Systemic Immunotherapy for Advanced and High-risk Melanoma in 2017

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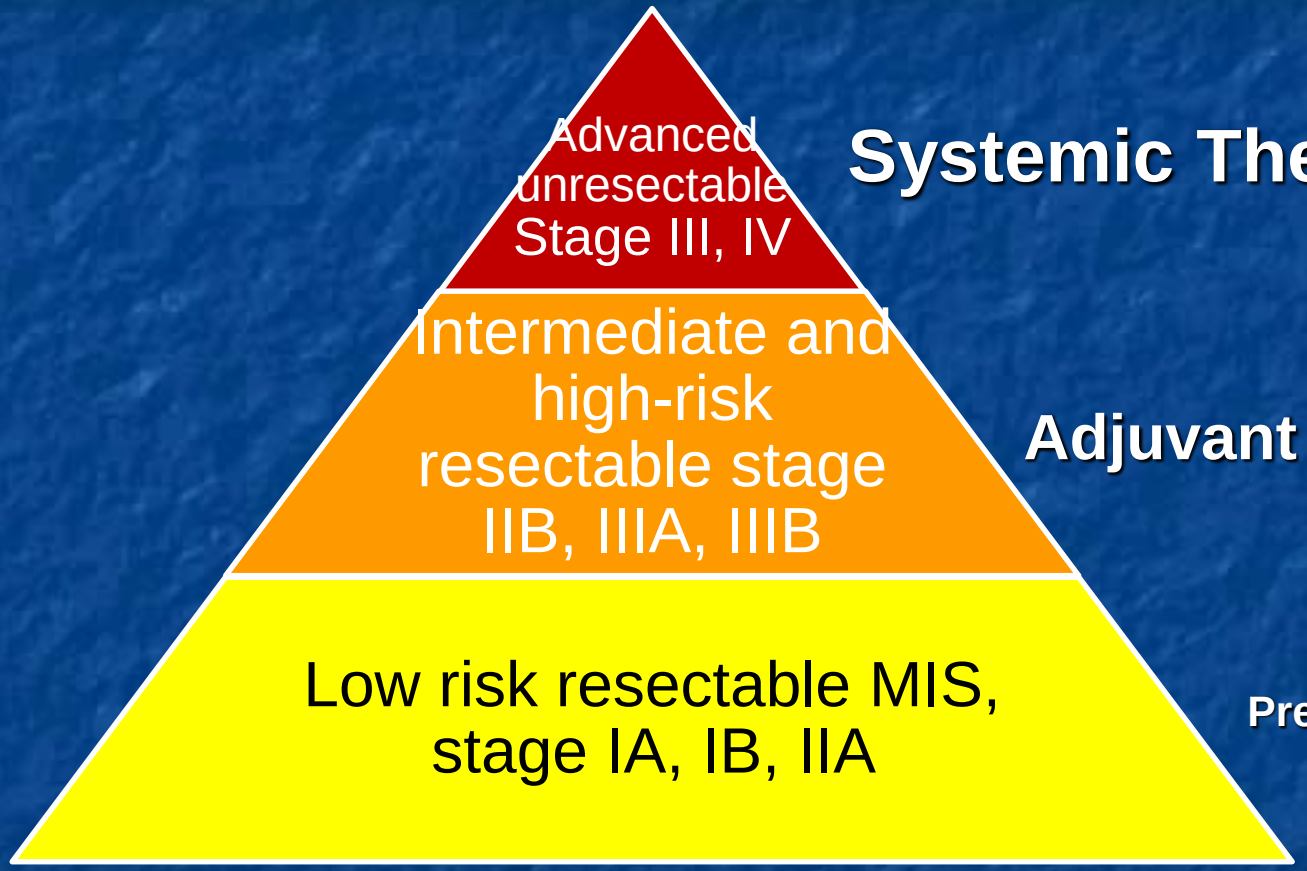
Distribution of Melanoma Burden by Stage



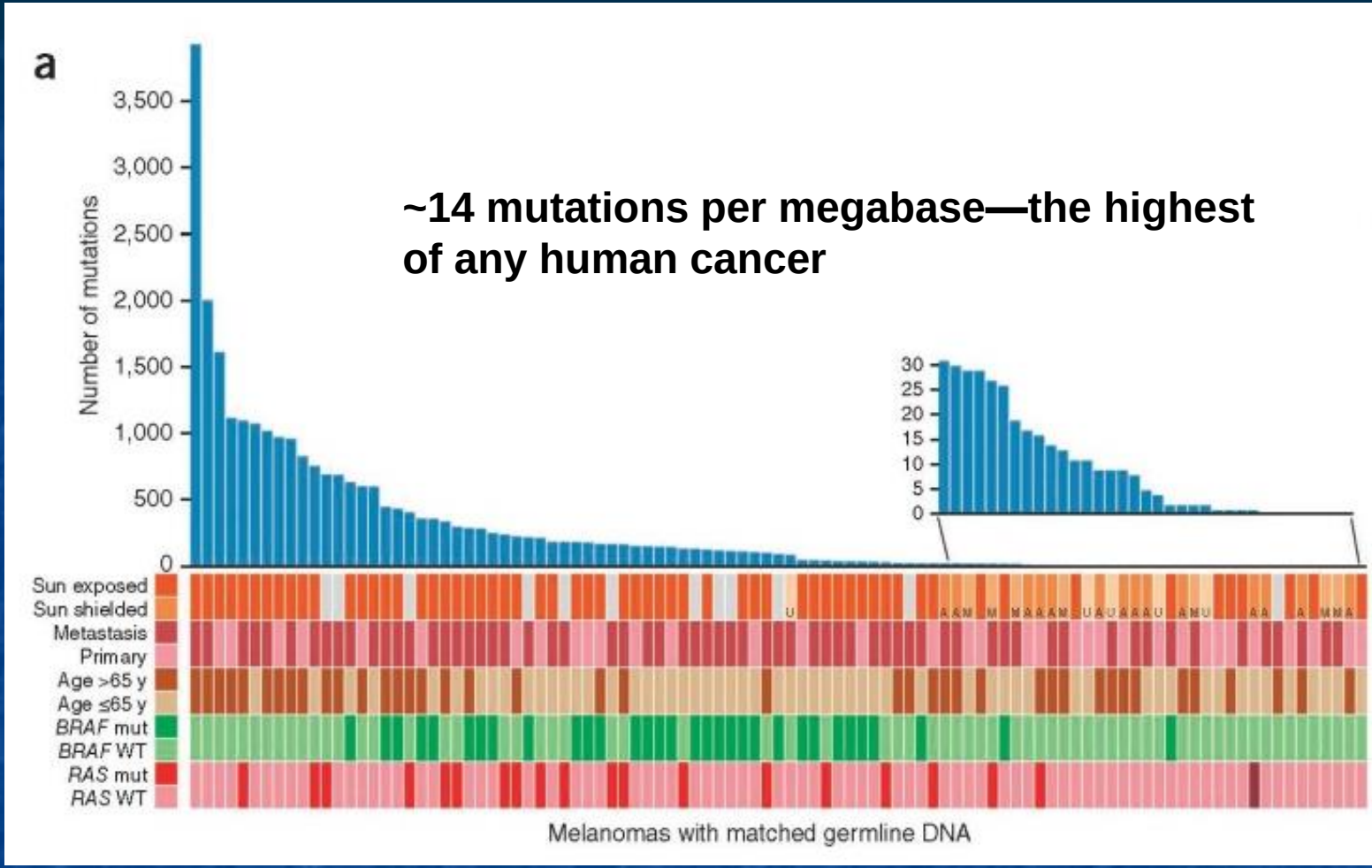
The burden of operable high-risk disease numerically dwarfs that of advanced melanoma while the burden of early disease exceeds both

Melanoma is an Immunogenic Tumor

Dialogue between Host and Tumor

- Primary melanoma is characterized by lymphocytic infiltrate (TIL)
  - TIL infiltrate at primary site has prognostic and potential predictive utility (PDL1)
  - TCGA analysis shows inflammatory infiltrate prognostic
- Melanoma spreads first and most frequently via lymphatics → nodal basin
  - Sentinel node mapping & biopsy adopted by AJCC for melanoma ≥1mm (1999), but
  - Few immunological or molecular studies of SLN to date
- Melanoma progression is associated with immune evasion and tolerance

Mutational Spectrum in Melanoma



Somatic nonsynonymous mutations across 99 matched melanoma samples: tumors represented as sun-exposed skin (dark orange bars) , sun-shielded skin (acral (A), mucosal (M) or uveal (U), shown in different shades of light orange) or unknown origin (gray bars). Primary compared to metastasis; age of the patients and BRAF, NRAS mutation status indicated. Mut, mutated; WT, wild type.

Krauthammer M, Kong Y, et al. Halaban R. Exome sequencing identifies recurrent somatic RAC1 mutations in melanoma. Nat Genet. 2012 Sep;44(9):1006-14. PMID: 22842228; PubMed Central PMCID: PMC3432702.

TCGA Lessons for Melanoma Immunotherapy

- No significant correlation of genomic classification with outcome
- Subclass with enriched immune gene expression associated with favorable OS
- Favorable ‘immune’ transcriptomic subclass is associated with LCK–a T cell signaling non-receptor TK, as well as lymphocyte infiltrate on pathology

Progress and Prospects for Systemic Melanoma Therapy

- Role of current available single agents
  - none w/ survival benefit (2010) →

    10 FDA approved and multiple pending (2017)
- Adjuvant setting as immunologically favorable window for improved results
  - One agent 1996-2015; anti-CTLA4 2015→ anti-PD1, and BRAF/MEK inhibitors 2017
  - Biomarkers needed for refined application
  - Neoadjuvant studies essential to progress

Immunotherapy of Melanoma

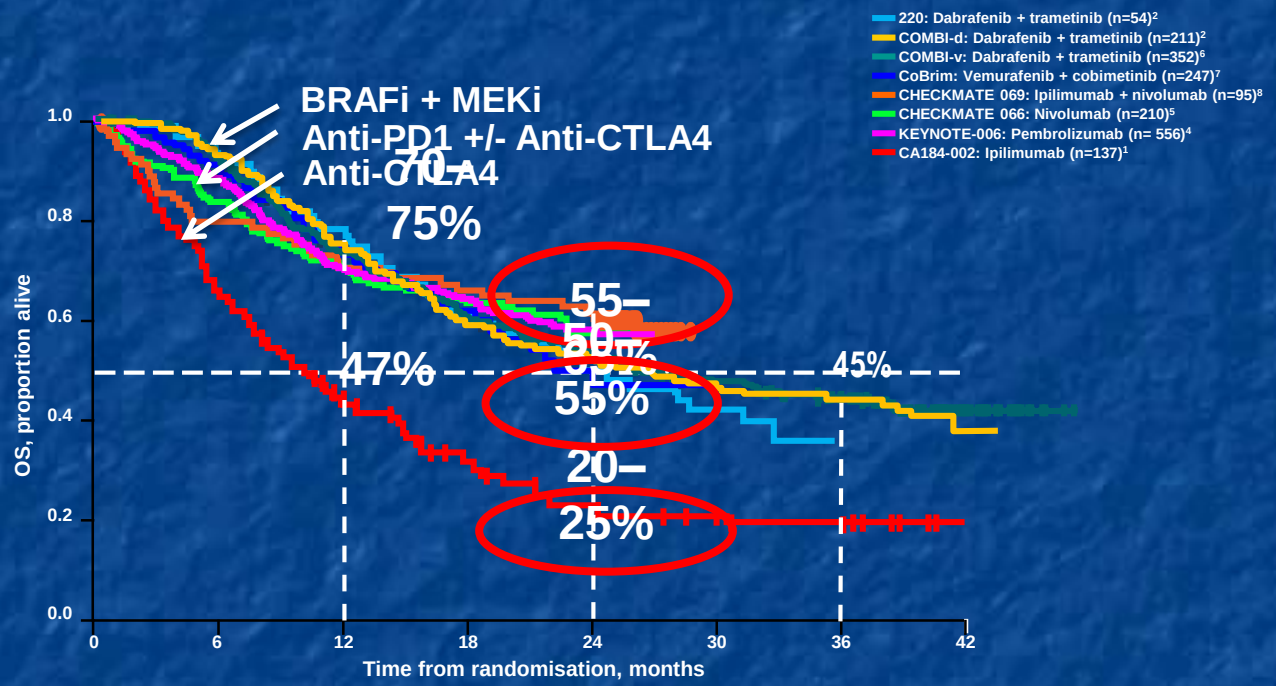
Advanced Disease

- High-dose bolus IL-2 (FDA approval 1998)
- Ipilimumab anti-CTLA4 blocking @ 3mg/kg (2011)
- Pembrolizumab and Nivolumab anti-PD1 mAbs (2014)
- Ipi-Nivo in BRAF WT, and now in BRAF mut (2015, 16)
- T-VEC in injectable met disease (2015)
  - Pending: PD-L1, TIM-3, LAG3, TIGIT …

Adjuvant Therapy

- High-dose IFNα (FDA approval 1996)
- Peg IFNα (FDA approval 2011)
- Ipilimumab anti-CTLA4 @ 10 mg/kg (2015)
  - Pending:
    - anti-PD1 Nivolumab, Pembrolizumab, Nivolumab/Ipilimumab
    - Combinations of anti-PD1 and IDO, 3rd Gen CBI
    - BRAFi, BRAFi/MEKi

Improving Overall Survival of Metastatic Melanoma



1. Hodi FS et al . NEJM 2010; 2. Flaherty Oral ASCO 2016; 3. Long GV et al Lancet 2015 & Flaherty K et al Oral ASCO 2016; 4. Robert C et al NEJM 2015; 372:2521 & Schachter J et al Oral ASCO 2016; 5. Robert C et al NEJM 2015; 372:320 and Atkinson V et al Poster SMR 2015; 6. Robert C Oral ESMO 2016; 7. Atkinson V et al . Oral SMR 2015; 8. Postow MA et al Oral AACR 2016;

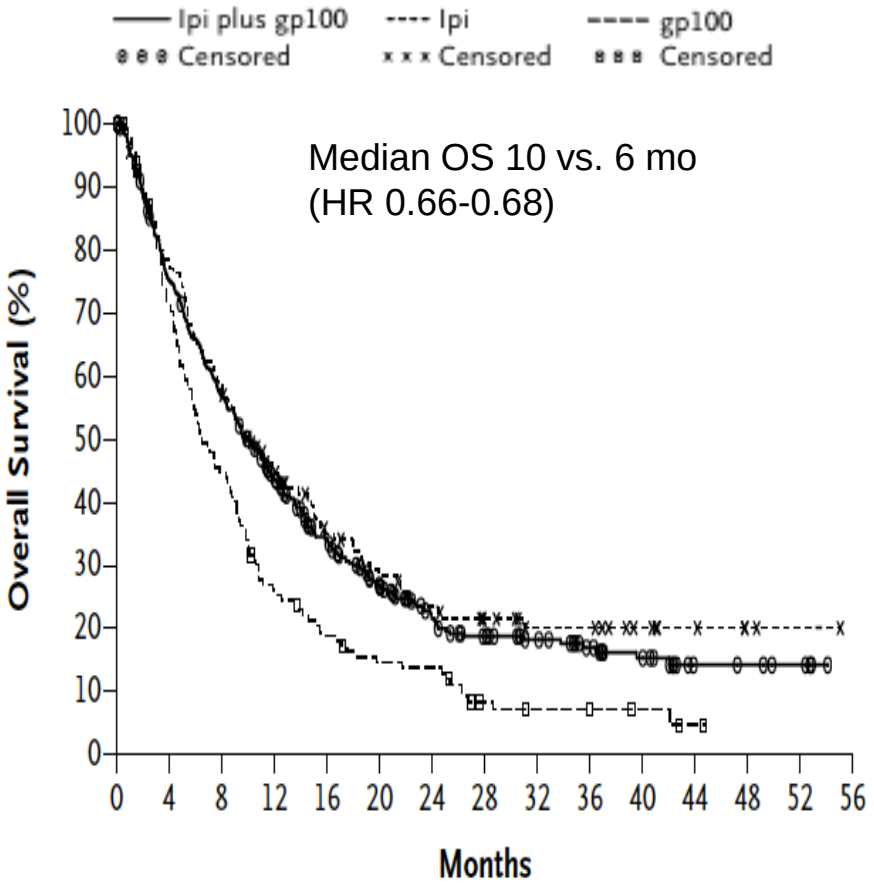
Slide Courtesy G V Long

Overall Survival for Advanced Melanoma Improved by anti-CTLA4 blocking mAb Ipilimumab

- mAb blocks the inhibitory receptor CTLA4 on immune cells
- Antitumor efficacy in murine tumor models alone enhanced with vaccines
- Synergism with vaccines not replicated in human melanoma
- Clinical benefits greatest in relation to endpoint of *overall survival*

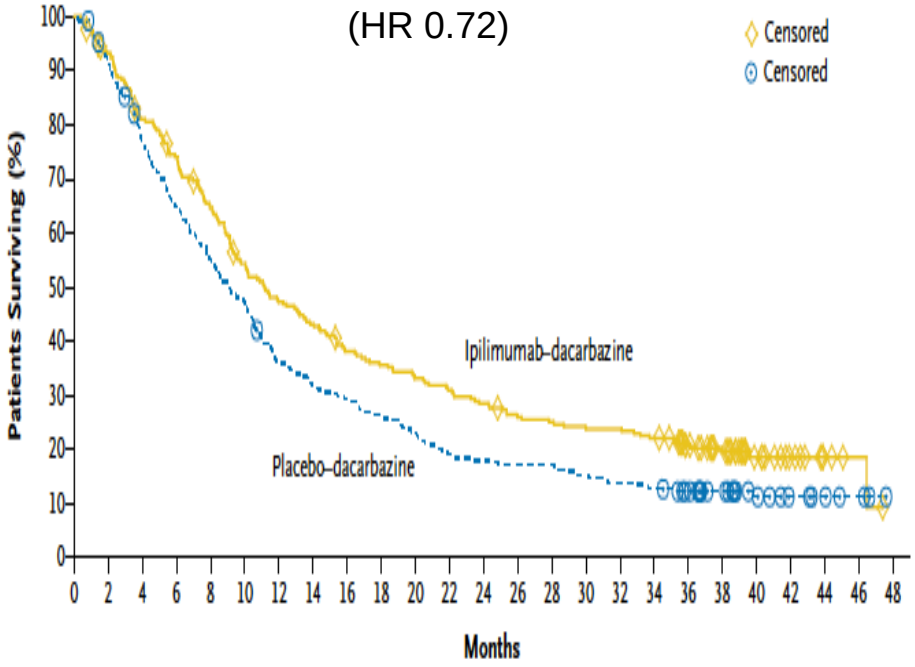
Improved Survival in Advanced Disease

Ipilimumab Results in Second and First Line



Median OS 10 vs. 6 mo
(HR 0.66-0.68)

3 mg/kg x 4 doses q3wks with or without gp100



Median OS 11.2 vs. 9.1 mo
(HR 0.72)

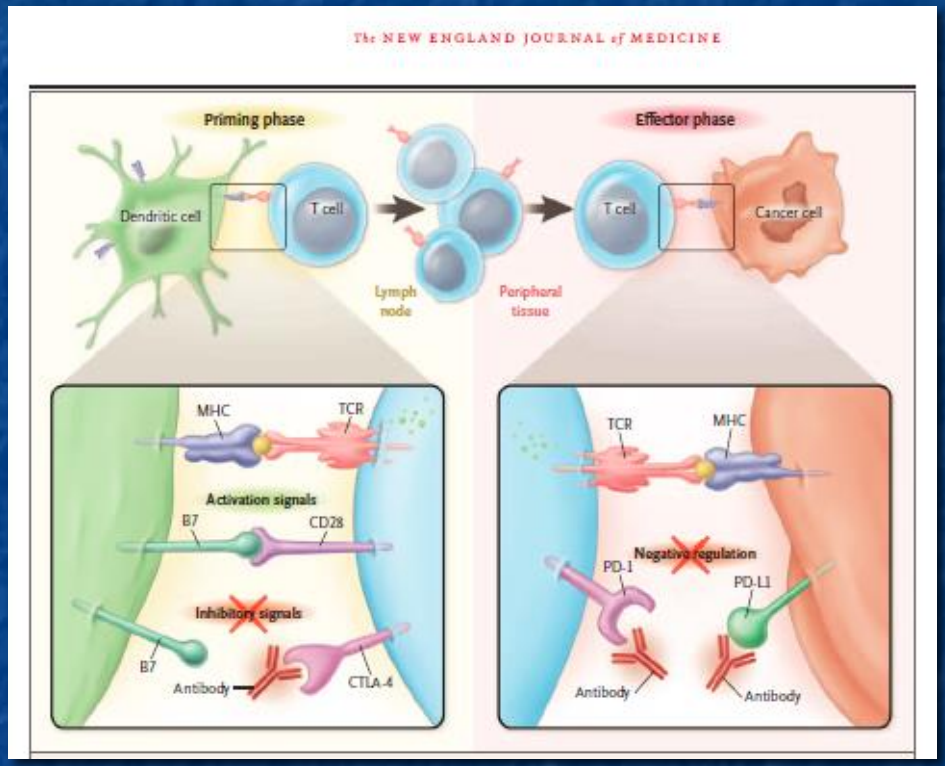
10 mg/kg x 4 doses q3wks then q3mos + dacarbazine

Hodi et al, NEJM 2010; Robert et al, NEJM 2011

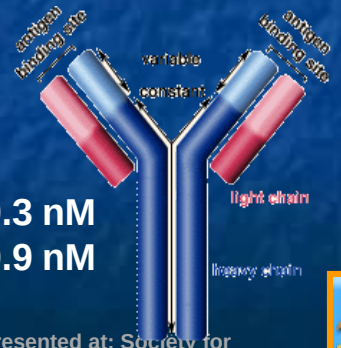
Toxicity of Ipilimumab: Immune-related AEs in up to 40%

- Skin
- Gastrointestinal
- Endocrine
- Liver

Second Generation Checkpoint Blockade



- CTLA-4–blocking antibodies release immune checkpoint at activation step of immune response to cancer
- PD-1–blocking antibodies release an immune checkpoint at effector step of immune response to cancer
  - Pembrolizumab is PD-1–blocking antibody with robust efficacy and manageable toxicity in patients with advanced melanoma[1-5]

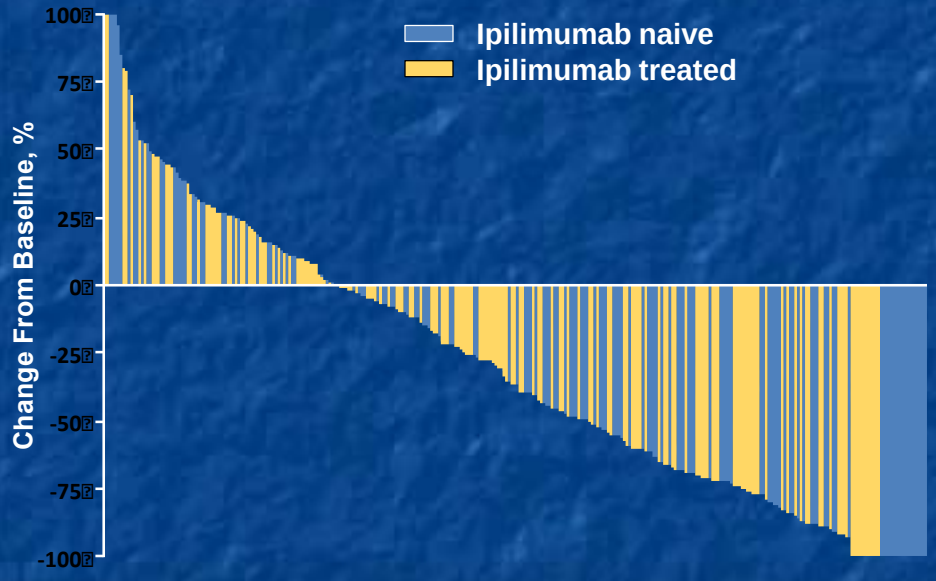


Human IgG4
K_D: ~29 pM
PD-L1 IC_{50}: ~0.1-0.3 nM
PD-L2 IC_{50}: ~0.5-0.9 nM

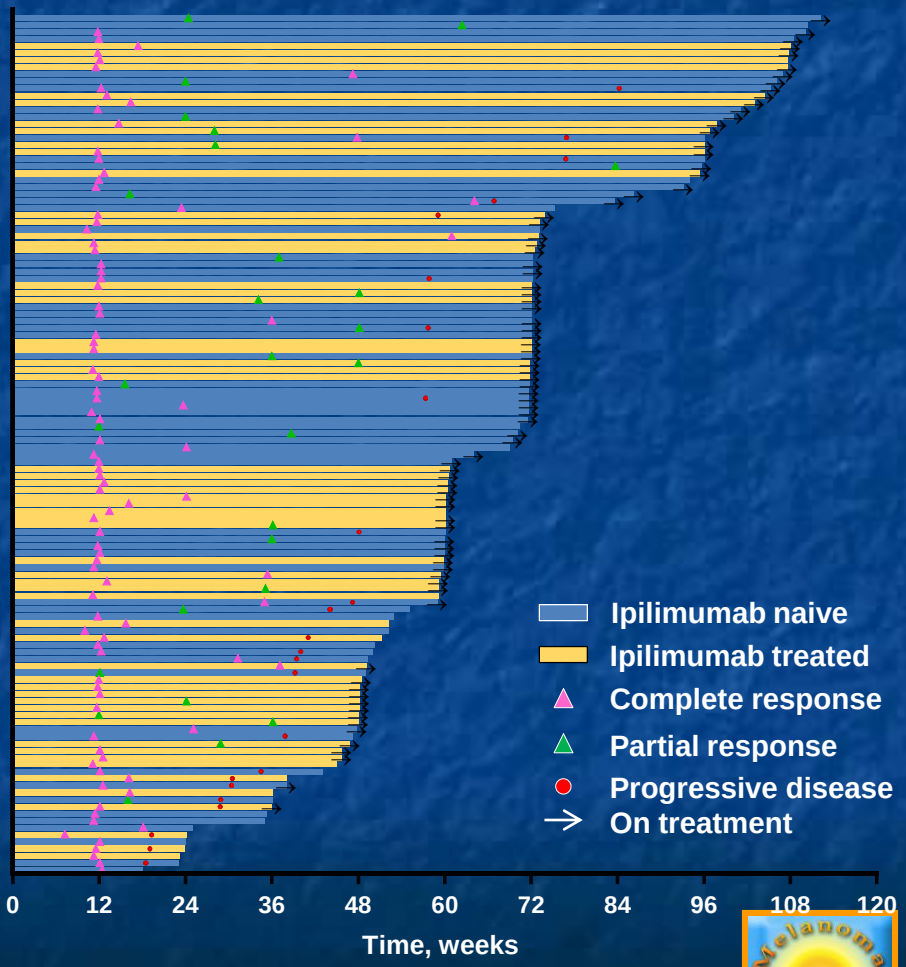
1. Hamid O et al. *N Engl J Med*. 2013;392:134-144; 2. Robert C et al. *Lancet*. 2014;384:1109-1117; 3. Daud A et al. Presented at: Society for Melanoma Research
2014 Annual Meeting; November 13-16, 2014; Zurich, Switzerland; 4. Robert C et al. Abstract LBA34. Presented at: ESMO 2014 Congress; September 26-30, 2014; Madrid, Spain; 5. Ribas A et al. Presented at: Society for Melanoma Research 2014 Annual Meeting; November 13-16, 2014; Zurich, Switzerland.

Anti-PD1 Pembrolizumab Efficacy in KEYNOTE-001

Maximum Percentage Change from Baseline in Tumor Size



Time to and Durability of Response



KEYNOTE-006 (NCT01866319): International, Randomized, Phase III Study

Patients

- Unresectable, stage III or IV melanoma
- ≤1 prior therapy, excluding anti–CTLA-4, PD-1, or PD-L1 agents
- Known *BRAF* status[b]
- ECOG PS 0-1
- No active brain metastases
- No serious autoimmune disease

R
1:1:1

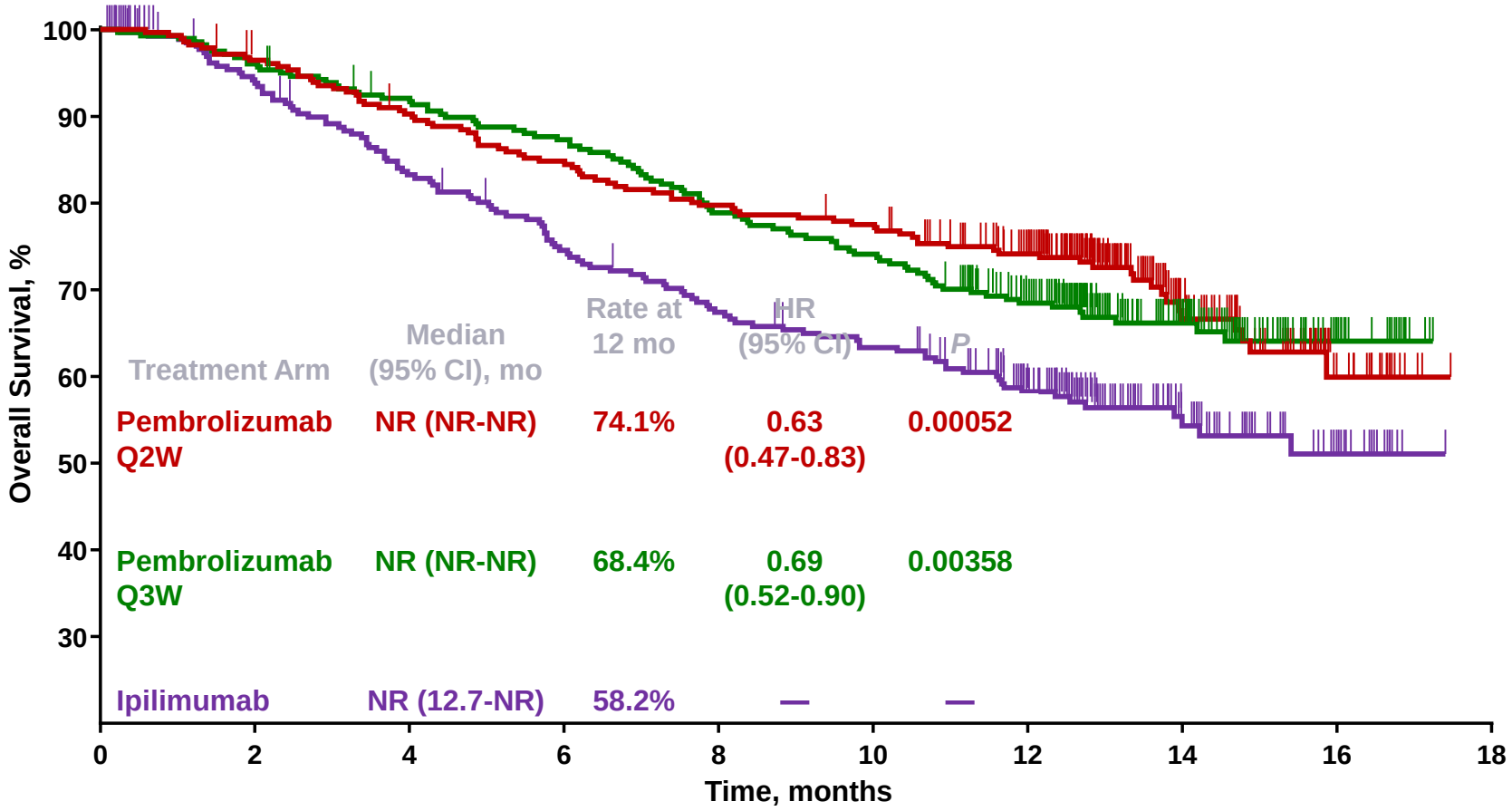
- **Pembrolizumab** 10 mg/kg IV Q2W
- **Pembrolizumab** 10 mg/kg IV Q3W
- **Ipilimumab** 3 mg/kg IV Q3W x 4 doses

Stratification factors:
- ECOG PS (0 vs 1)
- Line of therapy (first vs second)
- PD-L1 status (positive[c] vs negative)

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

[a]Patients enrolled from 83 sites in 16 countries.
[b]Prior anti-BRAF targeted therapy was not required for patients with normal LDH levels and no clinically significant tum related symptoms or evidence of rapidly progressing disease.
[c]Defined as membranous PD-L1 expression in ≥1% of tumor cells as assessed by IHC using the 22C3 antibody.

OS at the Second Interim Analysis (IA2)



No. at risk

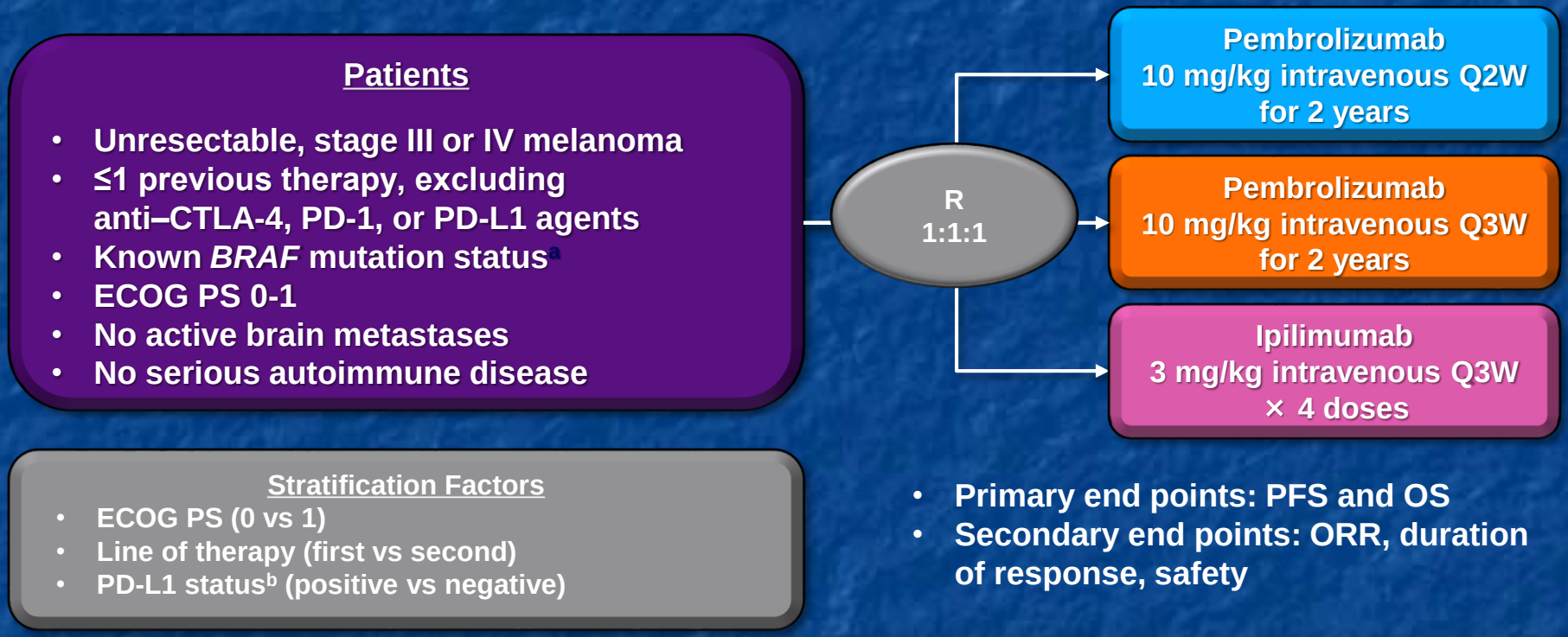
279	266	248	233	219	212	177	67	19	0
277	266	251	238	215	202	158	71	18	0
278	242	212	188	169	157	117	51	17	0

Analysis cut-off date: March 3, 2015.

Conclusions

- Pembrolizumab is superior to ipilimumab for
  - OS: risk of death reduced 31% to 37%
  - PFS: ~1.8-fold increase in 6-month rates
  - ORR: ~2.8-fold increase
- Favorable safety vs ipilimumab
- Similar efficacy, tolerability, for pembrolizumab schedules
- Results support first line use of pembrolizumab regardless of prior ipilimumab treatment

KEYNOTE-006 (NCT01866319) Study Update



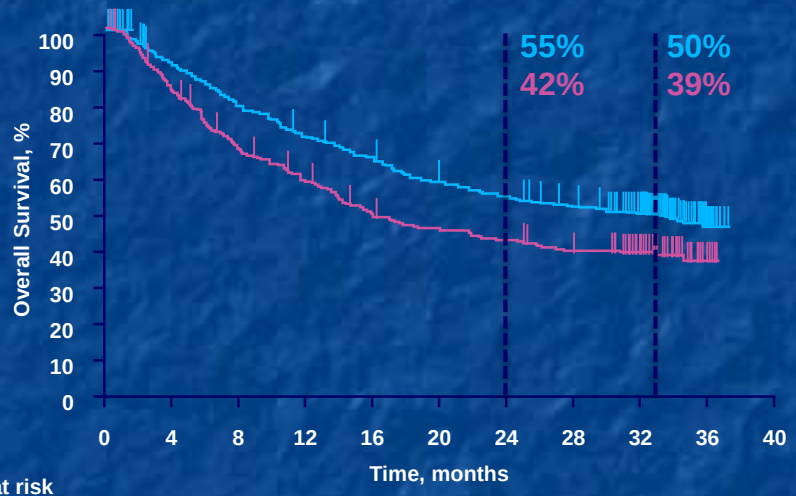
- Primary end points: PFS and OS
- Secondary end points: ORR, duration of response, safety

[a]Prior anti-BRAF targeted therapy was not required for patients with normal LDH levels and no clinically significant tumor-related symptoms or evidence of rapidly progressing disease. [b]Defined as ≥1% staining in tumor and adjacent immune cells as assessed by IHC (22C3 antibody).

Kaplan-Meier Estimates of Survival in Total Population (Median Follow-Up, 33.9 mo)

OS

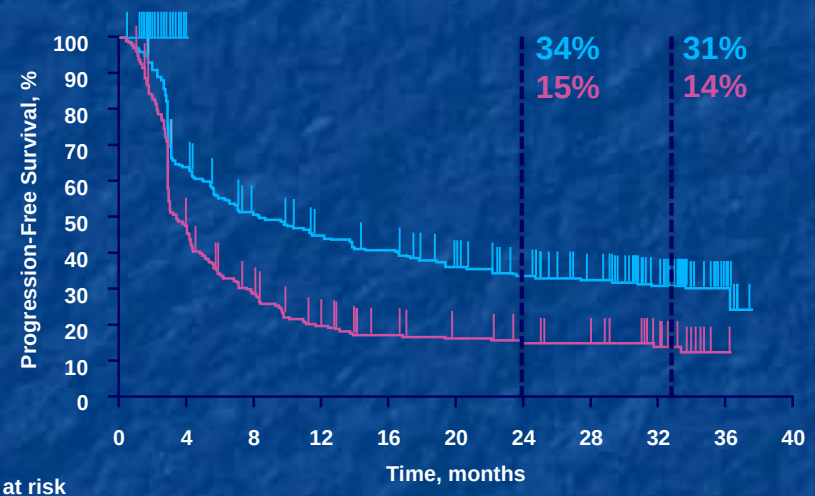
Arm	Events, n	HR (95% CI)	Median, mo (95% CI)
Pembrolizumab	278	0.70 (0.58-0.86)	32.3 (24.5-NR)
Ipilimumab	155	—	15.9 (13.3-22.0)



No. at risk											
Pembrolizumab	556	500	436	387	351	317	297	273	229	24	0
Ipilimumab	278	212	169	145	122	111	103	94	77	10	0

PFS per irRC by Investigator

Arm	Events, n	HR (95% CI)	Median, mo (95% CI)
Pembrolizumab	369	0.56 (0.47-0.67)	8.3 (6.5-11.2)
Ipilimumab	204	—	3.3 (2.9-4.1)



No. at risk											
Pembrolizumab	556	347	269	231	211	182	155	138	88	12	0
Ipilimumab	278	110	64	40	32	27	23	20	14	2	0

Analysis includes all randomized patients with measurable disease at baseline who received ≥1 pembrolizumab dose.
Data cutoff date: Nov 3, 2016.

Post Study Antineoplastic Therapy

Therapy, n (%)	Pembrolizumab N = 555	Ipilimumab N = 256
Any[a]	247 (44)	138 (54)
Immunotherapy	172 (31)	97 (39)
Anti–CTLA-4	137 (25)	13 (5)
Anti–PD-1	49 (9)[b]	86 (34)[c]
Anti–PD-L1	3 (<1)	2 (<1)
Anti–CLTA-4 + anti–PD-1	0	1 (<1)
BRAF inhibitor ± MEK inhibitor	130 (23)	81 (32)
Chemotherapy	64 (11)	32 (12)
Other therapy	11 (4)	13 (5)

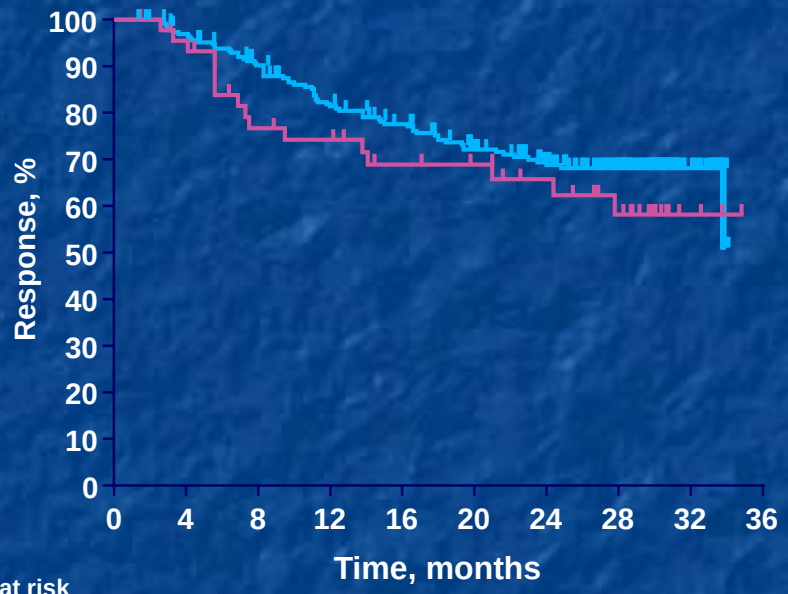
[a]Patients may have received ≥1 poststudy therapy. [b]27 received pembrolizumab; 22 received nivolumab. [c]44 received pembrolizumab; 42 received nivolumab.
Data cutoff date: Nov 3, 2016.

Tumor Response (irRC, investigator)

	Pembrolizumab N = 556	Ipilimumab N = 278
ORR, % (95% CI)	42 (38-46)	16 (12-21)
Best overall response, % (95% CI)		
CR	13 (11-16)	3 (1-6)
PR	29 (25-33)	14 (10-18)
SD	21 (18-25)	25 (20 -31)
PD	29 (26-33)	39 (33-45)

Analysis includes all randomized patients with measurable disease at baseline who received ≥1 pembrolizumab dose. Data cutoff date: Nov 3, 2016.

Kaplan-Meier Estimate of Response Duration (irRC, investigator)

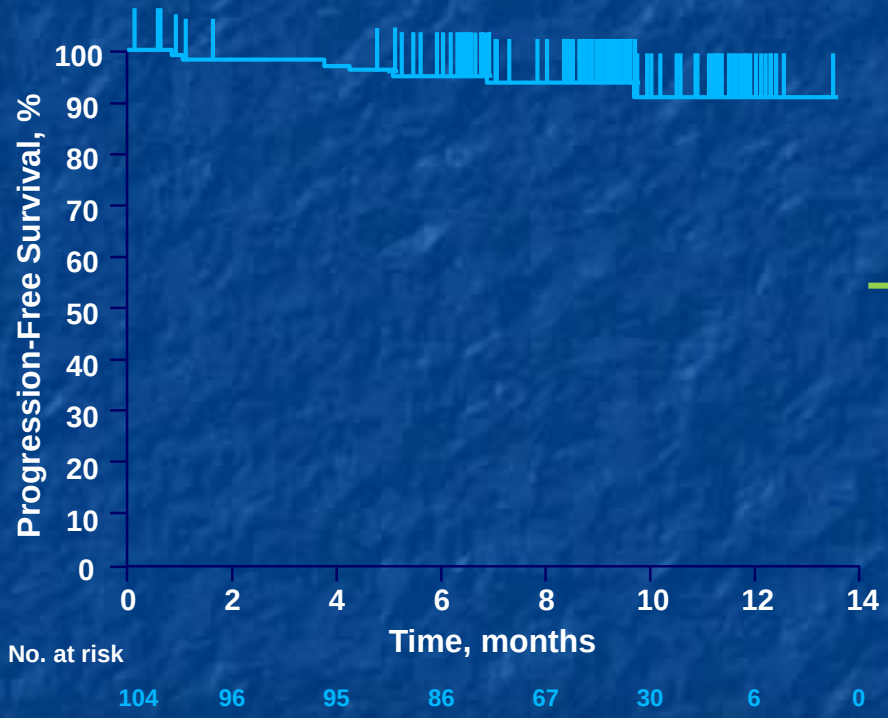


Arm	Responders, n	Median (range), months	Ongoing Response, n (%)[a]
Pembrolizumab	233	NR (1.0+ to 33.8+)	165 (71)
Ipilimumab	46	NR (1.1+ to 34.8+)	30 (65)

[a]Patients without progression, death, or new anticancer therapy. Data cutoff date: Nov 3, 2016.

Once achieved, responses with anti-PD1 are as durable (71%) ~ as anti CTLA4 (65%) at 3 years

PFS (irRC, investigator) From Last Pembrolizumab Dose to PD or Death in Patients Who Completed Protocol-Specified Time on Pembrolizumab (n = 104)

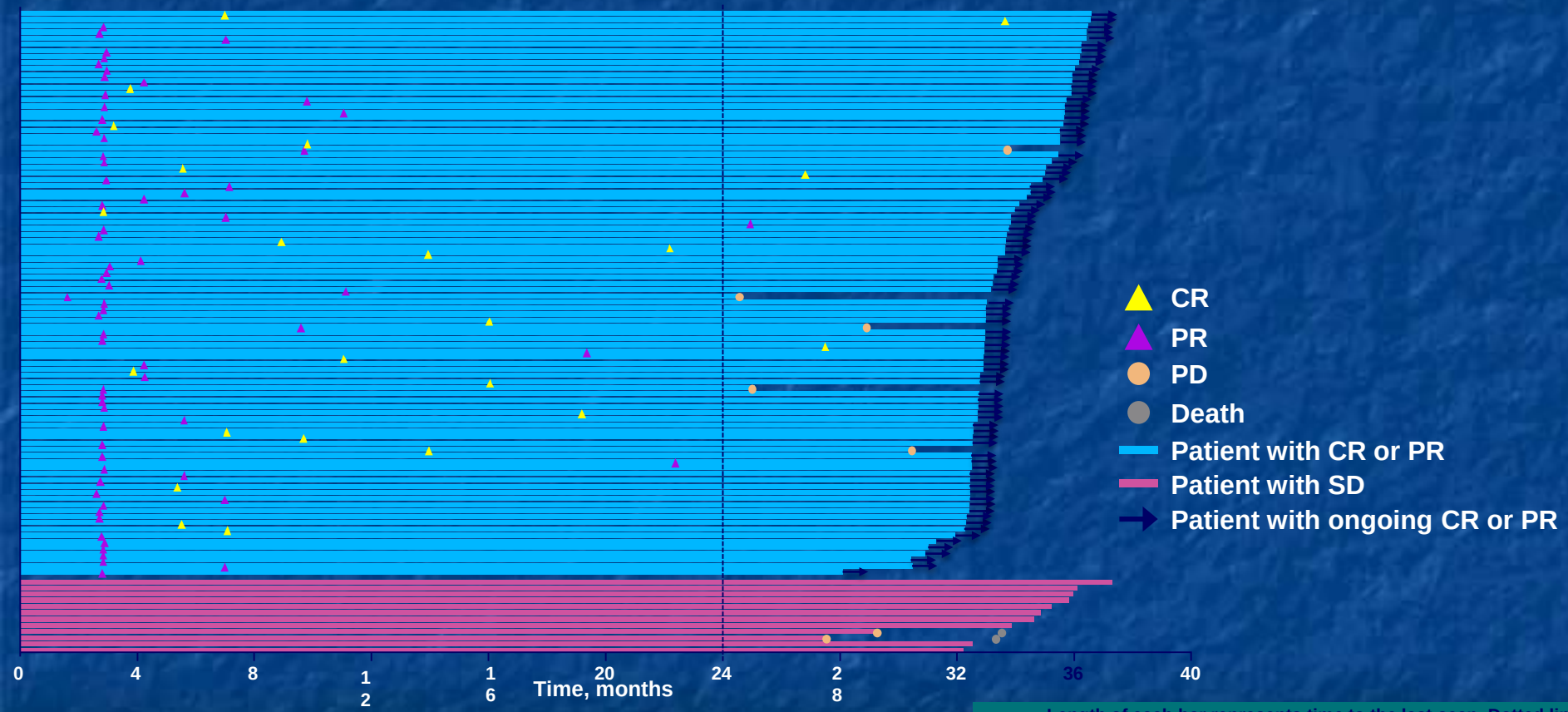


Patients who completed protocol-specified time on pembrolizumab, n	Estimated PFS, % (95% CI)	Median PFS
104	91 (80-96)	NR

- 102 (98%) patients were alive after a median of 9.7 months after completing pembrolizumab treatment

Data cutoff date: Nov 3, 2016.

Treatment Exposure and Response Duration in Patients Who Completed Protocol-Specified Time on Pembrolizumab (n = 104)



Length of each bar represents time to the last scan. Dotted line represents time of protocol-specified pembrolizumab discontinuation.
Data cutoff date: Nov 3, 2016.

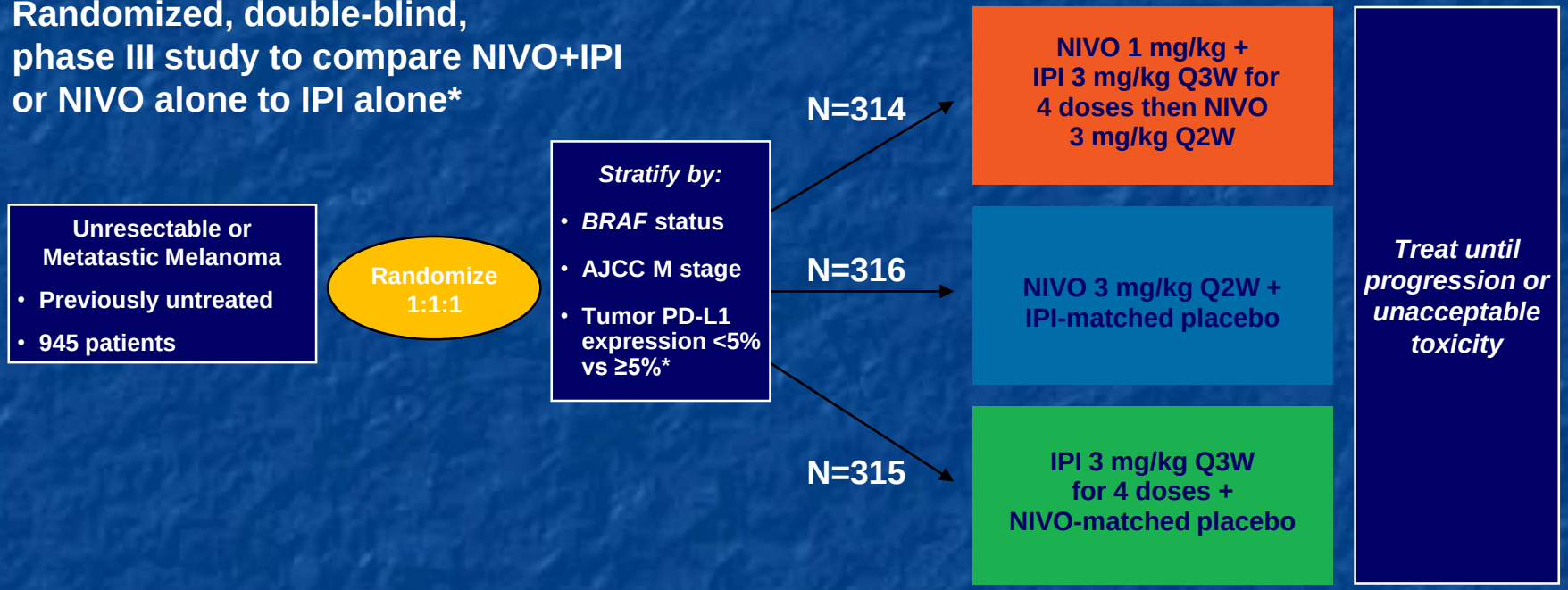
Summary and Conclusions

- After a median follow-up of nearly 3 years, superiority of pembrolizumab over ipilimumab was confirmed
  - Median OS: 32.3 vs 15.9 months
  - Median PFS: 8.3 vs 3.3 months
  - Favorable safety profile
- 91% of patients who completed 2 years of pembrolizumab treatment are progression free after median follow-up of 9.7 mos
- Data further support use of pembrolizumab as standard of care for patients with advanced melanoma

Robert et al Proc ASCO 2017

CheckMate 067: Study Design

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*

Study Endpoints: NIVO+IPI or NIVO vs IPI

- **Co-primary endpoints:**
  - PFS and OS (intent-to-treat population)
- **Secondary / exploratory endpoints:**
  - ORR by RECIST v1.1
  - Efficacy by tumor PD-L1 expression level
  - Safety profile (in patients who received ≥1 dose of study drug)
- **Current analysis:**
  - Per protocol, 644 deaths were projected to occur at 28 months (99% power to detect a HR of 0.65 for each NIVO-containing arm vs IPI)
    - actual number of deaths was 28% lower than anticipated (95% power to detect HR of 0.65 vs IPI)
  - The study was not powered for comparison between NIVO+IPI and NIVO

Updated Response To Treatment

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

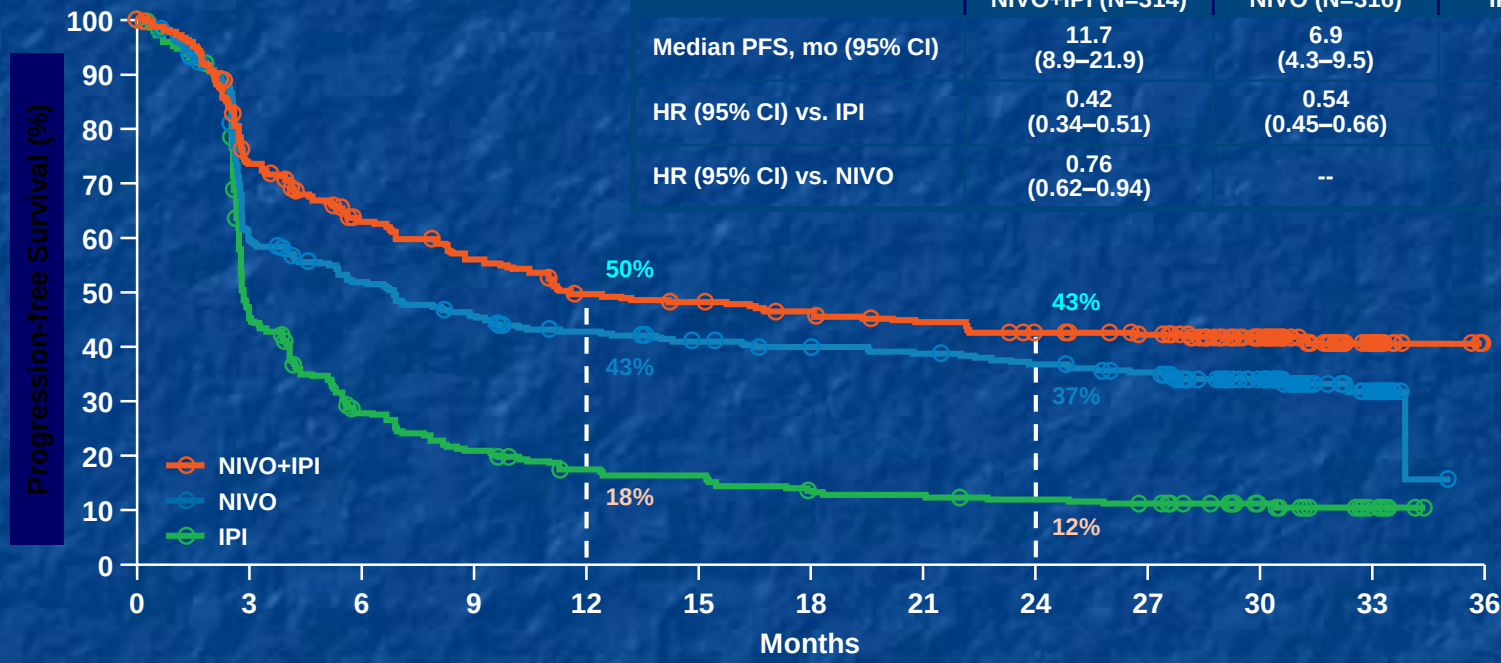
***By RECIST v1.1; NR = not reached.**

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

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

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:

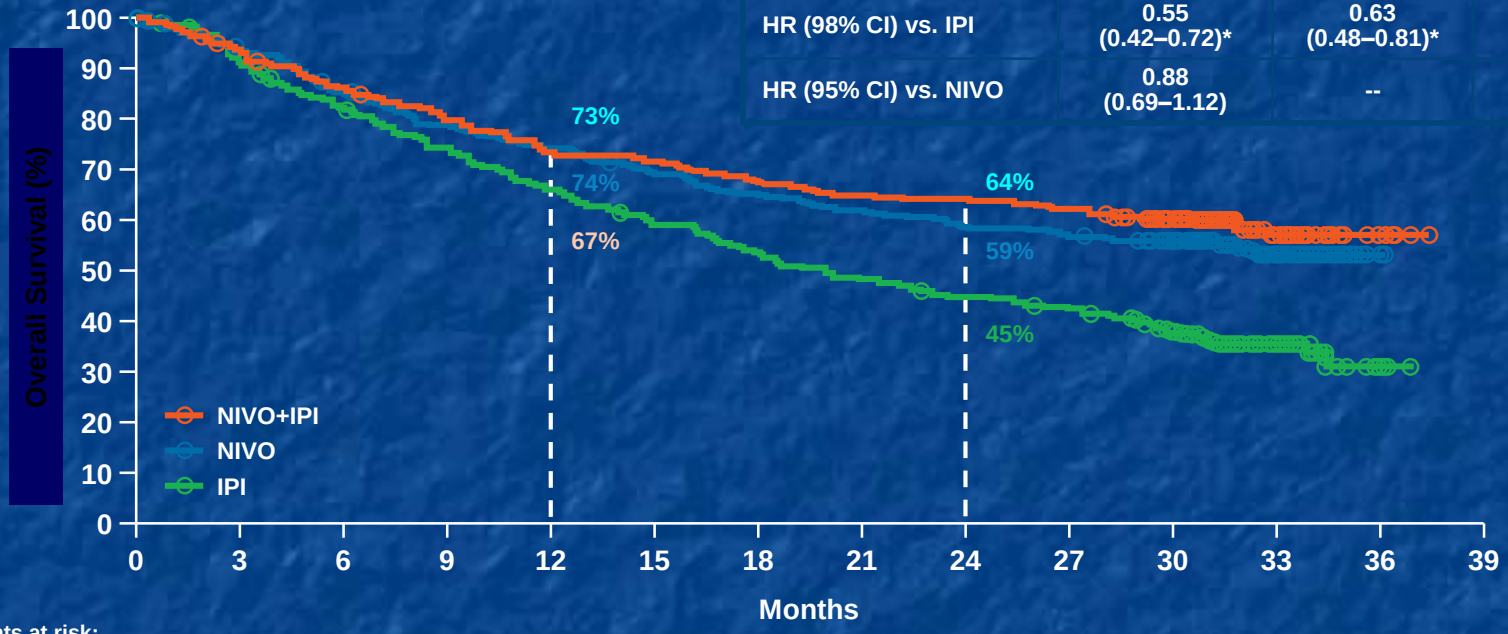
NIVO+ IPI	314	218	176	156	137	132	125	118	110	104	71	16	0
NIVO	316	178	151	132	120	112	107	103	97	88	62	16	0
IPI	315	136	77	58	46	43	35	33	30	27	16	5	0

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

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:

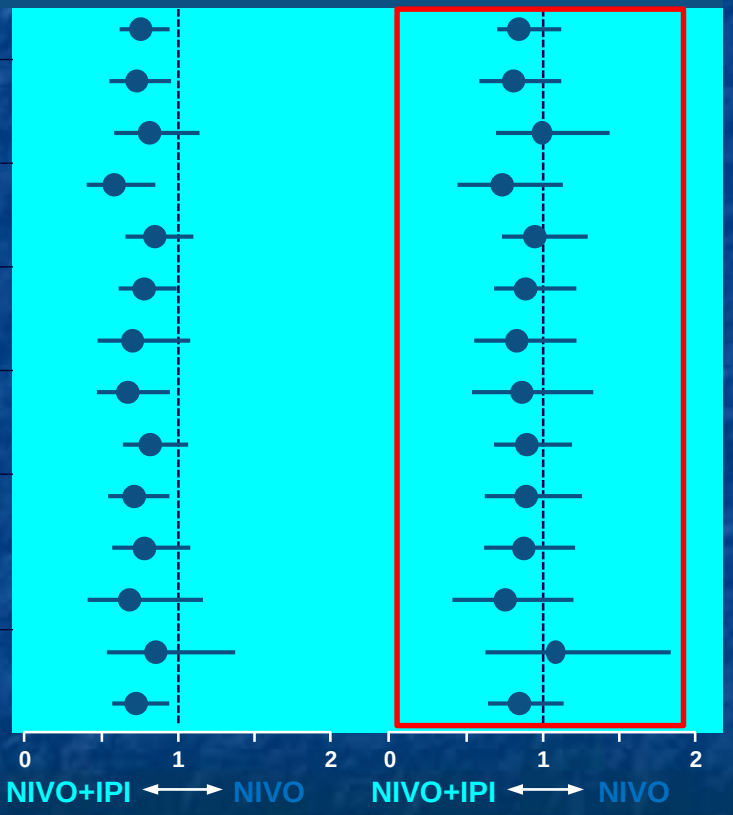
NIVO+IPI	314	292	265	247	226	221	209	200	198	192	170	49	7	0
NIVO	316	292	265	244	230	213	201	191	181	175	157	55	3	0
IPI	315	285	254	228	205	182	164	149	136	129	104	34	4	0

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

PFS and OS Subgroup Analyses (All Randomized Patients)

Descriptive comparison between NIVO+IPI and NIVO

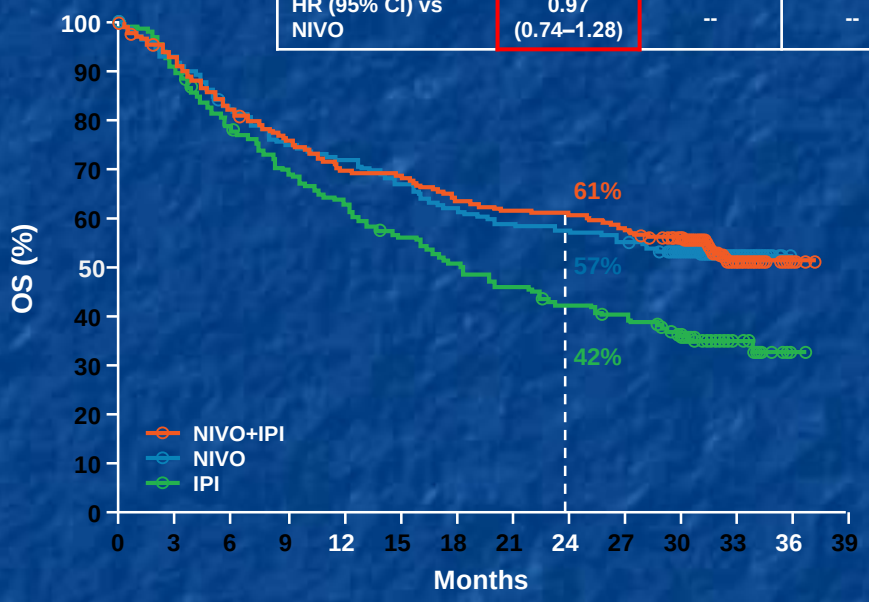
	Patients		Unstratified Hazard Ratio	
Subgroup	NIVO+IPI	NIVO	PFS	OS
Overall	314	316	0.77	0.89
<65 years	185	198	0.74	0.81
≥65 years	129	118	0.82	0.99
BRAF Mutant	102	98	0.60	0.71
BRAF Wild-type	212	218	0.86	0.97
ECOG PS = 0	230	237	0.79	0.91
ECOG PS = 1	83	78	0.72	0.82
M0/M1a/M1b	129	132	0.67	0.84
M1c	185	184	0.83	0.90
LDH ≤ ULN	199	197	0.72	0.89
LDH > ULN	114	112	0.79	0.86
LDH > 2 x ULN	37	37	0.70	0.71
PD-L1 ≥5%	68	80	0.87	1.05
PD-L1 <5%	210	208	0.73	0.84



OS in Patients with *BRAF* Wild-type and Mutant Tumors

BRAF Wild-type

	NIVO+IPI	NIVO	IPI
Median, mo (95% CI)	NR (27.6–NA)	NR (25.8–NR)	18.5 (14.8–23.0)
HR (95% CI) vs NIVO	0.97 (0.74–1.28)	--	--

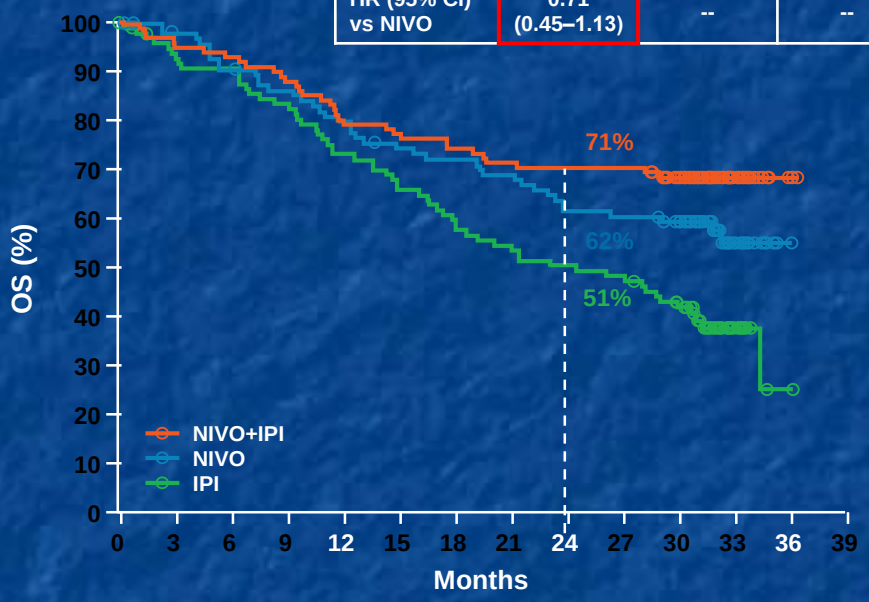


Patients at risk:

NIVO+IPI	212	194	170	157	144	142	133	127	126	120	108	31	5	0
NIVO	218	199	179	163	155	144	134	127	124	119	105	38	2	0
IPI	215	194	166	147	134	118	106	96	87	82	67	21	3	0

BRAF Mutant

	NIVO+IPI	NIVO	IPI
Median, mo (95% CI)	NR	NR (26.4–NR)	24.6 (17.9–31.0)
HR (95% CI) vs NIVO	0.71 (0.45–1.13)	--	--



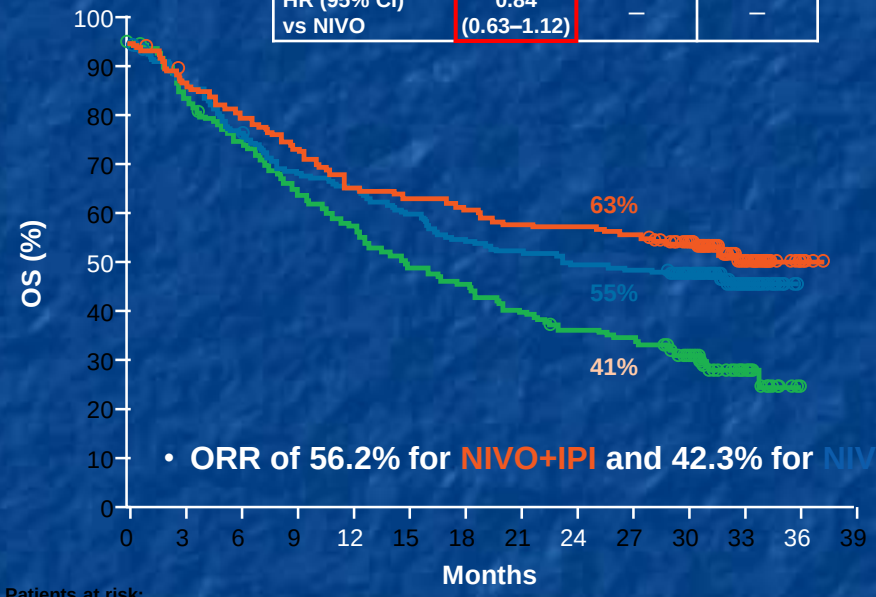
Patients at risk:

NIVO+IPI	102	98	95	90	82	79	76	73	72	72	62	18	2	0
NIVO	98	93	86	81	75	69	67	64	57	56	52	17	1	0
IPI	100	91	88	81	71	64	58	53	49	47	37	13	1	0

OS by Tumor PD-L1 Expression, 5% Cutoff

PD-L1 Expression Level <5%

	NIVO+IPI	NIVO	IPI
Median OS, mo (95% CI)	NR (31.8–NR)	NR (23.1–NR)	18.5 (13.7–22.5)
HR (95% CI) vs NIVO	0.84 (0.63–1.12)	–	–

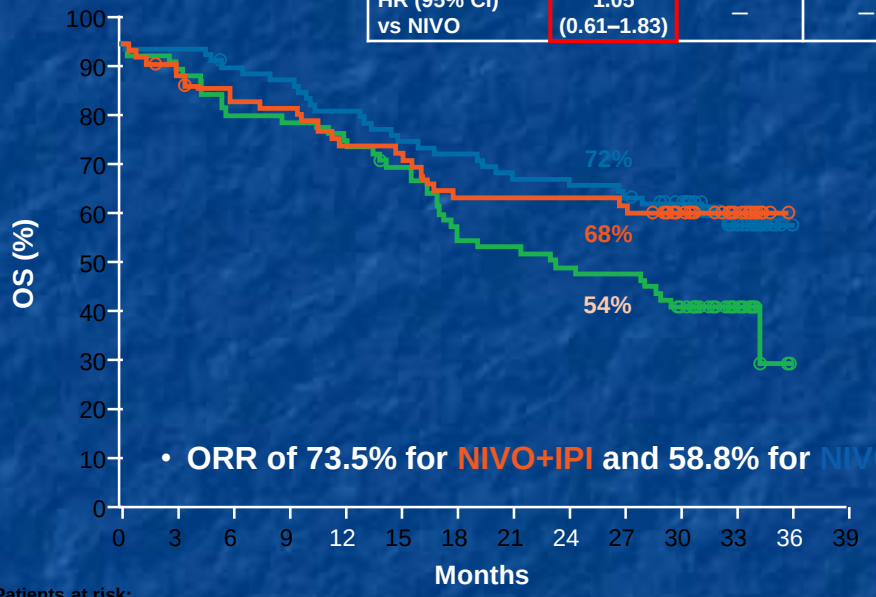


- ORR of 56.2% for NIVO+IPI and 42.3% for NIVO

Patients at risk:														
NIVO+IPI	210	194	178	163	146	144	139	131	130	127	116	34	7	0
NIVO	208	189	169	151	144	133	123	118	112	110	99	34	2	0
IPI	202	179	158	140	125	108	100	90	81	78	63	18	2	0

PD-L1 Expression Level ≥5%

	NIVO+IPI	NIVO	IPI
Median OS, mo (95% CI)	NR	NR	28.9 (18.1–NR)
HR (95% CI) vs NIVO	1.05 (0.61–1.83)	–	–



- ORR of 73.5% for NIVO+IPI and 58.8% for NIVO

Patients at risk:														
NIVO+IPI	68	63	56	55	52	50	45	45	45	44	35	11	0	0
NIVO	80	79	75	73	68	63	61	58	57	54	49	18	1	0
IPI	75	72	67	65	61	55	46	43	40	39	33	13	1	0

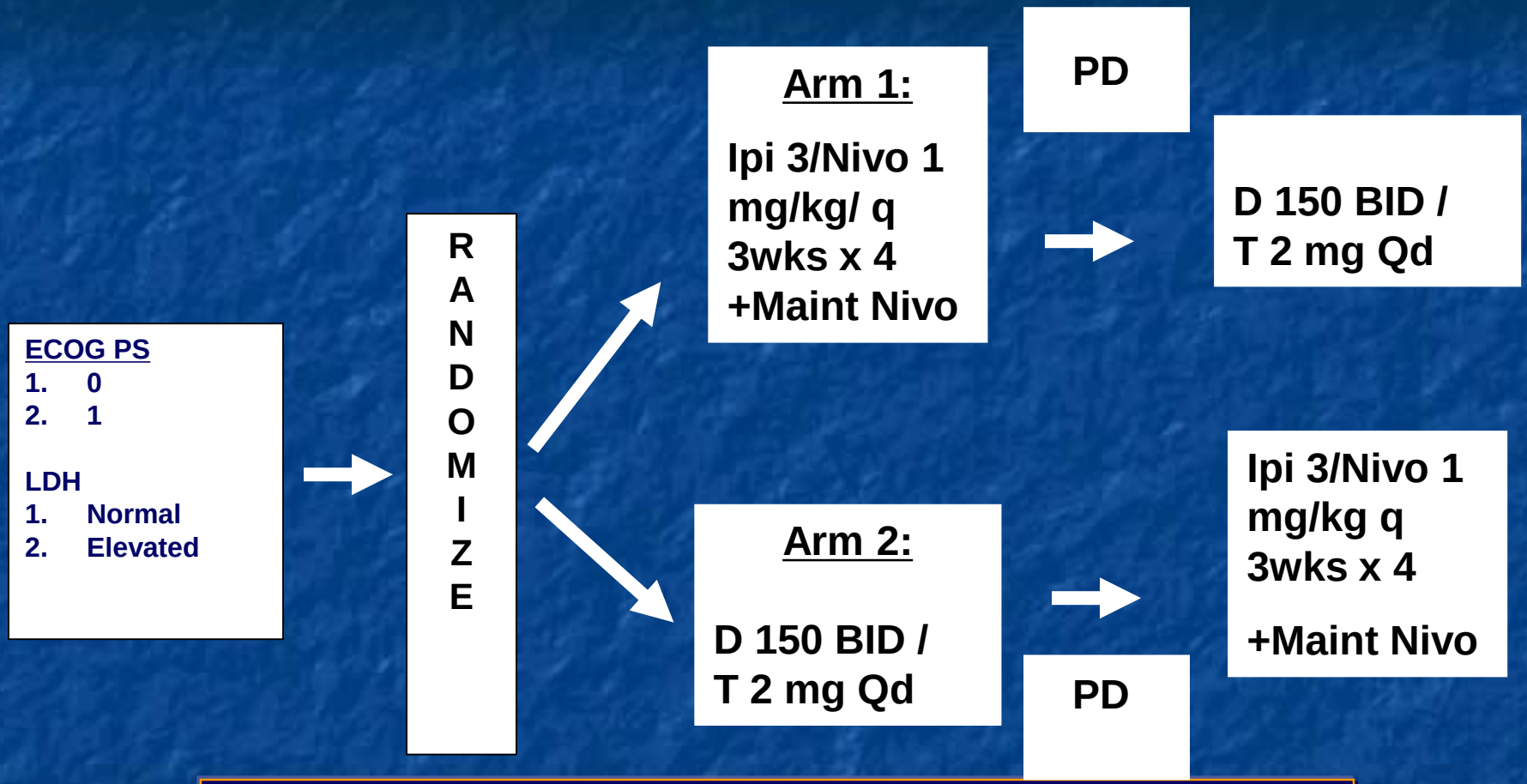
Conclusions

- NIVO+IPI and NIVO significantly improved OS and PFS vs. IPI alone in patients with untreated advanced melanoma
- NIVO+IPI resulted in numerically higher OS, PFS and ORR vs. NIVO alone
  - These are not statistically significantly better than NIVO in this analysis at maturity
  - Results consistently favored NIVO+IPI across clinically relevant subgroups, including PD-L1 expression <5% or <1%, mutant *BRAF*, and elevated LDH
  - Although similar prolongation of OS was observed with NIVO and NIVO+IPI for PD-L1 expression ≥5% or ≥1%, NIVO+IPI resulted in higher ORR regardless of PD-L1 expression
- For NIVO+IPI, median DOR & time to subsequent therapy are still not reached
- The safety profile of the combination is consistent with earlier experience, and early discontinuation due to AEs did not preclude benefit

Single Agent Anti-PD1 Blockade: Future Directions

- What duration of treatment is required?
  - Randomized discontinuation trial needed
- Adjuvant protocols
  - BMS 238 Study: Nivo vs. Ipi
  - US Intergroup S1404: Pembro vs. IFN or Ipi
  - EORTC: Pembro vs. placebo with crossover
- Combinations:
  - With other immunotherapy, targeted therapy, RT, Vaccines
- Biomarker refinement to select patients for optimal intervention for DFS, OS
- What initial therapy best for BRAFmut patient?

Phase III Intergroup Trial: EA6134
Ipi/Nivo → D/T vs D/T → Ipi/Nivo



ECOG led intergroup protocol EA6134
– Atkins, Chmielowski, Ribas and Kirkwood
Open and active July 2015

Additional Combinations of Potential Interest:

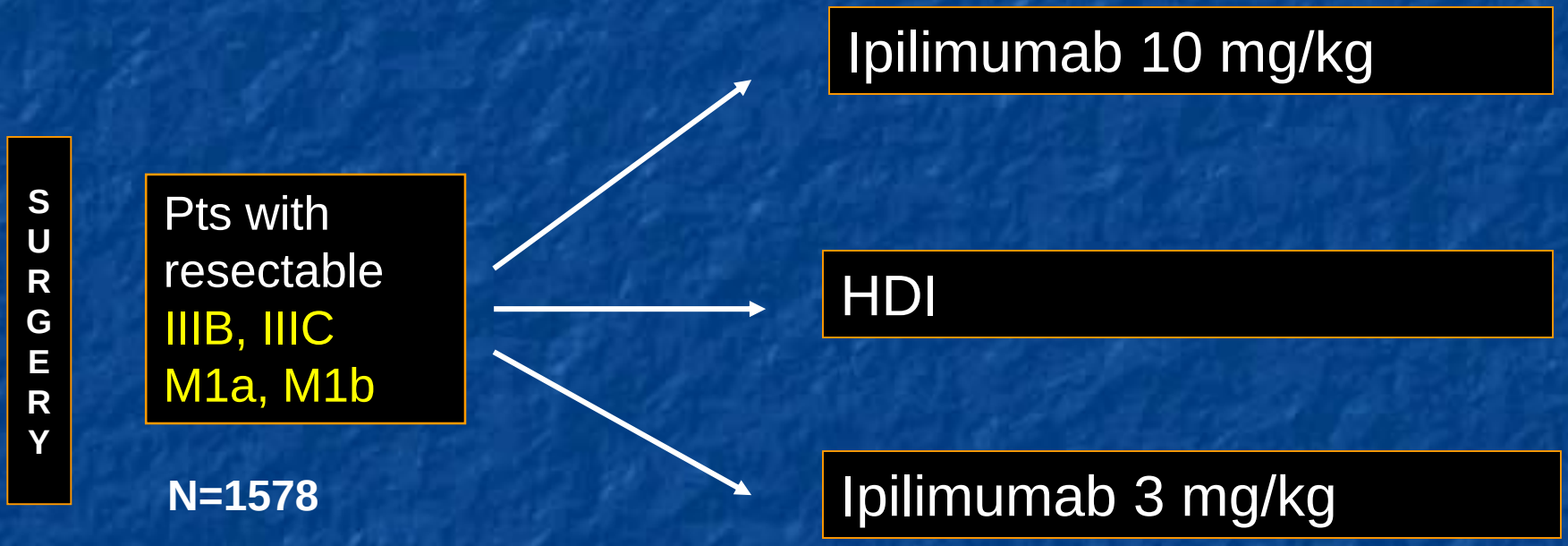
- Molecular inhibitors of tumor (BRAF+MEK)
- Immunotherapy doublets (anti-CTLA4/PD1 anti-CTLA4+IFN, anti-PD1+IFN, anti-PD1+IDO)
- Molecular inhibitors of tumor + Immunotherapy
  - Molecular inhibitors of tumor and Immunotherapy BRAFi+anti-PD1 (UPCI 15-131)

Adjuvant Immunotherapy of Melanoma

- Standard of Care: IFN (E1684) 1996→
  - New formulation PegIFN (EORTC 18991)
- New options with anti-CTLA4
  - Ipi 10 mg/kg vs Placebo EORTC 18071 2015→
  - Ipi 10 mg/kg or 3 mg/kg vs IFN E1609
- New options with anti-PD1
  - Pembrolizumab vs IFN S1404
  - Nivo vs Ipi BMS 238

US Intergroup Adjuvant Phase III Trial E1609: Ipilimumab vs. HDI

(Accrual of 1678 Adult Pts Completed Aug 2014)



Endpoints

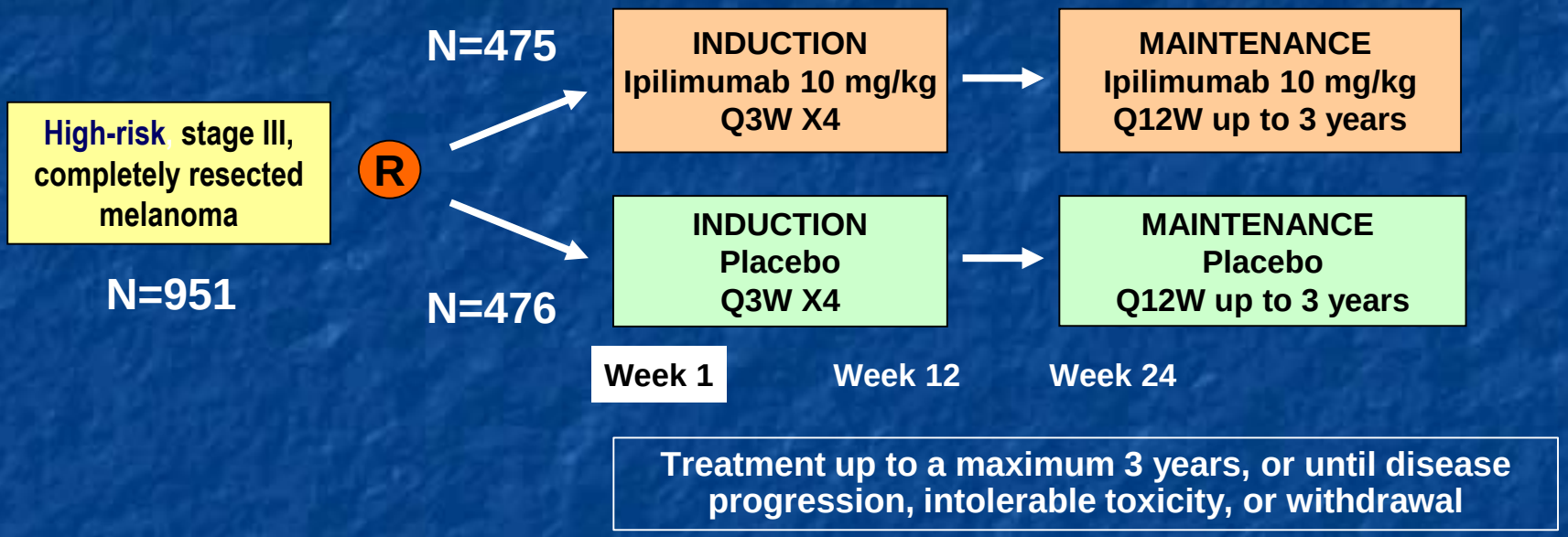
OS, RFS

QOL

Immunological correlates of RFS, OS

- **serial blood serum and lymphocytes**
- **baseline tissue blocks**

EORTC 18071/CA184-029: Study Design



Stratification factors:

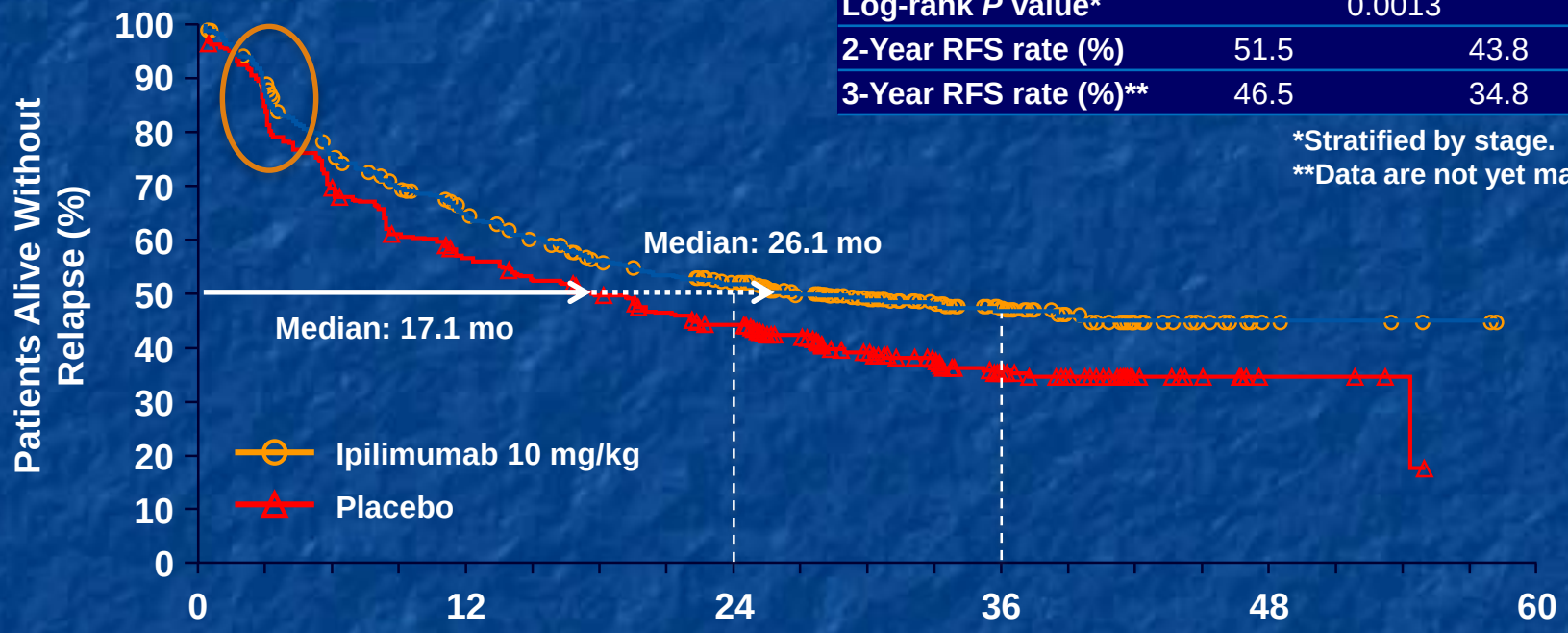
- Stage (IIIA vs IIIB vs IIIC 1-3 positive lymph nodes vs IIIC ≥4 positive lymph nodes)
- Regions (North America, European countries and Australia)

Eggermont et al., Proc ASCO 2014

Primary Endpoint: Recurrence-free Survival (IRC)

	Ipilimumab	Placebo
Events/patients	234/475	294/476
HR (95% CI)*	0.75 (0.64–0.90)	
Log-rank *P* value*	0.0013	
2-Year RFS rate (%)	51.5	43.8
3-Year RFS rate (%)**	46.5	34.8

*Stratified by stage.
**Data are not yet mature.



Patients at Risk

	O	N					
Ipilimumab	234	475	276	205	67	5	0
Placebo	294	476	260	193	62	4	0

Eggermont et al., Proc ASCO 2014

Deaths Related to Adjuvant Study Drug Treatment

- Five patients (1.1%) died of drug-related AEs in the ipilimumab group:
  - Three patients with colitis (2 with gastrointestinal perforations)
  - One patient with myocarditis
  - One patient with Guillain-Barré syndrome
- No deaths due to intervention in placebo group

Eggermont et al., Proc ASCO 2014

Intergroup Trial S1404

Stage IIIB-C (>N1) and IV (M1a, b)

- Pembrolizumab 200mg q 3 weeks x 1 yr

vs

- High-dose IFN (or FDA approved regimen)

  – Primary Endpoint: Overall Survival

  – Secondary Endpoints: RFS, QOL

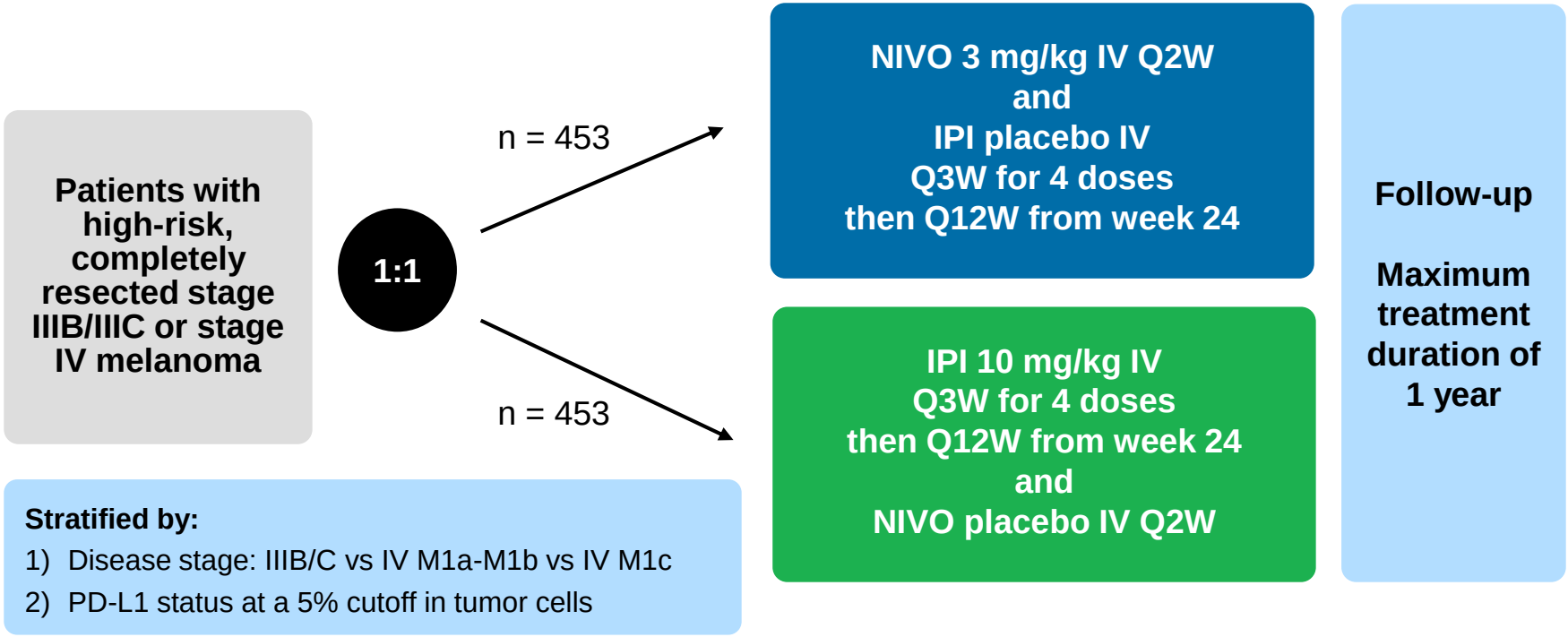
MADRID 2017 ESMO congress

Adjuvant Therapy With Nivolumab Versus Ipilimumab After Complete Resection of Stage III/IV Melanoma: A Randomized, Double-blind, Phase 3 Trial (CheckMate 238)

Jeffrey Weber,[1] Mario Mandala,[2] Michele Del Vecchio,[3] Helen Gogas,[4] Ana M. Arance,[5] C. Lance Cowey,[6] Stéphane Dalle,[7] Michael Schenker,[8] Vanna Chiarion-Sileni,[9] Ivan Marquez-Rodas,[10] Jean-Jacques Grob,[11] Marcus Butler,[12] Mark R. Middleton,[13] Michele Maio,[14] Victoria Atkinson,[15] Paola Queirolo,[16] Veerle de Pril,[17] Anila Qureshi,[17] James Larkin,[18]* Paolo A. Ascierto[19]*

[1]NYU Perlmutter Cancer Center, New York, New York, USA; [2]Papa Giovanni XIII Hospital, Bergamo, Italy; [3]Medical Oncology, National Cancer Institute, Milan, Italy; [4]University of Athens, Athens, Greece; [5]Hospital Clínic de Barcelona, Barcelona, Spain; [6]Texas Oncology-Baylor Cancer Center, Dallas, Texas, USA; [7]Hospices Civils de Lyon, Pierre Bénite, France; [8]Oncology Center Sf Nectarie Ltd., Craiova, Romania; [9]Oncology Institute of Veneto IRCCS, Padua, Italy; [10]General University Hospital Gregorio Marañón, Madrid, Spain; [11]Hôpital de la Timone, Marseille, France; [12]Princess Margaret Cancer Centre, Toronto, Ontario, Canada; [13]Churchill Hospital, Oxford, United Kingdom; [14]Center for Immuno-Oncology, University Hospital of Siena, Istituto Toscano Tumori, Siena, Italy; [15]Gallipoli Medical Research Foundation and Princess Alexandra Hospital, Woolloongabba, and University of Queensland, Greenslopes, Queensland, Australia; [16]IRCCS San Martino-IST, Genova, Italy; [17]Bristol-Myers Squibb, Princeton, New Jersey, USA; [18]Royal Marsden NHS Foundation Trust, London, UK; [19]Istituto Nazionale Tumori Fondazione Pascale, Naples, Italy; *Contributed equally to this study.

CA209-238: Study Design



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

Key Eligibility Criteria

- At least 15 years of age
- Eastern Cooperative Oncology Group performance status score of 0 or 1
- Histologically confirmed melanoma metastatic to regional lymph nodes or with distant metastases surgically rendered free of disease
  - Stage IIIB, IIIC, or stage IV melanoma by the American Joint Committee on Cancer 2009 classification, 7th edition
  - Complete regional lymphadenectomy or resection was required within 12 weeks of randomization
- Patients with ocular/uveal melanoma, systemic corticosteroid use >10 mg/day of prednisone or equivalent, or previous systemic therapy for melanoma were excluded
  - Acral and mucosal melanoma were allowed

Study Overview

Primary endpoint

- RFS: time from randomization until first recurrence (local, regional, or distant metastasis), new primary melanoma, or death

Secondary endpoints

- OS
- Safety and tolerability
- RFS by PD-L1 tumor expression
- HRQoL

Current interim analysis

- Primary endpoint (RFS), safety, and HRQoL
  - DMFS (exploratory)
- Duration of follow-up: minimum 18 months; 360 events

DMFS = distant metastasis-free survival; HRQoL = health-related quality of life

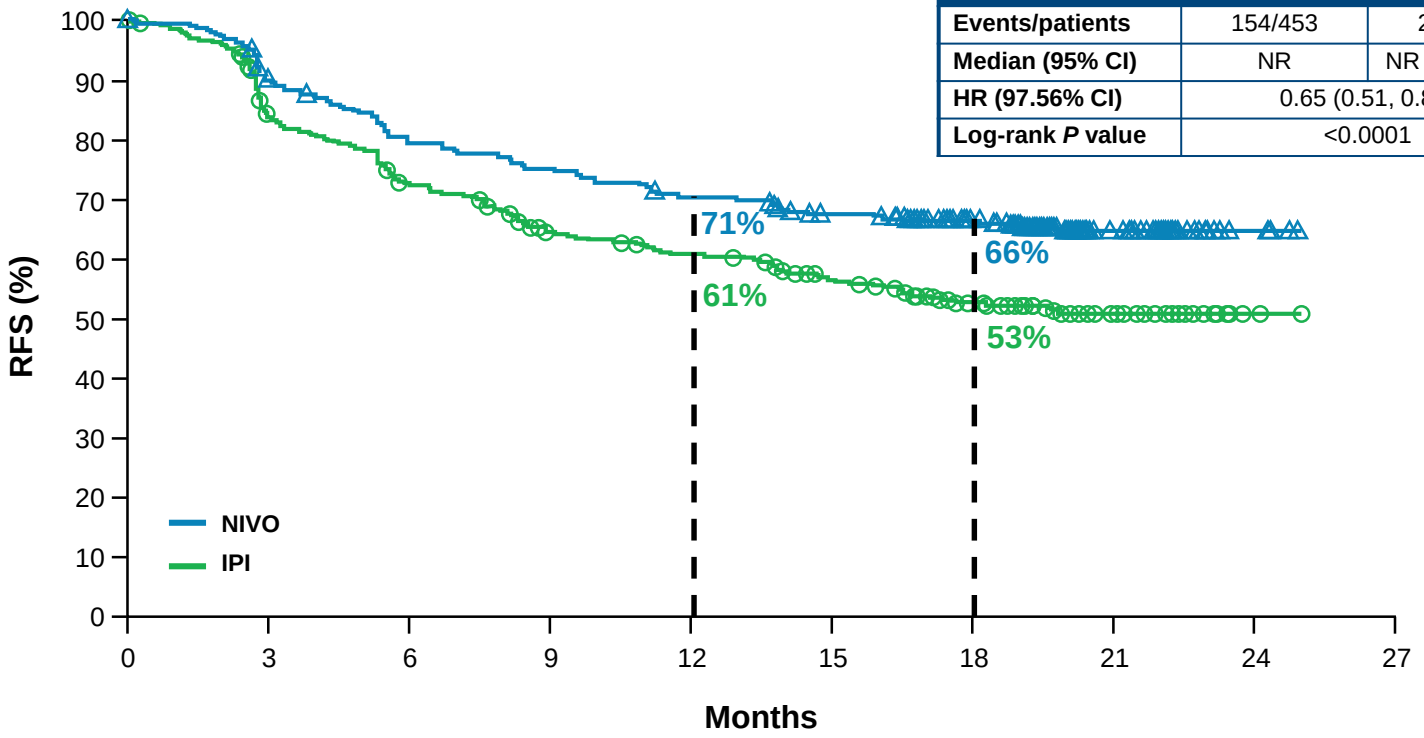
Baseline Patient Characteristics

	NIVO (n = 453)	IPI (n = 453)
Median age, years	56	54
Male, %	57	59
Stage, IIIB+IIIC, %	81	81
Macroscopic lymph node involvement (% of stage IIIB+IIIC)	60	58
Ulceration (% of stage IIIB+IIIC)	42	37
Stage IV, %	18	19
M1c without brain metastases (% stage IV)	17	17
PD-L1 expression ≥5%, %	34	34
***BRAF* mutation, %**	41	43
LDH ≤ ULN, %	91	91

- Most of the patients had cutaneous melanoma (85%), and 4% had acral and 3% had mucosal melanoma
- All 905 patients are off treatment; median doses were 24 (1-26) in the NIVO group and 4 (1-7) in the IPI group
- 397 patients completed 1 year of treatment (61% of the NIVO group and 27% of the IPI group)

Primary Endpoint: RFS

	NIVO	IPI
Events/patients	154/453	206/453
Median (95% CI)	NR	NR (16.6, NR)
HR (97.56% CI)	0.65 (0.51, 0.83)	
Log-rank *P* value	<0.0001	



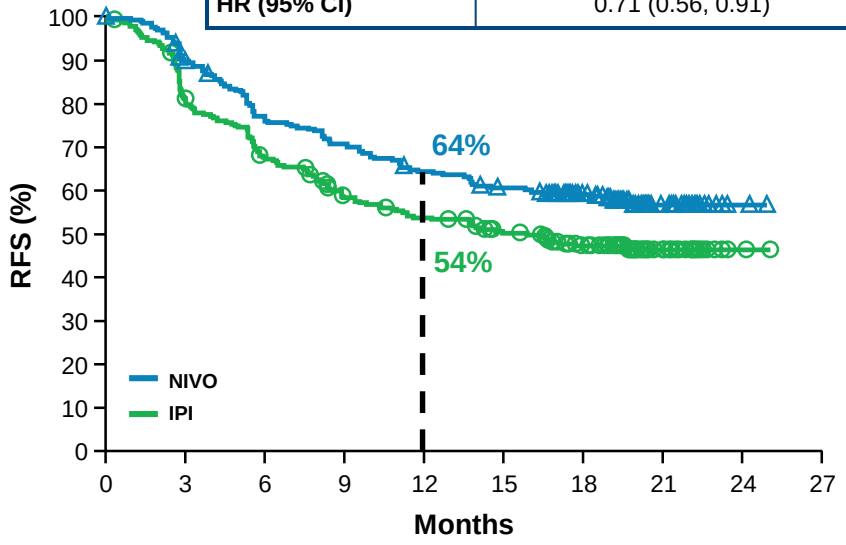
Number of patients at risk

NIVO	453	399	353	332	311	291	249	71	5	0
IPI	453	364	314	269	252	225	184	56	2	0

Subgroup Analysis of RFS: PD-L1 Expression Level

PD-L1 Expression Level <5%

	NIVO	IPI
Events/patients	114/275	143/286
Median (95% CI)	NR	15.9 (10.4, NR)
HR (95% CI)	0.71 (0.56, 0.91)	

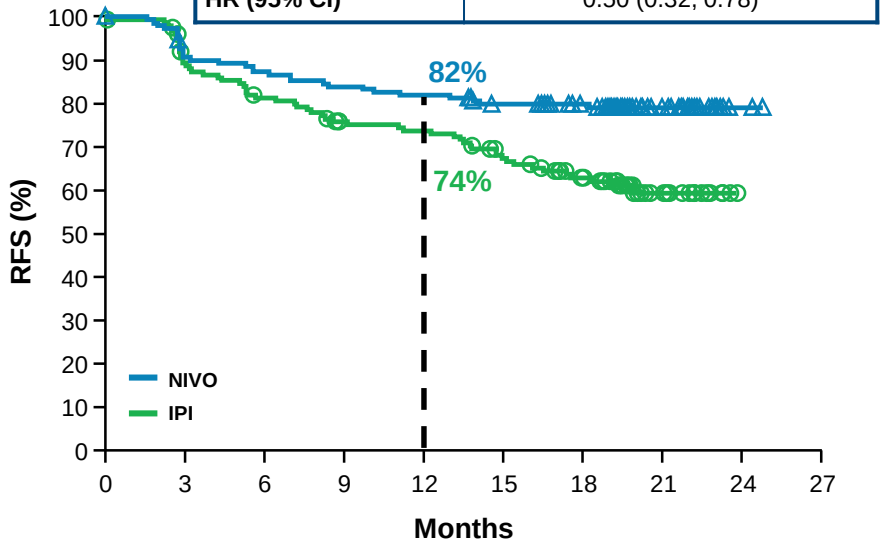


Number of patients at risk

NIVO	275	242	204	189	171	159	129	41	3	0
IPI	286	219	184	153	139	124	100	31	2	0

PD-L1 Expression Level ≥5%

	NIVO	IPI
Events/patients	31/152	57/154
Median (95% CI)	NR	NR
HR (95% CI)	0.50 (0.32, 0.78)	



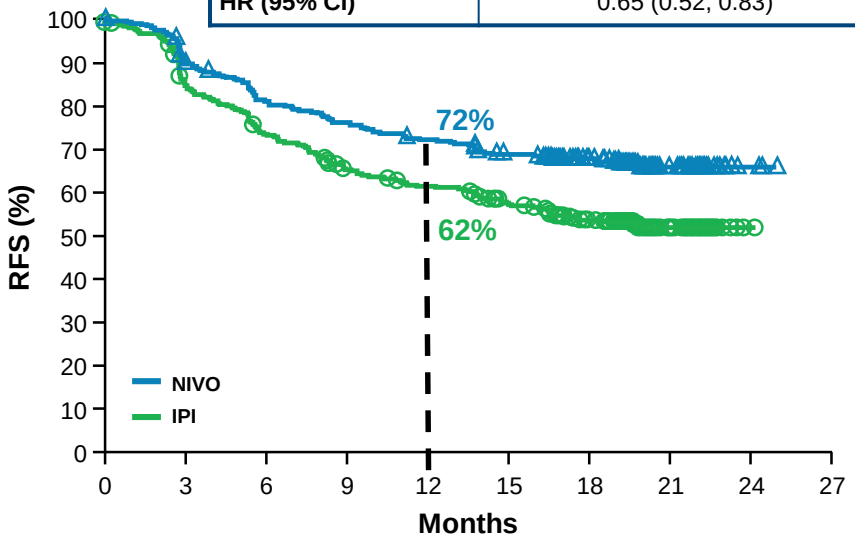
Number of patients at risk

NIVO	152	135	130	125	122	114	105	26	2	0
IPI	154	133	120	108	105	93	78	21	0	0

Subgroup Analysis of RFS: Disease Stage

Stage III

	NIVO	IPI
Events/patients	120/367	163/366
Median (95% CI)	NR	NR (16.6, NR)
HR (95% CI)	0.65 (0.52, 0.83)	

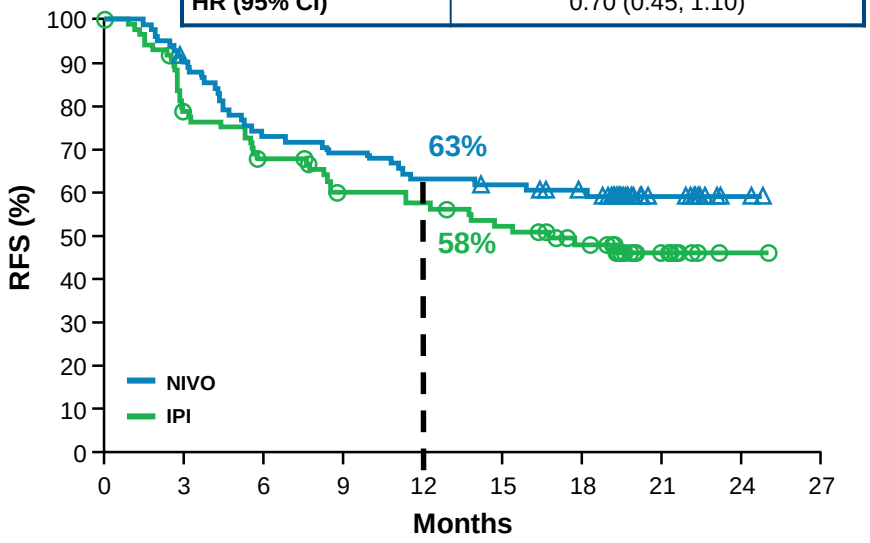


Number of patients at risk

NIVO	367	322	290	272	257	239	203	58	3	0
IPI	366	299	259	223	208	186	152	45	1	0

Stage IV

	NIVO	IPI
Events/patients	33/82	43/87
Median (95% CI)	NR (15.9, NR)	16.8 (8.5, NR)
HR (95% CI)	0.70 (0.45, 1.10)	



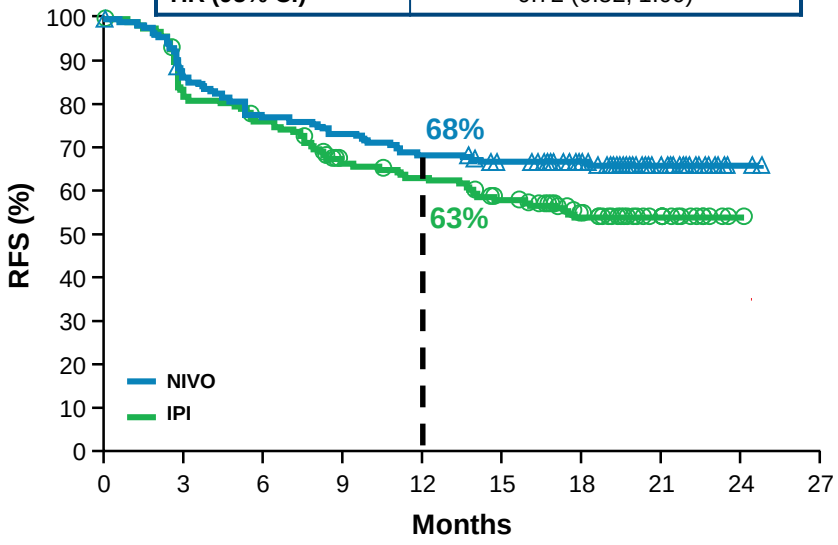
Number of patients at risk

NIVO	82	73	59	56	51	49	43	12	2	0
IPI	87	65	55	46	44	39	32	11	1	0

Subgroup Analysis of RFS: *BRAF* Mutation Status

BRAF Mutant

	NIVO	IPI
Events/patients	63/187	84/194
Median (95% CI)	NR	NR (16.1, NR)
HR (95% CI)	0.72 (0.52, 1.00)	

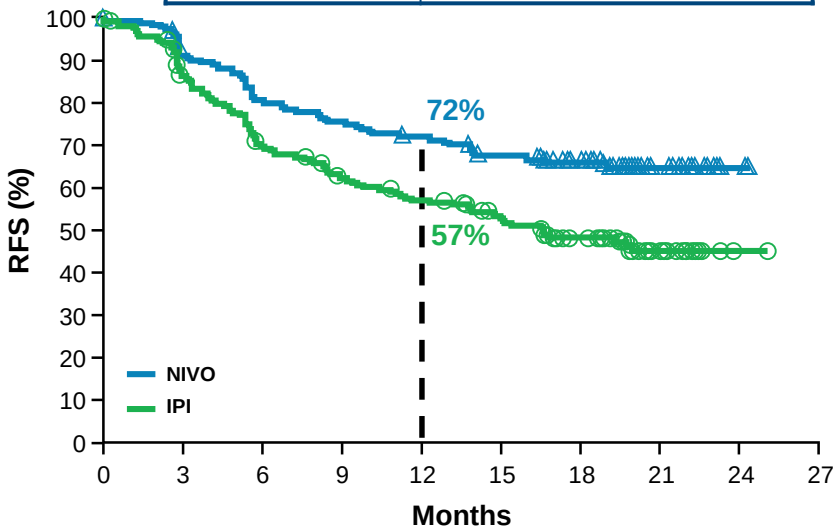


Number of patients at risk

NIVO	187	159	142	135	126	118	102	32	2	0
IPI	194	155	142	118	112	100	78	26	1	0

BRAF Wild type

	NIVO	IPI
Events/patients	67/197	105/214
Median (95% CI)	NR	16.6 (12.3, NR)
HR (95% CI)	0.58 (0.43, 0.79)	

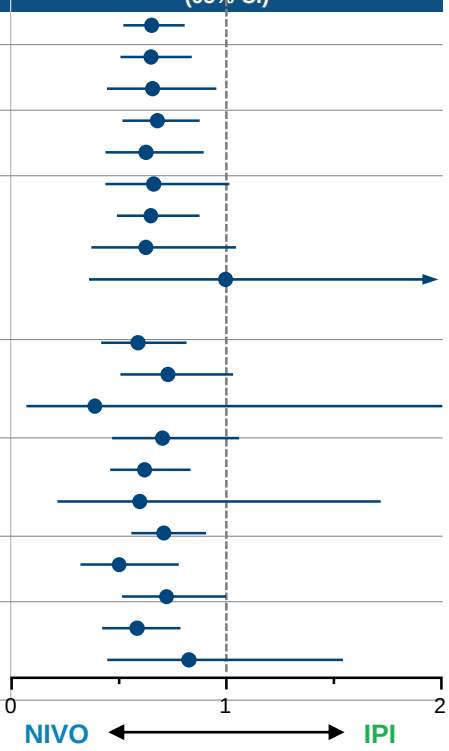


Number of patients at risk

NIVO	197	175	154	145	137	127	108	26	2	0
IPI	214	174	140	122	111	96	80	22	1	0

RFS: Prespecified Subgroups

Subgroup		No. of events/no. of patients		Unstratified HR (95% CI)
		NIVO 3 mg/kg	IPI 10 mg/kg	
Overall	Overall	154/453	206/453	0.66 (0.53, 0.81)
Age	<65 years	106/333	147/339	0.65 (0.51, 0.84)
	≥65 years	48/120	59/114	0.66 (0.45, 0.97)
Sex	Male	99/258	133/269	0.68 (0.53, 0.88)
	Female	55/195	73/184	0.63 (0.44, 0.89)
Stage (CRF)	Stage IIIb	41/163	54/148	0.67 (0.44, 1.00)
	Stage IIIc	79/204	109/218	0.65 (0.49, 0.87)
	Stage IV M1a-M1b	25/62	35/66	0.63 (0.38, 1.05)
	Stage IV M1c	8/20	8/21	1.00 (0.37, 2.66)
	Not reported	1/2	0/0	
Stage III: Ulceration	Absent	58/201	94/216	0.59 (0.42, 0.82)
	Present	60/153	64/135	0.73 (0.51, 1.04)
	Not reported	2/15	5/15	0.39 (0.07, 2.00)
Stage III: Lymph node involvement	Microscopic	41/125	55/134	0.71 (0.47, 1.07)
	Macroscopic	72/219	101/214	0.62 (0.46, 0.84)
	Not reported	7/25	7/18	0.60 (0.21, 1.72)
PD-L1 status	<5%/indeterminate	123/300	149/299	0.71 (0.56, 0.90)
	≥5%	31/152	57/154	0.50 (0.32, 0.78)
***BRAF* mutation status**	Mutant	63/187	84/194	0.72 (0.52, 1.00)
	Wild-type	67/197	105/214	0.58 (0.43, 0.79)
	Not reported	24/69	17/45	0.83 (0.45, 1.54)



Safety Summary

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

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

Conclusions

- Nivolumab showed a clinically and statistically significant improvement in RFS vs the active control of high-dose ipilimumab for patients with resected stages IIIB/IIIC and stage IV melanoma at high risk of recurrence (HR = 0.65, $P < 0.0001$)
  - 18-month RFS rates were 66% for nivolumab and 53% for ipilimumab
  - Benefit for nivolumab was observed across the majority of prespecified subgroups tested, including PD-L1 and *BRAF* mutation status
- Nivolumab has a superior safety profile in comparison with ipilimumab, with fewer grade 3/4 AEs and fewer AEs leading to treatment discontinuation
- Nivolumab has the potential to be a new standard treatment option for patients with resected stage IIIB, IIIC, and IV melanoma regardless of *BRAF* mutation

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

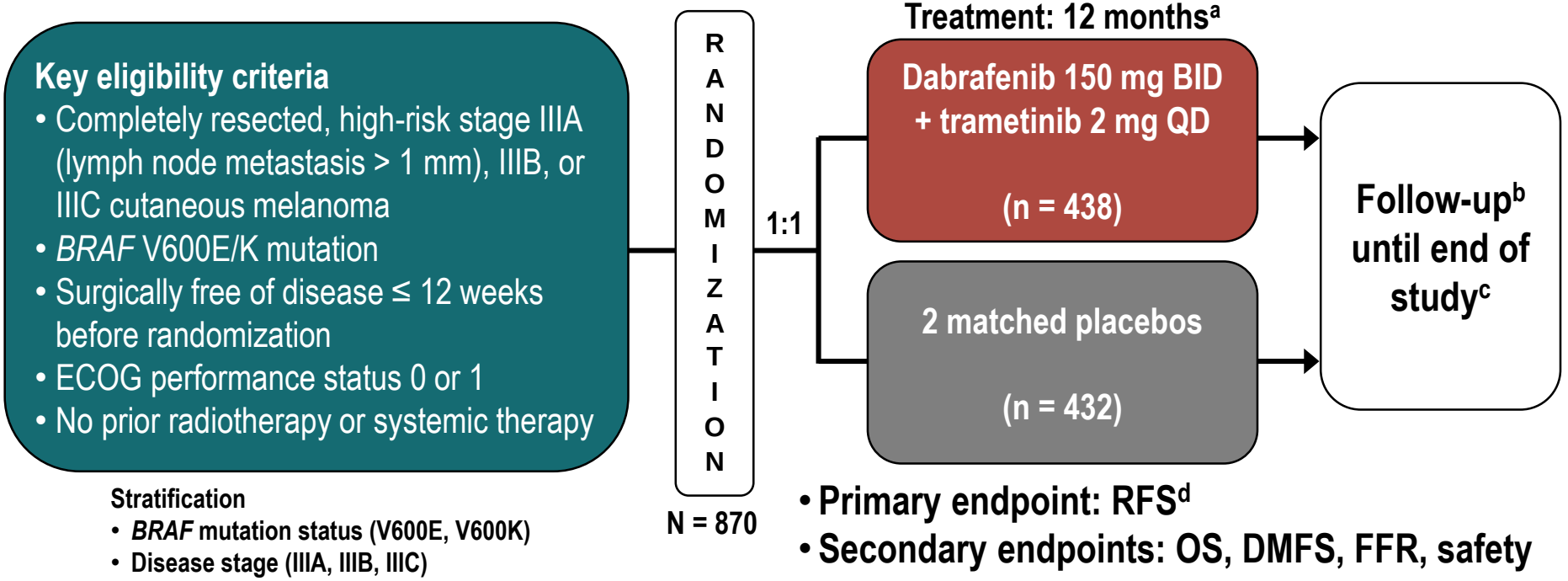
Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma

J. Weber, M. Mandala, M. Del Vecchio, H.J. Gogas, A.M. Arance, C.L. Cowey, S. Dalle, M. Schenker, V. Chiarion-Sileni, I. Marquez-Rodas, J.-J. Grob, M.O. Butler, M.R. Middleton, M. Maio, V. Atkinson, P. Queirolo, R. Gonzalez, R.R. Kudchadkar, M. Smylie, N. Meyer, L. Mortier, M.B. Atkins, G.V. Long, S. Bhatia, C. Lebbé, P. Rutkowski, K. Yokota, N. Yamazaki, T.M. Kim, V. de Pril, J. Sabater, A. Qureshi, J. Larkin, and P.A. Ascierto, for the CheckMate 238 Collaborators*

COMBI-AD: ADJUVANT DABRAFENIB PLUS TRAMETINIB FOR RESECTED STAGE III *BRAF* V600–MUTANT MELANOMA

Axel Hauschild, Mario Santinami, Georgina V. Long, Victoria Atkinson, Mario Mandalà, Vanna Chiarion-Sileni, James Larkin, Marta Nyakas, Caroline Dutriaux, Andrew Haydon, Caroline Robert, Laurent Mortier, Jacob Schachter, Ran Ji, Pingkuan Zhang, Bijoyesh Mookerjee, Jeff Legos, Richard Kefford, Reinhard Dummer, John M. Kirkwood

COMBI-AD: STUDY DESIGN



BID, twice daily; DMFS, distant metastasis–free survival; ECOG, Eastern Cooperative Oncology Group; FFR, freedom from relapse; OS, overall survival; QD, once daily; RFS, relapse-free survival. [a] Or until disease recurrence, death, unacceptable toxicity, or withdrawal of consent; [b] Patients were followed for disease recurrence until the first recurrence and thereafter for survival; [c] The study will be considered complete and final OS analysis will occur when ≈ 70% of randomized patients have died or are lost to follow-up; [d] New primary melanoma considered as an event.

STUDY ANALYSES AND ENDPOINTS

- Efficacy analyses included all patients (intent-to-treat population), and safety analyses included all patients who received ≥ 1 dose of randomized treatment (safety population)
- OS was to be tested only if the primary endpoint (RFS) significantly favored the combination arm
  - OS statistical significance boundary (O'Brien-Fleming) for first interim analysis, *P* = .000019
- All recurrence analyses were based on investigator assessment and defined as follows:
  - RFS: time from randomization to disease recurrence or death from any cause
    - Study was designed to provide > 90% power (assuming ≈ 410 RFS events observed) to detect an HR of 0.71 with an overall 2-sided type I error rate of 5%
  - DMFS: time from randomization to date of first distant metastasis or death, whichever occurred first
  - FFR: time from randomization to recurrence, with censoring of patients dying from causes other than melanoma or treatment-related toxicity

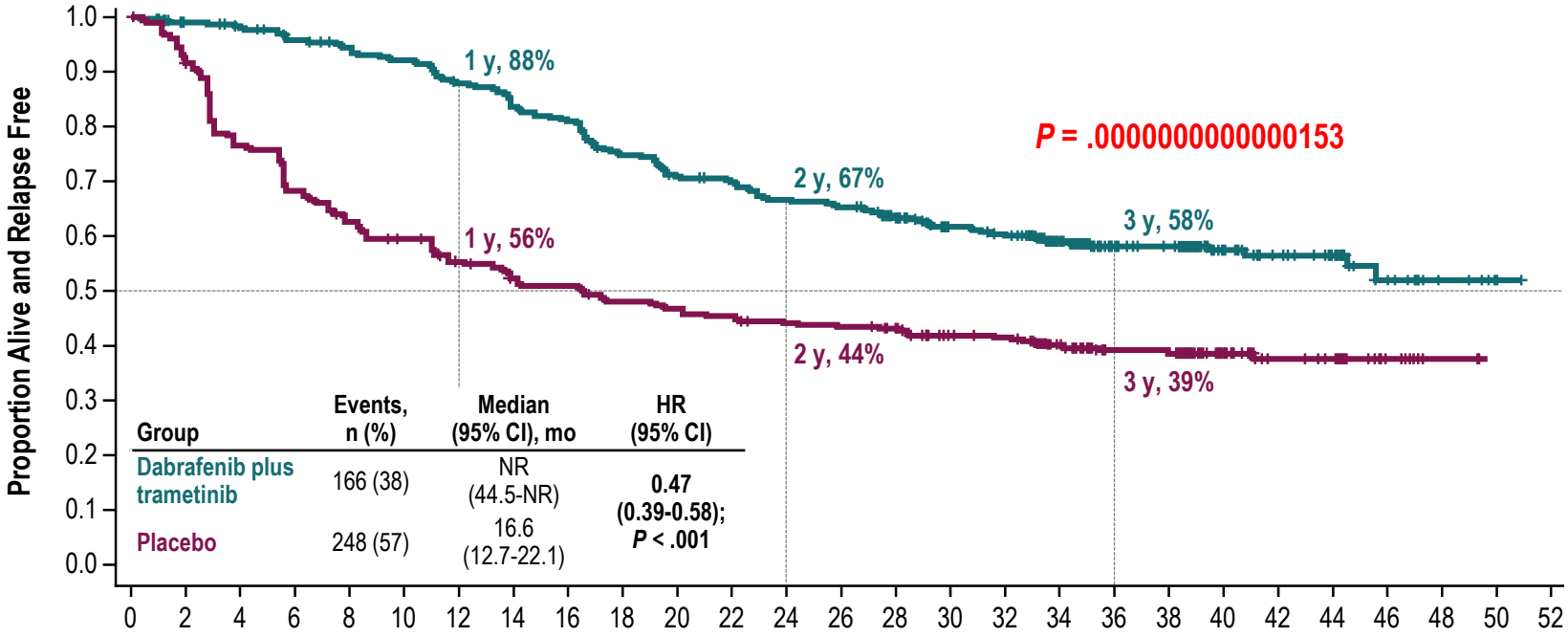
HR, hazard ratio.

BASELINE DEMOGRAPHICS AND PATIENT CHARACTERISTICS[a]

	Dabrafenib Plus Trametinib (n = 438)	Placebo (n = 432)	Total (N = 870)
Median age (range), years	50 (18-89)	51 (20-85)	50 (18-89)
Male, n (%)	195 (45)	193 (45)	388 (45)
***BRAF* mutation status, n (%)**			
V600E	397 (91)	395 (91)	792 (91)
V600K[b]	41 (9)	37 (9)	78 (9)
ECOG performance status of 0, n (%)	402 (92)	390 (90)	792 (91)
Disease stage, n (%)			
IIIA	83 (19)	71 (16)	154 (18)
IIIB	169 (39)	187 (43)	356 (41)
IIIC	181 (41)	166 (38)	347 (40)
III (unspecified)	5 (1)	8 (2)	13 (1)

[a] Reported for patients with available data; [b] One patient had both *BRAF* V600E and *BRAF* V600K mutations and was included in the V600K subset.

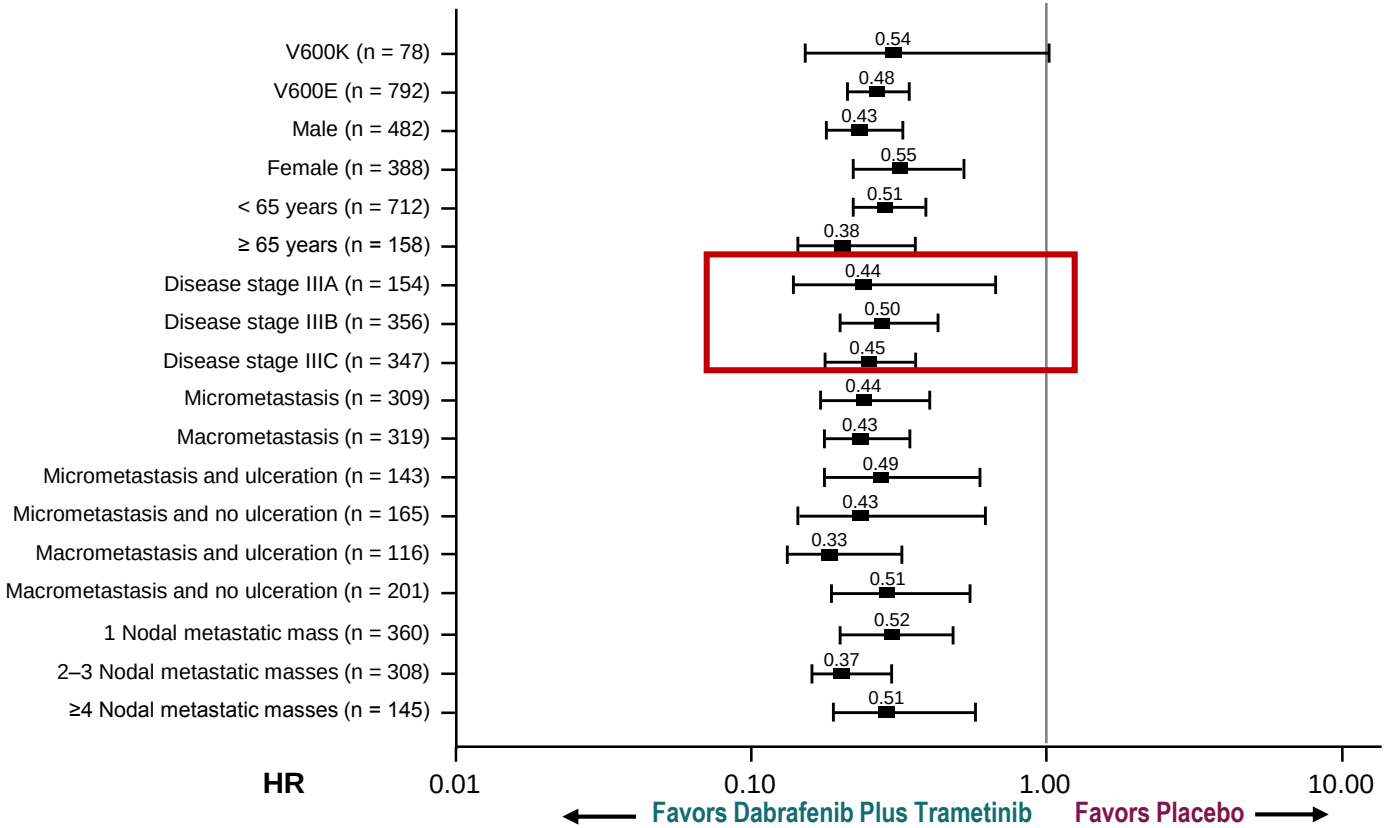
RELAPSE-FREE SURVIVAL (PRIMARY ENDPOINT)



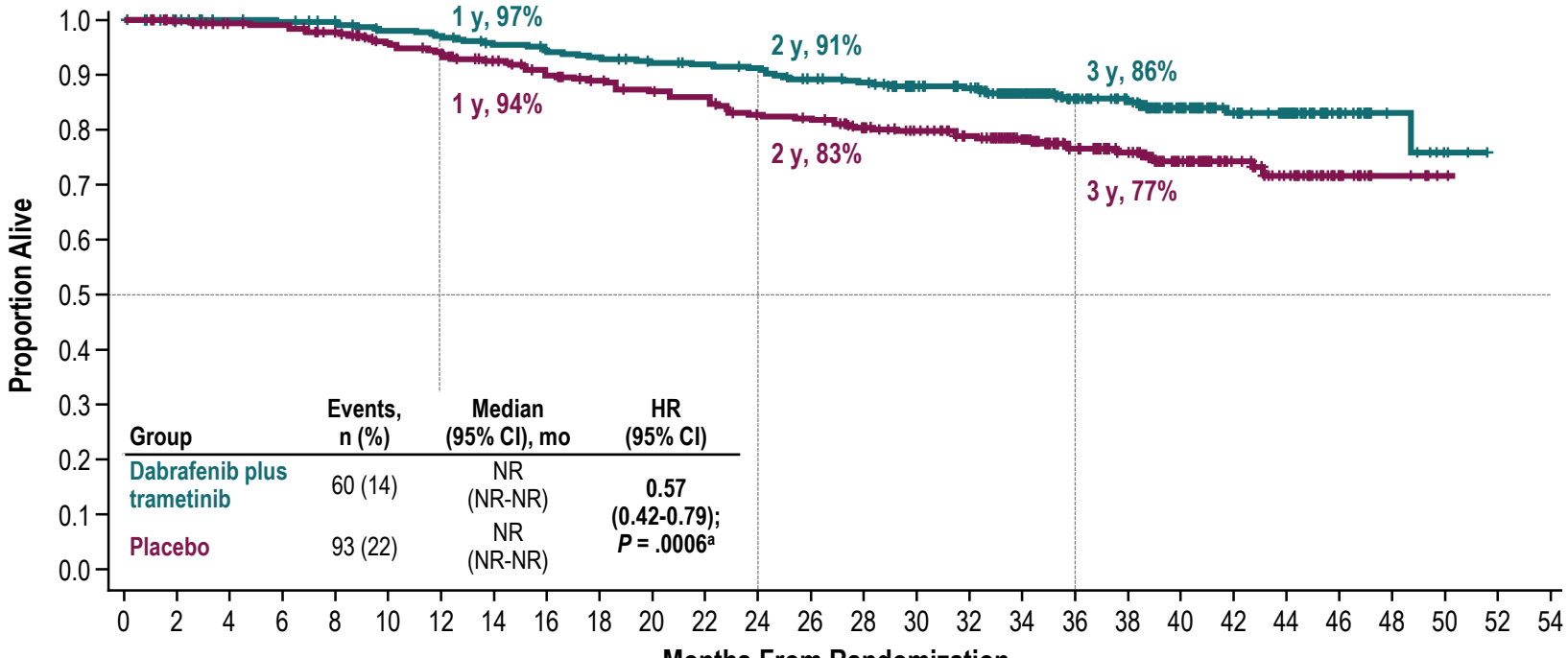
No. at Risk																											
Dabrafenib plus trametinib	438	413	405	392	382	373	355	336	325	299	282	276	263	257	233	202	194	147	116	110	66	52	42	19	7	2	0
Placebo	432	387	322	280	263	243	219	203	198	185	178	175	168	166	158	141	138	106	87	86	50	33	30	9	3	0	0

NR, not reached.

RELAPSE-FREE SURVIVAL BY SUBGROUP



OVERALL SURVIVAL (FIRST INTERIM ANALYSIS)



No. at Risk																												
Dabrafenib plus trametinib	438	426	416	414	408	401	395	387	381	376	370	366	362	352	328	301	291	233	180	164	105	82	67	28	12	5	0	0
Placebo	432	425	415	410	401	386	378	362	346	337	328	323	308	303	284	269	252	202	164	152	94	64	51	17	7	1	0	0

[a] Prespecified significance boundary (*P* = .000019).

POST-RECURRENCE THERAPY (SAFETY POPULATION)

Post-recurrence Therapy	Dabrafenib Plus Trametinib (n = 435)	Placebo (n = 432)
Any post-recurrence anticancer therapy, n (%)	148 (34)	217 (50)
Surgery	78 (18)	131 (30)
Radiotherapy	60 (14)	72 (17)
Any systemic post-recurrence anticancer therapy, n (%)	120 (28)	183 (42)
Small molecule–targeted therapy	63 (14)	137 (32)
Any BRAF inhibitor[a]	63 (14)	137 (32)
Any MEK inhibitor[b]	47 (11)	77 (18)
Immunotherapy	89 (20)	103 (24)
Anti–PD-1/PD-L1	71 (16)	68 (16)
Anti–CTLA-4	53 (12)	68 (16)
Interferon	6 (1)	11 (3)
T-VEC	0	1 (< 1)
Biologic therapy	1 (< 1)	1 (< 1)
Chemotherapy	20 (5)	23 (5)
Investigational treatment	6 (1)	19 (4)
Other therapy	2 (< 1)	0
Median time from disease recurrence to start of systemic post-recurrence therapy, excluding radiotherapy and surgery (range), weeks	7.1 (0-136)	7.3 (0-78)

CTLA-4, cytotoxic T-lymphocyte–associated 4; PD-1, programmed cell death 1; PD-L1 programmed cell death ligand 1; T-VEC, talimogene laherparepvec. [a] Included dabrafenib, vemurafenib, and encorafenib; [b] Included trametinib, cobimetinib, and binimetinib.

POST-RECURRENCE THERAPY AMONG PATIENTS WITH RELAPSE

Post-recurrence Therapy	Dabrafenib Plus Trametinib (n = 163 relapses)	Placebo (n = 247 relapses)
Any post-recurrence anticancer therapy, n (%)	148 (91)	217 (88)
Surgery	78 (48)	131 (53)
Radiotherapy	60 (37)	72 (29)
Any systemic post-recurrence anticancer therapy, n (%)	120 (74)	183 (74)
Small molecule–targeted therapy	63 (39)	137 (55)
Any BRAF inhibitor[a]	63 (39)	137 (55)
Any MEK inhibitor[b]	47 (29)	77 (31)
Immunotherapy	89 (55)	103 (42)
Anti–PD-1/PD-L1	71 (44)	68 (28)
Anti–CTLA-4	53 (33)	68 (28)
Interferon	6 (4)	11 (4)
T-VEC	0	1 (< 1)
Biologic therapy	1 (1)	1 (< 1)
Chemotherapy	20 (12)	23 (9)
Investigational treatment	6 (4)	19 (8)
Other therapy	2 (1)	0
Median time from disease recurrence to start of systemic post-recurrence therapy, excluding radiotherapy and surgery (range), weeks	7.1 (0-136)	7.3 (0-78)

CTLA-4, cytotoxic T-lymphocyte–associated 4; PD-1, programmed cell death 1; PD-L1 programmed cell death ligand 1; T-VEC, talimogene laherparepvec. [a] Included dabrafenib, vemurafenib, and encorafenib; [b] Included trametinib, cobimetinib, and binimetinib.

COMMON ADVERSE EVENTS

AEs, n (%)	Dabrafenib Plus Trametinib (n = 435)		Placebo (n = 432)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Any AE (> 20% with dabrafenib plus trametinib)[a]	422 (97)	180 (41)	380 (88)	61 (14)
Pyrexia	273 (63)	23 (5)	47 (11)	2 (< 1)
Fatigue	204 (47)	19 (4)	122 (28)	1 (< 1)
Nausea	172 (40)	4 (1)	88 (20)	0
Headache	170 (39)	6 (1)	102 (24)	0
Chills	161 (37)	6 (1)	19 (4)	0
Diarrhoea	144 (33)	4 (1)	65 (15)	1 (< 1)
Vomiting	122 (28)	4 (1)	43 (10)	0
Arthralgia	120 (28)	4 (1)	61 (14)	0
Rash	106 (24)	0	47 (11)	1 (< 1)

[a] Eleven patients (3%) in the treatment arm and 10 patients (2%) in the placebo arm had new primary melanomas; 8 (2%) and 7 (2%), respectively, had cutaneous squamous cell carcinoma/keratoacanthoma; 19 (4%) and 14 (3%), respectively, had basal cell carcinoma; and 10 (2%) and 4 (1%), respectively, had noncutaneous malignancies.

CONCLUSIONS

- This is the first randomized study of combination BRAF and MEK inhibition as melanoma adjuvant therapy
- Dabrafenib plus trametinib significantly reduced the risk of disease recurrence vs placebo in patients with resected high-risk, stage III, *BRAF* V600E/K–mutant melanoma (RFS HR, 0.47 [95% CI, 0.39-0.58]; $P < .001$)
  - Estimated 1-, 2-, and 3-year RFS rates with dabrafenib plus trametinib were 88%, 67%, and 58%, respectively
  - Similar RFS benefit was observed across patient subgroups, including all stage categories

CONCLUSIONS (CONT)

- In addition to RFS, OS improvement with dabrafenib plus trametinib was demonstrated (HR, 0.57 [95% CI, 0.42-0.79])
  - Similar rates of post-recurrence therapy in each arm attributes OS improvement to adjuvant dabrafenib plus trametinib treatment
- Manageable safety profile with combination dabrafenib and trametinib
- Dabrafenib plus trametinib is a novel adjuvant treatment option for *BRAF* V600–mutant melanoma

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ORIGINAL ARTICLE

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

G.V. Long, A. Hauschild, M. Santinami, V. Atkinson, M. Mandalà, V. Chiarion-Sileni, J. Larkin, M. Nyakas, C. Dutriaux, A. Haydon, C. Robert, L. Mortier, J. Schachter, D. Schadendorf, T. Lesimple, R. Plummer, R. Ji, P. Zhang, B. Mookerjee, J. Legos, R. Kefford, R. Dummer, and J.M. Kirkwood

ABSTRACT

Conclusions: Future of Systemic IO Therapy is Rational Combinations

- BRAF inhibitors increase melanoma antigen expression CD8+ T cell infiltration of melanoma
  - Rationale for combination of BRAF inhibitors with IFNα and other immunotherapy (UPCI 12-107)
- IFNα modulates tumor immune response & induces PDL1→ IFN + anti-PD1 combination (UPCI 13-105)
- IFNα modulates immunity that is complementary to anti-CTLA4→ IFNα + Ipilimumab
- Anti-CTLA4 and anti-PD1 provide complementary immunomodulation→ evaluation in advanced & adjuvant arenas

Thanks to our patients, program, and cooperative group members

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Melanoma and Skin Cancer SPORE

ECOG-ACRIN Melanoma Committee

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