SARCOMAS ULTRARRAROS

Dr. Javier Martínez Trufero

Universidad Europea de Madrid (UEM)

Sev. De Oncología Médica,

Hospital Univ. Miguel Servet,

Zaragoza

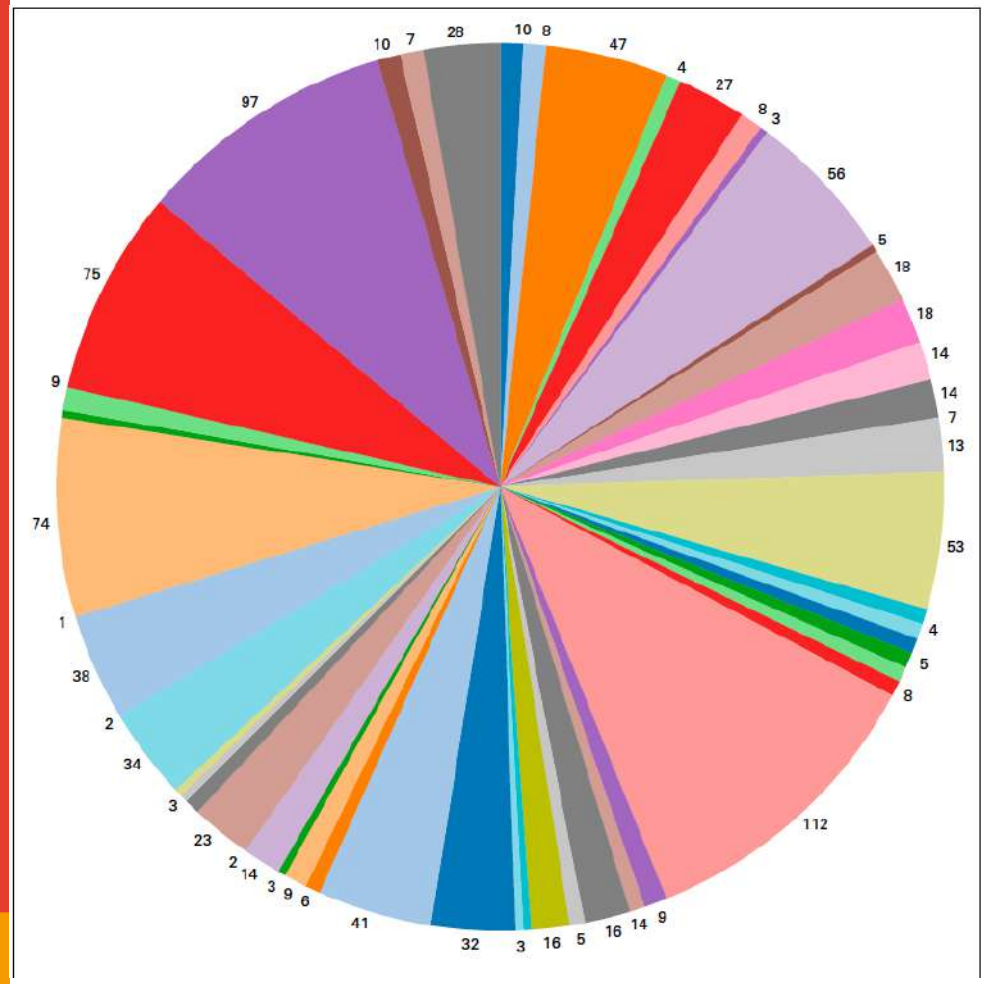
XIV CURSO AVANZADO DE SARCOMAS GEIS 2023

Universidad Europea

GEIS
GRUPO ESPAÑOL DE INVESTIGACIÓN EN SARCOMAS

Máster en Tumores Musculoesqueléticos

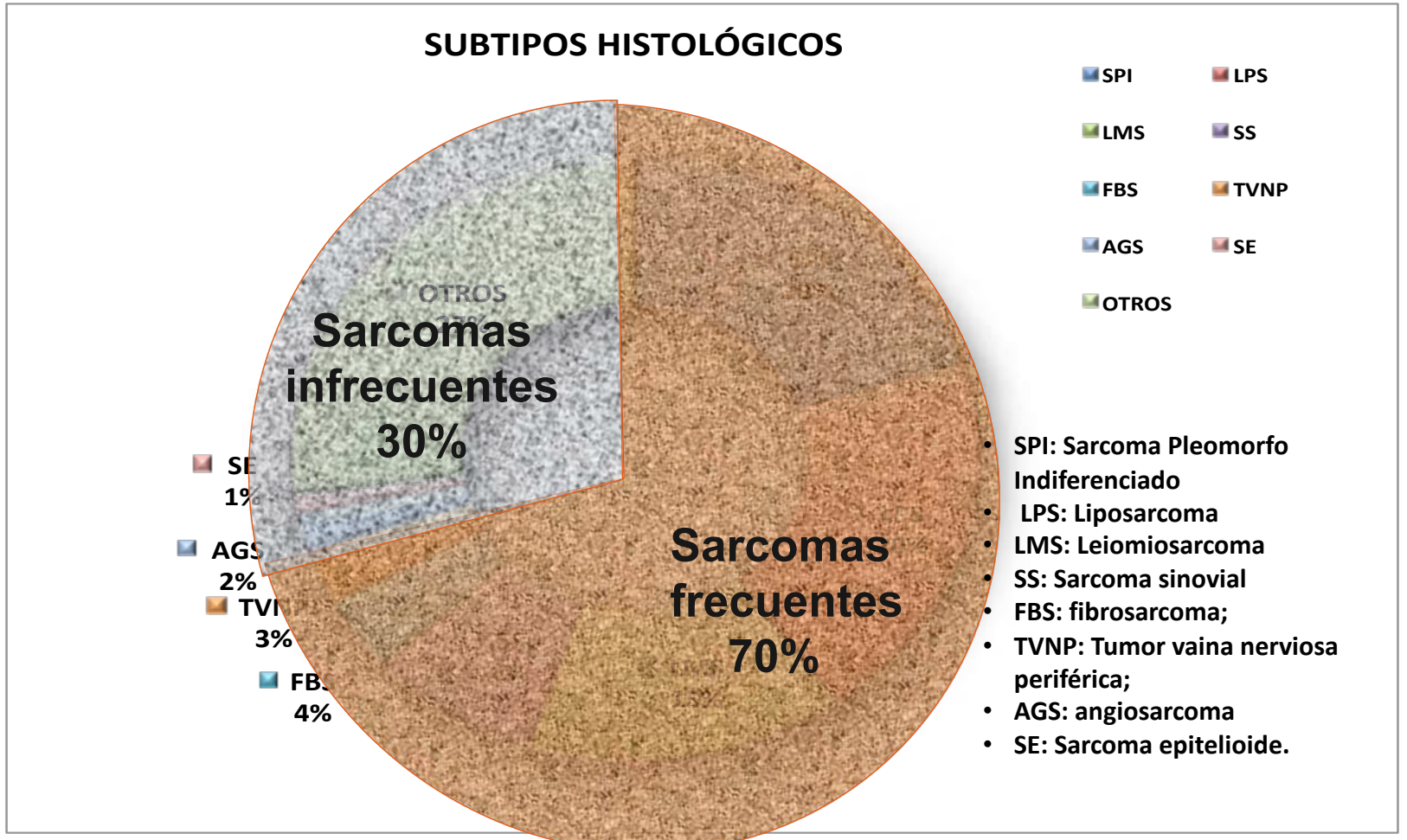
Subtipos de Sarcoma



- Alveolar rhabdomyosarcoma
- Alveolar soft part sarcoma
- Angiosarcoma
- Chondroblastic osteosarcoma
- Chondrosarcoma
- Clear cell sarcoma
- Dedifferentiated chondrosarcoma
- Dedifferentiated liposarcoma
- Dermatofibrosarcoma protuberans
- Desmoid/aggressive fibromatosis
- Desmoplastic small-round-cell tumor
- Embryonal rhabdomyosarcoma
- Endometrial stromal sarcoma
- Epithelioid hemangioendothelioma
- Epithelioid sarcoma
- Ewing sarcoma
- Extraskeletal myxoid chondrosarcoma
- Fibrosarcoma
- Follicular dendritic cell sarcoma
- Hemangioma
- Histiocytic dendritic cell sarcoma
- Inflammatory myofibroblastic tumor
- Intimal sarcoma
- Leiomyosarcoma
- Liposarcoma
- Low-grade fibromyxoid sarcoma
- Mesenchymal chondrosarcoma
- Metaplastic carcinosarcoma
- Myxofibrosarcoma
- Myxoid chondrosarcoma
- Myxoid/round-cell liposarcoma
- Ossifying fibromyxoid tumor
- Osteoblastic osteosarcoma
- Osteosarcoma
- Ovarian carcinosarcoma/malignant mixed mesodermal tumor
- Perivascular epithelioid cell tumor
- Pleomorphic liposarcoma
- Pleomorphic rhabdomyosarcoma
- Rhabdomyosarcoma
- Round cell sarcoma, NOS
- Sarcoma, NOS
- Sarcomatoid renal cell carcinoma
- Sclerosing epithelioid fibrosarcoma
- Secondary osteosarcoma
- Small cell osteosarcoma
- Solitary fibrous tumor/hemangiopericytoma
- Spindle cell rhabdomyosarcoma
- Synovial sarcoma
- Tenosynovial giant cell tumor diffuse type
- Undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma/high-grade spindle cell sarcoma
- Undifferentiated uterine sarcoma
- Uterine adenosarcoma
- Uterine carcinosarcoma/uterine malignant mixed müllerian tumor
- Uterine leiomyosarcoma
- Uterine perivascular epithelioid cell tumor
- Uterine sarcoma, other
- Well-differentiated liposarcoma

Carmagnani Pestana R, et al. JCO Precision Oncology April 25, 2019

Subtipos de Sarcoma

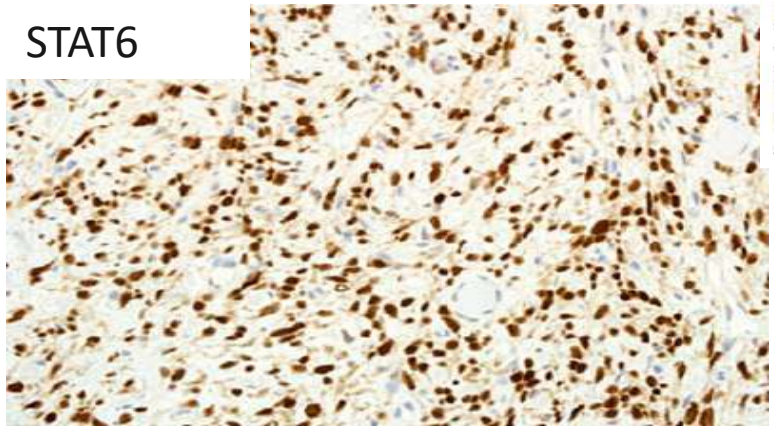


Carmagnani Pestana R, et al. JCO Precision Oncology April 25, 2019

Tumor fibroso solitario (TFS)

- Grupo de tumores .
- 5ª-6ª década . Igual ambos sexos .
- Sindrome de Doege-potter
- **Localizaciones:** serosas

STAT6

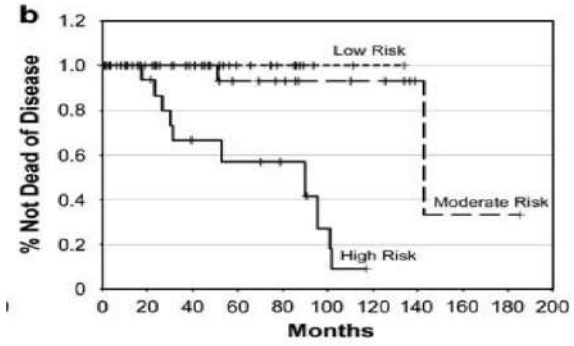


Fusiones génicas NAB2-STAT6

Table 5 Risk stratification model

Risk factor	*Score*
Age	
<55	0
⩾55	1
Tumor size (cm)	
<5	0
5 to <10	1
10 to <15	2
⩾15	3
Mitotic figures (/10 high-power fields)	
0	0
1–3	1
⩾4	2

Risk	*Total score*
Low	0–2
Moderate	3–4
High	5–6



- **Cirugía amplia : Gold-estándar**, con criterios similares a cualquier sarcoma.
- **RT-QT neo/adyuvante**: **no** evidencia de beneficio.

Thway K et al . Int J Surg Pathol. 2016 Jun;24(4):281-92

Tumor fibroso solitario (TFS)

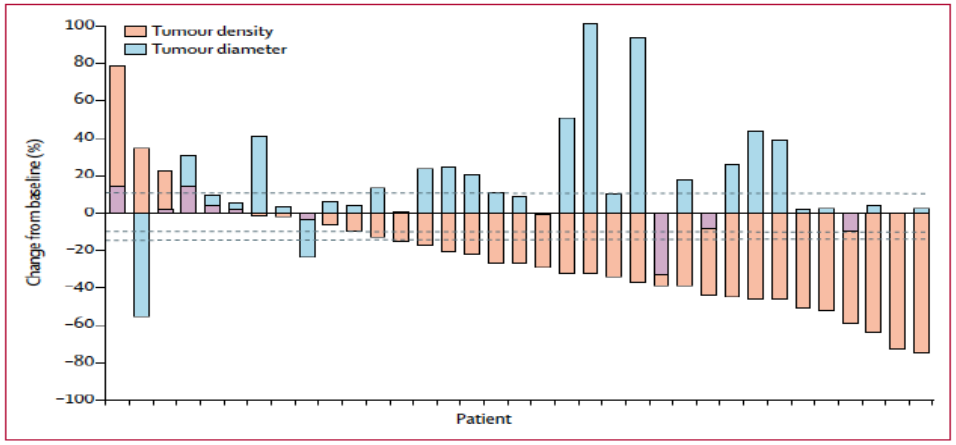
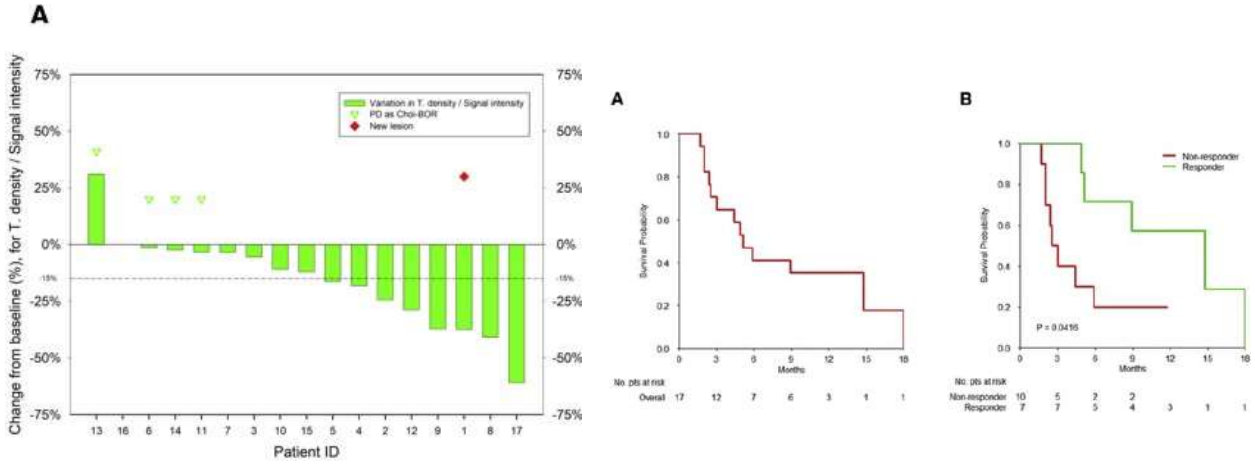


Figure 2: **Response to treatment by patient according to Choi criteria**
All patients in the per-protocol population shown (n=35). Tumour diameter was measured in mm and tumour density was measured in Hounsfield units. The dashed lines represent +10% of diameter increase, –10% of diameter decrease, –15% density decrease (CHOI criteria cutoffs). Purple bars are overlaps.

RESPUESTA	CHOI (%)	RECIST (%)
RP	51	6
SD	26	60
PD	23	34

Median PFS (Choi):5.57 m (4.51-6.62)
Median PFS (RECIST): 5.57 m(4.29-6.84)
Median OS: no alcanzada.



Best Choi response:
PR 7p (41.2%),SD 6p (35.3%), PD 4p (23.5%).
Choi-ORR: 41.2% (95%-CI: 18.4-67.1%).

PFS whole population : Median Choi-PFS: 5.1 m
PFS for patients responsive and nonresponsive by Choi (Median Choi-PFS 14.8 versus 2.8 m).

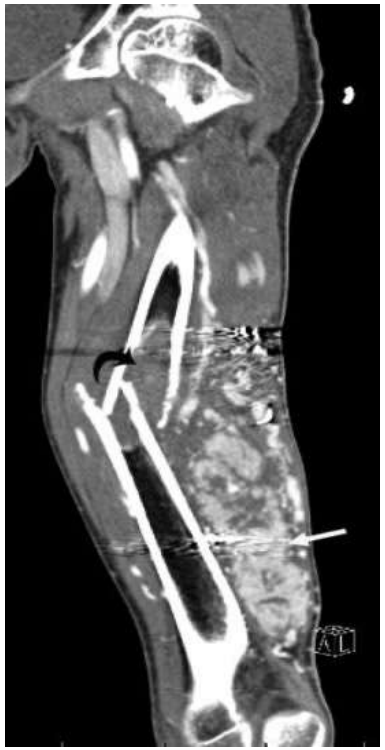
Martin-Broto et al. Lancet Oncol. 2019 Jan;20(1):134-144

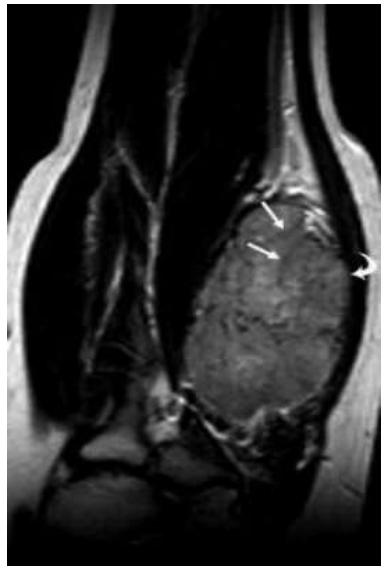
Stachiotti et al. Eur J Cancer. 2014 Nov;50(17):3021-8

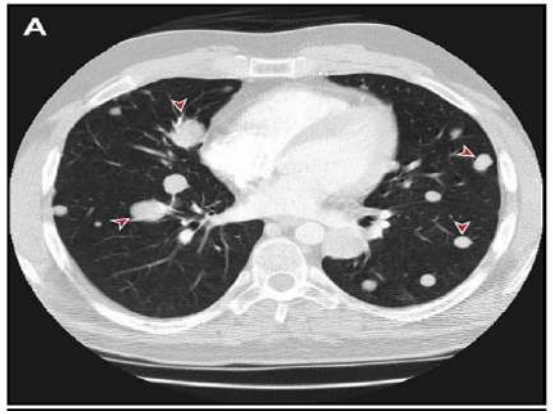
Sarcoma alveolar de partes blandas (SAPB)

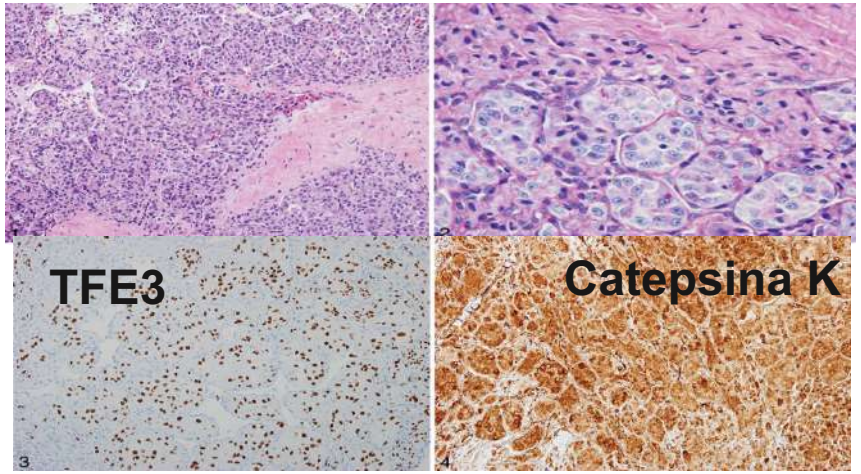
- 15-35 años.**Sexo:** mujeres (ratio 2:1) .
- **Localización :**
  - Adultos: mas frecuente en muslo o nalga.
  - Niños: mas frecuente en cabeza y cuello.

Etiologia : relacionan con la infección por Citomegalovirus.









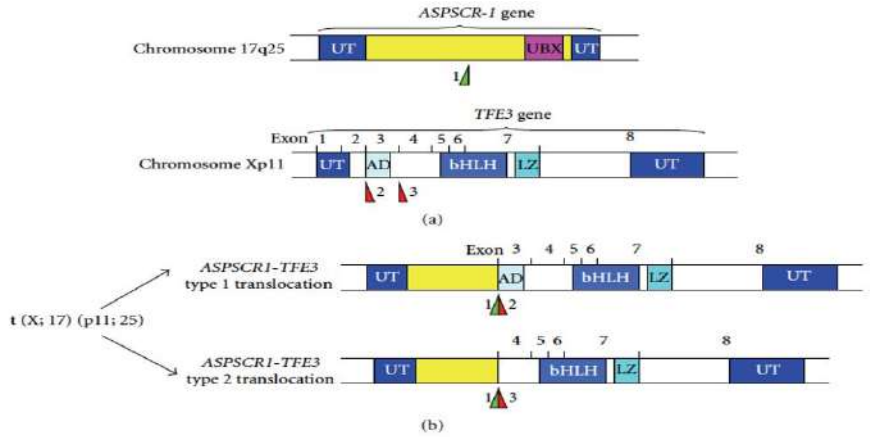


FIGURE 1: The t(X;17)(p11;25) translocation. (a) The ASPSCR-1 gene is located at chromosome 17q25 and the TFE3 gene at Xp11. The breakpoint found in the ASPSCR-1 gene is marked at "1", and the two defined breakpoints in the TFE3 gene are marked "2" and "3". (b) Following translocation, two variants of the ASPSCR-1-TFE3 fusion gene can be created. The Type 1 translocation retains the N-terminal activation domain of the TFE3 gene.

Jaber OI, et al. Arch Pathol Lab Med. 2015 Nov;139(11):1459-62
Jambhekar et al. WHO Classification of tumors of soft tissue and bone. 5th ed; vol 3 ; 2020. 297-299.

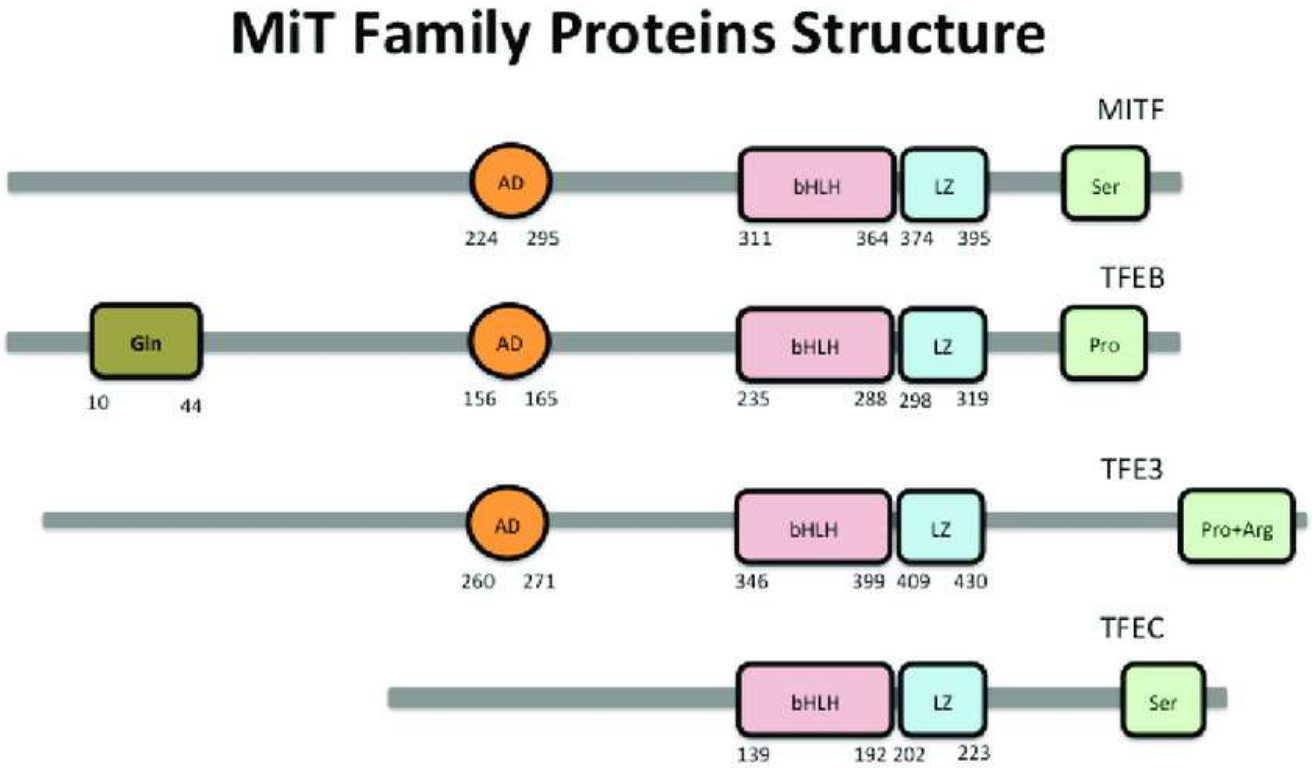
SAPB: familia de translocaciones MITF/MiT

Microphthalmia-associated transcription factor (MITF/MiT):

Familia de factores de transcripción bHLH-LZ: TFE3 (TFEA), TFEB, TFEC and MITF.

Neoplasias relacionadas:

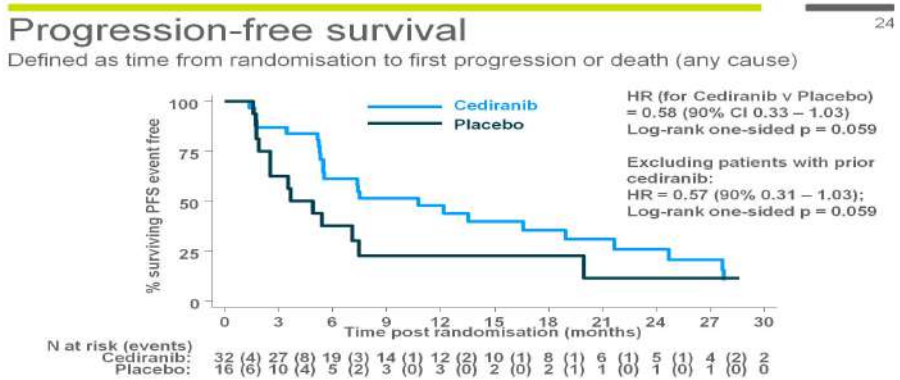
- Carcinoma células renales con translocaciones *ASPL-TFE3*/t(X;17)(p11.23;q25) o *MALAT1-TFEB*/t(6;11) (p21.1;q12),
- Perivascular epithelioid cell neoplasm (PEComa),
- Alveolar soft part sarcoma (ASPS),
- Epithelioid hemangioendothelioma,
- Ossifying fibromyxoid tumor (OFMT),
- Clear cell tumor with melanocytic differentiation and *ACTIN-MITF* translocation.



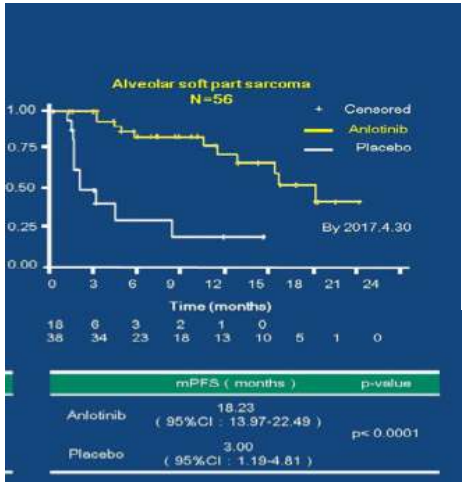
Wei S, et al. Histol Histopathol 2022, 37: 311-321

Sarcoma alveolar de partes blandas

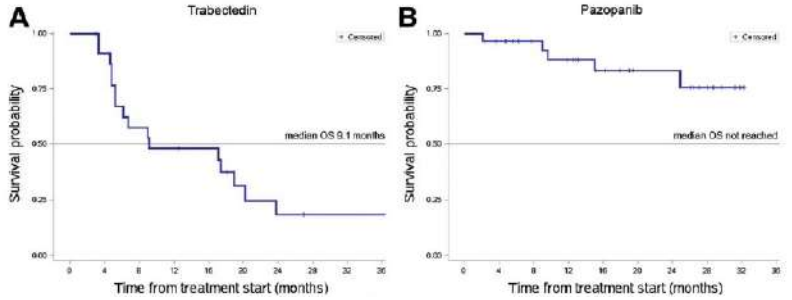
CEDIRANIB



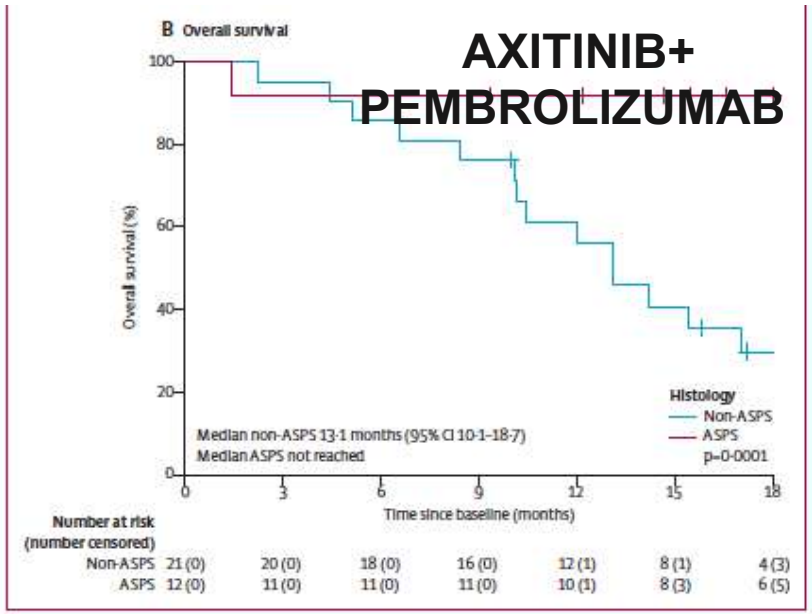
ANLOTINIB



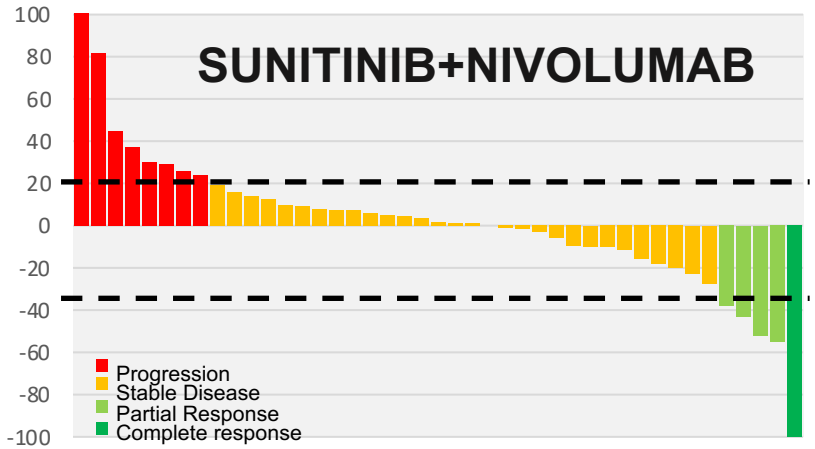
PAZOPANIB



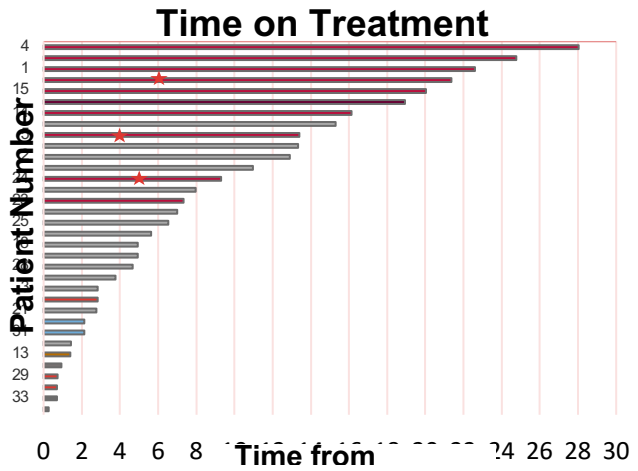
AXITINIB+ PEMBROLIZUMAB



SUNITINIB+NIVOLUMAB



ATEZOLIZUMAB



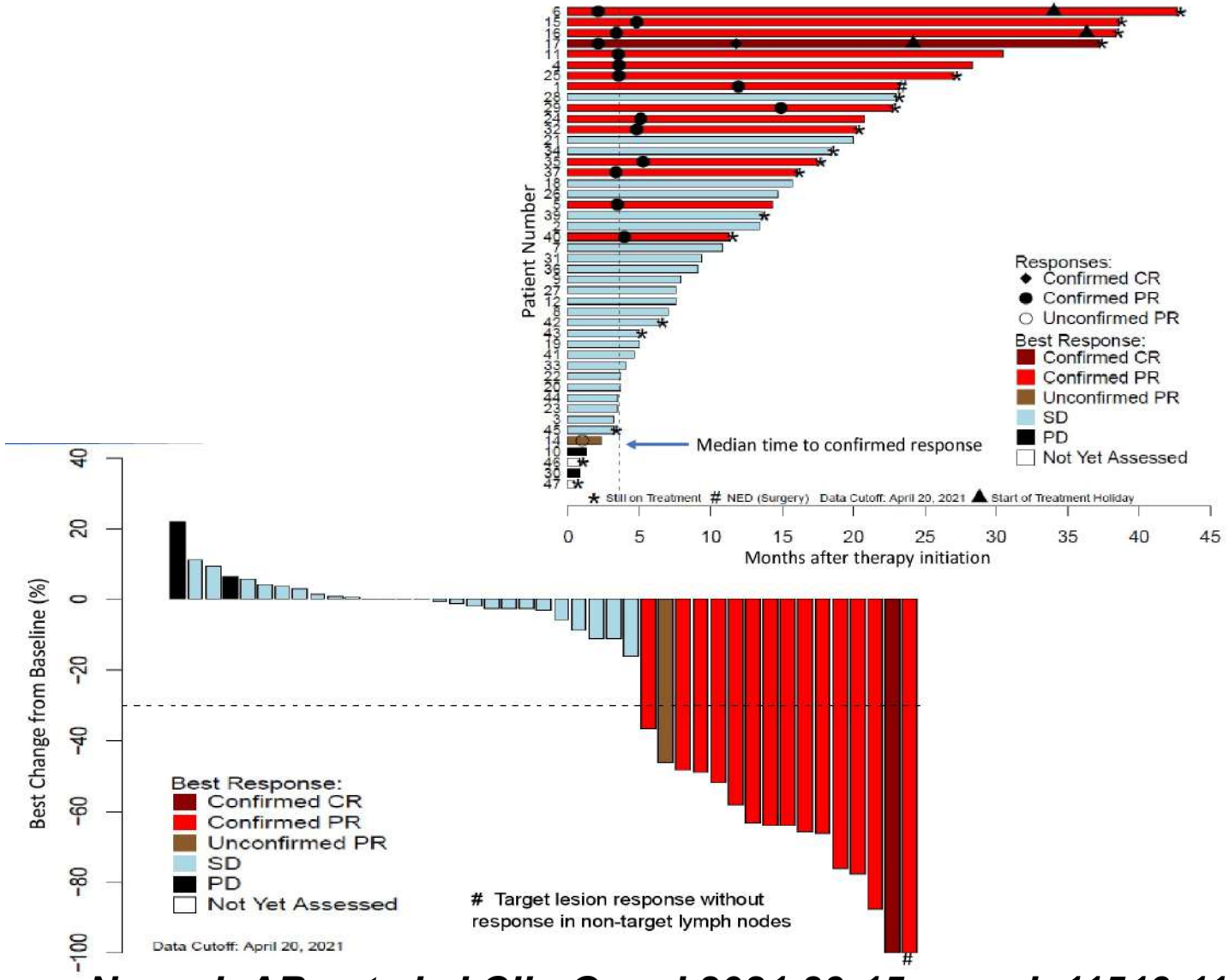
Salah S. J Clin Oncol 35, 2017 (suppl; abstr 110. Wilky BA. Lancet Oncol 2019; 20:837–848 Yang S. J Clin Oncol 36, 2018 (suppl; abstr 11572) Martin-Broto J. J Clin Oncol 36, 2018 (suppl; abstr 11515)O'Sullivan Coyne G, et al. CTOS 2019 Meeting; Nov 16. Paper 066

SAPB: Inmunoterapia. Atezolizumab (N=45)

Patient Outcomes

Best Response	No. of Patients
CR	01
PR	
confirmed	14*
unconfirmed	01
SD	25
PD	02
Total evaluable	43

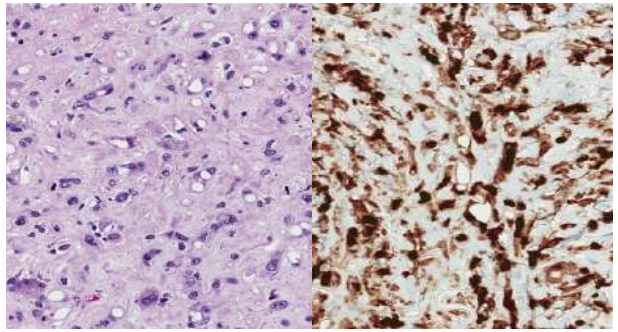
- Observed response rate: **37.2% (16/43)**
- Median time on study was **11.3 months** (range, 0.5–42.8)
- Median time to confirmed response: **3.5 months** (range, 2.1-14.9)
- Median duration of confirmed response: **16.6 months** (range, 7.4-40.6).
- **Three** patients have been on treatment holiday per protocol and have maintained PR after stopping therapy for a median of **8.6 months**



Naqash AR . et al. J Clin Oncol 2021 39:15_suppl, 11519-11519

Máster en Tumores Musculoesqueléticos

Hemangioendotelioma epitelioide



- Descrito en 1982.
- El mas frecuente y mejor caracterizado.
- Se considera maligno.
- Fusión WWTR1-CAMTA1 la mas frecuente .
- Afectación cutánea, partes blandas y visceral .
- Diseminación a distancia.

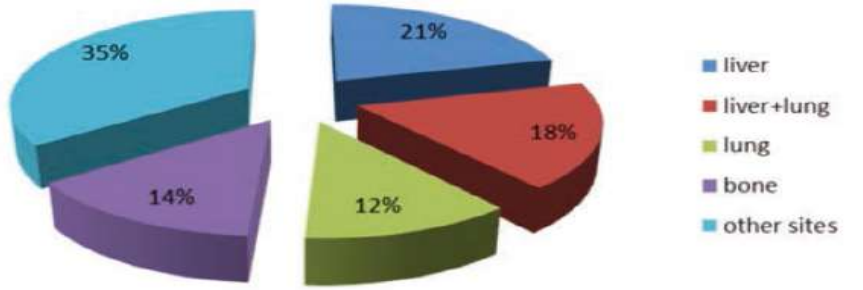


Figure 1. The most common epithelioid hemangioendothelioma presentations.

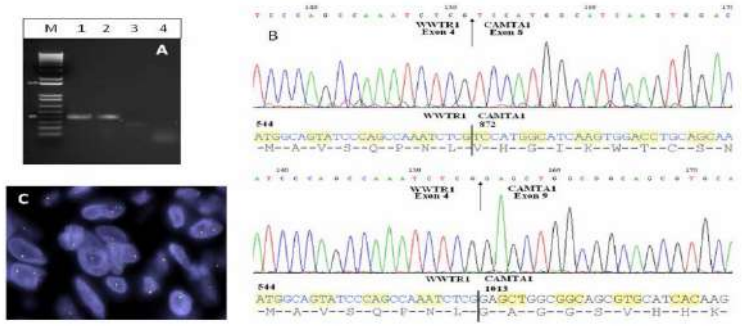


Figure 5.
RT-PCR detection of *WWTR1-CAMTA1* fusion transcript variants and FISH demonstration of fused *CAMTA1* and *WWTR1* signals. A. Gel electrophoresis showing amplified products in lanes 1–3, of two distinct sizes (M, size marker, lane 1, EHE#4, lane 2, EHE#6, lane 3, EHE#1, lane 4, negative control no-RNA). B. Sequencing of the 3 amplicons identified two molecular variants, with exon 4 of *WWTR1* being fused in-frame to either exon 8 (variant 1, upper panel) or exon 9 (variant 2, lower panel) of *CAMTA1*. C. FISH demonstration of fused signals, using probes centromeric to *CAMTA1* and telomeric to *WWTR1*.

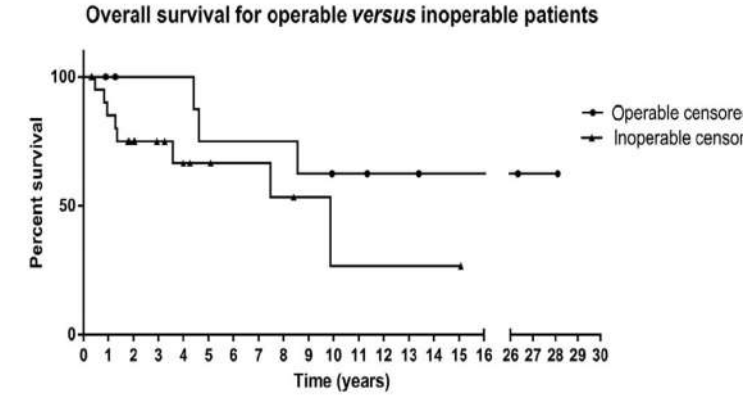


Figure 2. *Overall survival for operable vs. inoperable patients.*

HÍGADO: El trasplante hepático es el método curativo mas utilizado y aceptado

CAMTA1 -WWTR1

YAP1–TFE3

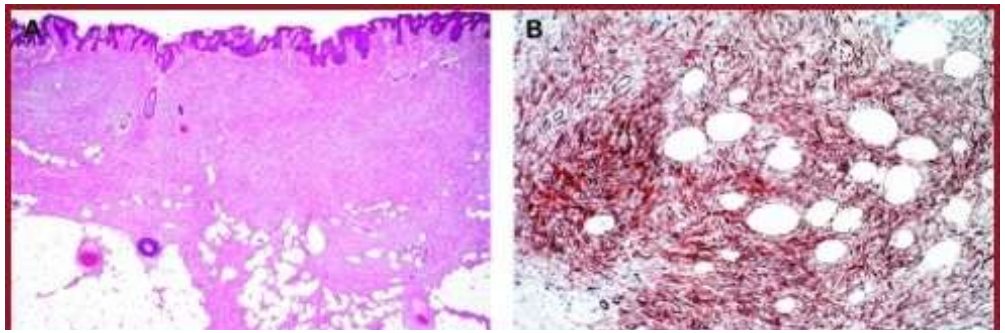
Errani C. Genes Chromosomes Cancer 2011;50:644-53 Antonescu CR. Genes Chromosomes Cancer 2013;52:775–784Rubin BP et al. WHO Classification of tumors of soft tissue and bone. 5th ed; vol 3 ; 2020. pp. 172-175

Hemangioendotelioma epitelioide

Estudio	N	Edad	sexo	Fármaco	Respuestas
Semenisty 2015	1	62	F	Pazopanib	PR
Bally 2015	1	48	F	Pazopanib	SD
Kollar 2017	10	NA	NA	Pazopanib	1CR, 1 PR, 4 SD
Saada 2014	1	51	F	Sunitinib	SD (6 años)
Prochilo 2013	1	72	F	Sunitinib	PR
Tolkach 2012	1	53	M	Sunitinib	PR
Zhengz 2017	1	44	M	Apatinib	PR
Kobayashi 2016	1	49	M	Sorafenib	PR

Bally O. Clinical Sarcoma Research. 2015;5:12. Semenisty V. BMC Cancer. 2015 May 13;15:402. Prochilo T. Case Reports in Oncology. 2013;6(1):90-97. Saada E. Oncol Res Treat. 2014;37(3):124-6. Kollár A. Acta Oncologica, 2017 Jan;56(1):88-92. Tolkach Y. Onkologie. 2012;35(6):376-8. Zheng Z. Medicine. 2017;96(45):e8507. Kobayashi. Case Rep Oncol. 2016 Feb 19;9(1):134-7.

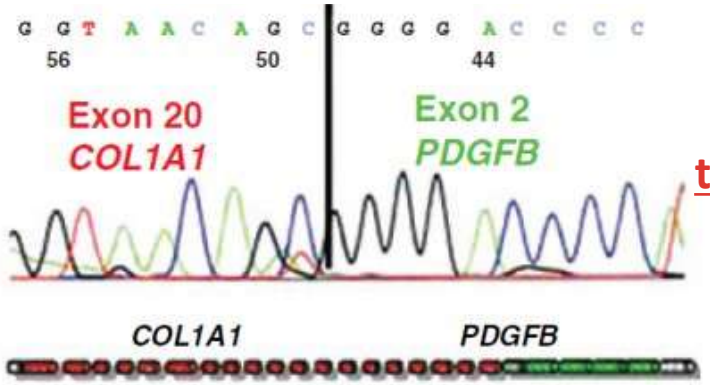
Dermatofibrosarcoma protuberans



IHQ:

+ difusa e intensa **para CD34 y vimentina**

- S-100, actina de músculo liso, desmina, queratinas, ag memb epitelial y estromelisina



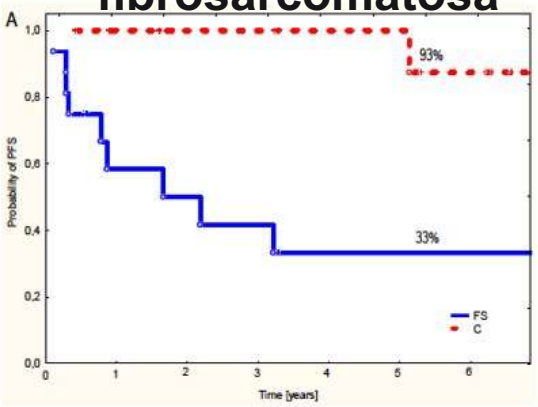
Translocación t(17;22)(q22;q13) que se observa en el 90%

- **0.8 a 4.5 casos nuevos/millón de hab/año y año.**
- **1-6% SPB**
- **0.1% tumores malignos**

Adultos jóvenes o de mediana edad.

Raza negra

Transformación fibrosarcomatosa



-Indicada Cirugía Mohs

- Indicada RT postoperatoria.

Dermatofibrosarcoma protuberans: imatinib .

Table 2. Response to Imatinib

Patient No.	Stage	Best Response	Duration of Imatinib (days)	Duration of Response to Imatinib (days)	Duration of Follow-Up (days)
1	Locally advanced	PR (disease-free after surgical resection)	698	685	845
2	Locally advanced	PR (disease-free after surgical resection)	62	62	699
3	Locally advanced	PR (disease-free after surgical resection)	141	141	572
4	Locally advanced	CR	457	457	536
5	Locally advanced	PR (disease-free after surgical resection)	139	139	258
6	Locally advanced	CR	188	188	267
7	Locally advanced	CR*	146	146	225
8	Locally advanced	CR*	88	88	88
9	Metastatic	PR	198	198	383
10	Metastatic	SD (Patient deceased day 32)	21	N/A	32

Abbreviations: PR, partial response; CR, complete response; SD, stable disease.
*Patients proceeded to resection, and complete response was confirmed by pathologic examination.

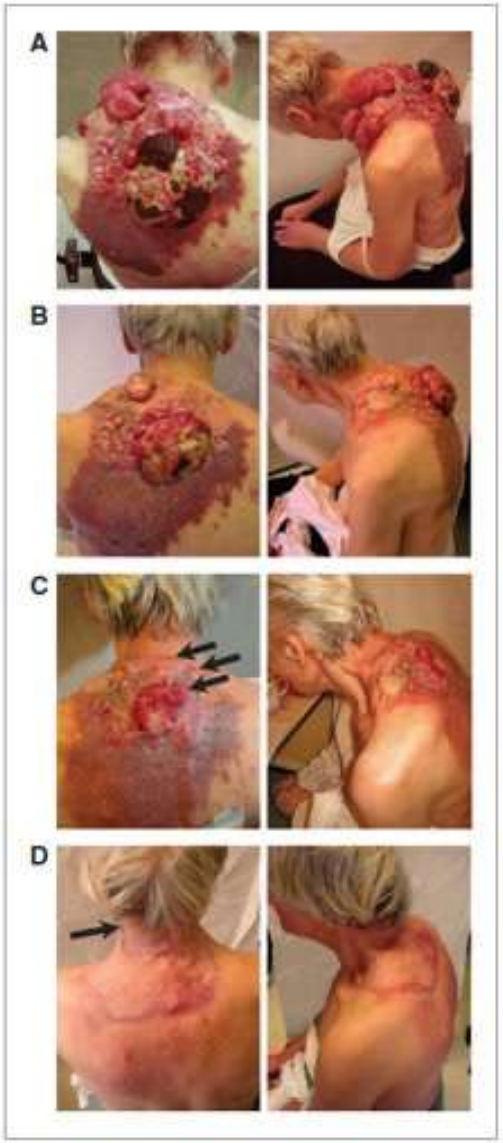
Table 2. Treatment characteristics, response, and follow-up (per protocol)

Patient ID	Longest tumor diameter at enrollment (method)	Longest tumor diameter at 6 weeks (method) response	Longest tumor diameter at 12 weeks (method) response	Duration of imatinib therapy (months)	Best overall response (diameter change by RECIST)	Progression during ongoing imatinib therapy (subsequent treatment)	Definitive surgery (months from onset of imatinib)	Safety margins at definiti surgery	Relapse after end of imatinib therapy (subsequent treatment)	Follow-up from onset of imatinib (months)
ADO-01	34 mm (Ultrasound)	25 mm (Ultrasound) SD	19 mm (Ultrasound) PR	3.0	PR (−42%)	None	Yes (3.1)	Unknown	None	97.3+
ADO-02	95 mm (Ultrasound)	92 mm (Ultrasound) SD	33 mm (Ultrasound) PR	2.8	PR (−65%)	None	Yes (3.2)	1.5 cm	None	29.9+
ADO-03	36 mm (MRI)	28 mm (Ultrasound) SD	22 mm (Ultrasound) PR	1.5	PR (−40%)	None	Yes (2.8)	0.5 cm	None	89.3+
ADO-04	50 mm (MRI)	35 mm (MRI) PR	29 mm (MRI) PR	2.8	PR (−42%)	None	Yes (2.9)	1.0 cm	None	82.9+
ADO-05	59 mm (MRI)	57 mm (MRI) SD	48 mm (MRI) SD	7.0	PR (−33%)	None	Yes (7.0)	1.0 cm	None	84.2+
ADO-06	183 mm (MRI)	165 mm (MRI) SD	125 mm (MRI) PR	6.3	PR (−45%)	Progression and new lesions in primary location at 5.7 months (surgery: CR)	Yes (6.5)	0.5 cm	Local recurrence at 7 months (imatinib: PD, sunitinib: PR, surgery: CR); distant metastasis at 35 months (radiation: PD)	48.3; Death by DFSP
ADO-07	92 mm (Ultrasound)	115 mm (Ultrasound) PD	NE (tumor excised)	1.5	PD (+25%)	Progression at 1.5 months (surgery: CR)	Yes (1.5)	Unknown	None	23.2+
ADO-09	17 mm (Ultrasound)	17 mm (Ultrasound) SD	15 mm (Ultrasound) SD	2.8	SD (−12%)	None	Yes (2.8)	1.0 cm	None	57.2+
ADO-10	27 mm (Ultrasound)	25 mm (Ultrasound) SD	40 mm (Ultrasound) PD	2.9	SD (−7%)	Progression at 2.9 months (surgery: CR)	Yes (2.9)	2.0 cm	None	79.5+
ADO-11	40 mm (MRI)	36 mm (MRI) SD	32 mm (MRI) SD	2.8	SD (−20%)	None	Yes (3.1)	1.0 cm	None	67.5+
ADO-12	60 mm (CT)	58 mm (CT) SD	62 mm (CT) SD	5.2	SD (±0%)	None	Yes (6.5)	Wide (limb amputation)	None	76.9+
ADO-13	45 mm (MRI)	45 mm (MRI) SD	45 mm (MRI) SD	3.3	SD (±0%)	None	Yes (3.3)	Unknown	None	76.7+
ADO-15	68 mm (MRI)	59 mm (MRI) SD	48 mm (MRI) PR	16.7	CR (clinical evaluation)	None	No (imatinib continued until CR)	NA	None	46.7; Death by other reason
ADO-16	40 mm (MRI)	ND	28 mm (MRI) PR	3.3	PR (−30%)	None	Yes (3.7)	2.0 cm	None	70.2+

NOTE: Course of treatment, outcome and follow-up of the (per protocol) patient population.
Abbreviations: NA, not applicable; ND, not done; NE, not evaluable; SD, stable disease.

- Fase II que da la aprobación por la FDA y EMEA
- N= 10. RC 4 y 5 RP

PUEDE PERMITE CIRUGÍAS MENOS MUTILANTES



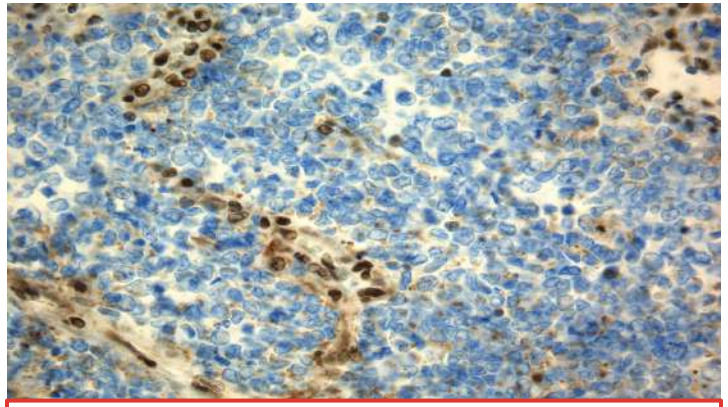
Beaziz J,et al. Cancers (Basel). 2021 May 6;13(9):2224.
Mc Arthuer et al. JCO. 2005

Sarcomas SWI/SNF deficientes

Table 1. SMARCB1-deficient malignant neoplasms.

SMARCB1-Deficient Mesenchymal Malignant Tumors	SMARCB1-Deficient Non-Mesenchymal Malignant Tumors
Extrarenal malignant rhabdoid tumor	Atypical teratoid rhabdoid tumor
Epithelioid sarcoma	Cribriform neuroepithelial tumor
Poorly differentiated chordoma	Renal medullary carcinoma
Epithelioid MPNST [1]	SMARCB1-deficient sinonasal carcinoma
Myoepithelial carcinoma	SMARCB1-deficient carcinoma of the GI tract
Myxoid extraskeletal chondrosarcoma	

[1] malignant peripheral nerve sheath tumor.

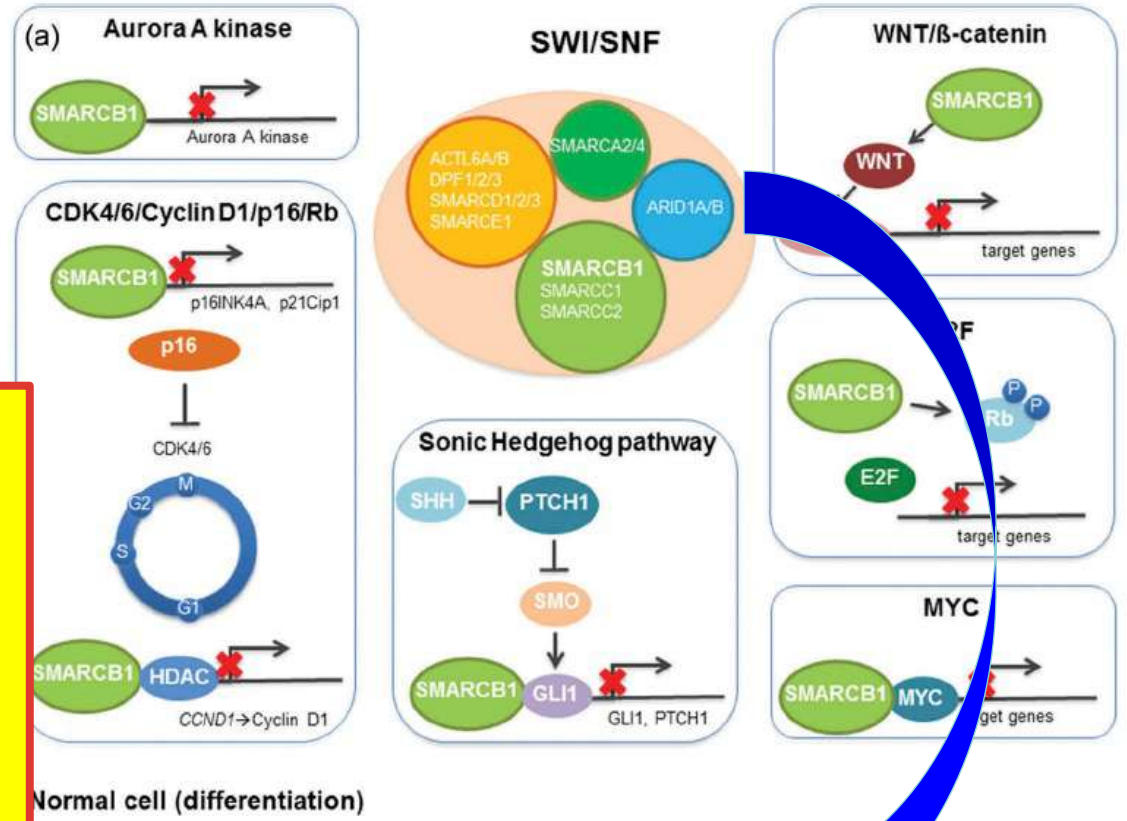


IHQ for INI1, the product of the SMARCB1 gene typically defective in ATRT. Note loss of brown staining in the nuclei of tumor cells with defective SMARCB1 as compared to retained staining of nuclei of vascular cells (internal positive control).

SWI/SNF Deficient tumors :

- Rhabdoid tumors.
- Small cell carcinoma ovary hypercalcaemic
- type (SCCOHT).
- SMARCA4 deficient undiferentiated tumors SMARCA4 uterine sarcomas.
- SMARCA4 undifferentiated sinunasal carcinomas
- Epitheliod sarcoma (SMARB1-def)

SWItch/Sucrose Non-Fermentable (SWI/SNF)



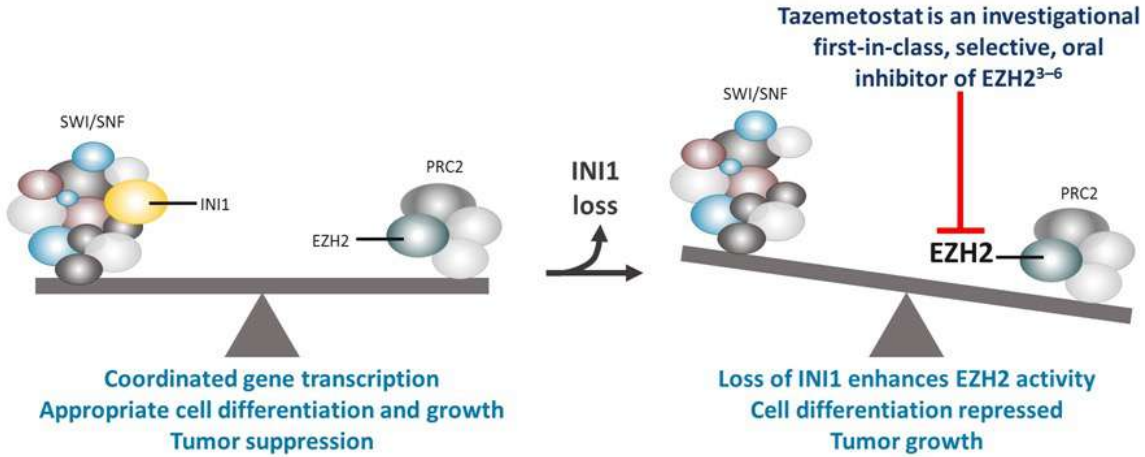
SMARCB1(INI-1)
SMARCA4
ARID1A

Nemes K, Frühwald MC. Expert Opin Ther Targets. 2018;22(4):365-379.

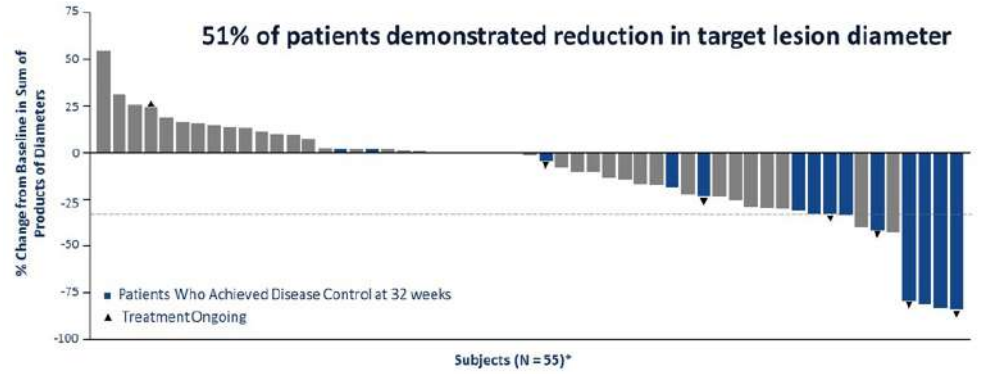
Sarcomas SWI/SNF deficientes

TAZEMETOSTAT IN EPITHELIOID SARCOMA.

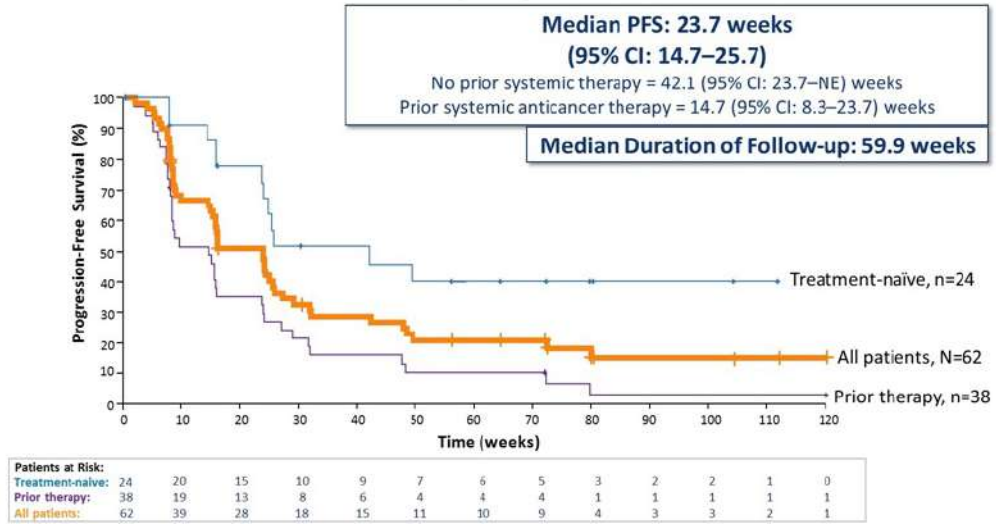
LOSS OF INI1 CREATES AN ONCOGENIC DEPENDENCY ON ENHANCER OF ZESTE HOMOLOG 2 (EZH2)



BEST PERCENT CHANGE IN SUM OF TARGET LESION DIAMETERS PER INVESTIGATOR ASSESSMENT



PROGRESSION-FREE SURVIVAL (PFS)



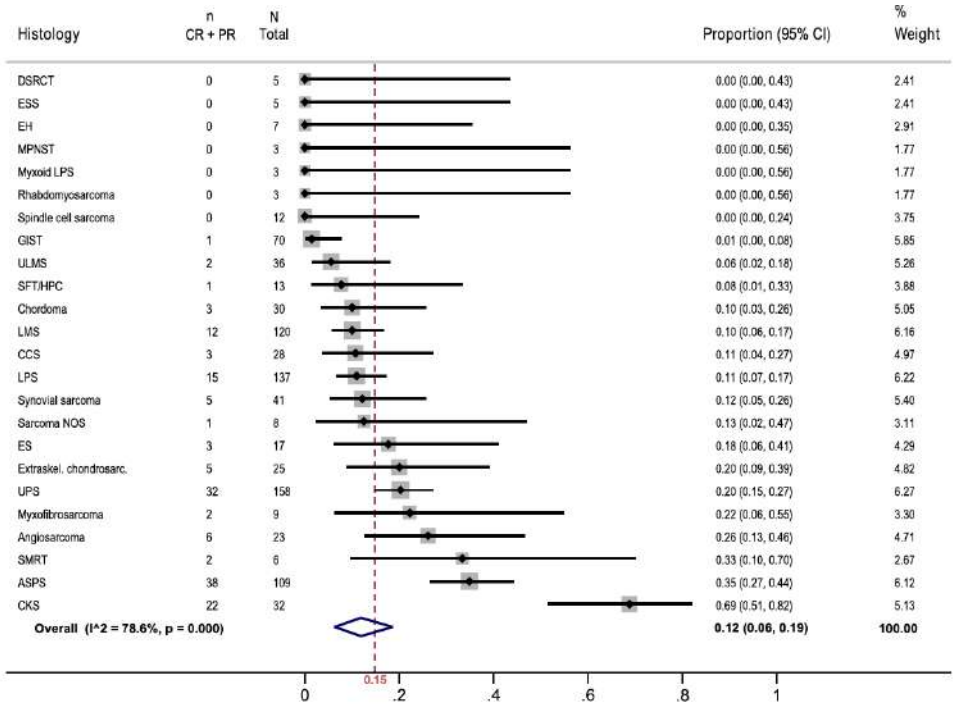
Stacchiotti S, et al. J Clin Oncol 37, 15_suppl (May 20, 2019) 11003-11003.

Sarcomas SWI/SNF deficientes

Table 2. Results of clinical studies evaluating ICI in monotherapy in SMARCB1-deficient sarcoma.

Reference	NCT Identifier/ Trial Name	Study Design	Study Description	Number of Patients	Specific Histotype	Best Response	Duration of Best Response
Paoluzzi, 2016		Retrospective series	Nivolumab in relapsed metastatic/unresectable sarcomas	2	ES	1 PR 1 PD	3.8 mth
Blay, 2019	NCT03012620/ AcSé	Phase II	Pembrolizumab for patients with selected rare cancer types	1	MRT	PR	NA
Georger, 2020	NCT02541604/ iMATRIX	Phase I/II	Atezolizumab in children and young adults with refractory or relapsed solid tumors, with known or expected PD-L1 expression	3	MRT	PR	NA
Georger, 2020	NCT02332668	Phase I/II	Pembrolizumab in pediatric patients with PD-L1-positive, advanced, relapsed, or refractory solid tumor	2 1	MRT ES	1 PR 1 PD PR	17.8 mth 11.8 mth
Forrest, 2020		Case report	Pembrolizumab	1	ES	SD	12 mth
			Nivolumab	1	PDC	PR	9 mth
			Pembrolizumab	1	MRT	SD	15 wk

Abbreviations: ES: epithelioid sarcoma; MRT: malignant rhabdoid tumor; PDC: poorly differentiated chordoma; PR: partial response; PD: progressive disease; SD: stable disease; NA: not available.

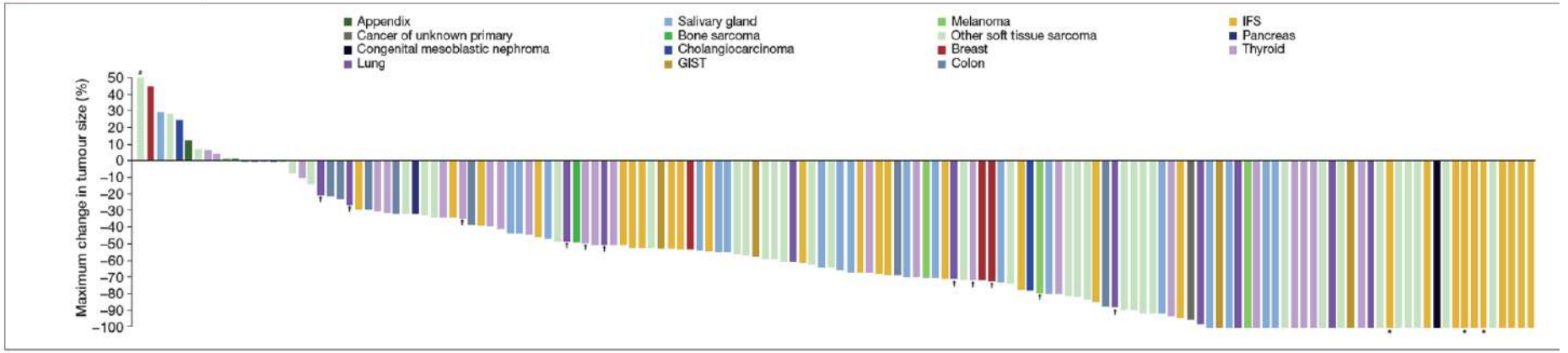


Ngo C,et al. Biomedicines. 2022 Mar 11;10(3):650.
M. Saerens et al. Eur J Cancer 2021: 152 , 165e182

Sarcomas con NTRK fusions

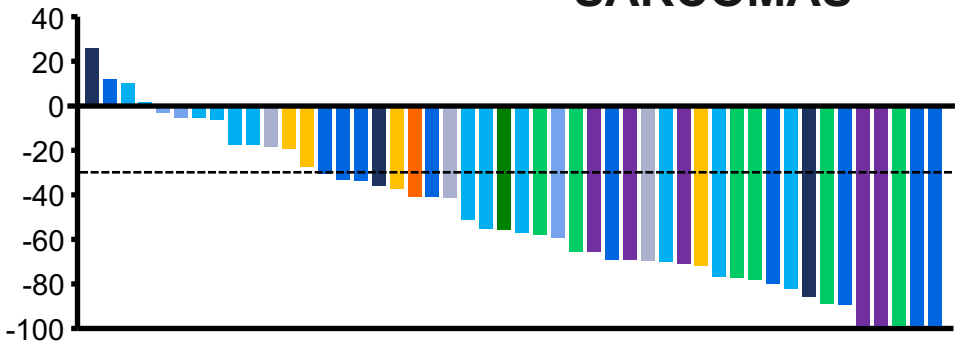
LAROTRECTINIB IN SARCOMAS HARBOURING TRK FUSIONS

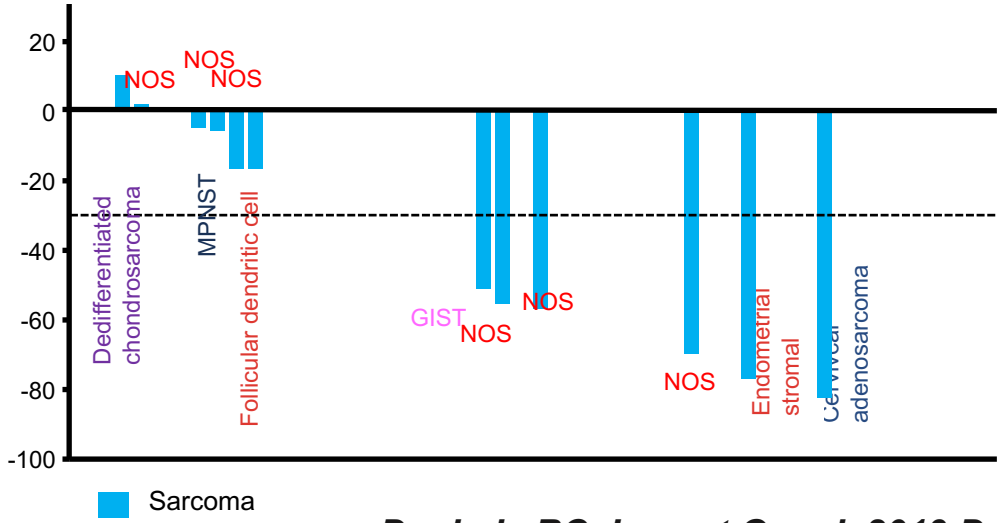
Figure 3. Maximum change in tumour size.



Excludes four patients who had clinical deterioration prior to an initial response assessment and six patients who were not evaluable due to insufficient time on therapy. †Patients with a pathological complete response. ‡Maximum change in tumour size of +93.2%. §Patients with brain metastases. GIST, gastrointestinal stromal tumour; IFS, infantile fibrosarcoma.

ENTRECTINIB *NTRK* FUSION+ SARCOMAS





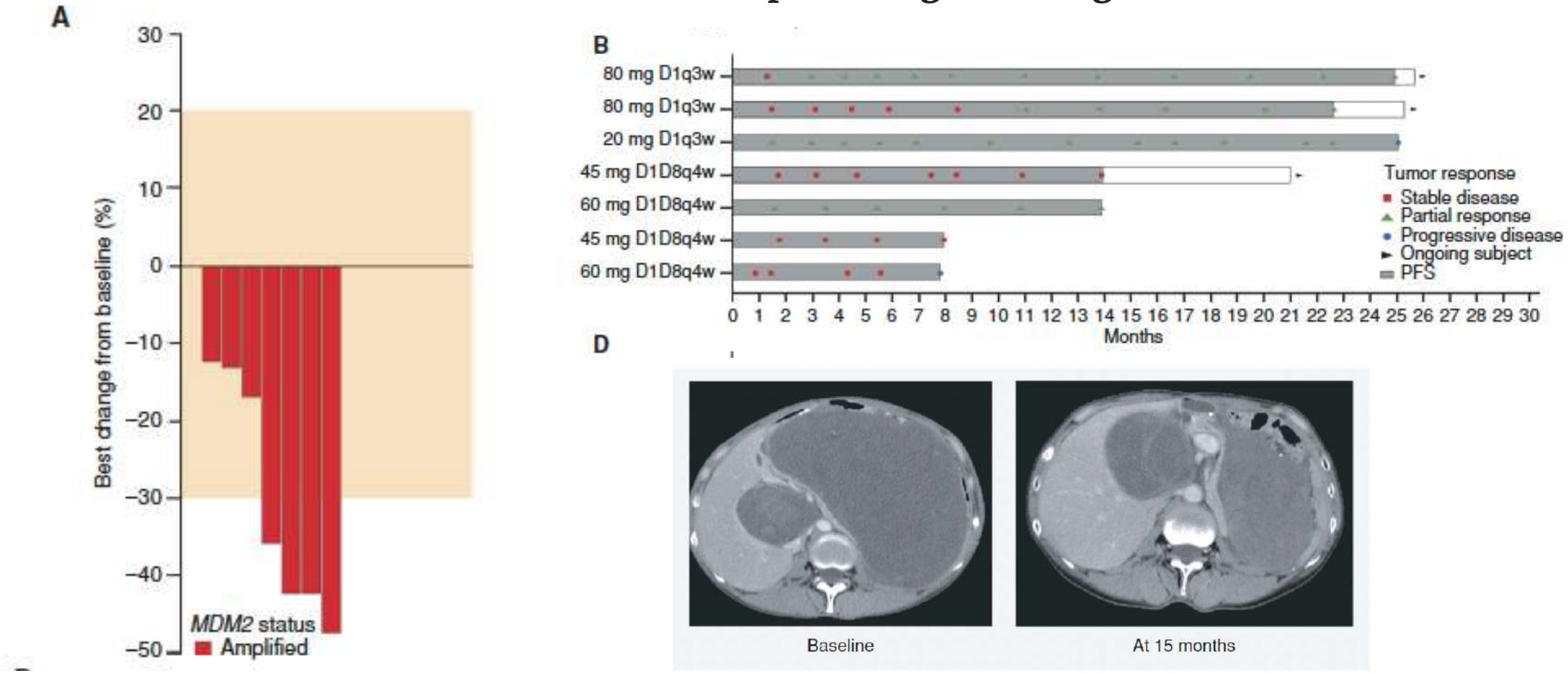
Doebele RC. Lancet Oncol. 2019 Dec 11..
Hong DS, Lancet Oncol. 2020 Apr;21(4):531-540.

Sarcomas huérfanos o ultrahuérfanos

- Fibrosarcoma Epitelioide Esclerosante
- Sarcoma fibromixoide de bajo grado
- **Liposarcoma bien diferenciado avanzado**
- Sarcoma Phyllodes
- ……

Liposarcoma bien diferenciado

MDM2-p53 Antagonist Brigimadlin



LoRusso P. Cancer Discov. 2023 Aug 4;13(8):1802-1813.

Universidad Europea

GEIS
GRUPO ESPAÑOL DE INVESTIGACIÓN EN SARCOMAS

Máster en Tumores Musculoesqueléticos