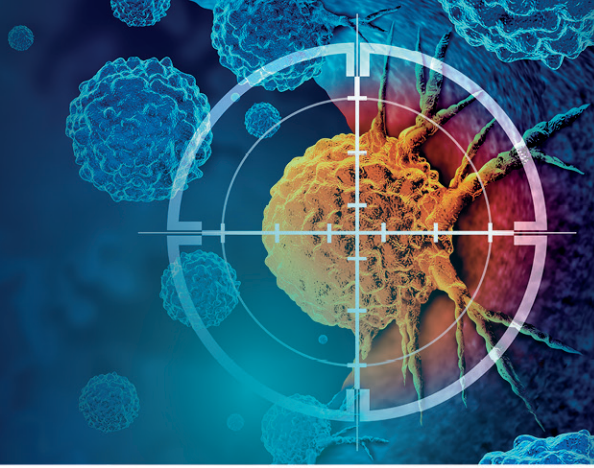
XVIII SIMPOSIUM

BASES BIOLÓGICAS DEL CÁNCER E INNOVACIÓN TERAPÉUTICA

MÁS DE 20 AÑOS A LA VANGUARDIA DE LA FORMACIÓN EN LA BIOLOGÍA Y TRATAMIENTO DEL CÁNCER



¿Qué debemos saber de la biología de los tumores GU? Empezando por lo básico

Ricardo Sánchez-Escribano, Oncología médica HCUV

Conflicto de intereses

- He recibido grant de investigación de Pfizer
- Colaboraciones para eventos educativos independientes de J&J, Bayer, Merck, IPSEN, MSD, Astellas, Ricordati Rare diseases, Rovi, BMS, Gillead, AZ
- Participado en advisory boards para Bayer, Astellas, Merck e IPSEN
- Recibido ayudas para cursos, congresos y bolsa de viaje de J&J, Bayer, Merck, IPSEN, MSD, Astellas, Ricordati Rare diseases, Rovi, BMS, Gillead, AZ
- Ni yo ni mis familiares poseemos acciones de ninguna compañía farmaceutica

AGENDA DE LA PRESENTACIÓN

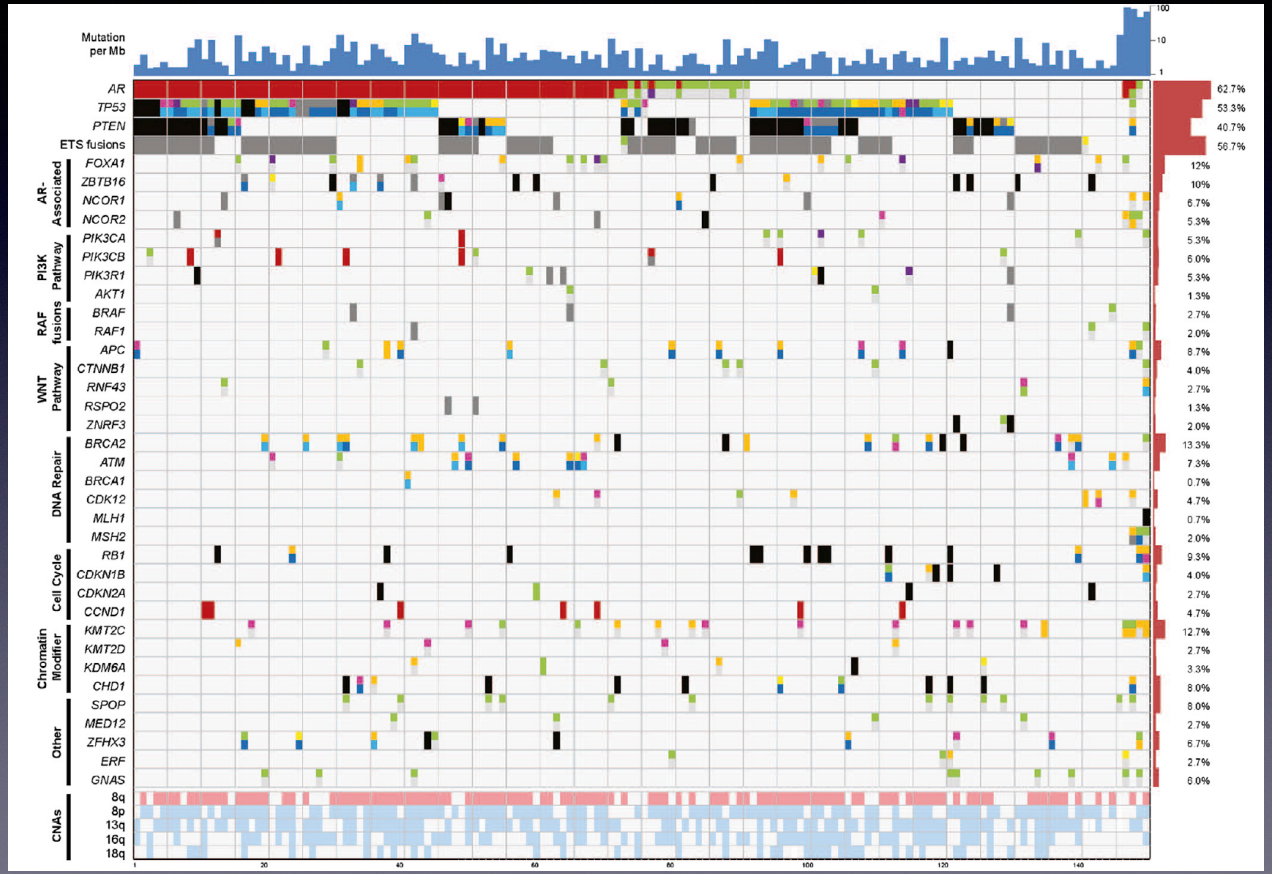
- **Lo básico de CÁNCER DE PRÓSTATA**
- **Lo básico de CÁNCER UROTELIAL**
- **Lo básico de CÁNCER DE RIÑÓN**

¿Qué debemos saber de la biología de los tumores GU?



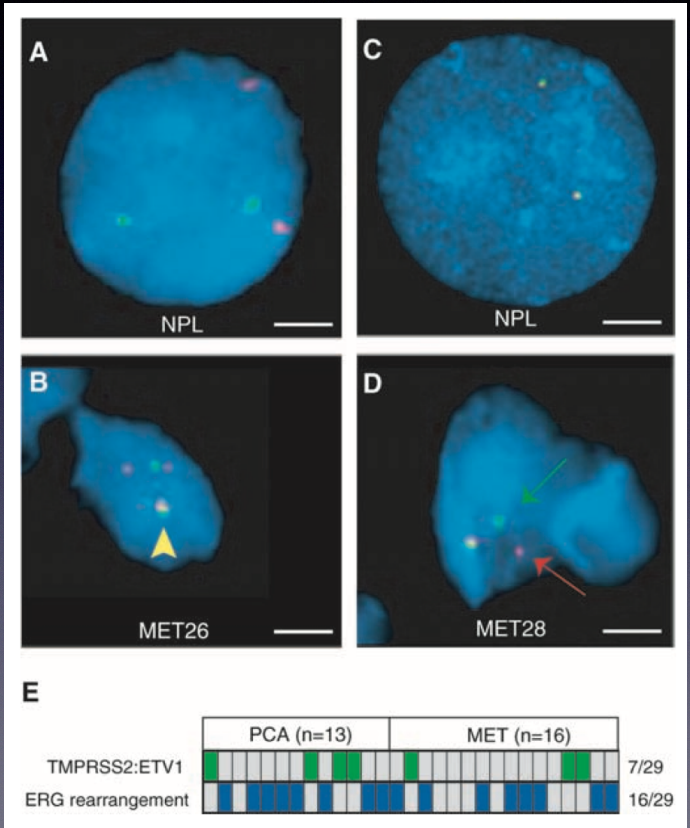
CÁNCER DE PRÓSTATA

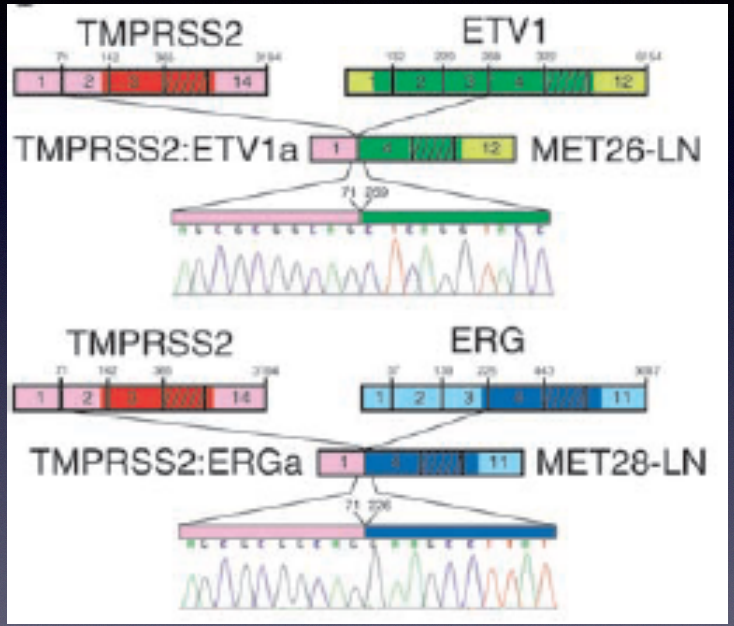
Taxonomía del CPRC



1. Robinson D, Van Allen EM, Wu YM, Schultz N, Lonigro RJ, Mosquera JM, et al. Integrative Clinical Genomics of Advanced Prostate Cancer. Cell. mayo de 2015;161(5):1215-28.

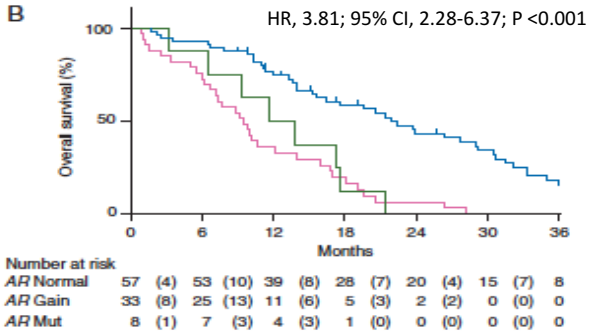
Fusión TMPRSS2-ETS family: evento oncogénico principal en >50% de CaP

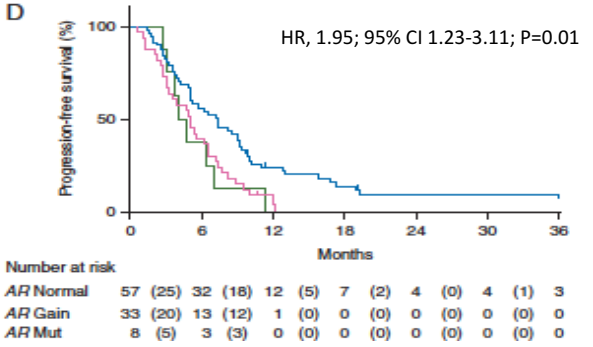




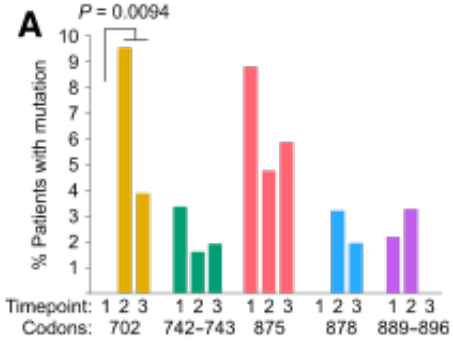
Tomlins SA, Rhodes DR, Perner S, Dhanasekaran SM, Mehra R, Sun XW, et al. Recurrent Fusion of *TMPRSS2* and ETS Transcription Factor Genes in Prostate Cancer. Science. 28 de octubre de 2005;310(5748):644-8.

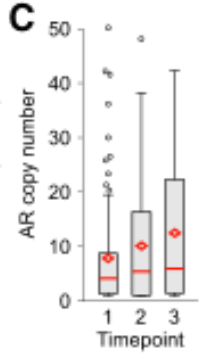
AR aberrations identify patients with worse outcome to new antiandrogens

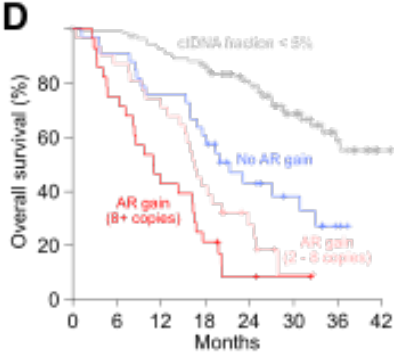


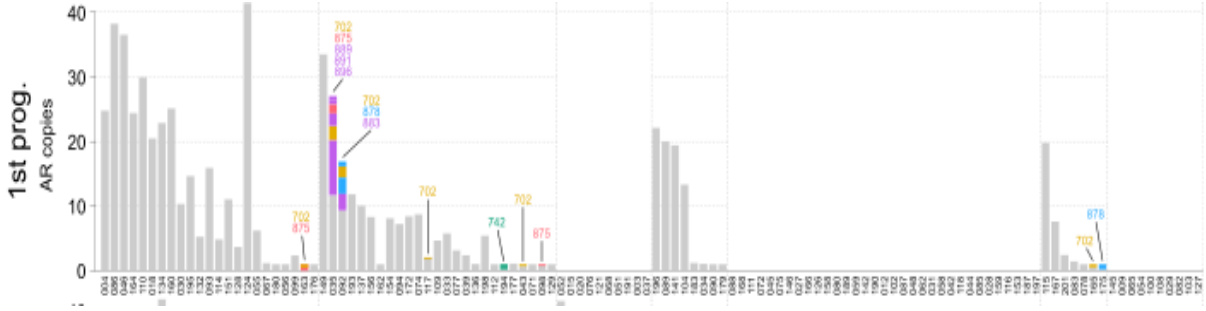


Conteduca V. Annals of Oncology 2017



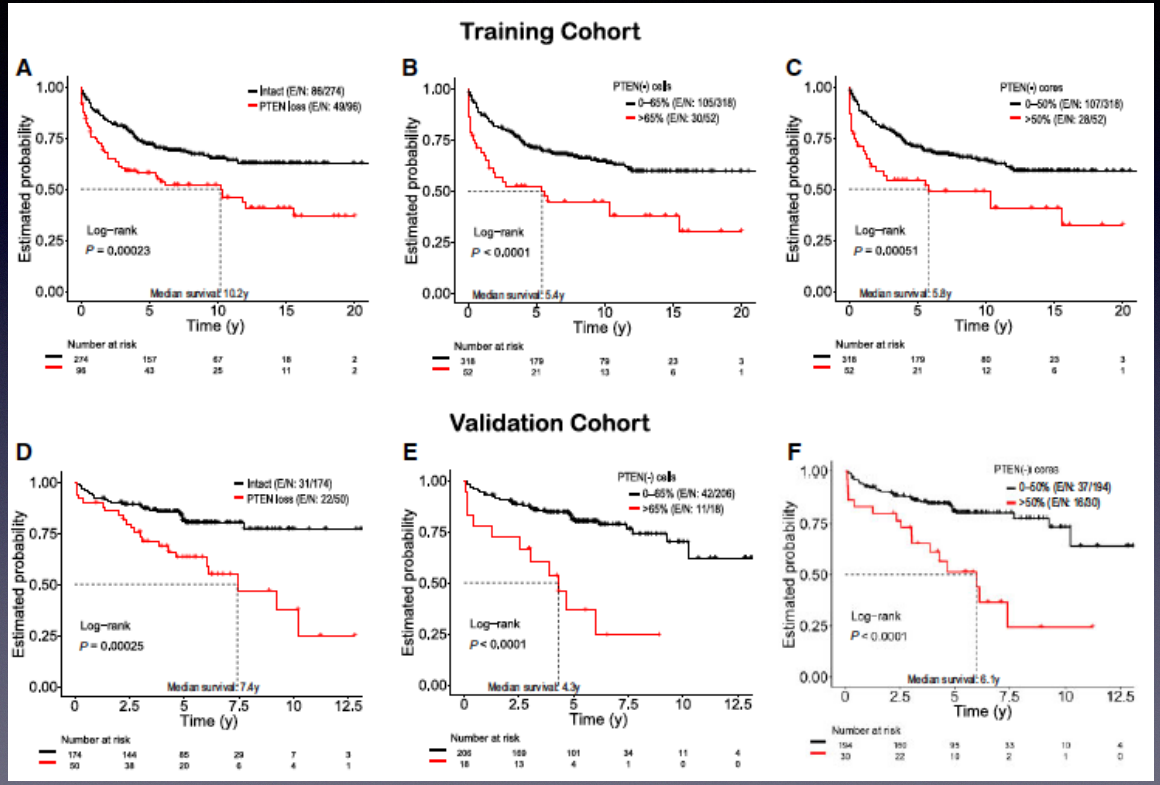






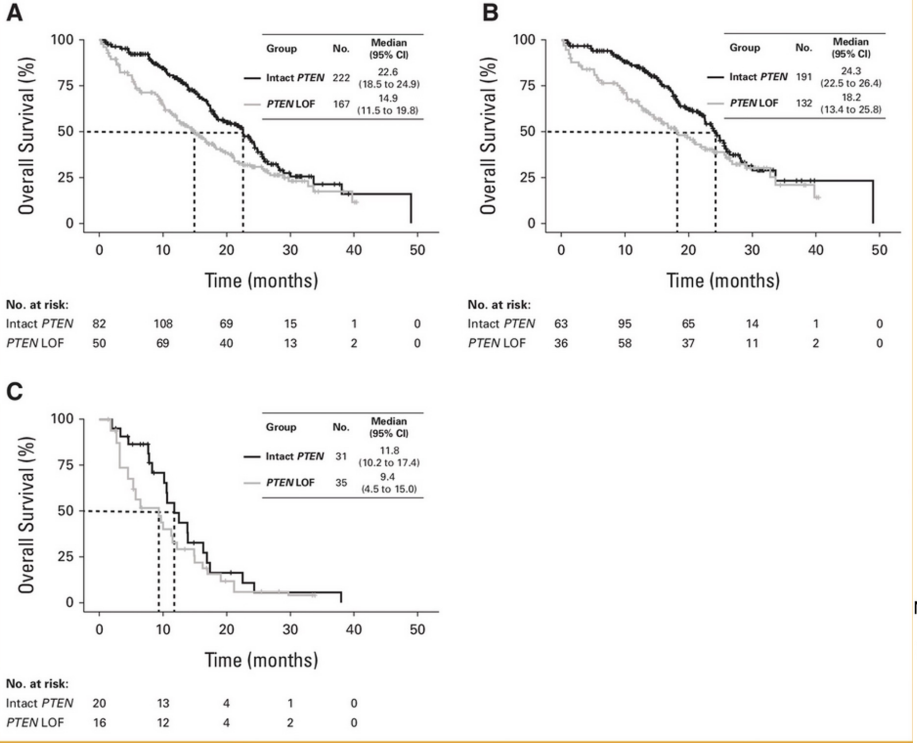
Annala M. Clin Cancer Res 2021

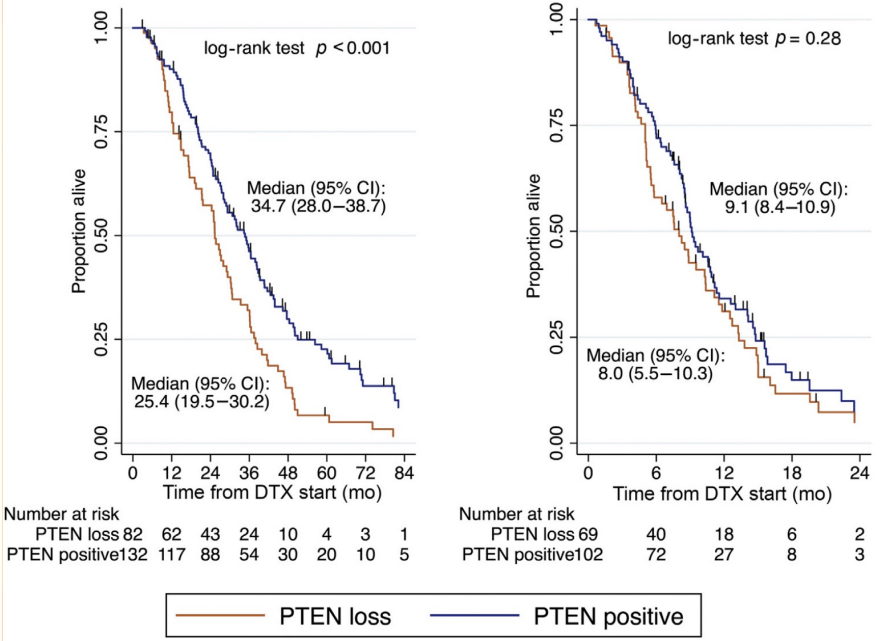
La pérdida de PTEN se asocia a mayor riesgo de recaída tras terapia local



Jamaspishvili T, Patel PG, Niu Y, Vidotto T, Caven I, Livergant R, et al. Risk Stratification of Prostate Cancer Through Quantitative Assessment of PTEN Loss (qPTEN). JNCI: Journal of the National Cancer Institute. 1 de noviembre de 2020;112(11):1098-104.

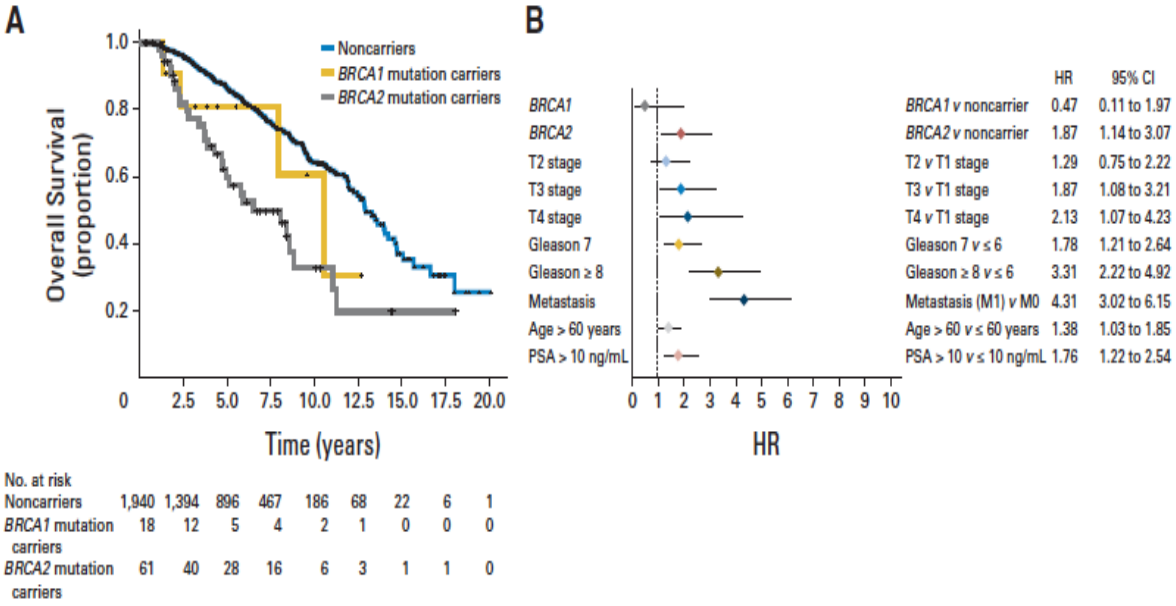
Efecto de pérdida de PTEN en las terapias sistémicas del CPRC





JCO Precis Oncol 8, e2300562(2024), [10.1016/j.euo.2018.02.006](https://doi.org/10.1016/j.euo.2018.02.006)

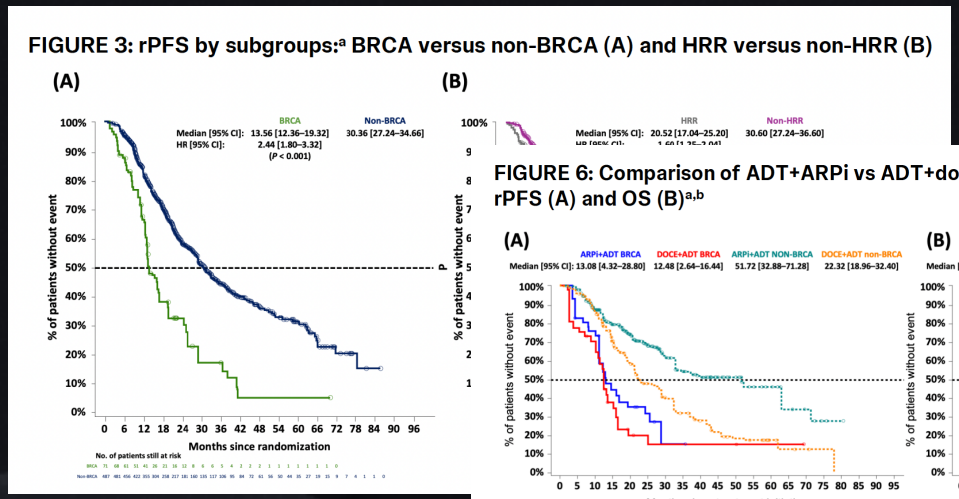
BRCAg are more aggresive:
higher risk of nodal involvement, distant metastasis and poor survival

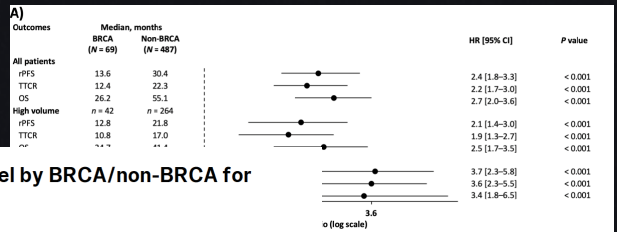


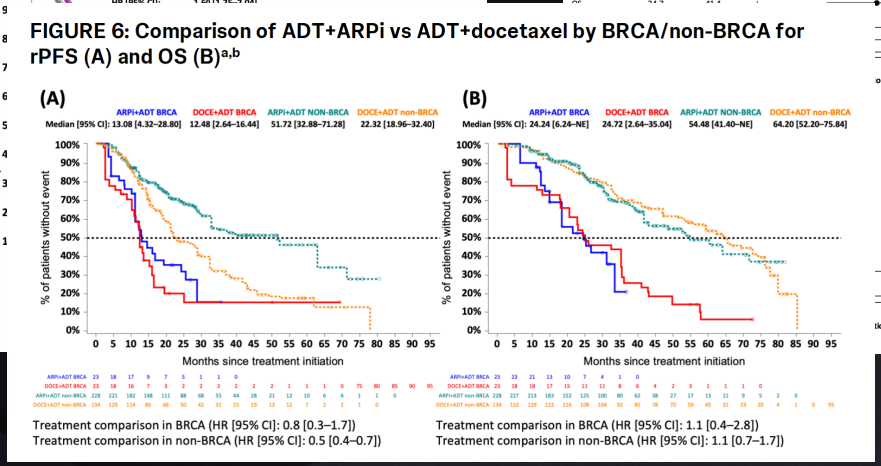
E. Castro. J Clin Oncol 2013

Valor pronóstico independiente en mHSPC

Estudio CAPTURE, cohorte Achilles

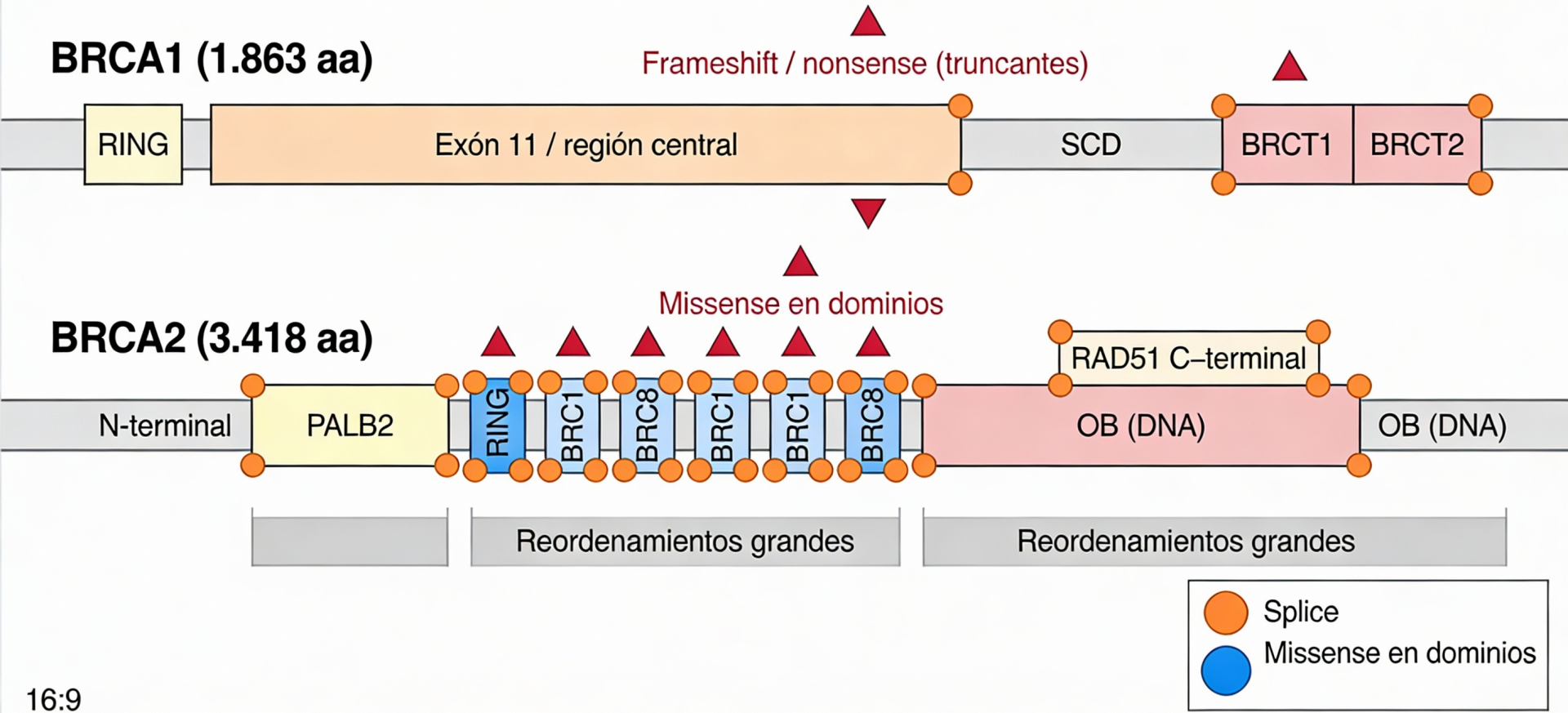






Presented by D. Olmos at the 2025 American Society of Clinical Oncology Annual Meeting; May 30–June 3, 2025; Chicago, IL, USA

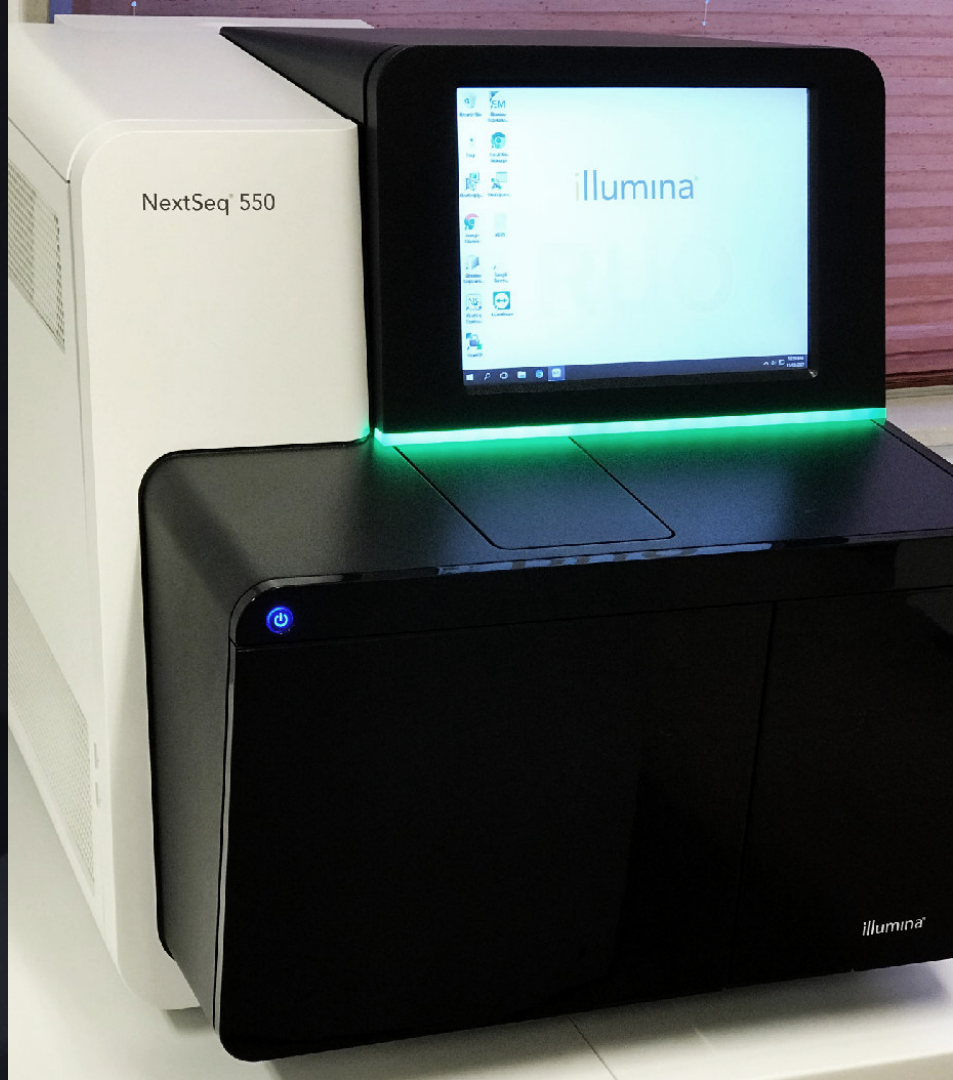
Mapa de BRCA1 y BRCA2 y tipos de mutaciones



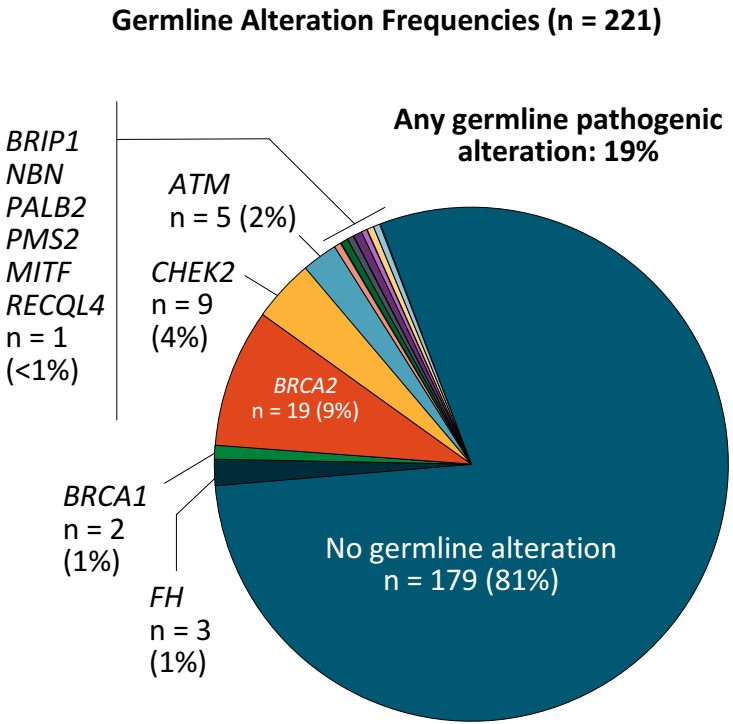
16:9

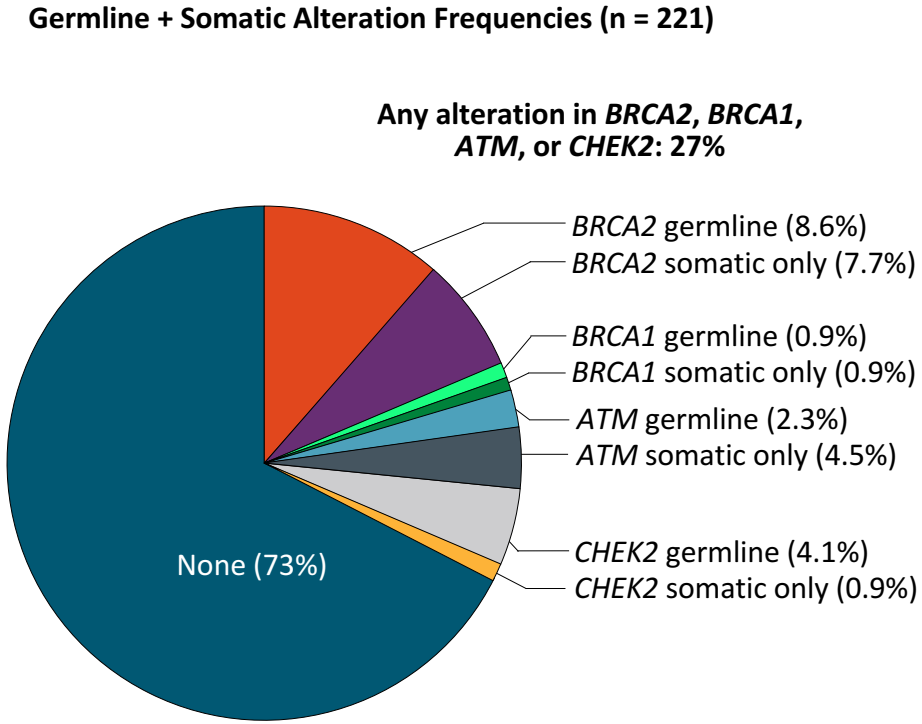
Determinación mutaciones HRR en Cáncer de próstata

- Empleo de paneles de NGS
  - Secuenciación por amplicones
  - Captura híbrida
- Muestras
  - Células nucleadas sanguíneas/mucosa oral/saliva (germinal)
  - Tejido tumoral (somática)
  - ctDNA, CTCs (somática)



Genomic Alterations Can Occur in Germline or Somatically, Can Be Identified by Clinical NGS Testing



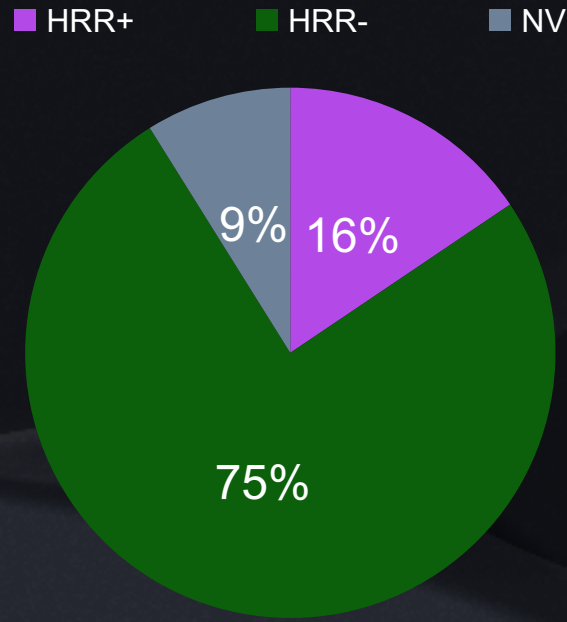


Abida. JCO Precis Oncol. 2017;PO.17.00029.

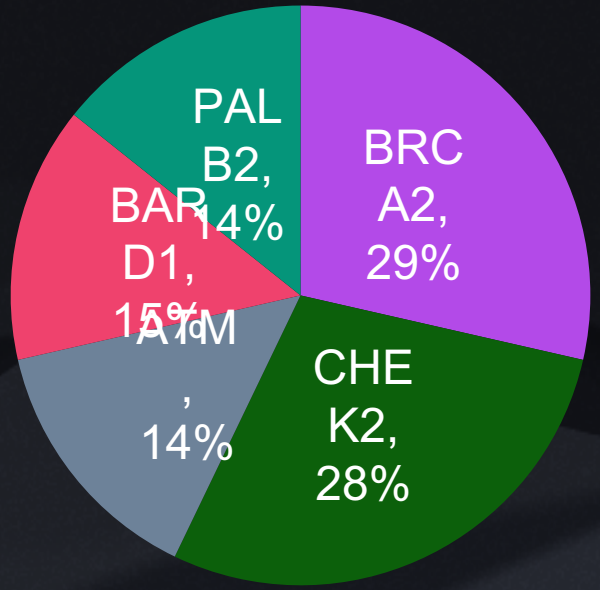
Slide credit: clinicaloptions.com

Datos de nuestro centro (HCUV 2022-2026)

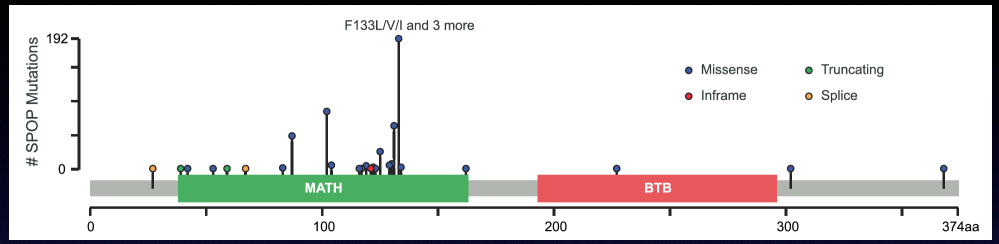
N = 47 casos (18 idBRCA, 26 Bioarray, 3 Foundation CdxLiquid)

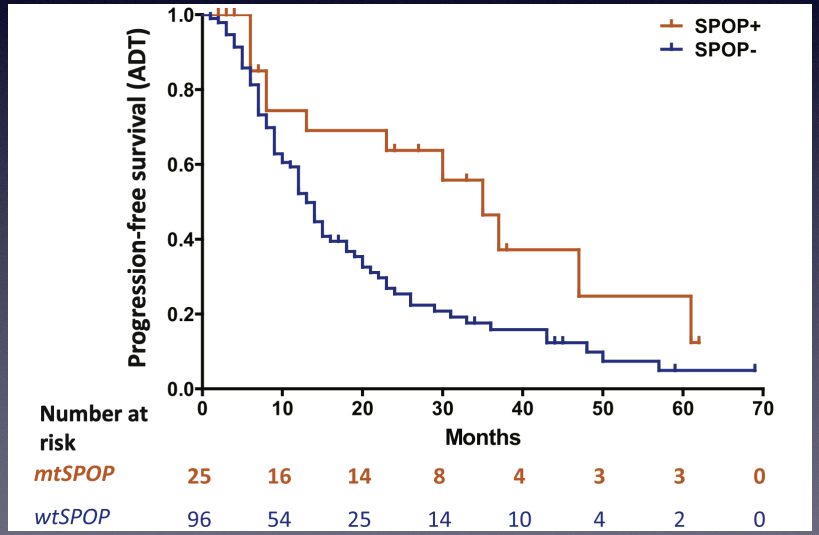


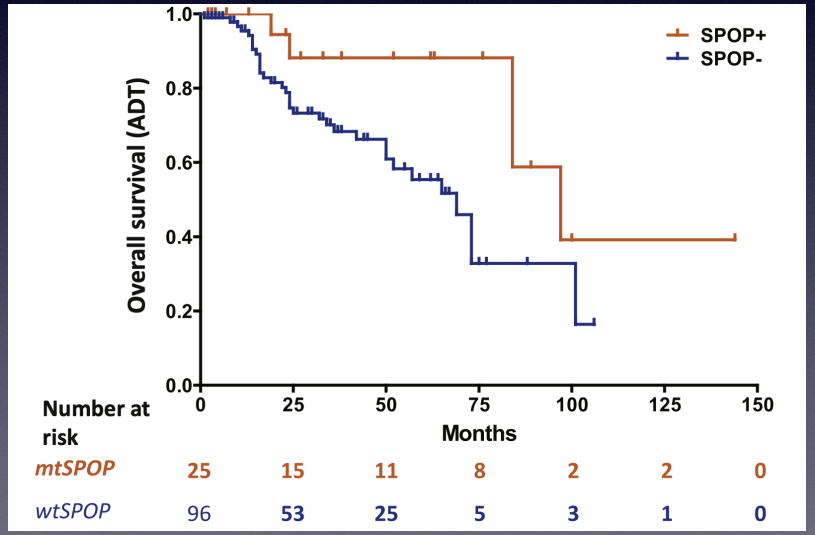
HRR+ (7 casos) 2 CHEK2, 2 BRCA2, 1 ATM, 1 BARD1, 1 PALB2



SPOP oncogen supresor relevante en CaP





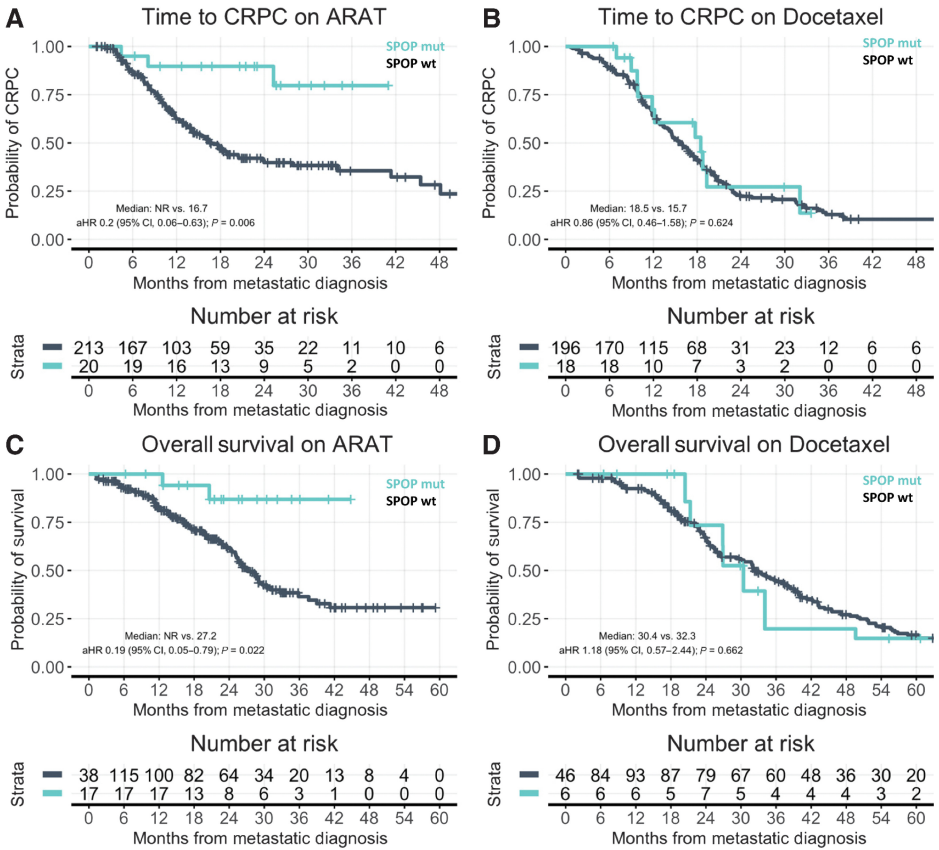


Swami U, Isaacsson Velho P, Nussenzveig R, Chipman J, Sacristan Santos V, Erickson S, et al. Association of SPOP Mutations with Outcomes in Men with De Novo Metastatic Castration-sensitive Prostate Cancer. European Urology. noviembre de 2020;78(5):652-6.

AACR American Association for Cancer Research

From: **SPOP Mutations as a Predictive Biomarker for Androgen Receptor Axis–Targeted Therapy in De Novo Metastatic Castration-Sensitive Prostate Cancer**

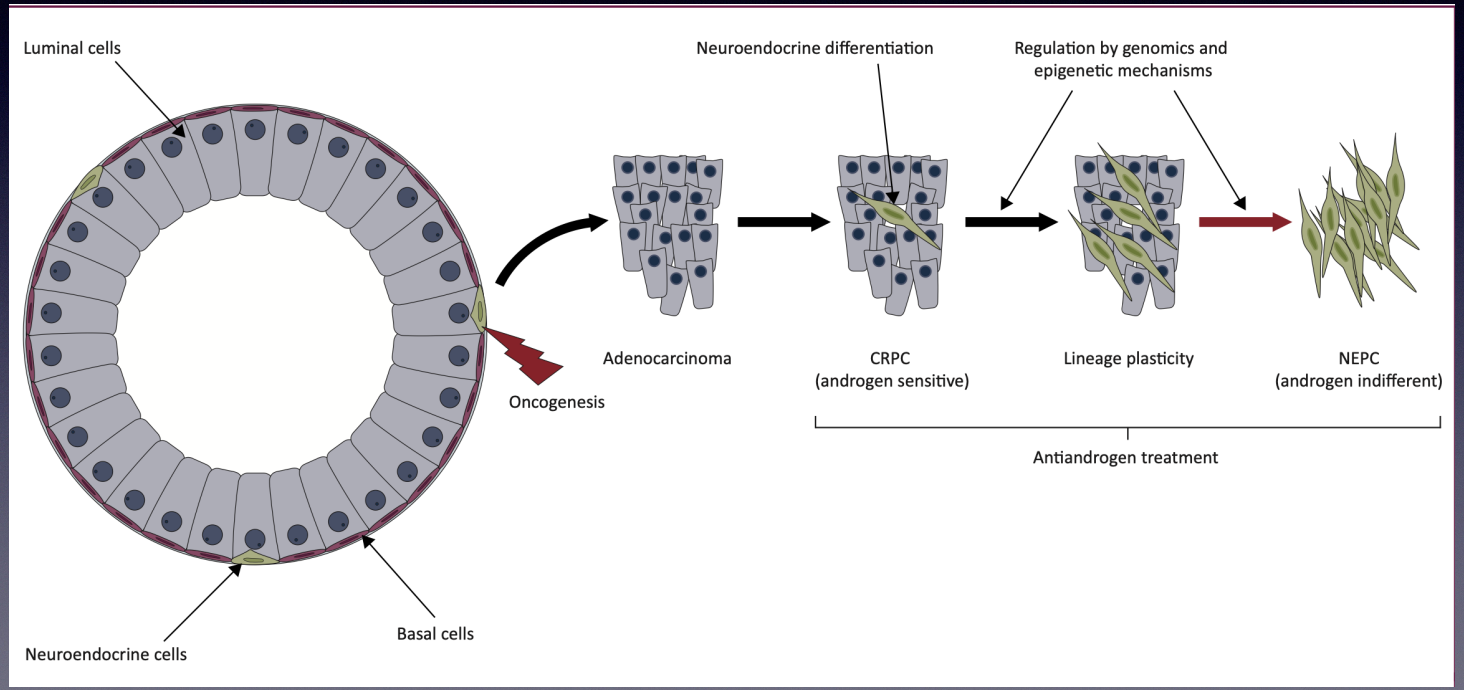
Clin Cancer Res. 2022;28(22):4917-4925. doi:10.1158/1078-0432.CCR-22-2228



Date of Download: 3/10/2026

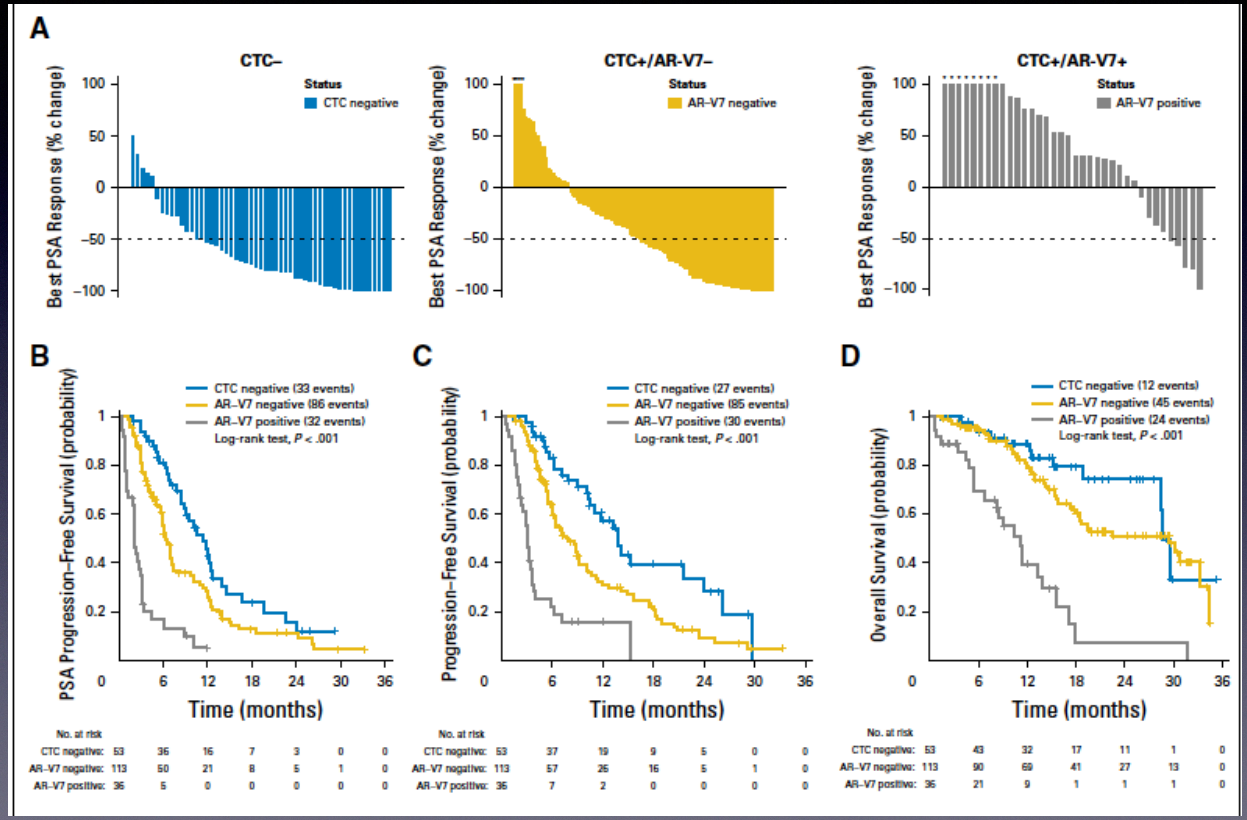
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Evolución a fenotipo andrógeno insensible: plasticidad de línea



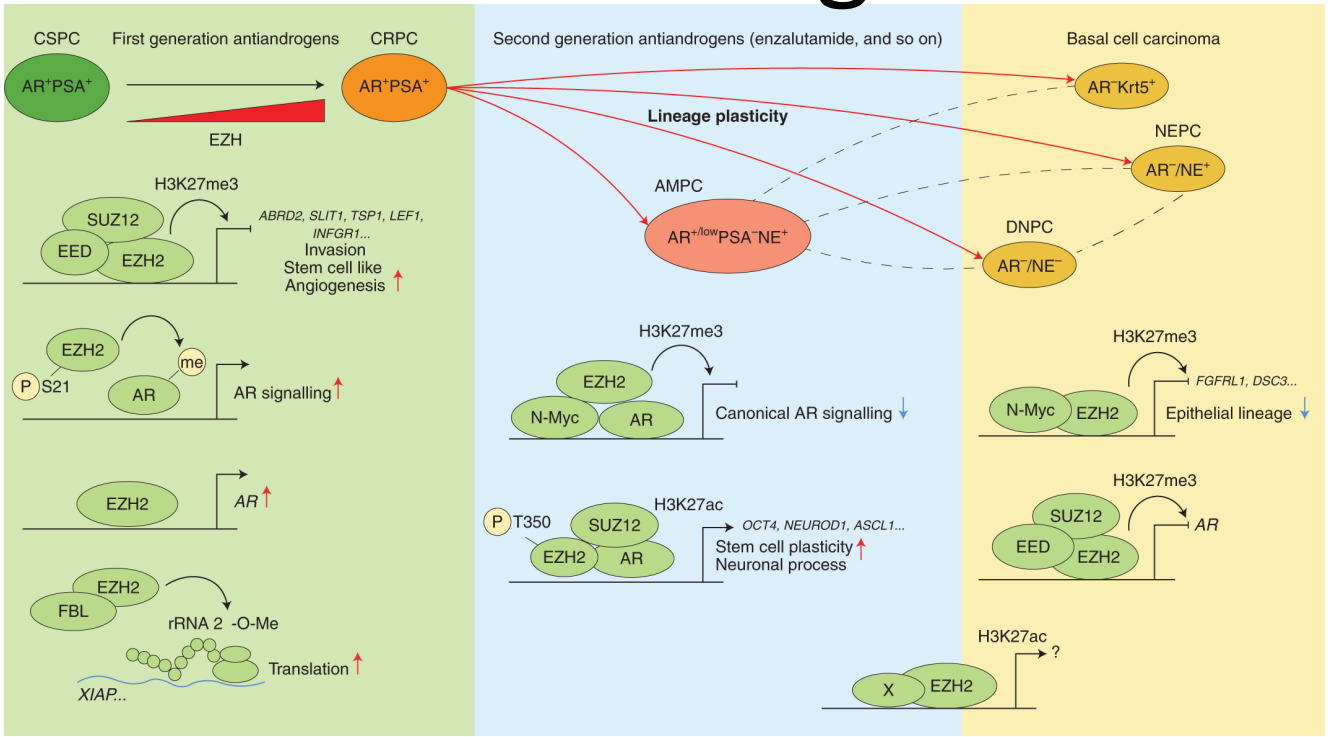
1. Ge R, Wang Z, Montironi R, Jiang Z, Cheng M, Santoni M, et al. Epigenetic modulations and lineage plasticity in advanced prostate cancer. Annals of Oncology. abril de 2020;31(4):470-9.

Splice variants: ARV7



Antonarakis ES, Lu C, Luber B, Wang H, Chen Y, Zhu Y, et al. Clinical Significance of Androgen Receptor Splice Variant-7 mRNA Detection in Circulating Tumor Cells of Men With Metastatic Castration-Resistant Prostate Cancer Treated With First- and Second-Line Abiraterone and Enzalutamide. JCO. 1 de julio de 2017;35(19):2149-56.

EZH2 en la carcinogenesis del CP



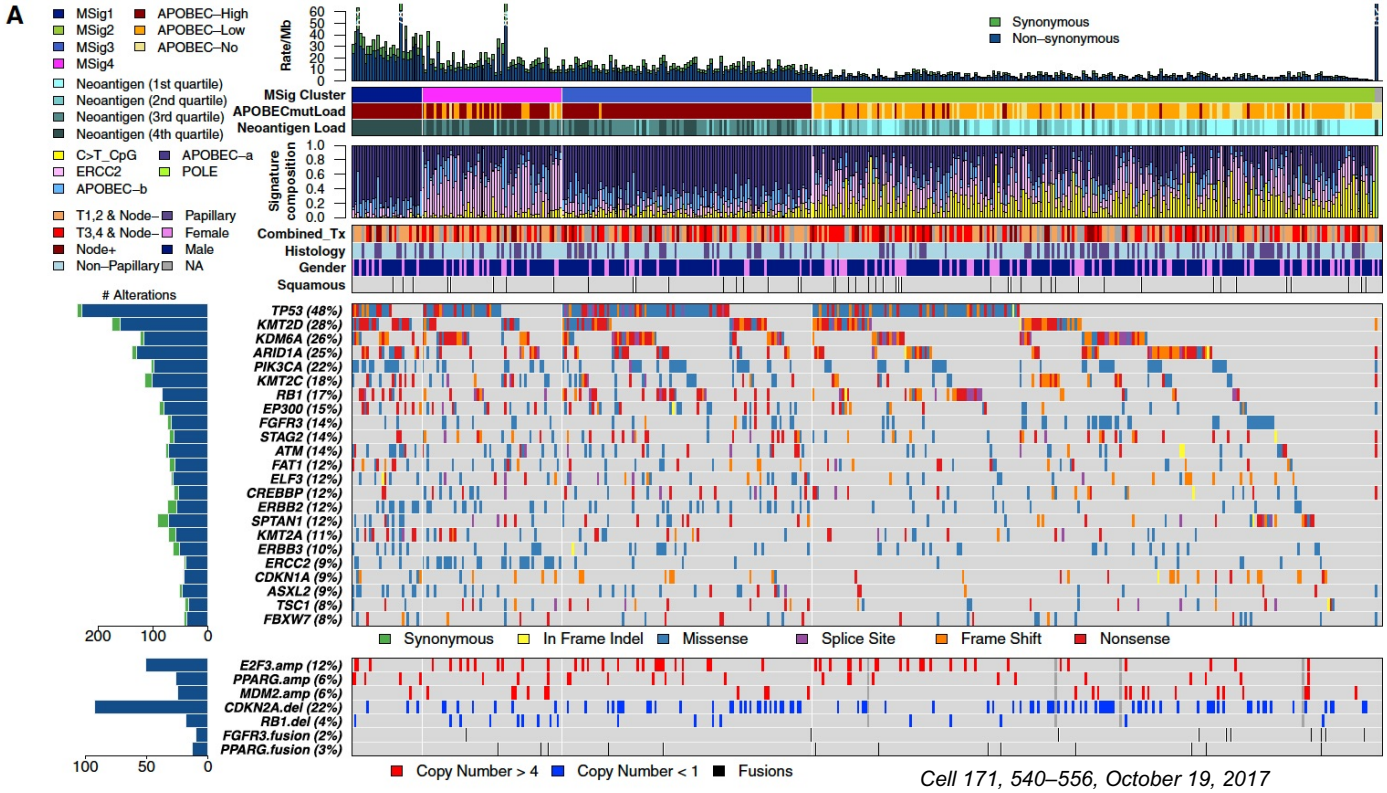
Nature Cell Biology | VOL 23 | September 2021 | 928–938

¿Qué debemos saber de la biología de los tumores GU?



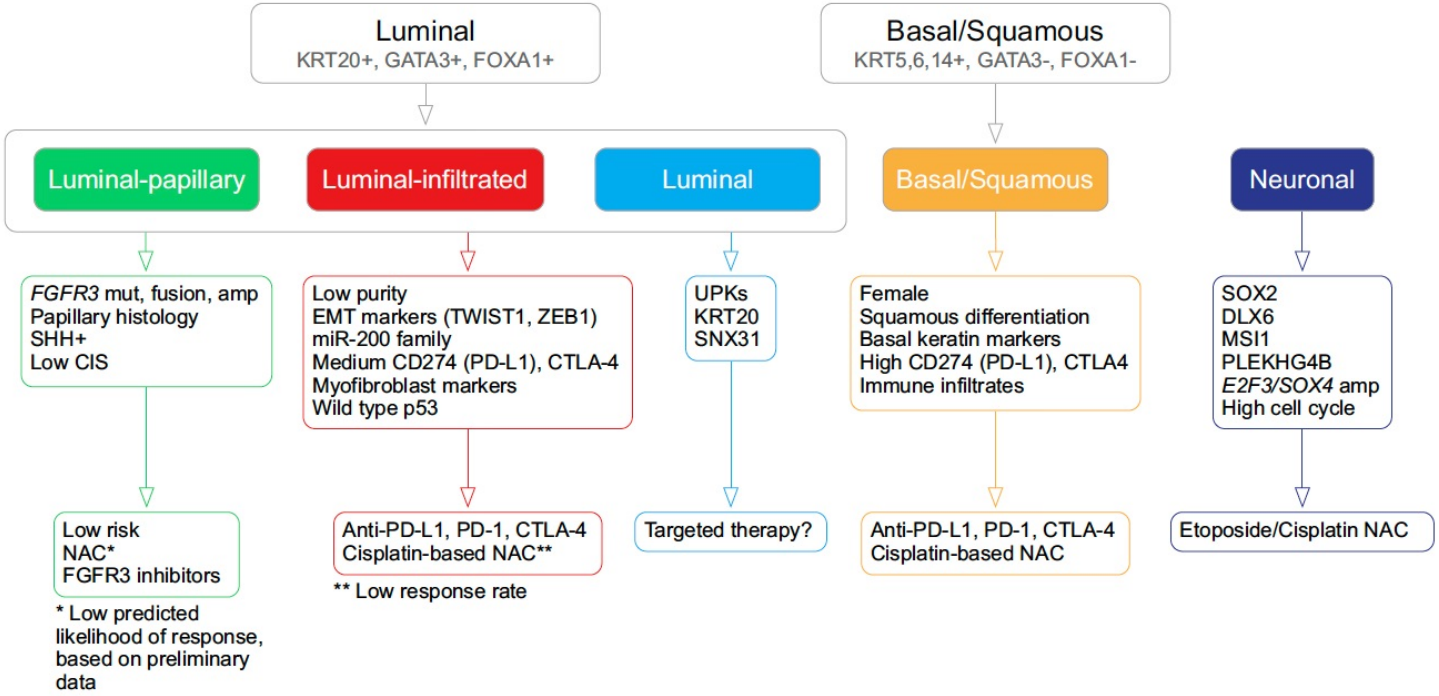
CÁNCER UROTELIAL

Panorama mutacional del cáncer de vejiga



Cell 171, 540–556, October 19, 2017

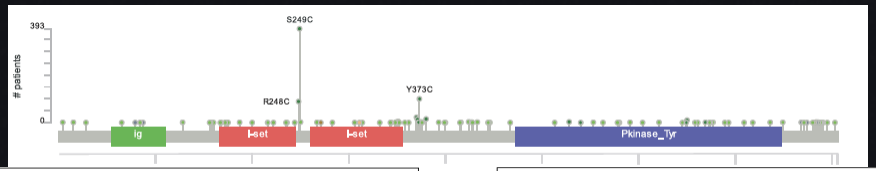
Subtipos intrínsecos



Cell 171, 540–556, October 19, 2017

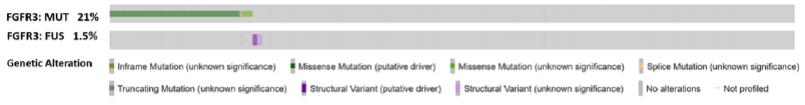
Alteraciones de FGFR en cáncer urotelial





A

GENIE Cohort v13.0-public: 3,482 samples/3,080 patients with Bladder Cancer

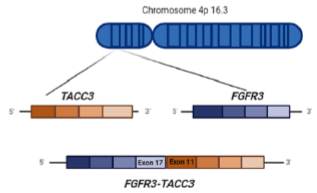


B

Gene	N	%
TACC3	18	85.7%
JAKMIP1	1	4.76%
TNIP2	1	4.76%
FAM184B	1	4.76%

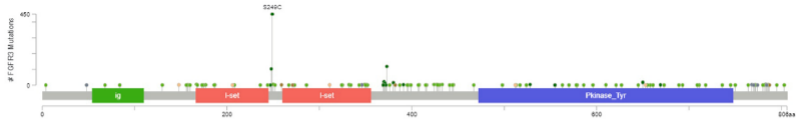
** Fusions of unknown oncogenic and biological significance (N)=28*

C



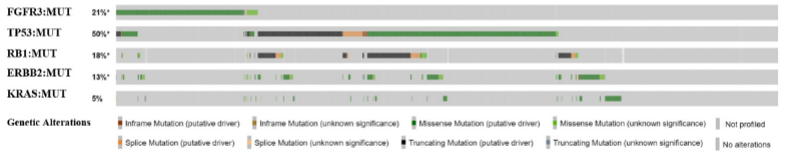
FGFR

A



GENIE Cohort v13.0-public: 3,482 samples/3,080 patients with Bladder cancer

B

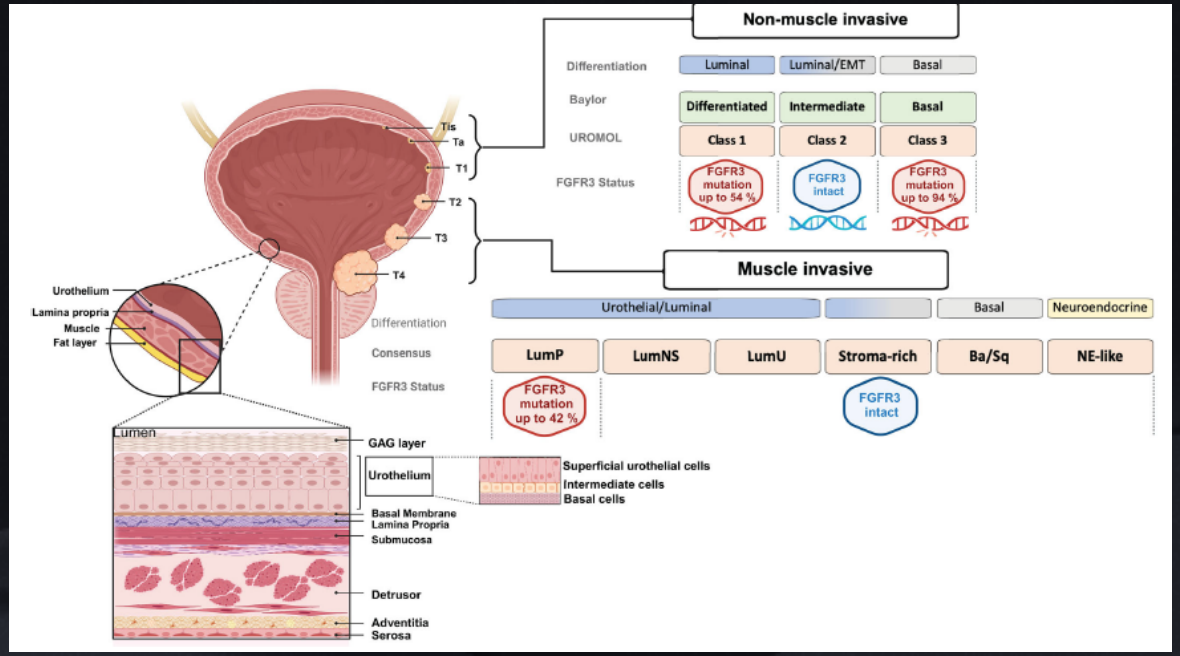


C

A	B	Total (100%)	Neither (%)	A Not B (%)	B Not A (%)	Both (%)	p-Value	q-Value
FGFR3: MUT	TP53: MUT	717	34%	9.2%	52.3%	4.5%	<0.001	<0.001
FGFR3: MUT	RB1: MUT	717	67.6%	12.5%	18.7%	1.1%	<0.001	0.002
FGFR3: MUT	KRAS: MUT	717	83.7	13.1%	2.6%	0.6%	0.387	0.553
FGFR3: MUT	ERBB2: MUT	717	72.1	11.4%	14.2%	2.23%	0.553	0.553

Cancer Treatment Reviews 115 (2023) 102530

Distribucion a lo largo de la enfermedad y subtipos



- 64% en NMIBC
- 16% en MIBC
- 34% Tracto superior

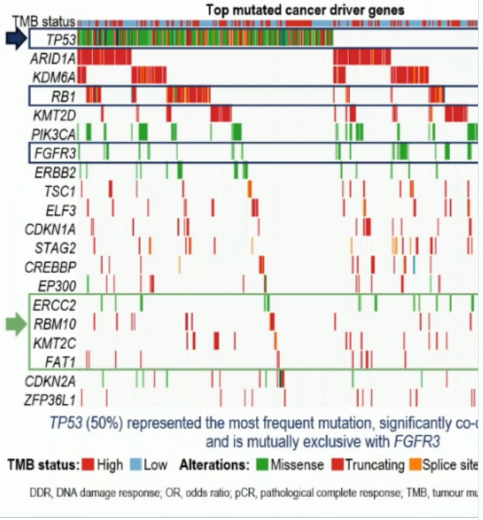
Cancer Communications. 2024;44:1189–1208.

Métodos de deteccion

- Next generation sequencing (NGS), detección de mutaciones y alteraciones de FGFR en tumor y sangre, puede detectar tanto fusiones como mutaciones puntuales
- PCR Kit especificos (eg QUIAGEN Therascan, SNapshot multiplex) para mutaciones puntuales
- Espectrometría de masas (uso investigacional)
- Análisis de preparaciones histopatológicas con IA (prescreening)
- Sistemas de conteo digital (NanoString)

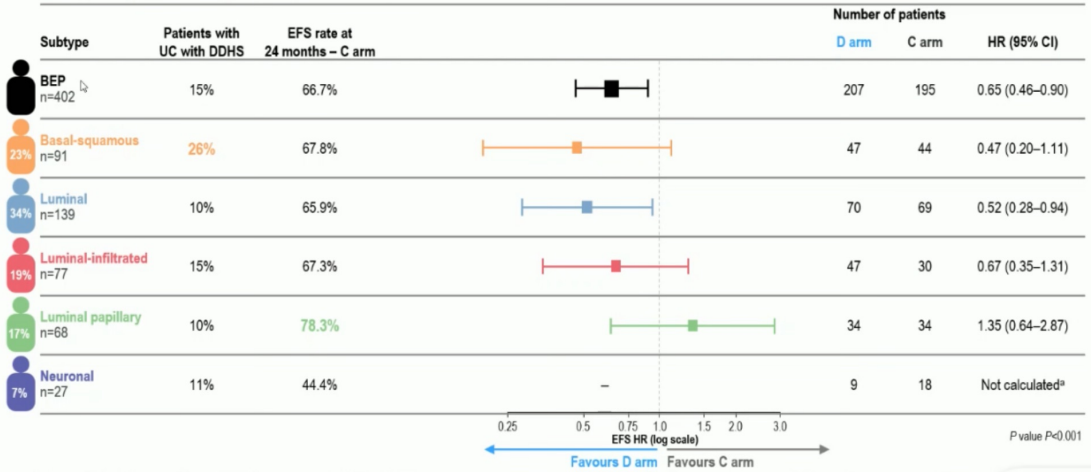
NIAGARA: Mutational Landscape & Association of Driver Alterations

Select DDR-related gene alterations were
combined-treatment arms



NIAGARA: EFS Benefit in MIBC Transcriptional Subtypes

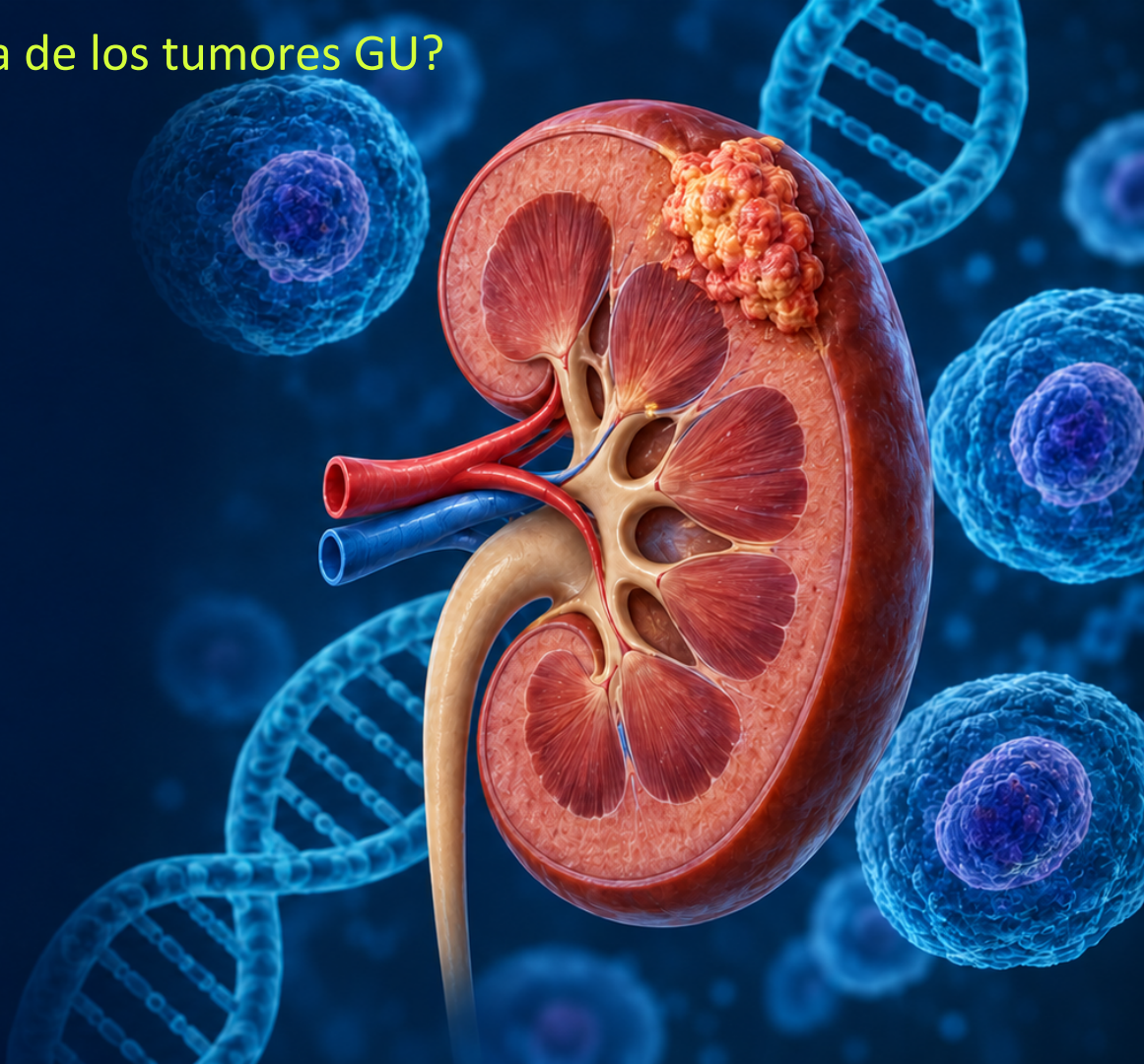
Addition of perioperative durvalumab to NAC appeared to improve EFS across most transcriptional subtypes, including basal-squamous



Graph depicts EFS HR (square) and 95% confidence intervals (lines), and was assessed by the Cox proportional hazards model, with treatment as the only covariate and ties handled by the Efron approach. A significant p-value provides evidence against the null hypothesis that observations are equally likely to fall into each category, suggesting the category probabilities are not all equal, p-value obtained from a Chi-squared test. [a]Not calculated as there are fewer than 20 patients per arm. BEP, biomarker-evaluable population; C, comparator; CI, confidence interval; D, durvalumab; DDHS, divergent differentiation or histological subtype; EFS, event-free survival; HR, hazard ratio; MIBC, muscle-invasive bladder cancer; NAC, neoadjuvant chemotherapy; UC, urothelial carcinoma.

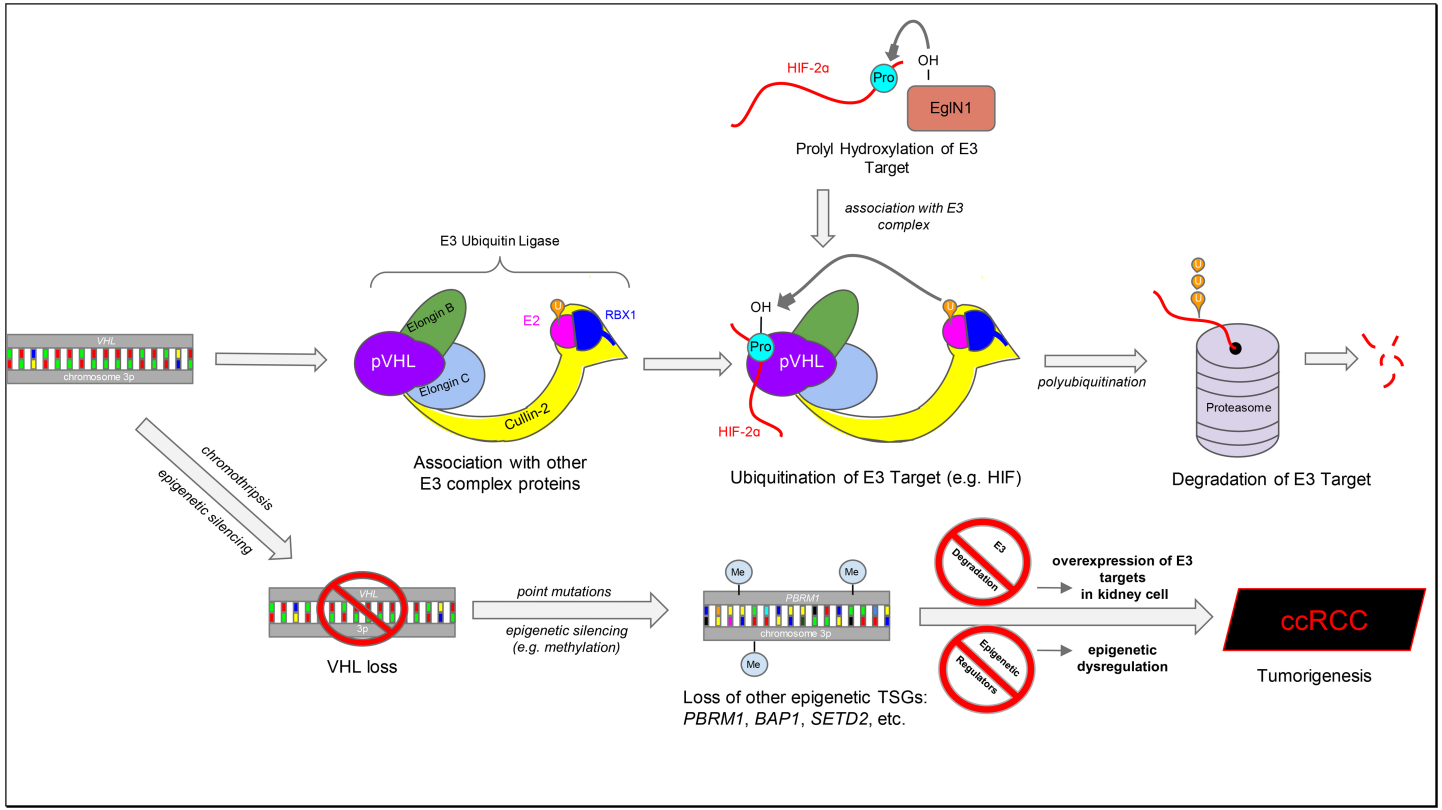
MADRID 2025 ESMO congress

¿Qué debemos saber de la biología de los tumores GU?



CÁNCER RENAL

Via VHL-HIF: la base en RCC



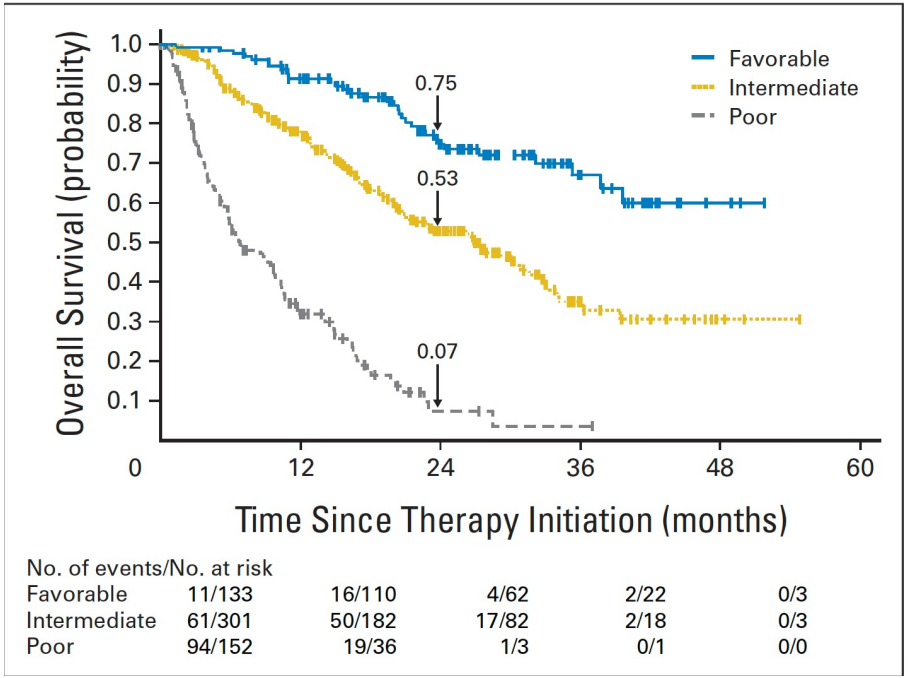
J Genet Genomics. 2021 Jul 9;48(7):552–559.

Casi 20 años del Heng score…

Table 3. Multivariable Analysis and Final Model

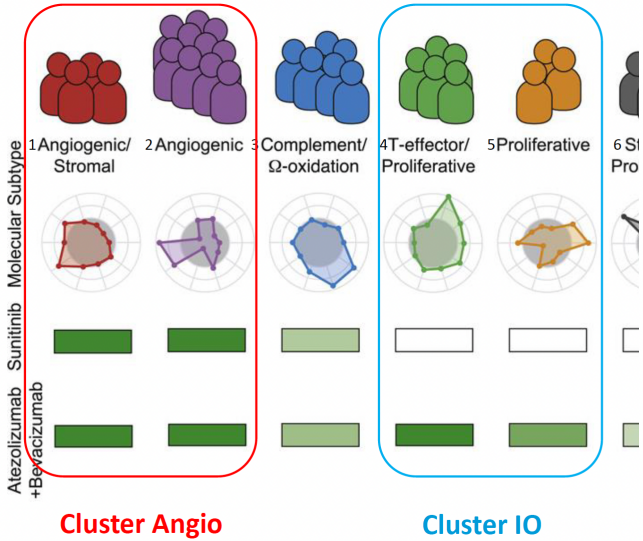
Parameter	Parameter Estimate ± SE	Hazard Ratio	95% CI	*P*
Clinical				
KPS < 80%	0.92 ± 0.14	2.51	1.92 to 3.29	< .0001
Time from diagnosis to treatment < 1 year	0.35 ± 0.13	1.42	1.09 to 1.84	.0098
Laboratory				
Hemoglobin < LLN	0.54 ± 0.14	1.72	1.31 to 2.26	.0001
Calcium > ULN	0.59 ± 0.17	1.81	1.29 to 2.53	.0006
Neutrophil count > ULN	0.88 ± 0.17	2.42	1.72 to 3.39	< .0001
Platelet count > ULN	0.40 ± 0.16	1.49	1.09 to 2.03	.0121

NOTE. Total number of patients = 564.
Abbreviations: SE, standard error; KPS, Karnofsky performance status; LLN, lower limit of normal; ULN, upper limit of normal.



J Clin Oncol 27:5794-5799.

OPTIC-RCC



Key Eligibility Criteria

- ECOG 0 or 1
- Metastatic clear cell RCC without prior systemic therapy in any setting
- Available tumor tissue for RNA-sequencing/cluster prediction



Simon's Minimax Two-Stage Design

Clusters 1/2 → **Nivolumab/Cabozantinib (N=26)**

- H_0: ORR ≤ 55%
- H_A: ORR > 75%

Stage I (N=12) ≥7/12 responders → **Stage II (N=14)** ≥18/26

Clusters 4/5 → **Ipilimumab/Nivolumab (N=28)**

- H_0: ORR ≤ 40%
- H_A: ORR > 70%

Stage I (N=16) ≥7/16 responders → **Stage II (N=12)** ≥15/28

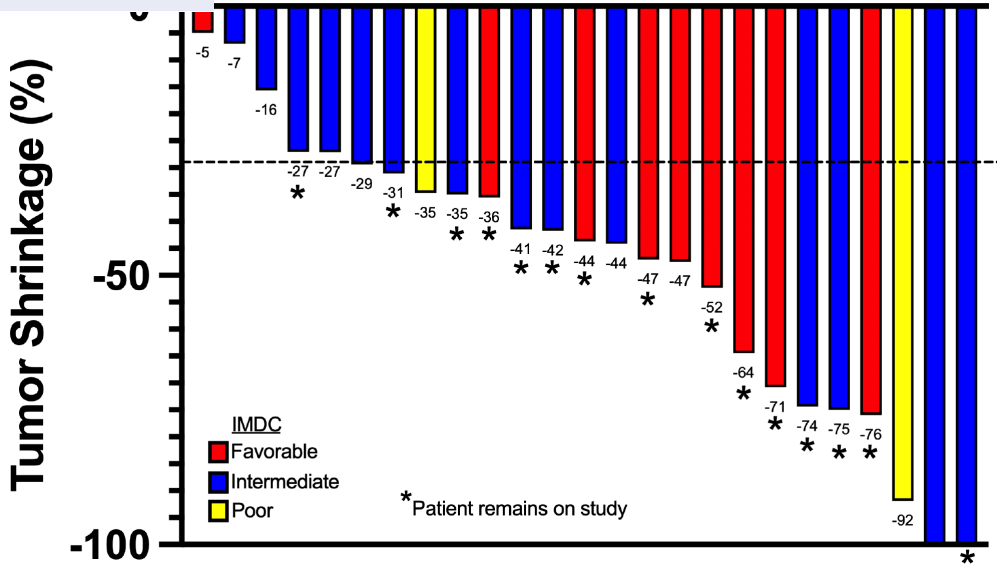
Remains open to accrual

Clusters 3/6/7 — Excluded from trial

- Primary Endpoint: Objective response rate (ORR)
- Secondary Endpoints: Progression free survival (PFS), depth of response >80% at 6 months, immune-related adverse events

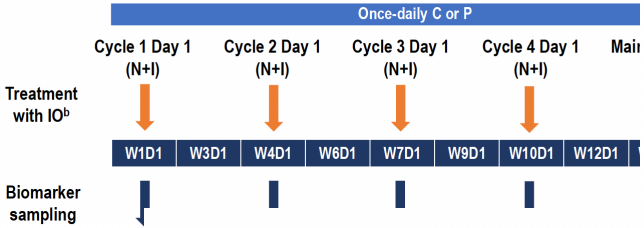
	Cluster 1/2 (n=25)*
Objective response – no. (%)	19 (76)
Best overall response – no. (%)	
Complete response	2 (8)
Partial response	17 (68)
Stable disease	6 (24)
Progressive disease	0 (0)
Patients with tumor burden reduction – no. (%)	25 (100)
% tumor shrinkage – median (range)	42 (5-100)

Depth of response



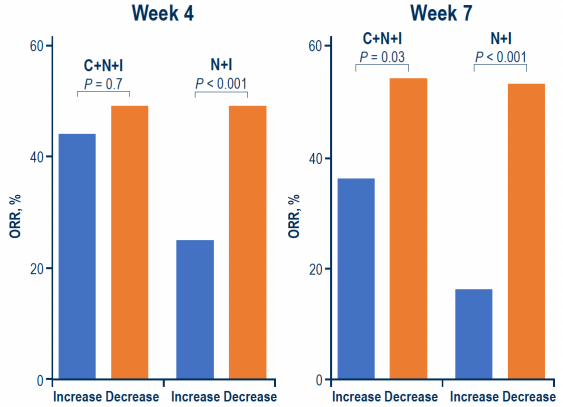
Biomarcadores sobre COSMIC 313: KIM-1

Monitorización KIM-1



Base
(prior to fi

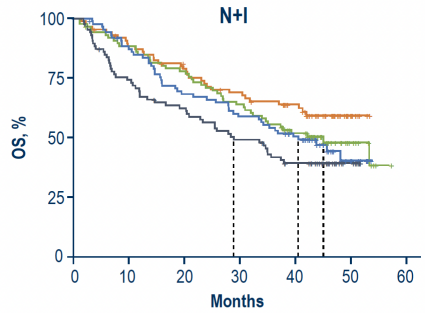
Patients with	
C+N+I	35
N+I	34



ast
+I

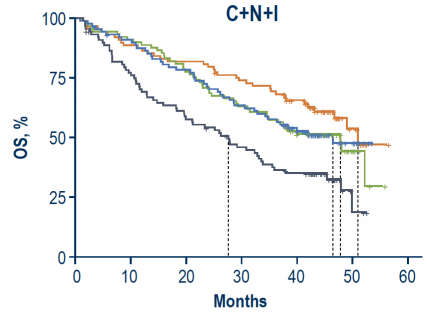
| Total
ests, n |
|---|
| 1461 |
| 1491 |

Kaplan-Meier OS analyses stratified by quartiles of baseline circulating KIM-1



Number at risk:

Q1 : 19–280 pg/mL	87	75	64	55	43	8	0
Q2: 282–1189 pg/mL	87	76	67	54	39	10	0
Q3: 1199–6212 pg/mL	87	75	58	50	39	6	0
Q4: 6393–85,909 pg/mL	86	63	52	41	30	7	0



Number at risk:

Q1 : 18–266 pg/mL	89	78	72	64	49	11	0
Q2: 268–1247 pg/mL	89	81	69	56	38	6	0
Q3: 1279–6743 pg/mL	89	79	68	55	38	10	0
Q4: 6815–77,057 pg/mL	89	66	50	38	27	2	0

PFS

	N+I		C+N+I	
Time point	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
W4D1	0.52 (0.39, 0.69)	**< 0.01**	0.75 (0.48, 1.17)	0.20
W7D1	0.35 (0.26, 0.47)	**< 0.01**	0.56 (0.39, 0.81)	**< 0.01**
W10D1	0.34 (0.25, 0.46)	**< 0.01**	0.65 (0.45, 0.94)	**0.024**
W14D1	0.32 (0.22, 0.44)	**< 0.01**	0.52 (0.36, 0.76)	**< 0.01**

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