CENTRO INTEGRAL ONCOLÓGICO
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TUMORES DE LOS ANEJOS CUTÁNEOS

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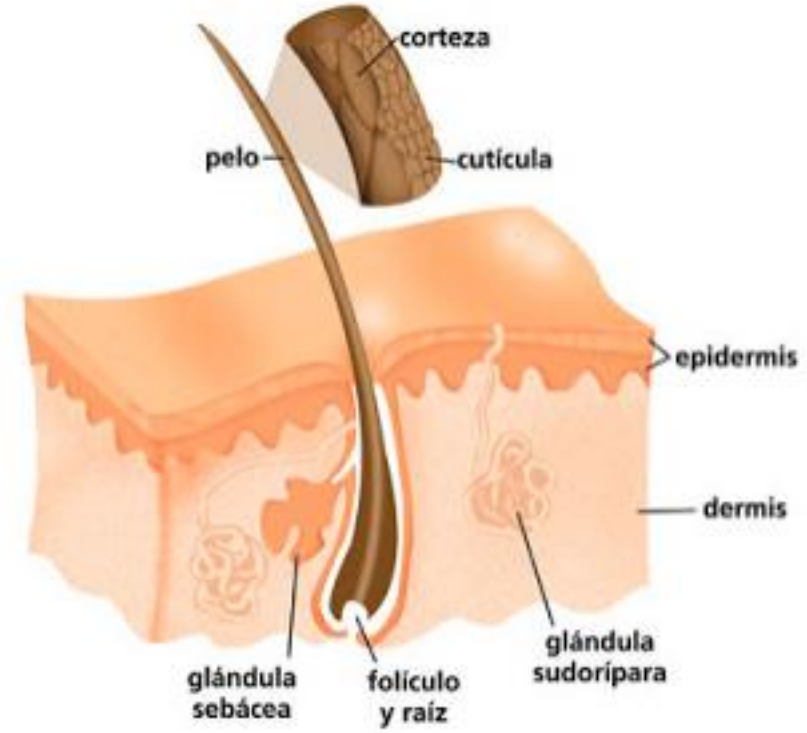
ANEJOS CUTÁNEOS

Estructuras dependientes de la piel.
GLÁNDULAS DE LA PIEL, PELO, UÑAS

Función: protección mecánica, aislamiento térmico, infecciones, impermeabilidad, radiaciones, sensación táctil



GENERALIDADES TUMORES DE LOS ANEJOS CUTANEOS

- **Grupo heterogéneo** de entidades de baja frecuencia de presentación, que puede plantear ciertas **dificultades diagnósticas**
- Origen es controvertido: a partir de **células madres pluripotenciales**, aceptándose principalmente dos líneas embriológicas: pilosebáceo-apócrina y ecrina
- **La mayoría son benignos**, aunque su contraparte maligna existe, siendo más infrecuente, localmente agresiva, potencialmente metastatizante y de presentación a edades más tardía
- Generalmente >2.5 cm
- Es de utilidad tratar de determinar su comportamiento biológico en cuanto a agresividad y potencial invasivo, dada su importancia en cuanto al tratamiento y pronóstico
- La **histopatología** es la herramienta más importante para su diagnóstico y clasificación
- El tratamiento de elección es la resección quirúrgica amplia, con disección ganglionar regional electiva

TUMORES ECRINOS Y APOCRINOS MALIGNOS	CARCINOMAS FOLICULARES	CARCINOMAS CON DIFERENCIACIÓN SEBACEA
Porocarcinoma **Hidradenocarcinoma** **Carcinoma adenoide quistico** Carcinoma mucinoso y carcinoma endocrino productor de mucina de las glandulas sudoriparas **Carcinoma anexial microquistico** **Adenocarcinoma digital papilar agresivo** **Enfermedad de Paget extramamaria** Carcinoma cutaneo cribiforme Carcinoma cutáneo secretor	Carcinoma tricoblastico Carcinoma triquilémico Carcinoma pilomatricial	**Carcinoma sebáceo**

PRECISION MEDICINE

GENOTIPE → PHENOTIPE

- Matching driver mutations with drugs

PHENOTIPE → GENOTIPE

- Analyzing excepcional responses of therapies

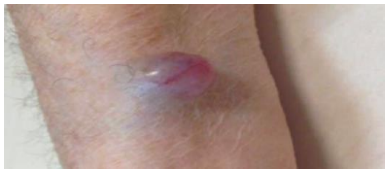
➢Baja frecuencia. Serie de casos

➢**La estrategia de hacer coincidir la terapia dirigida con los target biológicamente relevantes mediante el uso de técnicas de secuenciación (NGS**)

- 1. TUMORES ECRINOS Y APOCRINOS MALIGNOS

TUMORES ECRINOS Y APOCRINOS MALIGNOS
Porocarcinoma
Hidradenocarcinoma
Carcinoma adenoide quistico
Carcinoma mucinoso y carcinoma endocrino productor de mucina de las glandulas sudoriparas
Carcinoma anexial microquistico
Adenocarcinoma digital papilar agresivo
Enfermedad de Paget extramamaria
Carcinoma cutaneo cribiforme
Carcinoma cutáneo secretor

HIDRADENOMA NODULAR MALIGNO (ACROSPIROMA MALIGNO, HIDRADENOCARCINOMA NODULAR DE CÉLULAS CLARAS, HIDRADENOMA NODULAR MALIGNO DE CÉLULAS CLARAS)



- Surgen del **conducto intradérmico de las glándulas sudoríparas ecrinas**
- Hombres=Mujeres / 30 y 50 a
- Cara > EEII > Cuero cabelludo > tórax >cuello
- Constituyen un nódulo firme mayor de 3 cm, fijo a tejido circundante, rojizo-rosado, mal limitado, que puede ulcerarse
- Comportamiento agresivo con más del 50% de tasas de recurrencia local [2]
- Metástasis 60% : LN, pulmón, huesos, higado, cerebro
- Supervivencia 5ª: 65%
- Opciones de quimioterapia y hormonoterapia (Tamoxifeno) con distintas respuestas

[1]Mehregan AH, Hashimoto K, Rahbari H. Eccrine adenocarcinoma. A clinicopathologic study of 35 cases. Arch Dermatol. 1983;119(2):104–14
[2]Wilson KM, Jubert AV, Joseph JI. Sweat gland carcinoma of the hand (malignant acrospiroma). J Hand Surg [Am]. 1989;14(3):531–5.
Image: Courtesy of Elservier

J Cutan Pathol 2007: 34: 49–54
doi: 10.1111/j.1600-0560.2006.00570.x
Blackwell Munksgaard. Printed in Singapore

Journal of
Cutaneous Pathology

Metastatic hidradenocarcinoma with demonstration of *Her-2/neu* gene amplification by fluorescence *in situ* hybridization: potential treatment implications

- Overexpression of Her2/neu and gene amplification has been documented in one case of metastasizing malignant hidradenoma.
- 44 años. Hidradenocarcinoma en **pared torácica+ afectación ganglionar**
- Resección en bloque+ VA **(9/28)**
- **IHQ: AR+, RE+. HER-2/Nneu: +**
- **FISH HER2: amplificado** en tumor primario y metástasis ganglionar Ratio 2.5 y 3.5
- **Radioterapia + AC+ Trastuzumab adyuvante→ No evidencia de recidiva**

Recomendación: testar FISH HER2 y RRHH por IHQ en los hidradenocarcinomas

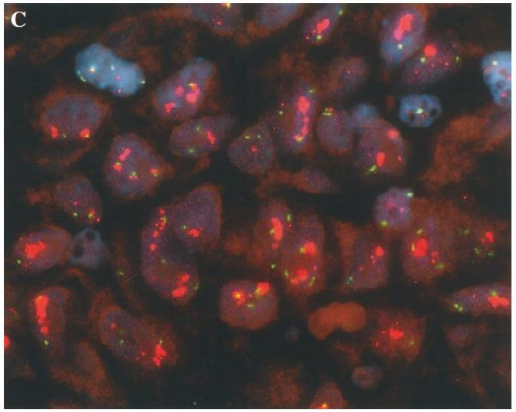


Fig. 2. Strong and diffuse immunoreactivity with anti-Her-2/*neu* within the primary tumor (A) and the lymph node metastasis (B). Note the lack of immunoreactivity within the area of the tumor corresponding to hidradenoma (upper left-hand aspect of panel A). Fluorescence *in situ* hybridization (FISH) for Her-2/neu demonstrates amplification in the primary tumor. Orange signal corresponds to the *Her-2/neu* locus of chromosome 17q. The green signal

GENES, CHROMOSOMES & CANCER 43:202–205 (2005)

BRIEF COMMUNICATION

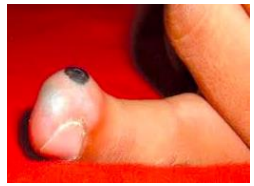
Clear Cell Hidradenoma of the Skin—a Third Tumor Type with a t(11;19)-Associated *TORC1–MAML2* Gene Fusion

Afrouz Behboudi,[1] Marta Winnes,[1] Ludmila Gorunova,[2] Joost J. van den Oord,[3] Fredrik Mertens,[2] Fredrik Enlund,[1] and Göran Stenman[1]*

[1]Lundberg Laboratory for Cancer Research, Department of Pathology, Göteborg University, Sahlgrenska University Hospital, Göteborg, Sweden
[2]Department of Clinical Genetics, Lund University Hospital, Lund, Sweden
[3]Department of Pathology, Laboratory of Morphology and Molecular Pathology, University Hospital Leuven, Katholieke Universiteit Leuven, Leuven, Belgium

- Translocaciones en varios carcinomas salivares y carcinomas pulmonares mucoepidermoides
- Translocaciones t **(11; 19) resulta en el gen de fusión TORC1-MAML2**
- Las consecuencias de esta fusión no han sido entendidas, MAML2 como **coactivador** para los receptores **Notch**
- Datos disponibles sugieren su expresión en tumores benignos o de bajo grado de malignidad

ADENOCARCINOMA PAPILAR DIGITAL AGRESIVO (ADPA)



- Tumor raro . Incidencia 0.08 por millón personas/año
- Se presenta como un nódulo en la superficie volar de los dedos de las manos y, con menos frecuencia , de los pies
- Excisión local/amputación digital es el tratamiento de elección . Estudio ganglionar y a distancia
- Altas tasas de recurrencia local: 30-50%
- Metástasis: 15 a 30 % de los casos: ganglios linfáticos y los pulmones
- No existen guías de tratamiento estándar ni tratamiento efectivo en la enfermedad metastásica
- El análisis de secuenciación mostró mutaciones **BRAF V600E** en uno de cada nueve tumores

Next-generation sequencing reveals rare genomic alterations in aggressive digital papillary adenocarcinoma☆,☆☆

Diana Bell, MD*, Phyu Aung, MD, PhD, Victor G. Prieto, MD, PhD, Doina Ivan, MD

Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX

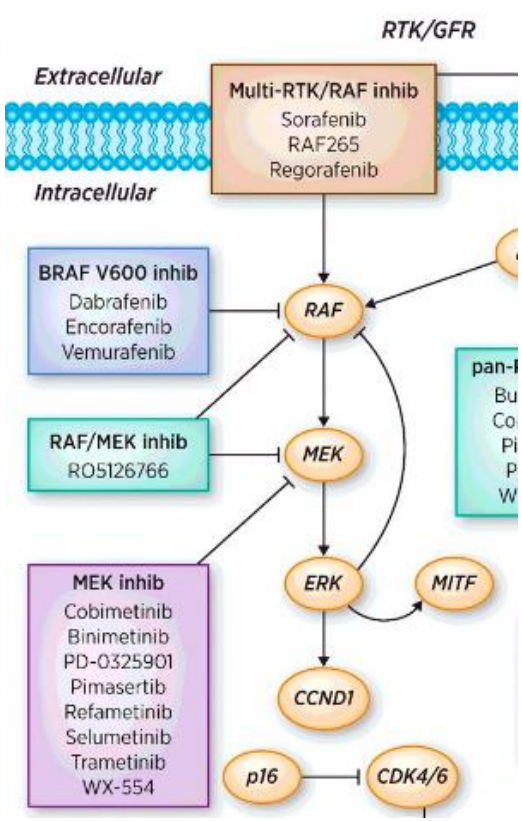
- Comprehensive genomic profiling of 9 ADPA cases
- Identification of a **BRAF-V600E (BRAF c.1799T>A p.V600E)** mutation in 1 patient (11%)
- Targeted therapy may be a treatment option for patients with metastatic ADPA if a relevant oncogene mutation is identified

Table
Demographic, clinicopathologic, and molecular characteristics of 9 patients with ADPA

Case	Age (y)/sex	Location	SLN status	Follow-up (mo)	Sequenom
1	52/F	Third finger	Negative	NED, 36	No mutations
2	48/F	Ankle	Negative	NED, 48	No mutations
3	41/M	Index finger	Positive (2/5)	NED, 54 mo	No mutations
4	58/M	Fifth finger	Negative	NED, 6	No mutations
5	39/F	Heel	Positive (1/4)	NED, 18	No mutations
6	58/F	Fifth finger	Positive	NED, 6	No mutations
7	57/M	Third finger	N/A	NED, 36	No mutations
8	40/M	Third finger	N/A	DOD, lung metastasis	No mutations
9	31/F	Ankle	Negative	NED, 12	BRAF c.1799T>A p.V600E

RAS/RAF/MEK/ERK mitogen-activated protein kinasa pathway

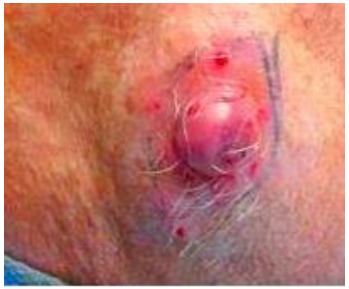
- Regula la proliferación celular, supervivencia, migración
- Mutación en distintos tumores: melanoma, CCR, ca papilar de tiroides..
- Inhibidores de BRAF:→Potencial terapéutico



Targeted therapy in combination trials in cutaneous advanced melanoma (52, 102, 103)

Drug	Molecular target	PubChem ID
MAPK Pathway		
Dabrafenib (GSK2118436)	BRAF V600	44462760
Encorafenib (LGX818)	BRAF V600	50922675
Vemurafenib (PLX4032)	BRAF V600	42611257
Cobimetinib (GDC-0973, XL-518)	MEK	16222096
Binimetinib (MEK162)	MEK	10288191
PD-0325901	MEK	9826528
Pimasertib (MSC-1936369B, AS-703026)	MEK	44187362
Refametinib (BAY 86-9766)	MEK	44182295
Selumetinib (AZD6244)	MEK	10127622
Trametinib (GSK1120212)	MEK	11707110
WX-554	MEK	Not listed
RO5126766 (CH5126766)	Dual RAF/MEK	16719221

POROCARCINOMA:



- Es una neoplasia de **alto grado**, la **más frecuente de las neoplasias malignas ecrinas** de anejos cutáneos
- 50% se origina *de novo*, o de un poroma evolucionado
- Mujeres >60 años de edad
- Predominio EEII (50%)
- Generalmente son placas planas, verrugosas o polipoides de 2 a 10 cm
- Su crecimiento es lento
- 2 patrones: intraepidérmico y el **dérmico (mal pronóstico: metástasis 20 % : piel, LN, pulmón, hígado, SNC, hueso**)
- Tecnicas secuenciación han mostrado mutaciones en EGFR, HRAS, TP53, RB1, ATM, ARID1A, PIK3CA y CDKN2A[1]

1. Harms PW, Hovelson DH, Cani AK, et al. Porocarcinomas harbor recurrent HRAS-activating mutations and tumor suppressor inactivating mutations. Hum Pathol 2016; 51:25.

Loss of heterozygosity of adenomatous polyposis coli gene in cutaneous tumors as determined by using polymerase chain reaction and paraffin section preparations

Naoki Ichihashi *, Yasuo Kitajima

Department of Dermatology, Gifu University School of Medicine, 40 Tukasa-machi, Gifu-city, 500-8705, Japan

Received 18 February 1999; received in revised form 21 April 1999; accepted 22 April 1999

- La pérdida de heterocigosidad (LOH) de APC se ha descrito hace más de una década
- La alteración en el gen de la poliposis adenomatosa (APC), que es un gen supresor de tumores, es uno de los eventos anteriores en la carcinogénesis de algunos adenocarcinomas.
- **57** casos consistieron en enfermedad extramamaria de Paget, carcinoma de células escamosas (SCC), poroma ecrino y porocarcinoma, tumor metastásico de adenocarcinoma rectal y melanoma maligno.
- Amplificación ADN mediante PCR El ADN fue examinado 9 **(tres de los siete poromas ecrinos, dos porocarcinomas ecrinos) mostraron LOH**

Table 1
LOH of APC in cutaneous tumors

	Informative/total	LOH/informative
Extramammary Paget's disease	11/14	0/11
Eccrine poroma	7/12	3/7
Eccrine porocarcinoma	2/3	2/2
Squamous cell carcinoma	5/14	0/5
Malignant melanoma	5/11	0/5
Metastasis of rectal carcinoma	2/3	2/2

Hum Pathol. 2016 May;51:25-31. doi: 10.1016/j.humpath.2015.12.015. Epub 2016 Jan 7.

Porocarcinomas harbor recurrent HRAS-activating mutations and tumor suppressor inactivatin mutations.

Harms PW[1], Hovelson DH[2], Cani AK[2], Omata K[2], Haller MJ[2], Wang ML[3], Arps D[4], Patel RM[4], Fullen DR[4], Wang M[3], Siddiqui J[5], Andea A[4], Tomlins SA[6].

5 porocarcinomas by next-generation sequencing using the Oncomine Comprehensive Assay:

- **En 4 (80%) de 5 tumores**, se identificó al menos 1 potencial driver oncogénico potencial
- **Mutaciones genes supresoras de tumores :**
  - TP53 (4/5, 80%)
  - RB1 (3/5, 60%)
  - ATM (2/5, 40%)
  - ARID1A (1/5, 20%)
  - CDKN2A (1/5, 20).

- **Mutaciones activadores de HRAS** 2 (40%) de 5: mutaciones en el exón 2 (p.G13D) y el exón 3 (p.Q61L) Hospot

- **Mutaciones en EGFR** en 2 (40%) de 5.

HRAS y EGFR como mutaciones driver en un subconjunto de poroma y porocarcinoma.
La inactivación de TP53 y RB1 también pueden contribuir a la tumorigénesis.
Implicaciones para la terapia dirigida en casos metastásicos o no resecables.

Pathology (■ 2017) ■(■), pp. 1–6

Targeted molecular profiling reveals genetic heterogeneity of poromas and porocarcinomas

MARTINA BOSIC[1], MARTINA KIRCHNER[2], DIMITRIJE BRASANAC[1], JONAS LEICHSENRING[2], AMELIE LIER[2], ANNA-LENA VOLCKMAR[2], CRISTIANO OLIVEIRA[2], IVO BUCHHALTER[2], FABIAN STÖGBAUER[2], SNEZANA ZIVKOVIC-PERISIC[3], BENJAMIN GOEPPERT[2], PETER SCHIRMACHER[2,4], ROLAND PENZEL[2], VOLKER ENDRIS[2] AND ALBRECHT STENZINGER[2,4]

[1]*Institute of Pathology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia;* [2]*Institute of Pathology, University of Heidelberg, Heidelberg, Germany;* [3]*Institute of Public Health 'Dr Milan Jovanovic Batut', Belgrade, Serbia; and* [4]*German Cancer Consortium (DKTK), Heidelberg, Germany*

- NGS of 50 cancer-related genes in **12 cases** (6 poromas and six porocarcinomas)
- Non-synonymous mutations were found in **2/3 in several tumor suppressors** (RB1, APC, CDKN2A and PTEN) and genes implicated in **PI3K-AKT and MAPK pathways** (ABL1, PDGFRA, PIK3CA, HRAS and PTEN)
- Hotspot HRAS mutation in 2 poromas (p.G13R and p.Q61R) and one porocarcinoma (p.G13C)
- P53 mutations were found in all porocarcinoma(not poromas)

Table 2 Mutated genes in poromas and porocarcinomas

Patient ID	Diagnosis	Gene	Exon	Mutations (nucleotide)	Mutations (amino acid)	Allele frequency (%)	Coverage (absolute reads)	COSMIC ID	COSMIC incidence	UV
1	P	*HRAS*	3	c.182A>G	p.Q61R	43.75	1437	COSM499	240	No
2	P	*ERBB4*	15	c.1771G>A	p.E591K	5	2982	COSM5590820	2	No
3	P	*HRAS*	2	c.37G>C	p.G13R	27.62	1404	COSM486	350	No
4	P	No mutation								
5	P	*APC*	16	c.4298C>T	p.P1433L	3.57	2130	COSM5880106	5	Yes
6	P	No mutation								
7	PC	No mutation								
8	PC	*TP53*	8	c.836G>A	p.G279E	18.92	741	COSM43714	42	No
		PTEN	7	c.640C>T	p.Q214*	9.06	2005	COSM1169525	2	Yes
9	PC	*TP53*	8	c.833C>T	p.P278L	28.02	1067	COSM10863	81	Yes
		TP53	6	c.640_642ATG>TA	p.H214fs*1	13.45	2523	No entry		No
		ABL1	4	c.715C>T	p.R239C	24.25	5299	No entry		No
		RB1	17	c.1654C>T	p.R552*	21.86	1704	COSM887	9	No
		PDGFRA	15	c.2023G>A	p.E675K	10.2	3168	No entry		No
		PIK3CA	10	c.1633G>A	p.E545K	9.1	2600	COSM763	1596	No
10	PC	*TP53*	8	c.916C>T	p.R306*	63.48	942	COSM145026	18	Yes
11	PC	No mutation								
12	PC	*HRAS*	2	c.37G>T	p.G13C	20.77	2104	COSM486	350	No
		TP53	8	c.833C>T	p.P278L	14.71	442	COSM10863	81	Yes
		CDKN2A	2	c.330_331GG>AA	p.W110*	15.83	1203	No entry		Yes
		CDKN2A	2	c.341C>T	p.P114L	15.11	1211	COSM12476	46	Yes
		RET	10	c.1865C>T	p.P622L	12.34	1232	No entry		Yes
		APC	16	c.4298C>T	p.P1433L	5.39	1798	COSM5880106	5	Yes

TUMOUR TYPE	POROMAS			POROCARCINOMAS				
Study	Harms et al. 2016	Present study	Summed results	Dias-Santagata et al. 2011	Le et al. 2012	Harms et al. 2016	Present study	Summed results
Technology	SS	NGS	/	SS	SS	NGS	NGS	/
Tested genes (N)	1	50	/	15	15	126	50	/
Examined cases (N)	17	6	6-23	4*	11	5	6	5-26
Mutations per case (N)	0-1	0-1	0-1	0-1	0-1	1-7	0-6	0-7
Mutated genes								
ABL1		0%	0%			0%	17%	9%
APC		17%	17%	0%	0%	0%	17%	4%
ARID1A						20%		
ATM		0%	0%			20%	0%	9%
CDKN2A		0%	0%			20%	17%	18%
EGFR		0%	0%	0%	0%	40%	0%	7%
ERBB2		0%	0%			20%	0%	9%
ERBB4		17%	17%			0%	0%	0%
HRAS	12%	33%	17%			40%	17%	12%
NCOR1						20%		20%
PBRM1						20%		20%
PDGFRA		0%	0%			0%	17%	9%
PIK3CA		0%	0%	25%	18%	0%	17%	9%
PTEN		0%	0%	0%	0%	0%	17%	4%
RB1		0%	0%			60%	17%	36%
RET		0%	0%			0%	17%	9%
TP53		0%	0%	0%	0%	80%	67%	31%

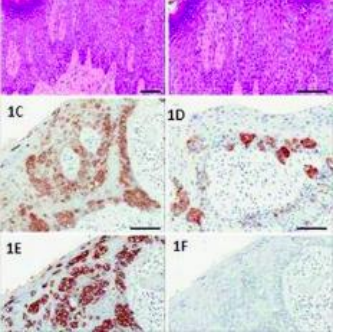
Mutation frequency	0%	25%	50%	75%	100%
	0%	25%	50%	75%	100%
	not tested				

Summary of genetic profiling studies on poromas and porocarcinomas. Technologies for detection of mutations, number of tested genes, number of examined nd mutational load were taken into consideration. The heat map visualises frequencies of mutations per gene and tumour type (poromas, orange; porocarcinomas, N, absolute number; NGS, next generation sequencing; SS, Sanger sequencing; *, four samples were tested from two patients and primary and metastatic tumours atched.

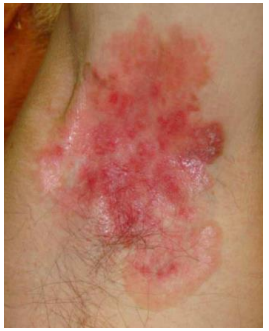
>supresores de tumores defectuosos en los porocarcinomas con respecto a poromas

papel de la mutagénesis inducida por TP53 y UV en el desarrollo de porocarcinomas

missense mutations (p.G279E and p.P278L): UV -RELATED



ENFERMEDAD DE PAGET EXTRAMAMARIA



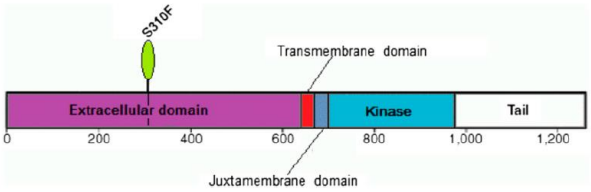
- Paget: Células con diferenciación gandular en la epidermis
- Se origina de las glándulas apocrinas o de queratinocitos germinales, tronculares "**totipotenciales" de las glándulas apocrinas o células Toker**
- Placas eccematosas bien demarcadas, predominantemente ubicadas en la **región anogenital** y con menor frecuencia en las **axilas**
- Puede concurrir una **2º neoplasia sincrónica : GU-GI : 9-32%**
- **Asociación familiar**
- Localizado: resección quirúrgica (1-1.5cm margen)+ terapia local: imiquimod, cremas 5FU→ buen pronóstico
- Esquemas QT:Mit C+5FU+ Epirrubicina, Vincristina, Cisplatino, Carbo-Docetaxel
- Enf avanzada: **50-60% sobreexpresión de HER2** :respuestas prolongadas con trastuzumab→ Testar
- Se han descrito mutaciones de las vías PIK3CA, AKT1 y RAS / RAF
- **Factores de mal pronóstico**: EMPD anorrectal, raditerapia en monoterapia,afectación dérmica, ganglionar o enfermedad avanzada y edad avanzada[1]
- Supervivencia 5 años: 50% para enferemedad avanzada[1]

Karam A, Dorigo O. Treatment outcomes in a large cohort of patients with invasive extramammary Paget's disease. Gynecol Oncol 2012;125:346–51

The Oncologist®

Treatment of Metastatic Extramammary Paget's Disease Associated With Adnexal Adenocarcinoma, With Anti-HER2 Drugs Based on Genomic Alteration ERBB2 S310F

- RE; 10-20% IH HER-2 FISH HER2 negativo
- AC X6: RP
- Letrozol mantenimineto.
- FoundationOne Mutación puntual: ERBB2 S310F
- Capecitabina-lapatinib: 1 año: RP



Case Report

Metastatic Extramammary Paget's Disease of Scrotum Responds Completely to Single Agent Trastuzumab in a Hemodialysis Patient: Case Report, Molecular Profiling and Brief Review of the Literature

- EPD escrotal EIV (ósea , ganglionar)
- Hemodialisis
- Trastuzumab 6mg/kg
- RC tras 3 ciclos. Mantenimiento > 1 año

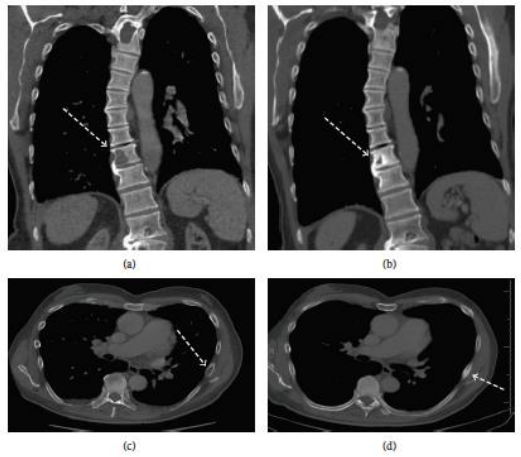


Figure 4: (a) Pretherapy T10 vertebral body lytic metastasis, (b) posttherapy T10 vertebral body becoming sclerotic, (c) pretherapy left 7th rib lytic metastasis, and (d) posttherapy left 7th rib met becoming sclerotic.

Case Report

Metastatic Extramammary Paget's Disease of Scrotum Responds Completely to Single Agent Trastuzumab in a Hemodialysis Patient: Case Report, Molecular Profiling and Brief Review of the Literature

Molecular profiling (Caris Life Science)

Table 1: Percent of cases by subtype with biomarker aberration and comparison of total EMPD versus MPD.

Primary tumor site	IHC																ISH		Sequencing	
	AR	BCRP	ER	Her2	MGMT	MRP1	PD-1	PD-L1	PDGFR	PR	PTEN*	RRM1*	TLE3	TOP2A	TOPO1	TS*	cMYC	EGFR	Her2	BRCA2	PIK3CA
Anus ($n = 2$)	0%	NT	0%	0%	0%	50%	NT	NT	NT	0%	50%	50%	NT	100%	0%	100%	NT	50%	NT	NT	NT
Scrotum ($n = 1$)	100%	NT	100%	0%	100%	NT	100%	100%	NT	0%	0%	0%	100%	100%	100%	0%	0%	NT	0%	100%	100%
Vulva ($n = 9$)	67%	67%	22%	44%	44%	75%	NT	NT	67%	11%	89%	67%	0%	44%	44%	89%	0%	0%	0%	NT	0%
All EMPD ($n = 12$)	**58%**	**67%**	**25%**	**33%**	**42%**	**70%**	**100%**	**100%**	**67%**	**8%**	**75%**	**58%**	**50%**	**58%**	**42%**	**83%**	**0%**	**11%**	**0%**	**100%**	**50%**
MPD ($n = 8$)	50%	33%	71%	36%	40%	75%	NT	NT	25%	43%	67%	100%	100%	20%	80%	100%	100%	0%	25%	NT	100%

Biomarker and technology used are shown for each subtype, as percent of total cases. A total of EMPDs are also compared to MPD. Percent in each box refers to overexpression of target proteins except for PTEN*, RRM1*, and TS*, where the percent refers to underexpression of the target. Genes in which no mutation was found: ABL1, AKT1, ALK, ATM, BRAF, BRCA1, BRCA2, CDH1, c-KIT, cMET, CSF1R, CTNNB1, EGFR, ERBB2, ERBB4, FBXW7, FGFR1, FGFR2, FLT3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, JAK2, JAK3, KDR, KRAS, MLH1, MPL, NOTCH1, NPM1, NRAS, PDGFRA, PIK3CA, PTEN, PTPN11, RB1, RET, SMAD4, SMARCB1, SMO, STK11, TP53, and VHL.
IHC, immunohistochemistry; ISH, fluorescence in situ hybridization.

Differences in protein expression leves, CN, gene mutations.

EMPD: (12): RE 25%, HER2: 33%, **PD-1: 100%, PD-L1: 100%, BRCA2: 100%, PTEN: 75%** PI3KCA: 50%

-Scrotum: ER and AR

-Vulva: HER2: 44%

MPD: (8): **RE 71%,** HER2: 36%, PTEN:67%, **PI3K;100%**

Peter Barth . Metastatic Extramammary Paget's Disease of Scrotum Responds Completely to Single Agent Trastuzumab in a Hemodialysis Patient: Case Report, Molecular Profiling and Brief Review of the Literature

OPCIONES TERAPÉUTICAS PROPUESTAS:

- Tratamiento hormonal: Si RE/RP +
- Terapia antiHERE2: Trastuzumab, Cape, Pertuzumab , T-DM1
- Inhibidores PI3KC
- CPI: PD-1, PD-L1

- IMPORTANCIA DE LA SECUENCIACIÓN*

CARCINOMA ADENOIDE QUISTICO (ACC)

- Variante del adenocarcinoma
- **Crecimiento lento: pero invasión local** y puede metastatizar
- Puede surgir en múltiples tipos de órgano: **más frecuente glándula salival (2º).** Otros: piel, mama, pulmón, próstata, glándula lagrimal, tracto genital femenino y tracto gastrointestinal
- El diagnóstico de ACC en la mitad inferior de la cara debe impulsar la evaluación de la diseminación local de ACC de las glándulas salivales
- ACC cutáneo, pronóstico más favorable que el salival
- Característica: translocación entre el **cromosoma 6q y 9p** y la identificación del gen de fusión resultante MYB-NFIB y causa la desregulación del gen MYB
- Extirpación quirúrgica con márgenes de 2cm. Radioterapia adyuvante

1. North JP, McCalmont TH, Fehr A, et al. Detection of MYB Alterations and Other Immunohistochemical Markers in Primary Cutaneous Adenoid Cystic Carcinoma. Am J Surg Pathol 2015; 39:1347.

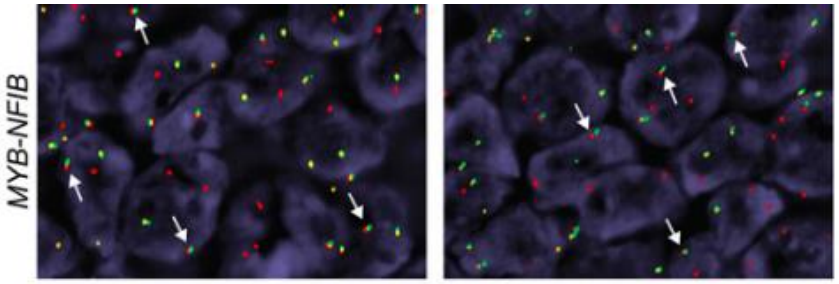
- No QT estándar: Cisplatino, doxorubicina en combinación con ciclofosfamida ORR: 25% , respuestas cortas[1,2,3]

1. Belani CP, Eisenberger MA, Gray WC. Preliminary experience with chemotherapy in advanced salivary gland neoplasms. Med Pediatr Oncol 1988;16:197–202. [PubMed]
2. Creagan ET, Woods JE, Rubin J, Schaid DJ. Cisplatin-based chemotherapy for neoplasms arising from salivary glands and contiguous structures in the head and neck. Cancer 1988;62:2313–2319. [PubMed]
3. Licitra L, Grandi C, Palma SD, et al. Cisplatin, doxorubicin and cyclophosphamide in advanced salivary gland carcinoma: a phase II trial of 22 patients. Ann Oncol 1996;7:640–642. [PubMed]
4, Hitre E, Takacsi-Nagy Z, Rubovszky G, et al. Cetuximab and platinum-based chemoradio- or chemotherapy of patients with epidermal growth factor receptor expressing adenoid cystic carcinoma: a phase II trial. Br J Cancer 2013;109:1117–1122

Combining EGFR inhibitors; platinum-based chemotherapy; and radiotherapy, when indicated, may be a viable treatment approach in ACC.

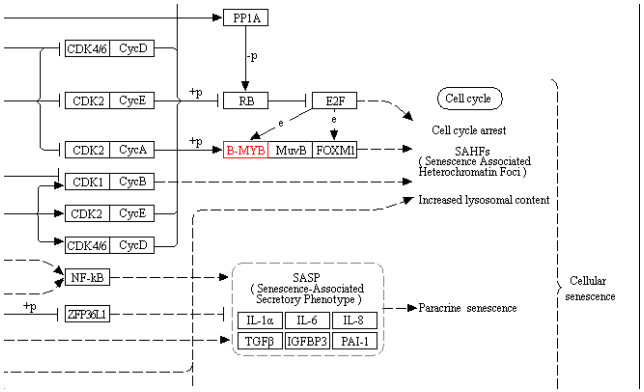
Objective responses were found in four **(44%)** patients with **locally advanced disease** and five **(42%)** patients with **metastatic disease**

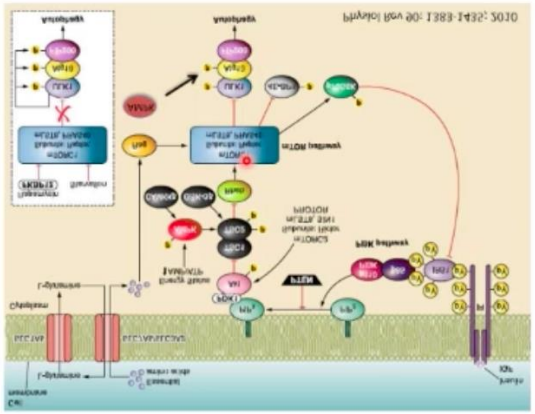
II	Cetuximab + RT + cisplatin or Cetuximab + cisplatin and 5-FU(*n* = 21^)	-Locally advanced ACC (*n* = 9): IV cetuximab loading dose 400 mg/m^2 1 week prior to radiation, followed by weekly IV cetuximab 250 mg/m^2 + concomitant RT + weeks 1, 3, 5 IV cisplatin 75 mg/m^2 on days 1, 21 and 42. -Metastatic ACC (*n* = 21): IV cetuximab loading dose 400 mg/m^2 in the 1st week of treatment followed by weekly IV cetuximab 250 mg/m^2 + IV cisplatin 75 mg/m^2 on day 1 + continuous 5-FU IV 1000 mg/m^2/day on days 1–4.	EGFR	Completed	-PFS - Secondary outcome : ORR, OS	-Locally advanced ACC (*n* = 9): Median PFS 64 months. 2 CR (22%), 2 PR (22%), 5 SD (55.6%), no PD (0%). OS was not reached. -Metastatic ACC (*n* = 12): Median PFS 13 months, Maximum PFS 48 months. 5 PR (42%), 7 SD (58%), no PD (0%). OS 24 months.	EudraCT 2006–001694-23 [58]



MYB-NFIB

- La translocación entre los cromosomas t (6; 9) (q22–23; p23–24), que resulta en el gen de fusión MYB-NFIB
- MYB-NFIB regula genes involucrados en el control del ciclo celular, la replicación /reparación del ADN y el procesamiento del ARN
- MYB-NFIB es un driver oncogénico y un target terapéutico regulado por la señalización de IGF1R dependiente de AKT





ARTICLE

Targeting the Oncogenic Transcriptional Regulator MYB in Adenoid Cystic Carcinoma by Inhibition of IGF1R/AKT Signaling

Mattias K. Andersson, Maryam K. Afshari, Ywonne Andrén, Michael J. Wick, Göran Stenman

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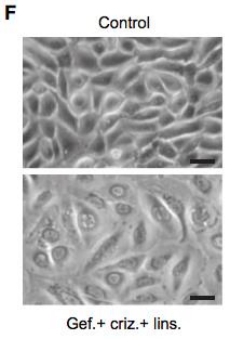
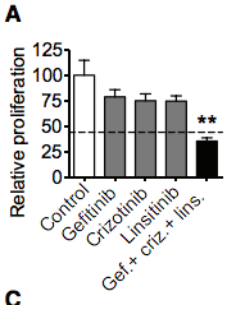
Correspondence to: Göran Stenman, DMD, PhD, Sahlgrenska Cancer Center, University of Gothenburg, Box 425, SE-405 30 Gothenburg, Sweden (e-mail: goran.stenman@gu.se).

- Estudios de cultivos celulares o tumores de 15 pacientes con ACC
- La fusión se regula a través de la señalización dependiente de AKT inducida por la **sobreexpresión de IGF1R** y se regula a la baja con la inhibición de IGF1R
- La coactivación del receptor del factor de crecimiento epidérmico (EGFR) y y MET promovió la proliferación de las células ACC,
- Terapia combinada con inhibidores IGFR1 / EGFR / MET inhibió sinérgicamente el crecimiento de xenoinjertos derivados del paciente
  - In our study, linsitinib only slightly reduced the growth of xenografted human ACCs
  - combined targeting of IGF1R, EGFR, and MET statistically significantly reduced MYB expression and the growth of xenografted human ACCs





Proliferation of ACC cells treated for 72 hours with inhibitory concentrations (IC25) of single and multiple tyrosine kinase inhibitors (

JNCI J Natl Cancer Inst (2017)

Expresión c-Kit: 90%

c-Kit have not shown efficacy as single agents in ACC

Downstream effectors of MYB, such as c-KIT, could pose an alternative approach to reduce MYB activity.

I	Imatinib (*n* = 4)	Oral 400 mg daily	c-kit	Completed	OR, SD	-No objective responses. -1 patient with SD (25%)	[50]
II	Imatinib (*n* = 16)	Oral 400 mg twice per day	c-kit	Completed	OR, SD	No objective responses. -9 patients with SD (56%)	[51]
II	Imatinib (*n* = 10)	Oral 400 mg daily, dose modification allowed.	c-kit	Completed	ORR	-No objective responses. -2 patients (20%) had SD, both for ≥ 6 months.	[52]
II	Imatinib + cisplatin (*n* = 28)	Oral imatinib 800 mg daily for 2 months, followed by cisplatin IV 80 mg/m^2 every 4 weeks with Oral imatinib 400 mg daily up to 6 cycles. Oral imatinib 400 mg daily after completion of chemotherapy.	c-kit	Completed	ORR[#]	-PR: 3 patients (11%). -SD: 19 patients (68%). -Median time to progression : 15 months-Median OS: 35 months.	[53]
II	Dasatinib (*n* = 40[+])	Oral 70 mg daily for 4 weeks in a 4-week cycle.	c-kit	Active, not recruiting	ORR, PFS	-No objective responses. -0 patient had PR (0%), 21 patients had SD (52%). -Median PFS was 4.8 months.	NCT00859937 [54]

CARCINOMA ANEXAL MICROQUÍSTICO (MAC)

- También conocido como carcinoma esclerosante de conductos del sudor
- Crecimiento lento pero localmente agresiva
- Se suele presentar en la zona central cara
- Deriva de células queratonociticas pluripotenciales
- FR: Inmunosupresión, exposición UV
- Escisión quirúrgica convencional con evaluación del margen patológico + radioterapia adyuvante
- No tratamiento estándar en la enfermedad metastásica metastásica

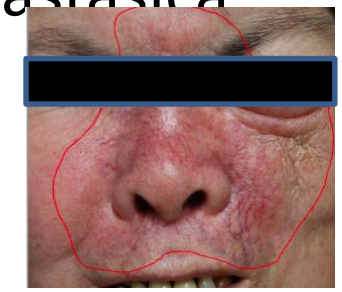


Photo Courtesy of T. Namiki

ANTICANCER RESEARCH *37*: 5109-5111 (2017)
doi:10.21873/anticanres.11929

Metastatic Microcystic Adnexal Carcinoma with DNA Sequencing Results and Response to Systemic Antineoplastic Chemotherapy

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[1]*Department of Oncology, Kunshan First People's Hospital Affiliated to Jiangsu University, Kunshan, P.R. China;*
[2]*Section of Satellite Oncology, Moffitt Cancer Center and Division of Hematology/Oncology, Morsani School of Medicine, University of South Florida, Tampa, FL, U.S.A.*

- Solo **4 casos de pacientes metastásicos** han sido reportados en la literatura y ninguno recibió terapia sistémica.
- MAC EIV (pulmón, hígado, LN, bazo)
- NGS con un panel de 435 genes para tumores sólidos
- Mutación en **TP53** y pérdidas cromosómicas en el inhibidor de la quinasa dependiente **de ciclina 2A (CDKN2A)** y el inhibidor de la quinasa dependiente de ciclina **2B(CDKN2B)**
- Carboplatino-Taxol x 4 ciclos con PR
- En PD, planeado para iniciar CDK4 / 6 inhibidores

Pilot Study of a Next-Generation Sequencing-Based Targeted Anticancer Therapy in Refractory Solid Tumors at a Korean Institution

Hyung Soon Park[1,2], Sun Min Lim[3], Sora Kim[4], Sangwoo Kim[4], Hye Ryun Kim[2], KyuBum Kwack[5], Min Goo Lee[1], Joo-Hang Kim[3], Yong Wha Moon[3]*

1 Department of Pharmacology and Brain Korea 21 Plus Project for Medical Sciences, Yonsei University College of Medicine, Seoul, Korea, 2 Division of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea, 3 Medical Oncology, Department of Internal Medicine, CHA Bundang Medical Center, CHA University, Seongnam, Korea, 4 Severance Biomedical Science Institute and Brain Korea 21 Plus Project for Medical Sciences, Yonsei University College of Medicine, Seoul, Korea, 5 Department of Biomedical Science, College of Life Science, CHA University, Seongnam, Korea

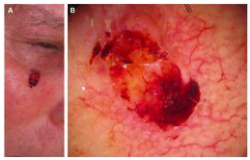
- FoundationOne NGS in 36 refractory solid tumors at a Korean institution
- Extracted tumor genomic DNA
- **BRAF mutation** in microcytic adnexal carcinoma
- **Sorafenib** target: PDFRG and RAF

Table 3. Outcomes of matched therapy.

Patient number	Age	ECOG status	Tumor type	Targeted mutation	Other mutation	Drug	Best response	TTP (months)
1	63	2	External auditory canal adenocarcinoma	PDGFRA (L710F)	FBXW7	Sorafenib	PR (-68%)	3.7
2	37	1	Parotid carcinosarcoma	PIK3CA (H1047R)	ROS1, ERBB3, TP53	Everolimus	PR (-30%)	5.8
3	48	1	Tracheal squamous cell carcinoma	PIK3CA (H1047R)	MAP2K1	Everolimus	SD (-21%)	6.7
4	49	3	Microcystic adnexal carcinoma of scalp	BRAF (D22G)	None	Sorafenib	PD	0.7
5	63	2	Esophagus adenocarcinoma	ERBB2 (P597H)	PIK3C2B, TP53	Afatinib	PD	0.9

ECOG, Eastern Cooperation Oncology Group; TTP, time to progression; PR, partial response; SD, stable disease; PD, progressive disease.

CARCINOMA SECRETOR ANÁLOGO MAMARIO CUTÁNEO (MASC)



- Tumores de bajo grado
- Se produce glándulas salivales (parótida) y mama
- Son análogos por la histopatología al carcinoma secretor de glándula mamaria
- Es un carcinoma de bajo grado del conducto sudoríparo causado por una translocación entre cromosomas **t (12; 15)** que produce el gen de fusión **ETV6-NTRK3[1]: 2010**
- Activación oncogénica del neurotrophic receptor tyrosine **NTRK1, NTRK2 y NTRK3** en tumores malignos humanos
- Involucran el dominio carboxi-terminal del receptor de tirosina

Courtesy of Luis Javier del Pozo, MD, Illes Balears, Spain.

Secretory Carcinoma of the Skin Harboring ETV6 Gene Fusions: A Cutaneous Analogue to Secretory Carcinomas of the Breast and Salivary Glands.AUBishop JA, Taube JM, Su A, Binder SW, Kazakov DV, Michal M, Westra WH SOAm J Surg Pathol. 2017;41(1):62.

Annals of Oncology Advance Access published March 16, 2016

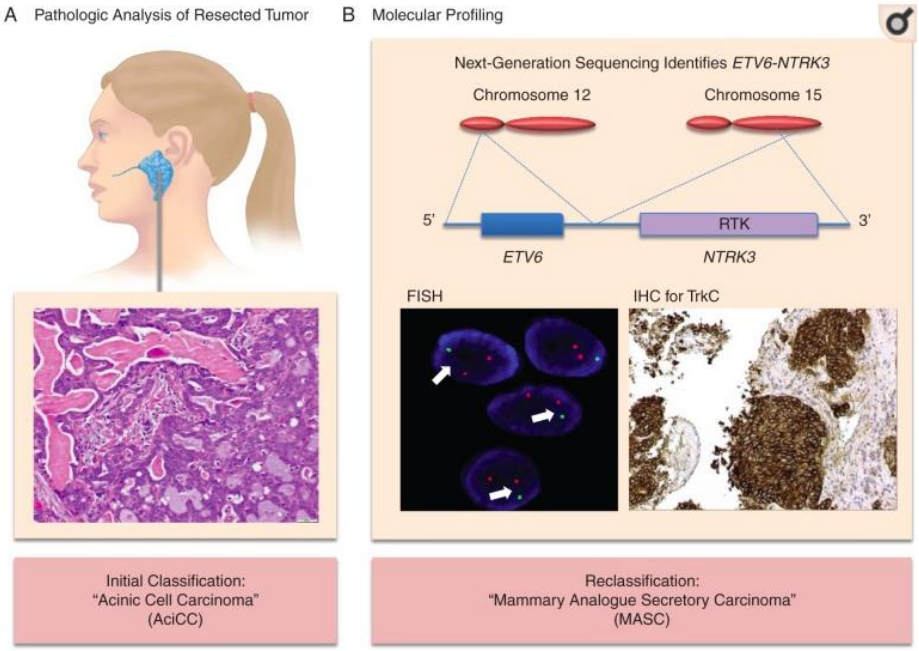
original article

Annals of Oncology 00: 1–7, 2016
doi:10.1093/annonc/mdw042

What hides behind the MASC: clinical response and acquired resistance to entrectinib after *ETV6-NTRK3* identification in a mammary analogue secretory carcinoma (MASC)

A. Drilon[1,2], G. Li[3], S. Dogan[4], M. Gounder[1,2], R. Shen[5], M. Arcila[4], L. Wang[4], D. M. Hyman[1,2], J. Hechtman[4], G. Wei[3], N. R. Cam[3], J. Christiansen[3], D. Luo[3], E. C. Maneval[3], T. Bauer[6], M. Patel[7], S. V. Liu[8], S. H. I. Ou[9], A. Farago[10], A. Shaw[10], R. F. Shoemaker[3], J. Lim[3], Z. Hornby[3], P. Multani[3], M. Ladanyi[4], M. Berger[4], N. Katabi[4], R. Ghossein[4] & A. L. Ho[1,2*]

pathology from a superficial parotidectomy

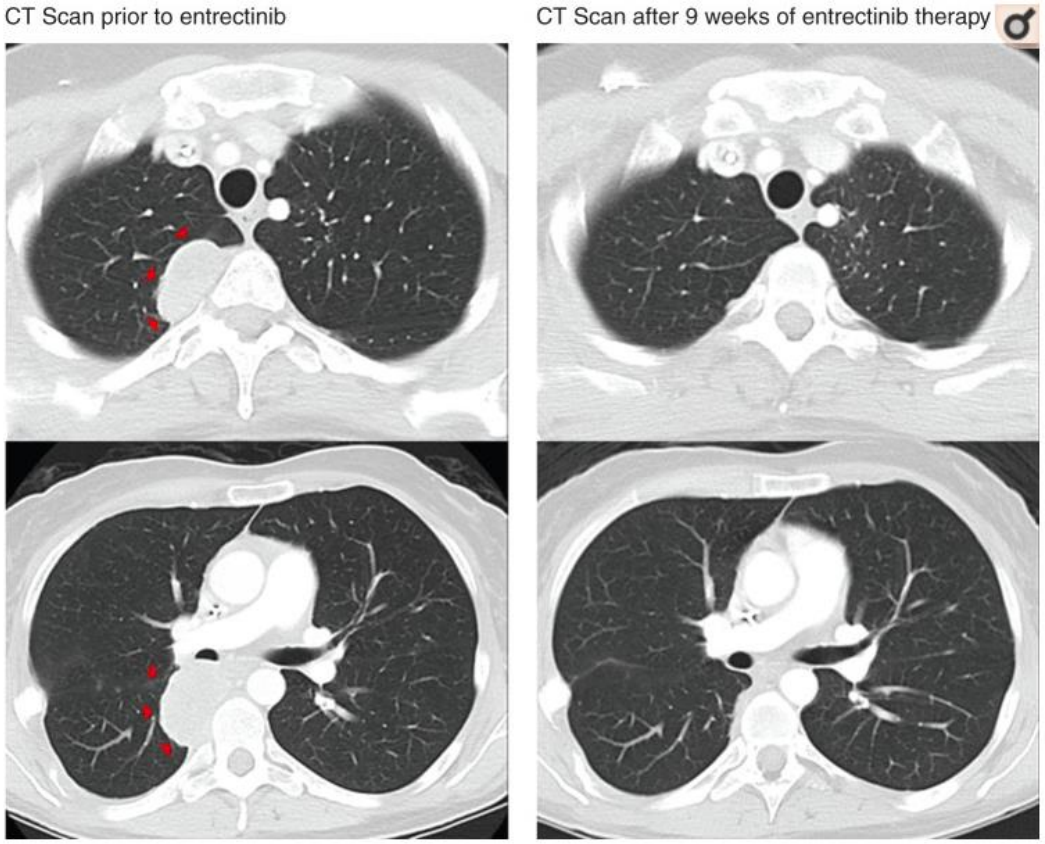


***ETV6-NTRK3* fusion** detected via broad, hybrid-capture-based **next-generation sequencing**.

Reciprocal **translocation between chromosome 12 and chromosome 15 resulted in fusion of *ETV6* exons 1–5 to *NTRK3* exons 15–20 containing the receptor tyrosine kinase (RTK) domain**.

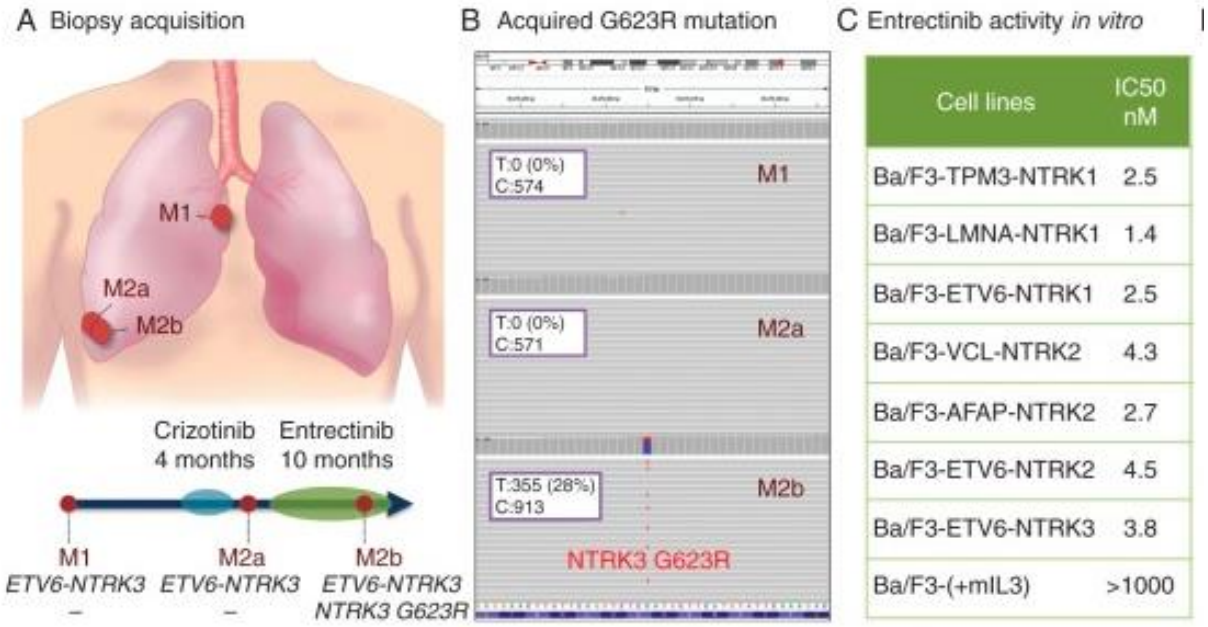
On the lower left, a **positive break-apart FISH) *NTRK3*** assay is shown with split signals (arrows).
On the lower right, **IHQ for TrkC revealed strong staining signifying TrkC** overexpression.

This alteration was targeted with the pan-Trk inhibitor **entrectinib (Ignyta),** which possesses potent in vitro activity against cell lines containing various NTRK1/2/3 fusions



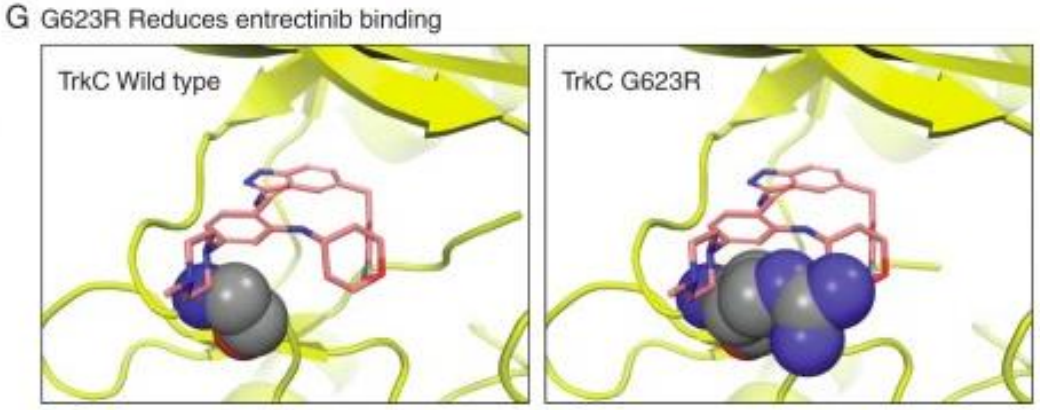
A durable partial response is achieved with entrectinib therapy in an *ETV6-NTRK3*-rearranged mammary analogue secretory carcinoma. Computed tomography (CT) imaging of the patient after progression on crizotinib and before entrectinib therapy is shown on the left. Repeat CT imaging at 9 weeks revealed a dramatic partial response to therapy (RECIST v1.1) with an interval decrease and resolution of pleural-based metastases in the right hemithorax (arrows). This response was confirmed at 13 weeks and further shrinkage was noted at 21 weeks. A best radiologic response of 89% reduction in tumor burden from baseline was achieved.

The development of clinical entrectinib resistance is mediated by the appearance of a novel ***NTRK3* G623R**



Cell lines	IC50 nM
Ba/F3-TPM3-NTRK1	2.5
Ba/F3-LMNA-NTRK1	1.4
Ba/F3-ETV6-NTRK1	2.5
Ba/F3-VCL-NTRK2	4.3
Ba/F3-AFAP-NTRK2	2.7
Ba/F3-ETV6-NTRK2	4.5
Ba/F3-ETV6-NTRK3	3.8
Ba/F3-(+mIL3)	>1000

broad, hybrid-capture-based next-generation sequencing confirmed the **appearance of an *NTRK3* G623R mutation after progression on entrectinib**



The substitution of arginine for glycine at position 623 results in steric hindrance that decreases the binding of entrectinib to mutant TrkC

- All suspected MASC neoplasms, including Acinic cell carcinomas and other morphologically similar low-grade salivary tumors, shouls undergo molecular profiling for **ETV6-NTRK**
- In a series of nonparotid AciCC cases, **79%** of tumors harbored ETV6-NTRK3 rearrangements, resulting in a change in diagnosis to MASC [1]

Bishop JA, Yonescu R, Batista D, Eisele DW, Westra WH. Most nonparotid “acinic cell carcinomas” represent mammary analog secretory carcinomas. Am J Surg Pathol 2013; 37: 1053–1057.

The NEW ENGLAND JOURNAL of MEDICINE

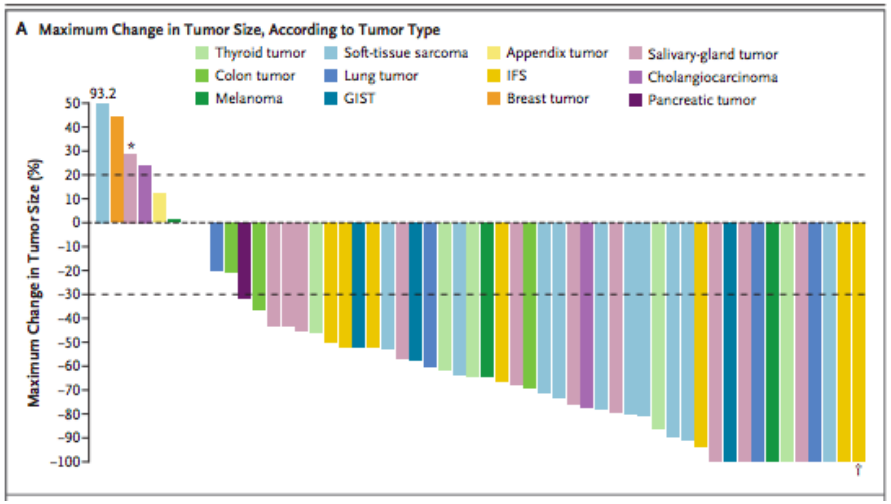
ORIGINAL ARTICLE

Efficacy of Larotrectinib in *TRK* Fusion–Positive Cancers in Adults and Children

A. Drilon, T.W. Laetsch, S. Kummar, S.G. DuBois, U.N. Lassen, G.D. Demetri, M. Nathenson, R.C. Doebele, A.F. Farago, A.S. Pappo, B. Turpin, A. Dowlati, M.S. Brose, L. Mascarenhas, N. Federman, J. Berlin, W.S. El-Deiry, C. Baik, J. Deeken, V. Boni, R. Nagasubramanian, M. Taylor, E.R. Rudzinski, F. Meric-Bernstam, D.P.S. Sohal, P.C. Ma, L.E. Raez, J.F. Hechtman, R. Benayed, M. Ladanyi, B.B. Tuch, K. Ebata, S. Cruickshank, N.C. Ku, M.C. Cox, D.S. Hawkins, D.S. Hong, and D.M. Hyman

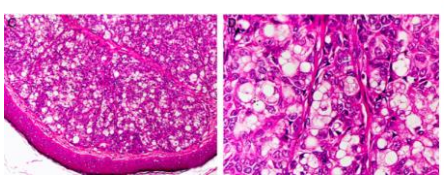
- N: **55 patients**
- **ORR 75%**
- **At 1 year, 71%** of the responses were ongoing and 55% of the patients remained progression-free
- The median duration of response and progression-free survival had not been reached
- Larotrectinib had marked and durable antitumor activity in patients with TRK fusion–positive cancer
- mammary analogue secretory carcinoma of the salivary gland (in 12 patients)

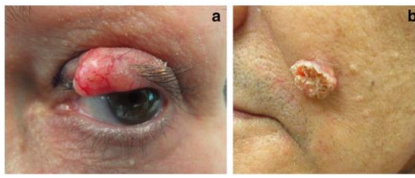
Tumor type — no. (%)	
Salivary-gland tumor	12 (22)
Other soft-tissue sarcoma‡	11 (20)
Infantile fibrosarcoma	7 (13)
Thyroid tumor	5 (9)
Colon tumor	4 (7)
Lung tumor	4 (7)
Melanoma	4 (7)
GIST	3 (5)
Cholangiocarcinoma	2 (4)
Appendix tumor	1 (2)
Breast tumor	1 (2)
Pancreatic tumor	1 (2)



2. TUMORES CON DIFERENCIACIÓN SEBACEA: CARCINOMA SEBACEO

- Es una de las 4 neoplasias **más agresivas** de la piel
- Región de cabeza y cuello: **área periocular**
- Pueden aparecer **esporádicamente** o en asociación con el **síndrome de Muir-Torre**
- Las mutaciones inactivadoras en el factor potenciador linfoide 1 (LEF1) y **los genes MMR (**MSH2, MLH1 y MSH6) se han implicado en esta familia de tumores[1,2]
- Tratamiento: extirpación quirúrgica con disección ganglionar.
- QT-RTpoco efectivas.
- **Pronóstico malo**; S 5 años: <30%





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2. Everett JN, Raymond VM, Dandapani M, et al. Screening for germline mismatch repair mutations following diagnosis of sebaceous neoplasm. JAMA Dermatol 2014; 150:1315
photo courtesy of Razieh Soltani Arabshahi, MD

SINDROME DE MUIR TORRE

- Síndrome de cáncer hereditario caracterizado por la presencia de al menos una **neoplasia sebácea y una neoplasia visceral**(CCR> GU, mama, hepatobiliar)
- Se transmite de **manera AD** y es una **variante del síndrome de Lynch**
- Las mutaciones de la **línea germinal** en los genes MSH2, MSH6, MLH1 y PMS2 de reparación del ADN (MMR) dan como resultado una **inestabilidad de microsatélites (MSI) y un fenotipo hipermutable**
- MSI puede evaluarse mediante **PCR o IHQ** del estado del gen MMR: La expresión nuclear ausente de MSH-2, MSH-6, MLH-1 o PMS-2 es indicativa de mutaciones de la línea germinal en estos genes
- La pérdida de MSH-2 es el patrón más común

Chemotherapy with **5FU, paclitaxel, and platinum** can be beneficial in controlling the disease. Tumour profiling and genotype-based chemotherapy could be a promising direction for future studies in this rare disease

TABLE I

Systemic chemotherapy for the treatment of metastatic sebaceous carcinoma: case reports

Reference	Regimen	Response	
		Type	Duration (months)
Koyama *et al.*, 1994[8]	Vinblastine 5 mg/m^2 and cisplatin 80 mg/m^2 for 3 cycles; doxorubicin 50 mg/m^2 and cisplatin 75 mg/m^2 for 2 cycles	Shrinkage of metastatic lesions; survived for 7 months on chemotherapy	7
Murthy *et al.*, 2005[9]	Carboplatin and 5-fluorouracil for 3 cycles, followed by radiotherapy	Shrinkage of tumour, enabling eyelid-sparing exenteration surgery	26
Husain *et al.*, 2008[10]	Carboplatin–docetaxel–bevacizumab for 2 cycles, followed by carboplatin–docetaxel for 1 cycle	Shrinkage of lung mass to 30%, after which surgery could be planned; survived till 6 months after report on case	>6
Osada *et al.*, 2011[11]	5-Fluorouracil 800 mg/m^2 on days 1–5 and cisplatin 80 mg/m^2 on day 1 monthly	Recurrence- and metastasis-free at 20 months	>20
Joshi *et al.*, 2012[12]	Every-3-weeks paclitaxel 175 mg/m^2 and carboplatin AUC 5 for 6 cycles	Completely resolved without recurrence at 6 months	>6
Jung *et al.*, 2013[13]	5-Fluorouracil 750 mg/m^2 and cisplatin 75 mg/m^2 on days 1–5 (2 patients treated: one for 8 cycles; one for 3 cycles); trial of doxorubicin for 2 cycles in 1st case	Chemotherapy stopped after 15 months because of intolerance; regression of cutaneous lesions after 3 months	15
Orcurto *et al.*, 2014[14]	5-Fluorouracil 750 mg/m^2 daily for 4 days, cisplatin 100 mg/m^2 and docetaxel 75 mg/m^2 every 3 weeks for 4 cycles; capecitabine 1000 mg/m^2 daily days 1–10 every 21 days	Complete response at more than 20 months	>20
Present report	5-Fluorouracil–oxaliplatin–leucovorin (FOLFOX) for 5 months, followed by paclitaxel for 9 months, followed by gemcitabine for 2.5 months	On FOLFOX, stable disease by CT at 5 months, but progression on CT at 7 months; stable disease on paclitaxel, but didn't tolerate; gemcitabine had no effect on progression	17

AUC = area under the curve; CT = computed tomography.

V. Kumar et al. Unusual presentation of metastatic sebaceous carcinoma and its response to chemotherapy: is genotyping a right answer for guiding chemotherapy in rare tumours?

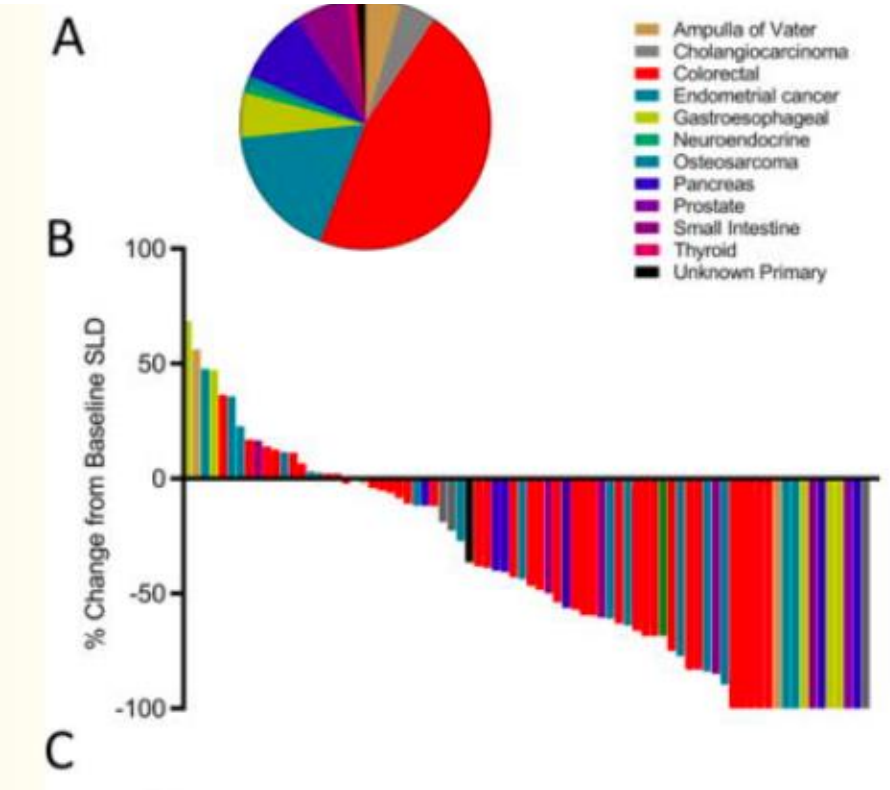
CANCER BIOMARKERS

Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade

Dung T. Le,[1,2,3] Jennifer N. Durham,[1,2,3*] Kellie N. Smith,[1,3*] Hao Wang,[3*] Bjarne R. Bartlett,[2,4*] Laveet K. Aulakh,[2,4] Steve Lu,[2,4] Holly Kemberling,[3] Cara Wilt,[3] Brandon S. Luber,[3] Fay Wong,[2,4] Nilofer S. Azad,[1,3] Agnieszka A. Rucki,[1,3] Dan Laheru,[3] Ross Donehower,[3] Atif Zaheer,[5] George A. Fisher,[6] Todd S. Crocenzi,[7] James J. Lee,[8] Tim F. Greten,[9] Austin G. Duffy,[9] Kristen K. Ciombor,[10] Aleksandra D. Eyring,[11] Bao H. Lam,[11] Andrew Joe,[11] S. Peter Kang,[11] Matthias Holdhoff,[3] Ludmila Danilova,[1,3] Leslie Cope,[1,3] Christian Meyer,[3] Shibin Zhou,[1,3,4] Richard M. Goldberg,[12] Deborah K. Armstrong,[3] Katherine M. Bever,[3] Amanda N. Fader,[13] Janis Taube,[1,3] Franck Housseau,[1,3] David Spetzler,[14] Nianqing Xiao,[14] Drew M. Pardoll,[1,3] Nickolas Papadopoulos,[3,4] Kenneth W. Kinzler,[3,4] James R. Eshleman,[15] Bert Vogelstein,[1,3,4] Robert A. Anders,[1,3,15] Luis A. Diaz Jr.[1,2,3]†‡

The genomes of cancers deficient in mismatch repair (MMR) contain exceptionally high numbers of somatic mutations. In a proof-of-concept study, we previously showed that colorectal cancers with MMR deficiency were sensitive to immune checkpoint blockade with anti-PD-1 antibodies. We have expanded this study to now evaluate efficacy of PD-1 blockade in patients with advanced MMR-deficient cancers across 12 different tumor types. Objective radiographic responses were observed in 53% of patients and complete responses were achieved in 21% of patients. Responses were durable with median progression-free and overall survival still not reached. Functional analysis in a responding patient demonstrated rapid in vivo expansion of neoantigen-specific T cell clones that were reactive to mutant neopeptides found in the tumor. These data support the hypothesis that the large proportion of mutant neoantigens in MMR-deficient cancers make them sensitive to immune checkpoint blockade, regardless of the cancers' tissue of origin.

N: 86
12 subtipos tumorales
Pembrolizumab
Fenotipo hipermutable:Neoantigenos: sensible CPI



CASE REPORT Open Access

Near complete response to Pembrolizumab in microsatellite-stable metastatic sebaceous carcinoma

Evidio Domingo-Musibay[1,6*], Paari Murugan[2,6], Alessio Giubellino[2,6], Sandeep Sharma[3], Daniel Steinberger[3], Jianling Yuan[4,6], Matthew A. Hunt[5,6], Emil Lou[1,6] and Jeffrey S. Miller[1,6]

- Carcinoma sebáceo EIV (cerebral, pulmonar, hepático, intestinal, LN, osea)
- **PDL1: 100% TC**
- Foundation Medicine: **microsatellite stable** and carried a mutational burden of **17mutations/Mb**

Table 1 Tumor genomic next generation sequencing (NGS) study reveals mutations in several genes, including somatic mutations in genes mutated in the sebaceous carcinoma COSMIC dataset (in bold)

Gene	Alteration	Subcellular localization	Pathway
LRP1B	G3156C, Q1125*	Plasma membrane	Receptor mediated endocytosis
CCND1	S41L	Nucleus; cytosol	Cyclin D1, cell cycle
TET2	P174H	Nucleoplasm	DNA demethylation
TP53	rearrangement, del exon 10-11	Nucleoplasm	DNA repair
FANCA	A816V, R685S	Nucleus	DNA repair
FGF6	A63T	Extracellular	Growth factor
MYST3	Q1681_Q1684del	Nucleolus; cytosol	Histone acetyltransferase (HAT)
KRAS	G12C	Cytosol	MAPK signalling
RBM10	F173fs*7	Nucleus	mRNA splicing
MET	amplification	Plasma membrane	Receptor tyrosine kinase
FGFR3	I539del	Endoplasmic reticulum	Receptor tyrosine kinase
FLT4	K520E, R658W	Nucleus; plasma membrane	Receptor tyrosine kinase
ROS1	N692H	Vesicles	Receptor tyrosine kinase
TERT	-124C>T	Nucleoplasm	Telomerase
WT1	R471S	Nucleoplasm	WT1 Transcription Factor
MYC	L435F	Nucleoplasm	MYC Transcription Factor
ZNF703	G406R	Nucleus	Transcriptional co-repressor
c11orf30	C1211S	Nucleoplasm	Trascriptional Repressor
FLCN	R320Q	Nucleus; cytosol	Tumor suppressor
TNFAIP3	R706Q	Cytosol	Ubiquitination

*denotes mutations causing a premature stop codon
fs denotes the presence of a frameshift mutation

mutations in:
-genes for regulatory transcription factors,
-**DNA repair** proteins
-**growth factor** receptors,
-targetable **MAPK** signaling proteins

CPI: pembrolizumab: RP mayor tras 6m

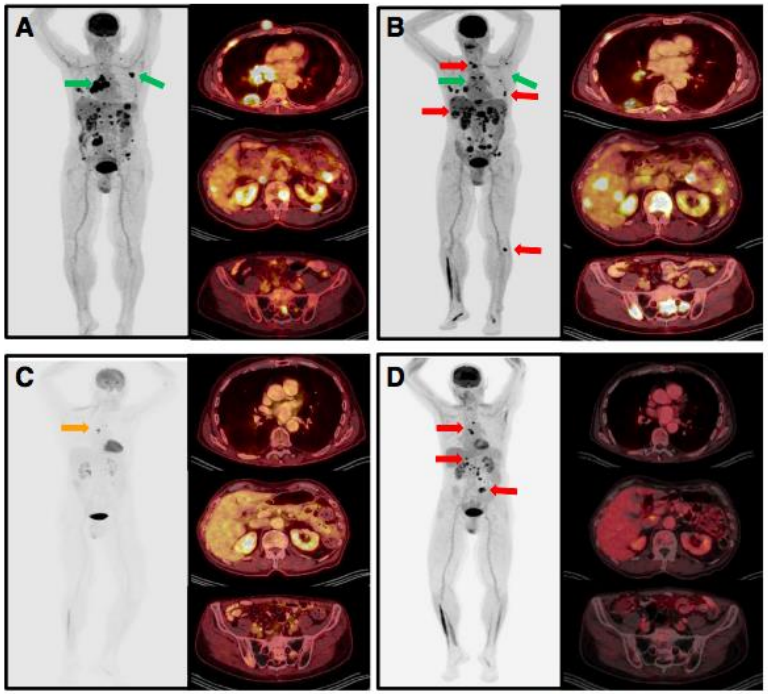


Fig. 3 Positron emission tomography (PET) maximum intensity projection (MIP) images and axial images from the chest, abdomen, and pelvis demonstrating the radiographic response to pembrolizumab therapy. **a** Baseline imaging shows extensive metastatic disease burden, and green arrows highlight lesions first to improve in lung, mediastinum, and axillary lymph nodes. **b** Imaging after 3 months (4 cycles) of pembrolizumab are consistent with mixed response and pseudoprogression, with several new hypermetabolic foci (red arrows) in soft tissue, liver and bone. **c** Imaging studies at 6 months shows a near complete response to 7 cycles of pembrolizumab, with regression of multiple hypermetabolic metastatic foci, and few small remaining foci of residual hypermetabolism in the chest and abdomen. **d** Imaging at 12 months shows persistent FDG avidity in mediastinal and abdominal lymph nodes and new FDG avid lesions in liver and small bowel (red arrows)

-patient's clinical response was associated with circulating CD8 + cytotoxic T lymphocytes in peripheral blood:

-The ongoing, durable response to checkpoint inhibition described in this report supports clinical testing of anti-PD1 checkpoint inhibitors **in MSS and MSI-high sebaceous carcinoma**

High expression of PD-1 and PD-L1 in ocular adnexal sebaceous carcinoma

Thomas J. Kandl, Oded Sagiv, Jonathan L. Curry, Jing Ning, Junsheng Ma, Courtney W. Hudgens, John Van Arnam, Jennifer A. Wargo, Bita Esmaeli & Michael T. Tetzlaff

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Further, we demonstrated that 50% of OASC specimens contained tumor cells expressing PD-L1, and these tumors were infiltrated by higher densities of PD-1 + T cells. Together, these observations suggest that the PD-1/PD-L1 axis is operational in a subset of primary OASCs, serving to inhibit the immune response and enable tumor progression, and further suggest that abrogation of the PD-1/PD-L1 axis through PD-1 blockade may be effective in the treatment of locally advanced or metastatic OASC.

Programmed death receptor Ligand 1 expression in eyelid sebaceous carcinoma: a consecutive case series of 41 patients

Shiqiong Xu,[1,†] Hong Yu,[2,†] Guohui Fu,[2] Xianqun Fan[1] and Renbing Jia[1]

TNM staging				PD-L1			
T	N	M	Staging	Percentage (%)	Intensity	PD-L1 lo/hi	Grade
T2c	N1	M1 lung	IV	1–50	++	Hi	Poor
T4c	N2	M0	III	>50	+++	Hi	Poor
T1c	N1	M0	III	1	+++	Hi	Moderate
T4d	N1	M0	III	<1	+	Lo	Poor
T4d	N2	M0	III	1–50	+++	Hi	Moderate
T4a	N1	M0	III	1–50	++	Hi	Moderate
T2c	N1	M0	III	<1	++	Lo	Poor
T1c	N1	M0	III	>50	+++	Hi	Poor
T4a	N1	M0	III	>50	+++	Hi	Poor
T2b	N1	M0	III	1–50	+++	Hi	Poor
T1b	N0	M0	IA	<1	+	Lo	Poor
T1b	N0	M0	IA	<1	+	Lo	Moderate
T3d	N0	M0	IIA	<1	+	Lo	Moderate
T1b	N0	M0	IA	1–50	++	Hi	Poor
T1b	N0	M0	IA	0	0	Lo	Moderate
T1b	N0	M0	IA	0	0	Lo	Poor
T3c	N0	M0	IIA	<1	++	Lo	Moderate
T1b	N0	M0	IA	1–50	+++	Hi	Moderate
T2c	N0	M0	IIA	1–50	+	Hi	Moderate
T1b	N0	M0	IA	<1	+	Lo	Poor
T1b	N0	M0	IA	1–50	++	Hi	Moderate
T1b	N0	M0	IA	1–50	++	Hi	Poor
T1b	N0	M0	IA	<1	+	Lo	Moderate
T1b	N0	M0	IA	<1	+	Lo	Moderate
T1b	N0	M0	IA	0	0	Lo	Poor
T4a	N0	M0	IIB	<1	+	Lo	Moderate
T1b	N0	M0	IA	<1	+	Lo	Poor
T1c	N0	M0	IA	<1	+	Lo	Poor
T2b	N0	M0	IIA	1–50	+++	Hi	Moderate
T1c	NO	MO	IA	<1	+	Lo	Poor
T1b	N0	M0	IA	1–50	+++	Hi	Moderate
T1c	N0	M0	IA	0	0	Lo	Poor
T2c	N0	M0	IIA	<1	+	Lo	Poor
T1c	N0	M0	IA	<1	+	Lo	Moderate
T2a	N0	M0	IB	1–50	++	Hi	Moderate
T1b	N0	M0	IA	1–50	+	Hi	Moderate
T3c	N0	M0	IIA	1–50	++	Hi	Poor
T1c	N0	M0	IA	1–50	+	Hi	Poor
T1c	N0	M0	IA	1–50	++	Hi	Moderate
T2c	N0	M0	IIA	0	0	Lo	Moderate
T1a	N0	M0	IA	<1	+	Lo	Poor

CONCLUSIONES

- Debido a su infrequencia, las características moleculares y el tratamiento de la enfermedad metastásica permanece desconocido
- El análisis del genoma de una paciente nos puede ayudar a encontrar nuevos oncogenes/genes supresores
- Objetivo: Idetificar mutaciones drivers para las que existan tratamiento que se esten aplicando actualmente en otras enfermedades
- La inclusión de estos pacientes en un consorcio de enfermedades raras y en ensayos clínicos multicéntricos diseñados para enfermedades raras, y el mayor avance en el conocimiento sobre marcadores específicos para terapia dirigida, proporcionaría información necesaria