XVII SIMPOSIUM
BASES BIOLÓGICAS DEL CÁNCER
E INNOVACIÓN TERAPÉUTICA

MÁS DE 20 AÑOS A LA VANGUARDIA DE LA FORMACIÓN
EN LA BIOLOGÍA Y TRATAMIENTO DEL CÁNCER

SALAMANCA, 22 Y 23 DE MAYO DE 2025

Innovación y evidencia: el presente del tratamiento sistémico adyuvante en melanoma

Guillermo Crespo Herrero. Hospital Universitario de Burgos

Conflictos de Interés

Consultor/asesor: BMS, Novartis, Ipsen, Janssen, Sanofi, Pierre Fabre

Ponente: Regeneron, Lilly, BMS, Roche, Ipsen, Pierre Fabre, Eisai, MSD, Novartis, Bayer, J&J, Astellas

Congresos/viajes: Pfizer, BMS, Ipsen, Roche, Pierre Fabre, MSD, Novartis, Merck, J&J, Bayer

Agenda

- **Adyuvancia**:
  - Estadios IIB/C:
    - KEYNOTE-716: Pembrolizumab vs placebo
    - CHECKMATE 76K: Nivolumab vs placebo
  - Estadios III:
    - KEYNOTE-54 / EORTC 1325: Pembrolizumab vs placebo
    - CHECKMATE 238: Nivolumab vs Ipilimumab
    - COMBI-AD: Dabrafebib-Trametinib vs placebo
- **Neoadyuvancia**
  - SWOG S1801: Pembrolizumab perioperatorio vs Pembrolizumab adyuvante
  - NADINA: Ipilimumab-Nivolumab neoady ± nivolumab ady vs nivolumab ady
- **Futuro**

¿Aumenta la SLE?

¿Cuál es la tasa de RCp?

¿Aumenta la supervivencia?

¿Qué toxicidades inmunomediadas?

¿Aumenta la SLE?

¿Cuál es la tasa de RCp?

¿Estoy curado?

¿Cuál es mi riesgo de recaída?

¿Cuál es mi riesgo de muerte?

¿Aumenta la supervivencia?

¿Qué toxicidades inmunomediadas?

¿Qué pasa si reaparece la enfermedad?

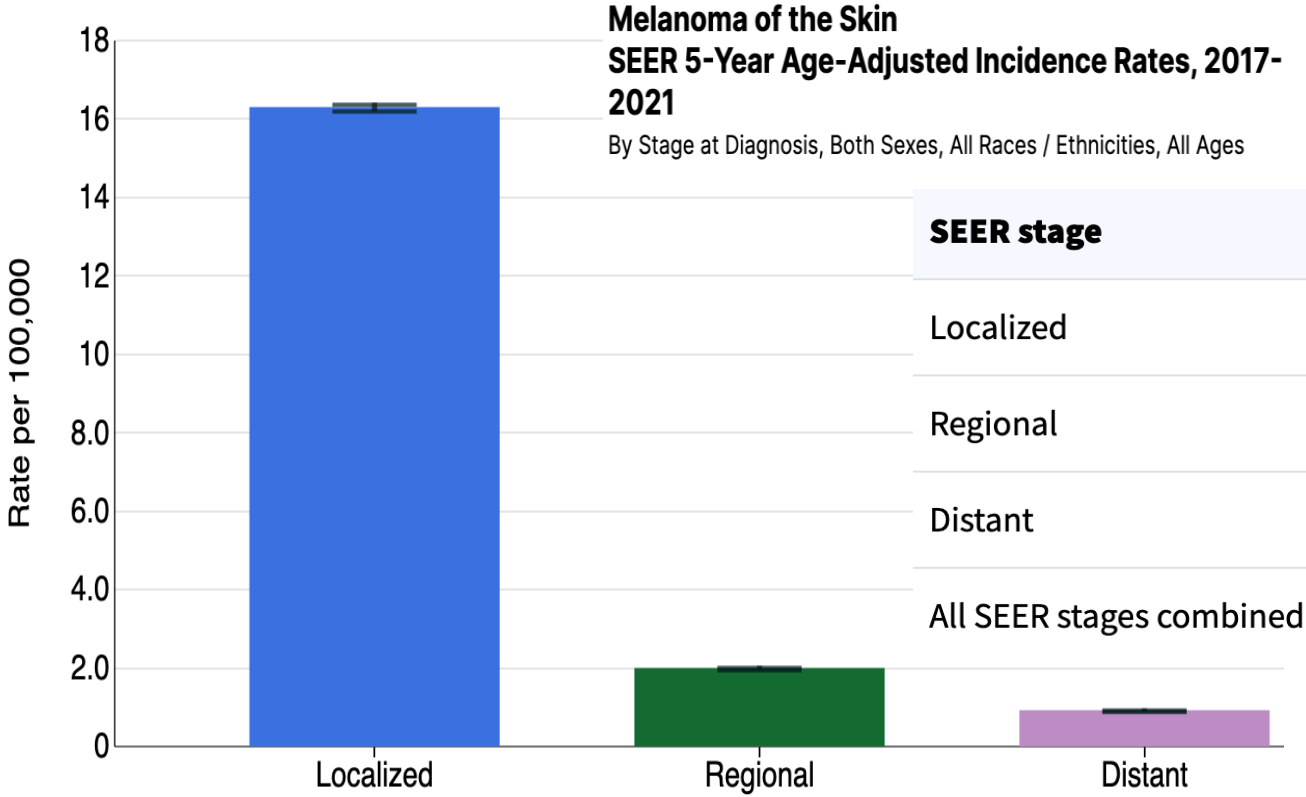
¿Qué toxicidades tendré?

¿Cuándo la adyuvancia?

El paciente en el centro, pero de verdad

- Alto riesgo de recaída
- Aumento de Supervivencia (¿↑ SLE?; ¿Tratamientos efectivos en enfermedad avanzada?)
- Tratamiento poco tóxico (o compensa el riesgo)

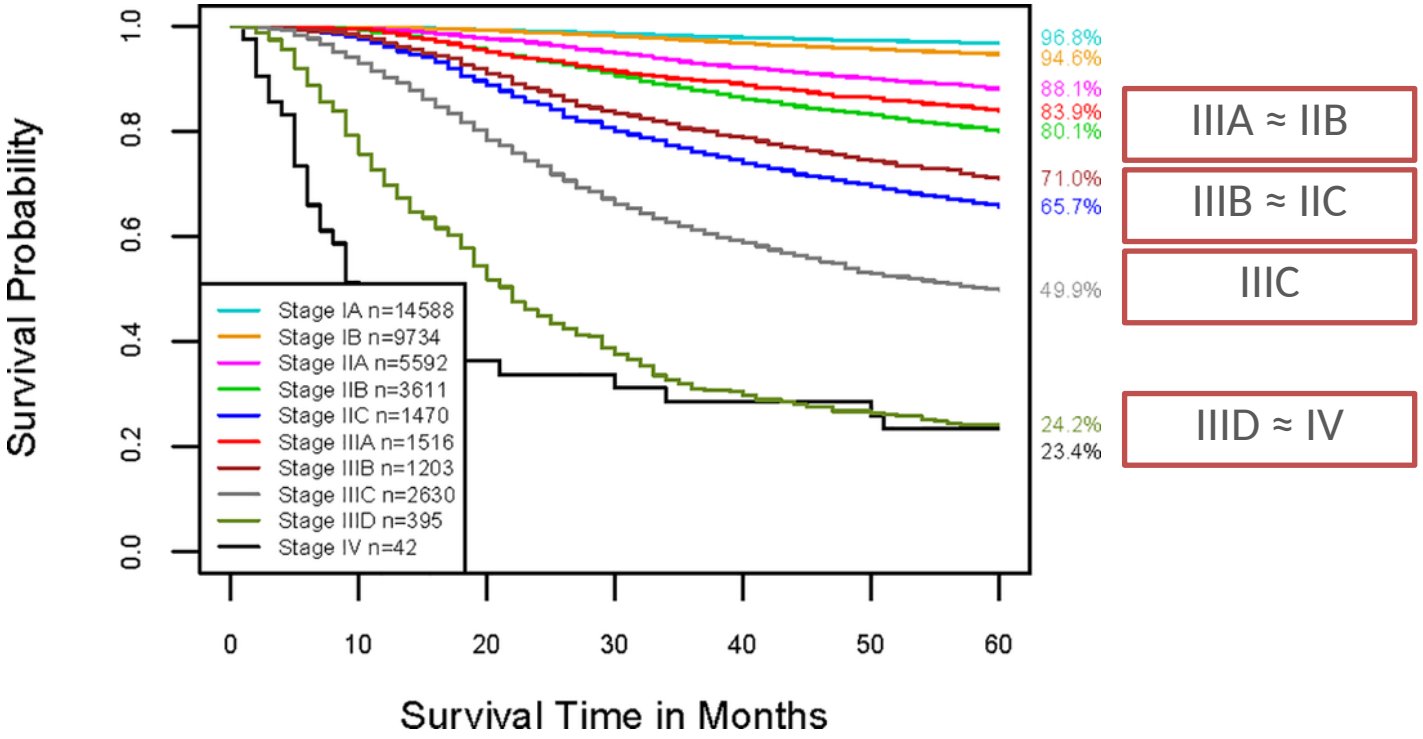
Incidencia y pronóstico



SEER stage	5-year relative survival rate
Localized	>99%
Regional	74%
Distant	35%
All SEER stages combined	94%

SEER Database

Incidencia y pronóstico

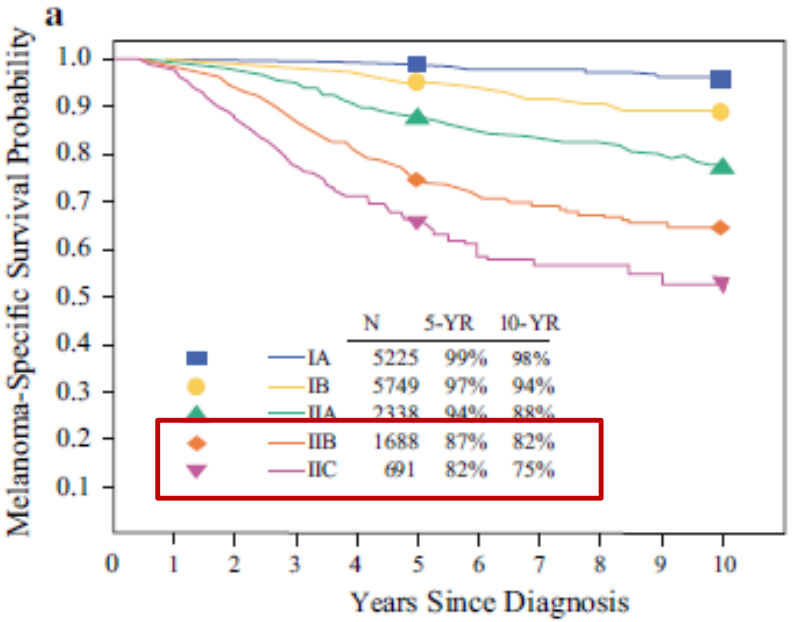


SEER Database

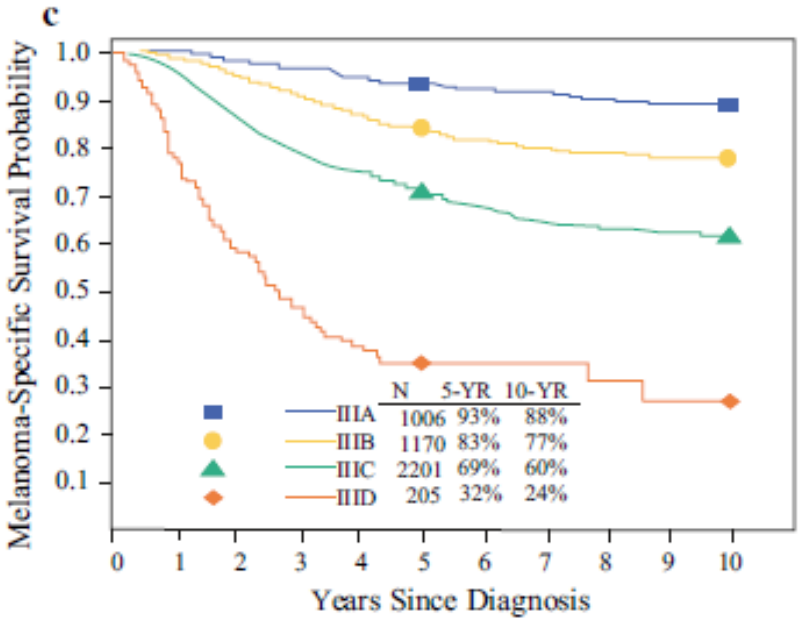
Incidencia y pronóstico

¿Qué hacer en IIB y IIIA?

Stage I-II



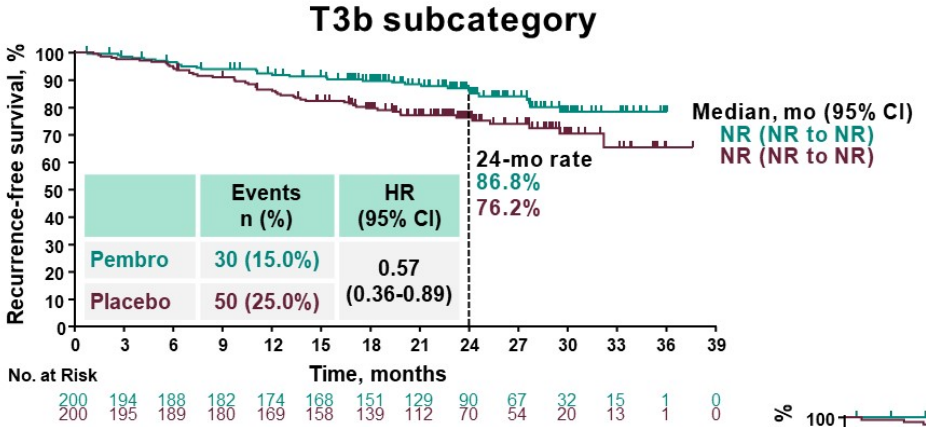
Stage III

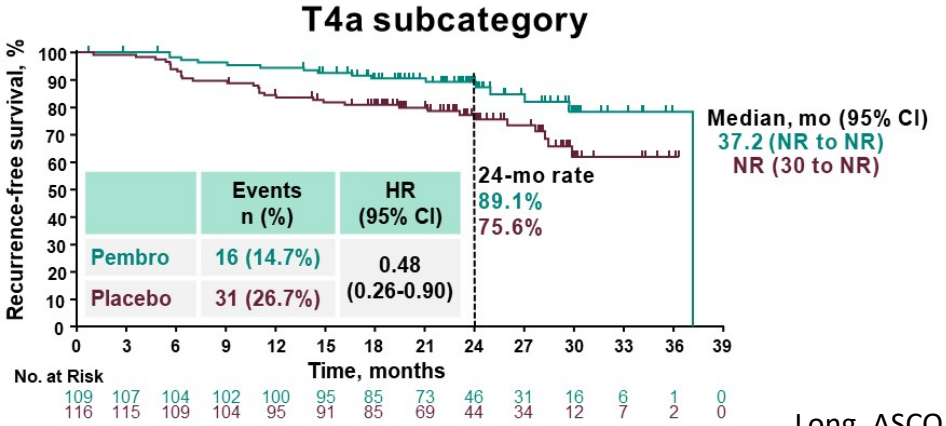


Gershenwald, Ann Surg Oncol 2018

Estadio IIB: ¿Estoy curado?

Keynote 716

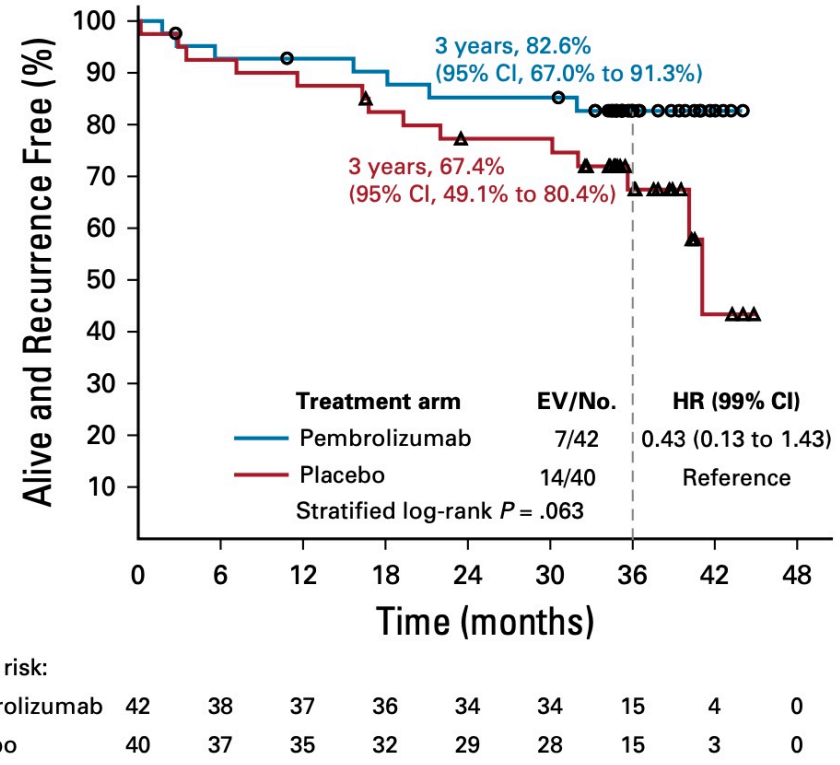




Long, ASCO 2022

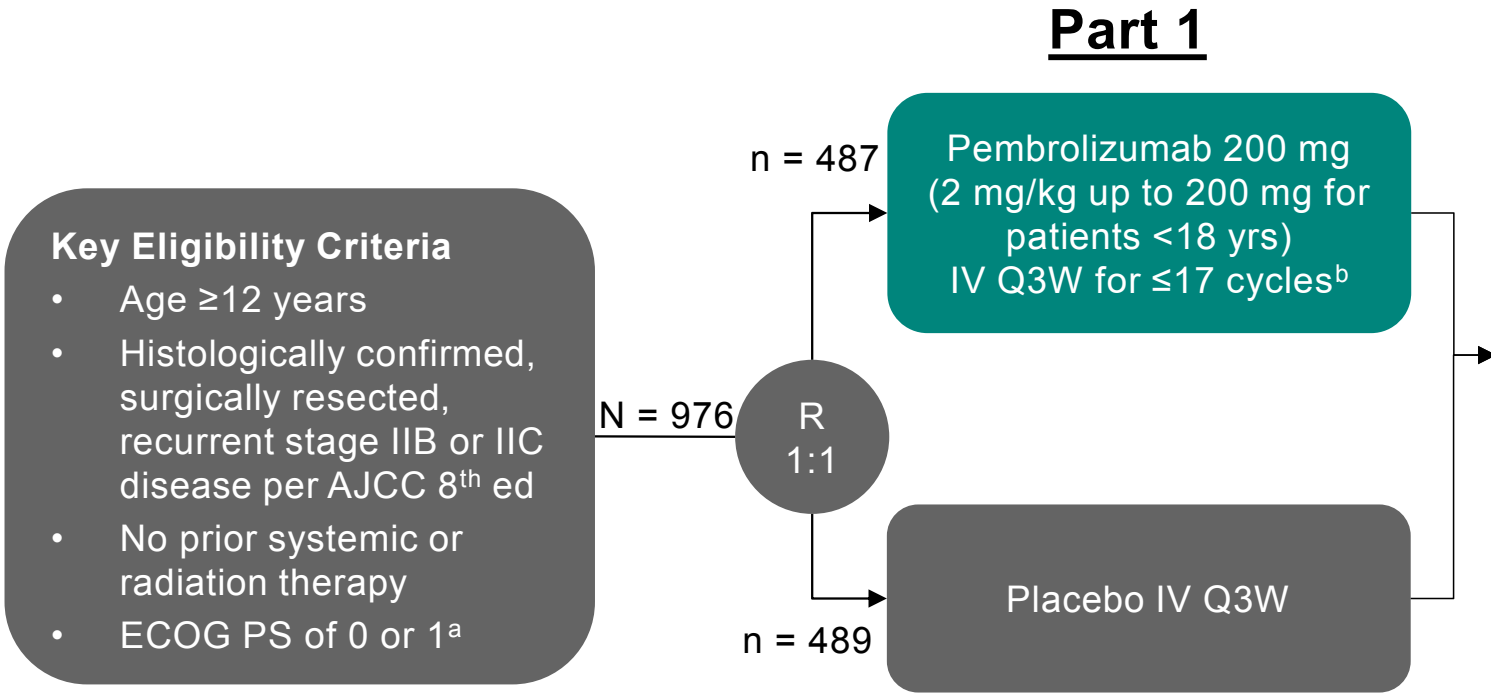
Estadio IIIA: ¿Estoy curado?

Keynote 054



Eggermont, JCO 2022

Estadio IIB/IIC: KEYNOTE 716

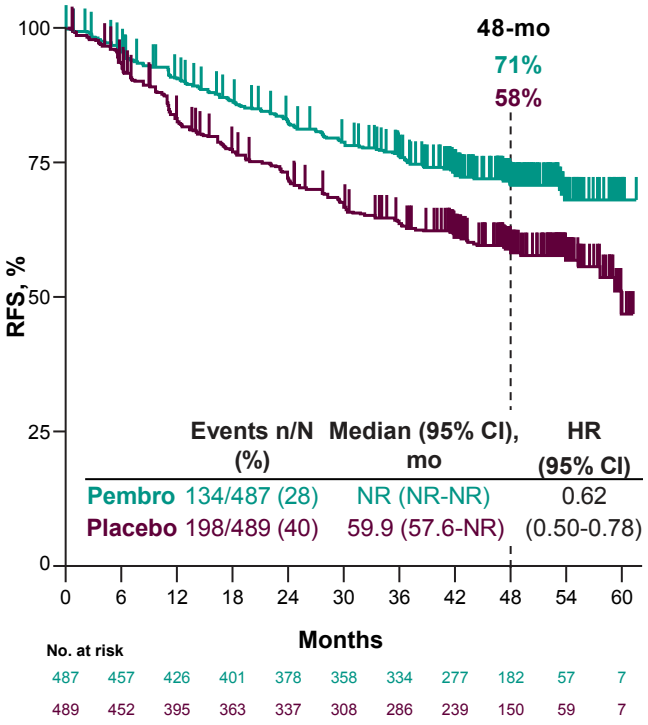


Follow up: 52.8 months

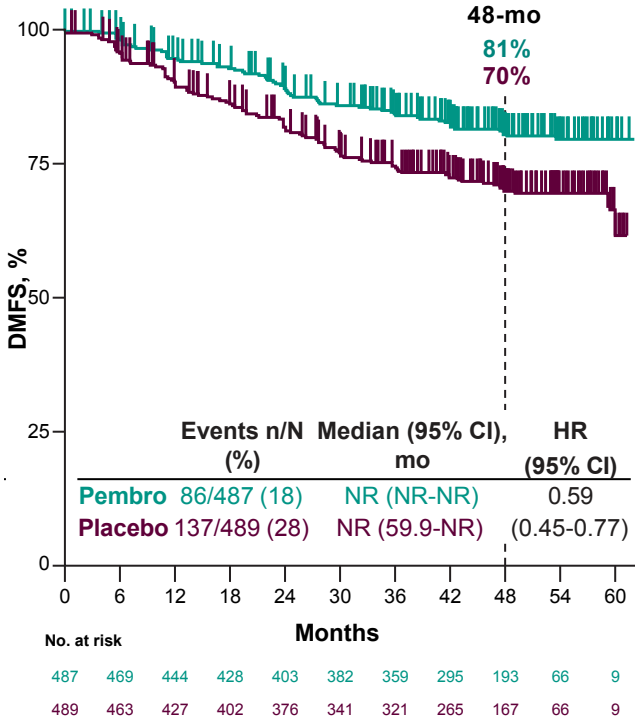
Luke, Lancet 2022; Luke, JCO 2024

Estadio IIB/IIC: KEYNOTE 716

RFS

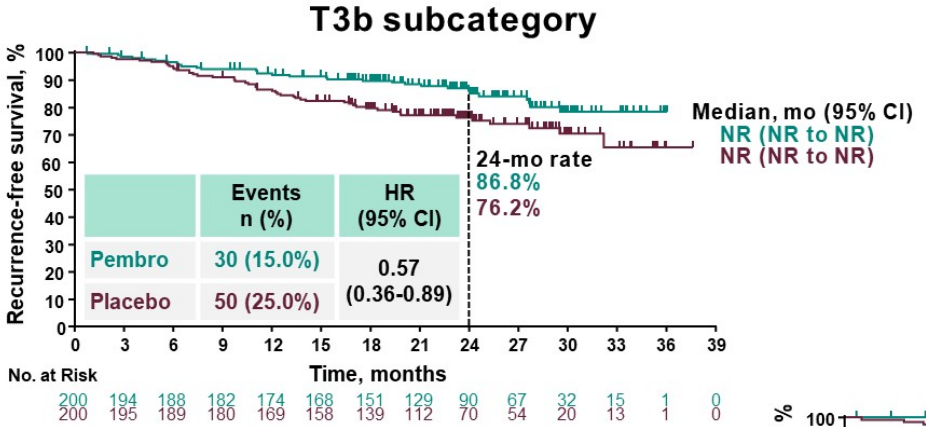


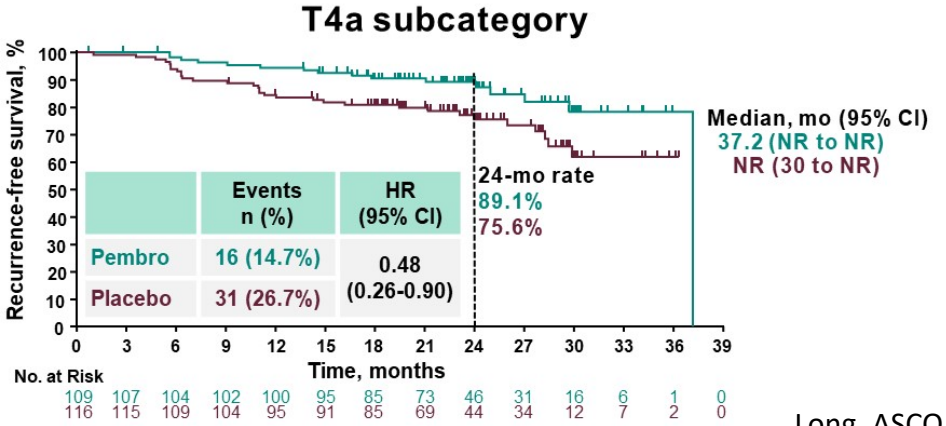
DMFS



Luke, Lancet 2022; Luke, JCO 2024

Estadio IIB/IIC: KEYNOTE 716

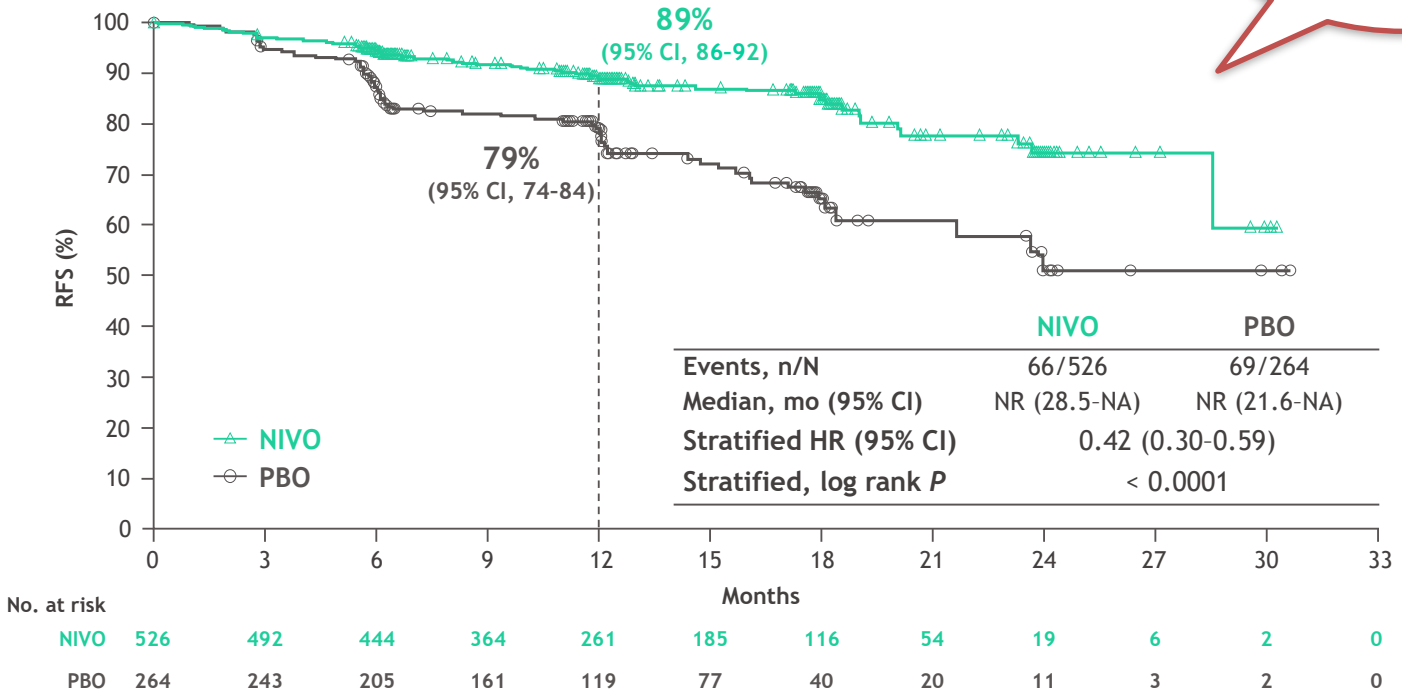




Long, ASCO 2022

Estadio IIB/IIC: CheckMate 76K

No financiado



Follow up: 15.8 months

Kirkwood, Nat Med 2023

¿Adyuvancia Estadio III?

Standard of care pre-2010		Surgery	Observation	Med RFS 25.6 mo[1] 5–yr RFS ~35%
		Surgery	Adjuvant IFN-α	HR 0.82 vs obn (DFS)[2]
2015 EORTC 18071		Surgery	Adjuvant CTLA-4	HR 0.75 vs obn (RFS)[3] 5–yr RFS ~41%

1. Eggermont AMM, et al. Lancet. 2008;372:117–126; 2. Mocellin S, et al. J Natl Cancer Inst. 2010;102:493–501;
3. Eggermont AMM, et al. N Engl J Med. 2016;375:1845–1855; 4. Eggermont AMM, et al. N Engl J Med. 2018;378:1789–1801;
5. Weber J, et al. N Engl J Med. 2017;377:1824–1835; 6. Patel SA, et al. ESMO 2022 & N Engl J Med. 2023;388:813–823;
7. Blank CU, et al. N Engl J Med. 2024;00:00–00; *1-yr EFS rates estimated from KM curve.

Long, ESMO 2024

Estadio III: CheckMate 238

Patients with:

- **High-risk, completely resected stage IIIB/ IIIC or stage IV (AJCC 7th edition) melanoma**
- **No prior systemic therapy**
- **ECOG 0-1**

1:1

n = 453

NIVO 3 mg/kg IV Q2W and IPI placebo IV Q3W for 4 doses then Q12W from week 24

n = 453

IPI 10 mg/kg IV Q3W for 4 doses then Q12W from week 24 and NIVO placebo IV Q2W

Follow-up

Maximum treatment duration of 1 year

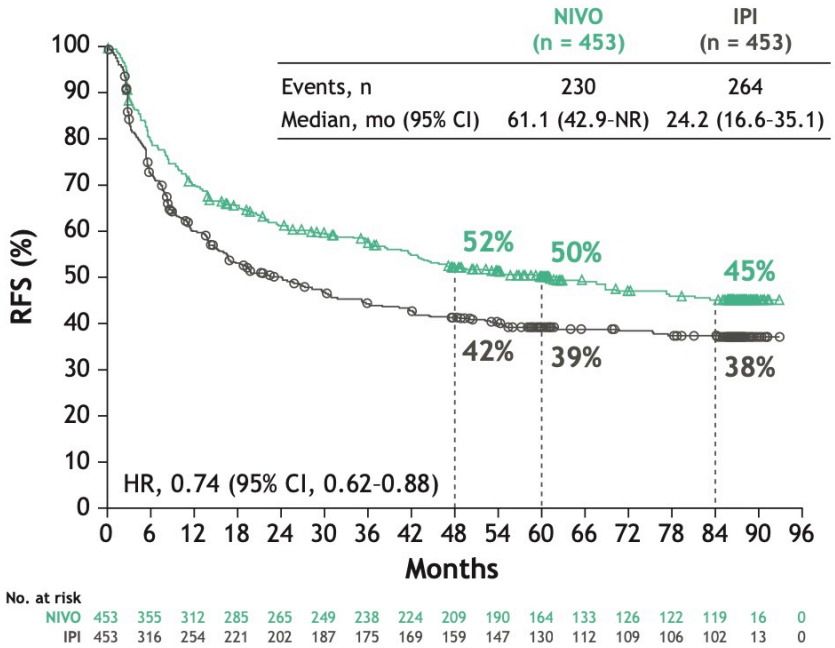
Stratified by:

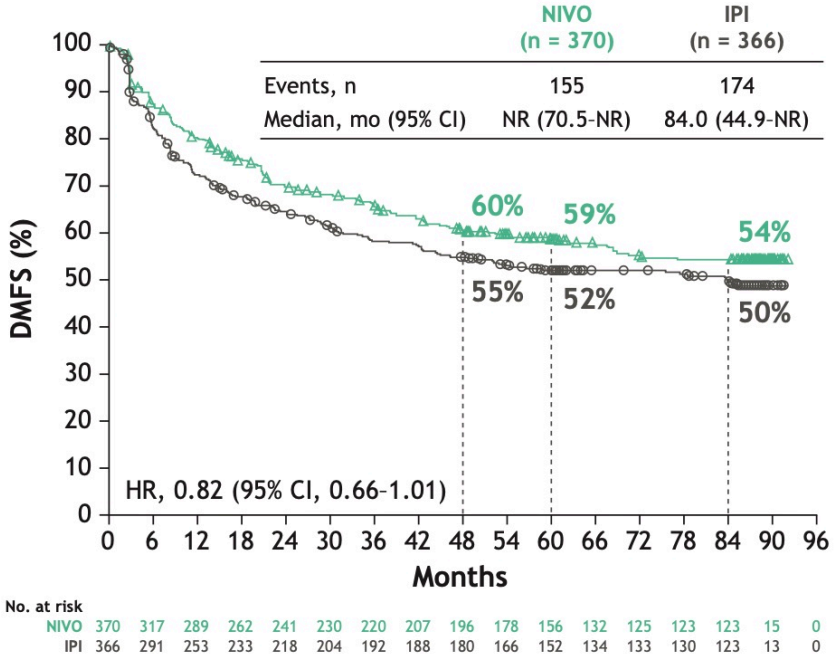
1) Disease stage: IIIB/C vs IV M1a-M1b vs IV M1c
2) PD-L1 status at a 5% cutoff in tumor cells

Minimum Follow up: 7 years

Weber, NEJM 2017; Ascierto, ESMO 2023

Estadio III: CheckMate 238

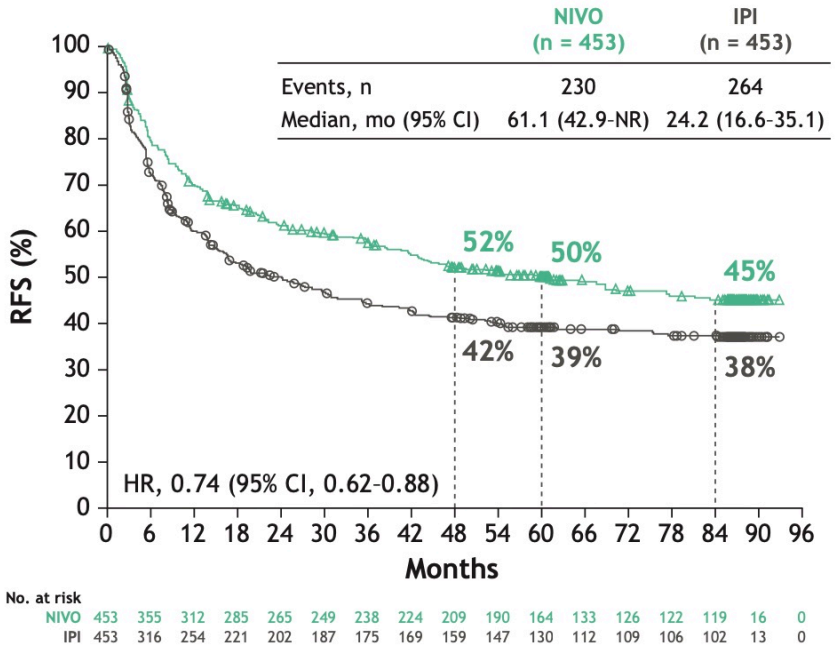


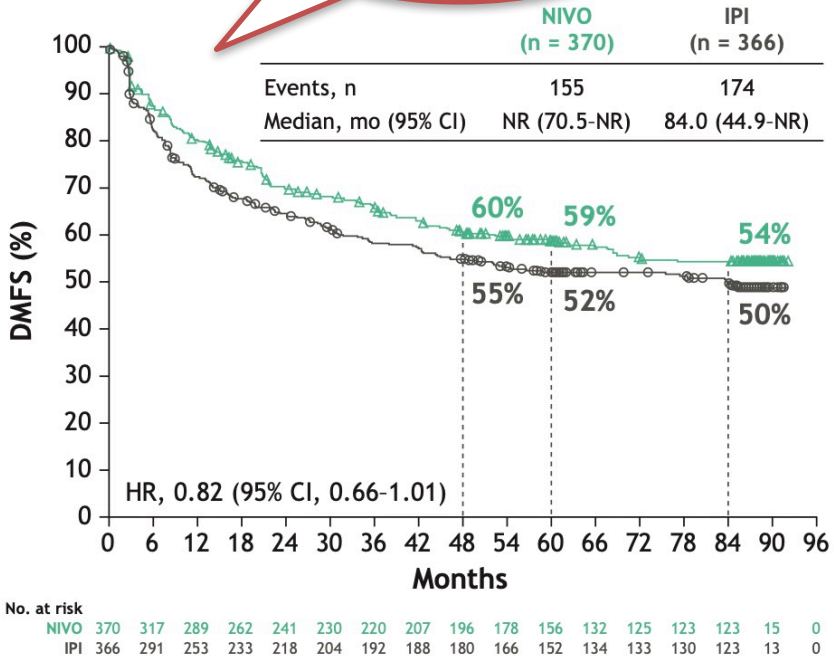


Weber, NEJM 2017; Ascierto, ESMO 2023

Estadio III: CheckMate 238

¿Hasta cuando hacer seguimiento?

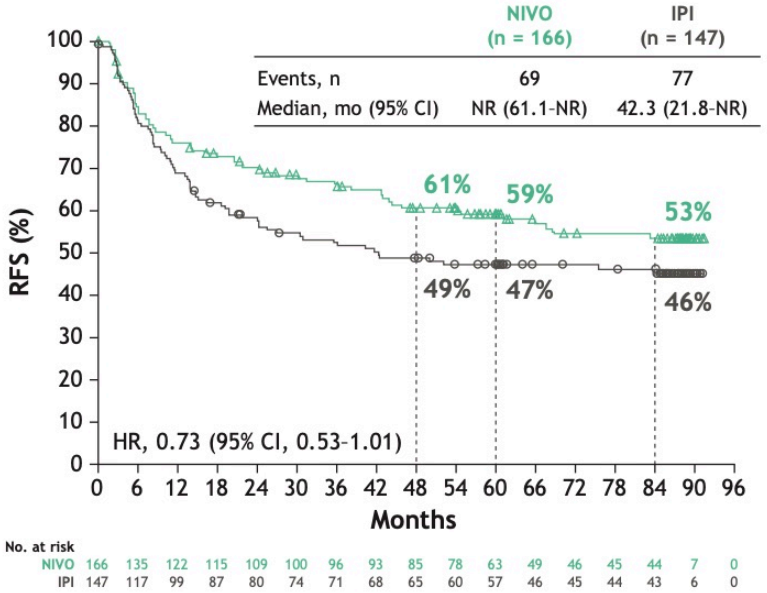




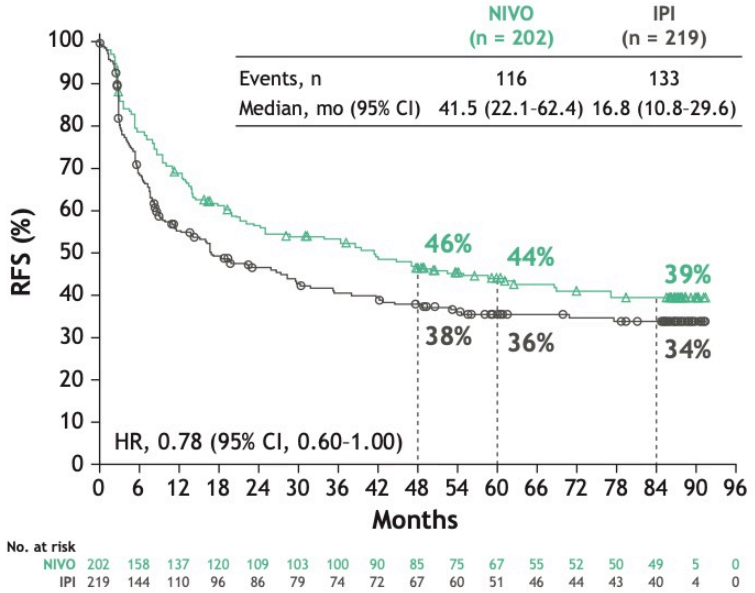
Weber, NEJM 2017; Ascierto, ESMO 2023

Estadio III: CheckMate 238

A. Stage IIIB



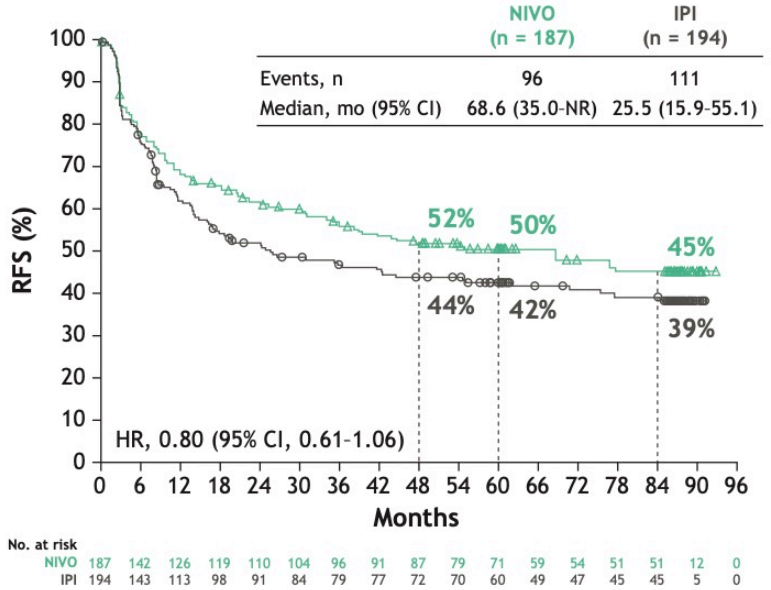
B. Stage IIIC



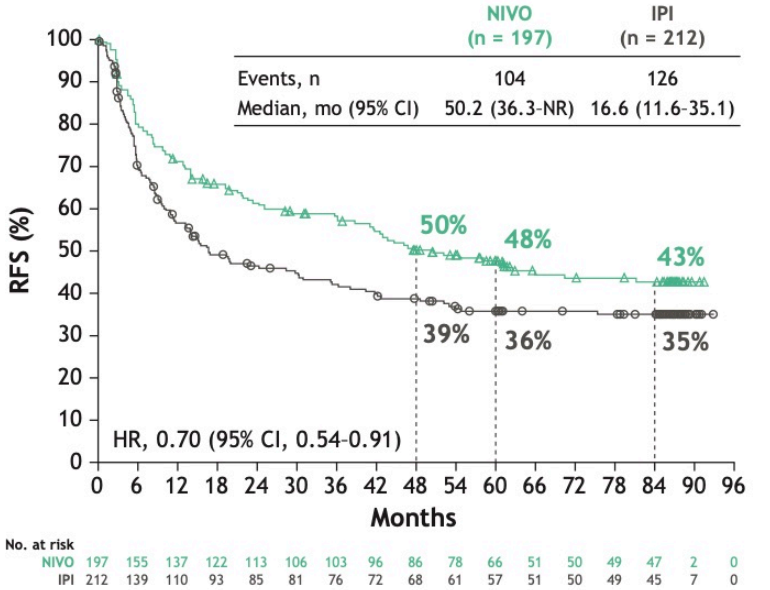
Weber, NEJM 2017; Ascierto, ESMO 2023

Estadio III: CheckMate 238

C. *BRAF* mutant



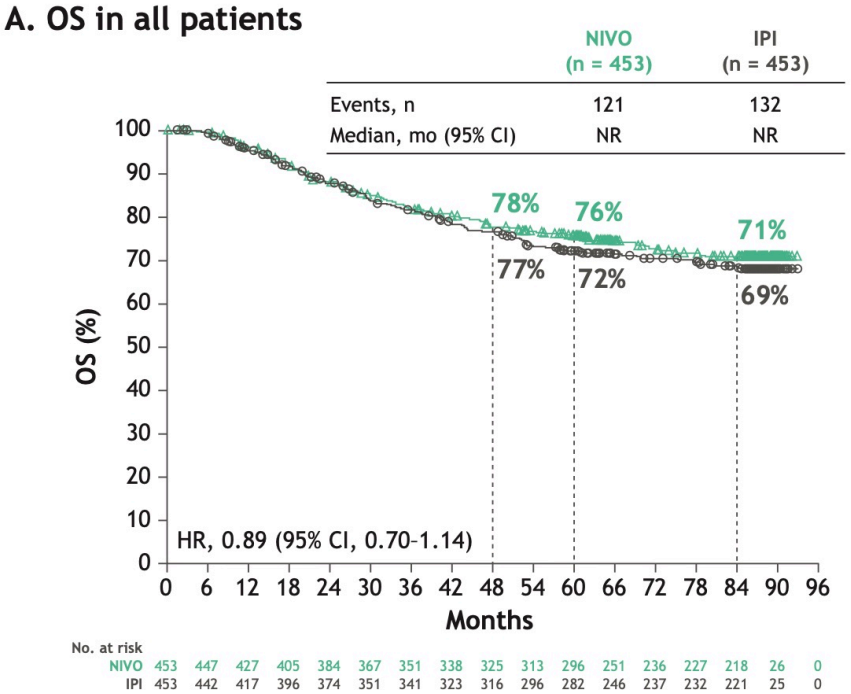
D. *BRAF* wild-type

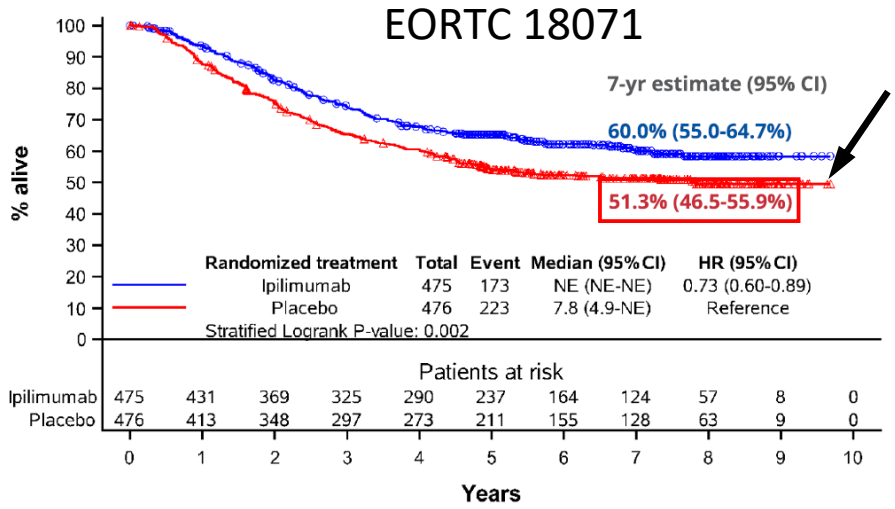


Weber, NEJM 2017; Ascierto, ESMO 2023

Estadio III: CheckMate 238

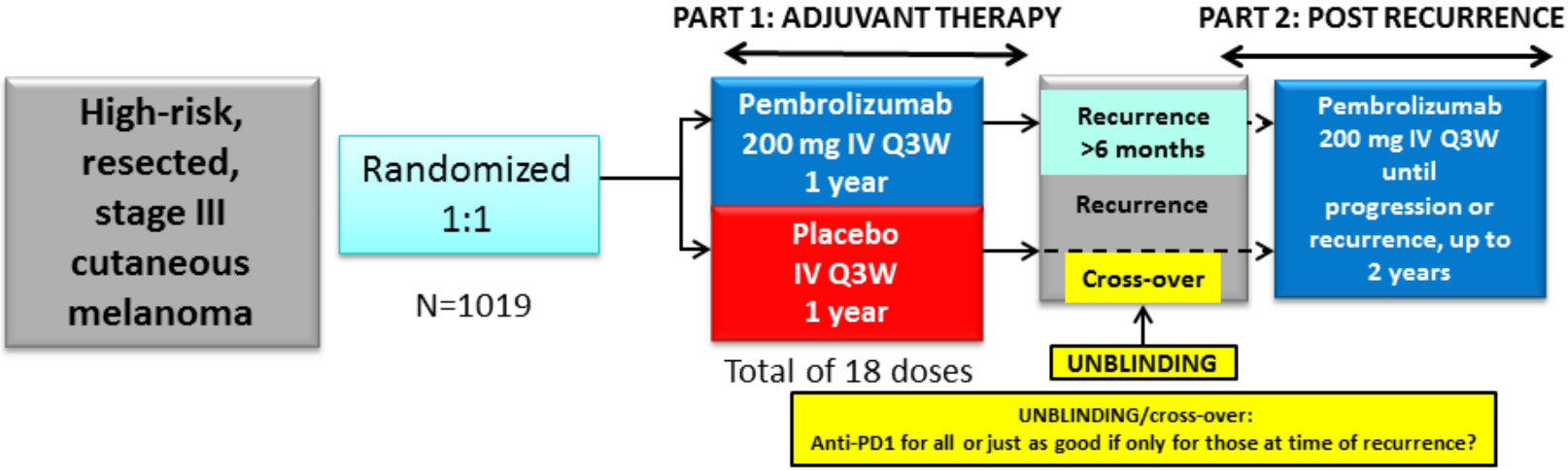
¿Beneficio en Supervivencia?





Weber, NEJM 2017; Ascierto, ESMO 2023; Eggermont, Eur J Cancer 2019

Estadio III: EORTC 1325/KEYNOTE 054



Stratification factors:

✓ **Stage**: IIIA (>1 mm metastasis) vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥4 positive lymph nodes

✓ **Region**: North America, European countries, Australia/New Zealand, other countries

Primary Endpoints:

- **RFS (per investigator) in overall population,** and **RFS in patients with PD-L1-positive tumors**

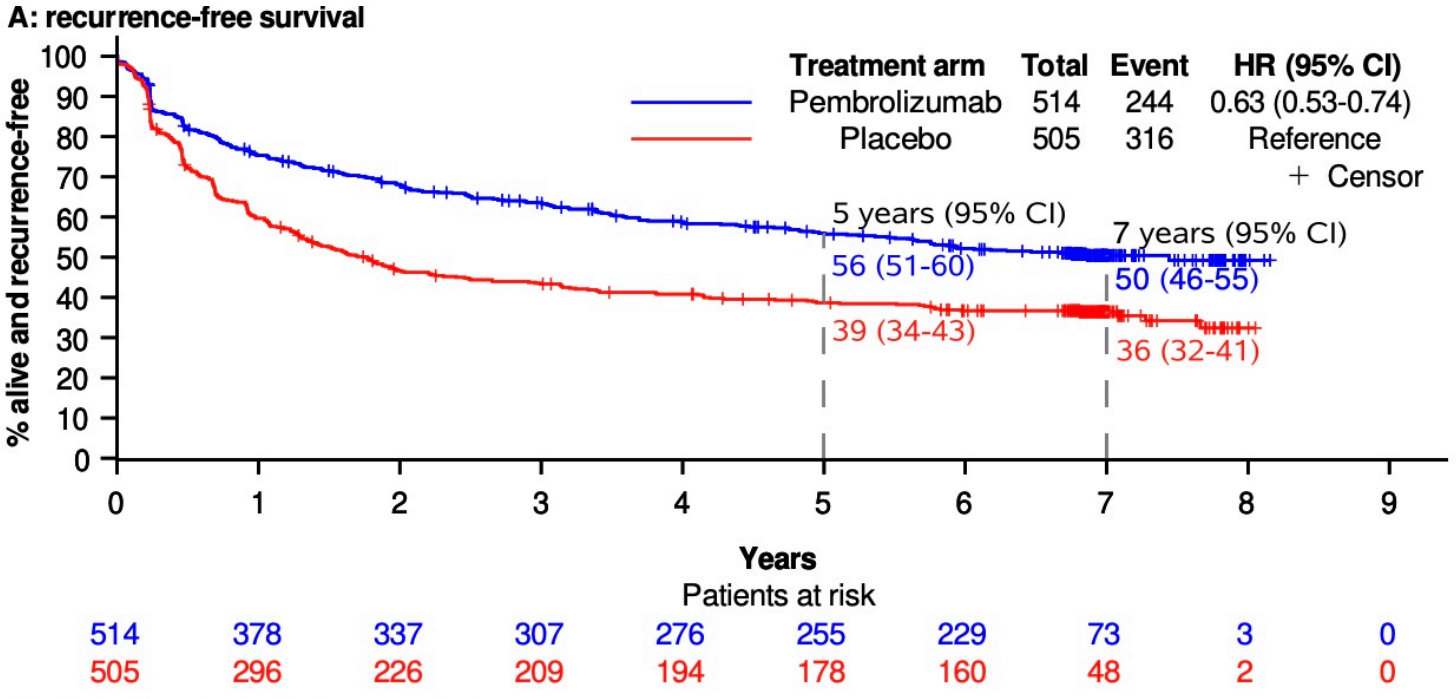
Secondary Endpoints:

- **DMFS and OS** in all patients, and in patients with PD-L1-positive tumors; **Safety, Health-related quality of life**

Minimum Follow up: 7 years

Eggermont, NEJM 2018; Eggermont, EJC 2024

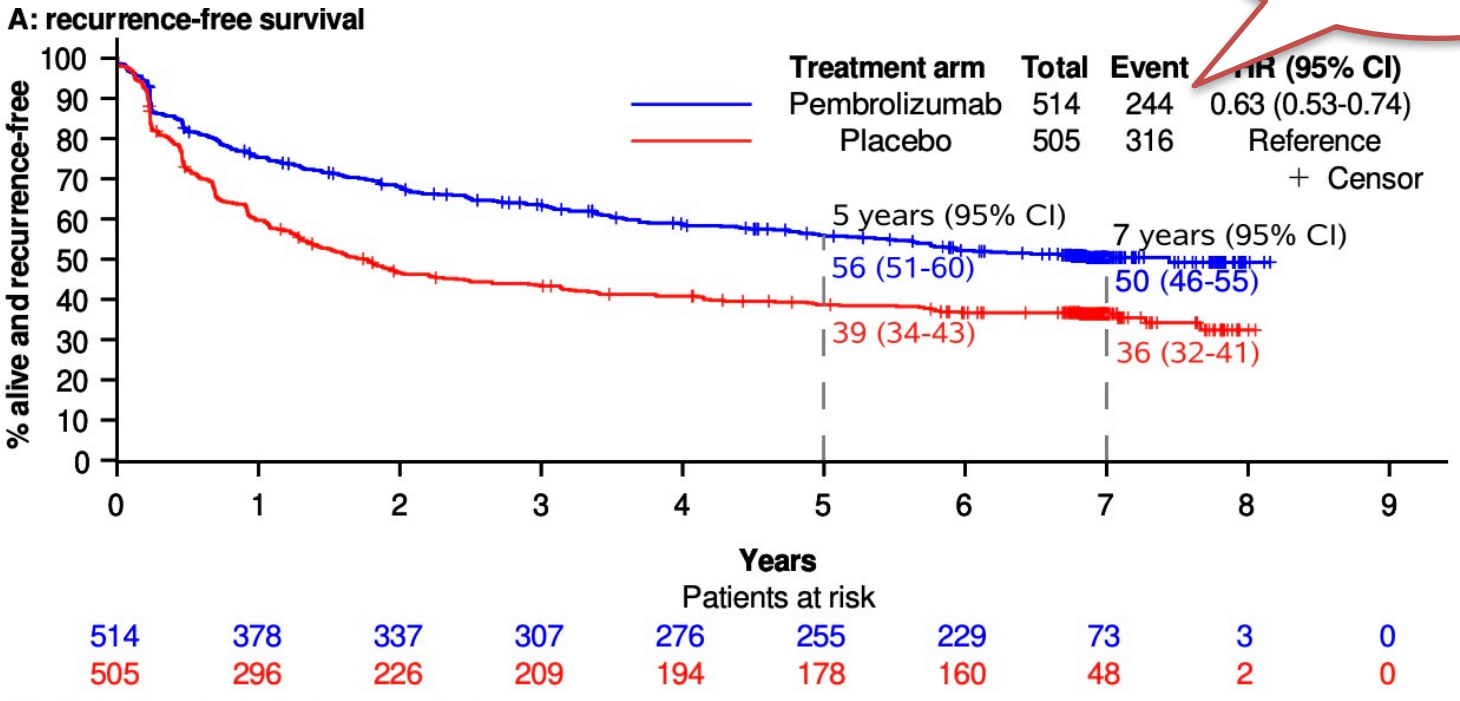
Estadio III: EORTC 1325/KEYNOTE 054



Eggermont, NEJM 2018; Eggermont, EJC 2024

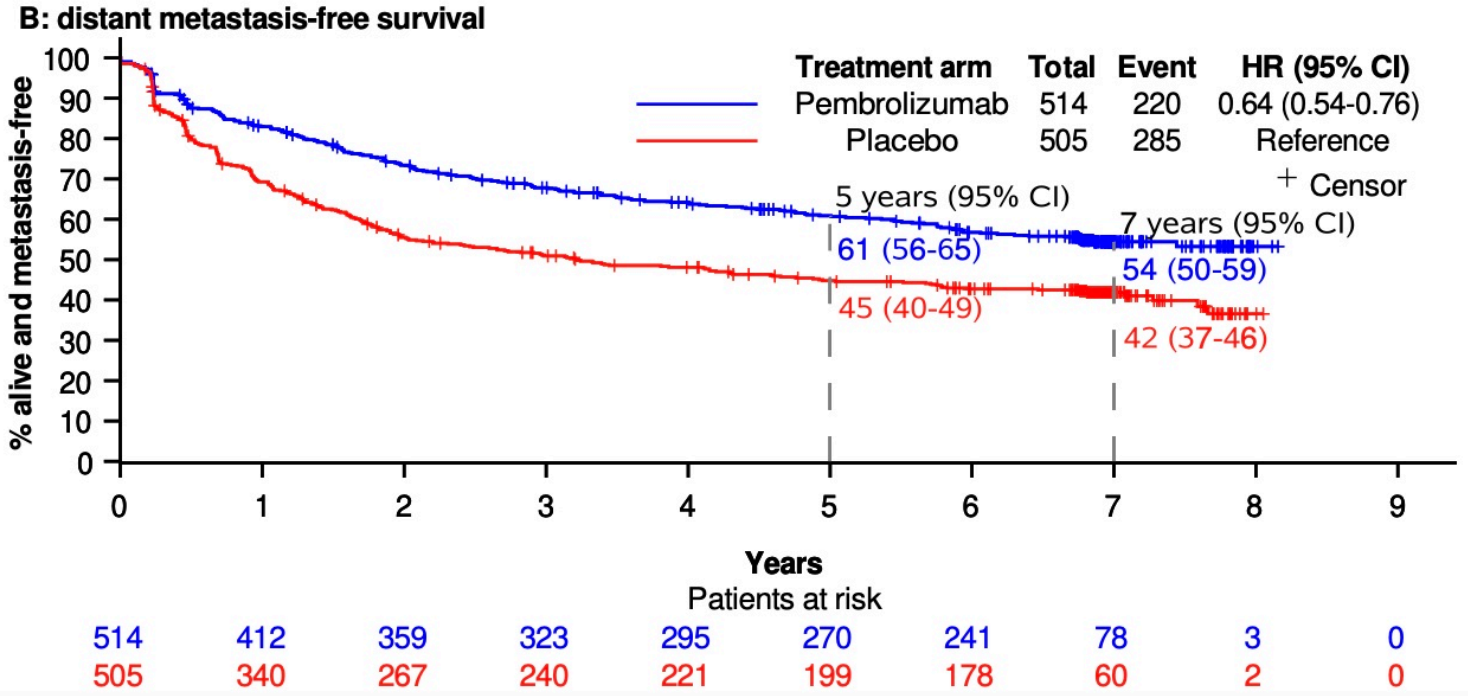
Estadio III: EORTC 1325/KEYNOTE

Desde 1-5-2025
financiados IIIA y IIIB



Eggermont, NEJM 2018; Eggermont, EJC 2024

Estadio III: EORTC 1325/KEYNOTE 054

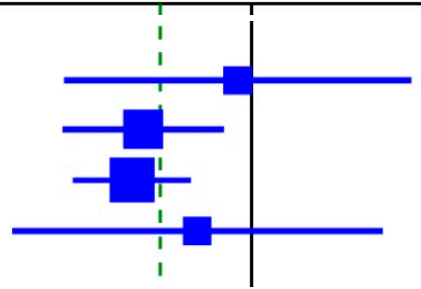


Eggermont, NEJM 2018; Eggermont, EJC 2024

Estadio III: EORTC 1325/KEYNOTE 054

¿Se benefician los IIIA?

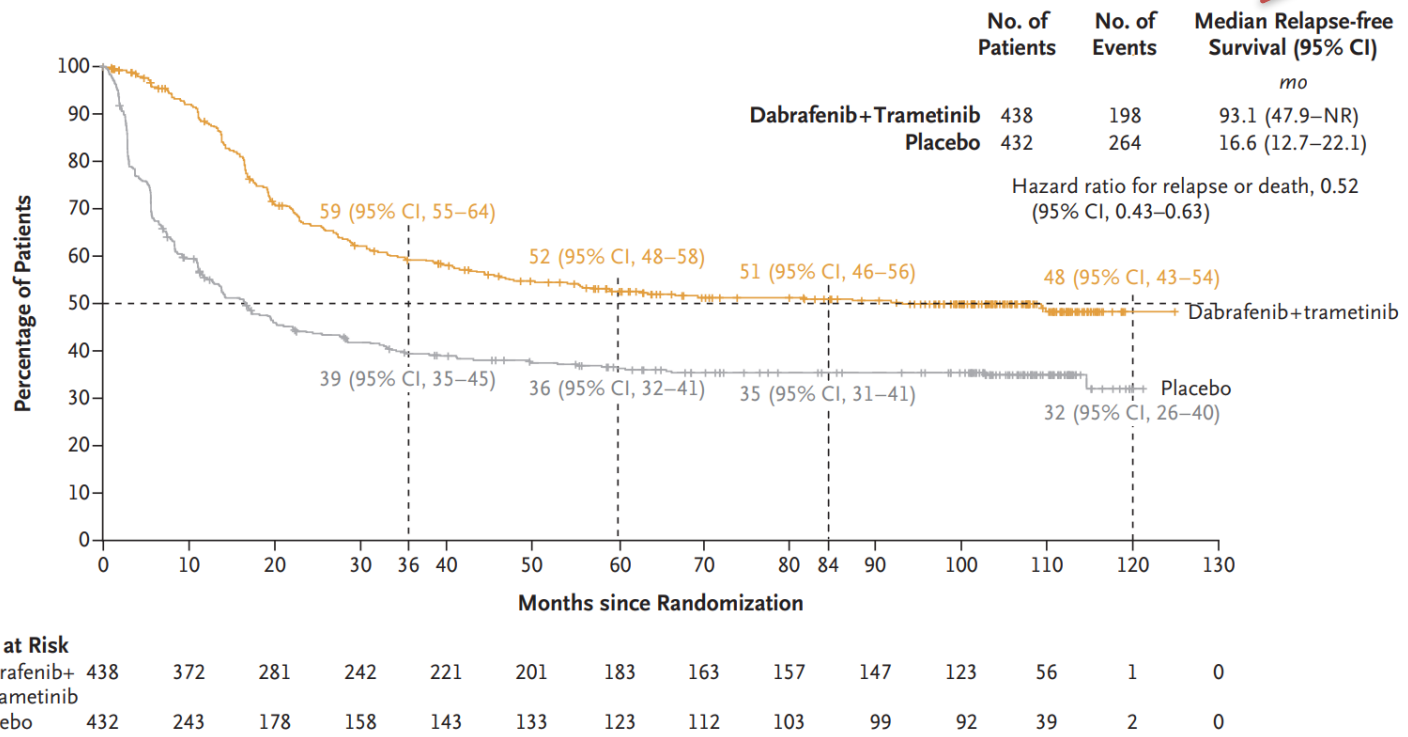
	Events / Patients Pembrolizumab	Placebo	HR (CI)		HR & CI (Pembrolizumab : Placebo)	Interaction test
AJCC-8 classification						
Stage IIIA	17 / 42	17 / 40	0.93	(0.38 ; 2.25)		p=0.431 (df=3)
Stage IIIB	63 / 163	107 / 189	0.58	(0.38 ; 0.87)		
Stage IIIC	136 / 267	167 / 239	0.54	(0.40 ; 0.73)		
Stage IIID	15 / 20	15 / 19	0.76	(0.30 ; 1.94)		
	N missing = 40					



Eggermont, NEJM 2018; Eggermont, EJC 2024

Estadio III: COMBI-AD

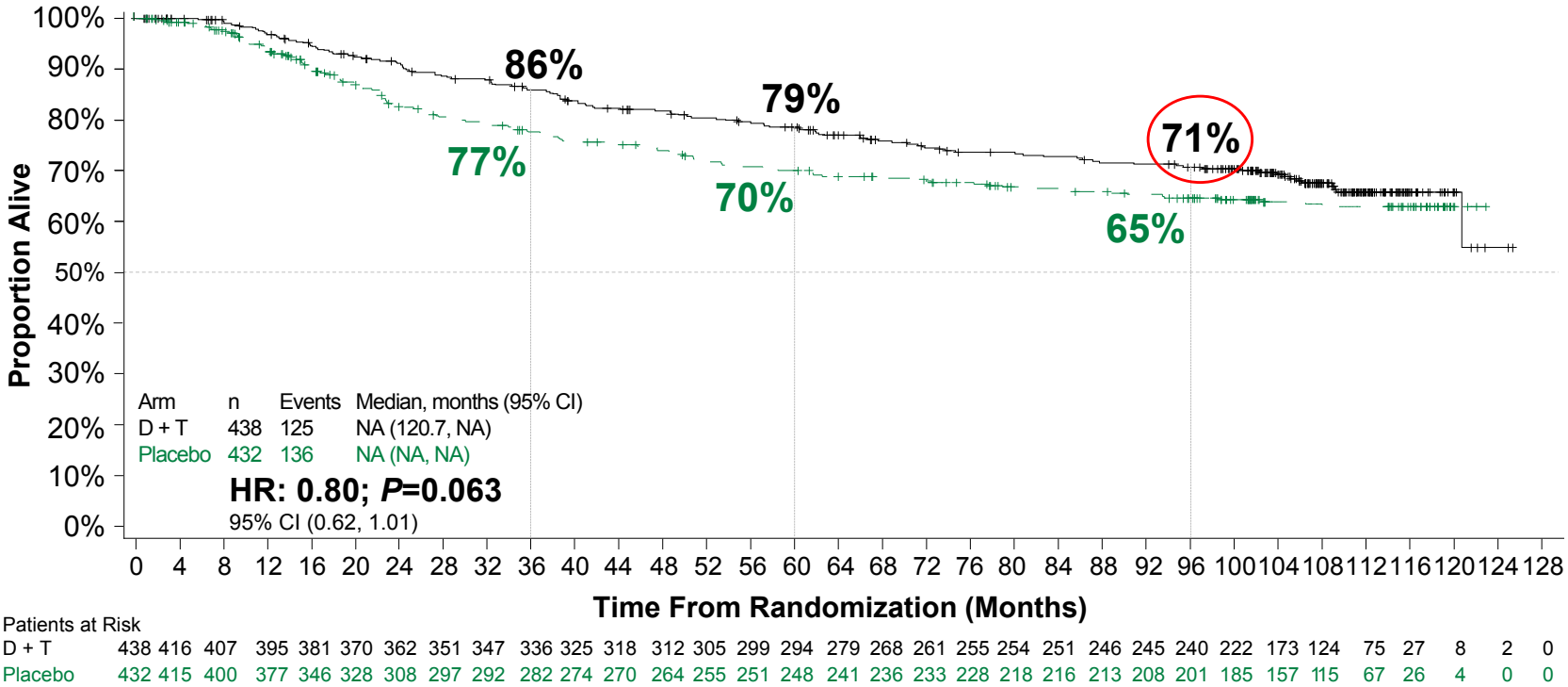
No financiado



Median Follow up: 100 months

Long, NEJM 2017; Long, NEJM 2024

Estadio III: COMBI-AD

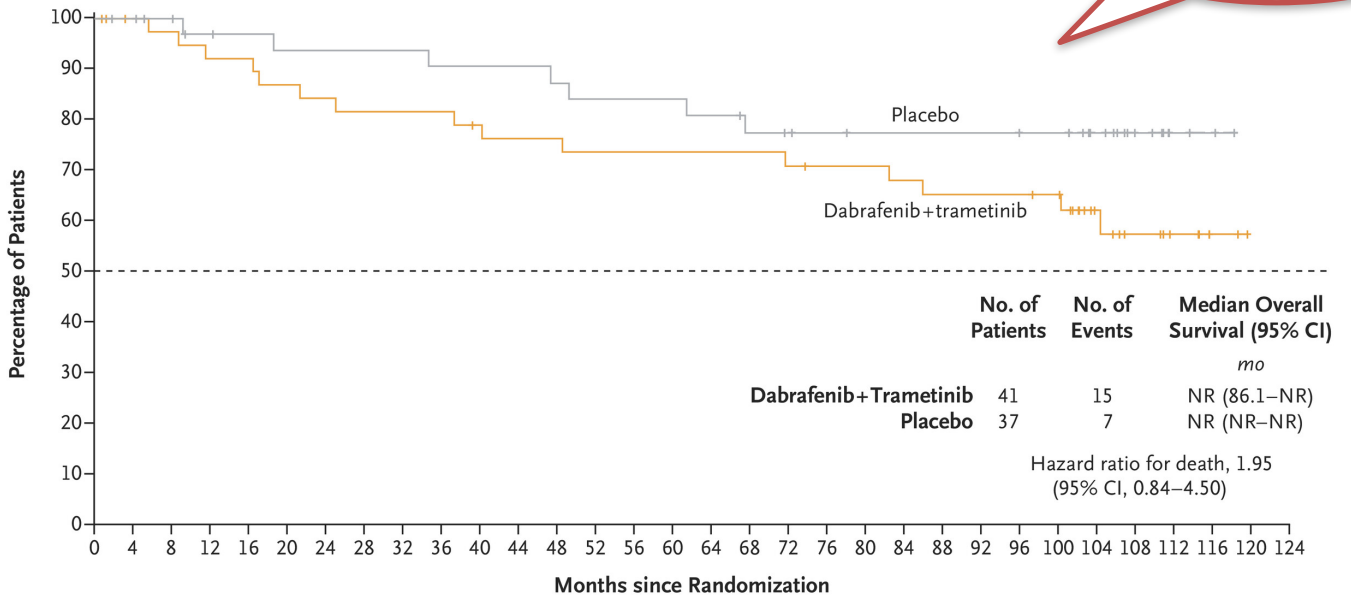


Long, NEJM 2017; Long, NEJM 2024

Estadio III: COMBI-AD

No beneficio en V600K

B Overall Survival with *BRAF* V600K Mutation



No. at Risk

Dabrafenib+ trametinib	41	38	37	35	35	33	32	31	31	31	29	28	28	27	27	27	27	27	26	25	25	24	23	23	23	22	13	9	6	2	0	0
Placebo	37	36	34	31	30	29	29	29	29	28	28	28	27	26	26	26	25	23	22	21	20	20	20	20	20	19	14	9	3	2	0	0

Long, NEJM 2017; Long, NEJM 2024

¿Tratamiento Estadio III?

Standard of care pre-2010		Surgery	Observation	Med RFS 25.6 mo[1] 5–yr RFS ~35%
		Surgery	Adjuvant IFN-α	HR 0.82 vs obn (DFS)[2]
2015 EORTC 18071		Surgery	Adjuvant CTLA-4	HR 0.75 vs obn (RFS)[3] 5–yr RFS ~41%
2017–18 KEYNOTE 054 CheckMate 238		Surgery	Adjuvant PD-1	HR 0.57 vs surgery alone (RFS)[4] HR 0.65 vs CTLA-4 (RFS)[5] 5–yr RFS ~55%

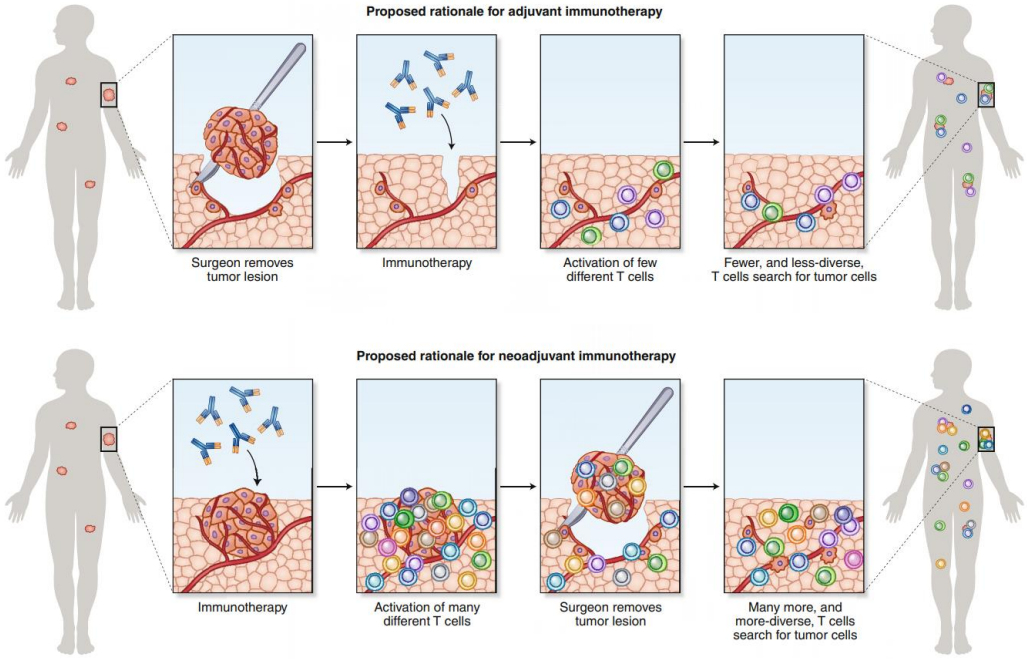
1. Eggermont AMM, et al. Lancet. 2008;372:117–126; 2. Mocellin S, et al. J Natl Cancer Inst. 2010;102:493–501;
3. Eggermont AMM, et al. N Engl J Med. 2016;375:1845–1855; 4. Eggermont AMM, et al. N Engl J Med. 2018;378:1789–1801;
5. Weber J, et al. N Engl J Med. 2017;377:1824–1835; 6. Patel SA, et al. ESMO 2022 & N Engl J Med. 2023;388:813–823;
7. Blank CU, et al. N Engl J Med. 2024;00:00–00; *1-yr EFS rates estimated from KM curve.

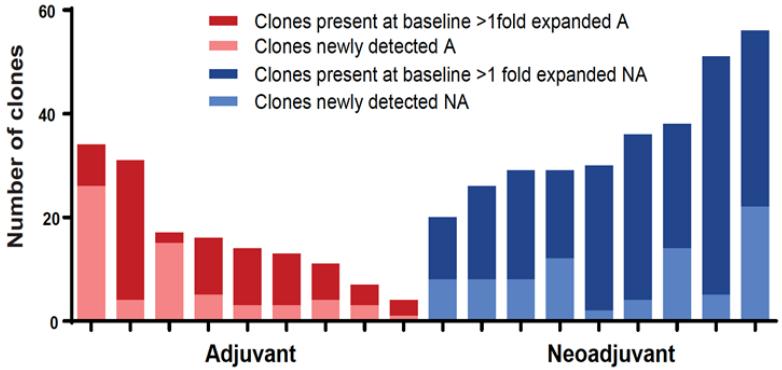
Long, ESMO 2024

¿Neoadyuvancia Estadio III?

Aumentar el número de antígenos

Información pronostica en la cirugía





Versluis, Nat Med 2020; Blank, Nat Med 2018

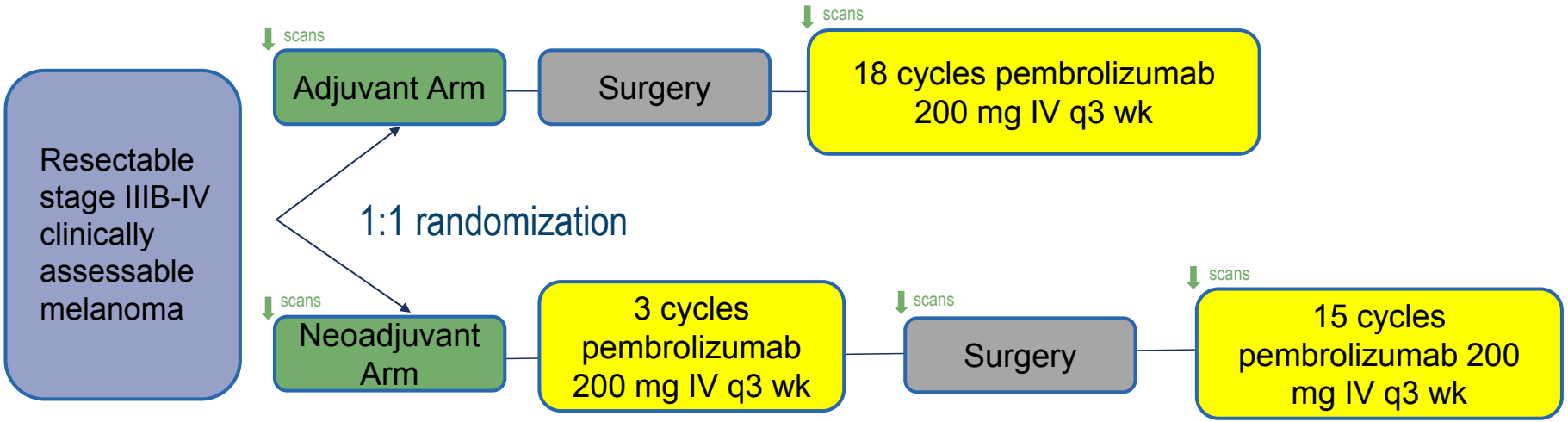
Respuesta Patológica

Pathological Response Category	Percent Viable Tumour Cells	Category
Pathological Complete Response (pCR)	0% viable tumour cells	Major Pathological Response **MPR**
Near Pathological Complete Response (near-pCR)	0 to ≤10% viable tumour cells	
Pathological Partial Response (pPR)	>10% and ≤50% viable tumour cells	**pPR**
Pathological Non-Response (pNR)	>50% viable tumour cells	**pNR**

Neoadyuvancia Estadio III: SWOG 1801

Fase II

Primary endpoint: Event-free survival



⬇radiographic assessment (scans)

Additional criteria: strata included AJCC 8th ed. stage and LDH, adjuvant radiation allowed, concomitant radiation & pembrolizumab was not allowed, brain metastasis excluded, uveal melanoma excluded

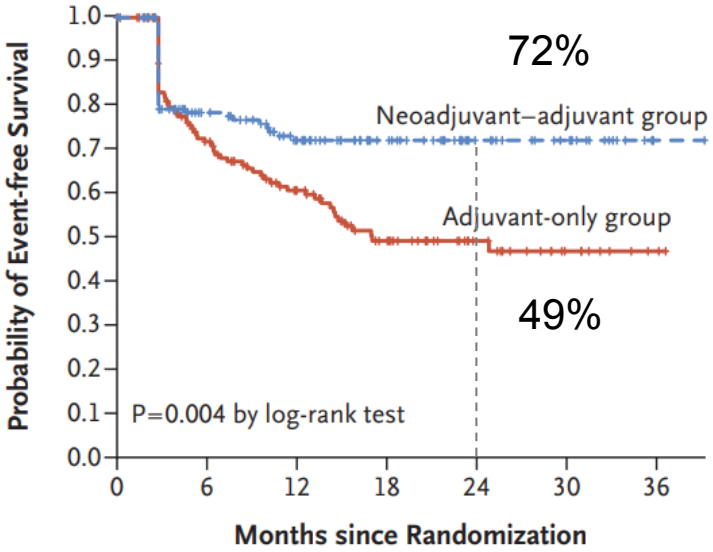
Surgery type and extent was required to be pre-specified and carried out regardless of radiologic response to therapy

Patel, NEJM 2023

Neoadyuvancia Estadio III: SWOG 1801

No aprobación EMA

Event-free survival



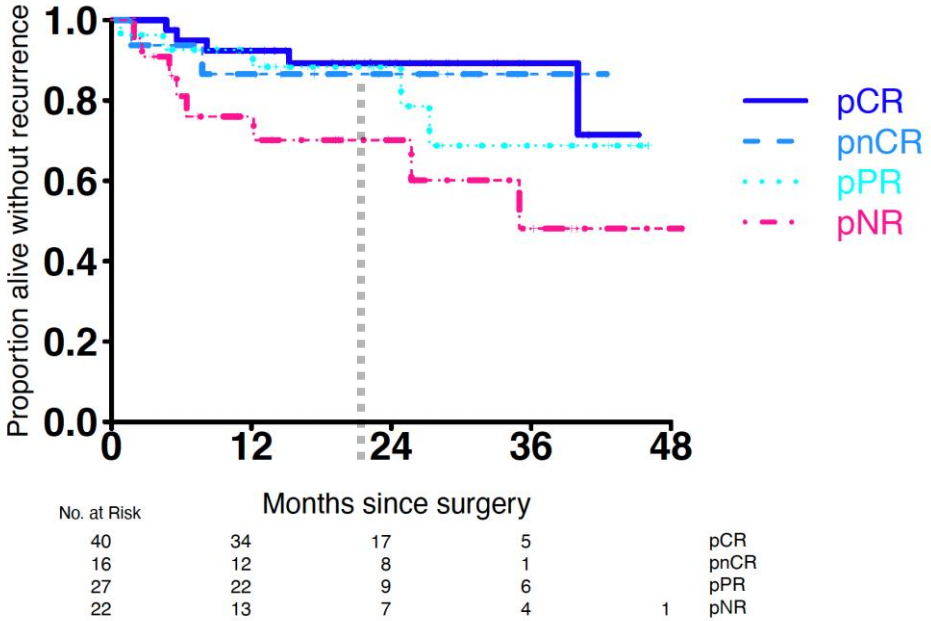
No. at Risk

Neoadjuvant–adjuvant group	154	96	69	46	25	17	1
Adjuvant-only group	159	98	67	40	22	10	2

Patel, NEJM 2023

Neoadyuvancia Estadio III: SWOG 1801

	n (%)	24-month RFS (95% CI)
pCR	40 (38%)	89% (80-100)
pnCR	16 (15%)	87% (71-100)
pPR	27 (26%)	88% (77-100)
pNR	22 (21%)	70% (53-94)
MPR	56 (53%)	88% (80-98)



Patel, NEJM 2023

Neoadyuvancia Estadio III: SWOG 1801

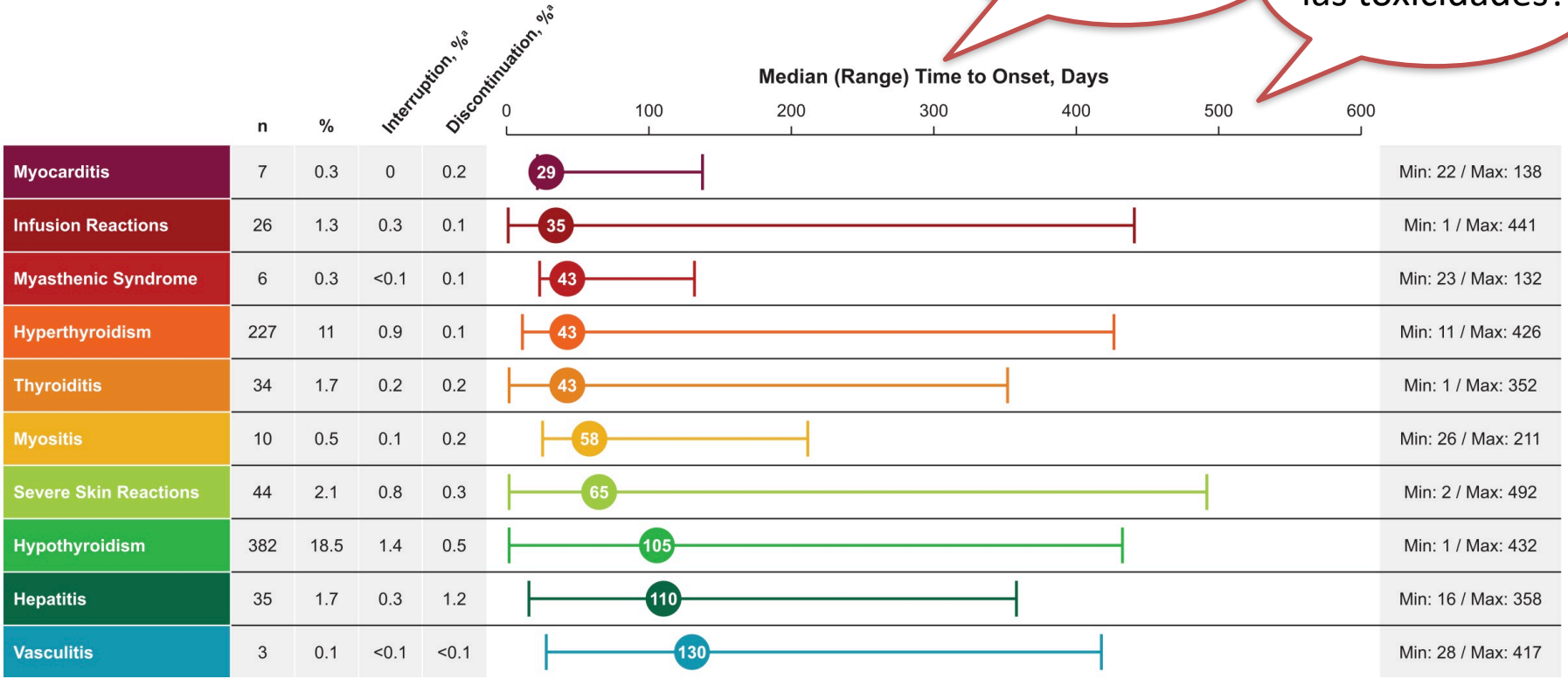
Grade 3-4 adverse events	Peri-operative	Adjuvant
Neoadjuvant pembrolizumab	11/152 (7%)	-
Surgery	9/127 (7%)	5/141 (4%)
Adjuvant pembrolizumab	14/113 (12%)	18/131 (14%)
Any treatment-related adverse event	12%	14%

Patel, NEJM 2023

Toxicidad anti PD-1

¿Son tan poco tóxicos?

¿Notificamos las toxicidades?



Luke, Eur J Cancer 2024

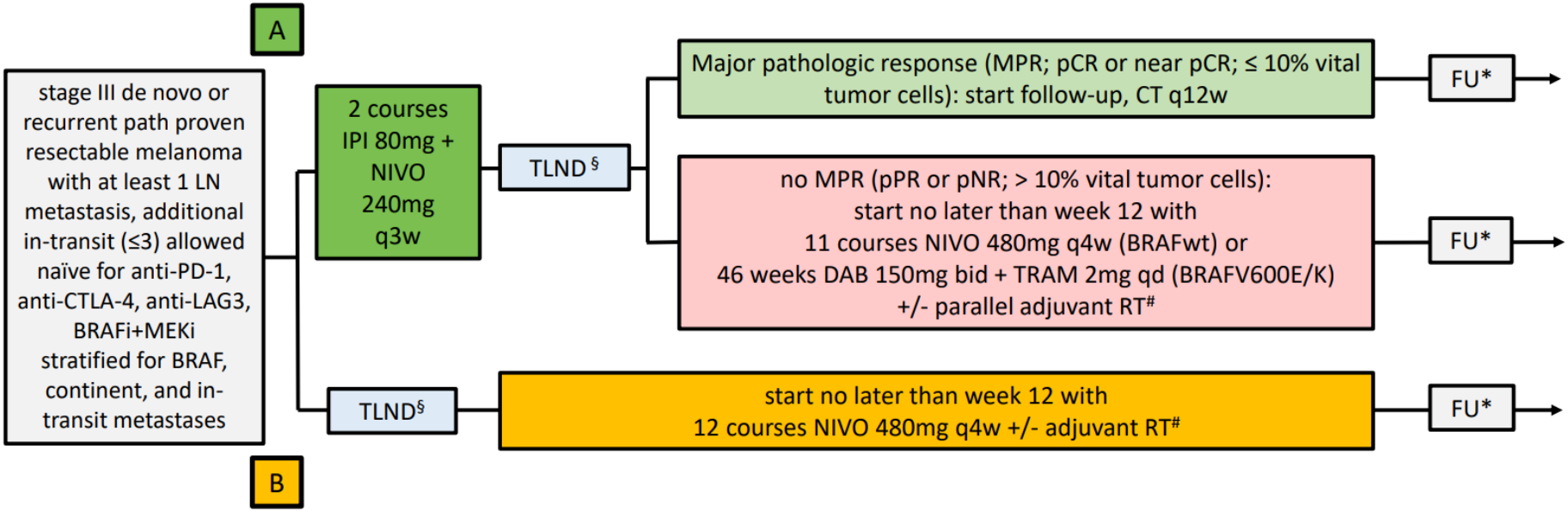
Toxicidad anti PD-1

¿Cómo explicamos al paciente este riesgo?

Colitis	62	3	1.2	1.2	148	Min: 2 / Max: 465
Pneumonitis	82	4	2	1.9	160	Min: 21 / Max: 431
Sarcoidosis	17	0.8	<0.1	0.4	167	Min: 37 / Max: 234
Myelitis	1	<0.1	0	<0.1	179	Min: 179 / Max: 179
Type 1 Diabetes Mellitus	17	0.8	0.2	0.5	190	Min: 37 / Max: 370
Adrenal insufficiency	38	1.8	0.5	0.5	194	Min: 22 / Max: 423
Nephritis	16	0.8	0.1	0.4	199	Min: 63 / Max: 424
Encephalitis	1	<0.1	0	0	203	Min: 203 / Max: 203
Hypophysitis	32	1.6	0.4	0.5	207	Min: 4 / Max: 422
Pancreatitis	6	0.3	0.1	<0.1	239	Min: 148 / Max: 399
Uveitis	3	0.1	0	<0.1	301	Min: 175 / Max: 326

Luke, Eur JK Cancer 2024

Neoadyuvancia Estadio III: NADINA

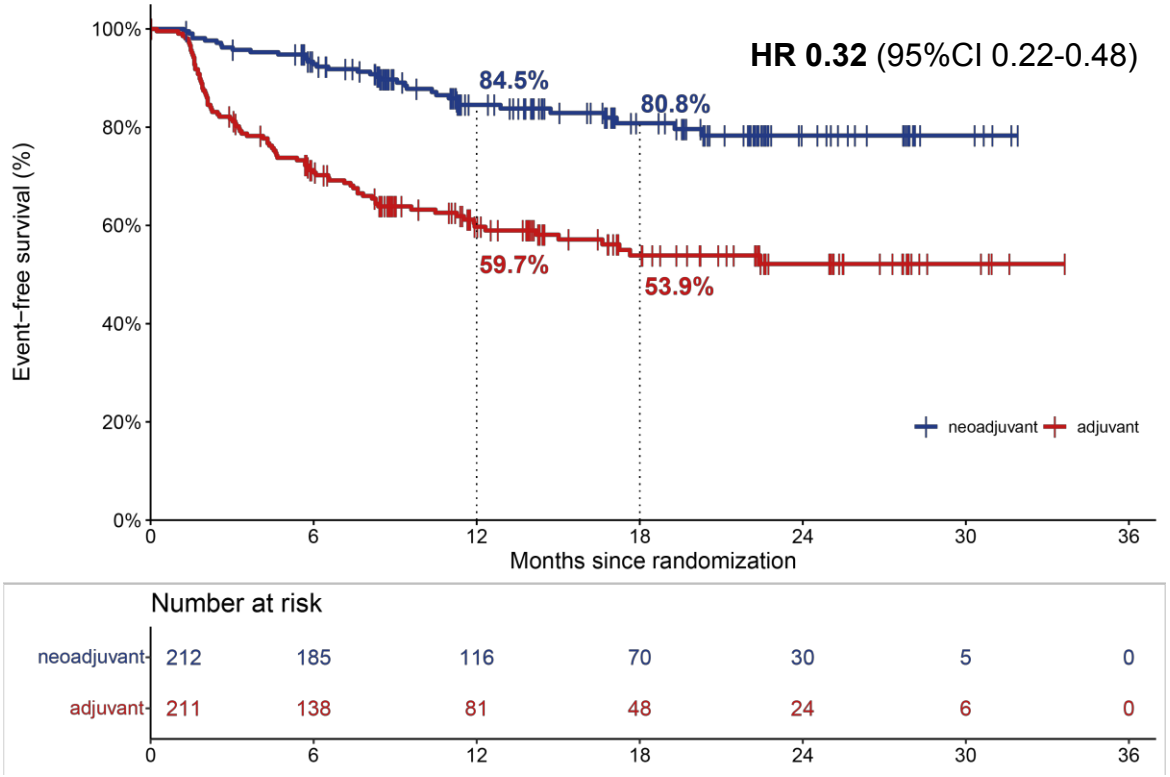


Median Follow up: 15.4 months

Blank, NEJM 2024; Lucas ESMO 2024

Neoadyuvancia Estadio III: NADINA

No aprobación EMA



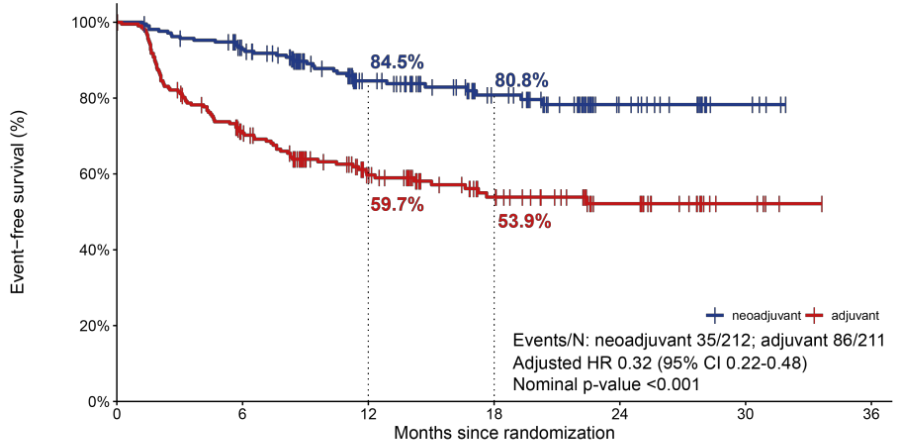
Major pathological response (MPR) 60.8%

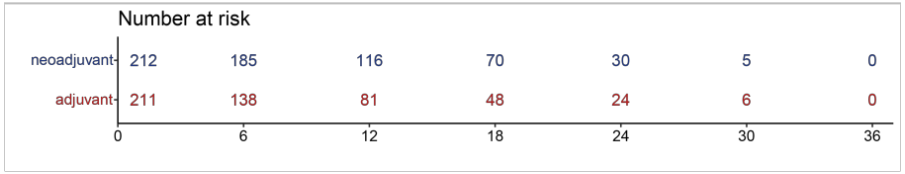
Pathological complete response (pCR) 49.1%

Blank, NEJM 2024; Lucas ESMO 2024

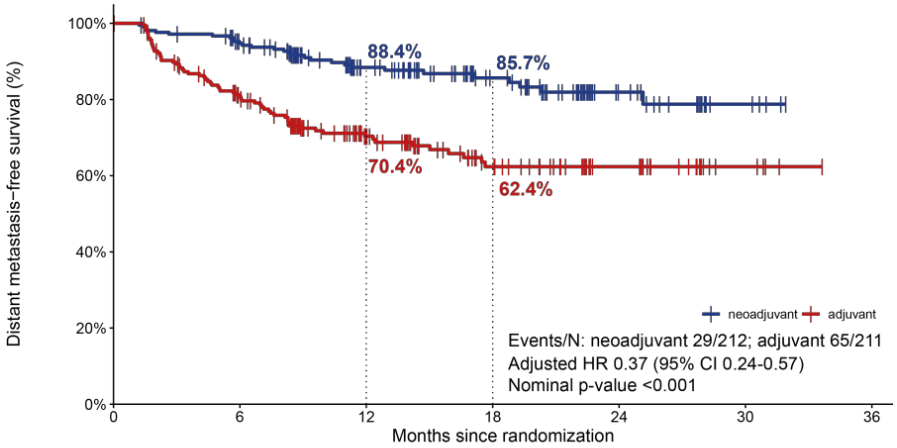
Neoadyuvancia Estadio III: NADINA

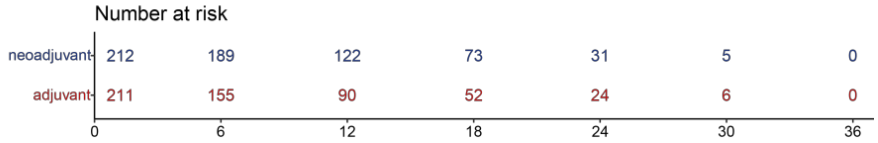
Event-free survival





Distant metastasis-free survival

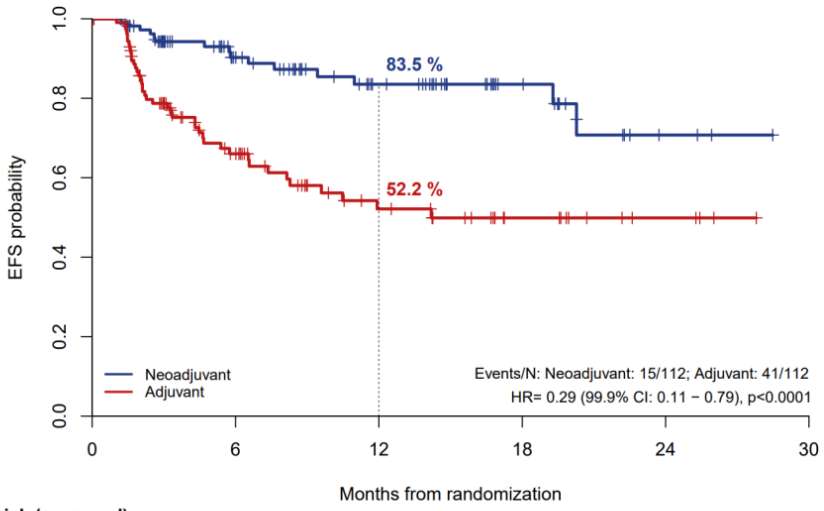




Blank, NEJM 2024; Lucas ESMO 2024

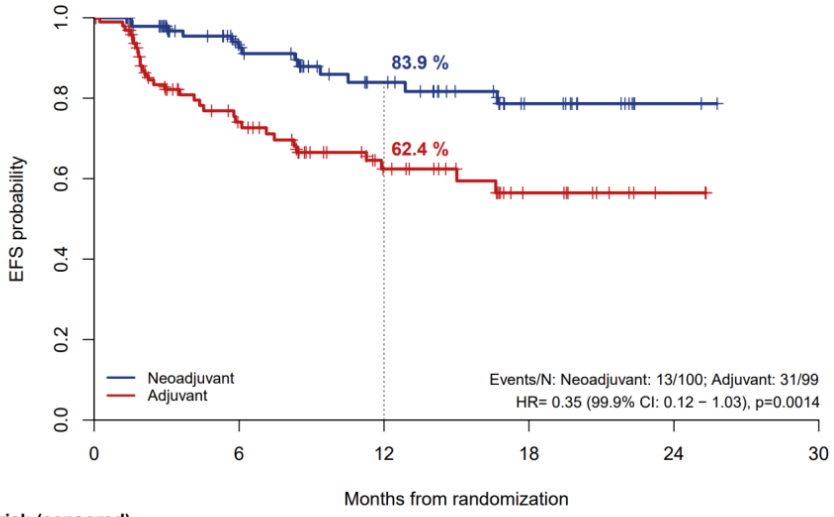
Neoadyuvancia Estadio III: NADINA

BRAF$^{V600E/K}$ mutation



# at risk (censored)										
Neoadjuvant	112	(0)	63	(40)	38	(61)	18	(81)	3	(94)
Adjuvant	112	(0)	48	(32)	25	(47)	11	(60)	4	(67)

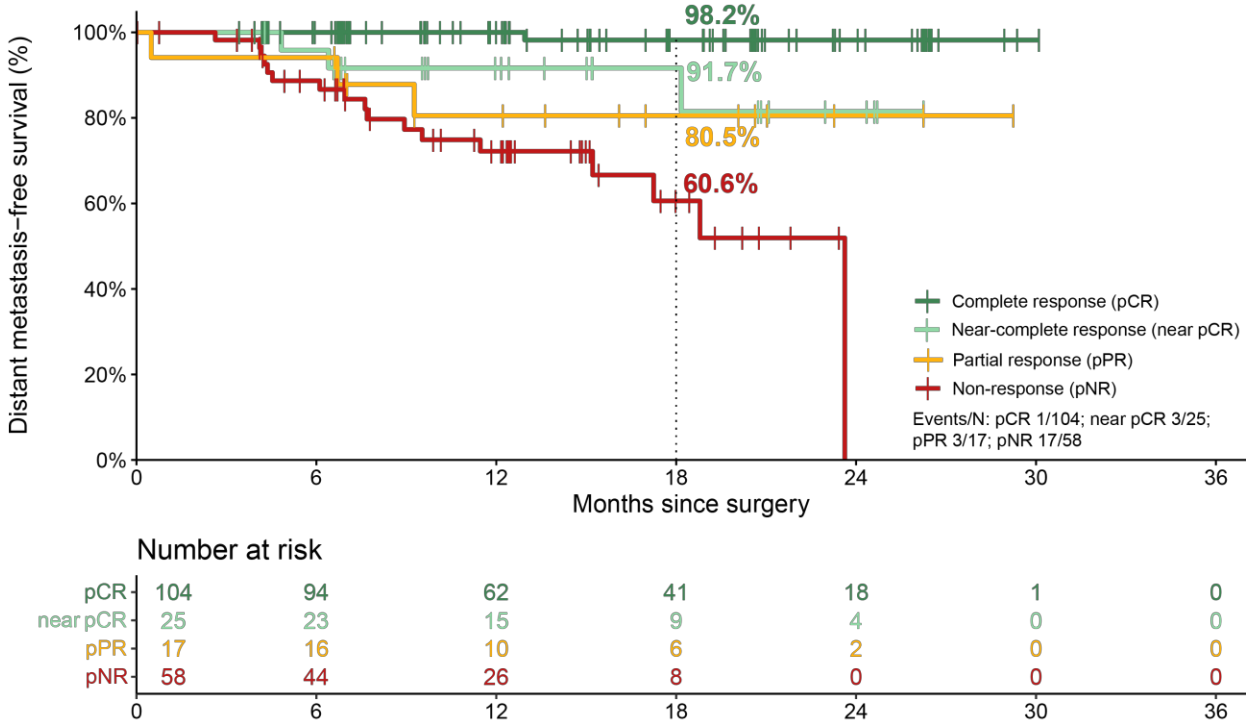
BRAF wildtype



# at risk (censored)										
Neoadjuvant	100	(0)	63	(31)	39	(50)	16	(71)	2	(85)
Adjuvant	99	(0)	52	(25)	28	(42)	12	(56)	2	(66)

Blank, NEJM 2024

Neoadyuvancia Estadio III: NADINA



Blank, NEJM 2024; Lucas ESMO 2024

Neoadyuvancia Estadio III: NADINA

	Neoadjuvant n=212	Adjuvant n=208
Any adverse event	204 (96.2%)	194 (93.3%)
Any grade ≥3 AE	100 (47.2%)	71 (34.1%)
Surgery related AE [1]	120 (60.6%)	151 (72.6%)
Surgery related grade ≥3 AE [1]	28 (14.1%)	30 (14.4%)
Systemic treatment related AE [2]	181 (85.4%)	123 (72.4%)
Systemic treatment related grade ≥3 AE [2]	63 (29.7%)	25 (14.7%)
Death due to treatment related AE	0	1 (0.5%)

Blank, NEJM 2024

¿Tratamiento Estadio III?

Standard of care pre-2010		Surgery	Observation	Med RFS 25.6 mo[1] 5–yr RFS ~35%
		Surgery	Adjuvant IFN-α	HR 0.82 vs obn (DFS)[2]
2015 EORTC 18071		Surgery	Adjuvant CTLA-4	HR 0.75 vs obn (RFS)[3] 5–yr RFS ~41%
2017–18 KEYNOTE 054 CheckMate 238		Surgery	Adjuvant PD-1	HR 0.57 vs surgery alone (RFS)[4] HR 0.65 vs CTLA-4 (RFS)[5] 5–yr RFS ~55%
2022 SWOG S1801	Neoadjuvant PD-1	Surgery	Adjuvant PD-1	**HR 0.58** vs adjuvant PD-1 (EFS)[6]
2024 NADINA	Neoadjuvant PD-1 plus CTLA-4	Surgery	Response-directed adjuvant PD-1 or BRAF/MEK	**HR 0.32** vs adjuvant PD-1 (EFS)[7]

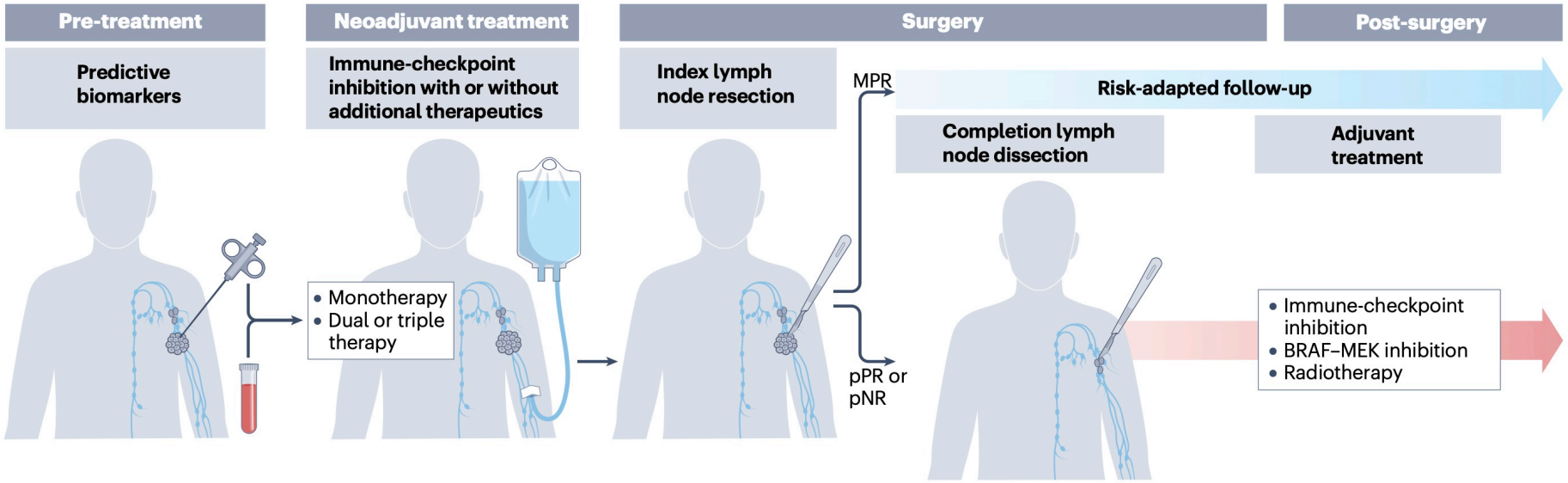
1. Eggermont AMM, et al. Lancet. 2008;372:117–126; 2. Mocellin S, et al. J Natl Cancer Inst. 2010;102:493–501;
3. Eggermont AMM, et al. N Engl J Med. 2016;375:1845–1855; 4. Eggermont AMM, et al. N Engl J Med. 2018;378:1789–1801;
5. Weber J, et al. N Engl J Med. 2017;377:1824–1835; 6. Patel SA, et al. ESMO 2022 & N Engl J Med. 2023;388:813–823;
7. Blank CU, et al. N Engl J Med. 2024;00:00–00; *1-yr EFS rates estimated from KM curve.

Long, ESMO 2024

Neoadyuvancia Estadio III

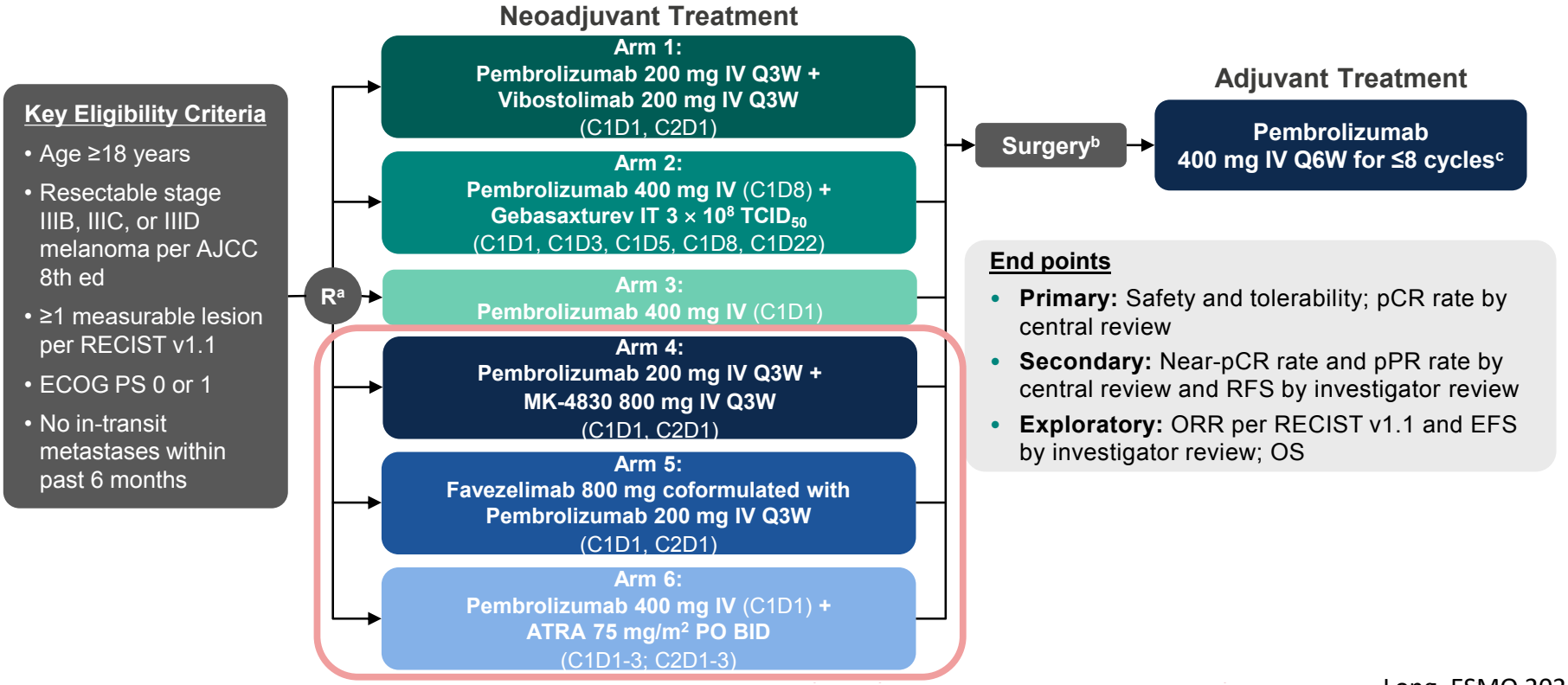
- Necesario mayor seguimiento
- Aumento de toxicidad (G3-4: 30% vs 12%)
- Muchos no recaen con anti PD-1: ¡Biomarcadores!
- ¿Es necesaria la parte adyuvante tras la neoadyuvancia?
- ¿Cambiar estrategia en no respondedores?
- ¿Cómo incorporarlo en práctica clínica?

Futuro



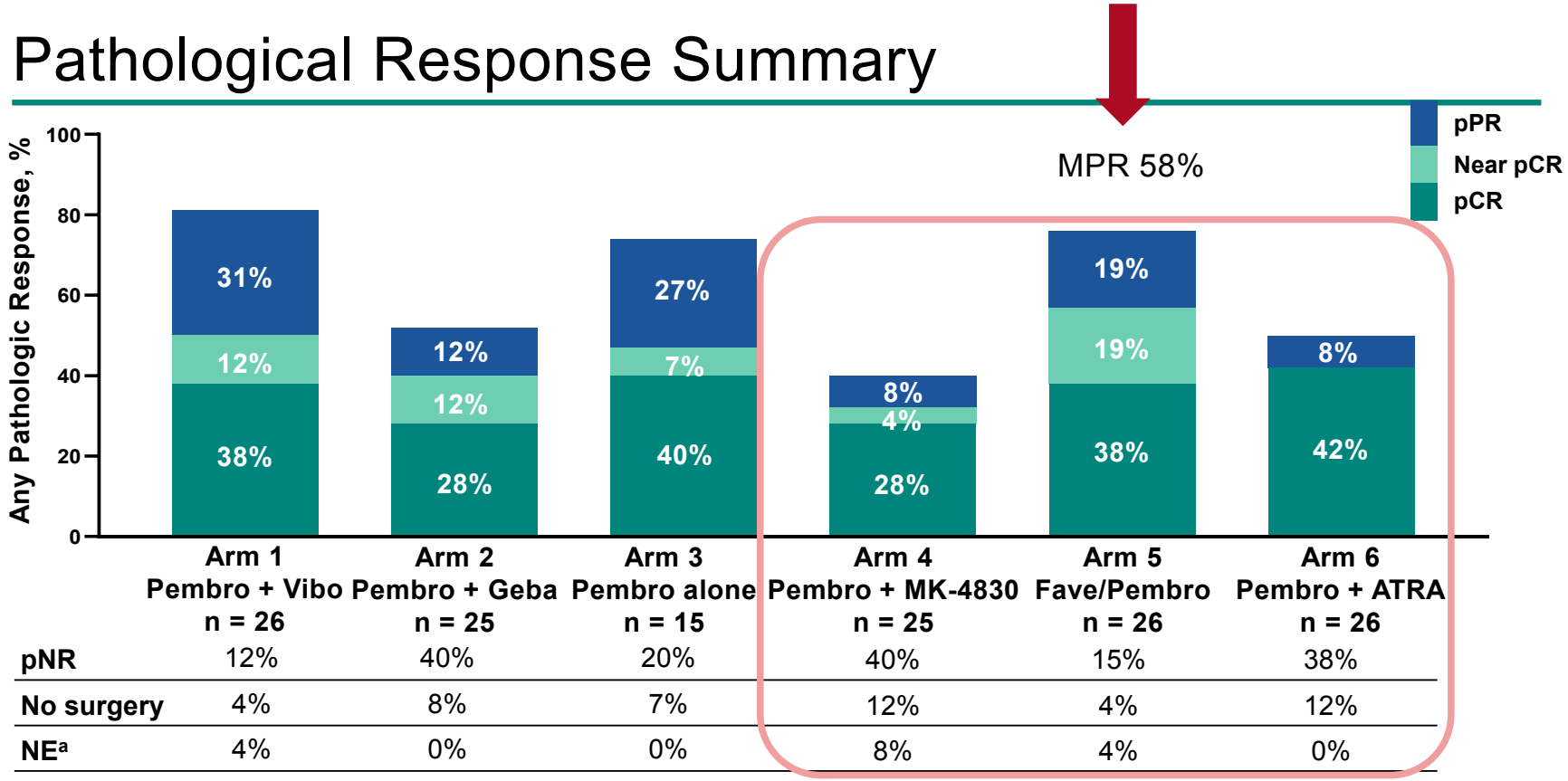
Lucas, Nat Rev Clin Onc 2023

KEYMAKER-U02 Substudy 02C Study Design (NCT04303169)



Long, ESMO 2024

Pathological Response Summary

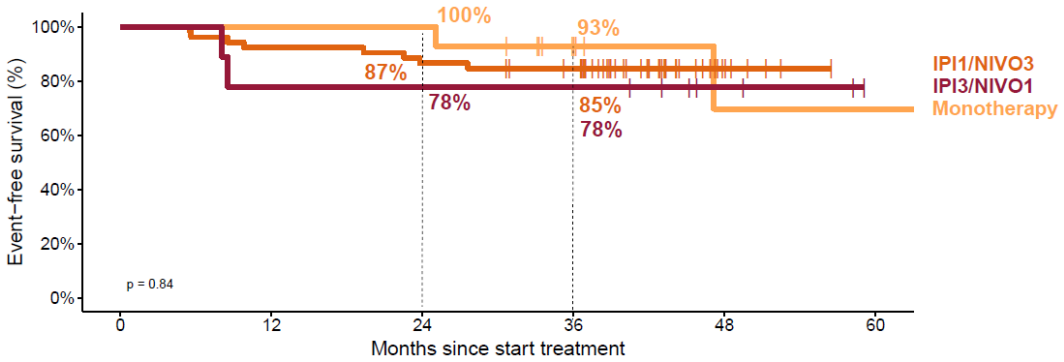


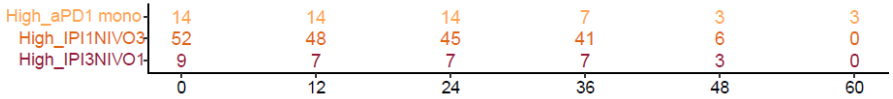
	Arm 1 Pembro + Vibo n = 26	Arm 2 Pembro + Geba n = 25	Arm 3 Pembro alone n = 15	Arm 4 Pembro + MK-4830 n = 25	Arm 5 Fave/Pembro n = 26	Arm 6 Pembro + ATRA n = 26
pNR	12%	40%	20%	40%	15%	38%
No surgery	4%	8%	7%	12%	4%	12%
NE[a]	4%	0%	0%	8%	4%	0%

Long, ESMO 2024

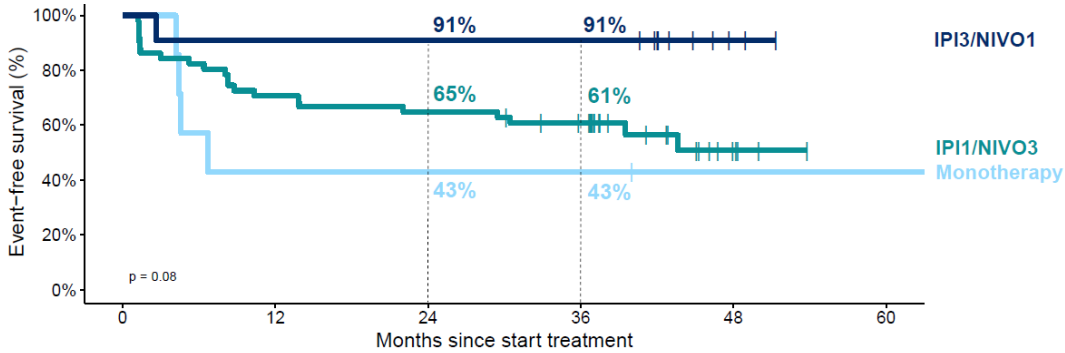
Biomarcadores

IFNγ high



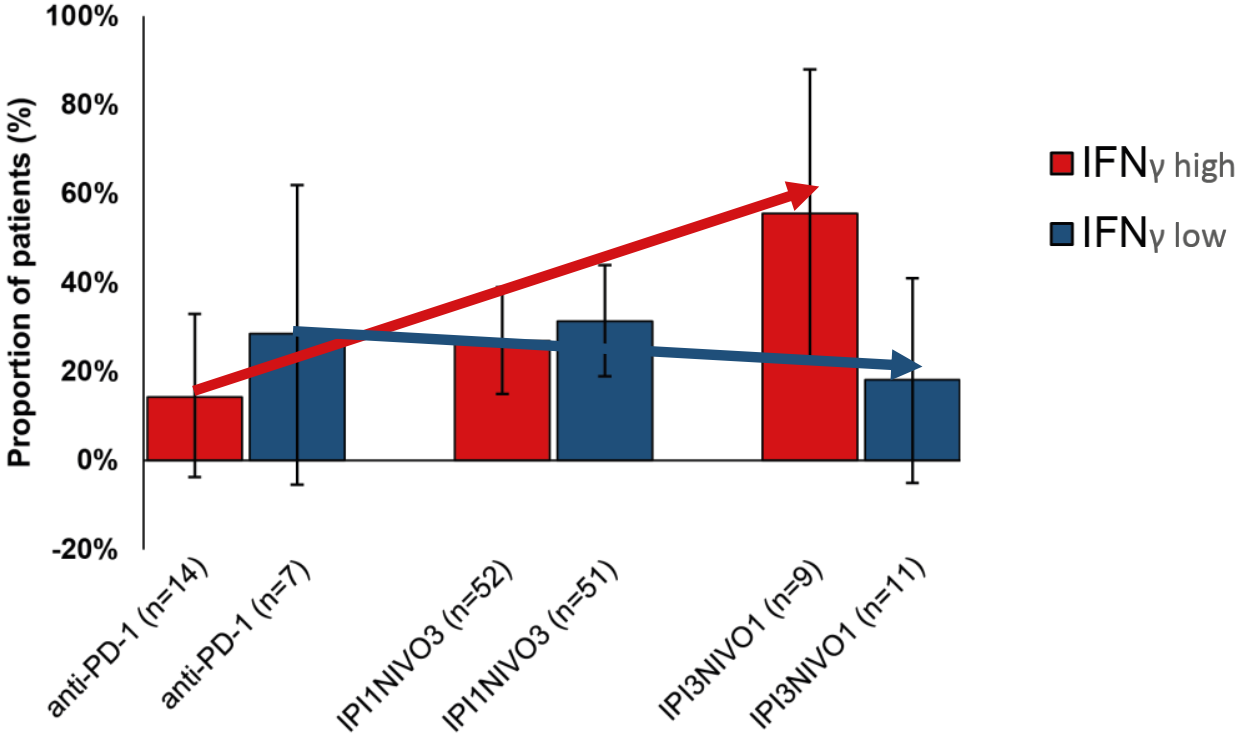


IFNγ low



Lucas, ESMO 2024

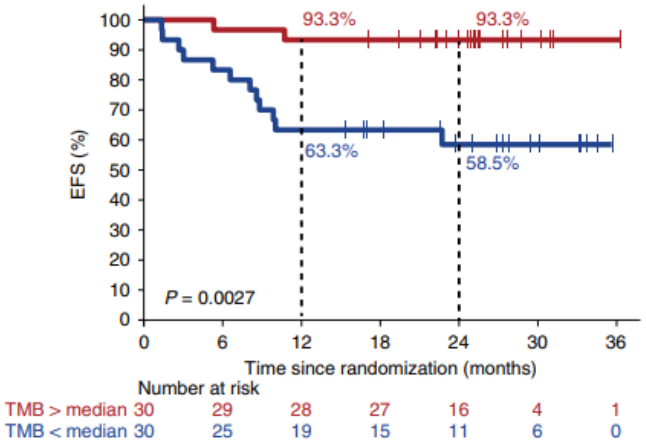
Biomarcadores



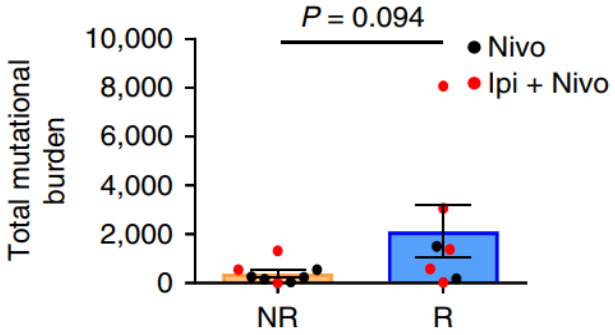
Lucas, ESMO 2024

Biomarcadores

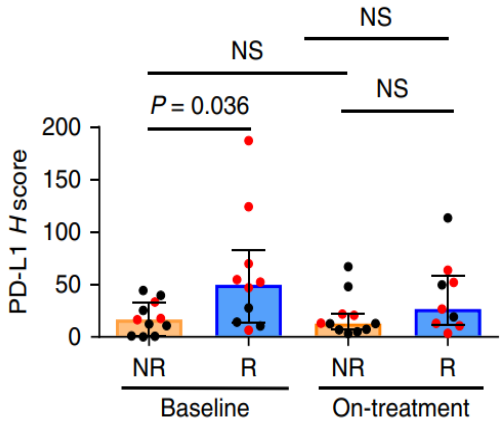
Tumor mutational burden (TMB)
OpACIN-neo



Tumor mutational burden (TMB)
Amaria et al.



PD-L1
Amaria et al.



Rozeman, Nat Med 2021; Amaria, Nat Med 2018

Conclusiones

- El tratamiento **adyuvante** del melanoma en estadios IIB/C y III con **anti–PD-1** mejora la **Supervivencia Libre de Recaída**
- La **neoadyuvancia** en estadio III clínico mejora la SLE y logra altas tasas de **Respuesta Patológica Mayor** y debemos incorporarla a la práctica clínica
- Se requieren **biomarcadores** para seleccionar la inmunoterapia más adecuada (anti–PD-1 ± anti–CTLA-4) en cada paciente
- Dado que muchos pacientes se pueden curar, es preciso tener en cuenta la posibilidad de **toxicidades crónicas**
- Es preciso incorporar nuevos fármacos o combinaciones para **pacientes no respondedores**
- Es necesario **involucrar al paciente** en la toma de decisiones