Optimal First Line Therapy for Newly Diagnosed Metastatic Melanoma Patients: Ipilimumab+Nivolumab

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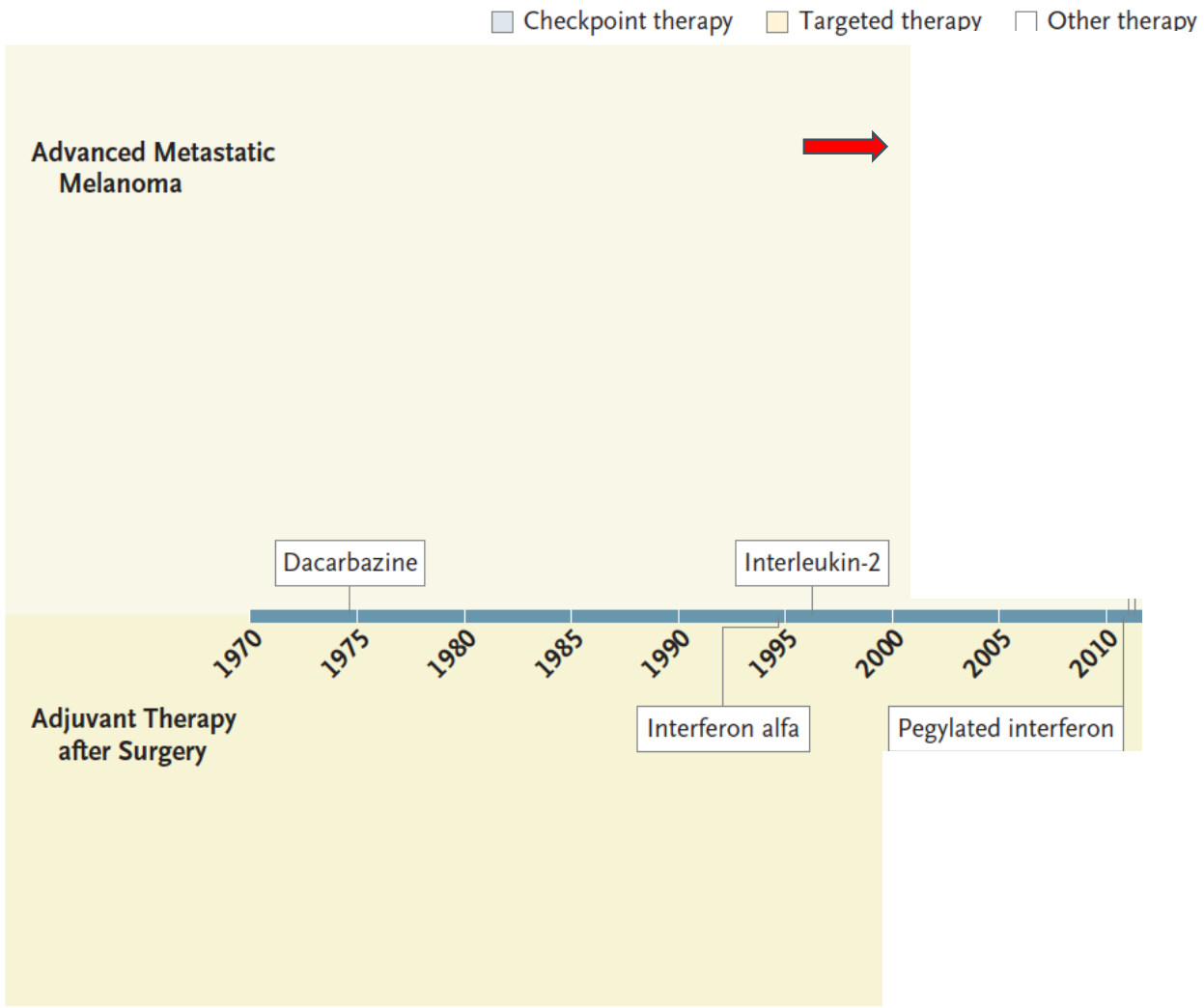
How we got here…



Relatlimab + nivolumab

Curti BD and Faries MB. NEJM. 2021 384;23:2229-2240

Immune-checkpoint inhibitors have revolutionized the treatment paradigm for advanced/metastatic melanoma

	Median OS
"The Dark Ages" Dacarbazine Interleukin-2 Interferon	6 months
"The Immunotherapy Era"	
Ipilimumab (anti-CTLA4) + nivolumab (anti-PD1) "Ipi/Nivo"	72 months
Relatlimab (anti-Lag3) + nivolumab (anti-PD1) "Rela/Nivo"	TBD

Ipi/Nivo has a durable effect

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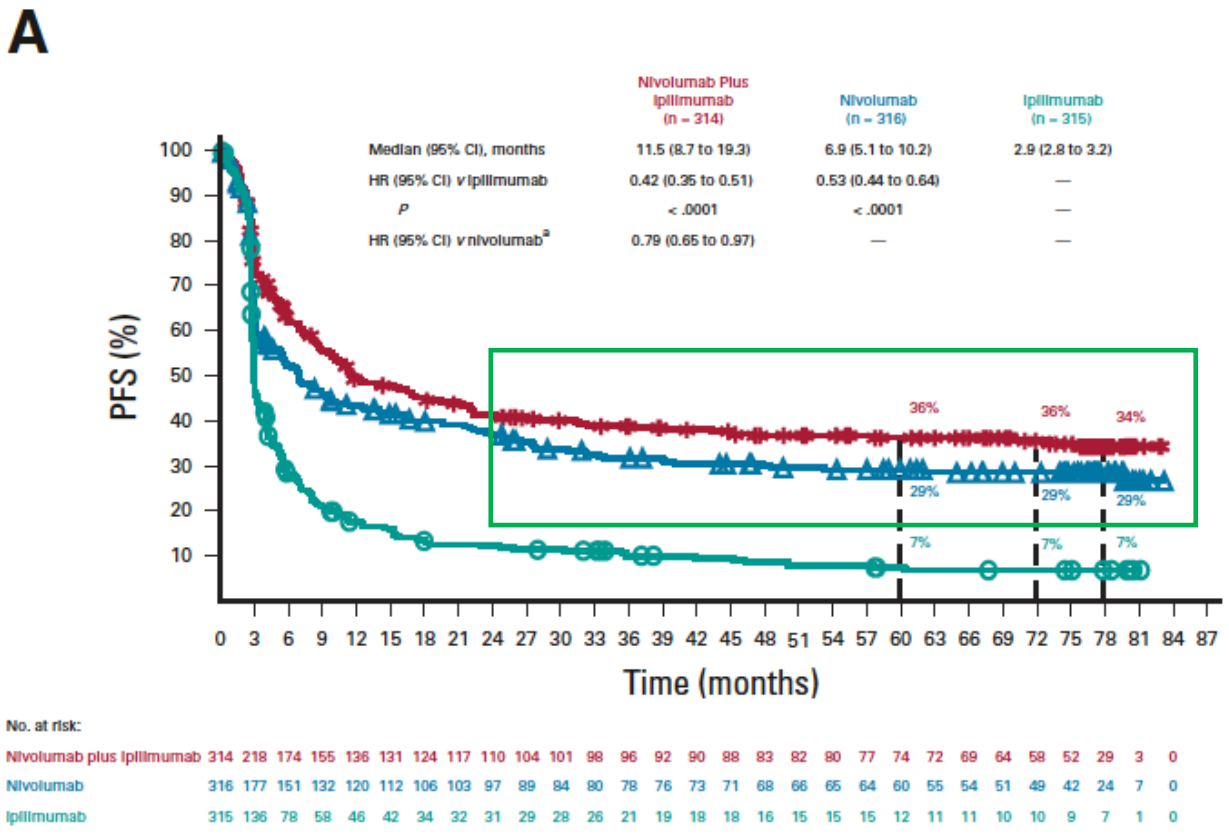

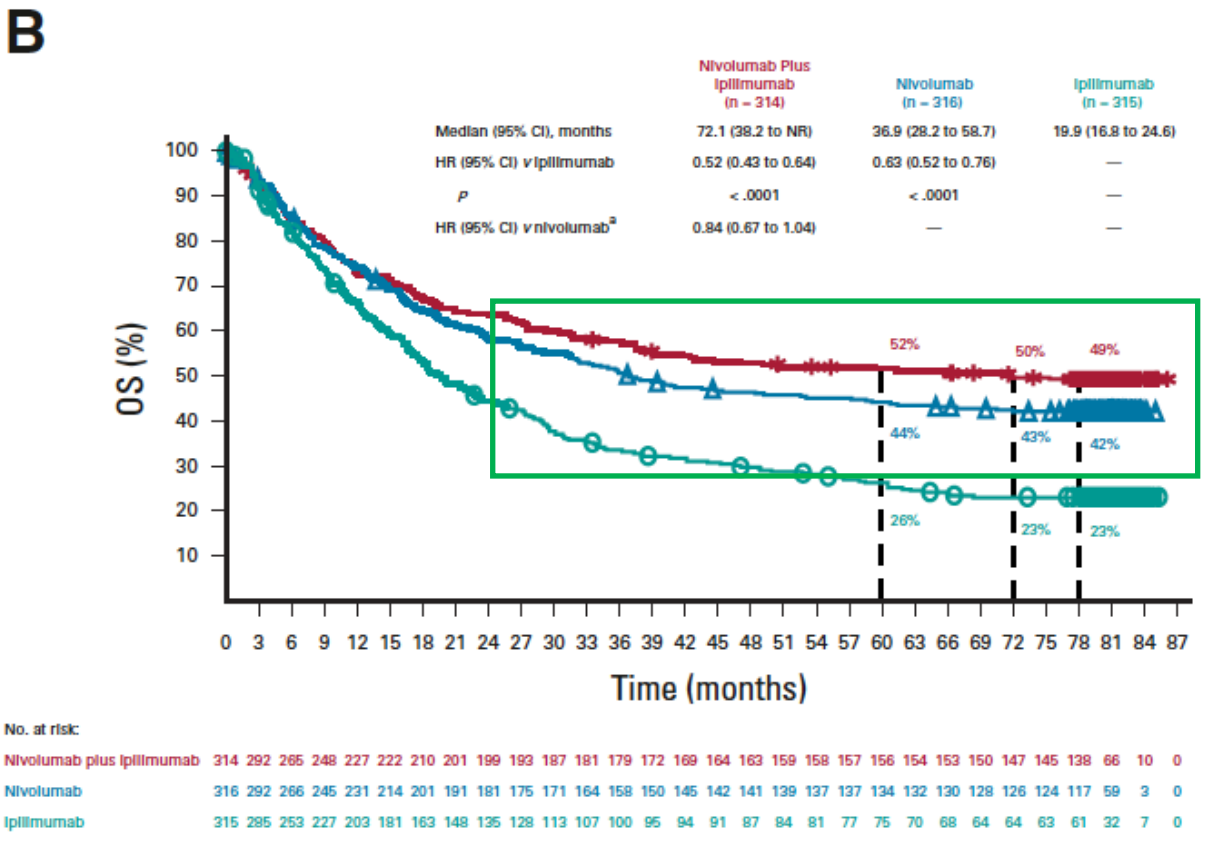

Wolchok et al. JCO. 2022 40(2):127-137

Ipi/Nivo has a long median treatment-free interval

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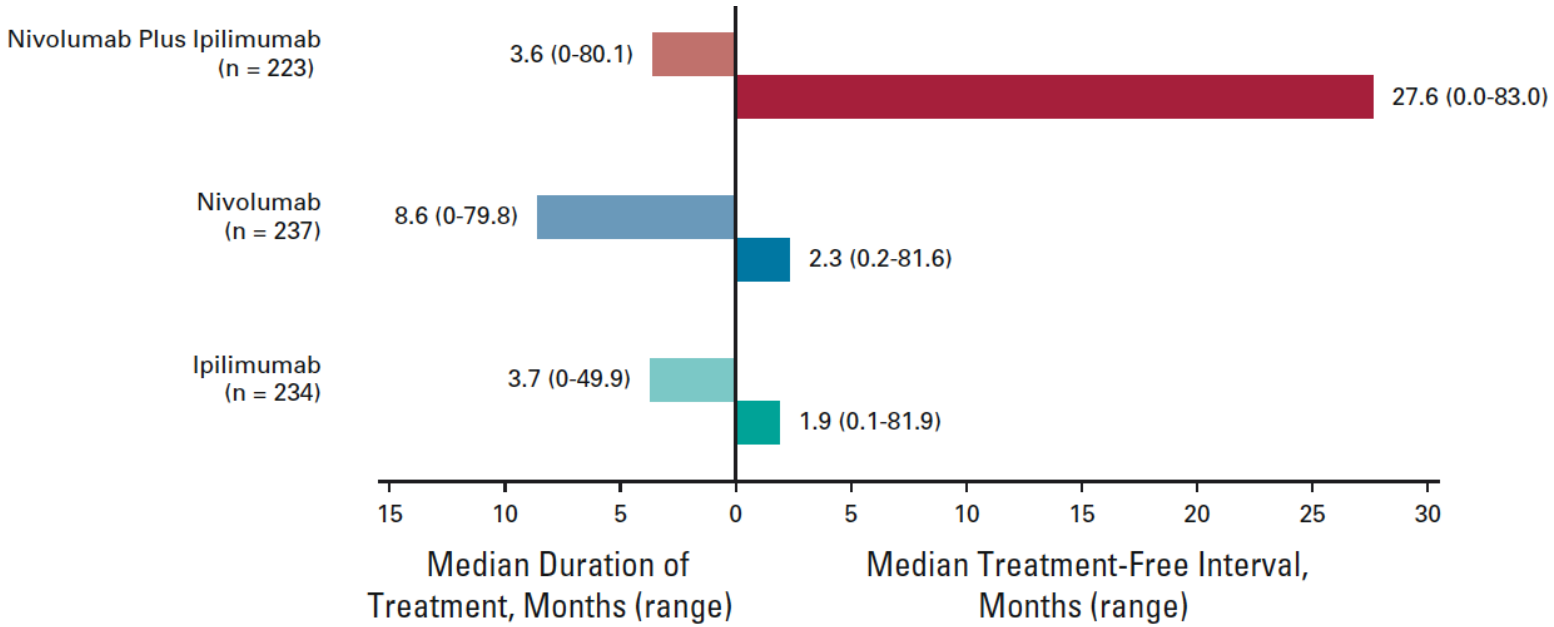
Wolchok et al. JCO. 2022 40(2):127-137

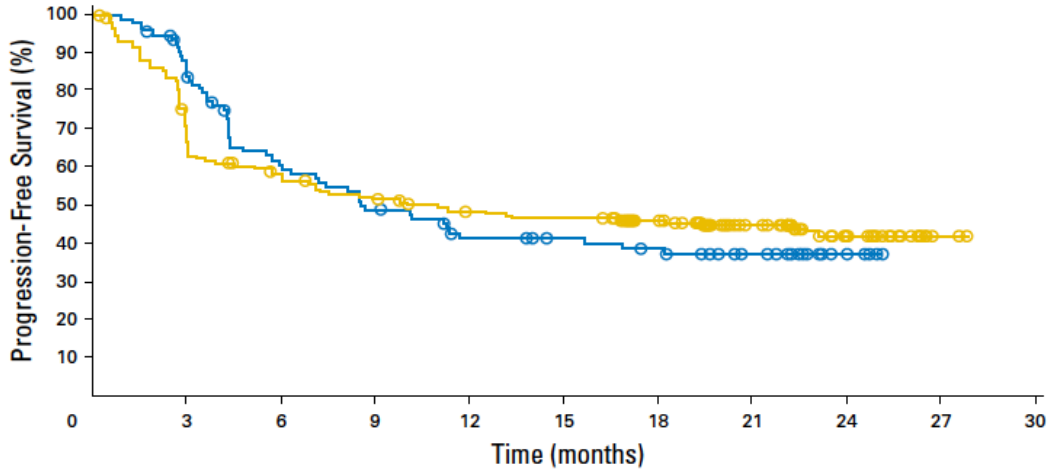


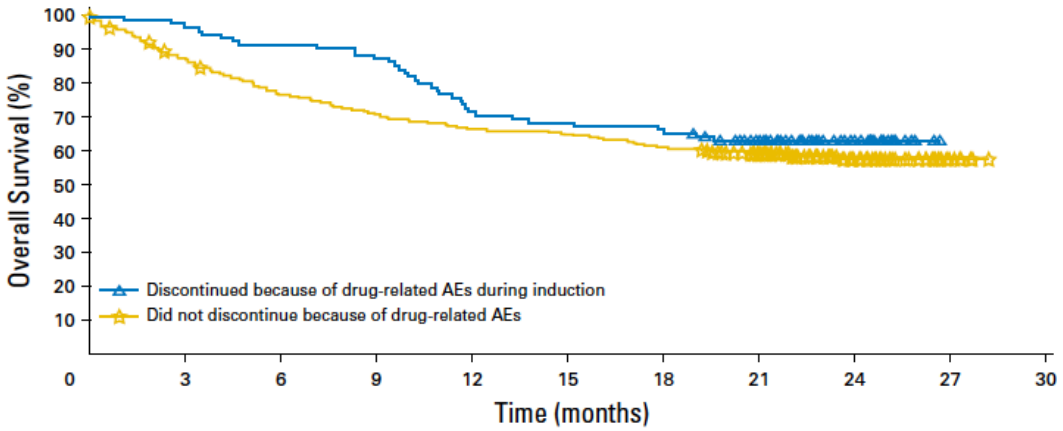
Caveats:

1. Study not powered to test Ipi/Nivo vs nivolumab monotherapy
2. Significant toxicity with Ipi/Nivo

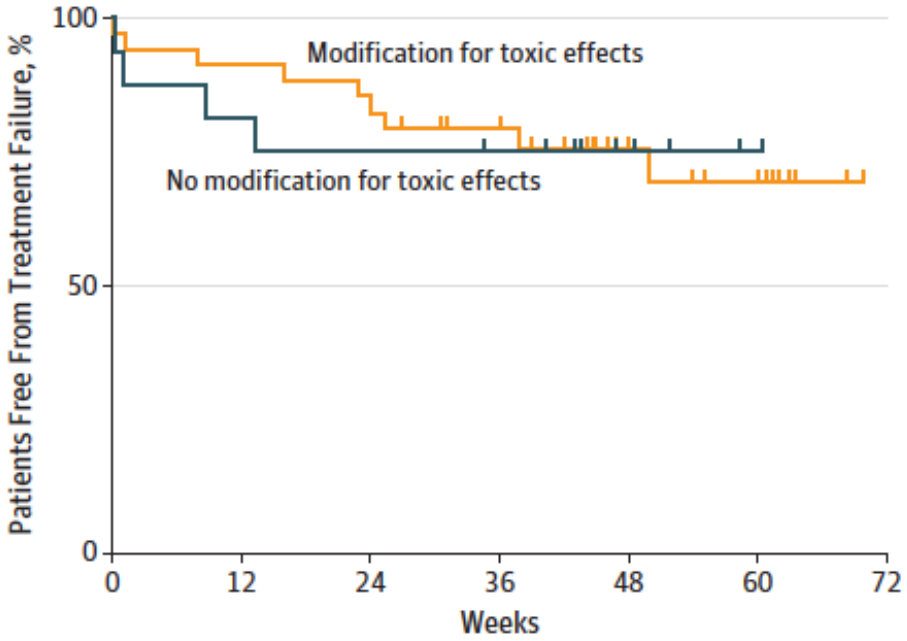
	Ipilimumab-Nivolumab		Nivolumab	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Treatment-related adverse events (%)	300 (96)	186 (59)	271 (87)	74 (24)
Led to discontinuation of treatment (%)	131 (42)	96 (31)	43 (14)	25 (8)

Similar outcomes for Ipi/Nivo-treated patients who discontinued therapy due to IRAEs





Schadendorf et al. JCO. 2017 35:3807-3814



No. at risk							
Modification	34	31	27	21	12	7	0
No modification	16	13	12	11	4	1	0

Shoushtari et al. JAMA Oncol. 2018;4(1):98-101

Approved “flip dose” to reduce toxicity:

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Patients randomized 1:1 to either

“Flip dose”: Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg

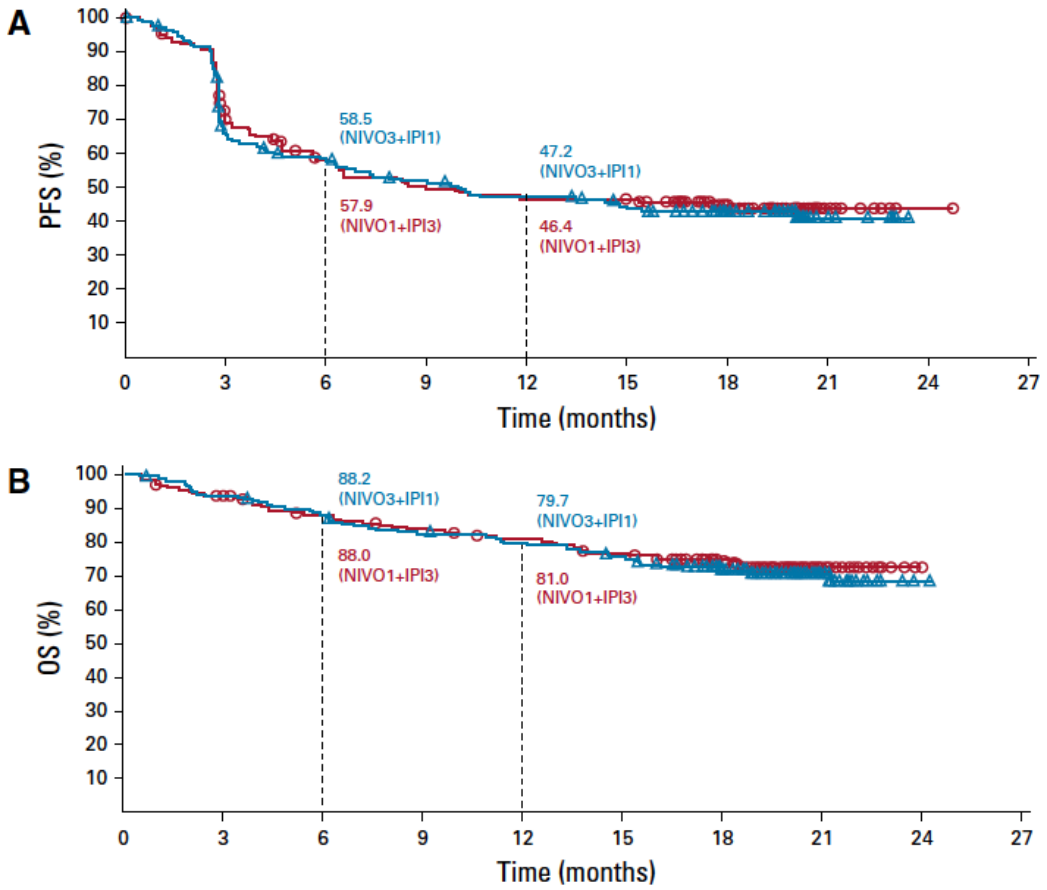
vs

Standard dose: Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg

Then, all patients received nivolumab 480 mg once every 4 weeks until disease progression or unacceptable toxicity

TABLE 2. Safety Summary

Variable	“Flip dose” NIVO3+IPI1 (n = 180)	Standard NIVO1+IPI3 (n = 178)
Treatment-related grade 3-5 AEs (95% CI), %	33.9 (27.0 to 41.3)	48.3 (40.8 to 55.9)
Difference (95% CI), %	−14.4 (−24.5 to −4.3)	
P	.006	
Treatment-related AEs	154 (85.6)	167 (93.8)
Grade 3 and 4	60 (33.3)	86 (48.3)
Grade 5	1 (0.6)	0
Serious AEs of any cause	86 (47.8)	113 (63.5)
Grade 3 and 4	61 (33.9)	85 (47.8)
Grade 5	6 (3.3)	3 (1.7)
Treatment-related AEs leading to discontinuation	43 (23.9)	59 (33.1)
Grade 3 and 4	30 (16.7)	49 (27.5)
Grade 5	1 (0.6)	0



Lebbe et al. JCO. 2019; 37:867-875

Improved efficacy of Ipi/Nivo in specific disease patient populations

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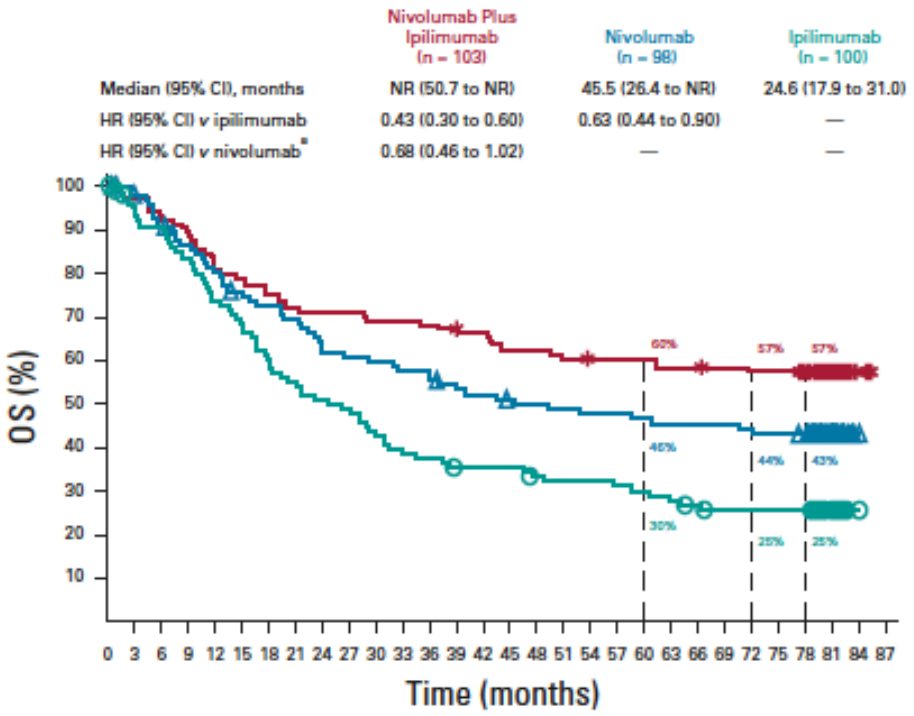
BRAF-mutated patients



Wolchok et al. JCO. 2022 40(2):127-137

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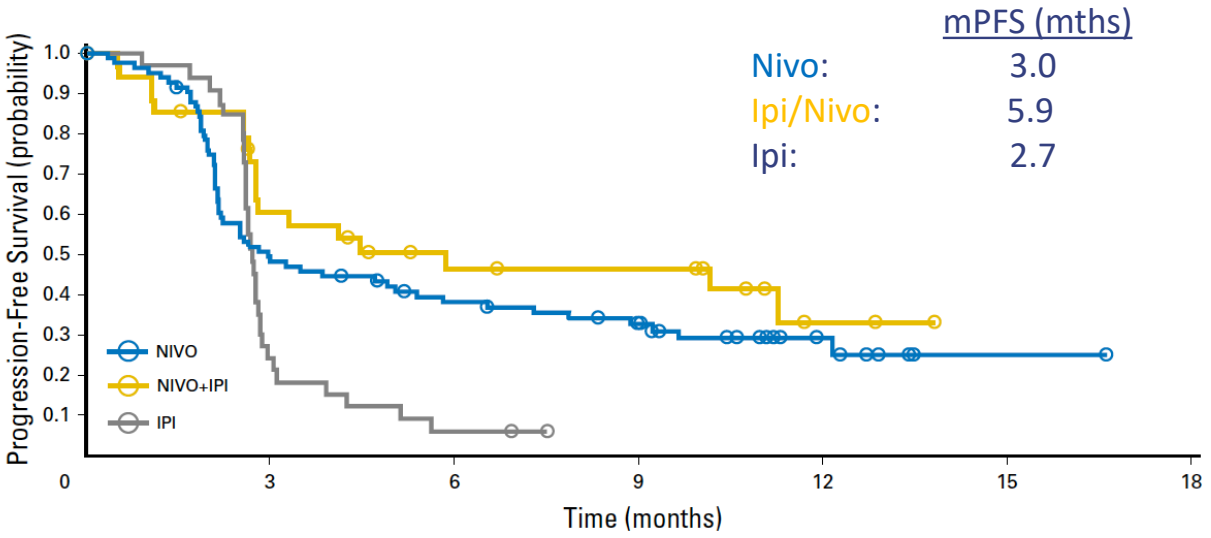
Patients with brain metastases

	Asymptomatic brain disease		Symptomatic brain disease	
	Intracranial	Extracranial	Intracranial	Extracranial
ORR	53.5%	48.5%	16.7%	22.2%
CR	33%	16%	17%	6%
PR	21%	33%	0%	17%
SD	4%	5%	0%	0%
PD	30%	17%	61%	39%
36-mth PFS	54.1%	-	18.9%	-
36-mth OS	71.9%	-	36.6%	-

Efficacy of Rela/Nivo in patients with brain metastases is unknown

Tawbi et al. Lancet Oncol. 2021; 22(12):1692-1704

Ipi/Nivo may have improved efficacy in mucosal melanoma, a rare and aggressive subtype



mPFS (mths)

Nivo: 3.0

Ipi/Nivo: 5.9

Ipi: 2.7

Response	Nivo (n = 86)	Ipi/Nivo (n = 35)	Nivo (n = 36)
Best overall response, No. (%)			
Complete response	5 (5.8)	1 (2.9)	0
Partial response	15 (17.4)	12 (34.3)	3 (8.3)
Stable disease	19 (22.1)	7 (20.0)	3 (8.3)
Progressive disease	40 (46.5)	11 (31.4)	27 (75.0)
Not evaluable	7 (8.1)	4 (11.4)	3 (8.3)
Objective response rate, % (95% CI)*	23.3 (14.8 to 33.6)	37.1 (21.5 to 55.1)	8.3 (1.8 to 22.5)

Limited efficacy data for Rela/Nivo in patients with mucosal melanoma

D'Angelo SP, Sosman JA, et al. *JCO*. 2016

Summary for Ipi/Nivo:

- Ipilimumab (3mg/kg q 3 weeks x 4 cycles) plus nivolumab (1mg/kg q 3 weeks x 4 cycles) has a durable clinical benefit with a median OS of 72 months
- Increased risk for toxicity but now our ability to manage toxicities have improved and modification/discontinuation of Ipi/Nivo does not significant decreased efficacy
- Efficacy data available for specific high-risk populations (elevated LDH, brain/liver metastases, symptomatic metastatic disease, rare melanoma subtypes)
- Option to use “flip dose”