



V SIMPOSIO  
GETHI

18/19

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Ilustre Colegio Oficial de Médicos de Madrid. Aula Jiménez Díaz. Madrid

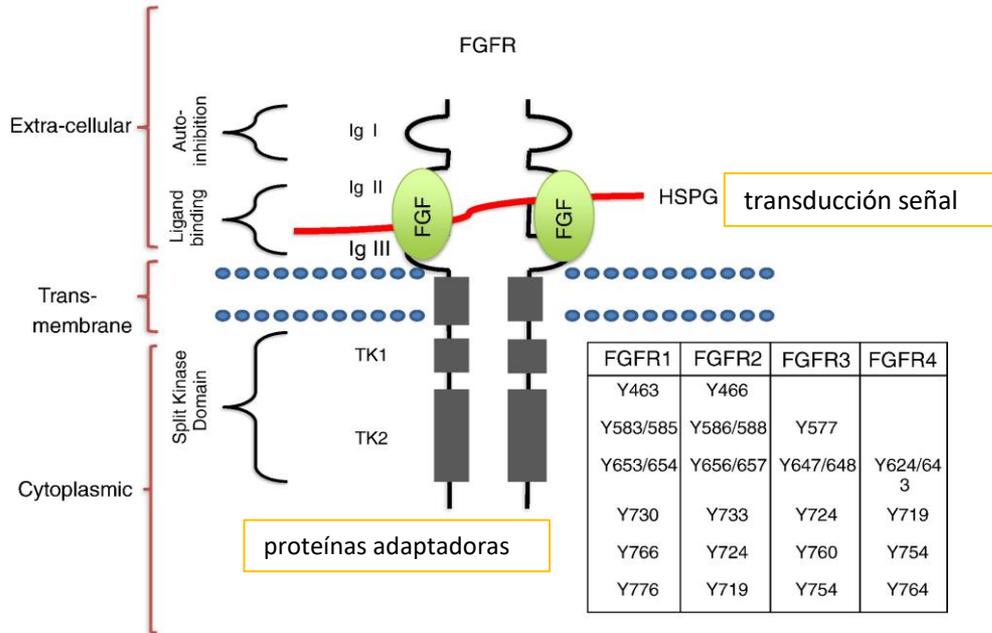
## FGFR EN TUMORES SÓLIDOS Y CÁNCER RARO ¿Qué alteraciones presentan y en qué tumores?

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# V SIMPOSIO GETHI

## FGFR

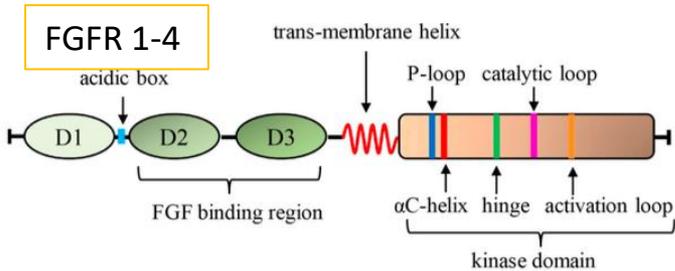
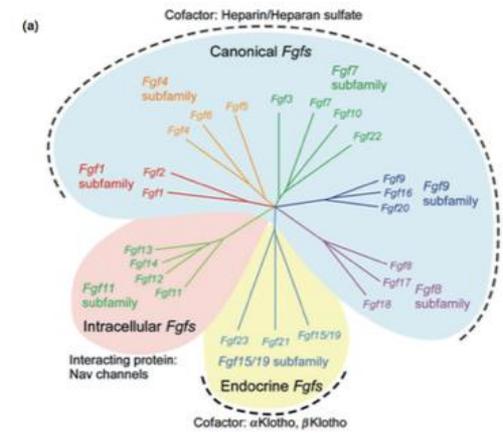
- Pertenece a la familia de RTK ( FGRF 1-4): afinidades de ligando y distribución tisular
- Regulan diversos procesos fisiológicos (osteogénesis)



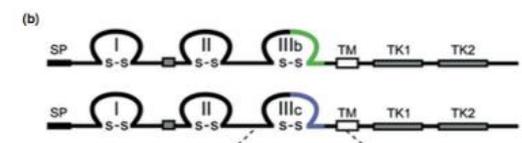
proteínas adaptadoras

transducción señal

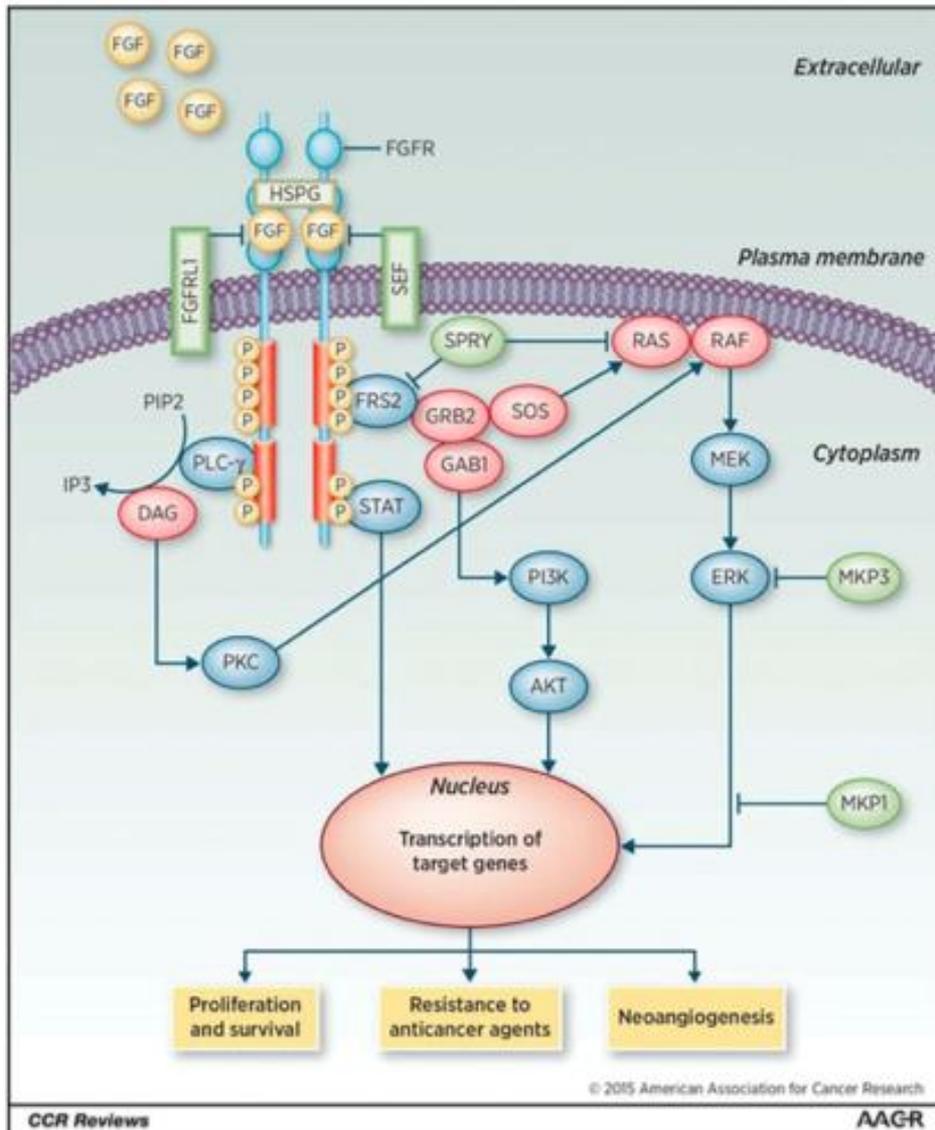
22 ligandos FGF



Complejo (FGF) –FGFR  
 2moléculas receptoras  
 2 FGF  
 1 cadena de proteoglicano de heparin sulfato



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1) Unión (FGF - HSPG)+ Ig FGFR :dimerización del receptor→ cambios conformacionales FGFR→ fosforilación de residuos TK intracelulares

2) Residuos TK funcionan como sitios de acoplamiento para diversas proteínas adaptadoras:

- **FGFR sustrato 2 (FRS2)**→GRB2, GAB1, SOS
- **Fosfolipasa C $\gamma$  (PLC $\gamma$ )**: fosforilación y activación → desencadena la liberación de calcio intracelular →activar los miembros dependientes de calcio de la familia de la **proteína quinasa C (PKC)**. También induce la señalización de MAPK a través de la **fosforilación de Raf**

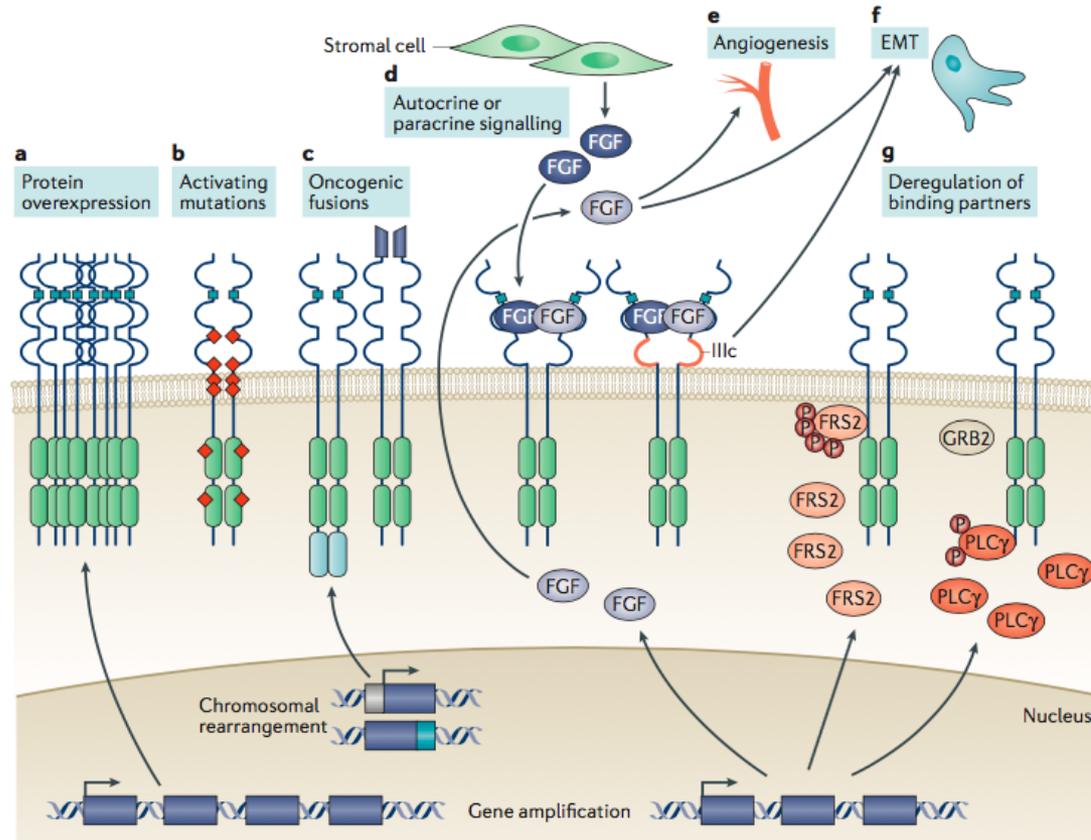
3) La unión de las proteínas adaptadoras a los FGFR conduce a la activación de múltiples vías de transducción de señales, incluidas las cuatro vías principales: **RAS-MAPK, PI3K-Akt, JAK/STAT** y **PLC $\gamma$**

La desregulación de la señalización de FGFR promueve la proliferación, supervivencia y desarrollo de resistencia a fármacos desarrollo de angiogénesis y evasión inmune

# V SIMPOSIO GETHI

## Mecanismos de señalización oncogénica de FGFR

- Amplificación génica → Sobreexpresión R
- Mutaciones con ganancia de función → cambio conformacional en el dominio kinasa/extracelular (activación indep de ligando)
- Translocaciones: proteínas de fusión:
- Sobreexpresión del ligando (tumor-estroma)



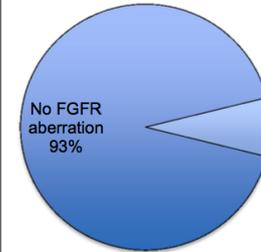
## Clinical Cancer Research

### THE FGFR LANDSCAPE IN CANCER: ANALYSIS OF 4853 TUMORS BY NEXT GENERATION SEQUENCING

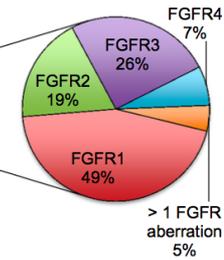
Teresa Helsten, Sheryl Elkin, Elisa Arthur, et al.

*Clin Cancer Res* Published OnlineFirst September 15, 2015.

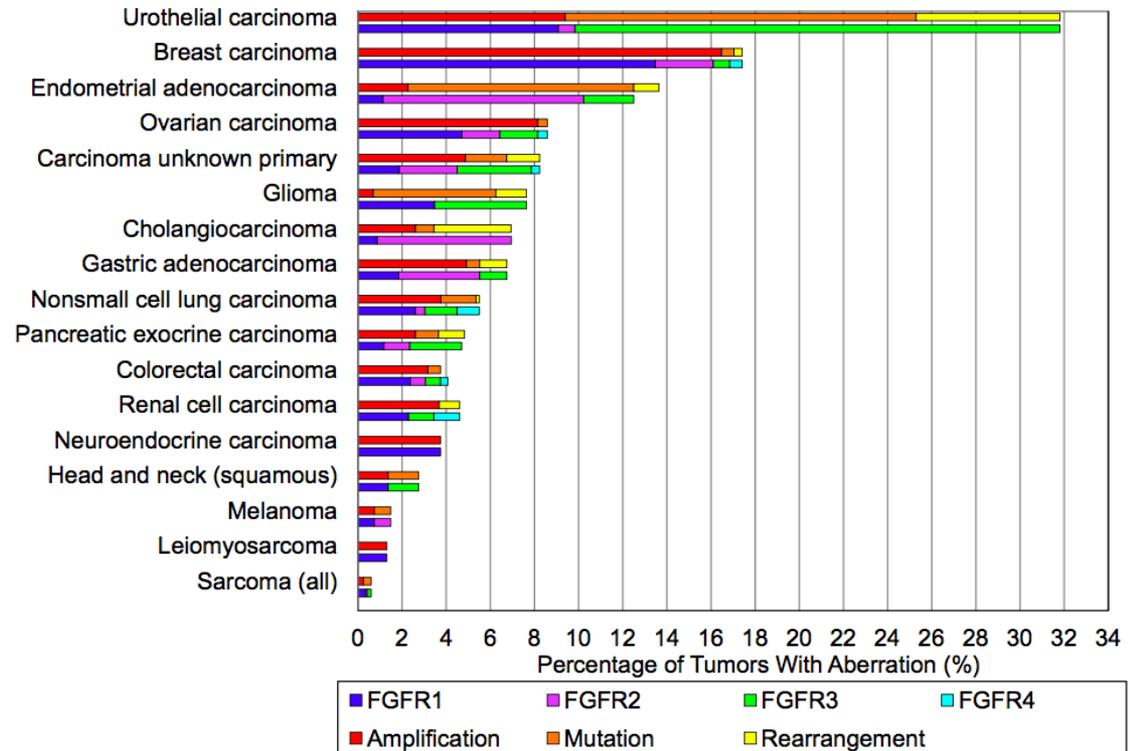
Frequency of FGFR Aberrations (4853 Patients)



Cases with FGFR Aberrations

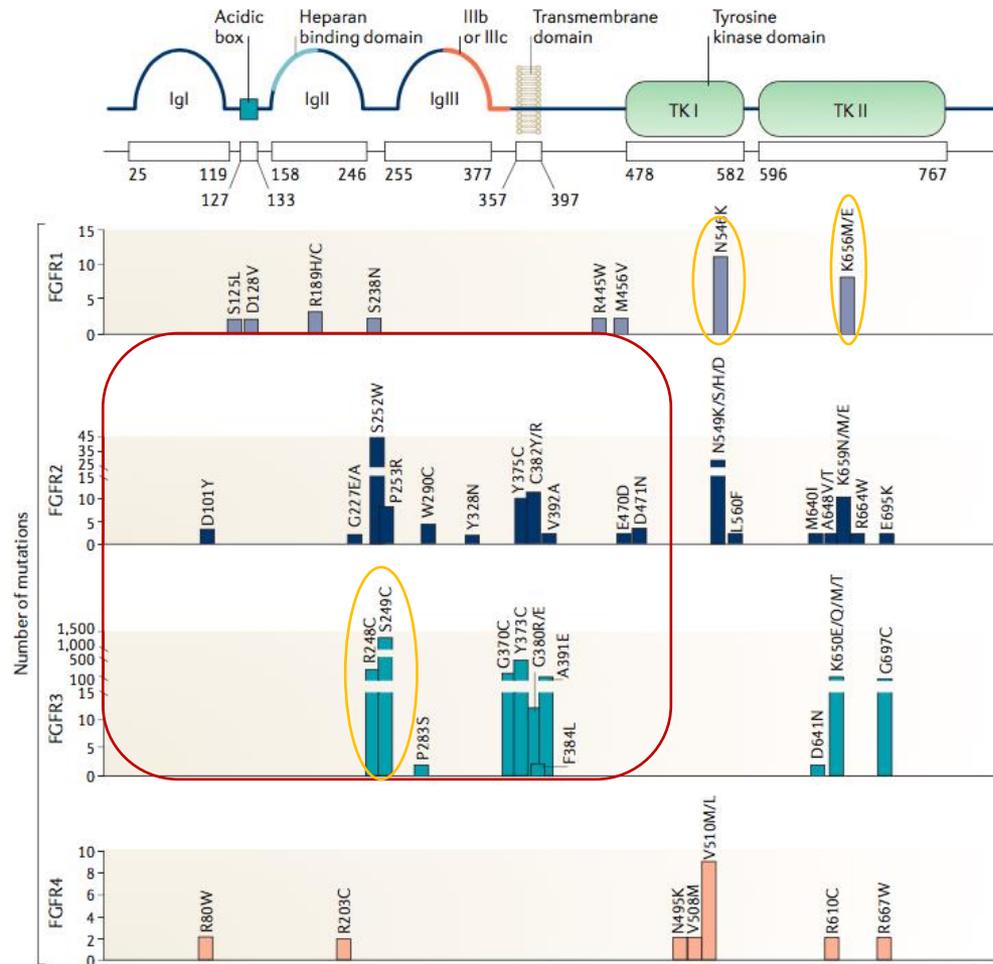


- Frequencies of FGFR aberrations in **4853 solid tumors –NGS–**
- FGFR aberrations **7.1% of cancers: gene amplification (66%) mutations (26%), rearrangements (8%)**
  - FGFR1 was affected in 3.5% of
  - FGFR3, in 2.0%
  - FGFR2, in 1.5%;
  - FGFR4, in 0.5%
- Cancers most commonly affected:
  - urothelial (32%)
  - breast (18%);
  - endometrial (~13%),
  - squamous lung cancers (~13%),
  - ovarian cancer (~9%)

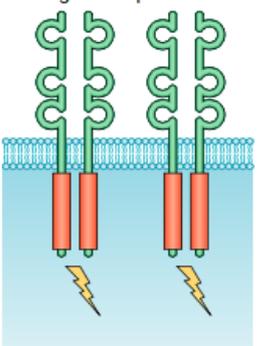


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Structure of fibroblast growth factor receptor and frequency of the receptors' somatic mutations with their relative locations



FGFR overexpression owing to gene amplification



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## AMPLIFICACIÓN FGFR

### FGFR1

- CPNCP : 17% -CPCP: 6%
- CA MAMA Luminal 15%: RRHH+ 5%: TN
- CA UROTELIAL: 9%
- CA ESÓFAGO: 9%
- CA CRC: 6%
- CA GÁSTRICO: 2%
- CyC: 5%
- CA OVARIO: 3%
- CA PANCREAS: 1%
- SARCOMAS: 3-20%

### FGFR2

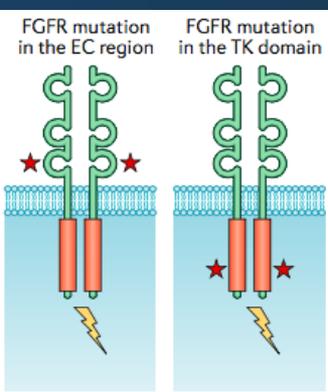
- CA GÁSTRICO :5-10%
- CA MAMA TN:2-4%

### FGFR3

- CA UROTELIAL

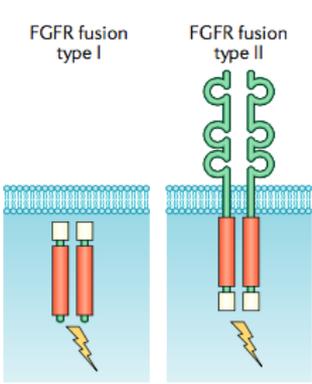
### FGFR4

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## MUTACIONES ACTIVANTES FGFR

FGFR1	FGFR2	FGFR3	FGFR4
<p>*RARAS</p> <ul style="list-style-type: none"><li>-CA MAMA: FGFR1(N546K)</li><li>-ASTROCITOMA PILOCÍTICO:5-8%</li></ul>	<p>*FRECUENTES</p> <ul style="list-style-type: none"><li>-ENDOMETRIAL:12%</li><li>-CPNM:4%</li><li>-CA GÁSTRICO: 4%</li><li>-CA UROTELIAL:2%</li><li>-CA MAMA: 1.4% (N549H/K)</li></ul>	<p>*FRECUENTES</p> <ul style="list-style-type: none"><li>-NMIBC: 75%</li><li>-MIBC:20%</li><li>-CA CERVIX: 5%</li></ul>	<p>RABDOMIOSARCOMA: K535, E550</p>



## FUSIONES

FGFR1	FGFR2	FGFR3	FGFR4
<ul style="list-style-type: none"><li>-Ca mama:FGFR1-ERLIN2</li></ul>	<ul style="list-style-type: none"><li>-Colangiocarc Intrah: 15%</li><li>-Ca pulmón</li><li>-Ca tiroides</li><li>-Ca de próstata</li></ul>	<ul style="list-style-type: none"><li>-Glioblastoma</li><li>-Ca vejiga: 2%</li><li>-Ca pulmón</li></ul>	

# V SIMPOSIO GETHI

Table 1 | **FGFR fusion partners**<sup>51,52,56</sup>

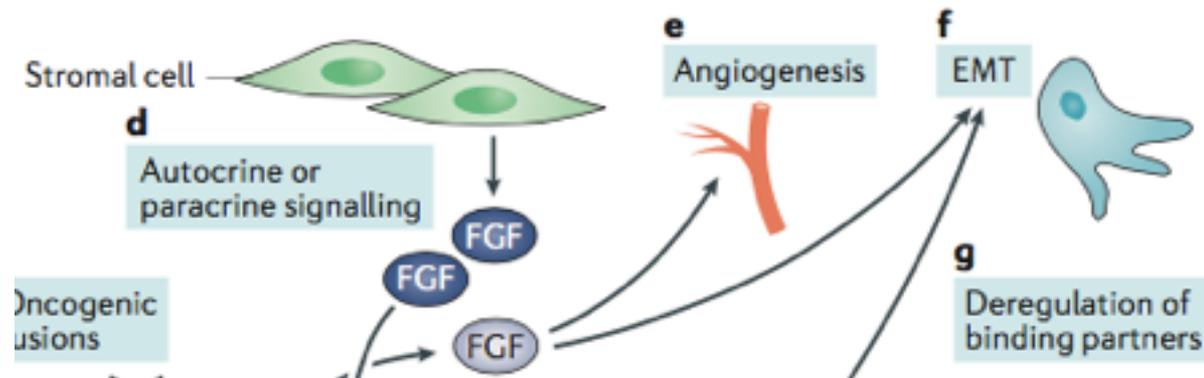
socios de fusión de FGFR contienen dominios de dimerización, que inducen la dimerización del receptor independiente del ligando y los efectos oncogénicos

Cancer type	5'-gene	3'-gene	Cases reported	Frame	Fusion type
Bladder cancer	FGFR3	TACC3	3/121	In-frame	Short
Breast cancer	FGFR1	ADAM18	1/1,019	Out-of-frame	Middle
	RHOT1	FGFR1	1/1,019	CDS-5UTR	InterChr
	NSD3	FGFR1	2/1,019	In-frame	Short
	FGFR2	CCDC6	1/1,019	In-frame	Long
Glioblastoma	FGFR3	TACC3	6/158	In-frame	Short
Head and neck squamous cell carcinoma	FGFR3	TACC3	2/300	In-frame	Short
	FGFR3	TPRG1	1/300	Out-of-frame	InterChr
Intrahepatic cholangiocarcinoma	FGFR2	AHCYL1	7/66	In-frame	InterChr
	FGFR2	BICC1	2/66	In-frame	InterChr
Low-grade glioma	FGFR3	ELAVL3	1/266	In-frame	InterChr
	FGFR3	TACC3	1/266	In-frame	Short
Lung adenocarcinoma	FGFR1	SLC20A2	1/487	CDS-5UTR	Middle
Lung squamous cell carcinoma	BAG4	FGFR1	1/220	In-frame	Short
	FGFR2	CCAR2	1/220	In-frame	InterChr
	CCAR2	FGFR2	1/220	CDS-5UTR	InterChr
	FGFR3	TACC3	5/220	In-frame	Short
Ovarian cancer	FGFR2	USP10	1/400	In-frame	InterChr
Prostate adenocarcinoma	SLC45A3	FGFR2	1/84	CDS-5UTR	InterChr
	FGFR3	AES	1/178	In-frame	InterChr
Thyroid carcinoma	FGFR2	OFD1	1/494	In-frame	InterChr
	VCL	FGFR2	1/494	In-frame	Long

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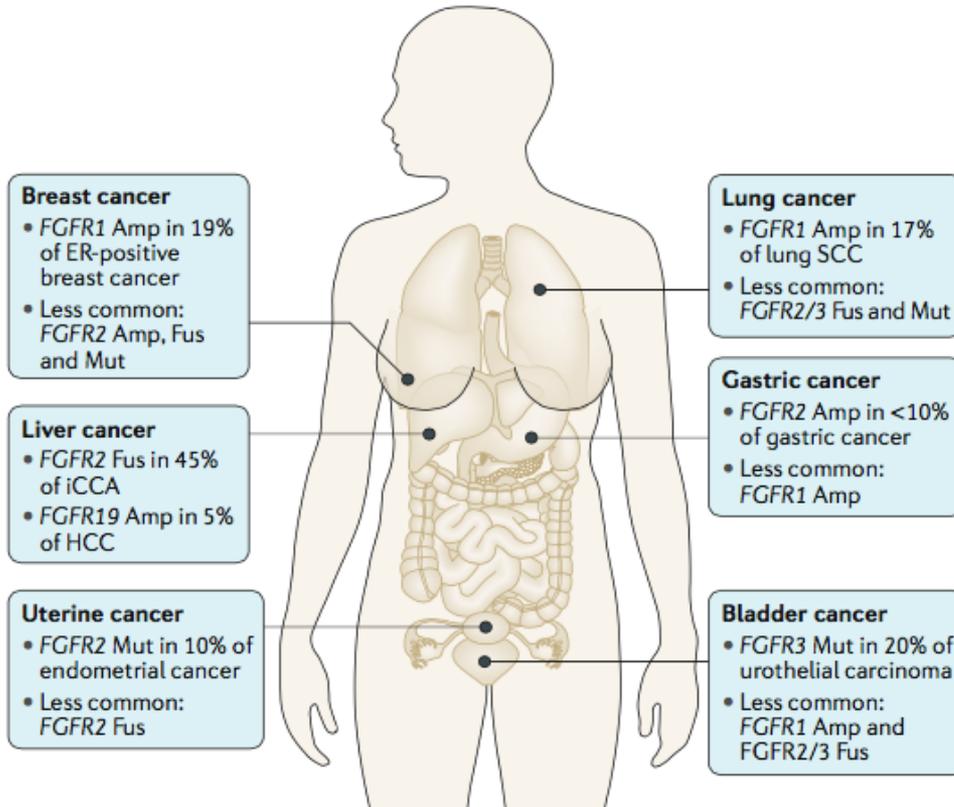
## *Señalización por ligando FGF, TEM y angiogenesis*

- FGF1, FGF2, FGF6, FGF8 ,endocrino FGF19 y FGF23
- FGF2 : cicatrización heridas, angiogénesis ( TEM)
- Niveles elevados FGF2 :pacientes resistentes a antiangiogénicos (pulmón, mama)



## Distribution of common FgFR-mutant cancers

### REVIEWS



Gene	Gene Amplifications	Point Mutations	Chromosomal Translocations	Splice Variants
<i>FGFR1</i>	Breast, ovarian, bladder, and lung cancer	Majority of cancers. Example: Melanoma	Stem cell leukemia/lymphoma (SCLL), GBM	IIIc: small cell lung carcinoma Iβ: breast cancer and GBM
<i>FGFR2</i>	Breast, gastric, lung cancer	Majority of cancers. Example: Endometrial carcinoma		IIIb: breast, endometrial, cervical, lung, pancreatic and colorectal cancer IIIc: prostate cancers
<i>FGFR3</i>	Bladder cancer	Majority of cancers. Example: bladder cancer	GBM, T-cell lymphoma and bladder	IIIc: bladder cancer
<i>FGFR4</i>	Colorectal cancer	Majority of cancers. Example: metastatic breast cancer and rhabdomyosarcoma		

Masaru Katoh, Nature Reviews 2018

Jimenez-Pascual A, Cells 2019

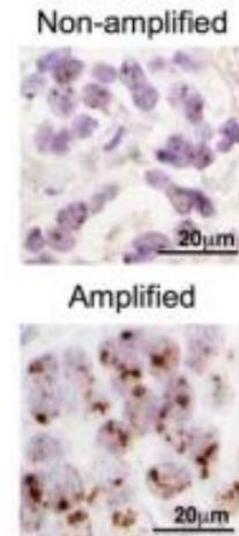
## CÁNCER DE MAMA

- **Amplificaciones de FGFR1** (8p11-12) son una de las alteraciones más comunes en pacientes con cáncer de mama de cualquier subtipo (15%)
- Ocurre con mayor frecuencia en pacientes con cáncer de mama positivo para el receptor de estrógenos (ER) (19%) y en aquellas con TNBC (4%)
- Coamplificación de FGF3, FGF4 y FGF19 :15% (TNBC) TCGA
- Fusiones (**FGFR2 – AFF3**, **FGFR2– CASP7** y **FGFR2 – CCDC6**)
- Mutaciones missense **FGFR2** en el segundo dominio extracelular (R203C) o el **dominio intracelular de tirosina quinasa** ( N549K y K659E)

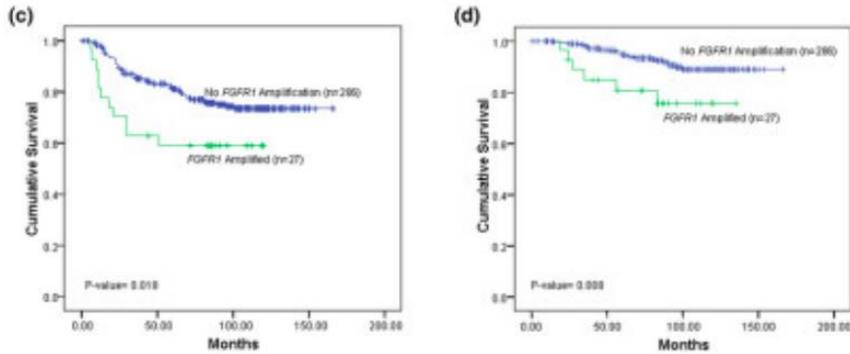
**Table 1**  
Most frequent genomic aberrations of the FGF/FGFR signaling pathway in breast cancer.

Gene	Amplification	Mutations	Fusions	References
<i>FGFR1</i>	8.7–23%	S125L K566R	<i>FGFR1-ZNF703</i>	[14–16, 23–24]
Amplicon 11q <i>FGFR2</i>	15–20% <1% (Overall) 4% (TNBC)	N549K R203C S587C	<i>FGFR2-AFF3</i>	[17–18] [14, 20, 23–24]
<i>FGFR3</i>	<1%	P689S		[14, 23]
<i>FGFR4</i>	2.3%	V550E A484T E326K		[14, 23]

FGFR: Fibroblast growth factor receptor; TNBC: Triple-negative breast cancer.



FGFR1 gene amplification was significantly correlated with shorter overall survival, mainly in HR-positive breast cancer



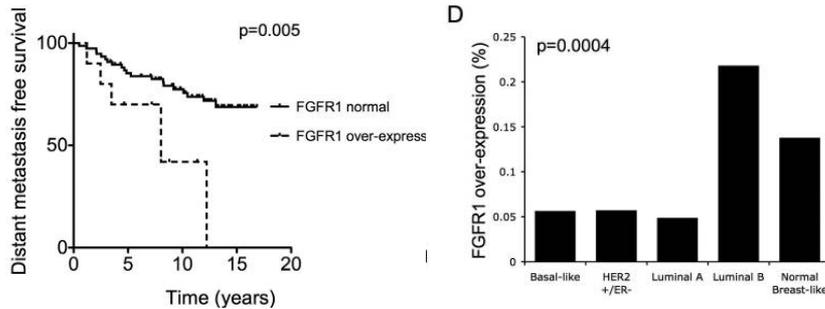
Casos positivos de receptores de estrógeno, supervivencia libre de enfermedad. (d) Casos positivos de receptores de estrógeno, supervivencia general

Elbauomy Elsheikh et al. Breast Cancer Res 2007

Cox proportional hazards analysis for predictors of disease-free and overall survival: effects of tumour grade, size, lymph node stage, oestrogen receptor (ER) status and FGFR1 status in ER-positive and ER-negative tumours

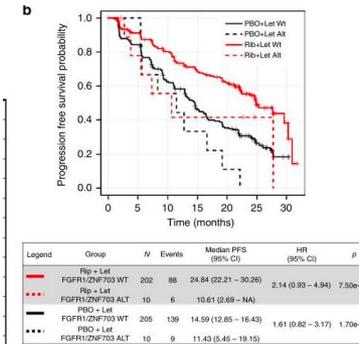
Variable	ER-positive tumours			ER-negative tumours		
	Hazard ratio	95% confidence interval	P value	Hazard ratio	95% confidence interval	P value
<b>Disease-free interval</b>						
Grade <sup>a</sup>	1.387	1.027–1.874	0.033	1.001	0.637–1.574	0.996
Tumour size $\geq 1.5$ cm <sup>b</sup>	1.551	0.926–2.595	0.095	2.348	1.092–5.052	0.029
Positive lymph node stage	1.407	0.879–2.252	0.155	2.597	1.563–4.315	0.000
FGFR1 amplification	2.250	1.184–4.274	0.013	1.104	0.440–2.774	0.833
<b>Overall survival</b>						
Grade <sup>a</sup>	2.600	1.471–4.594	0.001	1.673	0.731–3.829	0.223
Tumour size $\geq 1.5$ cm <sup>b</sup>	2.124	0.792–5.697	0.134	2.594	0.911–7.387	0.074
Positive lymph node stage	1.973	0.953–4.083	0.067	5.124	2.646–9.924	0.000
FGFR1 amplification	3.389	1.374–8.358	0.008	1.278	0.450–3.624	0.645

worse distant metastasis-free survival in FGFR1-overexpressing tumors and a higher frequency of FGFR1 amplification in the luminal B subtype



Turner et al. Cancer Res 2010

FGFR alterations correlate with poor outcome in ER+ breast cancers treated with CDK4/6 inhibitors and endocrine therapy

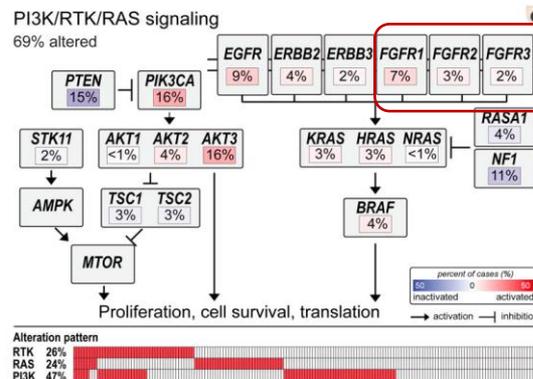


PFS in patients in the **MONALEESA-2** trial of **letrozole (Let) plus ribociclib (Rib)** vs. letrozole plus placebo (PBO) those with detectable FGFR1/ZNF703 amplification (ALT) in ctDNA had a PFS of **10.61 months vs. 24.84 months** in patients without FGFR1/ZNF703 amplification.

Luigi Formisano et al, Nature Communications 2019

## CÁNCER DE PULMÓN

- **Amplificación FGFR1(8P12):** una de las alteraciones más frecuentes
  - Escamoso (**17%**), células pequeñas (6%) adenocarcinoma (1%)
  - Tabaquismo
  - 12% estadios localizado NSCLC (21% of SCCs and 2% of adenocarcinomas)**temprano SSC**
  - 17% metástasis cerebrales de NSCLCs (19% of SCCs and 12% of adenocarcinomas)**evento tardío adenocarcinoma.**
- Mutaciones FGFR3 S249C (4% adenocarcinomas)
- Fusiones FGFR3–TACC3 (2% SCCs)
- Menos frecuentes (<1%): mutaciones FGFR2 W290C y FGFR2 K660E/N (orFGFR2cK659E/N) y fusión FGFR2–CIT



**Table 1**  
Principal genomic FGFR alterations in NSCLC.

Tumor type	Gene	Alteration	Incidence (%)	Refs.
Sq-NSCLC	FGFR1	Amplification	11–22	[25–33]
	FGFR1	Mutation	2	[37]
	FGFR2	Mutation	3–5	[37,38]
	FGFR3	Mutation	2–3	[37,38]
	FGFR4	Mutation	2	[37]
	FGFR3-TACC3	Translocation	1–3.5	[40,42]
	BAC4-FGFR1	Translocation	0.3–0.6	[40,42]
Ad-NSCLC	FGFR2-KIAA1967	Translocation	0.3	[40]
	FGFR1	Amplification	2.2–3.4	[31,35]
	FGFR3-TACC3	Translocation	0.5	[41,42]

Sq-NSCLC, squamous non small cell lung cancer; Ad-NSCLC, adenocarcinoma non small cell lung cancer.

La amplificación del gen FGFR1 es una alteración frecuente en el SCC del pulmón y parece ser un **marcador pronóstico favorable para las mujeres y particularmente para pacientes con SCC avanzado del pulmón (estadios III-IV)**

SCC of the lung (n=101)

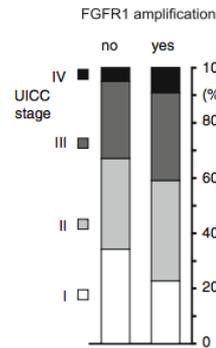
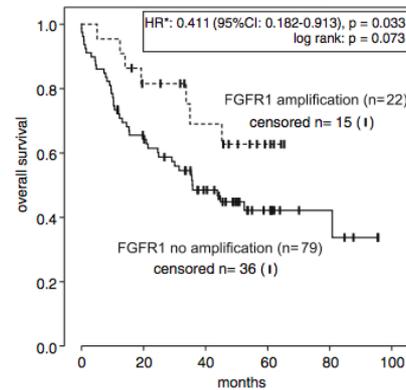
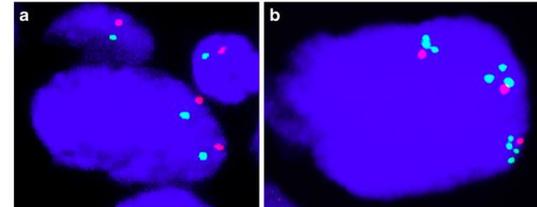


Fig. 1 Fluorescence in situ hybridization to identify the amplification of FGFR1 gene on SCC of the lung. **a** FGFR1 gene wild-type, FGFR1/CEN8 ratio 1.0. **b** FGFR1 gene amplification, FGFR1/CEN8 ratio > 2.0. ( $\times 100$  magnification). A dual color probe (ZytoVision, Bremerhaven) was used for FGFR1 (green) and centromere of chromosome 8 (red)



**metanálisis de 13 estudios** publicados en Sq-NSCLC mostró una tasa de amplificación de FGFR1 del 19%, significativamente **correlacionada con el tabaquismo** y la metástasis en los ganglios linfáticos. **No relación con OS**

**Table 2**  
Information of eligible studies.

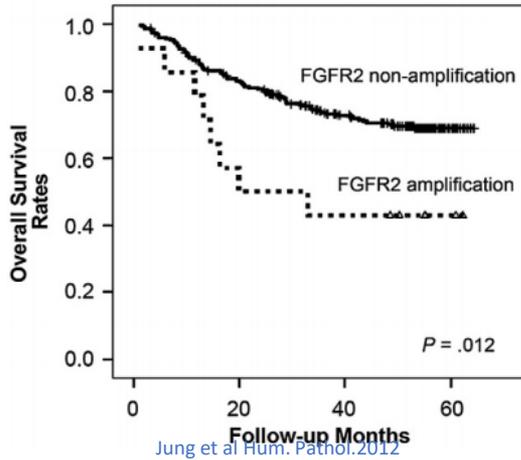
First author	Year	Source of Pts	Stage	Test method	Total Pts		Sq. Pts		Smoker Pts		Not smoker Pts	
					Number	AMP+ (%)	Number	AMP+ (%)	Number	AMP+ (%)	Number	AMP+ (%)
Weiss	2010	Switzerland	NA	FISH	232	NA	153	22.0%	153	17.65%	NA	NA
Dutt	2011	USA	I-IV	SNP	628	5.4%	46	19.6%	NA	NA	NA	NA
Goeke	2012	Germany	I-III	FISH	72	16.0%	72	16.0%	42	14.29%	2	0
Heist	2012	USA	I-IV	FISH	226	16.4%	226	16.4%	217	16.1%	9	22.2%
Kohler	2012	Germany	I-IV	FISH	260	7.7%	133	10.5%	NA	NA	NA	NA
Sasaki	2012	Japan	I-IV	RT-PCR	100	32.0%	65	41.5%	76	40.8%	24	4.2%
Schildhaus	2012	Germany	NA	FISH	347	17.3%	290	20.0%	NA	NA	NA	NA
Craddock	2013	Canada	I-IV	FISH	121	18.2%	121	18.2%	104	20.2%	4	0
Gadgeel	2013	USA	I-IV	RT-PCR	345	4.9%	136	5.2%	270	5.6%	NA	NA
Kim	2013	Korea	I-III	FISH	262	13.0%	262	13.0%	225	15.1%	37	0
Tran	2013	Australia	I-III	CS-ISH	264	18.6%	101	24.8%	165	21.8%	9	0
Ren	2013	China	I-IV	RT-PCR	59	50.8%	24	45.8%	29	55.20%	30	10.0%
Cihoric	2014	Switzerland	I-II	FISH	329	12.5%	169	20.7%	239	13.80%	18	5.6%

Sq: squamous cell carcinoma; Pts: patients; AMP+: FGFR1 amplification; CS-ISH: chromogenic with silver in situ hybridization; RT-PCR: real time PCR; SNP: single nucleotide polymorphism.

## CÁNCER GÁSTRICO

- **Amplificaciones FGFR2** :<10% de los pacientes con cáncer gástrico
- Asocian: invasión linfática/venosa, afectación ganglionar, metástasis a distancia, estadios avanzados y un pronóstico desfavorable
- El cáncer gástrico amplificado con FGFR2 es particularmente probable que tenga **complicaciones o recurrencia de la enfermedad peritoneal y / o metástasis ováricas (tumor de Krukenberg)**

313 casos, 14 (4.5%) mostraron amplificación del receptor 2 del factor de crecimiento de fibroblastos por hibridación fluorescente in situ. Se encontró que la amplificación del receptor 2 del factor de crecimiento de fibroblastos estaba asociada con un estadio pT más alto ( $P = .023$ ), un estadio pN más alto ( $P = .038$ ) y metástasis a distancia ( $P = .009$ ) y estaba significativamente asociado con una supervivencia más baja ( $p = 0,012$ )



**Table 3** Multivariate analysis of predictive factors for survival (Cox proportional hazards model)

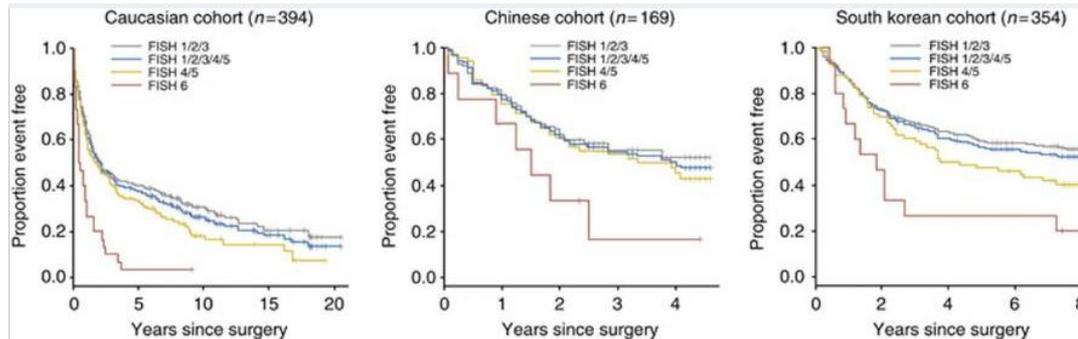
Parameters	Odds ratio (95% CI)	P
<i>FGFR2</i> amplification		.422
Positive vs negative	1.357 (0.644-2.860)	
pTNM stage		<.001
II vs I	5.817 (1.822-18.570)	
III vs I	30.153 (10.572-86.004)	
IV vs I	44.190 (14.859-131.421))	
Radical surgery		.003
R1 vs R0	1.913 (0.458-7.982)	
R2 vs R0	2.781 (1.529-5.058)	

Abbreviation: CI indicates confidence interval.

Blood vessel invasion			.039
Absent	9 (64.3%)	254 (84.9%)	
Present	5 (35.7%)	45 (15.1%)	
Lymphatic invasion			.012
Absent	1 (7.1%)	122 (40.8%)	
Present	13 (92.9%)	177 (59.2%)	
Tumor invasion			.015
Early carcinoma	0 (0.0%)	90 (30.1%)	
Advanced carcinoma	14 (100.0%)	209 (69.9%)	
T class			.023
T1	0 (0.0%)	90 (30.1%)	
T2	4 (28.6%)	50 (16.7%)	
T3	4 (28.7%)	103 (34.4%)	
T4a	6 (42.9%)	48 (16.1%)	
T4b	0 (0.0%)	8 (2.7%)	
N class			.038
pN0	2 (14.3%)	131 (43.8%)	
pN1	1 (7.1%)	44 (14.7%)	
pN2	3 (21.4%)	38 (12.7%)	
pN3a	6 (42.9%)	46 (15.4%)	
pN3b	2 (14.3%)	40 (13.4%)	
Distant metastasis			.009
Absent	9 (64.3%)	264 (88.3%)	
Present	5 (35.7%)	35 (11.7%)	
TNM stage			.032
I	2 (14.3%)	106 (35.5%)	
II	2 (14.3%)	77 (25.8%)	
III	5 (35.7%)	81 (27.1%)	
IV	5 (35.7%)	35 (11.7%)	

### Asociación del número de copias de FGFR2 con la supervivencia general

.La mediana de SG fue significativamente más corta en pacientes con GC amplificada con FGFR2 en comparación con pacientes con GC no amplificada con FGFR2 en cohortes del Reino Unido ( $P < 0,0001$ ) y coreanas ( $P = 0,0073$ ) mediante análisis univariado. Se observó una tendencia similar para la cohorte china, pero no alcanzó significación ( $P = 0,0646$ )



## CARCINOMA UROTELIAL

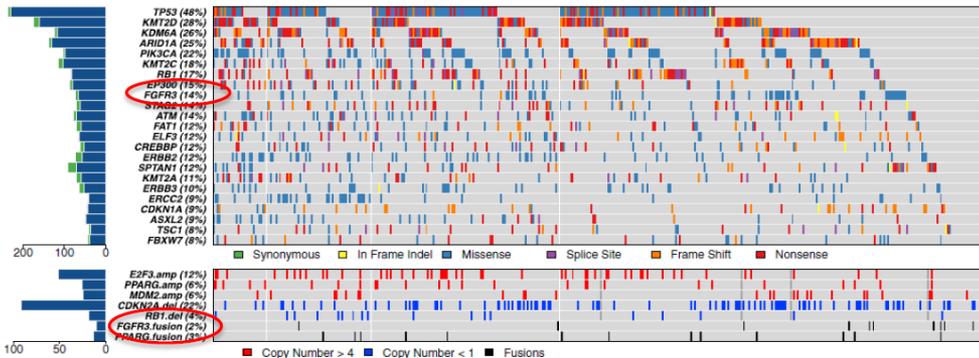
FGFR alterations occur very commonly in non-muscle-invasive bladder cancer (NMIBC) (~40-70%) but are also found in 15-20% of mUC and are enriched in immunologically “cold” luminal type 1 UC – based on recent molecular classification schemes for MIBC.

Cell

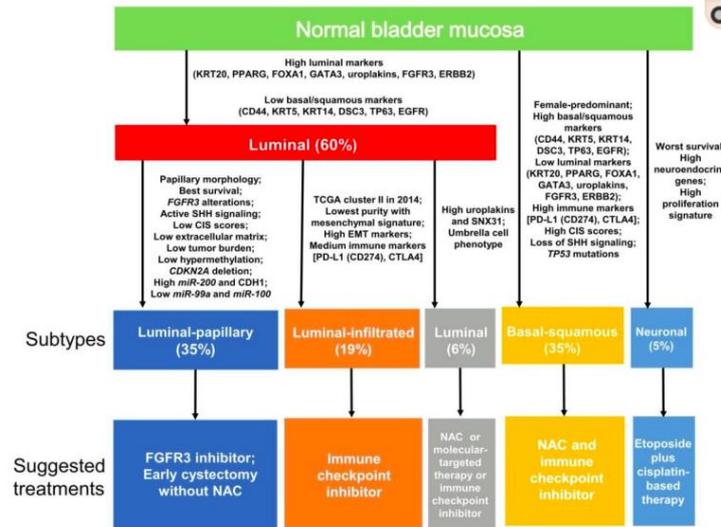
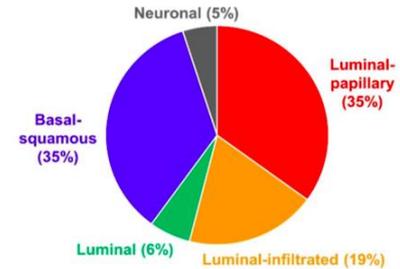
Article

### Comprehensive Molecular Characterization of Muscle-Invasive Bladder Cancer

A. Gordon Robertson,<sup>1,25</sup> Jaegil Kim,<sup>2,25</sup> Hikmat Al-Ahmadie,<sup>3</sup> Joaquim Bellmunt,<sup>4</sup> Guangwu Guo,<sup>5</sup> Andrew D. Cherniack,<sup>2</sup> Toshinori Hinoue,<sup>6</sup> Peter W. Laird,<sup>6</sup> Katherine A. Hoadley,<sup>7</sup> Rehan Akbani,<sup>8</sup> Mauro A.A. Castro,<sup>9</sup> Ewan A. Gibb,<sup>1</sup> Rupa S. Kanohi,<sup>9</sup> Dmitry A. Gordenin,<sup>10</sup> Sachet A. Shukla,<sup>5</sup> Francisco Sanchez-Vega,<sup>11</sup> Donna E. Hensel,<sup>12</sup> Bogdan A. Czerniak,<sup>13</sup> Victor E. Reuter,<sup>3</sup> Xiaoping Su,<sup>8</sup> Benilton de Sa Carvalho,<sup>14</sup> Vinicius S. Chagas,<sup>9</sup> Karen L. Mungall,<sup>1</sup> Sara Sadeghi,<sup>1</sup> Chandra Sekhar Pedamallu,<sup>2</sup> Yiling Lu,<sup>15</sup> Leszek J. Klimczak,<sup>16</sup> Jioxin Zhang,<sup>6</sup> Caleb Choo,<sup>1</sup> Akinyemi I. Ojesina,<sup>17</sup> Susan Bullman,<sup>2</sup> Kristen M. Leraas,<sup>18</sup> Tara M. Lichtenberg,<sup>18</sup> Catherine J. Wu,<sup>19</sup> Nicholas Schultz,<sup>11</sup> Gad Getz,<sup>2</sup> Matthew Meyerson,<sup>20</sup> Gordon B. Mills,<sup>16</sup> David J. McConkey,<sup>21</sup> TCGA Research Network, John N. Weinstein,<sup>8,22,\*</sup> David J. Kwiatkowski,<sup>23,\*</sup> and Seth P. Lerner<sup>24,26,\*</sup>

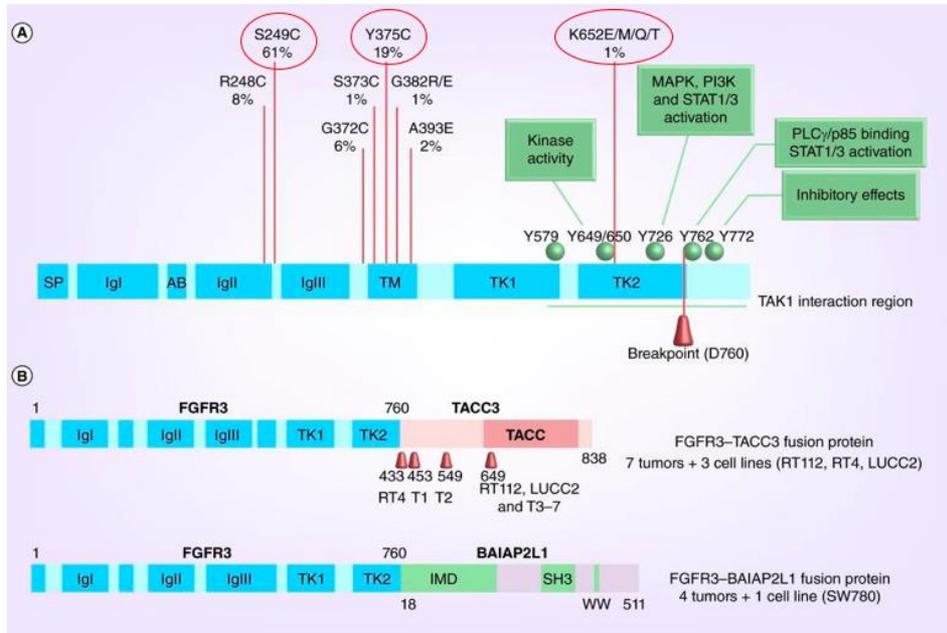


### Molecularly-distinct subtypes determined by TCGA



Categorization of muscle-invasive bladder cancer into five different subtypes based on mRNA expression by The Cancer Genome Atlas. Molecular and clinicopathological characteristics and suggested treatments for the five subtypes are summarized. CIS, carcinoma in situ; epithelial-mesenchymal transition; NAC, neoadjuvant chemotherapy; SHH, sonic hedgehog.

- Las mutaciones de FGFR3 más prevalentes son los cambios de Ser a Cys en el dominio extracelular que promueven la autodimerización y la activación de la señalización independiente del ligando (di Martino et al 2009).



Mutaciones missense: : FGFR3 S249C ,FGFR 3Y375C ( dimerización ind ligando)

Mutaciones menos frecuentes: FGFR3K652E / M

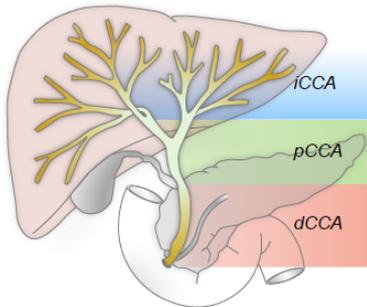
Fusiones FGFR3-TACC3 / FGFR-3-BAIA

Amplificaciones FGFR3 FGFR3K652E/M (activación constitutiva TK)

## COLANGIOCARCINOMA

### BACKGROUND

#### Cholangiocarcinoma



iCCA, pCCA, and dCCA correspond to intrahepatic, perihilar, and distal cholangiocarcinoma, respectively.

- Most common primary malignancy of the bile duct<sup>1</sup>
  - Worldwide incidence varies regionally (0.3–3.4 per 100,000 in North America and Eu)
    - Substantially higher incidence in certain regions of Asia, particularly Thailand
- First-line treatment for locally advanced or metastat cholangiocarcinoma (CCA) is gemcitabine/cisplatin: →
- Second-line chemotherapies have shown limited efficacy<sup>4–7</sup>
  - Progression-free survival: median 2.6–3.2 mo
  - Overall survival: median 6.2–7.2 months
  - Objective response rate: 7.7–9.5%
- Several actionable oncogenic alterations have been identified in CCA, including alterations involving FGFR2<sup>1–3</sup>
  - **FGFR2 fusions or rearrangements are**
    - Almost exclusively found in iCCA
    - Present in 10–16% of patients with iCCA in the United States and Europe<sup>4–6</sup>

Focal amplifications of FGF19 and FGFR2-containing gene fusions (FGFR2–KIAA1598, FGFR2–MGEA5, FGFR2–PPHLN1, FGFR2–TACC3 )

Intrahepáticos: **IDH1/2, FGFR2, BRAF**  
Extrahepáticos: KRAS, P53, CDKN2

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ORIGINAL REPORTS

**Cholangiocarcinoma With *FGFR* Genetic Aberrations: A Unique Clinical Phenotype**

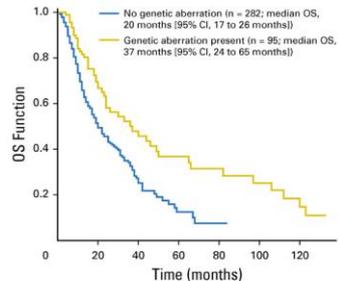
[Apurva Jain](#), [Mitesh J. Borad](#), [Robin Kate Kelley](#), [Ying Wang](#), [Reham Abdel-Wahab](#), [Funda Meric-Bernstam](#), ...

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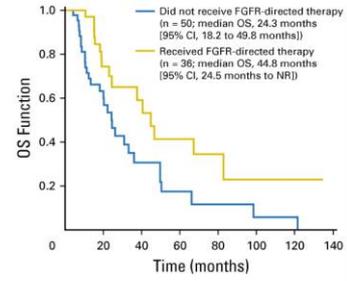
**n:377 →95 alteraciones *FGFR* (*FGFR2* :74→63 fusiones)**

Alteraciones *FGFR* mayor frecuencia en:

- **pacientes más jóvenes** ( $\leq 40$  años; 20%) ( $P < .001$ ),
- **Estadio precoz I / II v III / IV:** 35.8% v 22%, ( $P = .001$ )
- asociaron **SG más prolongada (37 v 20 meses,  $P < .001$ )**. Esta diferencia se mantuvo significativa después de excluir a 36 pacientes tratados con inhibidores de *FGFR*. No hubo diferencia de OS ( $P = .60$ ) con fusiones versus otras alteraciones de *FGFR* ( $n = 29$ ).
- **Mejor SG con terapia dirigida a *FGFR* en comparación con el tratamiento estándar ( $P = .01$ ).**



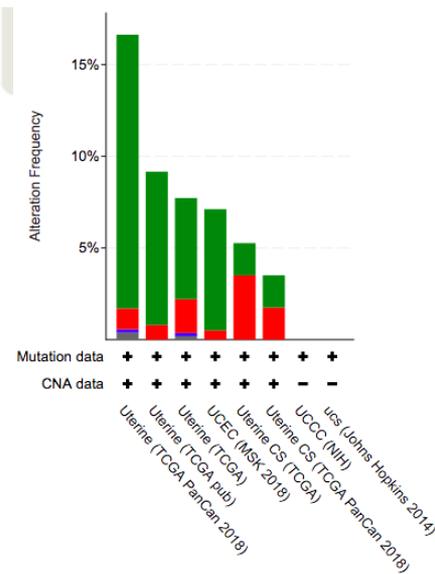
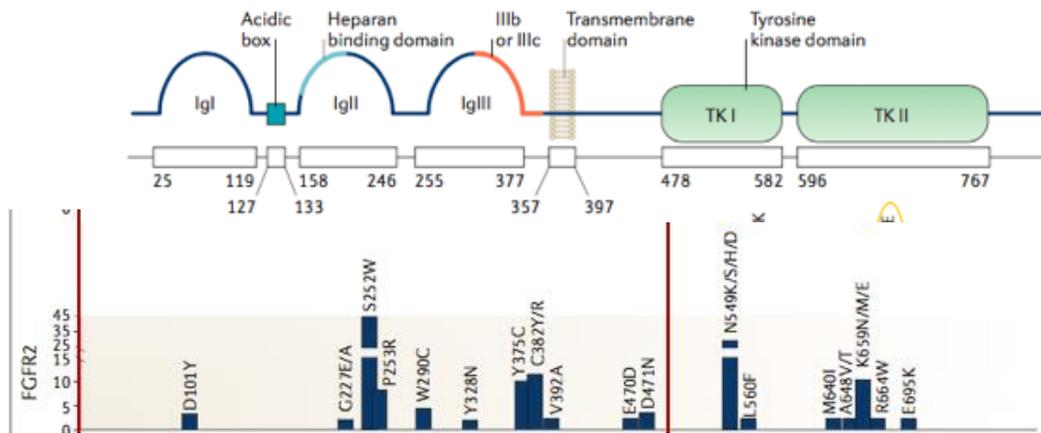
No. at risk:	0	20	40	60	80	100	120
No genetic aberration	282	105	26	7	1		
Genetic aberration present	95	48	22	15	11	8	5



No. at risk:	0	20	40	60	80	100	120	140
Did not receive FGFR-directed therapy	50	20	7	3	2	1	1	
Received FGFR-directed therapy	36	20	10	7	4	2	2	

## TUMORES GINECOLÓGICOS

**CÁNCER DE ÚTERO:** Mutaciones puntuales FGFR2: S252W, P253R, Y376C, C383R, N550K / H y K660E



**CÁNCER CERVIX, OVARIO O VULVA :** mutac FGFR2 o FGFR3 raras

## OTROS

**TUMORES CEREBRALES:** glioblastoma, glioma bajo grado, astrocitoma pilocítico, neuroblastomas olfatorio

- Glioblastoma: mutaciones FGFR1 (N546K and K656E) and FGFR3–TACC3
- Glioma bajo grado, astrocitoma pilocítico: FGFR1 duplicaciones dominio quinasa, mutaciones y fusiones
- Neuroblastoma olfatorio: fusiones (FGFR2–KIAA1598, FGFR2–CTNNA3 and FGFR3–TACC) y amplificaciones FGFR3

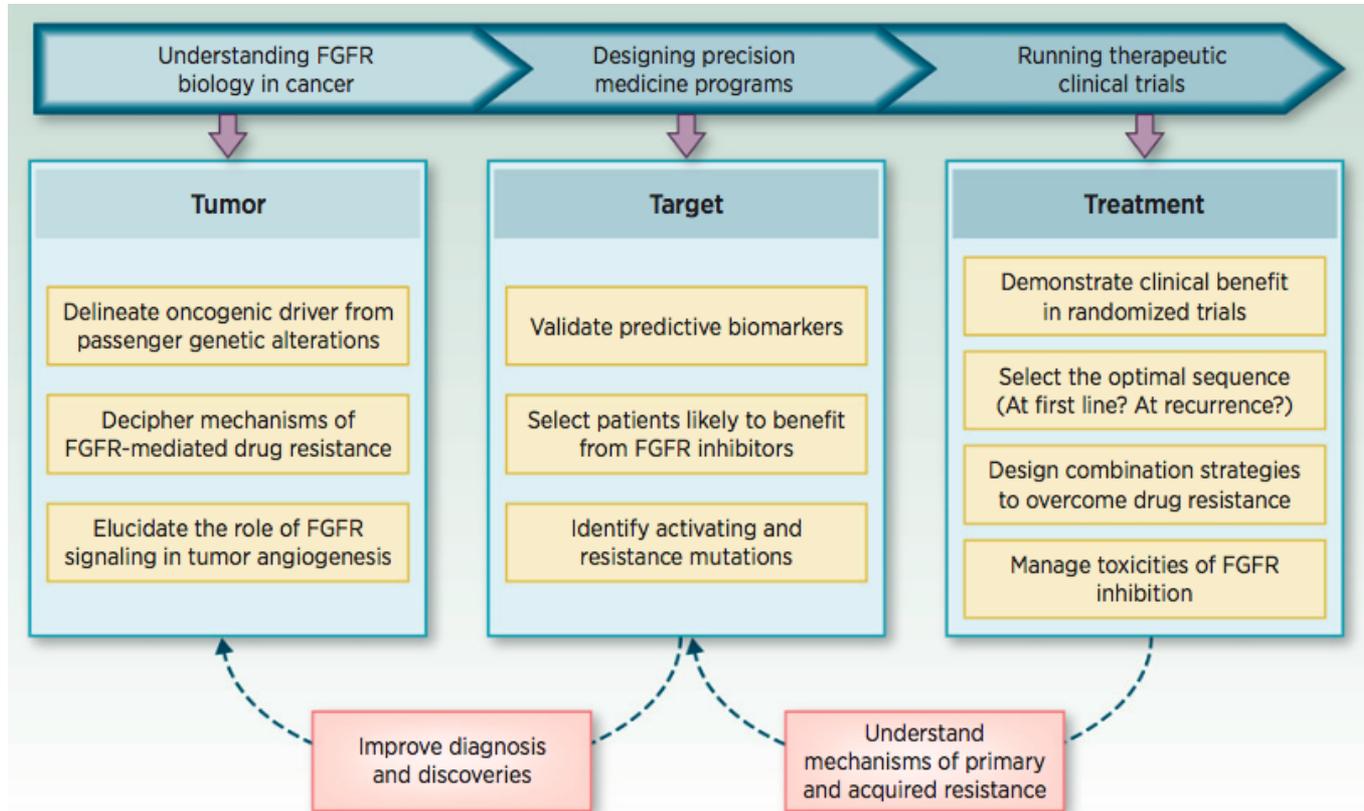
## OTROS

- FGFR1 N546K: Sarcoma Ewing ,GISTs, feocromocitomas
- FGFR3 K650M :melanoma acral,liposarcoma

# V SIMPOSIO GETHI

## FGFR research in cancer: from bench to bedside.

Overview of challenges and prospects for the development of FGFR-targeted therapies



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## CONCLUSIONES:

- Las aberraciones de FGFR son comunes en una amplia variedad de cánceres, siendo la mayoría amplificaciones o mutaciones activadoras
- La inhibición de FGFR es una opción terapéutica importante en múltiples tipos tumorales
- Debido a su relativa frecuencia y su fácil detección representan dianas terapéuticas atractivas para el desarrollo de fármacos
- Secuenciación para identificar anomalías moleculares accionables : medicina de precisión
- Hay varios ensayos en curso de fármacos inhibidores de FGFR con resultados prometedores