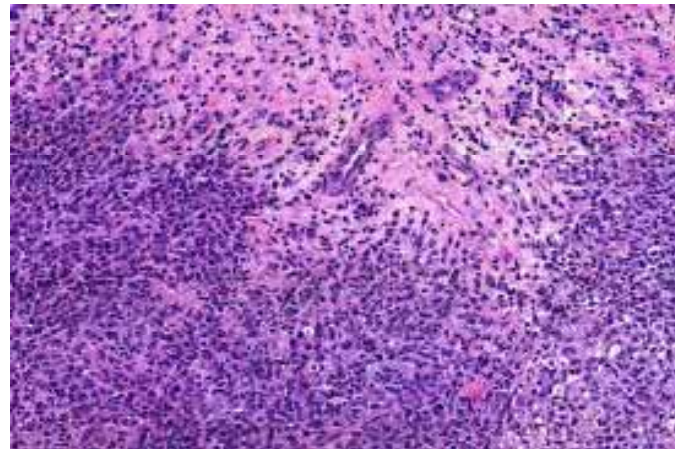


TRATAMIENTO ADYUVANTE DEL MELANOMA



Dr. Joaquín Gimeno Pelegrín
R4 Oncología Médica
HCU Lozano Blesa
Zaragoza

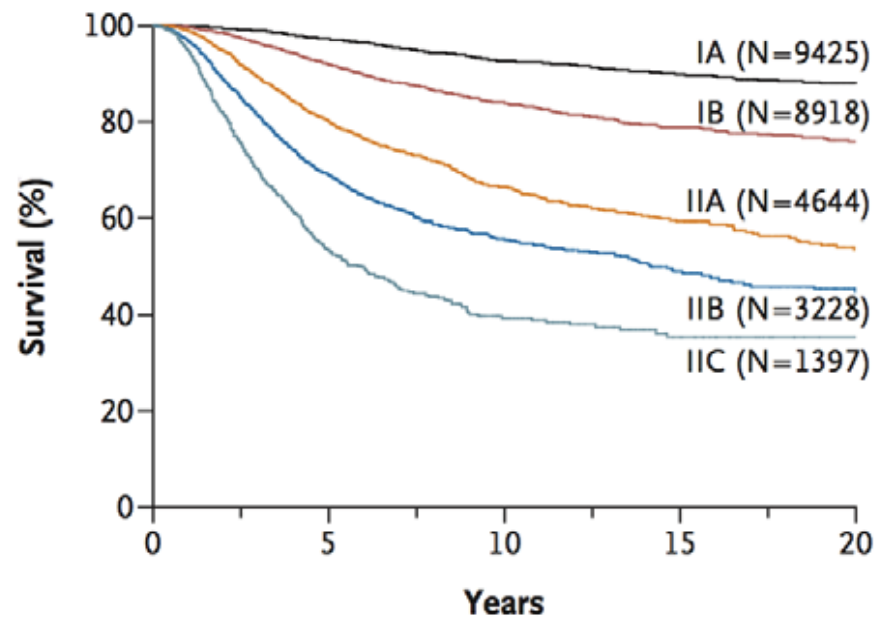
CLASIFICACION TNM

P		Tis	T1 ≤1mm		T2 1.01 - 2 mm		T3 2.01 - 4 mm		T4 > 4mm	
			a No ulcera	b Ulcerado	a No ulcera	b Ulcerado	a No ulcera	b Ulcerado	a No ulcera	b Ulcerado
MO			a No ulcera	b Ulcerado	a No ulcera	b Ulcerado	a No ulcera	b Ulcerado	a No ulcera	b Ulcerado
N0		0	IA	IB		IIA		IIB		IIC
N1 1 ad	a micro		IIIA	IIIB	IIIA	IIIB	IIIA	IIIB	IIIA	IIIB
	b macro		IIIB	IIIC	IIIB	IIIC	IIIB	IIIC	IIIB	IIIC
N2 2-3 ad	a micro		IIIA	IIIB	IIIA	IIIB	IIIA	IIIB	IIIA	IIIB
	b macro		IIIB	IIIC	IIIB	IIIC	IIIB	IIIC	IIIB	IIIC
	cin transit		IIIB	IIIC	IIIB	IIIC	IIIB	IIIC	IIIB	IIIC
N3 ≥ 4 ad			IIIC							

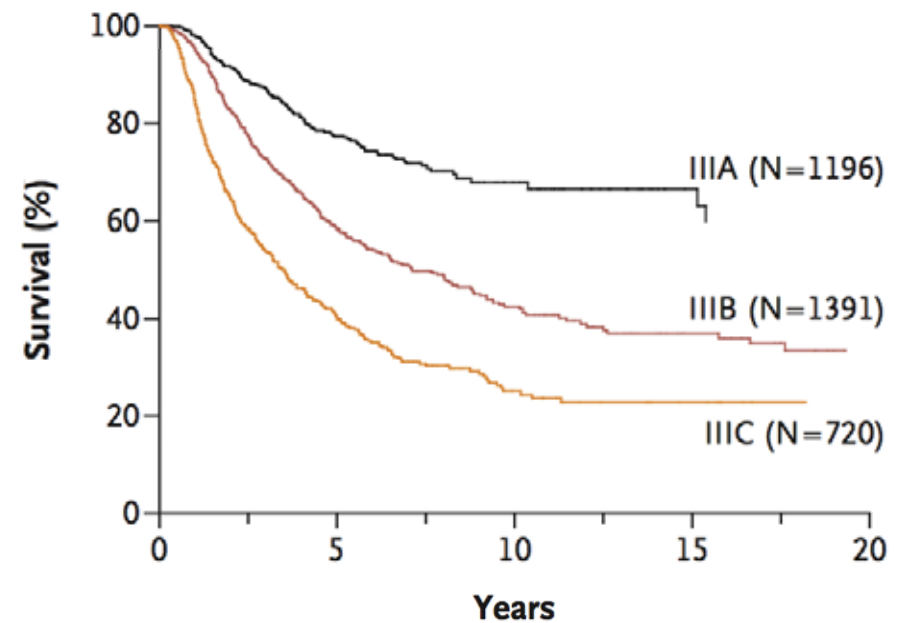
Pathological staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic stage 0 or stage IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.

MORTALIDAD POR ESTADIOS

A Stage I and Stage II Melanoma



B Stage III Melanoma



Cálculo de tasa de supervivencia



Individualized Melanoma Patient Outcome Prediction Tools

Developed based on the American Joint Committee on Cancer Melanoma Database

By Seng-jaw Soong PhD, Shouluan Ding PhD, Daniel G. Coit MD, Charles M. Balch MD, Jeffrey Gershenwald MD, John F. Thompson MD and the American Joint Committee on Cancer, Melanoma Task Force

[Disclaimer](#) [Main](#)

Patient with Regional Metastasis

Patient characteristics: Patient ID: No patient ID supplied.

Clinical

Age:

Lesion Site:

Pathological

Tumor Burden:

Number of Nodes:

Ulceration:

Tumor Thickness (mm):

Estimated Survival Rates (95% Confidence Interval)

1-Year	2-Year	5-Year	10-Year
75.7%	58.7%	36.9%	25.4%
(68.2% - 84%)	(49.2% - 69.9%)	(27.5% - 49.5%)	(16.4% - 39.4%)

<http://www.melanomaprognosis.org>



Una iniciativa de la SEOM para Residentes y Adjuntos Jóvenes

CLASIFICACION TNM

P		Tis	T1 ≤1mm		T2 1.01 - 2 mm		T3 2.01 - 4 mm		T4 > 4mm	
			a No ulcera	b Ulcerado	a No ulcera	b Ulcerado	a No ulcera	b Ulcerado	a No ulcera	b Ulcerado
MO			a No ulcera	b Ulcerado	a No ulcera	b Ulcerado	a No ulcera	b Ulcerado	a No ulcera	b Ulcerado
N0		0	IA	IB		IIA		IIB		IIC
N1 1 ad	a micro		IIIA	IIIB	IIIA	IIIB	IIIA	IIIB	IIIA	IIIB
	b macro		IIIB	IIIC	IIIB	IIIC	IIIB	IIIC	IIIB	IIIC
N2 2-3 ad	a micro		IIIA	IIIB	IIIA	IIIB	IIIA	IIIB	IIIA	IIIB
	b macro		IIIB	IIIC	IIIB	IIIC	IIIB	IIIC	IIIB	IIIC
	cin transit		IIIB	IIIC	IIIB	IIIC	IIIB	IIIC	IIIB	IIIC
N3 ≥ 4 ad		IIIC								

Pathological staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic stage 0 or stage IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.

TRATAMIENTO ADYUVANTE

- ▶ Los pacientes en los estadios IIB, IIC y III tienen un elevado riesgo de recaída, que se estima desde un 30 a un 80%.
- ▶ Es en estos estadios (estadios de alto riesgo) en los que se han centrado la realización de ensayos clínicos aleatorizados de tratamientos adyuvantes.
- ▶ De todos los fármacos investigados (dacarbacina, vacuna BCG, levamisol, megestrol...) el interferón alfa-2b ha demostrado a través de ensayos aleatorizados tener una eficacia en el tratamiento adyuvante del melanoma maligno de alto riesgo.

INTERFERON I (IFN)

- ▶ Interferón clase I, se produce en células dendríticas plasmocitoides en respuesta a infecciones u otros estímulos.
- ▶ Efecto antitumoral.
 - suprime la proliferación celular.
 - estimula la actividad antifagocitaria de los macrófagos.
 - Aumenta la actividad citotóxica específica de linfocitos.
 - Efecto apoptótico ⁽¹⁾.
 - Efecto antiangiogénico ⁽¹⁾.

⁽¹⁾ Davar. Journal of Skin Cancer. 2011

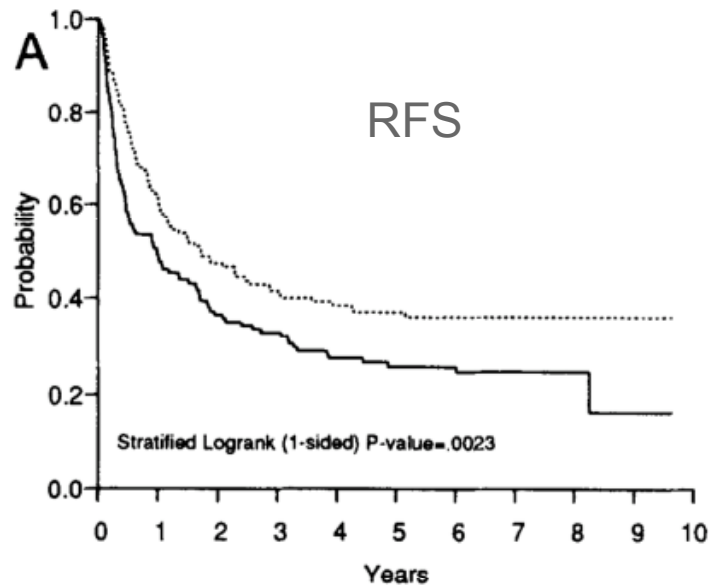
INTERFERON ALFA- 2b (IFNa-2b)

- ▶ IFNa altas dosis: > 10 MU/dosis.
- ▶ IFNa dosis intermedias: 5-10 MU/dosis.
- ▶ IFNa bajas dosis: <3 MU/dosis.

IFNa ALTAS DOSIS. ECOG 1684

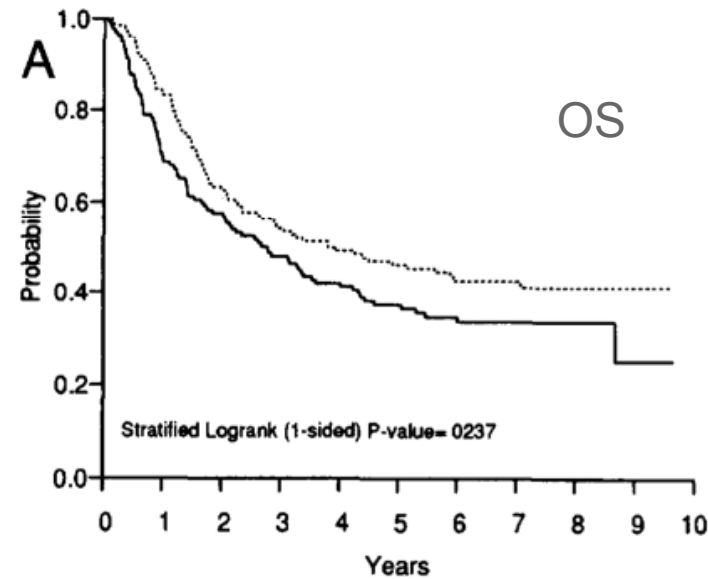
► Esquema de tratamiento:

- Inducción: IFNa-2b 20MU/m² iv 5 días a la semana x 4 semanas.
- Mantenimiento: IFNa-2b 10MU/m² sc 3 días a la semana x 48 sem.



Group	Time Interval				
	0-2	2-4	4-6	6-8	8-10
— OBS	87/137	12/49	2/37	1/23	1/4
..... IFN	75/143	12/66	3/52	0/35	0/14

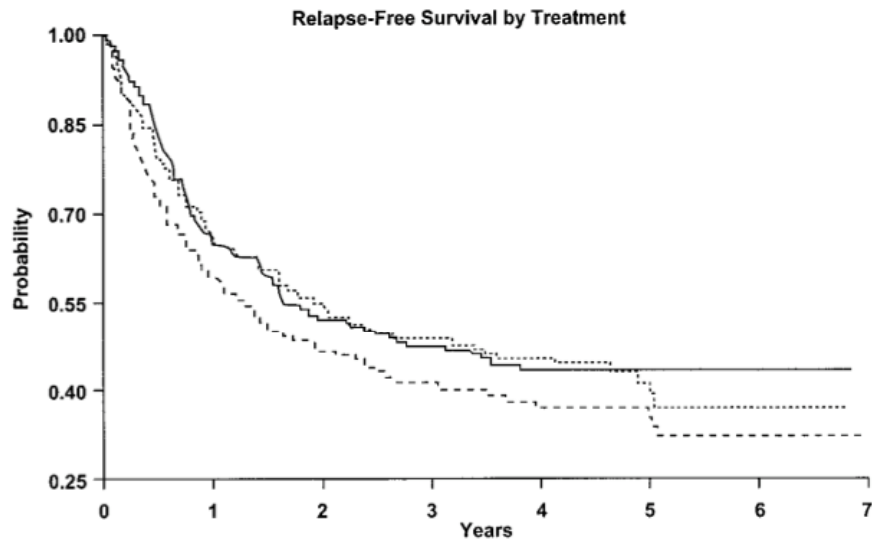
(# events/# at risk)



Group	Time Interval				
	0-2	2-4	4-6	6-8	8-10
— OBS	58/137	21/78	9/56	1/33	1/7
..... IFN	53/143	19/89	8/69	1/44	0/17

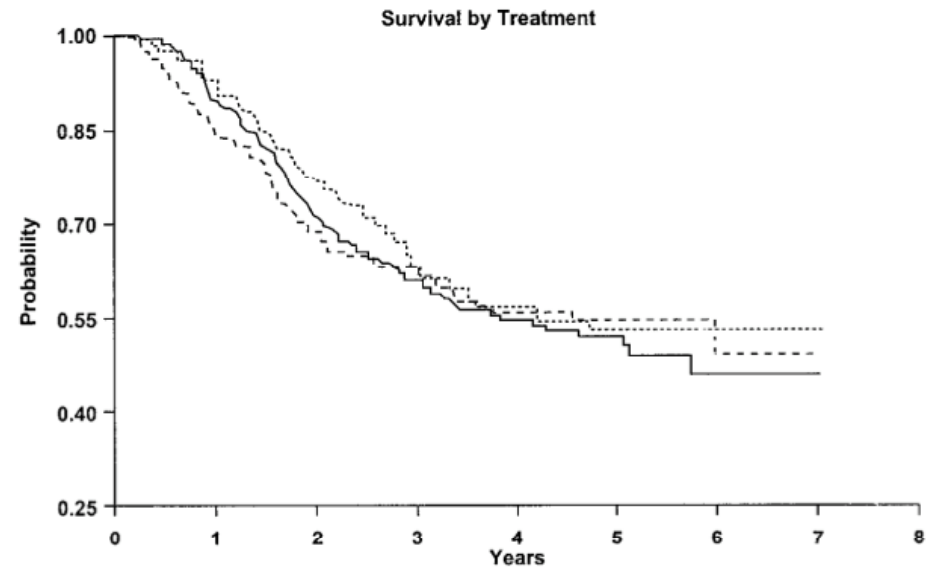
(# events/# at risk)

IFNa ALTAS DOSIS. INTERGROUP E1690/S911/C9190



Group	Time interval						
	0-1	1-2	2-3	3-4	4-5	5-6	6-7
— HDI	70/203	24/127	9/100	6/77	0/53	0/28	0/9
..... LDI	69/203	22/132	12/110	5/86	3/56	2/21	0/5
- - - - - Obs	78/202	24/112	10/87	6/71	1/45	2/22	0/3

(# events/# at risk)



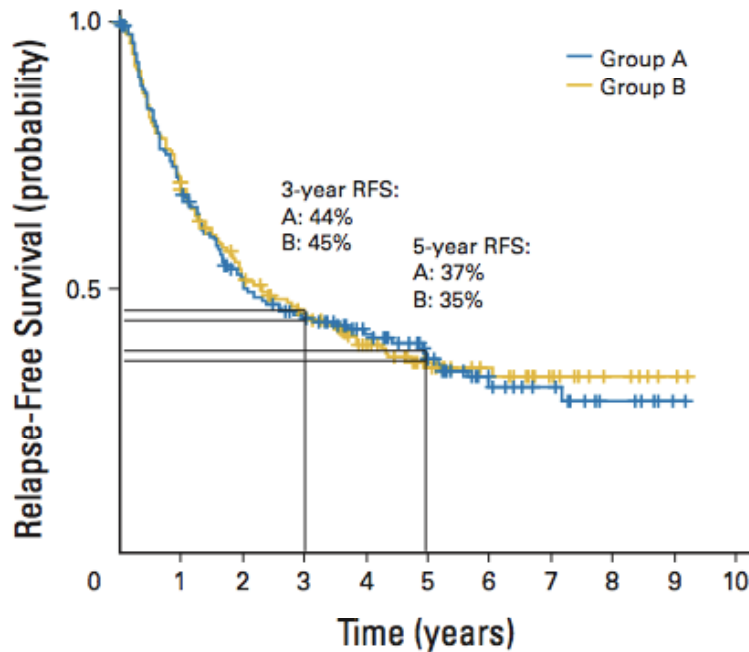
Group	Time interval							
	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8
— HDI	21/203	37/182	20/143	10/109	3/71	3/36	0/11	0/1
..... LDI	15/203	32/188	26/155	11/118	4/77	0/30	0/9	0/1
- - - - - Obs	31/202	31/170	12/137	11/115	1/75	1/37	0/8	0/0

(# events/# at risk)

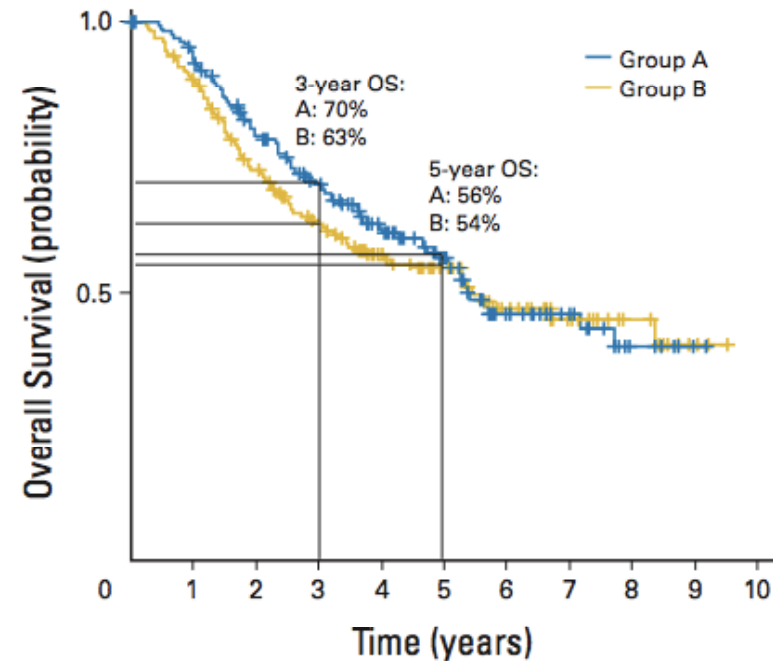
IFNa ALTAS DOSIS. ESTUDIO HeCOG

► Esquema de tratamiento:

- Inducción: IFNa-2b 15MU/m² iv 5 días a la semana x 4 semanas.
- Mantenimiento: IFNa-2b 10MU sc 3 días a la semana x 48 sem.



No. at risk	0	1	2	3	4	5	6	7	8	9	10
Induction only	177	117	82	67	50	35	18	11	6	1	
Induction plus maintenance	176	113	82	48	48	33	24	13	7	2	



No. at risk	0	1	2	3	4	5	6	7	8	9	10
Induction only	177	157	126	102	77	57	35	16	12	12	
Induction plus maintenance	176	147	115	90	67	51	32	19	11	4	

Pectasides D, Dafni U, Bafaloukos D, Skarlos D, Polyzos A, Tsoutsos D, et al. Randomized Phase III Study of 1 Month Versus 1 Year of Adjuvant High-Dose Interferon Alfa-2b in Patients With Resected High-Risk Melanoma. J. Clin. Oncol. 2009 Feb. 18;27(6):939-44.

IFNa ALTAS DOSIS. INTERGROUP TRIAL E1697

ASCO Home ▶ Meetings ▶ Abstracts ▶ 2011 ASCO Annual Meeting

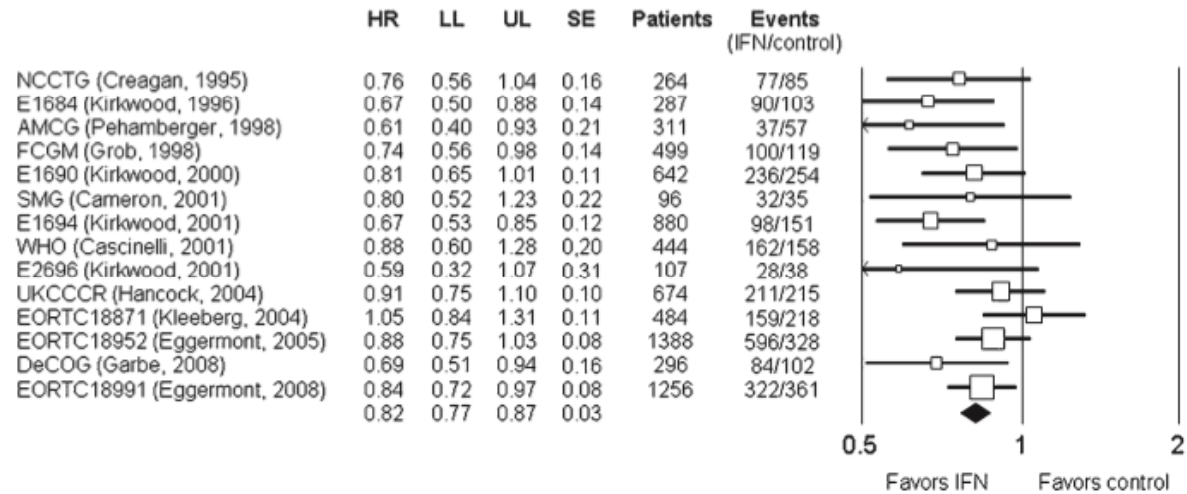
Randomized phase III trial of high-dose interferon alfa-2b (HDI) for 4 weeks induction only in patients with intermediate- and high-risk melanoma (Intergroup trial E 1697) .

year survival rate was 23.1% (95% CI, 16.1-30.1; n=553). Accrual to the trial has therefore been terminated.

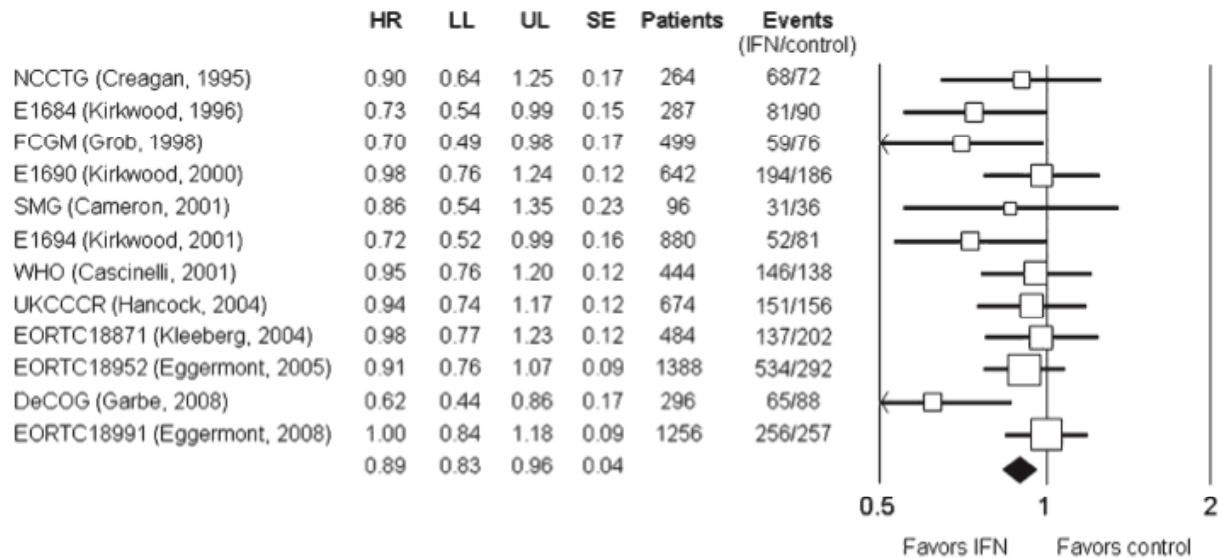
Conclusions: Adjuvant HDI induction with only 4 weeks therapy neither improved RFS nor OS over observation for pts with intermediate and high-risk melanoma. This trial supports the importance of HDI treatment duration and argues that the approved 1 year Interferon regimen of induction followed by maintenance remains the standard of care for pts with T4N0 or node positive disease.

IFNa METAANALISIS

RFS



OS



IFNa Análisis Combinado

A Pooled Analysis of Eastern Cooperative Oncology Group and Intergroup Trials of Adjuvant High-Dose Interferon for Melanoma

John M. Kirkwood, Judith Manola, Joseph Ibrahim, et al.

Clin Cancer Res 2004;10:1670-1677. Published online March 10, 2004.

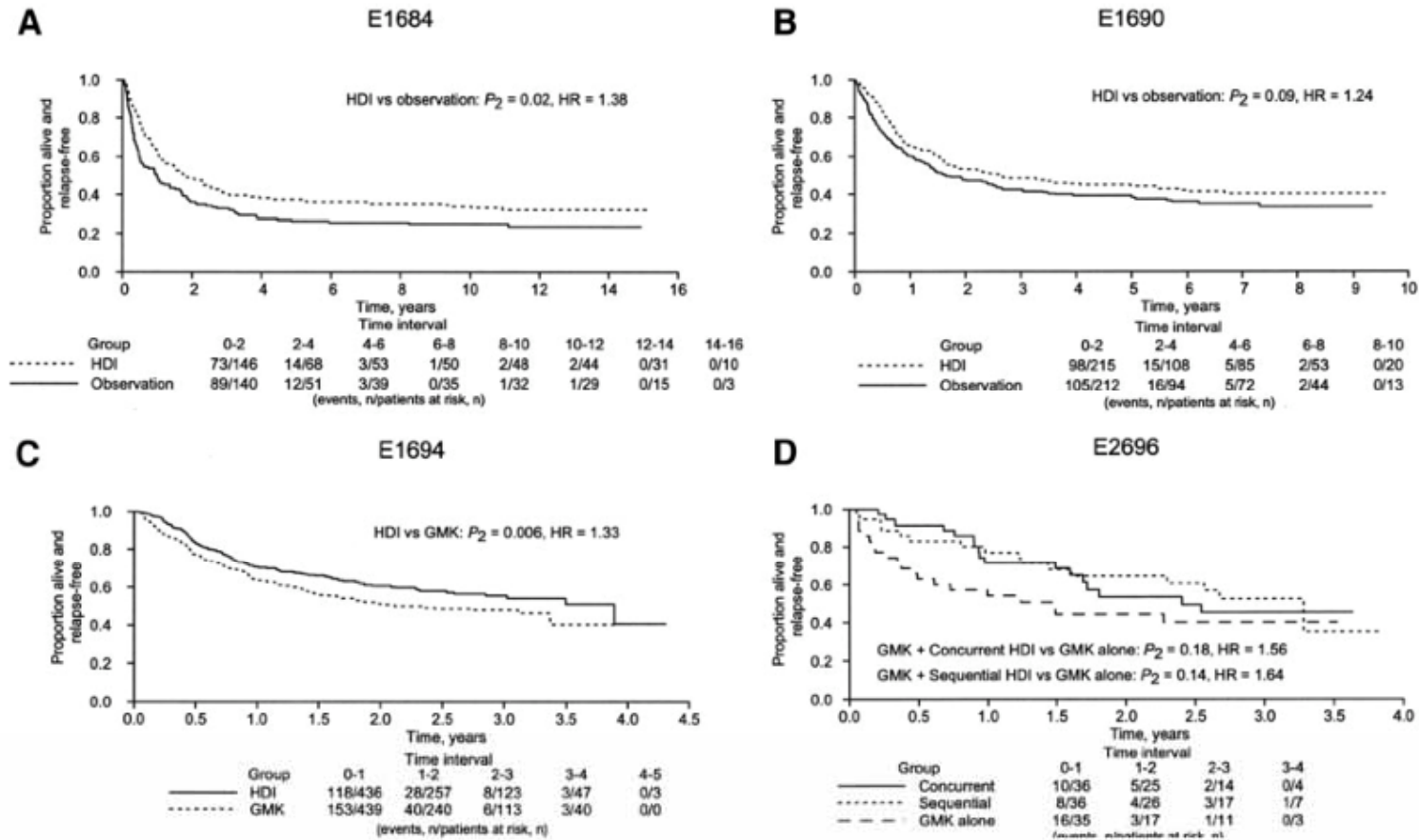


Fig. 1 Kaplan-Meier estimates of relapse-free survival for patients treated on (A) E1684 at median follow-up of 12.6 years, (B) E1690 at a median follow-up of 6.6 years, (C) E1694 at a median follow-up of 2.1 years, and (D) E2696 at a median follow-up of 2.8 years. HDI, high-dose IFN- α 2b; HR, hazard ratio; GMK, GM2/keyhole limpet hemocyanin.

IFNa Análisis Combinado

A Pooled Analysis of Eastern Cooperative Oncology Group and Intergroup Trials of Adjuvant High-Dose Interferon for Melanoma

John M. Kirkwood, Judith Manola, Joseph Ibrahim, et al.

Clin Cancer Res 2004;10:1670-1677. Published online March 10, 2004.

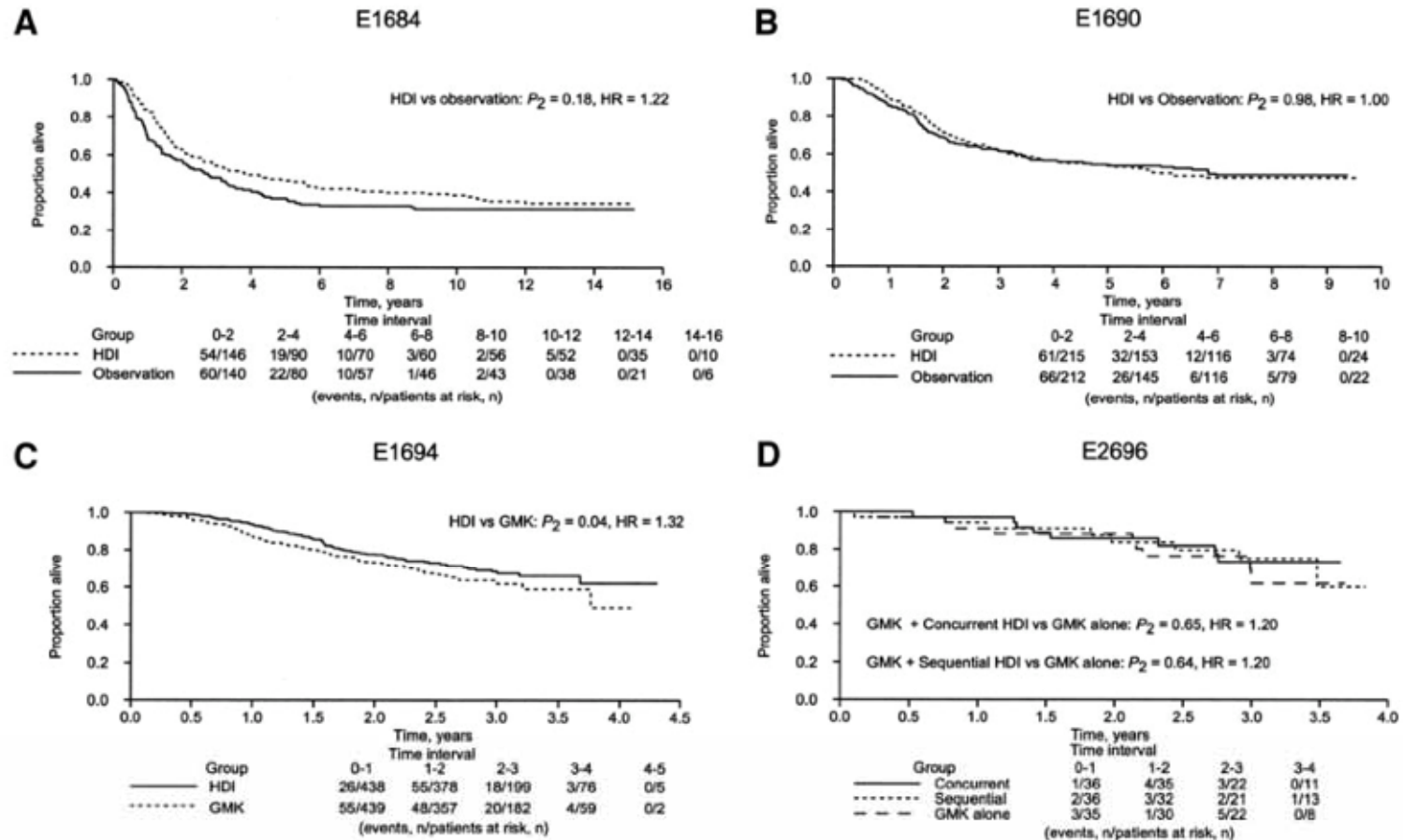


Fig. 2 Kaplan-Meier estimate of overall survival for patients treated on (A) E1684 at median follow-up of 12.6 years, (B) E1690 at a median follow-up of 6.6 years, (C) E1694 at a median follow-up of 2.1 years, and (D) E2696 at a median follow-up of 2.8 years. HDI, high-dose IFN- α 2b; R, hazard ratio; GMK, GM2/keyhole limpet hemocyanin.

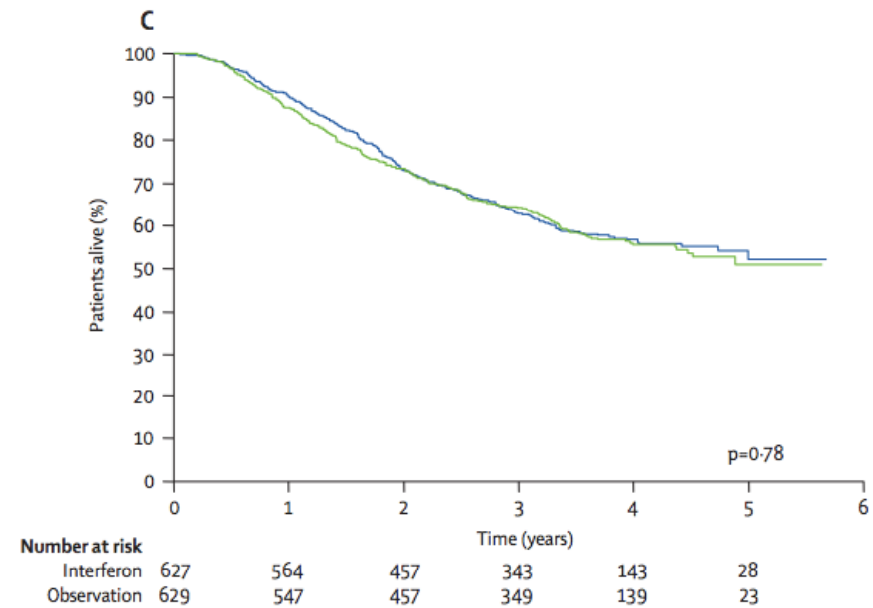
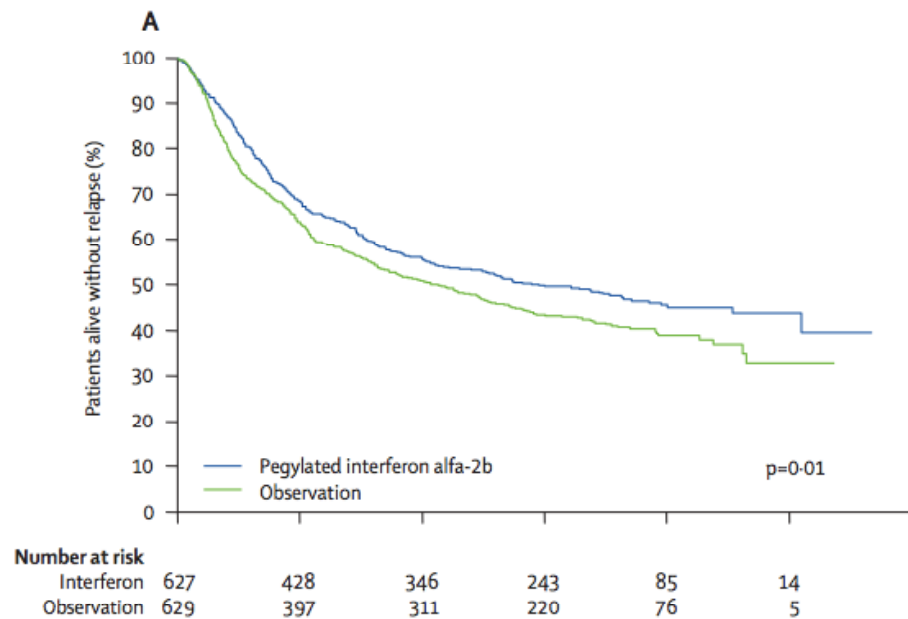
IFNa DOSIS INTERMEDIAS Y BAJAS

									Intermediate dose	
EORTC 18952 [31]	1388	II-III (T4N0M0/TanyN + M0)	IFN- α 2b for 1 yr versus 2 yrs versus observation	IV 10 MU 5 days a week for 4 weeks → then → SC 10 MU 3 days a week for 1 year OR SC 5 MU 3 days a week for 2 years	1.6	7.2% (NS)	5.4% (NS)	74		
EORTC 18991 [91]	1256	III (TanyN + M0)	PEG IFN- α 2b versus observation	SC 6 μ g/kg/week for 8 weeks → then → SC 3 μ g/kg/week for 5 years	3.8	45.6% versus 38.9% (NS)	NS	100		
									Low dose	
Austrian melanoma cooperative group (AMCG) [92]	311	II (T2-4N0M0)	IFN- α 2a versus observation	SC 3 MU 7 days a week for 3 weeks → then → SC 3 MU 3 days a week for 1 year	3.4	S	Not available	0		
French melanoma cooperative group (FCGM) [93]	499	II (T2-4N0M0)	IFN- α 2a versus observation	SC 3 MU 3 days a week for 18 months	>3	0.74 (HR), S	0.70 (HR), S	0		

INTERFERON PEGILADO. EORTC 18991

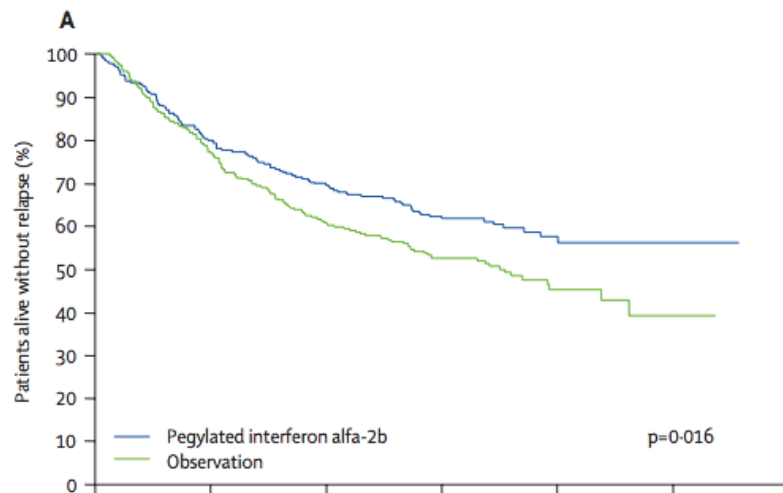
► Esquema de tratamiento:

- Inducción: IFNa-2b pegilado 6 µg/kg a week subcutaneously for 8 weeks.
- Mantenimiento: IFNa-2b pegilado 3 µg/kg per week subcutaneously for 5 years.

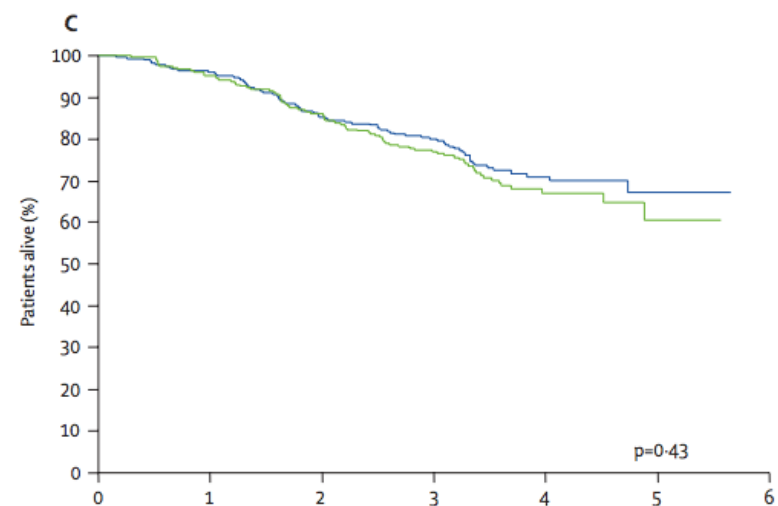


INTERFERON PEGILADO

Relapse-Free Survival (A) and Overall Survival (C) in stage III-N1 (microscopic nodal involent only) patients



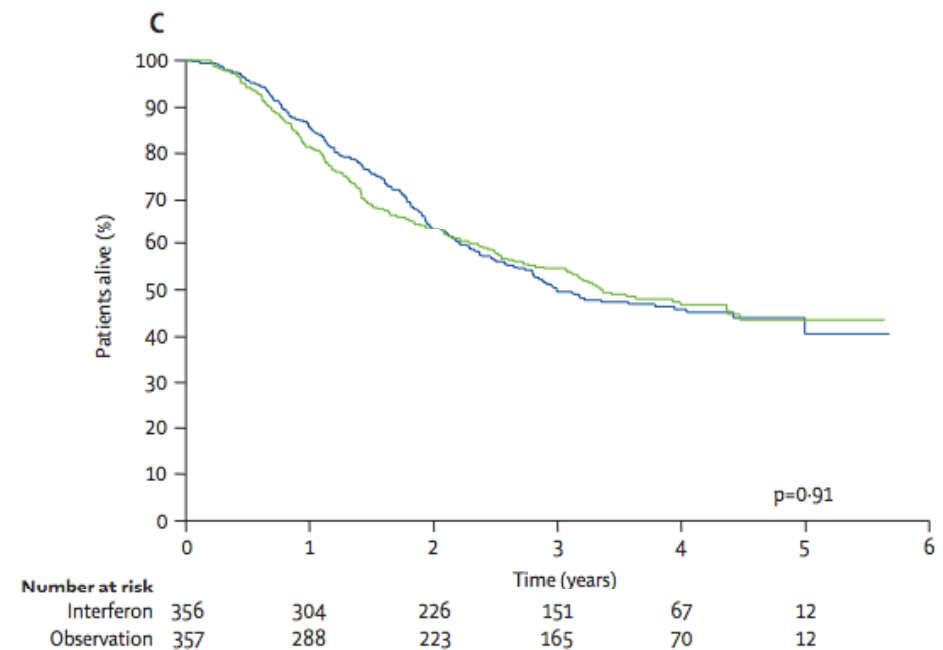
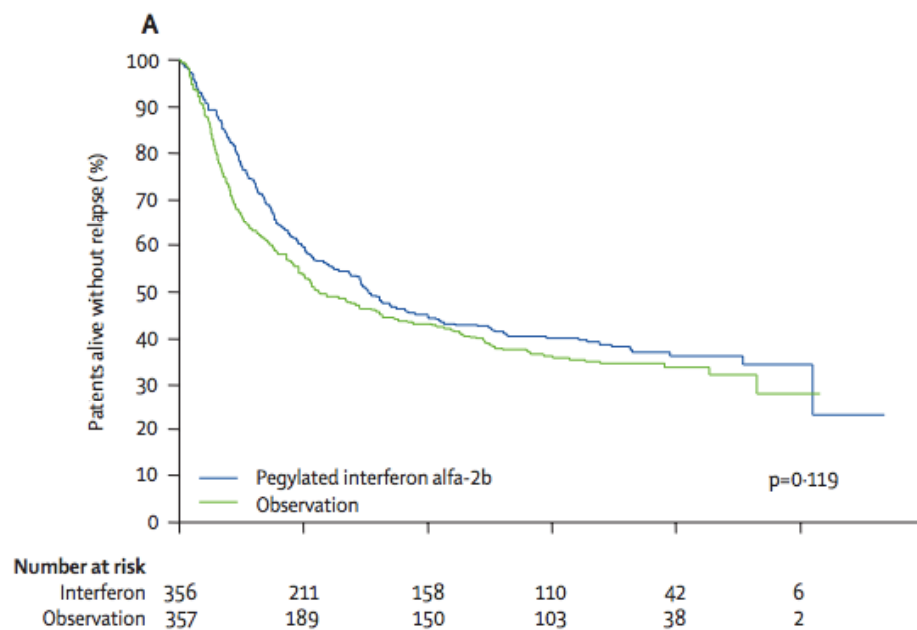
Number at risk						
Interferon	271	217	188	133	43	8
Observation	272	208	161	117	38	3



Number at risk						
Interferon	271	260	231	192	76	16
Observation	272	259	234	184	69	11

INTERFERON PEGILADO

Relapse-Free Survival (A) and Overall Survival (C) in stage III-N2 (palpable nodal involent) patients



IFNa-2b

TOXICIDAD

efecto secundario	% Grado 3-4	Comienzo	Comentario
Cansancio	21-24	Agudo y crónico	Descartar hipotiroidismo. Puede requerir ↓dosis
Leucopenia, anemia y trombopenia	26-60	Crónica > aguda	↓dosis si G3
Elevación enz hepáticas	14-29	Crónica > aguda	Potencialmente mortal. Requiere ↓dosis hasta recuperacion. Suspensión definitiva si G4.
Sdr. pseudogripal	18%	Aguda	Hidratación.
Nauseas y vómitos	5%	Aguda	Metoclopramida o similar.
Depresión.	2-10%	Crónica.	Antidepresivos.
Hipotiroidismo.	<5%	Crónica.	Levotiroxina.

IFNa-2b pegilado

TOXICIDAD

	Interferon group (N=608)			Observation group (N=613)		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Any	605 (99%)	246 (40%)	32 (5%)	484 (79%)	60 (10%)	14 (2%)
Fatigue	574 (94%)	89 (15%)	8 (1%)	252 (41%)	7 (1%)	0
Liver function test*	479 (79%)	64 (10%)	2 (<1%)	221 (36%)	8 (1%)	2 (<1%)
Pyrexia	454 (75%)	24 (4%)	1 (<1%)	53 (9%)	0	0
Headache	425 (70%)	24 (4%)	0	118 (19%)	4 (1%)	0
Myalgia	408 (67%)	22 (4%)	1 (<1%)	140 (23%)	3 (<1%)	0
Depression	360 (59%)	38 (6%)	1 (<1%)	153 (25%)	2 (<1%)	1 (<1%)

*Alanine and aspartate aminotransferases/bilirubin/alkaline phosphatase.

Table 5: Adverse events occurring in 4% or more of patients (grade 3 and 4)

RADIOTERAPIA ADYUVANTE

- ▶ Adenopatías múltiples.
- ▶ Adenopatías de gran tamaño.
- ▶ Desbordamiento capsular con afectación del tejido circundante.

RADIOTERAPIA ADYUVANTE

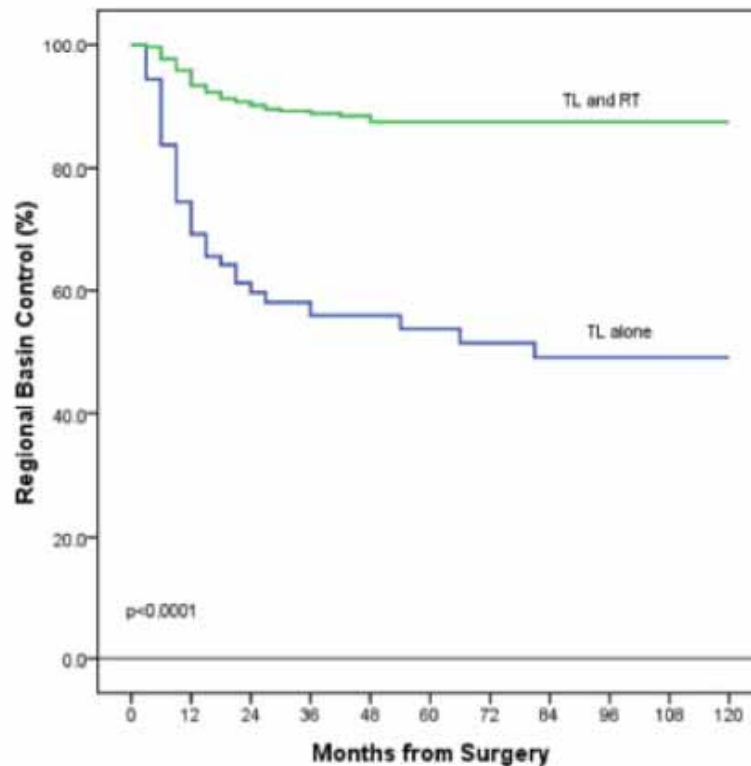


FIGURE 1. This chart illustrates regional lymph node basin control in patients with clinically advanced lymph node-metastatic melanoma who underwent therapeutic lymphadenectomy (TL) based on the presence or absence of adjuvant radiation therapy (RT).

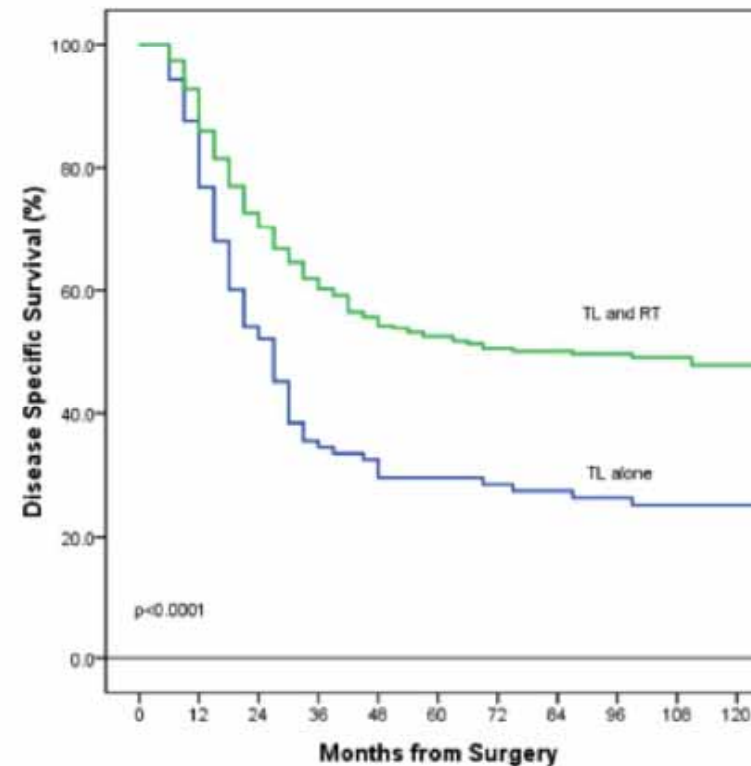


FIGURE 2. This chart illustrates disease-specific survival for patients with clinically advanced lymph node-metastatic melanoma who underwent therapeutic lymphadenectomy (TL) based on the presence or absence of adjuvant radiation therapy (RT).

TRATAMIENTO ADYUVANTE DEL MELANOMA

▶ Entonces.....¿Qué hacemos



GUIAS CLÍNICAS:

clinical practice guidelines

Annals of Oncology 21 (Supplement 5): v194–v197, 2010
doi:10.1093/annonc/mdq188

Melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

R. Dummer¹, A. Hauschild², M. Guggenheim³, L. Jost⁴ & G. Pentheroudakis⁵
On behalf of the ESMO Guidelines Working Group*

Adjuvant treatment in patients with resected macroscopic node involvement is preferentially applied in the context of randomized clinical trials in specialized centres. However, high-dose interferon $\alpha 2b$ is an approved indication for this therapeutic situation.

Adjuvant chemotherapies, mistletoe (*Viscum album*) extracts.



Una iniciativa de la SEOM para
Residentes y Adjuntos Jóvenes

GUIAS CLÍNICAS



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 3.2012 Melanoma

P		Tis	T1 ≤1mm		T2 1.01 - 2 mm		T3 2.01 - 4 mm		T4 > 4mm	
			a No ulcera	b Ulcerado	a No ulcera	b Ulcerado	a No ulcera	b Ulcerado	a No ulcera	b Ulcerado
MO			a No ulcera	b Ulcerado	a No ulcera	b Ulcerado	a No ulcera	b Ulcerado	a No ulcera	b Ulcerado
N0		0	IA	IB		IIA		IIB		IIC
N1 1 ad	a micro		IIIA	IIIB	IIIA	IIIB	IIIA	IIIB	IIIA	IIIB
	b macro		IIIB	IIIC	IIIB	IIIC	IIIB	IIIC	IIIB	IIIC
N2 2-3 ad	a micro		IIIA	IIIB	IIIA	IIIB	IIIA	IIIB	IIIA	IIIB
	b macro		IIIB	IIIC	IIIB	IIIC	IIIB	IIIC	IIIB	IIIC
	c in transit		IIIB	IIIC	IIIB	IIIC	IIIB	IIIC	IIIB	IIIC
N3 ≥ 4 ad			IIIC							

→ If Stage IIB, IIC:
Clinical trial
or
Observation
or
Interferon alfa¹
(category 2B)

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NCCN Guidelines Version 3.2012 Melanoma

ESTADIO III
Ganglio centinela positivo



Clinical trial
or
Observation
or
Interferon alfa^{1,0} (category 2B)

ESTADIO III
Adenopatías clínicas



Clinical trial
or
Observation
or
Interferon alfa^{1,0} (category 2B)
and/or
Consider RTP to nodal basin if
Stage IIIC with multiple nodes
involved or macroscopic
extranodal extension

GUIAS CLÍNICAS



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NCCN Guidelines Version 3.2012 Melanoma

ESTADIO III
en tránsito



→
**Clinical trial
or
Observation
or
Interferon alfa¹
(category 2B)**

CONCLUSION

- ▶ El IFNa-2b se mantiene como el único tratamiento activo en la adyuvancia en pacientes tratados quirúrgicamente de melanoma maligno con alto riesgo de recaída.(2B)
- ▶ La decisión de tratamiento debe ser individualizada, considerando el riesgo de recaída, presencia de comorbilidades y el deseo del paciente de una terapia agresiva o la aversión a toxicidades.

Y en el futuro...

- ▶ Ipilimumab
 - EORTC 18071 (Ipilimumab Vs Placebo; Stage III)
 - ECOG 1609 (Ipilimumab Vs HDI; Stage III)
- ▶ MAGE-A3.

¡Muchas gracias por vuestra atención!