GETTHI

Grupo Español de Oncología Transversal y Tumores Huérfanos e Infrecuentes

VII SIMPOSIO GETTHI

Sesión 3: Vías de desarrollo de la oncología transversal (I)

2 de diciembre de 2021 - *Formato virtual*

"NTRK-Tumours": fundamentos biológicos y resultados clínicos

Antonio Pérez-Martínez, Hospital Universitario La Paz, Madrid

1. Perspectiva histórica
2. Fundamentos biológicos
3. Ensayos clínicos
4. Experiencia Servicio de Hemato-Oncología Pediátrica Hospital Universitario La Paz

1. Perspectiva histórica

"Los orígenes del descubrimiento de los oncogenes TRK se remontan a la primavera de 1975 cuando los grupos de Harold Varmus y Mike Bishop, en colaboración con Peter Vogt, describieron por primera vez que el oncogén *src* responsable de los tumores inducidos por el virus del sarcoma de Rous NO ERA UN GEN VïRICO SINO UN GEN CELULAR, del genoma del pollo, transducido por el virus.

Este descubrimiento fue publicado al año siguiente en *Nature* y 13 años después, en 1989, les valió el Premio Nobel de Fisiología y Medicina a Harold Varmus y Mike Bishop".

Nature Vol. 260 March 11 1976

DNA related to the transforming gene(s) of avian sarcoma viruses is present in normal avian DNA

D. STEHELIN*
H. E. VARMUS
J. M. BISHOP

P. K. VOGT

Cortesía del Dr. Barbacid

"Estos resultados se presentaron por primera vez en la Conferencia Anual del NCI de 1975 que organizó el Instituto Nacional del Cáncer en Hershey, Pensilvania, que reunió a todos los jefes de grupo financiados por el programa especial del NCI sobre retrovirus oncogénicos.

El azar hizo que pudiera asistir a esa conferencia. De hecho, la primera conferencia a la que asistí desde mi llegada a los Estados Unidos en septiembre de 1974

Desde ese día, no pude quitarme de la cabeza la idea de que quizás los tumores humanos fueran también causados por genes celulares como el que dio origen al oncogén viral *src*, que podrían activarse como oncogenes bien por mutaciones espontáneas, bien por insultos carcinogénicos como el habito de fumar"

Cortesía del Dr. Barbacid

Pero en biología, las hipótesis tienen poco valor si no se demuestran experimentalmente

Por lo tanto, y durante un tiempo no pude encontrar la forma de poder probar esta hipótesis

Todo cambió una noche cuando recibí una llamada telefónica de mi amigo **Ángel Pellicer**, entonces becario postdoctoral en el laboratorio de Richard Axel en la Universidad de Columbia. Estaba muy emocionado porque acababa de demostrar que era posible transferir un gen de mamífero (el gen que codifica la timidina quinasa) a células de ratón en cultivo utilizando DNA genómico total.

Cell, Vol. 14, 725–731, July 1978, Copyright © 1978 by MIT

Biochemical Transfer of Single-Copy Eucaryotic Genes Using Total Cellular DNA as Donor

Michael Wigler, Angel Pellicer, Saul Silverstein*
and Richard Axel

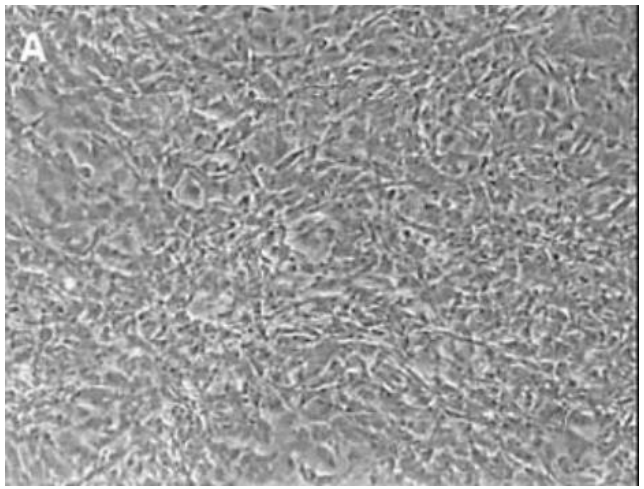
Cortesía del Dr. Barbacid

Estos resultados, publicados el verano siguiente en la revista CELL, demostraban que mediante una simple técnica de "transfección" iba a ser posible identificar cualquier gen de mamífero siempre que dicho gen proporcionara una ventaja selectiva, ya fuera crecer en un medio de cultivo especial como era el caso del gen de la timidina quinasa o inducir una transformación maligna que pudiera identificarse por el cambio de morfología en las células

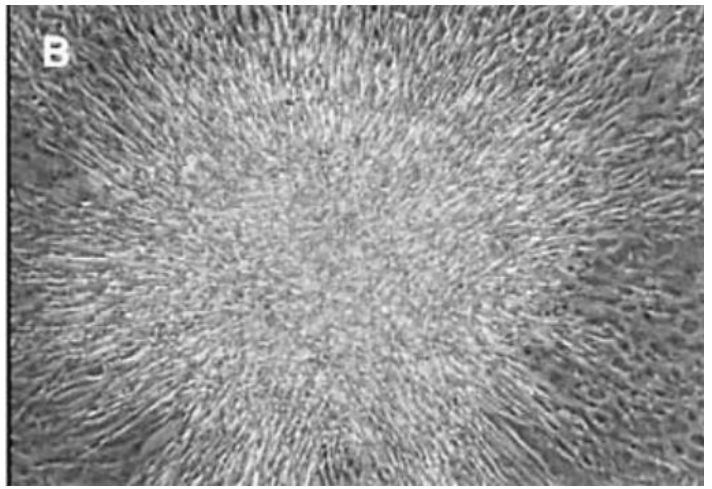
Tras viajar a Nueva York para aprender esta técnica de la mano de Ángel Pellicer, aislamos DNA genómico de unas treinta líneas celulares de tumores humanos y los usamos para transfectar células NIH3T3, una línea de fibroblastos embrionarios de ratón que, al sufrir una transformación maligna, adquirían unas características morfológicas que les hacían fácilmente diferenciables de las células normales

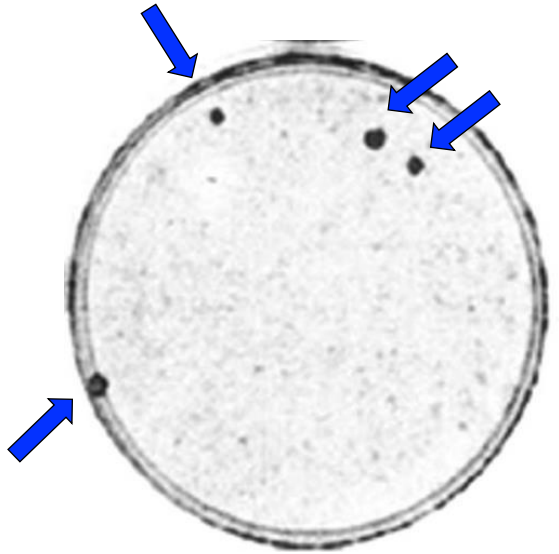
Cortesía del Dr. Barbacid

Pronto observamos que el DNA genómico aislado de una línea celular de carcinoma de vejiga denominada T24, producía de 4 a 5 focos de células transformadas por placa Petri.



Células NIH3T3 normales





"Focos"de células NIH3T3 transformadas por DNA aislado de células tumorales humanas T24 vistos al microscopio óptico (izquierda) y a simple vista (derecha)

Cortesía del Dr. Barbacid

"Este trabajo sentó las bases experimentales para el aislamiento, a finales de 1981, del primer oncogén humano, utilizando técnicas estándar de clonación de DNA, utilizando como sonda, secuencias repetitivas presentes en el DNA humano"

Proc. Natl. Acad. Sci. USA
Vol. 79, pp. 2845–2849, May 1982

Oncogenes in human tumor cell lines: Molecular cloning of a transforming gene from human bladder carcinoma cells

(transfection assays/*Alu* repetitive sequences)

SIMONETTA PULCIANI, EUGENIO SANTOS, ANNE V. LAUVER, LINDA K. LONG, KEITH C. ROBBINS, AND MARIANO BARBACID

Cortesía del Dr. Barbacid

"Un par de meses después de la publicación del aislamiento del primer oncogén humano pudimos CERRAR EL CÍRCULO, demostrando que, al igual que sucedió con el oncogén *src*, este gen humano ya había sido convertido en un oncogén anteriormente al ser transducido por un retrovirus murino aislado 16 años antes por la Dra. Janet Harvey

Por ello, este oncogén se denominó H-RAS: **H** por Harvey y RAS por "**RA**t **S**arcoma"

Reprinted from Nature, Vol. 298, No. 5872, pp. 343-347, 22 July 1982
© *Macmillan Journals Ltd., 1982*

T24 human bladder carcinoma oncogene is an activated form of the normal human homologue of BALB- and Harvey-MSV transforming genes

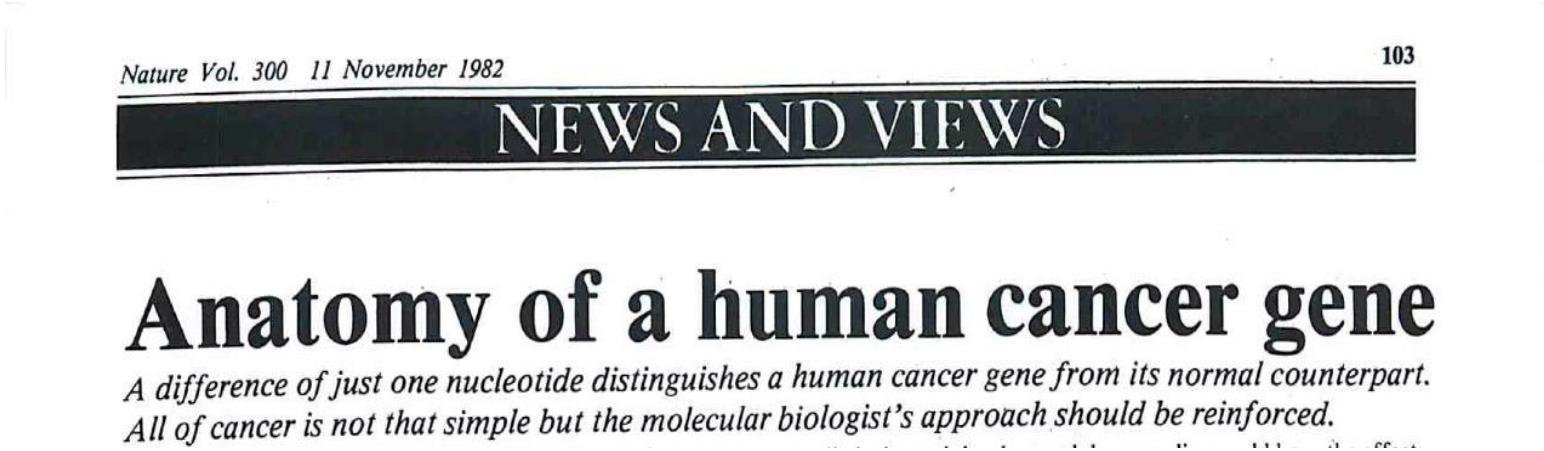
Eugenio Santos, Steven R. Tronick, Stuart A. Aaronson, Simonetta Pulciani & Mariano Barbacid

Laboratory of Cellular and Molecular Biology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20205, USA

Cortesía del Dr. Barbacid

"Estos resultados también sirvieron para poner en valor todo el trabajo realizado con retrovirus durante mas de dos décadas y que los oncólogos clínicos pensaron que no tenia nada que ver con el cáncer humano

El siguiente hito no se hizo esperar. Unos meses después, demostramos junto al grupo de Bob Weinberg del MIT que el oncogén H-RAS debía sus propiedades oncogénicas a una sola mutación puntual en su DNA, la primera mutación asociada con el desarrollo del cáncer humano"



Nature Vol. 300 11 November 1982 103

NEWS AND VIEWS

Anatomy of a human cancer gene

A difference of just one nucleotide distinguishes a human cancer gene from its normal counterpart. All of cancer is not that simple but the molecular biologist's approach should be reinforced.

Cortesía del Dr. Barbacid

"Durante este frenético periodo, y antes de saber que la activación oncogénica de H-RAS se debía a una simple mutación puntual, me quise asegurar que este los "oncogenes humanos" estaban presentes en los tumores de los pacientes y no se debían a las alteraciones que se producen en las líneas tumorales al ser crecidas en cultivo durante décadas

Por ello, conseguimos biopsias tumorales y repetimos todo el proceso experimental que nos había llevado al aislamiento del oncogen H-RAS de una línea celular.

Afortunadamente y tras un par de intentos, pudimos comprobar que efectivamente, las biopsias tumorales obtenida directamente de pacientes de cáncer también poseían oncogenes capaces de transformar células NIH3T3"

Cortesía del Dr. Barbacid

Reprinted from Nature, Vol. 300, No. 5892, pp. 539-542, 9 December 1982
© Macmillan Journals Ltd., 1982

Oncogenes in solid human tumours

Simonetta Pulciani, Eugenio Santos, Anne V. Lauver, Linda K. Long, Stuart A. Aaronson & Mariano Barbacid

Laboratory of Cellular and Molecular Biology, National Cancer Institute, Bethesda, Maryland 20205, USA

Table 1 Summary of DNAs isolated from naturally occurring human tumours tested for transformation of NIH 3T3 mouse cells in transfection assays

Type of tumour	Total tested	Positive in transfection assays
Carcinomas		
Bladder	2	0
Breast	2	0
Colon	2	2
Kidney	3	0
Lung	5	1
Ovary	4	0
Pancreas	2	1
Sarcomas		
Fibrosarcoma	4	0
Osteosarcoma	2	0
Rhabdomyosarcoma	2	1

Table 2 Summary of human oncogenes detected in our laboratory

Type of tumour	Source of DNA	Ref.	Oncogene	Relationship with retroviral *onc* genes
Carcinomas				
Bladder	T24 cells	21	*onc* A	*has, bas*
Bladder	A1698 cells		*onc* B	*kis*
Colon	Solid tumour 1665		*onc* C	—
Colon	Solid tumour 2033		*onc* D	—
Colon	A2233 cells		*onc* B	*kis*
Gall bladder	A1604 cells		*onc* B	*kis*
Lung	A2182 cells	8	*onc* B	*kis*
Lung	A427 cells	22	*onc* B	*kis*
Lung	Solid tumour 1615		*onc* B	*kis*
Pancreas	Solid tumour 1189		*onc* B	*kis*
Sarcomas				
Fibrosarcoma	HT-1080 cells	23	*onc* E	—
Rhabdomyosarcoma	Solid tumour 1085		*onc* B	*kis*

has, bas = H-RAS
kis = K-RAS
onc D = TRK
onc E = MET

Cortesía del Dr. Barbacid

NATURE VOL. 319 27 FEBRUARY 1986

A human oncogene formed by the fusion of truncated tropomyosin and protein tyrosine kinase sequences

Dionisio Martin-Zanca*, Stephen H. Hughes† & Mariano Barbacid*

* Developmental Oncology Section and † Gene Expression Section, Basic Research Program, Frederick Cancer Research Facility, Frederick, Maryland 21701, USA

A biologically active complementary DNA clone of a transforming gene present in a human colon carcinoma contains gene sequences of both tropomyosin and a previously unknown protein tyrosine kinase. The predicted protein (641 amino acids) encoded by this oncogene seems to have been formed by a somatic rearrangement that replaced the extracellular domain of a putative transmembrane receptor by the first 221 amino acids of a non-muscle tropomyosin molecule.

Cortesía del Dr. Barbacid

En base a estos datos moleculares decidimos renombrar oncD como **TRK** por es **T**ropomyosin **R**eceptor **K**inase y pronunciarlo "track".

En el editorial que la revista Nature encargó a Mike Bishop, éste sugirió que dado el proceso de generación de este oncogén mediante una fusion molecular, algo desconocido hasta entonces, deberiamos de haberlo llamado "**trick**"

Oncogenes

Tricks with tyrosine kinases

from J. Michael Bishop

discoverers of *onc*-D suggest that the gene be rechristened *trk* and that the acronym be pronounced 'track'. But as a bemused bystander, I find 'trick' more apt. □

Cortesía del Dr. Barbacid

En los años siguientes descubrimos que TRK representaba el prototipo de una pequeña familia de genes que codificaban por receptores tirosina quinasa, TrkB y TrkC

The EMBO Journal vol.8 no.12 pp.3701 – 3709, 1989

trkB, a novel tyrosine protein kinase receptor expressed during mouse neural development

Rüdiger Klein[1], Luis F.Parada[2], François Coulier[3,4] and Mariano Barbacid[1,3]

Cell, Vol. 66, 967–979, September 6, 1991

trkC, a New Member of the trk Family of Tyrosine Protein Kinases, Is a Receptor for Neurotrophin-3

Fabienne Lamballe, Rüdiger Klein, and Mariano Barbacid

A partir de aquí la comunidad científica empezó a llamar a estos genes **TrkA, TrkB y TrkC** cuando se trataba de genes de origen murino y **NTRK1, NTRK2 y NTRK3** cuando se trataba de genes humanos

Cortesía del Dr. Barbacid

Aunque no encontramos formas oncogencicas de TRKB o TRKC, pronto vimos que los genes TRK podían adquirir propiedades oncogénicas mediante múltiples mecanismos, sin necesidad de la participación de las secuencias de tropomiosina, siempre que se mantuviera su actividad catalítica tirosina quinasa tal y como se ha podido comprobar posteriormente

Proc. Natl. Acad. Sci. USA
Vol. 85, pp. 2964–2968, May 1988
Biochemistry

Frequent generation of oncogenes by *in vitro* recombination of *TRK* protooncogene sequences

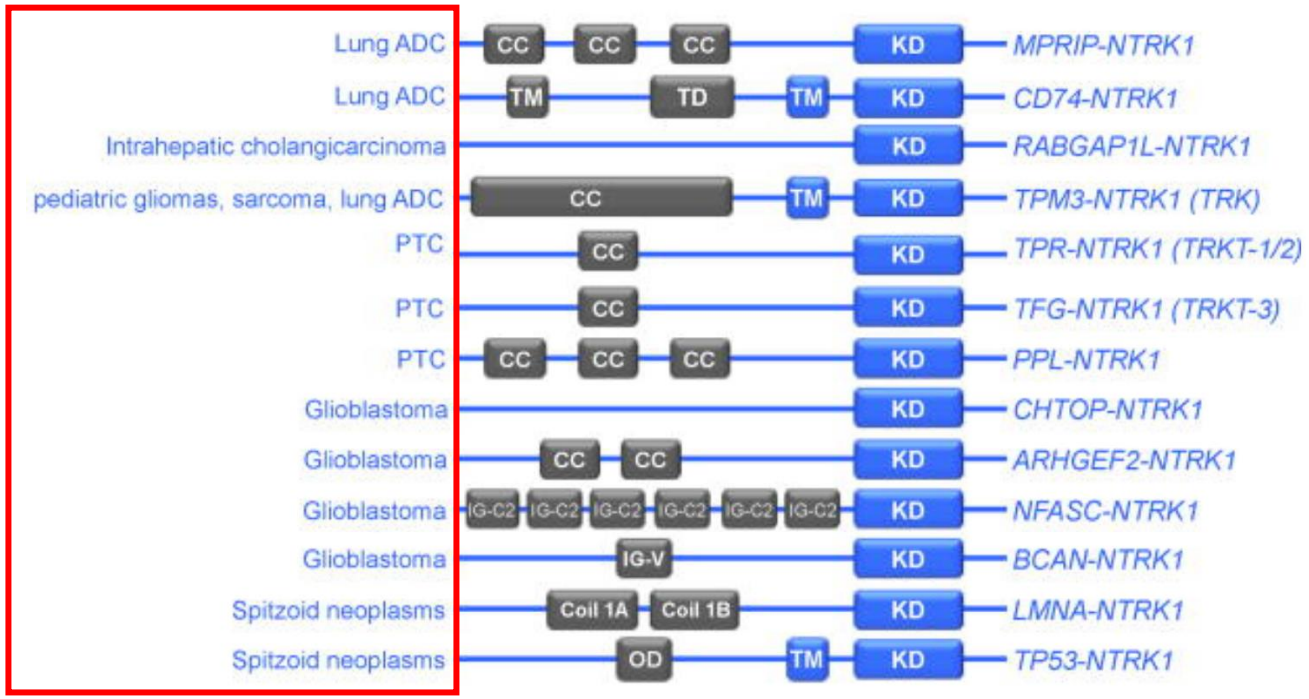
(tyrosine protein kinase/growth factor receptor/malignant transformation)

RALPH OSKAM, FRANÇOIS COULIER, MARY ERNST, DIONISIO MARTIN-ZANCA, AND MARIANO BARBACID

Basic Research Program, Frederick Cancer Research Facility, Frederick, MD 21701

Cortesía del Dr. Barbacid

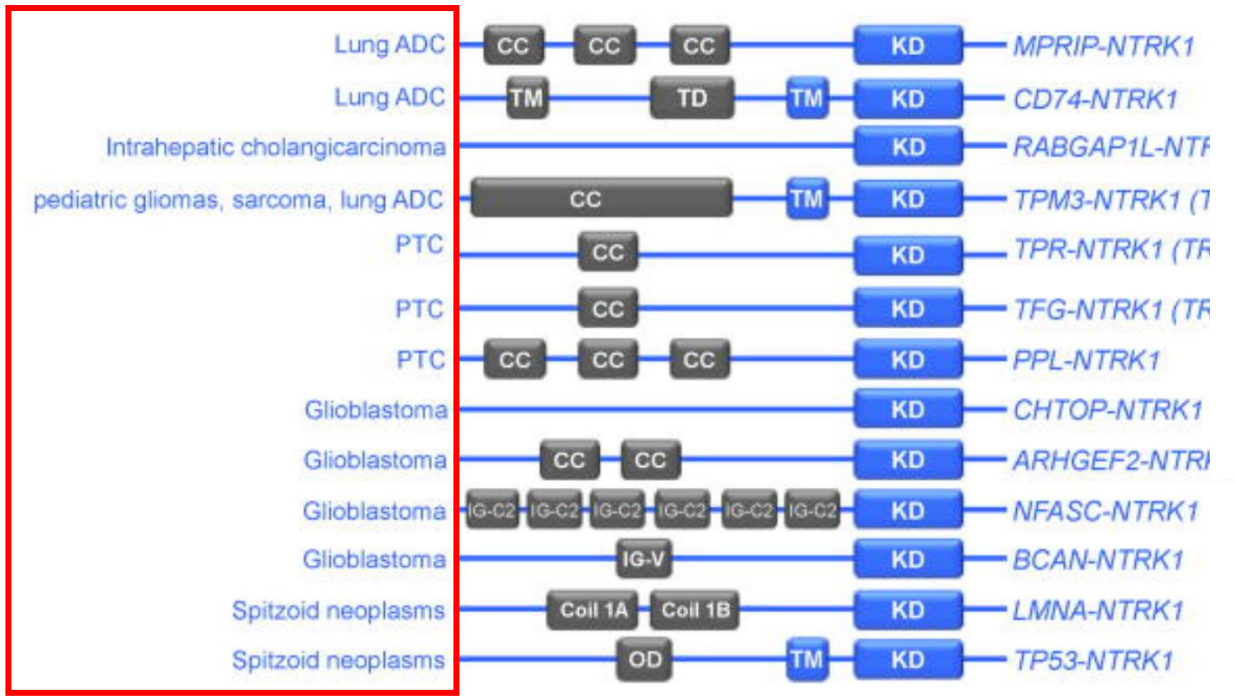
Oncogenes de fusion con NTRK1



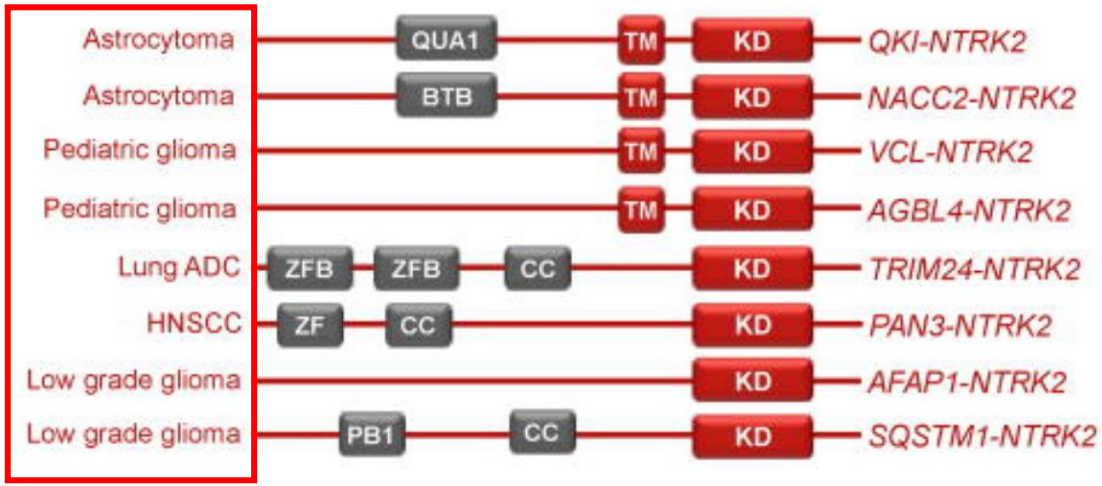
A. Vaishnavi et al., Cancer Discov., 2015

Cortesía del Dr. Barbacid

Oncogenes de fusion con NTRK1



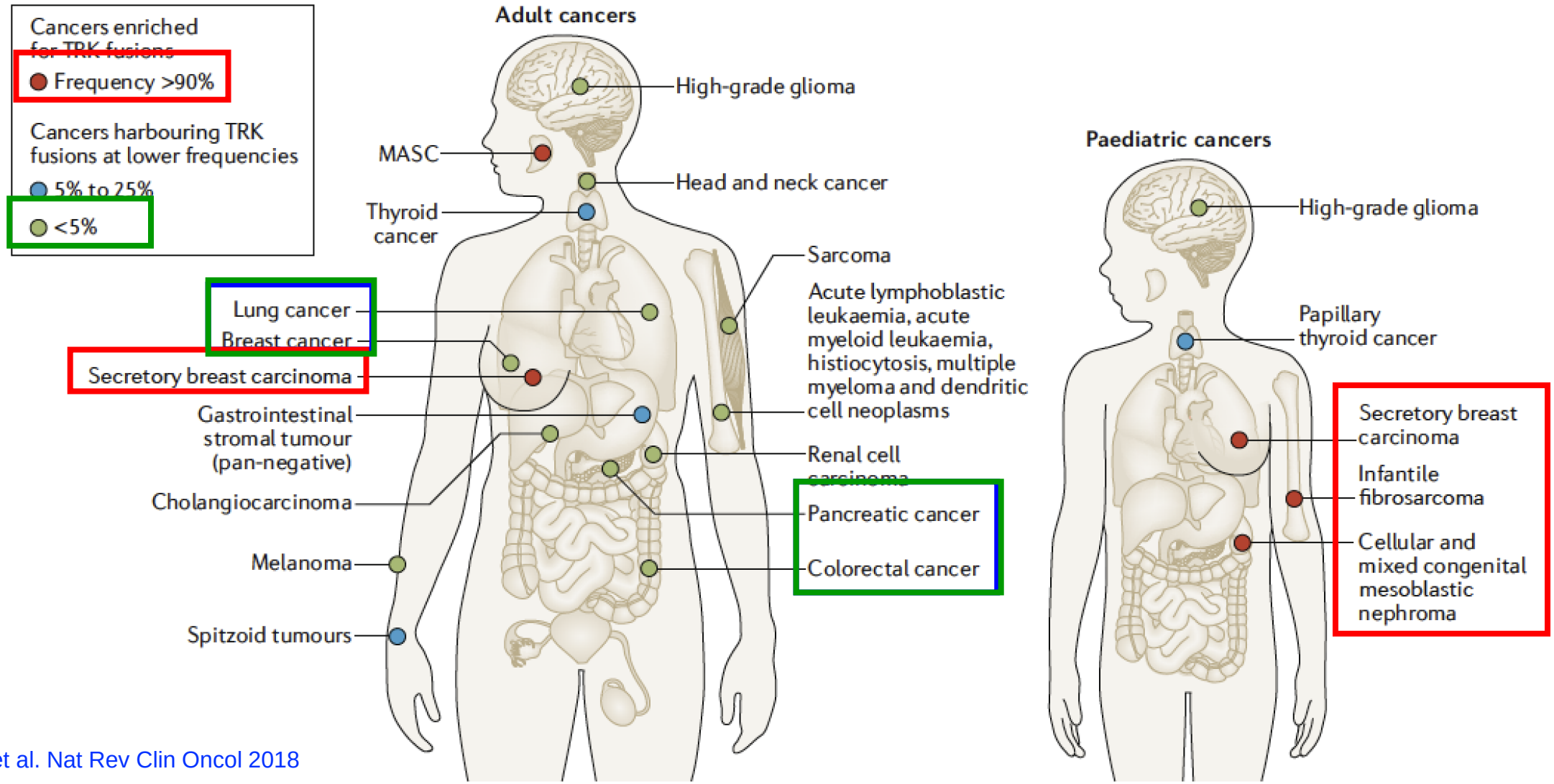
Oncogenes de fusion con NTRK2



Oncogenes de fusion con NTRK3

A. Vaishnavi et al., Cancer Discov., 2015

Distribution and frequency of NTRK fusions in adult and paediatric tumours



E. Cocco et al. Nat Rev Clin Oncol 2018

Histology	Screening Methodology	Rationale
Frequency of TRK fusions > 75%		
Infantile fibrosarcoma	IHC/FISH (*ETV6* and/or *NTRK3*)/RT-PCR; NGS if negative	High frequency of *ETV6-NTRK3* fusion; variant *NTRK3* and *NTRK1* fusions have been described
Cellular congenital mesoblastic nephroma	IHC/FISH (*ETV6* and/or *NTRK3*)/RT-PCR; NGS if negative	High frequency of *ETV6-NTRK3* fusion; variant *NTRK3* fusions have been described
Secretory breast cancer	IHC/FISH (*ETV6* and/or *NTRK3*)/RT-PCR; NGS if negative	High frequency of *NTRK3* fusions
Mammary analog secretory carcinoma of the salivary gland	IHC/FISH (*ETV6* and/or *NTRK3*)/RT-PCR; NGS if negative	High frequency of *NTRK3* fusions
Frequency of TRK fusions 10% to 40%		
Spitzoid melanomas	IHC/NGS	TRK fusions occur in 15%-25% of pediatric melanocytic neoplasms
Metastatic papillary thyroid cancer	IHC/NGS	TRK fusions (*NTRK1* and *NTRK3*) occur in approximately 25% of children, and *BRAF* activating mutations occur in approximately half of patients
High-grade gliomas, especially in young children	NGS	TRK fusions occur, especially in tumors of children < 3 years of age; patients have poor prognosis; IHC has not been validated in gliomas, which can have normal physiologic expression of TRK
Frequency of TRK fusions unknown or < 5%		
Undifferentiated or spindle cell sarcoma (without known defining fusion)	NGS	Prevalence of TRK fusions unknown but described; in addition to *NTRK*, other targetable fusions have been described
Inflammatory myofibroblastic tumor	IHC/NGS	TRK fusion tumors may share inflammatory myofibroblastic tumor–like morphology; mutually exclusive fusions of ALK and ROS1 also occur

Albert et al. JCO 2019

NTRK inhibitors approved by the FDA

NEJM; Feb 2018

ORIGINAL ARTICLE

Efficacy of Larotrectinib in *TRK* Fusion–Positive Cancers in Adults and Children

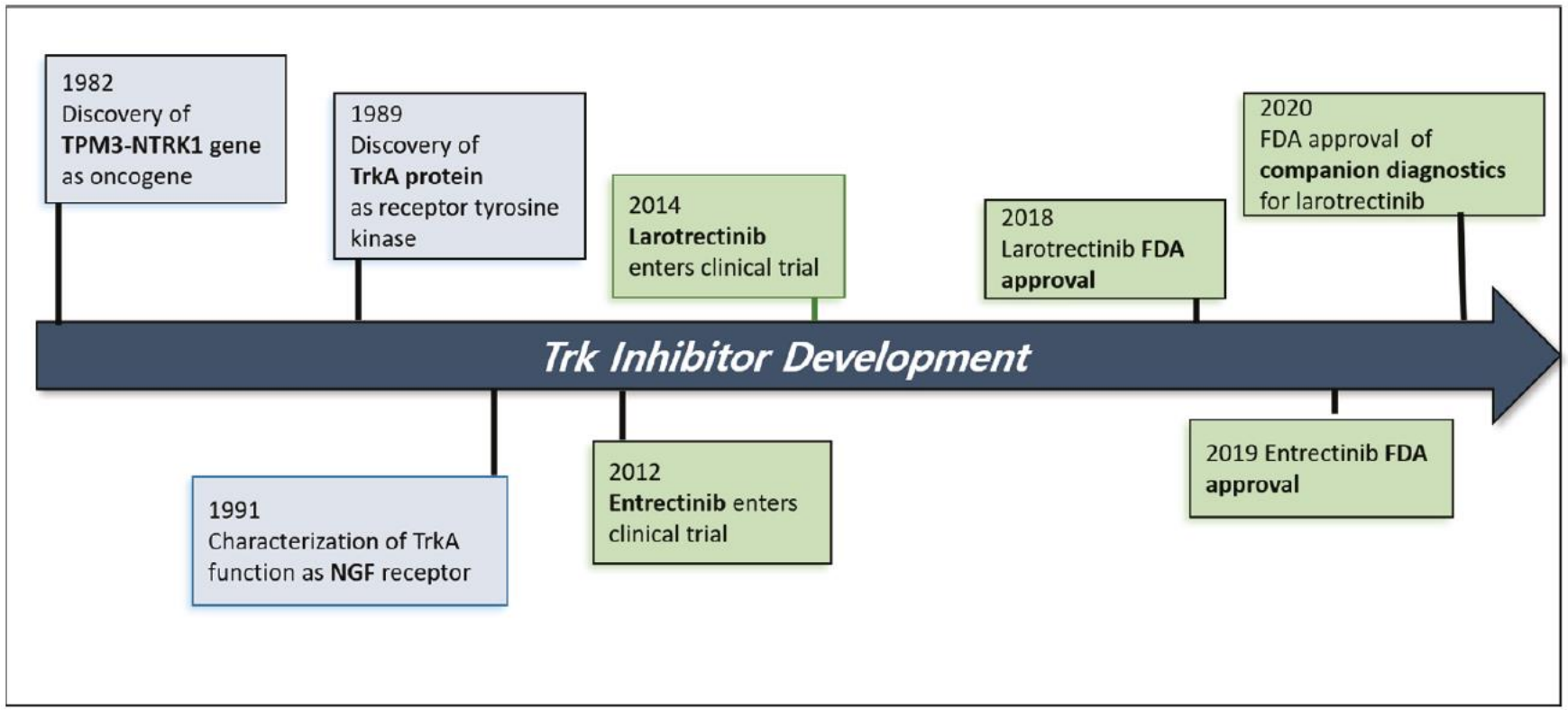
A. Drilon, T.W. Laetsch, S. Kummar, S.G. DuBois, U.N. Lassen, G.D. Demetri, M. Nathenson, R.C. Doebele, A.F. Farago, A.S. Pappo, B. Turpin, A. Dowlati, M.S. Brose, L. Mascarenhas, N. Federman, J. Berlin, W.S. El-Deiry, C. Baik, J. Deeken, V. Boni, R. Nagasubramanian, M. Taylor, E.R. Rudzinski, F. Meric-Bernstam, D.P.S. Sohal, P.C. Ma, L.E. Raez, J.F. Hechtman, R. Benayed, M. Ladanyi, B.B. Tuch, K. Ebata, S. Cruickshank, N.C. Ku, M.C. Cox, D.S. Hawkins, D.S. Hong, and D.M. Hyman

THE LANCET
Oncology
Volume 21, Issue 2, February 2020, Pages 271-282

Articles

Entrectinib in patients with advanced or metastatic *NTRK* fusion-positive solid tumours: integrated analysis of three phase 1–2 trials

Robert C Doebele MD [a, †], Alexander Drilon MD [b, c, †], Luis Paz-Ares MD [d], Prof Salvatore Siena MD [e, f], Prof Alice T Shaw MD [g], Anna F Farago MD [g], Collin M Blakely MD [h], Takashi Seto MD [i], Prof Byung Chul Cho MD [j], Diego Tosi MD [k], Benjamin Besse MD [l], Sant P Chawla MD [m], Prof Lyudmila Bazhenova MD [n], John C Krauss MD [o], Young Kwang Chae MD [p], Minal Barve MD [q], Ignacio Garrido-Laguna MD [r], Stephen V Liu MD [s] ... Prof George D Demetri MD [aj]



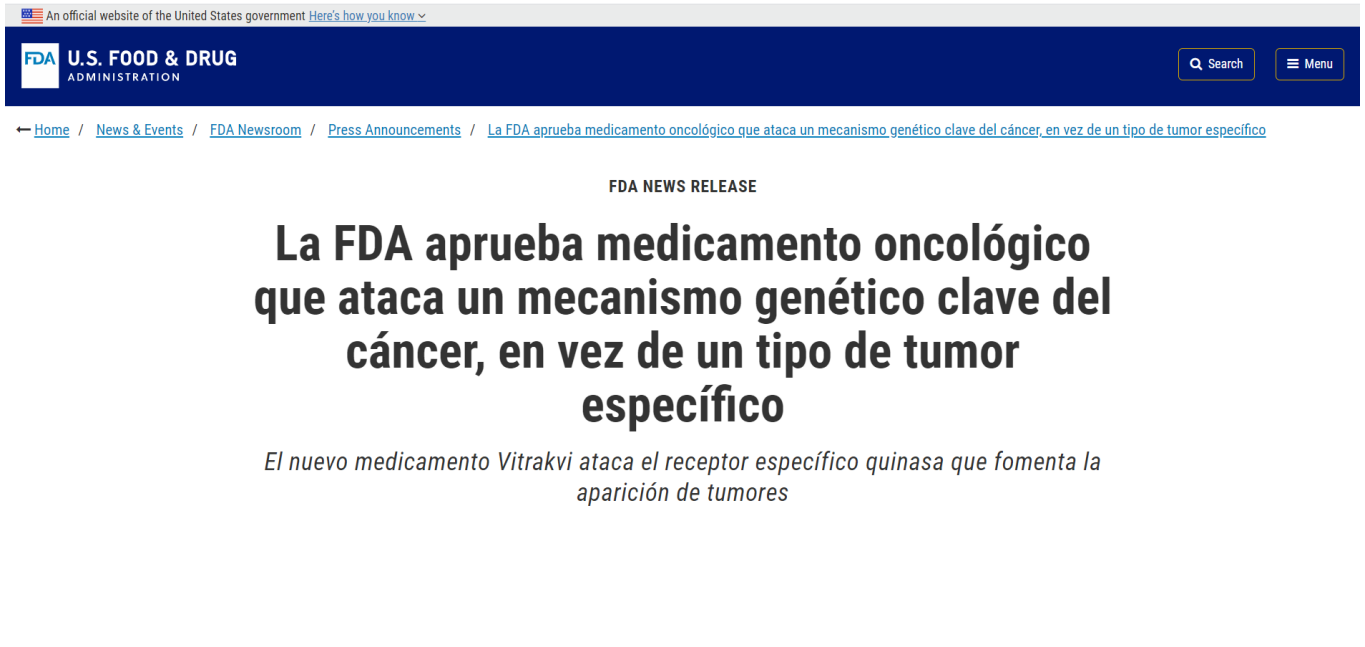
Sun-Young Han. Pharmaceuticals 2021

VII SIMPOSIO GETTHI

Sesión 3: Vías de desarrollo de la oncología transversal (I)

"NTRK-Tumours": fundamentos biológicos y resultados clínicos

Noviembre 2018 Larotrectinib, ARRY-470, LOXO-101, Vitrakvi, Bayer



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FDA U.S. FOOD & DRUG ADMINISTRATION

Search Menu

Home / News & Events / FDA Newsroom / Press Announcements / La FDA aprueba medicamento oncológico que ataca un mecanismo genético clave del cáncer, en vez de un tipo de tumor específico

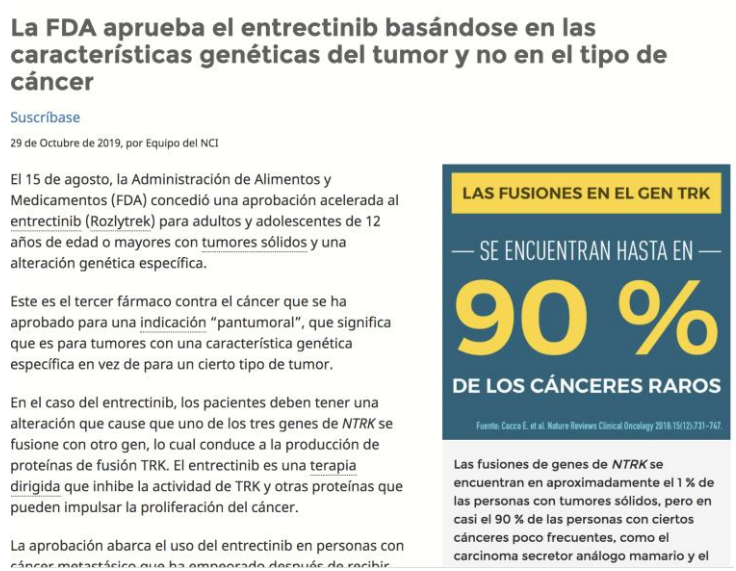
FDA NEWS RELEASE

La FDA aprueba medicamento oncológico que ataca un mecanismo genético clave del cáncer, en vez de un tipo de tumor específico

El nuevo medicamento Vitrakvi ataca el receptor específico quinasa que fomenta la aparición de tumores

Scott LJ. Drugs. 2019

Octubre 2019 Entrectinib, RXDX-101, NMS-E628 Rozlytrek, Roche



La FDA aprueba el entrectinib basándose en las características genéticas del tumor y no en el tipo de cáncer

Suscríbase

29 de Octubre de 2019, por Equipo del NCI

El 15 de agosto, la Administración de Alimentos y Medicamentos (FDA) concedió una aprobación acelerada al entrectinib (Rozlytrek) para adultos y adolescentes de 12 años de edad o mayores con tumores sólidos y una alteración genética específica.

Este es el tercer fármaco contra el cáncer que se ha aprobado para una indicación "pantumoral", que significa que es para tumores con una característica genética específica en vez de para un cierto tipo de tumor.

En el caso del entrectinib, los pacientes deben tener una alteración que cause que uno de los tres genes de *NTRK* se fusione con otro gen, lo cual conduce a la producción de proteínas de fusión TRK. El entrectinib es una terapia dirigida que inhibe la actividad de TRK y otras proteínas que pueden impulsar la proliferación del cáncer.

La aprobación abarca el uso del entrectinib en personas con

LAS FUSIONES EN EL GEN TRK

— SE ENCUENTRAN HASTA EN —

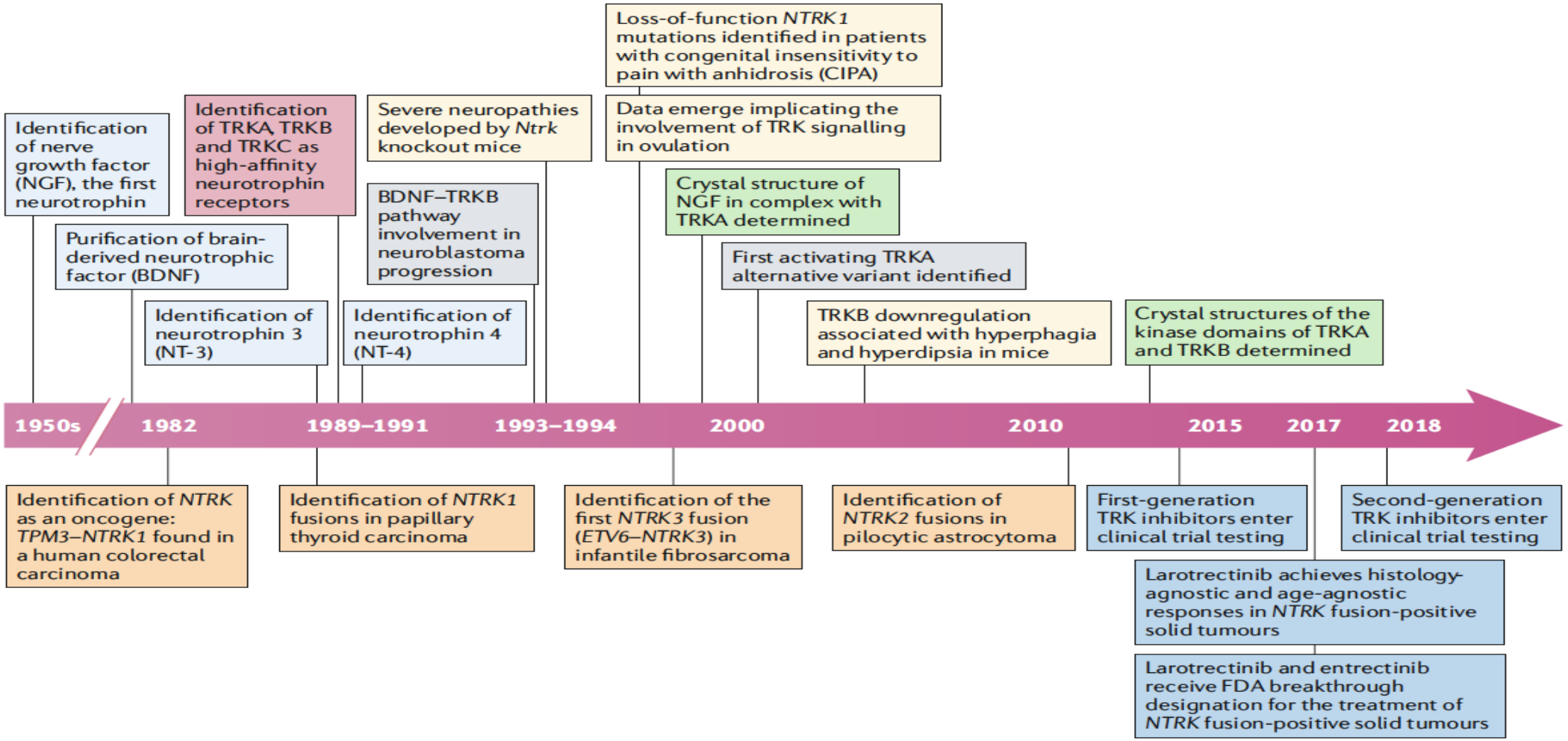
90 %

DE LOS CÁNCERES RAROS

Fuente: Cocco E. et al. Nature Reviews Clinical Oncology 2018;15(12):731–747.

Las fusiones de genes de *NTRK* se encuentran en aproximadamente el 1 % de las personas con tumores sólidos, pero en casi el 90 % de las personas con ciertos cánceres poco frecuentes, como el carcinoma secretor análogo mamario y el

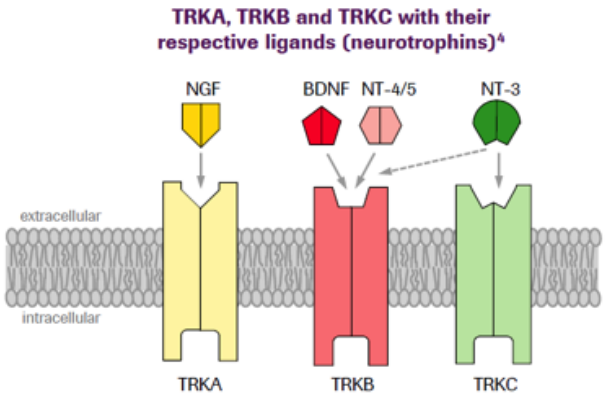
Al-Salama ZT, et al. Drugs. 2019



Cocco E. Nat Med Oncol 2018

2. Fundamentos biológicos

- Tropomyosin receptor kinases (Trk) are tyrosine kinases encoded by neurotrophic tyrosine/tropomyosin receptor kinase (NTRK) genes.
- Chromosomal rearrangement of NTRK genes is found in cancer tissues
- Drug development, known as tissue-agnostic development, larotrectinib and entrectinib approval
- Patients for tissue-agnostic clinical trials (basket trial) were selected based on the presence of NTRK gene rearrangement, independent of tumor type
- Several tumor types (rare cáncer) can be subjected to clinical trials at the same time
- Tumor-agnostic approach cannot be adopted for all oncogenic alterations



Criterios comunes de terapias tumor agnósticas[1]

- Los agentes terapéuticos potencialmente adecuados para indicaciones histológicas agnósticas y apropiados para ensayos clínicos de tipo “basket” deben cumplir ciertos criterios:

Biológicos

- Mecanismo establecido de acción independiente de la histología del tumor
- Ausencia de mecanismos de resistencia específicos de histología.
- Actividad clínica a través de histologías
- Eficacia en pacientes adultos y pediátricos
- Seguridad clínica

Regulatory

- Biomarcador validado
- Actividad clínica sustancial que lleve a suponer una superioridad frente al tratamiento estándar
- Seguimiento de la eficacia tras la aprobación y de la seguridad

Estadísticos

- La aleatorización puede ser difícil de realizar o inviable
- Diseño efectivo para permitir la evaluación de la heterogeneidad de la subpoblación
- Considerar la evaluación de los datos de fase II de indicación única antes de la agrupación
- Las respuestas son un sustituto de los *endpoints* clínicos

1. Pestana RC, Sen S, Hobbs BP, Hong DS. Histology-agnostic drug development - considering issues beyond the tissue. Nat Rev Clin Oncol. 2020;17(9):555-568.

Consenso internacional de tratamientos con indicación tumor-agnóstica[1]

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

JSCO—ESMO—ASCO—JSMO—TOS: international expert consensus recommendations for tumour-agnostic treatments in patients with solid tumours with microsatellite instability or *NTRK* fusions

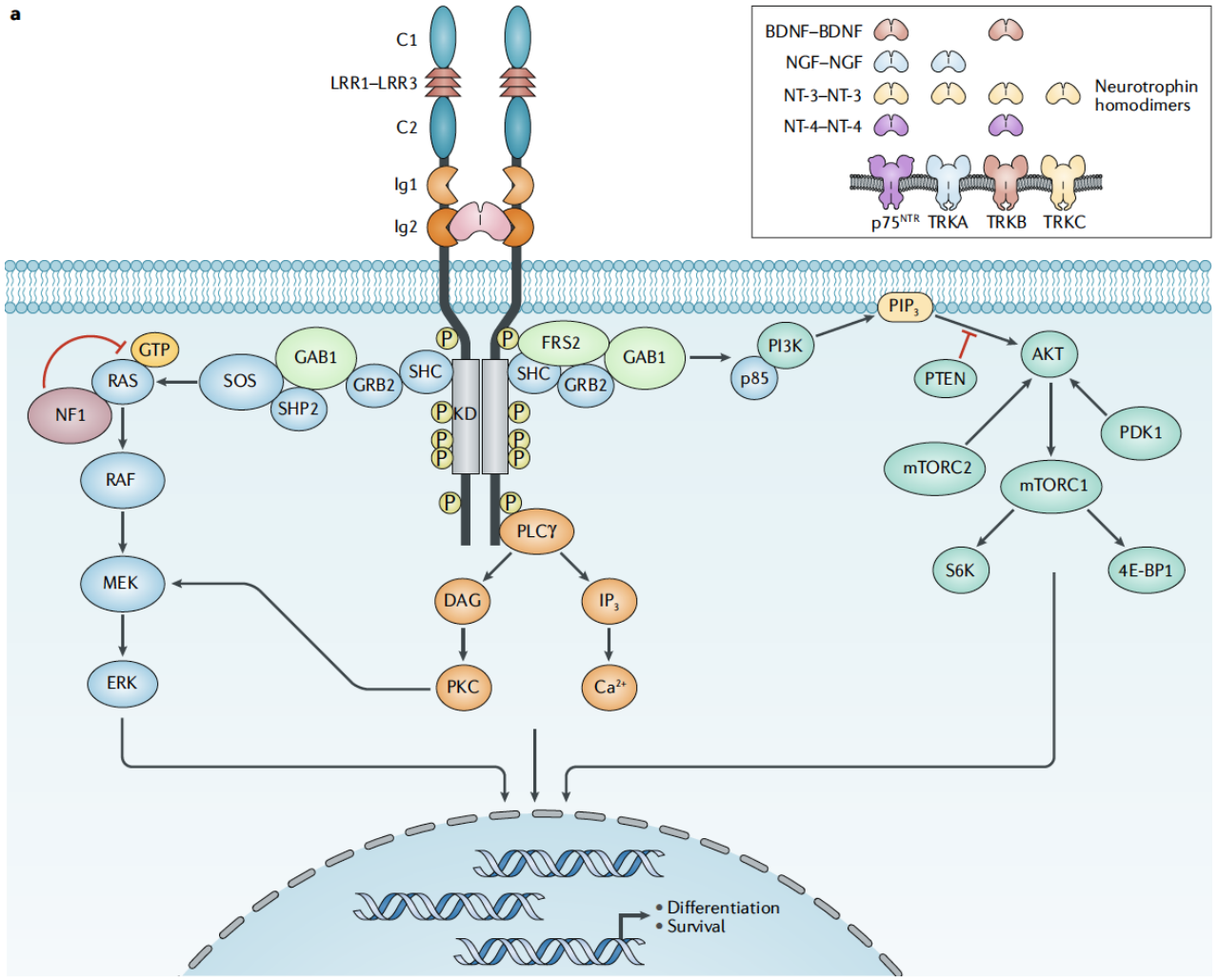
T. Yoshino[1*], G. Pentheroudakis[2], S. Mishima[1], M. J. Overman[3], K.-H. Yeh[4], E. Baba[5], Y. Naito[6], F. Calvo[7], A. Saxena[8], L.-T. Chen[9], M. Takeda[10], A. Cervantes[11], H. Taniguchi[1], K. Yoshida[12], Y. Kodera[13], Y. Kitagawa[14], J. Tabernero[15], H. Burris[16] & J.-Y. Douillard[17]

Table 1. The six identical clinical questions (CQs) formulated for the treatment and management of patients with MSI/dMMR or *NTRK* fusion-positive tumours from which two separate series of recommendations were developed, i.e. one series of clinical recommendations for each clinical situation

CQ no.	CQs
CQ1	Should all patients with solid tumours be tested for MSI/MMR or *NTRK* fusions?
CQ2	When is the optimal timing for tests for MSI/MMR or for *NTRK* fusions?
CQ3	Which tests are recommended for determining MSI/MMR status or *NTRK* fusions?
CQ4	What is the appropriate biospecimen for testing for MSI/MMR or *NTRK* fusions?
CQ5	Which treatment is recommended for MSI/dMMR patients or patients with *NTRK* fusions?
CQ6	Where in the treatment algorithm should immunotherapy be used in the treatment of patients with MSI/dMMR solid tumours or a TRK inhibitor be used in the treatment of patients with *NTRK* fusion-positive solid tumours?

dMMR, deficient in (DNA) mismatch repair; MSI, microsatellite instability; *NTRK*, neurotrophic tyrosine receptor kinase; TRK, tropomyosin receptor kinase.

1. Yoshino T, Pentheroudakis G, Mishima S, et al. JSCO-ESMO-ASCO-JSMO-TOS: international expert consensus recommendations for tumour-agnostic treatments in patients with solid tumours with microsatellite instability or NTRK fusions. *Ann Oncol.* 2020;31(7):861-872.



Cocco E. Nat Med Oncol 2018

- The Trk family is comprised of three isoforms, TrkA, TrkB, and TrkC, encoded by NTRK1, NTRK2, and NTRK3 abundantly expressed in the nervous system

- Ligands for Trk cell surface receptor tyrosine kinase are:
  - nerve growth factor (NGF) for TrkA,
  - brain-derived neurotropic factor or neurotropin 4 for TrkB,
  - aneurotropin 3 for TrkC

- Downstream signaling for Trk receptor kinases is primarily mediated by MAPK and PI3K

- neuronal development and differentiation have been reported as major functions

Sun-Young Han. Pharmaceuticals 2021

VII SIMPOSIO GETTHI

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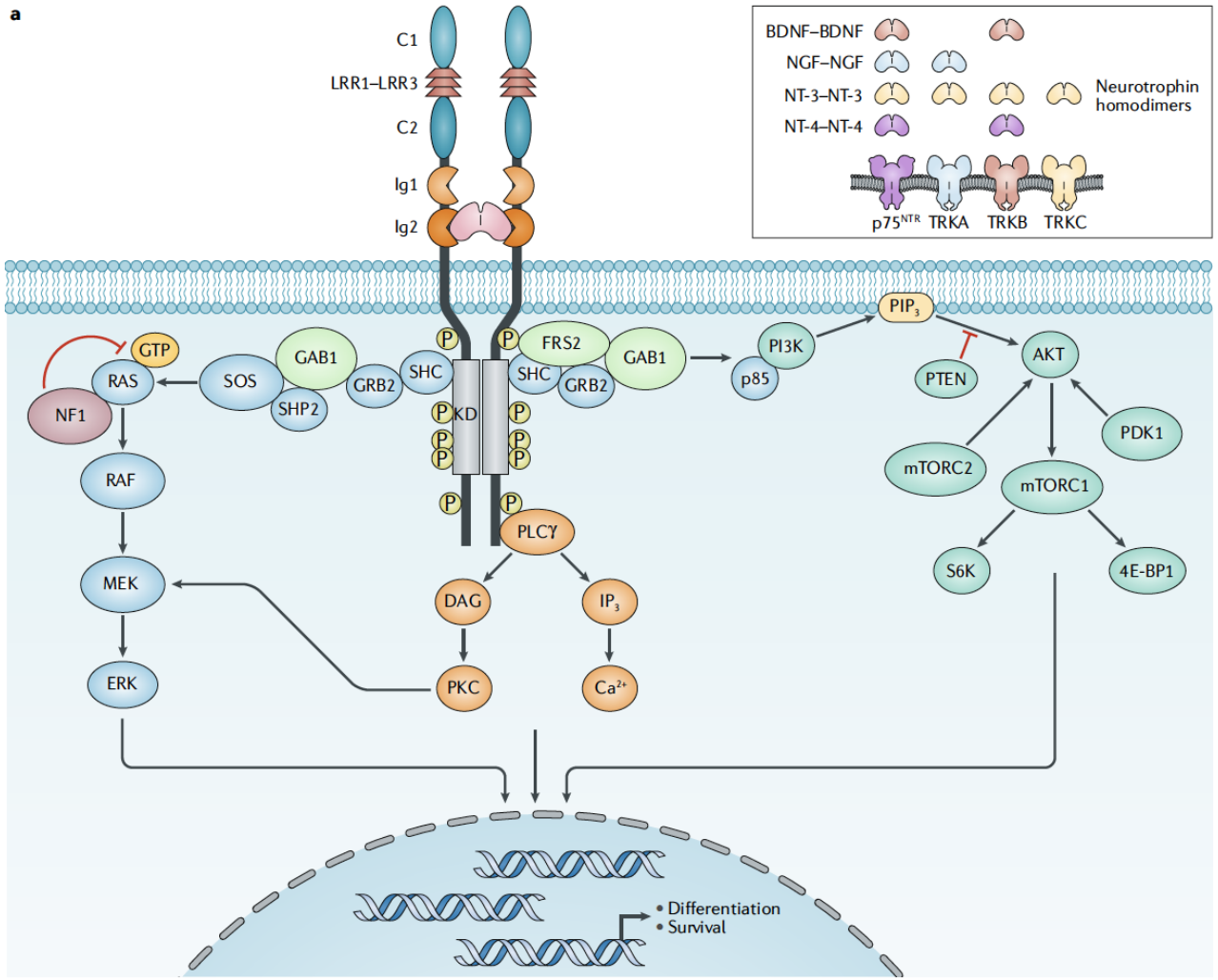
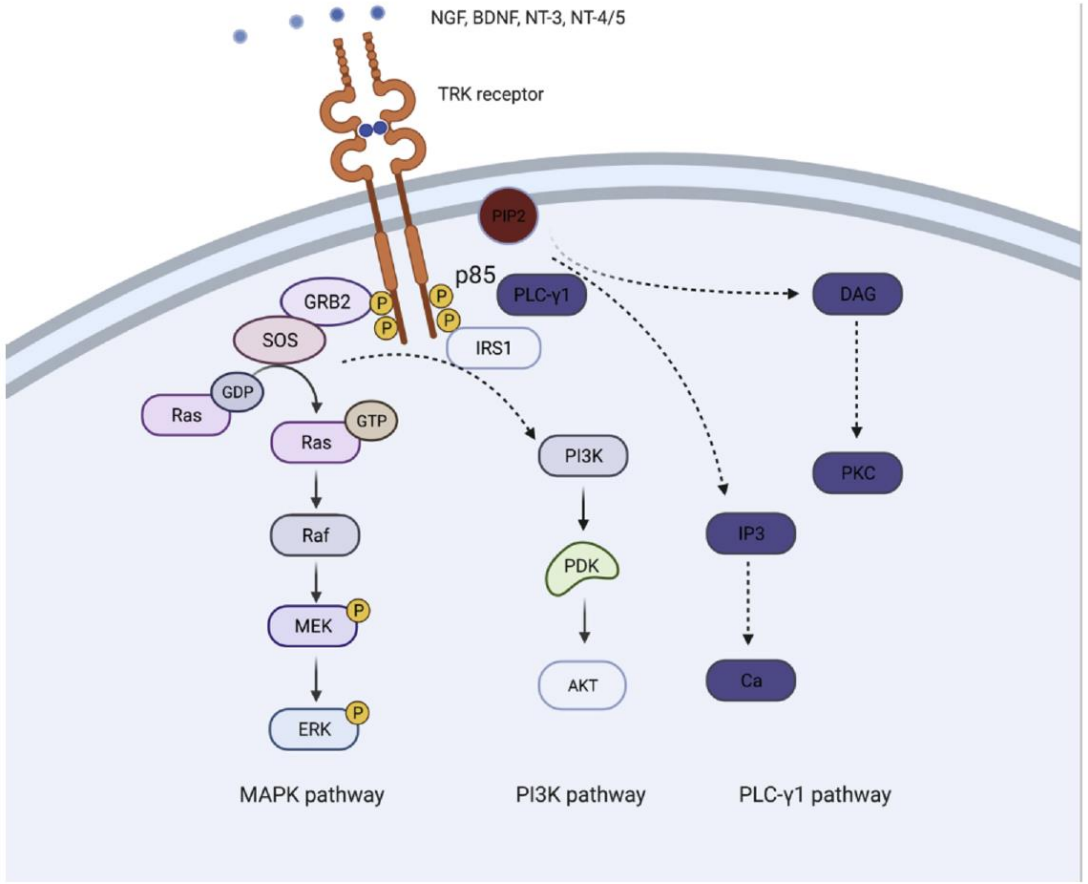


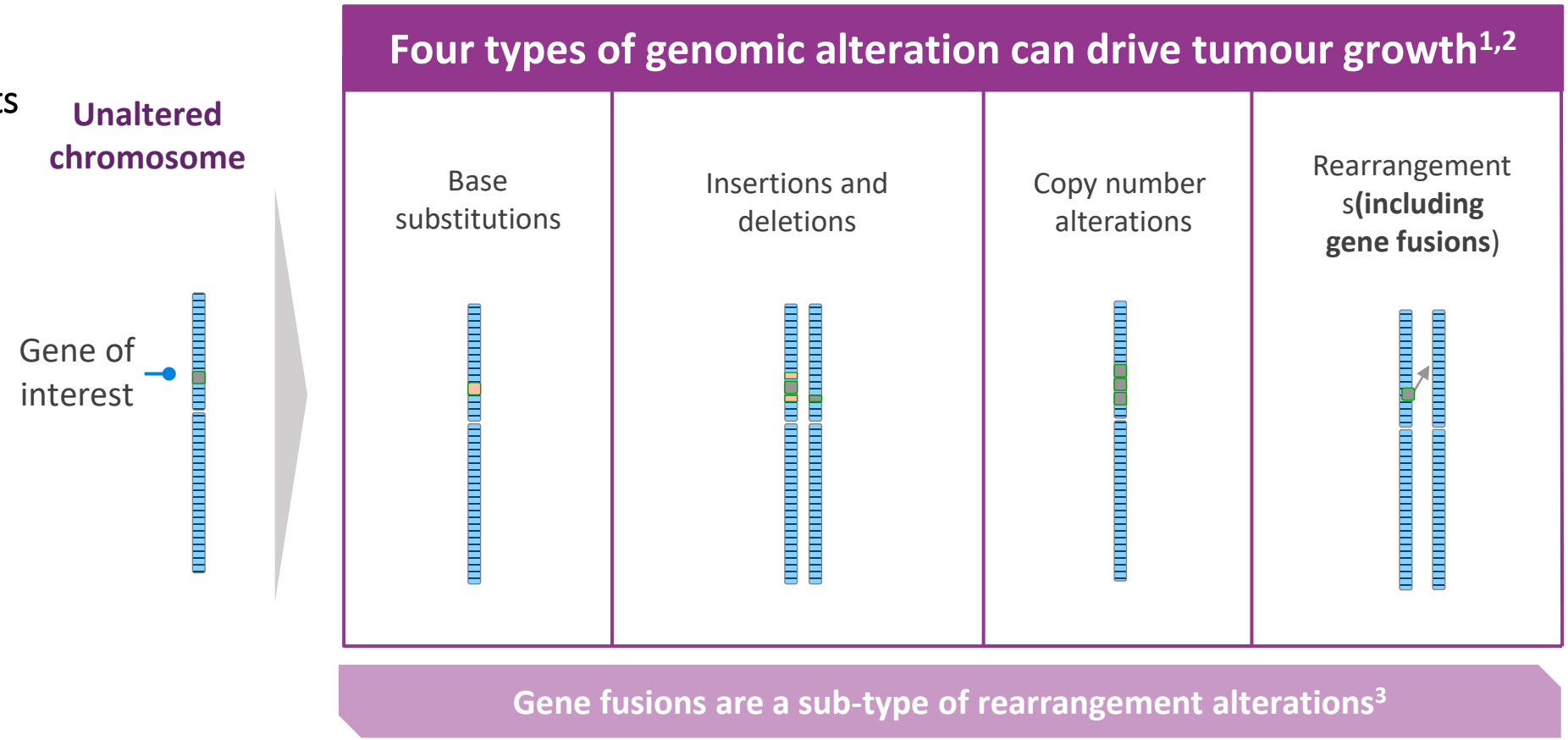
Cocco E. Nat Med Oncol 2018



Kojadinovic A, et al. Crit Rev Oncol Hematol. 2021

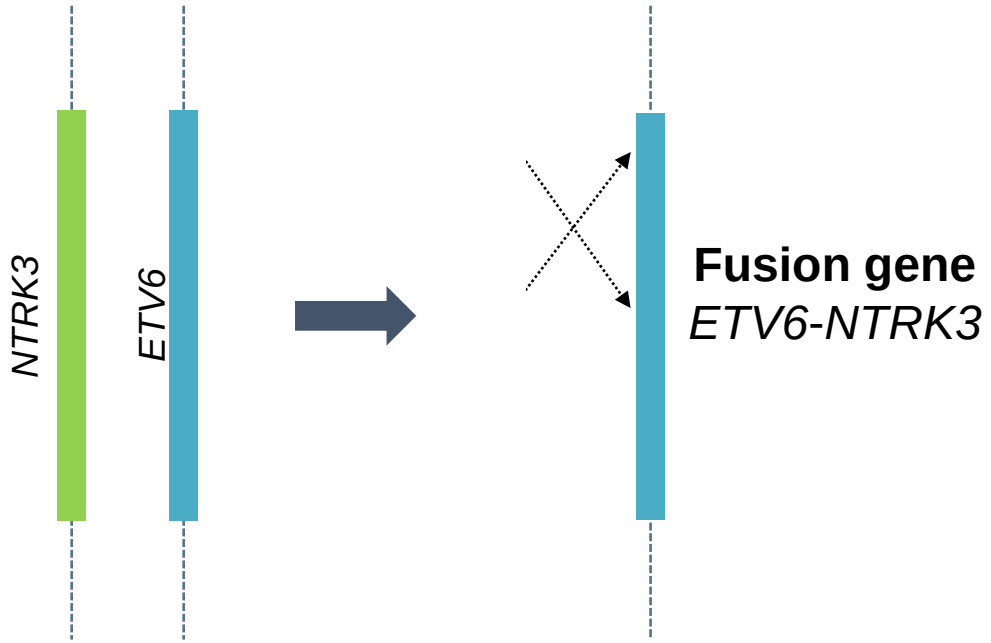
Mechanisms of Trk activation in cancer:

1. Somatic mutations
2. Activating splice variants
3. Trk overexpression
4. NTRK fusion



1. Stratton, M.R., et al. (2009) Nature 458:719-24;
2. Chin, L. and Gray, J.W. (2008) Nature 452:533-63; 3. Tomlins, A.S., et al. (2008) Neoplasia 10:177-88.

The most common Trk activation is fusion



Intrachromosomal or **interchromosomal** rearrangement yields a gene fusion

Gene fusions frequently act as **oncogenic drivers**

Number of different fusion partners observed

NTRK	**~80**
ROS1	**~30**
ALK	**~60**

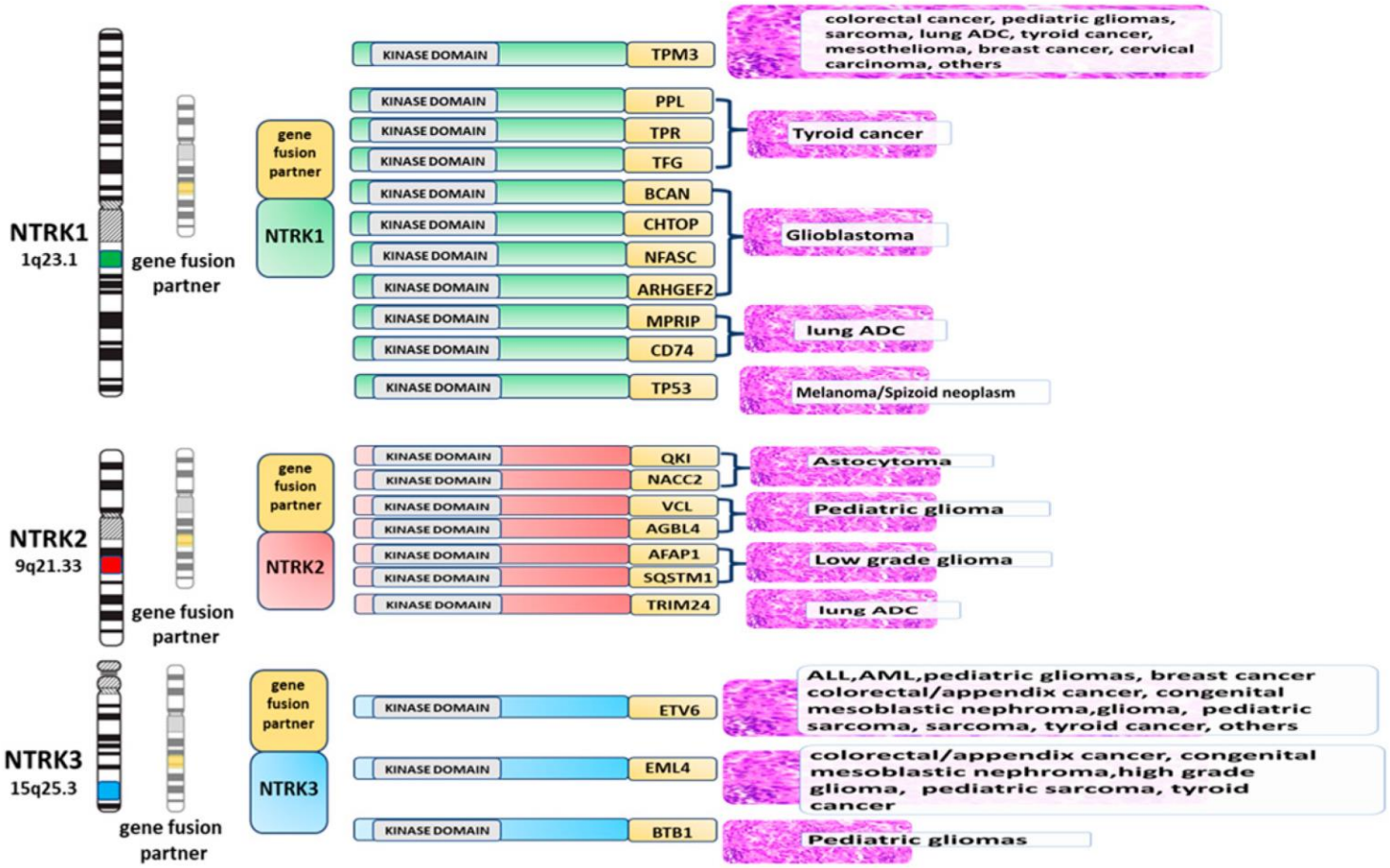
- Hsiao, et al. J Mol Diagn 2019; Klempner & Ou. Atlas Genet Cytogenet Oncol Haematol 2015 (updated 2017. Available at: http://atlasgeneticsoncology.org/Genes/ROS1ID42144ch6q22.html); Allouche. Atlas Genet Cytogenet Oncol Haematol 2010 (updated 2017. Available at: http://atlasgeneticsoncology.org/Genes/ALKID16.html)

Fusion involving NTRK1, NTRK2, and NTRK3 (NTRK kinase domain, with different partner genes)

1. The first NTRK fusion was tropomyosin 3 (TPM3)-NTRK1, colorectal cancer

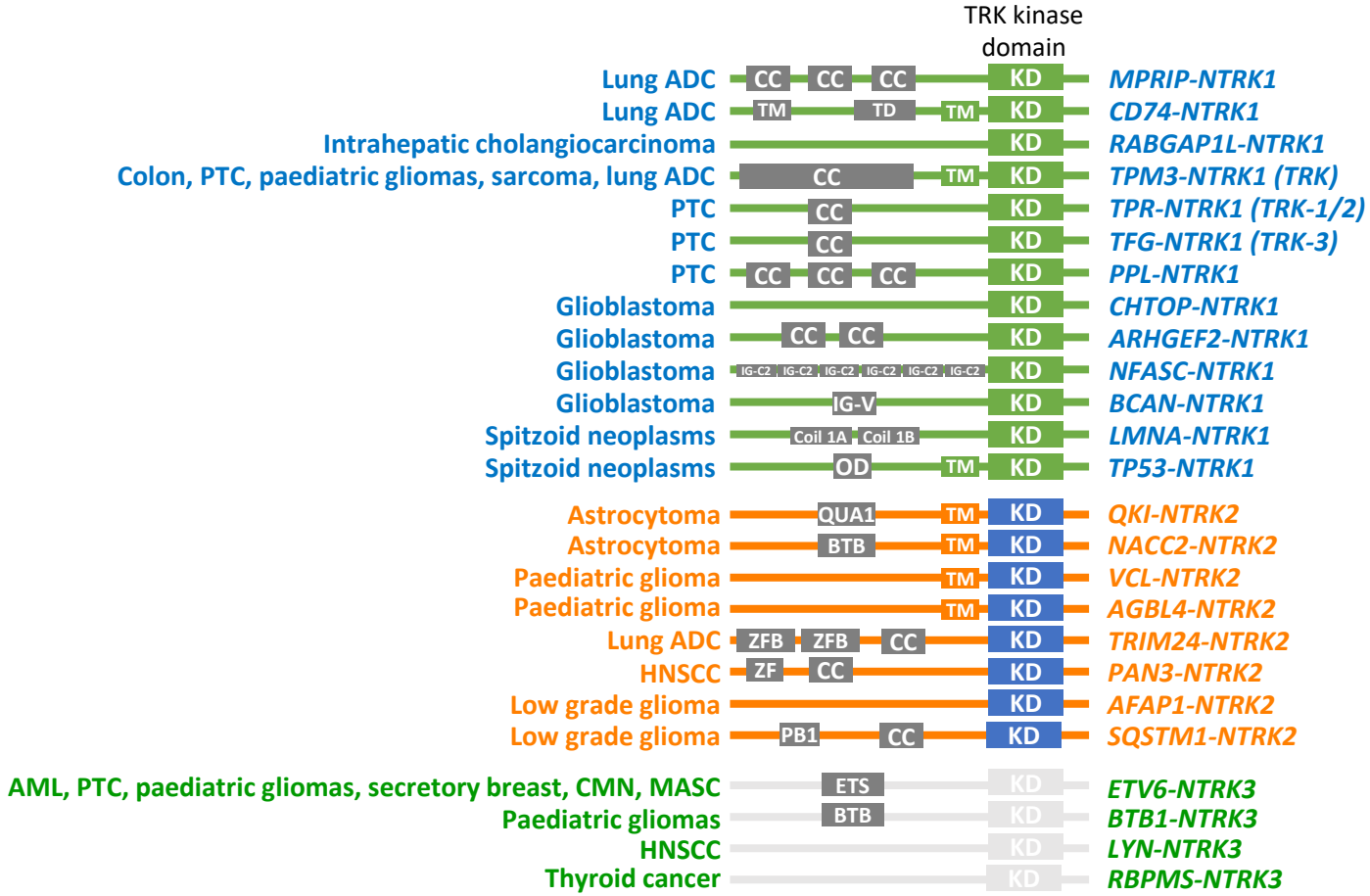
2. (TPR)-NTRK1 in thyroid cancer

3. (TRIM24)-NTRK2 and (ETV6)-NTRK3 in fibrosarcoma



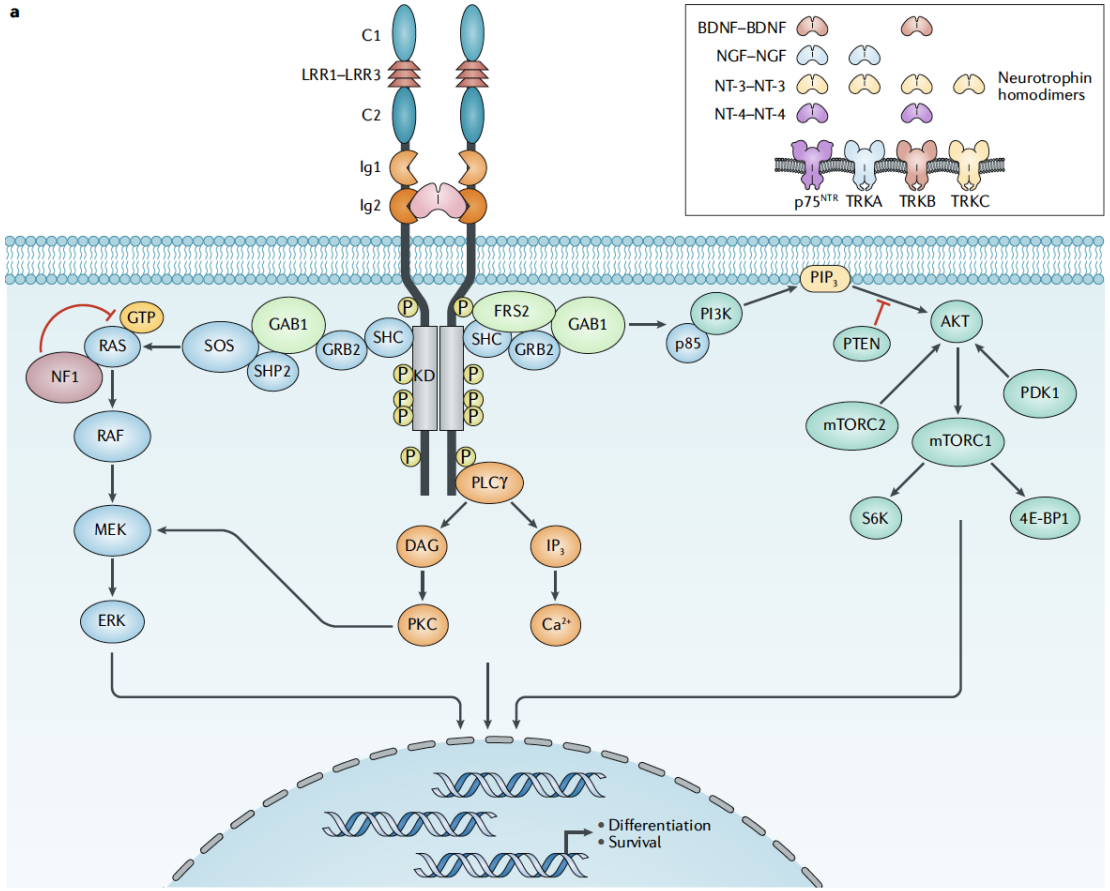
Zito Marino et al., 2020

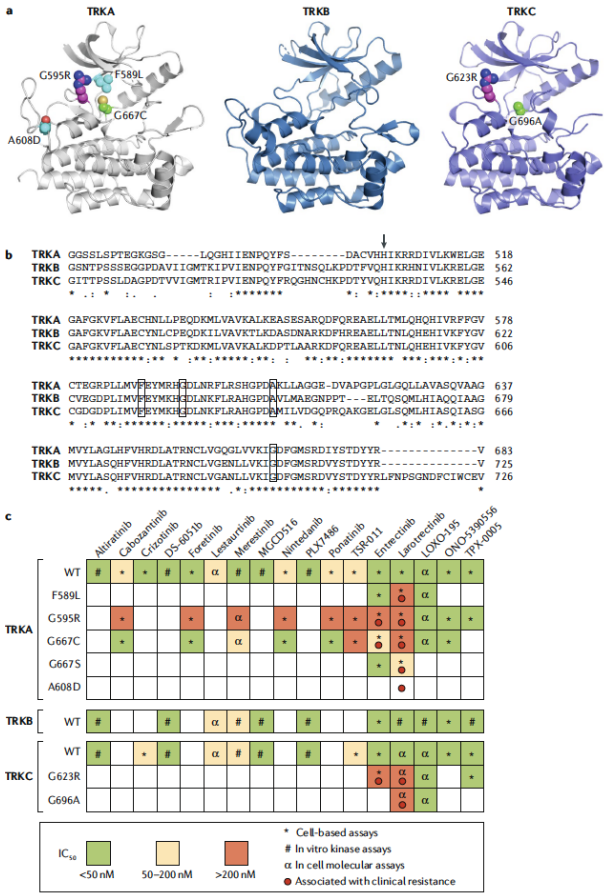
Multiple *NTRK* fusion partners reported in human malignancy



ADC: adenocarcinoma; AML: acute myeloid leukemia; BTB: bric-a-brac, tramtrack, and broad complex domain; CCD: coiled-coil domain; CMN: congenital mesoblastic nephroma; ETS: E26 transformation-specific domain; HNSCC: head and neck squamous cell cancer;
IG-C2: Immunoglobulin-like C2-type domain;
IG-V: Immunoglobulin-like V domain; MASC: mammary analogue secretory carcinoma; NTRK: neurotrophic TRK; OD: oligomerisation domain; PTC: papillary thyroid cancer; QUA1: Quaking 1 domain; TD: trimerisation domain; TPM3: tropomyosin-3; TRK; TRK: tropomyosin receptor kinase; ZF: zinc finger; ZFB: zinc finger B.

The fusion proteins activate Trk kinase, independent of ligand binding

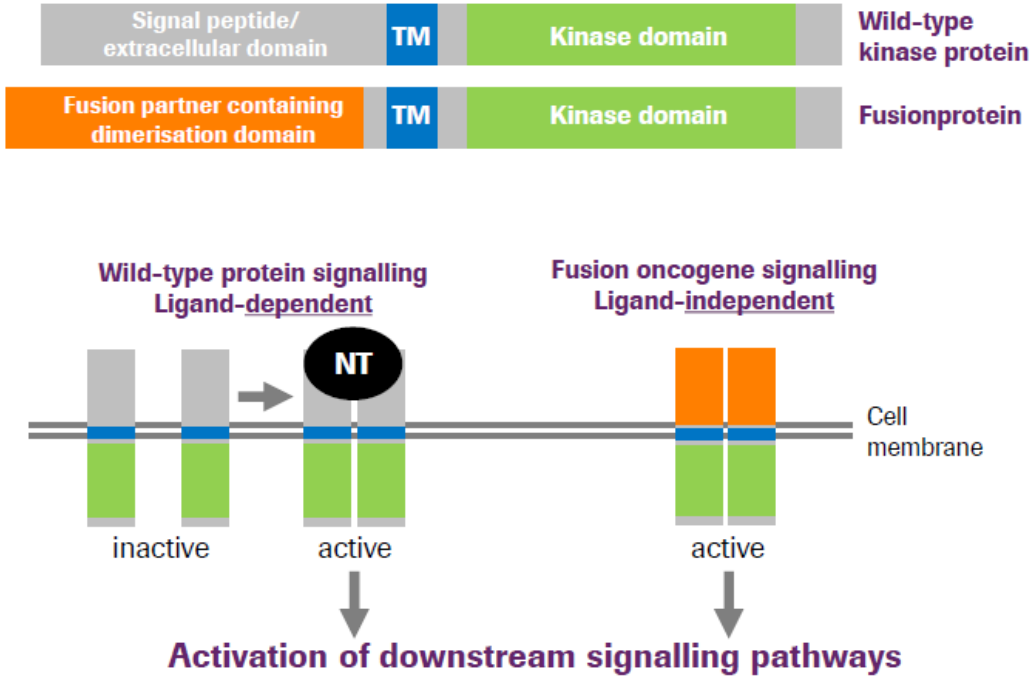




Cocco E. Nat Med Oncol 2018

NTRK GENE FUSIONS CAUSE CONSTITUTIVE ACTIVATION OR OVEREXPRESSION OF TRK PROTEINS DRIVING ONCOGENESIS

- TRKA/B/C are encoded by *NTRK*1/2/3 genes, respectively[1]
- Oncogenic activation of *NTRK* genes is typically caused by in-frame fusions leading to the expression of a chimeric protein, which retains the kinase domain, but not the ligand-binding domain[1-3]
- The oncogenic chimera is typically constitutively activated or overexpressed, leading to a constant signal cascade[1,2]
- The unrestrained activation of TRK-dependent pathways leads to cancer cell transformation, proliferation, migration and invasiveness[1]



NT: neurotrophin; NTRK: neurotrophic tropomyosin receptor kinase; RTK: receptor tyrosine kinase; TM: transmembrane domain; TRK: tropomyosin receptor kinase.

1. Ricciuti B, et al. (2017) Med Oncol 34:105; 2. Amatu A, et al. ESMO Open. 2016; 3. Vaishnavi A, et al. (2013) Nat Med 19:1469-72; 4. figure modified from Farago AF (2017) J Thorac Oncol.

MECHANISM OF ACTION OF TRK INHIBITORS

Orally bioavailable inhibitors of the tyrosine kinase domain of TrkA, TrkB, TrkC receptors[1]

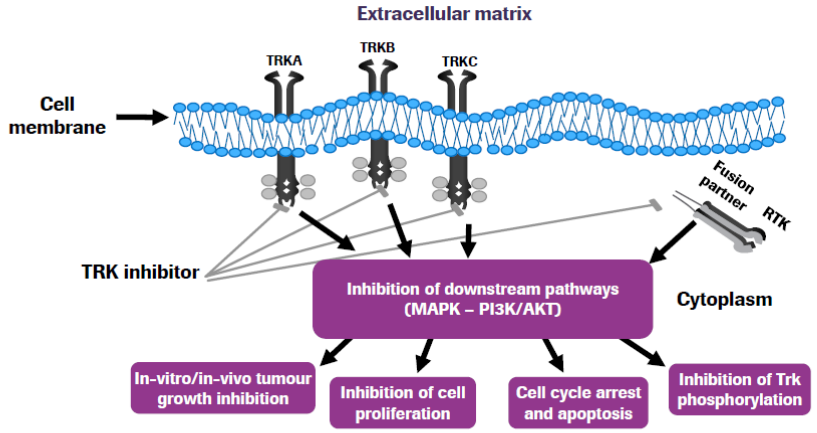


Table 1. TRK inhibitors

	Larotrectinib	Entrectinib	Selitrectinib	Repotrectinib
Generation				
First	✓	✓		
Second			✓	✓
Inhibits				
TRKA/B/C	✓	✓	✓	✓
ROS1		✓		✓
ALK		✓		✓
Resistance				
Inhibits most *NTRK* mutations			✓	✓

The features of four TRK tyrosine kinase inhibitors (larotrectinib, entrectinib, selitrectinib and repotrectinib) are summarised by tyrosine kinase inhibitor generation, major kinase targets and activity against resistance.

Drilon et al. Ann Oncol. 2019

- Producto experimental, no autorizado -

1. Rolfo, et al. Expert Opin Investig Drugs 2015;

3. Ensayos clínicos

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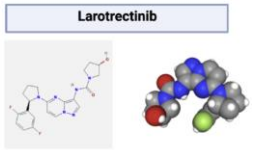
Sesión 3: Vías de desarrollo de la oncología transversal (I)

"NTRK-Tumours": fundamentos biológicos y resultados clínicos

Noviembre 2018

Larotrectinib, ARRY-470, LOXO-101, Vitrakvi, Bayer

For larotrectinib, the three trials which enrolled patients with advanced solid tumours:

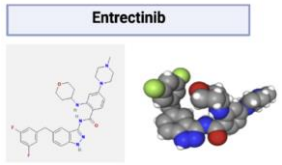


1. an adult phase I trial (NCT02122913),
2. a paediatric phase I/II trial (**SCOUT**)
3. an adult/adolescent phase II basket trial (**NAVIGATE**),

Octubre 2019

Entrectinib, RXDX-101, NMS-E628, Rozlytrek, Roche

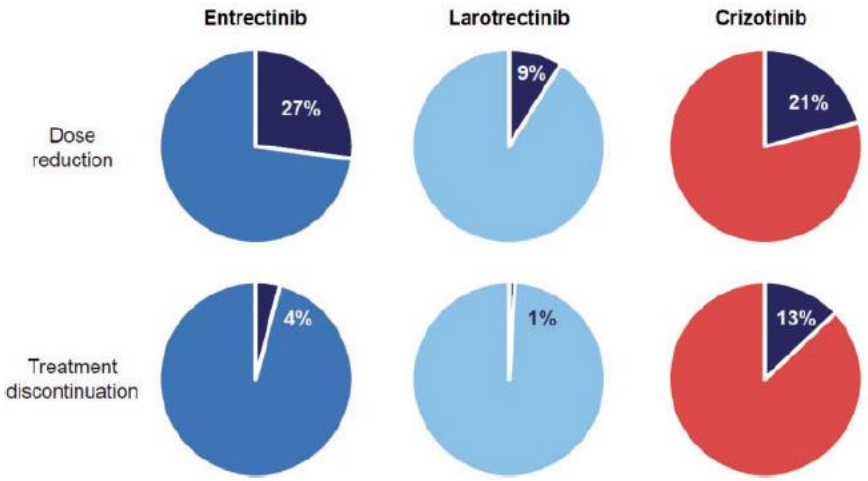
For entrectinib, the four contributory trials were:

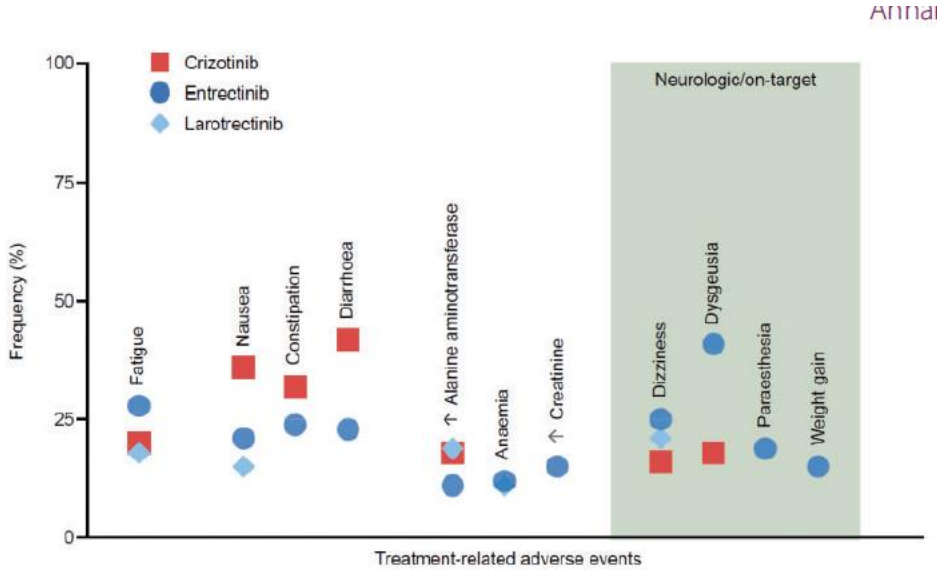


1. an adult phase I trial (**ALKA**-372-001, Italy),
2. a separate adult phase I trial (**STARTRK-1**, global),
3. a phase II basket trial (**STARTRK-2**),which enrolled patients with solid tumours harbouring NTRK1/2/3, ROS1 or ALK gene fusion,
4. phase I/Ib paediatric trial (**STARTRK-NG**) (2-21 years)

	Larotrectinib	Entrectinib	Entrectinib peds
TRK fusion-positive cancers, n	159	54	7
Age	1 month to 80 years	58 (range 21-83) years	>12 years
Histologies	salivary gland cancer (16%), infantile fibrosarcoma (15%), thyroid cancer (15%) and lung cancer (9%)	sarcoma (24%), lung cancer (19%), mammary analogue secretory carcinoma (13%) and breast cancer (11%)	high-grade gliomas (3), (CNS) embryonal tumour (1), melanoma (1) and infantil Fibrosarcoma (2)
NTRK fusions	NTRK1 (45%) or NTRK3 (53%)	NTRK1 (41%) or NTRK3 (57%)	NTRK3 (4)
ORR **CR/PR**	79% (95% CI 72% to 88%) 16/63%	ORR was 57% (95% CI 43% to 71%) -/-	All -/-
Median duration of response	Not reached	10.4 months	15 months
Intracraneal ORR **CR/PR**	55% (95% CI 23% to 83%) 27/27	36%	

	Larotrectinib	Entrectinib
Real data, n	>207	>355
Side effect	Fatigue 36% (grade 1 and 2)	Notable side effect: rise in creatinine, anemia, weigh gain
Dose reduction	16%	17%
Discontinuation	<1%	4%





Drilon et al. Ann Oncol. 2019

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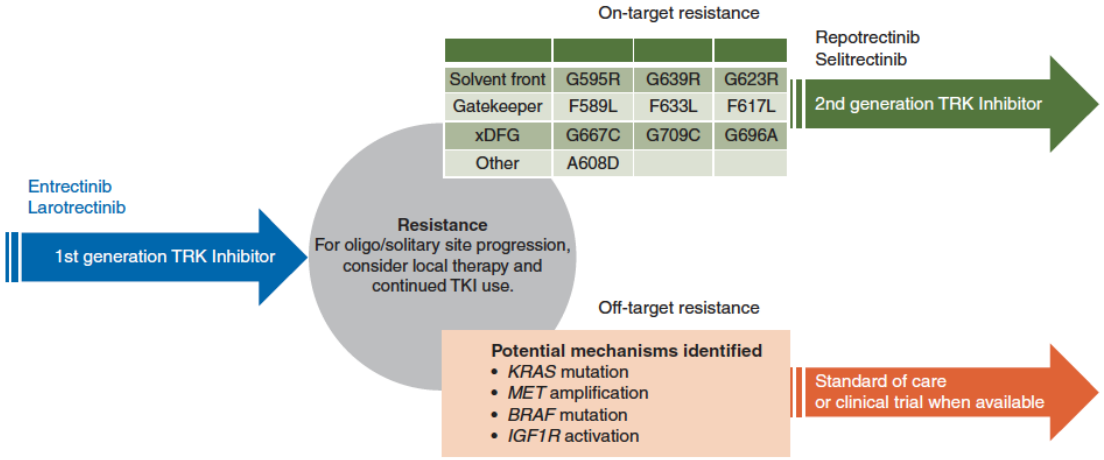

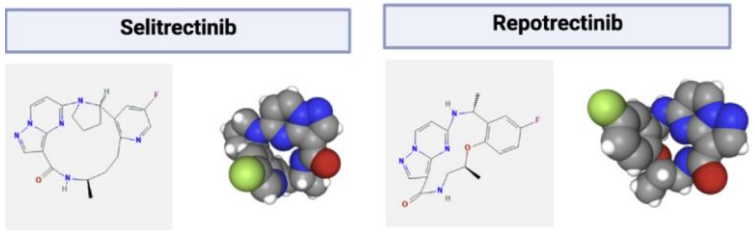

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Next generation (small size and highest activity)	Selitrectinib	Repotrectinib
Previous 1st NTRK	31	2
Trials on going	(NCT03215511)	(NCT03093116)
Histologies	Sarcoma (16%), gastrointestinal stromal tumour (13%) and pancreatic adenocarcinoma, mammary analogue secretory and breast carcinoma (10% each	mammary analogue secretory carcinoma and cholangiocarcinoma
NTRK fusions		NTRK1
ORR	45%	

Drilon et al. Ann Oncol. 2019

Noviembre 2018

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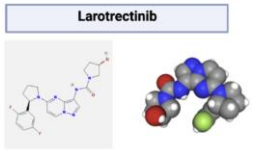

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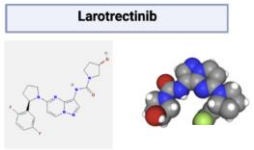

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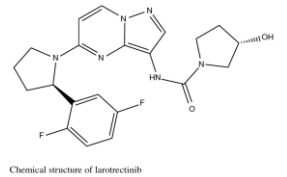
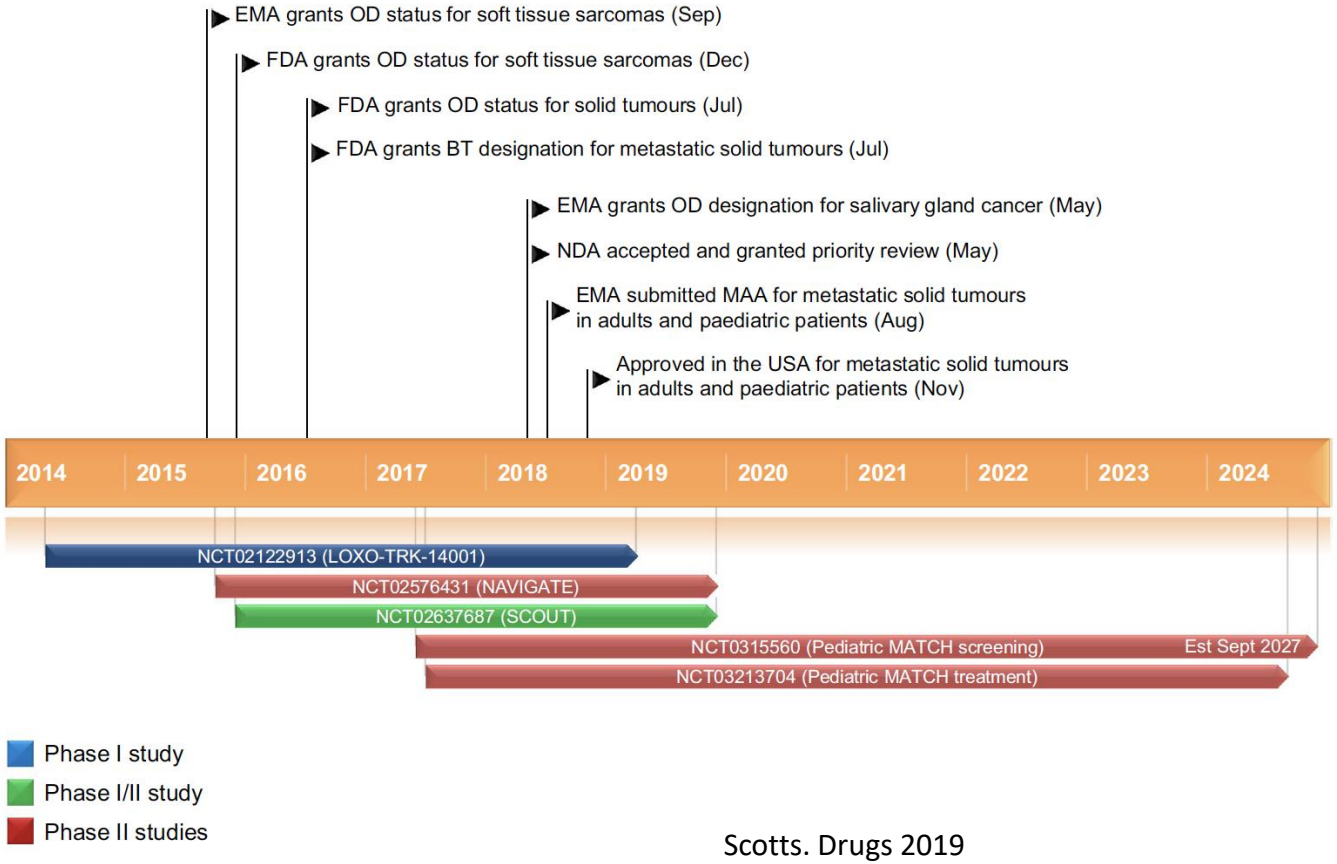

Chemical structure of larotrectinib



Features and properties of larotrectinib	
Alternative names	ARRY-470; LOXO-101; VITRAKVI®
Class	Amides, antineoplastics, pyrazoles, pyrimidines, pyrrolidines, small molecules
Mechanism of Action	TRKA receptor antagonists; TRKB receptor antagonists; TRKC receptor antagonists
Route of Administration	Oral
Pharmacodynamics	Binds to and inhibits TRKA, TRKB and TRKC, thereby preventing TRK activation, resulting in both the induction of cellular apoptosis and the inhibition of cell growth in tumours that overexpress TRK
Pharmacokinetics	Linear pharmacokinetics across doe range of 100–400 mg (i.e. 1–4 × recommended adult dose); t_{max} ≈ 1 h; bioavailability 34%; volume of distribution 48 L (intravenous dose); metabolized primarily by CYP3A4; 58 and 39% of a dose recovered in faeces and urine; mean clearance 98 L/h; half-life 2.9 h
Adverse reactions	
Most frequent (≥ 20% of pts)	Fatigue, nausea, dizziness, vomiting, anaemia, increased transaminase levels, cough, constipation, diarrhoea
ATC codes	
WHO ATC code	L01X-E53 (larotrectinib)
EphMRA ATC code	L1 (antineoplastic)
Chemical name	(3S)-N-(5-((2R)-2-(2,5-Difluorophenyl)pyrrolidin-1-yl)pyrazolo(1,5-a)pyrimidin-3-yl)-3-hydroxypyrrolidine- 1-carboxamide

t_{max} time to attain maximum plasma concentration, *TRK* tropomyosin receptor kinase

Scotts. Drugs 2019

Noviembre 2018

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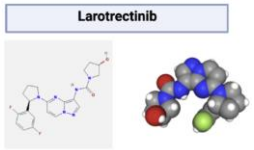
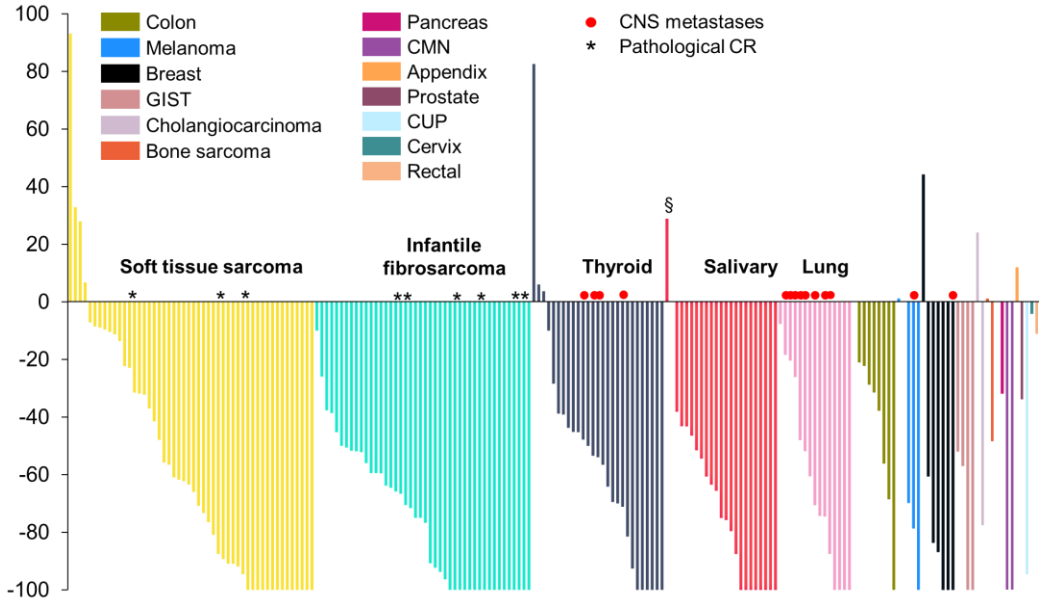


2. a paediatric phase I/II trial (SCOUT)

- Approved in more than 40 countries, including the US and Canada, for adult and pediatric patients with TRK fusion cancer

Post-hoc analysis of SCOUT

- A subset of pediatric patients enrolled in the SCOUT study (NCT02637687) discontinued larotrectinib without disease progression, including patients who underwent on-study surgical resection or entered a wait-and-see period following response according to physician discretion, as permitted



The objective of this analysis was to describe outcomes for pediatric patients with TRK fusion sarcoma who discontinued larotrectinib without evidence of prior disease progression

Noviembre 2018

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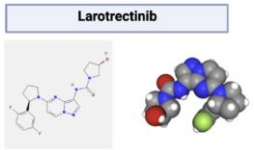

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	Surgical (n=15)					Non-surgical (n=16)
	Total surgical (n=15)	pCR (n=8)	R0 (n=2)	R1 (n=4)	R2 (n=1)	
Progressed, n (%)	3 (20)†	0	1 (50)*	1 (25)†	1 (100)	4 (25)

- None of the eight surgical patients discontinuing treatment after pCR had tumor progression during follow-up
- Two of the six (33.3%) other surgical patients had tumor progression
  - One of four R1; TTP 156 days
  - One of one R2; TTP 109 days
- One patient had tumor progression after discontinuation, resumed treatment and then had surgery*
  - One of two R0; TTP 27 days
- Four of the 16 (25%) non-surgical patients had tumor progression after discontinuation
  - TTP 41, 55, 84, and 251 days
- The median TTP after discontinuation for either surgical or non-surgical patients has not been reached

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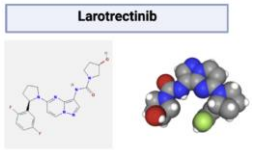

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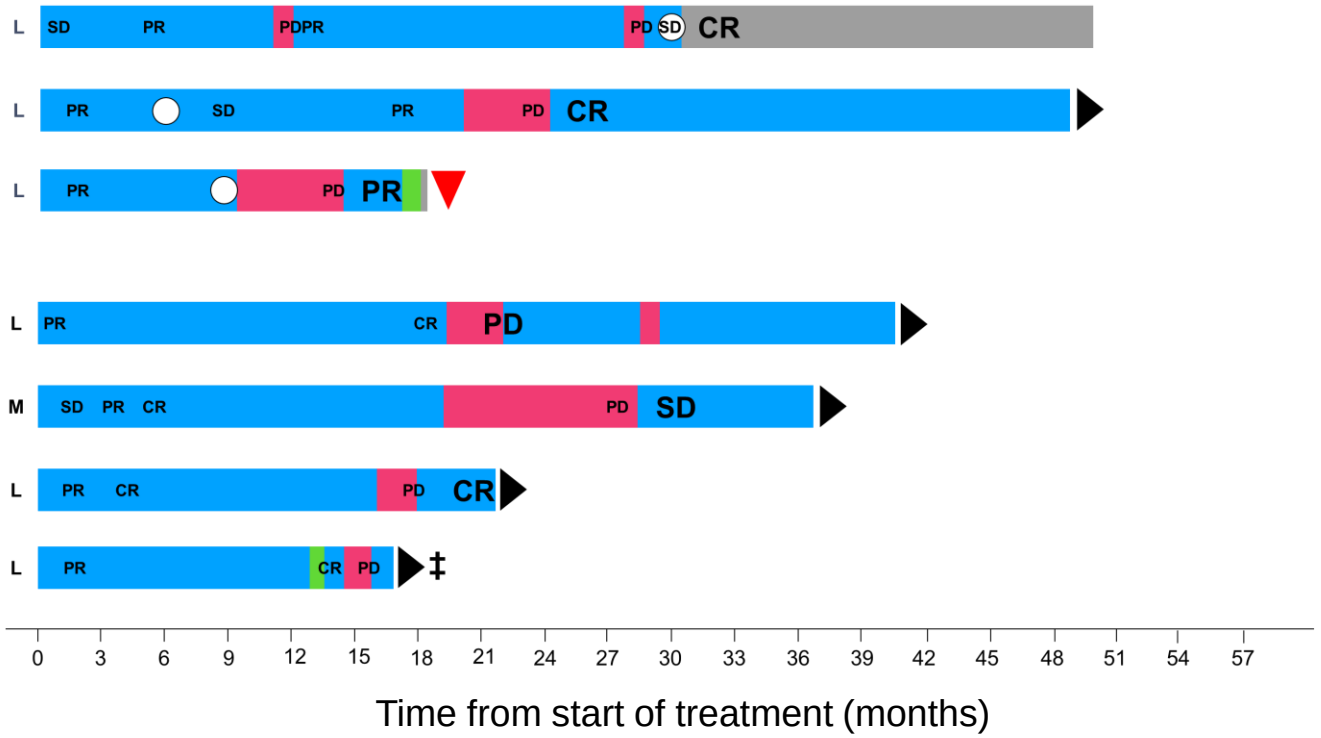


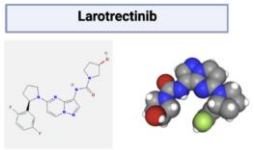
Conclusions

- Based on this exploratory analysis in 31 patients who discontinued larotrectinib treatment without disease progression:
  - **None of the eight patients who had surgical resection with pCR had tumor progression**
  - Two of six (33%) surgical patients without pCR had tumor progression
  - Most patients who discontinued without surgery had durable responses, although 4 of 16 (25%) had tumor progression
  - Four of six (67%) evaluable patients had objective response with re-challenge with larotrectinib following disease progression off therapy
- These results suggest that **discontinuation of larotrectinib may be feasible in selected patients**
- The optimal duration of treatment with larotrectinib in pediatric patients is a focus of an ongoing Children's Oncology Group trial (NCT03834961)

Noviembre 2018

Larotrectinib, ARRY-470, LOXO-101, Vitrakvi, Bayer

For larotrectinib, the three trials which enrolled patients with advanced solid tumours:

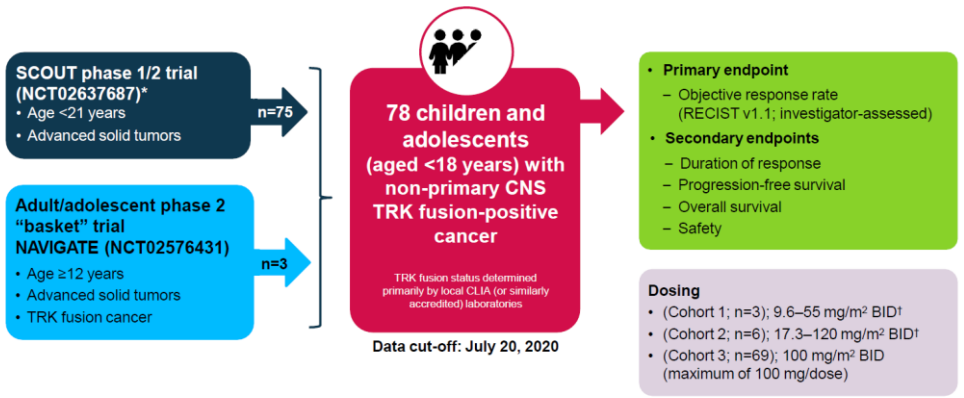


2. a paediatric phase I/II trial (SCOUT)

- Approved in more than 40 countries, including the US and Canada, for adult and pediatric patients with TRK fusion cancer

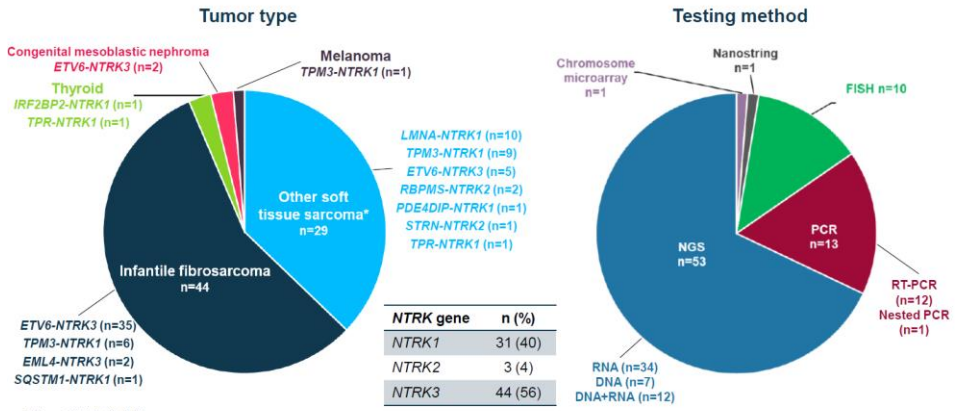
An expanded dataset

Study design



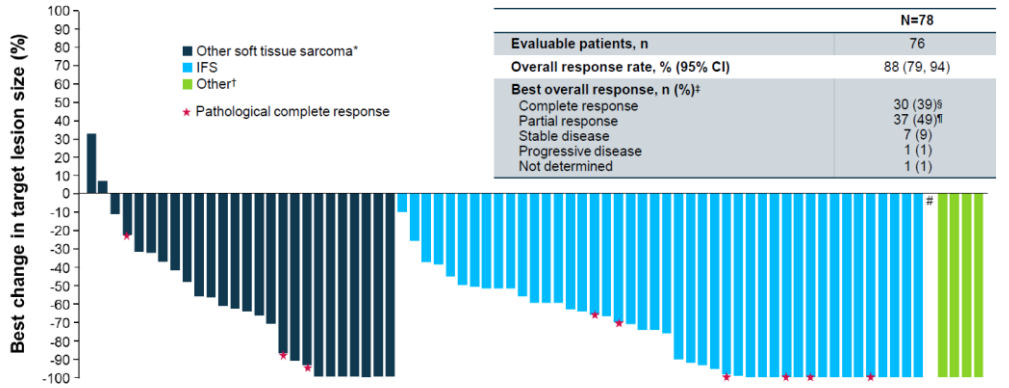
Analysis only includes patients with measurable disease at baseline.
*Presence of an *NTRK* gene fusion was not a general requirement for enrollment; †Dosing based on age and body surface area predicted by SimCyp modeling to yield equivalent exposures to adult patients treated with 100 mg (Cohort 1) and 150 mg (Cohort 2).
BID, twice daily; CLIA, Clinical Laboratory Improvement Amendments; CNS, central nervous system; RECIST, Response Evaluation Criteria in Solid Tumors.

Pediatric population by tumor type and testing method (N=78)



Data cut-off: July 20, 2020.
*Includes spindle cell (n=12), inflammatory myofibroblastic tumor (n=4), peripheral nerve sheath (n=4), soft tissue sarcoma not otherwise specified (n=5), and one each of myopericytoma, infantile myofibromatosis, lipofibromatosis, and small round cell.
FISH, fluorescence *in situ* hybridization; NGS, next-generation sequencing; PCR, polymerase chain reaction; RT, reverse transcription.

Best change in target lesion size

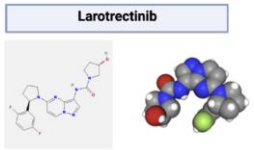


	N=78
Evaluable patients, n	76
Overall response rate, % (95% CI)	88 (79, 94)
Best overall response, n (%)‡	
Complete response	30 (39)§
Partial response	37 (49)¶
Stable disease	7 (9)
Progressive disease	1 (1)
Not determined	1 (1)

Noviembre 2018

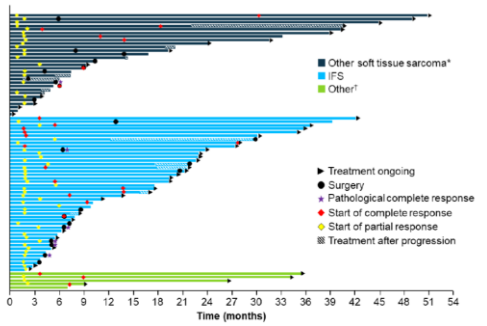
Larotrectinib, ARRY-470, LOXO-101, Vitrakvi, Baye

2. a paediatric phase I/II trial (SCOUT)



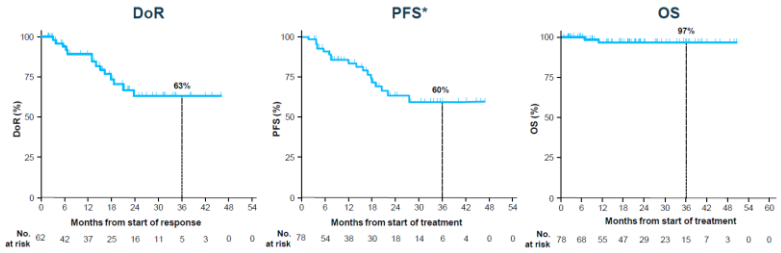
An expanded dataset

Duration of treatment



- Treatment duration ranged from 0.26+ to 50.6+ months
- Median time to response was 1.84 months (range 0.89–9.07)
- At the data cut-off:
  - 17 patients (22%) continued treatment post progression, with 10 patients (13%) on treatment post progression for ≥4 weeks
  - 33 patients (42%) had discontinued treatment
    - Tumor resection‡ (n=16)
    - Disease progression (n=10)
    - Adverse event§ (n=4)
    - Other (n=3)

Secondary efficacy endpoints

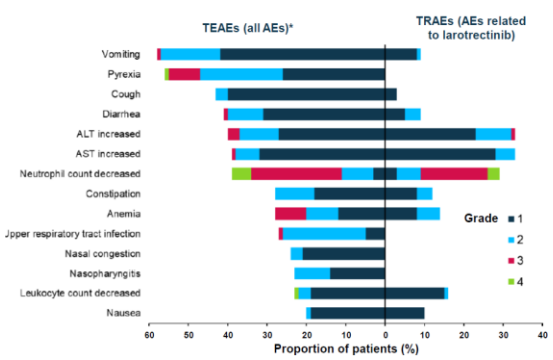


Median DoR, months (95% CI)	Not reached (21.2, NE)
Median follow up, months	20.7
36-month DoR, % (95% CI)	63 (47, 79)

Median PFS, months (95% CI)	Not reached (22.1, NE)
Median follow up, months	19.3
36-month PFS, % (95% CI)	60 (45, 75)

Median OS, months (95% CI)	Not reached (NE, NE)
Median follow up, months	21.1
36-month OS, % (95% CI)	97 (92, 100)

Safety (N=78)



- TRAEs were mainly grade 1 or 2
- Grade 3 or 4 TRAEs occurred in 22 patients (28%)
- Serious TRAEs occurred in four patients (5%)
- Three patients (4%) discontinued treatment due to TRAEs
- There were no grade 5 AEs
- Nine patients (12%) experienced neurologic TRAEs, the majority of which were grade 1 or 2
- Fractures occurred in eight patients (10%)
  - Seven grade 1 or 2, one grade 3
  - Causes include trauma (n=4), tumor-related (n=2), stress fracture (n=1), and unknown (n=1)
  - No fractures were considered by the investigators to be related to larotrectinib

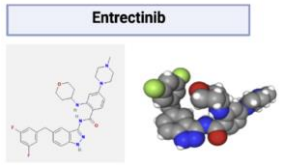
Conclusions

- In this expanded dataset with a longer follow up, larotrectinib continues to demonstrate rapid and durable tumor-agnostic efficacy with a robust survival benefit (36-month OS rate, 97%) in pediatric patients as young as 1 month of age with non-primary CNS TRK fusion cancer
- Larotrectinib had a favorable safety profile with no new safety signals identified, and only three patients discontinuing treatment due to a TRAE
  - Neurologic TRAEs were rare and mainly grade 1 or 2
- These results illustrate the importance of offering *NTRK* gene fusion testing to pediatric patients with solid tumors, especially those lacking the usual driver alterations

Octubre 2019

Updated entrectinib data from a phase 1/2 trial in children and adolescents with recurrent or refractory solid tumors, including primary central nervous system (CNS) tumors

Entrectinib, RXDX-101, NMS-E628, Rozlytrek, Roche



For entrectinib, the four contributory trials were:

1. an adult phase I trial (**ALKA**-372-001, Italy),
2. a separate adult phase I trial (**STARTRK-1**, global),
3. a phase II basket trial (**STARTRK-2**),which enrolled patients with solid tumours harbouring NTRK1/2/3, ROS1 or ALK gene fusion,
4. phase I/Ib paediatric trial (**STARTRK-NG**) (2-21 years)

STARTRK-NG:

	Entrectinib	Entrectinib peds
TRK fusion-positive cancers, n	54	7
Age	58 (range 21-83) years	>12 years
Histologies	sarcoma (24%), lung cancer (19%), mammary analogue secretory carcinoma (13%) and breast cancer (11%)	high-grade gliomas (3), (CNS) embryonal tumour (1), melanoma (1) and infantil Fibrosarcoma (2)
NTRK fusions	NTRK1 (41%) or NTRK3 (57%)	NTRK3 (4)
ORR **CR/PR**	ORR was 57% (95% CI 43% to 71%) -/-	All -/-
Median duration of response	10.4 months	15 months
Intracraneal ORR **CR/PR**	36%	

VII SIMPOSIO GETTHI

Sesión 3: Vías de desarrollo de la oncología transversal (I)

"NTRK-Tumours": fundamentos biológicos y resultados clínicos

Updated entrectinib data from a phase 1/2 trial in children and adolescents with recurrent or refractory solid tumors, including primary central nervous system (CNS) tumors

STARTRK-NG: study design

Pediatric and adolescent patients*
Total enrolled (N=39); data cut-off 5 Nov 2019

Dose-finding phase 1 (N=16)
Patients with relapsed or refractory solid tumors with/without target gene fusions
Dose level 250–750 mg/m²: Sequential assignment to escalating doses of entrectinib (3+3 design), initially dosed by BSA

250 mg/m²	400 mg/m²	550 mg/m²	750 mg/m²
(n=3)	(n=3)	(n=7)	(n=3)

Expansion phase 2 trial (N=23)†
Recommended dose level 550 mg/m² (n=14) OR
400 mg/m² in patients unable to swallow intact capsules (n=9)

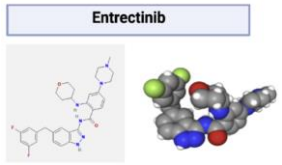
Cohort B: Primary CNS tumor with *NTRK/ROS1* fusion‡ (n=9)	*Enrollment discontinued* Cohort C: Neuroblastoma (n=3)	Cohort D: Extracranial solid tumor *NTRK/ROS1* fusion‡ (n=2)	*Enrollment discontinued* Cohort E:** Unable to swallow capsule (n=9)

**Cohort E:
- Primary CNS tumors (n=5)
- Extracranial solid tumors (n=4)

Primary endpoint: Objective response rate (ORR)
Secondary endpoints: Duration of response (DoR), progression-free survival (PFS), overall survival (OS) and safety

Octubre 2019

Entrectinib, RXDX-101, NMS-E628, Rozlytrek, Roche



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4. phase I/Ib paediatric trial (**STARTRK-NG**) (2-21 years)

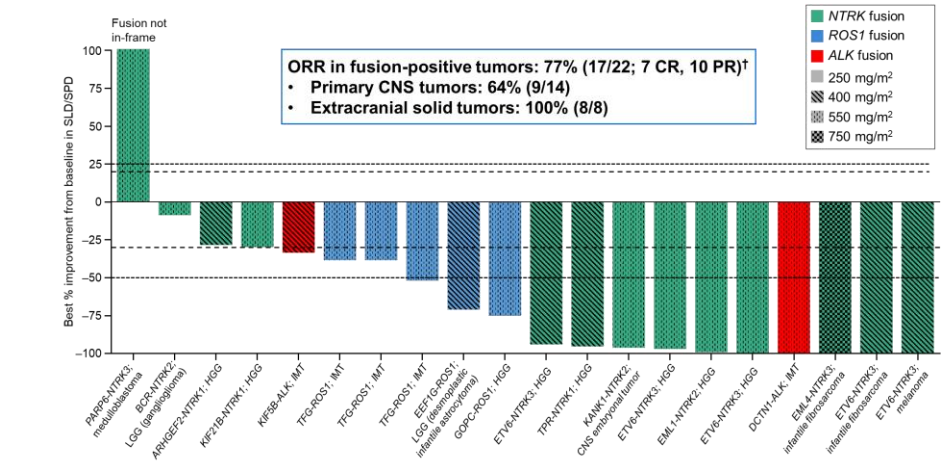
		Phase 1 dose-escalation (n=16)	Phase 2 (n=23)	All patients (N=39)
Age, years	Median (range)	9.5 (4–20)	4 (4.9mo–19yr)	7 (4.9mo–20yr)
Sex, n (%)	Male	10 (62.5)	11 (47.8)	21 (53.8)
	Female	6 (37.5)	12 (52.2)	18 (46.2)
Race, n (%)	White	13 (81.3)	20 (87)	33 (84.6)
	Black/African American	3 (18.8)	2 (8.7)	5 (12.8)
	Other	0	1 (4.3)	1 (2.6)
Karnofsky/Lansky score, n (%)*	60	0	1 (4.3)	1 (2.6)
	70	1 (6.7)	1 (4.3)	2 (5.3)
	80	2 (13.3)	7 (30.4)	9 (23.7)
	90	7 (46.7)	6 (26.1)	13 (34.2)
	100	5 (33.3)	8 (34.8)	13 (34.2)
Prior systemic therapies, n (%)	Chemotherapy	14 (87.5)	17 (73.9)	31 (79.5)
	Immunotherapy	7 (43.8)	4 (17.4)	11 (28.2)
	Targeted therapy†	3 (18.8)	0	3 (7.7)
	Monoclonal antibody	8 (50.0)	3 (13.0)	11 (28.2)
	Radiation	13 (81.3)	11 (47.8)	24 (61.5)
Tumor type, n (%)	Primary CNS	0	14 (60.9)	14 (35.9)
	Extracranial	5 (31.3)	5 (21.7)	10 (25.6)
	Neuroblastoma	11 (68.8)	4 (17.4)	15 (38.5)
Gene fusion, n (%)	*NTRK1/2/3*	1 (6.3)	13 (56.5)	14 (35.9)
	ROS1	1 (6.3)	4 (17.4)	5 (12.8)
	ALK	1 (6.3)	2 (8.7)	3 (7.7)
	None	13 (81.3)	4 (17.4)	17 (43.6)

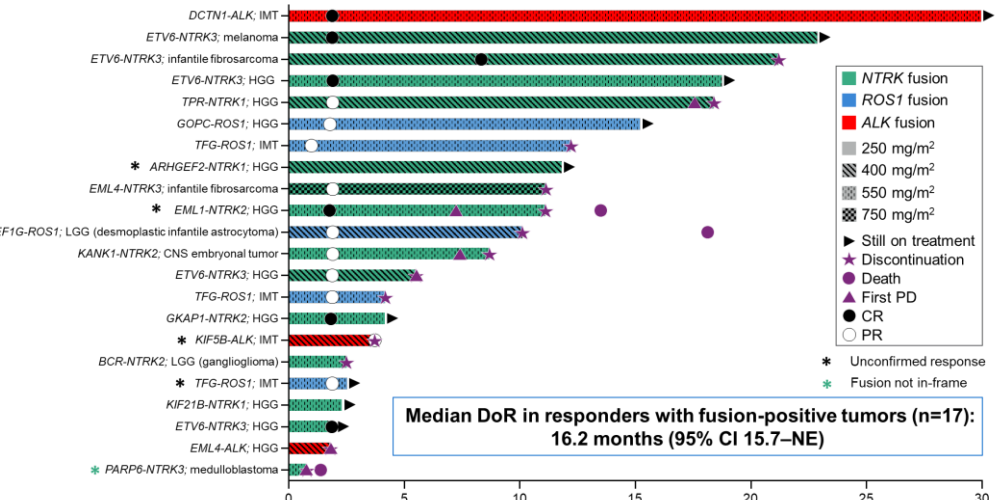
VII SIMPOSIO GETTHI

Sesión 3: Vías de desarrollo de la oncología transversal (I)

"NTRK-Tumours": fundamentos biológicos y resultados clínicos

Updated entrectinib data from a phase 1/2 trial in children and adolescents with recurrent or refractory solid tumors, including primary central nervous system (CNS) tumors



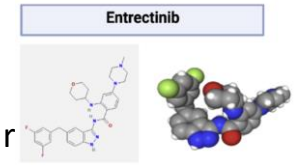


Octubre 2019

Entrectinib, RXDX-101, NMS-E628, Rozlytrek, Roche

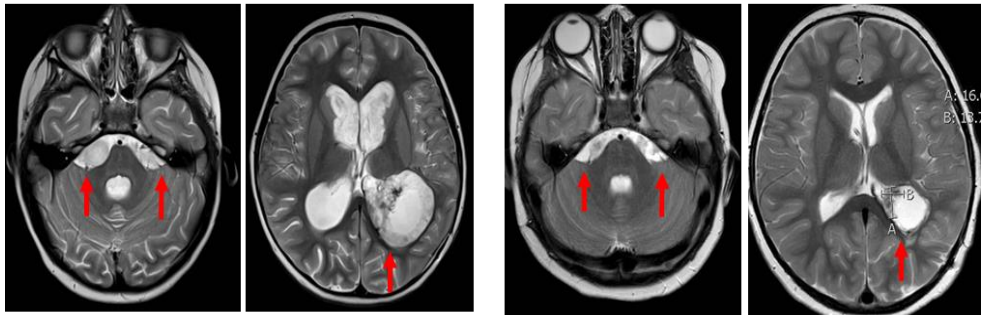
For entrectinib, the four contributory trials were:

4. phase I/Ib paediatric trial (**STARTRK-NG**) (2-21 year



Primary CNS tumor

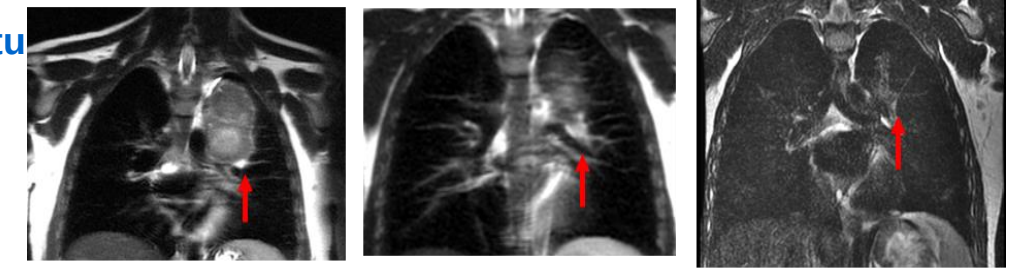
High-grade glioma: biphasic spindled and epithelioid glial neoplasm (*ETV6-NTRK3*)



Baseline — After 2 cycles

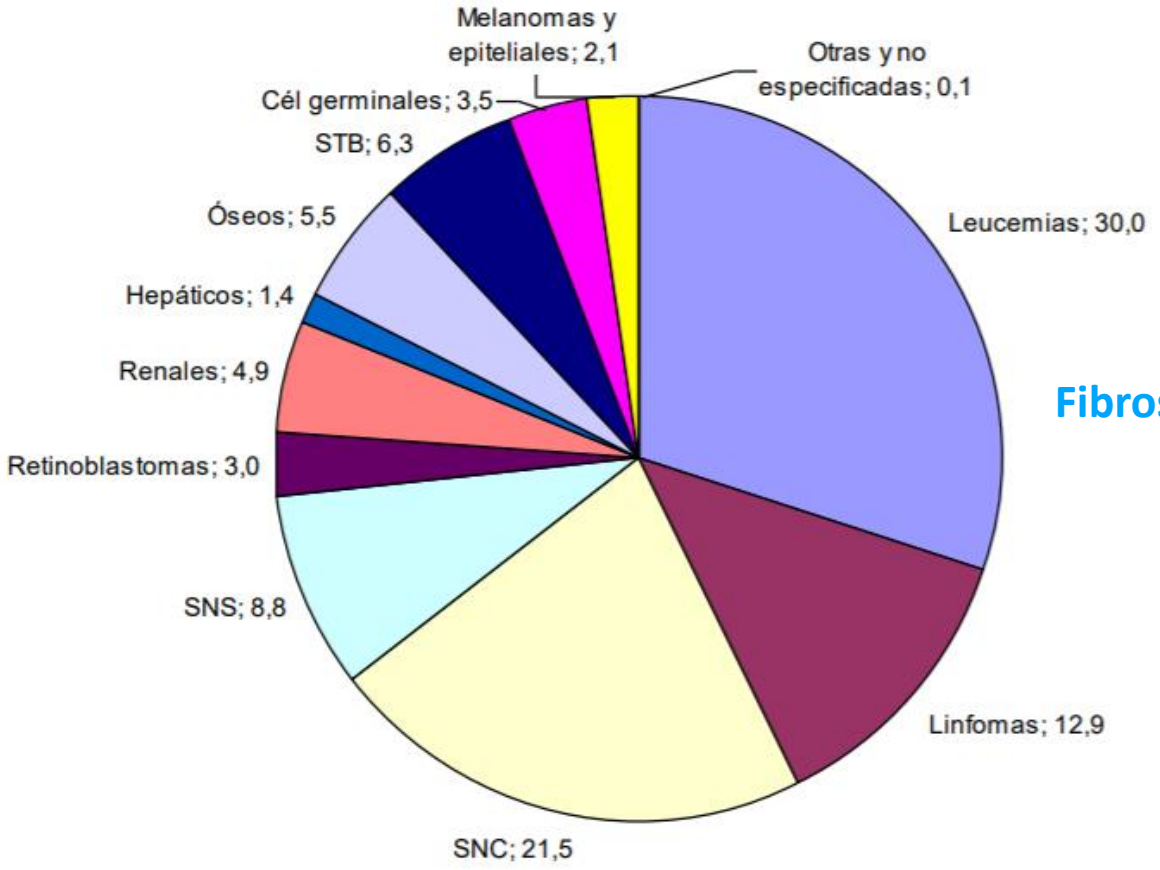
Extracranial solid tu

Inflammatory myofibroblastic tumor (*TFG-ROS1*)



Baseline — After 2 cycles — After 9 cycles

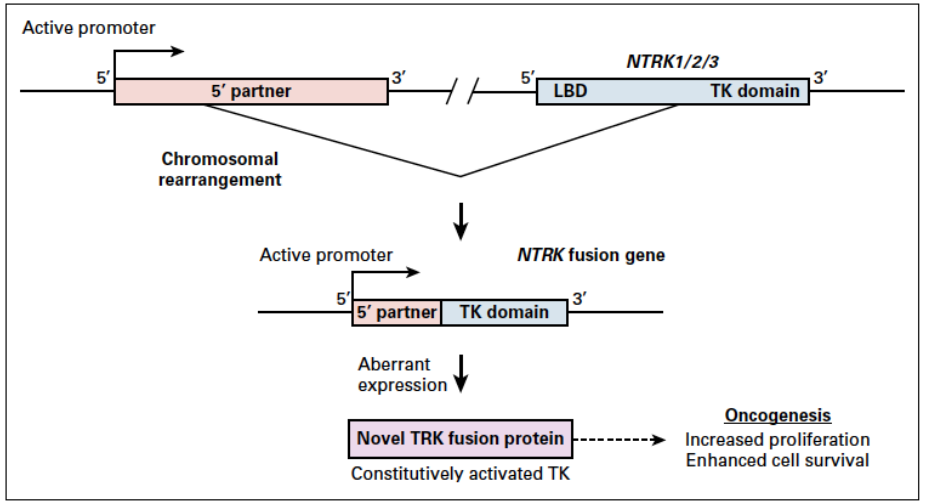
4. Experiencia Servicio de Hemato-Oncología Pediátrica Hospital Universitario La Paz



Fuente: RETI-SEHOP

- Neonatos y hasta menores de 2 años
- ♂ > ♀
- Translocación cromosómica t(12; 15) (p13; q25) y fusión génica **ETV6-NTRK3**
- Descrito en 1998 por Sorensen et al
- Diagnóstico por imagen, estudios anatomopatológicos y moleculares.
- Tratamiento: cirugía y/o quimioterapia.

Fibrosarcoma infantil

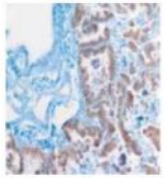


Albert et al. JCO 2019

Fibrosarcoma infantile: ETV6-NTRK3

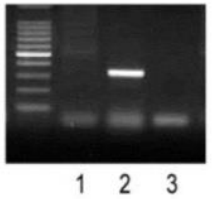
Immunohistochemistry (IHC)

- Detects protein expression, which may be attributable to a fusion event as it detects TRK protein (wild-type and fusion)[1]



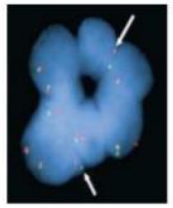
Reverse transcription polymerase chain reaction (RT-PCR)

- Detects known and unknown fusion transcripts in RNA[3]
- Cannot determine novel partner[2]



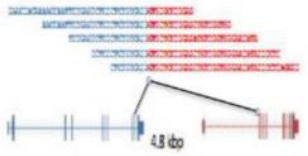
Fluorescence in situ hybridization (FISH)

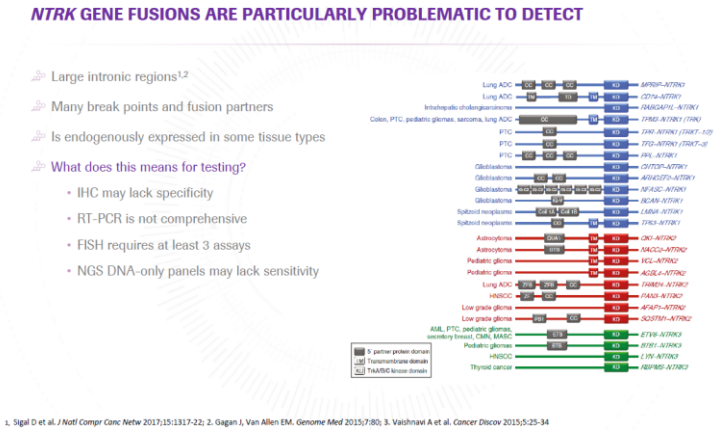
- Detects known gene rearrangements in DNA that may generate a fusion transcript[2]



Next-generation sequencing (NGS)

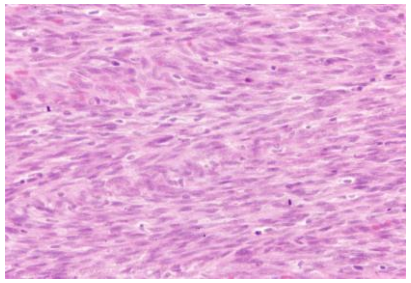
- Detects known and novel fusions with arbitrary breakpoints in DNA or RNA[2]
- The sensitivity and specificity of NGS assays vary widely[4]





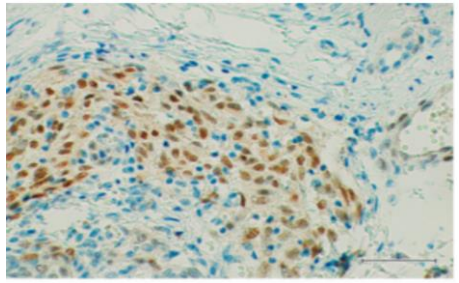
1. Sigal D et al. *J Natl Compr Canc Netw* 2017;15:1317-22; 2. Gagan J, Van Allen EM. *Genome Med* 2015;7:80; 3. Vaishnavi A et al. *Cancer Discov* 2015;5:25-34

IMAGEN HISTOLÓGICA



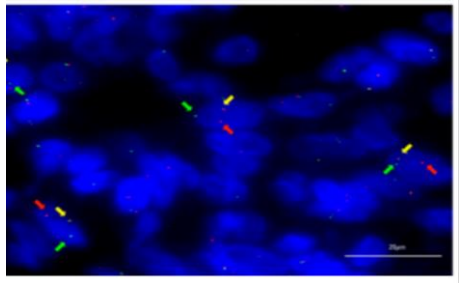
Fotografía cedida por el Dr. Pozo Kreilinger (Servicio de Anatomía Patológica del Hospital U. La Paz, Madrid).

INMUNOHISTOQUÍMICA



Fuente: Zito Marino et al., 2020

IMAGEN FISH



Fuente: Zito Marino et al., 2020

Table 1. Summary of main features, strengths and weaknesses of all available techniques to detect *NTRK* rearrangements

Method	Sensitivity	Specificity	Detection of all fusion genes	Detection of partner	Detection of expression	Screening
IHC	High[a]	High[b]	Yes	No	Yes	Yes
FISH[c]	High	High	One per probe	No	No	No
RNA seq NGS	High	High	Yes	Yes	Yes	Yes
DNA seq[c]	Moderate	High	Yes	Yes	No	Yes

[a]False negatives reported mainly in *NTRK3* fusions.
[b]In the absence of smooth muscle/neuronal differentiation.
[c]Detected rearrangements by DNA-based assays may not result in fusions, correlation with surgical pathology and predicted transcript (for sequencing) is needed.

(Marchiò et al., 2019)

(A) Immunohistochemistry

- Detects protein expression, which *may* be attributable to a fusion event.
  (A) Strong panNTRK antibody expression in *NTRK1* fusion–positive IFS.

(B) FISH

- Detects gene rearrangements in DNA that *may* generate a fusion transcript.
  (B) *ETV6* FISH break-apart probe demonstrating an *ETV6* rearrangement.

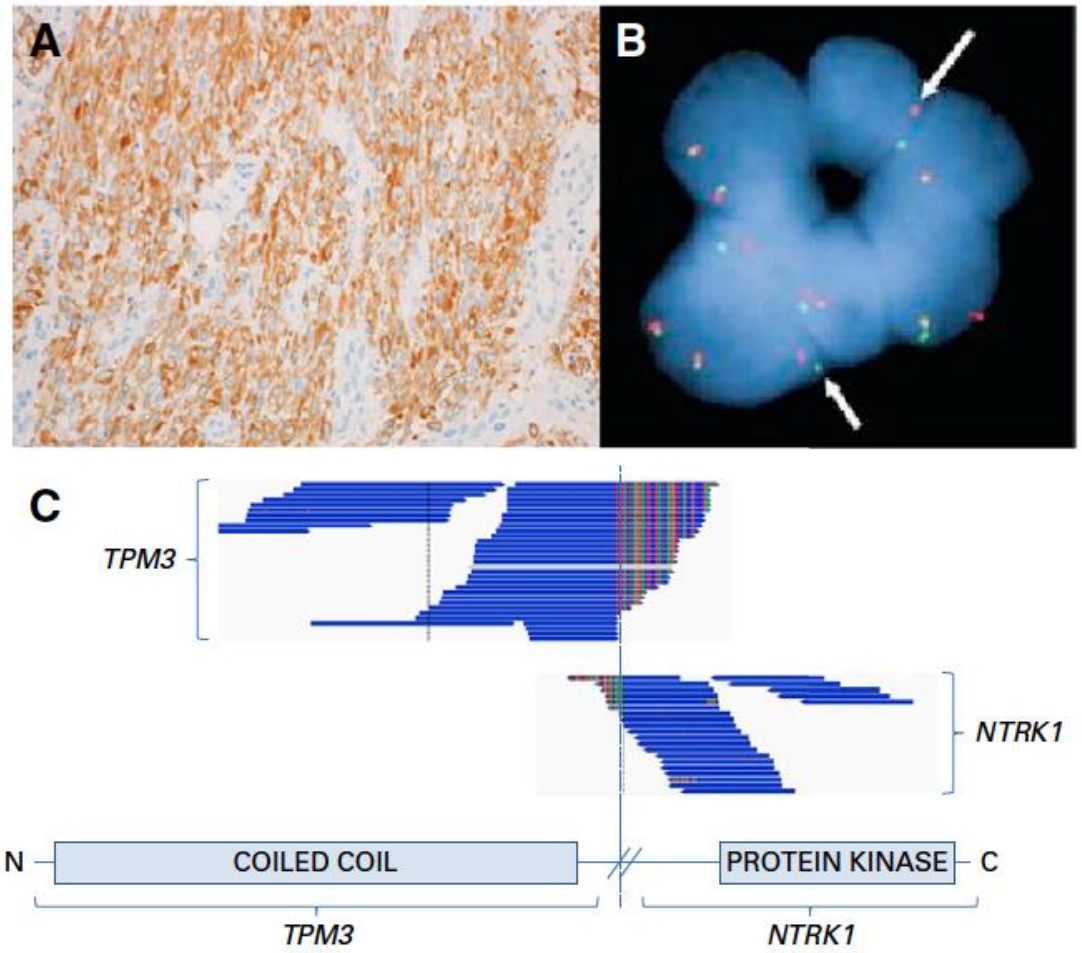
Reverse Transcriptase Polymerase Chain Reaction

- Detects known fusion transcripts in RNA.
- Detects 5′/3′ imbalance as a fusion signature, but cannot determine novel partner.

(C) Next-Generation Sequencing

- Detects known and novel fusions with arbitrary breakpoints in DNA or RNA.
- Exact capabilities depend on enrichment strategy and data analysis pipeline.

(C) Sequencing read piles aligned to the human genome and visualized using the Integrative Genomics Viewer. The rainbow plot shows discordant mate pairs in the tumor with one mate mapping to intron 7 of *TPM3* on chromosome 1 and the other mapping to intron 8 of *NTRK1* also on chromosome 1.



Albert et al. JCO 2019

ABORDAJE TUMOR AGNÓSTICO Y MEDICINA DE PRECISIÓN

- Terapias de precisión dirigidas a genes drugables.
- Terapias individualizadas.
- Reducción de efectos adversos y morbilidad.

Número total de sarcomas infantiles diagnosticados entre los años 2000-2020 en el Hospital Universitario La Paz.

En el periodo 2000-2020 se han diagnosticado 7 fibrosarcomas infantiles, lo que constituye un 2.5% de todos los sarcomas

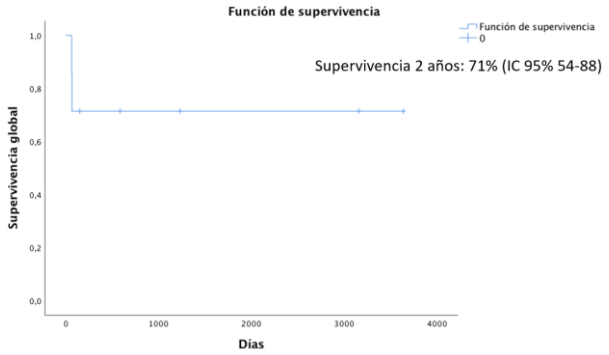
TIPO DE SARCOMA	FRECUENCIA
Ewing	64
Osteosarcoma	58
Rabdomiosarcoma	71
Sarcomas rabdoides	6
PNET	18 (incluye óseos, partes blandas y viscerales)
Otros sarcomas	60 (incluye fibromatosis, desmoplásicos y sarcomas varios)
TOTAL SARCOMAS	**277**

VII SIMPOSIO GETTHI

Sesión 3: Vías de desarrollo de la oncología transversal (I)

"NTRK-Tumours": fundamentos biológicos y resultados clínicos

PACIENTES	1	2	3	4	5	6	7
VARIABLES							
Género	Femenino	Masculino	Masculino	Masculino	Femenino	Femenino	Masculino
Procedencia	Alicante	Madrid	Madrid	Burgos	A Coruña	Madrid	Madrid
Fecha del diagnóstico	Día +1 de vida	Día +1 de vida	Semana 24 intraútero	+3 meses de vida	+9 meses de vida	Día +1 de vida	+3 meses de vida
Localización tumoral	Región axilar izquierda	Región lumbar, sobre nevus melanocítico gigante	Región cérvico-torácica izquierda	Región cervical alta (C2-C4)	Región pectoral derecha	Región retroperitoneal abdominal	Región cuadricipital de muslo izquierdo
Extensión tumoral al diagnóstico	Localmente avanzado	Localizado	Localmente avanzado	Localizado	Localizado	Localizado	Localizado
Estudio citogenético: fusión génica ETV6-NTRK3, translocación t(12;15)(p13.2;q25.3)	No estudiada	No estudiada	Negativo	Positivo	Negativo	Positivo	Positivo
Tratamiento	Cirugía: disección y extirpación de la tumoración en bloque	Cirugía: resección del nevus en su totalidad y cierre primario.	Ninguno	Cirugía : hemilaminectomía derecha descompresiva C2-C4 y resección tumoral subtotal + Quimioterapia adyuvante IVA	Cirugía: exéresis del tumor	Larotrectinib oral 25 mg cada 12 horas	Larotrectinib oral 25 mg cada 12 horas
Respuesta a tratamiento	R0	R0		R2	R1	R0	R0
Evolución	Libre de enfermedad	Libre de enfermedad	† (primeras 48 horas de vida)	† (67 días post-diagnóstico)	Libre de enfermedad	Libre de enfermedad	Libre de enfermedad
Seguimiento	9, 96 años	8, 65 años	-	-	3, 1 años	1, 61 años	0, 42 años

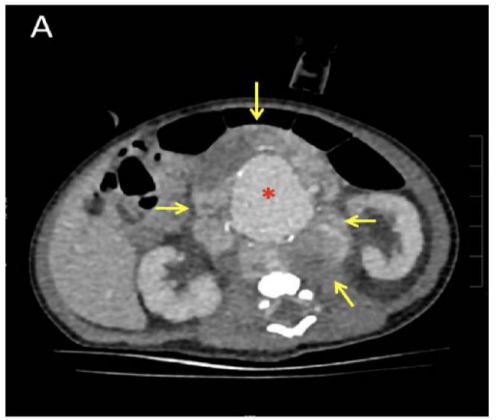


Treatment of infantile fibrosarcoma associated to an abdominal aortic aneurysm with larotrectinib: a case report

María Dolores Corral Sánchez [1], Víctor Galán Gómez [1], Ana Sastre Urgelles [1], Diego Plaza López de Sabando [1], Pedro Rubio Aparicio [1], Leopoldo Martínez Martínez [2], Eduardo Alonso Gamarra [3], José Juan Pozo Kreilinger [4], Rita María Regojo Zapata [4], Juan Carlos López Gutiérrez [5], Eugenia Antolín Alvarado [6], Felipe Gómez Martín [7], Ana María Sánchez Torres [8], Elena Marín Manzano [9], Luis González Del Valle [9], Antonio Pérez-Martínez [1,10]

Affiliations + expand

PMID: 33622165 DOI: 10.1080/08880018.2021.1889730



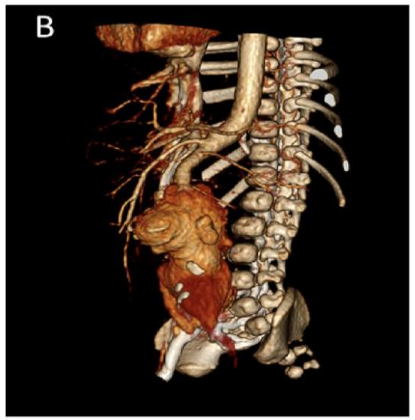


Table 1. Size of the IFS and the abdominal aortic aneurysm during the treatment with larotrectinib.

Time (months)	IFS (cm)	Abdominal aortic aneurysm (cm)
0	AP = 6.4; T = 4.8; CC = 9.4	AP = 3.4; T = 3.7; CC = 6.2
1	AP = 1.0; T = 1.4; CC = 3.0	AP = 3.7; T = 3.7; CC = 6.0
2	AP = 0.9; P = 0.5	AP = 3.7; T = 3.6; CC = 6.2
3	P = 0.6	AP = 4.0; T = 3.5; CC = 6.4
4	P = 0.6	AP = 3.9; T = 3.9; CC = 6.0
5	0	AP = 3.9; T = 3.7; CC = 6.3
6	0	AP = 3.3; T = 3.7; CC = 6.5
8	0	AP = 3.7; T = 3.5; CC = 6.3
9	0	–

Note. AP = anteroposterior; CC = craniocaudal; IFS = infantile fibrosarcoma; P = posterior; T = transversal.

Corral Sánchez et al. Pediatr Hematol Oncol. 2021.

- El jarabe de Daniela

Original Article | Published: 14 June 2013

Margin status and multimodal therapy in infantile fibrosarcoma

Jason P. Sulkowski, Mehul V. Raval & Marybeth Browne

Pediatric Surgery International **29**, 771–776 (2013) | Cite this article
550 Accesses | **16** Citations | Metrics

Abstract

Purpose

The rarity of infantile fibrosarcoma (IF)
The purpose of this study was to better d
the role of chemotherapy.

more rarely delays its presentation to 2 years of age [6]. CIFS occurs more commonly in males than females (3:2) [5]. CIFS affects Caucasians 68% of the time, and Blacks (16.1%) and Hispanics (8.9%) less commonly [4]. CIFS most commonly involves the extremities (51.8%) or trunk (23.7%), but 16.5% of the time presents in the head and neck region [4].

The differential diagnosis of CIFS includes spindle cell rhabdomyosarcoma and poorly differentiated embryonal rhabdomyosarcoma, infantile fibromatosis, malignant peripheral nerve sheath tumor, syno-

tral necrosis, hemorrhage, collagen formation and calcifications wi
often be encountered as well [12]. Variations with irregular bloo
vessels or minimal collagen have been documented [13]. Invasiv
findings include engulfed regions of muscle or adipose tissue. Thes
tumors stain with 100% positivity for vimentin [14]. CIFS is cha
acterized in up to 85% of cases by a specific chromosomal translocatio
t (12; 15)(p13; q25) coding for a ETV6-NTRK3 gene fusion [15]. Cy
togenetic and molecular evaluation using FISH and RT-PCR can b
employed to detect the ETV6-NTRK3 transcript characteristic of CIF
and solidify the diagnosis. This is also useful in eventual treatmer
among patients with tumors not amenable to surgical treatment as tu
mors positive for the ETV6-NTRK3 transcript tend to be more sensitiv
to chemotherapy [16].

were not observed in any of the noncellular fibromatoses or in myofibromatoses [20]. The ETS variant gene 6-neurotrophin 3 receptor gene (*ETV6-NTRK3*) gene fusion product identified by RT-PCR has been recognized as diagnostic of infantile fibrosarcoma. *ETV6-NTRK3* transcript was present in 87.2% of patients where the investigation was performed by the European Pediatric Soft Tissue Sarcoma Study Group [19]. Pavlick *et al.* found that 9 out of 2031 advanced cancers from patients less than 21-years old (0.44%) harbored *NTRK* fusions [21]. Notably, four of these cases were in children less than 2-years old for which infantile fibrosarcoma was consid-

- La **localización del FSI** más frecuente en este estudio fue en tronco (43%), seguida de la localización en esqueleto axial (29%), en esqueleto distal (14%) y en cuello (14%), **en contraste con lo descrito en otros estudios**, donde la localización más frecuente es en extremidades, seguida de tronco y cabeza y cuello.

- El estudio citogenético mediante RT-PCR o FISH realizado en cinco de los pacientes de esta serie de casos, objetivó que **el 60%** de los casos se caracterizaba por presentar la translocación cromosómica t(12; 15) (p13; q25) y la fusión génica ETV6-NTRK3, lo que supone, aproximadamente, **un 20% menos de lo descrito en la literatura.**

VII SIMPOSIO GETTHI

Sesión 3: Vías de desarrollo de la oncología transversal (I)

"NTRK-Tumours": fundamentos biológicos y resultados clínicos

Rapid, complete and sustained tumour response to the TRK inhibitor larotrectinib in an infant with recurrent, chemotherapy-refractory infantile fibrosarcoma carrying the characteristic ETV6-NTRK3 gene fusion

S S Bielack [1], M C Cox [2], P Klothaki [3], P Müller-Ab[illegible] K Simon-Klingenstein [4], S[illegible]

Affiliations + expand

PMID: 32223937 DOI: 10[illegible]

Results: After 4 days on treatment, the parents noted that the index tumour was visibly smaller and softer. The rapid tumour regression continued over the following weeks. On day 56 of treatment, the first scheduled control MRI showed the target lesion had shrunk to 1.2×1.2×0.8 cm (ca. 0.6 cm^3), corresponding to a complete response according to the Response Evaluation Criteria In Solid Tumors version 1.1. This response was maintained over subsequent follow-up visits, and on day 112 at the second control MRI the target lymph node was completely normal. At last follow-up, the disease remained in complete remission after 16 months on larotrectinib, with negligible toxicity and no safety concerns.

Conclusion(s): Selective TRK inhibition by larotrectinib offers a novel, highly specific and highly effective therapeutic option for IFS carrying the characteristic ETV6-NTRK3 gene fusion. Its use should be considered when surgery is not feasible. (NCT02637687).

HHS Public Access

Author manuscript

N Engl J Med. Author manuscript; available in PMC 2018 August 22.

Published in final edited form as:

N Engl J Med. 2018 February 22; 378(8): 731–739. doi:10.1056/NEJMoa1714448.

Efficacy of Larotrectinib in *TRK* Fusion–Positive Cancers in Adults and Children

A. Drilon, T.W. Laetsch, S. Kummar, S.G. DuBois, U.N. Lassen, G.D. Demetri, M. Nathenson, R.C. Doebele, A.F. Farago, A.S. Pappo, B. Turpin, A. Dowlati, M.S. Brose, L. Mascarenhas, N. Federman, J. Berlin, W.S. El-Deiry, C. Baik, J. Deeken, V. Boni, R. Nagasubramanian, M. Taylor, E.R. Rudzinski, F. Meric-Bernstam, D.P.S. Sohal, P.C. Ma, L.E. Raez, J.F. Hechtman, R. Benayed, M. Ladanyi, B.B. Tuch, K. Ebata, S. Cruickshank, N.C. Ku, M.C. Cox, D.S. Hawkins, D.S. Hong, and **D.M. Hyman**

The use of neoadjuvant larotrectinib in the management of children with locally advanced TRK fusion sarcomas

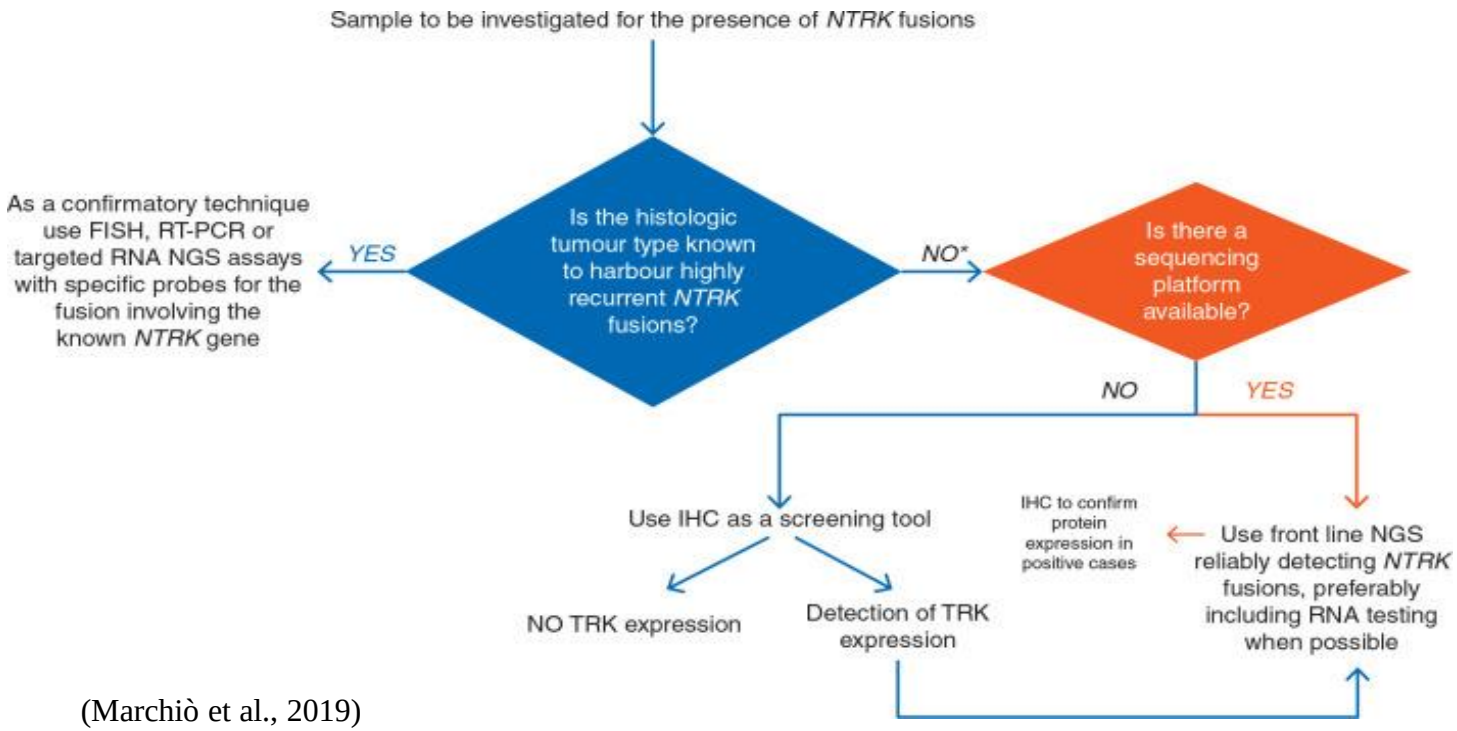
Steven G DuBois [1], Theodore W Laetsch [2], Noah Federman [3], Brian K Turpin [4], Catherine M Albert [5], Ramamoorthy Nagasubramanian [6], Megan E Anderson [7], Jessica L Davis [8], Hope E Qamoos [9], Mark E Reynolds [9], Scott Cruickshank [9], Michael C Cox [9], Douglas S Hawkins [5], Leo Mascarenhas [10], Alberto S Pappo [11]

Affiliations + expand

PMID: 30204247 PMCID: PMC6263791 DOI: 10.1002/cncr.31701

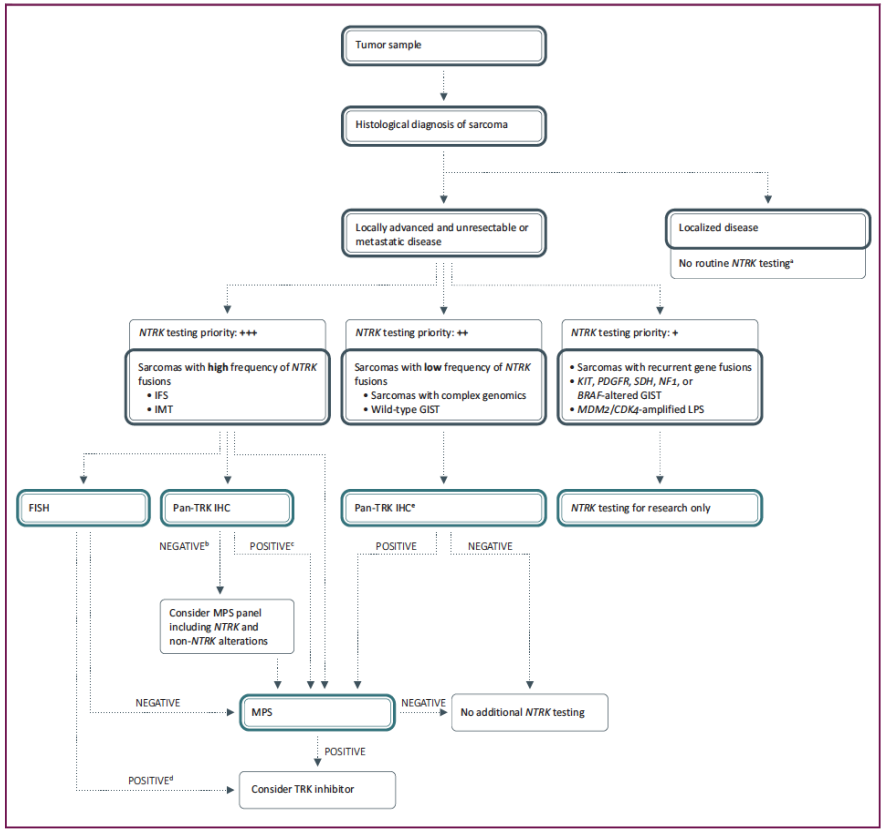
Conclusions: Children with locally advanced TRK fusion sarcomas may proceed to surgical resection after treatment with the selective TRK inhibitor larotrectinib, thereby sparing them the potentially significant morbidity noted with current approaches. These results support the evaluation of larotrectinib as presurgical therapy in children with newly diagnosed TRK fusion sarcomas.

- Algoritmo diagnóstico



(Marchiò et al., 2019)

Recommended algorithm of NTRK testing in sarcomas



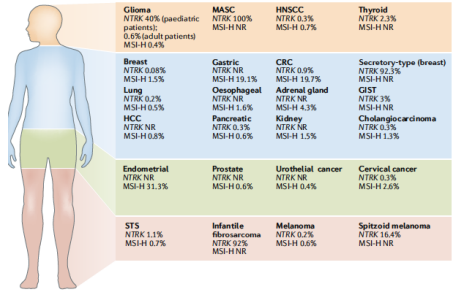
Demetri GD, et al. Ann Oncol. 2020;

- Importancia de la **implementación del abordaje tumor agnóstico** en la Oncología pediátrica, con el fin de alcanzar tratamientos individualizados, con mayor precisión y con menor tasa de efectos adversos y morbilidad asociados

- El abordaje tumor agnóstico podría ser una herramienta útil para llegar a conseguir una oncología pediátrica individualizada de calidad

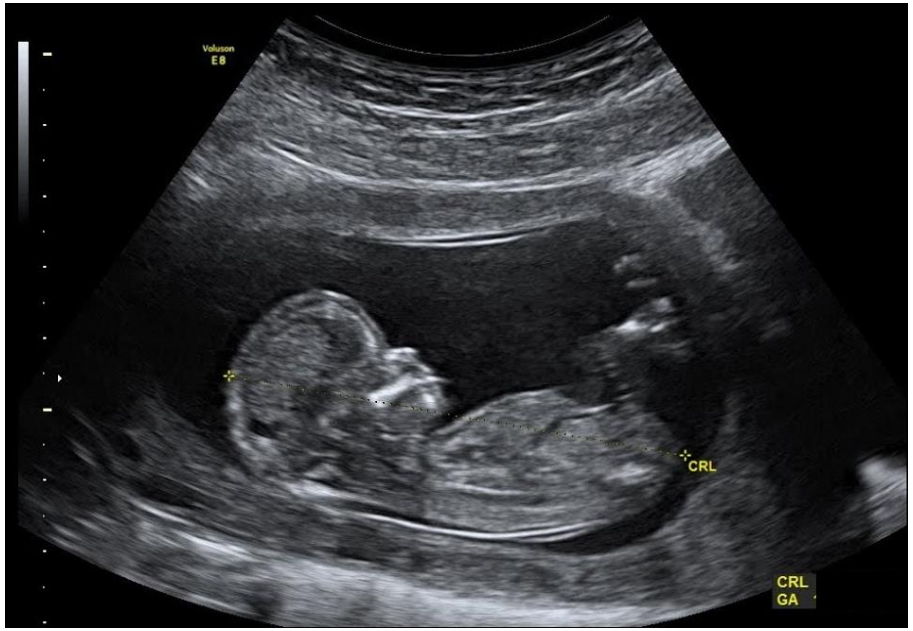
- La mayoría de los cánceres pediátricos no se han evaluado suficientemente para excluir la presencia de fusiones de TRK

- Por lo tanto, en niños con cualquier tumor sólido en recaída o refractario, se debe considerar la detección de fusiones de TRK, ya sea por IHC o por NGS, como parte de un perfil molecular amplio que también puede identificar otras dianas accionables



Pestana RC, et al. Nat Rev Clin Oncol. 2020

- Importancia de un **seguimiento adecuado durante el embarazo** mediante técnicas de imagen, como la ecografía, y de la **derivación temprana a centros de referencia** para el diagnóstico y tratamiento de sarcomas infantiles.



VII SIMPOSIO GETTHI

Sesión 3: Vías de desarrollo de la oncología transversal (I)

"NTRK-Tumours": fundamentos biológicos y resultados clínicos

UNIDAD DE TERAPIAS DIRIGIDAS EN CÁNCER INFANTIL

Adela Escudero López, PhD
Responsable de la Sección de Hematooncología Pediátrica. SºGenética (INGEMM)

Reunión de Terpias Dirigidas – Hospital Universitario la Paz
24 de junio de 2021

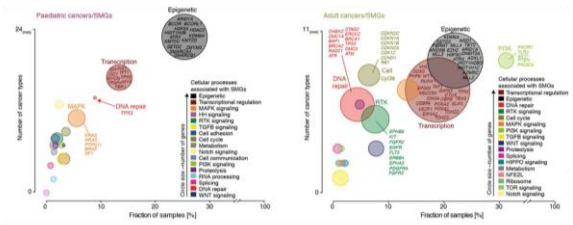
OTROS: Robot Eppendorf Hamilton, fragmentador COVARIS, termocicladores, equipo multiplexado, tplacas imantadas…

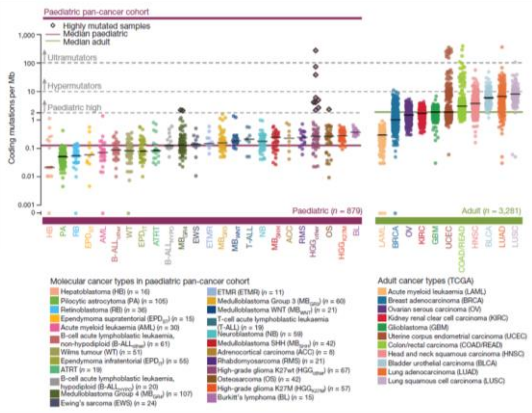
CORE DE GENÉTICA Y NGS (PREANALÍTICA-NGS-BIOINFORMÁTICA
- 3 FACULTATIVOS RESPONSABLES
- 8 TÉCNICOS DE LABORATORIO
- 3 BIOINFORMÁTICOS (2 ESPECIALIZADOS EN CÁNCER)

MÁS DE 10 AÑOS DE EXPERIENCIA EN NGS
MÁS DE 5000 MUESTRAS PROCESADAS POR NGS/AÑO
5 TECNOLOGÍAS
- 3 DE EXOMA
- TSO500 PARA CÁNCER DE PULMÓN
- CÁNCER HEREDITARIO

APOYO INVESTIGACIÓN

	PEDIATRIC	ADULT
Incidence	176 per 100,000	538,8 per 100,000
Cancer types	Leukemia/CNS	Breast/Lung/Prostate
Biology	Embryonal	Carcinoma
Somatic mutations	Limited	Abundant
Gene types	Different mutational profile	





Grobner et al. The landscape of genomic alterations across childhood cancers 2018

VII SIMPOSIO GETTHI

Sesión 3: Vías de desarrollo de la oncología transversal (I)

"NTRK-Tumours": fundamentos biológicos y resultados clínicos

SOMÁTICO

>100 pacientes diagnosticados de cáncer en edad pediática

27 pacientes Recaída/refreactarios

9/27 pacientes Terapia dirigida (30%)

5 pacientes recibieron

2 pacientes pendientes de recibirlo

3 pacientes respondieron

HULP: COMITÉ DE MEDICINA DE PRECISIÓN (V 9.00-10.00H)

SEHOP
SOCIEDAD ESPAÑOLA DE HEMATOLOGÍA Y ONCOLOGÍA PEDIÁTRICAS

MOLECULAR TUMOR BOARD

LEGEND cost

Innovative Therapies for Children with Cancer
ITCC European Consortium

Innovative Therapies for Children with Cancer in Europe

Prevalencia de alteraciones en tumores sólidos[1-4]

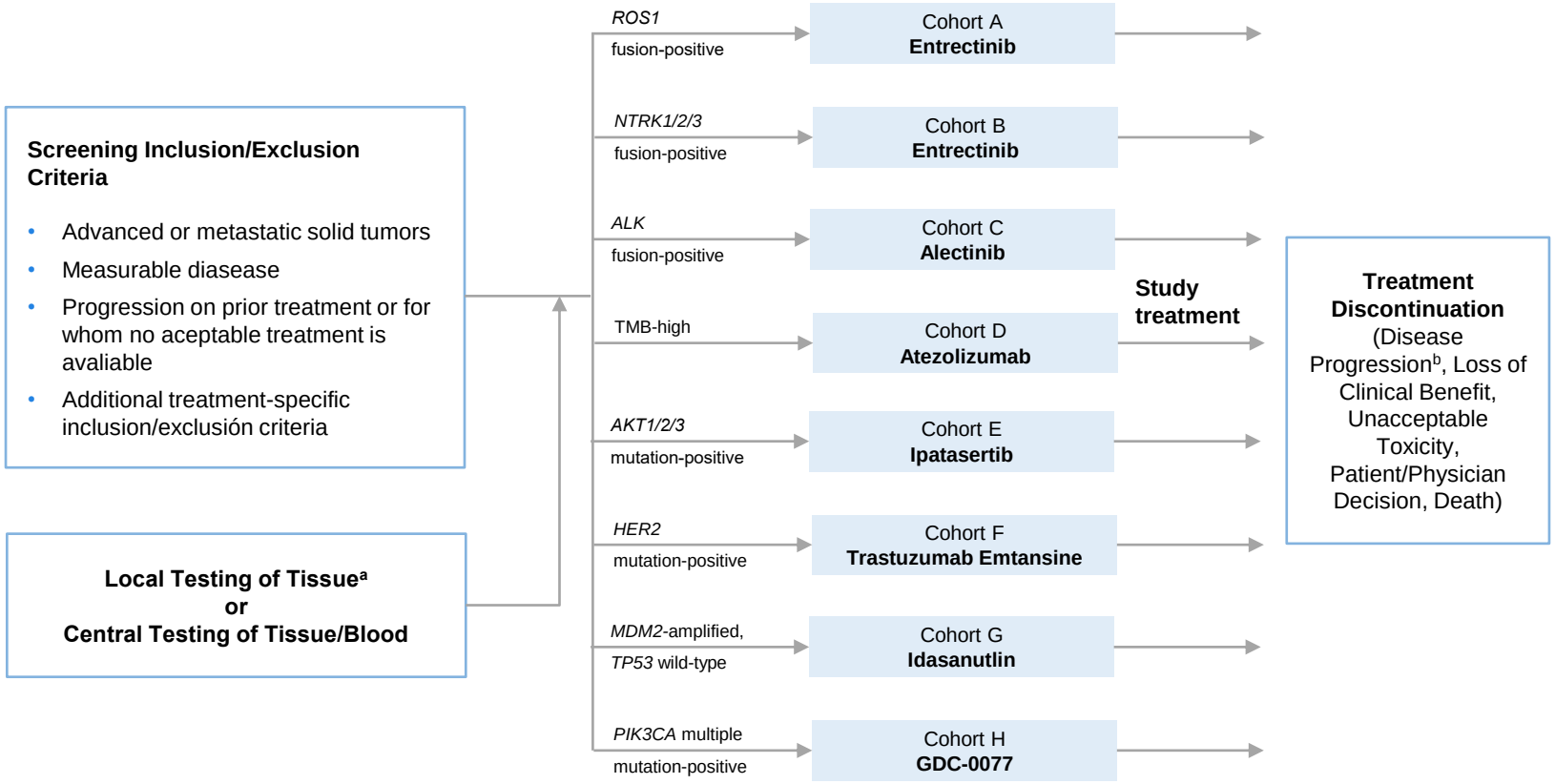
Cada uno de los 8 brazos de TAPISTRY se dirige a una población de pacientes con un biomarcador de **baja a muy, muy baja prevalencia.**

Biomarcador	Frecuencia
Fusión ROS1 (no NSCLC)	0,05%
Fusión NTRK1/2/3	0,10%
Fusión ALK (no NSCLC)	0,11%
Múltiples mutaciones PIK3CA	0,88%
Mutación AKT1/2/3	0,98%
Mutación HER2	1,48%
Amplificación MDM2, tipo salvaje TP53	2,58%
TMB alta (≥ 16 mut/Mb)	8,49%

1. Hartmaier RJ, Albacker LA, Chmielecki J, et al. High-Throughput Genomic Profiling of Adult Solid Tumors Reveals Novel Insights into Cancer Pathogenesis. Cancer Res. 2017;77(9):2464-2475. 2 Foundation Medicine 2019. 3. Ross JS, Ali SM, Fasan O, et al. ALK Fusions in a Wide Variety of Tumor Types Respond to Anti-ALK Targeted Therapy. Oncologist. 2017;22(12):1444-1450. 4. Schumacher TN, Schreiber RD. Neoantigens in cancer immunotherapy. Science. 2015;348(6230):69-74.

Estudio TAPISTRY[1]

Estudio de fase II, global, multicéntrico, abierto, de múltiples cohortes en pacientes con tumores sólidos no resecables, localmente avanzados o metastásicos que albergan alteraciones genómicas oncogénicas específicas o que tienen un nivel alto de TMB según lo identificado por un ensayo NGS.



1. https://clinicaltrials.gov/ct2/show/NCT04589845.

PROTOCOLO DE TERAPIAS DIRIGIDAS

Adela Escudero López, PhD
Responsable de la Sección de Hematooncología Pediátrica. SºGenética (INGEMM)
Reunión de Terpias Dirigidas – Hospital Universitario la Paz
24 de junio de 2021

La **caracterización genética y molecular** de todos los **tumores sólidos en población infantil** para ofrecer a los pacientes el **tratamiento** que mejor se adapte a su circunstancia, ya sea mediante la inclusión en un ensayo clínico si lo hubiera disponible, o mediante uso compasivo si se considera que es la mejor opción terapéutica para el paciente

¿A QUÉ TIPO DE TUMORES VA DIRIGIDO?

TODOS los tumores sólidos infantiles:

- Piezas o biopsias quirúrgicas
- Biopsias por radiología intervencionista donde sea factible lograr muestra suficiente

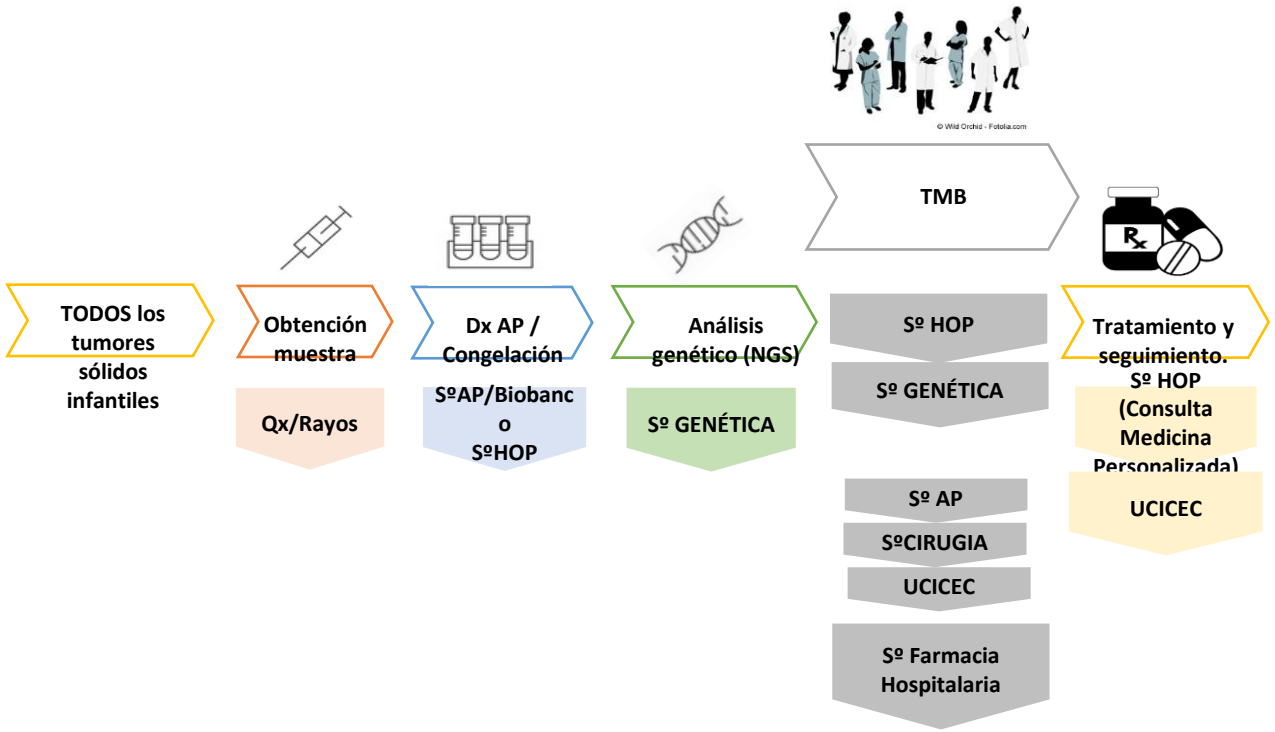
Al **DIAGNÓSTICO** o en la primera intervención que se le realice tras haber recibido tratamiento sistémico

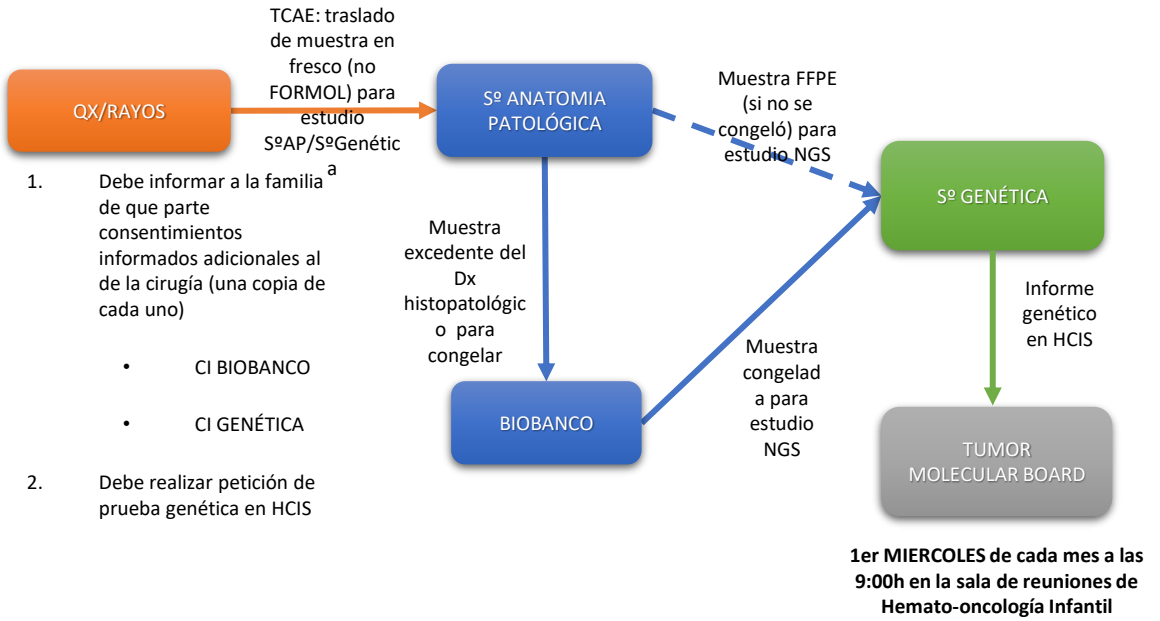
En caso de **RECAÍDAS**, si es posible obtener nuevas muestras

VII SIMPOSIO GETTHI

Sesión 3: Vías de desarrollo de la oncología transversal (I)

"NTRK-Tumours": fundamentos biológicos y resultados clínicos





- **Tipo de panel y versión**: mut4C v1
- **Nº de genes totales**: 622 genes
- **Nº de genes analizados** (relacionados con la patología)
  - DIANAS (191 genes)
  - LEUKEMIA (98 genes)
  - LEUKEMIA+FASTRACK (231 genes)

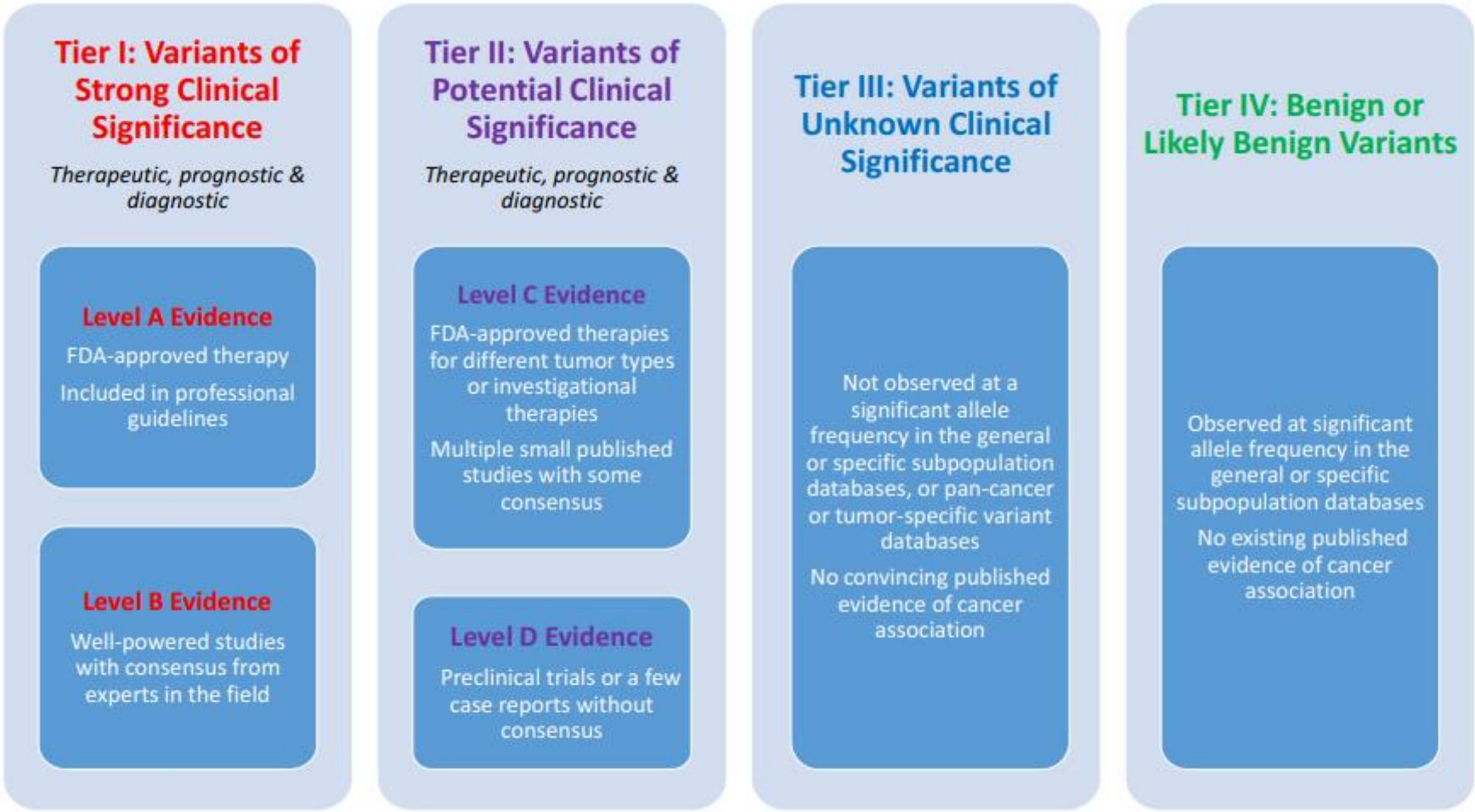
The ESMO scale for clinical actionability of molecular targets: ESCAT

Tier 1 – Ready for routine clinical use			
ESCAT evidence tier	**Required level of evidence**	**Clinical value class**	**Clinical implication**
I: Alteration-drug match is associated with improved outcome in clinical trials	I-A: prospective, randomised clinical trials show the alteration-drug match in a specific tumour type results in a clinically meaningful improvement of a survival end point I-B: prospective, non-randomised clinical trials show that the alteration-drug match in a specific tumour type results in clinically meaningful benefit as defined by ESMO MCBS 1.1 1-C: clinical trials across tumour types or basket clinical trials show clinical benefit associated with the alteration-drug match, with similar benefit observed across tumour types	Drug administered to patients with the specific molecular alteration has led to improved clinical outcome in prospective clinical trial(s)	Access to the treatment should be considered standard of care

- The new guidelines include six levels of clinical evidence for decision making according to implications for patient management

  - Tier I, targets ready for implementation in routine clinical decisions;
  - Tier II, investigational targets that likely define a patient population that benefits from a targeted drug but additional data are needed;
  - Tier III, clinical benefit previously demonstrated in other tumour types or for similar molecular targets;
  - Tier IV, preclinical evidence of actionability;
  - Tier V, evidence supporting co-targeting approaches; and
  - Tier X, lack of evidence for actionability.

- Grupo de trabajo de somáticas INGEMM (onco adultos, pediátrico y malformaciones vasculares)



VII SIMPOSIO GETTHI

Sesión 3: Vías de desarrollo de la oncología transversal (I)

"NTRK-Tumours": fundamentos biológicos y resultados clínicos

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RESEARCH (IdiPAZ)

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Carla Martín PhD
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Alfonso Navarro
Carmen Mestre
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Alicia Pernás

UCICEC/JACIE

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Victor Galán
Ana Sastre Urgellés
Diego Plaza López de Sabando
Pedro Rubio Aparicio
Isabel Martínez Romera

ADVANCED THERAPY UNIT PRODUCTION

Isabel Mirones PhD
Marta Cobo
Gema Casado

HEMATOLOGY AND CELL THERAPY

Raquel de Paz Arias PhD
Mercedes Gassior
Antonio Marcos
Ana Romero

GETTHI

Grupo Español de Oncología Transversal y Tumores Huérfanos e Infrecuentes

VII SIMPOSIO GETTHI

Sesión 3: Vías de desarrollo de la oncología transversal (I)

2 de diciembre de 2021 - *Formato virtual*

"NTRK-Tumours": fundamentos biológicos y resultados clínicos

Antonio Pérez-Martínez, Hospital Universitario La Paz, Madrid