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EXPERTS KNOWLEDGE SHARE

TRK FUSION-POSITIVE SARCOMAS AND LUNG CANCER

Prof. Robin Jones, Prof. Erin Rudzinski and

Prof. Christian Rolfo

19th October 2021

EXPERTS KNOWLEDGE SHARE

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THE OBJECTIVE OF THIS MEETING IS TO SHARE CURRENT OPINIONS ON HOW TO IDENTIFY, TEST AND TREAT TRK FUSION-POSITIVE SARCOMAS AND LUNG CANCER

YOUR OPPORTUNITY TO **DISCUSS AND SHARE LEARNINGS** ON A CHALLENGING TOPICS WITHIN THE AREA OF TRK FUSION-POSITIVE CANCER

A CHANCE TO HEAR THE **VIEWS OF EXPERTS** AND ALLOW THEM TO ANSWER THE QUESTIONS THAT ARE IMPORTANT TO YOU

DISCUSS **PATIENT CASE STUDIES AND QUESTIONS** THAT YOU HAVE SENT IN ADVANCE OF THIS EVENT

INTRODUCING THE SCIENTIFIC COMMITTEE

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The Royal Marsden Hospital NHS Foundation Trust & Institute of Cancer Research, London, UK

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DISCLAIMER

This meeting is based on an independent medical educational grant from Bayer. The programme is therefore independent; the content is not influenced by Bayer and is the sole responsibility of the experts

Please note:

The views expressed within this presentation are the personal opinions of the experts. They do not necessarily represent the views of the experts' academic institutions or the rest of the faculty

DETECTION OF TRK FUSION-POSITIVE SARCOMAS

Prof. Erin Rudzinski, MD

Seattle Children's Hospital,
Seattle, USA

DISCLOSURES

- Prof Rudzinski has nothing to disclose.

NTRK GENES

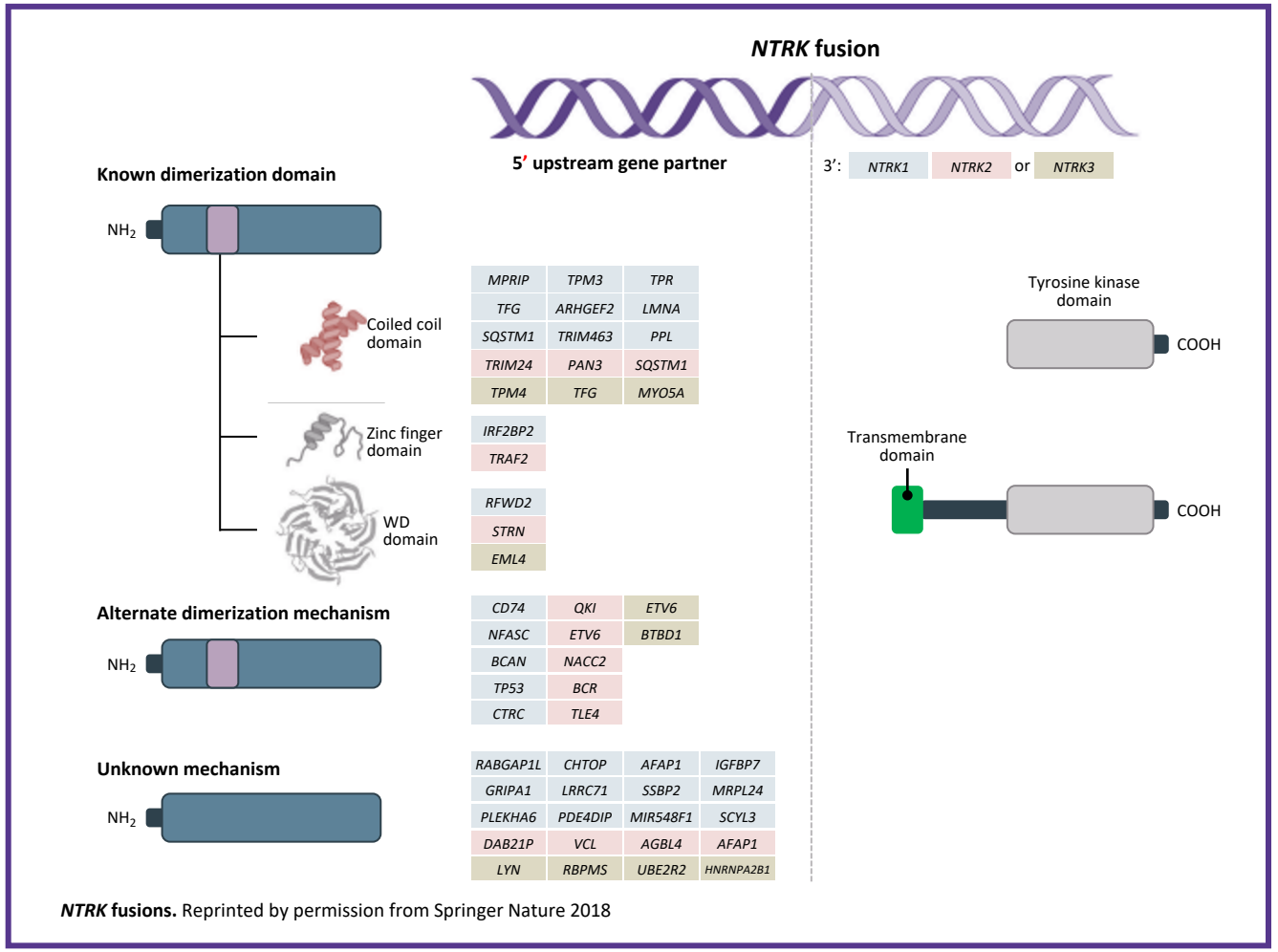
- Neurotrophic tropomyosin-receptor kinase genes (*NTRK1, NTRK2, NTRK3*)
- Encode tropomyosin receptor kinase proteins (TRKA, TRKB, TRKC)
- Normally expressed in peripheral and central nervous systems in embryonic development and in adult tissues
- Kinase domain activation leads to activation of downstream signalling of MAPK, PI3K and PKC pathways to promote neuron growth, differentiation and survival

MAPK, mitogen-activated protein kinase; NTRK, neurotrophic tyrosine receptor kinase; PI3K, phosphoinositide 3-kinase; PKC, protein kinase Cl; TRK, tropomyosin receptor kinase

Hechtman JF. Mod Pathol. 2021; doi: 10.1038/s41379-021-00913-8 (Online ahead of print)

NTRK FUSIONS

- **Intra- or inter-chromosomal gene rearrangements lead to the *NTRK* gene joining with a fusion partner gene**
- Over 80 different fusion partners identified
- This triggers constitutive activation of the TRK protein
- This promotes, through MAPK and/or PI3K pathways:
  - ↑ tumour proliferation
  - ↑ survival
  - ↑ invasion
  - ↑ angiogenesis



***NTRK* fusions.** Reprinted by permission from Springer Nature 2018

MAPK, mitogen-activated protein kinase; NTRK, neurotrophic tyrosine receptor kinase; PI3K, phosphoinositide 3-kinase; TRK, tropomyosin receptor kinase

Hechtman JF. Mod Pathol. 2021; doi: 10.1038/s41379-021-00913-8 (Online ahead of print)

NTRK FUSIONS IN SARCOMAS

NTRK, neurotrophic tyrosine receptor kinase

INCIDENCE OF *NTRK* FUSIONS IN SARCOMAS

VARIES IN PAEDIATRIC AND ADULTS TUMOURS

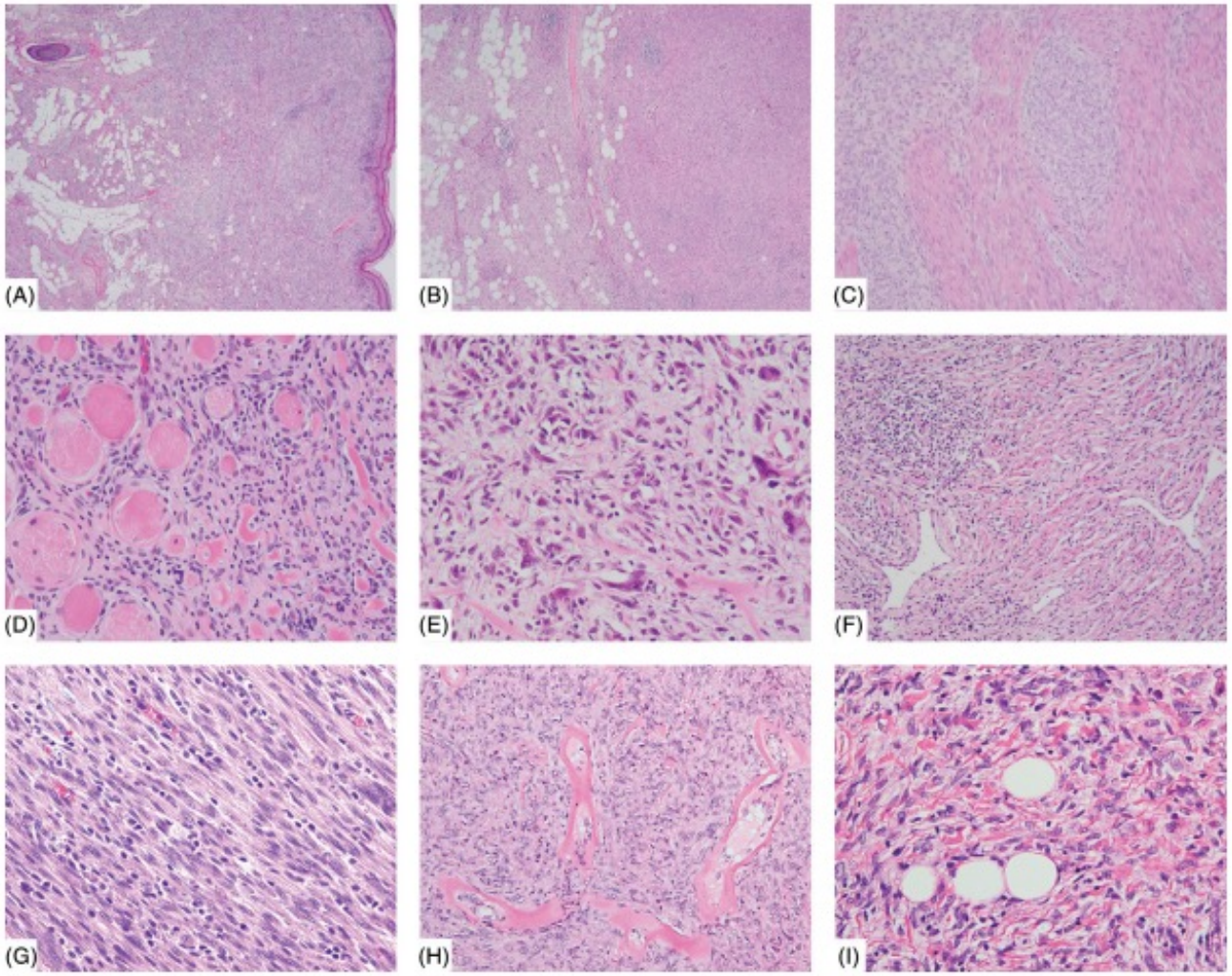
Diagnosis	Frequency
• Infantile fibrosarcoma	91%
• Inflammatory myofibroblastic tumour	18%
• Sarcoma (not otherwise specified)	0.68-1.17%

NTRK, neurotrophic tyrosine receptor kinase

Hechtman JF. Mod Pathol. 2021; doi: 10.1038/s41379-021-00913-8 (Online ahead of print)

NTRK FUSION HISTOLOGY

- Lipofibromatosis-like neural tumour
- Malignant peripheral nerve sheath tumour-like sarcomas
- Infantile fibrosarcoma-like
- Inflammatory myofibroblastic tumour-like



NTRK, neurotrophic tyrosine receptor kinase

Kao YC, et al. Genes Chromosomes Cancer. 2020; 59:575-83

INCIDENCE OF *NTRK* FUSIONS IN SARCOMAS

VARIES IN PAEDIATRIC AND ADULTS TUMOURS

Diagnosis	Frequency
• Infantile fibrosarcoma	91%
• Inflammatory myofibroblastic tumour	18%
• Sarcoma (not otherwise specified)	0.68-1.17%
• GIST	Anecdotal
• Bone sarcomas	Anecdotal

GIST, gastrointestinal stromal tumour; NTRK, neurotrophic tyrosine receptor kinase

Hechtman JF. Mod Pathol. 2021; doi: 10.1038/s41379-021-00913-8 (Online ahead of print)

Atiq MA, et al. Mod Pathol. 2021; 34:95-103; Lam SW, et al. Histopathology. 2021; doi: 10.1111/his.14432 (Online ahead of print)

TESTING APPROACHES

IMMUNOHISTOCHEMISTRY

- panTRK – targets TRKA, TRKB and TRKC
- Good screening tool – **fast** and **inexpensive**, requires **minimal tissue**
  - Sensitivity of 96-100% for *NTRK1/2* fusions
  - Sensitivity of 79% for *NTRK3* fusions
  - Patterns of staining correspond to gene involved
    - Cytoplasmic staining not specific for *NTRK* fusions
- Disadvantage is that it requires subsequent **molecular verification**

NTRK, neurotrophic tyrosine receptor kinase; TRK, tropomyosin receptor kinase

Hechtman JF. Mod Pathol. 2021; doi: 10.1038/s41379-021-00913-8 (Online ahead of print)

TESTING APPROACHES

FLUORESCENT IN SITU HYBRIDISATION (FISH)

- ETV6
  - Useful in tumours with **high prevalence of *ETV6-NTRK3*** fusions such as infantile fibrosarcoma, mammary analogue secretory carcinoma of salivary gland, secretory breast carcinoma
- *NTRK1/2/3*
- Advantages are **rapid** turn around time (1-3 days), requires relatively **little tissue**
- Disadvantages are potential for false negatives, relatively few places offer *NTRK1/2/3*

NTRK, neurotrophic tyrosine receptor kinase

Hechtman JF. Mod Pathol. 2021; doi: 10.1038/s41379-021-00913-8 (Online ahead of print)

TESTING APPROACHES

RT-PCR

- Some common paediatric panels may include *ETV6-NTRK3*
- Advantages include **cost**, moderate **turn around time** (1 week), relatively **little tissue**
- Disadvantages include **lack of detection of other fusion partners**

NTRK, neurotrophic tyrosine receptor kinase; RT-PCR, reverse transcription-polymerase chain reaction

Hechtman JF. Mod Pathol. 2021; doi: 10.1038/s41379-021-00913-8 (Online ahead of print)

TESTING APPROACHES

NEXT GENERATION SEQUENCING (DNA)

- Advantages include detection of **multiple fusion partners**, analyse for other alterations simultaneously
- Disadvantages include requirement for moderate **amount of tumour tissue, limited coverage of introns** (81% sensitivity – best at *NTRK1*), longer **turn around times** (2-4 weeks), **does not confirm gene fusion is functional**

NTRK, neurotrophic tyrosine receptor kinase

Hechtman JF. Mod Pathol. 2021; doi: 10.1038/s41379-021-00913-8 (Online ahead of print)

TESTING APPROACHES

NEXT GENERATION SEQUENCING (RNA)

- Advantages include detection of **multiple fusion partners**, detection is **partner agnostic, confirmation that the fusion gene is transcribed, not limited by gene size** (introns)
- Disadvantages include moderate **amount of tumour tissue**, subject to RNA **degradation** in older samples, longer **turn around times** (2-4 weeks)

Hechtman JF. Mod Pathol. 2021; doi: 10.1038/s41379-021-00913-8 (Online ahead of print)

TESTING APPROACHES

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OTHER

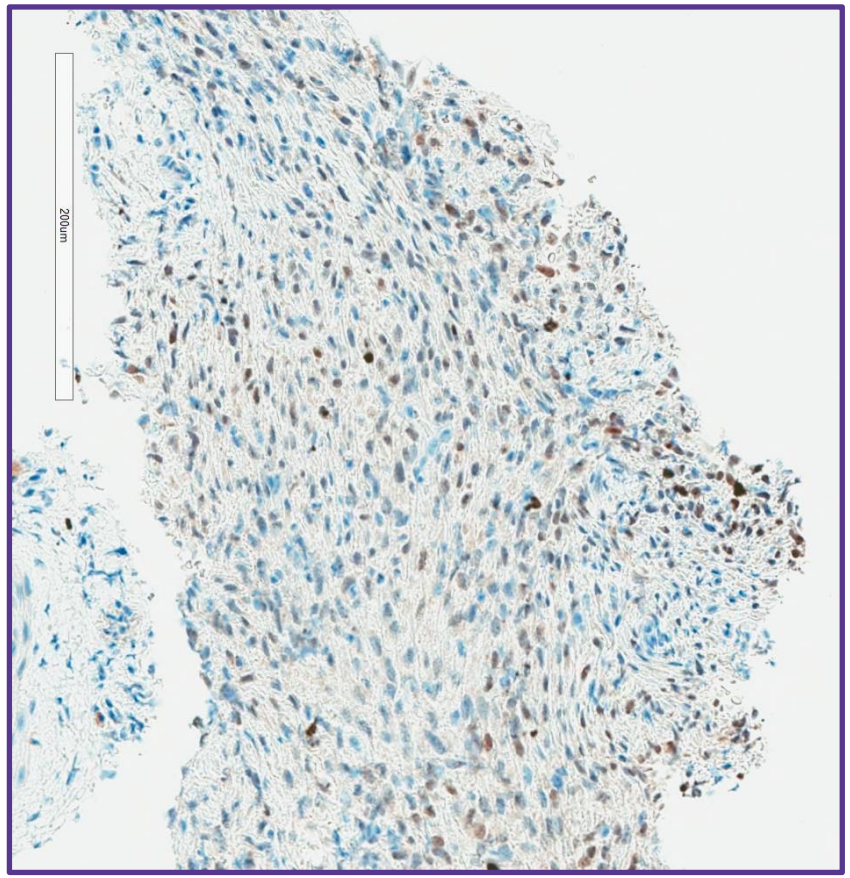
- Whole transcriptome
- Hybrid DNA/RNA panels
- Nanostring

Marchiò C. Ann Oncol. 2019;30(9):1417-1427. doi: 10.1093/annonc/mdz204

Hechtman JF. Mod Pathol. 2021; doi: 10.1038/s41379-021-00913-8 (Online ahead of print)

MY APPROACH…

- panTRK immunohistochemistry
  - Nuclear panTRK
  - Proceed to *ETV6* FISH, RT-PCR
  - NGS panel (RNA) for *NTRK3*
- panTRK immunohistochemistry
  - Cytoplasmic panTRK
  - Sequencing for *NTRK1/2* by (DNA or RNA)
    - *NTRK2* not picked up well by DNA
  - FISH, other
- Negative panTRK
  - Sequencing for multiple tyrosine kinases (RNA)



FISH, fluorescent in situ hybridisation; NGS, next-generation sequencing; NTRK, neurotrophic tyrosine receptor kinase; RT-PCR, reverse transcription-polymerase chain reaction; TRK, tropomyosin receptor kinase

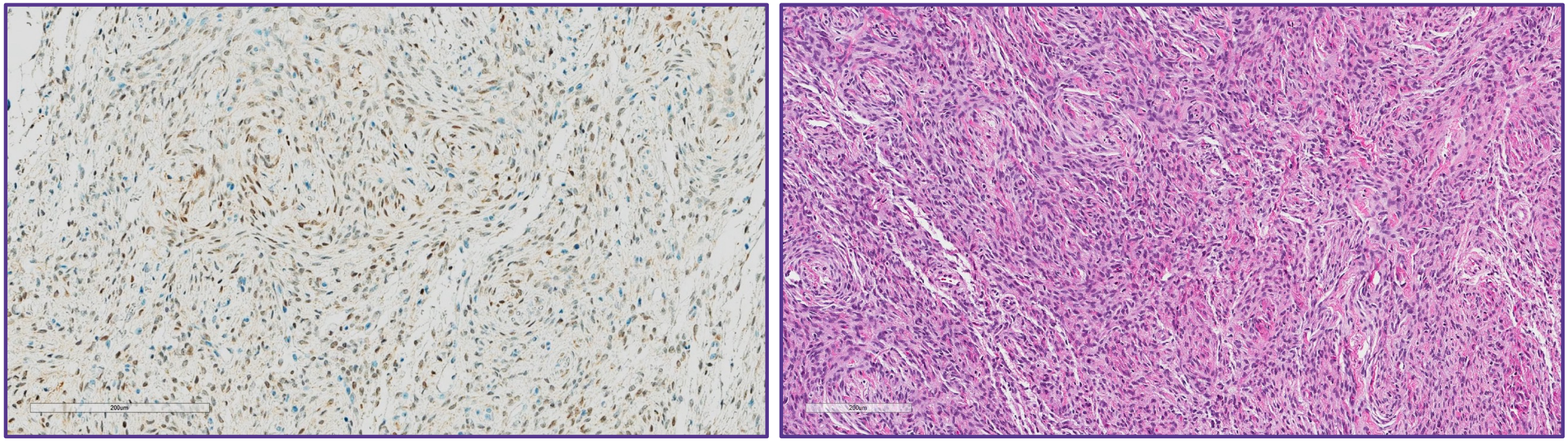
PRACTICAL EXPERIENCE

PEARLS FROM MY PRACTICE

- I have only seen nuclear panTRK staining in *NTRK3* fused cases
  - True even for cases that have failed initial sequencing attempts
- Monomorphic spindle cell tumours (in children / young adults) frequently harbour gene rearrangements
  - Infantile fibrosarcoma/lipofibromatosis-like neural tumour spectrum of tumours frequently harbour kinase gene alterations, including *NTRK*s
  - Quick to pursue RNA sequencing panels

NTRK, neurotrophic tyrosine receptor kinase; TRK, tropomyosin receptor kinase

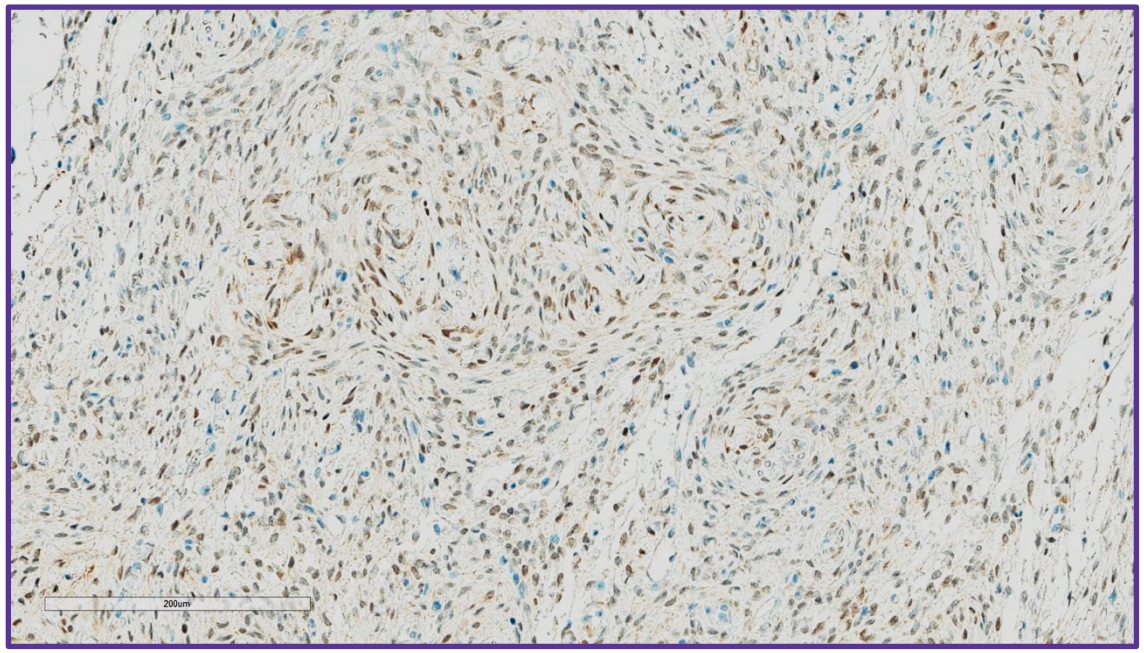
4-MONTH-OLD MALE WITH INTRADURAL/ EXTRA-AXIAL MASS

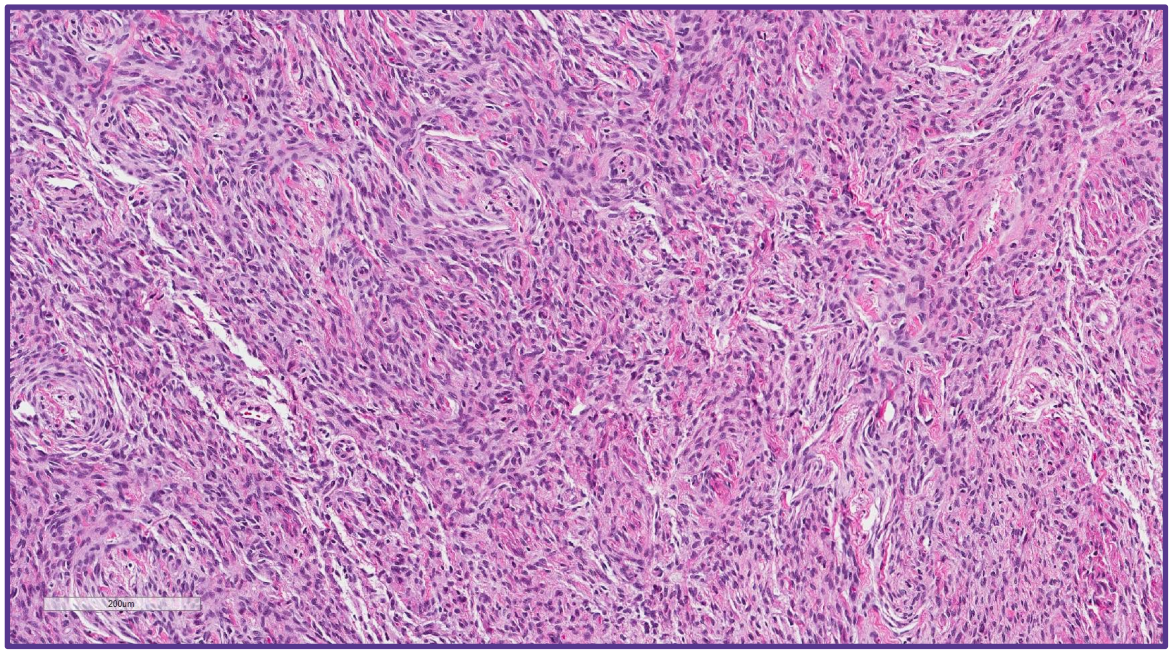


- Outside hospital sent for NTRK IHC – reported as equivocal → Sequencing eventually came back negative so sent for consultations.
- My repeat IHC showed diffuse nuclear panTRK staining → Sent for local RNA sequencing

NTRK, neurotrophic tyrosine receptor kinase

4-MONTH-OLD MALE WITH INTRADURAL/ EXTRA-AXIAL MASS





***KHDRBS1-NTRK3* fusion**

NTRK, neurotrophic tyrosine receptor kinase

TRK FUSION-POSITIVE SARCOMAS
CLINICAL DATA, SECOND GENERATION THERAPIES

Prof. Robin L Jones

Royal Marsden Hospital
Institute of Cancer Research, London, United Kingdom

DISCLOSURES

- Receipt of grants/research support:
  - MSD
  - GSK

- Receipt of consultation fees:
  - Adaptimmune, Astex, Athenex, Bayer, Boehringer Ingelheim, Blueprint, Clinigen, Eisai, Epizyme, Daichii, Deciphera, Immune Design, Immunicum, Karma Oncology, Lilly, Merck, Mundipharma, PharmaMar, Springworks, SynOx, Tracon

NTRK FUSION-POSITIVE TUMOURS

- Tropomyosin receptor kinase (TrK)
  - 3 trans-membrane proteins (Trk A, B + C receptors)
  - Encoded by the *NTRK1*, *2* + *3* genes
  - Expressed in human neuronal tissue
    - Function as high-affinity receptors for neurotrophins

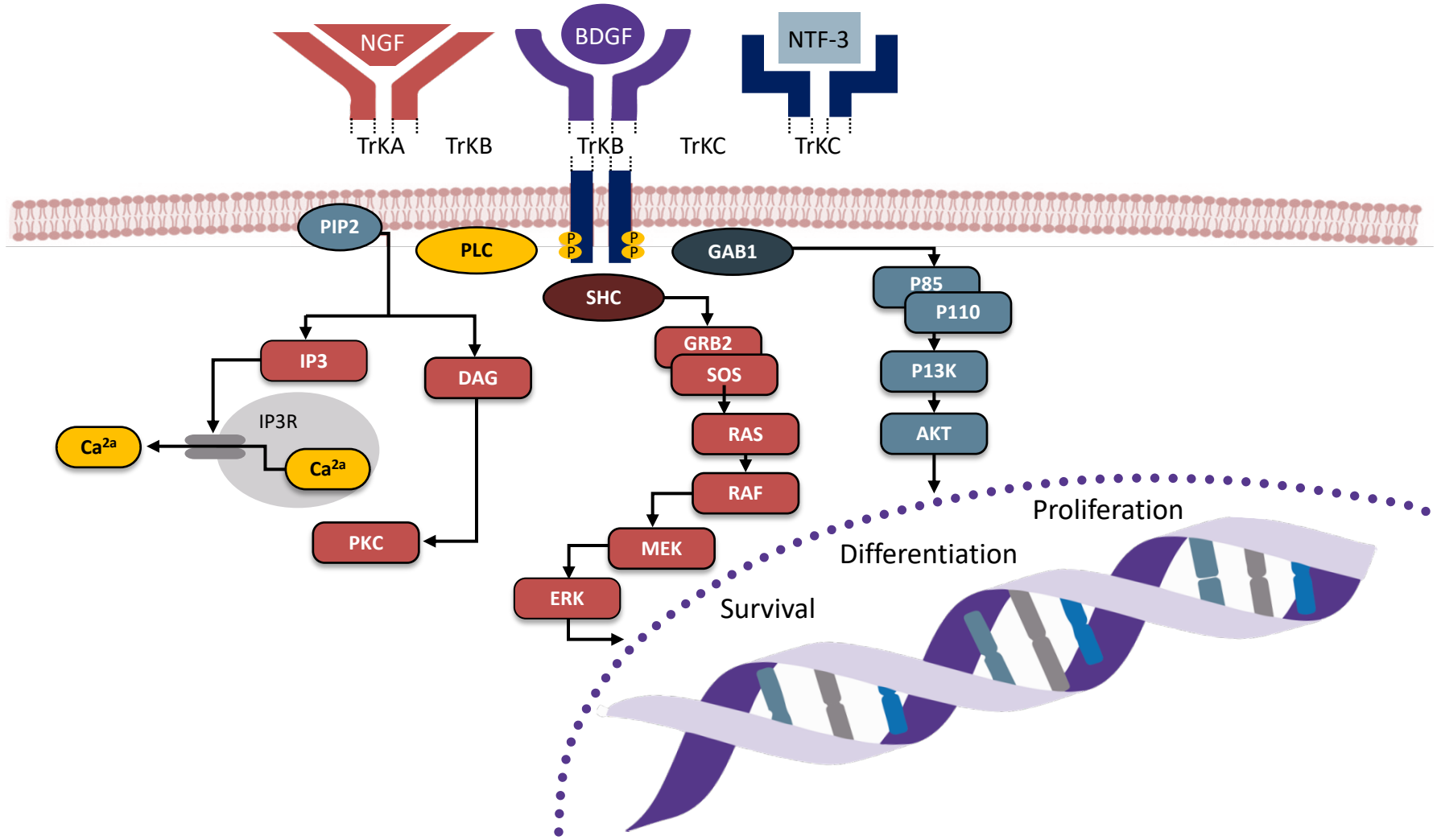
- Oncogenic *NTRK* gene fusions
  - Induce cell proliferation
  - Engage downstream signalling pathways

- Rare – occur in diverse range of tumours

NTRK, neurotrophic tyrosine receptor kinase; TRK, tropomyosin receptor kinase

Doebele RC, et al. Cancer Discov. 2015;5(10):1049-57; Wilding CP, et al. Curr Opin Oncol 2020;32(4):307-13

TRK RECEPTOR SIGNALLING



AKT, v-akt murine thymoma viral oncogene homologue; BDGF, brain-derived growth factor; DAG, diacyl-glycerol; ERK, extracellular signal-regulated kinase; GAB1, GRB2-associated-binding protein 1; GRB2, growth factor receptor-bound protein 2; IP3, inositol trisphosphate; IP3R, IP3 receptor; MEK, mitogen-activated protein kinase; NGF, nerve growth factor; NTF-3, neurotrophin -3; PI3K, phosphatidylinositol-4,5-biphosphate 3-kinase; PIP2, phosphatidylinositol 4,5-biphosphate; PKC, protein kinase C; PLC, phospholipase C; RAF, rapidly accelerated fibrosarcoma kinase; RAS, rat sarcoma kinase; SHC, Src homology 2 domain containing; Trk, tropomyosin receptor kinase

Amatu A, et al. ESMO Open 2016;1:e000023

NTRK FUSIONS IN SARCOMAS

- Established role
  - Infantile fibrosarcoma with *ETV6-NTRK3* gene fusions[1]
  - *KIT/PDGFRA w*ild-type GIST[2]
- Unclear which sarcoma subtypes are likely to harbour *NTRK* gene fusions
  - Screening methods are expensive + must be targeted
- Tumours with translocations of *EWSR1* in Ewing sarcoma or KIT in GIST are unlikely to harbour *NTRK* gene fusions
  - More research is required to confirm these observations
- Emerging tumours with *NTRK* fusions
  - Spindle cell tumours with *RAF1, BRAF* & *NTRK1/2* gene fusions[3]
  - Infantile fibrosarcoma-like with *BRAF* & *NTRK1* gene fusions[4,5]
  - Lipofibromatosis-like neural tumours with *NTRK1* gene fusions[6]
  - *NTRK3* gene fusions positive sarcomas[6]

GIST, gastrointestinal stromal tumour; NTRK, neurotrophic tyrosine receptor kinase; PDGFRA, platelet-derived growth factor receptor alpha

1. Fletcher CDM et al. WHO Classification of Tumours of Soft Tissue and Bone. 4th ed. Lyon, France: IARC Press; 2013; 2. Cocco E, et al. Nat Rev Clin Oncol. 2018;15:731-47;
3. Suurmeijer AJH, et al. Genes Chromosomes Cancer. 2018;57:611-21; 4. Kao Y-C, et al. Am J Surg Pathol. 2018;42:28-38;
5. Agaram NP, et al. Am J Surg Pathol. 2016;40:1407-16; 6. Suurmeijer AJH, et al. Genes Chromosomes Cancer. 2019;58:100-10

FREQUENCY OF *NTRK* GENE FUSIONS IDENTIFIED IN SARCOMAS

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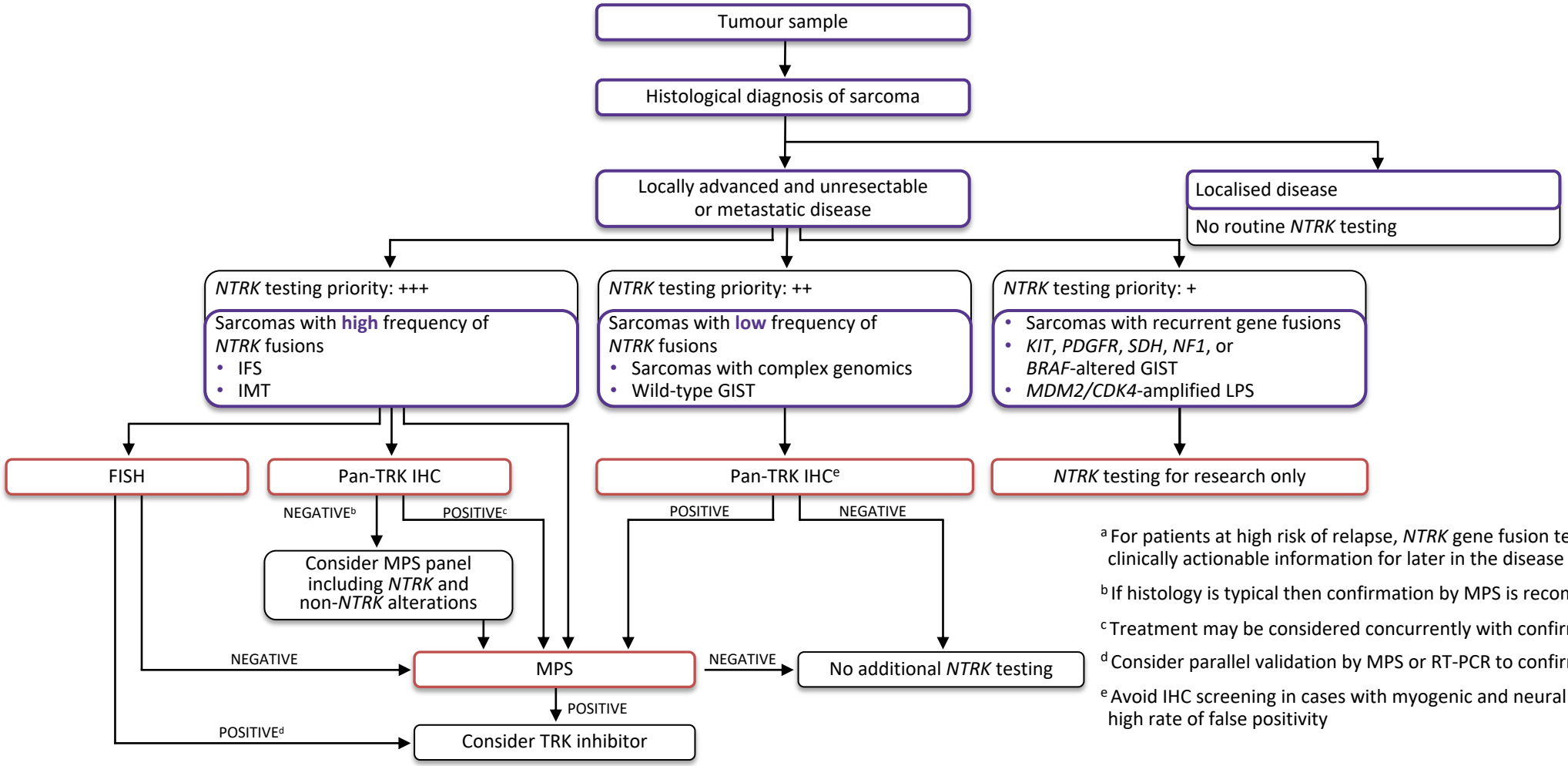
Study	Testing method	Proportion of patients with *NTRK* fusions identified	*NTRK* fusion-positive sarcoma subtypes	*NTRK* genes and fusion partners involved
Agaram et al.	FISH, RNA MPS	71% (10/14)	Lipofibromatosis-like tumour	1 *TPR-NTRK1* 1 *TPM3-NTRK1* 4 *LMNA-NTRK1*
Bourgeois et al.	RT-PCR	91% (10/11)	IFS	*ETV6-NTRK3*
Bui et al.	Targeted DNA MPS	0.7% (1/152)	Myopericytoma	NR
Chang et al.	Targeted RNA MPS	33% (3/9)	IMT	*ETV-NTRK3*
Chmielecki et al.	Targeted RNA MPS	1% (4/324)	IFS (n=2), assorted soft tissue sarcoma (n=1), haemangioma (n=1), bone sarcoma (n=1)	*SQSTM1-NTRK1* (n=1), other fusion partners NR
Church et al.	FISH	96% (25/26)	IFS	*NTRK3*
Croce et al.	Targeted RNA MPS	54% (7/13)	Uterine and vaginal sarcomas resembling fibrosarcoma	6 *TPM3-NTRK1*, 1 *EML4-NTRK3*
Gatalica et al.	Targeted RNA MPS	0.4% (2/478)	1 STS (poorly differentiated sarcoma with possible myofibroblastic differentiation), 1 uterine sarcoma (intermediate to high-grade sarcoma of uterine origin, with myxoid stroma and no specific line of differentiation)	1 *TPM3-NTRK1*, 1 *SPECC1L-NTRK3*
Rosen et al.	Targeted RNA MPS	1% (11/944)	Sarcoma NOS [9/770 (1%)], uterine sarcoma [2/174 (1%)]	NR
Shi et al.	Targeted DNA MPS	0.5% (1/186) overall [4% (1/24) in quad-negative tumours]	GIST	*ETV6-NTRK3*
Solomon et al.	Targeted DNA and/or RNA MPS	0.7% (13/1915) 18% (3/17)	IFS (n=2), lipofibromatosis-like neural tumour (n=2), uterine sarcoma (n=2), uterine high-grade pleomorphic sarcoma, high-grade spindle cell sarcoma, malignant spindle cell sarcoma, spindle cell sarcoma, angiosarcoma, S-100 positive malignant spindle cell neoplasm, low grade sarcoma (all n=1) IMT	*LMNA-NTRK1* (n=4), *TPM3-NTRK1* (n=3), *ETV6-NTRK3* (n=2), *TPR-NTRK1*, *TPM4-NTRK3*, *EEF1A1-NTRK3*, *PEAR1-NTRK1* (all n=1) *ETV6-NTRK3*
Stransky et al.	TCGA RNA-seq dataset	1% (1/103)	Sarcoma	*TPM3-NTRK1*
Surrey et al.	Targeted RNA MPS	4% (2/45)	Sarcomas (other)	1 *TFG-NTRK3*, 1 *RBPMS-NTRK3*
Suurmeijer et al.	FISH, targeted RNA MPS	60% (15/25)	Malignant peripheral nerve sheath tumour-like	8 *LMNA-NTRK1*, 3 *TPM3-NTRK1*, 1 *SPECC1L-NTRK2*, 1 *TPR-NTRK1*, 2 *NTRK1* with unknown fusion partners
Yamamoto et al.	MPS (TBC), IHC	5% (2/40)	IMT	*ETV6-NTRK3*
Zhu et al.	Targeted RNA MPS	3% (5/184)	Lipofibromatosis-like neural tumour (n=2), IFS (n=1), IMT (n=1), sarcoma NOS (n=1)	2 *ETV6-NTRK3*, 2 *TPM3-NTRK1*, 1 *LMNA-NTRK1*

FISH, fluorescent in situ hybridisation; GIST, gastrointestinal stromal tumour; IFS, infantile fibrosarcoma; IHC, immunohistochemistry; IMT, inflammatory myofibroblastic tumour; MPS, massive parallel sequencing; NOS, not otherwise specified; NR, not reported; NTRK, neurotrophic tyrosine receptor kinase; RT-PCR, reverse transcription polymerase chain reaction; STS, soft tissue sarcoma; TCGA, The Cancer Genome Atlas

Demetri GD, et al. Ann Oncol. 2020;31(11):1506-17

RECOMMENDED ALGORITHM FOR *NTRK* GENE FUSION TESTING IN SARCOMAS



[a] For patients at high risk of relapse, *NTRK* gene fusion testing might provide clinically actionable information for later in the disease course

[b] If histology is typical then confirmation by MPS is recommended

[c] Treatment may be considered concurrently with confirmatory MPS

[d] Consider parallel validation by MPS or RT-PCR to confirm that fusion is in-frame

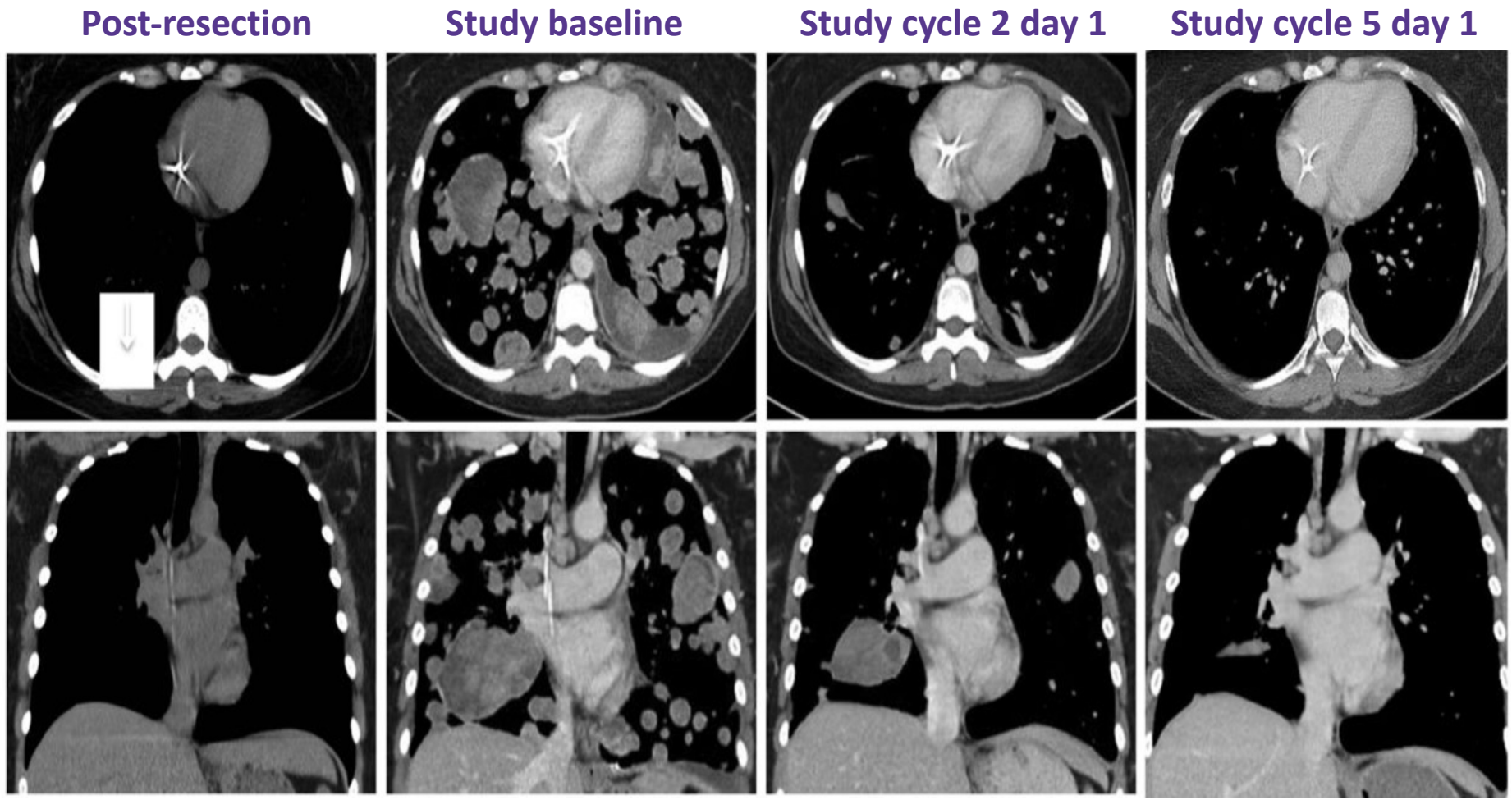
[e] Avoid IHC screening in cases with myogenic and neural differentiation due the high rate of false positivity

FISH, fluorescent in situ hybridisation; GIST, gastrointestinal stromal tumour; IFS, infantile fibrosarcoma; IHC, immunohistochemistry; IMT, inflammatory myofibroblastic tumour; LPS, liposarcoma; MPS, massive parallel sequencing; NTRK, neurotrophic tyrosine receptor kinase; RT-PCR, reverse transcription polymerase chain reaction; TRK tropomyosin receptor kinase

Demetri GD, et al. Ann Oncol. 2020;31(11):1506-17

LAROTRECTINIB IN SARCOMAS

RESPONSE IN SARCOMA WITH *LMNA-NTRK1* FUSION TO LAROTRECTINIB



NTRK, neurotrophic tropomyosin receptor kinase

Doebele RC, et al. Cancer Discov. 2015;5(10):1049-57

LAROTRECTINIB IN TRK FUSION-POSITIVE SARCOMAS

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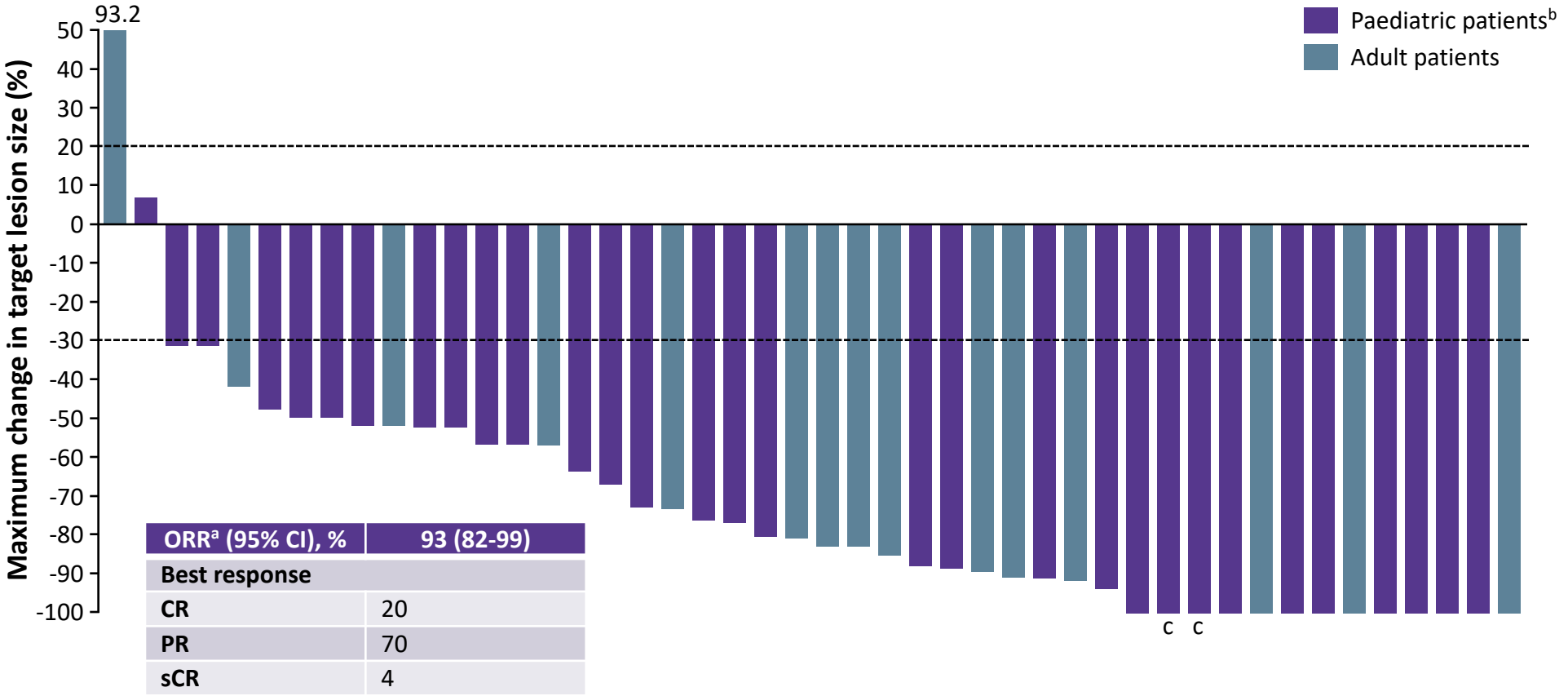
In this subset of patients with sarcoma: ORR = 93% across both adult and paediatric patients with *NTRK* gene fusions

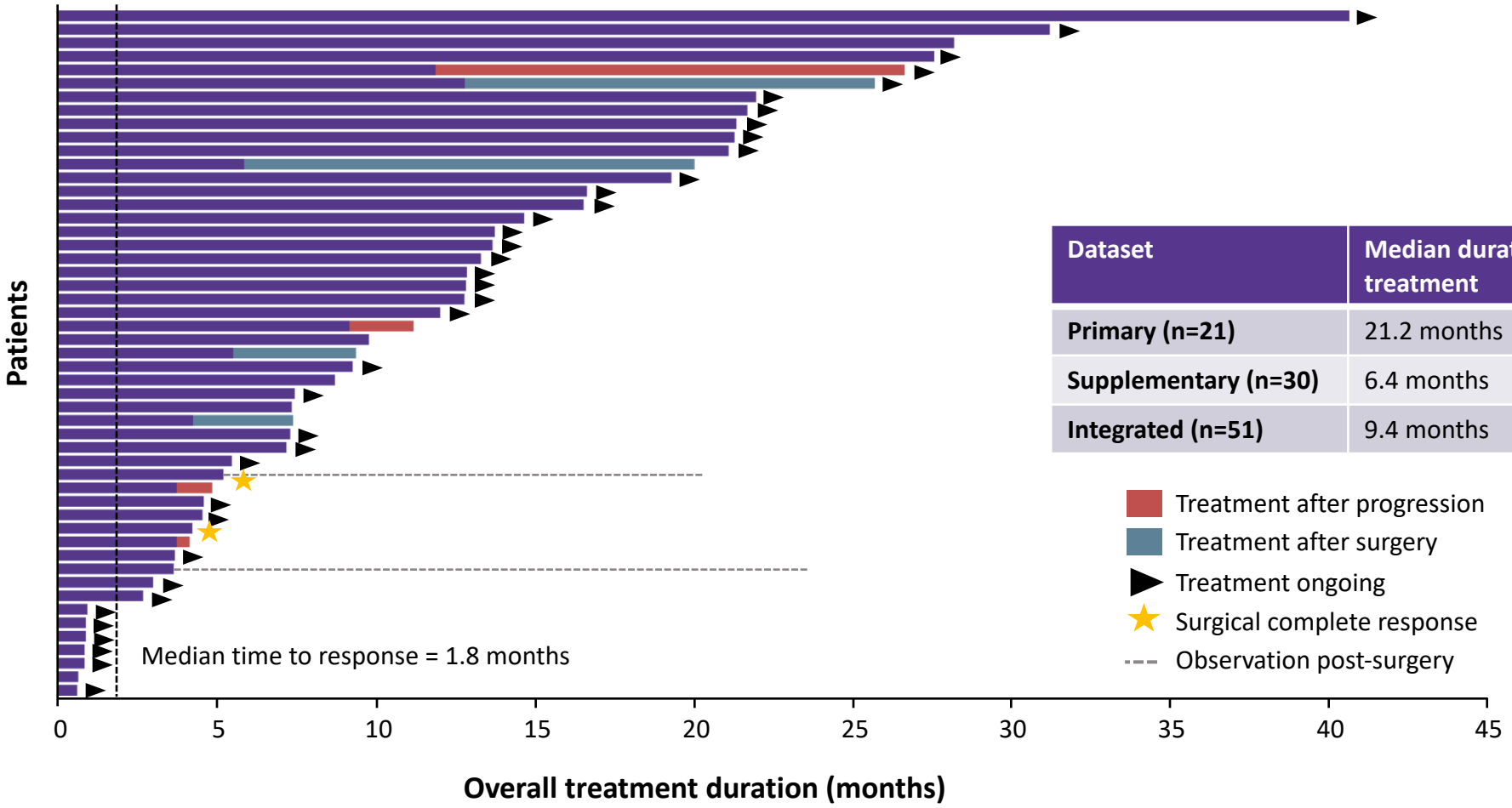


ORR[a] (95% CI), %	93 (82-99)
Best response	
CR	20
PR	70
sCR	4

Investigator response assessments, as of 30 July 2018

[a]n=46 patients; includes three unconfirmed PRs pending confirmation; does not include five patients continuing on study and awaiting initial response assessment
[b]Age <21 years; [c]sCR
CI, confidence interval; CR, complete response; ORR, objective response; PR, partial response; sCR, surgical complete response; TRK tropomyosin receptor kinase
Federman N, et al. CTOS. 2018

LAROTRECTINIB: DURATION OF TREATMENT



Dataset	Median duration of treatment
Primary (n=21)	21.2 months
Supplementary (n=30)	6.4 months
Integrated (n=51)	9.4 months

Investigator response assessments, as of 30 July 2018

Federman N, et al. CTOS. 2018

TRK-INHIBITION PROVIDES ROBUST RESPONSES IN PATIENTS WITH *NTRK* GENE FUSION-POSITIVE SARCOMA

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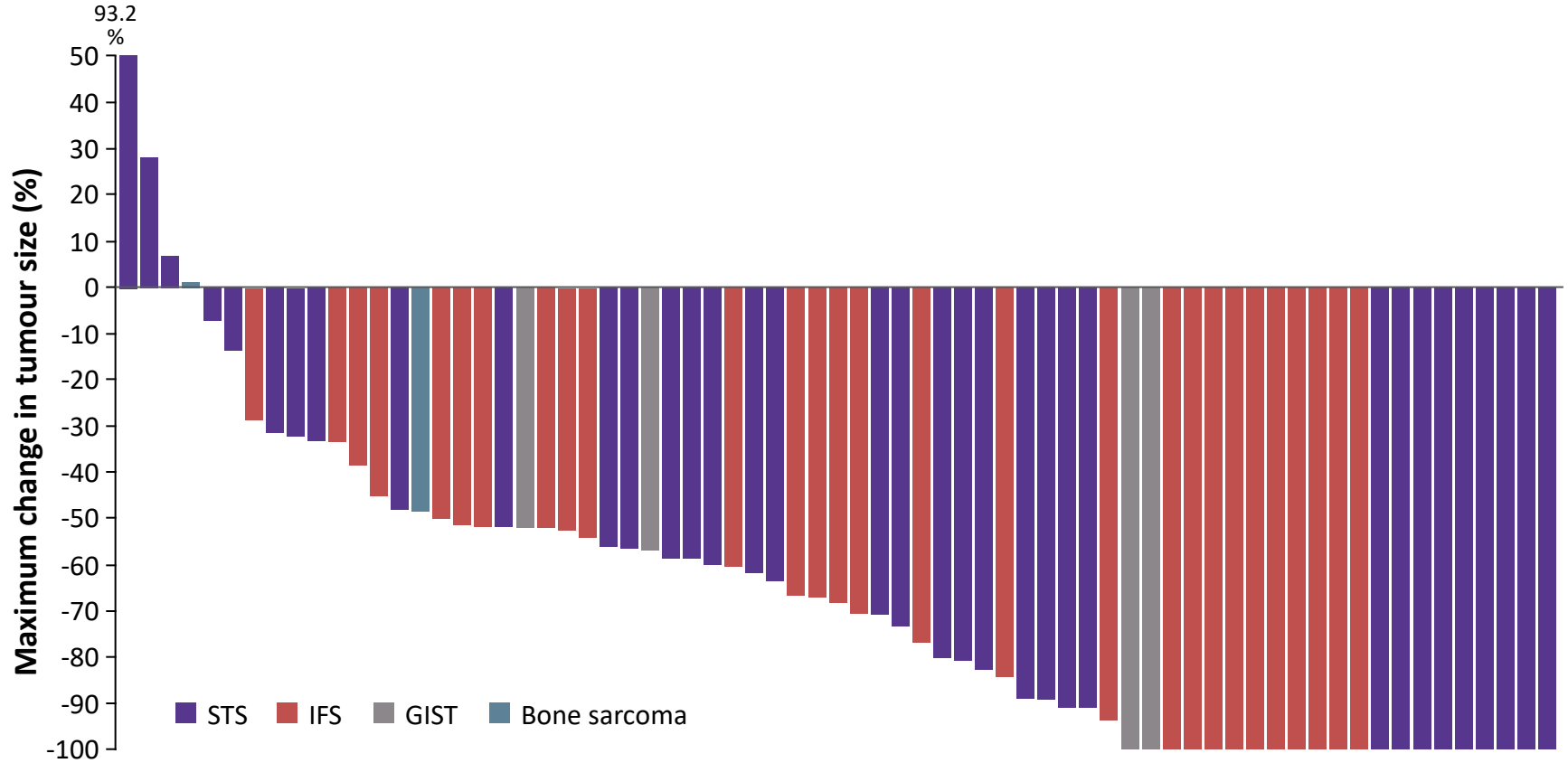
EFFICACY OF LAROTRECTINIB IN SARCOMAS HARBOURING TRK FUSIONS: BEST CHANGE IN TARGET LESIONS



Data cut-off: Feb 19, 2019

GIST, gastrointestinal stromal tumour; IFS, infantile fibrosarcoma; NTRK, neurotrophic tropomyosin receptor kinase; STS, soft tissue sarcoma; TRK, tropomyosin receptor kinase

Demetri GD, et al. CTOS 2019. Abstract #3254588. Oral presentation

TRK-INHIBITION PROVIDES DURABLE RESPONSES IN PATIENTS WITH *NTRK* GENE FUSION-POSITIVE SARCOMA

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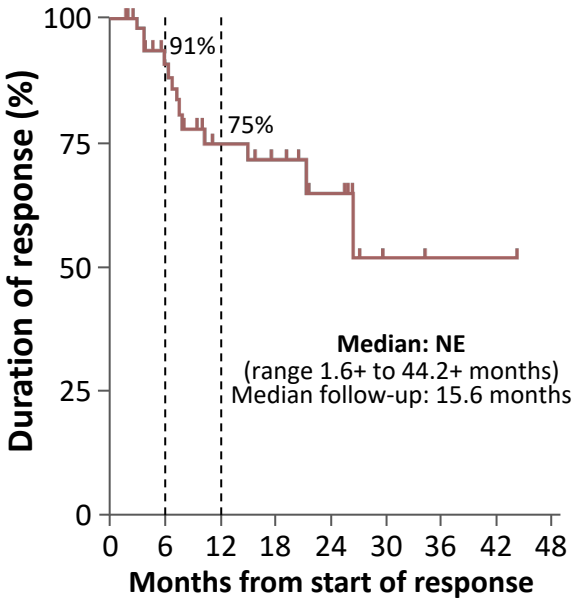
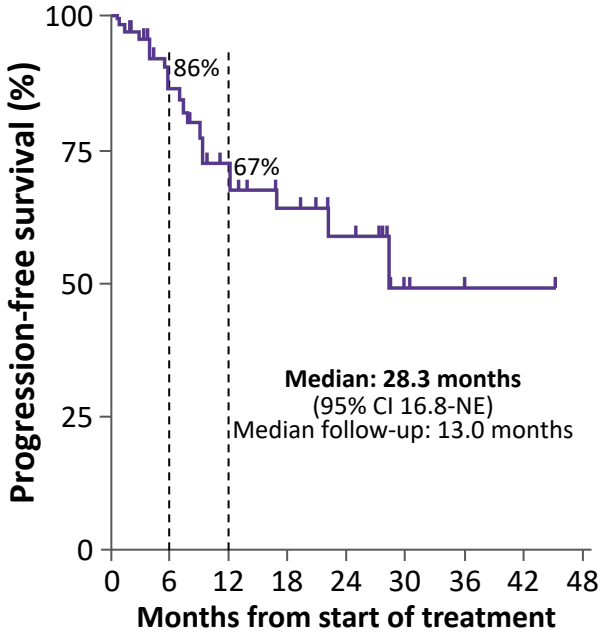
DURATION OF RESPONSE



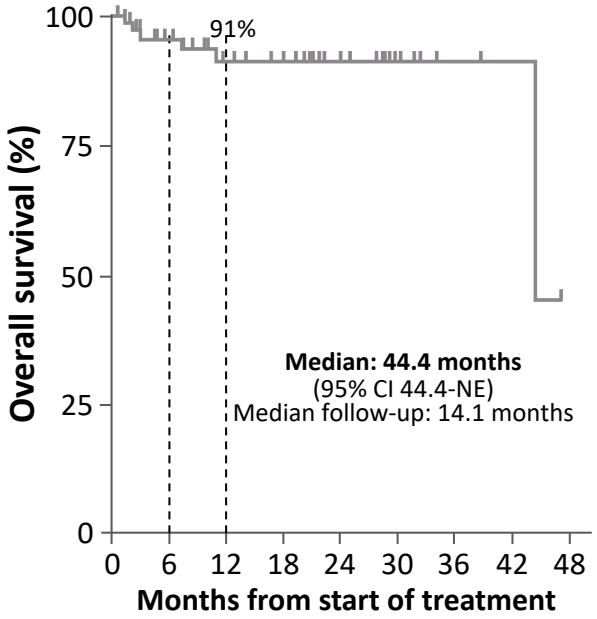
No. at risk	54	37	22	14	9	2	1	1	0

PROGRESSION-FREE SURVIVAL



	71	41	25	20	10	3	1	1	0

OVERALL SURVIVAL



	71	53	36	29	17	8	3	2	0

Data cut-off: Feb 19, 2019

CI, confidence interval; NE, not estimable; NTRK, neurotrophic tropomyosin receptor kinase; TRK, tropomyosin receptor kinase

Demetri GD, et al. CTOS 2019. Abstract #3254588. Oral presentation

LAROTRECTINIB IN TRK FUSION-POSITIVE SARCOMAS - TRIAL DESIGN

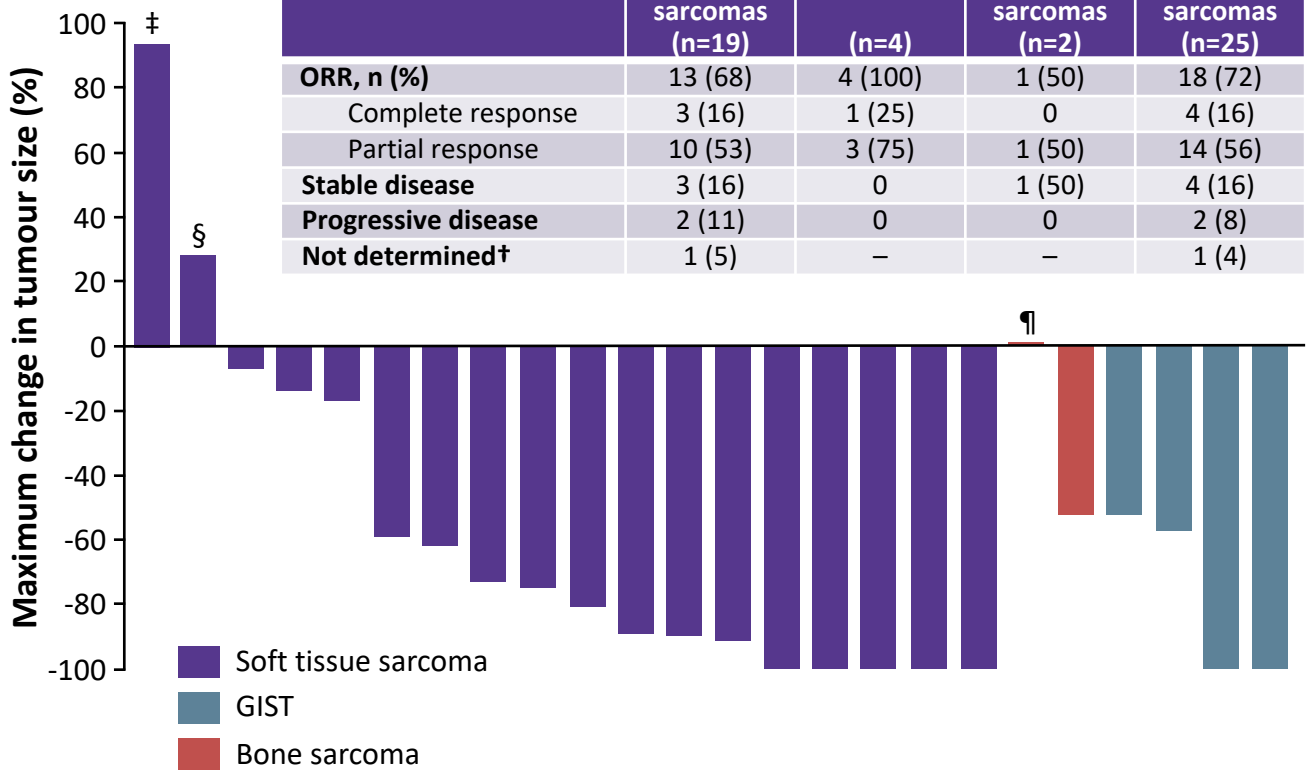
- Assessed the efficacy and safety of larotrectinib in adult patients with TRK fusion-positive sarcomas
- Adult patients aged ≥18 years with sarcomas harbouring an *NTRK* gene fusion and treated with larotrectinib were identified from three clinical trials:
  - NCT02122913
  - NCT02576431
  - NCT02637687
- Patients (N=25)
  - Soft tissue sarcoma (n=19)
  - Gastrointestinal stromal tumour (n=4)
  - Bone sarcoma (n=2)
- larotrectinib was administered orally at 100 mg BID (one patient received 150 mg BID)
- The primary endpoint was ORR, as assessed by investigators using RECIST v1.1
- Data cut-off: 15 July 2019

BID, twice a day; NTRK, neurotrophic tropomyosin receptor kinase; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors; TRK, tropomyosin receptor kinase

Kummar S, et al. Connective Tissue Oncology Society (CTOS) Virtual Meeting Eposter 106: 2020

LAROTRECTINIB IN TRK FUSION-POSITIVE SARCOMAS - EFFICACY

	Soft tissue sarcomas (n=19)	GISTs (n=4)	Bone sarcomas (n=2)	All adult sarcomas (n=25)
ORR, n (%)	13 (68)	4 (100)	1 (50)	18 (72)
Complete response	3 (16)	1 (25)	0	4 (16)
Partial response	10 (53)	3 (75)	1 (50)	14 (56)
Stable disease	3 (16)	0	1 (50)	4 (16)
Progressive disease	2 (11)	0	0	2 (8)
Not determined†	1 (5)	–	–	1 (4)



Endpoint	Iarotrectinib (N=25)
Primary endpoint	
ORR, n (%)	18 (72) (95% CI 51-88)
Secondary endpoints	
Time to response, median (range), mo	1.8 (0.9-3.5)
Duration of treatment, mo	Range, 0.1-51.6 Treatment ongoing in 10 patients (40%) at data cut-off
Median DoR, %	NE (95% CI 7.2-NE) at 22.9 mo (median FU) 64 (95% CI 41-87) at 24 mo
Median PFS, mo	28.3 (95% CI 6.8-NE) at 22.1 mo
Median OS, %	44.4 (95% CI 44.4-NE) at 21.4 mo (median FU) 91 (95% CI 80-100) at 24 mo

Data cut-off: 15 July 2019.

‡ Patient with malignant peripheral nerve sheath tumour who had progressive disease as best response; § Patient with synovial sarcoma who had progressive disease as best response; ¶ Patient with bone sarcoma with a maximum change in tumour size of 1.1%

CI, confidence interval; DoR, duration of response; FU, follow-up; GIST, gastrointestinal stromal tumour; mo, months; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival

Kummar S, et al. Connective Tissue Oncology Society (CTOS) Virtual Meeting Eposter 106: 2020

SAFETY: ADVERSE EVENTS OCCURRING ≥15% PATIENTS[1]

- AEs were mostly grade 1 or 2, and with 6 months additional follow up compared with the previous analysis,[2] there were no unexpected safety signals
- Grade 3 or 4 treatment-emergent AEs occurred in 11 patients (44%), with none attributed to larotrectinib
- Two patients had grade 5 AEs (neurofibrosarcoma and malignant neoplasm progression) and neither were attributed to larotrectinib
- Three patients (12%) permanently discontinued treatment due to treatment-emergent AEs
  - No patients permanently discontinued treatment due to a larotrectinib-related AE

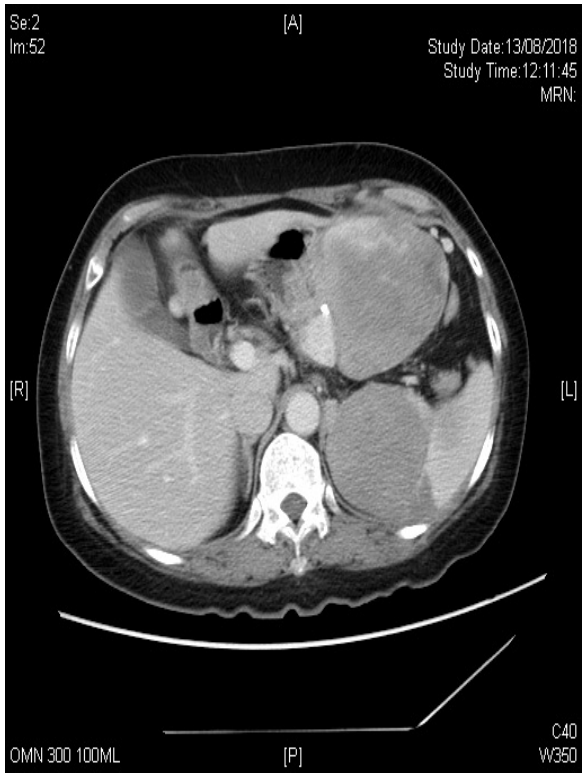
Preferred term	Treatment-emergent AEs, n (%)			Treatment-related AEs, n (%)	
	Grade 1 or 2	Grade 3	Any Grade	Grade 3	Any Grade
Constipation	12 (48)	0	12 (48)	0	5 (20)
Dizziness	9 (36)	0	9 (36)	0	6 (24)
Abdominal pain	7 (28)	1 (4)	8 (32)	0	1 (4)
Fatigue	7 (28)	1 (4)	8 (32)	0	3 (12)
Nausea	8 (32)	0	8 (32)	0	4 (16)
ALT increased	6 (24)	0	6 (24)	0	3 (12)
Anaemia	4 (16)	2 (8)	6 (24)	0	1 (4)
Back pain	6 (24)	0	6 (24)	-	-
Myalgia	6 (24)	0	6 (24)	0	5 (20)
Edema peripheral	6 (24)	0	6 (24)	0	2 (8)
Abdominal distension	5 (20)	0	5 (20)	0	1 (4)
Diarrhoea	5 (20)	0	5 (20)	0	1 (4)
Headache	5 (20)	0	5 (20)	0	3 (12)
Pain in extremity	5 (20)	0	5 (20)	0	1 (4)
Anxiety	3 (12)	1 (4)	4 (16)	-	-
Musculoskeletal chest pain	4 (16)	0	4 (16)	-	-
Urinary tract infection	3 (12)	1 (4)	4 (16)	-	-
Vomiting	4 (16)	0	4 (16)	0	2 (8)
Weight increased	2 (8)	2 (8)	4 (16)	0	2 (8)

AE, adverse event

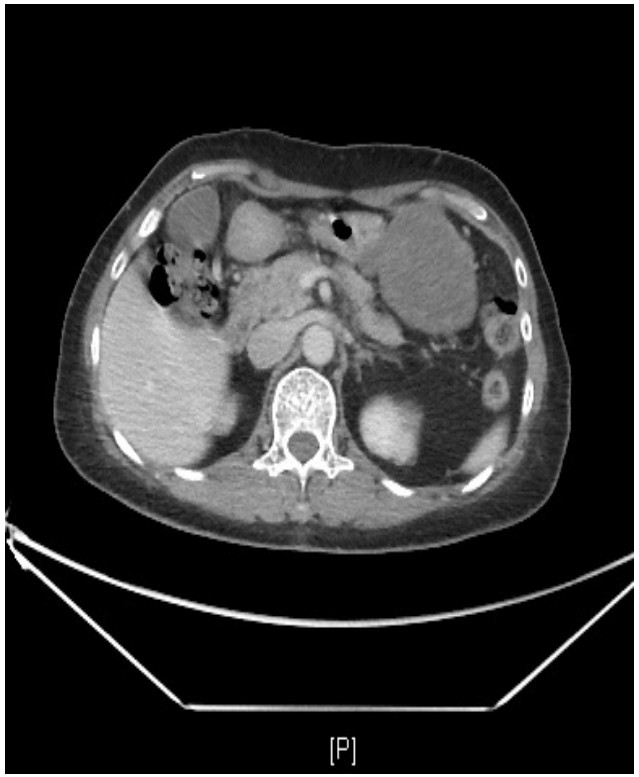
1. Kummar S, et al. Connective Tissue Oncology Society (CTOS) Virtual Meeting Eposter 106: 2020; 2. Demetri GD, et al. CTOS Abstract #3254588: 2019

ENTRECTINIB IN SARCOMAS

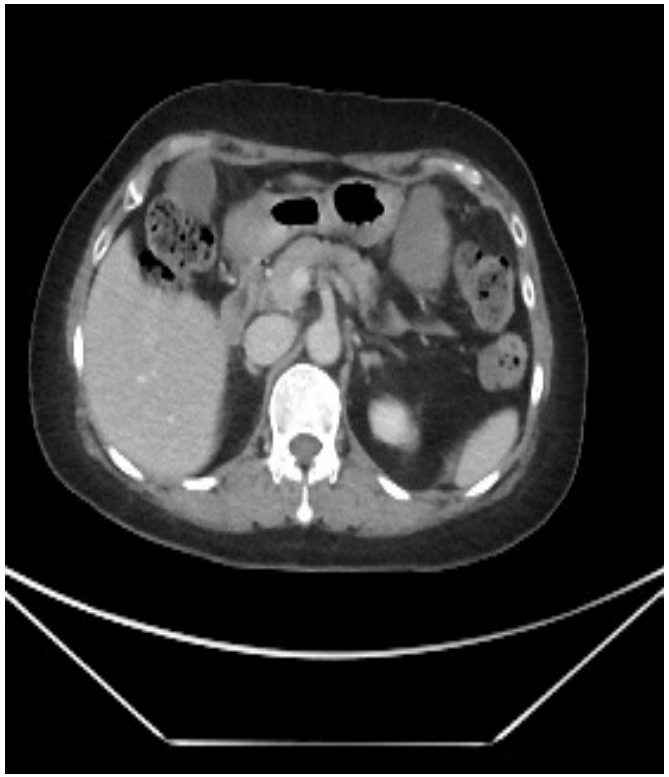
RADIOLOGICAL RESPONSE IN A PATIENT WITH A HIGH GRADE SARCOMA WITH HISTIOCYTIC DIFFERENTIATION (*ETV6:NTRK3* EXON 14) TREATED WITH ENTRECTINIB (CLINICAL TRIAL)



Baseline



~ 3 months after treatment



Nadir achieved at ~6 months after treatment

NTRK, neurotrophic tropomyosin receptor kinase

ENTRECTINIB IN SARCOMAS – TRIAL DESIGN

- Combined analysis of
  - ALKA-372-001
  - NCT02097810[1]
  - NCT02568267[2]

- Sarcoma cohort
  - RECIST response rate: 6/12 (50%)
  - Six with stable disease

- Most treatment related adverse events Grade 1 or 2
  - Serious treatment-related adverse events: 30/ 355 (9%) patients

RECIST, Response Evaluation Criteria in Solid Tumors

1.ClinicalTrials.gov (NCT02097810); 2. ClinicalTrials.gov (NCT02568267)

Doebele RC, et al. Lancet Oncol. 2020;21(2):271-282

SECOND GENERATION TRK INHIBITORS – ONGOING CLINICAL TRIALS

- Phase 1/ 2 Loxo-195
  - Previously treated with TRK inhibitors
  - NCT03215511[1]

- repotrectinib (TPX-0005)
  - Next generation pan-TRK, ROS1 + ALK tyrosine kinase inhibitor
  - Phase 1/ 2 in 6 cohorts (NCT03093116[2])
  - One cohort = pre-treated TRK fusion positive solid tumours

TRK, tropomyosin receptor kinase

1. ClinicalTrials.gov (NCT03215511); 2. ClinicalTrials.gov (NCT03093116)

MECHANISMS OF RESISTANCE

- Acquired resistance[1,2,3]
- More research needed[1]
- Mutations leading to secondary resistance described[2,3]
- On-target mutations involving *NTRK* kinase domain[2]
- TRK xDFG mutations confer resistance to type I next-generation TRK inhibitors[2]
  - designed to maintain potency against several kinase domain mutations
- Off-target resistance[3]
  - Patients pre-treated TRK inhibitors + in patient-derived models
  - Mediated by genomic alterations that converge to activate mitogen-activated protein kinase (MAPK) pathway

MAPK, mitogen-activated protein kinase; NTRK, neurotrophic tropomyosin receptor kinase; TRK, tropomyosin receptor kinase

1. Russo M, et al. Cancer Discov. 2016;6(1):36-44; 2. Cocco E, et al. Cancer Discov. 2021;11(1):126-41; 3. Cocco E, et al. Nat Med. 2019;25(9):1422-7

CONCLUSIONS

TRK inhibitors

- High response rate with long durability in patients with TRK fusion sarcomas
- Favourable safety profile and well tolerated

Importance of identifying *NTRK* gene fusions in patients with sarcomas

- To enable these patients to potentially benefit from TRK-targeted therapy

NTRK, neurotrophic tropomyosin receptor kinase; TRK, tropomyosin receptor kinase

DETECTION OF TRK FUSION-POSITIVE LUNG CANCERS

Prof. Erin Rudzinski, MD

Seattle Children's Hospital,
Seattle, USA

INCIDENCE OF GENE FUSIONS IN LUNG CANCER

NTRK connect® POWERED BY COR2ED

Gene	Common alteration	Incidence
ROS1	Rearrangement	1-2%
ALK	Rearrangement	2-7%
BRAF	V600E	1-2%
NTRK	Rearrangement	0.2%
MET	Amplification	0.34%
MET	Exon 14 skipping	2-3%
EGFR	Common (exon 19, 21)	30-50%
EGFR	Uncommon (exon 20, G719X, L585R, other)	12%
RET	Rearrangement	1-2%
HER2	Mutations	2-4%
KRAS	Mutations	20-30%
NRG1	Rearrangement	0.2-0.8%

ALK, anaplastic lymphoma kinase; BRAF, v-raf murine sarcoma viral oncogene homolog B1; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; KRAS, Kirsten rat sarcoma viral oncogene homolog; MET, hepatocyte growth factor receptor gene; NRG1, neuregulin 1; NTRK, neurotrophic tyrosine receptor kinase; RET, rearranged during transfection; ROS1, c-ros oncogene 1

Melosky B, et al. Lung Cancer. 2021; 160:136-51 (modified)

INCIDENCE OF GENE FUSIONS IN LUNG CANCER

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Melosky B, et al. Lung Cancer. 2021; 160:136-51 (modified)

INCIDENCE

- *NTRK* fusions occur in NSCLC lung cancer at approximately 0.1-0.3%
  - 10× more common in tumours with no other oncogenic drivers
  - *NTRK1* may be more common than *NTRK2/3*
- *NTRK* fusions mutually exclusive with other oncogenic drivers
  - However, may occur as a resistance mechanism to other TKI therapies

Frequency of *NTRK* fusions among consecutively tested unique patients with NSCLC

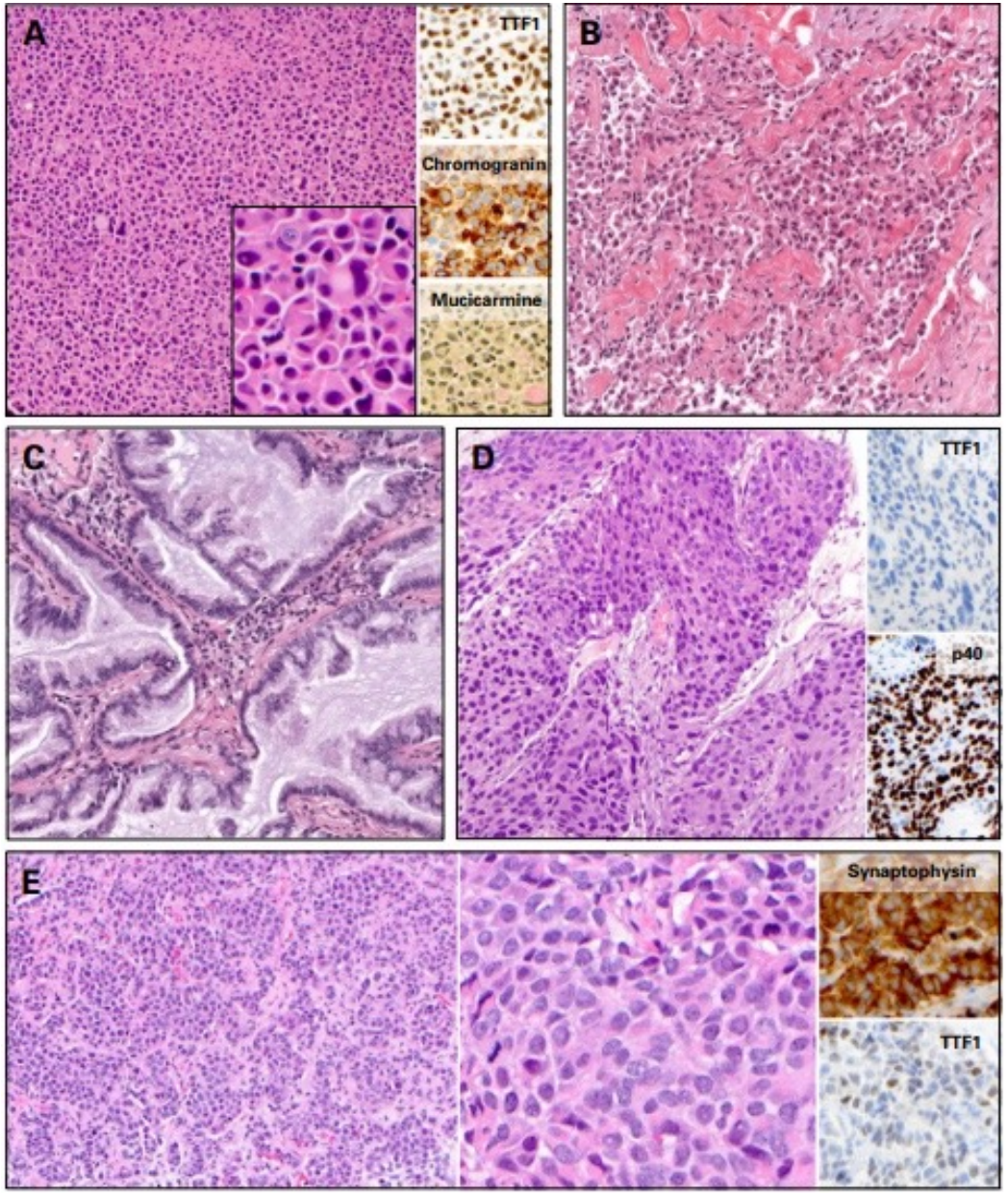
Fusion	MGH	MSKCC	Total	Frequency, % (95% CI)
No. of NSCLCs screened	1,804	3,608	4,872	
NTRK1	2	4	6	0.12 (0.5 - 0.27)
NTRK2	0	1	1	0.02 (0.00 - 0.11)
NTRK3	2	2	4	0.08 (0.02 - 0.21)
All *NTRK*	4	7	11	0.23 (0.11 - 0.40)

CI, confidence interval; MGH, Massachusetts General Hospital; MSKCC, Memorial Sloan Kettering Cancer Center; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; TKI, tyrosine kinase inhibitor

Harada G, et al. Lung Cancer. 2021; 161:108-13; Farago AF, et al JCO Precis Oncol. 2018; 2018:PO.18.00037

NTRK FUSIONS ACROSS TUMOUR TYPES/HISTOLOGIES

- Described across a variety of patient ages (median age range= 48y (range from 25-86) and tumour types/histologies



A: Adenocarcinoma (solid growth pattern, diffuse neuroendocrine differentiation, signet ring cells); B: Adenocarcinoma (poorly-differentiated, solid and single-cell growth patterns); C: Mucinous adenocarcinoma; D: Squamous cell carcinoma; E: Neuroendocrine carcinoma (well-differentiated morphology, increased mitotic activity)
NTRK, neurotrophic tyrosine receptor kinase
Farago AF, et al JCO Precis Oncol. 2018; 2018:PO.18.00037

TESTING APPROACHES

NTRK connect® POWERED BY COR2ED

SINGLE GENE-TESTING

- FISH for *NTRK1/2/3*
  - Advantages are rapid turn around time (1-3 days), requires relatively little tissue
  - Disadvantages are potential for false negatives, relatively few places offer *NTRK1/2/3*

- RT-PCR
  - Advantages include cost, moderate turn around time (1 week), relatively little tissue
  - Disadvantages include lack of detection of other fusion partners

FISH, fluorescent in situ hybridisation; NTRK, neurotrophic tyrosine receptor kinase; RT-PCR, reverse transcription-polymerase chain reaction

Hechtman JF. Mod Pathol. 2021; doi: 10.1038/s41379-021-00913-8 (Online ahead of print)

TESTING APPROACHES

NEXT GENERATION SEQUENCING

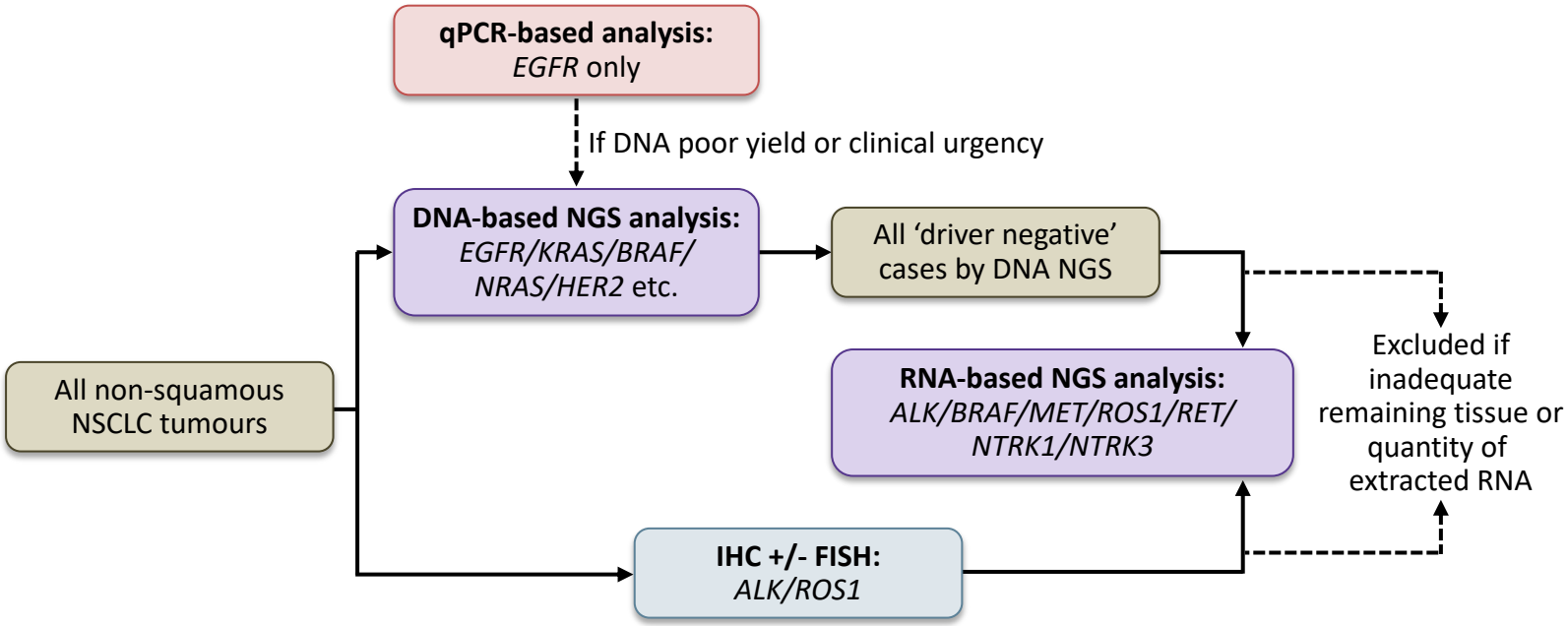
- DNA-based
  - Advantages include analyse variety of gene groups frequently altered in lung cancer including point mutations, amplifications and tumour mutational burden
  - Disadvantages include requires moderate amounts of tumour tissue, limited coverage of introns (81% sensitivity – best at *NTRK1*) and turn around times (2-4 weeks)
- RNA-based
  - Advantages include confirmation that the fusion gene is transcribed, not limited by gene size (introns), and detection is partner agnostic
  - Disadvantages include moderate amounts of tumour tissue, subject to RNA degradation in older samples, turn around times (2-4 weeks)

NTRK, neurotrophic tyrosine receptor kinase

Hechtman JF. Mod Pathol. 2021; doi: 10.1038/s41379-021-00913-8 (Online ahead of print)

WORKFLOWS

- Multiple published approaches
- Depend on institutional resources



ALK, anaplastic lymphoma kinase; BRAF, v-raf murine sarcoma viral oncogene homolog B1; EGFR, epidermal growth factor receptor; FISH, fluorescent in situ hybridisation; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; KRAS, Kirsten rat sarcoma viral oncogene homolog; MET, hepatocyte growth factor receptor gene; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; qPCR, quantitative polymerase chain reaction; RET, rearranged during transfection; ROS1, c-ros oncogene 1

Moore DA, et al. Lung Cancer. 2021; 161:55-9

TESTING APPROACHES

OTHER

- Immunohistochemistry
- Nanostring

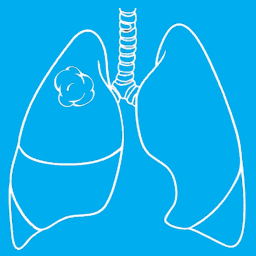
TREATMENT OF TRK FUSION-POSITIVE LUNG CANCERS

Prof. Christian Rolfo, MD

Centre of Thoracic Oncology
Tisch Cancer Institute Icahn School of Medicine at Mount Sinai, New York, USA

Clinical data with larotrectinib and entrectinib in NSCLC, 2nd gen TKIs and mechanisms of resistance

Christian Rolfo, MD, PhD, MBA, Dr.hc
Professor in Medicine
Icahn School of Medicine, Mount Sinai
Associate Director of Clinical Research
Center for Thoracic Oncology
The Tisch Cancer Institute
Mount Sinai, New York, NY, US



Center for Thoracic Oncology

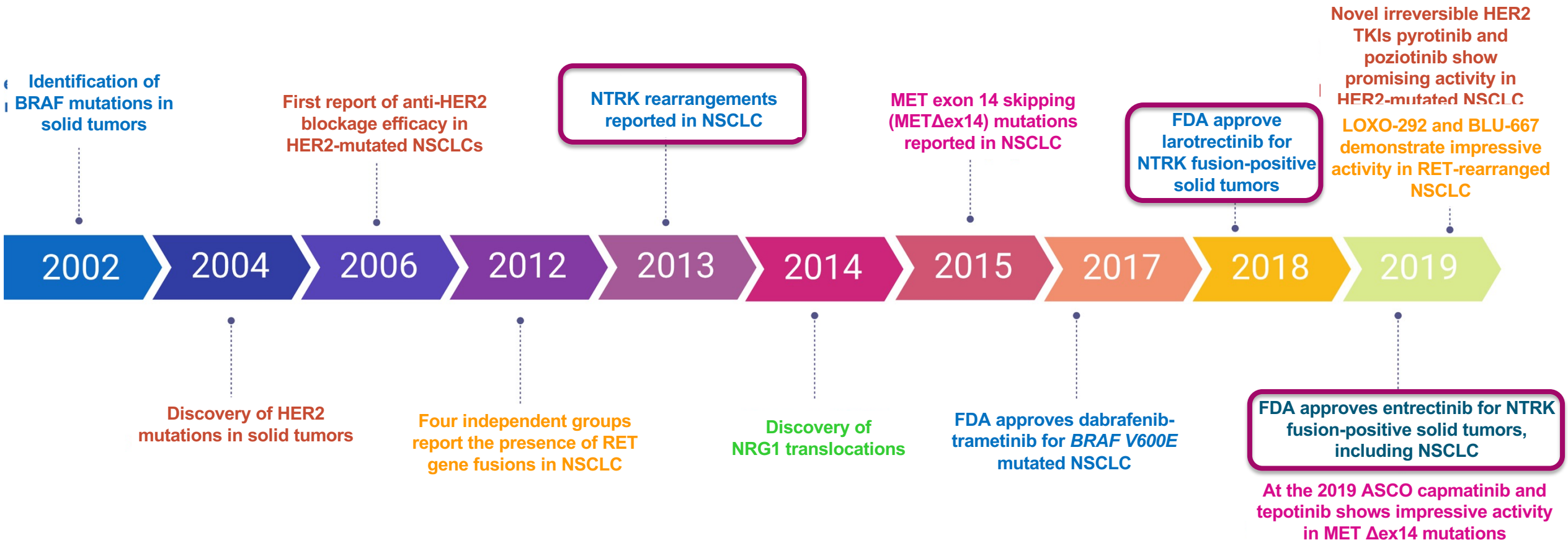
Mount Sinai
The Tisch Cancer Institute

Disclosures

Research grants	Lung Cancer Research Foundation-Pfizer Grant 2019 NIH U54 grant
Personal financial interests	Speaker: MSD, Roche, Astra Zeneca
	Advisory board: Inivata, ArcherDx, EMD Serono, Novartis, Boston Pharmaceuticals, Pfizer, Eisai, Blueprint, Mirati, COR2ED, Daiichi Sankyo
Non-financial interests	Research Collaboration: GuardantHealth
Leadership roles	Deputy chair Educational Committee IALSC - President ISLB (International Society of Liquid Biopsy) - Educational Chair: OLA Oncology Latin American Association Scientific Committee Member at ESO (European School of Oncology).

IALSC, International Society for the Study of Lung Cancer; ISLB, International Society of Liquid Biopsy

Milestones in the story of novel oncogene drivers in advanced NSCLC



ASCO, American Society of Clinical Oncology; FDA, Food and Drug Administration; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; TKI, tyrosine kinase inhibitor

Adapted from Russo A (Rolfo C), et al. Curr Oncol Rep. 2020;22(5):48

Clinical activity of larotrectinib in patients with TRK fusion cancers

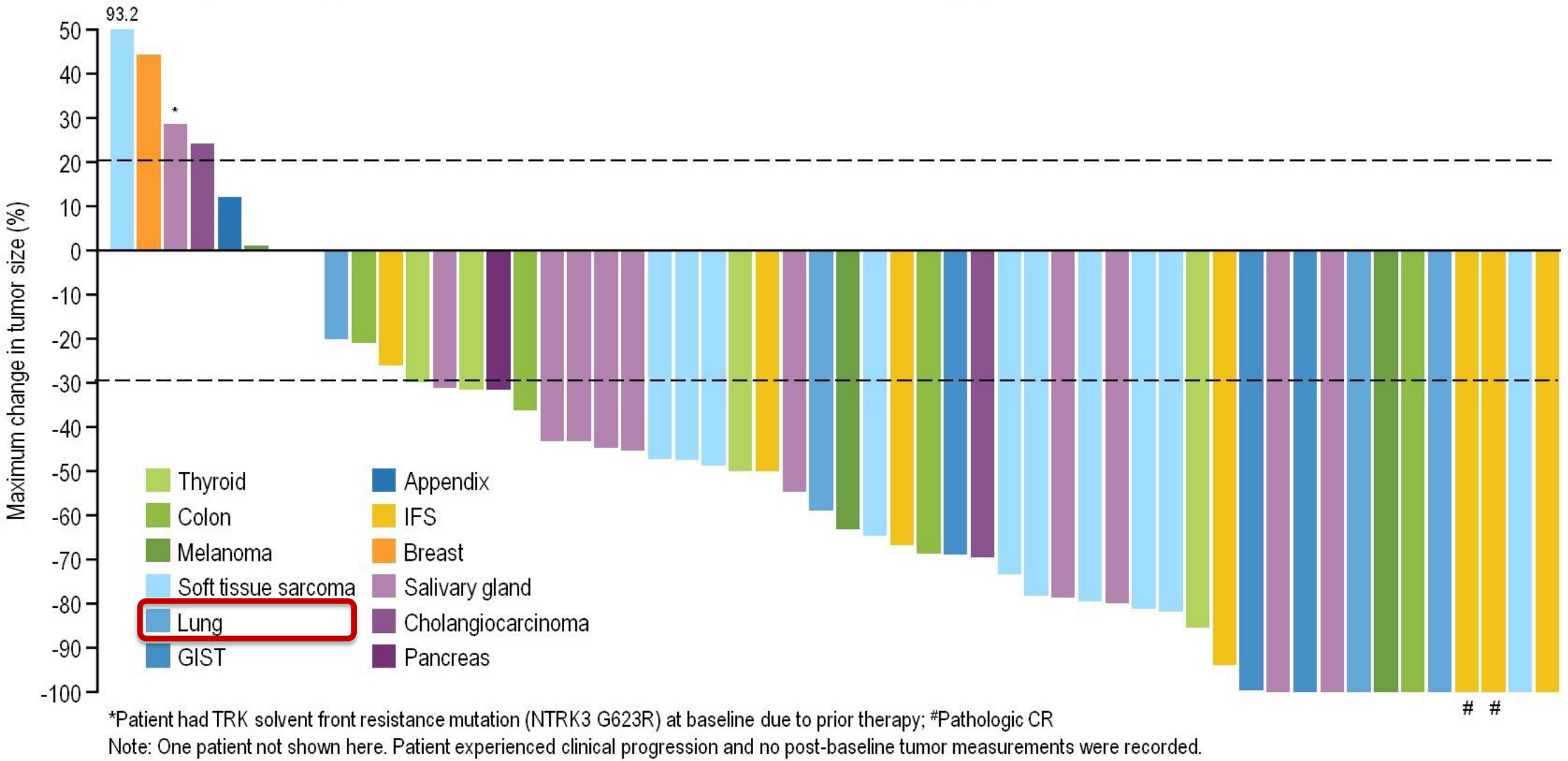
	Enrolled patients with confirmatory response data available (n=50)	All enrolled patients (n=55)*
Objective response rate (95% CI)	**76%** (62–87%)	**78%** (65–88%)
Partial response	**64%**	**65%***
Complete response	**12%**	**13%***
Stable disease	12%	11%
Progressive disease	12%	11%

*Includes unconfirmed responses with confirmatory scans pending (4 PR, 1 CR). All remain in response and ongoing on study.

CI, confidence interval; CR, complete response; PR, partial response; TRK, tropomyosin receptor kinase

Presented By David Hyman at 2017 ASCO Annual Meeting

Larotrectinib Efficacy regardless of tumor type



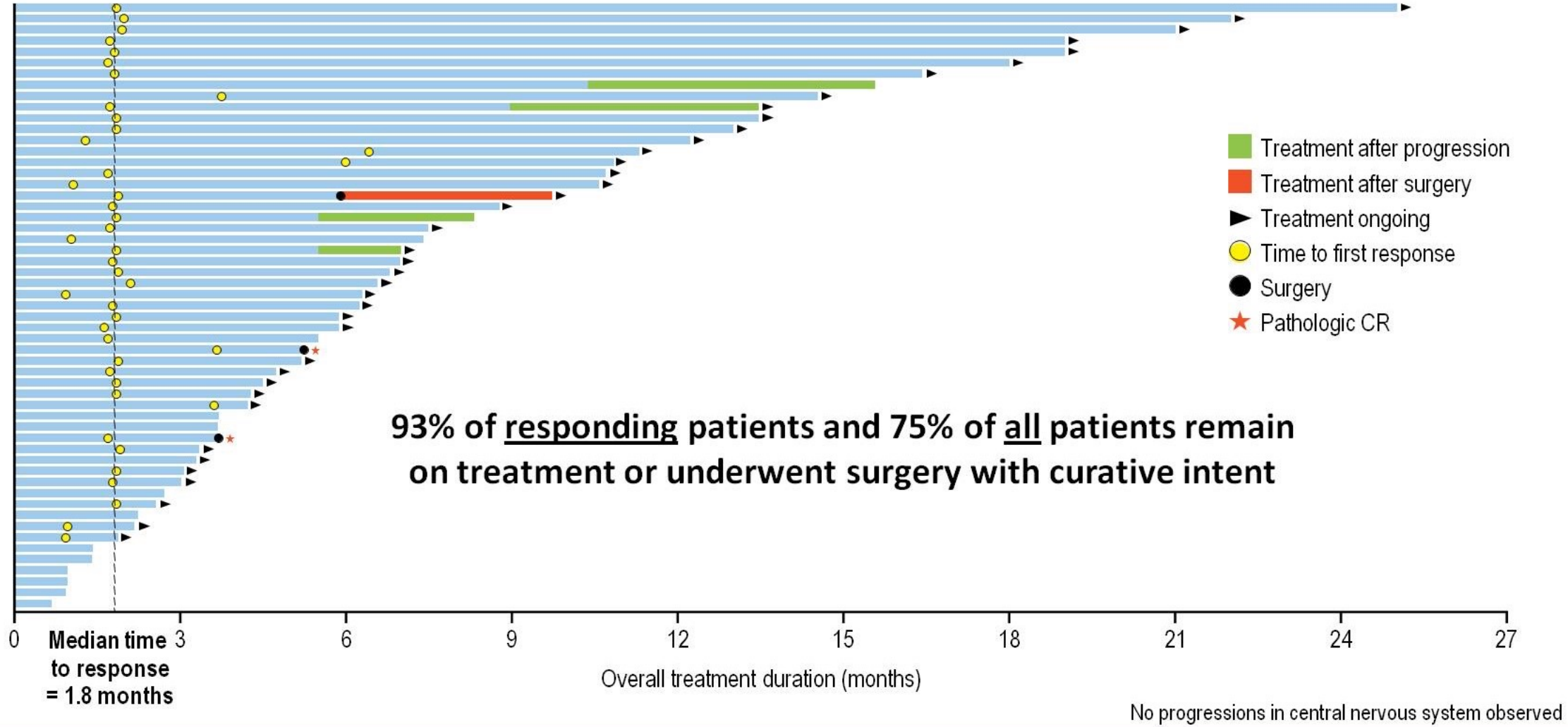
*Patient had TRK solvent front resistance mutation (NTRK3 G623R) at baseline due to prior therapy; #Pathologic CR

Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.

GIST, Gastrointestinal stromal tumor; IFS, infantile fibrosarcoma

Presented By David Hyman at 2017 ASCO Annual Meeting

Duration of larotrectinib therapy



CR, complete response

Presented By David Hyman at 2017 ASCO Annual Meeting

Efficacy and safety of larotrectinib in patients with *NTRK* fusion-positive lung cancer

Study design

Adult phase I trial (NCT02122913)
- Age ≥18 years
- Advanced solid tumors

n=1

Phase II basket trial (NAVIGATE, NCT02576431)
- Age ≥12 years
- Advanced solid tumors
- TRK fusion cancer

n=19

20 patients with TRK fusion lung cancer

TRK fusion status determined by local CLIA-accredited (or similar) laboratories

Data cut-off: July 20, 2020

Primary endpoint
- Best ORR per IRC and INV (RECIST v1.1)

Secondary endpoints
- Duration of response
- Progression-free survival
- Overall survival
- Safety

Larotrectinib dose
- Larotrectinib, 100 mg BID continuously
- 28-day cycles

Baseline demographics

	N=20
Prior therapies,‡ n (%)	
Surgery	10 (50)
Radiotherapy	9 (45)
Systemic therapy§	19 (95)
Number of prior systemic therapies, n (%)	
0	1 (5)
1	6 (30)
2	3 (15)
≥3	10 (50)
Best response to most recent systemic therapy, n (%)	
Partial response	3 (15)
Stable disease	5 (25)
Progressive disease	5 (25)
Other¶	7 (35)

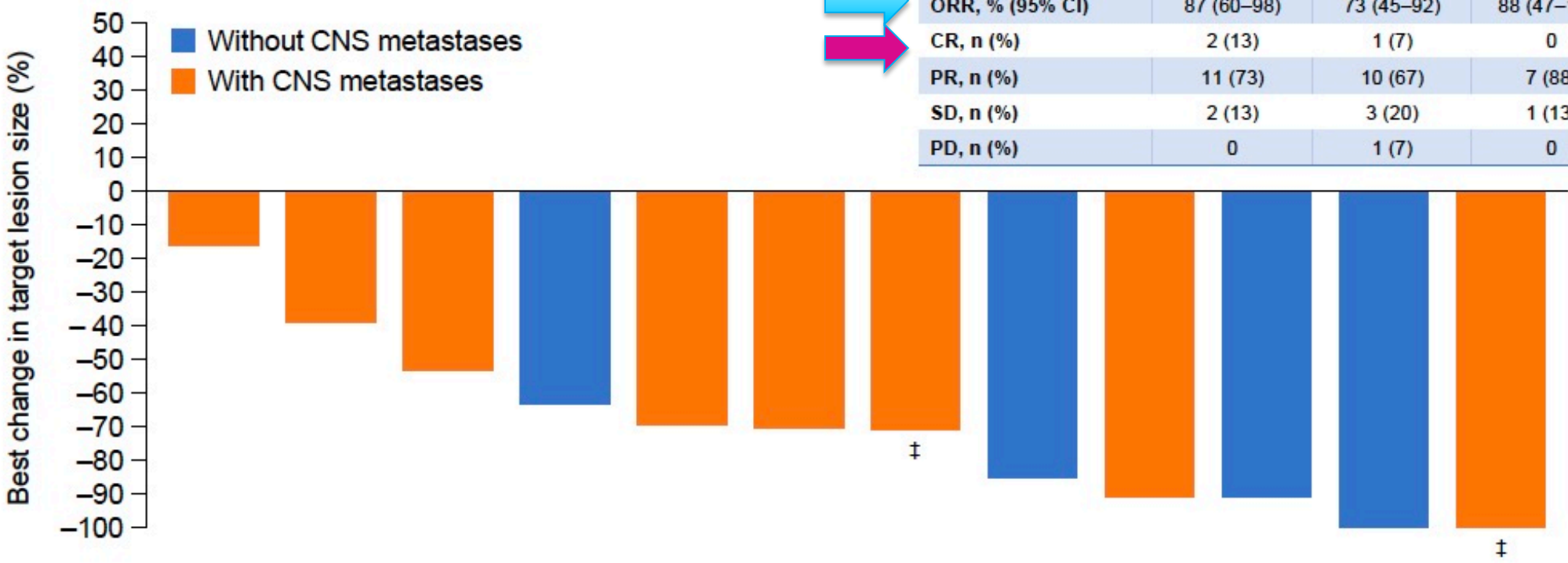
Baseline demographics

	N=20
Age, median (range), years	48.5 (25.0–76.0)
Sex, n (%)	
Male	10 (50)
Female	10 (50)
Race, n (%)	
White	9 (45)
Asian	8 (40)
Other	2 (10)
American Indian or Alaska Native	1 (5)
ECOG performance status, n (%)	
0	8 (40)
1	10 (50)
2	1 (5)
3	1 (5)
Histology, n (%)	
Adenocarcinoma	19 (95)
Neuroendocrine carcinoma	1 (5)†
CNS metastases, n (%)	
No	10 (50)
Yes	10 (50)
Previous radiotherapy	2 (10)

BID, twice daily; CLIA, clinical laboratory improvement amendments; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; INV, investigator-assessed; IRC, independent review committee; NTRK, neurotrophic tyrosine receptor kinase; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors; TRK, tropomyosin receptor kinase

Drilon A, et al. WCLC 2021. Abstract P53.02. Poster presentation.

Best response to larotrectinib per IRC in patients with *NTRK* fusion-positive lung cancer

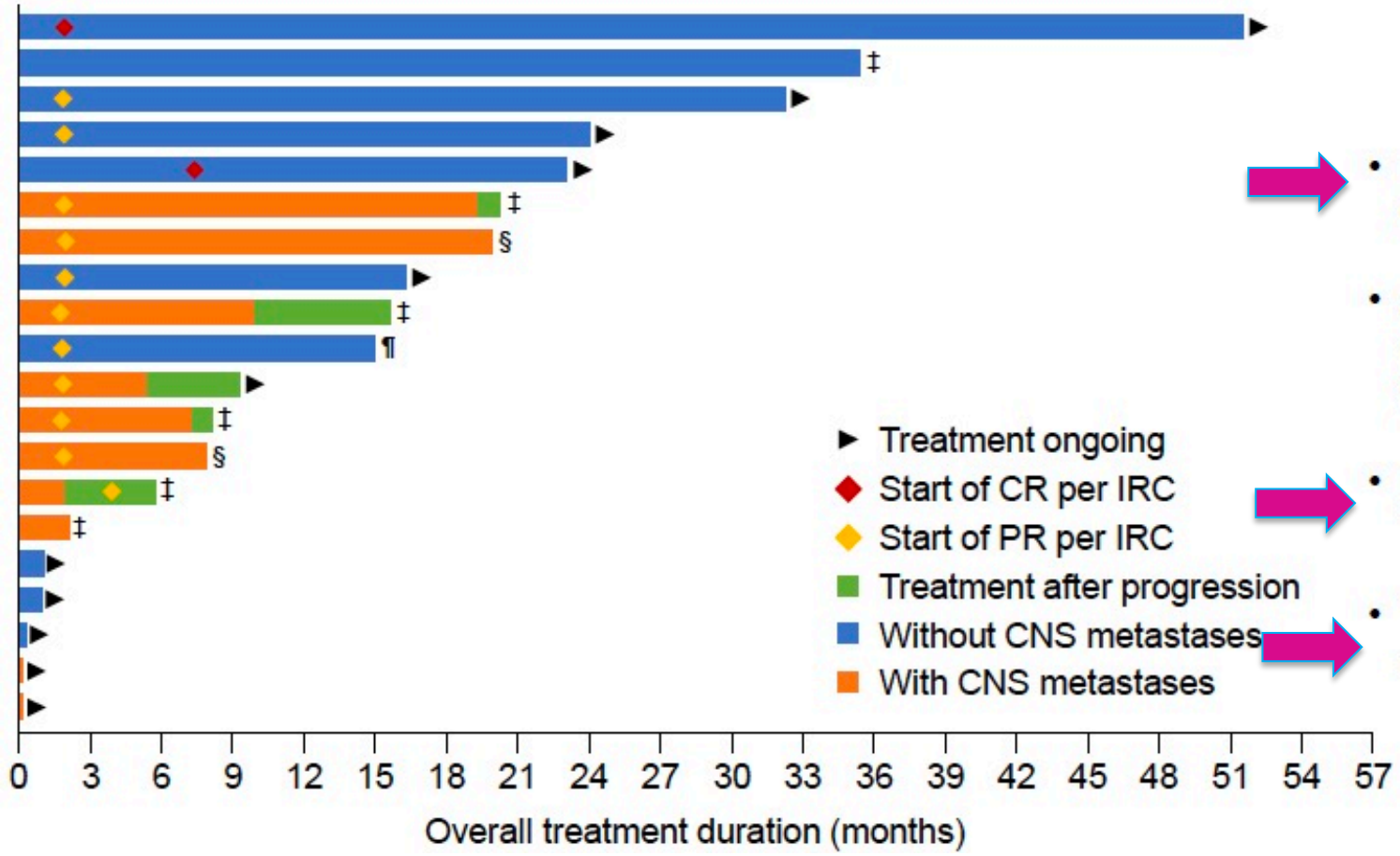


	All patients		Patients with CNS metastases	
	IRC	INV	IRC	INV
Evaluable patients, n	15	15	8	8
ORR, % (95% CI)	87 (60–98)	73 (45–92)	88 (47–100)	63 (25–91)
CR, n (%)	2 (13)	1 (7)	0	0
PR, n (%)	11 (73)	10 (67)	7 (88)	5 (63)
SD, n (%)	2 (13)	3 (20)	1 (13)	2 (25)
PD, n (%)	0	1 (7)	0	1 (13)

BID, twice daily; CLIA, clinical laboratory improvement amendments; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; INV, investigator-assessed; IRC, independent review committee; NTRK, neurotrophic tyrosine receptor kinase; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors; TRK, tropomyosin receptor kinase

Drilon A, et al. WCLC 2021. Abstract P53.02. Poster presentation.

Treatment duration with larotrectinib in patients with *NTRK* fusion-positive lung cancer



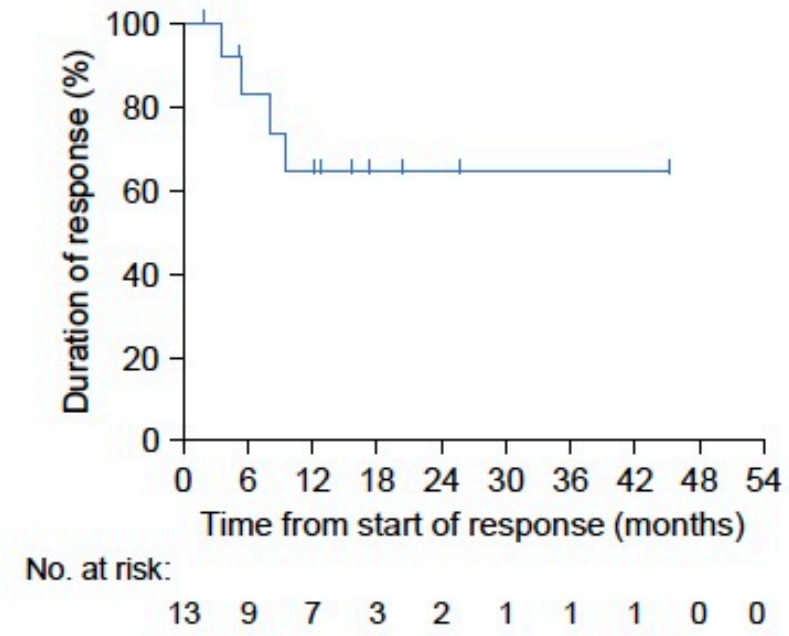
- Duration of treatment ranged from 0.03+ to 51.5+ months
- At the data cut-off, 7 patients (35%) had progressed with 5 (25%) continuing treatment post-progression
- Median time to response per IRC was 1.84 months (range: 1.68–7.33 months)
- Treatment ongoing in 11 patients (55%) at data cut-off

CNS, central nervous system; CR, complete response; IRC, independent review committee; NTRK, neurotrophic tyrosine receptor kinase; PR, partial response; SD, stable disease

Drilon A, et al. WCLC 2021. Abstract P53.02. Poster presentation.

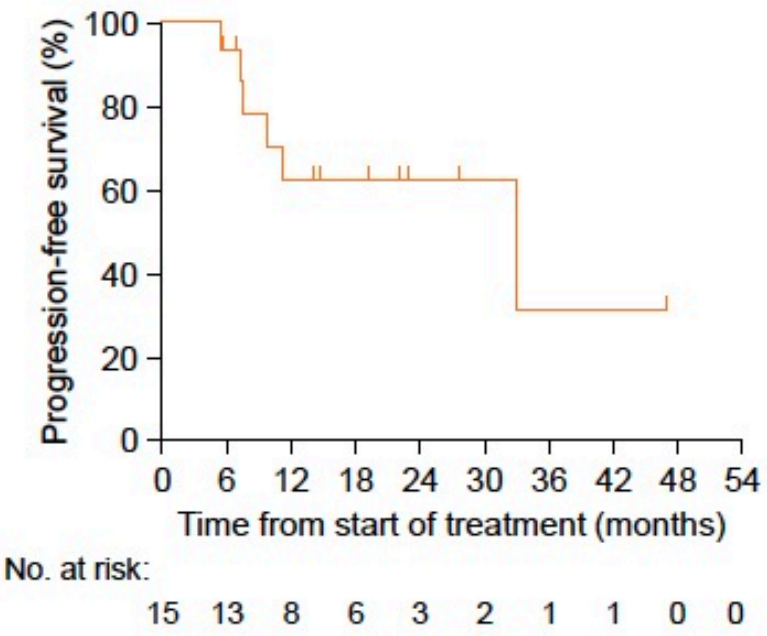
DoR, PFS, and OS with larotrectinib in patients with *NTRK* fusion-positive lung cancer (per IRC)

DoR



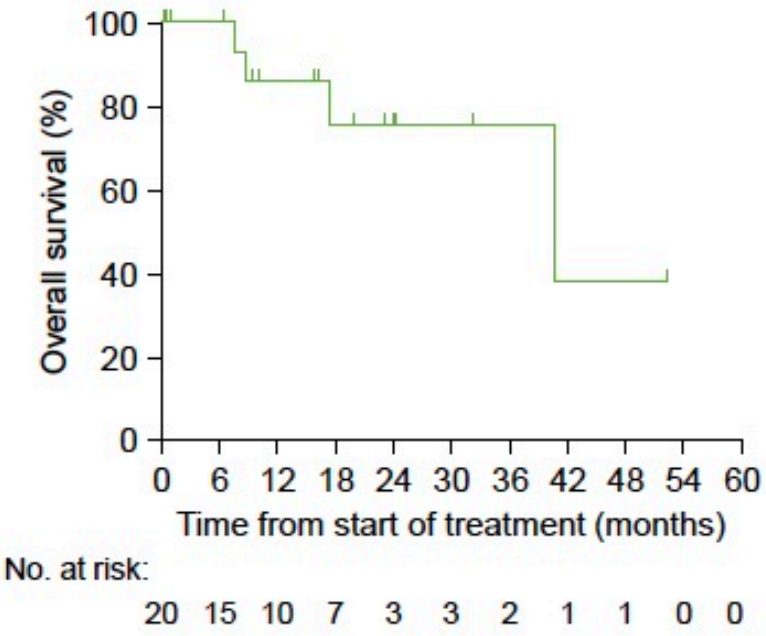
Median DoR, months (95% CI)	Not reached (5.5–NE)
Median follow-up, months	15.6
12-month DoR, %	64

PFS



Median PFS, months (95% CI)	33 (7.6–NE)
Median follow-up, months	22.1
12-month PFS, %	62

OS



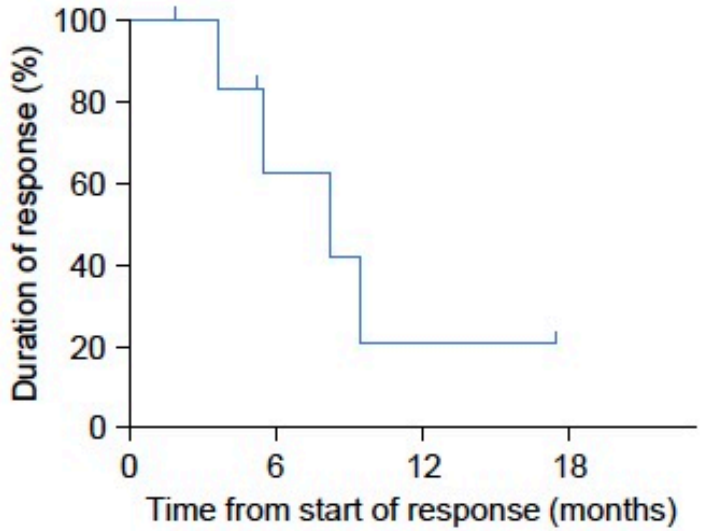
Median OS, months (95% CI)	40.7 (17.2–NE)
Median follow-up, months	16.2
12-month OS, %	86

CI, confidence interval; DoR, duration of response; IRC, independent review committee; NE, not estimable; NTRK, neurotrophic tyrosine receptor kinase; OS, overall survival; PFS, progression-free survival

Drilon A, et al. WCLC 2021. Abstract P53.02. Poster presentation.

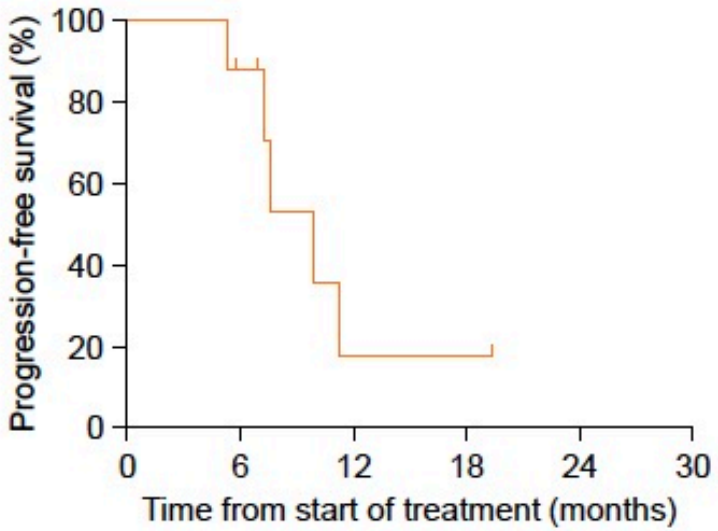
larotrectinib activity in patients with *NTRK* fusion-positive lung cancer with CNS metastases

DoR



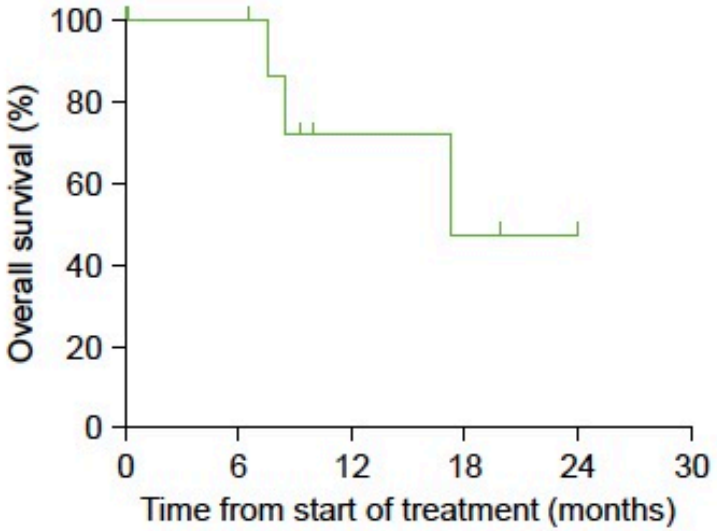
Median DoR, months (95% CI)	8.2 (3.6–NE)
Median follow-up, months	17.4
12-month DoR, %	21

PFS



Median PFS, months (95% CI)	9.9 (5.3–NE)
Median follow-up, months	19.3
12-month PFS, %	18

OS

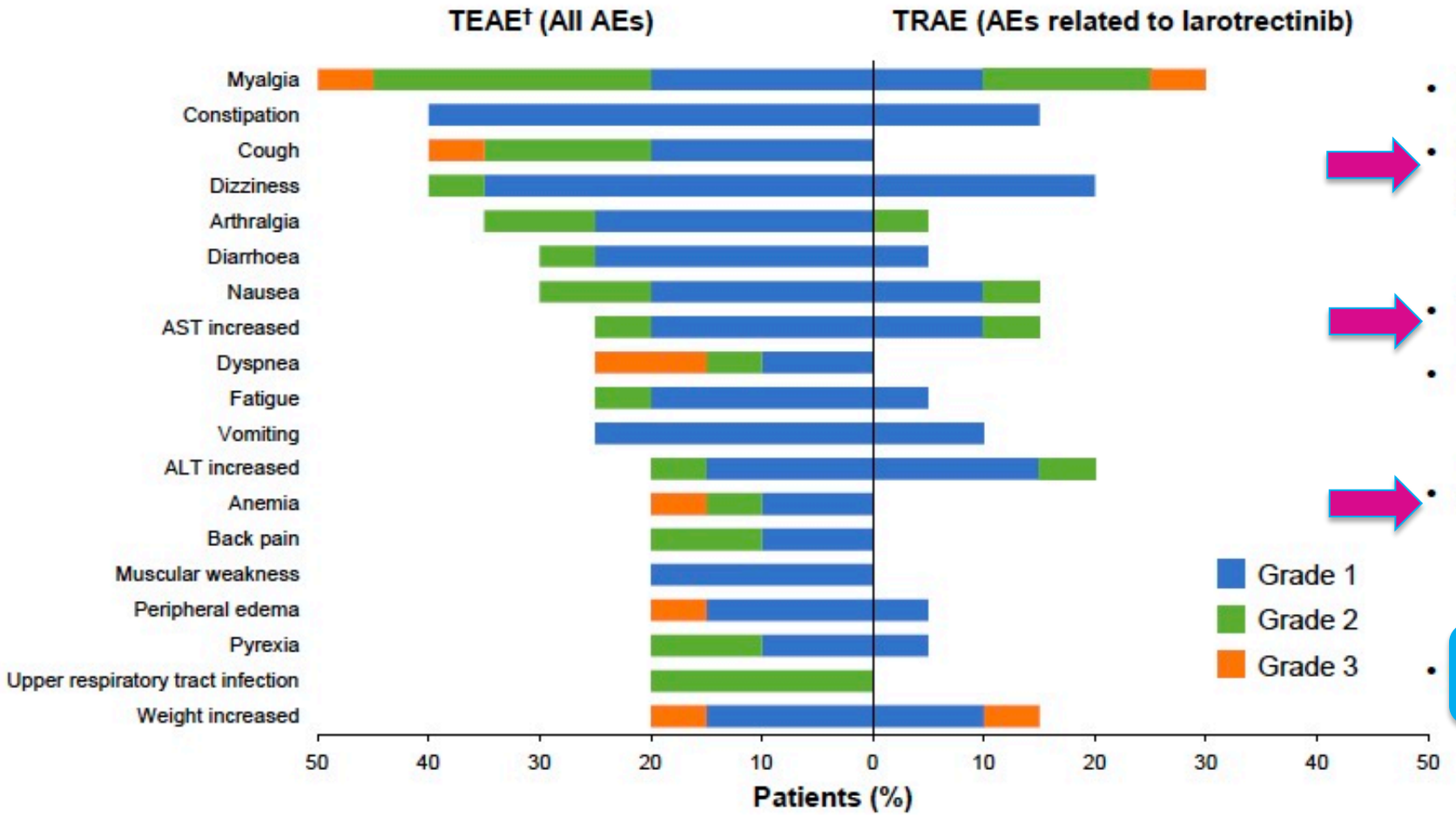


Median OS, months (95% CI)	17.2 (7.6–NE)
Median follow-up, months	10
12-month OS, %	71

CI, confidence interval; CNS, central nervous system; DoR, duration of response; NE, not estimable; NTRK, neurotrophic tyrosine receptor kinase; OS, overall survival; PFS, progression-free survival

Drilon A, et al. WCLC 2021. Abstract P53.02. Poster presentation.

Safety of larotrectinib in patients with *NTRK* fusion-positive lung cancer

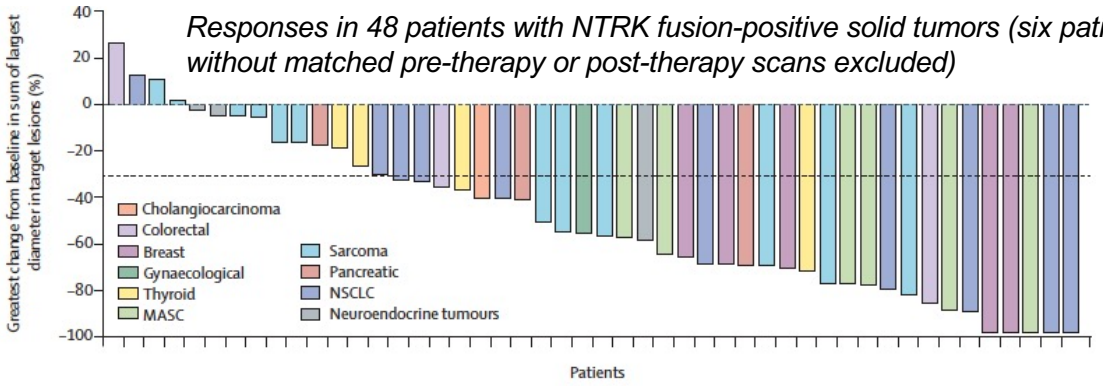


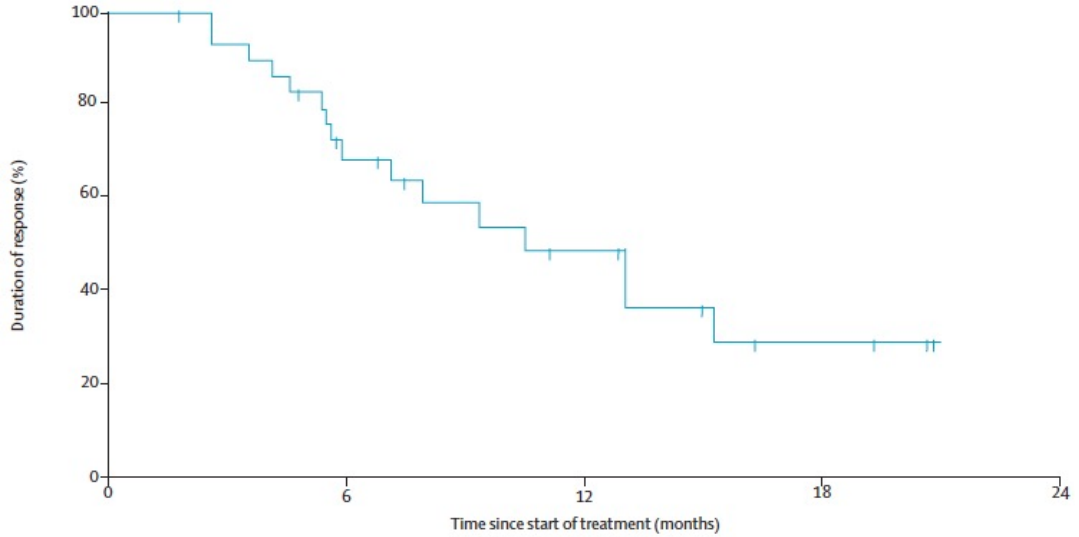
- TEAEs were mainly Grade 1–2
- Grade 3 TRAEs occurred in 2 (10%) patients:
  - Hypersensitivity,‡ myalgia, and weight increased
- There were no Grade 4 TEAEs
- 1 (5%) patient had a Grade 5 TEAE
  - Cardiac arrest unrelated to larotrectinib
- 2 patients had dose reductions due to TRAEs
  - Grade 2 AST and Grade 2 ALT increase in 1
  - Grade 2 neutrophil count decrease in 1
- No patients discontinued treatment due to TEAEs

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NTRK, neurotrophic tyrosine receptor kinase; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event;
Drilon A, et al. WCLC 2021. Abstract P53.02. Poster presentation.

Entrectinib

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





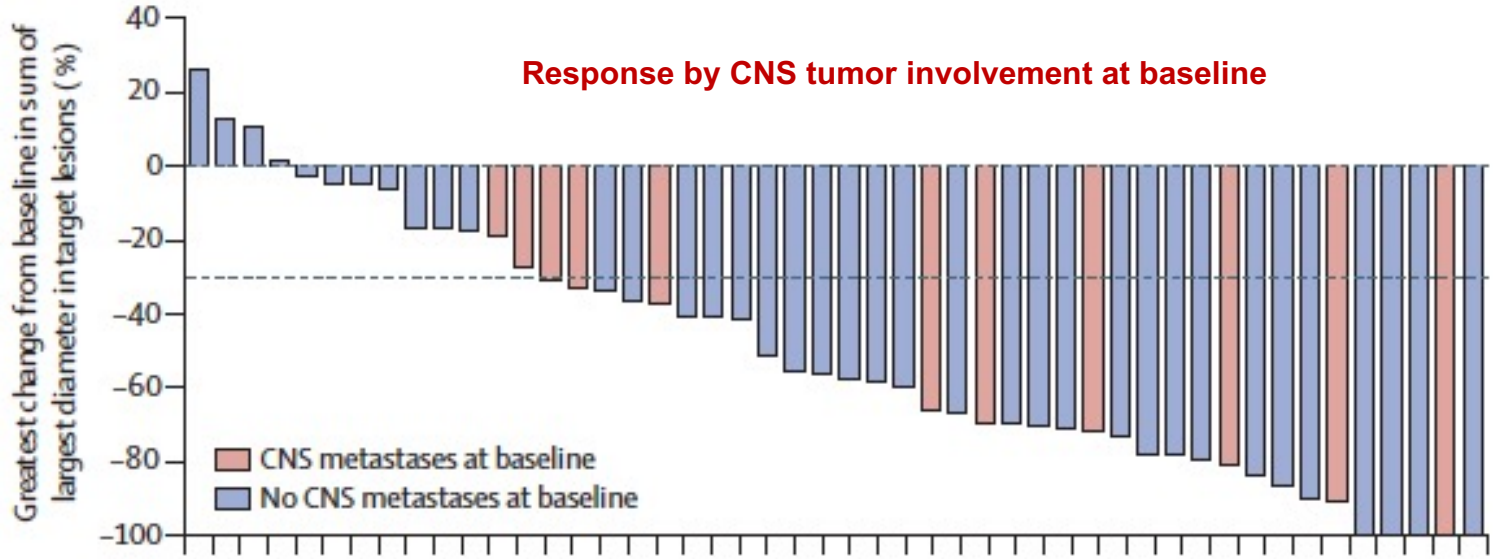
- **31 of 54 patients had an objective response (57%; 95% CI 43.2-70.8)**
- **7% CR and 50% PR**

Median duration of response: 10 months (95% CI 7.1 to NE)

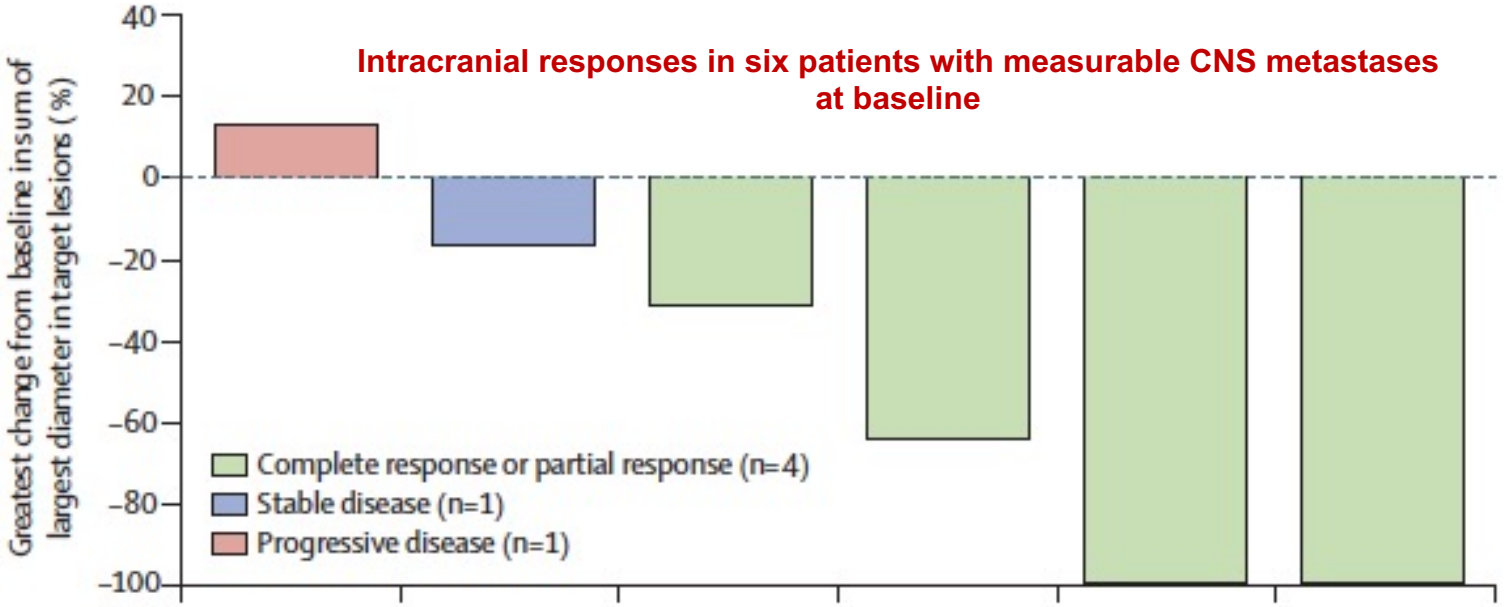
CNS, central nervous system; CR, complete response; CRC, colorectal carcinoma; CUP, cancer of unknown primary; GI, gastrointestinal; MASC, mammary analogue secretory carcinoma; mets, metastases; ND, not determined; NE, not estimable; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; SLD, sum of longest diameters

Rolfo C. ASCO 2020, Doebele RC, et al. Lancet Oncol. 2020;21:271-82; Bazhenova L, et al. Ann Oncol. 2021;32(suppl_5): S583-S620 (ESMO 2021 poster presentation)

Response by CNS tumor involvement at baseline



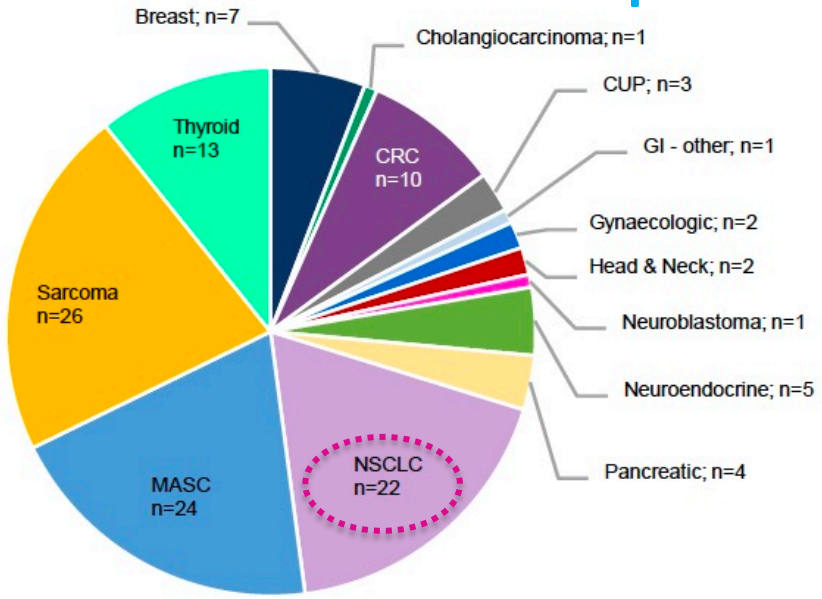
Intracranial responses in six patients with measurable CNS metastases at baseline

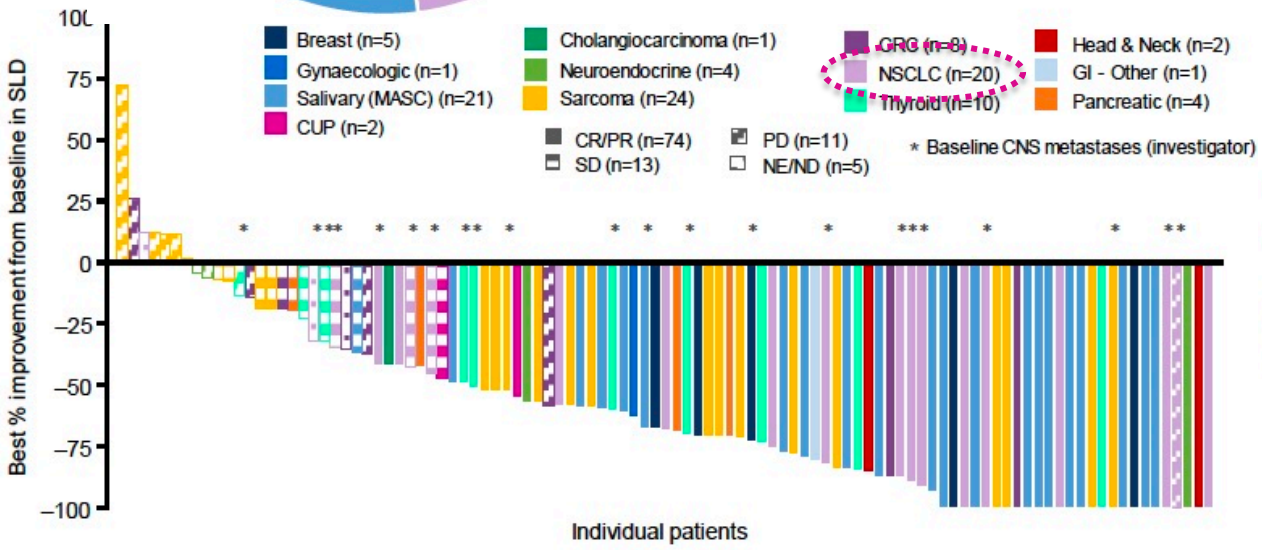


CNS, central nervous system

Rolfo C. ASCO 2020, Doebele RC, et al. Lancet Oncol. 2020;21:271-82

entrectinib in *NTRK* fusion-positive solid tumors: ESMO 2021 updated analysis





Parameter	Efficacy population (N=121)	Baseline CNS metastases‡ (n=26)	No baseline CNS metastases‡ (n=95)
ORR*, n (%) 95% CI	74 (61.2) 51.9–69.9	15 (57.7) 36.9–76.7	59 (62.1) 51.6–71.9
Complete response, n (%)	19 (15.7)	2 (7.7)	17 (17.9)
Partial response, n (%)	55 (45.5)	13 (50.0)	42 (44.2)
Stable disease, n (%)	13 (10.7)	4 (15.4)	9 (9.5)
Progressive disease, n (%)	13 (10.7)	2 (7.7)	11 (11.6)
Non-CR/PD, n (%)	6 (5.0)	0	6 (6.3)
Missing or unevaluable†, n (%)	15 (12.4)	5 (19.2)	10 (10.5)
Median time to response*, months (95% CI)	1.0 (0.9–1.0)	1.7 (0.9–2.8)	1.0 (0.9–1.0)
Median DoR*, months (95% CI)	20.0 (13.0–38.2)	17.2 (6.0–29.4)	29.0 (12.9–NE)
Median PFS*, months (95% CI)	13.8 (10.1–19.9)	11.7 (4.7–30.2)	13.8 (10.2–20.8)
Median OS, months (95% CI)	33.8 (23.4–46.4)	19.9 (7.9–NE)	37.1 (23.9–NE)

Tumour types (n≥4)*	n	ORR, % (95% CI)	DoR, months (95% CI)
NSCLC	22	63.6 (40.7–82.8)	19.9 (10.4–29.4)

CI, confidence interval; CNS, central nervous system; CR, complete response; CRC, colorectal carcinoma; CUP, cancer of unknown primary; DoR, duration of response; ESMO, European Society for Medical Oncology; GI, gastrointestinal; MASC, mammary analogue secretory carcinoma; ND, not determined; NE, not estimable; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; PD, progressive disease; PFS, progression-free survival; PR, primary response; ORR, objective response rate; OS, overall survival; SD, stable disease

Bazhenova L, et al. Ann Oncol. 2021;32(suppl_5): S583-S620 (ESMO 2021 poster presentation)

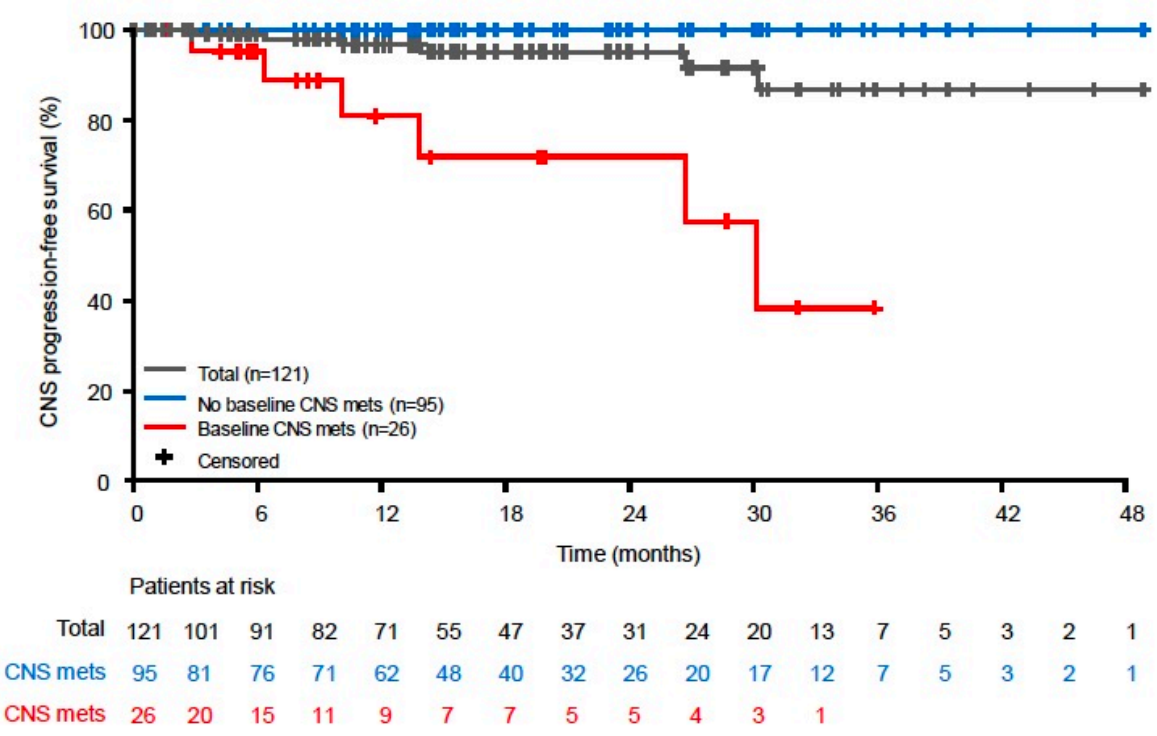
CNS activity of entrectinib in *NTRK* fusion-positive solid tumors

Parameter	Baseline CNS metastases (BICR) (N=19)	Measurable baseline CNS metastases (BICR) (N=11)
Intracranial ORR, n (%) (95% CI)	10 (52.6) (28.9–75.6)	7 (63.6) (30.8–89.1)
Complete response, %	6 (31.6)	3 (27.3)
Partial response, %	4 (21.1)	4 (36.4)
Median intracranial DoR, months (95% CI)	17.2 (7.4–NE)	22.1 (7.4–NE
Median intracranial PFS, months (95% CI)	10.1 (6.3–26.7)	19.9 (5.9–NE

BICR, blinded independent central review; CNS, central nervous system; NE, not estimable.

- With additional clinical experience, entrectinib continues to demonstrate durable overall and intracranial responses, regardless of CNS status at baseline:
  - In patients without baseline CNS metastases, ORR was **62.1%** (17 CR) and median DoR was **29.0 months**
  - In patients with baseline CNS metastases, ORR was **57.7%** and median DoR was **17.2 months**.
- Entrectinib can address the unmet need of a **CNS-active treatment** in patients with *NTRK* fusion-positive solid tumours.

Time to CNS Progression



BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; CR, complete response; DoR, duration of response; mets, metastases; NE, not estimable; NTRK, neurotrophic tyrosine receptor kinase; ORR, objective response rate; PFS, progression-free survival

Bazhenova L, et al. Ann Oncol. 2021;32(suppl_5): S583-S620 (ESMO 2021 poster presentation)

Safety of entrectinib in *NTRK* fusion-positive solid tumors: ESMO 2021 updated analysis

TRAEs reported in ≥10% of patients Patients, %	*NTRK* fusion-positive safety population (n=193)	Overall safety population (N=626)
Dysgeusia	35.2	35.9
Diarrhoea	31.1	25.9
Fatigue	27.5	28.8
Weight increase	27.5	27.3
Constipation	25.9	25.1
Blood creatinine increase	25.9	21.2
Dizziness	24.9	26.8
Oedema peripheral	18.1	16.1
Anaemia	17.1	15.7
Nausea	16.6	20.3
AST increase	16.6	13.1
ALT increase	15.5	12.5
Paraesthesia	11.9	15.8
Myalgia	10.9	14.4
Vomiting	10.9	13.6
Arthralgia	5.2	10.2

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ESMO, European Society for Medical Oncology; NTRK, neurotrophic tyrosine receptor kinase; TRAE, treatment-related adverse event

Bazhenova L, et al. Ann Oncol. 2021;32(suppl_5): S583-S620 (ESMO 2021 poster presentation).

Summary of larotrectinib and entrectinib activity in *NTRK* fusion-positive NSCLC

	Larotrectinib (n = 20)	Entrectinib (n = 13)
Age, median (range)	48.5 (25–76) years	60 (46–77) years
CNS metastases at baseline, n (%)		
No	10 (50)	5 (38)
Yes	10 (50)	8 (62)
Previously treated with radiotherapy	2 (10)	5 (38)
***NTRK* fusion**, n (%)		
NTRK1	16 (80)	8 (61)
NTRK2	0	1 (8)
NTRK3	4 (20)	4 (31)
Tumor histology, n (%)		
Adenocarcinoma	19 (95)	9 (69)
Squamous Cell carcinoma	0	2 (16)
Neuroendocrine carcinoma	1 (5)	0
NSCLC - NOS	0	2 (16)

	Larotrectinib (n = 20)	Entrectinib (n = 13)
ORR (95% CI)	73% (45–92%)	69% (39–91%)
-CR/PR rate	7%/67%	8%/61%
Median DoR, months (95% CI)	33.9 (5.6–33.9)	NE (5.6-NE)*
Median PFS, months (95% CI)	35.4 (5.3–35.4)	14.9 (4.7–NE)
Median OS, months (95% CI)	40.7 (17.2-NE)	14.9 (5.9–NE)

*n = 9.

CI, confidence interval; CNS, central nervous system; CR, complete response; DoR, duration of response; NE, not estimable; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response

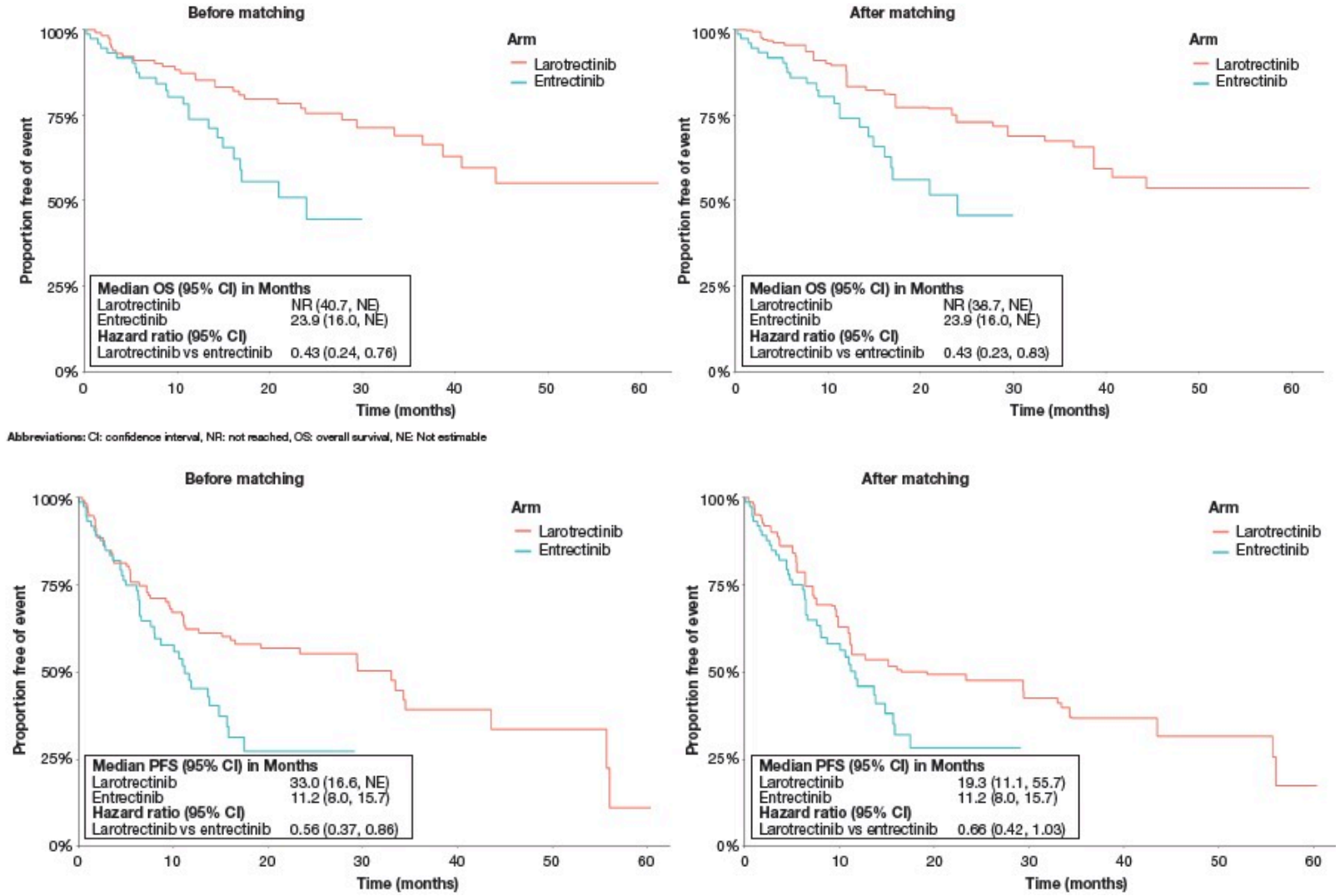
Harada G (Drilon A), et al. Lung Cancer. 2021;161:108-113

Matching-adjusted indirect comparison for treatment of TRK fusion cancer with larotrectinib versus entrectinib

Comparison of OS Kaplan Meier curves before and after matching

- Using an MAIC to compare outcomes of adult patients, OS, CR, and DoR favored larotrectinib before and after matching compared to entrectinib. PFS and ORR were favorable for larotrectinib but not statistically different. Safety outcomes were comparable and low for both treatments

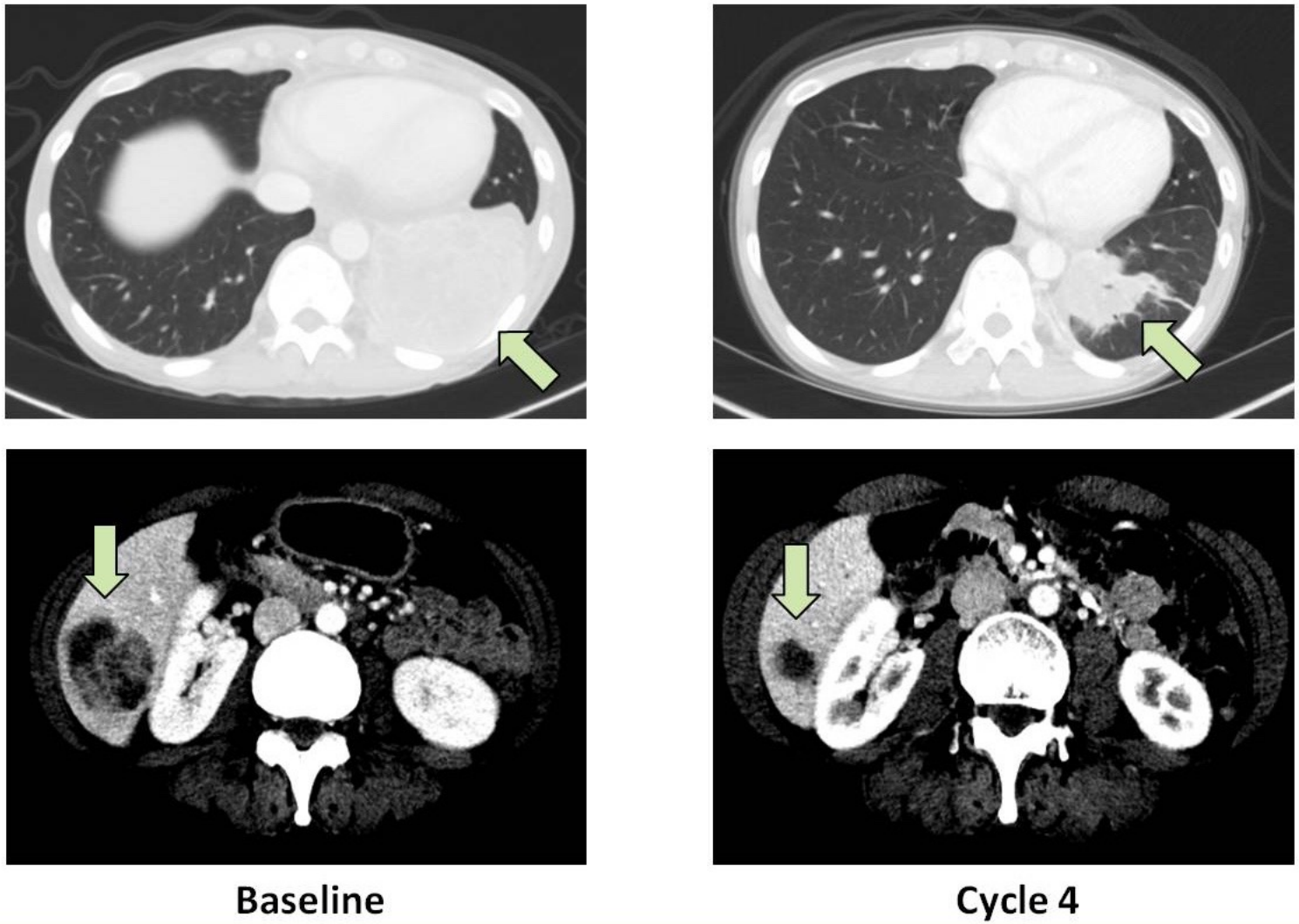
Comparison of PFS Kaplan Meier curves before and after matching



CI, confidence interval; CR, complete response; DoR, duration of response; MAIC, matching-adjusted indirect comparison; NE, not estimable; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TRK, tropomyosin receptor kinase

Garcia-Foncillas J, et al. Ann Oncol. 2021;32(suppl_5): S382-S406 (ESMO 2021 poster presentation).

SQSTM1-NTRK1 lung cancer patient case



45F NSCLC & paraneoplastic hypertrophic osteoarthropathy

Prior therapy: platinum/pemetrexed

Larotrectinib ongoing in month 8, resolution of paraneoplastic symptoms

NSCLC, non-small cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase

Presented By David Hyman at 2017 ASCO Annual Meeting

Comparison of selected FDA-approved or under clinical development TRK inhibitors

Drug	Target(s)	IC_{50} against TRKs in cell lines	CNS penetration	Activity against *NTRK* secondary mutations	Development phase in *NTRK* fusion-positive tumors	Approval status
Larotrectinib	TRKA/B/C	9.8–25 nM	Brain-plasma ratio in mice of 0.03-0.23	No	II	FDA approved
Entrectinib	TRKA/B/C, ROS1, ALK	0.1-1.7 nM*	Brain-plasma ratio in mice of 0.6-1	No	II	FDA approved
Selitrectinib (LOXO-195)	TRKA/B/C	≤5 nM	Brain-plasma ratio in mice of 0.021 ± 0.004	Yes	I/II	FDA orphan drug designation
Repotrectinib (TPX-0005)	TRKA/B/C, ROS1, ALK	<0.2 nM	Brain-plasma ratio in mice of 0.0281-0.0577	Yes	I/II	Not approved
DS-6051b	TRKA/B/C, ROS1	~3-20 nM	Not reported	Yes	I	Not approved

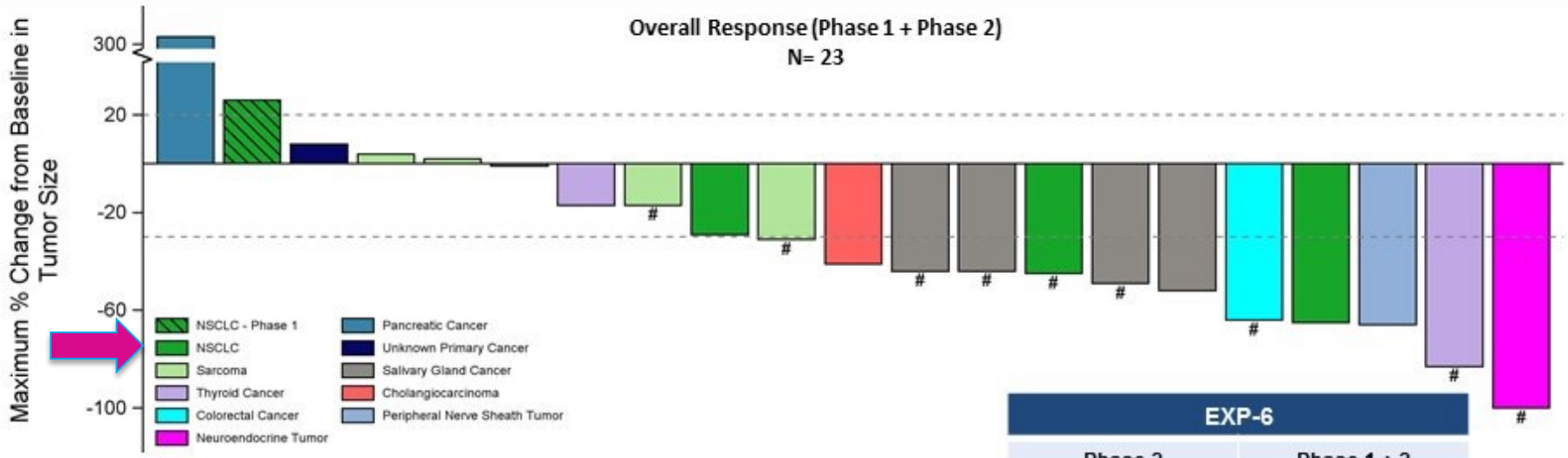
*enzymatic assays

Abbreviations: TRK, Tropomyosin receptor kinase; nM, nanomolar; IC_{50}, half maximal inhibitory concentration; CNS, central nervous system; ROS1, c-ros oncogene 1; ALK, anaplastic lymphoma kinase; FDA, Food and Drug Administration.

Rolfo C. Lancet Oncol. 2020;21;472-4

Repotrectinib Preliminary Efficacy

Preliminary Efficacy: *NTRK*+ TKI-Pretreated Advanced Solid Tumor Patients



Patient remains on treatment.
1 patient not displayed due to discontinuing treatment prior to first post-baseline scan.
1 patient not displayed due target lesion measurement not performed at the post-baseline scan.

	EXP-6	
	Phase 2 (N=22)	Phase 1 + 2 (N=23)
Confirmed ORR (cORR) (95% CI)	45%* (24 – 68)	43%* (23 – 66)
Duration of Response (range in months)	1.9+– 15.1 n=10	1.9+– 15.1 n=10

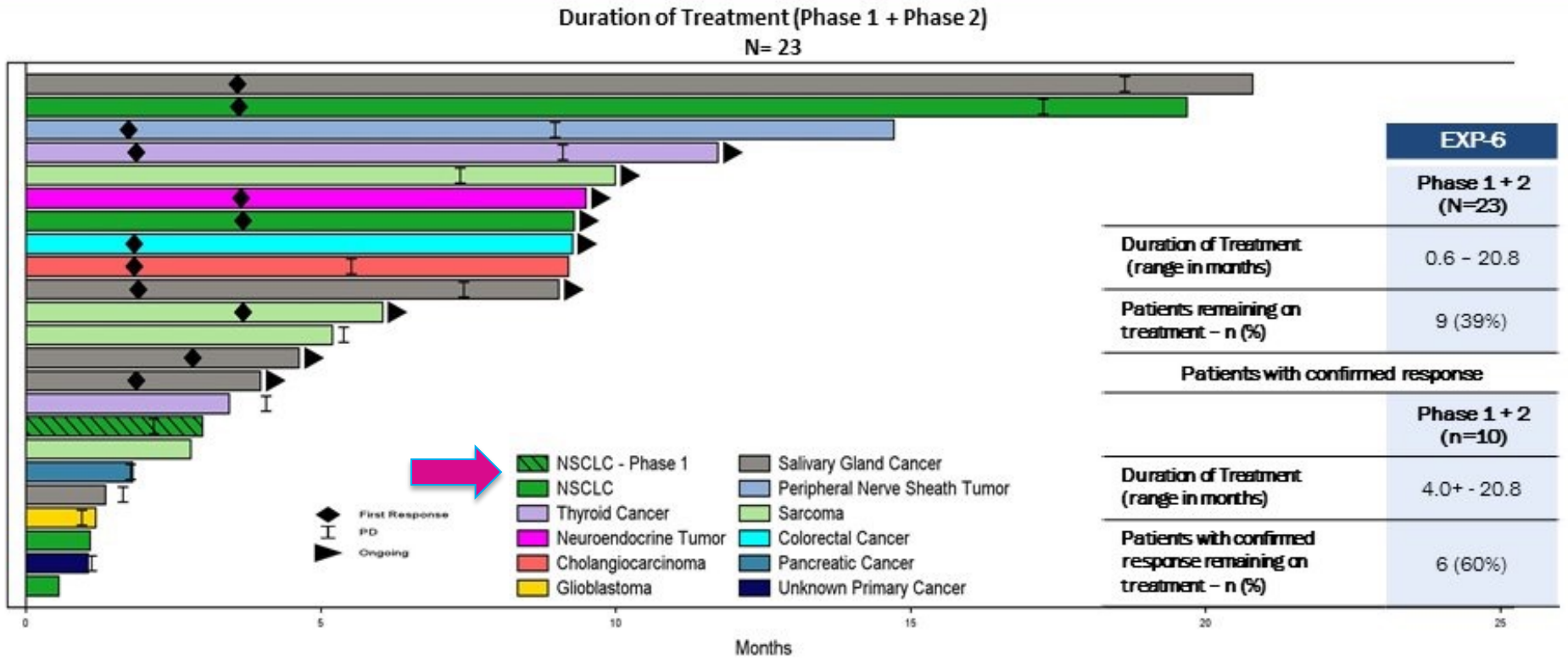
*At time of the 26 August 2021 data cut off, 3 patients in Phase 2 EXP-6 had unconfirmed PR (uPR). One uPR has been confirmed by scans that were entered after the 26 August 2021 data cut off and is included in the cORR; the other 2 uPR patients are on treatment awaiting confirmatory scans. Phase 2: RECIST v1.1 assessed by Physician Assessment. Phase 1: RECIST v1.1 assessed by Blinded Independent Central Review (BICR) with data cutoff date of 22 July 2019 for patients with baseline measurable disease and ≥ 1 post-baseline scan. Phase 1 patients treated at or above the Phase 2 recommended dose.

AACR-NCI-EORTC VIRTUAL INTERNATIONAL CONFERENCE ON MOLECULAR TARGETS AND CANCER THERAPEUTICS

Besse B. et al, OCT 2021

Repotrectinib Preliminary Efficacy

Duration of Treatment: *NTRK*+ TKI-Pretreated Advanced Solid Tumor Patients



EXP-6	Phase 1 + 2 (N=23)
Duration of Treatment (range in months)	0.6 - 20.8
Patients remaining on treatment – n (%)	9 (39%)
Patients with confirmed response	
	Phase 1 + 2 (n=10)
Duration of Treatment (range in months)	4.0+ - 20.8
Patients with confirmed response remaining on treatment – n (%)	6 (60%)

Phase 2 data cutoff date 26 August 2021 (responses confirmed by Physician Assessment).
Phase 1 data cutoff date 22 July 2019 for responses confirmed by BICR and 26 August 2021 for duration of treatment.

Besse B. et al, OCT 2021

Repotrectinib Preliminary Efficacy

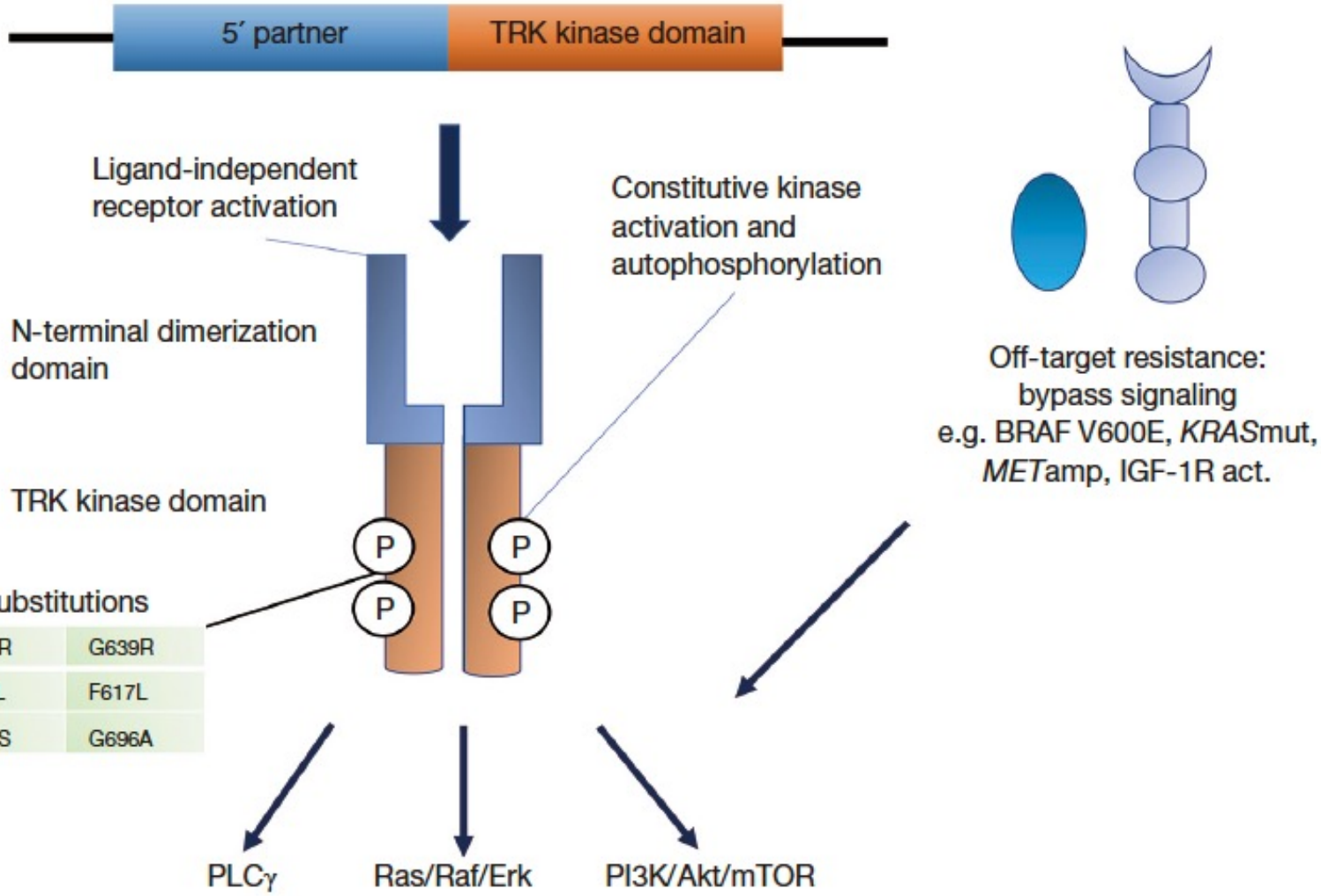
Safety Summary: Phase 1 and Phase 2 Combined

All Treated Patients (N=301)					
	TEAEs (≥15% of patients)			TRAEs	
Adverse Events	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3 n (%)	Grade 4 n (%)
Dizziness	181 (60.1)	7 (2.3)	0	7 (2.3)	0
Dysgeusia	132 (43.9)	1 (0.3)	0	1 (0.3)	0
Constipation	101 (33.6)	1 (0.3)	0	0	0
Paraesthesia	87 (28.9)	3 (1.0)	0	3 (1.0)	0
Dyspnea[a]	84 (27.9)	18 (6.0)	3 (1.0)	1 (0.3)	0
Anaemia	82 (27.2)	24 (8.0)	1 (0.3)	10 (3.3)	0
Fatigue	73 (24.3)	5 (1.7)	0	2 (0.7)	0
Nausea	62 (20.6)	3 (1.0)	0	0	0
Muscular weakness	57 (18.9)	5 (1.7)	0	3 (1.0)	0
Ataxia	51 (16.9)	0	0	0	0

- Repotrectinib was generally well tolerated
- Most TRAEs were Grade 1 or 2
- The most commonly-reported TEAE remains low-grade dizziness (60%)
  - 76% (138/181) were Grade 1
  - 11 (4%) patients reported ataxia in the absence of dizziness
  - No events of dizziness or ataxia led to treatment discontinuation
- Dose modifications due to TEAEs
  - 27% with TEAEs that led to dose reduction
  - 11% with TEAEs that led to drug discontinuation

[a] One patient reported Grade 5 dyspnea.
Note: 2 Grade 4 TRAEs of transient CPK increase and no Grade 5 TRAEs. TEAE = treatment-emergent adverse event; TRAE = treatment-related adverse event. Data cutoff date 26 August 2021.

Mechanisms of resistance to TRK inhibitors



Solvent front	G595R	G623R	G639R
Gatekeeper	F589L	F633L	F617L
xDFG	G667C	G667S	G696A

IGF-1R act., insulin-like growth factor 1 receptor activation; TRK, tropomyosin receptor kinase

Ekman S. Transl Lung Cancer Res. 2020;9:2535-44

Please test your patients!

at least to determine those who will not have a benefit of Immunotherapy!

Christian.Rolfo@mssm.edu

@ChristianRolfo

Thanks

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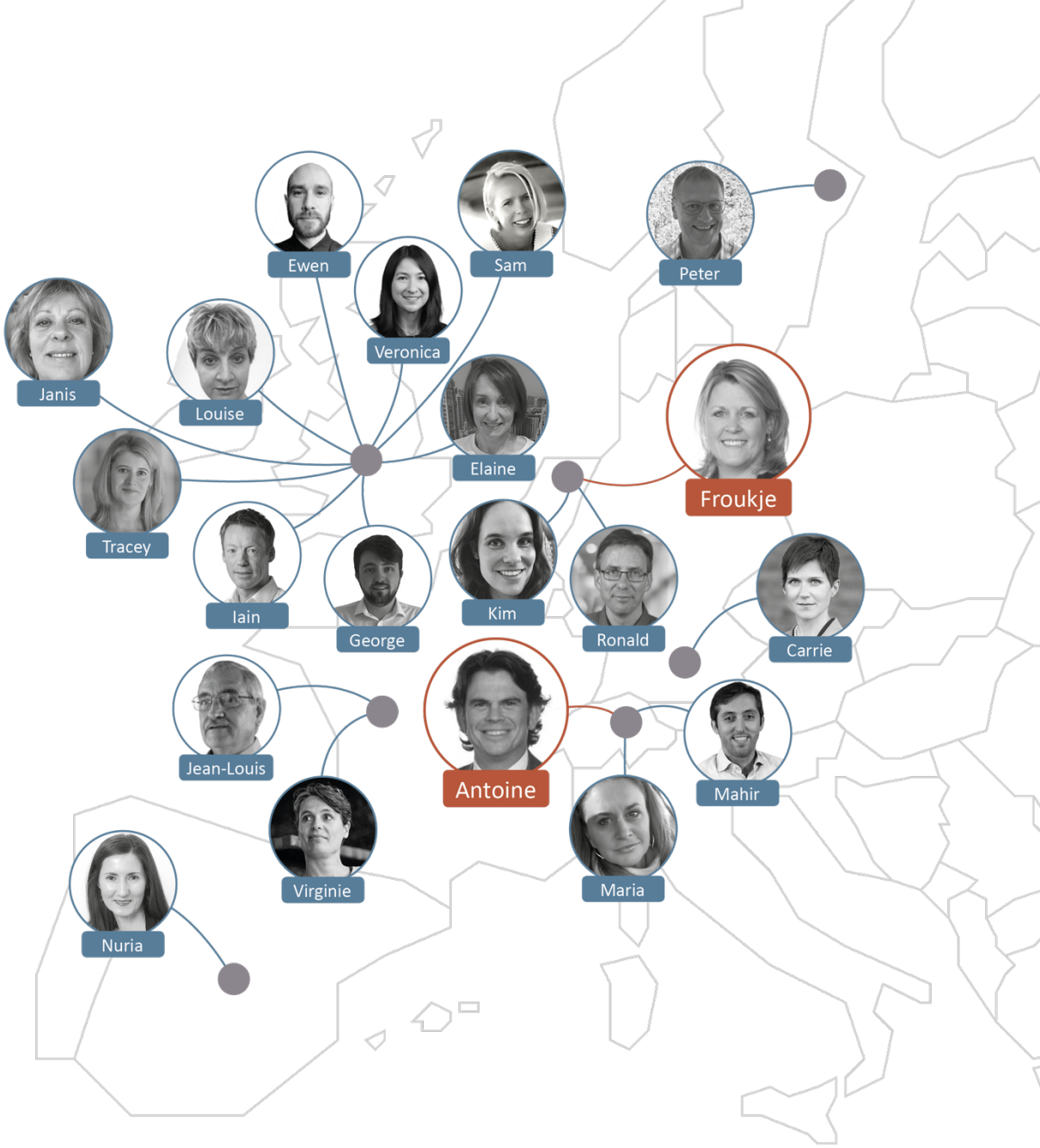

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