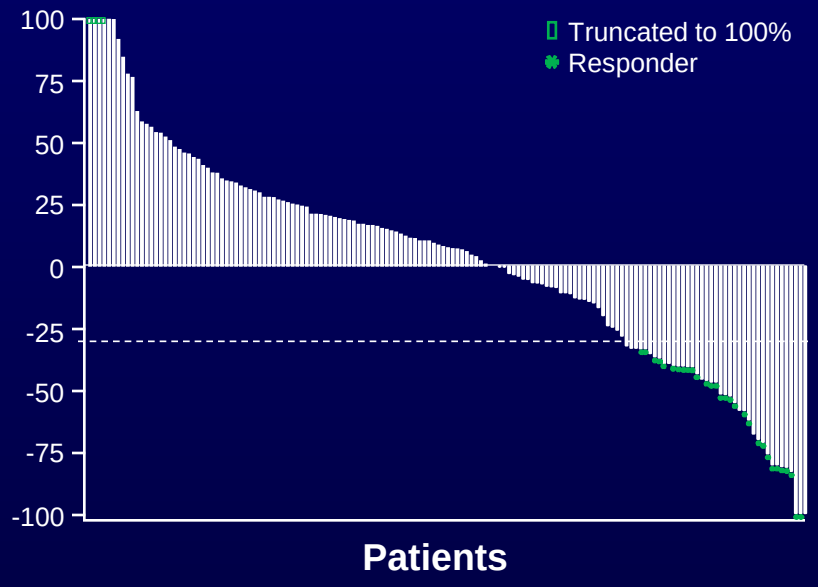
CI = confidence interval, HR = hazard ratio; mo = month

Ca209-066: Objective Response by RECIST v1.1

Nivolumab
ORR 40% (95% CI, 33–47%)



Dacarbazine
ORR 14% (95% CI, 10–19%)



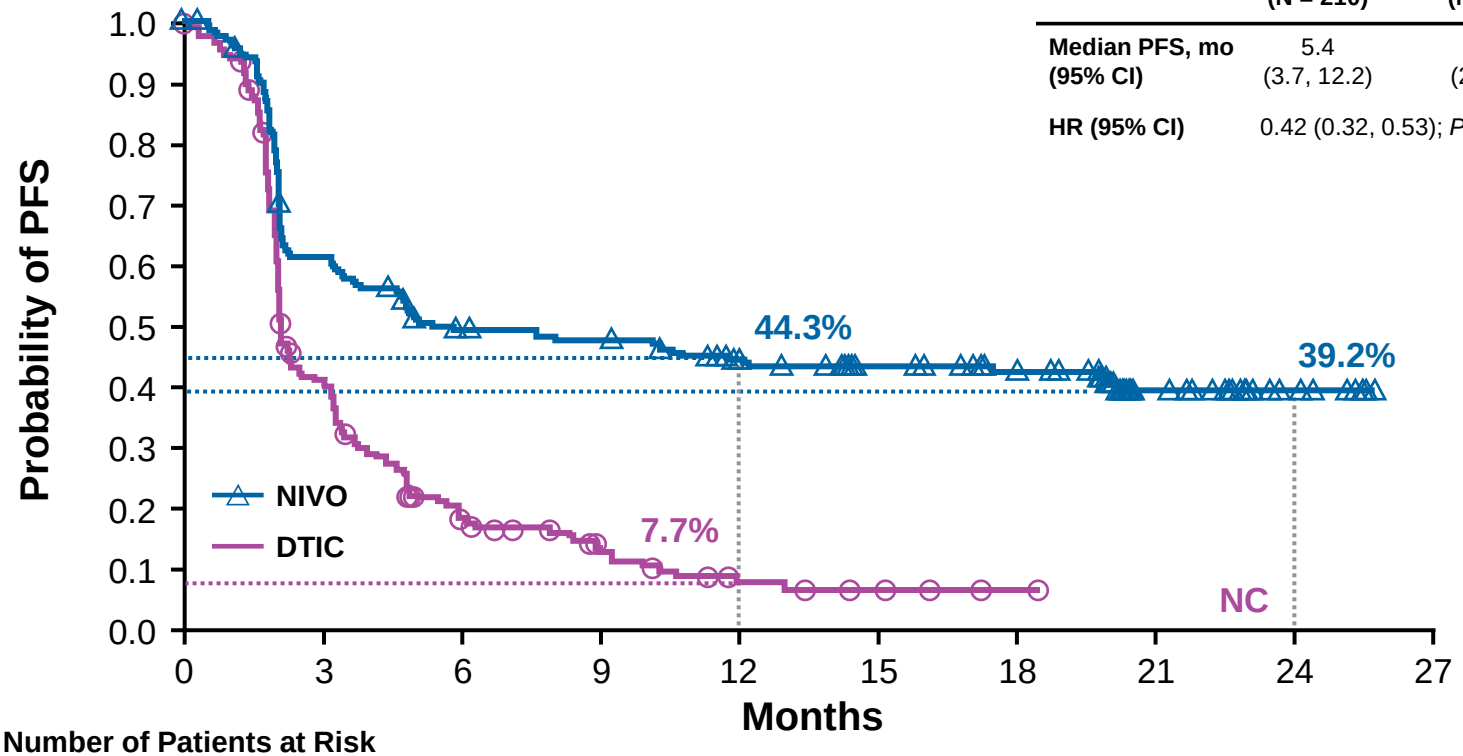
Odds ratio for response 4.06 (95% CI, 2.52–6.54; *P* < 0.0001)

Showing only patients with both baseline and at least one post-baseline measurement of target lesion.

Robert et al. N Engl J Med 2015 Jan 22;372(4):320-30

Progression-Free Survival – NIVO vs DTIC

	NIVO (N = 210)	DTIC (N = 208)
Median PFS, mo (95% CI)	5.4 (3.7, 12.2)	2.2 (2.1, 2.5)
HR (95% CI)	0.42 (0.32, 0.53); *P* < 0.0001	

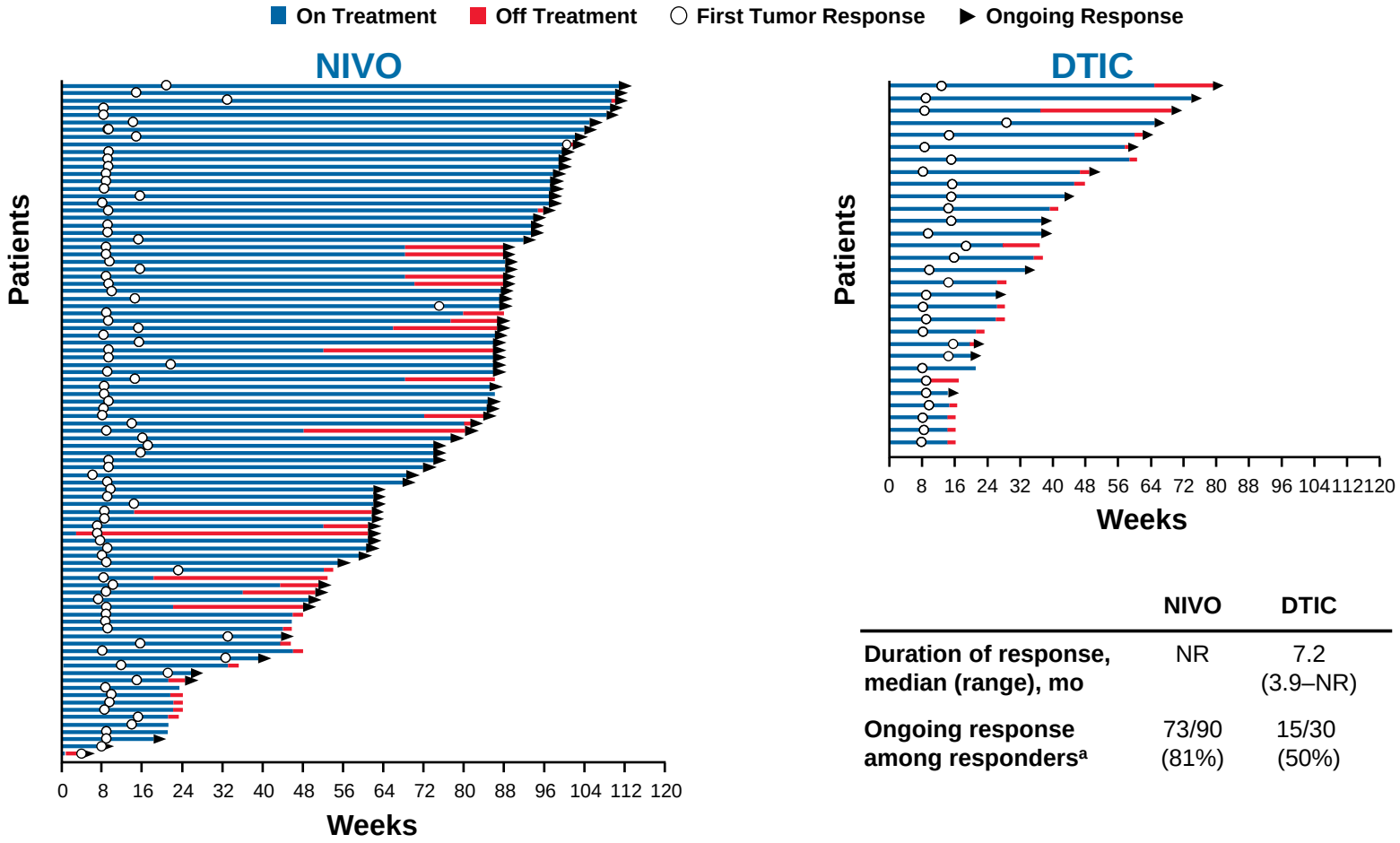


Number of Patients at Risk

NIVO	210	119	92	88	76	61	52	23	7	0
DTIC	208	75	33	17	7	4	1	0	0	0

CI = confidence interval; HR = hazard ratio; mo = month; NC = not calculated

Time to and Durability of Response

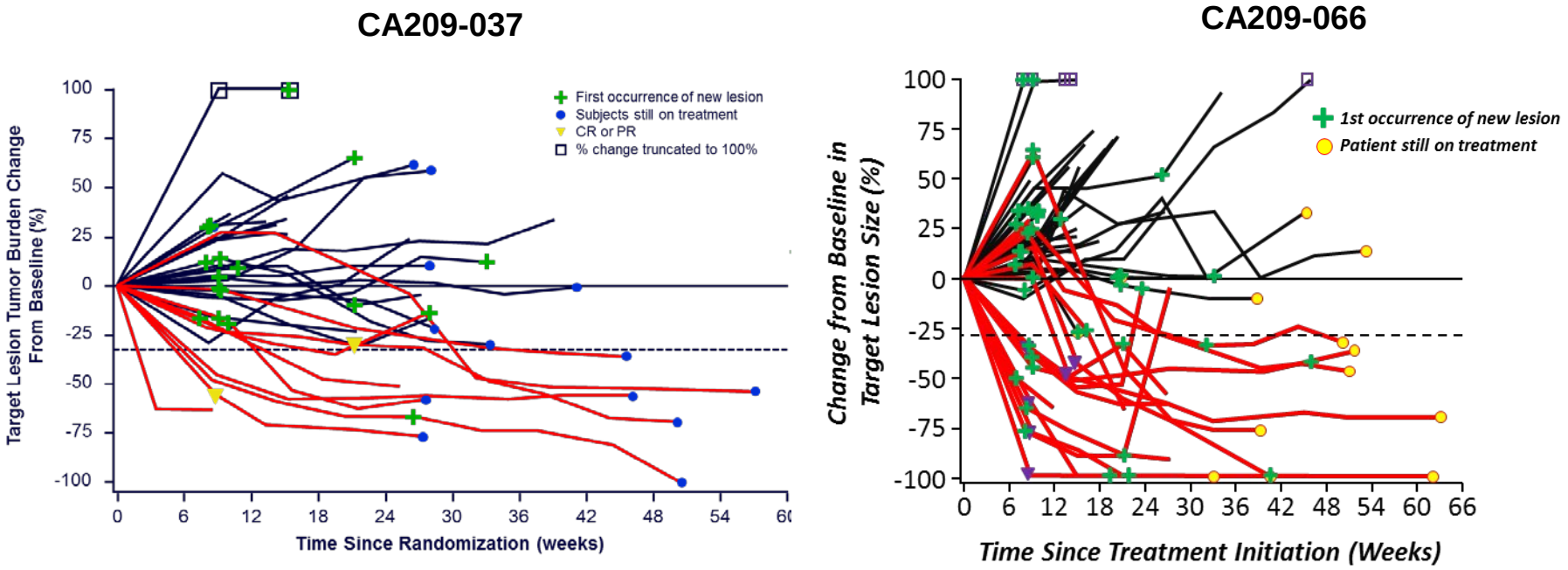


	NIVO	DTIC
Duration of response, median (range), mo	NR	7.2 (3.9–NR)
Ongoing response among responders[a]	73/90 (81%)	15/30 (50%)

[a]At the time of the last follow-up

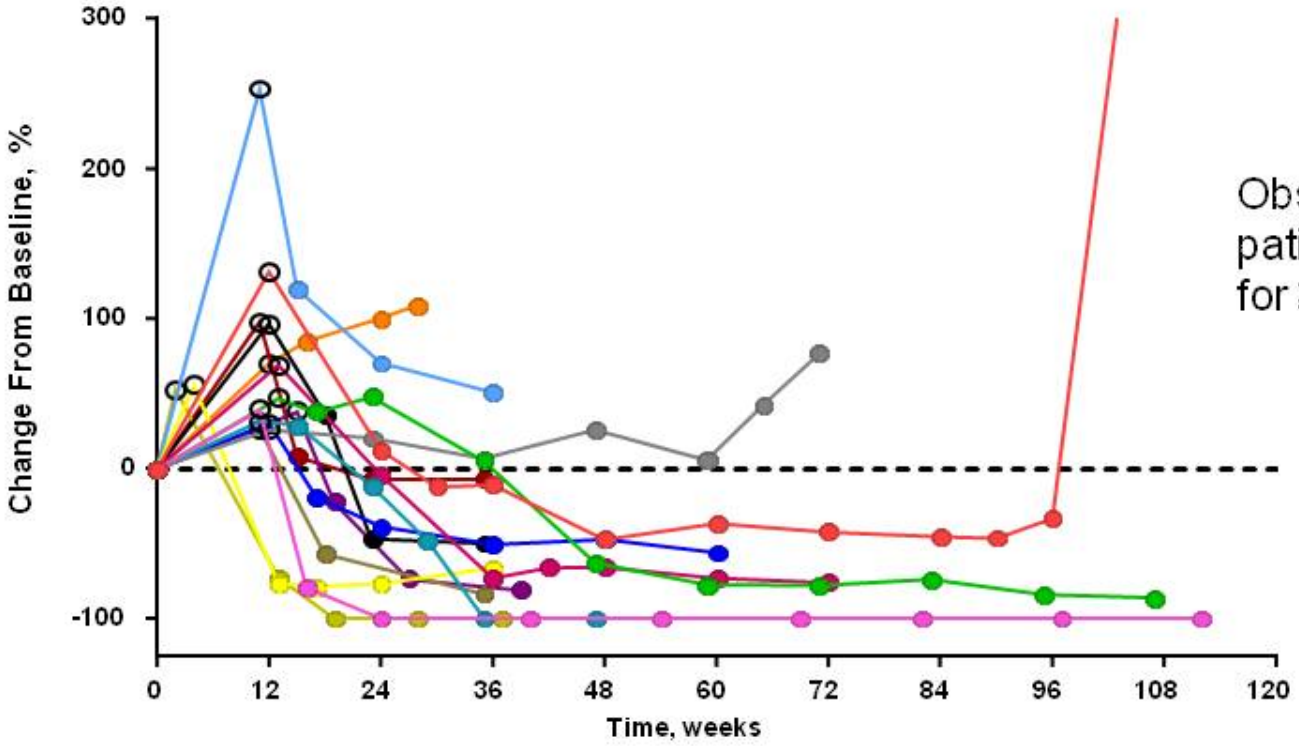
mo = month; NR = not reached

Unconventional responses in patients treated with nivolumab



- In both the two randomised phase III studies (CA209-037 and CA209-066) there was a 8% of patients who progressed according with RECIST v1.1 criteria, but achieved or maintained a ≥ 30% reduction in the target lesion tumour burden ("immune-related, unconventional response pattern")
- For this reason, together the classical RECIST criteria, we must consider immuno-related criteria even for nivolumab treatment

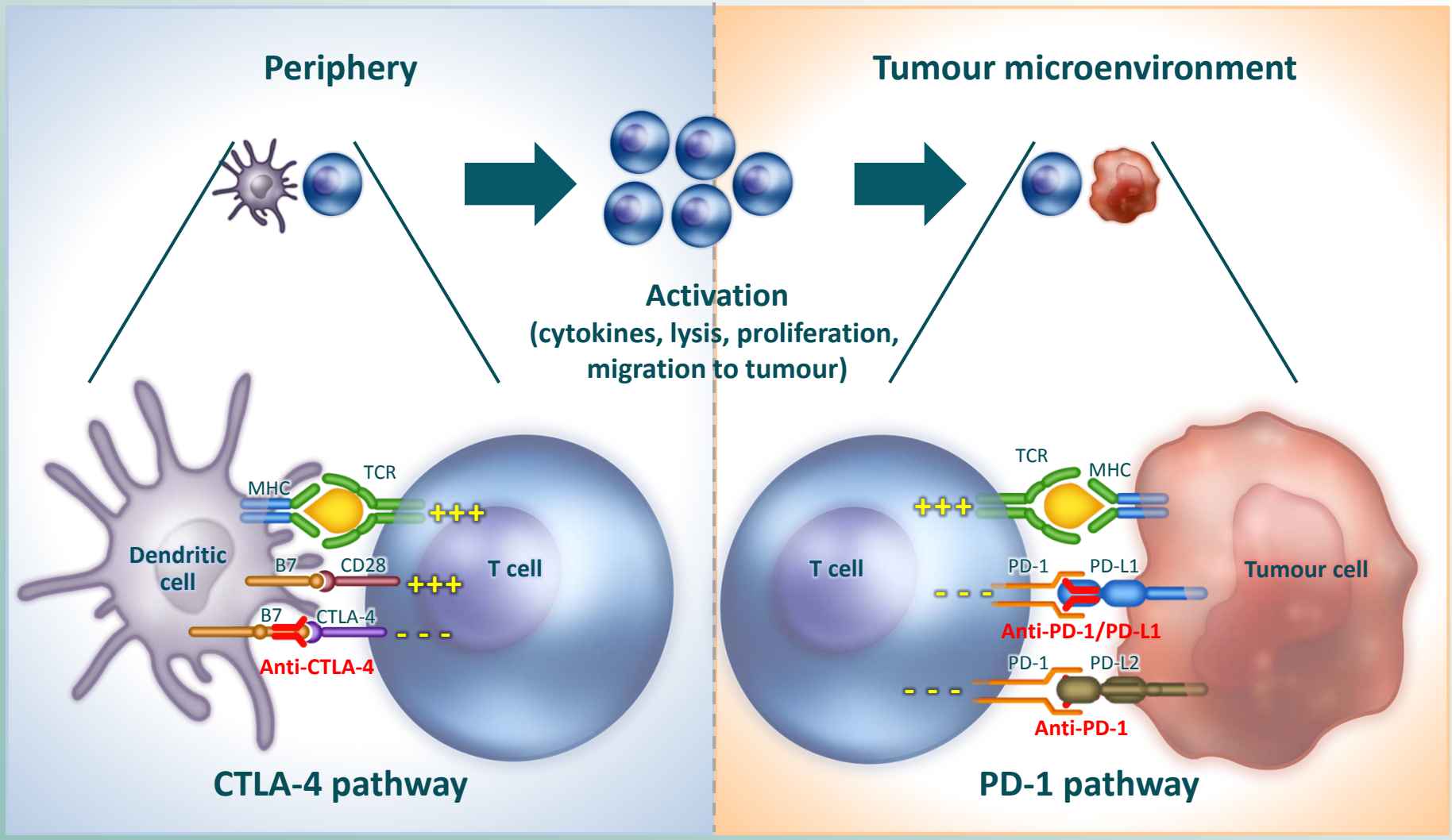
Early Pseudoprogression (irRC, Central Review)



Observed in 15 of 327 (4.6%) patients followed by imaging for ≥28 weeks

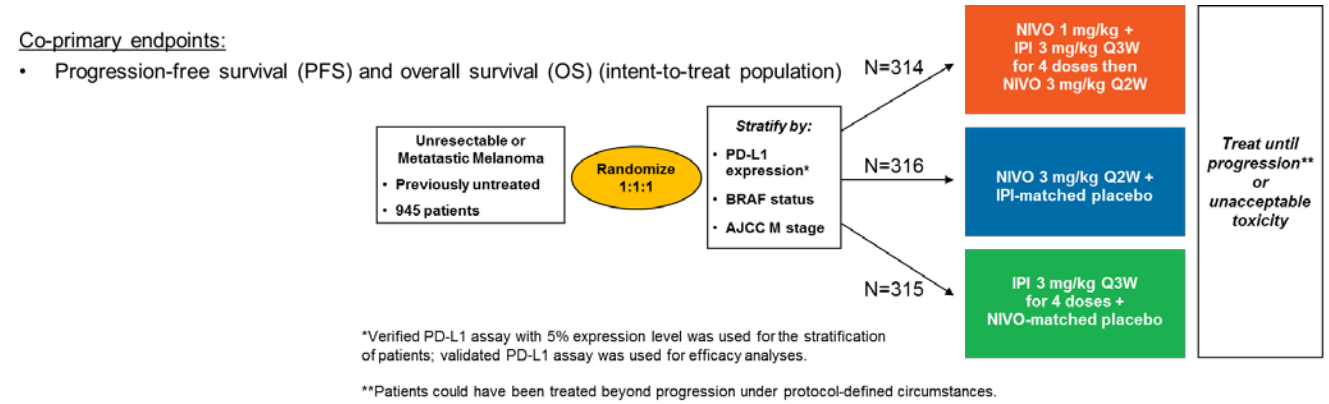
Circles represent times of radiologic assessment. Open circles represent the time at which the 25% threshold for pseudoprogression was crossed.
Analysis cutoff: October 2014

Targeting CTLA-4 and PD-1 pathways



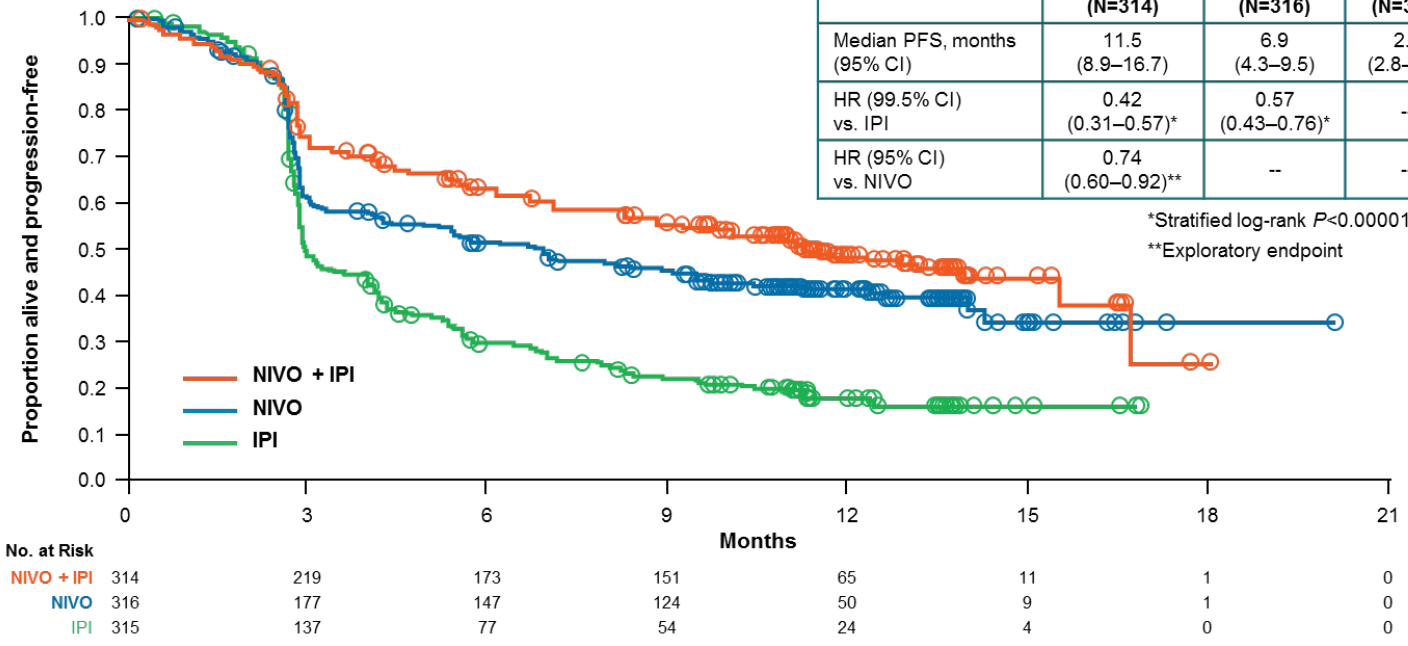
Wolchock J, et al. JCO 2013 Volume 31, Issue 15_suppl ; abstr 9012^

Ipilimumab plus nivolumab - results from the three arms randomized phase 3 study in untreated advanced melanoma patients with ipilimumab/nivolumab or nivolumab alone vs ipilimumab alone (CA209-067): NIVO + IPI resulted in a longer PFS



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

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

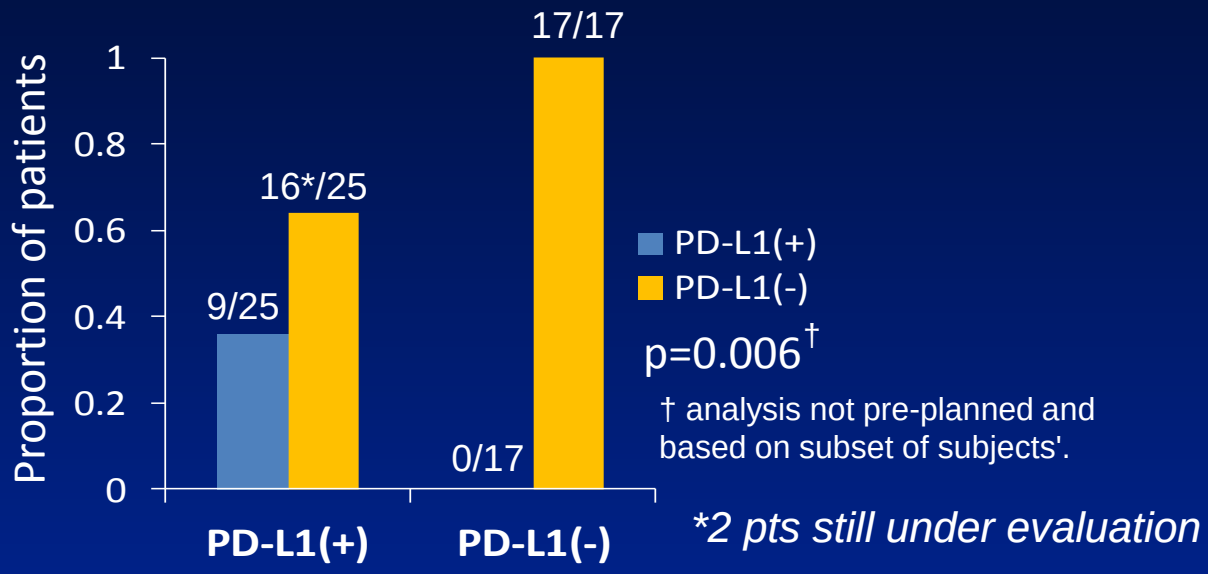


Larkin J et al. N Engl J Med 2015;373:23-34

Candidate Predictive Biomarker: Tumor PD-L1 Expression

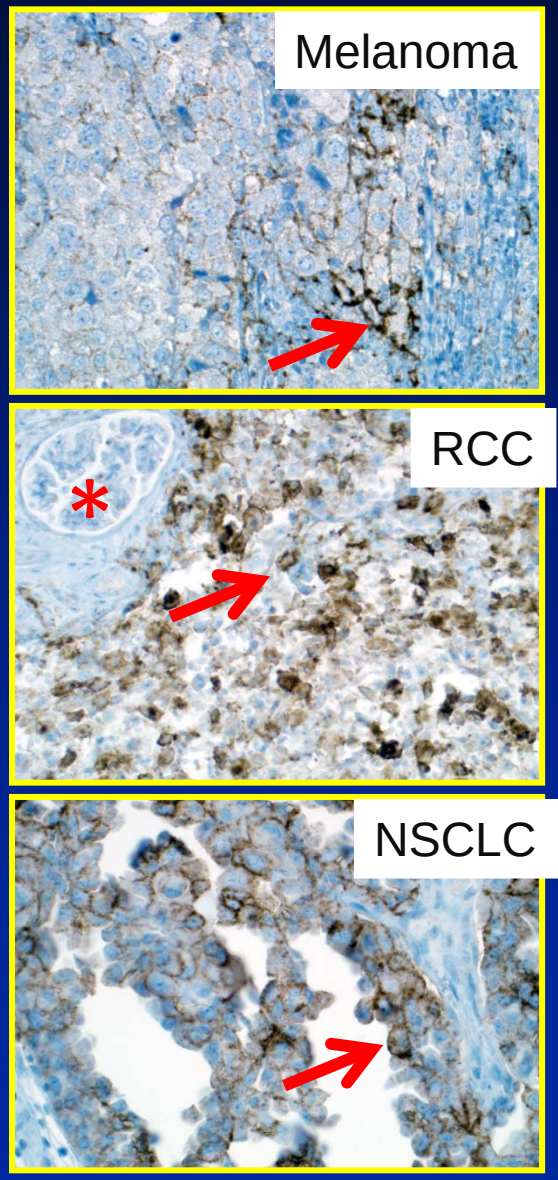
Correlation of PD-L1 expression in pretreatment tumor biopsies with clinical outcomes

42 pts include 18 MEL, 10 NSCLC, 7 CRC, 5 RCC, and 2 CRPC.



**2 pts still under evaluation*

Association Between Pretreatment Tumor PD-L1 Expression and Clinical Response			
Response Status	**PD-L1 Positive no. (%)**	**PD-L1 Negative no. (%)**	**Total no. (%)**
CR/PR	**9 (36)**	**0**	**9 (21)**
Nonresponder	**16* (64)**	**17 (100)**	**33 (79)**
All Patients	**25**	**17**	**42**



Topalian S, et al. NEJM 2012;366:2443-2454.

Tumor PD-L1 Expression as candidate predictive biomarker: response according to PD-L1 expression in NSCLC and melanoma

Subsequent experiences showed that there is a 15-20% of patients PD-L1 negative who respond. Moreover, in the phase I study with the combination ipilimumab/nivolumab, the ORR was similar in both the groups (PD-L1 positive and negative). (*Simeone et al. Melanoma Manag. 2015; 2:41–50*)

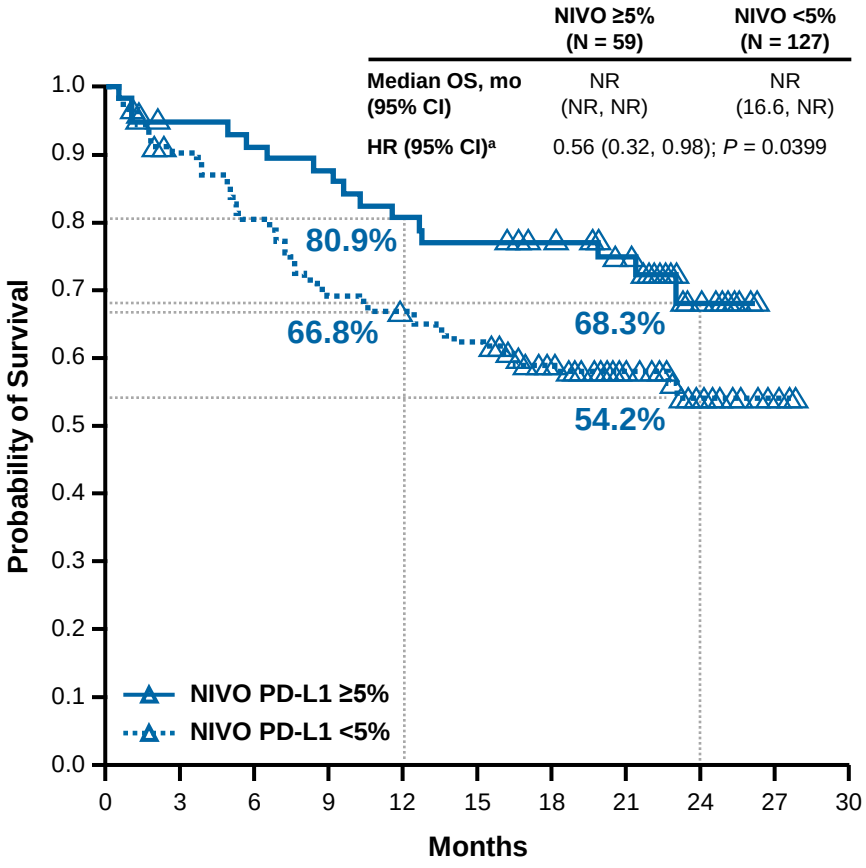
	Tumour	PDL1+ Positive ORR n/N (%)	PDL1- Negative ORR n/N (%)
MPDL3280A (Hamid ASCO 2013)	Melanoma	4/15 (27)	3/15 (20)
Nivolumab (Weber ASCO 2013)	Melanoma	8/12 (67)	6/32 (19)
Nivolumab (Grosso ASCO 2013)	Melanoma	7/16 (44)	3/18 (17)
Nivolumab (Topalian, N Engl J Med, 2012)	NSCLC	9/25 (36)	0/17 (0)
Nivolumab (Antonia, WCLC 2013)	NSCLC	5/31 (16)	4/32 (13)
Pembrolizumab (Garon, WCLC 2013)	NSCLC	4/7 (57)	2/22 (9)
MPDL3280A3 (Horn, WCLC 2013)	NSCLC	8/26 (31)	4/20 (20)
Nivolumab/ Ipilimumab (Callahan ASCO 2013)	NSCLC	4/10 (40)	8/17 (47)

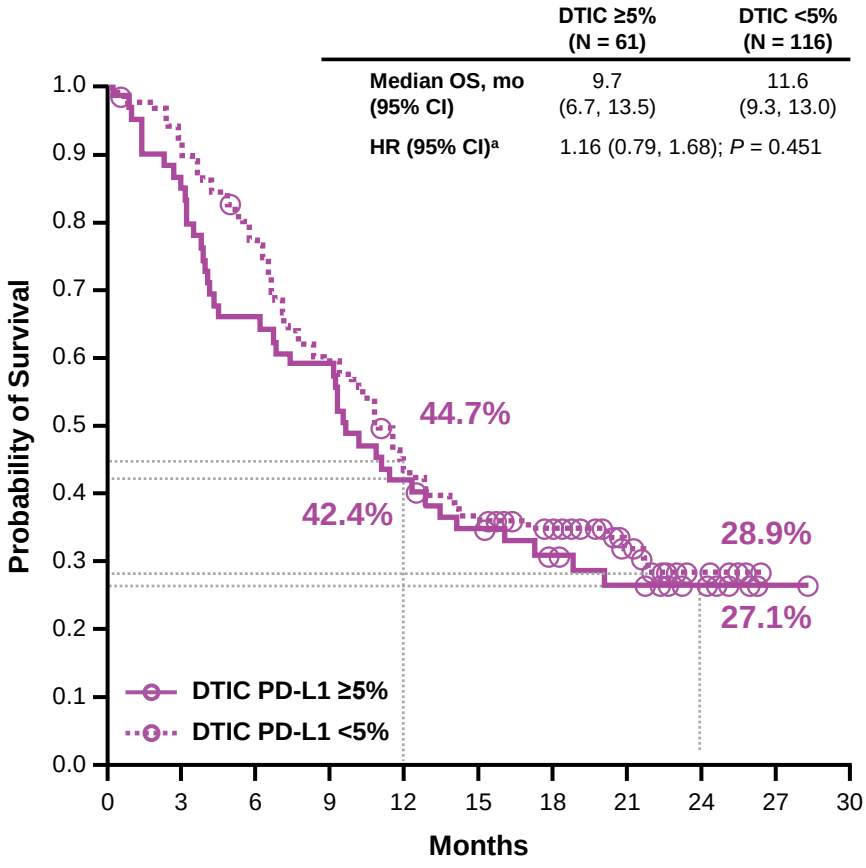
Key questions

- Variability in tissue collection timing, cell sampling, types of assay, IHC criteria

1. Antonia SJ, et al. Poster presentation at WCLC 2013. J Thorac Oncol 2013;8(Suppl 2):abstract: P2.11-035; 2. Garon EB, et al. Oral presentation at WCLC 2013. J Thorac Oncol 2013;8(Suppl 2):abstract: MO18.02; 3. Horn L, et al. Mini-Oral presentation at WCLC 2013. J Thorac Oncol. 2013;8(Suppl 2):abstract: MO18.01. Bottom table Presented by: Walter J. Urba, MD, PhD

OS by PD-L1 expression level (5%)



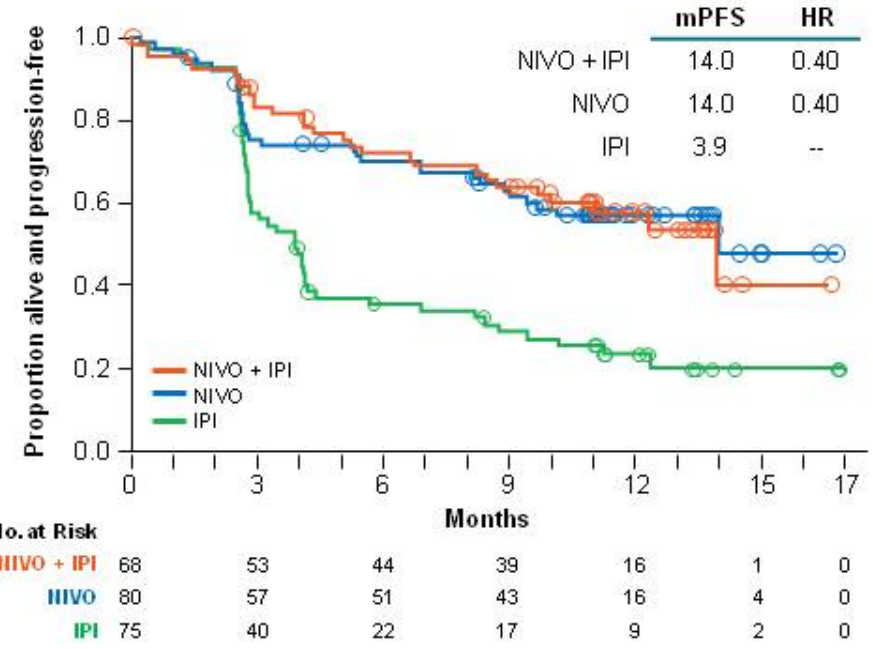


[a]Hazard ratios expressed as PD-L1 ≥5% over PD-L1 <5%

CI = confidence interval; HR = hazard ratio; mo = month; NR = not reached

PFS by PD-L1 Expression Level (5%)

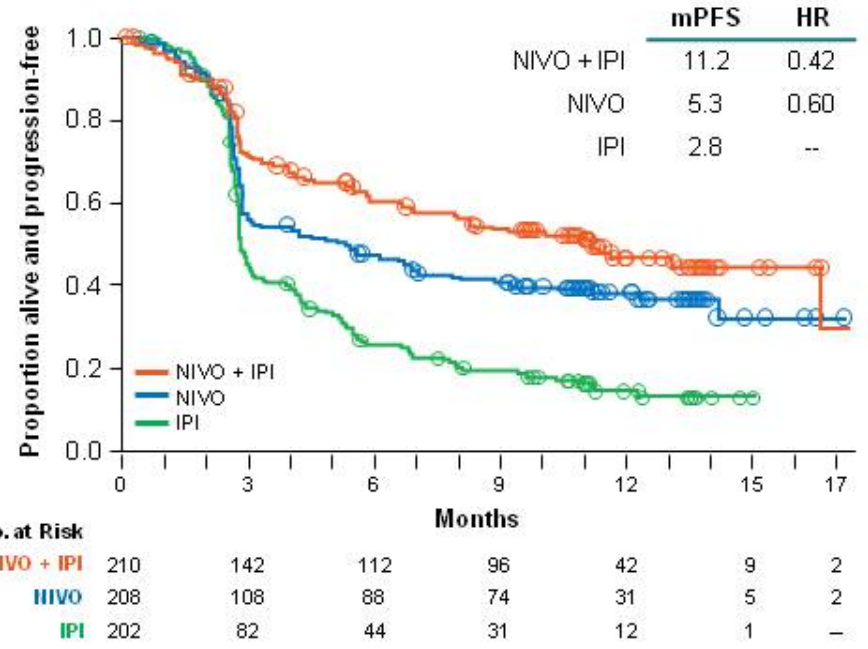
PD-L1 ≥5%*



	mPFS	HR
NIVO + IPI	14.0	0.40
NIVO	14.0	0.40
IPI	3.9	--

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

PD-L1 <5%*



	mPFS	HR
NIVO + IPI	11.2	0.42
NIVO	5.3	0.60
IPI	2.8	--

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

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

PRESENTED AT: ASCO Annual '15 Meeting

Presented By Jedd Wolchok at 2015 ASCO Annual Meeting

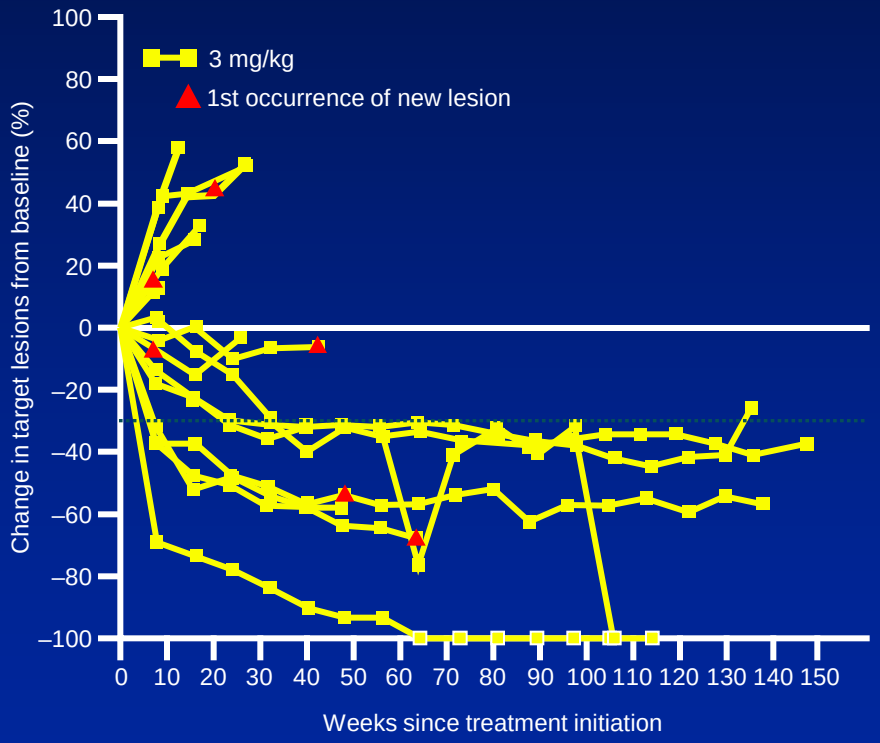
PD-L1 as a potential biomarker: % of Pts PD-L1 positive in the different clinical trials

Study	Pts PDL1+ Positive (%)
CA209-037 (Weber J et al. LO 2015)	49
CA209-066 (Robert C et al. NEJM 2014)	35
Ca209-067 (Larkin J et al. NEJM 2015) ipi/nivo arm	21,7
Ca209-067 (Larkin J et al. NEJM 2015) nivo arm	**25,3**
Keynote 006 (Robert C et al. NEJM 2015) pembro every 2 wks	**80,6**
Keynote 006 (Robert C et al. NEJM 2015) pembro every 3 wks	79,8
Keynote 002 (Puzanov I et al. ASCO 2015)	69
Keynote 001 (Daud A et al SMR 2014))	77

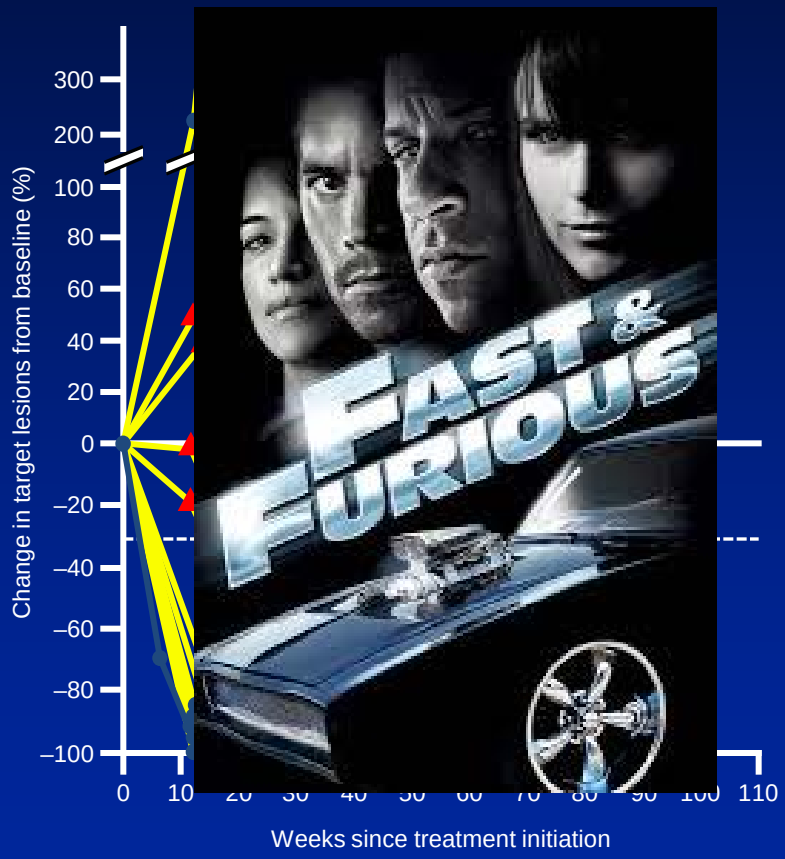
Ascierto PA et al. J Trans Med 2015; 13:213

Changes in Target Lesions: Comparing Nivolumab Alone and in Combination

Nivolumab monotherapy



Nivolumab + ipilimumab

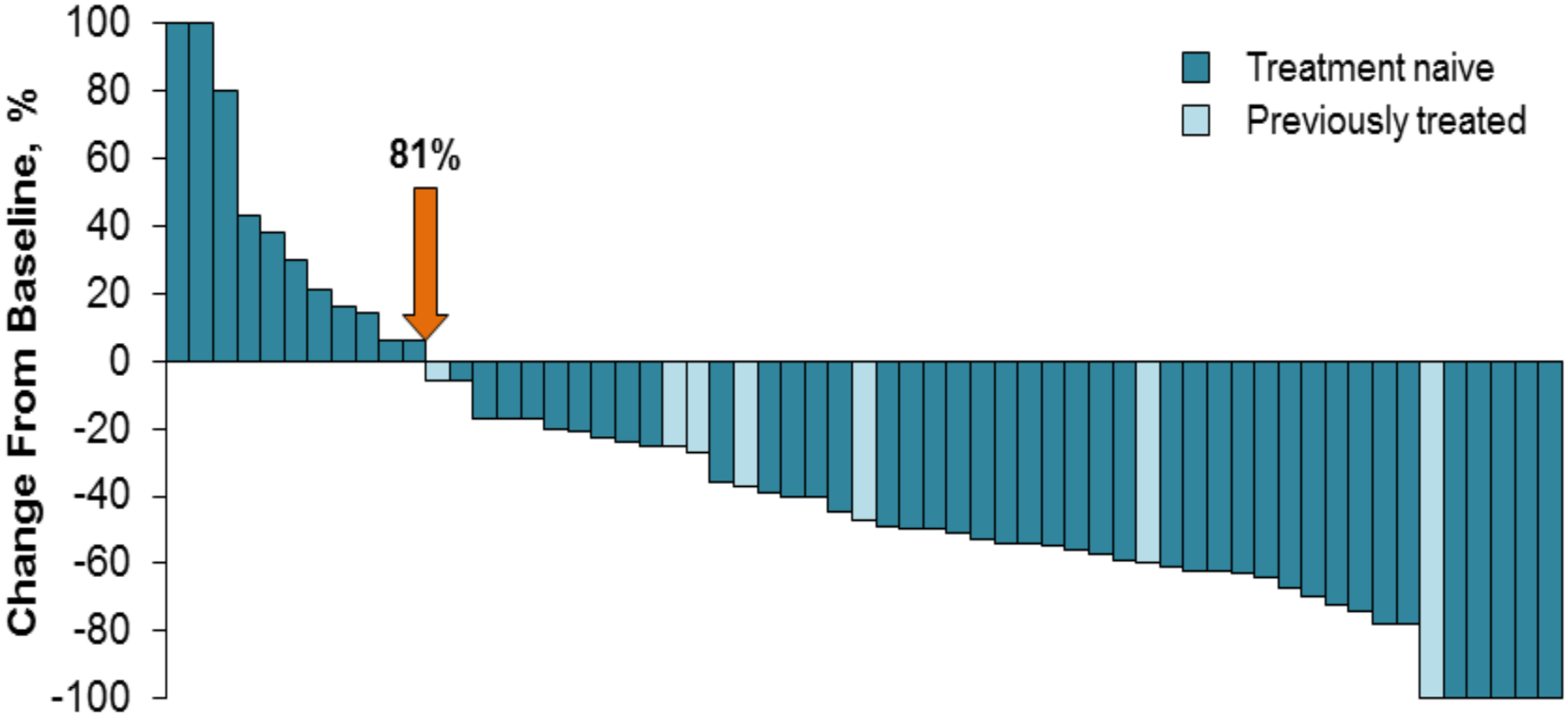


Horizontal line at −30% = threshold for defining objective response (partial tumour regression) in absence of new lesions or non-target disease according to RECIST

Wolchok JD, et al. J Clin Oncol 2013;31(suppl): abstract 9012^;
Sznol M, et al. J Clin Oncol 2013;31(suppl): abstract CRA9006^

G V Long et al. SMR 2015.

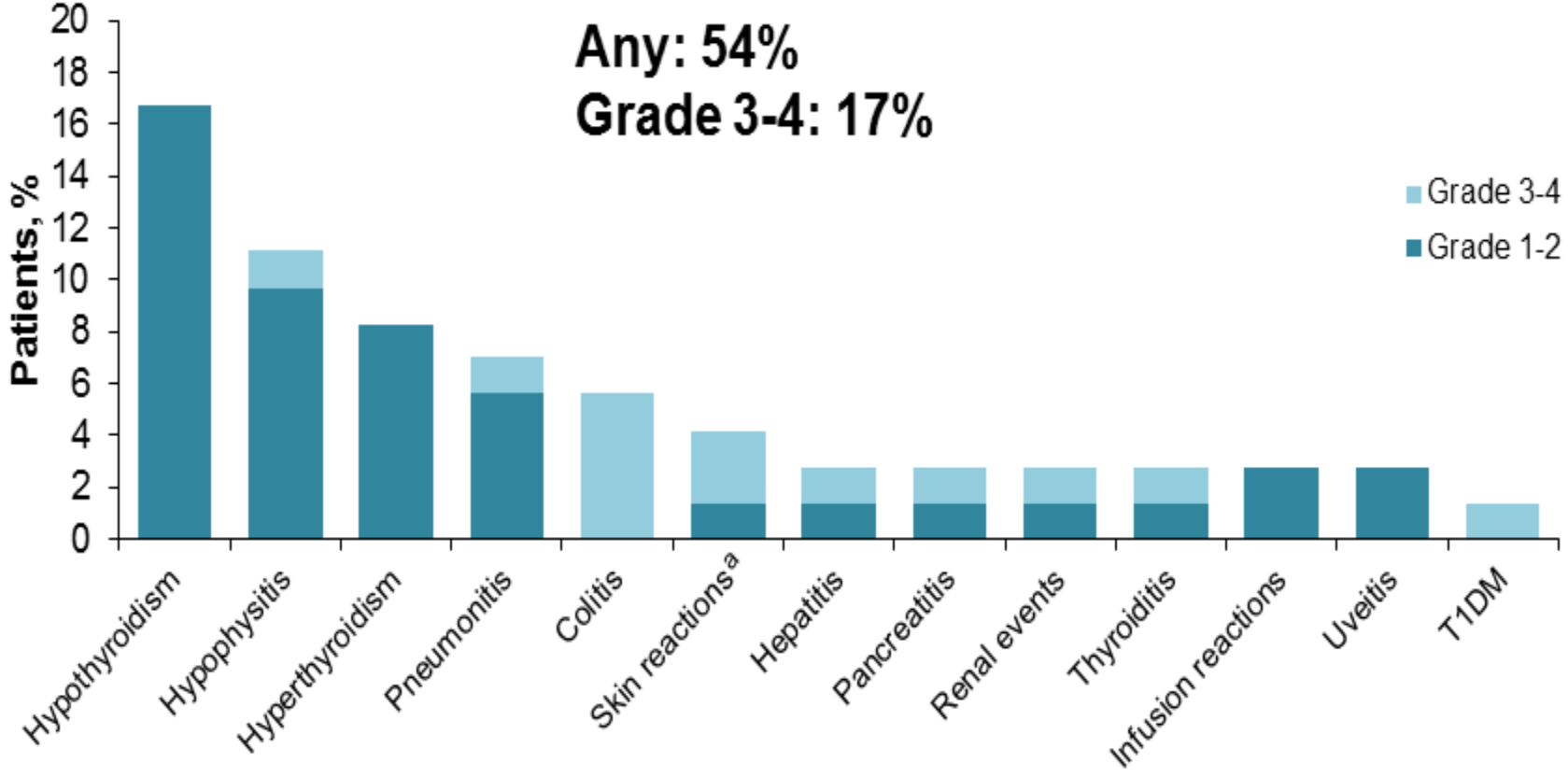
Change From Baseline in Target Lesions by Central Review (n = 59[a])



[a]Tumor size assessed in patients with ≥1 postbaseline assessment per central review.
Data cutoff date: August 31, 2015.

G V Long et al. SMR 2015.

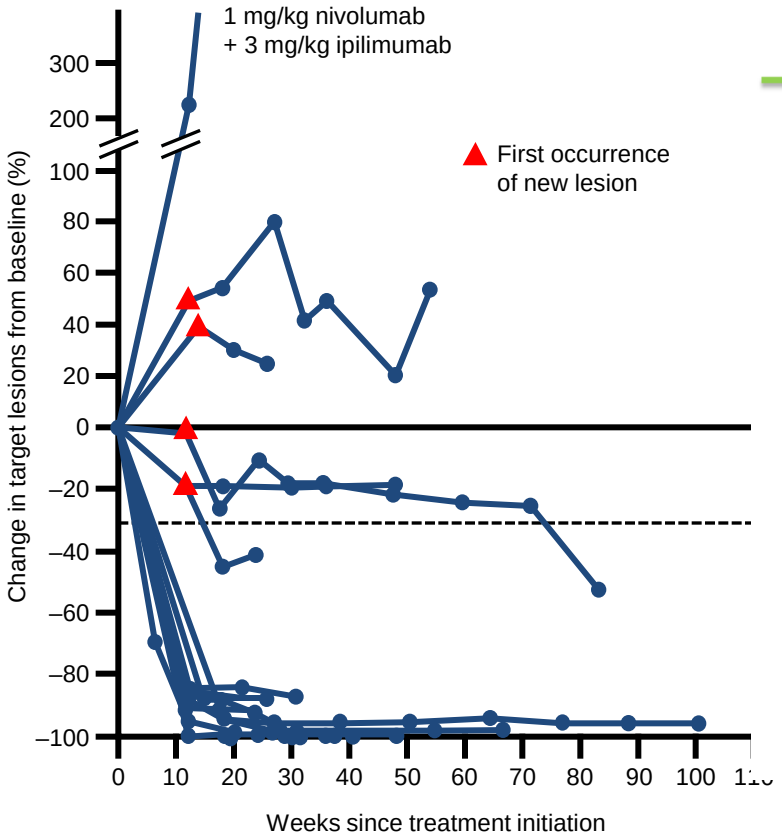
Immune-Mediated AEs



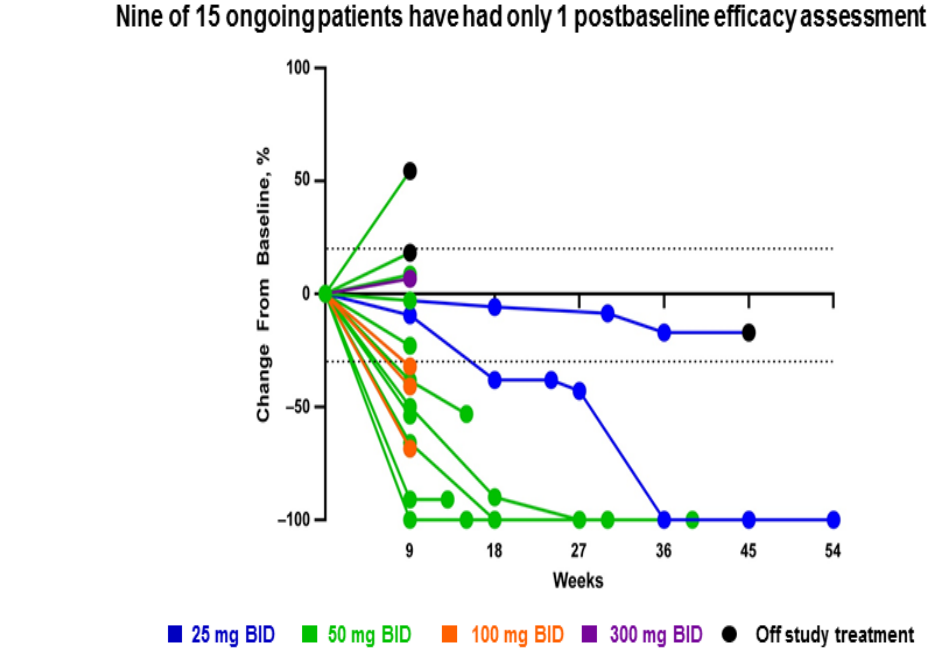
[a]Skin reactions include 1 case each of grade 2 dermatitis exfoliative, grade 3 rash, and grade 3 rash pruritic.
Events were considered regardless of attribution by investigator. Similar preferred terms were combined. Data cutoff date: August 31, 2015.

Changes in Target Lesions: Comparing Nivo/Ipi and Pembro/Epacadostat

Nivolumab + ipilimumab



Percent Change From Baseline in Target Lesions Over Time: Melanoma



Horizontal line at −30% = threshold for defining objective response (partial tumour regression) in absence of new lesions or non-target disease according to RECIST

Wolchok JD, et al. J Clin Oncol 2013;31(suppl): abstract 9012^;
Sznol M, et al. J Clin Oncol 2013;31(suppl): abstract CRA9006^

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