IV Simposio

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Monográfico de Tumores cutáneos infrecuentes

ESCLEROSIS TUBEROSA Y SD DE GORLIN: EJEMPLOS DE TERAPIA PERSONALIZADA EN CÁNCER HEREDITARIO

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CENTRO INTEGRAL ONCOLÓGICO hm CIOCC

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DISCLOSURES

- Advisory role: Amgen, BMS, GSK, Novartis, MSD, Roche, Celegene, Pierre Fabre, Bioncotech, Regeneron, Sanofi, Merck Serono, Astra Zeneca.
- Non remunerated scientific advisor: Biosequence/Onco DNA
- Travel accommodation and congress: BMS, GSK, Roche, MSD, Amgen, Bioncotech
- Clinical trial participation as PI: BMS, GSK, Roche, Novartis, MSD, Amgen, Ab Science, Bioncotech, Aduro, Merck Serono, Iovance.
- If you find something I have missed, please e-mail me: ivanpantic@hotmail.com

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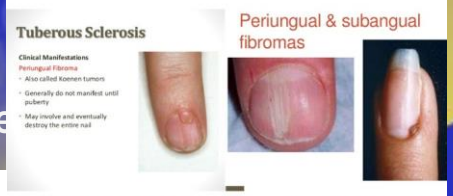
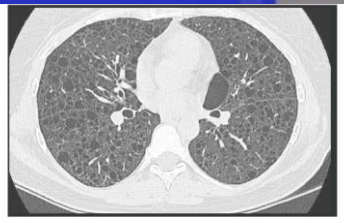
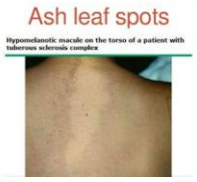
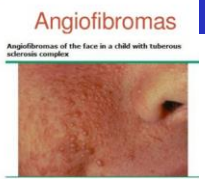
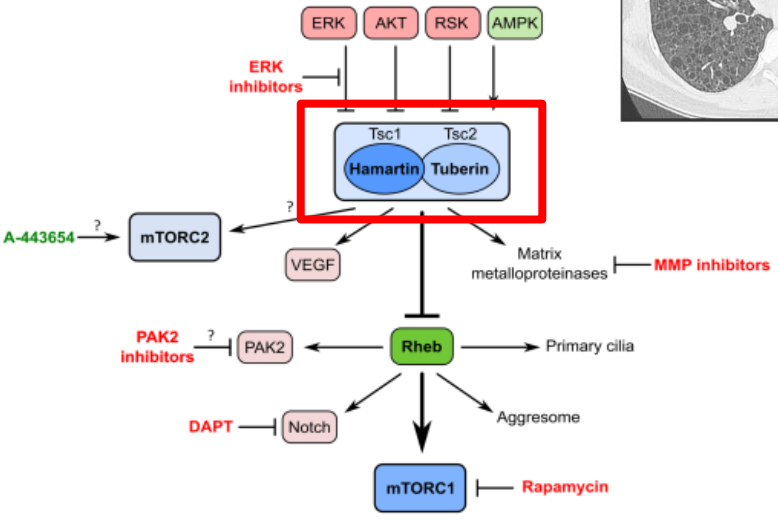
ESCLEROSIS TUBEROSA











Brain
70–80% Subependymal nodule
5–20% Subependymal giant cell astrocytoma (SEGA)
70% Cortical tubers★

Eyes
30–50% Retinal hamartoma
~39% Chorioretinal hypo-pigmented lesions

20–40% Forehead plaque
75–90% Facial angiofibroma

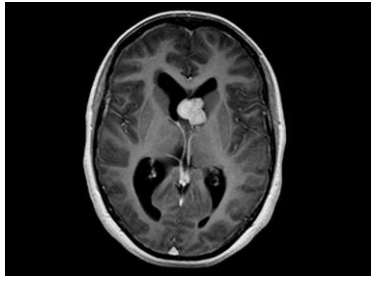
Lungs
30–40% of women Lymphangioleio-myomatosis★

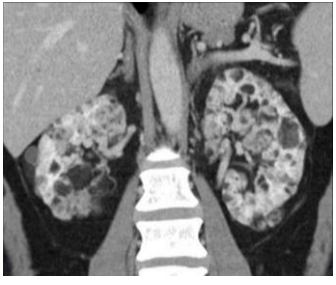
47–67% Cardiac rhabdomyomas

Kidneys
50% Angiomyolipoma★
26% Cystic disease★
2.4% Renal cell carcinoma

Skin
~50% Shagreen patch
~100% Hypopigmented macules★

Nail bed
88% Ungual fibromas

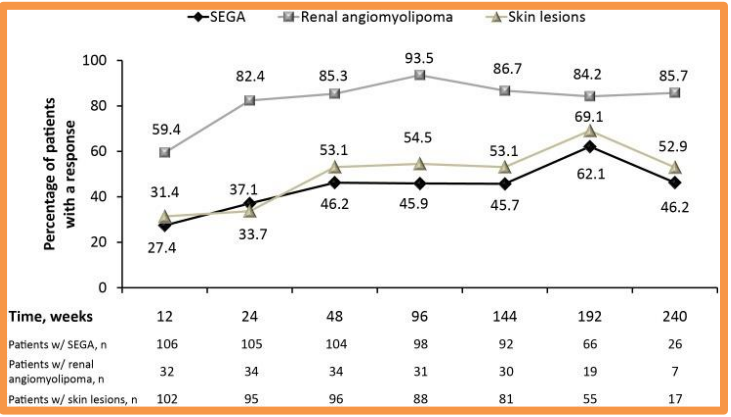




Neuman 2011 EMBO Molecular Medicine
Switon 2016 IUBMB Life.

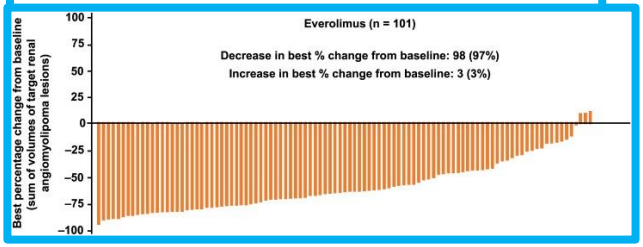
EXIT 1, 2 and 3: phase 3 everolimus vs placebo

EXIT-1 patients with new or growing TSC-related SEGA

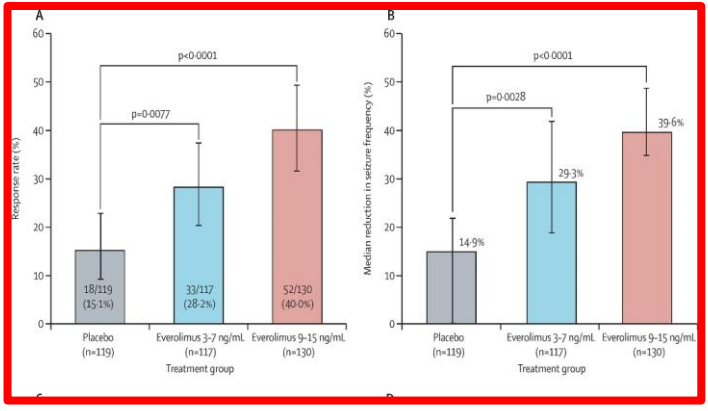


Time, weeks	12	24	48	96	144	192	240
Patients w/ SEGA, n	106	105	104	98	92	66	26
Patients w/ renal angiomyolipoma, n	32	34	34	31	30	19	7
Patients w/ skin lesions, n	102	95	96	88	81	55	17

EXIT-2 patients with angiomyolipomas and/or lymphangioleiomiomatosis



EXIT-3 patients with resistant epilepsy



France 2016 PLoS One
Brisler 2017 PLoS One
French 2016 Lancet

GORLIN

SÍNDROME DE GORLIN

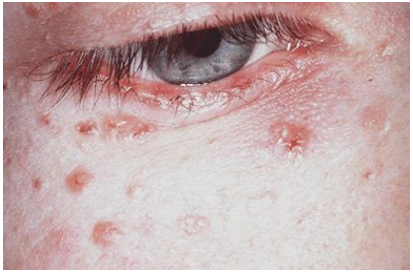
Mutación en gen de PTCH

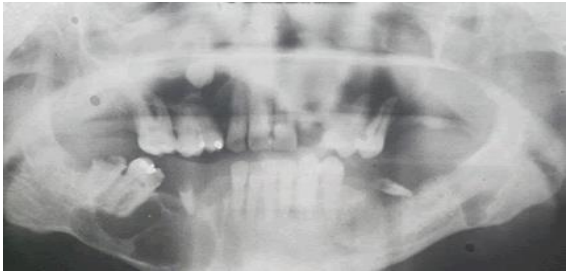
Autosómico dominante

Predisposición a carcinoma basocelular, meduloblastoma, quistes odontogénicos y otros tumores

Hipersensibilidad a rayos UV y radiaciones ionizantes

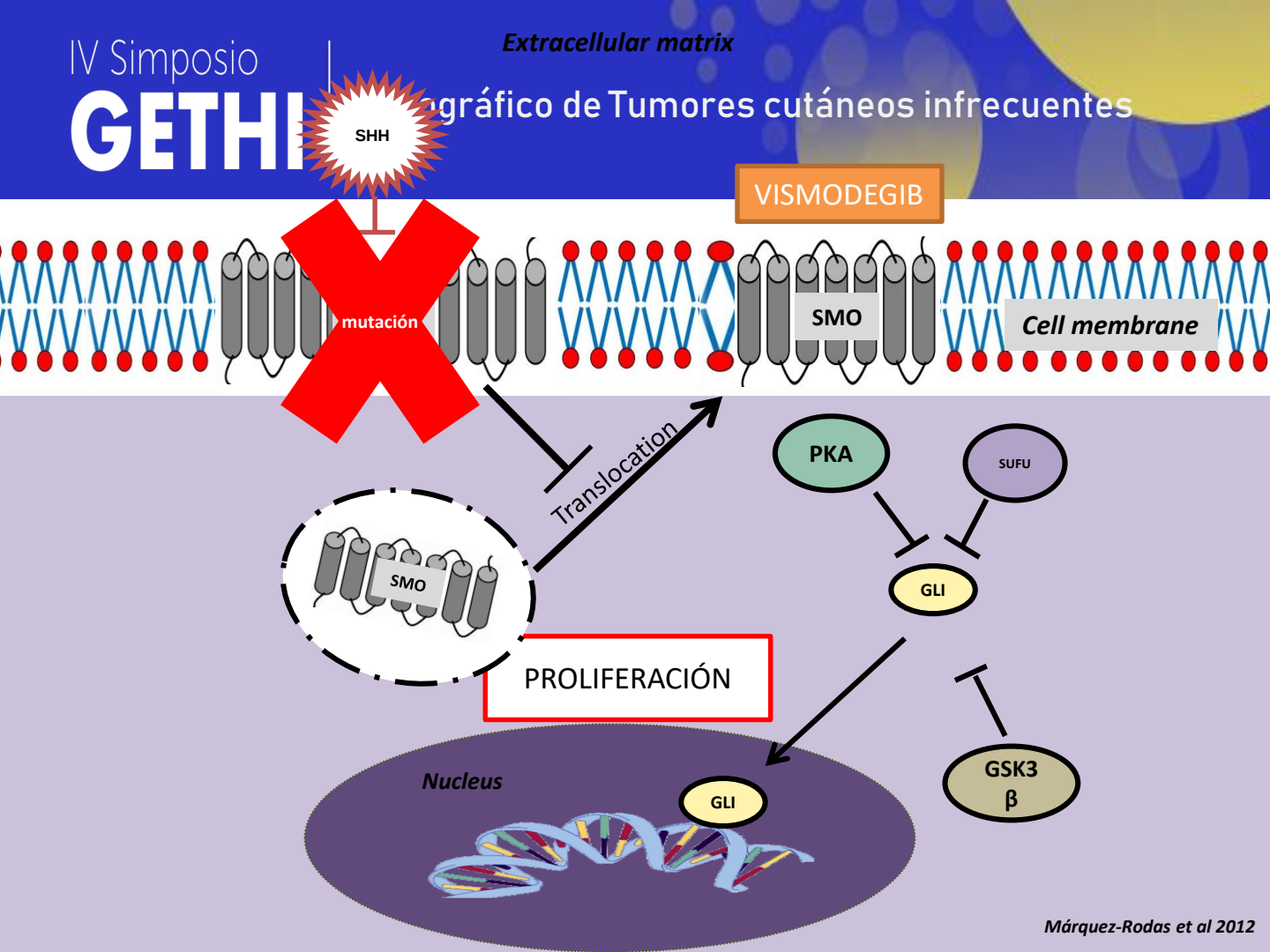
Mutaciones **somáticas** muy frecuentes en CBC y meduloblastoma esporádicos





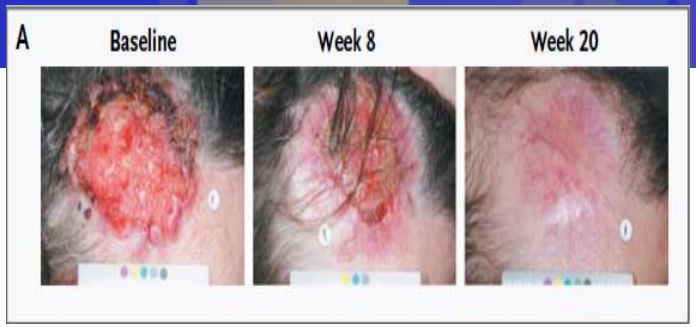
NCHPEG.org

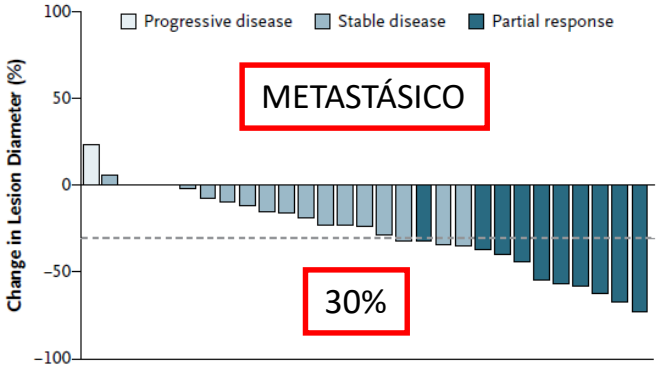
...gráfico de Tumores cutáneos infrecuentes

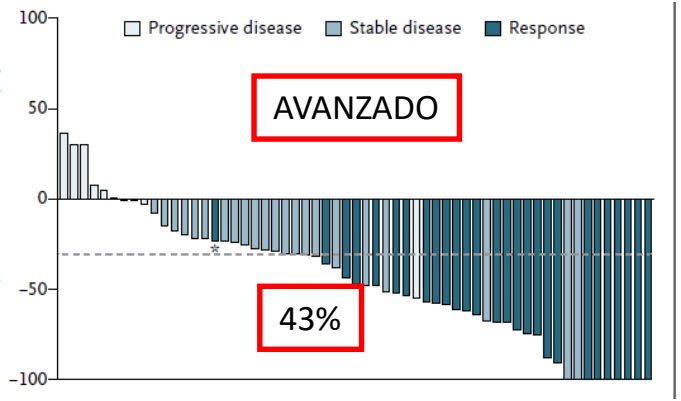


Márquez-Rodas et al 2012

Vismodegib in basal cell carcinoma







Mediana 9,5 meses de SLP

Sekulic 2012

¿FUNCIONA DISTINTO VISMODEGIB EN SD DE GORLIN?

Chang *et al. Orphanet Journal of Rare Diseases* (2016) 11:120
DOI 10.1186/s13023-016-0506-z

Orphanet Journal of Rare Diseases

RESEARCH Open Access

Safety and efficacy of vismodegib in patients with basal cell carcinoma nevus syndrome: pooled analysis of two trials

Anne Lynn S. Chang[1*], Sarah T. Arron[2], Michael R. Migden[3], James A. Solomon[4,5,6], Simon Yoo[7], Bann-Mo Day[8], Edward F. McKenna[8] and Aleksandar Sekulic[9]

Chang Orphanet 2016

22/104 (21%)

19/119 (16%)

Table 1 Patient demographics and baseline disease characteristics[a]

	Erivance BCC ($N = 104$)			EAS ($N = 119$)			
	laBCC		mBCC	laBCC		mBCC	
	BCCNS ($n = 22$)	Non-BCCNS ($n = 49$)	Non-BCCNS ($n = 33$)	BCCNS ($n = 12$)	Non-BCCNS ($n = 50$)	BCCNS ($n = 7$)	Non-BCCNS ($n = 50$)
Median age, years (range)	47 (21–71)	67 (38–101)	62 (38–92)	52 (26–79)	67 (40–92)	58 (37–71)	63 (24–100)
Female, *n* (%)	10 (45)	22 (45)	9 (27)	6 (50)	13 (26)	3 (43)	9 (18)
WCBP, *n* (%)	3 (33)	1 (2)	2 (6)	4 (33)	2 (4)	1 (14)	1 (2)
ECOG PS, *n* (%)							
0–1	22 (100)	44 (90)	32 (97)	12 (100)	46 (92)	7 (100)	45 (90)
2	0	5 (10)	1 (3)	0	4 (8)	0	5 (10)
Target lesions, *n* (%)							
1	13 (59)	35 (71)	9 (27)	4 (33)	30 (60)	4 (57)	20 (40)
2	4 (18)	8 (16)	4 (12)	2 (17)	11 (22)	0	10 (20)
≥3	5 (23)	6 (12)	20 (61)	6 (50)	9 (18)	3 (43)	20 (40)
Prior treatment, *n* (%)							
Surgery	21 (96)	41 (84)	32 (97)	12 (100)	45 (90)	7 (100)	47 (94)
Radiotherapy	1 (5)	21 (43)	19 (58)	1 (8)	19 (38)	2 (29)	33 (66)
Systemic therapy	5 (23)	3 (6)	10 (30)	2 (17)	9 (18)	2 (29)	18 (36)
Surgery contraindicated, *n* (%)	18 (82)	25 (51)	NA	7 (58)	28 (56)	NA	NA

BCCNS basal cell carcinoma nevus syndrome, *EAS* expanded access study, *ECOG PS* Eastern Cooperative Oncology Group performance status, *laBCC* locally advanced basal cell carcinoma, *mBCC* metastatic basal cell carcinoma, *NA* not available, *WCBP* women of childbearing potential

[a]There were no patients with BCCNS with mBCC in the ERIVANCE BCC study; therefore, this column is omitted in the table

Chang Orphanet 2016

TASA Y CALIDAD DE RESPUESTAS

Table 2 Investigator-assessed BORR (efficacy-evaluable patients) comparing BCCNS and non-BCCNS patient groups

	Erivance BCC (*N* = 96)			EAS (*N* = 95)			
	laBCC		mBCC	laBCC		mBCC	
	BCCNS (*n* = 21)	Non-BCCNS (*n* = 42)	Non-BCCNS (*n* = 33)	BCCNS (*n* = 12)	Non-BCCNS (*n* = 44)	BCCNS (*n* = 6)	Non-BCCNS (*n* = 33)
BORR, *n* (%) [95 % CI]	17 (81) [58–95]	21 (50) [34–66]	15 (46) [28–64]	4 (33) [10–65]	22 (50) [35–65]	3 (50) [12–88]	9 (27) [13–46]
Complete response	8 (38)	12 (29)	0	1 (8)	5 (11)	2 (33)	0
Partial response	9 (43)	9 (21)	15 (46)	3 (25)	17 (39)	1 (17)	9 (27)
Stable disease	3 (14)	12 (29)	15 (46)	6 (50)	21 (48)	3 (50)	17 (52)
Progressive disease	1 (5)	5 (12)	2 (6)	2 (17)	0	0	3 (9)
Not evaluable or missing	0	4 (10)	1 (3)	2 (17)	1 (2)	0	4 (12)

BCCNS basal cell carcinoma nevus syndrome, *BORR* best overall response rate, *CI* confidence interval, *EAS* expanded access study, *laBCC* locally advanced basal cell carcinoma, *mBCC* metastatic basal cell carcinoma

Chang Orphanet 2016

ESTUDIO STEVIE n= 1215

Table 4
Best confirmed overall response rate in patients with histologically confirmed and measurable disease by Gorlin syndrome status.

Efficacy parameter	Locally advanced BCC		Metastatic BCC		Total	
	With Gorlin n = 213	Without Gorlin n = 884	With Gorlin n = 5	Without Gorlin n = 84	With Gorlin n = 218	Without Gorlin n = 968
Patients with measurable disease at baseline, n	208	863	5	79	213	942
Best overall response rate						
Responder, n (%)	170 (81.7)	566 (65.6)	4 (80.0)	27 (34.2)	174 (81.7)	593 (63.0)
95% CI	75.8–86.7	62.3–68.8	28.4–99.5	23.9–45.7	75.8–86.6	59.8–66.0
Complete response, n (%)	95 (45.7)	263 (30.5)	1 (20.0)	3 (3.8)	96 (45.1)	266 (28.2)
Partial response, n (%)	75 (36.1)	303 (35.1)	3 (60.0)	24 (30.4)	78 (36.6)	327 (34.7)
Stable disease, n (%)	31 (14.9)	236 (27.3)	1 (20.0)	38 (48.1)	32 (15.0)	274 (29.1)
Progressive disease, n (%)	1 (0.5)	20 (2.3)	–	9 (11.4)	1 (0.5)	29 (3.1)
Missing or not evaluable, n (%)	6 (2.9)	41 (4.8)	–	5 (6.3)	6 (2.8)	46 (4.9)
Median time to response, (95% CI), months	2.9 (2.8–3.7)	3.7 (3.0–3.7)	2.0 (1.0–NE)	NE (6.5–NE)	2.9 (2.8–3.7)	3.7 (3.7–3.8)
Median duration of response,[a] (95% CI), months	28.8 (24.8–NE)	18.7 (16.8–21.1)	15.1 (13.9–16.2)	11.0 (8.3–NE)	28.8 (24.8–NE)	18.5 (16.4–20.8)

BCC = basal cell carcinoma; CI = confidence interval; NE = not estimable.
Data are n (%) based on the number of patients with measurable disease at baseline.
[a] Analysis based on responders only.

Table 2
TEAEs by length of exposure.

TEAE by preferred term	Number of events (events per 100 patient–years)	
	Occurring <12 months' treatment (808.9 patient–years)	Occurring ≥12 months' treatment (288.1 patient–years)
Any grade	8578 (1060.5)	1128 (391.6)
Muscle spasm	793 (98.0)	14 (4.9)
Alopecia	732 (90.5)	15 (5.2)
Dysgeusia	647 (80.0)	16 (5.6)
Weight decreased	454 (56.1)	39 (13.5)
Decreased appetite	281 (34.7)	22 (7.6)
Asthenia	269 (33.3)	22 (7.6)
Ageusia	209 (25.8)	4 (1.4)
Nausea	208 (25.7)	10 (3.5)
Fatigue	190 (23.5)	11 (3.8)
Diarrhoea	160 (19.8)	37 (12.8)
Arthralgia	110 (13.6)	14 (4.9)
Constipation	105 (13.0)	11 (3.8)
Headache	87 (10.8)	5 (1.7)
Vomiting	90 (11.1)	12 (4.2)
Anaemia	60 (7.4)	29 (10.1)

N. Basset-Séguin et al. / European Journal of Cancer 86 (2017) 334–348

¿PODEMOS MEJORAR LA TOLERANCIA? DOSIS INTERMITENTES

Two intermittent vismodegib dosing regimens in patients with multiple basal-cell carcinomas (MIKIE): a randomised, regimen-controlled, double-blind, phase 2 trial

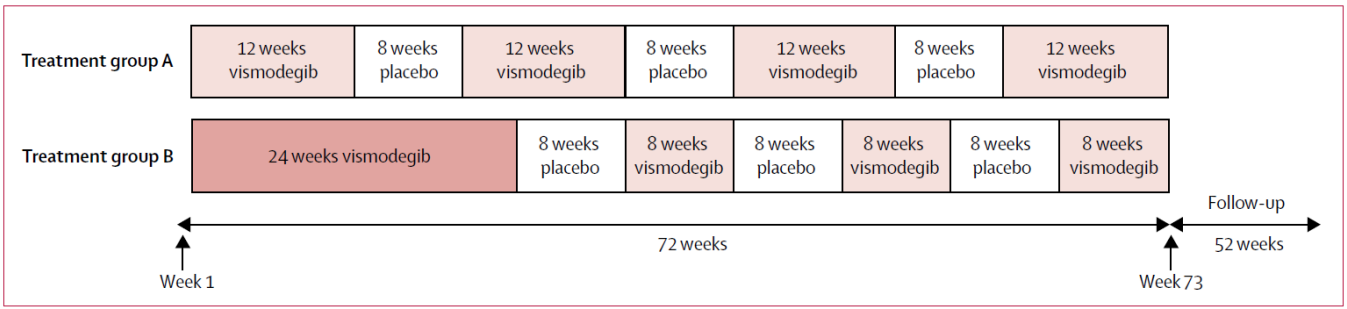


Figure 1: Treatment schedules

PACIENTES CON CBC MULTIPLES CANDIDATOS A CXA

Dreno Lancet Oncol 2017

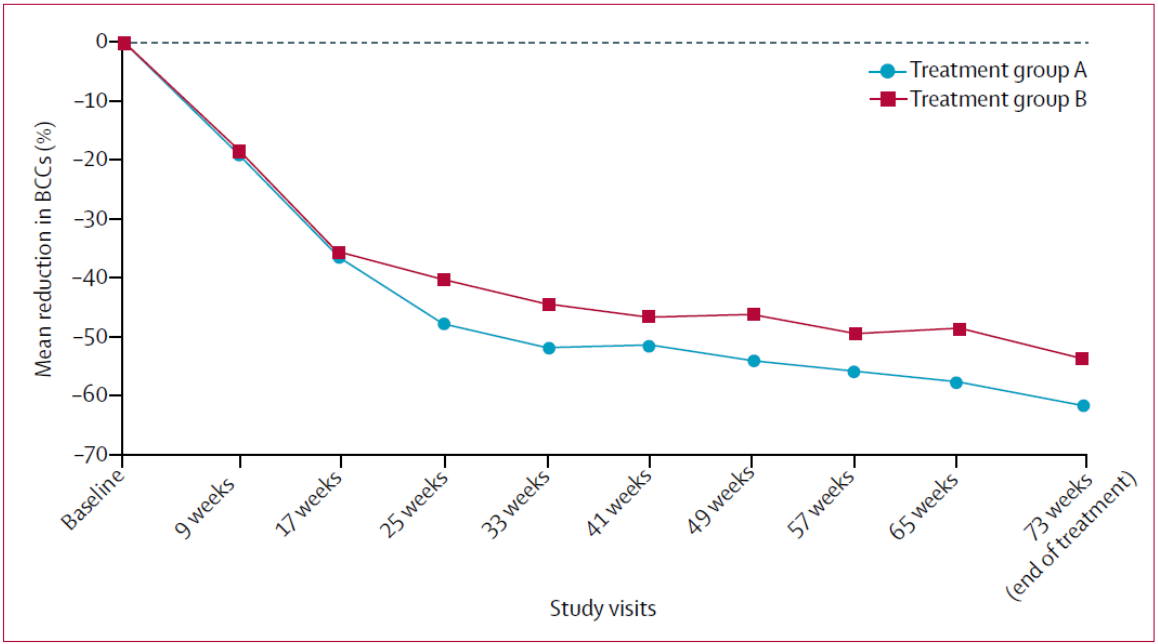


***Figure 3*: Mean percentage reduction from baseline in the number of clinically evident basal-cell carcinomas**
All patients who received treatment are included at all timepoints (treatment group A, n=114; treatment group B, n=113). Each treatment cycle was 4 weeks. BCCs=basal cell carcinomas.

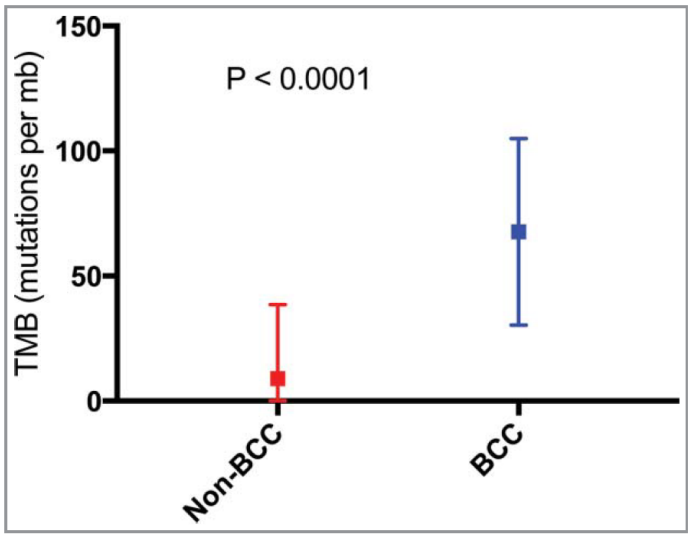
Dreno Lancet Oncol 2017

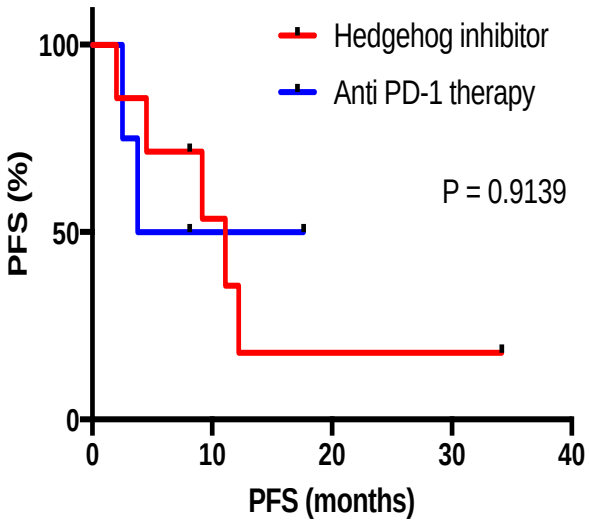
	Treatment group A (n=114)			Treatment group B (n=113)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
All	113 (99%)	30 (26%)	3 (3%)	110 (97%)	36 (32%)	4 (4%)
Muscle spasm	79 (69%)	4 (4%)	0	81 (72%)	12 (11%)	0
Dysgeusia	74 (65%)	1 (1%)	0	73 (65%)	2 (2%)	0
Alopecia	72 (63%)	0	0	73 (65%)	0	0
Fatigue	24 (21%)	0	0	26 (23%)	0	0
Weight decreased	23 (20%)	1 (1%)	0	21 (19%)	0	0
Decreased appetite	21 (18%)	0	0	15 (13%)	2 (2%)	0
Diarrhoea	20 (18%)	0	0	17 (15%)	1 (1%)	0
Nausea	23 (20%)	0	0	14 (12%)	1 (1%)	0
Asthenia	15 (13%)	0	0	19 (17%)	1 (1%)	0
Arthralgia	18 (16%)	0	0	16 (14%)	0	0
Myalgia	18 (16%)	0	0	12 (11%)	0	0
Ageusia	14 (12%)	0	0	12 (11%)	1 (1%)	0
Headache	11 (10%)	0	0	12 (11%)	0	0
Blood creatine phosphokinase increased	10 (9%)	1 (1%)	0	11 (10%)	4 (4%)	0
Pneumonia	0	2 (2%)	0	2 (2%)	0	0
Hypophosphataemia	0	0	0	0	3 (3%)	0
γ-Glutamyltransferase increased	0	2 (2%)	0	4 (4%)	0	0
Abscess limb	1 (1%)	0	0	1 (1%)	2 (2%)	0

30%ABANDONOS VS 23%

Dreno Lancet Oncol 2017

¿INMUNOTERAPIA?





Goodman Oncoimmunology 2018

CONCLUSIONES

- La hiperactivación de la vía mTOR es una oportunidad para tratamiento específico en esclerosis tuberosa
  - Disminución de SEGAs, epilepsia y aparentemente disfunción pulmonar por linfangioleiomiomatosis
- Las mutaciones en PTCH, tanto somáticas como germinales, son una vía de hiperactivación de SMO que conllevan a otra oportunidad terapéutica en CBC
  - Toxicidad como gran problema
  - Estrategias intermitentes