Genómica en el consultorio

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#UroOncoIAF

IAF INSTITUTO ALEXANDER FLEMING

BLADDER CANCER IN LATINAMERICA BLATAM

AAOC 50 DESDE 1967 AÑOS ASOCIACIÓN ARGENTINA DE ONCOLOGÍA CLÍNICA

FUNDACION PARA LA INVESTIGACION Y PREVENCION DEL CANCER FUCA

Uro Target Urooncología

Conflictos de Interés

- Honorarios recibidos de Bayer, AstraZeneca, Raffo, MSD, Bayer, Bristol, Roche, Merck, Pfizer, Nutricia, GBT, IPSEN, FMI.
- Participo como investigador en múltiples estudios clínicos que involucran estas drogas en estas indicaciones

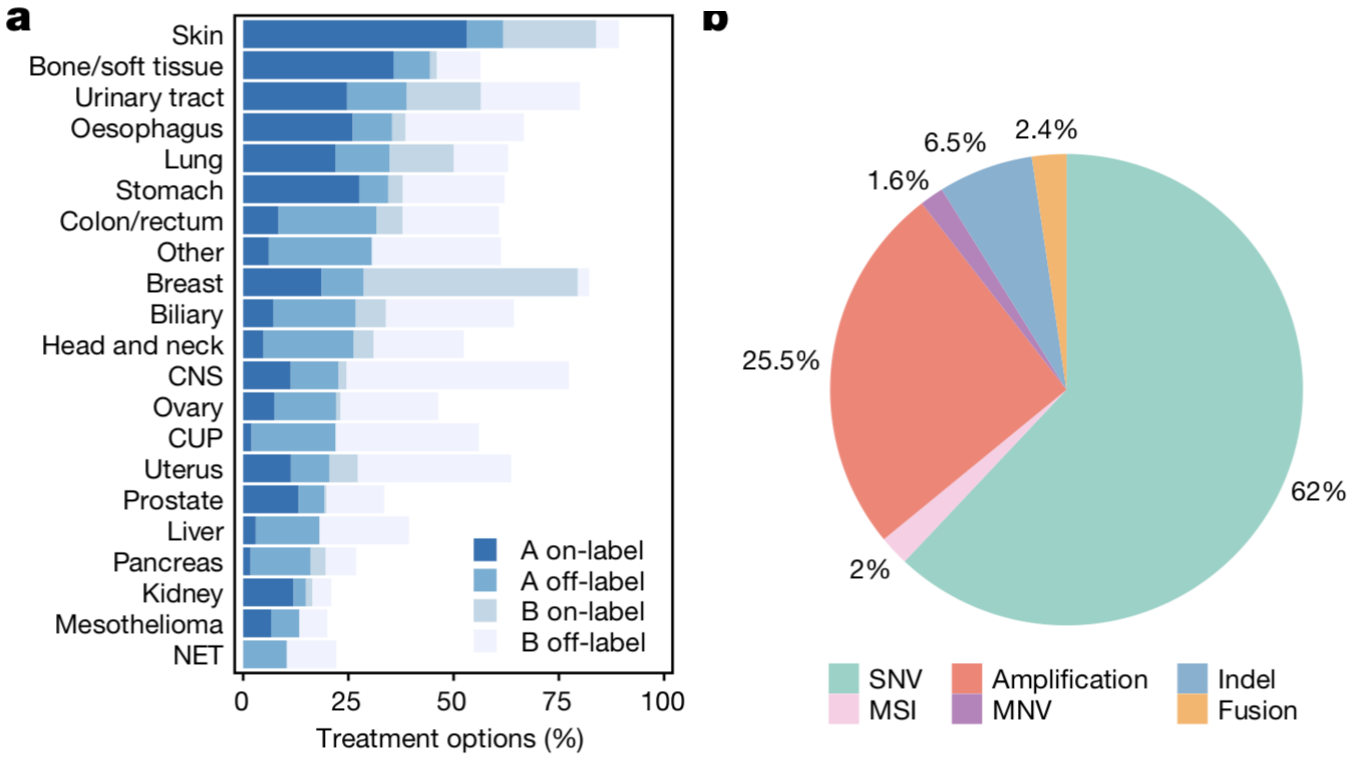
Flujo de trabajo en la genómica aplicada a la Medicina de Precisión

Good *et al,* Genome Biology 2014

Prevalencia de accionabilidad genómica en análisis pan-cancer whole genome

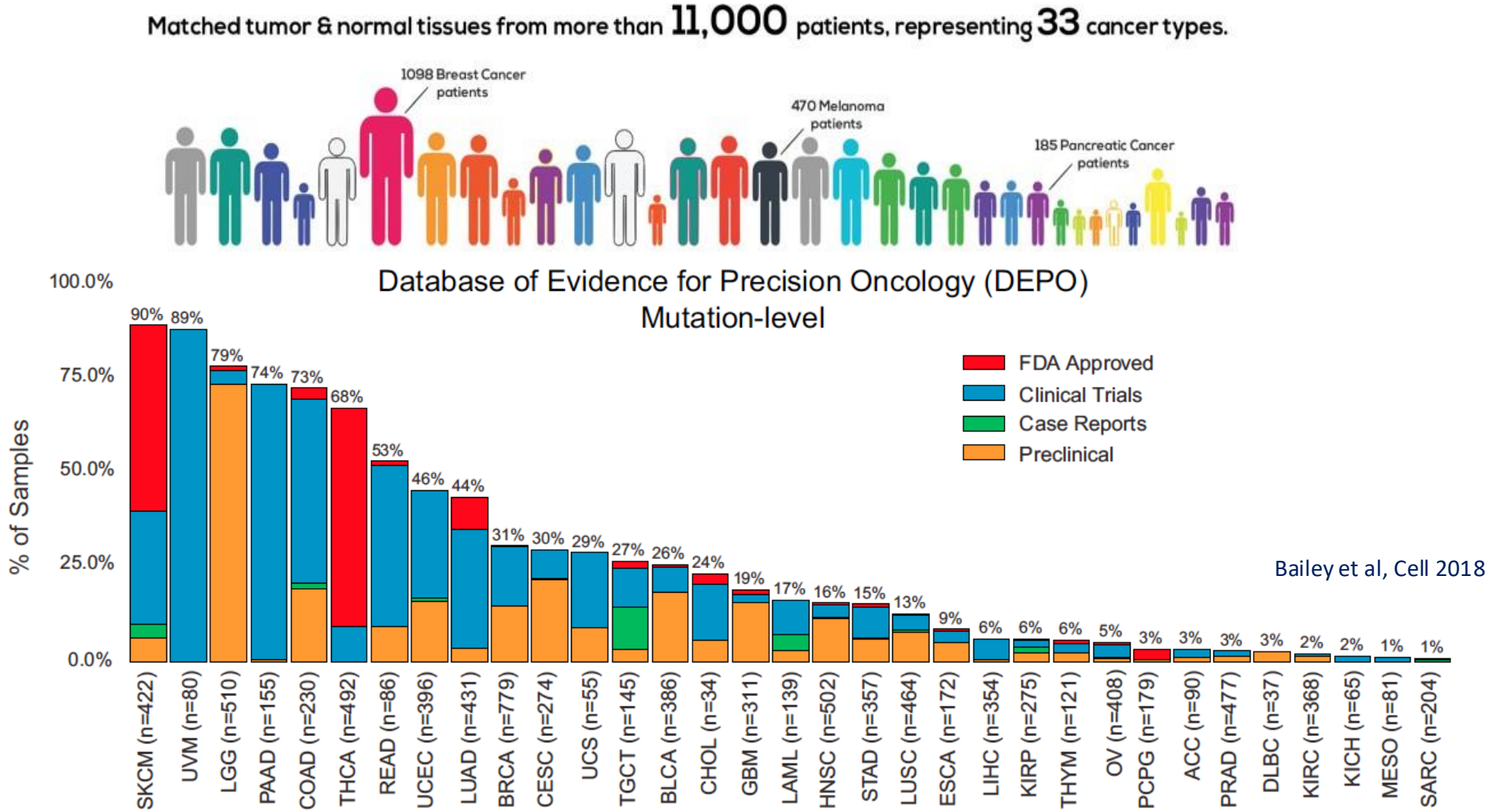
Article

Pan-cancer whole-genome analyses of metastatic solid tumours



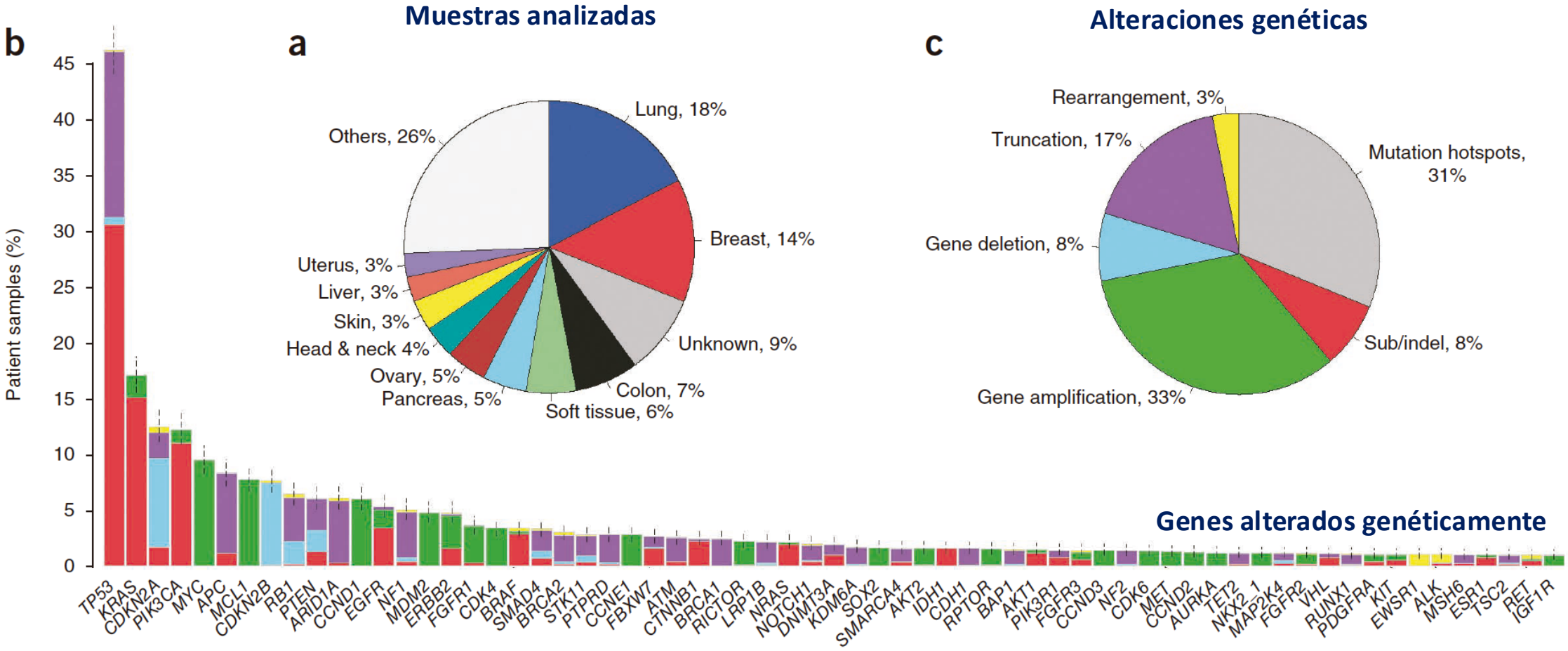
Priestley et al, Nature 2019

Accionabilidad clínica de la base TCGA (The Cancer Genome Atlas)
Whole exome sequencing (n=11,000)



Bailey et al, Cell 2018

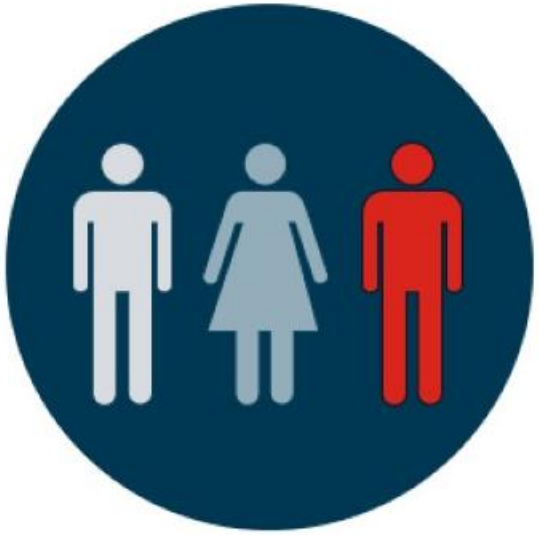
Alteraciones somáticas reveladas por un estudio de Foundation Medicine
Panel de 324 genes (n=10,000)



Frampton and Foundation Medicine coauthors, Nature Biotechnology 2013

La importancia de la Medicina de Precisión

Tratamiento individualizado



Menos efectos adversos

Costo efectiva

Aumento de la sobrevida

Por que es necesario un Molecular Tumor Board

Testeo Genómico

Reporte Genómico

Match terapéutico

Aprobaciones de la EMA y FDA en Medicina de Precisión en Oncología

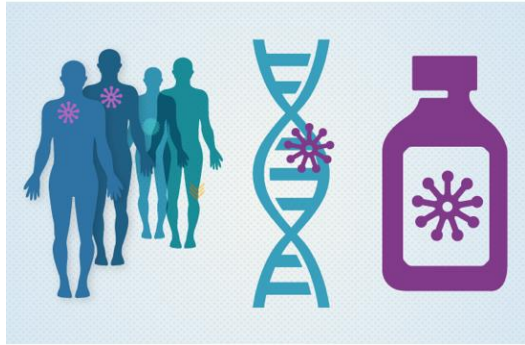


Table 1 FDA and EMA approved biomarker matching targeted drugs and routine molecular pathology testing [2, 3]

Gene/protein	Anticancer agent	Indications	Biomarker	Routine testing
ALK	Crizotinib, ceritinib, alectinib, lorlatinib, brigatinib	NSCLC	*ALK* translocation	FISH, IHC
Androgen receptor (AR)	Abiraterone, enzalutamide, dalurotamide, apalutamide	Prostate cancer	AR expression	IHC
BCL-2	Venetoclax	Chronic myeloid leukemia	BCL-2 protein expression, *BCL-2* amplification/ translocation	IHC, FISH
BCR/ABL	Imatinib, dasatinib, nilotinib, bosutinib, ponatinib	Chronic myeloid leukemia	*BCR/ABL1* fusion	IHC (FISH, DNA/ RNA sequencing), PCR[1]
BRAF	Dabrafenib+trametinib, vemurafenib+cobimetinib, encorafenib+binimetinib	Melanoma, NSCLC, anaplastic thyroid cancer, hairy cell leukemia	*BRAF* V600E/K mutations	IHC, PCR[1], DNA sequencing
BRCA	Olaparib, talazoparib, rucaparib	Breast cancer, ovarian cancer	Germline/somatic *BRCA* 1/2 mutations	DNA sequencing
C-KIT, PDGFR	Imatinib	Gastrointestinal stromal tumor	*c-KIT* Exon 9 and 11 mutations, *PDGFR* mutations	IHC, DNA sequencing
PDGFRB	Imatinib	Myelodysplastic/ myeloproliferative syndromes	*PDGFRB* rearrangement	FISH
Estrogen/ progesterone receptors (ER/PR)	Tamoxifen, raloxifene, fulvestrant, toremifine	Breast cancer	ER/PR expression	IHC
erBB2/HER-2	Trastuzumab, pertuzumab, ado-trastuzumab, emtansine, neratinib	Breast cancer, gastric cancer	HER-2 protein expression, *HER-2* amplification	IHC, FISH
EGFR	Gefitinib, erlotinib, afatinib, dacomitinib	NSCLC	*EGFR* exon 19 deletion, exon 21 L858R mutation	DNA sequencing, PCR[1]
	Osimertinib		*EGFR* T790M mutation	
FGFR2/3	Erdafitinib	Bladder cancer	*FGFR3* mutations, *FGFR2/3* fusions	DNA sequencing, FISH
FLT3	Midostaurin, gilteritinib	Acute myeloid leukemia	*FLT3* mutations	DNA sequencing, PCR[1]
IDH1/2	Ivosidenib, enasidenib	Acute myeloid leukemia	*IDH1/2* mutations	IHC, DNA sequencing
MET	Crizotinib (breakthrough designation)	NSCLC	*MET* amplification, *MET* exon 14 alterations	FISH, DNA/RNA sequencing
MSI-H or dMMR	Pembrolizumab	MSI-H or dMMR solid tumors	MLH1, MSH2, MSH6, PMS2 protein expression, MSI high	IHC, DNA sequencing, PCR[1]
	Nivolumab and ipilimumab	Colorectal cancer		
NTRK	Larotrectinib, entrectinib	Solid tumors with NTRK fusions	*NTRK* protein expression, *NTRK* fusion	IHC, FISH, DNA/RNA sequencing
PI3KCA	Alpelisib	Breast cancer	*PI3KCA* mutation	DNA sequencing
PI3K (alpha and delta)	Copanlisib	Follicular lymphoma	*PI3K* mutation	DNA sequencing
PI3K (delta and gamma)	Duvelisib	Chronic lymphocytic leukemia, small lymphocytic lymphoma	*PI3K* mutation	DNA sequencing
RAS (negative predictor)	Cetuximab, panitumumab	Colorectal cancer	*KRAS/NRAS* wildtype	DNA sequencing
RET	LOXO-292 (breakthrough designation)	NSCLC, medullary thyroid cancer	*RET* fusion, *RET* mutation	FISH, DNA/RNA sequencing
ROS1	Crizotinib, entrectinib	NSCLC	*ROS* translocation	FISH, DNA/RNA sequencing

AR androgen receptor, *dMMR* deficient mismatch repair, *ER* estrogen receptor, *FISH* fluorescence in situ hybridization, *IHC* immunohistochemistry, *MSI-H* high levels of microsatellite instability, *NSCLC* non-small cell lung cancer, *PR* progesterone receptor

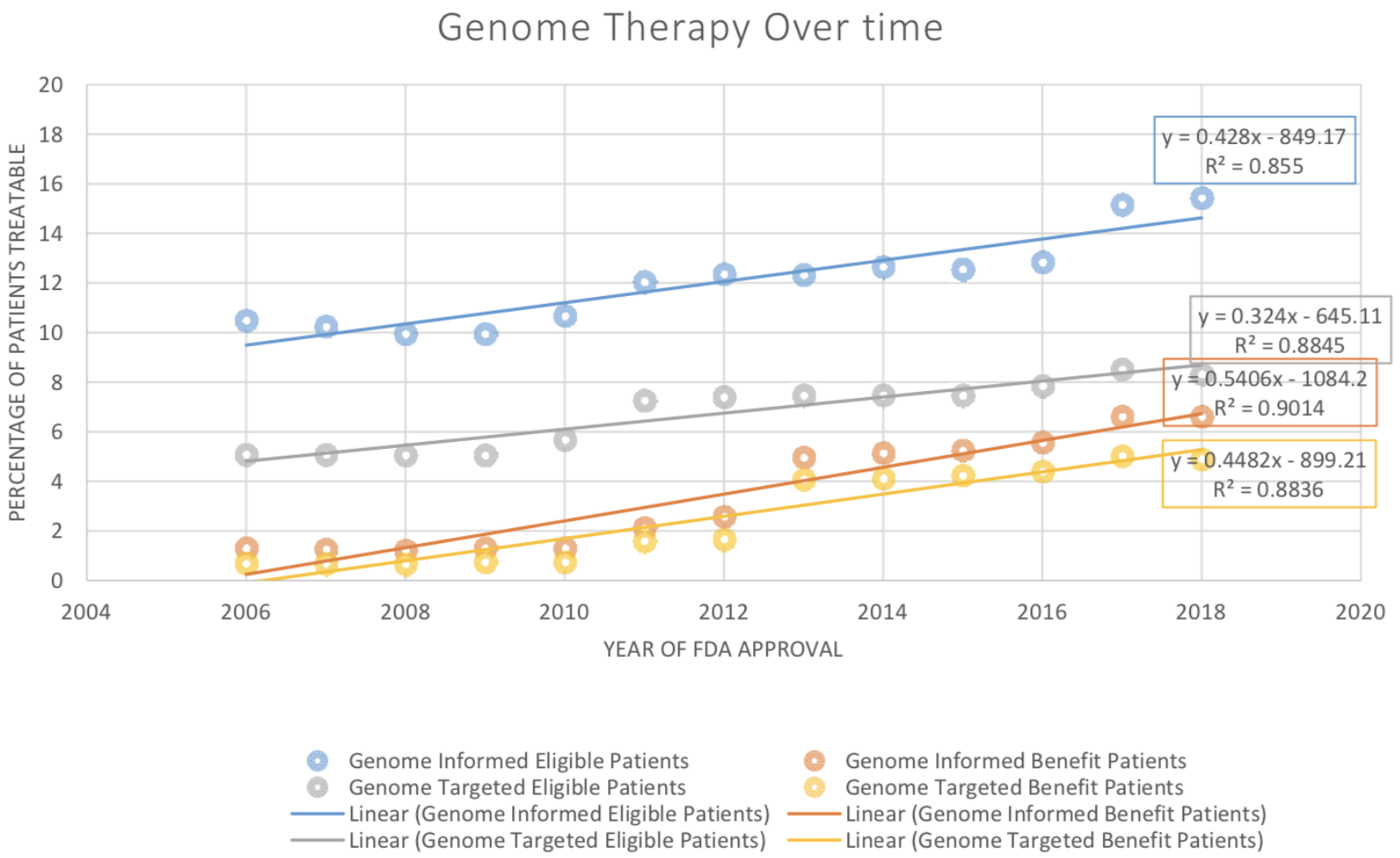
[1]Applications of PCR may include fragment analysis, quantitative PCR, and restriction fragment length polymorphisms

Malone *et al,* Genome Medicine, 2020

Terapias emergentes “Genomics-guided”

ATM mut	Prostate	Olaparib
BRAF L596/K601 mut	Melanoma	Trametinib
CDK4 amp	Sarcomas	Abemaciclib, Palbociclib, Ribociclib
ESR1 mut	Breast	Fulvestrant
EZH2 mut	Lymphoma	Tazemetostat
HRAS mut	Head & Neck	Tipifarnib
JAK2 fus	Leukemia	Ruxolitinib
KRAS G12C mut	Lung	AMG510
MAP2K1 mut	Ovarian, Melanoma, Lung	Cobimetinib, Trametinib
MTOR mut	Renal, Bladder	Everolimus, Temsirolimus
NRAS mut	Melanoma	Cobimetinib, Binimetinib
PALB2 mut	Pancreas, Prostate	Olaparib
PTCH1 mut	Skin, Embryonal	Vismodegib, Sonidegib
RET fus/mut	Lung, Thyroid	Selpercatinib, pralsetinib

Beneficio terapéutico basado en terapias dirigidas



2019

~17% Genome-informed

~11% Genome-targeted

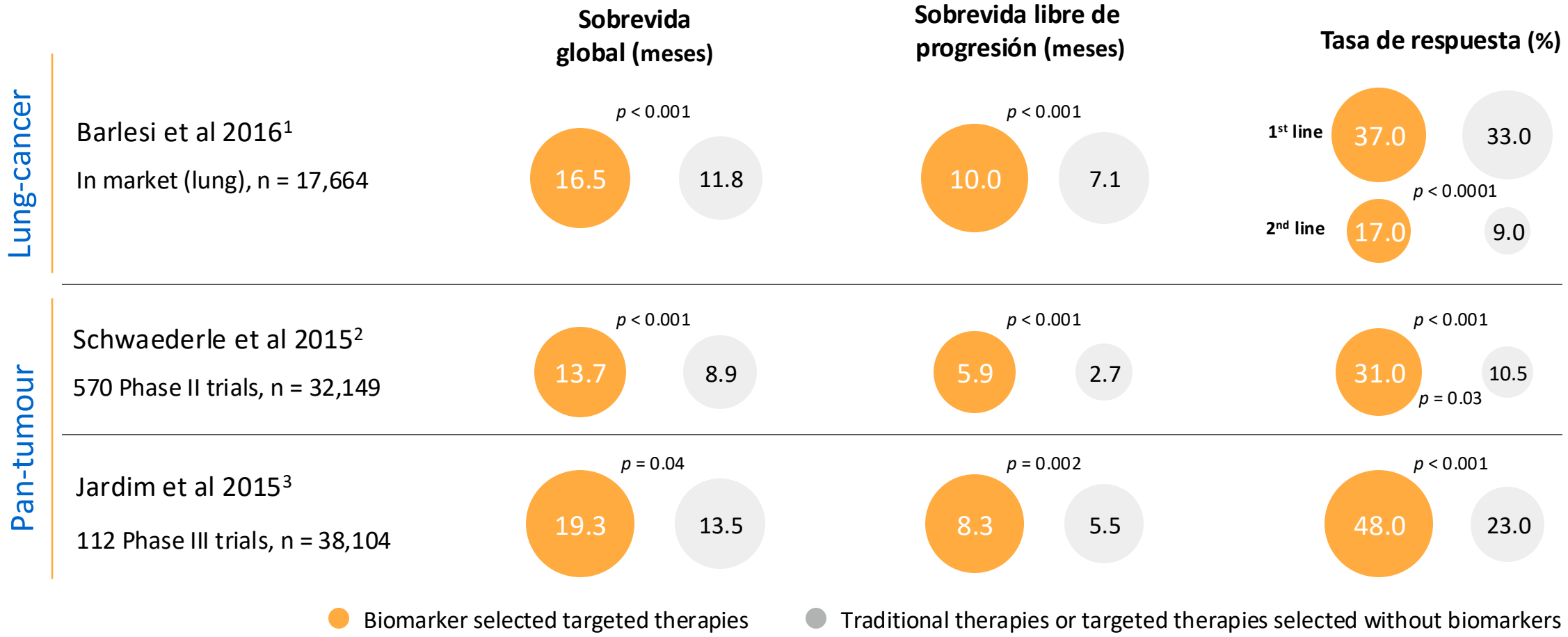
~8% Benefit genome-informed

~6% Benefit genome-targeted

~50% benefit

Marquart et al, JAMA Oncology, 2018

Los ensayos clínicos con selección de pacientes por biomarcadores tienen mejores resultados que los estudios sin biomarcadores



1. Barlesi, F., et al. (2016) *Lancet* 87:1415-26;
2. Schwaederle, M., et al. (2015) *JCO* 33:3817-25;
3. Jardim, D.L., et al. (2015) *J Natl Cancer Inst* 107.

Transformación de la Oncología en los últimos años

¿Cómo ponemos esto en práctica?

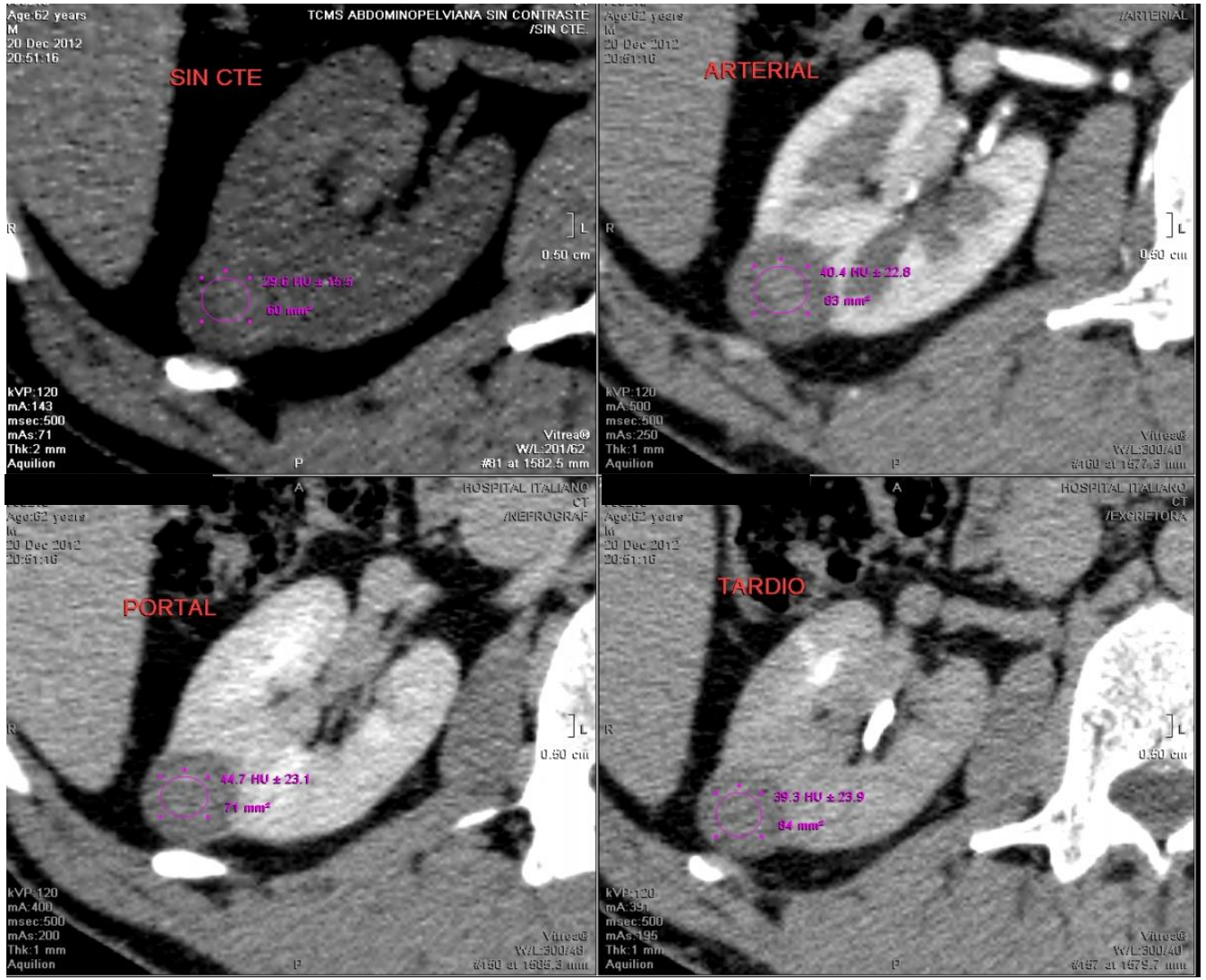
Caso Clínico

Paciente DD, de 45 años

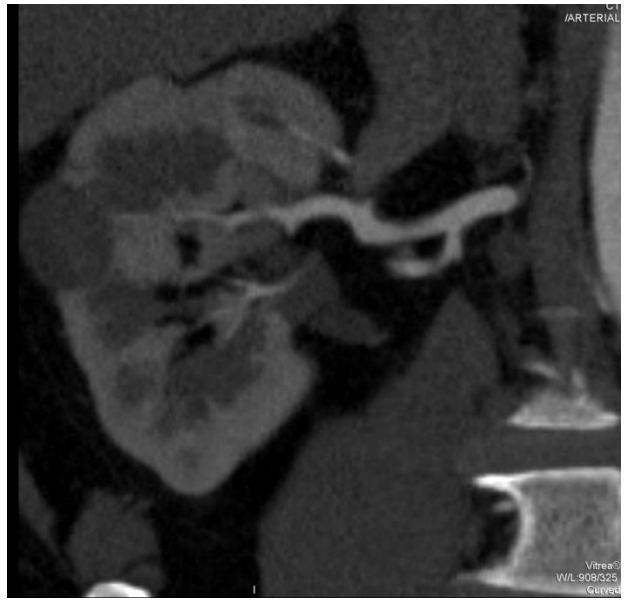
2013:

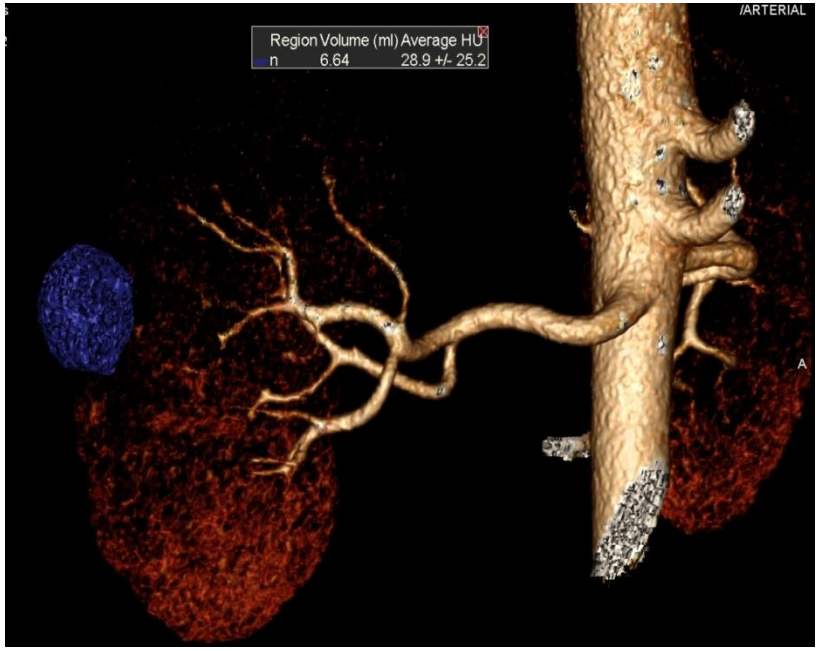
Por dolor en fosa lumbar

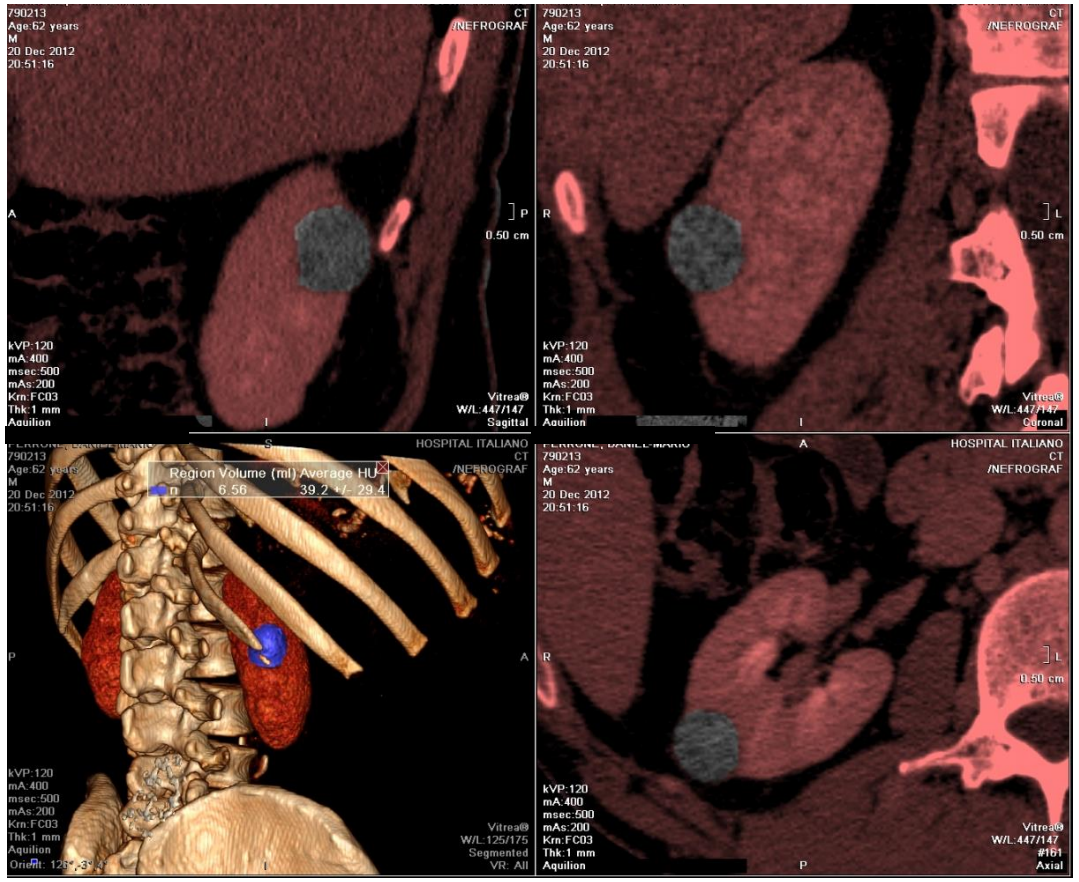
Eco abdominal:



Caso Clínico







- Marzo 2013: Nefrectomía parcial laparoscópica.
- AP: CA DE CELULAS CLARAS (GRADO DE FUHRMAN III) pT2. MARGEN LIBRE.

Caso Clínico

2015: Recaída ganglionar retroperitoneal: cirugía R0

2017: Recaída ganglionar múltiples sitios. Inicia Sunitinb

Toxicidad: mucositis, astenia, diarrea, HTA, coloración amarillenta de la piel, elevación de transaminasas.
Ajuste de dosis, (reducción), esquema 2-1,

Caso Clínico

Dic 2018: Progresión adenopatías retroperitoneales.

Conducta:

1: Segunda con Nivolumab? ✓

2: Segunda Línea con Axitinib?

3: Lenvatinib/everolimus?

4: Perfilado molecular del tumor?

FOUNDATIONONE®

Patient Name [redacted]

Report Date
28 November 2017

Tumor Type
Kidney renal carcinoma

Date of Birth	08 September 1972	**Medical Facility**	Instituto Alexander Fleming		
Sex	Female	**Ordering Physician**	Martin Angel	**Specimen Received**	03 November 2017
FMI Case #	TRF286346	**Additional Recipient**	Not Given	**Specimen Site**	Not Provided
Medical Record #	Not Given	**Medical Facility ID #**	201693	**Date of Collection**	09 June 2017
Specimen ID	134895/2B	**Pathologist**	Not Provided	**Specimen Type**	Block

ABOUT THE TEST:

FoundationOne™ is a next-generation sequencing (NGS) based assay that identifies genomic alterations within hundreds of cancer-related genes.

PATIENT RESULTS

- 7 genomic findings
- 2 therapies associated with potential clinical benefit
- 0 therapies associated with lack of response
- 11 clinical trials

TUMOR TYPE: KIDNEY RENAL CARCINOMA

Genomic Alterations Identified†

NF2 splice site 241-6_266del32
FH splice site 904+1G>A
GNAS P308L
LRP1B loss exons 4-20
MLH1 K618del – subclonal*

Additional Findings†

Microsatellite status MS-Stable
Tumor Mutation Burden TMB-Low; 1 Muts/Mb

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THERAPEUTIC IMPLICATIONS

Genomic Findings Detected	FDA-Approved Therapies (in patient's tumor type)	FDA-Approved Therapies (in another tumor type)	Potential Clinical Trials
NF2 splice site 241-6_266del32	Everolimus Temsirolimus	None	Yes, see clinical trials section
FH splice site 904+1G>A	None	None	Yes, see clinical trials section
GNAS P308L	None	None	None
LRP1B loss exons 4-20	None	None	None
Microsatellite status MS-Stable	None	None	None
MLH1 K618del - subclonal	None	None	None

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Dic 2018: Progresión, nódulos pulmonares y adenopatías retroperitoneales.

Conducta:

1: Segunda con Nivolumab?

2: Segunda Línea con Axitinib?

3: Lenvatinib/everolimus? ✓

Cambió la conducta

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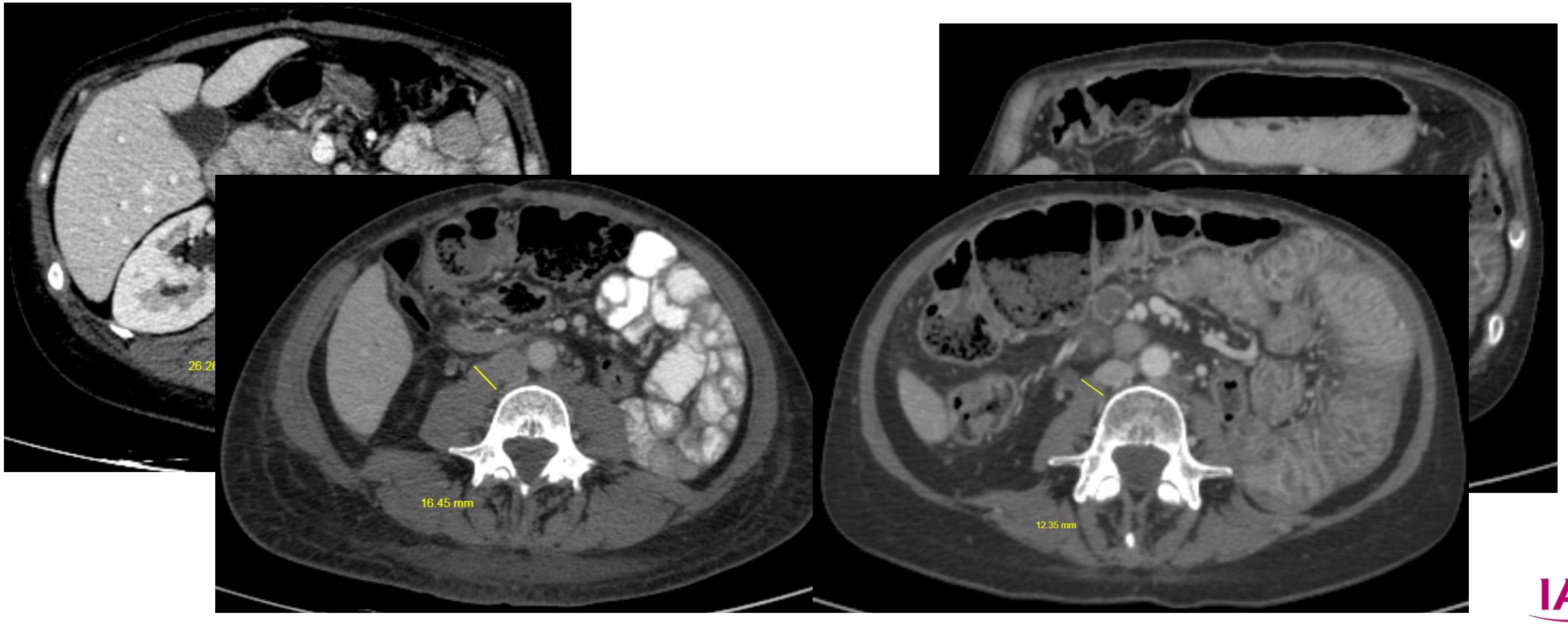
Cambió la conducta

dec 2018

06 feb 2019



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Caso Clínico

HG, 63 años
En 2014: diagnóstico de angiosarcoma de cuero cabelludo.
Resección completa.
2017: metástasis esplénica y hepática.
Entre 2017 y 2018:
1° línea: Doxorrubicina
2° Línea: Paclitaxel semanal
3° Línea: Pazopanib
4° Línea: Ifosfamida

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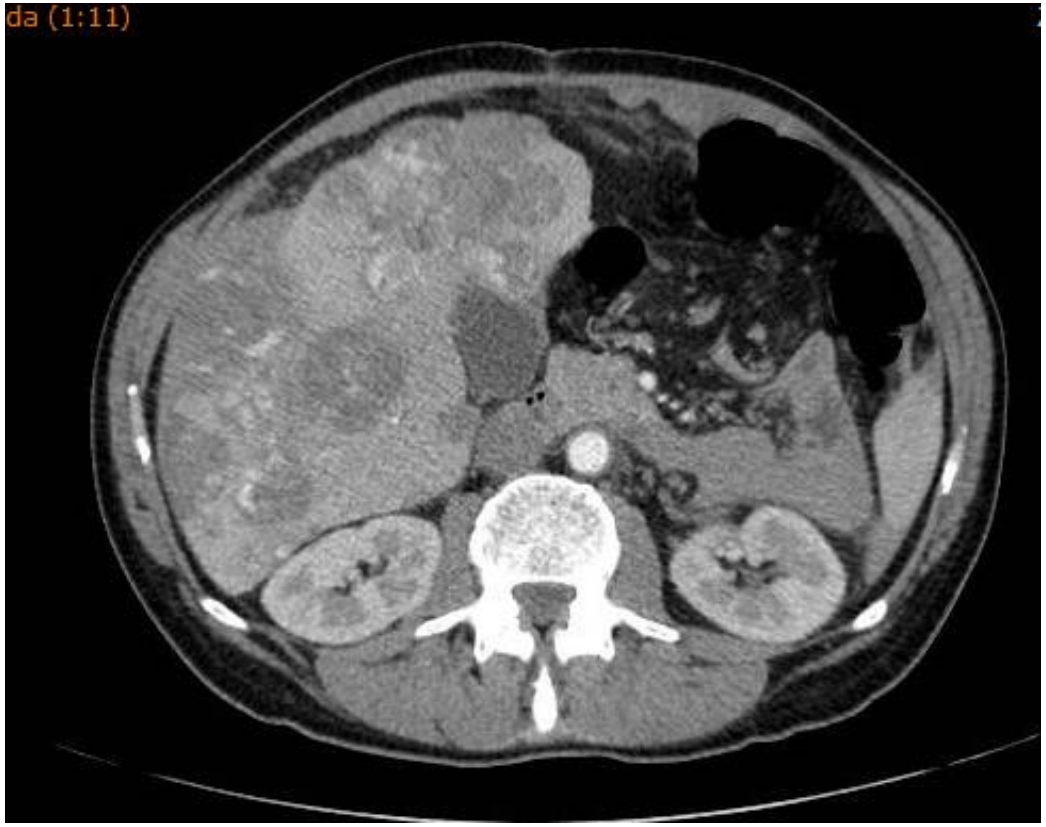
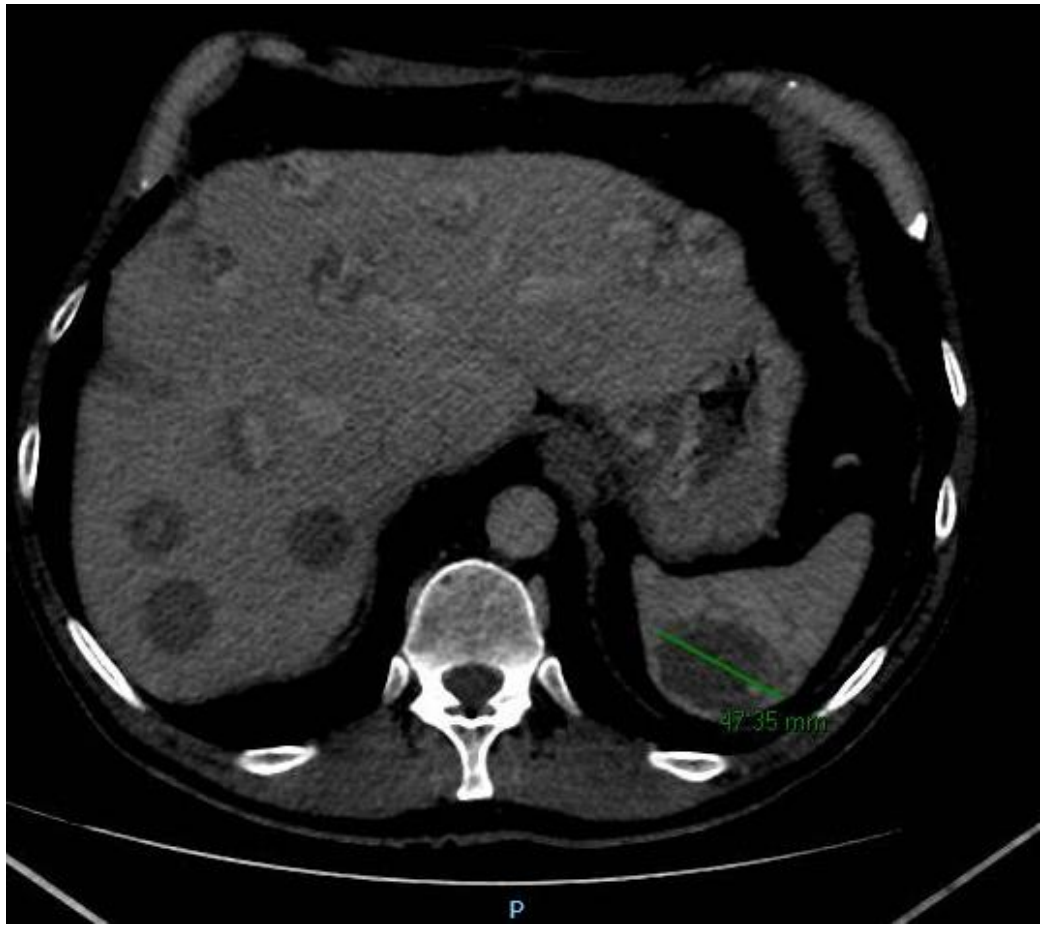
Caso Clínico

HG, 63 años. 2014: angiosarcoma de cuero cabelludo. Resección completa.
2017: metástasis esplénica y hepática. 1° línea: Doxorrubicina; 2° Línea: Paclitaxel W;
3° línea: Pazopanib; 4° Línea: Ifosfamida.





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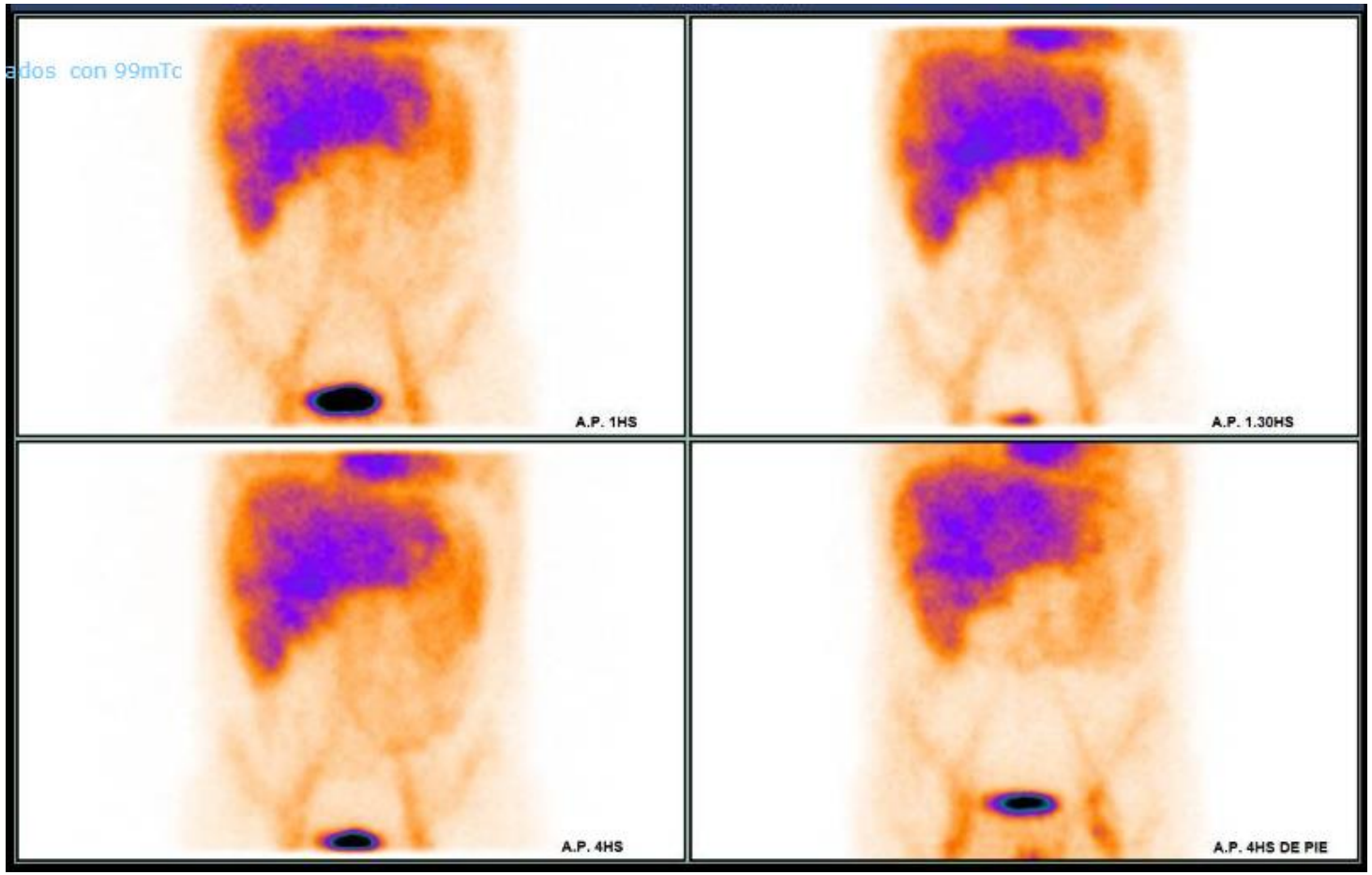

γScan:

GR marcados:

Positivo para sangrado de las lesiones Hepáticas

ECOG PS: 2

GOT/GPT x 2

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Caso Clínico

FOUNDATIONONE Heme

Patient Name	Report Date	Tumor Type
[redacted]	19 April 2018	Liver angiosarcoma

Date of Birth	06 August 1956	**Medical Facility**	Instituto Alexander Fleming		
Sex	Male	**Ordering Physician**	Martin Angel	**Specimen Received**	23 March 2018
FMI Case #	TRF332580	**Additional Recipient**	Not Given	**Specimen Site**	Liver
Medical Record #	250342	**Medical Facility ID #**	201693	**Date of Collection**	02 February 2018
Specimen ID	BS-18-D12878 (84101)	**Pathologist**	Not Provided	**Specimen Type**	Block

ABOUT THE TEST:

FoundationOne Heme™ is a next-generation sequencing (NGS) based assay that identifies genomic alterations within hundreds of cancer-related genes.

PATIENT RESULTS

17 genomic findings

9 therapies associated with potential clinical benefit

0 therapies associated with lack of response

29 clinical trials

TUMOR TYPE: LIVER ANGIOSARCOMA

Genomic Alterations Identified†

FGFR3 K650T
PIK3CA P104L, P124L
ARFRP1 amplification
CDKN2A p16INK4a A57fs*89 and p14ARF P72fs*100, p16INK4a Q50*
EPHA3 E930K
GNAS amplification
MAP3K14 splice site 1420_1420+1GG>AA
PCLO S4231F
TOP1 amplification
TP53 L265R, R267W, Y205D
ZNF217 amplification

Additional Findings†

Microsatellite status MS-Stable
Tumor Mutational Burden TMB-High; 59 Muts/Mb

† For a complete list of the genes assayed and performance specifications, please refer to the Appendix

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Caso Clínico

please refer to the Appendix

THERAPEUTIC IMPLICATIONS

Genomic Findings Detected	FDA-Approved Therapies (in patient's tumor type)	FDA-Approved Therapies (in another tumor type)	Potential Clinical Trials
FGFR3 K650T	Pazopanib	Ponatinib	Yes, see clinical trials section
PIK3CA P104L, P124L	None	Temsirolimus Everolimus	Yes, see clinical trials section

Progresión

ECOG 2

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Invest New Drugs (2013) 31:1602–1608
DOI 10.1007/s10637-013-0028-7

PHASE II STUDIES

Multicenter phase II
with metastatic or re
sarcomas after failur

Changhoon Yoo · Jeeyun Lee · Sun Y
Kyong Hwa Park · Tae Min Kim · Yu
Hyo Jin Lee · Kyung Hee Lee · Jin-H

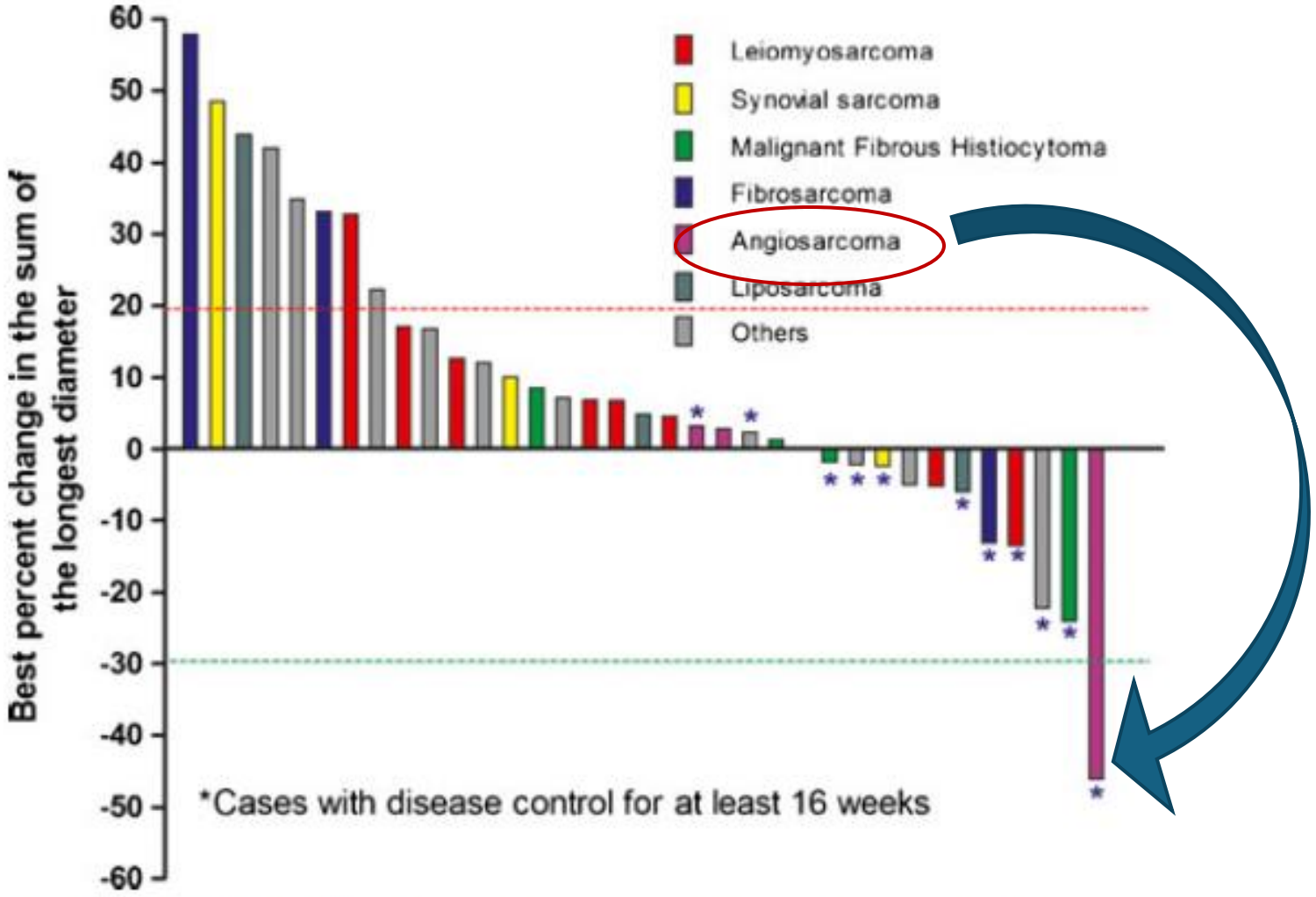

Fig. 1 Waterfall plots of the best percent change in the sum of the longest tumor diameter

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Toxicidad

Table 3 Adverse events occurring in ≥10 % of patients

Adverse events	Total (n = 41)			
	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	11 (27 %)	0 (0 %)	0 (0 %)	0 (0 %)
Anemia	9 (22 %)	1 (2 %)	0 (0 %)	0 (0 %)
Thrombocytopenia	9 (22 %)	2 (5 %)	1 (2 %)	0 (0 %)
Pain	5 (12 %)	13 (32 %)	2 (5 %)	0 (0 %)
Stomatitis	8 (20 %)	5 (12 %)	3 (7 %)	0 (0 %)
Diarrhea	2 (5 %)	1 (2 %)	1 (2 %)	0 (0 %)
Asthenia	5 (12 %)	13 (32 %)	2 (5 %)	0 (0 %)
Skin rash	8 (20 %)	7 (17 %)	0 (0 %)	0 (0 %)
Elevated AST	9 (22 %)	0 (0 %)	0 (0 %)	0 (0 %)
Elevated ALT	9 (22 %)	0 (0 %)	0 (0 %)	0 (0 %)
Hypoalbuminemia	8 (20 %)	0 (0 %)	0 (0 %)	0 (0 %)
Hyperglycemia	25 (61 %)	4 (10 %)	5 (12 %)	1 (2 %)
Hypertriglyceridemia	13 (32 %)	0 (0 %)	0 (0 %)	0 (0 %)

AST aspartate aminotransferase, *ALT* alanine aminotransferase

Caso Clínico

Genomic Findings Detected	FDA-Approved Therapies (in patient's tumor type)	FDA-Approved Therapies (in another tumor type)	Potential Clinical Trials
Tumor Mutational Burden TMB-High; 59 Muts/Mb	None	Atezolizumab Avelumab	Yes, see clinical trials section

Genomic Findings Detected	FDA-Approved Therapies (in patient's tumor type)	FDA-Approved Therapies (in another tumor type)	Potential Clinical Trials
Tumor Mutational Burden TMB-High; 59 Muts/Mb	None	Atezolizumab Avelumab Durvalumab Nivolumab Pembrolizumab	Yes, see clinical trials section
P72fs*100, p16INK4a Q50*			
EPHA3 E930K	None	None	None
GNAS amplification	None	None	None
MAP3K14 splice site 1420_1420+1GG>AA	None	None	None
Microsatellite status MS-Stable	None	None	None
PCLO S4231F	None	None	None
TOP1 amplification	None	None	None
TP53 L265R, R267W, Y205D	None	None	None
ZNF217 amplification	None	None	None

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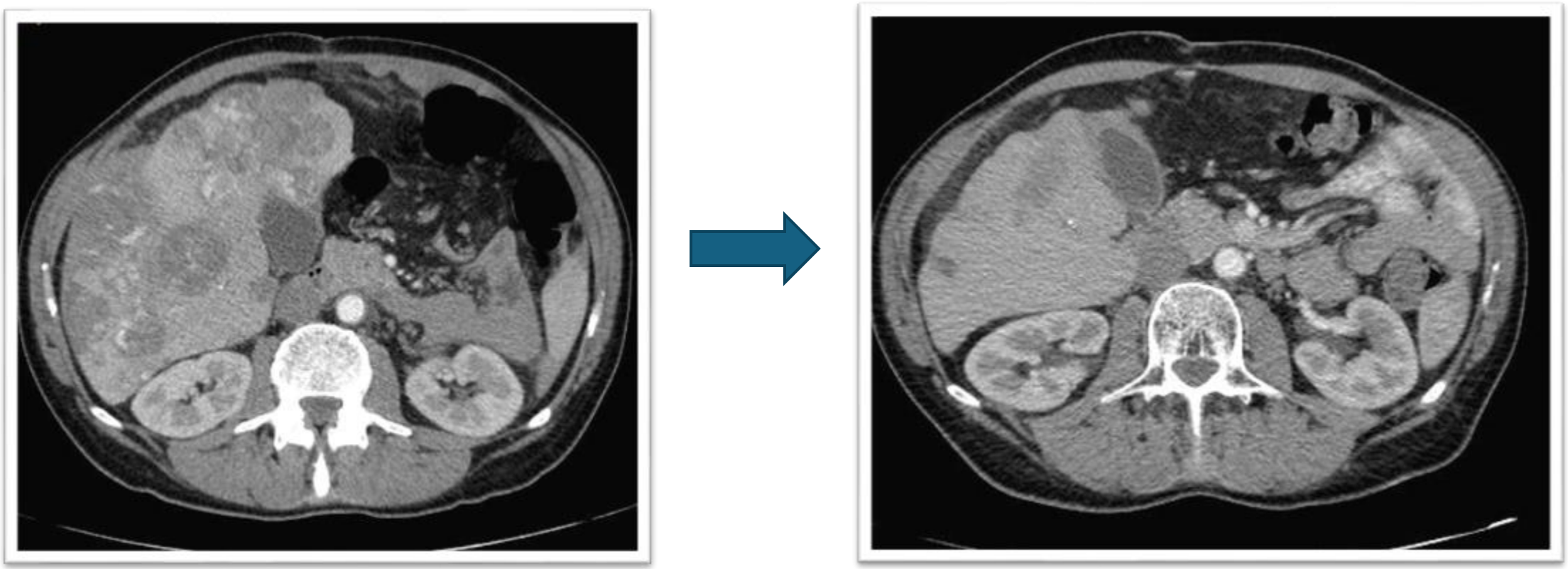
Inició Atezolizumab 1200 mg Cada 21 días



Mejoría del hepatograma

ECOG PS 0

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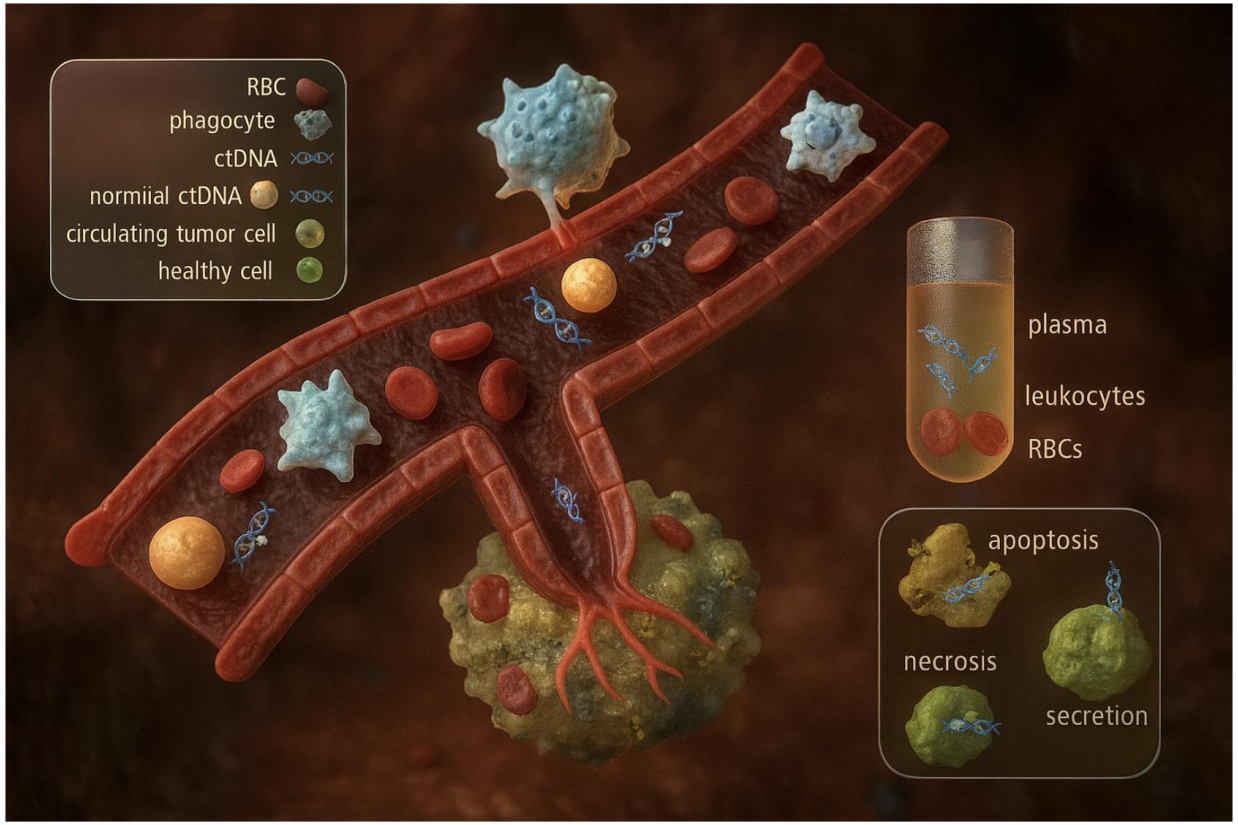
¿Por qué el ADN tumoral circulante (ctDNA) para la evaluación de la MRD?



- Las células neoplasicas liberan **ADN tumoral circulante (ctDNA)** en el torrente sanguíneo.
- ctDNA es una poderosa herramienta que se puede medir para evaluar la ausencia o presencia de **enfermedad molecular residual (MRD)**

Hahn AW, Nussenzveig RH, Maughan BL, Agarwal N. Cell-free Circulating Tumor DNA (ctDNA) in Metastatic Renal Cell Carcinoma (mRCC): Current Knowledge and Potential Uses. Kidney Cancer. 2019;3:7-13.

ctDNA

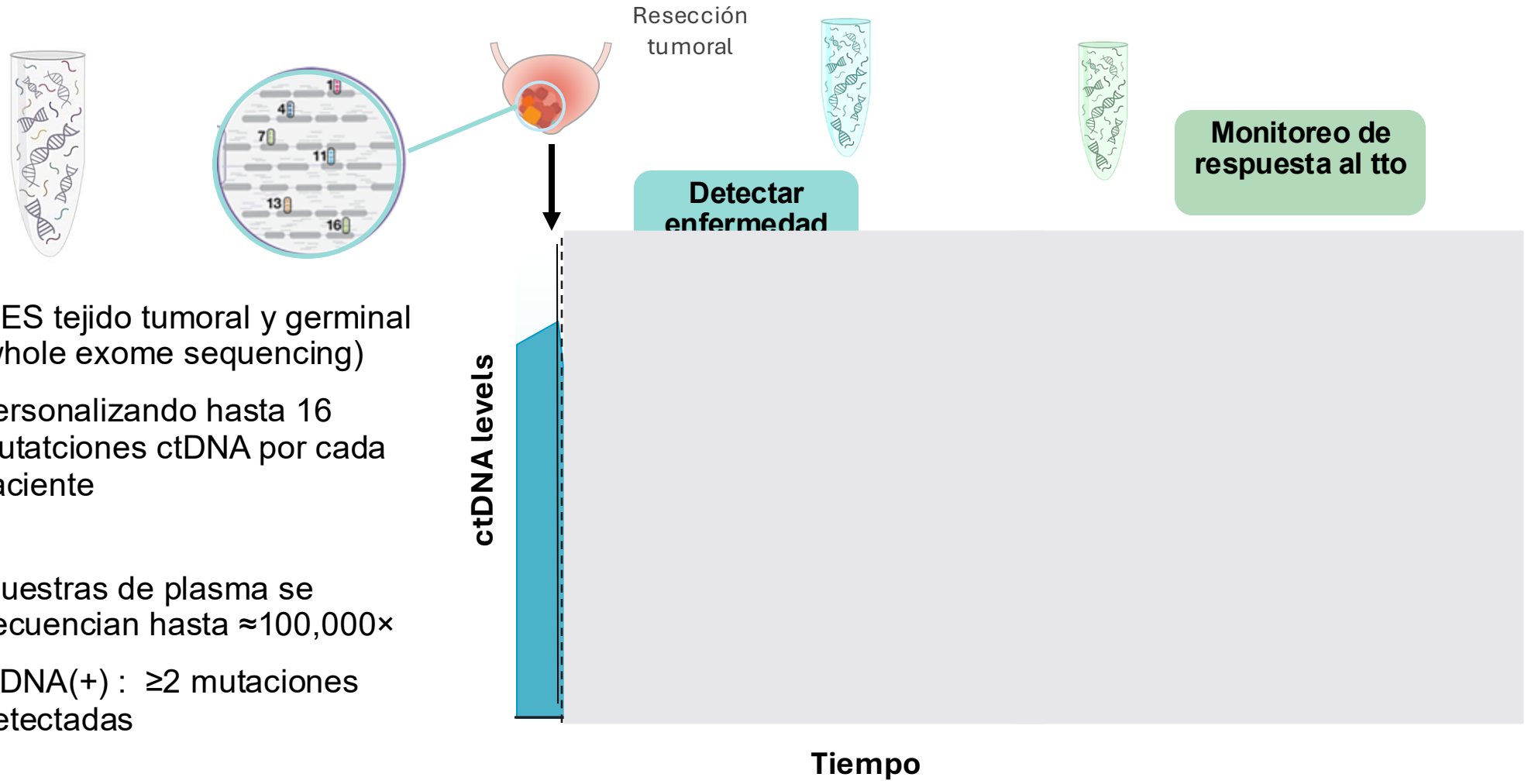
Límite de Detección:

Puede detectar **ctDNA** a una **variante de frecuencia alélica (VAF) de < 0.1% a 0.01%**

Determinar Resultado Positivo:

Alta especificidad (**> 99.5%**) al requerir la **detección de al menos dos mutaciones para una llamada positiva de ctDNA**, lo que conduce a **menos falsos positivos**.

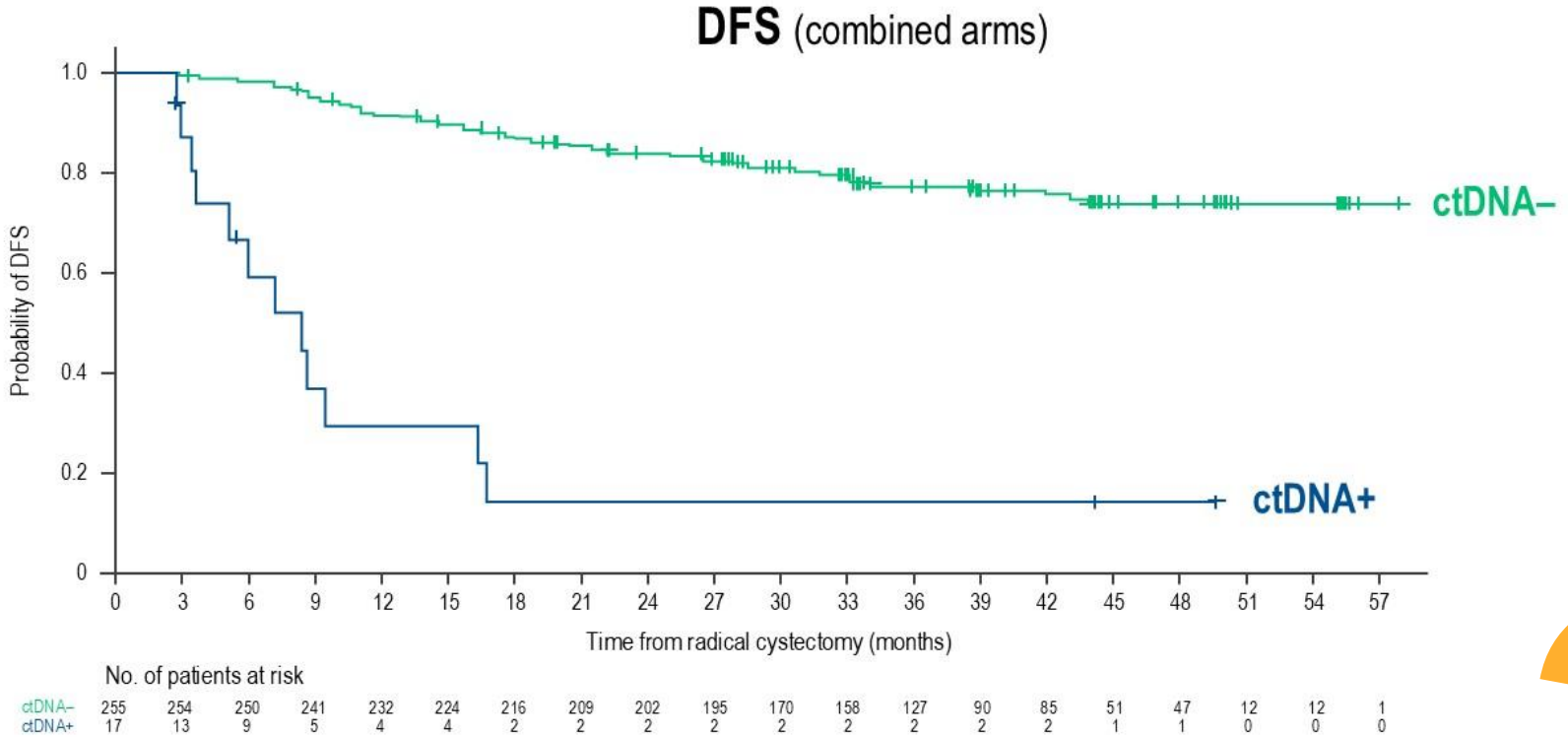
Evaluación de ctDNA en IMvigor010[1]



1. WES tejido tumoral y germinal (whole exome sequencing)
2. Personalizando hasta 16 mutatciones ctDNA por cada paciente
3. Muestras de plasma se secuencian hasta ≈100,000×
4. ctDNA(+) : ≥2 mutaciones detectadas

Powles et al. IMvigor010 ctDNA
https://bit.ly/2IxYllE

NIAGARA Post-Cystectomy: ctDNA Detection Was Prognostic for DFS



ctDNA– vs ctDNA+ **HR, 0.09** (95% CI, 0.05–0.18)

- **BEP post-cystectomy ctDNA+ = 9%**

BEP, biomarker evaluable population; CI, confidence interval; ctDNA, circulating tumor DNA; DFS, disease-free survival; HR, hazard ratio.

Participant & Sample Information

Screening Number:	100873
Year of Birth:	1976
Biological Sex:	Female
Protocol ID:	BO42843
Time Point:	Surveillance W18
Natera Case ID:	11410179
Cancer Type:	Muscle Invasive Bladder Cancer (MIBC)
Block ID:	117181-10G
Tissue Collected:	22MAR2023
Tissue Received:	21JUL2023
Blood-WES Collected:	13JUL2023
Blood-WES Received:	15JUL2023
Blood-ctDNA Collected:	26JAN2024
Blood-ctDNA Received:	29JAN2024
Blood-ctDNA Kit Barcode:	29413184-2-SB

Clinical Site

PI Name:	Martin Angel
Site Number:	343952
Site Address:	Cramer 1180, Buenos Aires, N/A C1426ANZ, AR
Report Date:	02FEB2024

natera | Signatera™ Residual disease test (MRD)

ABOUT THIS TEST:
Signatera is a bespoke mPCR-NGS assay for the detection of circulating tumor DNA (ctDNA) in the plasma of patients previously diagnosed with cancer. Individual-specific mutation signatures are identified by upfront tissue and matched normal whole-exome sequencing.

CAUTION- Investigational device
Limited by Federal (or United States) law to investigational use.
FOR PERFORMANCE EVALUATION ONLY

FINAL RESULTS SUMMARY

ctDNA Not Detected ⊖

Blood-ctDNA Collection Date: 26JAN2024

T3 N0 M0: NAC --> ypT3 ypN1 M0
3 años libre de enfermedad
Evitamos tratamiento sistémico

Participant & Sample Information

Screening Number:	100833
Year of Birth:	1966
Biological Sex:	Male
Protocol ID:	BO42843
Time Point:	Surveillance W0
Natera Case ID:	9736008
Cancer Type:	Muscle Invasive Bladder Cancer (MIBC)
Block ID:	118494
Tissue Collected:	17MAY2023
Tissue Received:	26JUN2023
Blood-WES Collected:	08JUN2023
Blood-WES Received:	12JUN2023
Blood-ctDNA Collected:	19JUL2023
Blood-ctDNA Received:	20JUL2023
Blood-ctDNA Kit Barcode:	26923329-2-SB

Clinical Site

PI Name:	Martin Angel
Site Number:	343952
Site Address:	Cramer 1180, Buenos Aires, N/A C1426ANZ, AR
Report Date:	10AUG2023

natera | Signatera™ Residual disease test (MRD)

ABOUT THIS TEST:
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FINAL RESULTS SUMMARY

ctDNA Positive ⊕

Blood-ctDNA Collection Date: 19JUL2023

T3 N0 M0: NAC --> ypT2 ypN0 M0
Inicia “Adyuvancia” 7 meses post Cx.
1 año libre de enfermedad desde fin de “Adyuvancia”

No Solo encontrar el target .....
Sino darle en el centro

Comité Molecular de Tumores o Tumor Molecular Boards (CMT/TMB)

- Equipo multidisciplinario
- Función: asistir en la interpretación de resultados de testeo de tumores y su utilidad clínica

Genetistas

Oncólogos

Bio-informáticos

Investigadores clínicos

Terceros Pagadores

Biólogos

Asesores genéticos en Oncología

Patólogos

IAF
INSTITUTO ALEXANDER FLEMING

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Implementation of a molecular tumour board in LATAM: the impact on treatment decisions for patients evaluated at Instituto Alexander Fleming, Argentina

Martín Osvaldo Angel[1,a], Carmen Pupareli[2], Tomas Soule[3], Florencia Tsou[2,b], Mariano Leiva[4], Federico Losco[1,c], Federico Esteso[5,d], Juan Manuel O´Connor[5,e], Romina Luca[5], Fernando Petracci[6,f], Romina Girotti[7], Yamil Damián Mahmoud[7,g], Claudio Martín[2,h] and Matías Chacón[8,i]

The value of virtual molecular tumor boards for informed clinical decision-making

Martín Angel[*,1], Mutlu Demiray[2], Umut Dişel[3], João Passos[4]

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Mensaje final…

La biología tumoral ya es parte de nuestro consultorio…

No lo podemos negar…

El problema es que no confundamos…

Expectativa

Tumores con mutaciones accionables

- Discutir en TMB
- Acceso
- Costos
- Beneficio Clínico

Muchas Gracias

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