ONCOLOGIA AL FEMMINILE 2015

Un filo sottile per coniugare i progressi scientifici con la pratica clinica, le linee guida e l'etica

Risultati e Prospettive nel Melanoma Maligno

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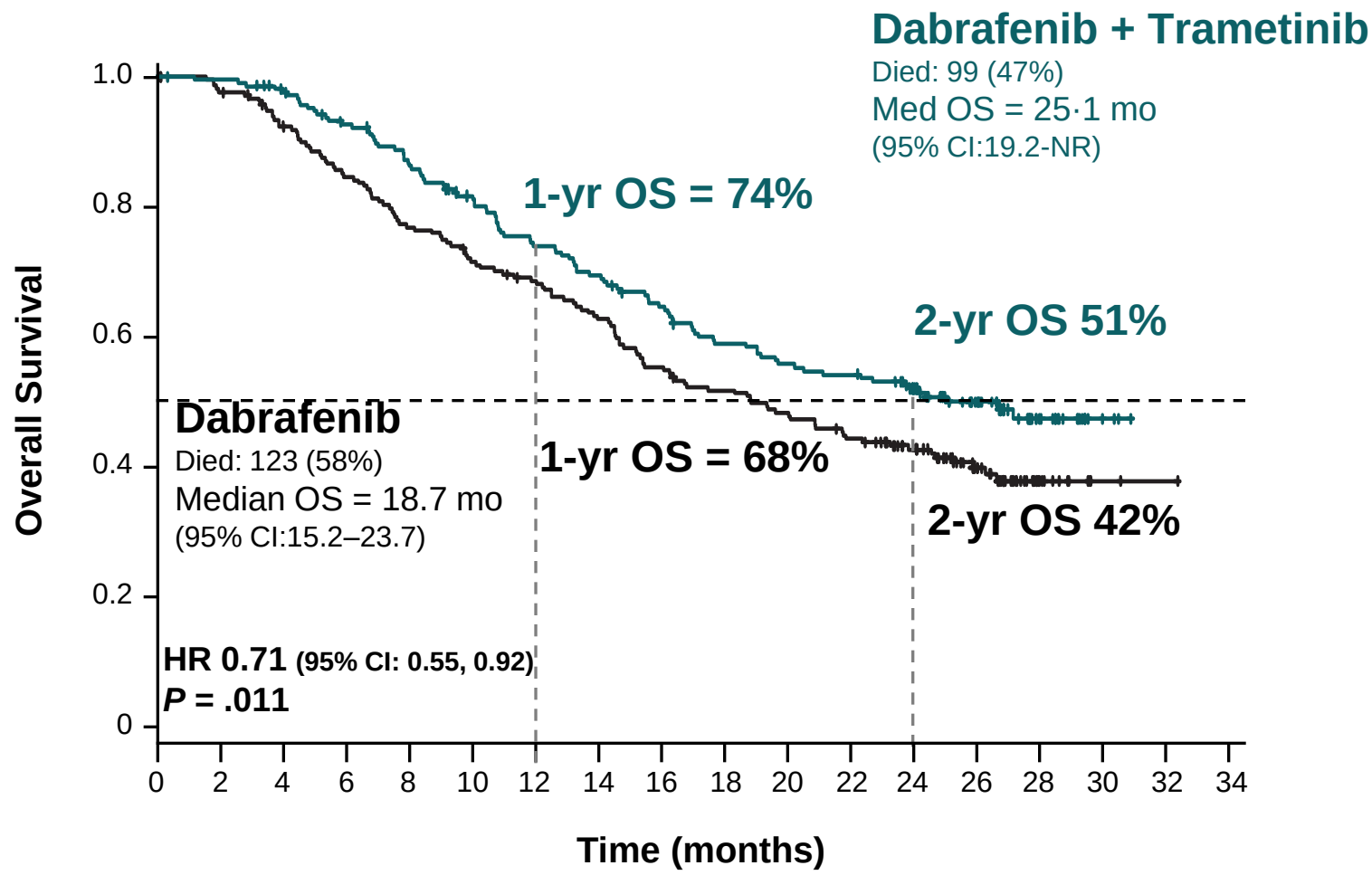
Trattamento del melanoma non operabile nel 2015 in Italia

Melanoma BRAF mutato	Melanoma non BRAF mutato
• Combo D+T (DL 648) • Combo V+C (EAP / DL 648) • Studio Clinico (Columbus o Combo MB) Cardiopatia e/o patologia oculare • Dabrafenib o Vemurafenib	• Ipilimumab • Nivolumab o pembrolizumab (EAP) • Studio clinico (NIBIT M2) • Chemioterapia Metastasi cerebrali sintomatiche, patologia autoimmune, PS 2 RT, SRT, S, CT, se risposta IPI, BSC

COMBI-d: Overall Survival



Number at risk

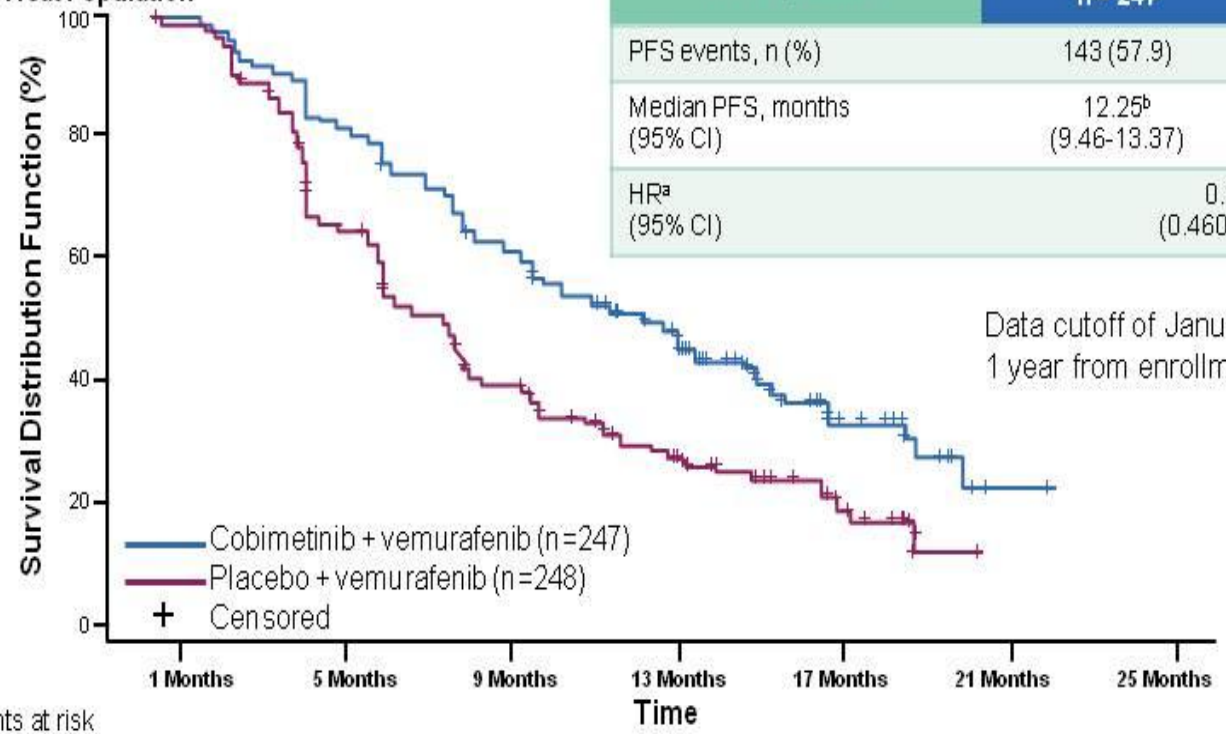
Dabrafenib + trametinib	211	208	200	187	174	159	144	135	124	112	106	103	88	53	21	3	0	0
Dabrafenib + placebo	212	206	191	175	159	147	138	127	111	104	95	88	70	42	10	2	1	0

Dabrafenib+Trametinib med follow up 20 mo (range 0-30 mo); Dabrafenib med follow up 16 mo (range 0-32 mo).

Long GV, et al. *Lancet*. 2015.

coBRIM Updated Investigator-Assessed PFS

Kaplan-Meier Plot for PFS
Intent-to-Treat Population



ITT Population	Cobi + Vem n = 247	Pbo + Vem n = 248
PFS events, n (%)	143 (57.9)	180 (72.6)
Median PFS, months (95% CI)	12.25[b] (9.46-13.37)	7.20[b] (5.55-7.49)
HR[a] (95% CI)	0.58[b] (0.460-0.719)	

Data cutoff of January 16, 2015 was 1 year from enrollment of last patient

No. of patients at risk

Vemurafenib + cobimetinib	238	215	190	168	142	116	79	46	21	8	1
Vemurafenib + placebo	240	205	150	115	87	67	45	30	17	3	

[a]Stratified HR.
[b]The median PFS was 6.2 months in Pbo + Vem, and 9.9 months in Cobi + Vem (HR, 0.51; 95% CI, 0.39-0.68) at the May 9, 2014 data cutoff.
Larkin J et al. *N Engl J Med.* 2014;371:1867-1876.

Presented By James Larkin at 2015 ASCO Annual Meeting

COMBI-d: Post-Progression Systemic Therapy

	Dabrafenib + Placebo[a] n = 212n (%)	Dabrafenib + Trametinib[b] n = 211n (%)
Study treatment continued post progression[c]	65 (31)	62 (29)
Subsequent anti-cancer therapy[d]	108 (51)	70 (33)
Ipilimumab	59 (28)	37 (18)
BRAF inhibitor (vemurafenib and/or dabrafenib)	29 (14)	18 (9)
Pembrolizumab or nivolumab	14 (7)	6 (3)
Chemotherapy regimens	66 (31)	45 (21)
Other	14 (7)	4 (2)

[a]35 (17%) remained on study treatment at data cut.

[b]64 (30%) remained on study treatment at data cut.

[c]Received study treatment for at least 15 days after disease progression.

[d]Study treatment is not included.

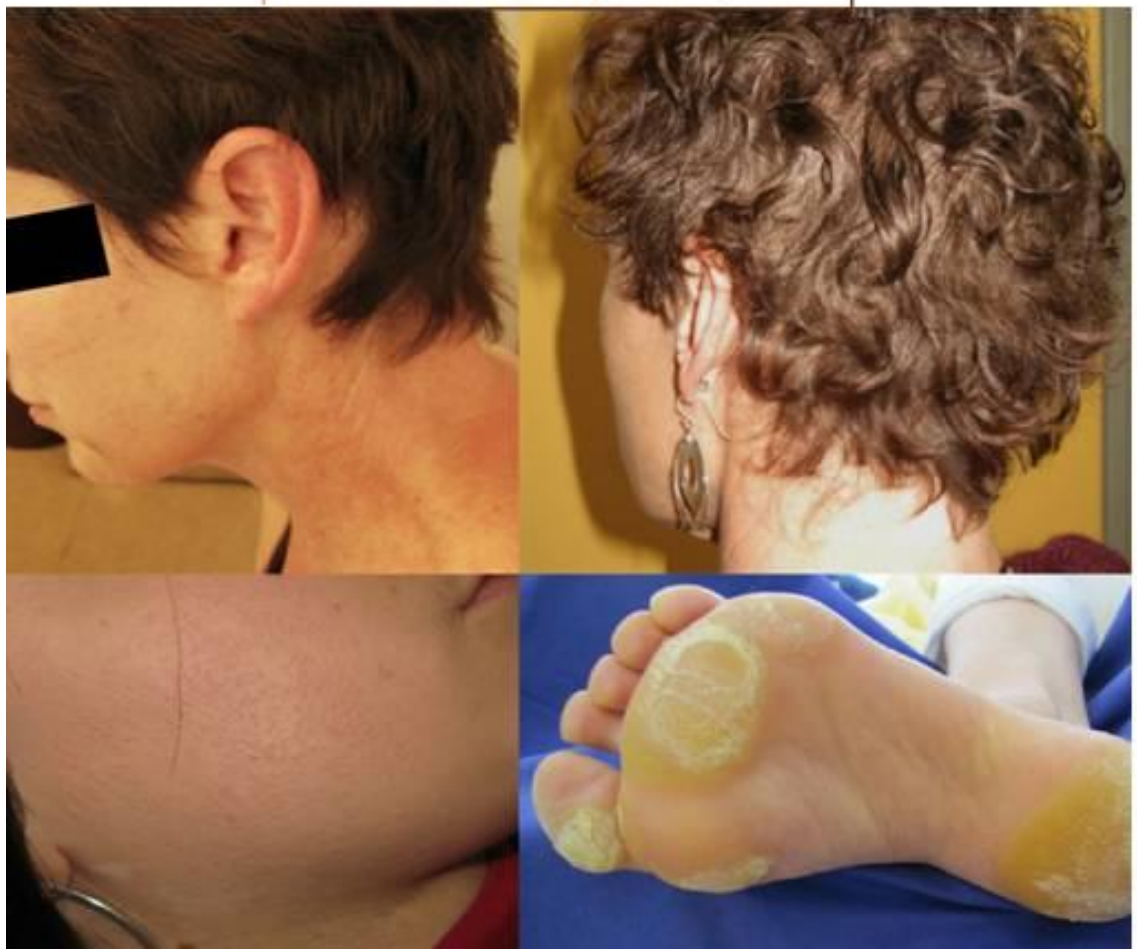
OPEN ACCESS Freely available online

PLOS ONE

RASopathic Skin Eruptions during Vemurafenib Therapy

Jeannine D. Rinderknecht, Simone M. Goldinger, Sima Rozati, Jivko Kamarashev, Katrin Kerl, Lars E. French, Reinhard Dummer*, Benedetta Belloni

March 2013 | Volume 8 | Issue 3 | e58721



RAS Mutations Are Associated With the Development of Cutaneous Squamous Cell Tumors in Patients Treated With RAF Inhibitors

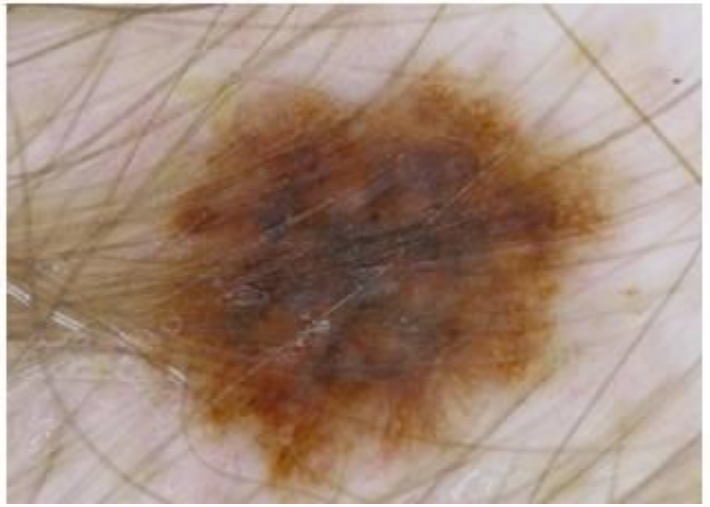
JCO.2011.

Patrick A. Oberholzer, Damien Kee, Piotr Dziunycz, Antje Sucker, Nyam Kamsukom, Robert Jones, Christine Roden, Clinton J. Chalk, Kristin Ardlie, Emanuele Palescandolo, Adriano Piris, Laura E. MacConaill, Caroline Robert, Günther F.L. Hofbauer, Grant A. McArthur, Dirk Schadendorf, and Levi A. Garraway

Atypical Melanocytic Proliferations and New Primary Melanomas in Patients With Advanced Melanoma Undergoing Selective *BRAF* Inhibition

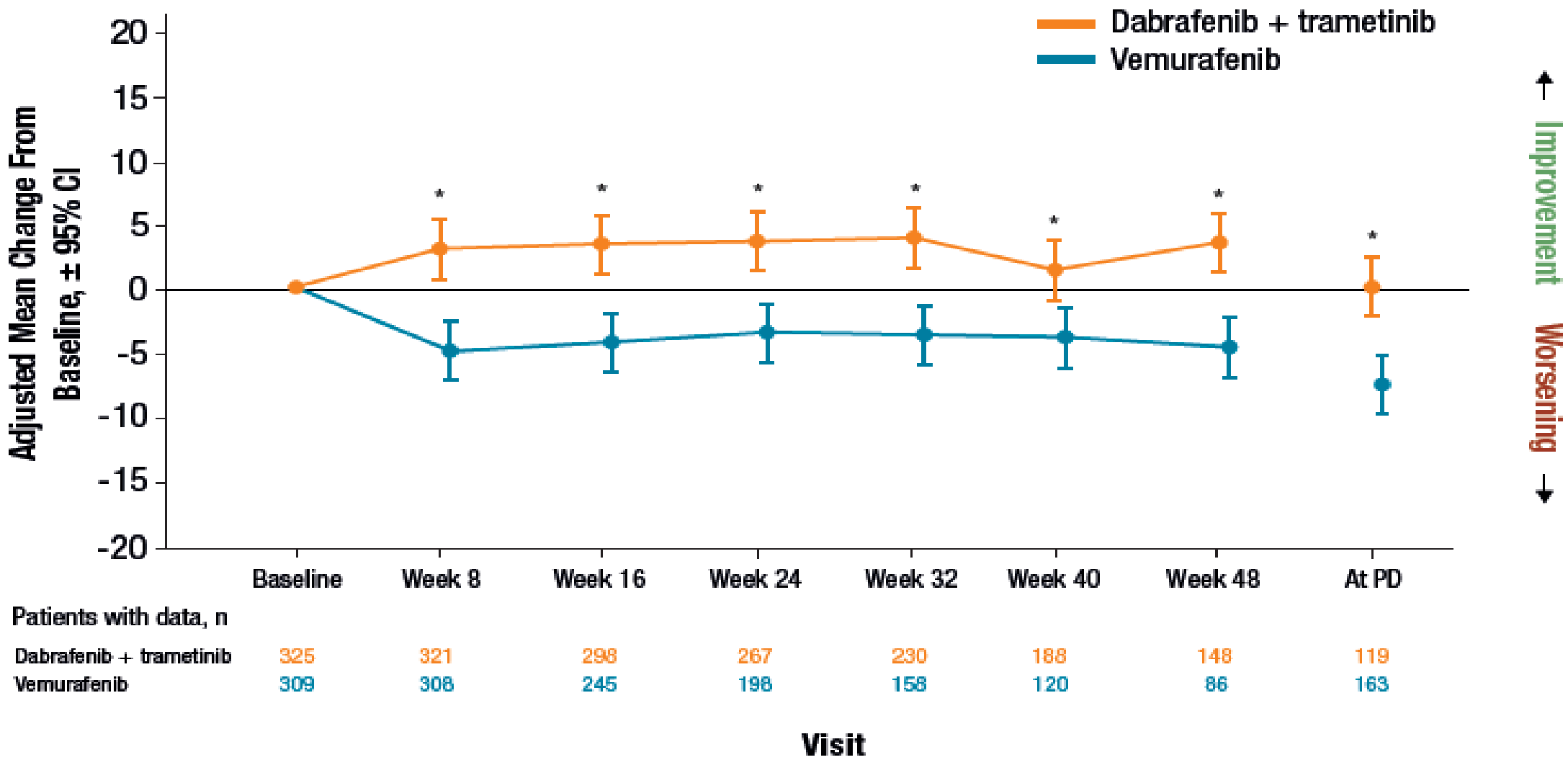
J Clin Oncol 30. © 2012

Lisa Zimmer, Uwe Hillen, Elisabeth Livingstone, Mario E. Lacouture, Klaus F. [illegible], Friederike Egberts, Axel Hauschild, Mohammed Kashani-Sabet, Simone M. Goldinger, Reinhard Dummer, Georgina V. Long, Grant McArthur, André Scherag, Antje Sucker, and Dirk Schadendorf



ASCO Annual '15 Meeting

Figure 2. EORTC QLQ-C30 Global Health Status Score Changes From Baseline



Scelta terapeutica nei pazienti BRAF mutati: cosa discutere ?

Terapia	RR%	mTTR	mRDT	ToxG3/4	mPFS	mOS	1-y S	2-y S
Combo[1]	**69**	1	12.9	32	**11.4**	**25**	**74**	51
IPI[2]	12-15	4	19.3	56.3 20	2 ?	11.2	47.3	28.5
Nivo[3,5]	40	2.1	NR	11.-16	5.1-6.7	NR	72.9	NR
Pembro[4]	34	3	NR	13	5.5	NR	74	NR

1 GV long Lancet 2015,
2 C Robert NEJM 2011
3 C Robert NEJM 2014
4 C Robert NEJM 2015
5 J Larkin NEJM 2015

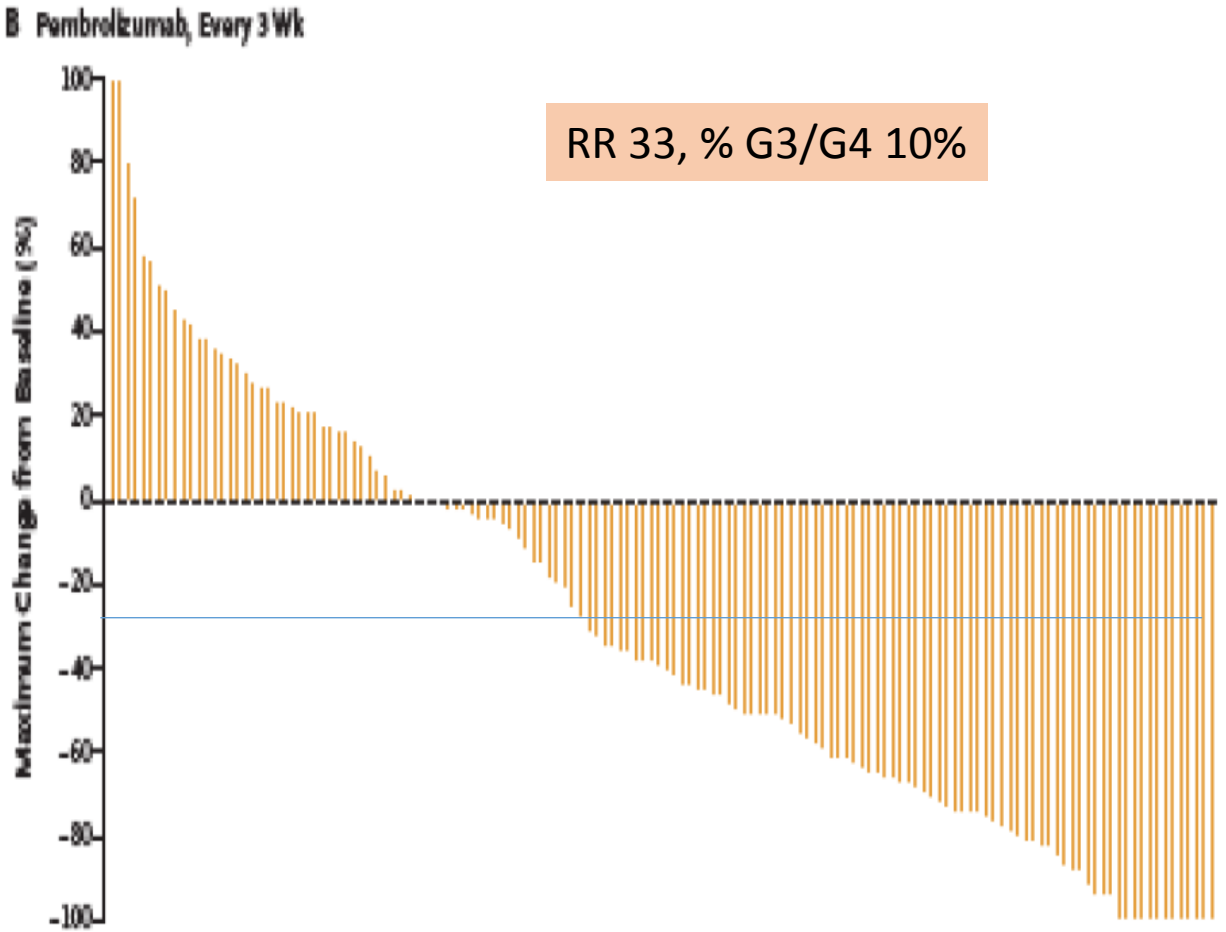
Scelta terapeutica nei pazienti BRAF mutati: cosa discutere ?

Terapia	Somministst	QOL	Durata Te	Toxi ricov/rev	Costi	Ferti	Interfer lavoro
Combo	Orale cont	++++	illimitata	+++/-	???	?	minima
IPI	90' q 21	---	73 gg	++/---	+++	?	modesta
Nivo	60' q 14	?	illimitata	++/--	???	?	media
Pembro	30' q 21	?	illimitata	++/-	???	?	media

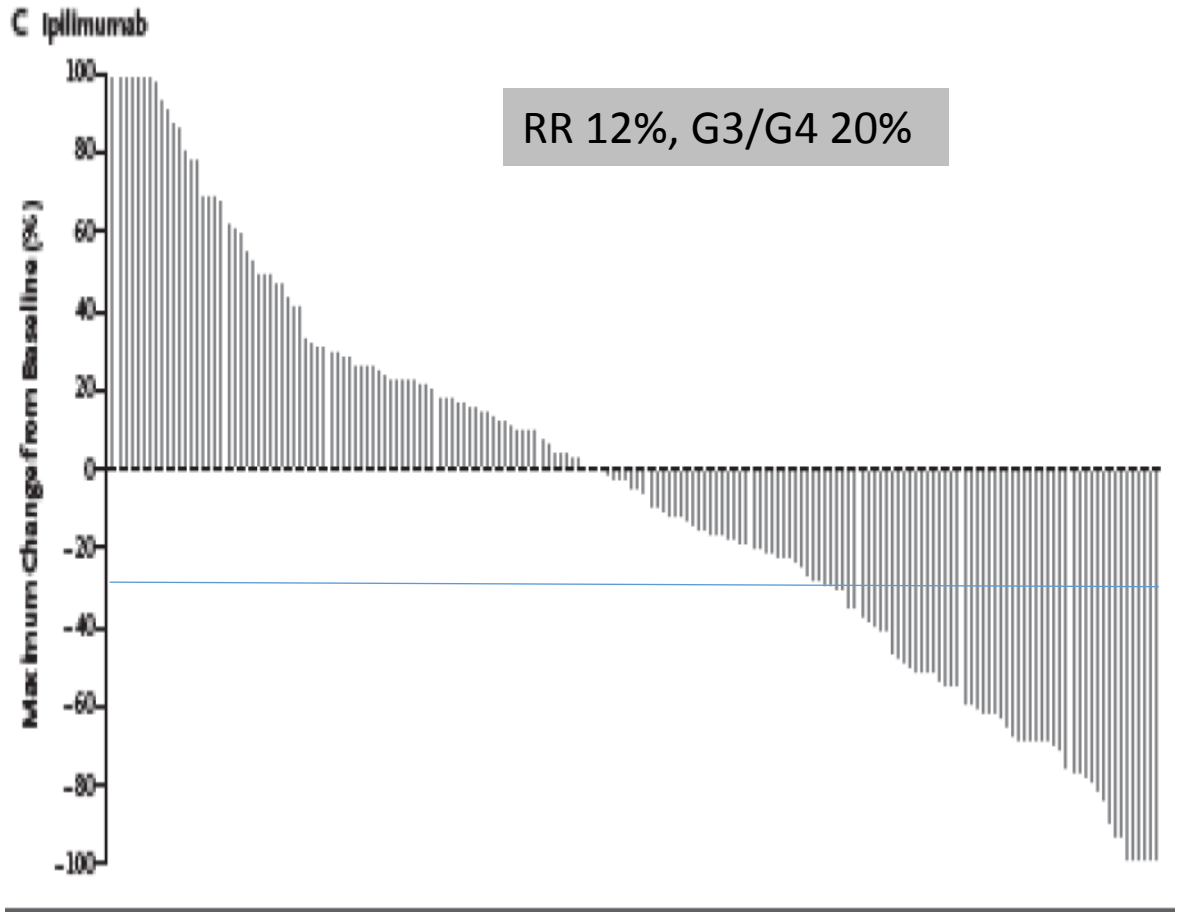
Pembrolizumab versus Ipilimumab in Advanced Melanoma

N ENGL J MED 372;26 NEJM.ORG JUNE 25, 2015

C Robert et al.



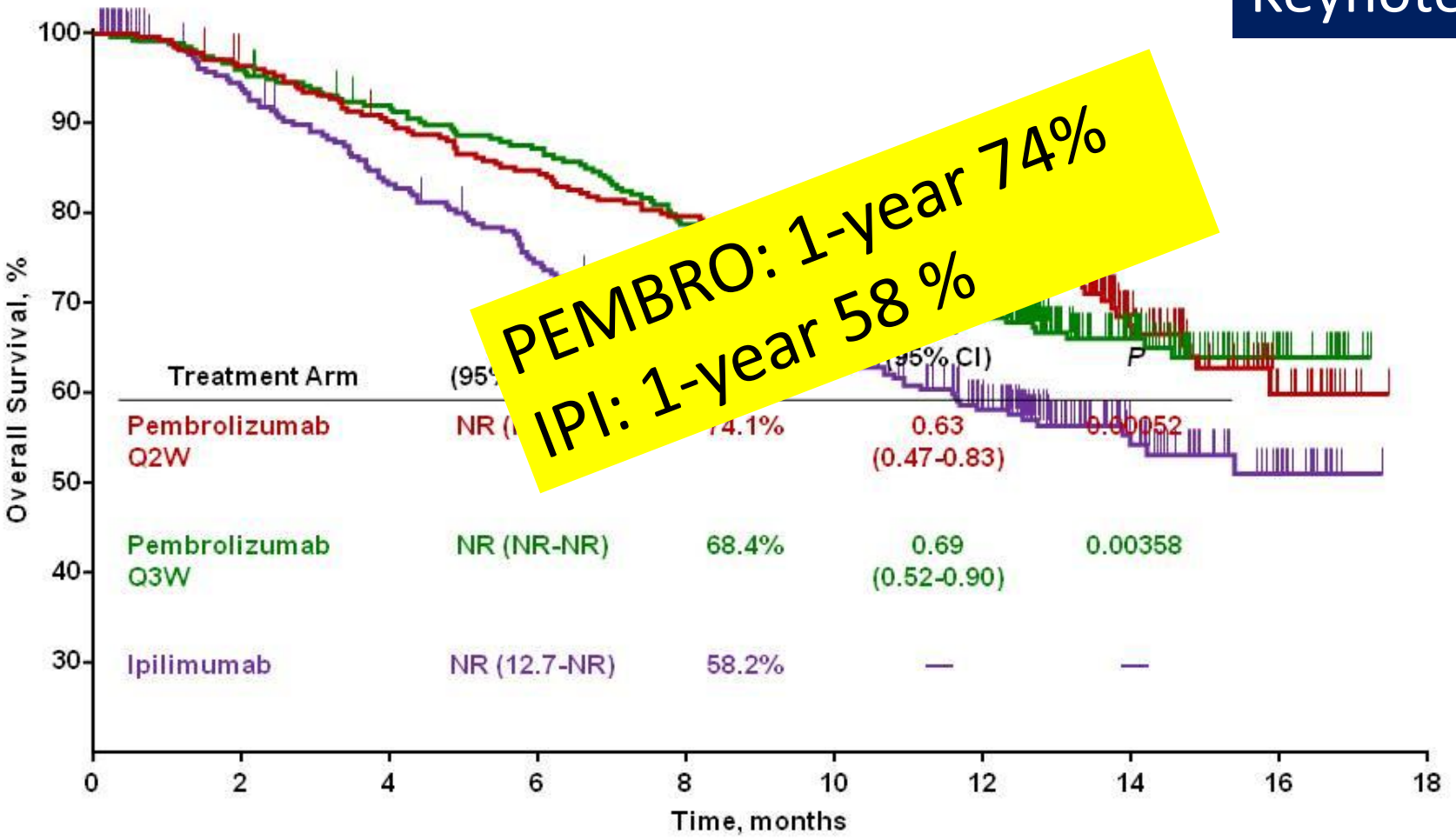
RR 33, % G3/G4 10%



RR 12%, G3/G4 20%

OS at the Second Interim Analysis

Keynote-006



PEMBRO: 1-year 74%
IPI: 1-year 58 %

NEJM, Robert et al 2015

Analysis cut-off date: March 3, 2015.

Presented By Lynn Schuchter at 2015 ASCO Annual Meeting

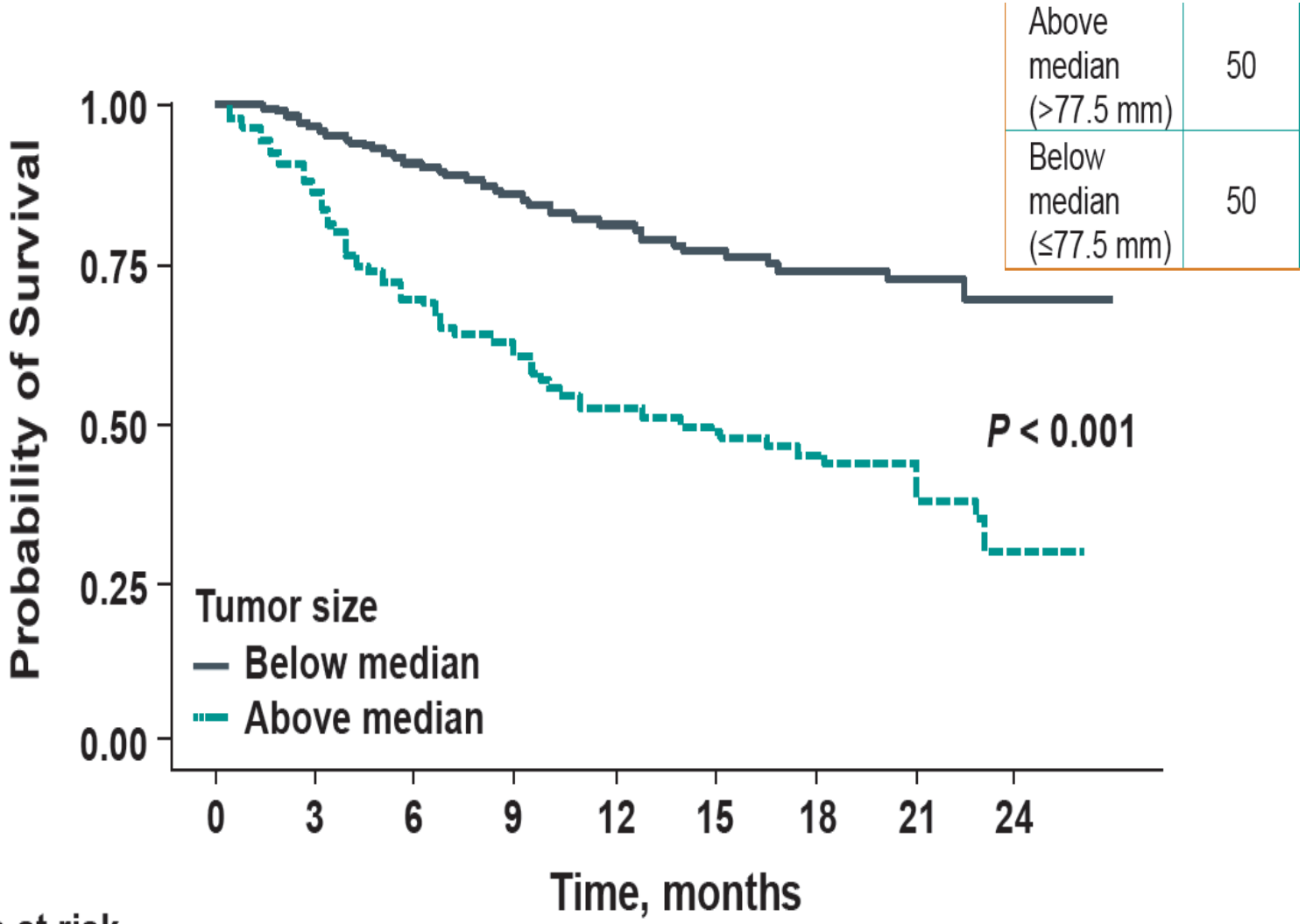
Baseline Tumor Size Is an Independent Prognostic Factor for Overall Survival in Patients With Metastatic Melanoma Treated With the Anti–PD-1 Monoclonal Antibody Pembrolizumab (MK-3475)

Table 3. Analysis of Independent Predictors of OS

Factors	Hazard Ratio	*P*	Independent (BIC)
Baseline tumor size ≥ median	2.35	<0.001	Yes
Elevated LDH	1.70	0.002	Yes
ECOG PS	1.52	0.020	Yes
BRAF mutant	1.56	0.021	No
M1c	1.08	0.68	No
IPI naive	0.89	0.50	No

ASCO 2014

Baseline Tumor Size Is an Independent Prognostic Factor for Overall Survival in Patients With Metastatic Melanoma Treated With the Anti–PD-1 Monoclonal Antibody Pembrolizumab (MK-3475)



Numbers at risk

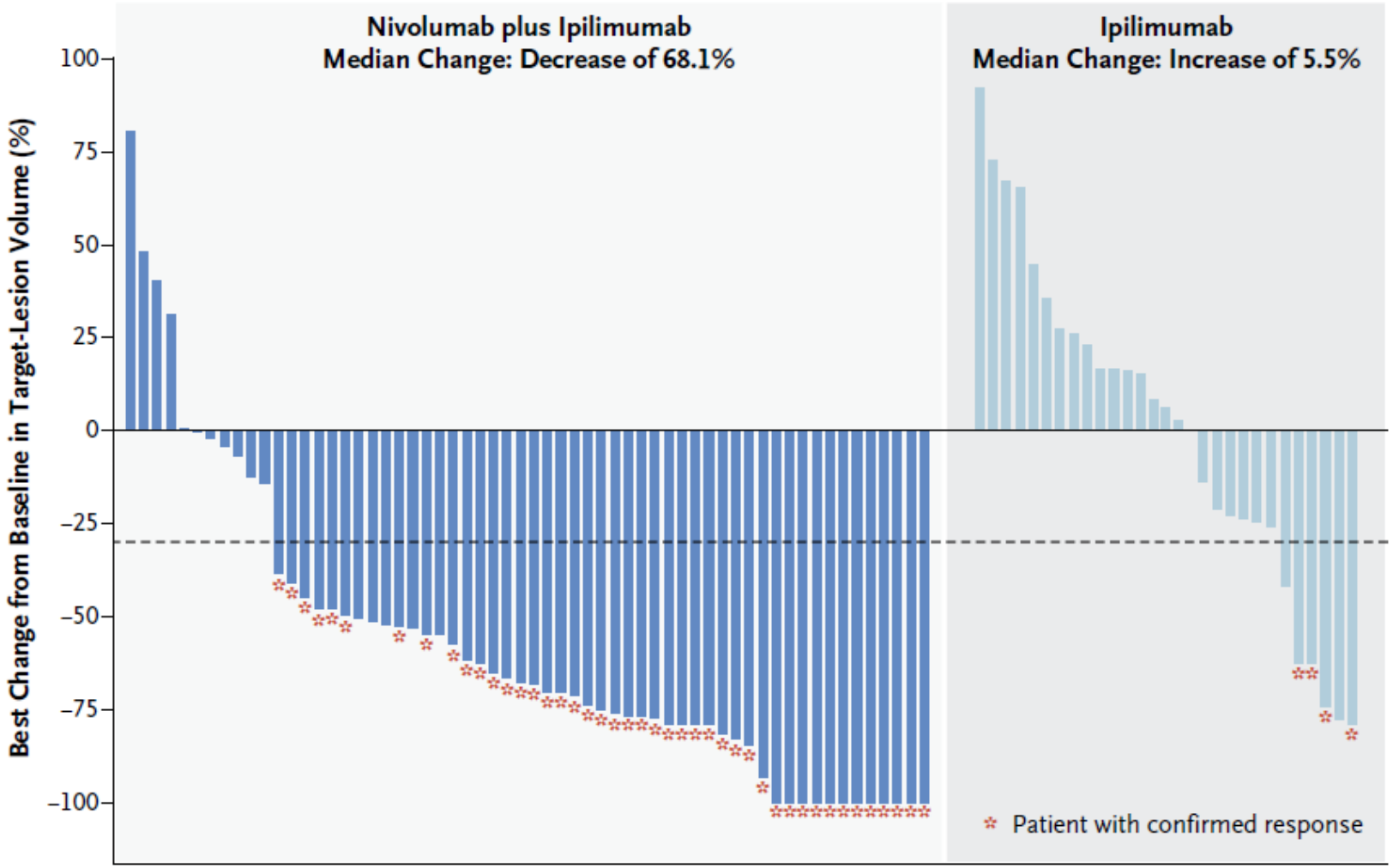
Below median	183	177	162	153	132	103	55	44	19
Above median	182	151	121	104	82	60	24	16	5

ASCO 2014

Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma

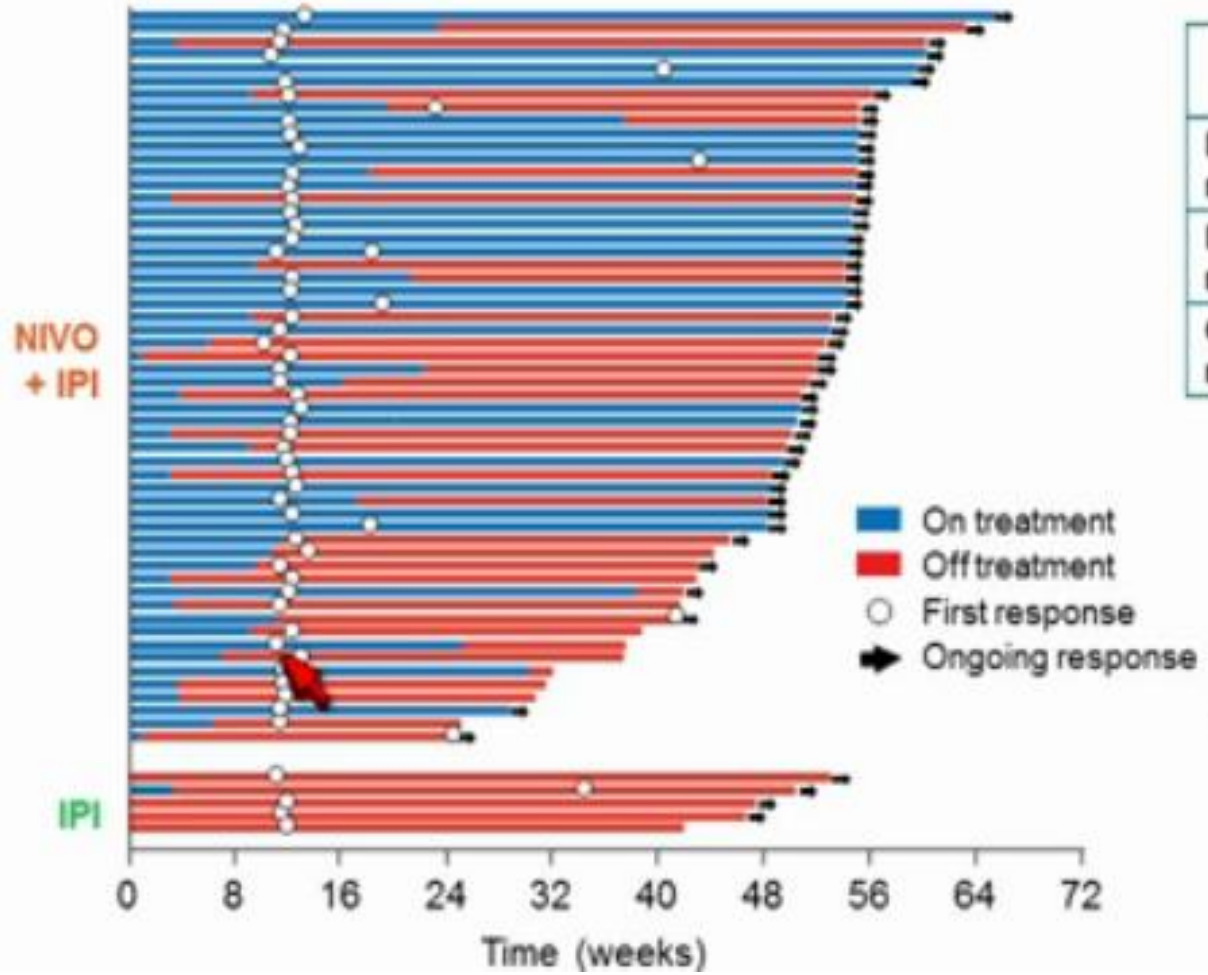
N ENGL J MED 372;21 NEJM.ORG MAY 21, 2015

M.A Postow et a.l



IPI+Nivo	vs	IPI
ORR= 59%		11%
CR= 22%		0%
PD= 16%		47%
G3/G4= 54%		24%

Time to and Durability of Response (All Randomized Responders)



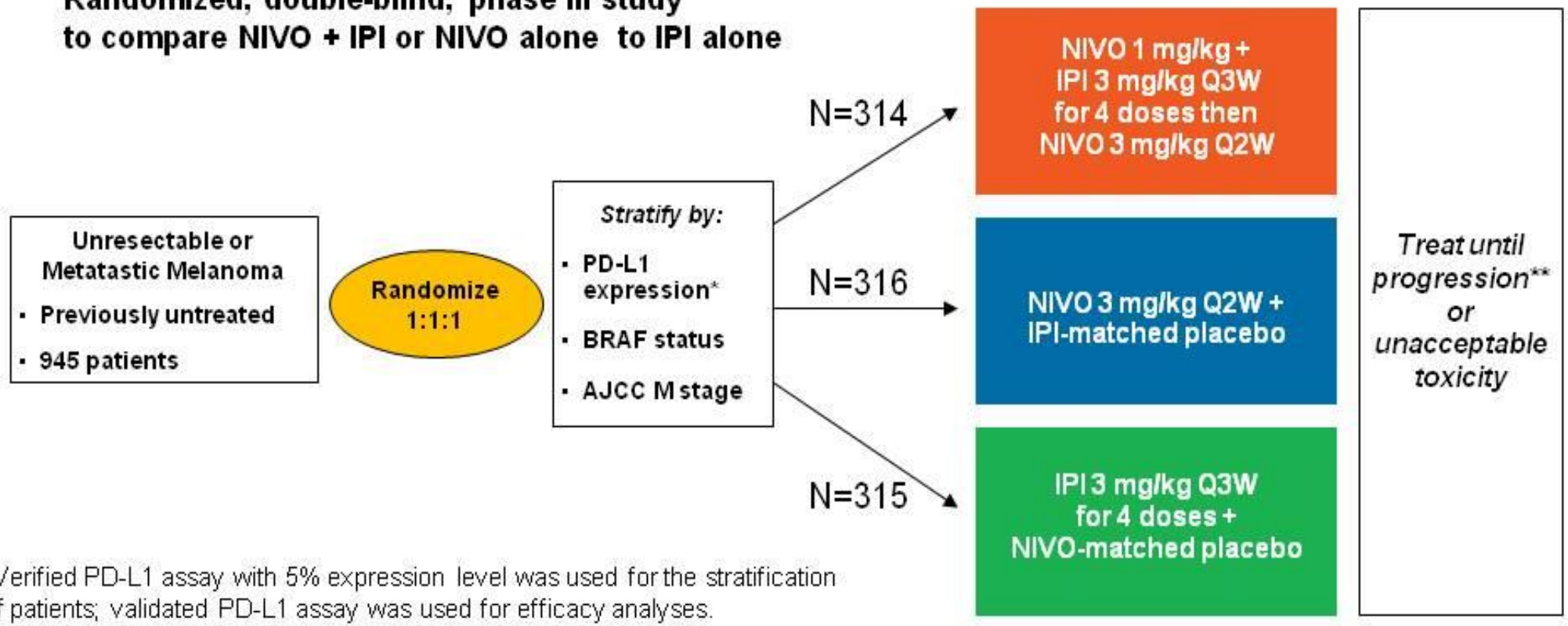
	NIVO + IPI (N = 95)	IPI (N = 47)
Median time to response, months (range)[a]	2.8 (2.3, 9.9)	2.7 (2.5, 7.9)
Median duration of response, months (range)[a]	NR (0–12.1)[b]	NR (3.5–9.8)[b]
Ongoing response among responders, n (%)[a]	46/56 (82)	4/5 (80)

[a]Minimum follow-up of 11 months from date of randomization
[b]Censored data (response ongoing)
NR = not reached

- 68% of patients (30/44) who discontinued the NIVO + IPI combination due to drug-related toxicity experienced a complete or partial response

CA209-067: Study Design

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



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

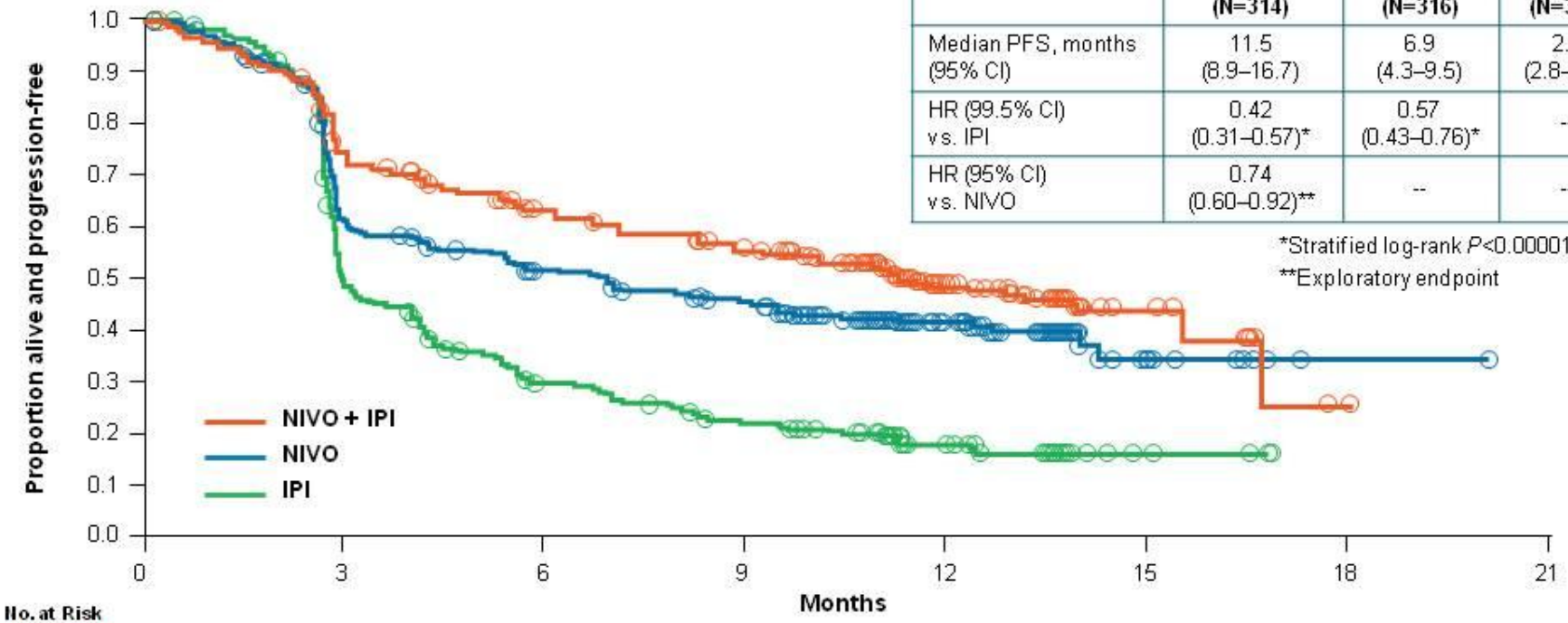
**Patients could have been treated beyond progression under protocol-defined circumstances.

PFS (Intent-to-Treat)

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

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

**Exploratory endpoint



No. at Risk								
NIVO + IPI	314	219	173	151	65	11	1	0
NIVO	316	177	147	124	50	9	1	0
IPI	315	137	77	54	24	4	0	0

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Safety Summary

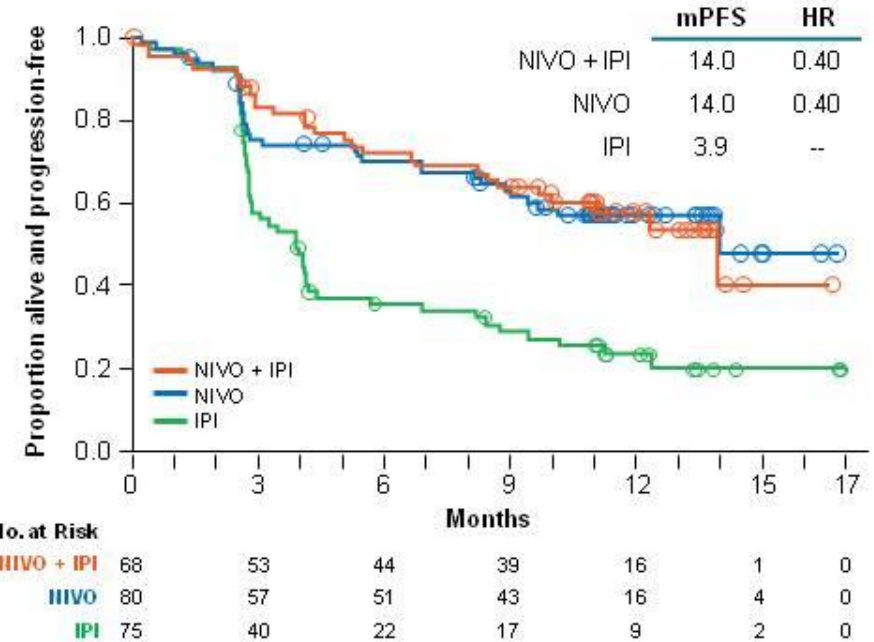
Patients Reporting Event, %	NIVO + IPI (N=313)		NIVO (N=313)		IPI (N=311)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Treatment-related adverse event (AE)	95.5	55.0	82.1	16.3	86.2	27.3
Treatment-related AE leading to discontinuation	36.4	29.4	7.7	5.1	14.8	13.2
Treatment-related death*	0		0.3		0.3	

*One reported in the NIVO group (neutropenia) and one in the IPI group (cardiac arrest).

- 67.5% of patients (81/120) who discontinued the NIVO + IPI combination due to treatment-related AEs developed a response

PFS by PD-L1 Expression Level (5%)

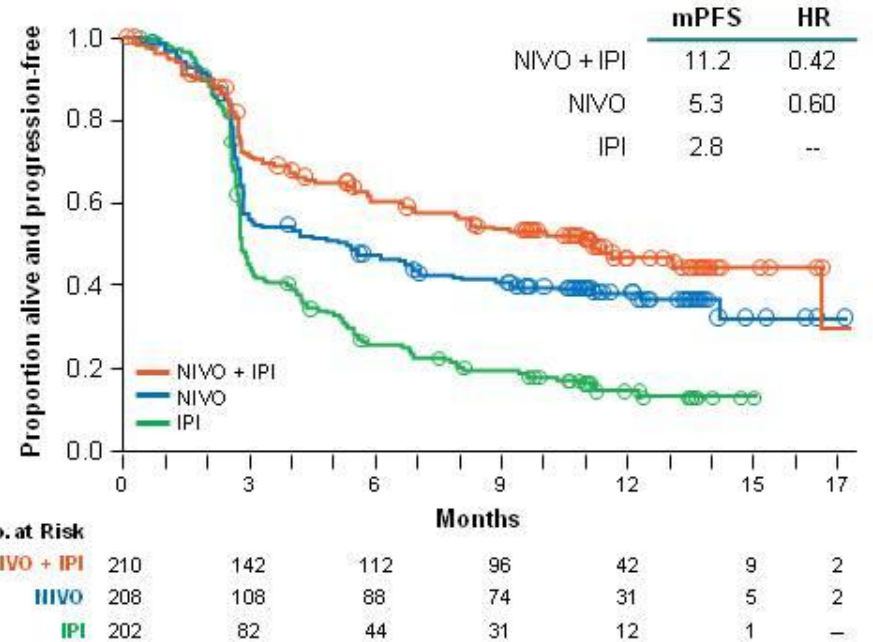
PD-L1 ≥5%*



	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.

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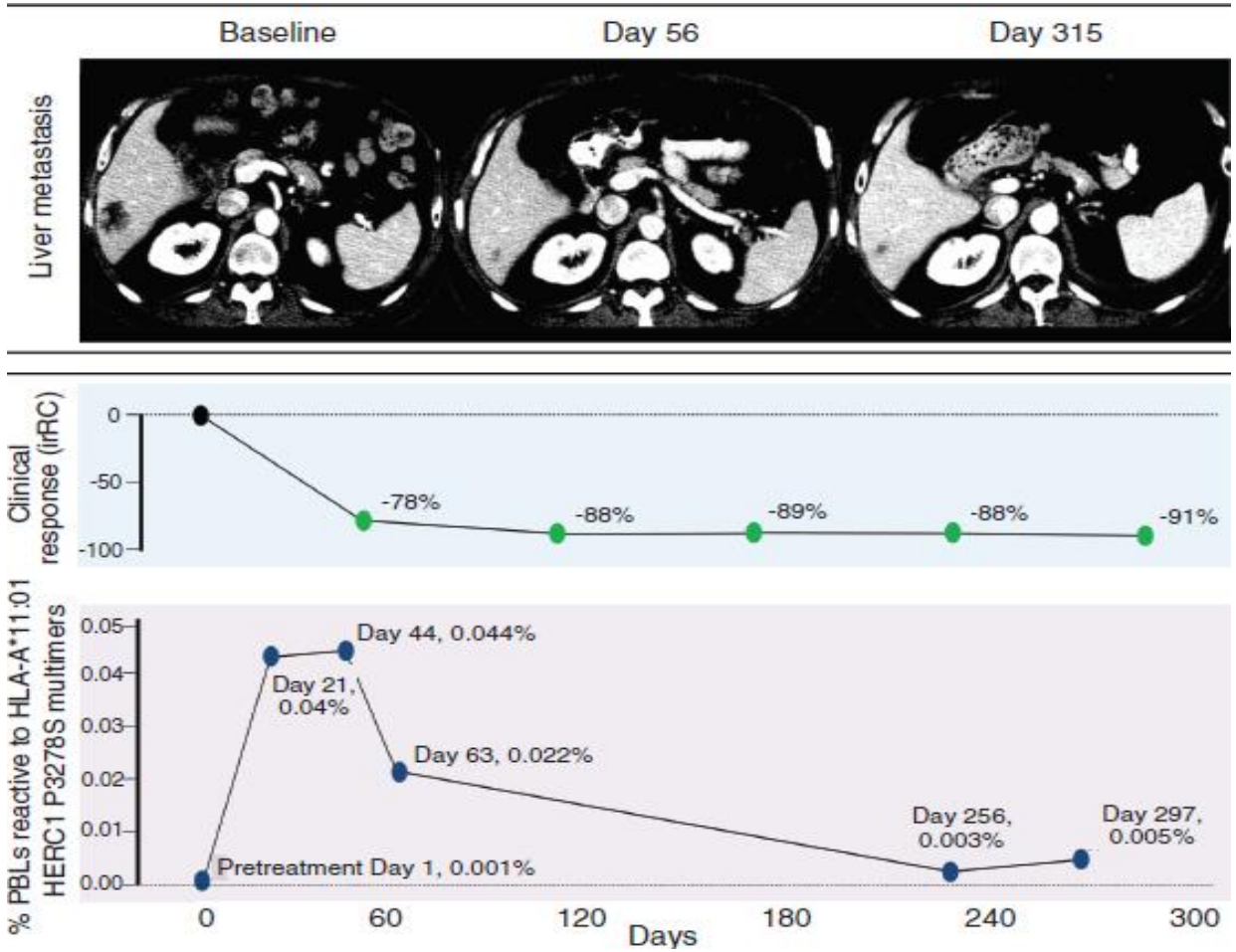
Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer

NA.Rizvi et al Science

3 APRIL 2015 • VOL 348 ISSUE 6230



Next Steps BRAF Targeted Therapy

Building on the Backbone

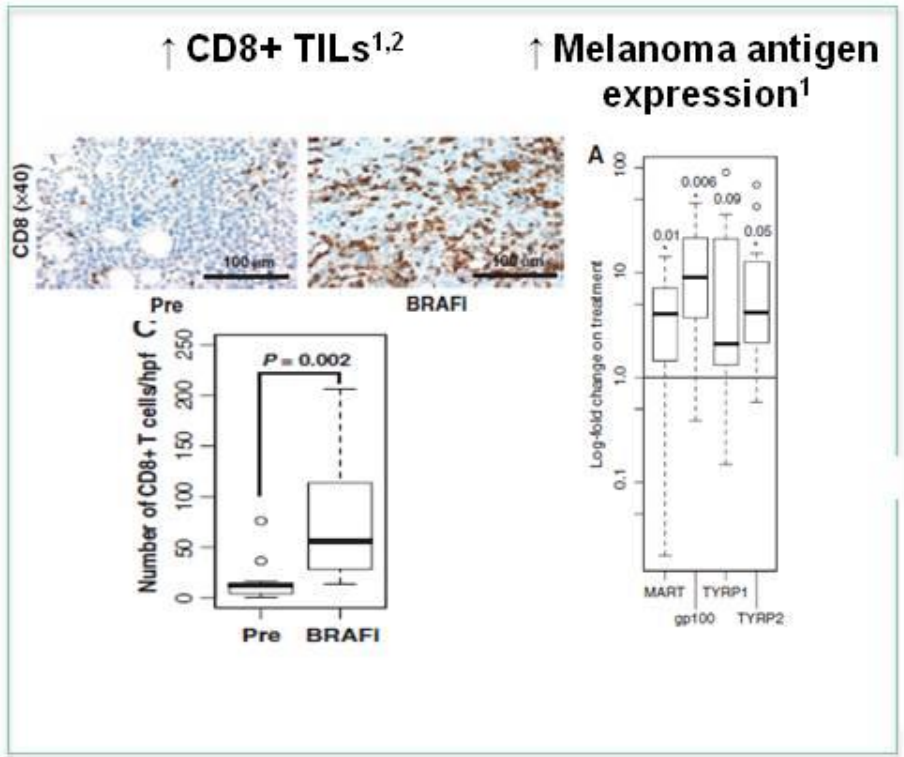
Doublet Therapy: BRAFi and MEKi

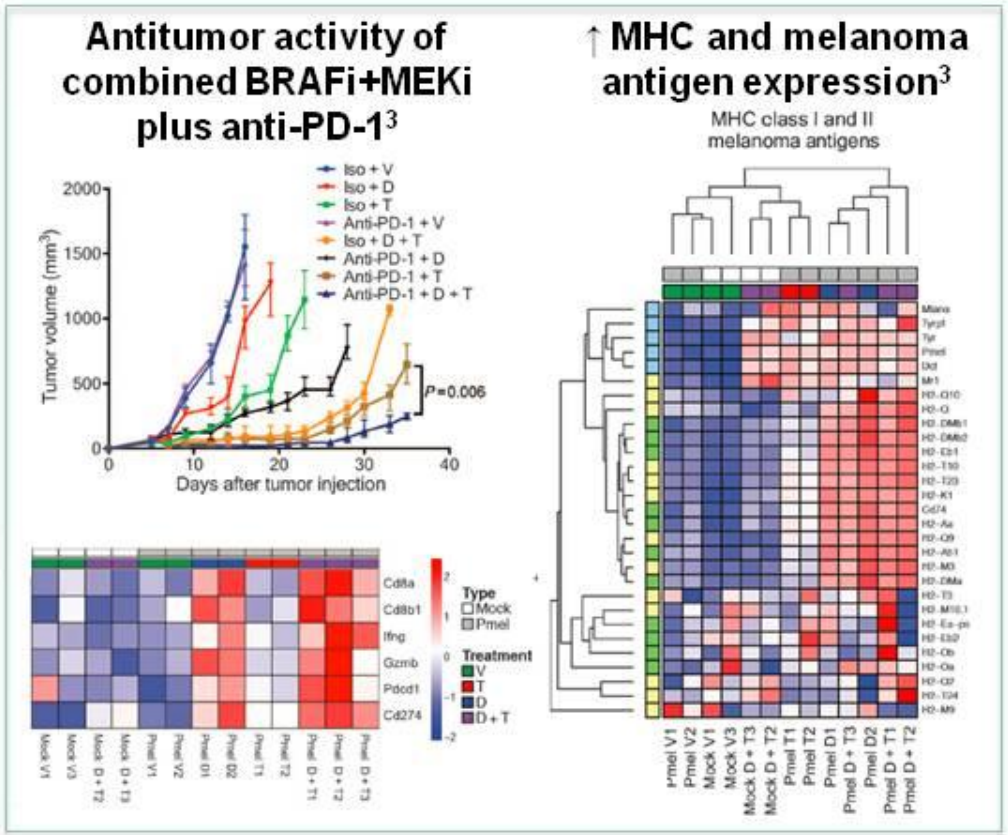
Upfront Triple Therapy
BRAFi + MEKi + Drug X

Drug X at Progression
BRAFi +MEKi → Drug X

PI3K/ MTOR/AKT
Anti-VEGF
CDK 4/6
C-Met
FGF
Autophagy
Etc, etc

BRAF/MEK inhibition modulates the immune microenvironment





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

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

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

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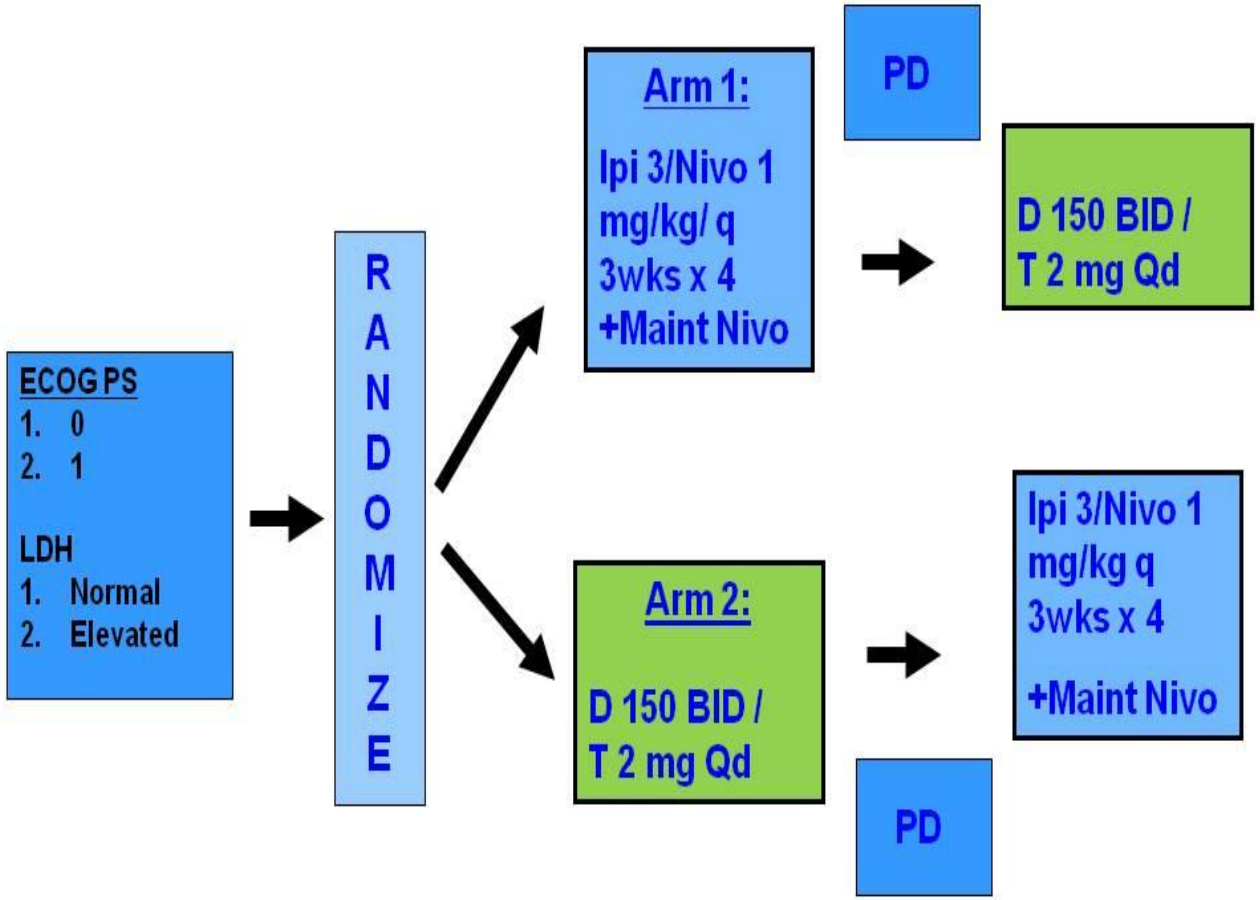
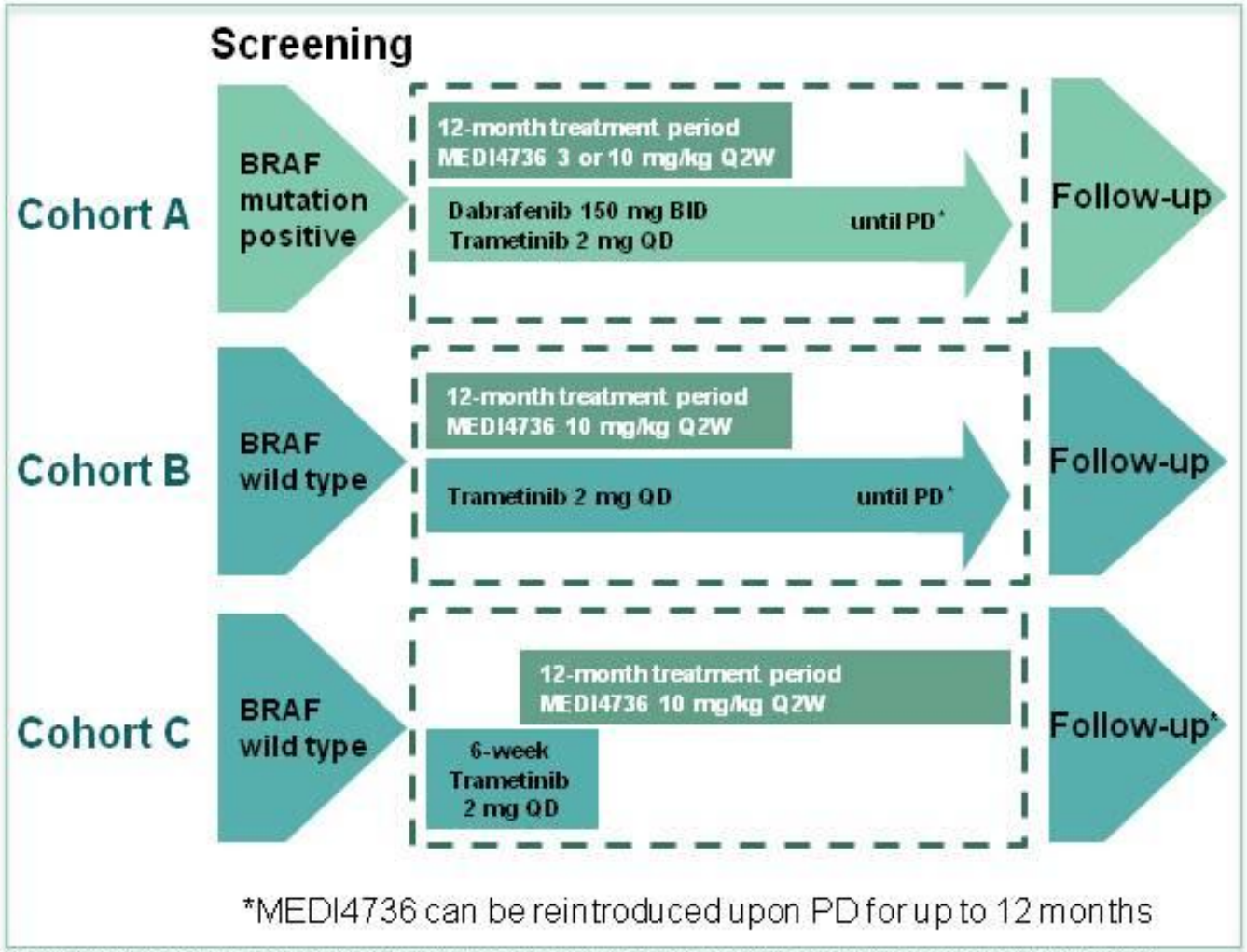
EA6134: Ipi/Nivo to D/T vs D/T to Ipi/Nivo



Presented By Lynn Schuchter at 2015 ASCO Annual Meeting

Study design and population

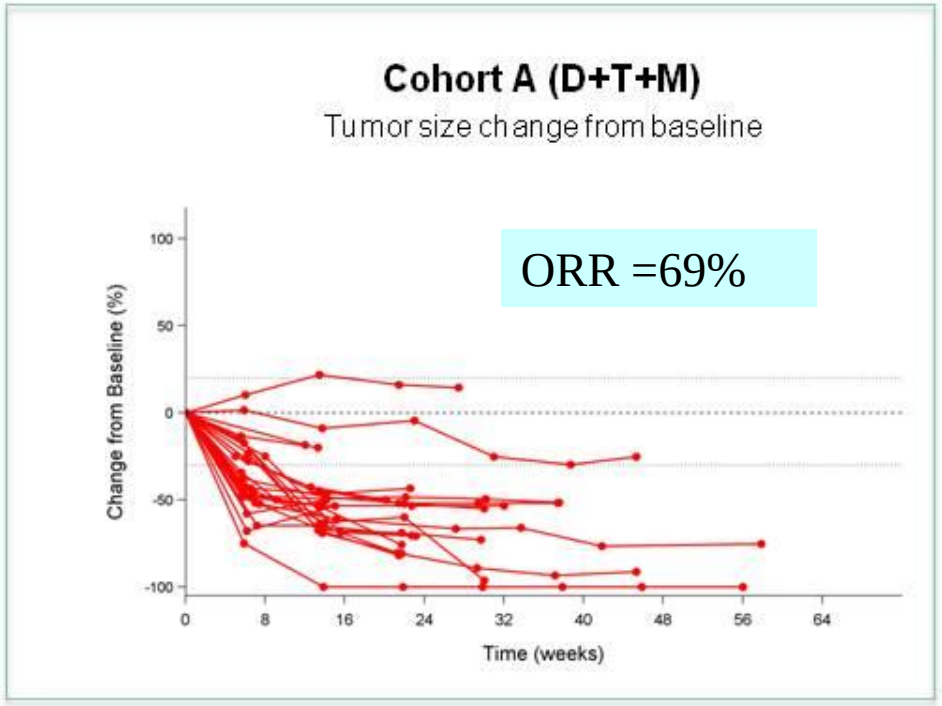


- **Key inclusion criteria**
  - Stage IIIC/IV melanoma
  - BRAF mutation status
    - Cohort A: confirmed $BRAF^{V600E/K}$ mutation positive
    - Cohort B and C: confirmed $BRAF^{V600E/K}$ mutation negative
  - ECOG PS 0–1
  - Adequate organ and marrow function
  - Prior immunotherapy permitted:
    - anti-CTLA-4
    - anti-PD-1/anti-PD-L1
  - Measurable disease required

- **Key exclusion criteria**
  - Active or prior autoimmune disease
  - Prior BRAF or MEK inhibitor therapy
  - Prior severe or persistent irAE

BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group Performance Status; irAE, immune-related adverse event; PD, progressive disease; Q2W, every 2 weeks; QD, once daily; SD, stable disease

Tumor size change and time to response: Cohort A



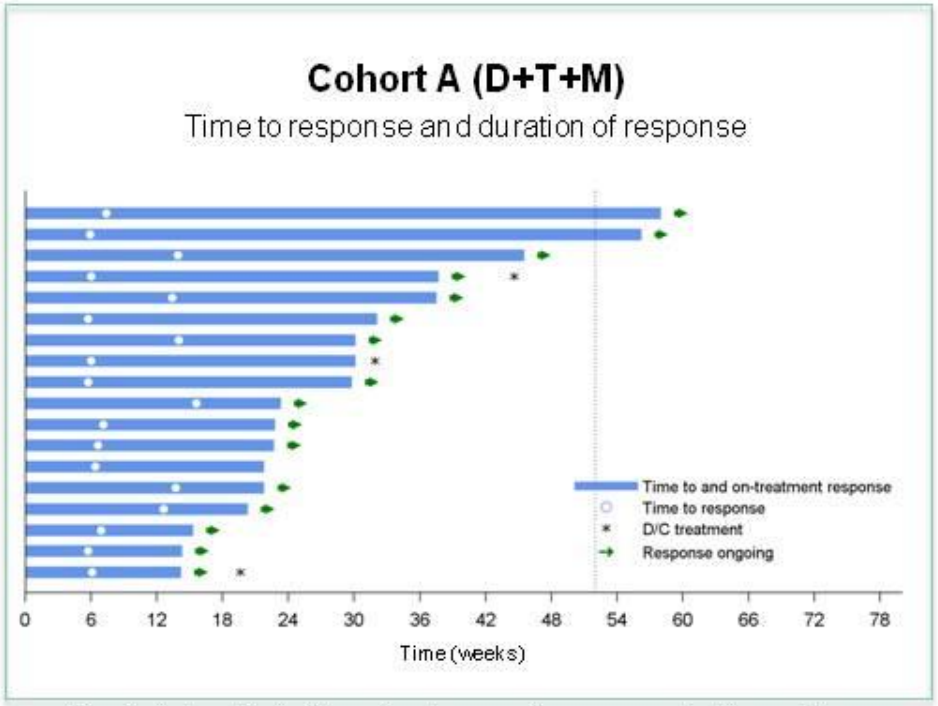


Figure includes subjects with confirmed response in response evaluable population;
D/C treatment=Discontinuation of the regimen

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

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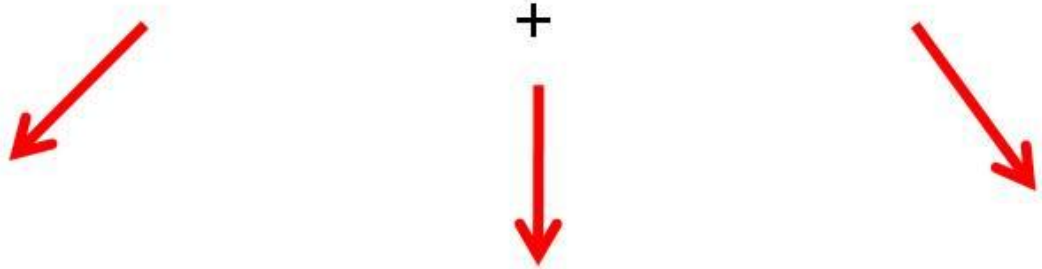
Next Steps Immunotherapy

Building on the Backbone

Monotherapy vs Doublet Therapy
PD-1 alone or PD-1 and Ipi

Triple Therapy ?

+



Vaccine Strategies

Other immunotherapies
GM-CSF
IDO inhibitors
OX40
LAG 3

Radiation: RadVax
Anti-VEGF


Opportunity
Just Ahead


Thanks