The Royal Marsden NHS
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Single agent anti-PD1 vs combination: how to choose

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Disclosures

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- Support from NIHR RM/ICR Biomedical Research Centre for Cancer

Aim

The Guardian February 2016: ‘The closest thing yet to a cure for terminal cancer?’

https://www.theguardian.com/science/2016/feb/04/revolutionary-drug-immune-system-advanced-cancer

Data

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma

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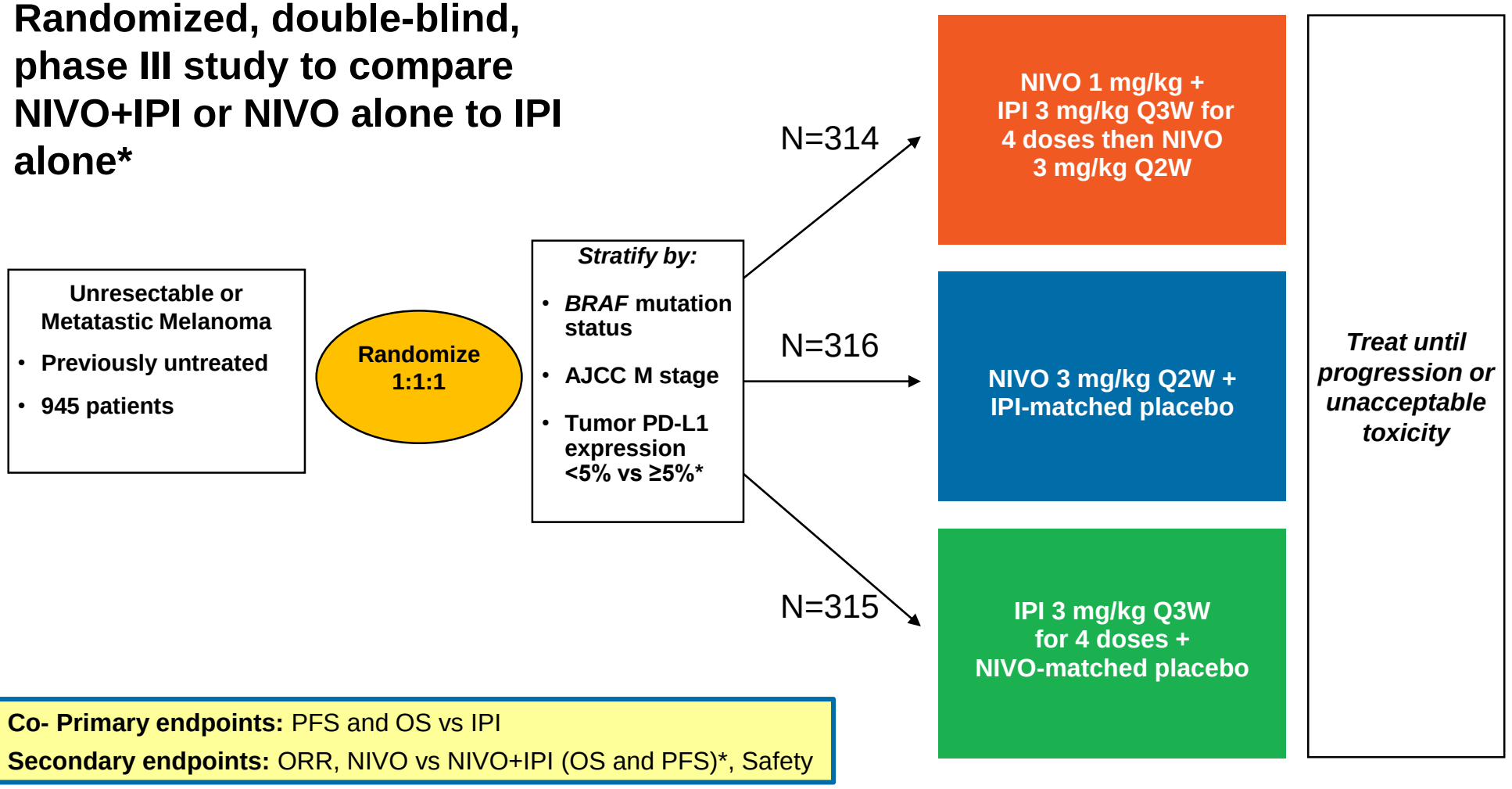
Checkmate 067: Study Design

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



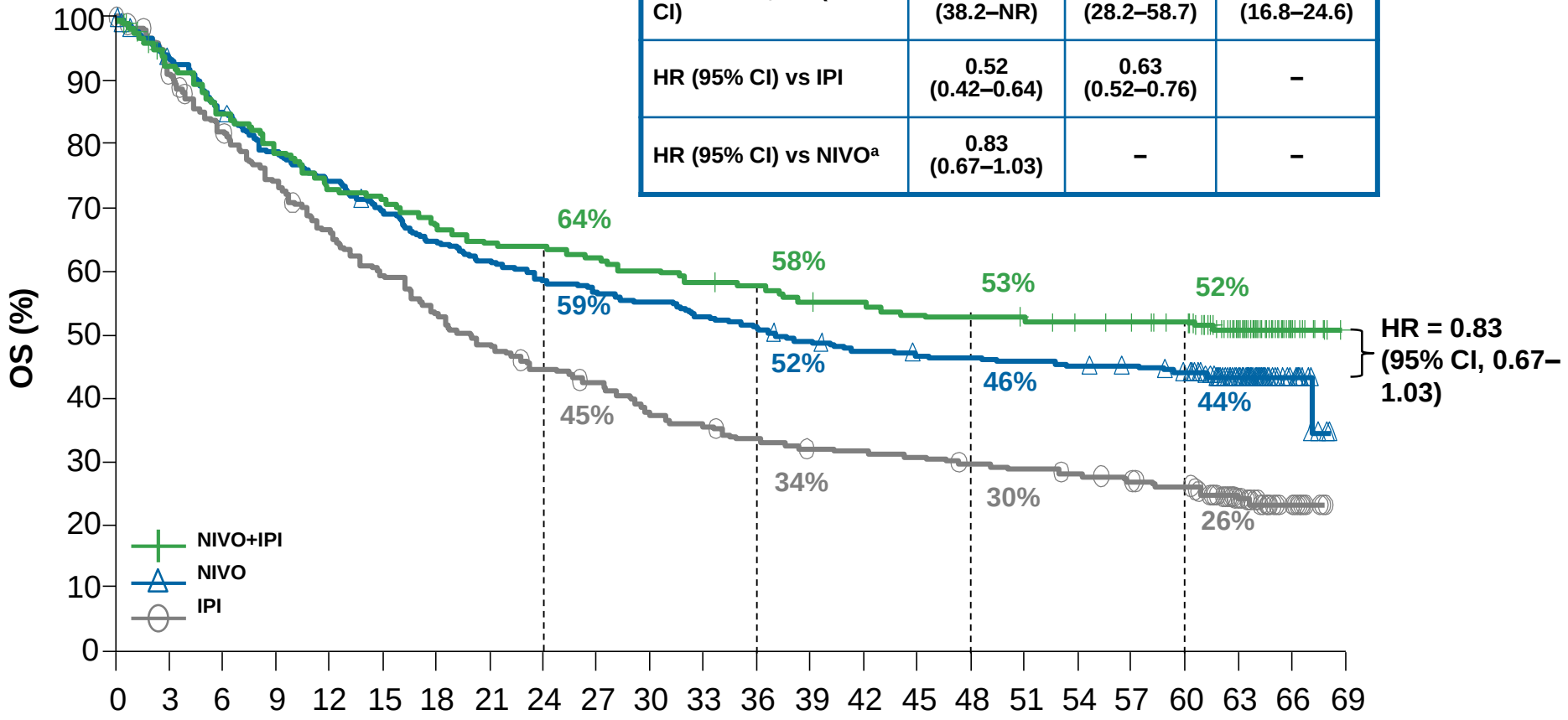
Co- Primary endpoints: PFS and OS vs IPI

Secondary endpoints: ORR, NIVO vs NIVO+IPI (OS and PFS)*, Safety

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

Overall Survival

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
HR (95% CI) vs IPI	0.52 (0.42–0.64)	0.63 (0.52–0.76)	–
HR (95% CI) vs NIVO[a]	0.83 (0.67–1.03)	–	–



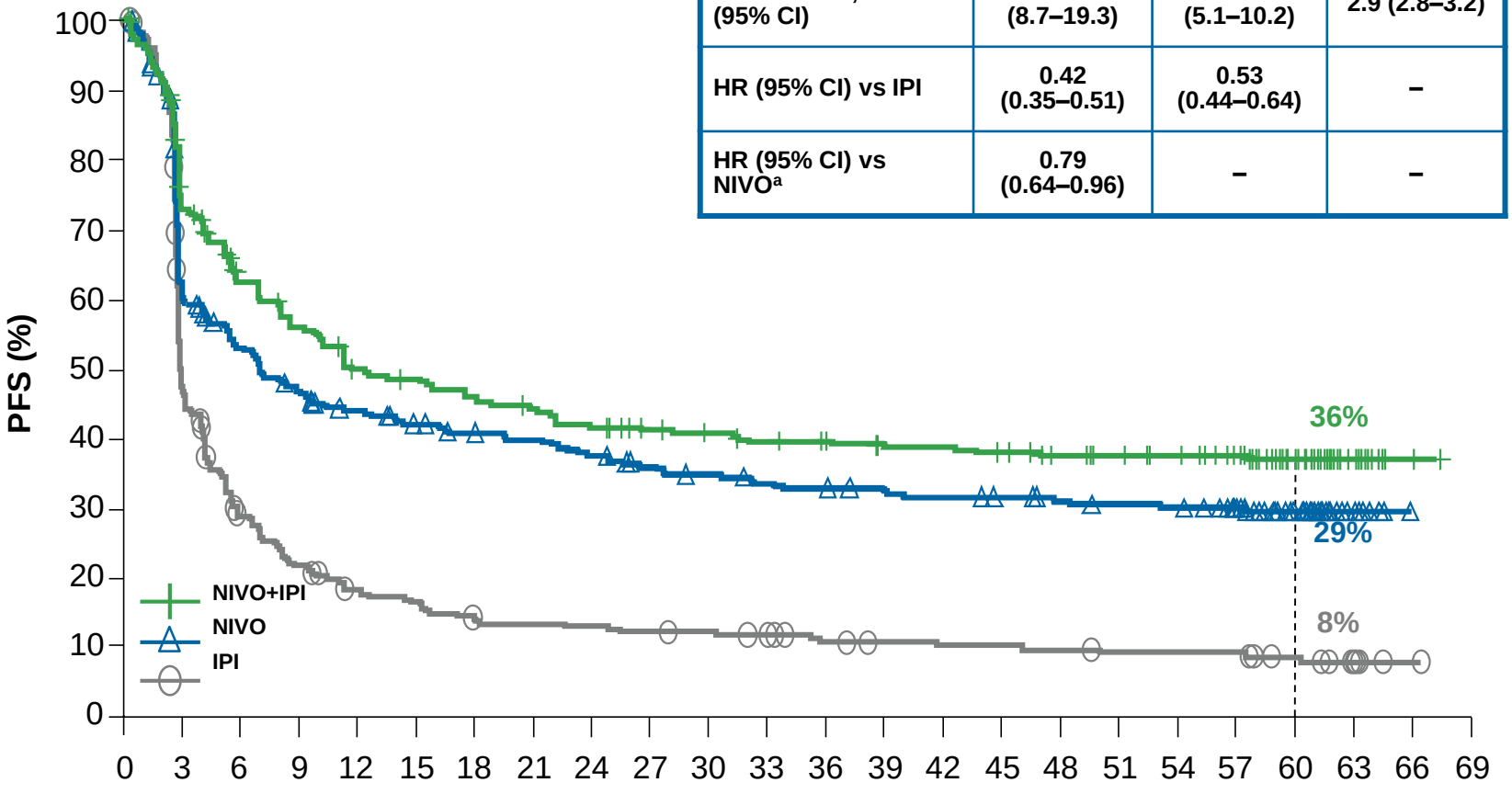
No. at risk

NIVO+IPI	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	157	155	150	92	14	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	135	130	78	14	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	73	36	12	0

[a]Descriptive analysis. 1. Larkin J, et al. Oral presentation at the AACR Annual Meeting; April 1–5, 2017; Washington DC, USA. Abstract CT075; 2. Wolchok JD, et al. *N Engl J Med* 2017;377:1345–1356; 2. Hodi FS, et al. *Lancet Oncol* 2018;19:1480–1492.

Progression-Free Survival

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median PFS, mo (95% CI)	11.5 (8.7–19.3)	6.9 (5.1–10.2)	2.9 (2.8–3.2)
HR (95% CI) vs IPI	0.42 (0.35–0.51)	0.53 (0.44–0.64)	–
HR (95% CI) vs NIVO[a]	0.79 (0.64–0.96)	–	–



No. at risk

NIVO+IPI	314	218	174	155	136	131	124	117	110	104	101	97	95	91	90	88	82	79	76	69	45	19	2	0
NIVO	316	177	151	132	120	112	106	103	97	88	84	80	78	76	73	71	68	66	65	60	40	13	1	0
IPI	315	136	78	58	46	42	34	32	31	29	28	26	21	19	18	18	17	15	15	15	11	8	1	0

[a]Descriptive analysis.

Response rate

Table 1. Response to Treatment.*

Variable	Nivolumab plus Ipilimumab (N=314)	Nivolumab (N=316)	Ipilimumab (N=315)
Best overall response — no. (%)†			
Complete response	69 (22)	60 (19)	18 (6)
Partial response	114 (36)	81 (26)	42 (13)
Stable disease	38 (12)	30 (9)	69 (22)
Progressive disease	74 (24)	121 (38)	159 (50)
Unable to determine	19 (6)	24 (8)	27 (9)
Objective response‡			
Patients with response			
No.	183	141	60
% (95% CI)	58 (53–64)	45 (39–50)	19 (15–24)
Estimated odds ratio (95% CI)§	6.35 (4.38–9.22)	3.54 (2.46–5.10)	—
P value§	<0.001	<0.001	—
Median duration of response (95% CI) — mo			
Intention-to-treat population	NR¶	NR (50.4–NR)	14.4 (8.3–53.6)
BRAF mutation status			
Patients with *BRAF* mutations	NR (21.0–NR)	55.0 (20.6–NR)	14.4 (6.9–NR)
Patients without *BRAF* mutations	NR (42.4–NR)	NR (50.4–NR)	19.2 (6.0–56.4)
Metastasis stage			
M10/M1a/M1b	NR (NR–NR)	NR (36.3–NR)	13.4 (6.0–31.3)
M1c	NR (15.8– NR)	NR (26.2–NR)	47.4 (5.1–NR)
PD-L1 expression level			
<5%	NR (40.1–NR)	NR (50.4–NR)	12.8 (5.3–53.6)
≥5%	NR (18.1–NR)	NR (26.7–NR)	31.3 (6.1–NR)
Lactate dehydrogenase level			
≤ULN	NR (44.0–NR)	NR (45.7–NR)	22.3 (6.9–56.4)
>ULN	NR (25.4–NR)	NR (13.8–NR)	11.6 (1.8–NR)
Patients with complete response	NR (NR–NR)	NR (NR–NR)	NR (13.3–NR)
Continued response — no. of patients/ total no. (%)	57/69 (83)	49/60 (82)	13/18 (72)
Patients with partial response	19.8 (10.2–NR)	25.1 (16.4–NR)	8.3 (4.2–14.4)
Continued response — no. of patients/ total no. (%)	56/114 (49)	37/81 (46)	11/42 (26)

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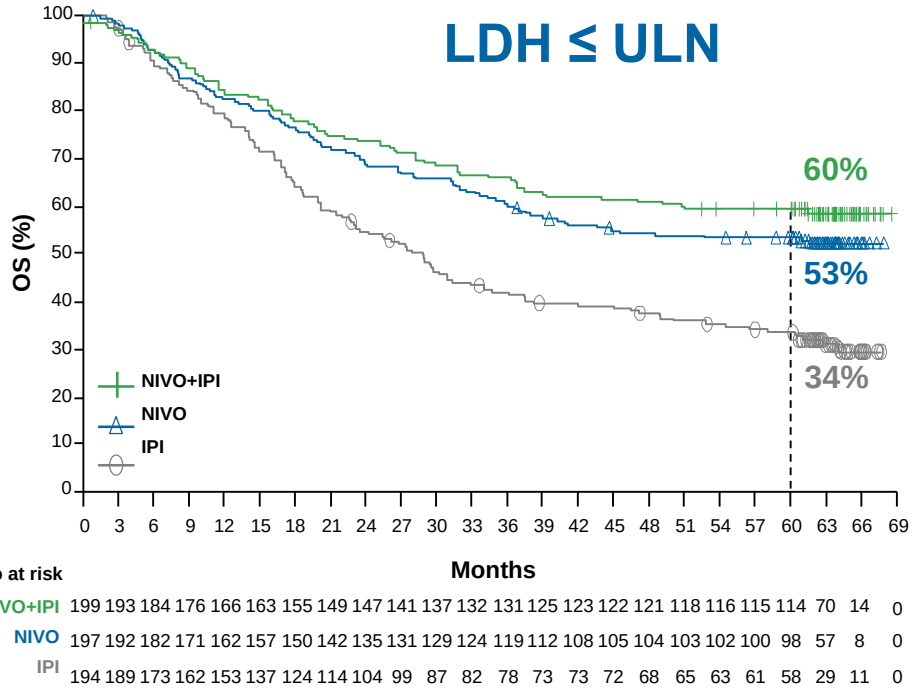
OS by LDH Level

- Improved OS with NIVO+IPI and NIVO vs IPI regardless of baseline LDH levels

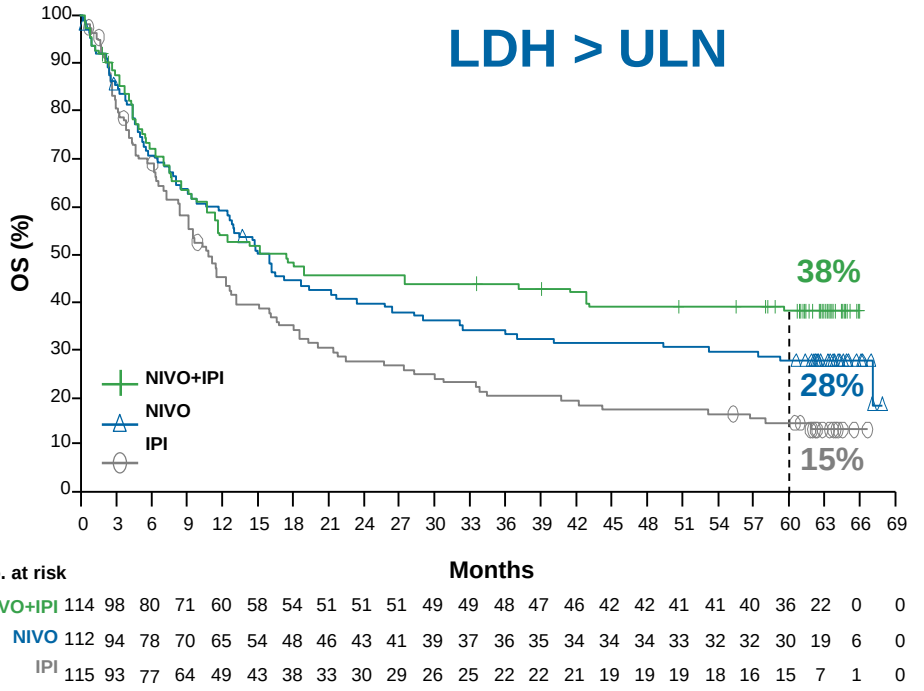
	NIVO+IPI (n = 199)	NIVO (n = 197)	IPI (n = 194)
Median, mo (95% CI)	NR	NR (40.2–NR)	28.8 (22.7–34.0)
HR (95% CI) vs IPI	0.48 (0.37–0.64)	0.58 (0.44–0.76)	–
HR (95% CI) vs NIVO[a]	0.83 (0.62–1.12)	–	–

	NIVO+IPI (n = 114)	NIVO (n = 112)	IPI (n = 115)
Median, mo (95% CI)	17.4 (10.7–42.6)	16.0 (11.7–21.7)	10.9 (8.4–13.1)
HR (95% CI) vs IPI	0.58 (0.43–0.79)	0.71 (0.53–0.96)	–
HR (95% CI) vs NIVO[a]	0.82 (0.59–1.13)	–	–



No at risk

NIVO+IPI	199	193	184	176	166	163	155	149	147	141	137	132	131	125	123	122	121	118	116	115	114	70	14	0
NIVO	197	192	182	171	162	157	150	142	135	131	129	124	119	112	108	105	104	103	102	100	98	57	8	0
IPI	194	189	173	162	153	137	124	114	104	99	87	82	78	73	73	72	68	65	63	61	58	29	11	0



No. at risk

NIVO+IPI	114	98	80	71	60	58	54	51	51	51	49	49	48	47	46	42	42	41	41	40	36	22	0	0
NIVO	112	94	78	70	65	54	48	46	43	41	39	37	36	35	34	34	34	33	32	32	30	19	6	0
IPI	115	93	77	64	49	43	38	33	30	29	26	25	22	22	21	19	19	19	18	16	15	7	1	0

[a]Descriptive analysis. LDH, lactate dehydrogenase; ULN, upper limit of normal.

Safety Summary

- No new safety signals were observed with the additional follow-up
- No additional deaths due to study drug toxicity were reported since the prior analysis[a]

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 AE, %	96	59	87	23	86	28
Treatment-related AE leading to discontinuation, %	42	31	13	8	15	14
Treatment-related death, n (%)	2 (1)		1 (< 1)		1 (< 1)	

- Survival outcomes were not impacted by discontinuing NIVO+IPI early due to a TRAE[b]
  - Patients who discontinued NIVO+IPI during induction due to a TRAE had 5-year PFS (35%) and OS rates (51%) similar to patients in the overall population (36% and 52%, respectively)

[a]Previously reported treatment-related deaths were cardiomyopathy and liver necrosis for NIVO+IPI (n = 1 each; both occurred > 100 days after last treatment), neutropenia for NIVO (n = 1), and colonic perforation for IPI (n = 1); [b]Post-hoc analysis. TRAE, treatment-related adverse event.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain

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Immunotherapy for Brain Metastases

Table 2. Response to Treatment.

Variable	Intracranial (N=94)	Extracranial (N=94)	Global (N=94)
Best overall response — no. (%)*			
Complete response	24 (26)	7 (7)	8 (9)
Partial response	28 (30)	40 (43)	40 (43)
Stable disease for ≥6 mo	2 (2)	6 (6)	5 (5)
Progressive disease	31 (33)	28 (30)	33 (35)
Could not be evaluated†	9 (10)	13 (14)	8 (9)
Objective response‡			
No. of patients	52	47	48
Percent of patients (95% CI)	55 (45–66)	50 (40–60)	51 (40–62)
Clinical benefit§			
No. of patients	54	53	53
Percent of patients (95% CI)	57 (47–68)	56 (46–67)	56 (46–67)

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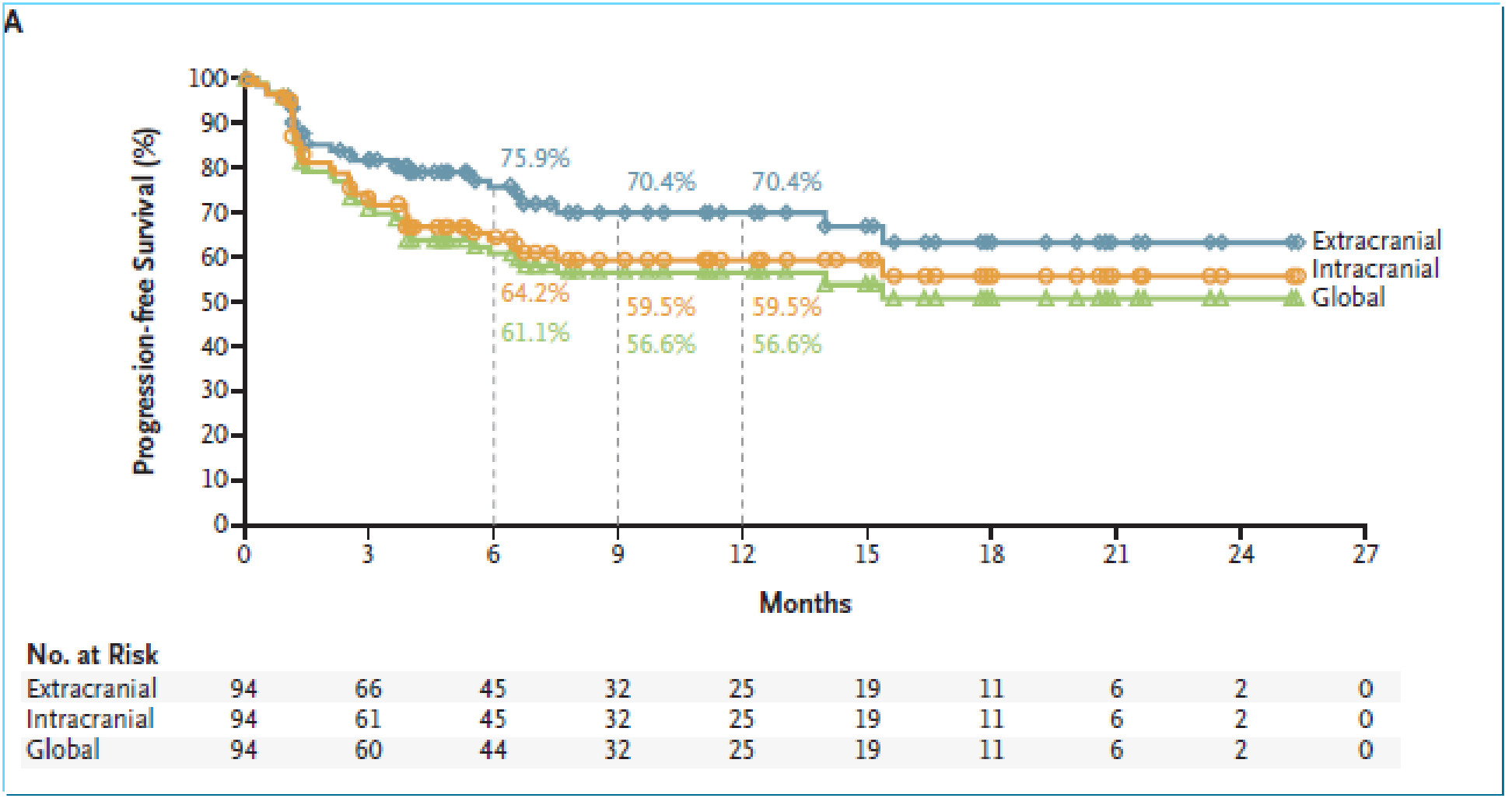
Immunotherapy for Brain Metastases



No. at Risk										
Extracranial	94	66	45	32	25	19	11	6	2	0
Intracranial	94	61	45	32	25	19	11	6	2	0
Global	94	60	44	32	25	19	11	6	2	0

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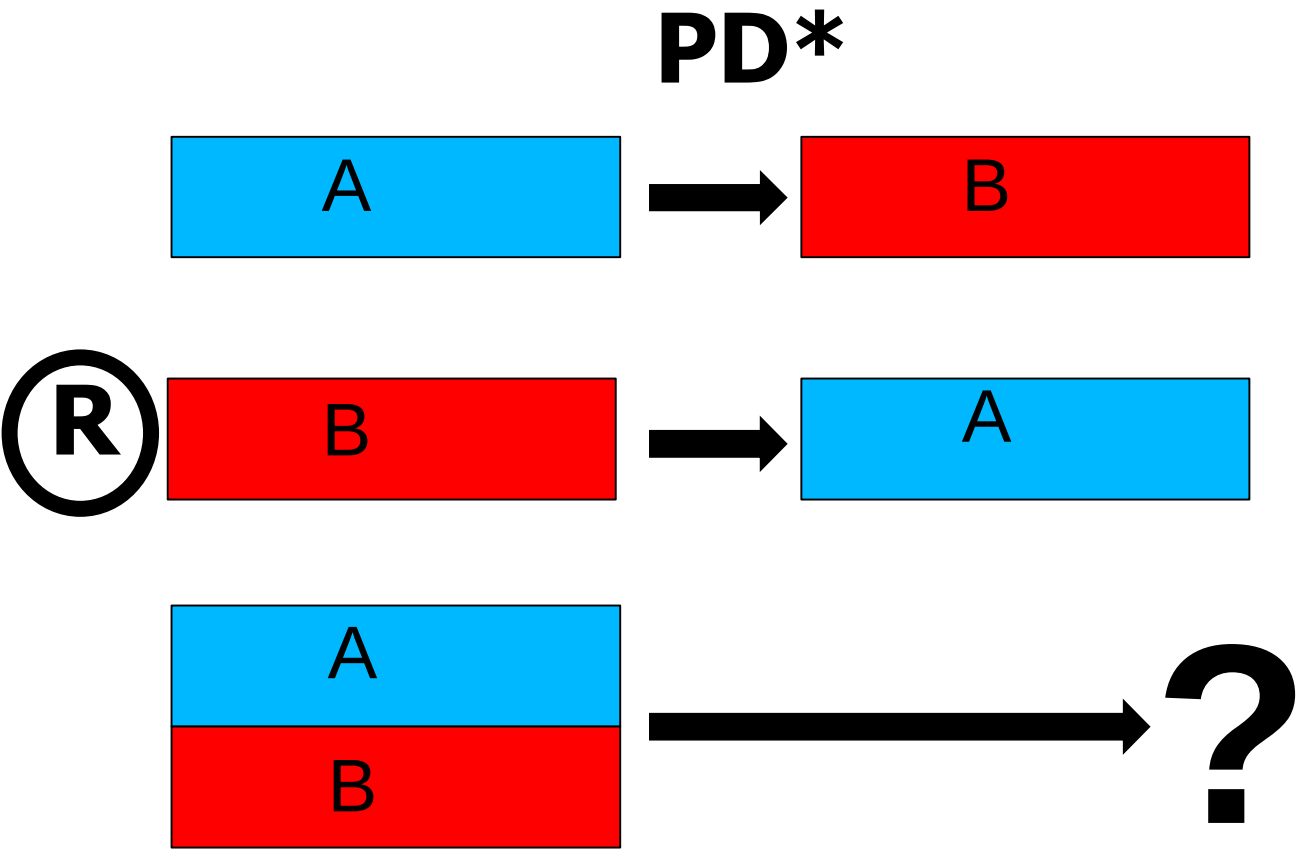
Interpretating data in clinical practice

Combine or sequence?



Efficacy readout e.g. overall survival, time to strategy failure / PFS_2

Toxicity and QoL readouts important too as combinations can be toxic

*need not be at progressive disease; could be at maximum response, after a fixed time or contingent on a biomarker

What information do we need to select patients ?

Compliance in reporting side effects?

Is 2nd line feasible?
(or is there only 1
shot on goal?)

High LDH?

Brain metastases?

Performance status?

Tempo/bulk/bad biology?

Contraindications to CPI?
Relative/absolute??

Summary

- Anti-PD1 therapy (combo and mono) is given with curative intent in Stage 4 melanoma
- Significant side effects can therefore be justified
- Nevertheless, patients need to be able to report side effects, be fit enough to withstand them and their treatment
- Age is not a contraindication to combination therapy
- I believe there are few absolute contraindications
- In my view combination therapy is preferred for brain metastases, high LDH and bad biology disease
- But it is also more active than single agent in good biology disease…

The Royal Marsden NHS
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Acknowledgements

- Our patients and their families
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