CAMPUS SEOM

Área de formación virtual SEOM

Melanoma y otros tumores cutáneos

Dra. Begoña Campos Balea
Hospital Universitario Lucus Augusti

SEOM
Sociedad Española
de Oncología Médica

Disclosures

- **Speaker & Advisor:**
  - BMS, Roche, MSD, Astra Zeneca, Novartis, Pierre Fabre, Sanofi, Rovi, Leo Pharma

- **Travel and educational expenses:**
  - BMS, Roche, MSD, Lilly, Astra Zeneca, Novartis, Sanofi, Pierre Fabre, Rovi, Leo Pharma

Indice

Indice

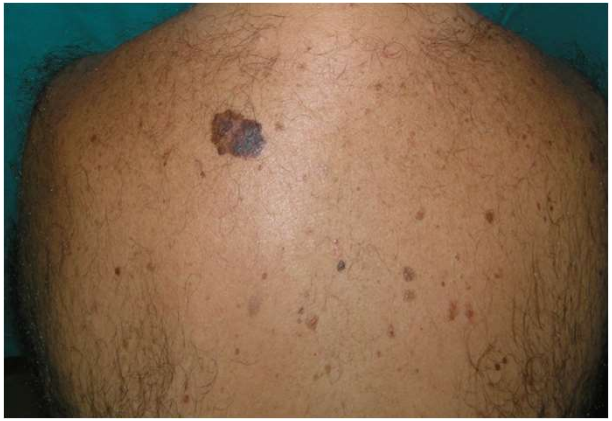
- MELANOMA

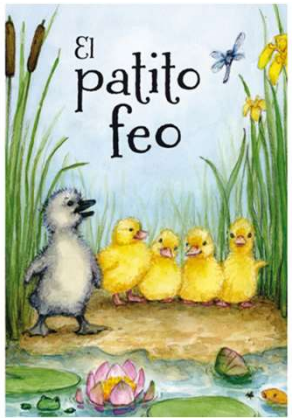
  - Epidemiología, estadiaje, testing molecular.
  - Enfermedad Localizada: cirugía y tratamiento adyuvante.
  - Enfermedad metastásica: tratamiento terapia dirigida e inmunoterapia.

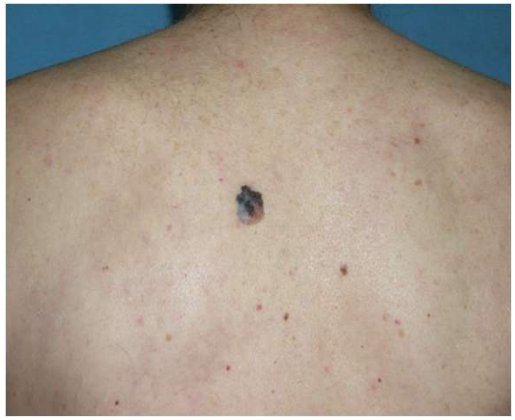
- CARCINOMA DE CÉLULAS ESCAMOSAS CUTÁNEO
- CARCINOMA BASOCELULAR CUTÁNEO
- CARCINOMA DE MERKEL

Melanoma


ABCDE del melanoma: guía para establecer el riesgo de melanoma
A
ASIMETRÍA: las dos mitades del lunar no encajan
B
BORDES: los bordes son irregulares o desiguales
C
COLOR: se presentan múltiples manchas que cambian (negras, marrones, rojas, bronceadas, azules o rosas)
D
DIAMETRO: mayor de 6 mm
E
EVOLUCIÓN: cambios en el aspecto y los síntomas, como sangrado, supuración o picor




El
patito
feo



Incidencia y mortalidad

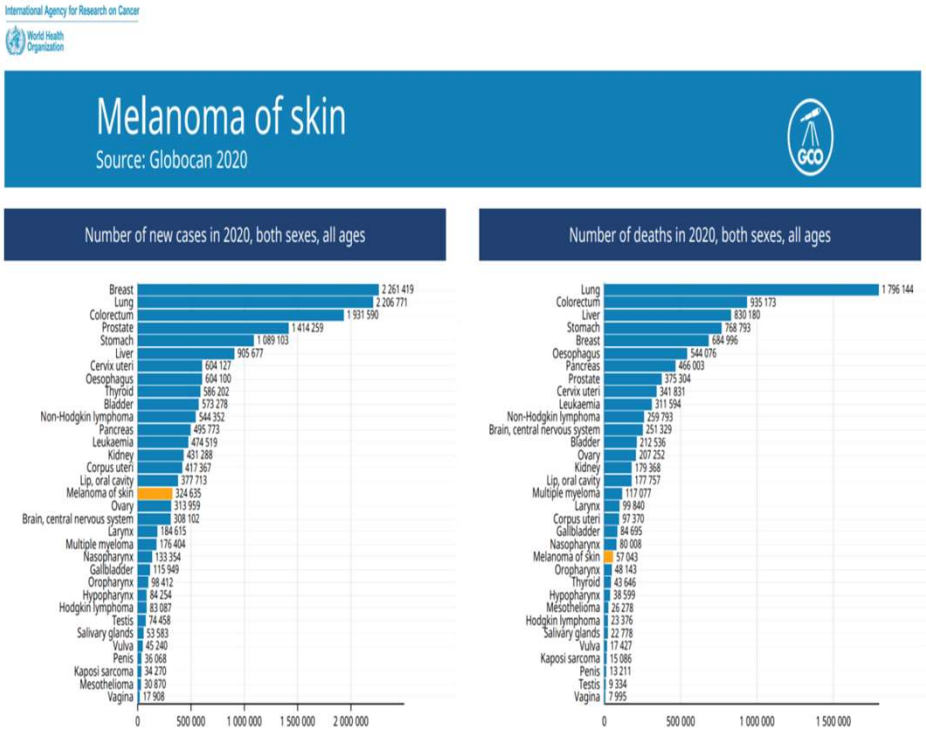


Tabla 2. Estimación del número de nuevos casos de cáncer en España para el año 2023 según tipo tumoral (excluidos los cánceres cutáneos no melanoma) (ambos sexos).

TIPO TUMORAL	N
Cavidad oral y faringe	7.882
Esófago	2.302
Estómago	6.932
Colon	28.465
Recto	14.256
Hígado	6.695
Vesícula biliar	2.648
Páncreas	9.280
Laringe	3.378
Pulmón	31.282
Melanoma de piel	8.049
Mama	35.001
Cérvix uterino	2.326
Cuerpo uterino	7.171
Ovario	3.584
Próstata	29.002
Testículo	1.510
Riñón (sin pelvis)	8.626
Vejiga urinaria	21.694
Encéfalo y sistema nervioso	4.072
Tiroides	6.084
Linfoma de Hodgkin	1.539
Linfomas no hodgkinianos	9.943
Mieloma	3.082
Leucemias	6.411
Otros	18.046
Todos excepto piel no melanoma	279.260

Fuente: Red Española de Registros de Cáncer (REDECAN).

Tabla 5. Fallecimientos por tumores en España en 2021, por causa, ambos sexos.

	Total
Tumores	113.662
Tumor maligno del labio, de la cavidad bucal y de la faringe	2.451
Tumor maligno del esófago	1.780
Tumor maligno del estómago	4.838
Tumor maligno del colon	11.021
Tumor maligno del recto, de la porción rectosigmoide y del ano	4.017
Tumor maligno del hígado y vías biliares intrahepáticas	5.066
Tumor maligno del páncreas	7.663
Otros tumores malignos digestivos	2.515
Tumor maligno de la laringe	1.158
Tumor maligno de la tráquea, de los bronquios y del pulmón	22.438
Otros tumores malignos respiratorios e intratorácicos	476
Tumores malignos del hueso y de los cartílagos articulares	352
Melanoma maligno de la piel	1.056
Otros tumores malignos de la piel y de los tejidos blandos	1.675
Tumor maligno de la mama	6.614
Tumor maligno del cuello del útero	697
Tumor maligno de otras partes del útero	1.628
Tumor maligno del ovario	1.979
Tumores malignos de otros órganos genitales femeninos	626
Tumor maligno de la próstata	5.889
Tumores malignos de otros órganos genitales masculinos	180
Tumor maligno del riñón, excepto pelvis renal	2.270
Tumor maligno de la vejiga	4.464
Otros tumores malignos de las vías urinarias	1.770
Tumor maligno del encéfalo	3.175
Otros tumores malignos neurológicos y endocrinos	624
Tumor maligno de sitios mal definidos, secundarios y de sitios no especificados	4.836

Aunque no es el tumor cutáneo más frecuente, sí es el causante del 80% de las muertes por estos tumores

Año 2021 en España:

incidencia: 8049 casos nuevos

mortalidad: 1056 pacientes

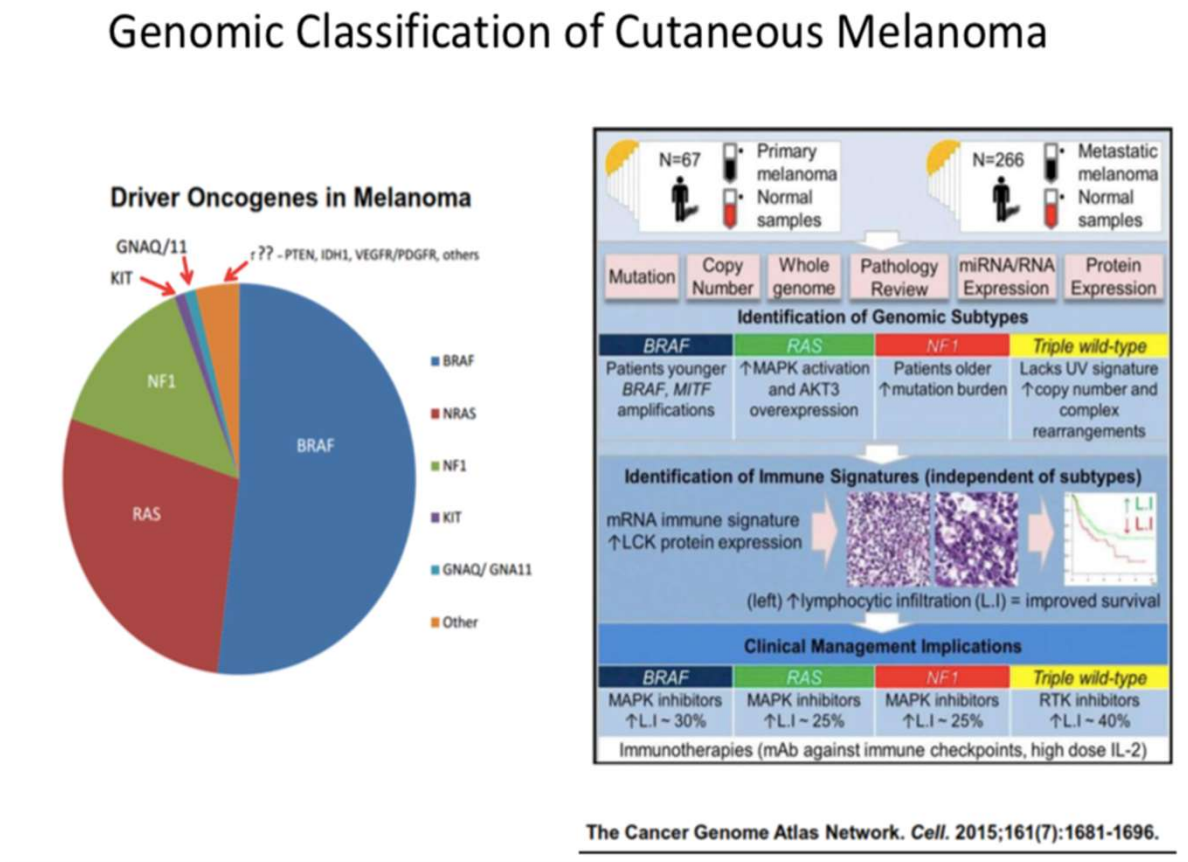
https://seom.org/images/Las_cifras_del_Cancer_en_Espana_2023.pdf

Factores de riesgo

- Nevus
- Factores genéticos
- Fenotipo cutáneo
- Historia familiar MC
- Historia personal MC

- **¡¡Exposición solar!!**

Test moleculares



- Es recomendado solicitar las siguientes mutaciones driver y determinaciones para un diagnóstico confirmado de melanoma estadio IIB, IIC, III (resecable o no) y IV:

- **BRAF V600**
- **NRAS**
- **c-kit**
  - en estadio IV
  - preferiblemente melanoma de mucosas y lentiginoso acral
- Expresión PDL-1 (Nivo + Ipi financiado en PDL1 negativos, entre otros)

- Únicamente tenemos opciones de **tratamiento dirigido** para los melanomas con **mutaciones BRA**F, pero la determinación del resto de mutaciones es importante para identificar pacientes con posibilidades futuras de tratamientos emergentes y para poder derivarlos a unidades con ensayos clínicos dirigidos.

Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-upAnnals of Oncology 30: 1884–1901, 2019. Majem M et all SEOM clinical guideline for the management of cutaneous melanoma (2020). Clin Transl Oncol. 2021 May;23(5):948-960. doi: 10.1007/s12094-020-02539-9. Epub 2021 Mar 2. PMID: 33651321..

Estadificación del Melanoma AJCC 8ª edición

Table 1 Melanoma staging AJCC 8th edition

T category	Thickness	Ulceration status
TX: Primary tumor thickness cannot be assessed (e.g., diagnosis by curettage)	Not applicable	Not applicable
T0: No evidence of primary tumor (e.g., 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	With ulceration
	0.8–1.0 mm	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

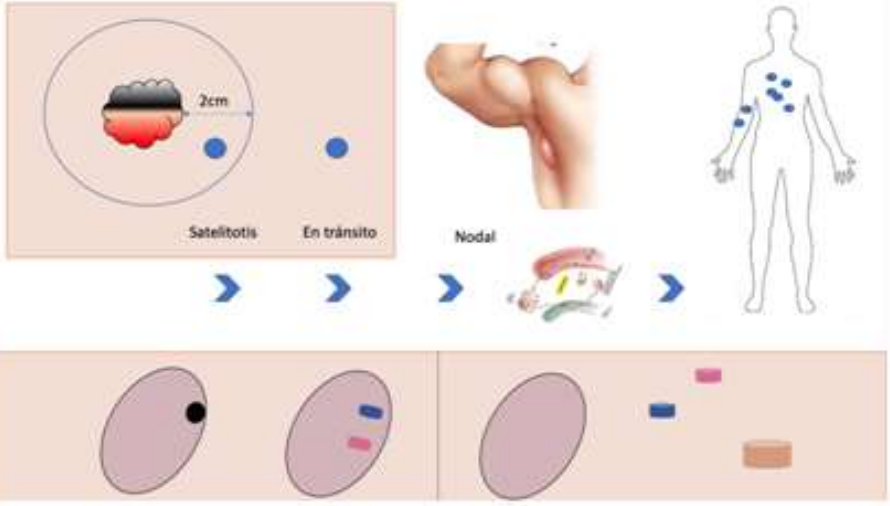
N category	No. of tumor-involved regional lymph nodes	Presence of in-transit, satellite, and/or microsatellite metastases
NX	Regional nodes not assessed (e.g., sentinel lymph node biopsy not performed, regional nodes previously removed for another reason) Exception: pathological N category is not required for T1 melanomas, use clinical N information	No
N0	No regional metastases detected	No
N1	One tumor involved node or any number of in-transit, satellite, and/or microsatellite metastases with no tumor involved nodes	
N1a	One clinically occult (i.e., 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 any number of in-transit, satellite, and/or microsatellite metastases with one tumor-involved node	
N2a	Two or three clinically occult (i.e., 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 any number of 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 (i.e., detected by SLN biopsy)	No
N3b	Four or more, at least one of which was clinically detected, or the 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

M category	Anatomic site	LDH level
M0	No evidence of distant metastasis	Not applicable
M1	Evidence of distant metastasis	See below
M1a	Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node	Not recorded or unspecified
M1a(0)		Not elevated
M1a (1)		Elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b(0)		Not elevated
M1b (1)		Elevated

Table 1 (continued)

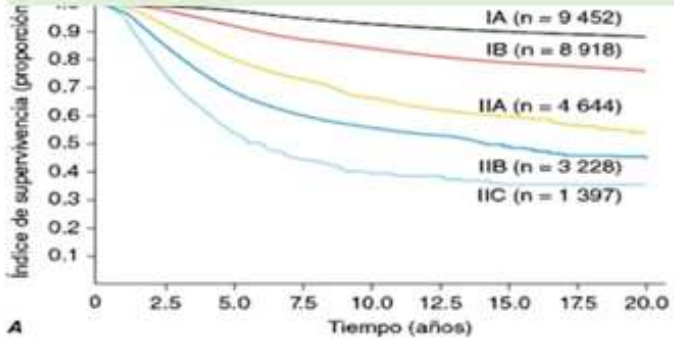
M category	Anatomic site	LDH level
M1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)		Not elevated
M1c (1)		Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
M1d(0)		Not elevated
M1d (1)		Elevated

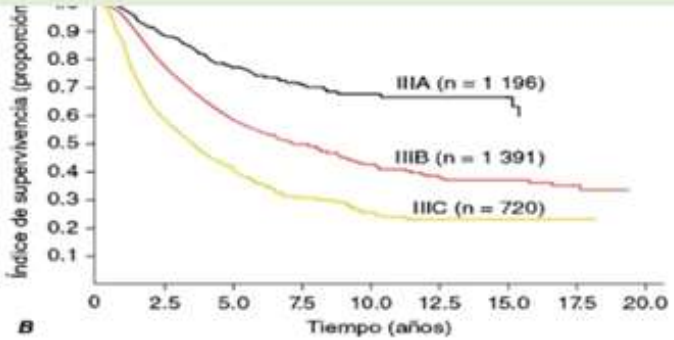
T	N	M	Stage group
Tis	N0	M0	0
T1a	N0	M0	IA
T1b–T2a	N0	M0	IB
T2b–T3a	N0	M0	IIA
T3b–T4a	N0	M0	IIB
T4b	N0	M0	IIC
Any T, Tis	≥N1	M0	III
Any T	Any N	M1	IV

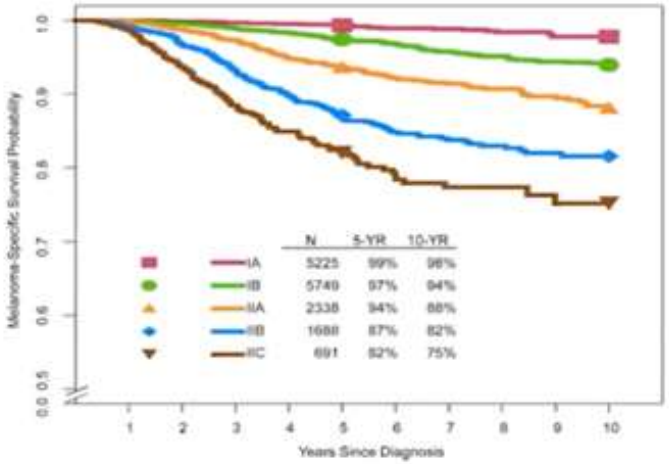


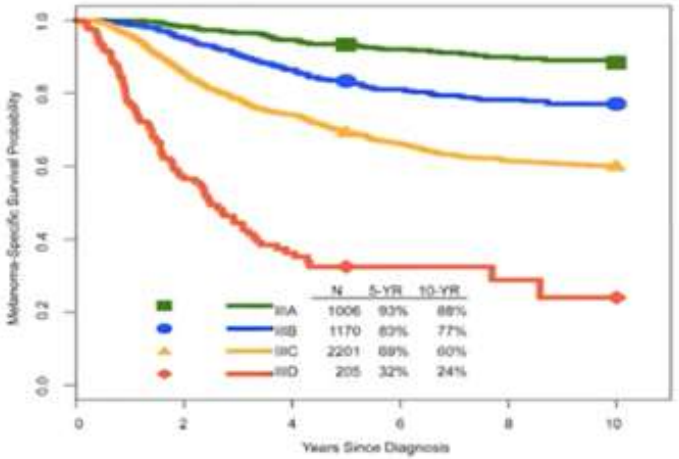
Maiem M et all SEOM clinical guideline for the management of cutaneous melanoma (2020).

Importante selección de pacientes: impacto del estadio en el riesgo de recaída y probabilidad de supervivencia







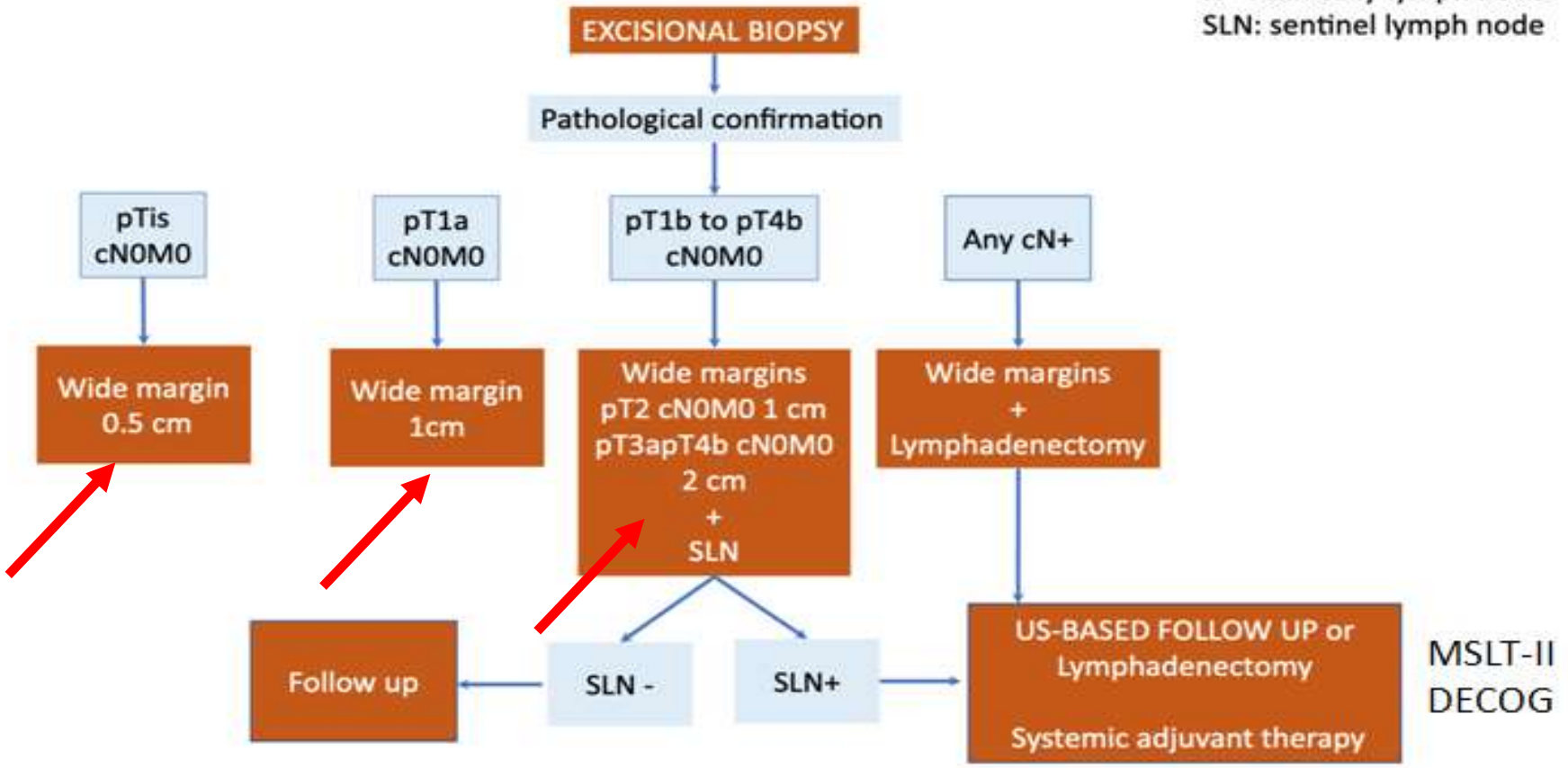


TNM AJCC 8th Edición

1. American Joint Committee on Cancer (AJCC) Cancer Staging System, 8th ed. Amin MB, ed. New York: Springer; 2017. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of the 2009 AJCC melanoma staging and classification. *J Clin Oncol*. 2009;27(36):6199-6206

Algoritmo de tratamiento Enfermedad localizada

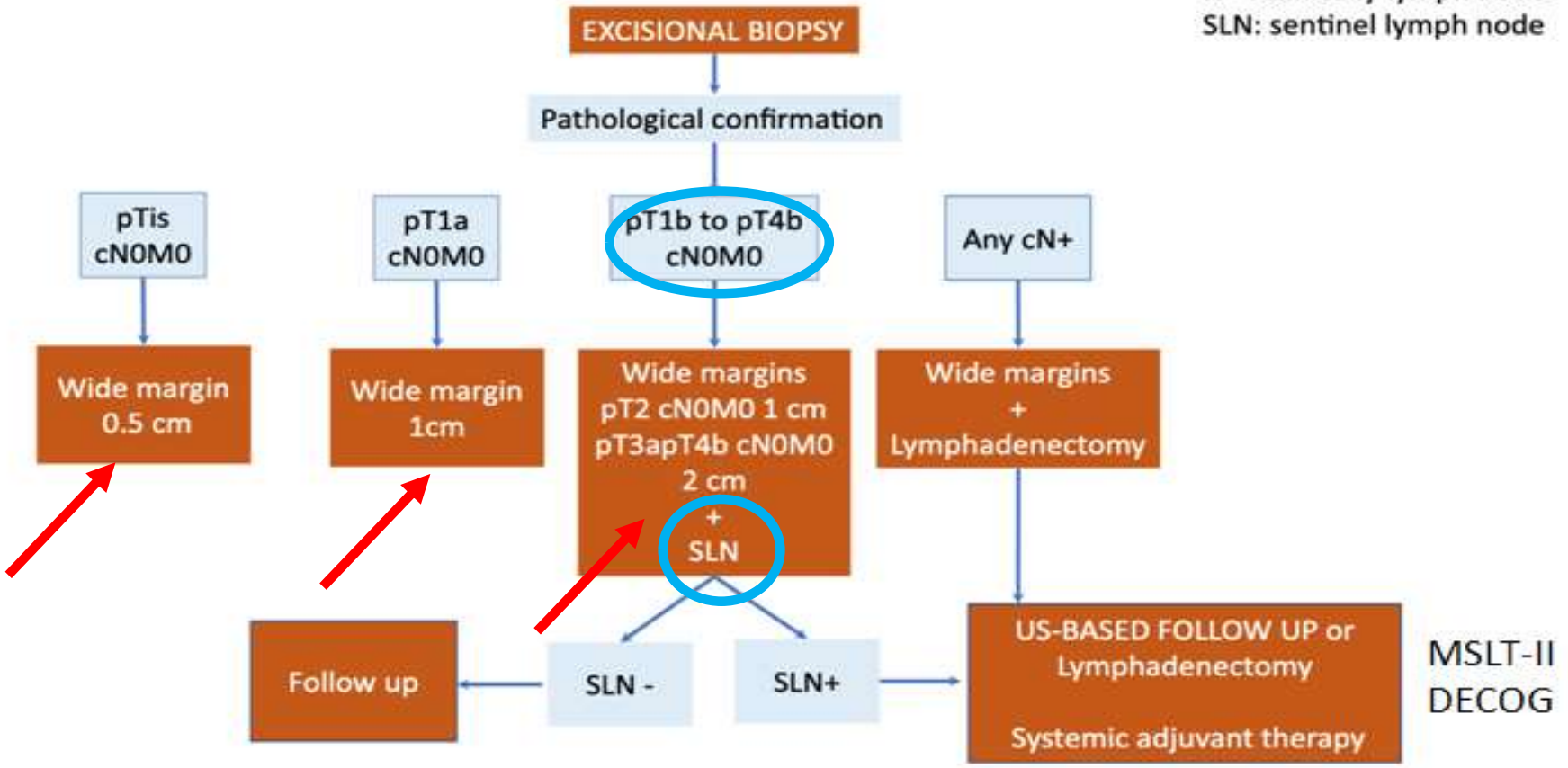
N+ : clinically lymph node
SLN: sentinel lymph node



Maiem M et all SEOM clinical guideline for the management of cutaneous melanoma (2020).

Algoritmo de tratamiento Enfermedad localizada

N+ : clinically lymph node
SLN: sentinel lymph node

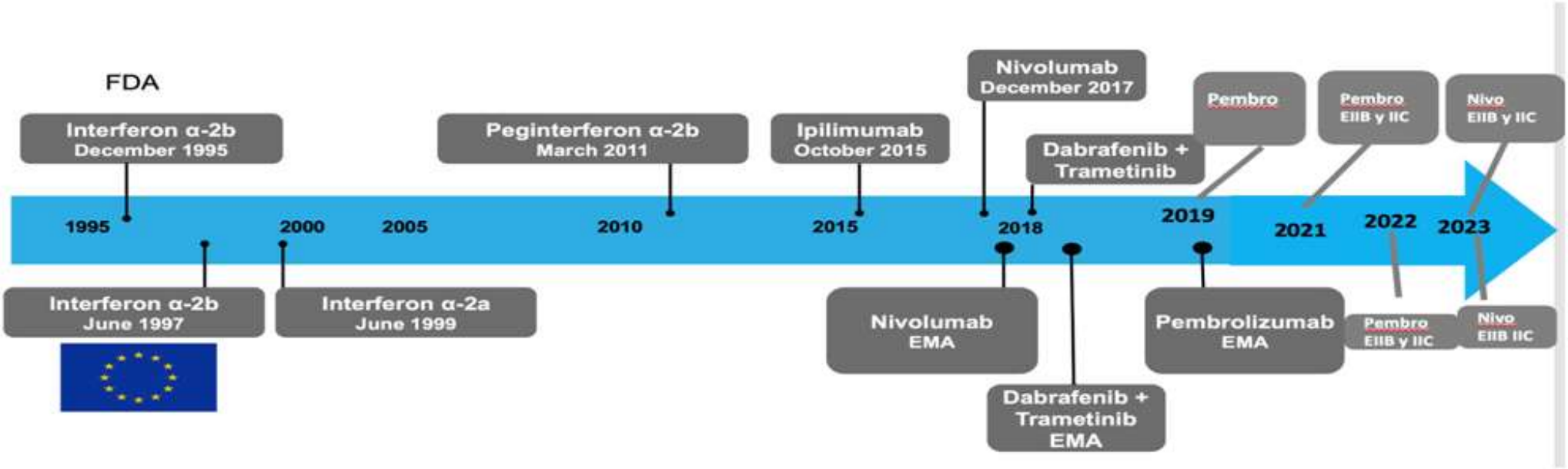


Maiem M et all SEOM clinical guideline for the management of cutaneous melanoma (2020).

Adyuvancia en melanoma

Tratamiento adyuvante melanoma

Aprobaciones tratamiento adyuvante en melanoma EIII y EII

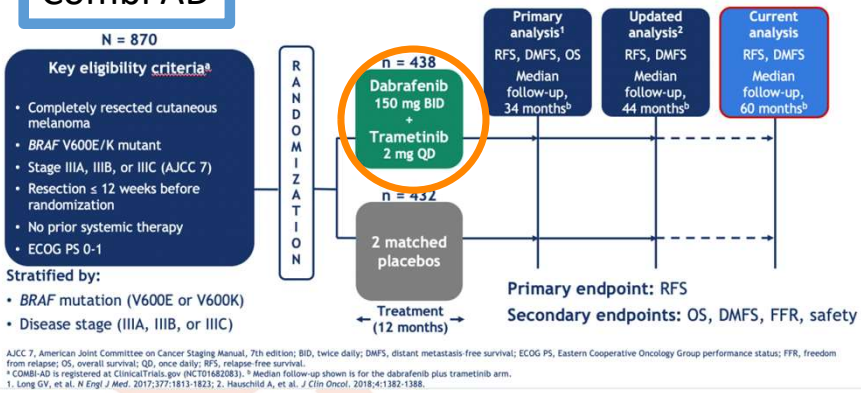


Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow upAnnals of Oncology 30: 1884–1901, 2019. Maiem M et all SEOM clinical guideline for the management of cutaneous melanoma (2020). Clin Transl Oncol. 2021 May;23(5):948 960. doi: 10.1007/s12094 020 02539 9. Epub 2021 Mar 2. PMID: 33651321. Adaptada de ANA Arance.GEM2019.

ADYUVANCIA

CAMPUS SEOM
Área de formación virtual SEOM

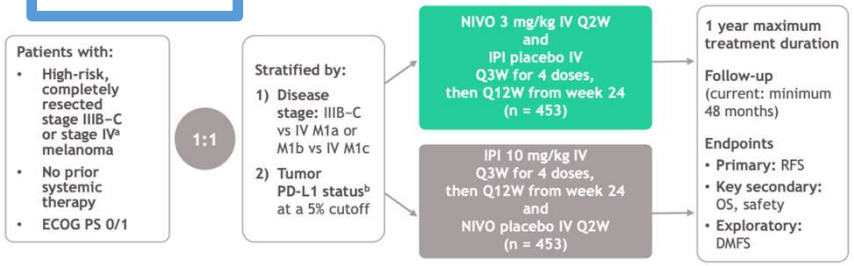
Combi AD



AJCC 7, American Joint Committee on Cancer Staging Manual, 7th edition; BID, twice daily; DMFS, distant metastasis-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; FFR, freedom from relapse; OS, overall survival; QD, once daily; RFS, relapse-free survival.
[a] COMBI-AD is registered at ClinicalTrials.gov (NCT01682083). [b] Median follow-up shown is for the dabrafenib plus trametinib arm.
1. Long GV, et al. *N Engl J Med*. 2017;377:1813-1823; 2. Hauschild A, et al. *J Clin Oncol*. 2018;4:1382-1388.

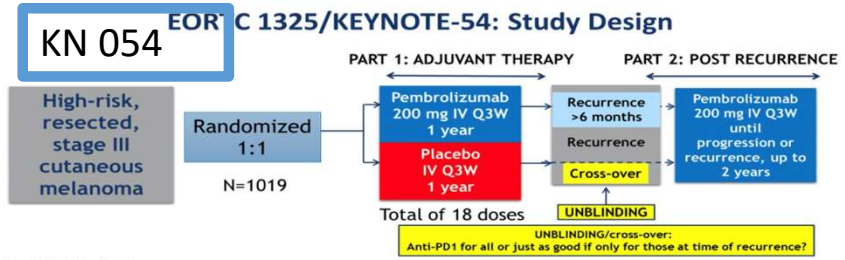
- Estadios III
- Frente a placebo

CM 238



- Estadios IIIB-IIIC y IV resecados
- **Frente a Ipilimumab**

KN 054

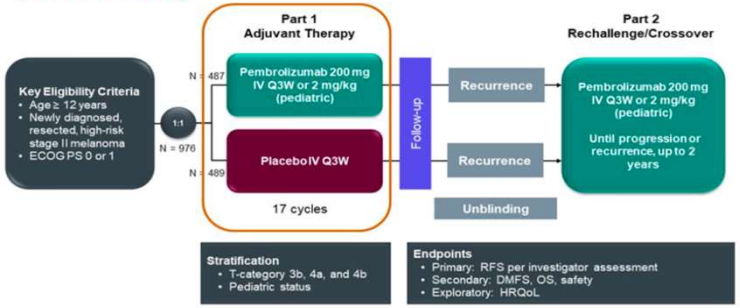


Stratification factors:
✓ **AJCC-7 Stage**: IIIA (>1 mm metastasis) vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥4 positive lymph nodes
✓ **Region**: North America, European countries, Australia/New Zealand, other countries

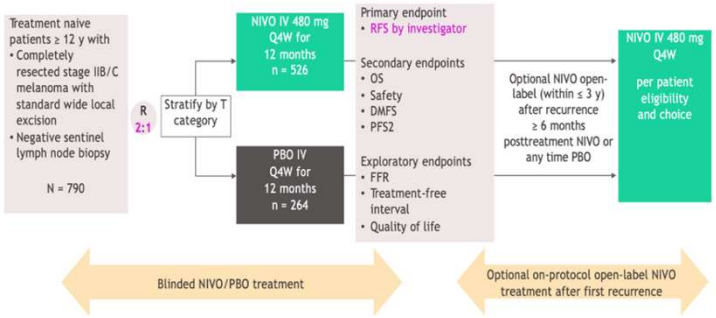
Primary Endpoints:
• **RFS (per investigator) in overall population**, and **RFS in patients with PD-L1-positive tumors**
Secondary Endpoints:
• **DMFS and OS** in all patients, and in patients with PD-L1-positive tumors; **Safety, Health-related quality of life**

- Estadios III
- Frente a placebo

KEYNOTE-716 Study Design



CM 76k



- Estadios IIB/C
- Frente a placebo

Hauschild.ASCO 2020.Dummer et all.NEJM sep 2020
Ascierto et all.Lancet sept 2020.Weber. Weber J, et al. SMR 2021.
Eggermont AMM, et al. N Eng J Med 2022
Luke J, et al. ASCO 2023
Long GV, et al. SMR 2022

ADYUVANCIA

OBJETIVO PRIMARIO: RFS

CAMPUS SEOM
Área de formación virtual SEOM

	COMBI-AD	CM 238	KN 054	KN 716	CM 76k
SLR (%)	52 vs 36	50 vs 39	55 vs 38	76.2 vs 63.4	89 vs 79
SLM (%)	65 vs 54	59 vs 52	61 vs 44	84.4 vs 74.4	92 vs 87
EA g.3-4 (%)	31	14	15	17	10
Discont. EA (%)	26	4	ND	17	17
TOX.PERSISTENTE					
Tiroidea	--	21	20	15	19
DM	--	3	2	0.4	1
Insuf. adrenal	--	1.5	1	2.1	2
	Datos a 5 años			Datos a 3 años	Datos a 1 año

Hauschild.ASCO 2020.Dummer et all.NEJM sep 2020
Ascierto et all.Lancet sept 2020.Weber. Weber J, et al. SMR 2021.
Eggermont AMM, et al. N Eng J Med 2022
Luke J, et al. ASCO 2023
Long GV, et al. SMR 2022
Almudena Garcia Castaño.SEOM2023

En resumen…

Adyuvancia según evidencia científica

- **Estadios IIB/IIC**
  - Pembrolizumab/Nivolumab
- **Estadios IIIA** (N1 con > 1 mm)
  - Dabrafenib + Trametinib (BRAFm)
  - Pembrolizumab
- **Estadio IIIB/IIIC/IIID**
  - Dabrafenib + Trametinib (BRAFm)
  - Pembrolizumab/Nivolumab
- **Estadio IV resecado**
  - Nivolumab

Adyuvancia financiada en España

- **Estadios IIB/IIC**
  - Pembrolizumab/Nivolumab
- **Estadios IIIA** (N1 con > 1 mm)
  - ~~Dabrafenib + Trametinib (BRAFm)~~
  - Pembrolizumab
- **Estadio IIIB/IIIC/IIID**
  - ~~Dabrafenib + Trametinib (BRAFm)~~
  - Pembrolizumab/Nivolumab
- **Estadio IV resecado**
  - Nivolumab

Melanoma metastásico

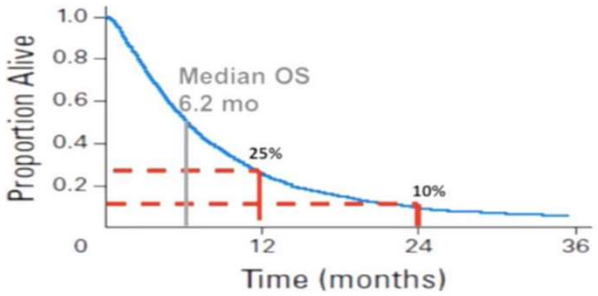
Terapias dirigidas

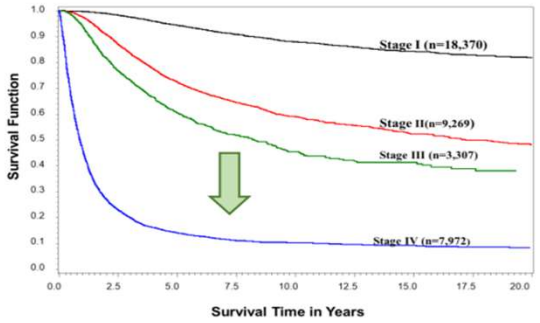
Inmunoterapia

Melanoma Metastásico

El pasado…

Supervivencia Global del Melanoma Metastásico del Meta-análisis de 2008

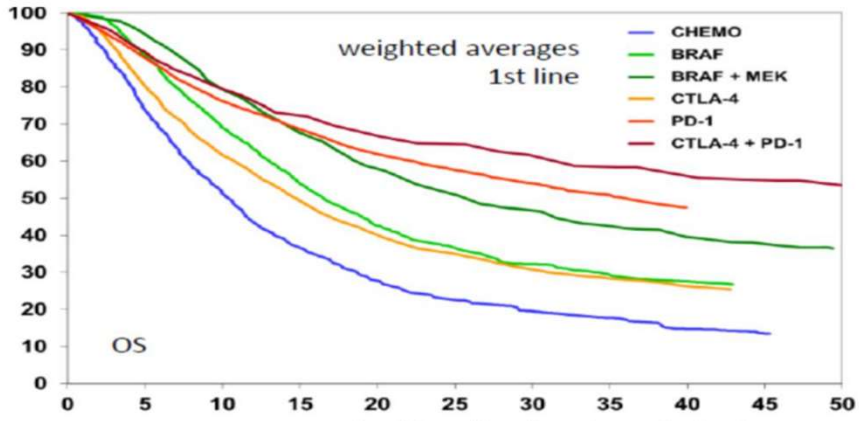




Balch et al, CA Cancer J Clin 2004

El presente…

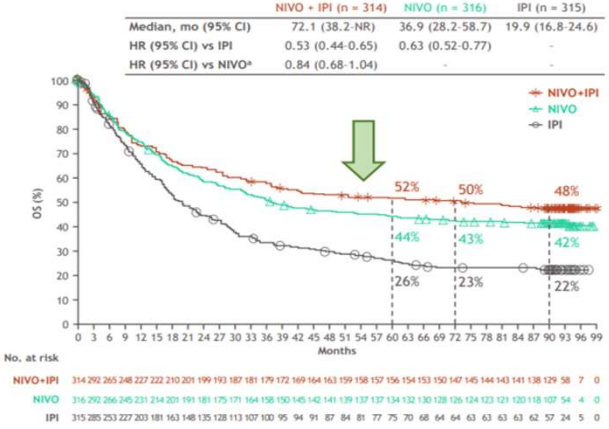
SG en 1L Melanoma avanzado



Response rates

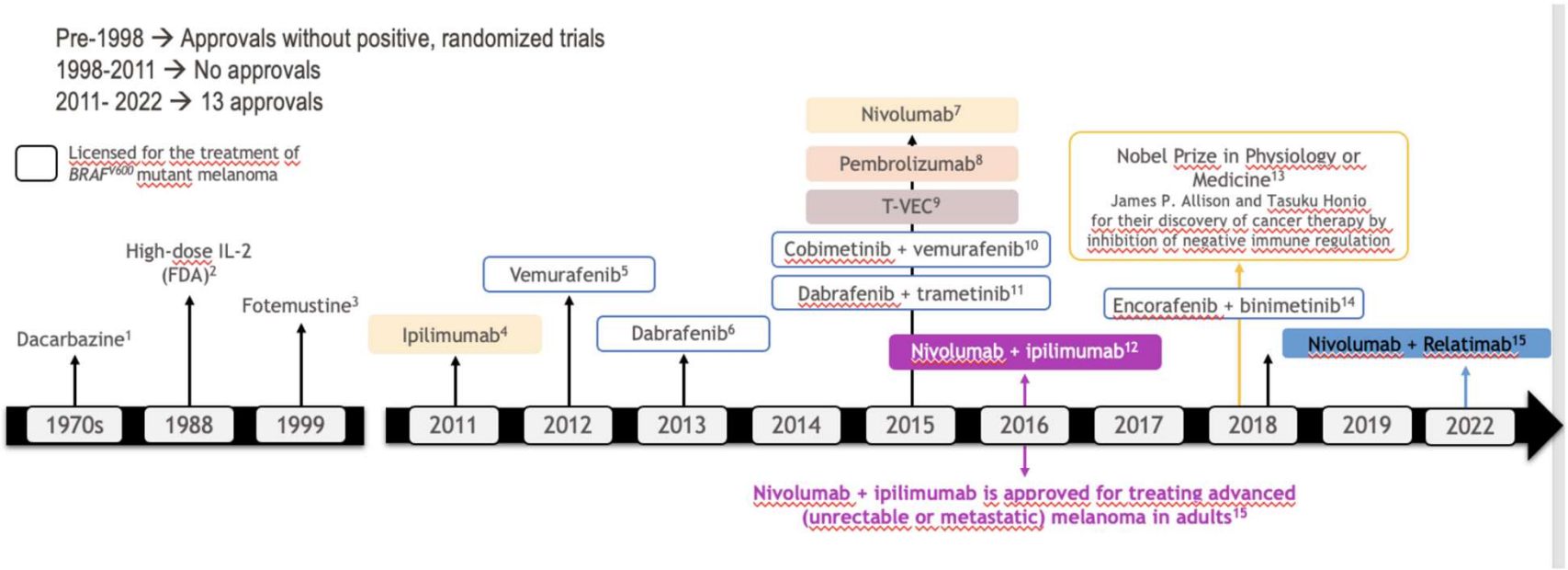
Anti-PD1/CTLA4:	50-55%
Anti-PD1:	35-40%
Anti-BRAF/MEK:	70%
Anti-BRAF:	50%
Anti-CTLA4:	15-20%
Chemo:	10-15%

Ugurel S *et al Eur J Cancer* 2020



Hodi FS et al, ASCO 2022

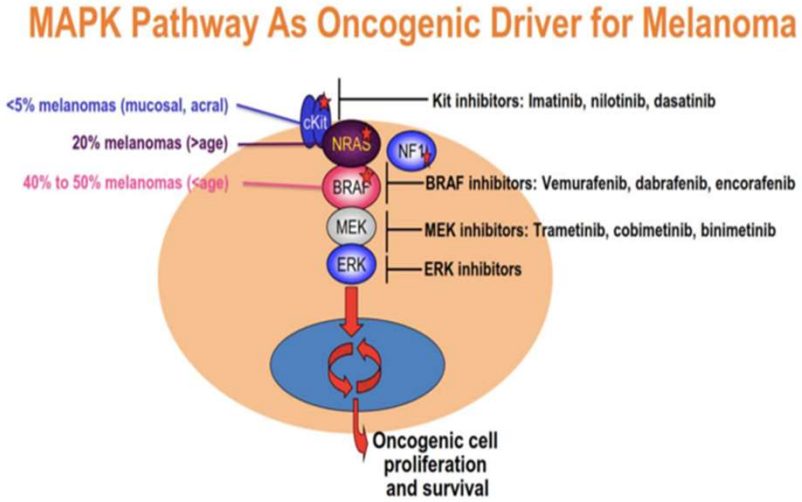
Arsenal terapeútico para el melanoma avanzado

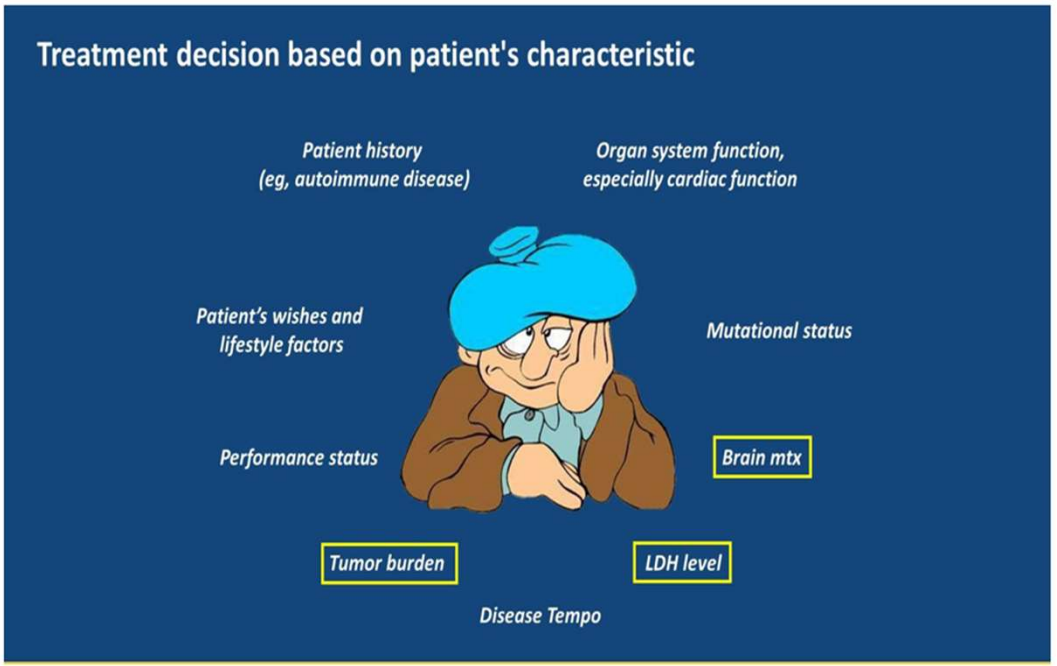


All treatments have been granted market authorisation by the EMA, unless otherwise stated. MOA, mechanisms of action; mOS, median overall survival; BRAF, B-Raf proto-oncogene; T-VEC, talimogene laherparepvec.

1. Dacarbazine SmPC. Available at: https://cima.aemps.es/cima/pdfs/es/ft/62333/62333_ft.pdf. 2. Interleukin-2 SmPC. Available at: https://cima.aemps.es/cima/pdfs/es/ft/62287/FichaTecnica_62287.html.pdf. 3. Fotemustine SmPC. Available at: https://cima.aemps.es/cima/pdfs/es/ft/62561/FichaTecnica_62561.html.pdf. 4. Yervoy (ipilimumab) EPAR. Available at https://bit.ly/2HKYrVk. 5. Zelboraf (vemurafenib) EPAR. Available at http://bit.ly/2yv9Ro7. 6. Tafinlar (dabrafenib) EPAR. Available at http://bit.ly/2hoic54. 7. Opdivo (nivolumab) EPAR. Available at https://bit.ly/2HSwQxq. 8. Keytruda (pembrolizumab) EPAR. Available at http://bit.ly/2hlLyVm. 9. Imlygic (T-VEC) EPAR. Available at http://bit.ly/2yvzh52. 10. Cotellic (cobimetinib) EPAR. Available at https://bit.ly/2KxoME6. 11. Novartis Press Release, September 2015. Available at http://bit.ly/1L03WoK. 12. Opdivo (nivolumab) Variation Assessment Report. Available at https://bit.ly/2Ic3Bct. 13. Press release: The Nobel Prize in Physiology or Medicine 2018. Available at: https://www.nobelprize.org/prizes/medicine/2018/press-release/. 14. Pierre Fabre Press Release, September 2018. Available at: https://bwnews.pr/2MP210x. 15. Nivolumab SmPC (2020, AEMPS). 15-In July 2022, the CHMP has adopted a positive opinion for the marketing authorization of Opdualag™ for the first-line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents from 12 years of age with expression of PD-L1<1% in tumor cells.

Selección del tratamiento





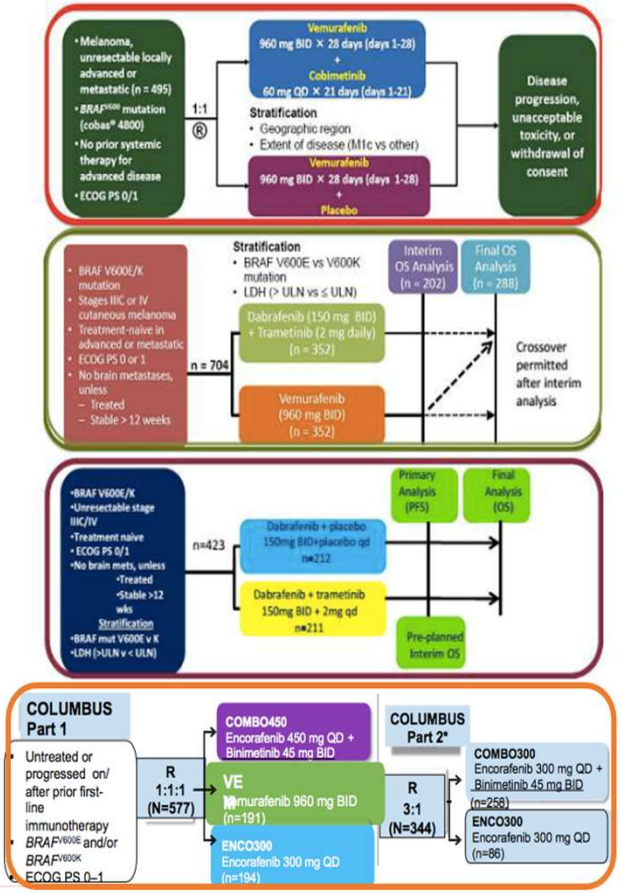
Xing Y, et al. *Cancer*. 2010;116(9):2234-2241. Curtin JA, et al. *N Engl J Med*. 2005;353(20):2135-2147. Curtin JA, et al. *J Clin Oncol*. 2006;24(26):4340-4346. Van Raamsdonk CD, et al. *N Engl J Med*. 2010;363(23):2191-2199. Ribas A, et al. *J Clin Oncol*. 2011;29(suppl): Abstract 8509.

Adaptada Paolo Ascierto at 2019 ASCO Annual Meeting

Terapias dirigidas

Diseño ensayos clínicos

- COBRIM (PFS)
- COMBI-v (OS)
- COMBI-d (PFS)
- COLUMBUS (PFS)



1.Robert et al NEJM 20152. Long G.V. et al. NEJM 2014.3.Larkin et al NEJM 20144..Dummer ASCO 2018

- **Características de los pacientes** similares:
  - Mediana edad: ~55 años
  - Sexo masculino: 51-60%
  - PS 0: ~70%
  - LDH elevada: <% en Columbus (24-29) y > en CoBRIM (43-46)
  - BRAF V600E: 70-90%
  - M1c: ~60-65%
  - IO previa solo en COLUMBUS

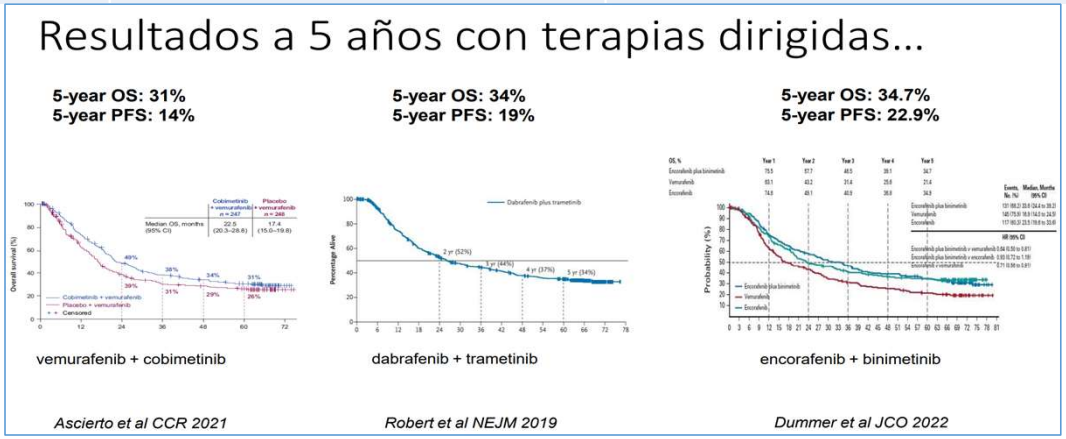
- **Brazo comparador:**
  - **Vemurafenib en monoterapia**

  (en el Combi-D, dabrafenib)
  - Datos muy homogéneos
    - PFS: 7m
    - RO: 50%
    - SG: 17m

Dummer R. et al Lancet Oncol 2018; Long G.V. et al. NEJM 2014; Long G.V. et al Lancet 2015; Long G.V. Ann Oncol 2017, Robert C. et al NEJM 2014, Robert C. et al ESMO 2016; Larkin J. et al NEJM 2014, Ascierto P.A. et al Lancet Oncol 2016. Hamid O. et al Cancers 2020. McArthur.SMR 2019. Dreno et al. J Clin Oncol 36, ASCO 2018 (suppl; abstr 9522). Dummer, Lancet Oncol 2018. Ascierto, Eur J Cancer 2020. Dummer, JCO.2022.

Terapias dirigidas: eficacia y tolerancia

	COMBIv/COMBId	CoBRIM	COLUMBUS
RO (%)	67	70	64
SLP a 5 años (%)	19	14	22.9
SGm (meses)	25.9	22.5	33
SG a 5 años (%)	34	31	34.7
Tox. g.3-4 (%)	48	65	64
Suspensión del tratamiento (%)	14	15	14



Dummer R. et al Lancet Oncol 2018; Long G.V. et al. NEJM 2014; Long G.V. et al Lancet 2015; Long G.V. Ann Oncol 2017, Robert C. et al NEJM 2014, Robert C. et al ESMO 2016; Larkin J. et al NEJM 2014, Ascierto P.A. et al Lancet Oncol 2016. Hamid O. et al Cancers 2020. McArthur.SMR 2019. Dreno et al. J Clin Oncol 36, ASCO 2018 (suppl; abstr 9522). Dummer, Lancet Oncol 2018. Ascierto, Eur J Cancer 2020. Dummer, JCO.2022.

Efectos adversos. Terapia dirigida

- La **mediana de tiempo de resolución de los efectos adversos es <3 meses** en la mayoría de los casos, excepto para reducción del valor de LVEF (vemurafenib monoterapia).
- La mayoría de los **efectos adversos son manejables con reducción de dosis** de alguno de los dos fármacos o ambos.
- La mayoría de efectos adversos **responden correctamente al manejo médico ambulatorio**.
- La **discontinuación por toxicidad** en terapia dirigida **es infrecuente**.

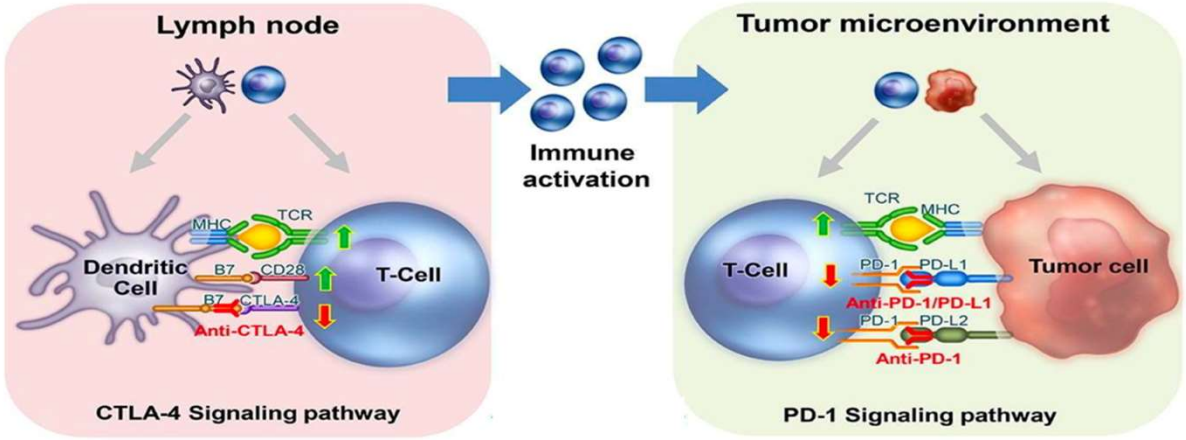
Table 4. Select adverse drug reactions, warnings, and precautions.

ADR, %	D/T * n = 209		V/C n = 247		E/B † n = 192	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
General						
Pyrexia	57 ‡	7	28	2	18	4
Peripheral edema	25	1.4	12.6 [31]	NR	13	1
Chills	31	0	10	0	0	0
Gastrointestinal disorders						
Nausea	34	0.5	41	1	41	2
Vomiting	25	1.0	24	1	30	2
Diarrhea	30	1.4	60	6	36	3
Arthralgia	26	0.9	36 [31]	2.4 [31]	26	1
Skin						
Rash	42	0	73 [37]	17 [37]	22	1
Acneiform dermatitis	10 [33]	NR	16 [31]	2 [31]	4.4 [23]	0 [23]
PPE syndrome	5 [33]	NR	6 [34]	0 [34]	6.2 [23]	0 [23]
cuSCC §	3	NR	6	NR	2.6	0
Basal cell carcinoma	3.3	NR	4.5	NR	1.6	0
LV dysfunction ¶	6 #	NR	9 [34]	2 [34]	7	1.6 **
reatine kinase increased ‡‡	Not monitored ‡‡		79	14	58	5
Photosensitivity §§	2 [31]	NR	46	4	4 [23]	0.4 [23]
Liver function tests ‡‡						
ALT increased	44	3.8	68	11	29	6
AST increased	60	4.3	73	8	27	3
ALP increased	50	1.0	71	7	21	1
Hemorrhage	19	1.9	13	1	19	3.2
Ocular toxicity						
Serous retinopathy	Not monitored ##		26 †††	NR	20 †††	3
Visual impairment	NR	NR	15 ‡‡‡	<1	20 ‡‡‡	0
Uveitis	2 [33]	NR	2 [34]	NR	4	0
'enous thromboembolism	2.8 §§§	NR	NR	NR	6	0
ECG QT prolonged	0.8 [33]	0 [33]	NR	1.6 [31]	0.5 ###	0
Hypertension	25	6	15	4	11	6

1.Robert et al NEJM 2015.2.Larkin et al NEJM 2014.Dummer ASCO 2018. hamid O. et al Cancers 2020

Inmunoterapia

Anti-CTLA-4 y Anti-PD1, mecanismos de acción: distintos pero complementarios



- Induces de novo anti-tumor T-cell responses[1,2]
- Enables adaptation to evolving tumor[2,3]
- Promotes emergence of memory T-cells[4]
- Causes compensatory increase in tumor PD-L1[2]

- Restores anti-tumor T-cell function[5,6]
- Enhances pre-existing T-cell response[5]
- Increase cytokine production[7]

- Anti-CTLA4: Ipilimumab
- Anti-PD1:
  - Pembrolizumab
  - Nivolumab
- Anti-CTLA4 + Anti-PD1:
  - Nivolumab + Ipilimumab
- Anti-PD1 + anti-LAG3:
  - Nivolumab + Relatlimab

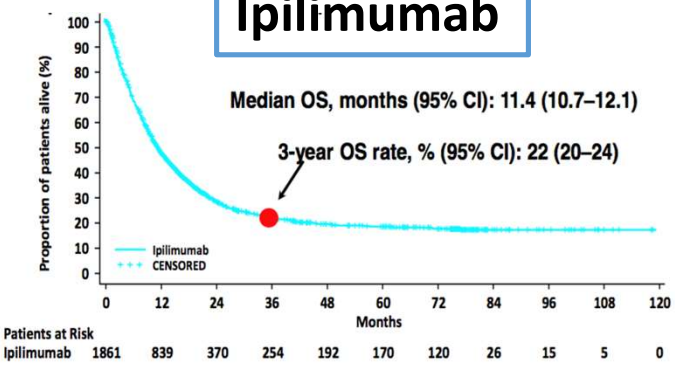
Figure extracted from Hassel JC, et al. Cancer Treat Rev. 2017[8]
CTLA-4, cytotoxic T-lymphocyte antigen 4; PD-1, programmed cell death protein 1; APC, antigen presenting cell; TCR, T cell receptor; MHC, major histocompatibiloty complex.

1. Pardoll DM. Nat Rev Cancer 2012;12:252-264. 2. Wei SC, et al. Cancer Discov 2018;8:1069-1086. 3. Wei SC, et al. Immunity 2019;50:1084-1098. 4. Das R, et al. J Immunol 2015;194:950-959.
5. Wang C, et al. Cancer Immunol Res 2014;2:846-856. 6. Brahmer JR, et al. J Clin Oncol 2010;28:3167-3175. 7. Hamanishi J, et al. Proc Natl Acad Sci U S A 2007;104:3360-3365. 8. Hassel JC, et al. Cancer Treat Rev. 2017;57:36-49.

Inmunoterapia en monoterapia

CAMPUS SEOM
Área de formación virtual SEOM

Ipilimumab

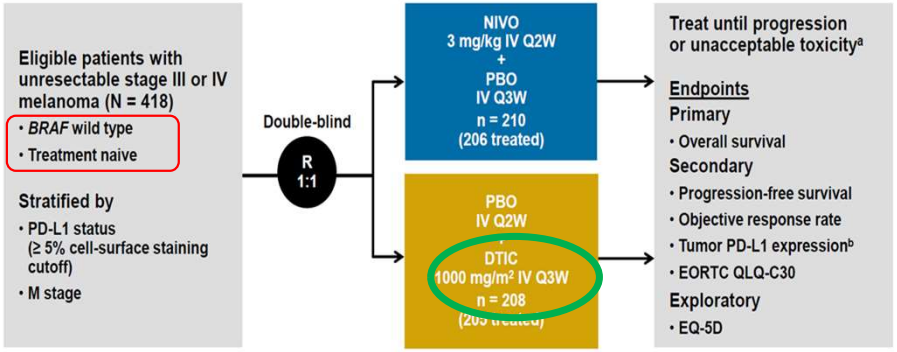



Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma

- Pooled analysis (12 estudios, 1861 pacientes pretratados/ no tratados)
- Se observa "aplanamiento de la curva" a los 36 meses.
- Largos SUPERVIVIENTES

	CM 066	KN 006	
SGm (meses)	37.3	32.7	1ª L:38.7
			2ª L: 23.5
SG a 5 años (%)	39	40	1ª L:43
			2ª L: 32
SLPm (meses)	5.1	3.4	

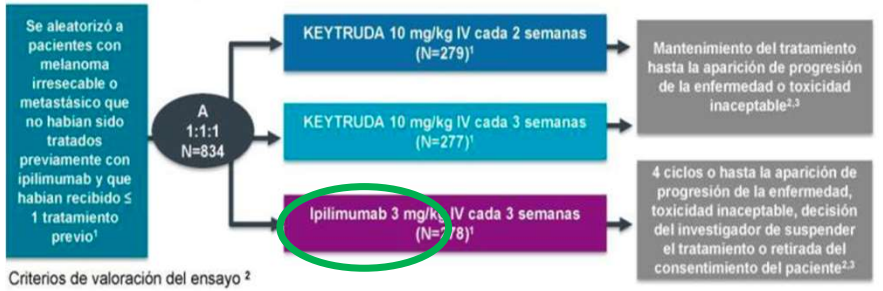
CM 066: Study Design and Endpoints[1-3]



KN 006:

36% BRAFm
65% en 1ª línea

- Ensayo de fase 3, abierto, multicéntrico, aleatorizado y controlado en el que participaron pacientes con melanoma avanzado (irresecable o metastásico) no tratados previamente con ipilimumab y que habían recibido no más de un tratamiento sistémico previo[1]



Criterios de valoración del ensayo [2]

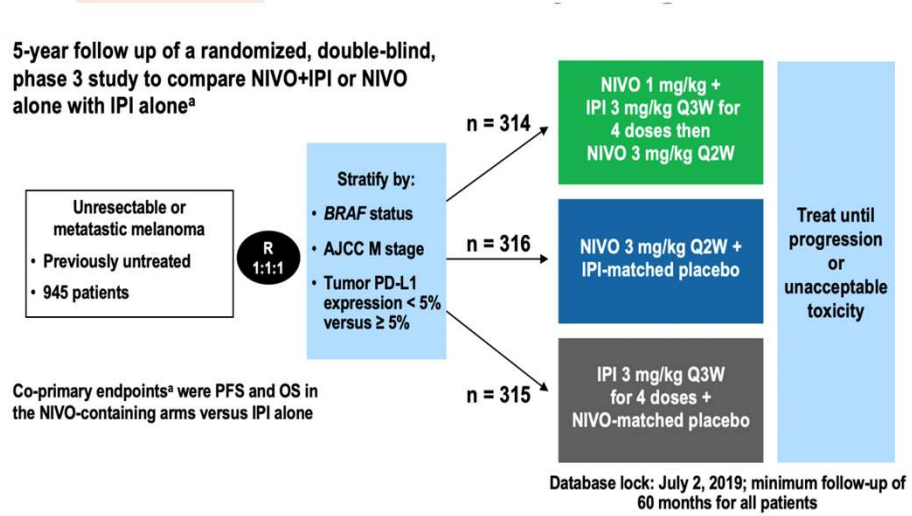
- Principales: SLP evaluada mediante una EROI conforme a los criterios RECIST, versión 1.1, y SG

Robert et al. NEJM 2014; Robert et al. *Journal of Clinical Oncology* 2020 383937-3946. Robert C, et al. N Engl J Med. 2015;372:2521-2532. Robert C. Lancet Oncol. 2019 Sep;20(9):1239-1251.

Doblete de inmunoterapia

CAMPUS SEOM
Área de formación virtual SEOM

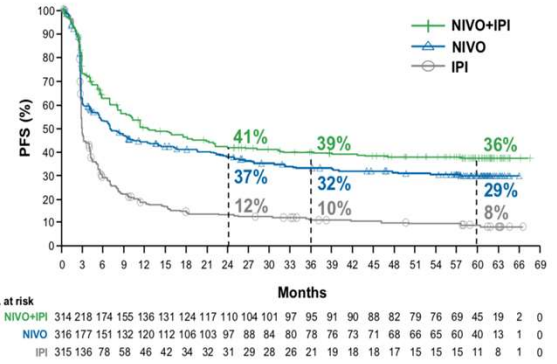
CM 067: ANTI-PD-1 + ANTI-CTLA-4



NCT01844505
[a]The study was not powered for a comparison between NIVO+IPI and NIVO.AJCC, American Joint Committee on Cancer.

Progression-Free Survival

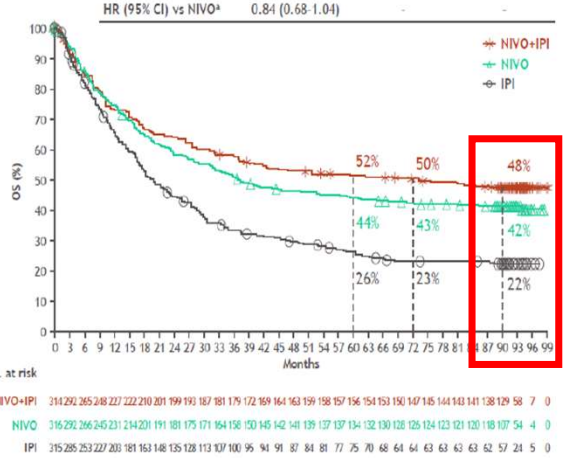
	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median PFS, mo (95% CI)	11.5 (8.7–19.3)	6.9 (5.1–10.2)	2.9 (2.8–3.2)
HR (95% CI) vs IPI	0.42 (0.35–0.51)	0.53 (0.44–0.64)	–
HR (95% CI) vs NIVO[a]	0.79 (0.64–0.96)	–	–



[a]Descriptive analysis. NR, not yet reached. Larkin J, et al. *N Engl J Med* 2019:381:1535–1546.

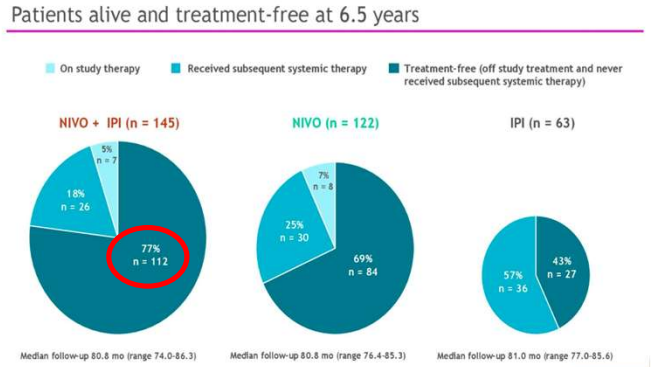
Overall Survival

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median, mo (95% CI)	72.1 (38.2-NR)	36.9 (28.2-58.7)	19.9 (16.8-24.6)
HR (95% CI) vs IPI	0.53 (0.44-0.63)	0.65 (0.52-0.77)	–
HR (95% CI) vs NIVO[a]	0.84 (0.68-1.04)	–	–



Características de los pacientes bien balanceadas:
- M1c ~ 58%
- LDH elevada~ 36%
- PDL1 + ~ 23%
- BRAFm ~ 31%

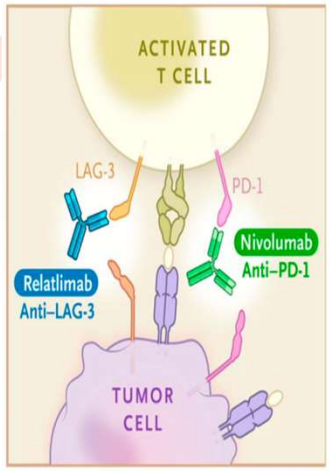
Toxicidad g.3-4 (%): 31 vs 8 vs 14
Pero la SG no se ve resentida en el brazo de N + I en caso de cese de tratamiento por toxicidad
(SG 51 vs 52%)

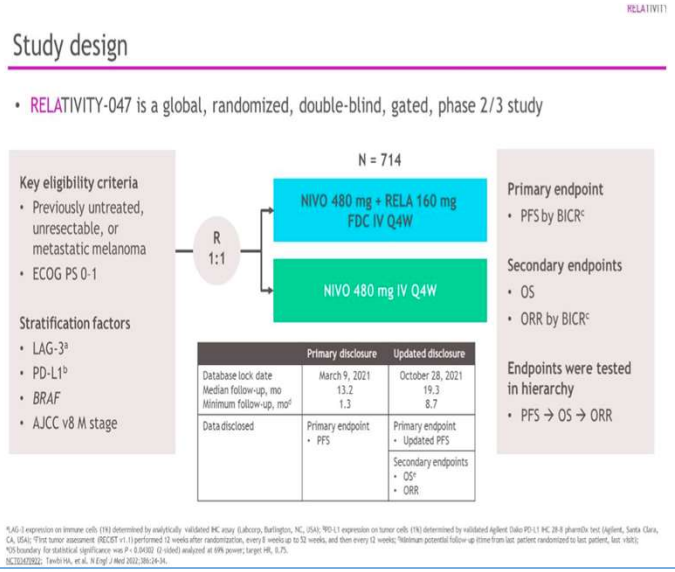


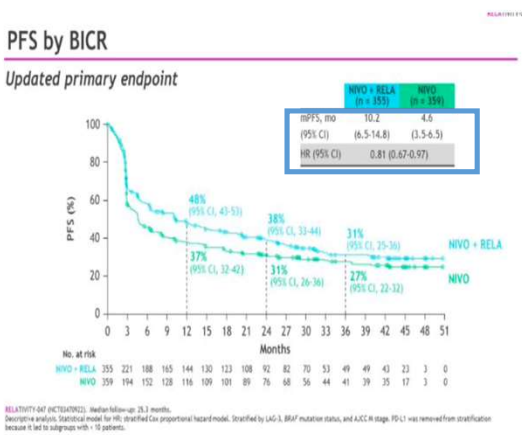
Larkin J et al. *N Engl J Med* 2019. Hodi FS, et al. Long-term survival in advanced melanoma for patients treated with nivolumab plus ipilimumab in CheckMate067. Póster #9522. J Clin Oncol 40, 2022 (suppl16). Presentado en la reunión de la Sociedad Americana de Oncología Clínica (ASCO); Junio 2022; Chicago, IL (USA). Wolchok.ASCO2021.

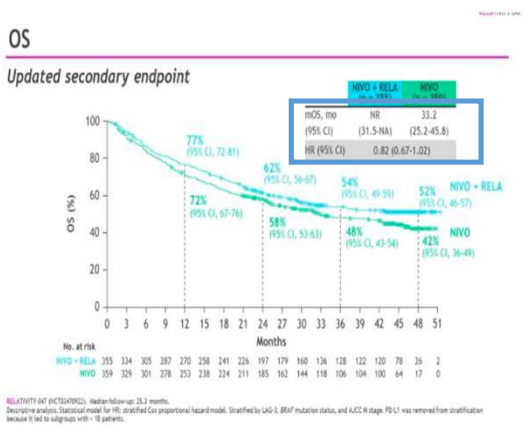
Doblete de inmunoterapia

RELATIVITY-047 : Anti-PD1 +Anti LAG









Confirmed ORR by BICR	NIVO + RELA (n = 355)	NIVO (n = 359)
ORR % (95 CI)	44 (38-49)	34 (29-39)

Características de los pacientes bien balanceadas pero…

- M1c: 42.5 vs 35.4%; M1d 1.7 vs 3.1%
- > 3 localizaciones mtx: 31.5 vs 24.2%
- LDH elevada: 36.6-35.7%
- Tratamiento neoadyuvante: 9.3 vs 7.5%
- PDL1 -: 59 %; BRAFm: 38.5%; LAG 3 +: 75%
- Incluye pacientes con melanoma acral (11.5%) y de mucosas (7.1%)

Mediana de seguimiento de 2 años:

- SLP a 3 años: 31 vs 27%
- SG a 4 años: 52 vs 42%
- Tox g.3-4: 21.1 vs 11.1%
- Discontinuidad del tratamiento por tox: 9 vs 3.6%

TAWBI, Hussein A., et al. Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. *New England Journal of Medicine*, 2022, vol. 386, no 1, p. 24-34. . 2. Relatlimab and nivolumab vs nivolumab in previously untreated metastatic or unresectable melanoma: overall survival and response rates from RELATIVITY-047 (CA224-047) Georgina V. Long, ASCO 2022. Presentation number 360385. 3. Nivolumab (NIVO) + relatlimab (RELA) vs NIVO in previously untreated metastatic or unresectable melanoma: OS and ORR by key subgroups from RELATIVITY-047 Hussein A. Tawbi. ASCO 2022. Presentation Number 9505. Tawbi HA, ASCO 2023

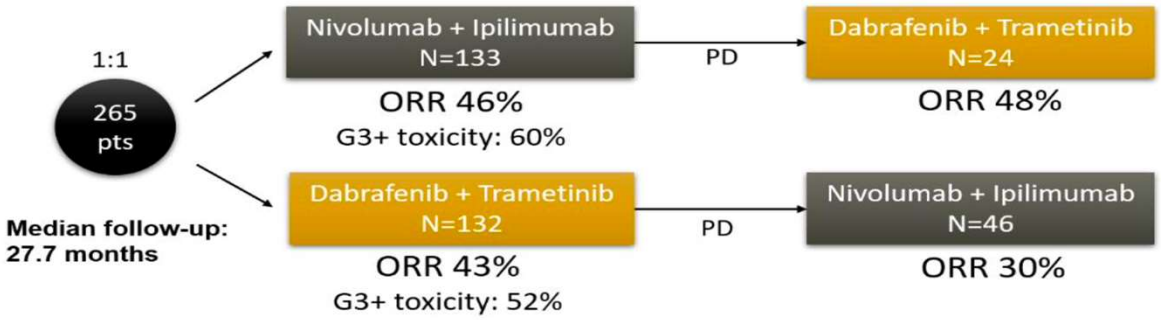
Dreamseq Trial : phase 3

La mejor secuencia en caso de BRAFm?

CAMPUS SEOM
Área de formación virtual SEOM

June 2023

AIM: to compare the efficacy and toxicity of the sequence of nivolumab/ipilimumab followed by dabrafenib/trametinib to the converse sequence
PATINETS: treatment-naive BRAFV600-mutant advanced melanoma, ECOG 0-1



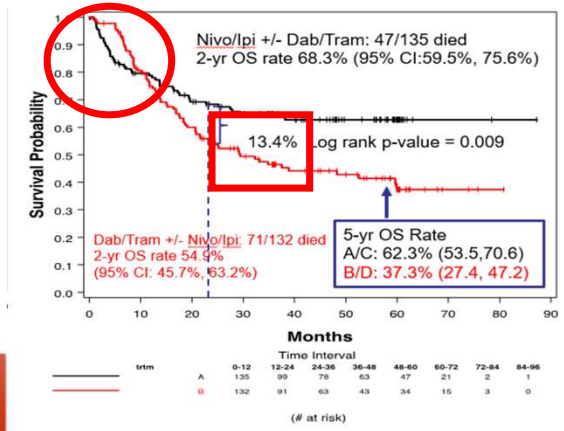
2-year OS

72%

vs

52%

p=0.0095

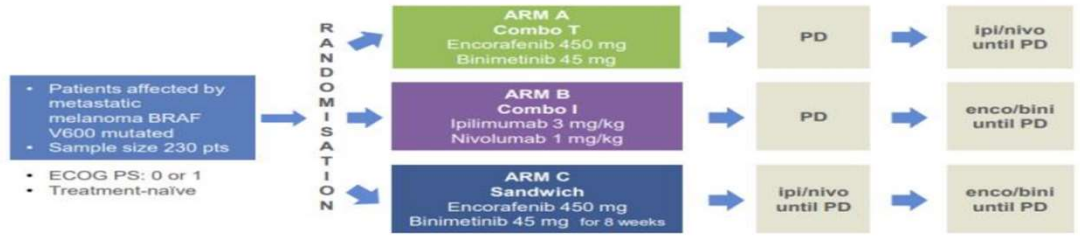


CONCLUSION:
- **the treatment sequence beginning with Nivolumab+Ipilimumab resulted in superior OS**
- **The difference became evident at 10 months**

Atkins M. et al. J Clin Oncol. 2022 SEP

Georgetown | Lombardi

SEQUENTIAL COMBO IMMUNO AND TARGET THERAPY (SECOMBIT) STUDY: STUDY DESIGN



Primary endpoint:
- OS

Secondary endpoints:
- PFS
- Total PFS
- Time to second progression
- % patients alive at 2–3 years
- Best ORR
- DOR

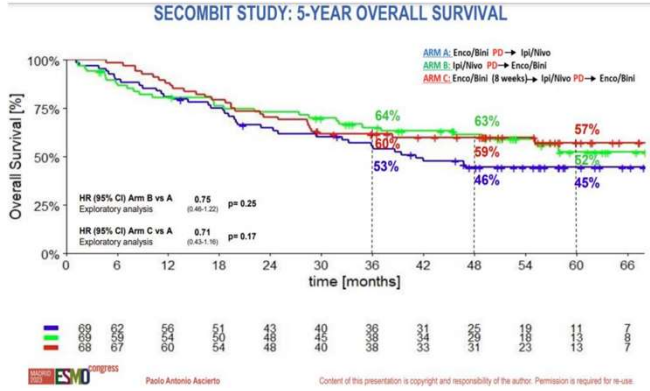
Stratification Factors:
- IIIb/c – M1a – M1b
- M1c with LDH ≤ 2ULN
- M1c with LDH > 2 ULN

Current analysis: First patient randomized November 2016. Database lock 31st June 2022: 48 months PFS rate, total PFS at 48 months, OS at 48 months, preliminary biomarkers report. Duration of follow-up: the median follow-up estimated with the reverse Kaplan-Meier method is **43 months** (IQR: 37-51).

Clinicaltrials.gov: NCT02631447

PARIS 2022 ESMO congress

Paolo Antonio Ascierto



Por subgrupos mejores resultados en caso de LDH elevada y de Mtx en SNC

Toxicidad de la inmunoterapia en melanoma metastásico

CAMPUS SEOM
Área de formación virtual SEOM

Symptoms such as
- Unilateral or bilateral weakness
- Sensory alterations
- Paresthesia

Symptoms such as
- Pruritus
- Rash

Signs such as
- Abnormal liver function tests (eg. AST, ALT) or total bilirubin

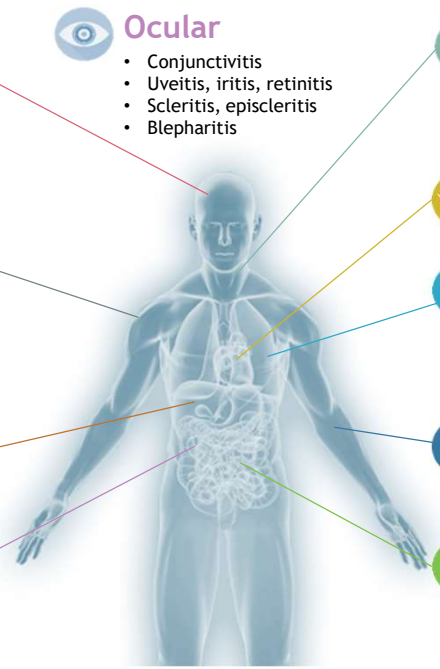
Signs such as
- Gradually rising creatinine
- Hematuria
- Ankle edema

Neurologic
- Neuropathy
- Myelopathy
- Guillain-Barre syndrome
- Myasthenia gravis-like syndrome
- Encephalitis
- Meningitis

Skin
- Dermatitis, erythroderma
- Psoriasis
- Vitiligo
- Toxic epidermal necrolysis
- Stevens-Johnson syndrome

Hepatic
- Hepatitis

Renal
- Nephritis
- Lupus-like glomerulonephritis



Ocular
- Conjunctivitis
- Uveitis, iritis, retinitis
- Scleritis, episcleritis
- Blepharitis

Endocrine
- Hypo or hyperthyroidism
- Hypophysitis, hypopituitarism
- Adrenal insufficiency
- Type 1 diabetes

Signs and symptoms such as
- Fatigue, headache
- Mental status changes
- Abdominal pain, Hypotension, abnormal thyroid function tests and/or serum chemistries

Cardiotoxicity
- Myocarditis, pericarditis, vasculitis

Symptoms such as
- Non-specific symptoms (eg. fatigue, muscle pain)*

Pulmonary
- Pneumonitis
- Pleuritis
- Interstitial lung disease

Signs and symptoms such as
- Radiographic changes
- Shortness of breath
- Chest pain
- New cough

Musculoskeletal
- Arthralgia, arthritis
- Myalgia, myositis

Signs and symptoms such as
- Joint pain/swelling/erythema
- Muscle discomfort
- Muscle weakness

Gastrointestinal
- Colitis
- Ileitis
- Pancreatitis
- Gastritis
- GI perforation

Signs and symptoms
- Diarrhea
- Abdominal pain
- Blood or mucus in stool
- Bowel perforation
- Peritoneal signs
- Ileus

Grade 3/4 adverse events
- Anti-PD-1: 10-14%
- Anti-PD-1 + anti-CTLA-4: 48-58%
- Anti-PD-1 + Anti-LAG-3: 22%

IirAEs, immune-related adverse events; AST/ALT, aspartate/alanine aminotransferase.

1. Naidoo J, et al. J Clin Oncol 2017;35(7):709-717. 2. Naidoo J, et al. Ann Oncol 2015;26(12):2375-2391. 3. Villadolid J, et al. Transl Lung Cancer Res 2015;4(5):560-575. 4. Weber JS, et al. Oncologist 2016;21(10):1230-1240. 5. Champiat S. et al Annals Oncol. 2016; 27(4):559-574.

ASCO Special Articles

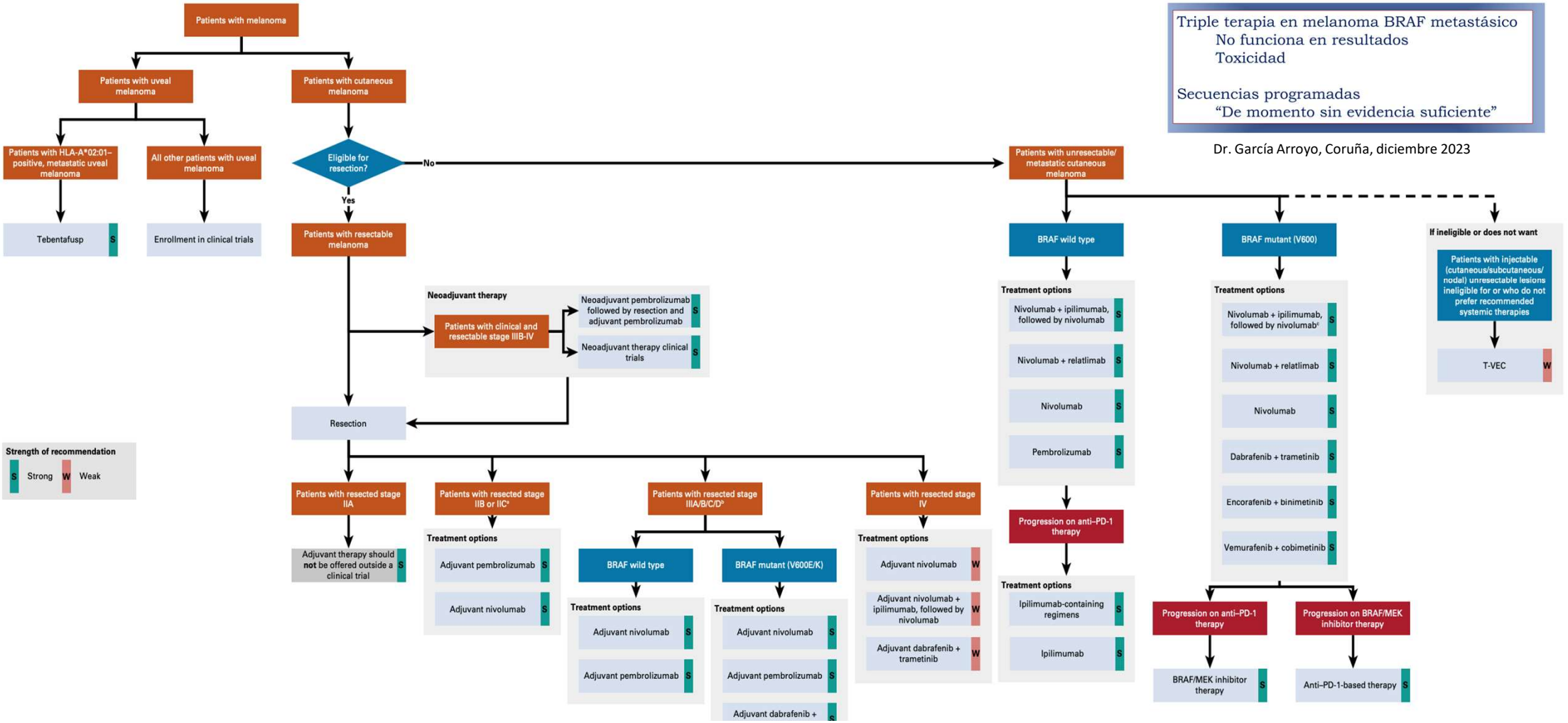
Systemic Therapy for Melanoma: ASCO Guideline Update

Rahul Seth, DO[1]; Sanjiv S. Agarwala, MD[2]; Hans Messersmith, MPH[3]; Krishna C. Alluri, MD[4]; Paolo A. Ascierto, MD[5]; Michael B. Atkins, MD[6]; Kathryn Bollin, MD[7]; Matias Chacon, MD[8]; Nancy Davis, MD[9]; Mark B. Faries, MD[10]; Pauline Funchain, MD[11]; Jason S. Gold, MD[12]; Samantha Guild, JD[13]; David E. Gyorki, MBBS[14]; Varinder Kaur, MD[15]; Nikhil I. Khushalani, MD[16]; John M. Kirkwood, MD[17]; Jennifer Leigh McQuade, MD[18]; Michael O. Meyers, MD[19]; Anthony Provenzano, MD[20]; Caroline Robert, MD, PhD[21]; Mario Santinami, MD[22]; Amikar Sehdev, MPH, MD[23]; Vernon K. Sondak, MD[16];

Triple terapia en melanoma BRAF metastásico
No funciona en resultados
Toxicidad

Secuencias programadas
"De momento sin evidencia suficiente"

Dr. García Arroyo, Coruña, diciembre 2023



Melanoma uveal

Uveal melanoma

- Uveal melanoma (UM) is the most frequent intraocular malignant tumor in adults
- Up to 50% patients develop distant metastases, often to the liver
- Benchmarks (Historical) for:
  - mPFS 3.3 m and 6m-PFS rate 27%
  - mOS 10.2 m and 6m-OS rate 43%

Khoja et al. Annals Oncol 2019; 30: 1370-80

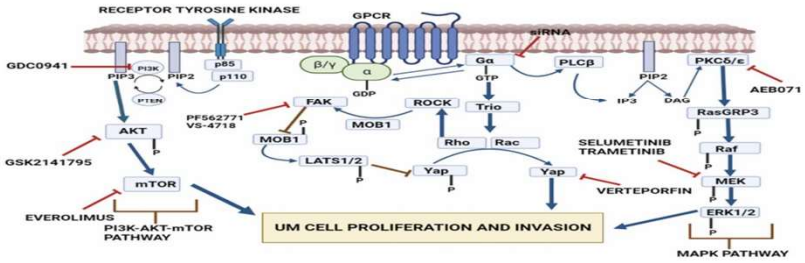
ICI are largely ineffective in mUM

- Meta-analysis 24 trials* of ICIs†, OS data available for 950 patients receiving different treatment lines[1]
  - Overall median OS was **11.5** (95% CI: 9.5–13.8) months, with a 1-year OS of **48.6%** (95% CI: 42.3–55.8%)
  - For first-line treatment only, median OS was **11.5** (95% CI: 9.2–14.6) months
  - For second- and subsequent-line treatment, median OS was **11.2** (95% CI: 8.7–13.7) months
- This meta-analysis included two prospective studies of ipilumumab plus nivolumab (ipi+nivo)[2,3]
  - The reported 1-year OS for ipi+nivo used as **first-line** treatment was **52%**[2]
  - The reported 1-year OS for ipi+nivo used as **mixed-line** treatment was **56%**[3]

*Articles published between 2012 and 2022; †These included anti-CTLA4 (n=7 studies; n=245 patients); anti-PD(L)1 (n=13 studies; n=408 patients); combined anti-CTLA4/anti-PD1 (n=8 studies; n=315 patients)
1L, first-line treatment; 2L+, second-line and beyond treatment; CI, confidence interval; IC, investigator's choice; mUM, metastatic uveal melanoma; OS, overall survival; PFS, progression free survival

1. Pham JP, et al. Melanoma Res 2023;33(4):31
2. Piulats JM, et al. J Clin Oncol 2021;39(6):58
3. Pelster MS, et al. J Clin Oncol 2021;39(6):59

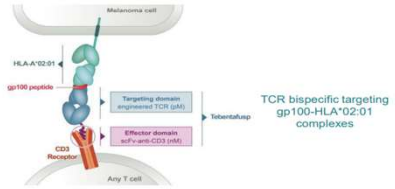
Targeted strategies in Uveal Melanoma



Khan SA, Crit Rev Oncol Hemat Nov 2023

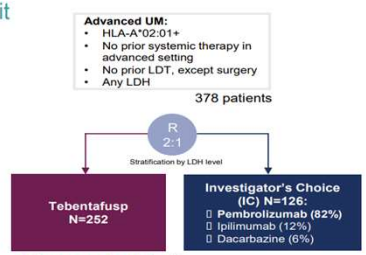
IMCgp100-202: First Positive phase 3 study in mUM

First TCR therapeutic to demonstrate survival benefit



TCR bispecific targeting gp100-HLA*02:01 complexes

- Bispecific, soluble TCR therapeutic
- Affinity-enhanced TCR fused to anti-CD3
- Designed to redirect T cells to gp100+ melanocytic cells



Primary endpoint: OS
Secondary endpoints: ORR, PFS, DCR, DoR, Safety

- Baseline characteristics were well balanced[1]
- Minimum follow-up for OS: 36 months

MADRID 2023 ESMO congress

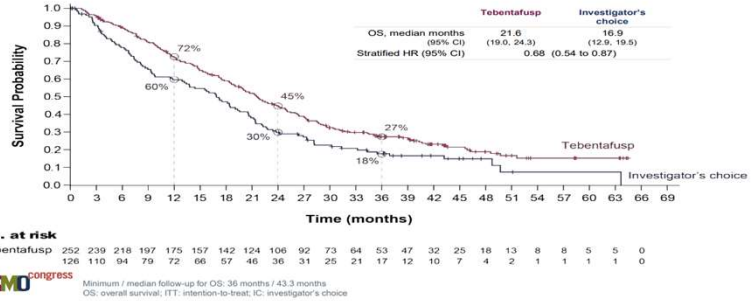
1. Nathan et al. *N Engl J Med* 2021; 385:1196-1206
HLA: human leukocyte antigen; LDT: liver directed therapy; LDH: lactate dehydrogenase; TCR: T cell receptor; UM: uveal melanoma
OS: overall survival; ORR: overall response rate; PFS: progression free survival; DCR: disease control rate; DoR: duration of response

Piperno-Neumann S, ESMO 2023

IMCgp100-202: First Positive phase 3 study in mUM

3-year update: OS in ITT

OS benefit of tebentafusp maintained vs IC at 3-year follow-up



MADRID 2023 ESMO congress

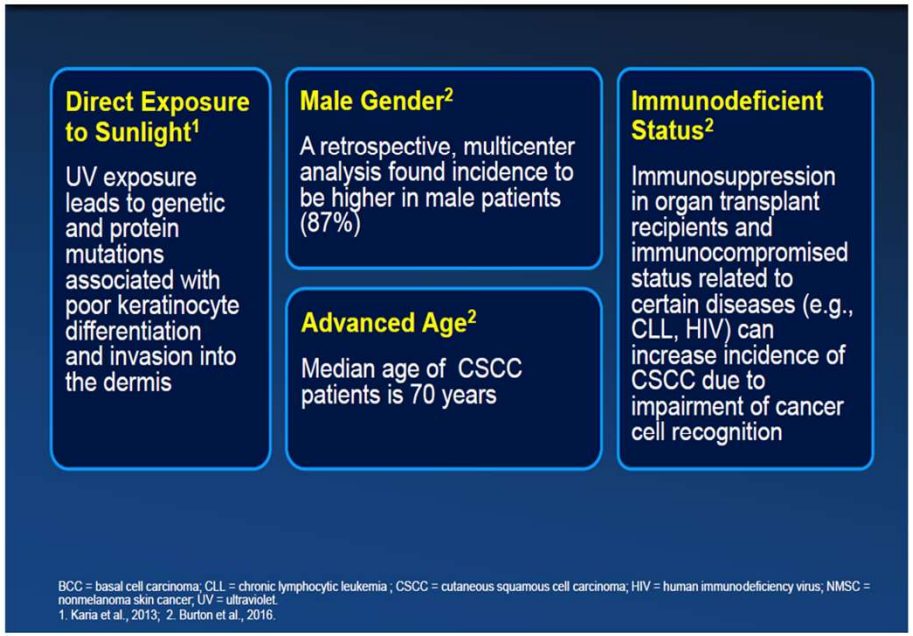
Minimum / median follow-up for OS: 36 months / 43.3 months
OS: overall survival; ITT: intention-to-treat; IC: investigator's choice

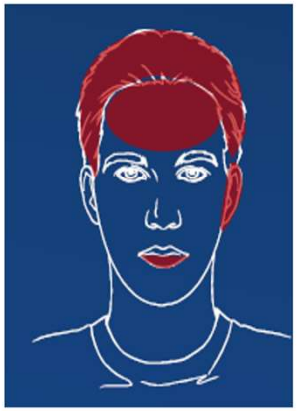
Piperno-Neumann S, ESMO 2023

Perfil de toxicidad distinto: Síndrome de liberación de citoquinas

Indice

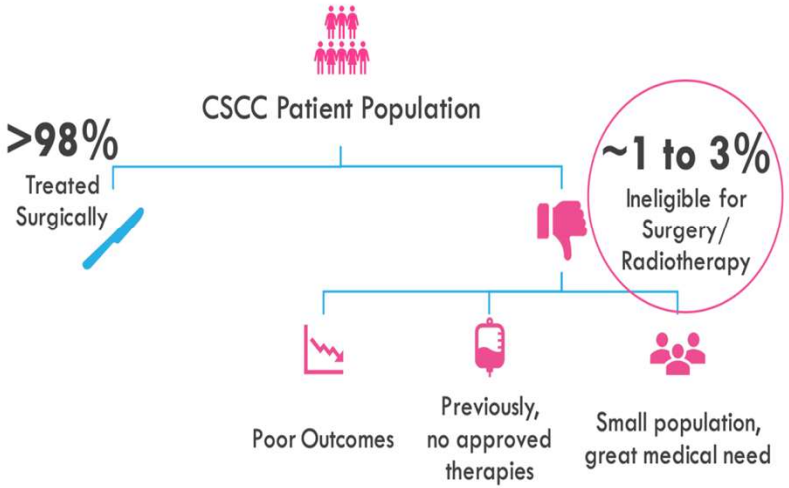
La incidencia del CCCE se asocia con varios factores de riesgo, destacando la exposición directa al sol (20% de tumores cutáneos)





70% of all CSCCs occur on the head and neck

-Most frequently involved locations are the lower lip, external ear and periauricular region, forehead, and scalp



2º tumor cutáneo no melanoma más frecuente, tras los basocelulares
Varones agricultores, pescadores… (exposición crónica)
70% en cabeza y cuello
> 98% tratamiento quirúrgico exclusivo

Schmults CD, et al. JAMA Dermatol. 2013;149(5):541-547.

Tratamiento sistémico

Radiotherapy

Platinum-Based Chemotherapy

- No established standard regimen
- Short-lived remissions (average duration: 3 mo) in up to 60% of patients

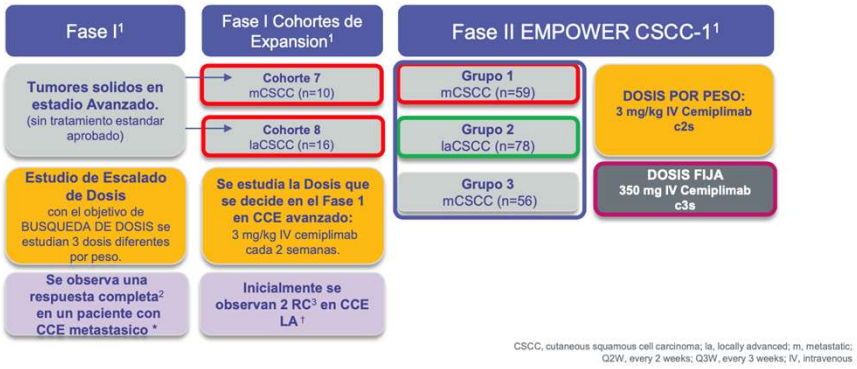
Mutation-Driven Targeted Therapy

- EGFR/pan-HER inhibitors
  - Cetuximab (RR: 28%)
  - Panitumumab(RR: 31%)
  - Dacomitinib (RR ASCO 2017: 28%)

Immunotherapy

- Change of immunosuppressive treatment in organ transplant recipients (OTR) toward mTOR inhibitors
- PD-1 antibodies: cemiplimab

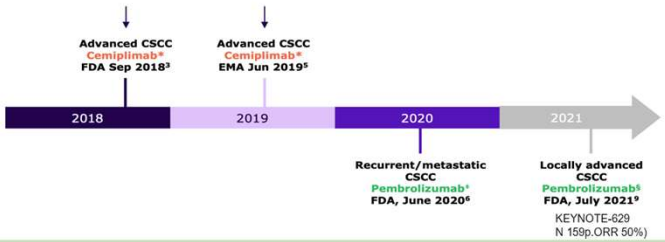
Paolo Ascierto.ESMO22



CSCC, cutaneous squamous cell carcinoma; la, locally advanced; m, metastatic; Q2W, every 2 weeks; Q3W, every 3 weeks; IV, intravenous

1. Migden MR et al, N Engl J Med 2018;379:341–51; 2. Falchook GS, et al. J Immunother Cancer. 2016;4:70; 3. Papadopoulos K, et al. Presentation at 2017 American Society of Clinical Oncology, Chicago, IL. J Clin Oncol. 2017;35(15_suppl):9503; 4. Cemiplimab SmPC, available at https://www.medicines.org.uk/emc; accessed August 2019; 5 Midgen et al Lancet Oncol. 2020 Feb;21(2):294-305.

Inmuno checkpoint inhibitors en CCCE



El tratamiento con anti PD-1 está indicado para pacientes con CSCC localmente avanzado o metastásico no subsidiarios de cirugía o radioterapia curativa.

Of the currently available checkpoint inhibitors, only cemiplimab* is approved in the treatment of advanced CSCC in the US, EU, Canada, and Brazil[1]

Pembrolizumab is only approved in the treatment of advanced CSCC in the US[5-6].

Note: Comparison of clinical trials and their efficacy and safety results cannot be made because study methodologies and trial conditions differ from one clinical trial to another, and even from one drug to another. Additionally, baseline characteristics of patients can vary among studies

*Currently available agents as of July 12, 2019; †In the US approved as cemiplimab-rwlc[3]

BMS, Bristol-Myers Squibb; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; EMD, Emmanuel Merck, Darmstadt; MSD, Merck Sharp & Dohme; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; PI, prescribing information; SmPC, summary of product characteristics

1. LIBTAYO® PI; 2. LIBTAYO® SmPC; 3. OPDIVO® PI; 4. OPDIVO® SmPC; 5. KEYTRUDA® PI; 6. KEYTRUDA® SmPC; 7. COSIBELIMAB, ESMO 2020

Fase I: 26 p; RO 50%; Mediana tiempo respuesta→ 2.3 meses

Fase II:

- **E**n el 66.3% de los pacientes administrado en 1ª línea
- RO: 46%
- Control de enfermedad: 72.5%
- SLP: 22.1m
- SG a 2 años:61.8%:
- Perfil toxicidad aceptable con EAs ≧ 3 < 20% y mejoría significativa en calidad de vida con el cemiplimab (QLQ-30).

Tratamiento sistémico

Radiotherapy

Platinum-Based Chemotherapy

- No established standard regimen
- Short-lived remissions (average duration: 3 mo) in up to 60% of patients

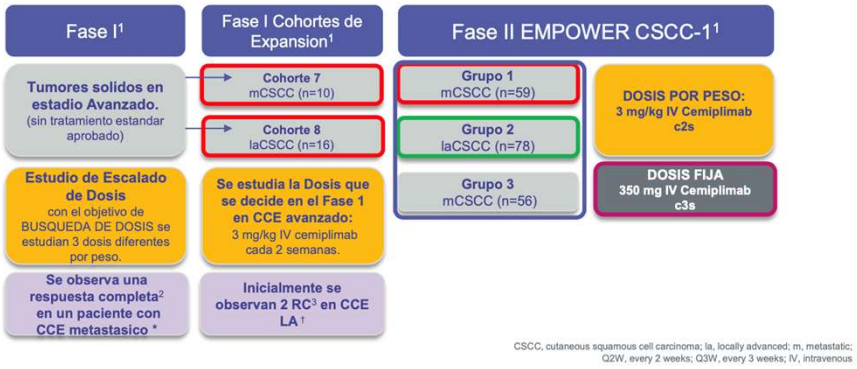
Mutation-Driven Targeted Therapy

- EGFR/pan-HER inhibitors
  - Cetuximab (RR: 28%)
  - Panitumumab(RR: 31%)
  - Dacomitinib (RR ASCO 2017: 28%)

Immunotherapy

- Change of immunosuppressive treatment in organ transplant recipients (OTR) toward mTOR inhibitors
- PD-1 antibodies: cemiplimab

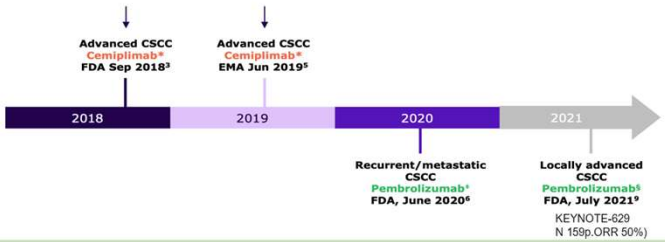
Paolo Ascierto.ESMO22



CSCC, cutaneous squamous cell carcinoma; la, locally advanced; m, metastatic; Q2W, every 2 weeks; Q3W, every 3 weeks; IV, intravenous

1. Migden MR et al, N Engl J Med 2018;379:341–51; 2. Falchook GS, et al. J Immunother Cancer. 2016;4:70; 3. Papadopoulos K, et al. Presentation at 2017 American Society of Clinical Oncology, Chicago, IL. J Clin Oncol. 2017;35(15_suppl):9503; 4. Cemiplimab SmPC, available at https://www.medicines.org.uk/emc; accessed August 2019; 5 Midgen et al Lancet Oncol. 2020 Feb;21(2):294-305.

Inmuno checkpoint inhibitors en CCCE



El tratamiento con anti PD-1 está indicado para pacientes con CSCC localmente avanzado o metastásico no subsidiarios de cirugía o radioterapia curativa.

Of the currently available checkpoint inhibitors, only cemiplimab* is approved in the treatment of advanced CSCC in the US, EU, Canada, and Brazil[1]

Pembrolizumab is only approved in the treatment of advanced CSCC in the US[5-6].

Note: Comparison of clinical trials and their efficacy and safety results cannot be made because study methodologies and trial conditions differ from one clinical trial to another, and even from one drug to another. Additionally, baseline characteristics of patients can vary among studies

*Currently available agents as of July 12, 2019; †In the US approved as cemiplimab-rwlc[3]

BMS, Bristol-Myers Squibb; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; EMD, Emmanuel Merck, Darmstadt; MSD, Merck Sharp & Dohme; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; PI, prescribing information; SmPC, summary of product characteristics

1. LIBTAYO® PI; 2. LIBTAYO® SmPC; 3. OPDIVO® PI; 4. OPDIVO® SmPC; 5. KEYTRUDA® PI; 6. KEYTRUDA® SmPC; 7. COSIBELIMAB, ESMO 2020

Cemiplimab no financiado en España

Fase I: 26 p; RO 50%; Mediana tiempo respuesta→ 2.3 meses

Fase II:

- **E**n el 66.3% de los pacientes administrado en 1ª línea
- RO: 46%
- Control de enfermedad: 72.5%
- SLP: 22.1m
- SG a 2 años:61.8%:
- Perfil toxicidad aceptable con EAs ≧ 3 < 20% y mejoría significativa en calidad de vida con el cemiplimab (QLQ-30).

Indice

EPIDEMIOLOGÍA

- El carcinoma basocelular de piel es un tumor frecuente
  - 75-80% de los tumores cutáneos
- Riesgo de segundo BCC: 44% en 3 años
- Localmente avanzados: 1-10%
  - Deben ser evaluados en comité multidisciplinar
  - Pueden ser candidatos a tratamiento sistémico
- Rara vez metastatiza : 0.003%–0.5%

Criterios de alto riesgo de CBCC

CAMPUS SEOM
Área de formación virtual SEOM

- ✓ Diámetro
  - ✓ ≥ 20 mm tronco/extremidades
  - ✓ ≥ 10 mm en mejillas/frente/cuello
  - ✓ ≥ 6 mm en otras zonas de la cara
- ✓ Bordes mal definidos
- ✓ Inmunosupresión
- ✓ Radioterapia previa
- ✓ Subtipos:
  - ✓ morfea, basoescamoso, infiltrativo, mixto, nodular, esclerosante
- ✓ Infiltración perineural

Criterios que contraindican la cirugía y la RT en CBCIa Nägeli MC, Dummer R. Vismodegib (Erivedge). Schweiz Med Forum 2014; 14: 284–286.
>5 CBC en pacientes con síndromes genéticos
CBC>10 mm recidivado tras 2 cirugías en localizaciones críticas
CBC que infiltra hueso, cartílago u otras estructras
CBC recidivante tras múltiples cirugías/RT
CBC en pacientes no candidatos a anestesia general

Inhibidores de la vía de hedgehog

Vismodegib

FDA Enero´12
EMA Julio´13
AEMPS Agosto´13
CCB LA o M sin opciones de cir/RT

Sonidegib

FDA Julio´15
EMA Agosto´15
AEMPS Agosto´15
CCB LA sin opciones de cir/RT

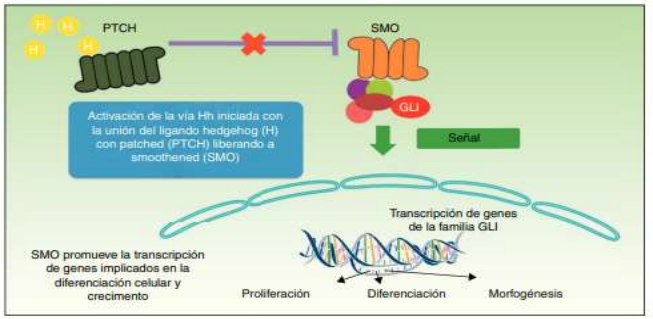


Figura 1 Activación de la vía Hedgehog (Hh).

Ridky, 2007; ACS, 2012; Rubin et al, 2005; Housman et al, 2003; Christenson et al, 2005; Marcil et al, 2000.J. Dreier et al, B J Dermatol, 2014 .NCCN 1/2021

Tratamiento sistémico

Estudio pivotal ERIVANCE

	CBCm (n = 33)		CBC-la (n = 63)	
	IRF (Obj1º)	INV (Obj2º)	IRF (Obj1º)	INV (Obj2º)
Respondedores (ORR) (Respuesta completa + parcial)	30.3% (n=10)	45.5% (n=15)	42.9% (n=27)	60.3% (n=38)
Enfermedad Estable	63.6%	45.5%	38.1%	23.8%
Progresión	3.0%	6.1%	12.7%	9.5%
No evaluable	3.0%	3.0%	6.3%	6.3%
IC95% para la respuesta objetiva	(15.6 – 48.2)	(28.1 – 62.2)	(30.5 – 56.0)	(47.2 – 71.7)
p-valor	0.0011		<0.0001	

75% beneficio clínico (respuesta o ausencia de progresión en 24 semanas)

	CBCm (n = 33)		CBC-la (n = 63)	
	Análisis Primario (26 de Noviembre 2010)	Análisis Final a 30 meses (30 de Mayo de 2013)	Análisis Primario (26 de Noviembre 2010)	Análisis Final a 30 meses (30 de Mayo de 2013)
Duración mediana de Respuesta (meses)	12.9m	14.8m	7.6m	26.2m
IC95%	5.6-12.9	5.6-17.0	7.4-NE	9.0-37.6

Tiempo medio hasta la MÁXIMA REDUCCIÓN DEL TUMOR (5.5-6.7 meses)

Table 1. Efficacy of sonidegib (18-month analysis) and vismodegib (21-month analysis) in patients with laBCC per RECIST criteria.

Patients with laBCC	Sonidegib 200 mg QD [25] Central View RECIST-like	Vismodegib 150 mg QD [26] Central View RECIST
	n = 66	*n* = 63
ORR, *n* (%); 95% CI	40 (60.6); 47.8–72.4	30 (47.6); 35.5–60.6
CR, *n* (%)	14 (21.2)	14 (22.2)
PR, *n* (%) DCR 92.3%	26 (39.4)	16 (25.4) DCR 82.5%
SD, *n* (%)	20 (30.3)	22 (34.9)
PD, *n* (%)	1 (1.5)	8 (12.7)
Unknown, *n* (%)	5 (7.6)	3 (4.8)
DOR, median, months	26.1	9.5

RECIST, response evaluation criteria in solid tumors; QD, once daily; ORR, objective response rate; CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; DOR, duration of response.

Cemiplimab ha mostrado eficacia tras fallo o intolerancia a iHH

Sekulic A et al. New Engl J Med 2012;366:2171–9. Sekulic et al. ASCO 2014; Sekulic et al. JAAD 2015.Dummer.JEADV2020.Stratigos et al.Lancet Oncol 2021

Efectos adversos

Estrategias de tratamiento
Reducción de dosis
Dosis intermitentes
Detención y retratamiento a la progresión.

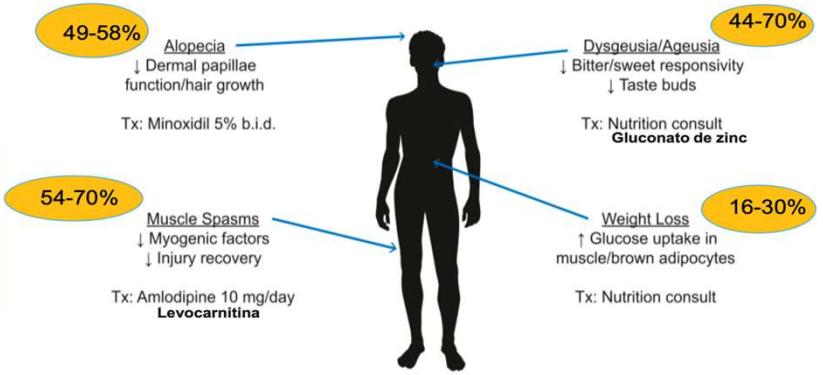


Figure 1. Adverse events associated with hedgehog pathway inhibitors [19, 21, 26, 29]. Abbreviations: b.i.d., twice daily; Tx, treatment.

Lacouture ME Characterization and Management of Hedgehog Pathway Inhibitor-Related Adverse Events Oncol 2016
Heckmann SM Zinc Gluconate in the Treatment of Dysgeusia a Randomized Clinical Trial J Dent Res 2005
Cannon JGD Levocarnitine for vismodegib-associated muscle spasms *JEADV 2018*

M Lacouture The Oncologist 2016;21:1–12 .Chacón.SEOM23

Indice

EPIDEMIOLOGÍA

- ✓ Es un tumor neuroendocrino que se origina en las células de Merkel (derivadas de la cresta neural), sin función clara.
- ✓ Es un tumor cutáneo raro, <1% de tumores cutáneos
  - ✓ En torno a 2800 casos en Estados Unidos al año
  - ✓ Su incidencia se ha triplicado en los últimos 30 años
    - ✓ Aumento esperanza de vida
    - ✓ Inmunosupresión
    - ✓ Exposición UV
- ✓ Gran mortalidad, SG a 10 años 57% en EEUU y 47% en Europa
  - ✓ Duplica en letalidad a la del melanoma

AEIOU

***A**syntomatic; **E**xpanding rapidly; **I**nmunosuppressed; **O**ld; **U**V exposed*

Heath M, Jaimes N, Lemos B, Mostaghimi A, Wang LC, Peñas PF, et al. Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: The AEIOU features. J Am Acad Dermatol. 2008;58:375–81.

Eigentler TK. Clinical course and prognostic factors of Merkel cell carcinoma of the skin. Br J Dermatol. 2009;161:90–4.

FACTORES DE RIESGO

Schadendorf 2017 EJC
Feng 2008 Science

TRATAMIENTO LOCAL

- ✓ **Cirugía primario +/-RDT único tratamiento curativo**
  - ✓ 1-2 cm margen
  - ✓ ganglio centinela en ganglios clínica y radiológicamente negativos
- ✓ **Linfadenectomía** en ganglios positivos clínicos o tras BSGC+
- ✓ **Radioterapia adyuvante**: fundamental en estadio I/II, aumenta SG
  - Ganglios clínicamente negativos:
    - Zona tumoral a todos, salvo < 1cm y sin invasión linfovascular
  - Lecho ganglionar:
    - Ganglio centinela positivo y no linfadenectomía
    - Ganglio centinela no posible o negativo con riesgo de falso negativo (por ej, cabeza y cuello)

Adaptada Ivan Marquez.2019. Schadendorf 2017 EJC. IPT avelumab2020. Iwona Ługowska.ESMO23

Schadendorf 2017 EJC.NCCN 2021.Adaptada Ivan Márquez.2019

- ✓ Enfermedad quimiosensible pero rápidamente quimiorresistente
- ✓ Regímenes basados en Platino/etopósido,alquilantes,taxanos...
  - No basados en estudios aleatorizados
- ✓ Racional para inmunoterapia

- Mayor frecuencia en inmunodeprimidos.
- Casos de regresión espontánea.
- Infiltración linfocitaria = mejor pronóstico.

Tratamiento sistémico

JAVELIN Merkel 200:prospectivo no aleator en CCM metastásico

~40% 2 o + líneas previas

Primer fármaco aprobado por la FDA y EMA, para los pacientes con carcinoma metastásico de células de Merkel.

N=200 (estimado) Ensayo fase II, abierto, multicéntrico para evaluar la actividad clínica y seguridad de avelumab (MSB0010718C) en sujetos con CCM metastásico[1].

Pacientes[1]:
- Histológicamente probado CCMm
- ECOG PS 0–1

Parte A: han recibido al menos una línea de quimioterapia **(n=88)**[2,3]

Parte B: no han recibido ningún tratamiento sistémico para el CCMm **(n=112)**[4]

Evaluación tumoral cada 6 semanas (RECIST v1.1; IERC)

Avelumab 10 mg/kg IV (1-h infusión) cada 2 sem*
Hasta progresión de la enfermedad, o toxicidad inaceptable u otro criterio médico que obligue a la suspensión.

Parte A:
"Endpoint" Primario:
- **Mejor respuesta objetiva confirmada**

Endpoints 2º:
- DoR, PFS, OS, seguridad, Ac-Ave, PK

Parte B:
"Endpoint" Primario:
- **Respuesta objetiva duradera**

Endpoints 2º:
- DoR, PFS, OS, seguridad, Ac-Ave, PK

Respuesta (N=88)	Resultados preliminares (≥6 meses de seguimiento)	≥1 año de seguimiento	≥36 meses de seguimiento
ORR, % (95% IC)	**31.8 (21.9–43.1)**	**33.0 (23.3–43.8)**	33.0 (23.3-43.8)
Confirmada BOR, n (%)			
CR	8 (9.1)	10 (11.4)	10 (11.4)
PR	20 (22.7)	19 (21.6)	19 (21.6)
SD	9 (10.2)	9 (10.2)	9 (10.2)
PD	32 (36.4)	32 (36.4)	32 (36.4)
No-CR/no-PD	1 (1.1)*	0	
No evaluable	18 (20.5)	18 (20.5)	18 (20.5)
Duración de la Respuesta	**n=28**	**n=29**	**N=29**
Mediana DOR, meses (95% IC)	NE (8.3, –)	NE (18.0, –)	40.5 (18.0-NE)
Rango	2.8–17.5+	2.8–23.3+	2.8-41.5
6-meses DRR,† % (95% IC)	**29.1 (19.5–38.8)**	**30.6 (20.9–40.3)**	
Proporción de la respuesta a 1 año, % (95% IC)	N/A	**23.9 (15.4–34.1)**	
Respuestas con ≥6-meses de duración,‡ % (95% IC)	**92 (70–98)**	**93 (74–98)**	93 (75-98)
Respuestas con ≥1-año duración,‡ % (95% IC)	N/A	**74 (53–87)**	71 (51-85)
Respuestas con ≥2-año duración,‡ % (95% IC)	N/A	N/A	67 (47-82)
Respuestas con ≥3-año duración,‡ % (95% IC)	N/A	N/A	52 (26-73)

Tasa supervivencia a 3 años 32% vs 0% QT

Variables de eficacia (Parte B) (según RECIST v1.1, CIRCV)	Resultados (N=116)
Tasa de respuesta objetiva (TRO) Tasa de respuesta, RC+RP** n (%) (IC del 95%)	46 (39,7%) (30,7, 49,2)
Mejor respuesta global (MRG) confirmada Respuesta completa (RC)** n (%) Respuesta parcial (RP)** n (%)	19 (16,4%) 27 (23,3%)
Duración de la respuesta (DR)a Mediana, meses (IC del 95%) Mínima, máxima (meses) ≥ 3 meses mediante K-M (IC del 95%) ≥ 6 meses mediante K-M (IC del 95%) ≥ 12 meses mediante K-M (IC del 95%) ≥ 18 meses mediante K-M (IC del 95%) ≥ 24 meses mediante K-M (IC del 95%)	18,2 (11,3, no estimable) 1,2, 28,3 89% (75, 95) 78% (63, 87) 66% (50, 78) 52% (34, 67) 45% (25,63)
Supervivencia libre de progresión (SLP) Mediana de la SLP, meses (IC del 95%) Tasa de SLP a los 3 meses por K-M (IC del 95%) Tasa de SLP a los 6 meses por K-M (IC del 95%) Tasa de SLP a los 12 meses por K-M (IC del 95%) Tasa de SLP a los 24 meses por K-M (IC del 95%)	4,1 (1,4; 6,1) 51% (42, 60) 41% (32, 50) 31% (23, 40) 20% (12, 30)

Los TRAEs más frecuentes fueron reacciones infusionales, fiebre, fatiga y erupción

1. NCT02155647. Available at ClinicalTrials.gov (accessed November 2020). 2. Kaufman HL et al. Lancet Oncol 2016;17:1374–85; 2. Ficha técnica de Bavencio®. Octubre 2020. Disponible en: https://cima.aemps.es/cima/dochtml/ft/1171214001/FT_1171214001.html#1-nombre-del-medicamento

EMA Y FDA approval for **Avelumab**

FDA for approval for **Pembrolizumab**

Muchas gracias por vuestra atención

Y mucha suerte en el examen!!

SEOM
Sociedad Española de Oncología Médica