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PANMEP

PROGRAMA ANDALUZ DE FORMACIÓN EN MEDICINA PERSONALIZADA Y DE PRECISIÓN

EXPERTO UNIVERSITARIO EN MEDICINA PERSONALIZADA Y DE PRECISIÓN

DIAGNÓSTICO MOLECULAR

ORGANIZAN:

- **Consejería de Salud y Consumo**, Fundación Progreso y Salud - IAVANTE
- **Universidad Internacional de Andalucía**

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Junta de Andalucía
Consejería de Salud y Consumo

Casos prácticos I

Federico Rojo

Caso 1.

Alteración de ALK

Mujer 68 años

Sin antecedentes tabáquicos

Antecedentes: HTA

5/22: Estudiada por Neumología como NÓDULO EN LSD A ESTUDIO por lesión en LSD objetivada en TC de tórax. Nódulo de contorno mal definido de unos 15 mm en segmento anterior del LSD. Se identifican varios pequeños nódulos periféricos milimétricos bilaterales.

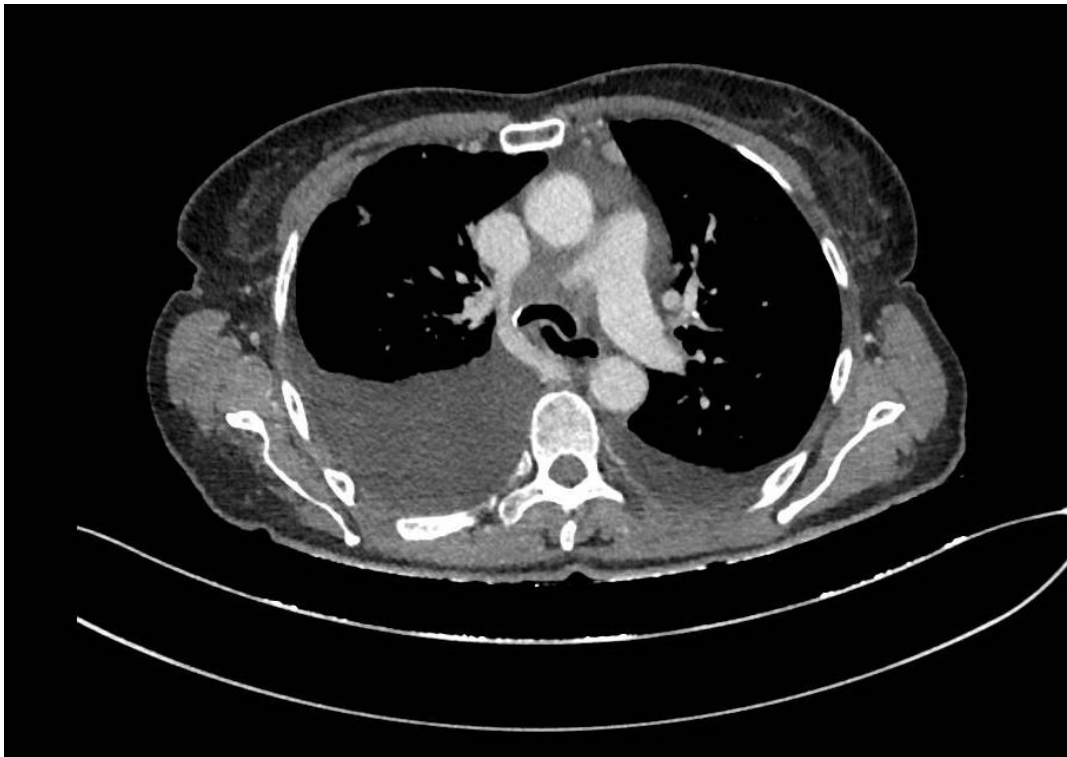
Adenopatías paratraqueal en hilio pulmonar derecho y en espacio subcarinal

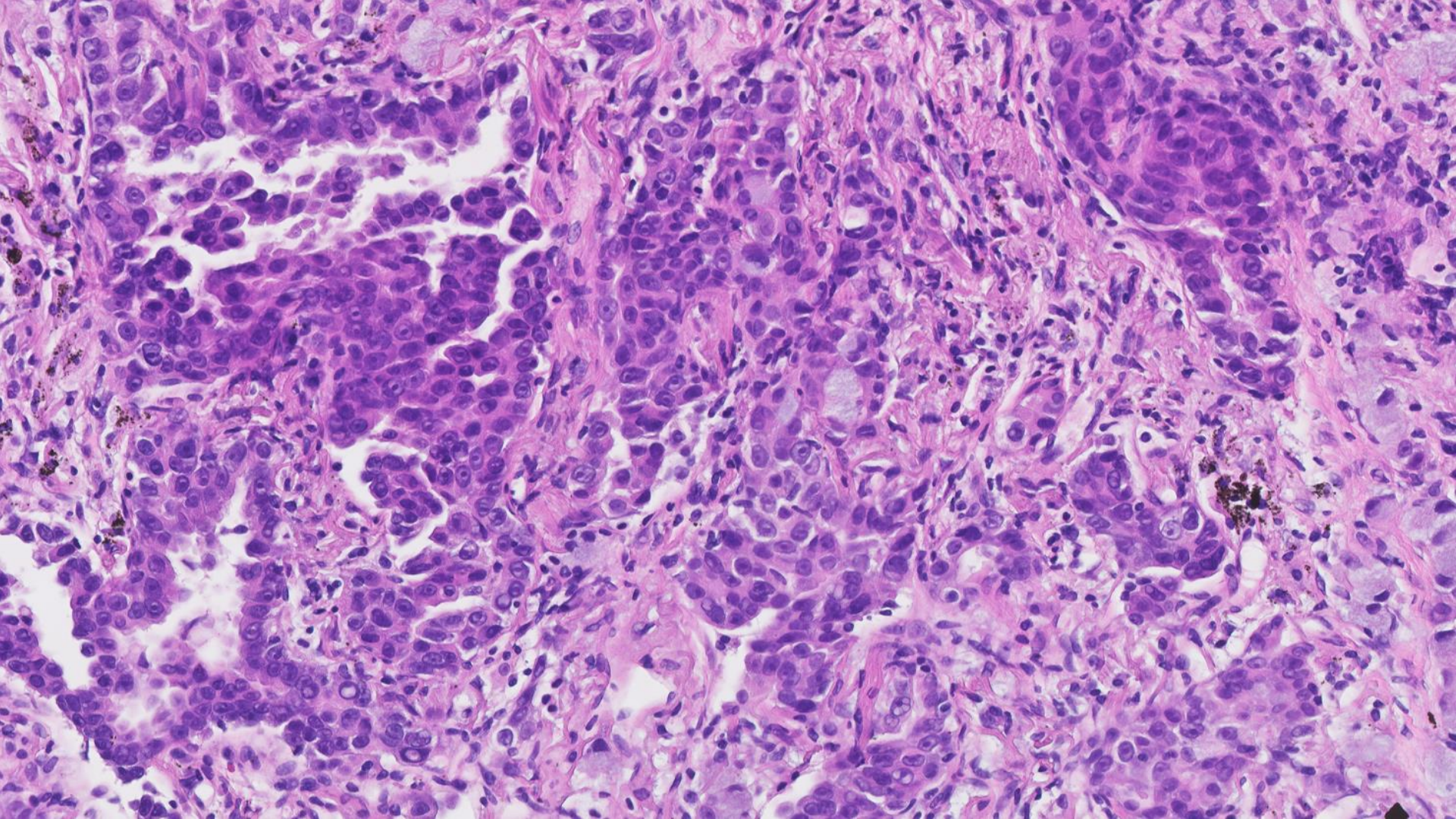
Captación en PET-TC con 18FDG

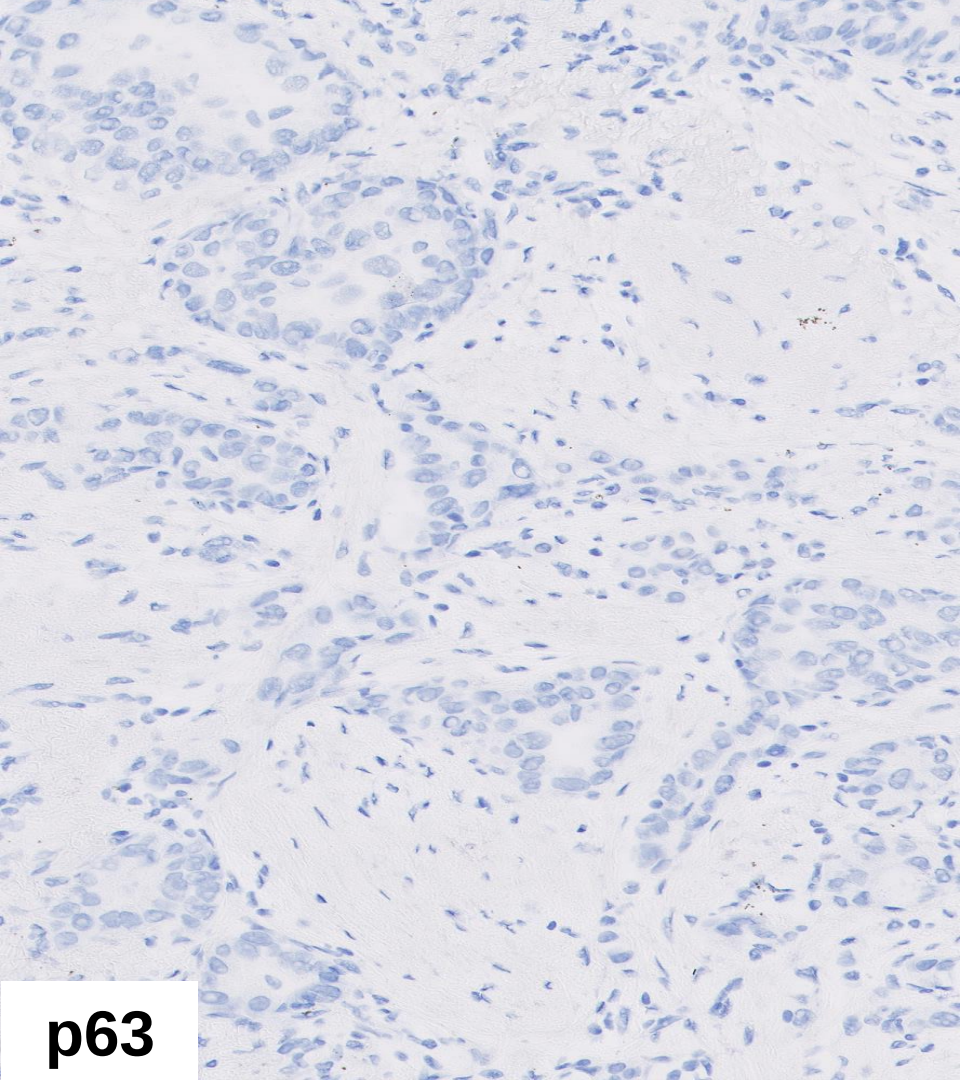
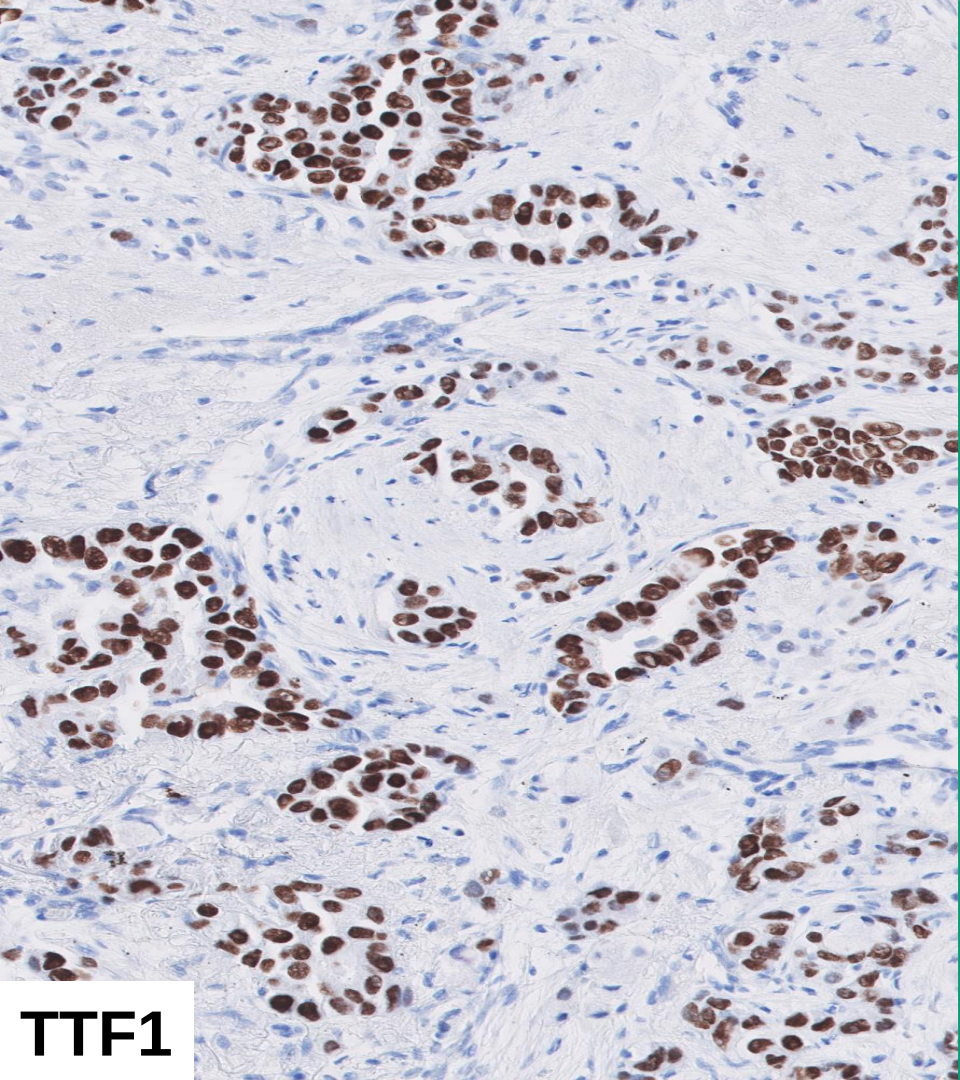
N. MALIGNA DE BRONQUIO Y PULMON

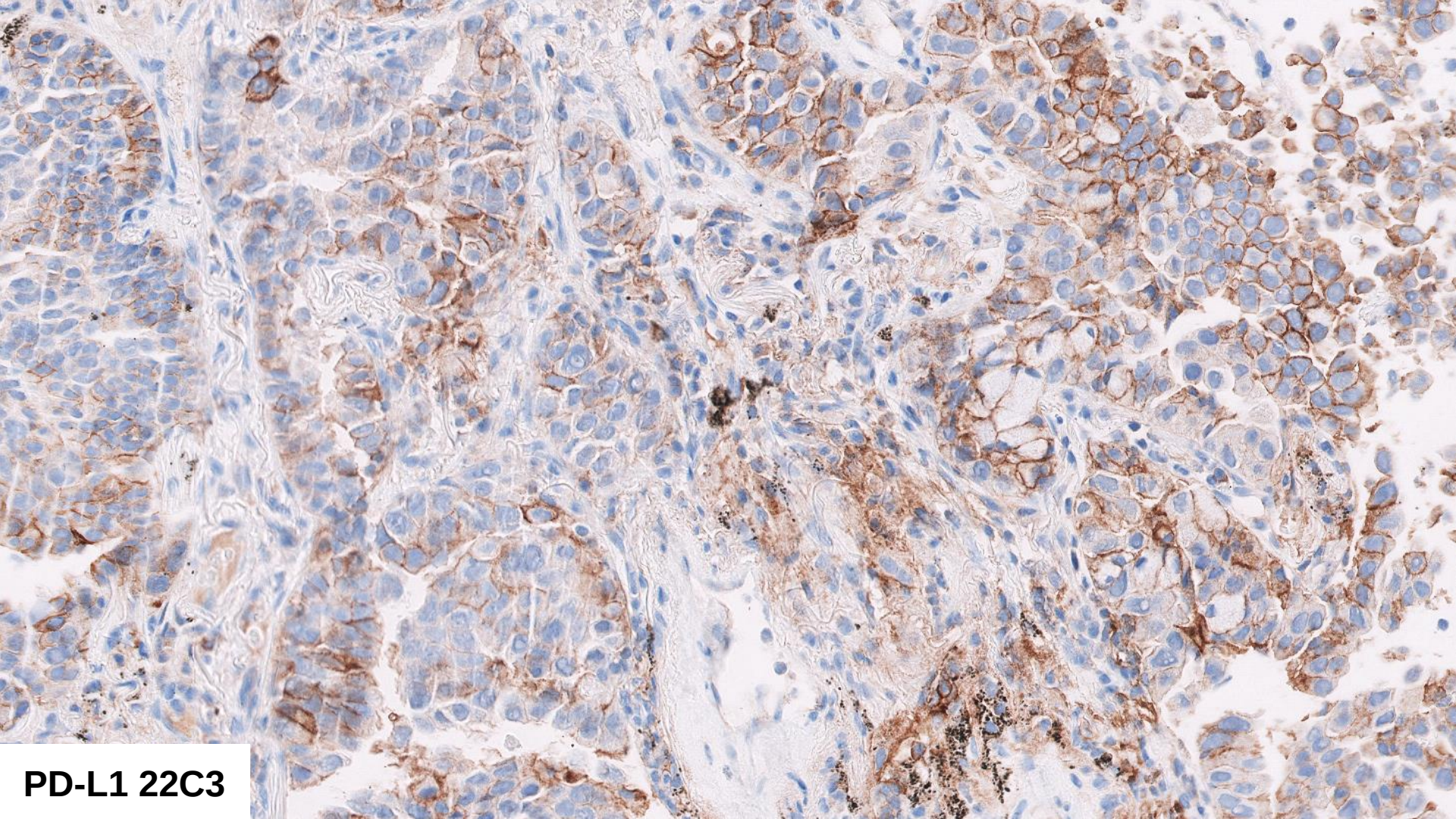
SIN ESPECIFICAR T: 4 N: x M: 1 Estadío: IV

BAG de la lesión pulmonar

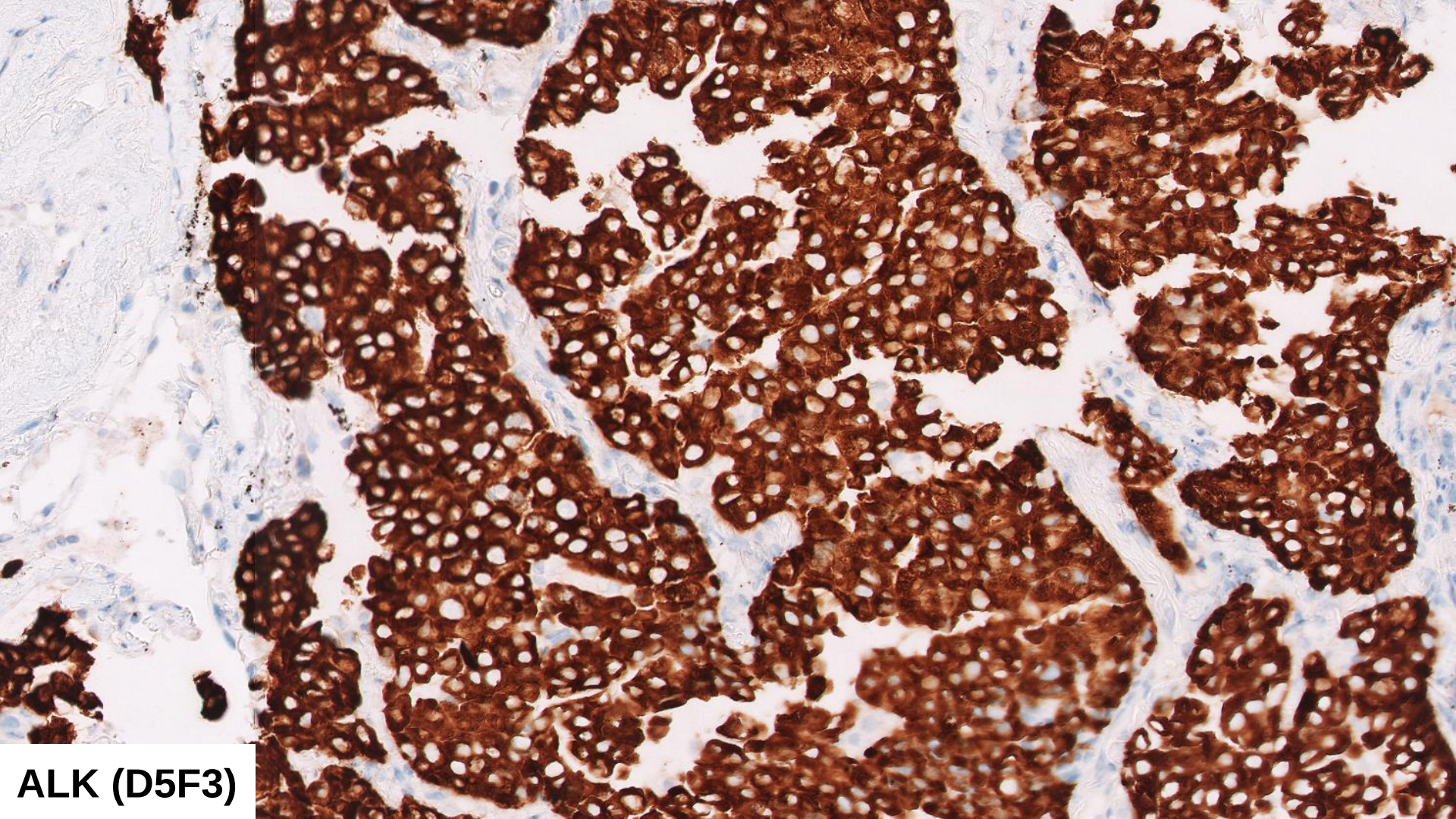








PD-L1 22C3



ALK (D5F3)

Action OncoKitDx

Secuenciadores compatibles	Illumina NextSeq500, Illumina NextSeq2000, Illumina HiSeq, Illumina NovaSeq
Número de reacciones	20
Número de muestras por run	Mid Output v2.5 kit (150 cycles): 12 muestras High Output v2.5 kit (150 cycles): 32 muestras
Secuenciación	Paired-end (2 x 75 ciclos)
Cantidad de ADN por muestra	50-200 ng
Calidad de ADN recomendada	DIN >3
Región genómica analizada	500 Kb
Genes diana	SNVs e INDELS: AKT1*, ALK, ARID1A, ATM, ATRX, BAP1, BRAF, BRCA1, BRCA2, CDH1, CHEK2, CTNNB1, EGFR, ERBB2, ESR1, FGFR1, FGFR4, GNA11, GNAQ, H3F3A, HIST1H3B, HIST1H3H, HRAS, IDH1, IDH2, KIT, KRAS, MAP2K1, MET, MLH1, MSH2, MSH6, MTOR, MYC, NRAS, NTRK2, NTRK3, PALB2, PBRM1, PDGFRA, PIK3CA, PMS2 + 5'UTR, PTEN, POLD1, POLE, RET, ROS1, SDHA, SDHB, SDHD, TERT + 5'UTR, TSC1*, TSC2*, TP53 y VHL. * Secuenciación de <i>hotspot</i> SVs: ALK (intrón 19), ATP1B1 (intrones 3 y 4), BRAF (intrones 7, 8, 9 y 10), EGFR (intrones 7, 23, 24 y 25), ETV6 (intrones 4 y 5), FGFR2 (intrón 17 y región 3'UTR), FGFR3 (intrón 17 y región 3'UTR), NTRK1 (intrones 8, 9, 10, 11 y 12), NTRK2 (intrones 12 y 15), RET (intrones 9, 10 y 11) y ROS1 (intrones 31, 32, 33, 34 y 35).
	ADN procedente de sangre periférica, tejido fresco, congelado y paraafinado

Perfil mutacional obtenido:

Variantes patogénicas:

Traslocación ALK exón 19 (chr2:29,446,394) :: EML4 (chr2:42,522,654, +) (56 lecturas). No se identifican alteraciones en EGFR (exones 18, 19, 20 y 21), traslocaciones de ROS1 o RET, amplificación de MET, mutaciones del sitio de splicing del exón 14 de MET, mutaciones puntuales en KRAS (codones 12/13 y 61), mutaciones en BRAF (V600), ni mutaciones o inserciones en el exón 20 de ERBB2 (HER2).

Otras alteraciones identificadas:

Variantes de significado incierto**:

IDH2(NM_002168.2)Exón8 c.992C>T; p.Thr331Met (53%)

** Se consideran Variantes de significado incierto aquellos cambios a nivel nucleotídico cuya repercusión no es conocida hasta la fecha. Estos cambios no deben considerarse de valor clínico. Son susceptibles a reclasificaciones futuras por consorcios especializados.

Inestabilidad de microsatélites:

No se identifica inestabilidad de microsatélites, fracción de inestabilidad 0,14 (marcadores inestables 14 de 103 analizados) (MSS 0-0.17)

Caso 1.

Alteración de ALK

Carcinoma de pulmón, estadio IV con afectación secundaria adenopática, pulmonar, hepática y suprarrenal, ALK+.

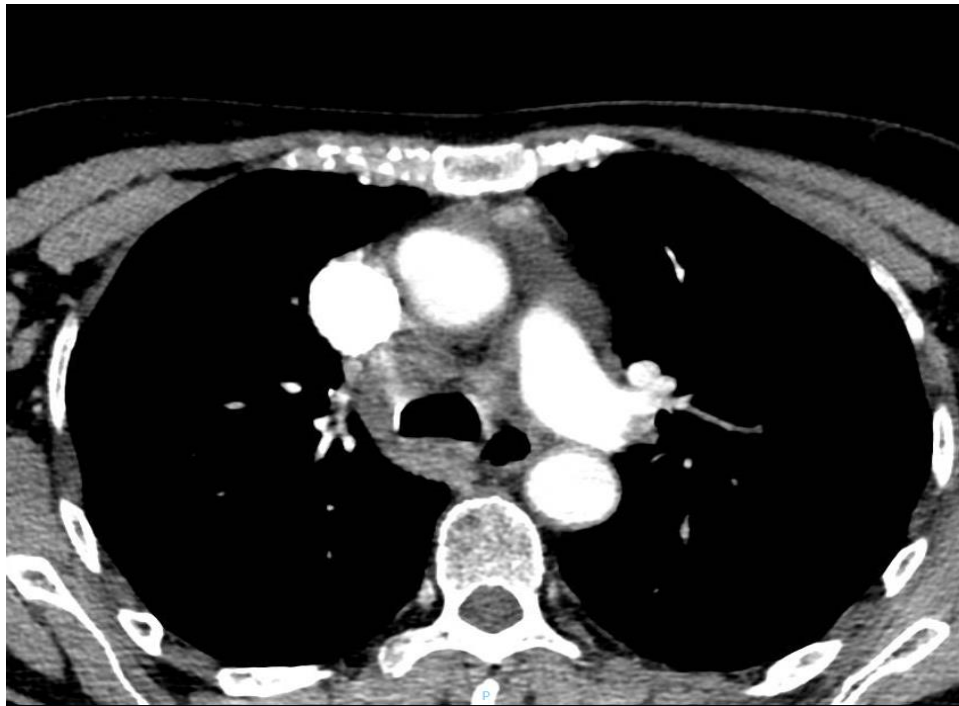
6/22 Inicia tratamiento dirigido con alectinib.

9/22 Primera reevaluación precoz: Disminución de nódulo de contorno mal definido y peor definición con perdida de nodularidad de nódulo satélite configurando aspecto de opacidad focal mal definida.

Disminución en número y tamaño de pequeños nódulos bilaterales.

Disminución de tamaño y de captación de adenopatías mediastínicas (paratraqueales altas y bajas bilaterales, prevasculares, espacio subcarinal) e hiliares bilaterales sugiriendo componente necrótico post-tratamiento.

Disminución de tamaño de lesiones focales hepáticas.



Caso 2. Alteración de ALK

Caso 2.

Alteración de ALK

Mujer 61 años

Ex-fumadora de 20 cigarrillos/día desde 2021

Antecedentes médicos: HTA y diabetes,
EPOC moderado fenotipo bronquítico crónico
no agudizador.

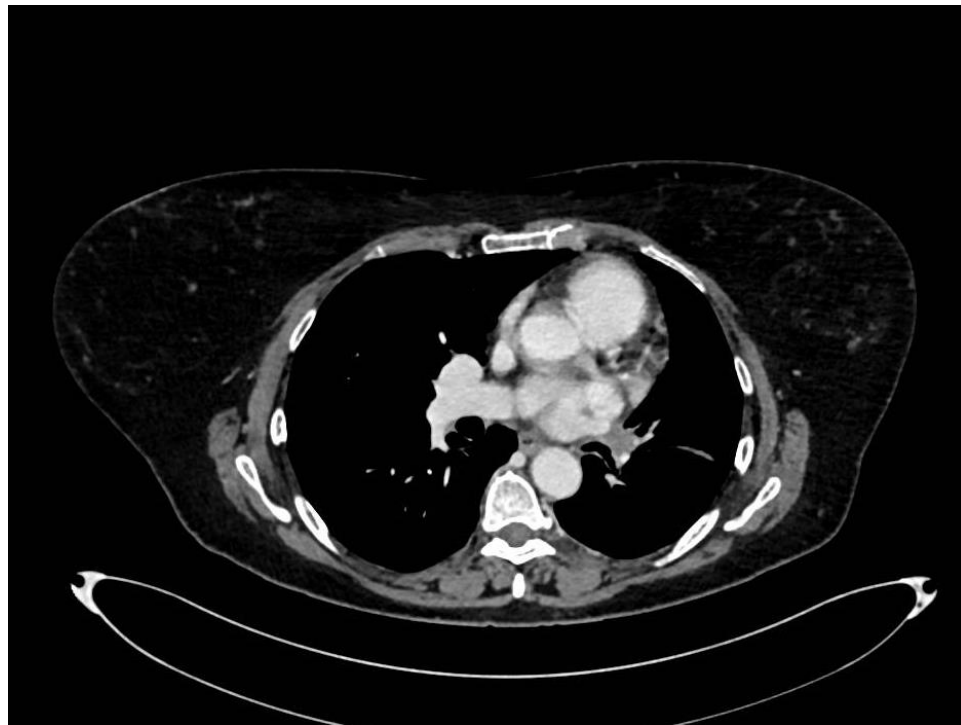
01/22. Diagnóstico Oncológico:

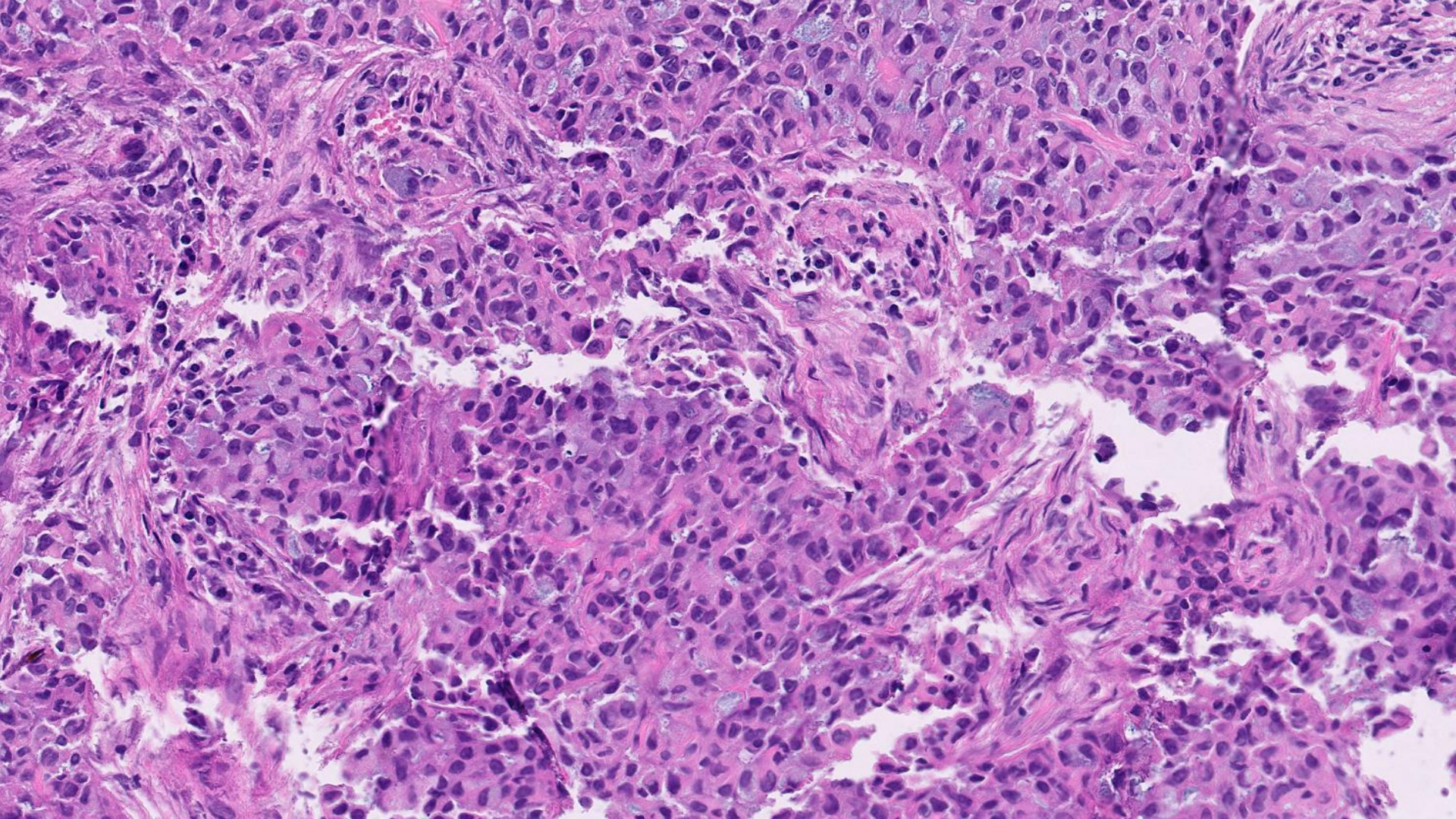
Adenocarcinoma de pulmón, estadio IV

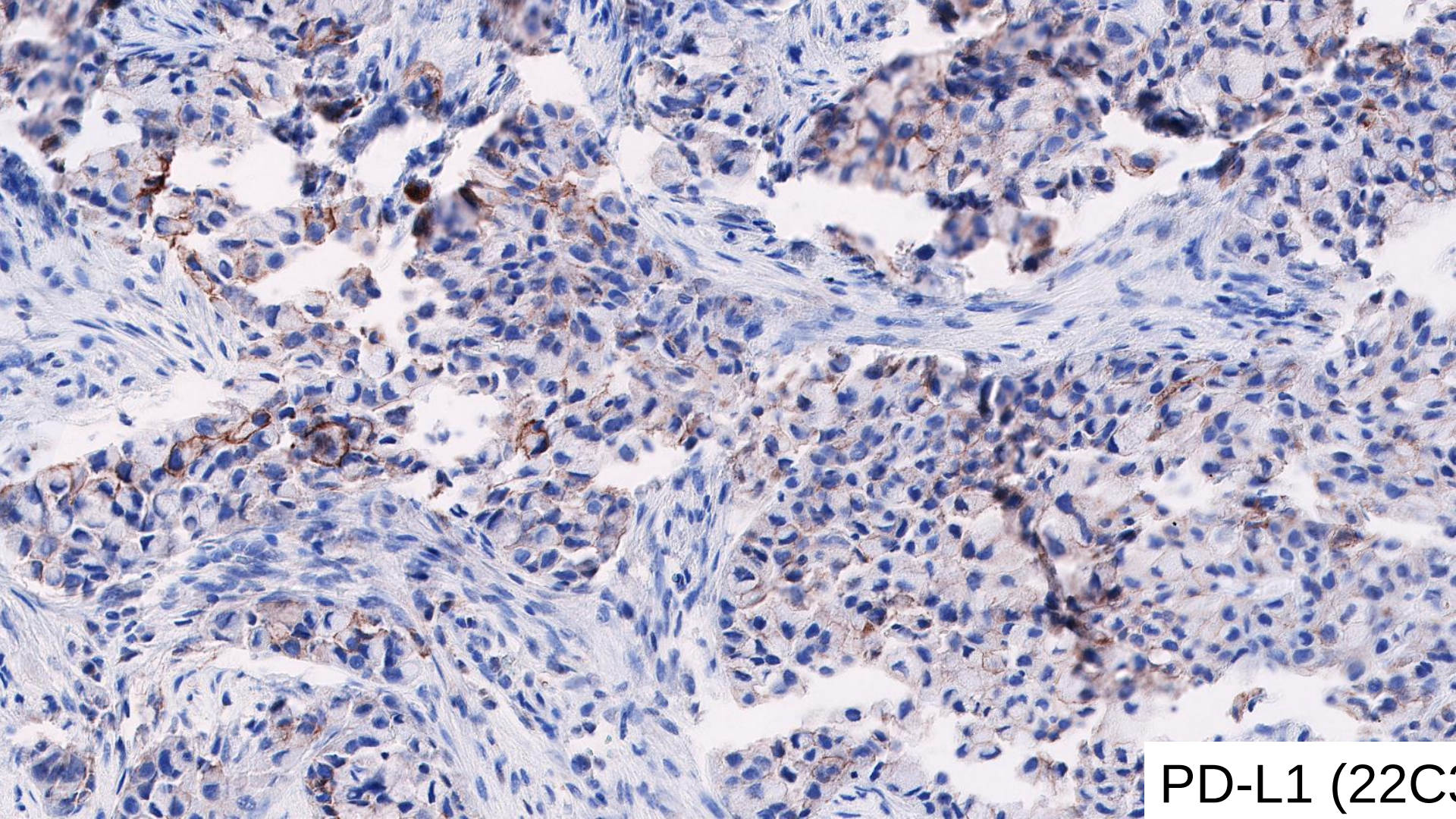
TC: Masa pulmonar parahiliar izquierda, de
aproximadamente 3,2 cm, que asocia
atelectasia de la língula, segmento
anteromedial basal y lateral basal del LII.

Derrame pleural izquierdo leve.

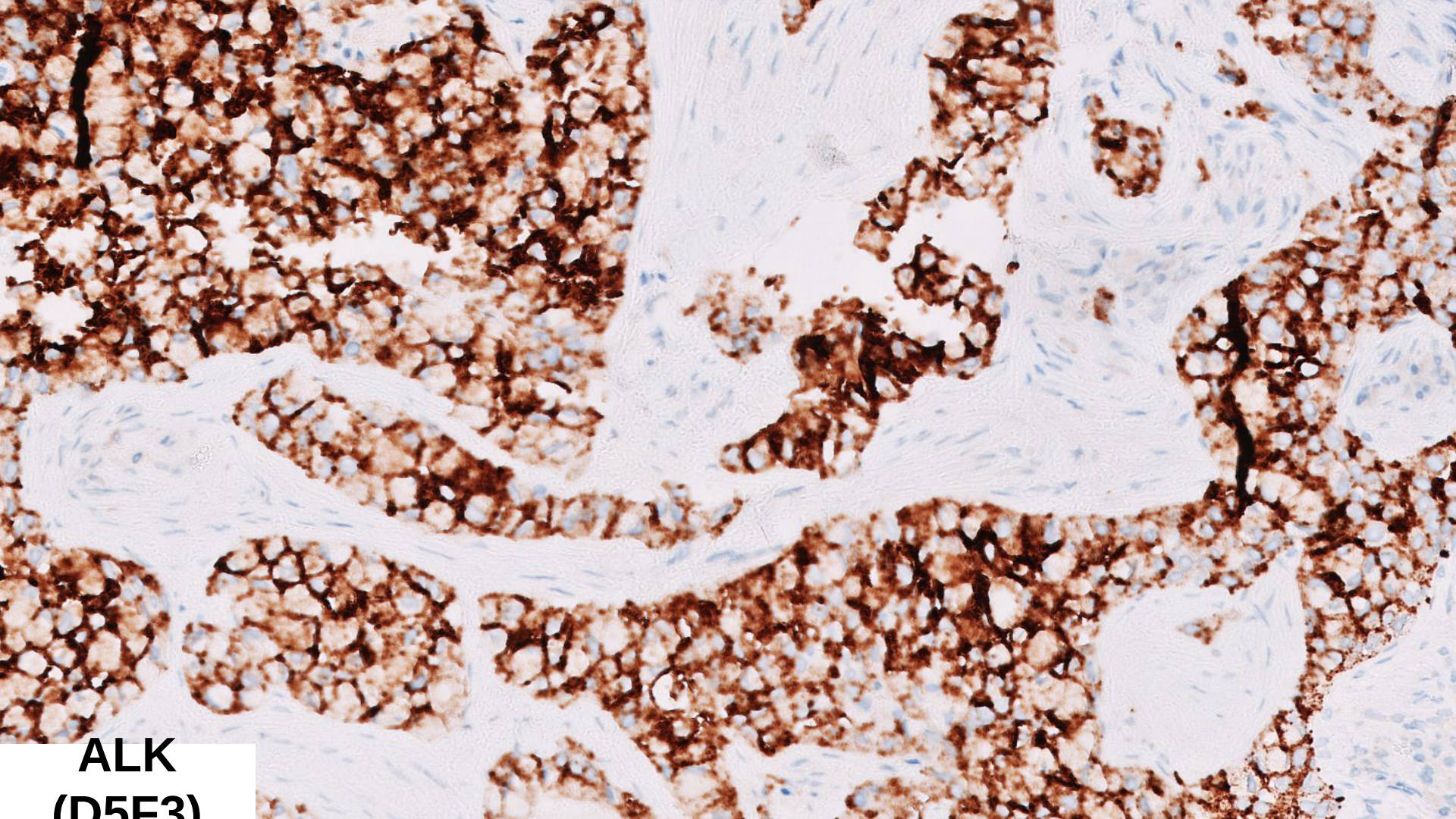
BAG de masa pulmonar







PD-L1 (22C3)



**ALK
(D5E3)**



Action OncoKitDx

Perfil mutacional obtenido:

Variantes patogénicas:

Traslocación ALK exón 19 (chr2:29447951) :: AC007682.1 (chr2:51322755) (6 lecturas).

Esta traslocación se identifica entre los exones 19 y 20 de ALK con la región no codificante AC007682.1 (LOC730100), situada en el cromosoma 2, próxima a EML4. Esta traslocación no está descrita en las bases de datos y se desconocen sus implicaciones en la activación de ALK y su valor predictivo de beneficio a inhibidores selectivos.

No se identifican alteraciones en EGFR (exones 18, 19, 20 y 21), traslocaciones de ROS1 o RET, amplificación de MET, mutaciones del sitio de splicing del exón 14 de MET, mutaciones puntuales en KRAS (codones 12/13 y 61), mutaciones en BRAF (V600), ni mutaciones o inserciones en el exón 20 de ERBB2 (HER2).

Otras alteraciones identificadas:

Variantes de significado incierto**:

CTNNB1 (NM_001904.3): Exón 6/15 c.879C>A p.Phe293Leu (VAF 5,58%)

ATM (NM_000051.3): Exón 13/63 c.1937C>T p.Ser646Leu (VAF 59,07%)

** Se consideran Variantes de significado incierto aquellos cambios a nivel nucleotídico cuya repercusión no es conocida hasta la fecha. Estos cambios no deben considerarse de valor clínico. Son susceptibles a reclasificaciones futuras por consorcios especializados.

Inestabilidad de microsatélites:

No se identifica inestabilidad de microsatélites, fracción de inestabilidad 0,14 (marcadores inestables 14 de 103 analizados) (MSS 0-0.17)

Caso 2.

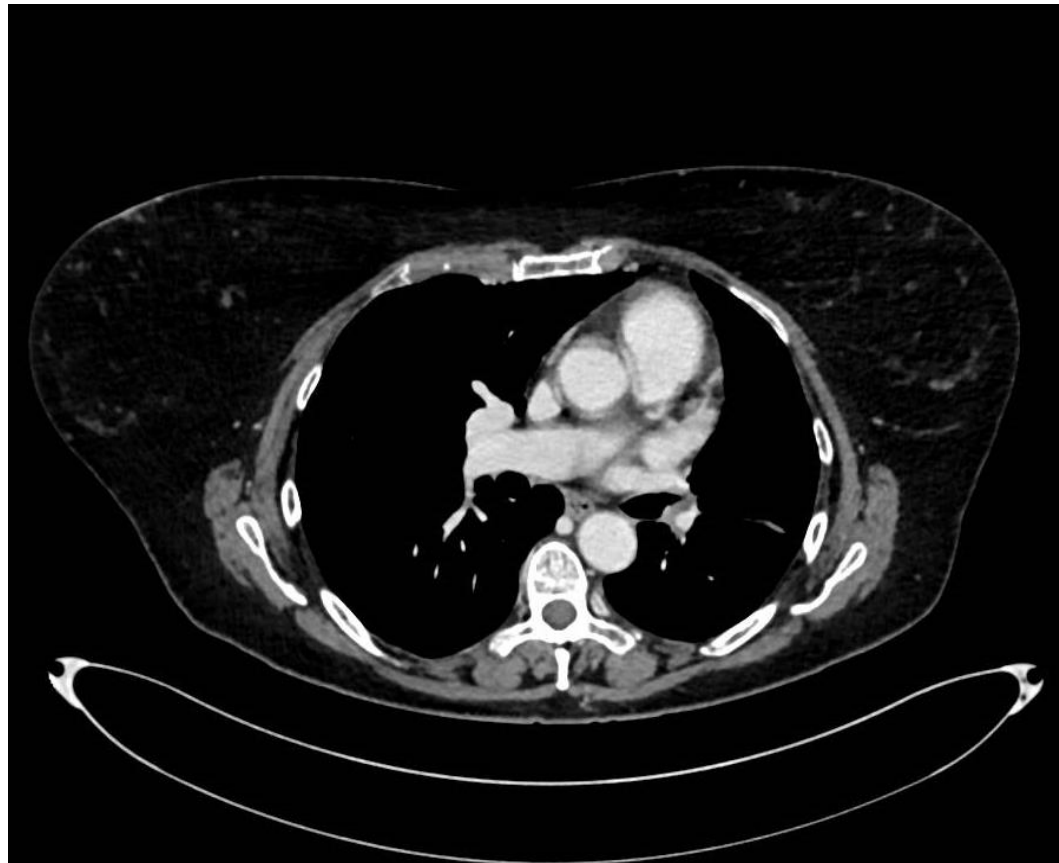
Alteración de ALK

2/22: Alectinib 1200mg/dia

5/22: RP mayor, con re-expansión pulmonar casi completa. Resolución del derrame pleural izquierdo.

12/22: estabilidad de la pequeña densidad de partes blandas de unos 15 mm en región hiliar izquierda, adyacente al bronquio de la língula.

Adenopatías no de tamaño significativo. Sin cambios significativos respecto al estudio previo.



Caso 3.

Alteración de ALK

Caso 3.

Alteración de ALK

Hombre 56 años, ex-fumador desde hace 10 años (IPA = 3.2). Inicio a los 36, lo dejó a los 42 - 10 cig/día (leve exposición al tabaco)

Antecedentes: HTA

Historia actual: Remitido por centro privado ante diagnóstico de ADC de pulmón, estadio IVA (T4N3M1a).

Comienza el estudio en mayo 2022, con disfonía de 2 meses de evolución.

Rx de tórax: masa de LSI.

Estudio de marcadores en biopsia líquida.

Patient ID: Guardant Sample A052684802 Report ID: A052684802.220615_NB501022_0978_AHV3K7BG
Report Date: Jun 18, 2022 Disease: XL.nof1report
Gender: male Lung adenocarcinoma

1. Summary

CLINICALLY RELEVANT ALTERATIONS

TIER 1: VARIANTS OF STRONG CLINICAL SIGNIFICANCE

Predictive Variants

Marker	Alteration	Therapies approved in this indication	Therapies approved in other indications	May indicate resistance to therapies	Trials
ALK	EML4-ALK fusion	Crizotinib (A), Brigatinib (A), Ceritinib (A), Alectinib (A), Lorlatinib (A)	None	None	Yes

Prognostic and Diagnostic Variants: None

TIER 2: VARIANTS OF POTENTIAL CLINICAL SIGNIFICANCE: NONE

GUIDELINES

Marker-Alteration	Summary
ALK-EML4-ALK fusion	For non-small cell lung carcinoma (NSCLC) patients with tumors harboring ALK rearrangement, the ESMO Clinical Practice Guidelines highlight crizotinib, alectinib, and brigatinib (I, A) and ceritinib (I, B) as therapy options, and note that alectinib, brigatinib, and ensartinib have been associated with longer progression-free survival, and alectinib with lower toxicity, as compared with crizotinib. For patients with CNS involvement, alectinib (III, A), brigatinib (III, B), or ceritinib (IV, B) are recommended (2020; ESMO Guidelines_NSCLC 2020).

INTERACTIONS: NONE

OTHER ALTERATIONS

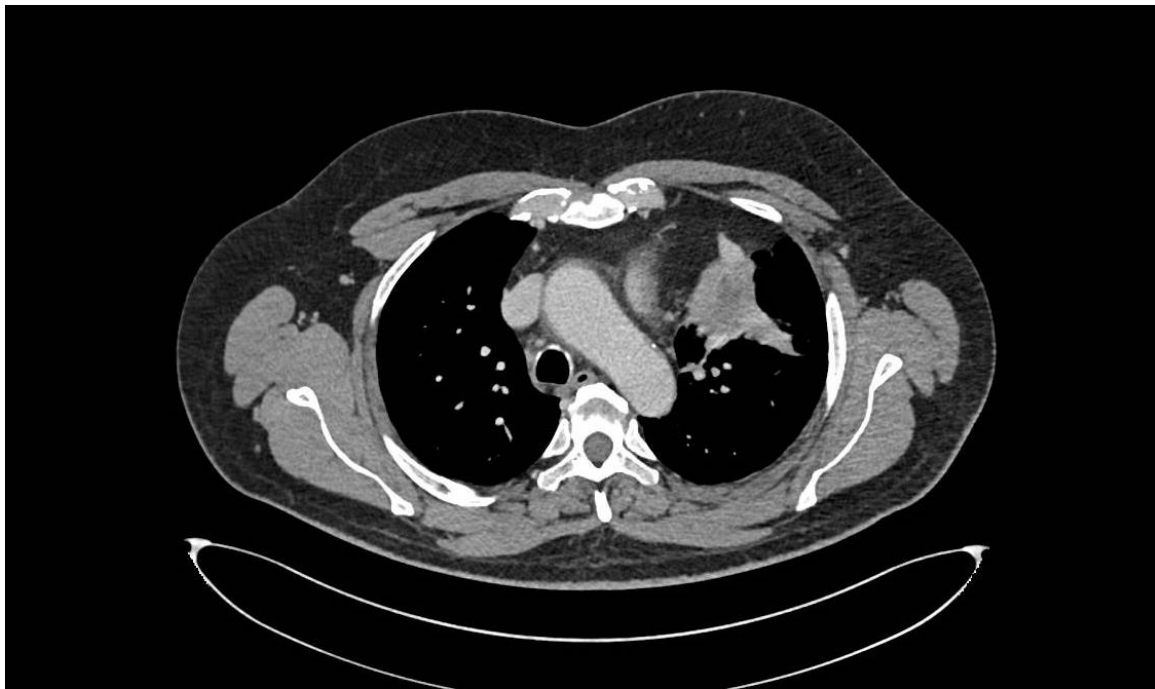
TIER 3: VARIANTS OF UNCERTAIN CLINICAL SIGNIFICANCE: NONE

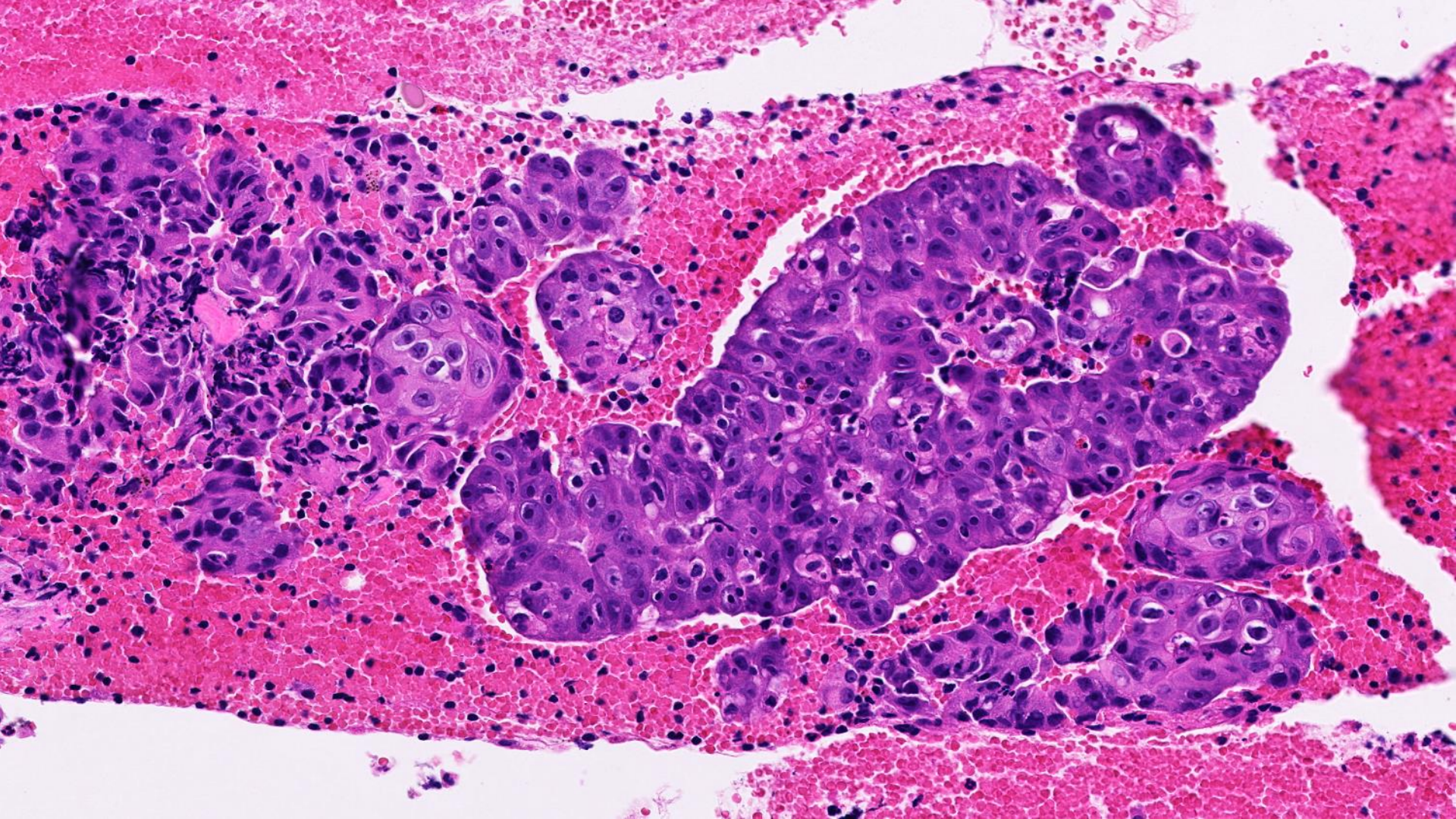
TIER 4: BENIGN OR LIKELY BENIGN VARIANTS: NONE

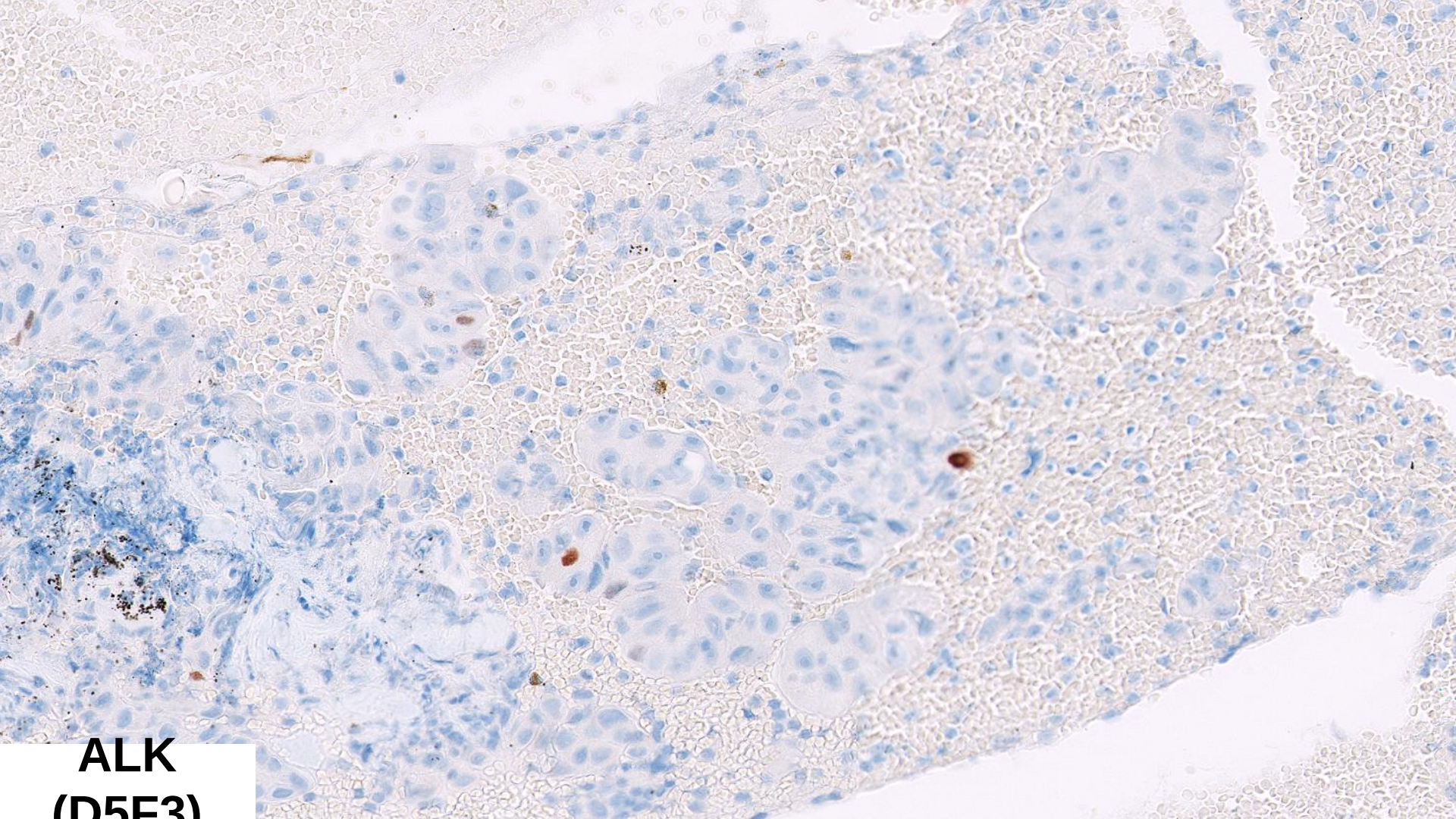
Caso 3.

Alteración de ALK

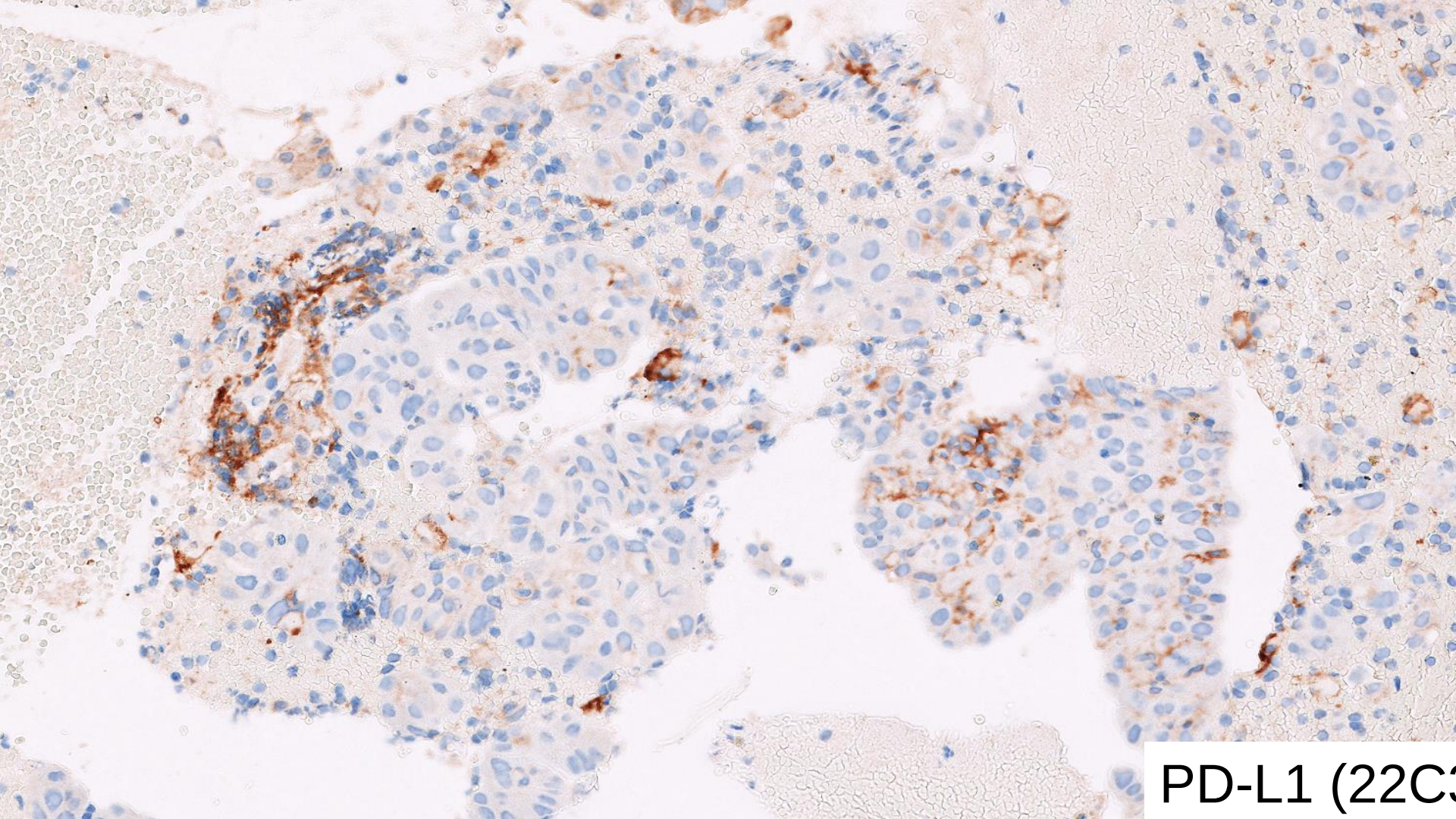
Pruebas: PET-TC y TC tórax y
broncoscopia. Masa pulmonar 9cm, en
LSI. Contacta con pleura mediastínica e
infiltra estructuras broncovasculares.
Nódulos pulmonares en LID, de 10mm y
LII, de 8mm, sugerentes de metástasis.
Captación patológica en adenopatía en
nivel IV dcho, supraclaviculares bilaterales
y múltiples mediastínicas prevasculares,
paratraqueales bilaterales, subcarinales,
paraórticas y subaórticas, hiliares
izquierdas y periesofágica derecha.
PAAF EBUS de mediastino
región 4R : ADENOCARCINOMA
PRIMARIO PULMONAR. Estudio
inmunohistoquímico CKAE1/AE3. TTF1 y
napsina. Negativo para p63.







ALK
(D5E3)



PD-L1 (22C3)

Caso 3.

Alteración de ALK

Situación clínica con deterioro físico, aumento de síntomas.

Control 09/22: Aumento de la masa en LSI, con incremento de la afectación adenopática mediastínica, hiliar y de carina. Crecimiento de los nódulos en LID y LII, y aparición de lesiones satélites.

Se solicita confirmación de perfil molecular sobre EBUS.





Action OncoKitDx

Perfil mutacional obtenido:

Variantes patogénicas:

Se detecta una fusión de ALK::EML4 asociada a una delección en la posición 2:29447107::2:42524443.

Esta fusión es de patrón no convencional ALK::EML4, asociada a una delección (2:29447107::2:42524443) entre ambos genes, sin inversión de sus secuencias. No existe evidencia clínica de la eficacia de los inhibidores de tirosina-quinasa en estas variantes.

Otras alteraciones identificadas:

Variantes de significado incierto**:

ERBB2(NM_000535.5)Exón 7 c.892G>A;p.Ala298Thr (VAF 52.22%)

SDHA(NM_004168.2)Exón10 c.1414G>A;p.Glu472Lys (VAF 5%)

CHEK2(NM_001005735.1) c.449-5T>A; (VAF 41%)

** Se consideran Variantes de significado incierto aquellos cambios a nivel nucleotídico cuya repercusión no es conocida hasta la fecha. Estos cambios no deben considerarse de valor clínico. Son susceptibles a reclasificaciones futuras por consorcios especializados.

Inestabilidad de microsatélites:

No se identifica inestabilidad de microsatélites, fracción de inestabilidad 0.14 (marcadores inestables 15 de 110 analizados) (MSS 0-0.17)

Have you explored our new Comparative Genome Viewer (CGV) yet?

Genome Data Viewer

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Homo sapiens

(human)

Assembly: GRCh37.p13 (GCF_000001405.25) • Chr 2 (NC_000002.11)

Search assembly

Location, gene or phenotype

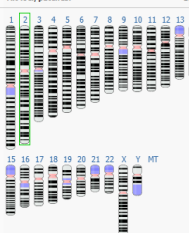
Examples

Assemblies

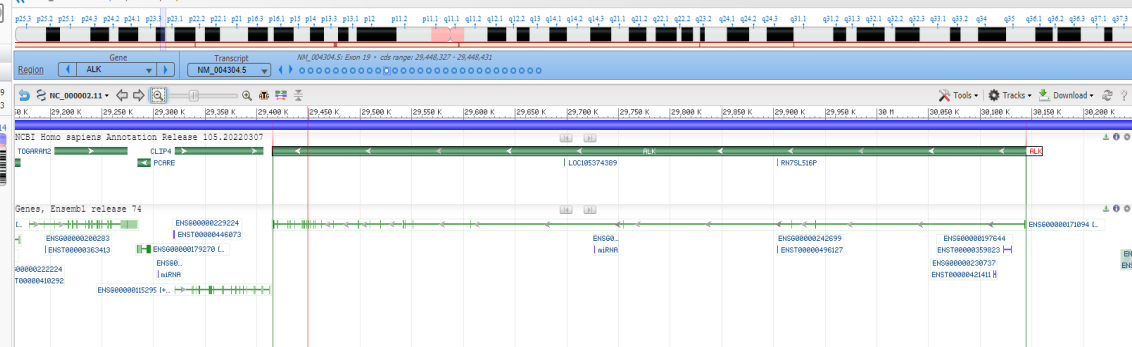
Ideogram View

Unplaced/unlocalized scaffolds:

Alt loci/patches:



NC_000002.11: 29,165,969 - 30,256,306



Have you explored our new Comparative Genome Viewer (CGV) yet?

Genome Data Viewer

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Homo sapiens

(human)

Assembly: GRCh37.p13 (GCF_000001405.25) • Chr 2 (NC_000002.11)

Search assembly

Location, gene or phenotype

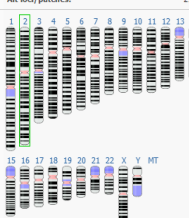
Examples

Assemblies

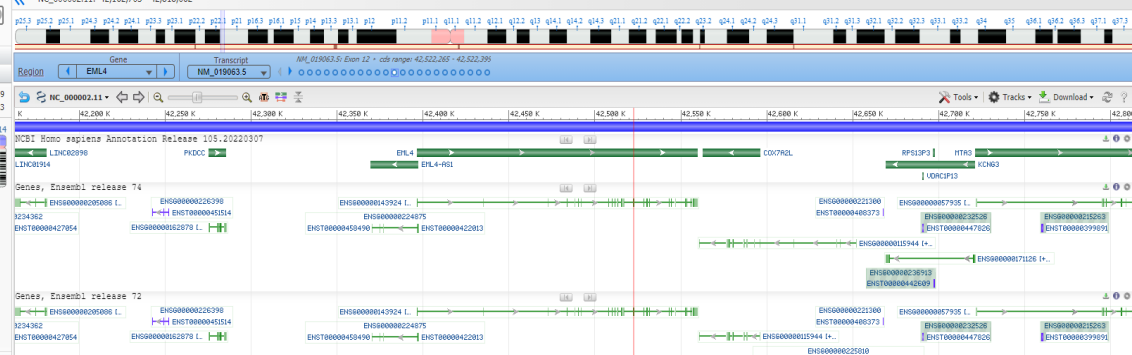
Ideogram View

Unplaced/unlocalized scaffolds:

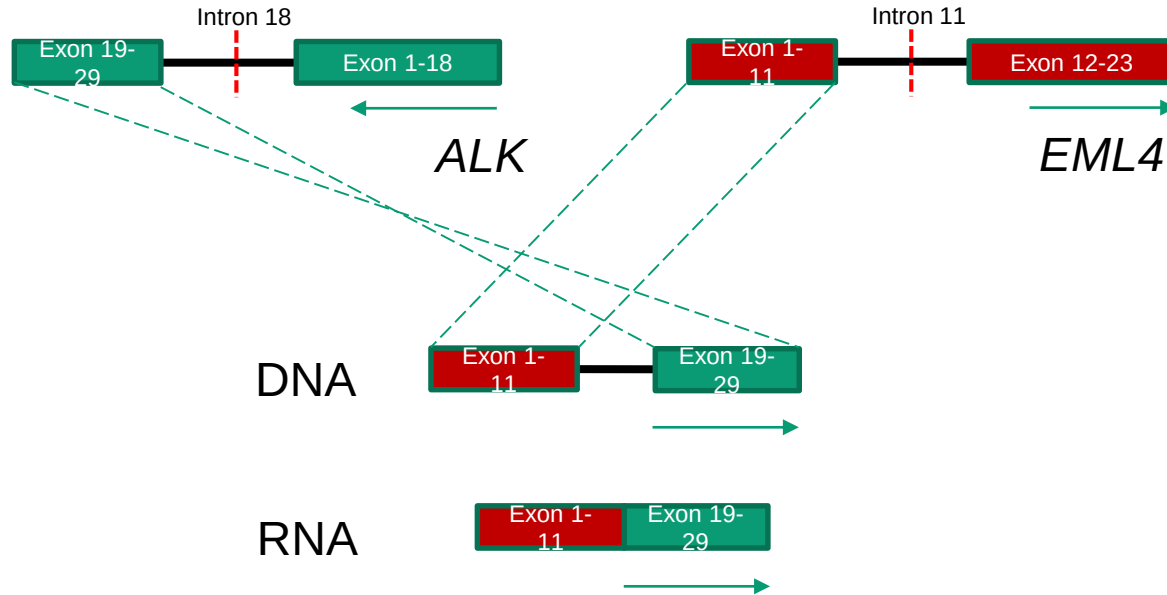
Alt loci/patches:



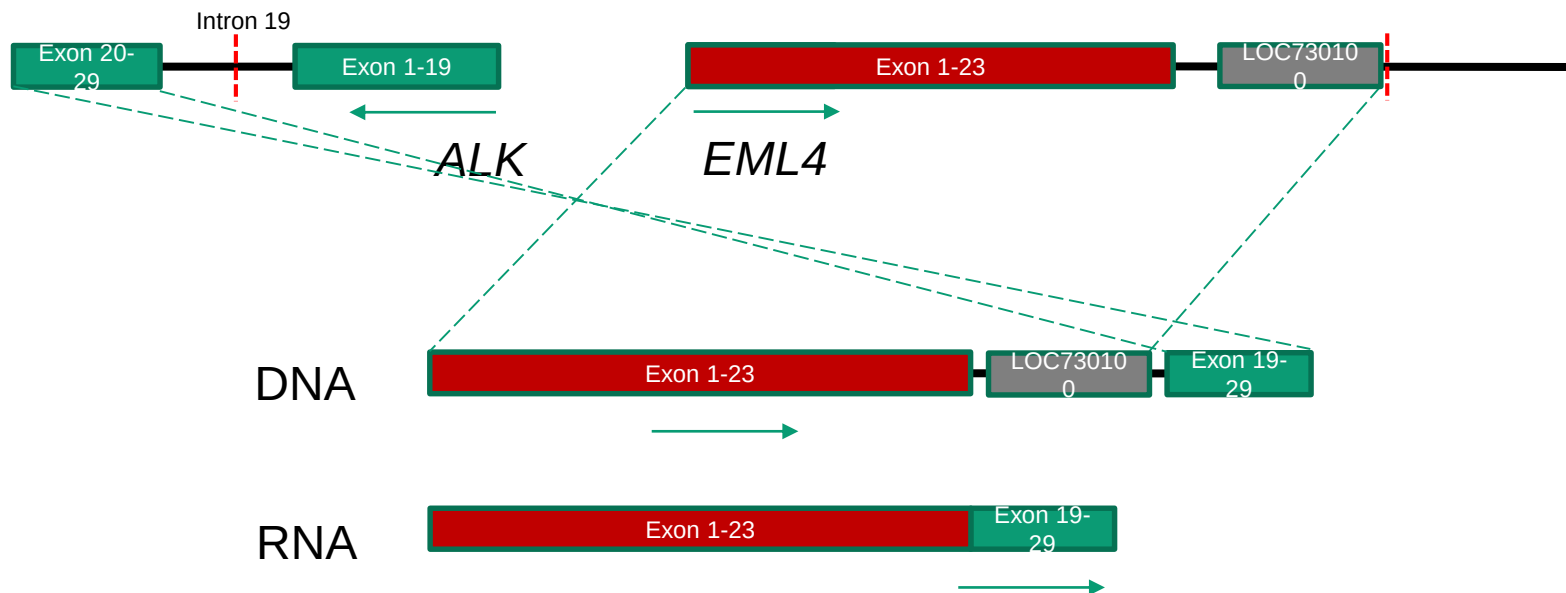
NC_000002.11: 42,162,703 - 42,818,062



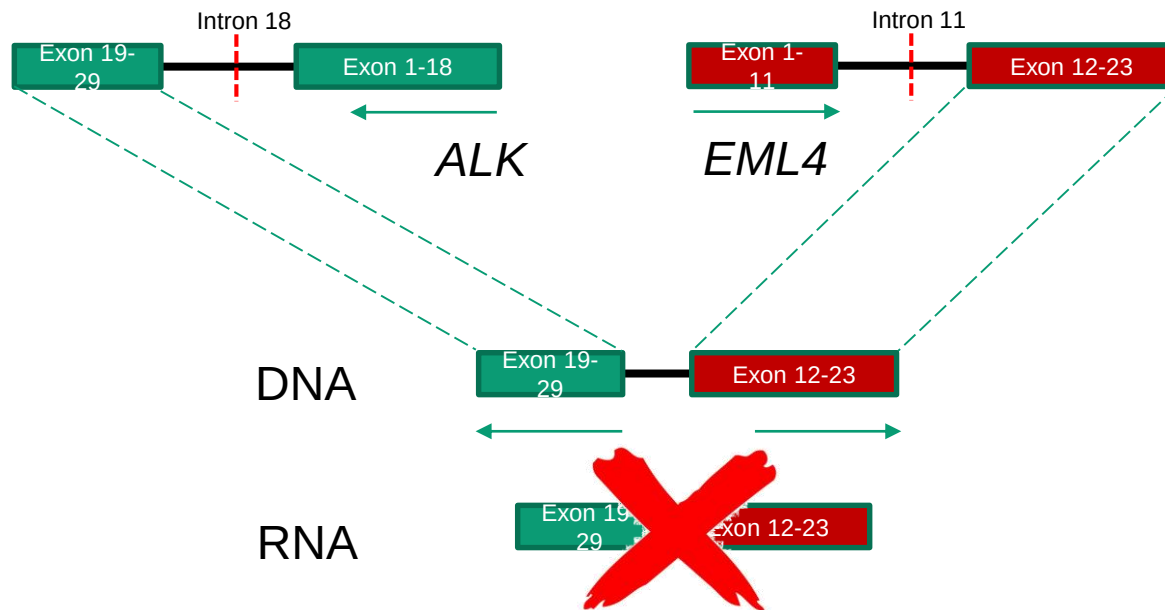
Chromosome 2



Chromosome 2

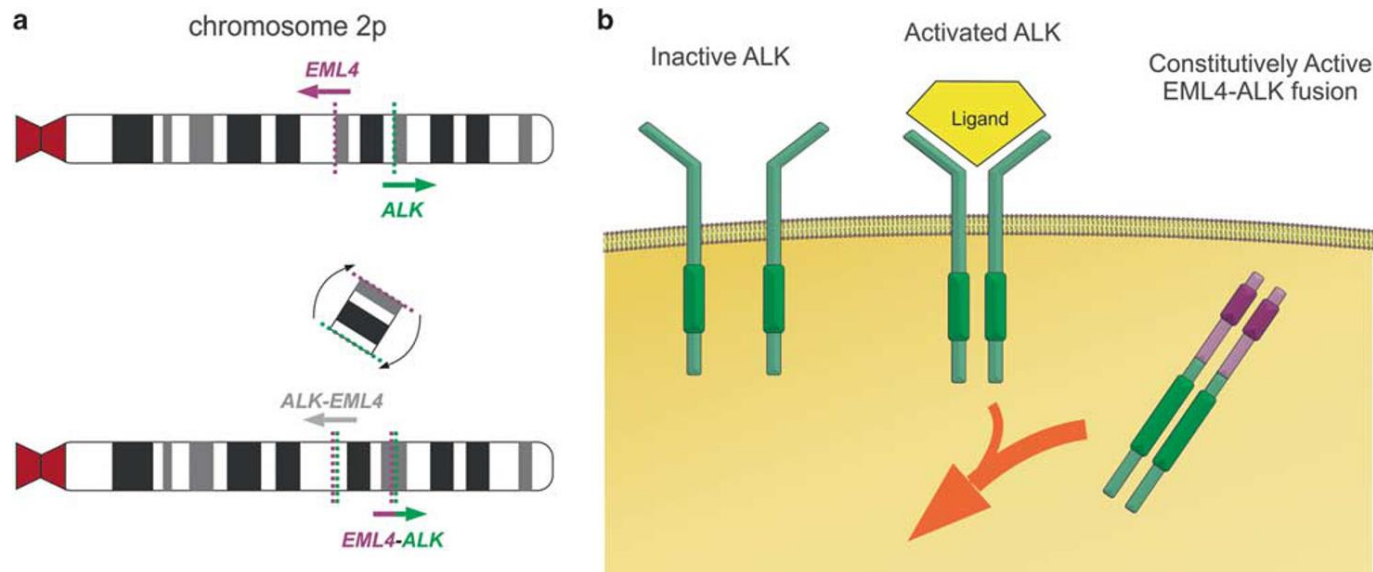


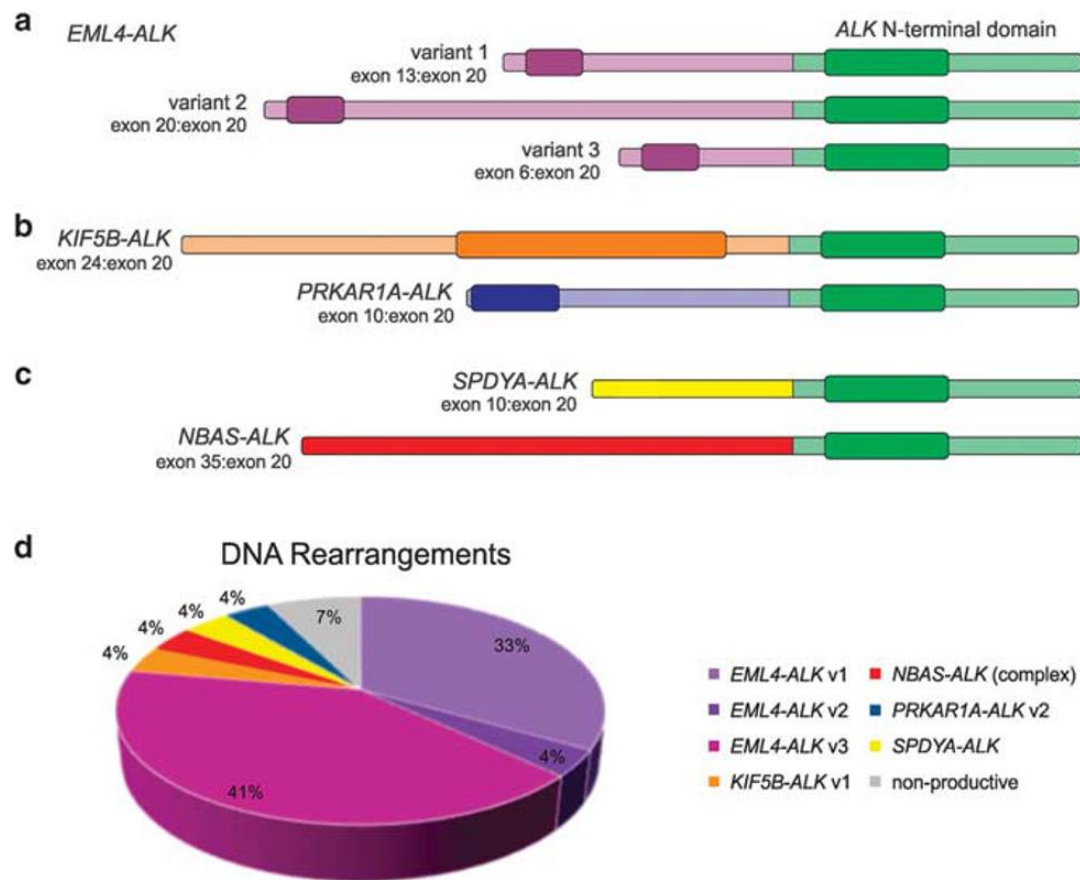
Chromosome 2



Genomic heterogeneity of *ALK* fusion breakpoints in non-small-cell lung cancer

Jason N Rosenbaum¹, Ryan Bloom², Jason T Forsy³, Jeff Hiken³, Jon R Armstrong³, Julie Branson⁴, Samantha McNulty⁴, Priya D Velu¹, Kymberlie Pepin⁵, Haley Abel⁶, Catherine E Cottrell⁷, John D Pfeifer⁴, Shashikant Kulkarni⁸, Ramaswamy Govindan⁵, Eric Q Konnick⁹, Christina M Lockwood⁹ and Eric J Duncavage⁴





Catalog of 3 Fusion Partners in ALK-positive NSCLC Circa 2020

Sai-Hong Ignatius Ou, MD, PhD,^{1,a} Viola W. Zhu, MD, PhD,² Misako Nagasaka, MD^{3,c}^aDepartment of Medicine, Division of Hematology-Oncology, Chao Family Comprehensive Cancer Center, University of California Irvine School of Medicine, Orange, California^bDepartment of Oncology, Karmanos Cancer Institute/Wayne State University School of Medicine, Detroit, Michigan^cDepartment of Advanced Medical Innovations, St. Marianna University Graduate School of Medicine, Kawasaki, Kanagawa, Japan

Received 4 February 2020; accepted 5 February 2020

Table 1. Catalog of Fusion Partners in ALK+ NSCLC

Fusion No.	Fusion Partner	Year Published in Print/ Presented	Chromosomal Location	Fusion Breakpoint	Response to ALK TKI at the Time of Publication	Tumor Source	Method of Detection	Variant Frequency in Tumor	FISH/ IHC	References ^a
1	EML4	2007	2p21	(E13, A21) (E20, A21)	Not treated with ALK TKI	Tumor	PCR/Sanger sequencing	NR	ND/ND	Soda, 2007 ¹
2	TFG	2007	3q12.2	(T3, A20)	Not treated with ALK TKI	Cell line/ Tumor	5'RACE PCR DNA sequencing	NR	ND/ND	Rikova, 2007 ²
3	KIF5B	2009	10p11.22	(K24, A20)	Not treated with ALK TKI	Tumor	RT-PCR	NR	+/+	Takeuchi, 2009 ⁶
4	KLC1	2012	14q32.33	(K9, A 20)	Not treated with ALK TKI	Tumor	RT-PCR	NR	+/+	Takeuchi, 2012 ⁸
5	STRN	2013	2p22.2	(S3, A20)	PR to crizotinib	Plasma	DNA NGS	1%	ND/ND	Yang, 2013 ¹⁵
6	HIP1	2014	7q11.23	(H2, A20)	Not treated with ALK TKI	Tumor	RNA sequencing	NR	ND/ND	Yang, 2014 ¹⁴
7	TPR	2014	14q32.33	(T15, A20)	Not treated with ALK TKI	Tumor	PCR	NR	+/+	Choi, 2014 ¹⁷
8	BIRC6	2015	2p22.3	(B2, A20)	PR to crizotinib	Tumor	DNA NGS	NR	+/+	Shan 2015 ¹⁸
9	DCTN1	2015	2p13.1	(D26, A20)	NR	Tumor	DNA NGS	NR	+/+	Ilyevleva, 2015 ¹⁹
10	SQT4T	2015	5q35.3	(S5, A20)	NR	Tumor	DNA NGS	NR	+/+	Ilyevleva, 2015 ¹⁹
11	SOCS5	2015	2p21	NR	NR	Tumor	NGS	NR	+/+	Drilon, 2015 ²⁰
12	SEC31A	2016	4q21.22	(S21, A20)	Adjuvant setting, not treated with ALK TKI	Tumor	NGS	NR	+/+	Kim, 2016 ²¹
13	CLTC	2016	17q23.1	(C31, A20)	Unknown	Tumor	NGS	NR	NR/ NR	Ali, 2016 ²²
14	PKNA1A	2016	17q24.2	(P5, A20)	PR to crizotinib	Tumor	NGS	NR	+/+	Ali, 2016 ²²
15	PPM1B	2016	2p21	(P1, A20)	PR to crizotinib	Tumor	NGS	NR	NR/ NR	Ali, 2016 ²²
16	EP32A2	2016	2p11.2	(E2, A20)	PR to crizotinib	Tumor	NGS	NR	+/+	Ali, 2016 ²²
17	CRMI1	2016	2p22.2	NR	NR	Tumor	NGS	NR	NR/ NR	Tan, 2016 ²³
18	CEBP2	2017	2p22.2	(C2, A20)	Not treated with ALK TKI	Tumor	NGS	25.3%	+/+	Li, 2017 ²⁴
19	PCALM	2017	11q14.2	(P19, A20)	Not treated with ALK TKI	Tumor	NGS	10.2%	NR	Xu, 2017 ²⁵
20	CLPI1	2017	12q24.31	(C22, A20)	PR to crizotinib	Tumor	Targeted RNA sequencing	NR	+/+	Vendrell, 2017 ²⁵
21	BCL11A	2017	2p16.1	(B4, A20)	PR to crizotinib	Tumor and plasma	DNA NGS	54.2% (PFPE) 14.9% (plasma)	ND/ND	Tian, 2017 ²⁶
22	GCC2	2017	2q12.3	(G12, A20)	NR	Tumor	RT-PCR, NGS	NR	+/+	Noh, 2017 ²⁷
23	LMO7	2017	13q22.2	(L15, A20)	NR	Tumor	RT-PCR, NGS	NR	+/+	Noh, 2017 ²⁸
24	PHACTR1	2017	6p24.1	(P7, A20)	NR	Tumor	RT-PCR, NGS	NR	+/+	Noh, 2017 ²⁸
25	CNTN2	2018	6p21.2	(C2, A20)	No with crizotinib, SD with pemterexed	Tumor	NGS	~7.5%	+/+	Du, 2018 ²⁹
26	VIT	2018	2p22.2	(V7, A20)	PR to alectinib	Tumor	NGS	NR	+/+	Hu, 2018 ³
27	DYSF	2018	2p13.2	NR	Extracranial PR but intracranial progression to crizotinib	Pleural effusion	DNA NGS	23.7%	ND/+	Yin 2018 ³¹
28	ITGA4	2018	2q32.1	NR	Extracranial PR but intracranial progression to crizotinib	Pleural effusion	DNA NGS	15.2%	ND/+	Yin, 2018 ³¹
29	PLEKHA7	2018	11p15.2-p15.1	(P26, A19)	PR to alectinib + osimertinib	Plasma	DNA NGS	NR	ND/ND	Schrock, 2018 ³²
30	CLU1	2018	7q22.1	(C8, A20)	PR to crizotinib	Tumor	NGS	11%	NR/ NR	Zhang 2018 ³³
31	VKORC1L1	2018	7q11.21	(V1, A20)	PR with crizotinib and alectinib	Plasma	NGS	NR	+/+	Zhu, 2018 ³⁴
32	FBXO36	2018	2q36.3	NR	PR to crizotinib	Tumor	NGS	NR	ND/+	Xu, 2018 ³⁵
33	SPTBN1	2018	2p16.2	NR	NR	Plasma	NGS	NR	NR/ NR	Ramalingam, 2018 ³⁷
34	ENL6	2018	2p16.1	(E1, A20)	PR to crizotinib	Tumor	NGS	NR	ND/+	Lin, 2018 ³⁸
35	FBXO17	2018	2p16.3	(F1, A20)	PR to crizotinib	Tumor	NGS	NR	ND/+	Lin, 2018 ³⁸
36	CLIP4	2018	2p23.2	(C7, A20)	NR	Tumor	NGS	NR	ND/+	Zhu, 2018 ³⁹
37	CAMKMT	2019	2p21	(C3, A20)	Not treated with ALK TKI	Tumor	NGS	NR	+/+	Hu, 2019 ⁴⁰
38	NCOA1	2019	2p23.3	(N21, A20)	PR to crizotinib, PFS > 18 months	Tumor	NGS	NR	ND/+	Cao, 2019 ⁴¹
39	MYT1L	2019	2p25.3	(M14, A20)	PR on crizotinib, PD on ceritinib and alectinib	Tumor	NGS	NR	+/+	Tsou, 2019 ⁴²
40	SBRD1	2019	2p21	(S20, A20)	Not treated with ALK TKI	Tumor	NGS	2.6%	ND/+	Hou, 2019 ⁴³
41	SRSF2A	2019	2p23.1	(S1, A20)	NR	Tumor	NGS	NR	ND/+	Hou, 2019 ⁴⁴

Fusion No.	Fusion Partner	Year Published in Print/ Presented	Chromosomal Location	Fusion Breakpoint	Response to ALK TKI at the Time of Publication	Tumor Source	Method of Detection	Variant Frequency in Tumor	FISH/ IHC	References ^a
42	NTRK2 (R64A 1486)	2019	2q36.3	(N3, A20)	NR	Tumor	NGS	NR	ND/-	Zhao, 2019 ⁴⁵
43	MNP1B	2019	17p11.2	(M21, A20)	PR to crizotinib	Tumor	RNA sequencing	NR	+/+	Fan, 2019 ⁴⁶
44	ADAM17	2019	2p35.1	(A4, A20)	PR to alectinib	Plasma	DNA NGS	3.68%	NR/ NR	Supplee, 2019 ⁴⁸
45	ALK	2019	2p23.2-p23.1	(A6, A20)	NR	Plasma	DNA NGS	26.63%	NR/ NR	Supplee, 2019 ⁴⁸
46	LPIN1 ^b	2019	2p25.1	NR	Response to crizotinib + erlotinib	Tumor	NGS	NR	NR/ NR	Supplee 2019 ⁴⁸
47	WDRCP	2019	2p15	(W17, A20)	PR to crizotinib	Tumor	DNA NGS	52.6%	+/+	He, 2019 ⁴⁷
48	CEP55	2019	10q23.33	(C3, A20)	NR	Tumor	DNA NGS	NR	NR/ NR	Couëtoux du Tertre, 2019 ⁴⁸
49	ERC1 ^c	2019	12p13.33	(E15, A20)	NR	Tumor	DNA NGS	NR	NR/ NR	Couëtoux du Tertre, 2019 ⁴⁸
50	SLC16A7 ^c	2019	12p13.33	NR	NR	Tumor/ plasma	DNA NGS	NR	NR/ NR	Zhou, 2019 ⁴⁹
51	THNP2	2019	12q14.1	(S1, A20)	PR to crizotinib prolonged PFS	Tumor/ plasma	DNA NGS	NR	NR/ NR	Couëtoux du Tertre, 2019 ⁴⁸
52	ATAD2B	2019	4p16.3	(T5, A20)	PR to crizotinib	Tumor/ plasma	DNA NGS	0.1% (plasma) 3.3% (tumor)	ND/+	Feng, 2019 ⁵⁰
53	SLMAP	2019	2p24.1-p23.3	(A1, A20)	Treated with crizotinib	Tumor	DNA NGS	NR	ND/+	Bai, 2019 ⁵¹
54	FBN1	2019	3p14.3	(S12, A20)	Unknown, adjuvant treatment with crizotinib	Tumor	Anchored Multiplex RNA sequencing	NR	+/+	Paga, 2019 ⁵²
55	SWAP70	2019	15q21.1	NR	NR	Tumor/ plasma	DNA NGS	NR	NR/ NR	Zhou, 2019 ⁵³
56	TCF12	2019	15q21.1	NR	NR	Tumor/ plasma	DNA NGS	NR	NR/ NR	Zhou, 2019 ⁵³
57	TRIM66	2019	15p15.4	NR	NR	Tumor/ plasma	DNA NGS	NR	NR/ NR	Zhou, 2019 ⁵³
58	WNK3	2019	3p11.22	NR	NR	Tumor/ plasma	DNA NGS	NR	NR/ NR	Zhou, 2019 ⁵³
59	AKAPBL	2019	19p13.12	NR	esartinib	plasma	DNA NGS	NR	NR/ NR	Horn, 2019 ⁵³
60	SPECC1L	2019	22q11.23	(S9, A20)	Not treated with ALK TKI	Tumor	DNA NGS	NR	NR/ NR	Pan, 2019 ⁵⁴
61	PRKCB	2019	16p11.2-p12.1	(P2, A19)	PR to crizotinib, disappearance of PRKCB-ALK fusion variant	Tumor and plasma	NGS	2.6% (tumor) 0.8% (plasma)	NR/ NR	Luo, 2019 ⁵⁵
62	CDK15 ^c	2019	2q33.1	(C10, A19)	NR	Tumor	DNA NGS	NR	NR/ NR	Wen, 2019 ⁵⁶
63	LCLAT1	2019	2p23.1	NR	NR	Tumor	DNA NGS	NR	NR/ NR	Wen, 2019 ⁵⁶
64	MP1	2019	11q22.1	NR	NR	Tumor	DNA NGS	NR	NR/ NR	Wen, 2019 ⁵⁶
65	PLEKHA2 (ISCLL)	2020	19p36.21	(P7, A20)	SD to crizotinib and brigatinib	Tumor	NGS	NR	ND/+	Li, 2020 ⁵⁷
66	DCHS1	2020	11p15.4	NR	PR or SD to esartinib	Tumor	NGS	NR	NR/ NR	Yang, 2020 ⁵⁸
67	PPFIBP1	2020	12p11.23-p11.22	NR	PR or SD to esartinib	Tumor	NGS	NR	NR/ NR	Yang, 2020 ⁵⁸
68	ATP13A4	2020	3q29	(A9, A19)	NR	Tumor	NGS	NR	NR/ NR	Tian, 2020 ⁵⁹
69	C12orf75	2020	12q23.3	(C1, A20)	NR	Tumor	NGS	NR	NR/ NR	Tian, 2020 ⁵⁹
70	ERES1	2020	2p21	(E1, A20)	NR	Tumor	NGS	NR	NR/ NR	Tian, 2020 ⁵⁹
71	FAM179A (TOGARAKM)	2020	2p23.2	(F1, A20)	NR	Tumor	NGS	NR	NR/ NR	Tian, 2020 ⁵⁹
72	FLTR	2020	12q23.2	(F13, A20)	NR	Plasma	NGS	NR	NR/ NR	Zhang, 2020 ⁶⁰
73	LIMD1	2020	2q31.31	(L2, A20)	NR	Tumor	NGS	NR	NR/ NR	Tian, 2020 ⁶⁰
74	LINC03227	2020	13q12.12	(L2, A20)	NR	Tumor	NGS	NR	NR/ NR	Tian, 2020 ⁶⁰
75	LOC491460	2020	7q33.1	(L1, A20)	SD to crizotinib	Tumor	NGS	NR	NR/ NR	Tian, 2020 ⁶⁰
76	LYPD1	2020	8q21.2	(L3, A20)	NR	Tumor	NGS	NR	NR/ NR	Tian, 2020 ⁶⁰
77	RBMO2	2020	10q25.2	(R1, A20)	NR	Tumor	NGS	NR	NR/ NR	Tian, 2020 ⁶⁰
78	TACR1	2020	12p12	(T1, A20)	PR to crizotinib	Tumor	NGS	NR	NR/ NR	Tian, 2020 ⁶⁰
79	ZANCF	2020	2q42.2	(Z1, A20)	NR	Tumor	NGS	NR	NR/ NR	Tian, 2020 ⁶⁰
80	TTC27	2020	2p22.3	(T12, A20)	NR	Tumor	NGS	NR	NR/ NR	Tian, 2020 ⁶⁰
81	TUBB8	2020	6p21.33	(T3, A20)	NR	Tumor	NGS	NR	NR/ NR	Tian, 2020 ⁶⁰
82	SMPD4	2020	2q11.1	(S1, A20)	NR	Tumor	NGS	NR	NR/ NR	Tian, 2020 ⁶⁰
83	SORCS1	2020	10q25.1	(S10, A20)	NR	Tumor	NGS	NR	NR/ NR	Tian, 2020 ⁶⁰
84	LINC00211	2020	2p22.2	(L7, A20)	PR with crizotinib and alectinib, SD with lorlatinib	CSF	NGS	33.2%	NR/+	Li, 2020 ⁶¹
85	SOS1	2020	2p22.1	(S2, A20)	PR to crizotinib	FFPE	NGS	NR	ND/ ND	Chen, 2020 ⁶²
86	C9orf73	2020	9q22.32	(C12, A20)	NR	FFPE	NGS	22.4%	ND/+	Zhang, 2020 ⁶³
87	CYBBRD1	2020	2q31.1	(C21, A20)	NR	FFPE	NGS	12.5%	ND/ NR	Zhang, 2020 ⁶³
88	MTA3 ^c	2020	2p21	(M6, A 20)	SD with crizotinib, no response to alectinib	FFPE	NGS	15.3%	ND/ NR	Zhang, 2020 ⁶³
89	THADA	2020	2p21	(T25, A20)	SD to crizotinib, PR to ceritinib	Plasma	NGS	0.3%	ND/ NR	Zhang, 2020 ⁶⁴

Table 2. List of Chromosomal Locations of Intergenic Translocations With Potential Fusion Partners

No.	Year Published in Print/Presented	Chromosomal Location	Potential Fusion Partner Gene	Response to ALK TKI at the Time of Publication	Tumor Source	Method of Detection	Variant Frequency in Tumor	FISH/ IHC	References
1	2019	12q23.3	<i>RIC8B</i>	NR	Tumor	NGS	NR	ND/NR	Zhao, 2019 ⁴⁴
2	2019	2p21	<i>LOC388942</i> (<i>LINC01913</i>)	NR	Tumor	NGS	NR	ND/NR	Zhao, 2019 ⁴⁴
	2020	2p21	<i>LOC388942</i> (<i>LINC01913</i>)	NR	Tumor	NGS	NR	NR/NR	Tian, 2020 ⁵⁹
3	2019	2q22.1-q22.2	<i>LRP1B</i>	NR	Tumor	NGS	NR	ND/NR	Zhao, 2019 ⁴⁴
4	2019	2p16.2	<i>MIR4431</i>	NR	Tumor	NGS	NR	ND/NR	Zhao, 2019 ⁴⁴
5	2019	2p23.3	<i>CENPA/DPYSL5</i>	PR to crizotinib	Tumor	NGS	NR	+/+	Fei, 2019 ⁶³
6	2020	18q12.1	<i>CDH2</i>	NR	Tumor	NGS	NR	NR/NR	Tian, 2020 ⁵⁹
7	2020	18q12.2	<i>CELF4</i>	NR	Tumor	NGS	NR	NR/NR	Tian, 2020 ⁵⁹
8	2020	2p23.3	<i>CENPA</i>	PR to crizotinib	Tumor	NGS	NR	NR/NR	Tian, 2020 ⁵⁹
9	2020	15q13.3	<i>CHRNA7</i>	PR to crizotinib	Tumor	NGS	NR	NR/NR	Tian, 2020 ⁵⁹
10	2020	2q14.3	<i>CNTNAP5</i>	NR	Tumor	NGS	NR	NR/NR	Tian, 2020 ⁵⁹
11	2020	2p21	<i>COX7A2L</i>	NR	Tumor	NGS	NR	NR/NR	Tian, 2020 ⁵⁹
12	2020	2p13.2	<i>DYSF</i>	NR	Tumor	NGS	NR	NR/NR	Tian, 2020 ⁵⁹
13	2020	2p16.3	<i>FSHR</i>	NR	Tumor	NGS	NR	NR/NR	Tian, 2020 ⁵⁹
14	2020	13q12.11	<i>GJB6</i>	NR	Tumor	NGS	NR	NR/NR	Tian, 2020 ⁵⁹
15	2020	3q22.3	<i>LINC01210</i>	NR	Tumor	NGS	NR	NR/NR	Tian, 2020 ⁵⁹
16	2020	2p22.3	<i>MEMO1</i>	NR	Tumor	NGS	NR	NR/NR	Tian, 2020 ⁵⁹
17	2020	2p22.3	<i>MIR548AD</i>	NR	Tumor	NGS	NR	NR/NR	Tian, 2020 ⁵⁹
18	2020	4q31.1	<i>MGST2</i>	NR	Tumor	NGS	NR	NR/NR	Tian, 2020 ⁵⁹
19	2020	2q11.2	<i>PDCL3</i>	NR	Tumor	NGS	NR	NR/NR	Tian, 2020 ⁵⁹
20	2020	2p22.2	<i>QPCT</i>	NR	Tumor	NGS	NR	NR/NR	Tian, 2020 ⁵⁹
21	2020	2p23.3	<i>RAB10</i>	NR	Tumor	NGS	NR	NR/NR	Tian, 2020 ⁵⁹
22	2020	2p22.1	<i>SLC8A1</i>	NR	Tumor	NGS	NR	NR/NR	Tian, 2020 ⁵⁹
23	2020	2q32.3	<i>STK17B</i>	NR	Tumor	NGS	NR	NR/NR	Tian, 2020 ⁵⁹
24	2020	6q24.1-q24.2	<i>VTAT</i>	NR	Tumor	NGS	NR	NR/NR	Tian, 2020 ⁵⁹
25	2020	2p22.2	<i>CDC42EP3^d</i>	No response to crizotinib and alectinib	Plasma	NGS	13.0%	ND/+	Zhang, 2020 ⁶⁰
26	2020	19q13.42	<i>PR11-433C9.2</i> (<i>PRPF31</i>)	NR	Tumor	NGS	18.6%	ND/NR	Zhang, 2020 ⁶⁰
27	2020	3p22.1	<i>RPSA</i>	NR	Tumor	NGS	7.9%	ND/+	Zhang, 2020 ⁶⁰
28	2020	2p23.3	<i>UBXN2A</i>	NR	Tumor	NGS	25.4%	ND/NR	Zhang, 2020 ⁶⁰

Intergenic Breakpoints Identified by DNA Sequencing Confound Targetable Kinase Fusion Detection in NSCLC

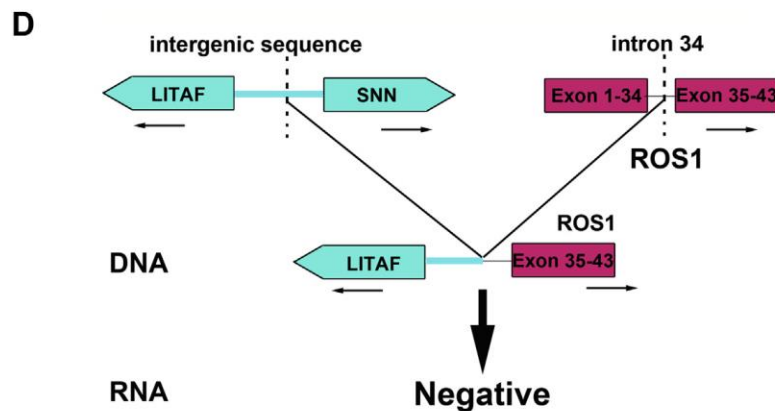
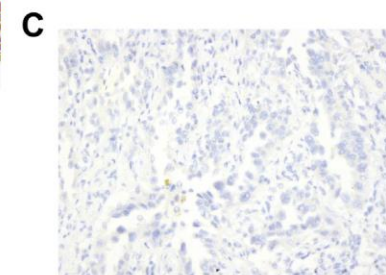
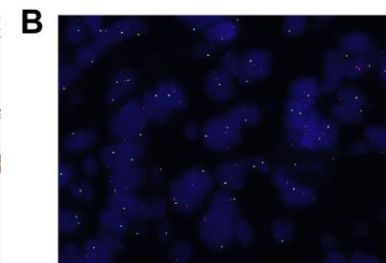
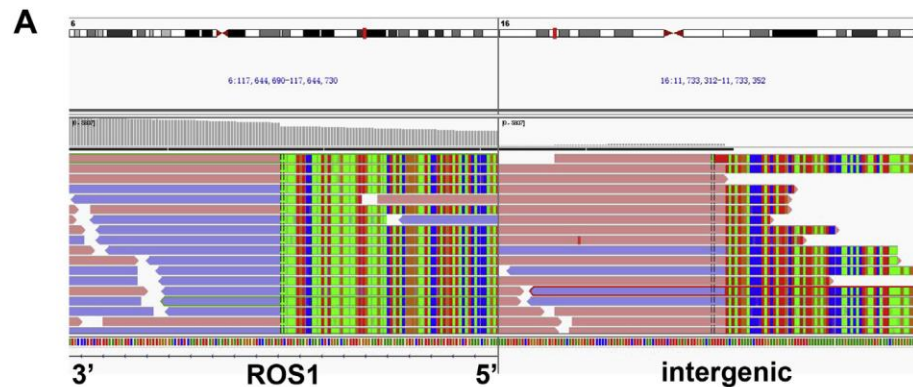
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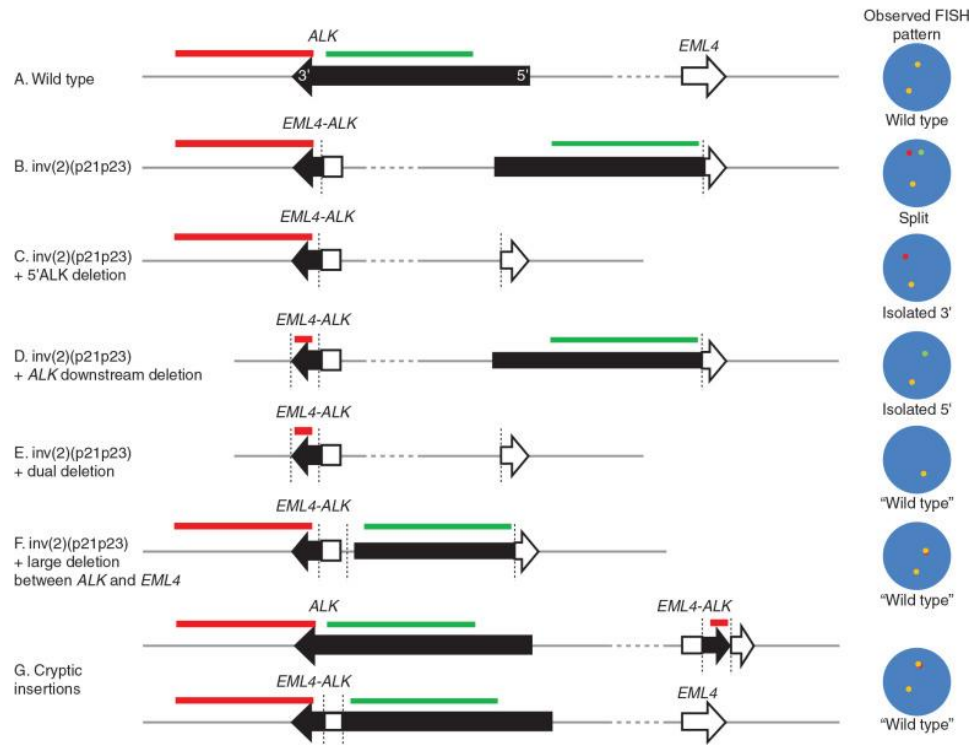
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Prospective and clinical validation of ALK immunohistochemistry: results from the phase I/II study of alectinib for ALK-positive lung cancer (AF-001JP study)

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Caso 4.

Carcinoma de pulmón con mutación de EGFR

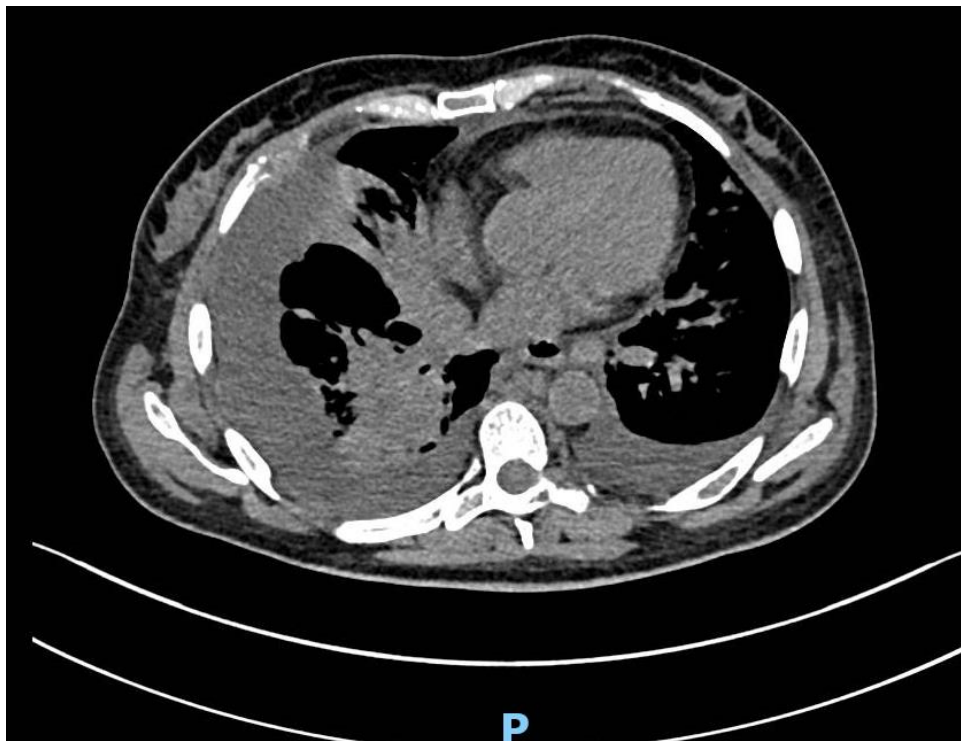
Caso 4.

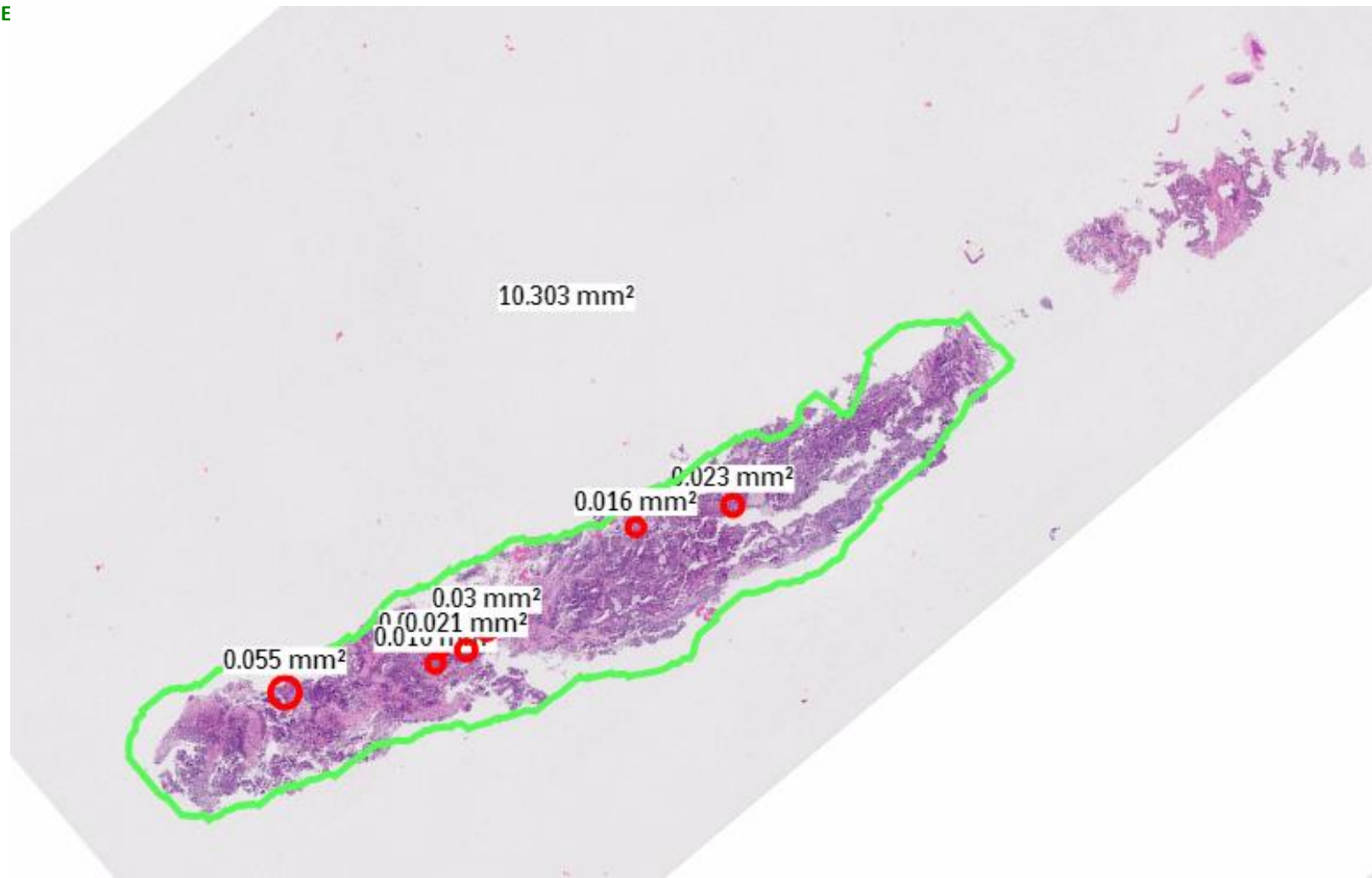
Carcinoma de pulmón con mutación de EGFR

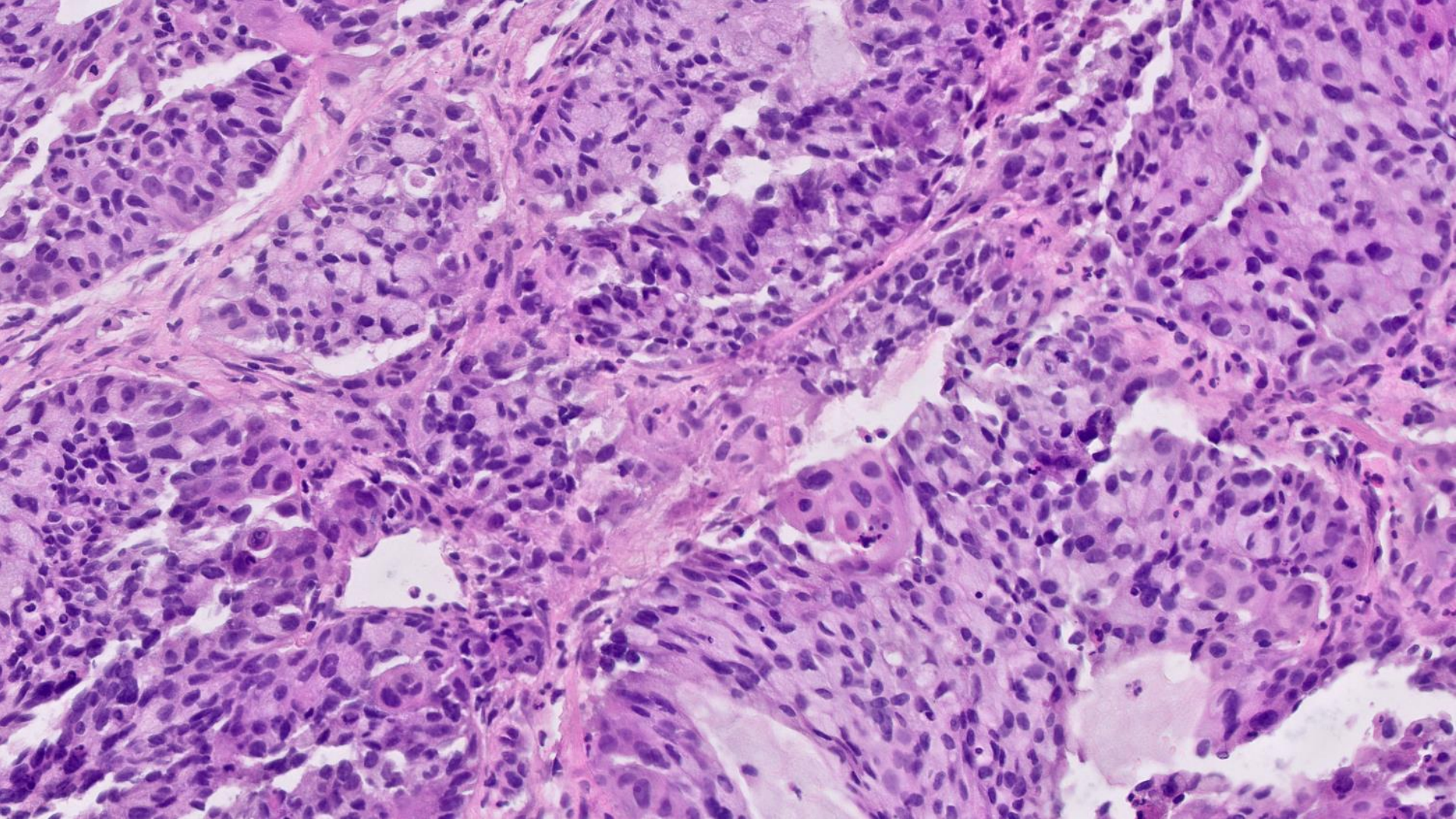
Mujer de 59 años, sin antecedentes personales de interés. Historia familiar con tía materna ca ovario, tía materna ca colon, tía materna ca páncreas y tío materno ca estómago (edades entre 60-70 años). Tío paterno ca colon (85 años).

No fumadora. Historia de asma con dolor en HCD y aumento de tos reciente.

Diagnóstico Oncológico Febrero 2022 : Masa parenquimatosa heterogénea en LID de 7,8 cm. Múltiples lesiones de aspecto metastásico en el parénquima hepático la de mayor tamaño de unos 55 mm en lóbulo caudado. Adenopatías hiliares hepáticas, retroperitoneales y periesofágicas. Derrame pericárdico de hasta 17 mm de espesor máximo. Leve cuantía de derrame pleural derecho. N. MALIGNA DE BRONQUIO PRINCIPAL T: x N: x M: 1 Estadío: IV ECOG: 0

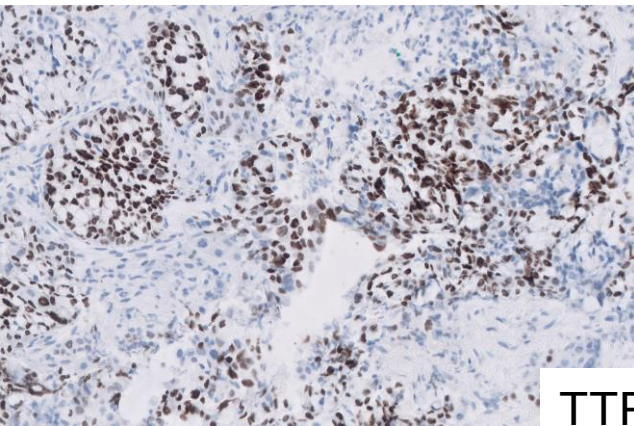




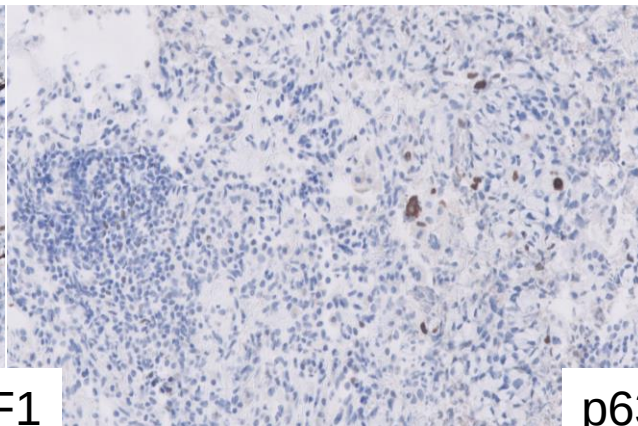


Caso 4.

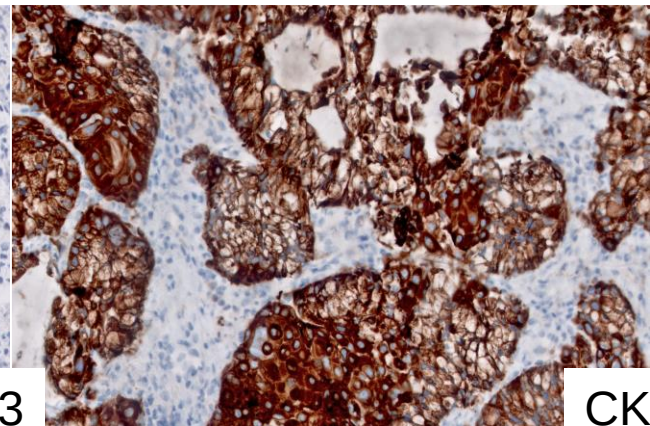
Carcinoma de pulmón con mutación de EGFR



TTF1



p63



CK



Action OncoKitDx

Perfil mutacional obtenido:

Variantes patogénicas:

EGFR (NM_005228.3): Exón 19/28 c.2239_2250del p.Leu747_Ala750del (VAF 55,31%). Mutado EGFR delección exón 19
No se identifican traslocaciones de ALK, ROS1 o RET, amplificación de MET, mutaciones del sitio de splicing del exón 14 de MET, mutaciones puntuales en KRAS (codones 12/13 y 61), mutaciones en BRAF (V600), ni mutaciones o inserciones en el exón 20 de ERBB2 (HER2).

Otras alteraciones identificadas:

Otras variantes patogénicas:

Amplificación de EGFR, 8,43 copias

Caso 4.

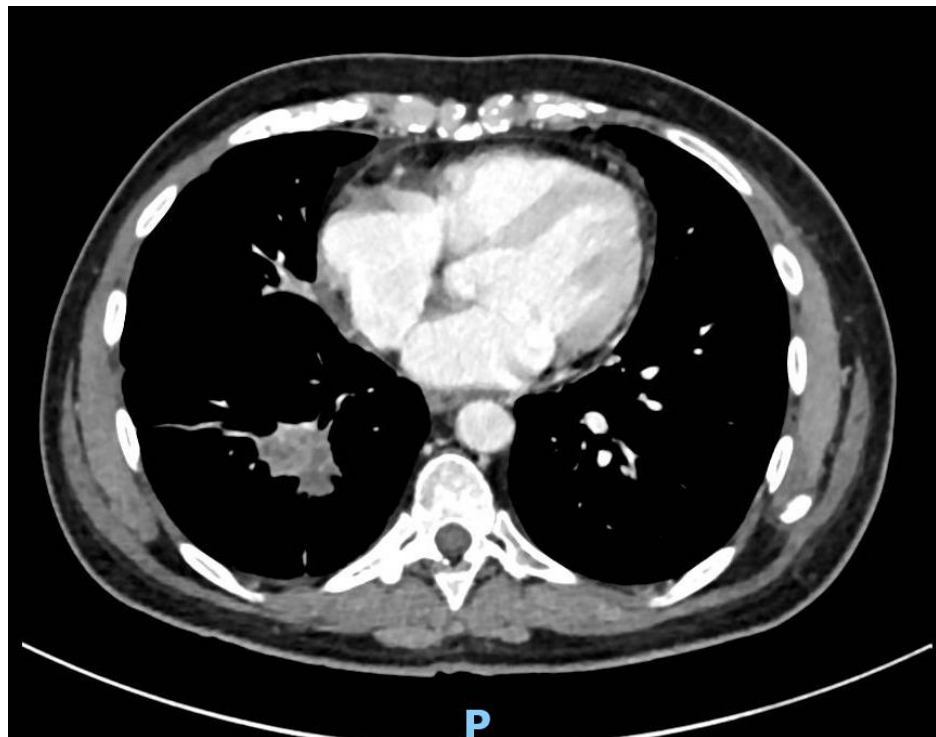
Carcinoma de pulmón con mutación de EGFR

Carcinoma de células no pequeñas estadio IVB (hepáticas y ganglionares).

EGFR del19

PD L1 0%. ALK y NTRK negativos Marzo 2022: Inicia tratamiento con Osimertinib, con excelente respuesta.

Respuesta en pulmón y regresión de lesiones adenopáticas y hepática

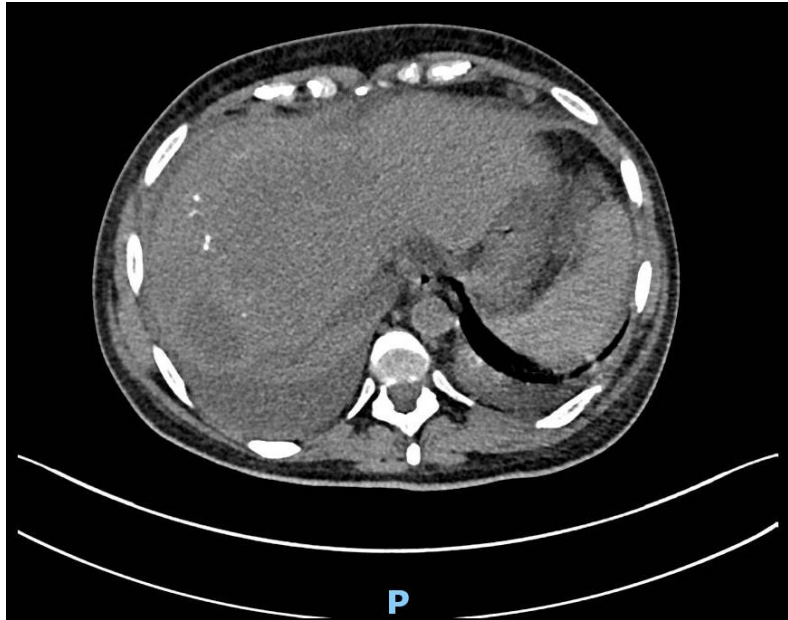


Caso 4.

Carcinoma de pulmón con mutación de EGFR

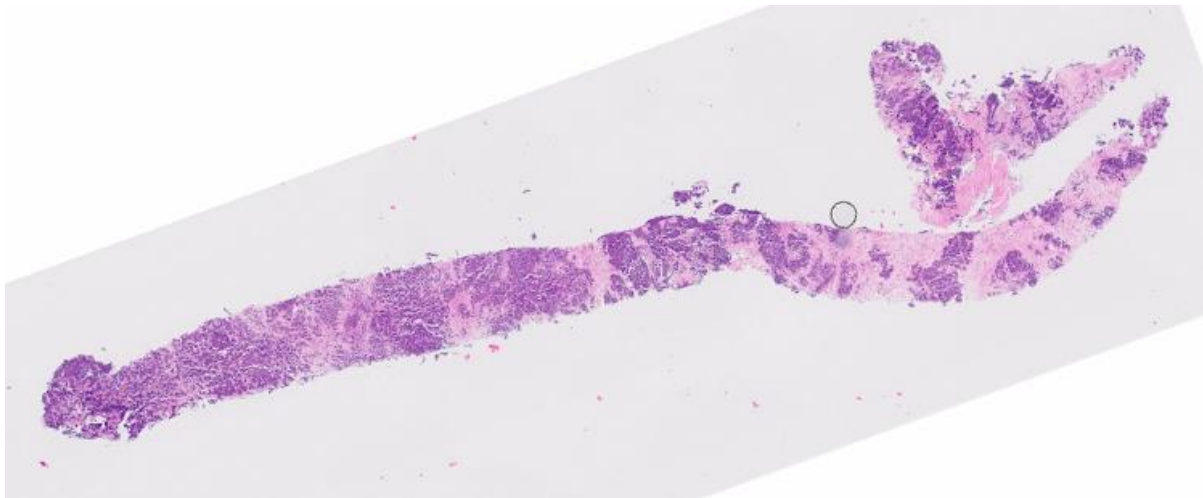
Julio 2023: Progresión pulmonar con afectación hepática importante y 3 lesiones de 14, 8 y 5 mm en SNC.

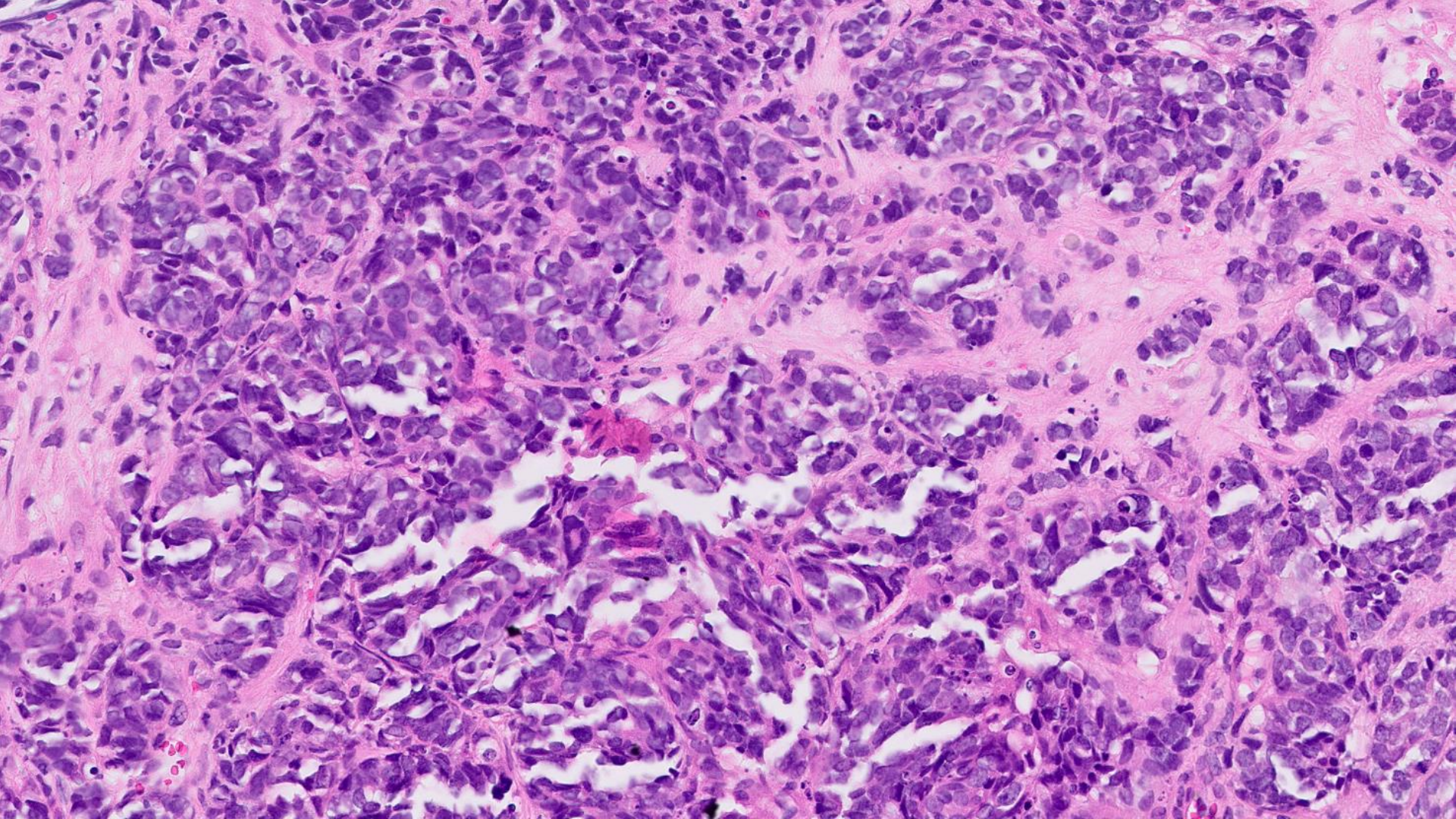
1 metástasis ósea en soma C4.

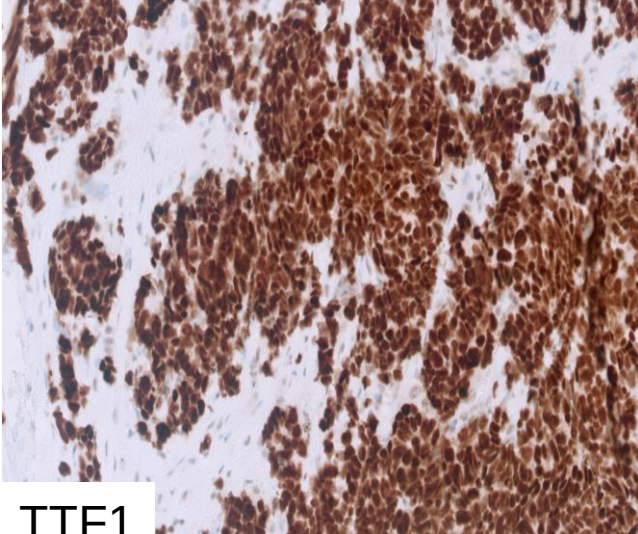


Caso 4.

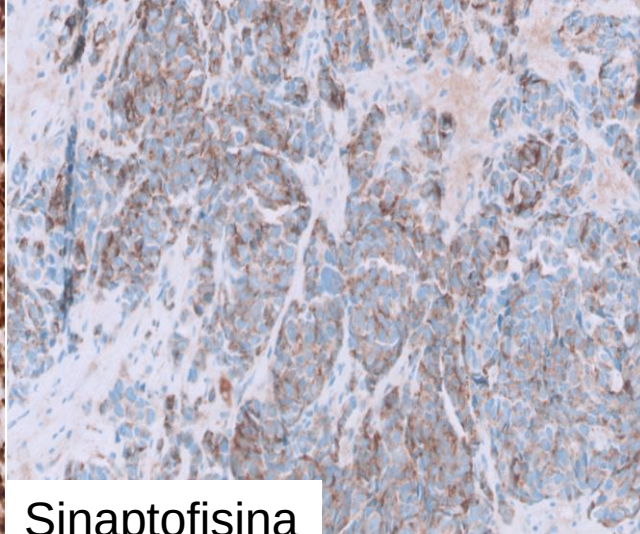
Carcinoma de pulmón con mutación de EGFR



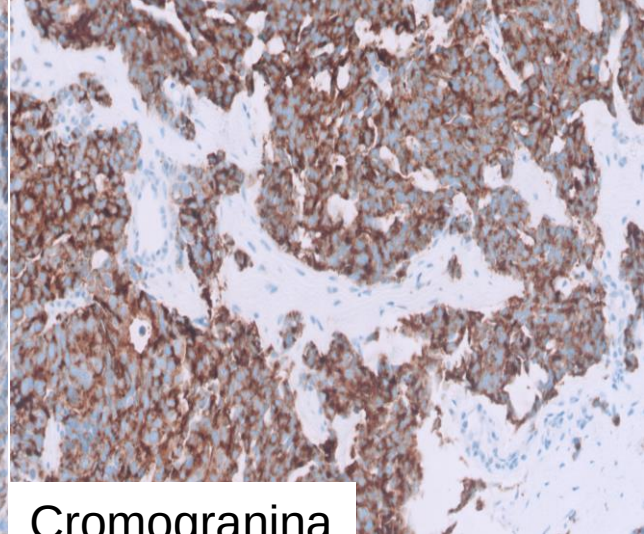




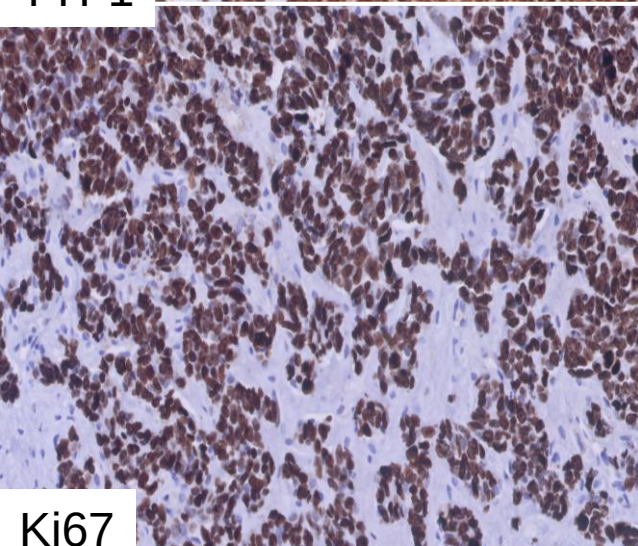
TTF1



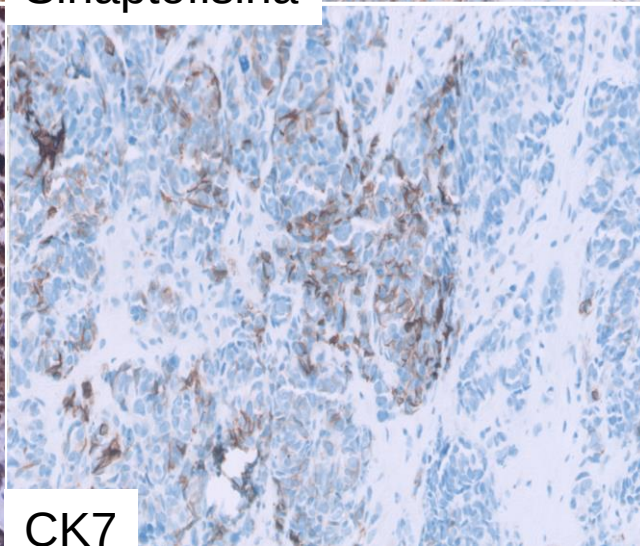
Sinaptofisina



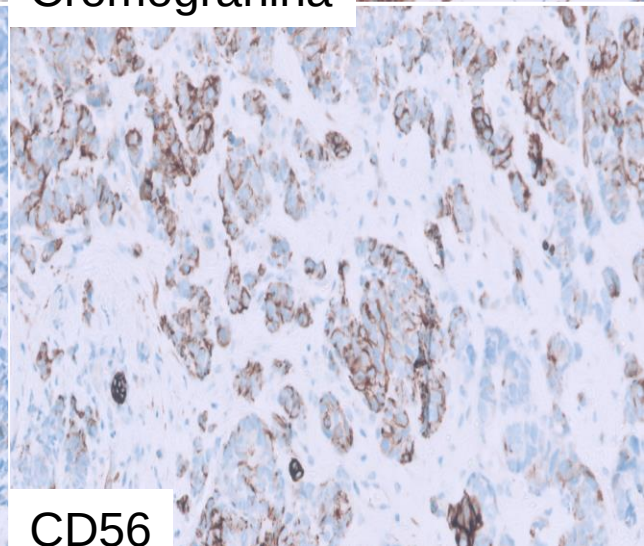
Cromogranina



Ki67



CK7



CD56

Caso 4.

Carcinoma de pulmón con mutación de EGFR

Cilindros tisulares constituidos por una proliferación neoplásica densamente celular, de hábito epitelial y con parcial morfología fusocelular, que crece formando masas sólidas irregulares, nidos o cordones y como células sueltas, en un estroma fibroescleroso. Las células son de tamaño intermedio, citoplasma eosinófilo no definido y núcleo hipercromático, denso, con ocasional y pequeño nucleolo.

TTF1: positivo, difuso e intenso

Cromogranina: positivo, en la gran mayoría de las células

Sinaptofisina: positivo difuso

CK7: positivo parcheado

P63: positivo parcheado nuclear, en células aisladas

CK20: negativo

Ki67: 90%

Diagnóstico: Carcinoma con características morfológicas e inmunofenotipo congruente con Carcinoma de células pequeñas.



Action OncoKitDx

Perfil mutacional obtenido:

Variantes patogénicas:

EGFR (NM_005228.3): Exón 19/28 c.2239_2250del p.Leu747_Ala750del (VAF 70%). Mutado EGFR delección exón 19
No se identifican traslocaciones de ALK, ROS1 o RET, amplificación de MET, mutaciones del sitio de splicing del exón 14 de MET, mutaciones puntuales en KRAS (codones 12/13 y 61), mutaciones en BRAF (V600), ni mutaciones o inserciones en el exón 20 de ERBB2 (HER2).

Otras alteraciones identificadas:

Variantes patogénicas:

HRAS NM_005343.2 :Exón 2/6 c.38G>T p.Gly13Val (VAF:1,11%)

Variantes de significado incierto**:

EGFR (NM_005228.3): Exón 19/28 c.2251A>C p.Thr751Pro (VAF 62%)

Caso 4.

Carcinoma de pulmón con mutación de EGFR

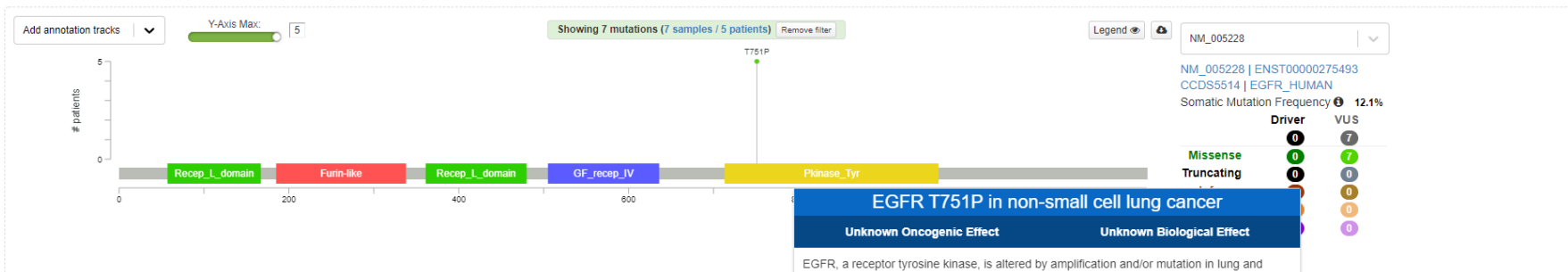

Data Sets Web API Tutorials/Webinars FAQ News Visualize Your Data About cBioPortal Installations

Modify Query
Combined Study (40285 samples)
Querying 40285 samples / 37648 patients in 36 studies
EGFR

Queried gene is altered in
• 4796 (13%) of queried patients
• 5493 (14%) of queried samples

OncoPrint
Cancer Types Summary
Plots
Mutations
Structural Variants Beta!
Comparison/Survival
CN Segments
Pathways
Download

EGFR



7 Mutations: includes 2 duplicate mutations in patients with multiple samples (page 1 of 1)

Study of Origin	Sample ID	Cancer Type Detailed	Protein Change	Ann
Lung Adenocarcinoma (CPTA...	C3N-02067	Lung Adenocarcinoma	T751P	
Non-Small Cell Lung Cancer ...	CRUK0012-R1	Non-Small Cell Lung Cancer	T751P	
Non-Small Cell Lung Cancer ...	CRUK0012-R2	Non-Small Cell Lung Cancer	T751P	
Non-Small Cell Lung Cancer ...	CRUK0012-Pre-ctDNA	Non-Small Cell Lung Cancer	T751P	
Lung Adenocarcinoma Met O...	P-0020803-T01-WES	Lung Adenocarcinoma	T751P	
Lung Adenocarcinoma Met O...	P-0026255-T01-WES	Lung Adenocarcinoma	T751P	
Metastatic Non-Small Cell Lu...	NCI-L-081-01	Lung Adenocarcinoma	T751P	

Showing 1-7 of 7 Mutations: includes 2 duplicate

Columns (10 / 625)

T751P

IC	Allele Freq (T)	# Mut in Sample
7	0.26	30
7	0.19	66
7	0.13	63
7		17
7	0.09	197
7	0.16	94
7	0.28	6

The information above is intended for research purposes only and should not be used as a substitute for professional diagnosis and treatment.

Caso 4.

Carcinoma de pulmón con mutación de EGFR

 varsome

EGFR(NM_005228.5):c.2251A>C

hg38

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Editions

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Demo

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Join

chr7-55174788-A-C (EGFR:p.T751P)

Submit to ClinVar

Link publication

Classify

Share

API Link

Favorites

Variant 

Explain

Chromosome

Position

REF Sequence

ALT Sequence

Variant type

Cytoband

HGVS

RS ID

Gene symbol

chr7

55174788

A

C

SNV

7p11.2

EGFR(NM_005228.5):c.2251A>C
p.(Thr751Pro)

rs2128954841 |  dbSNP

EGFR

 UCSC genome browser  Mastermind  TraP Score

This variant has been viewed 15 times on VarSome.

Connect with past and future viewers of this variant...

 VarSome.com is for research use only. Find out about our clinically certified platform: VarSome Clinical.

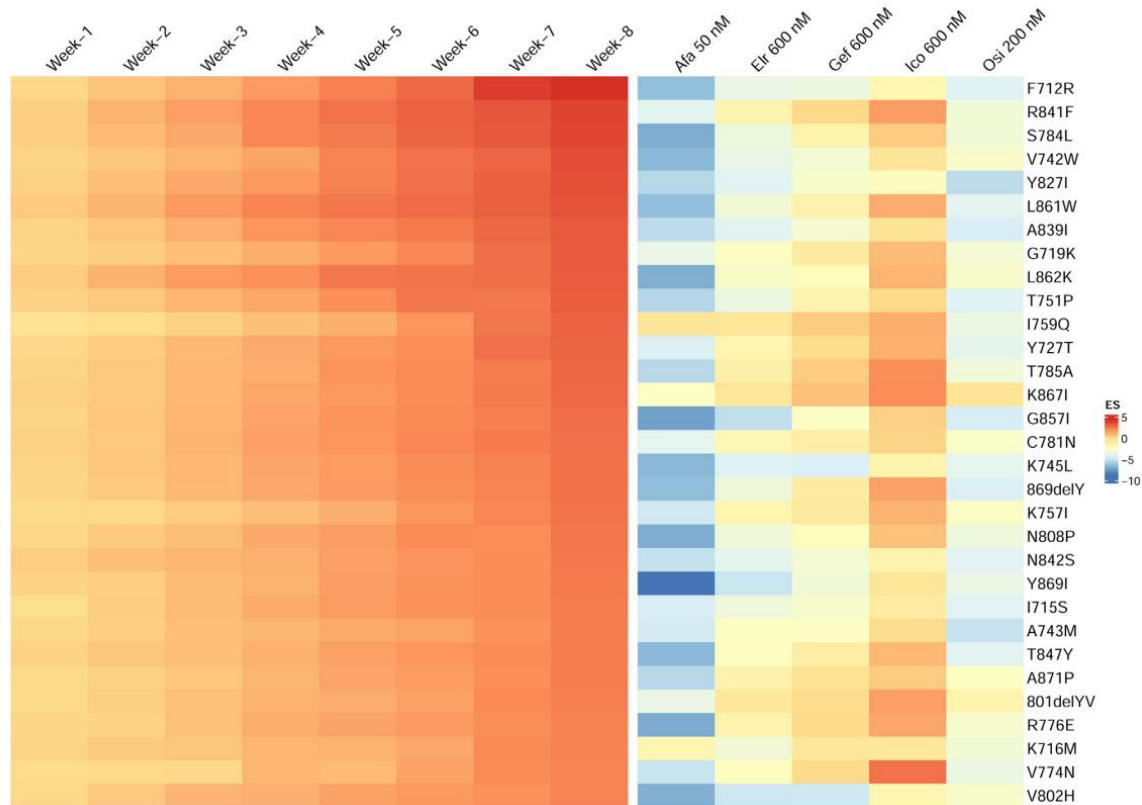


Original Research Article

Defining the sensitivity landscape of EGFR variants to tyrosine kinase inhibitors



Lei An^{a,*}, Yueqiang Wang^{b,*}, Guangyao Wu^a, Zhenxing Wang^a, Zeyuan Shi^a, Chang Liu^c, Chunli Wang^c, Ming Yi^d, Chenguang Niu^e, Shaofeng Duan^e, Xiaodong Li^a, Wenxue Tang^{f,g}, Kongming Wu^a, Shuqing Chen^{b,*}, Hongen Xu^{f,g,*}



Caso 5.

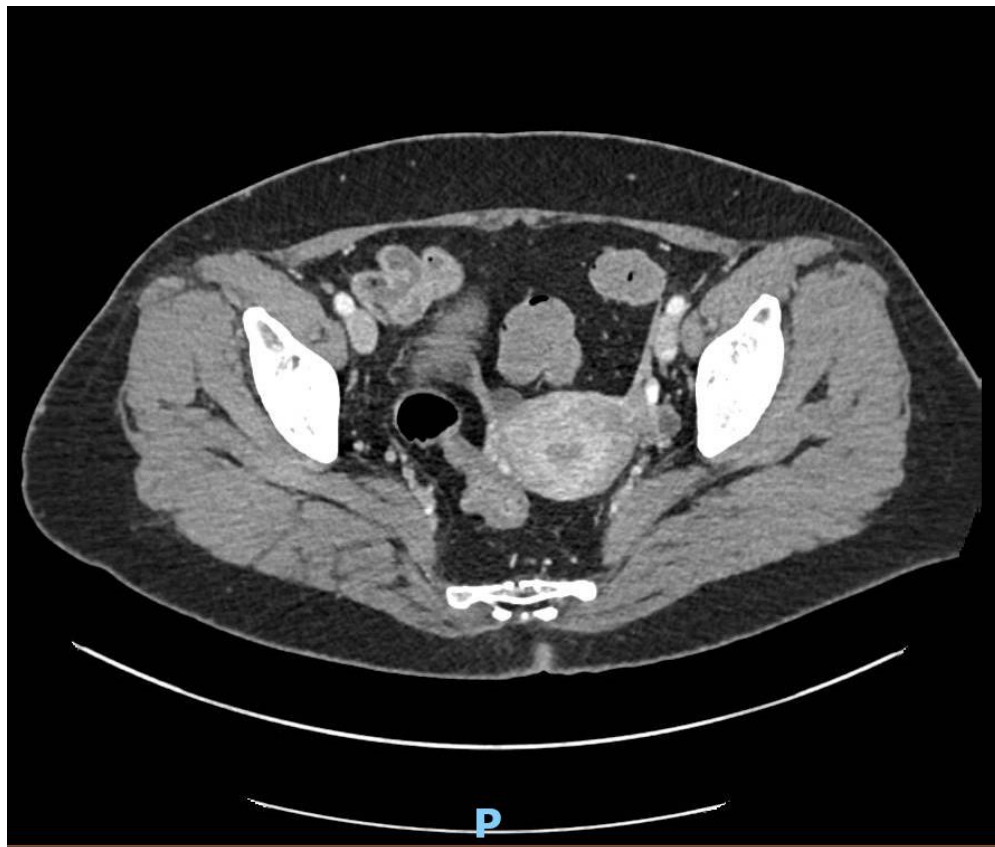
Clasificación molecular en cáncer de endometrio

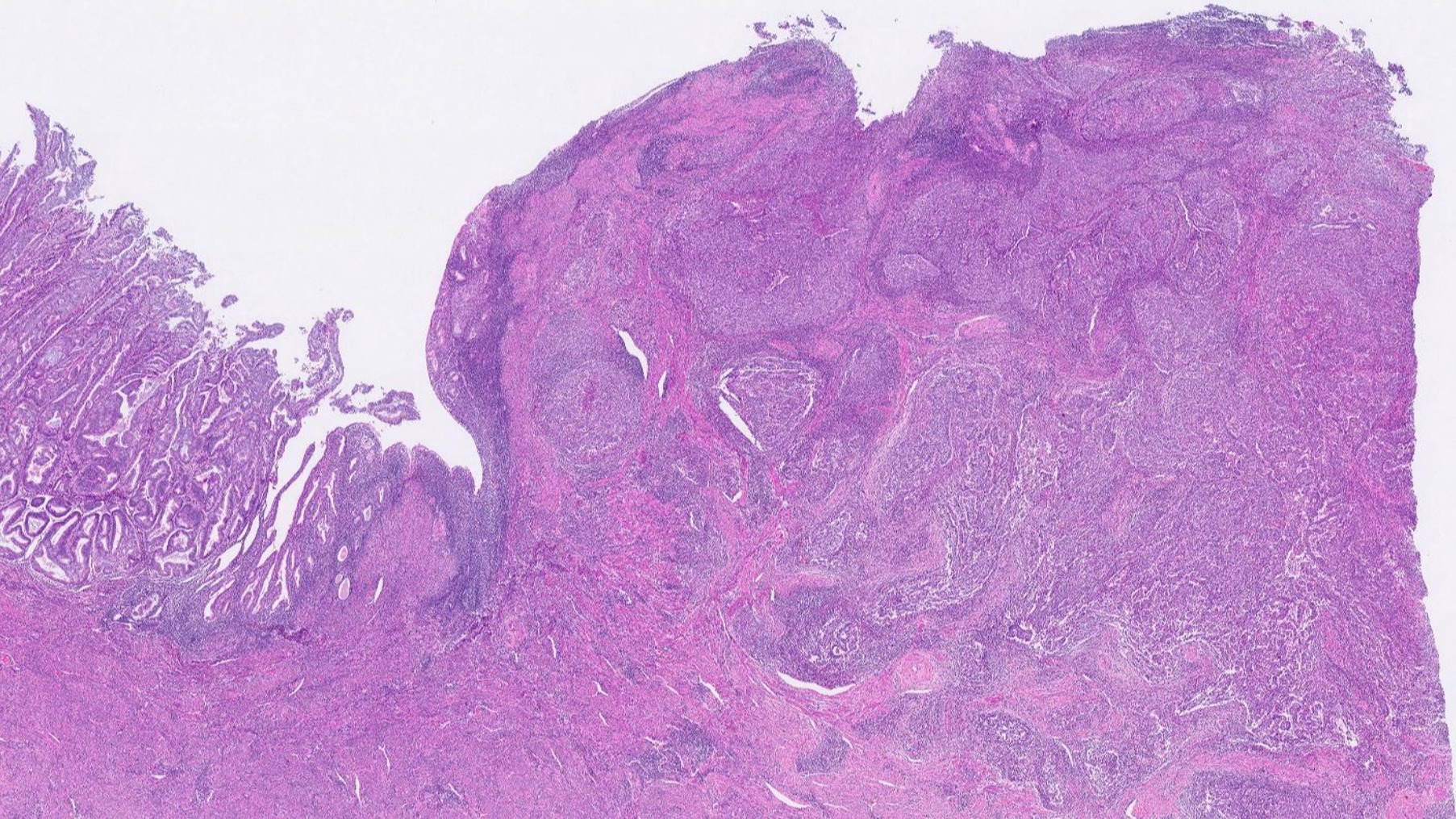
Caso 5.

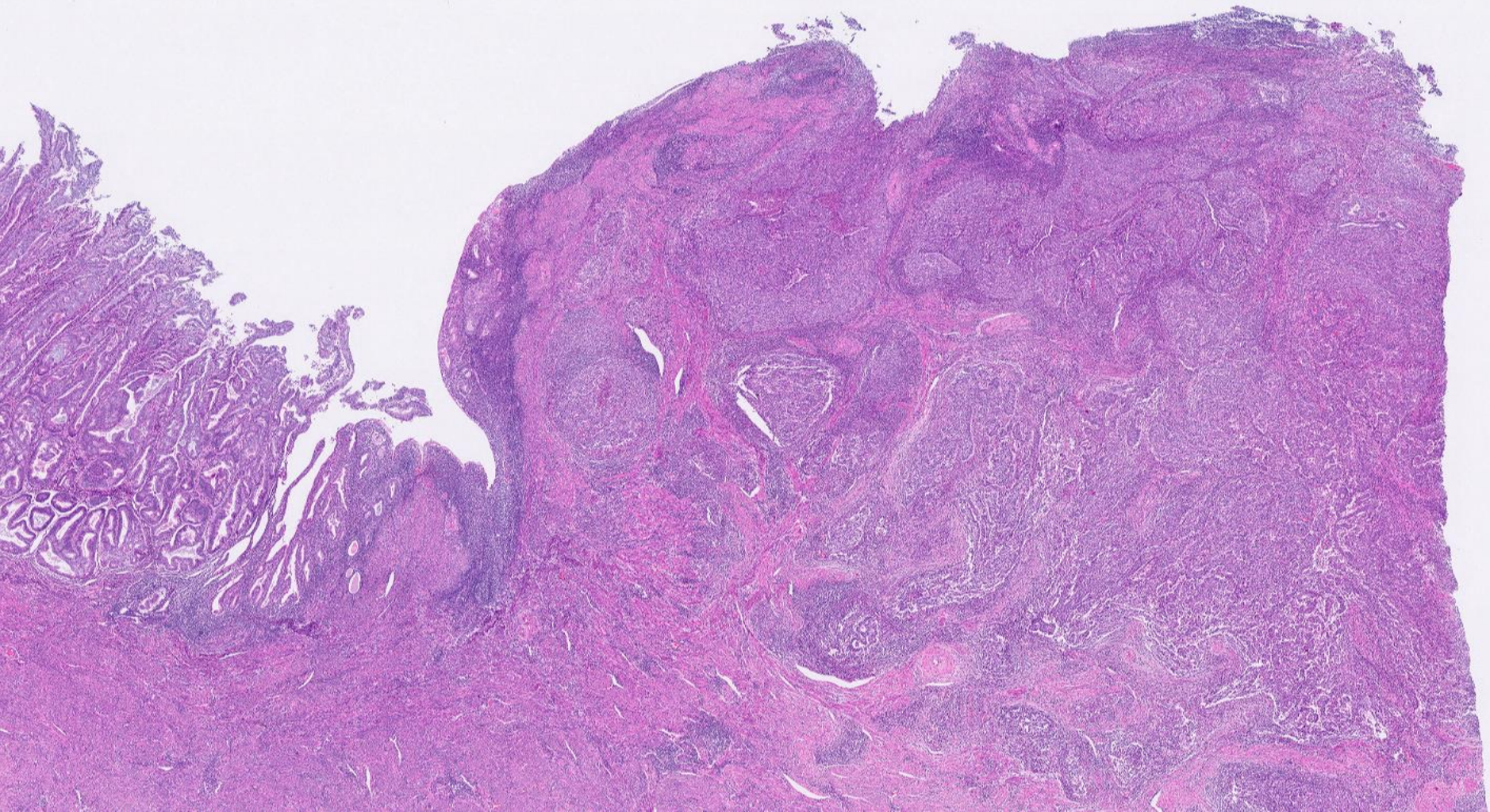
Clasificación molecular en cáncer de endometrio

Mujer de 53 años que acude para realizar histerectomía + doble anexectomía+ BSGC por ca de endometrio No antecedentes Familiares de ca de mama o ginecológico. Mq: 17 años G2P2 Menopausia 51 años. Última citología: hace 2 meses en matrona de centro de salud.

TC: Útero con endometrio con dilatación cavidad endometrial con formaciones hiperrefringentes irregulares en su interior, con afectación de miometrio, compatible con Estadio II. No patología anexial. No LL 02/21. Histerectomía total + doble anexectomía + ganglio centinela pélvico.







ADENOCARCINOMA ENDOMETRIAL de TIPO ENDOMETRIOIDE grado 3 (FIGO)(grado arquitectural 3- grado nuclear 3) con áreas bien diferenciadas, subtipo molecular de BAJO RIESGO en la muestra remitida.

p53: wild type.

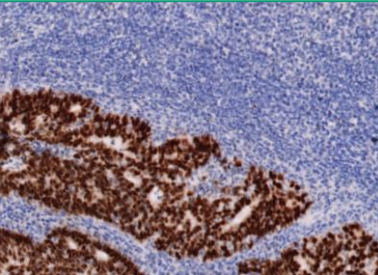
WT1: negativo.

p16: negativo

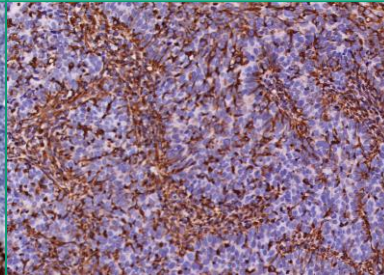
CK7: positivo áreas diferenciadas, negativo áreas pobremente diferenciadas.

CK20 negativo.

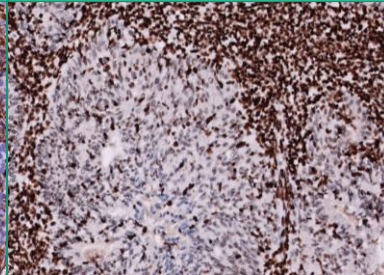
RE



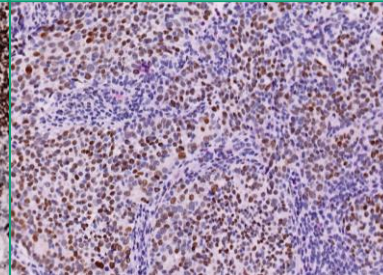
VIM



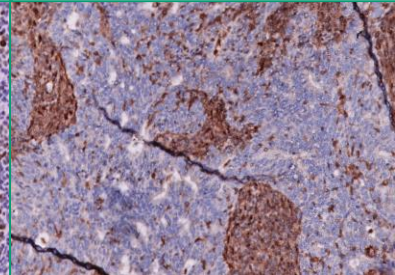
ARID1A



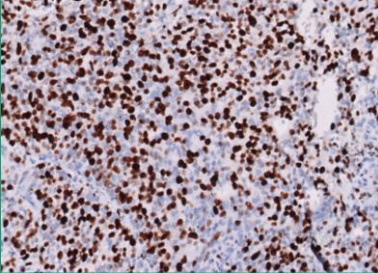
PAX8



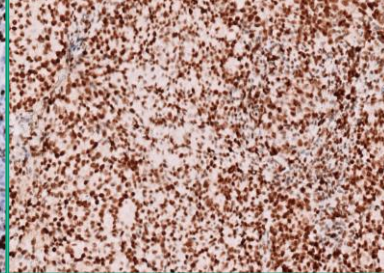
PTEN



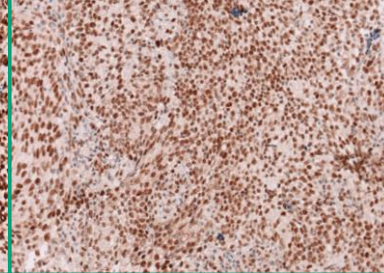
Ki67



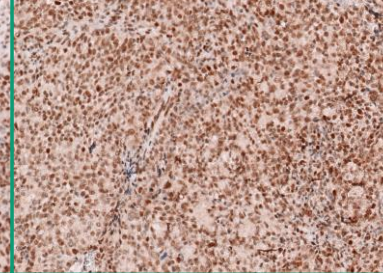
MLH1



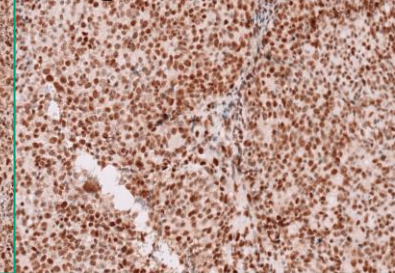
MSH2



MSH6



PMS2



Perfil mutacional obtenido:

Variantes patogénicas:

POLE (NM_006231.2)Exón 14 c.1366G>C ; p.Ala456Pro VAF :30,8%

Otras alteraciones identificadas:

Variantes patogénicas:

PTEN (NM_000314.4)Exón 1 c.19G>T ; p.Glu7Ter VAF :21,04%

PIK3CA (NM_006218.2)Exón 2 c.263G>A ; p.Arg88Gln VAF :27,16%

Variantes probablemente patogénicas:

ARID1A (NM_006015.4)Exón 20 c.5299G>T ; p.Glu1767Ter VAF :6,24%

CTNNB1 (NM_001904.3)Exón 3 c.110C>A ; p.Ser37Tyr VAF :18,78%

PBRM1 (NM_018313.4)Exón 17 c.2128C>T ; p.Arg710Ter VAF :6,69%

EGFR (NM_005228.3)Exón 18 c.2174C>T ; p.Thr725Met VAF :5,68%

ATM (NM_000051.3)Exón 37 c.5623C>T ; p.Arg1875Ter VAF :6,45%

ATRX (NM_000489.3)Exón 9 c.2342G>A ; p.Arg781Gln VAF :18,6%

Variantes de significado incierto**:

MSH2 (NM_000251.2)Exón 9 c.1432C>T ; p.Leu478Phe VAF :18,7%

IDH1 (NM_005896.2)Exón 9 c.1036C>T ; p.Leu346Phe VAF :5,7%

FGFR4 (NM_001291980.1)Exón 5 c.535A>G ; p.Thr179Ala VAF:46,81%

ROS1 (NM_002944.2)Exón 33 c.5397G>T ; p.Gln1799His VAF :6,42%

ESR1 (NM_000125.3)Exón 2 c.470G>A ; p.Arg157Gln VAF :5,75%

PMS2 (NM_000535.5)Exón 11 c.1981G>A ; p.Glu661Lys VAF :16,76%

MET (NM_001127500.1)Exón 10 c.2360C>A ; p.Ser787Ter VAF :23,94%

NTRK2 (NM_006180.3)Exón 15 c.1427A>C ; p.Lys476Thr VAF :19,7%

PTEN (NM_000314.4)Exón 8 c.834C>A ; p.Phe278Leu VAF :8,28%

BRCA2 (NM_000059.3)Exón 10 c.1811A>C ; p.Lys604Thr VAF :5,55%

MAP2K1 (NM_002755.3)Exón 7 c.765G>T ; p.Glu255Asp VAF :21,46%

NTRK3 (NM_002530.3)Exón 10 c.964G>A ; p.Glu322Lys VAF :20,57%

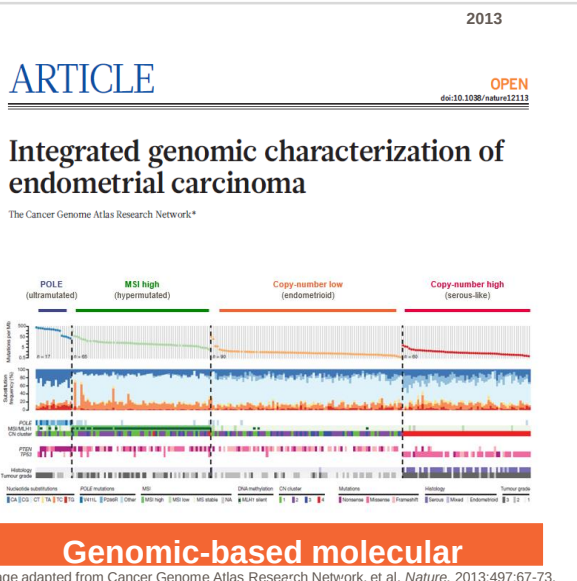
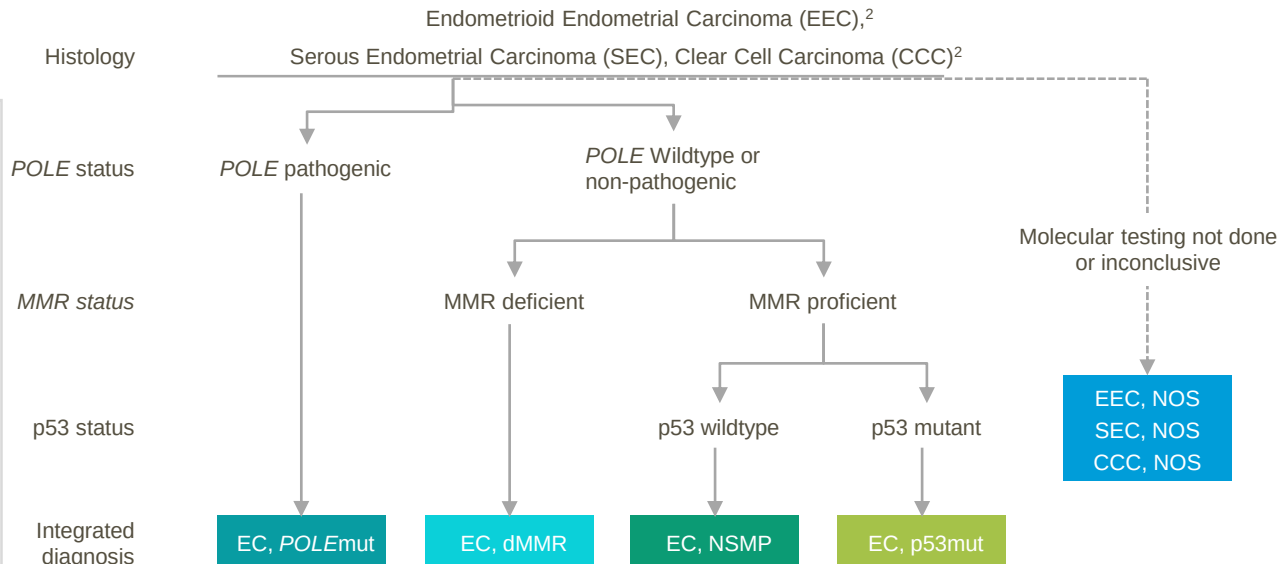
CDH1 (NM_004360.3)Exón 7 c.871G>A ; p.Asp291Asn VAF :5,51%

ATRX (NM_000489.3)Exón 30 c.6617A>G ; p.Glu2206Gly VAF :5,07%

Inestabilidad de microsatélites:

No se identifica inestabilidad de microsatélites, fracción de inestabilidad 0,28 (marcadores inestables 100 de 110 analizados) (MSS 0-0.17)

Estratificación del riesgo en cáncer de endometrio



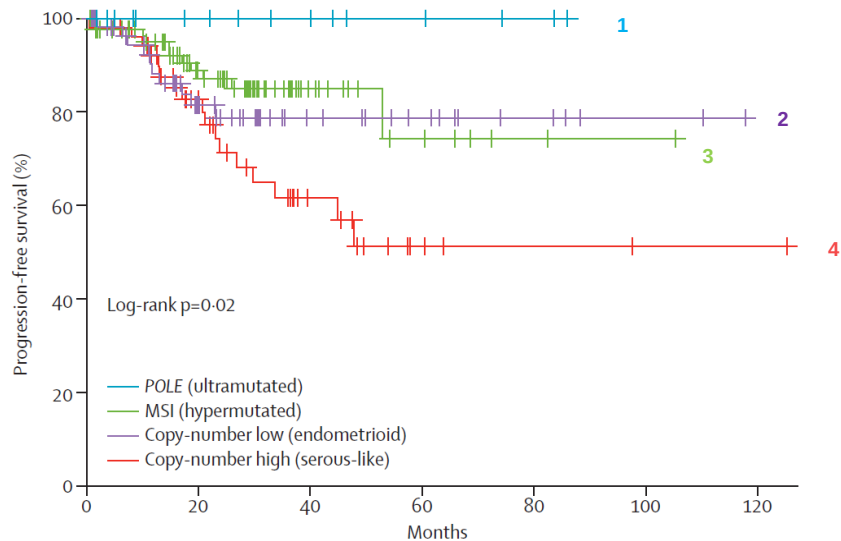
Los tumores de endometrio pueden clasificarse en 4 subgrupos moleculares

Subgrupos moleculares TCGA ²

	1	2	3	4
	POLE 5-10%	MSI-high 25-30%	Copy number low 45%	Copy number high 25%
Mutation load				
Somatic copy number alterations load				
Histology	Endometrioid	Endometrioid	Endometrioid	Serous and endometrioid
Grade				
PI3K alterations				
KRAS mutation				
TP53 mutation	35%	5%	1%	>90%
Prognosis	Excellent	Intermediate	Intermediate	Poor

POLE y MSI-H tienen una alta carga mutacional tumoral: suelen caracterizarse por un alto número de TILs y una alta expresión de puntos de control inmunitarios ³

PFS según subgrupo molecular ²

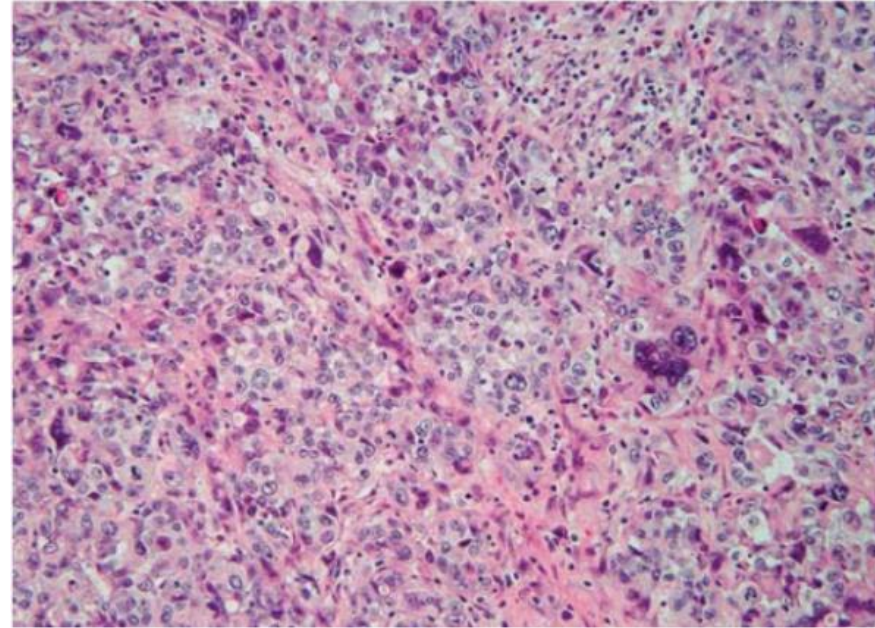


Estos subgrupos moleculares se correlacionan con el pronóstico de la enfermedad ^{1,2}

Subtipos moleculares en cáncer de endometrio

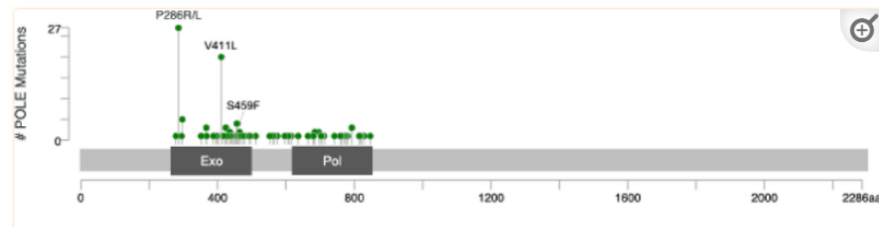
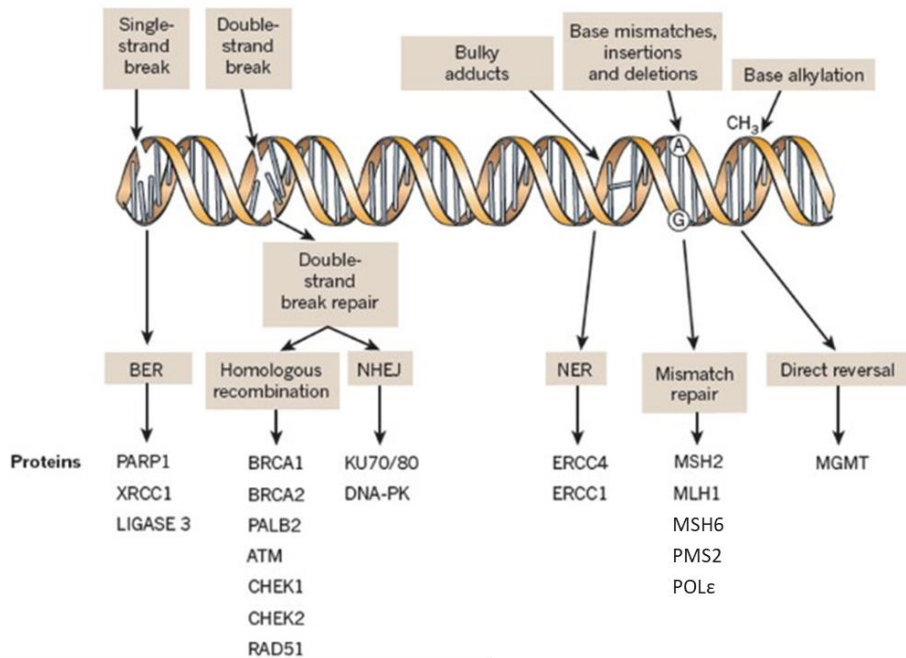
POLE

- 5 -10%
- Carcinomas ultramutados ($100-230 \times 10^{-6}/\text{Mb}$)
- Endometrioides casi siempre
- Heterogeneidad morfológica intratumoral-
morfológica ambigua (seroso-endometrioides).
- Alto grado: atipia de alto grado parcheada (bizarra)
- TILs
- Mujeres más jóvenes.
- No relacionados con Índice de masa corporal.
- Excelente pronóstico.
- Potencial beneficio a la inmunoterapia



Subtipos moleculares en cáncer de endometrio

POLE

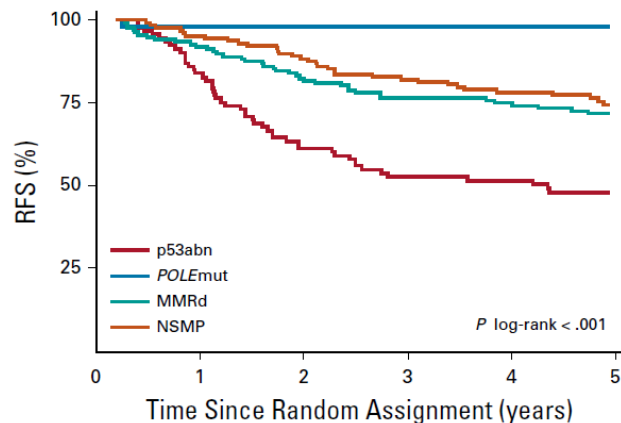


Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit From Adjuvant Therapy

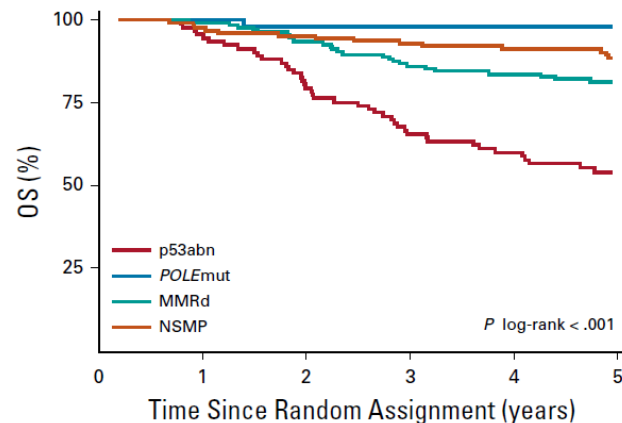
Alicia León-Castillo, MD¹; Stephanie M. de Boer, MD²; Melanie E. Powell, MD³; Linda R. Mileskin, MBBS⁴; Helen J. Mackay, MD⁵; Alexandra Leary, MD, PhD⁶; Hans W. Nijman, MD, PhD^{6,7}; Naveena Singh, MD, MBBS⁸; Pamela M. Pollock, PhD⁹; Paul Bessette, MD¹⁰; Anthony Fyles, MD¹¹; Christine Haie-Meder, MD¹²; Vincent T. H. B. M. Smit, MD, PhD¹; Richard J. Edmondson, MD¹³; Hein Putter, MD¹⁴; Henry C. Kitchener, MD¹³; Emma J. Crosbie, MD, PhD¹³; Marco de Bruyn, PhD⁷; Remi A. Nout, MD²; Nanda Horeweg, MD, PhD²; Carien L. Creutzberg, MD, PhD²; and Tjalling Bosse, MD, PhD¹ on behalf of the TransPORTEC consortium

This analysis confirms the excellent survival of patients with *POLE*mut EC even in those with advanced-stage and nonendometrioid histologies, with no differences between adjuvant treatment received. This favorable clinical outcome is thought to be the result of the patients' enhanced T-cell response due to their high mutational burden.²⁴

A



B



Caso 5.

Clasificación molecular en cáncer de endometrio

Decisión CM: No tratamiento adyuvante (EBRT $\pm$ brachytherapy $\pm$ systemic therapy), seguimiento.

12/22: Libre de enfermedad

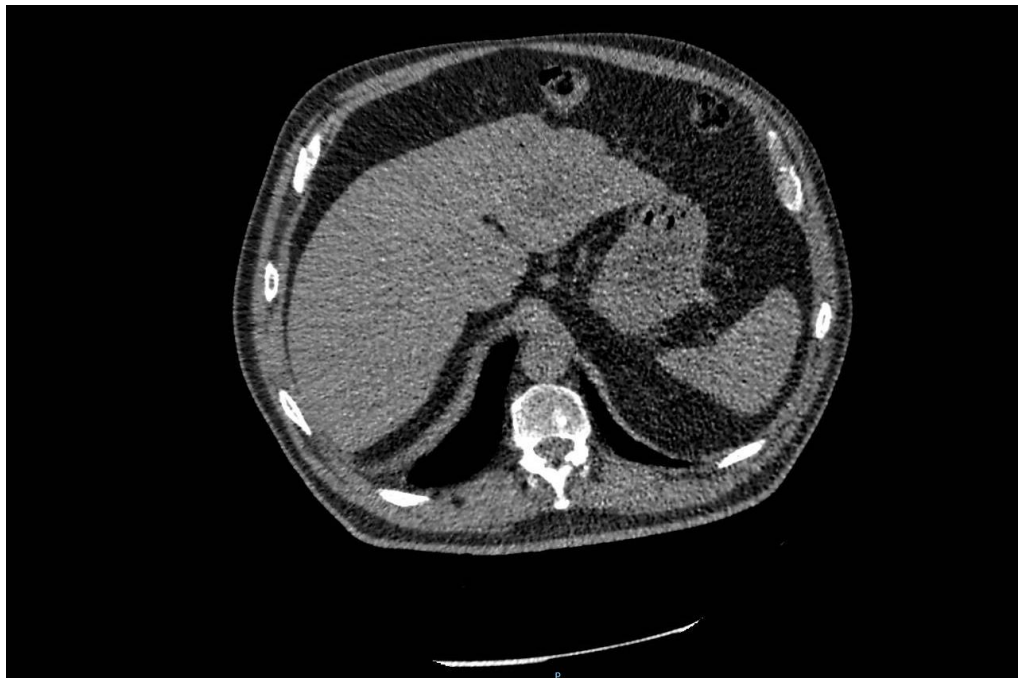
Caso 6.

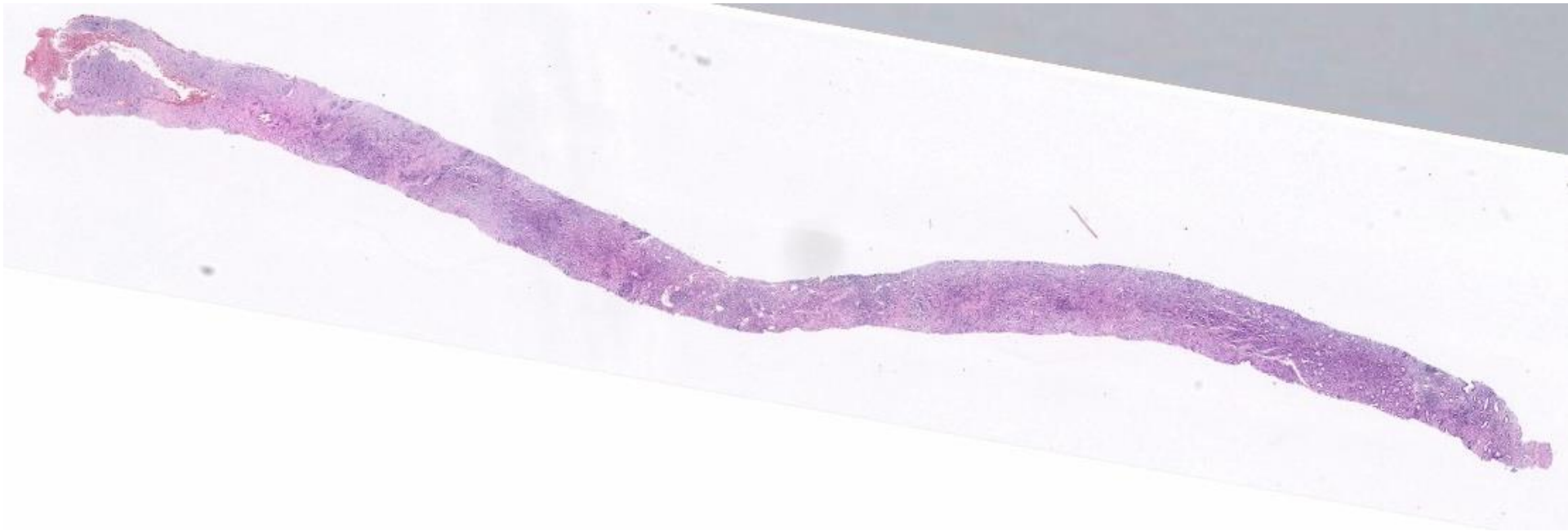
Dianas terapéuticas en colangiocarcinoma

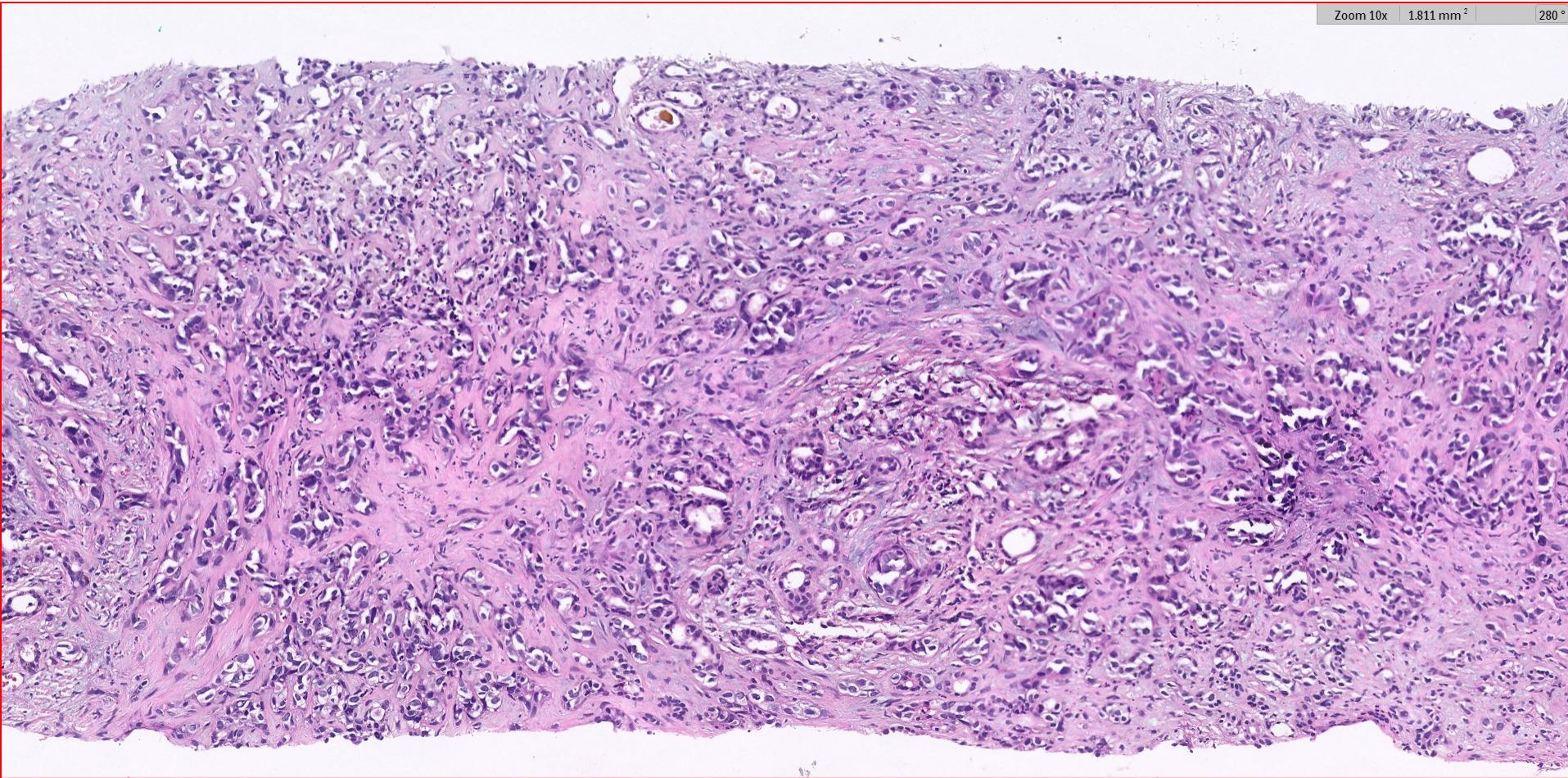
Caso 6.

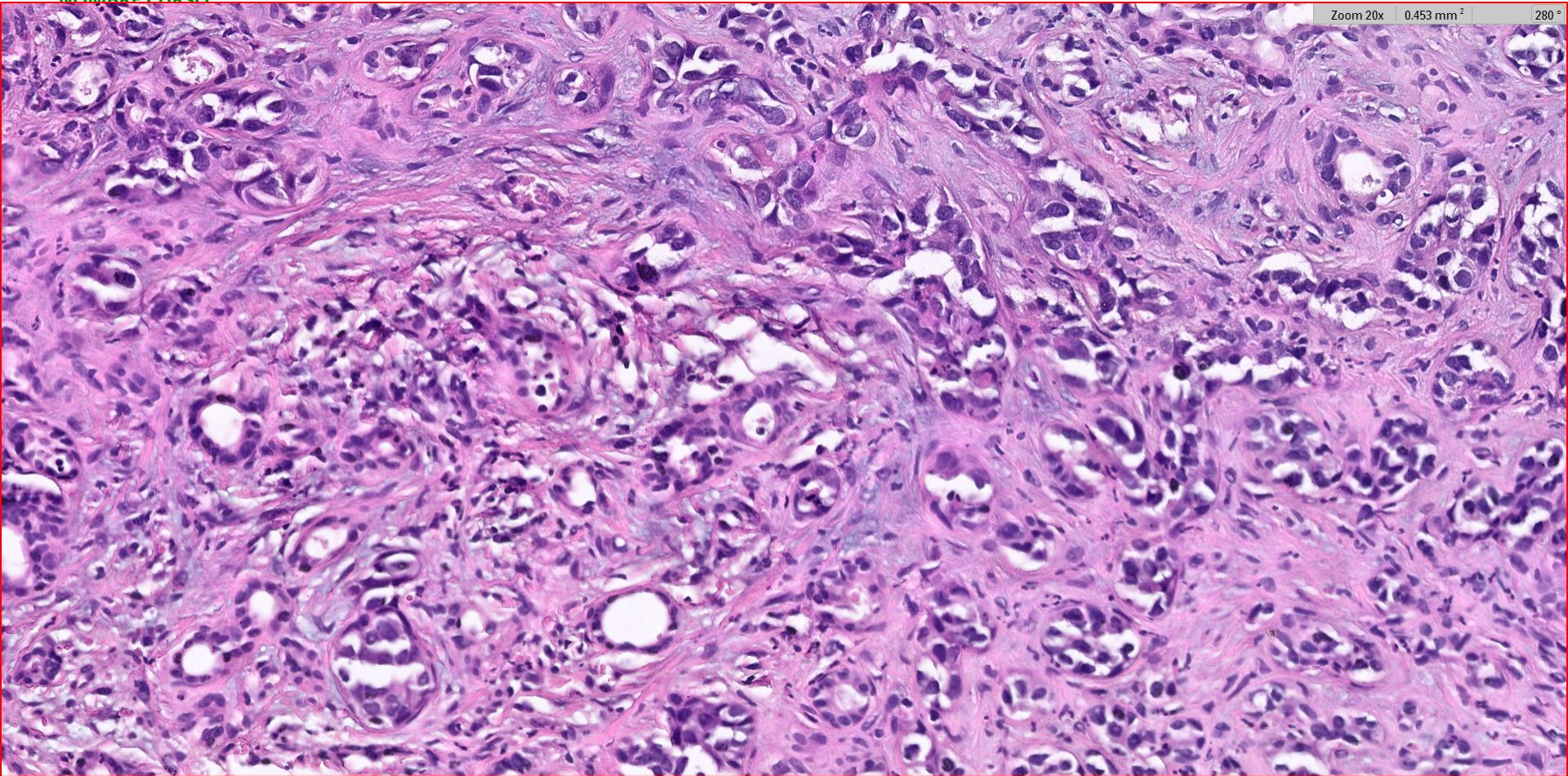
Dianas terapéuticas en colangiocarcinoma

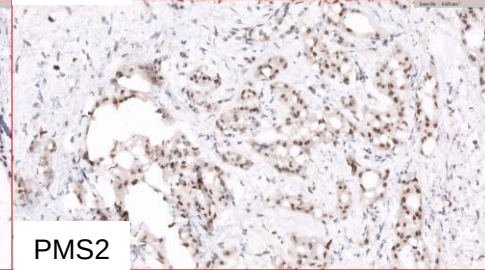
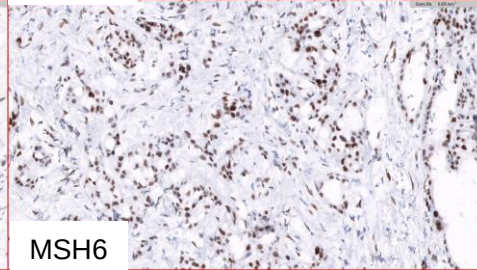
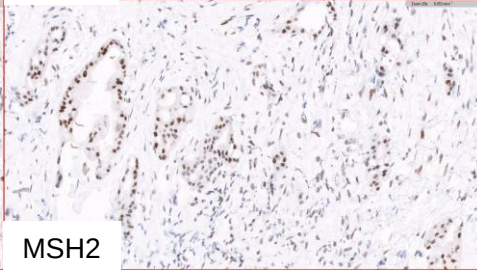
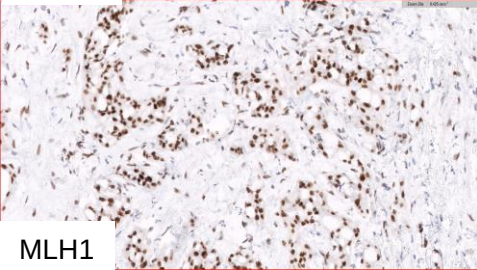
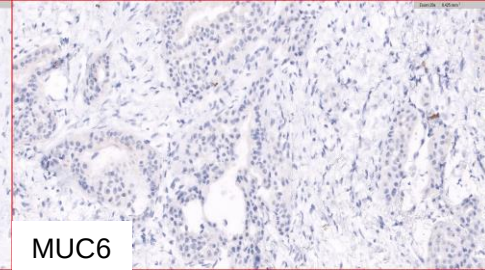
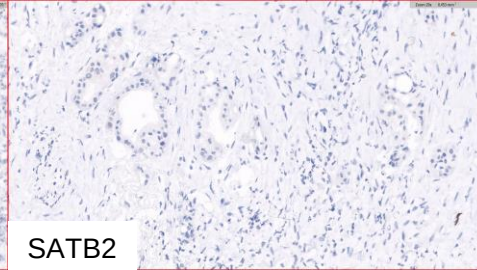
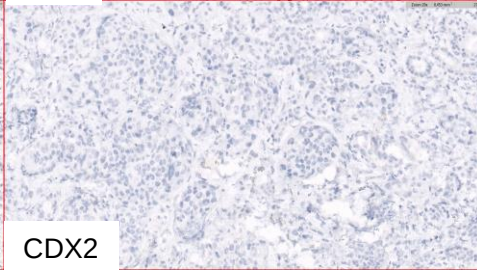
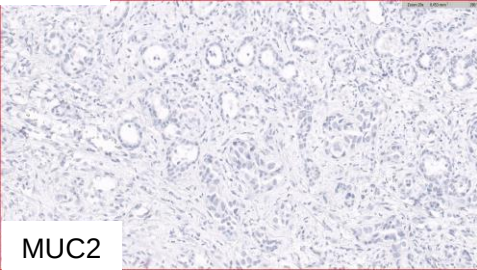
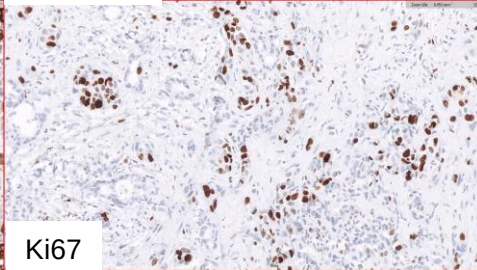
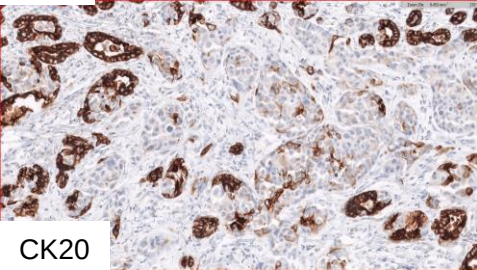
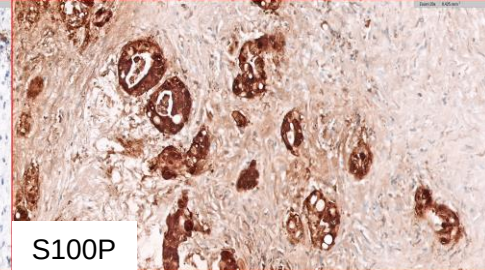
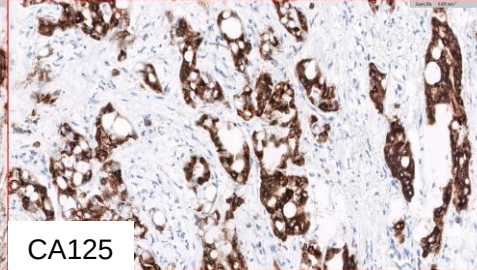
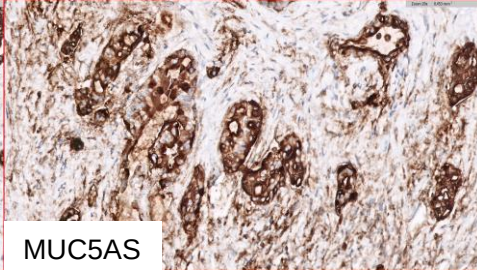
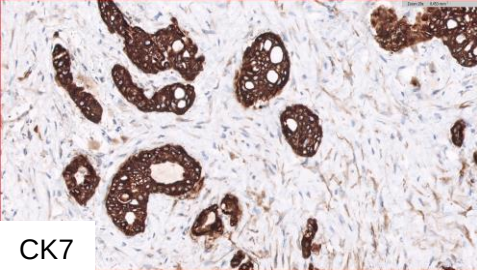
- Varón de 65 años, con antecedentes de consumo alcohólico y exfumador (IPA 75), diabetes y dislipemia. En tratamiento por su patología descrita.
- Enfermedad pulmonar obstructiva crónica con obstrucción leve.
- Adenomas de colon con displasia leve en 2016.
- Paciente incluido en programa de cribado de cáncer de pulmón en el centro, desde Dic/2019, donde se realiza TC screening, detectándose LOEs hepáticas en Marzo/2020 en el segmento II y III de 6 cm y en el segmento IVA de 1.5 cm.
- BAG hepática.











Caso 6.

Dianas terapéuticas en colangiocarcinoma

BAG hepática:

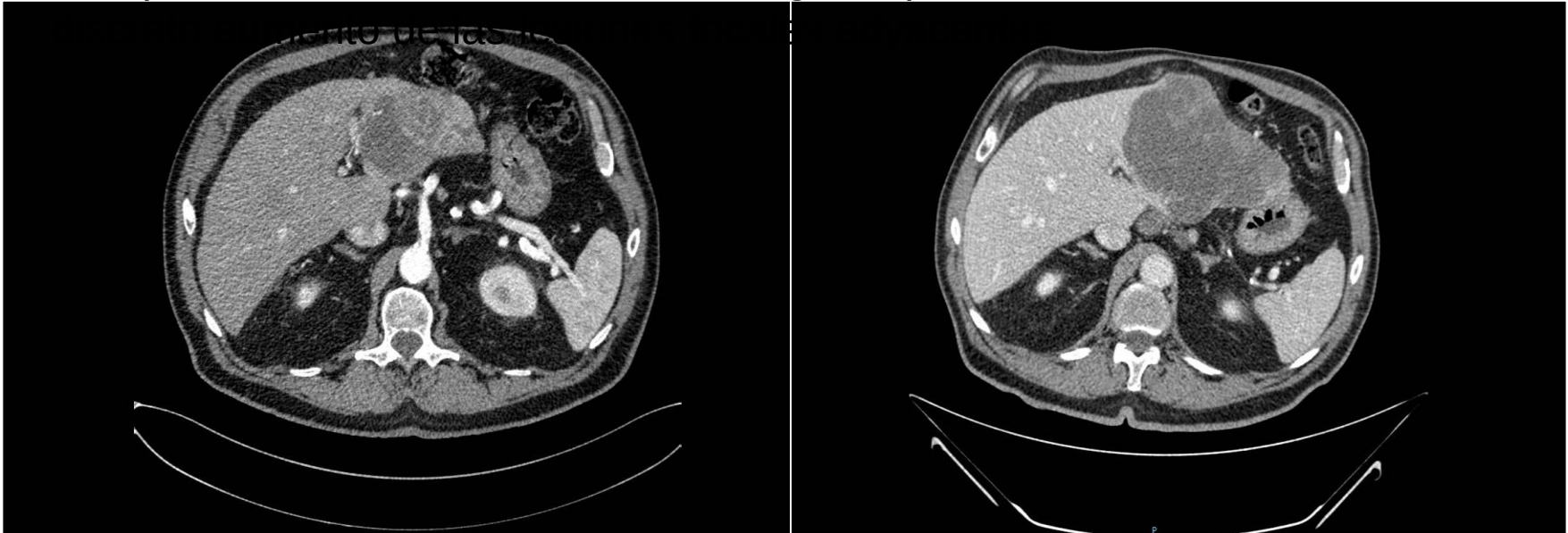
Tejido hepático con infiltración por Adenocarcinoma de patrón pancreatobiliar moderadamente diferenciado.

En caso de corresponder clínicamente a una lesión primaria hepática, el tumor es compatible con colangiocarcinoma.

Caso 6.

Dianas terapéuticas en colangiocarcinoma

- Inicia tratamiento con capecitabina, con progresión a los 6 meses (Nov/2020).
- Se propone segunda línea con FOLFOX. Tras 4 ciclos, progresión (sin respuesta a 2º línea FOLFOX, Ene/2021): masa en lóbulo hepático izquierdo, de unos 13 cm, que impronta la cápsula anterior extendiéndose a la grasa peritoneal. se observa también



Action OncoKitDx

Secuenciadores compatibles	Illumina NextSeq500, Illumina NextSeq2000, Illumina HiSeq, Illumina NovaSeq
Número de reacciones	20
Número de muestras por run	Mid Output v2.5 kit (150 cycles): 12 muestras High Output v2.5 kit (150 cycles): 32 muestras
Secuenciación	Paired-end (2 x 75 ciclos)
Cantidad de ADN por muestra	50-200 ng
Calidad de ADN recomendada	DIN >3
Región genómica analizada	500 Kb
Genes diana	SNVs e INDELS: AKT1*, ALK, ARID1A, ATM, ATRX, BAP1, BRAF, BRCA1, BRCA2, CDH1, CHEK2, CTNNB1, EGFR, ERBB2, ESR1, FGFR1, FGFR4, GNA11, GNAQ, H3F3A, HIST1H3B, HIST1H3H, HRAS, IDH1, IDH2, KIT, KRAS, MAP2K1, MET, MLH1, MSH2, MSH6, MTOR, MYC, NRAS, NTRK1, NTRK2, NTRK3, PALB2, PBRM1, PDGFRA, PIK3CA, PMS2 + 5'UTR, PTEN, POLD1, POLE, RET, ROS1, SDHA, SDHB, SDHD, TERT + 5'UTR, TSC1*, TSC2*, TP53 y VHL. * Secuenciación de <i>hotspot</i> SVs: ALK (intrón 19), ATP1B1 (intrones 3 y 4), BRAF (intrones 7, 8, 9 y 10), EGFR (intrones 7, 23, 24 y 25), ETV6 (intrones 4 y 5), FGFR2 (intrón 17 y región 3'UTR), FGFR3 (intrón 17 y región 3'UTR), NTRK1 (intrones 8, 9, 10, 11 y 12), NTRK2 (intrones 12 y 15), RET (intrones 9, 10 y 11) y ROS1 (intrones 31, 32, 33, 34 y 35).
	ADN procedente de sangre periférica, tejido fresco, congelado y parafinado

Variantes patogénicas:

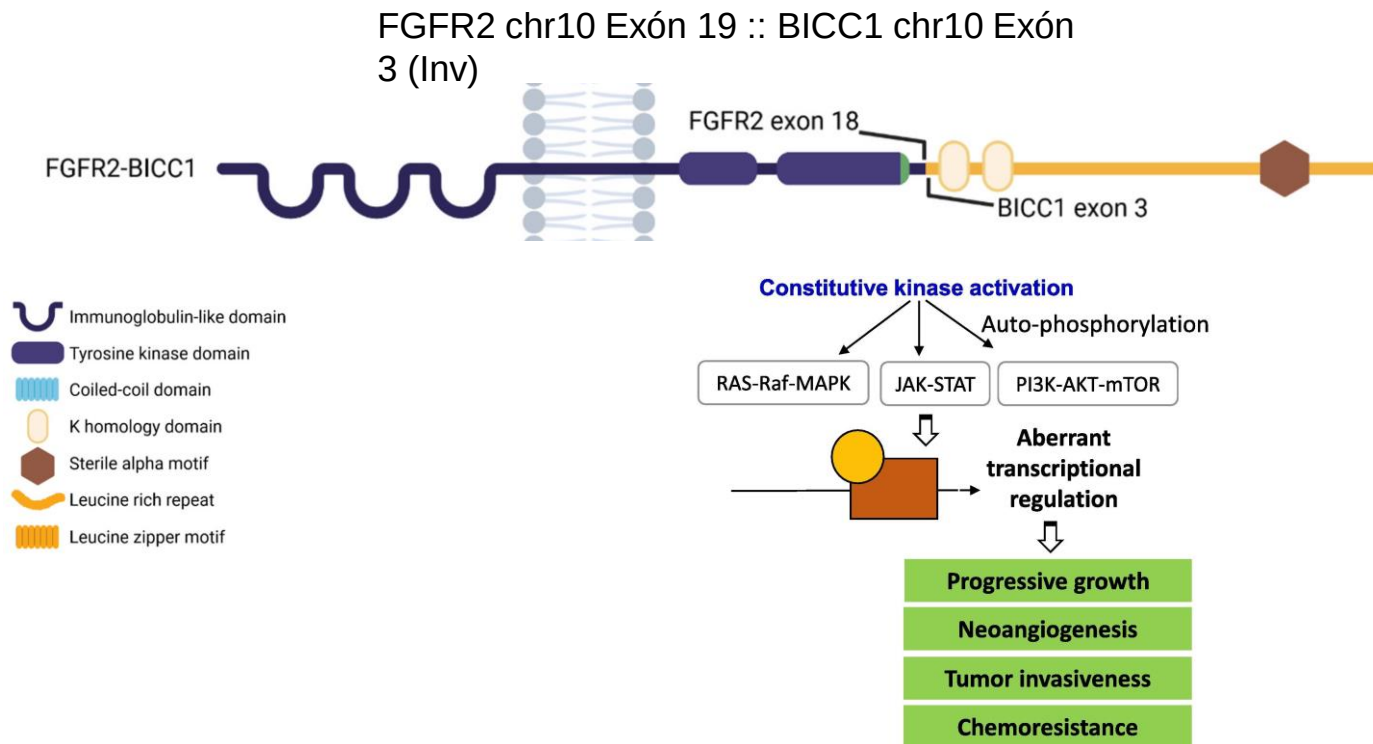
- FGFR2 chr10 Exón 19:29448317 :: BICC1 chr10 Exón 3 (Inv):42253550 (124 lecturas)

Variantes de significado incierto:

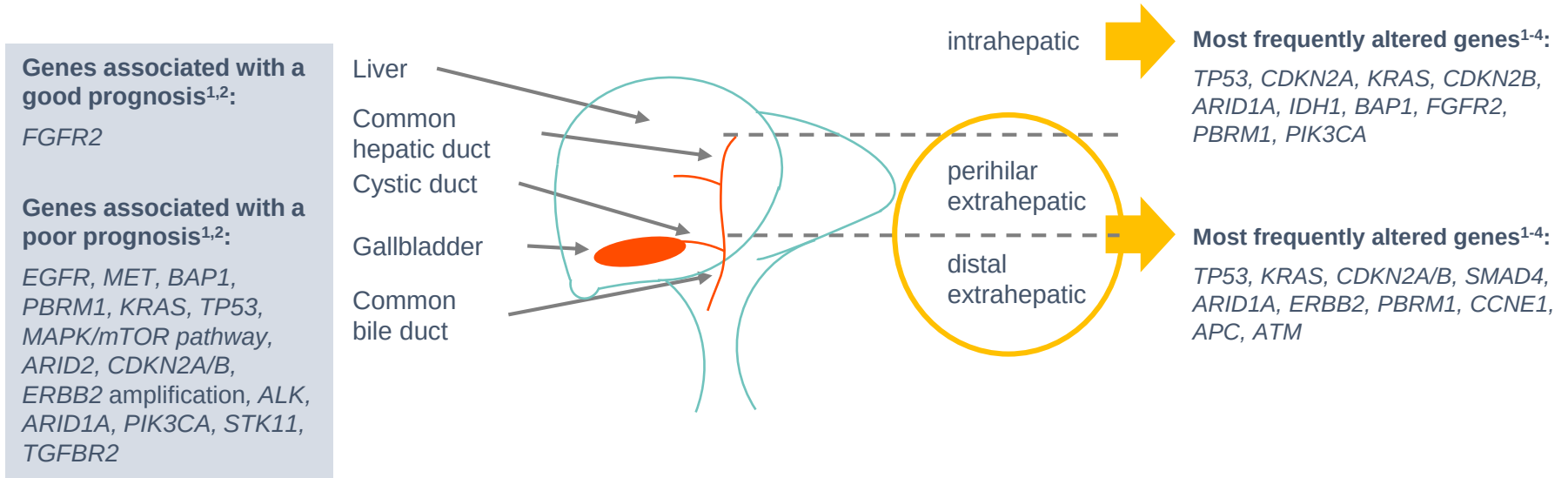
- GNAQ: NM_002072.3. Exón2 c.286A>T; p.Thr96Ser (VAF 7%)
- BAP1: NM_004656.3. Exón 15; c.1946G>A;

Caso 6.

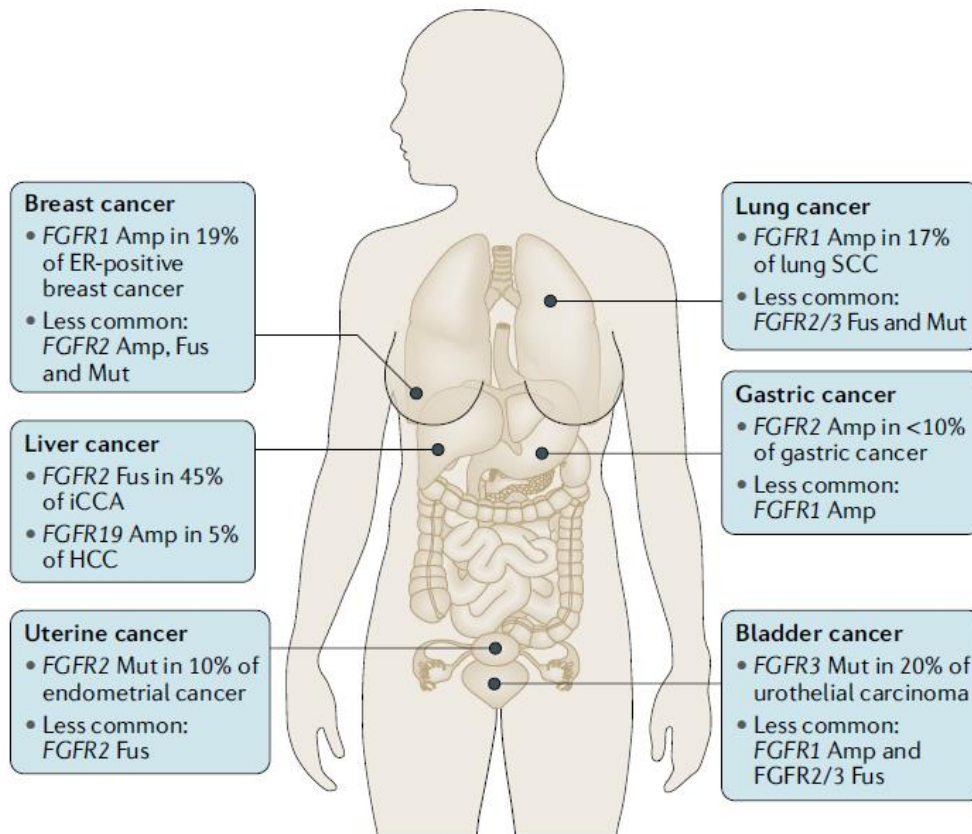
Dianas terapéuticas en colangiocarcinoma



Each location has a different genomic profile and signature alterations



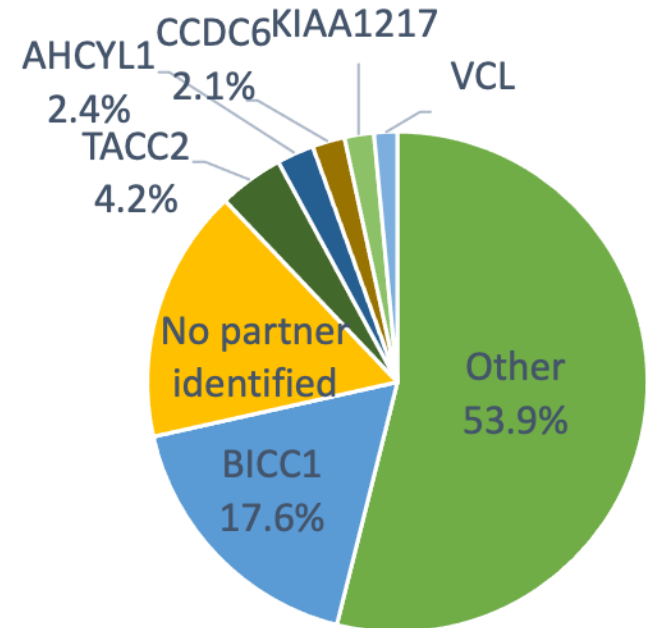
Mechanisms of oncogenic FGFR signaling



FGFR2 rearrangement partners are diverse in intrahepatic CCA

- **FGFR2 rearrangements** occur with a **variety** of **distinct partners**
- **Recurrent partners account for > 33%** of all rearrangements
- **FGFR2 GA** are typically mutually exclusive with other kinase drivers but **co-occur** with **mutations** in the **mTOR / PIK3CA / AKT pathways**, highlighting the need for **further clinical trials** of **FGFR inhibitors**
- **FGFR2 fusions frequently co-occurred in intrahepatic cholangiocarcinoma** with **BAP1 GAs** and were **mutually exclusive** from other targetable kinases, high gLOH, IDH1/2 SVs, KRAS GAs

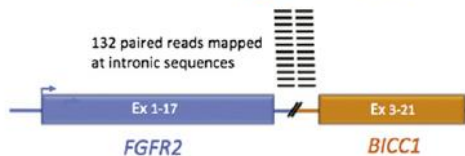
Distribution of FGFR2 fusion partners



Chromosome 10

BICC1 *FGFR2*

132 paired reads mapped
at intronic sequences



FGFR2-BICC1 fusion gene*

Protein domains



**FGFR2-BICC1* known fusion based on chimeric read support for *BICC1-FGFR2* rearrangement with same breakpoint

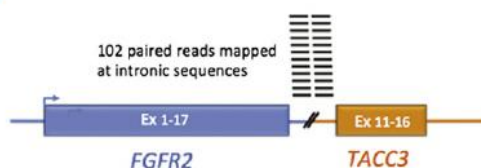
Chromosome 4

TACC3

Chromosome 10

FGFR2

102 paired reads mapped
at intronic sequences



FGFR2-TACC3 fusion gene

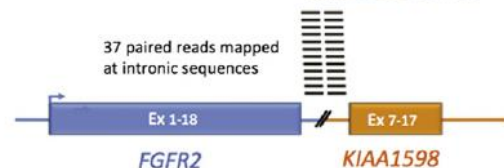
Protein domains



Chromosome 10

KIAA1598 *FGFR2*

37 paired reads mapped
at intronic sequences



FGFR2-KIAA1598 fusion gene

Protein domains



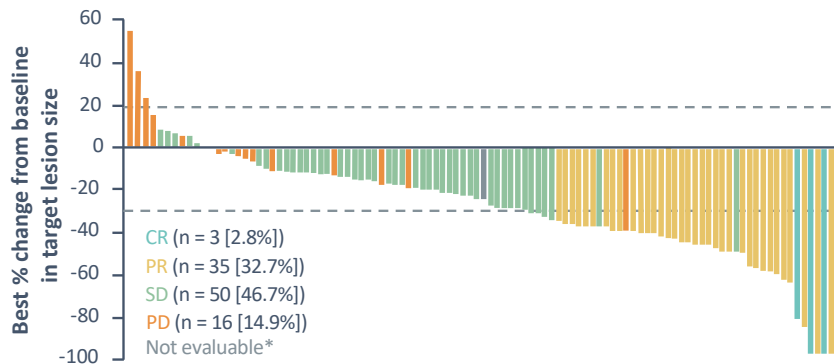
Inhibitor (manufacturer)	Target (IC ₅₀ *)	Clinical trial identifier	Cancer type
Non-selective inhibitors			
Dovitinib (Novartis)	FLT3 (1 nM), c-KIT (2 nM); FGFR1 (8 nM), VEGFR3 (also known as FLT4) (8 nM), FGFR3 (9 nM) and VEGFR1 (also known as FLT1) (10 nM)	NCT01719549	FGFR2-amplified gastric cancer
		NCT01732107	FGFR3-mutated or -overexpressed urothelial cancer
		NCT01223027	Metastatic renal cell cancer
Ponatinib (ARIAD Pharmaceuticals)	ABL (<1 nM), PDGFRα (1.1 nM), VEGFR2 (1.5 nM), FGFR1 (2.2 nM) and c-SRC (5.4 nM)	NCT02265341	FGFR2 fusions in biliary cancer
		NCT02272998	FGFR genetically aberrant advanced-stage cancers
Lucitanib (Clovis Oncology)	VEGFR1 (7 nM), VEGFR3 (10 nM), FGFR1 (18 nM), VEGFR2 (25 nM) and FGFR2 (83 nM)	NCT01283945	FGFR1-amplified advanced solid tumours
		NCT02202746	FGFR genetically aberrant metastatic breast cancer
		NCT02053636	FGFR1/11q-amplified ER+ metastatic breast cancer
		NCT02109016	Any FGF-related aberration in advanced or metastatic lung cancer

Selective inhibitors				
AZD4547 (AstraZeneca)	FGFR1 (<1 nM), FGFR3 (1.8 nM), FGFR2 (2.5 nM) and VEGFR2 (24 nM)	NCT02664935	FGFR genetically aberrant NSCLC	
		NCT02117167	FGFR genetically aberrant metastatic NSCLC	
		NCT02154490	FGFR genetically aberrant SCLC	
NVP-BGJ398 (Novartis)	FGFR1 (<1 nM), FGFR3 (1 nM), FGFR2 (1.4 nM), FGFR3 (K650E) (4.9 nM) and FGFR4 (60 nM)	NCT01004224	FGFR1–3 genetically aberrant solid tumours, FGFR1-amplified squamous cell lung cancer and FGFR3-mutated or fused bladder cancer	
		NCT01697605	FGFR genetically aberrant advanced solid tumours in an Asian population	
		NCT01928459	FGFR genetically aberrant advanced solid tumours with PIK3CA mutations	
		NCT01975701	Glioma subtypes with FGFR1–TACC1 fusion, FGFR3–TACC3 fusion and/or activating mutation in FGFR1–3	
		NCT02160041	FGFR genetically aberrant solid and/or haematological cancers	
		NCT02150967	FGFR genetically aberrant advanced or metastatic cholangiocarcinoma	
JNJ-42756493 (Janssen)	FGFR1 (<1 nM), FGFR2 (<1 nM), FGFR4 (<1 nM), FGFR3 (1.05 nM) and FGFR3 (G697C) (1.9 nM)	NCT02421185	FGFR19-amplified advanced hepatocellular carcinoma	
		NCT02365597	FGFR genetically aberrant advanced or metastatic urothelial cancer	
		NCT02699606	Asian participants with NSCLC, gastric cancer, urothelial cancer, oesophageal cancer and cholangiocarcinoma	
LY2874455 (Lilly)	FGFR1 (2.8 nM), FGFR2 (2.6 nM), FGFR3 (6.4 nM), FGFR4 (6 nM) and VEGFR2 (7 nM)	NCT01212107	Advanced-stage cancer	

Inhibitor (manufacturer)	Target (IC ₅₀ *)	Clinical trial identifier	Cancer type
Selective inhibitors (cont.)			
TAS120 (Taiho Oncology)	FGFR1 (3.9 nM), FGFR2 (1.3 nM), FGFR3 (1.6 nM) and FGFR4 (8.3 nM)	NCT02052778	FGFR genetically aberrant advanced solid tumours or multiple myeloma
Debio-1347 (Debiopharm International)	FGFR2 (7.6 nM), FGFR1 (9.3 nM) and FGFR3 (22 nM)	NCT01948297	FGFR1–3 genetically aberrant solid tumours
Ligand trap and antibodies			
FP-1039 (GlaxoSmithKline)	FGF2 (0.023 µg ml ⁻¹)	NCT01868022	FGFR genetically aberrant solid malignancies in combination with paclitaxel and carboplatin or docetaxel
FPA114 (Five Prime Therapeutics)	FGFR2-IIb	NCT02318329	Advanced solid tumours
MFGR18775 (Genentech)	FGFR3	NCT01363024	Advanced solid tumours

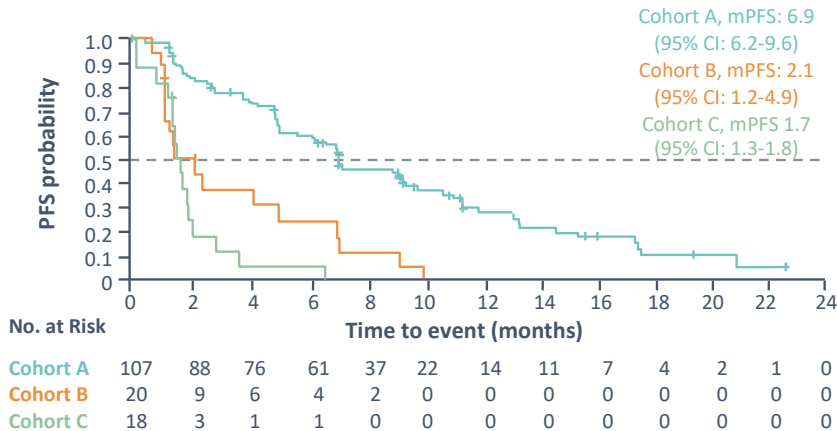
FIGHT-202: Pemigatinib has potential therapeutic benefit in *FGFR2* rearranged / fusion advanced CCA patients

Change from baseline in target lesion size (cohort A)



- ORR in cohort A: 35.5% (95% CI, 26.5% – 45.4%), with 3 complete responses¹
- ORR in cohorts B and C was zero¹
- DOR in cohort A: 9.1 months²

Median progression-free survival



- OS[†] in cohort A: 21.1 months (95% CI: 14.8 - NE)¹
- OS in cohorts B and C was 6.7 (95% CI: 2.1 - 10.6) and 4.0 (95% CI: 2.3 - 6.5) respectively¹

Pemigatinib has been approved as the first treatment for adults with previously treated advanced CCA harbouring *FGFR2* gene fusions²

Coloured bars: confirmed responses per RECIST. *Patient had decrease in target lesion size but was not evaluable for response per RECIST;

[†] OS data were not mature at cut-off.

CGP: comprehensive genomic profiling; CI: confidence interval; CR: complete response; DOR: duration of response; NE: not estimable; OR: overall response rate;

OS: overall survival; PD: progressive disease; PFS: progression-free survival; RECIST 1.1: response evaluation criteria in solid tumours v1.1; SD: stable disease.

1. Abou-alfa, G.K., et al. (2020) Lancet Oncol doi: 10.1016/S1470-2045(20)30109-1. [Epub ahead of print]; 2. FDA Press Release (2020) Available at: <https://www.fda.gov/news-events/press-announcements/fda-approves-first-targeted-treatment-patients-choleangiocarcinoma-cancer-bile-ducts>. (Accessed July 2020).

First-in-Human Study of Highly Selective FGFR2 Inhibitor, RLY-4008, in Patients With ICC and Other Advanced Solid Tumors



The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. [Know the risks and potential benefits](#) of clinical studies and talk to your health care provider before participating. Read our [disclaimer](#) for details.

ClinicalTrials.gov Identifier: NCT04526106

[Recruitment Status](#) : Recruiting

[First Posted](#) : August 25, 2020

[Last Update Posted](#) : May 5, 2022

See [Contacts and Locations](#)

Sponsor:

Relay Therapeutics, Inc.

Information provided by (Responsible Party):

Relay Therapeutics, Inc.

Criteria

Key Inclusion Criteria

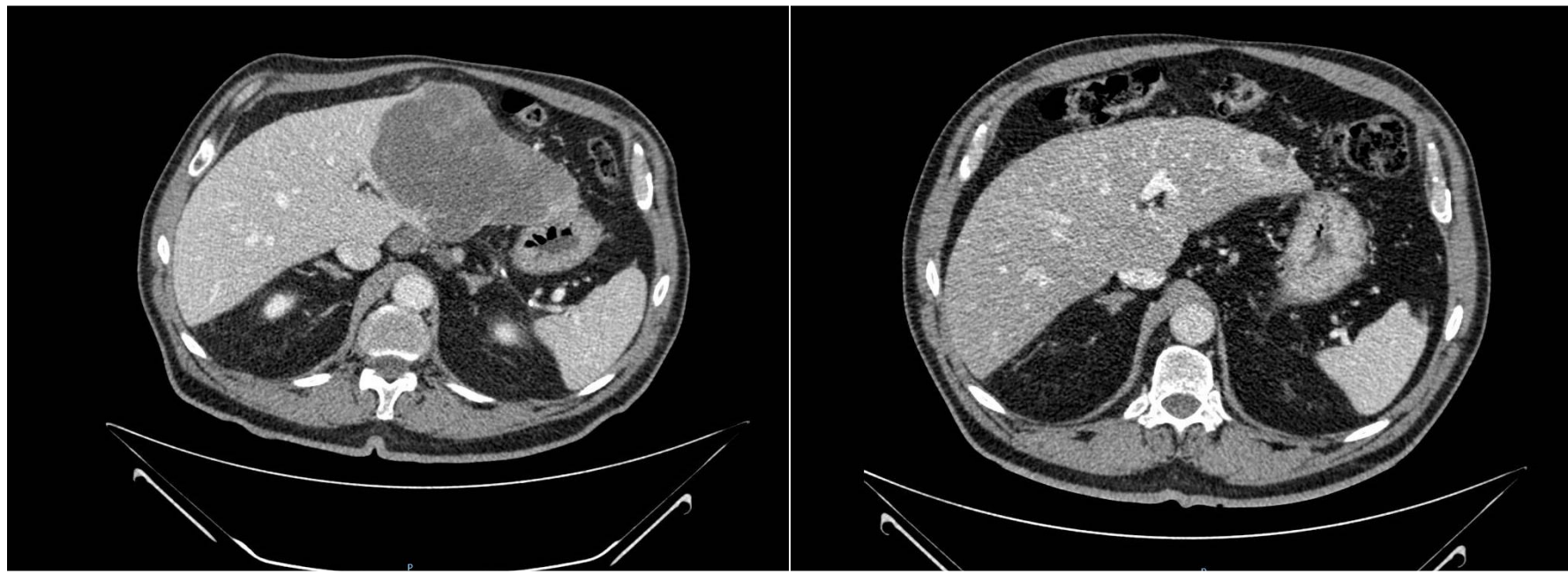
- Histologically or cytologically confirmed unresectable or metastatic solid tumor
- Documented FGFR2 gene fusion, mutation, or amplification per local testing of blood and/or tumor
- Additional FGFR2 alterations/tumor types may be considered for the Part 1 dose escalation
- Part 2 dose expansion patients must additionally meet the group requirements detailed below.
 - Group 1: patient must have a confirmed diagnosis of unresectable or metastatic ICC with FGFR2 fusion (per local assessment of blood and/or tumor) and has received prior treatment with a pan-FGFR inhibitor (eg, pemigatinib, erdafitinib, infigratinib, futibatinib).
 - Group 2: patient must have a confirmed diagnosis of unresectable or metastatic ICC with FGFR2 fusion (per local assessment of blood and/or tumor) and has NOT received prior treatment with a pan-FGFR inhibitor (eg, pemigatinib, erdafitinib, infigratinib, futibatinib).
 - Group 3: patient has an unresectable or metastatic solid tumor with FGFR2 fusion (per local assessment of blood and/or tumor) other than ICC.
 - Group 4: patient has an unresectable or metastatic solid tumor with FGFR2 amplification (per local assessment of blood and/or tumor).
 - Group 5: patient has an unresectable or metastatic solid tumor with an oncogenic FGFR2 mutation (per local assessment of blood and/or tumor).

Spain

Hospital Universitari Vall d'Hebron Barcelona, Spain, 08035	Recruiting
Hospital Universitario Fundación Jiménez Díaz- START MADRID Madrid, Spain, 28040	Recruiting
Hospital Universitario HM Sanchinarro-START MADRID-CIOCC Madrid, Spain, 28050	Recruiting
Clinica de Universidad de Navarra Pamplona, Spain, 31008	Recruiting
Hospital Clínico Universitario de Valencia Valencia, Spain, 46010	Recruiting

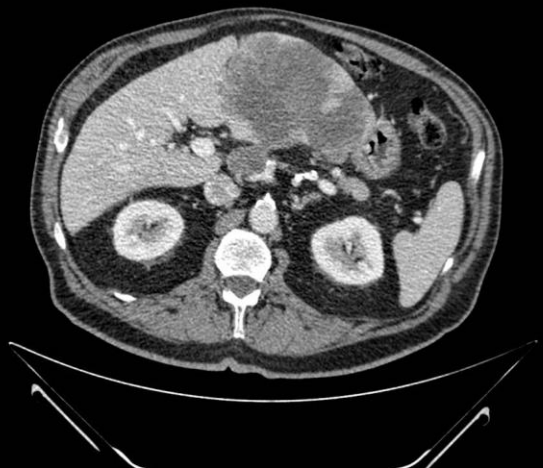
Dianas terapéuticas en colangiocarcinoma

- Inicia tratamiento con RLY4008 (A First-in-Human Study of Highly Selective FGFR2 Inhibitor, RLY-4008, in Patients With Intrahepatic Cholangiocarcinoma (ICC) and Other Advanced Solid Tumors, Cohorte 2) (Mar/2021).
- Evaluación Jul/2021: Respuesta parcial, con reducción de masa en lóbulo hepático izquierdo (1.8cm), de aspecto regresivo y sin evidencia de lesiones adyacentes.



Dianas terapéuticas en colangiocarcinoma

- Evaluación Mar/2022: Progresión de la enfermedad, con hígado con aumento de tamaño de la masa en lóbulo hepático izquierdo, de unos 14 cm, adenopatías en hilio hepático, de hasta 22 mm, y retroperitoneales, la más grande de unos 18 mm de eje corto. Nódulos de nueva aparición, los más evidentes de aproximadamente 6 mm en segmento anterior del lóbulo superior derecho, 8 mm y 9 mm en segmento apical del lóbulo inferior derecho y 7 mm en lingula.



Caso 7.

Tumor glial del adulto

Caso 7.

Tumor glial del adulto

Mujer de 67 años que acude a urgencias por cuadro subagudo de varios días de evolución de debilidad en extremidades izquierdas, alteración en el habla, decaimiento general y dificultades cognitivas con somnolencia. Ingresa en urgencias el 13/1/22 por presentar caída en el domicilio, sin pérdida de conciencia ni TCE. Ha conseguido subir a la cama para coger el móvil y llamar a su hijo.

La paciente pasó el covid recientemente (19/12-29/12), a raíz de lo cual percibe empeoramiento de los síntomas antes referidos. No comenta otra sintomatología acompañante, no fiebre, no cefalea, no nauseas, no disnea, no dolor torácico, no sintomatología digestiva.

E.N.: Consciente y orientada en las tres esferas. Algo inatenta, con cierta lentitud en las respuestas y tendencia al sueño. Reacciona a la llamada y abre ojos, siendo capaz de comprender y obedecer ordenes verbales, con cierta lentitud en las respuestas motoras. Lenguaje coherente sin claros elementos difásicos. Habla levemente disártrica pero totalmente inteligible.

PP.CC: perimétrica por confrontación sin claro déficit campimétrico. V normal. VII: leve asimetría en musculatura hemifacial izquierda. Pares bajos: conservados. Motor: claudicación en maniobras antigravitatorias con extremidades izquierdas. Balance motor compatible con hemiparesia B-C izquierda 4/5. RCP indiferente bilateral. Sensitivo: normal. Cerebelo: dismetría d-n y t-r acorde al grado de paresia. Marcha: sin alteraciones.

Caso 7.

Tumor glial del adulto

TC craneal sin contraste: Se observa lesión / masa infiltrativa aparentemente intraaxial, levemente más hiperdensa que el parénquima cerebral adyacente, centrado en porción medial del lóbulo temporal derecho que se extiende hacia hemimesencéfalo y hemiprotuberancia ipsilateral, y rodea prácticamente todo el ventrículo lateral derecho. Debido a estas características infiltrativas, la lesión resulta difícil de medir. Asocia edema vasogénico en el parénquima cerebral circundante a nivel del lóbulo temporal derecho y condiciona efecto de masa sobre los surcos de la convexidad con colapso parcial del sistema ventricular y desplazamiento de la línea media hacia la izquierda de aproximadamente 5 mm. Hallazgos que sugieren tumor primario de SNC vs metástasis como primera posibilidad.



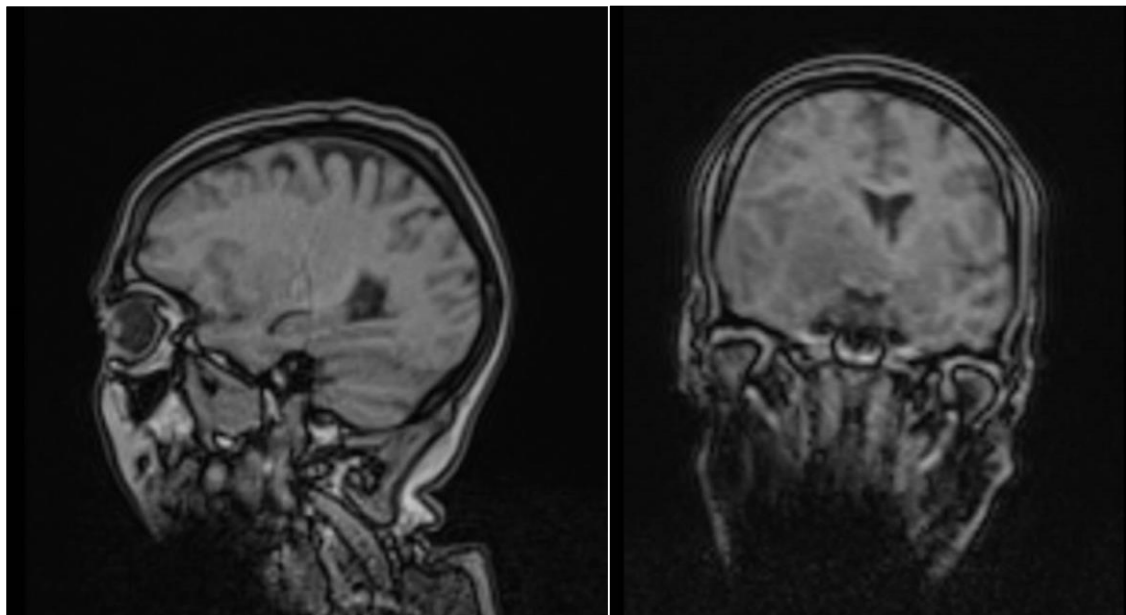
Caso 7.

Tumor glial del adulto

RM CRANEAL: Lesión parenquimatosa en caudado, periatral, ínsula, ganglios basales, hipotálamo, amígdala, hipocampo, giro parahipocampal, polo temporal anterior, hemimesencéfalo y hemiprotuberancia derechas, cintillas ópticas y cuerpos mamilares, con hiperseñal en TR largo, sin clara restricción en difusión ni captación postcontraste.

Ejerce efecto de masa con impronta sobre el ventrículo lateral derecho y III ventrículo y desviación de línea media hacia la izquierda de 7 mm e incipiente herniación uncal y trastentorial descendente.

OD: Tumor glial difuso

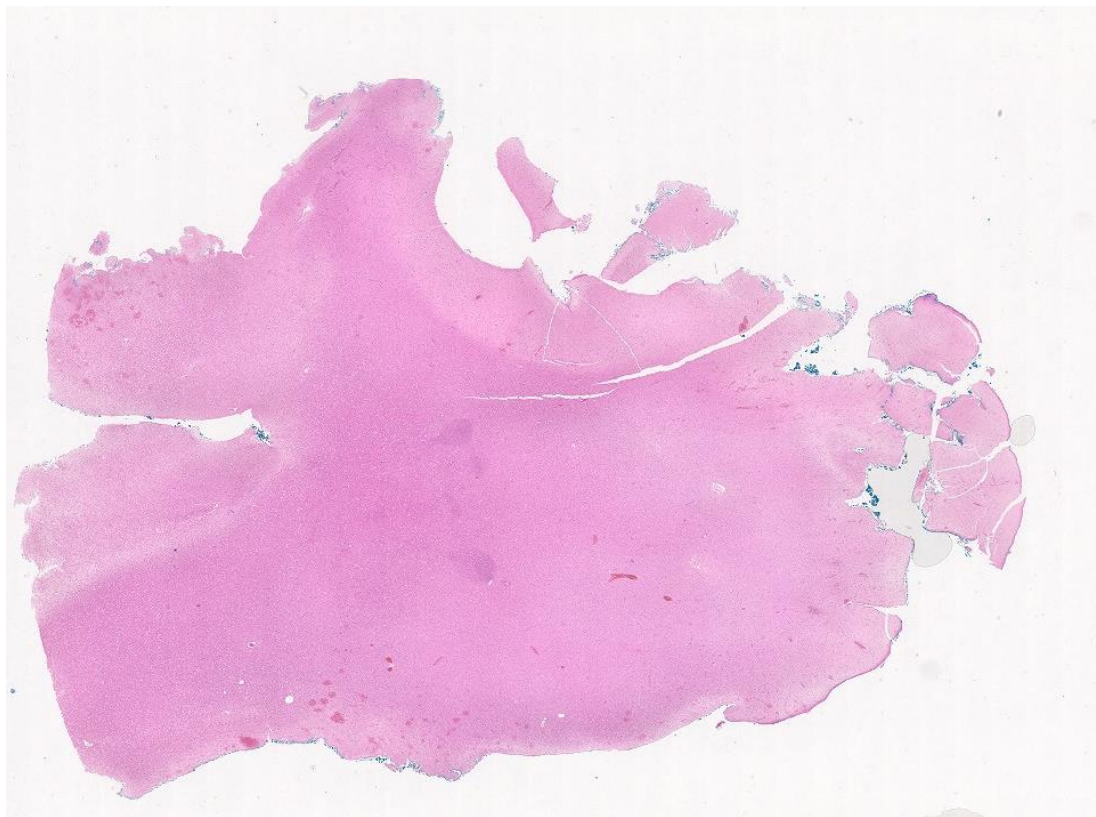


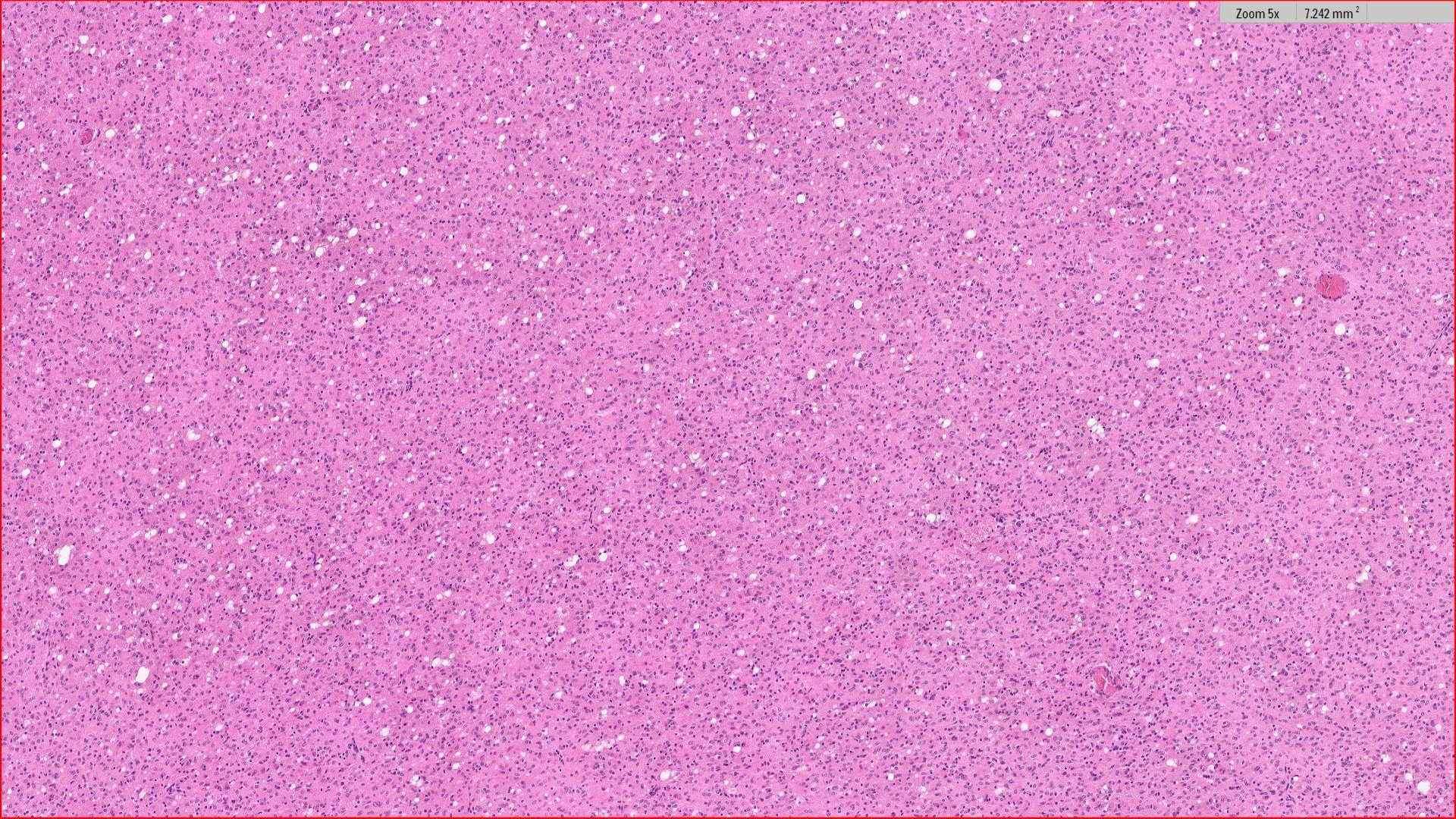
Caso 7.

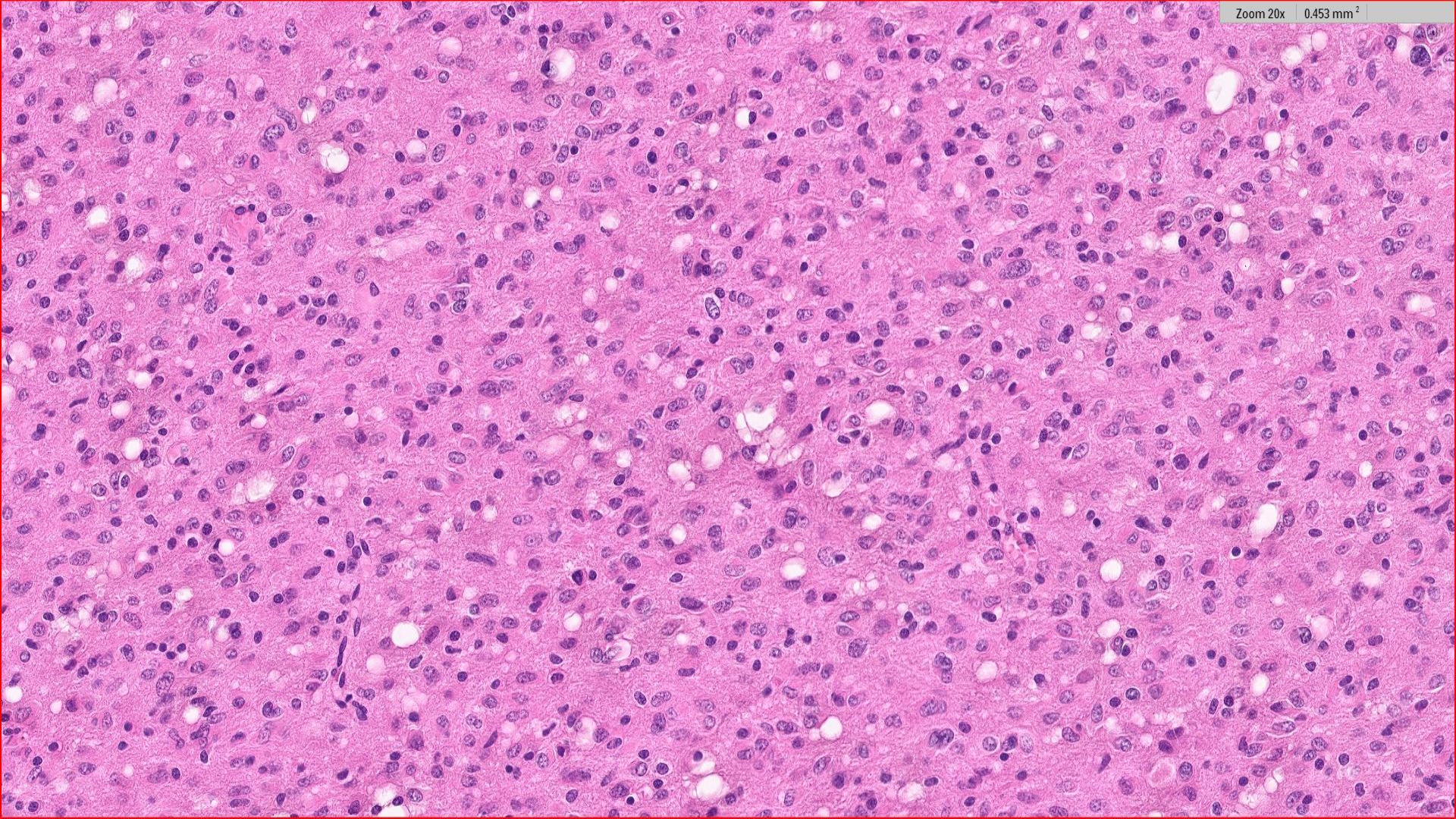
Tumor glial del adulto

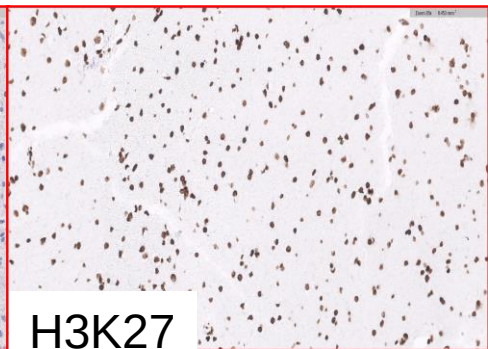
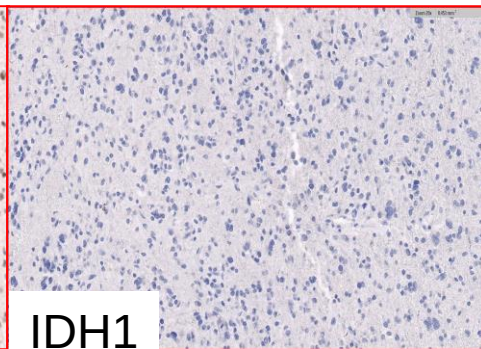
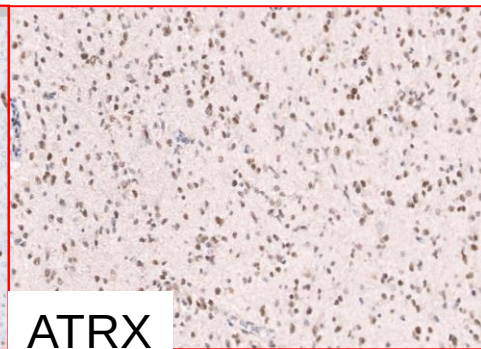
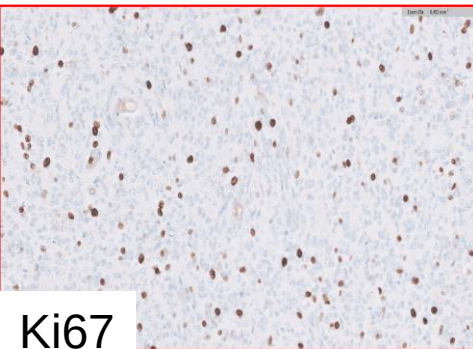
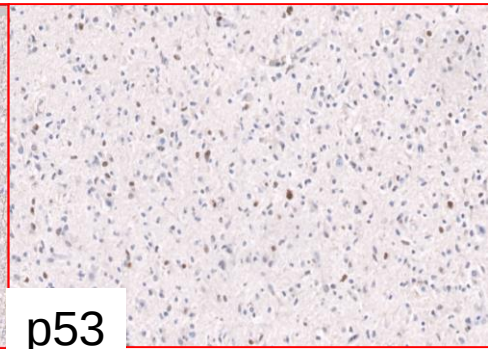
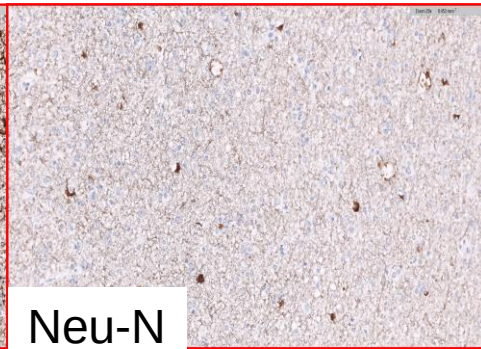
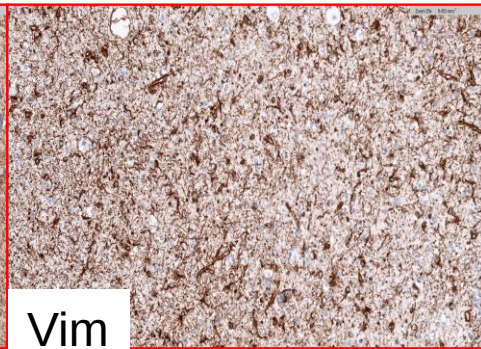
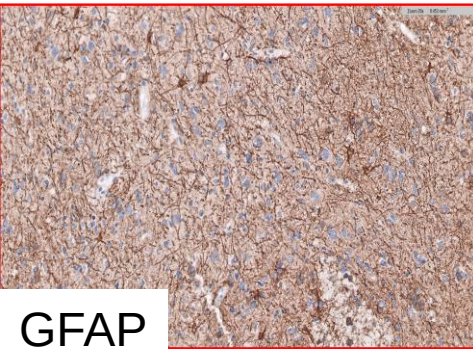
15/2/22: Craneotomía con lobectomía temporal derecha.

Se remiten fragmentos de parénquima cerebral que miden 7 x 4 x 1cm. Se realiza estudio morfológico.









Caso 7.

Tumor glial del adulto

Cerebro, resección:

- Clasificación histopatológica: Tumor glial difuso del adulto, astrocitoma
- Grado SNC OMS: 3
- Pendiente de caracterización molecular

The 2021 WHO Classification of Tumors of the Central Nervous System: a summary

Table 2 Key Diagnostic Genes, Molecules, Pathways, and/or Combinations in Major Primary CNS Tumors

Tumor Type	Genes/Molecular Profiles Characteristically Altered ^a
Astrocytoma, IDH-mutant	IDH1, IDH2, ATRX, TP53, CDKN2A/B
Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted	IDH1, IDH2, 1p/19q, TERT promoter, CIC, FUBP1, NOTCH1
Glioblastoma, IDH-wildtype	IDH-wildtype, TERT promoter, chromosomes 7/10, EGFR
Diffuse astrocytoma, MYB- or MYBL1-altered	MYB, MYBL1
Angiocentric glioma	MYB
Polymorphous low-grade neuroepithelial tumor of the young	BRAF, FGFR family
Diffuse low-grade glioma, MAPK pathway-altered	FGFR1, BRAF
Diffuse midline glioma, H3 K27-altered	H3 K27, TP53, ACVR1, PDGFRA, EGFR, EZHIP
Diffuse hemispheric glioma, H3 G34-mutant	H3 G34, TP53, ATRX
Diffuse pediatric-type high-grade glioma, H3-wildtype, and IDH-wildtype	IDH-wildtype, H3-wildtype, PDGFRA, MYCN, EGFR (methyloyme)
Infant-type hemispheric glioma	NTRK family, ALK, ROS, MET
Pilocytic astrocytoma	KIAA1549-BRAF, BRAF, NF1
High-grade astrocytoma with piloid features	BRAF, NF1, ATRX, CDKN2A/B (methyloyme)
Pleomorphic xanthoastrocytoma	BRAF, CDKN2A/B
Subependymal giant cell astrocytoma	TSC1, TSC2
Chordoid glioma	PRKCA
Astroblastoma, MN1-altered	MN1
Ganglion cell tumors	BRAF
Dysembryoplastic neuroepithelial tumor	FGFR1
Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters	Chromosome 14, (methyloyme)
Papillary glioneuronal tumor	PRKCA

Papillary glioneuronal tumor	PRKCA
Rosette-forming glioneuronal tumor	FGFR1, PIK3CA, NF1
Myxoid glioneuronal tumor	PDGFRA
Diffuse leptomeningeal glioneuronal tumor	KIAA1549-BRAF fusion, 1p (methyloyme)
Multinodular and vacuolating neuronal tumor	MAPK pathway
Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)	PTEN
Extraventricular neurocytoma	FGFR (FGFR1-TACC1 fusion), IDH-wildtype
Supratentorial ependymomas	ZFTA, RELA, YAP1, MAML2
Posterior fossa ependymomas	H3 K27me3, EZHIP (methyloyme)
Spinal ependymomas	NF2, MYCN
Medulloblastoma, WNT-activated	CTNNB1, APC
Medulloblastoma, SHH-activated	TP53, PTCH1, SUFU, SMO, MYCN, GLI2 (methyloyme)
Medulloblastoma, non-WNT/non-SHH	MYC, MYCN, PRDM6, KDM6A (methyloyme)
Atypical teratoid/rhabdoid tumor	SMARCB1, SMARCA4
Embryonal tumor with multilayered rosettes	C19MC, DICER1
CNS neuroblastoma, FOXR2-activated	FOXR2
CNS tumor with BCOR internal tandem duplication	BCOR
Desmoplastic myxoid tumor of the pineal region, SMARCB1-mutant	SMARCB1
Meningiomas	NF2, AKT1, TRAF7, SMO, PIK3CA; KLF4, SMARCE1, BAP1 in subtypes; H3K27me3; TERT promoter, CDKN2A/B in CNS WHO grade 3
Solitary fibrous tumor	NAB2-STAT6
Meningeal melanocytic tumors	NRAS (diffuse); GNAQ, GNA11, PLCB4, CYSLTR2 (circumscribed)
Adamantinomatous craniopharyngioma	CTNNB1
Papillary craniopharyngioma	BRAF

Qué marcadores moleculares son imprescindibles en los gliomas de adultos para su diagnóstico?

OPEN



EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood

Michael Weller¹✉, Martin van den Bent², Matthias Preusser³, Emilie Le Rhun^{4,5,6,7}, Jörg C. Tonn⁸, Giuseppe Minniti⁹, Martin Bendszus¹⁰, Carmen Balana¹¹, Olivier Chinot¹², Linda Dirven^{13,14}, Pim French¹⁵, Monika E. Hegi¹⁶, Asgeir S. Jakola^{17,18}, Michael Platten^{19,20}, Patrick Roth¹, Roberta Rudà²¹, Susan Short²², Marion Smits²³, Martin J. B. Taphoorn^{13,14}, Andreas von Deimling^{24,25}, Manfred Westphal²⁶, Riccardo Soffietti²¹, Guido Reifenberger^{27,28} and Wolfgang Wick^{29,30}

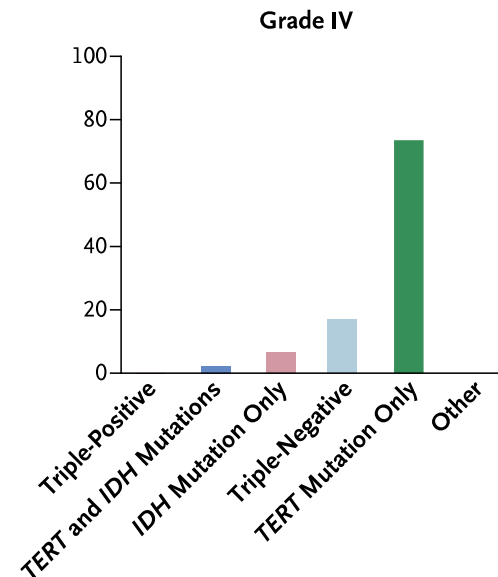
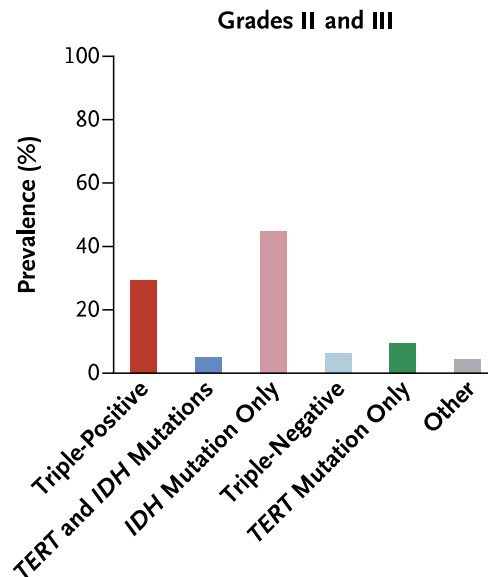
On the basis of the WHO classification and cIMPACT-NOW recommendations, the following molecular biomarkers are central to categorizing diffuse gliomas in adults:

- IDH1/2 mutations
- 1p/19q co-deletion
- Histone H3 K27M mutation
- Histone H3.3 G34R/V mutation
- *TERT* promoter mutation
- *EGFR* gene amplification
- chromosome 7 gain combined with chromosome 10 loss (the +7/−10 signature)
- homozygous deletions on 9p21 involving the *CDKN2A* and *CDKN2B* gene loci (*CDKN2A/B* homozygous deletion)

Glioma Groups Based on 1p/19q, *IDH*, and *TERT* Promoter Mutations in Tumors

Jeanette E. Eckel-Passow, Ph.D., Daniel H. Lachance, M.D.,
Annette M. Molinaro, Ph.D., Kyle M. Walsh, Ph.D., Paul A. Decker, M.S.,
Hugues Sicotte, Ph.D., Melike Pekmezci, M.D., Terri Rice, M.P.H.,
Matt L. Kosel, B.S., Ivan V. Smirnov, Ph.D., Gobinda Sarkar, Ph.D.,
Alissa A. Caron, B.S., Thomas M. Kollmeyer, M.S., Corinne E. Praska,
Anisha R. Chada, B.A., Chandralekha Halder, B.S., Helen M. Hansen, B.A.,
Lucie S. McCoy, M.P.H., Paige M. Bracci, Ph.D., Roxanne Marshall, B.S.,
Shichun Zheng, Ph.D., Gerald F. Reis, M.D., Ph.D., Alexander R. Pico, Ph.D.,
Brian P. O'Neill, M.D., Jan C. Buckner, M.D., Caterina Giannini, M.D., Ph.D.,
Jason T. Huse, M.D., Ph.D., Arie Perry, M.D., Tarik Tihan, M.D., Ph.D.,
Mitchell S. Berger, M.D., Susan M. Chang, M.D., Michael D. Prados, M.D.,
Joseph Wiemels, Ph.D., John K. Wiencke, Ph.D., Margaret R. Wrensch, Ph.D.,
and Robert B. Jenkins, M.D., Ph.D.

N Engl J Med 2015;372:2499-508.

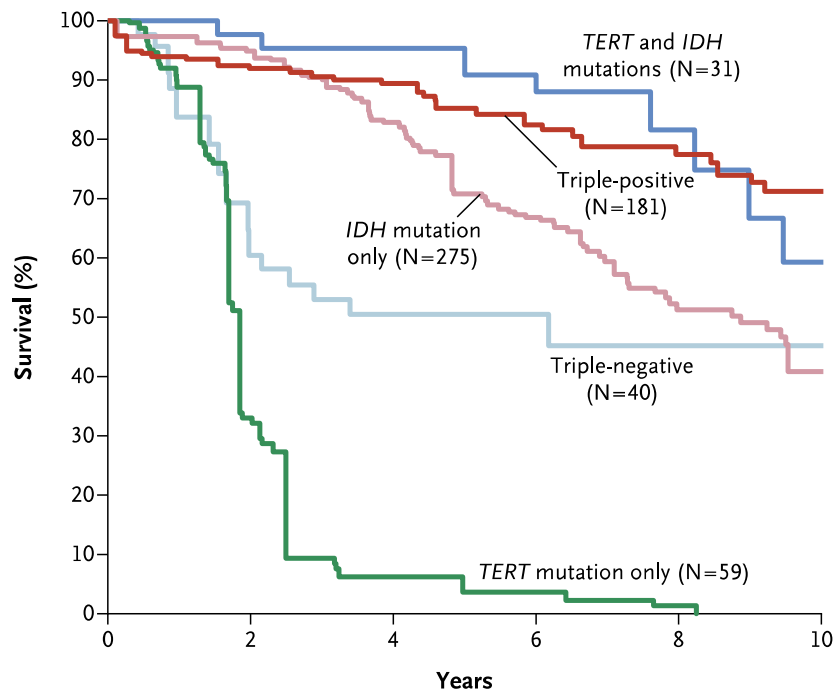


- Gliomas were classified into five principal groups on the basis of three tumor markers.
- Among 615 grade II or III gliomas, 29% had all three alterations (i.e., were triple- positive), 5% had *TERT* and *IDH* mutations, 45% had only *IDH* mutations, 7% were triple-negative, and 10% had only *TERT* mutations; 5% had other combinations.
- Among 472 grade IV gliomas, less than 1% were triple-positive, 2% had *TERT* and *IDH* mutations, 7% had only *IDH* mutations, 17% were triple-negative, and 74% had only *TERT* mutations.

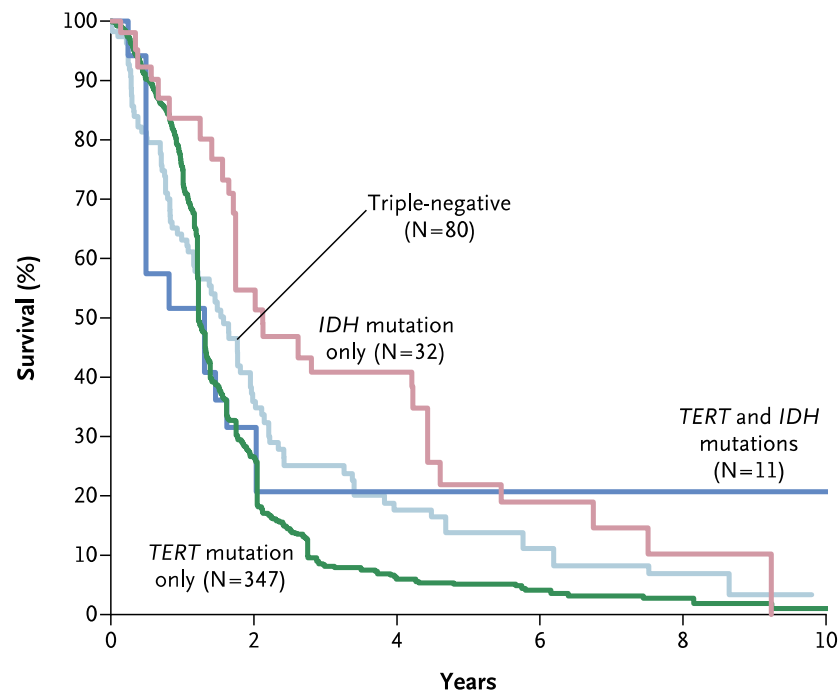
Glioma Groups Based on 1p/19q, IDH, and TERT Promoter Mutations in Tumors

N Engl J Med 2015;372:2499-508.

A Grades II and III



B Grade IV



MGMT

The New England Journal of Medicine

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VOLUME 343

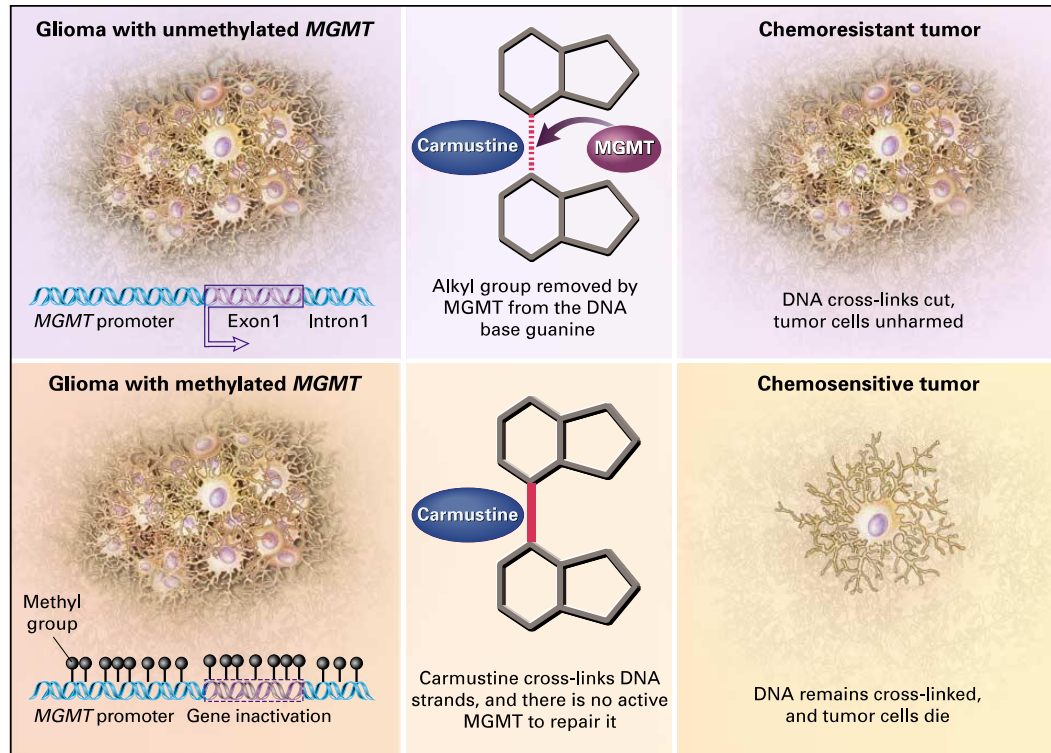
NOVEMBER 9, 2000

NUMBER 19



INACTIVATION OF THE DNA-REPAIR GENE *MGMT* AND THE CLINICAL RESPONSE OF GLIOMAS TO ALKYLATING AGENTS

MANEL ESTELLER, M.D., PH.D., JESUS GARCIA-FONCILLAS, M.D., PH.D., ESTHER ANDION, B.Sc.,
STEVEN N. GOODMAN, M.D., PH.D., OSCAR F. HIDALGO, M.D., VICENTE VANACLOCHA, M.D., STEPHEN B. BAYLIN, M.D.,
AND JAMES G. HERMAN, M.D.



Cómo abordar el diagnóstico integrado de los tumores gliales?

CIMPACT-NOW: Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy, 2018 recommendations

IDH mutations in cancer

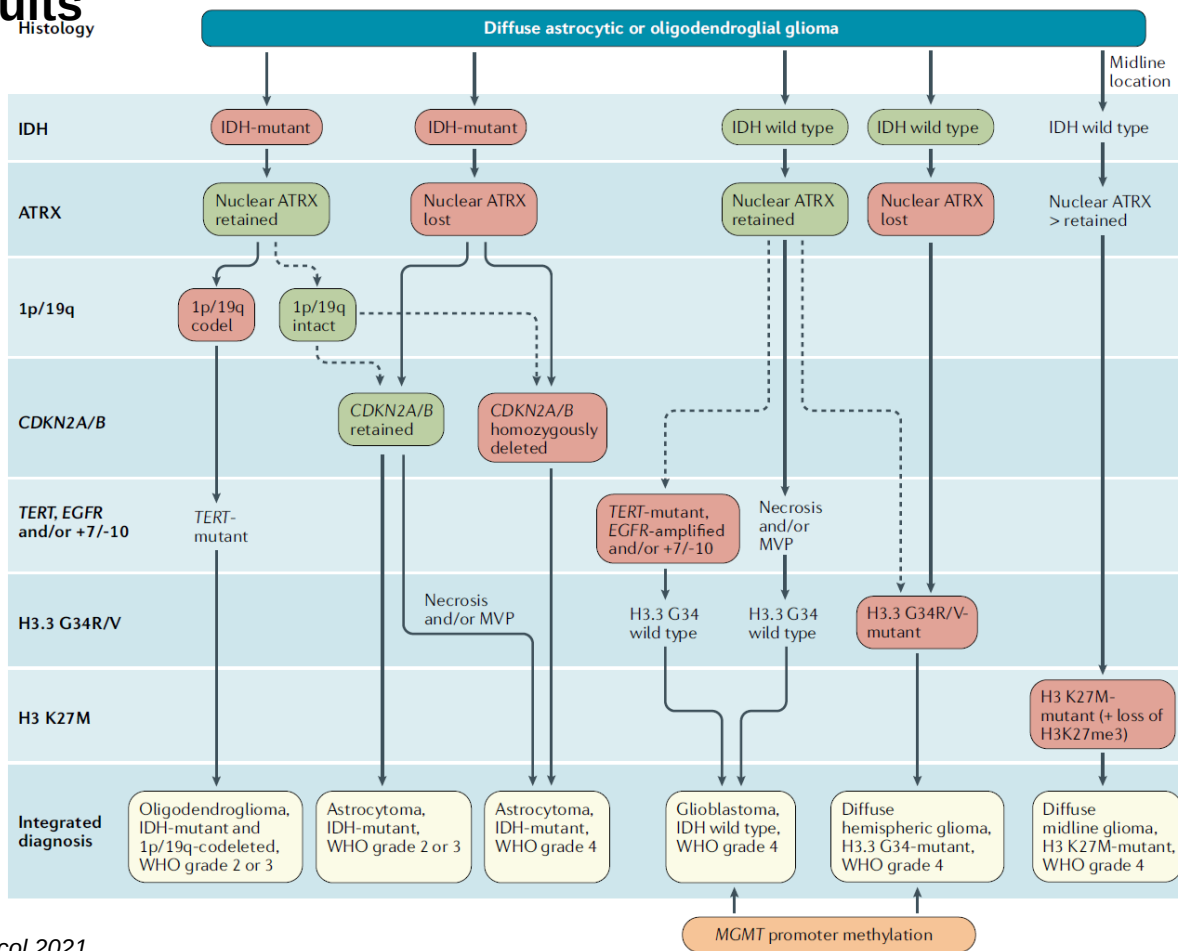
Diffuse gliomas corresponding histologically to WHO grade 2 or 3 that are immunohistochemically negative for IDH1 expression should be sequenced for less common *IDH1* and for *IDH2* mutations.

CIMPACT-NOW: Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy, 2018 recommendations

The minimal molecular criteria for identifying an IDH-wildtype diffuse astrocytic glioma that, despite appearing histologically as a WHO grade II or III neoplasm, would follow an aggressive clinical course more closely resembling that of an IDH-wildtype glioblastoma:

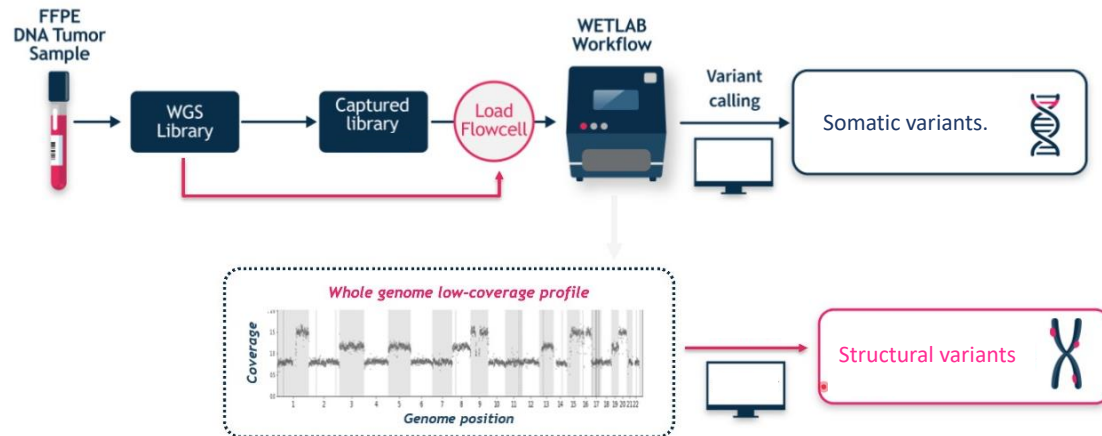
1. EGFR amplification OR
2. Combined whole chromosome 7 gain and whole chromosome 10 loss (+7/-10) OR
3. TERT promoter mutation

Diagnostic algorithm for the integrated classification of the major diffuse gliomas in adults



Action OncoKitDx

Secuenciadores compatibles	Illumina NextSeq500, Illumina NextSeq2000, Illumina HiSeq, Illumina NovaSeq
Número de reacciones	20
Número de muestras por run	Mid Output v2.5 kit (150 cycles): 12 muestras High Output v2.5 kit (150 cycles): 32 muestras
Secuenciación	Paired-end (2 x 75 ciclos)
Cantidad de ADN por muestra	50-200 ng
Calidad de ADN recomendada	DIN >3
Región genómica analizada	500 Kb
Genes diana	SNVs e INDELS: AKT1*, ALK, ARID1A, ATM, ATRX, BAP1, BRAF, BRCA1, BRCA2, CDH1, CHEK2, CTNNB1, EGFR, ERBB2, ESR1, FGFR1, FGFR4, GNA11, GNAQ, H3F3A, HIST1H3B, HIST1H3H, HRAS, IDH1, IDH2, KIT, KRAS, MAP2K1, MET, MLH1, MSH2, MSH6, MTOR, MYC, NRAS, NTRK1, NTRK2, NTRK3, PALB2, PBRM1, PDGFRA, PIK3CA, PMS2 + 5'UTR, PTEN, POLD1, POLE, RET, ROS1, SDHA, SDHB, SDHD, TERT + 5'UTR, TSC1*, TSC2*, TP53 y VHL. * Secuenciación de <i>hotspot</i> SVs: ALK (intrón 19), ATP1B1 (intrones 3 y 4), BRAF (intrones 7, 8, 9 y 10), EGFR (intrones 7, 23, 24 y 25), ETV6 (intrones 4 y 5), FGFR2 (intrón 17 y región 3'UTR), FGFR3 (intrón 17 y región 3'UTR), NTRK1 (intrones 8, 9, 10, 11 y 12), NTRK2 (intrones 12 y 15), RET (intrones 9, 10 y 11) y ROS1 (intrones 31, 32, 33, 34 y 35).
	ADN procedente de sangre periférica, tejido fresco, congelado y parafinado





Action OncoKitDx

Perfil mutacional obtenido:

- IDH1 (NM_005896.4):c.102C>T (p.Tyr34=) (VAF 68,6%)
- IDH2 nativo
- Promotor TERT nativo
- H3F3A nativo
- H3K27 nativo
- ATRX nativo
- PTEN (NM_000314.4): c.302T>C; p.Ile101Thr (VAF 33,9%)

Inestabilidad de microsatélites:

No se identifica inestabilidad de microsatélites, fracción de inestabilidad 0,14 (marcadores inestables 14 de 103 analizados) (MSS 0-0.17)

IAVANTE IDH1 (NM_005896.4):c.102C>T (p.Tyr34=) (VAF 68,6%)

 National Library of Medicine
National Center for Biotechnology Information

Log in

ClinVar
Genomic variation as it relates to human health

Search by gene symbols, location, HGVS expressions, c-dot, p-dot, conditions, and more

Search ClinVar ?

Advanced search

About Access Submit Stats FTP Help

Were new search queries using location, c-dot, and p-dot helpful?  

[Follow](#)  Print  Download

NM_005896.4(IDH1):c.102C>T (p.Tyr34=)

[Cite this record](#)

Interpretation: Likely benign

Review status: ☆☆☆ criteria provided, single submitter

Submissions: 1 (Most recent: Mar 14, 2019)

Last evaluated: May 18, 2018

Accession: VCV000741270.1

Variation ID: 741270

Description: single nucleotide variant

Variant details

[Conditions](#)[Gene\(s\)](#)

NM_005896.4(IDH1):c.102C>T (p.Tyr34=)

Allele ID: 747188

Variant type: single nucleotide variant

Variant length: 1 bp

Cytogenetic location: 2q34

Genomic location: 2: 208251450 (GRCh38) GRCh38 UCSC
2: 209116174 (GRCh37) GRCh37 UCSC

HGVS:	Nucleotide	Protein	Molecular consequence
	NM_005896.4:c.102C>T	NP_005887.2:p.Tyr34=	synonymous
	NM_001282386.1:c.102C>T	NP_001269315.1:p.Tyr34=	synonymous
	NM_001282387.1:c.102C>T	NP_001269316.1:p.Tyr34=	synonymous

... more HGVS

Protein change: -

Other names: -

Canonical SPDI: NC_000002.12:208251449:G:A

Functional consequence: -

Global minor allele frequency (GMAF): -

Allele frequency: The Genome Aggregation Database (gnomAD) 0.00001
The Genome Aggregation Database (gnomAD), exomes 0.00003
Exome Aggregation Consortium (ExAC) 0.00004
Trans-Omics for Precision Medicine (TOPMed) 0.00000

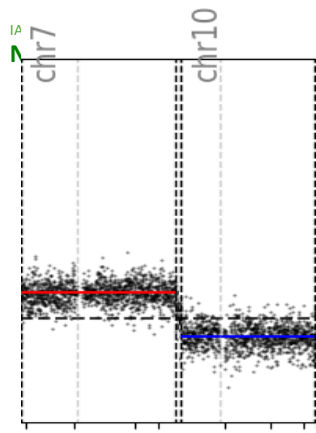
Links: dbSNP: rs753580953
VarSome

Submitted interpretations and evidence

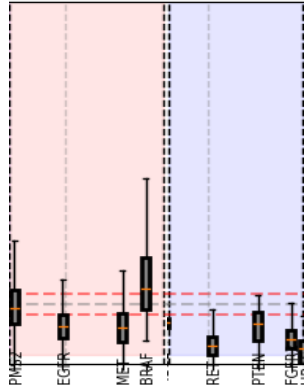
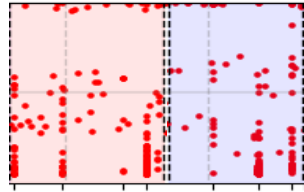
Interpretation (Last evaluated)	Review status (Assertion criteria)	Condition (Inheritance)	Submitter	More information
Likely benign (May 18, 2018)	criteria provided, single submitter (Invitae Variant Classification Sherlock (9/6/2015)) Method: clinical testing	not provided Affected status: unknown Allele origin: germline	Invitae Accession: SCV001062687.1 Submitted: (Mar 14, 2019)	

Functional evidence

There is no functional evidence in ClinVar for this variation. If you have generated functional data for this variation, please consider submitting that data to ClinVar.



Positive for combined chromosome 7 gain
and chromosome 10 loss (+7/−10
signature)



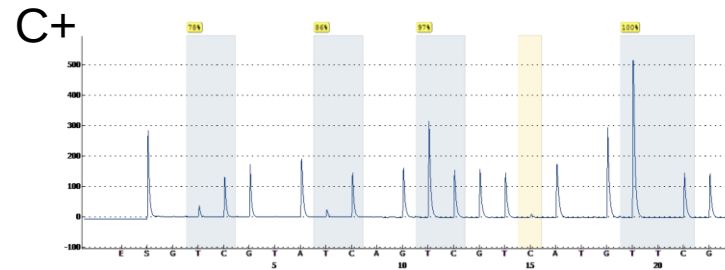
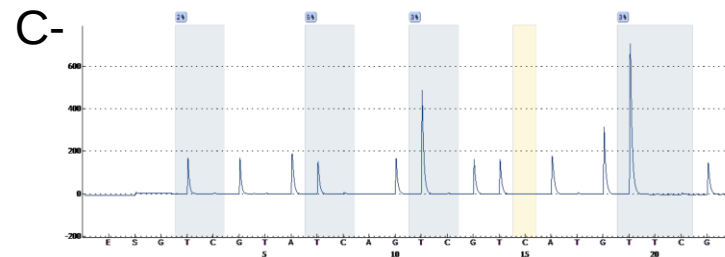
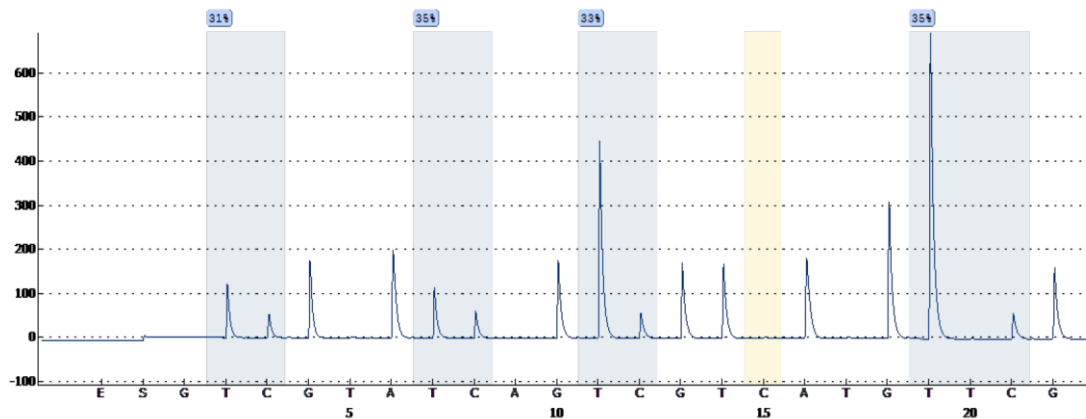
IAVANTE
NOMBRE CURSO

Hallazgos moleculares



MGMT Pyro Kit

Estudio de metilación del promotor del gen MGMT



Caso 7.

Tumor glial del adulto

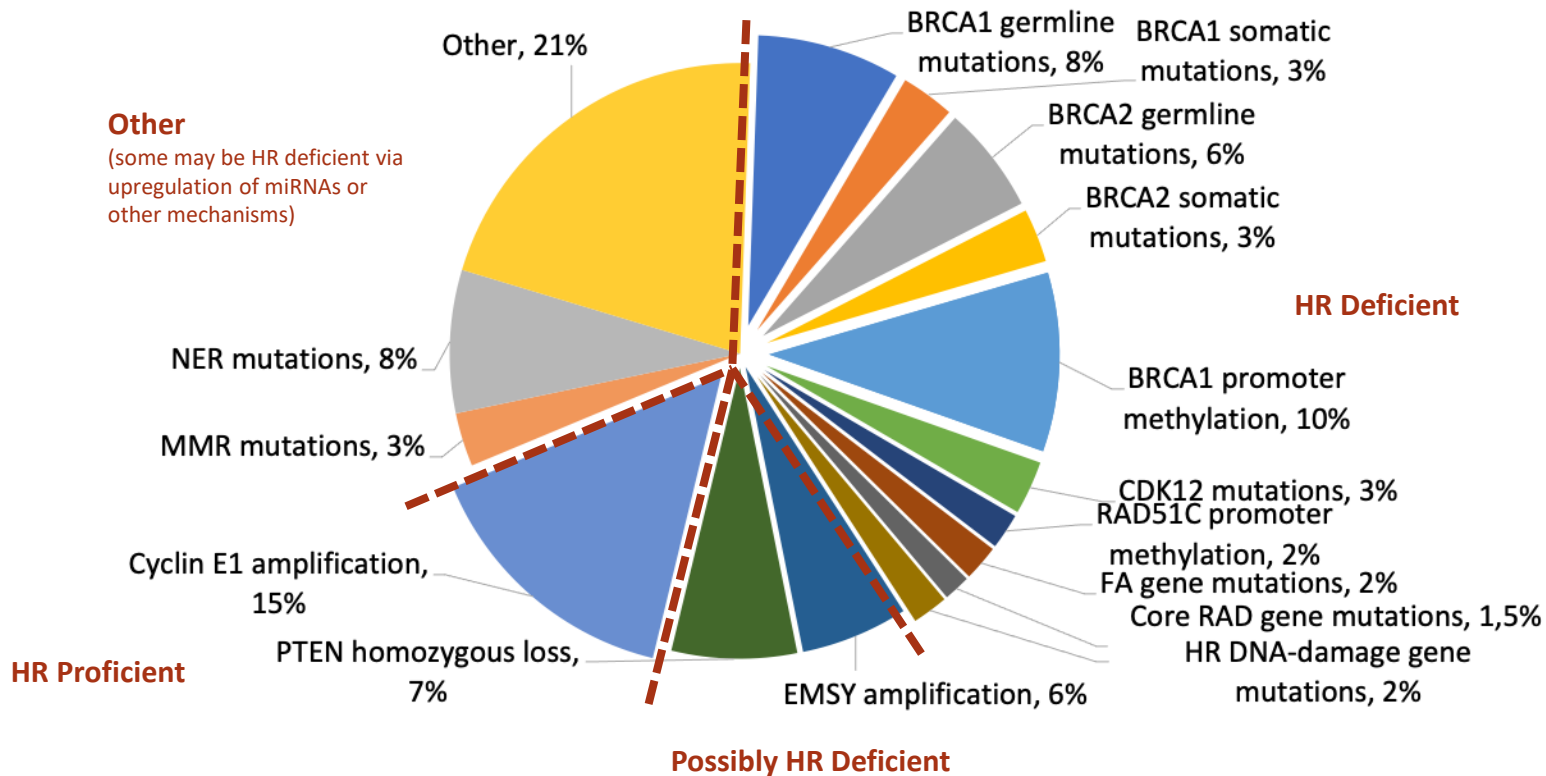
Cerebro, resección:

- Diagnóstico integrado: Glioblastoma IDH nativo
- Clasificación histopatológica: Glioma astrocítico difuso
- Grado SNC OMS: 4
- Perfil molecular: IDH1/2 nativo, ATRX conservado, CDKN2A/B conservado, TERT nativo, EGFR no amplificado, firma citogenética +7/-10, H3.3 nativo, H3K27M nativo
- Hipermetilación del promotor de MGMT

Caso 8.

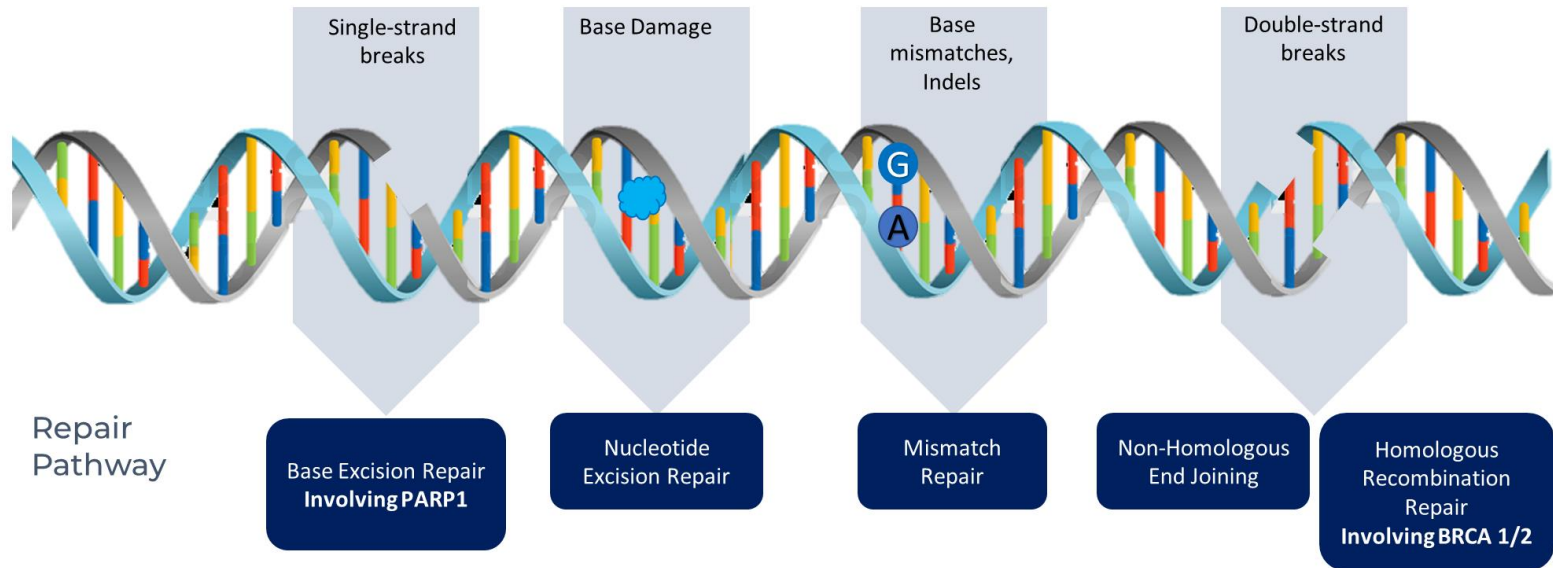
Estudio de HRD en cáncer de ovario

Molecular landscape in high grade epithelial ovarian cancer



In healthy cells, DNA damage is repaired via 5 key pathways

Type of DNA Damage



Synthetic lethality: PARP inhibitors in BRCA1/2 mutant cancer

NATURE | VOL 434 | 14 APRIL 2005

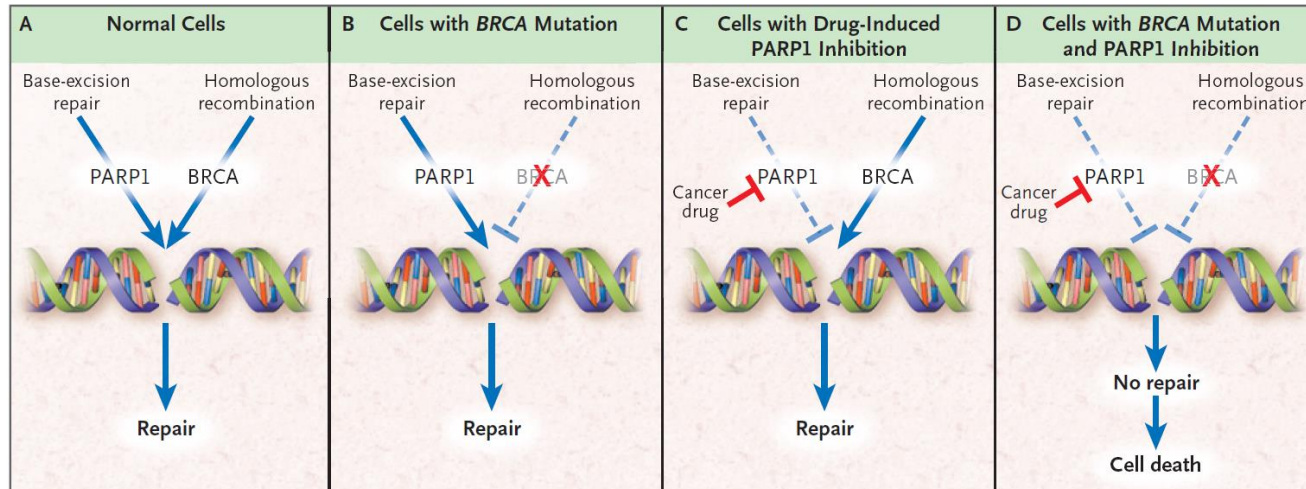
Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase

Helen E. Bryant¹, Niklas Schultz², Huw D. Thomas³, Kayan M. Parker¹, Dan Flower¹, Elena Lopez¹, Suzanne Kyle³, Mark Meuth¹, Nicola J. Curtin³ & Thomas Helleday^{1,2}

NATURE | VOL 434 | 14 APRIL 2005

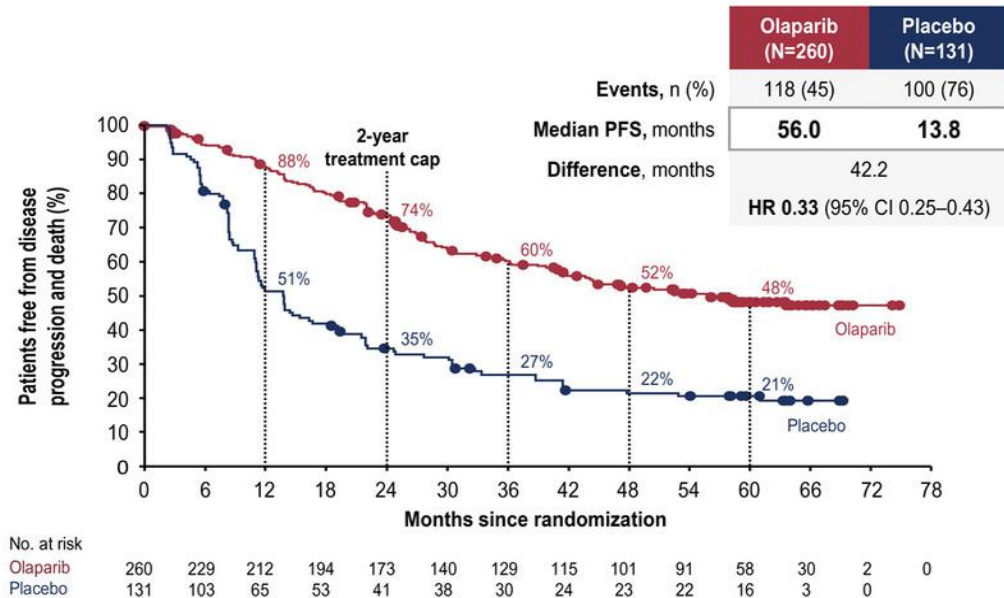
Targeting the DNA repair defect in *BRCA* mutant cells as a therapeutic strategy

Hannah Farmer^{1,2,4}, Nuala McCabe^{1,2,4}, Christopher J. Lord^{2,4}, Andrew N. J. Tutt^{2,3}, Damian A. Johnson², Tobias B. Richardson², Manuela Santarosa^{2,†}, Krystyna J. Dillon⁴, Ian Hickson⁴, Charlotte Knights⁴, Niall M. B. Martin⁴, Stephen P. Jackson^{4,5}, Graeme C. M. Smith⁴ & Alan Ashworth^{1,2}



SOLO-1: PFS in BRCAm HGOC

Maintenance therapy with olaparib provided a substantial benefit with regard to PFS among women with newly diagnosed advanced ovarian cancer and a BRCA1/2 mutation

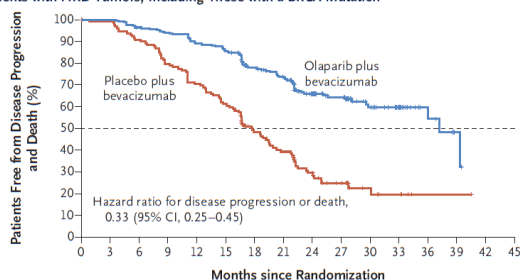


PAOLA-1: PFS according to BRCA and HRD status

The PAOLA-1 trial in patients with advanced HGOC demonstrated that adding maintenance olaparib to bev provides a sustancial PFS benefit, particularly in HRD-positive patients and irrespective of BRCaM status

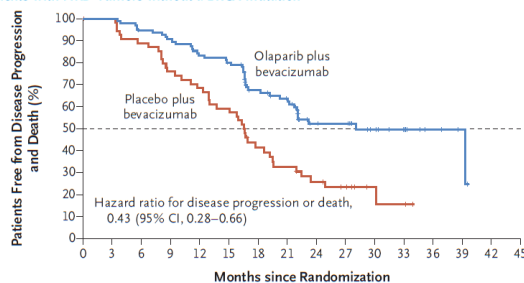
HRD positive

C Patients with HRD Tumors, Including Those with a BRCA Mutation



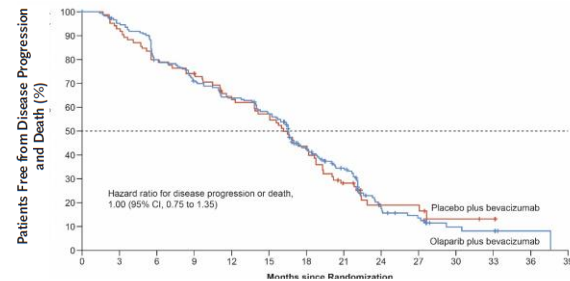
	Olaparib + bevacizumab (n=255)	Placebo + bevacizumab (n=132)
Events, n (%)	87 (34)	92 (70)
Median PFS, months	37.2*	17.7
Δ Median PFS, months	19.5	
HR (95% CI)	0.33 (0.25–0.45)	

D Patients with HRD Tumors without a BRCA Mutation



	Olaparib + bevacizumab (n=97)	Placebo + bevacizumab (n=55)
Events, n (%)	43 (44)	40 (73)
Median PFS, months	28.1*	16.6
Δ Median PFS, months	11.5	
HR (95% CI)	0.43 (0.28–0.66)	

HRD negative



	Olaparib + bevacizumab (n=282)	Placebo + bevacizumab (n=137)
Events, n (%)	193 (68)	102 (74)
Median PFS, months	16.9	16.0
Δ Median PFS, months	0.9	
HR (95% CI)	0.92 (0.72–1.17)	

Las guías ESMO recomiendan considerar el test HRD para identificar pacientes de nuevo diagnóstico que puedan beneficiarse de terapias con PARPi



SPECIAL ARTICLE

Available online 28 September 2020

ESMO recommendations on predictive biomarker testing for homologous recombination deficiency and PARP inhibitor benefit in ovarian cancer

R. E. Miller^{1,2}, A. Leary³, C. L. Scott^{4,5}, V. Serra⁶, C. J. Lord^{7,8}, D. Bowtell^{4,5}, D. K. Chang^{9,10}, D. W. Garsed^{4,5}, J. Jonkers¹¹, J. A. Ledermann¹², S. Nik-Zainal^{13,14}, I. Ray-Coquard^{15,16}, S. P. Shah¹⁷, X. Matias-Guiu¹⁸, E. M. Swisher¹⁹ & L. R. Yates^{20,21}

En el contexto de un diagnóstico reciente, es **razonable utilizar una prueba validada de HRD basada en la cicatriz** para:

- Establecer la magnitud del beneficio conferido por el uso de iPARP en BRCAwt HGSC
- Identificar el subgrupo de pacientes con BRCAwt con menos probabilidades de beneficiarse del tratamiento con iPARP

HRD test	Test level of evidence	Clinical validity	Clinical utility	
			1L maintenance	PSR disease
Germline BRCA mutations	I	Good	Good	Good
Tumour BRCA mutations	I	Good	Good	Good
Somatic BRCA mutations	I/II	Good/fair	Good	Good
Non-BRCA HRR gene mutations	II	Marginal	No evidence	Marginal
HR genomic scar assays:				
GIS	I	Good	Good	Good
LOH	II	Good	No evidence	Good

En el contexto de un diagnóstico reciente, **se recomienda de forma rutinaria la prueba g/sBRCAm** para identificar a los pacientes con HGSC que deben recibir un iPARP

En la actualidad, la **cantidad de evidencia es insuficiente** para determinar la validez clínica de los genes individuales o de los paneles de **genes HRR no BRCA para predecir la respuesta al iPARP** y se necesitan más datos recopilados de forma prospectiva.

Permanent footprint of genomic changes that causes genomic scars is used as an approach to identify HRD

Etiology of HRD

CAUSE

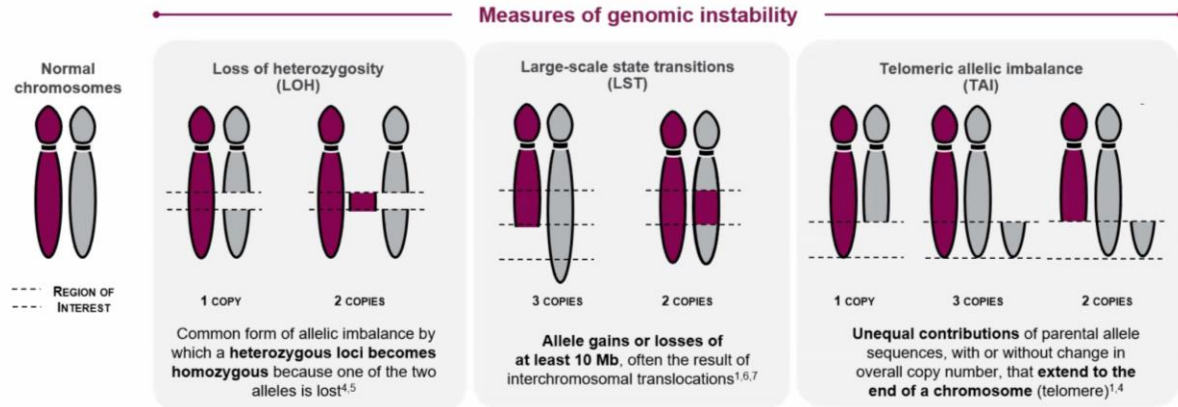


EFFECT

HRD phenotype

Tumor BRCA1/2 mutation

Genomic Instability



A single chromosome change can meet the definition for more than one measure of genomic instability.⁸

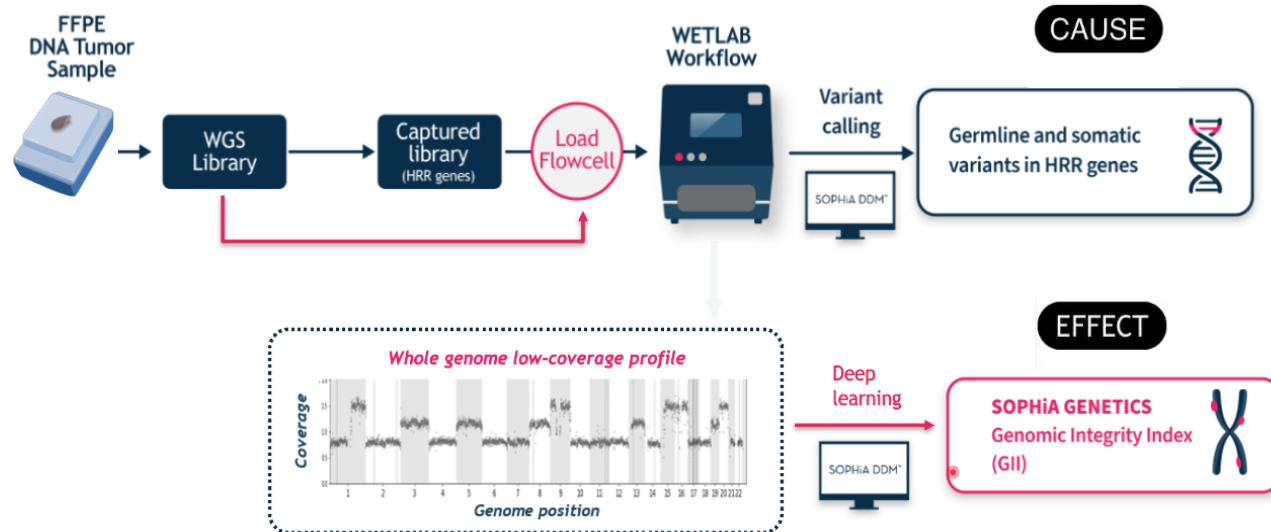
HRD landscape: Commercial solutions

Myriad-based			Alternative Dx partner Kits								Academic LDTs				
	Illumina TSO500 + HRD	Satellite Lab Myriad	AmoyDx HRD Focus	SOPHiA DDM HRD	Thermo Fisher Onco Scan	Thermo Fisher OCA+	QIAGEN QIAseq HRD Panel	F1CDx Roche	OncoDNA Onco DEEP	SeqOne HRD	Agilent CGH-array	sWGS Curie	LDT Baclesse	LDT CGFL	FOCI RAD51
Availability	June 2022	Q4 2021	V1: Dec 2020 V2: Mar 2021	Feb 2022	Q4 2021	March 2021	Q4 2021	Before 2019	Sept 2022	No date	Yes	Yes	Yes	Sept 2022	No
Algorithm	Myriad	Myriad	AmoyDx	Sophia Genetics	Thermo Fisher	No score	Qiagen	LOH Score	Integra-gen	SeqOne	Internal	Internal	internal	internal	IF
Design	CGP+ HRD	HRD (GIS)	BRCA1/2 +HRD	28 HRR genes+ sWGS	SNP Array (no BRCA)	CGP	15 HRR+ HRD	CGP+ HRD	CGP+BRCA 1/2+ HRD score	HRR+ sWGS	CGH-array	sWGS - HRD	CGP+ HRD	BRCA1/2 +sWGS	HRD
Platform	Illumina NextSeq/ NovaSeq	Illumina Next/ NovaSeq	Illumina NextSeq NovaSeq	Illumina NextSeq	Affymetrix GeneChip	Thermo Fisher	Compatible with all major NGS platforms	NA	Twist Bioscience Illumina	Illumina Next/ NovaSeq	Agilent	Illumina Next/ NovaSeq	Illumina NextSeq	Illumina NextSeq	IF

1. Pujade-Lauraine E, et al. *Int J Gynecol Cancer* 2021; **31** (Supplement 3): Abstract 201. 2. Ray-Coquard I, et al. *Ann Oncol* 2023; **34**: 681–692.
3. <https://investor.illumina.com/news/press-release-details/2022/Illumina-Launches-Research-Test-Codeveloped-with-Merck-to-Unlock-Deeper-Insights-into-the-Tumor-Genome/default.aspx> (accessed Aug 2023).
4. <https://emea.illumina.com/content/dam/illumina/gcs/assembled-assets/marketing-literature/tso500-HRD-data-sheet-m-gl-00748/tso500-HRD-data-sheet-m-gl-00748.pdf> (accessed Aug 2023).
5. Buisson A, et al. Presented at ESGO 2022. [Poster PA-065]. 6. Boidot R, et al. Presented at ESMO Gynaecological Cancers Congress 2023. [Abstract 39MO]. 7. Loverix L, et al. Presented at SGO 2022. [Oral 16].
8. Christinat Y, et al. *JCO Precis Oncol* 2023; **7**: e2200555. 9. Callens C, et al. Presented at ESMO Gynaecological Cancers Congress. [Abstract 38MO]. 10. Leman R, et al. *Int J Gynecol Cancer* 2022; **32** (Supplement 2): A280.

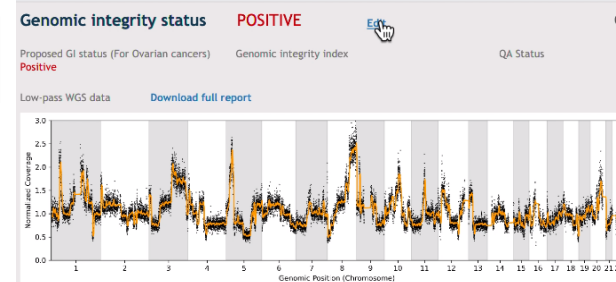
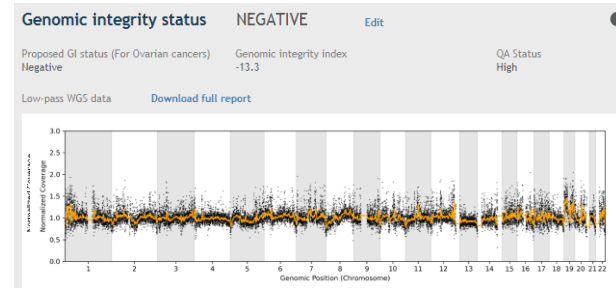
Sophia HRD Solution: Gene Panel and Genomic Integrity analysis

Variant calls + **Genomic integrity index** = HRD status



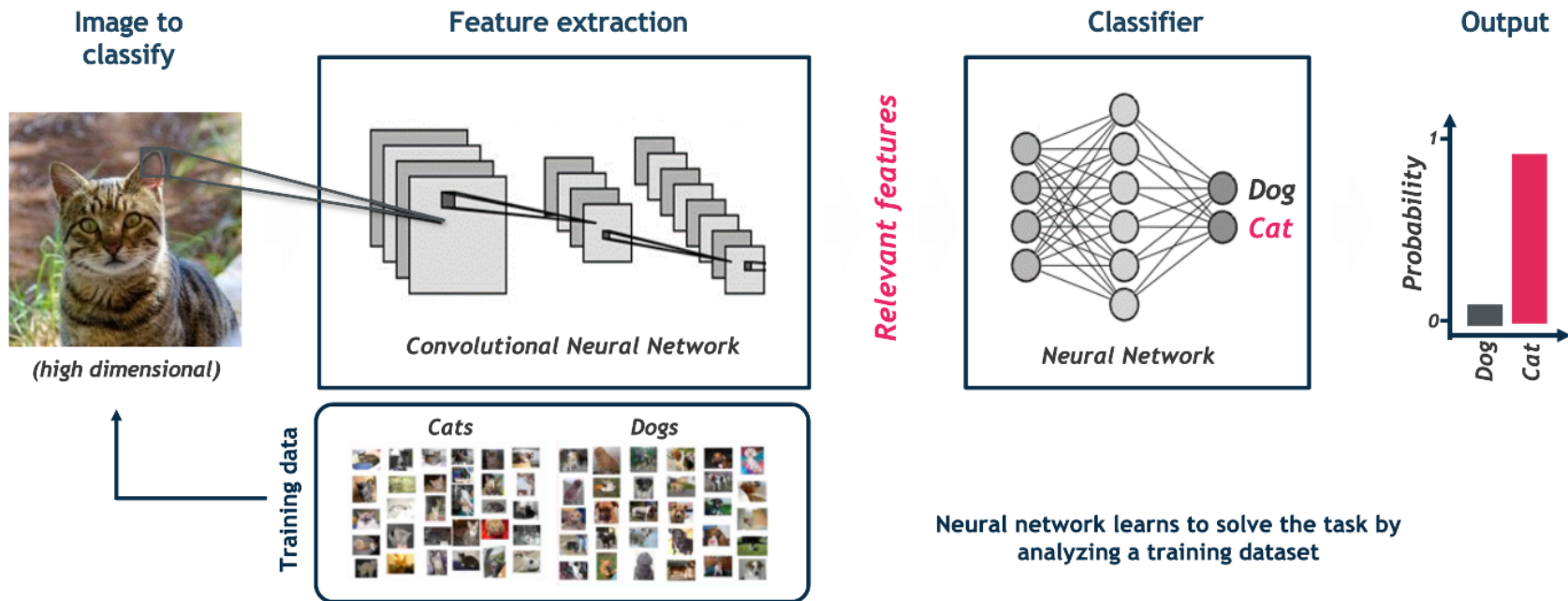
HRR genes

<i>AKT1</i>	<i>CDK12</i>	<i>FGFR1</i>	<i>PPP2R2A</i>
<i>ATM</i>	<i>CHEK1</i>	<i>FGFR2</i>	<i>RAD51B</i>
<i>BARD1</i>	<i>CHEK2</i>	<i>FGFR3</i>	<i>RAD51C</i>
<i>BRCA1</i>	<i>ESR1</i>	<i>MRE11</i>	<i>RAD51D</i>
<i>BRCA2</i>	<i>FANCA</i>	<i>NBN</i>	<i>RAD54L</i>
<i>BRIP1</i>	<i>FANCD2</i>	<i>PALB2</i>	<i>TP53</i>
<i>CCNE1</i>	<i>FANCL</i>	<i>PIK3CA</i>	<i>PTEN</i>



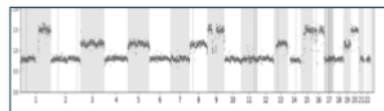
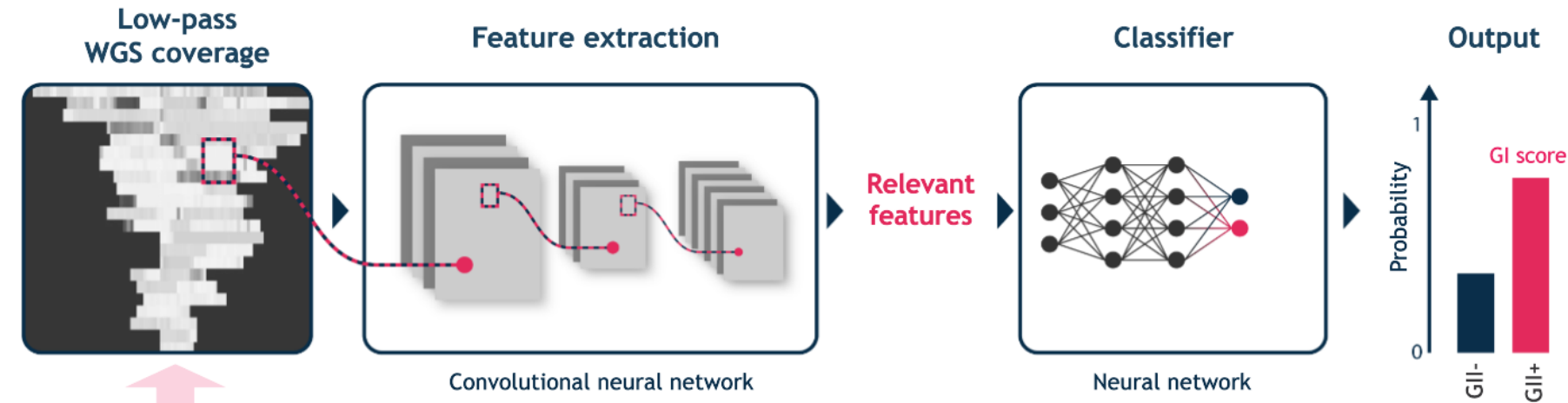
Deep learning-based Sophia HRD solution

- Deep learning is a powerful tool to solve classification tasks (e.g., establish if an image shows a cat or a dog)
- Learn relevant features that in traditional algorithms were hand-engineered by experts



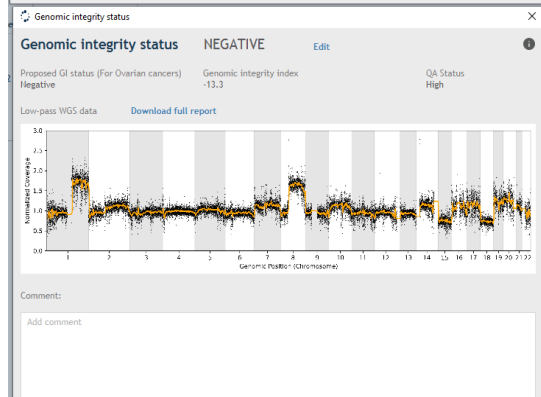
Deep learning-based Sophia HRD solution

- Transform low-pass WGS (~1x) coverage profile into an “image”
- Use a convolutional neural network to classify images as HRD positive and HRD negative

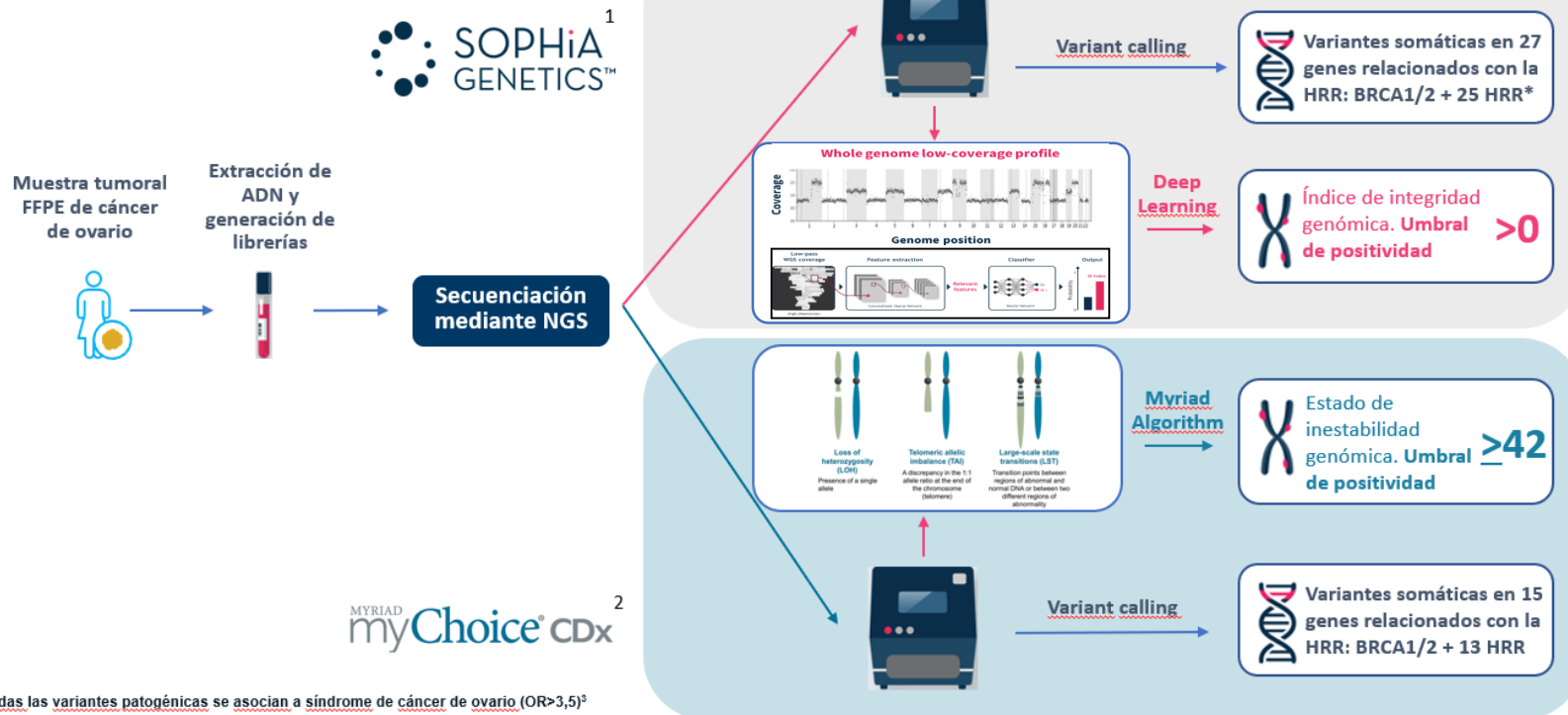


SOPHiA GENETICS
Genomic Integrity Index





Comparativa del HRD mediante los Kits HRD SOPHiA y Myriad MyChoice Dx Plus



1. SOPHiA genetics technical sheet. Available at: <https://www.sophiagenetics.com/clinical/oncology/solid-tumors/homologous-recombination-deficiency-solutions/> (Last accessed June 2022)

2. Instrucciones de envío de muestras Myriad myChoice CDx Plus (myChoiceCDxPLUS_Instr._14_07_20_EN).

3. Manchanda R, Gaba F, Talaulikar V et al. Risk-Reducing Salpingo-Oophorectomy and the Use of Hormone Replacement Therapy Below the Age of Natural Menopause. BJOG. 2022 Jan;129(1):e16-e34.

iD-BRCA HRD: Spanish Lab Network for BRCA/HRD testing



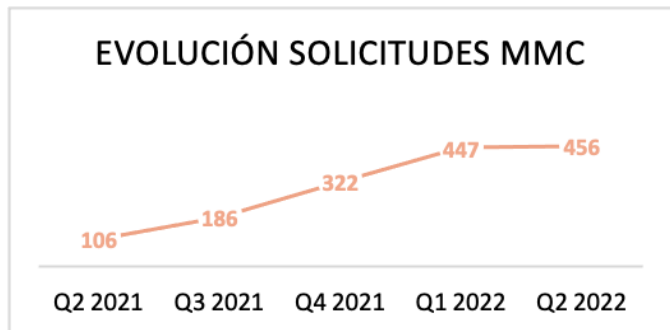
- **Análisis de tejido tumoral**
 - **Determinación de HRD mediante NGS (Sophia DDM HRD Solution o TSO500 Illumina)**
 - **4 centros:**
 - **ICO-HU. Bellvitge**
 - **H. Gral. Valencia**
 - **Fundación Jimenez Díaz**
 - **CHU Santiago**
- (+1 adicional en 2023 → H. Clínico San Carlos)
- **Reporte de resultados estandarizado**

Resultados del test HRD en España: Modelo *send out* Myriad myChoice CDx Plus

MYRIAD
myChoice[®]CDx^{PLUS}

1 Más de 1300 muestras analizadas

Centros con reunión de activación	106
Centros Firmados	97
Centros Activos en envío de muestras	90



Total

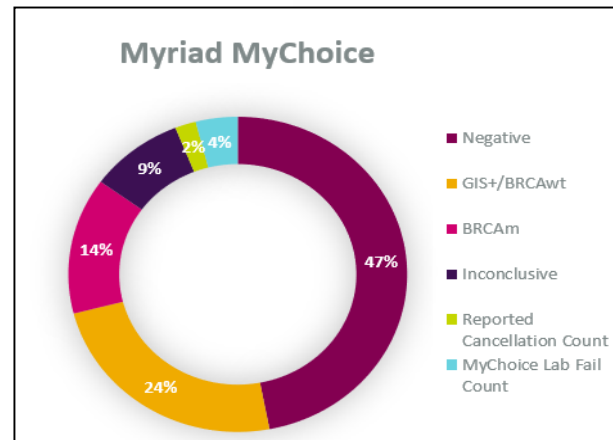
1517



Analyzed

1322

2 38% de las muestras fueron HRD +



16 días TAT

HRD Positivity	HRD Negative	Undetermined
38%	47%	9%

Experiencia test HRD en rutina en España reportada hasta el 2º semestre del 2023

1. Samples requested

SAMPLE REQUEST EVOLUTION -
LOCAL PLATFORM



 **2270**

2. Report of results

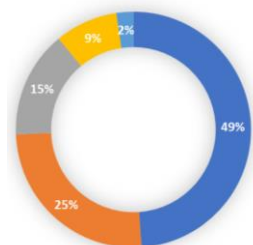


Max. TAT 4 weeks



202 Centers with access to
local platform

3. Results BRCA/HRD local platform



■ Negative
■ GIS+/BRCAwt
■ BRCAm
■ Inconclusive
■ Reported Cancellation Count

2022

2023

4. Results of others genes HRR

HRR Gene	Prevalence
CCNE1 Amplification	5,8%
BRIP1	2,3%
PALB2	1,4%
Rad51c	1,1%
Rad51d	1,2%

N=2265

Prevalencia de alteraciones en genes HRR vs GIS.

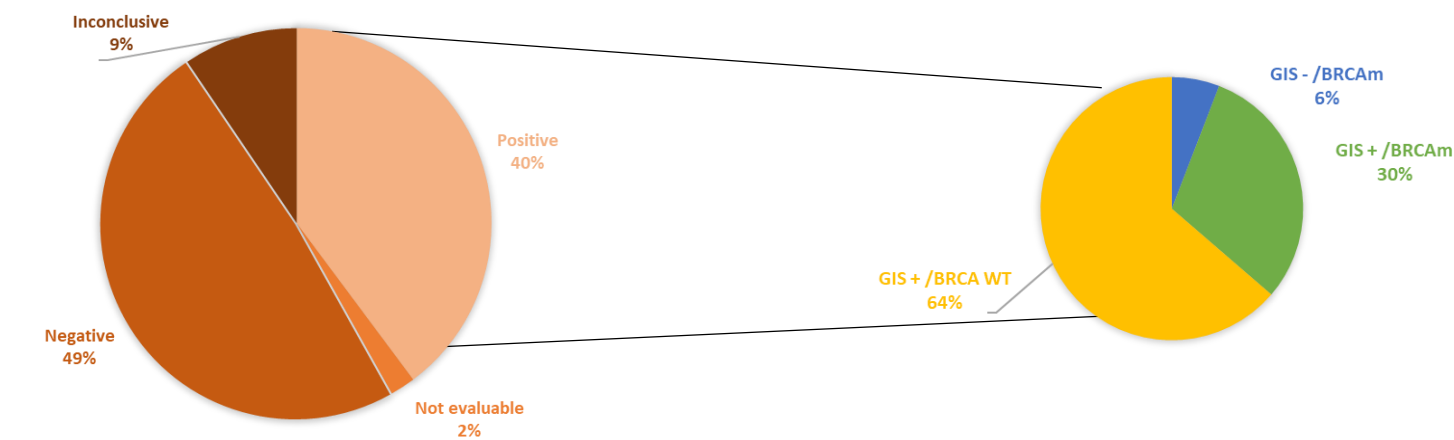
Plataforma local



Resultados de 5 genes HRR

HRR Gene	Frequency	GIS +	GIS -	Co-mutations
CCNE1 Amplification	5,32% (43)	11,6% (5)	88,4% (38)	1 (BRCA2)
BRIP1	2,35% (19)	36,80%(7)	63,2% (12)	1 (PALB2)
PALB2	1,98% (16)	62,5%(10)	37,5% (6)	4 (BRCA1) 3 (BRCA2) 1 (Rad51c) 1(Rad51d)
Rad51c	1,11% (9)	33,3% (3)	66,6% (6)	1 (PALB2)
Rad51d	1,24% (10)	80% (8)	20% (2)	1 (PALB2)

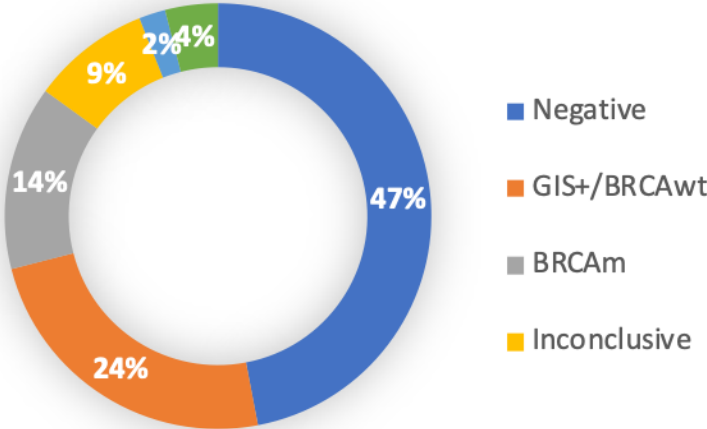
Plataforma local HRD en España – 2538 muestras reportadas en el Q3 2022 – Q2 2023



Reference Site	Samples Reported	Inconclusive	Negative	Positive	Not Evaluable
Hospitals A ,B, C & D	2270	9% (±3%)	49% (±1%)	40% (±3%)	2% (±3%)

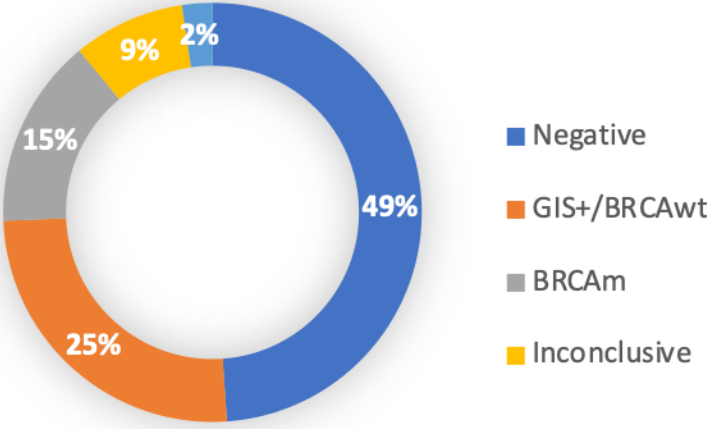
Plataforma local HRD en España – 2538 muestras reportadas en el Q3 2022 – Q2 2023

Myriad MyChoice



Time: Q2 2021-Q2 2022
N= 1322

Local platform



Time: Q3 2022-Q2 2023
N= 2270

Caso 8

Mujer 54 años, sin antecedentes de interés
Estudiada en Medicina Interna por dolor abdominal desde mayo 22

TAC abdomino-pélvico 08/22. Hallazgos compatibles con neoplasia anexial de 123 x 85 mm, con carcinomatosis peritoneal y metástasis ganglionares, hepáticas y pulmonares.

Diagnóstico Oncológico 1: N. MALIGNA DE OVARIO T: 3 N: x M: 1 Estadio: IV

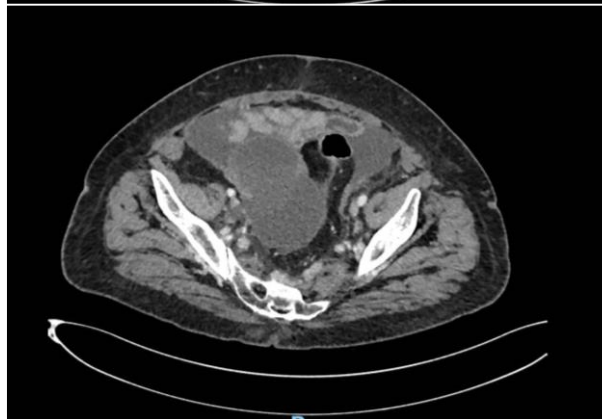
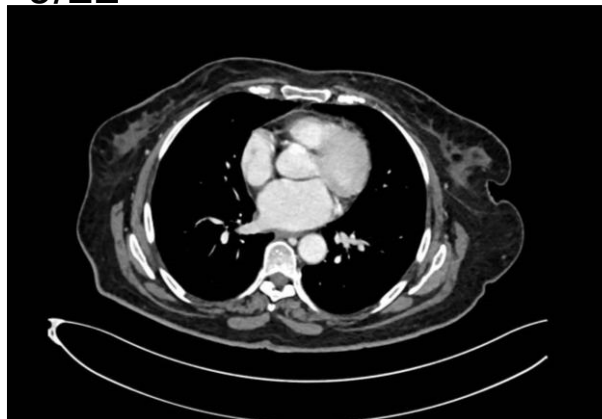
Laparoscopia diagnostica: CARCINOMA SEROSO DE ALTO GRADO de probable origen ovárico, tubárico o peritoneal.

Estudios complementarios p53: alterado (sobreexpresión). WT1: positivo difuso. PAX8: positivo difuso. Calretinina: negativo. Receptores de estrógenos: + focal Receptores de progesterona: negativo. p16: positivo intenso, continuo, difuso. CK7: positivo. CK20 negativo. PTEN: no se evidencia pérdida de expresión. Ki67: 49 %. ARID1A: no se evidencia pérdida de expresión. Líquido ascítico, citología: Citología positiva.

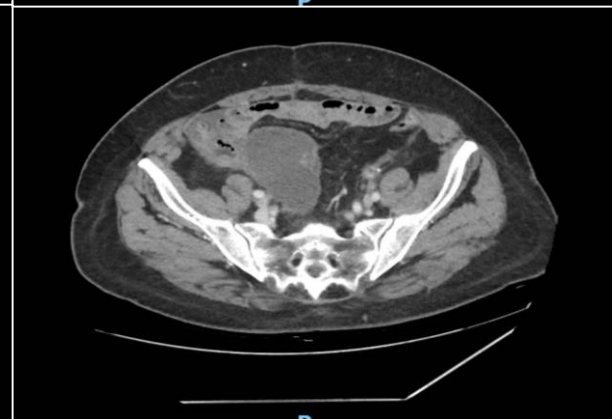
Inicia tratamiento 9/22: CBP + paclitaxel + BVZ x 6 y posterior BVZ de mantenimiento.

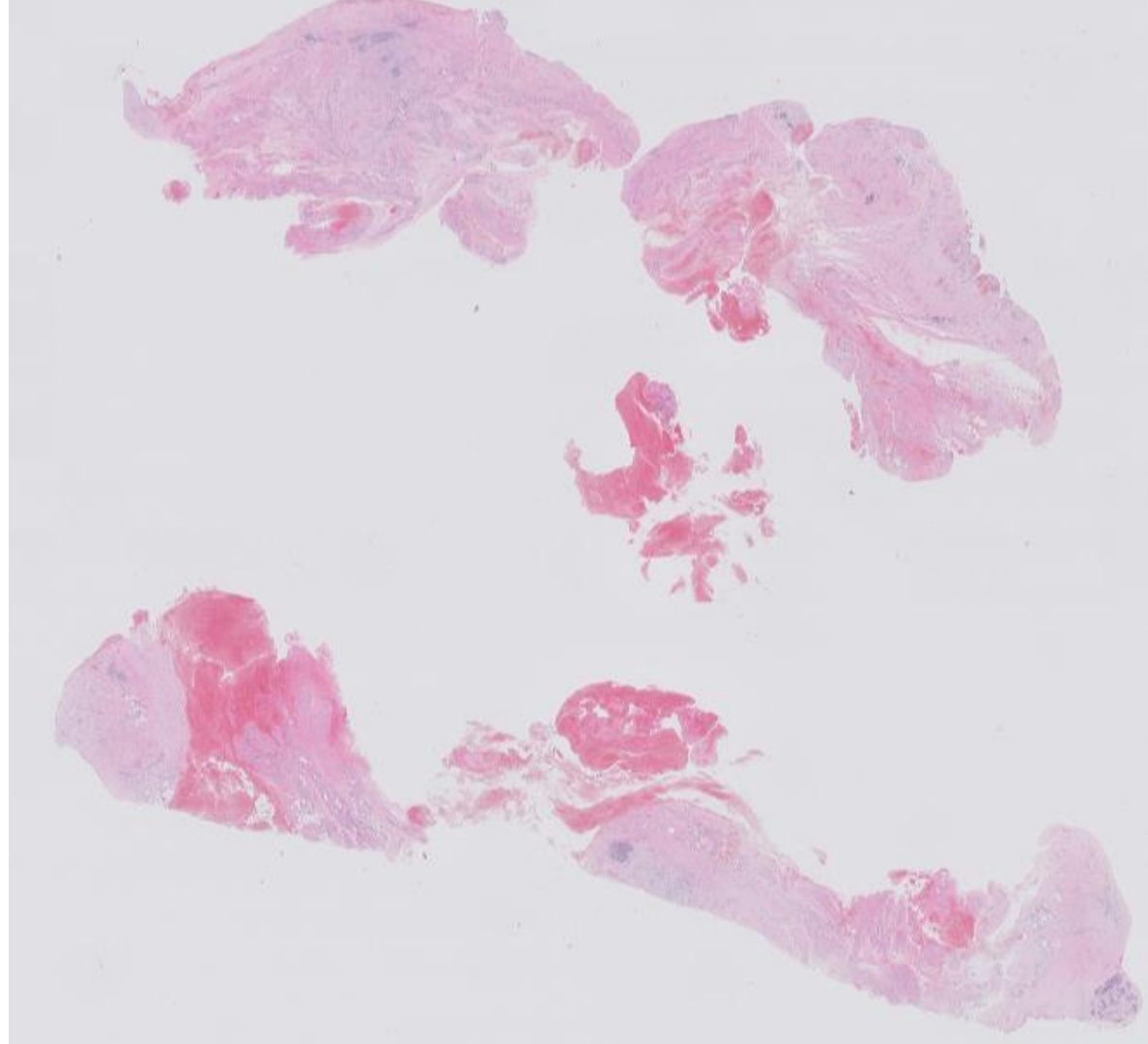
11/22 Mejoría clínica y radiológica, con disminución de los nódulos pulmonares, de la masa pélvica y de la ascitis.

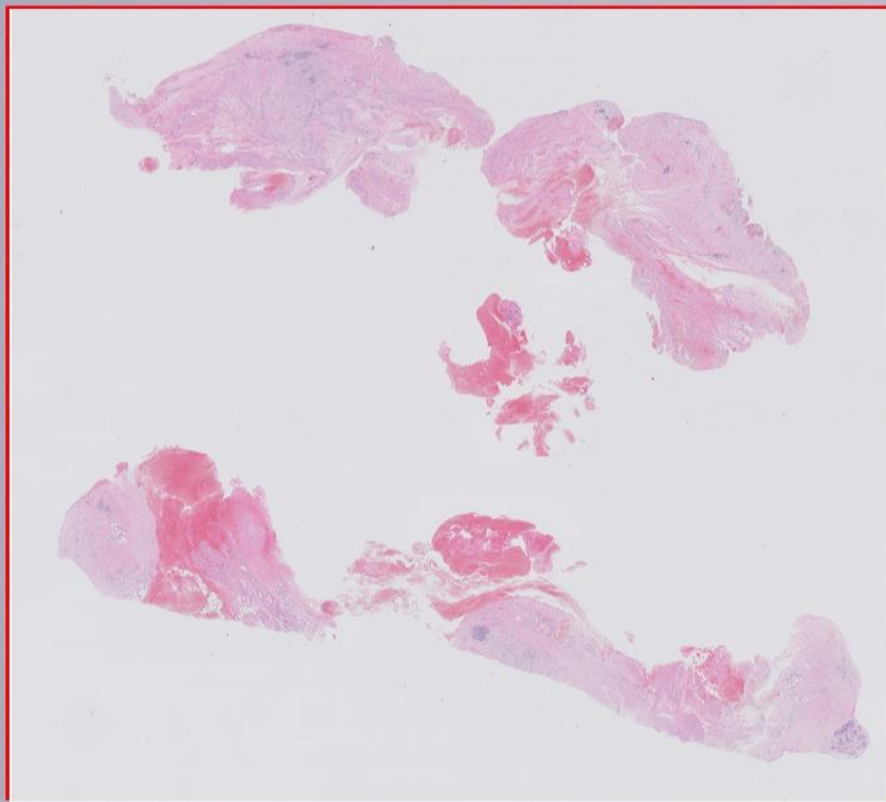
9/22

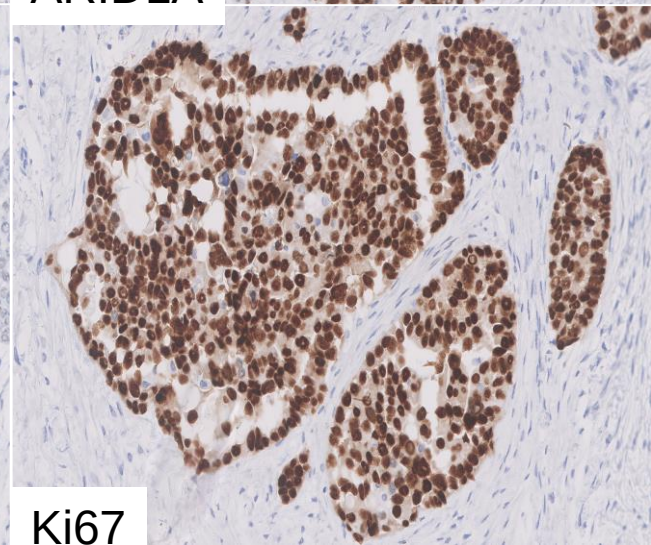
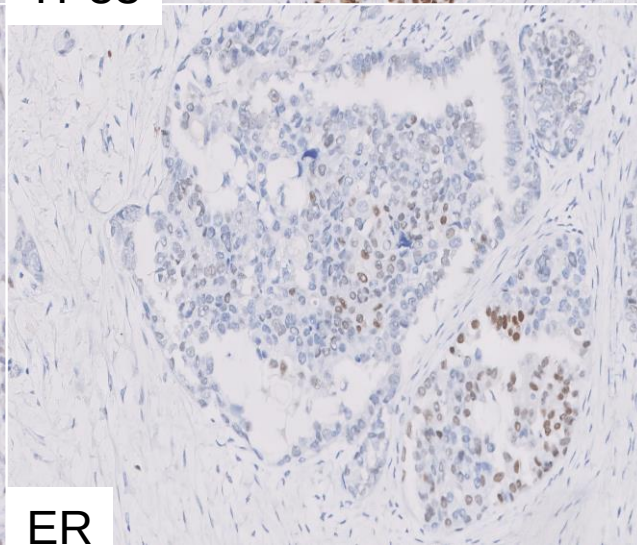
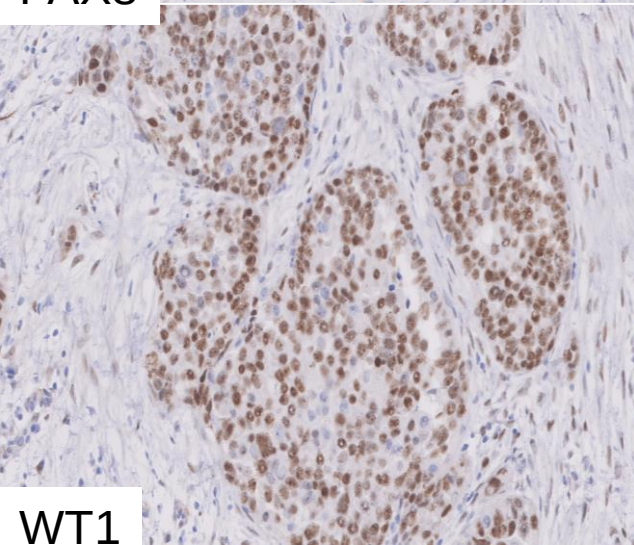
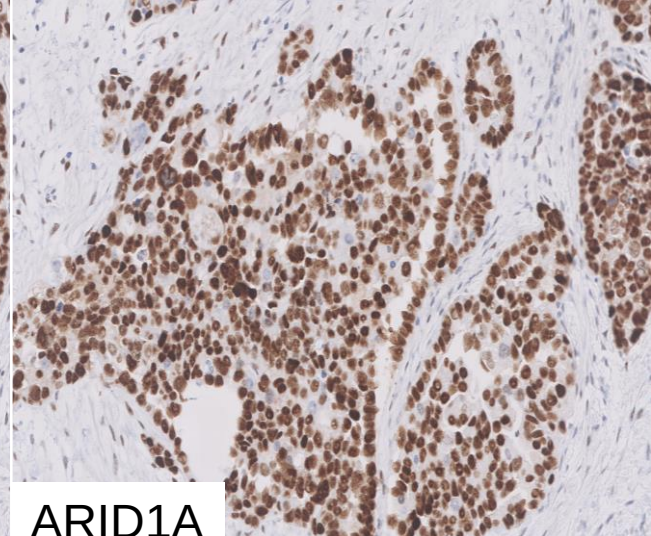
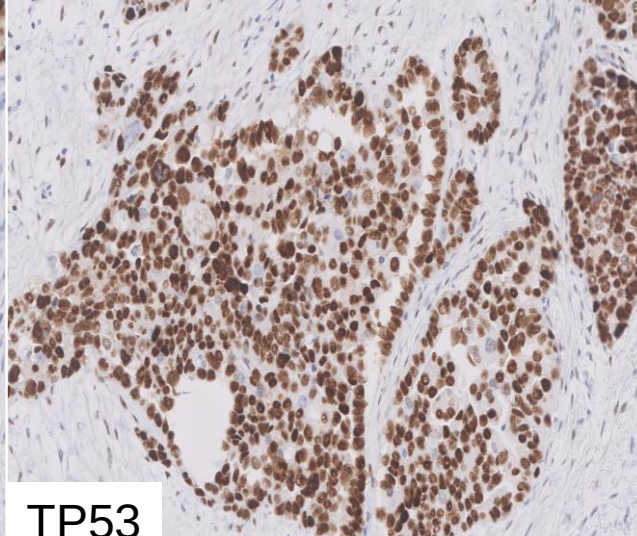
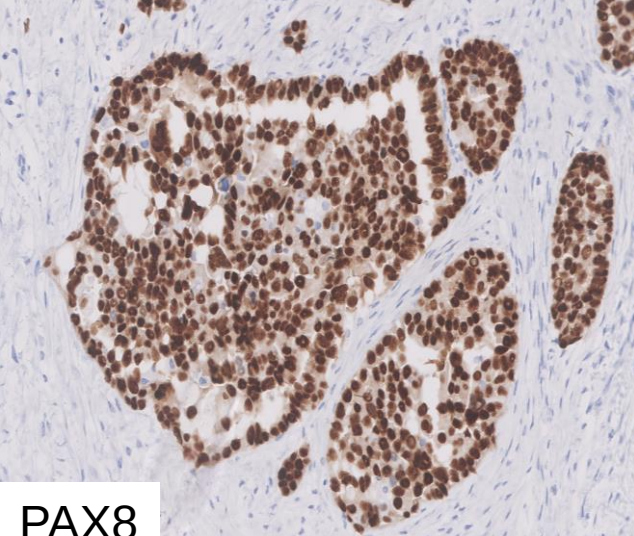


11/22









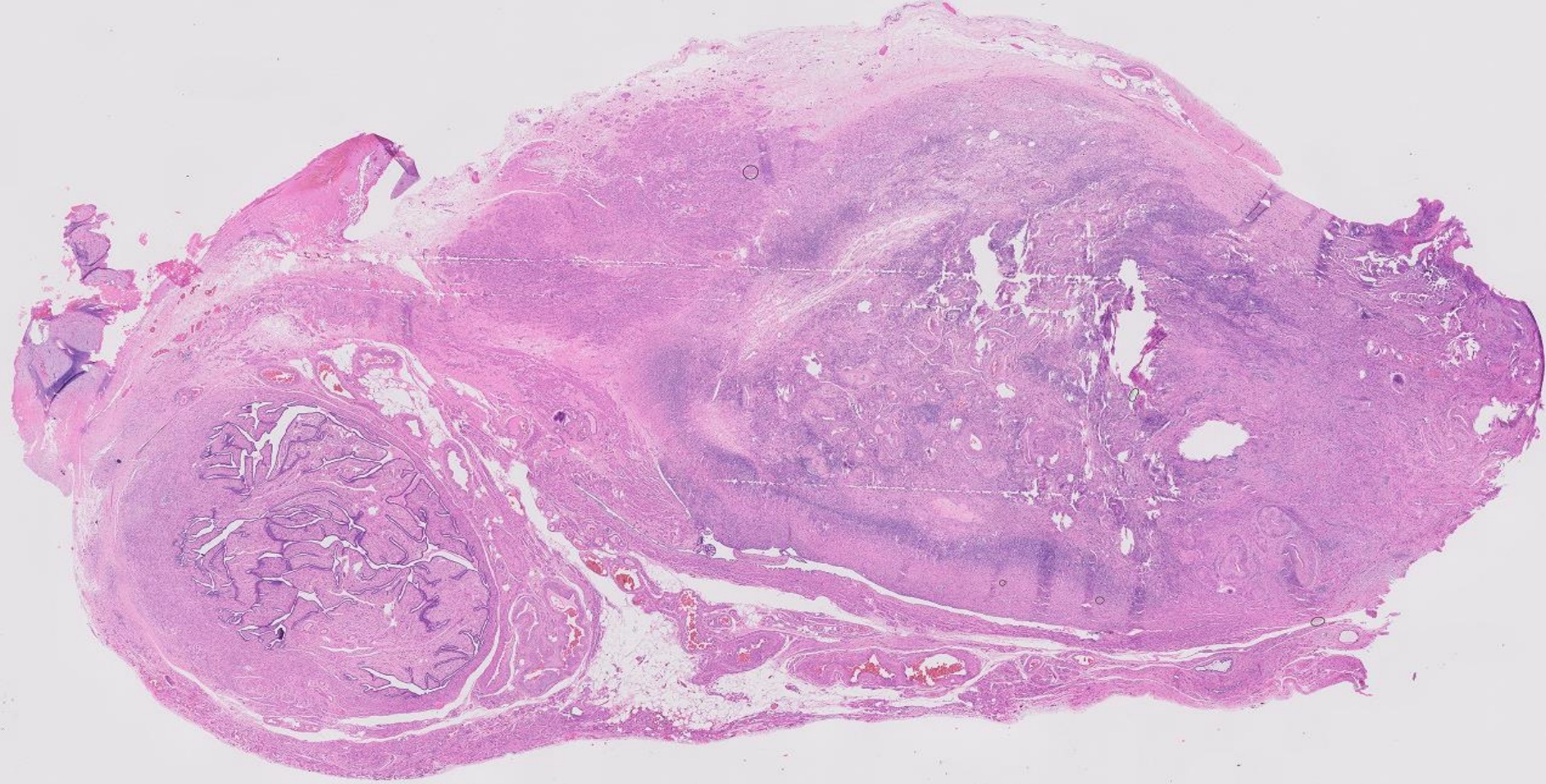
Tratamiento: Cirugía citorreductora tras 6 ciclos + SBRT nódulo pulmonar

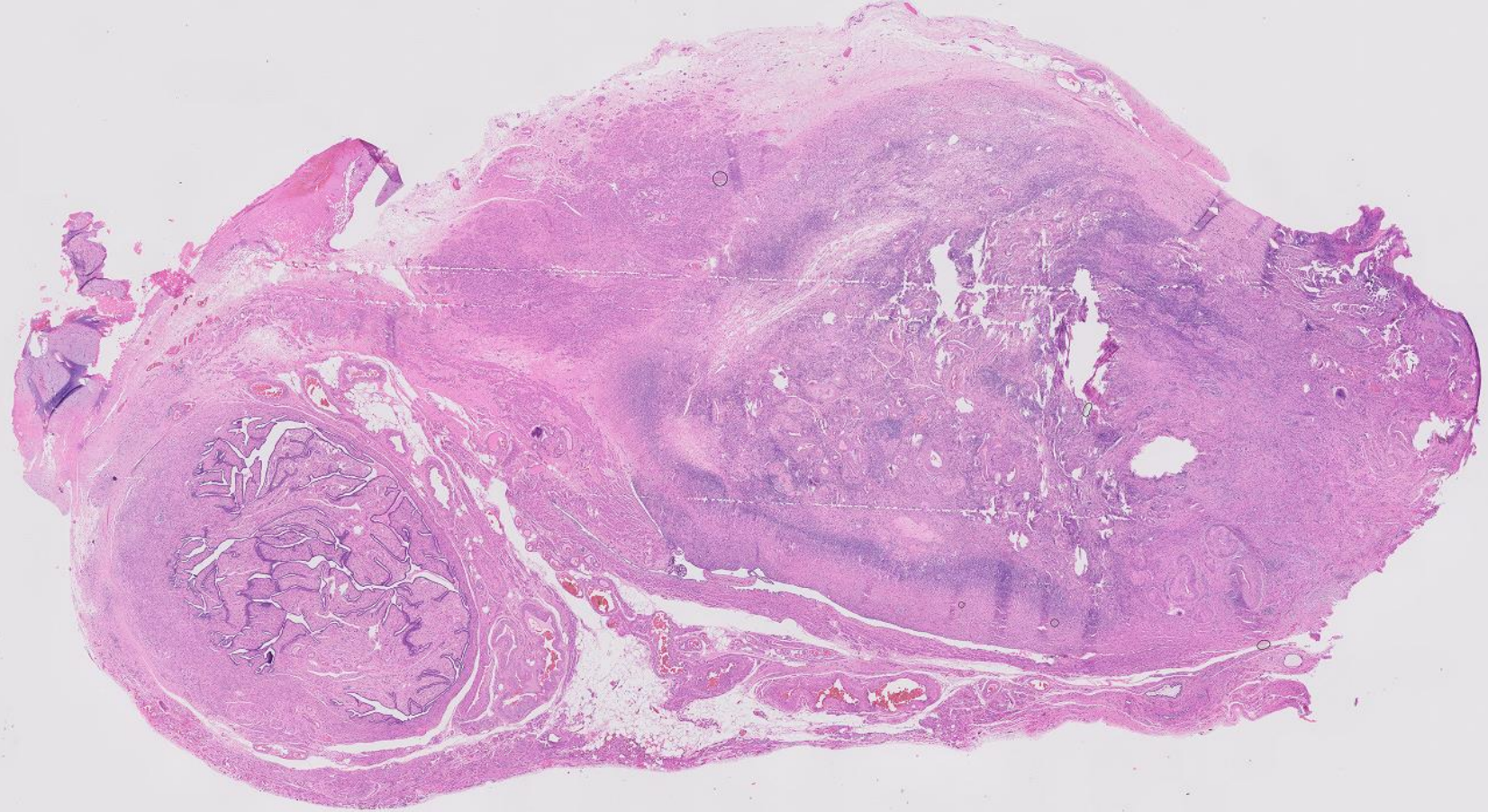
CARCINOMA SEROSO DE ALTO GRADO presente en:

- OVARIO DERECHO: con extensa necrosis tumoral (más del 90 % de toda la tumoración) y presencia de carcinoma residual. Se identifica estroma ovárico residual en la periferia y remanente de pared tubárica atrapada en la fibrosis periférica.
- TROMPA IZQUIERDA: afectación extrínseca de la pared por carcinoma.
- BIOPSIA PERITONEAL: múltiples focos de carcinoma infiltrante (extensión del foco mayor de 12,3 mm).
- LIGAMENTO REDONDO HEPÁTICO: se identifica carcinoma en la grasa alrededor del ligamento (extensión del carcinoma de 3 mm).
- IMPLANTE MESO-COLON: fibrosis con mínimo foco de carcinoma residual (menor de 1 mm).
- EPIPLON: focos de carcinoma infiltrante en las lesiones macroscópicas de 7 cm y 3 cm. Presencia de un ganglio linfático en grasa de epiplon con infiltración por carcinoma.
- No se ha visto invasión linfovascular.

- pTNM (8va ed.2017)/FIGO(2014): ypT3c/(IIIC) pN0 L0 V0

Efecto del tratamiento (2): Respuesta tumoral apreciable en el tumor viable, comprendiendo desde la regresión multifocal o difusa asociada a cambios fibroinflamatorios con tumor viable a la regresión extensa asociada a los cambios fibroinflamatorios con tumor residual multifocal.





SOPHiA DDM Dx HRD status: POSITIVO

Inestabilidad genómica (GIS): POSITIVO

Índice de inestabilidad genómica: 11.5 (valor de inestabilidad genómica mayor o igual a 0 confiere un GIS positivo)

Mutaciones BRCA1/BRCA2:

No se han identificado mutaciones en BRCA1/BRCA2

The screenshot displays the SOPHiA DDM software interface. At the top, a navigation bar includes 'Interpretation 1', 'SAMPLE #364276 623-3211', 'RUN 28/04/2023', 'F_ID RUN23_2023-APR-28', and 'S13'. Below this, a 'Virtual Panel' sidebar on the left shows 'GENES 123', 'VARIANTS 14', 'RETAINED 109', and 'LOW CONFIDENCE 11'. The main content area is divided into several sections: 'Patient' (Herrea Cervajal Garcia [F.ID]), 'Text Information' (SOPHiA DDM HRD status), 'Project' (Interpretation 1, Draft), 'Documents', and 'Clinical Results'. A modal window titled 'SOPHiA DDM HRD status' is open, showing 'Proposed SOPHiA DDM HRD status (For Ovarian cancers) Positive'. It includes a table of biomarkers and a comment field. To the right, 'SNVs/Indels Prediction' shows a green arc with 'D: 123' and 'Prediction'. Below it, 'SNVs/Indels Pathogenicity Flags' shows a green arc with '1' and 'Ch'. The 'Actionability' section shows a green arc with '14: 2' and '15: 2'. The bottom right corner features a 'Test Information' panel with 'ROUTINE ILL10217_FPRE_CH1_huSeq_2 v4.5.360' and a 'Public Databases' list.

SOPHiA DDM HRD status POSITIVE

Proposed SOPHiA DDM HRD status (For Ovarian cancers) Positive

Reported supporting biomarkers	Proposed	Final	
☒ Genomic integrity status	Positive	POSITIVE	View
☒ BRCA Status	Negative	NEGATIVE	View
☒ HRR Status		Not considered	View
☐ CCNE1 Status		Not considered	View

Comment:

Add comment

SNVs/Indels Prediction

D: 123

Prediction

SNVs/Indels Pathogenicity Flags

1^{Ch}

Actionability

14: 2 15: 2

ACTIONABILITY

Test Information

ROUTINE ILL10217_FPRE_CH1_huSeq_2 v4.5.360

Root virtual panel version 1.1

BDS Number

No BDS Number Existing

Public Databases

Database	Version
ClinVar	v02020817
COSSMIC	v2
dbNSFP	v2.9
dbNSFP (hg38)	v4.1
dbSNP	v194
ESP	9400
ESP (hg38)	6000
Ensembl	v0.3.1
G1000	v5.20190902
GenAD EpiCov	v02011121
GenAD	v2.1
GenAD (hg38)	v2.1.1
OMIM	21/05/10
JAX-CKB	v02011210

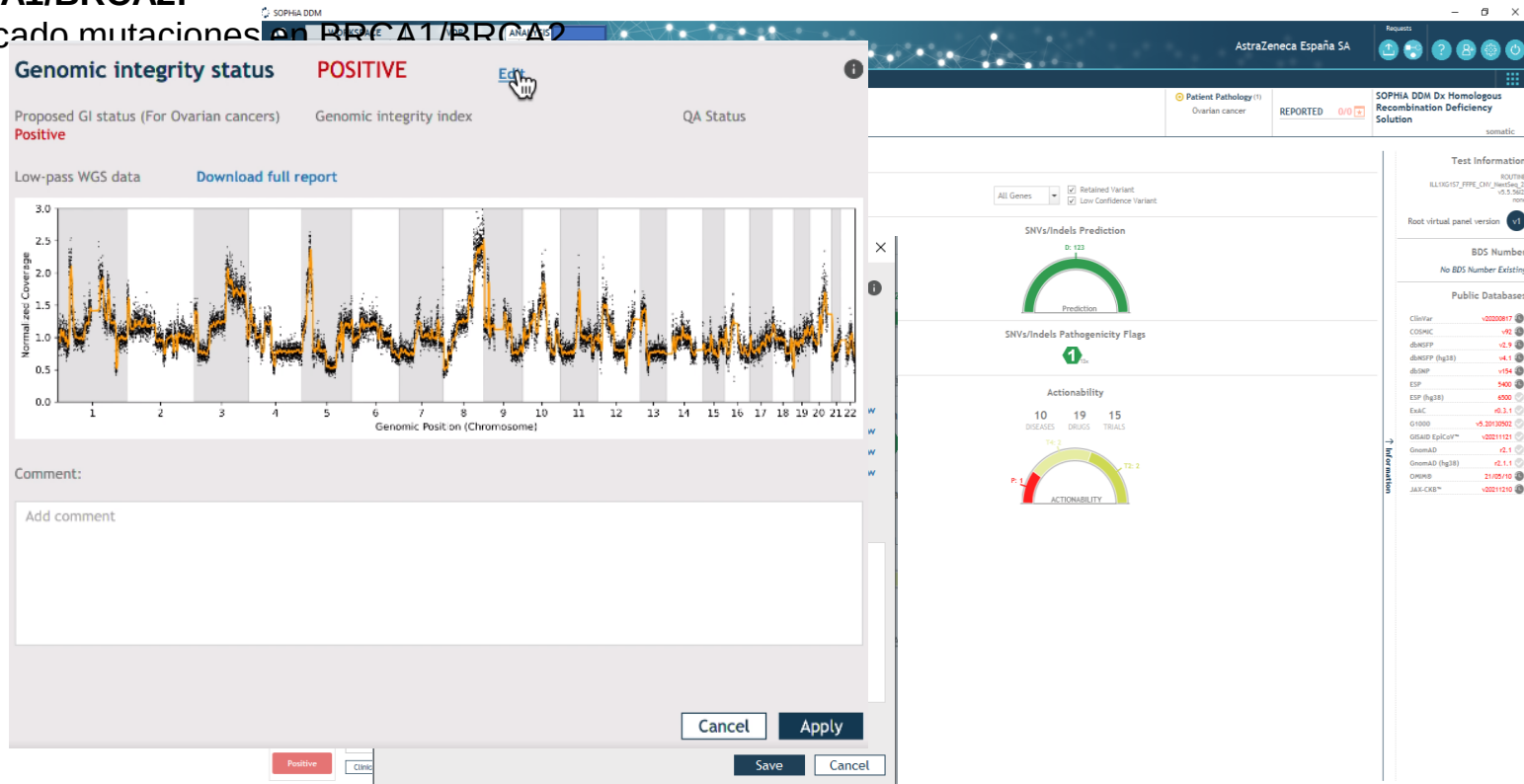
SOPHiA DDM Dx HRD status: POSITIVO

Inestabilidad genómica (GIS): POSITIVO

Índice de inestabilidad genómica: 11.5 (valor de inestabilidad genómica mayor o igual a 0 confiere un GIS positivo)

Mutaciones BRCA1/BRCA2:

No se han identificado mutaciones en BRCA1/BRCA2



SOPHiA DDM Dx HRD status: POSITIVO

Inestabilidad genómica (GIS): POSITIVO

Índice de inestabilidad genómica: 11.5 (valor de inestabilidad genómica mayor o igual a 0 confiere un GIS positivo)

Mutaciones BRCA1/BRCA2:

No se han identificado mutaciones en BRCA1/BRCA2

The screenshot displays the SOPHiA DDM Dx Homologous Recombination Deficiency Solution interface. A modal window titled "Genomic integrity status" is open, showing a "POSITIVE" result for the proposed GI status (For Ovarian cancers). The genomic integrity index is 11.5, and the QA status is "Positive". The interface also shows a "Test Information" panel on the right, including the patient's name, the test name, and a list of public databases. The bottom of the screen features a "Cancel" button and an "Apply" button.

Genomic integrity status **POSITIVE**

Proposed GI status (For Ovarian cancers) **Positive**

Genomic integrity index 11.5

QA Status **Positive**

Low-pass WGS data [Download full report](#)

3.0

Test Information

ROUTINE
ILLINOIS_FPH_CHT_SortSeq_2
v5.5.2020
none

Root virtual panel version 1.0

BDS Number
No BDS Number Existing

Public Databases

Database	Version
ClinVar	v0200817
COSSMIC	v92
dbNSFP	v2.9
dbNSFP (hg38)	v4.1
dbSNP	v194
ESP	9400
ESP (hg38)	8000
Ensembl	v92.1.1
G1000	v5.2019002
IGVAD EpiCov	v0201121
OmniAD	v2.1
OmniAD (hg38)	v2.1.1
OMIM	21/05/10
JAX-CKB	v0201210

Cancel **Apply**

Positive **Cancel** **Save** **Cancel**

Tratamiento: 12 ciclos adicionales de paclitaxel semanal + bevacizumab para seguir con olaparib de mantenimiento

5/23, sin evidencia de progresión

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Gracias por su atención

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