THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Immunotherapy and Targeted Therapy in Melanoma

Jennifer McQuade, MD, MA, MS

Assistant Professor, Melanoma Medical Oncology

UT MD Anderson Cancer Center

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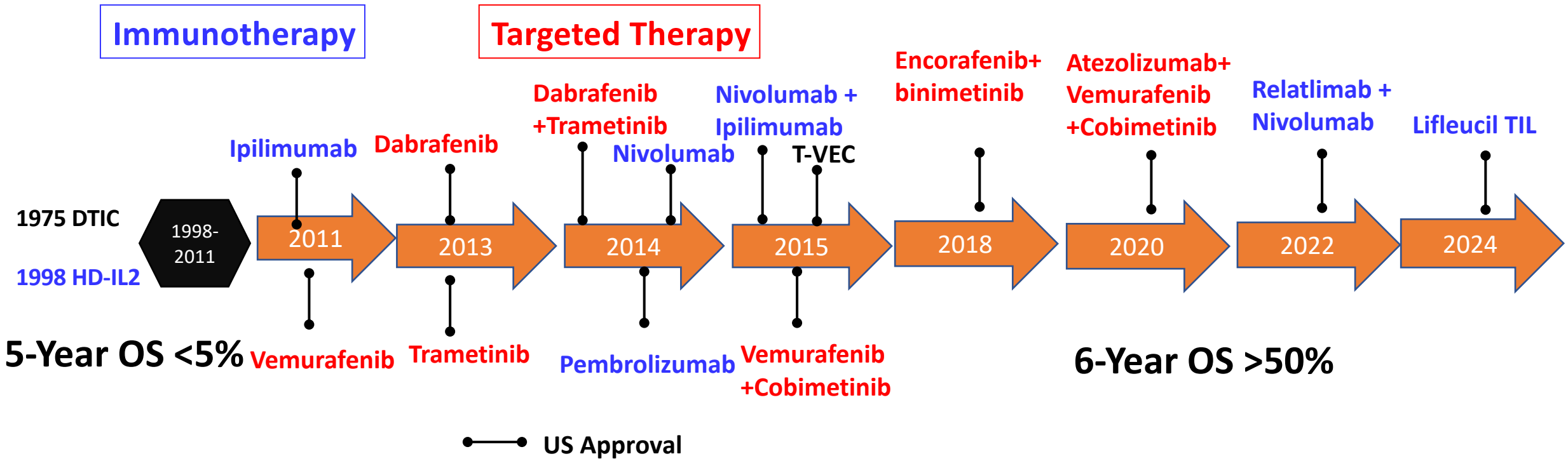
Metastatic Disease

Approved Agents for Stage IV Melanoma

Pre-1998	Approvals w/o (+) randomized trials
1998-2011	No approvals
2011-2024	**14 approvals**



CheckMate 067: Ipi/Nivo vs Nivo vs Ipi

	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, mths (95% CI)	**NR** (NR–NR)	**31.1** (31.1–NR)	**18.2** (8.3–NR)

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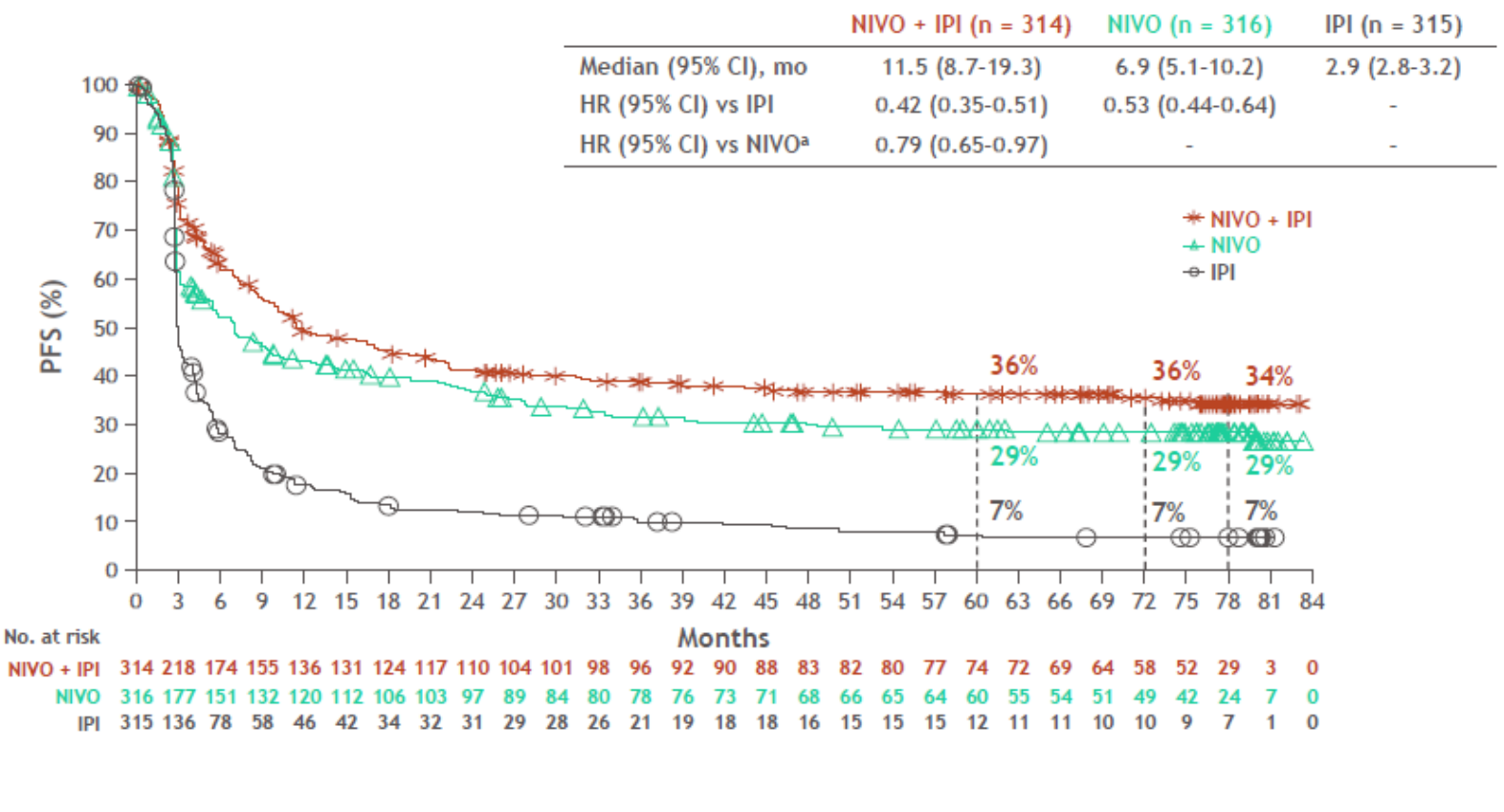
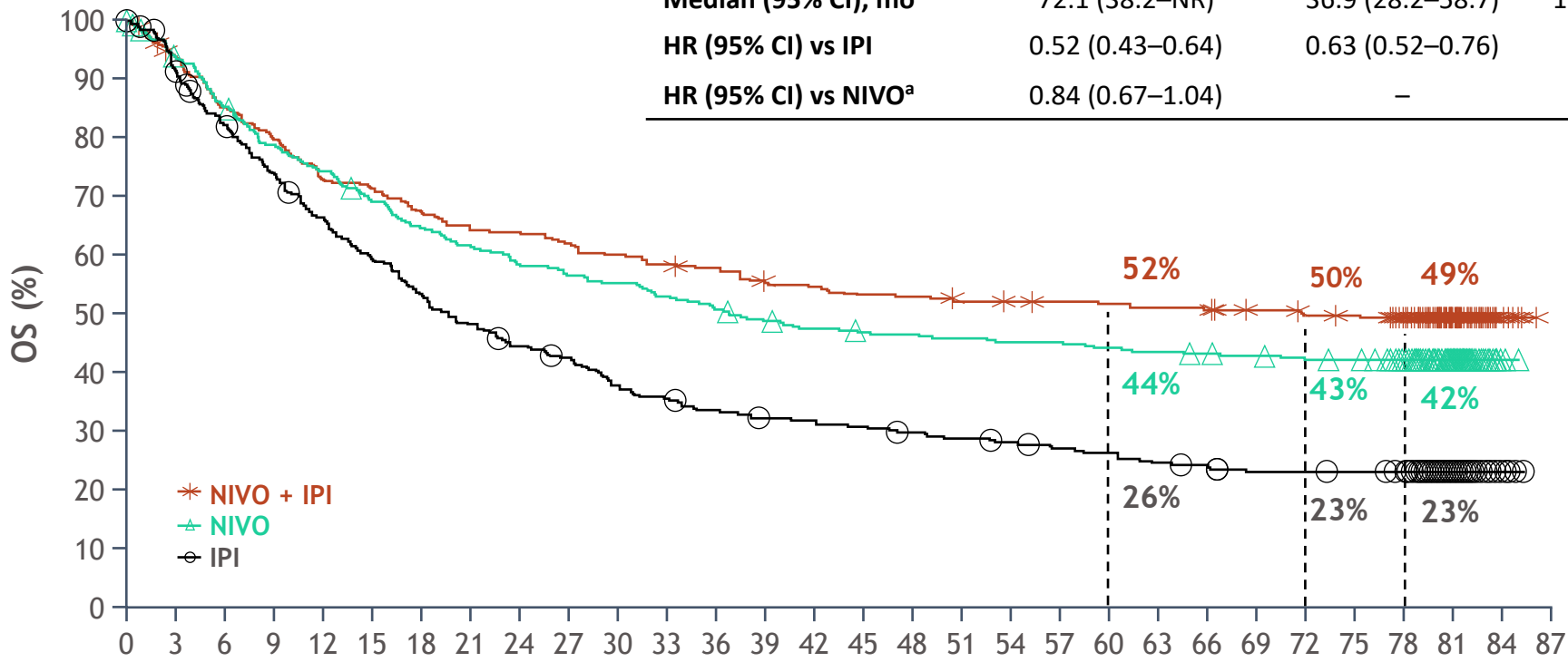


Wolchok, ASCO 2015; Larkin NEJM 2015

Adapted from Wolchock et al. ASCO 2021, Abstract 9506

CheckMate 067: 6.5-year Overall survival

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median (95% CI), mo	72.1 (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
HR (95% CI) vs IPI	0.52 (0.43–0.64)	0.63 (0.52–0.76)	–
HR (95% CI) vs NIVO[a]	0.84 (0.67–1.04)	–	–



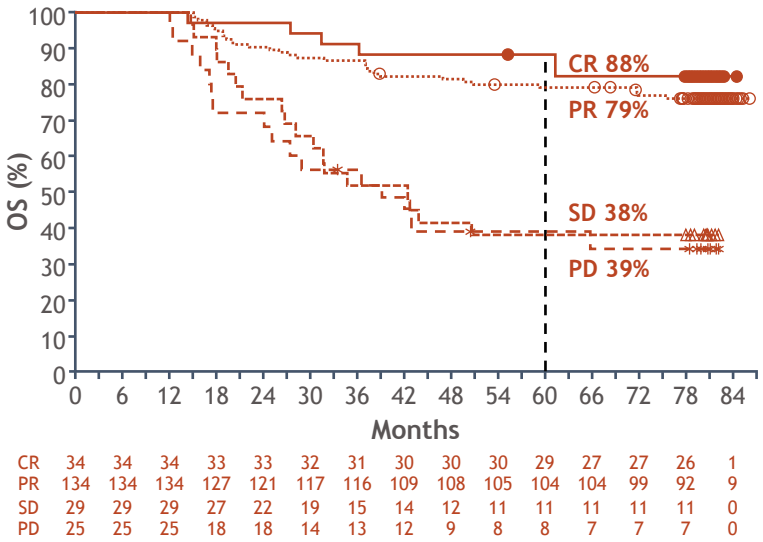
No. at risk																													
NIVO + IPI	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	158	157	156	154	153	150	147	145	138	66	10	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	137	134	132	130	128	126	124	117	59	3	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	75	70	68	64	64	63	61	32	7	0

[a]Descriptive analysis.

Wolchock, JD, et al., *JCO, Jan 2022 .*

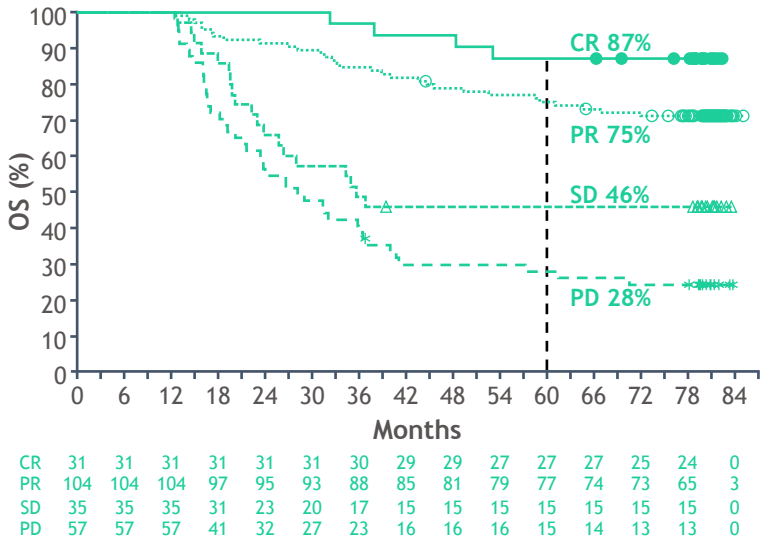
OS by best overall response, 12-month landmark analysis[a]

NIVO + IPI



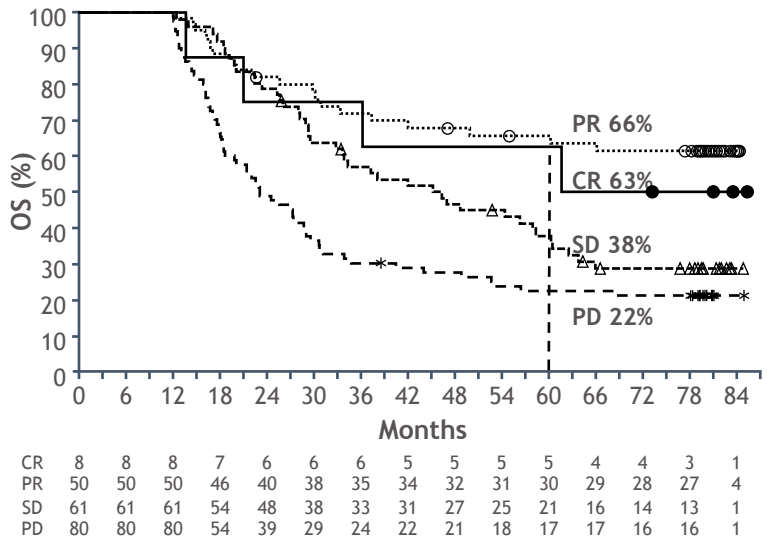
CR	34	34	34	33	33	32	31	30	30	30	29	27	27	26	1
PR	134	134	134	127	121	117	116	109	108	105	104	104	99	92	9
SD	29	29	29	27	22	19	15	14	12	11	11	11	11	11	0
PD	25	25	25	18	18	14	13	12	9	8	8	7	7	7	0

NIVO



CR	31	31	31	31	31	31	30	29	29	27	27	27	25	24	0
PR	104	104	104	97	95	93	88	85	81	79	77	74	73	65	3
SD	35	35	35	31	23	20	17	15	15	15	15	15	15	15	0
PD	57	57	57	41	32	27	23	16	16	16	15	14	13	13	0

IPI

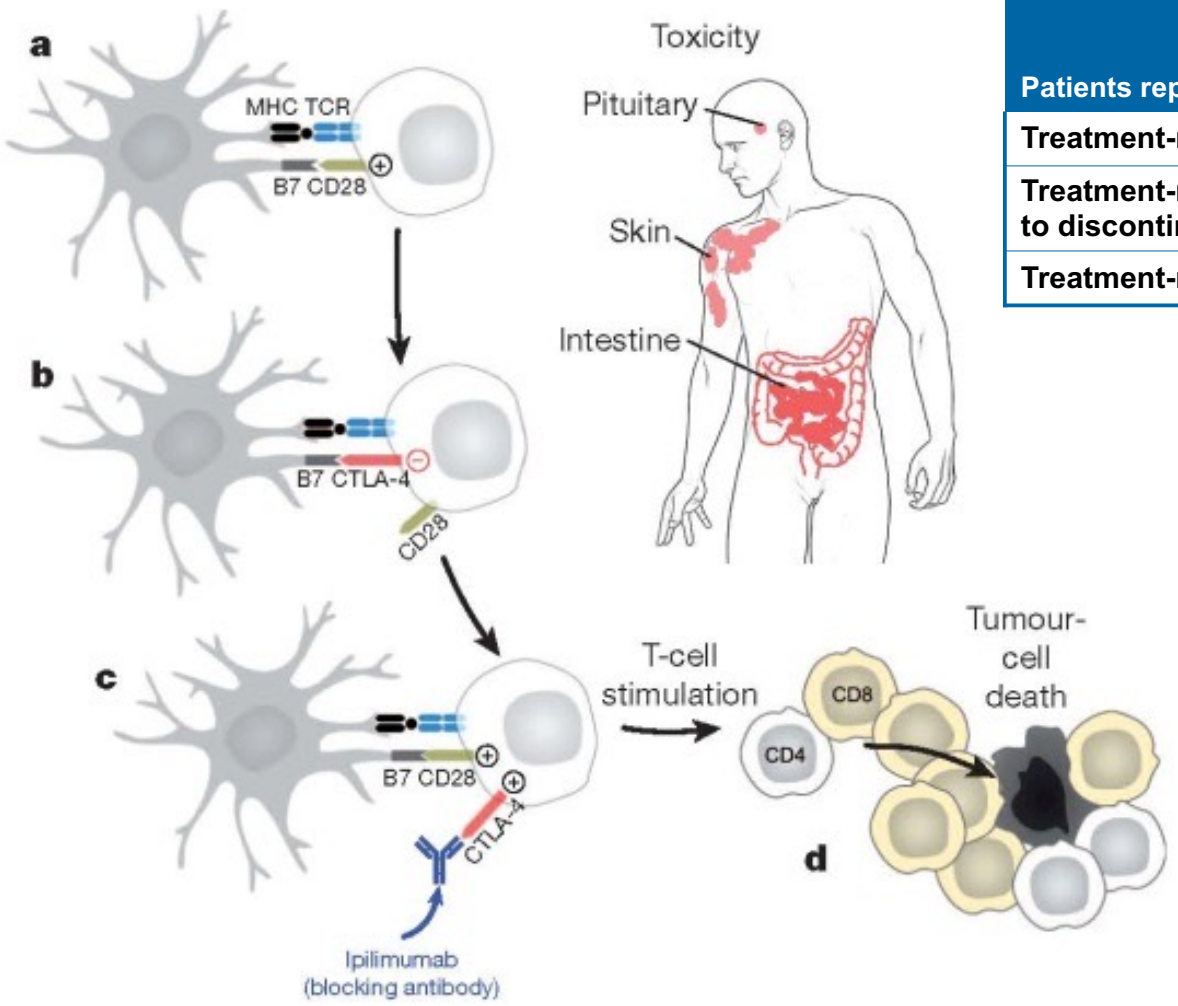


CR	8	8	8	7	6	6	6	5	5	5	5	4	4	3	1
PR	50	50	50	46	40	38	35	34	32	31	30	29	28	27	4
SD	61	61	61	54	48	38	33	31	27	25	21	16	14	13	1
PD	80	80	80	54	39	29	24	22	21	18	17	17	16	16	1

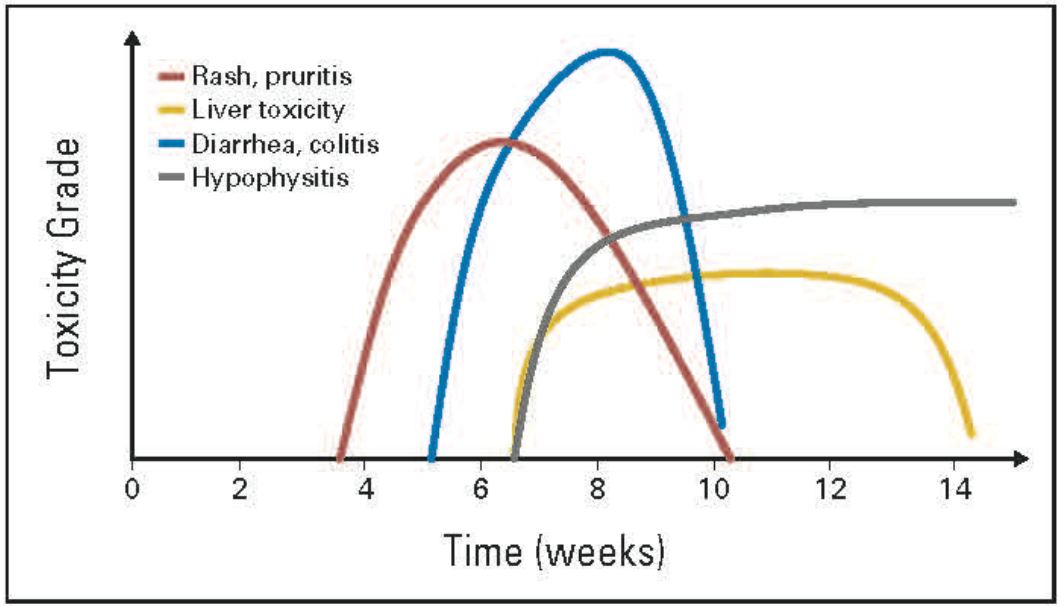
- **Patients with a best overall response of a CR, PR, SD, or PD at 12 months were followed for OS**

Wolchock, JD, et al., *JCO, Jan 2022 .*

Toxicity organs, incidence, patterns



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, %	95.8	**59.1**	86.3	**22.4**	86.2	27.7
Treatment-related AE leading to discontinuation, %	40.3	**30.4**	12.5	**8.0**	15.1	13.5
Treatment-related death, n (%)	2 (0.6)		1 (0.3)		1 (0.3)	

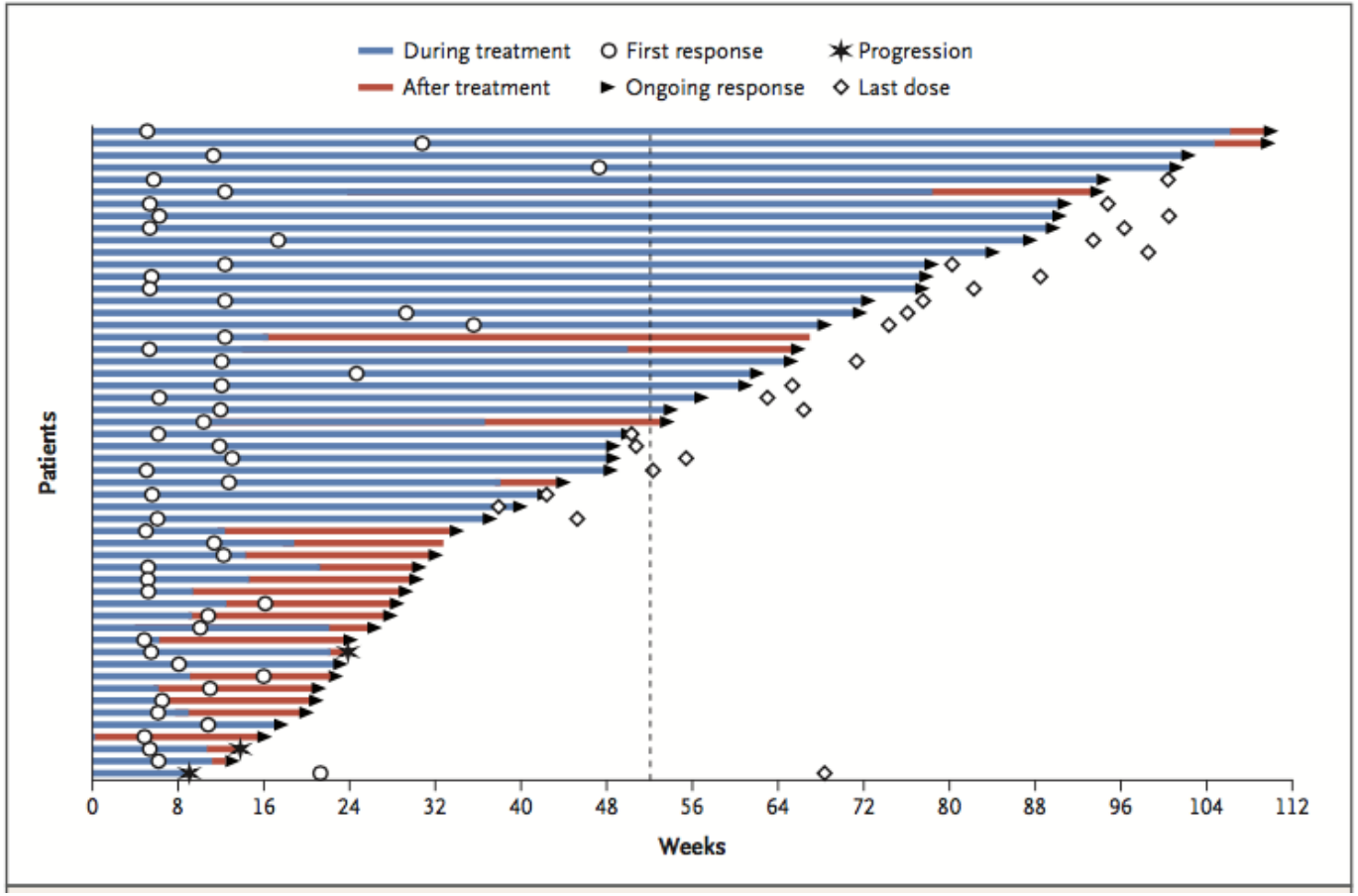


Weber, et al., *The Oncologist, 2016.*

CheckMate-204: Phase 2 of Ipi + Nivo in MBM in Asymptomatic Patients

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)

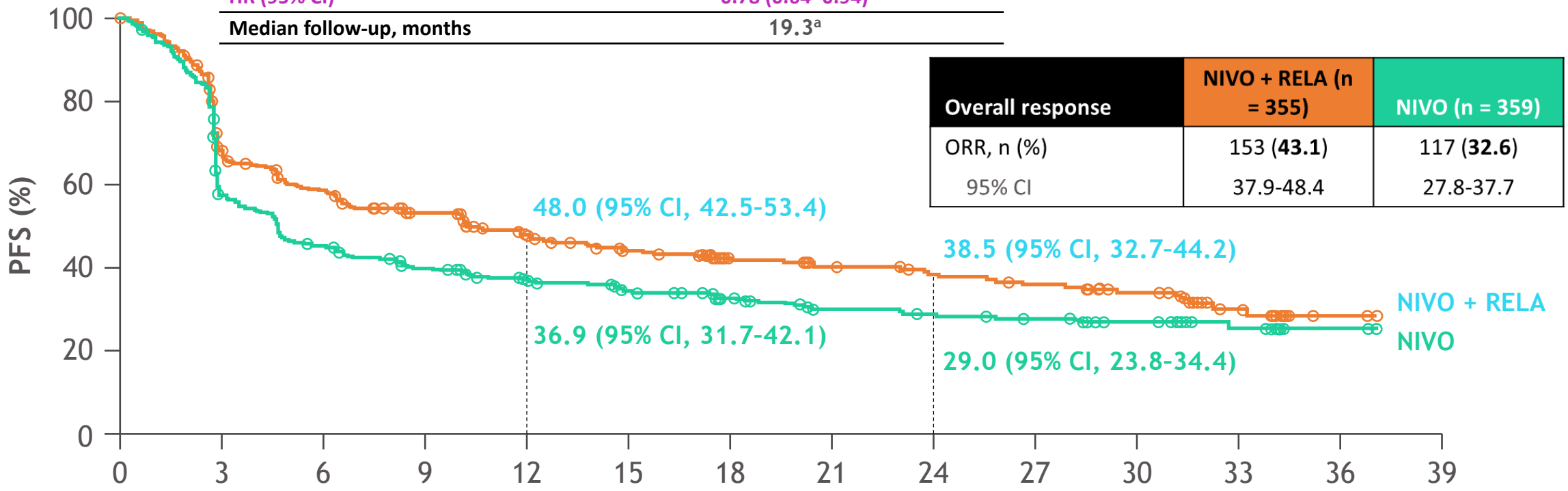


Tawbi et al, NEJM 2017

Relativity-047- Nivo/Rela vs Nivo

	NIVO + RELA (n = 355)	NIVO (n = 359)
Median PFS, months	**10.22**	**4.63**
(95% CI)	(6.51–14.75)	(3.48-6.44)
HR (95% CI)	**0.78 (0.64–0.94)**	
Median follow-up, months	**19.3[a]**	

Overall response	NIVO + RELA (n = 355)	NIVO (n = 359)
ORR, n (%)	153 (**43.1**)	117 (**32.6**)
95% CI	37.9-48.4	27.8-37.7



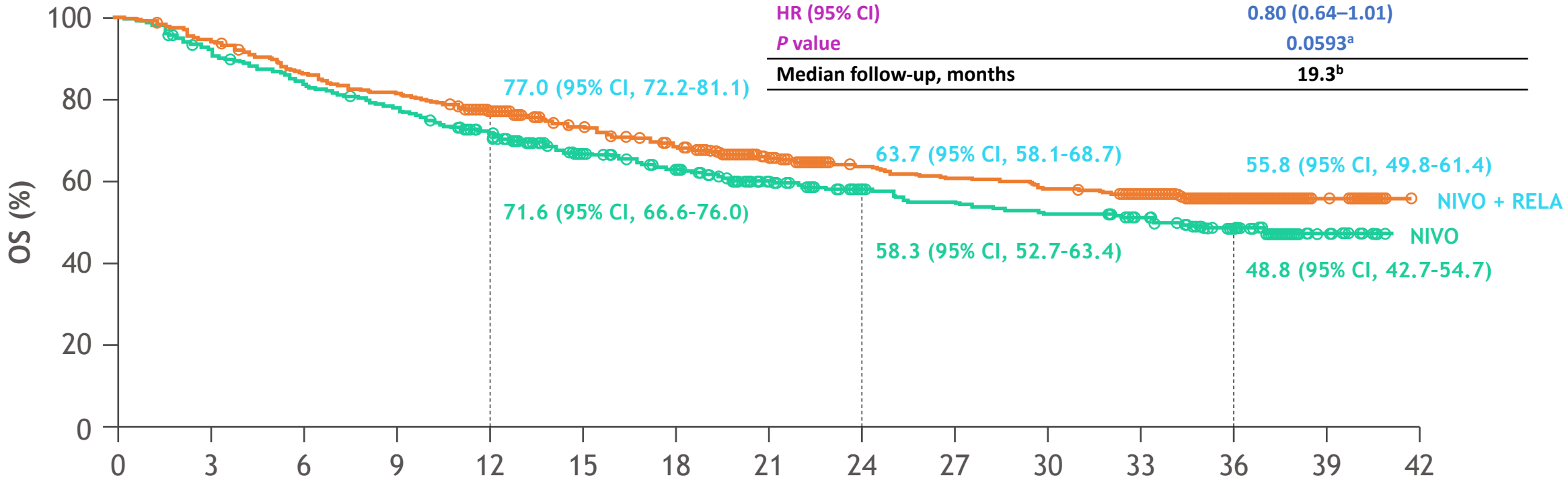
No. at risk													
NIVO + RELA	355	223	189	159	130	106	82	70	64	59	48	20	2	0
NIVO	359	192	150	124	98	82	67	52	49	45	33	15	3	0

Statistical model for HR and *P* value: stratified Cox proportional hazard model. Stratified by LAG-3, *BRAF*, and AJCC M stage. PD-L1 was removed from stratification because it led to subgroups with < 10 patients. Database lock date: October 28, 2021.

[a]Minimum potential follow-up (time from last patient randomized to last patient, last visit) was 8.7 months.

Secondary endpoint: overall survival

	NIVO + RELA (n = 355)	NIVO (n = 359)
Median OS, months	NR	34.10
(95% CI)	(34.20–NR)	(25.23–NR)
HR (95% CI)	0.80 (0.64–1.01)	
***P* value**	0.0593[a]	
Median follow-up, months	19.3[b]	



No. at risk															
NIVO + RELA	355	334	305	287	261	227	203	167	145	139	133	109	50	9	0
NIVO	359	329	301	277	240	202	182	155	126	119	113	96	42	8	0

Statistical model for HR and *P* value: stratified Cox proportional hazard model and stratified log-rank test. Stratified by LAG-3, *BRAF*, and AJCC M stage. PD-L1 was removed from stratification because it led to subgroups with < 10 patients. Database lock date: October 28, 2021.
[a]OS boundary for statistical significance was $P < 0.04302$ (2-sided) analyzed at 69% power; target HR, 0.75; [b]Minimum potential follow-up (time from last patient randomized to last patient, last visit) was 8.7 months.

Safety summary

- RELA + NIVO FDC was associated with a manageable safety profile and without unexpected safety signals

AE, n (%)	RELA + NIVO (n = 355)		NIVO (n = 359)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Any AE	345 (97.2)	143 (40.3)	339 (94.4)	120 (33.4)
TRAE	288 (81.1)	67 (18.9)	251 (69.9)	35 (9.7)
Leading to discontinuation	52 (14.6)	30 (8.5)	24 (6.7)	11 (3.1)
TRAE ≥ 10%				
Pruritus	83 (23.4)	0	57 (15.9)	2 (0.6)
Fatigue	82 (23.1)	4 (1.1)	46 (12.8)	1 (0.3)
Rash	55 (15.5)	3 (0.8)	43 (12.0)	2 (0.6)
Arthralgia	51 (14.4)	3 (0.8)	26 (7.2)	1 (0.3)
Hypothyroidism	51 (14.4)	0	43 (12.0)	0
Diarrhea	48 (13.5)	3 (0.8)	33 (9.2)	2 (0.6)
Vitiligo	37 (10.4)	0	35 (9.7)	0

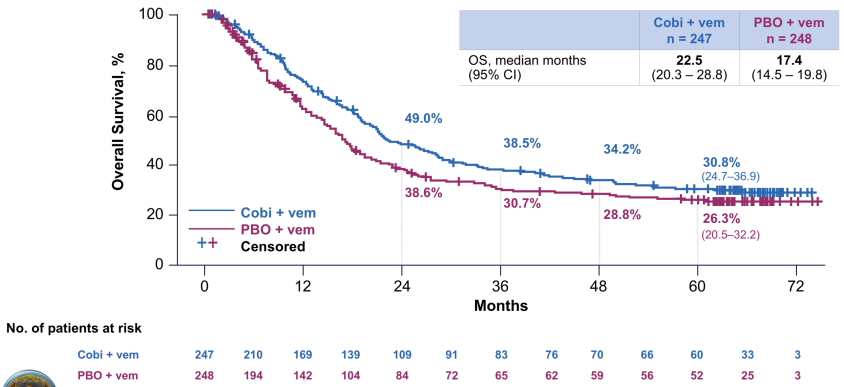
- Treatment-related deaths: RELA + NIVO (n = 3) – hemophagocytic lymphohistiocytosis, acute edema of the lung, and pneumonitis; NIVO (n = 2) – sepsis and myocarditis, and worsening pneumonia

AE, adverse event. Includes events reported between first dose and 30 days after last dose of study therapy. Other grade 3/4 TRAEs that were associated with any grade TRAEs occurring in <10% of patients not shown.

Three different dual targeted combinations: dabrafenib + trametinib, vemurafenib+cobimetinib, encorafenib+binimetinib

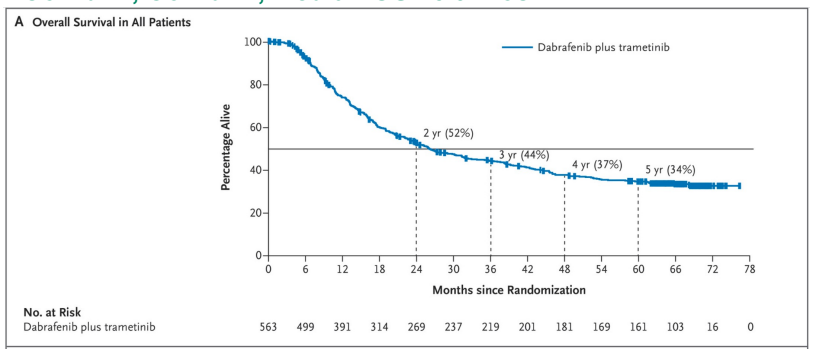
5 year survival rates

Co-BRIM, Median OS 22.5 mos



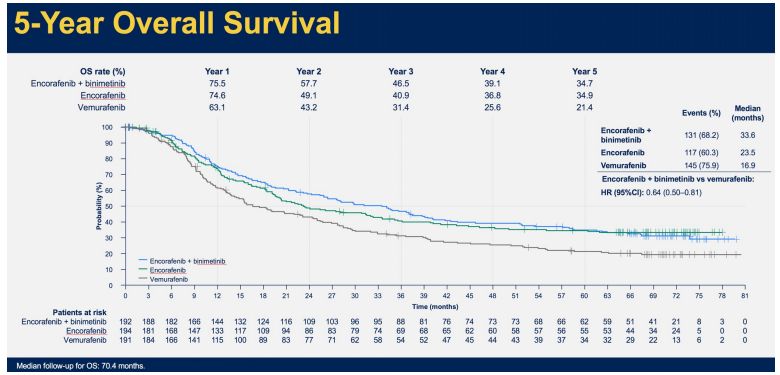
McArthur et al., *SMR* 2019

Combi-V, Combi-D, Median OS 25.9 mos



Robert et al., *N Engl J Med.* 2019

COLUMBUS, Median OS 33.6 mos



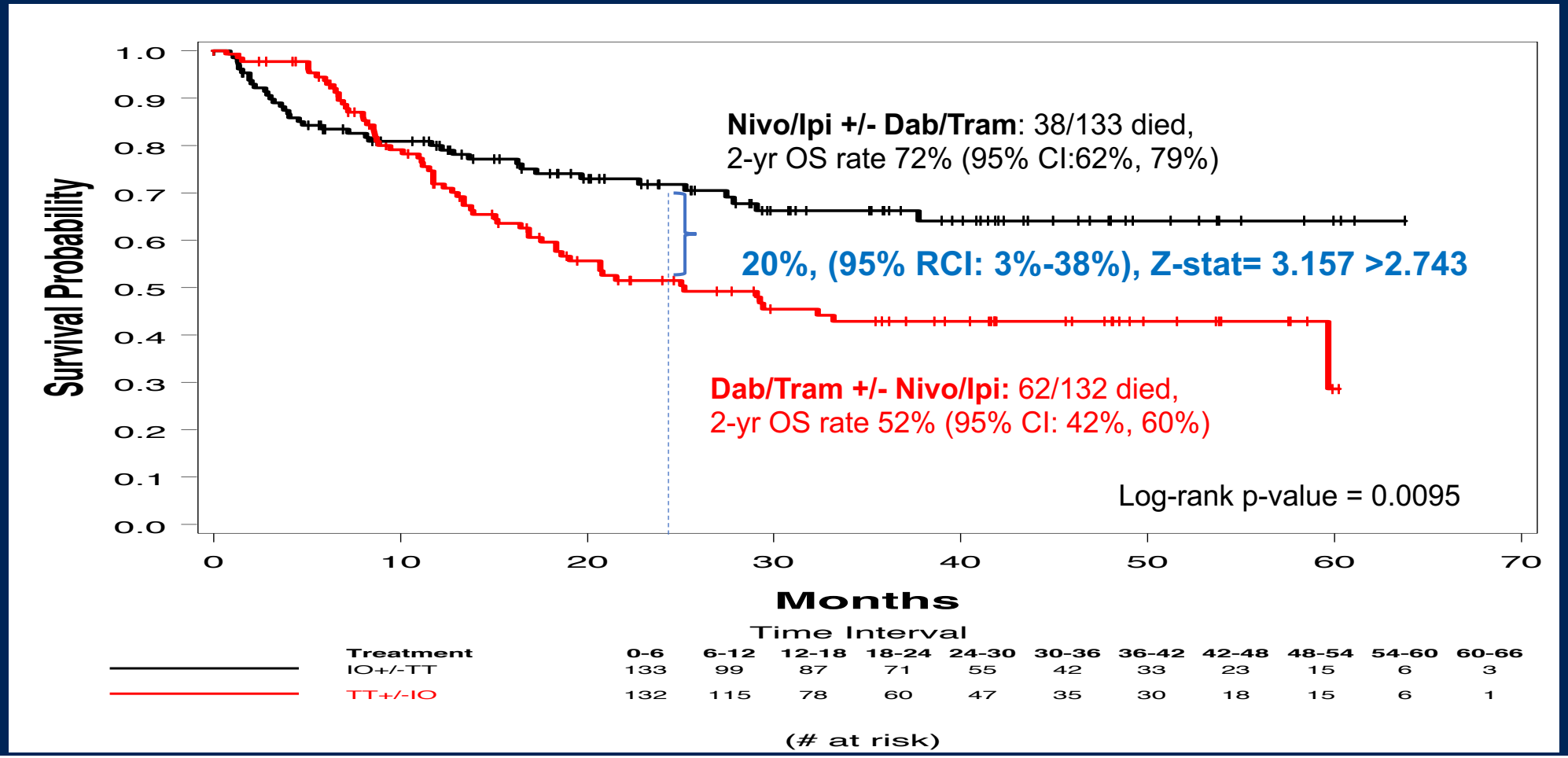
Dummer et al., ASCO 2021, abstract 9507

Dual targeted therapy and AEs

	COMBI-D	COMBI-V	Enco/Bini (COLUMBUS)	coBRIM
Toxicity (% all/ % ≥Gr 3)	DT	DT	EB	VC
Pyrexia	52 / 7	53 / 4	18/4	26 / 2
Photosensitivity		4 / 0	5 / 1	28 / 2
Nausea	20 / 0	36 / 1	41/2	40 / 1
Arthralgia	16 / <1	24 / 1	26/1	32 / 2
ALT up	10 / 2		13/6**	23 / 11
Hyperkeratosis	6 / 0	4 / 0	14/1	10 / 0
Hand-foot	6 / <1	4 / 0	7/0	
cuSCC	3 / 3	1 / 1	4/0	1 / 1
EF down	4 / 1	8 / 4	8/2	8 / 1

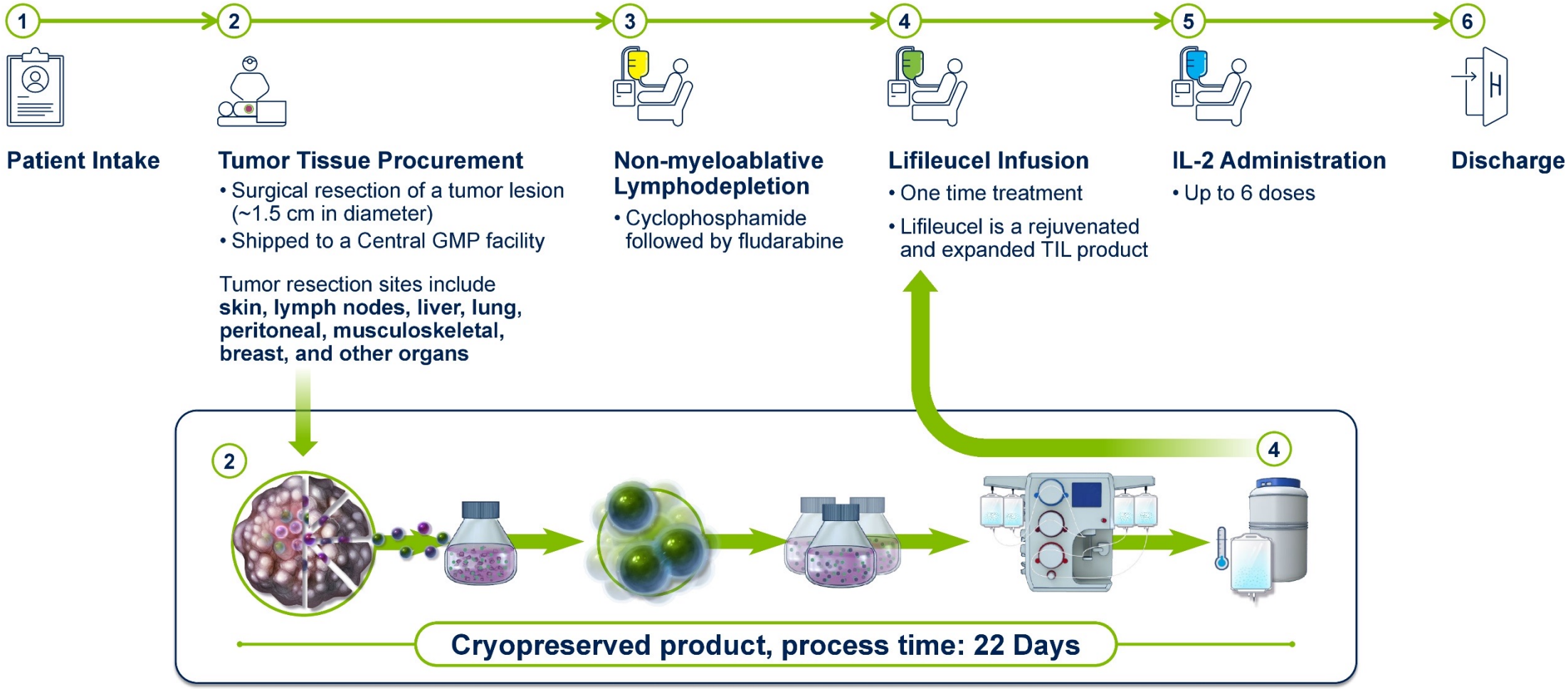
Ryan Sullivan, MD

DREAMseq: start with Ipi/nivo or Dab/Tram?
Overall Survival (OS)



PRESENTED BY: Michael B. Atkins, MD

Patient Journey and TIL Manufacturing



GMP, good manufacturing practices; IL-2, interleukin-2; NMA-LD, non-myeloablative lymphodepletion; TIL, tumor infiltrating lymphocytes.

Presented By: **James M. G. Larkin, MD, FRCP, PhD**

Baseline Patient and Disease Characteristics

Characteristic	N=66
Gender, n (%)	
Female	27 (41)
Male	39 (59)
Age, years	
Median	55
Min, max	20, 79
Prior Therapies, n (%)	
Mean number of prior therapies	3.3
Anti–PD-1 / Anti–PD-L1	66 (100)
Anti–CTLA-4	53 (80)
Anti–PD-1 + Anti–CTLA-4	34 (52)
BRAFi / MEKi	15 (23)
Progressive Disease for ≥1 Prior Therapy, n (%)	
Anti–PD-1 / Anti–PD-L1	65 (99)
Anti–CTLA-4	41 (77)*
ECOG Performance Status, n (%)	
0	37 (56)
1	29 (44)

Characteristic	N=66
BRAF Mutation Status, n (%)	
Mutated V600E or V600K	17 (26)
Wild type	45 (68)
Unknown	3 (5)
Other	1 (2)
Tumor PD-L1 Expression, n (%)	
PD-L1 positive (TPS ≥5%)	23 (35)
PD-L1 negative (TPS <5%)	26 (39)
LDH, n (%)	
≤ULN	39 (59)
>1 to 2 × ULN	19 (29)
>2 × ULN	8 (12)
Target Lesions Sum of Diameter (mm)	
Mean (SD)	106 (71)
Min, max	11, 343
Number of Target and Non-Target Lesions	
>3, n (%)	51 (77)
Mean (SD)	6 (2.7)
Liver and / or brain lesions, n (%)	28 (42)

Patients had:

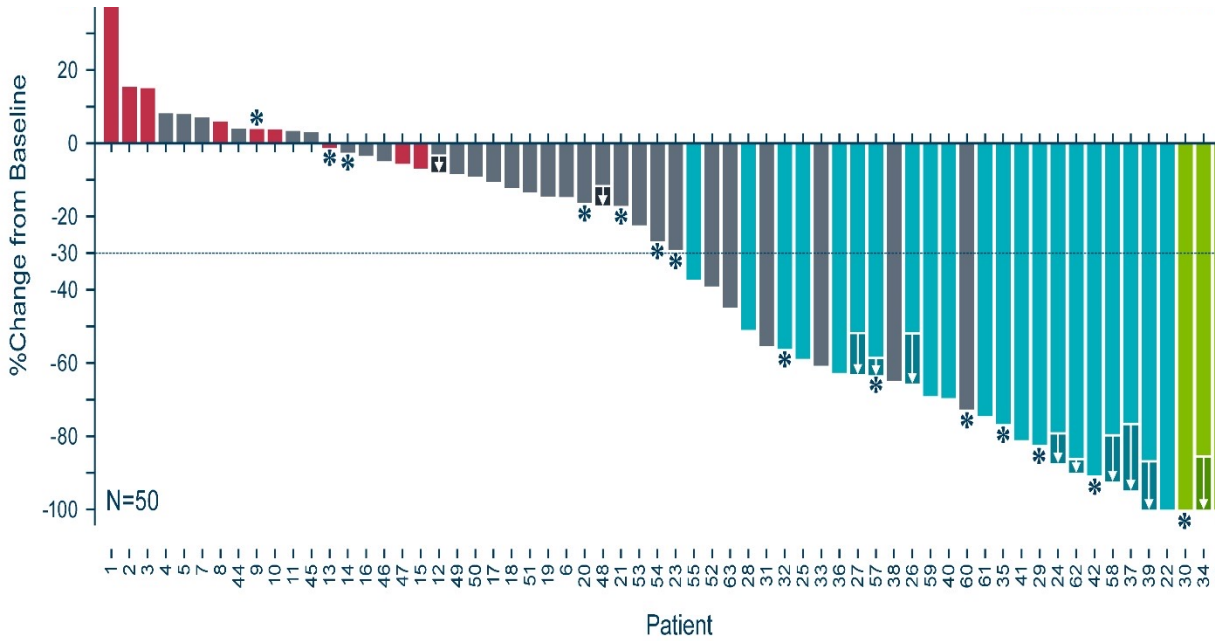
- **Mean of 3.3 prior therapies, ranging from 1–9**
- **High tumor burden at baseline**

*Percent is calculated based on number of patients who received prior anti–CTLA-4.
BRAFi, BRAF inhibitor; CTLA-4, cytotoxic T-lymphocyte antigen-4; ECOG, Easter Cooperative Oncology Group; LDH, lactate dehydrogenase; MEKi, MEK inhibitor; mm, millimeter; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1; SD, standard deviation; TPS, tumor proportion score; ULN, upper limit of normal.

 |

Objective Response Rate

Response, n (%)	N=66
Objective Response Rate	**24 (36.4)**
Complete response	3 (4.5)
Partial response	21 (31.8)
Stable disease	29 (43.9)
Progressive disease	9 (13.6)
Non-evaluable*	4 (6.1)
Disease control rate	53 (80.3)
Median Duration of Response	**Not Reached**
Min, max (months)	2.2, 38.5+



*Cox proportional hazards regression model.
†Assuming the data follow exponential distribution.
DOR, duration of response; HR, hazard ratio; LDH, lactate dehydrogenase; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand-1; ULN, upper limit of normal.

Summary on Targeted Therapy for Metastatic Disease

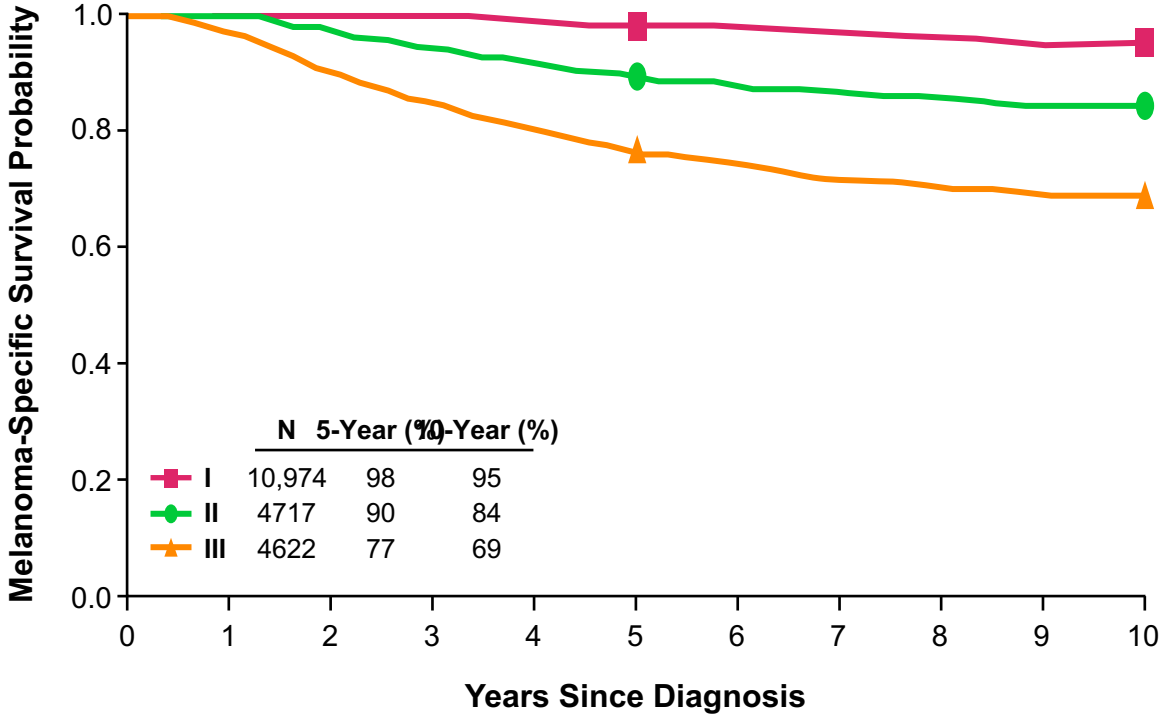
- BRAF is the most common mutation in cutaneous melanoma but is rarely identified in other melanoma sub-types (acral, mucosal, uveal)
- Combination BRAF+MEKi is superior to BRAFi alone in terms of PFS/OS and tolerability
- Development of resistance to these agents is expected and associated with development of aggressive disease
- Use of imatinib or other similar TKIs can be useful in pts with KIT mutated disease
- Targeted agents for NRAS mutations are being explored

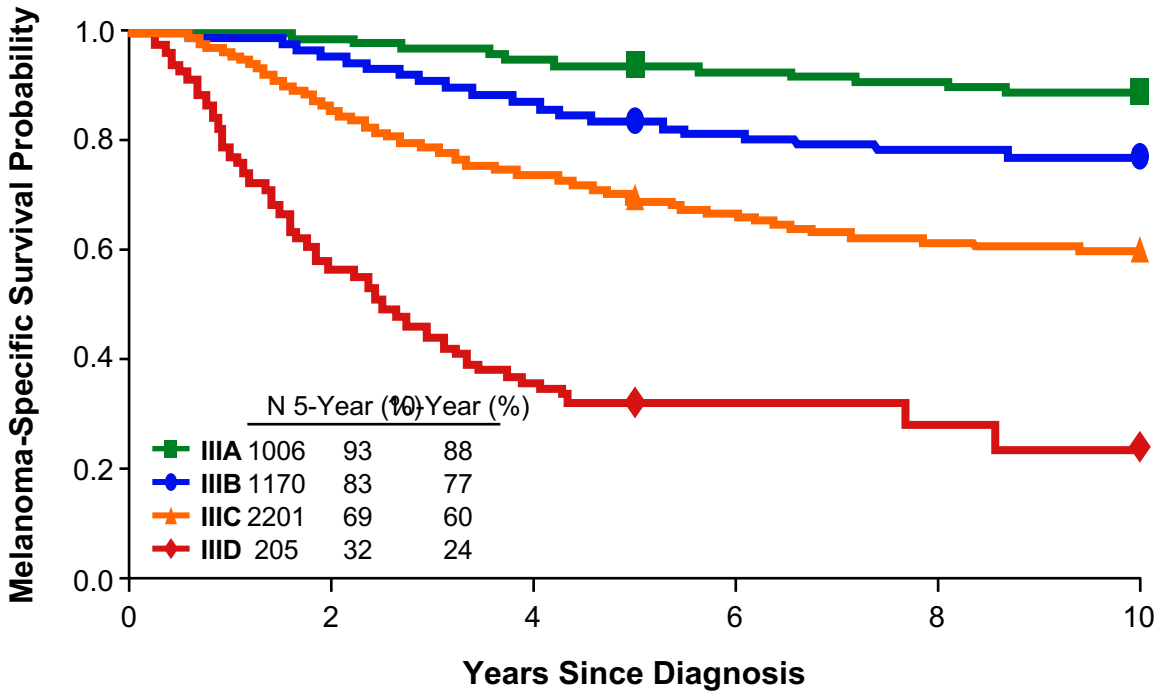
Summary on Immunotherapy

- These agents have the potential to produce prolonged duration of benefit and are thus used preferentially for the management of metastatic disease
- Ipi + Nivo is associated with 49% OS at 6.5 years but is associated with high-grade IRAEs
- Nivo/relatlimab is now FDA approved for use in stage IV melanoma based on favorable data in treatment naïve patents
- TVEC has a role in management of patients with isolated, small volume cutaneous or LN disease
- In patients with BRAF V600 mutations, OS is improved for upfront ipi/nivo followed by braf/mek at progression
- Vem/cobi/atezo is FDA approved for use in 1st line setting for patients with BRAF mutations

Adjuvant treatment

Melanoma-Specific Survival Stage I-III: AJCC 8th Edition



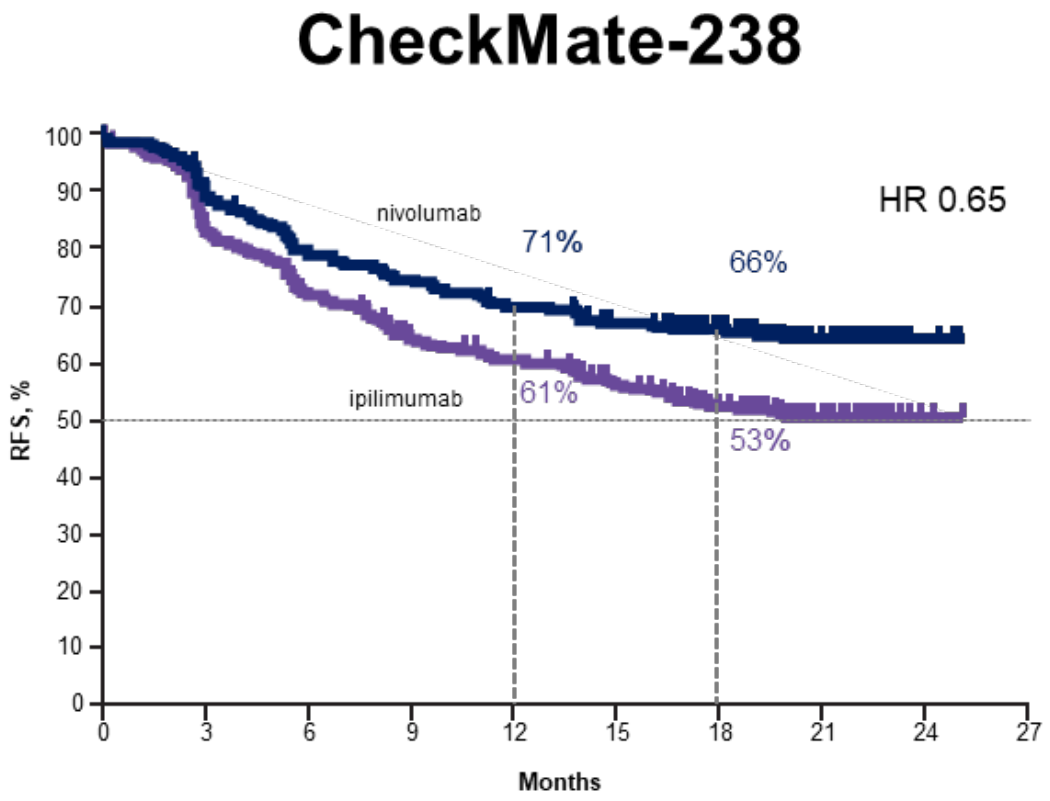


Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin*. 2017; doi:10.3322/caac.21409.

Anti-PD1 Adjuvant Immune Checkpoint Therapy for Stage III Melanoma

***Trials required CLND and size of LN metastasis >1mm for IIIA patients

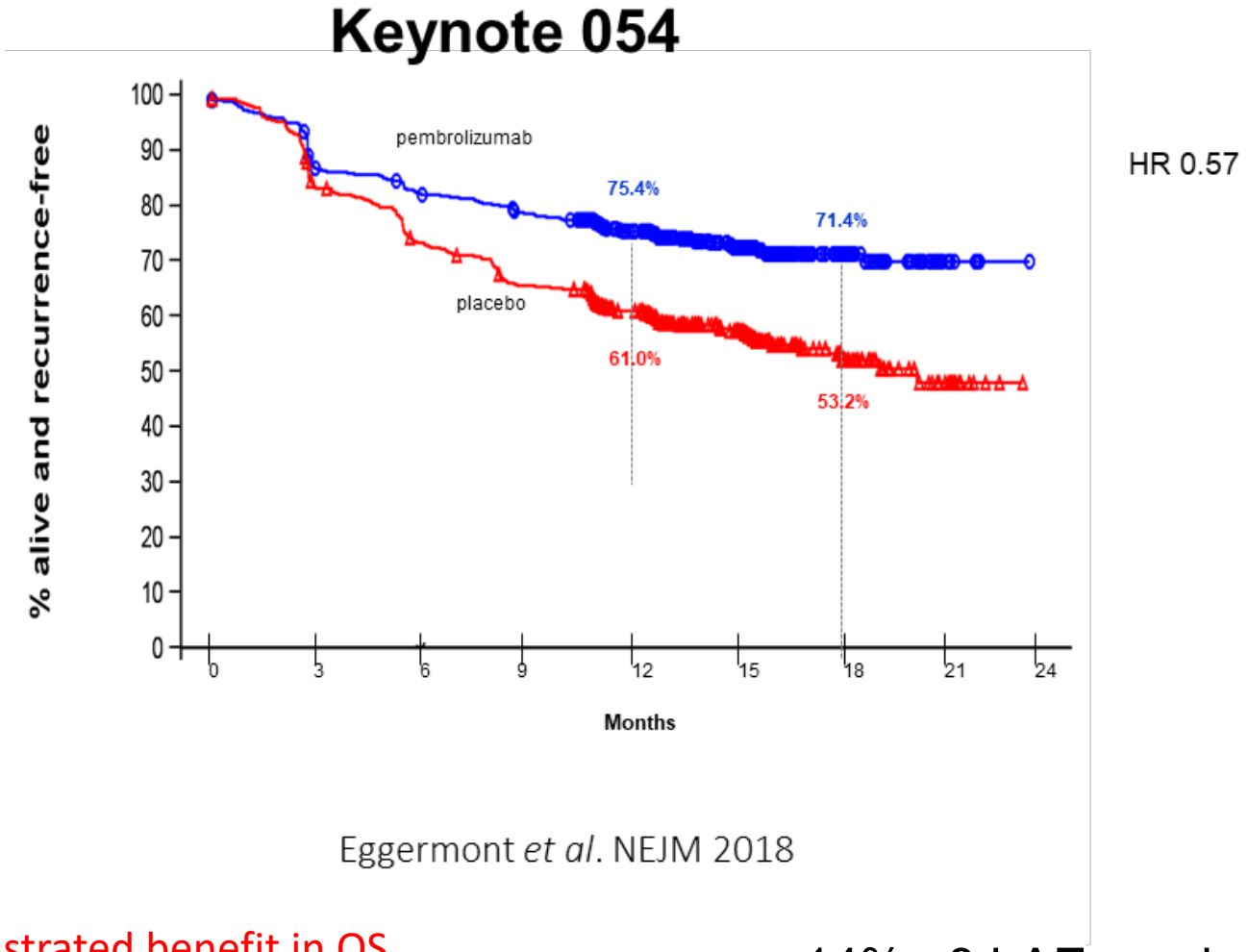
Resected stage IIIB-IIIC, IV melanoma N=906:
Nivo vs Ipi



Weber *et al*. NEJM 2017

14% g3 irAE nivo
46% g3 irAE ipi

Resected stage IIIA-IIIC melanoma N=1019:
Pembro vs placebo

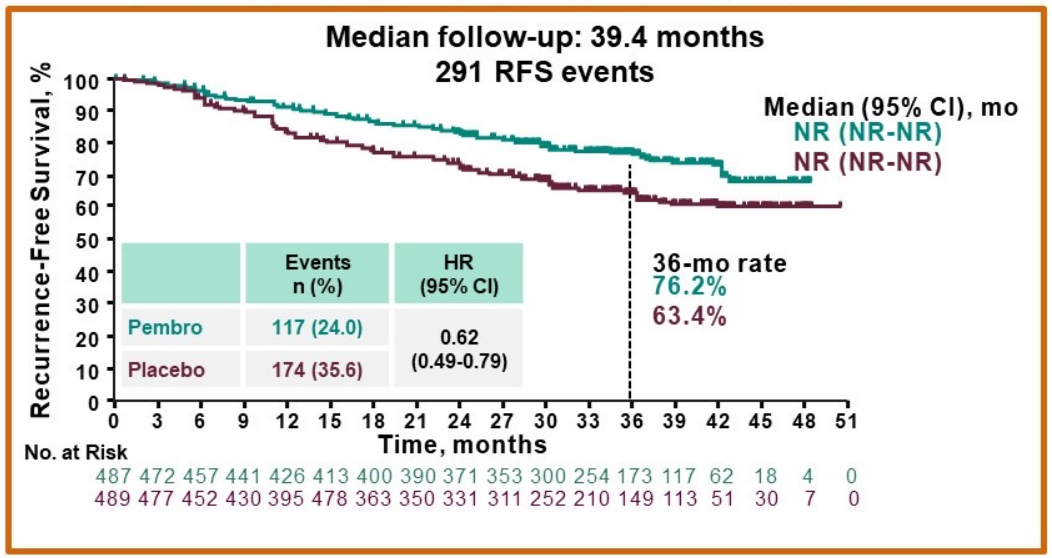


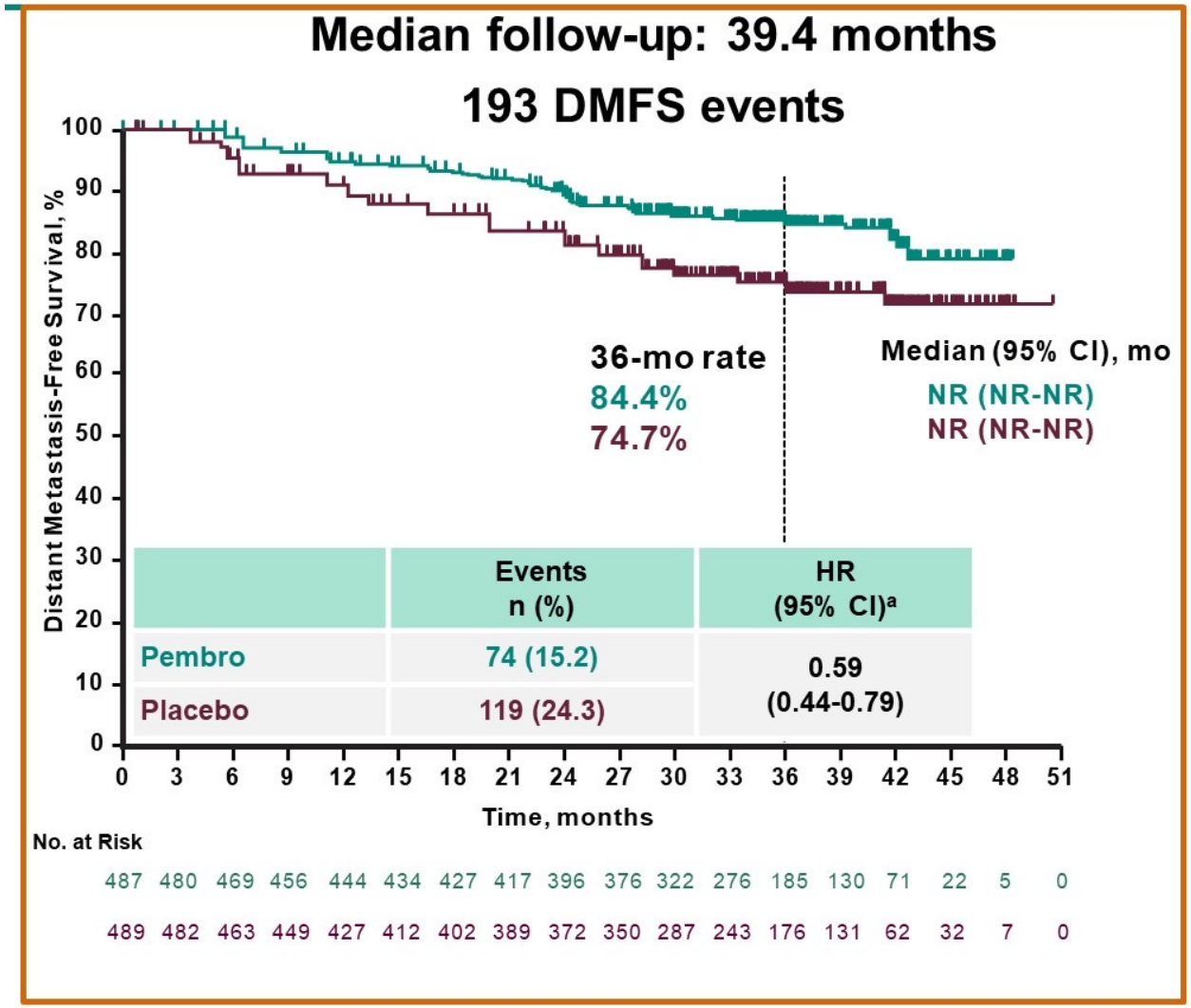
Eggermont *et al*. NEJM 2018

14% g3 irAE pembro

No demonstrated benefit in OS

Keynote 716: Adjuvant PD1 for High-Risk Stage IIB/IIC Melanoma

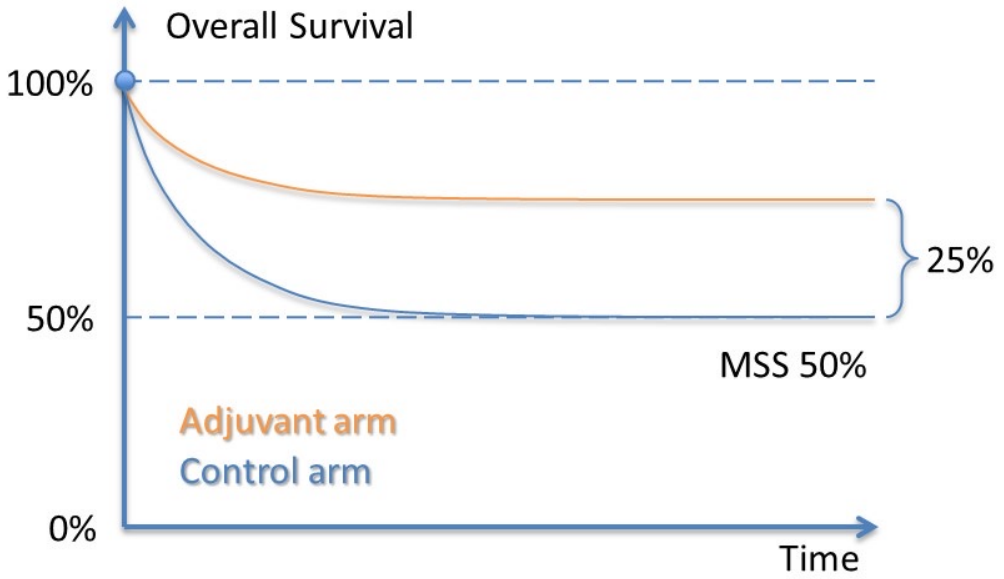




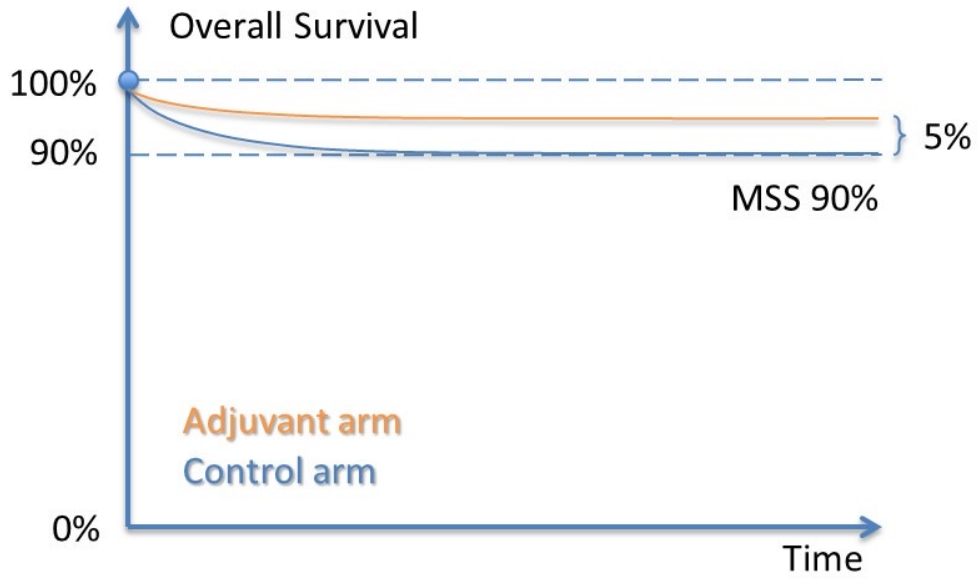
17% g3 irAE pembro

Number needed to treat in the adjuvant setting

Individual patient risks impact directly the number needed to treat (NNT) or to harm (NNH)



HR 0.5 and absolute benefit: 25%
NNT[1]: 1/0.25 = 4



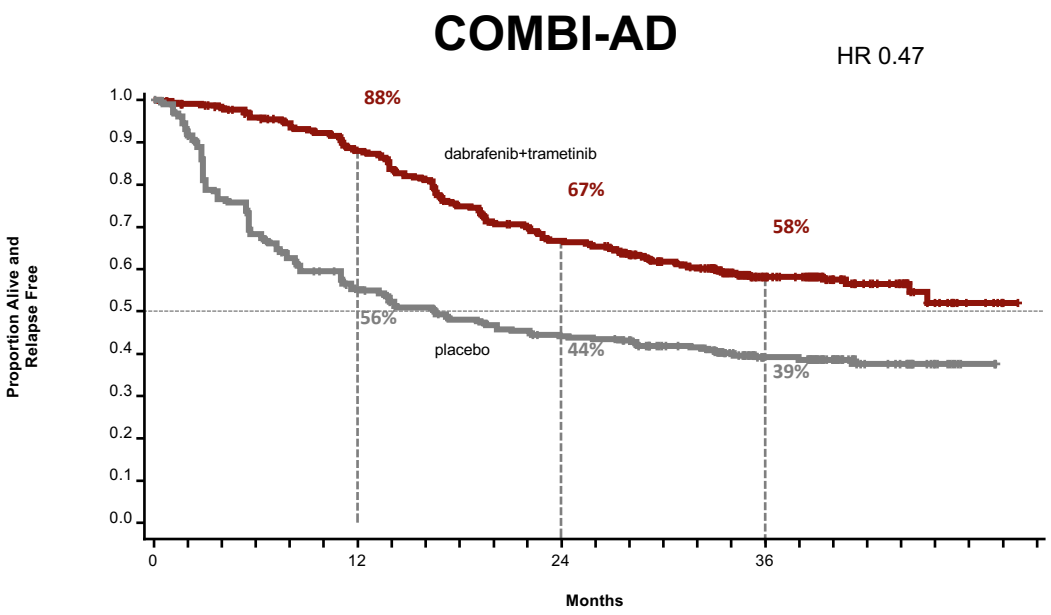
HR 0.5 and absolute benefit: 5%
NNT: 1/0.05 = 20

[1]NNT is computed as $1/(I_u-I_e)$, where I_e is the incidence of bad outcome in the exposed group and I_u that of the unexposed group; MSS, melanoma specific survival

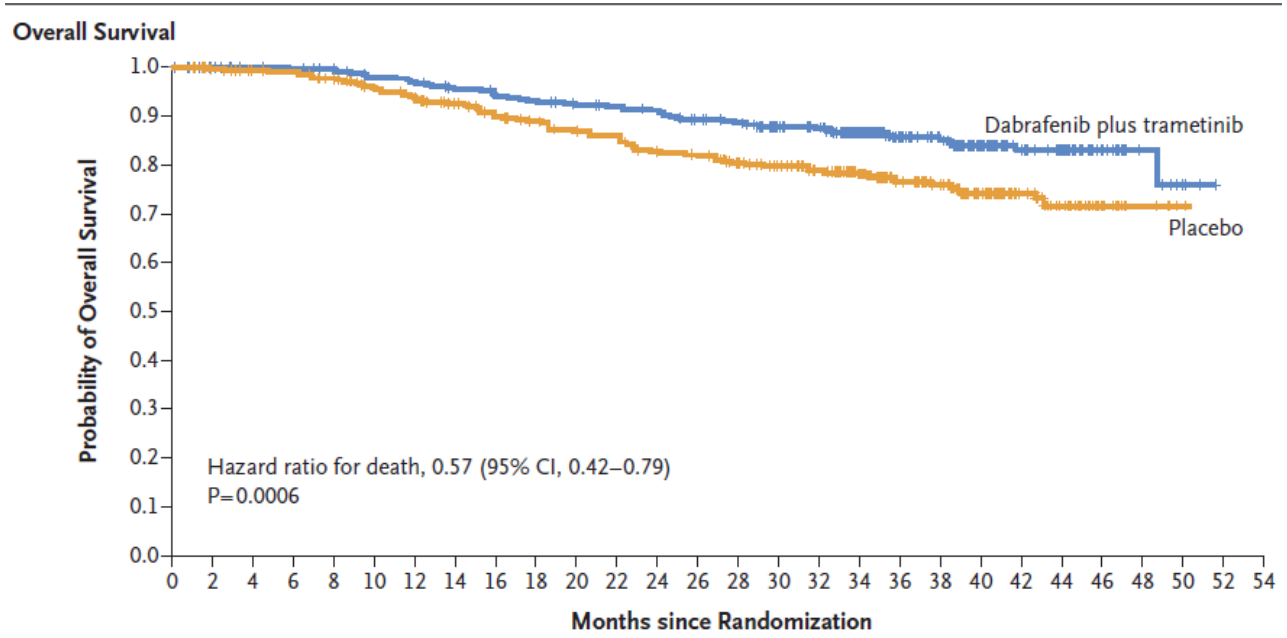
Adjuvant BRAF Directed Therapy for Stage III BRAF Mutated Melanoma

***Trial required CLND and size of LN metastasis >1mm for IIIA patients

Resected stage IIIA-IIIC melanoma
BRAF V600 E or K
N=807



Long et al. NEJM 2017



Hauschild et al. J Clin Oncol 2018

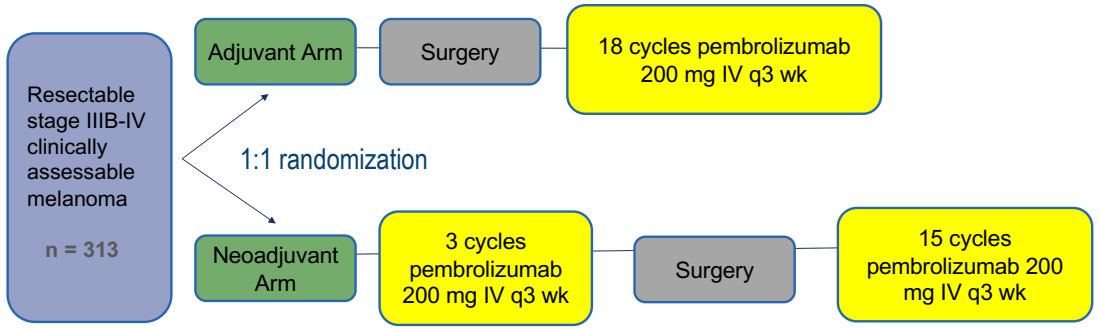
66% dose holds
38% dose reduction
26% stopped early

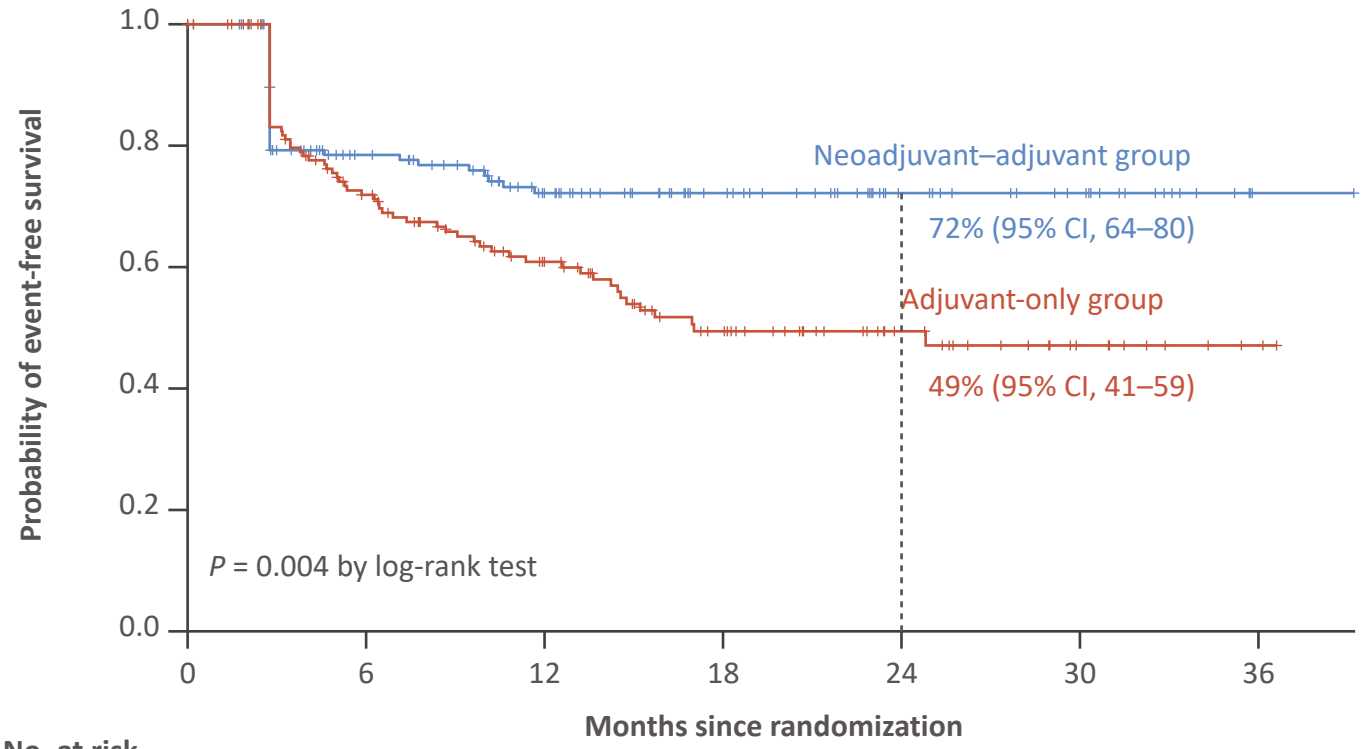
Summary on Adjuvant Medical Therapy

- Pembrolizumab is now FDA approved for adjuvant use in resected stage IIB/IIC melanoma
- Both nivolumab and pembrolizumab improve RFS and are associated with 14% ≥G3 toxicity rate. No proven OS benefit
- Ipi + nivo is NOT used for adjuvant therapy in stage III disease (does improve outcomes in resected Stge IV)
- Dabrafenib + trametinib improves PFS AND OS and tends to not be associated with permanent side effects
- There is no head-to-head data on which adjuvant regimen is optimal in a patient with BRAF mutated disease

Neoadjuvant treatment

S1801 : Neoadjuvant vs adjuvant Nivo



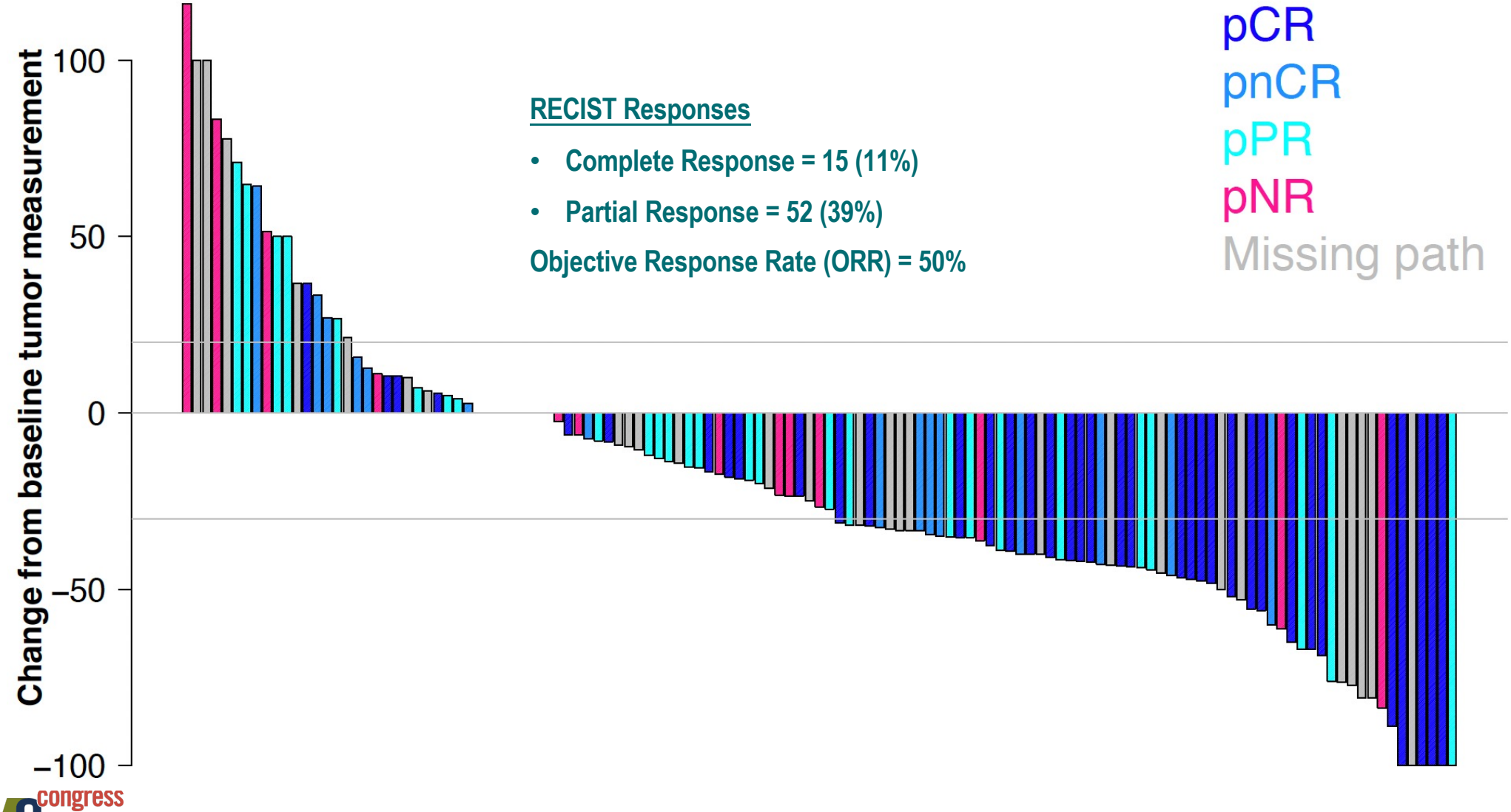


No. at risk							
Neoadjuvant-adjuvant	154	96	69	46	25	17	1
Adjuvant-only	159	98	67	40	22	10	2

Patel et al. NEJM 2023

S1801 waterfall plot of RECIST responses

Assessed after 3 cycles of neoadjuvant immunotherapy



Combination neoadjuvant immunotherapy regimens

Trial/Regimen	# of doses	N	pCR Rate	ORR	≥G3 Toxicity
Amaria et al.[1] **Ipi 3 + Nivo 1** Nivo 240mg	Up to 3 Up to 4	11 12	45% 25%	73% 25%	**73%** 8%
Blank et al.[2-3] OpACIN **Ipi 3 + Nivo 1**	2	10	33%	50%	**90%**
Rozeman et al.[3-4] OpACIN-Neo **Ipi 3 + Nivo 1** **Ipi 1 + Nivo 3** Ipi 3 + Nivo 3	2 2 4	30 30 26	47% 57% 23%	63% 57% 35%	**40%** **20%** 50%
Huang et al.[5] Pembro 200mg	1	29	19%	n/a	0%

1: Amaria et al. Nat Med 2018; 24: 1649-54; 2: Blank et al Nat Med 2018; 24: 1655-61; 3: Rozeman et al. 2021 27: 256-63 4: Rozeman et al. Lancet Oncol 2019; 20: 948-60; 5: Huang et al. Nat Med 2019; 25: 454-61