Generalitat de Catalunya
Departament de Salut

ICO 10 MÉS 10
Institut Català d'Oncologia

Germans Trias i Pujol
Hospital
Institut Català de la Salut

IGTP

Optimizing Immunotherapy

New Approaches, Biomarkers, Sequences and Combinations

Immunotherapy in the clinic
Melanoma

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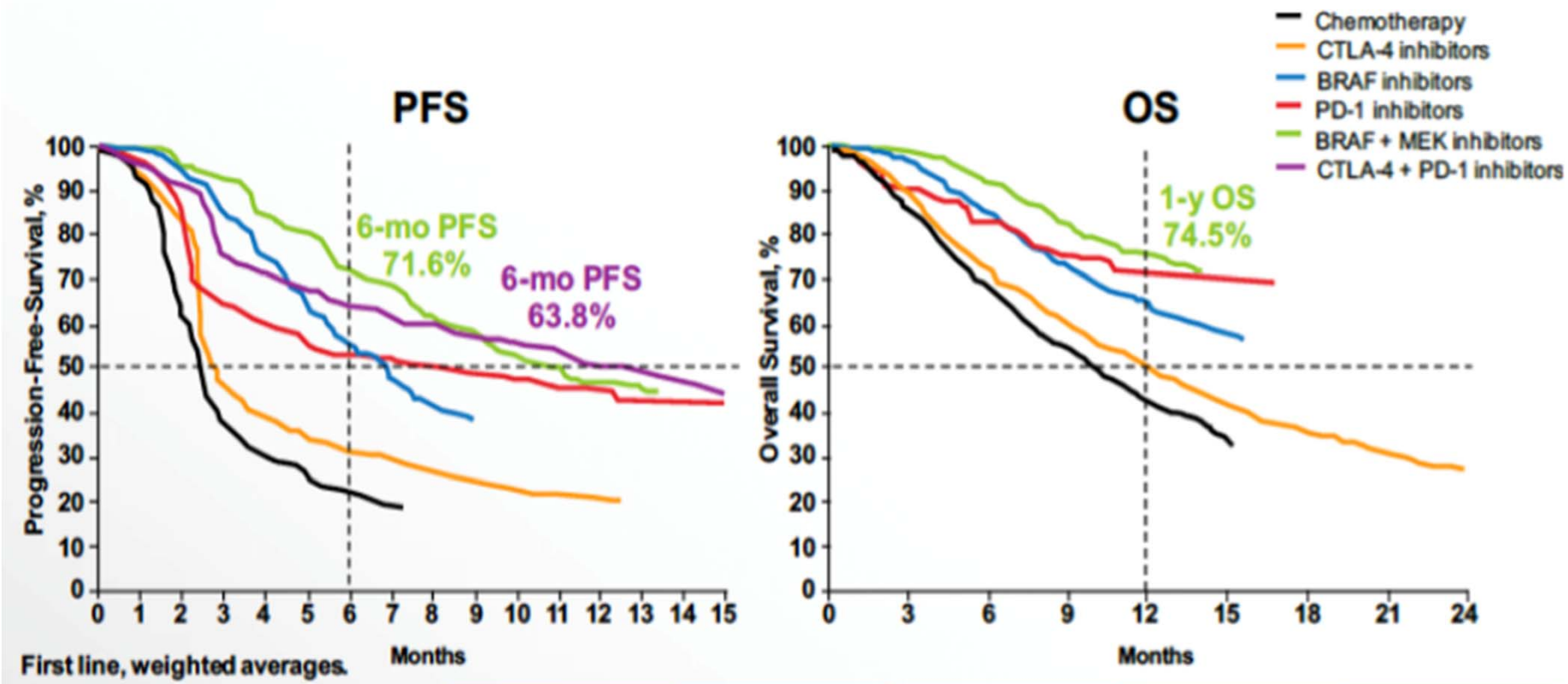
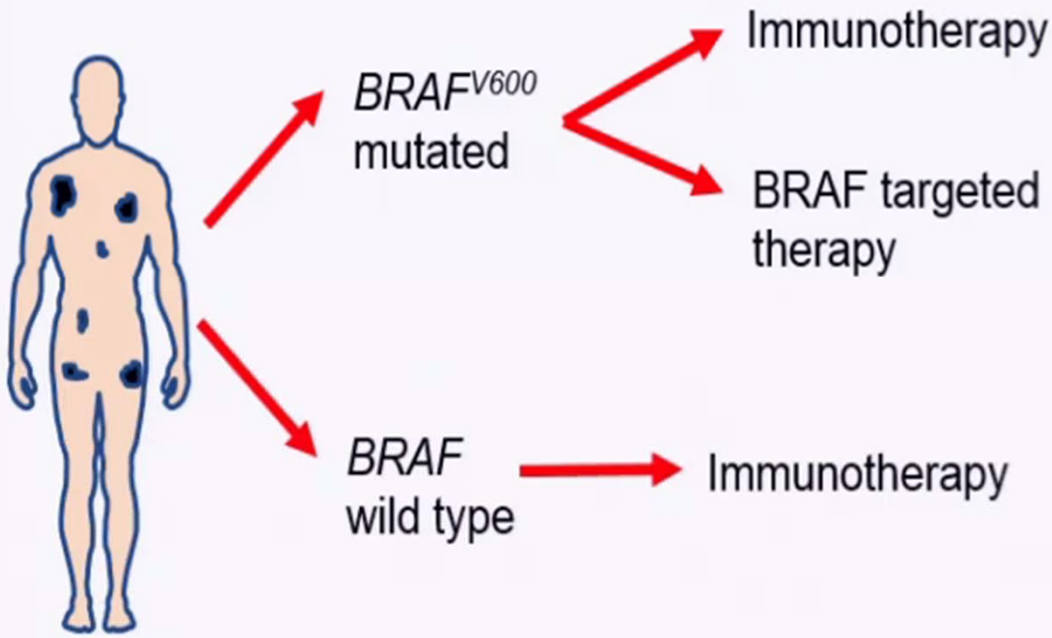
PRBB Auditorium, Barcelona
20 de Octubre del 2017

Metastatic Melanoma: Overall Survival



	Chemotherapy	CTLA-4 Inhibitor	BRAF Inhibitors	PD-1 Inhibitors	BRAF + MEK Inhibitors	CTLA-4 + PD-1 Inhibitors
6-mo PFS (95% CI), %	22.1 (19.1-25)	31 (27-35.1)	56 (53.3-58.8)	51 (46.4-55.6)	71.6 (68.2-75)	63.8 (58.7-68.9)
1-yr OS (95% CI), %	42.2 (37.2-47.2)	50.1 (45.4-54.8)	64.4 (58.1-70.7)	71.9 (60.7-83)	74.5 (70.7-78.4)	73%

Treatment options for a patient with metastatic melanoma



National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2017
Melanoma

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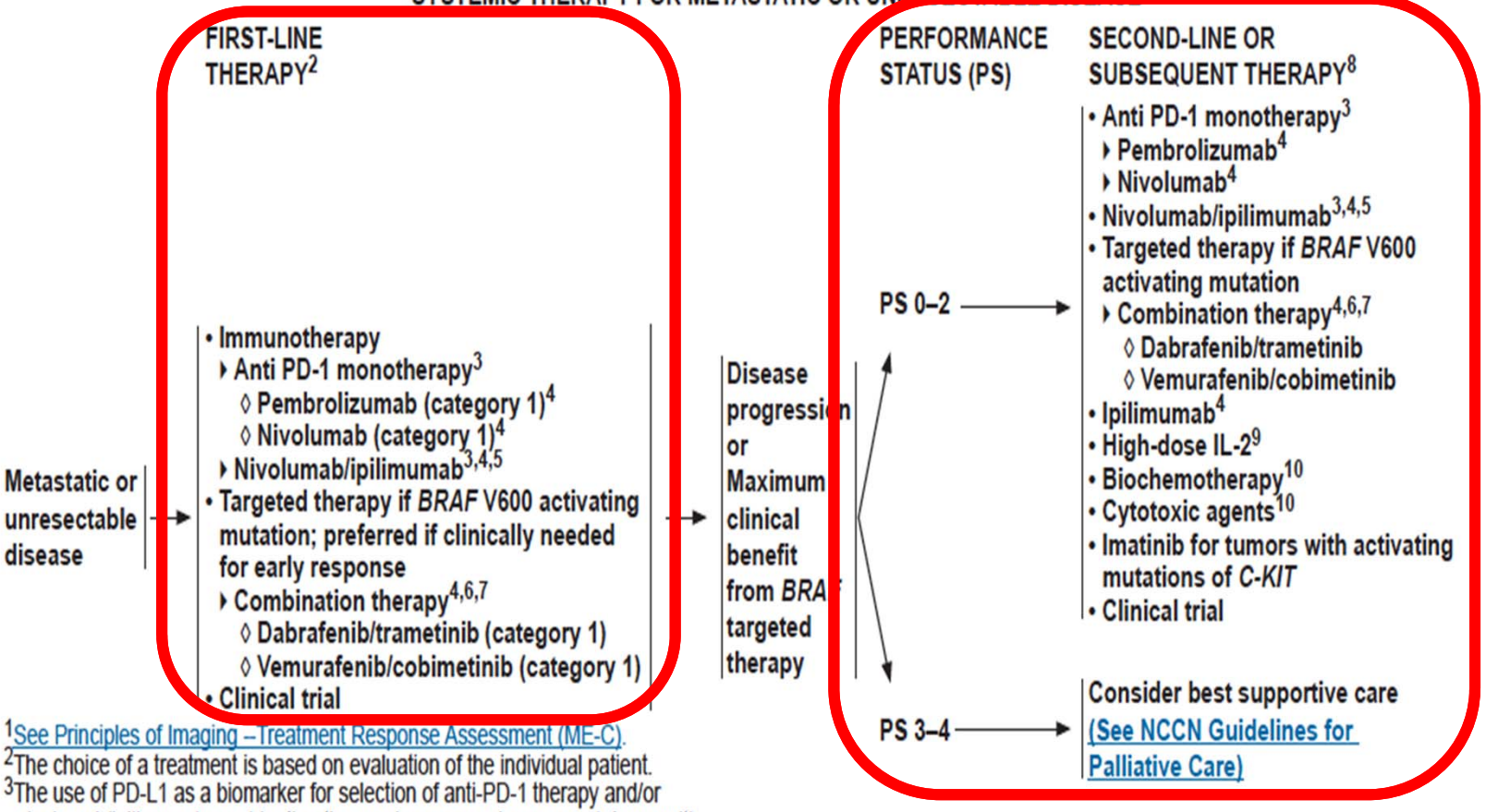
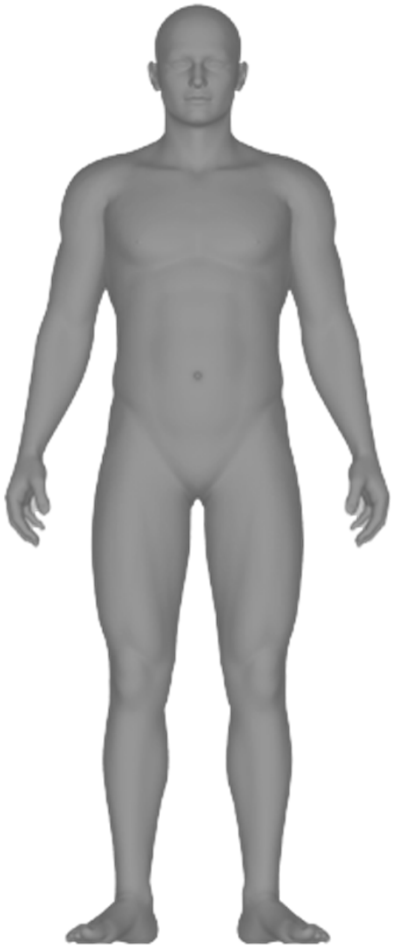
Discussion

SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE[1]



[1] See Principles of Imaging – Treatment Response Assessment (ME-C).
[2] The choice of a treatment is based on evaluation of the individual patient.
[3] The use of PD-L1 as a biomarker for selection of anti-PD-1 therapy and/or nivolumab/ipilimumab combination therapy is an emerging research issue with non-uniform application among the NCCN Member Institutions (category 2B).

Selection of treatment in melanoma



Co-morbilities

Brain mets

ECOG

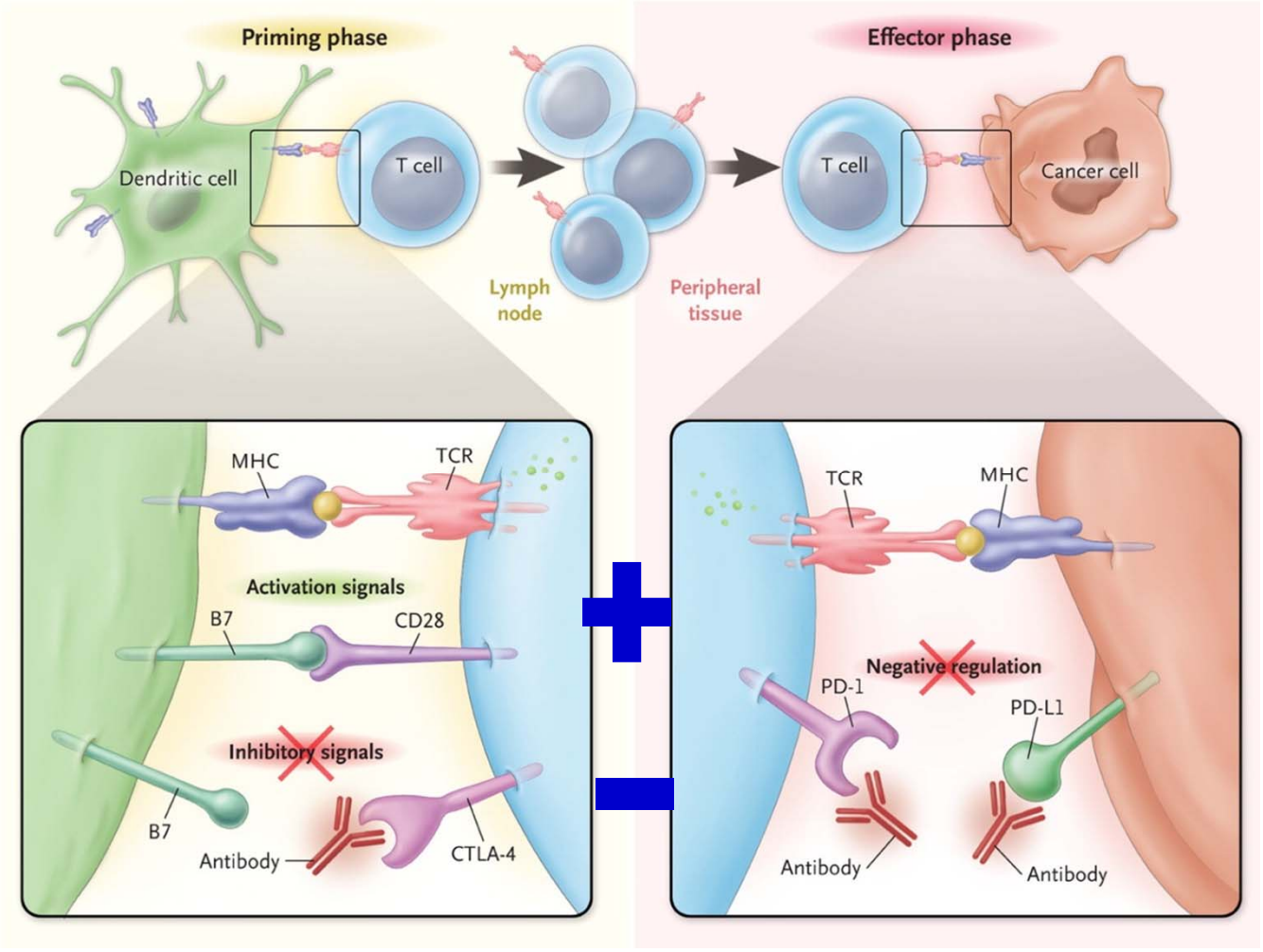
BRAF

Tumor burden

Resectability

LDH

CTLA-4 and PD-1/L1 Checkpoint Blockade for Cancer Treatment



Ipilimumab induces durable tumor responses in a subset of patients

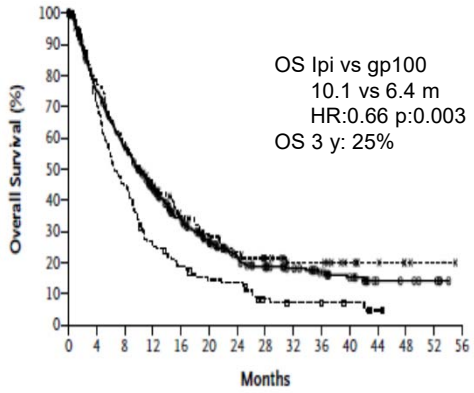
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian Quirt, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.D., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.

A Overall Survival



No. at Risk

Ipi plus gp100	403	297	223	163	115	81	54	42	33	24	17	7	6	4	0
Ipi	137	106	79	56	38	30	24	18	13	13	8	5	2	1	0
gp100	136	93	58	32	23	17	16	7	5	5	3	1	0	0	0

N Engl J Med. 2010 Aug 19;363(8):711-23.

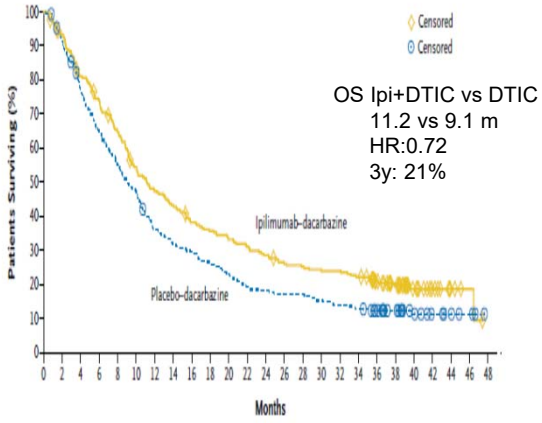
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma

Caroline Robert, M.D., Ph.D., Luc Thomas, M.D., Ph.D., Igor Bondarenko, M.D., Ph.D., Steven O'Day, M.D., Jeffrey Weber M.D., Ph.D., Claus Garbe, M.D., Celeste Lebbe, M.D., Ph.D., Jean-François Baurain, M.D., Ph.D., Alessandro Testori, M.D., Jean-Jacques Grob, M.D., Neville Davidson, M.D., Jon Richards, M.D., Ph.D., Michele Maio, M.D., Ph.D., Axel Hauschild, M.D., Wilson H. Miller, Jr., M.D., Ph.D., Pere Gascon, M.D., Ph.D., Michal Lotem, M.D., Kaan Harmankaya, M.D., Ramy Ibrahim, M.D., Stephen Francis, M.Sc., Tai-Tsang Chen, Ph.D., Rachel Humphrey, M.D., Axel Hoos, M.D., Ph.D., and Jedd D. Wolchok, M.D., Ph.D.

A

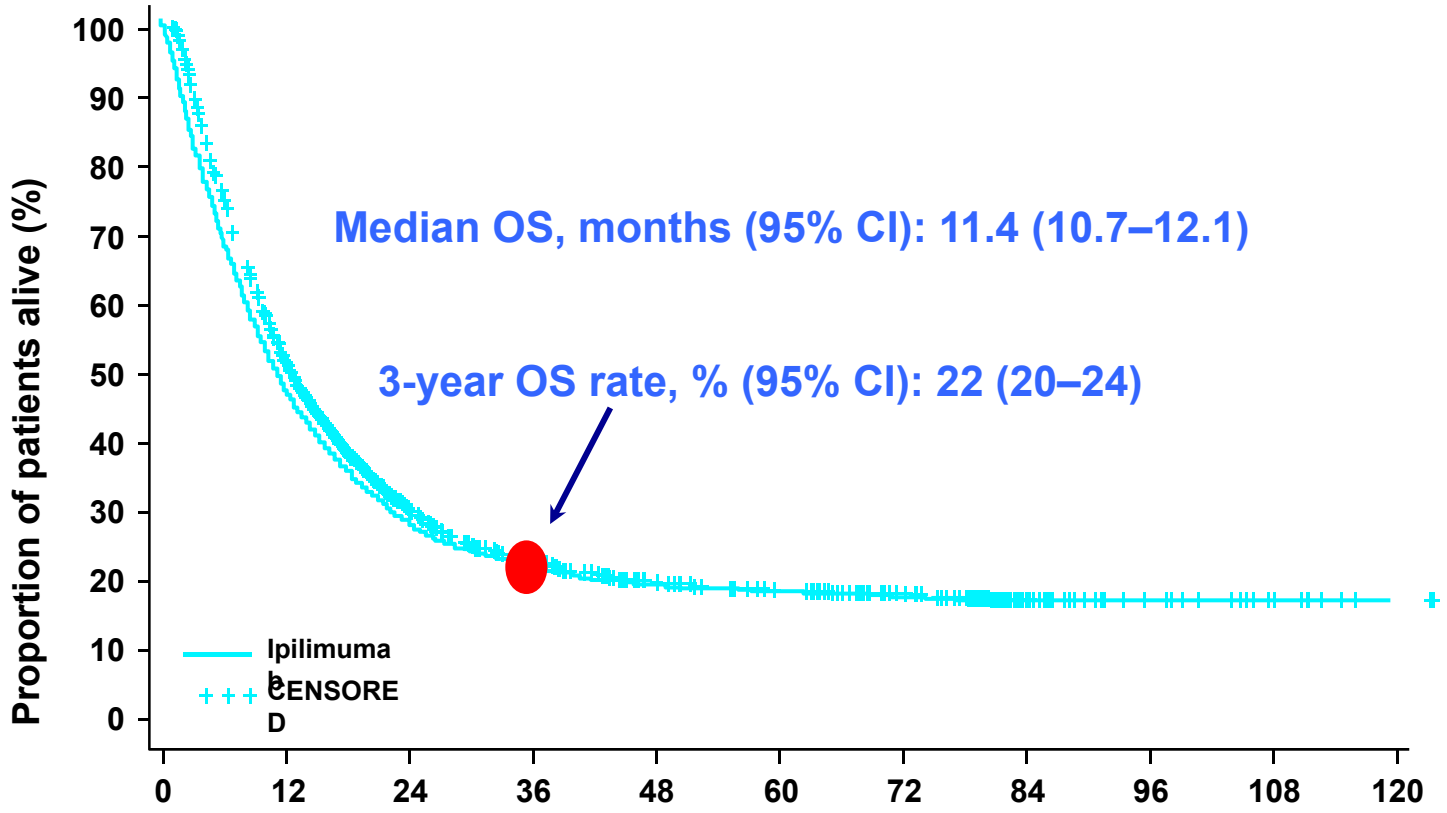


No. at Risk

Ipilimumab-dacarbazine	250	230	199	181	157	131	114	104	91	85	79	74	68	61	59	56	56	52	41	31	17	10	4	2	0
Placebo-dacarbazine	252	229	190	160	136	116	89	78	72	64	56	47	44	42	42	37	34	31	26	19	11	7	5	3	0

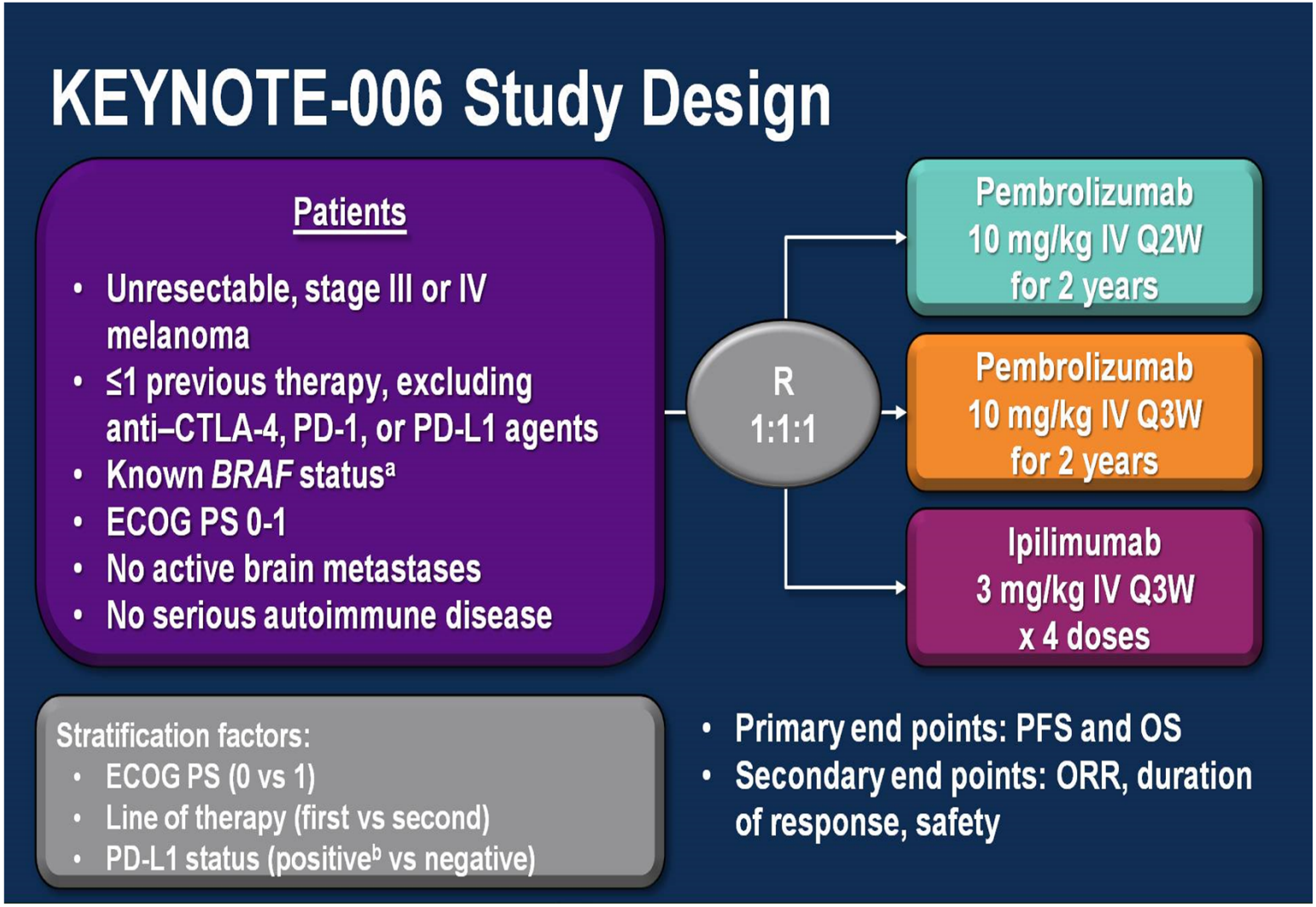
N Engl J Med. 2011 Jun 30;364(26):2517-26.

Pooled OS Analysis Including EAP Data: 4846 Patients



Patients at Risk											
Ipilimumab	1861	839	370	254	192	170	120	26	15	5	0

Keynote-006 Phase III: Pembrolizumab vs Ipilimumab

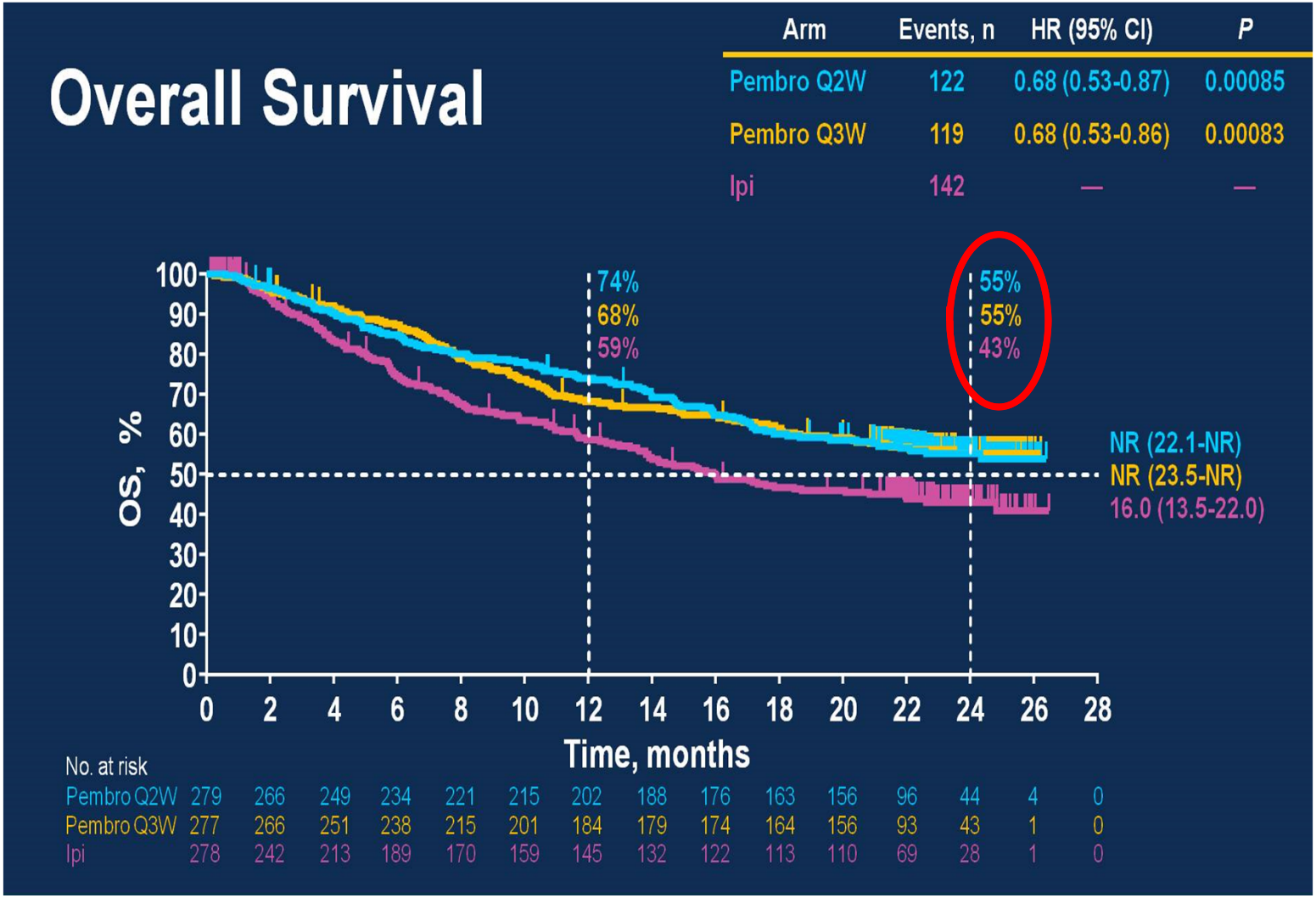


Keynote-006 Phase III: Characteristics

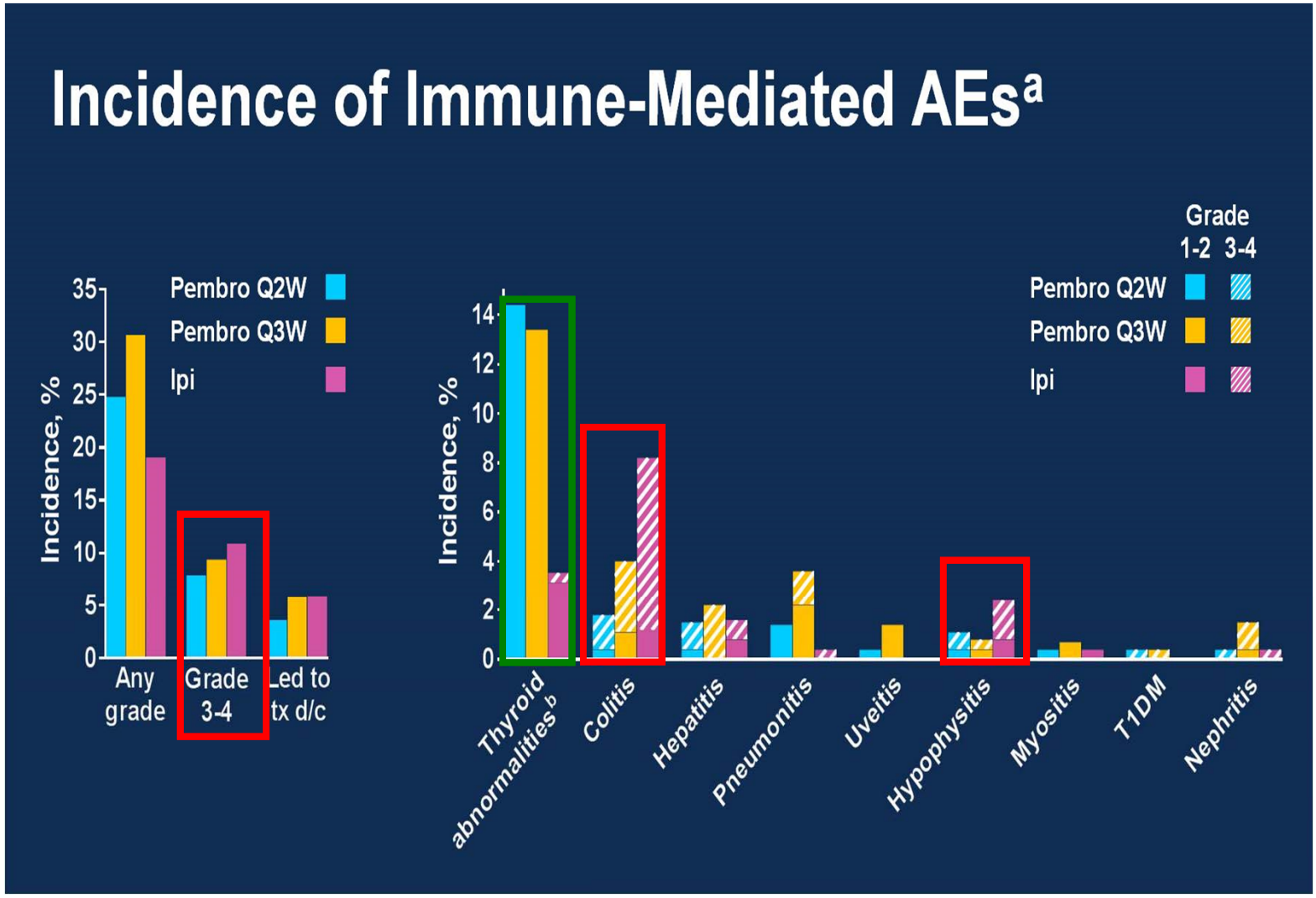
Baseline Characteristics

Characteristic	Pembrolizumab Q2W N = 279	Pembrolizumab Q3W N = 277	Ipilimumab N = 278
Age, median (range), years	61 (18-89)	63 (22-89)	62 (18-88)
Men	161 (58%)	174 (63%)	162 (58%)
ECOG PS 0	196 (70%)	189 (68%)	188 (68%)
Elevated LDH	81 (29%)	98 (35%)	91 (33%)
BRAF^{V600} mutant	98 (35%)	97 (35%)	107 (38%)
PD-L1 positive[a]	225 (81%)	221 (80%)	225 (81%)
M1c disease	179 (64%)	189 (68%)	178 (64%)
1 previous therapy	96 (34%)	92 (33%)[b]	97 (35%)

Keynote-006 Phase III: Overall Survival



Keynote-006 Phase III: AES

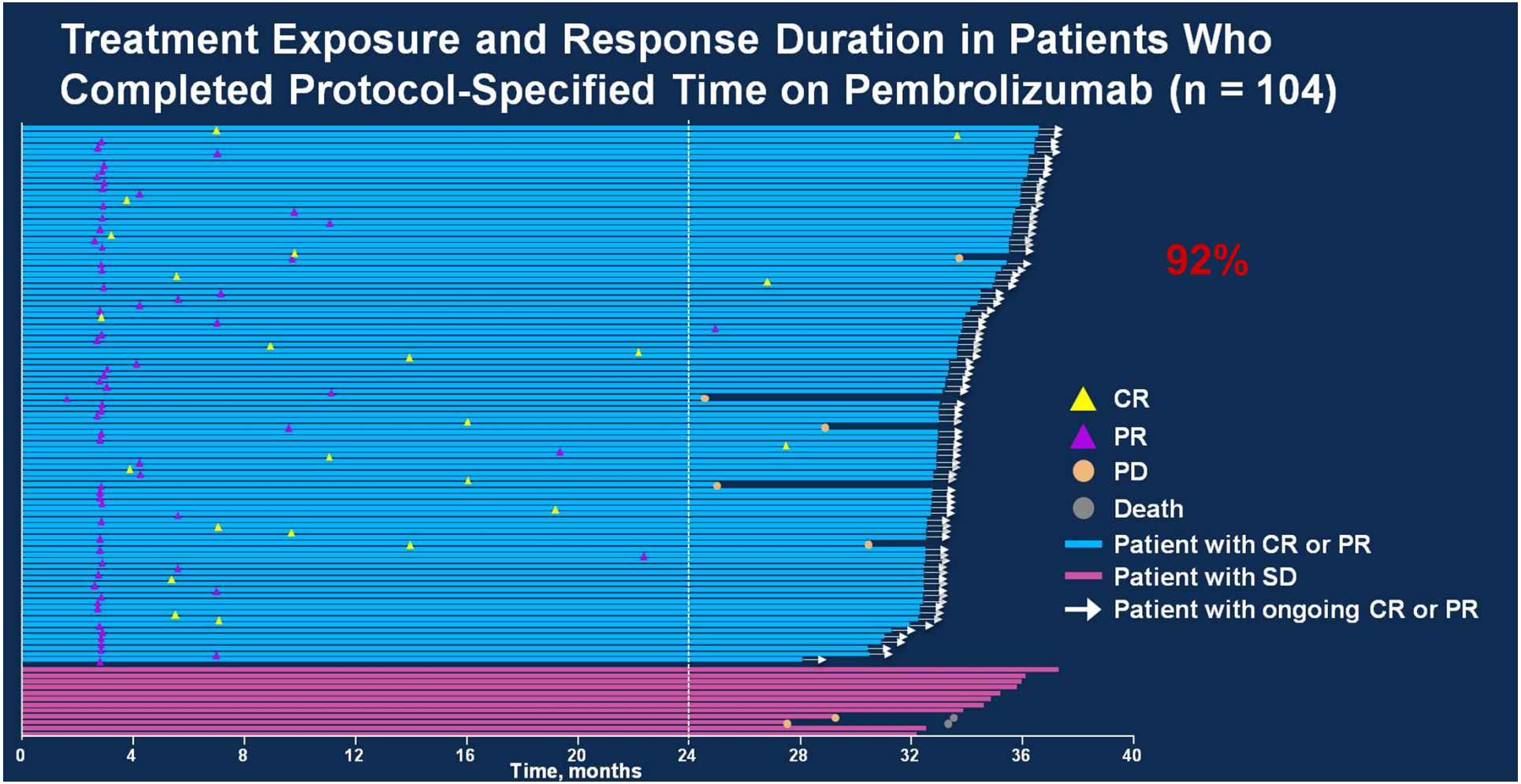


Keynote-006 Phase III: Discontinuation

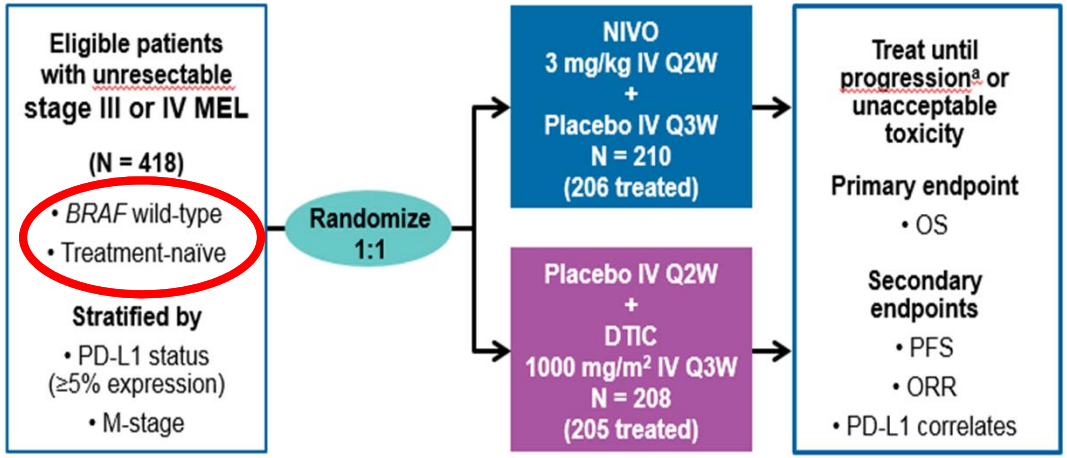
Exposure and AE Summary

	Pembro Q2W N = 278	Pembro Q3W N = 277	Ipilimumab N = 256
Time on therapy, weeks			
Median (range)	28.1 (0.1-108.1)	24.0 (0.1-111.1)	9.0 (0.1-13.1)
Mean (SD)	44.6 (37.2)	41.7 (37.7)	7.2 (3.1)
Treatment-related AEs[a]			
Any grade	229 (82%)	213 (77%)	190 (74%)
Grade 3-4	46 (17%)	46 (17%)	50 (20%)
Led to death (grade 5)	1 (<1%)[b]	0	0
Led to discontinuation	19 (7%)	30 (11%)	23 (9%)

Keynote-006

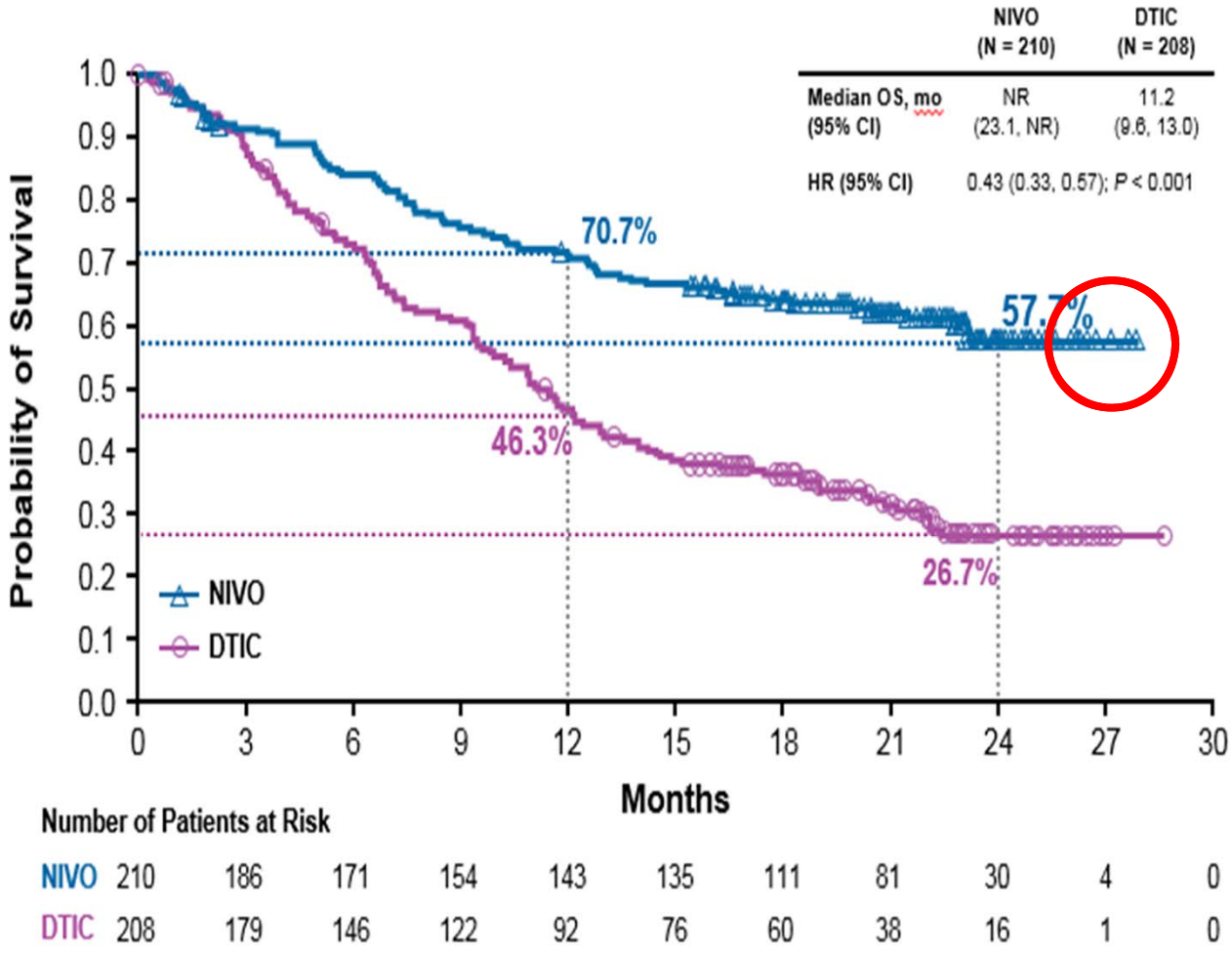

Treatment Exposure and Response Duration in Patients Who Completed Protocol-Specified Time on Pembrolizumab (n = 104)
92%
CR
PR
PD
Death
Patient with CR or PR
Patient with SD
Patient with ongoing CR or PR
0
4
8
12
16
20
24
28
32
36
40
Time, months

CA209-066: Nivolumab in Previously Untreated Melanoma without BRAF Mutation



	NIVO (N = 210)	DTIC (N = 208)
Age, years		
Median (range)	64 (18–86)	66 (26–87)
Gender, %		
Male	58	60
ECOG performance status, %		
0	71	58
1	29	40
M-stage, %		
M0/M1a/M1b	39	39
M1c	61	61
Baseline LDH level, %		
≤ ULN	62	64
> ULN	38	36
PD-L1 status, %		
Positive (≥5% expression)	35	36
Negative/indeterminate	65	64

CA209-066: Overall Survival



- Median follow-up was 18.5 months for NIVO and 10.9 months for DTIC (2 year OS rates are estimated)

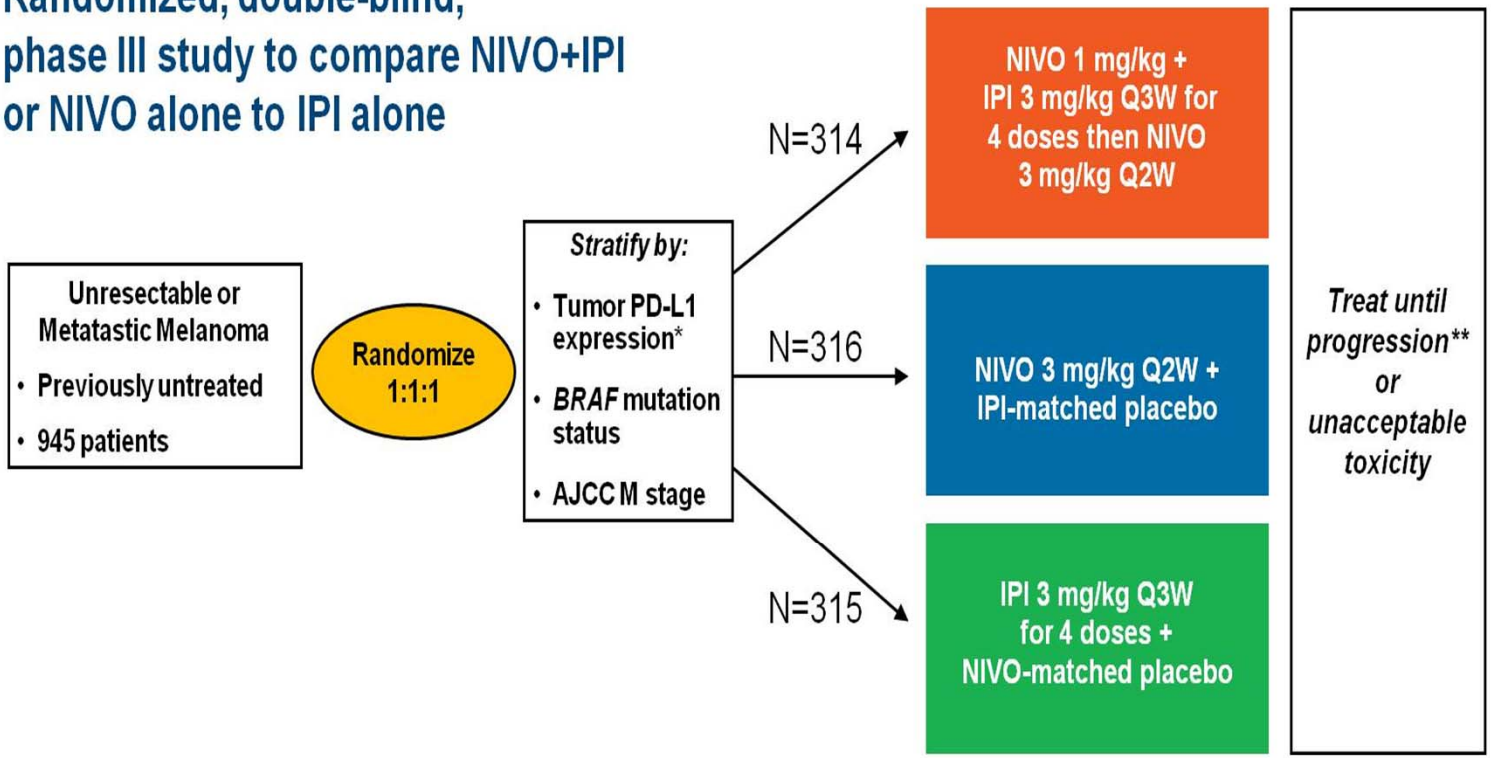
CA209-066: Safety data

Patients reporting AE, %[a]	NIVO (N = 206)		DTIC (N = 205)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
All treatment-related select AEs	58	6	31	2
Skin	41	2	15	0
Pruritus	22	<1	5	0
Rash	18	<1	3	0
Gastrointestinal	19	1	16	<1
Diarrhea	18	<1	16	<1
Colitis	2	<1	0	0
Hepatic	5	2	4	1
Elevated ALT	2	1	2	<1
Elevated AST	2	<1	2	<1
Endocrine	9	2	1	0
Hypothyroidism	5	0	1	0
Hyperthyroidism	3	<1	0	0
Pulmonary	3	<1	0	0
Pneumonitis	2	<1	0	0
Renal	2	<1	<1	0
Renal failure	1	0	0	0

	NIVO (N = 206)		DTIC (N = 205)	
Patients reporting AE, n (%)	Any grade	Grade 3–4	Any grade	Grade 3–4
Treatment-related	159 (77)	27 (13)	159 (78)	35 (17)
Treatment-related leading to discontinuation	12 (6)	7 (3)	7 (3)	4 (2)

CA209-067: Study Design

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



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

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

Baseline Patient Characterisitics

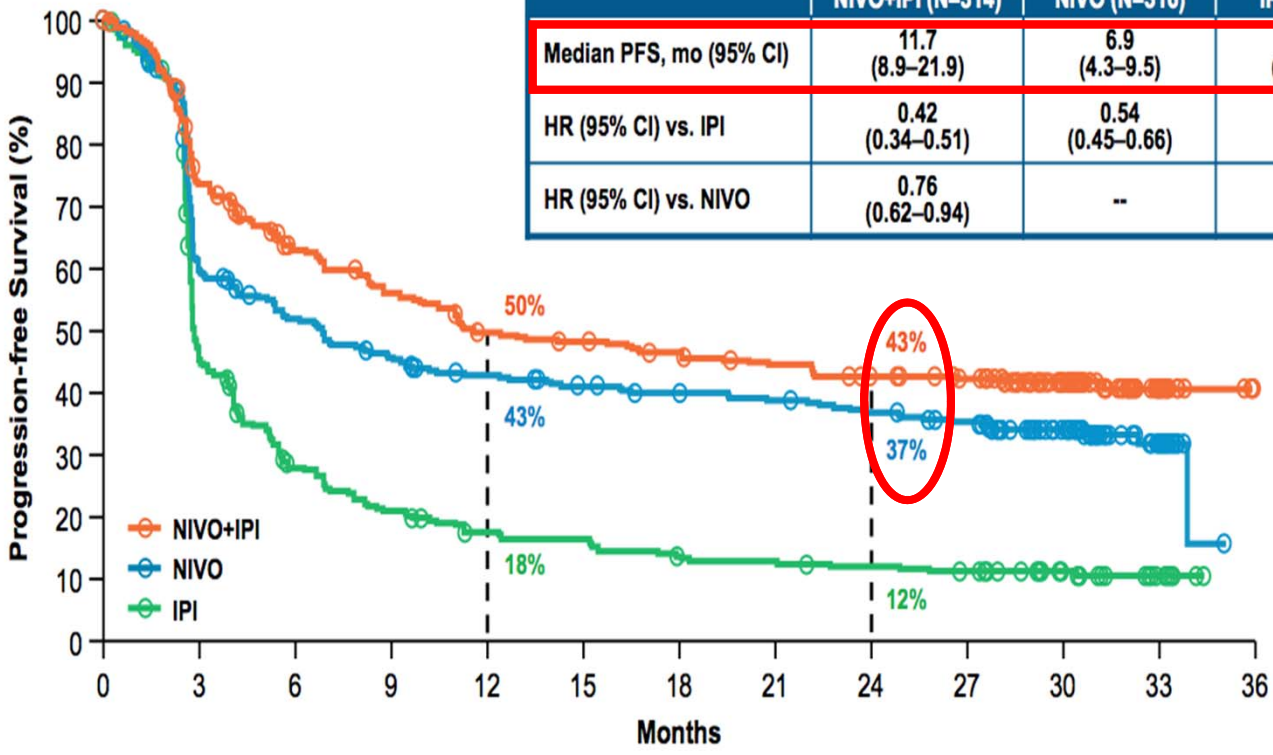
	NIVO + IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median age, years (range)	61 (18–88)	60 (25–90)	62 (18–89)
Age ≥65 years	41.1%	37.3%	42.2%
Sex — Male	65.6%	63.9%	64.1%
ECOG performance status of 0*	73.2%	75.3%	71.1%
M stage — M1c	57.6%	58.2%	58.1%
LDH — >ULN	36.3%	35.4%	36.5%
LDH — >2x ULN	11.8%	11.7%	9.5%
Brain metastases	3.5%	2.5%	4.8%
PD-L1 expression ≥5%**	21.7%	25.3%	23.8%
BRAF V600 mutant	32.2%	31.6%	30.8%

*Remaining patients had an ECOG PS of 1, except for one patient with a PS of 2 (NIVO) and one unreported (NIVO + IPI).

**Pre-treatment tumor specimens were centrally assessed by PD-L1 immunohistochemistry (using a validated BMS/Dako assay).

CA209-067: 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:

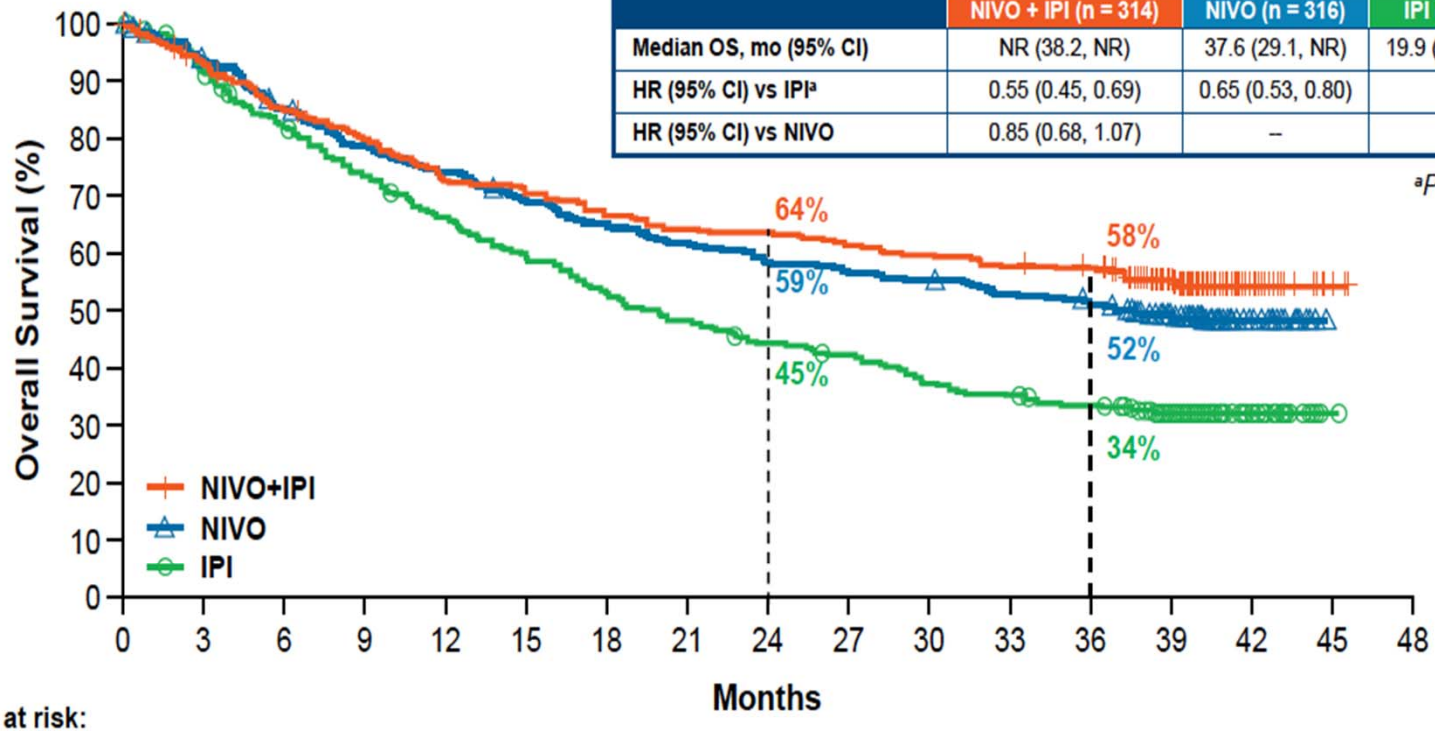
NIVO+ IPI	314	218	176	156	137	132	125	118	110	104	71	16	0
NIVO	316	178	151	132	120	112	107	103	97	88	62	16	0
IPI	315	136	77	58	46	43	35	33	30	27	16	5	0

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

CA 209-067: Overall Survival

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2, NR)	37.6 (29.1, NR)	19.9 (16.9, 24.6)
HR (95% CI) vs IPI[a]	0.55 (0.45, 0.69)	0.65 (0.53, 0.80)	--
HR (95% CI) vs NIVO	0.85 (0.68, 1.07)	--	--

[a]$P < 0.0001$



Patients at risk:

NIVO+IPI	314	292	265	247	226	221	209	200	198	192	186	180	177	131	27	3	0
NIVO	316	292	265	244	230	213	201	191	181	175	171	163	156	120	28	0	0
IPI	315	285	253	227	203	181	163	148	135	128	117	107	100	68	20	2	0

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)

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

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

Subsequent Therapies: All randomized Patients

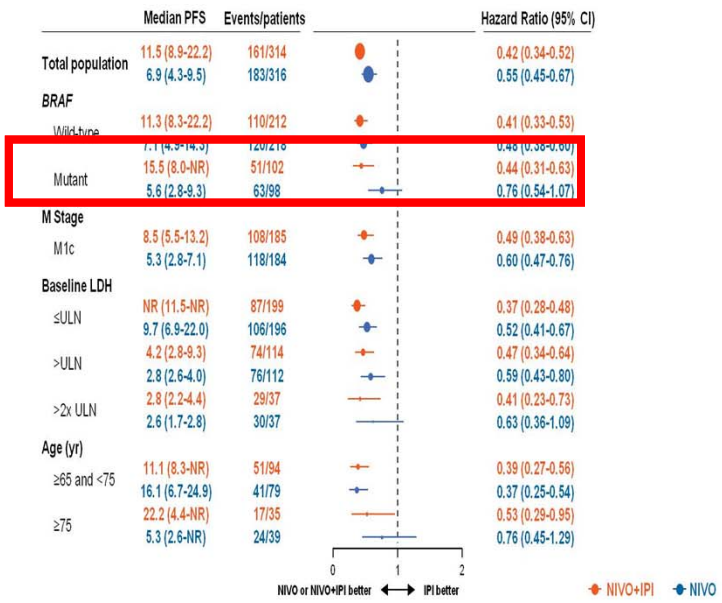
	NIVO+IPI (N=314)	NIVO (N=316)	IPI (N=315)
Any subsequent therapy, n (%)*	129 (41)	169 (54)	225 (71)
Systemic therapy	100 (32)	140 (44)	196 (62)
Anti-PD-1 agents	30 (10)	32 (10)	132 (42)
Anti-CTLA-4	19 (6)	83 (26)	12 (4)
BRAF inhibitors	40 (13)	57 (18)	68 (22)
MEK inhibitors	30 (10)	38 (12)	39 (12)
Investigational 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

*Patients may have received more than 1 subsequent therapy (e.g. radiation, surgery and systemic therapies)

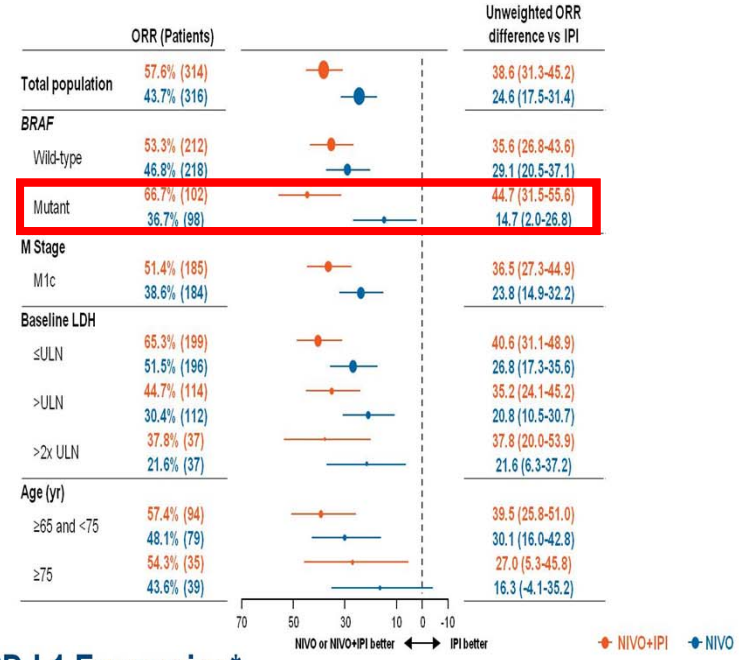
**Other than investigational immunotherapy, BRAF inhibitors, and MEK inhibitors

Mono vs Combo Immunotherapy

PFS in Patient Subgroups (18 month follow-up)



ORR in Patient Subgroups (18 month follow-up)



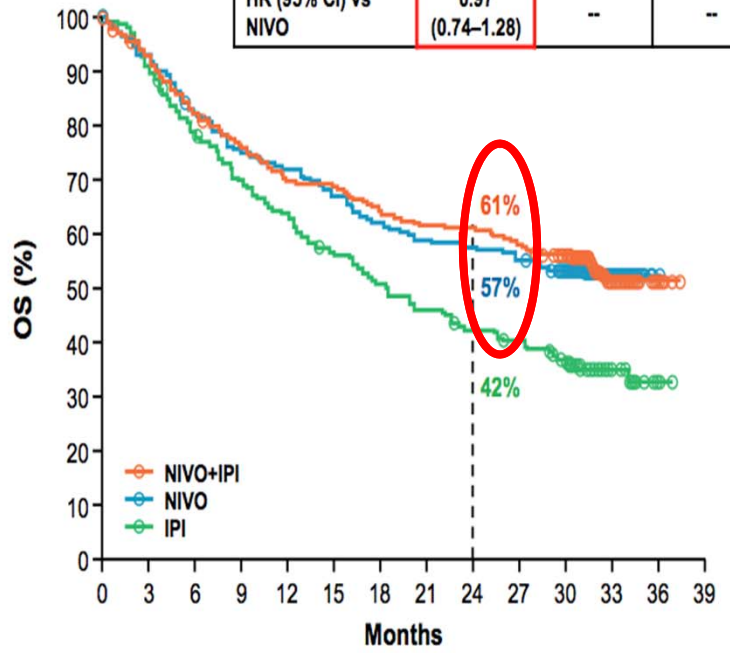
Response to Treatment by Tumor PD-L1 Expression*

		NIVO+IPI	NIVO	IPI
PD-L1 (≥5%)	ORR, % (95% CI)	**72.1** (59.9–82.3)	**57.5** (45.9–68.5)	**21.3** (12.7–32.3)
	Median Duration of Response (months)	NR	20.7	NR
PD-L1 (<5%)	ORR, % (95% CI)	**54.8** (47.8–61.6)	**41.3** (34.6–48.4)	**17.8** (12.8–23.8)
	Median Duration of Response (months)	NR	22.3	18.2

CA 209-067 OS: Benefit in BRAFm

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)	--	--

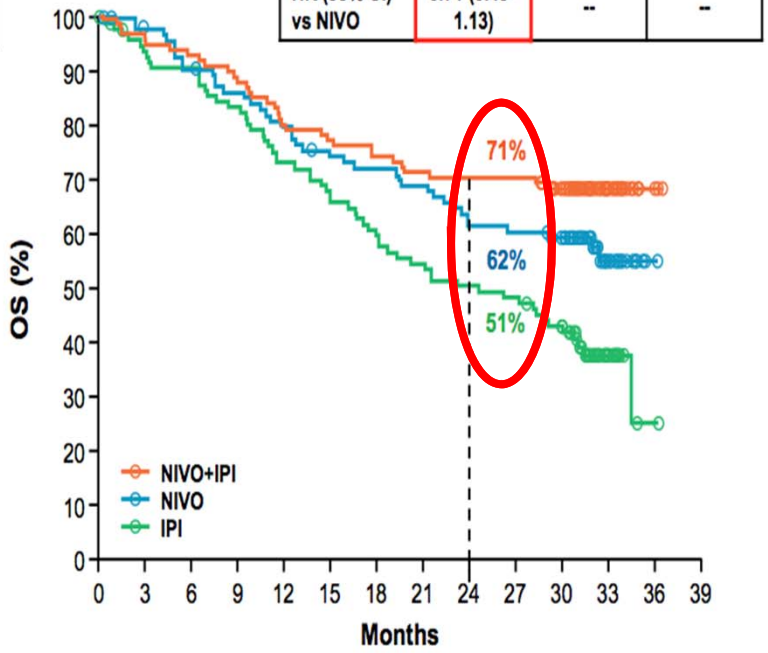


Patients at risk:

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

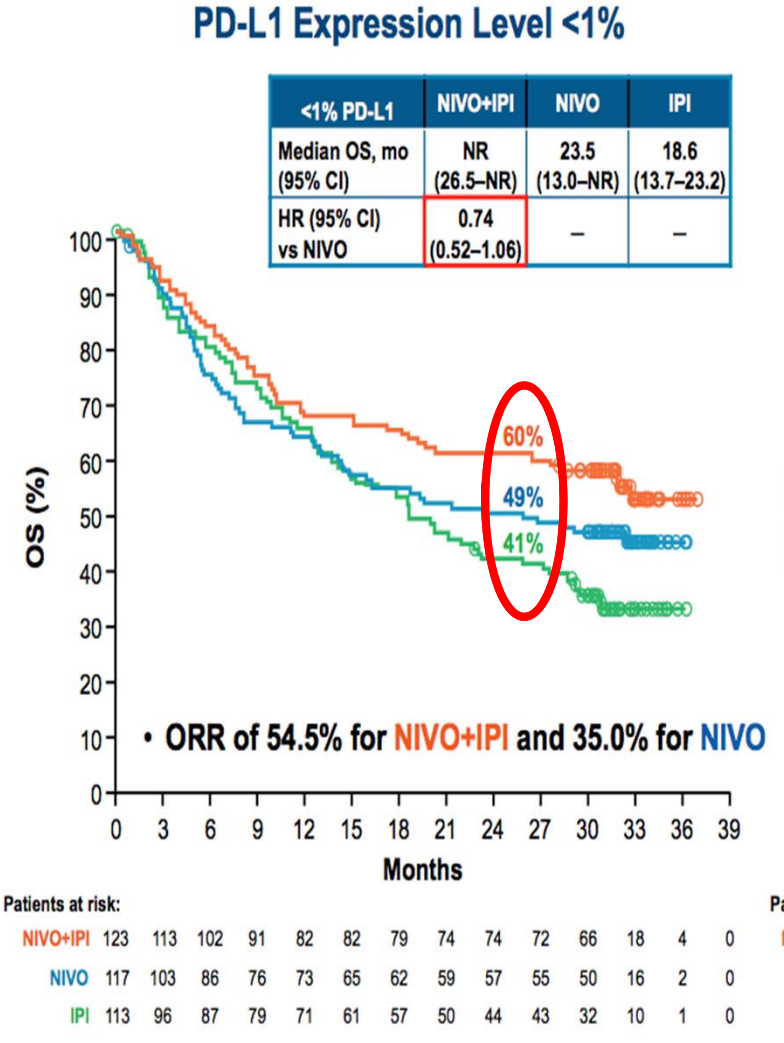
	NIVO+IPI	NIVO	IPI
Median, mo (95% CI)	NR	NR (26.4–NR)	24.6 (17.9–31.0)
HR (95% CI) vs NIVO	0.71 (0.45–1.13)	--	--

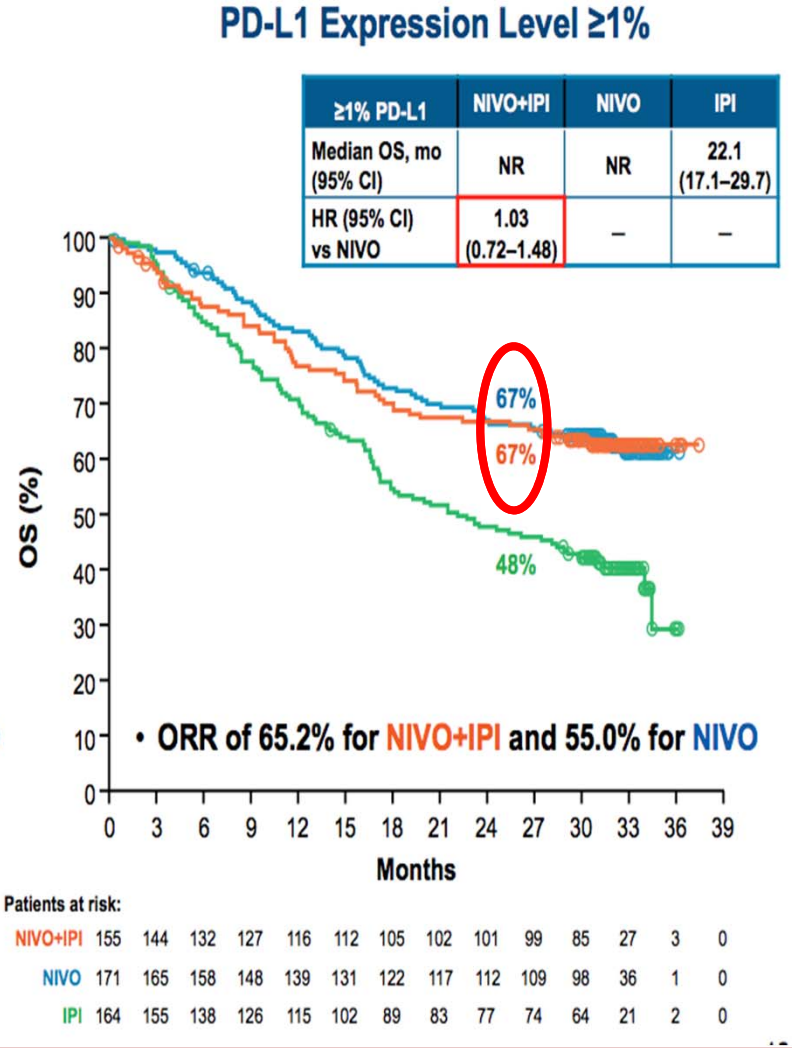


Patients at risk:

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

CA209-067 OS: Similar outcomes in PD-L1 ≥ 1%





CA 209-067: Selected related AEs

	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
Skin AEs, %	60.4	5.8	43.8	2.2	54.7	2.9
Rash	28.4	2.9	22.7	0.3	21.2	1.6
Pruritus	35.1	1.9	20.4	0.3	36.3	0.3
Gastrointestinal AEs, %	47.6	15.3	21.7	2.9	37.3	11.6
Diarrhea	45.4	9.6	20.8	2.2	33.8	6.1
Colitis	11.5	8.0	2.2	1.0	11.3	8.0
Endocrine AEs, %	32.3	5.8	15.7	1.6	11.6	2.6
Hypothyroidism	16.0	0.3	9.3	0	4.5	0
Hyperthyroidism	10.2	1.0	4.5	0	1.0	0
Hepatic AEs, %	31.6	19.8	7.3	2.6	7.4	1.6
Elevated ALT	17.9	8.6	3.8	1.0	3.9	1.6
Elevated AST	15.7	6.1	4.2	1.0	3.9	0.6
Pulmonary AEs, %	7.3	1.0	1.6	0.3	1.9	0.3
Pneumonitis	6.7	1.0	1.3	0.3	1.6	0.3
Renal AEs, %	6.4	1.9	1.0	0.3	2.6	0.3
Elevated creatinine	4.2	0.3	0.6	0.3	1.6	0

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

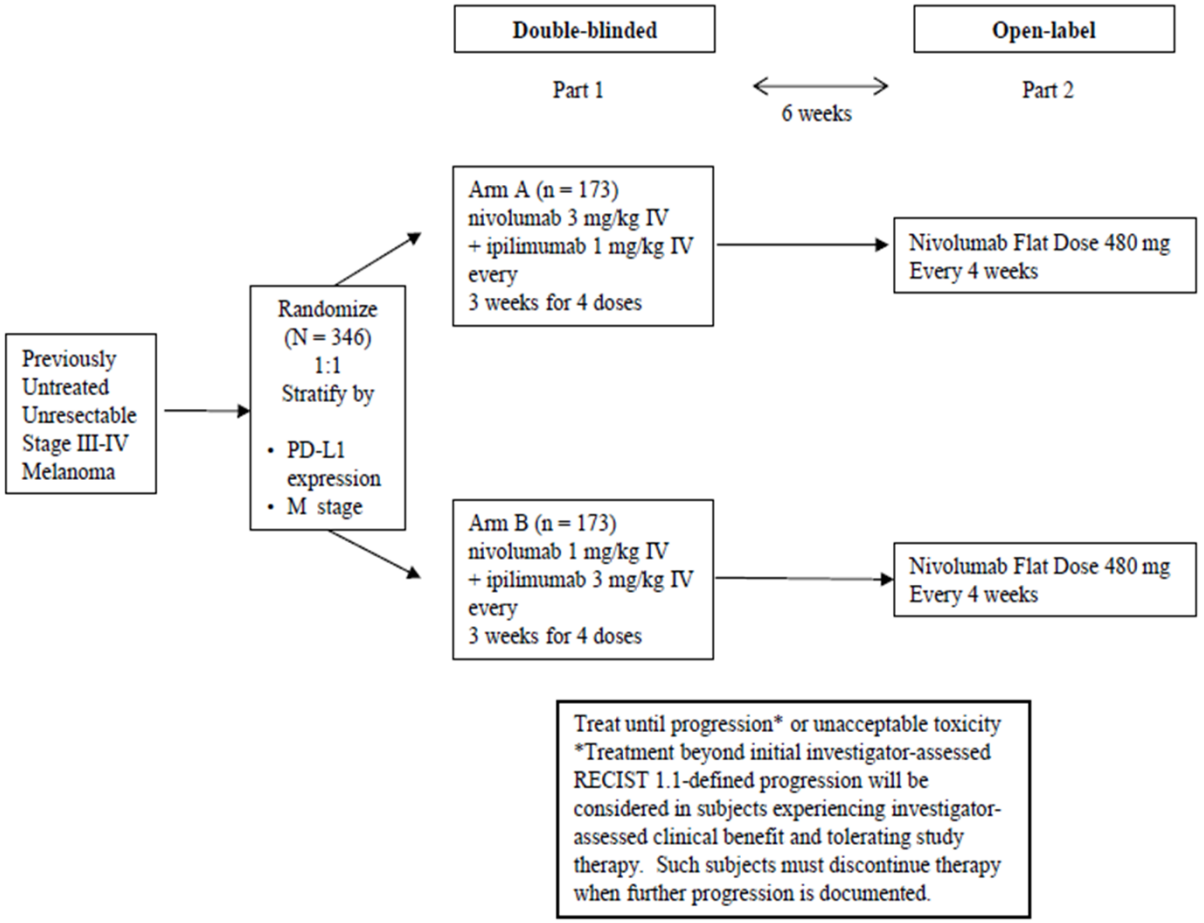
	NIVO+IPI (N=313)		NIVO (N=313)		IPI (N=311)	
Patients reporting event, %	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Treatment-related adverse event (AE)	95.8	58.5	86.3	20.8	86.2	27.7
Treatment-related AE leading to discontinuation	39.6	31.0	11.5	7.7	16.1	14.1
Treatment-related death, n (%)	2 (0.6)[a]		1 (0.3)[b]		1 (0.3)[b]	

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

[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).[1]

CA 209511: Phase IIIb/IV, Randomized, Double Blinded

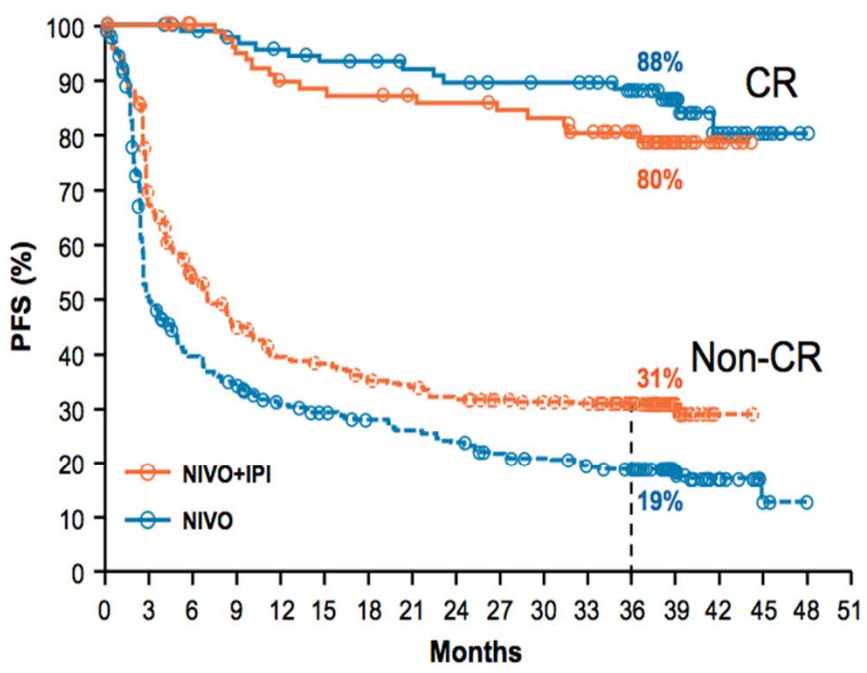
- OP: AEs
- OS: ORR, PFS, OS, QoL



Questions?

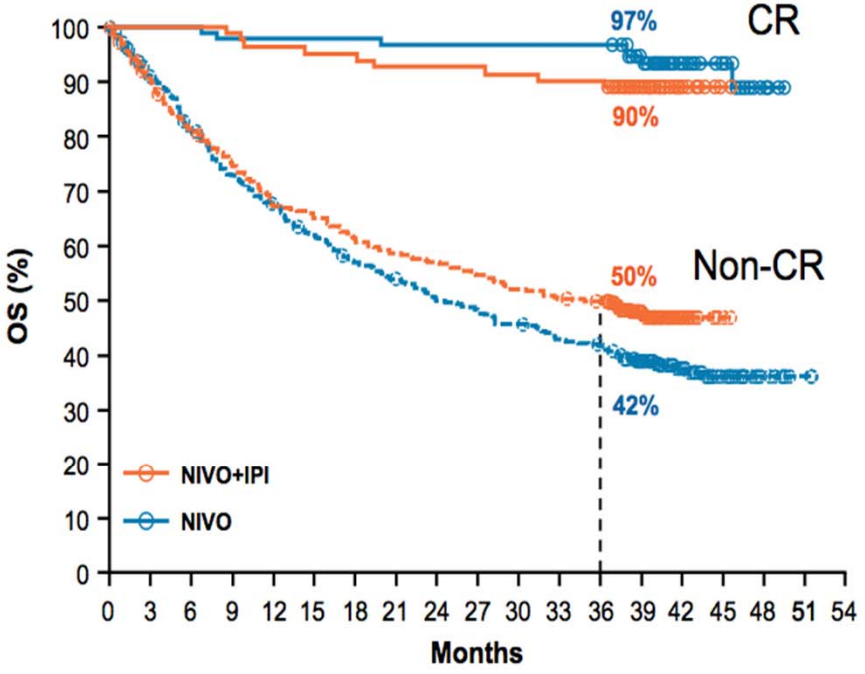
- How long to treat with anti-PD-1?
- Sequences: BRAFi/Anti PD-1 first?
- New Combos: Triplets, IDOi…
- Selection treatment: Biomarkers

PFS and OS: Pooled CR and Non-CR for NIVO+IPI and NIVO



Patients at risk:

NIVO+IPI	327	205	155	128	110	106	98	92	85	80	76	72	55	17	1	0	0	0
NIVO	434	204	155	133	114	104	97	90	82	72	67	62	56	33	15	3	1	0



Patients at risk:

NIVO+IPI	327	392	260	240	216	210	196	187	182	174	166	160	156	95	19	2	0	0	0
NIVO	434	386	344	308	283	258	239	224	208	197	189	177	169	137	63	28	9	2	0

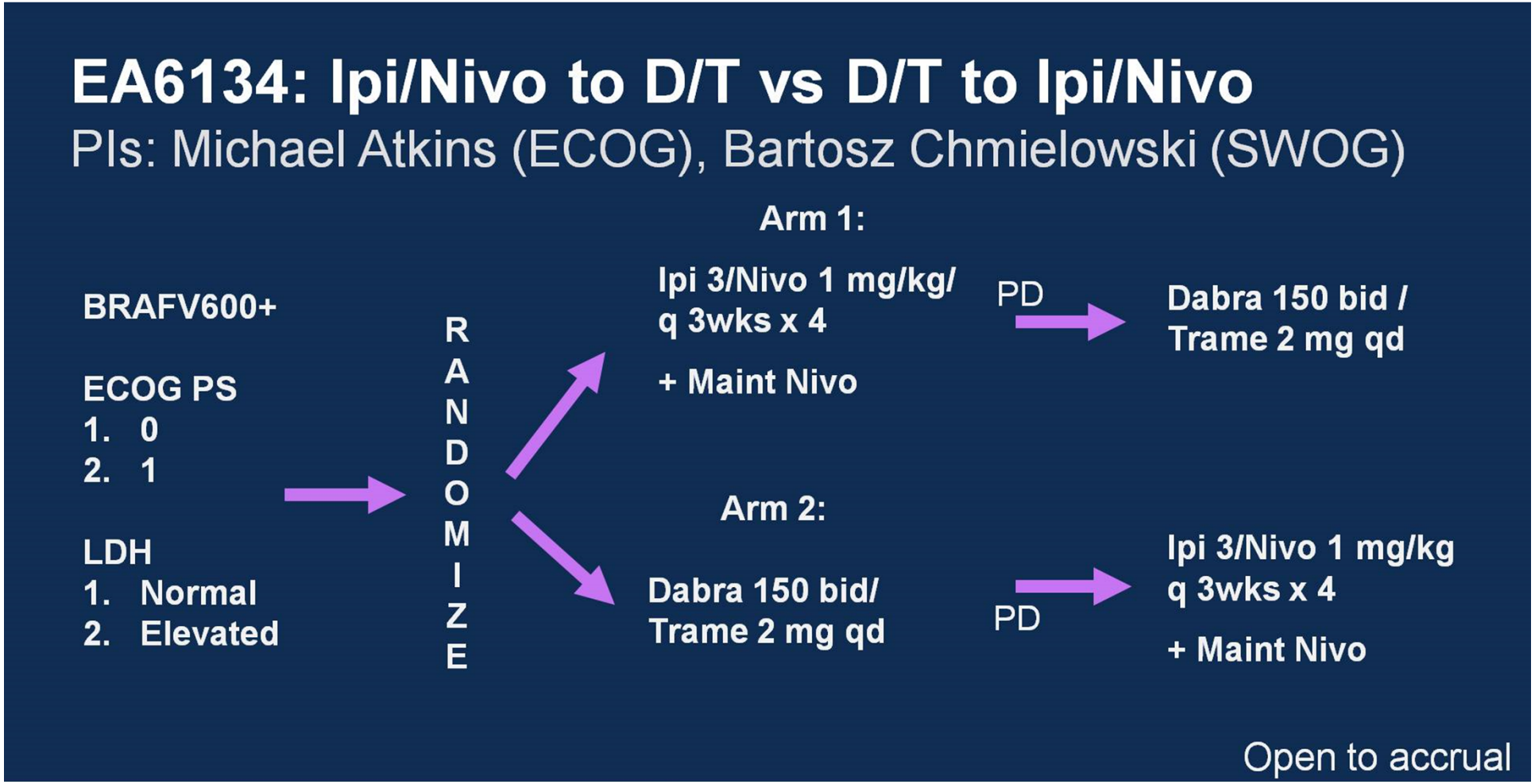
Post-treatment Therapy

	NIVO+IPI		NIVO	
	CR (n = 82)	Non-CR (n = 327)	CR (n = 92)	Non-CR (n = 434)
Any subsequent therapy, n (%)	13 (16)	154 (47)	18 (20)	279 (64)
Systemic therapy	6 (7)	123 (38)	9 (10)	233 (54)
Anti-PD-1 agents	4 (5)	46 (14)	6 (7)	66 (15)
Anti-CTLA-4	2 (2)	18 (6)	5 (5)	153 (35)
BRAF inhibitors	3 (4)	43 (13)	0	59 (14)
MEK/NRAS inhibitors	1 (1)	37 (11)	1 (1)	45 (10)
Median time to subsequent systemic therapy, months (95% CI)[a]	NR (NR, NR)	26.6 (17.5, NR)	NR (NR, NR)	9.2 (7.3, 15.2)
Patients free of subsequent systemic therapies at 3 years, %[a]	92	48	93	32

[a]Excludes patients who died and never received subsequent therapy

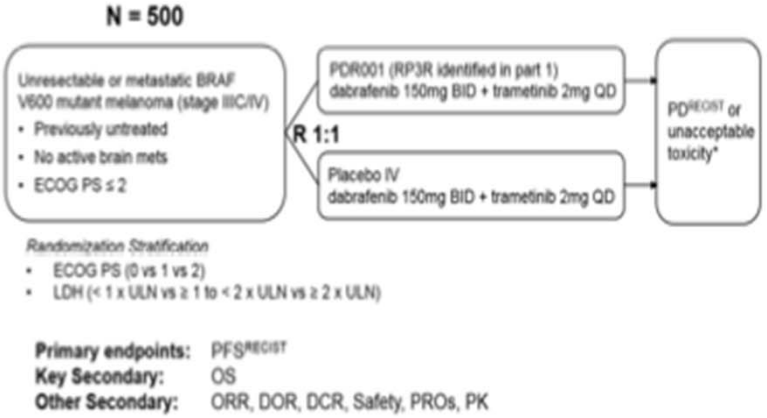
CTLA-4 = cytotoxic T-lymphocyte antigen 4; NR = not reached; PD-1 = programmed death 1

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



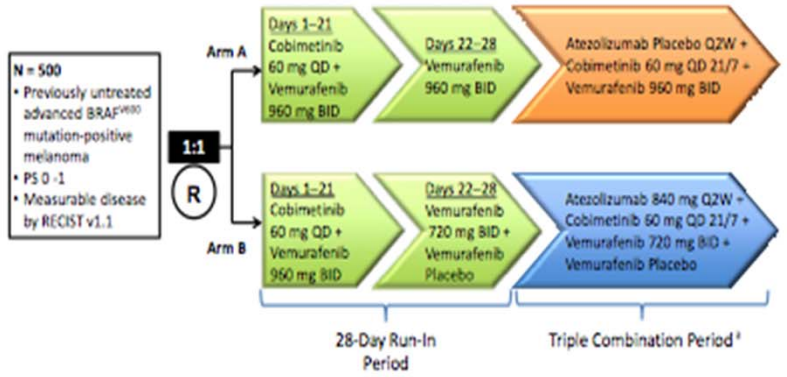
TRIPLETS

Combi-i



*Treatment beyond PD^Recist is permitted if all of the following criteria are met: (1) subject has irSD, irPR or unconfirmed irPD according irRECIST, (2) the treatment will not delay an imminent intervention to prevent serious complications, (3) tolerance of study treatment, and (4) stable performance status

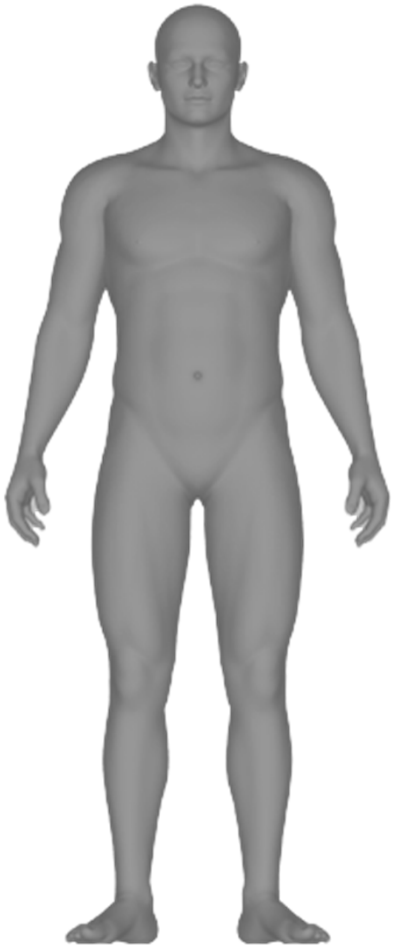
Trilogy



21/7 = treatment on Days 1–21 followed by no treatment on Days 22–28; BID = twice daily; PS = performance status; QD = once daily; Q2W = every 2 weeks; R = randomization; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

[a] Study treatment will continue until investigator-determined disease progression (or confirmed progression 4–8 weeks later, for clinically stable patients with a favorable benefit-risk ratio), death, unacceptable toxicity, withdrawal of consent, or pregnancy, whichever occurs first.

Selection of treatment in melanoma



Co-morbilities

Brain mets

ECOG

BRAF

Tumor burden

Resectability

LDH

Many combination avenues
> 800 clinical trials

+ radiotherapy

+ other checkpoint-I
TIM 3; LAG 3

+ macrophage-I
CSFR1

+ chemo

+ other IT
- 41BB
- OX-40
- CD40
- GITR
- ICOS
- IDO

+ local tt
- Ipi
- Oncol virus
- TLR agonist

+ cancer vaccines

+ Adopt C T

+ targeted therapies
BRAF, MEK

+ epigenetic modifiers
HDAC

+ NK activation

Conclusions

Anti-PD-1/CTL4

- Anti-PD-1 better than Anti-CTL4 (RR,PFS,OS)
- Anti-PD-1 showed longer survivors (OS 3y 43%).
- AntiPD-1 more favourable than Anti-CTL4.
- Combo Ipi+Nivo: Benefit OS(descriptive analysis), exploratory data OS (BRAFm, PDL-1-), Higher toxicity.
- Selection treatment: Based clinical characterisitics, not selection by biomarkers (PDL-1 weak biomarker)

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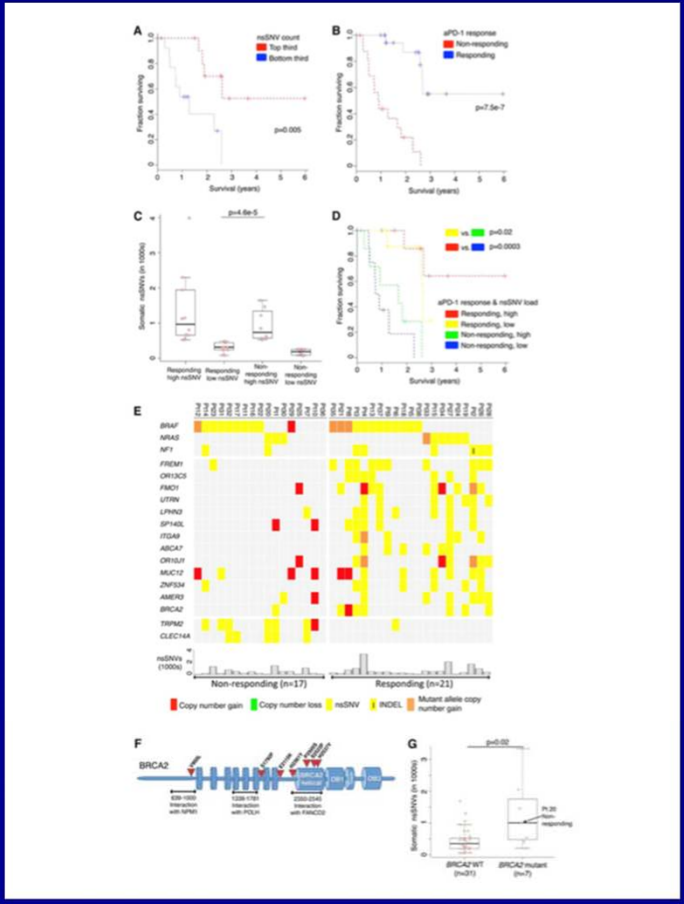
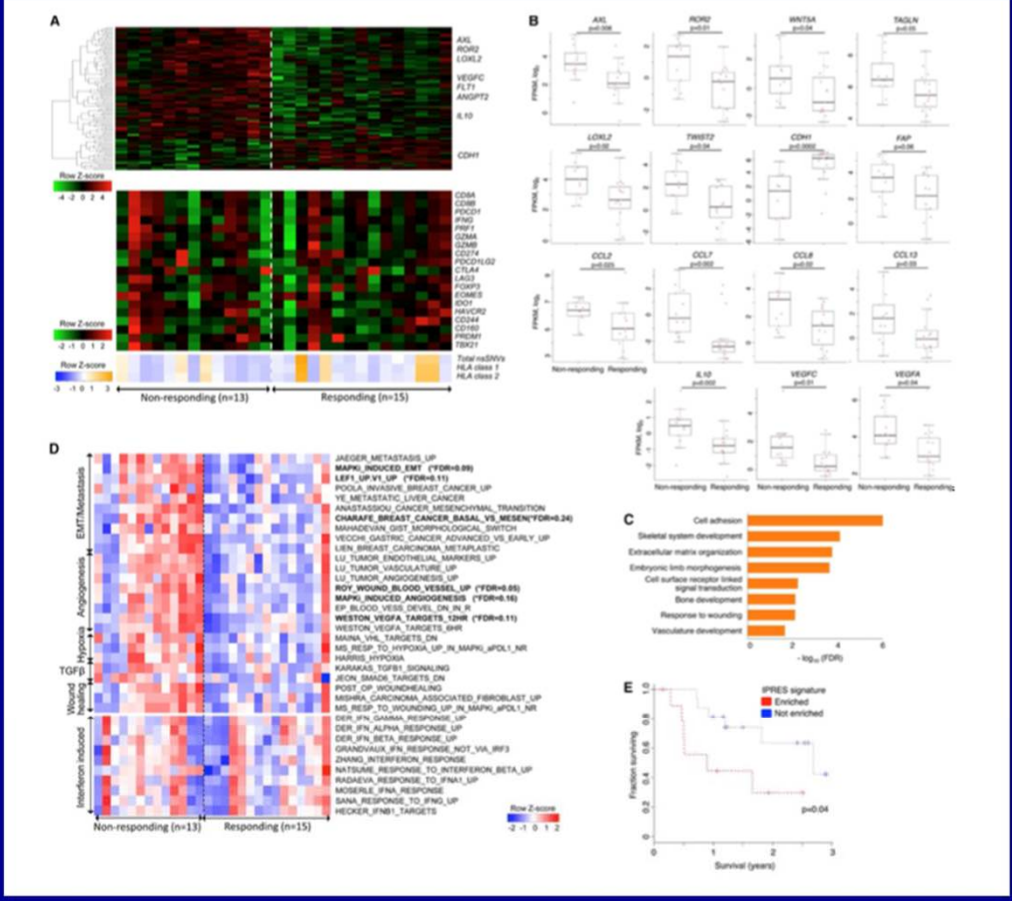
Hospital Verge de la Cinta
C. de les Esplanetes, 14
43500 Tortosa

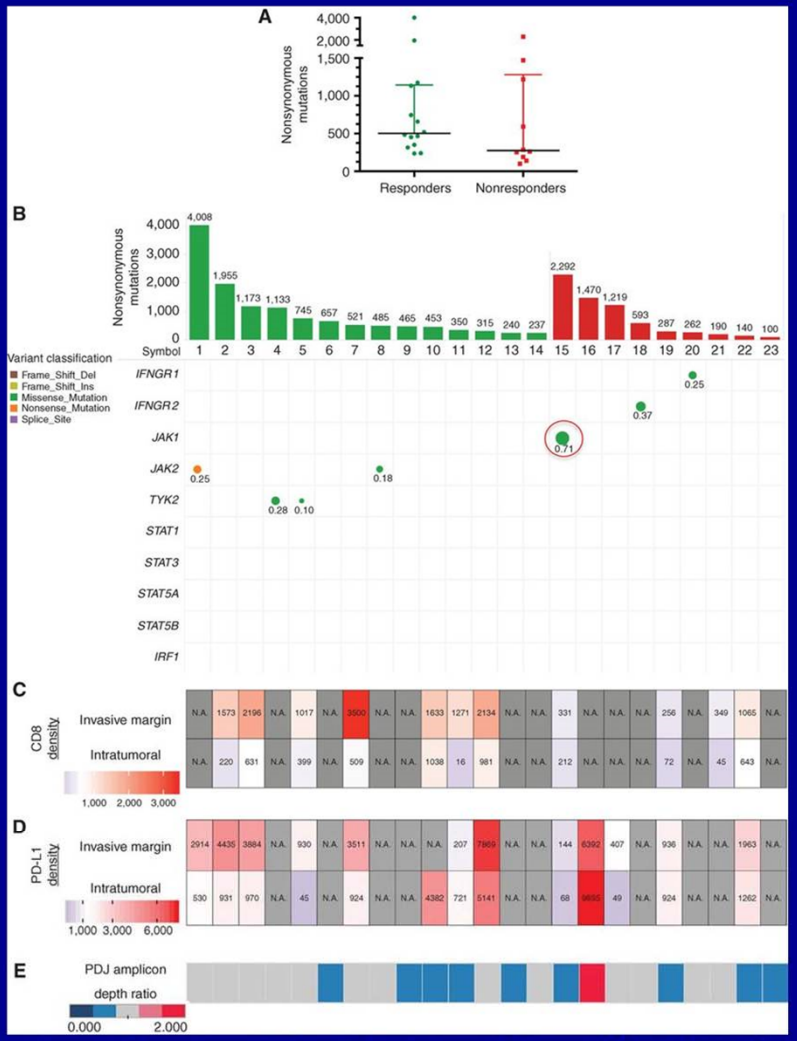
Genomic and Expression Profiles Associated with PD-1 Resistance: IPRES





Hugo, W et al Cell 2016 Concurrence of a tumor cell mesenchymal phenotype with an angiogenesis- and wound healing-related inflammatory microenvironment

Mutational load and mutations in the interferon signaling pathway among patients with advanced melanoma with or without response to anti–PD-1 blockade therapy.



Daniel Sanghoon Shin et al. Cancer Discov 2017;7:188-201

AACR American Association for Cancer Research
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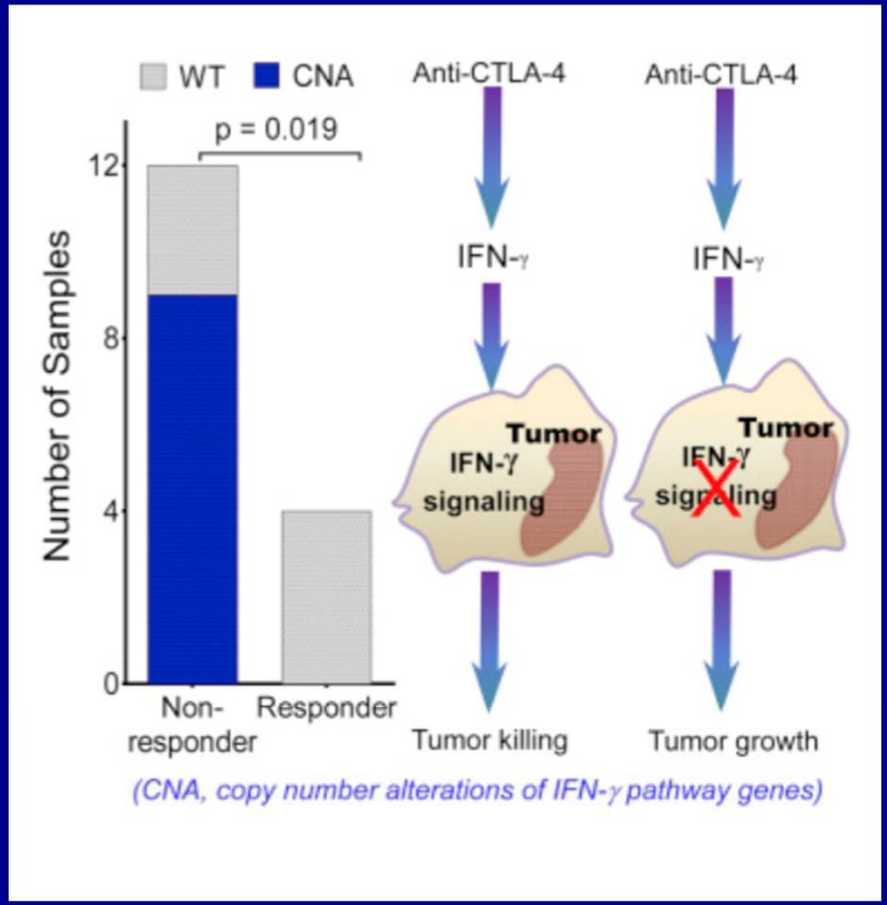
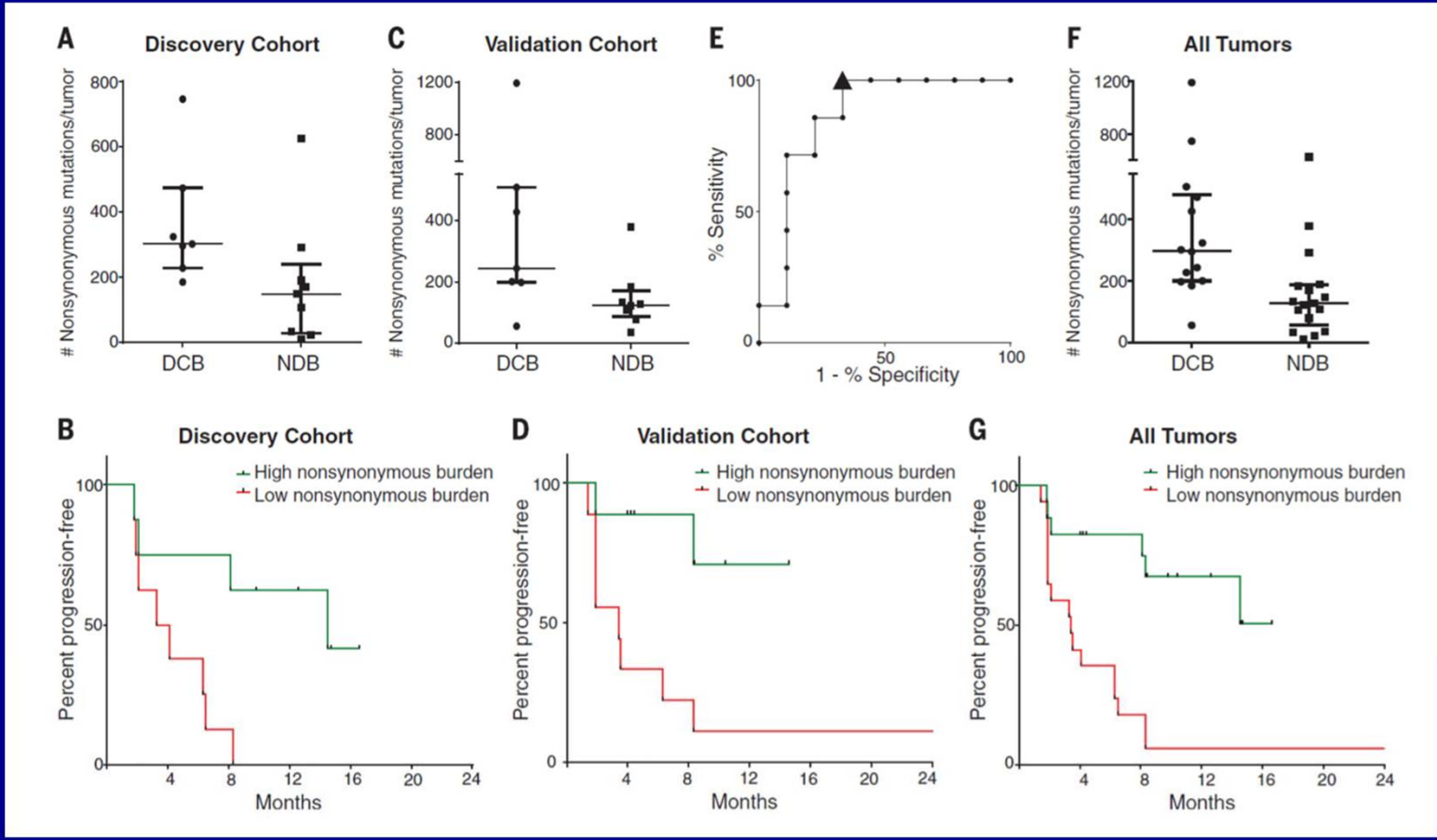
Copy number alterations of IFN-gamma genes associated with resistance to CTLA-4 blockade



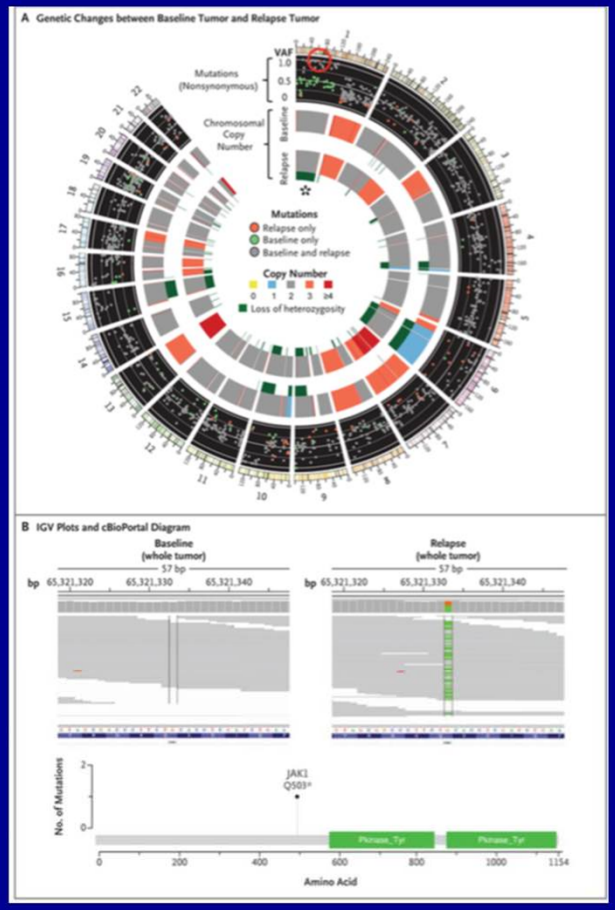
Gao, J et al Cell 2016

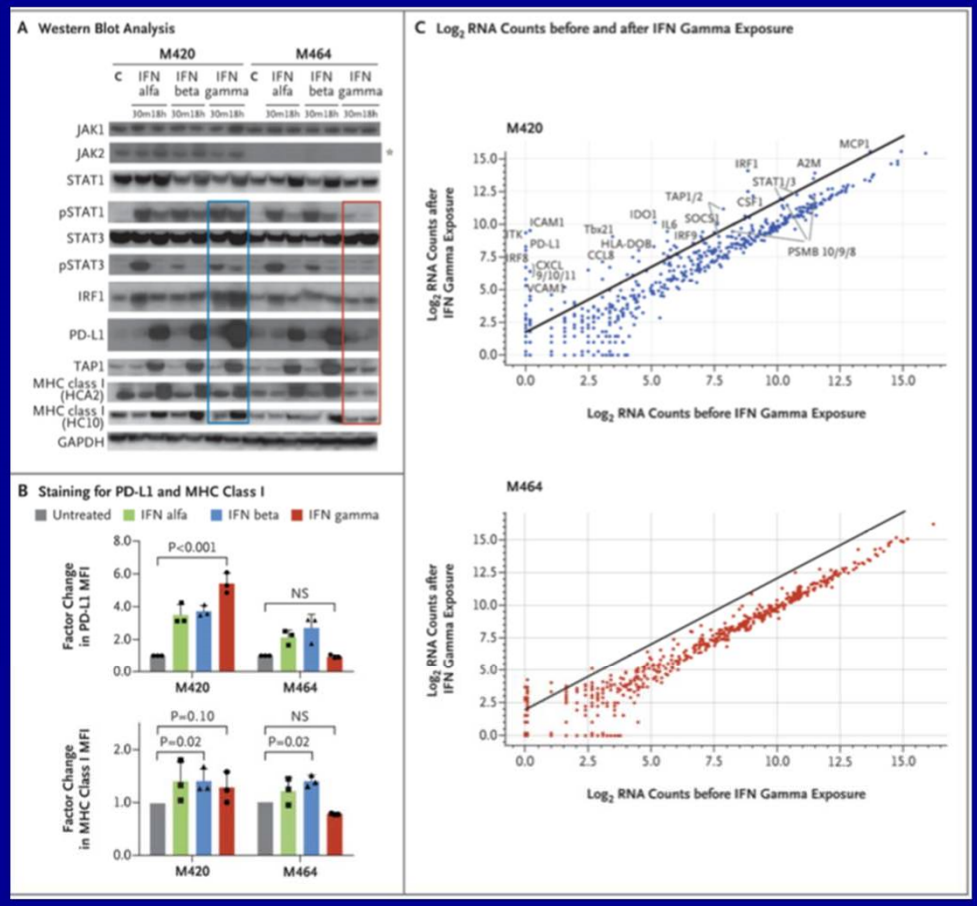
Mutational burden associated with clinical benefit of PD-1 blockade



Rizvi, N et al Science 2015

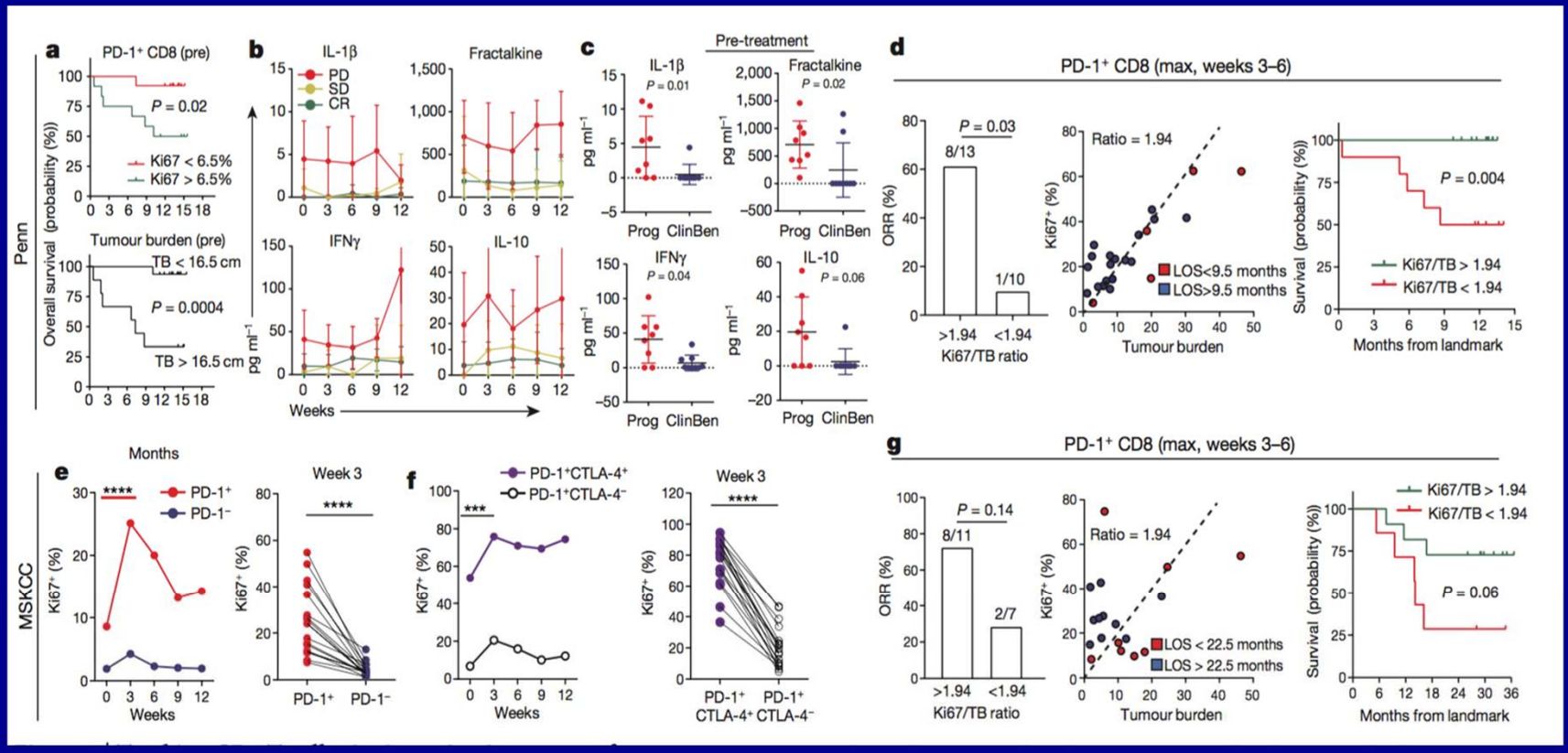
JAK 1/2 mutations associated with acquired resistance to PD-1 blockade





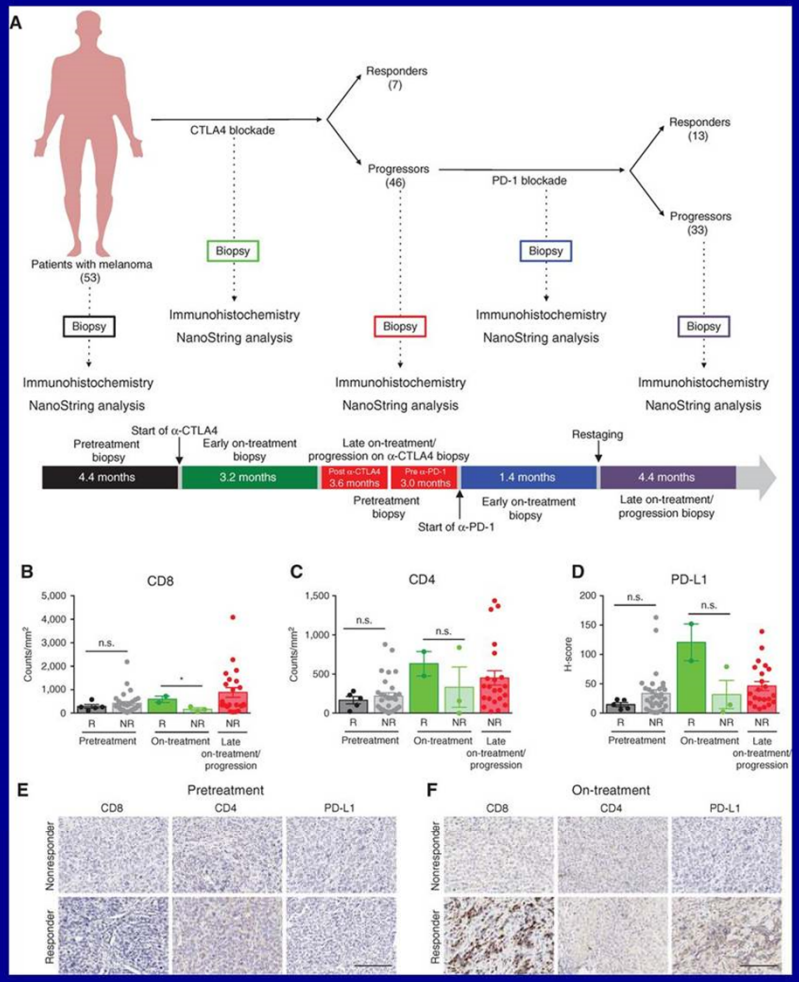
Zaretsky, J et al NEJM 2016

Composite tumor burden and PD-1+/CD8 T cells are associated with PD-1 response



Huang, AC et al Nature 2017

Immune profiling in early on-treatment biopsies is predictive of response to CTLA4 blockade in a unique cohort of patients treated with sequential CTLA4 and PD-1 blockade.



Pei-Ling Chen et al. Cancer Discov 2016;6:827-837

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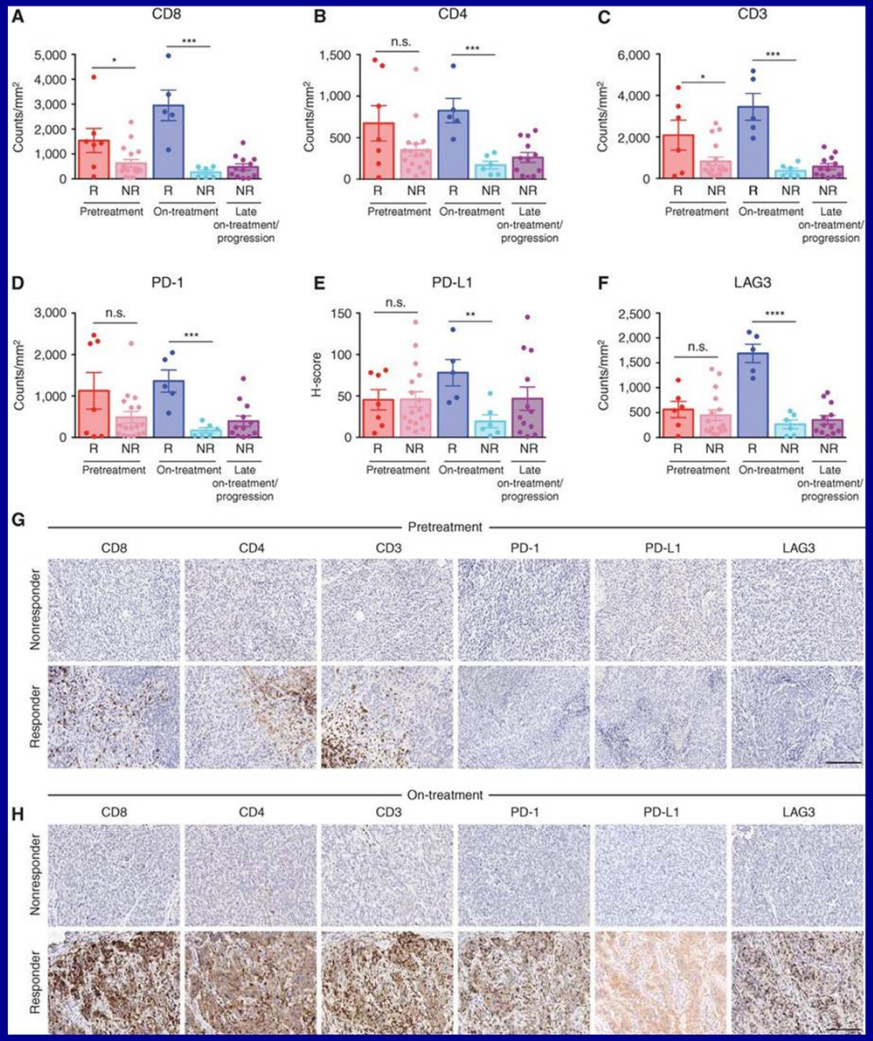
Immune profiling in early on-treatment biopsies is highly predictive of response to PD-1 blockade.



Pei-Ling Chen et al. Cancer Discov 2016;6:827-837

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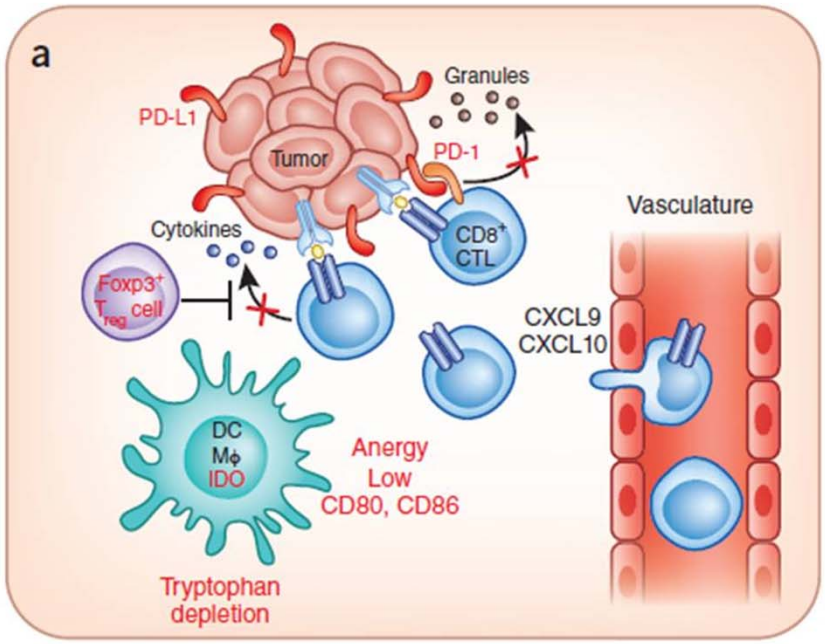
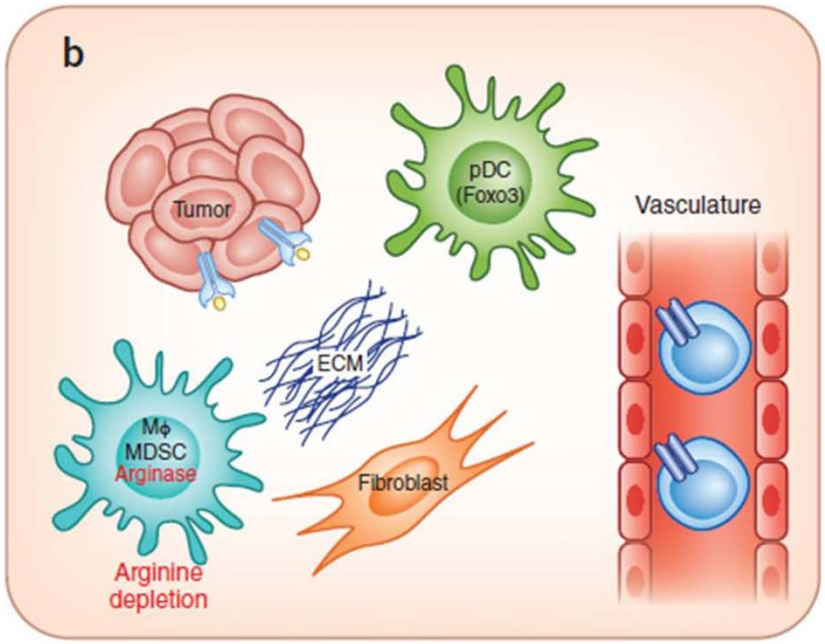
Working model: immunobiology of T cell-inflamed and non-inflamed tumor microenvironment

T cell-inflamed



- Chemokines
- CD8⁺ T cells
- Type I IFN signature
- Immune escape: Inhibitory pathways
- ***Most immunotherapy responders have this phenotype***

Non-T cell-inflamed

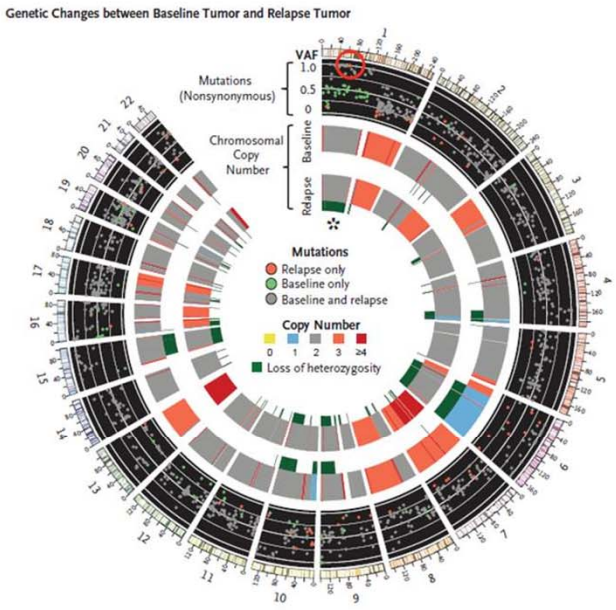


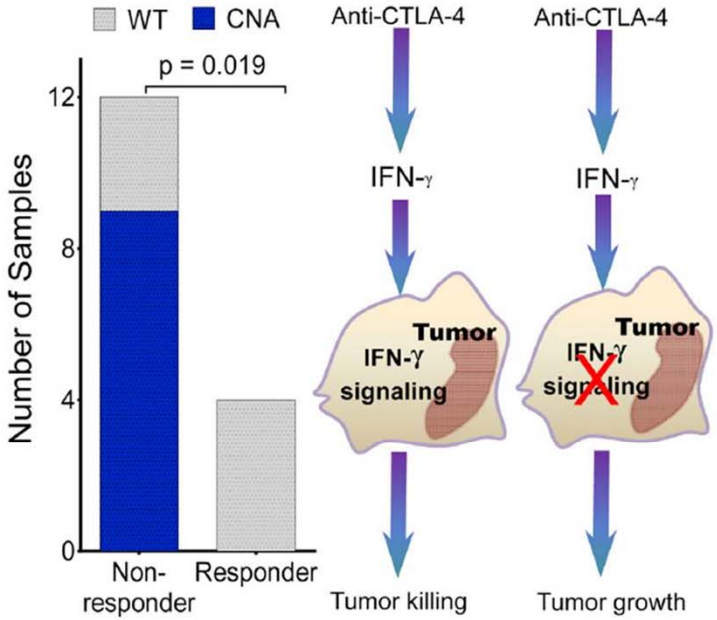
- Low inflammatory signature
- Absent intratumoral CD8⁺ T cells
- Immune escape: T cell exclusion

Nature Immunol. 2013

Genetic resistances to immunotherapies

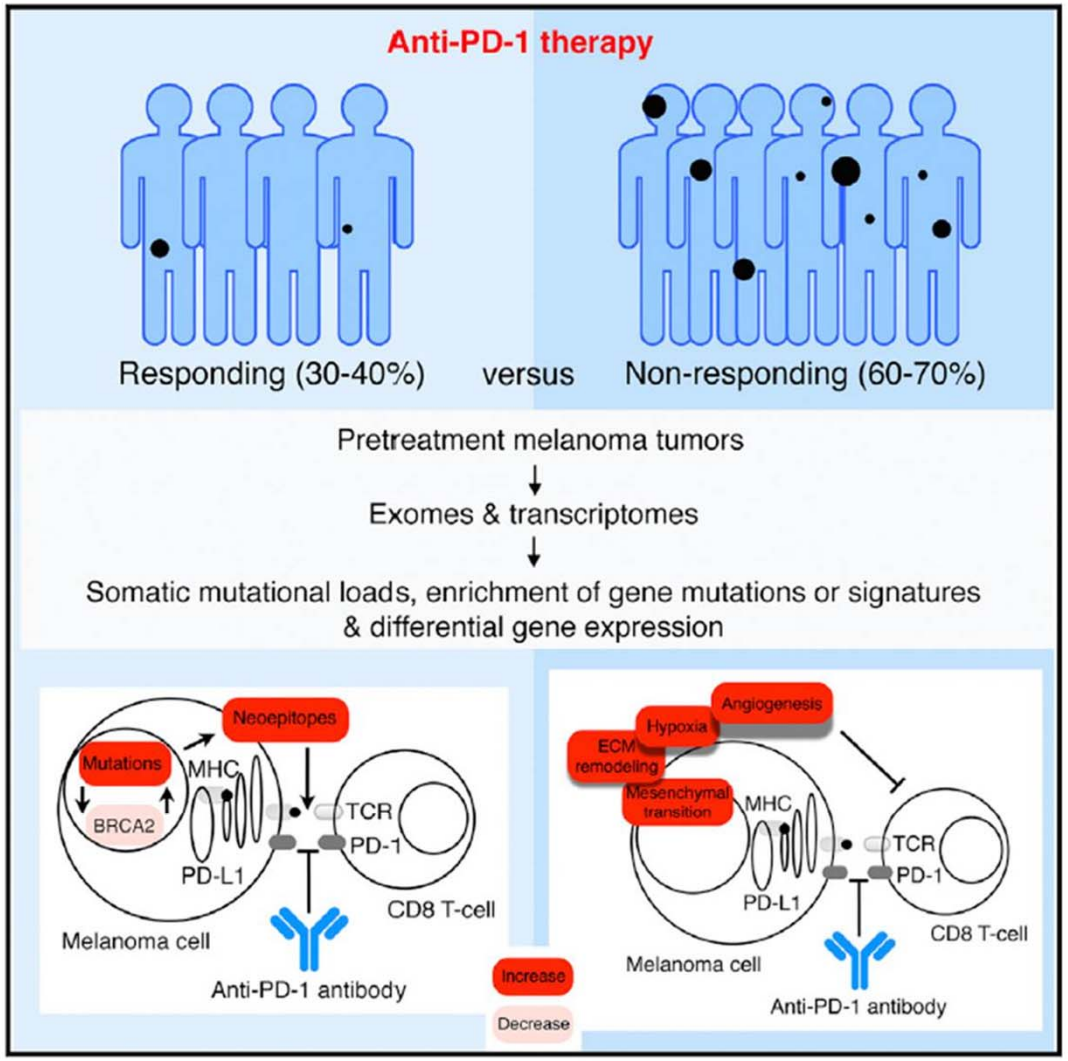
- Mutation-derived modification of the INF-γ signaling pathway or loss of Cl I expression



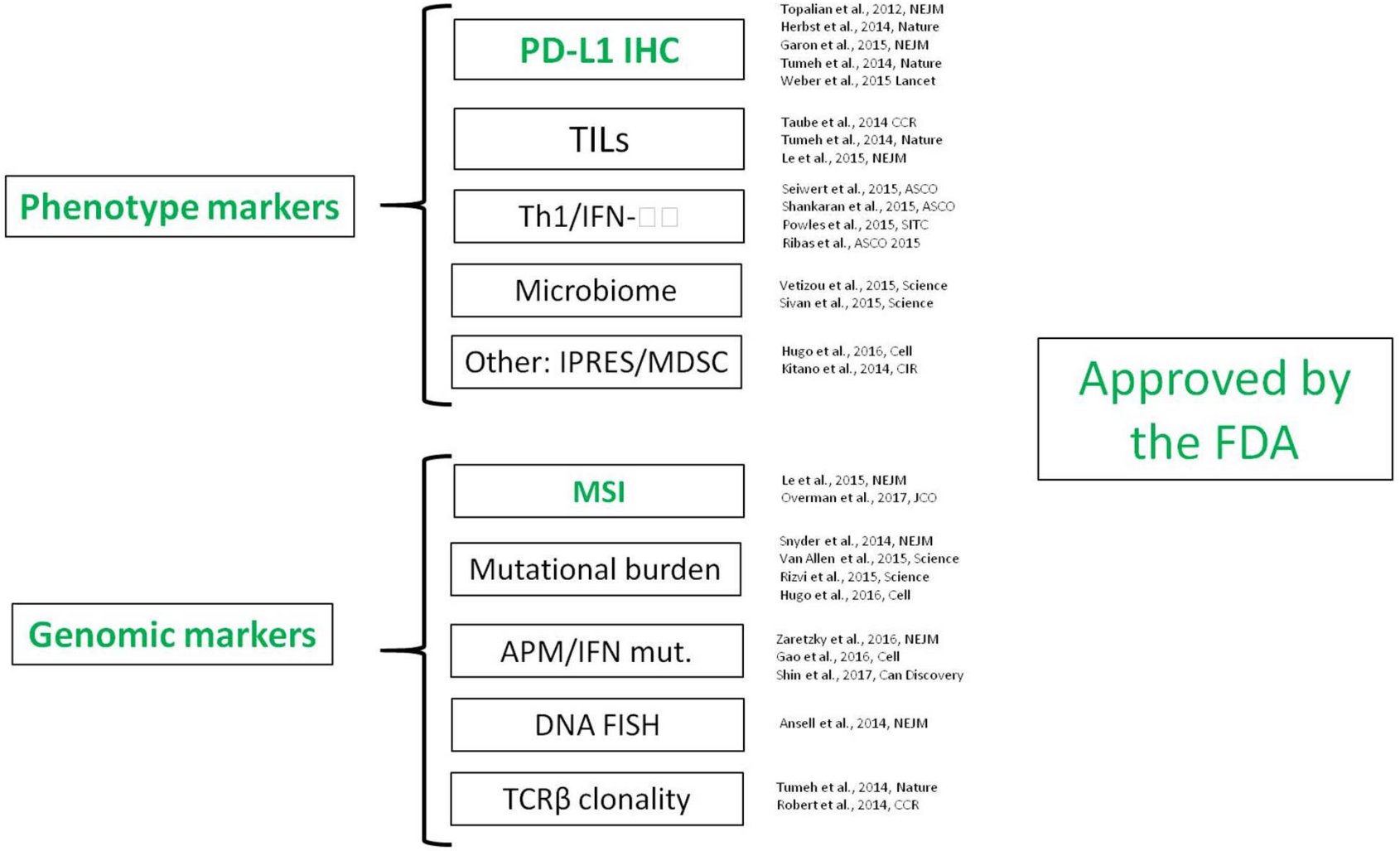


Zaretsky et al, NEJM 2016; Gao et al et al, Cell 2016, Sucker et al Nat Com 2017; Shin et al Cancer Discocery 2017

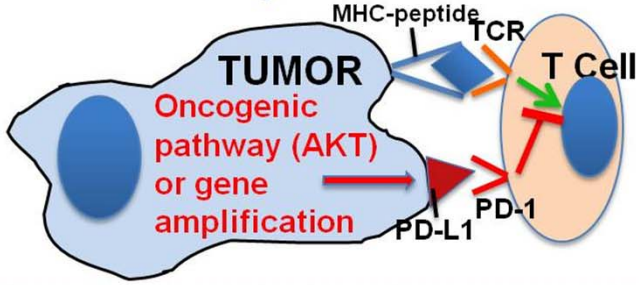
Innate anti-PD-1 signature (IPRES) for primary resistance



Hugo et al, Cell 2016

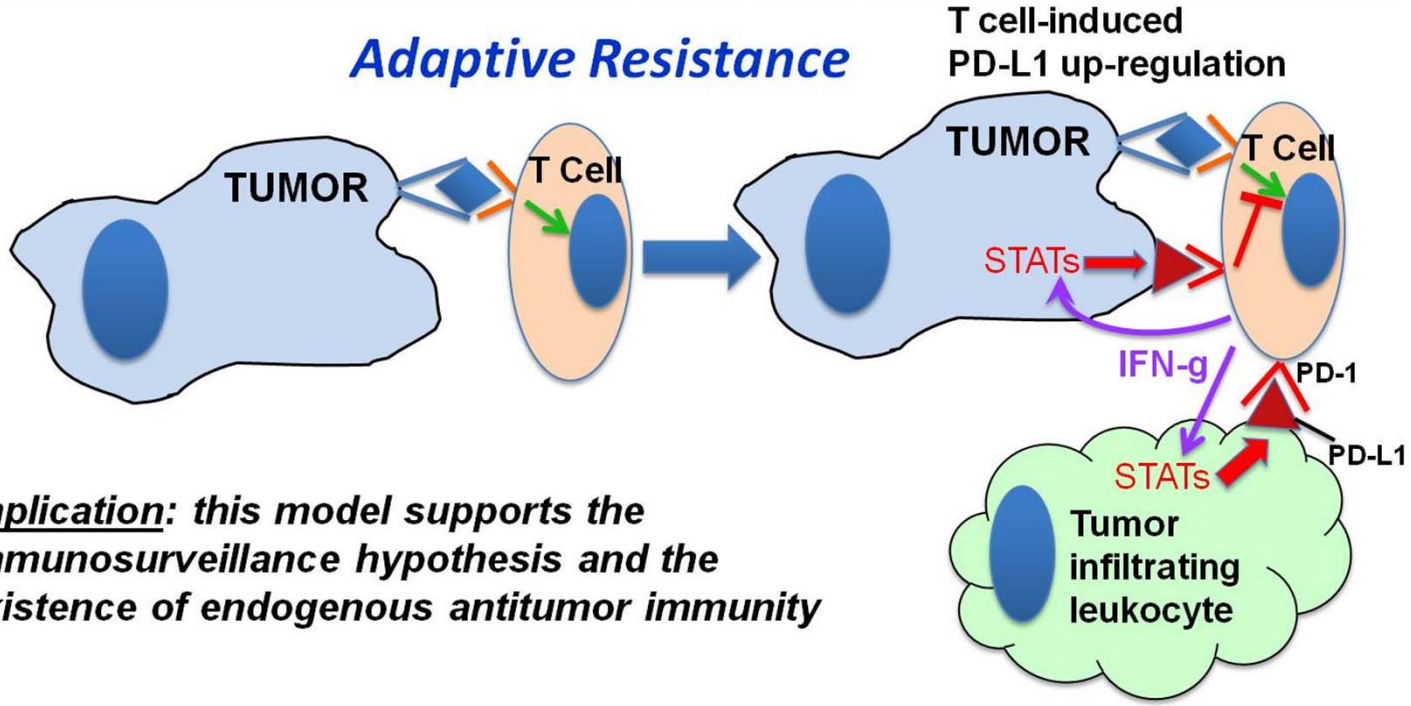

Phenotype markers
PD-L1 IHC
Topalian et al., 2012, NEJM
Herbst et al., 2014, Nature
Garon et al., 2015, NEJM
Tumeh et al., 2014, Nature
Weber et al., 2015 Lancet
TILs
Taube et al., 2014 CCR
Tumeh et al., 2014, Nature
Le et al., 2015, NEJM
Th1/IFN-□□
Seiwert et al., 2015, ASCO
Shankaran et al., 2015, ASCO
Powles et al., 2015, SITC
Ribas et al., ASCO 2015
Microbiome
Vetizou et al., 2015, Science
Sivan et al., 2015, Science
Other: IPRES/MDSC
Hugo et al., 2016, Cell
Kitano et al., 2014, CIR
Genomic markers
MSI
Le et al., 2015, NEJM
Overman et al., 2017, JCO
Mutational burden
Snyder et al., 2014, NEJM
Van Allen et al., 2015, Science
Rizvi et al., 2015, Science
Hugo et al., 2016, Cell
APM/IFN mut.
Zaretzky et al., 2016, NEJM
Gao et al., 2016, Cell
Shin et al., 2017, Can Discovery
DNA FISH
Ansell et al., 2014, NEJM
TCRβ clonality
Tumeh et al., 2014, Nature
Robert et al., 2014, CCR
Approved by the FDA

Innate (tumor cell intrinsic) Resistance



Constitutive tumor signaling induces PD-L1 on tumor cells

Adaptive Resistance



- ***<u>Implication</u>: this model supports the immunosurveillance hypothesis and the existence of endogenous antitumor immunity***

TRACTAMENTS

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