

XVII SIMPOSIUM **BASES BIOLÓGICAS DEL CÁNCER E INNOVACIÓN TERAPÉUTICA**

MÁS DE 20 AÑOS A LA VANGUARDIA DE LA FORMACIÓN
EN LA BIOLOGÍA Y TRATAMIENTO DEL CÁNCER

SALAMANCA, 22 Y 23 DE MAYO DE 2025

OPCIONES TERAPÉUTICAS Y NUEVOS HORIZONTES EN EL TRATAMIENTO DEL MELANOMA MALIGNO AVANZADO

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Hospital General Universitario Gregorio Marañón

Universidad Complutense de Madrid

23-5-2025

CONFLICTOS DE INTERÉS

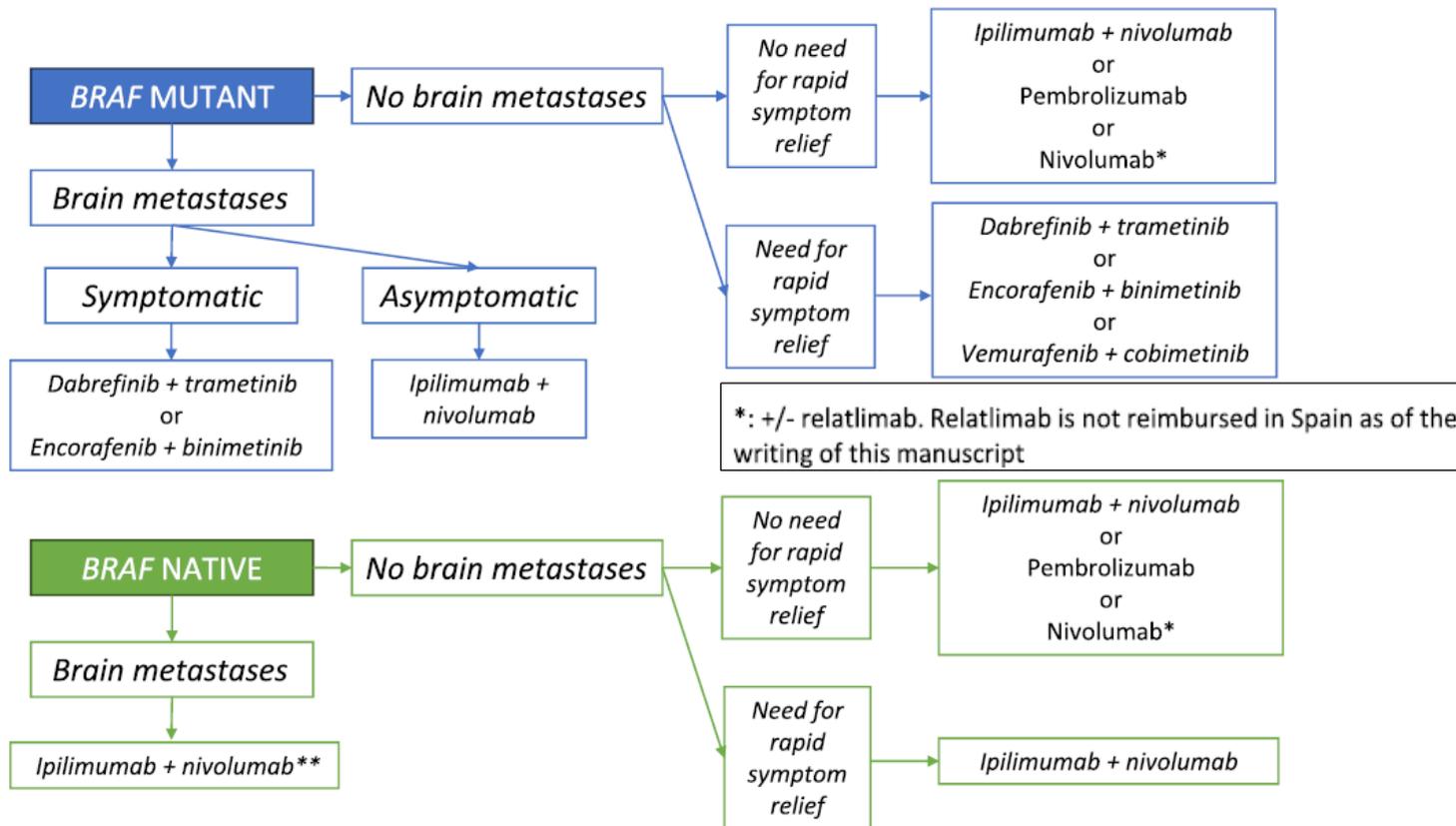
Advisory role: Amgen, Astra Zeneca, BiolineRx, BMS, Celegene, GSK, Highlight Therapeutics, Immunocore, Merck Serono, MSD, Novartis, Pierre Fabre, Regeneron, Roche, Sanofi, Sun Pharma

Travel accommodation and congress: Amgen, BMS, GSK, Highlight Therapeutics, MSD, Novartis, Pierre Fabre, Roche, Sun Pharma

Clinical trial participation as PI: Ab Science, Aduro, Agenus, Alkermes, Amgen, Astra Zeneca, Biontech, BMS, Erasca, Genentech, GSK, Highlight Therapeutics, Idera, Immunocore, Incyte, Iovance, Kartos, Merck Serono, MSD, Novartis, Pfizer, Regeneron, Roche, Sairopa.

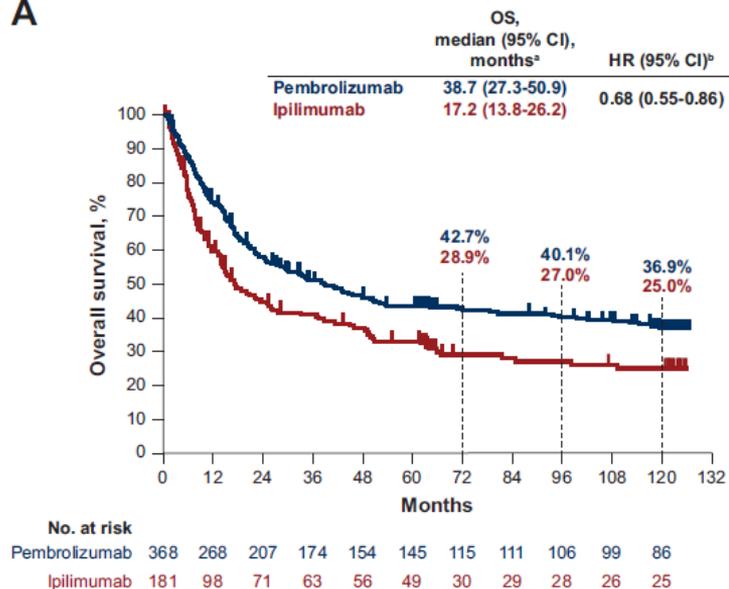
If you find something I have missed, please e-mail me: ivanpantic@hotmail.com

BASÁNDONOS EN LAS GUÍAS SEOM-GEM 2023



BRAF NATIVO, NO MTS SNC: PEMBROLIZUMAB KN 006

A



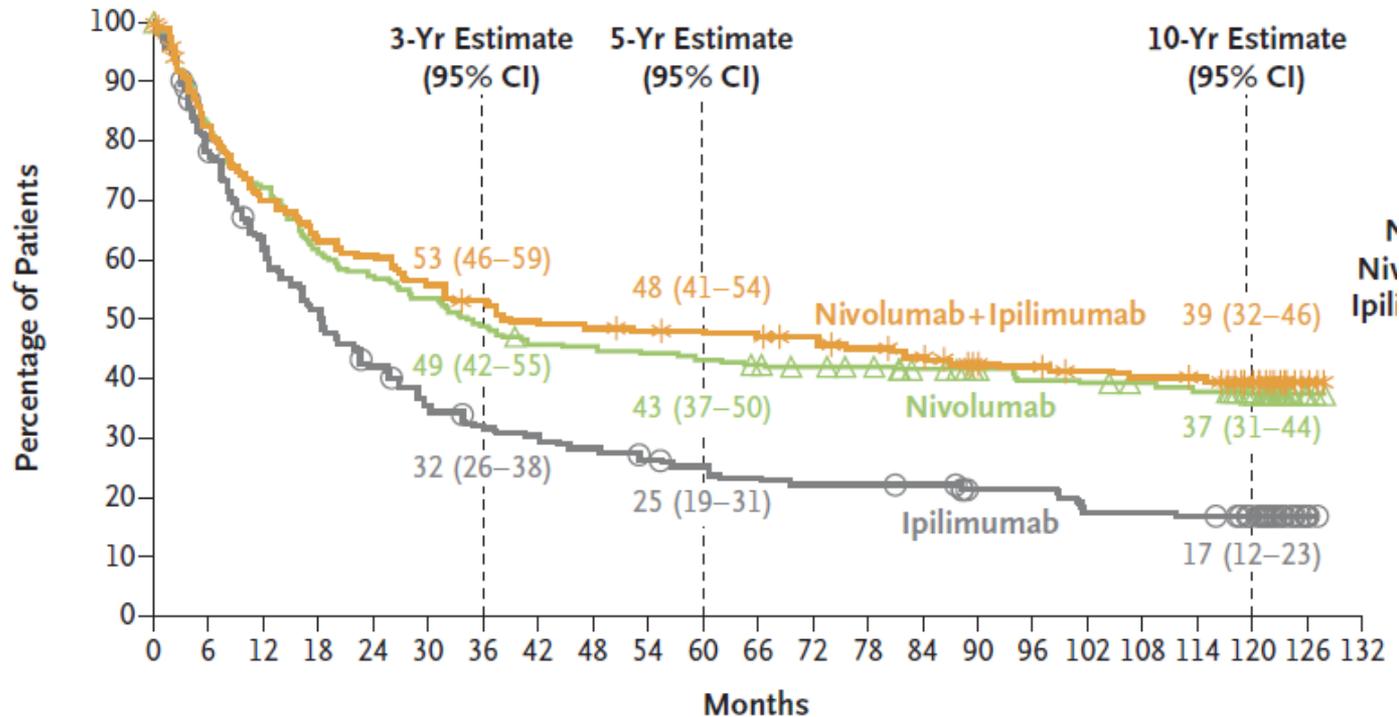
Subgroup	Events/ patients	Hazard ratio (95% CI) ^a
Overall	533/834	0.71 (0.60–0.85)
BRAF subgroup		
<i>BRAF</i> -wild type	339/525	0.74 (0.59–0.93)
<i>BRAF</i> -mutant; no prior BRAFi/MEKi	92/163	0.56 (0.37–0.86)
<i>BRAF</i> -mutant; prior BRAFi/MEKi	98/139	0.73 (0.48–1.10)
LDH level		
Normal	328/548	0.78 (0.62–0.98)
Elevated	194/270	0.60 (0.44–0.80)
Tumor size		
<10 cm	321/536	0.72 (0.58–0.91)
≥10 cm	140/186	0.64 (0.45–0.91)
Brain metastases		
Yes	50/80	0.56 (0.32–0.98)
No	477/748	0.73 (0.60–0.88)

0.1 0.5 1

Favors pembrolizumab

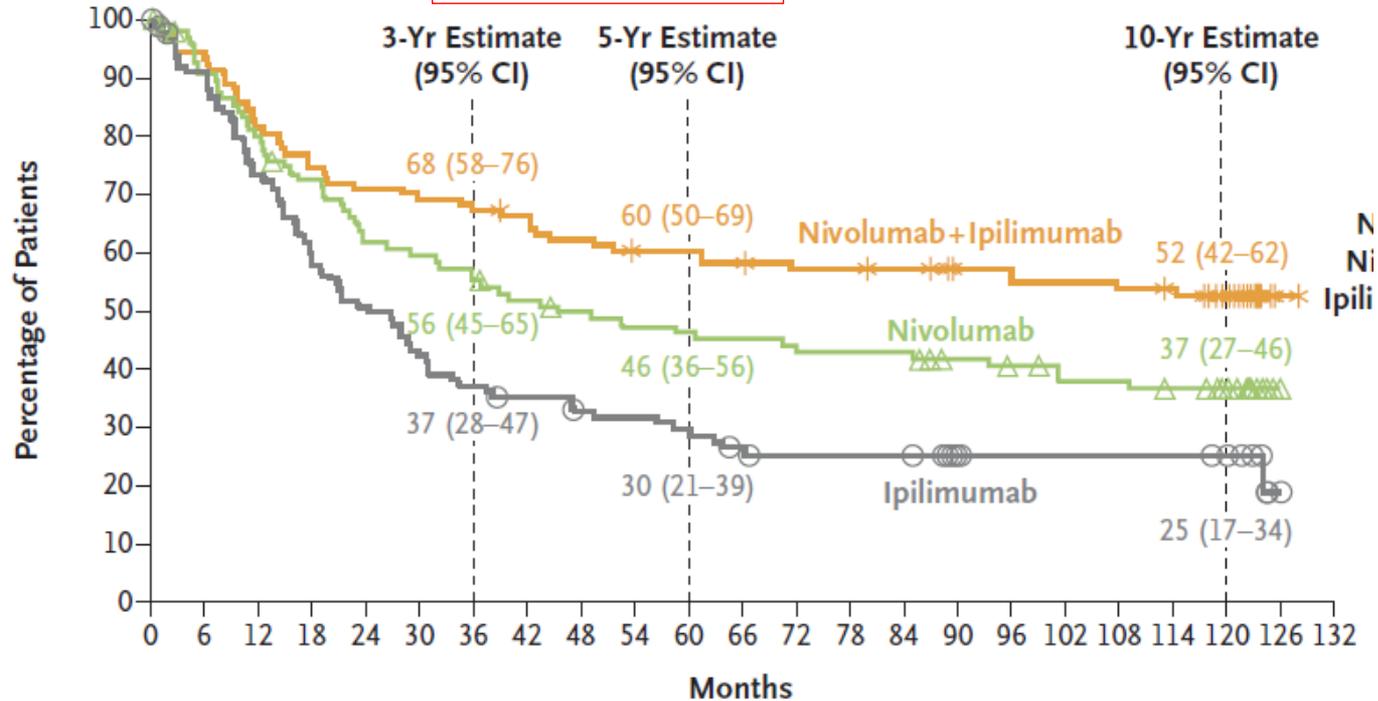
BRAF NATIVO, NO MTS SNC: NIVOLUMAB +/- IPILIMUMAB CM 067

B Overall Survival among Patients without BRAF Mutations



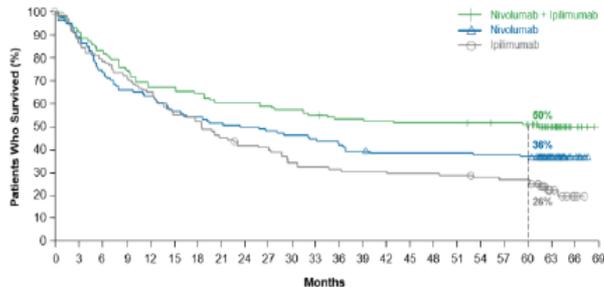
BRAF MUTADO, NO MTS SNC: NIVOLUMAB +/- IPILIMUMAB CM 067

A Overall Survival among Patients with BRAF Mutations

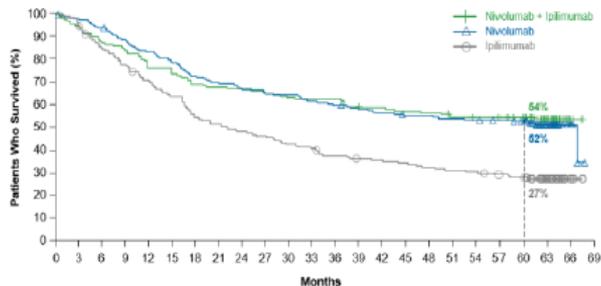


NIVOLUMAB, SIN METASTASIS CEREBRALES, INDEPENDIENTE DE BRAF, ¿CON O SIN IPILIMUMAB? PAPEL DEL PD-L1

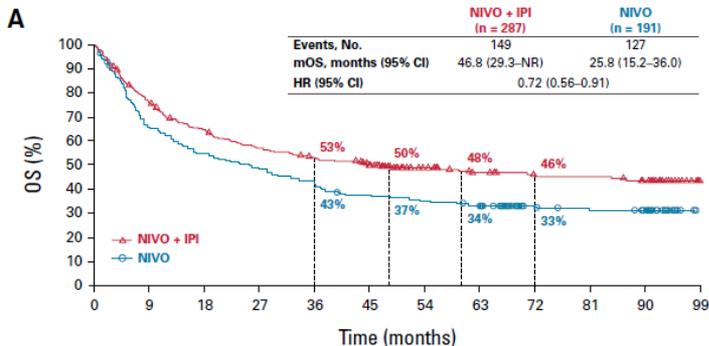
(A) PD-L1 expression level <1%



(B) PD-L1 expression level ≥1%

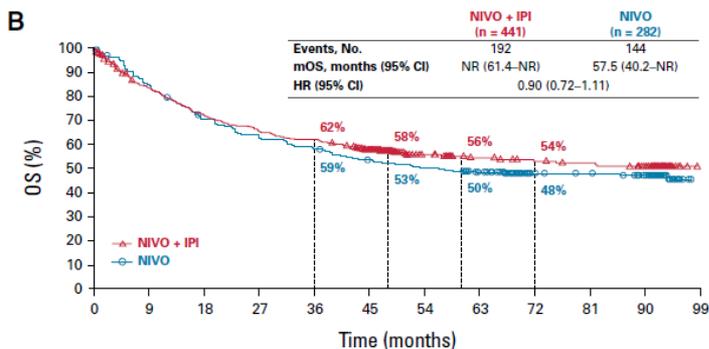


CM067



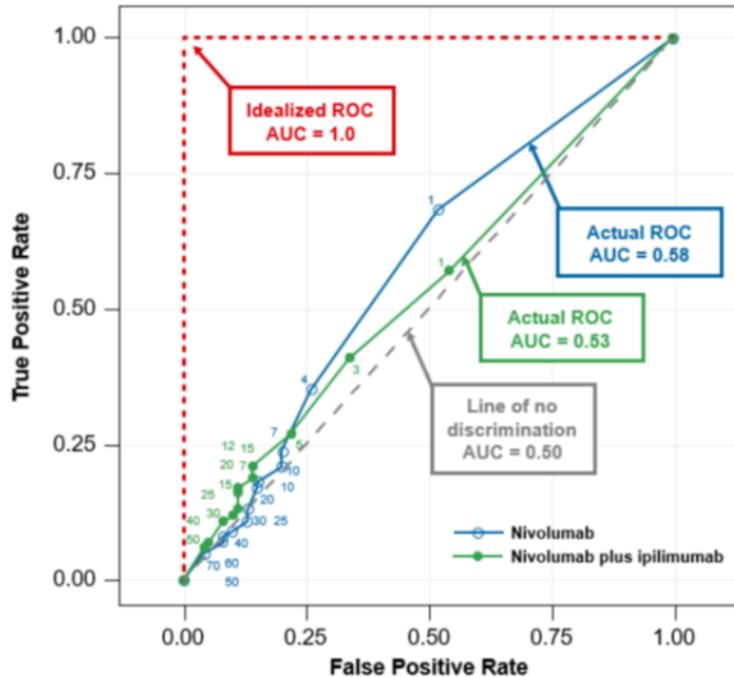
No. at risk:

	287	216	182	160	146	126	74	63	57	56	50	0
NIVO + IPI	287	216	182	160	146	126	74	63	57	56	50	0
NIVO	191	123	103	92	81	70	66	59	41	37	33	0



Time (months)
POOLED ANALYSIS

PARADOJAS DE LA REGULACIÓN



YERVOY en combinación con nivolumab está indicado para el tratamiento del melanoma avanzado (irreseccable o metastásico) en adultos. En relación con nivolumab en monoterapia se ha establecido un aumento de la supervivencia libre de progresión (SLP) y supervivencia global (SG) para la combinación de nivolumab con ipilimumab, solo en los pacientes con baja expresión de PD L1 en el tumor (ver las secciones 4.4 y 5.1).

* Más información

Modificación	Situación expediente indicación
YERVOY en combinación con nivolumab está indicado para el tratamiento del melanoma avanzado (irreseccable o metastásico) en adultos y adolescentes a partir de 12 años (ver sección 4.4). En relación con nivolumab en monoterapia se ha establecido un aumento de la supervivencia libre de progresión (SLP) y supervivencia global (SG) para la combinación de nivolumab con ipilimumab, s [redacted] e [redacted] ver las secciones 4.4 y 5.1).	Sin petición de financiación

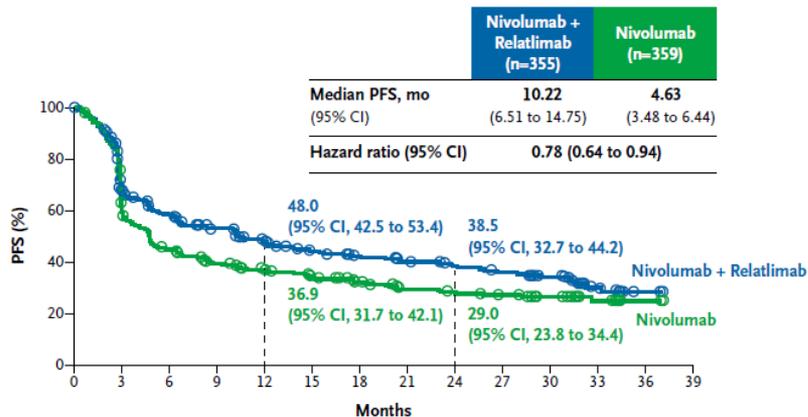
Resuelto

Sí, financiada indicación autorizada

CM067 estratificó para PD-L1<5%; ¿Qué es baja expresión?; ¿Qué anticuerpo usamos para la determinación?; ¿Qué score?

NIVOLUMAB, SIN METASTASIS CEREBRALES, INDEPENDIENTE DE BRAF, ¿CON O SIN RELATLIMAB (ANTI LAG-3)?

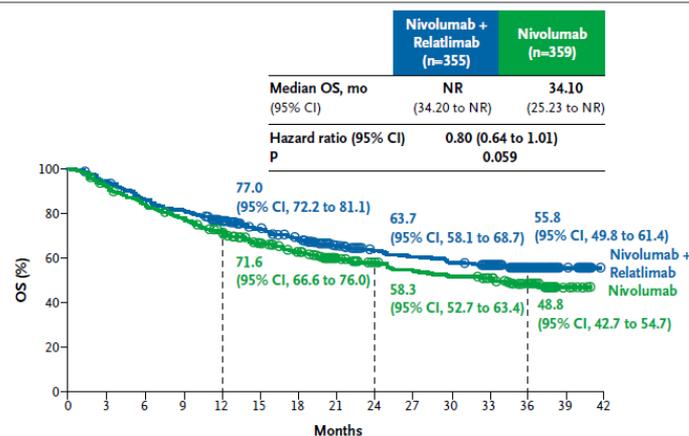
A



No. at risk

Nivolumab + Relatlimab	355	223	189	159	130	106	82	70	64	59	48	20	2	0
Nivolumab	359	192	150	124	98	82	67	52	49	45	33	15	3	0

B



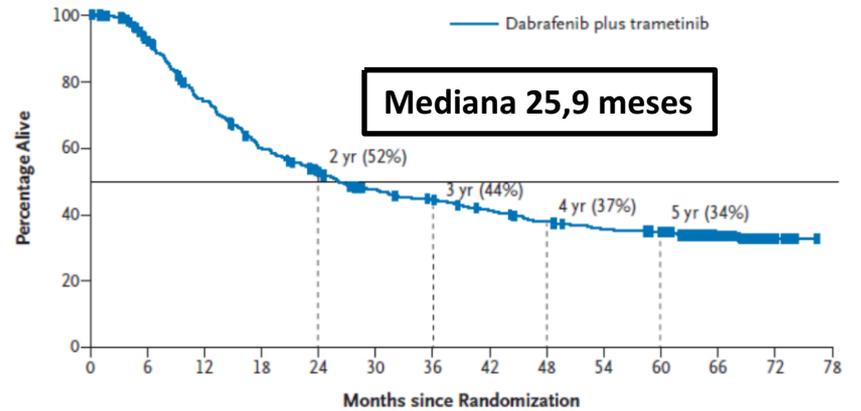
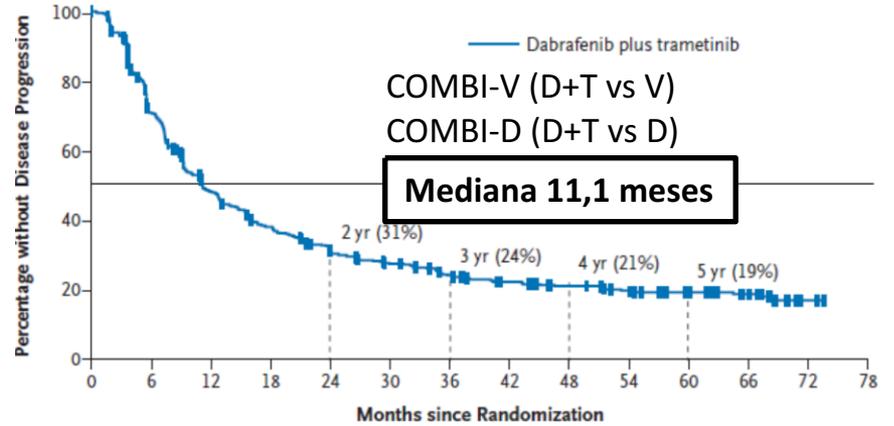
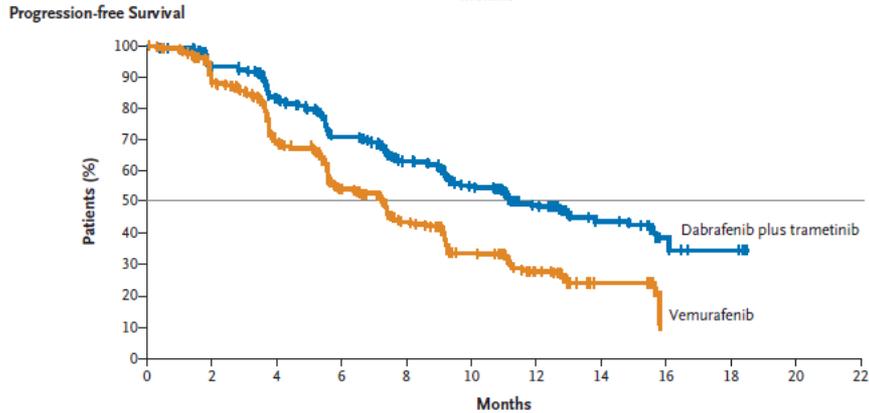
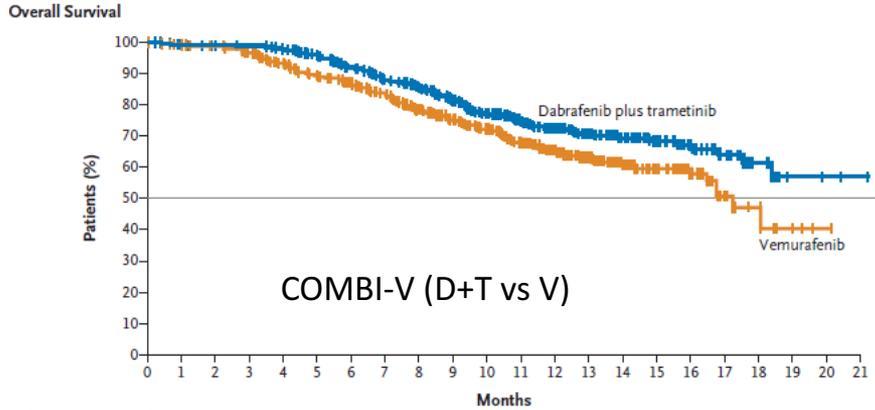
No. at risk

Nivolumab + Relatlimab	355	334	305	287	261	227	203	167	145	139	133	109	50	9	0
Nivolumab	359	329	301	277	240	202	182	155	126	119	113	96	42	8	0

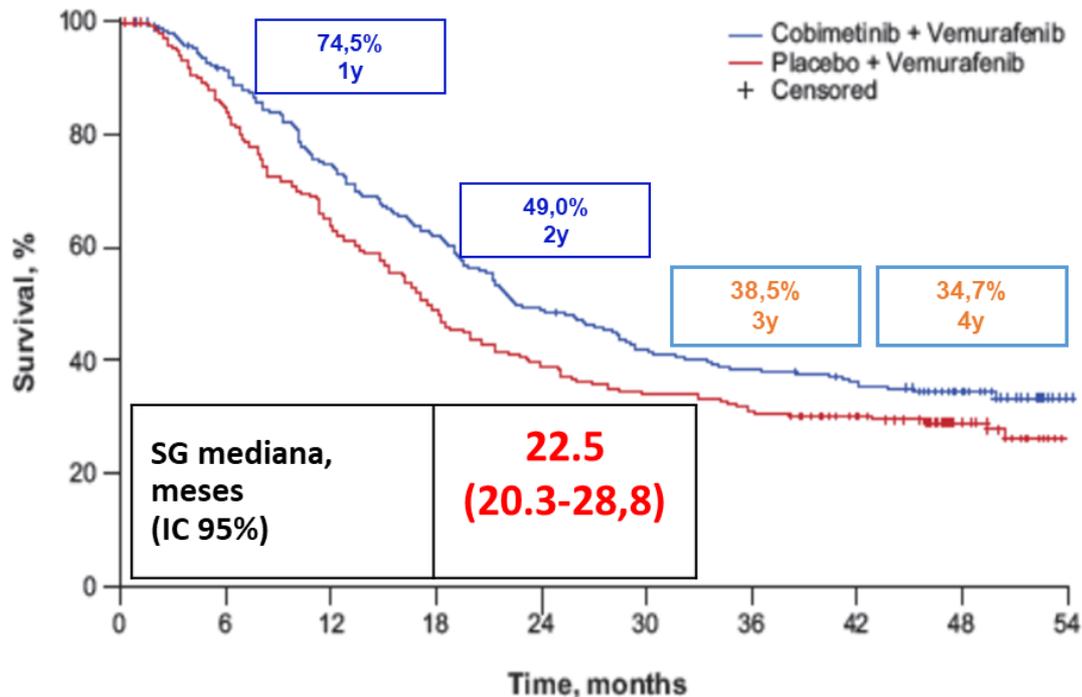
Indicaciones autorizadas	Indicación autorizada	Situación expediente indicación	Resolución expediente de financiación indicación
	Opdulag está indicado para el tratamiento de primera línea del melanoma avanzado (irresecable o metastásico) en adultos y adolescentes a partir de 12 años de edad con expresión de PD-L1 menor 1% en las células tumorales.	Resuelto	No incluida

Long 2023 NEJM evidence
<https://www.sanidad.gob.es/profesionales/medicamentos>

BRAF MUTADO Y TERAPIA DIRIGIDA: DABRAFENIB + TRAMETINIB



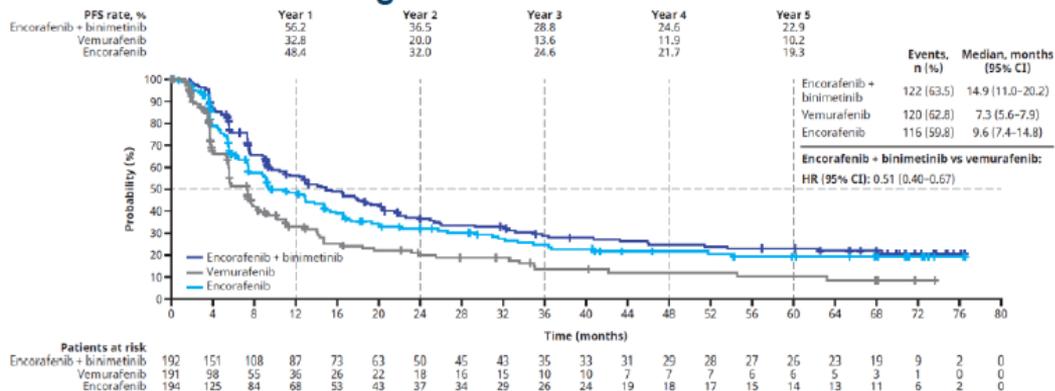
BRAF MUTADO Y TERAPIA DIRIGIDA: VEMURAFENIB + COBIMETINIB



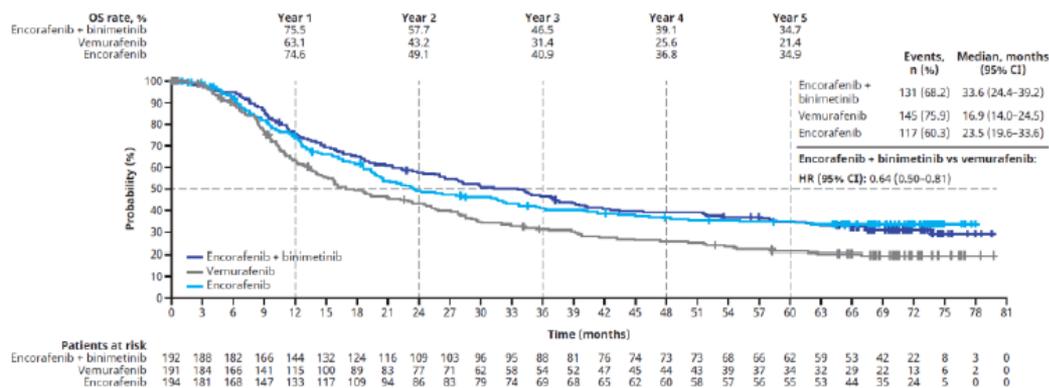
	0	6	12	18	24	30	36	42	48	54									
Cobimetinib + Vemurafenib	247	232	210	192	169	152	139	123	109	100	91	87	83	80	76	73	44	19	1
Placebo + Vemurafenib	248	230	194	165	142	126	108	94	85	77	73	72	66	64	63	58	34	16	—

BRAF MUTADO Y TERAPIA DIRIGIDA: ENCORAFENIB + BINIMETINIB

Progression-Free Survival



Overall Survival

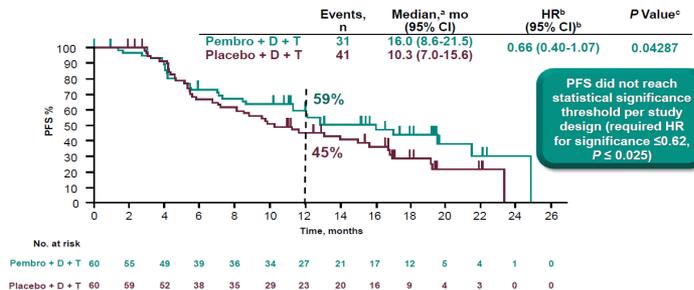


BRAF MUTADO: ¿COMBINACIÓN?

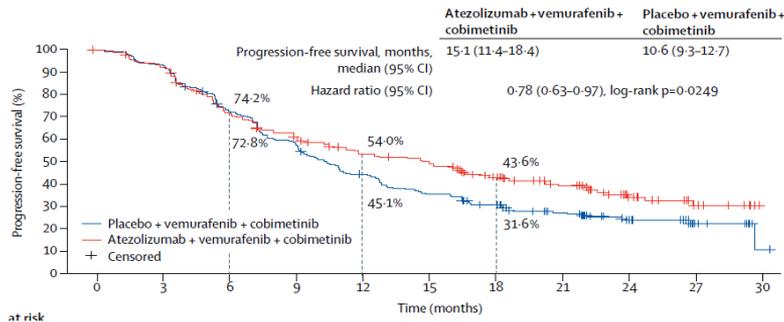
KEYNOTE 022



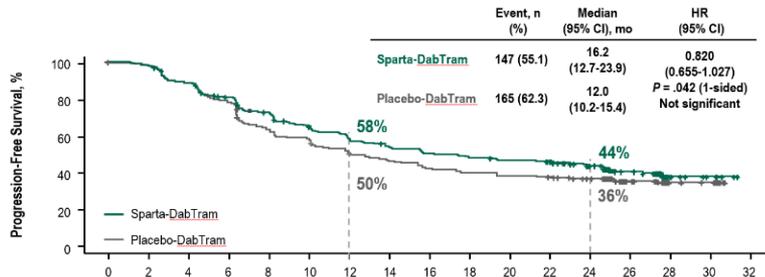
Progression-Free Survival



IMSPIRE 150

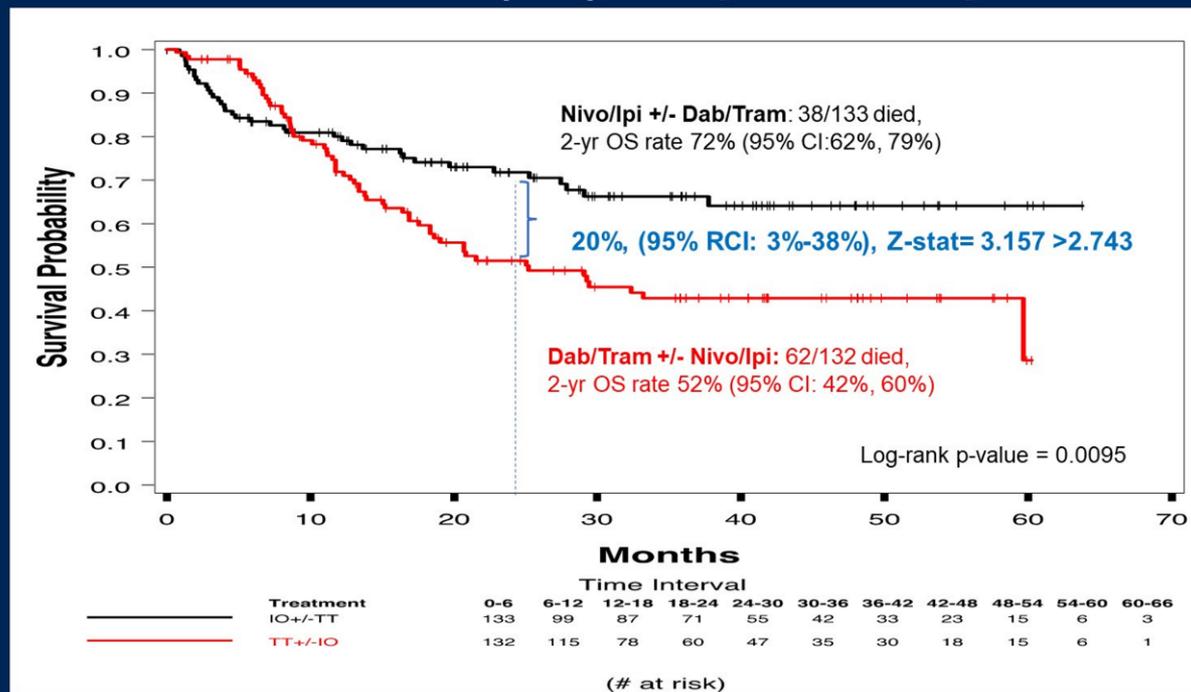


COMBI-I



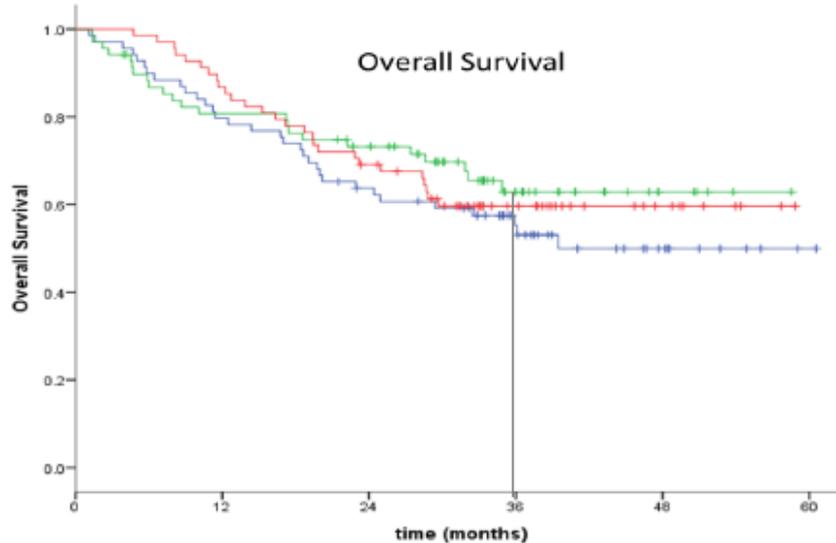
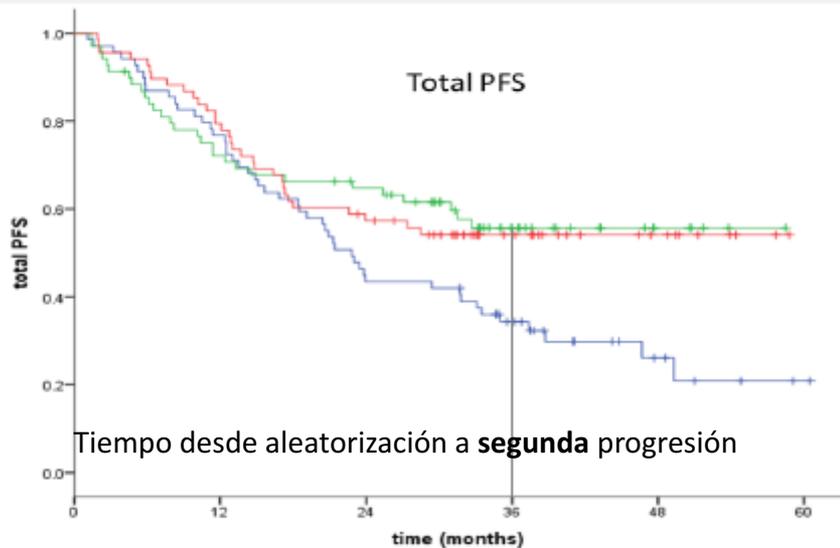
BRAF MUTADO: ¿SECUENCIA? DREAMSEQ

Overall Survival (OS): Step 1 +/- Step 2



24 ptes rama IO, Murieron sin recibir D+T

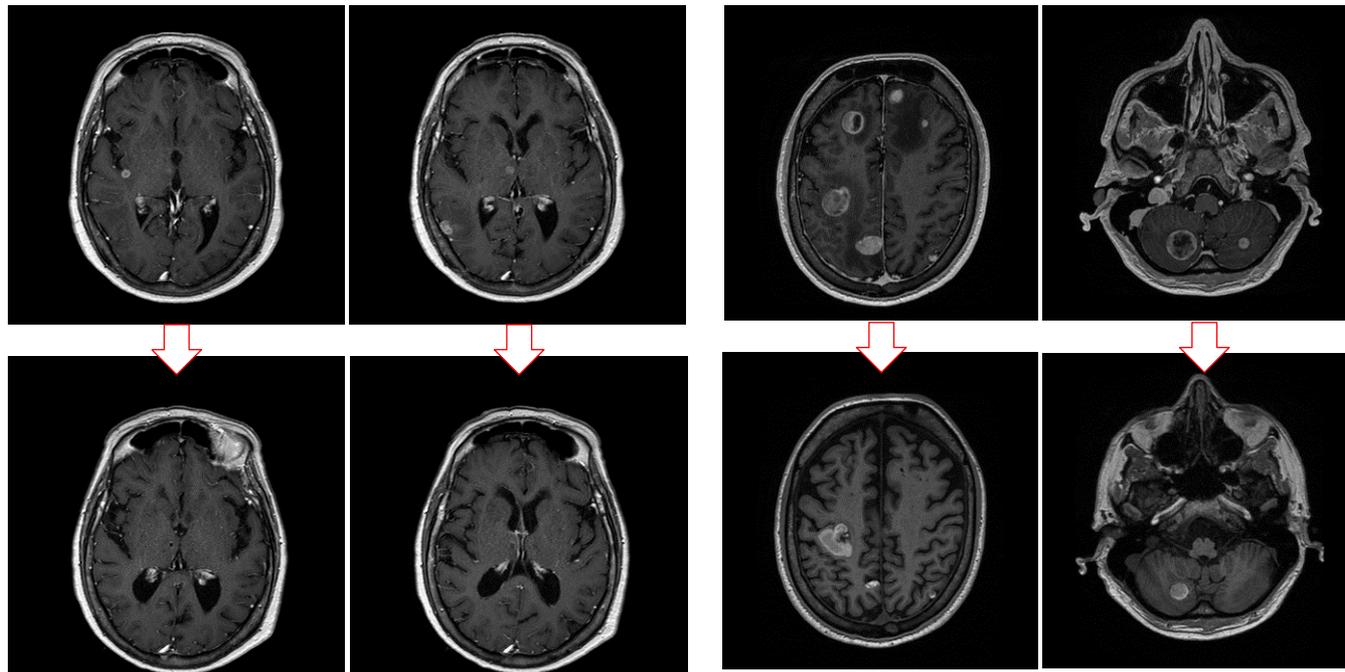
BRAF MUTADO: ¿SECUENCIA/INDUCCIÓN TD? SECOMBIT



ARM A:	69	53	30	19
ARM B:	69	49	42	19
ARM C:	68	53	38	19

	2-year tPFS	3-year tPFS	2-year OS	3-year OS	5	42	25	9	1
Arm A	44%	34%	62%	53%	4	46	20	6	0
Arm B	65%	56%	73%	63%	9	46	22	8	0
Arm C	57%	54%	69%	60%					

METÁSTASIS CEREBRALES: ESCENARIOS MUY DISTINTOS



1) Asymptomatic, ECOG 0, no esteroideos
CR with IPI+NIVO

2) Symptomatic, **ECOG 3**, high dose steroids
PR with ENCO+BINI

IPIILIMUMAB + NIVOLUMAB EN PACIENTES ASINTOMÁTICOS: CM204

ABC Best Intracranial RECIST Response

	A: Nivo+Ipi N=35	B: Nivo N=25	C: Nivo [†] N=16
Intracranial Response, n (%)	18 (51%)	5 (20%)	1 (6%)
CR	9 (26%)	4 (16%)	0 (0%)
PR	9 (26%)	1 (4%)	1 (6%)
SD	2 (6%)	0 (0%)	2 (13%)
PD	14 (40%)	19 (76%)	13 (81%)
NE*	1 (3%)	1 (4%)	0 (0%)

- Median duration of intracranial response not reached in any arm

NE = Not Evaluable

*Pts who deceased prior to wk 12 = PD

[†]Leptomeningeal, previous local treatment or symptoms

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2021 ASCO ANNUAL MEETING

ABC Best Intracranial RECIST Response: Drug Treatment Naïve Patients

	A: Nivo+Ipi N=27	B: Nivo N=19
Intracranial Response, n (%)	16 (59%)	4 (21%)
CR	8 (30%)	3 (16%)
PR	8 (30%)	1 (5%)
SD	2 (7%)	0 (0%)
PD	8 (30%)	14 (74%)
NE*	1 (4%)	1 (5%)

- Median duration of intracranial response not reached in any arm

NE = Not Evaluable

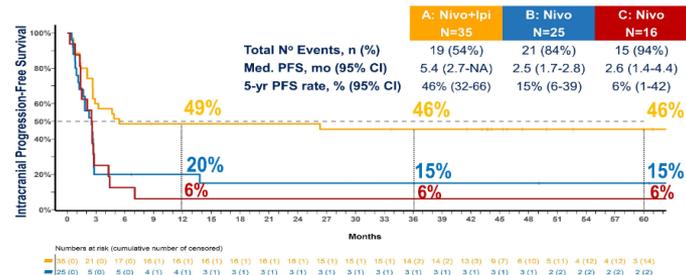
*Pts who deceased prior to wk 12 = PD

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2021 ASCO ANNUAL MEETING

ABC Intracranial Progression-Free Survival

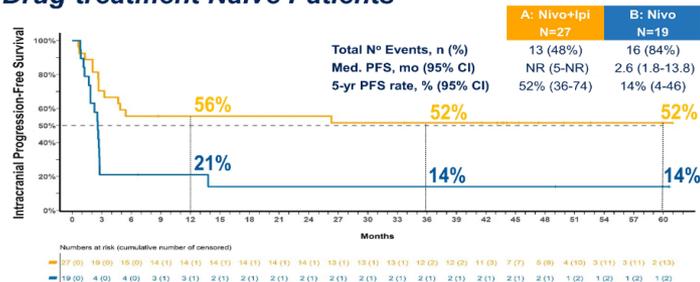


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2021 ASCO ANNUAL MEETING

ABC Intracranial Progression-Free Survival Drug-treatment Naïve Patients



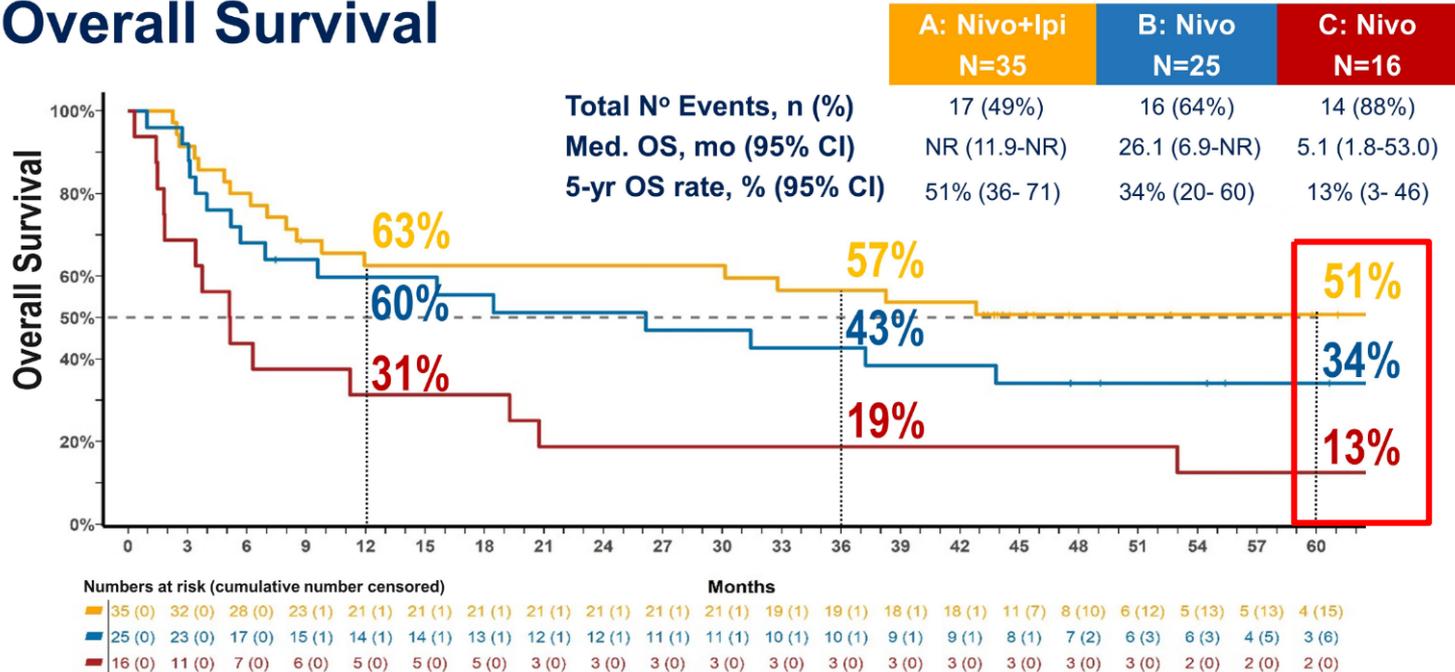
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2021 ASCO ANNUAL MEETING

IPILIMUMAB + NIVOLUMAB: ABC

Overall Survival



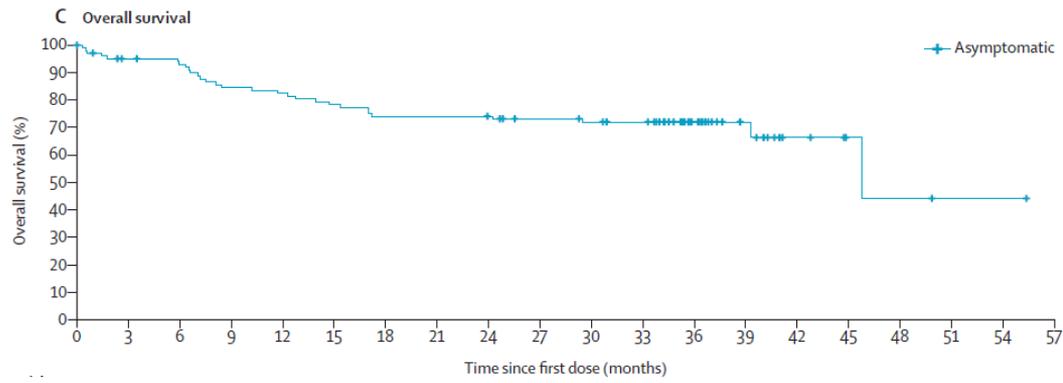
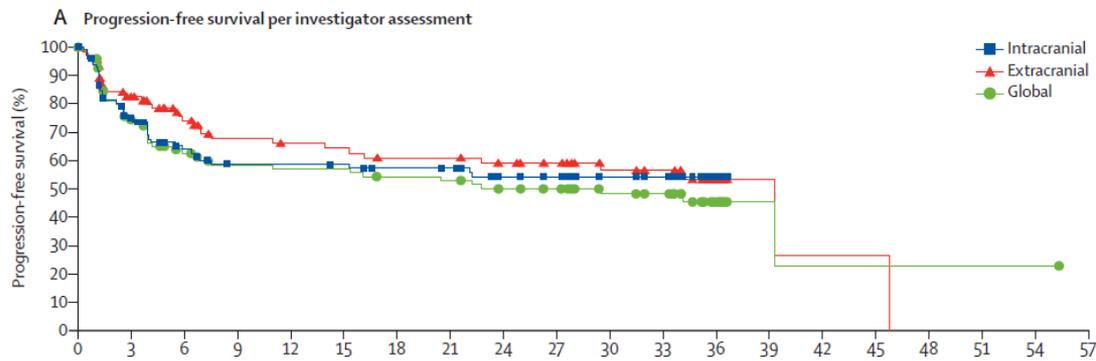
- Death solely due to intracranial progression in 8/76 (17%) patients (1 Cohort A, 4 Cohort B, 3 Cohort C)

IPIILIMUMAB + NIVOLUMAB EN PACIENTES ASINTOMÁTICOS: CM204

	Asymptomatic patients (n=101)		
	Intracranial	Extracranial	Global
Best overall response*			
Complete response	33 (33%)	16 (16%)	17 (17%)
Partial response	21 (21%)	33 (33%)	35 (35%)
Stable disease ≥6 months	4 (4%)	5 (5%)	4 (4%)
Progressive disease	30 (30%)	17 (17%)	26 (26%)
Not evaluable for clinical benefit rate	13 (13%)	30 (30%)	19 (19%)
Death prior to first on-study assessment	2 (2%)	3 (3%)	3 (3%)
Early discontinuation due to study toxicity	1 (1%)	1 (1%)	1 (1%)
Stable disease <6 months	6 (6%)	14 (14%)	10 (10%)
No extracranial disease at baseline	NA	7 (7%)	0
Other†	4 (4%)	5 (5%)	5 (5%)
Objective response rate‡	54/101 (53.5, 43.3-63.5)	49/101 (48.5, 38.4-58.7)	52/101 (51.5, 41.3-61.6)
Clinical benefit rate§	58/101 (57.4, 47.2-67.2)	54/101 (53.5, 43.3-63.5)	56/101 (55.4, 45.2-65.3)
Duration of response			
Ongoing responders/patients with objective response (%)	46/54 (85%)	38/49 (78%)	40/52 (77%)
Median (95% CI), months	NR (NR-NR)	NR (32.8-NR)	NR (32.8-NR)

ASYMPTOMATIC

mOS (m)	NR
%OS 36m	72
mBrainPFS (m)	NR (54% at 36 m)

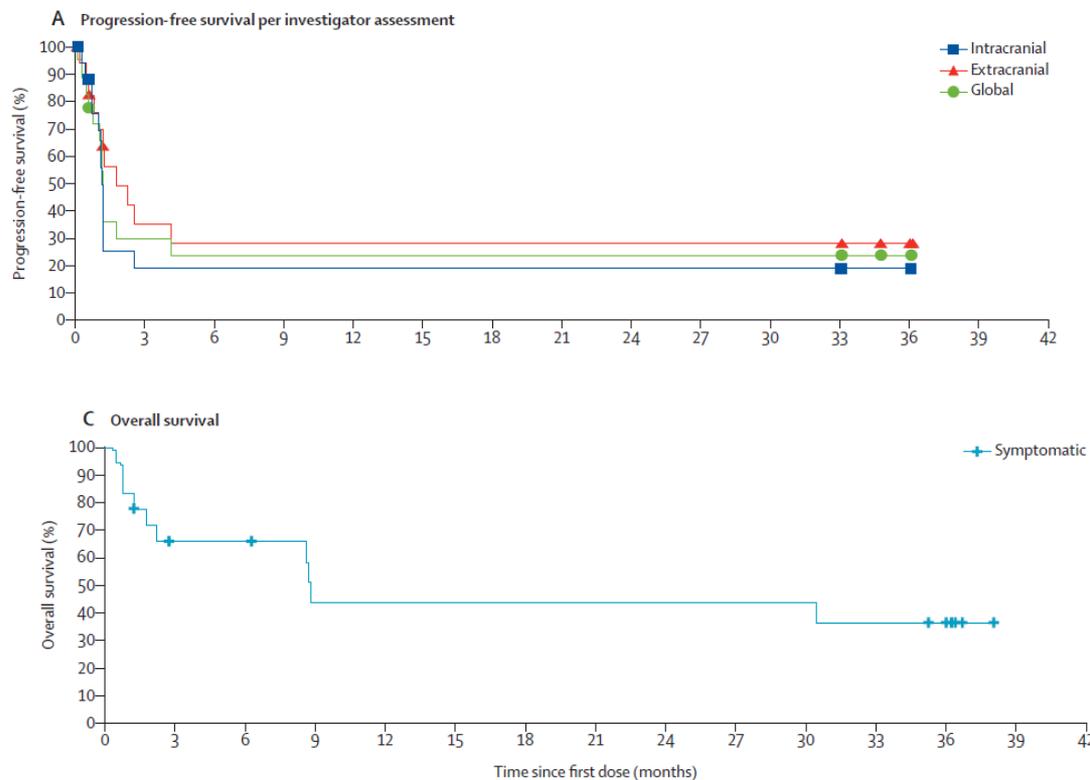


IPIILIMUMAB + NIVOLUMAB EN PACIENTES SINTOMÁTICOS: CM204

	Symptomatic patients (n=18)		
	Intracranial	Extracranial	Global
Best overall response*			
Complete response	3 (17%)	1 (6%)	1 (6%)
Partial response	0	3 (17%)	3 (17%)
Stable disease ≥6 months	0	0	0
Progressive disease	11 (61%)	7 (39%)	10 (56%)
Not evaluable for clinical benefit rate	4 (22%)	7 (39%)	4 (22%)
Death prior to first on-study assessment	2 (11%)	1 (6%)	1 (6%)
Early discontinuation due to study toxicity	0	0	0
Stable disease <6 months	2 (11%)	3 (17%)	1 (6%)
No extracranial disease at baseline	NA	1 (6%)	0
Other†	0	2 (11%)	2 (11%)
Objective response rate‡	3/18 (16.7, 3.6-41.4)	4/18 (22.2, 6.4-47.6)	4/18 (22.2, 6.4-47.6)
Clinical benefit rate§	3/18 (16.7, 3.6-41.4)	4/18 (22.2, 6.4-47.6)	4/18 (22.2, 6.4-47.6)
Duration of response			
Ongoing responders/patients with objective response (%)	3/3 (100%)	4/4 (100%)	4/4 (100%)
Median (95% CI), months	NR (NR-NR)	NR (NR-NR)	NR (NR-NR)

SYMPTOMATIC

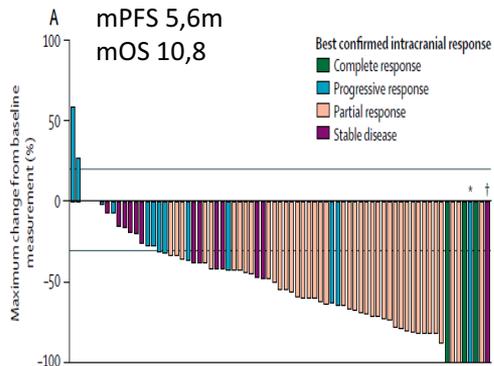
mOS (m)	9 (aprox)
%OS 36m	36
mBrainPFS (m)	1,2 (0,7-1,2)



DABRAFENIB + TRAMETINIB: COMBI-MB

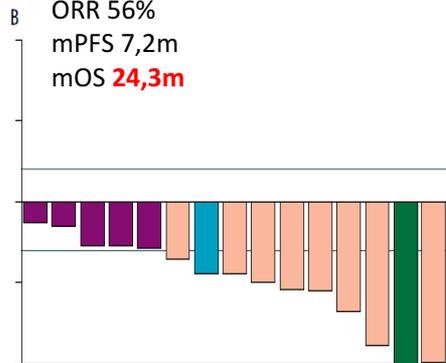
ASYMPTOMATIC: ORR 58%

mPFS 5,6m
mOS 10,8



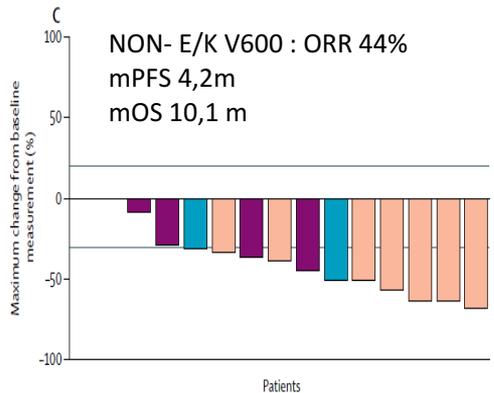
PREVIOUS LOCAL TREATMENT:

ORR 56%
mPFS 7,2m
mOS **24,3m**



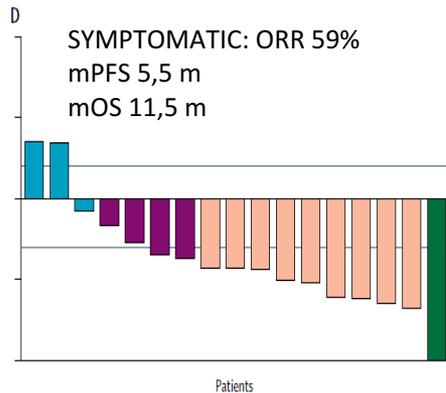
NON- E/K V600 : ORR 44%

mPFS 4,2m
mOS 10,1 m



SYMPTOMATIC: ORR 59%

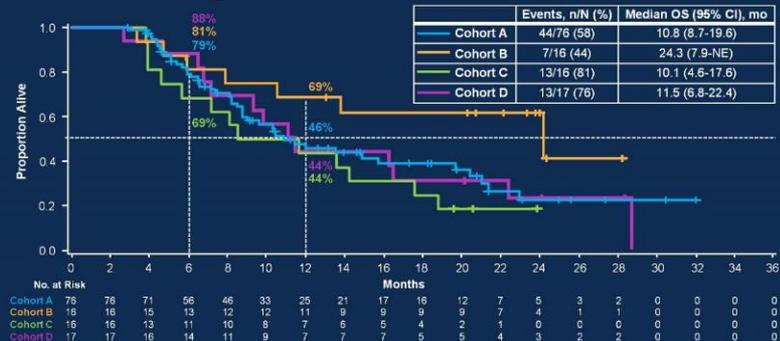
mPFS 5,5 m
mOS 11,5 m



Progression-Free Survival

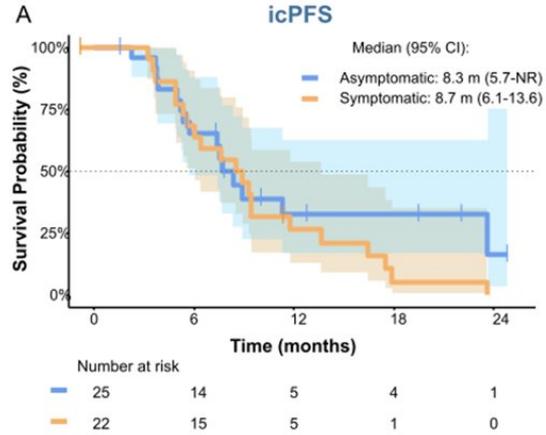
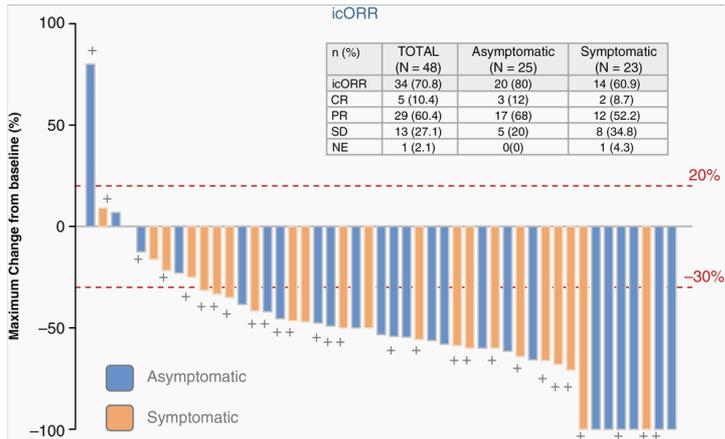


Preliminary Overall Survival



ENCORAFENIB + BINIMETINIB: GEM1802/EBRAIN

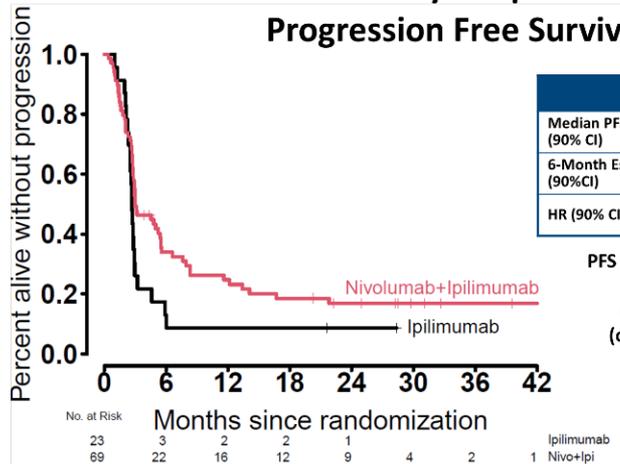
Figure 1. Confirmed maximum reduction in intracranial target lesion (at any time) in patients with symptomatic and ...



ENFERMEDAD METASTÁSICA POST PD-1 (+/-BRAF/MEKINH)

SEGUNDA LÍNEA POST PD-1: IPILIMUMAB+NIVOLUMAB VS IPILIMUMAB

Primary Endpoint Progression Free Survival

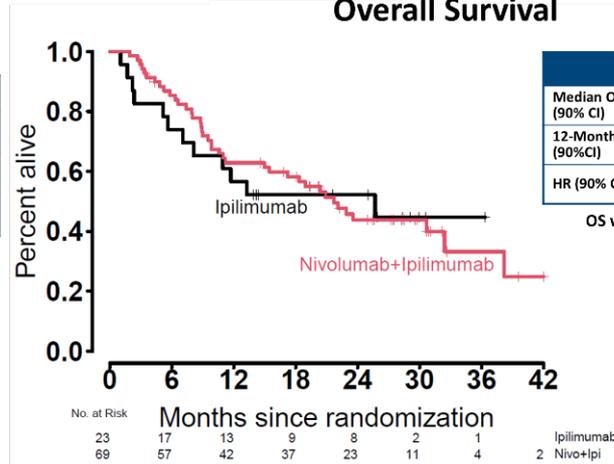


	NIVO+IPI (N=69)	IPI (N=23)
Median PFS, mo (90% CI)	3.0 (2.8, 5.3)	2.7 (2.5, 2.9)
6-Month Estimate (90%CI)	34% (25%, 44%)	13% (4%, 27 %)
HR (90% CI) vs. IPI	0.63 (0.41, 0.97)	--

PFS was statistically significantly improved with nivo+ipi compared to ipi (one-sided p-value = 0.037)

Median Duration of Follow-Up: 28.3 months

Overall Survival



	NIVO+IPI (N=69)	IPI (N=23)
Median OS, mo (90% CI)	21.7 (15.4, 32.4)	25.7 (8.1, NR)
12-Month OS (90%CI)	63% (52%, 72%)	57% (38%, 71%)
HR (90% CI) vs. IPI	0.93 (0.54, 1.60)	--

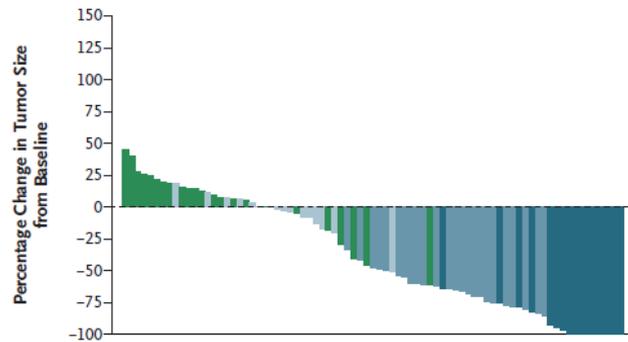
OS was not statistically different with nivo+ipi compared to ipi (one-sided p-value = 0.408)

Median Duration of Follow-up: 27.3 months

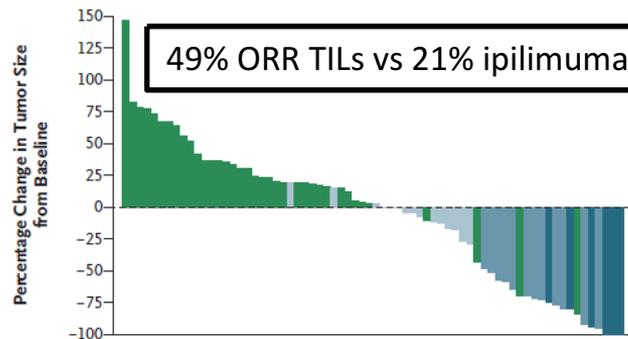
ENSAYO CLÍNICO TILs ACADÉMICOS VS IPILIMUMAB.

Best Overall Response: ■ Progressive disease ■ Stable disease ■ Partial response ■ Complete response

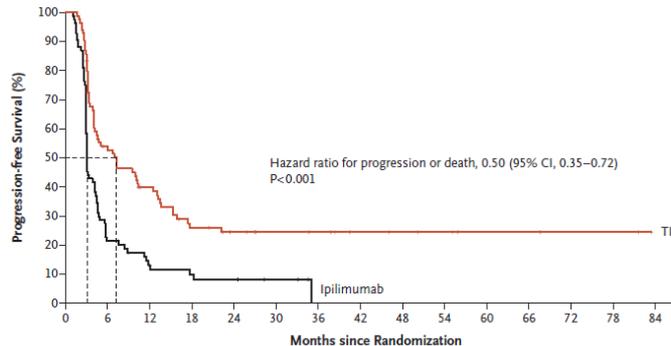
A TIL Group



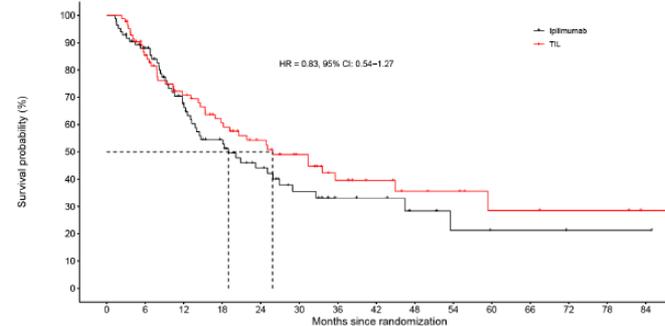
B Ipilimumab Group



49% ORR TILs vs 21% ipilimumab



Risk	84	41	29	18	14	11	10	7	6	5	3	2	2	0
imab	84	17	8	6	5	3	0	0	0	0	0	0	0	0
TIL	84	41	29	18	14	11	10	7	6	5	3	2	2	0



Number at risk	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84
Ipilimumab	84	69	47	34	23	15	9	0	5	3	2	2	1	1	1
TIL	84	68	51	40	31	23	15	11	8	7	4	4	3	3	1

mPFS 7,2 vs 3,1 meses
mOS 26 vs 19 meses

- 199 incluidos, 168 aleatorizados
 - 1 de cada 6-7 no recibe TILs
- 89% post PD-1 (11% naïve)
 - No aparentes dif en SG *naïve* vs *experienced*, pero N pequeña...
- LDH <2x

CONCLUSIONES (MAYO 2025)

- Primera línea, por defecto: inmunoterapia basada en anti PD-1
- En España (entorno público): nivolumab o pembrolizumab
- Ipilimumab + nivolumab si:
 - MTS cerebrales (especialmente asintomáticas)
 - PD-L1 negativo
- Terapia dirigida (sólo *BRAF*+)
 - Segunda línea post PD-1
 - Primera línea si contraindicación absoluta o necesidad **muy urgente** de respuesta
 - Metástasis cerebrales **sintomáticas**
 - Decisión claramente informada de paciente
- Post PD-1 (+/-*BRAF*) es un terreno aún por definir: ENSAYO CLÍNICO