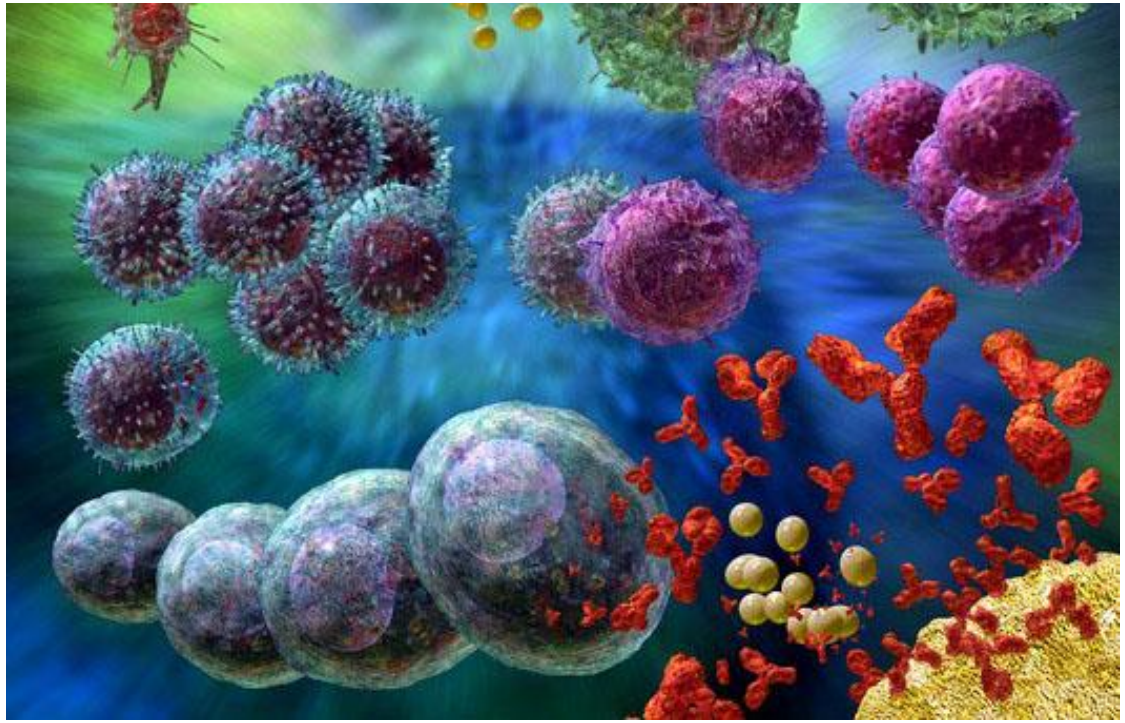


Il melanoma

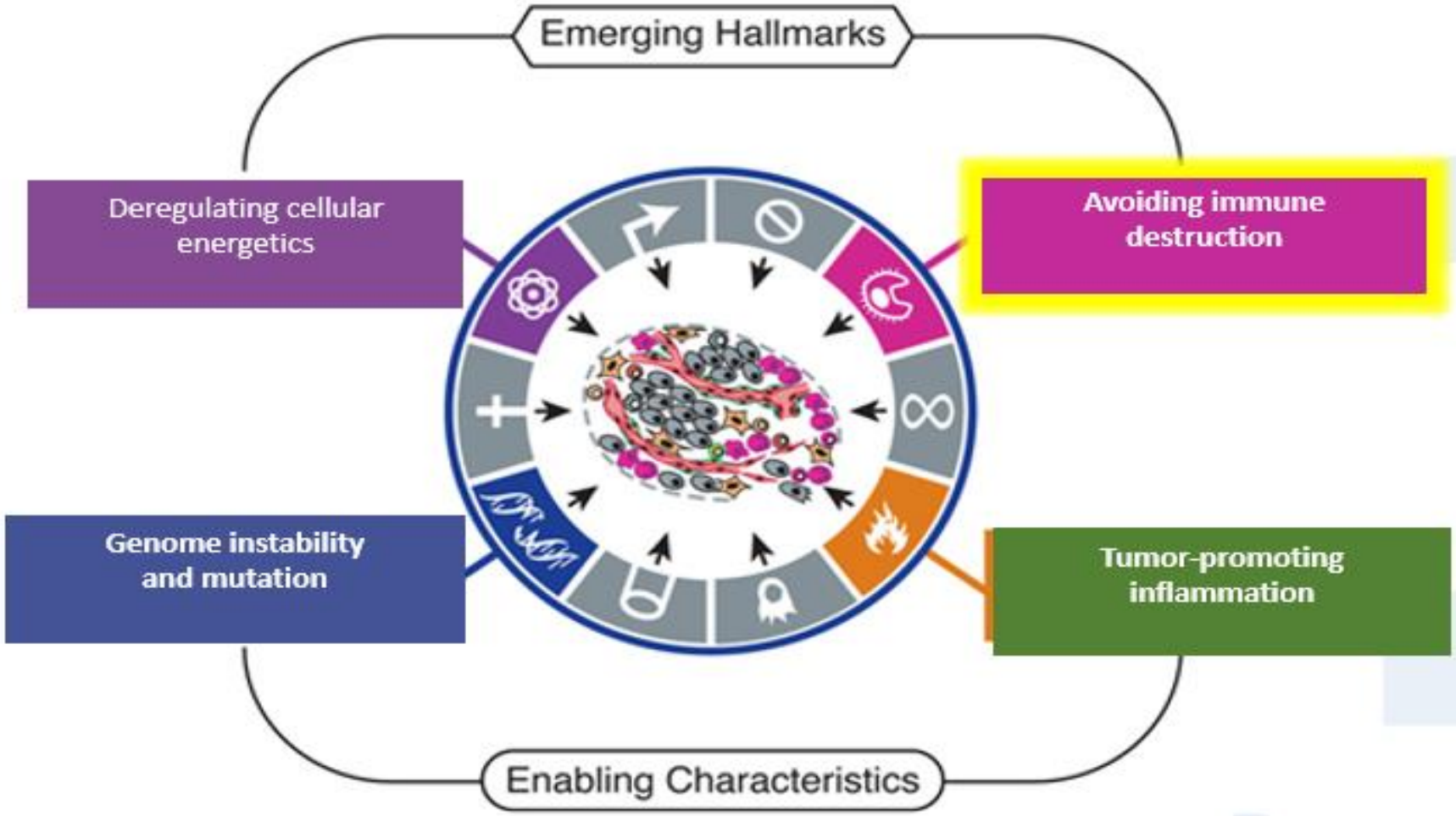
Vanna Chiarion Sileni
vanna.chiarion@iov.veneto.it

AGENDA

- ✓Using the immune system to fight melanoma
- ✓Where we are in melanoma treatment
- ✓Where we are going

Hallmarks of cancer cells 2011

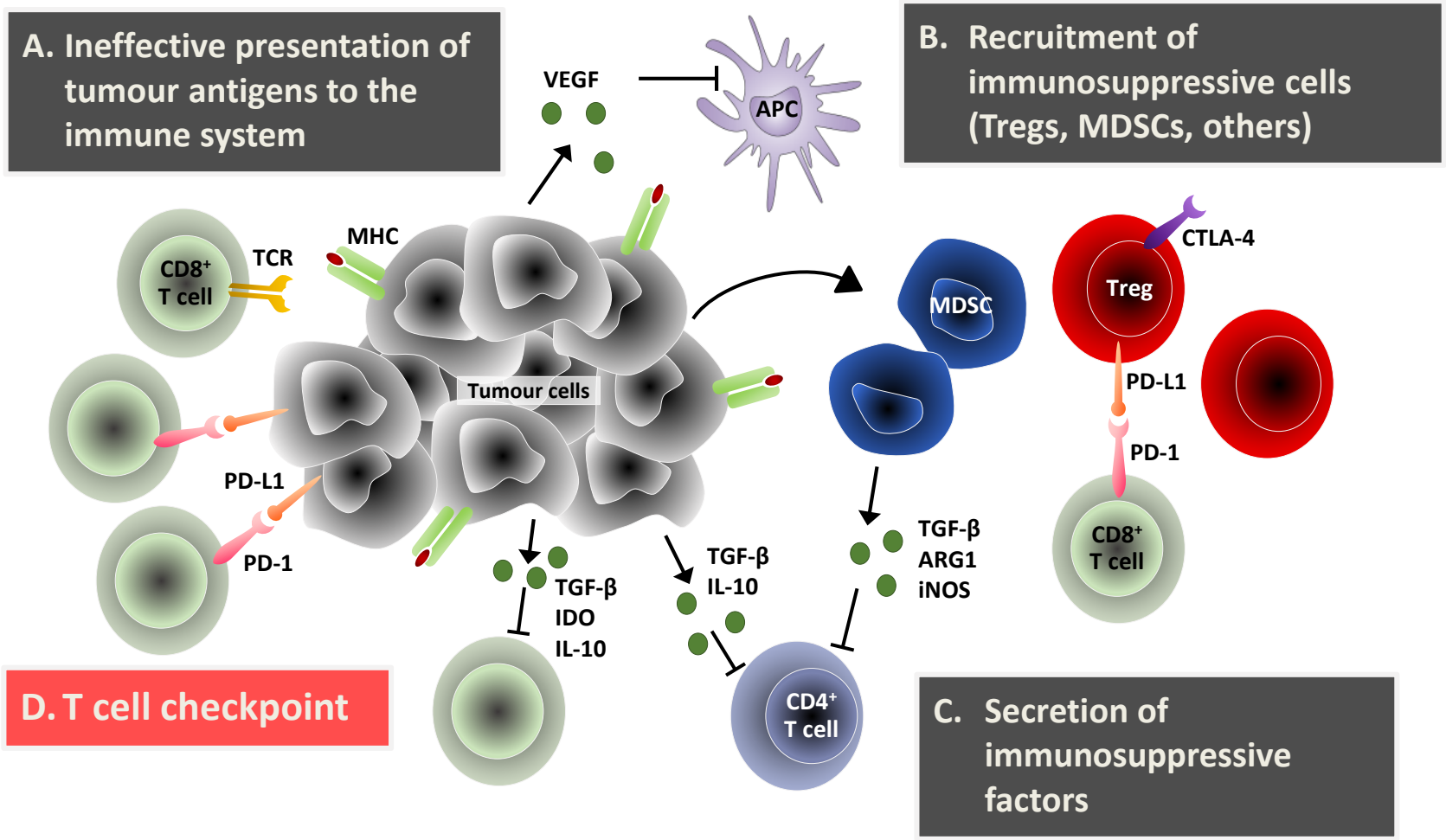
The role of tumor microenvironment and immunity



Hanahan and Weinberg, Cell, 2011

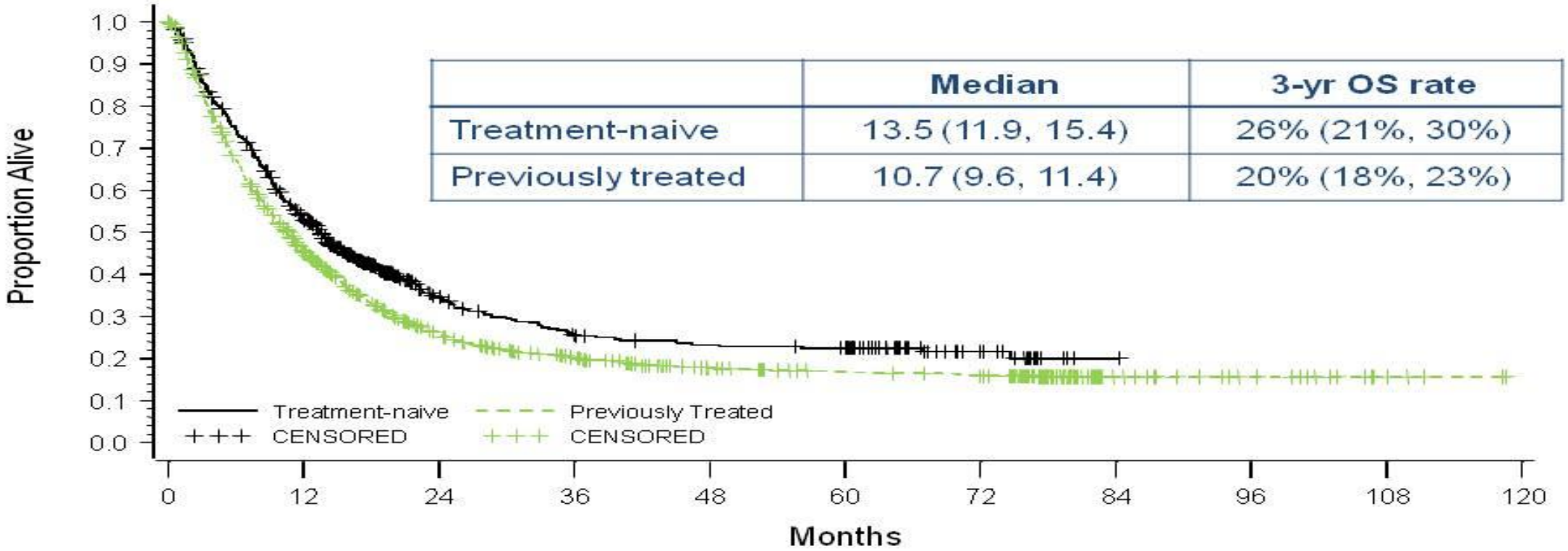
Tumours Use Various Mechanisms to Escape the Immune System

Immune escape mechanisms are complex and frequently overlapping



Vesely MD, et al. Ann Rev Immunol 2011;29:235–71

Subset Ipilimumab OS Analyses by Prior Therapy (N=1861)*



	Median	3-yr OS rate
Treatment-naive	13.5 (11.9, 15.4)	26% (21%, 30%)
Previously treated	10.7 (9.6, 11.4)	20% (18%, 23%)

Patients at Risk

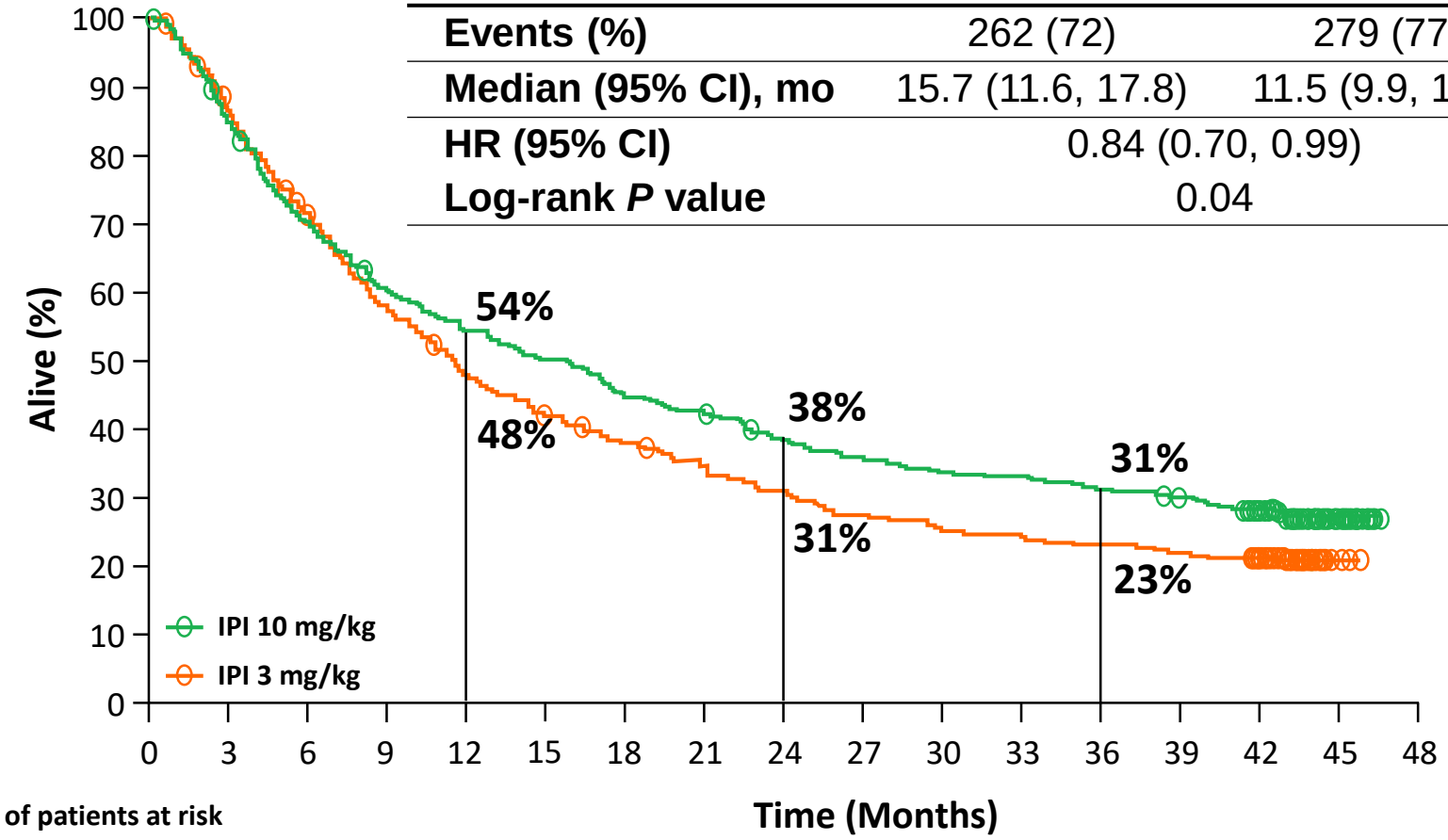
Treatment-naive	604	301	106	74	64	60	18	1	0	0	0
Previously treated	1257	538	264	180	128	110	102	25	15	5	0

*Non-randomized subset analyses.

Presented By Axel Hauschild at 2014 ASCO Annual Meeting

OS: Randomized Patients

OS	IPI 10 mg/kg n = 365	IPI 3 mg/kg n = 362
Events (%)	262 (72)	279 (77)
Median (95% CI), mo	15.7 (11.6, 17.8)	11.5 (9.9, 13.3)
HR (95% CI)	0.84 (0.70, 0.99)	
Log-rank *P* value	0.04	



Number of patients at risk

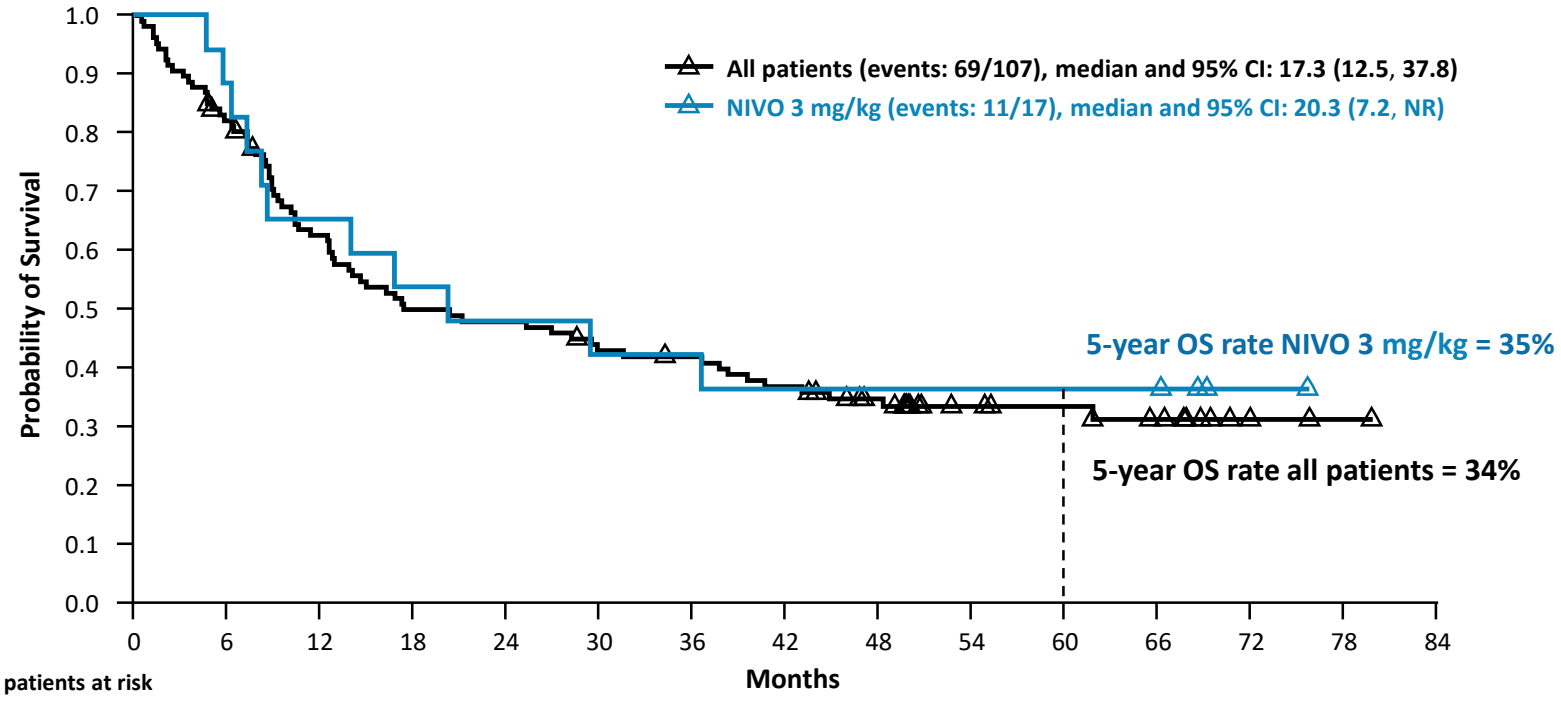
IPI 10 mg/kg	365	306	253	217	196	181	161	151	137	126	120	118	111	105	94	16	0
IPI 3 mg/kg	362	310	253	205	168	146	131	118	107	95	87	83	80	76	71	8	0

CI = confidence interval.

Minimum OS follow-up: ~43 mo

NIVO Monotherapy: 5-Year OS in *Pretreated* Patients (CA209-003)

- Data from long-term follow-up of phase 1 study

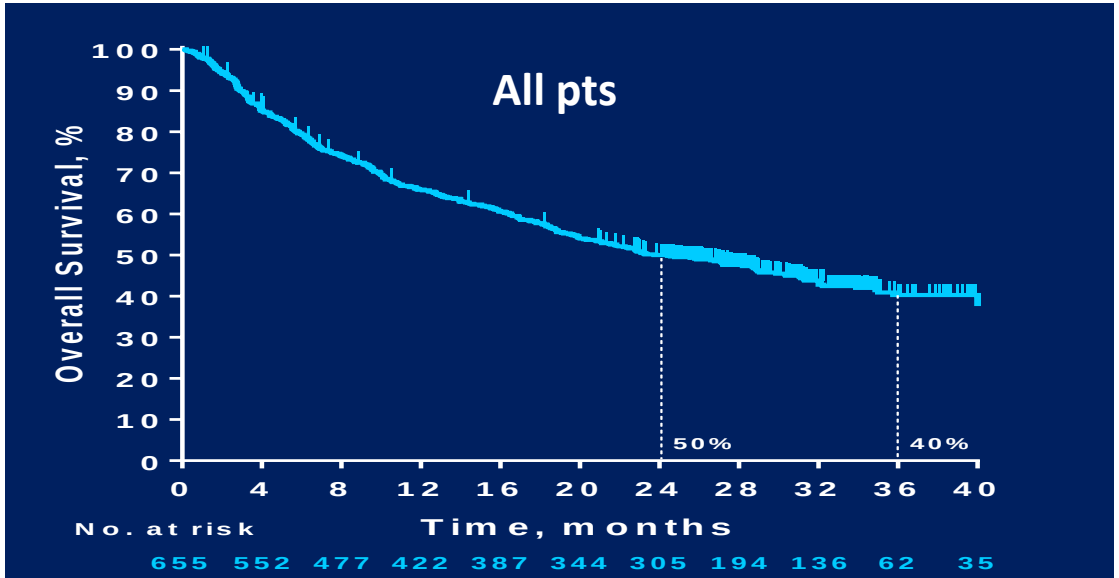


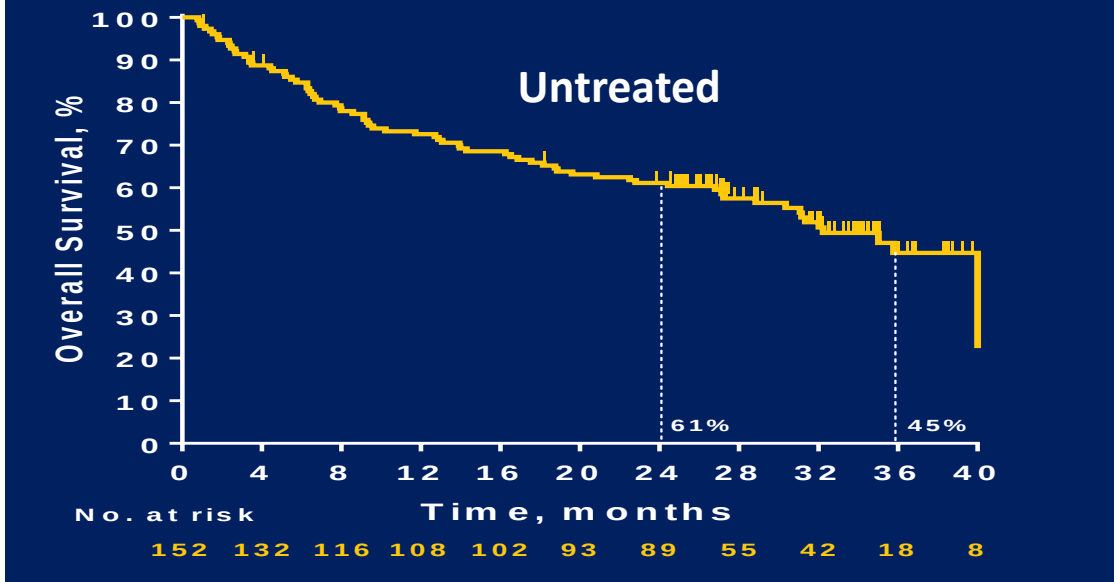
Number of patients at risk															
All patients	107	86	64	51	49	43	41	36	29	17	15	12	3	1	0
NIVO 3 mg/kg	17	15	11	9	8	7	7	6	6	6	6	6	1	0	

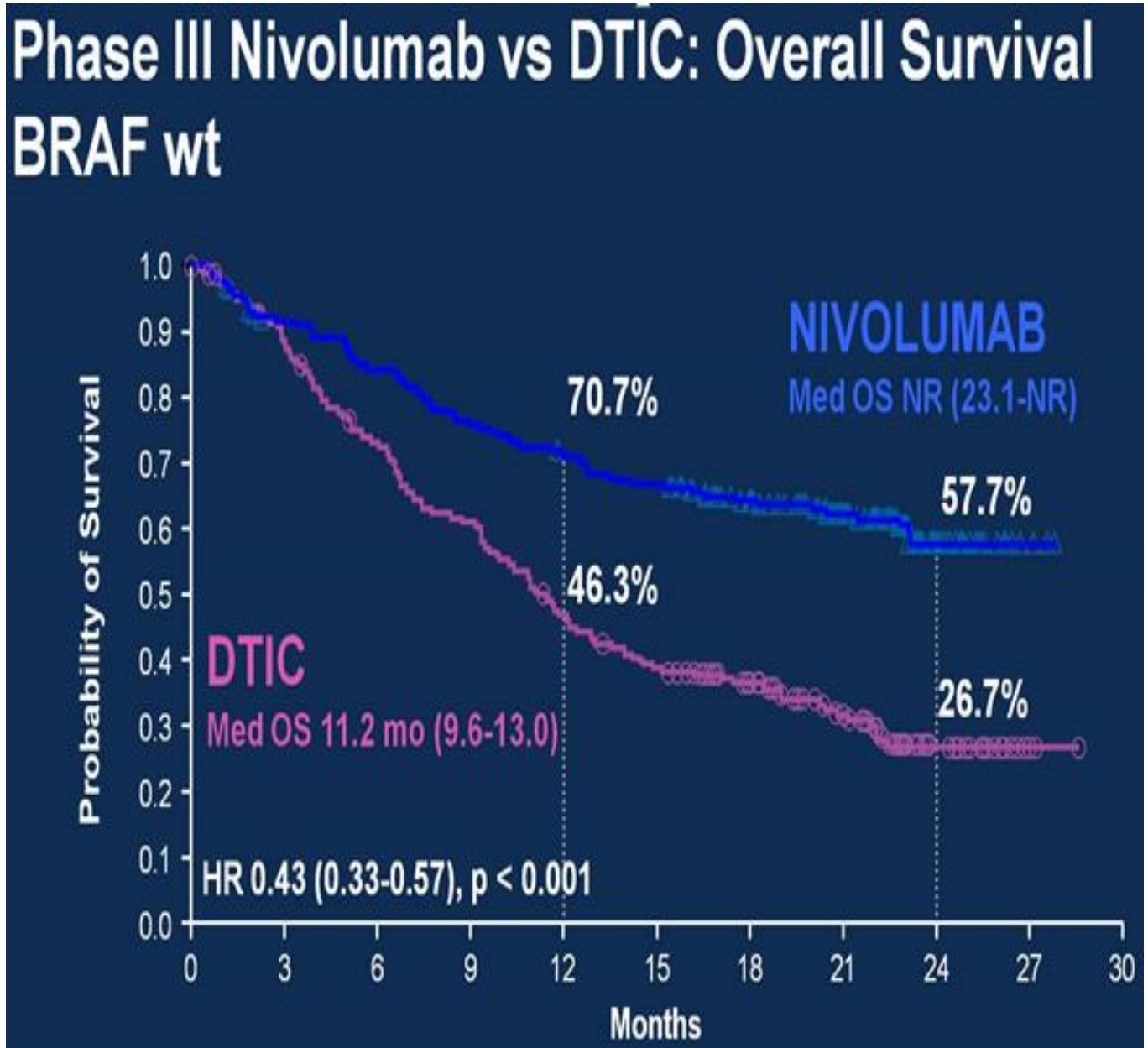
1. Hodi FS et al. Presented at AACR 2016; abstract CT001. 2. Topalian SL et al. *N Engl J Med*. 2012;366:2443-2454

Better activity and efficacy in untreated patients

3-Year OS With Pembrolizumab KEYNOTE-001



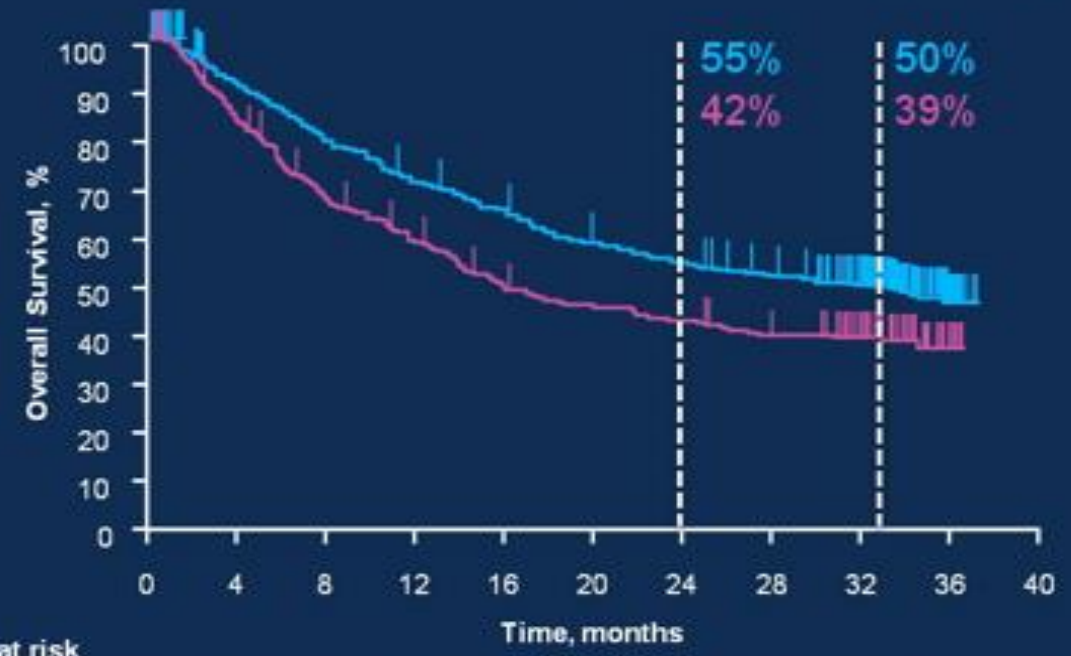




Kaplan-Meier Estimates of Survival in Total Population (Median Follow-Up, 33.9 mo)

OS

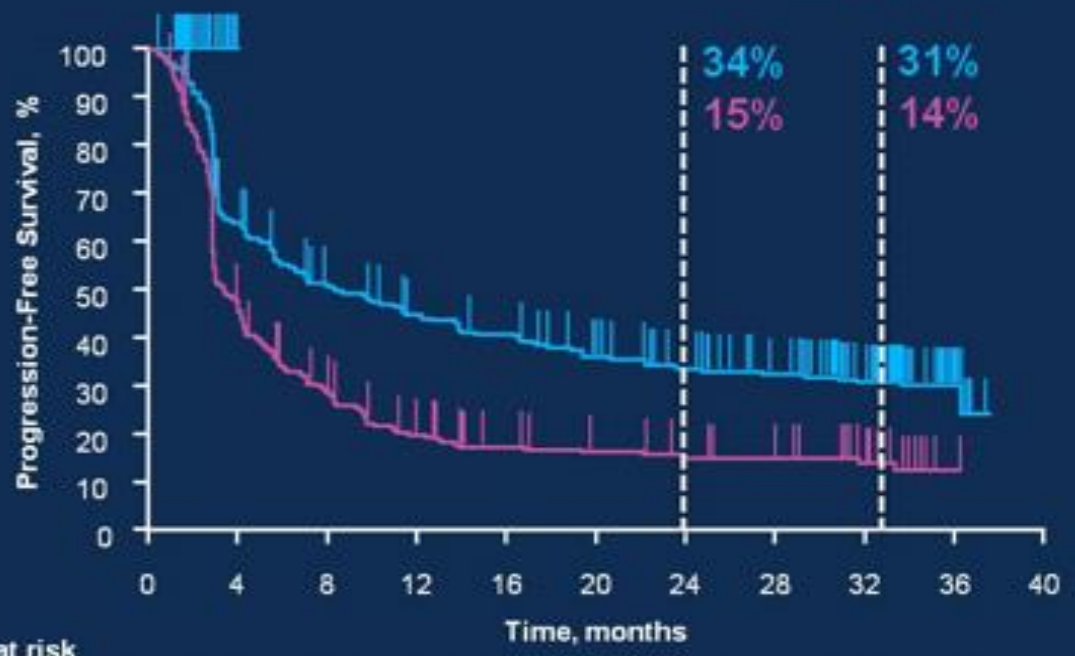
Arm	Events, n	HR (95% CI)	Median, mo (95% CI)
Pembrolizumab	278	0.70 (0.58-0.86)	32.3 (24.5-NR)
Ipilimumab	155	—	15.9 (13.3-22.0)



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)



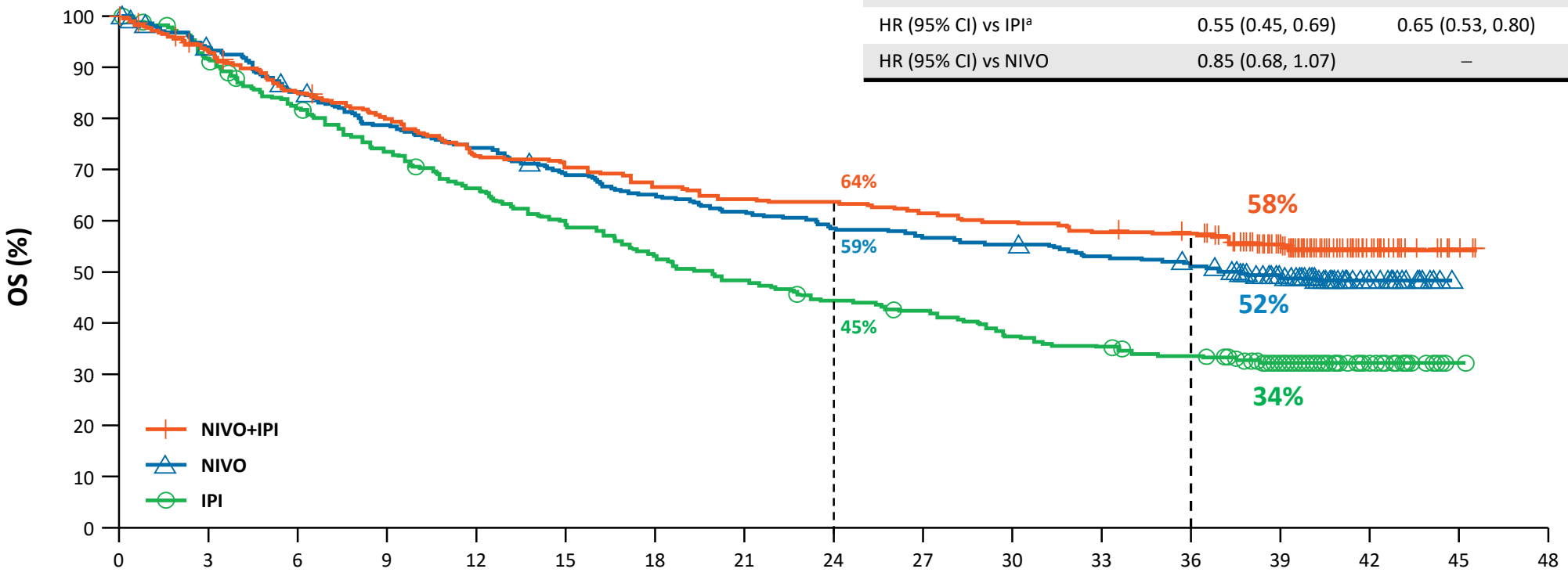
No. at risk											
Pembrolizumab	556	347	269	231	211	182	155	138	88	12	0
Ipilimumab	278	110	64	40	32	27	23	20	14	2	0

ASCO 2017

Checkmate-067: OS Intent-to-Treat

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, months (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]$P < 0.001$.

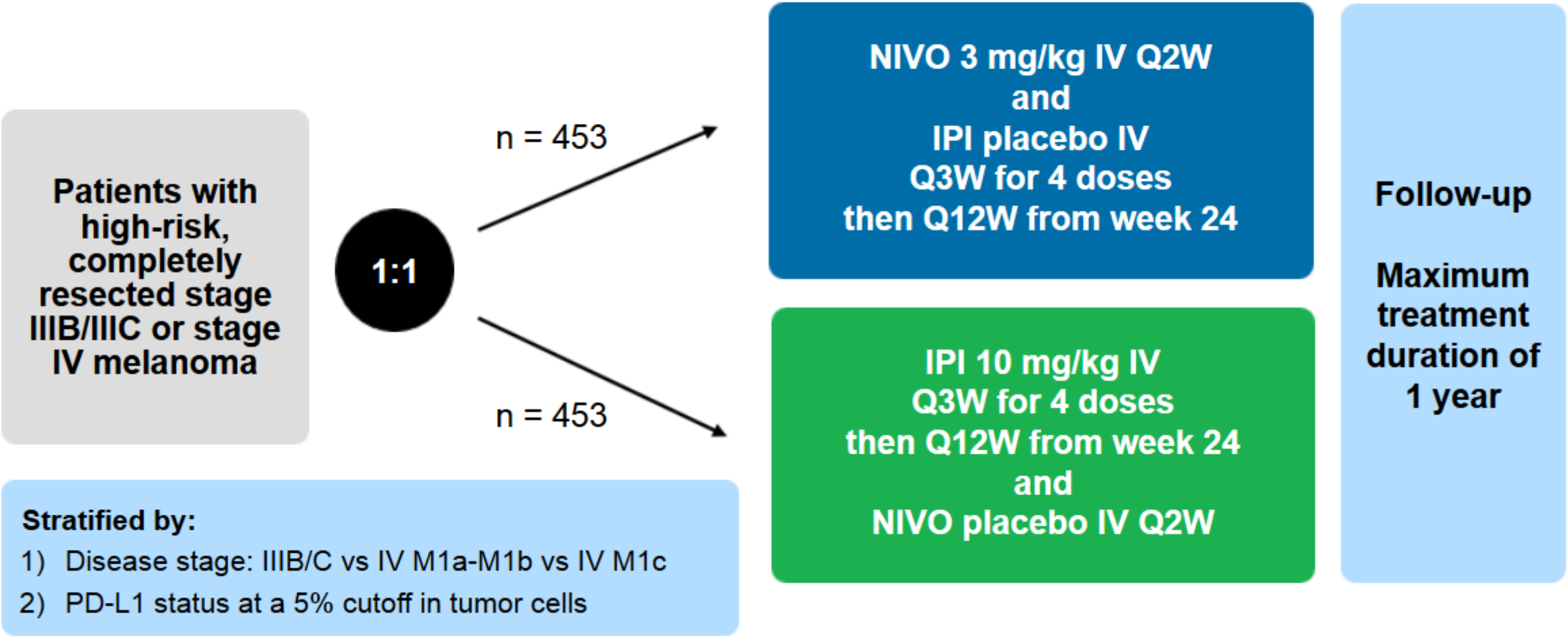


Patients at risk:

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	113	107	100	68	20	2	0

Database lock: May 24, 2017. Minimum follow-up of 36 months.
Adapted from Wolchok JD et al. *N Engl J Med.* 2017;Sep 11. doi: 10.1056/NEJMoa1709684. [Epub ahead of print].

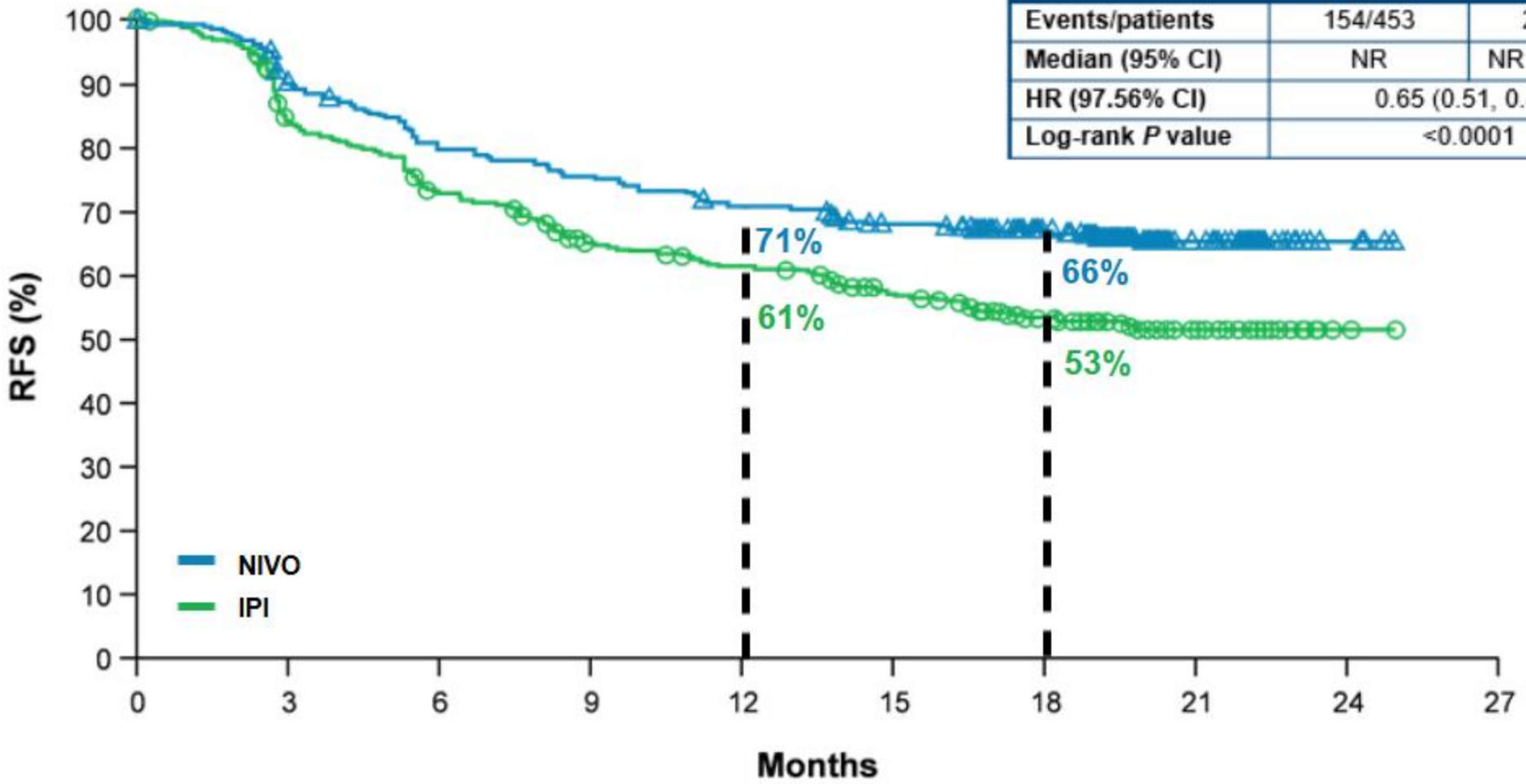
CA209-238: Study Design



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

Primary Endpoint: RFS

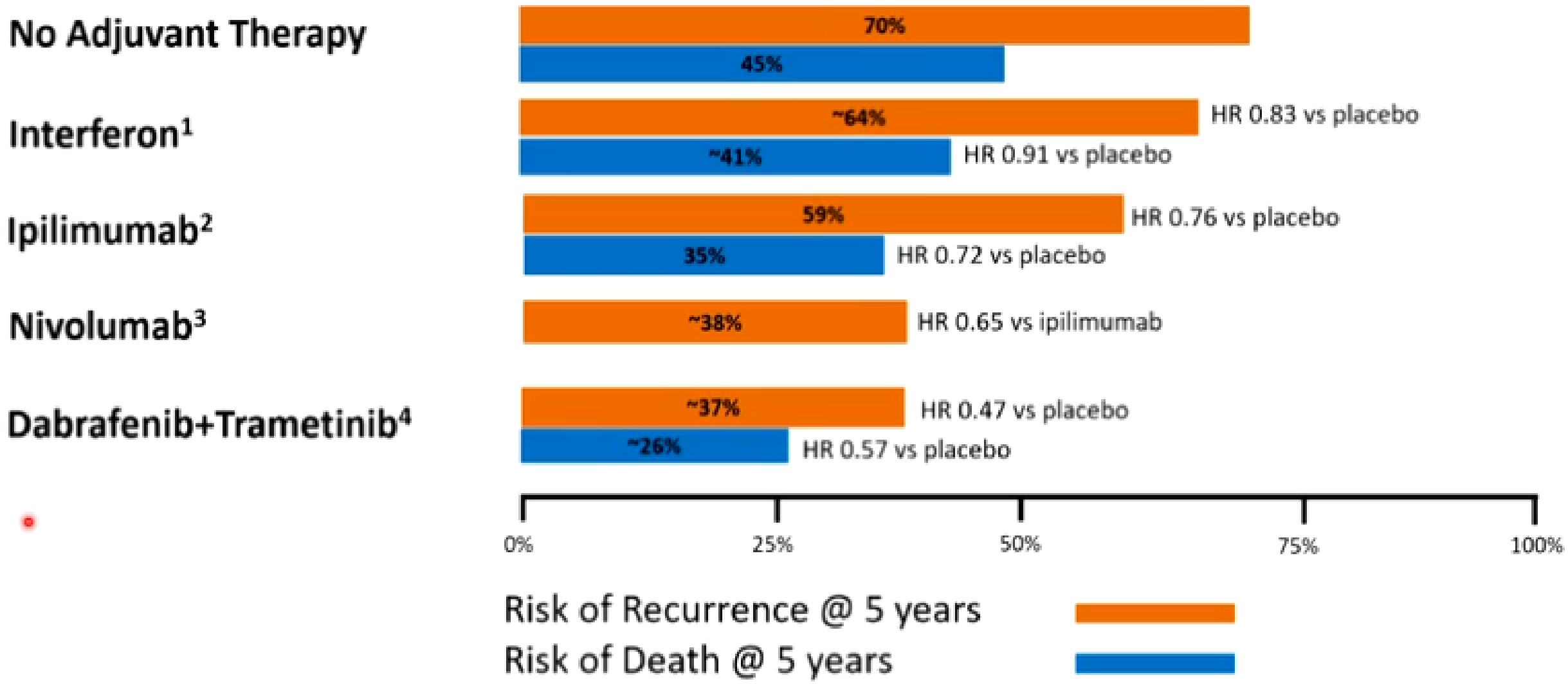
	NIVO	IPI
Events/patients	154/453	206/453
Median (95% CI)	NR	NR (16.6, NR)
HR (97.56% CI)	0.65 (0.51, 0.83)	
Log-rank *P* value	<0.0001	



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

Stage III Melanoma & Adjuvant Systemic Therapy



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

Melanoma Institute Australia

A Randomized Phase 2 Study of Nivolumab or Nivolumab plus Ipilimumab in Patients with Melanoma Brain Metastases: The Anti-PD1 Brain Collaboration (ABC)

Georgina V. Long, Victoria Atkinson, Alexander M. Menzies, Serigne Lo, Alexander Guminski, Michael P. Brown, Maria Gonzalez, Katrina Diamante, Shahneen Sandhu, Richard A. Scolyer, Louise Emmett, Grant A. McArthur.

ASCO ANNUAL MEETING '17 #ASCO17 Presented by Georgina V. Long

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]

[1]University of Texas, MD Anderson Cancer Center, Houston, TX, USA, [2]Moffitt Cancer Center and Research Institute, Tampa, FL, USA, [3]University of California-San Francisco, San Francisco, CA, USA, [4]The Angeles Clinic and Research Institute, Los Angeles, CA, USA, [5]Dana-Farber Cancer Institute, Boston, MA, USA, [6]University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA, [7]University of Colorado Comprehensive Cancer Center, Aurora, CO, USA, [8]University of Michigan, Ann Arbor, MI, USA, [9]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA, [10]Georgetown-Lombardi Comprehensive Cancer Center, Washington DC, USA, [11]Roswell Park Cancer Institute, Buffalo, NY, USA, [12]Winship Cancer Institute of Emory University, Atlanta, GA, USA, [13]Stanford University Hospital, Palo Alto, CA, USA, [14]University of Pittsburgh Medical Center, Pittsburgh, PA, USA, [15]Bristol-Myers Squibb, Princeton, NJ, USA, [16]Department of Medical Oncology, City of Hope, Duarte, CA, USA

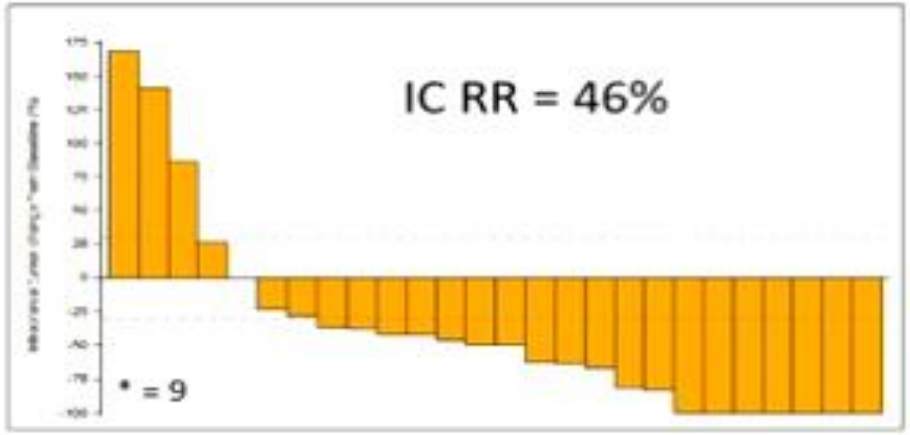
ASCO ANNUAL MEETING '17 #ASCO17 Abstract Number 9507

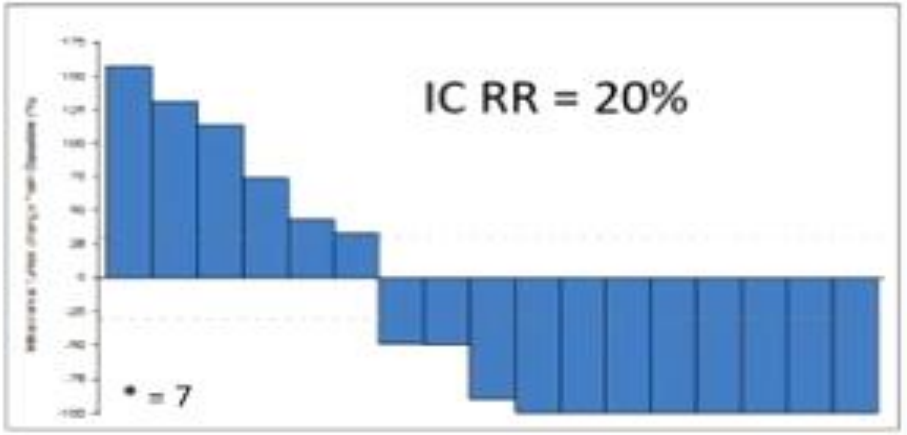
Intracranial Response

Cohort A: Nivo+Ipi

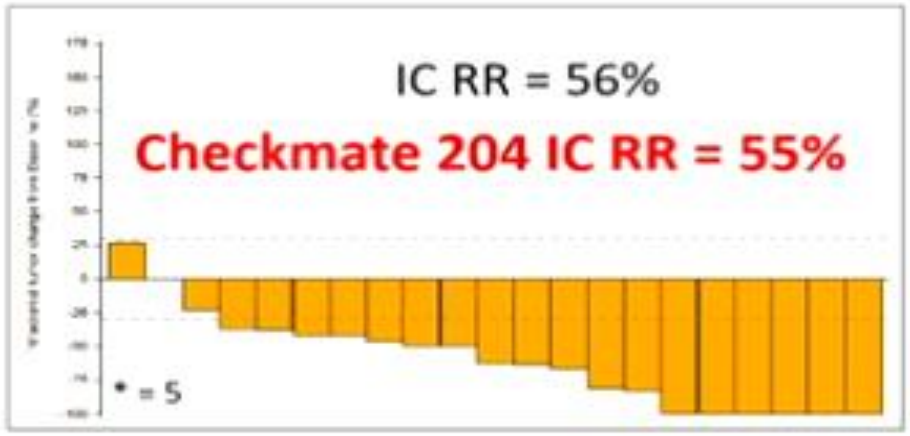
Cohort B: Nivo alone

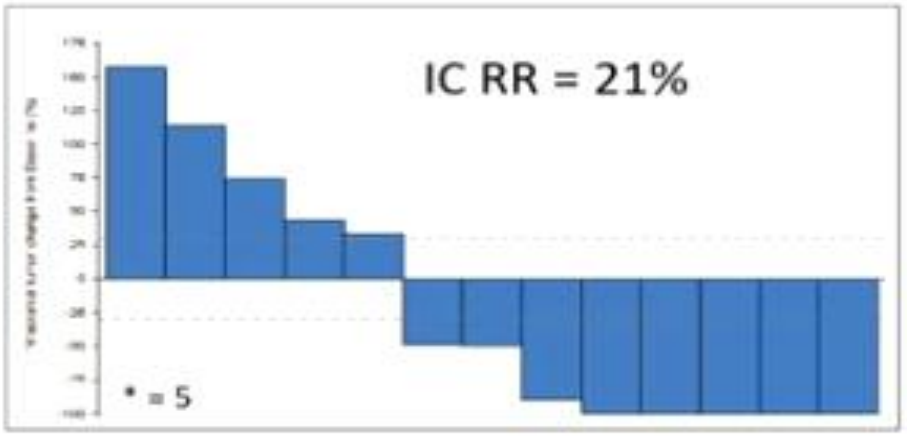
All Patients





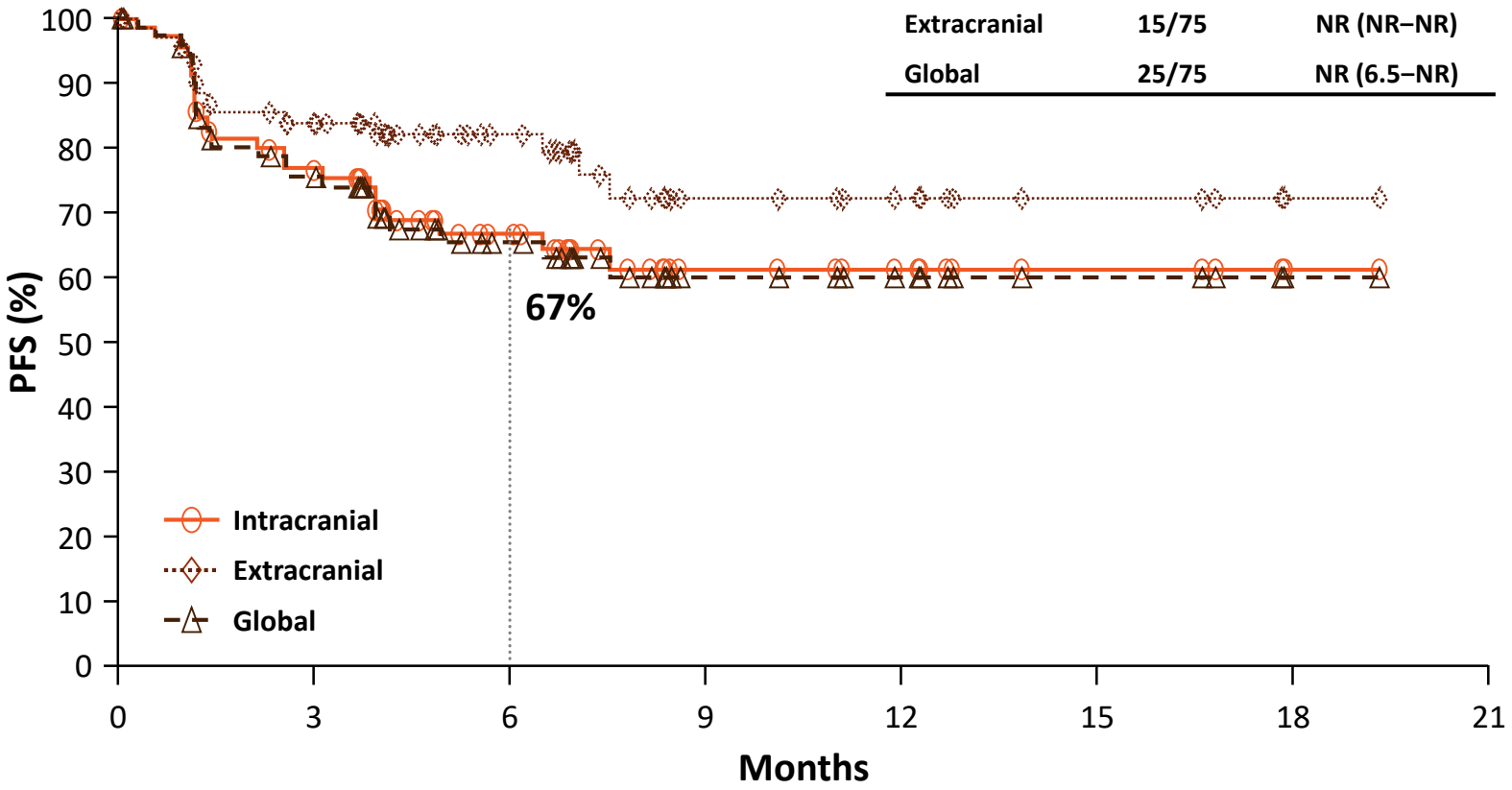
BRAF/MEKi Naive





PFS

	Events/patients	Median (95% CI)
Intracranial	24/75	NR (7.5–NR)
Extracranial	15/75	NR (NR–NR)
Global	25/75	NR (6.5–NR)

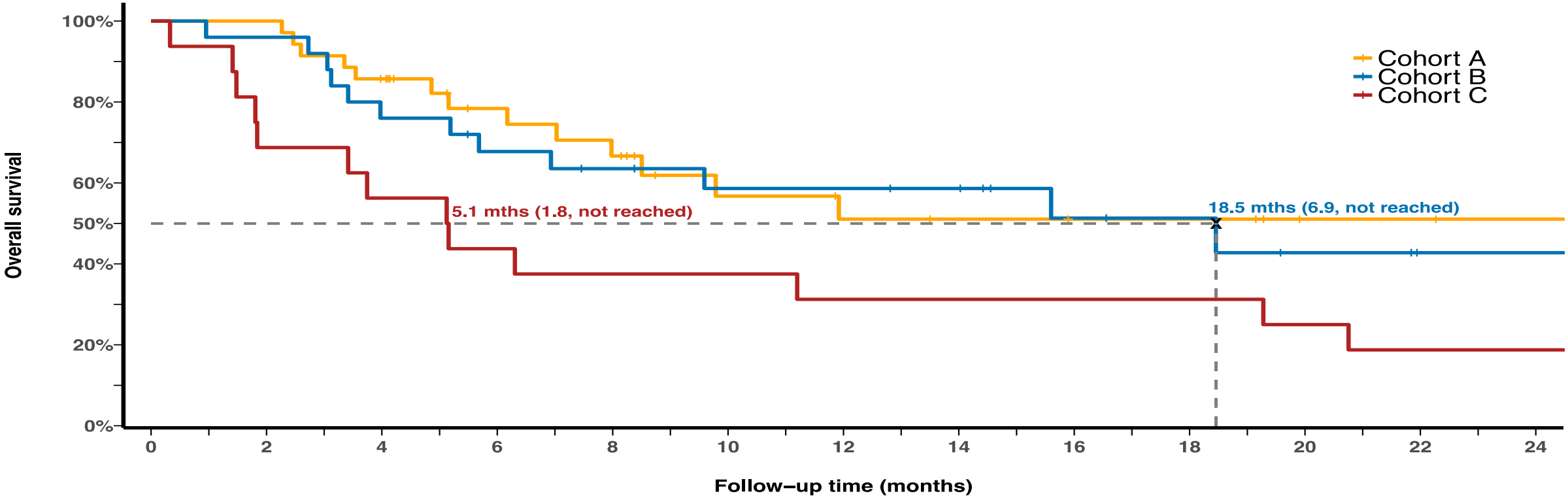


Number of patients at risk

Intracranial	75	50	30	14	10	5	1	0
Extracranial	75	52	31	14	10	5	1	0
Global	75	49	29	14	10	5	1	0

Overall Survival ABC study

	A: Nivo+Ipi N=35	B: Nivo N=25	C: Nivo N=12
Total Nº Events, n (%)	13 (37%)	12 (48%)	13 (81%)
Med. OS, mo (95% CI)	**NR (8.5 – NR)**	**18.5 (6.9 – NR)**	5.1 (1.8– NR)
6-mo OS rate, % (95% CI)	78% (65 – 94)	68% (52 – 89)	44% (25 – 76)



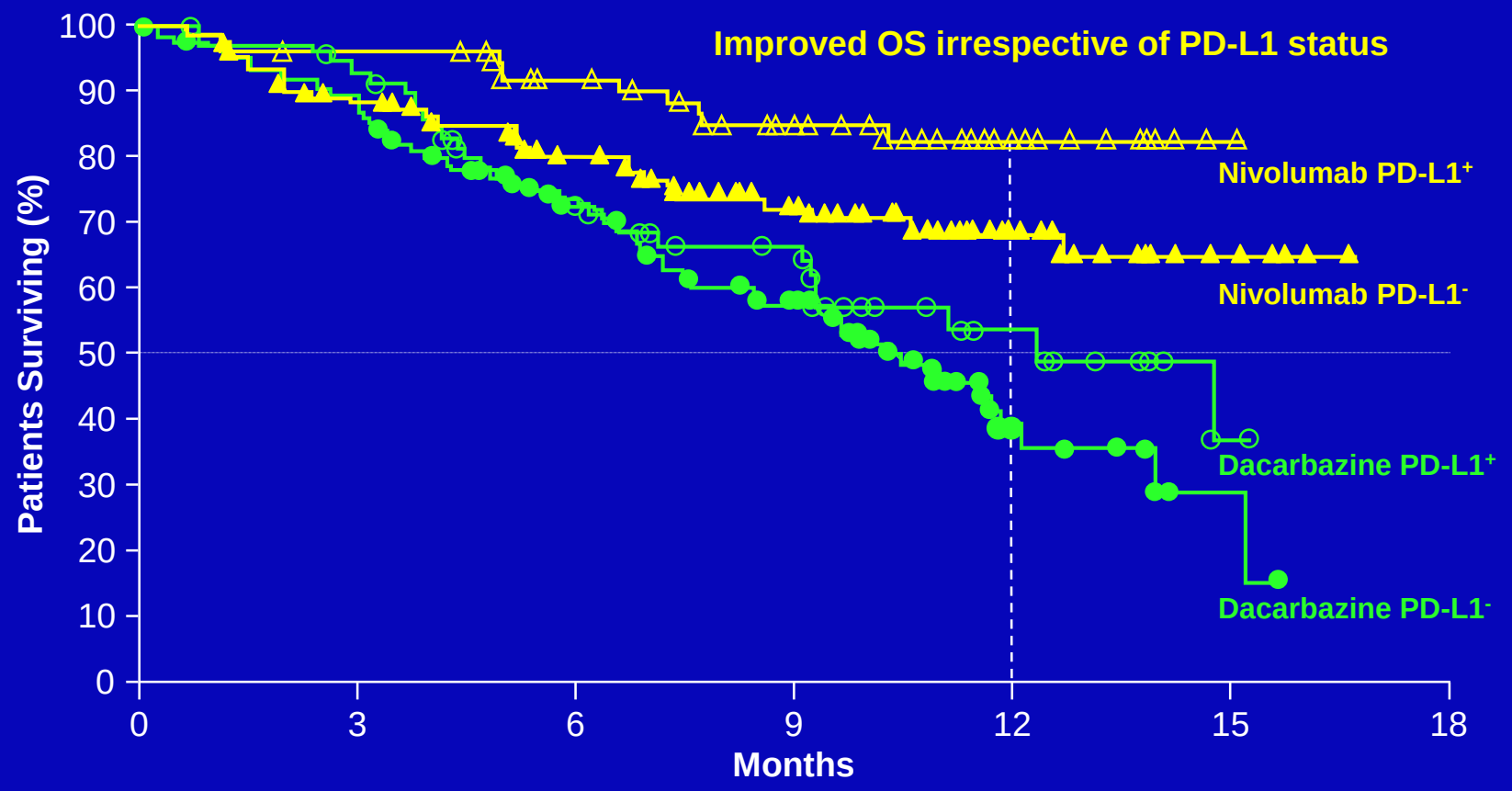
Numbers at risk (cumulative number of censored)

Cohort A	35 (0)	35 (0)	28 (2)	20 (8)	17 (8)	11 (12)	9 (13)	8 (14)	7 (15)	7 (15)	4 (18)	4 (18)	3 (19)
Cohort B	25 (0)	24 (0)	19 (0)	16 (1)	14 (2)	12 (3)	12 (3)	11 (4)	7 (7)	6 (8)	4 (9)	2 (11)	2 (11)
Cohort C	16 (0)	11 (0)	9 (0)	7 (0)	6 (0)	6 (0)	5 (0)	5 (0)	5 (0)	5 (0)	4 (0)	3 (0)	3 (0)

How to select ?

- ***Something simple (tumour volume/LDH)***
- ***Something solvable (PD-L1)***
- ***Something much more complex (tumour/immune interaction, T cell infiltration, gene signature, DNA repair deficiencies, mutation burden, gut microbiome….)***

OS by PD-L1 Status*



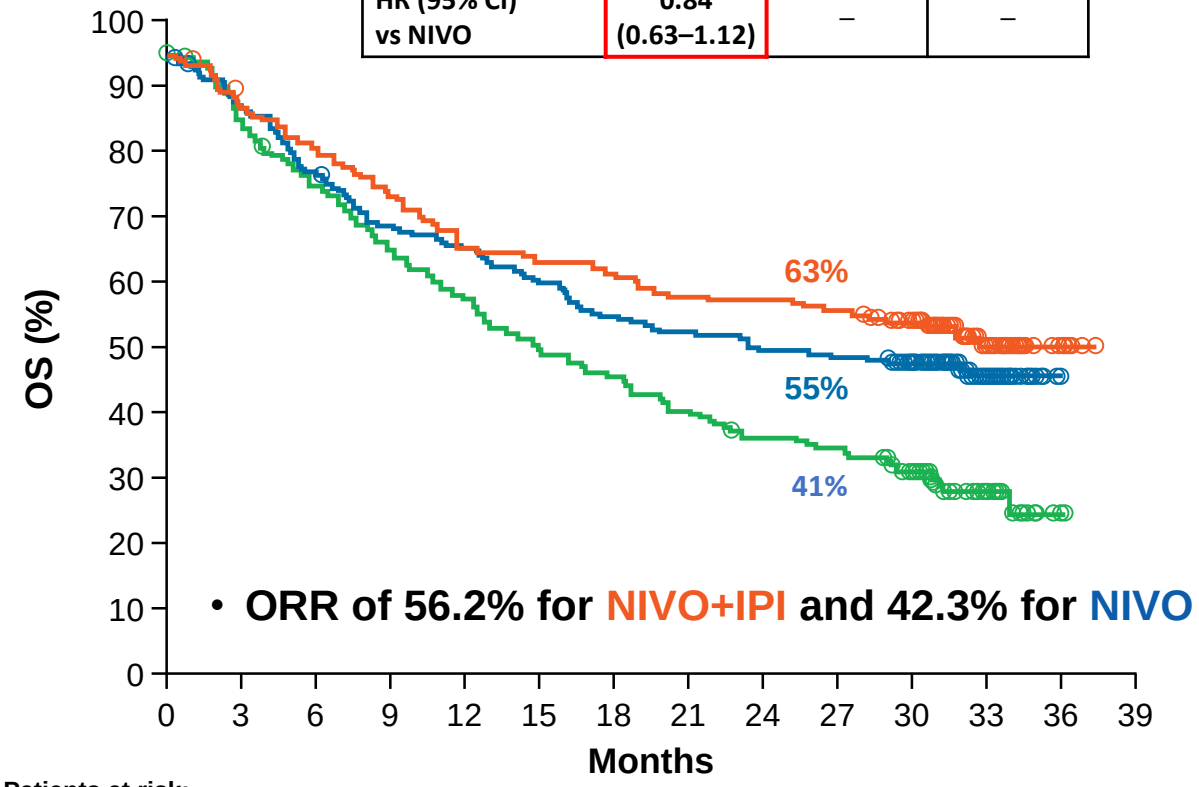
Patients at Risk							
Dacarbazine PD-L1$^-$	74	69	56	39	18	1	0
Nivolumab PD-L1$^-$	128	108	88	63	26	7	0
Dacarbazine PD-L1$^+$	74	64	44	30	11	1	0
Nivolumab PD-L1$^+$	126	107	78	52	11	2	0

*PD-L1 positive: ≥ 5% tumor cell surface staining. PD-L1 negative: < 5% tumor cell surface staining. NR=not reached.
Based on 5 August 2014 database lock.

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)	–	–



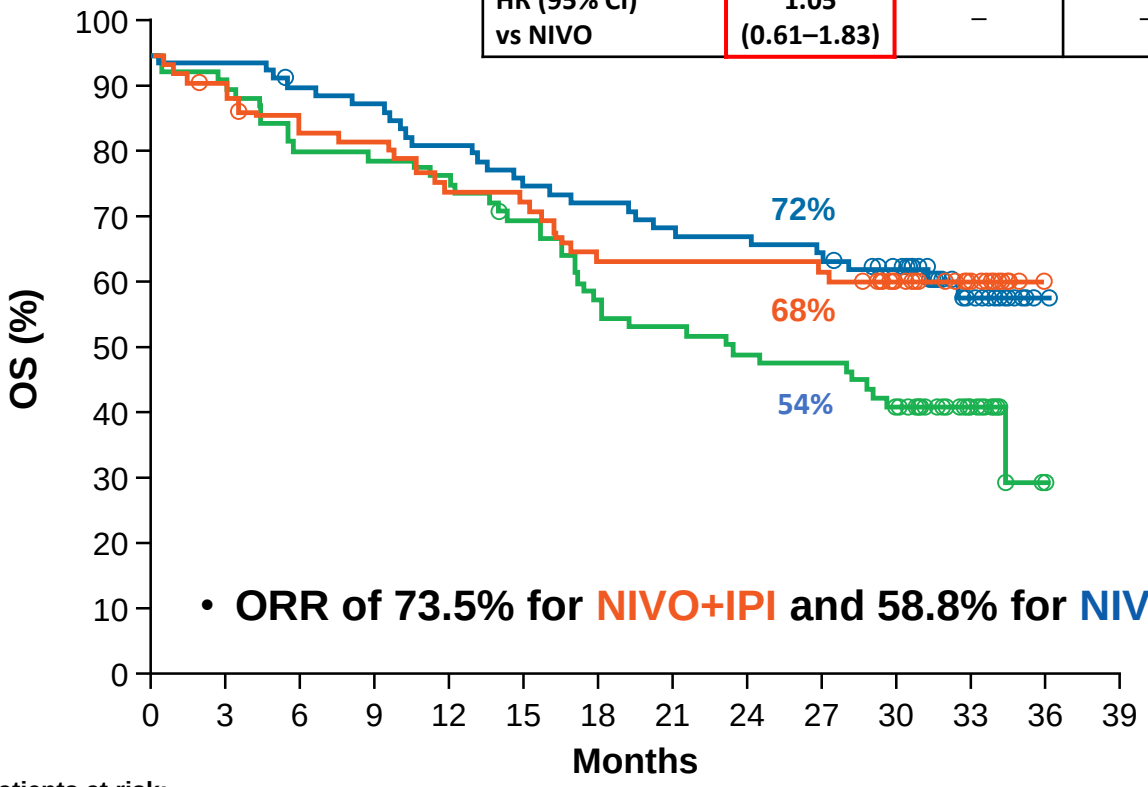
- ORR of 56.2% for NIVO+IPI and 42.3% for NIVO

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

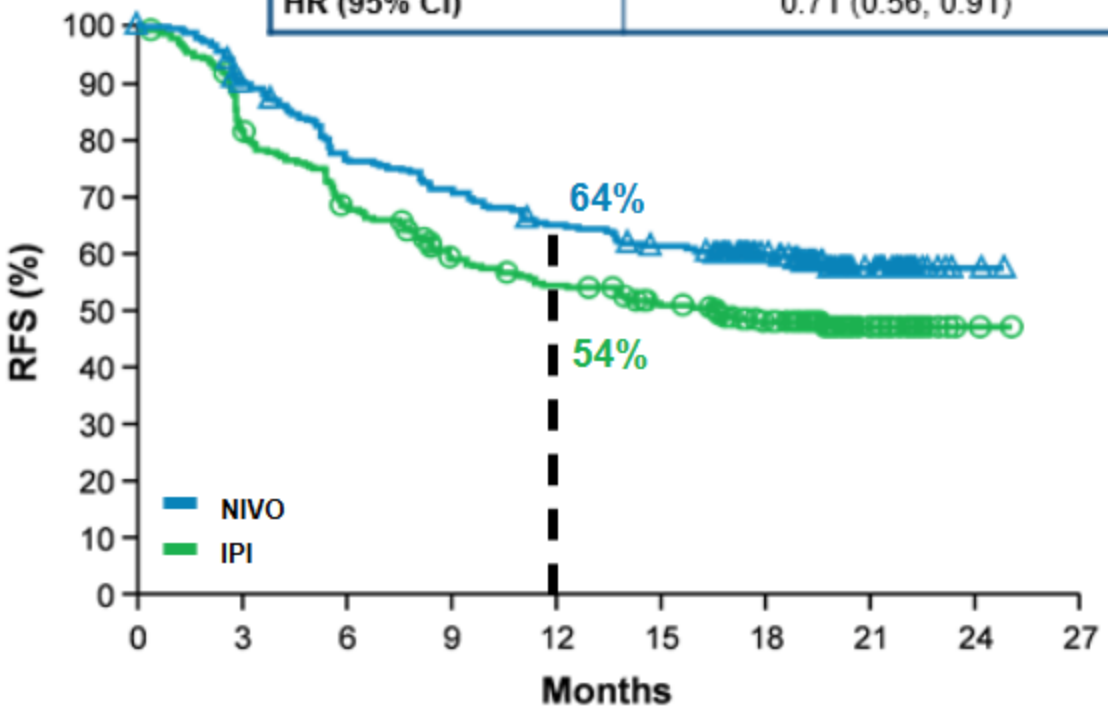
Patients at risk:

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

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)	

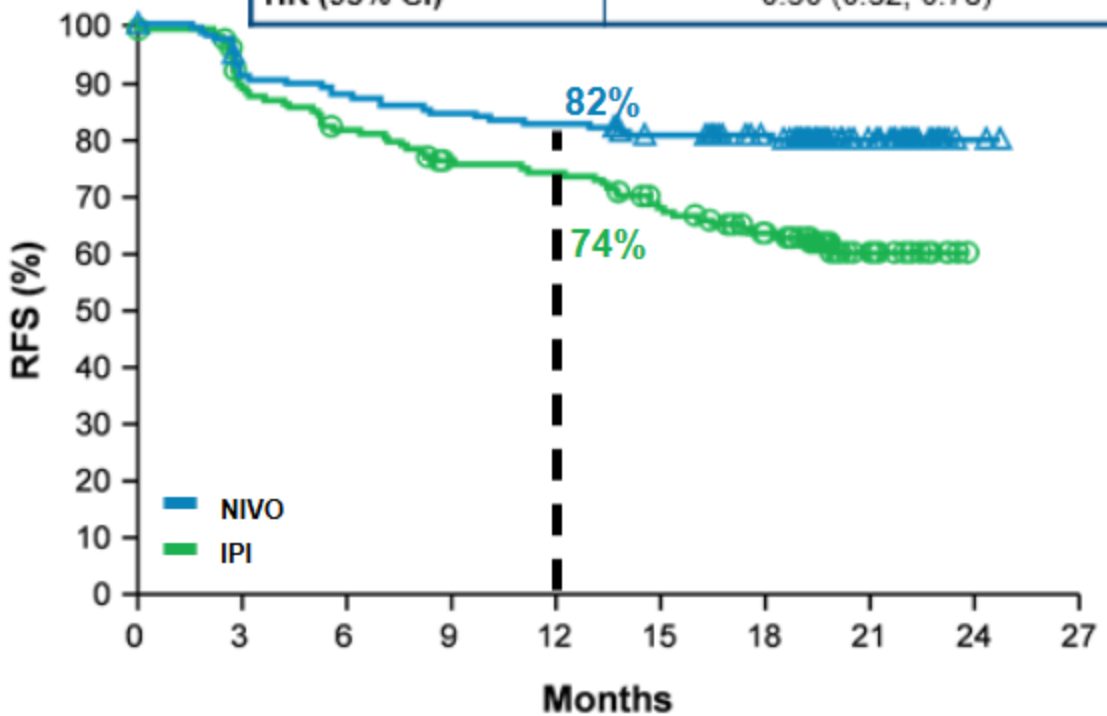


Number of patients at risk

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)	

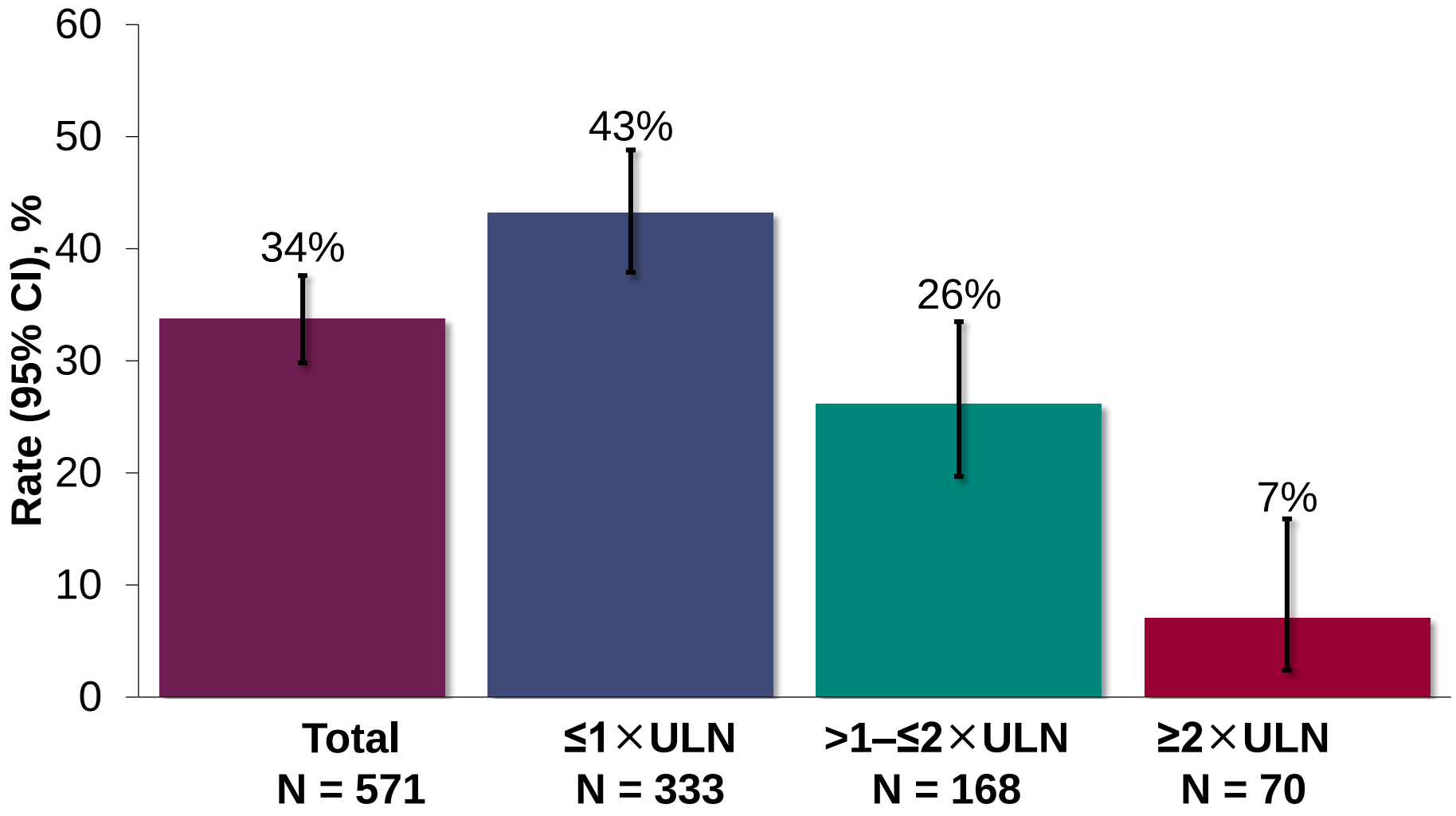


Number of patients at risk

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

Keynote 001 ORR: LDH ≤1 vs >1–≤2 vs >2×ULN

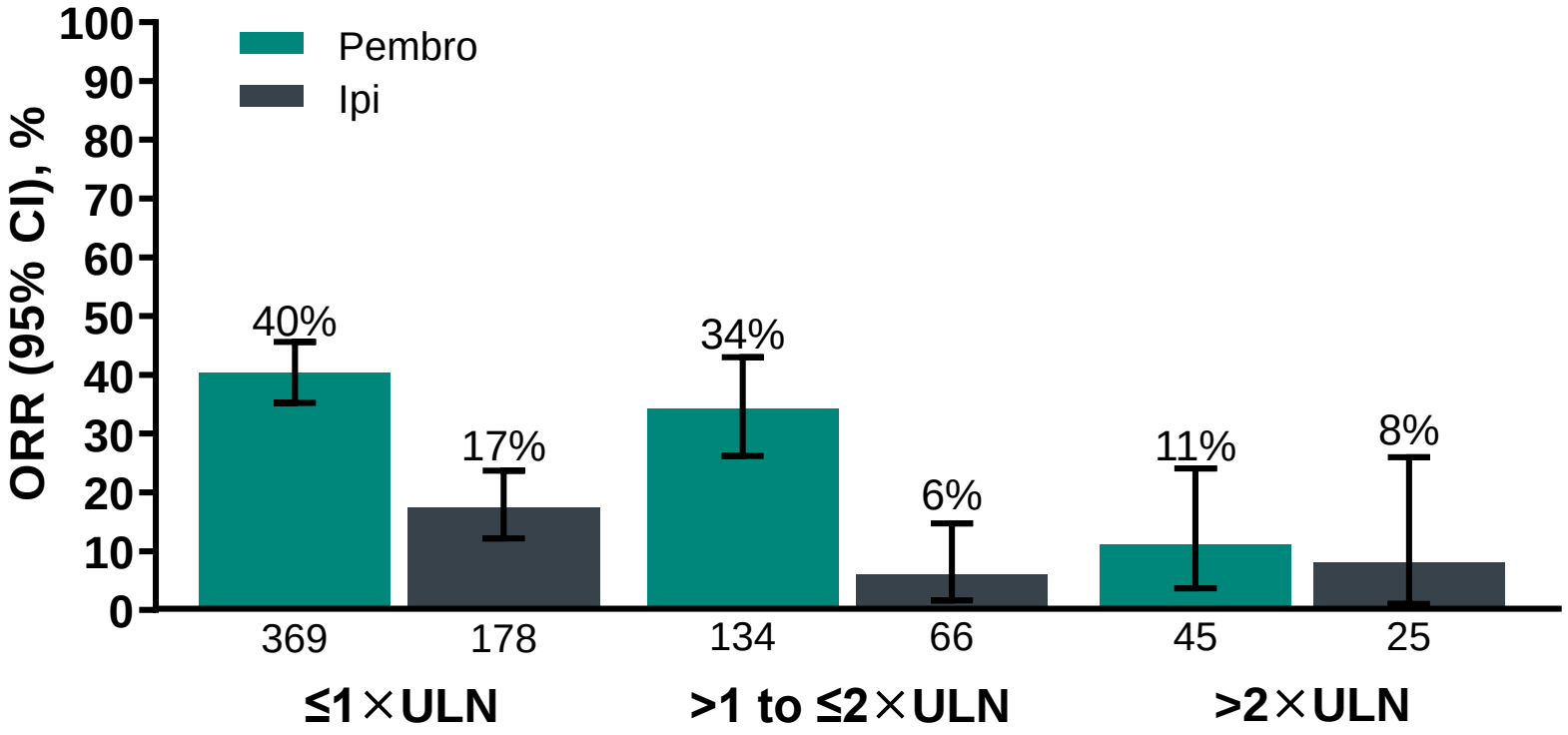
(RECIST v1.1, Central Review)



Bar height represents ORR. Error bars represent the 95% CI.
Data shown for patients with known LDH and centrally evaluable disease at baseline.
Data cutoff date: Sep 18, 2015 (median follow-up, 32 months).

KEYNOTE-006

(Blank et al. SMR 2016, Poster 24)

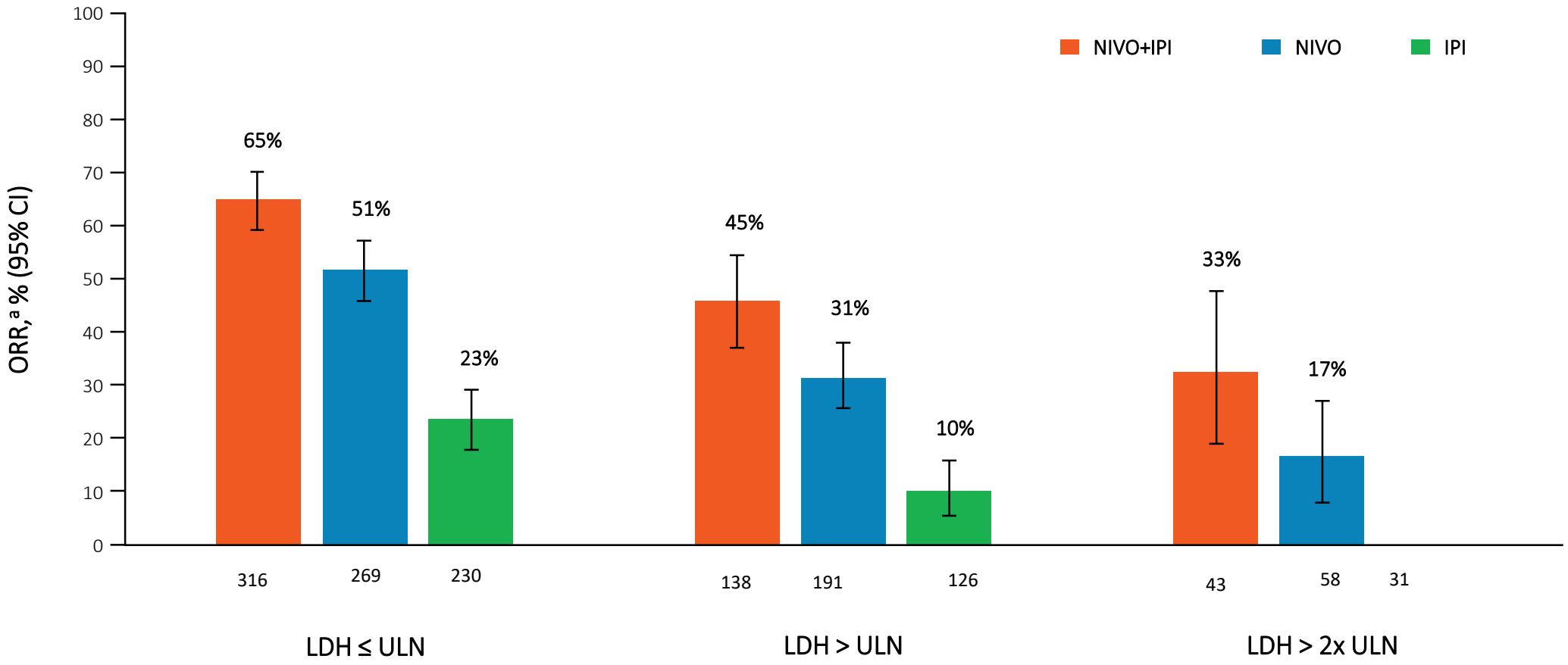


	≤1×ULN		>1 to ≤2×ULN		>2×ULN	
Responders, n	149	31	46	4	5	2
Ongoing[a]	70%	74%	74%	75%	80%	100%

[a]Responders without subsequent PD.

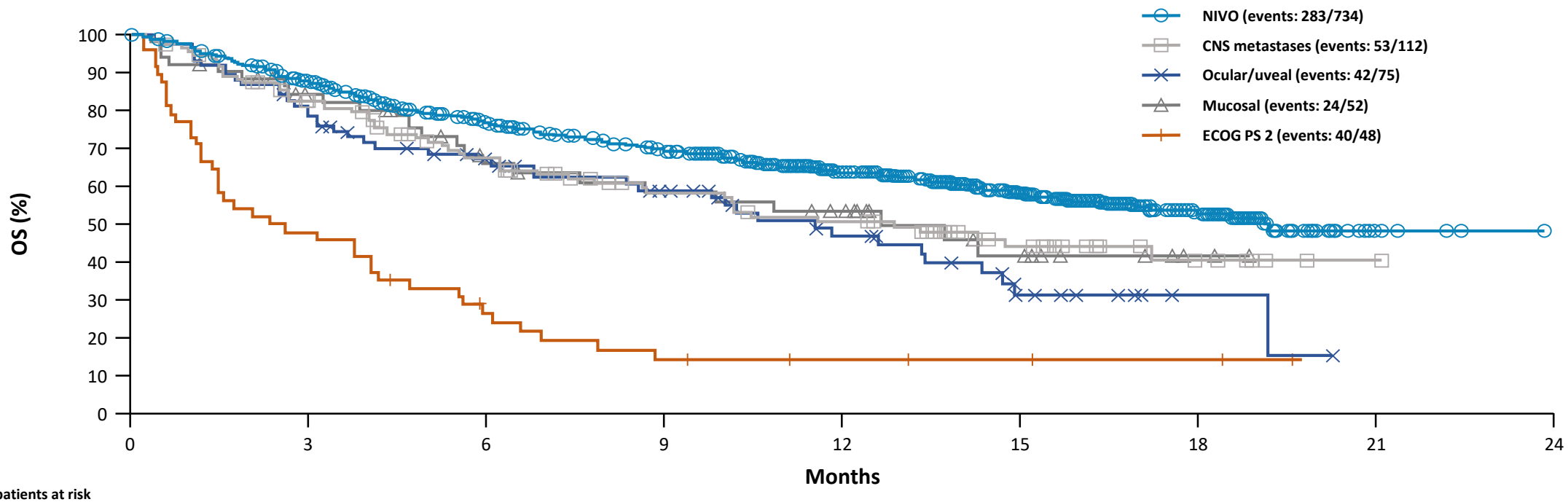
Blank C et al. Poster presented at SMR 2016; Nov 6-9, 2016; Boston, MA.

Best Response to Treatment: Checkmate 067



[a]By RECIST v1.1.

OS in All Treated Patients and in Key Subgroups

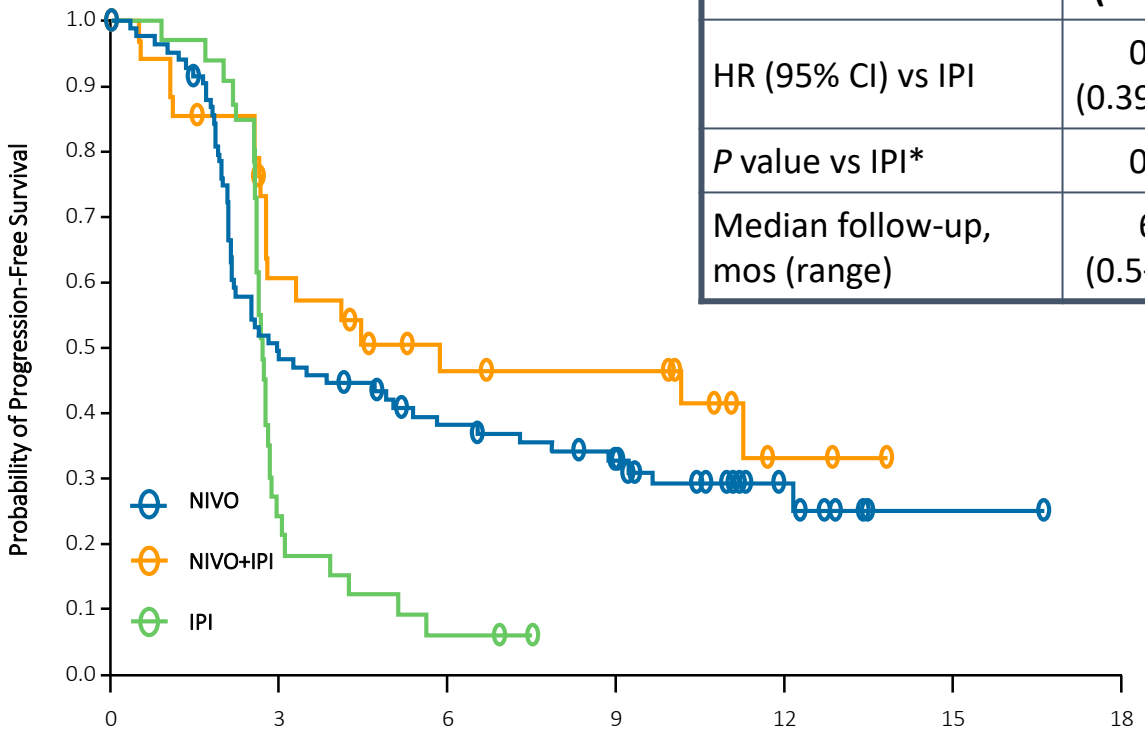


Number of patients at risk									
NIVO	734	620	505	422	343	201	62	5	0
CNS metastases	112	86	62	46	39	22	9	1	0
Ocular/uveal	75	58	43	34	22	9	2	0	0
Mucosal	52	39	27	23	19	10	2	0	0
ECOG PS 2	48	23	11	6	4	3	2	0	0

	Total (N = 734)	ECOG PS 2 (n = 48)	Uveal (n = 75)	Mucosal (n = 52)	CNS (n = 112)
Median OS, ms (95% CI)	19 (17, NR)	2 (1, 4)	11 (7, 15)	13 (6, NR)	13 (9, NR)
OS 12 ms (95% CI)	63 (60, 67)	14 (6, 26)	47 (34, 59)	53 (38, 67)	51 (40, 60)

PFS – Mucosal Melanoma

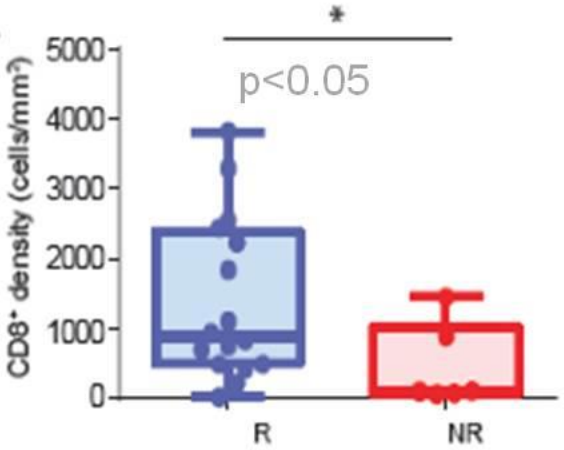
	NIVO (N=86)	NIVO+IPI (N=35)	IPI (N=36)
Median, mos (95% CI)	**3.0 (2.2–5.4)**	**5.9 (2.8–NR)**	**2.7 (2.6–2.8)**
HR (95% CI) vs IPI	0.61 (0.39–0.96)	0.42 (0.23–0.75)	--
P value vs IPI*	0.12	0.003	--
Median follow-up, mos (range)	6.2 (0.5–17.4)	8.1 (0.5–16.9)	8.6 (1.9–17.1)

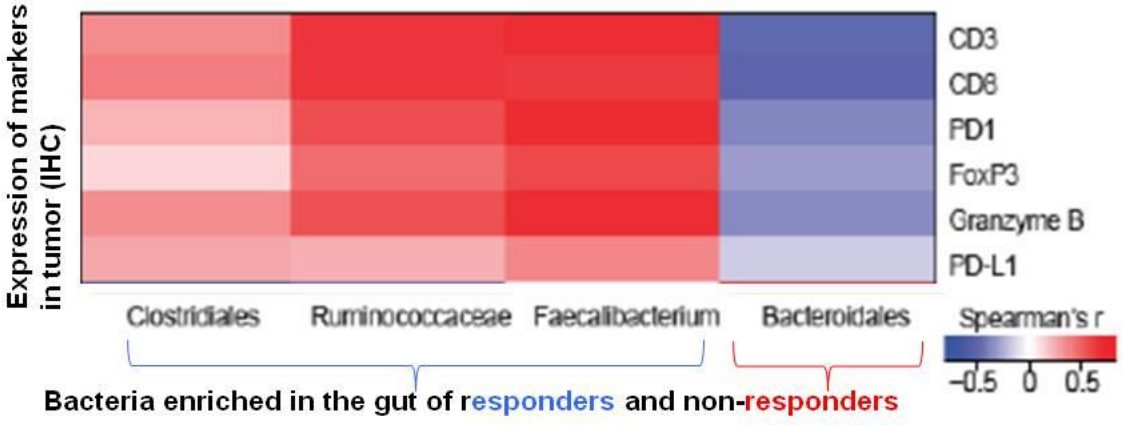


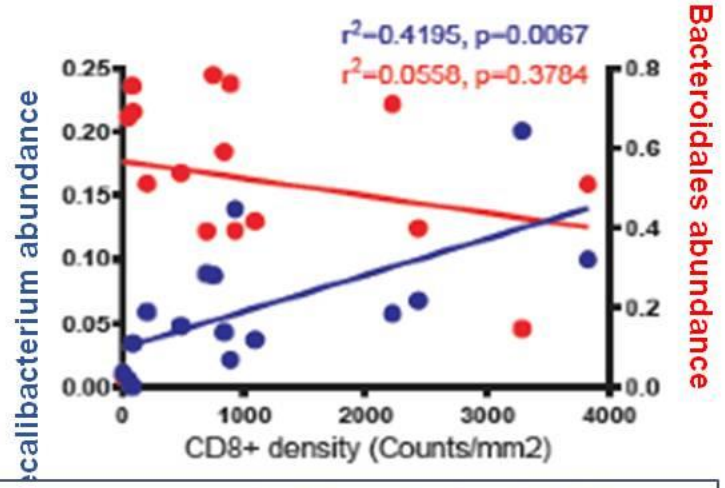
*Unstratified log-rank test.

Number of Patients at Risk							
NIVO	86	40	29	22	7	1	0
NIVO+IPI	35	19	12	11	2	0	--
IPI	36	8	2	0	0	0	--

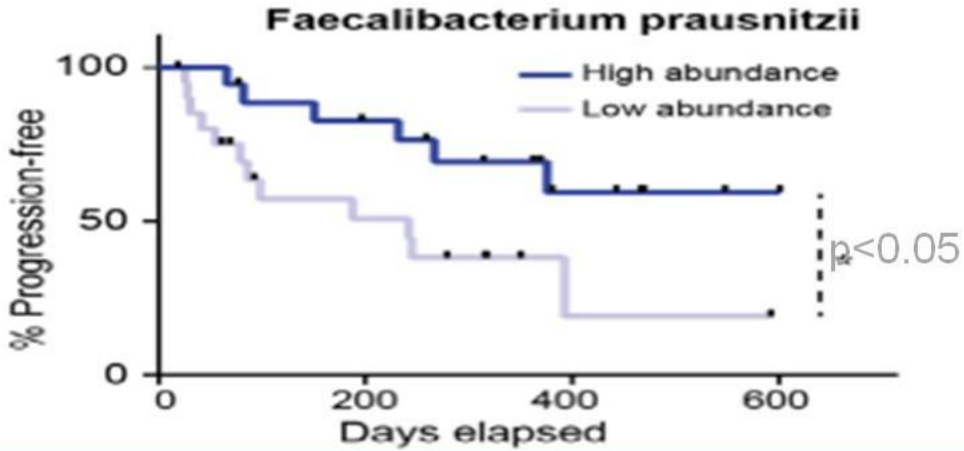
Anti-tumor immune responses were assessed and were compared to the composition of the gut (fecal) microbiome in patients on anti-PD-1

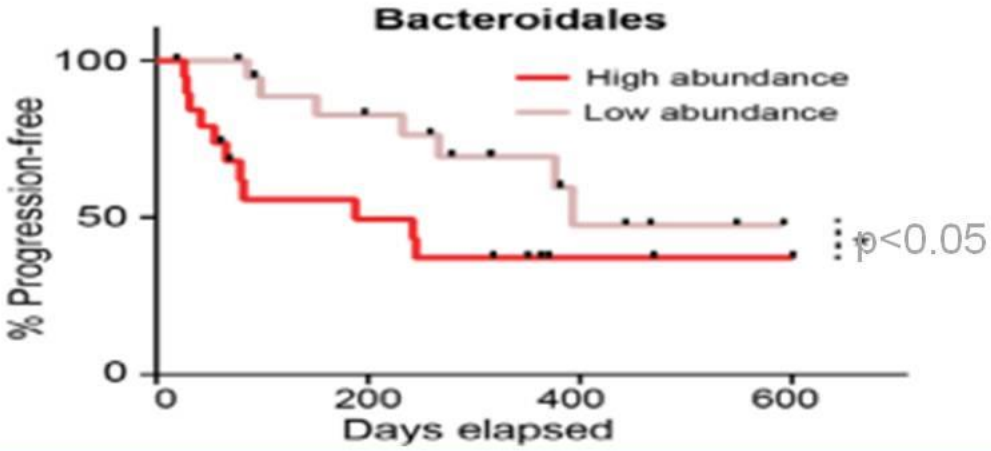






High abundance of Ruminococcus & Faecalibacteria in the gut was associated with cytotoxic T cells in TME





Differences in composition of the gut microbiome were associated with differences in PFS on aPD-1

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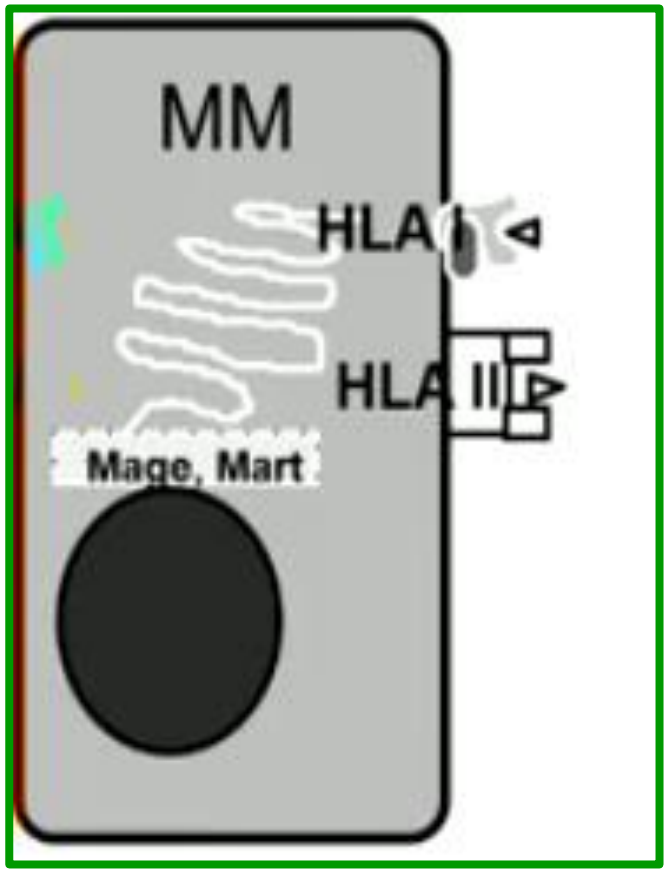
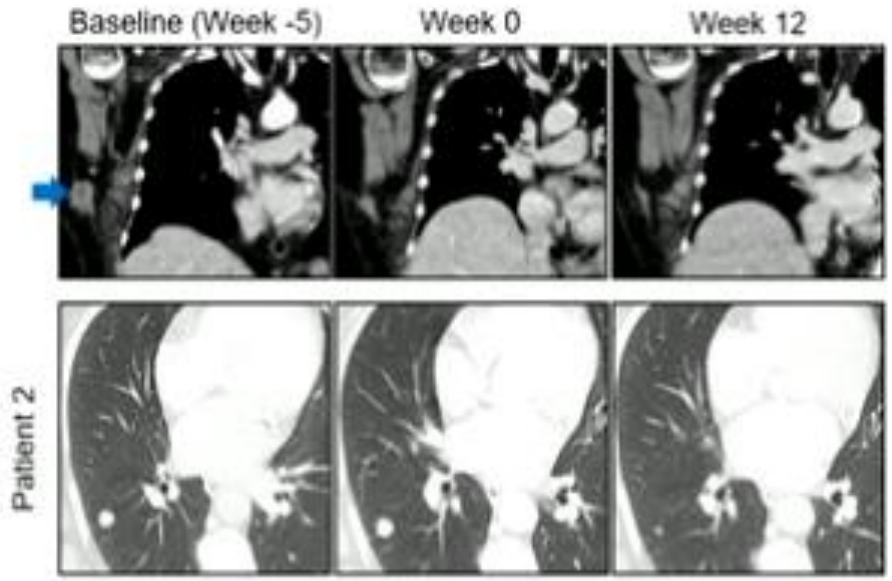
Strategies to overcome PD1 resistance



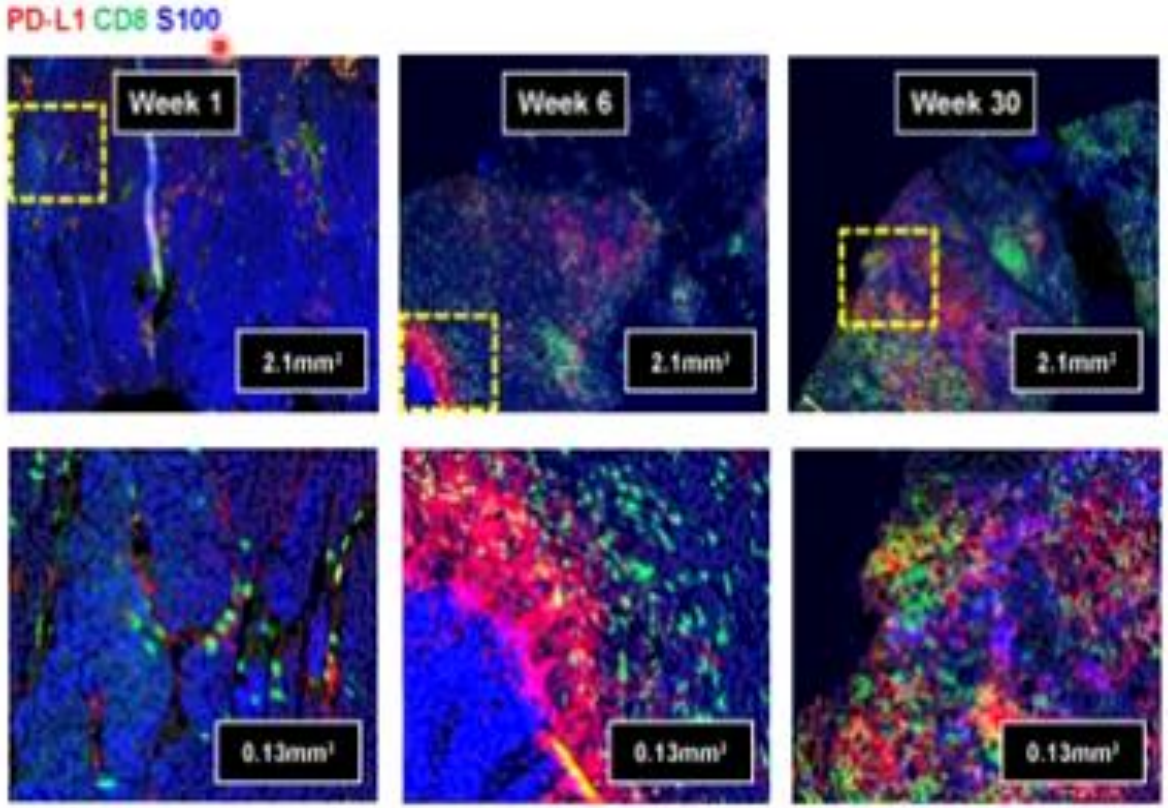
Cold Tumors	Oncolytic virotherapy, MEKi
IDO high	IDO inhibitors
Lag 3	Anti Lag3 Ab

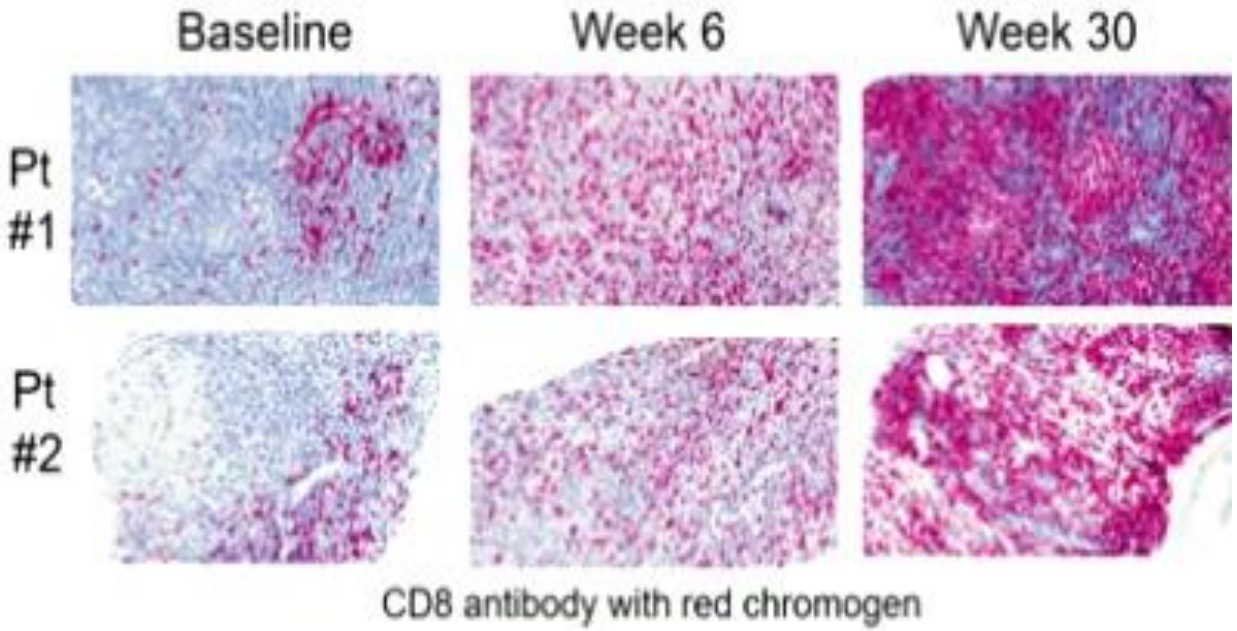
MASTERKEY-265: T-Vec + pembrolizumab

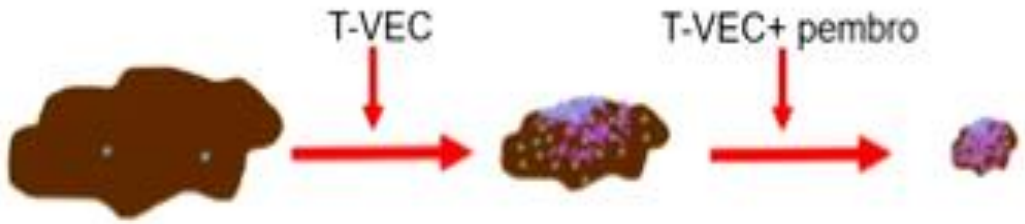


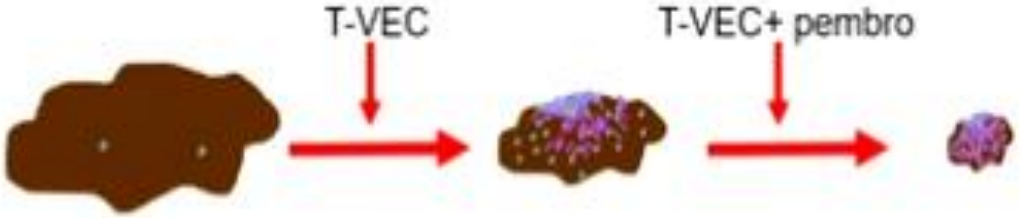
62% objective response rate
33% complete response rate

T-VEC increases tumor CD8 and PD-L1 in patients responding to combination with pembrolizumab



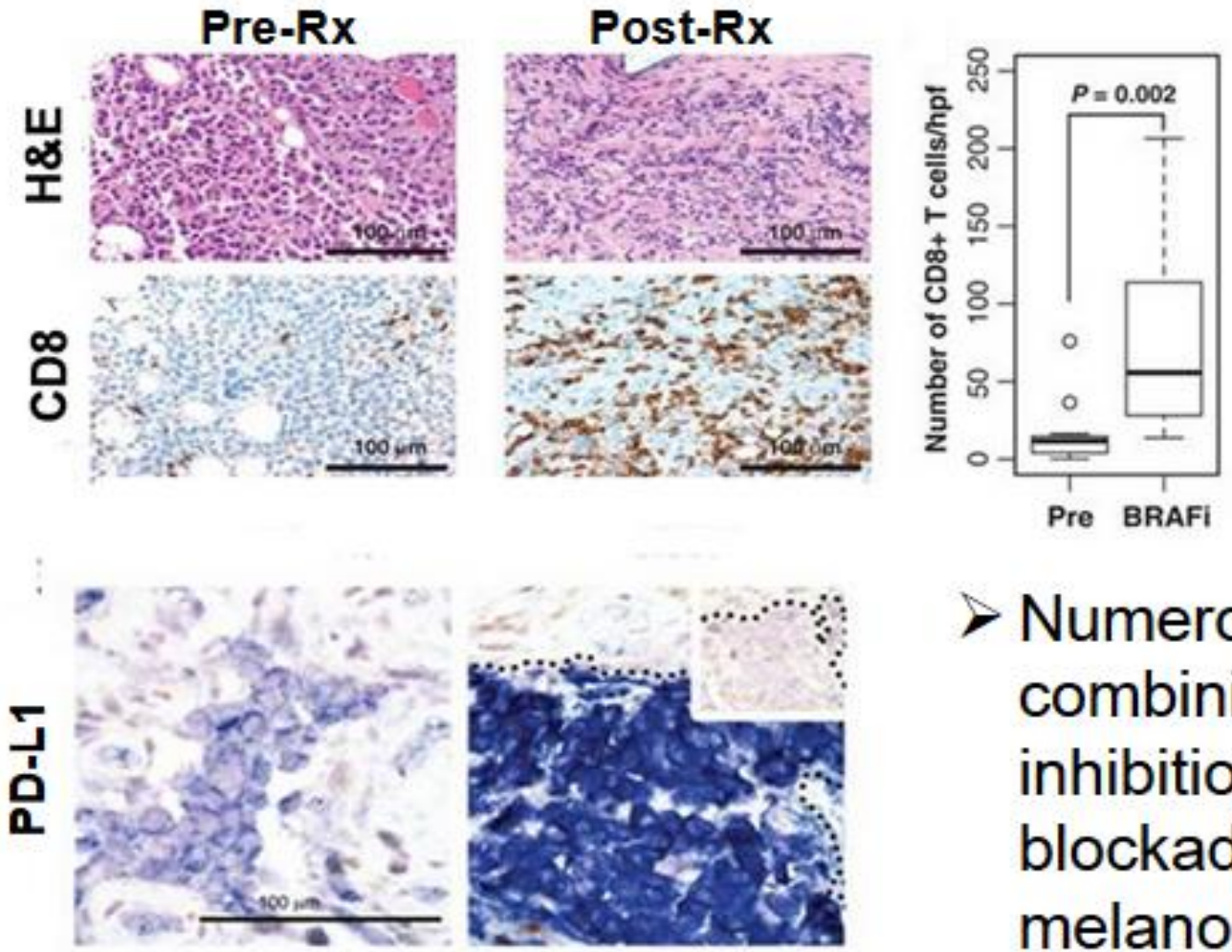






A. Ribas et al.Cell 2017,170:1109-1119

Selective BRAF inhibition in BRAFmut human melanoma is associated with increased CD8+ T cell infiltration and tumor PD-L1 expression

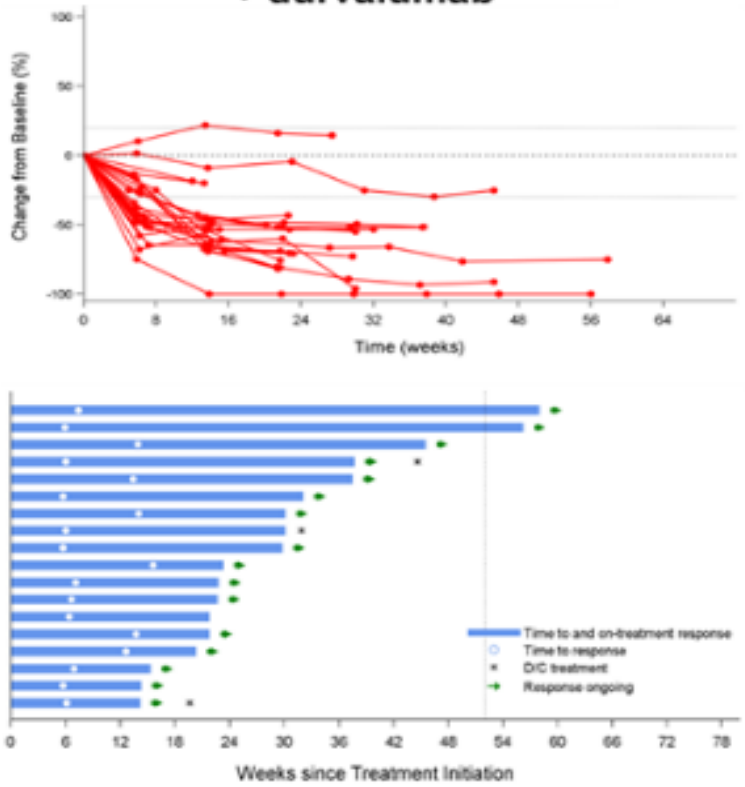


Frederick, Wargo, et al., Clin Cancer Res 2013

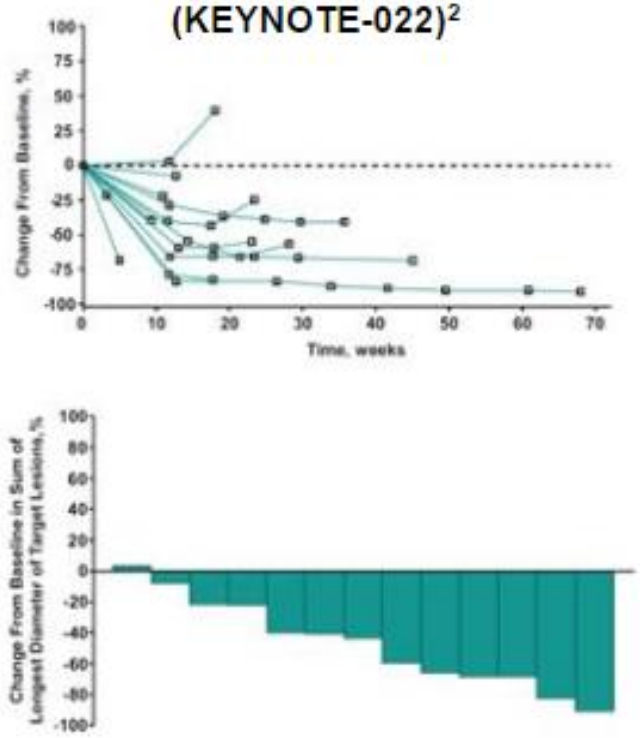
- Numerous clinical trials combining BRAF±MEK inhibition with PD-1/PD-L1 blockade are underway in melanoma

Phase 1 Clinical Trials of BRAFi+MEKi+Anti-PD-1/L1

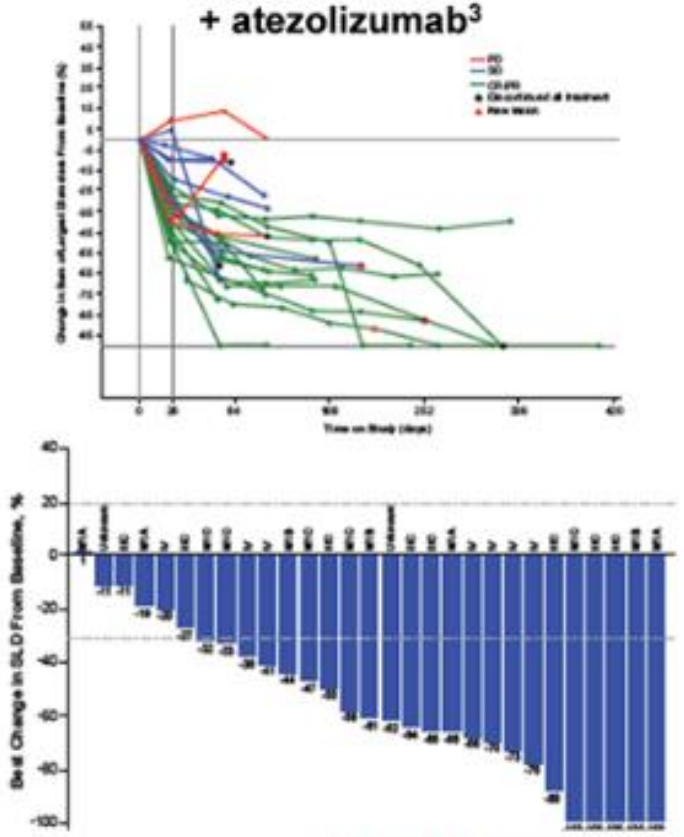
Dabrafenib + trametinib + durvalumab[1]



Dabrafenib + trametinib + pembrolizumab (KEYNOTE-022)[2]

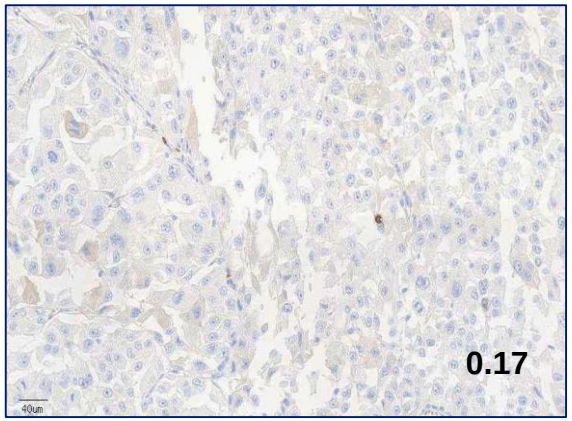
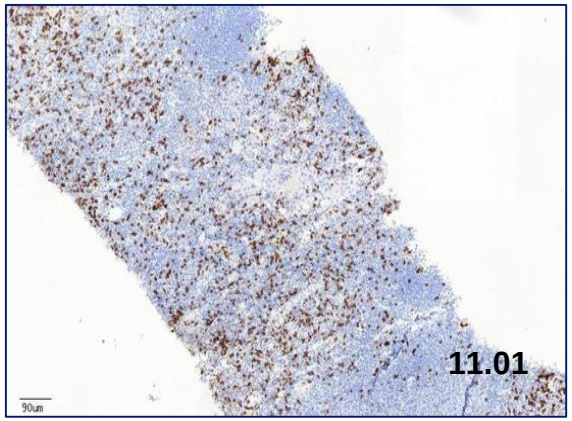
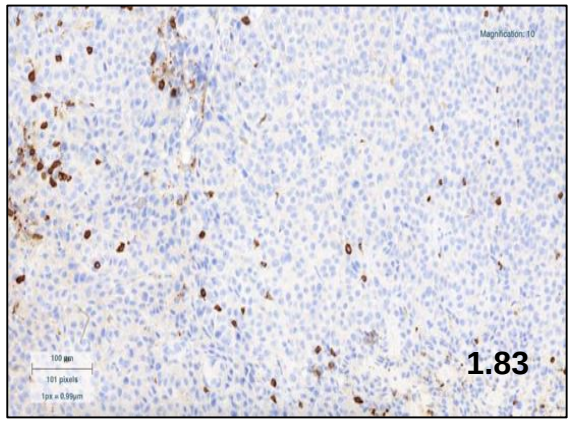
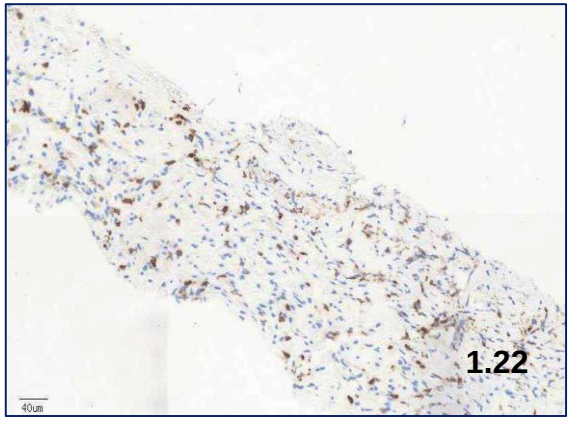
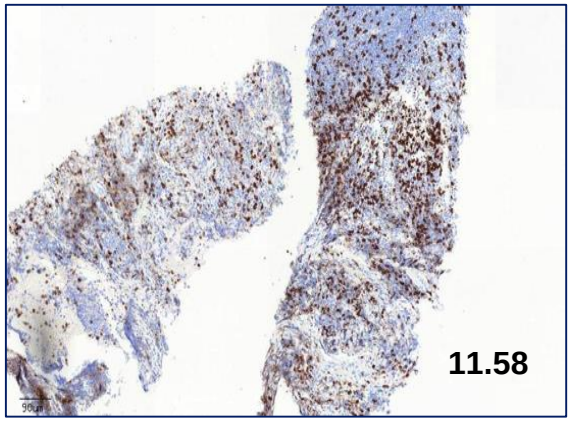
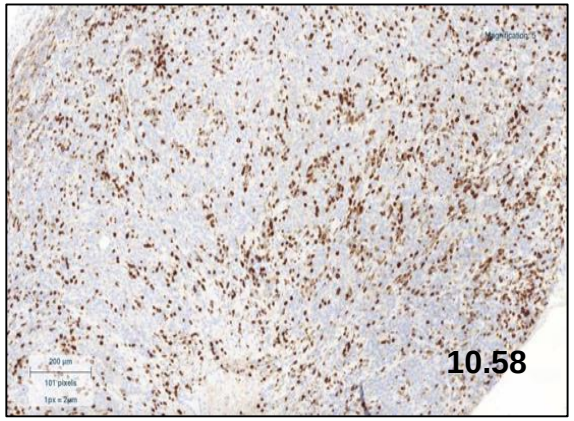


Vemurafenib + cobimetinib + atezolizumab[3]



1. Ribas et al. *J Clin Oncol* 33, 2015 (suppl, abstr 3003 ASCO). 2. Ribas et al. *J Clin Oncol* 34, 2016 (suppl; abstr 3014 ASCO). 3. Hwu et al. *Annals of Oncology* 27; 2016 (supp 6; abstr 1109PD ESMO).

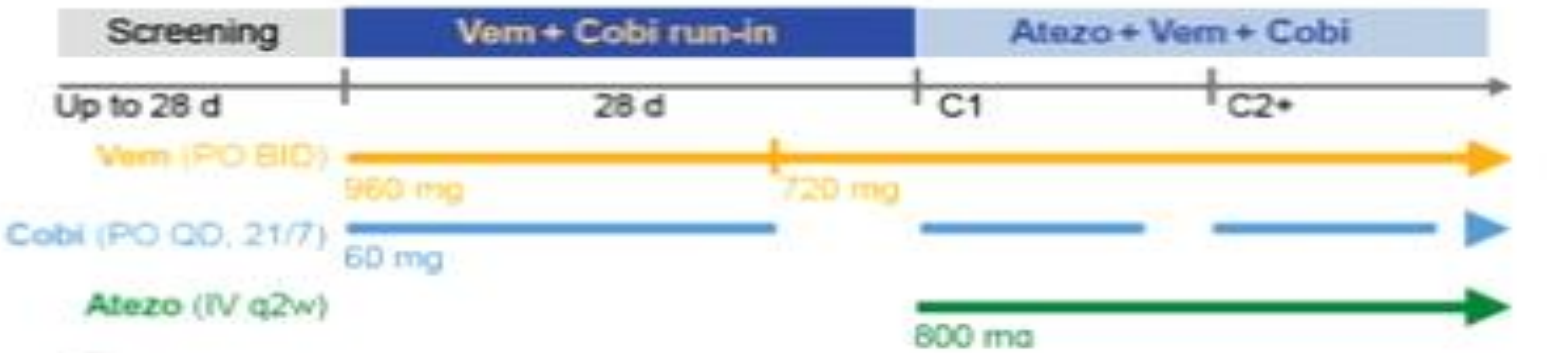
Tumor CD8+ T Cells Before and After Cobi + Vem Doublet Treatment Phase

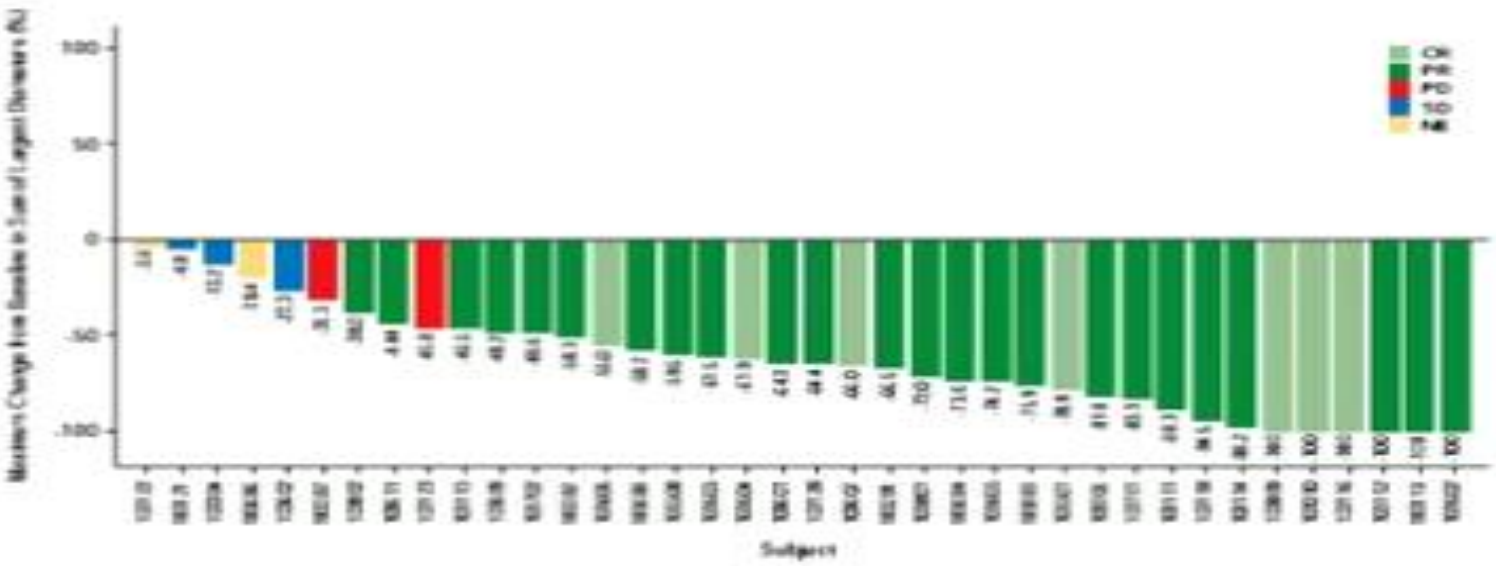
	Patient 1 (CR) (MD Anderson Cancer Center)	**Patient 2 (CR)** (Massachusetts General Hospital)	**Patient 3 (SD)** (Massachusetts General Hospital)
Pre-treatment			
Post-cobi+vem doublet treatment			

CD8 expression was assessed centrally by ICH. Numbers in each panel represent percentage of CD8 cells in the tumor center.

Vemurafenib + cobimetinib + atezolizumab

	GP28384 Cobi+ Vemu+ atezo
N	39
High LDH (%)	22.2
M1C (%)	25.6
III or M1a (%)	43.4
ORR (%)	81.6
CR (%)	18.4
Grade 3/5 AE (%)	41
Median FU (months)	10.1

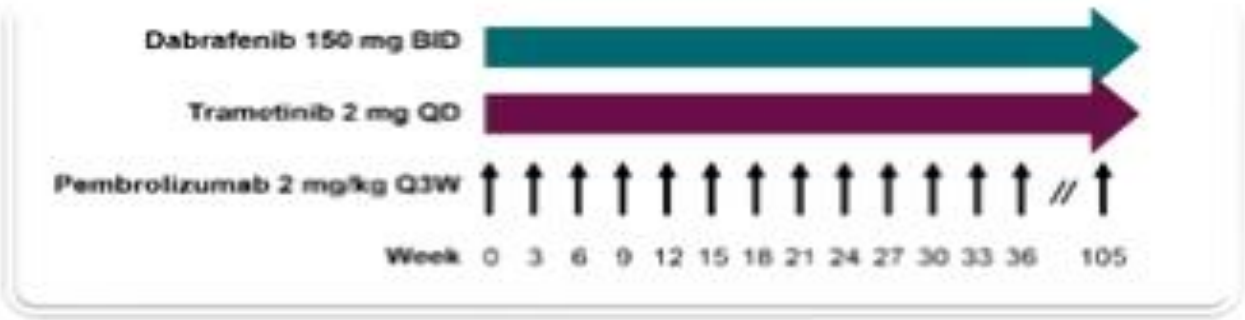


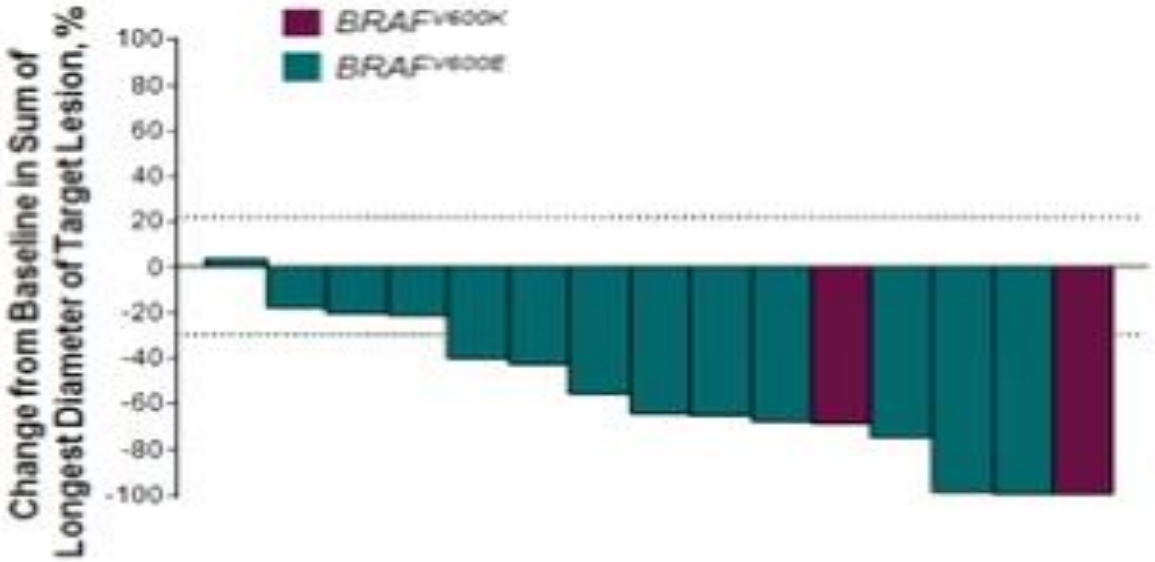


Sullivan et al ASCO 2017

Keynote 022 Pembrolizumab + dabrafenib + trametinib

	Keynote 22 Pembro + Dabra+ Trame
N	15
High LDH (%)	NR
M1C (%)	53
M1a (%)	13
ORR (%)	67
CR (%)	13
Grade 3/5 AE (%)	73
Median FU (months)	19.7

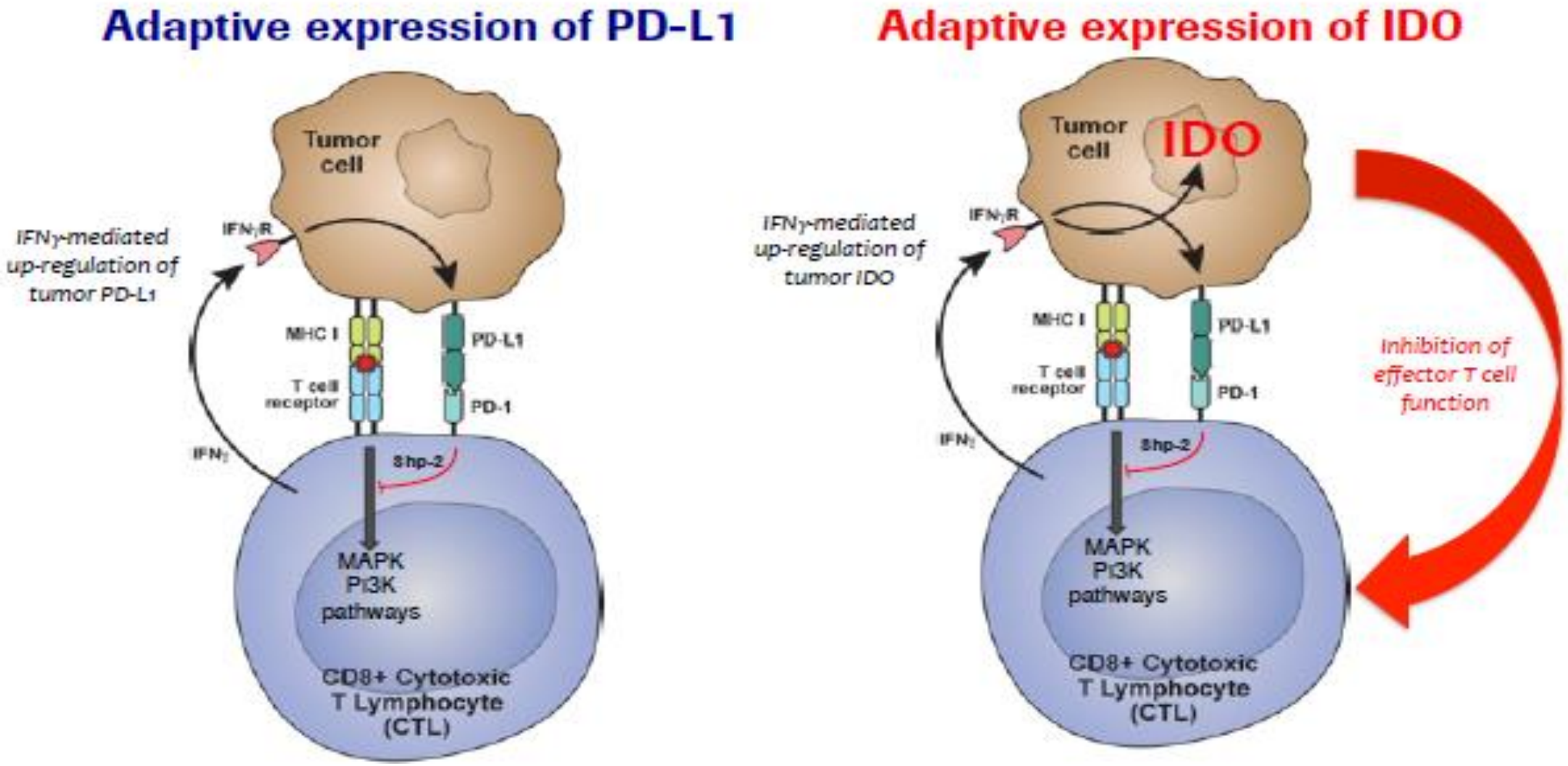




Ribas ESMO 2017,

IDO (indoleamine di-oxygenase)

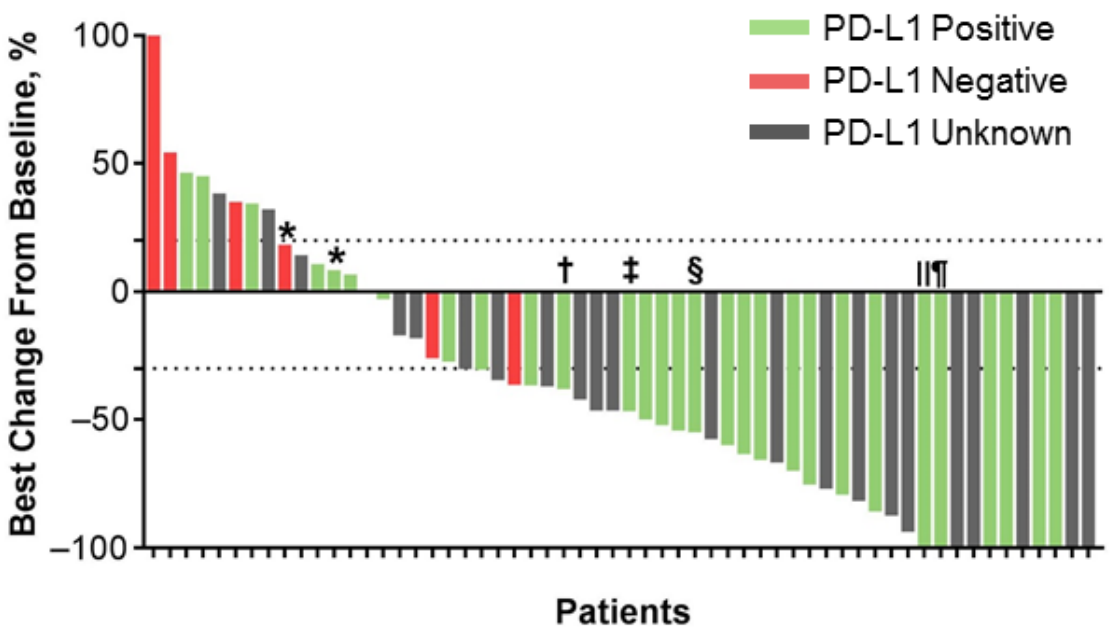
Another suppressor of effector T cells



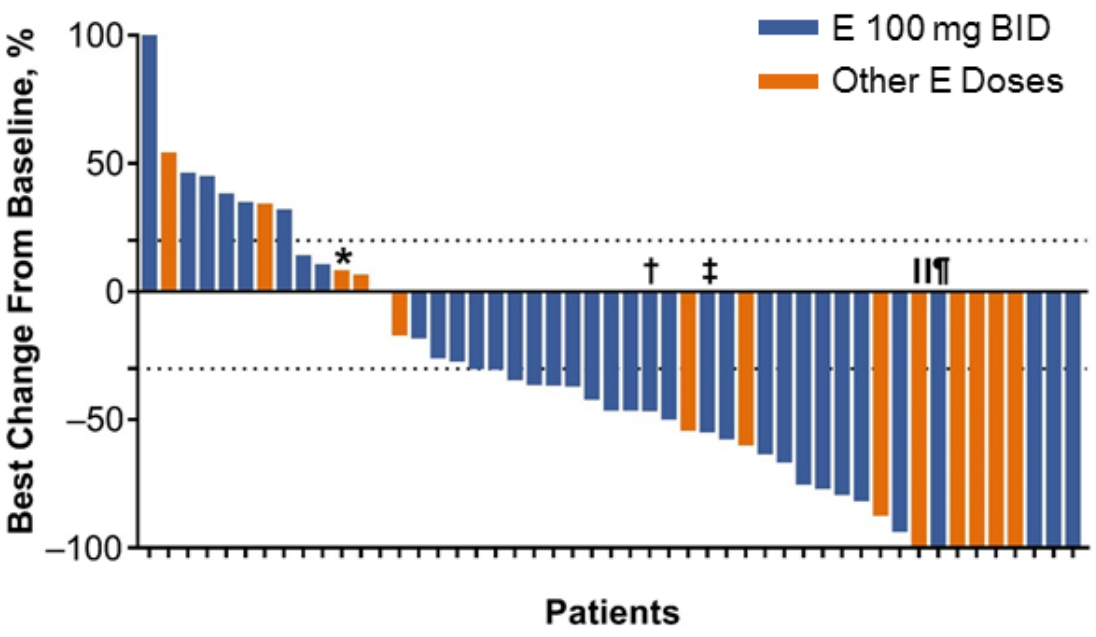
Best Percentage Change From Baseline in Target Lesions

Epacadostat Plus Pembrolizumab, P1/2 Advanced Melanoma

All Patients



Treatment-Naive Patients

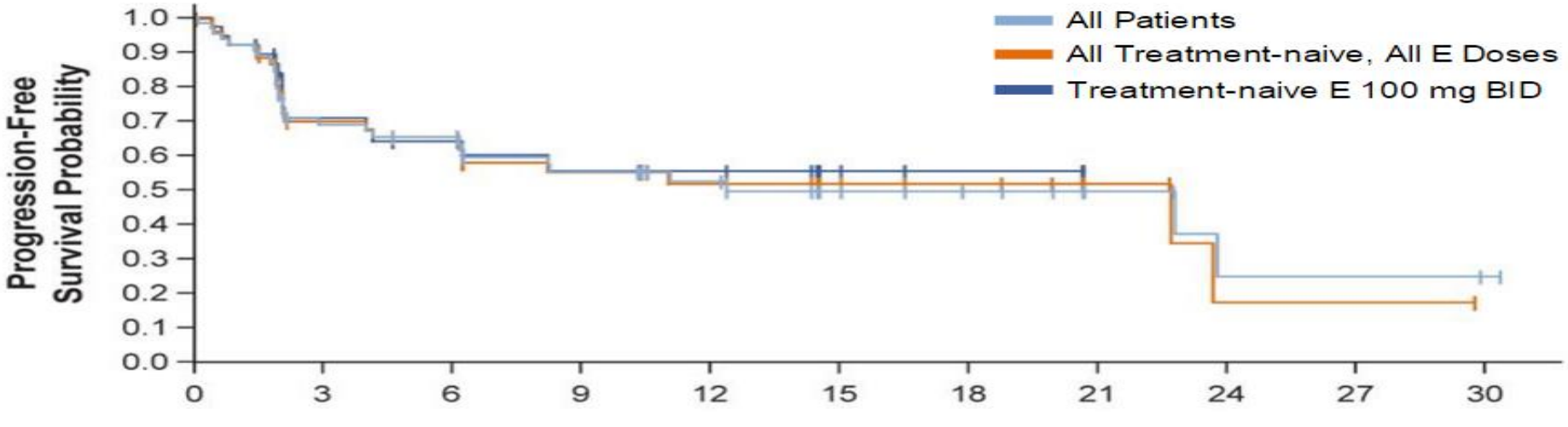


CR, complete response; DCR, disease control rate; E, epacadostat, irRECIST, immune-related RECIST; MEL, melanoma; ORR, objective response rate; PD, progressive disease; PD-L1, programmed death ligand 1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Note: PD-L1 positive defined as MEL Score ≥2 (membranous PD-L1 expression in ≥1% of tumor cells or inflammatory cells in nests of tumor cells) as assessed by immunohistochemistry using the 22C3 antibody. * SD per target lesion but PD per RECIST v1.1. † PR per target lesion but PD per RECIST v1.1. ‡ PR per target lesion but SD per RECIST v1.1. § PD per target lesion per RECIST v1.1 (PR per irRECIST). ‖ CR per target lesion but PD per new lesion per RECIST v1.1 (PR per irRECIST); ¶ CR per target lesion but PR per RECIST v1.1 (nontarget lesions still present).

Progression-Free Survival

Epacadostat Plus Pembrolizumab, P1/2 Advanced Melanoma



Patients at risk, n											
All melanoma	65	38	35	26	19	13	10	5	2	2	1
All treatment-naive	54	31	28	20	15	11	9	4	1	1	0
Treatment-naive 100 mg BID	39	21	18	12	8	4	2	0	0	0	0

Variable	All Patients (N=65)	Treatment-Naive for Advanced Disease (n=54)	Treatment-Naive for Advanced Disease, E 100 mg (n=39)
Median PFS, months (90% CI)	12.4 (6.2, 23.8)	22.8 (6.2, 23.8)	NR (4.2, NR)
PFS rate, % (90% CI)			
6 months	65 (54, 74)	65 (53, 75)	64 (49, 76)
12 months	52 (40, 63)	52 (38, 64)	55 (39, 69)
18 months	49 (37, 60)	52 (38, 64)	55 (39, 69)

O. Hamid, ESMO 2017

Treatment-Related Adverse Events (≥10%)

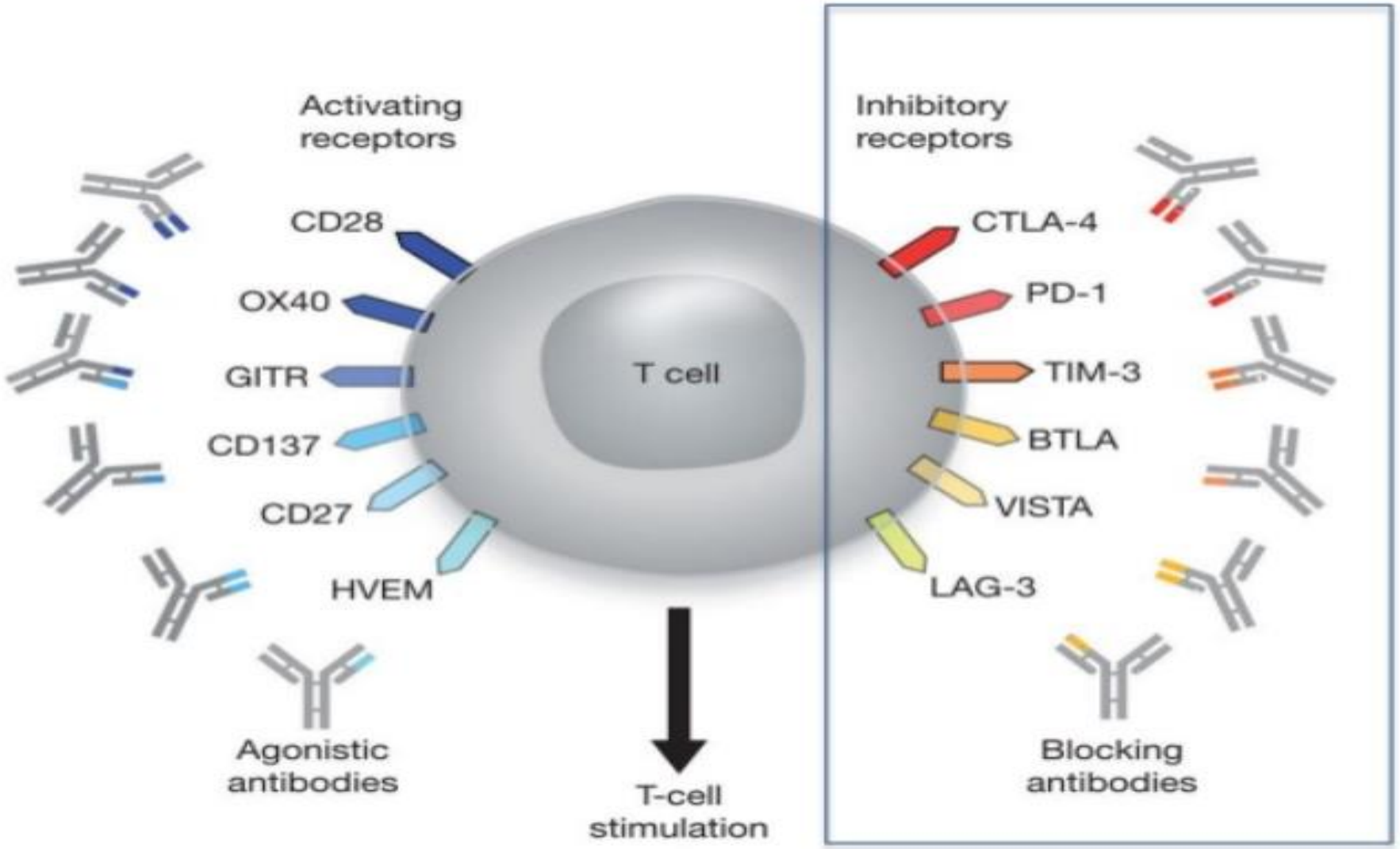
Epacadostat Plus Pembrolizumab, P1/2 Advanced Melanoma

Adverse Event, n (%)	All Grade (N=65)	Grade 3/4* (N=65)
Total	**52 (80)**	**13 (20)**
Rash†	30 (46)	3 (5)
Fatigue	28 (43)	1 (2)
Pruritus‡	19 (29)	0
Arthralgia	11 (17)	1 (2)
Diarrhea	10 (15)	0
AST increased	8 (12)	2 (3)
Nausea	8 (12)	0
ALT increased	7 (11)	2 (3)
Lipase increased	7 (11)	4 (6)

- Treatment-related adverse events led to dose interruptions in 16 patients (25%)
- Treatment-related adverse events led to dose reductions in 7 patients (11%)
- 4 patients (6%) discontinued due to treatment-related adverse events
  - Arthralgia (n=2 patients); autoimmune hepatitis and lipase increased (n=1 patient each)
  - These adverse events resolved in all but 1 patient (arthralgia) as of data cutoff
- Treatment-related serious adverse events were arthralgia, autoimmune hepatitis, and colitis (n=1 patient each)
  - These adverse events resolved and were manageable with supportive care
- No treatment-related adverse events led to death

O. Hamid, ESMO 2017

T-cell Targets for Immunoregulatory Antibody Therapy



I Mellman *et al. Nature* **480**, 480-489 (2011) doi:10.1038/nature10673

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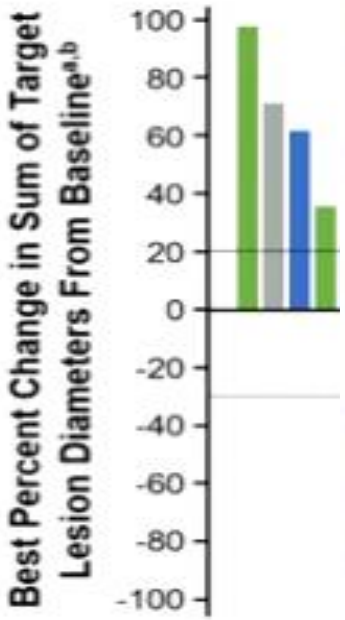
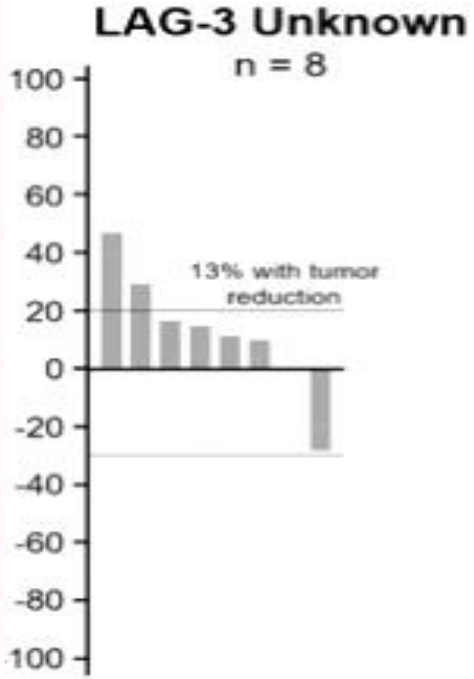
respective of



	Nivo+ relatlimab
N	61
High LDH (%)	24
M1C (%)	47.5
III M1a (%)	18.8
ORR (%)	11.5
CR (%)	1.6
Grade 3/5 AE (%)	10
Median FU (months)	4.1



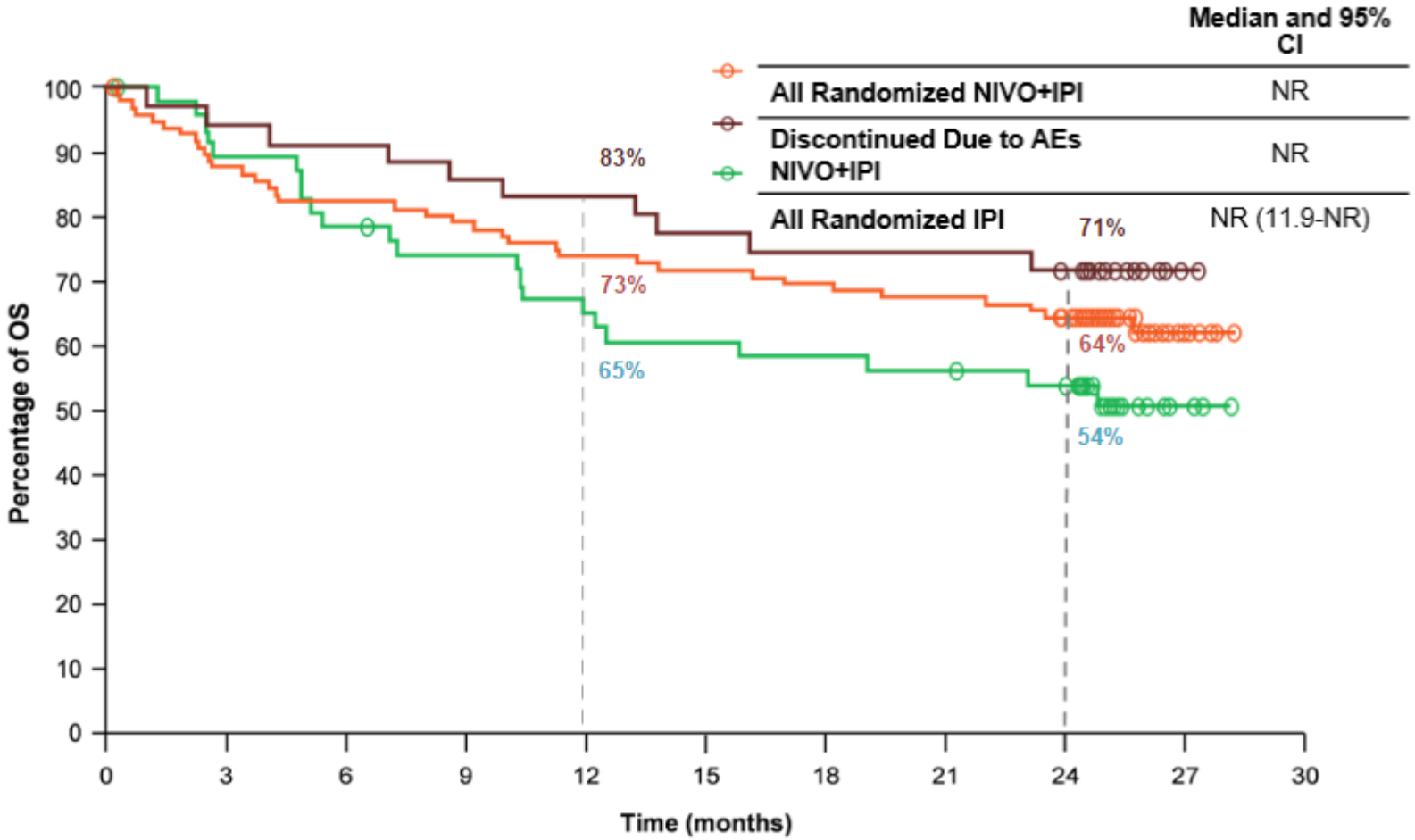
*Six patients who had clinical pr

getting full scans were not included

Key-point issues with patients on immune-therapy

- ✓How long to treat ?
- ✓Safety monitoring: how often, how long, physical or remote
- ✓Predictive biomarkers
- ✓How to deal with the long term survivors ?
- ✓Cost and Value

CA209-069: Overall Survival at 2 Years of Follow Up



Number of patients at risk:

Nivolumab + Ipilimumab	95	82	77	74	69	67	65	63	57	6	0
Nivolumab + Ipilimumab	35	33	32	30	29	27	26	26	24	1	0
Ipilimumab	47	41	36	33	29	27	26	25	22	3	0

- Subsequent systemic therapies were used in 64% of IPI patients, 28% of NIVO+IPI patients and in 31% of NIVO+IPI patients who discontinued due to treatment-related AEs

Hodi et al ASCO 2016

Disposition of Patients Who Completed Protocol-Specified Time on Pembrolizumab[a] (median follow-up, 9.7 mo)

556 patients received pembrolizumab

104 (19%) completed pembrolizumab

24 (23%) CR

- 23 ongoing responses
- 1 PD[b]
  - 1 received second course of pembrolizumab

68 (65%) PR

- 64 ongoing responses
- 4 PD[b]
  - 3 received second course of pembrolizumab

12 (12%) SD

- 10 ongoing SD
- 2 deaths[b,c]

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[a]Includes patients completing ≥21.6 months of treatment.
[b]From end of pembrolizumab treatment.
[c]Both deaths were a result of PD. Data cutoff date: Nov 3, 2016.

3. Can we stop?

- **PD1 ?Yes**
  - KN-001: 97% who stop in CR progression-free (med 10mo F/U)[1]
  - KN-006: 91% who stop @ 2y progression-free (med 9mo F/U)[2]
  - Series: 98% who stop after med 14.5mo progression-free (med 11mo F/U)[3]

- MAPKi
  - Series: 50% who discontinue in CR progression-free (med F/U 15mo)[4,5]
  - 220: Only 4% still on drug but PFS 13% at 5 years[6]

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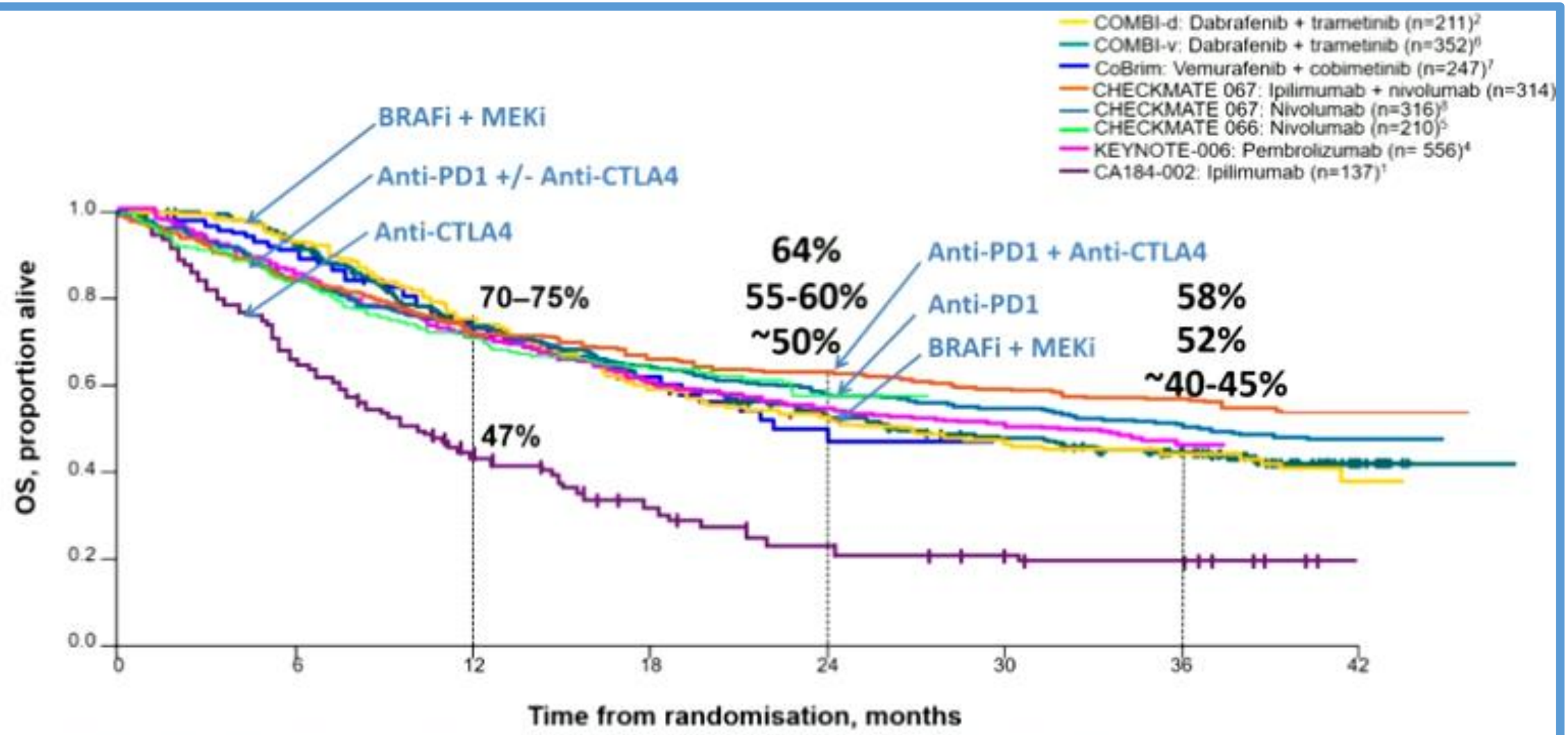
1. Robert C et al. ASCO 2016 (abstr 9503)
2. Robert C et al. ASCO 2017 (abstr 9504)
3. Jansen Y et al. ASCO 2017 (abstr 9539)
4. Carlino MS et al. Br J Cancer. 2016;115(11):1280-4
5. Tolk H et al. Mel Res. 2015;25(4):362-6
6. Long GV et al. ASCO 2017 (abstr 9505)

Overall Survival in Melanoma



1. Hodi FS et al. NEJM 2010; 2. Long GV. Oral ASCO 2017; 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 & Atkinson V et al. Poster SMR 2015; 6. Robert C Oral ESMO 2016; 7. Atkinson V et al. Oral SMR 2015; 8. Larkin J et al. Oral AACR 2017

Presented by Georgina V Long, MIA

SECOMBIT Study

- Prospective randomized phase II study to evaluate the best sequential approach with combo immunotherapy (ipilimumab/nivolumab) followed by combo target therapy (dabrafenib/ trametinib) and vice-versa
- Patients affected by metastatic melanoma BRAF V600 mutated
- Sample size 230 pts

ARM A
Combo T
LGX 450 mg
MEK 162 45 mg
→ **PD** → **Combo IT until PD**

ARM B
Combo I
Ipilimumab 3 mg/Kg
Nivolumab 1mg /Kg
→ **PD** → **Combo TT until PD**

ARM C
Sandwich
LGX 450 mg
MEK 162 45 mg for 8 weeks
→ **Combo IT until PD** → **Combo TT until PD**

This study is designed as a phase II randomized trial with no formal comparative test.

Endpoints:

Primary – OS

Secondary – PFS, Total PFS (TPFS): the time to the second progression, % patients alive at 2-3 years, BORR;

Duration of Response, Toxicity, Biomarkers study

Immunotherapy is a reality in the treatment of melanoma…. a better understanding of all involved players is mandatory to improve the results