DATOS CLÍNICOS EN TUMORES PORTADORES DE FUSIÓN NTRK
PUESTA AL DÍA

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Disclosure Information

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- Speaking: MSD, Bristol-Myers, Roche, Boehringer Ingelheim, Pfizer, Novartis, Astra-Zeneca, Lilly, Takeda, Bayer
- Grant support: None
- Other: None

INNOVATION CHANGES THE GAME…

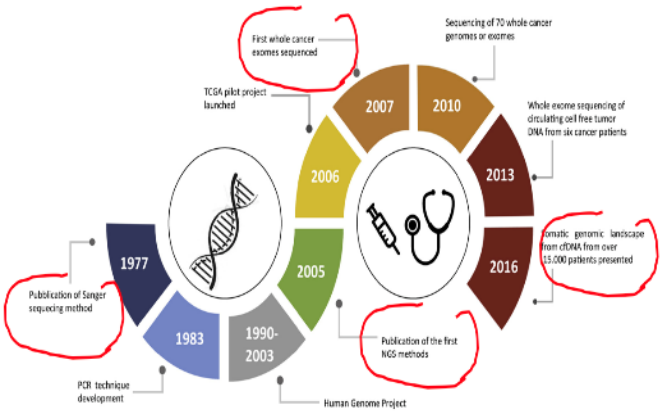
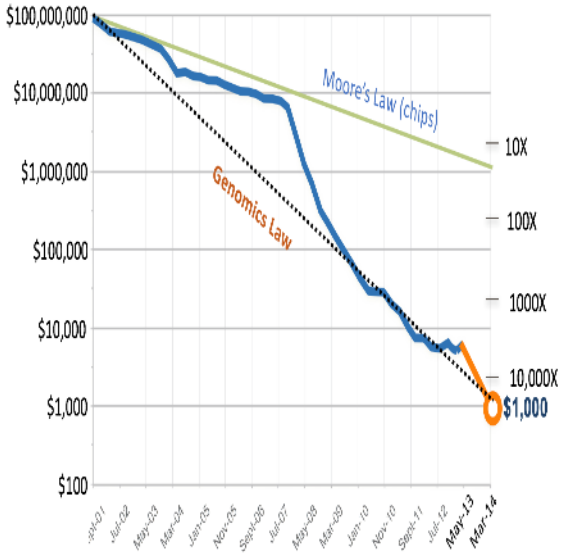


Fig. 1. Timeline of major achievements in sequencing technologies.

Morganti S, et al. Crit Rev Oncol 2019



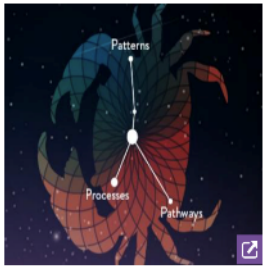
The Cancer Genome Atlas Program

The Cancer Genome Atlas (TCGA), a landmark cancer genomics program, molecularly characterized over 20,000 primary cancer and matched normal samples spanning 33 cancer types. This joint effort between the National Cancer Institute and the National Human Genome Research Institute began in 2006, bringing together researchers from diverse disciplines and multiple institutions.

Over the next dozen years, TCGA generated over 2.5 petabytes of genomic, epigenomic, transcriptomic, and proteomic data. The data, which has already lead to improvements in our ability to diagnose, treat, and prevent cancer, will remain publicly available for anyone in the research community to use.

TCGA Outcomes & Impact

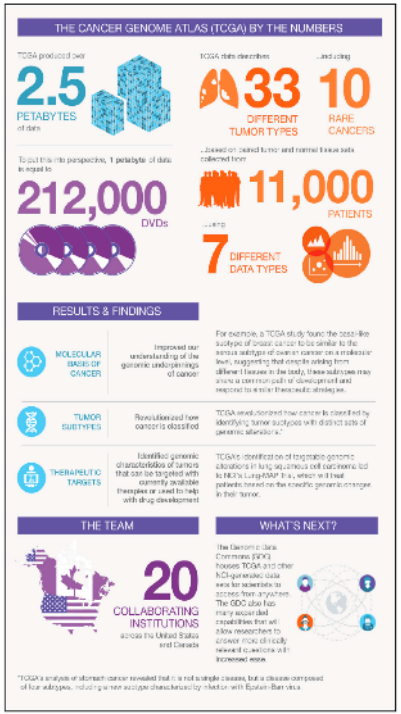
TCGA has changed our understanding of cancer, how research is conducted, how the disease is treated in the clinic, and more.



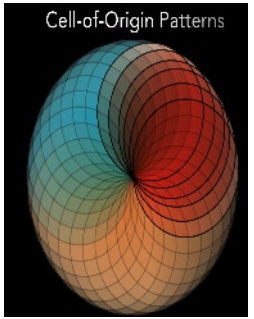
TCGA's PanCancer Atlas

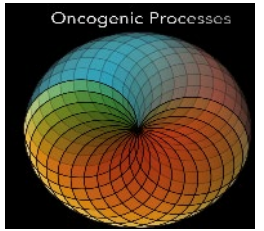
A collection of cross-cancer analyses delving into overarching themes on cancer, including cell-of-origin patterns, oncogenic processes and signaling pathways. Published in 2018 at the program's close.

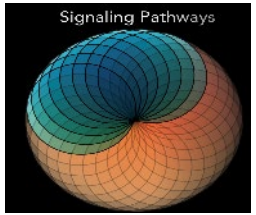
https://www.cancer.gov › research › structural-genomics



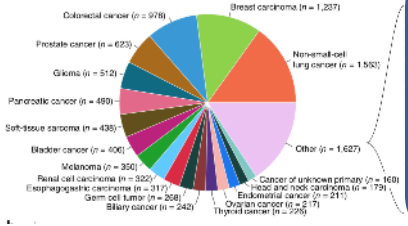
Hutter C, Cell 2018

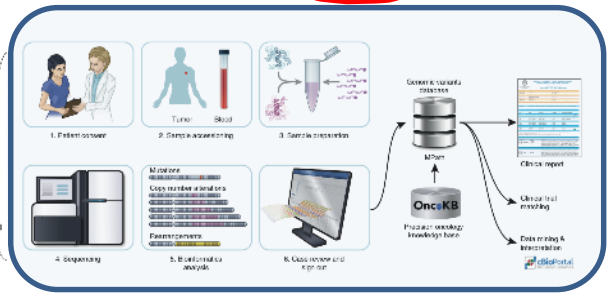


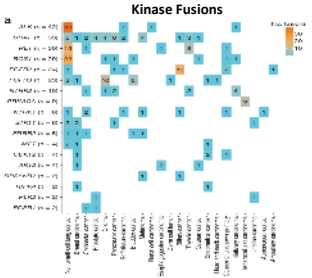


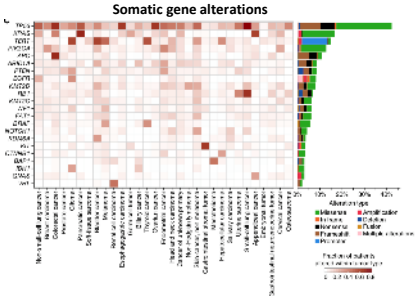


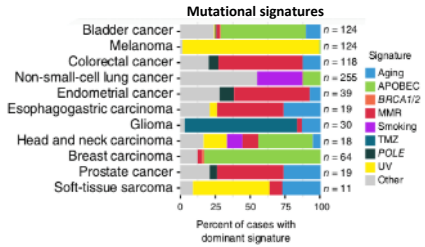
Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients

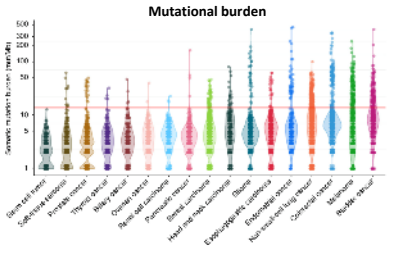






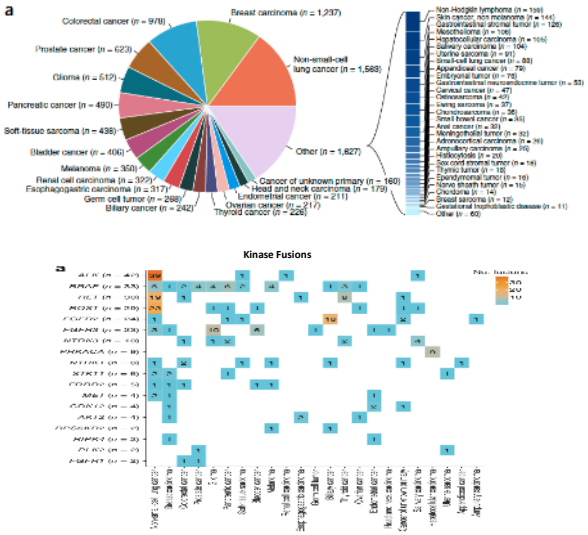






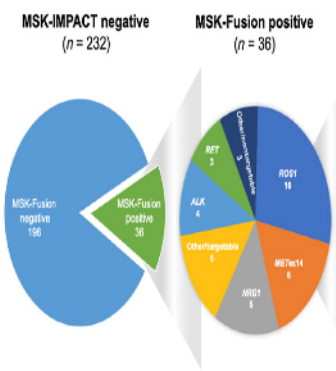
Zehir, Nature Medicine 2017

DNA vs RNA: RNA sequencing can maximize the likelihood of driver detection conjuntion with DNA sequencing



Zehir, Nature Medicine 2017

RNA –seq may rescue 14% fusions: 92% actionable



Clinical benefit of matched targeted therapy (n = 10)

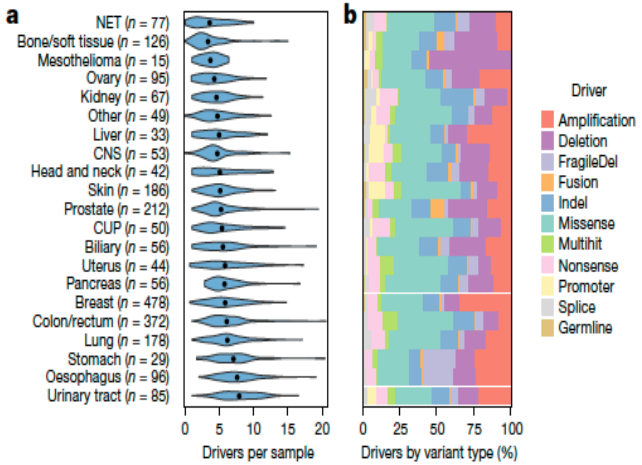
Rearrangement	Matched therapy	Best response*
EML4-ALK	Alectinib	SD
CD74-ROS1	Entrectinib	SD
SQSTM1-NTRK3	Larotrectinib	PR**
STRN-NTRK2	Larotrectinib	SD
CD74-ROS1	Entrectinib	PR**
CD74-NRG1	Afatanib	SD
MET Exon14 Skipping	Crizotinib	SD
SLC34A2-ROS1	Crizotinib	PD
SLC34A2-ROS1	Crizotinib	SD
SDC4-NRG1	Afatinib	PD

Benayed R, et al. Clin Cancer Res 2019

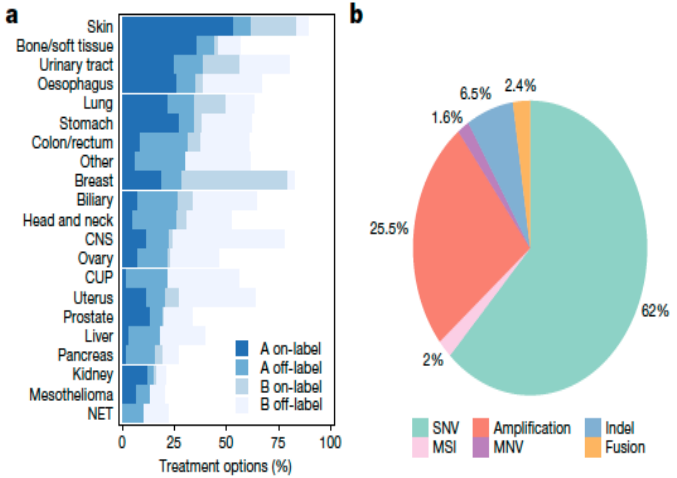
Treatment decisions may be complex: PRIORITAZING

Which driver gene alterations or pathway changes must guide targeted therapy selection?

The mean number of total driver was 5.7



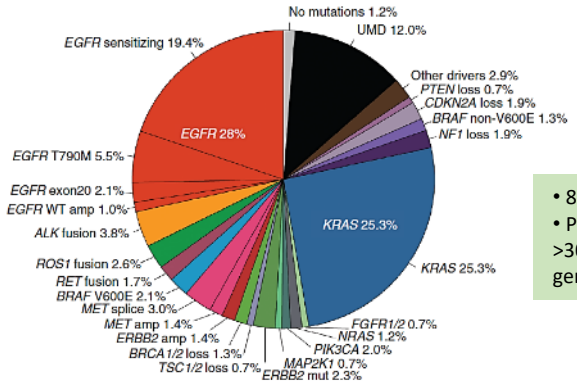
Clinical association and actionability



Priestley et al. Nature 2019

A NEW TREATMENT PARADIGM

Molecular subtyping of pulmonary adenocarcinoma in 2020



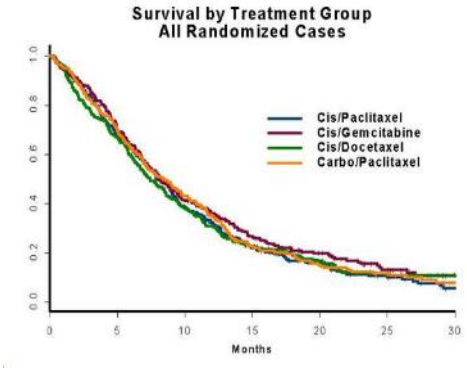
- 860 patients
- Prospective analysis of >300 cancer-associated genes

87% of potentially actionable alterations

Jordan EJ, et al. Cancer Discov 2017

Believers or non believers…

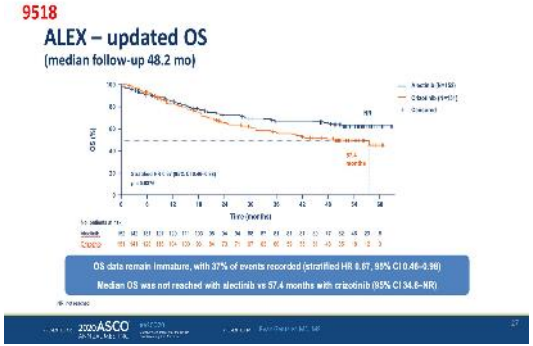
UNSELECTED POPULATION



ORR: 20-30%
mPFS: 5-6 months
mOS: 8-10 months
2 year survival rate: 11%
5 year survival rate: 0%

Schiller J, et al. N Enl J Med 2012

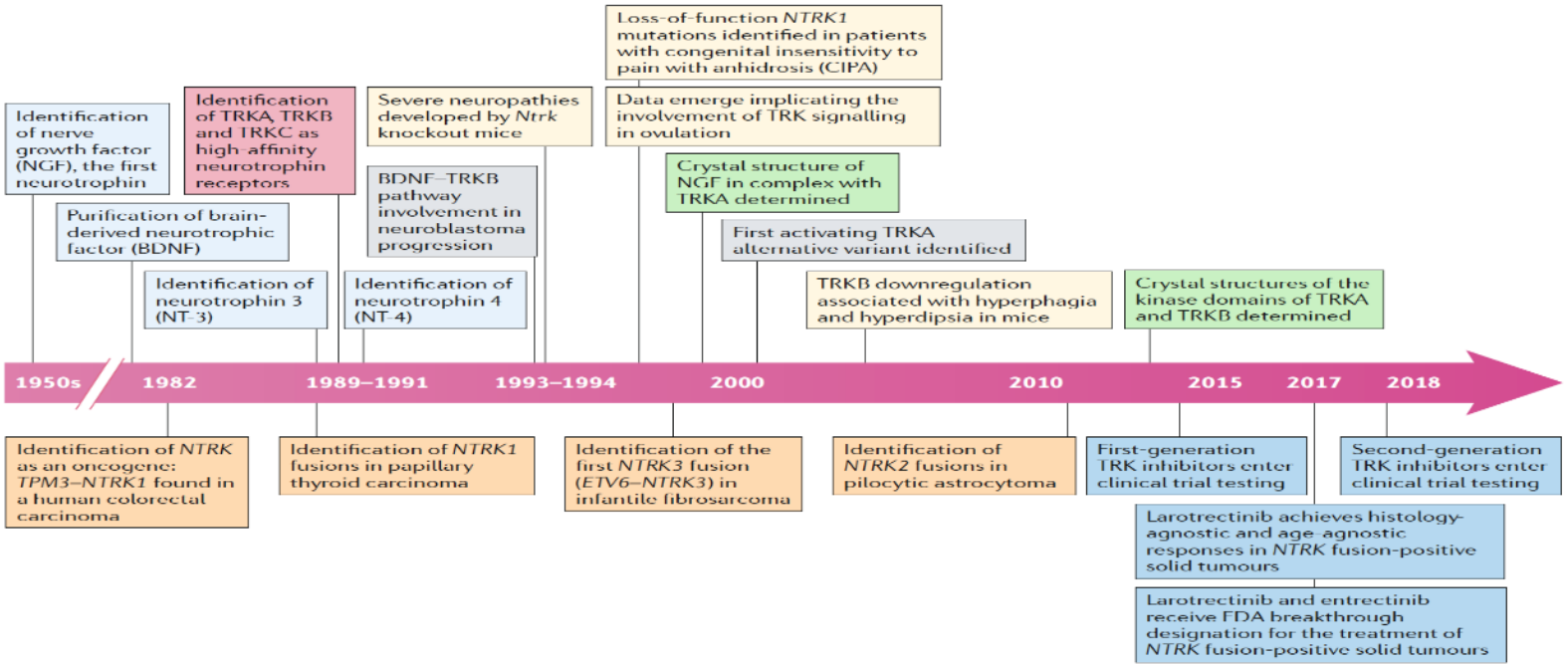
ALK +NSCLC



ORR: 80%
mPFS: <u>34m</u>
mOS: NR
2 year survival rate: 72%
5 year survival rate: 64%

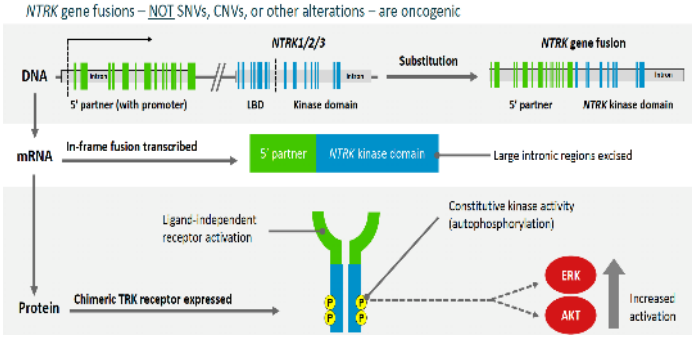
Peters S, N Engl J Med 2018
Peters S, ASCO 2020

A not so new target… but the best example of agnostic target: NTRK

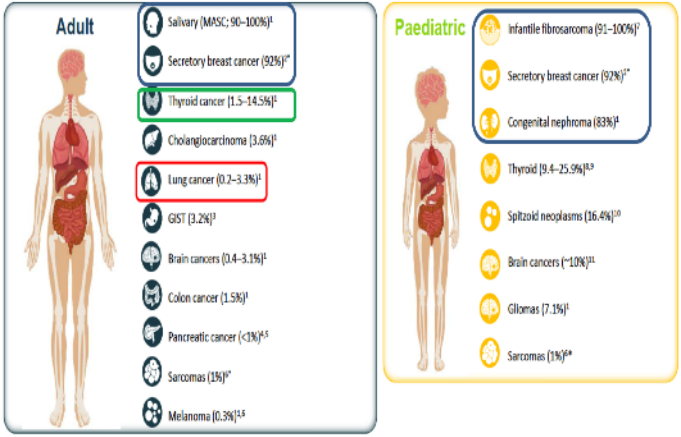


Cocco E et al. Nat Reviews 2018

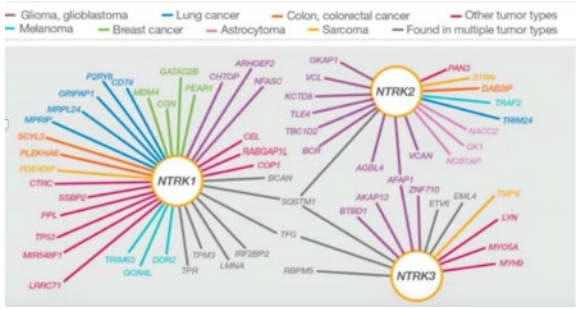
ACTIVATING *NTRK* FUSIONS RESULTS IN TRK FUSION PROTEINS THAT ARE ONCOGENIC DRIVERS



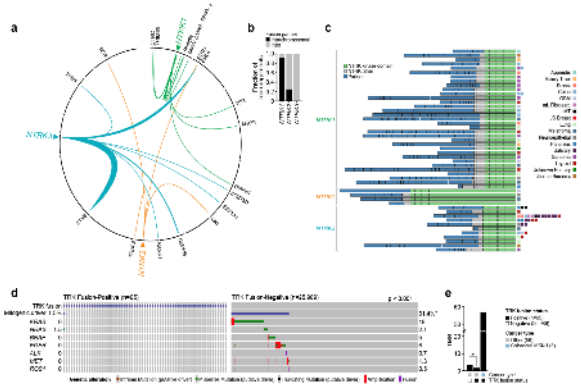
SEVERAL CANCER HISTOLOGIES, DIVERSE AGES…



SEVERAL FUSION PARTNERS

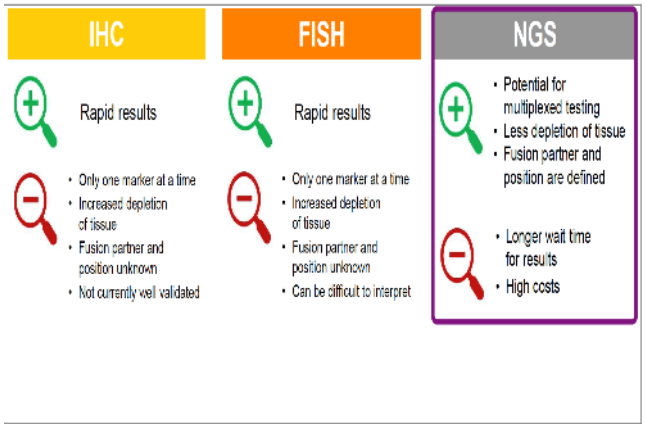


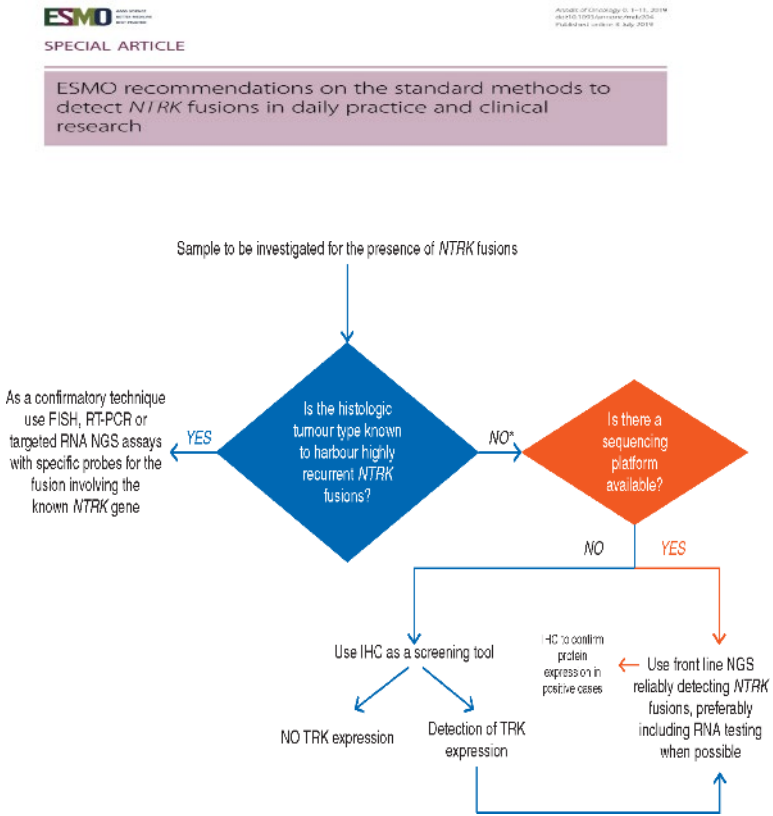
RARITY OF CO-OCCURRENCE OF TRK FUSION WITH OTHER CANONICAL ONCOGENES.



Amatu et al. ESMO Open 2016
Vaishnavi et al. Cancer Disc 2015
Penautl-Llorca et al. J Clin Pathol 2019
Hyman et al. ASCO 2017
Rosen EY, et al. Clin Cancer Res 2020

ESMO proposed NRTK gene fusion detection algorithm





Marchió et al. Ann Oncol 2019

INTERNATIONAL EXPERT CONSENSUS

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

SPECIAL ARTICLE

JSCO—ESMO—ASCO—JSMO—TOS: international expert cor
recommendations for tumour-agnostic treatments in patien
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. Calv
L.-T. Chen[9], M. Takeda[10], A. Cervantes[11], H. Taniguchi[1], K. Yoshida[12], Y. Kodera[13], Y. Kitagawa[14], J. Tabern
J.-Y. Douillard[17]

Table 3. Summary of the expert recommendations for the treatment of patients with solid tumours with *NTRK* fusions

CQ1. Should all patients with solid tumours be tested for *NTRK* fusion?	
1-1	Patients with **advanced (unresectable or metastatic)** solid tumours **without** actionable and **driver gene mutations/ fusions/amplifications** should be tested for *NTRK* fusion. [LoE: V, GoR: B, **LoA: A = 100%**]
1-2	Patients with **advanced (unresectable or metastatic)** solid tumours which are **highly likely to harbour *NTRK* fusions** should be tested for *NTRK* fusion, especially *ETV6-NTRK3* fusion. [LoE: V, GoR: A, **LoA: A = 100%**]
1-3	Patients with **advanced (unresectable or metastatic)** solid tumours other than above (CQ1-1 and 1-2) should be considered for testing for *NTRK* fusions. [LoE: V, GoR: A, **LoA: A = 100%**]
1-4	**Patients with locally-advanced tumours with a high incidence of *NTRK* fusions should be tested when considering neoadjuvant therapy before resection.** [LoE: V, GoR: **B, LoA: A = 100%**]
CQ2. When is the optimal timing for tests for *NTRK* fusion?	
	***NTRK* fusion testing** should be **considered** before or during the standard treatment of advanced (unresectable or metastatic) solid tumour. [LoE: V, GoR: **B, LoA: A = 100%**]
CQ3. Which tests are recommended for determining *NTRK* fusions?	
3-1	IHC is not recommended for confirming *NTRK* fusion. It may be used for screening to enrich patients with *NTRK* fusion. [LoE: V, GoR: B, **LoA: A = 100%**]
3-2	*In situ* hybridisation (ISH, e.g. FISH) for *ETV6-NTRK3* fusion is recommended for patients with tumours which are highly likely to harbour *NTRK* fusions. ISH is not recommended for patients other than the above. [LoE: V, GoR: B, **LoA: A = 100%**]
3-3	RT-PCR for *ETV6-NTRK3* fusion is recommended for patients with tumours which are highly likely to harbour *NTRK* fusions. [LoE: V, GoR: B, **LoA: A = 100%**]
3-4	NGS which detects *NTRK* fusion is recommended for testing for *NTRK* fusion. [LoE: V, GoR: C, **LoA: A = 100%**]
CQ4. What is the appropriate biospecimen for testing for *NTRK* fusions?	
	Both fresh samples as well as archival tissue samples properly fixed and preserved are appropriate for testing. [LoE: V, GoR: B, **LoA: A = 100%**]
CQ5. Which treatment is recommended for patients with *NTRK* fusions?	
	TRK inhibitors are strongly recommended for patients with *NTRK* fusions. [LoE: III, GoR: A, **LoA: A = 100%**]

Qs) formulated for the
/dMMR or *NTRK* fusion-
es of recommendations
ommendations for each

ours be tested for MSI/

sts for MSI/MMR or for

determining MSI/MMR

nen for testing for MSI/

for MSI/dMMR patients

should immunotherapy
its with MSI/dMMR solid
d in the treatment of
solid tumours?

satellite instability; *NTRK*,
receptor kinase.

Yoshino T, *Ann Oncol.* 2020;31(7):861-872.

Personalized Medicine in NSCLC

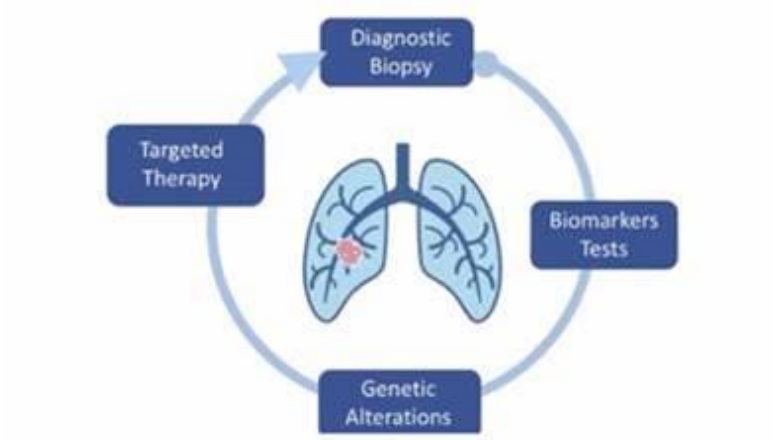
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 29 (Supplement 4): iv192–iv237, 2018
doi:10.1093/annonc/mdy275

CLINICAL PRACTICE GUIDELINES

Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

D. Planchard[1], S. Popat[2], K. Kerr[3], S. Novello[4], E. F. Smit[5], C. Faivre-Finn[6], T. S. Mok[7], M. Reck[8], P. E. Van Schil[9], M. D. Hellmann[10] & S. Peters[11], on behalf of the ESMO Guidelines Committee*



NSCLC Recommendations
ESMO Guidelines 2020

1 **"Test-Systematically"**

- ***EGFR***mut
- ***ALK***rearr
- ***ROS1***rearr
- ***BRAF***mut
- ***NTRK***rearr
- **PD-L1**

2 **'Should-test'**

- ***RET***rearr
- ***MET*** skipp/amp
- ***HER2***mut
- ***KRAS***mut

Planchard D et al. Ann Oncol 2018. Updated version 15 September 2020 and online publication: https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer

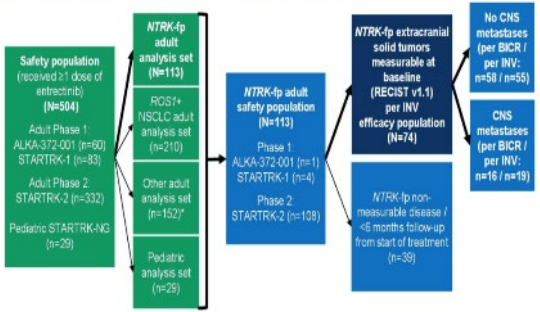
The main actors…

	Larotrectinib	Entrectinib
TKI Generation		
First	✓	✓
Drug Inhibits		
TRKA/B/C	✓	✓
ROS1		✓
ALK		✓
Contributory Trials		
Adult/Adolescent Trials	NAVIGATE Phase I Trial	STARTRK-2 STARTRK-1 ALKA-372001
Pediatric Trials	Phase I/II	STARTRK-NG

Presented by Dr. Planchard ESMO 2019

Entrectinib in patients with NTRK Fusion-positive solid tumors: an integrated analysis

Efficacy and safety populations enrolled in the integrated analysis



*ROS1+ non-NSCLC, *ALK* fusion-positive, no gene fusion. INV, investigator; BICR, blinded independent central review.

Results: patient demographics and baseline characteristics

Characteristic		*NTRK*-fp (N=74)
Age, years	Median (range)	57.0 (21–83)
Sex, n (%)	Female	39 (52.7)
	Male	35 (47.3)
Race, n (%)	White	52 (70.3)
	Asian	13 (17.6)
	Black	2 (2.7)
	Not reported	7 (9.5)
ECOG performance status, n (%)	0	30 (40.5)
	1	34 (45.9)
	2	10 (13.5)
Prior lines of systemic therapy, n (%)	0	20 (27.0)
	1	21 (28.4)
	2	20 (27.0)
	≥3	13 (17.6)
Any previous therapy, n (%)	Chemotherapy	60 (81.1)
	Targeted therapy	18 (24.3)
	Hormonal therapy	9 (12.2)
	Immunotherapy	9 (12.2)
CNS metastases at baseline*, n (%)	Yes	16 (21.6) / 19 (25.7)
	No	58 (78.4) / 55 (74.3)
Prior radiotherapy (RT) of the brain†, n (%)	Yes	11 (68.8)
	No	5 (31.2)
Time from end of brain RT to first dose‡, n (%)	<2 months	5 (45.5)
	>2 months–<6 months	4 (36.4)
	≥6 months	2 (18.2)

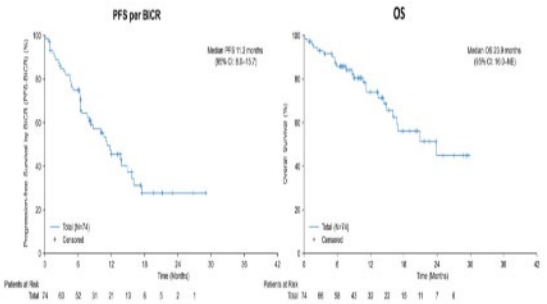
*BICR assessed / INV assessed. †Patients with baseline CNS metastases per BICR. ‡Patients with baseline CNS metastases per BICR and prior brain RT.

Systemic efficacy per BICR in patients with *NTRK*-fp solid tumors

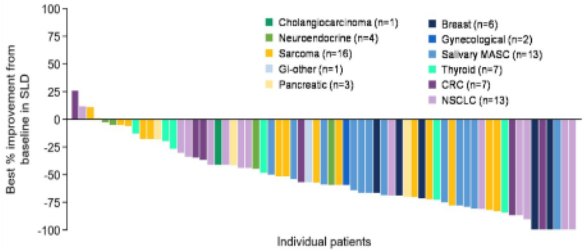
Parameter	Efficacy population (N=74)	Baseline CNS metastases‡ (n=16)	No baseline CNS metastases‡ (n=58)
ORR*, n (%) 95% CI	47 (**63.5**) 51.5–74.4	10 (**62.5**) 35.4–84.8	37 (**63.8**) 50.1–76.0
Complete response (CR), n (%)	5 (6.8)	0	5 (8.6)
Partial response (PR), n (%)	42 (56.8)	10 (62.5)	32 (55.2)
Stable disease (SD), n (%)	9 (12.2)	4 (25.0)	5 (8.6)
Progressive disease (PD), n (%)	6 (8.1)	1 (6.3)	5 (8.6)
Non-CR/PD, n (%)	3 (4.1)	0	3 (5.2)
Missing or unevaluable†, n (%)	9 (12.2)	1 (6.3)	8 (13.8)
DoR*			
Median, months (95% CI)	12.9 (9.3–NE)	6.0 (4.2–NE)	12.9 (9.3–NE)

*BICR assessed, RECIST v1.1. †Includes patients with unevaluable on-study scans or those who discontinued prior to obtaining adequate scans to evaluate or confirm response. ‡CNS metastases status determined by BICR. NE, not estimable.

Survival outcomes in patients with *NTRK*-fp solid tumors



Best individual response per BICR, by tumor type



Patients with missing SLD percent change are excluded from the plot. SLD, sum of longest diameters. GI, gastrointestinal. CRC, colorectal cancer. NSCLC, non-small-cell lung cancer. MASC, mammary analogue secretory carcinoma.

ORR 63%
DoR 12.9m
mPFS 11.2m
mOS 23.9m

Rolfo C, et al. ASCO 2020

Updated integrated analysis from three phase I/II entrectinib studies

Efficacy population* (N=74)
Adult patients with locally advanced/metastatic *NTRK* fusion-positive, TRK-inhibitor-naïve solid tumours, and ≥6 months of follow-up

ALKA-372-001 (n=1)
Phase I, dose-escalation study

STARTRK-1 (n=2)
Phase I, dose-escalation study

STARTRK-2 (n=71)
Phase II, multicentre, global basket study
Entrectinib 600mg once daily

- **Criteria for inclusion of patients with CNS disease:**
  - Both measurable and non-measurable baseline CNS disease were allowed if asymptomatic or controlled with prior CNS-directed therapy

- **Primary endpoints:†**
  - ORR
  - DoR

- **Secondary endpoints:†**
  - PFS and OS
  - **Intracranial ORR and DoR‡**
  - Safety and tolerability

Safety population§ (N=504)
Patients receiving ≥1 dose of entrectinib (all tumour types and gene rearrangements)

Data cut-off: 31 Oct 2018. *Disease burden assessed by BICR using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 after cycle 1 (4 weeks) then every 8 weeks *NTRK* fusion confirmed by nucleic acid-based methods (fluorescence in-situ hybridisation, quantitative PCR, DNA- or RNA-based next-generation sequencing); †Per BICR (RECIST v1.1); ‡Patients with measurable and non-measurable CNS lesions at baseline; §Patients from ALKA-372-001, STARTRK-1, STARTRK-2, and STARTRK-NG
BICR, blinded independent central review; DoR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival

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Baseline characteristics

Baseline characteristics		Patients with *NTRK* fusion-positive tumours (N=74)
Age, years	Median (range)	57.0 (21–83)
Sex, %	Female / Male	52.7 / 47.3
Race, %	White / Asian / Black / Not reported	70.3 / 17.6 / 2.7 / 9.5
ECOG performance status, %	0 / 1 / 2	40.5 / 45.9 / 13.5
Prior lines of systemic therapy, %	0 / 1 / 2 / ≥3	27.0 / 28.4 / 27.0 / 17.6
Any previous therapy, %	Chemotherapy / targeted therapy hormone therapy / immunotherapy	81.1 / 24.3 12.2 / 12.2
CNS metastases at baseline*, %	Yes / No	25.7 / 74.3
Prior radiotherapy of the brain†	Yes / No	68.4 / 31.6
Time from end of brain radiotherapy to first entrectinib dose‡	<2 months 2 months–<6 months ≥6 months	38.5 30.8 30.8

19 patients with investigator-assessed CNS metastases at baseline

16 patients confirmed to have baseline CNS metastases per BICR

- NSCLC (n=8/13 total)
- Thyroid (n=4/7)
- Sarcoma (n=2/16)
- Salivary (n=1/13)
- Breast (n=1/6)

*Investigator assessed; †Patients with baseline CNS metastases per investigator. Data for patients with BICR-assessed CNS metastases: 68.8% (Yes) / 31.2% (No)
‡Patients with baseline CNS metastases per investigator and prior brain RT. Data for patients with BICR-assessed CNS metastases: 45.5% (<2 mos) / 36.4% / (2–<6 mos) / 18.2% (≥6 mos) ECOG, Eastern Cooperative Oncology Group; RT, radiotherapy

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Intracranial response per BICR

High intracranial response rates seen in patients with baseline CNS metastases

Intracranial response	Patients with *NTRK* fusion-positive solid tumours and baseline CNS metastases per BICR	
	Measurable (n=8)	Measurable / non-measurable* (n=16)
Intracranial ORR, % (95% CI)	**62.5 (24.5–91.5)**	**50.0 (24.7–75.4)**
CR, n (%)	1 (12.5)	4 (25.0)
PR, n (%)	4 (50.0)	4 (25.0)
SD, n (%)	1 (12.5)	1 (6.3)
PD, n (%)	1 (12.5)	1 (6.3)
Non-CR/non-PD, n (%)	0	5 (31.3)*
Missing/unevaluable, n (%)	1 (12.5)	1 (6.3)

*As per RECIST v1.1 responses for patients with non-measurable CNS lesions could only be categorised as CR, non-CR/non-PD, or PD; non-measurable lesions included small lesions (longest diameter <10mm or pathological lymph nodes with ≥10 to <15mm short axis). CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease

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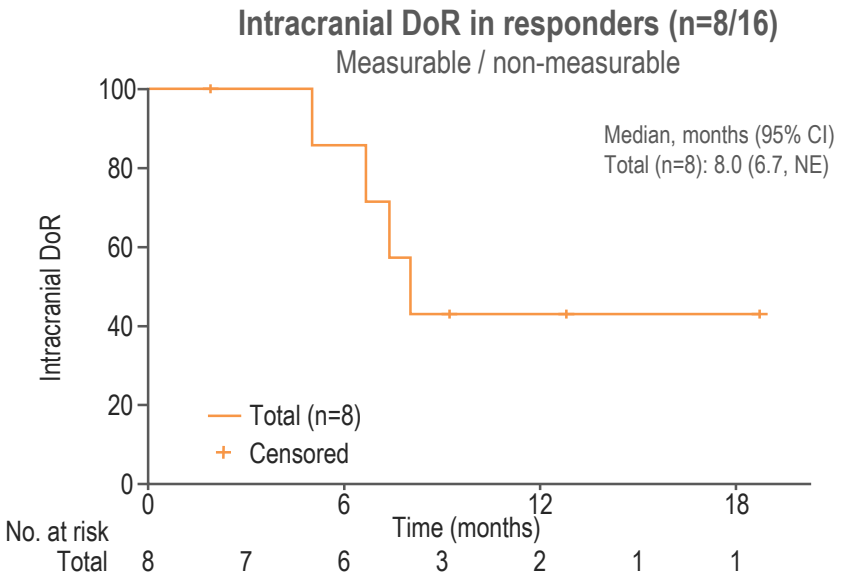
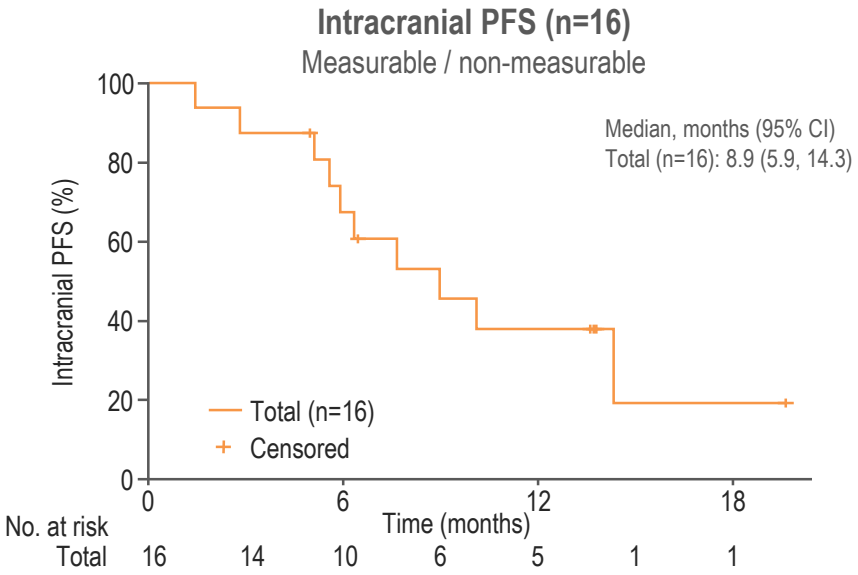
Intracranial DoR and PFS





Intracranial outcomes	Patients with *NTRK* fusion-positive solid tumours and baseline CNS metastases per BICR	
	Measurable (n=8)	Measurable / non-measurable* (n=16)
Median intracranial DoR in responders, months (95% CI)*	NE (5.0–NE)	8.0 (6.7–NE)
Median intracranial PFS, months (95% CI)†	10.1 (2.8–NE)	8.9 (5.9–14.3)

*Events occurred in 2 patients with measurable lesions and 4 patients with measurable/non-measurable lesions

†Intracranial PFS events occurred in 4 patients (2 PD, 2 deaths) with measurable lesions and 10 patients (3 PD, 7 deaths) with measurable/non-measurable lesions

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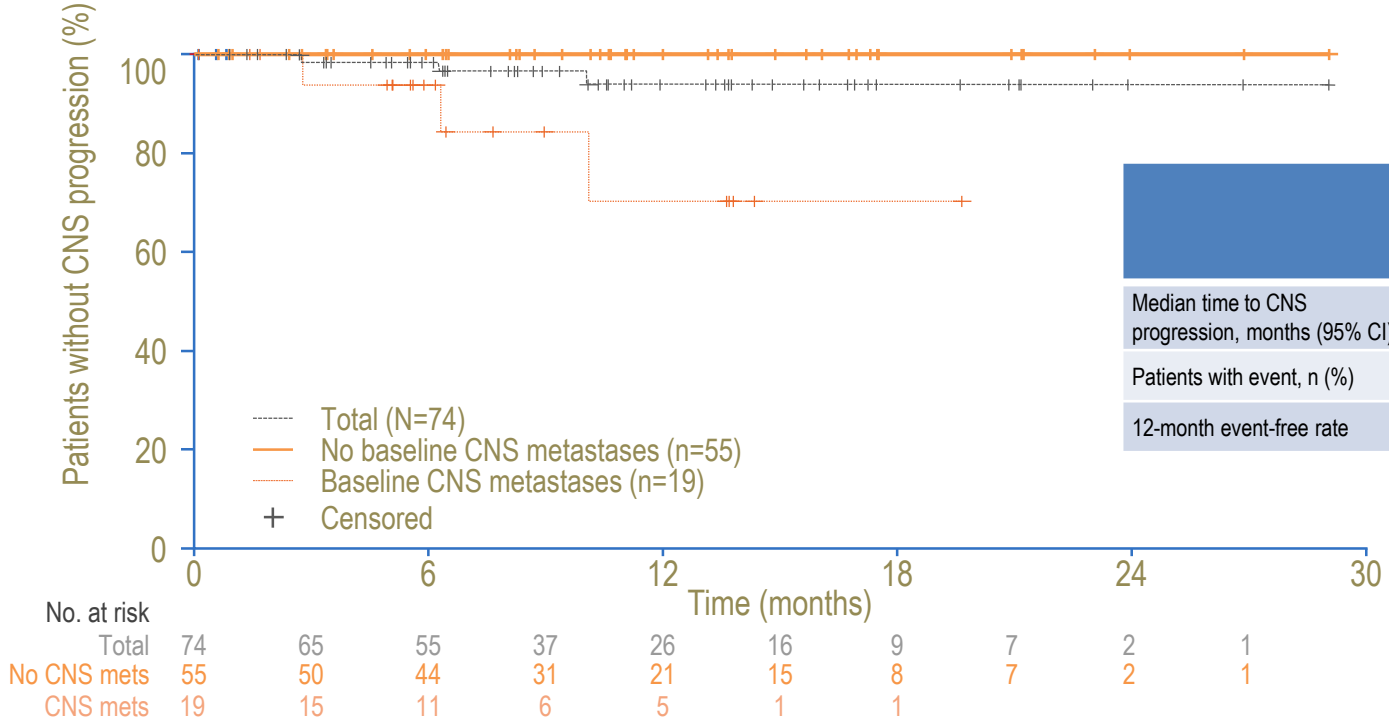
Time to CNS progression (deaths censored)

Rates of detected CNS progression confirmed by scans were very low*



	All patients (N=74)	No baseline CNS mets* (n=55)	Baseline CNS mets (n=19)
Median time to CNS progression, months (95% CI)	NE (NE)	NE (NE)	NE (10.1–NE)
Patients with event, n (%)	3 (4.1)	0	3 (15.8)
12-month event-free rate	0.94	1.00	0.70

Baseline CNS metastases assessed by investigator. Time to CNS progression: only confirmed CNS progression counted as an event (death censored). *As regular CNS scans in patients without baseline CNS metastases were not mandated by the protocol, CNS follow-up for patients in this subgroup was not comprehensive, but based on imaging elicited by symptomatic progression or routine CNS scans where customary. Patients with baseline CNS metastases underwent regular CNS scans

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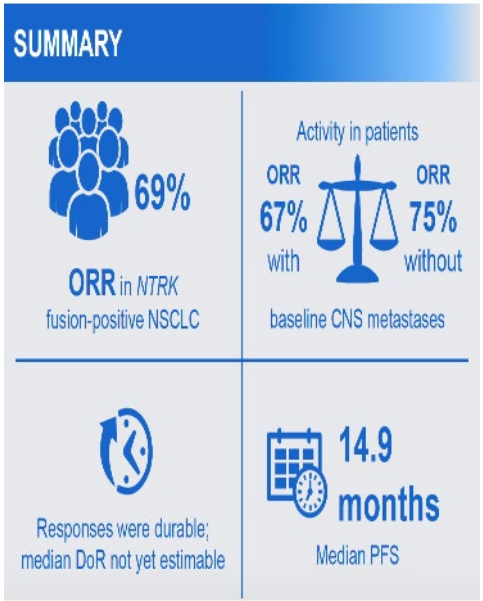
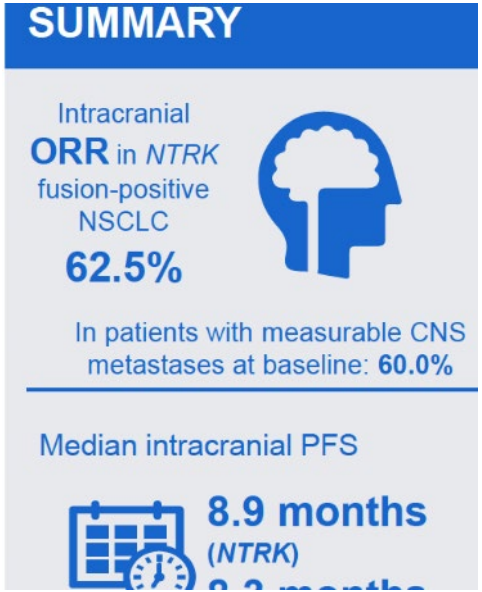
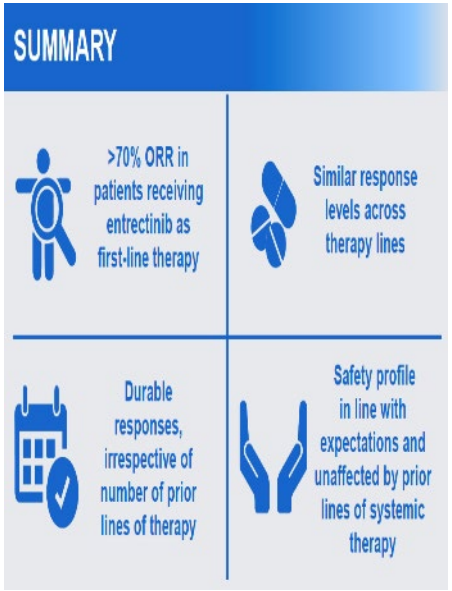
Systemic and intracranial efficacy of entrectinib in patients with *NTRK* or *ROS1* fusion-positive NSCLC with CNS metastases at baseline

Table 1. Baseline characteristics

	NTRK fusion-positive NSCLC (N=13)
Median age, years	60
Sex, female, n (%)	7 (53.8)
Histology, n (%)	
Adenocarcinoma†	9 (69.2)
Squamous cell carcinoma	2 (15.4)
NSCLC NOS	2 (15.4)
Adenosquamous carcinoma	0
Prior chemotherapy in any setting, n (%)	13 (100)
Prior lines of therapy in metastatic setting, n (%)	
0	3 (23.1)
1	4 (30.1)
≥2	6 (46.2)
CNS metastases at baseline,* n (%)	8 (61.5)
Measurable	5 (38.5)
Prior radiotherapy of the brain, n (%)	5 (38.5)
≥2 months prior	3 (60.0)
WBRT	0
Stereotactic RT	0
WBRT ± stereotactic RT	1 (20.0)



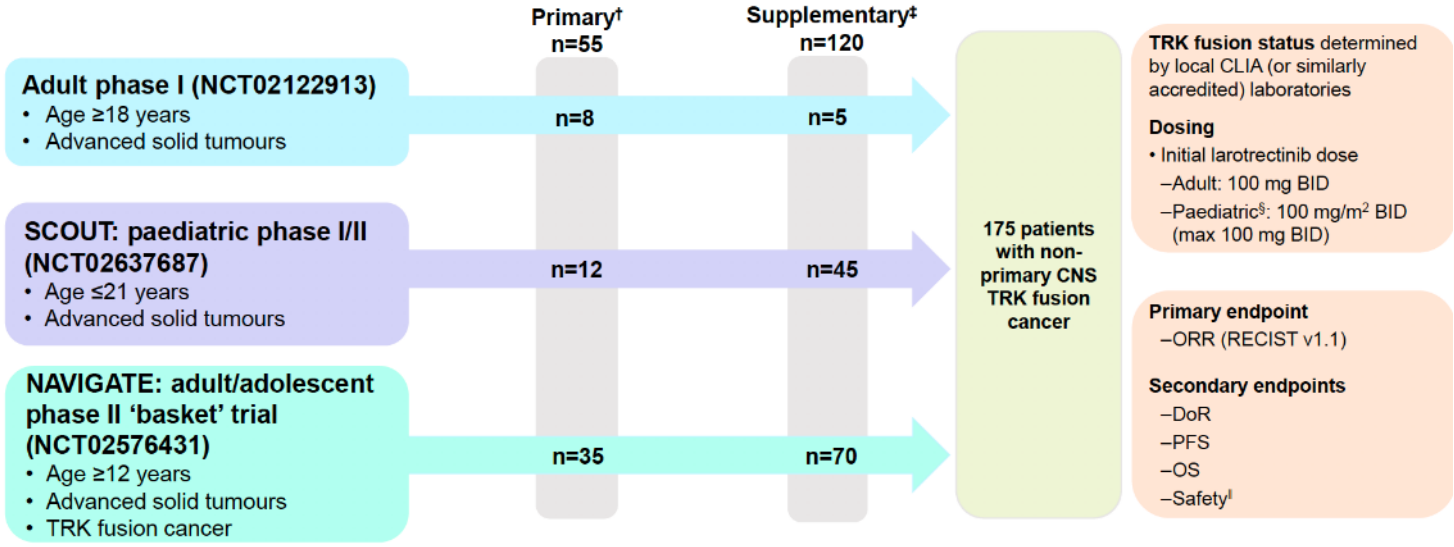




Dziadziuszko R, et al. ESMO 2020
Drilon A, et al. ESMO 2020
Liu SV et al. ESMO 2020

Larotrectinib
Integrated dataset

Study design

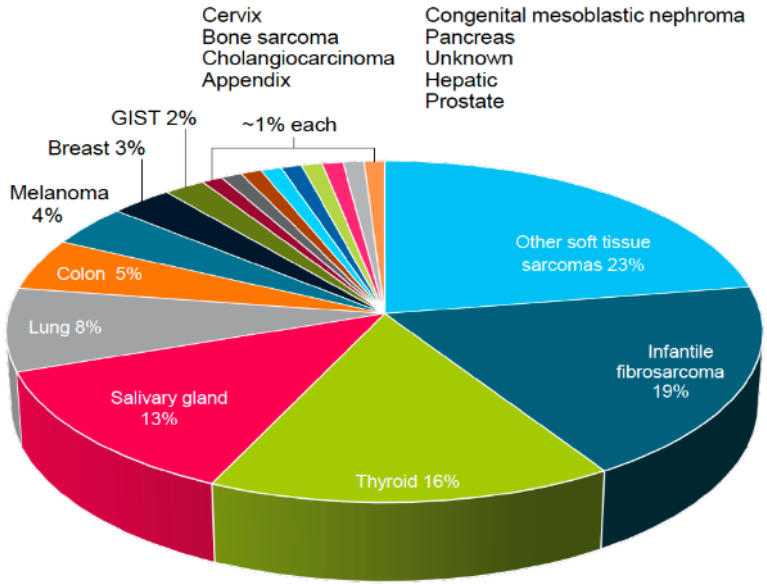


Data cut-off: 15 July 2019

†The primary dataset comprises those original patients included in the primary report with longer follow-up. ‡The supplementary dataset comprises the additional patients included in this analysis. §The starting dose was determined by SimCyp® modelling which predicted that the doses needed to match the larotrectinib exposure in adults given 100 mg BID are 9.6, 17, 28, 39, 49, 55, and 55 mg/m² for patients aged 1–3 months, 3–6 months, 6 months–1 year, 1–2 years, 2–6 years, 6–12 years, and 12–18 years, respectively. ¶The safety population included all patients enrolled in one of the three clinical trials, who received at least one dose of larotrectinib, regardless of TRK fusion status (n=279). BID, twice daily; CLIA, Clinical Laboratory Improvement Amendments; DoR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TRK, tropomyosin receptor kinase.

Baseline characteristics

	Integrated dataset (N=175)
Sex, n (%)	
Male	86 (49)
Female	89 (51)
Age, median (range), years	43 (0.1–84)
Paediatric (<18), n (%)	59 (34)
Adult (≥18), n (%)	116 (66)
ECOG PS, n (%)	
0	85 (49)
1	67 (38)
2	20 (11)
3	3 (2)
Known CNS metastasis at enrolment, n (%)	14 (8)
Number of prior systemic therapies, median (range)	1 (1–10)
Number of prior systemic therapies, n (%)	
0	44 (25)
1	50 (29)
2	35 (20)
≥3	46 (26)
***NTRK* gene fusion, n (%)**	
NTRK1	72 (41)
NTRK2	6 (3)
NTRK3†	97 (55)

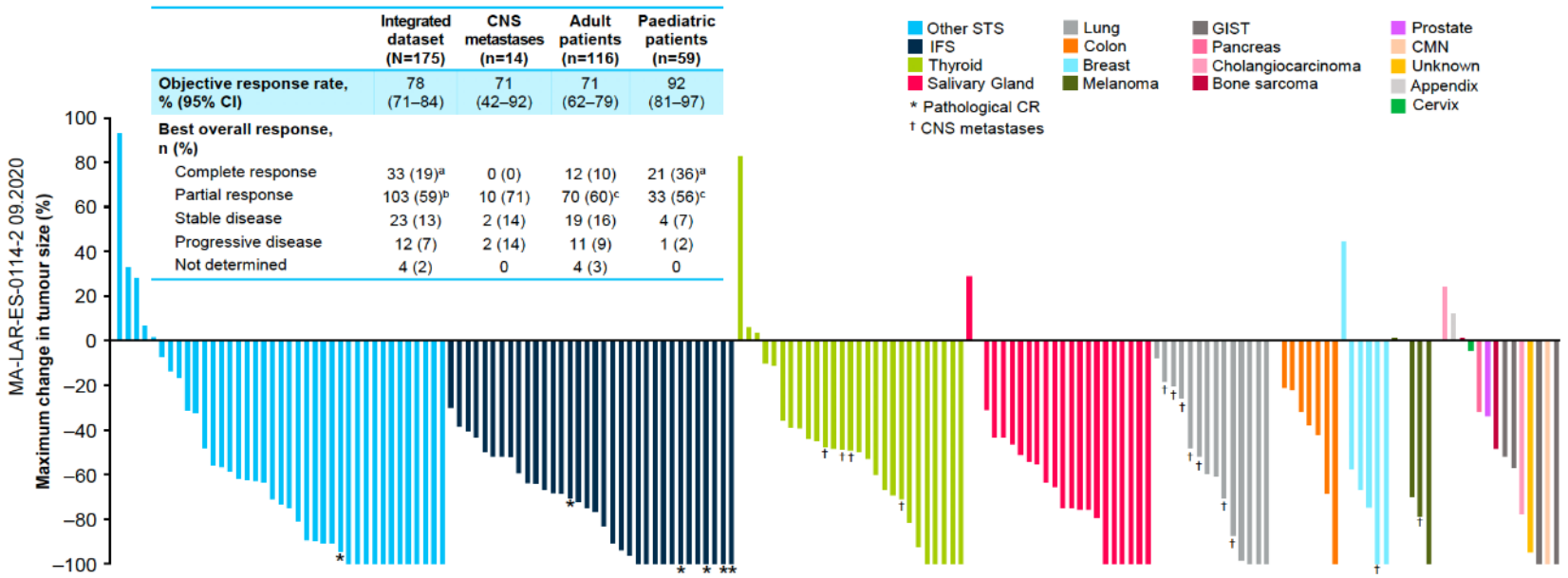


†Fusion inferred in 9 of 97 patients.
CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; GIST, gastrointestinal stromal tumour; *NTRK*, neurotrophic tyrosine receptor kinase; TRK, tropomyosin receptor kinase.

McDermott et al. ESMO 2020

Best response to larotrectinib by tumour type

	Integrated dataset (N=175)	CNS metastases (n=14)	Adult patients (n=116)	Paediatric patients (n=59)
Objective response rate, % (95% CI)	78 (71–84)	71 (42–92)	71 (62–79)	92 (81–97)
Best overall response, n (%)				
Complete response	33 (19)[a]	0 (0)	12 (10)	21 (36)[a]
Partial response	103 (59)[b]	10 (71)	70 (60)[c]	33 (56)[c]
Stable disease	23 (13)	2 (14)	19 (16)	4 (7)
Progressive disease	12 (7)	2 (14)	11 (9)	1 (2)
Not determined	4 (2)	0	4 (3)	0



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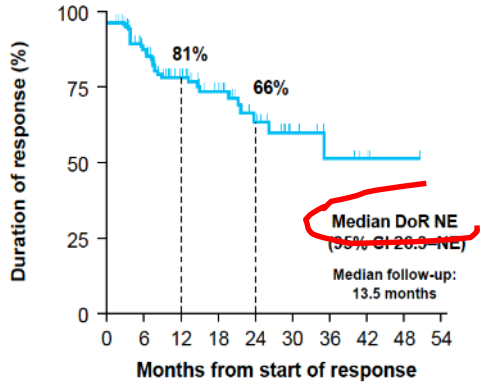
DoR, PFS and OS

MA-LAR-ES-0114-2 09.2020

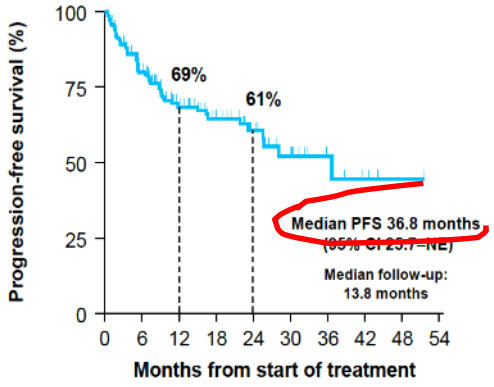
DoR



No. at risk 132 90 57 39 21 11 5 3 1 0

- Median DOR: NE (95% CI 26.3–NE)
- Median follow-up: 13.5 months
- Rate of ongoing response at 12 months: 81% (95% CI 73–89)
- Rate of ongoing response at 24 months: 66% (95% CI 53–78)

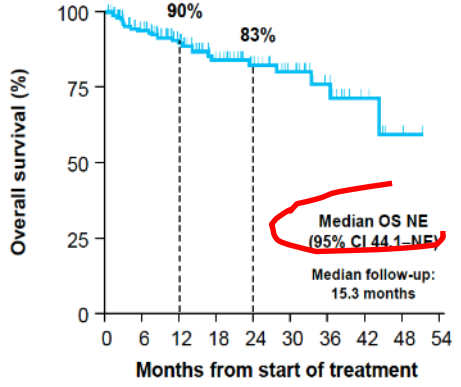
PFS



No. at risk 175 114 66 46 27 16 7 4 1 0

- Median PFS: 36.8 (95% CI 25.7–NE)
- Median follow-up: 13.8 months
- PFS rate at 12 months: 69% (95% CI 61–76)
- PFS rate at 24 months: 61% (95% CI 51–70)

OS



No. at risk 175 140 93 64 43 30 17 7 2 0

- Median OS: NE (95% CI 44.1–NE)
- Median follow-up: 15.3 months
- OS rate at 12 months: 90% (95% CI 85–95)
- OS rate at 24 months: 83% (95% CI 75–90)

In the 14 evaluable patients with brain metastases, at a median follow-up of 9.5 months, **the median DoR was 14.8 months (95% CI 3.7–NE)** and the 12-month DoR rate was 61% (95% CI 26–96).

Activity of Larotrectinib in Adult Patients with TRK Fusion Cancer: An Expanded Data Set

Figure 1: Patient population by tumor type (N=116)

A total of 116 adult patients with TRK fusion cancer across 17 tumor types were included in this analysis.

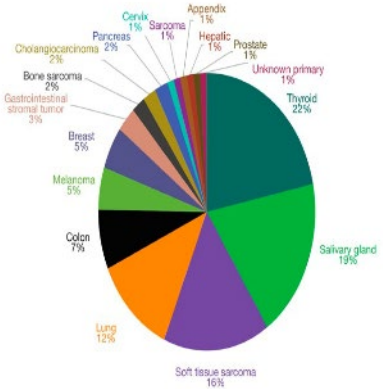
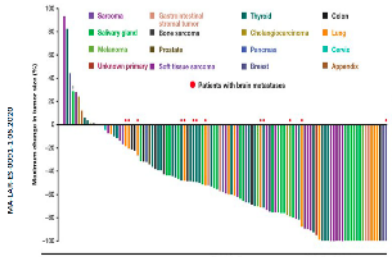


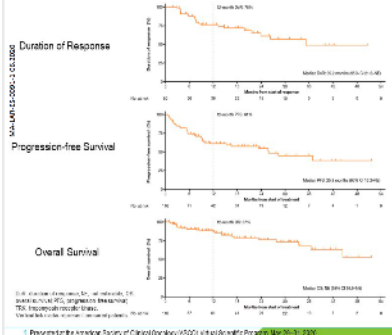
Figure 2: Tumor response in adult patients with TRK fusion cancer



- The **ORR was 71%** (95% confidence interval [CI] 62–79).
- Responses were observed irrespective of tumor type or gene type (*NTRK1–3*).
- Fourteen (12%) patients had brain metastases at baseline.
  - The ORR for these patients was 71% (95% CI 42–92).

	All patients (n=116)	Patients with brain metastases (n=14)
ORR, % (95% CI)	71 (62–79)	71 (42–92)
Best response, n (%)		
CR	12 (10)	3
PR	70 (60)	10 (71)
SD	19 (16)	2 (14)
PD	11 (9)	2 (14)
Not determined	4 (3)	3

Figure 3: Duration of Response, Progression-free Survival, and Overall Survival



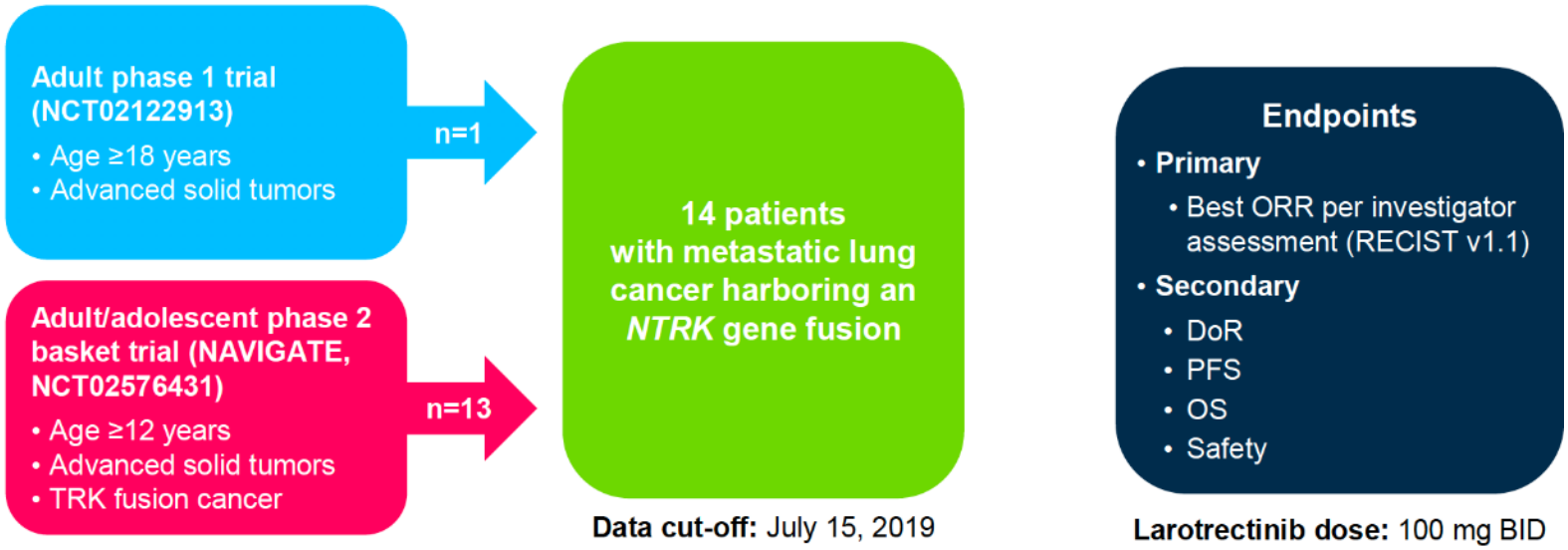
- The **median DoR was 35.2 months** (95% CI 21.6–not estimable [NE]) at a median follow-up of 17.4 months
- The longest ongoing treatment duration approached 4 years and 4 months (range of treatment: 0.1 to 51.6+ months).
- The **median PFS was 25.8 months** (95% CI 15.2–NE) at a median follow-up of 14.6 months. The rate of PFS at ≥12 months was 61%.
- The **median OS** was not reached (95% CI 36.5–NE) at a median follow-up of 15.8 months. The rate of OS at ≥12 months was 87%.

ORR 71%
DoR 35.2m
mPFS 25.8m
mOS NR

Drilon A, et al. ASCO 2020

ACTIVITY OF LAROTRECTINIB IN TRK FUSION LUNG CANCER

Study design



Data cut-off: July 15, 2019

Larotrectinib dose: 100 mg BID

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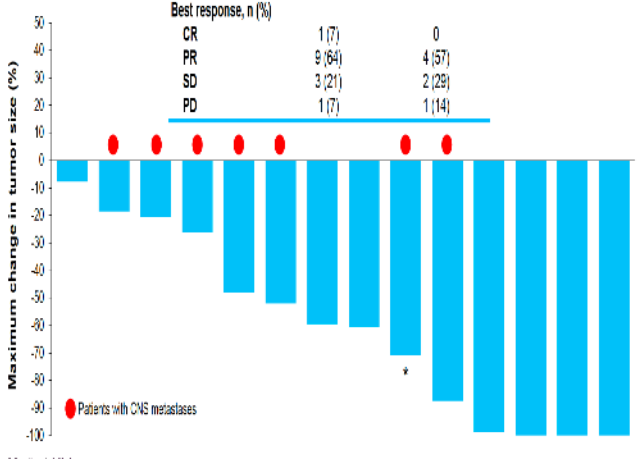
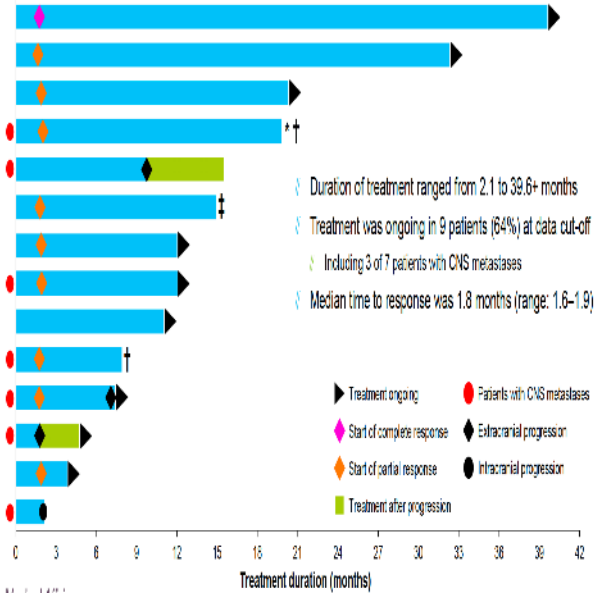
ORR 71%
DOT 2.1 to 39.6
mPFS NR
mDoR NE
mOS NE

Best response to larotrectinib

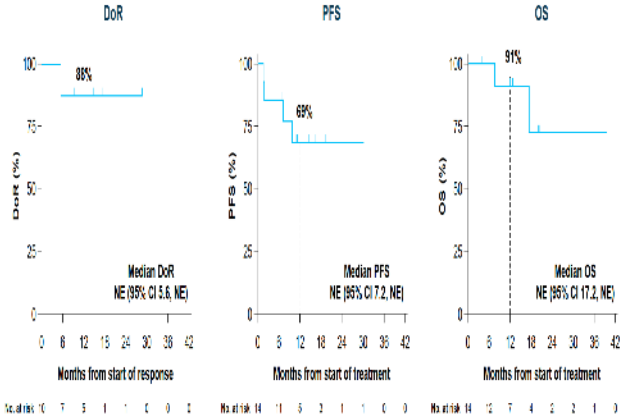
	All patients (N=14)	Patients with CNS metastases (n=7)
ORR, % (95% CI)	71 (42, 92)	57 (18, 90)
Best response, n (%)		
CR	1 (7)	0
PR	9 (64)	4 (57)
SD	3 (21)	2 (29)
PD	1 (7)	1 (14)



Treatment duration



DoR, PFS, and OS



- DoR rate at 12 months was 88% (95% CI 65, 100)
- PFS rate at 12 months was 69% (95% CI 43, 84)
- OS rate at 12 months was 91% (95% CI 74, 100)

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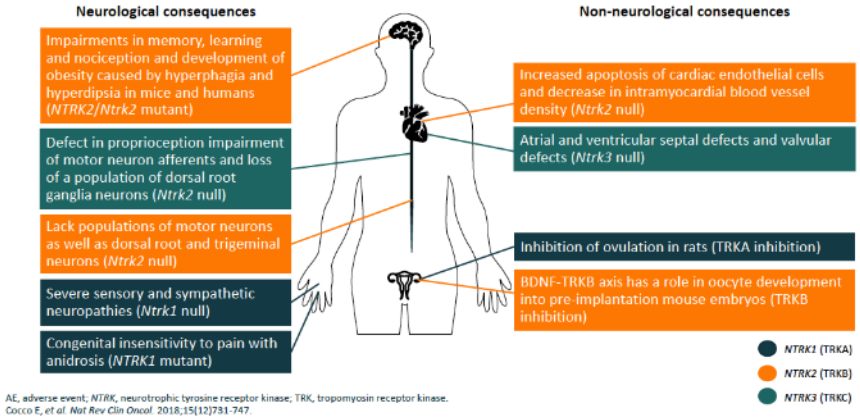
On-target AEs can occur with TRK inhibition

TRK receptor regulates normal funcions:

- NTRK1 → Pain, thermoregulation
- NTRK2 → movement, memory, appetite
- NTRK3 → proprioception



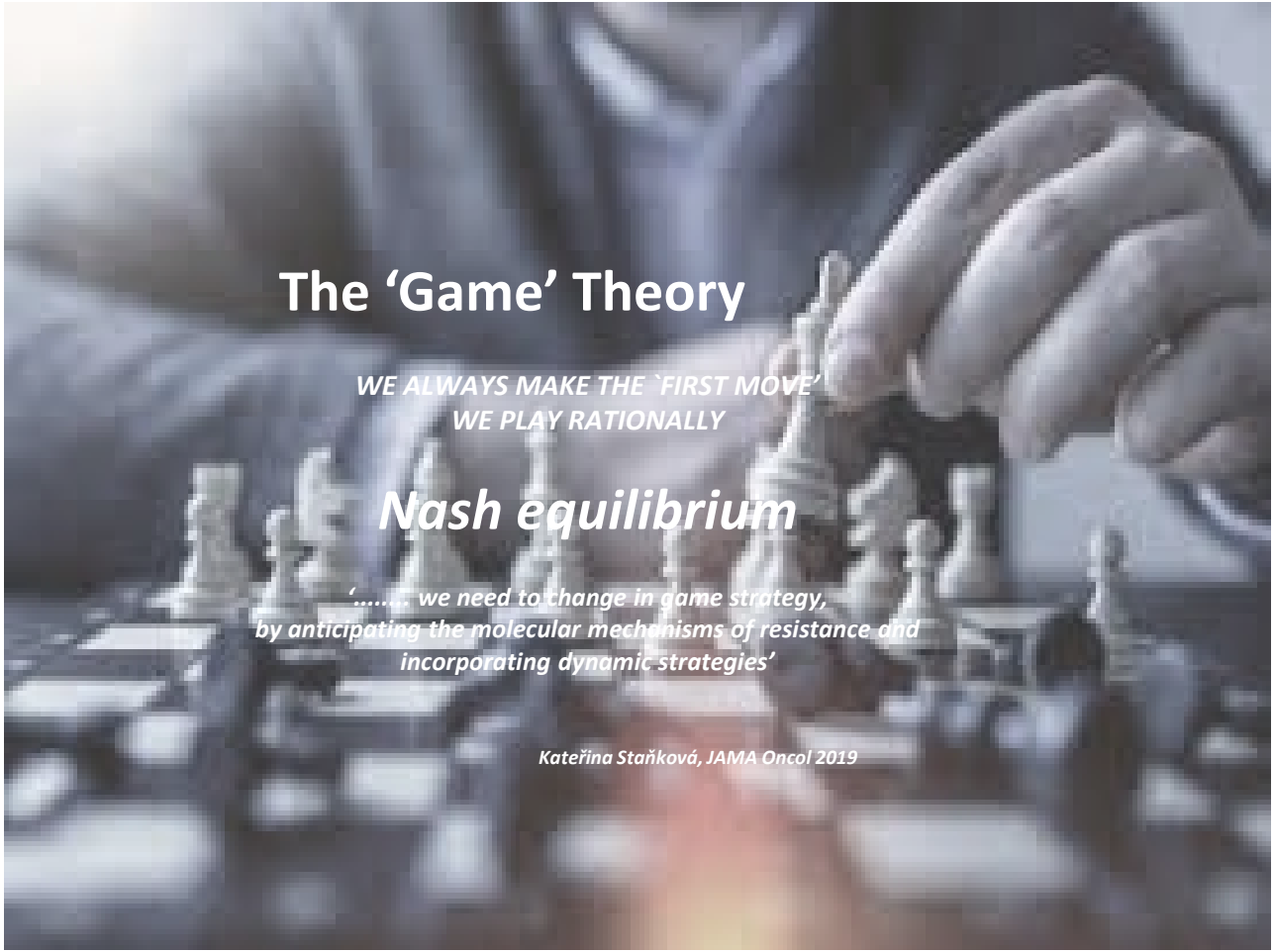
AE, adverse event; *NTRK*, neurotrophic tyrosine receptor kinase; TRK, tropomyosin receptor kinase.
Cocco E, *et al. Nat Rev Clin Oncol.* 2018;15(12):731-747.

	Larotrectinib treatment-emergent AEs in ≥15% of patients (n=207)[1]		Entrectinib treatment-related AEs in ≥10% of patients (n=355)[2]	
	Grade 1/2	Grade 3	Grade 1/2	Grade 3
Dysgeusia (%)	–	–	41.1	0.3
Dizziness (%)	28	1	24.8	0.6
Weight gain (%)	–	–	14.4	5.1
Paraesthesias (%)	–	–	18.9	0
Frequency of dose modification	Among patients with TRK fusion-positive cancer: Dose reduction – 11/122 (9%) Discontinuation due to an AE – 1/122 (<1%)		Treatment-related AEs in the overall safety population leading to: Dose reduction – 27.3% Dose interruption – 25.4% Discontinuation – 3.9%	

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

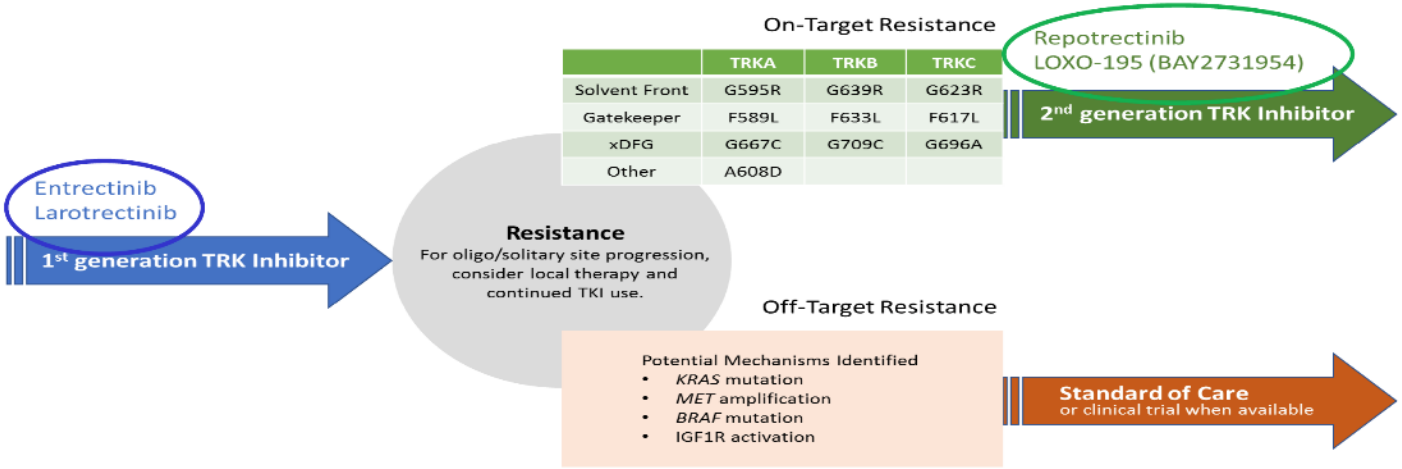
• *Larotrectinib is the first tumour-agnostic drug to be approved in the European Union for the treatment of adult and paediatric patients with solid tumours that display a NTRK gene fusion and who have no satisfactory treatment options [**III, A**; ESMO-MCBS v1.1 score: 3]*

•*Entrectinib: in August 2020, the EMA granted a conditional marketing authorisation to entrectinib as monotherapy indicated for the treatment of adult and paediatric patients 12 years of age and older with solid tumours expressing a NTRK gene fusion who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have not received a prior NTRK inhibitor or have no satisfactory treatment options [**III, B**; ESMO-MCBS v1.1 score: 3]*



Courtesy Dr. Reguart

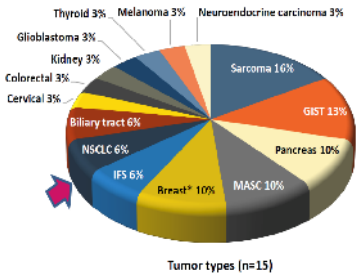
Potential treatment algorithm for TRK fusion positive cancers



Planchard D. ESMO 2019

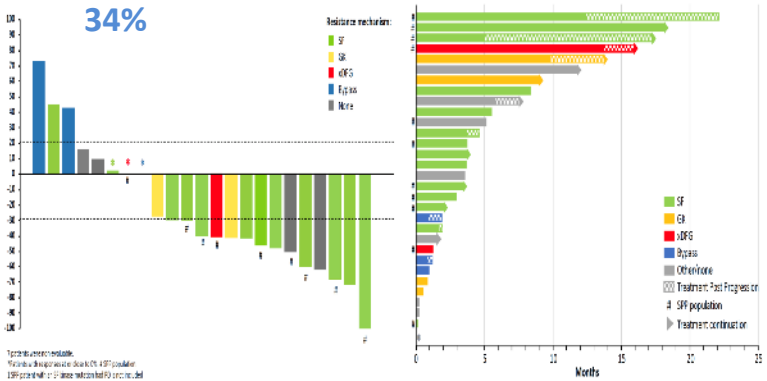
LOXO 195: a 2nd generation TRK inhibitor

Characteristic	Total (N=31)
Gender n (%)	
Female	22 (71)
Male	9 (30)
Median age (range), years	37 (1.25–72)
Pediatric (≤18), n (%)	7 (23)
Adult (>18), n (%)	24 (77)
Prior TKI^, n (%)	31 (100)
Larotrectinib	21 (69)
Entrectinib	9 (28)
PLX7486	1 (3)
Median duration# of prior TRK TKI, months (range)	11 (2-30)
TRK fusion, n (%)	
NTRK1	15 (48)
NTRK2	1 (3)
NTRK3	15 (48)
Enrollment, n (%)	
Phase I	20 (65%)
SPP	11 (35%)



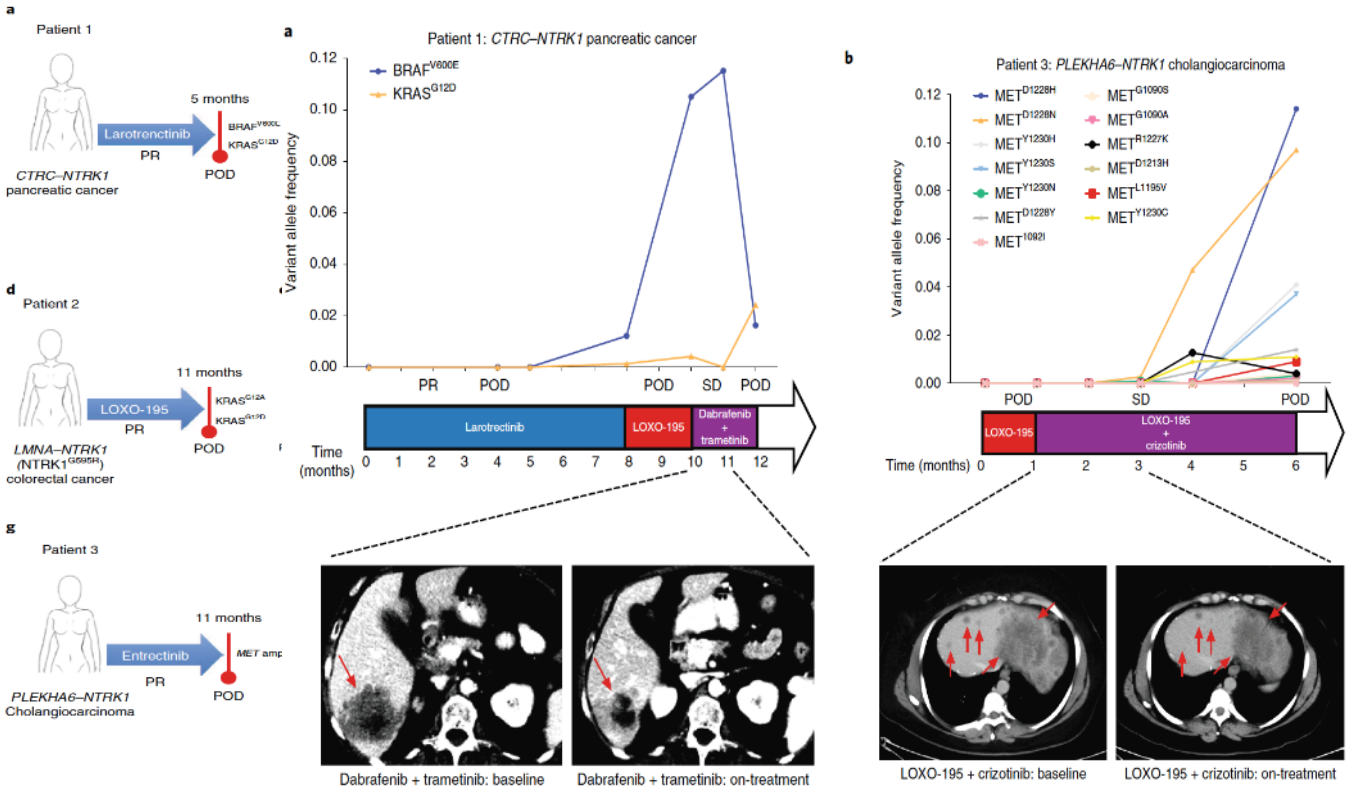
Tumor types (n=15)

NSCLC: RR 34%

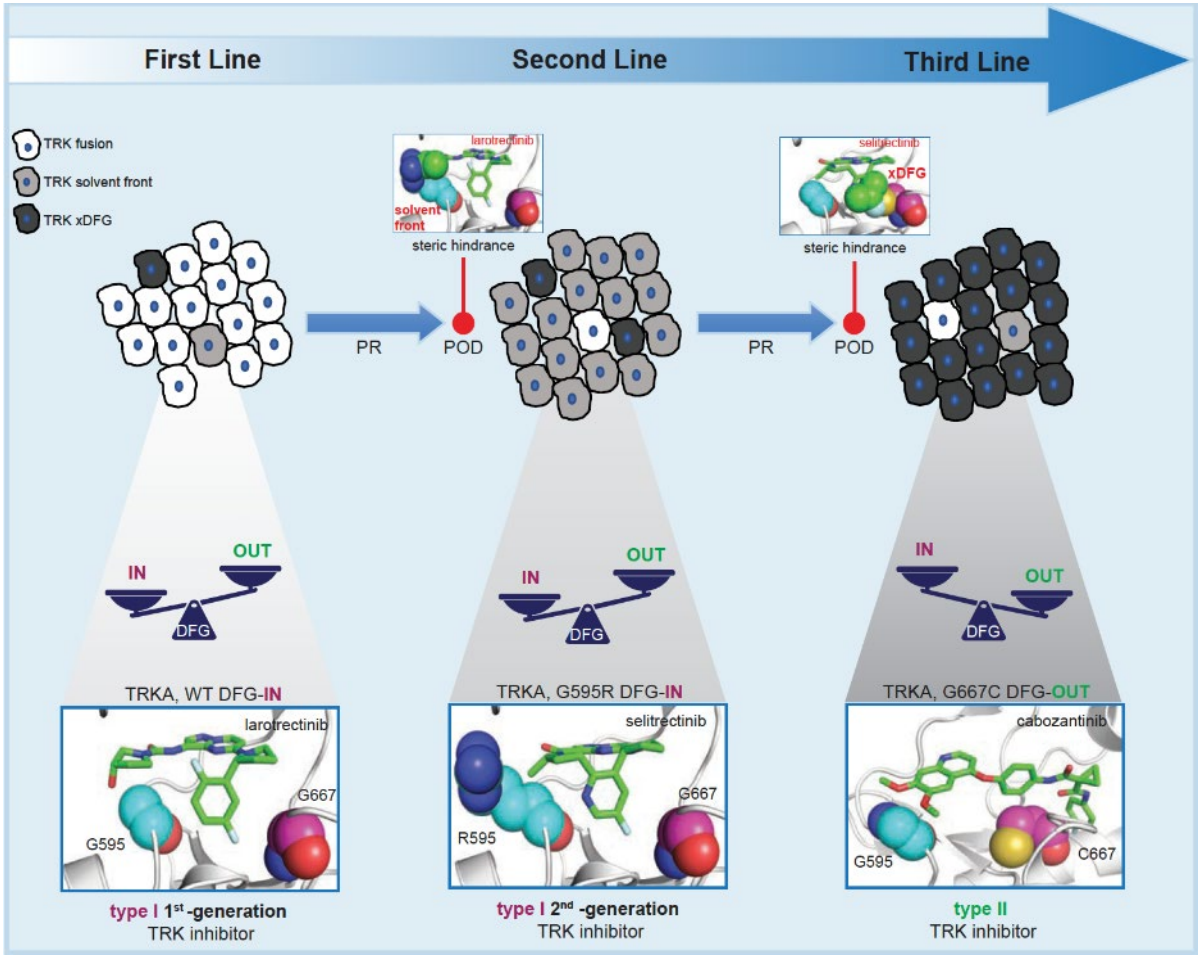


Hyman D, et al. AACR 2019

Off target resistance to NTRKi



Cocco et al. Nature Med 2019



Cocco et al. Cancer Discovery 2020

LET´S DO IT…

Genómica

Guía profesional y plan político para que la medicina de precisión impregne el SNS

GACETA MÉDICA

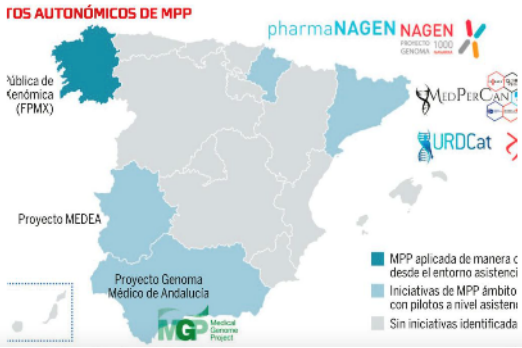
Clamor por un plan estatal en Medicina Personalizada de Precisión

Los expertos coinciden en que la medicina personalizada de precisión es una apuesta del presente

LA RAZON | SALUD

A la espera de un Plan Nacional de Medicina Especializada

Un informe recoge todas las iniciativas que hay a día de hoy en esta área a nivel autonómico



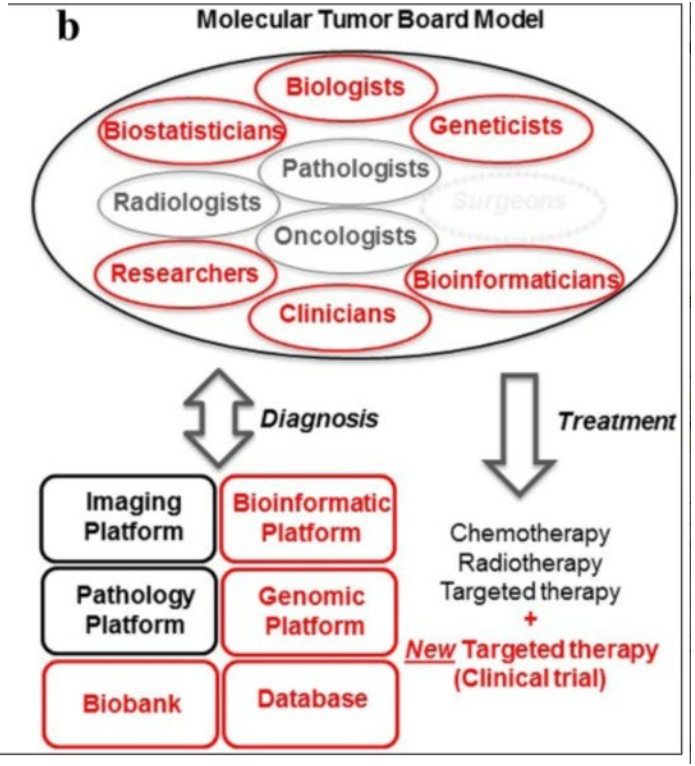
redacción médica

Los oncólogos proponen crear un Plan Estratégico de Medicina de Precisión

Ruth Vera, presidenta de la SEOM, ha defendido en el Senado la necesidad de que este proyecto esté dotado de recursos

MTBs are the logical evolution of the traditional tumor boards in the era of genomic medicine

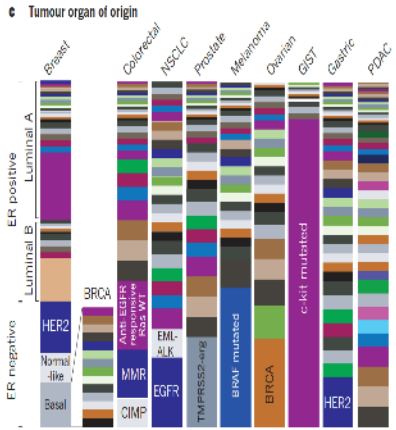
- Expert teams
- Sample availability: biopsy, rebiopsy…
- Technology
- Bioinformatics
- Adequate time-frame
- Quality assurance programs
- Link to a innovative clinical trials program

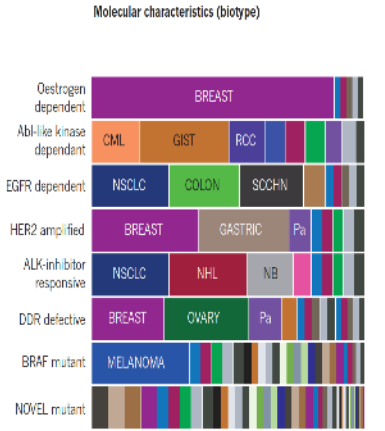


Stoekle HC et al. Sci Eng Ethics 2018

A DIFFERENT WAY TO DO CLINICAL TRIALS…

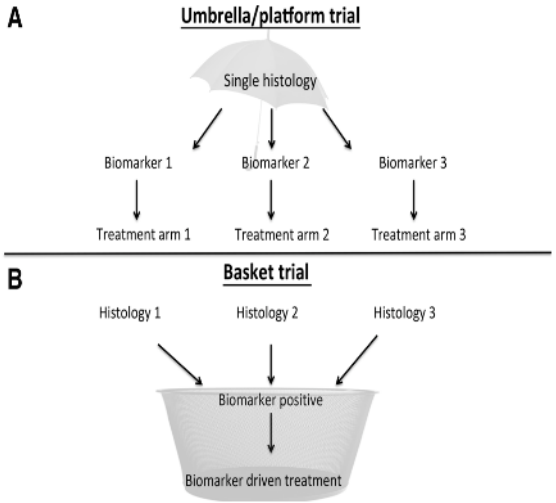
Challenges with Novel Clinical Trial Designs





UMBRELLA TRIALS

BASKET TRIALS



Cecchini M, et al. Clin Cancer Res 2019

The Era of Precision in Medicine…
NTRK: a new era in precision medicine

- ***Cancer: never more a single disease***
  - We have reached unprecedented survival rates
  - NTRK: a “must do it” and new player

- ***Genomic testing***: a true therapeutic revolution
  - If you don´t look for genetic alterations…forget the concept of precision medicine
  - Tumor tissue availability
  - Role of liquid biopsy…the immediate present/future

- Drug access…such an issue

- ***Education, collaboration, validation, evaluation, equity…***