Approcci di medicina personalizzata in Oncologia

Antonella Isacchi

Director Biotechnology & Kinase Platform Coordinator

Nerviano Medical Sciences

6 luglio 2018

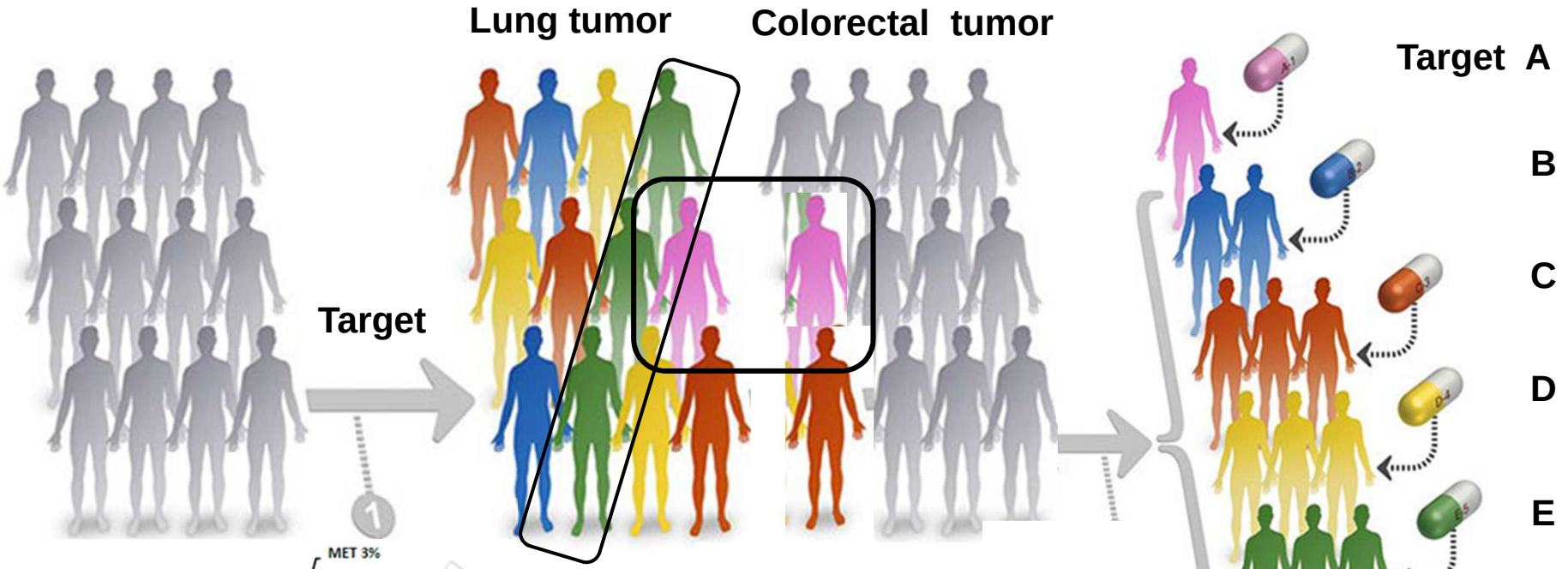
Nerviano Medical Sciences (NMS)

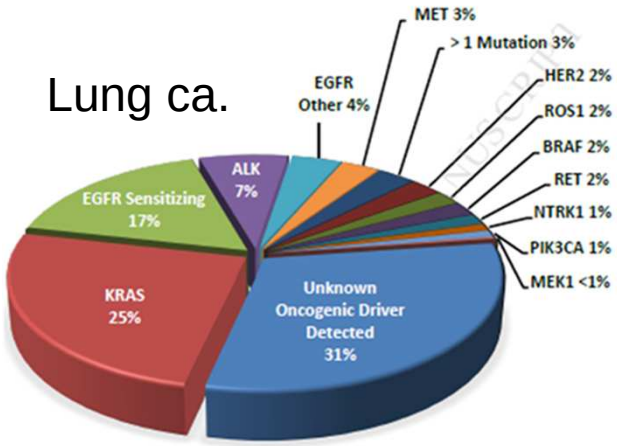
NERVIANO MEDICAL SCIENCES

- Nerviano Medical Sciences (NMS) is a research-based company dedicated to the discovery and development of innovative drugs for the treatment of cancer.
- NMS has a fully integrated R&D expertise from target identification and discovery to preclinical and clinical development, with proven capability to bring innovative oncology drugs to the clinic.
- We cover all operational aspects of preclinical drug development and manufacturing through our affiliates.

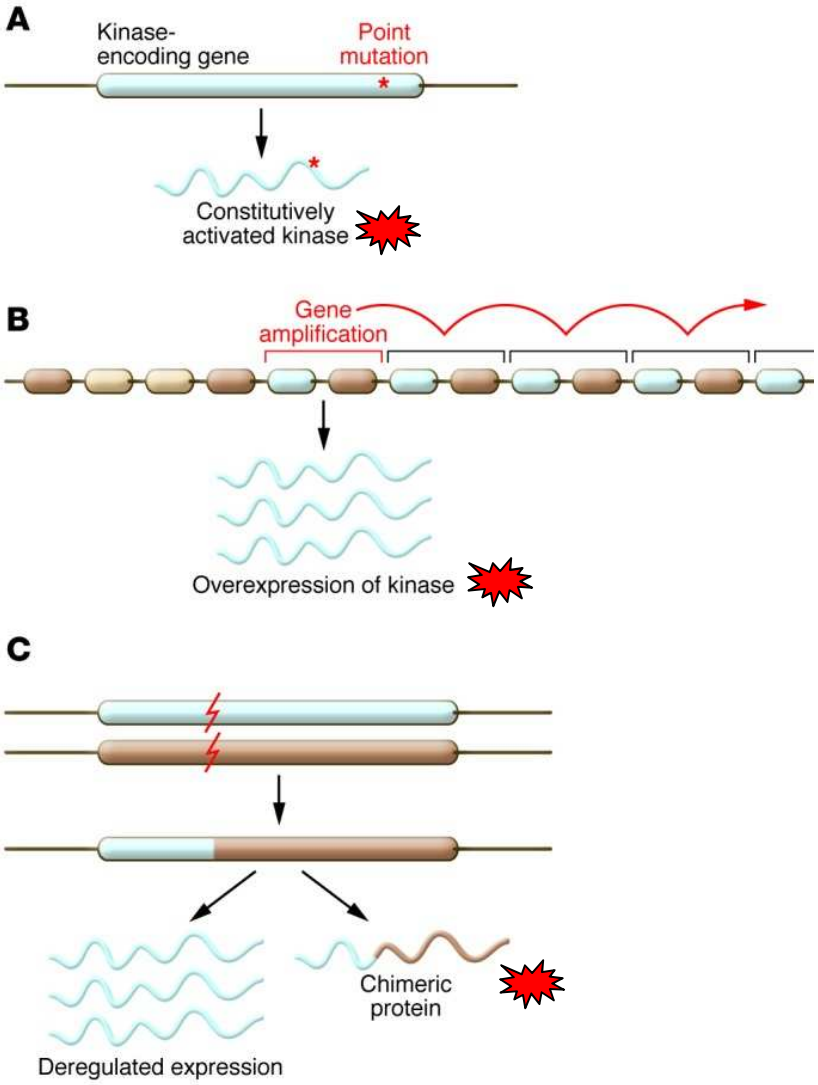
Personalized medicine in Oncology

Treatment designed to meet specific characteristics of individual patient's tumor





Kinases are activated by genomic alterations in tumor subsets



Kinases are a large family of enzymes that control many cellular processes

They are very important drug targets because:

✓ They become activated in cancers due to genetic alterations: biological relevance

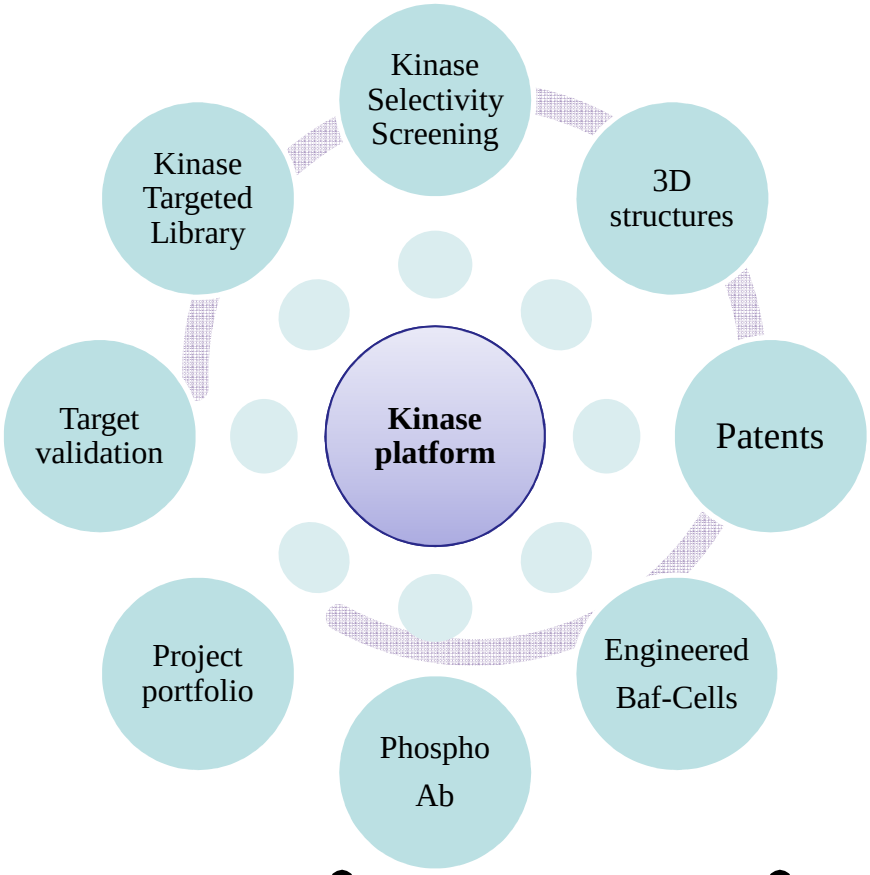
✓ They can be inhibited by drugs that bind the conserved ATP pocket : druggability

Modified from:
Targeting cancer with kinase inhibitors
Gross et al. J. Clin. Inv. (2015)

The Kinase platform

Economy of scale and project growth

- An infrastructure of know how and tools specific for kinases
- A proprietary kinase target libraries of 90,000+ compounds (from 100 chemical classes with extensive patent coverage)
- The platform facilitates the progression of all kinase projects from target to clinical candidate
- It generates economy of scale and secures growth of our project portfolio



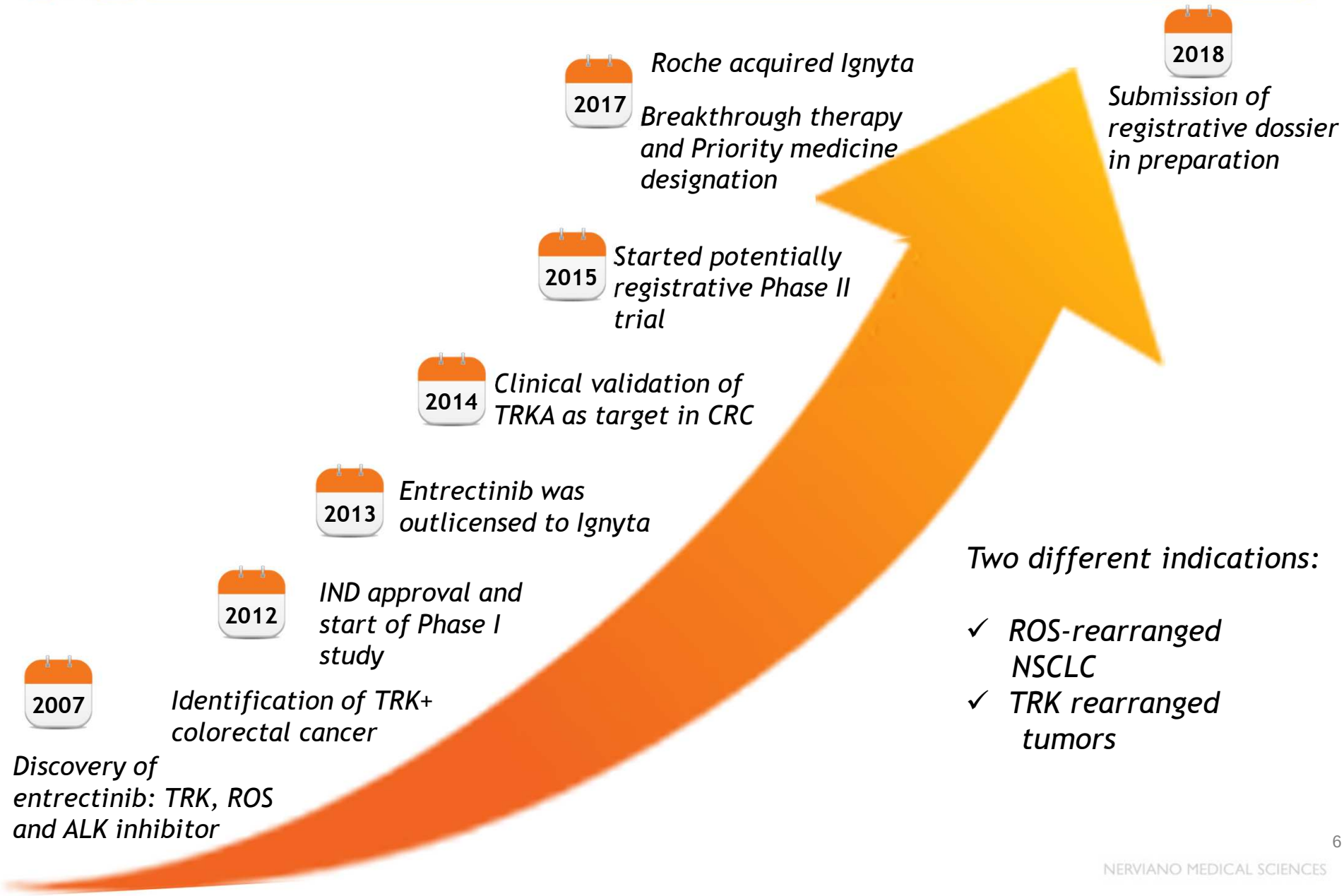
Kinase Targeted Library (KTL)
90,000+ proprietary cpds
ATP/purine competitors
Robust IP position

Kinase Selectivity Screening (KSS)
>100 kinase assays
fully automatized
> 800,000 IC50s

Kinase 3D Structures
In house protein production and crystallization
ca. 500 structures solved

Tumor cell lines
> 30 kinase dep. cell lines
> 500 tumor cell lines with genomic background

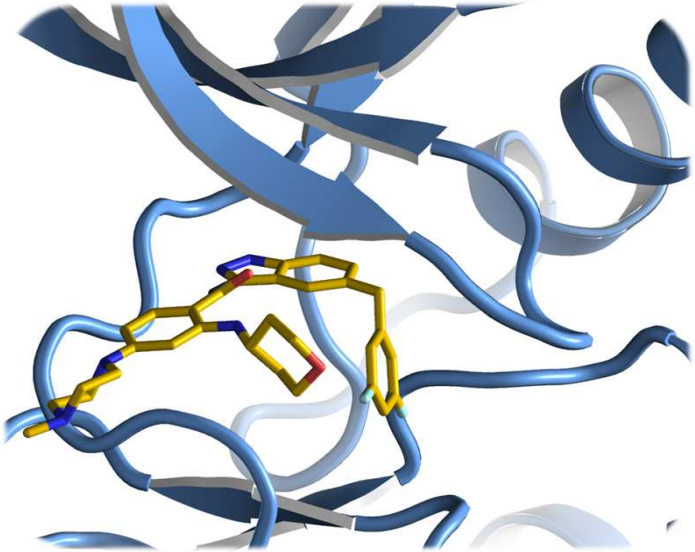
Entrectinib - A success story

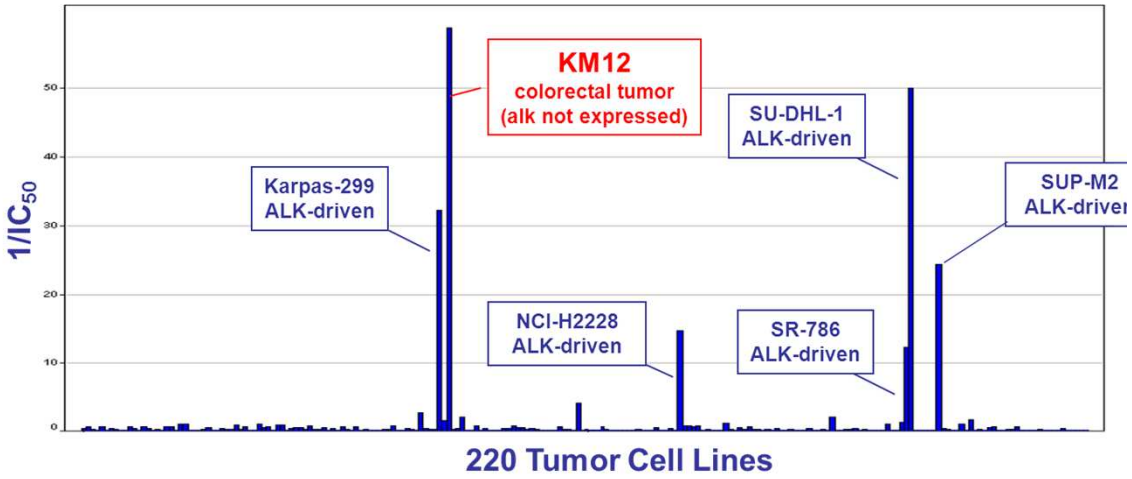


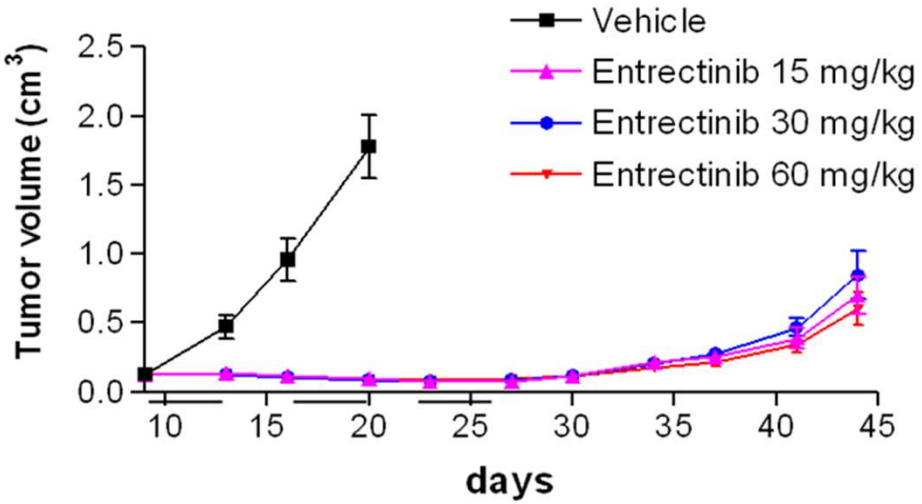
Two different indications:

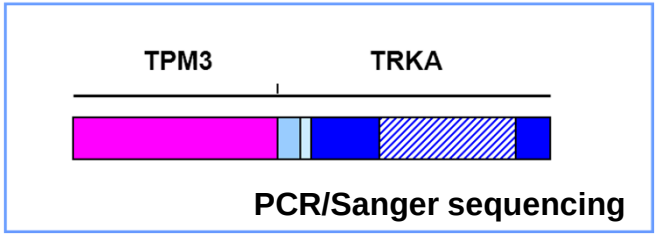
- ✓ *ROS-rearranged NSCLC*
- ✓ *TRK rearranged tumors*

CRC cell line driven by TRKA rearrangement is sensitive to entrectinib

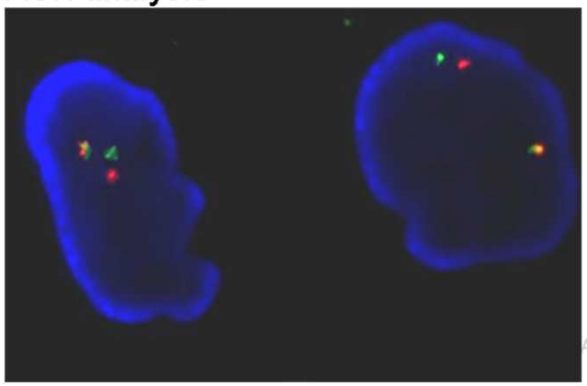






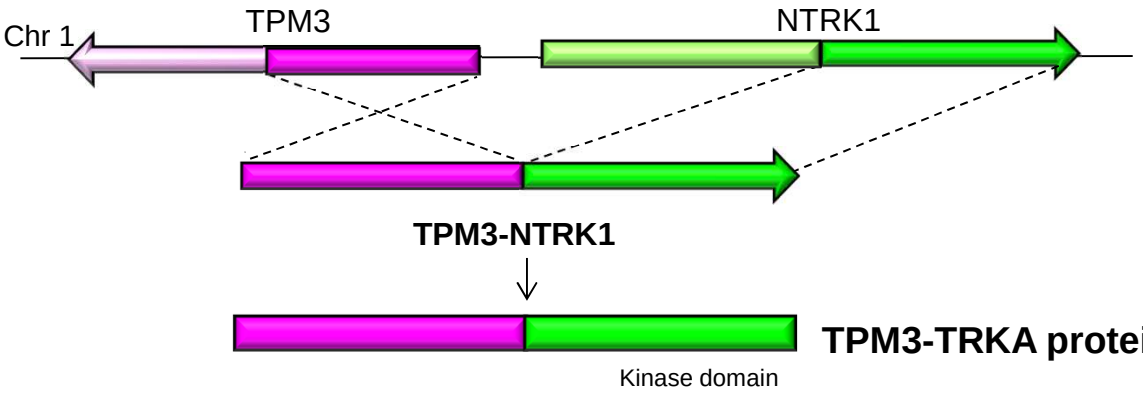


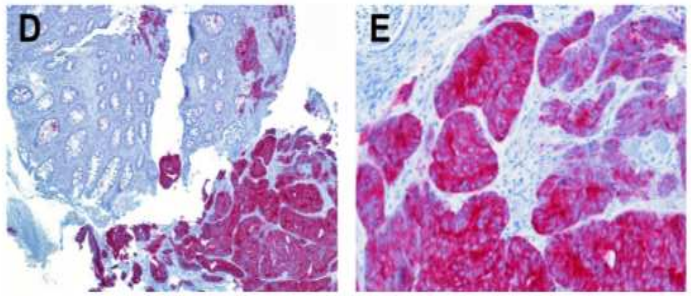
FISH analysis



Identification of TRK rearrangements in CRC tumors

TMP3-TRKA rearrangement in colorectal cancer patient

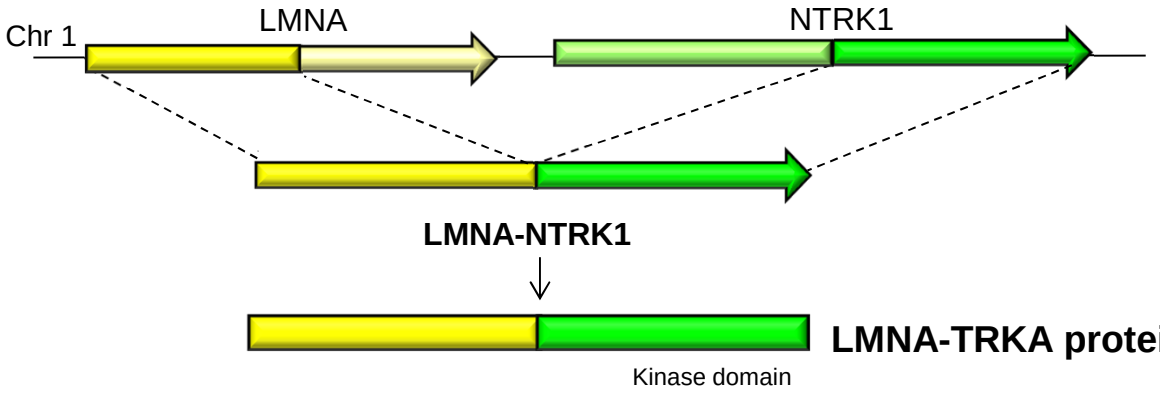


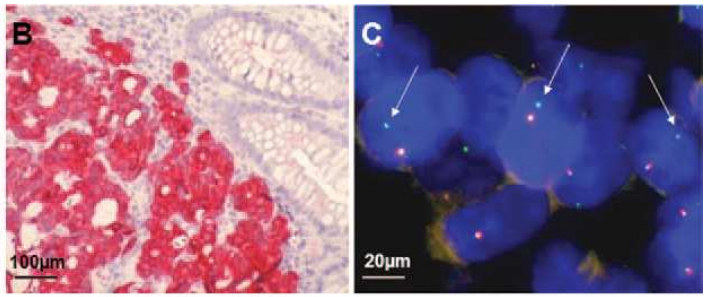


Identified by PCR/Sanger sequencing and IHC

Ardini E et al. Molecular Oncology 2014

LMNA-TRKA rearrangement in colorectal cancer patient





Identified by RACE and IHC

Sartore-Bianchi A et al. J Natl Cancer Inst. 2015

Identification of TRKA as a target in CRC patients

OXFORD

JNCI J Natl Cancer Inst (2016) 108(1): djv306

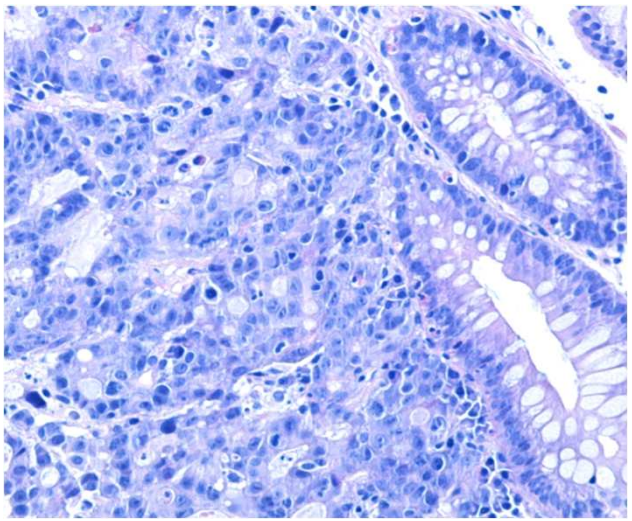
doi:10.1093/jnci/djv306
First published online November 12, 2015
Brief Communication

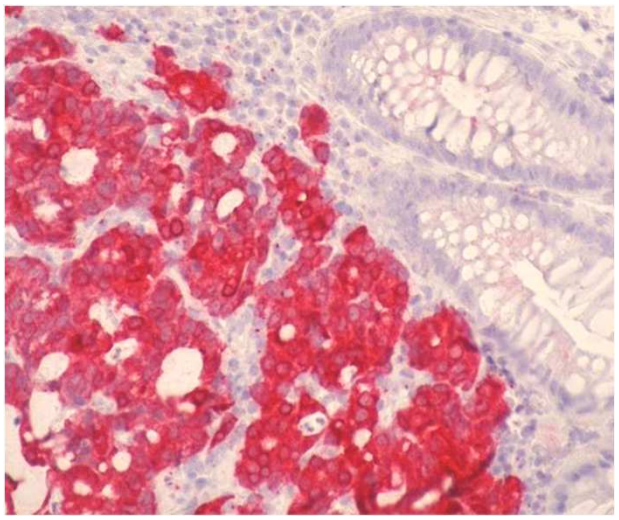
BRIEF COMMUNICATION

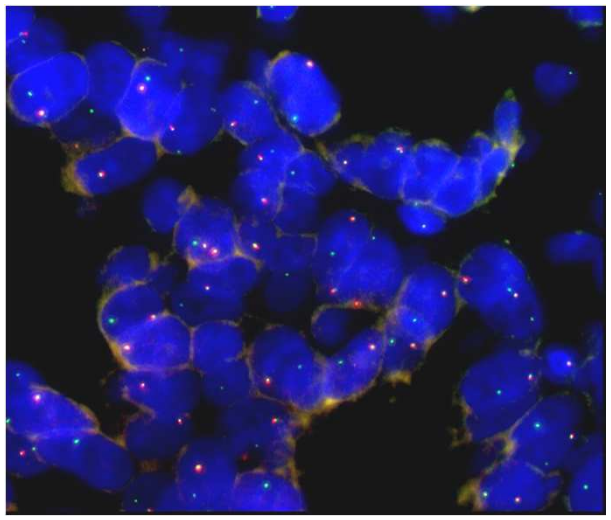
Sensitivity to Entrectinib Associated With a Novel LMNA-NTRK1 Gene Fusion in Metastatic Colorectal Cancer

Andrea Sartore-Bianchi, Elena Ardini, Roberta Bosotti, Alessio Amatu, Emanuele Valtorta, Alessio Somaschini, Laura Raddrizzani, Laura Palmeri, Patrizia Banfi, Erica Bonazzina, Sandra Misale, Giovanna Marrapese, Antonella Leone, Rachele Alzani, David Luo, Zachary Hornby, Jonathan Lim, Silvio Veronese, Angelo Vanzulli, Alberto Bardelli, Marcella Martignoni, Cristina Davite, Arturo Galvani, Antonella Isacchi, Salvatore Siena

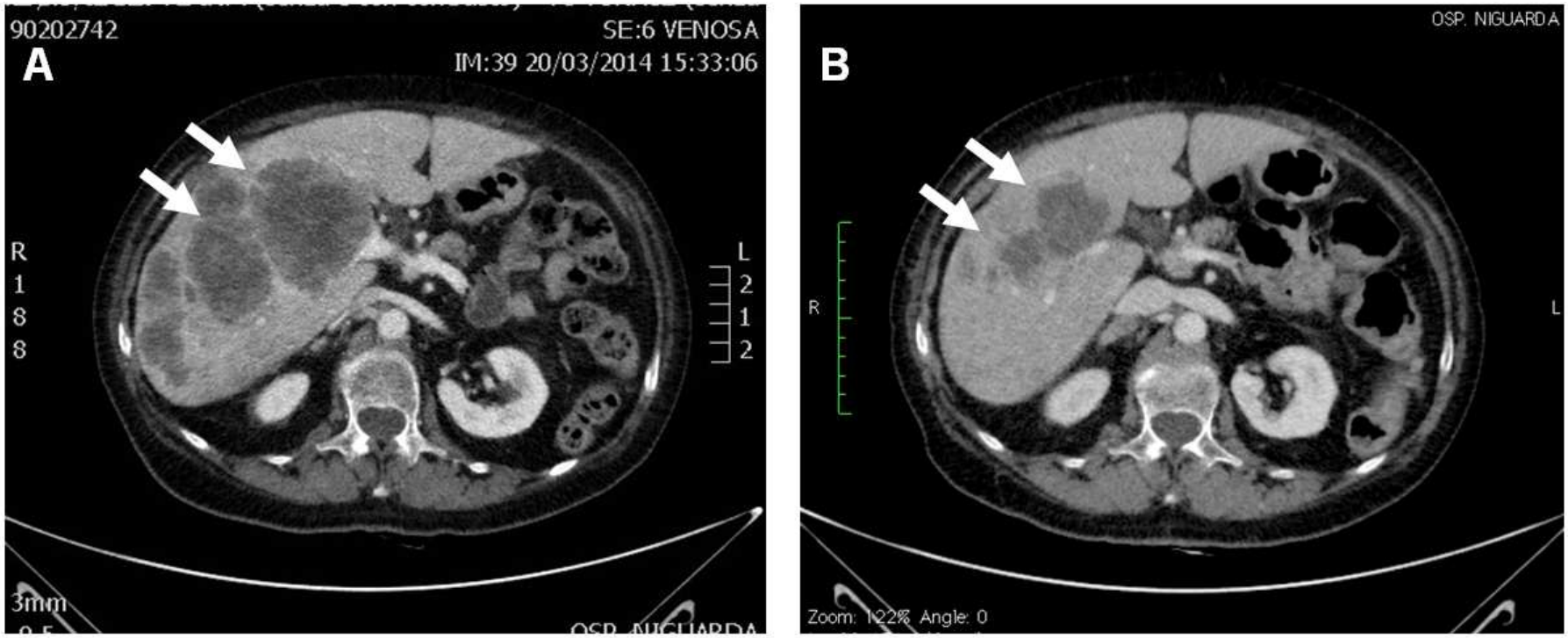
Affiliations of authors: Niguarda Cancer Center, Ospedale Niguarda Ca' Granda, Milan, Italy (ASB, AA, EV, LP, EB, GM, SV, AV, SS); Nerviano Medical Sciences S.r.l Nerviano, Milan, Italy (EA, RB, AS, LR, PB, AL, RA, AG, AI); Candiolo Cancer Institute – FPO, IRCCS, Candiolo, Torino, Italy (SM, AB); University of Torino, Department of Oncology, Candiolo, Torino, Italy (AB); FIRC Institute of Molecular Oncology (IFOM), Milano, Italy (SM); Ignyta, Inc., San Diego, CA (DL, ZH, JL); Clioss S.r.l. Nerviano, Milan, Italy (MM, CD); Università degli Studi di Milano, Milan, Italy (SS).







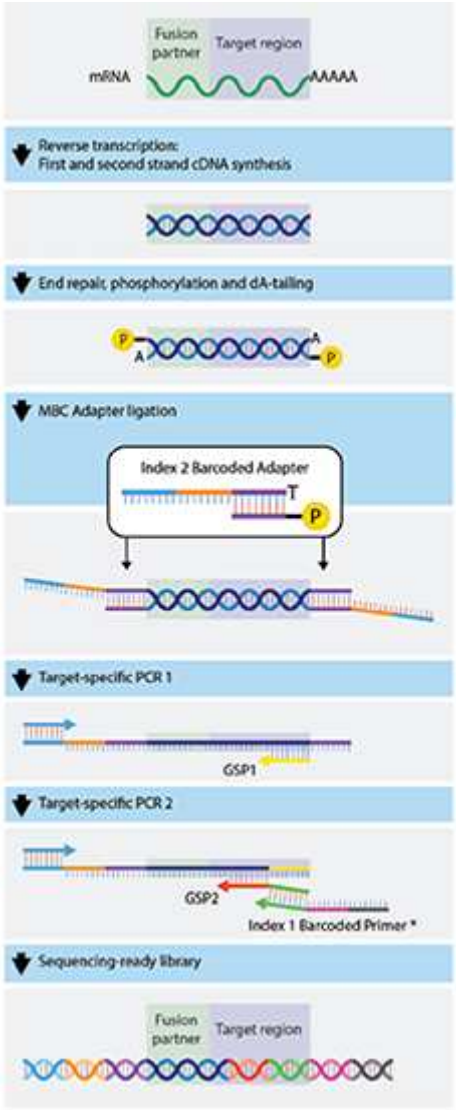
Clinical validation of TRKA as a target in CRC patients



CT Scans Showing the Response to Entrectinib.
The baseline abdominal CT scan of March 2014 shows massive liver involvement with largest lesions originating in hepatic segments 7 and 5 measuring 9 and 8.5 cm in longest diameter, respectively (**Panel A**, arrows). After one cycle of treatment with Entrectinib, objective tumor response as per Response Evaluation Criteria in Solid Tumors (RECIST) criteria was ascertained with the hepatic masses in the same segments measuring 6.5 and 5.3 cm (**Panel B**, arrows).

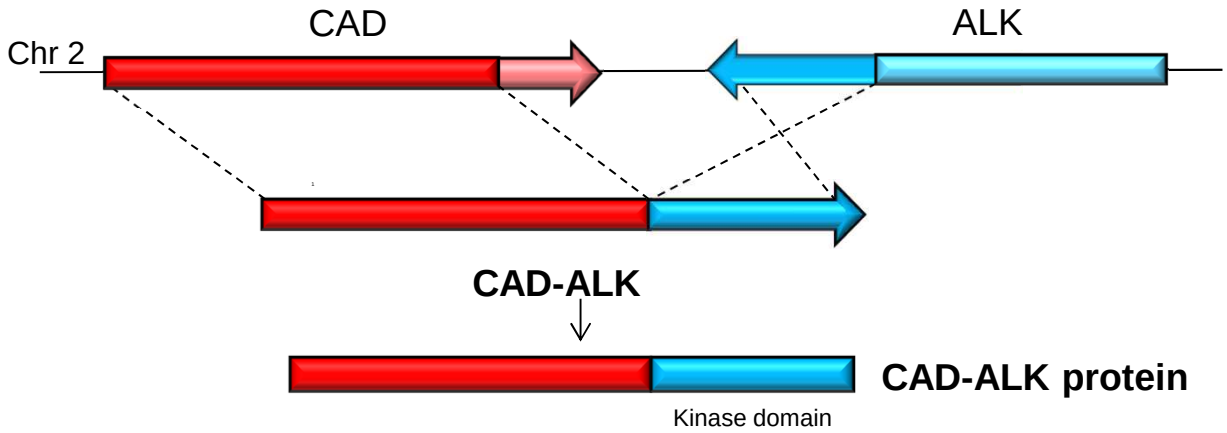
From: Sartore-Bianchi et al J Natl Cancer Inst. 2015; 108: djv306

Identification of ALK and TRK rearrangement in CRC by NGS



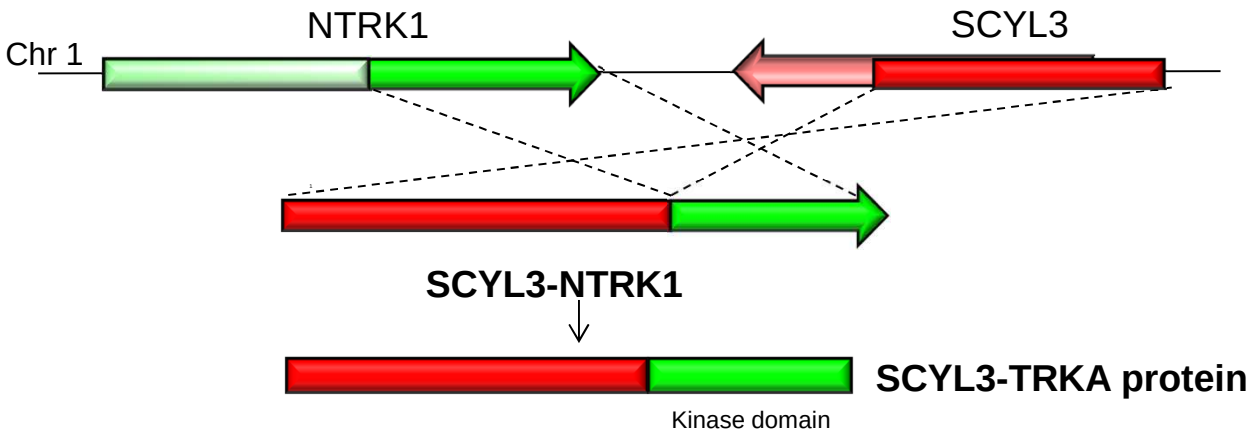
NGS *Archer*® FusionPlex®

CAD-ALK rearrangement in colorectal cancer patient



Amatu et al., Br J Cancer.2015

SCYL3-NTRK1 rearrangement in colorectal cancer patient



Milione M et al., Oncotarget 2017

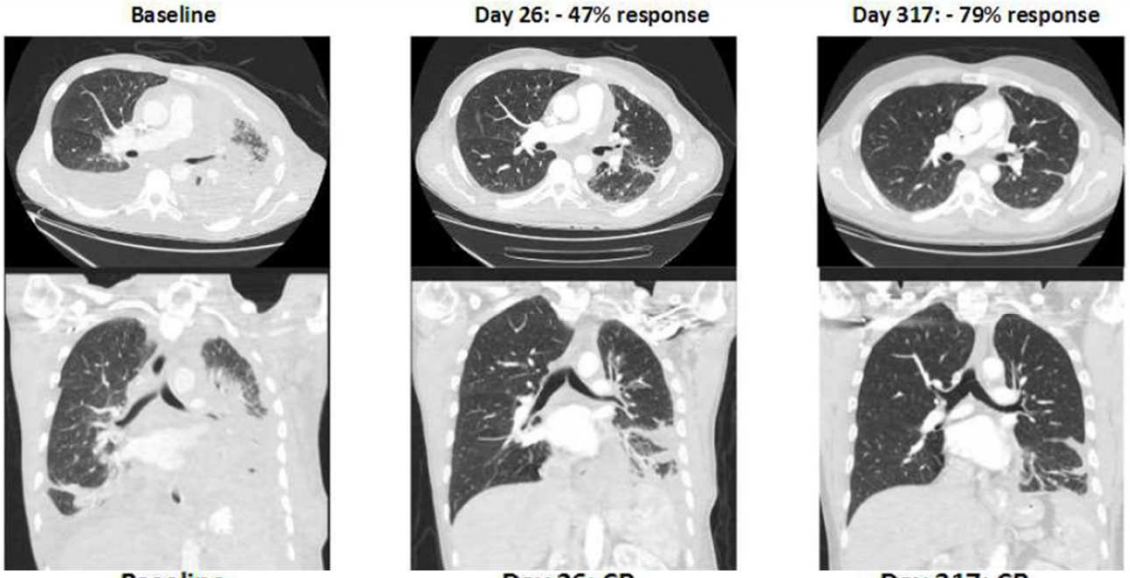
NTRK1, 2 and 3 are rearranged in different tumor types

Table 1 Reported gene fusions involving NTRK genes along with the corresponding tumour

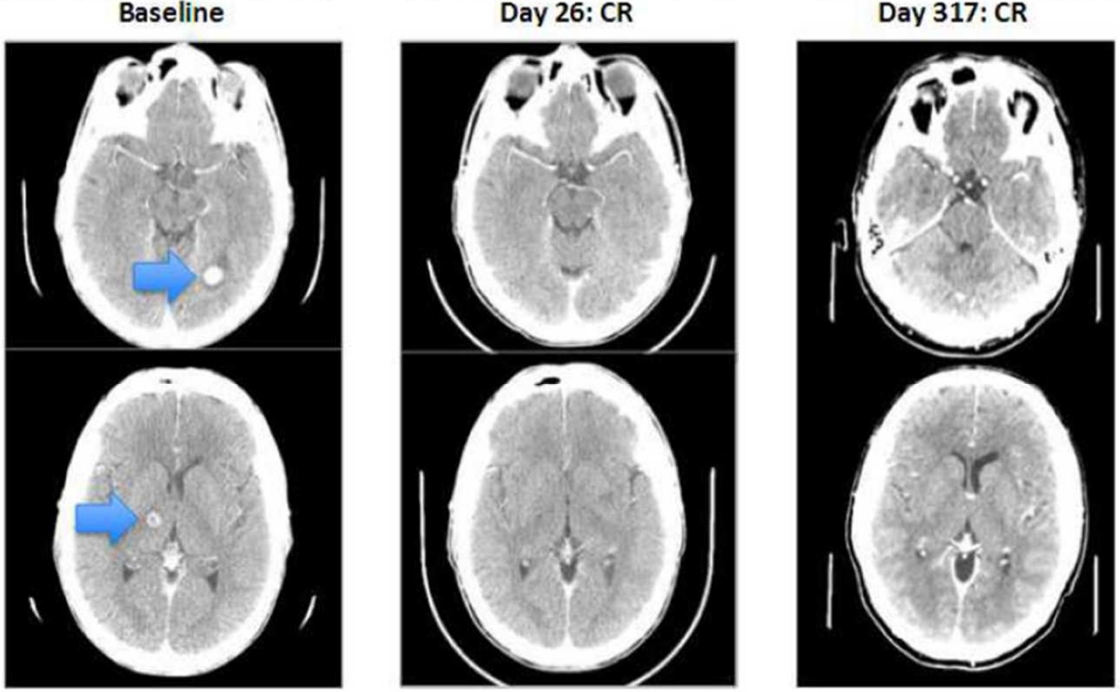
Gene fusion	Cancer type	Authors (year)
NTRK1		
LMNA-NTRK1	Colorectal	Sartore-Bianchi *et al* (2016)
	Soft tissue sarcoma	Doebele *et al* (2015)
	Spitzoid melanomas	Wiesner *et al* (2014)
	AYA sarcoma	Morosini *et al* (2015)
	Congenital infantile fibrosarcoma	Wong *et al* (2015)
TPM3-NTRK1	Colorectal	Lee *et al* (2015), Créancier *et al* (2015), Ardini *et al* (2014)
	Papillary thyroid carcinomas	Bongarzone *et al* (1989), Butti *et al* (1995)
	Glioblastoma	Wu *et al* (2014)
SQSTM1-NTRK1	NSCLC	Farago *et al* (2015)
NTRK1-SQSTM1	NSCLC	Siena *et al* (2015)
NFASC-NTRK1	Glioblastoma multiforme	Frattini *et al* (2013), Kim *et al* (2014)
BCAN-NTRK1	Glioblastoma multiforme	Kim *et al* (2014), Frattini *et al* (2013)
PPL-NTRK1	Thyroid carcinoma	Farago *et al* (2015)
RFWD2-NTRK1	Large cell neuroendocrine tumour (lung)	Fernandez-Cuesta *et al* (2014)
CD74-NTRK1	Lung adenocarcinomas	Vaishnavi *et al* (2013)
MPRIP-NTRK1	Lung adenocarcinomas	Vaishnavi *et al* (2013)
RABGAP1L-NTRK1	ICC	Ross *et al* (2014)
TFG-NTRK1	Thyroid carcinomas	Greco *et al* (1995)
TP53-NTRK1	Spitzoid melanomas	Wiesner *et al* (2014)
NTRK2		
Unknown-NTRK1	Appendiceal adenocarcinoma	Braghiroli *et al* (2016)
AFAP1-NTRK2	Low-grade glioma	Stransky *et al* (2014)
AGBL4-NTRK2	Glioblastoma	Wu *et al* (2014)
NACC2-NTRK2	Pilocytic astrocytomas	Jones *et al* (2013)
PAN3-NTRK2	Head and neck squamous cell carcinoma	Wu *et al* (2014)
QKI-NTRK2	Pilocytic astrocytomas	Jones *et al* (2013)
TRIM24-NTRK2	Lung adenocarcinoma	Wu *et al* (2014)
VCL-NTRK2	Glioblastoma	Wu *et al* (2014)
NTRK3		
ETV6-NTRK3	Glioblastoma	Zhang *et al* (2013)
	Glioblastoma	Wu *et al* (2014)
	MASC	Tognon *et al* (2002), Ito *et al* (2015), Del Castillo *et al* (2015)
	Ductal carcinoma	Makretsov *et al* (2004), Arce *et al* (2005), Lagree *et al* (2011), Pinto *et al* (2014)
	Fibrosarcoma	Morerio *et al* (2004), Punnett *et al* (2000)
	Congenital mesoblastic nephroma	Watanabe *et al* (2002)
	Radiation-associated thyroid cancer	Leeman-Neill *et al* (2014)
	AML	Kralik *et al* (2011), Eguchi *et al* (1999), Knezevich *et al* (1998)
	GIST	Brenca *et al* (2015)
	MASC of salivary gland	Urano *et al* (2015), Skàlovà *et al* (2015)
	Papillary thyroid cancer	Leeman-Neill *et al* (2014), Seungbok Lee *et al* (2014)
	Colorectal	Hechtman *et al* (2015)
BTBD1-NTRK3	Glioblastoma	Wu *et al* (2014)

Modified from Amatu etal. ESMO open

Entrectinib clinical efficacy in a TRK positive lung patient



Extracranial Response



Intracranial Response

Remains on entrectinib and clinically progression-free at >12 months

Images courtesy of Farago and Shaw, MGH

Stop fRETting the Target: Next-Generation RET Inhibitors Have Arrived

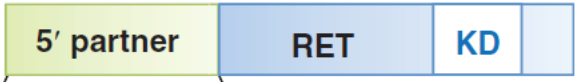
Wade T. Iams[1] and Christine M. Lovly[2]

July 2018 CANCER DISCOVERY

RET-driven cancers

RET fusions

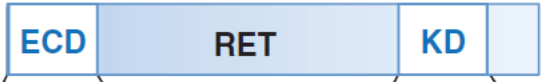
NSCLC (~1%–2%)[4]
PTC (~10%)[4]
Pancreatic cancer (<1%)[3]



KIF5B	NCOA4	TBLXR1
CCDC6	GOLGA5	FGFR1OP
NCOA	TRIM24	EML4
TRIM33	TRIM27	EPHA5
CUX1	KTN1	SQSTM1
KIAA1217	RFG9	PARD3
FRMD4A	ERC1	PICALM
KIAA1468	HOOK3	AFAP1L2
CCDC6	PCM1	PPFIBP2
PRKAR1A	AKAP13	ACBD5
FKBP15	SPECC1L	MYH13

RET mutations

MTC (>60%)[4]
Breast cancer (<1%)[3]
Endometrial cancer (<1%)[3]
Merkel cell carcinoma (<1%)[3]
Colorectal cancer (<1%)[3]
Sarcoma (<1%)[3]
Melanoma (<1%)[3]
Gastric cancer (<1%)[3]



C634W	C630R/Y	E768D	Y806C
G533C	D631Y	L790F	A883F
C609F/G/R/S/Y	C634F/G/R/S/W/Y	Y791F	S891A
C611F/G/S/Y/W	K666E	V804M	M918T
C618F/R/S	C620F/R/S	V804L	

RET inhibitors

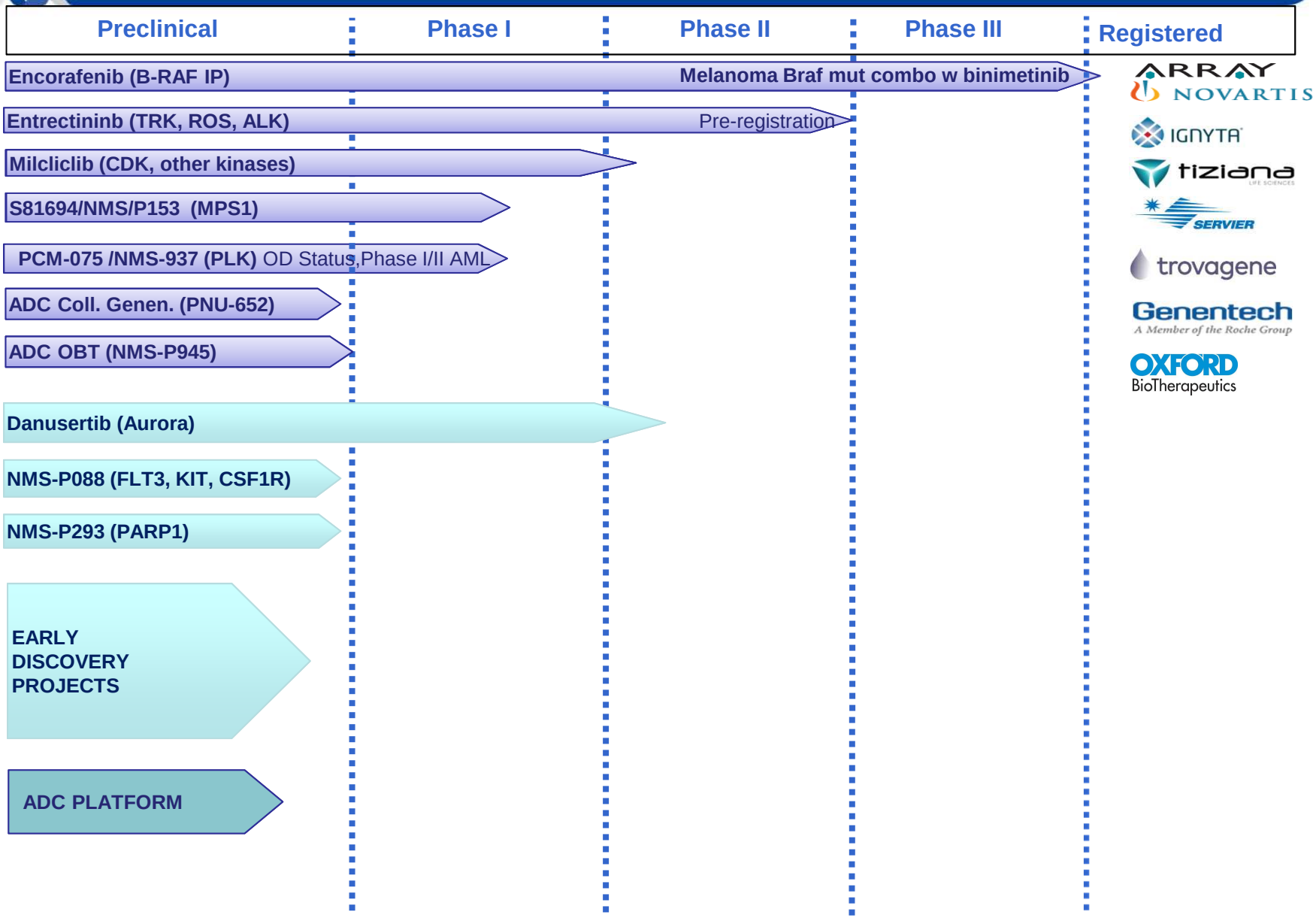
MKIs that target RET

Vandetanib
Cabozantinib
RXDX-105
Lenvatinib
Sorafenib
Sunitinib
Dovitinib
Alectinib
Ponatinib
Regorafenib
Nintedanib
Apatinib
Motesanib

"Next-generation" RET inhibitors

BLU-667
LOXO-292

NMS Oncology Project Pipeline



For further information, please visit: www.nervianoms.com