Optimización del tratamiento del melanoma metastásico

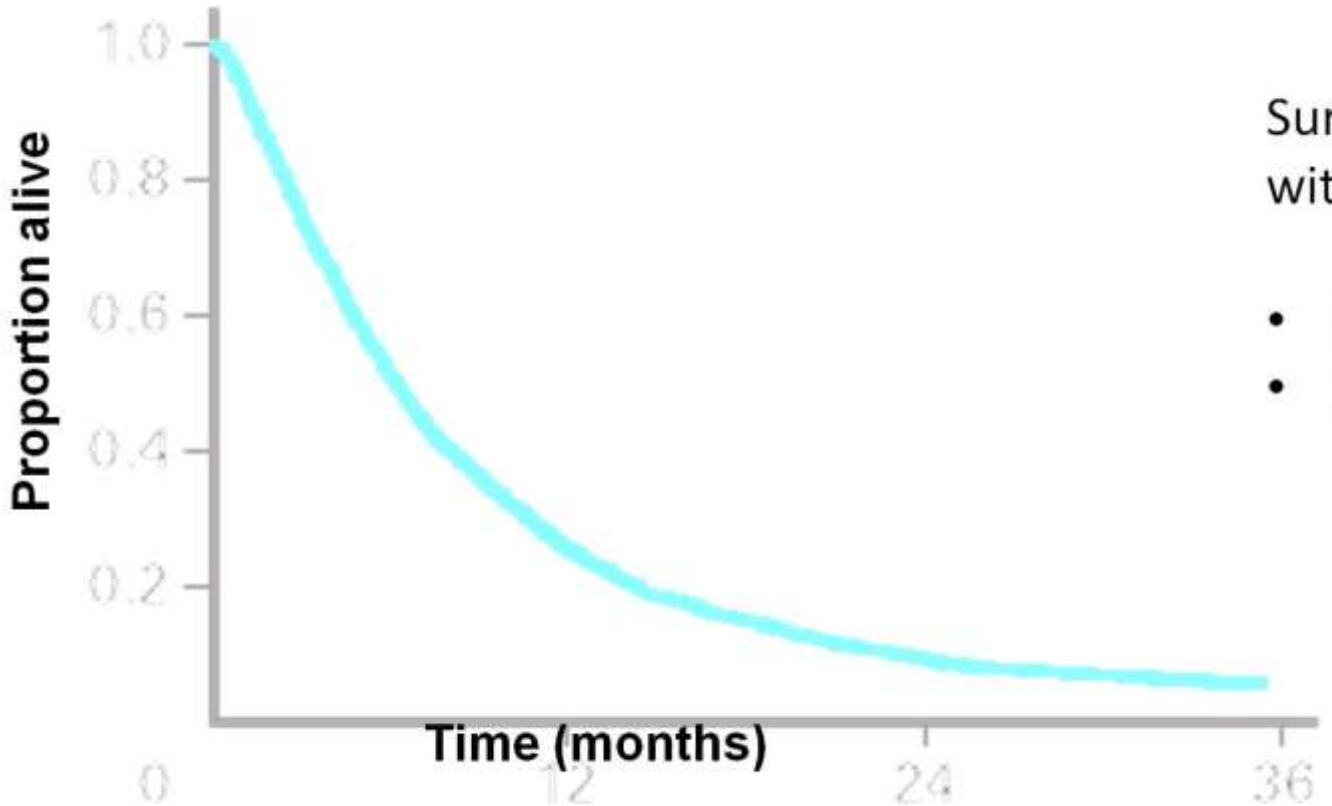
Pedro M. Bence

Médico Oncólogo

Unidad funcional de Sarcoma y Melanoma, Instituto de Oncología Ángel H. Roffo, Universidad de Buenos Aires.

Fundación CIDEA.

Overall Survival for Metastatic Melanoma before 2011

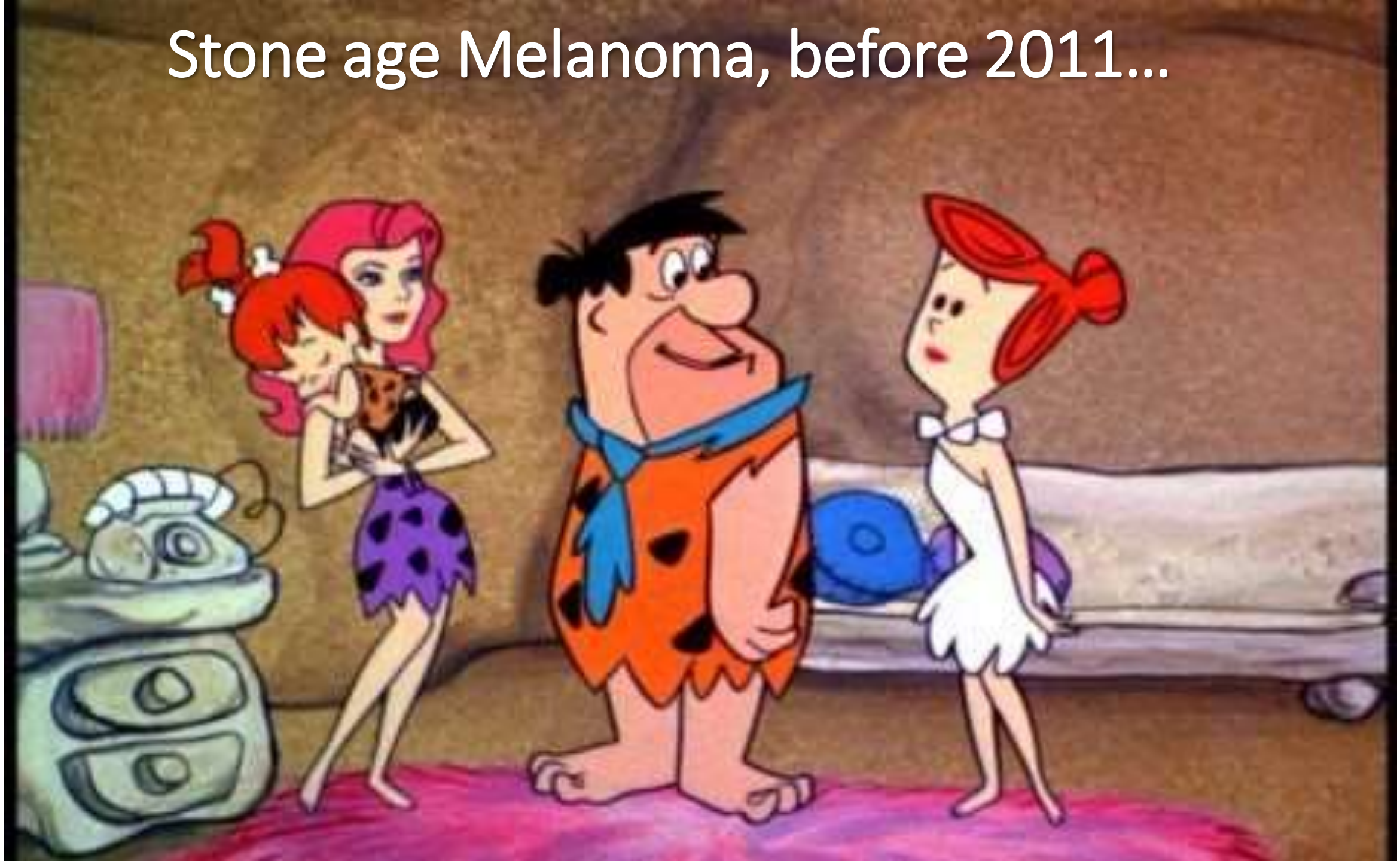


Adapted from Korn 2008

Survival data from 42 Phase II trials with over 2.100 stage IV patients:

- 12 month OS: 25.5 %,
- median OS: 6.2 months

Stone age Melanoma, before 2011…

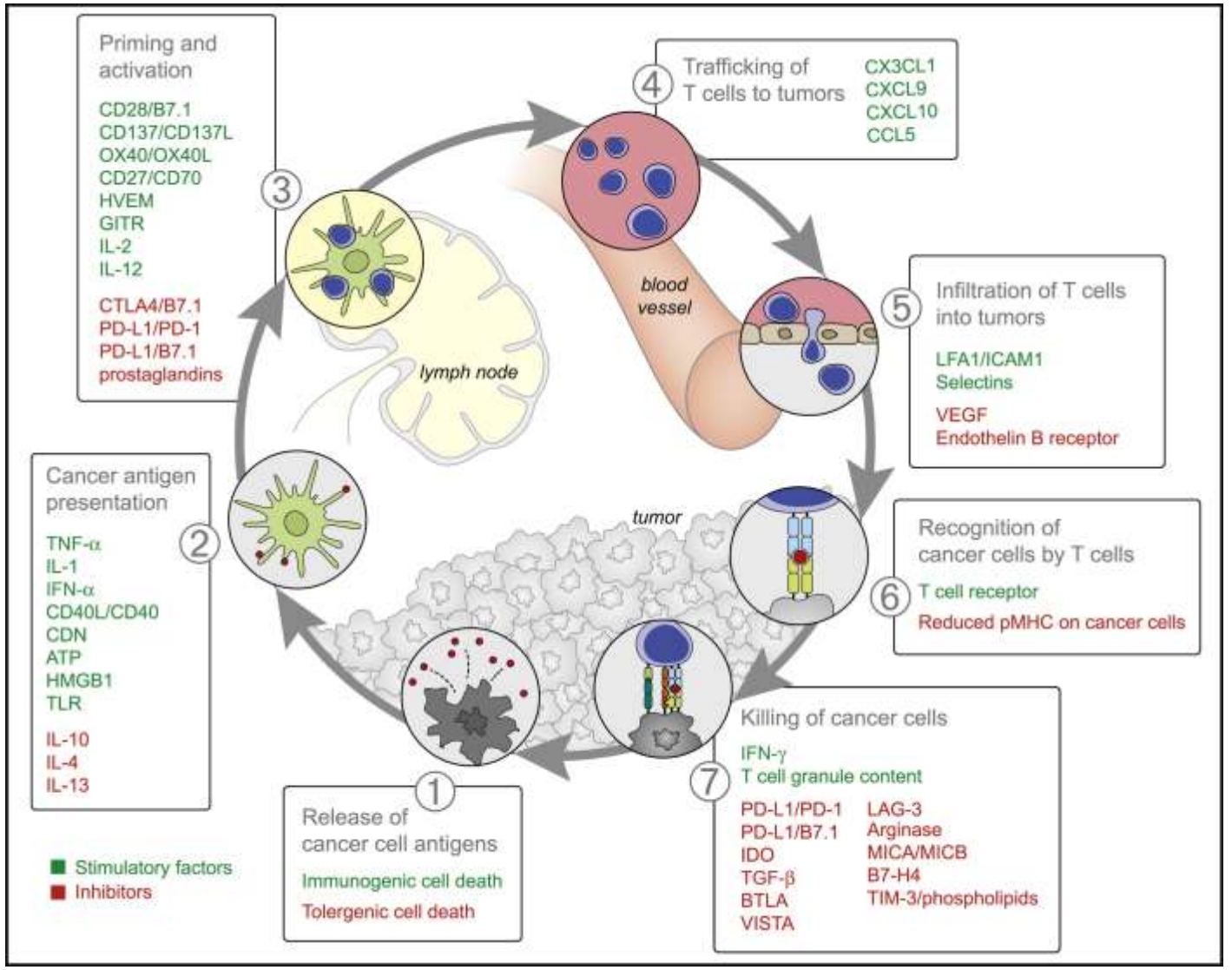


INMUNOTERAPIA

- ANTI PD-1
  - PEMBROLIZUMAB (KEYNOTE 006)
  - NIVOLUMAB (CHECKMATE 066- 067)

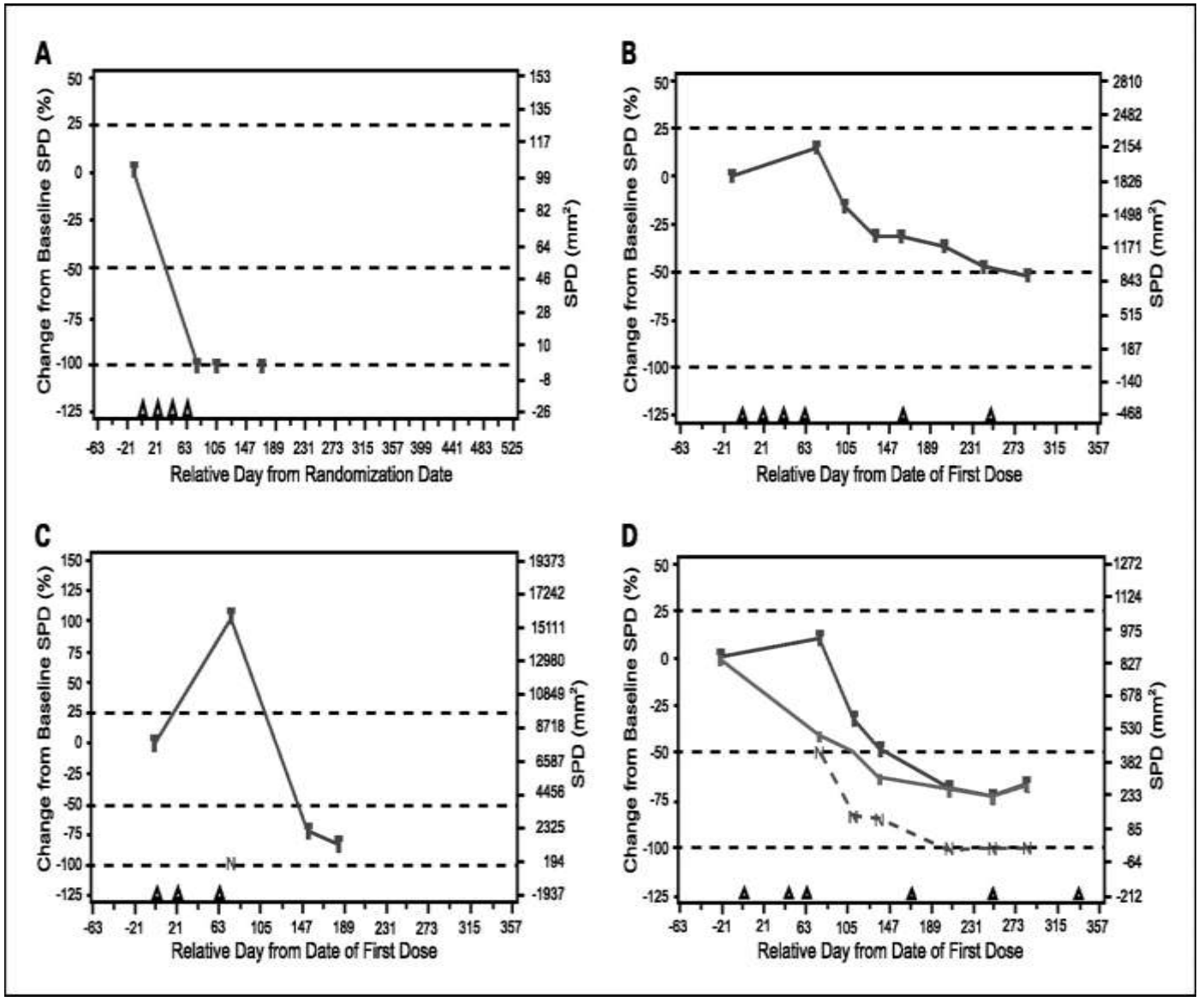
- ANTI PD-1 + …
  - ANTI CTLA4: NIVOLUMAB + IPILIMUMAB (CHECKMATE 067)
  - ANTI LAG-3: NIVOLUMAB + RELATLIMAB (RELATIVITY-047)
  - INHIBIDORES DE BRAF + MEK… IMspire, Keynote 022

Respuesta Inmune

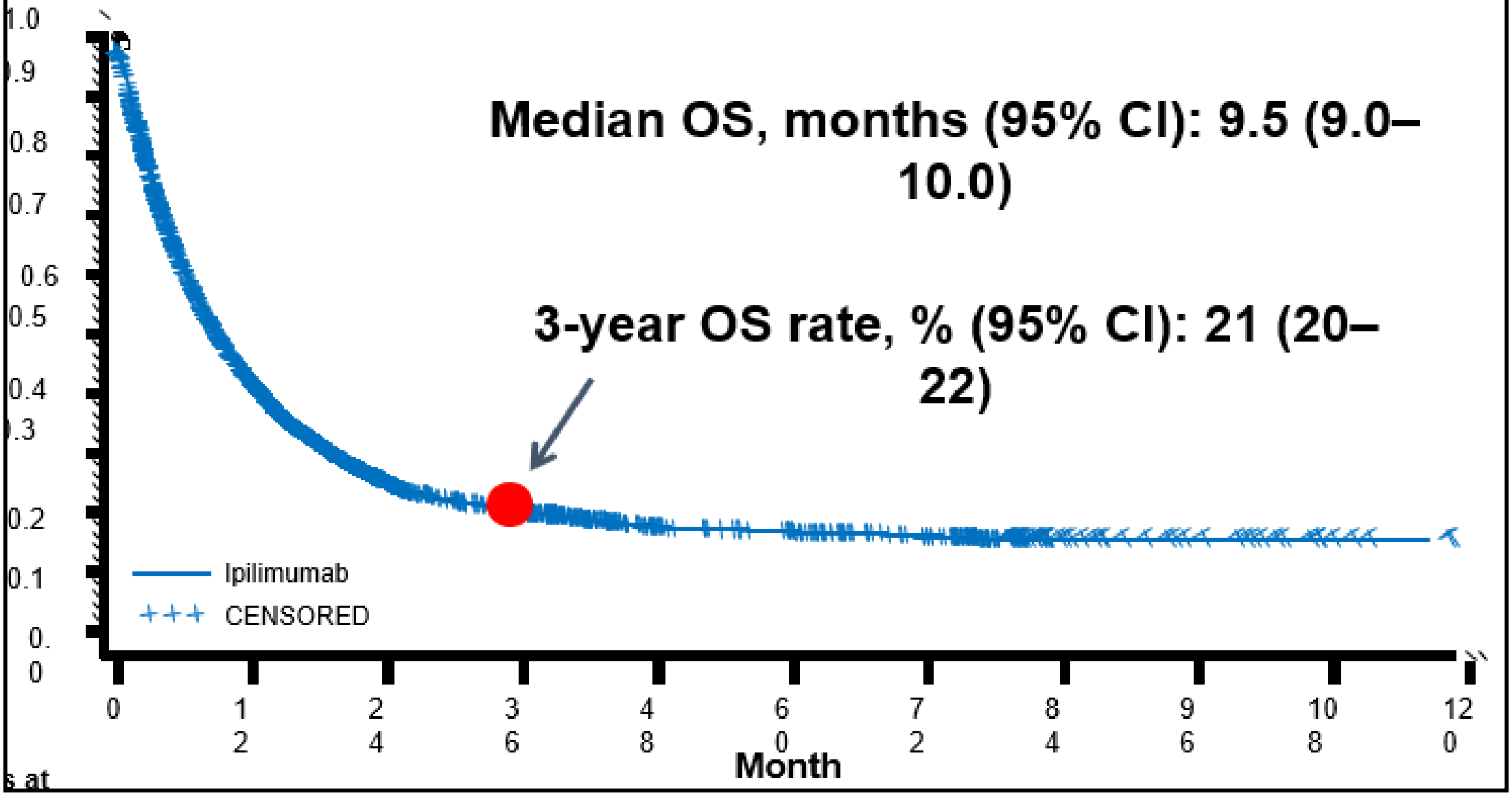


Immunity 2013 39, 1-10DOI: (10.1016/j.immuni.2013.07.012)

Cambio en los criterios de respuesta

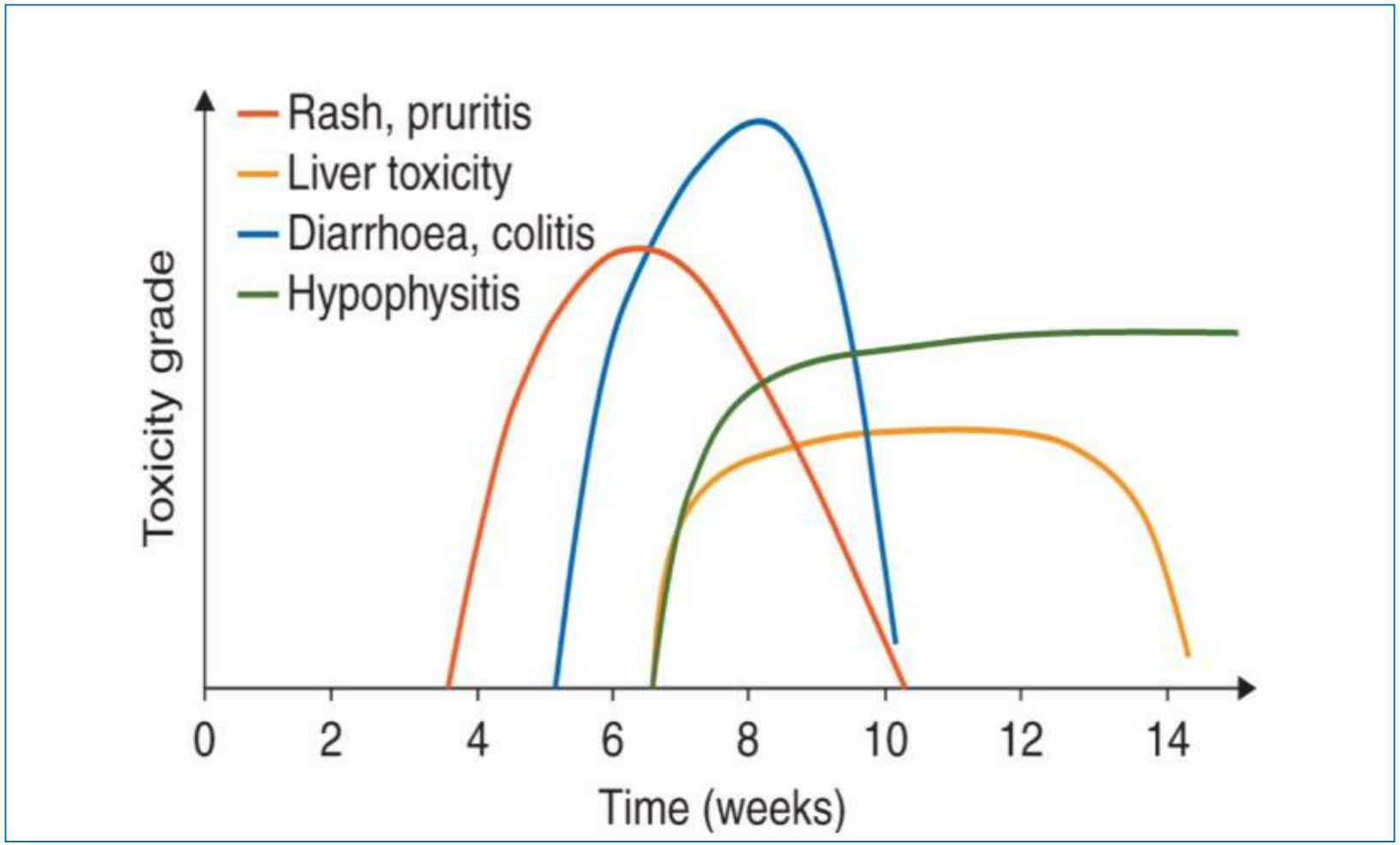


Ipilimumab Pooled OS Analysis Including EAP Data: 4846 Patients



Anti CTLA-4. Ipilimumab

Ipilimumab Pooled OS Analysis Including EAP Data: 4846 Patients

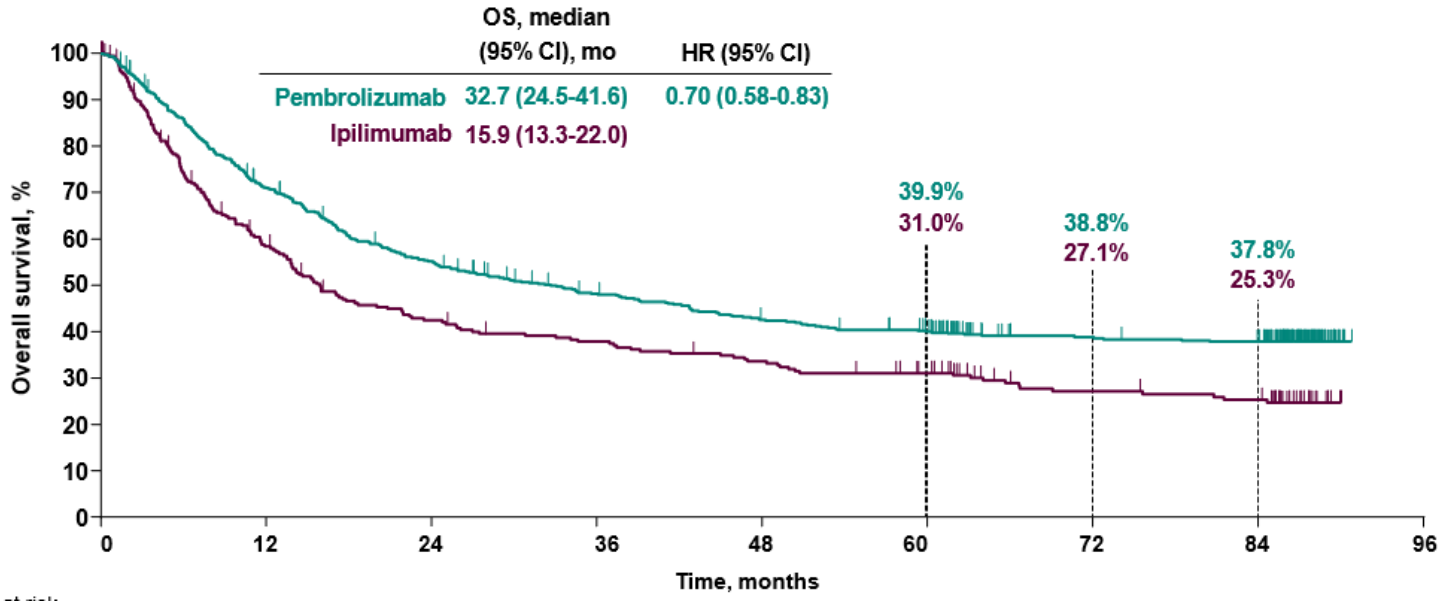


PEMBROLIZUMAB

KEYNOTE 006

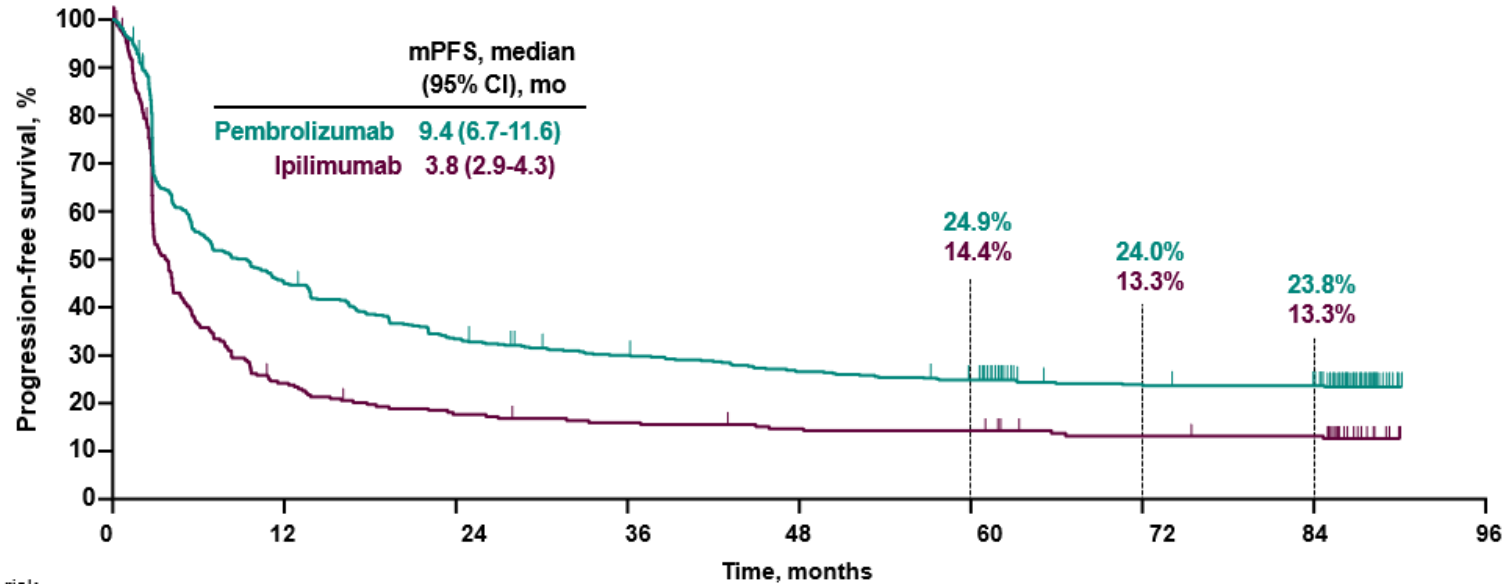
OS by Randomized Treatment

ITT Population



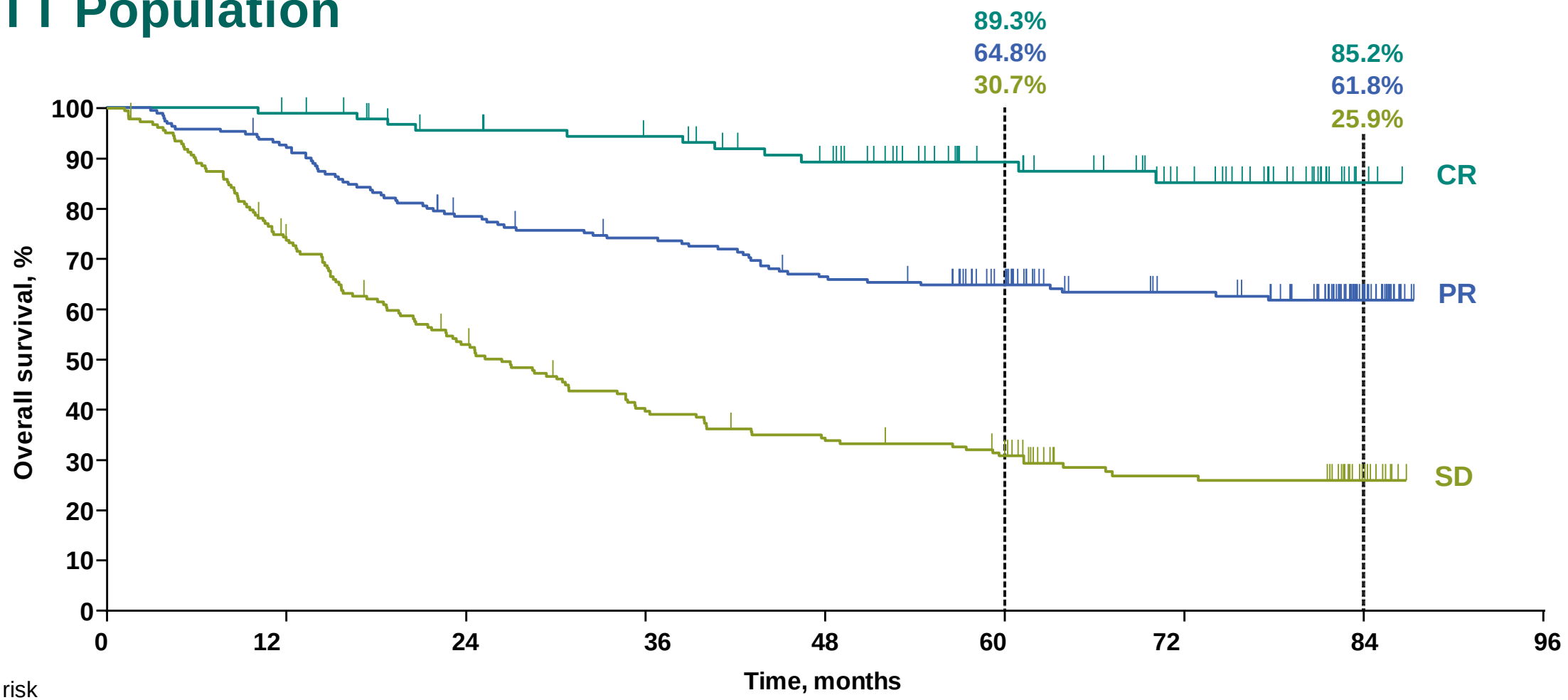
Modified PFS

ITT Population



OS From BOR by BOR with Pembrolizumab

ITT Population



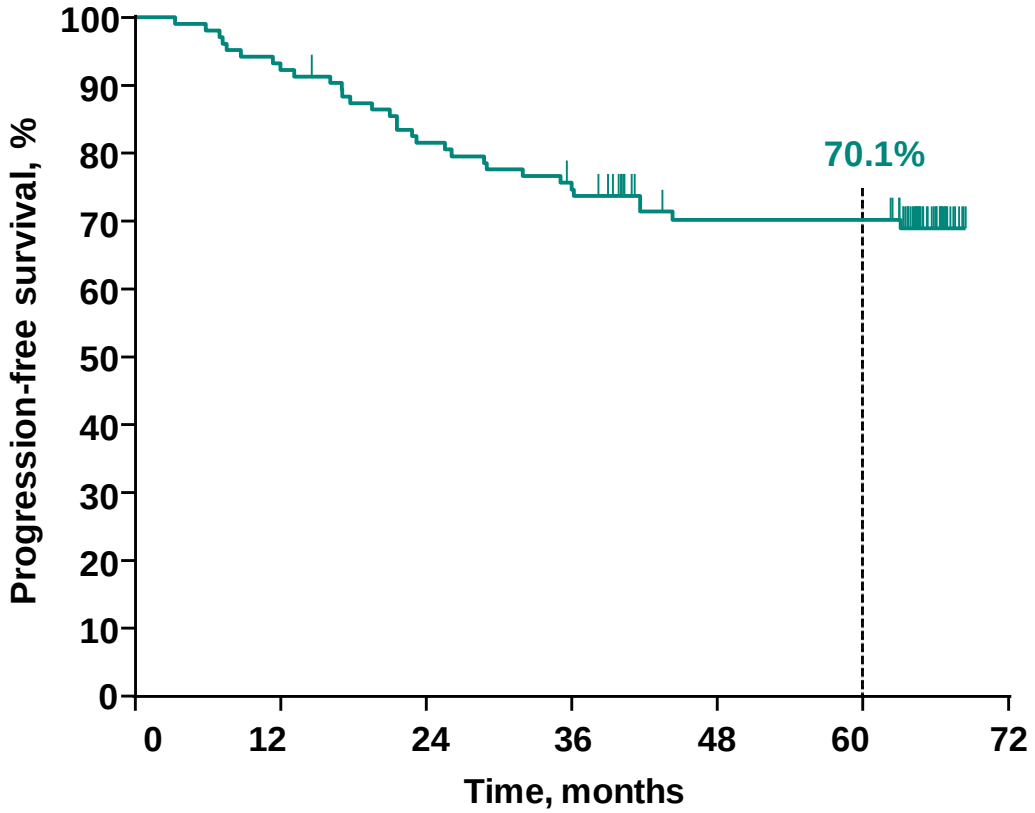
No. at risk

CR	93	91	82	78	68	48	34	3	0
PR	191	175	146	136	121	104	82	31	0
SD	184	132	93	68	58	50	31	14	0

Database cut-off: April 19, 2021.

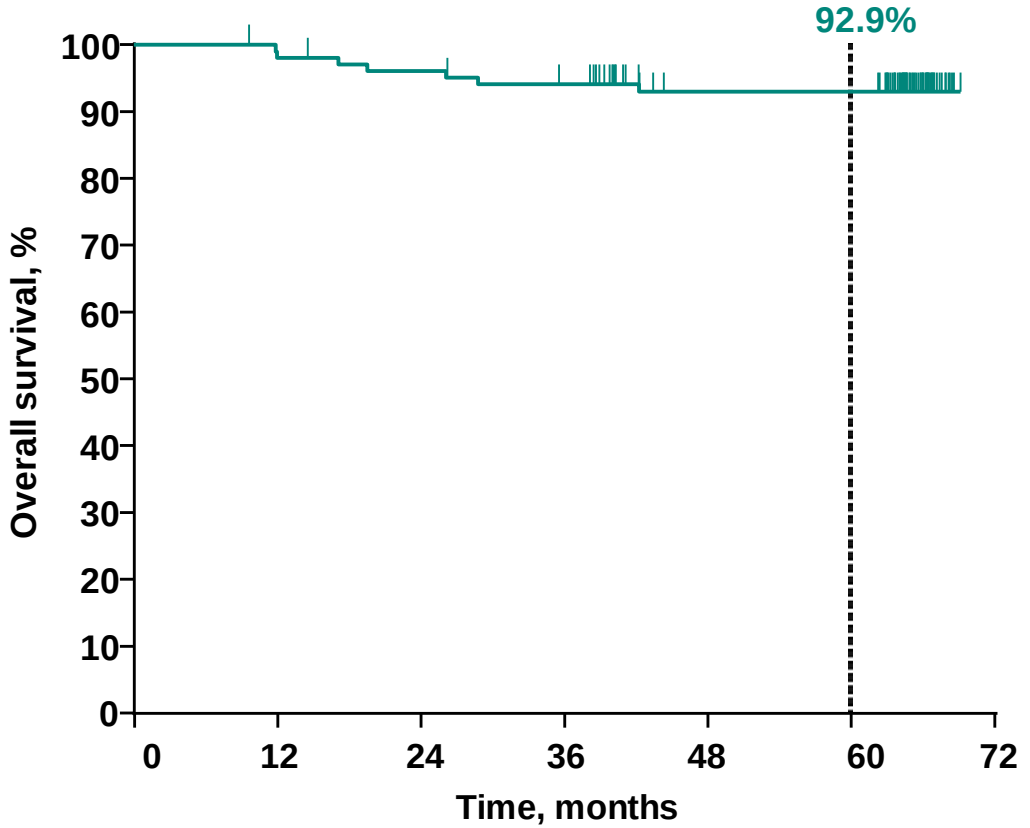
Modified PFS and OS

Participants Who Completed ≥94 Weeks of Pembrolizumab with SD or Better



No. at risk

Pembrolizumab	103	96	83	76	60	60	0

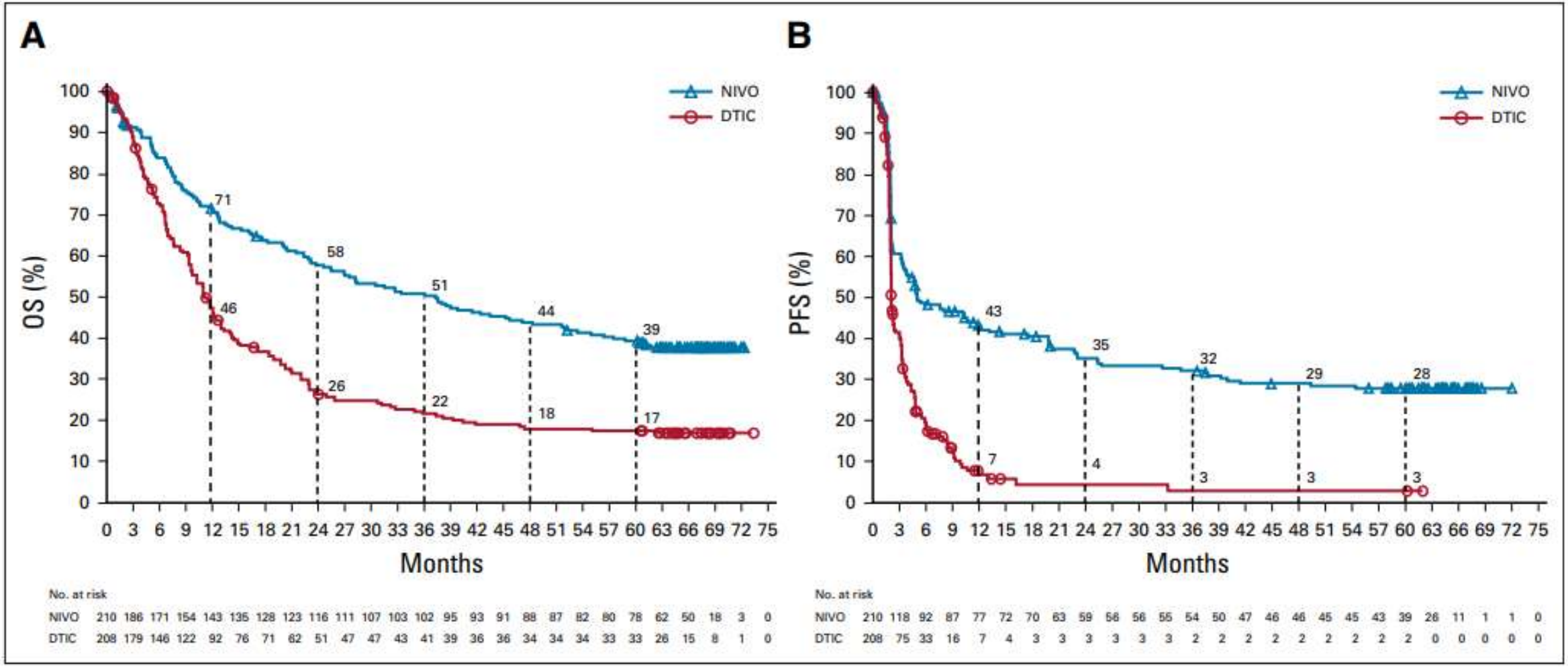


No. at risk

Pembrolizumab	103	101	97	93	76	76	0

Database cut-off: April 19, 2021.

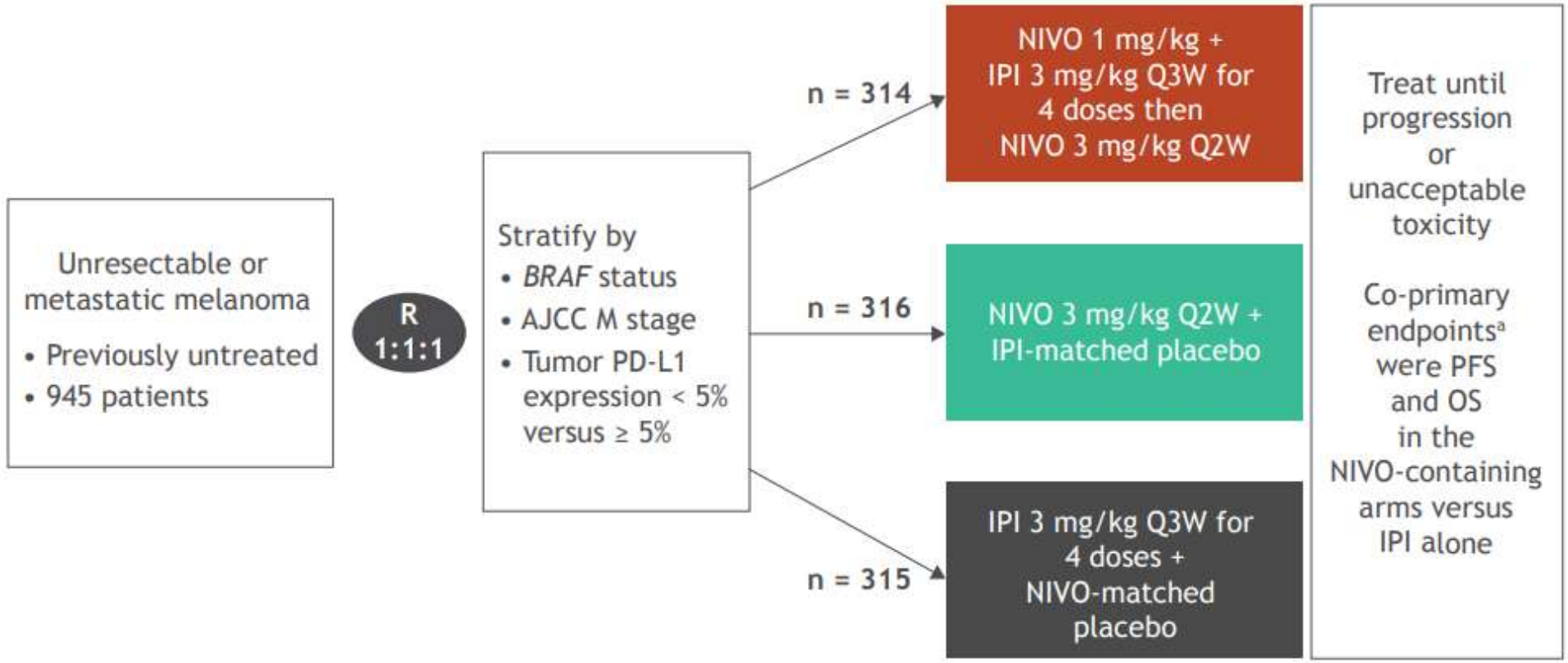
Five-Year Outcomes With Nivolumab in Patients With Wild-Type BRAF Advanced Melanoma



Robert C, et al. J Clin Oncol 2020,38:3937-3946

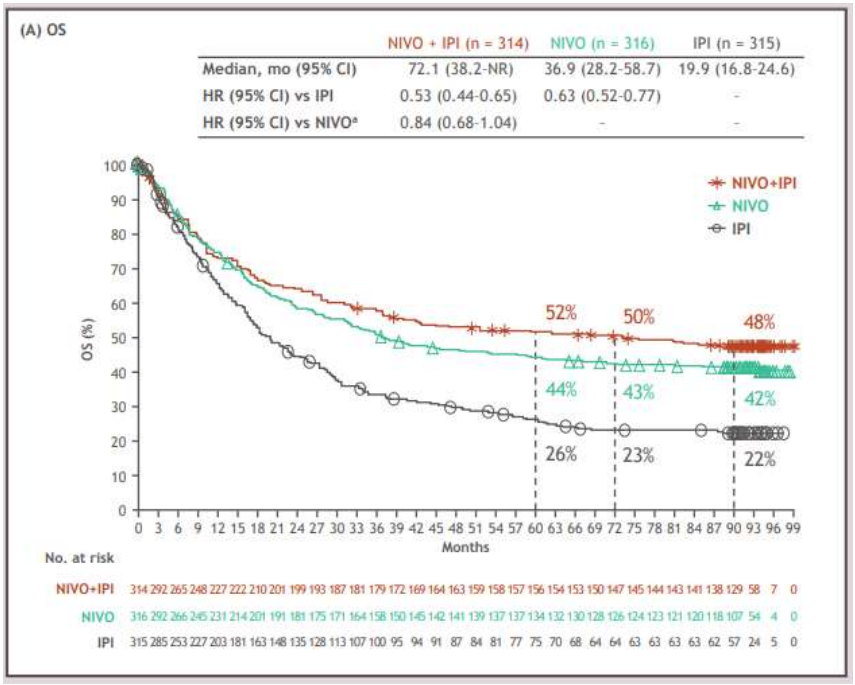
CHECKMATE 067

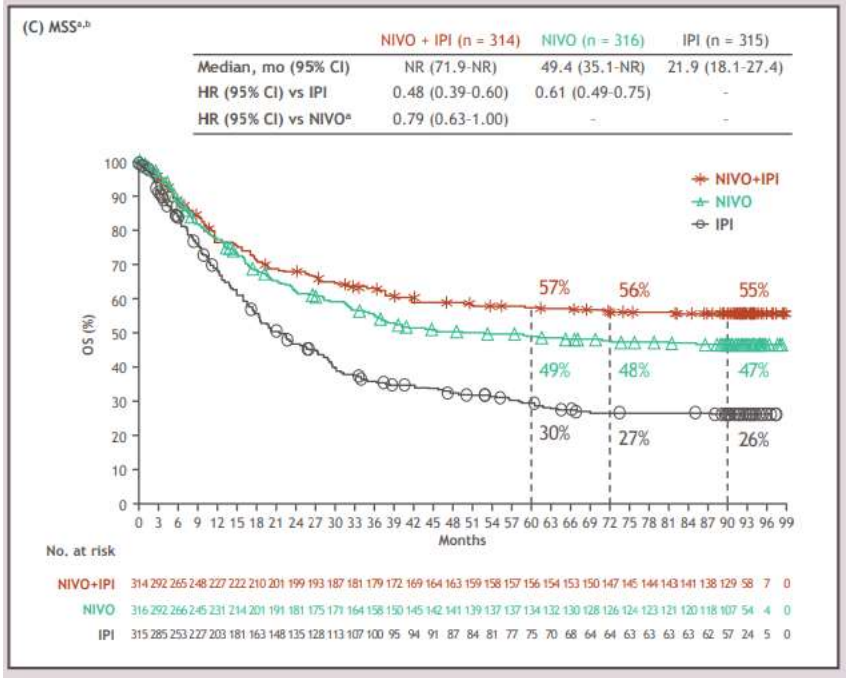
Figure 1. CheckMate 067 study design

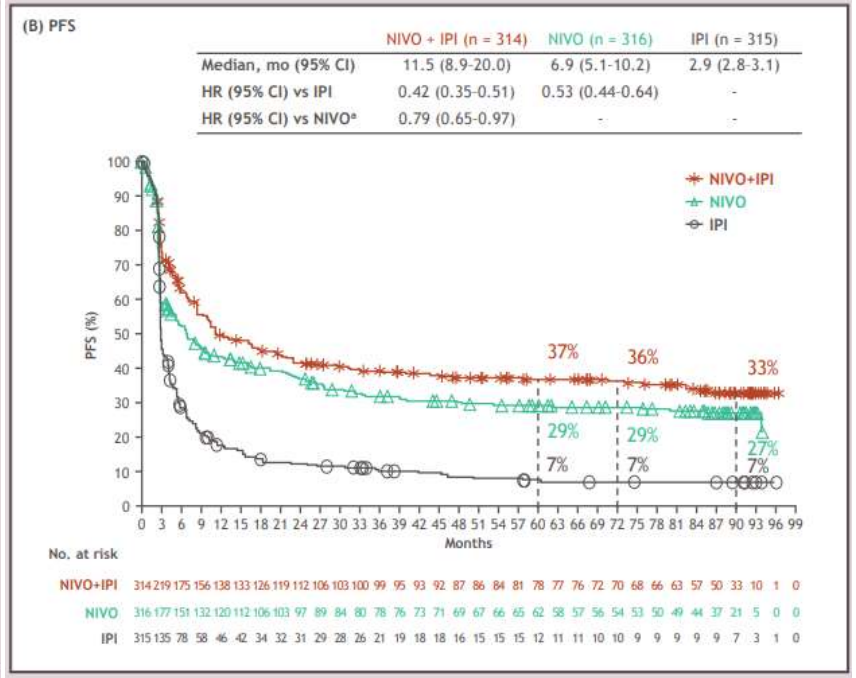


Hodi S, et al. ASCO 2022. Abs 9522.

CHECKMATE 067

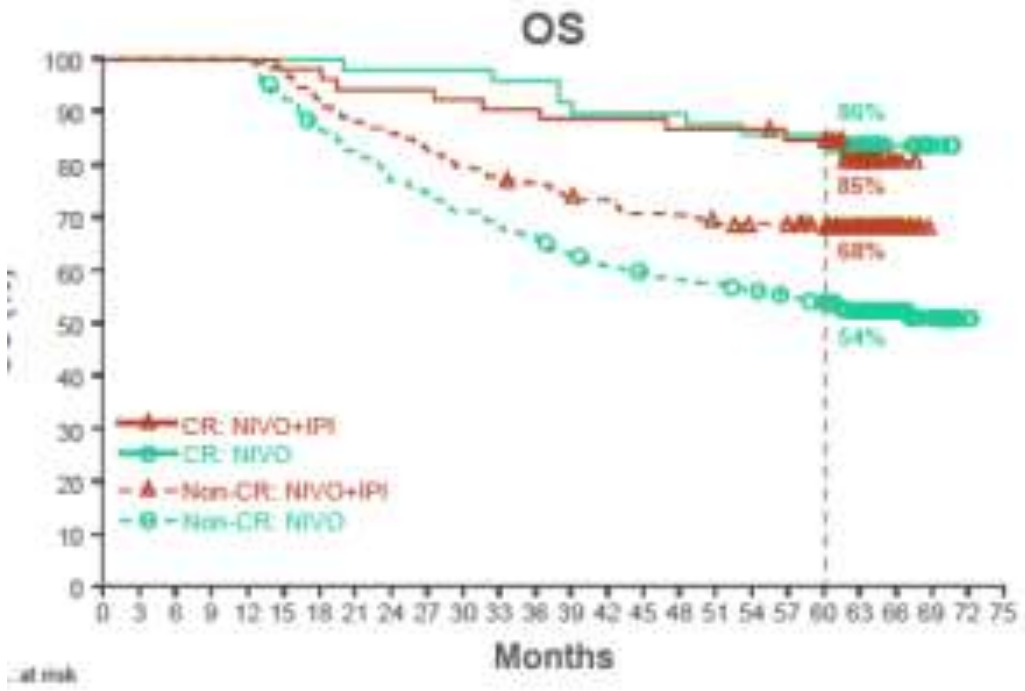


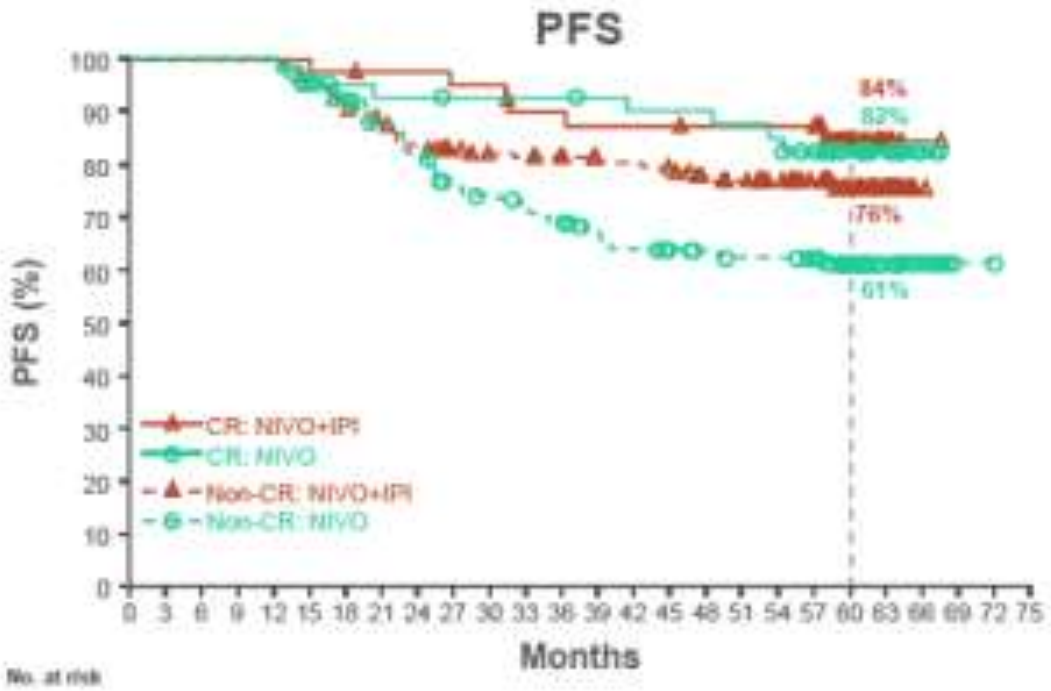




Hodi S, et al. ASCO 2022. Abs 9522.

CHECKMATE 067

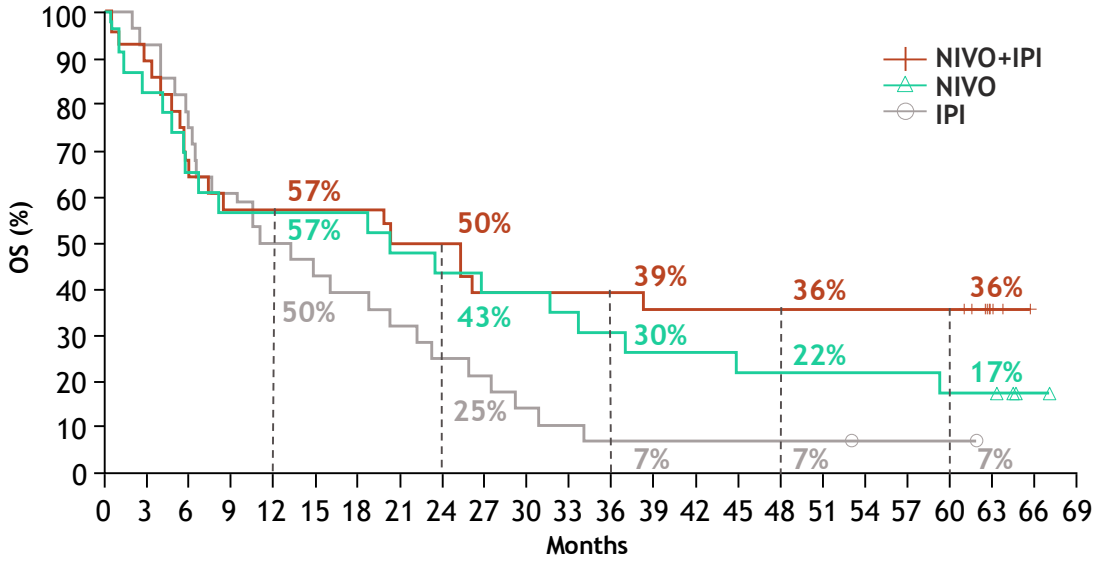




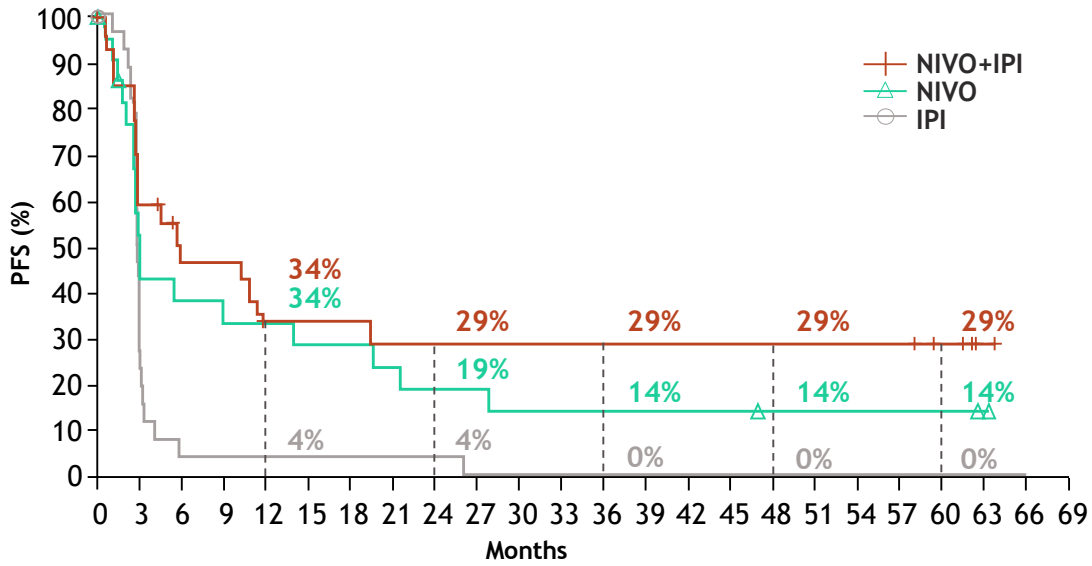
Hodi S, et al. ASCO 2022. Abs 9522.

Figure 4. OS and PFS in the mucosal and ITT populations

Mucosal	NIVO+IPI (n = 28)	NIVO (n = 23)	IPI (n = 28)
Median OS, mo (95% CI)	22.7 (5.6-NR)	20.2 (5.6-33.6)	12.1 (6.4-20.2)
HR (95% CI) vs IPI	0.52 (0.28-0.96)	0.71 (0.39-1.30)	-
HR (95% CI) vs NIVO[a]	0.73 (0.38-1.39)	-	-



Mucosal	NIVO+IPI (n = 28)	NIVO (n = 23)	IPI (n = 28)
Median PFS, mo (95% CI)	5.8 (2.7-19.3)	3.0 (2.5-13.9)	2.6 (2.6-2.8)
HR (95% CI) vs IPI	0.34 (0.18-0.64)	0.49 (0.26-0.92)	-
HR (95% CI) vs NIVO[a]	0.69 (0.36-1.33)	-	-



	NIVO+IPI		NIVO		IPI	
	Mucosal (n = 28)	ITT[7] (n = 314)	Mucosal (n = 23)	ITT[7] (n = 316)	Mucosal (n = 28)	ITT[7] (n = 315)
ORR, % (95% CI)	43 (24-63)	58 (53-64)	30 (13-53)	45 (39-50)	7 (1-24)	19 (15-24)
Best overall response, n (%)						
Complete response	4 (14)	69 (22)	1 (4)	60 (19)	0 (0)	18 (6)
Partial response	8 (29)	114 (36)	6 (26)	81 (26)	2 (7)	42 (13)

[a]Descriptive analysis; [b]12-, 24-, 36-, and 48-month rates are data on file.

METASTASIS CEREBRALES

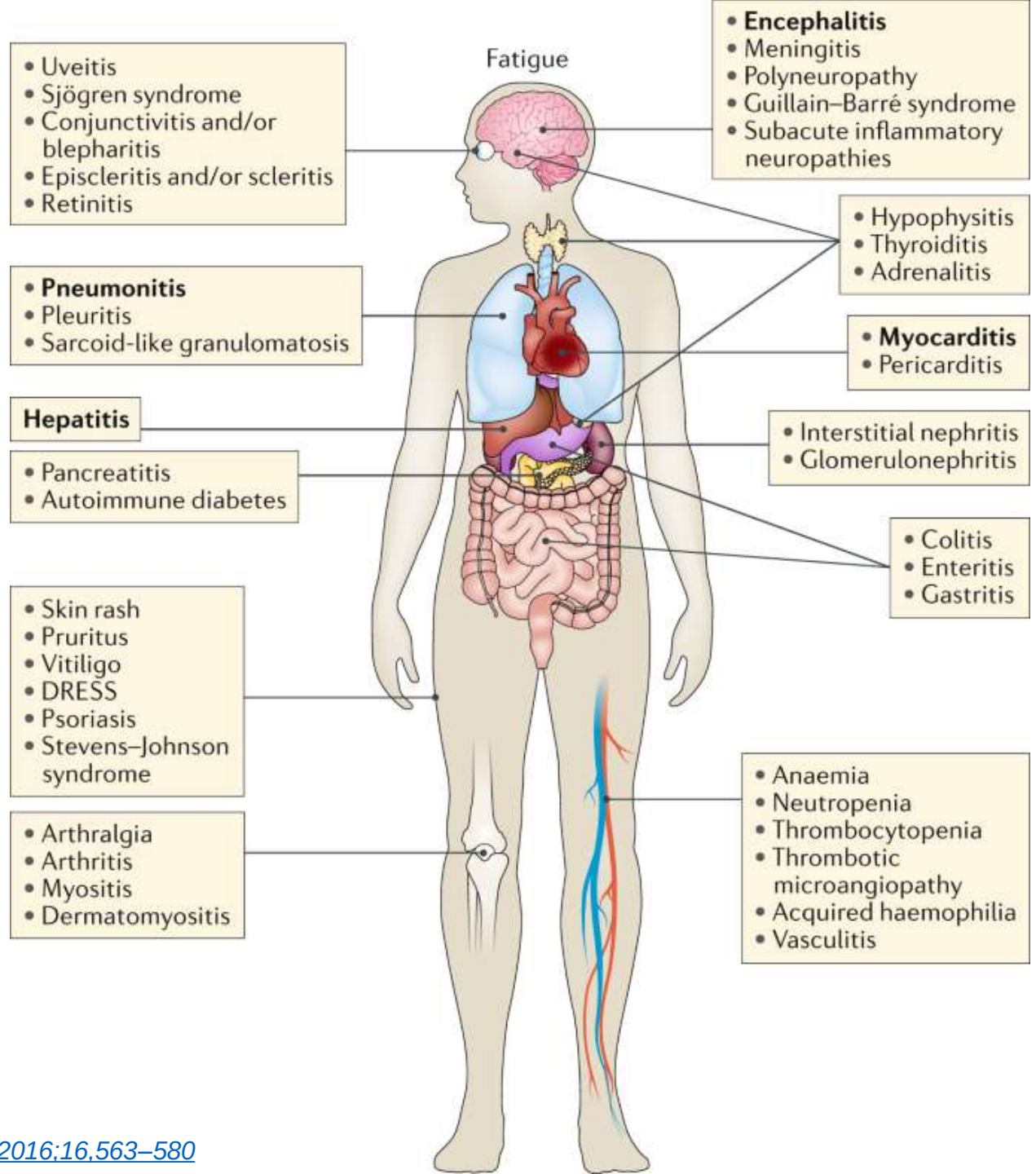
Promising results in 3 studies

Clinical Trial Title	Agents Tested	Patients	Response in brain (Complete or partial response or stable disease)
CheckMate 204 Study	Ipilimumab/ Nivolumab	75	60% (21% Complete)
ABC Study	Ipi/Nivo vs Nivolumab alone	75	Ipi/Nivo- 50% (15% Complete) Nivo- 24%
Combi MB Study	Dabrafenib/ Trametinib	125	75%-88%

CONCLUSIONES

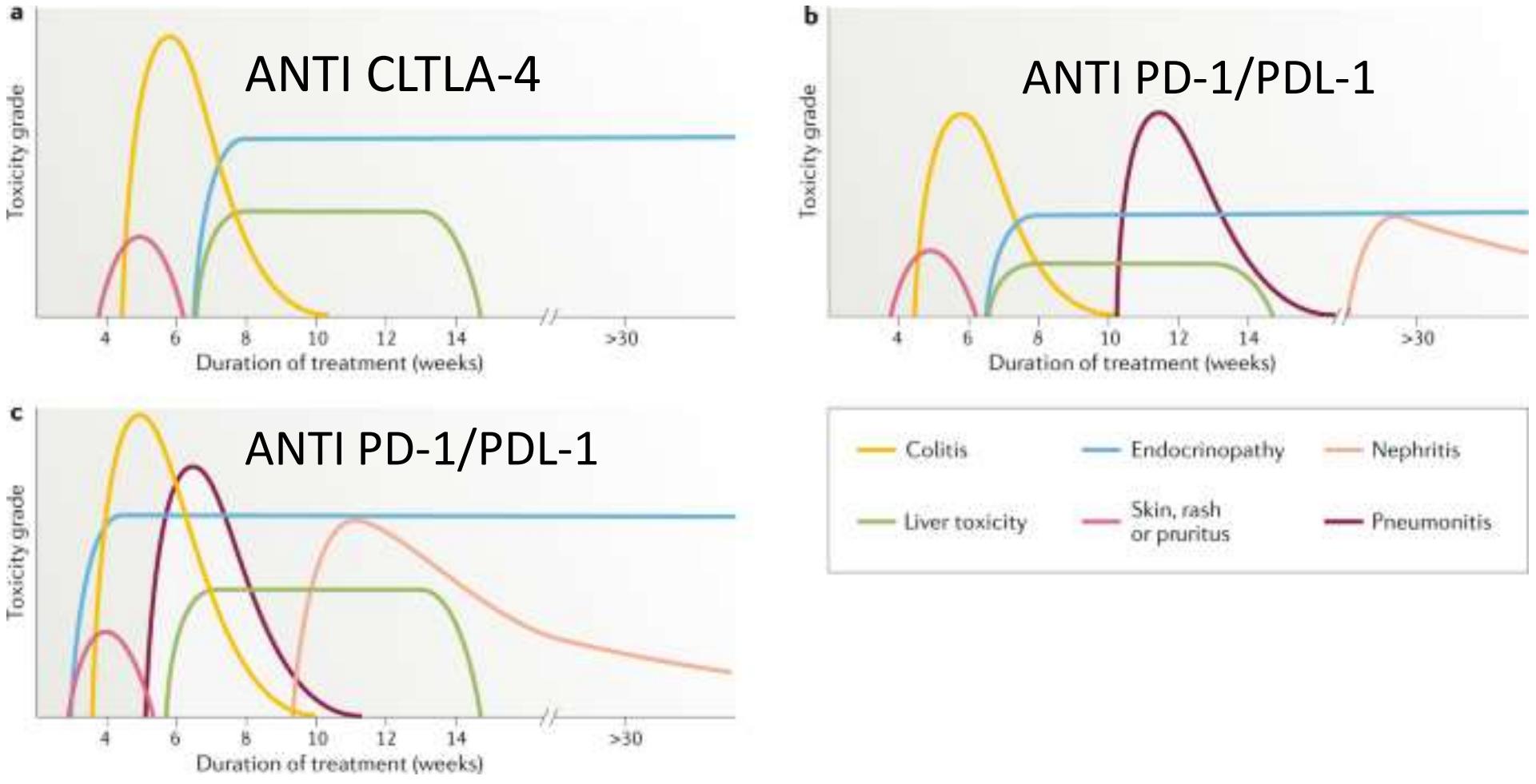
- ANTI PD1-1:
  - SLP a 5 años 25-29%, a 7 años 24-27%
  - SG a 5 años 39-44%, a 7 años 37.8-43%
- ANTI PD-1 + ANTI CTLA-4
  - SLP a 5 años 26%, a 7 años 33%
  - SG a 5 años 48%, a 7 años 52%.

APROXIMADAMENTE 9 DE CADA 10 PACIENTES CON RC Y 2 DE CADA 3 PACIENTE CON RP MANTIENEN LA RESPUESTA INCLUSO A 7 AÑOS



Nature Reviews Clinical Oncology 2016;16,563–580

CINÉTICA DE TOXICDADES



Nature Reviews Clinical Oncology 2016;16,563–580

CHECKMATE 067

Table 2. Treatment-Related Adverse Events.*

Event	Nivolumab plus Ipilimumab (N=313)		Nivolumab (N=313)		Ipilimumab (N=311)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with event (percent)					
Any treatment-related adverse event	300 (96)	184 (59)	270 (86)	67 (21)	268 (86)	86 (28)
Rash	93 (30)	10 (3)	72 (23)	1 (<1)	68 (22)	5 (2)
Pruritus	112 (35)	6 (2)	67 (21)	1 (<1)	113 (36)	1 (<1)
Vitiligo	28 (9)	0	29 (9)	1 (<1)	16 (5)	0
Maculopapular rash	38 (12)	6 (2)	15 (5)	2 (1)	38 (12)	1 (<1)
Fatigue	119 (38)	13 (4)	114 (36)	3 (1)	89 (29)	3 (1)
Asthenia	30 (10)	1 (<1)	25 (8)	1 (<1)	17 (5)	2 (1)
Pyrexia	60 (19)	2 (1)	21 (7)	0	21 (7)	1 (<1)
Diarrhea	142 (45)	29 (9)	67 (21)	9 (3)	105 (34)	18 (6)
Nausea	88 (28)	7 (2)	41 (13)	0	51 (16)	2 (1)
Vomiting	48 (15)	7 (2)	22 (7)	1 (<1)	24 (8)	1 (<1)
Abdominal pain	26 (8)	1 (<1)	18 (6)	0	28 (9)	2 (1)
Colitis	40 (13)	26 (8)	7 (2)	3 (1)	35 (11)	24 (8)
Headache	35 (11)	2 (1)	24 (8)	0	25 (8)	1 (<1)
Arthralgia	43 (14)	2 (1)	31 (10)	1 (<1)	22 (7)	0
Increased lipase level	44 (14)	34 (11)	27 (9)	14 (4)	18 (6)	12 (4)
Increased amylase level	26 (8)	9 (3)	20 (6)	6 (2)	15 (5)	4 (1)
Increased aspartate aminotransferase level	51 (16)	19 (6)	14 (4)	3 (1)	12 (4)	2 (1)
Increased alanine aminotransferase level	60 (19)	27 (9)	13 (4)	4 (1)	12 (4)	5 (2)
Decreased weight	19 (6)	0	10 (3)	0	4 (1)	1 (<1)
Hypothyroidism	53 (17)	1 (<1)	33 (11)	0	14 (5)	0
Hyperthyroidism	35 (11)	3 (1)	14 (4)	0	3 (1)	0
Hypophysitis	23 (7)	5 (2)	2 (1)	1 (<1)	12 (4)	5 (2)
Decreased appetite	60 (19)	4 (1)	36 (12)	0	41 (13)	1 (<1)
Cough	25 (8)	0	19 (6)	2 (1)	15 (5)	0
Dyspnea	36 (12)	3 (1)	19 (6)	1 (<1)	12 (4)	0
Pneumonitis	22 (7)	3 (1)	5 (2)	1 (<1)	5 (2)	1 (<1)
Treatment-related adverse event leading to discontinuation	123 (39)	95 (30)	37 (12)	24 (8)	49 (16)	43 (14)

N Engl J Med 2017; 377:1345-1356

How to choose PD1 monotherapy versus combination?

	NIVO+IPI (N=313)		NIVO (N=313)	
	Any Grade	G 3-4	Any Grade	G 3-4
Skin AEs, %	60.4	5.8	43.8	2.2
Rash	28.4	2.9	22.7	0.3
Pruritus	35.1	1.9	20.4	0.3
Gastrointestinal AEs, %	47.6	15.3	21.7	2.9
Diarrhea	45.4	9.6	20.8	2.2
Colitis	11.5	8.0	2.2	1.0
Endocrine AEs, %	32.3	5.8	15.7	1.6
Hypothyroidism	16.0	0.3	9.3	0
Hyperthyroidism	10.2	1.0	4.5	0
Hepatic AEs, %	31.6	19.8	7.3	2.6
Elevated ALT	17.9	8.6	3.8	1.0
Elevated AST	15.7	6.1	4.2	1.0
Pulmonary AEs, %	7.3	1.0	1.6	0.3
Pneumonitis	6.7	1.0	1.3	0.3
Renal AEs, %	6.4	1.9	1.0	0.3
Elevated creatinine	4.2	0.3	0.6	0.3

Larkin et al. *N Engl J Med.* 2015; Wolchok et al. *N Engl J Med.* 2017

RELATIVITY (NIVOLUMAB -/+ RELATLIMAB)

Safety summary

AE, n (%)	NIVO + RELA (n = 355)		NIVO (n = 359)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Any AE	352 (99.2)	154 (43.4)	344 (95.8)	126 (35.1)
TRAE	297 (83.7)	75 (21.1)	260 (72.4)	40 (11.1)
Leading to discontinuation	54 (15.2)	32 (9.0)	26 (7.2)	13 (3.6)
TRAE ≥ 10%				
Pruritus	87 (24.5)	0	59 (16.4)	2 (0.6)
Fatigue	83 (23.4)	5 (1.4)	47 (13.1)	1 (0.3)
Rash	59 (16.6)	3 (0.8)	48 (13.4)	2 (0.6)
Hypothyroidism	55 (15.5)	0	46 (12.8)	0
Arthralgia	53 (14.9)	3 (0.8)	29 (8.1)	1 (0.3)
Diarrhea	53 (14.9)	4 (1.1)	36 (10.0)	2 (0.6)
Vitiligo	45 (12.7)	0	42 (11.7)	0
Treatment-related deaths[a]	4 (1.1)	0	2 (0.6)	0

DBL date: October 28, 2021. Median follow-up: 19.3 mo. 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.
[a]Treatment-related deaths: NIVO + RELA (n = 4) – hemophagocytic lymphohistiocytosis, acute edema of the lung, pneumonitis, and multiorgan failure; NIVO (n = 2) – sepsis and myocarditis, and worsening pneumonia.

RELATIVITY (NIVOLUMAB -/+ RELATLIMAB)

Immune-mediated AEs

Immune-mediated AE category,[a] n (%)	NIVO + RELA (n = 355)		NIVO (n = 359)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Hypothyroidism/thyroiditis	66 (18.6)	0	53 (14.8)	0
Rash	39 (11.0)	3 (0.8)	28 (7.8)	5 (1.4)
Diarrhea/colitis	25 (7.0)	5 (1.4)	12 (3.3)	5 (1.4)
Hyperthyroidism	23 (6.5)	0	25 (7.0)	0
Hepatitis	21 (5.9)	15 (4.2)	11 (3.1)	6 (1.7)
Adrenal insufficiency	19 (5.4)	6 (1.7)	4 (1.1)	0
Pneumonitis	14 (3.9)	2 (0.6)	7 (1.9)	2 (0.6)
Hypophysitis	10 (2.8)	2 (0.6)	4 (1.1)	1 (0.3)
Nephritis and renal dysfunction	7 (2.0)	4 (1.1)	5 (1.4)	4 (1.1)
Hypersensitivity	5 (1.4)	0	5 (1.4)	0

- Additional AE of interest: myocarditis (any grade) occurred in 6 (1.7%) patients with NIVO + RELA and 2 (0.6%) with NIVO. Troponin monitoring was performed for the first 2 months of treatment per protocol

DBL date: October 28, 2021. Median follow-up: 19.3 mo.
[a]Includes AEs of any grade occurring in ≥ 1% of patients considered by investigators to be potentially immune-mediated that met the following criteria: occurred within 100 days of the last dose, regardless of causality; treated with immune-modulating medication with no clear alternative etiology; or had an immune-mediated component.

CONCLUSIONES

- ANTI CTLA-4:
  - TOXICIDAD SEVERA EN CERCA DE 30% DE LOS PACIENTES, A EXPENSAS DE 15% DE SUSPENSIONES POR EA. TR
- ANTI PD1-1:
  - TOXICIDADES SEVERAS RONDAN 15%, TASA DE SUSPENSION POR TOXICIDAD CERCANA AL 7% TR
- ANTI PD-1 + ANTI CTLA-4
  - TOXICIDADES SEVERAS CERCANAS AL 60%, CERCA DE LA MITAD DE LOS PACIENTES SUSPENDEN TRATAMIENTO POR EVENTOS ADVERSOS TR
- ANTI PD-1 + ANTI LAG-3
  - TOXICIDADES SEVERAS CERCANAS AL 20%, CON SUSPENSIONES POR EA DE 10% TR

MUCHAS GRACIAS!