Melanoma e Inmunoterapia

Simposio BMS Inmunoterapia del Cáncer

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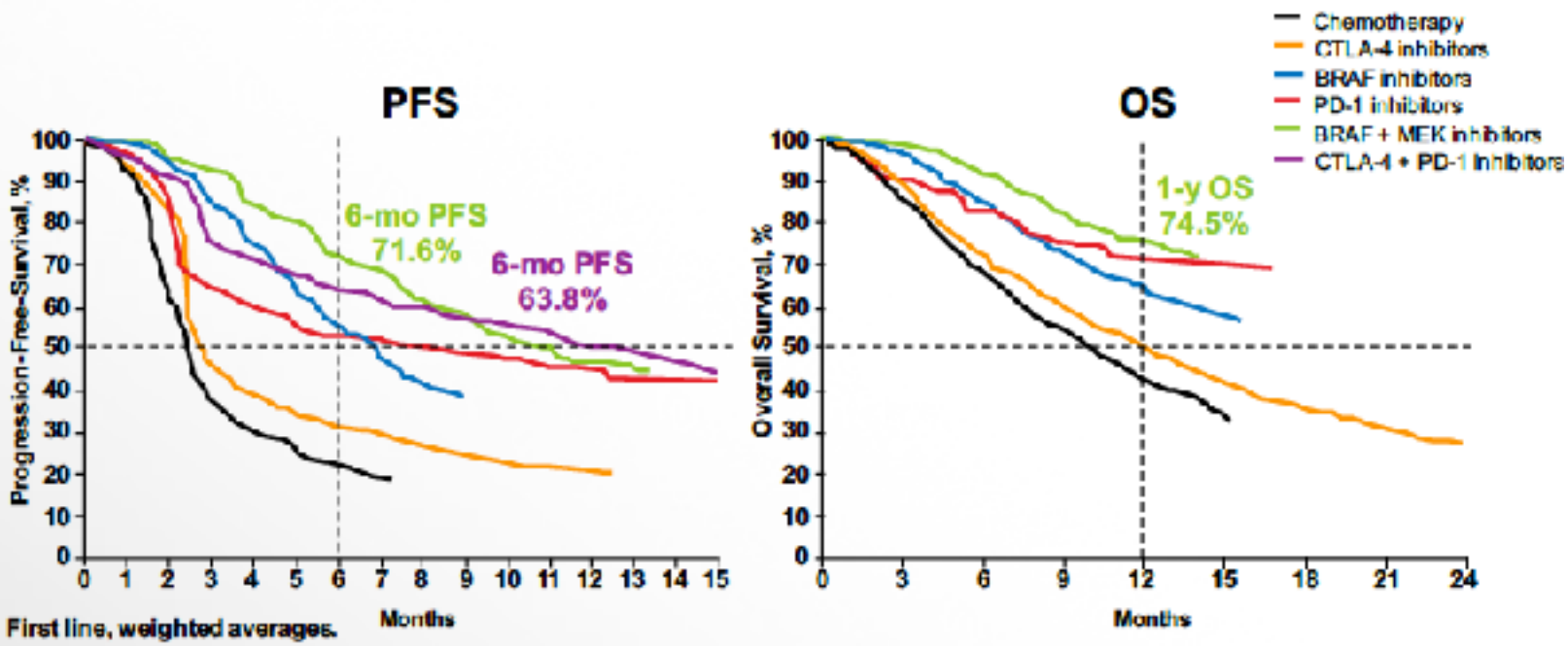
Epidemiología

- Incidencia en aumento: se duplica cada 10-20 años
- Representa un 2.5% de los canceres y un 1-2% de las muertes por cáncer
- Representa 4% canceres de piel y 79% muertes por esta causa
- En España en 1997 era la 16^{ava} causa de muerte por cáncer en el hombre y la 19^{ava} en la mujer
- Aproximadamente un centenar de casos metastasicos al año en la comunidad Valenciana
- Un tercio de melanomas metastaticos ocurren en menores de 50 años
- Hasta 2010 ningún tratamiento había mejorado la supervivencia
- Hasta 2010 la mediana de supervivencia era de 6 meses y a los 5 años vivian menos de un 5% de los pacientes

Jemal A et al. 2007. CA Cancer J Clin. 2007; 57:43-66

Grandes Avances en poco tiempo



First line, weighted averages.

	Chemotherapy	CTLA-4 inhibitor	BRAF inhibitors	PD-1 inhibitors	BRAF + MEK inhibitors	CTLA-4 + PD-1 inhibitors
6-mo PFS (95% CI), %	22.1 (19.1-25)	31 (27-35.1)	56 (53.3-58.8)	51 (46.4-55.6)	71.6 (68.2-75)	63.8 (58.7-68.9)
1-yr OS (95% CI), %	42.2 (37.2-47.2)	50.1 (45.4-54.8)	64.4 (58.1-70.7)	71.9 (60.7-83)	74.5 (70.7-78.4)	

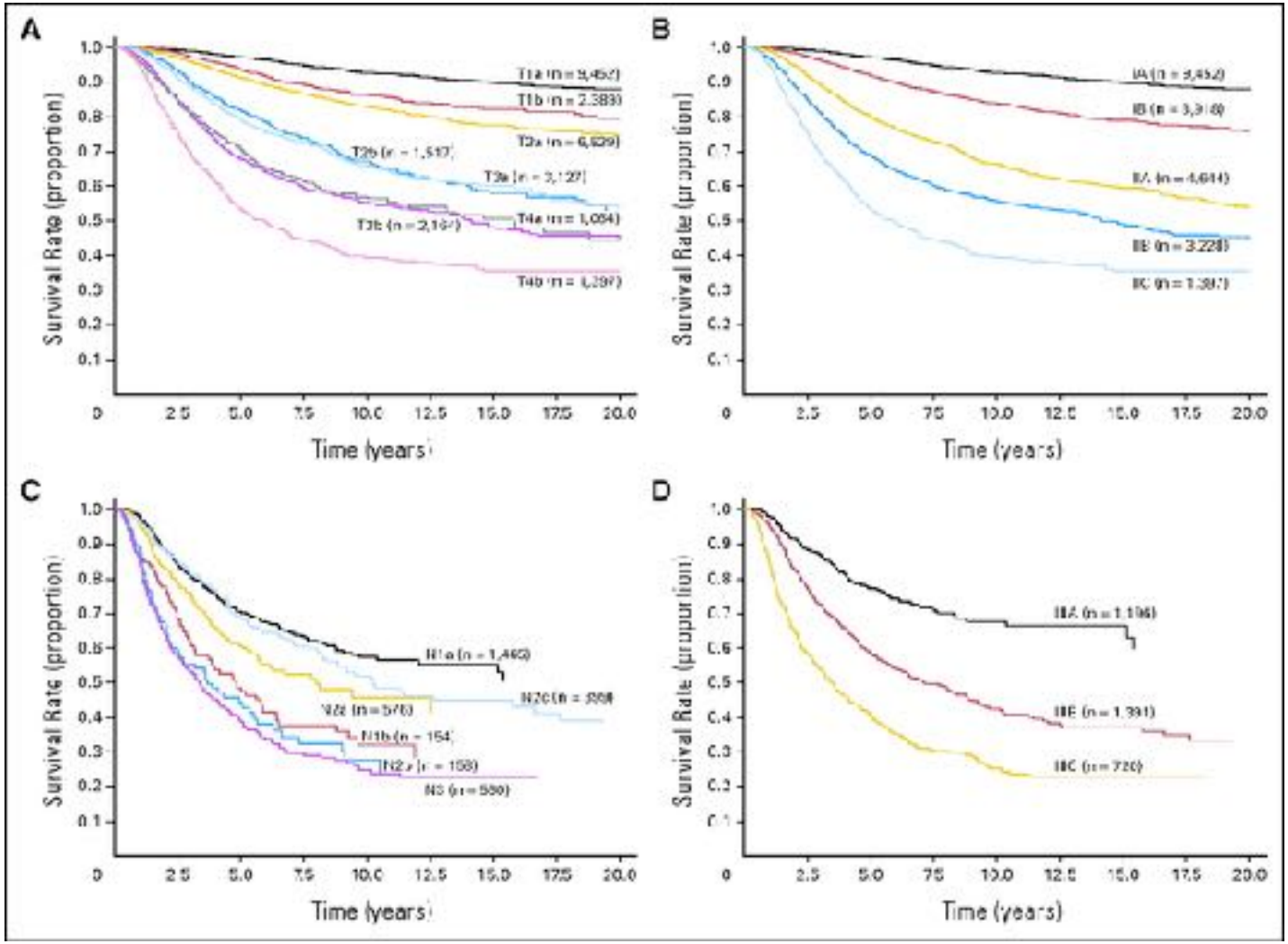
Ugurel S. et al. Eur J Cancer. 2016;53:125-134

¿Quienes necesitan tratamiento?

- Melanoma avanzado (Estadio III)
  - Recaídas en el 50 a 80%
  - Tasa de supervivencia a los 5 años de 25-70%
- Melanoma metastásico (Estadio IV)
  - No había tratamiento que haya mejorado la supervivencia hasta 2010
  - Mediana de supervivencia de 6 meses antes de nuevos tratamientos

Tratamiento medico del melanoma estadio III

Necesidad de tratamiento



Balch CM et al. JCO 2009: 6199-6206

Tratamiento adyuvante con interferón: E1684

Interferon Alfa-2b Adjuvant Therapy of High-Risk Resected Cutaneous Melanoma: The Eastern Cooperative Oncology Group Trial EST 1684

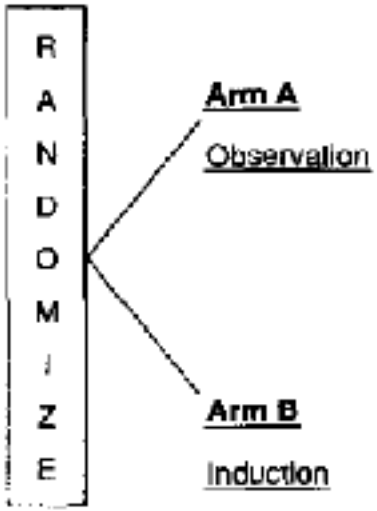
By John M. Kirkwood, Mylo Hunt Strawderman, Marc S. Ernstoff, Thomas J. Smith, Ernest C. Borden, and Ronald H. Blum

Indicaciones:

- Melanoma de alto riesgo IIB, IIC, III (alto riesgo)
- Tras cirugía de metástasis completamente resecadas

Esquema

- IFN-α-2b 20 Mi/m2 iv, 5 días a la semana/ 4 semanas
- IFN-α-2b 10 Mi/m2, sc 3 veces a la semana/ 48 semanas



Induction

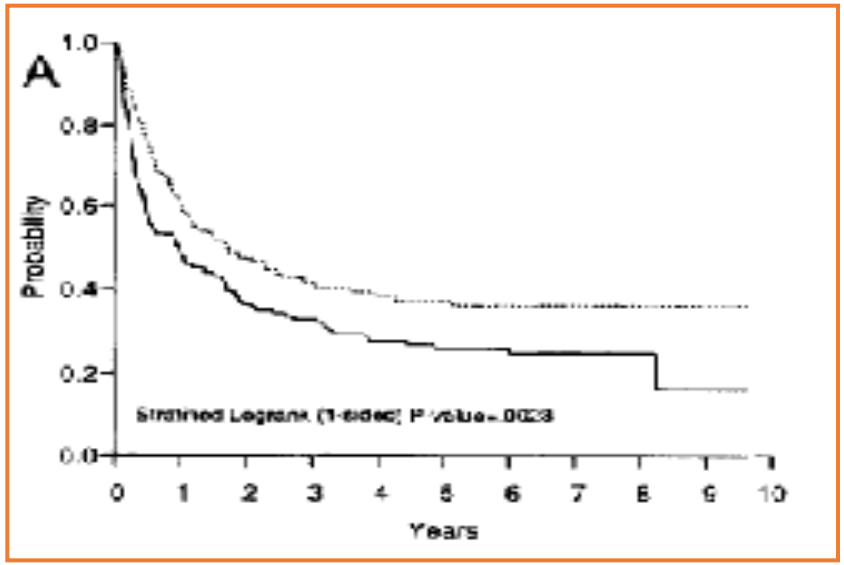
IFN alfa-2b 20 × 10^6 u/M^2 IV × 5/7 days q week × 4 weeks

Consolidation/Maintenance

10 × 10^6 u/M^2 SC 3 ×/week × 48 weeks

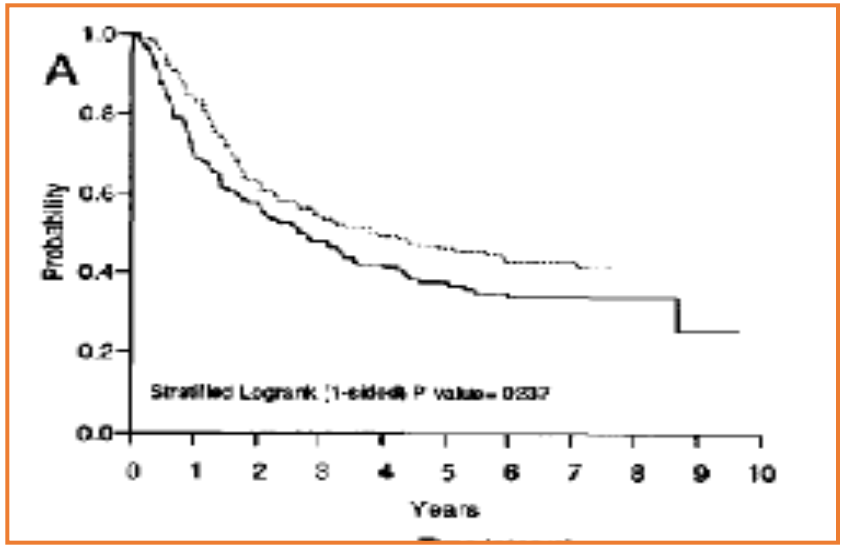
Kirkwood JM, el al. J Clin Oncol 14:7-17 1996

Tratamiento adyuvante con interferón : E1684



	SLP 5 años	SV 5 años
IFN alfa 2b	37%	46%
Observación	26%	37%

Aprobación FDA y EMA



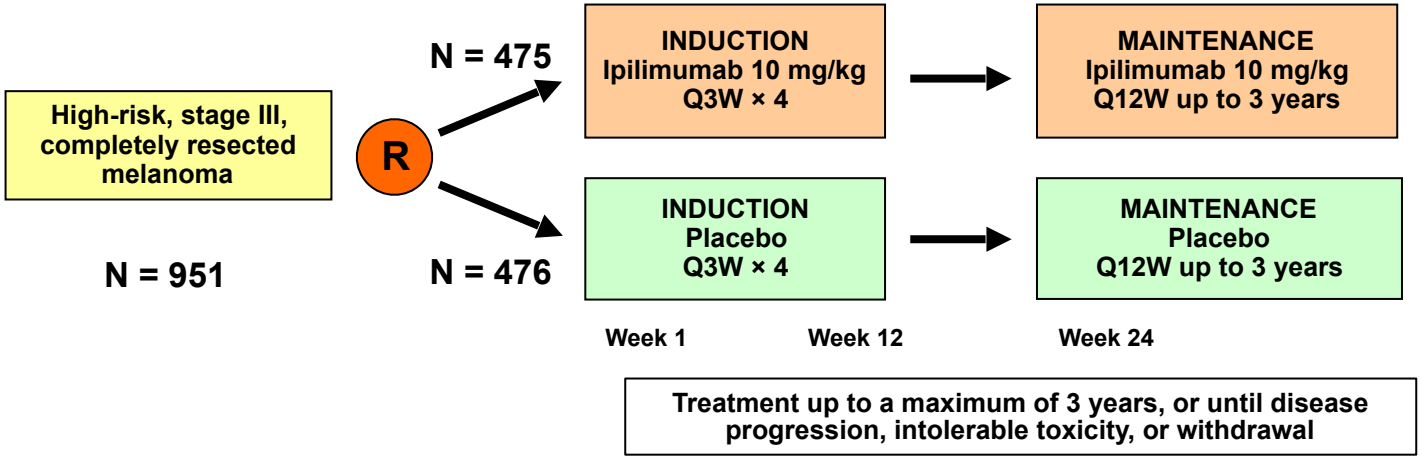
* Un análisis posterior de los resulados, con una mediana de seguimiento de 12.6 años continuo mostrando una mejoría significativa en SLP. Sin embargo, desaparece el beneficio de SG

Kirkwood JM, el al. J Clin Oncol 14:7-17 1996

** Kirkwood JM, el al. J Clin Oncol 2001; 19*

EORTC 18071: Diseño del estudio

Randomized, double-blind, phase 3 study evaluating the efficacy and safety of ipilimumab in the adjuvant setting for high-risk melanoma



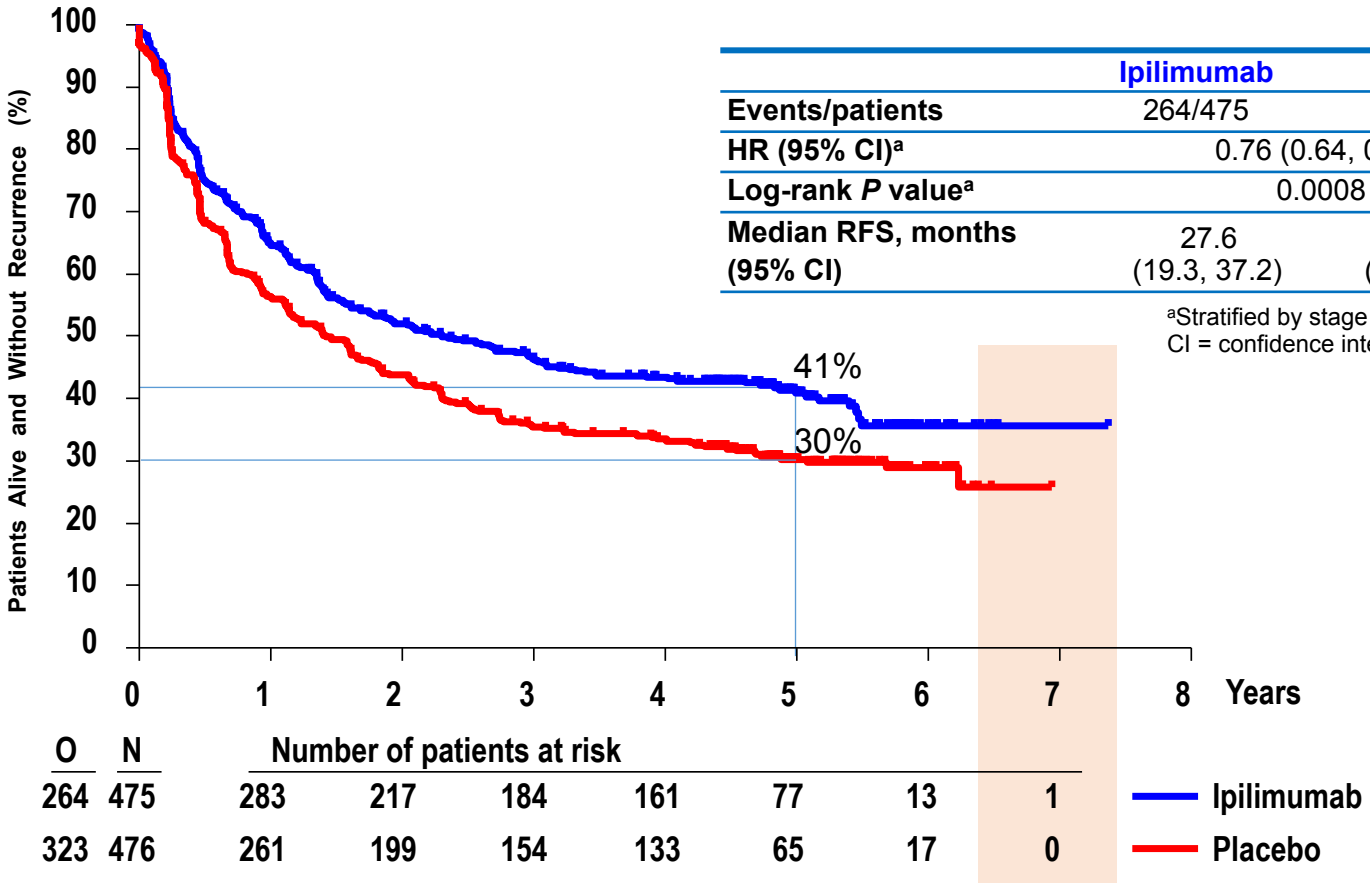
Stratification factors

- Stage (IIIA vs IIIB vs IIIC 1-3 positive lymph nodes vs IIIC ≥4 positive lymph nodes)
- Regions (North America, European countries, and Australia)

Enrollment Period: June 2008 to July 2011

Q3W = every 3 weeks; Q12W = every 12 weeks; R = randomization.

Resultados SLP



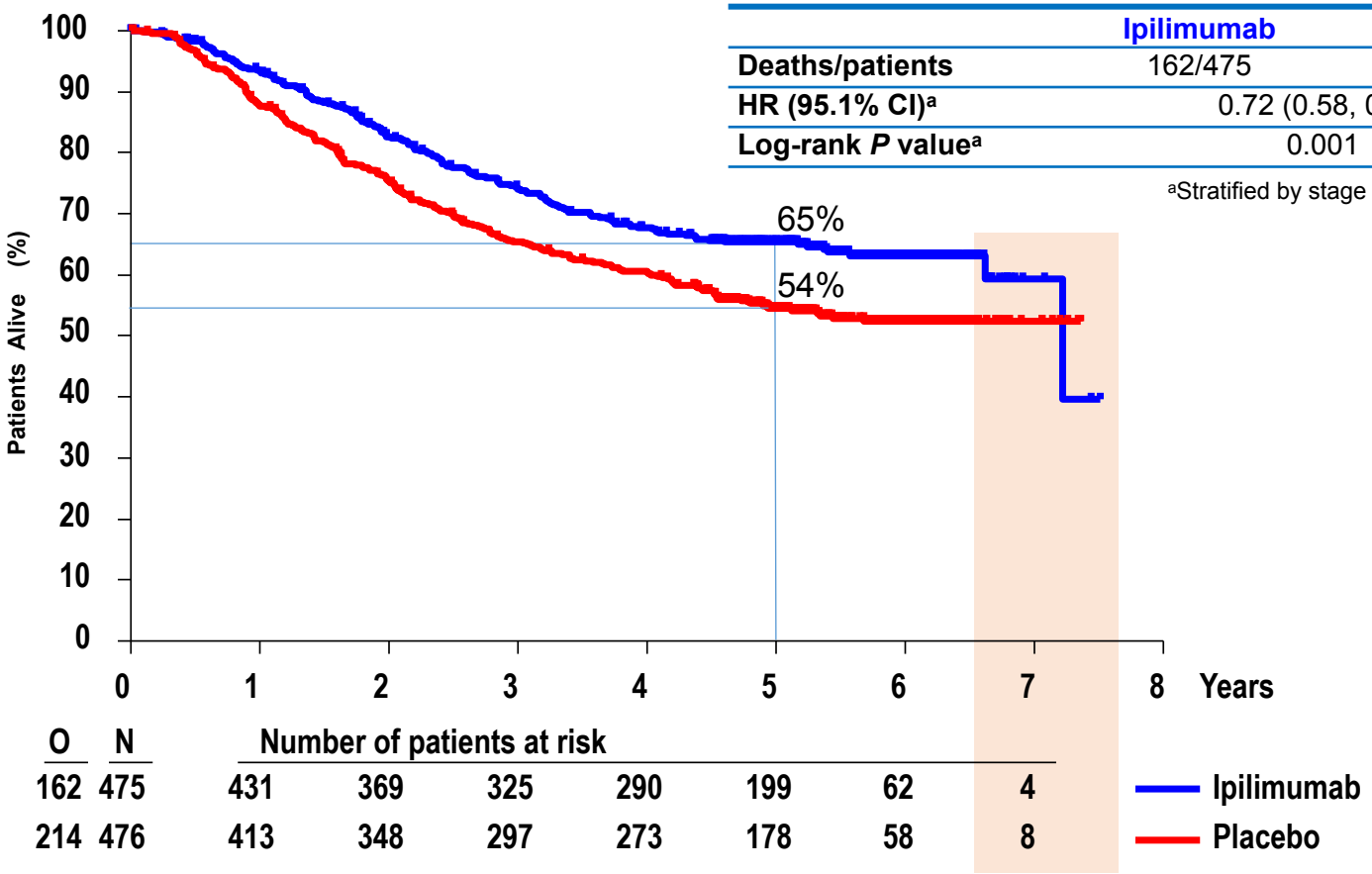
	Ipilimumab	Placebo
Events/patients	264/475	323/476
HR (95% CI)[a]	0.76 (0.64, 0.89)	
Log-rank *P* value[a]	0.0008	
Median RFS, months (95% CI)	27.6 (19.3, 37.2)	17.1 (13.6, 21.6)

[a]Stratified by stage provided at randomization.
CI = confidence interval.

Resultados SG

	Ipilimumab	Placebo
Deaths/patients	162/475	214/476
HR (95.1% CI)[a]	0.72 (0.58, 0.88)	
Log-rank *P* value[a]	0.001	

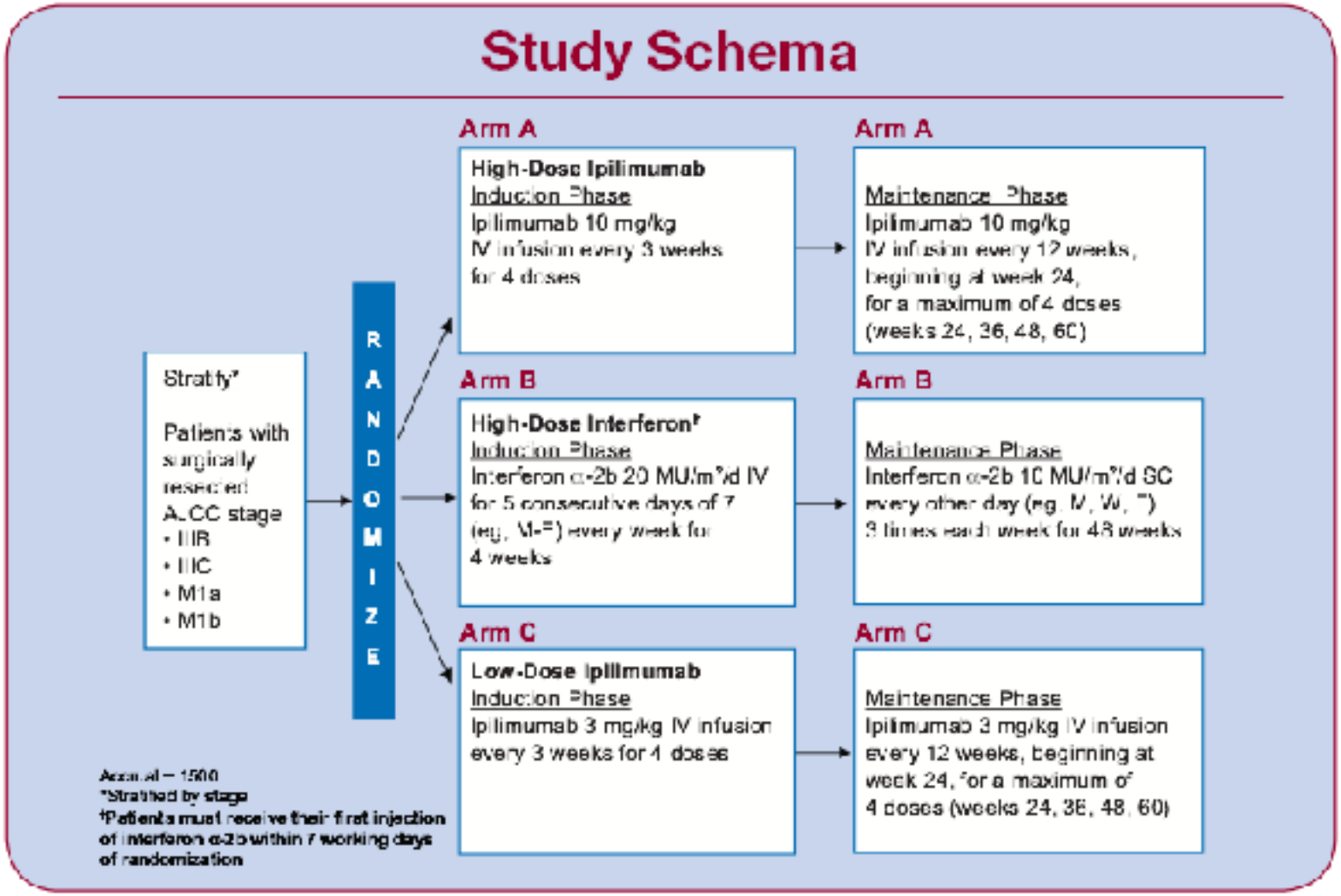
[a]Stratified by stage provided at randomization.



Motivos fin de tratamiento

	Ipilimumab (n = 471)	Placebo (n = 474)
Discontinuation, %	100	100
Reasons for discontinuation, %		
Normal completion (received study drug for entire 3 years)	13.4	30.2
Disease recurrence	28.7	59.5
AE related to study drug	49.7	1.9
Other reasons[a]	8.2	8.4
Median doses, per patient, n	4.0	8.0
Receiving ≥1 maintenance dose, %	42.0	70.0
Receiving ≥7 doses (1 year of therapy), %	28.9	56.8

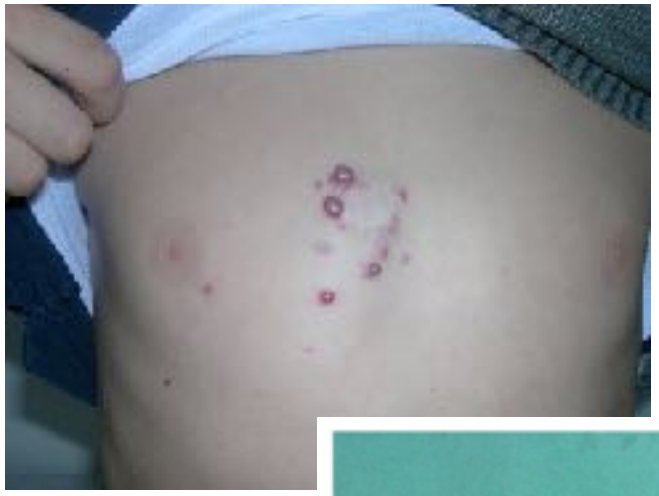
E1609 Trial

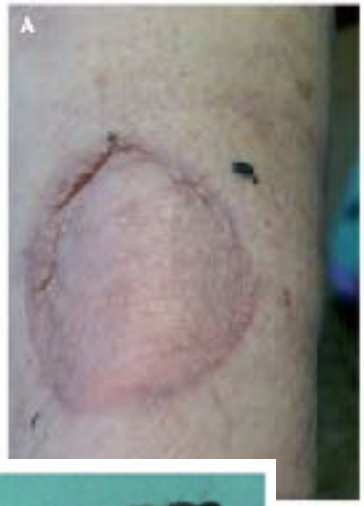

Study Schema
Stratify*
Patients with surgically resected AJCC stage
• IIIB
• IIIC
• M1a
• M1b
RANDOMIZE
Arm A
High-Dose Ipilimumab
Induction Phase
Ipilimumab 10 mg/kg
IV infusion every 3 weeks
for 4 doses
Arm A
Maintenance Phase
Ipilimumab 10 mg/kg
IV infusion every 12 weeks,
beginning at week 24,
for a maximum of 4 doses
(weeks 24, 36, 48, 60)
Arm B
High-Dose Interferon†
Induction Phase
Interferon α-2b 20 MU/m²/d IV
for 5 consecutive days of 7
(eg, M-F) every week for
4 weeks
Arm B
Maintenance Phase
Interferon α-2b 10 MU/m²/d SC
every other day (eg, M, W, F)
3 times each week for 48 weeks
Arm C
Low-Dose Ipilimumab
Induction Phase
Ipilimumab 3 mg/kg IV infusion
every 3 weeks for 4 doses
Arm C
Maintenance Phase
Ipilimumab 3 mg/kg IV infusion
every 12 weeks, beginning at
week 24, for a maximum of
4 doses (weeks 24, 36, 48, 60)
Accrual – 1500
*Stratified by stage
†Patients must receive their first injection of interferon α-2b within 7 working days of randomization

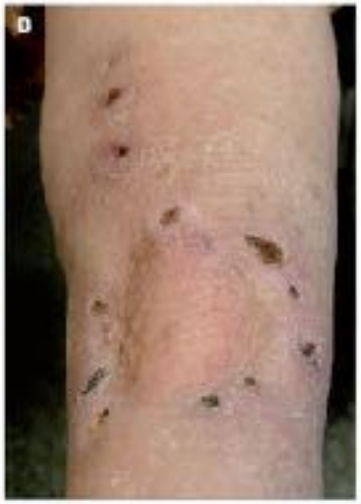
Anticuerpos anti PD-1

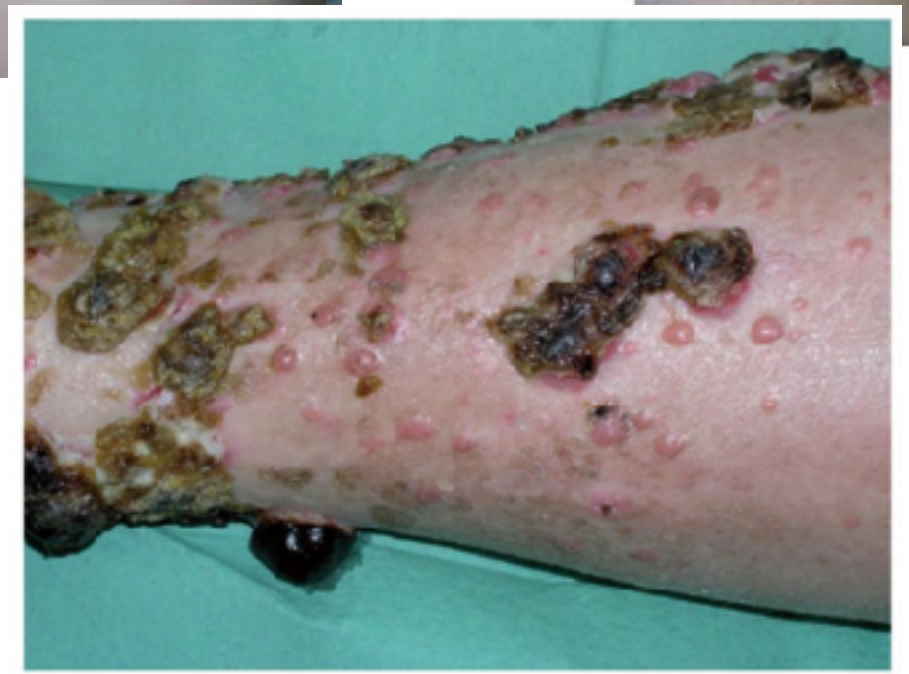
- Checkmate 238
  - Ipilimumab 10 mg/kg vs Nivolumab 3 mg/kg
  - Estadio IIIb-c y IV resecado
  - Objetivo SLP
  - En seguimiento (¿ASCO 2017?)
- Keynote 054
  - Pembrolizumab 200 mg vs placebo
  - Estadio IIIa-c resecado
  - Objetivo SLP
  - En seguimiento (¿ASCO 2017?)
- SWOG S1404
  - Pembrolizumab 200 mg vs IFN HD o Ipilimumab
  - Pacientes estadio IIIa (N2a) IIIb-c y IV resecados
  - Objetivo SLP y OS
  - Reclutando

N2c y N3 Satelitosis y metástasis en transito

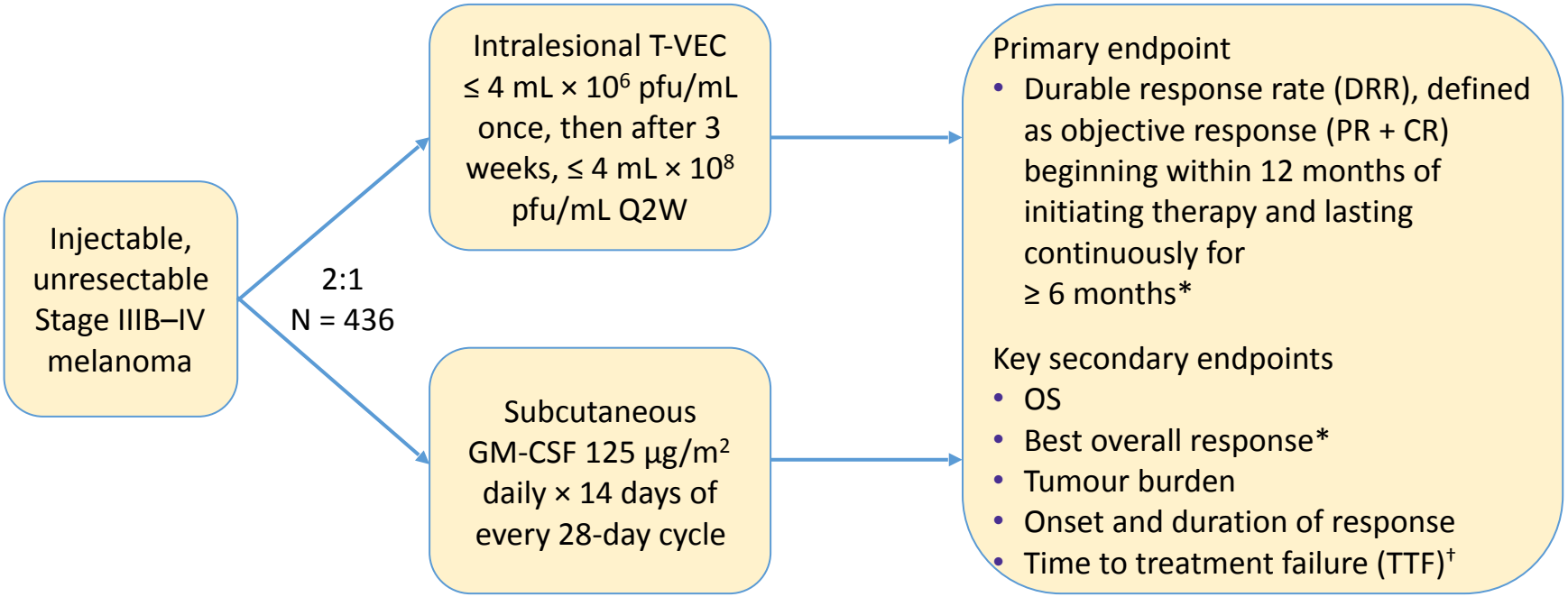








OPTIM Diseño y Objetivos



Randomisation stratification:
1. Disease stage
2. Prior non-adjuvant systemic treatment
3. Site of disease at first recurrence
4. Presence of liver metastases

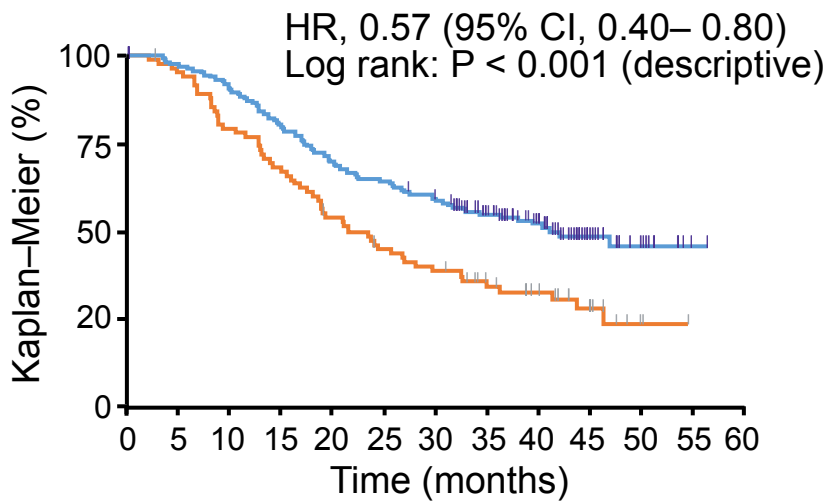
Patients enrolled between May 2009 and July 2011. Discontinuation of treatment because of progressive disease per response assessment criteria was not required before 24 weeks unless alternate therapy was clinically indicated.

† *Responses were determined using modified WHO criteria by a blinded EAC; TTF was defined as time from baseline to first clinically relevant disease progression for

Study 005/05: Andtbacka RHI, et al. J Clin Oncol 2015;33:2780–8.

Supervivencia por estadio de enfermedad

Stage IIIB/C, IV M1a

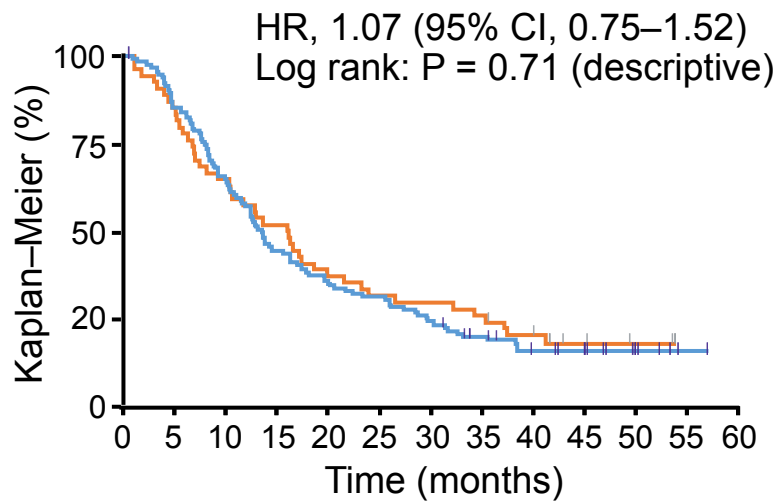


Risk set, n

T-VEC	163	157	146	129	113	104	93	73	51	23	10	1	0
GM-CSF	86	78	65	55	43	35	30	22	17	10	2	0	0

	Events/n, %	Median (95% CI), months
T-VEC	80/163 (49)	41.1 (30.6–NE)
GM-CSF	57/86 (66)	21.5 (17.4–29.6)

Stage IV M1b/c



Risk set, n

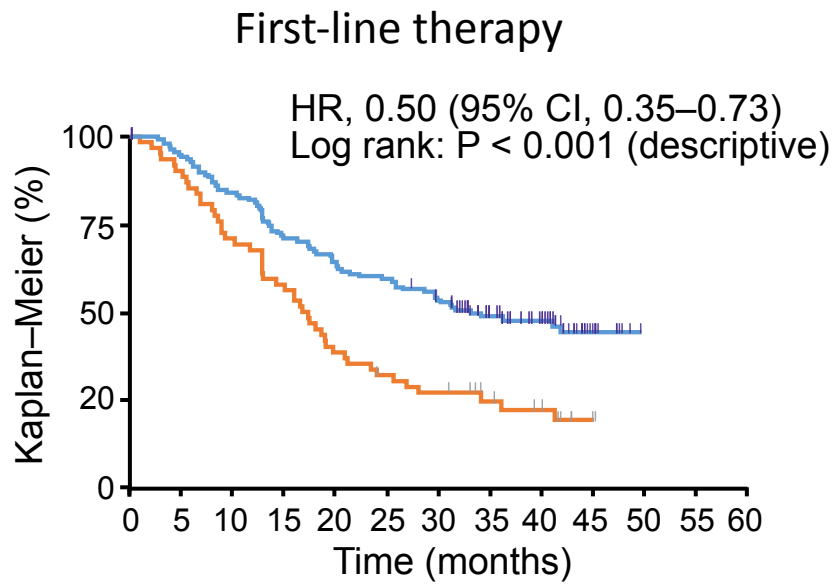
T-VEC	131	112	84	58	46	41	32	22	15	13	6	1	0
GM-CSF	55	46	35	28	20	17	16	14	10	5	3	0	0

	Events/n, %	Median (95% CI), months
T-VEC	109/131 (83)	13.4 (11.4–16.2)
GM-CSF	44/55 (80)	15.9 (10.2–19.7)

NE, not evaluable.

Andtbacka RHI, et al. J Clin Oncol 2015;33:2780–8.

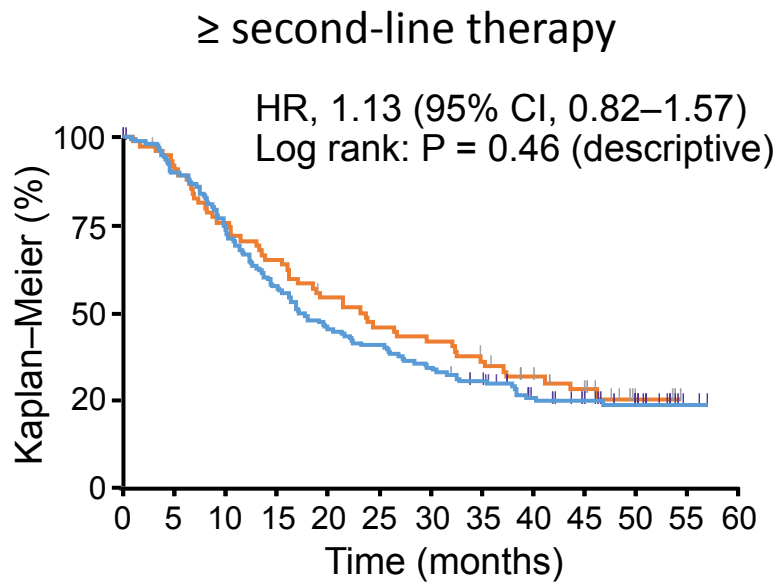
Supervivencia por línea de tratamiento



Risk set, n

T-VEC	138	130	116	98	89	82	72	50	37	12	0
GM-CSF	65	56	44	35	24	19	16	11	8	2	0

	Events/n, %	Median (95% CI), months
T-VEC	73/138 (53)	33.1 (25.9–NE)
GM-CSF	48/65 (74)	17.0 (12.8–20.9)



Risk set, n

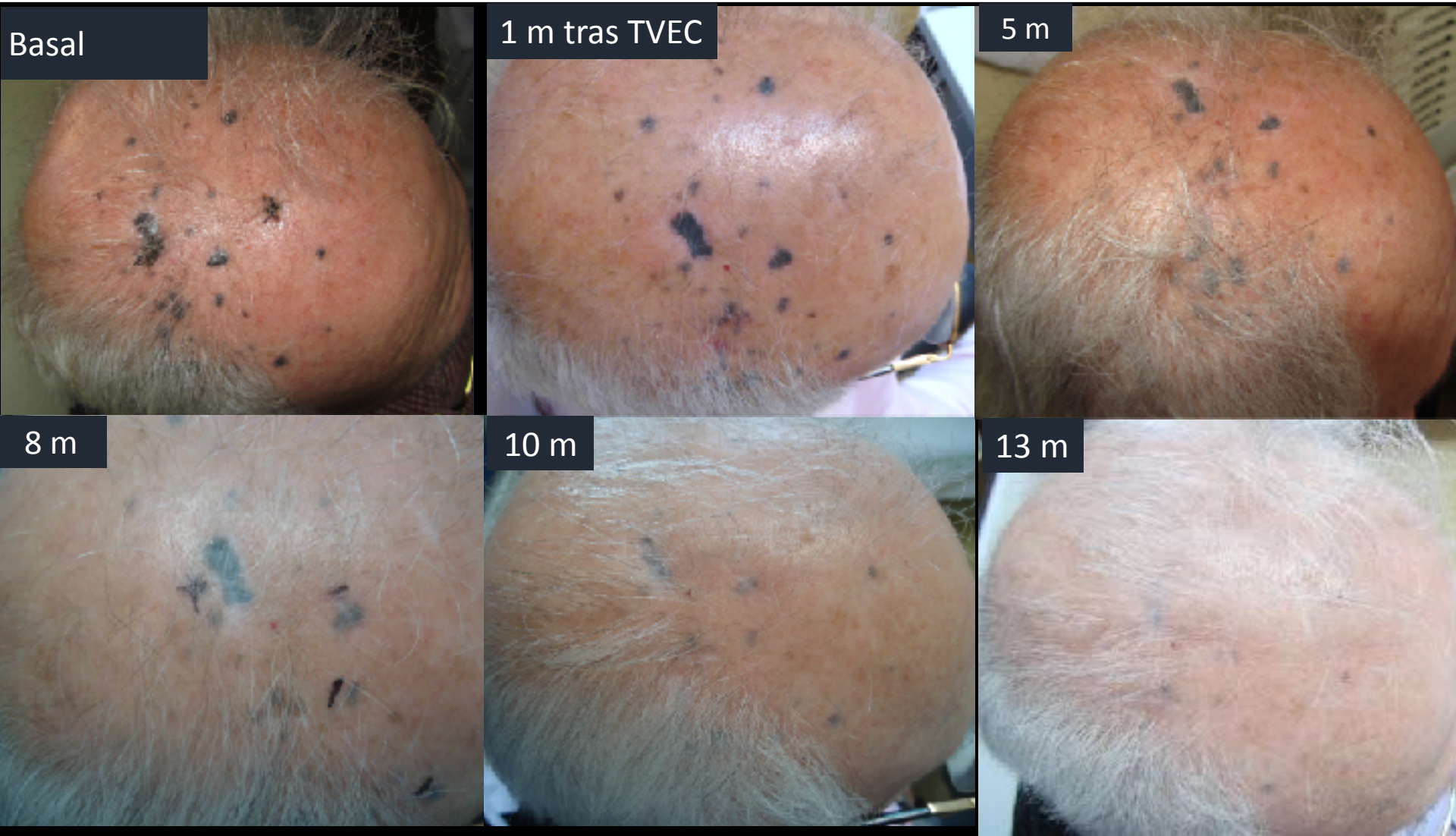
T-VEC	157	139	114	89	70	63	53	45	29	24	16	2	0
GM-CSF	76	68	56	48	39	33	30	25	19	13	5	0	0

	Events/n, %	Median (95% CI), months
T-VEC	116/157 (74)	17.1 (14.3–22.3)
GM-CSF	53/76 (70)	23.2 (16.2–32.4)

*Prior non-adjuvant systemic treatment.

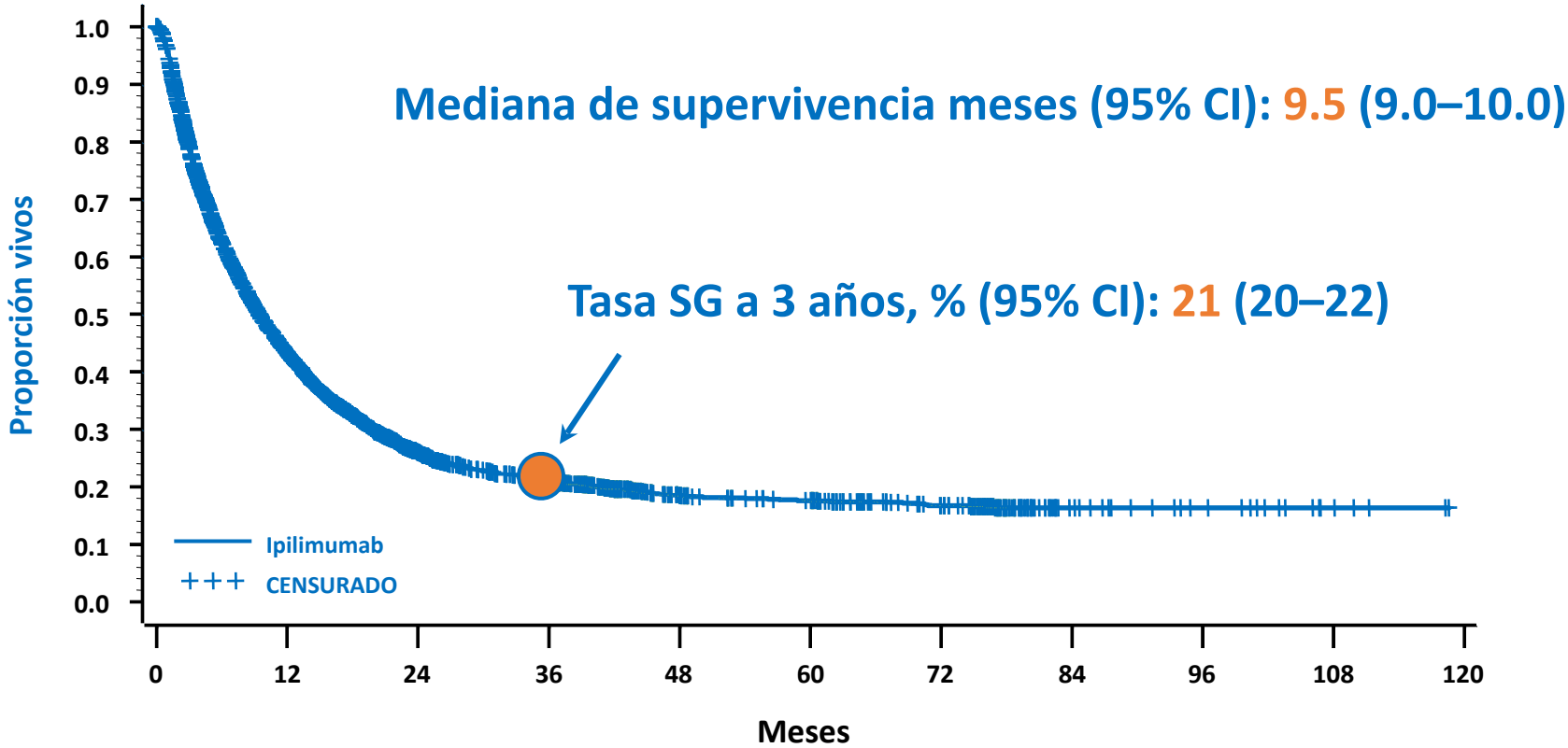
Andtbacka RHI, et al. J Clin Oncol 2015;33:2780–8.

Caso del HGUV dentro de EC



Inmunoterapia del melanoma metastatico

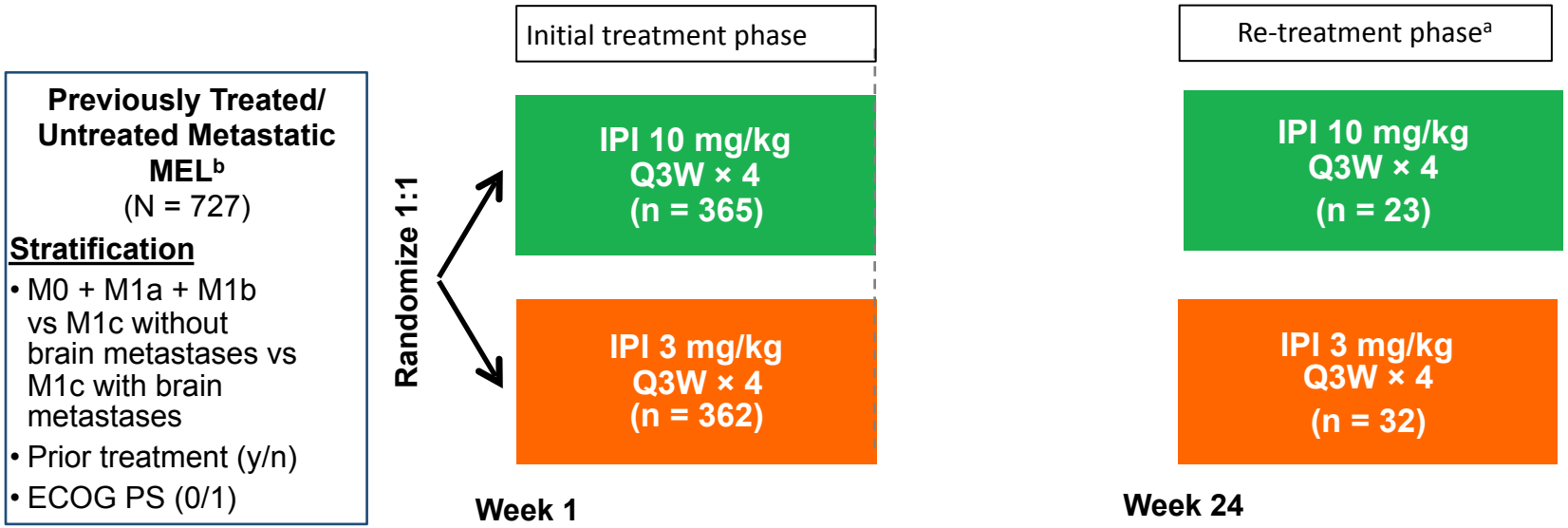
SG Ipilimumab pool incluido EAP: 4846 pacientes



Pacientes en Riesgo											
Ipilimumab	4846	1786	612	392	200	170	120	26	15	5	0

Schadendorf D, et al. Eur J Cancer 2013;49(suppl 2): abstract 24LBA

CA184-169: Diseño

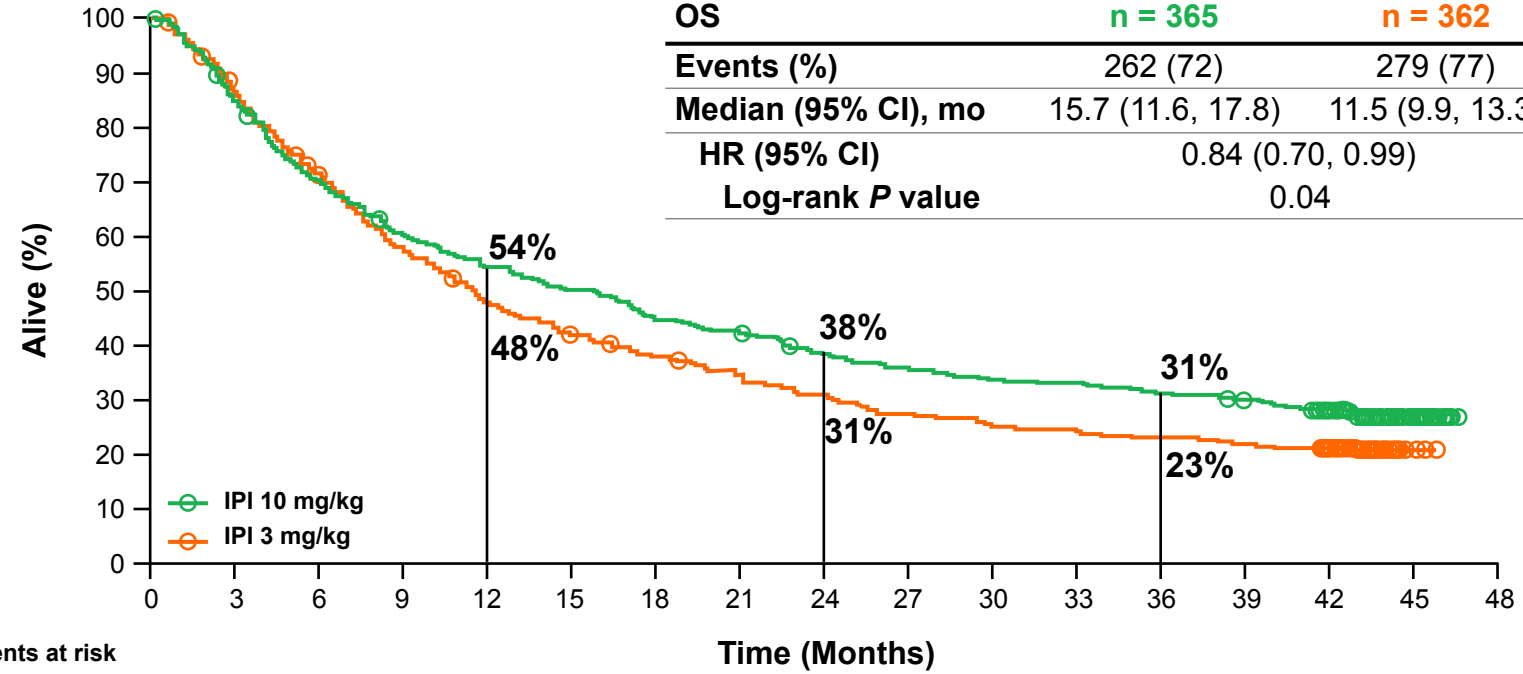


- **Enrollment period:** March 2012 to August 2012
- No crossover allowed between treatment arms

[a]After initial response (or stable disease ≥3 months) and subsequent progressive disease in the absence of intolerable toxicity.
[b]Patients could not be treated with BRAF/PD-1 therapy.
ECOG PS = Eastern Cooperative Oncology Group performance status; Q3W = every 3 weeks.

Supervivencia global

OS	IPI 10 mg/kg n = 365	IPI 3 mg/kg n = 362
Events (%)	262 (72)	279 (77)
Median (95% CI), mo	15.7 (11.6, 17.8)	11.5 (9.9, 13.3)
HR (95% CI)	0.84 (0.70, 0.99)	
Log-rank *P* value	0.04	



Number of patients at risk

IPI 10 mg/kg	365	306	253	217	196	181	161	151	137	126	120	118	111	105	94	16	0
IPI 3 mg/kg	362	310	253	205	168	146	131	118	107	95	87	83	80	76	71	8	0

Minimum OS follow-up: ~43 mo

Seguridad

	IPI 10 mg/kg n = 364		IPI 3 mg/kg n = 362	
AEs during initial treatment phase	**Any grade**	**Grades 3-5**	**Any grade**	**Grades 3-5**
AEs, %	95	59	93	52
Treatment-related AEs, %	79	34	63	19
Serious AEs, %	64	53	51	43
AEs leading to discontinuation, %	31	26	19	16
Immune-related AEs, %	74	30	54	14

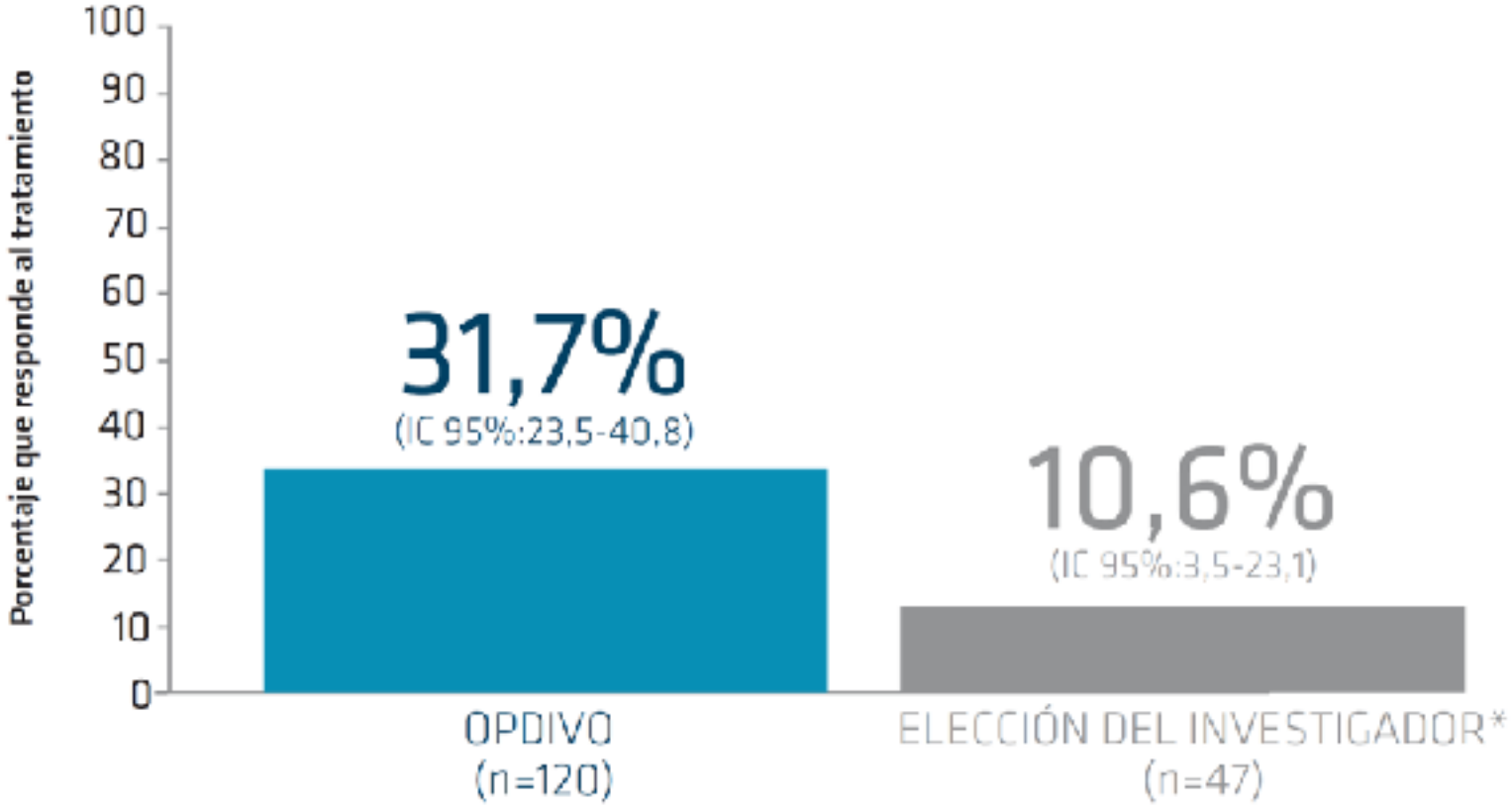
- During the entire study period, study-drug toxicity led to death in
  - 4 patients (1%) in the 10 mg/kg arm
    - Diarrhea leading to general deterioration, fulminant colitis, multi-organ failure, bowel perforation
  - 2 patients (<1%) in the 3 mg/kg arm
    - Multifocal colon perforation, myocardial infarction from complications of diarrhea and colitis

CheckMate 037: Diseño

Estudio de fase III aleatorizado, controlado, abierto

1. Weber J, D'Angelo SP, Minor D et al. Lancet Oncol 2015;16:375-84.

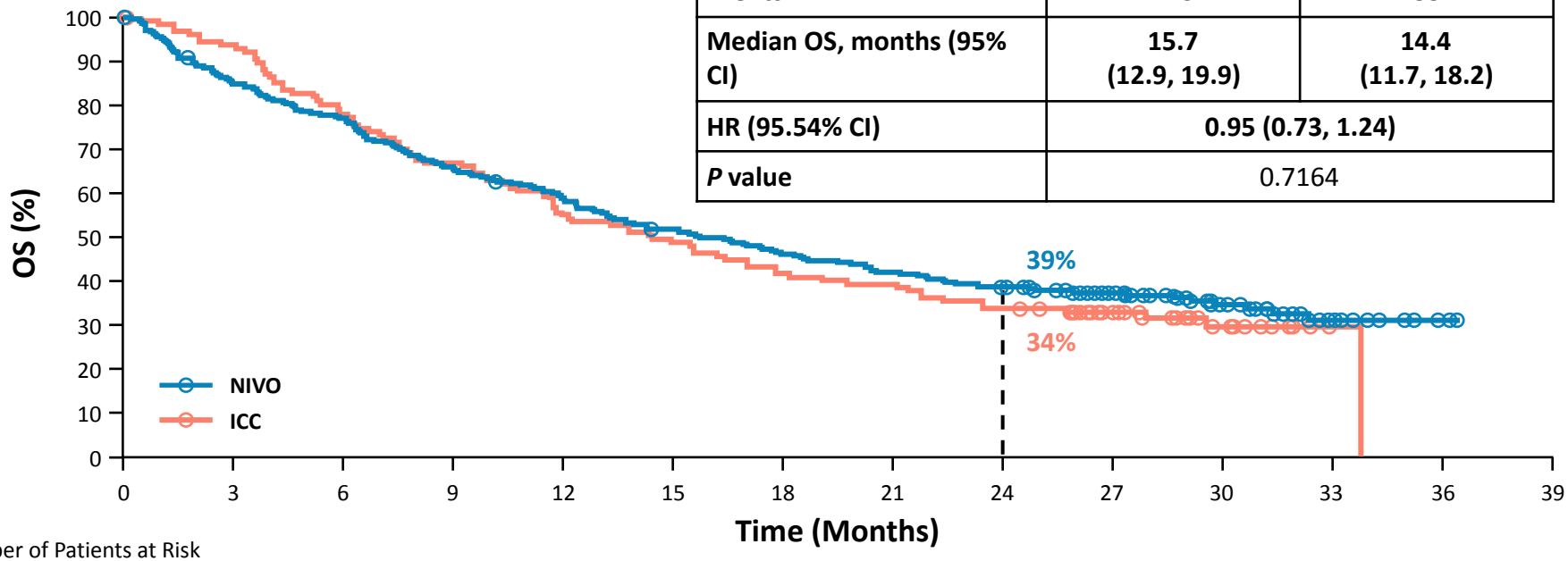
Objetivo principal: Tasa de respuesta objetiva en el ensayo CheckMate037[1]



1. Weber J, D'Angelo SP, Minor D et al. Lancet Oncol 2015;16:375-84.

CheckMate 037 supervivencia global

	NIVO (n = 272)	ICC (n = 133)
Events	175	88
Median OS, months (95% CI)	**15.7 (12.9, 19.9)**	**14.4 (11.7, 18.2)**
HR (95.54% CI)	**0.95 (0.73, 1.24)**	
***P* value**	0.7164	

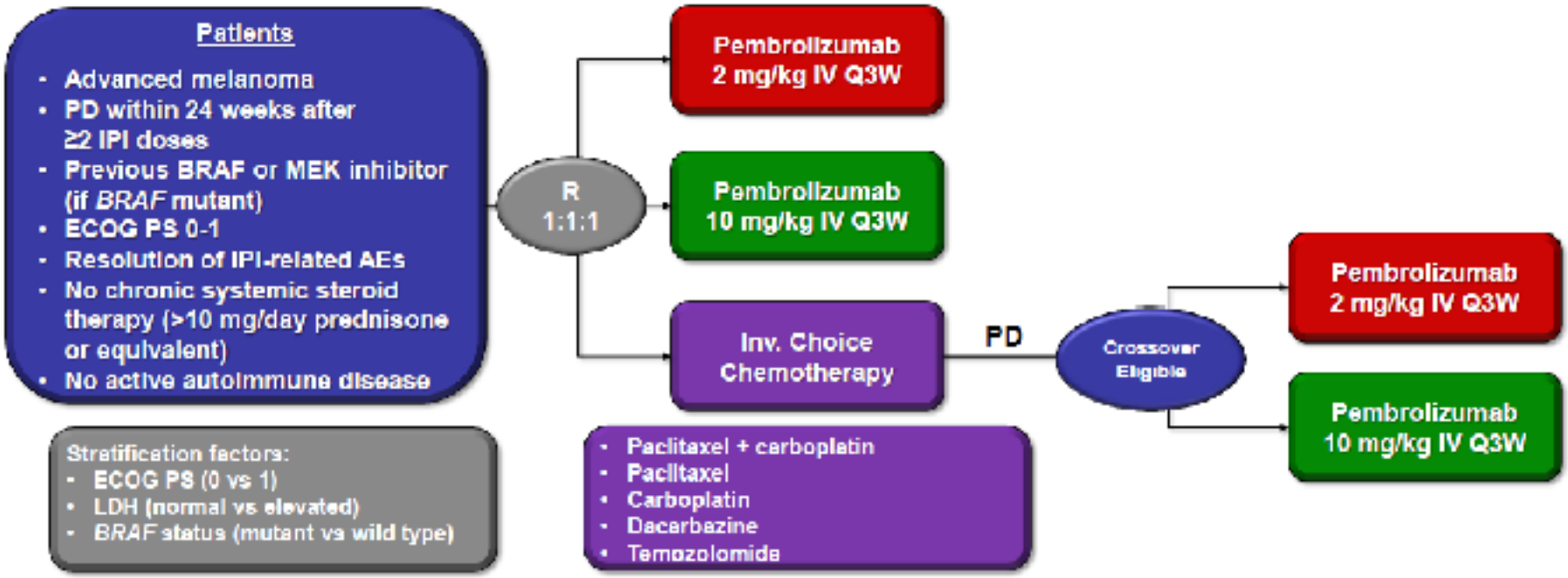


Number of Patients at Risk

NIVO	272	230	208	178	158	138	123	112	103	71	44	16	3	0
ICC	133	119	99	85	70	62	53	49	43	28	14	2	0	0

- 62% in the **ICC** group received subsequent systemic therapy, including 40% who received pembrolizumab
- 40% in the **NIVO** group had subsequent systemic therapy

Diseño Keynote 002



Antoni Ribas SMR Meeting 2014

Respuestas Keynote 002

	Pembrolizumab 2 Q3W n = 180	Pembrolizumab 10 Q3W n = 181	Chemotherapy n = 179
Best overall response			
Complete response	2%	3%	0%
Partial response	19%	23%	4%
Stable disease	18%	17%	18%

- $P < 0.0001$ each for pembrolizumab 2 mg/kg Q3W and 10 mg/kg Q3W vs chemotherapy
- $P = 0.21$ for pembrolizumab 10 mg/kg Q3W vs 2 mg/kg Q3W

ORR (95% CI)	21% (15%-28%)	25% (19%-32%)	4% (2%-9%)
Duration of response, wk			
Median	NR	NR	37
Range	6+ to 50+	5+ to 48+	7+ to 41
Ongoing responses	92%	87%	63%

Antoni Ribas SMR Meeting 2014

SLP Keynote 002 (Revisión Central)

A

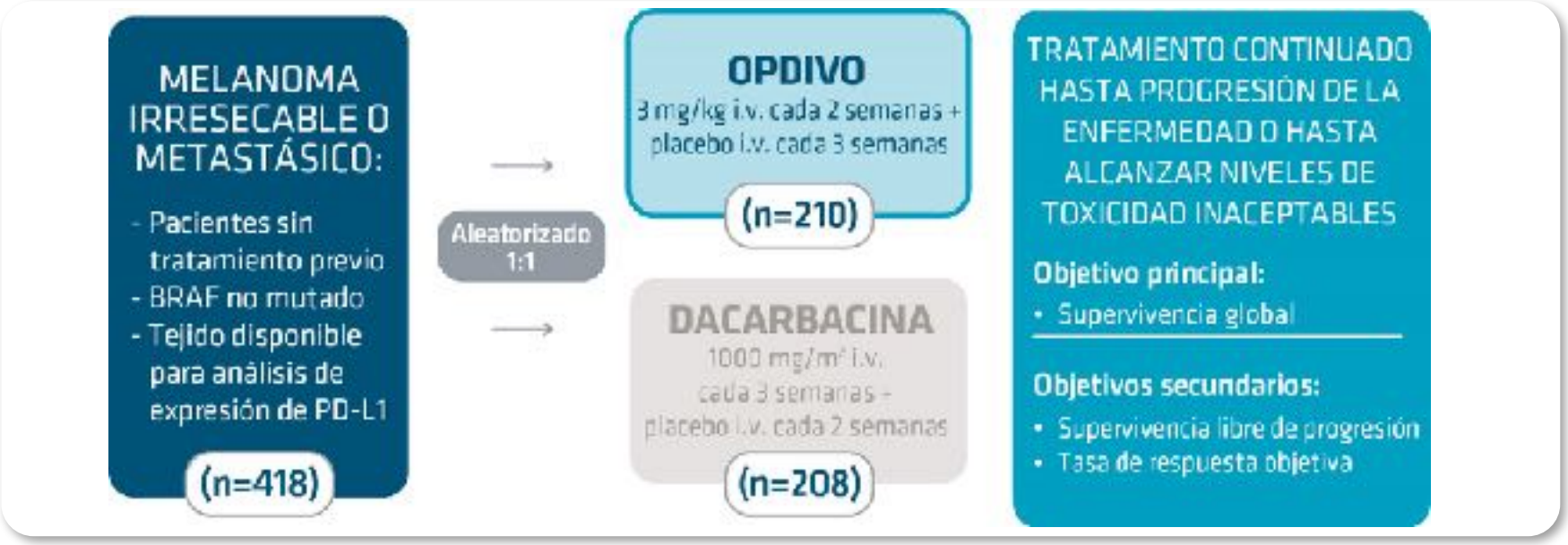
Arm	Median (95% CI), mo	Rate at 6 mo	Rate at 9 mo	Mean,[a] mo
Pembro 2 Q3W	2.9 (2.8-3.8)	34%	24%	5.4
Pembro 10 Q3W	2.9 (2.8-4.7)	38%	29%	5.8
Chemotherapy	2.7 (2.5-2.8)	16%	8%	3.6

Pembrolizumab 10 mg/kg	181	158	82	55	39	15	5	1	1	0
Chemotherapy	179	128	43	22	15	4	2	1	0	0

Antoni Ribas, Lancet Oncol 2015; 16: 908-18

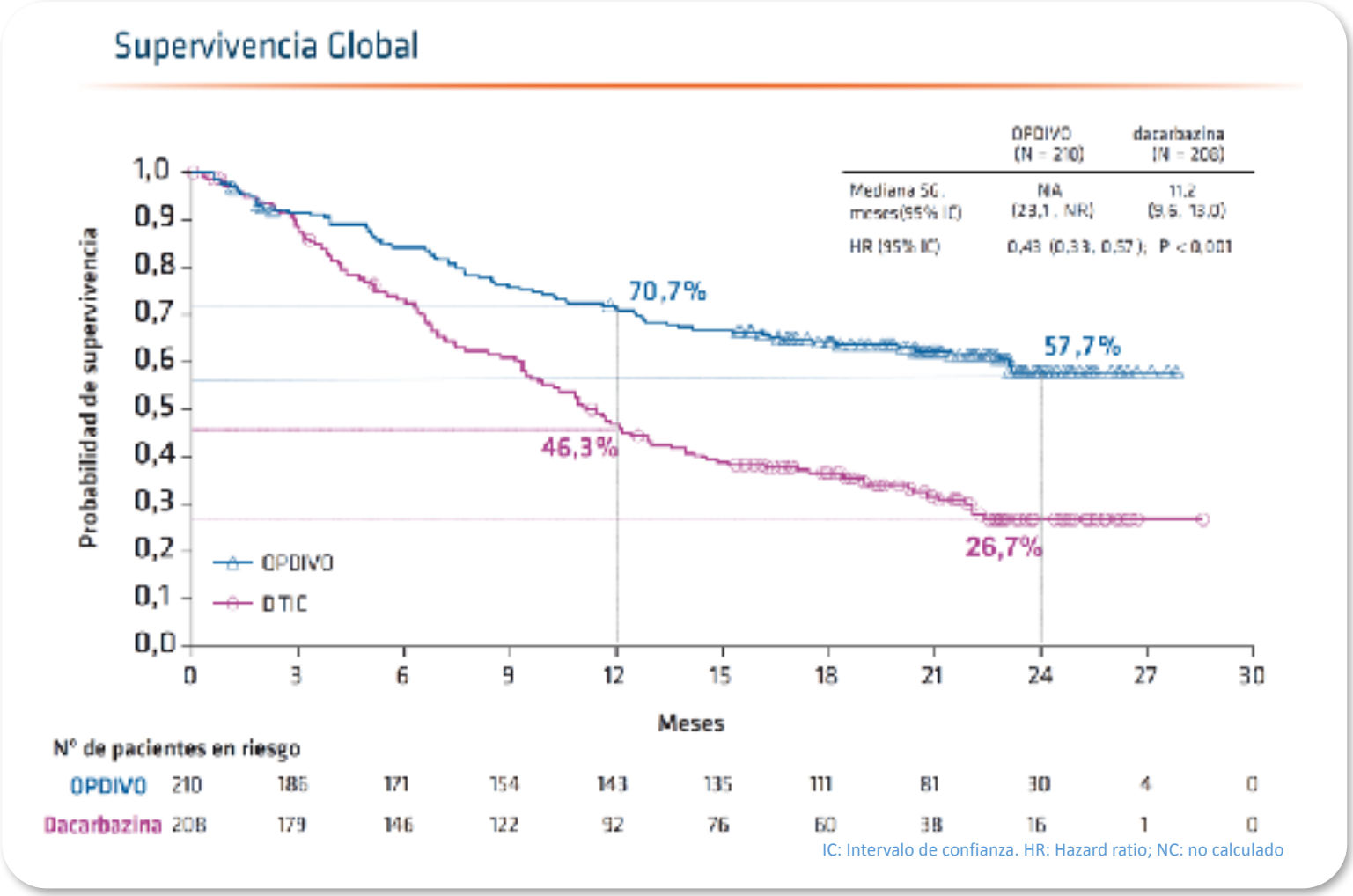
CheckMate 066: Diseño del estudio

Estudio de fase III, aleatorizado, doble ciego



1. Robert C, Long GV, Brady B, et al. N Engl J Med 2015;372(4):320-30.

CheckMate 066: Supervivencia global



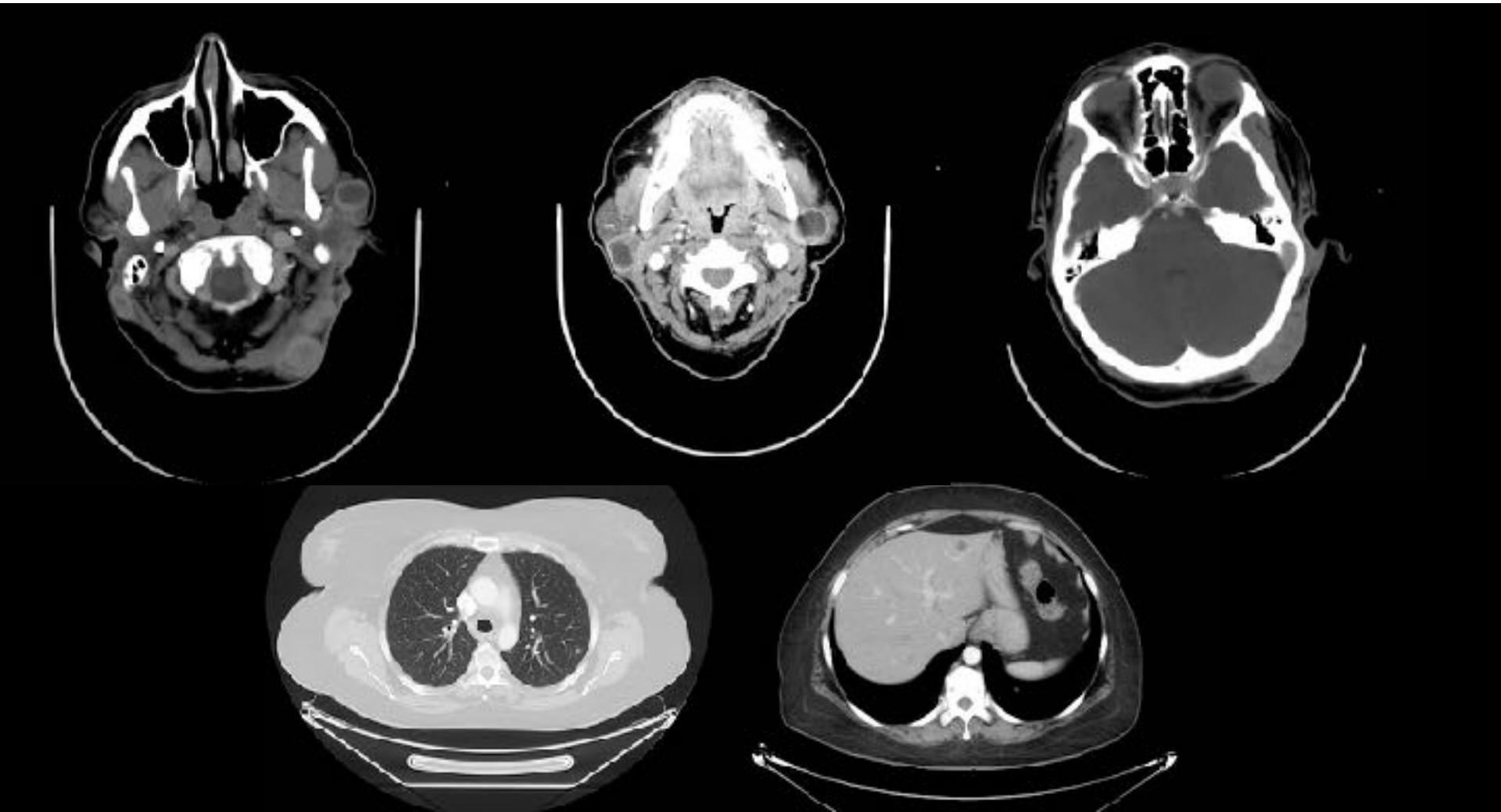
IC: Intervalo de confianza. HR: Hazard ratio; NC: no calculado

1. Atkinson V, Ascierto PA, Long GV, et al. Two-Year Survival and Safety Update in Patients With Treatment-Naïve Advanced Melanoma (MEL) Receiving Nivolumab or Dacarbazine in CheckMate 066. Presented at Society for Melanoma Research (SMR) 2015 International Congress; November 18–21, 2015; San Francisco, California, USA

Caso Clínico 1: Diagnostico

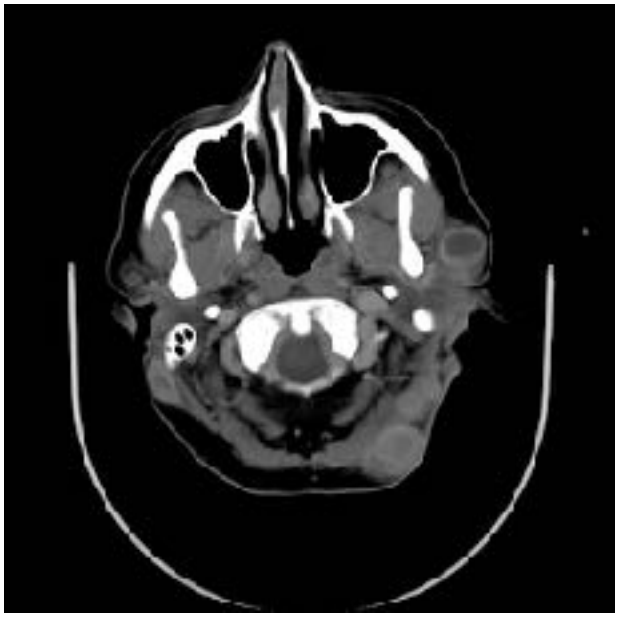
- Mujer de 51 años con antecedentes de
  - Melanoma de extensión superficial de 1.2 mm y ganglio centinela negativo en Febrero de 2013
  - Sobrepeso
- En Noviembre de 2013 nota aparición de nódulos subcutáneos en cuero cabelludo y dolorimiento facial.
- TAC objetiva Adenopatías cervicales bilaterales, múltiples nódulos subcutáneos en calota, múltiples nódulos pulmonares bilaterales de pequeño tamaño sugestivos de metástasis y un nódulo hepático
- La analítica muestra LDH de 427 mUI (208-378)
- B-RAF wild-type
- Con diagnostico de melanoma estadio IVc se remite a nuestro centro para valoración de tratamiento.
- Se propuso participar a la paciente en ensayo CM 066 y la paciente acepto

Caso clínico 1: Imagen Inicial

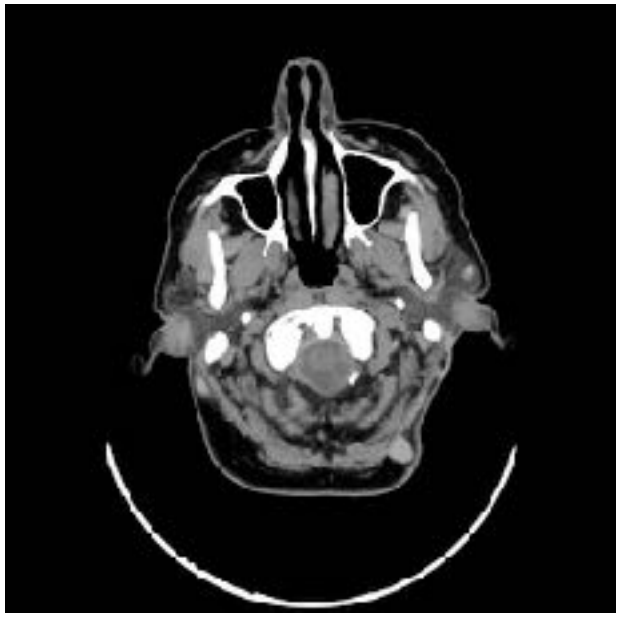


Caso clínico 1: Situación actual

- En la actualidad la paciente continua con Nivolumab manteniendo la respuesta parcial 38 meses tras diagnostico de enfermedad IVc
- Se ha discutido con la paciente la posibilidad de interrumpir el tratamiento pero no lo desea

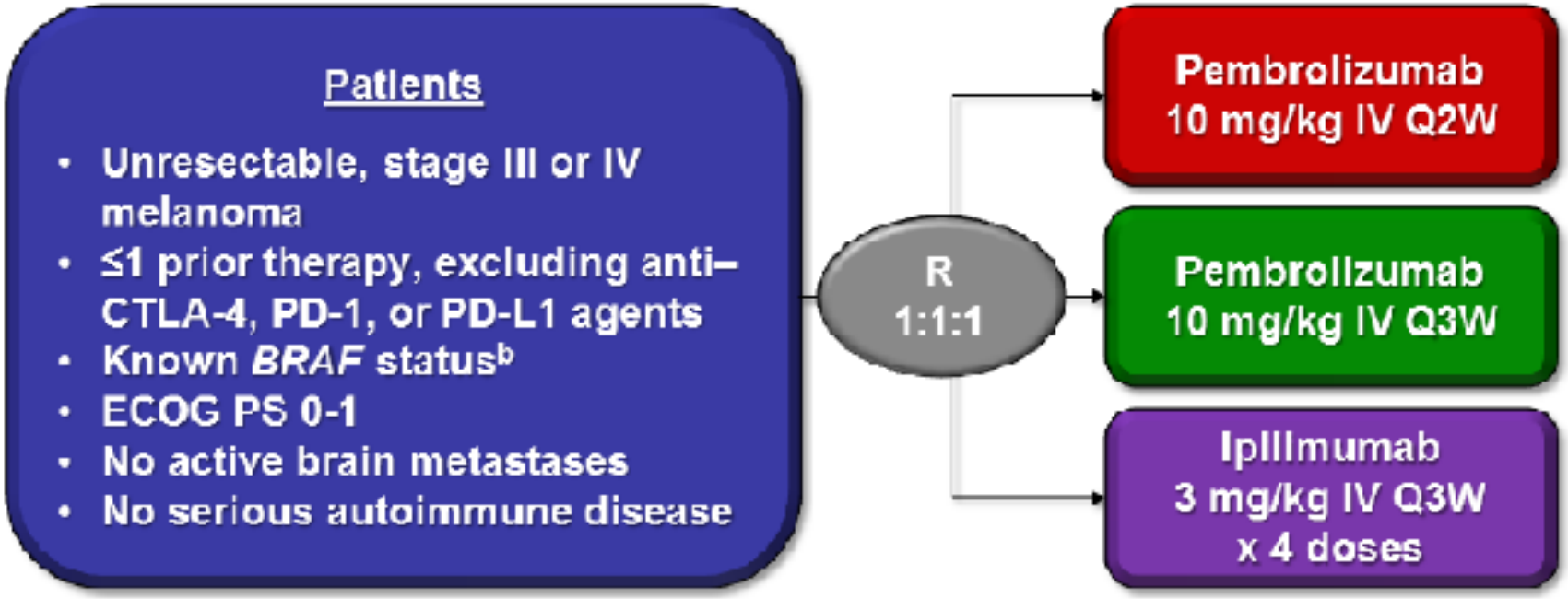


Nov 2014



Feb 2017

Diseño Keynote 006



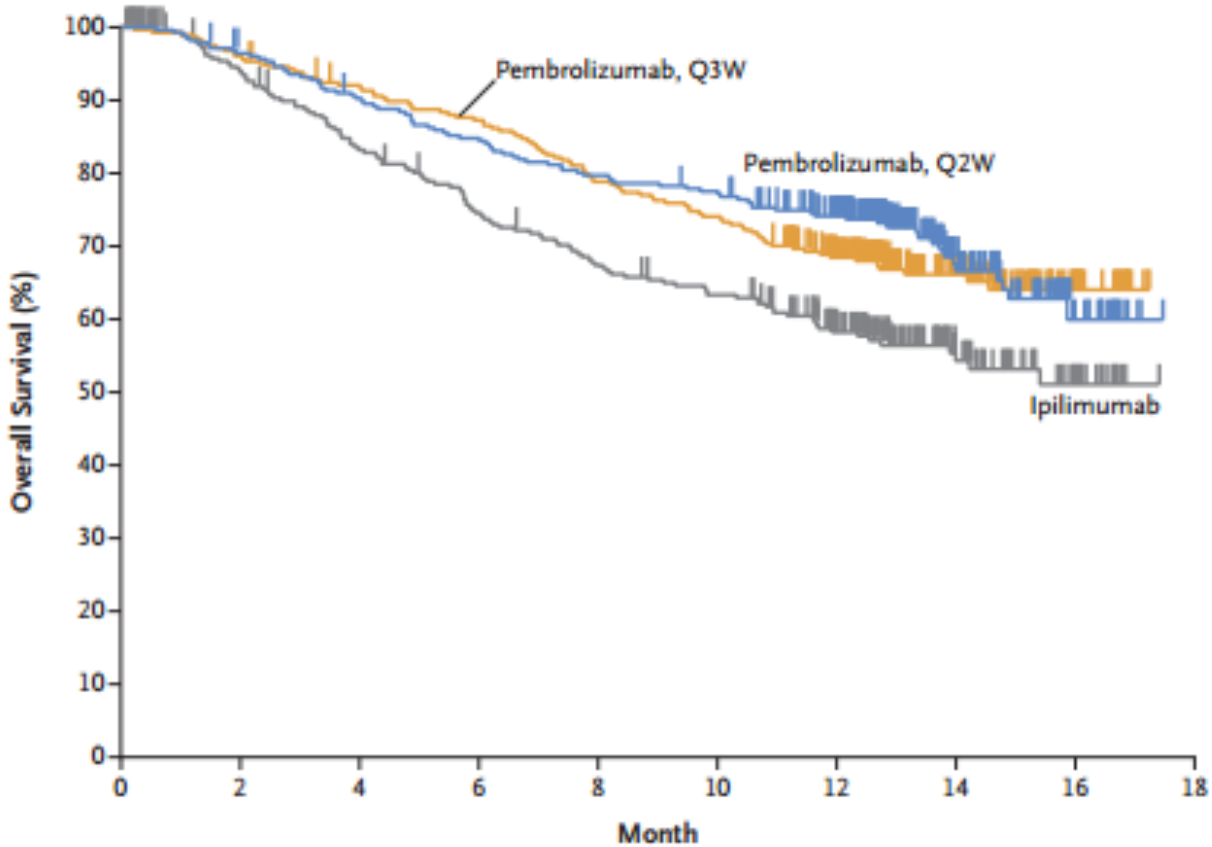
Stratification factors:
- ECOG PS (0 vs 1)
- Line of therapy (first vs second)
- PD-L1 status (positive[c] vs negative)

- Primary end points: PFS and OS
- Secondary end points: ORR, duration of response, safety

Antoni Ribas AACR 2015 Abstract CT101

Ipilimumab vs Pembrolizumab primera línea

B Overall Survival

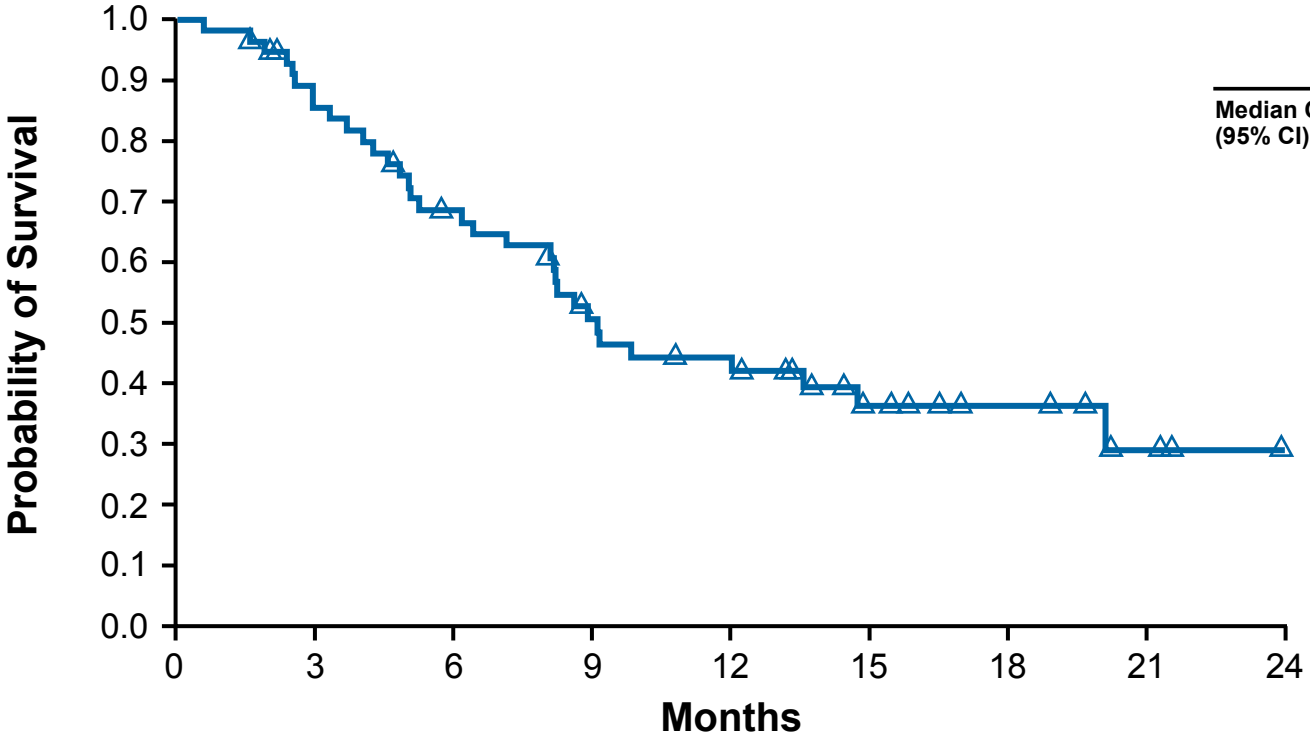


No. at Risk										
Pembrolizumab, Q2W	279	266	248	233	219	212	177	67	19	0
Pembrolizumab, Q3W	277	266	251	238	215	202	158	71	18	0
Ipilimumab	278	242	212	188	169	157	117	51	17	0

Robert et all. NEJM. April 2015

DOI: 10.1056/NEJMoa1503093

Fallos a nivolumab en el CM 066



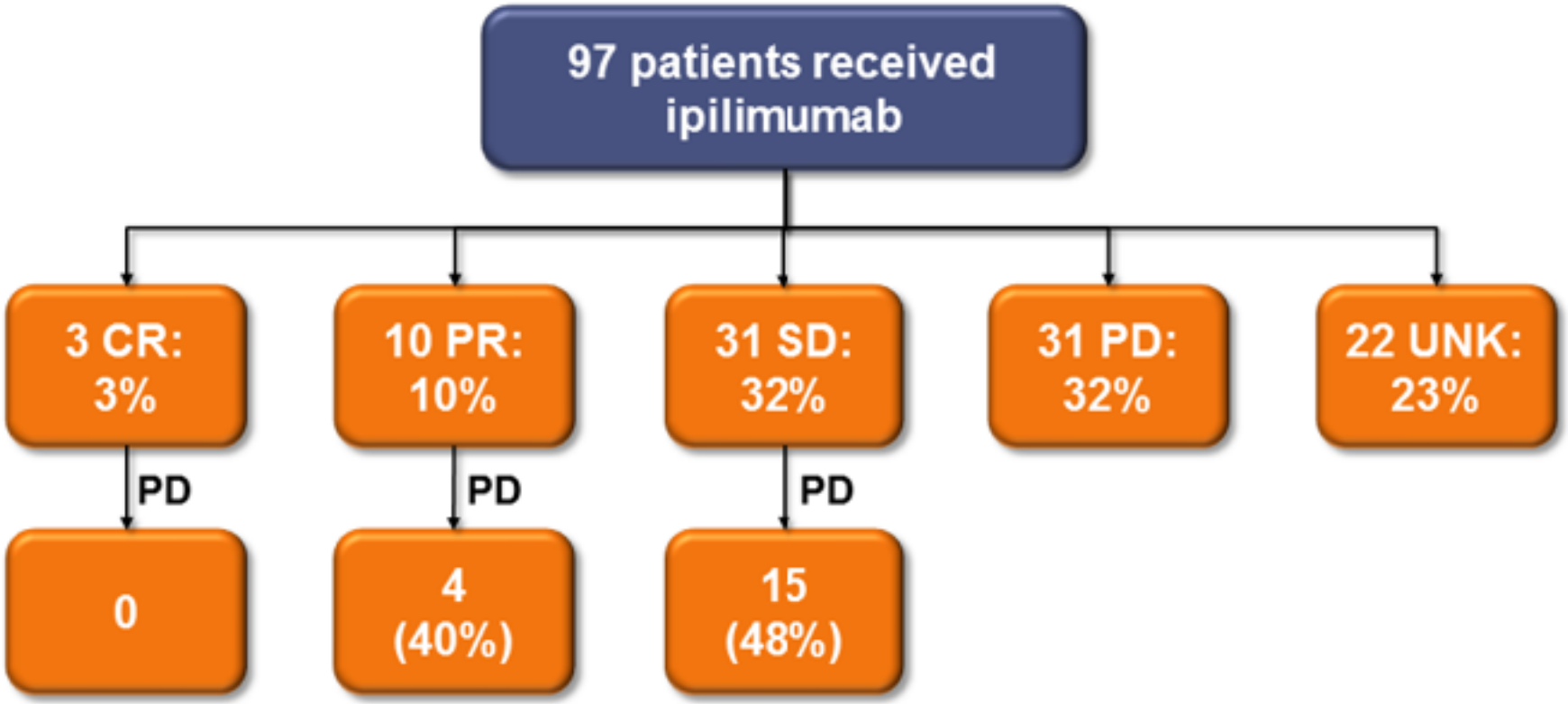
	NIVO to IPI (N = 57)
Median OS, mo (95% CI)	9.0 (7.1, 14.7)

Number of Patients at Risk									
NIVO to IPI	57	46	35	24	19	11	7	3	0

- Among these patients, ORR was 8.8% (n = 5, all PR) after the start of IPI

CI = confidence interval; mo = month

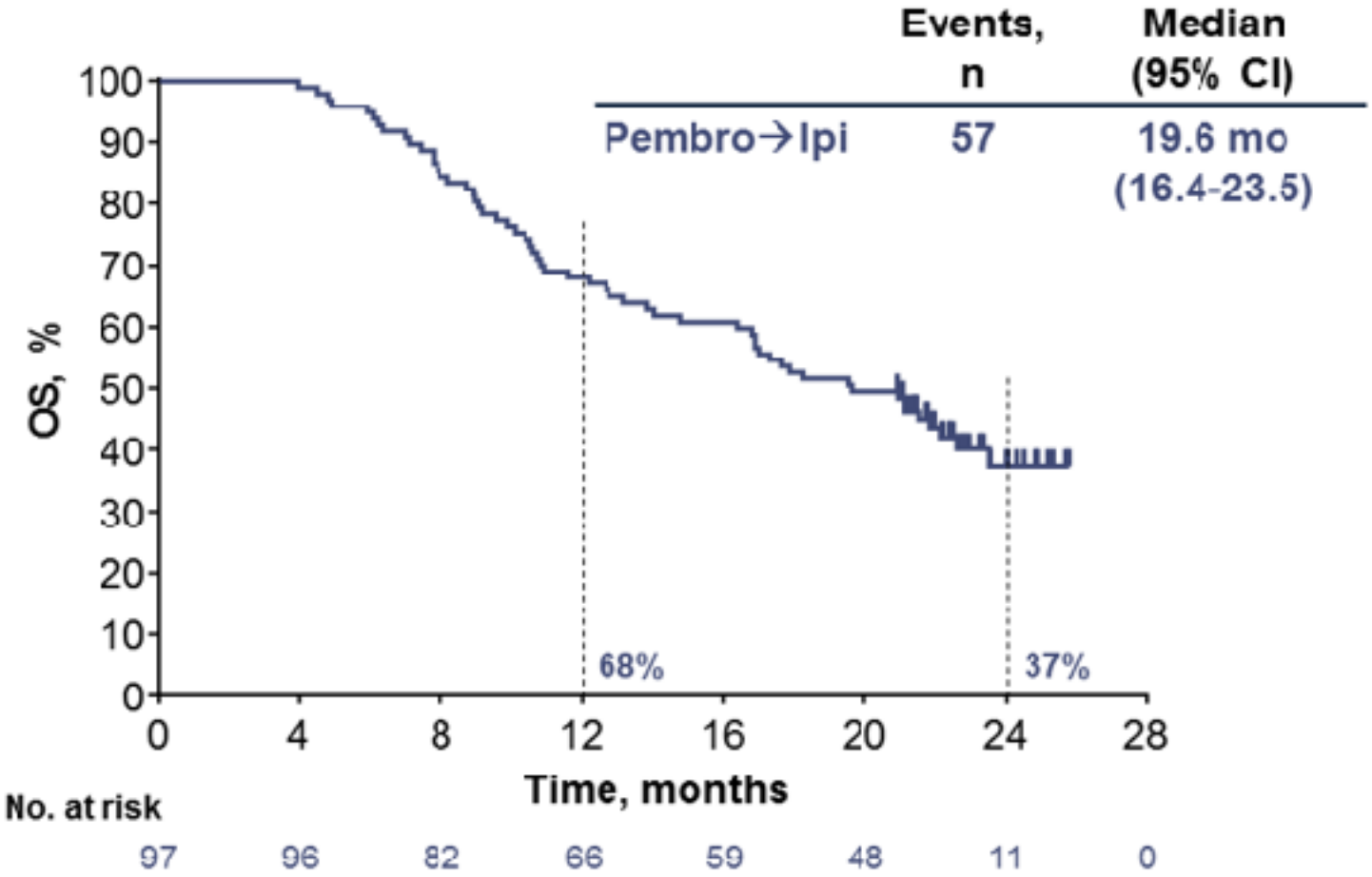
Respuestas Ipilimumab tras pembrolizumab KN 006



13% ORR in KEYNOTE 006 Ipilimumab Arm[1]

Long, SMR 2016

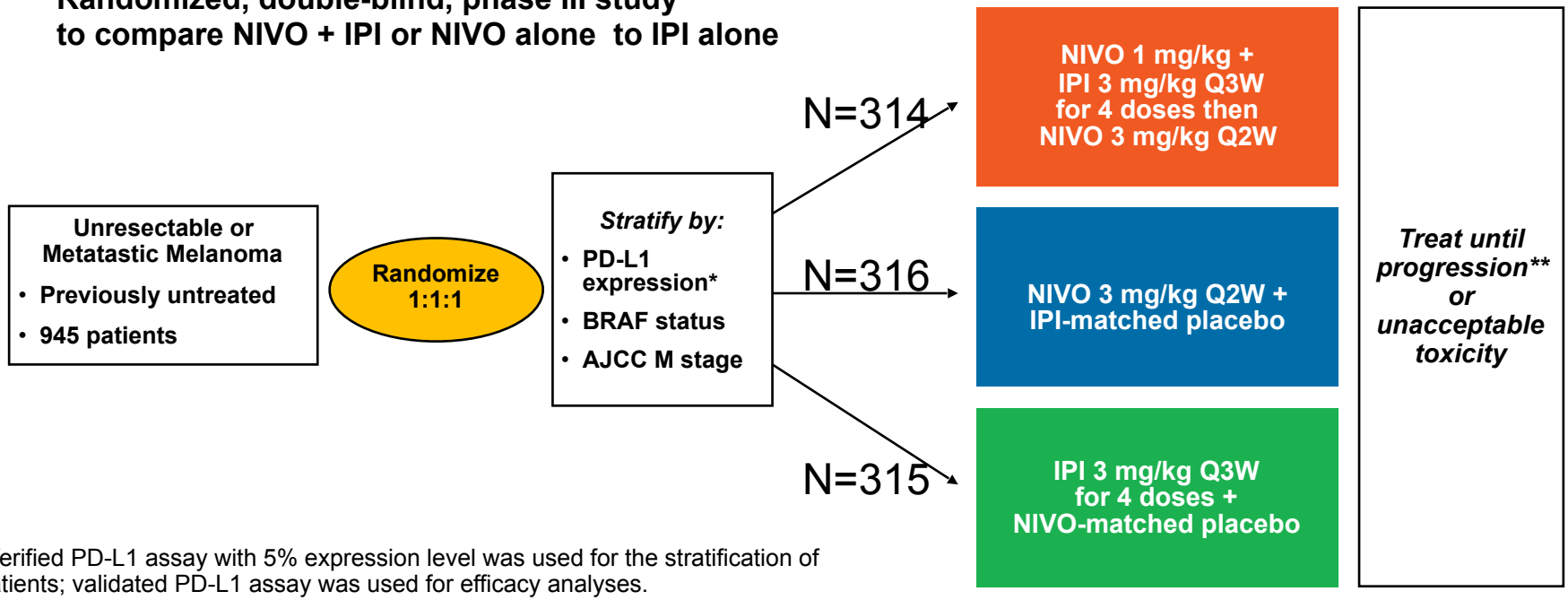
Supervivencia Ipilimumab tras pembrolizumab KN006



Long, SMR 2016

Ipilimumab + Nivolumab

Randomized, double-blind, phase III study to compare NIVO + IPI or NIVO alone to IPI alone



*Verified PD-L1 assay with 5% expression level was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses.

**Patients could have been treated beyond progression under protocol-defined circumstances.

Wolchok et al. ASCO 2015 LBA 1

Respuesta a tratamiento

	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, months (95% CI)	NR (NR–NR)	31.1 (31.1–NR)	18.2 (8.3–NR)

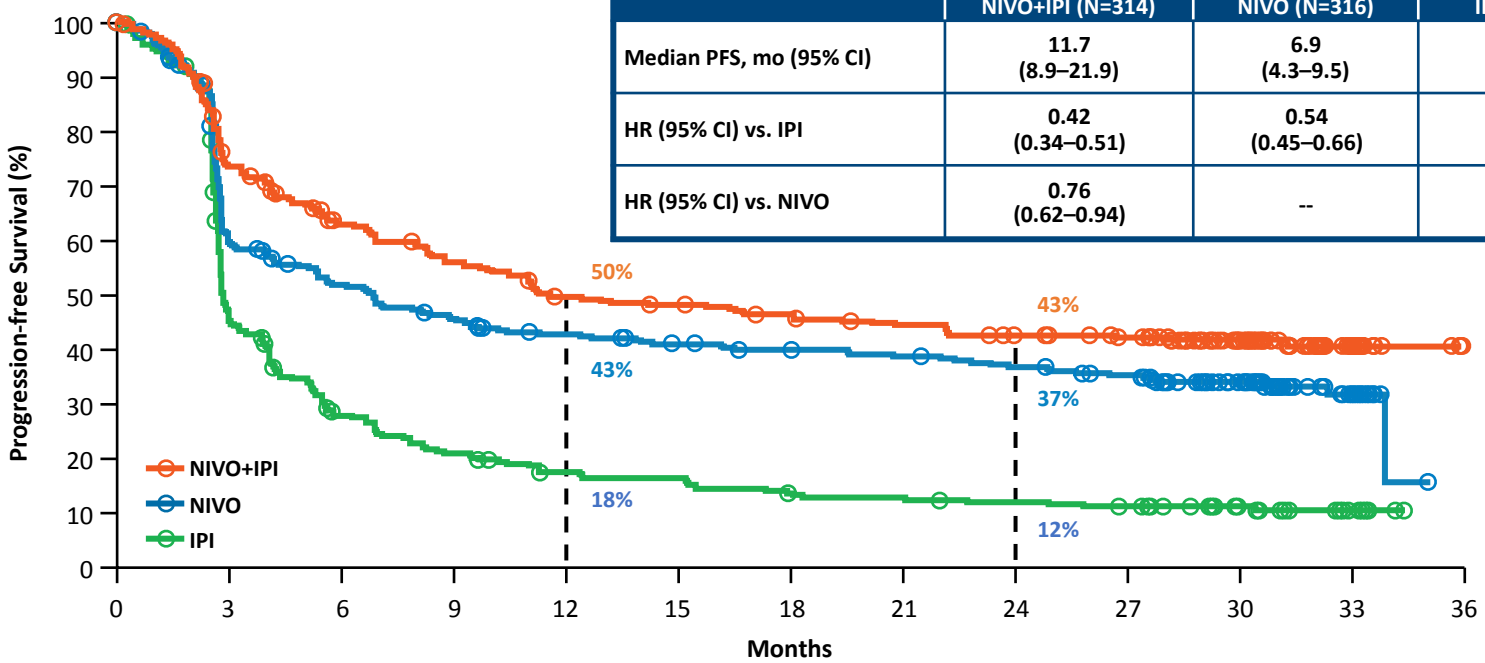
*By RECIST v1.1; NR = not reached.

- At the 18-month DBL, the CR rate for NIVO+IPI, NIVO and IPI was 12.1%, 9.8% and 2.2%, respectively

Database lock: Sept 13, 2016, minimum f/u of 28 months

Supervivencia libre de progresión

	NIVO+IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median PFS, mo (95% CI)	11.7 (8.9–21.9)	6.9 (4.3–9.5)	2.9 (2.8–3.2)
HR (95% CI) vs. IPI	0.42 (0.34–0.51)	0.54 (0.45–0.66)	--
HR (95% CI) vs. NIVO	0.76 (0.62–0.94)	--	--



Patients at risk:

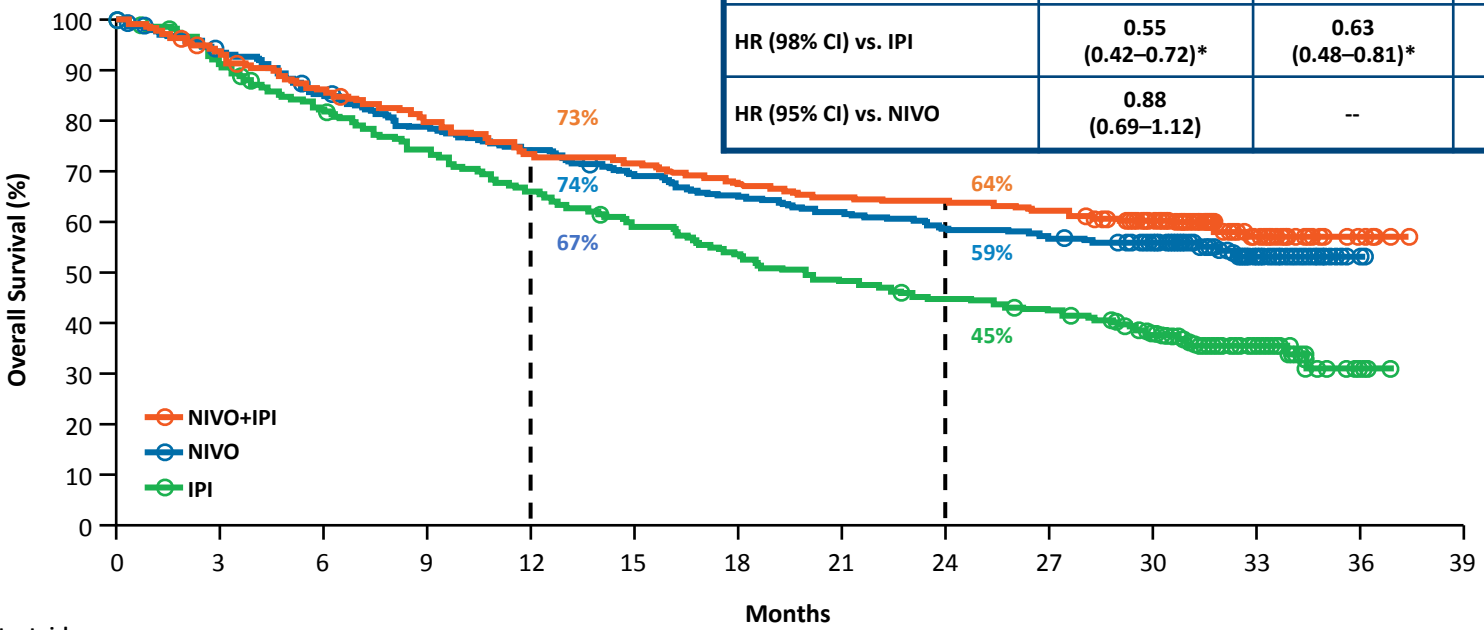
NIVO+ IPI	314	218	176	156	137	132	125	118	110	104	71	16	0
NIVO	316	178	151	132	120	112	107	103	97	88	62	16	0
IPI	315	136	77	58	46	43	35	33	30	27	16	5	0

Database lock: Sept 13, 2016, minimum f/u of 28 months

Supervivencia global

	NIVO+IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median OS, mo (95% CI)	NR	NR (29.1–NR)	20.0 (17.1–24.6)
HR (98% CI) vs. IPI	0.55 (0.42–0.72)*	0.63 (0.48–0.81)*	--
HR (95% CI) vs. NIVO	0.88 (0.69–1.12)	--	--

*P<0.0001



Patients at risk:

NIVO+IPI	314	292	265	247	226	221	209	200	198	192	170	49	7	0
NIVO	316	292	265	244	230	213	201	191	181	175	157	55	3	0
IPI	315	285	254	228	205	182	164	149	136	129	104	34	4	0

Database lock: Sept 13, 2016, minimum f/u of 28 months

Safety Summary

- With an additional 19 months of follow-up, safety was consistent with the initial report[1]

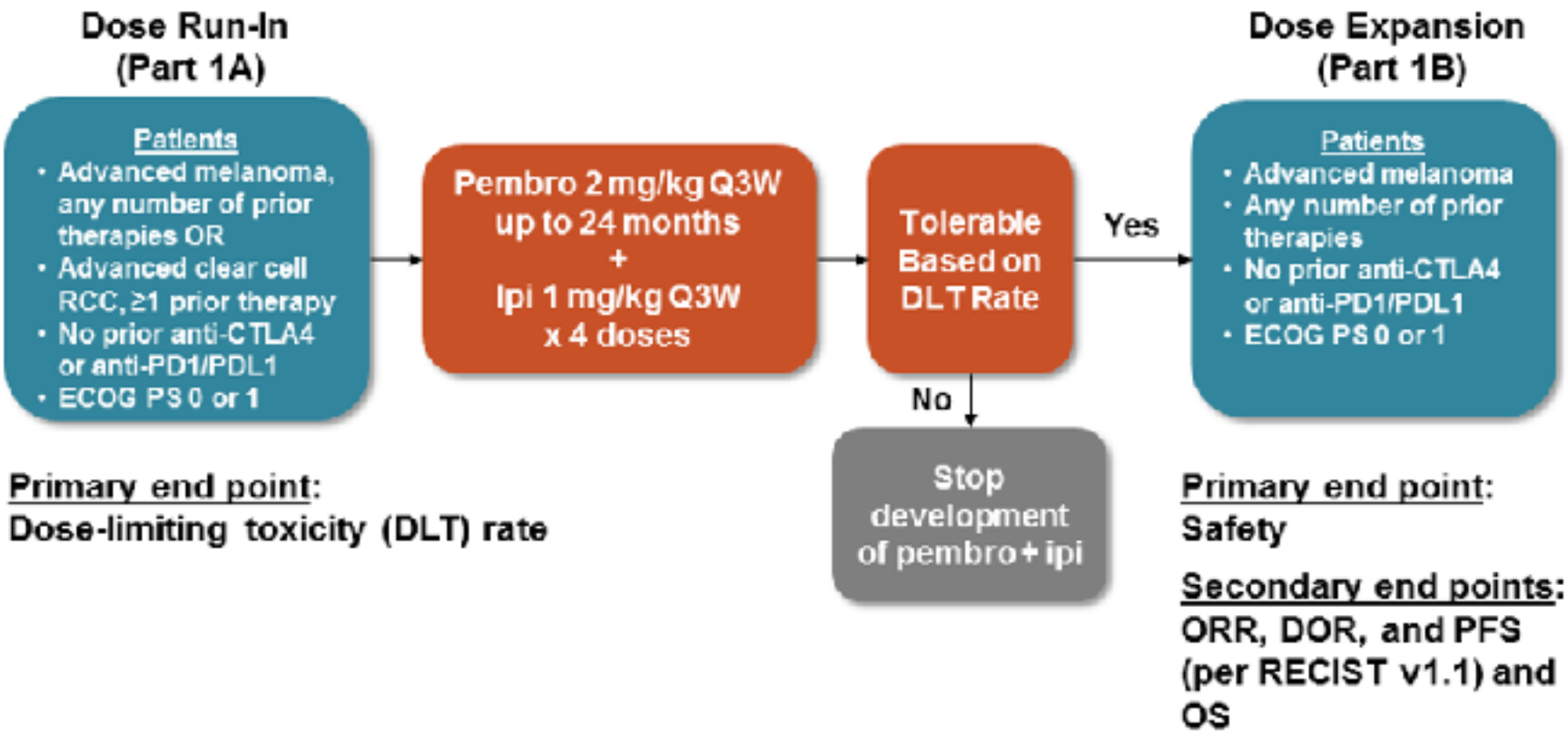
	NIVO+IPI (N=313)		NIVO (N=313)		IPI (N=311)	
Patients reporting event, %	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Treatment-related adverse event (AE)	95.8	58.5	86.3	20.8	86.2	27.7
Treatment-related AE leading to discontinuation	39.6	31.0	11.5	7.7	16.1	14.1
Treatment-related death, n (%)	2 (0.6)[a]		1 (0.3)[b]		1 (0.3)[b]	

- Most select AEs were managed and resolved within 3-4 weeks (85–100% across organ categories)
- ORR was 70.7% for pts who discontinued NIVO+IPI due to AEs, with median OS not reached

[a]Cardiomyopathy (NIVO+IPI, n=1); Liver necrosis (NIVO+IPI, n=1). Both deaths occurred >100 days after the last treatment.
[b]Neutropenia (NIVO, n=1); colon perforation (IPI, n=1).[1]

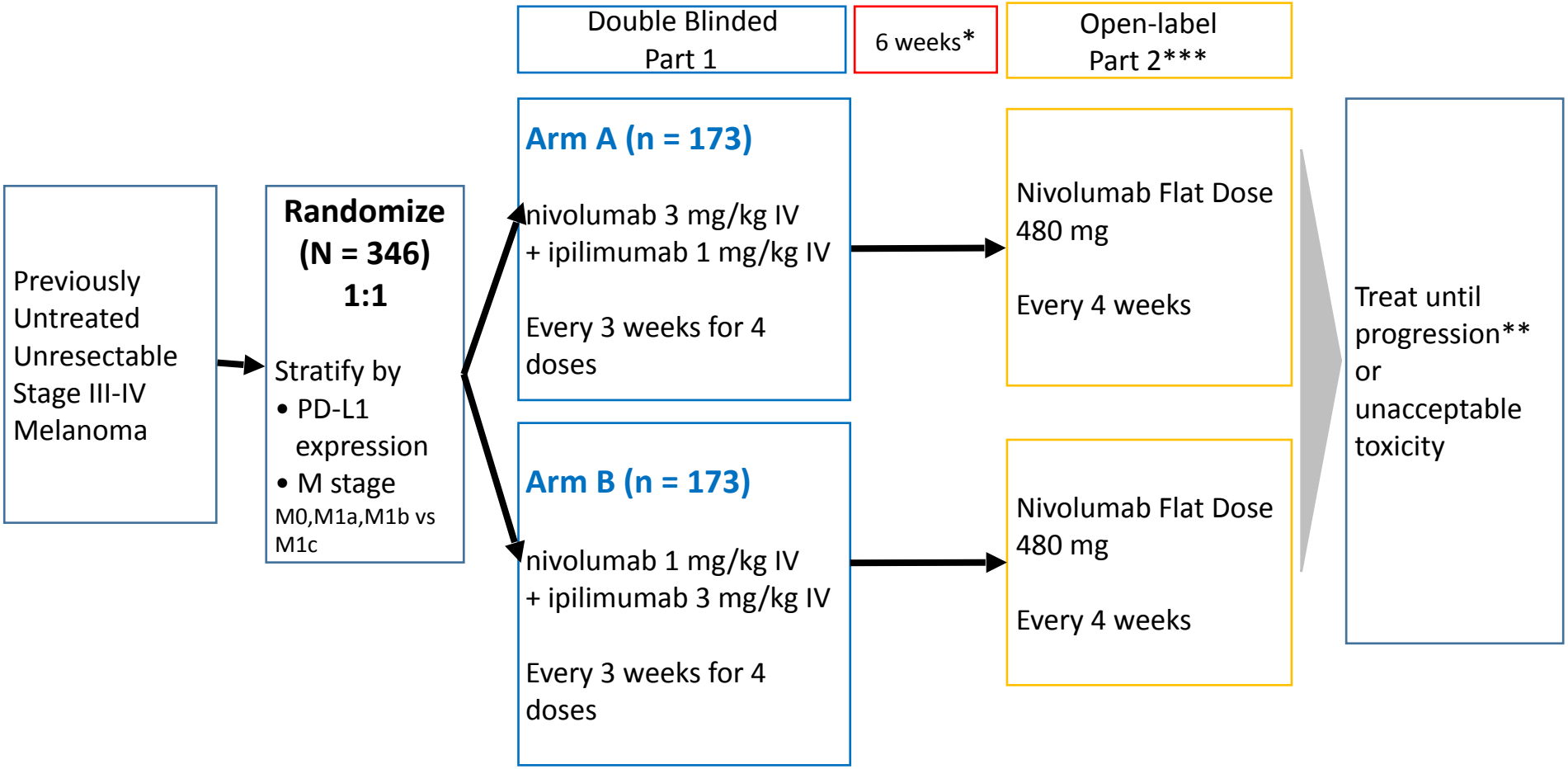
1. Larkin J, et al. *NEJM* 2015;373:23–34.

Ipilimumab + Pembrolizumab KN029



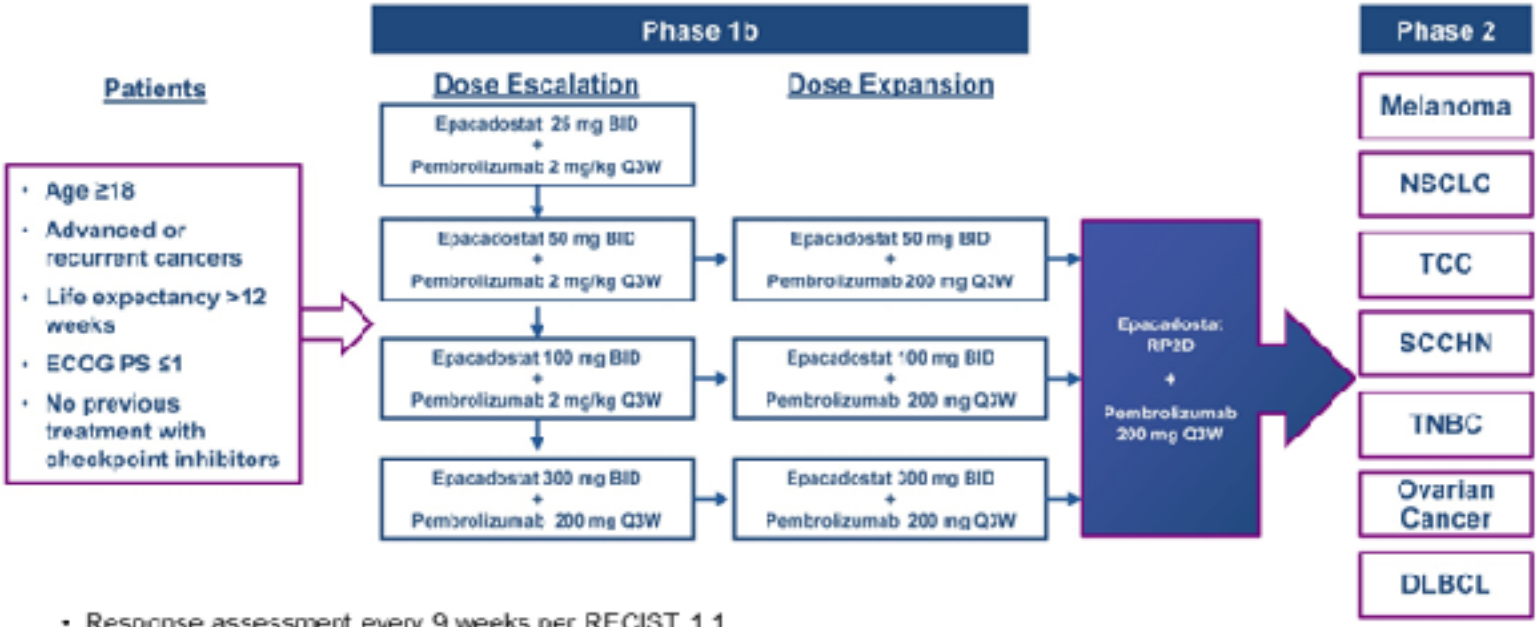
G V Long et al. SMR 2015.

Diseño estudio CA-209-511



Disponible HGU desde Mayo 2016

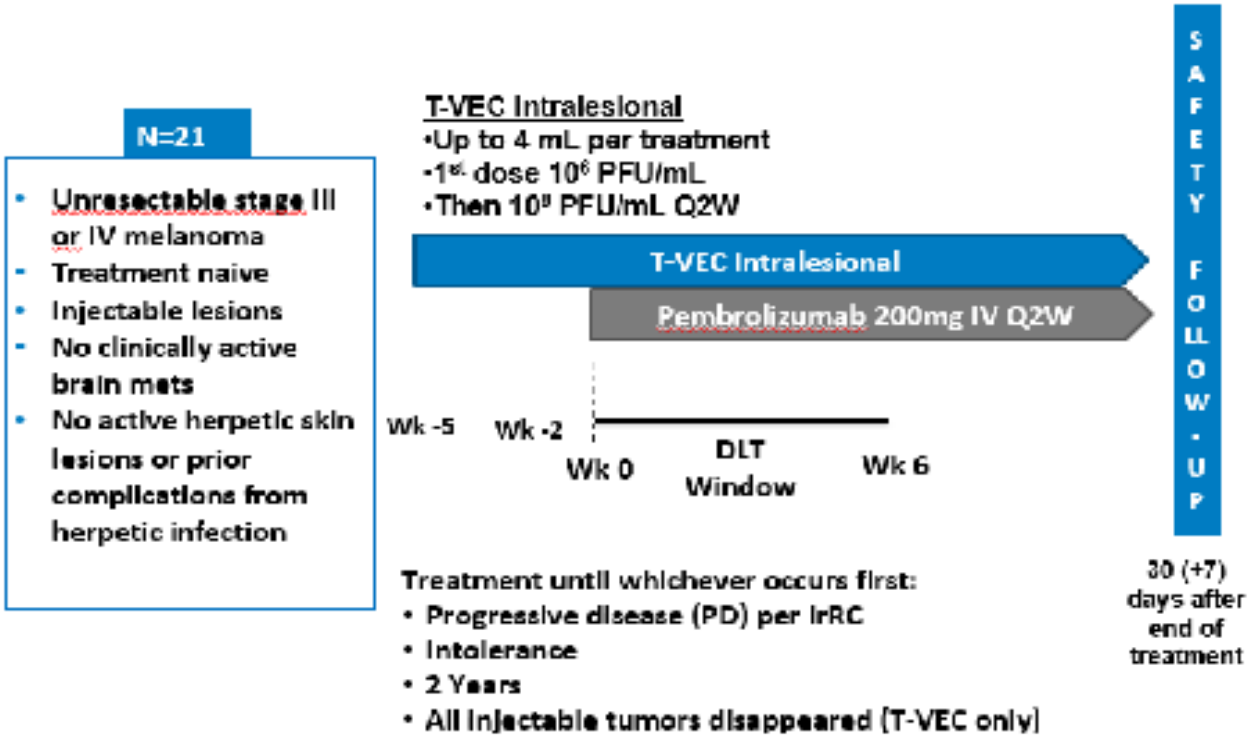
Pembrolizumab + Epacadostat



- Response assessment every 9 weeks per RECIST 1.1

SMR, O. Hamid, November 21, 2015

Pembrolizumab + T-VEC (MK 265)



GV Long SMR 2015

Conclusiones

- La inmunoterapia ha sido el primer tratamiento en modificar la historia natural y supervivencia del melanoma
- En la actualidad hay 5 fármacos de inmunoterapia autorizados es esta patología
- El futuro inmediato son las combinaciones de las que ya tenemos una aprobada (Ipilimumab mas Nivolumab)
- El la selección del tratamiento es cada vez mas compleja y debe realizarse en comités multidisciplinares
  - El farmacéutico hospitalario debería formar parte de ellos
- La actividad investigadora es muy importante en la Comunidad Valenciana ofreciendo grandes posibilidades para los pacientes