La genómica en la selección de tratamientos oncológicos en tumores infrecuentes y de origen desconocido

Carmen Beato

HUV Macarena T. urológicos, TBI,TOD

DISCLOSURES

COMUNICACIÓN PATROCINADA POR ROCHE

INDICE

INDICE

Los tumores raros….

- Son tumores **infrecuentes**, prevalencia < 6 individuos/100.000 habitantes/año.

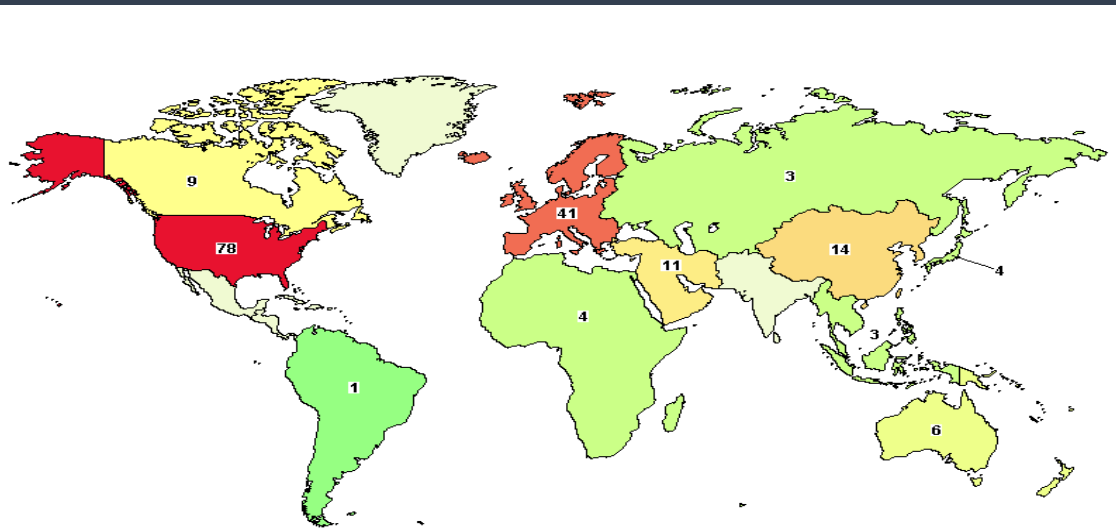
El **término infrecuente** es un **término relativo**, más allá de hacer referencia a su **baja incidencia** o **aparición esporádica** (por ej. feocromocitoma, carcinoma adenoide quístico, ependimoma, etc.), puede hacer referencia a **variantes histológicas raras de tumores frecuentes** (por ej. carcinoma sarcomatoide dentro de los carcinomas no microcíticos de pulmón), e incluso a **tumores con un comportamiento clínico atípico** (metástasis que aparecen décadas después del diagnóstico tras abordaje terapéutico quirúrgico y sin manifestaciones clínicas durante esos años).

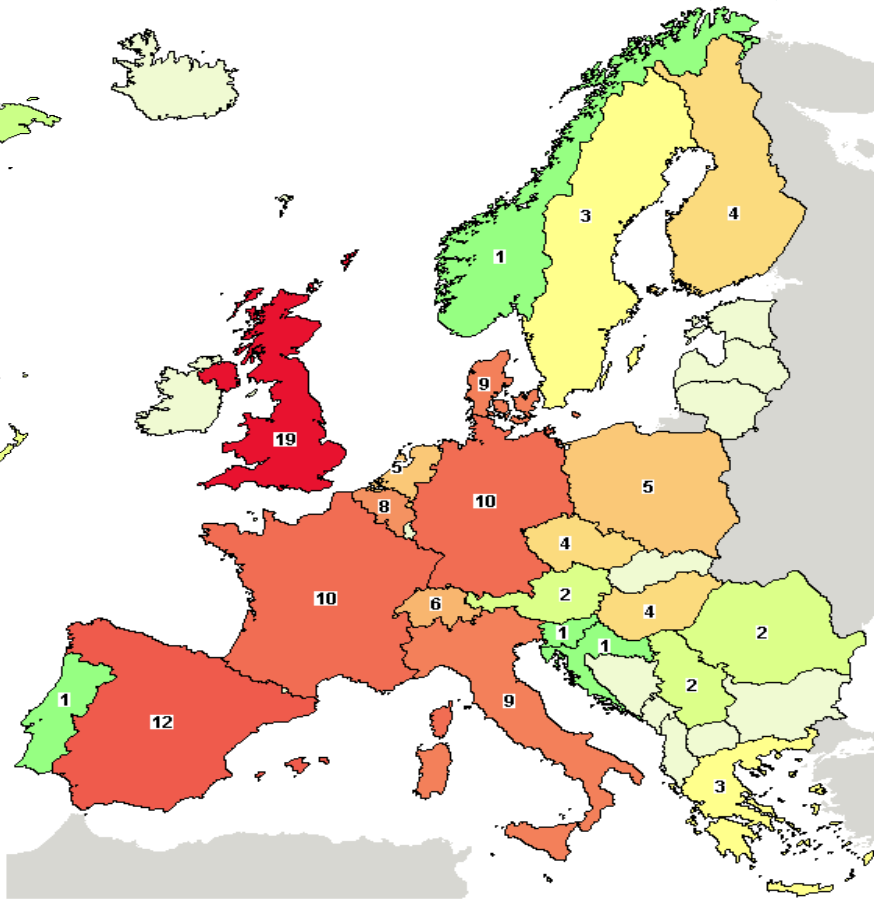
- Son tumores **huérfanos**, con escasas opciones terapéuticas disponibles (sin tratamientos aprobados con indicación terapéutica específica).

Los retos en el estudio de los tumores raros….

- ✓ En comparación con los tipos tumorales más comunes, en el caso de los tumores raros existe poca evidencia en cuanto a la mejor manera de tratarlos. Las guías clínicas rara vez hacen alusión a estas entidades. Por norma general aconsejan la inclusión del paciente en un ensayo clínico, pero no abundan los ensayos clínicos en estos tipos de tumores. Por ello, el acceso a fármacos es aún limitado, falta de agentes específicamente aprobados para el tratamiento de tumores raros.

12 EC ABIERTOS EN ESPAÑA, EN TODOS ES CRITERIO DE INCLUSIÓN “CARCINOMA UROTELIAL DE VEJIGA”





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Include only open studies Exclude studies with Unknown status

Rank	Status	Study
1	Recruiting	A Phase III Study of Atezolizumab Treatment Versus Observation as Adjuvant Therapy in Patients With PD-L1 Positive, High Risk Muscle Invasive Bladder Cancer After Cystectomy [IMvigor010] Condition: Bladder Cancer, Cancer Intervention: Biological: Atezolizumab (MPDL3280A)
2	Not yet recruiting	Study of MEDI4736 With or Without Tremelimumab Versus Standard of Care Chemotherapy in Bladder Cancer Condition: Bladder Cancer Interventions: Drug: MEDI4736; Drug: Tremelimumab; Drug: Cisplatin; Drug: Carboplatin; Drug: Gemcitabine
3	Recruiting	Pre-TURBT TC-3 Gel Intravesical Instillation in NMIBC Condition: Carcinoma of Urinary Bladder, Superficial Interventions: Device: 40 mg MMC gel; Other: Standard of care MMC mixed with water; Device: 80 mg MMC gel
4	Recruiting	A Study of MPDL3280A Compared With Chemotherapy in Patients With Locally Advanced or Metastatic Urothelial Bladder Cancer Condition: Bladder Cancer Interventions: Drug: Chemotherapy; Drug: MPDL3280A
5	Recruiting	Phase I / II Study of ColoAd1 by Sub-acute Fractionated IV Dosing in Cancer Patients Conditions: Solid Tumours of Epithelial Origin; Metastatic Colorectal Cancer; Metastatic Bladder Cancer Intervention: Biological: ColoAd1
6	Recruiting	A Dose Escalation Study in Adult Patients With Advanced Solid Malignancies

4.4. Survival

Overall, rare cancer survival was worse than common cancer survival. Relative survival was lower at 1 year and continued

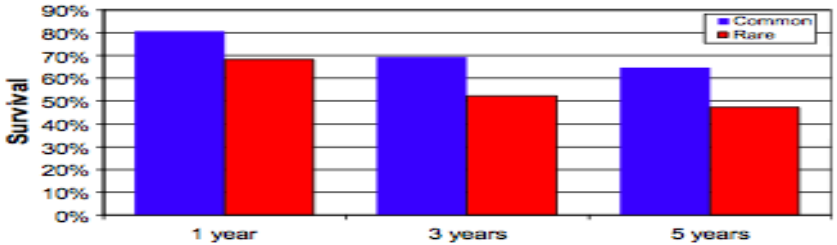


Fig. 3 – RARECARE estimates of relative survival for rare and common cancers in EU27 by year since diagnosis.

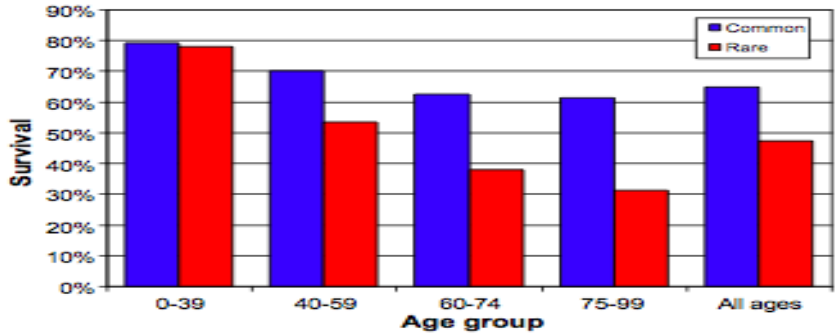


Fig. 4 – RARECARE estimates of relative survival for rare and common cancers in EU27 by age group.

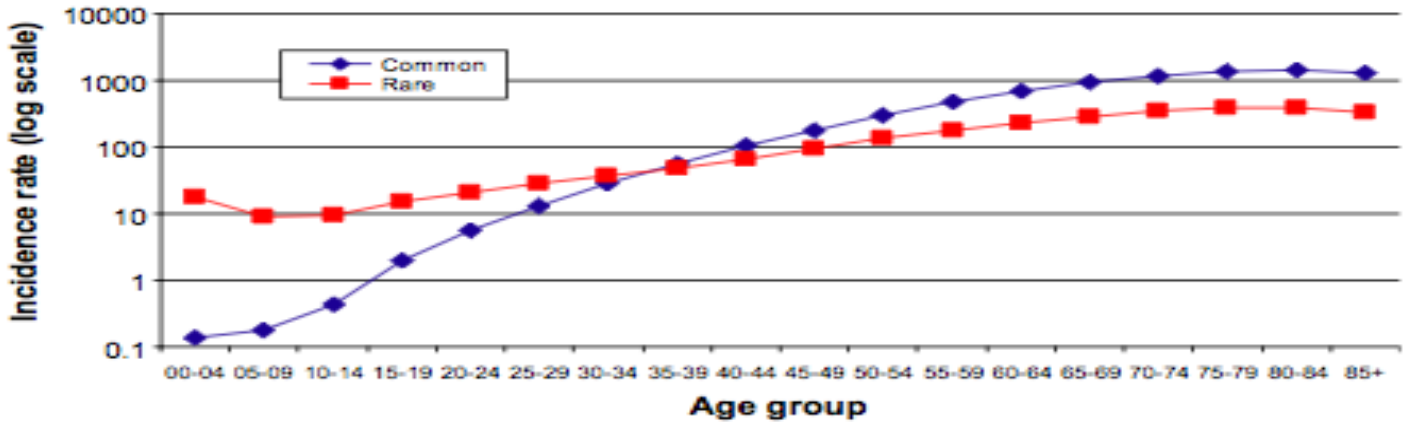


Fig. 2 – RARECARE estimates of age-specific incidence rates for rare and common cancers in EU 27.

EUROPEAN JOURNAL OF CANCER 47 (2011) 2493–2511

Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejconline.com

Rare cancers are not so rare: The rare cancer burden in Europe

Gemma Gatta [a,*], *Jan Maarten van der Zwan* [b], *Paolo G. Casali* [c], *Sabine Siesling* [b], *Angelo Paolo Dei Tos* [d], *Ian Kunkler* [e], *Renée Otter* [b], *Lisa Licitra* [f], *Sandra Mallone* [g], *Andrea Tavilla* [g], *Annalisa Trama* [a], *Riccardo Capocaccia* [g], *The RARECARE working group*

[a] *Department of Preventive and Predictive Medicine, Fondazione IRCSS, Istituto Nazionale dei Tumori, Via Venezian 1, 20133 Milan, Italy*
[b] *North East Netherlands Cancer Registry, Comprehensive Cancer Centre North East, P.O. Box 330, 9700 AH Groningen, The Netherlands*
[c] *Department of Cancer Medicine, Fondazione IRCSS, Istituto Nazionale dei Tumori, Via Venezian 1, 20133 Milan, Italy*
[d] *Department of Pathology, General Hospital of Treviso, Via Borgo Cavalli 42, 31100 Treviso, Italy*
[e] *Department of Clinical Oncology, Western General Hospital, Crewe Road South, Edinburgh EH4 2XU, UK*
[f] *Head and Neck Cancer Medical Oncology Unit, Fondazione IRCSS, Istituto Nazionale dei Tumori, Via Venezian 1, 20133 Milan, Italy*
[g] *Department of Cancer Epidemiology, Istituto Superiore di Sanità, Viale Regina Elena 299, Rome, Italy*

Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet—a population-based study

*Gemma Gatta, Riccardo Capocaccia, Laura Botta, Sandra Mallone, Roberta De Angelis, Eva Ardanaz, Harry Comber, Nadya Dimitrova, Maarit K Leinonen, Sabine Siesling, Jan M van der Zwan, Liesbet Van Eycken, Otto Visser, Maja P Žakelj, Lesley A Anderson, Francesca Bella, Kaire Innos, Renée Otter, Charles A Stiller, Annalisa Trama, for the RARECAREnet working group**

Added value of this study

With the new project 'Information network on rare cancer' (RARECAREnet), we updated the burden of rare cancer and provided indicators of the centralisation of patients with rare cancer in seven European countries. We estimated about 650 000 new diagnoses of rare cancers occur yearly in Europe, with an incidence of 115 of 100 000 per year. The incidence rose by 0·5% annually, due to overdiagnosis (eg, thyroid carcinoma) or improved diagnosis (eg, neuroendocrine tumours [NET], gastrointestinal stromal tumour [GIST]) or increases in exposure to risk factors (such as HPV). 5-year survival for rare cancers (49%) is still lower than for common cancers (63%), but

Summary

Background Rare cancers pose challenges for diagnosis, treatments, a cancers is scant. The RARECARE project defined rare cancers as t 100 000 people in European Union (EU). We updated the estimates trends in incidence and survival, and provide information about cent

Methods We analysed data from 94 cancer registries for more t European incidence and survival in 2000–07 and the correspond calculated as the number of new cases divided by the corresp relative survival was calculated by the Ederer-2 method. Seven r Netherlands, Slovenia, and the Navarra region in Spain) provided additional data for hospitals treating about 220 000 cases diagnosed in 2000–07. We also calculated hospital volume admission as the number of treatments provided by each hospital rare cancer group sharing the same referral pattern.

Findings Rare cancers accounted for 24% of all cancers diagnosed in the EU during 2000–07. The overall incidence rose annually by 0·5% (99·8% CI 0·3–0·8). 5-year relative survival for all rare cancers was 48·5% (95% CI 48·4 to 48·6), compared with 63·4% (95% CI 63·3 to 63·4) for all common cancers. 5-year relative survival increased (overall 2·9%, 95% CI 2·7 to 3·2), from 1999–2001 to 2007–09, and for most rare cancers, with the largest increases for haematological tumours and sarcomas. The amount of centralisation of rare cancer treatment varied widely between cancers and between countries. The Netherlands and Slovenia had the highest treatment volumes.

Interpretation Our study benefits from the largest pool of population-based registries to estimate incidence and survival of about 200 rare cancers. Incidence trends can be explained by changes in known risk factors, improved diagnosis, and registration problems. Survival could be improved by early diagnosis, new treatments, and improved case management. The centralisation of treatment could be improved in the seven European countries we studied.

INDICE

1. Contexto: Tumores de baja incidencia
2. La medicina de precisión como oportunidad en TBI
3. Foundation one
4. Experiencia de nuestro hospital
5. CUPISCO

LA MEDICINA DE PRECISIÓN COMO OPORTUNIDAD EN TBI

Los retos en el estudio de los tumores raros….

- ✓ Para los principales tipo tumorales, la validez clínica de la anotación molecular y el impacto en el manejo del paciente oncológico son una realidad en la actualidad.

ARTICLE

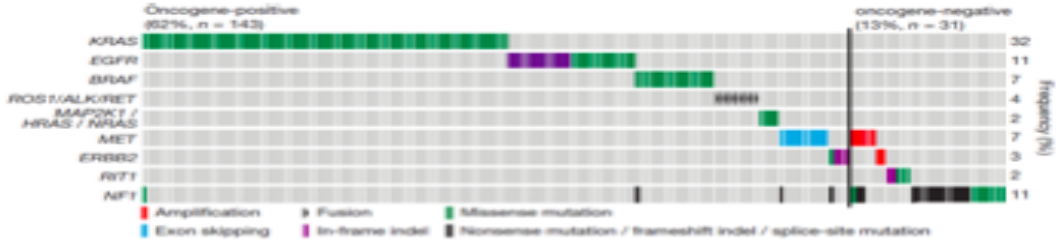
OPEN

doi:10.1038/nature13385

Collisson et al. Nature 2014; 511: 543-50

Comprehensive molecular profiling of lung adenocarcinoma

The Cancer Genome Atlas Research Network*



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Muzny et al. Nature 2012; 487: 330-7

Comprehensive molecular characterization of human colon and rectal cancer

The Cancer Genome Atlas Network*

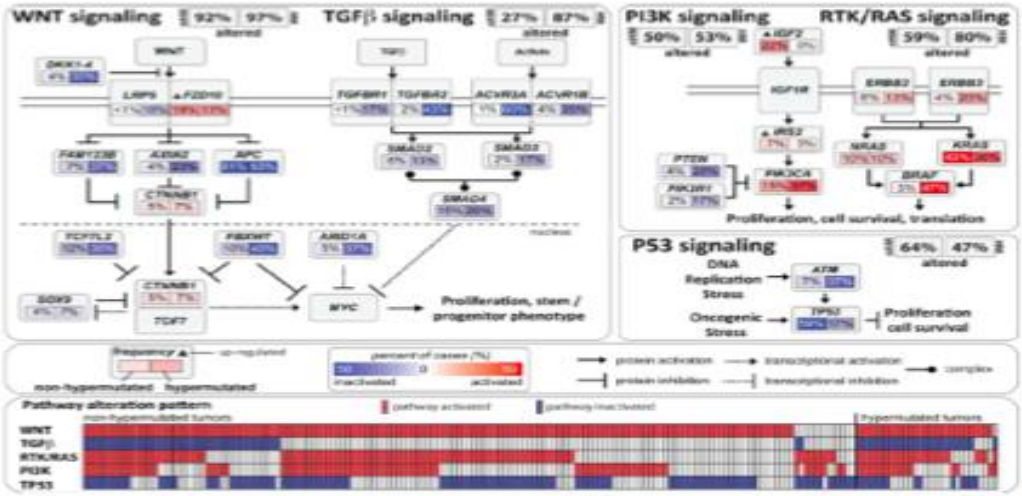

Figure 4. Diversity and frequency of genetic changes leading to deregulation of signaling pathways in CRC

LA MEDICINA DE PRECISIÓN COMO OPORTUNIDAD EN TBI

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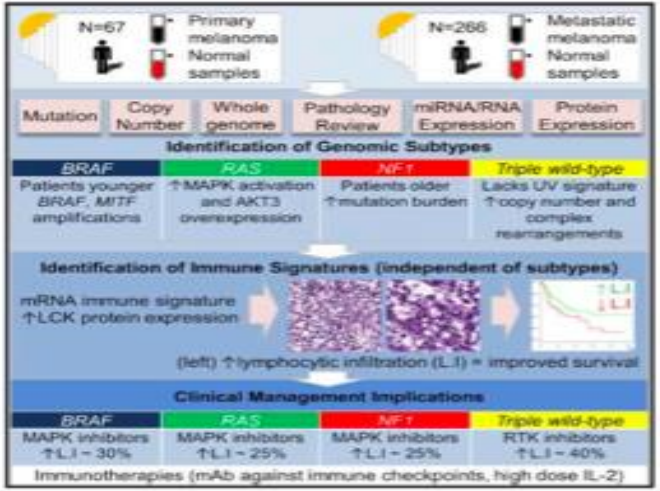
Akbani et al. Cell 2015; 161:1681-96

Genomic Classification of Cutaneous Melanoma

Graphical Abstract



Authors

The Cancer Genome Atlas Network

Figure 4. Diversity and Frequency of Genetic Changes Leading to Deregulation of Signaling Pathways in CRC

Huérfanos e Infrecuentes

Cancer

LA MEDICINA DE PRECISIÓN COMO OPORTUNIDAD EN TBI

Los retos en el estudio de los tumores raros....

NIH THE CANCER GENOME ATLAS
National Cancer Institute
National Human Genome Research Institute

✓ Inicio de proyectos en el campo de los tumores raros, ha permitido la caracterización de algunos tipos:

- Carcinoma adrenocortical *(Cancer Cell 2016; 29: 723-36)*
- Colangiocarcinoma
- Carcinoma renal cromófobo *(Cancer Cell 2014; 26: 319-30)*
- Mesotelioma
- Paraganglioglioma/feocromocitoma
- Tumor testicular de células germinales
- Timoma
- Melanoma uveal
- Carcinosarcoma uterino
- Carcinoma papilar de tiroides *(Cell 2014; 159 : 676-90)*

LA MEDICINA DE PRECISIÓN COMO OPORTUNIDAD EN TBI

Los retos en el estudio de los tumores raros....

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HHS Public Access
Author manuscript
Nat Genet. Author manuscript; available in PMC 2014 January 01.
Ho et al. Nat Genet. 2013; 45: 791-8

The Mutational Landscape of Adenoid Cystic Carcinoma

Contents lists available at SciVerse ScienceDirect
Cancer Treatment Reviews
journal homepage: www.elsevierhealth.com/journals/ctrv
ELSEVIER

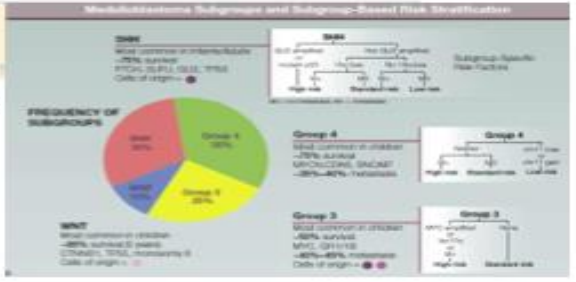
Tumour Review
Thymoma and thymic carcinoma in the target therapies era
Lamarca et al. Cancer Treat Rev 2013; 39: 413-20

frontiers in Oncology
Noujaim et al. Front Oncol 2015; 5: 186

Epithelioid sarcoma: opportunities for biology-driven targeted therapy

NIH Public Access
Author Manuscript

SnapShot: Medulloblastoma
Rusert et al. Cancer Cell 2014; 26: 940



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 0: 1–8, 2018
doi:10.1093/annonc/mdy263

SPECIAL ARTICLE

A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)

J. Mateo[1], D. Chakravarty[2], R. Dienstmann[1], S. Jezdic[3], A. Gonzalez-Perez[4], N. Lopez-Bigas[4,5], C. K. Y. Ng[6], P. L. Bedard[7], G. Tortora[8,9], J. -Y. Douillard[3], E. M. Van Allen[10], N. Schultz[2], C. Swanton[11], F. André[12*] & L. Pusztai[13]

		data		
	IV: pre-clinical evidence of actionability	IV-A: evidence that the alteration or a functionally similar alteration influences drug sensitivity in preclinical *in vitro* or *in vivo* models IV-B: actionability predicted *in silico*	Actionability is predicted based on preclinical studies, no conclusive clinical data available	Treatment should 'only be considered' in the context of early clinical trials. Lack of clinical data should be stressed to patients
Combination development	V: alteration-drug match is associated with objective response, but without clinically meaningful benefit	Prospective studies show that targeted therapy is associated with objective responses, but this does not lead to improved outcome	Drug is active but does not prolong PFS or OS, probably in part due to mechanisms of adaptation	Clinical trials assessing drug combination strategies could be considered
	X: lack of evidence for actionability	No evidence that the genomic alteration is therapeutically actionable	There is no evidence, clinical or preclinical, that a genomic alteration is a potential therapeutic target	The finding should not be taken into account for clinical decision

INDICE

FOUNDATIONONE CDx™

Applies **next-generation sequencing** to identify **genomic alterations across 324 cancer-related genes** known to be **drivers of solid tumors** plus select **introns of 28 genes**[1]

Microsatellite instability (MSI) + tumor mutational burden (TMB) testing

A **single solution** for simultaneous assessment of MSI and TMB biomarkers – previously separate and **time- and labor-intensive** tests. Will provide **additional** and **relevant genomic clues** as to which patients may **benefit the most** from certain immunotherapies

FOUNDATIONONE®LIQUID

A **liquid biopsy Assay for Circulating Tumor** DNA, interrogating **all** known classes of genomic alteration across **70 genes.** Provides validated, **blood-based profiling when tissue biopsy may not be feasible**[3]

Microsatellite instability (MSI)

A single solution for assessment of MSI – previously separate and time- and labor-intensive tests. Will provide additional and relevant genomic clues as to which patients may benefit the most from certain targeted or immunotherapies

FOUNDATIONONE™ Heme

Designed to analyze and interpret **DNA sequence** information of **405 genes** and **RNA sequence (cDNA)** information of **265 commonly rearranged genes** in **hematologic malignancies, sarcomas and pediatric tumors**[2]

Microsatellite instability (MSI) + tumor mutational burden (TMB) testing

A **single solution** for simultaneous assessment of MSI and TMB biomarkers – previously separate and **time- and labor-intensive** tests. Will provide **additional** and **relevant genomic clues** as to which patients may **benefit the most** from certain immunotherapies

Cobertura de tumores solidos, hematológicos y sarcomas (incluyendo tumores pediátricos)

Ficha técnica de Foundation One ; 2. Ficha ténica de Foundation One Heme; 3. Ficha técnica de Foundation ACT
Disponibles en https://www.rocheplus.es/es_es/foundation-medicine.html

FOUNDATION MEDICINE®

Roche

Understanding how FoundationOne CDx differs from FoundationOne

is the first **FDA-approved**, broad companion diagnostic for all solid tumours[1,2] in the U.S.

has **proven concordance** with multiple CDx tests and regulatory approval based on analytical and clinical validation of > 6,300 samples[3,4]

provides **clear** test results[5] with all guideline-recommended genes* and genomic signatures on the first page[6]

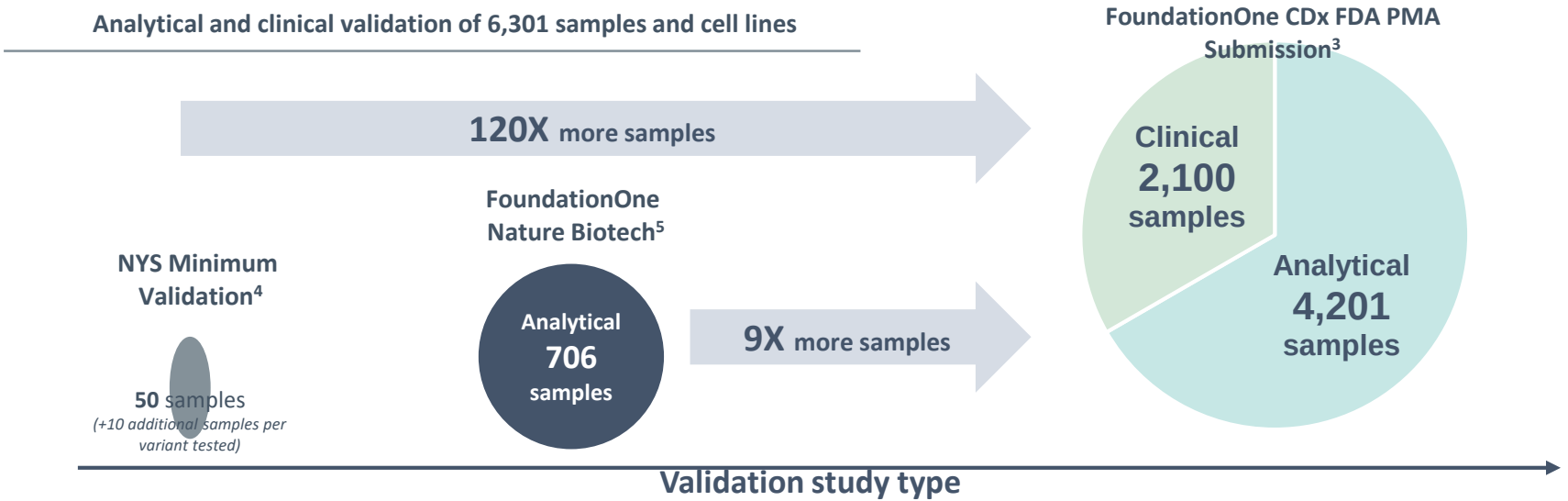
Includes an **updated gene list**, to provide relevant insights to help personalise patients' treatment plans[7]

*As of March 2018. For EU report, therapies may have been approved through a centralised EU procedure or a national procedure in an EU Member State.
CDx: companion diagnostic; FDA: US food and drug administration.

1. FoundationOne® CDx FDA Approval (2017) Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019a.pdf (Accessed June 2018);
2. FoundationOne CDx™ Technical Specifications (2017) Available at: www.foundationmedicine.com/genomic-testing/foundation-one-cdx (Accessed June 2018);
3. Next Generation Sequencing (NGS) guidelines for somatic genetic variant detection (2015) Available at: https://www.wadsworth.org/sites/default/files/WebDoc/1300145166NextGenSeq_ONCO_Guidelines.pdf (Accessed June 2018);
4. FoundationOne CDx™ clinical validation (2017) Available at: http://www.foundationmedicine.com/genomic-testing/foundation-one-cdx (Accessed June 2018);
5. Foundation Medicine website (2017) FoundationOne®CDx Available at: https://www.foundationmedicine.com/genomic-testing/foundation-one-cdx (Accessed July 2018); 6. FoundationOne CDx™ Sample Report (2018) Available at: www.foundationmedicine.com/genomic-testing/foundation-one-cdx (Accessed June 2018); 7. Roche FMI data on file.

FoundationOne CDx has undergone stringent validation processes

FoundationOne CDx has been validated with 6,300 samples; over 120 times more than the typical number of patient samples for laboratory test validation*[1,2] and 9 times more samples as compared with FoundationOne[3]



*According to NYS guidance. CGP: comprehensive genomic profile; NYS: New York state (guidelines); PMA: premarket approval.

1. FoundationOne CDx™ clinical validation (2017) Available at: http://www.foundationmedicine.com/genomic-testing/foundation-one-cdx (Accessed June 2018); 2. Next Generation Sequencing (NGS) guidelines for somatic genetic variant detection (2015) Available at: https://www.wadsworth.org/sites/default/files/WebDoc/1300145166/NextGenSeq_ONCO_Guidelines.pdf (Accessed June 2018);
3. FoundationOne CDx PMA Submission (2017); 4. https://www.horizondiscovery.com/reference-standards/what-are-reference-standards/quality-controlled/new-york-state-guidelines; 5. Frampton, G., et. al. (2013) *Nat Biotech* 31:1023-31.

Analytical validation studies for FoundationOne CDx vs other NGS tests

Concordant with an externally validated NGS method at an Academic Medical Center*

	PPA	NPA
All short variants	94.6%	99.9%
Substitutions	96.6%	99.9%
Insertions & deletions	83.4%	99.9%

* The detection of alterations by FoundationOne CD (F1CDx) assay was compared to results of an externally validated NGS assay (evNGS). Overall there were 157 overlapping genes between the two assays. The comparison between short alterations, including base substitutions and short indels, detected by F1CDx and the orthogonal method included 188 samples from 46 different tumours. Differences in variants of unknown significance (VUS) alteration calls between the platform were noted, and are expected based on differences in filtering employed by F1CDx and evNGS. Negative predictive value and positive predictive value were also calculated and were found to be different than percent agreement because the two platforms filter VUS differently. Discordant alterations not related to VUS filtering were primarily caused by deletions with low allelic fraction in homopolymer regions. The F1CDx variant calling pipeline imposes a filter based on MAF of ≥0.10 for indels in homopolymer regions to reduce the likelihood of calling false positives resulting from artifacts introduced by the technology. As such, the difference observed was due to varying filter thresholds between the two platforms. For additional concordance results for the CDx-associated variants, refer to the Summary of Clinical Studies.

Concordant with FoundationOne**

	PPA	NPA
All variants	98.6%	99.9%
All short variants	99.1%	99.9%
Substitutions	99.4%	99.9%
Insertions & deletions	97.0%	99.9%
All copy number variants	94.3%	99.9%
Amplifications	94.0%	99.9%
Losses	94.8%	99.8%
Rearrangements	100.0%	99.9%

**To support the use of retrospective data generated using FoundationOne® (F1 LDT), a concordance study was conducted with F1CDx[1]. This study evaluated a test set of 165 specimens. PPA and NPA between the F1CDx and F1 LDT, using the F1 assay as the reference method, was calculated for all alterations, as well as for alterations binned by type: short variants, copy number alterations (CNAs) and rearrangements. A total of 2325 variants, including 2026 short variants, 266 CNAs and 33 rearrangements were included in the study.

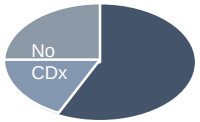
CDx: companion diagnostic; CNA: copy number alterations; evNGS: externally validated NGS; F1CDx: FoundationOne CDx; LDT: laboratory developed test; NGS: next-generation sequencing; NPA: negative predictive agreement; PPA: positive predictive agreement; VUS: variants of unknown significance.

1. FoundationOne® CDx Technical Information (2017) Available at:https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019C.pdf (Accessed July 2018).

Broad clinical utility across common cancers

% patients with genomic alterations that the FoundationOne CDx platform is clinically validated to detect[1-6]

CRC

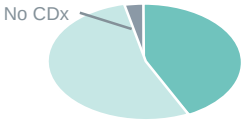


61-75% of patients[1]

KRAS wildtype
59% - 70%

NRAS wildtype
2% - 5%

Melanoma



39-94% of patients[2]

BRAF V600E
36% - 75%

BRAF V600K
2% - 19%

NSCLC

20-39% of patients[3]

EGFR exon 19 deletions
8% - 17%; *EGFR exon 21 L858R*
6% - 11%; EGFR exon 20 T790M
1% at diagnosis, 33% - 62% acq. resistance; ALK rearrangements
5% - 8%; BRAF V600E
1% - 2%

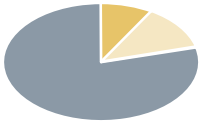
Ovarian

13-28% of Patients[4]

BRCA1
8% - 19%

BRCA2
5% - 9%

Breast

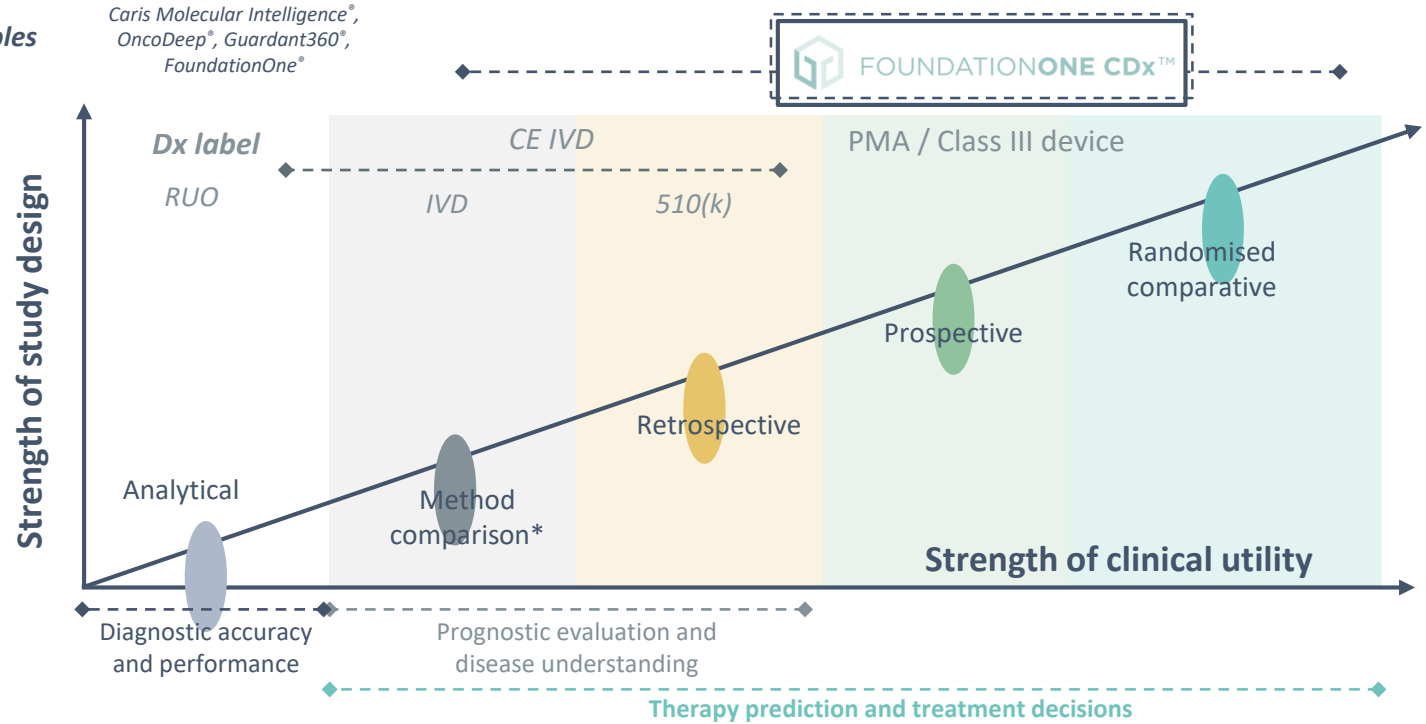


13-23% of patients[5]

ERBB2 (HER2)
amplification
13% - 23%

CDx: companion diagnostic; CRC: colorectal cancer; NSCLC: non-small cell lung cancer. Roth et al., 2010; 20008640, Amado et al., 2008; 18316791, Doullard et al., 2013; 24024839, Heinemann et al., 2014; 25088940, Price et al., 2015; 25742472, De Roock et al., 2012; 20619739, Vaughn et al., 2011; 21305640, Peeters et al., 2013; 23325582. 2 (Melanoma). Greaves et al., 2013; 23273605, Davies et al., 2002; 12068308, Hodis et al., 2012; 22817889, Menzies et al., 2012; 22535154, Colombino et al., 2012; 22614978, Long et al., 2011; 21343559. 3 (NSCLC). Vanderlaen et al., 2018; 29413057, Kris et al., 2014; 24846037, D'Angelo et al., 2011; 21482987, Esteban et al., 2015; 25766256, Han et al., 2017; 29110846, Barlesi et al., 2016; 26777916, Hata et al., 2013; 24105277, Tanaka et al., 2017; 28978102, Sequist et al., 2011; 21430269, Oxnard et al., 2011; 21135146; Palk et al., 2011; 21483012. 4 (Ovarian). Yang et al., 2011; 21990299, Cancer Genome Atlas Research Network., 2011; 21720365, Zhang et al., 2011; 21324516, Pennington et al., 2013; 24240112. 5 (Breast). Cancer Genome Atlas Network et al., 2012; 23000897, Owens et al., 2004; 15140287, Chmielecki et al., 2014; 25480824, Bartlett et al., 2001; 11745673. 6. Data from FoundationCoreTM knowledgebase.

The clinical utility of FoundationOne CDx is supported by a strong body of evidence



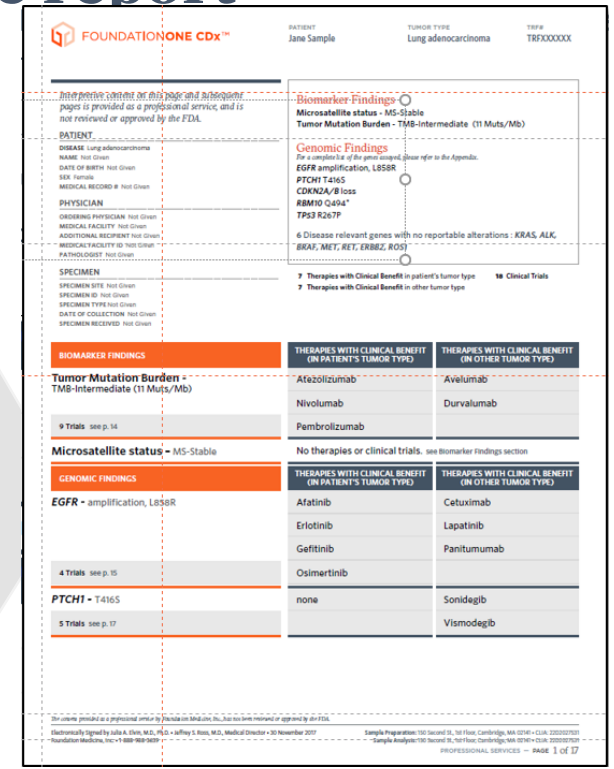
Caris Molecular Intelligence® is a trademark of Caris Life Science; OncoDeep® is a trademark of OncoDNA, Guardant360® is a trademark of Guardant Health; and FoundationOne® is a trademark of Foundation Medicine®; * A comparison against a predicate device which has already been clinically validated (ex cobas EGFR, Ventana HER2, etc). CE IVD: CE marked *in-vitro* diagnostic; Dx: diagnostic; IVD: *in-vitro* diagnostics; PMA: premarket approval; RUO: research use only.

Approved therapies that patients may respond to are clearly displayed on page one of the report

1. Therapies With Clinical Benefit (In patient's tumour type)
2. Therapies With Clinical Benefit (In other tumour type)
3. Clinical trials listed with simple page-number references

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE) (1)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE) (2)
Tumour Mutation Burden - TMB-Intermediate (11 Muts/Mb)	Atezolizumab	Avelumab
	Nivolumab	Durvalumab
(3) 9 Trials see p. 14	Pembrolizumab	
Microsatellite status - MS-Stable	No therapies or clinical trials. see Biomarker Findings section	

GENOMIC FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE) (1)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE) (2)
***EGFR* -** amplification, L858R	Afatinib	Cetuximab
	Erlotinib	Lapatinib
	Gefitinib	Panitumumab
(3) 4 Trials see p. 15	Osimertinib	
***PTCH1* -** T416S	none	Sonidegib
(3) 5 Trials see p. 17		Vismodegib



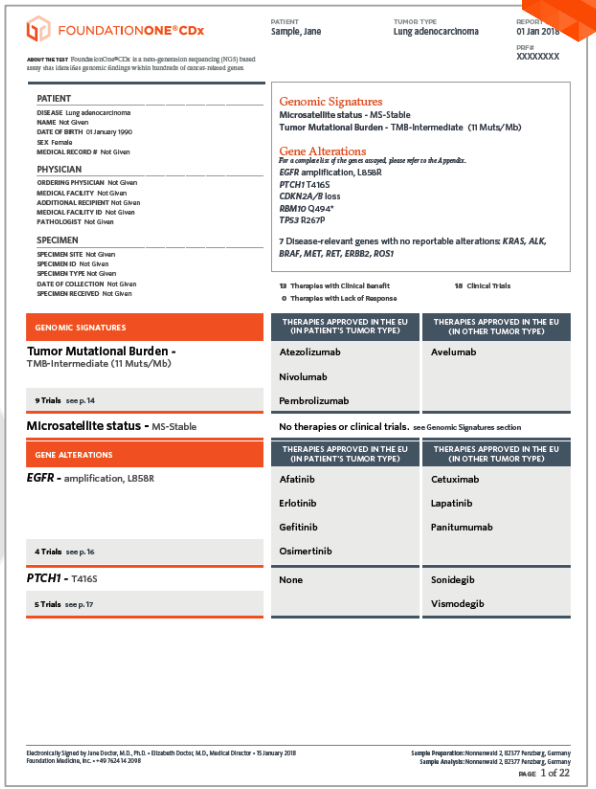
CDx: companion diagnostic; FDA: US food and drug administration.
FoundationOne CDx™ Sample Report (2018) Available at: www.foundationmedicine.com/genomic-testing/foundation-one-cdx (Accessed June 2018).

EU approved therapies that patients may respond to are clearly displayed on page one of the report

EU REPORT

1. Therapies With Clinical Benefit (In patient's tumour type)
2. Therapies With Clinical Benefit (In other tumour type)
3. Clinical trials listed with simple page-number references

GENOMIC SIGNATURES	1 THERAPIES APPROVED IN THE EU (IN PATIENT'S TUMOR TYPE)	2 THERAPIES APPROVED IN THE EU (IN OTHER TUMOR TYPE)
Tumor Mutational Burden - TMB-Intermediate (11 Muts/Mb)	Atezolizumab Nivolumab Pembrolizumab	Avelumab
3 9 Trials see p. 14		
Microsatellite status - MS-Stable	No therapies or clinical trials. see Genomic Signatures section	
GENE ALTERATIONS	**1 THERAPIES APPROVED IN THE EU (IN PATIENT'S TUMOR TYPE)**	**2 THERAPIES APPROVED IN THE EU (IN OTHER TUMOR TYPE)**
***EGFR* -** amplification, L858R	Afatinib Erlotinib Gefitinib Osimertinib	Cetuximab Lapatinib Panitumumab
3 4 Trials see p. 16		
***PTCH1* -** T416S	None	Sonidegib Vismodegib
3 5 Trials see p. 17		



CDx: companion diagnostic; FDA: US food and drug administration.
FoundationOne CDx Sample Report www.rochefoundationmedicine.com/reporting (Accessed June 2018).

Foundation One Liquid, nueva versión actualizada disponible en España desde el 3 de Septiembre 2018

FOUNDATIONONE®LIQUID

A **liquid biopsy Assay for Circulating Tumor** DNA, interrogating **all** known classes of genomic alteration across **70 genes.** Provides validated, **blood-based profiling when tissue biopsy may not be feasible**[3]

Novedades de la versión 2.0

- Mayor sensibilidad analítica (ventaja competitiva)(especialmente en frecuecias de mutalcion alélica >0,5%
- Mas genes: ahora 70
- Nuevo look
- Inclusion MSI
- Publicacion validación Analitica The Journal of Molecular diagnostics

Aumento y mejora en el proceso analítico (sensibilidad y Valor Predictivo Positivo (PPV), sobre toda la lista de genes analizados para sustituciones e inserciones, usando una amplia distribución de frecuencias de mutación alélica (MAF) clínicamente relevantes, y profundizando hasta niveles muy bajos.

—> FACT demuestra una alta **concordancia** con Foundation One*, donde el **83%** de las variantes detectadas en tejido también se detectaron en ctDNA.

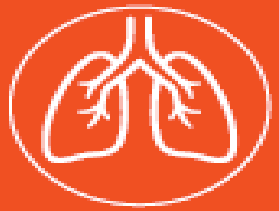
—> estudio **comparativo con múltiples técnicas ortogonales** revelaron que **no existen falsos positivos** en el estudio realizado para esta validación.

El artículo concluye diciendo que el test de Foundation ACT (ctDNA) es altamente sensible para detectar ctDNA en sangre, y puede identificar por tanto posibles opciones clínicas en los pacientes con cáncer avanzado

FOUNDATION MEDICINE® | Roche

FoundationOne Liquid:
High concordance with FoundationOne, our tissue-based comprehensive genomic profiling service*[8–10]

- Validated across a broad range of solid tumour types[2]
- In several studies of lung, breast and gastrointestinal cancers, a large percentage of alterations detected in tumour tissue were also detected in circulating tumour DNA[†8-10]



Lung

78%

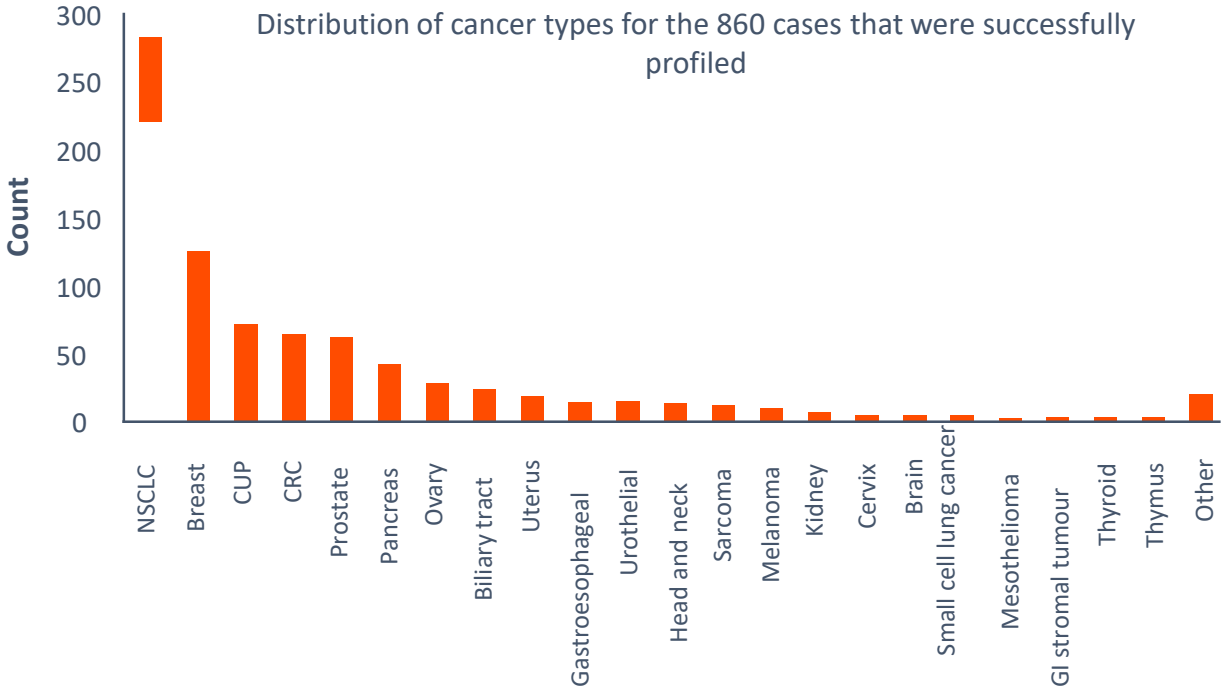
Breast

89%

Gastrointestinal

>90%

Frequency of cancer types profiled in the validation paper reflect distribution in commercial volume



Of 860 cases profiled

- 32.9% were NSCLC
- 14.9% were breast cancer
- 8.5% were CUP

CRC: colorectal cancer; CUP: cancer of unknown primary; GI: gastrointestinal; NSCLC: non-small cell lung cancer.
Clark, T.A., et al. (2018) *J Mol Diagn* (in press).

INDICE

CASOS CLÍNICOS EXPERIENCIA: BUSCANDO ENSAYOS CLÍNICOS.

IMPACTO EN LA PRÁCTICA CLÍNICA DE LAS PLATAFORMAS NGS: EXPERIENCIA PILOTO

INTRODUCCIÓN Y OBJETIVOS.

La secuenciación genómica exhaustiva revela información de genes accionables que intervienen en los procesos de división celular. A diferencia de la determinación de genes concretos, que identifican un número limitado de alteraciones, la aproximación diagnóstica mediante Comprehensive genomic profiling (CGP) permite determinar sustituciones de bases, inserciones, deleciones, alteraciones en el número de copias y reordenamientos. En los estudios solicitados pudimos conocer también el estado de inestabilidad de microsatélites y la carga mutacional.

El objetivo de nuestro trabajo es exponer el impacto del estudio molecular Next Generetion Sequencing (NGS) en el diagnóstico y tratamiento de estos tumores.

MATERIAL Y MÉTODOS.

Solicitamos estudio NGS en 12 pacientes con neoplasias de diversa histología. El criterio de selección de las mismas fue la percepción subjetiva del beneficio. De este modo, se seleccionaron 3 casos de tumores huérfanos por baja prevalencia (carcinoma de pene, carcinoma de uretra de histología escamosa, carcinoma de uretra de histología adenocarcinoma), 1 caso de tumor de origen desconocido, 2 casos de tumores de evolución atípica (mama triple negativo y melanoma BRAF wild type) y 6 casos de neoplasias progresadas a múltiples líneas de tratamiento y sin opciones terapéuticas en la actualidad (5 casos de neoplasias ginecológicas y un caso de carcinoma de próstata). De estos casos, 9 fueron valorables por ser la muestra satisfactoria.

RESULTADOS.

La **tabla 1** muestra el beneficio en cada caso.

Diagnóstico histológico	Calidad de la muestra / Alteración molecular	Alternativa terapéutica
Carcinoma escamoso de uretra metastásico	KRAS G12C RAF1 amplification CDKN1A G72fs*69 CREBBP Q1619fs*16 MLL2 L494fs*436 NOTCH2 W10* RB1 P777fs*33 TERT promoter -124C>T TP53 E258Q, R273L Microsatellite status MS-Stable Tumor Mutation Burden TMB-Intermediate; 11 Muts/Mb	• Beneficio esperado de inmunoterapia. • Cuatro terapias aprobadas en otra indicación. • EC potenciales
Adenocarcinoma de uretra metastásico	Muestra insuficiente	
Carcinoma de pene localmente avanzado	CCND1 amplification CD274 (PD-L1) amplification PDCD1LG2 (PD-L2) amplification ATR E54* FGF19 amplification FGF3 amplification FGF4 amplification FOXP1 duplication exons 12-14 JAK2 amplification PIK3CG amplification — equivocal‡ TP53 R248W Microsatellite status MS-Stable Tumor Mutation Burden TMB-Intermediate; 15 Muts/Mb	• Beneficio esperado de inmunoterapia. • Ocho terapias aprobadas en otra indicación. • EC potenciales
Tumor de origen desconocido metastásico	Genomic Alteration Identified† ROS1 G1196R Microsatellite status MS-Stable Tumor Mutation Burden TMB-Low; 0 Muts/Mb	• No terapias en indicación ni otra indicación. • No candidata a EC
Melanoma metastásico	BRAF V600E	• Cambio de estatus de BRAF. • Cuatro terapias aprobadas en indicación y una fuera de indicación. • EC potenciales
Carcinoma de mama triple negativo metastásico	NF1 Q1174* MYC amplification TP53 R110fs*13 Microsatellite status MS-Stable Tumor Mutation Burden TMB-Low; 1 Muts/Mb	• Impicación pronóstica conocida. • Dos terapias aprobadas fuera de indicación. • EC potenciales
Carcinoma de próstata metastásico	AR amplification TMPRSS2 TMPRSS2 ERG fusion ARID1B rearrangement intron 11 CCNE1 amplification CIC loss IGF1R amplification TP53 R110fs*13, R196* Microsatellite status MS-Stable Tumor Mutation Burden TMB-Low; 4 Muts/Mb	• Nueve terapias aprobadas en indicación. • EC potenciales
Carcinoma endometrioide de endometrio metastásico	KRAS G12A PTEN A126T PIK3R1 N564D Microsatellite status MS-Stable Tumor Mutation Burden TMB-Low; 3 Muts/Mb	• Cuatro terapias aprobadas fuera de indicación. • EC potenciales
Carcinoma de ovario metastásico	TP53 V157G RBM10 Q155fs*21 Microsatellite status MS-Stable Tumor Mutation Burden TMB-Low; 1 Muts/Mb	• EC potenciales
Carcinoma de endometrio metastásico	PTEN R130G APC S1465fs*3 ARID1A K974* TP53 R273C Microsatellite status MS-Stable Tumor Mutation Burden TMB-Low; 5 Muts/Mb	• Dos terapias aprobadas fuera de indicación. • EC potenciales
Carcinoma de ovario metastásico	Muestra insuficiente	
Carcinoma de ovario metastásico	Muestra insuficiente	

CONCLUSIONES. Los estudios de NGS suponen una nueva oportunidad para la orientación terapéutica. La posibilidad de dirigir a los pacientes a ensayos clínicos con criterios de selección moleculares podría ser una de las aplicaciones más directas de estas nuevas herramientas diagnósticas.

MATERIAL Y MÉTODOS

Solicitamos estudio NGS en 12 pacientes con neoplasias de diversa histología. El criterio de selección de las mismas fue la **percepción subjetiva del beneficio**. S**e seleccionaron 3 casos de tumores huérfanos** (carcinoma de pene, carcinoma de uretra de histología escamosa, carcinoma de uretra de histología adenocarcinoma), **1 caso de tumor de origen desconocido**, **2 de evolución atípica** (mama triple negativo y melanoma BRAF wild type) y **6 casos de neoplasias progresadas a múltiples líneas de tratamiento y sin opciones terapéuticas** (5 ginecológicas y un caso de carcinoma de próstata). De estos casos, **9 fueron valorables por ser la muestra satisfactoria**.

Melanoma metastásico	BRAF V600E	• Cambio de estatus de BRAF. • Cuatro terapias aprobadas en indicación y una fuera de indicación. • EC potenciales
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Carcinoma de próstata metastásico	AR amplification TMPRSS2 TMPRSS2 ERG fusion ARID1B rearrangement intron 11 CCNE1 amplification CIC loss IGF1R amplification TP53 R110fs*13, R196* Microsatellite status MS-Stable Tumor Mutation Burden TMB-Low; 4 Muts/Mb	• Nueve terapias aprobadas en indicación. • EC potenciales
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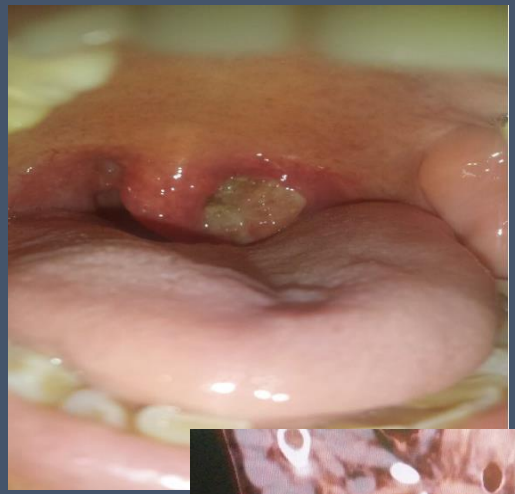
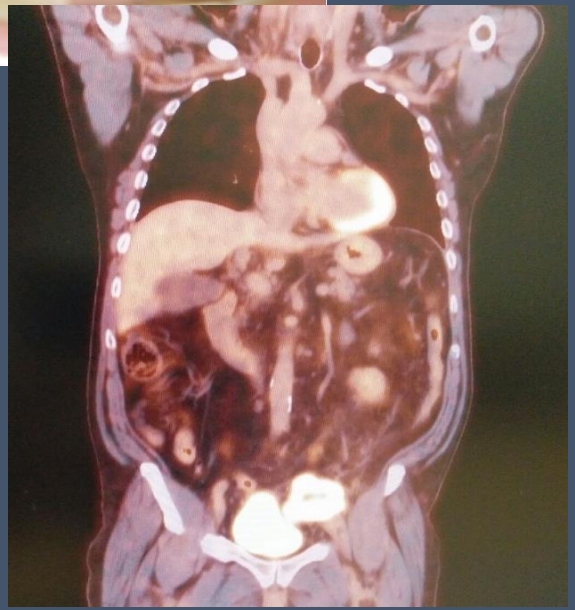
Carcinoma de ovario metastásico	Muestra insuficiente	
Carcinoma de ovario metastásico	Muestra insuficiente	

Diagnóstico histológico	Calidad de la muestra	Alteración molecular	Alternativa terapéutica
Carcinoma escamoso de uretra metastásico	KRAS G12C RAF1 amplification CDKN1A G72fs*69 CREBBP Q1619fs*16 MLL2 L494fs*436 NOTCH2 W10* RB1 P777fs*33 TERT promoter -124C>T TP53 E258Q, R273L Microsatellite status MS-Stable Tumor Mutation Burden TMB-Intermediate; 11 Muts/Mb		• Beneficio esperado de inmunoterapia. • Cuatro terapias aprobadas en otra indicación. • EC potenciales
Adenocarcinoma de uretra metastásico	Muestra insuficiente		
Carcinoma de pene localmente avanzado	CCND1 amplification CD274 (PD-L1) amplification PDCD1LG2 (PD-L2) amplification ATR E54* FGF19 amplification FGF3 amplification FGF4 amplification FOXP1 duplication exons 12-14 JAK2 amplification PIK3CG amplification — equivocal‡ TP53 R248W Microsatellite status MS-Stable Tumor Mutation Burden TMB-Intermediate; 15 Muts/Mb		• Beneficio esperado de inmunoterapia. • Ocho terapias aprobadas en otra indicación. • EC potenciales
Tumor de origen desconocido metastásico	Genomic Alteration Identified† ROS1 G1196R Microsatellite status MS-Stable Tumor Mutation Burden TMB-Low; 0 Muts/Mb		• No terapias en indicación ni otra indicación. • No candidata a EC





CASO 2

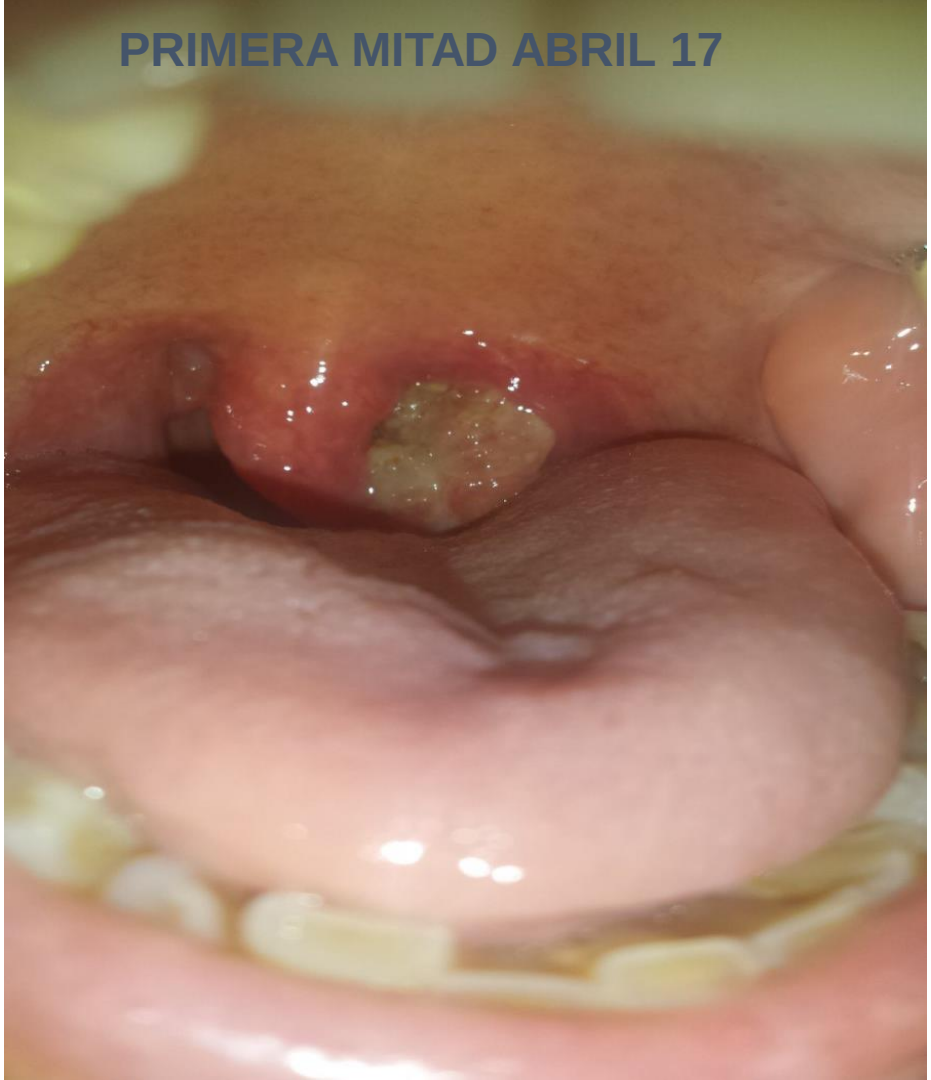
AP**:** Carcinoma urotelial de alto grado pTXG3 Lx con amplias áreas de necrosis. La inmunohistoquímica describió citoqueratina y GATA débil, negativo para PSA, CD 138 y para sinaptofisina.

1º linea CARBO-TAXOL: RC

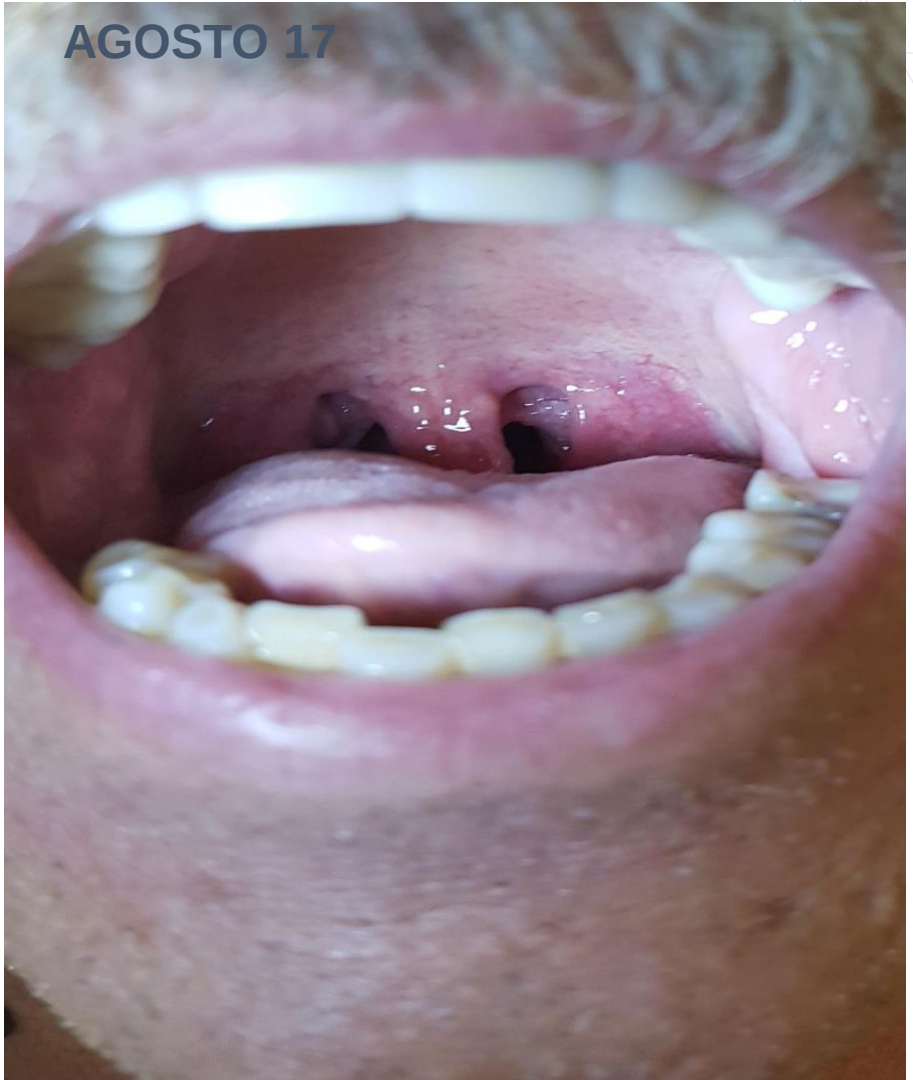
A los 5 meses (febrero 2017) consulta con ORL por odinofagia + lesión en **amígdala izquierda** que no mejora con tratamiento antibiótico.

Biopsia: carcinoma pobremente diferenciado.

PRIMERA MITAD ABRIL 17



AGOSTO 17



ABOUT THE TEST:

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

PATIENT RESULTS

12 genomic findings

4 therapies associated with potential clinical benefit

0 therapies associated with lack of response

10 clinical trials

TUMOR TYPE: NASOPHARYNX AND PARANASAL SINUSES UNDIFFERENTIATED CARCINOMA

Genomic Alterations Identified†

KRAS G12C
RAF1 amplification
CDKN1A G72fs*69
CREBBP Q1619fs*16
MLL2 L494fs*436
NOTCH2 W10*
RB1 P777fs*33
TERT promoter -124C>T
TP53 E258Q, R273L

Additional Findings†

Microsatellite status MS-Stable

Tumor Mutation Burden TMB-Intermediate; 11 Muts/Mb

† For a complete list of the genes assayed and performance specifications, 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
KRAS G12C	None	Cobimetinib Trametinib	Yes, see clinical trials section
RAF1 amplification	None	Cobimetinib Regorafenib Sorafenib Trametinib	Yes, see clinical trials section
CDKN1A G72fs*69	None	None	None
CREBBP Q1619fs*16	None	None	None

For further information and assistance please call Roche Customer Care: +49 7624 14 2098 or email at europe.foundationmedicine@roche.com

Electronically Signed by Jeffrey S. Ross, M.D. | Jeffrey S. Ross, M.D., Medical Director | 11 January 2018

Sample Preparation: Nonnenwald 2, 82377 Penzberg, Germany
Sample Analysis: Nonnenwald 2, 82377 Penzberg, Germany

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
A Multiarm, Open-label, Phase 1b Study of MLN2480 (an Oral A-, B-, and CRAF Inhibitor) in Combination With MLN0128 (an Oral mTORC 1/2 Inhibitor), or Alisertib (an Oral Aurora A Kinase Inhibitor), or Paclitaxel, or Cetuximab, or Irinotecan, in Adult Patients With Advanced Nonhematologic Malignancies	Phase 1	Aurora kinase A, EGFR, RAFs, mTORC1, mTORC2	Toulouse cedex 09 (France), Villejuif cedex (France), Pennsylvania, Bordeaux cedex (France), Madrid (Spain), Massachusetts, Malaga (Spain), Barcelona (Spain), Texas, London (United Kingdom), Oxford (United Kingdom), Manchester (United Kingdom)	NCT02327169
A Phase Ib/IIa Study of AZD2014 in Combination With Selumetinib in Patients With Advanced Cancers	Phase 1 / Phase 2	mTORC1, MEK, mTORC2	London (United Kingdom)	NCT02583542
A Sequential Phase I Study of MEK1/2 Inhibitors PD-0325901 or Binimetinib Combined With cMET Inhibitor PF-02341066 in Patients With RAS Mutant and RAS Wild Type (With Aberrant c-MET) Colorectal Cancer	Phase 1	MET, ALK, ROS1, MEK, AXL, TRKC, TRKA	Oxford (United Kingdom)	NCT02510001
Targeted Agent and Profiling Utilization Registry (TAPUR) Study	Phase 2	ABL, CDK4, PARP, EGFR, DDR2, PDGFRs,	North Dakota, Pennsylvania, Washington, Illinois, Georgia, Arizona, Utah, North Carolina, Oklahoma, South Dakota,	NCT02693535

Hospitales Universitarios Virgen Macarena

CASO 2

VALOR DE LA CARACTERIZACIÓN MOLECULAR Y DEL MICROAMBIENTE INMUNE EN TUMORES DE ORIGEN DESCONOCIDO: CARCINOIDE DE BAJO GRADO Y ORIGEN DESCONOCIDO.

Pablo Espejo García, Carmen Beato Zambrano, Lourdes Sevilla Ortega, Francisco Valdivia García, Luis de la Cruz Merino. Hospital Universitario Virgen Macarena.

INTRODUCCIÓN Y OBJETIVOS

Los TOD son considerados una p
beneficio de alguna terapia sob
molecular y del microambiente in

Por otro lado, según la literat
aproximadamente del 3 al 5 %
minuciosa evaluación anatomo-p
para su estudio y las diferentes
inmunohistoquímica.

MATERIAL Y MÉTODOS

Presentamos las caracterís
moleculares e inmunes extraída
un perfil de Next Genera
Sequencing (NGS) en una pac
con TOD de histología carcinoi
bajo grado, inicialmente tipifi
como de histología poco diferen
y origen desconocido.

RESULTADOS

Los hallazgos objetivados fueron
una baja carga de mutaciones t
CD8+ fueron consideradas baja
neoplasias pancreáticas si bien r
no ha sido caracterizada y su e
cáncer, lo que podría indicar su
han demostrado dar como resul
inhibidores no serían eficaces en

CONCLUSIONES

El proceso diagnóstico de los TO
solicitud del estudio molecular m
descrito en este contexto y con u

FOUNDATIONONE®

Patient Name	Report Date	Tumor Type
2503810573, ES	**04 January 2018**	**Pancreas neuroendocrine tumor (pNET)**

Date of Birth	01 June 1955	**Medical Facility**	Hospital Universitario Virgen Macarena		
Sex	Female	**Ordering Physician**	Beato, Carmen	**Specimen Received**	20 December 2017
FMI Case #	PRF500973	**Additional Recipient**	Not Given	**Specimen Site**	Liver
Medical Record #	Not Given	**Medical Facility ID #**	500261	**Date of Collection**	20 July 2017
Specimen ID	B17-12407 A1	**Pathologist**	Dr. Rios Martin, Juan Jose	**Specimen Type**	Block

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PATIENT RESULTS

3 genomic findings

0 therapies associated with potential clinical benefit

0 therapies associated with lack of response

0 clinical trials

TUMOR TYPE: PANCREAS NEUROENDOCRINE TUMOR (PNET)

Genomic Alteration Identified†

ROS1 G1196R

Additional Findings†

Microsatellite status MS-Stable

Tumor Mutation Burden TMB-Low; 0 Muts/Mb

Servicio Andaluz de Salud CONSEJERÍA DE SALUD

THERAPEUTIC IMPLICATIONS

Genomic Findings Detected	FDA-Approved Therapies (in patient's tumor type)	FDA-Approved Therapies (in another tumor type)	Potential Clinical Trials
Microsatellite status MS-Stable	None	None	None
ROS1 G1196R	None	None	None
Tumor Mutation Burden TMB-Low; 0 Muts/Mb	None	None	None

Informe RAECO (Ensayos Clínicos en Andalucía) - Tumores Sólidos, fase 1*

Patología	Ensayo	Línea	Centros
T. Sólidos	Fase II abierto de Entrectinib en TS avanzados o metastásicos que albergan reordenamiento de los genes NTRK1/2/3 ROS o ALK	Politratados	HUVR H. Málaga
T. Sólidos	ESTUDIO MULTICENTRICO FASE 2 NIVOLUMAB EN COMBINACION CON IPILIMUMAB PARA PACIENTES CON TUMORES PEDIATRICOS SOLIDOS AVANZADOS	1ª línea o posteriores	HUVM
T. Sólidos	A Phase 1b/2 dose escalation and cohort expansion study of the safety, tolerability and efficacy of a novel transforming growth factor–Receptor I Kinase Inhibitor (Galunisertib) administered in combination with Anti–	NA	H. Málaga

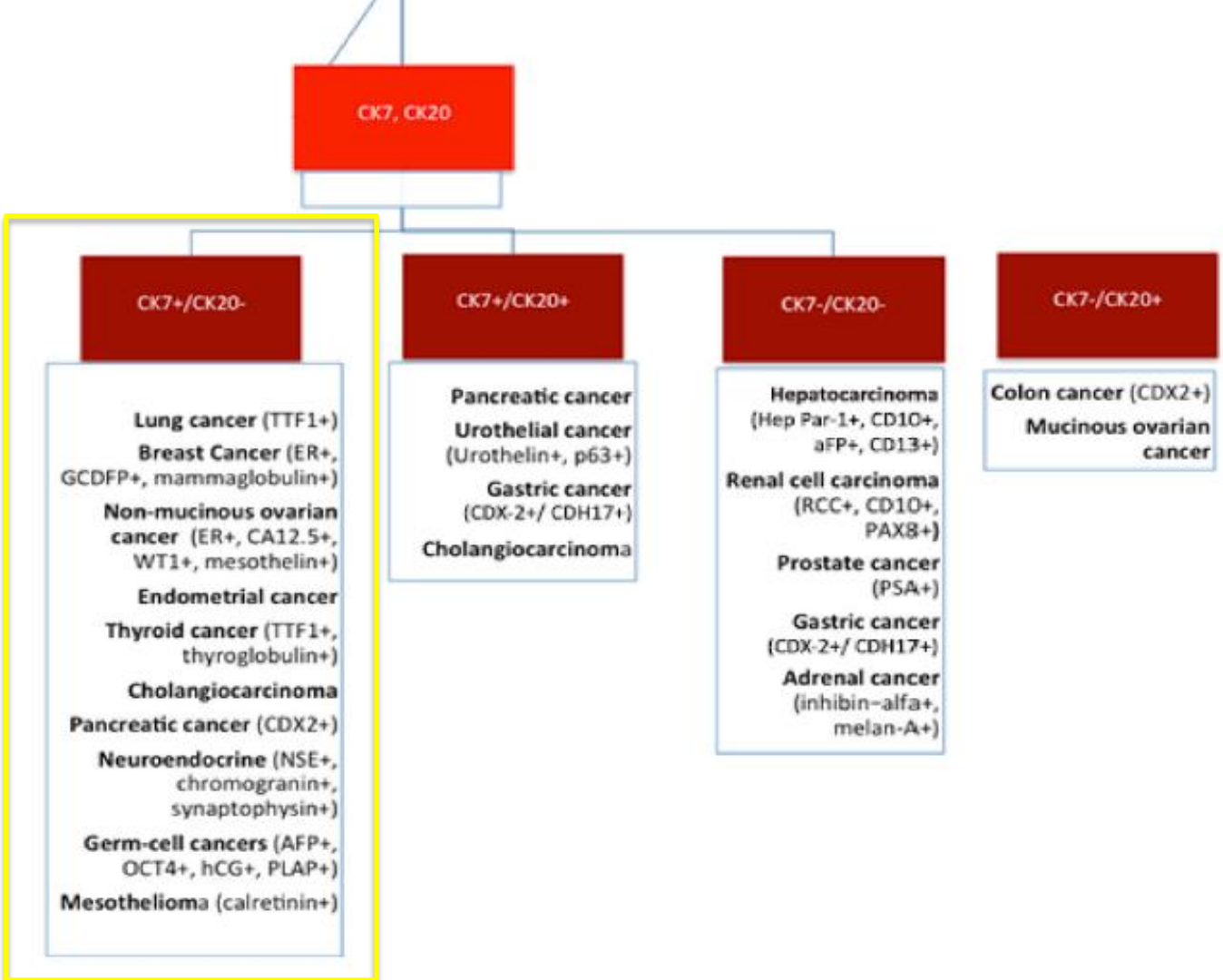
THERAPEUTIC IMPLICATIONS

Genomic Findings Detected	FDA-Approved Therapies (in patient's tumor type)	FDA-Approved Therapies (in another tumor type)	Potential Clinical Trials
Microsatellite status MS-Stable	None	None	None
ROS1 G1196R	None	None	None
Tumor Mutation Burden TMB-Low; 0 Muts/Mb	None	None	None

● ***ROS1***
G1196R

Gene and Alteration: The ROS1 oncogene encodes a tyrosine kinase of the insulin receptor family that plays a role in regulating cellular growth and differentiation by activating several signaling pathways, including those involving mitogen-activated protein kinase ERK1/2, phosphatidylinositol 3-kinase (PI3K), protein kinase B (AKT), STAT3, and Vav3[47]. The ROS1 alteration observed here has not been characterized and its effect on function is unclear; however, it has been reported in the context of cancer, which may indicate biological relevance. In addition, only ROS1 fusions have been found to result in constitutive activation of ROS1, suggesting ROS1 inhibitors may not be relevant in this case.

Frequency and Prognosis: ROS1 mutations have been reported in less than 1% of pancreatic malignancies in the COSMIC database, being most prevalent in pancreatic ductal adenocarcinoma, and have not been a significant topic of investigation in this disease context (Mar 2017).


CK7, CK20
CK7+/CK20-
Lung cancer (TTF1+)
Breast Cancer (ER+, GCDFP+, mammaglobulin+)
Non-mucinous ovarian cancer (ER+, CA12.5+, WT1+, mesothelin+)
Endometrial cancer
Thyroid cancer (TTF1+, thyroglobulin+)
Cholangiocarcinoma
Pancreatic cancer (CDX2+)
Neuroendocrine (NSE+, chromogranin+, synaptophysin+)
Germ-cell cancers (AFP+, OCT4+, hCG+, PLAP+)
Mesothelioma (calretinin+)
CK7+/CK20+
Pancreatic cancer
Urothelial cancer (Urothelin+, p63+)
Gastric cancer (CDX-2+/ CDH17+)
Cholangiocarcinoma
CK7-/CK20-
Hepatocarcinoma (Hep Par-1+, CD10+, aFP+, CD13+)
Renal cell carcinoma (RCC+, CD10+, PAX8+)
Prostate cancer (PSA+)
Gastric cancer (CDX-2+/ CDH17+)
Adrenal cancer (inhibin-alfa+, melan-A+)
CK7-/CK20+
Colon cancer (CDX2+)
Mucinous ovarian cancer

PATIENT RESULTS

13 genomic findings

8 therapies associated with potential clinical benefit

0 therapies associated with lack of response

11 clinical trials

TUMOR TYPE: PENIS SQUAMOUS CELL CARCINOMA (SCC)

Genomic Alterations Identified†

CCND1 amplification
CD274 (PD-L1) amplification
PDCD1LG2 (PD-L2) amplification
ATR E54*
FGF19 amplification
FGF3 amplification
FGF4 amplification
FOXP1 duplication exons 12-14
JAK2 amplification
PIK3CG amplification – equivocal#
TP53 R248W

Additional Findings†

Microsatellite status MS-Stable
Tumor Mutation Burden TMB-Intermediate; 15 Muts/Mb

THERAPEUTIC IMPLICATIONS

Genomic Findings Detected	FDA-Approved Therapies (in patient's tumor type)	FDA-Approved Therapies (in another tumor type)	Potential Clinical Trials
CCND1 amplification	None	Abemaciclib Palbociclib Ribociclib	Yes, see clinical trials section
CD274 (PD-L1) amplification	None	Nivolumab Pembrolizumab Atezolizumab Avelumab Durvalumab	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
PDCD1LG2 (PD-L2) amplification	None	Atezolizumab Pembrolizumab Nivolumab Avelumab Durvalumab	Yes, see clinical trials section

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
An Open-label, Multicenter, Dose Escalation Phase Ib Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Therapeutic Activity of RO7009789 (CD40 Agonist) in Combination With MPDL3280A (ANTI−PD-L1) in Patients With Locally Advanced and/or Metastatic Solid Tumors.	Phase 1	PD-L1, CD40	(Canada), (Denmark), (France), (Netherlands), (Spain)	NCT02304393
An Open-Label, Multicenter Phase Ib Study of The Safety and Tolerability of Atezolizumab (Anti-PD-L1 Antibody) Administered in Combination With Bevacizumab and/or Other Treatments in Patients With Solid Tumors	Phase 1	PD-1, VEGFR1, VEGFR2	California, Colorado, Connecticut, District of Columbia, Massachusetts, Minnesota, New York, North Carolina, Tennessee, (Korea, Republic of)	NCT02715531
A Phase 1 Dose Escalation and Cohort Expansion Study of the Safety, Tolerability, and Efficacy of Anti-LAG-3 Monoclonal Antibody (BMS-986016) Administered Alone and in Combination With Anti-PD-1 Monoclonal Antibody (Nivolumab, BMS-936558) in Advanced Solid Tumors	Phase 1/Phase 2	LAG-3, PD-1	Illinois, Maryland, Massachusetts, Michigan, New York, Oregon, Pennsylvania, Washington, Amsterdam (Netherlands), Barcelona (Spain), Copenhagen (Denmark), Essen (Germany), Greater London (United Kingdom), Helsinki (Finland)	NCT01968109

CASO CLÍNICO ASISTENCIAL

CASO 4

- **Varón, 36 años**.
- Sin hábitos tóxicos ni enfermedades de interés.
- Acude a Urgencias el 1/05/18 por **dolor y distensión abdominal** asociado a **síndrome constitucional** (pérdida de unos 5 kg de peso en el último mes).
- Exploración: Buen estado general. Eupneico. Bien perfundido e hidratado. Exploración orofaríngea sin hallazgos. Auscultación cardiopulmonar normal. Abdomen con dolor a la palpación en epigastrio, hipocondrio derecho y **hepatomegalia** de unos 2-3 traveses de dedo.
- Pruebas complementarias: Analítica de urgencias: hipertransaminasemia leve (GOT: 66 UI/l; GPT: 63 UI/l). Ecografía abdominal: **hígado** de contornos lobulados, **con múltiples lesiones nodulares de naturaleza probablemente metastásica**.
- Ingresa en Medicina Interna para estudio.

Caso de las Dras. Marta Espinosa y Lourdes Sevilla, presentado en GETHI 2018

- **Marcadores tumorales** normales, salvo:
  - Ca 125: 428 U/ml (5,0-35,0)
  - Ca 15,3: 200 U/ml (2,0-37,0)
  - Beta-2 microglobulina: 2,52 mg/l (0,80-2,20).

- **Gastroscopia** y **colonoscopia**: sin hallazgos de interés.

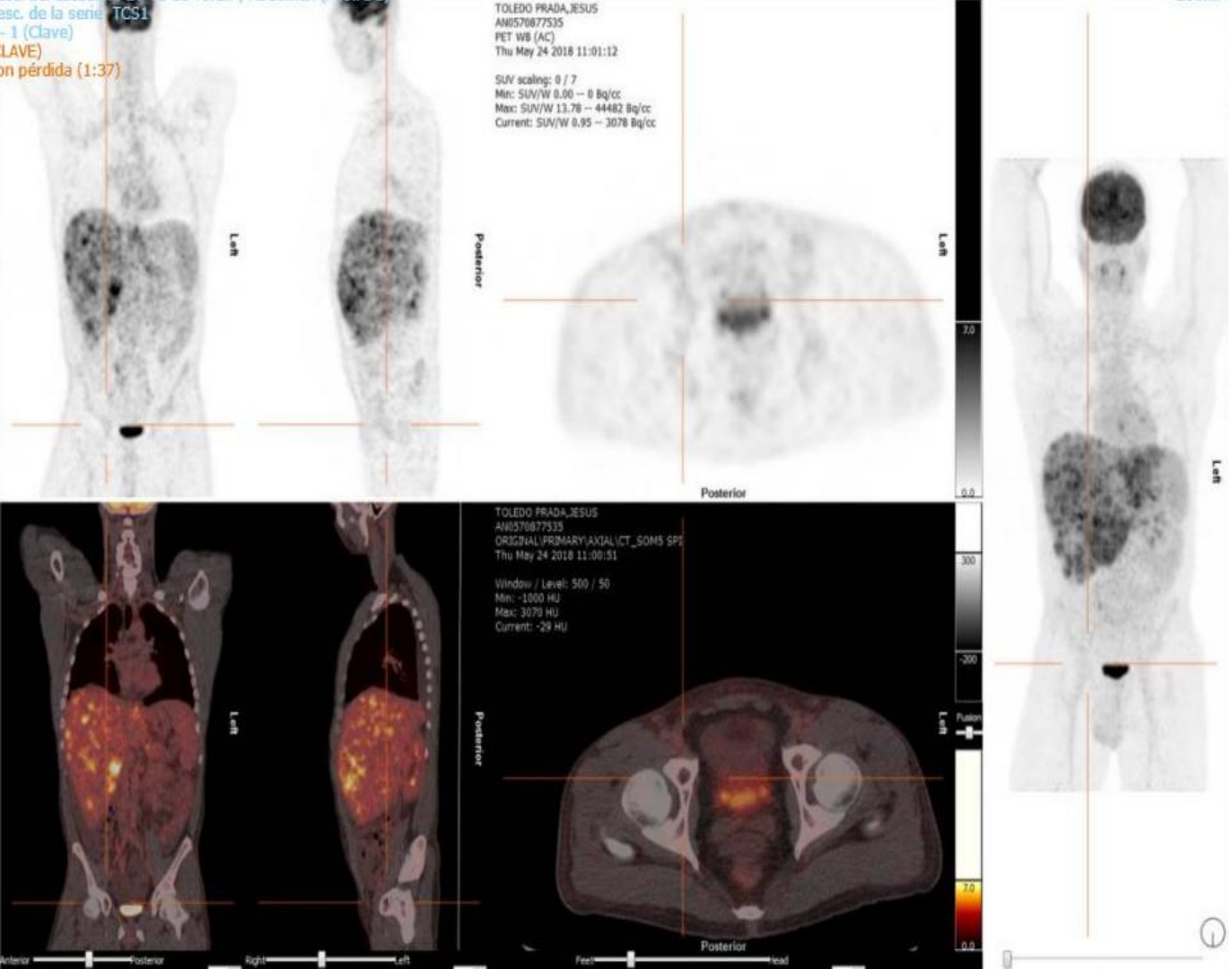
- **TAC de tórax, abdomen y pelvis**:

  - Tórax: No se observan nódulos pulmonares. Mínimo derrame pleural izquierdo. Signos de tromboembolismo pulmonar subsegmentario, sin áreas de infarto pulmonar.

  - Abdomen: Hepatomegalia con incontables lesiones hipodensas ocupantes de espacio. Lesión hipodensa en cuerpo pancreático de unos 27x17 mm con posible infiltración de arteria esplénica. Pequeñas adenopatías perihepáticas y retroperitoneales. Trombosis de venas ilíaca común e interna izquierdas.

  - Conclusión: Proceso neoplásico avanzado, probablemente se trate de un tumor primario pancreático con múltiples metástasis hepáticas, adenopatías y ascitis.

- **Ecoendoscopia**: Adenopatía de 1 cm en cabeza pancreática y varias en hilio hepático. Numerosas lesiones ocupantes de espacio hepáticas sólidas y quísticas, realizándose punción de ambos tipos de lesiones y enviando muestras a citología y microbiología.



PET-TAC:

Hepatomegalia con múltiples lesiones hipermetabólicas sugestivas de malignidad.

Posible lesión de moderada tasa de proliferación celular en cuerpo pancreático.

Ascitis y derrame pleural de moderada cuantía.

- **Hallazgos citológicos indicativos de carcinoma.**

- La neoplasia está constituida por grupos cohesivos de células de pequeño tamaño con escaso citoplasma y núcleos redondeados con nucleolo evidente.

- El índice de proliferación valorado con Ki67 es del 40%.

- **Estudio inmunohistoquímico**:
  - PanCK positiva
  - CK7 negativa, CK20 negativa
  - Marcadores neuroendocrinos (sinaptofisina, cromogranina y CD56) negativos.
  - TTF1 negativo.
  - PLAP negativa.

- **Estos hallazgos permiten descartar origen neuroendocrino, pulmonar y gastrointestinal.**

NEOPLASIA (CARCINOMA) DE ORIGEN DESCONOCIDO con afectación hepática múltiple, ascitis y adenopática/masa adyacente a cuerpo pancreático.

- 22/05/18: Primer ciclo QT según esquema **Carboplatino-Paclitaxel** (cada 21 días).

- Gran mejoría clínica.

- Cita en CCEE de Oncología Médica.
  - BAG hepática para repetir IHQ.
  - Foundation one

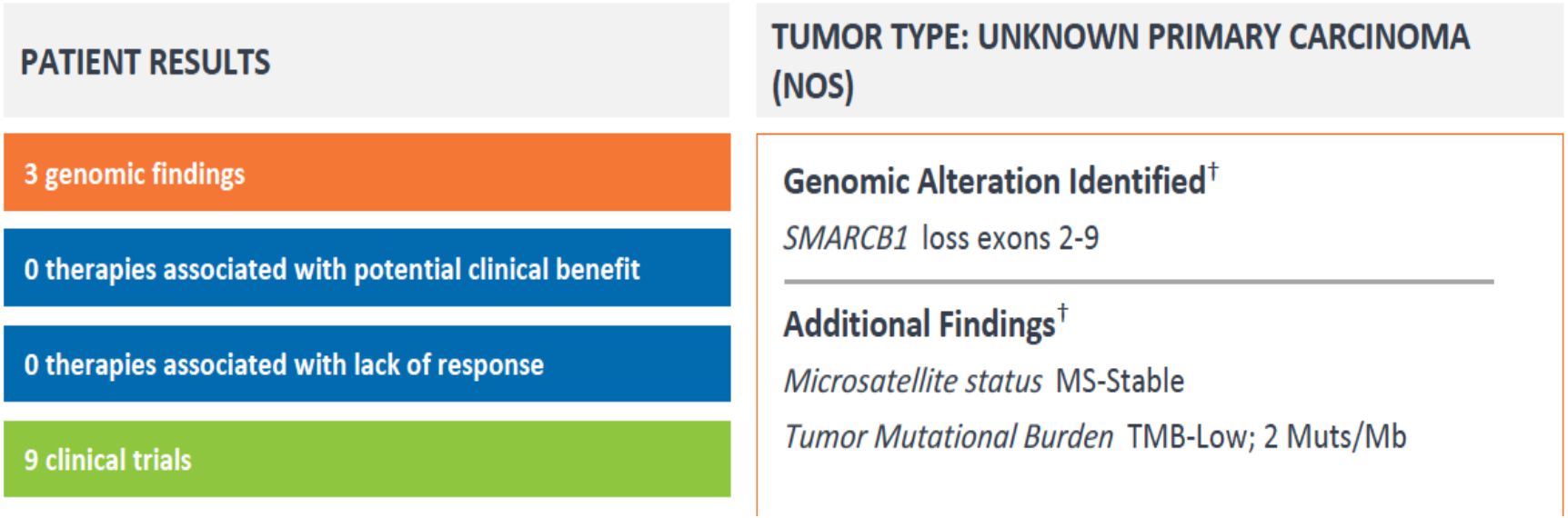
BAG HEPÁTICA:

Adenocarcinoma poco diferenciado.

- Estudio inmunohistoquímico:
  - Positivo para panCK y GATA3 (<5% del tumor).
  - Negativo para CK7, CK20, RCC, p63, MelanA, PSA, ERG, cromogranina, sinaptofisina, CD10, CD30, PLAP, PAX8 y Heppar1.
  - Con la inmunotinción para alfa-fetoproteína existe una muy débil positividad.

FOUNDATION ONE:

- Alteración genómica identificada: **SMARCB1 (loss exons 2-9).** Presente en:
  - 65% de los **tumores rabdoides**.
  - 7% de los tumores del SNC.
  - 2% de los tumores intestinales.
  - 2% de los tumores óseos.



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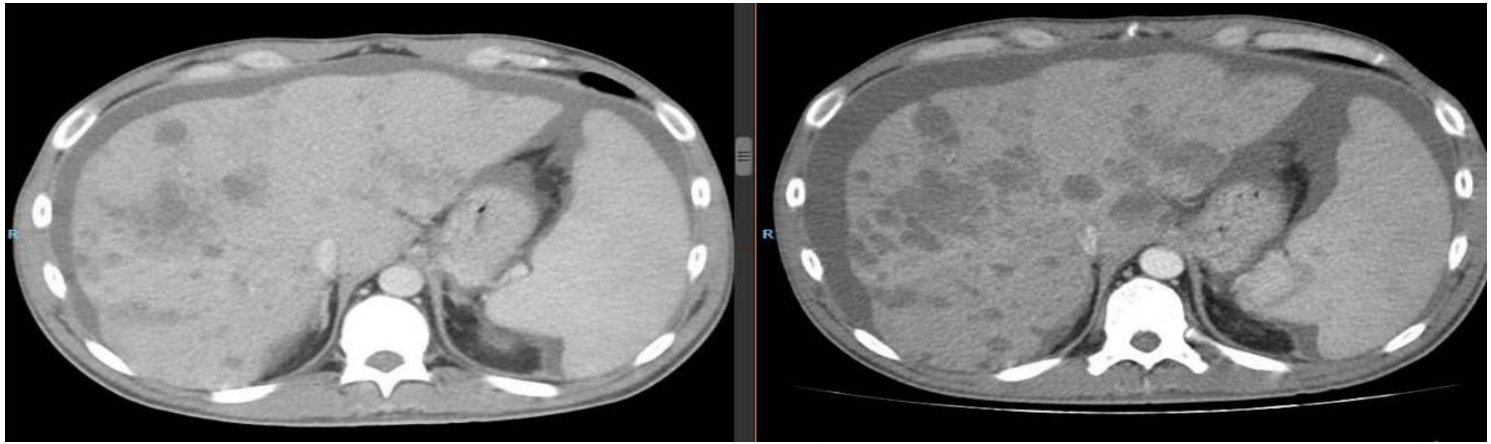
  - 2% de los tumores óseos.

Octubre/18:

- **TAC de reevaluación a los 6 ciclos: progresión de la enfermedad** a nivel hepático con aumento de la ascitis.



PENDIENTE DE INCLUSIÓN EN EC GETHI NIVORARE

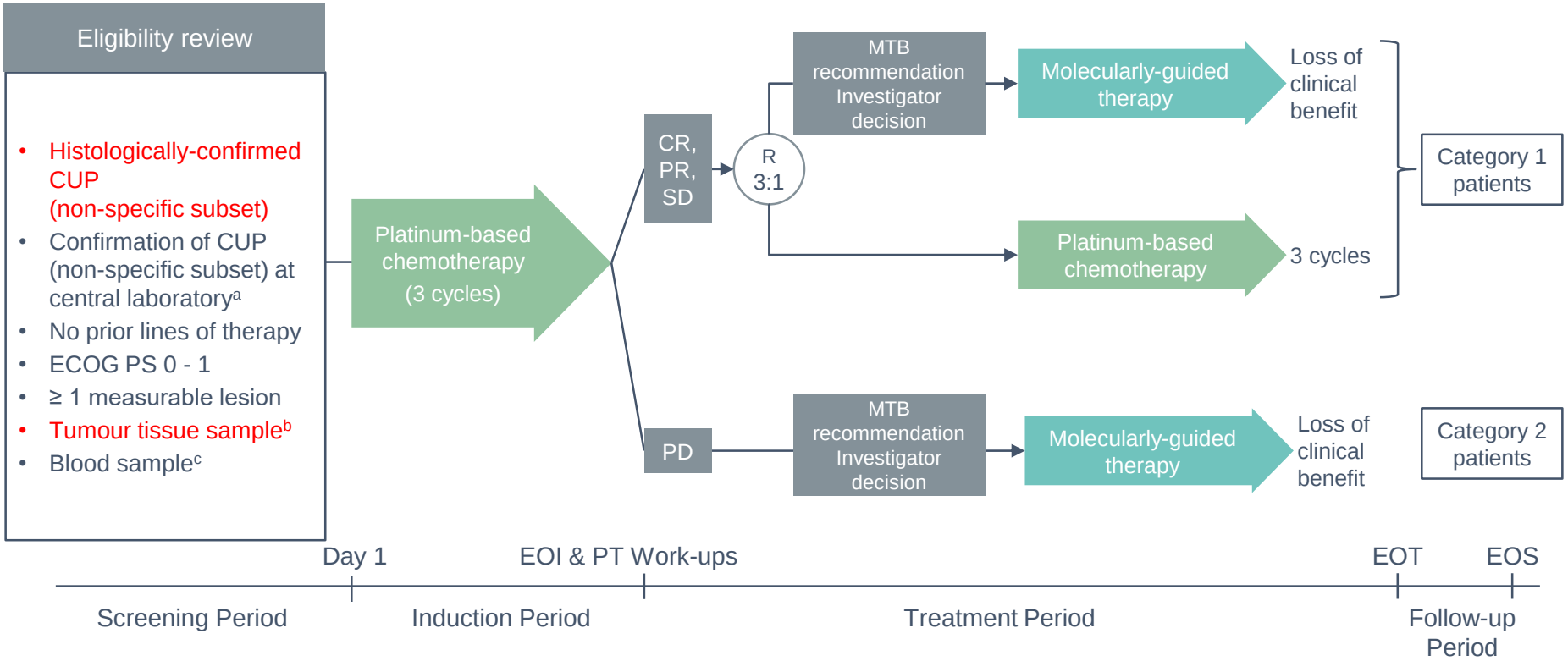
CUPISCO

Cancer of unknown primary (CUP) study

MX39795 – A phase II trial comparing the efficacy and safety of targeted therapy or cancer immunotherapy guided by genomic profiling versus platinum-based chemotherapy in patients with CUP

FOUNDATION MEDICINE® | Roche

Study overview



[a-c]: [For an explanation of footnotes please refer to Figure 2 in the Study protocol.]
CR: complete response; CUP: cancer of unknown primary; ECOG PS: Eastern Cooperative Oncology Group performance status; EOI: end of induction; EOT: end of treatment; MTB: molecular tumour board;
PD: progressive disease; PR: partial response; PT: pre-treatment; R: randomisation; SD: stable disease.

CUPISCO

Main Inclusion criteria

- Histological diagnosis of CUP (non-specific subset), with available report, as determined by the study site's local laboratory on a contemporaneous tissue sample. Types:
  - **Adenocarcinoma of unknown primary site (ACUP)**
  - **Poorly differentiated adenocarcinoma of unknown primary site**
  - **Poorly differentiated carcinoma of unknown primary**
- Naïve to systemic therapy for CUP
- Appropriate candidates for platinum-based doublet chemotherapy
- **ECOG performance status scores of 0 or 1**
- Must have at least one lesion that is measurable according to RECIST v1.1

CUPISCO

IMPORTANTE! Criterios de exclusión

Los pacientes que cumplan cualquiera de los criterios siguientes no podrán participar en el estudio:

* CPD escamoso.

* Pacientes con cualquiera de las neoplasias específicas distintas de CPD que aparecen identificadas en la guía sobre CPD de la ESMO (Fizazi y cols. 2015), entre ellas:

* Cáncer no epitelial.

* Tumor extragonadal de células germinativas.

* Pacientes pertenecientes a cualquiera de los siguientes subgrupos de CPD con pronóstico favorable:

* Carcinoma poco diferenciado con distribución en la línea media.

CUPISCO

IMPORTANTE! Criterios de exclusión

.

* Mujeres con adenocarcinoma papilar de la cavidad peritoneal.

* Mujeres con adenocarcinoma que afecta exclusivamente a los ganglios linfáticos axilares.

* Carcinoma escamoso de los ganglios linfáticos cervicales.

* Tumores neuroendocrinos poco diferenciados.

* Varones con metástasis óseas blásticas y PSA elevado.

* Pacientes con un tumor único, pequeño y potencialmente resecable.

* CPD de tipo cáncer de colon.

CUPISCO

Puntos clave

- Haber realizado todas las pruebas diagnósticas necesarias para descartar tumores de origen conocido según perfil paciente/localización metástasis
- Importancia colaboración **PATÓLOGO**: Diagnóstico local CUP según ESMO 2015. Panel básico:
  - *Leukocyte Common Antigen (LCA)*
  - *Octamer-binding transcription factor 4 (OCT4)*
  - *Human Melanoma Black 45 (HMB45)*
  - *Pan-cytokeratin (pan-CK), panel as used per local practice*
- Disponer de muestra suficiente de tejido **(≤ 3 meses)** para *Foundation Medicine*. Si no, se puede realizar nueva biopsia

Sites participating in Spain

Site	Investigator	
H. Clínic Barcelona	Aleix Prat Aparicio	
H. 12 de Octubre	Juan Antonio Núñez Sobrino	
H. Virgen Macarena	Carmen Beato Zambrano	
Complejo Hospitalario de Navarra	Esteban Salgado Pascual	
H. La Fe	Alejandra Giménez Ortiz	
H. Ramón y Cajal	Federico Longo Muñoz	
H. Clínico San Carlos	Antonio Casado Herráez	
H. Sant Joan Despí (Moisés Broggi)	Ferrán Losa Gaspà	
H. Quirón Madrid	Federico González González	
ICO Bellvitge (H. Duran i Reynals)	Gemma Soler González	

Thank you

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