Update from ASCO & AACR: the latest developments in treatment

CANCER RESEARCH UK | OXFORD CENTRE

We live in an immunotherapy world…

Additional data on combination Ipi/Nivo treatment

Final results of the national AVAST-M trial

Activity of treatments when there are brain metastases

[New checkpoint inhibitors]

Where now for adjuvant therapy?

AACR American Association for Cancer Research
ANNUAL MEETING 2017 WASHINGTON, DC
Abstract Number CT075

Overall Survival Results From a Phase III Trial of Nivolumab Combined With Ipilimumab in Treatment-naïve Patients With Advanced Melanoma (CheckMate 067)

James Larkin,[1] Vanna Chiarion-Sileni,[2] Rene Gonzalez,[3] Piotr Rutkowski,[4] Jean-Jacques Grob,[5] C. Lance Cowey,[6] Christopher D. Lao,[7] Dirk Schadendorf,[8] Pier Francesco Ferrucci,[9] Michael Smylie,[10] Reinhard Dummer,[11] Andrew Hill,[12] John Haanen,[13] Michele Maio,[14] Grant McArthur,[15] Dana Walker,[16] Linda Rollin,[16] Christine Horak,[16] F. Stephen Hodi,[17,*] Jedd D. Wolchok[18,*]

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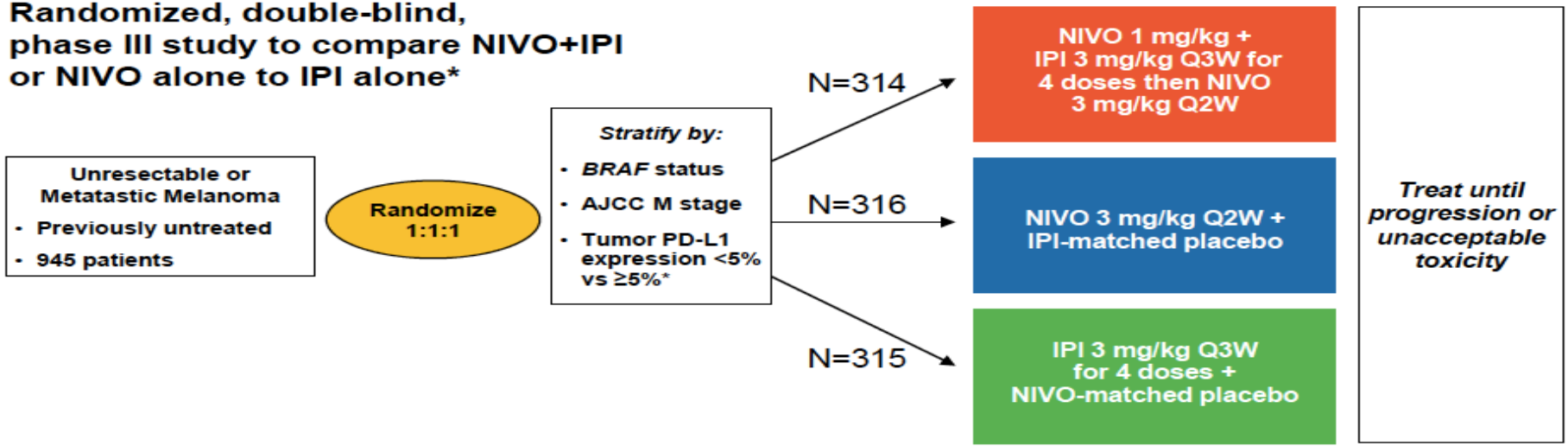
CheckMate 067: Study Design

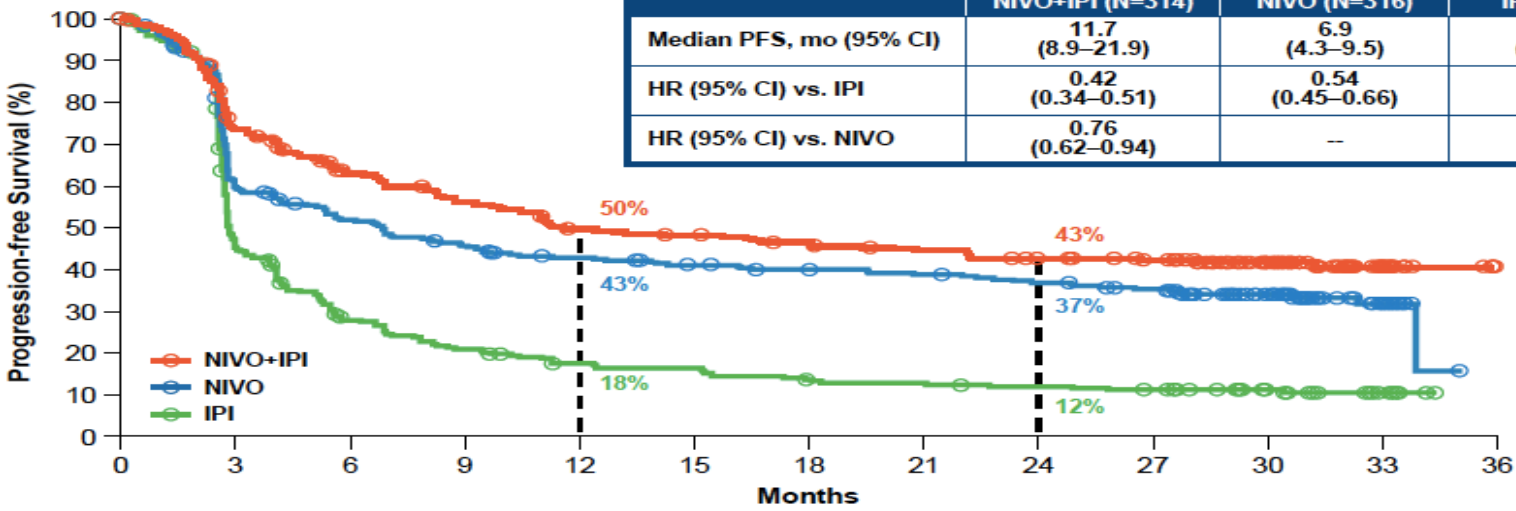
Randomized, double-blind, phase III study to compare NIVO+IPI or NIVO alone to IPI alone*



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

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)	--	--



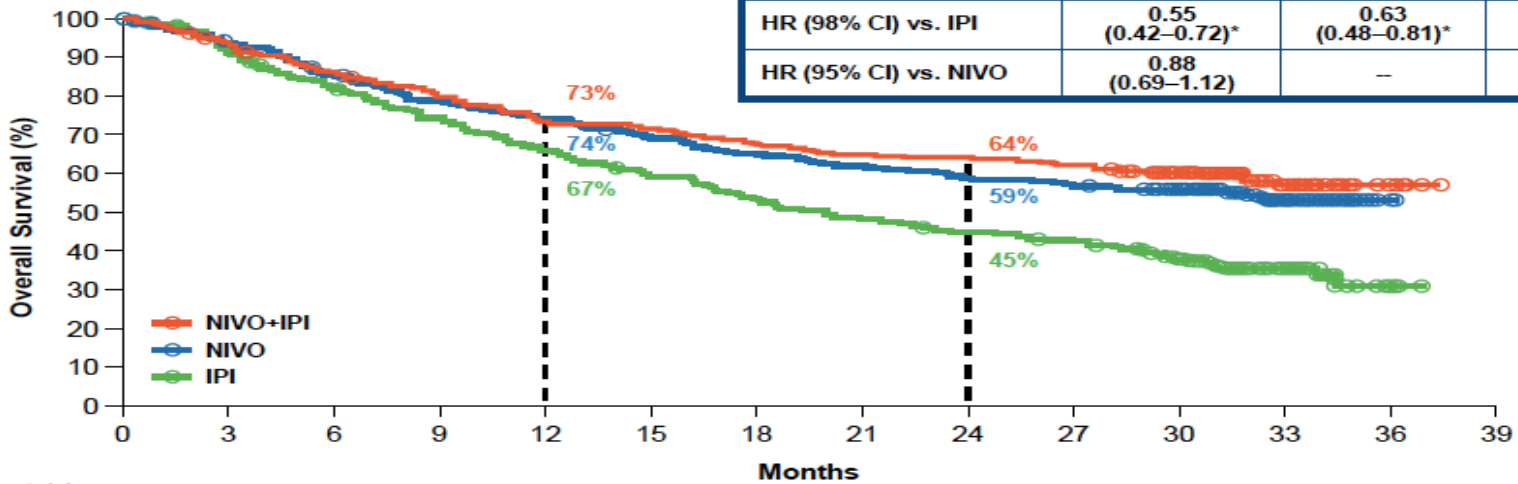
Patients at risk:

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

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



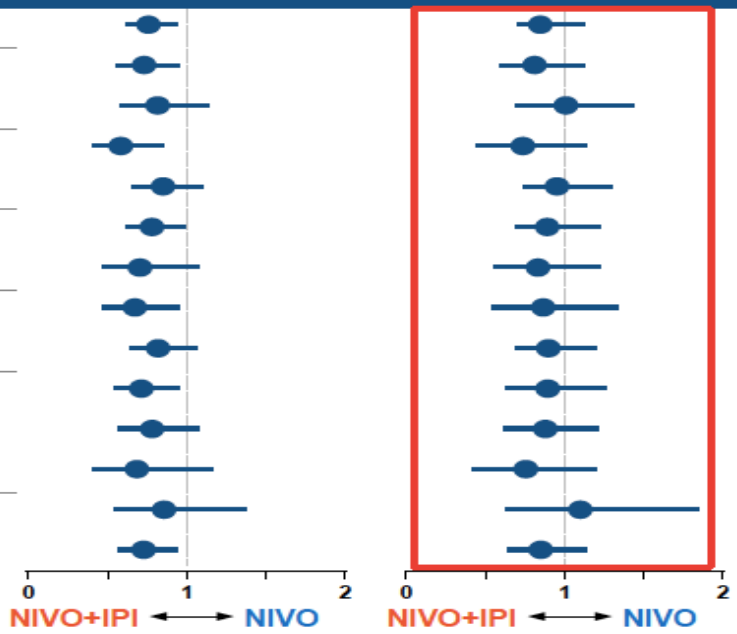
Patients at risk:

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

PFS and OS Subgroup Analyses (All Randomized Patients)

Descriptive comparison between NIVO+IPI and NIVO

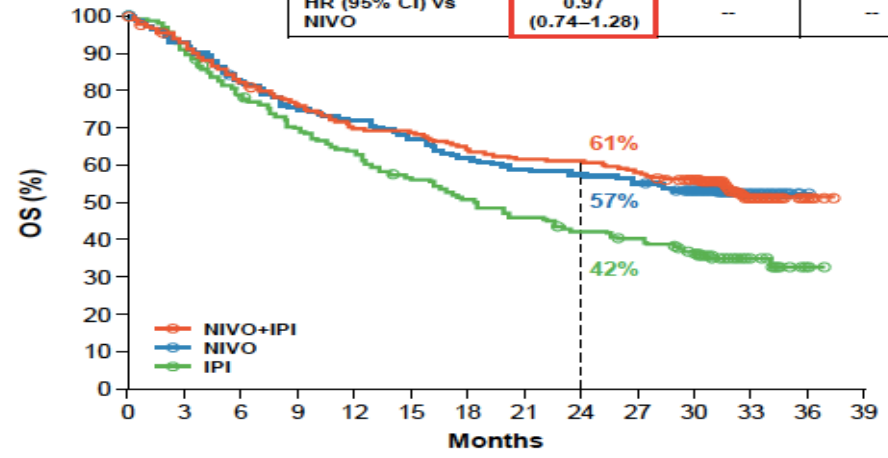
Subgroup	Patients		Unstratified Hazard Ratio	
	NIVO+IPI	NIVO	PFS	OS
Overall	314	316	0.77	0.89
<65 years	185	198	0.74	0.81
≥65 years	129	118	0.82	0.99
BRAF Mutant	102	98	0.60	0.71
BRAF Wild-type	212	218	0.86	0.97
ECOG PS = 0	230	237	0.79	0.91
ECOG PS = 1	83	78	0.72	0.82
M0/M1a/M1b	129	132	0.67	0.84
M1c	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)	--	--

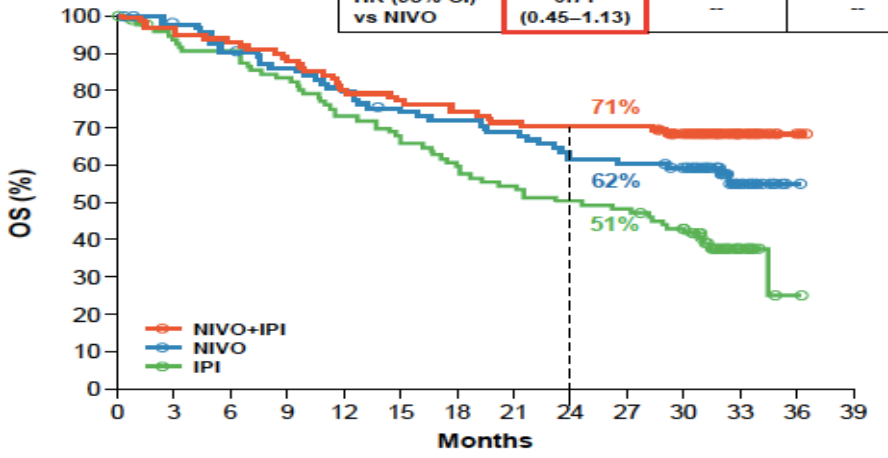


Patients at risk:

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)	--	--



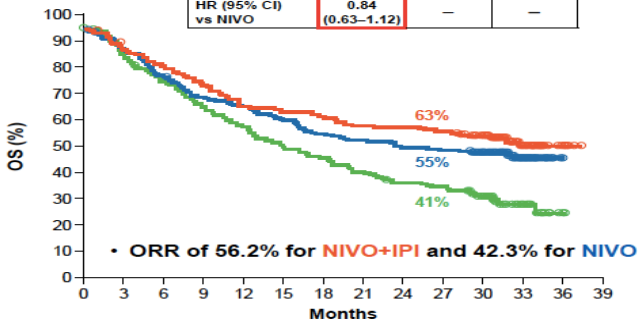
Patients at risk:

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

PD-L1 Expression Level <5%

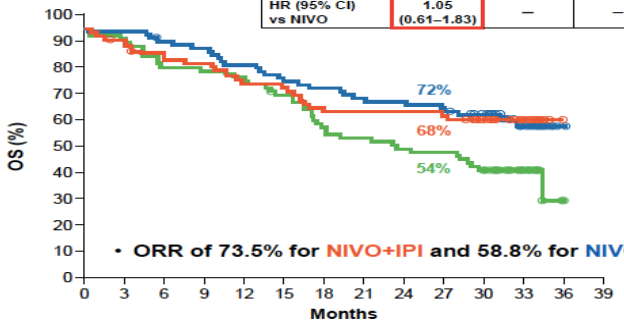
	NIVO+IPI	NIVO	IPI
Median OS, mo (95% CI)	NR (31.8–NR)	NR (23.1–NR)	18.5 (13.7–22.5)
HR (95% CI) vs NIVO	0.84 (0.63–1.12)	—	—



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

PD-L1 Expression Level ≥5%

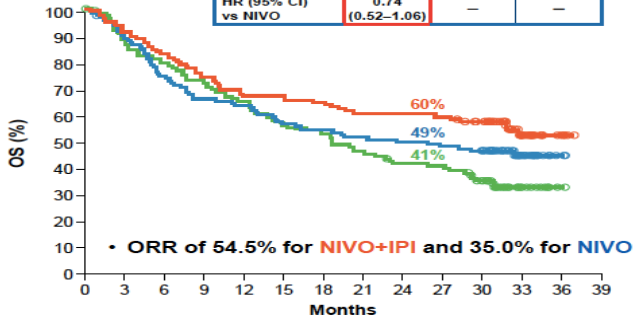
	NIVO+IPI	NIVO	IPI
Median OS, mo (95% CI)	NR	NR	28.9 (18.1–NR)
HR (95% CI) vs NIVO	1.05 (0.61–1.83)	—	—



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

PD-L1 Expression Level <1%

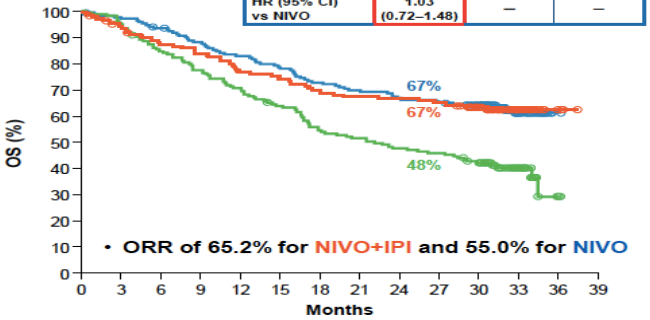
<1% PD-L1	NIVO+IPI	NIVO	IPI
Median OS, mo (95% CI)	NR (26.5–NR)	23.5 (13.0–NR)	18.6 (13.7–23.2)
HR (95% CI) vs NIVO	0.74 (0.52–1.06)	—	—



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

PD-L1 Expression Level ≥1%

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



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

Safety Summary

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

	NIVO+IPI (N=313)		NIVO (N=313)		IPI (N=311)	
Patients reporting event, %	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Treatment-related adverse event (AE)	95.8	58.5	86.3	20.8	86.2	27.7
Treatment-related AE leading to discontinuation	39.6	31.0	11.5	7.7	16.1	14.1
Treatment-related death, n (%)	2 (0.[illegible])[a]		1 (0.3)[b]		1 (0.3)[b]	

So what does it mean…

The benefits of combination immunotherapy aren't clear

The high chance of shrinking the tumour will be important for some people

Side effects will matter more for others

The hunt for better combinations is on

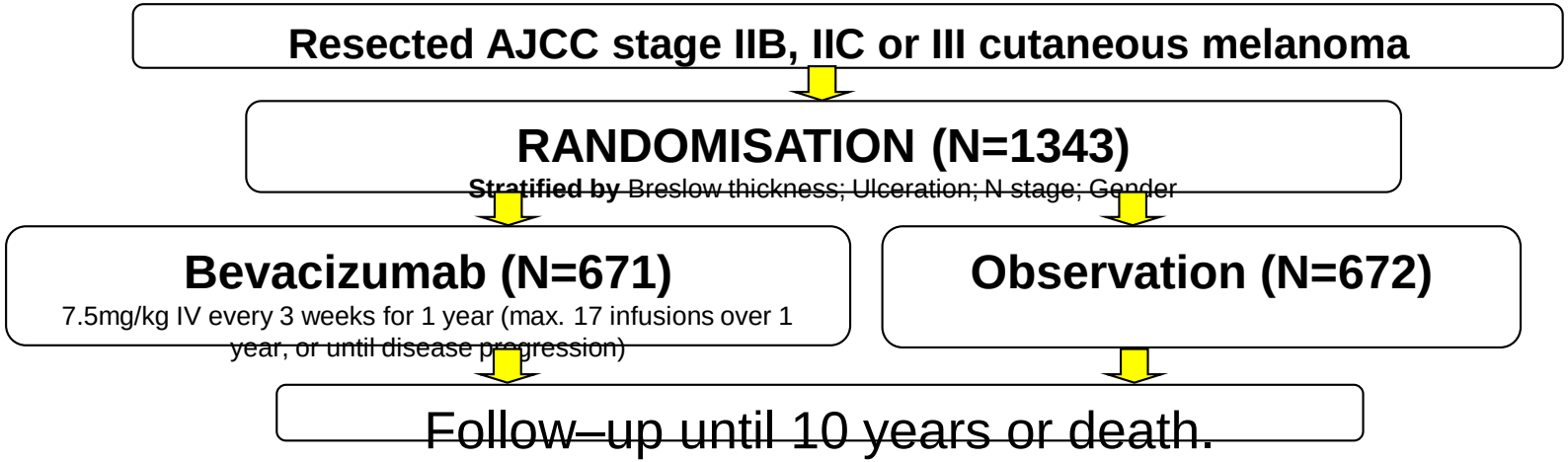
Adjuvant bevacizumab as treatment for melanoma patients at high risk of recurrence: Final results of the AVAST-M trial

- Pippa G Corrie, Andrea Marshall, Paul D Nathan, Paul Lorigan, Martin Gore, Saad Tahir, Guy Faust, Charles G Kelly, Maria Marples, Sarah J Danson, Ernest Marshall, Stephen J Houston, Ruth E Board, Ashita M Waterston, Jenny P Nobes, Mark Harries, Satish Kumar, Gemma Young, Emily Barker, Janet A Dunn, Mark Middleton

Trial funded by Cancer Research UK (grant ref. C7535/A6408 and C2195/A8466)

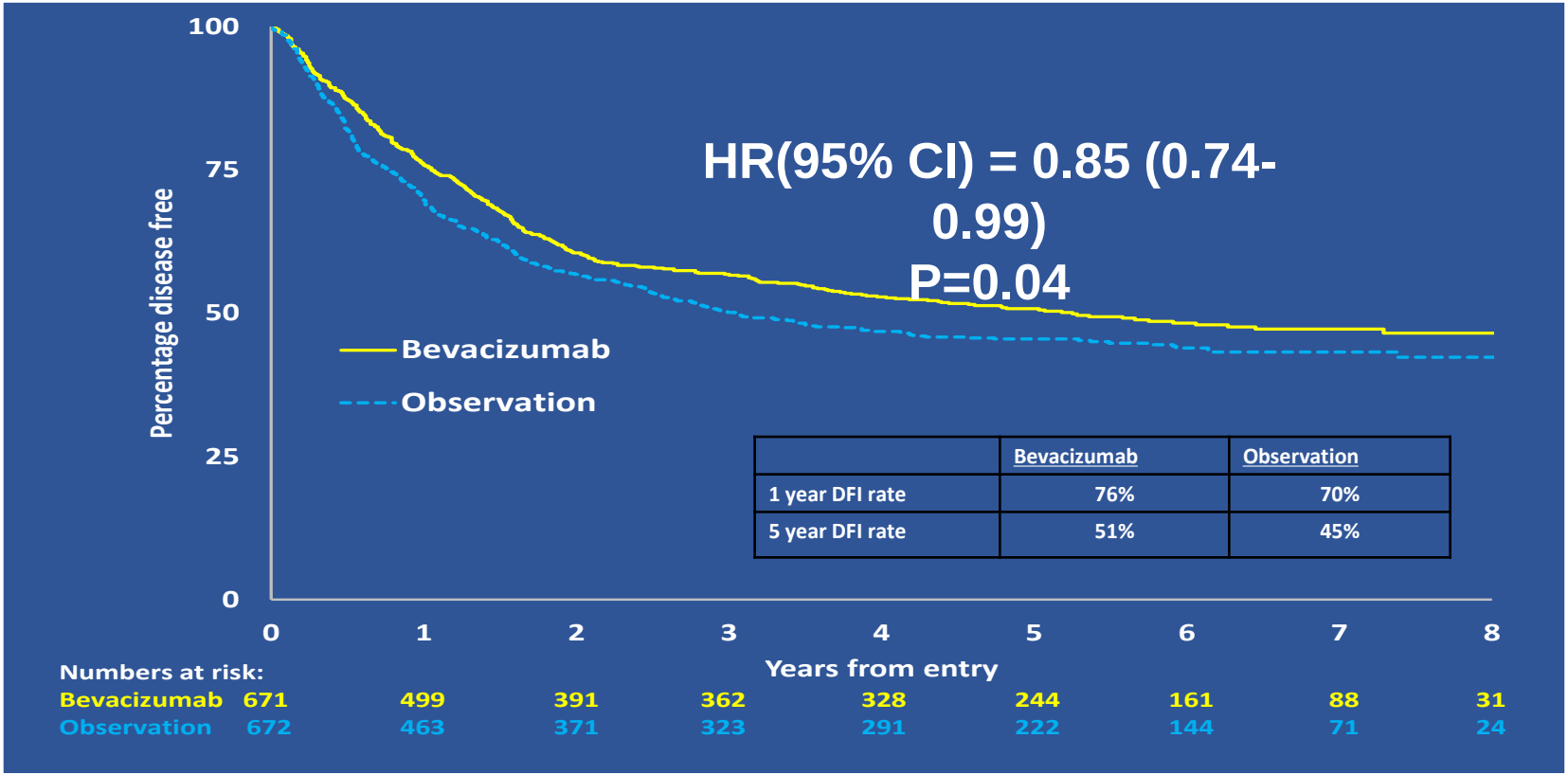
ISRCTN81261306; EudraCT Number: 2006-005505-64

AVAST-M Trial Design



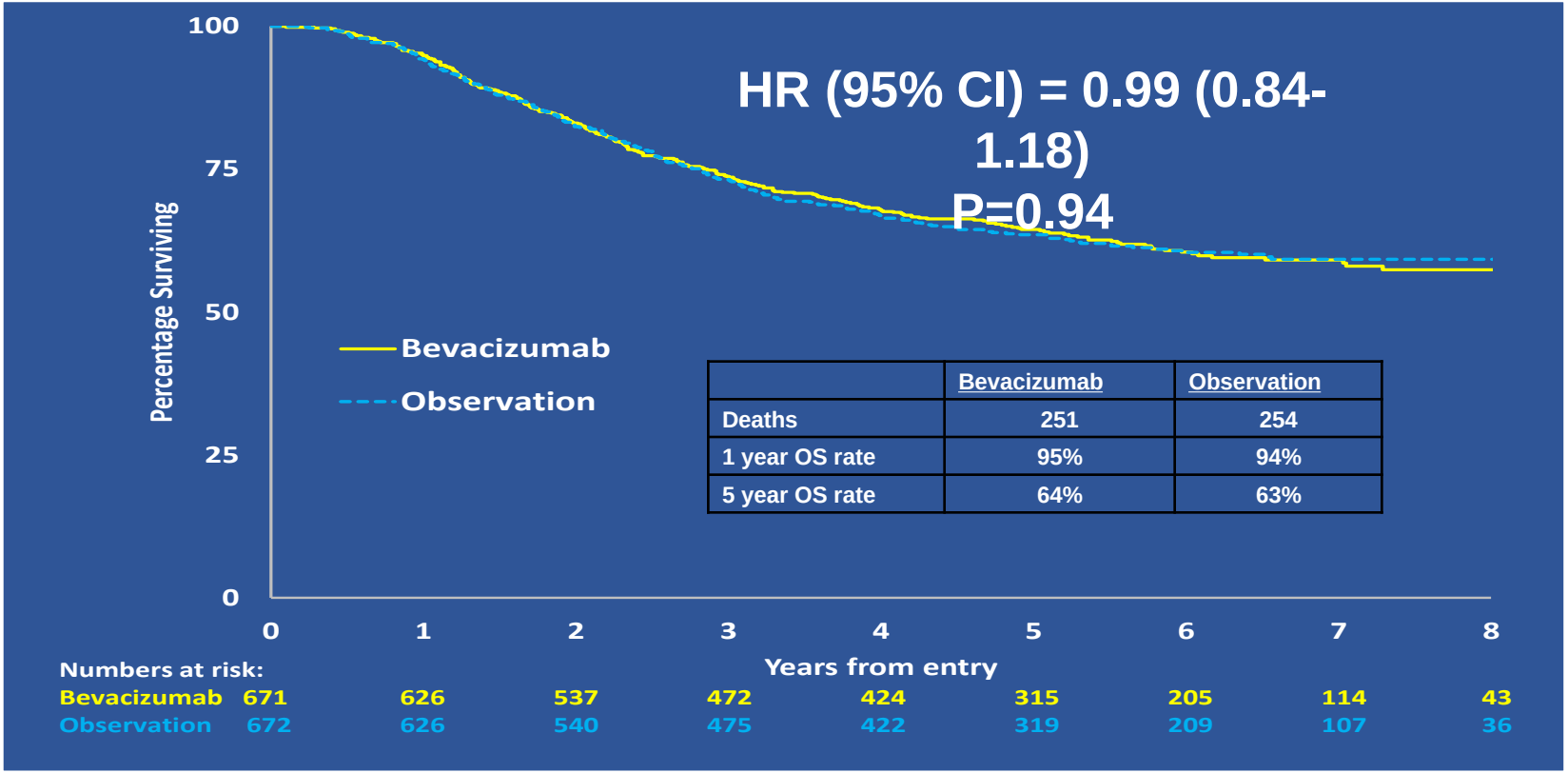
Presented by: Dr Pippa Corrie

Disease-free Interval (DFI)



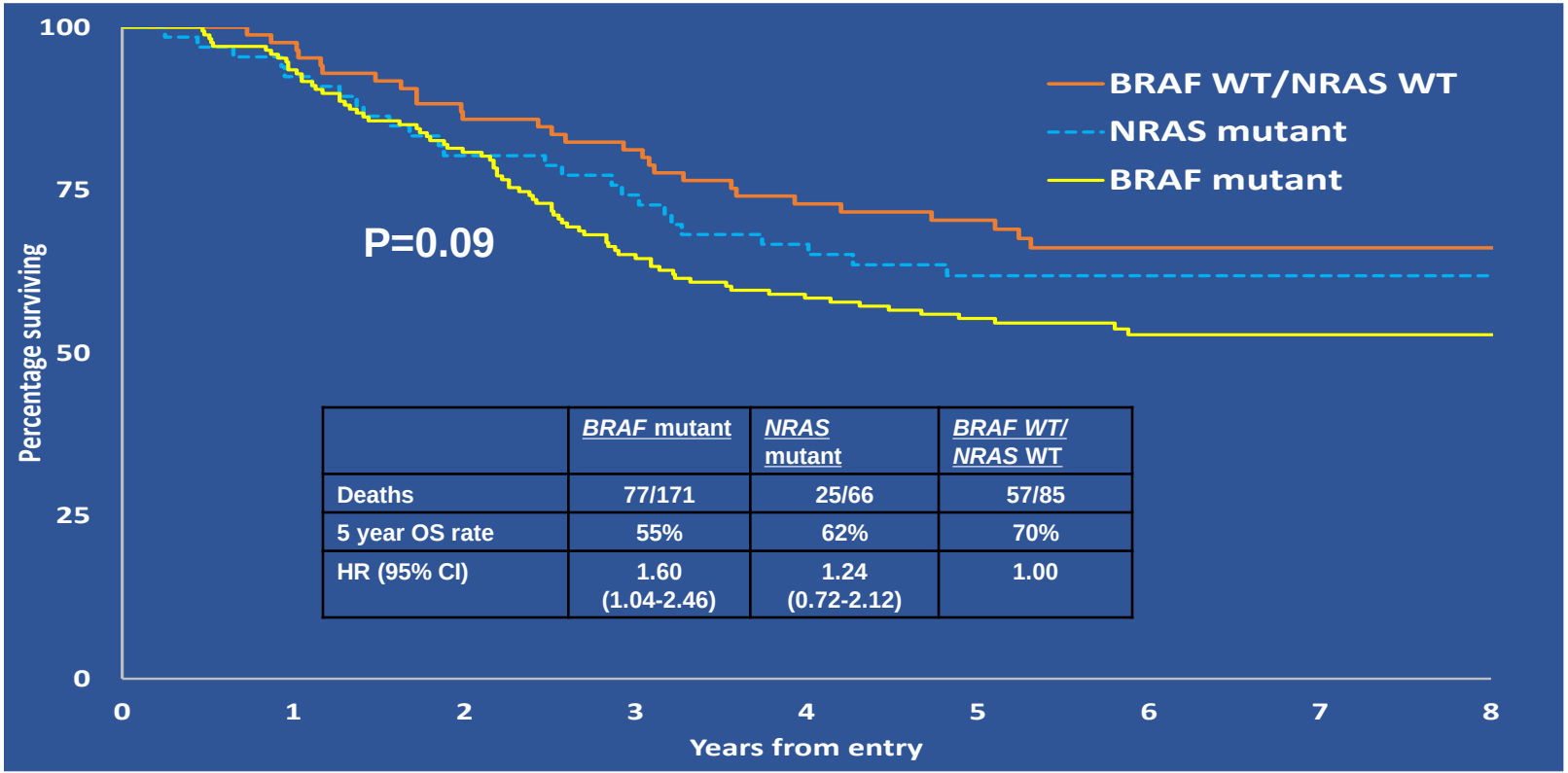
	Bevacizumab	Observation
1 year DFI rate	76%	70%
5 year DFI rate	51%	45%

Overall Survival



	Bevacizumab	Observation
Deaths	251	254
1 year OS rate	95%	94%
5 year OS rate	64%	63%

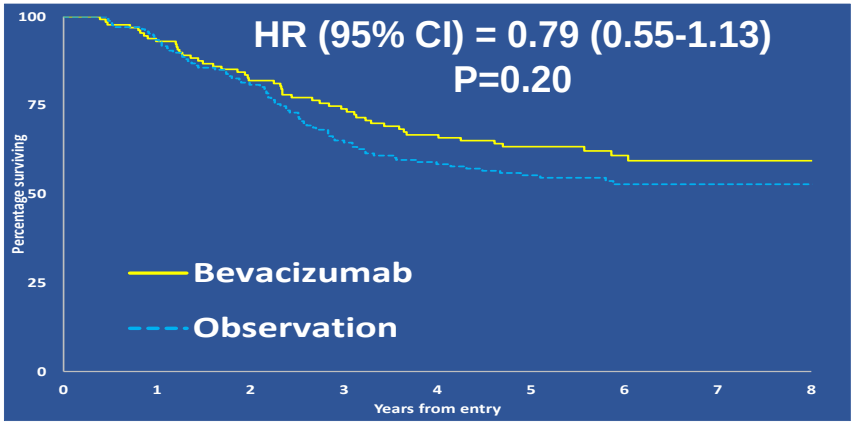
OS By *BRAF* And *NRAS* Status For Observation Arm Patients



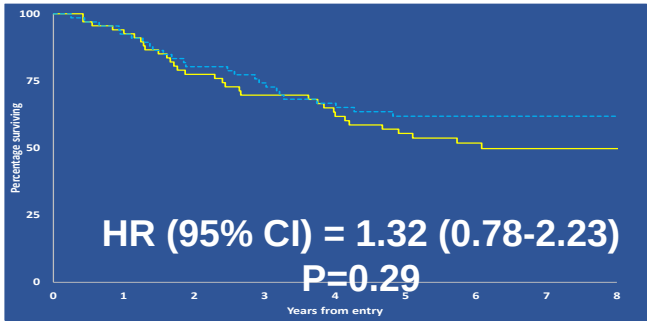
	BRAF mutant	*NRAS* mutant	*BRAF WT/ NRAS* WT
Deaths	77/171	25/66	57/85
5 year OS rate	55%	62%	70%
HR (95% CI)	1.60 (1.04-2.46)	1.24 (0.72-2.12)	1.00

OS By Trial Arm By *BRAF/NRAS* Status

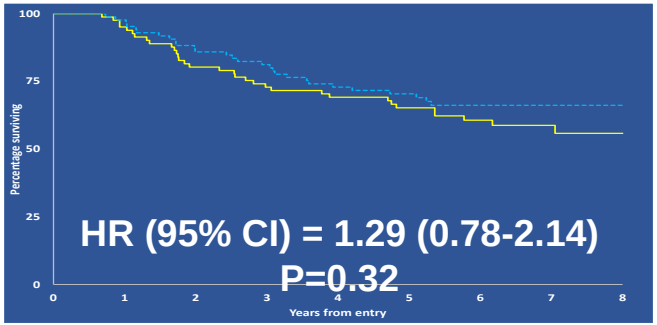
BRAF mutant melanoma



NRAS mutant melanoma



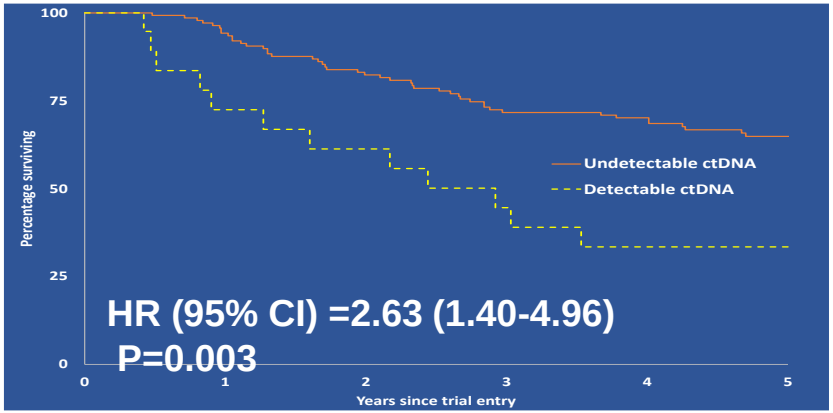
BRAF WT/ NRAS WT melanoma



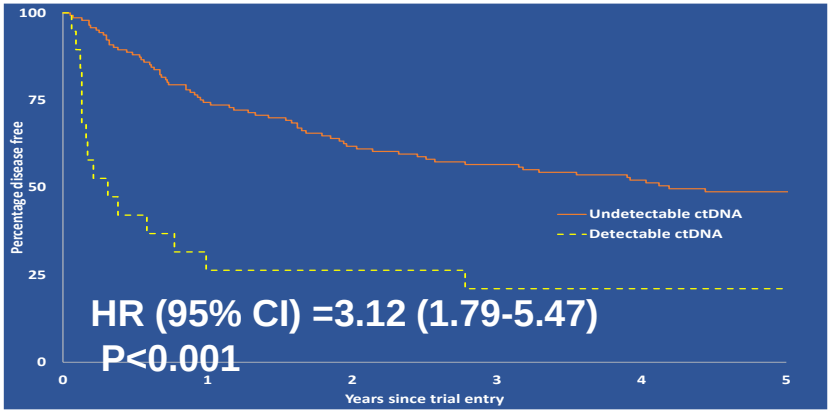
Impact of Mutant *BRAF* And *NRAS* ctDNA On Overall Survival

- ctDNA assessed in plasma of patients whose tumours had either a *BRAF* or *NRAS* mutation, using ddPCR
- ctDNA detected in plasma from 19 of 152 patients collected at baseline, within 12 weeks of surgical clearance

Overall Survival



Disease Free Interval



So what does it mean…

Adjuvant bevacizumab isn't going to be a useful treatment

Although it delays recurrence it doesn't help people live longer

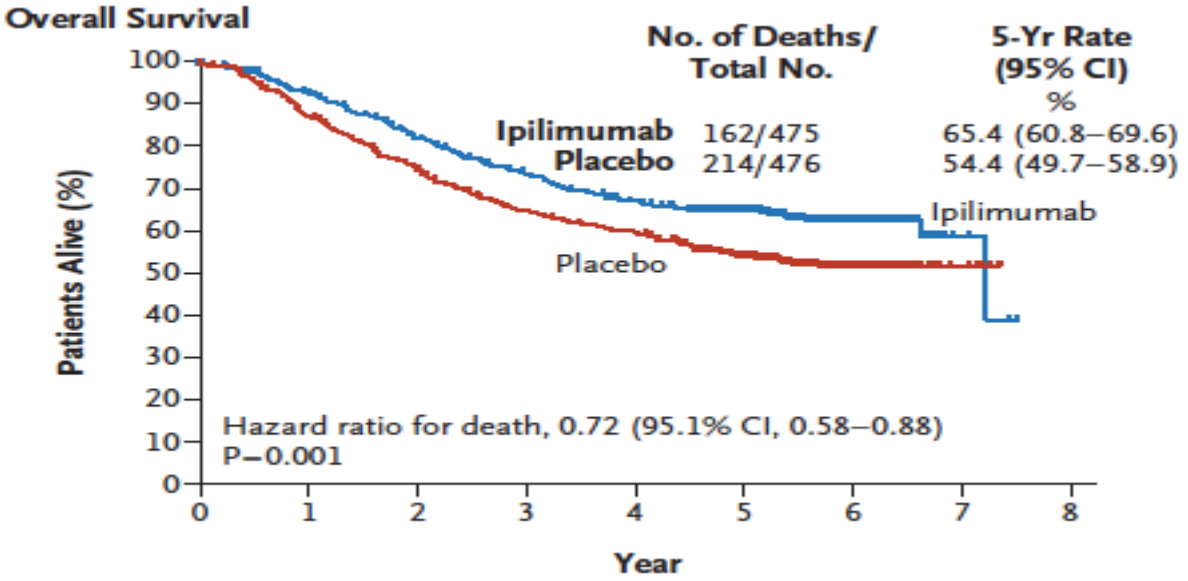
We may be able to use ctDNA to identify people at very high risk of relapse

BRAF and NRAS mutations were associated with worse outcomes in the observation arm

The interplay between angiogenesis, the mutations in some melanomas and the immune system need more study

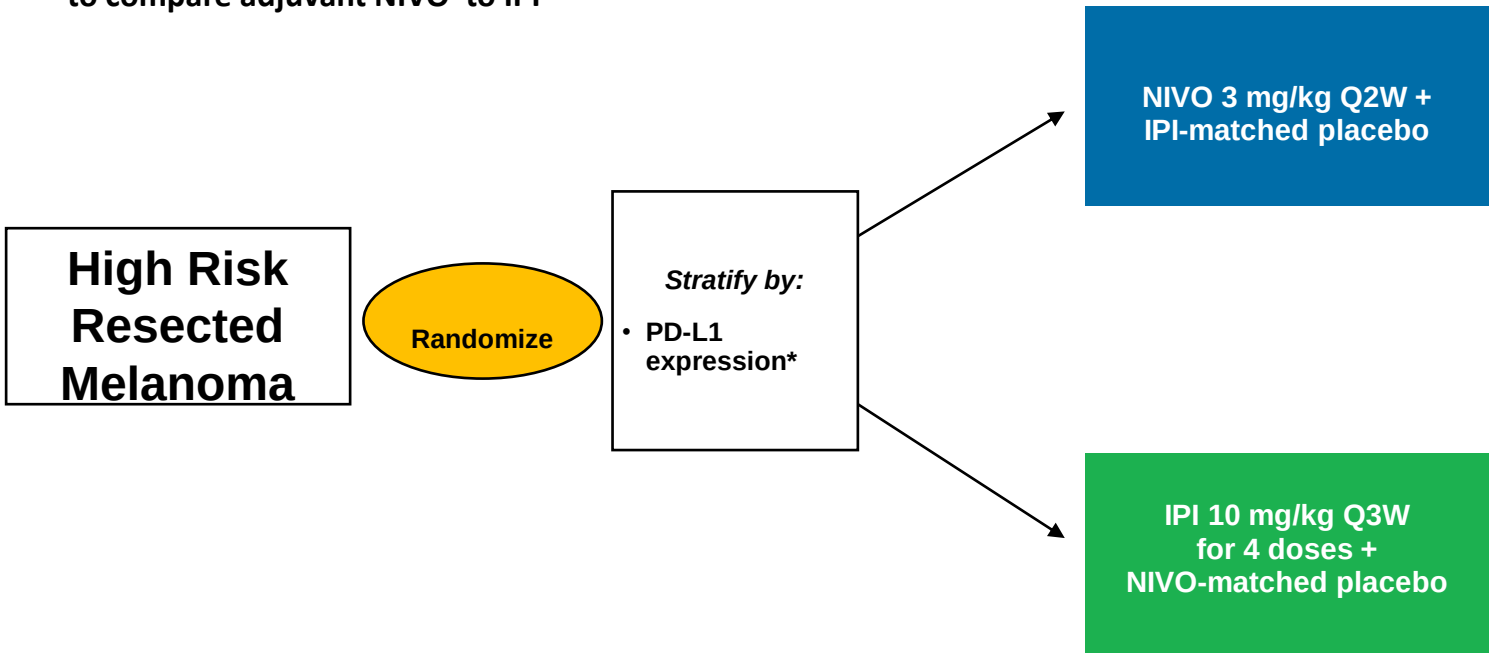
Where now for adjuvant therapy?

High dose ipilimumab works but is toxic



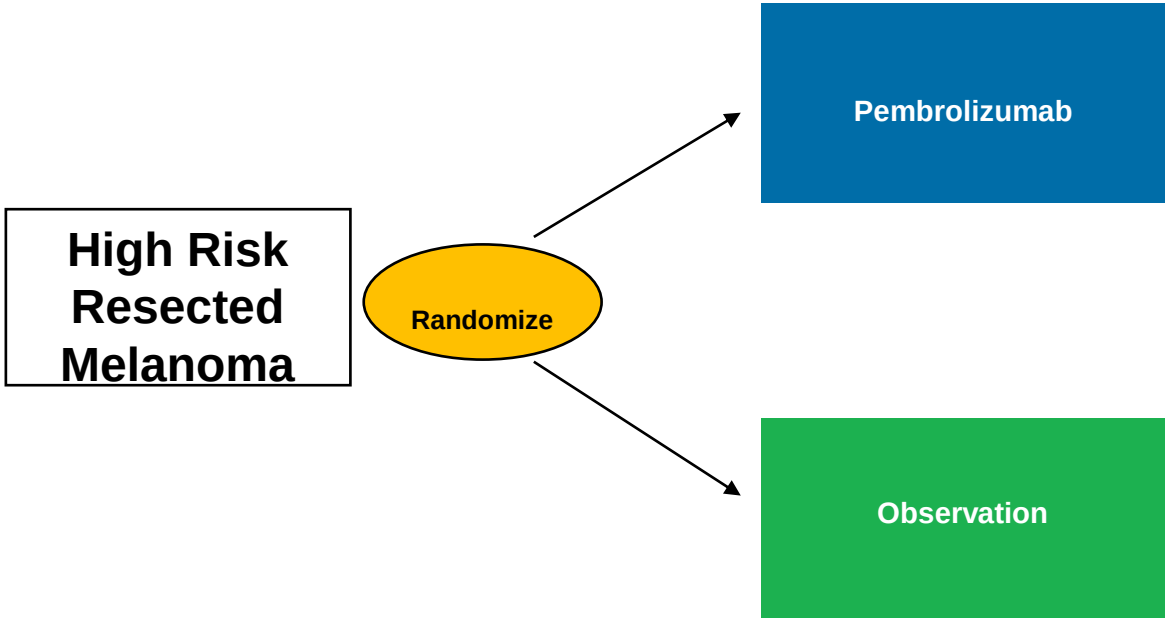
Checkmate 238

Randomized, double-blind, phase III study to compare adjuvant NIVO to IPI



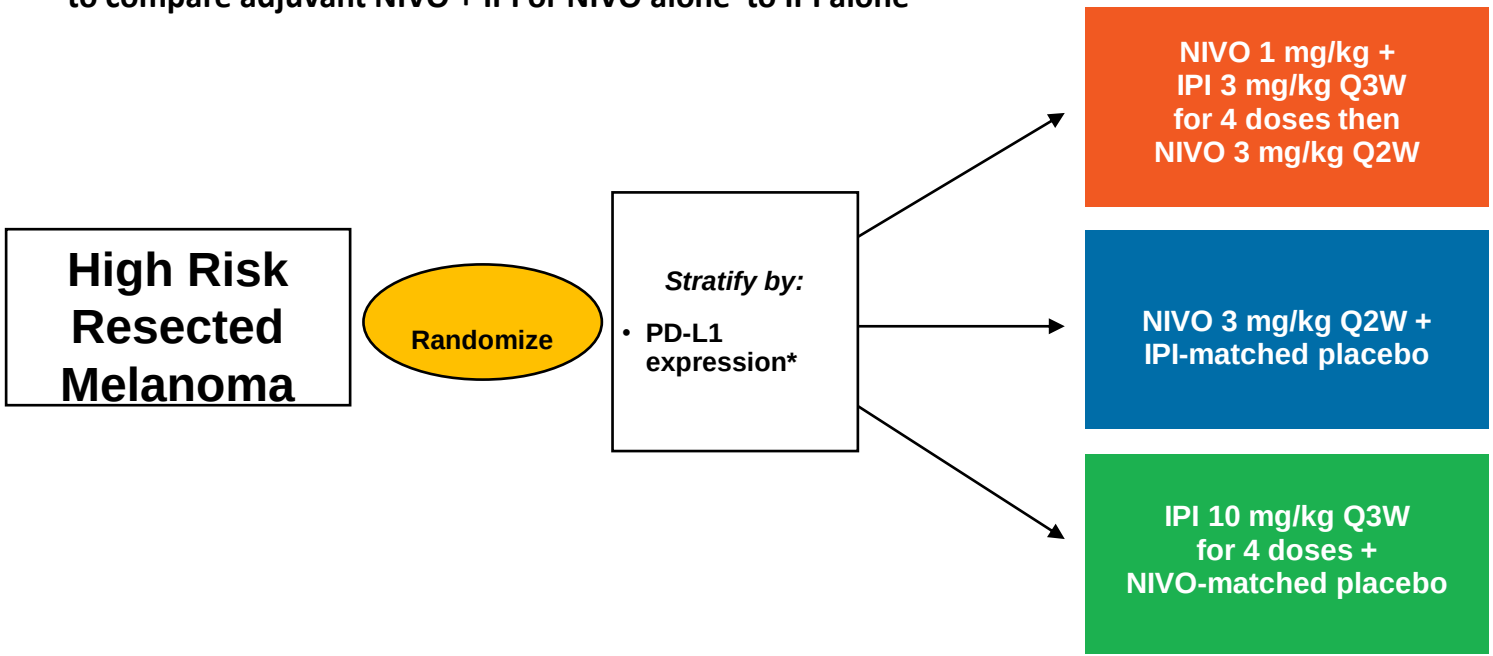
EORTC Pembrolizumab Trial

Randomized, double-blind, phase III study to compare adjuvant Pembro to observation



Checkmate 915

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



So what does it mean…

The best adjuvant treatment approach is uncertain

Ipilimumab works, but is toxic and the benefits of using it early versus saving it for later are unclear

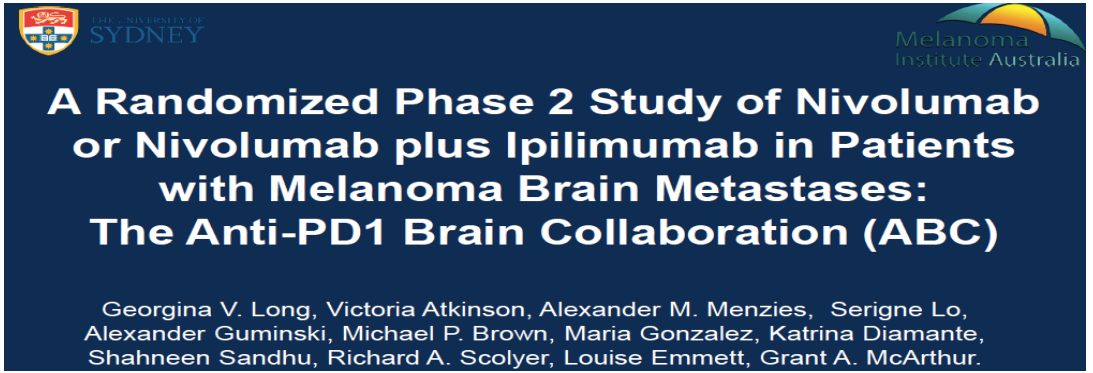
Trials to see if PD-1 is an option here are in progress

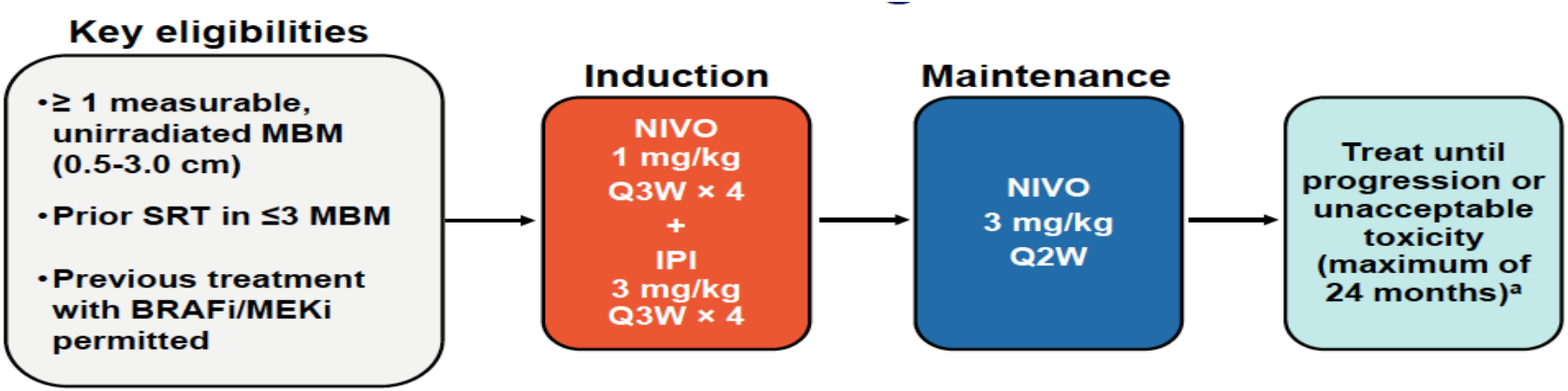
A new study will launch this month comparing these 2 options with combined Ipi/Nivo

Can we treat brain metastases effectively?

Efficacy and Safety of Nivolumab▼ Plus Ipilimumab▼ in Patients with Melanoma Metastatic to the Brain: Results of the Phase II Study CheckMate 204

Hussein Tawbi,[1] Peter Forsyth,[2] Alain Algazi,[3] Omid Hamid,[4] F. Stephen Hodi,[5] Stergios Moschos,[6] Nikhil Khushalani,[2] Rene Gonzalez,[7] Christopher Lao,[8] Michael Postow,[9] Michael B. Atkins,[10] Marc Ernstoff,[11] Igor Puzanov,[11] Ragini Kudchadkar,[12] Reena Thomas,[13] Ahmad Tarhini,[14] Joel Jiang,[15] Alexandre Avila,[15] Sheena Demelo,[15] Kim Margolin[16]



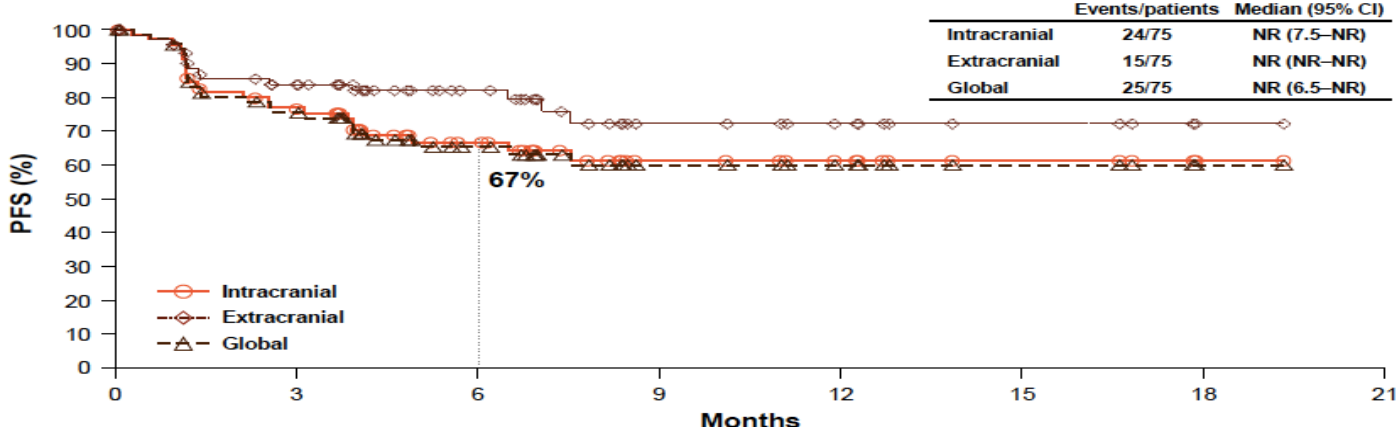


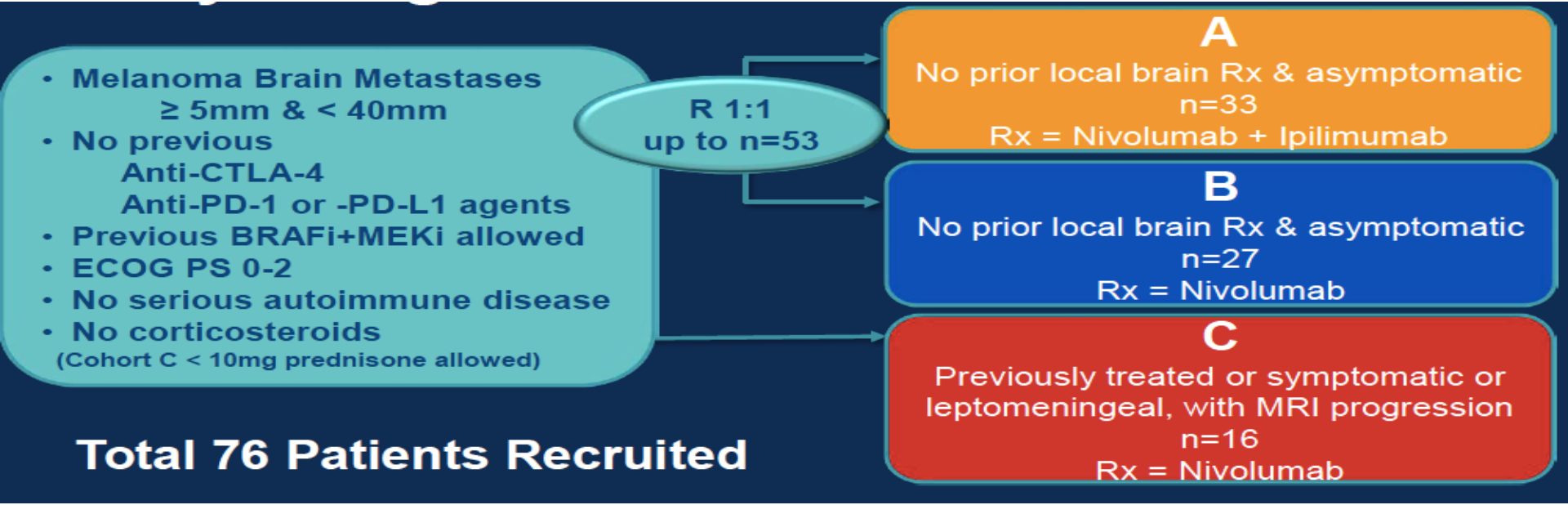
- Exclusion criteria included neurological symptoms; steroids > 10 days; WBRT; prior treatment with checkpoint inhibitors; leptomeningeal disease

Response to Treatment – All Patients (N = 75)

	Global	Intracranial	Extracranial
Best overall response, n (%)			
Complete response	4 (5)	16 (21)	5 (7)
Partial response	36 (48)	25 (33)	32 (43)
Stable disease	4 (5)	4 (5)	2 (3)
Progressive disease[a]	18 (24)	18 (24)	16 (21)
Not evaluable[b]	13 (17)	12 (16)	20 (27)
Objective response rate, % (95% CI)	53 (41–65)	55 (43–66)	49 (38–61)
Clinical benefit rate[c], % (95% CI)	59 (47–70)	60 (48–71)	52 (40–64)

PFS

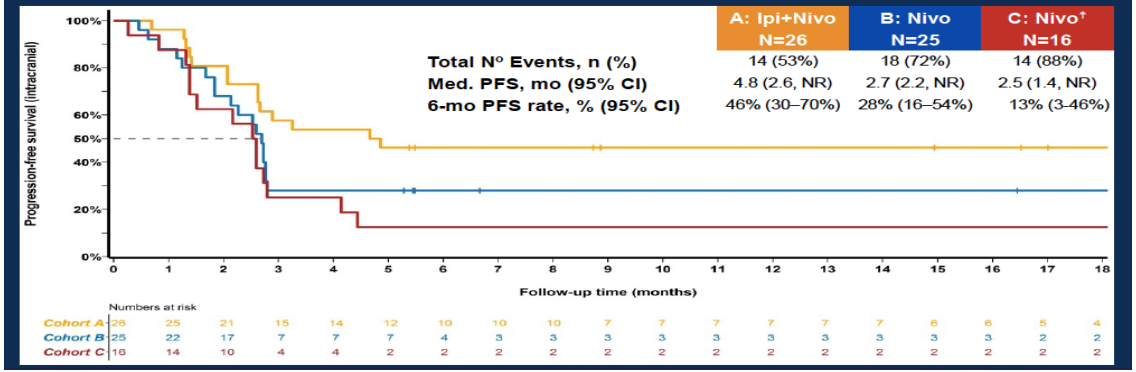



• Melanoma Brain Metastases
≥ 5mm & < 40mm
• No previous
Anti-CTLA-4
Anti-PD-1 or -PD-L1 agents
• Previous BRAFi+MEKi allowed
• ECOG PS 0-2
• No serious autoimmune disease
• No corticosteroids
(Cohort C < 10mg prednisone allowed)
R 1:1
up to n=53
A
No prior local brain Rx & asymptomatic
n=33
Rx = Nivolumab + Ipilimumab
B
No prior local brain Rx & asymptomatic
n=27
Rx = Nivolumab
C
Previously treated or symptomatic or leptomeningeal, with MRI progression
n=16
Rx = Nivolumab
Total 76 Patients Recruited

Best Intracranial RECIST Response

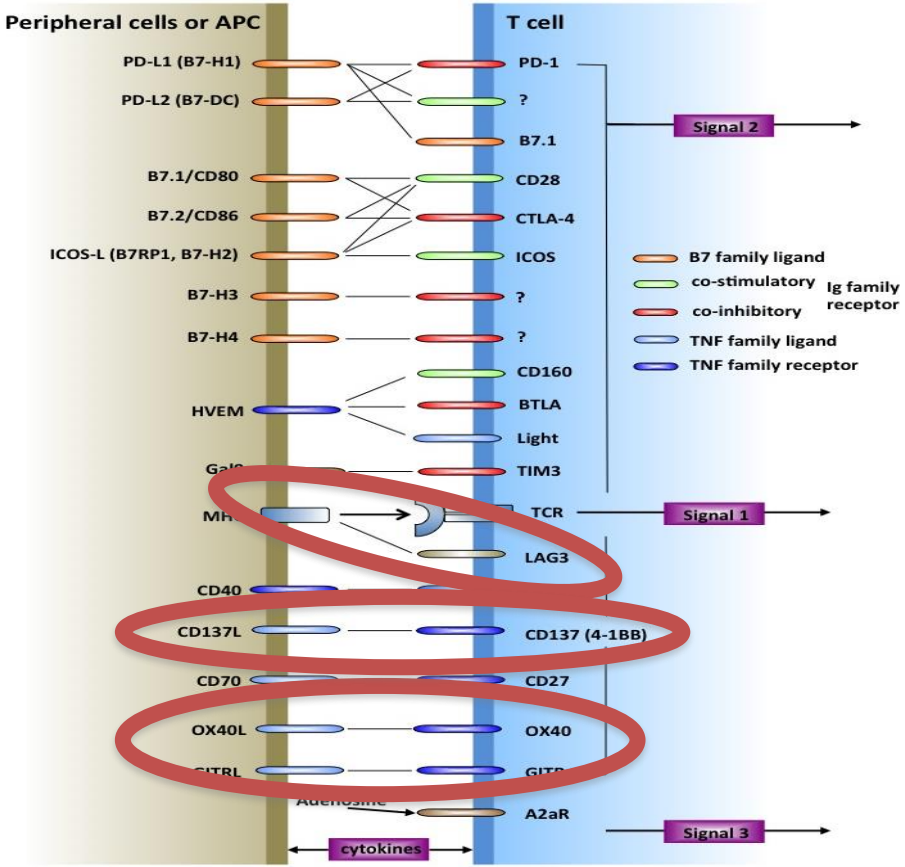
	A: Ipi+Nivo N=26	B: Nivo N=25	C: Nivo† N=16
Intracranial Response, n (%)	**11 (42%)**	**5 (20%)**	**1 (6%)**
CR	4 (15%)	3 (12%)	0
PR	7 (27%)	2 (8%)	1 (6%)
SD	2 (8%)	1 (4%)	4 (25%)
PD	12 (46%)	18 (72%)	11 (69%)
NE*	1 (4%)	1 (4%)	0

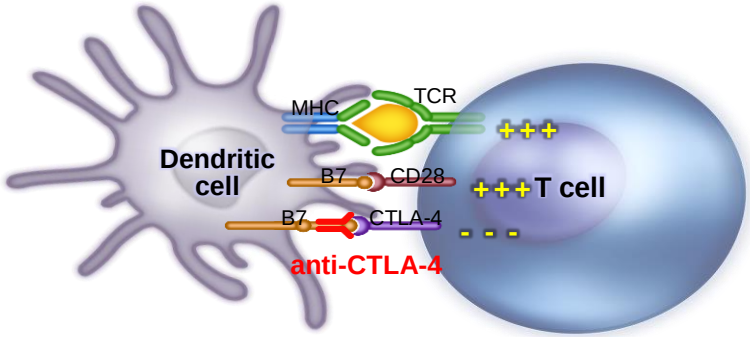
Intracranial Progression Free Survival



	A: Ipi+Nivo N=26	B: Nivo N=25	C: Nivo† N=16
Total Nº Events, n (%)	14 (53%)	18 (72%)	14 (88%)
Med. PFS, mo (95% CI)	4.8 (2.6, NR)	2.7 (2.2, NR)	2.5 (1.4, NR)
6-mo PFS rate, % (95% CI)	46% (30–70%)	28% (16–54%)	13% (3-46%)

Manipulating more checkpoints





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Oxford Biomedical Research Centre

NHS National Institute for Health Research

NCRI National Cancer Research Institute

Thanks for Listening

CANCER RESEARCH UK

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octo Oncology Clinical Trials Office

OCTRU Oxford Clinical Trials Research Unit

UKCRC Registered Clinical Trials Units

OCTRU is a UKCRC Registered Clinical Trials Unit
OCTRU is a joint venture between the Centre for Statistics in Medicine (CSM) and the Oncology Clinical Trials Office (OCTO) both based at the University of Oxford

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