VII SIMPOSIO GETTHI

GETTHI
Grupo Español de Oncología Transversal y Tumores Huérfanos e Infrecuentes

Sesión 4: Vías de desarrollo de la oncología transversal (II)

16 de diciembre de 2021 - *Formato virtual*

Alteraciones conocidas en la familia FGFR y sus implicaciones

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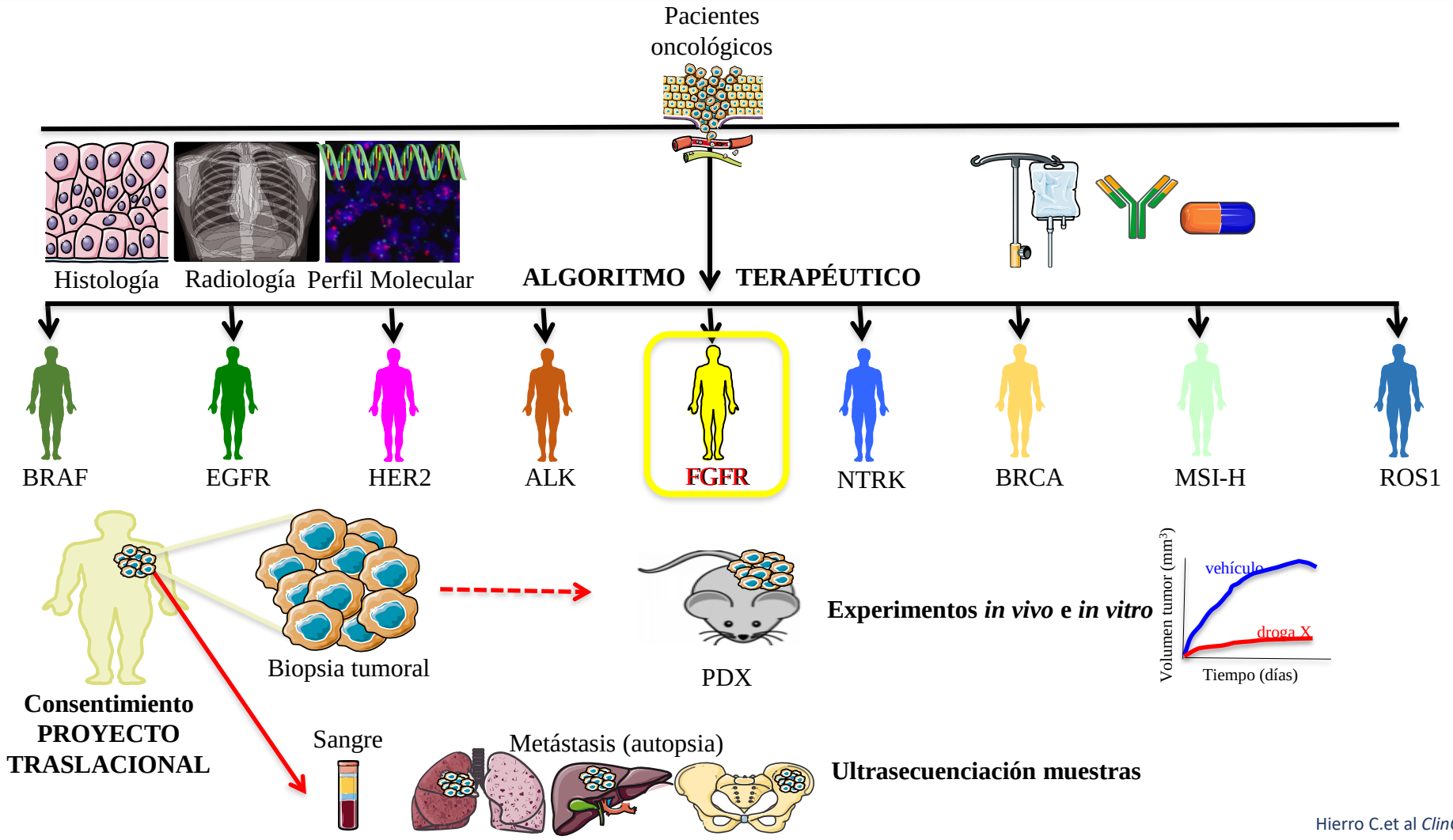
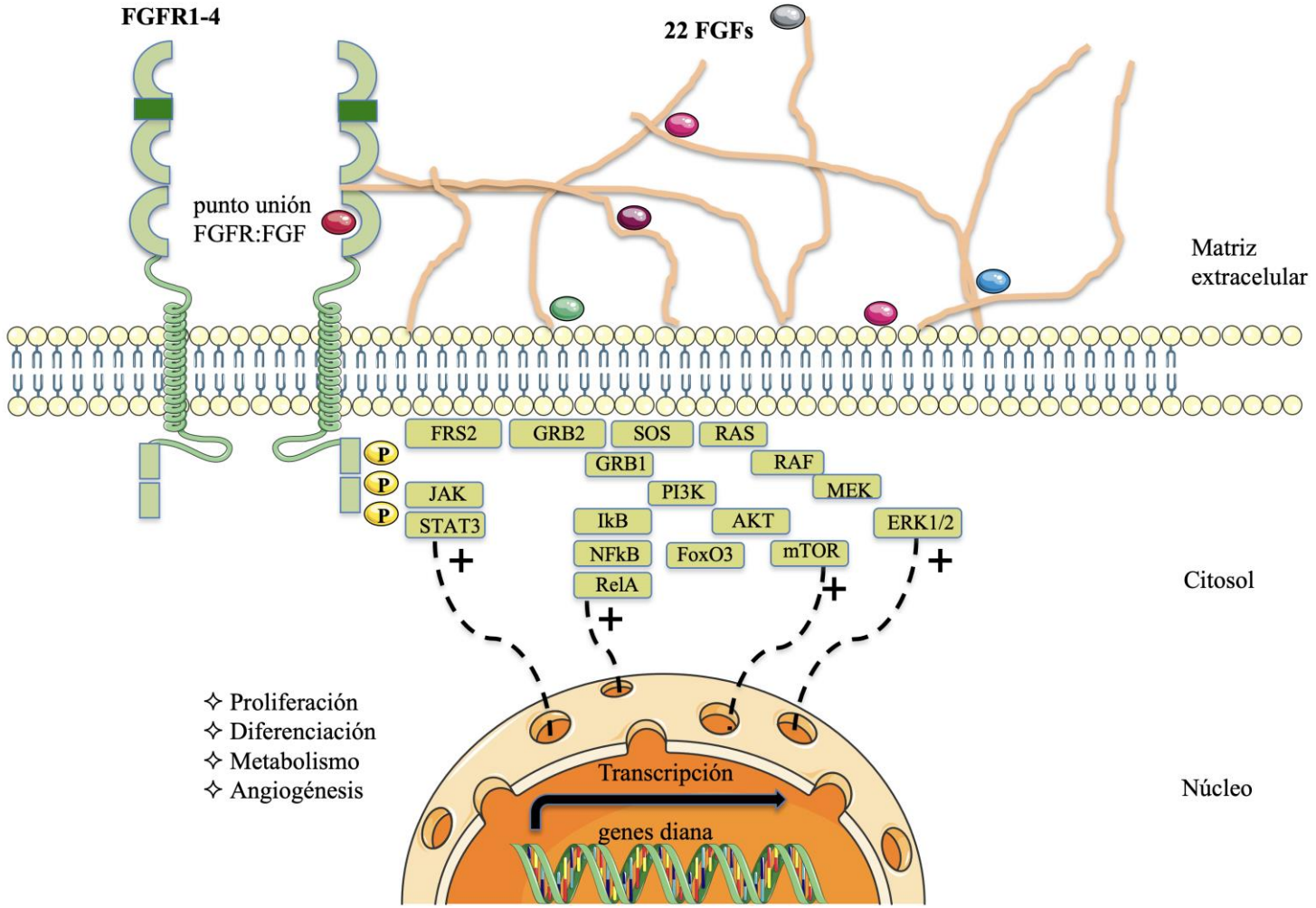
1. Desarrollo clínico precoz de nuevos fármacos y pacientes seleccionados molecularmente



Hierro C.et al *ClinCancerRes* 2019 Jun 1; 25(11):3210-3219

2. Biología molecular de la vía del *FGFR:FGF*



Dienstmann R.et al *AnnOncol* 2014; 25: 552-563

3. Alteraciones génicas en la vía del *FGFR:FGF* en tumores humanos

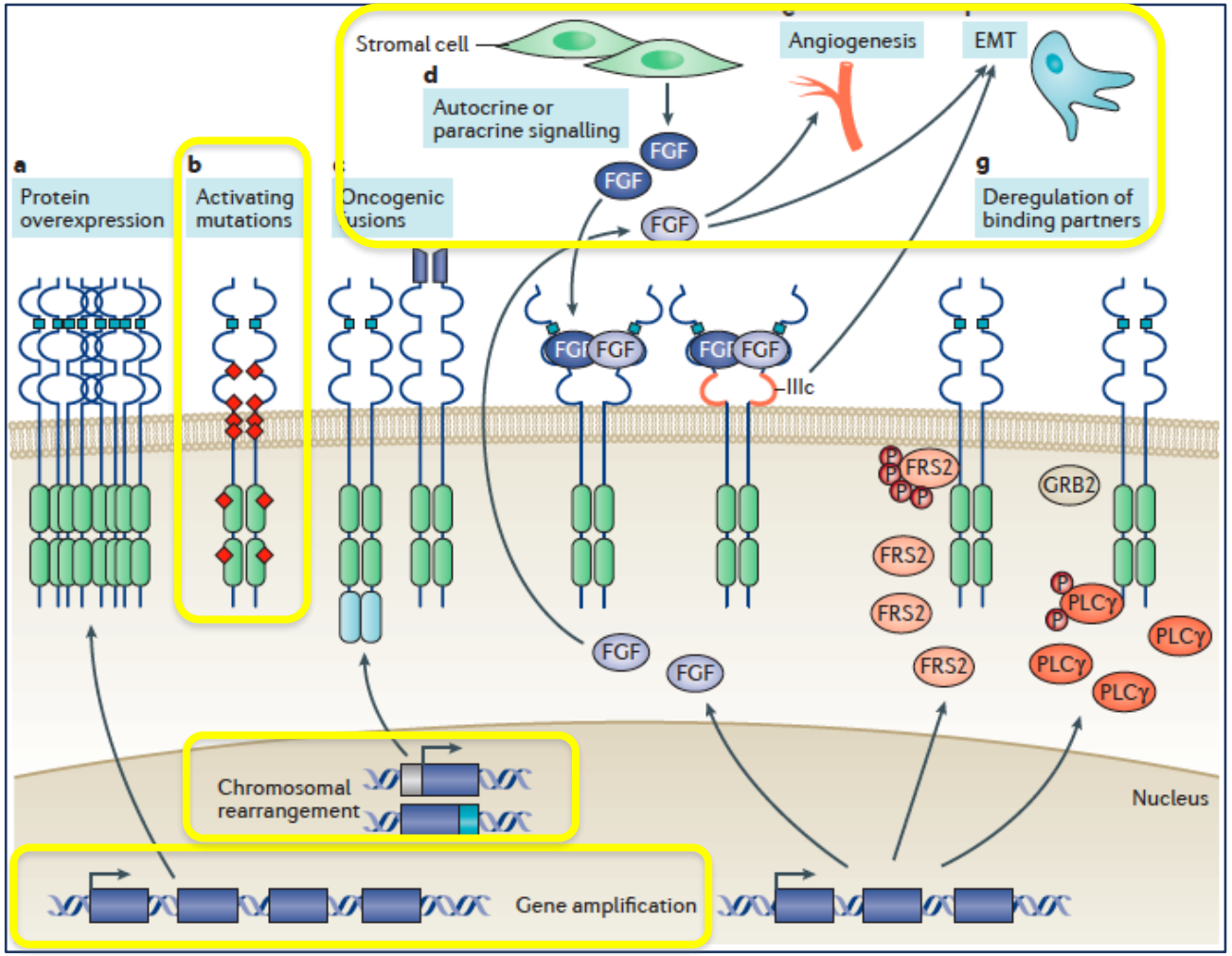
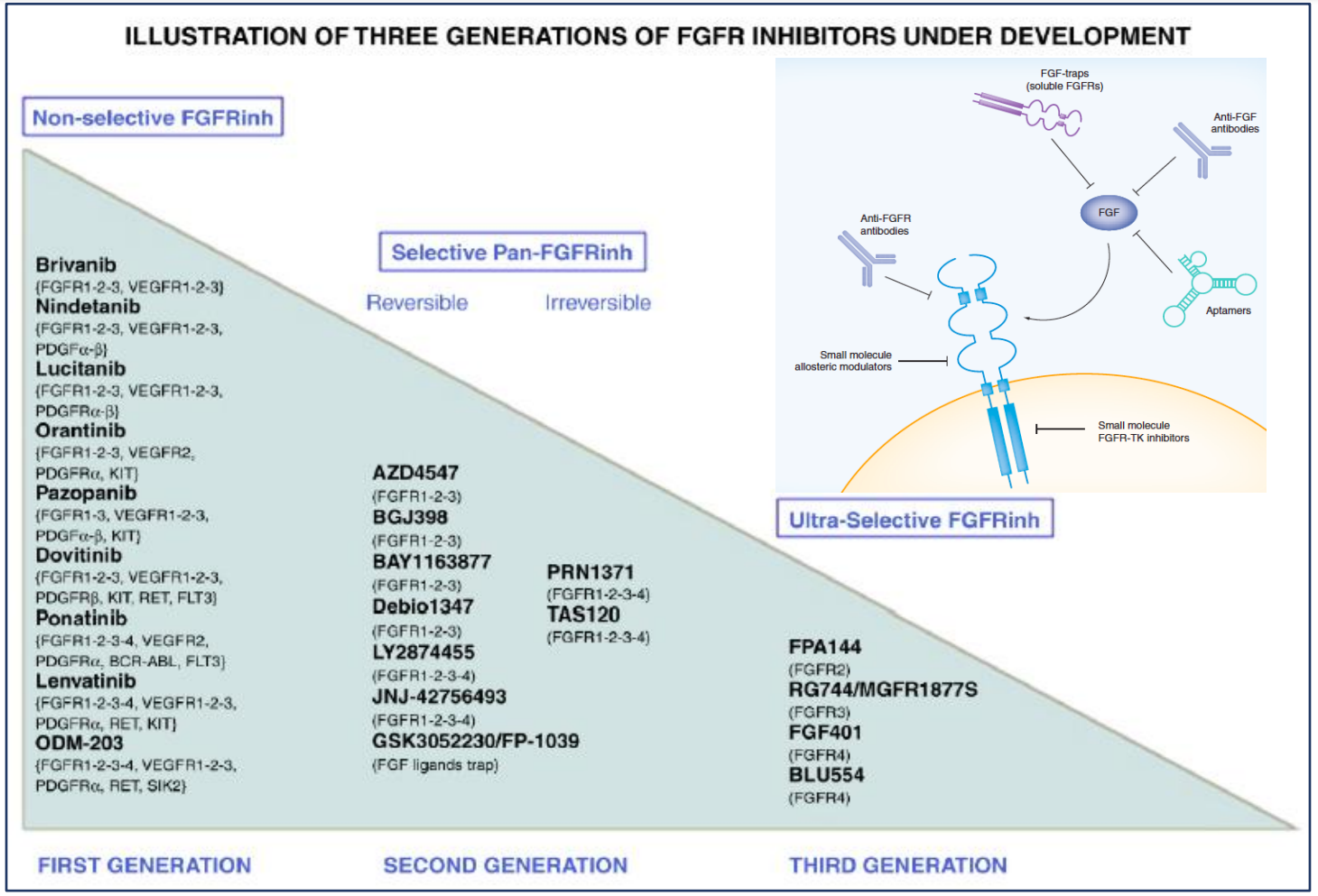


Table 1. Most Frequent FGFR/FGF Genomic Alterations in Human Solid Tumors

Tumor Type	FGFR/FGF Aberration	Prevalence (%)
Squamous NSCLC	FGFR1 amplification	10-20%
	11q amplification	12%
Adenocarcinoma NSCLC	FGFR1 amplification	6%
	11q amplification	4%
Small cell lung cancer	FGFR1 amplification	6%
Squamous head & neck cancer	FGFR1 amplification	10%
Squamous esophageal cancer	FGFR1 amplification	9%
Gastric cancer	FGFR2 amplification	7%
	FGFR2 mutation	4%
Hepatocellular cancer	FGFR4 and βKlotho overexpression	40%
	FGFR4 and βKlotho overexpression +- FGF19 overexpression	15%
Biliary tract cancer	FGFR2 translocations	13%
Colorectal cancer	FGFR4 amplification and FGF19 overexpression	4%
Hormone receptor–positive breast cancer	FGFR1 amplification	10%
	11q amplification	15%
Triple-negative breast cancer	FGFR1 amplification	4%,
	FGFR2 amplification	4%
Ovarian cancer	FGFR1 amplification	4%
	12q amplification	12%
Endometrial cancer	FGFR2 mutation	12%
	FGFR1 amplification	4%
Cervical cancer	FGFR3 Mutation	25%
Urothelial cancer (muscle-invasive)	FGFR1 amplification	11%
	FGFR3 mutation	15%
	FGFR3-TACC3 translocation	6%
Prostate cancer	FGFR1 amplification	8%
Glioblastoma	FGFR3-TACC3 translocation	3-7%
Melanoma	FGFR1 mutation	4%
	FGFR2 mutation	9%
	FGFR4 mutation	4%
Rhabdomyosarcoma	FGFR4 mutation	8%
Osteosarcoma	FGFR1 amplification	18%

Babina IS.et al *NatRevCancer* 2017; 17: 318-332
Hierro C.et al_*SeminOncol* 2015;42:801-819

4. Desarrollo de fármacos inhibidores del *FGFR*



Hierro C.et al Chapter 5; Vol 3 *Targeting Cell Survival Pathways to Enhance Response to Chemotherapy*. Elsevier©; 2018. p. 102-121
Herbert C. et al *PharmPatAnal* 2014;3(6):585-612

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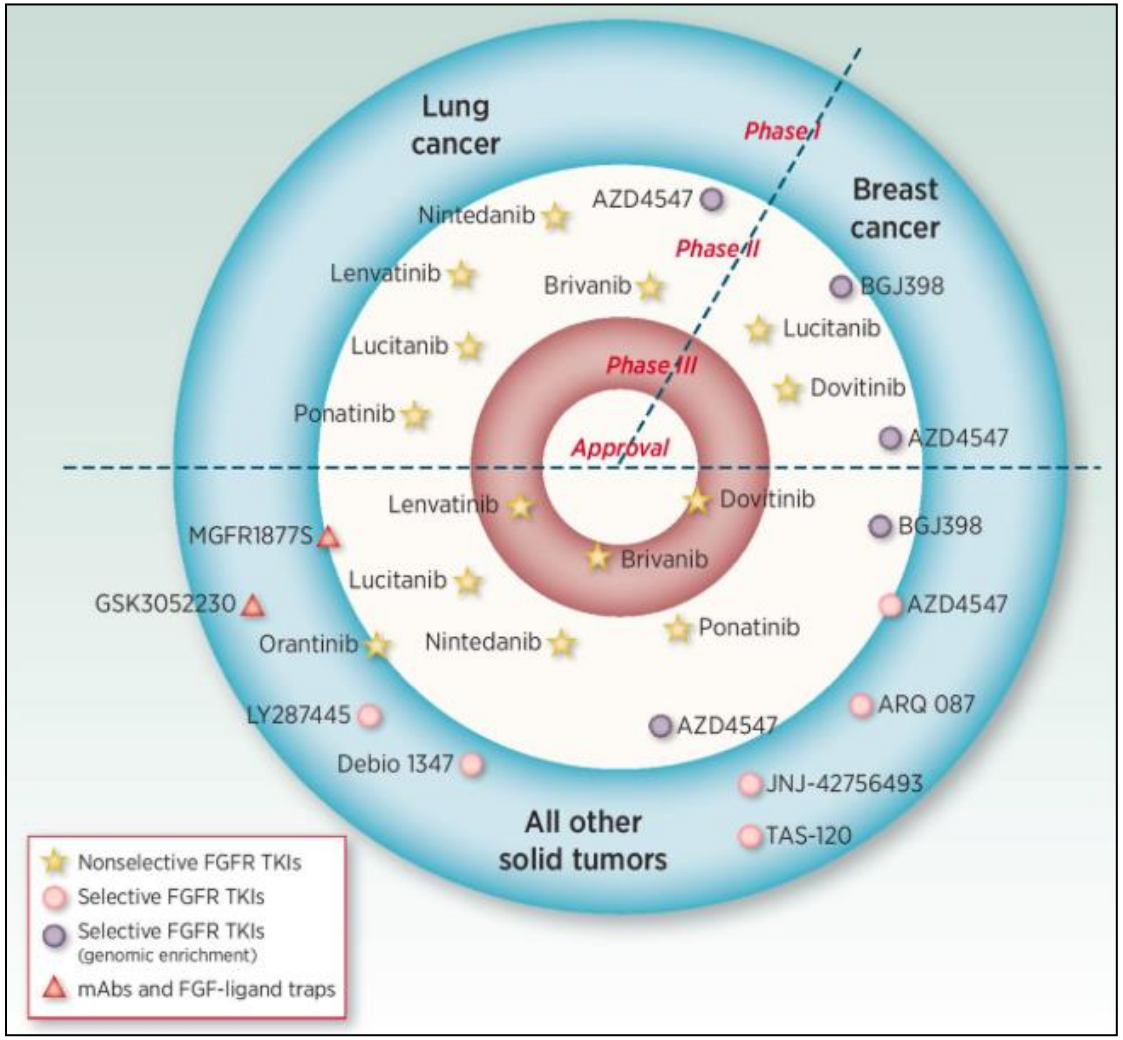

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FDA grants accelerated approval to erdafitinib for metastatic urothelial carcinoma

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Drug Information Soundcast in Clinical Oncology (D.I.S.C.O.)

Approved Drug Products with Therapeutic

On April 12, 2019, the Food and Drug Administration granted accelerated approval to erdafitinib (BALVERSA, Janssen Pharmaceutical Companies) for patients with locally advanced or metastatic urothelial carcinoma, with susceptible FGFR3 or FGFR2 genetic alterations, that has progressed during or following platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.

Patients should be selected for therapy based on an FDA-approved companion diagnostic for erdafitinib. Today, the FDA also approved the *therascreen*® FGFR RGQ RT-PCR Kit, developed by QIAGEN, for use as a companion diagnostic for this therapeutic indication.

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FDA grants accelerated approval to pemigatinib for cholangiocarcinoma with an FGFR2 rearrangement or fusion

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Drug Information Soundcast in Clinical Oncology (D.I.S.C.O.)

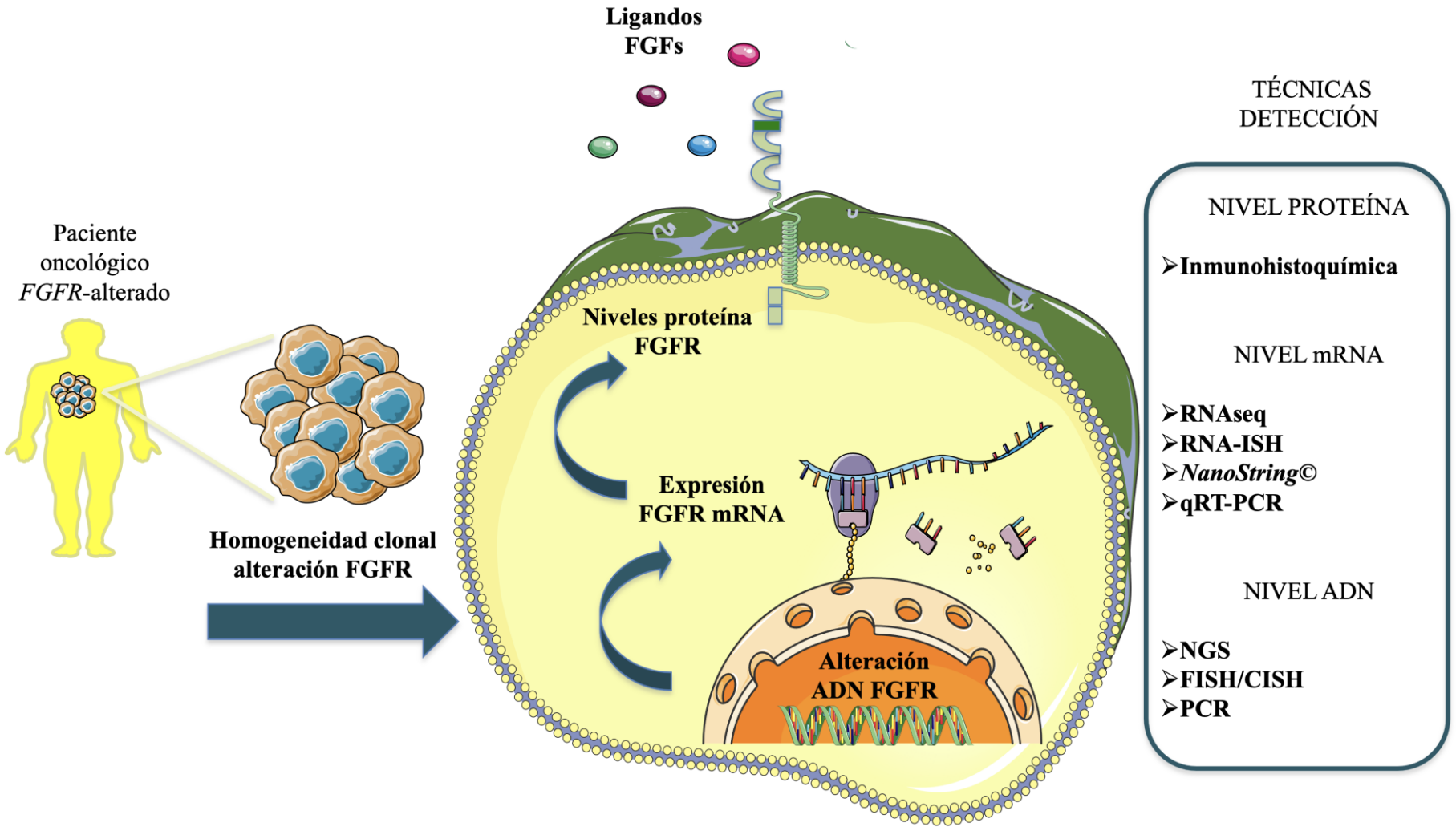
On April 17, 2020, the Food and Drug Administration granted accelerated approval to pemigatinib (PEMAZYRE, Incyte Corporation) for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement as detected by an FDA-approved test.

The FDA also approved the FoundationOne® CDX (Foundation Medicine, Inc.) as a companion diagnostic for patient selection.

Touat M.et al *ClinCancerRes*; 2015 Jun 15;21(12):2684-94

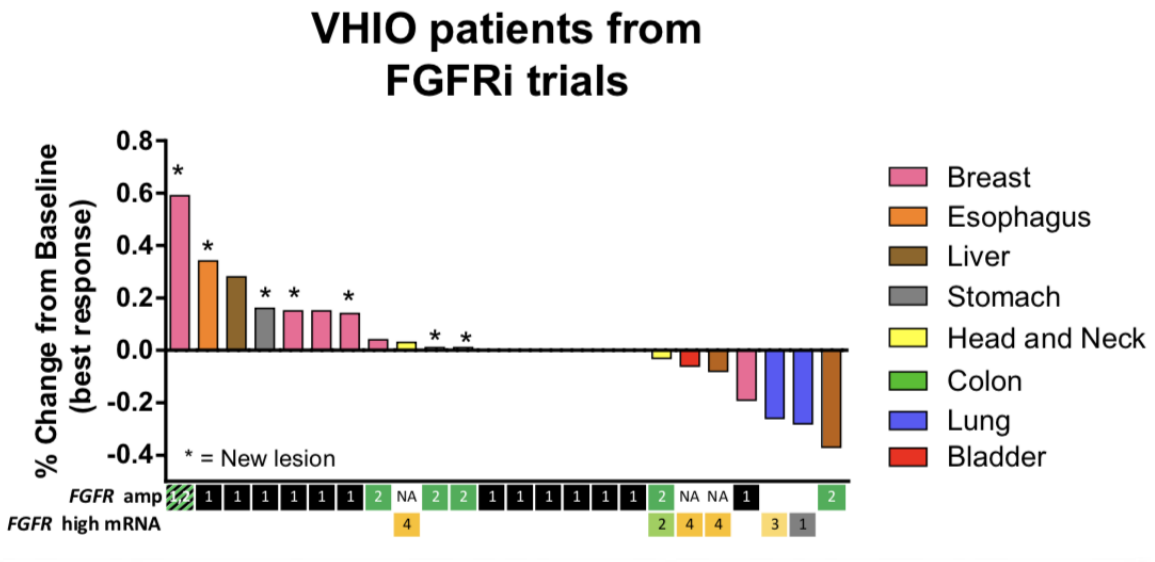
www.fda.gov

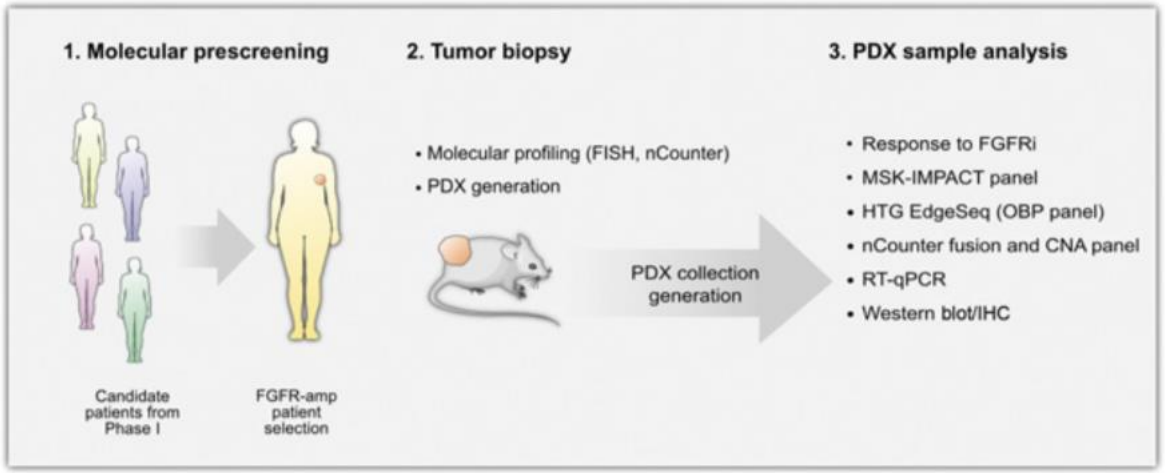
5. Potenciales biomarcadores predictivos de respuesta a los FGFRinh

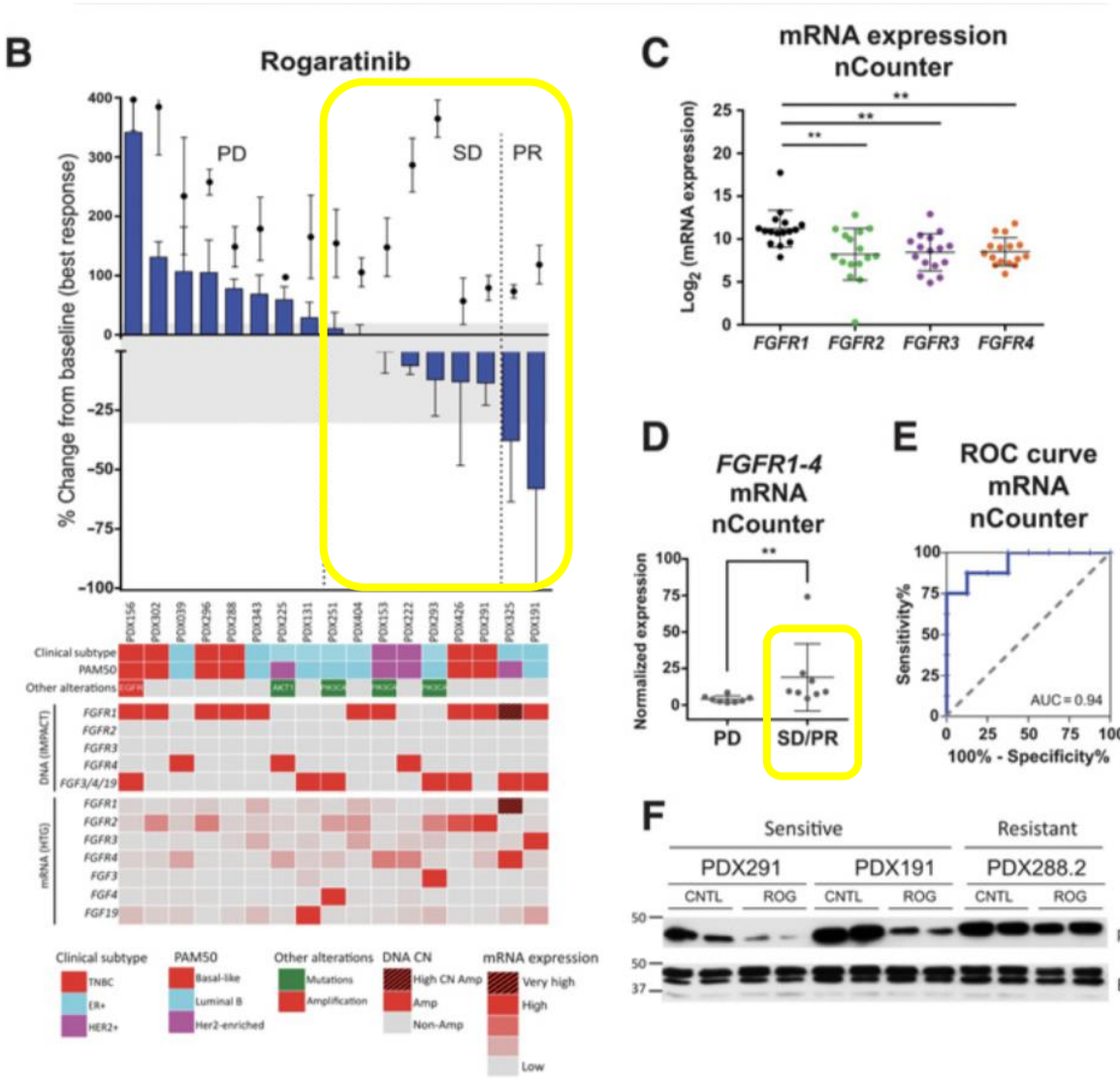


Hierro C.et al *AnnOnc* 2017; 28: 1207-1216

High FGFR1–4 mRNA Expression Levels Correlate with Response to Selective FGFR Inhibitors in Breast Cancer

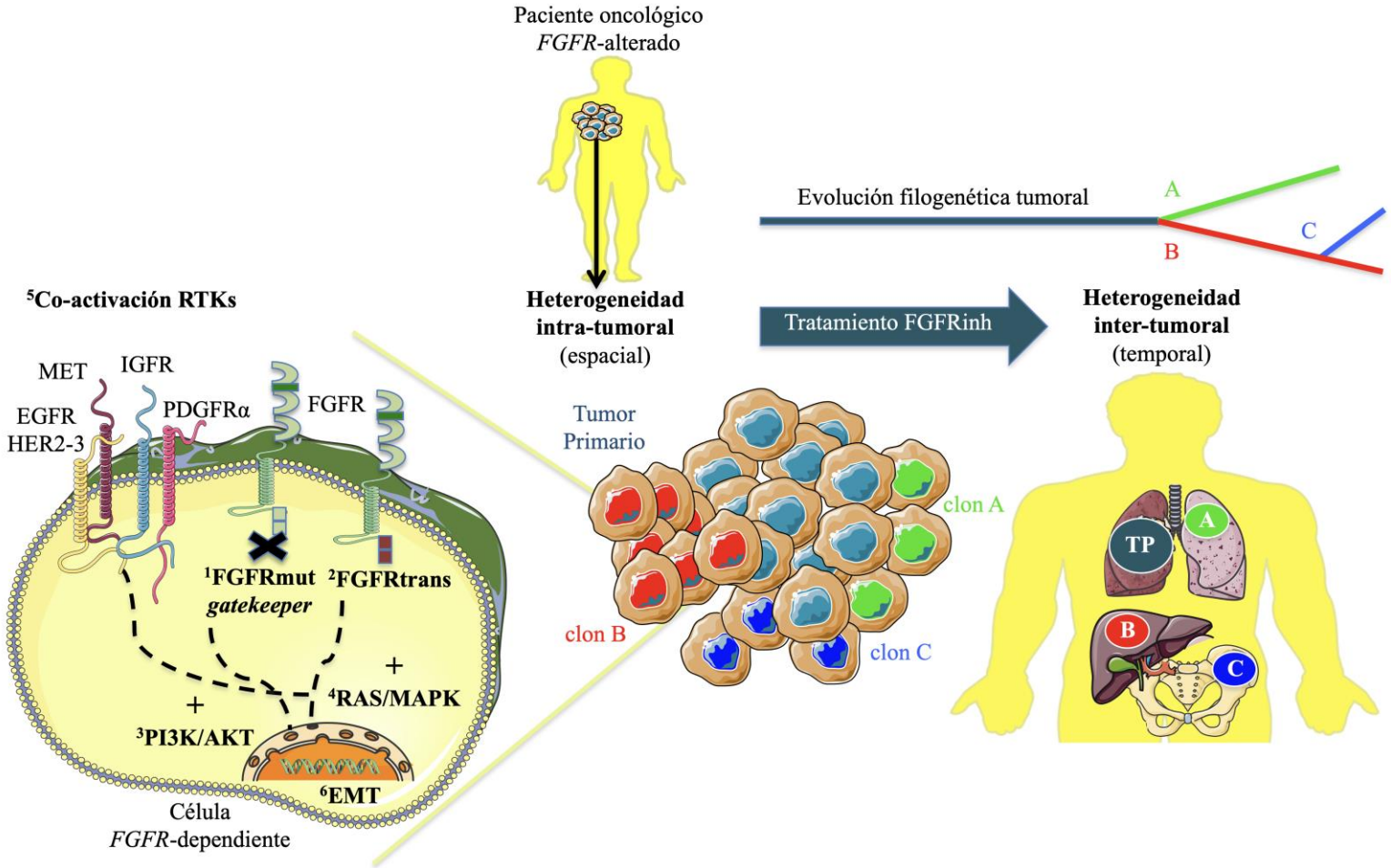




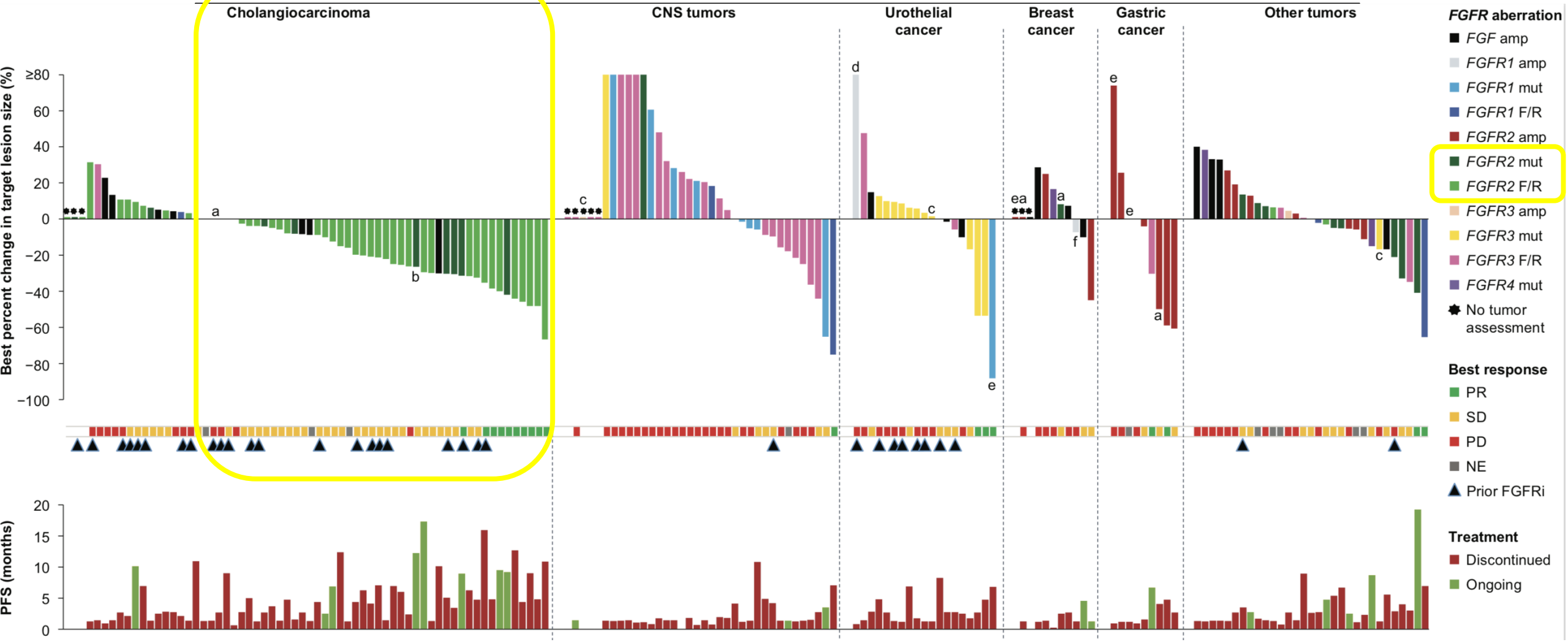


Sánchez-Guixé.et al *ClinCancerRes* 2021 Sep 30:clincanres.CCR-21-1810-A.2021

6. Mecanismos de resistencia a los FGFRinh



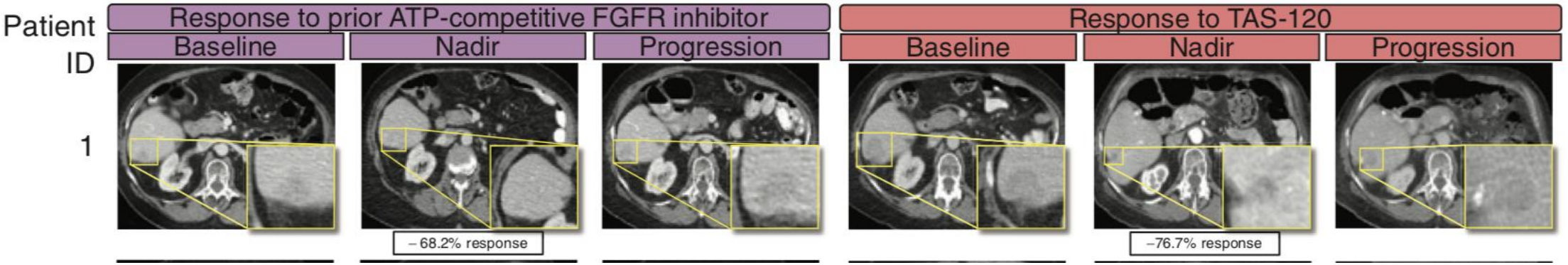
Gerlinger M.et al *NEnglJMed* 2012; 366: 883-892; Fidler IJ.et al *Science* 1982; 217: 998-1003; [1]Goyal L.et al *CancerDiscov* 2019;9(8):1064-79; [2]Kim SY.et al *Oncotarget* 2017 Feb 28;8(9):15014-15022; [3]Datta J.et al *MolCancerTher* 2017;16(4):614-24; [4]Bockorny B.et al *MolCancerTher* 2018;17(7):1526-39; [5]Wang J.et al *Oncogene* 2015; 34(17): 2167-77; [6]Grygielewicz P.et al *GastricCancer* 2014; Nov 19



Meric-Bernstam F.et al *CancerDiscov* 2021 Sep 22:candisc.0697.2021

TAS-120 Overcomes Resistance to ATP-Competitive FGFR Inhibitors in Patients with FGFR2 Fusion–Positive Intrahepatic Cholangiocarcinoma

Patient ID	FGFR2 fusion	First FGFR inhibitor	PFS (months)	BOR	Intervening therapies between 1st and 2nd FGFR inhibitor	Interval between 1st and 2nd FGFR inhibitor (months)	Second FGFR inhibitor	PFS (months)	BOR
1	*FGFR2-SORBS1*	BGJ398	12.6	–68.2%	None	1.2	TAS-120	15.8	–76.7%



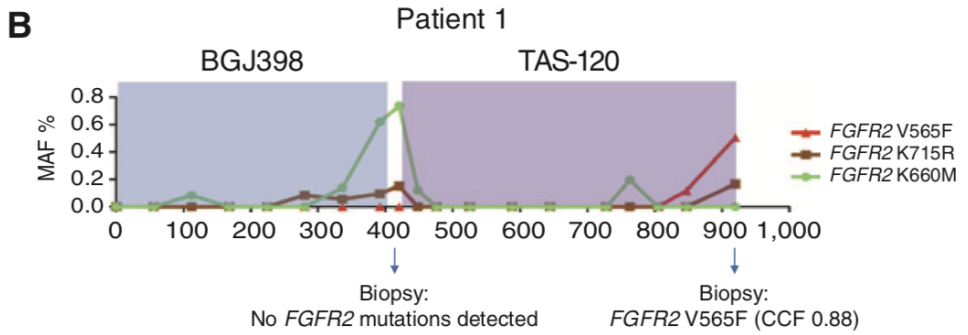


Table 1B. FGFR2 mutations detected in ctDNA and tumor biopsies

Patient ID	FGFR2 fusion	Post-progression BGJ398/Debio 1347, prior to TAS-120		Post-progression TAS-120	
		ctDNA	Tumor biopsy	ctDNA	Tumor biopsy
1	*FGFR2-SORBS1*	K660M, K715R	None detected	V565F[a]	V565F[b]

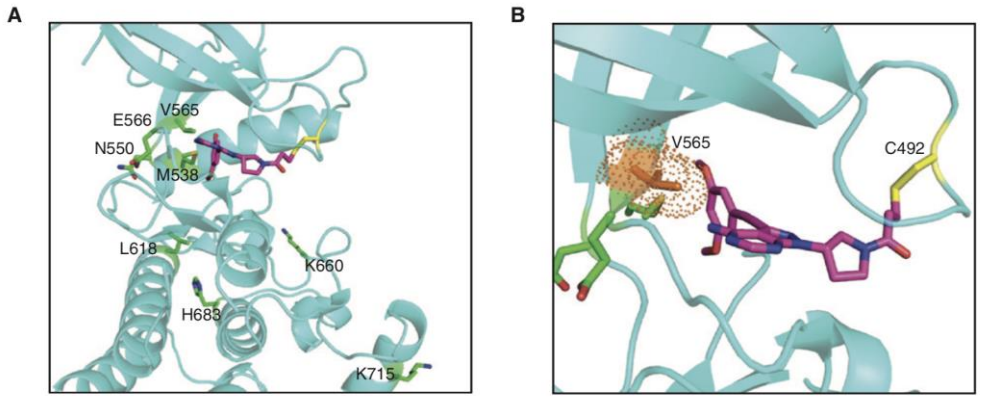


Figure 4. Structural modeling of secondary FGFR2 kinase domain mutations with TAS-120. **A,** Model showing TAS-120 docked into the binding pocket of WT FGFR2. Amino acid residues corresponding to mutations conferring resistance to ATP-competitive FGFR inhibitors are highlighted. Structural representations were prepared using PyMOL. **B,** A close-up view of TAS-120 in ATP-binding pocket of WT FGFR2. The gatekeeper residue (V565) is in close proximity to the dimethoxy phenyl group of TAS-120.

Goyal L.et al *CancerDiscov* 2019 Aug;9(8):1064-1079

7. Conclusiones

1. La vía FGFR:FGF desempeña un rol importante en múltiples procesos del cuerpo humano, que van desde la organogénesis hasta el metabolismo y la angiogénesis

2. Se han descrito distintas alteraciones moleculares implicando los genes FGFR:FGF en múltiples tipos tumorales

3. Las células neoplásicas *FGFR*-dependientes presentan un aumento de la proliferación celular, angiogénesis y resistencia a los fármacos quimioterápicos

4. Existen datos incipientes de eficacia con inhibidores del FGFR, pero es imprescindible seleccionar aquellos pacientes candidatos que, por sus características moleculares, presenten mayores probabilidades de obtener beneficio

5. Identificar biomarcadores predictivos de respuesta a los inhibidores del FGFR será clave para un desarrollo exitoso de estos agentes dirigidos

6. Los estudios fase I/*basket* agnósticos de histología y los protocolos traslacionales asociados han demostrado ser cruciales para avanzar en el conocimiento de la biología molecular de la vía y los posibles mecanismos de resistencia a los inhibidores

Gracias

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