TRATAMIENTO SISTÉMICO DEL CARCINOMA BASOCELULAR - CERTEZAS Y DUDAS

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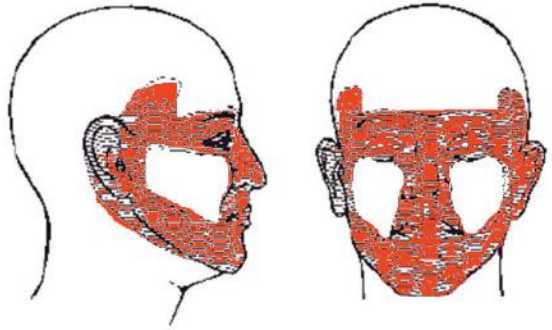
CLÍNIC BARCELONA Hospital Universitari

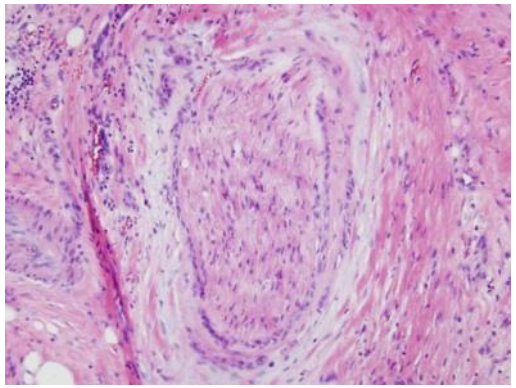
Conflictos de interés

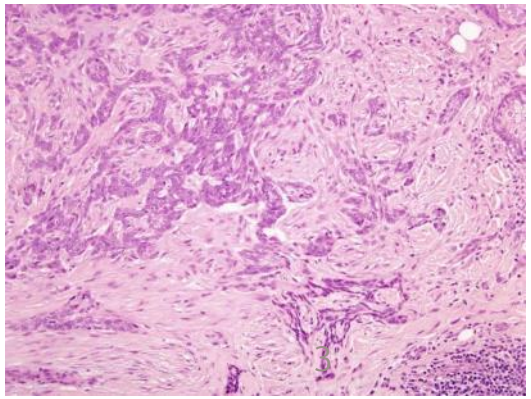
- Xarxa catalana de cancer cutáneo no melanoma (Roche , SunPharma)
- Ponencias (Roche, Sunpharma)
- Asistencia a cursos (Roche, Sunpharma).
- Ensayo clínico PH-L119IL2TNFBASK-04/21 (Philogen)

“Difficult-to-treat tumours”

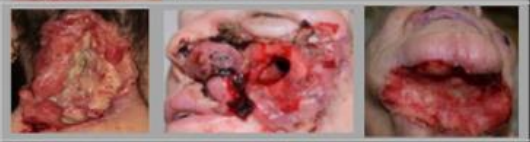


- (1) Dificultad técnica en mantener la **función y estética** debido al tamaño o localización (ojos, nariz, labios y oídos) del tumor
- (2) **Márgenes mal definidos** a menudo asociados con subtipo morfeiforme o recurrencia previa.
- (3) **Recurrencias multiples** previas en la cara
- (4) **Radioterapia previa**
- (5) **Infiltración de hueso / cartílago** o estructuras cuya resección curativa es improbable
- (6) **Negativa del paciente** a aceptar resultados de la cirugía
- (7) **Co-morbilidades** del paciente que interfieren en la cirugía





Clasificación EADO

Risk	Stage		Characteristics		Illustrative pictures	DTT-BCC Group (part 1)
Easy To Treat and low risk of recurrence	Common BCC	I	Low-risk common BCC	**None of the other stages characteristics.** *Recurrences only come from blind treatments, or insufficient surgical margins.*		*Not included*
Increasingly Difficult To Treat and increasing risk of recurrence	Common BCC	IIA	Common BCC but somewhat DTT	Common BCC but management is more complex than usual for any reason linked to the tumor (location requiring technical skill, poorly defined tumor borders, prior recurrence) and/or to the patient (poor general status, comorbidities, or unwillingness to cooperate ...). *Good results and low rate of recurrence expected with surgery even if technically complicate, when the patient cooperates.*		*1*
	Common BCC	IIB	DTT-BCC mainly due to multiplicity of common BCC	Very high number of common BCC (>10) or multiple complex BCC (> 5) in the setting of apparently sporadic cases or in Gorlin syndrome*. *When at least 1 of the multiple BCC can be classified III or IV, the patient will be classified accordingly, and not IIB		*2*
	Advanced BCC	IIIA	Locally advanced DTT-BCC out of critical areas	Large and/or destructive tumors in non-critical or functionally significant areas. *Deemed curable without expected functional mutilations.*		*3*
	Advanced BCC	IIIB	Locally advanced DTT-BCC in critical areas	Large and/or or destructive tumors in critical or functionally important areas (periorificial, nose, ...). *Deemed curable by surgery, but functional impairment and/or mutilation are inevitable.*		*4*
	Advanced BCC	IIIC	Extremely advanced DTT- BCC	Giant and/or deeply invasive tumors involving extracutaneous tissue (bone, muscles, vital or sensorial structures) responsible for an extreme clinical situation. *Cure cannot be expected by surgery whatever its extent.*		*5*
	Metastatic BCC	IV		Distant metastases*. *Whatever the initial BCC staging, patient must be classified IV when metastatic.		*Not included*

Ketty P et al. European Journal of Cancer 192 (2023) 113254

Eficacia ERIVANCE (Vismodegib) Investigator Review

laBCC	RECIST Vismodegib 150mg (n=63)[2] 39 months
ORR (CR + PR), n (%; 95% CI)	38 (**60.3%**;47-72)
CR, n (%)	20 (31.7%)
PR, n (%)	18 (28.6%)
SD, n (%)	15 (23.8%)
PD, n (%)	6 (9.5%)
UNK, n (%)	4 (6.3%)
DCR (CR+PR+SD), %	**84%**

DCR: Disease control rate

Data about MBCC and 800 mg dose are not shown because they are not in the label

laBCC, locally advanced Basal Cell Carcinoma; ORR, objective response rates; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; UNK, unknown

1. Gutzmer et al. BMC Cancer. 2021 Nov 19;21(1):1244.
2. Sekulic A, et al. BMC Cancer. 2017 16;17(1):332.

ESTUDIO STEVIE. VISMODEGIB

	CBC-la (n=1077)
Tiempo a respuesta, mediana (IC95%)	3.7 meses (2.9-3.7)
Mejor Respuesta Global, % (IC95%)	**68.5% (65.7-71.3)**
Respuesta completa	33.4% (360)
Respuesta parcial	35.1% (378)
Enfermedad estable	25.1% (270)
Progresión	1.9% (21)
No evaluable	4.5% (48)
Duración de la Respuesta, mediana (IC95%)	**23.0 meses (20.4-26.7)**

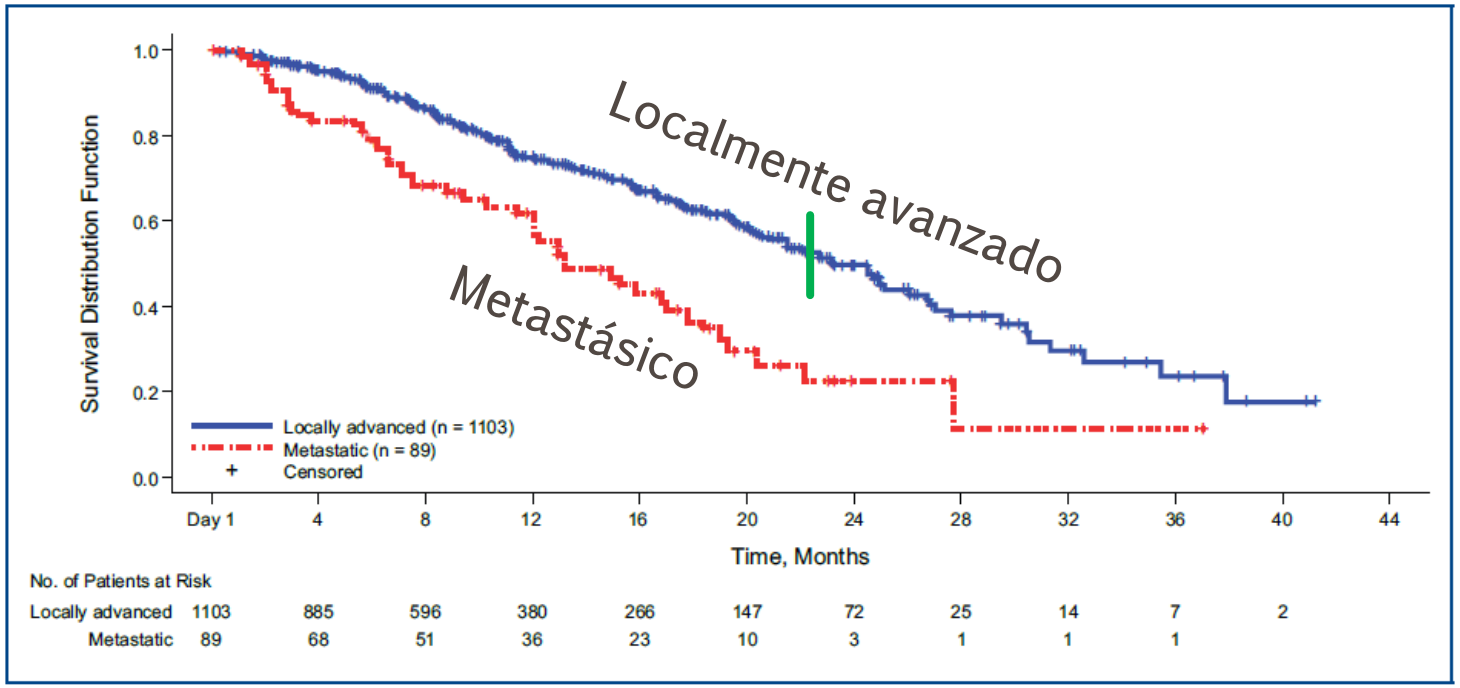
DCR 93,6%

Basset-Seguin. EJC 2017

STEVIE
Resultados de Supervivencia libre de progresión

	CBCm (n=96)	CBC-la (n=1119)
SLP, mediana (IC95%)	13.1 meses (12.0-17.7)	23.2 meses (21.4-26.0)

Figure 2. Kaplan-Meier curve of PFS.

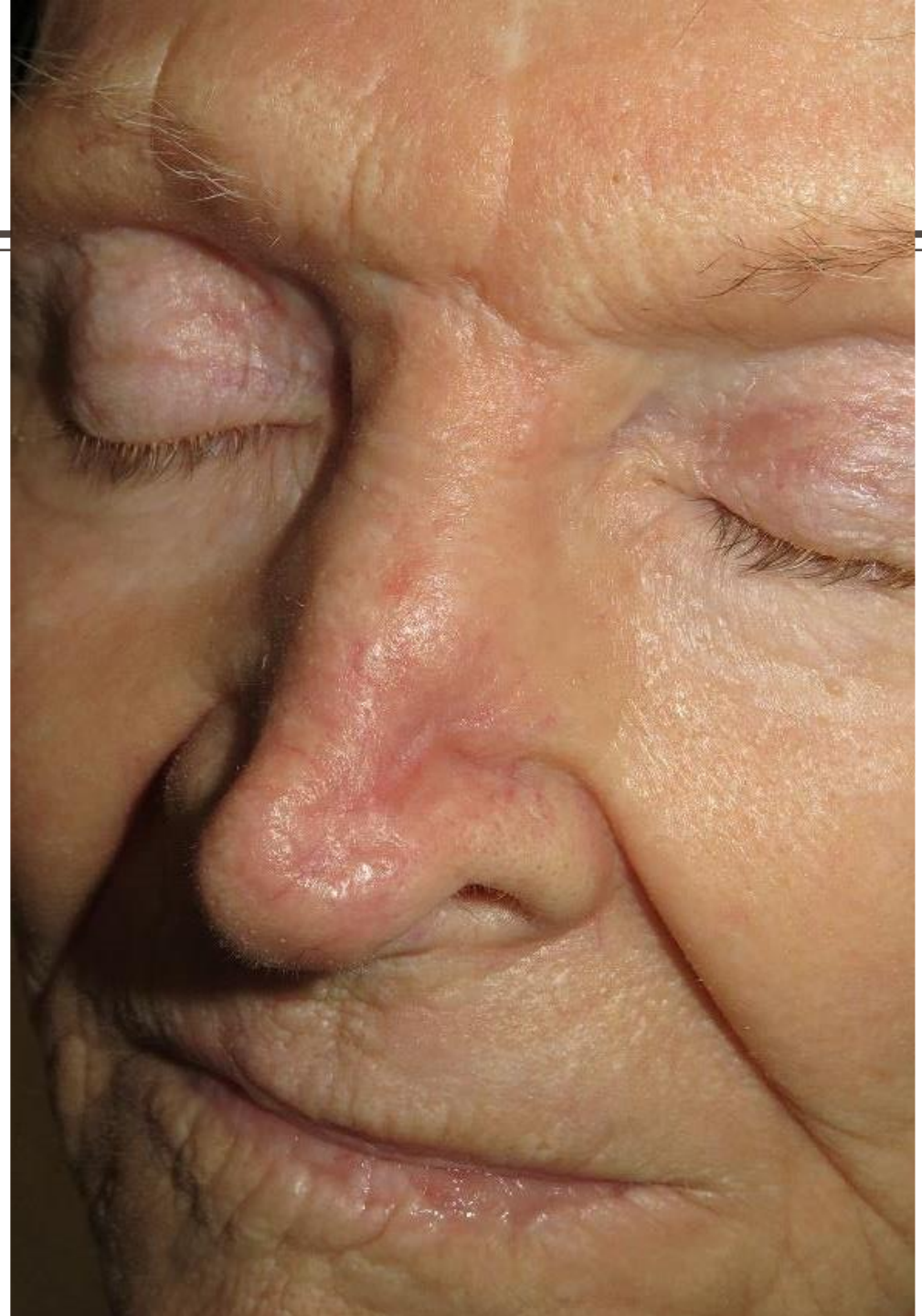


PFS, progression-free survival.

Hansson. ASCO 2016

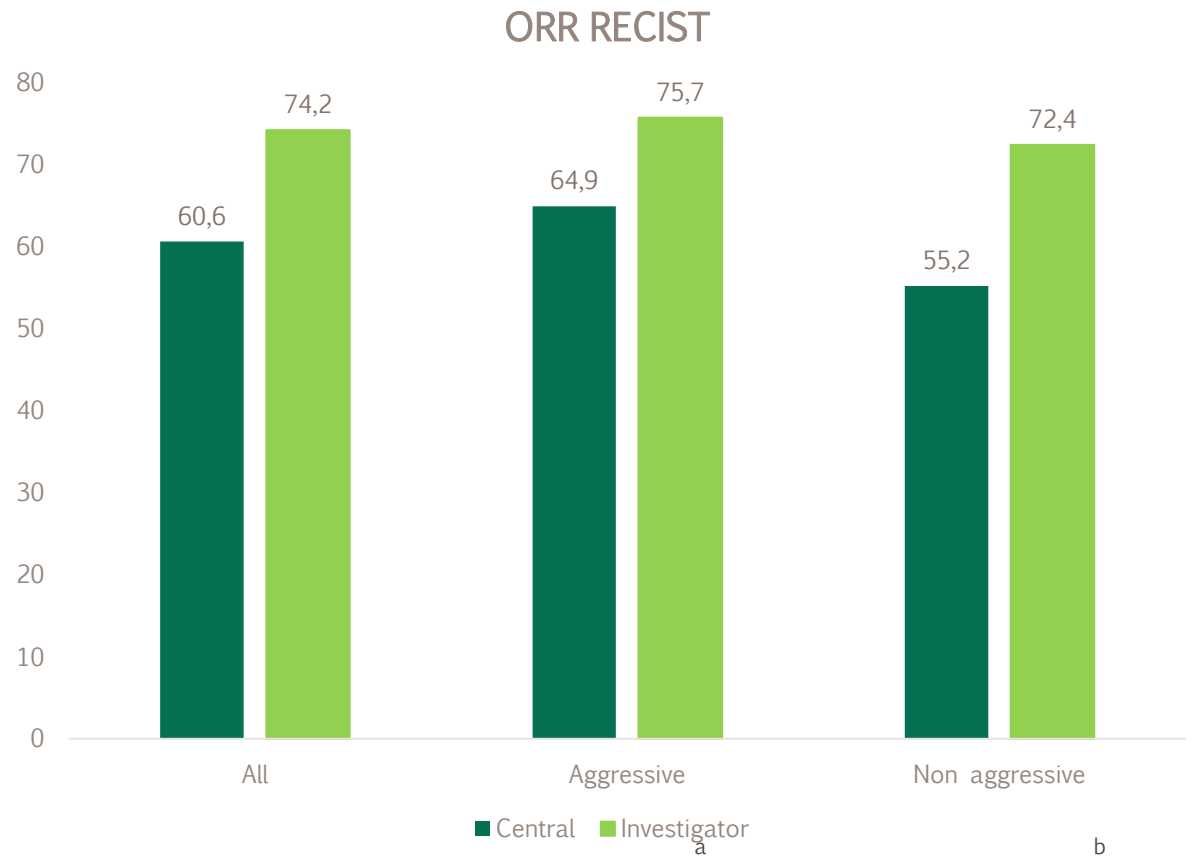

blayco
TELIC
GROUP


blayco
TELIC
GROUP



¿Se puede predecir qué basocelulares responderán?

Según parámetros histológicos



[a]Includes basosquamous, micronodular infiltrative, multifocal, and sclerosing histological subtypes
[b]Includes nodular and superficial histological subtypes

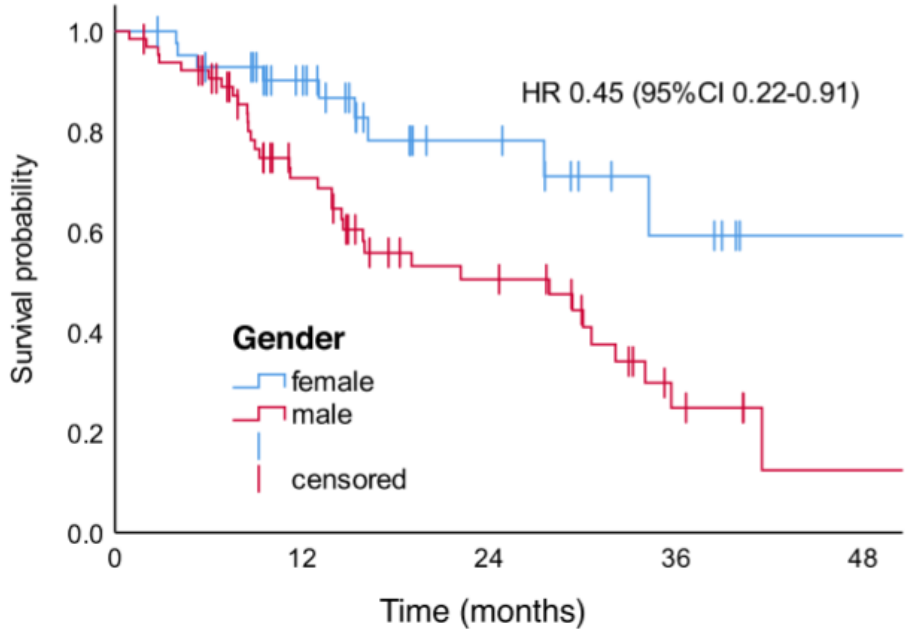
ERIVANCE. Gutzmer et al. BMC Cancer. 2021 Nov 19;21(1):1244.

Respuesta según parámetros clínicos:

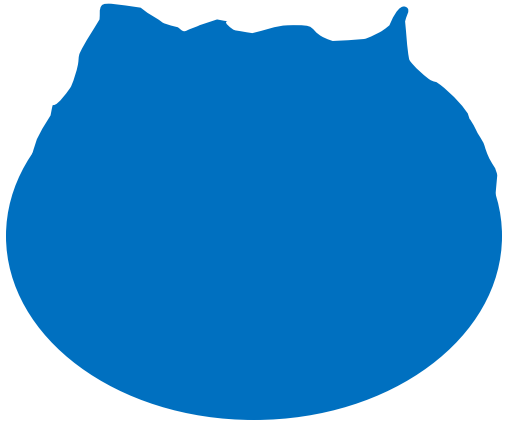
Multicenter Study > J Eur Acad Dermatol Venereol. 2022 Aug;36(8):1219-1228.
doi: 10.1111/jdv.18070. Epub 2022 Apr 5.

Analysis of efficacy and safety of vismodegib therapy in patients with advanced basal cell carcinoma – real world multicenter cohort study

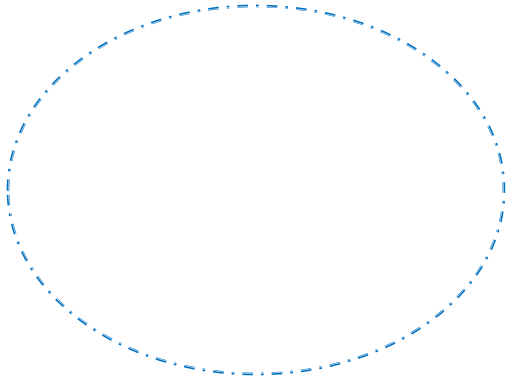
M Słowińska [1], M Dudzisz-Śledź [2], P Sobczuk [2 3], I Łasińska [4 5], A Pietruszka [6],



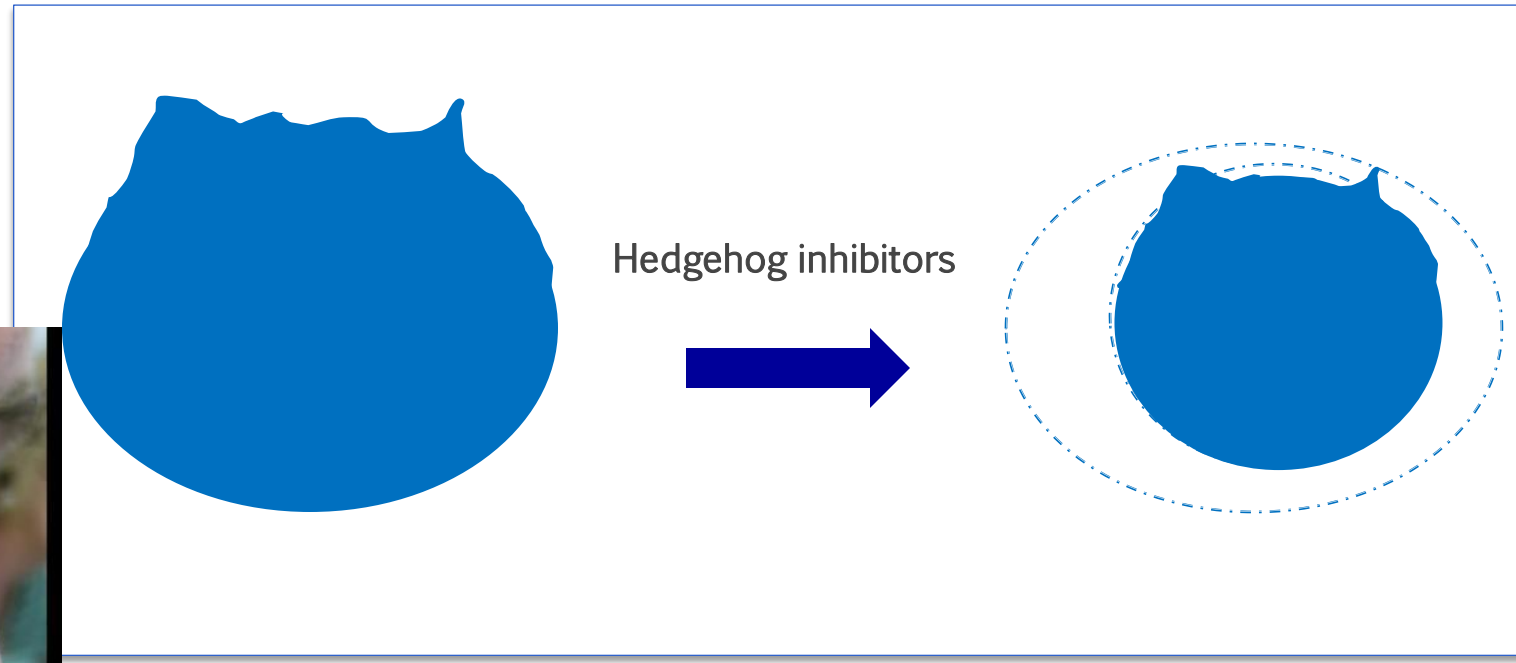
Modelos de respuesta a inhibidores de hedgehog



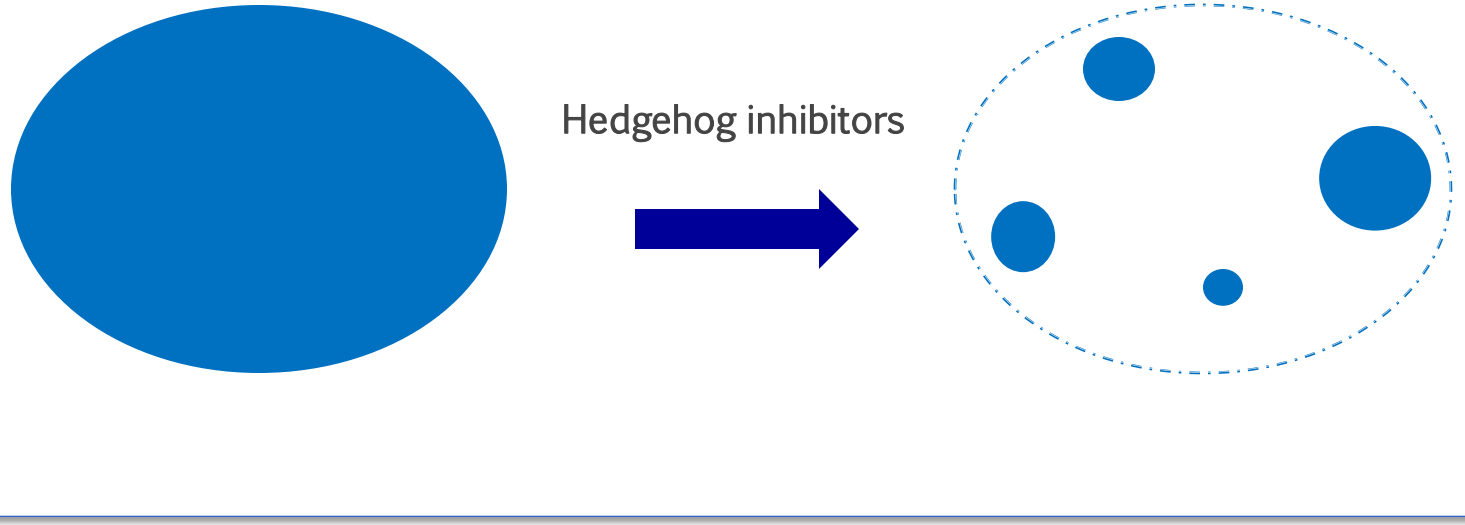
Hedgehog inhibitors

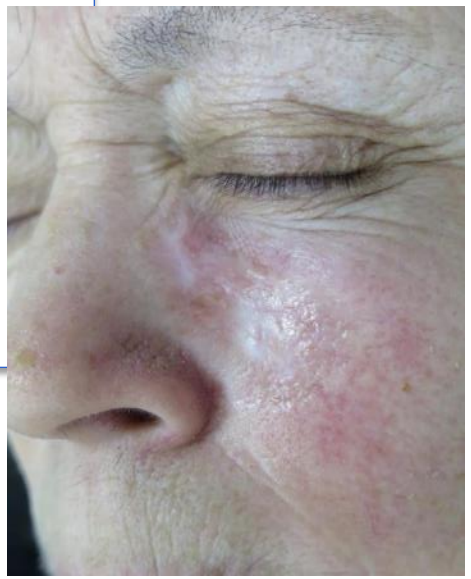


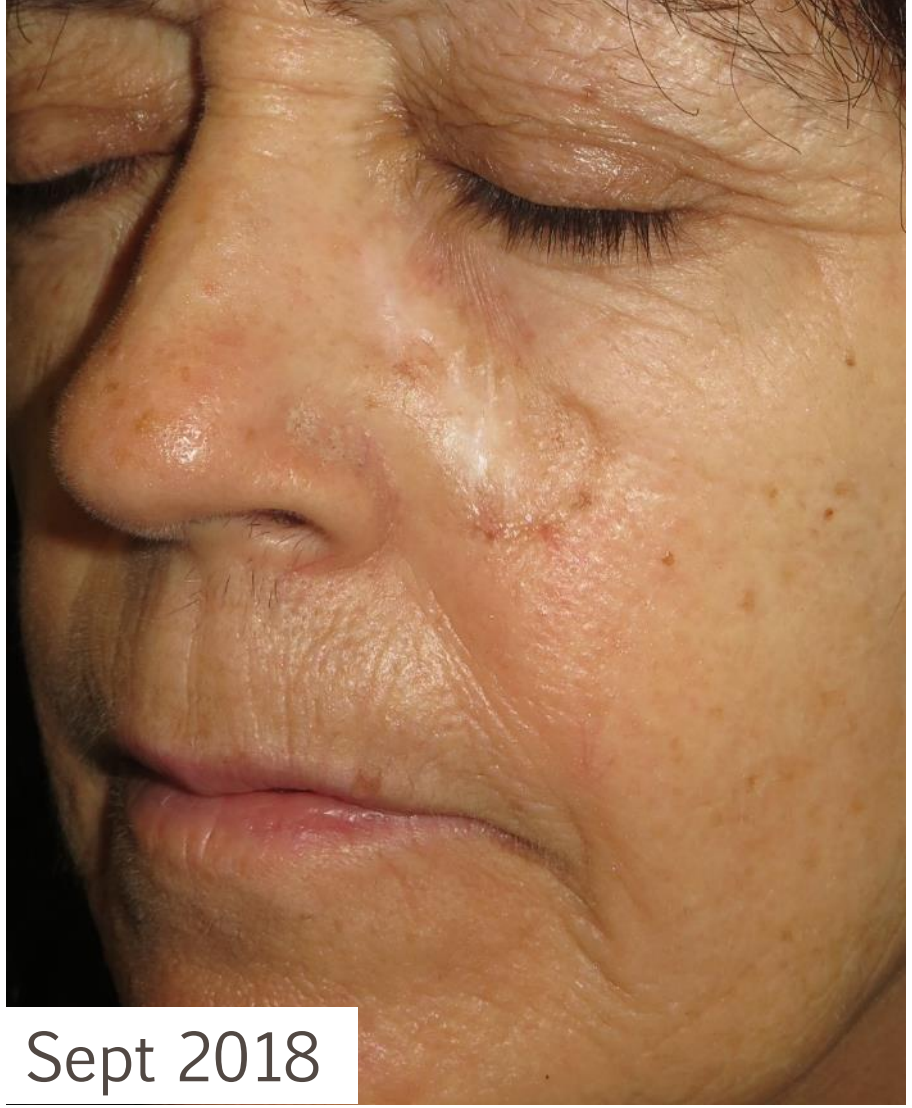
Modelos de respuesta a inhibidores de hedgehog



Modelos de respuesta a inhibidores de hedgehog



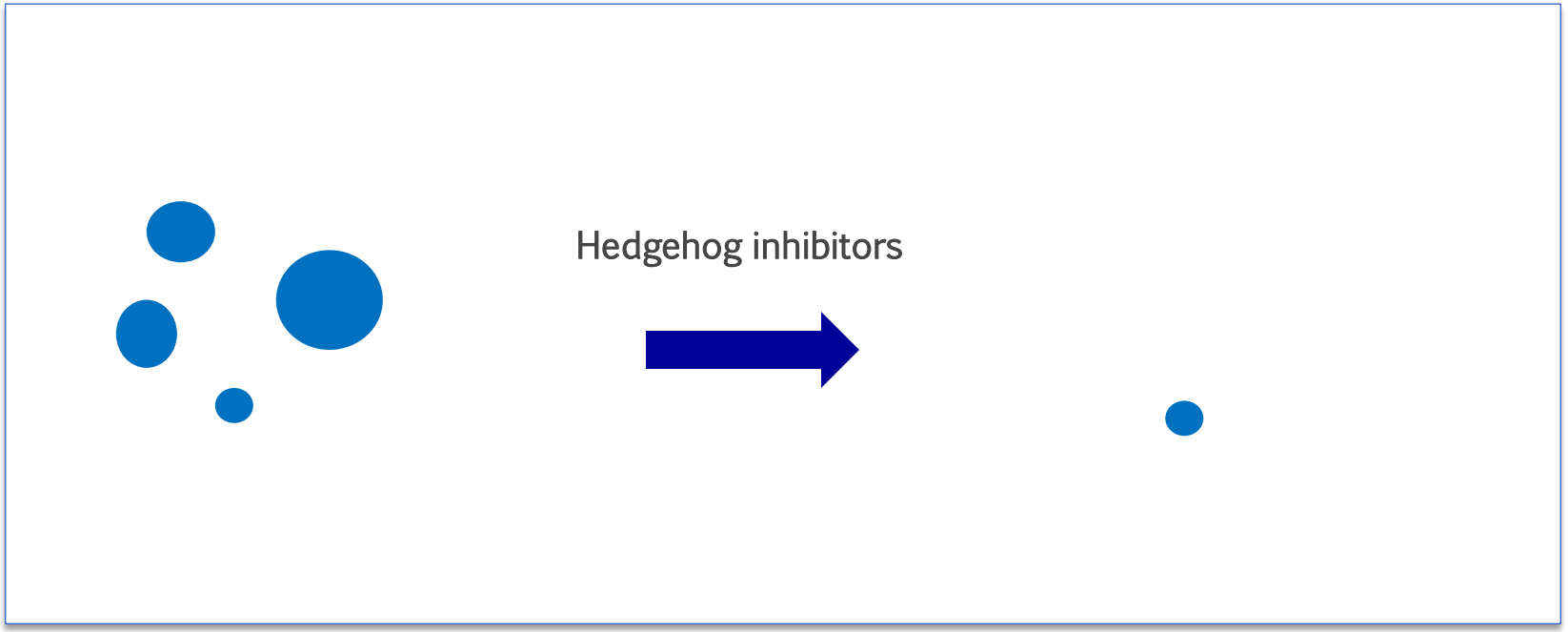




Sept 2018

Febrero 2019

Modelos de respuesta a inhibidores de hedgehog



PRE-VISMODEGIB

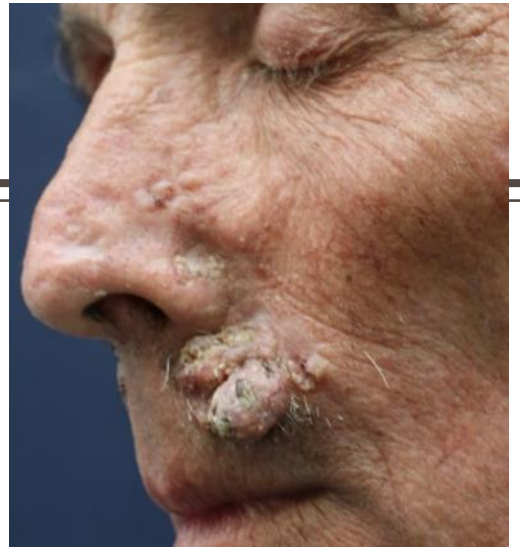
POST-VISMODEGIB

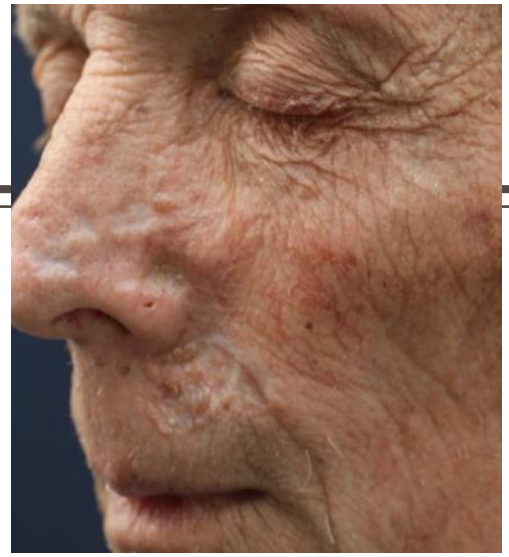
PRE-VISMODEGIB

POST-VISMODEGIB

PRE-VISMODEGIB

POST-VISMODEGIB





8 July 2016
T0 Vismodegib

T 1 month

T 5 months

¿Se pueden comparar Vismodegib y Sonidegib?

Comparativa Vismodegib/Sonidegib

	BOLT	ERIVANCE
laBCC	RECIST Sonidegib 200mg (n=66)[1*] 42 months	RECIST Vismodegib 150mg (n=63)[2] 39 months
ORR (CR + PR), n (%; 95% CI)	49 (**74.2%**; 62-84)	38 (**60.3%**;47-72)
CR, n (%)	19 (28.8%)	20 (31.7%)
PR, n (%)	30 (45.5%)	18 (28.6%)
SD, n (%)	11 (16.7%)	15 (23.8%)
PD, n (%)	1 (1.5%)	6 (9.5%)
UNK, n (%)	5 (7.6%)	4 (6.3%)
DCR (CR+PR+SD), %	**91%**	**84%**

Tiempo medio a respuesta máxima similar: 6 meses

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Stevie: DCR 93,6%

Tiempo medio a respuesta máxima similar: 6 meses

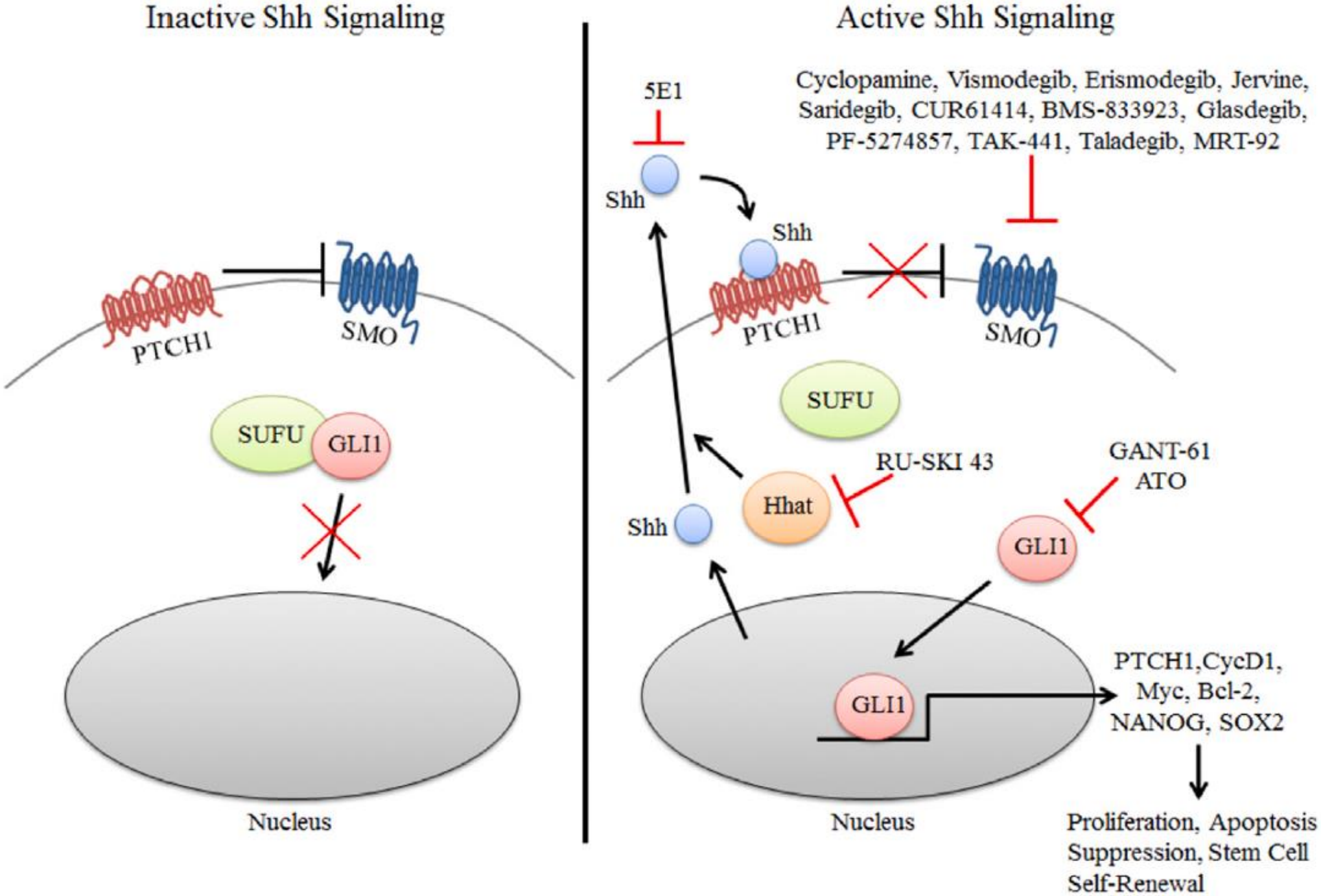
Resistencias primarias

	BOLT	ERIVANCE
laBCC	RECIST Sonidegib 200mg (n=66)[1]* 18 months	RECIST Vismodegib 150mg (n=63)[2] 21 months^
ORR (CR + PR), n (%; 95% CI)	40 (60.6%; 47.8-72.4)	30 (47.6%; 36-61)
CR, n (%)	14 (21.2%)	14 (22.2%)
PR, n (%)	26 (39.4%)	16 (25.4%)
SD, n (%)	20 (30.3%)	22 (34.9%)
PD, n (%)	1 (1.5%)	8 (12.7%)
UNK, n (%)	5 (7.6%)	3 (4.8%)
DCR (CR+PR+SD), %	90.9%	83%

STEVIE:1.9%

^After 21 months no central review data available

Los que resisten…


Inactive Shh Signaling
PTCH1
SMO
SUFU
GLI1
Nucleus
Active Shh Signaling
5E1
Cyclopamine, Vismodegib, Erismodegib, Jervine,
Saridegib, CUR61414, BMS-833923, Glasdegib,
PF-5274857, TAK-441, Taladegib, MRT-92
Shh
Shh
PTCH1
SMO
SUFU
RU-SKI 43
GANT-61
ATO
Hhat
Shh
GLI1
GLI1
PTCH1,CycD1,
Myc, Bcl-2,
NANOG, SOX2
Nucleus
Proliferation, Apoptosis
Suppression, Stem Cell
Self-Renewal

Resistencias primarias a inhibidores hedgehog

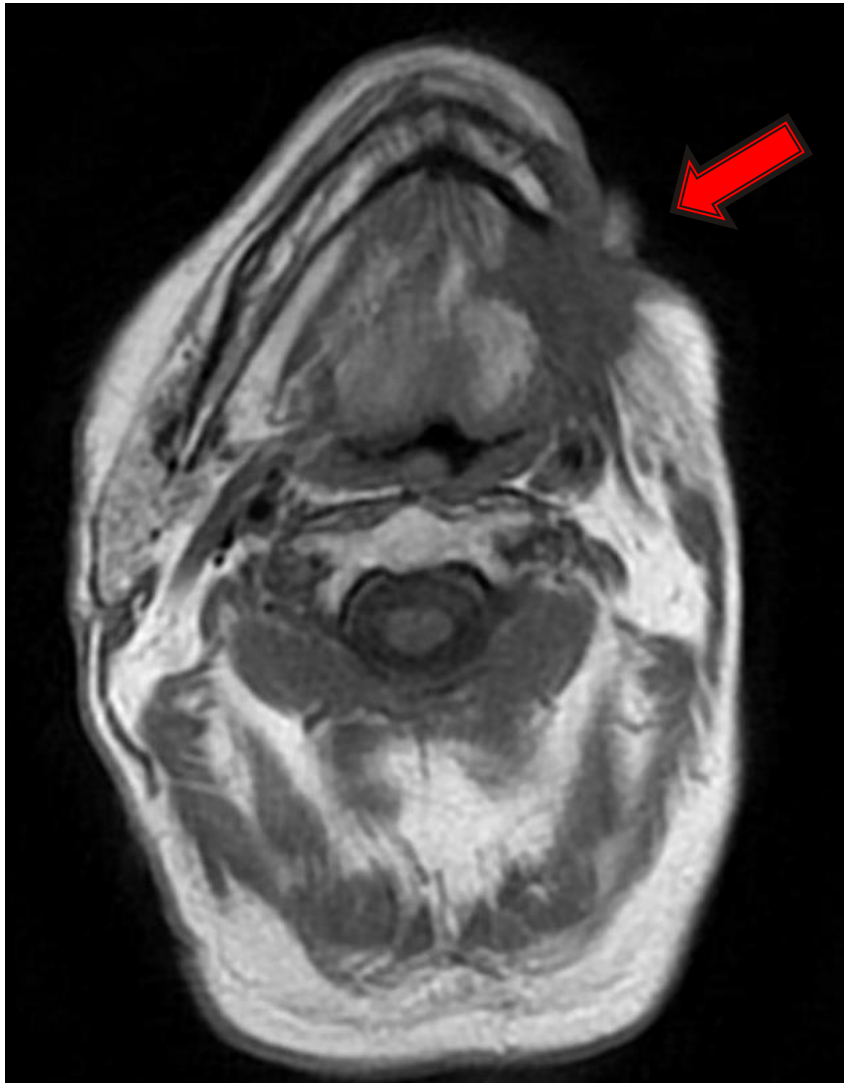
- Perfil genético diferente según subtipos histológicos.
  - CBC superficial vs nodular
  - CBC superficial mutaciones PATCH, NOTCH1
  - Frecuentes las mutaciones en CSMD1, NOTCH1, DPP10, TERT, DPH3, P53

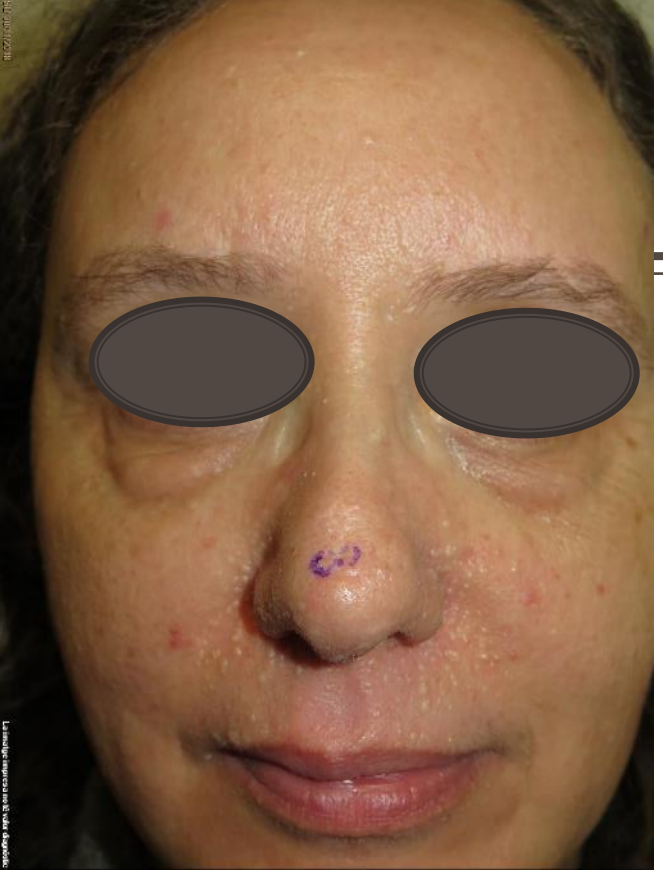
› Sci Rep. 2021 Jun 24;11(1):13206. doi: 10.1038/s41598-021-92592-3.

Molecular alterations in basal cell carcinoma subtypes

Lucia Di Nardo [# 1], Cristina Pellegrini [# 2], Alessandro Di Stefani [3], Francesco Ricci [4], Barbara Fossati [3], Laura Del Regno [3], Carmine Carbone [5], Geny Piro [5], Vincenzo Corbo [6], Pietro Delfino [6], Simona De Summa [7], Maria Giovanna Maturo [2], Tea Rocco [2], Giampaolo Tortora [5 8], Maria Concetta Fargnoli [2], Ketty Peris [9 10]

Resistencias PRIMARIAS a inhibidores hedgehog

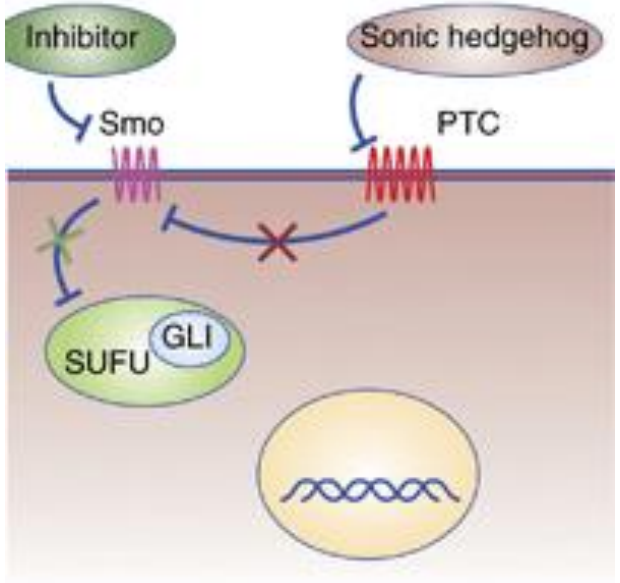




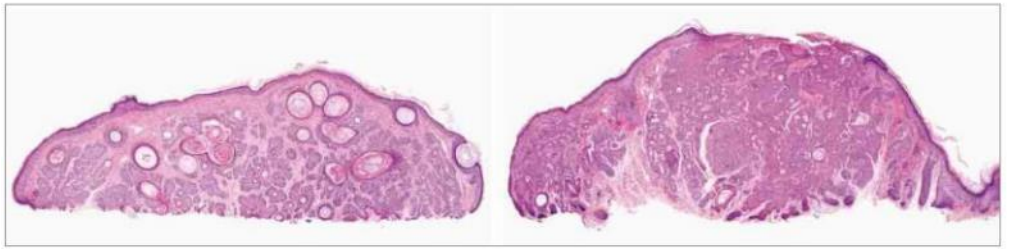
Case Report/Case Series

Multiple Hereditary Infundibulocystic Basal Cell Carcinoma Syndrome Associated With a Germline *SUFU* Mutation

Joshua M. Schulman, MD; Dennis H. Oh, MD, PhD; J. Zachary Sanborn, PhD; Laura Pincus, MD; Timothy H. McCalmont, MD; Raymond J. Cho, MD, PhD

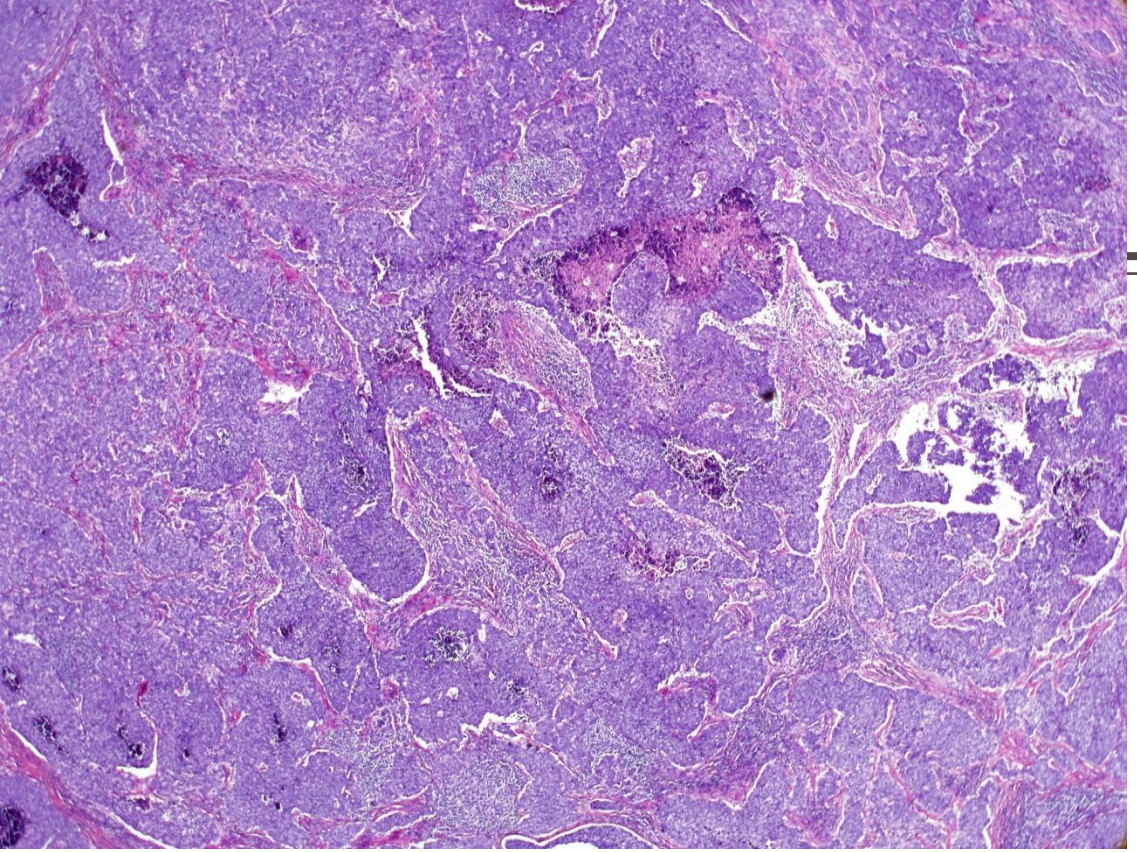


C Photomicrographs of patient's tumors

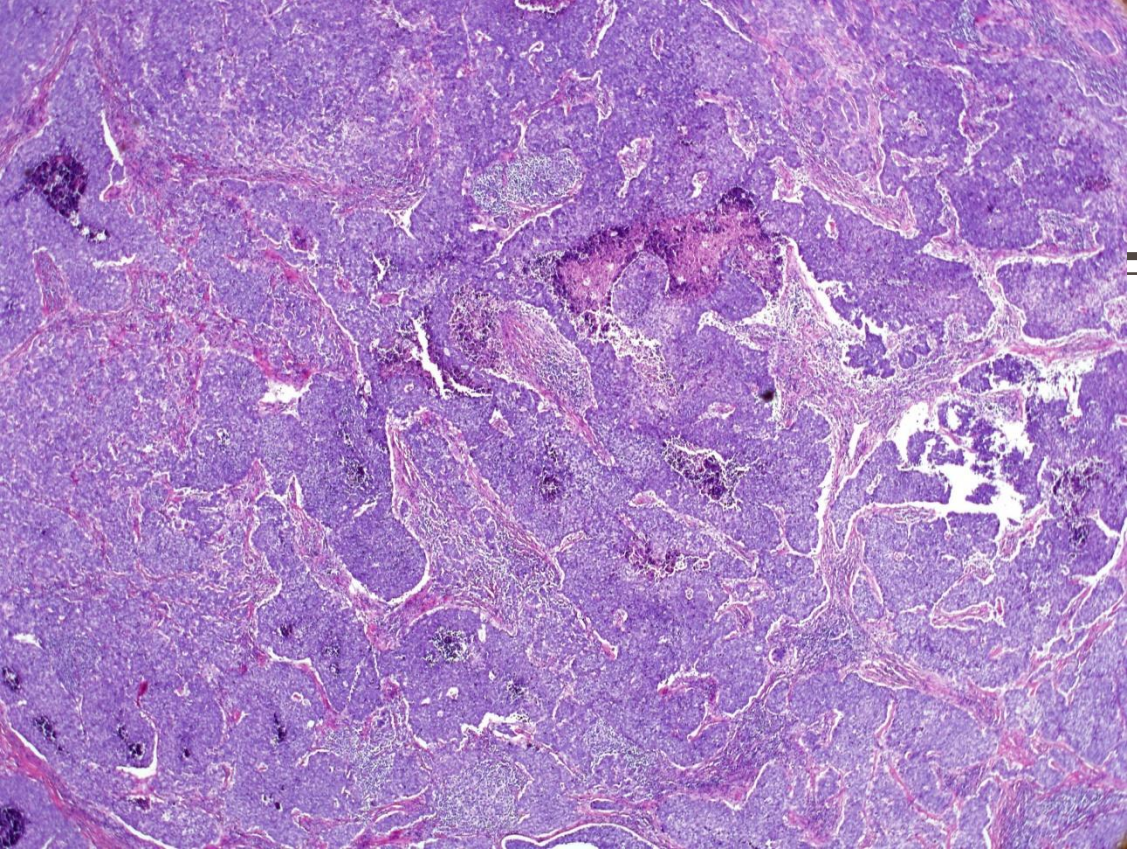


Varón. 83 años. Carcinoma basocelular con diferenciación escamosa.

3 meses post-vismodegib



- EMA +
- BER-EP4 débil



- EMA +
- BER-EP4 débil

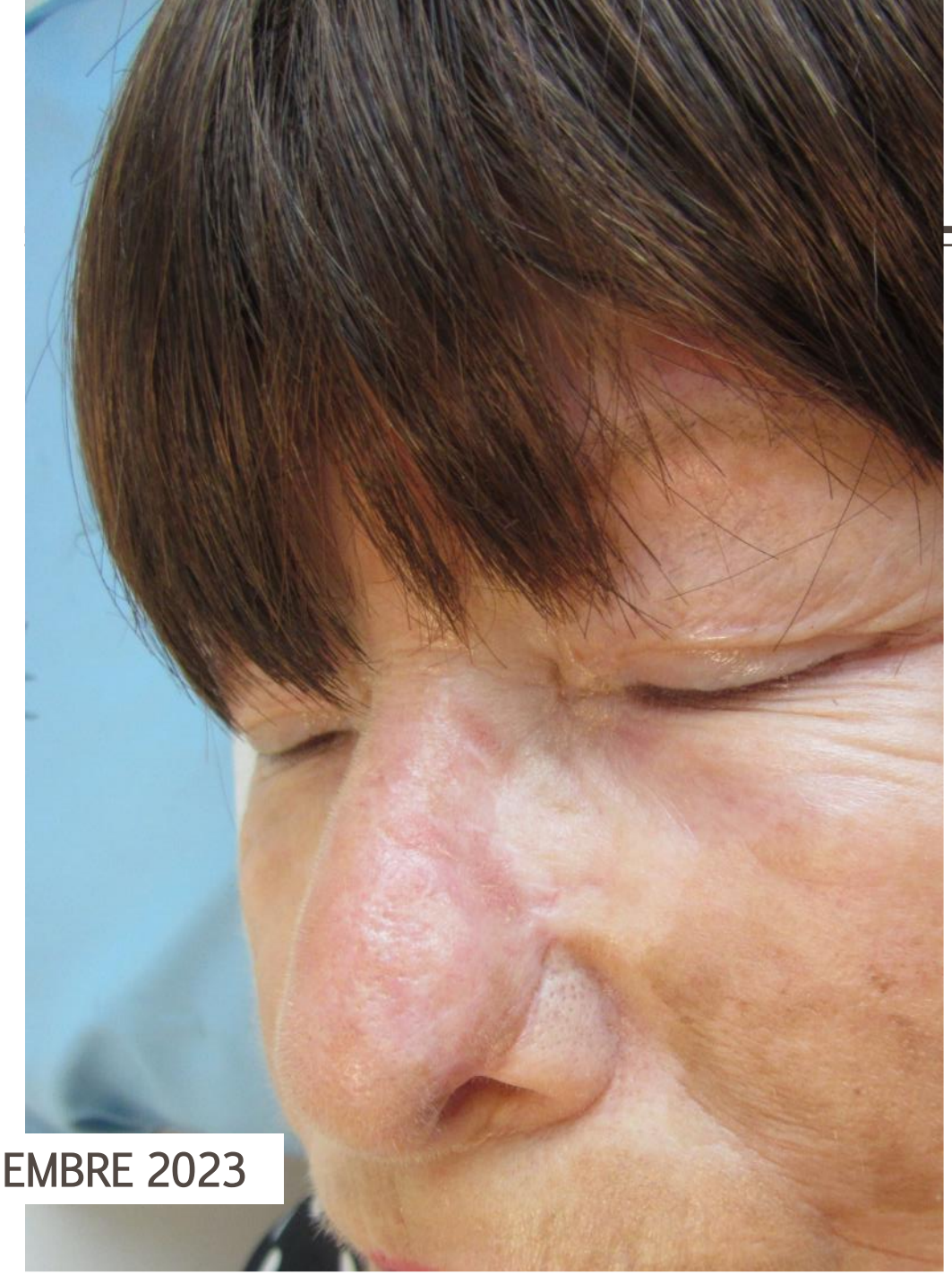
CARCINOMA ESCAMOSO BASALOIDE

VISMODEGIB

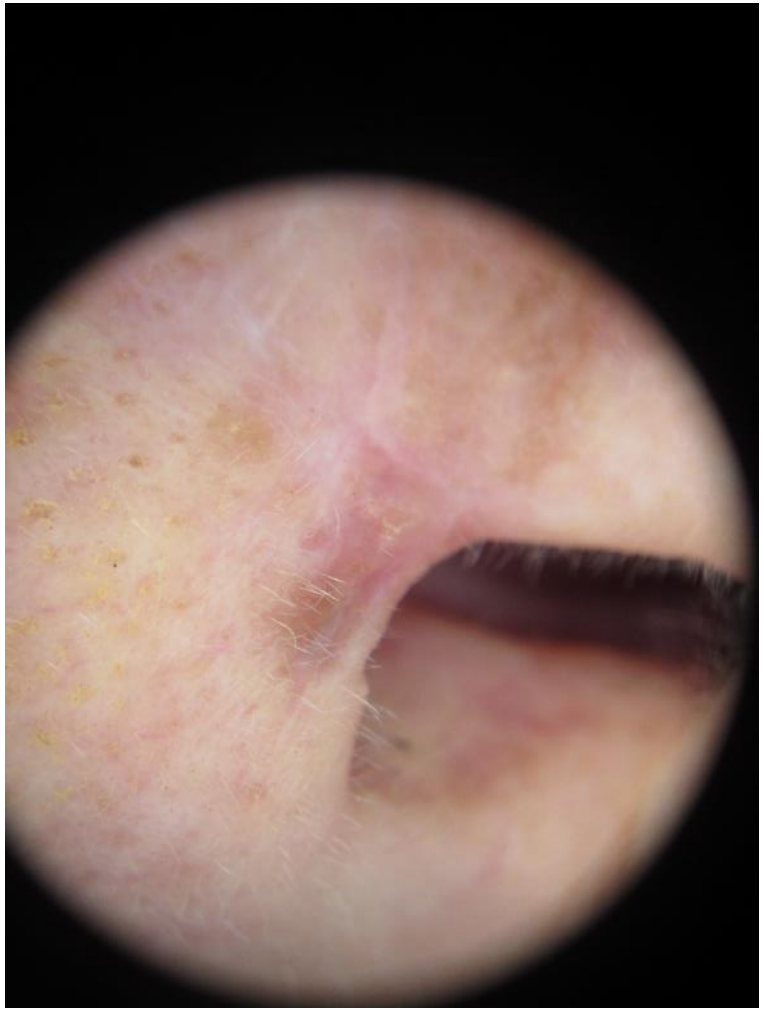
Los que reaparecen…

- Mujer 75 años
- Periodista
- Vida social +++
- Cirugía de Mohs previa + recidiva

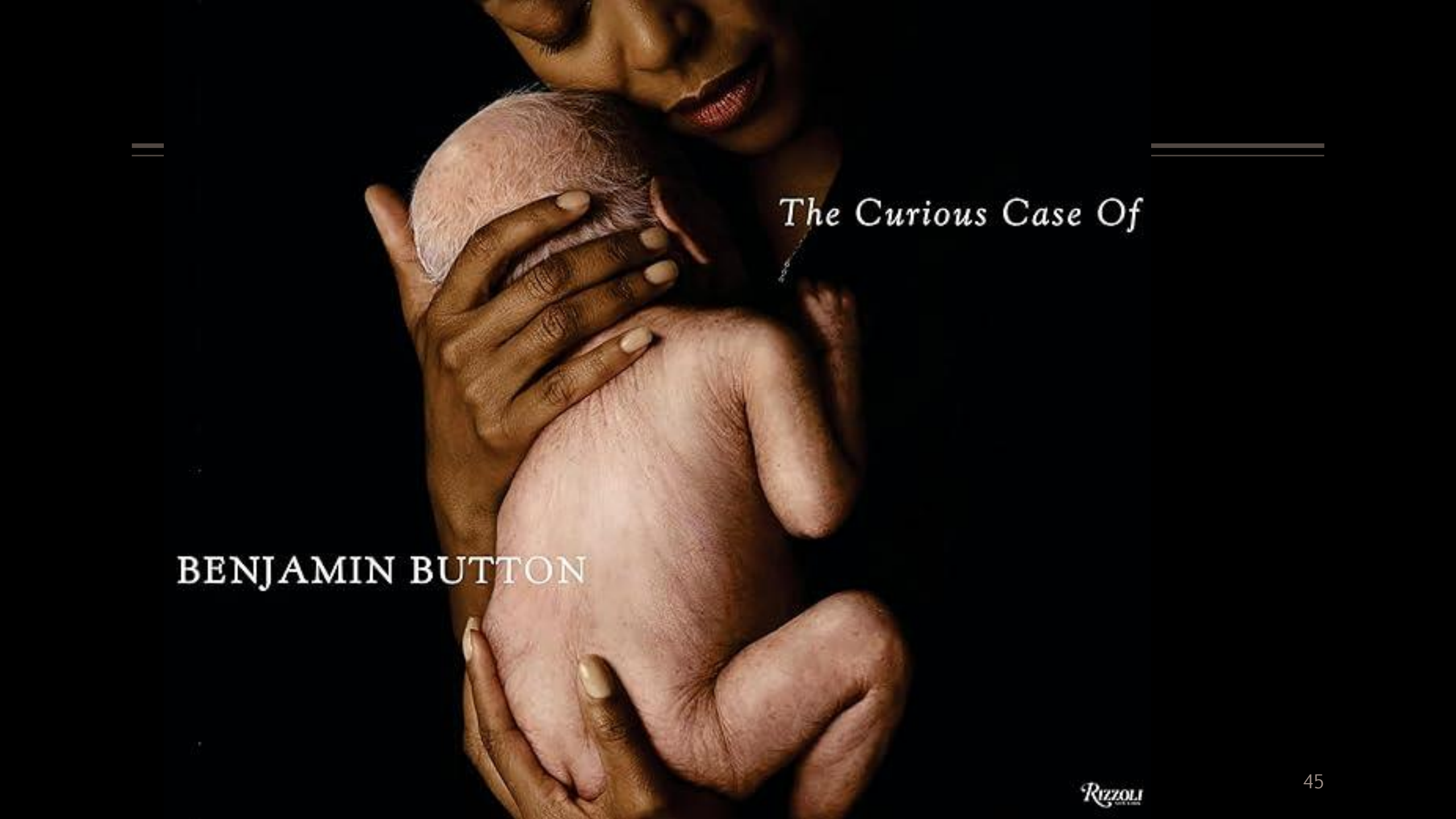
Vismodegib



SEPTIEMBRE 2023



Febrero 2024


The Curious Case Of
BENJAMIN BUTTON
RIZZOLI

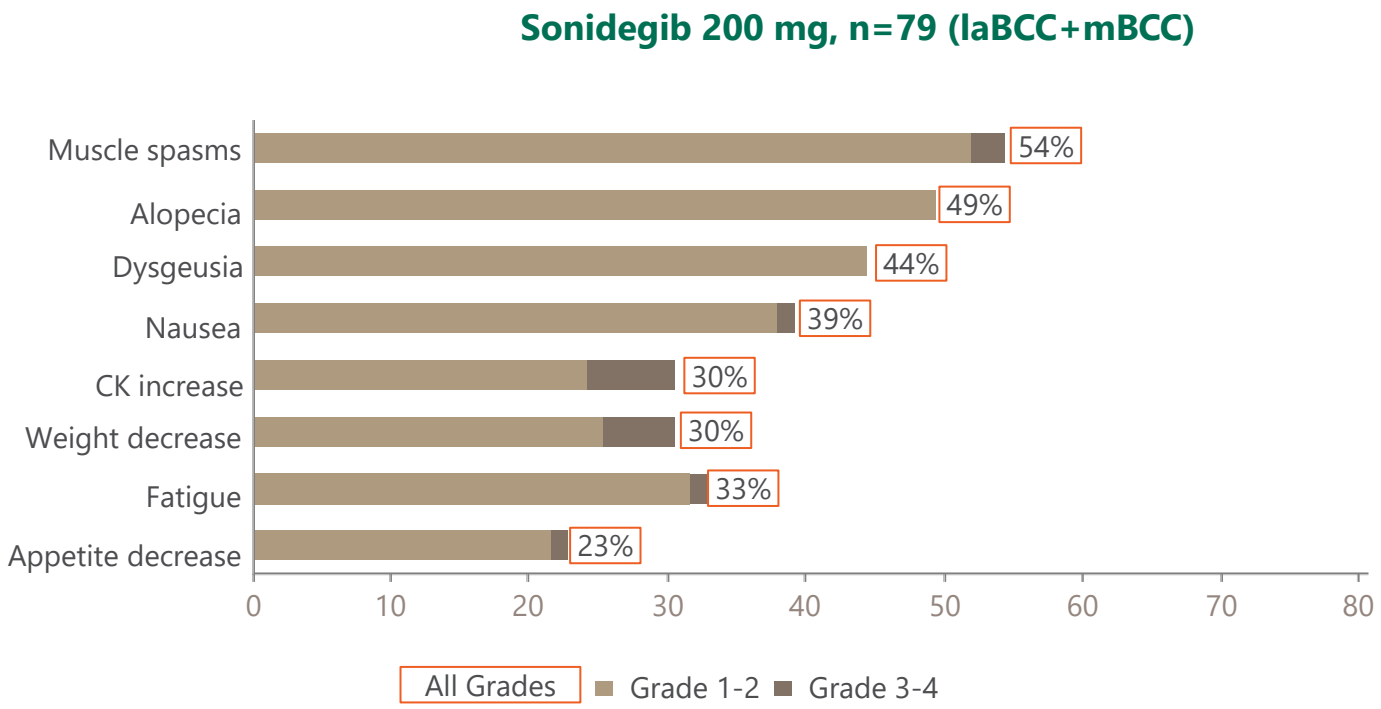
Efectos adversos inhibidores hedgehog/Vismodegib

25-30% **de los pacientes dejan el tratamiento por los efectos adversos**

Efecto adverso	Porcentaje
Espasmos musculares	66%
Alopecia	62%
Disgeusia	55%
Disminución peso	41%
Disminución apetito	25%
Astenia	24%

- Basset-Seguin. Estudio Stevie EJC 2017

Efectos adversos al Sonidegib

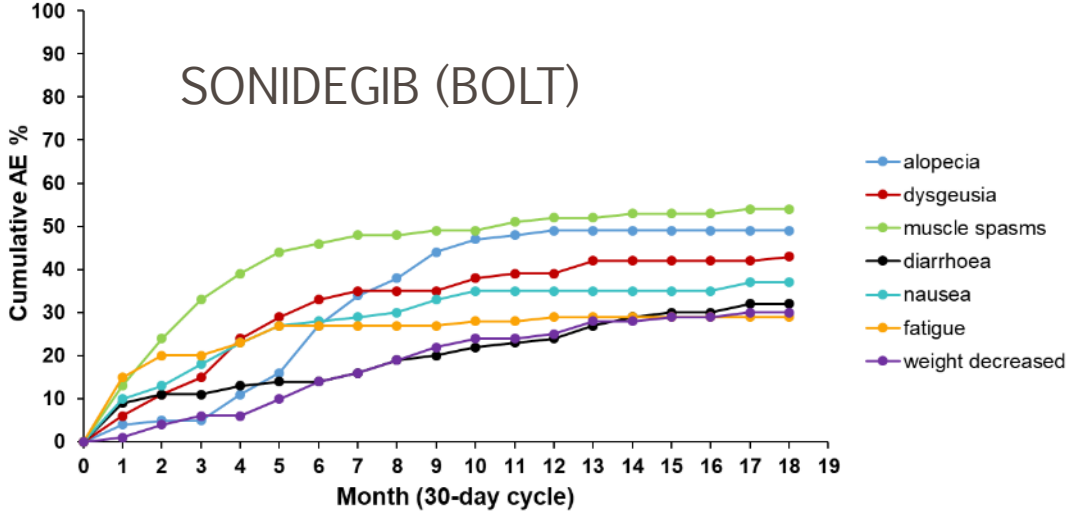


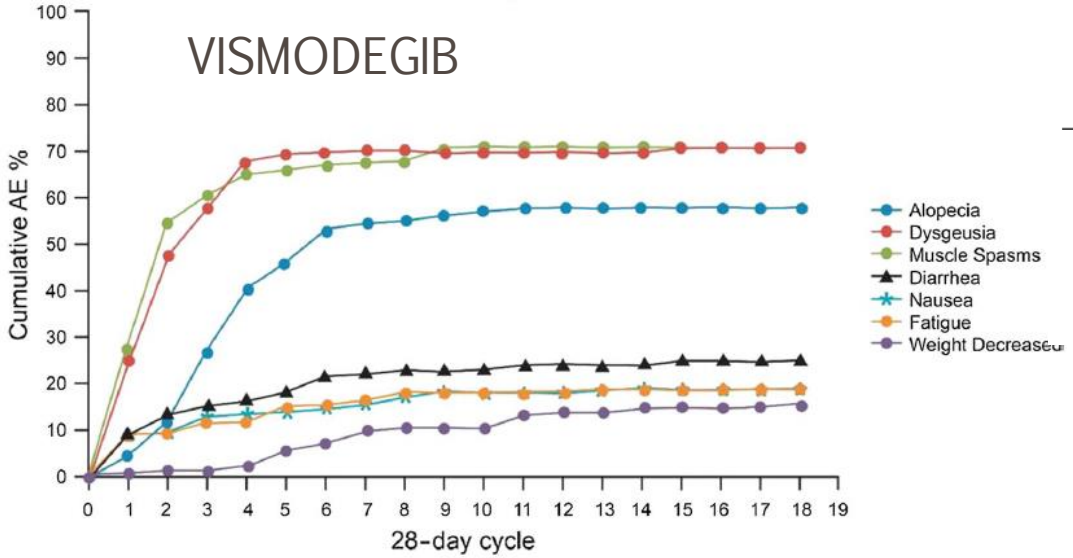
AEs, adverse events; CK, creatine phosphokinase

1. Dummer et al. Br J Dermatol. 2020 Jun;182(6):1369-1378. 2. Odomzo summary of product characteristics 2021

Efectos adversos Vismodegib-Sonidegib

Gutzmer et al. Dermatol Ther (Heidelb). 2021 Oct;11(5):1839-1849

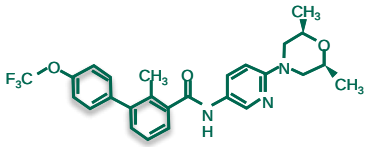
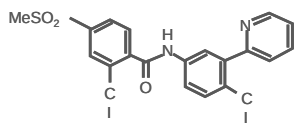




Expanded access study of patients with advanced basal cell carcinoma treated with the Hedgehog pathway inhibitor, vismodegib

Anne Lynn S. Chang, MD,[a] James A. Solomon, MD, PhD,[b,c,d] John D. Hainsworth, MD,[e] Leonard Goldberg, MD,[f] Edward McKenna, PharmD, BCOP,[g] Bann-mo Day, PhD,[g] Diana M. Chen, MD,[g] and Glen J. Weiss, MD[h]
Stanford, California; Ormond Beach and Orlando, Florida; Nashville, Tennessee; Urbana, Illinois; Houston, Texas; San Francisco, California; and Scottsdale, Arizona

Chang et al. J Am Acad Dermatol. 2014 Jan;70(1):60-9

	Odomzo® (sonidegib)	Vismodegib
Molecular structure	 [1]	 [3]
Dosing	200 mg orally once daily (empty stomach)*[2]	150 mg orally once daily [4]
Approved dose modifications	Alternate day dosing [2]	None
Half-life (T ½)	~28 days [2]	~4 days [4]
Plasma peak concentration (Cmax)	1030 ng/ml [1]	11449 ng/ml [5]
Lowest plasma concentration (Cmin)	890 ng/ml [1]	10493 ng/ml [5]
Skin concentration	6-fold higher in skin than in plasma [2]	Not measured
Apparent volume of distribution (Vss/F)	9170 litres [2]	16.4-26.6 litres [4]

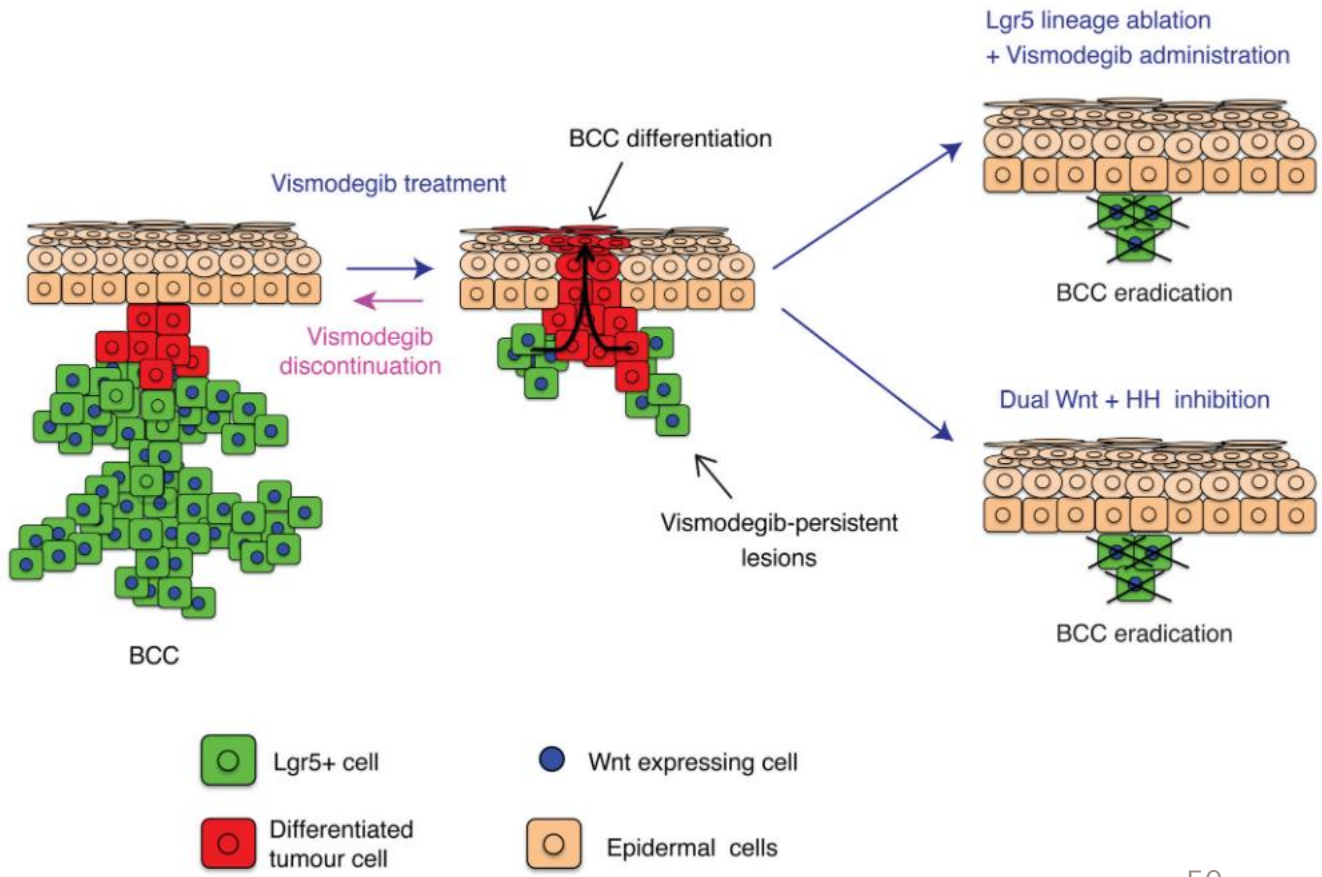
* ≥2 hours after a meal or ≥1 hour before the following meal

1. Odomzo® US prescribing information 2019. 2. Odomzo® summary of product characteristics 2019. 3. Erivedge® US prescribing information 2019. 4. Erivedge® summary of product characteristics 2019. 5. Sharma MR, Clin Cancer Res. 2013 Jun 1;19(11):3059-67. 6. Dummer et al. J Eur Acad Dermatol Venereol. 2020 Sep;34(9):1944-1956.

Nature. 2018 Oct;562(7727):434-438. doi: 10.1038/s41586-018-0603-3. Epub 2018 Oct 8.

A slow-cycling LGR5 tumour population mediates basal cell carcinoma relapse after therapy

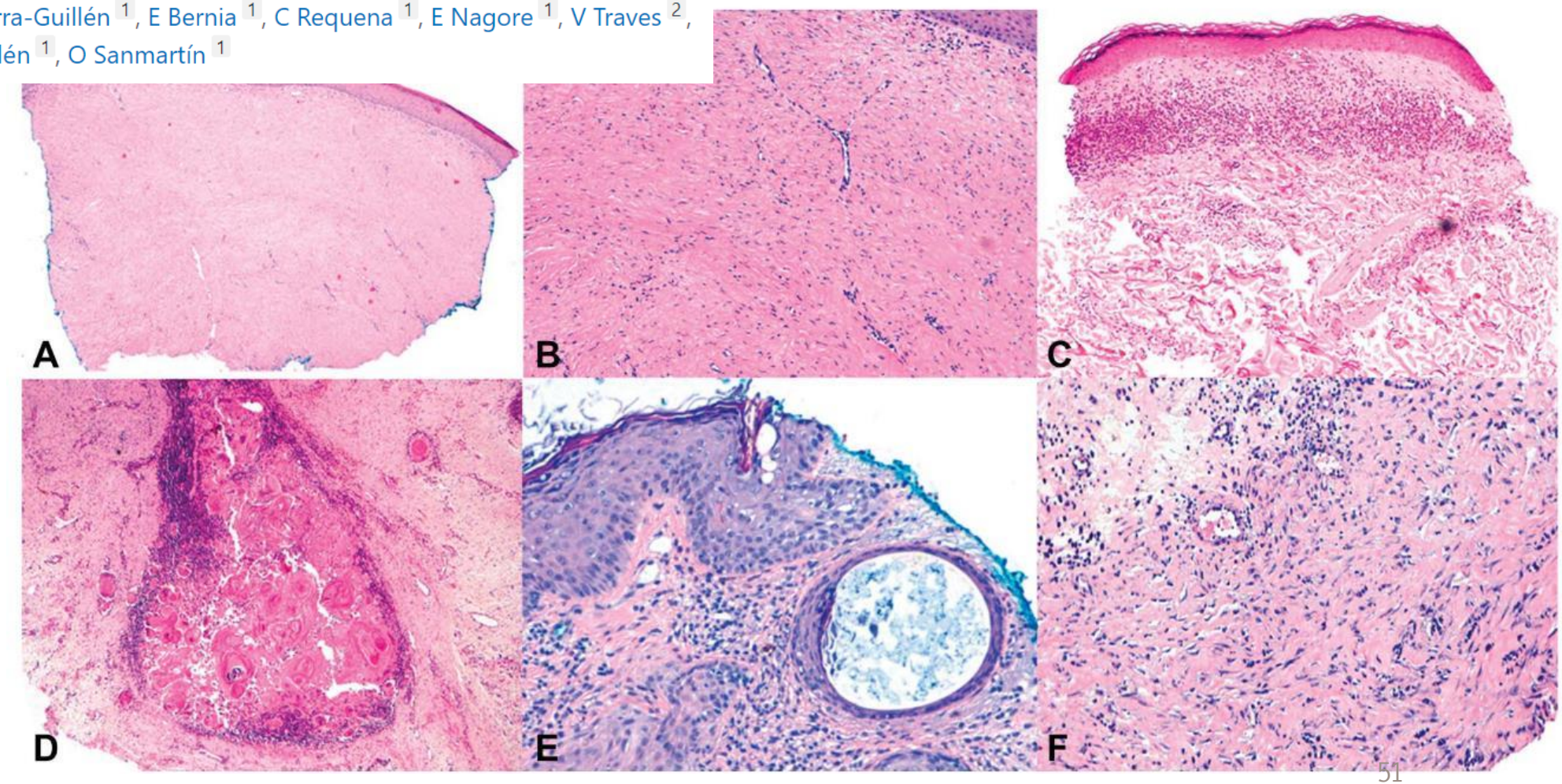
Adriana Sánchez-Danés [1], Jean-Christophe Larsimont [1], Mélanie Liagre [1], Eva Muñoz-Couselo [2 3], Gaëlle Lapouge [1], Audrey Brisebarre [1], Christine Dubois [1], Mariano Suppa [4], Vijayakumar Sukumaran [1], Véronique Del Marmol [4], Josep Tabernero [2 3], Cédric Blanpain [5 6]



Am J Dermatopathol. 2019 Oct;41(10):711-717. doi: 10.1097/DAD.0000000000001384.

Histologic Changes During Treatment With Vismodegib in Locally Advanced Basal Cell Carcinoma: A Series of 19 Cases

B Bancalari [1], B Llombart [1], C Serra-Guillén [1], E Bernia [1], C Requena [1], E Nagore [1], V Traves [2], L Calomarde [1], A Diago [1], C Guillén [1], O Sanmartín [1]



ActaDV

INVESTIGATIVE REPORT

Comparative Analyses of Tumour Volume Doubling Times for Periocular and Non-periocular Head and Neck Basal Cell Carcinomas

Andre Boo Shern KHOO[1], Patrick Kin Yoong GOON[2], Holger SUDHOFF[3#] and Peter Kin Cho GOON[1#]

[1]Department of Dermatology, Addenbrooke's Hospital, Hills Road, Cambridge, Cambridgeshire, [2]Department of Plastic Surgery, Lister Hospital, Coreys Mill Lane, Stevenage, Hertfordshire, UK, and [3]Department of Otorhinolaryngology and Head & Neck Surgery, Bielefeld University Hospital, Bielefeld, Germany

[#]Co-senior author.

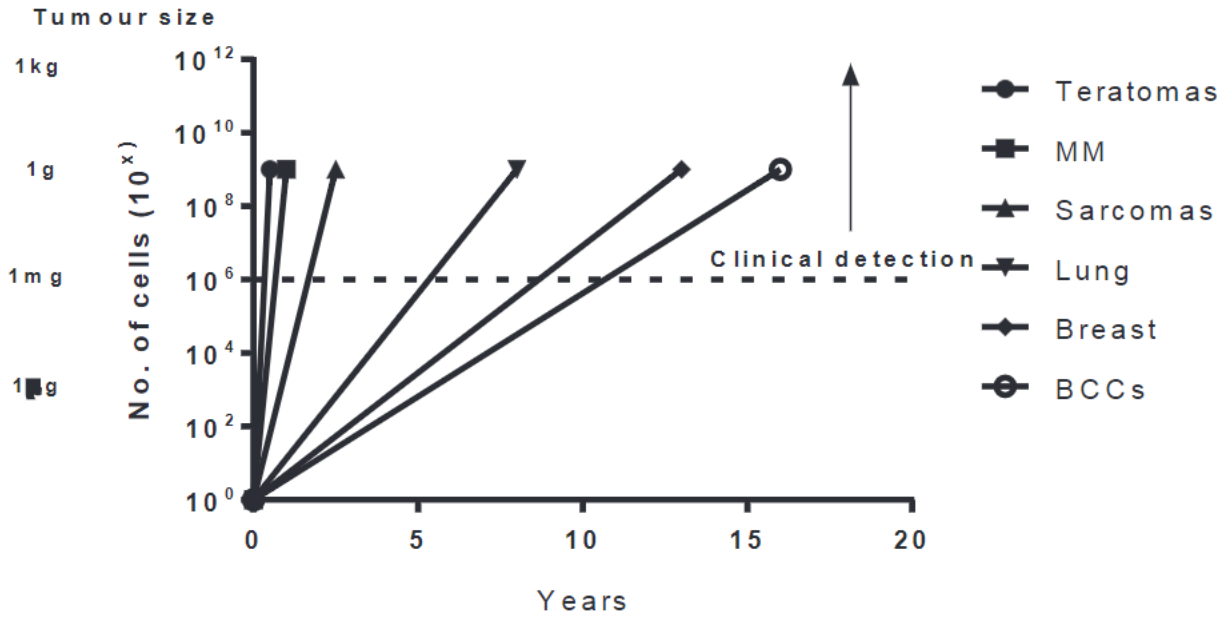
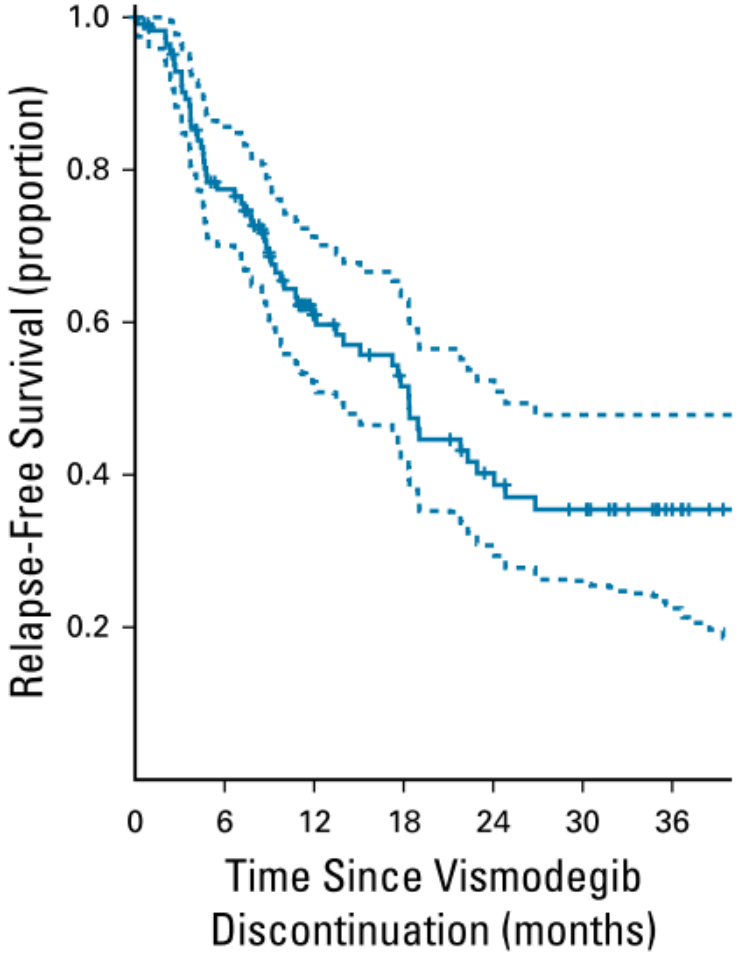


Fig. 3. Growth rates (estimated) for different solid tumours in comparison to nodular basal cell carcinomas (BCCs).

Recaída tres suspensión de Vismodegib



Observational Study > J Clin Oncol. 2019 Dec 1;37(34):3275-3282. doi: 10.1200/JCO.18.00794. Epub 2019 Oct 14.

Follow-Up of Patients With Complete Remission of Locally Advanced Basal Cell Carcinoma After Vismodegib Discontinuation: A Multicenter French Study of 116 Patients

Florian Herms [1 2], Jerome Lambert [1 2], Jean-Jacques Grob [3], Luc Haudebourg [1 2],

35% de respuestas mantenidas 36 meses después de haber obtenido respuesta completa.

=

65% recurrencias.

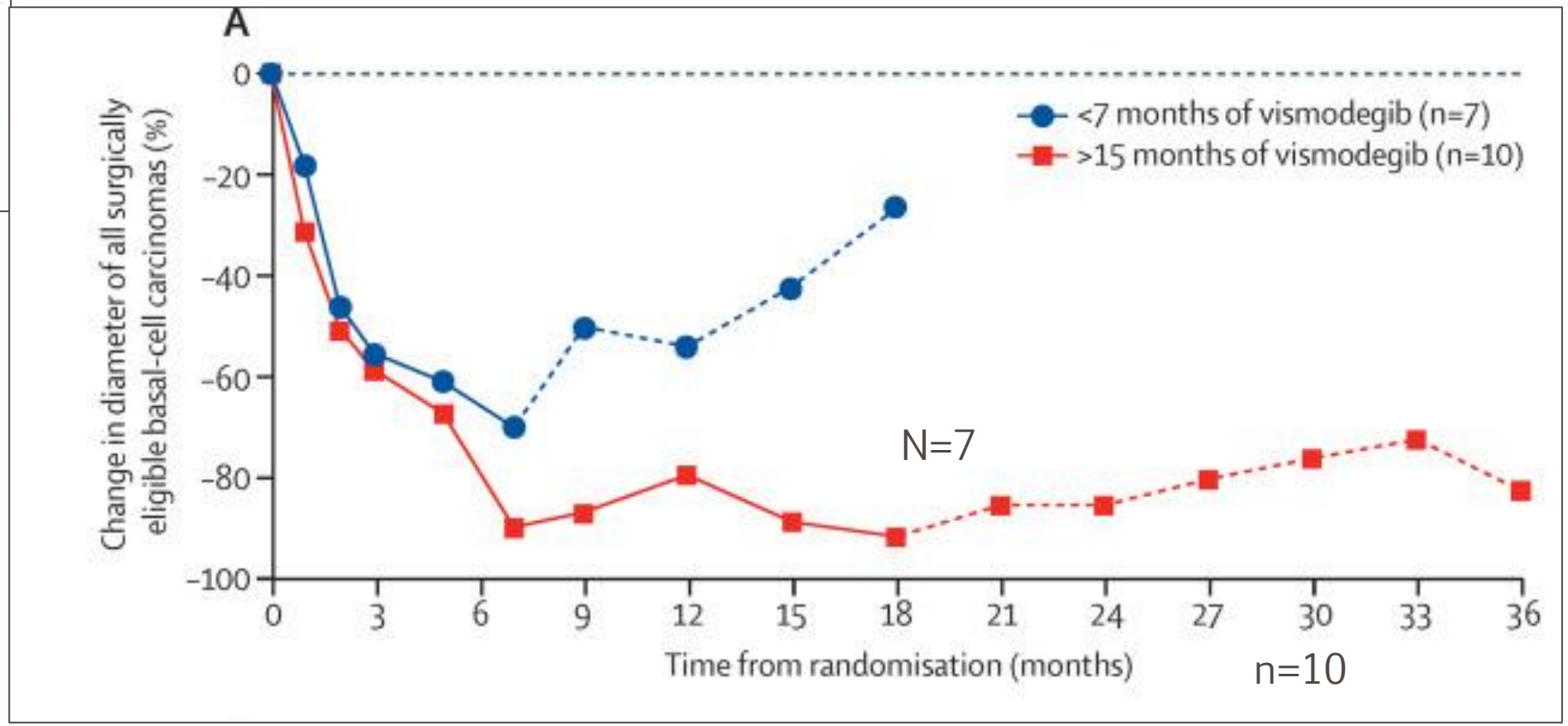
Respuesta completa a los 3 años en el 12% de los pacientes

THE LANCET
Oncology
Volume 17, Issue 12, December 2016, Pages 1720-1731

Articles

Inhibition of the hedgehog pathway in patients with basal-cell nevus syndrome: final results from the multicentre, randomised, double-blind, placebo-controlled, phase 2 trial

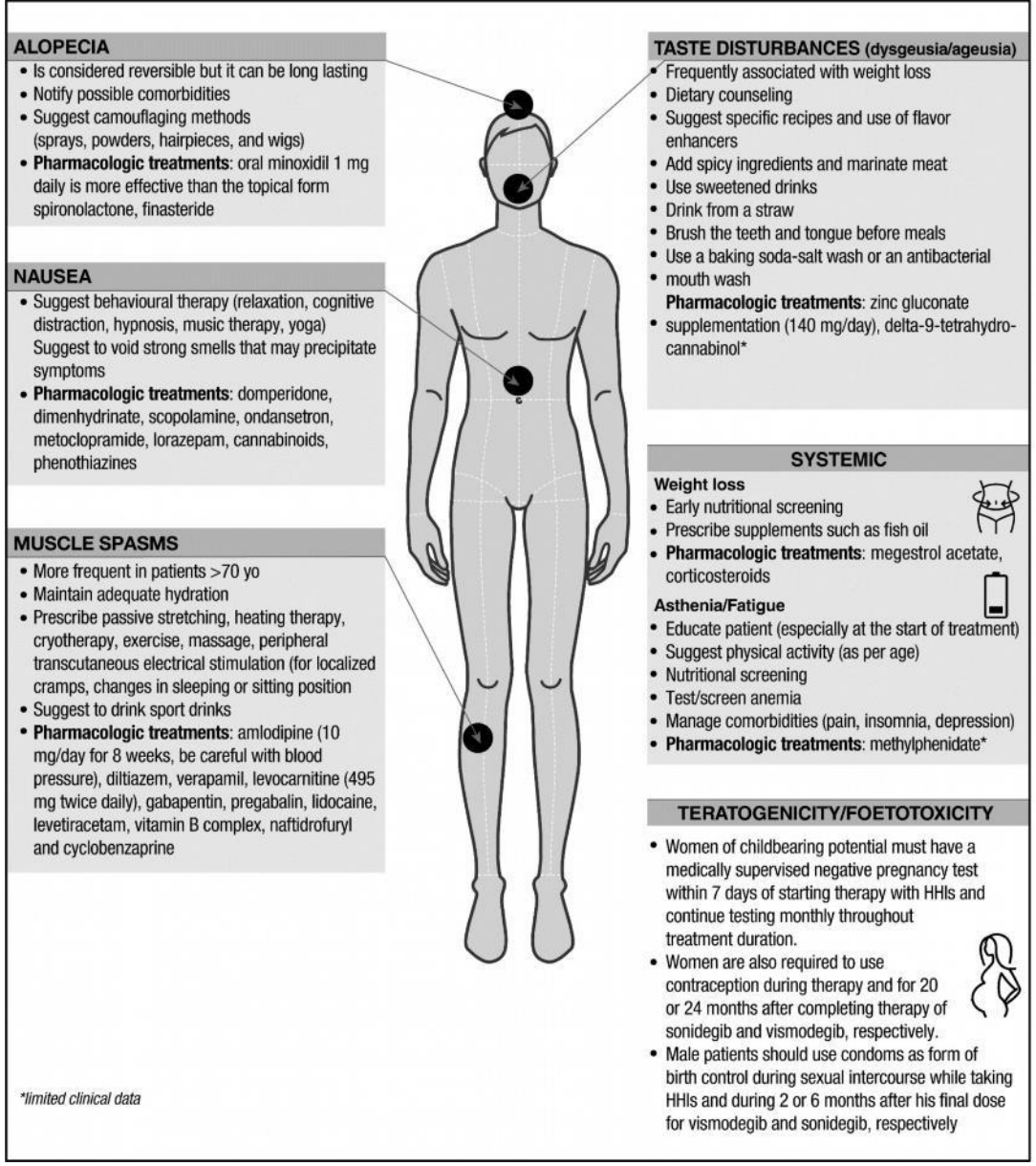
Jean Y Tang MD [a, b, †], Mina S Ally MD [a, b, †], Anita M Chanana BS [a], Julian M Mackay-Wiggan MD [c], Michelle Aszterbaum MD [d], Joselyn A Lindgren MS [a], Grace Ulerio BA [c], Melika R Rezaee BA [a], Ginny Gildengorin PhD [a], Jaddeen Marji MD [c], Charlotte Clark MD [c], Prof David R Bickers MD [c], Dr Ervin H Epstein Jr MD [a, *]



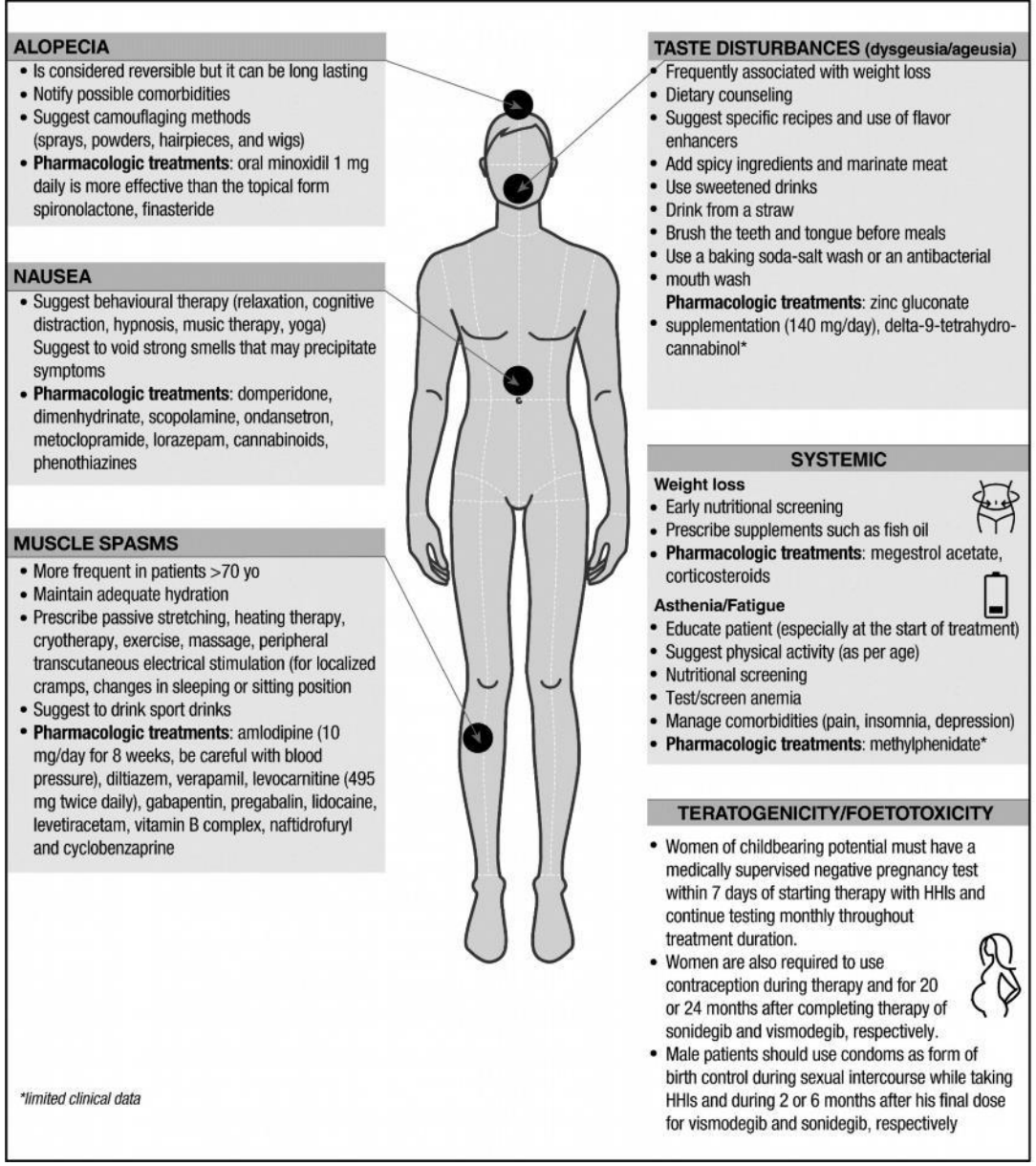
- **SI SE SUSPENDE EL IHH, EL BASOCELULAR RECIDIVA (LENTO PERO SEGURO)**

- **CUANTO MAS SE ALARGE EL TRATAMIENTO, MENOS RECIDIVA (EVIDENCIA POBRE)**

- **¿QUÉ HACER PARA NO SUSPENDER EL TRATAMIENTO?**



Bossi et al. Long-term strategies for management of advanced basal cell carcinoma with hedgehog inhibitors. Crit Rev Oncol Hematol. 2023 Jul 11;189:104066



› Cancers (Basel). 2022 May 19;14(10):2496. doi: 10.3390/cancers14102496.

Eight Years of Real-Life Experience with Smoothened Inhibitors in a Swiss Tertiary Skin Referral Center

Lara E Grossmann [1], Egle Ramelyte [1], Mirjam C Nägeli [1], Reinhard Dummer [1]

Affiliations + expand

PMID: 35626100 PMCID: PMC9139771 DOI: 10.3390/cancers14102496

- Muscle spasms could be subjectively reduced with quinine sulfate (200–250 mg twice a day). Some patients also benefited from peroral magnesium or muscle relaxants such as tizanidine.
- With a 2 months on/2 months off intermittent treatment we were able to avoid total alopecia, which was an important prerequisite for starting therapy, especially for women.

Bossi et al. Long-term strategies for management of advanced basal cell carcinoma with hedgehog inhibitors. Crit Rev Oncol Hematol. 2023 Jul 11;189:104066

COMO MANEJAR LOS EFECTOS ADVERSOS DE LOS INHIBIDORES DE HEDGEHOG

Grado 1-2: INTERMITENCIA

Pautas:

-Cada/48 hs (<resistencias?)

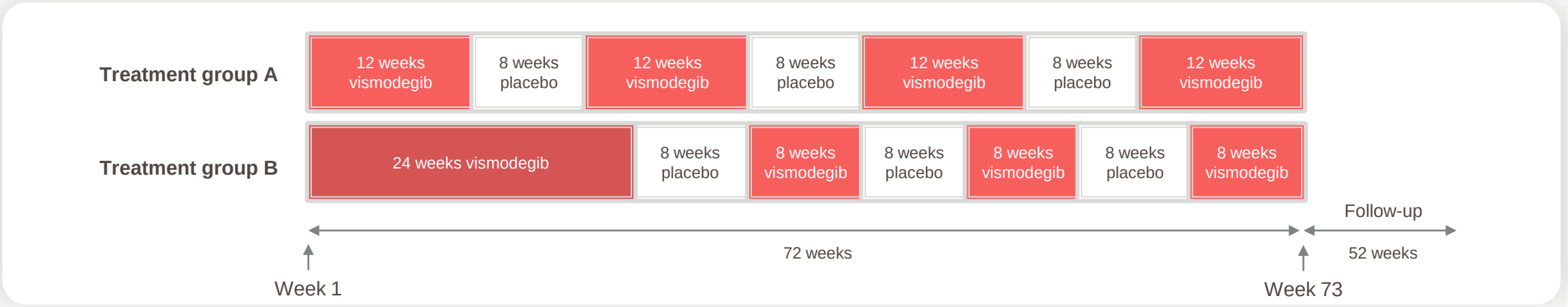
-Suspensión intermitente:

- 12 semanas tratamiento/8 descanso

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

Brigitte Dréno, Rainer Kunstfeld, Axel Hauschild, Scott Fosko, David Zloty, Bruno Labeille, Jean-Jacques Grob, Susana Puig, Frank Gilberg, Daniel Bergström, Damian R Page, Gary Rogers, Dirk Schadendorf

Dos regimens intermitentes de Vismodegib en pacientes con multiples CBC (Gorlin y no Gorlin)



	MIKIE[1] N=229	STEVIE[2] N=1215	ERIVANCE[3] N=104
EAs que llevan a suspensión	23% Group A: 20%, Group B: 34%	31%	57%*

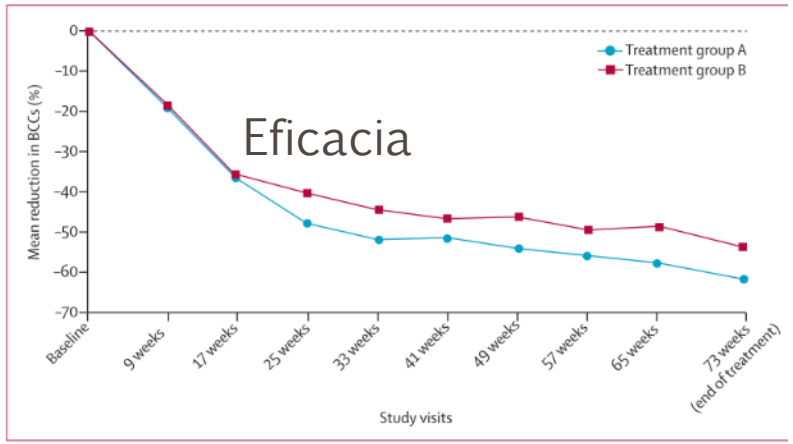


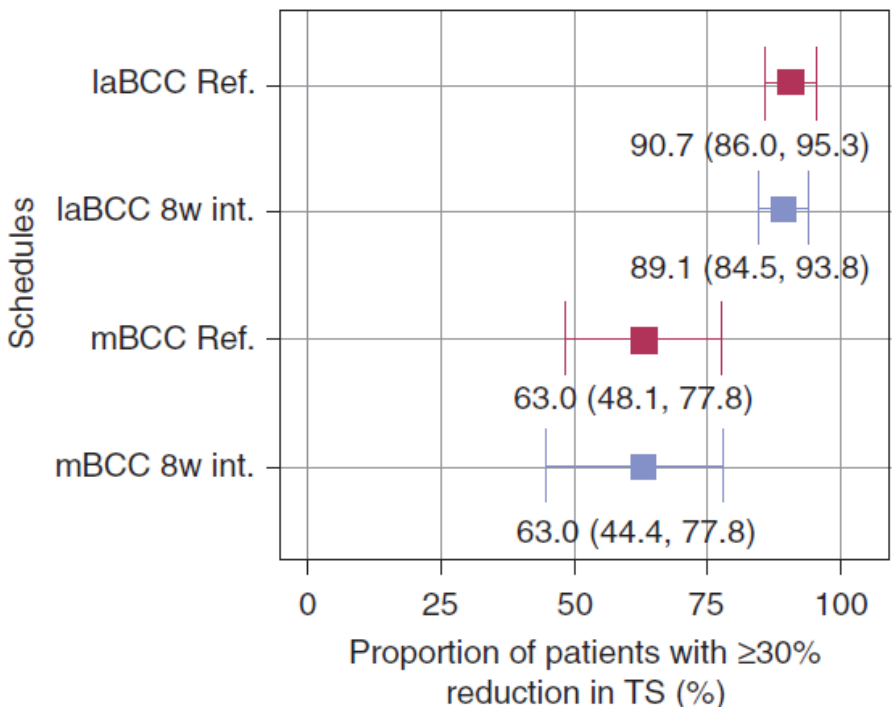
Figure 3: Mean percentage reduction from baseline in the number of clinically evident basal-cell carcinomas

1. Dréno B *et al. Lancet Oncol*

Vismodegib Efficacy in Advanced Basal Cell Carcinoma Maintained with 8-Week Dose Interruptions: A Model-Based Evaluation

JID Open

Journal of Investigative Dermatology (2021) **141,** 930–933; doi:10.1016/j.jid.2020.07.036



Pascal Chanu[1,*], *Luna Musib*[2], *Xin Wang*[2], *Sravanthi Cheeti*[2], *Sandhya Girish*[2], *Rene Bruno*[3], *Tong Lu*[2], *Josina Reddy*[4], *Jin Y. Jin*[2,5] and *Ivor Caro*[4,5]

[1]*Department of Clinical Pharmacology, Genentech/Roche, Lyon, France;* [2]*Department of Clinical Pharmacology, Genentech, Inc, South San Francisco, California, USA;* [3]*Department of Clinical Pharmacology, Genentech/Roche, Marseille, France; and* [4]*Product Development Oncology, Genentech/Roche, South San Francisco, California, USA*

[5]*These authors contributed equally to this work.*

[*]*Corresponding author e-mail: pascal.chanu@roche.com*

¿En definitiva, cuando escogemos los IHH en práctica clínica?

¿Qué recomendamos?

Cirugía agresiva pero factible….:

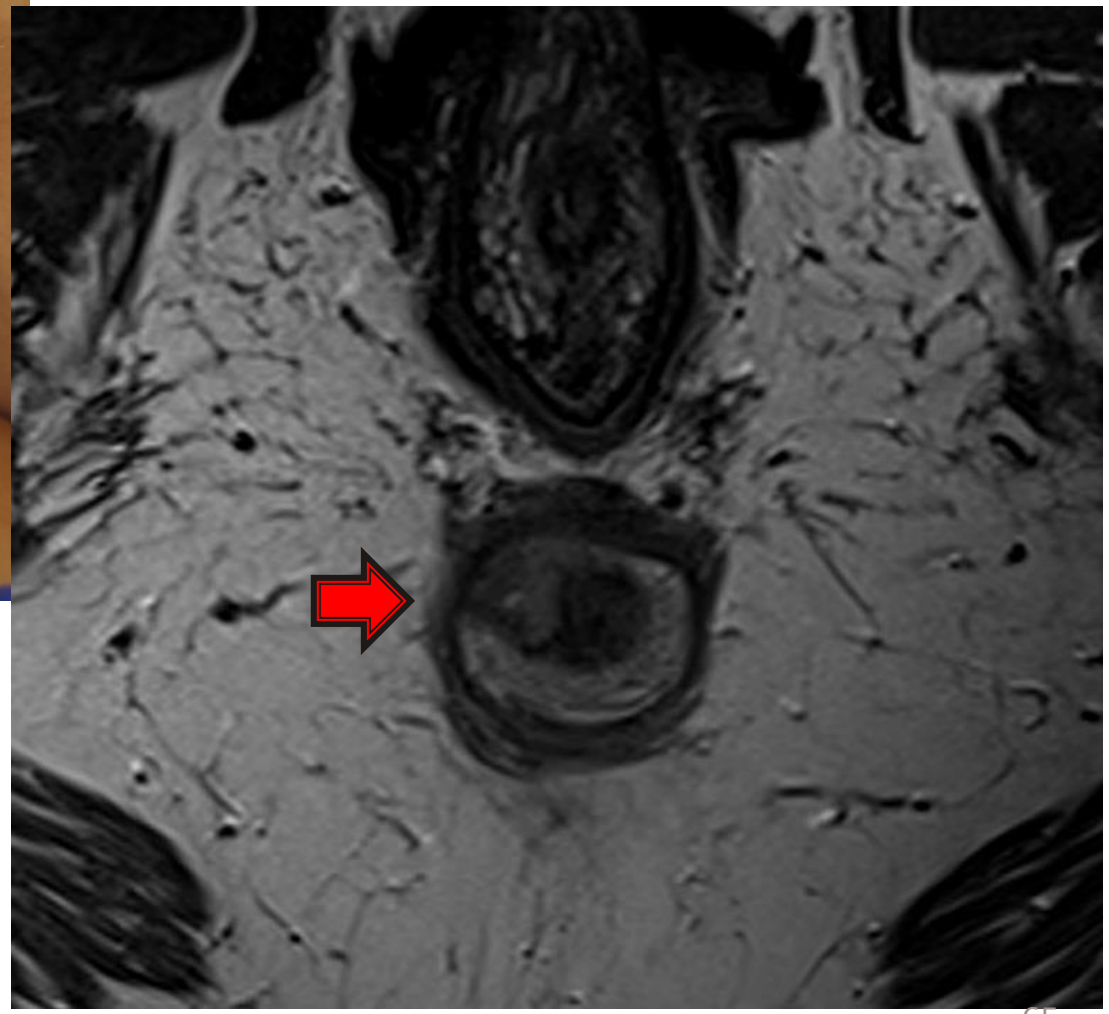
-Pacientes **jóvenes:** Recomendamos la Cirugía.

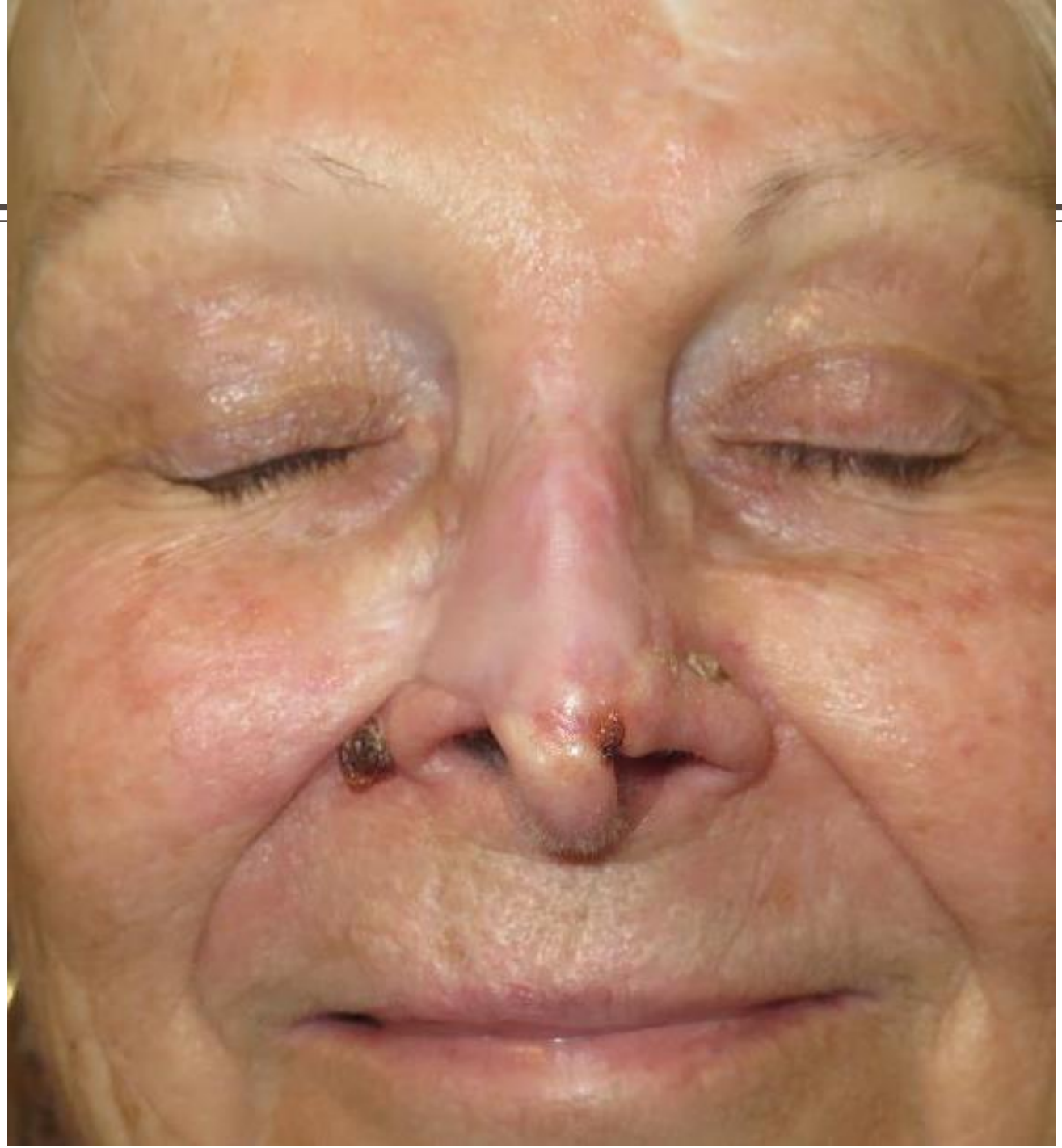
En tumores expansivos plantear IHH en neoadyuvancia

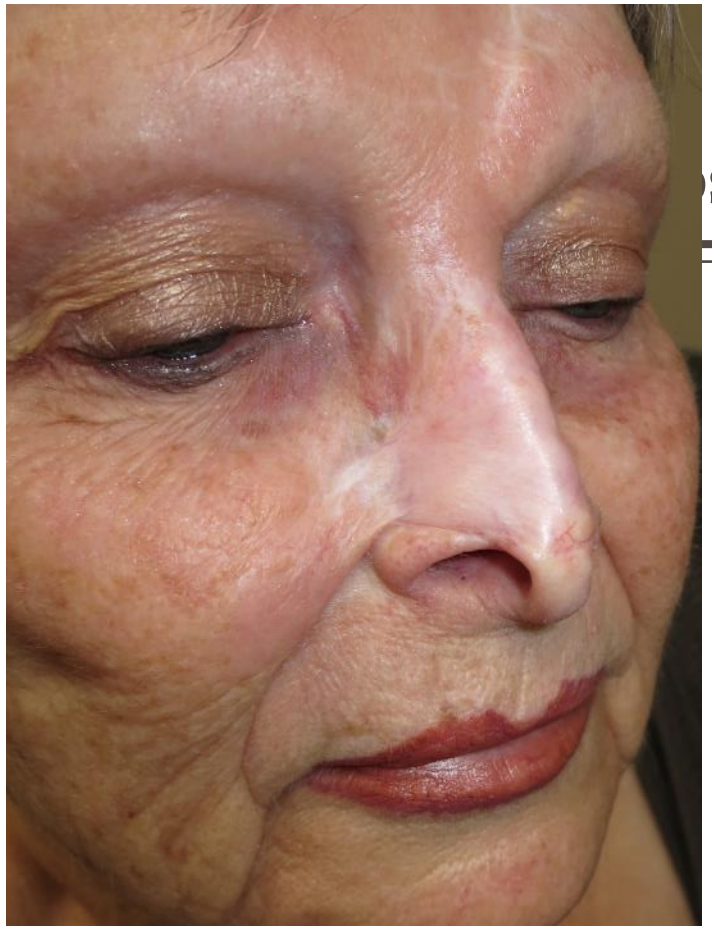
-**Edad avanzada**, ECOG >2, tumores múltiples ancianos, Gorlin: Planteamos IHH como primera opción.

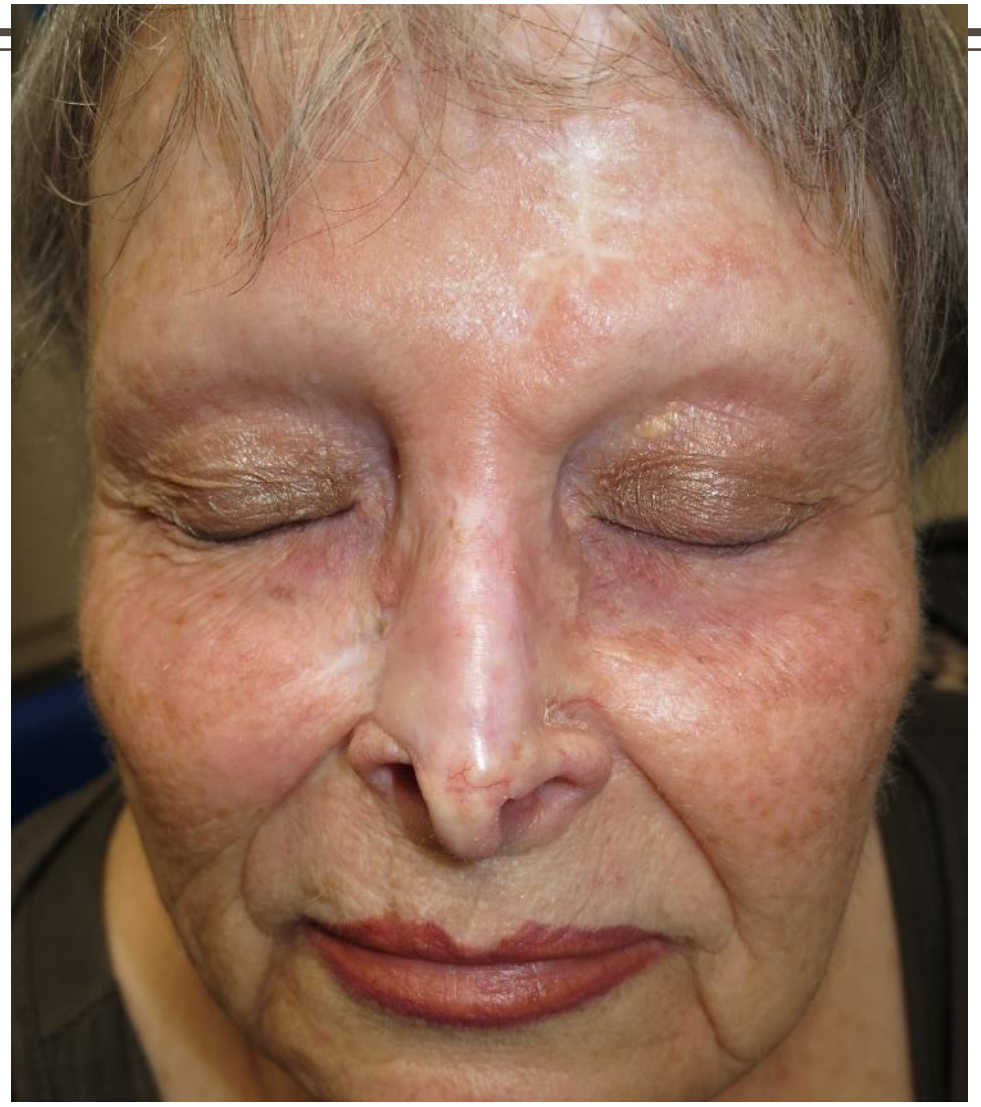
Inoperables (mutilación, co-morbilidades, preferencia paciente..):

-RDT/IHH



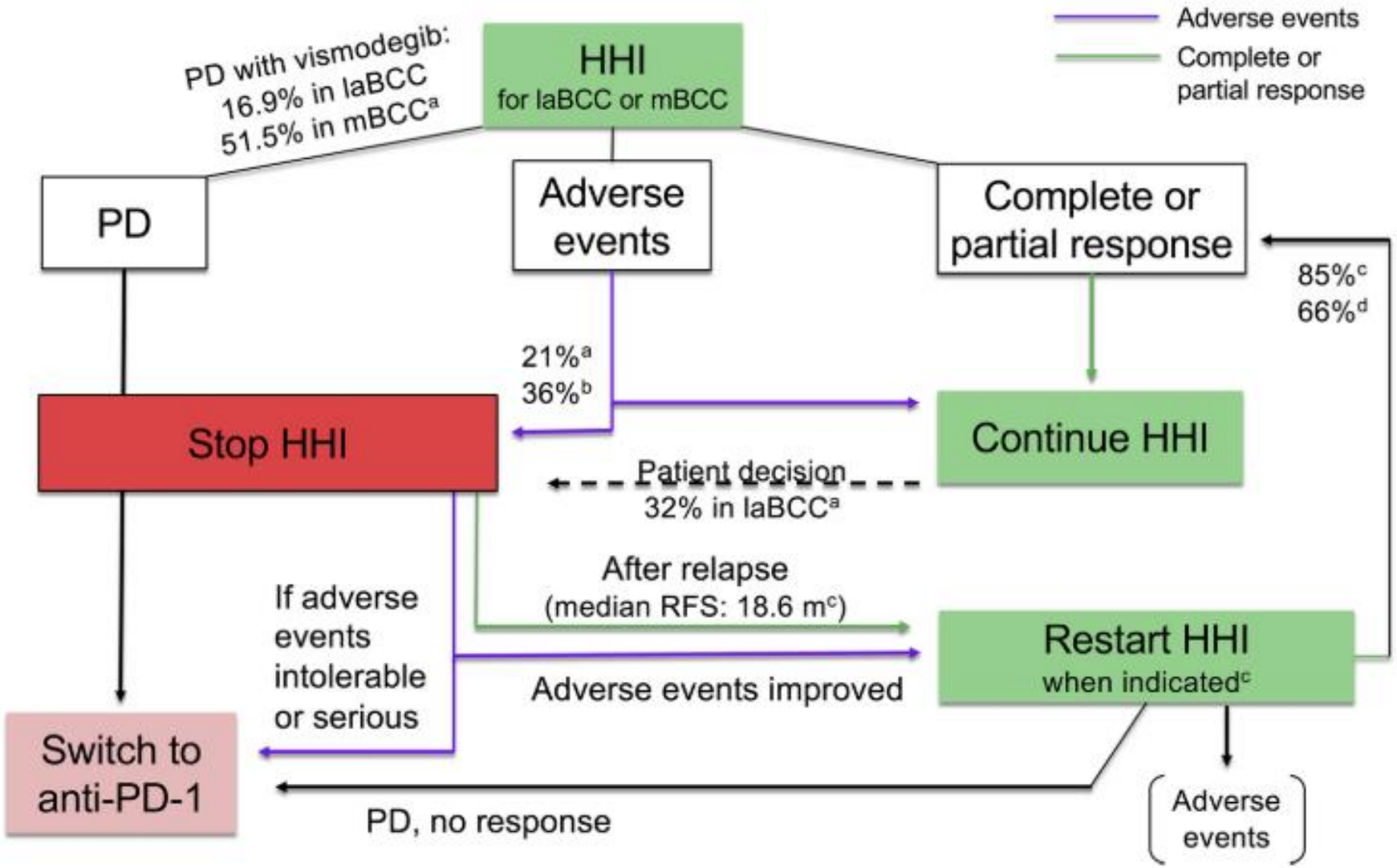






SONIDEGIB
DICIEMBRE 2023

VISMODEGIB



Dessinioti and Stratigos. ***Immunotherapy and its timing in advanced basal cell carcinoma treatment.*** *Dermatol Pract Concept 2023.*

¿Inducen la aparición de carcinoma escamoso cutáneo los IHH?

Real Life Xarxa Catalana

Dermatology. 2023;239(5):685-693. doi: 10.1159/000530813. Epub 2023 May 31.

Real-World Experience with Vismodegib on Advanced and Multiple BCCs: Data from the RELIVIS Study

Verónica Ruiz-Salas [1], Sebastian Podlipnik [2 3], Alejandra Sandoval-Clavijo [2 3], Onofre Sanmartin-Jiménez [4], Eduardo Bernia-Petit [4], Montserrat Bonfill-Ortí [5], Patricia Bassas-Freixas [6], Mireia Yebenes-Marsal [7], Ángeles Flórez-Menéndez [8], Joaquim Solá-Ortigosa [9], Miquel Just-Sarobé [10], Rafael Aguayo-Ortiz [11], Emili Masferrer I Niubó [12], Mónica Quintana-Codina [13], Gustavo Deza [14], Ane Jaka [15], Maria José Fuentes [15], Javier Cañueto [16], Agustí Toll [2 3]

Carcinomas escamosos:

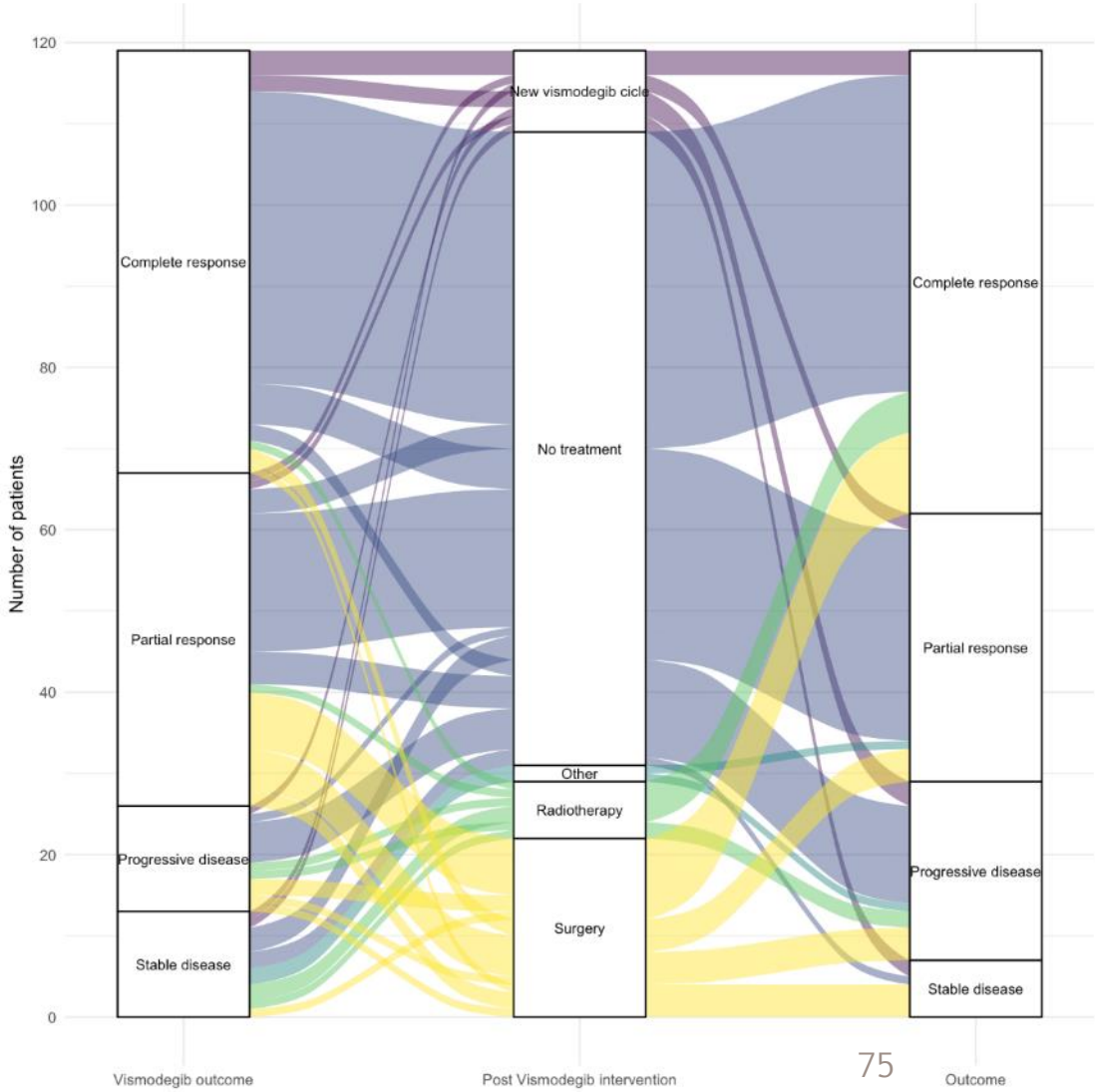
- 12%
- 58% invasivos
- Fuera de área de CBC 63,5%

NEOADYUVANCIA

Real Life Vismodegib

- 133 pacientes
- Respuestas parciales (RP): 31,6%
- Respuestas completas: (RC): 45,9%
  - Recurrencias: 31 %
- **34% otros tratamientos post vismodegib.**

(**42,5% de las RP**, 56% de las recaídas tras RC)



NEOADYUVANCIA PRE-CIRUGÍA

Fig. 2. BCC of right forehead and upper eyelid with orbital invasion (case 1). Pre-vismodegib (A) and 4 months since treatment initiation (B). C, One year later.

Periocular and Orbital laBCC (n=15)

67% COMPLETE RESPONSE (10)

20% PARTIAL RESPONSE (3)

13% PROGRESSION AFTER PARTIAL RESPONSE (2)

-1 progressión=Exanteration

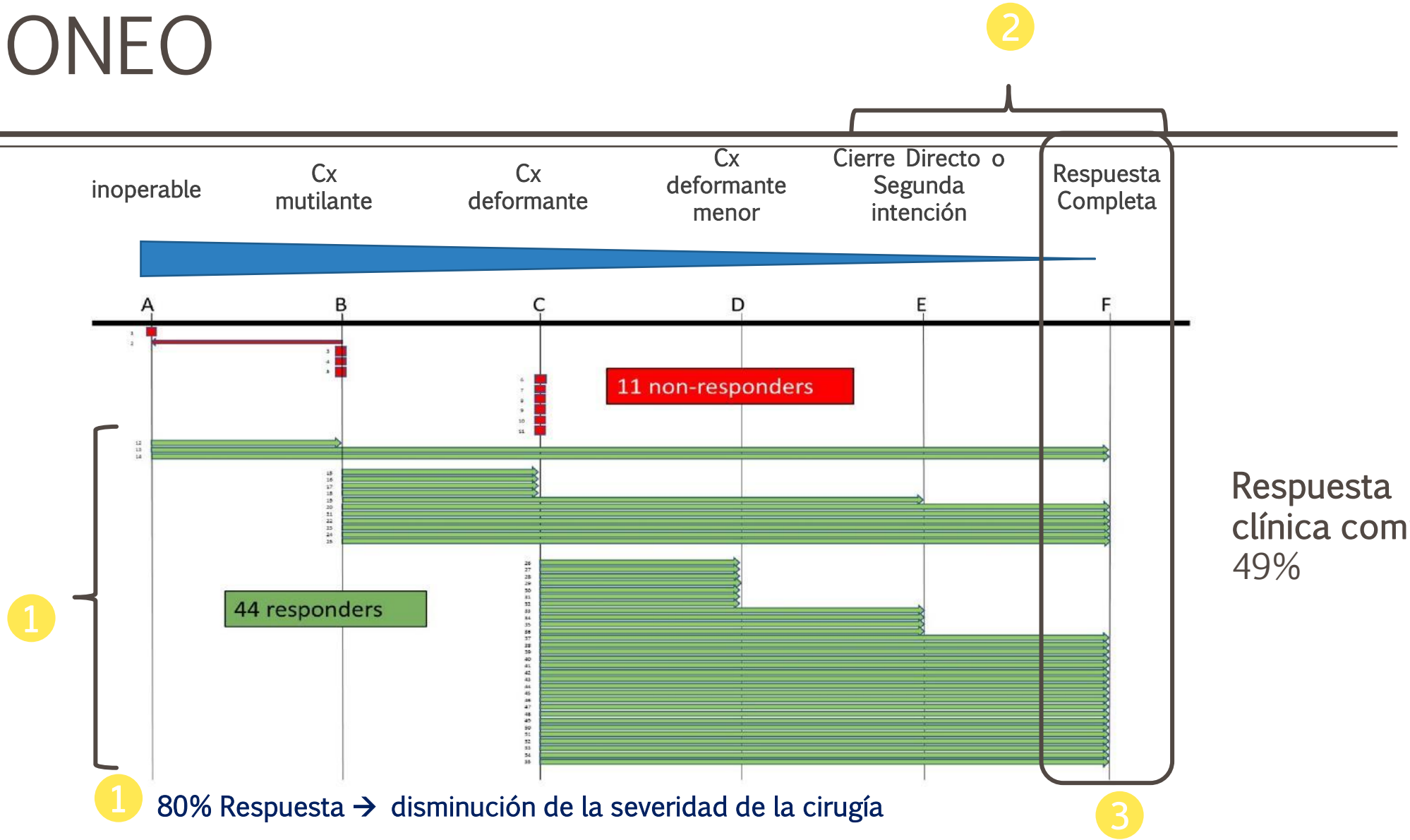
-1 intervention
-2 observation

Exanteration x 2

3/10 patients with orbital invasion required exanteration

Wong et al, PRSGlobal open 2017

VISMONEO

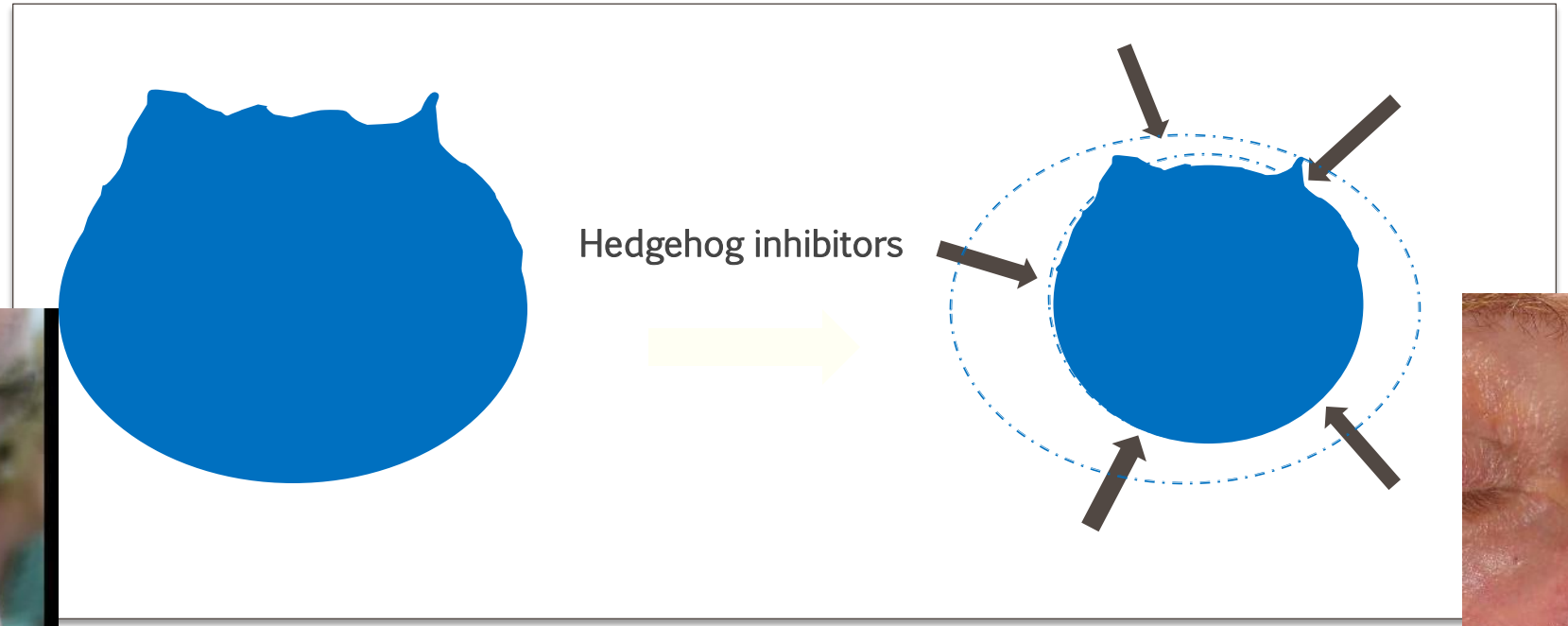


Respuesta clínica completa: 49%

1. 80% Respuesta → disminución de la severidad de la cirugía
2. 58% Sutura sencilla y respuesta completa
3. 49% Respuesta Completa → se evita la cirugía

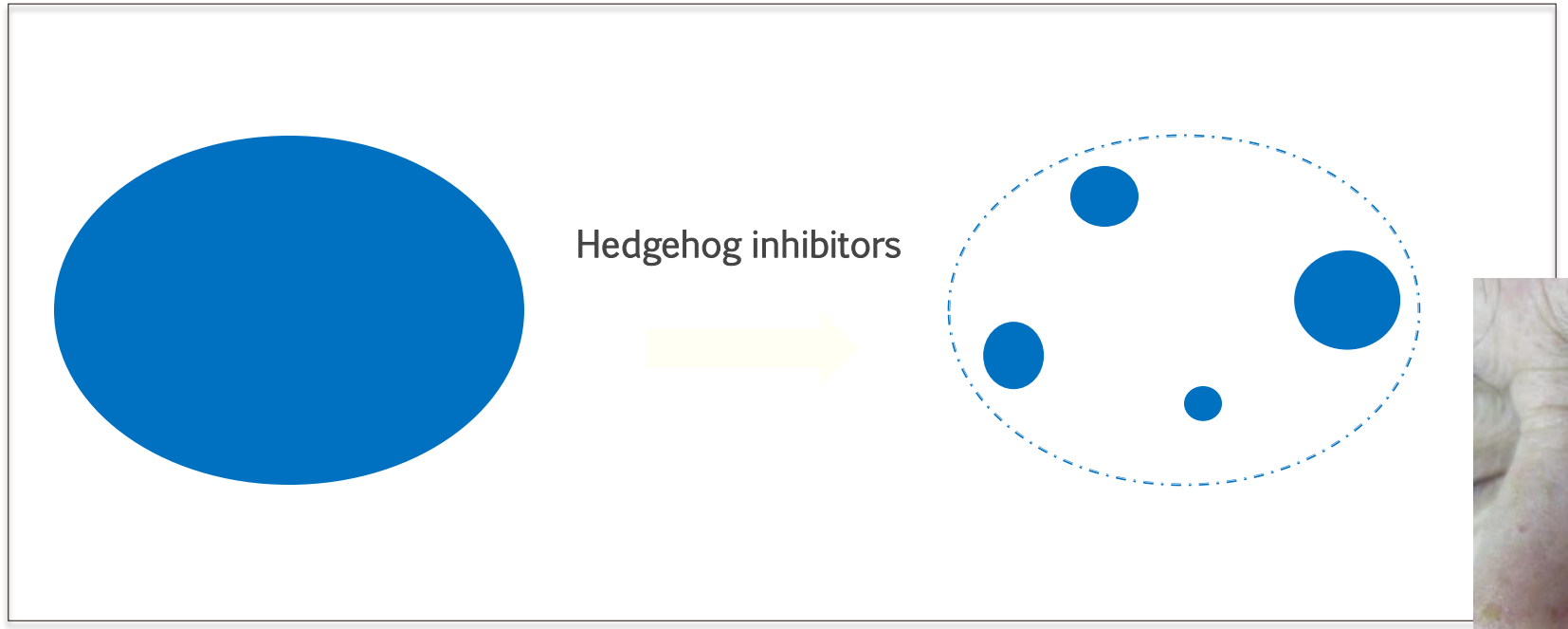
J Clin Oncol 36, 2018 (suppl; abstr 9509) ASCO 2018, L Mortier

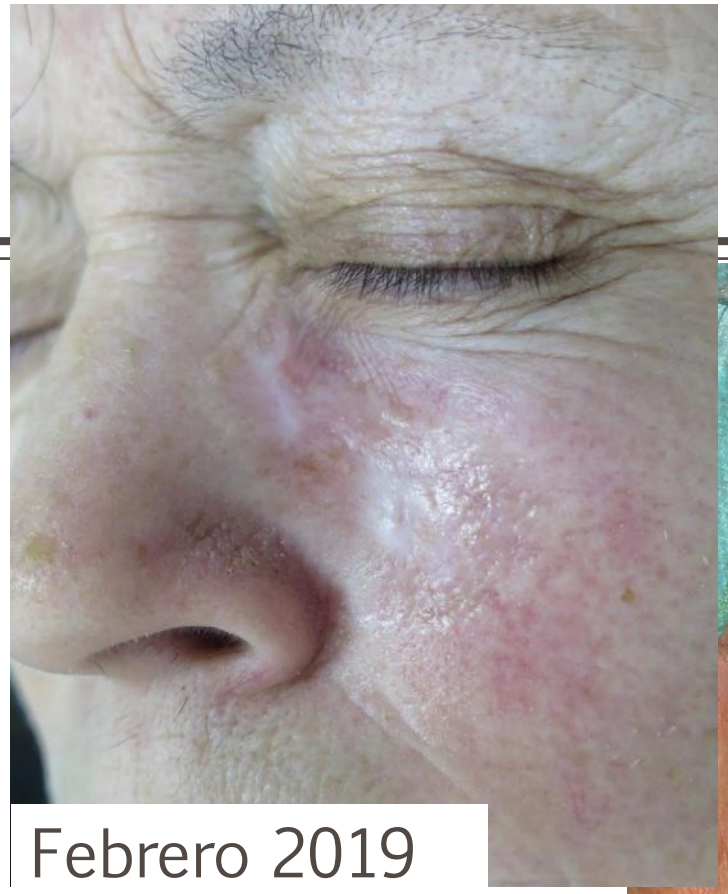
Modelos de respuesta a inhibidores de hedgehog



9 meses
Vismodegib

Modelos de respuesta a inhibidores de hedgehog





Febrero 2019

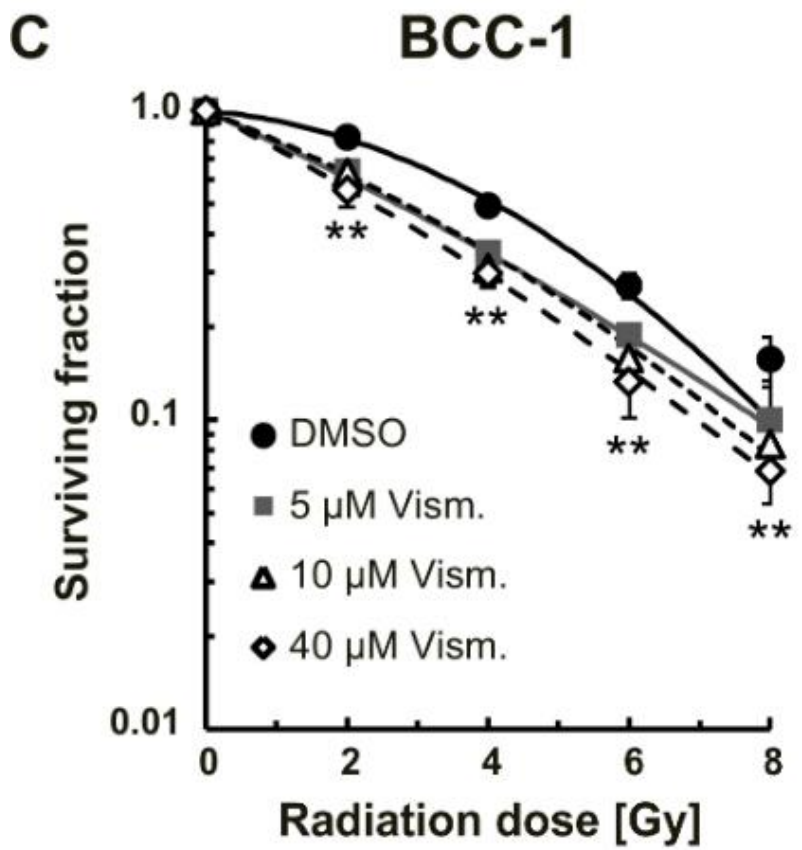
Abril 2019

¿Facilitan los IHH la respuesta a la RDT?

Int J Mol Sci. 2018 Sep; 19(9): 2485.
Published online 2018 Aug 23. doi: 10.3390/ijms19092485
PMCID: PMC6164565
PMID: 30142876

Radiation Sensitization of Basal Cell and Head and Neck Squamous Cell Carcinoma by the Hedgehog Pathway Inhibitor Vismodegib

Stephanie Hehlgans,[1,*†] Patrick Booms,[2,†] Ömer Güllülü,[1] Robert Sader,[2] Claus Rödel,[1] Panagiotis Balermpas,[1] Franz Rödel,[1,†] and Shahram Ghanaati[2,†]



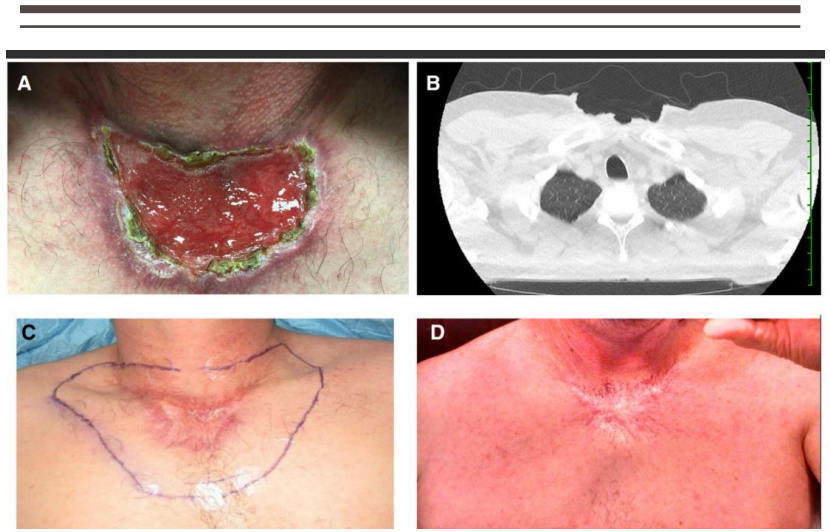
Oncologist. 2021 Dec;26(12):e2247-e2253. doi: 10.1002/onco.13959. Epub 2021 Sep 14.

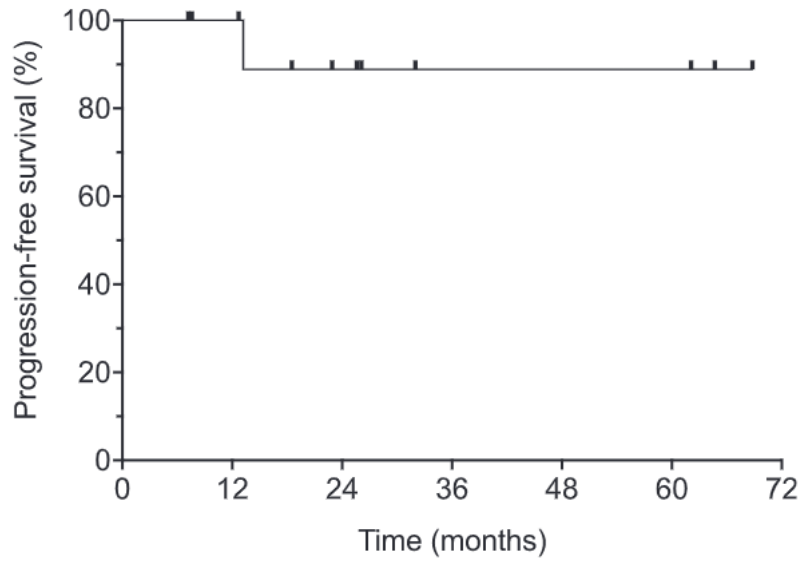
Hedgehog Inhibitor Induction with Addition of Concurrent Superficial Radiotherapy in Patients with Locally Advanced Basal Cell Carcinoma: A Case Series

Joshua P Weissman [1 2], Wolfram Samlowski [2 3 4], Raul Meoz [2 3 4]

UPN	Age	Sex	Ethnicity	BW stage	Site	Comorbidities	HHI	HHI dose (mg/d)	HHI duration (months)	RT fx (cGy)	RT dose (cGy)	Elapsed time (days)
1	72	F	W	T3	Head	AF	S	200	4.5	250	5,500[a]	30
2	56	M	W	T3	Head	Smoker	S	200	5	200	6,600	48
3	87	F	W	T2b	Head	Stroke	S	200	2.5	200	5,075[a]	53
4	88	M	W	T3	Head	none	S	200	3.8	250	5,750[a]	31
5	95	F	H	T3	Head	N/A	S	200	3.3	250	5,000[a]	29
6	60	F	W	T2b	Head	N/A	S	200	2.1	200	5,000[a]	30
7	71	M	W	T3	Head	Stroke, CAD, colon CA	S	200	6.3	200	6,400[a]	52
8	61	M	W	T3	Shoulder	none	S	200	2.6	250	5,000[a]	28
9	79	M	W	T3	Ankle	none	V	150	11.7	200	5,000[a]	28
10	45	M	W	T3	Chest	Smoker	V	150	2.7	200	6,000[a]	35
11	55	M	W	T3	Head	none	V	150	6.8	200	6,600	76
12	61	M	W	T3	Head	Smoker, bladder CA	V	150	4.2	250	5,500[a]	30

[a]Electron beam therapy.





- 12 pacientes.
- Retrospectivo.
- T3= tumores > o igual 4 cms
- PFS 40 meses: 89%

ENSAYOS PROSPECTIVOS

- 2 BRAZOS:
  - INHIBIDOR DE HEDGEHOG VS INHIBIDOR HEDGEHOG+ RADIOTERAPIA.
  - RDT VS INHIBIDOR DE HEDGEHOG + RDT

ENSAYOS PROSPECTIVOS

- 2 BRAZOS:
  - INHIBIDOR DE HEDGEHOG VS INHIBIDOR HEDGEHOG + RADIOTERAPIA.
  - ~~RDT VS INHIBIDOR DE HEDGEHOG + RDT~~

ENSAYOS PROSPECTIVOS

- 2 BRAZOS:
  - INHIBIDOR DE HEDGEHOG VS INHIBIDOR HEDGEHOG + RADIOTERAPIA.
  - ~~RDT VS INHIBIDOR DE HEDGEHOG + RDT~~

- 1 BRAZO:
  - RADIOTERAPIA + VISMODEGIB. 1 BRAZO.
  - VISMODEGIB + RADIOTERAPIA. 1 BRAZO.

J Clin Oncol. 2024 Apr 17:JCO2301708. doi: 10.1200/JCO.23.01708. Online ahead of print.

Phase II, Single-Arm Trial of Induction and Concurrent Vismodegib With Curative-Intent Radiation Therapy for Locally Advanced, Unresectable Basal Cell Carcinoma

Christopher A Barker [1], Suzanne Dufault [2], Sarah T Arron [3], Alan L Ho [4], Alain P Algazi [5],

- 24 pacientes.
- 3 meses inducción con vismodegib
- Control locoregional 91% al año.
- Supervivencia libre de progresión 5 años: 78%

Diciembre 2022 INICIO DE VISMODEGIB

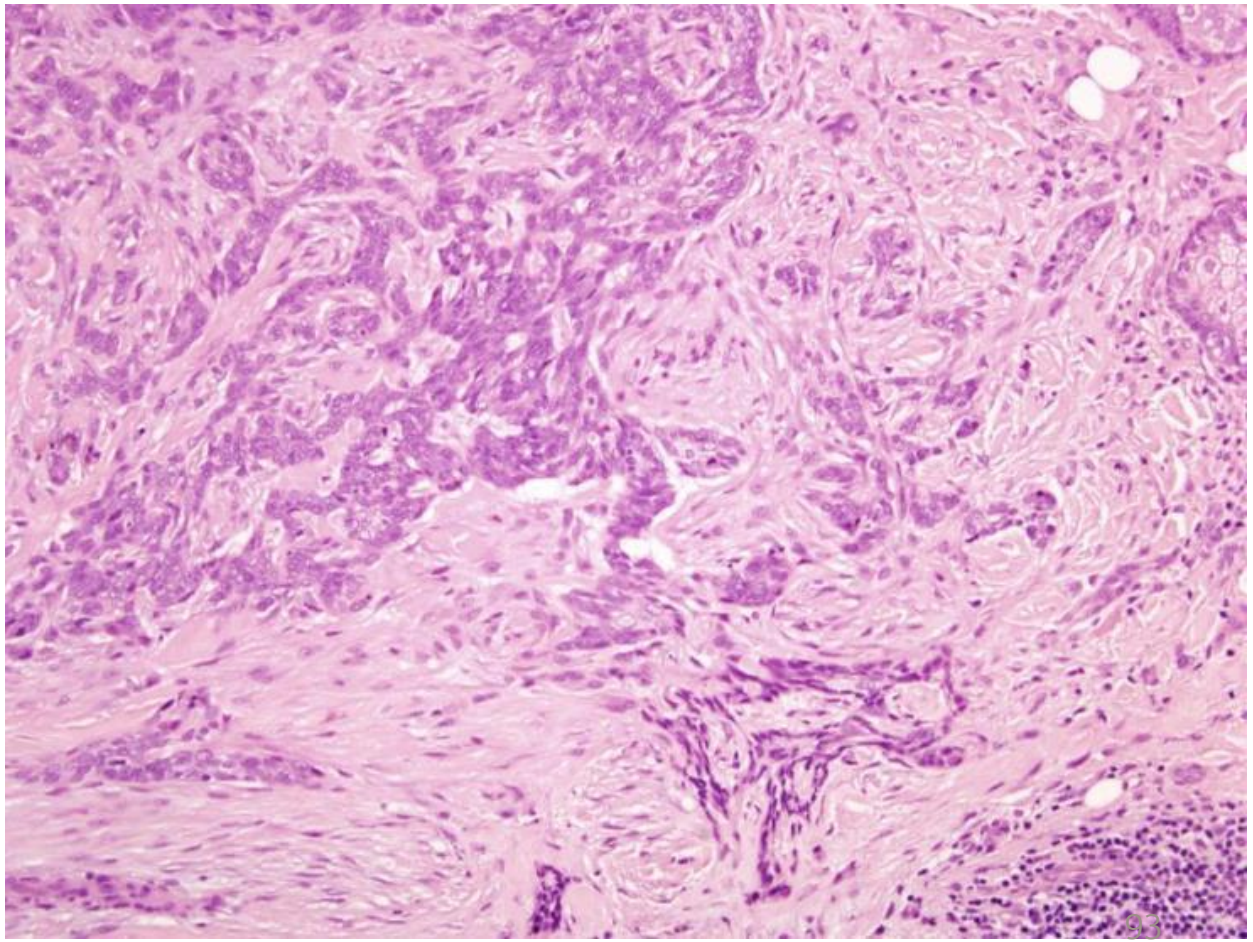
Agosto 23

POST-RDT. ORTOVOLTAJE. 11 GY X 3

Inmunoterapia en carcinoma basocelular ¿Funciona?

Inmunoterapia en carcinoma basocelular

- Tumor con carga mutacional alta.
- Poco “inmunoreactivo” (frío)



Clinical Trial > Lancet Oncol. 2021 Jun;22(6):848-857. doi: 10.1016/S1470-2045(21)00126-1.
Epub 2021 May 14.

Cemiplimab in locally advanced basal cell carcinoma after hedgehog inhibitor therapy: an open-label, multi-centre, single-arm, phase 2 trial

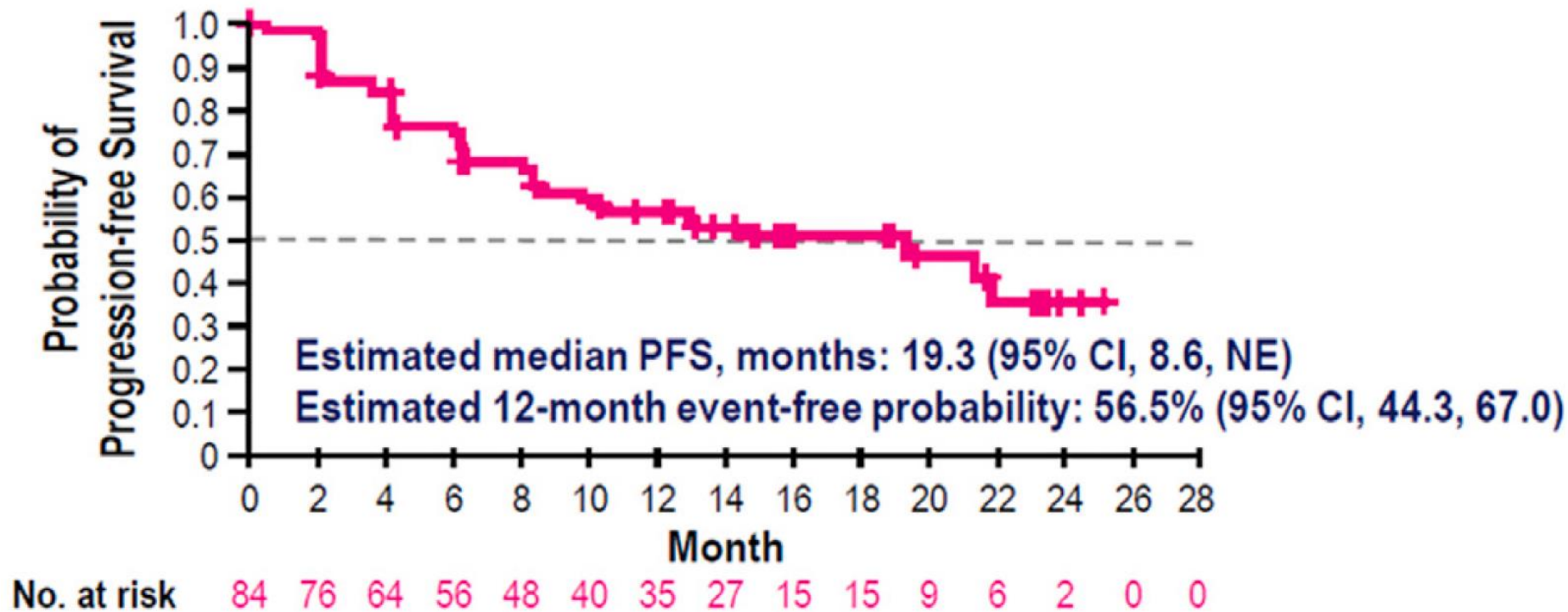
Alexander J Stratigos [1], Aleksandar Sekulic [2], Ketty Peris [3], Oliver Bechter [4], Sorilla Prey [5],

- Fase II.
- Cemiplimab 350 mgs/3 semanas.
- 84 pacientes con CBCla. Media seguimiento 15 meses.
- **31% respuestas objetivas** (6% RC; 25% RP)
- Tiempo medio a respuesta: **4,3 meses** (CEC 1,9 meses)
- Independiente de expresión de PD-L1
- Efectos adversos grado 3-4: 48%. HTA, colitis, prurito…

Clinical Trial > Lancet Oncol. 2021 Jun;22(6):848-857. doi: 10.1016/S1470-2045(21)00126-1. Epub 2021 May 14.

Cemiplimab in locally advanced basal cell carcinoma after hedgehog inhibitor therapy: an open-label, multi-centre, single-arm, phase 2 trial

Alexander J Stratigos [1], Aleksandar Sekulic [2], Ketty Peris [3], Oliver Bechter [4], Sorilla Prey [5],



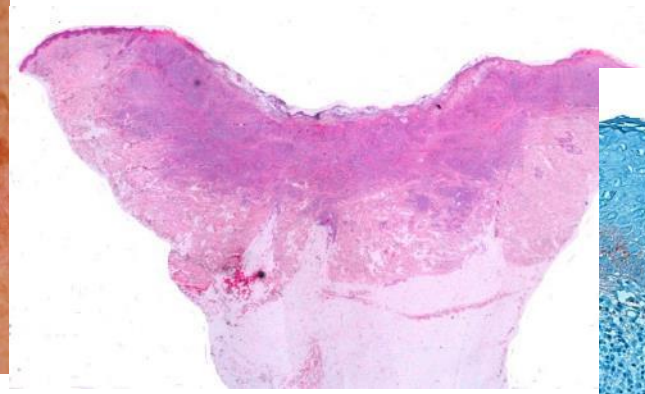
Regeneron - R2810-ONC-1620

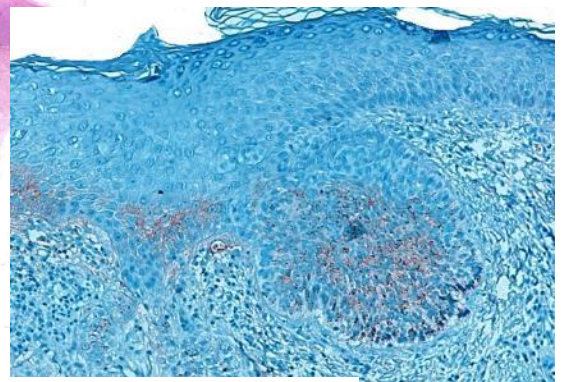
31/7/2018


22/10/2020

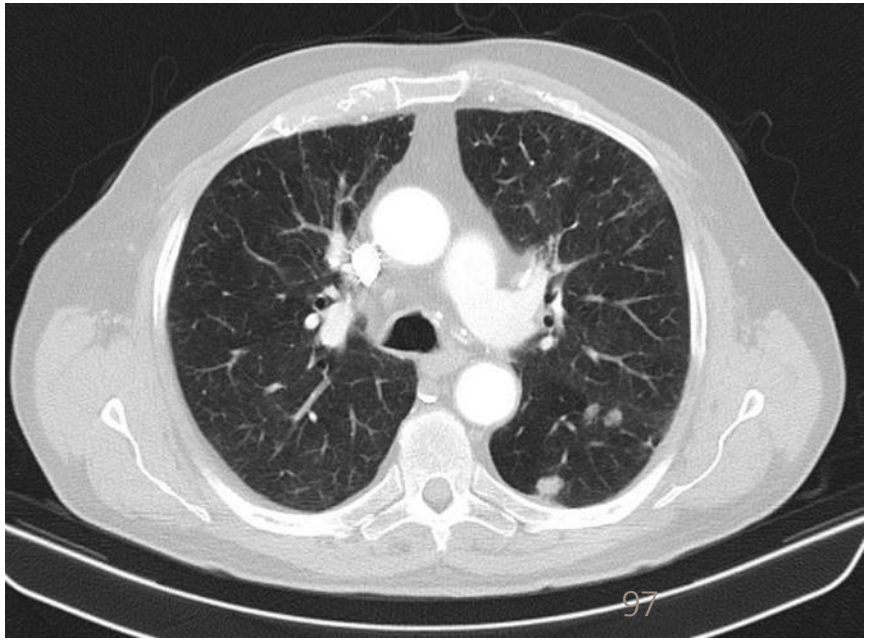
Regeneron - R2810-ONC-1620

- Varón de 80 años.
  - Carcinoma basocelular con diferenciación neuroendocrina con metástasis ganglionares y pulmonares.
  - Tratamiento previo con Vismodegib y QT con progresión

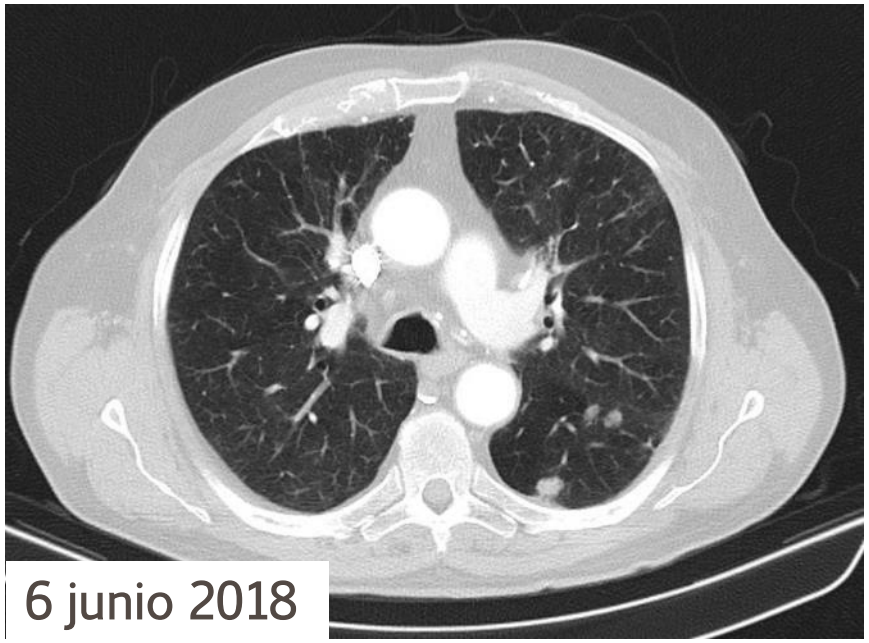




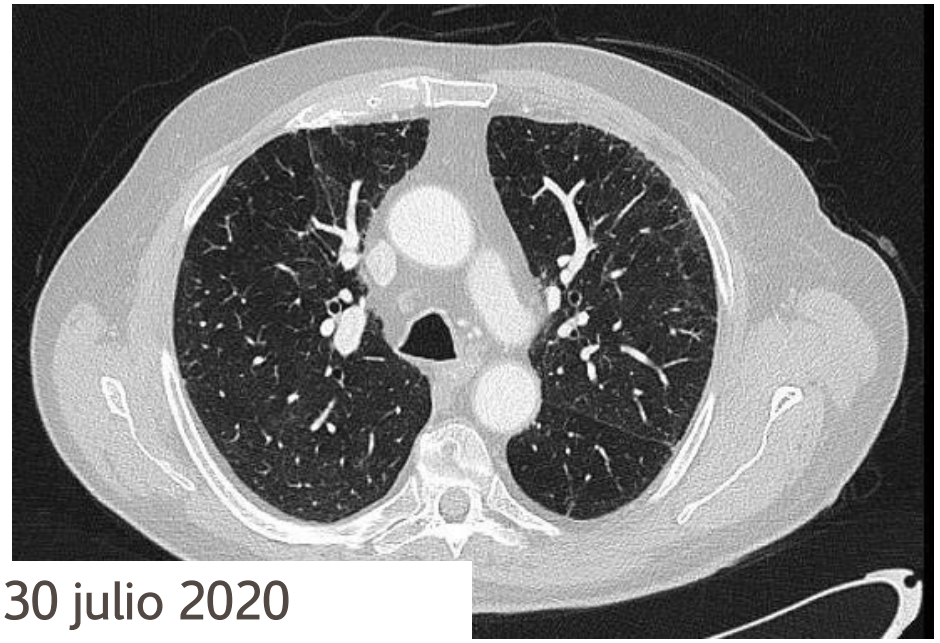
Cromogranina



Regeneron - R2810-ONC-1620



6 junio 2018



30 julio 2020

Tratamiento hasta marzo de 2020.

› Clin Exp Dermatol. 2024 Mar 18:llae099. doi: 10.1093/ced/llae099. Online ahead of print.

Metastatic basal cell carcinoma with neuroendocrine differentiation. Complete response to cemiplimab

Ignasi Marti-Marti [1], Susana Puig [1 2 3], Raquel Albero-González [4], Emili Masferrer [5], Pablo Iglesias [1], Javiera Pérez-Anker [1], Laura Serra-García [1], Xavier Tarroch [6], Neus Curcó [5], Agustí Toll [1]

Clinical Trial > Eur J Cancer. 2022 Dec;177:103-111. doi: 10.1016/j.ejca.2022.09.013.
Epub 2022 Oct 11.

Safety and efficacy of nivolumab, an anti-PD1 immunotherapy, in patients with advanced basal cell carcinoma, after failure or intolerance to sonic Hedgehog inhibitors: UNICANCER AcSé NIVOLUMAB trial

Marie Véron [1], Sylvie Chevret [2], Jean-Jacques Grob [3], Marie Beylot-Barry [4], Philippe Saiag [5],

- Fase II. 32 pacientes (29 CBCIa, 3 CBCm)
- Nivolumab.
- Evaluación semana 12:
  - RC: 3,1%
  - RP: 18,8%

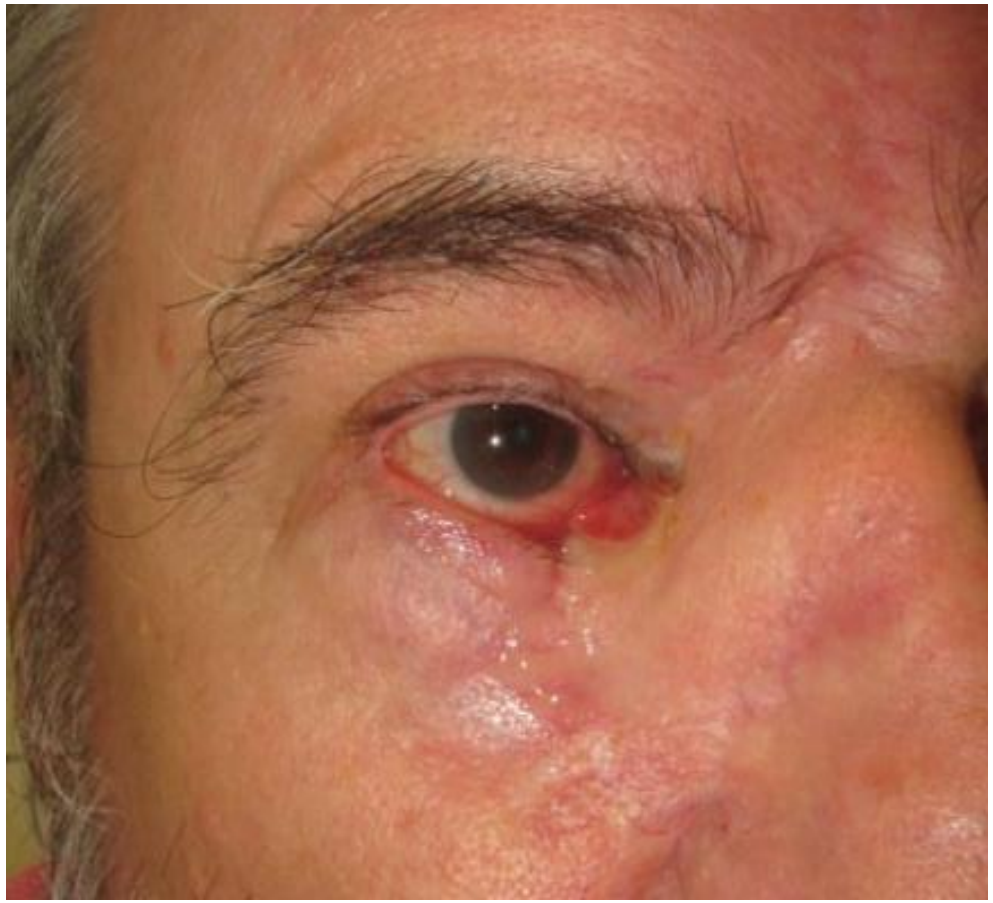
- Varón 70 años
- Sde depresivo.
- CBC no invasión órbita por RNM
- Vismodegib. Respuesta parcial.
- CMM.

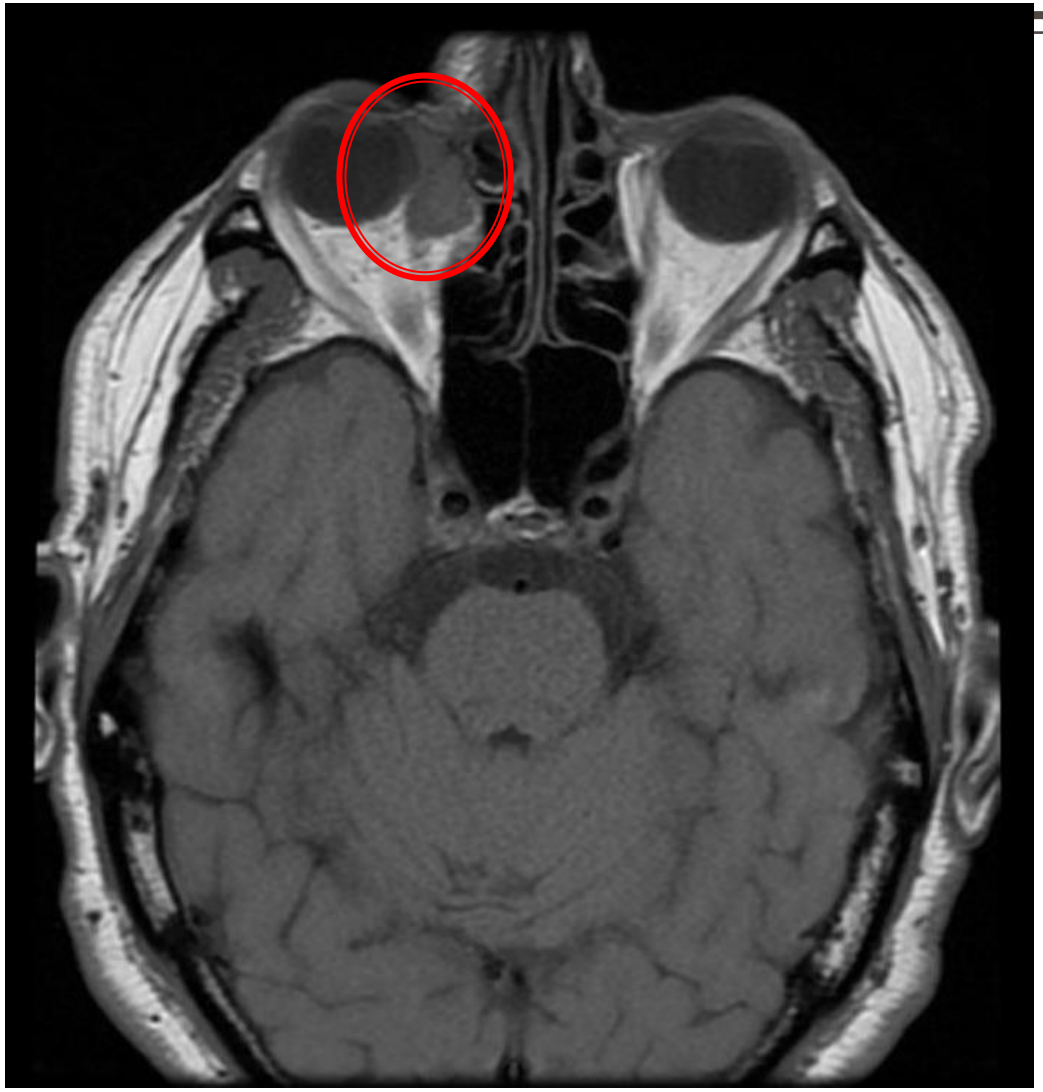
- Varón 70 años
- Sde depresivo.
- CBC no invasión órbita por RNM
- Vismodegib. Respuesta parcial.
- CMM. Márgenes afectos en profundidad
- Se propone enucleación en comité

Descartado por el paciente.

- Varón 70 años

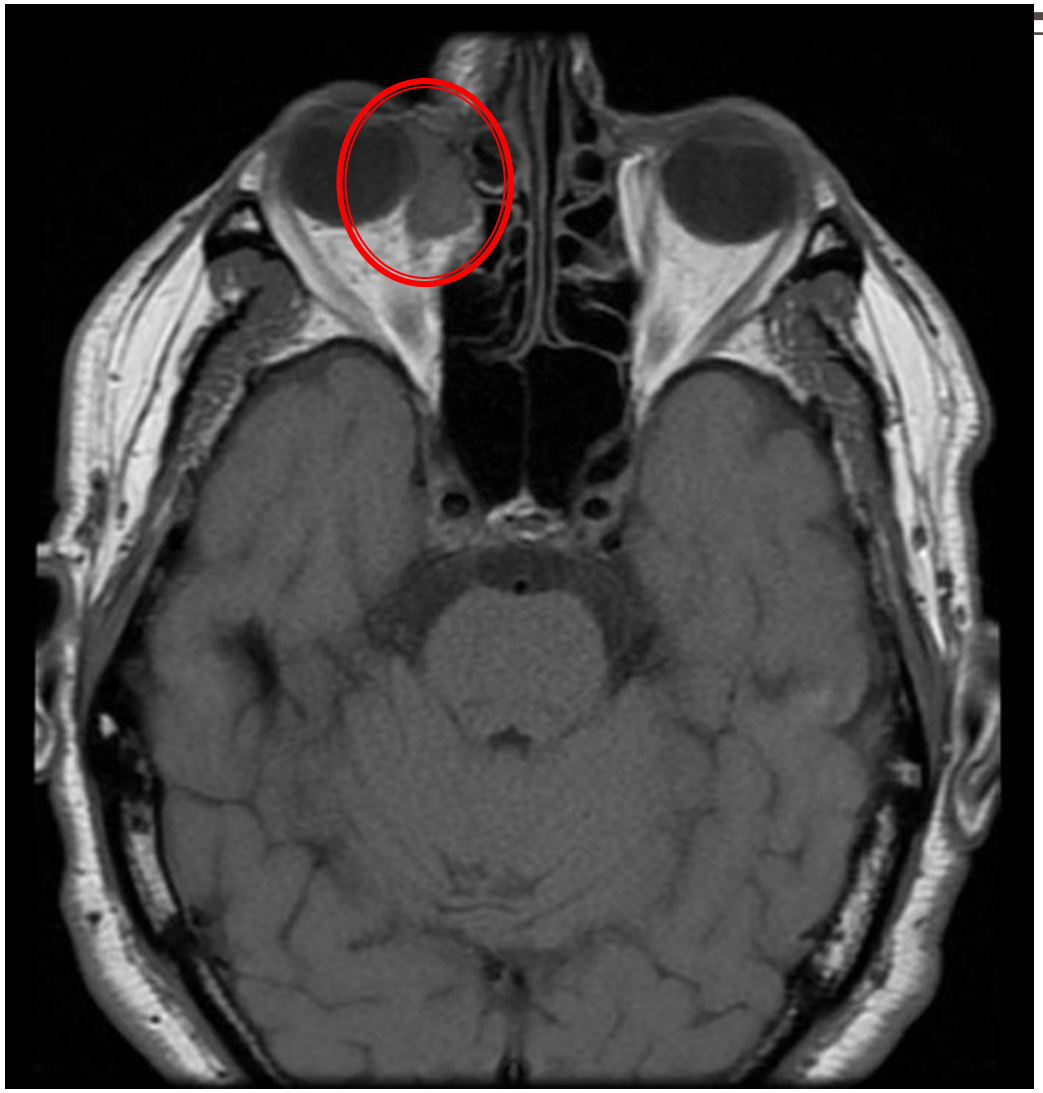
Recidiva a los 12 meses (Junio 2023) con confirmación histológica.





Julio 2023

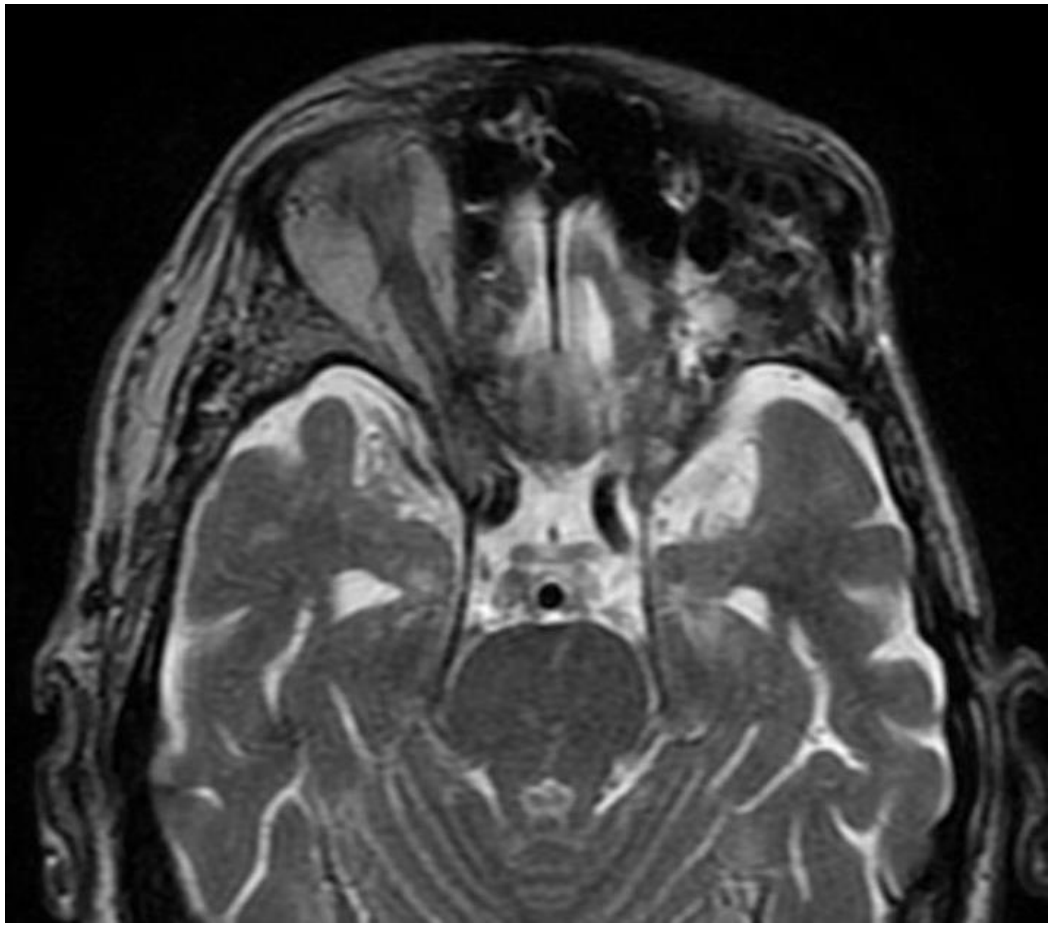
Nivolumab



Julio 2023

Marzo 2024

- Varón 80 años
- Tratamientos previos:
  - Cirugía/enucleación
  - Vismodegib.
  - Sonidegib



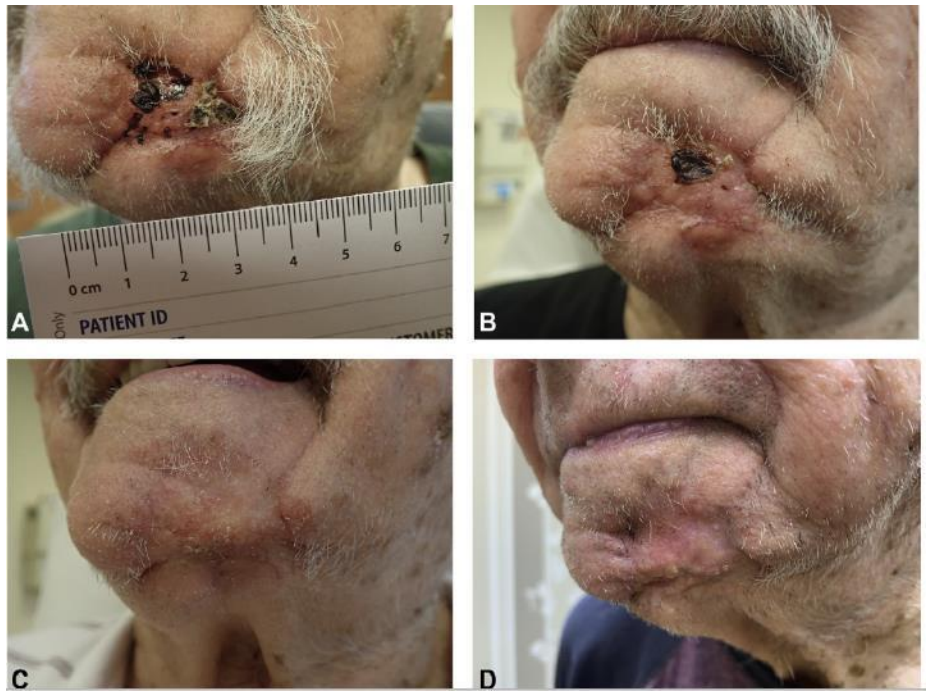
Pembrolizumab

Combinación de fármacos sistémicos. ¿Cuáles?

Case Reports > JAAD Case Rep. 2020 Nov 24;7:107-109. doi: 10.1016/j.jdcr.2020.11.014.
eCollection 2021 Jan.

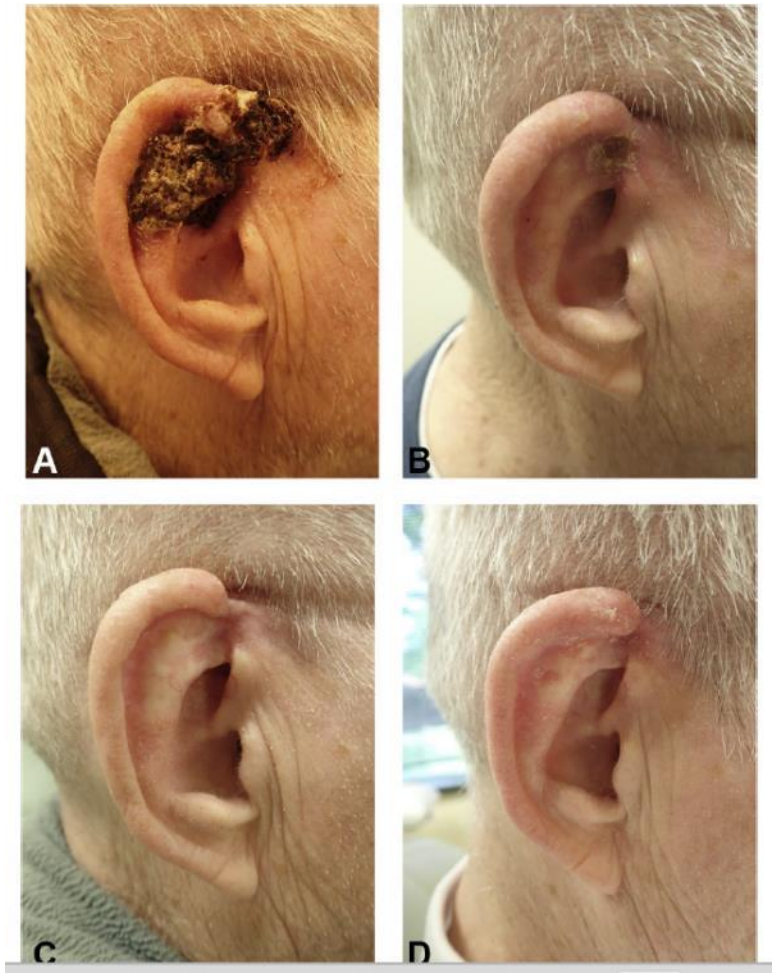
Vismodegib dose reduction effective when combined with itraconazole for the treatment of advanced basal cell carcinoma

Jaeyoung Yoon [1]



Vismodegib 150 / semana
Itraconazol 200/dia

X 28 semanas



Vismodegib 150 . 2 v/semana
Itraconazol 100/dia

X 21semanas

Ensayos clínicos activos en carcinoma basocelular

Tratamiento	BCC
Sonidegib+Cemiplimab	x
IFx-Hu2 vaccine	x
Nivolumab	x
Nivolumab+Relatlimab	x
T-VEC	x

Neoadyuvancia	BCC
Pembrolizumab	x
Cemiplimab	x

Muchas gracias

atoll@clinic.cat

Universitat de Barcelona

CLÍNIC BARCELONA Hospital Universitari