II CURSO
DE RESIDENTES
DE SAOM

13 y 14 DE ABRIL 2018
GRANADA

Organizado por:

Sociedad Andaluza de Oncología Medica

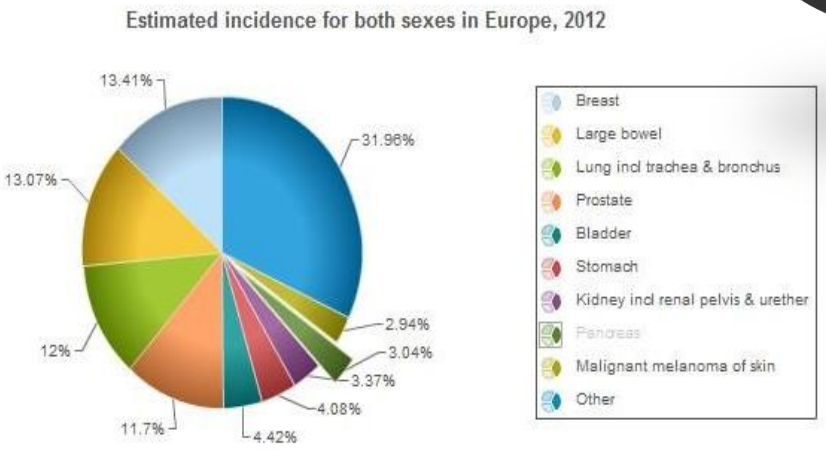
¿Es útil la Adyuvancia del Melanoma Maligno?

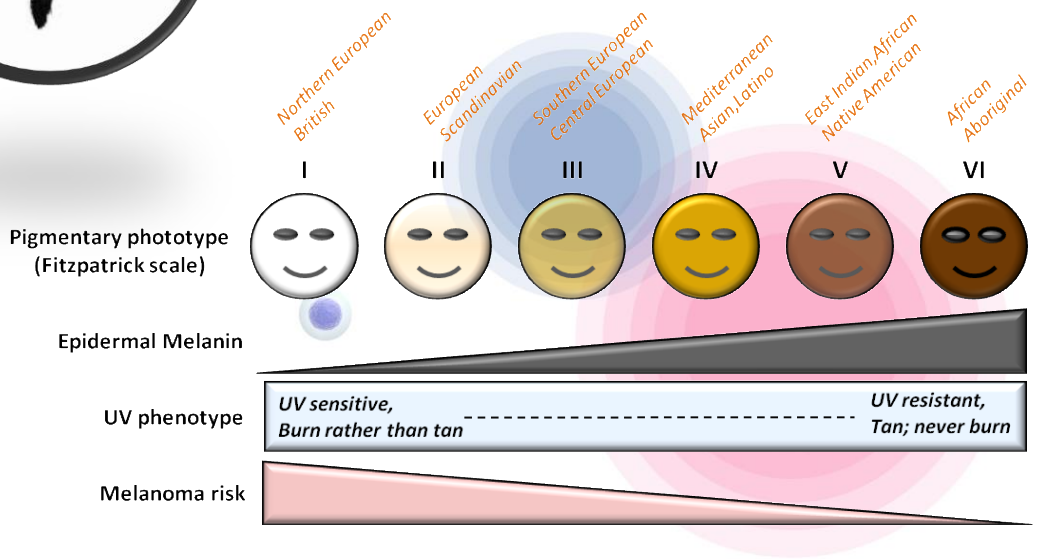
Ana Godoy Ortiz , R4

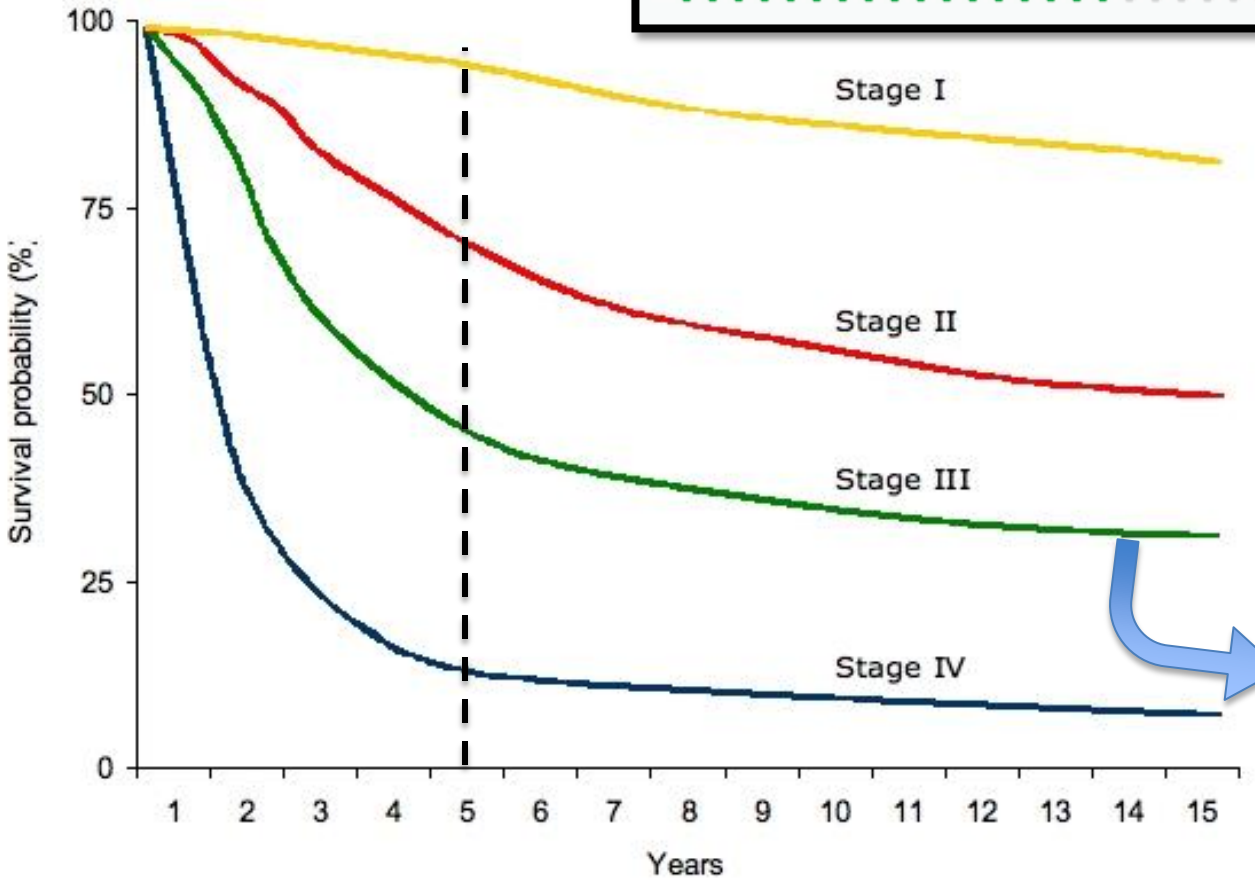
Hospital Regional y Hospital Universitario Virgen de la Victoria, Málaga


Equator
Cutaneous Melanoma Incidence (per 100,000 individuals)
4.1 +
1.8–4.1
0.89–1.6
0.48–0.89
< 0.48
No Data

9th


Estimated incidence for both sexes in Europe, 2012
13.41%
31.96%
13.07%
2.94%
3.04%
3.37%
12%
4.08%
11.7%
4.42%
Breast
Large bowel
Lung incl trachea & bronchus
Prostate
Bladder
Stomach
Kidney incl renal pelvis & urether
Pancreas
Malignant melanoma of skin
Other


Northern European British
European Scandinavian
Southern European Central European
Mediterranean Asian,Latino
East Indian,African Native American
African Aboriginal
I
II
III
IV
V
VI
Pigmentary phototype (Fitzpatrick scale)
Epidermal Melanin
UV phenotype
UV sensitive, Burn rather than tan
UV resistant, Tan; never burn
Melanoma risk



Población muy heterogénea

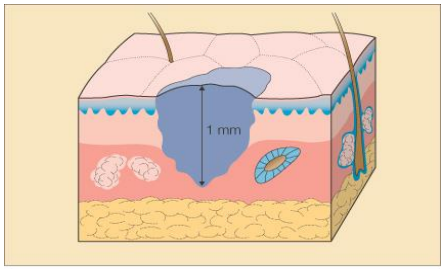
STAGING

AJCC, TNM 8th ed. 2017

T Category	Thickness	Ulceration Status
TX: primary tumor thickness cannot be assessed (eg, diagnosis by curettage)	Not applicable	Not applicable
T0: no evidence of primary tumor (eg, unknown primary or completely regressed melanoma)	Not applicable	Not applicable
Tis (melanoma *in situ*)	Not applicable	Not applicable
T1	≤1.0 mm	Unknown or unspecified
T1a	<0.8 mm	Without ulceration
T1b	<0.8 mm 0.8–1.0 mm	With ulceration With or without ulceration
T2	>1.0–2.0 mm	Unknown or unspecified
T2a	>1.0–2.0 mm	Without ulceration
T2b	>1.0–2.0 mm	With ulceration
T3	>2.0–4.0 mm	Unknown or unspecified
T3a	>2.0–4.0 mm	Without ulceration
T3b	>2.0–4.0 mm	With ulceration
T4	>4.0 mm	Unknown or unspecified
T4a	>4.0 mm	Without ulceration
T4b	>4.0 mm	With ulceration

Definition of Regional Lymph Node (N)

Extent of regional lymph node and/or lymphatic metastasis		
N Category	**Number of tumor-involved regional lymph node**	**Presence of in-transit, satellite, and/or microsatellite metastases**
NX	Regional nodes not assessed (eg, SLN biopsy not performed, regional nodes previously removed for another reason) **Exception**: pathological N category is not required for T1 melanomas, use cN.	No
N0	No regional metastases detected	No
N1	One tumor-involved node or in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes	
N1a	One clinically occult (ie, detected by SLN biopsy)	No
N1b	One clinically detected	No
N1c	No regional lymph node disease	Yes
N2	Two or three tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with one tumor-involved node	
N2a	Two or three clinically occult (ie, detected by SLN biopsy)	No
N2b	Two or three, at least one of which was clinically detected	No
N2c	One clinically occult or clinically detected	Yes
N3	Four or more tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with two or more tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases	
N3a	Four or more clinically occult (ie, detected by SLN biopsy)	No
N3b	Four or more, at least one of which was clinically detected, or presence of any number of matted nodes	No
N3c	Two or more clinically occult or clinically detected and/or presence of any number of matted nodes	Yes



Rigel et al: Cancer of the Skin © 2005 Elsevier Inc.

Breslow, ulceration, mitotic rate, lymph nodes…[TILs?]

STAGING

AJCC, TNM 8th ed. 2017

When T is...	And N is...	And M is...	Then the clinical stage group is...
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IB
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
Any T, Tis	≥N1	M0	III
Any T	Any N	M1	IV

When T is...	And N is...	And M is...	Then the pathological stage group is...
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IA
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T0	N1b, N1c	M0	IIIB
T0	N2b, N2c, N3b, or N3c	M0	IIIC
T1a/b-T2a	N1a or N2a	M0	IIIA
T1a/b-T2a	N1b/c or N2b	M0	IIIB
T2b/T3a	N1a-N2b	M0	IIIB
T1a-T3a	N2c or N3a/b/c	M0	IIIC
T3b/T4a	Any N ≥N1	M0	IIIC
T4b	N1a-N2c	M0	IIIC
T4b	N3a/b/c	M0	IIID
Any T, Tis	Any N	M1	IV

OVERVIEW TREATMENT OPTIONS IN MELANOMA

	Loco-regional		Systemic			
	Surgery	**Radio-therapy**	**Chemo-therapy**	**Inmune checkpoints**	**Targeted-therapy**	
Stage I	**STANDARD**			**?**	**?**	ADJUVANT
Stage II	**STANDARD**			Ongoing!	**BRIM8**	
Stage III	**STANDARD**	Cave 		**EORTC 18071 & Checkmate 238**	**BRIM8 & Combi-AD**	
Stage IV	*Selected*	Palliation	*Option*	**STANDARD**	**STANDARD**	METASTATIC

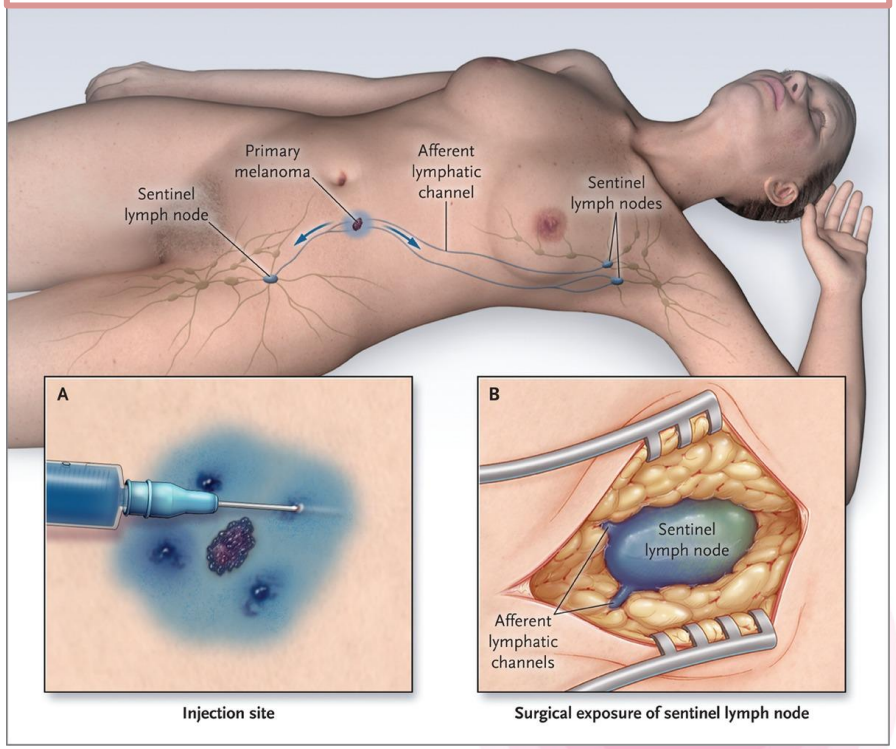
SLNB

IB-T1b (< 0.8 mm + ulceración y 0.8-1 mm +/- ulceración) o **IA-T1a** (< 0.8 mm con otros FR)*
OFRECER Y DISCUTIR CON EL PACIENTE

IB-T2a y II (> 1 mm)**
INDICACIÓN CLARA

- **PRECISIÓN EN ESTADIAJE**
- **INFORMACION PRONÓSTICA**
- Aumento tasa de control regional enf. Ganglionar *sin impacto en supervivencia*
- **Selección pacientes para terapia adyuvante**
- Selección candidatos a ECs

RISK-STRATIFY

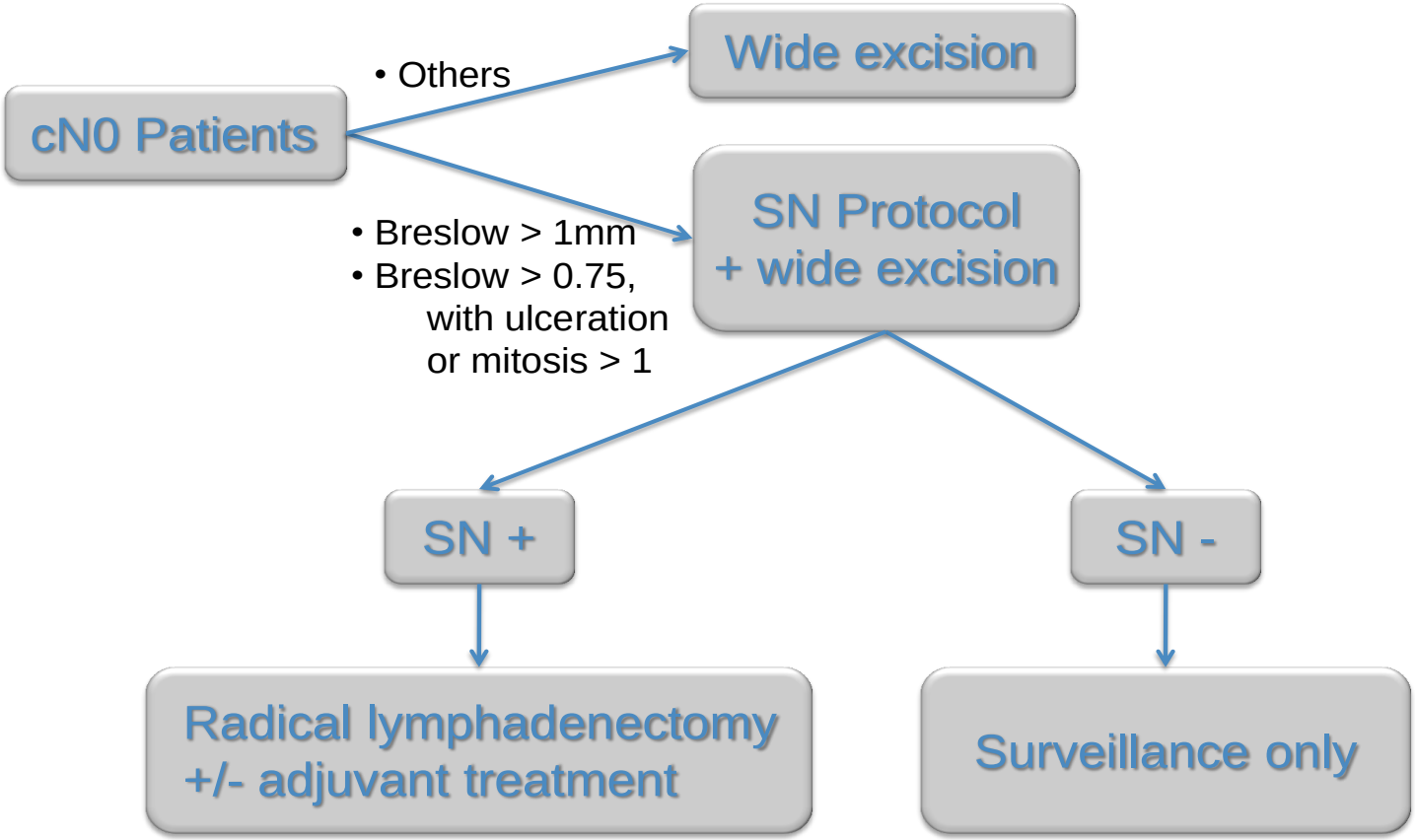


Recomendaciones según estadio CLINICO y por la 8th edición;
*Probabilidad de SLNB positivo 5-10%
**Probabilidad de SLNB positivo > 10%

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 FEBRUARY 13, 2014 VOL. 370 NO. 7

Final Trial Report of Sentinel-Node Biopsy versus Nodal Observation in Melanoma

D.L. Morton, J.F. Thompson, A.J. Cochran, N. Mozzillo, O.E. Nieweg, D.F. Roses, H.J. Hoekstra, C.P. Karakousis, C.A. Puleo, B.J. Coventry, M. Kashani-Sabet, B.M. Smithers, E. Paul, W.G. Kraybill, J.G. McKinnon, H.-J. Wang, R. Elashoff, and M.B. Faries, for the MSLT Group*

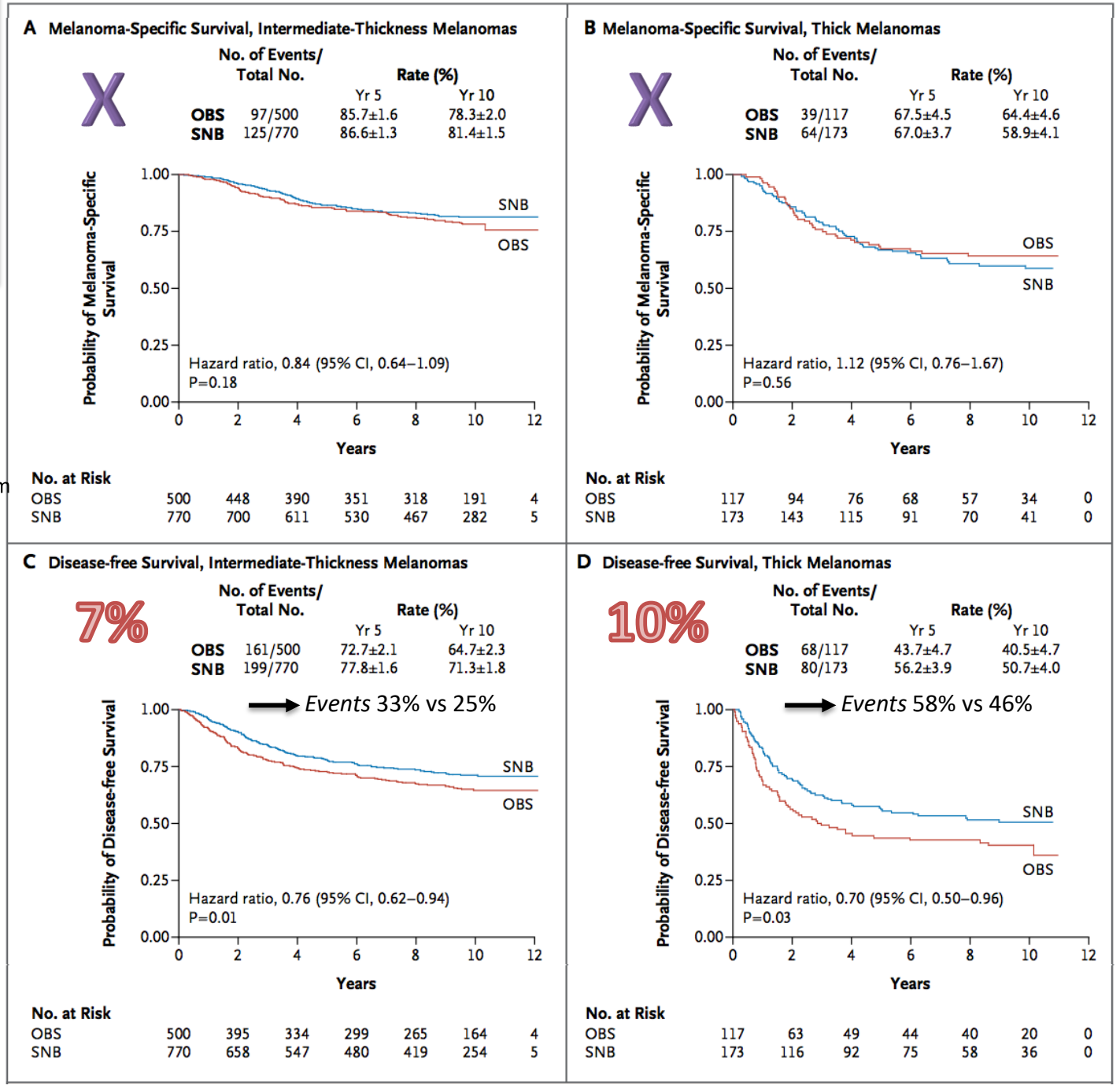


MSLT-1 Final analysis

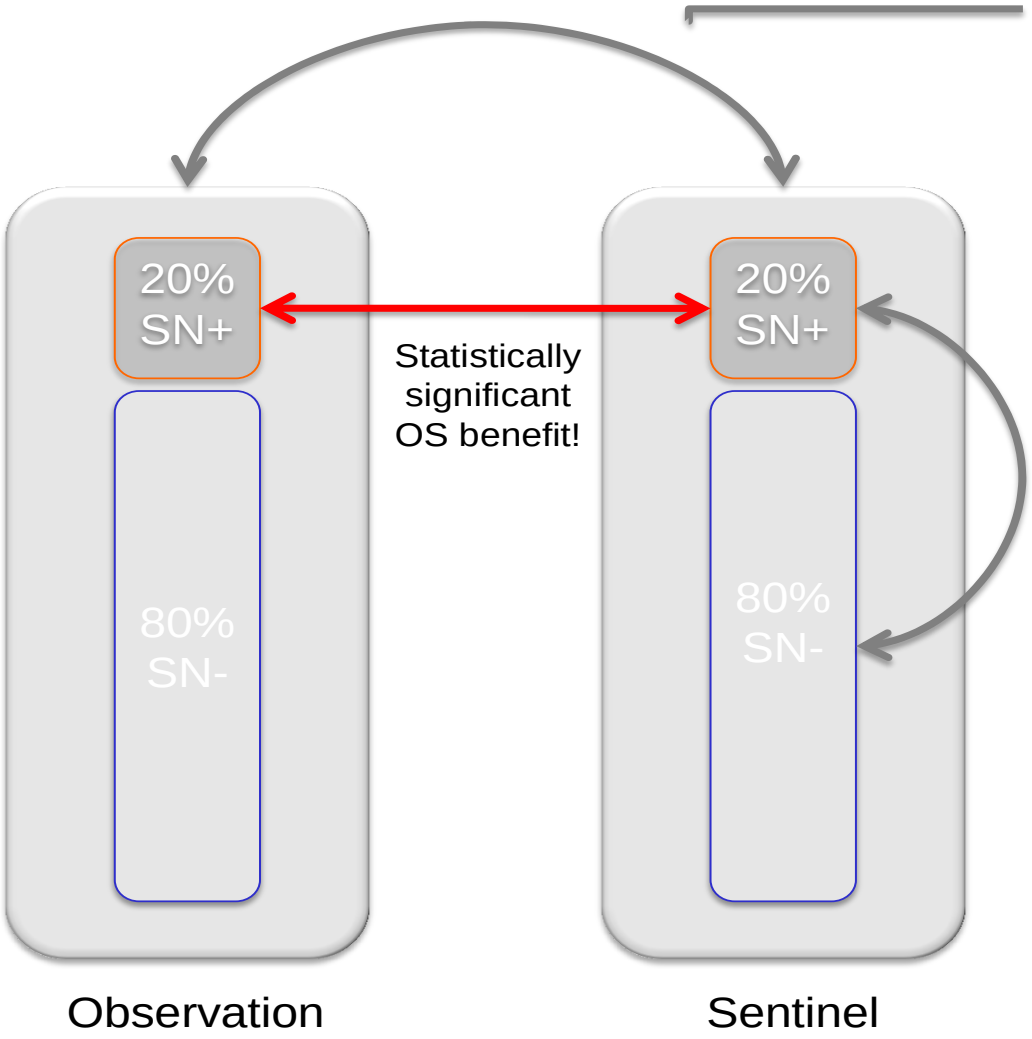
Morton et al, NEJM 2014

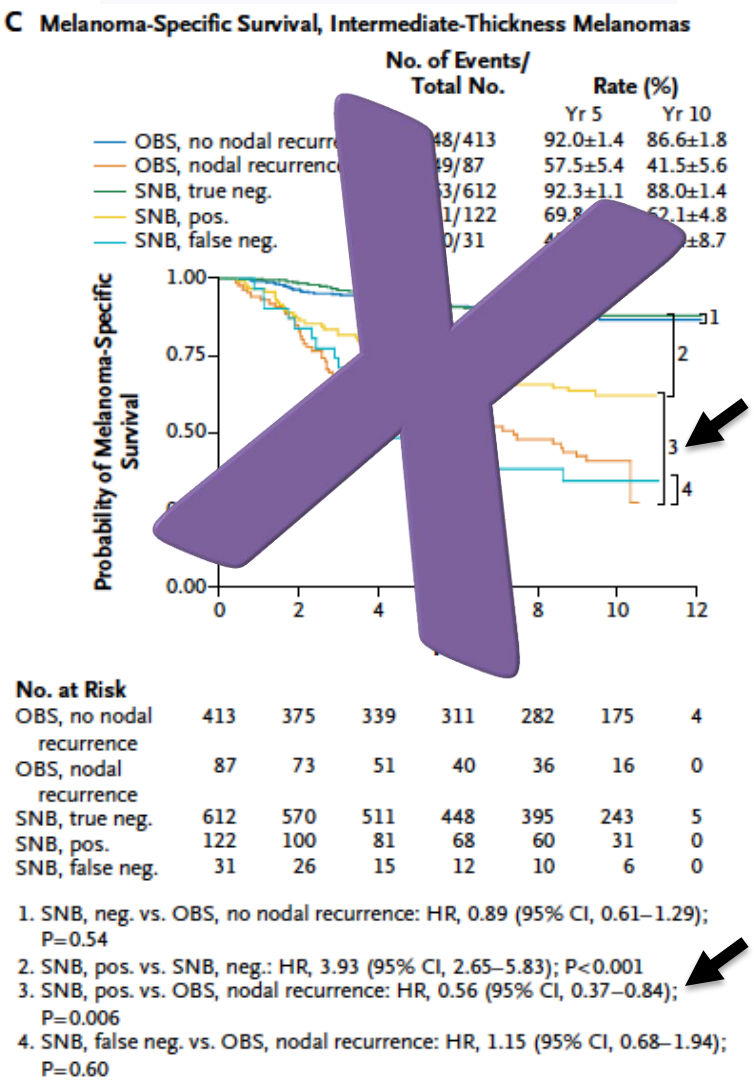
Intermediate thickness
1.2 to 3.5 mm

Thick
> 3.5 mm



INTERPRETRACIÓN “ERRÓNEA” DEL MSLT-I





Morton & al, *NEJM* 2014

II CURSO DE RESIDENTES DE SAOM

GRANADA, 13 y 14 DE ABRIL 2018

Organizado por:

SAOM Sociedad Andaluza de Oncología Médica

SLNB +

MSLT-II

Faries MB et al.
NEJM 2017

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 8, 2017 VOL. 376 NO. 23

Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma

M.B. Faries, J.F. Thompson, A.J. Cochran, R.H. Andtbacka, N. Mozzillo, J.S. Zager, T. Jahkola, T.L. Bowles, A. Testori, P.D. Beitsch, H.J. Hoekstra, M. Moncrieff, C. Ingvar, M.W.J.M. Wouters, M.S. Sabel, E.A. Levine, D. Agnese, M. Henderson, R. Dummer, C.R. Rossi, R.I. Neves, S.D. Trocha, F. Wright, D.R. Byrd, M. Matter, E. Hsueh, A. MacKenzie-Ross, D.B. Johnson, P. Terheyden, A.C. Berger, T.L. Huston, J.D. Wayne, B.M. Smithers, H.B. Neuman, S. Schneebaum, J.E. Gershenwald, C.E. Ariyan, D.C. Desai, L. Jacobs, K.M. McMasters, A. Gesierich, P. Hersey, S.D. Bines, J.M. Kane, R.J. Barth, G. McKinnon, J.M. Farma, E. Schultz, S. Vidal-Sicart, R.A. Hoefer, J.M. Lewis, R. Scheri, M.C. Kelley, O.E. Nieweg, R.D. Noyes, D.S.B. Hoon, H.-J. Wang, D.A. Elashoff, and R.M. Elashoff

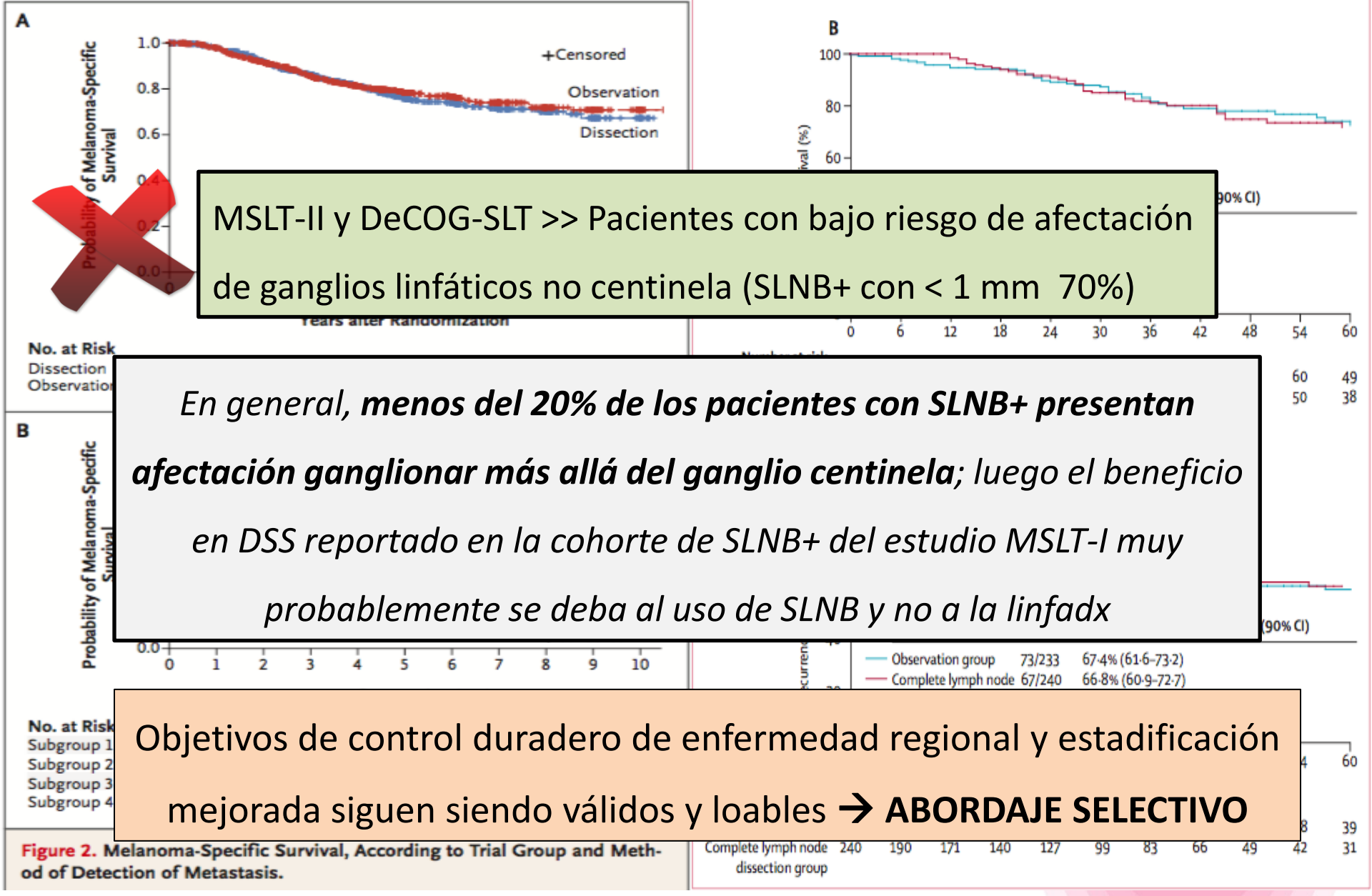
DeCOG-SLT

Leiter U et al.
Lancet Oncol 2016

Complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma (DeCOG-SLT): a multicentre, randomised, phase 3 trial

Ulrike Leiter, Rudolf Stadler*, Cornelia Mauch, Werner Hohenberger, Norbert Brockmeyer, Carola Berking, Cord Sunderkötter, Martin Kaatz, Klaus-Werner Schulte, Percy Lehmann, Thomas Vogt, Jens Ulrich, Rudolf Herbst, Wolfgang Gehring, Jan-Christoph Simon, Ulrike Keim, Peter Martus, Claus Garbe, for the German Dermatologic Cooperative Oncology Group (DeCOG)*

CLOSED EARLY



MSLT-II y DeCOG-SLT >> Pacientes con bajo riesgo de afectación de ganglios linfáticos no centinela (SLNB+ con < 1 mm 70%)

En general, ***menos del 20% de los pacientes con SLNB+ presentan afectación ganglionar más allá del ganglio centinela****; luego el beneficio en DSS reportado en la cohorte de SLNB+ del estudio MSLT-I muy probablemente se deba al uso de SLNB y no a la linfadx*

Objetivos de control duradero de enfermedad regional y estadificación mejorada siguen siendo válidos y loables → **ABORDAJE SELECTIVO**

Figure 2. Melanoma-Specific Survival, According to Trial Group and Method of Detection of Metastasis.

A. Melanoma-Specific Survival (MSS)
B. MSS RT-PCR or pathological assessment
C. Disease-free survival

B. Overall survival
C. Recurrence-free survival

Faries MB et al. NEJM 2017

Leiter U et al. Lancet Oncol 2016

II CURSO DE RESIDENTES DE SAOM
GRANADA, 13 y 14 DE ABRIL 2018
Organizado por:
SAOM
Sociedad Andaluza de Oncología Medica

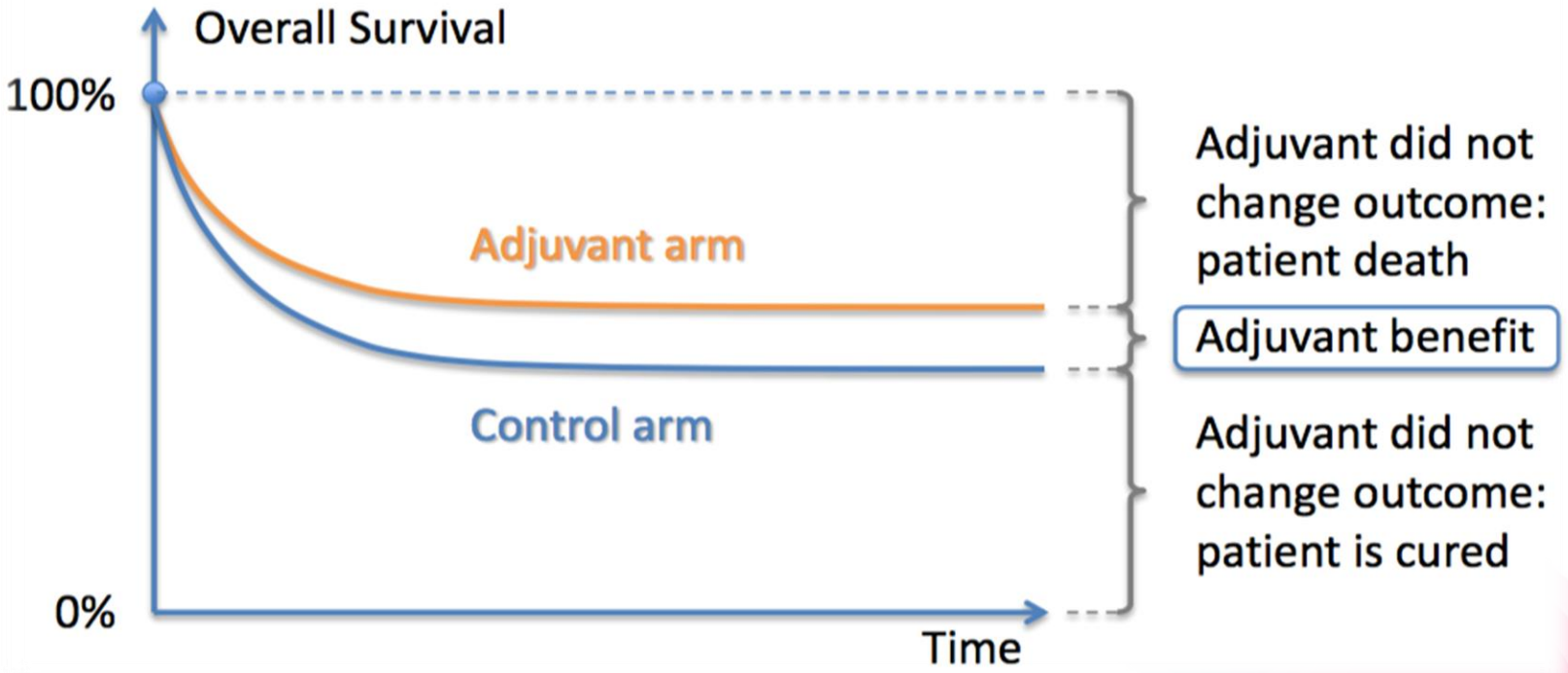
ADJUVANT THERAPY: Opciones antes de septiembre 2017

Cirugía

Radioterapia (Cave)

Interferons

Ipilimumab



In typical adjuvant trials, this results in a large number of **patients needed to treat**:

- Adjuvant Interferon - Cochrane Review (Mocellin 2013):
  - 35 participants in order to prevent 1 death
  - 97% of patients exposed for no benefit

II CURSO DE RESIDENTES DE SAOM
GRANADA, 13 y 14 DE ABRIL 2018
Organizado por:
SAOM
Sociedad Andaluza de Oncología Médica

IMMUNE MODULATIONS:

IFNa-2b

- **Señalización celular**
  - ✓ INF se une al receptor 1 y 2 de INF, activando TYK2 y **JAK1+2/STAT**
- **Efectos inmunes**
  - ✓ Activación de células dendríticas *(*Santini,*J ExpMed 2000)*
  - ✓ **Regulación positiva de MHC y presentación de antígeno (Ag)** *(*Cresswell, *Traffic 2000*)
  - ✓ Aumento de CD3 y CD11c en el infiltrado tumoral (Moshow&al, JCO 2006)
- **Otros efectos**
  - Efecto apoptotico mediado por AP o 2L/TRAIL (Chawla-Sarkar, *Apoptosis 2003*)
  - Efecto antiangiogenico por inhibición directa de células endoteliales (Folkman, *Nature Rev.Drug Discovery 2007*)

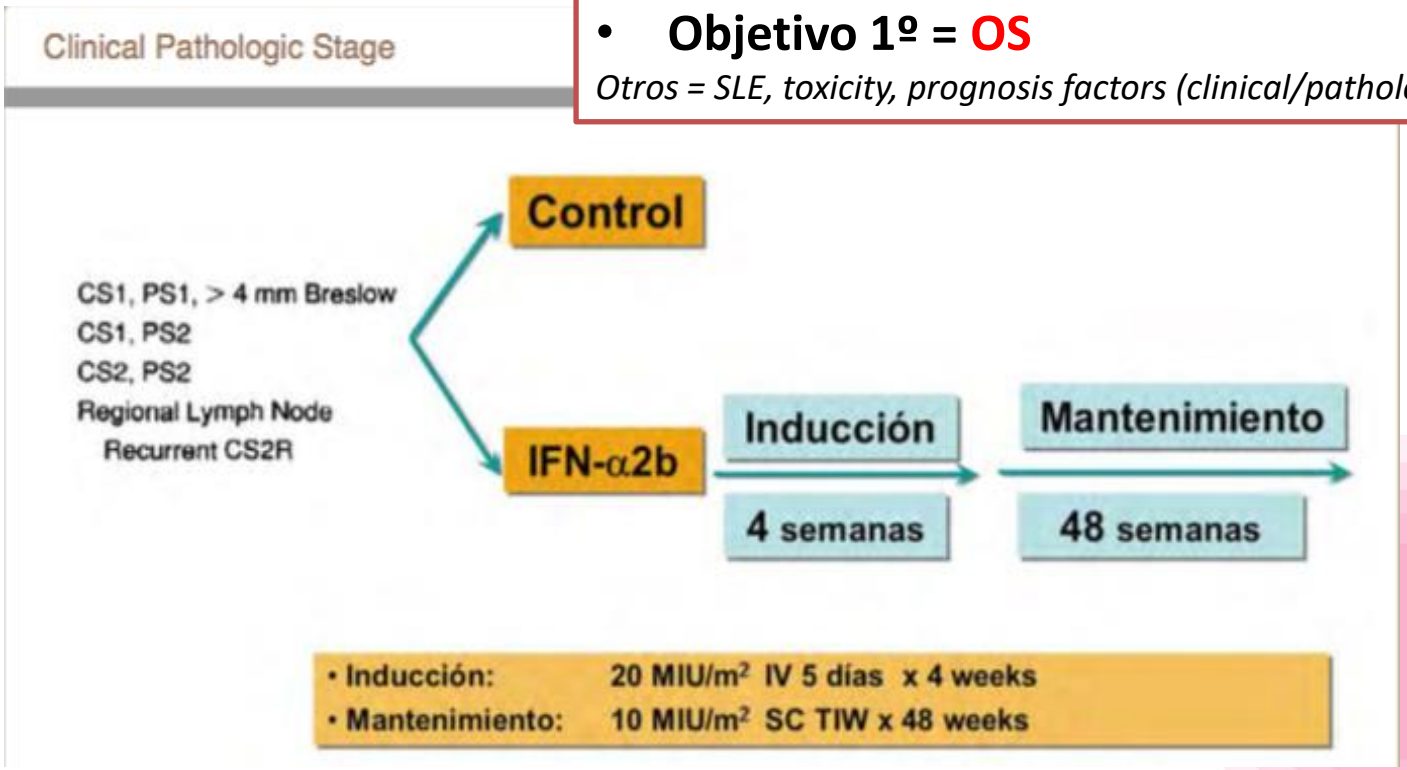
High dose INFa

> 10 MU/dosis

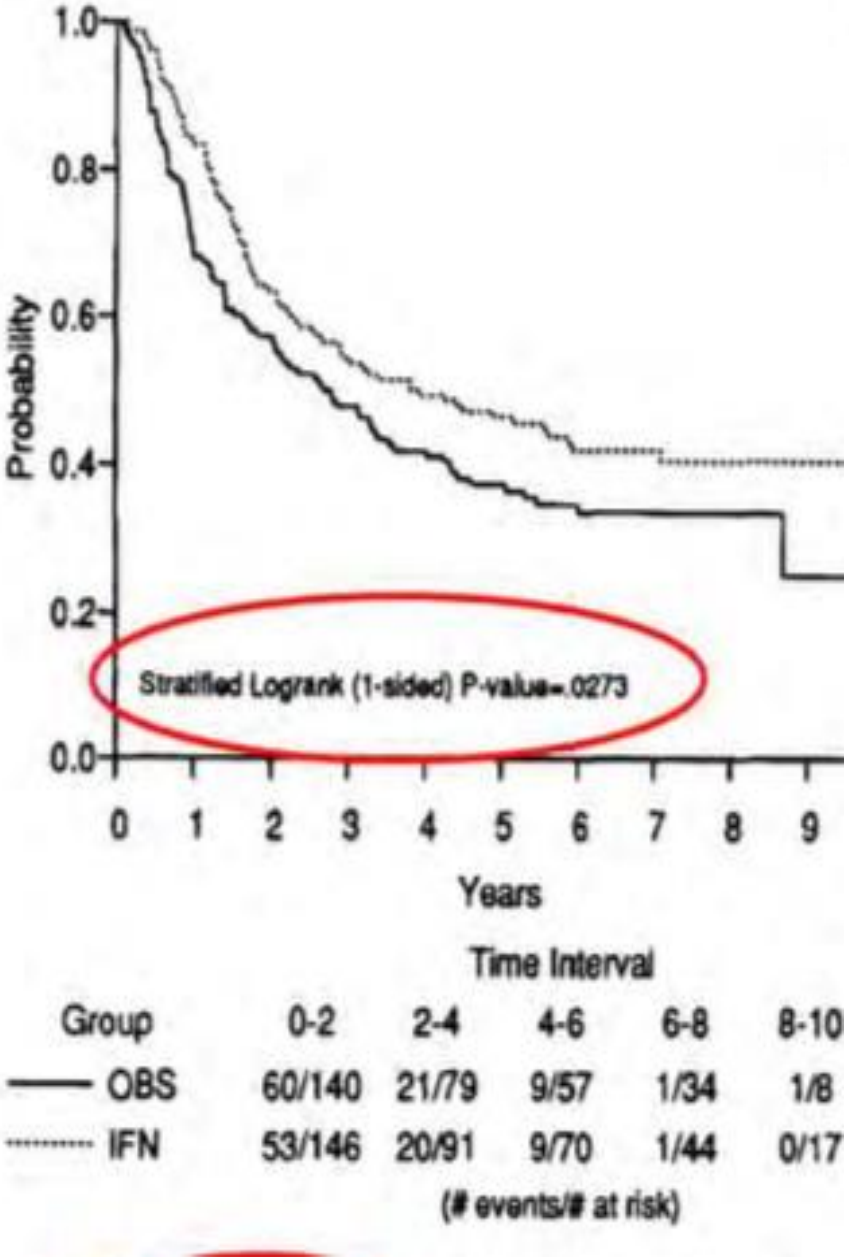
ECOG-1684

- **287 pacientes**
- T4, N1-N2b (*6th edition TNM)*
- **Objetivo 1º = OS**

Otros = SLE, toxicity, prognosis factors (clinical/pathological)



Kirkwood JM et al. J Clin Oncol. 1996 Jan;14(1):7-17



Analysis of survival (ITT)

Table 4. Cox Model Results Based on 280 Noncancelled Patients

Factor	Relapse-Free Survival Hazards Ratio	Relapse-Free Survival P	Overall Survival Hazards Ratio	Overall Survival P
Treatment with IFN	0.61	.0013	0.67	.0115
Time from diagnosis to randomization v < 30 days				
Days from diagnosis to randomization 30-40	0.68	.0364	0.66	.0379
Days from diagnosis to randomization > 40	0.50	.0002	0.54	.0020

6,9 años de seguimiento	
Mediana de SLE	**1.72** vs **0.98** años (p=.0023)
Mediana de SG	**3.82** vs **2.78** años (p=.0273)
SLE a 5 años	**37%** vs **26%**
SG a 5 años	**46%** vs **37%**

Table 6. Toxic Events by Type and Degree

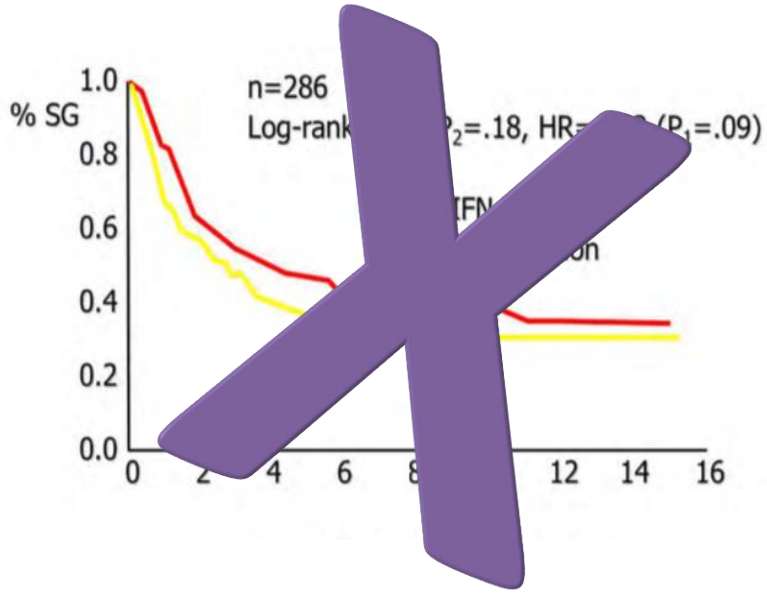
Type	Grade (N = 143) 1	2	3	4	5
Constitutional*	18	53	64	5	0
Myelosuppression	37	57	34	0	0
Hepatotoxicity	30	39	20	0	2
Neurologic	31	47	33	7	0
Worst grade/patient	2	30	96	13	2

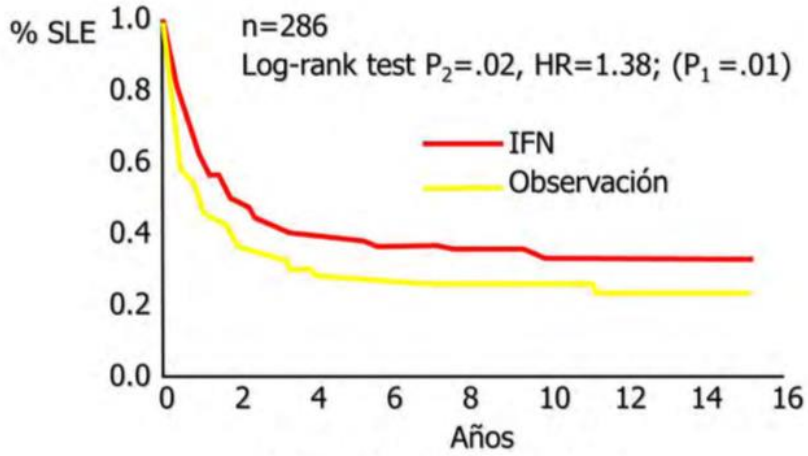
*Worst grade of any constitutional toxicity, including fever, chill, and flu-like symptoms: fatigue, malaise, diaphoresis.

76%

Kirkwood JM et al. J Clin Oncol. 1996 Jan;14(1):7-17

E1684: SLE a 12,6 años	
Control	24% (34 pacientes)
IF alfa2b I P^2=.02	35% (51 pacientes).



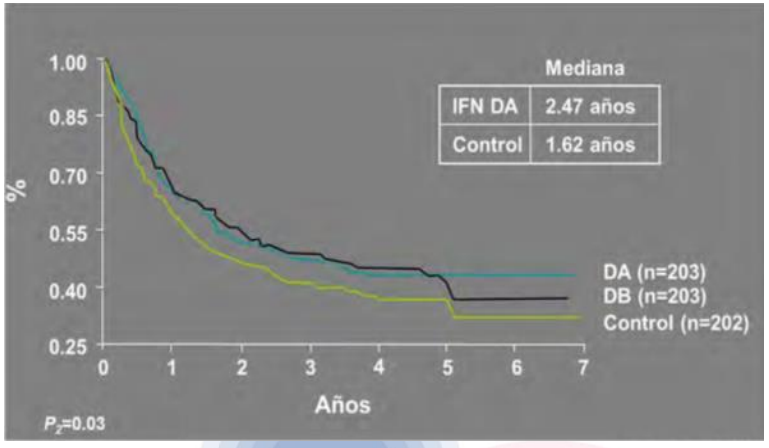


Kirkwood et al. Clin Cancer Res 10:1670, 2004

Observación
vs
IFN a dosis bajas - 3MU 3/d/sem x 2a.
IFN a dosis altas (E1684)
n = 642 (608)

ECOG-1690

- **Objetivo primario = DFS**
- **OS →**
  - Dosis altas vs control
  - Dosis bajas vs control
  - Dosis altas vs bajas
- **Estratificación**: METASTASIS GANGLIONARES
  - **No palpables (**25% pT4N0)
    - 24% T4N0 (Ix), 5% T4N0 (SLNB)
  - Palpables
  - Recidiva ganglionar regional
    - **51% N + recurrente**



IFN vs Control (4,3 años de seguimiento)	
Mediana de SLE	**2,4** vs **1,6** años (p=.03)
Mediana de SG	**5,1** vs **6** años X
SLE a 5 años	**44%**
SG a 5 años	**52%**

Kirkwood et al. J Clin Oncol 18:2444, 2000

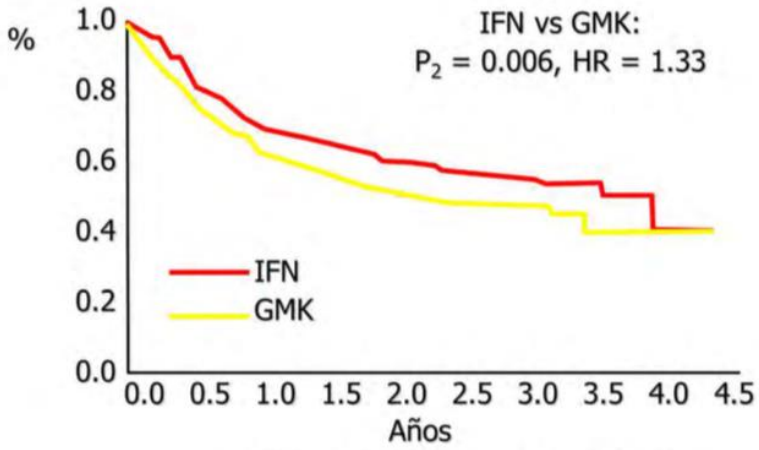
ECOG-1694

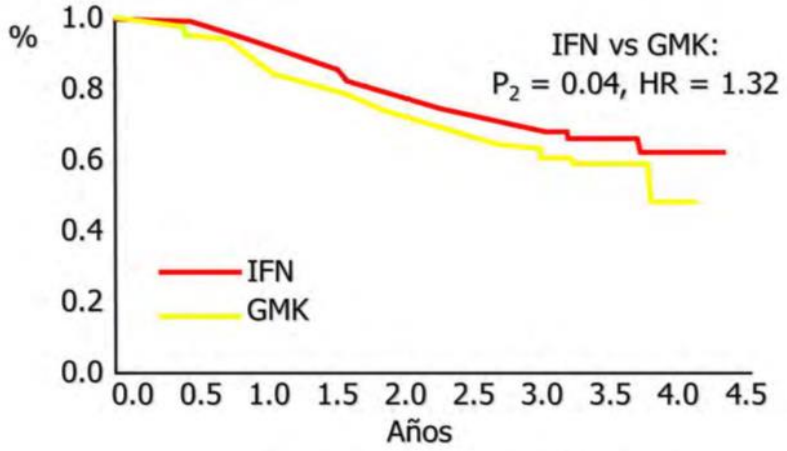
Gangliosido GM2, (GMK vaccine, Progenics, Inc., Tarrytown NY USA):

1 mL/sc días 1, 8, 15, 22, y cada 12 sem. (sem. 12-96)

n = 808 (774) → GMK (vacuna)

n = 808 (774) → IFNa2b Altas dosis





Kirkwood et al. Clin Cancer Res 10:1670,, 2004

Cooperative Group/IP	Eligibility	N	Treatment/Agent/Dosage/ Duration	IMPACTO	
				DFS	OS
ECOG 1684	**T4, ≥ N1**	287	IFNa2b 20 MU/m2/d UV x1 mo 10 MU/m2 SC TIW x 1 mos	+	-
				6.9 – 12.6 yrs	
ECOG 1690	**T4**N0 **T4, ≥ N1** N+ recurr	642	IFNa2b 20 MU/M2/d IV x 1 mo 10 MU/m2 SC TIW x 11 mos vs 3 MU/d SC TIW x 2 yrs	+	-
				4.3 – 6.6 yrs	
ECOG 1694	**T4,** N1	880	IFNa2b 20 MU/m2/d IV x 1 mo 10 MU/m2 SC TIW x 11 mos vs GMK vaccine x 96 wks	+	+
				At 1.3 – 2.1 yrs	

HDI vs Obs *(yrs)*

ECOG 1684:

DFS → 1.72 vs 0.98 (p = 0.0023, HR = 1.42)

OS → 3.82 vs 2.78 (p = 0.0237, HR = 1.28)

ECOG 1690:

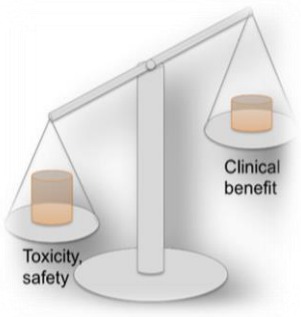
DFS → 2.47 vs 1.62 (p = 0.03, HR = 1.28)

OS → 5.12 vs 5.96 (p = NS, HR = 1.00)

ECOG 1694:

DFS → NR vs 1.88 (p = 0.0015, HR = 1.47)

OS → NR vs NR (p = 0.009, HR = 1.52)



ECOG 1684 y ECOG 1694

IFN-a2b HD en melanoma de alto riesgo prolonga SLE y SG

FDA & EMA: IFN-a2b x 1 año como tratamiento adyuvante de Melanoma de alto riesgo en los 56 meses posteriores a la resección *(42 días de la linfadenectomía).*

Intermediate dose INFa

5-10 MU/dosis

Trial	Size	Stage	Treatment schedule	DFS		OS	
				HR	p	HR	p
EORTC 18952 Eggermont 2005	1418 Pts.	IIB-III	INFα2b 10 MU, d1-5 x4w, SC + 10 MU, 3x/w x12m, SC or 10 MU, 3x/w x24m, SC	0.81	0.12	0.88	0.40
NORDIC, Hansson 2011	855 Pts.	IIB-III	INFα2b 10 MU, d1-5 x4w, SC + 10 MU, 3x/w x12m, SC or 10 MU, 3x/w x24m, SC	0.83	0.05	0.88	0.47

EORTC 18991

Peg-IFN

Low dose INFa

<3 MU/dosis

Trial	Size	Stage	Treatment schedule	DFS		OS	
				HR	p	HR	p
EORTC 18871 Kleeberg 2004	830 Pts.	II-III	INFα2b 1 MU, 3x/w, x 12 m	0.96	> 0.50	0.96	> 0.70
UKCCCR Hancock 2004	674 Pts.	IIB, III	INFα2a 3 MU, 3x/w, x 24 m	0.94	0.60	0.91	0.30
ECOG 1690 Kirkwood 2000	642 Pts.	IIB,III	INFα2b 3 MU, 3x/w, x 24 m	0.90	0.17	0.93	0.81
FCGM Grob 1998	499 Pts.	II	INFα2a 3 MU, 3x/w, x 18 m	0.75	0.035	0.72	0.059 (!)
DeCOG Garbe 2008	444 Pts.	III	INFα2a 3 MU, 3x/w, x 24 m	0.69	0.018	0.62	0.0045
WHO Cascinelli 2001	444 Pts.	III	INFα2a 3 MU, 3x/w, x 36 m	0.95	0.50	0.96	> 0.50
AMCG Pehamberger 1998	311 Pts.	II	INFα2a, 3 MU daily, x3w + 3 MU, 3x/w, x12 m	0.62	0.02	0.83	NS
SMG Cameron 2001	96 Pts.	IIB, III	INFα2b 3 MU, 3x/w, x 6 m	0.72	NS at > 2 years	0.81	> 0.20

EORTC 18991

Peg-IFNa-2b

Patients (N = 1256): Resected TxN1-2M0 melanoma, within 7 wks of lymphadenectomy

Randomization

Observation

Stratified by:

- Microscopic (N1) vs palpable (N2)
- 1 vs 2-4 vs 5+ nodes
- Breslow
- Ulceration
- Gender and site

Peg-IFN alfa-2b

- Induction (8 wks) 6 µg/kg/wk
- Maintenance (5 years or distant metastasis) 3 µg/kg/wk
- Dose reduction to 3, 2, 1 to maintain performance status

Primary Endpoints:

- Relapse-free survival
- Distant metastasis-free survival

Eggermont AM et al. Lancet 2008; 372: 117-26
Eggermont AM et al. JCO 2012

Outcomes at 3.8 years maturity

Outcome (ITT)	2007	
	HR (95% CI)	p
RFS	**0.82 (0.71-0.96)**	**0.01**
DMFS	0.88 (0.75-1.03)	0.11
OS	0.98 (0.82-1.16)	0.78

3-year RFS rate
45.6% versus 38.9%

- Enfermedad N2 sin beneficio significativo en ninguno de los objetivos del estudio
- Mediana de tolerancia de tratamiento = 14 meses
- **31% discontinuaron tratamiento** por eventos adversos
- **Toxicidad grado ¾ → 32%**
  - ✓ *Astenia 16%, hepatotoxicidad 11% y depresión 6%*

Eggermont AM et al. Lancet 2008; 372: 117-26

7-year RFS rate
39.1% versus 34.6%

Resultados a 7.6a[1] inferiores en comparación con 3.82a[2] FUP

Outcome (ITT)	2007		
		0.96 (0.82-1.11)	0.57

FDA: Aprobación en 2011 de Peg-IFNa adyuvante para melanoma de alto riesgo *(alternativa si intolerancia a HD IFNa2b)*

- Mediana de tolerancia de tratamiento = 14 meses
- **31% discontinuaron tratamiento** por eventos adversos
- **Toxicidad grado ¾ → 45%**

1. Eggermont AM et al. JCO 2012
2. Eggermont AM et al. Lancet 2008; 372: 117-26

- Estadio IIIA (N1,microscopic) beneficio significativo en RFS y DMFS en 2007

  LA MEJORA A LOS 7.6 AÑOS YA NO ES ESTADÍSTICAMENTE SIGNIFICATIVA

Outcome N1 (ITT)	2007		2011	
	HR (95% CI)	p	HR (99% CI)	p
RFS	0.73	0.016	0.82 (0.61-1.10)	0.08
DMFS	0.75	0.034	0.86 (0.63-1.17)	0.22
OS	0.88	0.43	0.86 (0.62-1.21)	0.26

- Enfermedad N2 sin beneficio significativo en ninguno de los objetivos del estudio

1. Eggermont AM et al. JCO 2012
2. Eggermont AM et al. Lancet 2008; 372: 117-26

Meta-analysis	RCT (n)	RFS	OS	Comment
Ives[1] 2017 	18	+ HR: 0.86; 95% CI: 0.81 – 0.91; P < 0.00001 **IFN vs Obs** • 5 ys = 3,5% • 10 ys = 2.7%	-/+ HR: 0,90; 95% CI: 0.85 – 0.97; P < 0.003 **IFN vs Obs** • 5 ys = 3% • 10 ys = 2.8%	*E1694 no incluido* **Mayor beneficio con IFN a altas dosis** **NNT = 33**
Wheatley[2] 2003 	13	+ HR: 0.87; 95% CI: 0.81 – 0.93; P = 0.00006	+ HR: 0.9; 95% CI: 0.84 – 0.97; P = 0.008	**Beneficio absoluto en OS del 3% a los 5 años** (CI: 1 to 5%) **NNT = 20**
Mocellin[3] 2010 	14	+ HR: 0.82; 95% CI: 0.77 – 0.87; P < 0.001	+ HR: 0.89; 95% CI: 0.83 – 0.96; P = 0.002	18% risk reduction DFS 11% risk reduction OS **NNT = 35**

1. Ives NJ et al. JCO 2007 ; Eur Jour Cancer 82 (2017): 171-183
2. Wheatley K et al. Cancer Treat Rev. 2003 Aug;29(4):241-52
3. Mocellin S et al. J Natl Cancer Inst. 2010 Apr 7;102(7):493-501.

APPROVED BY FDA & EMA

- **Toxicidad importante**
- Mejora de PFS
- **OS** (metanalisis) **= impacto marginal** (3%)
- **La relación dosis-respuesta y duración del tratamiento no clarificada**
  - PFS: ningún esquema optimo de tratamiento superior a otro
  - OS: sin asociación entre resultados y dosis o duración del tratamiento
- *"La duración factible del tratamiento debe ser 1 año e IFN HD, el esquema adyuvante a recomendar"* (pre-IPI)
  - *PegIFN (en US) como opción alternativa si IFN a2b no se tolera*

¿EL BENEFICIO CLINICO JUSTIFICA LA TOXICIDAD?

- ✗ **No hay consenso internacional**
- ✗ Guias clínicas divergentes

¿QUÉ OPCIONES NOS QUEDAN PARA PROGRESAR?

Mejor selección en la población de pacientes

Búsqueda de biomarcadores predictivos... ✓

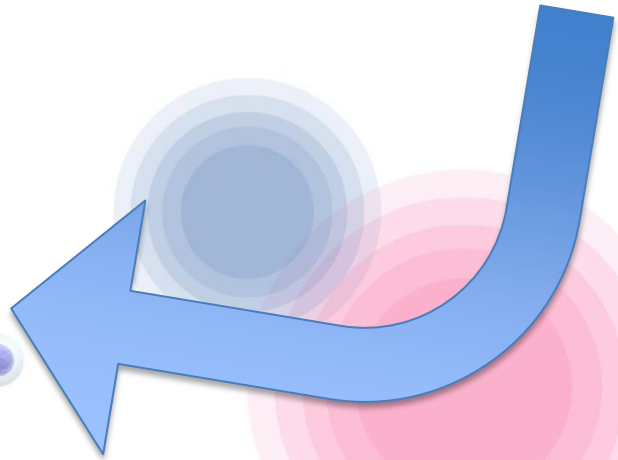
EORTC 8991

Stage III N1 & ulcerated

Mayor beneficio PegIFN
(OS < 9 vs 3.7 años)

Outcome N1, ulcerated (ITT)	2007[2]	
	HR (99% CI)	p
RFS	**0.72 (0.46-1.13)**	**0.06**
DMFS	0.65 (0.41-1.04)	0.02
OS	**0.59 (0.35-0.97)**	**0.006**

	Outcome OS 2011 based on primary tumor ulceration[1]	
	HR (99% CI)	p
Ulcerated	0.81 (0.58-1.14)	**0.11**
Not ulcerated	1.05 (0.79-1.41)	0.64



1. Eggermont AM et al. JCO 2012
2. Eggermont AM et al. Lancet 2008; 372: 117-26

EORTC 18952

Long term follow up of the EORTC 18952 trial of adjuvant therapy in resected stage IIB–III cutaneous melanoma patients comparing intermediate doses of interferon-alpha-2b (IFN) with observation: Ulceration of primary is key determinant for IFN-sensitivity

Alexander M.M. Eggermont [a,*], Stefan Suciu [b], Piotr Rutkowski [c], Willem H. Kruit [d], Cornelis J. Punt [e], Reinhard Dummer [f], François Salès [g], Ulrich Keilholz [h], Gaetan de Schaetzen [b], Alessandro Testori [i], for the EORTC Melanoma Group

Table 1
Patient characteristics by treatment group.

	13-month IFN N = 553 (%)	25-month IFN N = 556 (%)	Observation N = 279 (%)	All N = 1388 (%)
Stage				
IIB	141 (25.5)	142 (25.5)	73 (26.2)	356 (25.6)
III N1	119 (21.5)	107 (19.2)	57 (20.4)	283 (20.4)
III N2	293 (53.0)	307 (55.2)	149 (53.4)	749 (54.0)
Ulceration status				
Ulceration	165 (29.8)	204 (36.7)	106 (38.0)	475 (34.2)
No ulceration	285 (51.5)	265 (47.7)	135 (48.4)	685 (49.4)
Unknown	103 (18.6)	87 (15.6)	38 (13.6)	228 (16.4)
Stage & Ulceration status				
IIb/III-N1 & Ulceration	101 (18.3)	125 (22.5)	60 (21.5)	286 (20.6)
IIb/III-N1 & No Ulceration	139 (25.1)	109 (19.6)	62 (22.2)	310 (22.3)
III-N2 & Ulceration	64 (11.6)	79 (14.2)	46 (16.5)	189 (13.6)
III-N2 & No Ulceration	146 (26.4)	156 (28.1)	73 (26.2)	375 (27.0)
Unknown ulceration status	103 (18.6)	87 (15.6)	38 (13.6)	228 (16.4)

A.M.M. Eggermont et al. / European Journal of Cancer 55 (2016) 111e121

Intermediate dose INFa

~~EORTC 18952~~

- Mediana de seguimiento: 11 años
- RFS y DMFS → Impacto **borderline** en la población general para el esquema de 25 meses de tratamiento
- OS → **ausencia de significado estadístico**
- ESTADIO → Sin ningún beneficio en estadio III-N2

- **ULCERACION**

…Factor predictivo clave para sensibilidad y beneficio de IFN…

A.M.M. Eggermont et al. / European Journal of Cancer 55 (2016) 111e121

EORTC 18952

Long term follow up of the EORTC 18952 trial of adjuvant therapy in resected stage IIB–III cutaneous melanoma patients comparing intermediate doses of interferon-alpha-2b (IFN) with observation: Ulceration of primary is key determinant for IFN-sensitivity

Alexander M.M. Eggermont [a,*], Stefan Suciu [b], Piotr Rutkowski [c], Willem H. Kruit [d], Cornelis J. Punt [e], Reinhard Dummer [f], François Salès [g], Ulrich Keilholz [h], Gaetan de Schaetzen [b], Alessandro Testori [i], for the EORTC Melanoma Group

ULCERATED

"Distint biologic entity"

		RFS	DMFS	OS
Primary ulcerated (33%)	13 months	0.82 (0.57-1.18) p = 0.16		0.80 (0.54-1.18) p = 0.13
	25 months	**0.61** (0.42-0.89) **p = 0.0008**	0.57 (0.39-0.85) **p = 0.0003**	0.59 (0.39-0.88) **p = 0.0008**

A.M.M. Eggermont et al. / European Journal of Cancer 55 (2016) 111e121

Adjuvant interferon-α for the treatment of high-risk melanoma: An individual patient data meta-analysis

Natalie J. Ives [a], Stefan Suciu [b], Alexander M.M. Eggermont [c], John Kirkwood [d], Paul Lorigan [e], Svetomir N. Markovic [f], Claus Garbe [g], Keith Wheatley [h,*] on behalf of the International Melanoma Meta-Analysis Collaborative Group (IMMCG)

- IFN beneficio en términos de reducción de riesgo de recurrencia con mínimo beneficio en OS → **diferencias absolutas pequeñas**
- **No hay evidencia de que los resultados difieran según la duración del tratamiento o la dosis** total programada.
- No hubo evidencia de que el beneficio de IFN fuera distinto para los diferentes tipos de pacientes, a excepción de aquellos con **ulceración del primario…**

Ives et al. Eur Jour Cancer 82 (2017): 171-183

EORTC 18952

EORTC 18991

Adjuvant interferon-α for the treatment of high-risk melanoma: An individual patient data meta-analysis

Natalie J. Ives [a], Stefan Suciu [b], Alexander M.M. Eggermont [c], John Kirkwood [d], Paul Lorigan [e], Svetomir N. Markovic [f], Claus Garbe [g], Keith Wheatley [h,*] on behalf of the International Melanoma Meta-Analysis Collaborative Group (IMMCG)

OS ulcerated (IFN vs no IFN)

5 years = 46% vs 38.1%

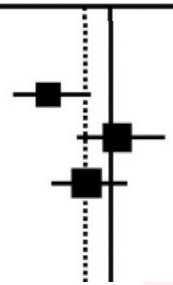
10 years = 38.5% vs 28%

9.7 % SD 3-5

(logrank 2P = 0.0002)

Stratum	Deaths/Patients IFN	Deaths/Patients No IFN	Statistics (O–E)	Statistics Var.	HR & 99% CI (IFN : No IFN)
Ulceration:					
Yes	506/898	369/545	–50·6	189·8	0.77 (0.64, 0.92)
No	719/1429	455/893	5·9	260·6	1.02 (0.87, 1.20)
Unknown/Missing	618/1112	560/949	–26·7	277·1	0.91 (0.78, 1.06)

Test for heterogeneity between yes/no subgroups: $\chi^2_1 = 9{\cdot}2$; P = 0·002



OS

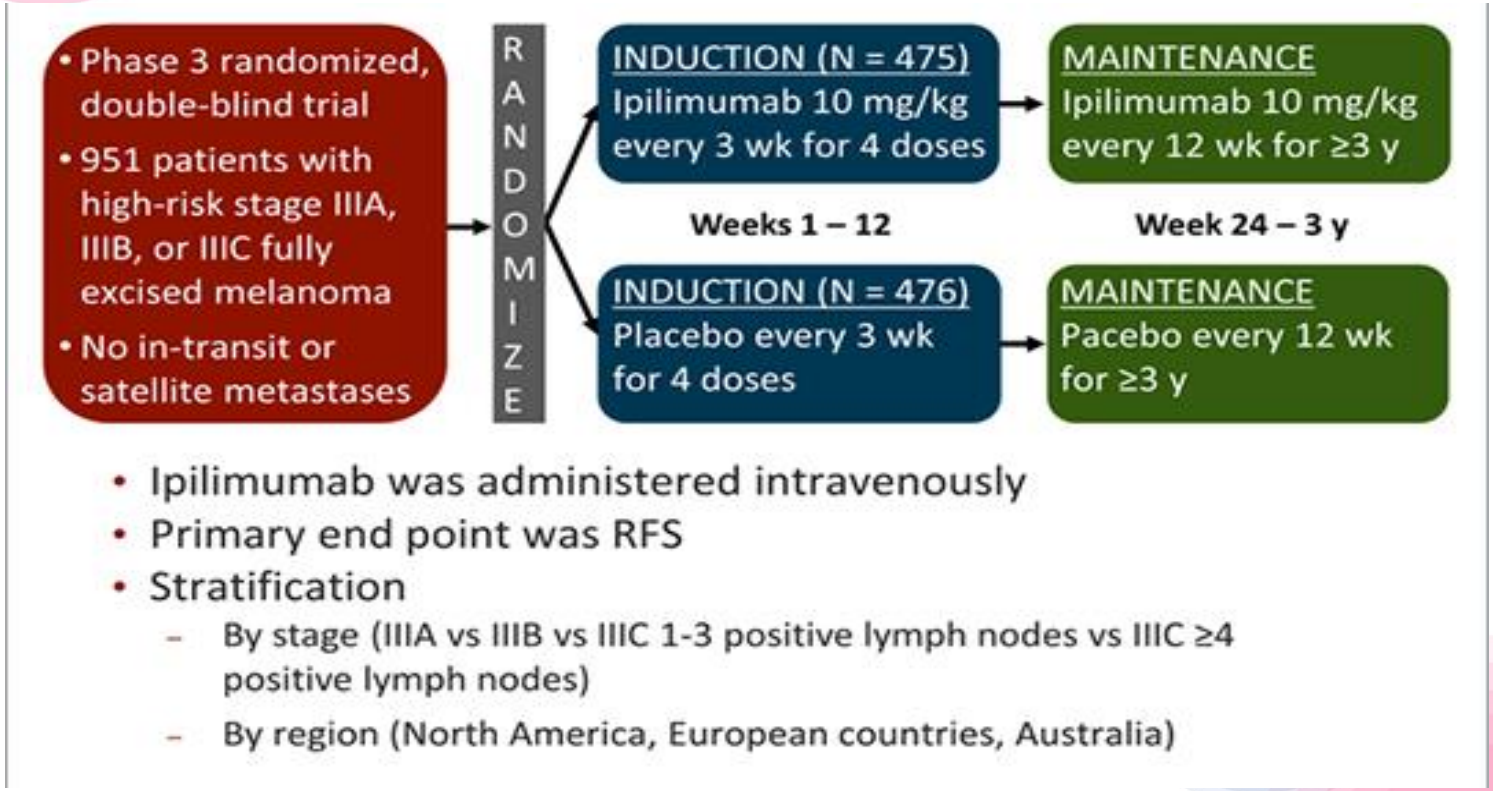
NNT = 9 (yes) vs 100 (no)

Ives et al. Eur Jour Cancer 82 (2017): 171-183

II CURSO DE RESIDENTES DE SAOM
GRANADA, 13 y 14 DE ABRIL 2018
Organizado por:
SAOM
Sociedad Andaluza de Oncología Médica

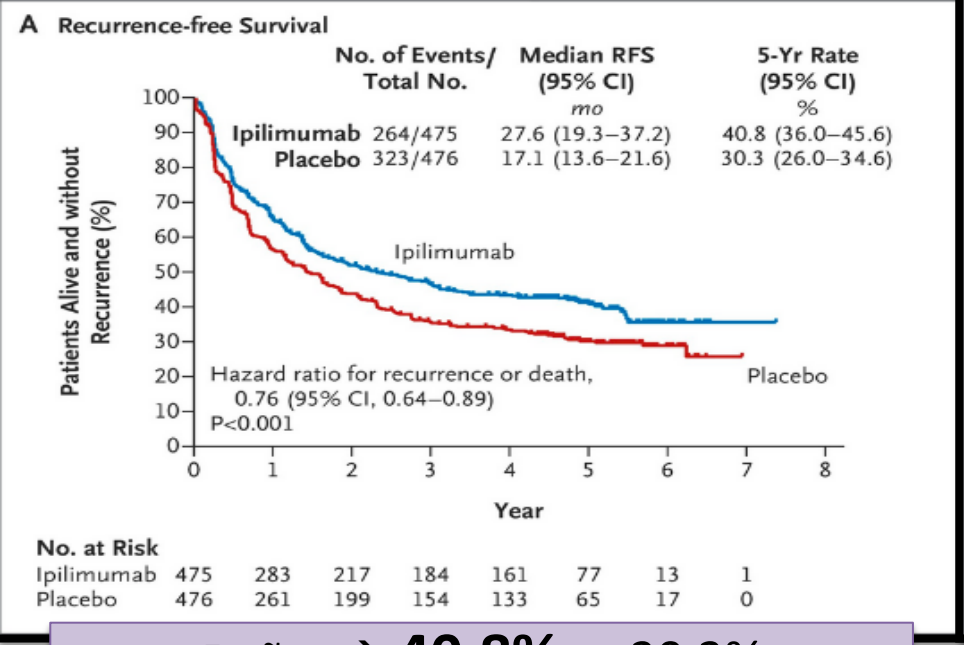
IMMUNOTHERAPY
&
TARGETED-THERAPY

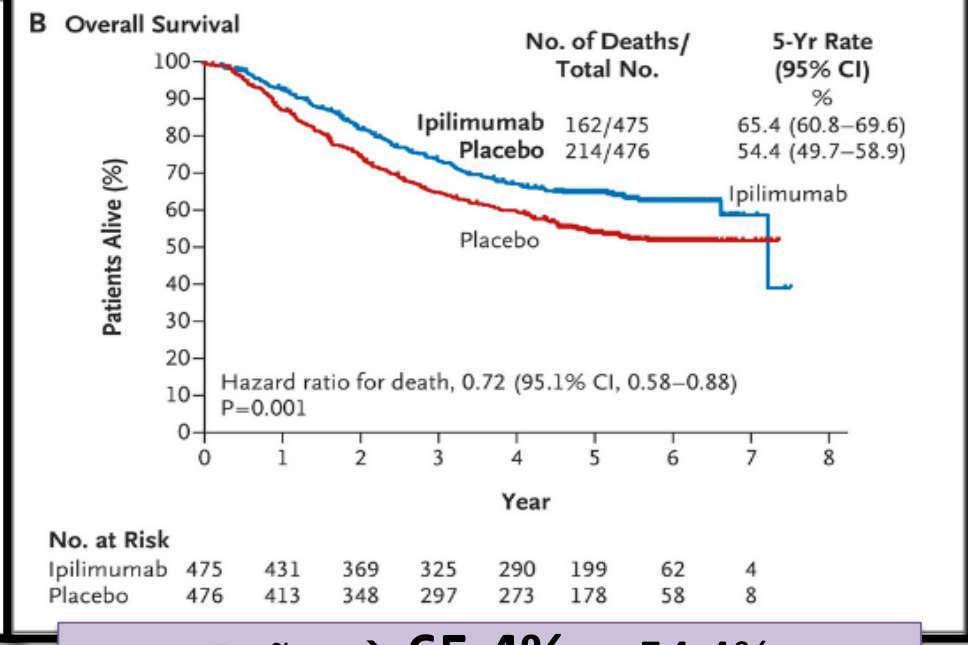
EORTC 18071



- **Importante** IIIA = metástasis en ganglios debía ser **> 1 mm**
- *Fue diseñado antes de la aprobación de ipilimumab a 3 mg/kg*

Eggermont AM et al. Lancet Oncol. 2015; 16:522-530
Eggermont AM et al. NEJM 2016;375:1875-1855





5 años → **40.8%** vs 30.3%

HR 0.76 (95%CI, 0.64-0.89); **p < 0.001**

5 años → **65.4%** vs 54.4%

HR 0.72 (95%CI, 0.58-0.88); **p = 0.001**

- **Status de BRAF desconocido**
- **IMPORTANTE TOXICIDAD**
  - **54% G3/4** (41.6% irAEs)
  - **> 50% discontinuaron tratamiento** (251 pts en el brazo de ipi)
    - ✓ *38.6 (182 pts) % dentro de las 12 ss tras la randomización*
  - **5 muertes** relacionadas con el tratamiento

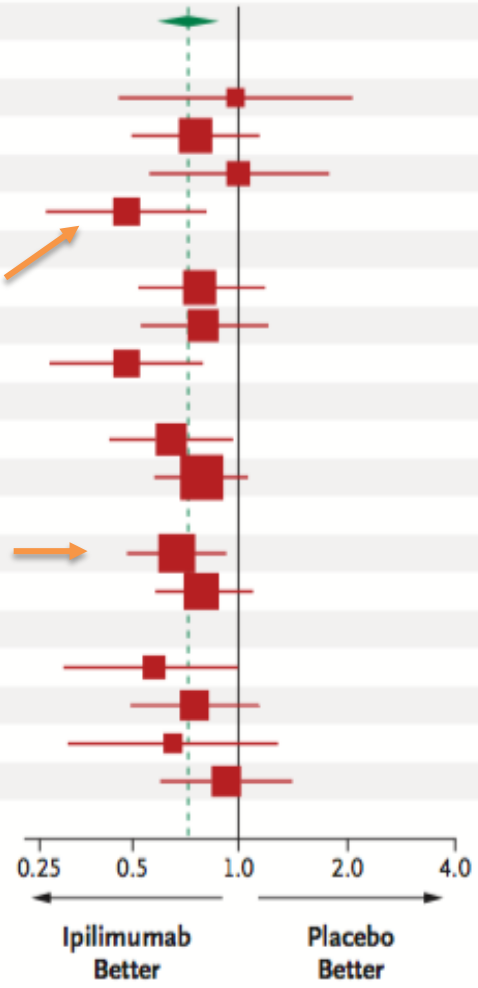
DOSE-INTENSITY

1 year = 28.3% pts

3 years = 13.4% (63/475)

Eggermont AM et al. NEJM 2016;375:1875-1855

Subgroup	Ipilimumab	Placebo	Hazard Ratio (95% or 99% CI)	P Value
	no. of deaths/total no.			
All patients	162/475	214/476	0.72 (0.59–0.88)	0.001
Disease stage				0.07
IIIA	24/98	22/88	0.98 (0.46–2.09)	
IIIB	68/213	85/207	0.75 (0.50–1.14)	
IIIC with 1–3 positive lymph nodes	34/69	45/83	1.00 (0.56–1.80)	
IIIC with ≥4 positive lymph nodes	36/95	62/98	0.48 (0.28–0.81)	
No. of positive lymph nodes				0.09
1	65/217	82/220	0.79 (0.52–1.21)	
2 or 3	61/163	70/158	0.83 (0.53–1.30)	
≥4	36/95	62/98	0.48 (0.28–0.81)	
Type of positive lymph node				0.21
Microscopic	54/210	76/193	0.61 (0.39–0.96)	
Macroscopic	108/265	138/283	0.80 (0.58–1.11)	
Ulceration				0.29
Yes	73/197	110/203	0.64 (0.44–0.94)	
No	79/257	88/244	0.80 (0.54–1.20)	
Lymph-node and ulceration status				0.35
Microscopic and ulceration	28/99	43/88	0.54 (0.29–0.99)	
Macroscopic and ulceration	45/98	67/115	0.76 (0.46–1.23)	
Microscopic and no ulceration	21/104	29/97	0.62 (0.30–1.29)	
Macroscopic and no ulceration	58/153	59/147	0.90 (0.56–1.45)	



Eggermont AM et al. NEJM 2016;375:1875-1855

- **A 5 años FUP, Ipilimumab mejoró resultados melanoma de alto riesgo y estadio III**
  - ✓ Tasas de supervivencia a 5a= OS 11%, DMFS 9% y RFS 11% > placebo
  - ✓ Beneficio incierto/ausente para estadio IIIA; *IIIB-C con 1-3 gg ?*
- **> 50% grado 3/4**
- **> 50% discontinuaron tratamiento** = *Los resultados no pueden probar ni refutar el valor de la terapia de mantenimiento*
- *3 mg probablemente iguales resultados*

APROBADO POR LA FDA (2015) estadio III, a 10 mg/kg

Eggermont AM et al. NEJM 2016;375:1875-1855

Preliminary Safety and Efficacy of the Ipilimumab Arms in U.S. Intergroup E1609: A Phase III of Adjuvant Ipilimumab (3 or 10 mg/kg) vs. High-Dose Interferon α-2b for Resected High-Risk Melanoma

Ahmad A. Tarhini[1], Sandra J. Lee[2], F. Stephen Hodi[3], Uma N. M. Rao[1], Gary I. Cohen[4], Omid Hamid[5], Laura F. Hutchins[6], Jeffrey A. Sosman[7], Harriet M. Kluger[8], Vernon K. Sondak[9], Henry B. Koon[10], Donald P. Lawrence[11], Kari L. Kendra[12], David R. Minor[13], Carrie B. Lee[14], Mark R. Albertini[15], Lawrence E. Flaherty[16], Teresa M. Petrella[17], John M. Kirkwood[1]

[1]University of Pittsburgh, Pittsburgh, Pennsylvania; [2]Dana Farber Cancer Institute – ECOG-ACRIN Biostatistics Center, Boston, Massachusetts; [3]Dana Farber Cancer Institute, Boston, Massachusetts; [4]Greater Baltimore Medical Center, Baltimore, Maryland; [5]The Angeles Clinic & Research Institute, Los Angeles, California; [6]University of Arkansas, Little Rock, Arkansas; [7]Northwestern University, Chicago, Illinois; [8] Yale University, New Haven, Connecticut; [9]H. Lee Moffitt Cancer Center, Tampa, Florida; [10]Case Western Reserve University, Cleveland, Ohio; [11]Massachusetts General Hospital, Boston, Massachusetts; [12]Ohio State University, Columbus, Ohio; [13]Sutter-California Pacific Medical Center, San Francisco, California; [14]University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; [15]University of Wisconsin, Madison, Wisconsin; [16]Wayne State University/Karmanos Cancer Institute, Detroit, Michigan; [17]Odette Cancer Center, Toronto, Ontario

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17 Presented by: Ahmad Tarhini, MD, PhD

ECOG-ACRIN cancer research group
Reshaping the future of patient care

- **Melanoma de alto riesgo resecado** (*estratificado por estadio IIIB, IIIC, M1a, M1b*) a **ipi10** o **ipi3** vs **HDI.**
- Activado 5/25/11 y reclutamiento completado en 8/15/14
  - ✓ **Reclutamiento a ipi10 suspendido por toxicidad** (23/09 – 16/11/2013)
  - ✓ Población final –> 1670 pacientes (511 ipi10, 523 ipi3 y 636 HDI)
- **RFS y OS como objetivos primarios**
- Seguridad
  - Eventos adversos relacionados (AEs) fueron reportados en 503 ipi10 y 516 ipi3 pts.

≥ G3 AEs
57% ipi 10 vs 36.4% ipi 3

Discontinuación de tratamiento
(*during the initial 4 dose induction phase*)
53.8% ipi 10 vs 35.2% ipi 3

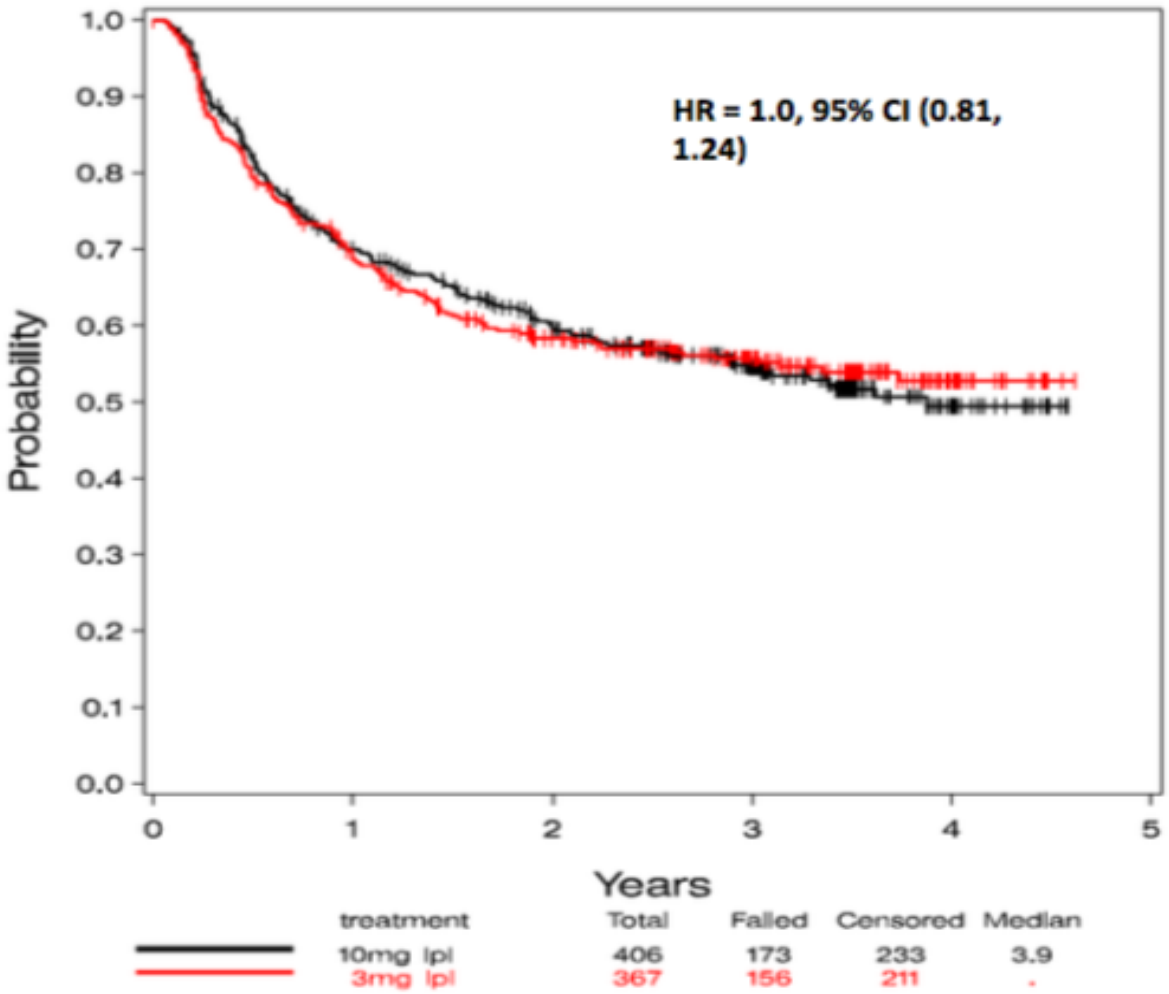
ASCO 2017: Presented by Ahmad Tarhini, MD. PhD

Median FUP
of 3.1 years

Drug Related Deaths

IPI 3 : 2pts
IPI 10 : 8 pts

RFS: Ipi10 vs. Ipi3 Adjuvant Therapy (unplanned interim analysis)



Seguridad relativa y el RFS preliminar, no comparativa de los brazos Ipi3 vs Ipi10 partir del 3/2/17

ASCO 2017: Presented by Ahmad Tarhini, MD. PhD

Adjuvant Therapy With Nivolumab Versus Ipilimumab After Complete Resection of Stage III/IV Melanoma: A Randomized, Double-blind, Phase 3 Trial (CheckMate 238)

Jeffrey Weber,[1] Mario Mandala,[2] Michele Del Vecchio,[3] Helen Gogas,[4] Ana M. Arance,[5] C. Lance Cowey,[6] Stéphane Dalle,[7] Michael Schenker,[8] Vanna Chiarion-Sileni,[9] Ivan Marquez-Rodas,[10] Jean-Jacques Grob,[11] Marcus Butler,[12] Mark R. Middleton,[13] Michele Maio,[14] Victoria Atkinson,[15] Paola Queirolo,[16] Veerle de Pril,[17] Anila Qureshi,[17] James Larkin,[18*] Paolo A. Ascierto[19*]

906 pts

- High-risk completely resected
- Stage IIIB/C or IV
- **1º endpoint --> RFS** (ITT)
- *Complete regional lymphadenectomy required within 12 weeks before randomization*

Median follow-up 18 months

R

NIVOLUMAB
3 mg/kg every 2 weeks
(n = 453)

IPILIMUMAB
***10 mg/kg** every 3 weeks for 4 doses, then every 12 weeks*
(n = 453)

Follow-up

Maximun treatment duration of 1 year

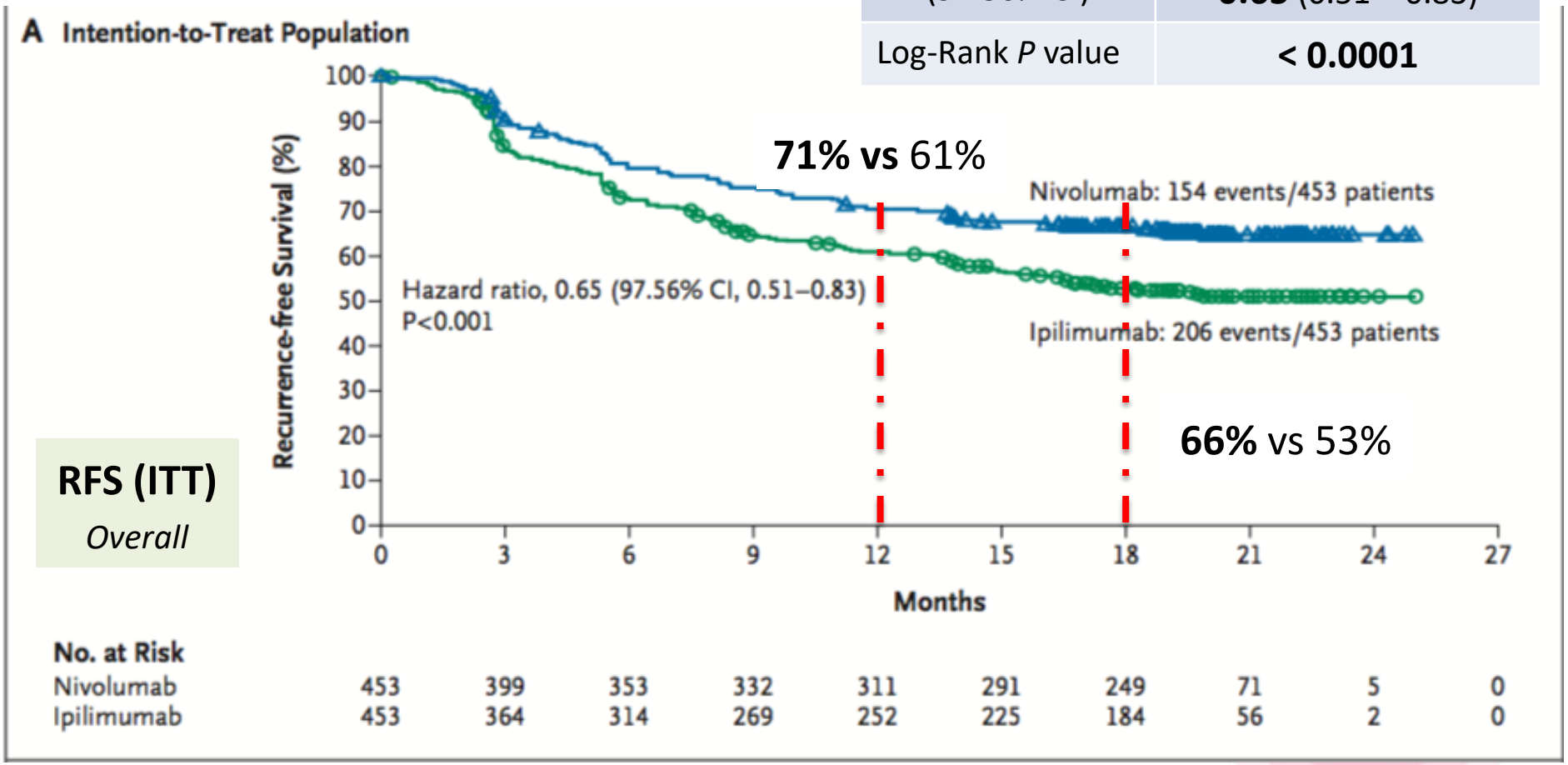
Weber et al. N Engl J Med 2017; 377:1824-1835

	NIVO (N =435)	IPI (N =453)
Disease stage — no. (%)		
IIIB	163 (36.0)	148 (32.7)
IIIC	204 (45.0)	218 (48.1)
IV	82 (18.1)	87 (19.2)
Other or not reported	4 (1.0)	0
Type of lymph-node involvement in stage III — no./total no. (%)		
Microscopic	125/369 (33.9)	134/366 (36.6)
Macroscopic	219/369 (59.3)	214/366 (58.5)
Not reported	25/369 (6.8)	18/366 (4.9)
Tumor ulceration in stage III — no./total no. (%)		
Yes	153/369 (41.5)	135/366 (36.9)
No	201/369 (54.5)	216/366 (59.0)
Not reported	15/369 (4.1)	15/366 (4.1)
Tumor PD-L1 expression — no. (%)		
<5%	275 (60.7)	286 (63.1)
≥5%	152 (33.6)	154 (34.0)
Could not be determined or not reported	26 (5.7)	13 (2.9)
BRAF status — no. (%)		
Mutation	187 (41.3)	194 (42.8)
No mutation	197 (43.5)	214 (47.2)
Not reported	69 (15.2)	45 (9.9)
LDH ≤ ULN, %	91	91

Weber et al. N Engl J Med 2017; 377:1824-1835

	NIVO	IPI
Events/patients	154/453	206/453
Median (95% CI)	NR	NR
HR (97.56% CI)	**0.65** (0.51 – 0.83)	
Log-Rank *P* value	**< 0.0001**	

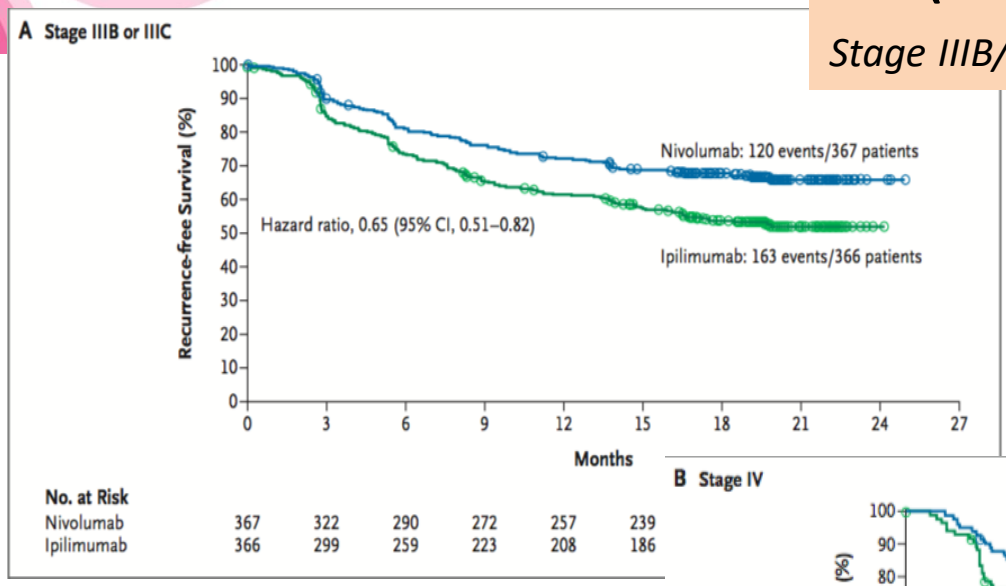
RFS (ITT)
Overall



Weber et al. N Engl J Med 2017; 377:1824-1835

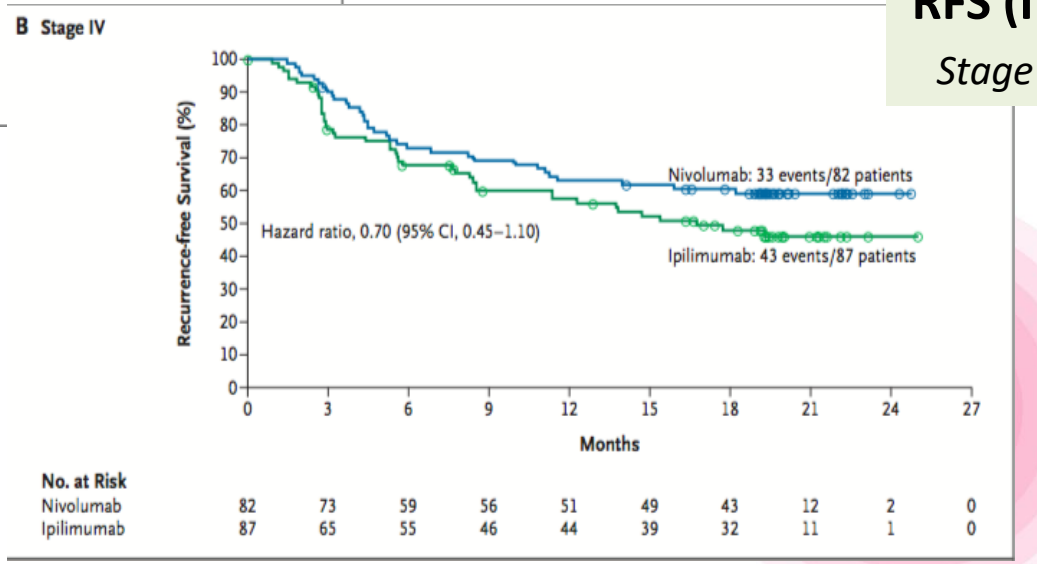
RFS (ITT)

Stage IIIB/C



RFS (ITT)

Stage IV

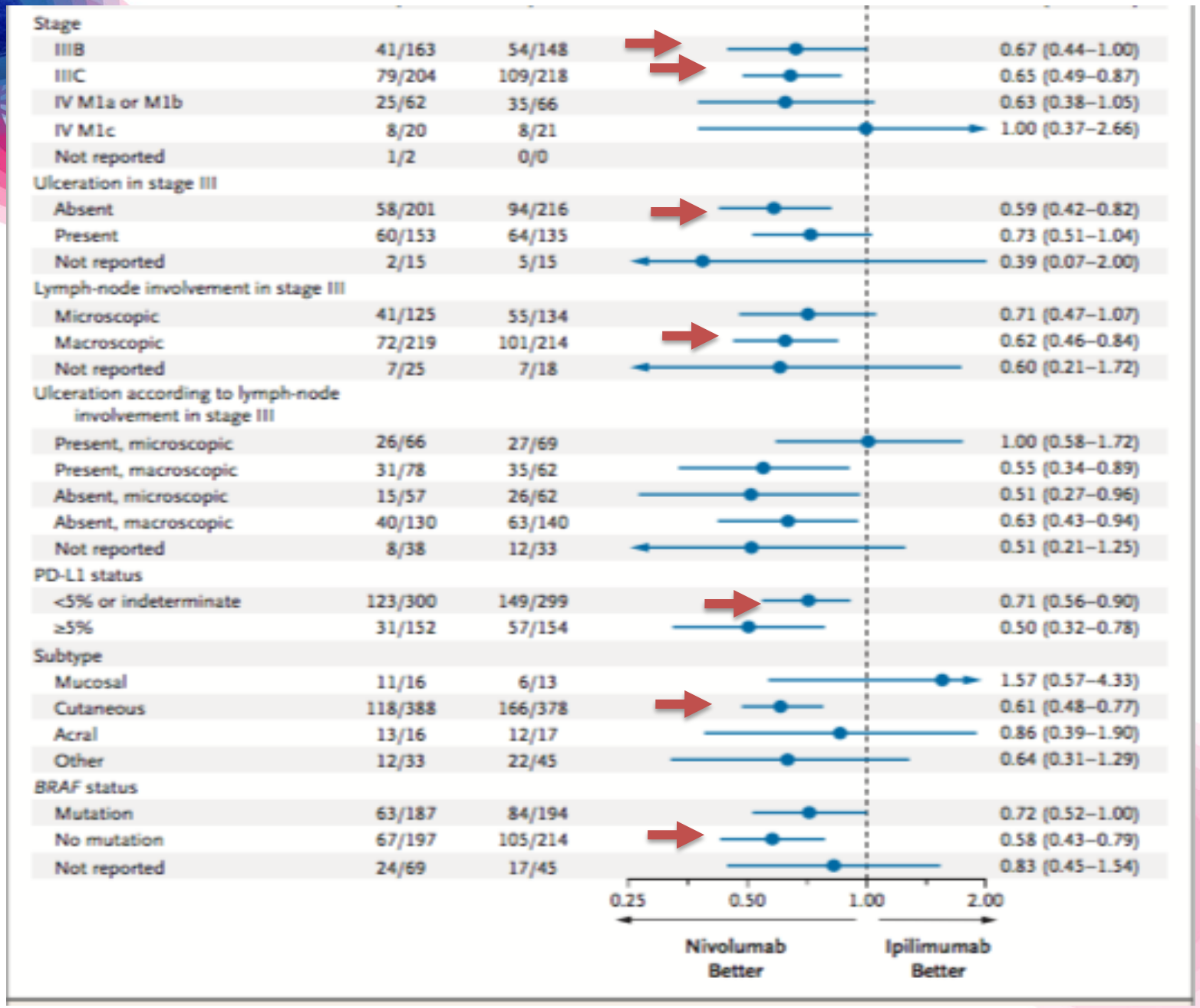


Weber et al. N Engl J Med 2017; 377:1824-1835

- Toxicidad → **G3/4 =** 14% vs **45.9%** con **Ipilimumab**
  - ✓ 2 muertes debidos a efectos adversos en el brazo de ipilimumab (>100 días tras tratamiento)
  - ✓ Discontinuación por efectos adversos de cualquier grado = 9.7% vs **42.6%**

- Beneficio de nivolumab sobre ipilimumab independientemente de…
  - **PD-L1 status (**<5% vs ≥ 5%)
  - Todos los subgrupos, incluidos estadio, edad, ulceración del primario y **status de *BRAF***

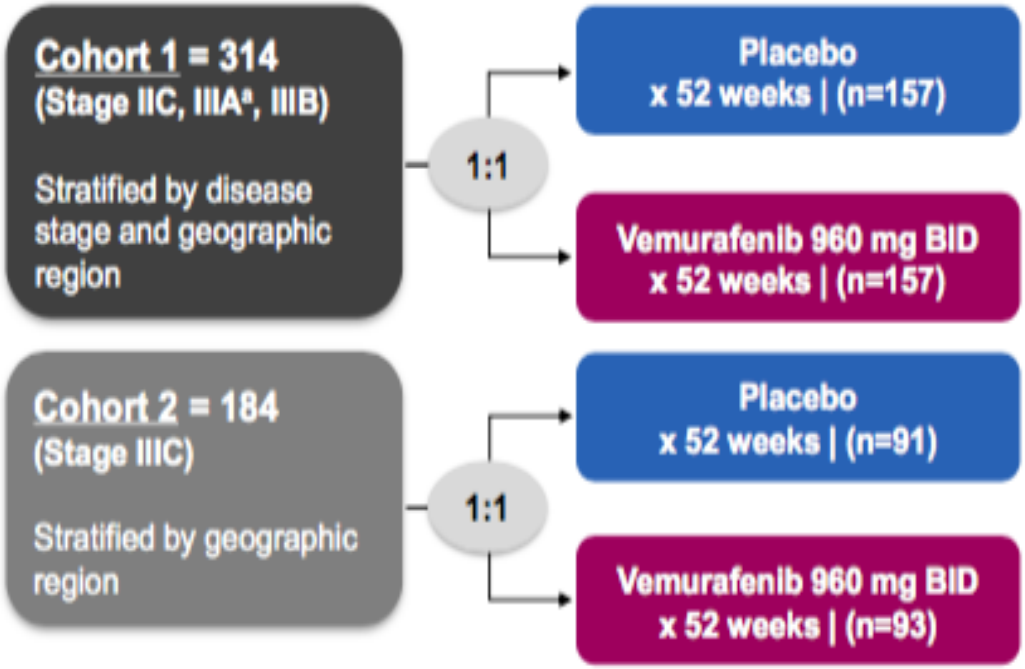
Weber et al. N Engl J Med 2017; 377:1824-1835



Weber et al. N Engl J Med 2017; 377:1824-1835

BRIM8: a randomized, double-blind, placebo-controlled study of adjuvant vemurafenib in patients with completely resected *BRAF*$^{V600+}$ melanoma at high risk for recurrence

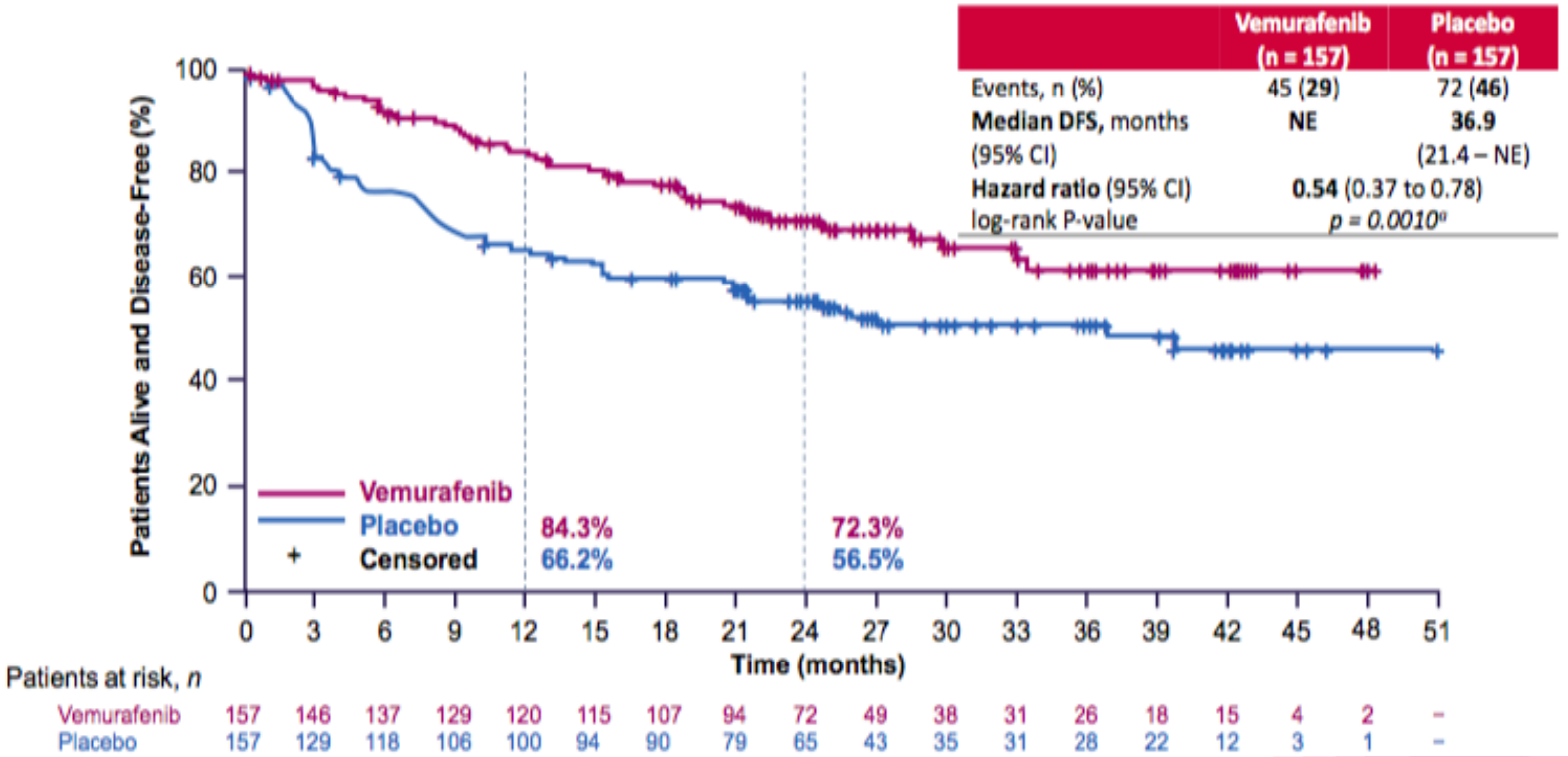
Karl Lewis,[1] Michele Maio,[2] Lev Demidov,[3] Mario Mandalà,[4] Paolo A. Ascierto,[5] Christopher Herbert,[6] Andrzej Mackiewicz,[7] Piotr Rutkowski,[8] Alexander Guminski,[9] Grant Goodman,[10] Brian Simmons,[10] Chenglin Ye,[10] Yibing Yan,[10] Dirk Schadendorf[11]



- **Primary endpoint**
  - DFS
- **Secondary endpoints**
  - DMFS
  - OS
  - Safety
  - HRQoL

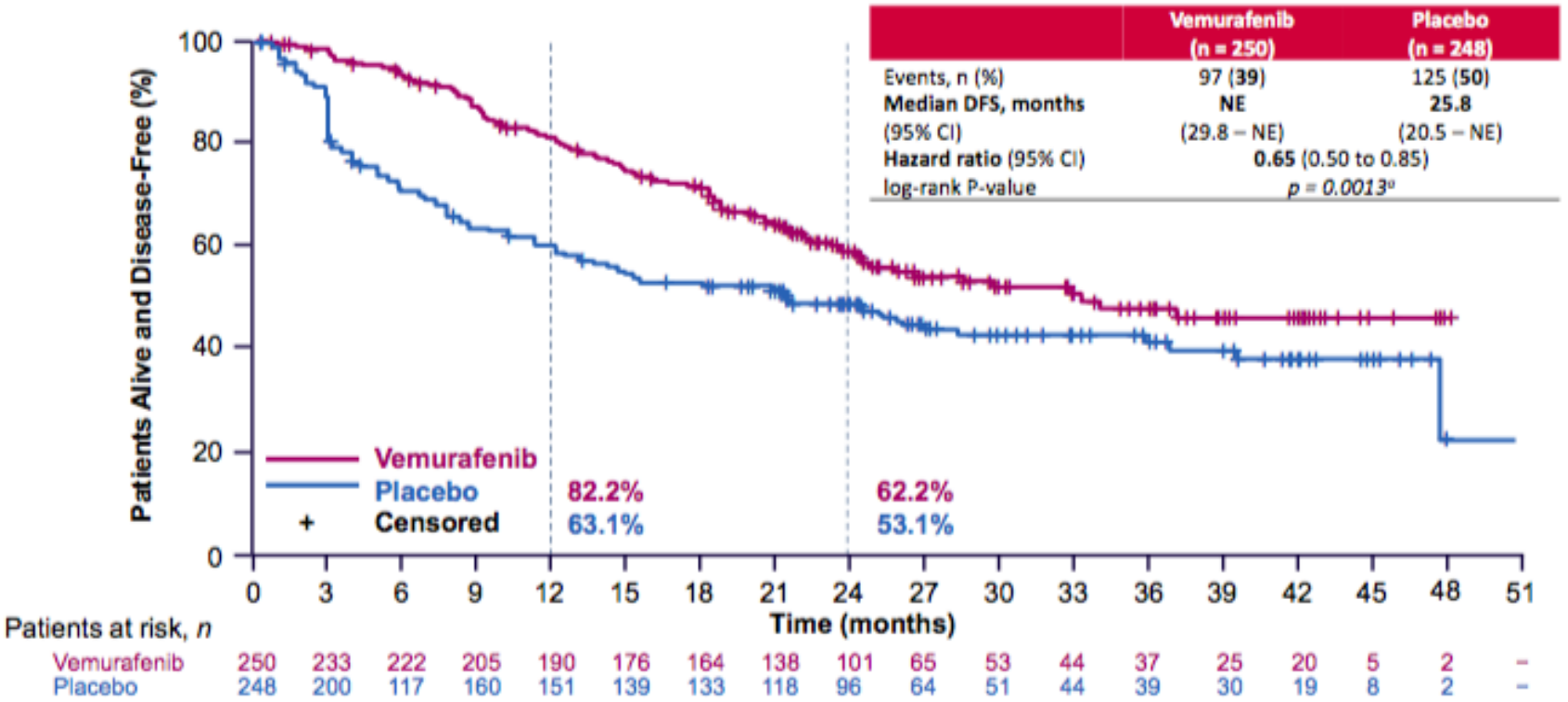
Maio M et al. Lancet Oncol. 2018 Feb 21. pii: S1470-2045 (18) 30106-2.

BRIM8: Primary DFS (Cohort 1, stage IIC – IIIB)



Maio M et al. Lancet Oncol. 2018 Feb 21. pii: S1470-2045 (18) 30106-2.

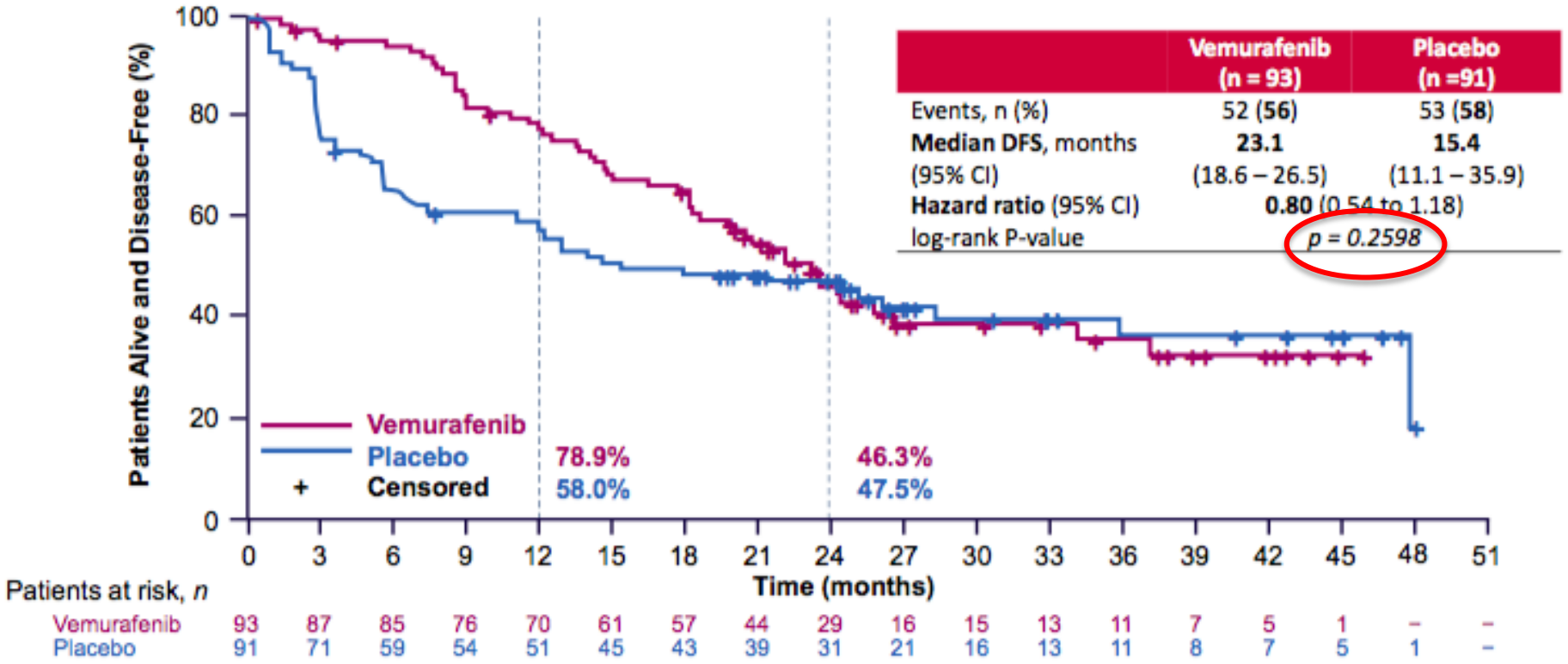
Pre-specified exploratory DFS analysis in **pooled ITT population**



	Vemurafenib (n = 250)	Placebo (n = 248)
Events, n (%)	97 (39)	125 (50)
Median DFS, months	**NE**	**25.8**
(95% CI)	(29.8 – NE)	(20.5 – NE)
Hazard ratio (95% CI)	**0.65** (0.50 to 0.85)	
log-rank P-value	*p = 0.0013*[a]	

Maio M et al. Lancet Oncol. 2018 Feb 21. pii: S1470-2045 (18) 30106-2.

BRIM8: Primary DFS (Cohort 2, stage IIIC)



	Vemurafenib (n = 93)	Placebo (n =91)
Events, n (%)	52 (56)	53 (58)
Median DFS, months	**23.1**	**15.4**
(95% CI)	(18.6 – 26.5)	(11.1 – 35.9)
Hazard ratio (95% CI)	**0.80** (0.54 to 1.18)	
log-rank P-value	*p = 0.2598*	

Maio M et al. Lancet Oncol. 2018 Feb 21. pii: S1470-2045 (18) 30106-2.

- Estadio IIC = solo 27 pacientes!!
- Seguridad

Vemurafenib (247 pts) vs Placebo (247 pts)

- ✓ Discontinuado (%)→ **20** vs 2
- ✓ Intensidad de dosis(%) → **82** vs 99
- ✓ **G3-4** (%) → **57** vs 15
- ✓ **G5** (%) → < 1* vs 0

- Conclusión: <u>No se cumplió el objetivo primario del estudio</u>

EL EFECTO NO FUE ESTADÍSTICAMENTE SIGNIFICATIVO

Maio M et al. Lancet Oncol. 2018 Feb 21. pii: S1470-2045 (18) 30106-2.

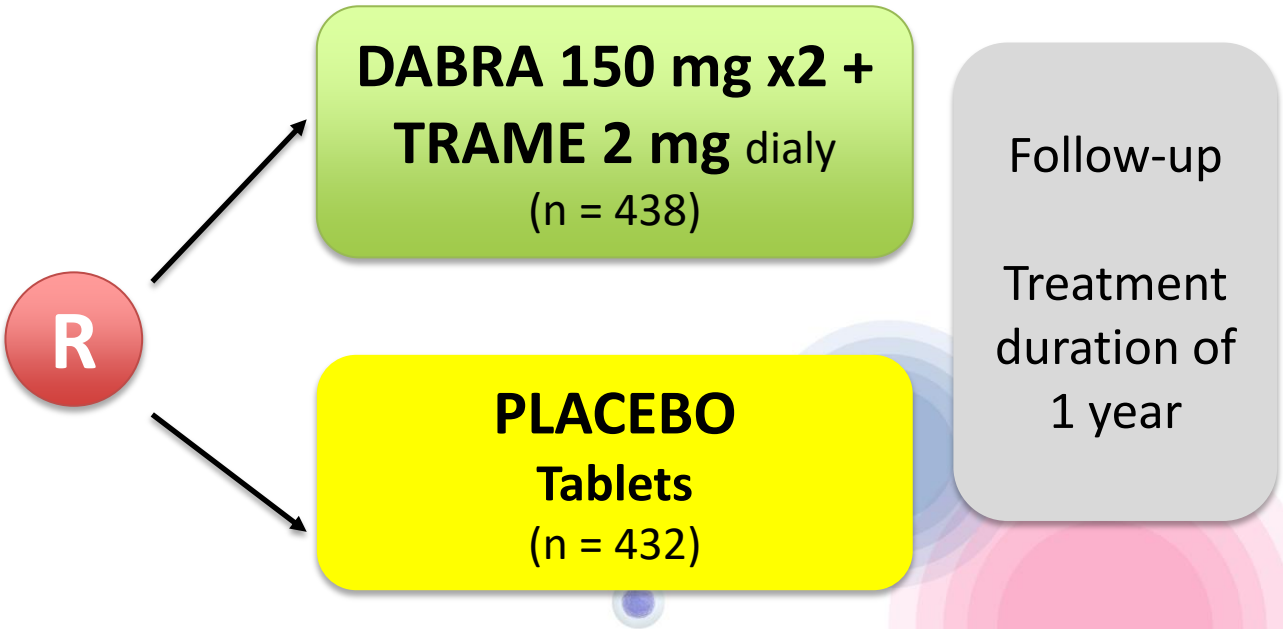
COMBI-AD: Adjuvant Dabrafenib plus trametinib for Resected Stage III *BRAf* V600–Mutant melanoma

Axel Hauschild, Mario Santinami, Georgina V. Long, Victoria Atkinson, Mario Mandalà, Vanna Chiarion-Sileni, James Larkin, Marta Nyakas, Caroline Dutriaux, Andrew Haydon, Caroline Robert, Laurent Mortier, Jacob Schachter, Ran Ji, Pingkuan Zhang, Bijoyesh Mookerjee, Jeff Legos, Richard Kefford, Reinhard Dummer, John M. Kirkwood

870 pts

- High-risk completely resected
- Stage III
- *1º endpoint* : **RFS** (New primary melanoma considered as an event).
- *2º endpoints*: **OS, DMFS, FFR, Safety**
- *BRAF mutation:* **V600E y V600K**

Median follow-up of 2.8 years,



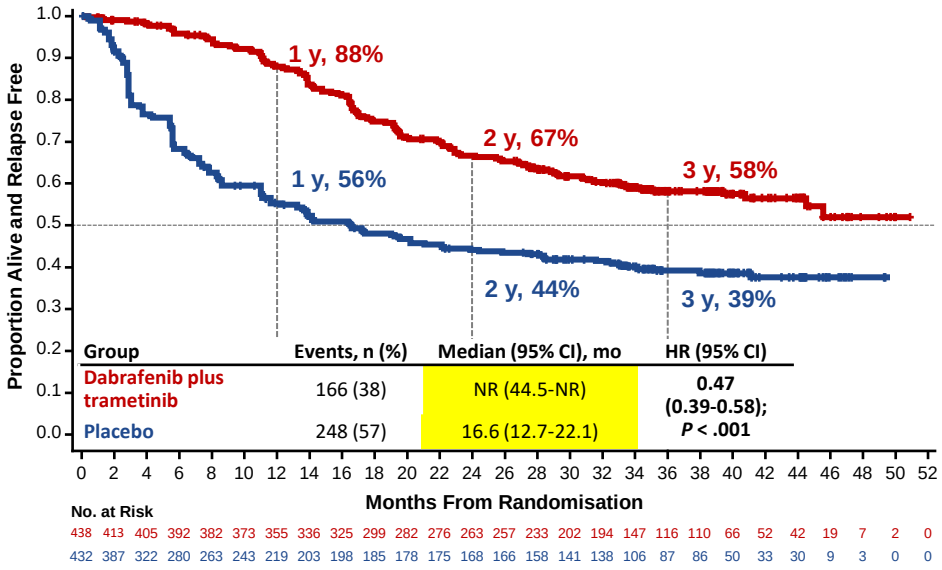
Gv Long et al. N Engl J Med. 2017 Nov 9; 377 (19): 1813-1823.

	Dabrafenib Plus Trametinib (n = 438)	Placebo (n = 432)	Total (N = 870)
Median age (range), years	50 (18-89)	51 (20-85)	50 (18-89)
Male, n (%)	195 (45)	193 (45)	388 (45)
***BRAF* mutation status, n (%)**			
V600E	397 (91)	395 (91)	792 (91)
V600K[b]	41 (9)	37 (9)	78 (9)
ECOG performance status of 0, n (%)	402 (92)	390 (90)	792 (91)
Disease stage, n (%)			
IIIA	83 (19)	71 (16)	154 (18)
IIIB	169 (39)	187 (43)	356 (41)
IIIC	181 (41)	166 (38)	347 (40)
III (unspecified)	5 (1)	8 (2)	13 (1)
Number of positive lymph nodes, n (%)			
1	177 (40)	183 (42)	360 (41)
2 or 3	158 (36)	150 (35)	308 (35)
≥ 4	73 (17)	72 (17)	145 (17)
Type of lymph node involvement, n (%)			
Microscopic	152 (35)	157 (36)	309 (36)
Macroscopic	158 (36)	161 (37)	319 (37)
Not reported	128 (29)	114 (26)	242 (28)
Primary tumour ulceration, n (%)			
Yes	179 (41)	177 (41)	356 (41)
No	253 (58)	249 (58)	502 (58)
In-transit disease, n (%)			
Yes	51 (12)	36 (8)	87 (10)
No	387 (88)	395 (91)	782 (90)

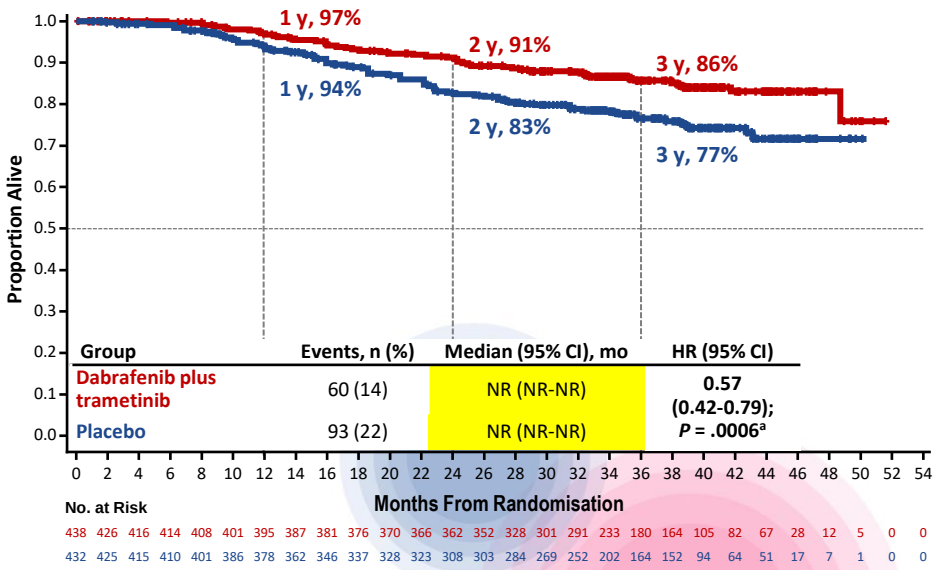
	Dabrafenib Plus Trametinib (n = 435)[a]	Placebo (n = 432)	Total (N = 867)
Patient status, n (%)			
Died	60 (14)	93 (22)	153 (18)
Ongoing in follow-up[b]	331 (76)	277 (64)	608 (70)
Withdrawn	47 (11)	62 (14)	109 (13)
Reasons for study withdrawal, n (%)			
Lost to follow-up	11 (3)	18 (4)	29 (3)
Investigator discretion	5 (1)	4 (< 1)	9 (1)
Withdrew consent	31 (7)	40 (9)	71 (8)

COMBI-AD Primary Analysis

Relapse-Free Survival (primary endpoint)



Overall Survival

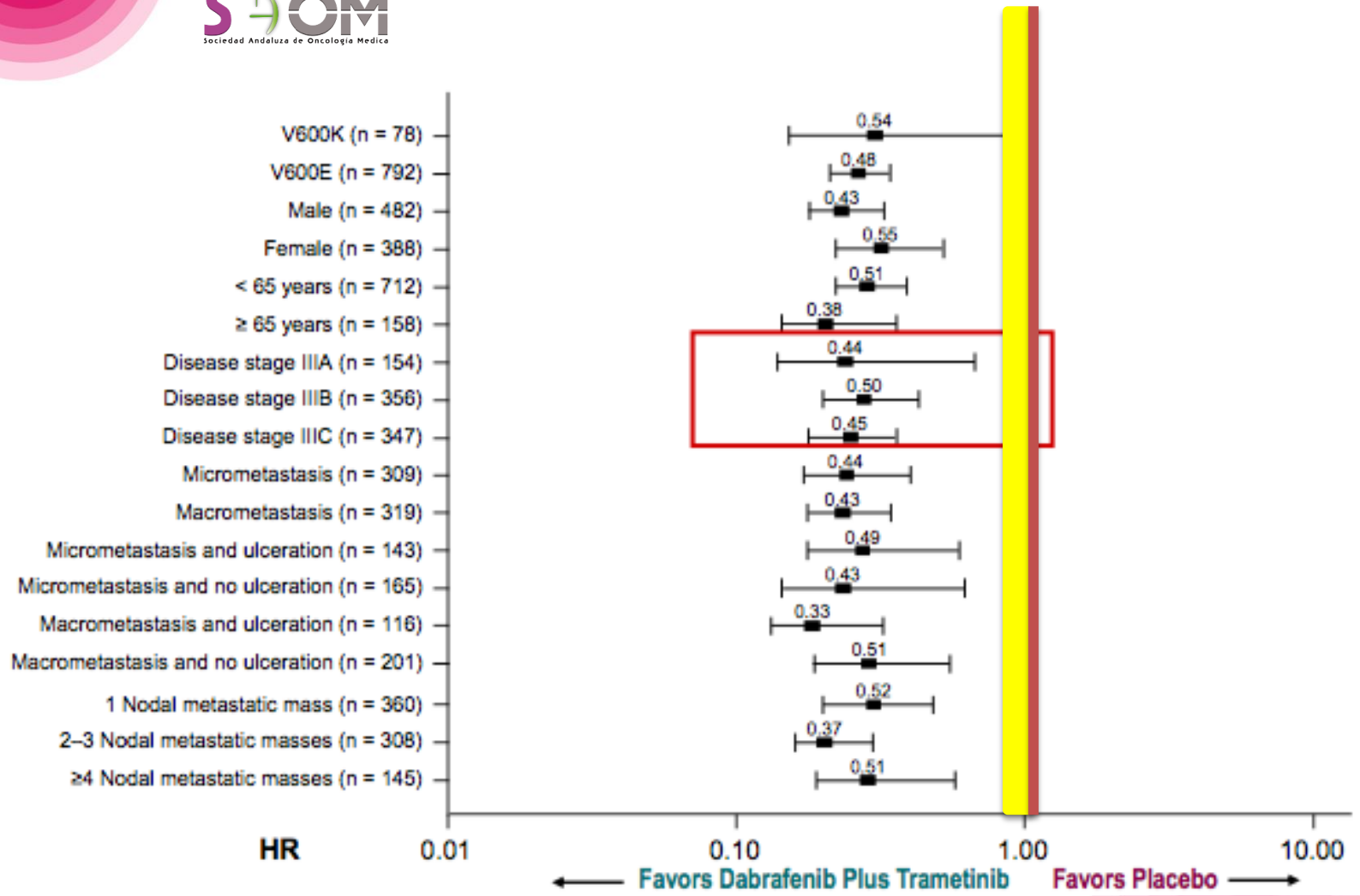


Data cutoff: 30 June 2017.

[a] Prespecified significance boundary (P = .000019); next interim analysis planned when 50% of events have occurred.
NR, not reached.
Long GV, et al. *N Engl J Med*. 2017 Sep 10. [Epub ahead of print].

PRESENTED BY GV LONG AT WCM/SMR 2017

Gv Long et al. N Engl J Med. 2017 Nov 9; 377 (19): 1813-1823.



Gv Long et al. N Engl J Med. 2017 Nov 9; 377 (19): 1813-1823.

Seguridad

- AEs mas frecuentes en el brazo experimental fueron pirexia y astenia (63% y 47% respectivamente)

AE Category, n (%)	Dabrafenib Plus Trametinib (n = 435)	Placebo (n = 432)
Any AE	422 (97)	380 (88)
AEs related to study treatment	398 (91)	272 (63)
Grade 3/4 AEs related to study treatment	136 (31)	21 (5)
Any SAE	155 (36)	44 (10)
SAEs related to study treatment	117 (27)	17 (4)
AEs leading to dose interruption	289 (66)	65 (15)
AEs leading to dose reduction	167 (38)	11 (3)
AEs leading to treatment discontinuation[a]	114 (26)	12 (3)
Fatal AEs related to study drug	0	0

Gv Long et al. N Engl J Med. 2017 Nov 9; 377 (19): 1813-1823.

Guías clínicas

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

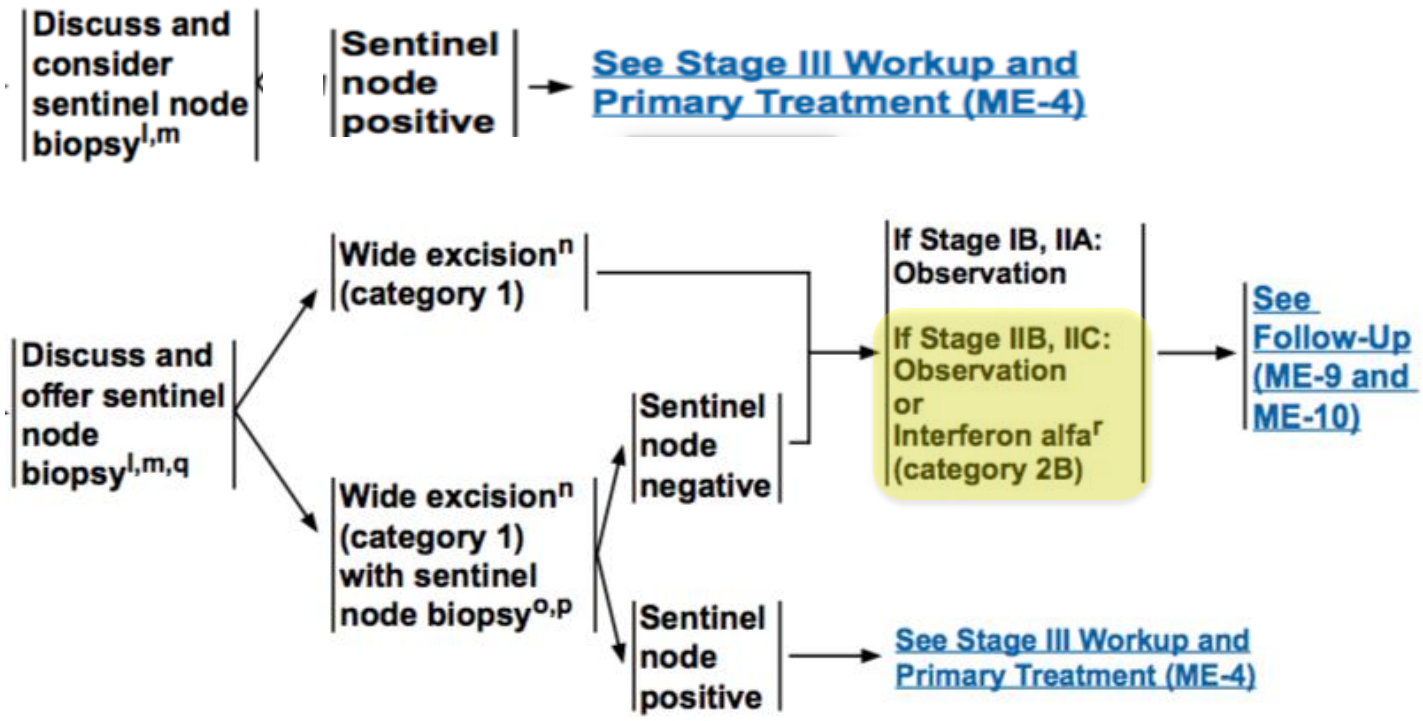
Melanoma

Version 2.2018 — January 19, 2018

NCCN.org

Stage IB (T1b) (<0.8 mm thick with ulceration or 0.8–1.0 mm thick ± ulceration)[i]

Stage IB (T2a) or II (>1 mm thick, any feature, N0)[q]



[x] Interferon can be given as high-dose alfa interferon for one year or as peginterferon alfa-2b for up to 5 years. Adjuvant interferon has been shown to improve DFS (category 1), but there is no impact on overall survival.

NOTE: All recommendations are category 2A unless otherwise indicated.

II CURSO DE RESIDENTES DE SAOM

GRANADA, 13 y 14 DE ABRIL 2018

Organizado por:

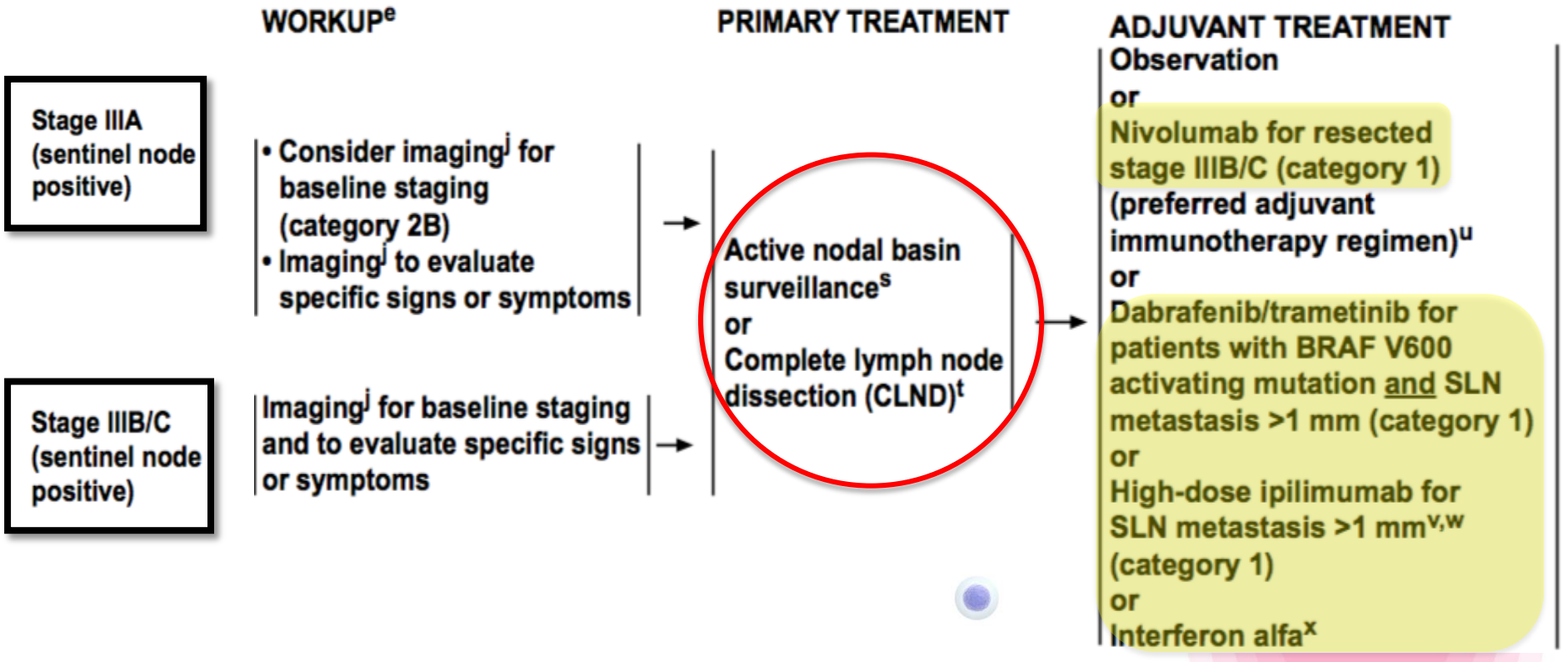
SAOM Sociedad Andaluza de Oncología Médica

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Melanoma

Version 2.2018 — January 19, 2018

NCCN.org



[x] Interferon can be given as high-dose alfa interferon for one year or as peginterferon alfa-2b for up to 5 years. Adjuvant interferon has been shown to improve DFS (category 1), but there is no impact on overall survival.

NOTE: All recommendations are category 2A unless otherwise indicated.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Melanoma

Version 2.2018 — January 19, 2018

NCCN.org

ADJUVANT TREATMENT

CLINICAL/ PATHOLOGIC STAGE	WORKUP[e]	PRIMARY TREATMENT	Locoregional option:	Systemic options:
Stage III (clinically positive node[s])	• FNA preferred, if feasible, or core, incisional, or excisional biopsy • Imaging[j] for baseline staging and to evaluate specific signs or symptoms	Wide excision of primary tumor[n] (category 1) + complete therapeutic lymph node dissection[y]	• Consider RT to nodal basin in selected high-risk patients based on location, size, and number of involved nodes, and/or macroscopic extranodal extension[z,aa] (category 2B)	• Observation • Nivolumab (category 1) (preferred adjuvant immunotherapy regimen)[u] • Dabrafenib/trametinib for patients with *BRAF* V600 activating mutation (category 1) • High-dose ipilimumab[v] (category 1) • Interferon alfa[x] • Biochemotherapy (category 2B)[bb]

[x] Interferon can be given as high-dose alfa interferon for one year or as peginterferon alfa-2b for up to 5 years. Adjuvant interferon has been shown to improve DFS (category 1), but there is no impact on overall survival.

NOTE: All recommendations are category 2A unless otherwise indicated.

II CURSO DE RESIDENTES DE SAOM

GRANADA, 13 y 14 DE ABRIL 2018

Organizado por:

clinical practice guidelines

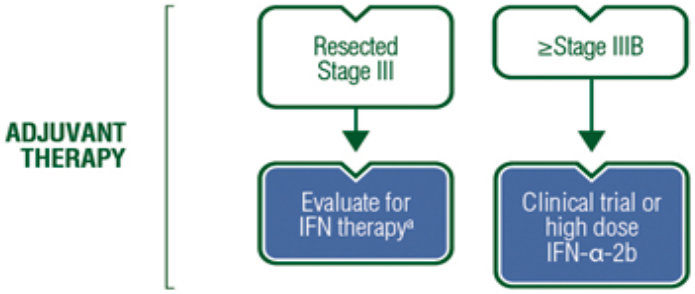
Annals of Oncology 26 (Supplement 5): v126–v132, 2015
doi:10.1093/annonc/mdv297

Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

R. Dummer[1], A. Hauschild[2], N. Lindenblatt[3], G. Pentheroudakis[4] & U. Keilholz[5], on behalf of the ESMO Guidelines Committee*

[1]Department of Dermatology, University Hospital Zürich, Zürich, Switzerland; [2]Department of Dermatology, University Hospital Schleswig-Holstein, Kiel, Germany; [3]Division of Plastic and Reconstructive Surgery, University Hospital Zürich, Zürich, Switzerland; [4]Ioannina University Hospital, Ioannina, Greece; [5]Charité Comprehensive Cancer Center, Charité-Universitätsmedizin, Berlin, Germany

Sentinel LN biopsy in melanoma with a tumour thickness of >1 mm and >0.75 mm and additional risk factors such as ulceration or mitotic rate (pT1b) are recommended for precise staging [II, B] [14]. A complete lymphadenectomy of regional LNs must be discussed with the patient, if the sentinel node was found positive for metastases [III, C]. However, this procedure offers just a relapse-free survival (RFS) benefit without proven effect on overall survival (OS) [15]. Sentinel LN biopsy should be carried out only in experienced centres.



[a]Patients with microscopic regional nodal involvement and/or ulcerated primaries most likely to benefit IFN, interferon

Clin Transl Oncol (2018) 20:69–74
https://doi.org/10.1007/s12094-017-1768-1

CLINICAL GUIDES IN ONCOLOGY

SEOM clinical guideline for the management of malignant melanoma (2017)

A. Berrocal[1] · A. Arance[2] · V. E. Castellon[3] · L. de la Cruz[4] · E. Espinosa[5] · M. G. Cao[6] · J. L. G. Larriba[7] · I. Márquez-Rodas[8] · A. Soria[9] · S. M. Algarra[10]

Surgery		
All melanoma suspected lesion must be biopsied	A	1a
Surgical margins should be Breslow adapted	A	1a
Melanomas of more than 1 mm should undergo sentinel node biopsy	A	1a
Melanomas of 0.75 mm should undergo sentinel node biopsy if there are risk factors	B	1a
Lymph node resection should be performed if sentinel node is positive or clinically evident	A	2a
Solitary metastases must be surgically removed	B	2b
Adjuvant therapy		
High risk melanoma patients could receive interferon adjuvant therapy	B	1a
If surgical margins are affected adjuvant radiotherapy may be added	B	2b
Adjuvant radiotherapy should be considered if more than 3 nodes are present, one is larger than 3 cm or capsule is broken	C	1b

CONCLUSIONES

- DeCOG & MSLT-II = **LINFADENECTOMÍA en SLNB ¿Sí o No?**
  - Necesidad de adaptación de los hallazgos de estos estudios en los próximos estudios en adyuvancia
  - Búsqueda de soluciones para perfeccionar la estadificacion y estratificación pronóstica de pacientes mediante el tratamiento quirúrgico

BUT…

Perdida de información para el calculo de riesgo

Hasta ahora necesario para la toma de decisión de tratamiento adyuvante !!!

- *Still rol for IFN therapy?*
  - ✓ Continua sin un papel bien definido en la configuración del tratamiento adyuvante para el melanoma
  - ✓ **EN ZONAS DEL MUNDO DONDE NO HAY OTRAS OPCIONES** (*viability/price*)
  - ✓ **"SOLO" en primario ulcerado** y estadio **III N+ microscópico**
- *Still role ipilimumab in near future? (US)*
  - ✓ 4 dosis a 3 mg/kg vs alternativas

TRAS LA APROBACION DE NIVO y D+T, PROBABLEMENTE NO

"THE BEST PERFORMERS IN STAGE IV ARE THE BEST PERFORMERS IN THE ADJUVANT SETTING"

- **BRAF$_i$ monoterapia** (stage IIC & IIIB/IIIC)

  FUTURO (MUY) INCIERTO

- **BRAF-MEK$_i$** *(stage IIIA, IIIB & IIIC)*

  Claro **beneficio para RFS-DMFS-OS en estadio III BRAF mutated** y consistente en todos los subgrupos

- **Anti-PDL1** *for all ? (stage IIIB/C & IV resecado)*

  PENDING OVERAL SURVIVAL DATE

  Preferiblemente **BRAF wild-type** (BRAF mutado = HR (95% CI) 0.72 (0.52 – 1.00)

YOU ONLY GET ONE SKIN

PROTECT IT FROM SUN DAMAGE

thanks so much!!