The Royal Marsden NHS
NHS Foundation Trust

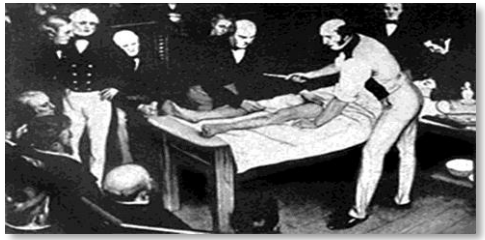
Melanoma: From Chemotherapy to Targeted Therapy and Immunotherapy

What every patient needs to know

James Larkin

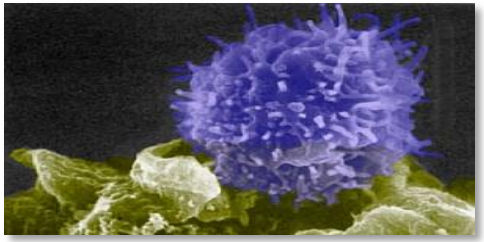
ICR The Institute of Cancer Research

Melanoma Therapy 1846 - 2017



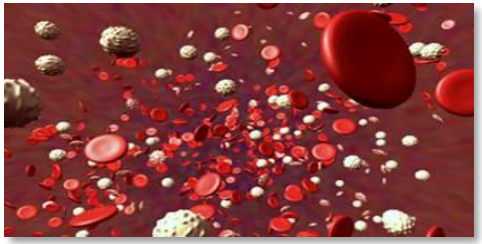
Surgery
1846

Cytotoxic Chemotherapy
1946

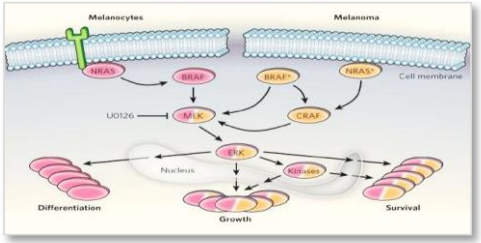


Checkpoint Inhibitors
Ipilimumab 2011
Nivolumab 2014
Pembrolizumab 2014

Radiation Therapy
1901

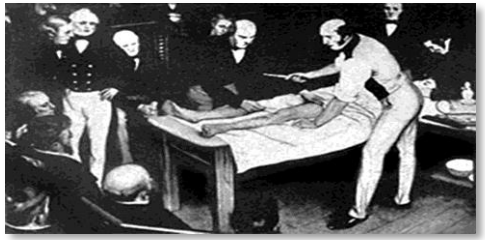


Cytokines
Interferon-α 1995
Interleukin-2 1998



Targeted Therapies
Vemurafenib 2011
Trametinib 2013
Dabrafenib 2013
Cobimetinib 2015

Melanoma Therapy 1846 - 2017



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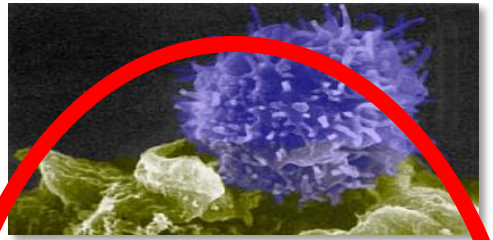

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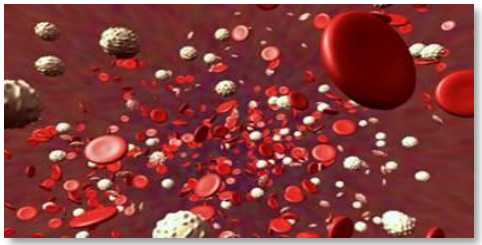

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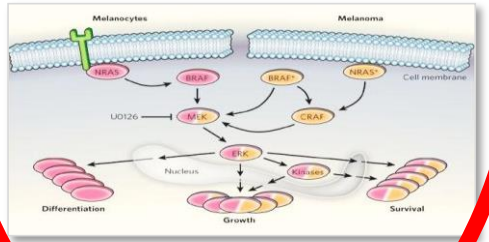

Targeted Therapies
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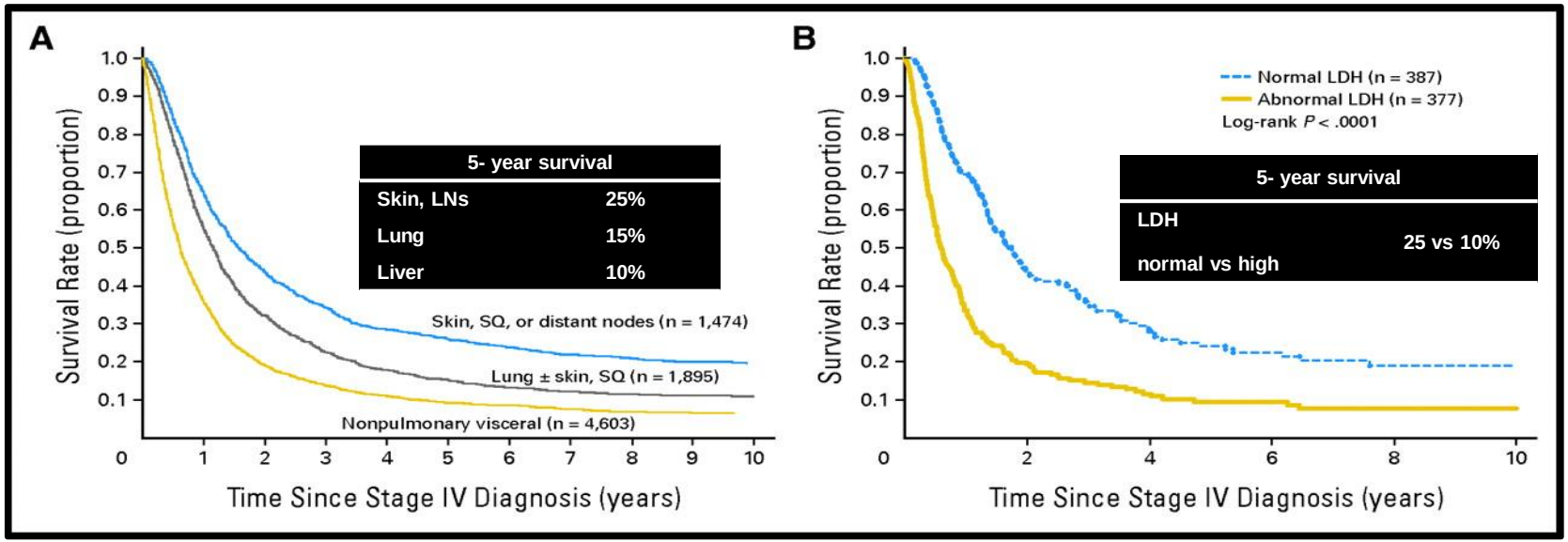
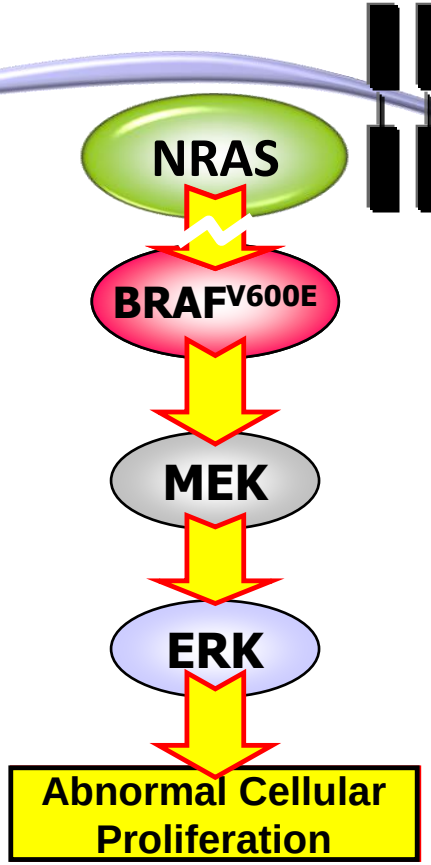
Cobimetinib 2015

Historical survival of stage 4 melanoma: median 6-9 months



Balch JCO 2009

Targeted Therapies



KIT ~ 2%

BRAF ~ 40%

NRAS ~ 20%

GNAQ ~ 2%

Curtin NEJM 2005; Curtin JCO 2006

The story starts here…

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Mutations of the *BRAF* gene in human cancer

Helen Davies[1,2], Graham R. Bignell[1,2], Charles Cox[1,2], Philip Stephens[1,2], Sarah Edkins[1], Sheila Clegg[1], Jon Teague[1], Hayley Woffendin[1], Mathew J. Garnett[3], William Bottomley[1], Neil Davis[1], Ed Dicks[1], Rebecca Ewing[1], Yvonne Floyd[1], Kristian Gray[1], Sarah Hall[1], Rachel Hawes[1], Jaime Hughes[1], Vivian Kosmidou[1], Andrew Menzies[1], Catherine Mould[1], Adrian Parker[1], Claire Stevens[1], Stephen Watt[1], Steven Hooper[3], Rebecca Wilson[3], Hiran Jayatilake[4], Barry A. Gusterson[5], Colin Cooper[6], Janet Shipley[6], Darren Hargrave[7], Katherine Pritchard-Jones[7], Norman Maitland[8], Georgia Chenevix-Trench[9], Gregory J. Riggins[10], Darell D. Bigner[10], Giuseppe Palmieri[11], Antonio Cossu[12], Adrienne Flanagan[13], Andrew Nicholson[14] Judy W. C. Ho[15], Suet Y. Leung[16], Siu T. Yuen[16], Barbara L. Weber[17], Hilliard F. Seigler[18], Timothy L. Darrow[18], Hugh Paterson[3], Richard Marais[3], Christopher J. Marshall[3], Richard Wooster[1,6], Michael R. Stratton[1,4] & P. Andrew Futreal[1]

Davies Nature 2002

and continues here…

The NEW ENGLAND JOURNAL of MEDICINE

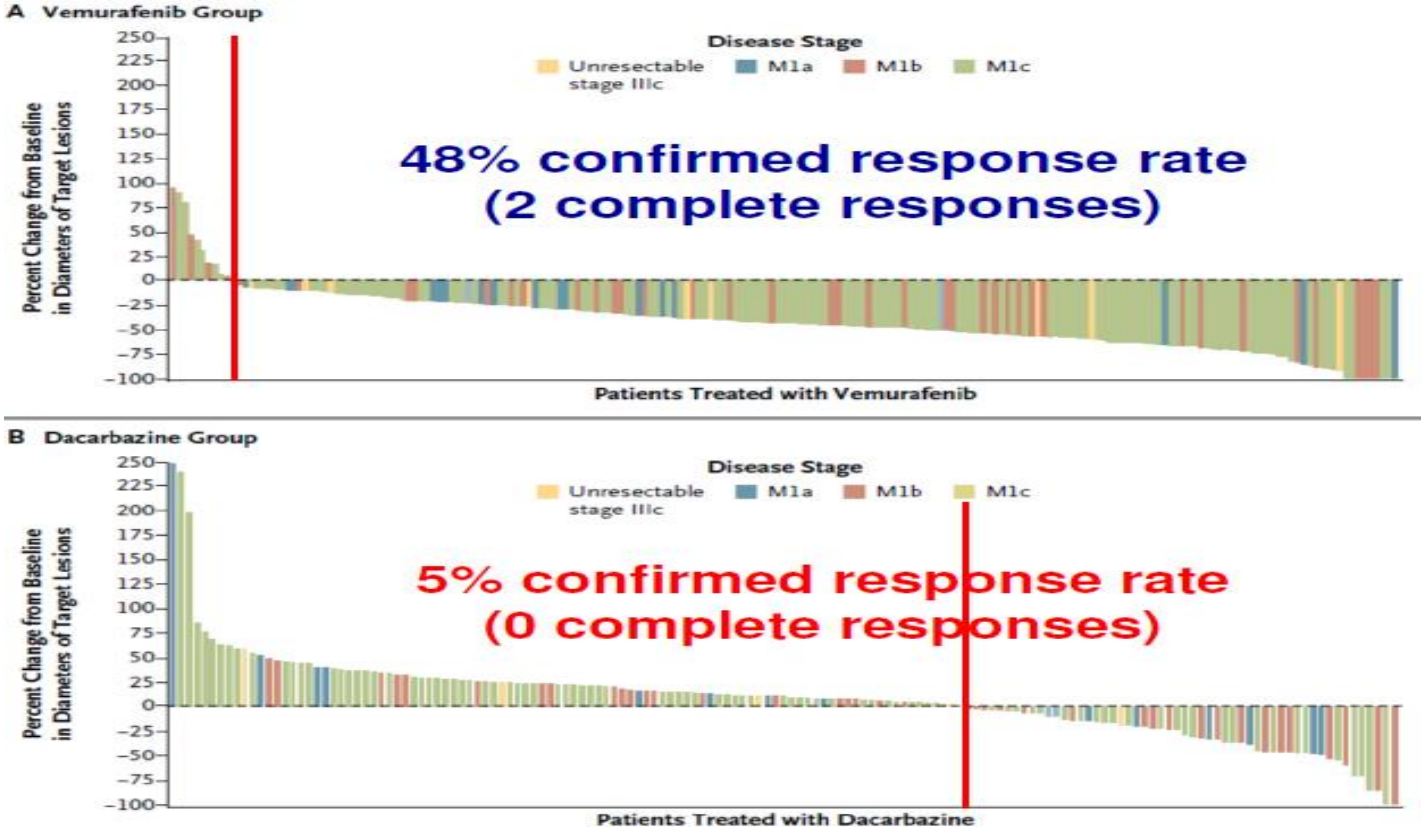
ORIGINAL ARTICLE

Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

Paul B. Chapman, M.D., Axel Hauschild, M.D., Caroline Robert, M.D., Ph.D., John B. Haanen, M.D., Paolo Ascierto, M.D., James Larkin, M.D., Reinhard Dummer, M.D., Claus Garbe, M.D., Alessandro Testori, M.D., Michele Maio, M.D., David Hogg, M.D., Paul Lorigan, M.D., Celeste Lebbe, M.D., Thomas Jouary, M.D., Dirk Schadendorf, M.D., Antoni Ribas, M.D., Steven J. O'Day, M.D., Jeffrey A. Sosman, M.D., John M. Kirkwood, M.D., Alexander M.M. Eggermont, M.D., Ph.D., Brigitte Dreno, M.D., Ph.D., Keith Nolop, M.D., Jiang Li, Ph.D., Betty Nelson, M.A., Jeannie Hou, M.D., Richard J. Lee, M.D., Keith T. Flaherty, M.D., and Grant A. McArthur, M.B., B.S., Ph.D., for the BRIM-3 Study Group*

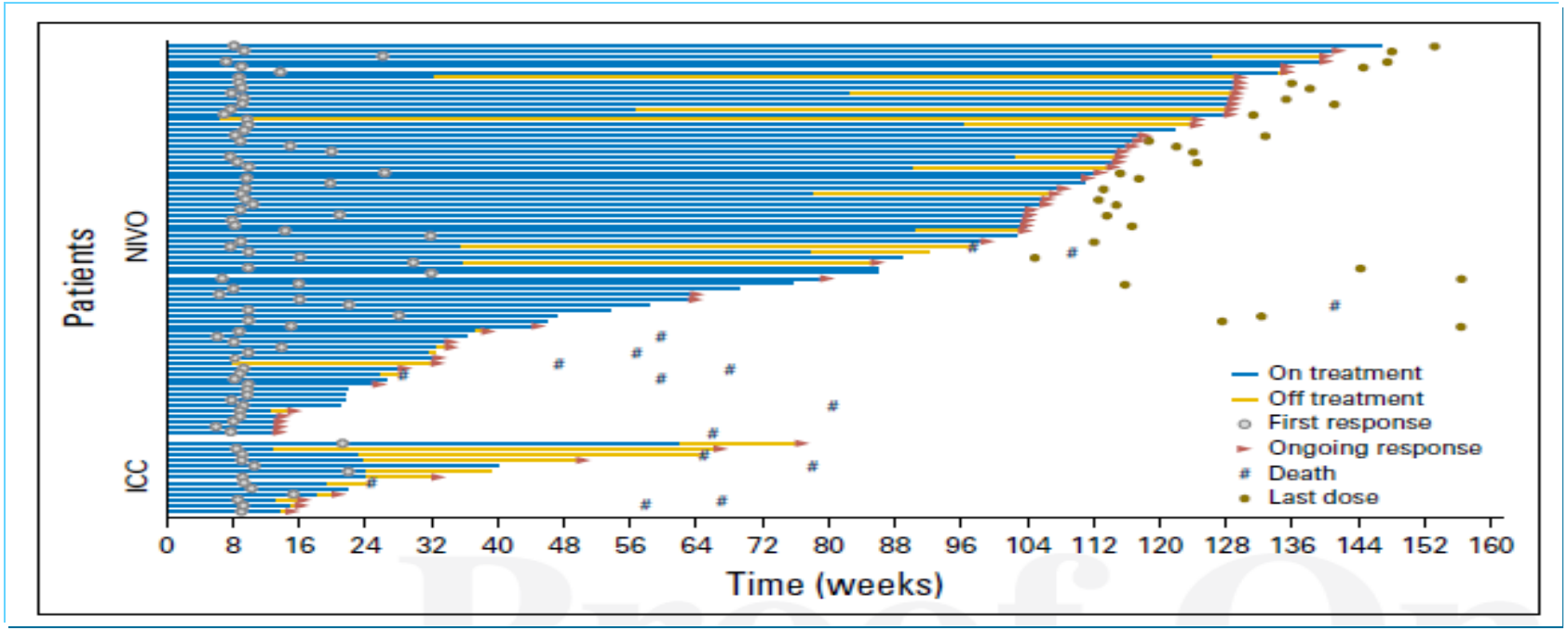
Chapman NEJM 2011

BRIM-3: Tumour shrinkage



Chapman NEJM 2011

More about chemotherapy: CM 037



Larkin JCO in press

More about chemotherapy: CM 037

Table 2. Response to Treatment via IRRC Analysis

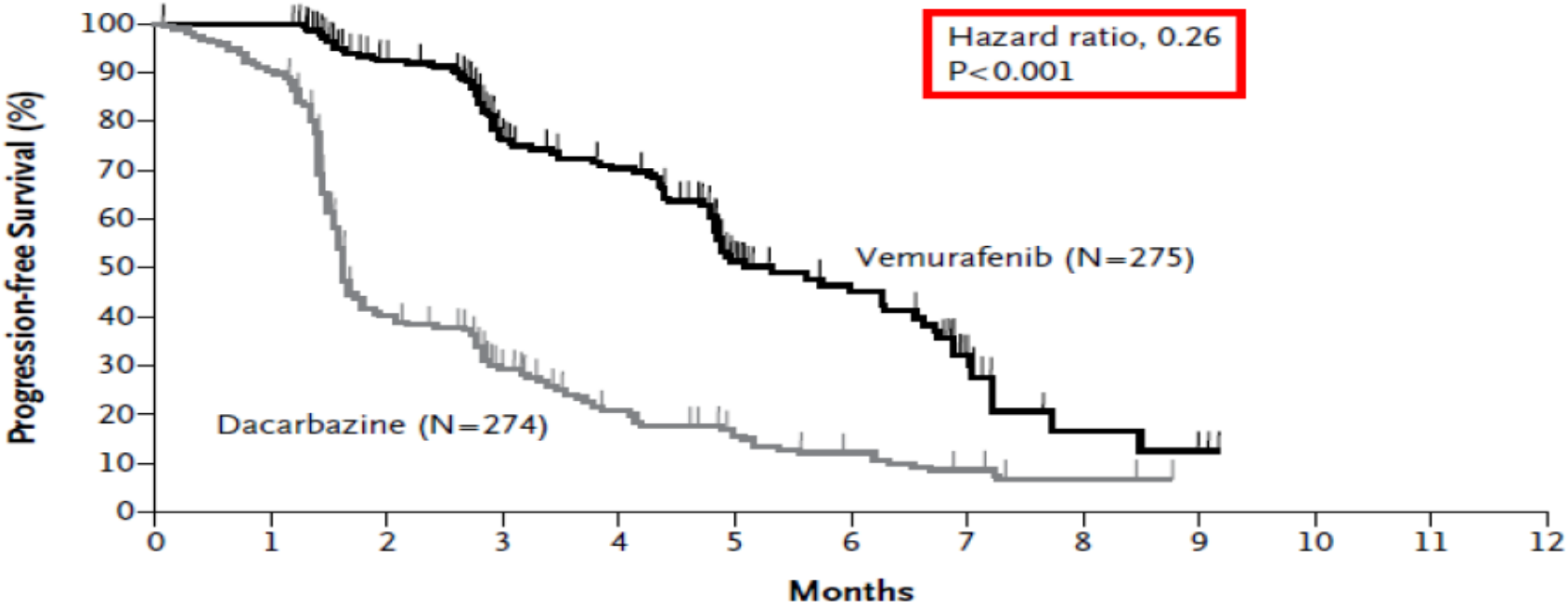
Response	IRRC	
	Nivolumab (n = 272)	ICC (n = 133)
Best overall response,* No. (%)		
Complete response	17 (6)	1 (1)
Partial response	57 (21)	12 (9)
Stable disease	55 (20)	37 (28)
Progressive disease	113 (42)	36 (27)
Unable to determine	30 (11)	47 (35)
Objective response†		
No. of patients (%; 95% CI)	74 (27; 22 to 33)	13 (10; 5 to 16)
Difference in ORR (95% CI)	17 (10 to 24)	
Median time to objective response (95% CI), months	2.2 (1.4 to 7.4)	2.1 (1.9 to 5.1)
Median duration of response (95% CI), months	31.9 (25.9 to 31.9)	12.8 (3.0 to NR)

Abbreviations: ICC, investigator's choice chemotherapy; IRRC, independent radiologic review committee; NR, not reached; ORR, overall response rate.
*RECIST v1.1.
†Complete response plus partial response.

Larkin JCO in press

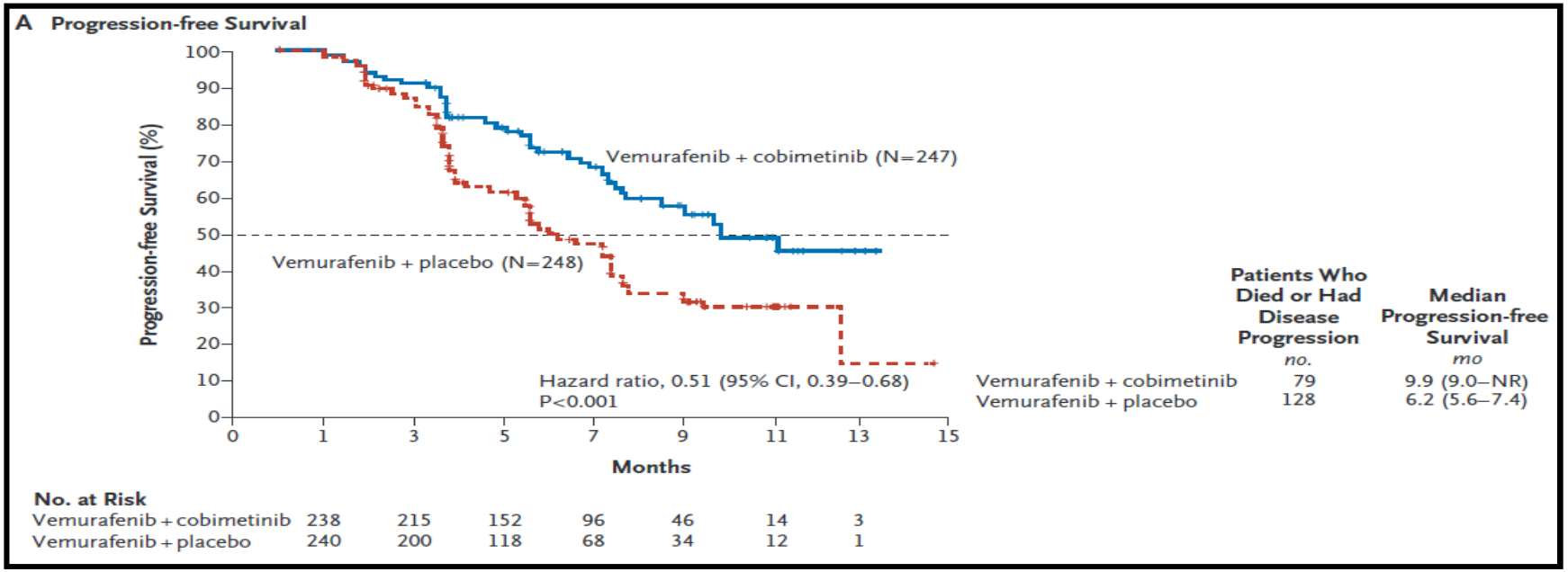
BRIM-3: Progression free survival

Median PFS 5.3 vs 1.6 months



Chapman NEJM 2011

BRAFi + MEKi vs BRAFi
vemurafenib + cobimetinib vs vemurafenib



	Patients Who Died or Had Disease Progression	Median Progression-free Survival
	no.	*mo*
Vemurafenib + cobimetinib	79	9.9 (9.0–NR)
Vemurafenib + placebo	128	6.2 (5.6–7.4)

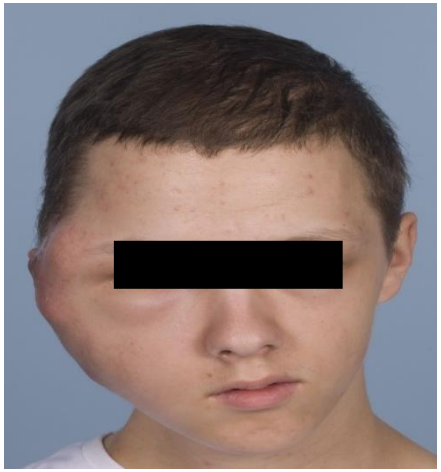
Larkin NEJM 2014

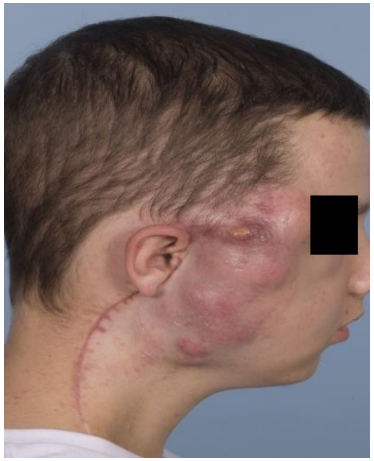
BRAFi + MEKi vs BRAFi: 3 RCTs

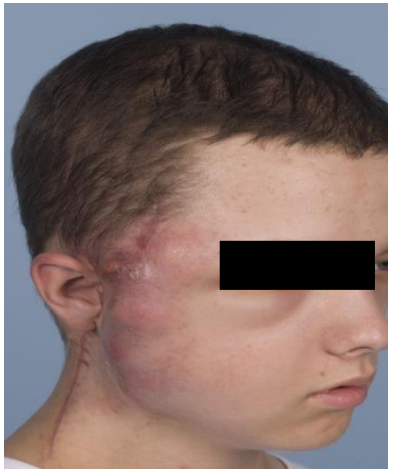
Trial	Progression Free Survival medians
Dabrafenib + trametinib vs vemurafenib[1]	11.4 vs 7.3 mos HR 0.56, p<0.001
Dabrafenib + trametinib vs dabrafenib[2]	9.3 vs 8.8 mos HR 0.75, p=0.03
Vemurafenib + cobimetinib vs vemurafenib[3]	9.9 vs 6.2 mos HR 0.51, p<0.0001

Robert NEJM 2015 Long NEJM 2014 Larkin NEJM 2014

17 year old with advanced melanoma







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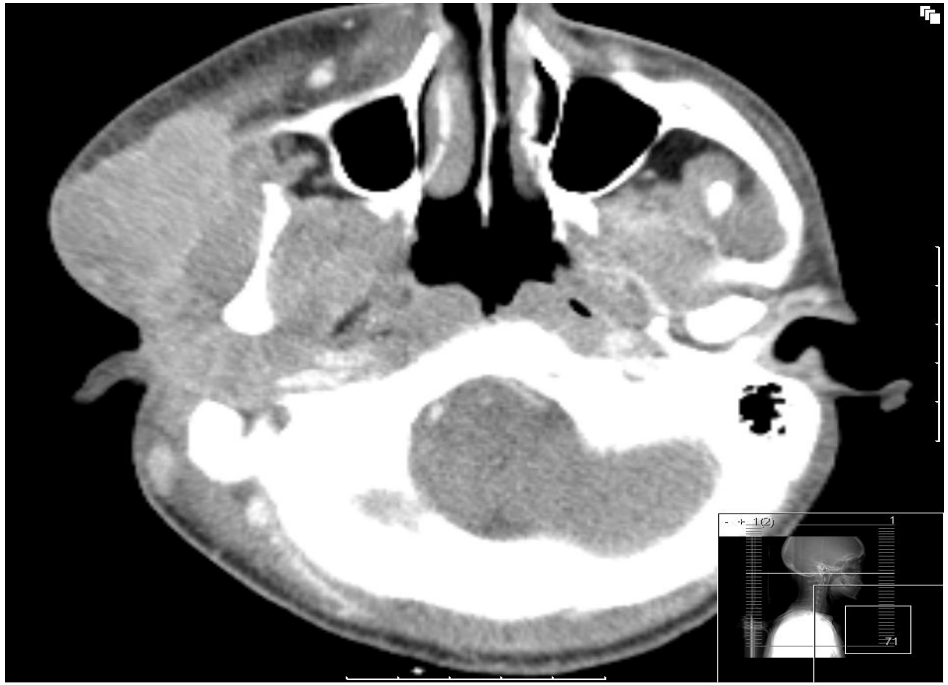
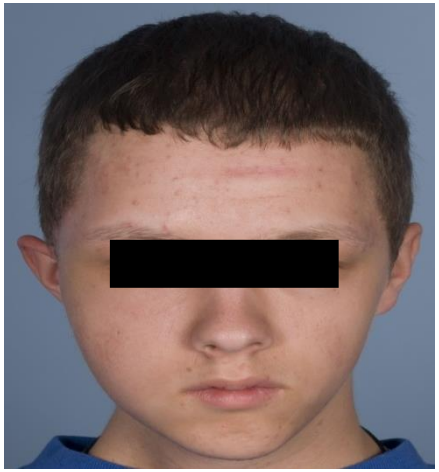
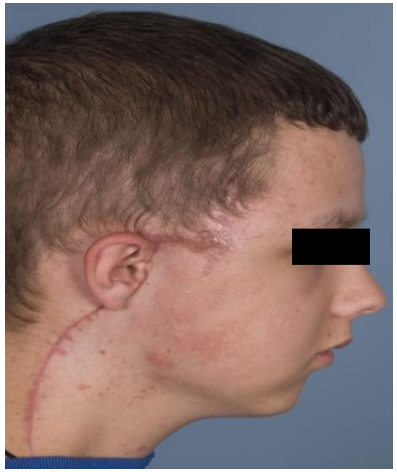
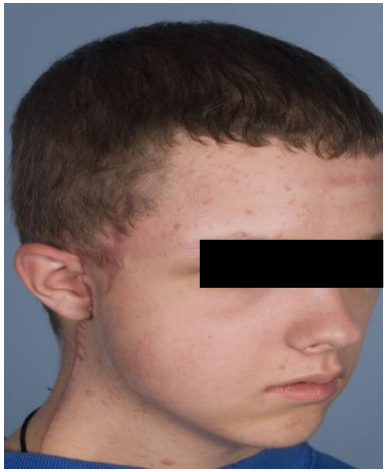


Day 9 BRAF inhibitor therapy







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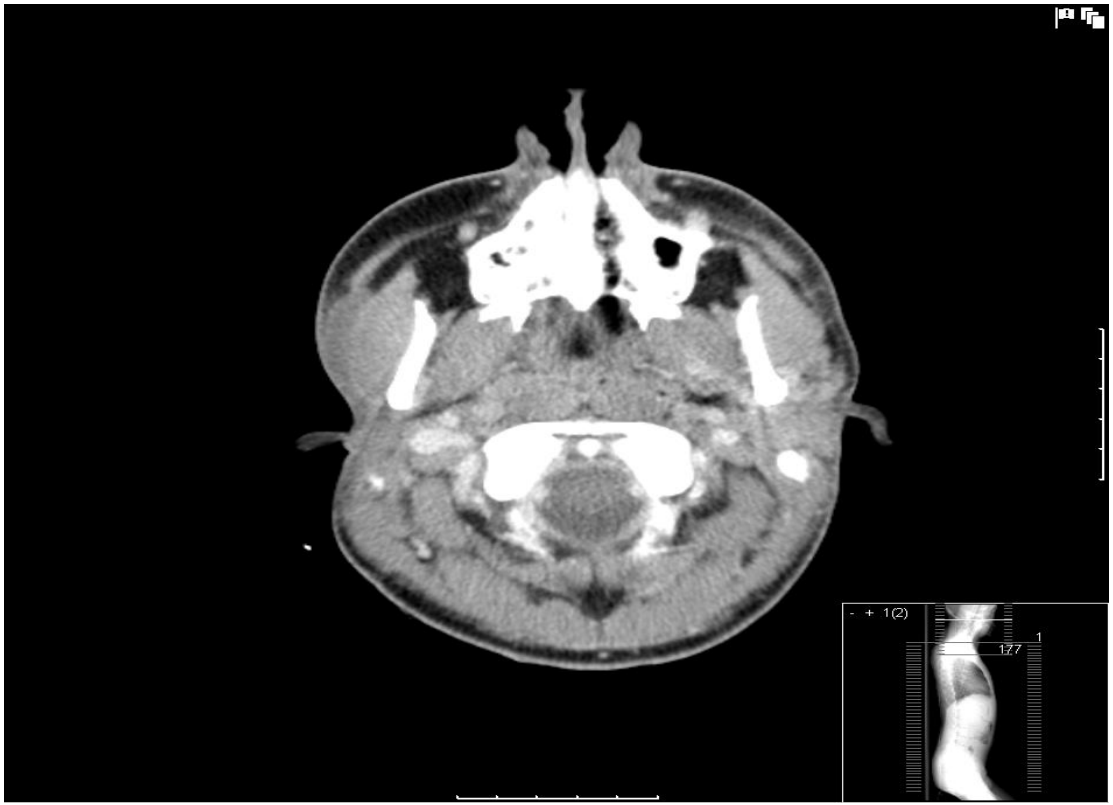

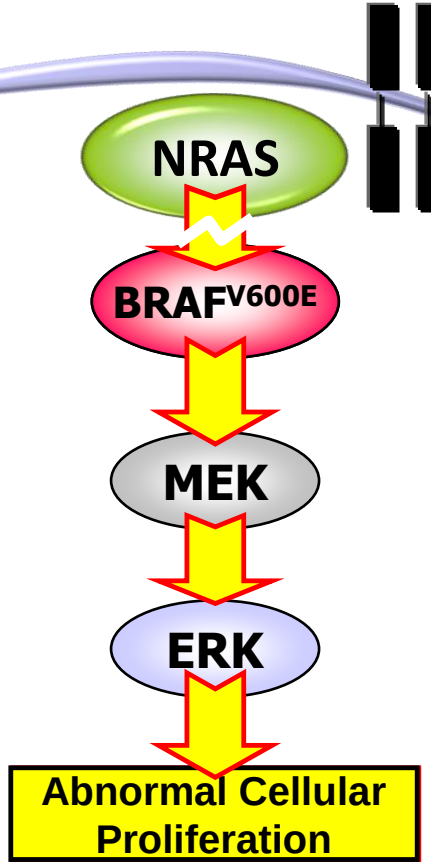

KIT ~ 2%

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Challenges for Targeted Therapy

Challenges for Targeted Therapy

RESISTANCE

TO

TREATMENT

Checkpoint Inhibitors

Immune stimulation

Interferon — **Interleukin 2**

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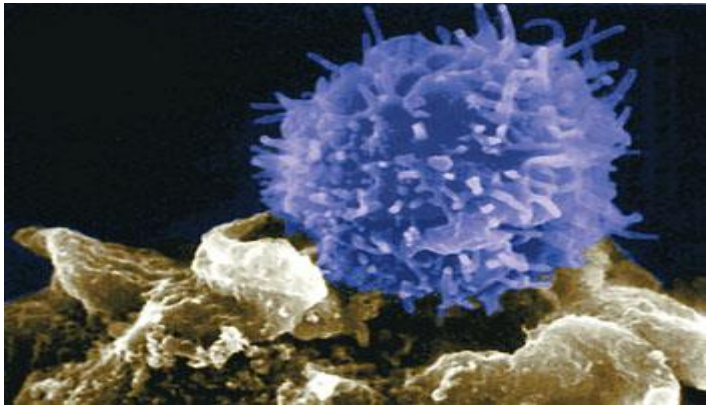

Immune stimulation

Interferon

Interleukin 2

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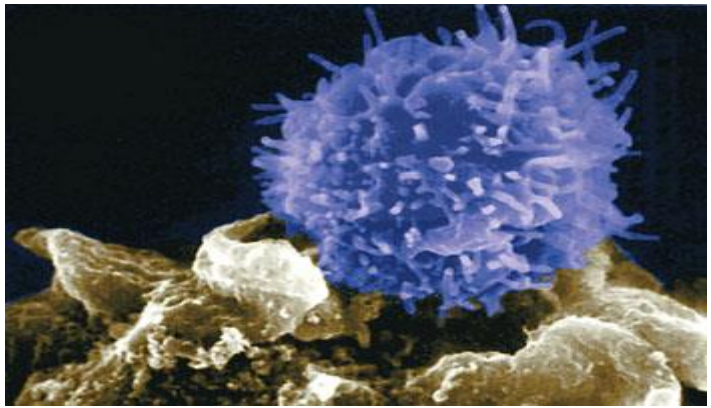

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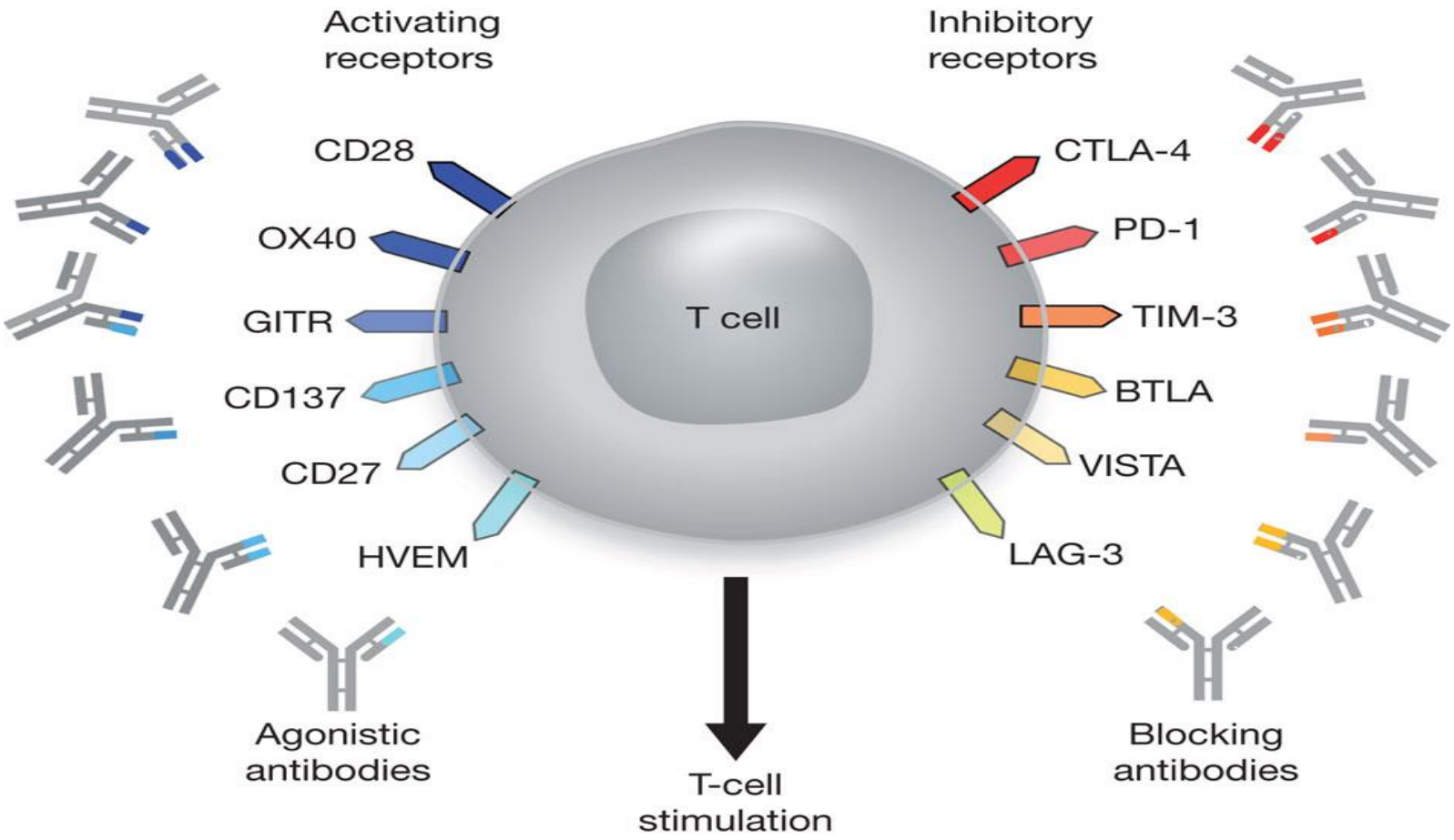
CTLA4

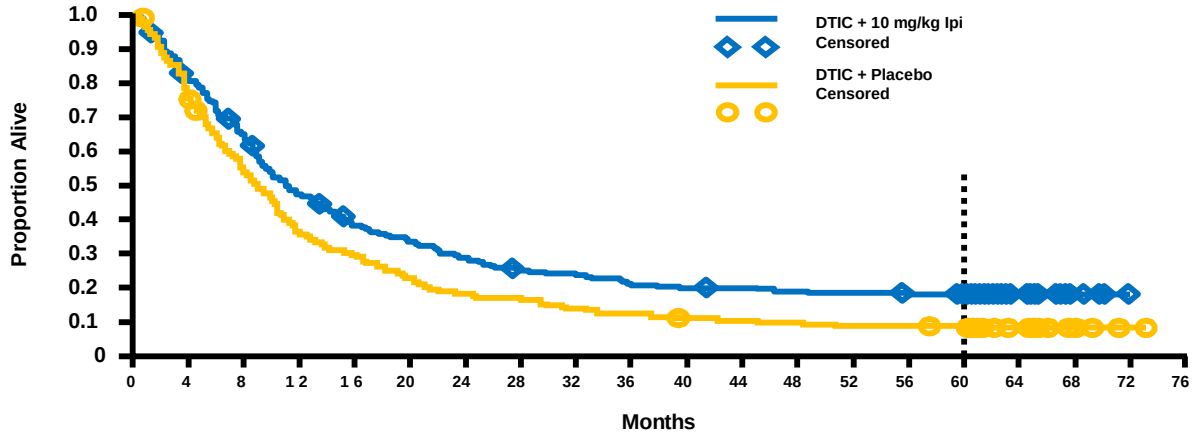
PD1

Immune checkpoint inhibitors



Mellman Nature 2012

5-year OS analysis DTIC +/- ipilimumab



Treatment group	Median OS, months	Overall survival rate, %				
		1-year	2-year	3-year	4-year	5-year
Ipi + DTIC	11.2	47.6%	28.9%	21.3%	19.1%	18.2%
Plac + DTIC	9.1	36.4%	17.8%	12.1%	9.7%	8.8%

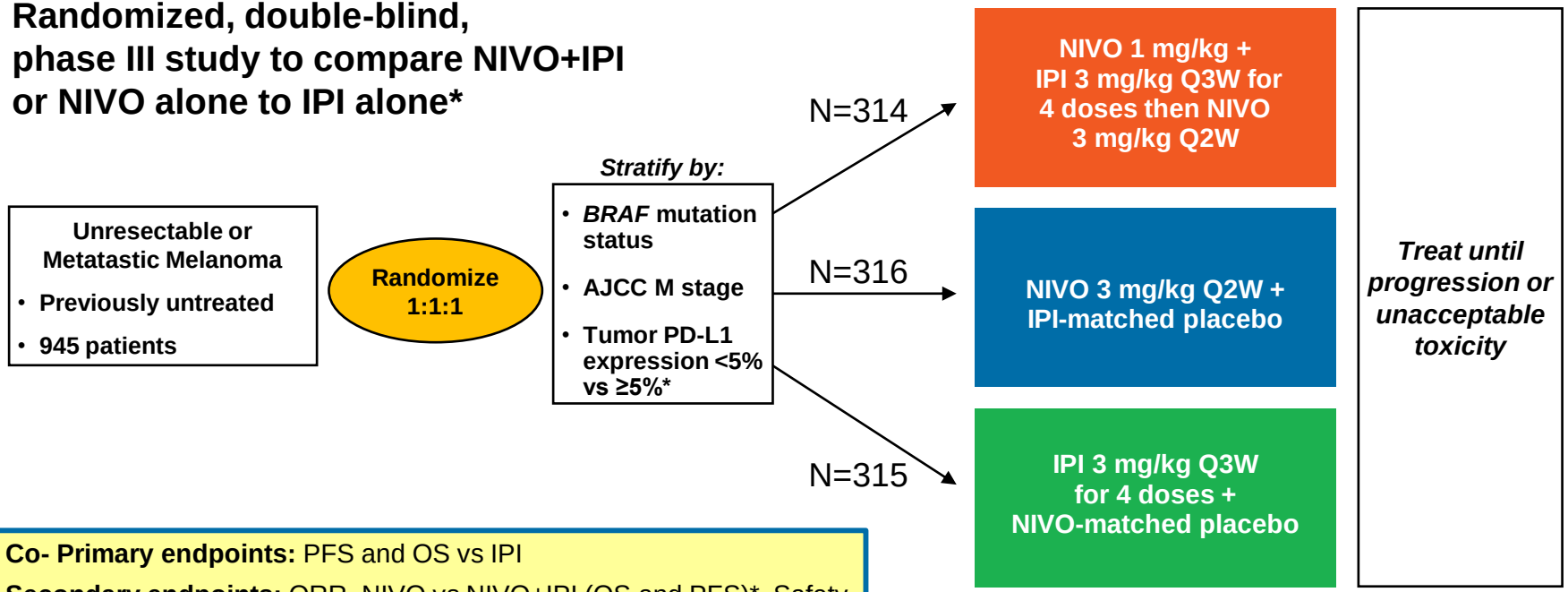
PLATEAU

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

CA209-067: 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

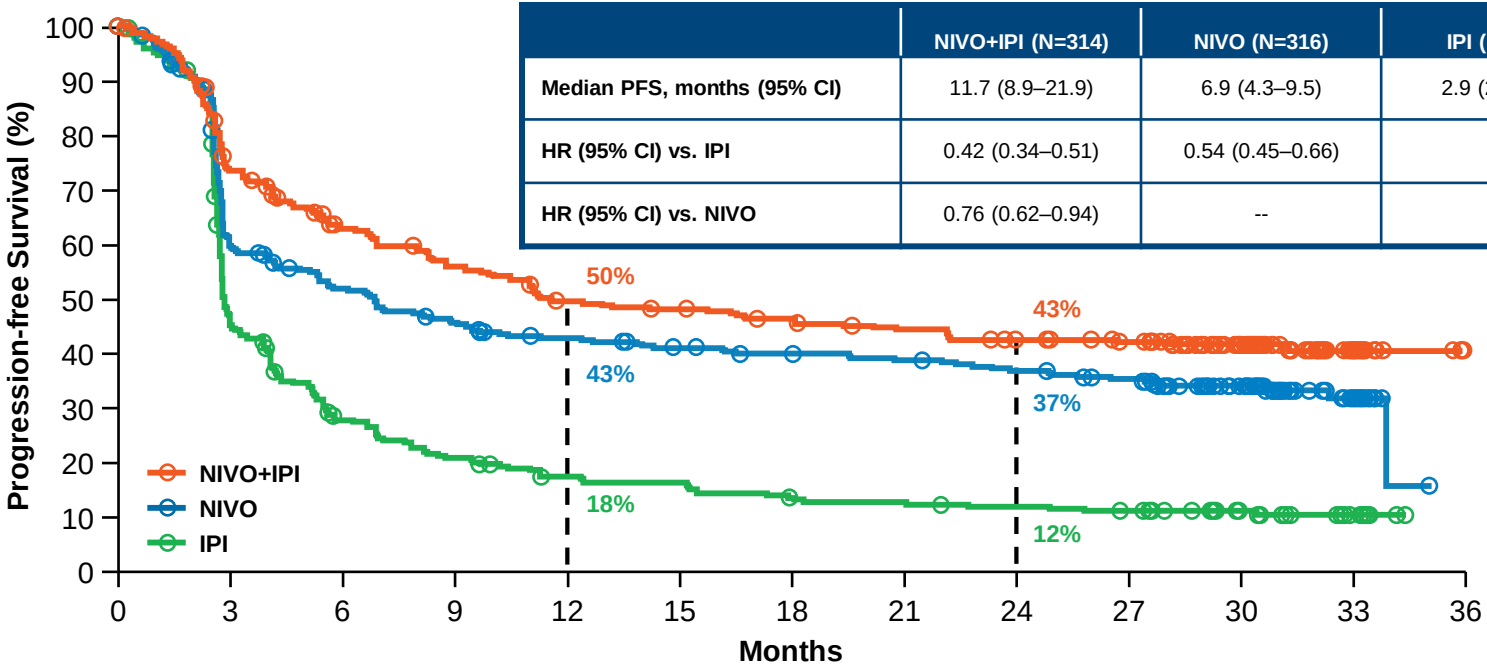
Database lock: Sept 13, 2016 (median follow-up ~30 months in both NIVO-containing arms)

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

Larkin AACR 2017

Updated Progression-Free Survival

	NIVO+IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median PFS, months (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)	--	--



Number of 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

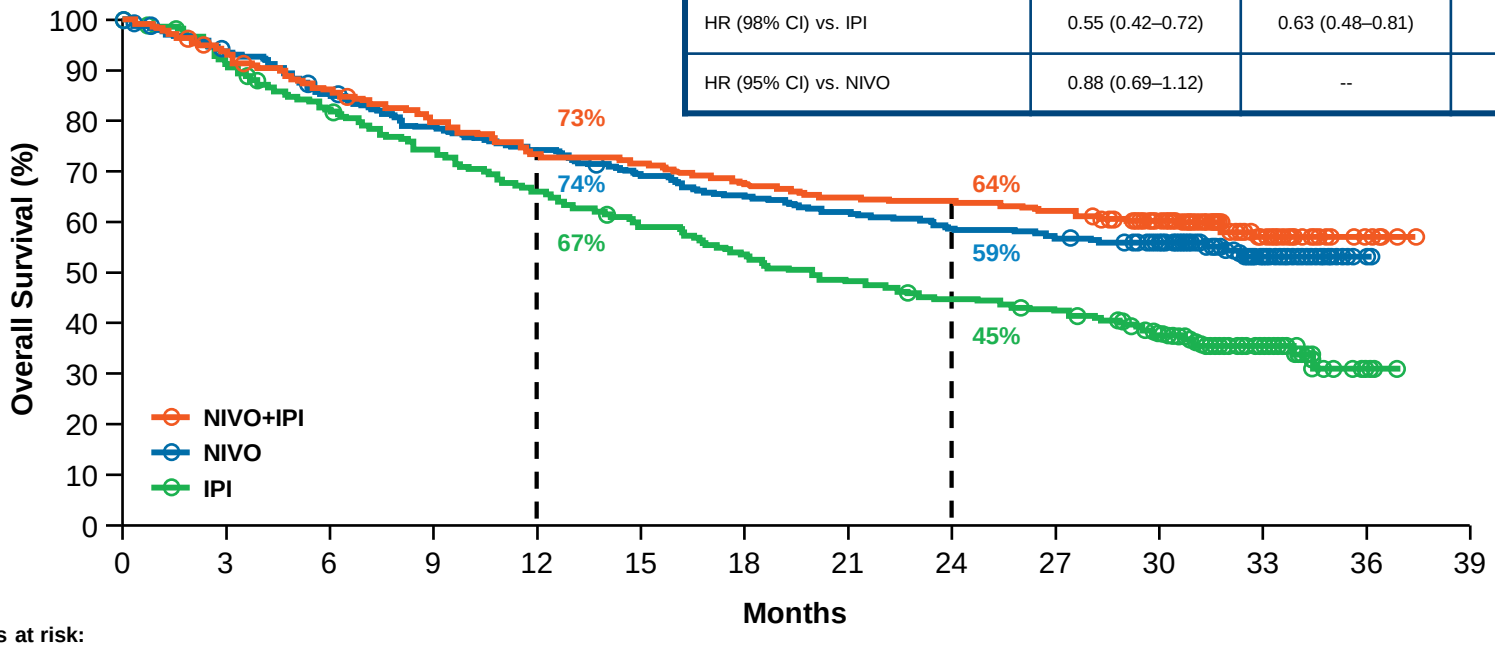
Database lock: Sept 13, 2016

Updated Response To Treatment

	NIVO+IPI (N=314)	NIVO (N=316)	IPI (N=315)
ORR, % (95% CI)*	**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)

Overall Survival

	NIVO+IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median OS, months (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)	--	--



Number of 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

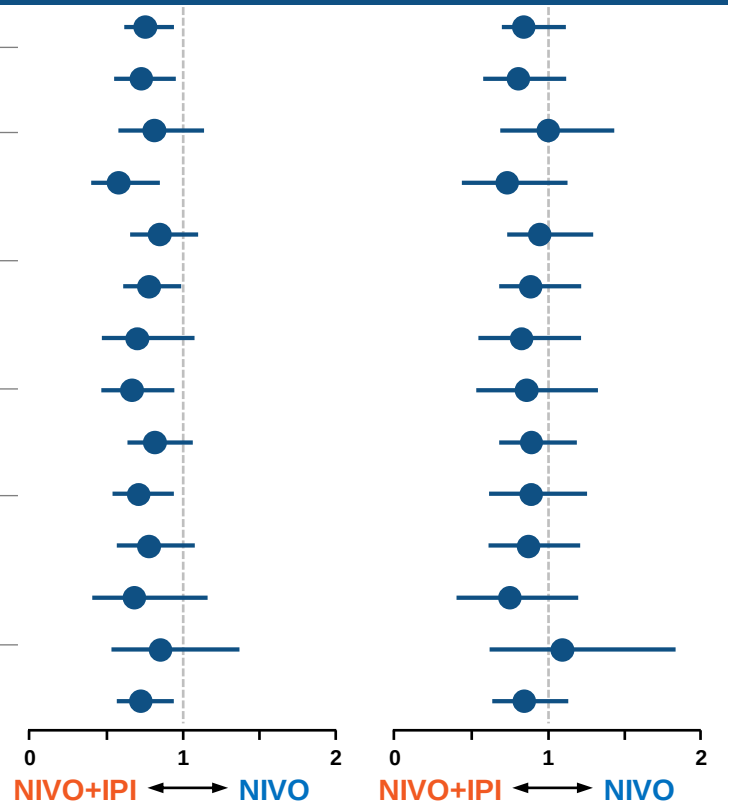
Subsequent Therapies: All Randomized Patients

	NIVO+IPI (N=314)	NIVO (N=316)	IPI (N=315)
Any subsequent therapy, n (%)*	129 (41)	169 (54)	225 (71)
Systemic therapy	100 (32)	140 (44)	196 (62)
Anti-PD-1 agents	30 (10)	32 (10)	132 (42)
Anti-CTLA-4	19 (6)	83 (26)	12 (4)
BRAF inhibitors	40 (13)	57 (18)	68 (22)
MEK/NRAS Inhibitors	30 (10)	38 (12)	39 (12)
Investigational agents**	8 (3)	6 (2)	15 (5)
Median time to subsequent systemic therapy, mo (95% CI)	NR (NR–NR)	26.8 (18.0–NR)	8.5 (7.3–9.7)
2 year % of pts free of subsequent therapies	65.8	53.8	24.7

PFS and OS Subgroup Analyses (All Randomized Patients)

Descriptive comparison between NIVO+IPI and NIVO

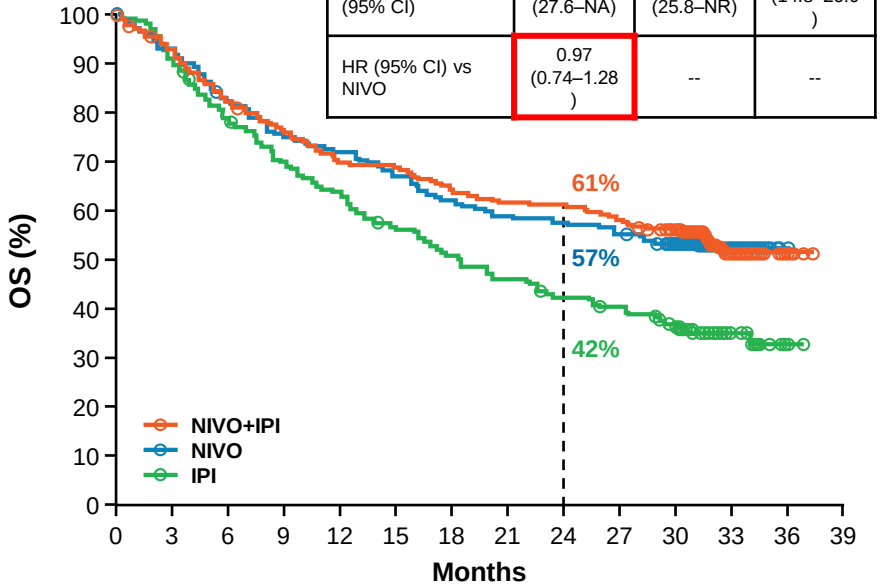
Subgroup	Patients		Unstratified Hazard Ratio	
	NIVO+IPI	NIVO	PFS	OS
Overall	314	316	0.77	0.89
<65 years	185	198	0.74	0.81
≥65 years	129	118	0.82	0.99
BRAF Mutant	102	98	0.60	0.71
BRAF Wild-type	212	218	0.86	0.97
ECOG PS = 0	230	237	0.79	0.91
ECOG PS = 1	83	78	0.72	0.82
M0/M1a/M1b	129	132	0.67	0.84
M1c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

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)	--	--

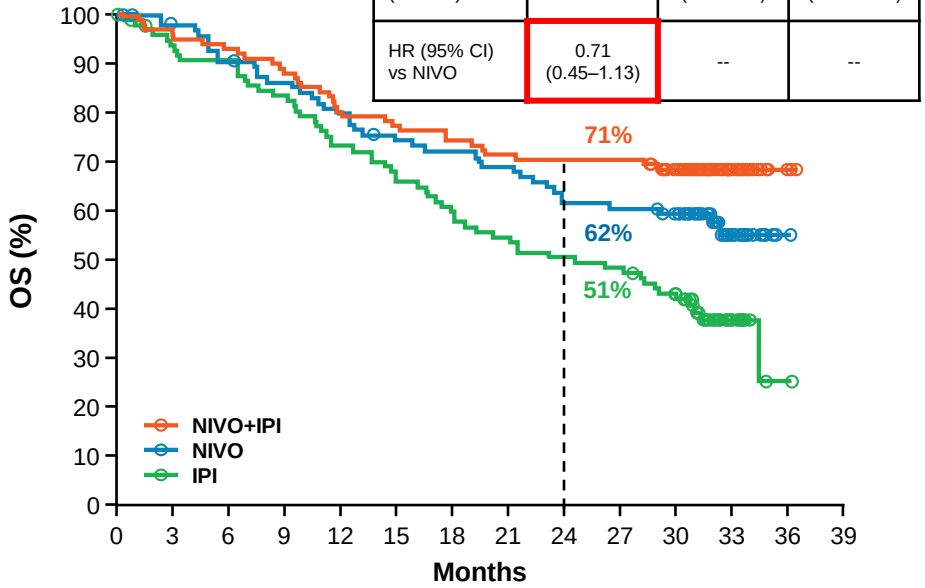


Number of patients at risk:

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)	--	--



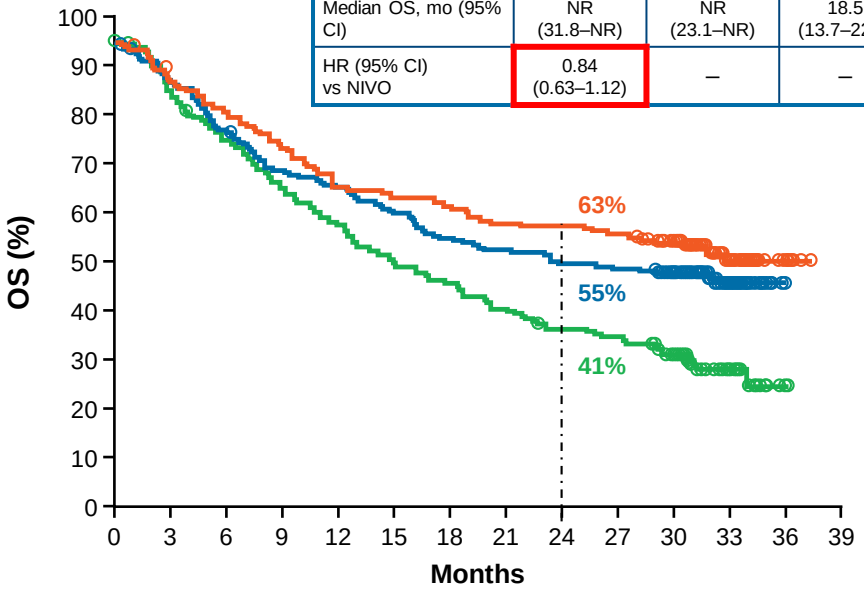
Number of patients at risk:

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

Tumor 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)	–	–

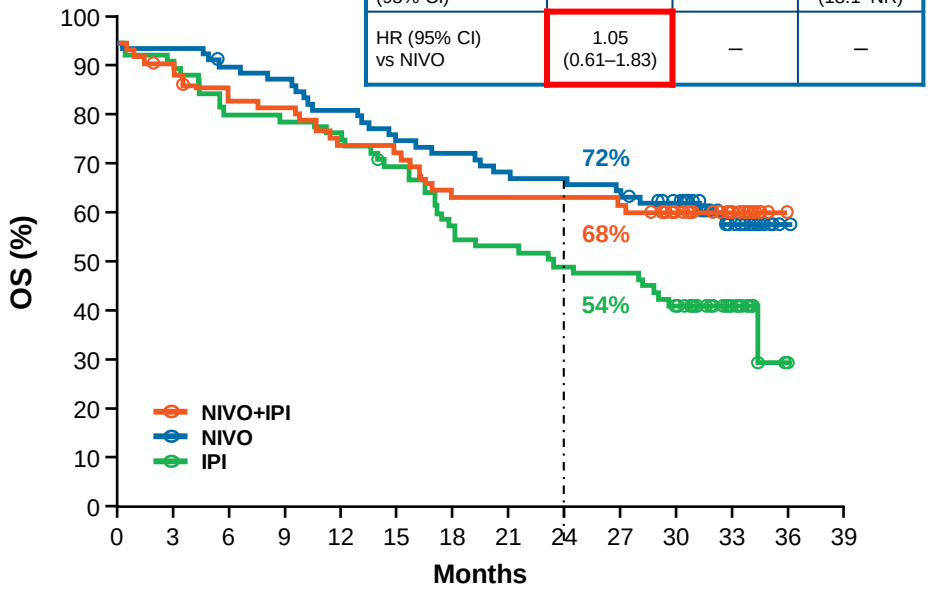


Number of patients at risk:

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

Tumor 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)	–	–



Number of 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

Response to Treatment by Tumor PD-L1 Expression

		NIVO+IPI	NIVO	IPI
PD-L1 (≥5%)	**ORR, %** (95% CI)	**73.5** (61.4–83.5)	**58.8** (47.2–69.6)	**21.3** (12.7–32.3)
	Median Duration of Response (months)	NR	NR	NR
PD-L1 (<5%)	**ORR, %** (95% CI)	**56.2** (49.2–63.0)	**42.3** (35.5–49.3)	**17.8** (12.8–23.8)
	Median Duration of Response (months)	NR	NR	18.2

Safety Summary

- Updated safety information, with an additional 19 months of follow-up, was consistent with the initial report (Larkin et al. *NEJM* 2015;373:23–34)

	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 (0.6)[a]		1 (0.3)[b]		1 (0.3)[b]	

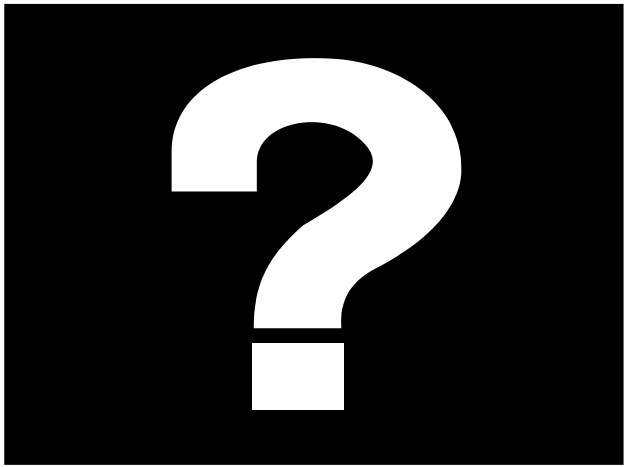
- ORR was 70.7% for pts who discontinued NIVO+IPI due to AEs, with median OS not reached
- Most select AEs were managed and resolved within 3-4 weeks (85–100% across organ categories)

[a]Cardiomyopathy (NIVO+IPI, N=1); Liver necrosis (NIVO+IPI, N=1). Both deaths occurred >100 days after the last treatment.
[b]Neutropenia (NIVO, N=1); colon perforation (IPI, N=1).

What information do we need to select patients for targeted and immunotherapies?

Therapy schedule

Disease tempo



Chance of success

Patient preference

Disease distribution

Performance status

Need for rapid response

Adverse events

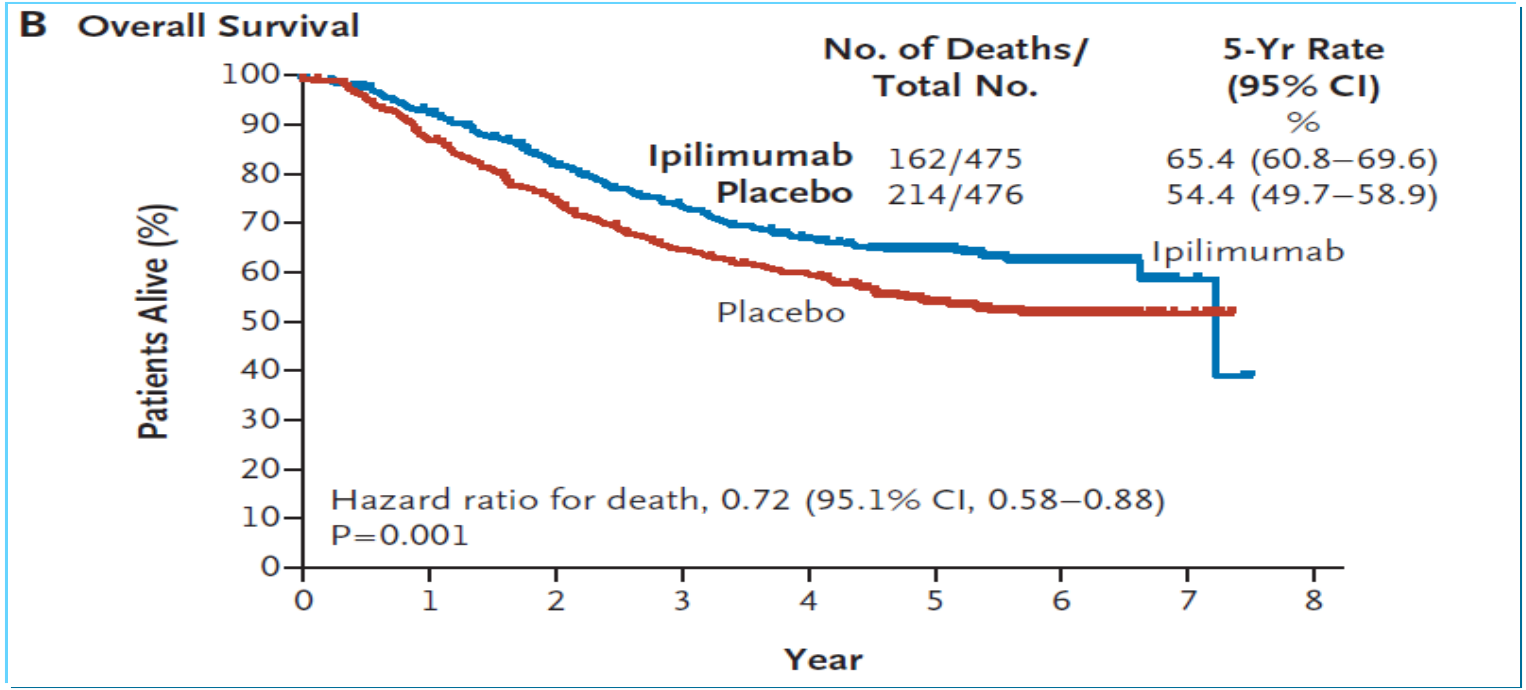
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy

A.M.M. Eggermont, V. Chiarion-Sileni, J.-J. Grob, R. Dummer, J.D. Wolchok, H. Schmidt, O. Hamid, C. Robert, P.A. Ascierto, J.M. Richards, C. Lebbé, V. Ferraresi, M. Smylie, J.S. Weber, M. Maio, L. Bastholt, L. Mortier, L. Thomas, S. Tahir, A. Hauschild, J.C. Hassel, F.S. Hodi, C. Taitt, V. de Pril, G. de Schaetzen, S. Suciu, and A. Testori

Adjuvant Ipilimumab in Melanoma



Summary

- Advanced melanoma historically regarded as generally untreatable with drugs
- Targeted therapy a major innovation in cancer therapeutics based on understanding biology
- Resistance generally inevitable in advanced disease though after less than a year on average
- Immune checkpoint inhibitors generally well tolerated and active in multiple tumour types
- Anti-CTLA4 therapy probably ‘curative’ in a small number of patients with advanced melanoma
- Lots of work still to do; I hope the last 5 years are just the beginning

Acknowledgements

- Our patients and their families

- Melanoma Clinical Trials Team, Royal Marsden, led by Sister Kim Edmonds

- Samra Turajlic and Martin Gore

- Collaborators in the UK and internationally in industry, academia and advocacy groups

Thank you