XXIV

Simposio de Revisiones en Cáncer

"Tratamiento médico del cáncer en el año 2022"

Una nueva realidad para los pacientes largos supervivientes.
Avanzando hacia estadios tempranos de la enfermedad con la IO

Dicho de otro modo: adyuvancia.

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Hospital General Universitario Gregorio Marañón
8-2-2022

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CONFLICTOS DE INTERÉS

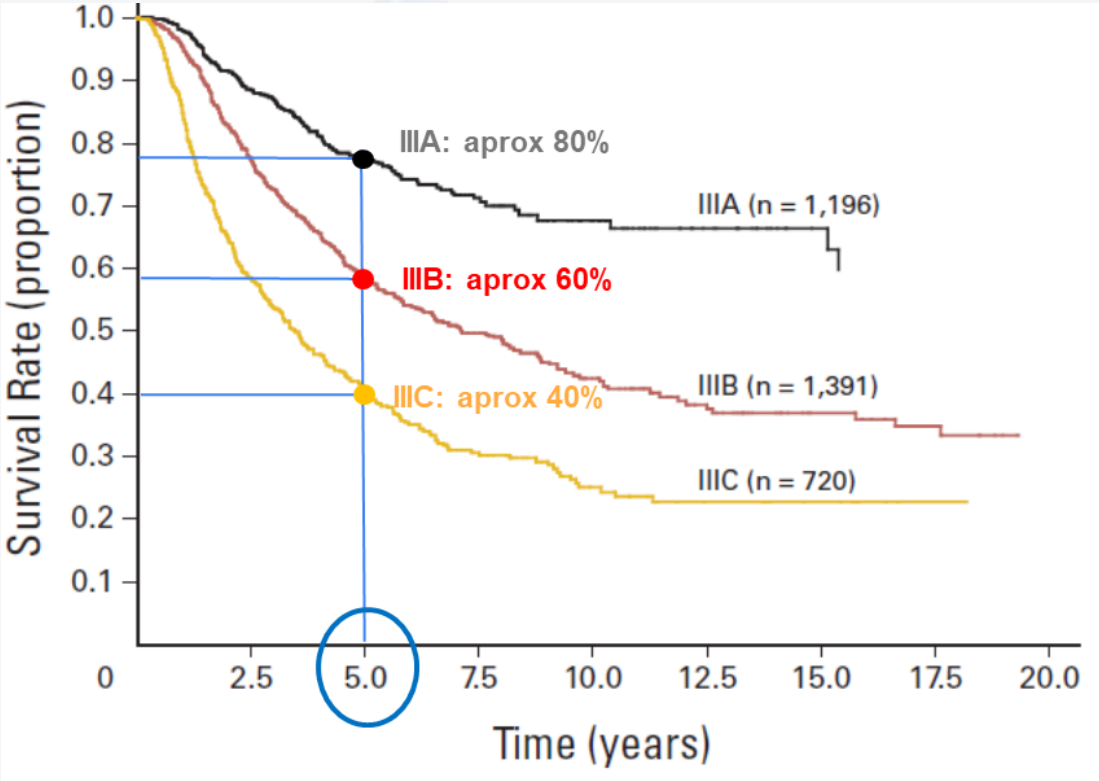
- Advisory role: Amgen, BMS, GSK, Novartis, MSD, Roche, Celegene, Pierre Fabre, Highlight Therapeutics (formerly Bioncotech), Regeneron, Sanofi, Merck Serono, Astra Zeneca, BiolineRx, Sun Pharma.

- Travel accommodation and congress: BMS, GSK, Roche, MSD, Amgen, Highlight Therapeutics, Novartis

- Clinical trial participation as PI: BMS, GSK, Roche, Novartis, MSD, Amgen, Ab Science, Array, Highlight Therapeutics, Aduro, Idera, Merck Serono, Iovance, Genentech, Biontech, Incyte, Kartos, 4SC, BiolineRx, Nektar therapeutics.

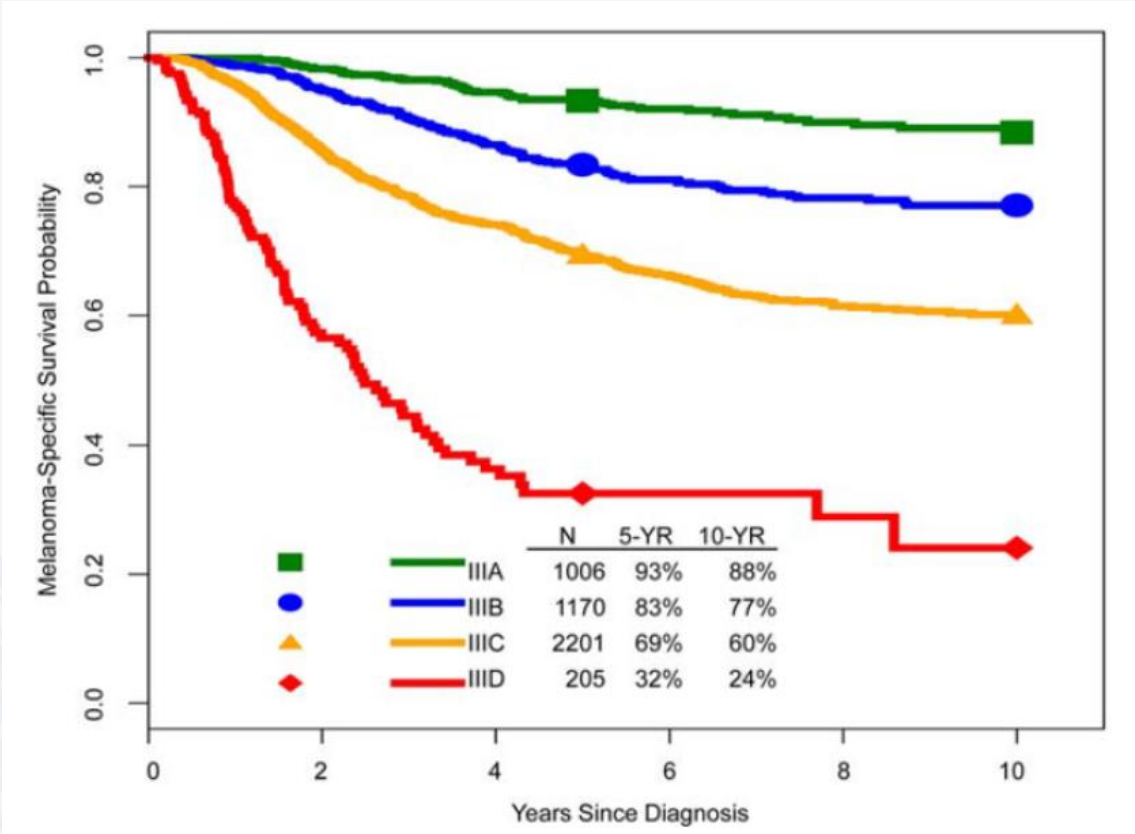
- If you find something I have missed, please e-mail me: ivanpantic@hotmail.com

¿DE DÓNDE PARTIMOS?



AJCC 7: clasificación usada en CM238 y demás ensayos pivotales

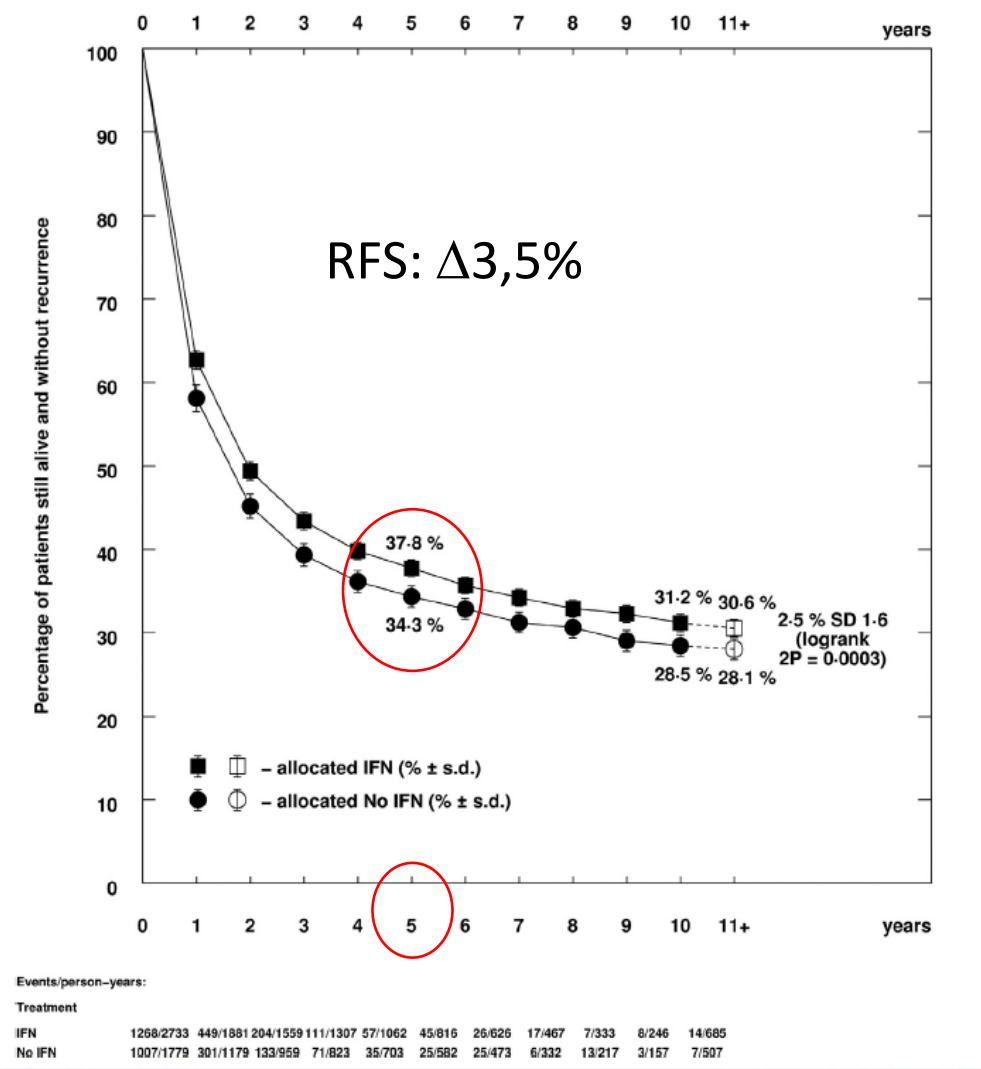
Estadio III=3307/30946 **(10,7%)**

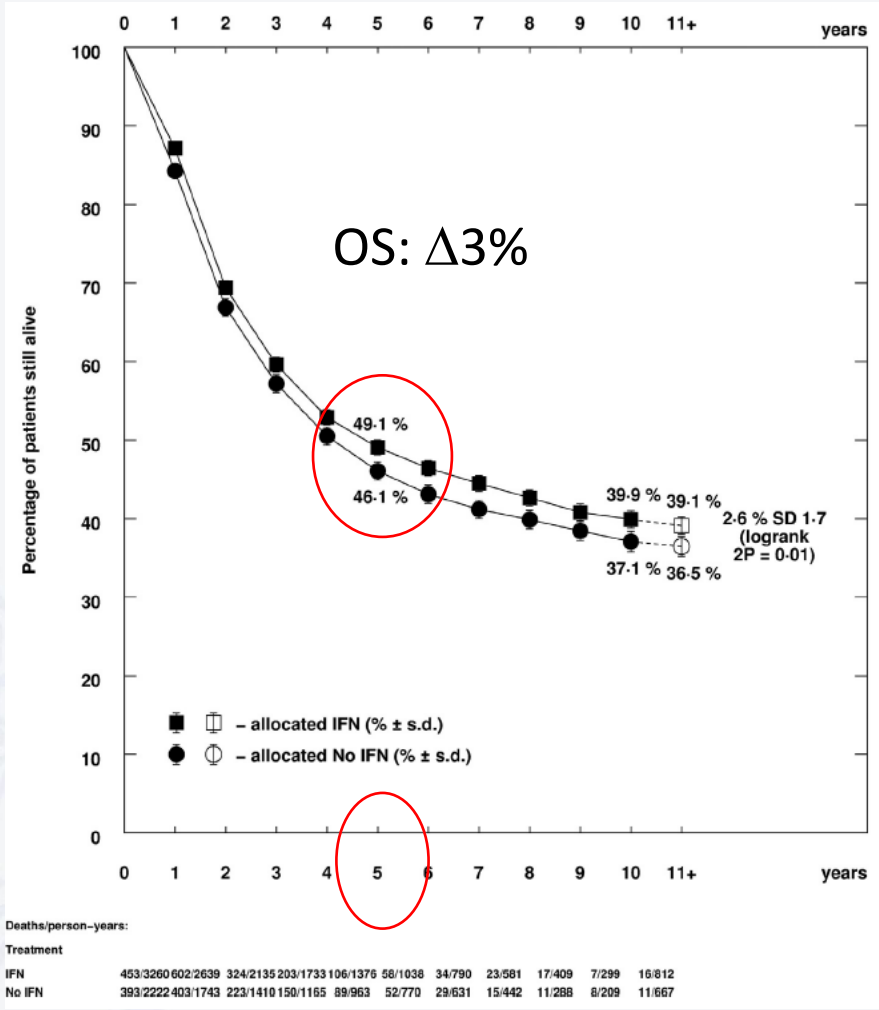


AJCC 8: clasificación usada en ensayos era post PD-1 y post BRAF/MEK

Balch 2009 J Clin Oncol
Gershenwald 2017 Ca Cancer J Clin

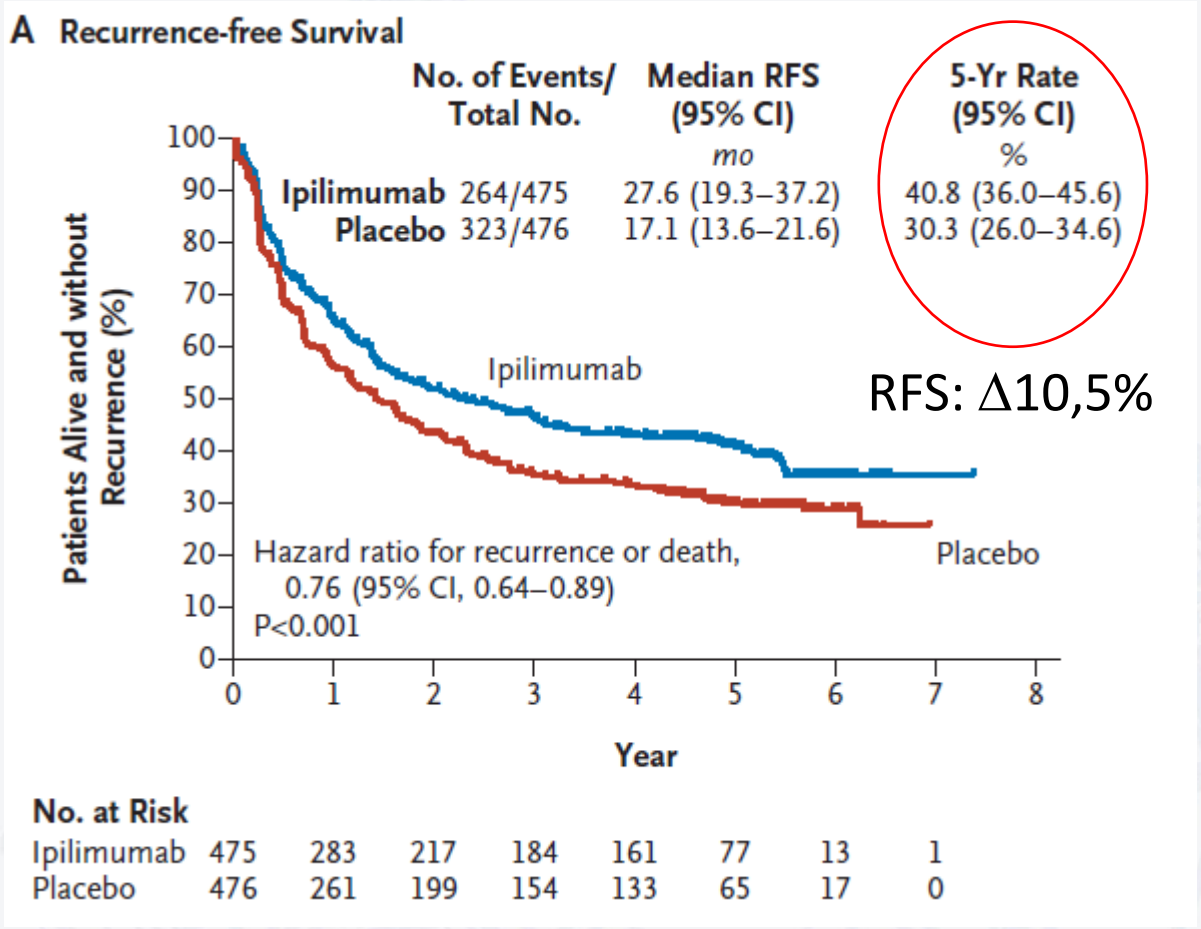
Interferón: meta-análisis



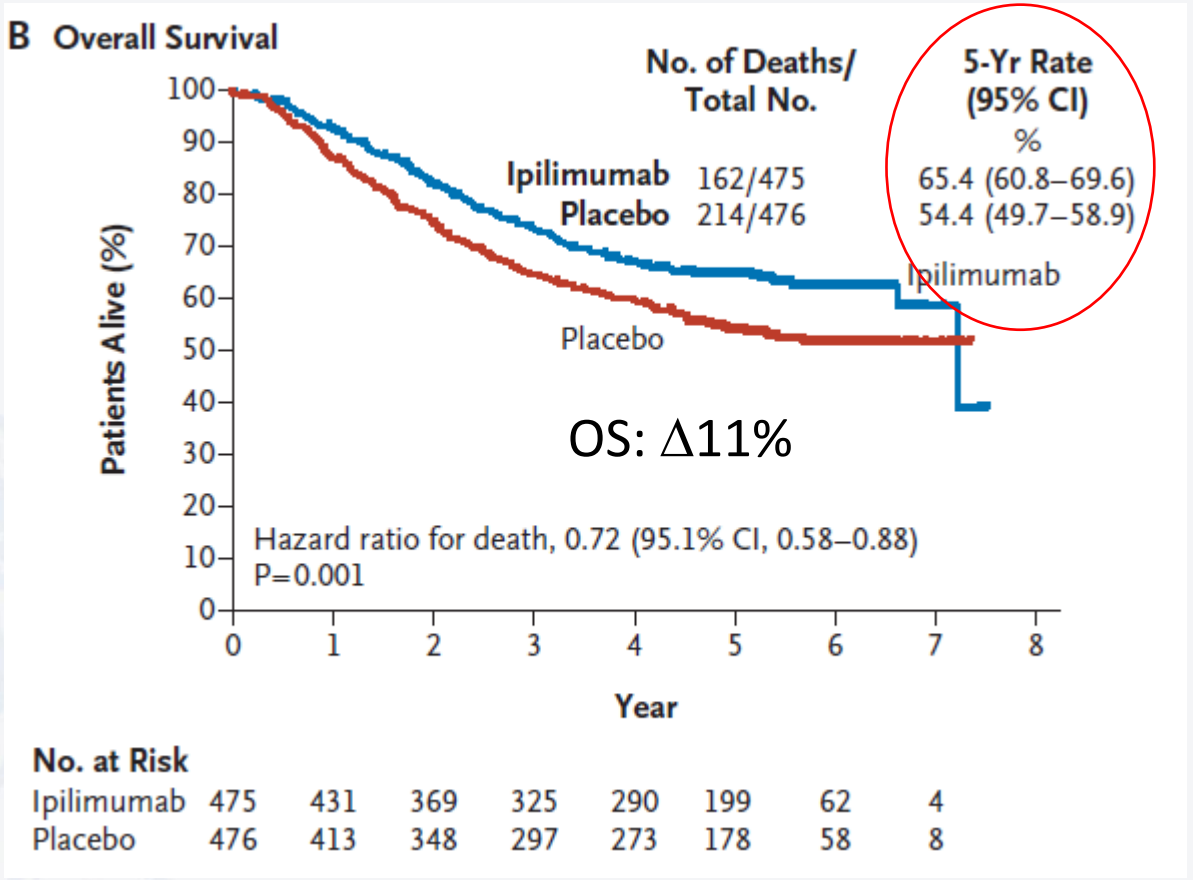


Ives 2017 Eur J Cancer

EORTC 18071: IPI VS PLB



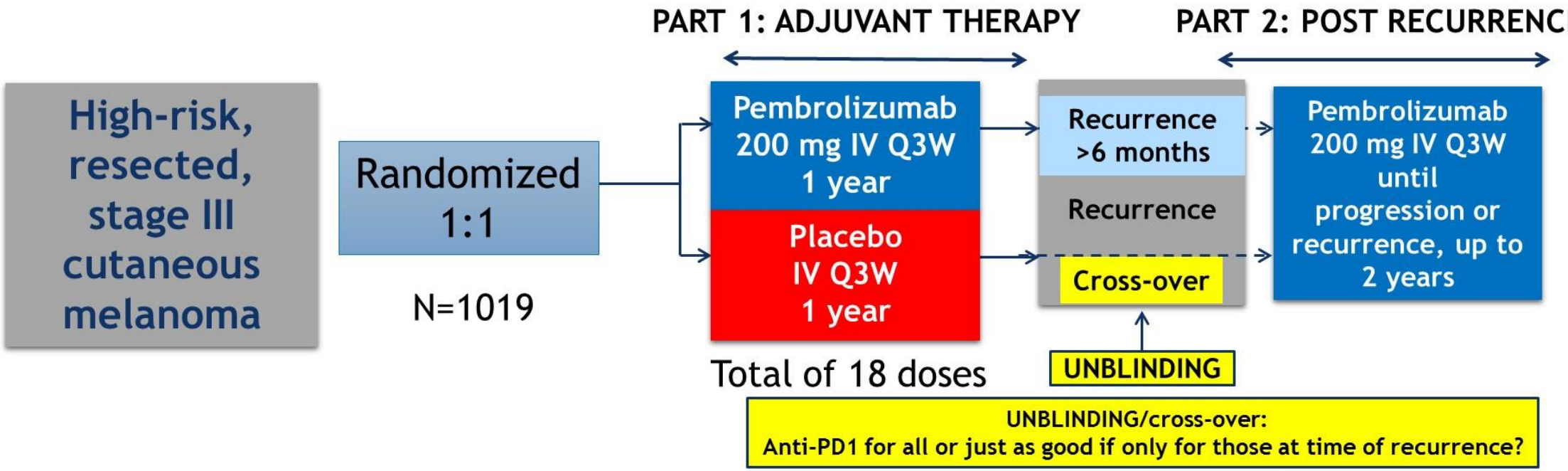
RFS: Δ10,5%



OS: Δ11%

Eggermont 2016 NEJM

EORTC 1325/KEYNOTE-54: Study Design



Stratification factors:

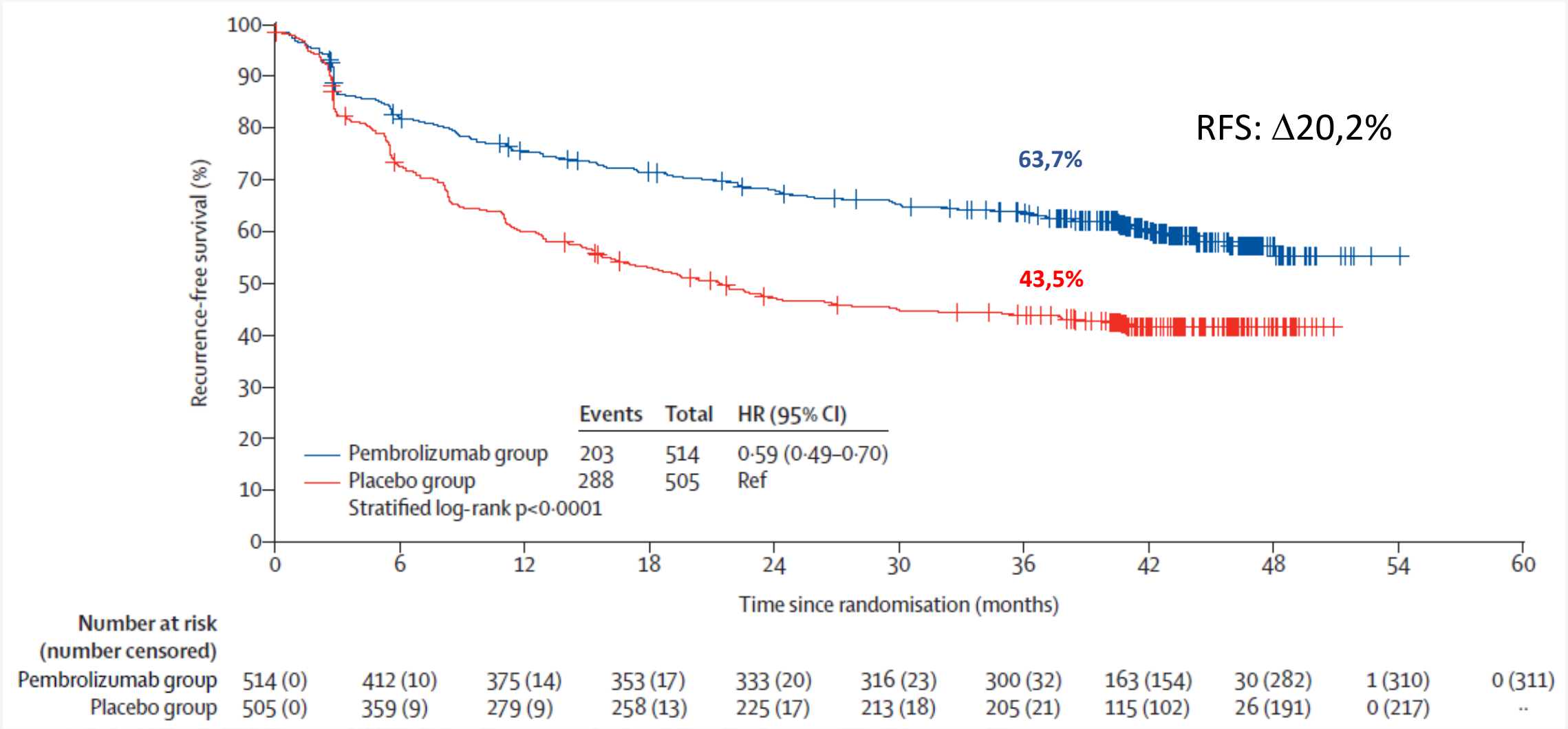
- ✓ **AJCC-7 Stage**: IIIA (>1 mm metastasis) vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥4 positive lymph nodes
- ✓ **Region**: North America, European countries, Australia/New Zealand, other countries

Primary Endpoints:

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

Secondary Endpoints:

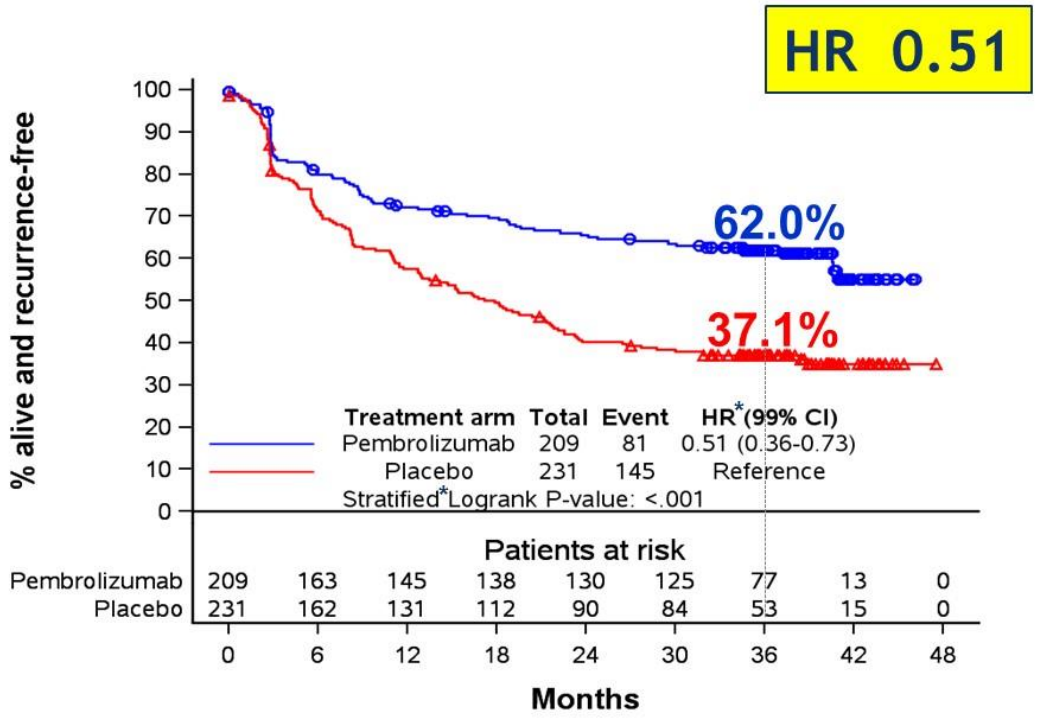
- **DMFS and OS** in all patients, and in patients with PD-L1-positive tumors; **Safety, Health-related quality of life**



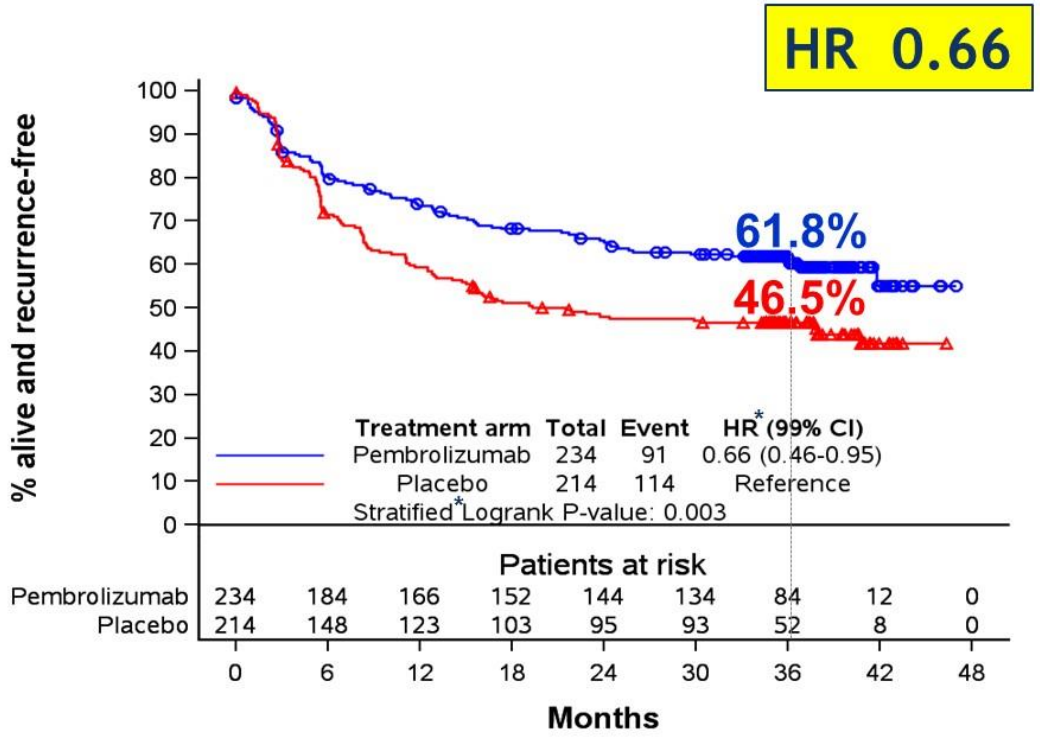
Eggermnot 2021 Lancet Oncol

RFS according to BRAF-V600 E-K mutation status

BRAF-mutated (n=440)



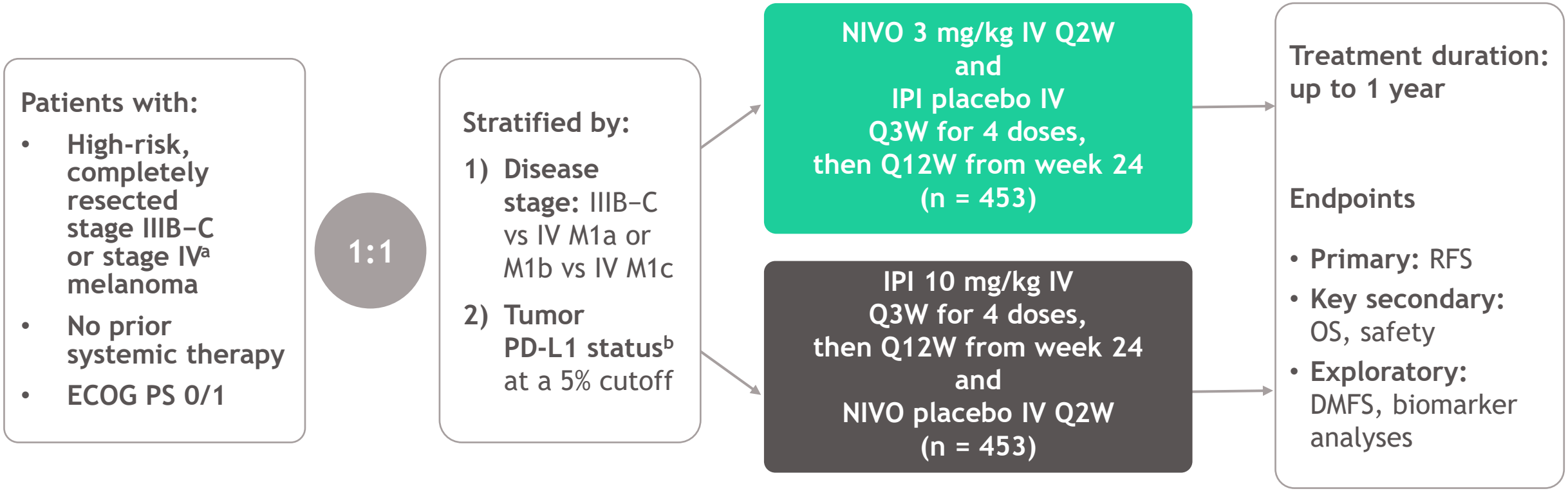
BRAF-WT (n=448)



*Stratified by stage given at randomization

Presented By Alexander Eggermont at TBD

CheckMate 238 study design



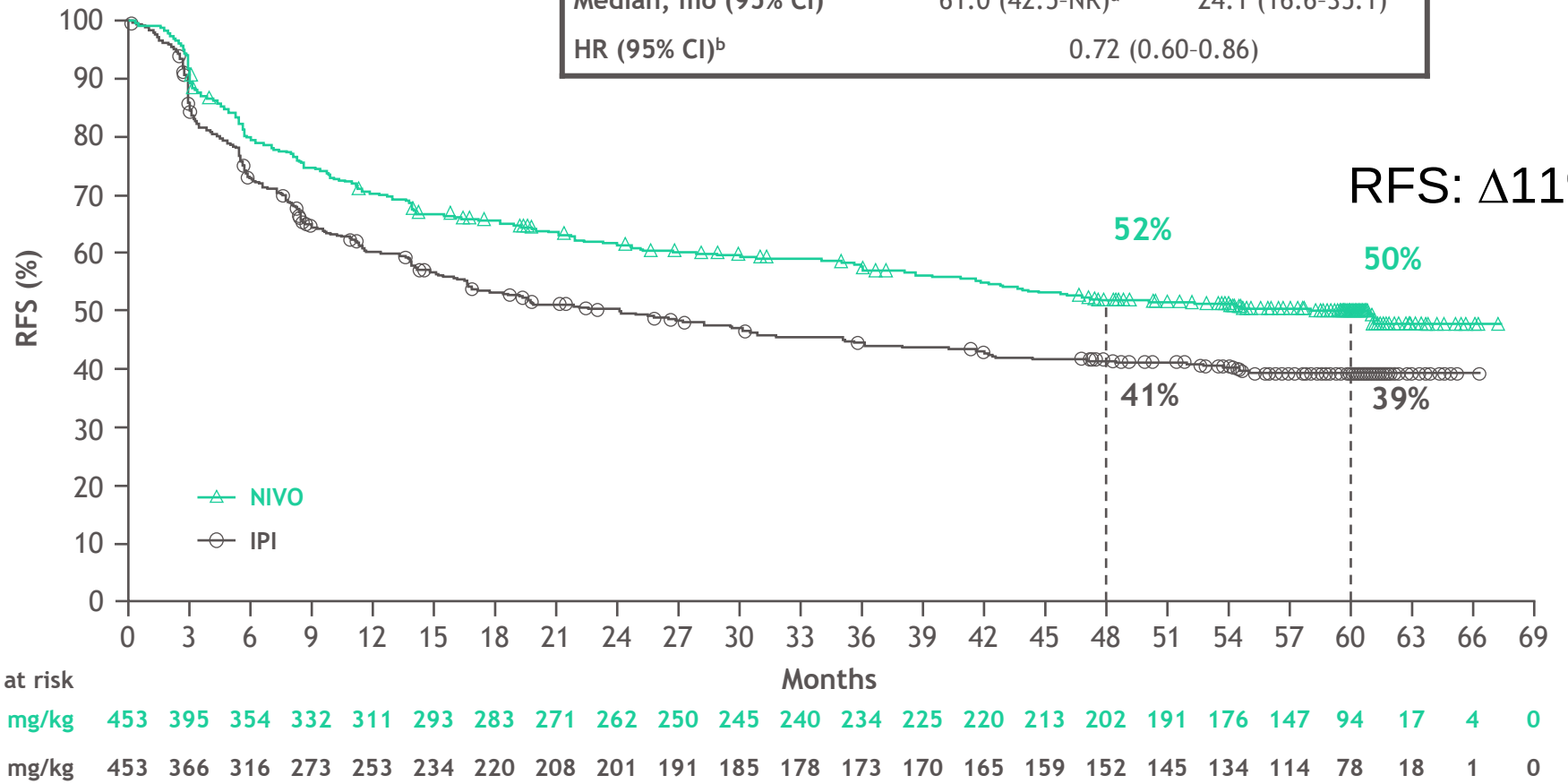
- Current analysis (database lock Mar 12, 2021; minimum 62.0 months follow-up)
  - Median follow-up of 61.5 months for NIVO and 61.2 months for IPI
  - Updated RFS with subgroup analyses, DMFS, and OS
  - Exploratory biomarker analysis
  - Safety analysis was not updated: all patients off study treatment > 100 days at 18-month analysis

NCT02388906.[a]Per American Joint Committee on Cancer, Cancer Staging Manual, 7th Edition; [b]PD-L1 IHC 28-8 pharmDx assay.
PD-L1, programmed death-ligand 1; PS, performance status.

Weber SMR 2021

Primary endpoint: 60-month RFS update in all patients

	NIVO (n = 453)	IPI (n = 453)
Events, n	218	257
Median, mo (95% CI)	61.0 (42.5-NR)[a]	24.1 (16.6-35.1)
HR (95% CI)[b]	0.72 (0.60-0.86)	



No. at risk																							
NIVO 3 mg/kg	453	395	354	332	311	293	283	271	262	250	245	240	234	225	220	213	202	191	176	147	94	17	4	0
IPI 10 mg/kg	453	366	316	273	253	234	220	208	201	191	185	178	173	170	165	159	152	145	134	114	78	18	1	0

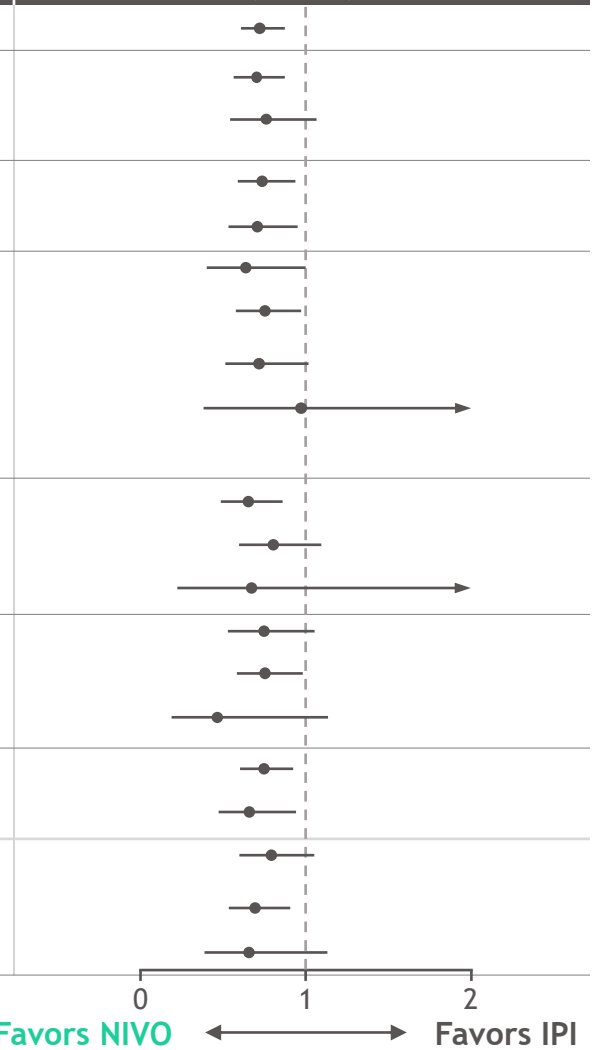
- New events since 4-year database lock: 6 (NIVO – 4 regional, 2 distant) and 4 (IPI – 1 each of local, distant, new primary, and death)

[a]Median not stable. [b]Stratified. Mo, month; NR, not reached.

Weber SMR 2021

60-Month RFS update: pre-specified subgroup analysis

Subgroup		NIVO n/N	IPI n/N	Unstratified HR (95% CI)
Overall	Overall	218/453	257/453	0.73 (0.61–0.87)
Age	< 65 years	147/333	184/339	0.70 (0.57–0.88)
	≥ 65 years	71/120	73/114	0.76 (0.55–1.06)
Sex	Male	131/258	157/269	0.74 (0.59–0.93)
	Female	87/195	100/184	0.71 (0.54–0.95)
Stage	IIIB	65/166	74/147	0.72 (0.52–1.01)
	IIIC	111/202	131/219	0.76 (0.59–0.97)
	IV M1a–M1b	32/62	43/66	0.64 (0.40–1.01)
	IV M1c	9/20	9/21	0.98 (0.39–2.47)
	Not reported	1/1	0/0	–
Stage III: ulceration	Absent	81/201	115/213	0.65 (0.49–0.87)
	Present	89/155	83/137	0.81 (0.60–1.09)
	Not reported	6/14	7/16	0.67 (0.22–2.02)
Stage III: lymph node involvement	Microscopic	58/128	72/134	0.75 (0.53–1.06)
	Macroscopic	109/217	122/214	0.75 (0.58–0.98)
	Not reported	9/25	11/18	0.47 (0.19–1.13)
Tumor PD-L1 status[b]	< 5% or indeterminate	161/300	183/299	0.75 (0.61–0.93)
	≥ 5%	57/153	74/154	0.66 (0.47–0.94)
***BRAF* mutation status[c]**	Mutant	90/187	106/194	0.80 (0.60–1.05)
	Wild-type	100/197	125/212	0.69 (0.53–0.90)
	Not reported	28/69	26/47	0.66 (0.39–1.13)

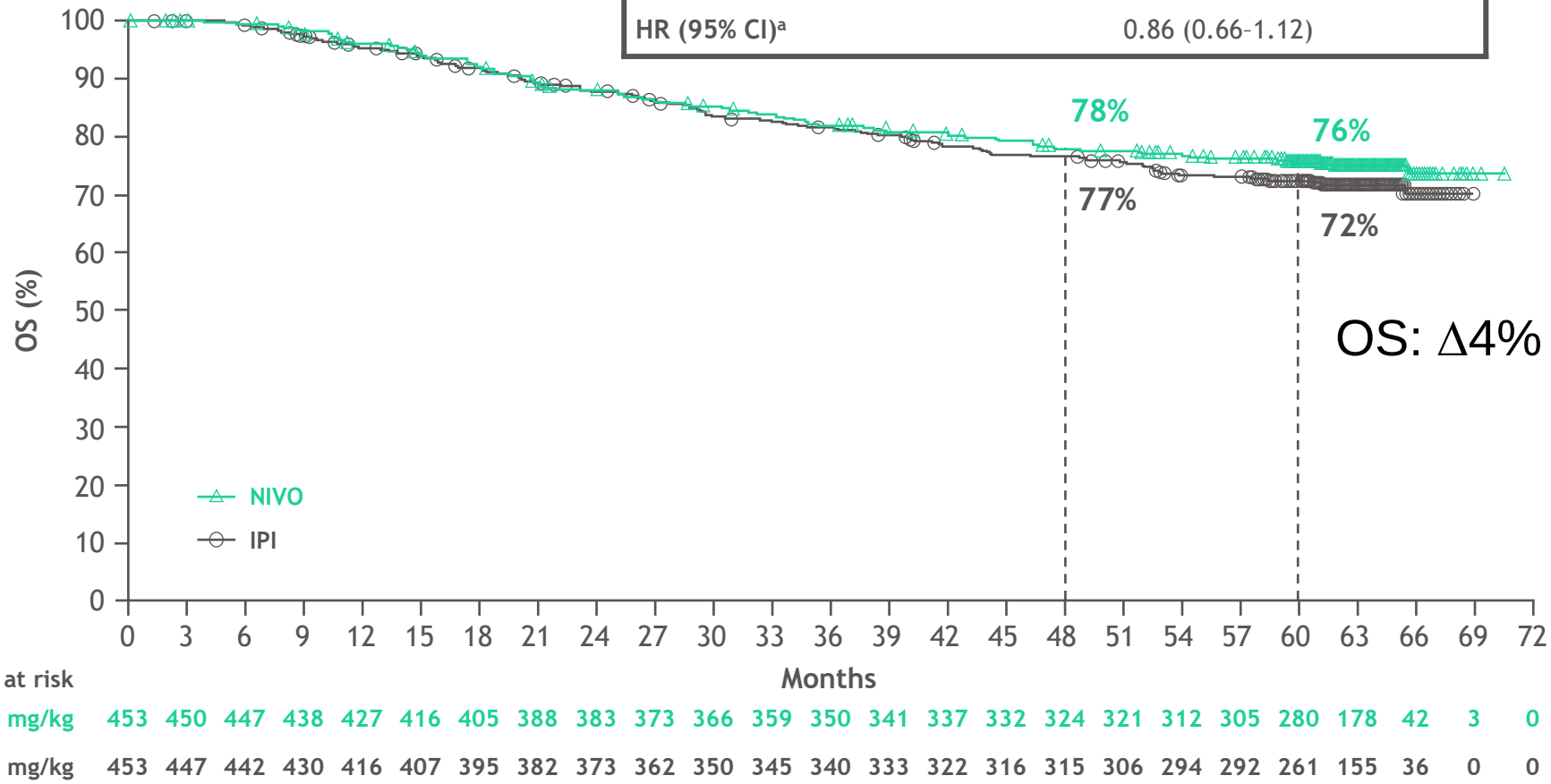


[a]Stratified HR = 0.72 (95% CI, 0.60–0.86); [b]PD-L1 IHC 28-8 pharmDx assay; status determined as percentage of tumor cells; [c]V600E/K.
PD-L1, programmed death-ligand 1.

Weber SMR 2021

Secondary endpoint: 60-month OS update in all patients

	NIVO (n = 453)	IPI (n = 453)
Events, n	108	120
Median, mo (95% CI)	NR	NR
HR (95% CI)[a]	0.86 (0.66–1.12)	



OS: Δ4% (NS)

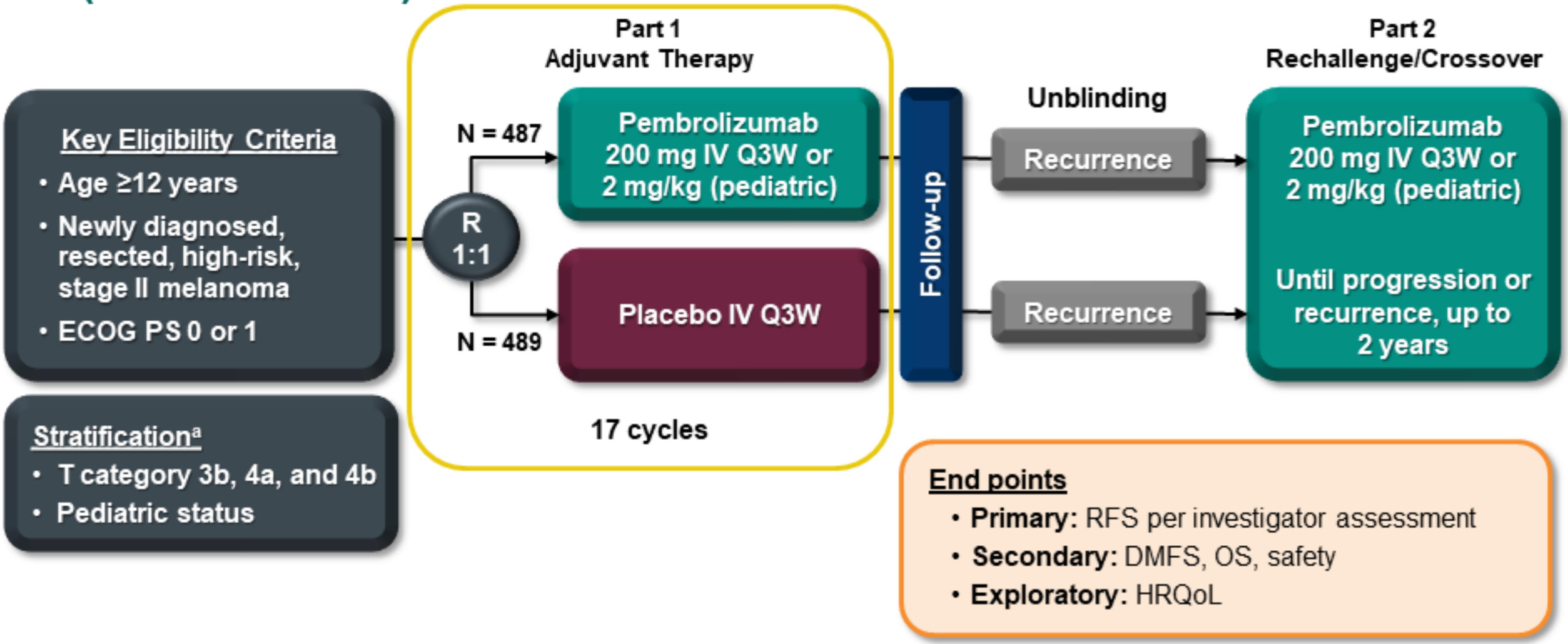
No. at risk																								
NIVO 3 mg/kg	453	450	447	438	427	416	405	388	383	373	366	359	350	341	337	332	324	321	312	305	280	178	42	3	0
IPI 10 mg/kg	453	447	442	430	416	407	395	382	373	362	350	345	340	333	322	316	315	306	294	292	261	155	36	0	0

- 228 of 302 anticipated events (75%); 17 new deaths since 4-year database lock (8 NIVO and 9 IPI), mainly attributed to disease

[a]Stratified. NR, not reached.

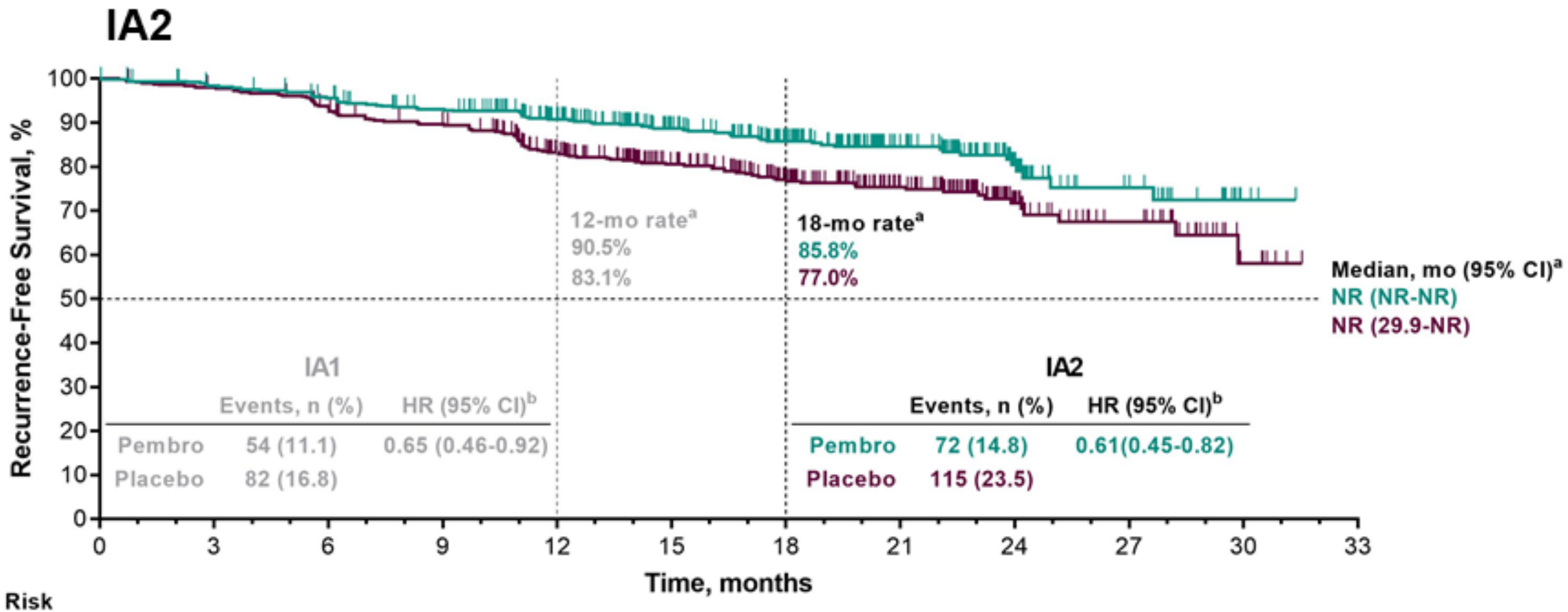
Weber SMR 2021

KEYNOTE-716 Study Design
(NCT03553836)



[a]*BRAF*-mutation status and PD-L1 status were not prespecified stratification factors due to tissue availability.

Recurrence-Free Survival

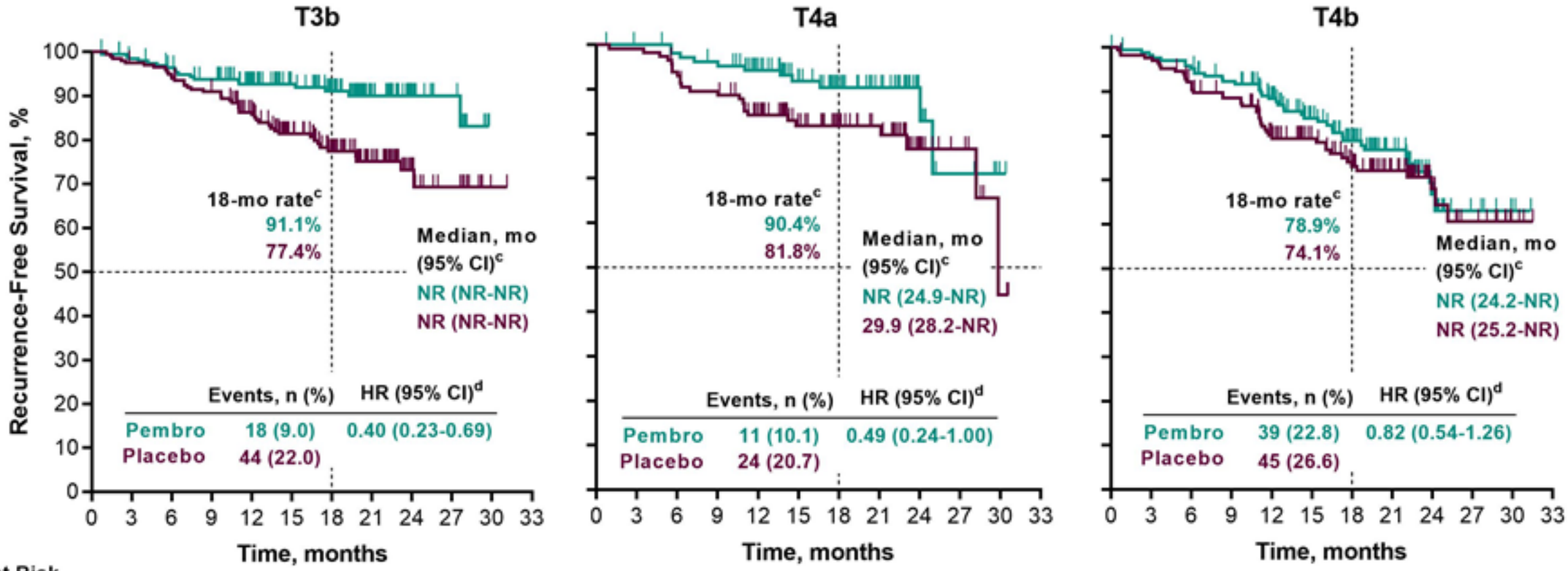


No. at Risk												
Pembrolizumab	487	471	454	432	369	300	229	149	60	28	3	0
Placebo	489	476	451	425	352	273	213	151	63	34	6	0

Luke SMR 2021

[a]From product-limit (Kaplan-Meier) method for censored data. [b]Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by melanoma T category (T3b vs T4a vs T4b). IA1 data cutoff: December 04, 2020. IA2 data cutoff: June 21, 2021.

RFS:T Category Subgroups[a,b]



No. at Risk

Pembrolizumab	200	193	186	177	151	124	97	60	26	14	0	0	109	107	104	101	86	69	49	34	12	5	1	0	171	166	161	152	130	105	81	54	21	8	2	0
Placebo	200	194	188	179	149	114	87	56	23	13	1	0	116	115	108	102	87	66	51	40	16	9	2	0	169	164	152	143	116	93	75	55	24	12	3	0

Luke SMR 2021

[a]Based on actual baseline tumor stages IIB and IIC collected on eCRF; 2 patients had T3a melanoma. [b]Two patients with Nx, 5 with N1c, and 2 with stage IV disease were not included in the T category analysis. [c]From product-limit (Kaplan-Meier) method for censored data. [d]Based on Cox regression model with Efron's method of tie handling with treatment as a covariate. Data cutoff: June 21, 2021.

CONCLUSIONES

- La adyuvancia basada en pembrolizumab o nivolumab (BRAF+ y -) presentan beneficio clínicamente relevante en pacientes con melanoma estadio III resecado
    - Particularmente IIIB-C-D
    - Más dudoso IIIA
    - Sin evidencia en IIIA<1mm
- Pembrolizumab presenta beneficio en disminución de riesgo de recaída en pacientes con melanoma estadio IIB-C resecado
    - Necesitamos más seguimiento para ponderar mejor el balance riesgo/beneficio

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Gracias

ARÁN