Activity of Larotrectinib in Sarcoma Patients with TRK Fusion Cancer

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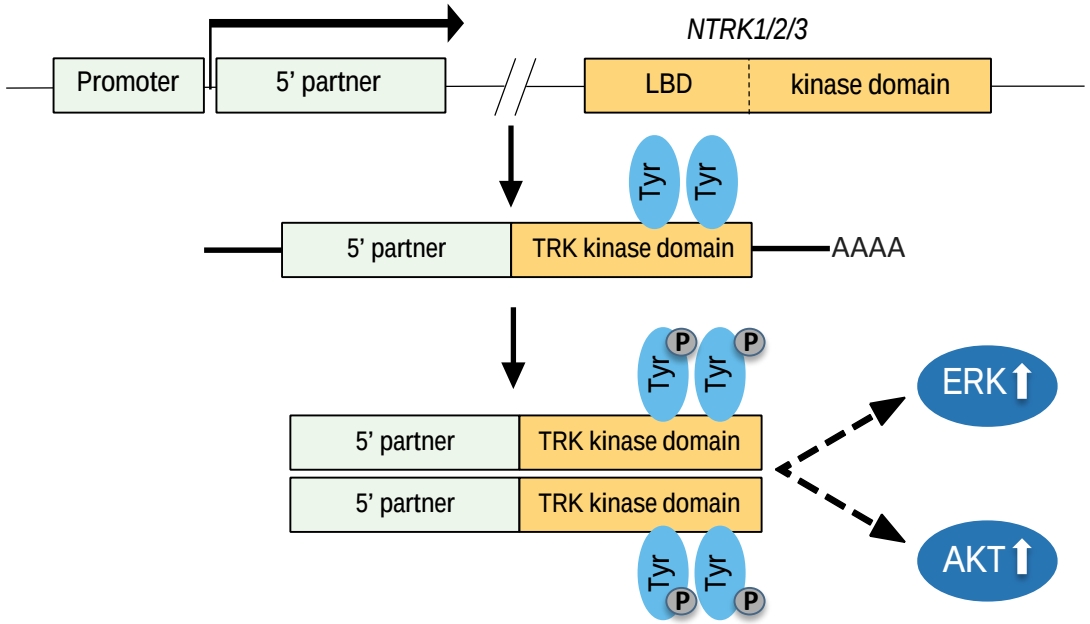
TRK fusions are oncogenic drivers

- After embryonal development, tropomyosin receptor kinases (TRK) expression is primarily limited to the nervous system[1]
- 3 structurally related neurotrophin receptors encoded by 3 distinct genes that regulate specific normal functions[2-6]
  - *NTRK1* → TRKA → Pain, thermoregulation
  - *NTRK2* → TRKB → Movement, memory, mood, appetite, body weight
  - *NTRK3* → TRKC → Proprioception
- Recurrent chromosomal fusion events have been identified across diverse pediatric and adult cancers[7-13]



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Estimated frequency of TRK fusions varies across tumor types

≤5%

CNS
- ✓ Astrocytoma[1]
- ✓ Low-grade glioma[2]
- ✓ Glioblastoma[3]

GI
- ✓ Colorectal cancer[2,4]
- ✓ Cholangiocarcinoma[5]
- ✓ Pancreatic cancer[6]

Head and Neck
- ✓ Squamous cell carcinoma[2]

Lung
- ✓ Adenocarcinoma[2,7]
- ✓ Large cell neuroendocrine carcinoma[8]

Other
- ✓ Acute myeloid leukemia[9]
- ✓ Breast-invasive carcinoma[2]
- ✓ Melanoma[2]
- ✓ Adult sarcoma[2]

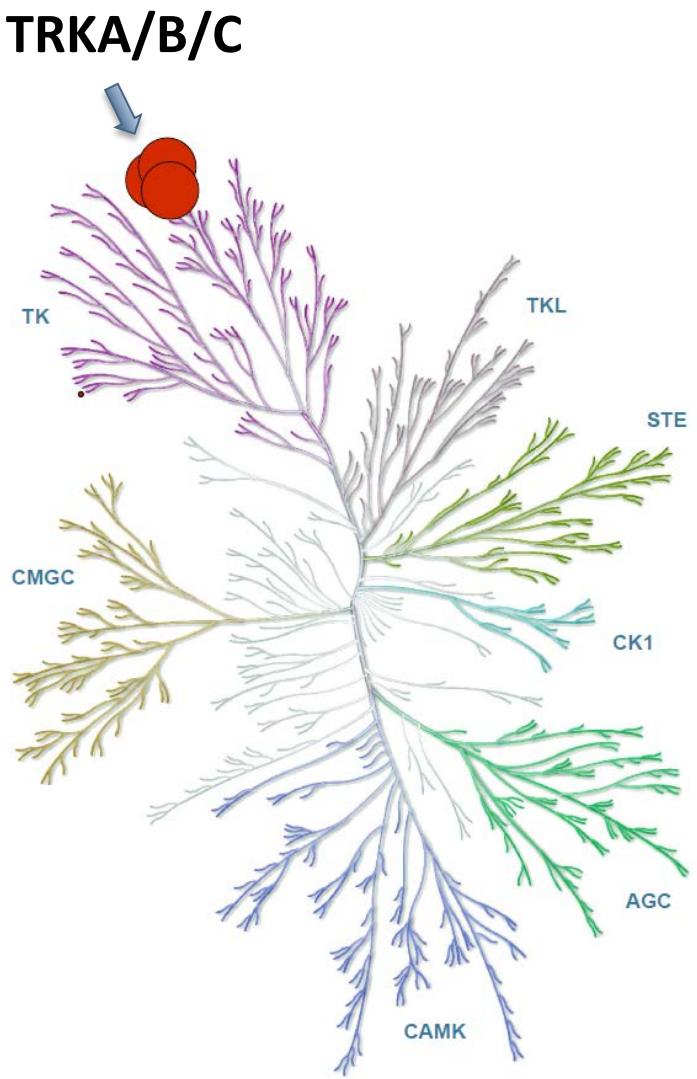
5%-25%
- ✓ Congenital mesoblastic nephroma[10,11]
- ✓ Recurrent papillary thyroid cancer[12]
- ✓ Pontine glioma[13]
- ✓ Spitzoid melanoma[14]
- ✓ Pediatric and young adult soft tissue sarcomas[15]
- ✓ Pan-negative gastrointestinal stromal tumors (GIST)[16]

≥75%
- ✓ Mammary analogue secretory carcinoma (MASC) of the salivary gland[17]
- ✓ Secretory breast carcinoma[18]
- ✓ Infantile fibrosarcoma[19]

1. Jones DT, et al. *Nat Genet.* 2013;45:927-934. 2. Stransky N, et al. *Nat Commun.* 2014;5:4846. 3. Kim J, et al. *PLoS One.* 2014;9:3. 4. DeBraud F, et al. ASCO. 2014 (abstr 2502). 5. Ross JS, et al. *Oncologist.* 2014;19: 235-242. 6. Bailey P, et al. *Nature* 2016;531:47-52. 7. Vaishnavi A, et al. *Nat Med.* 2013;19:1469-1472. 8. Fernandez-Cuesta L, et al. AACR. 2014 (abstr 1531). 9. Kralik JM, et al. *Diag Path.* 2011;6:19. 10. Argani P, et al. *Mod Path.* 2000;13:29. 11. Rubin BP, et al. *Amer J Path.* 1998;153:1451-1458. 12. Leeman-Neill RJ, et al. *Cancer.* 2014;120:799-807. 13. Wu G, et al. *Nat Genet.* 2014;46:444-450. 14. Wiesner T, et al. *Nat Commun*. 2014;5:3116. 15. Morosini D, et al. ASCO. 2015 (abstr 11020). 16. Brenca M, et al. *J Path*. 2016;238:543-549. 17. Bishop JA, et al. *Hum Pathol.* 2013;44:1982-1988. 18. Tognon C, et al. *Cancer Cell.* 2002;2:367-376. 19. Bourgeois JM, et al. *Am J Surg Pathol*. 2000;24:937-946.

Larotrectinib: a highly selective and potent inhibitor of all TRKs

- Larotrectinib is a highly potent small-molecular inhibitor against TRKA, TRKB, TRKC (5–11 nM IC_{50} in cellular assays)[1]
- Highly selective, with little of no interaction with other kinase and non-kinase targets
  - limited inhibition of other kinases and >1,000x selective over other off targets[1]
- Demonstrated activity in CNS disease[2]
- Liquid formulation allows dosing of children and infants from birth, and delivers equivalent pharmacokinetics as capsules
- Larotrectinib is highly active against TRK fusion cancer with durable responses in both children and adults[3]



IC_{50}, half maximal inhibitory concentration.

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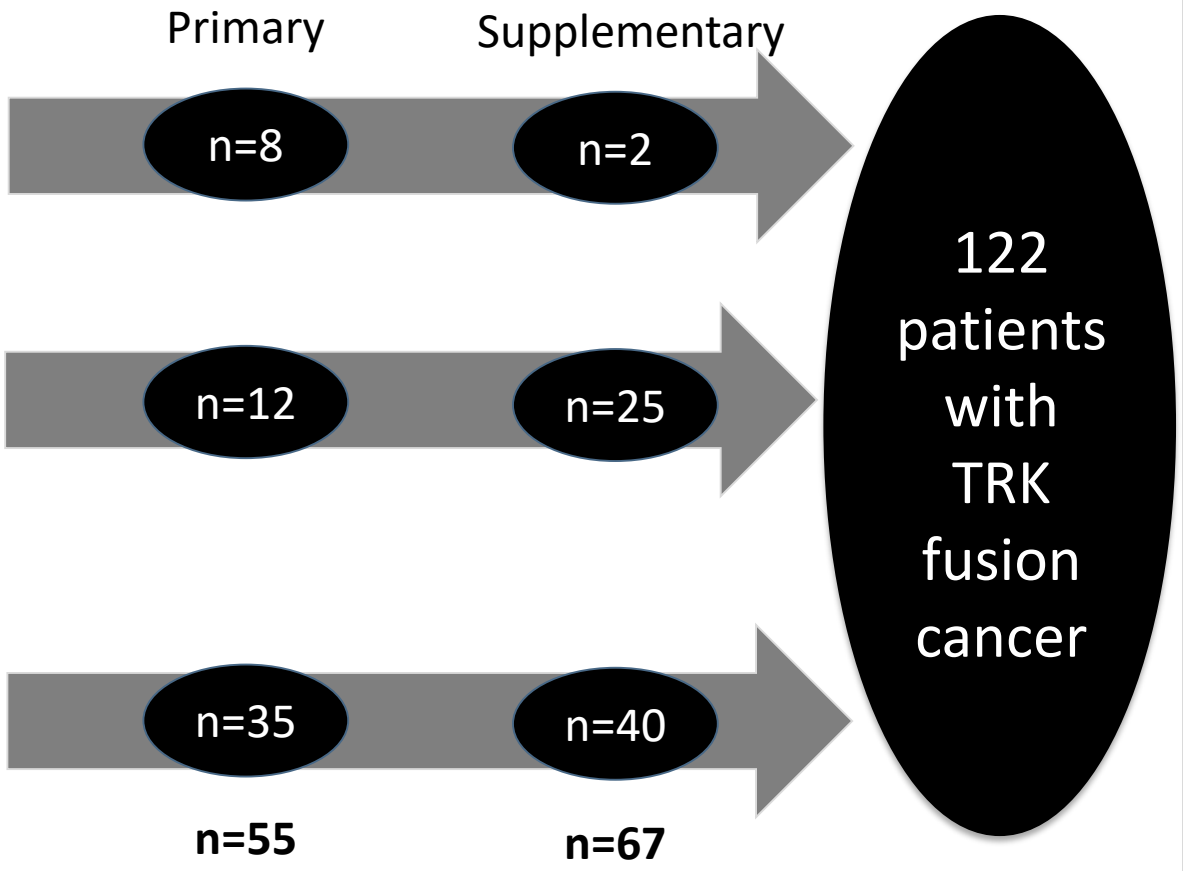
,3. Drilon et al. *NEJM* 2018 378:731-739, Laetsch et al. *Lanc Onc*. 2018 19:705-714.

Patients with TRK fusion cancer: Integrated dataset

Adult phase I
- Age ≥18 years
- Advanced solid tumors

SCOUT: pediatric phase I/II
- Age ≤21 years
- Advanced solid tumors

NAVIGATE: adult/adolescent phase II 'basket' trial
- Age ≥12 years
- Advanced solid tumors
- TRK fusion cancer

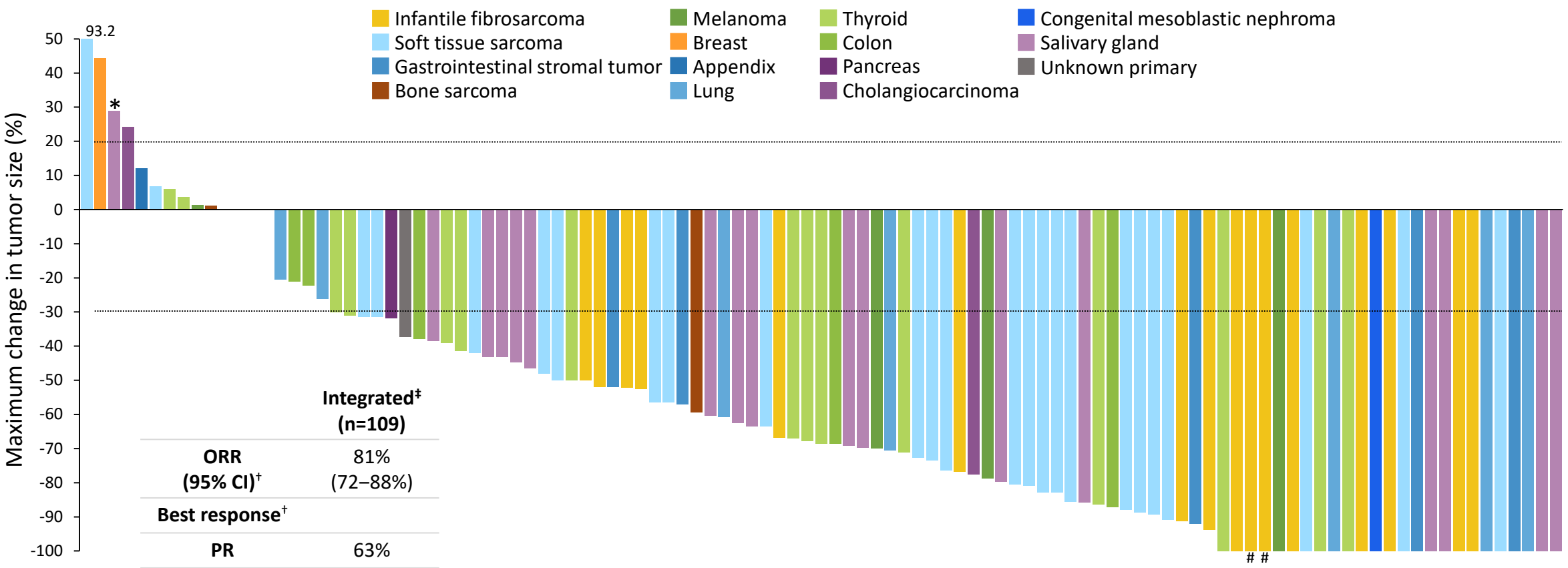


- **TRK fusion status** determined by local CLIA (or similarly accredited) laboratories
- **Primary endpoint**
  - Best objective response rate (RECIST 1.1)
- **Secondary endpoints**
  - Duration of response
  - Progression-free survival
  - Safety
- **Dosing**
  - Single-agent larotrectinib, administered predominantly at 100 mg BID continuously
  - Treatment beyond progression permitted if patient continuing to benefit

Data cut-off: 30 July 2018

BID, twice-daily; CLIA, clinical laboratory improvement amendments; RECIST, Response Evaluation Criteria In Solid Tumors
Lassen et al. presented at ESMO 2018

Integrated dataset: Larotrectinib is efficacious regardless of tumor type



	Integrated‡ (n=109)
ORR (95% CI)†	81% (72–88%)
Best response†	
PR	63%
CR	17%

‡Includes 9 unconfirmed PRs pending confirmation; does not include 13 patients continuing on study and awaiting initial response assessment *Patient had TRKC solvent front resistance mutation (G623R) at baseline due to prior therapy; #Surgical CR; †RECIST 1.1
Note: Two patients not shown here. These patients discontinued treatment prior to any post-baseline tumor measurements.
CR, complete response; ORR, objective response rate; PR, partial response
Lassen et al. presented at ESMO 2018

Investigator response assessments, as of 30 July 2018

Sarcoma subset - baseline characteristics and demographics

Characteristic	Primary (n=21)	Supplementary (n=30)	Integrated (n=51)
Gender, n (%)			
Male	12 (57)	13 (43)	25 (49)
Female	9 (43)	17 (57)	26 (51)
Median age (range), years	5.3 (0.3–61.0)	9.7 (0.1–61.0)	9.4 (0.1–61.0)
Age group, n (%)			
<2 years	6 (29)	11 (37)	17 (33)
2–<6 years	5 (24)	1 (3)	6 (12)
6–<15 years	1 (5)	11 (37)	12 (24)
15–39 years	4 (19)	2 (7)	6 (12)
≥40 years	5 (24)	5 (17)	10 (20)
***NTRK* gene fusion, n (%)**			
NTRK1	9 (43)	13 (43)*	22 (43)*
NTRK2	1 (5)	1 (3)	2 (4)
NTRK3	8 (38)	14 (47)	22 (43)
Inferred *NTRK3*	3 (14)	2 (7)	5 (10)

*One patient had an *LMNA-NTRK1* fusion per non-CLIA certified laboratory report

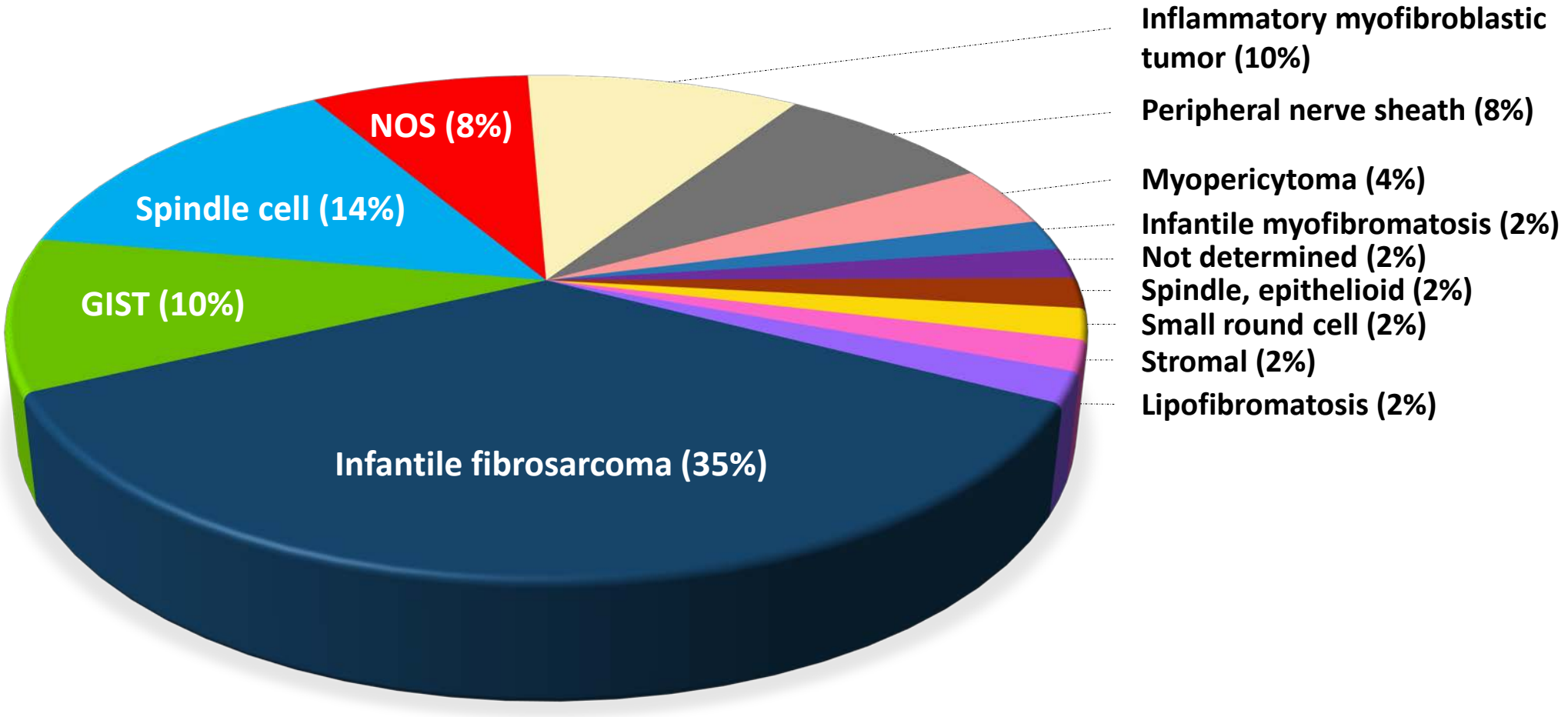
Sarcoma subset - baseline characteristics and demographics (2)

Characteristic	Primary (n=21)	Supplementary (n=30)	Integrated (n=51)
No. of prior systemic regimens, n (%)			
0	5 (24)	9 (30)	14 (27)
1	7 (33)	10 (33)	17 (33)
2	4 (19)	6 (20)	10 (20)
≥3	5 (24)	5 (17)	10 (20)
Disease Status at enrollment, n (%)			
Metastatic	12 (57)	18 (60)	30 (59)
Locally advanced	9 (43)	12 (40)	21 (41)
ECOG PS, n (%)			
0	10 (48)	20 (67)	30 (59)
1	9 (43)	6 (20)	15 (29)
2	2 (10)	4 (13)	6 (12)

ECOG PS, Eastern Cooperative Oncology Group performance status

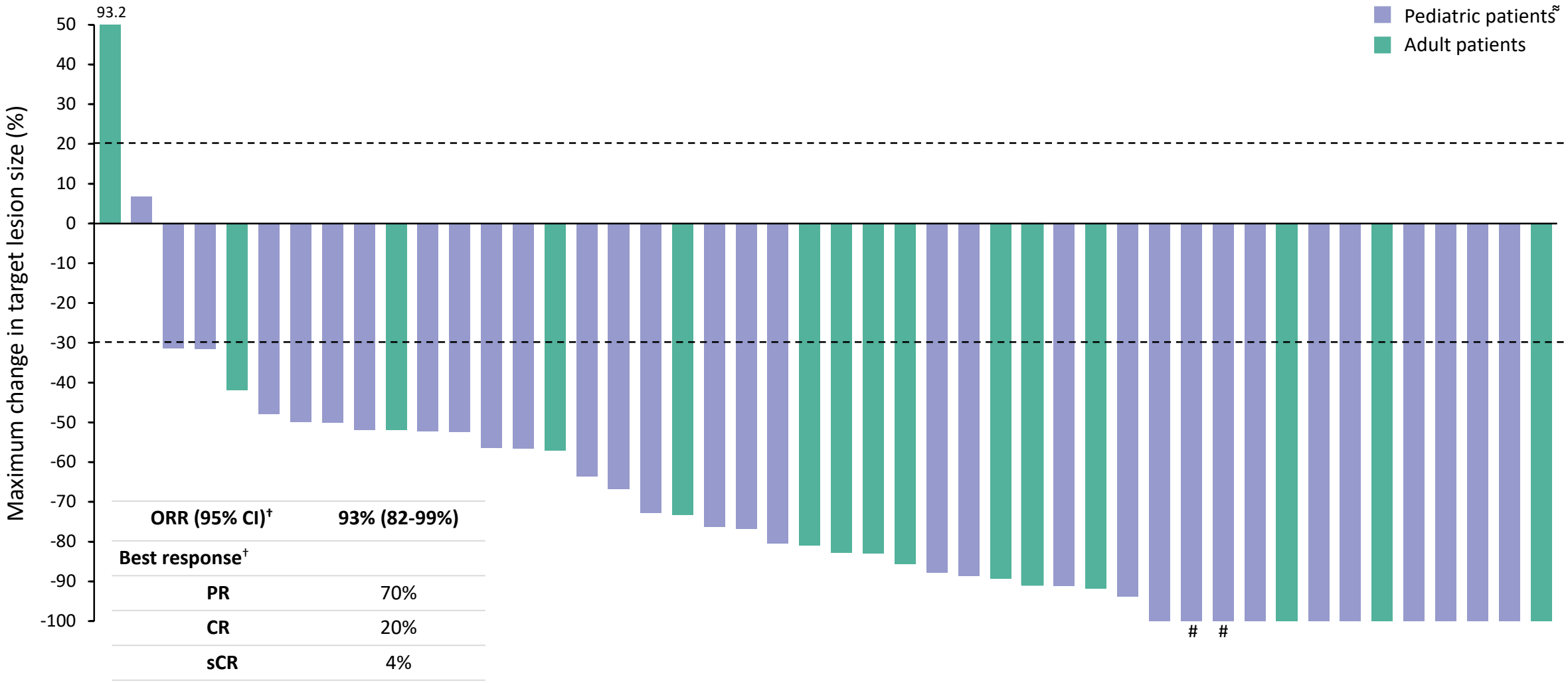
Data cut-off 30 July 2018

TRK fusion sarcoma patients (n=51) – subtypes*



* Based on Investigator assessment

Efficacy of larotrectinib in patients with TRK fusion sarcoma

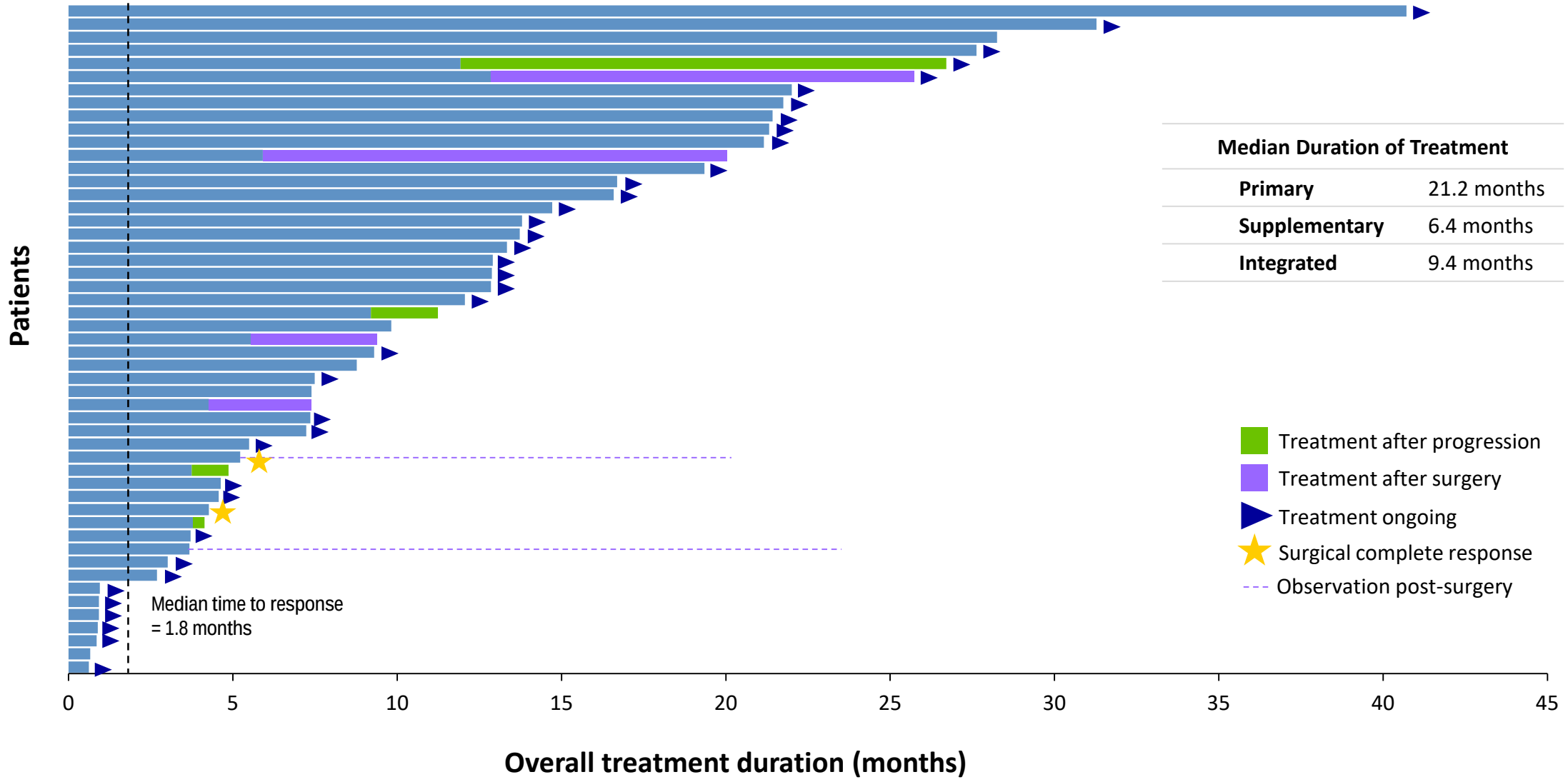


ORR (95% CI)†	**93% (82-99%)**
Best response†	
PR	70%
CR	20%
sCR	4%

†n=46 patients; includes 3 unconfirmed PRs pending confirmation; does not include 5 patients continuing on study and awaiting initial response assessment.
≈Age <21 years. #sCR. CR, complete response; ORR, objective response; PR, partial response; sCR, surgical complete response

Investigator response assessments, as of 30 July 2018

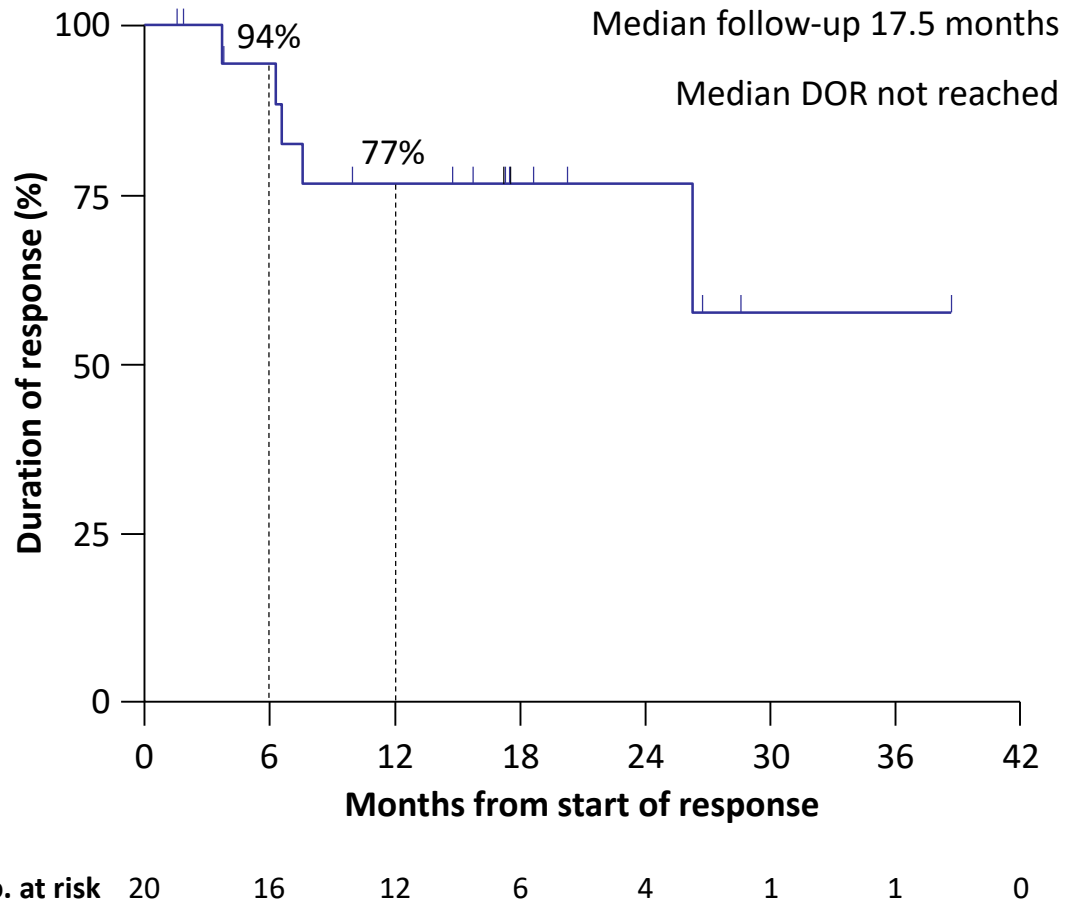
Duration of treatment in patients with sarcoma



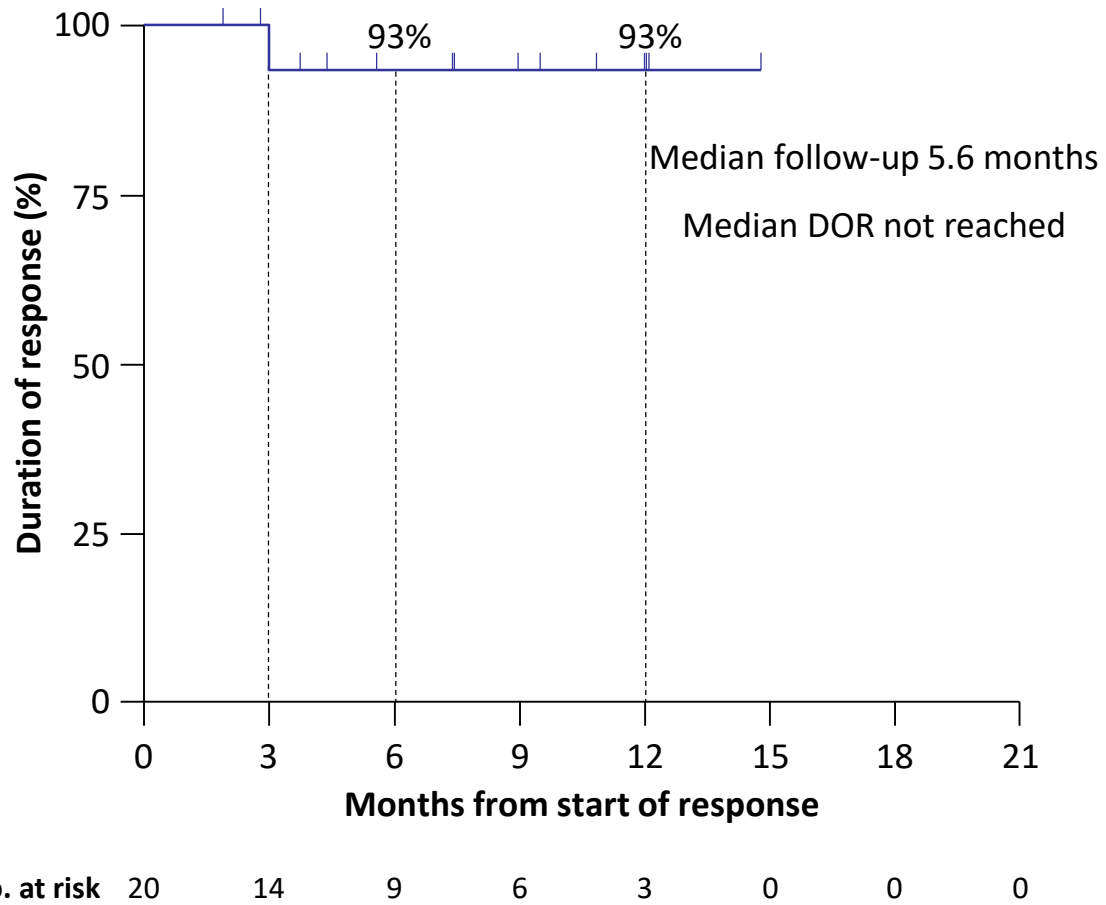
Investigator response assessments, as of 30 July 2018

Sustained responses with larotrectinib in patients with sarcoma

Primary dataset*



Supplementary dataset*



*In patients with confirmed complete or partial responses
DOR, duration of response

Investigator response assessments, as of 30 July 2018

Adverse events with larotrectinib: ≥15% in safety database (n=207)

	Treatment-emergent AEs (%)					Treatment-related AEs (%)		
	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total
Fatigue	18	15	3	–	36	<1	–	18
Dizziness	25	3	1	–	29	<1	–	21
Nausea	24	3	1	–	29	1	–	15
Constipation	22	5	<1	–	27	–	–	12
Anemia	10	7	10	–	27	2	–	11
ALT increased	17	5	3	<1	26	2	<1	21
AST increased	18	5	3	–	26	1	–	19
Cough	23	3	<1	–	26	–	–	1
Diarrhea	16	6	1	–	23	–	–	5
Vomiting	17	6	<1	–	23	–	–	10
Pyrexia	12	5	<1	<1	18	–	–	1
Dyspnea	10	6	2	–	18	–	–	1
Headache	13	4	–	–	16	–	–	4
Myalgia	12	3	1	–	16	<1	–	7
Peripheral edema	12	4	–	–	15	–	–	7

- 11 (9%) of 122 patients with TRK fusion cancer required dose reductions – all maintained tumor regression on reduced dose
- 1 (<1%) of 122 patients with TRK fusion cancer discontinued larotrectinib due to an adverse event

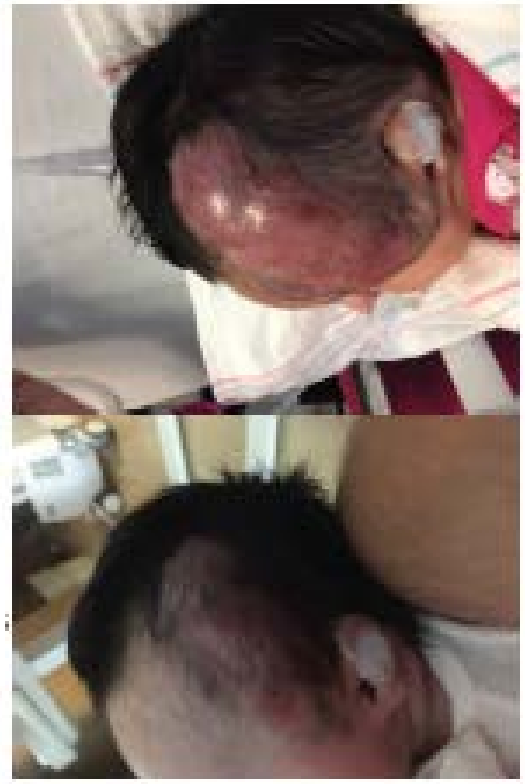
AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase

Data cut-off 30 July 2018

Patient with *ETV6-NTRK3* Infantile Fibrosarcoma

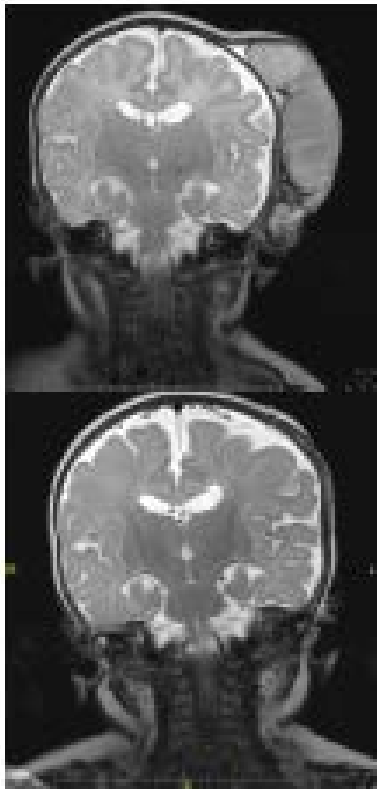
Baseline

After four doses



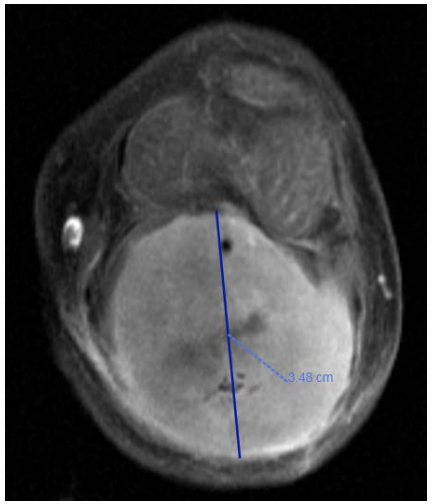
Baseline

Before Cycle 3

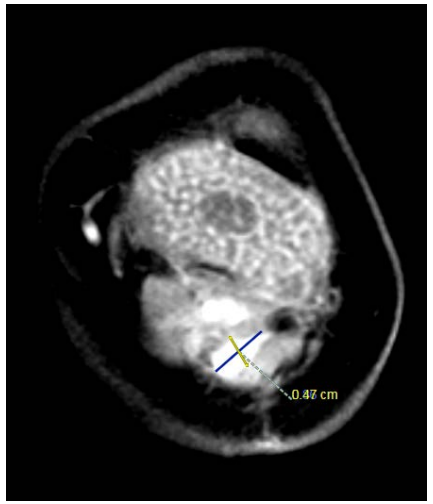


- 31-day-old infant with IFS of the scalp
- Rapid recurrence following surgical resection
- Marked clinical improvement after four doses of larotrectinib
- CR after 2 cycles of larotrectinib
- Remains on therapy after 23 cycles

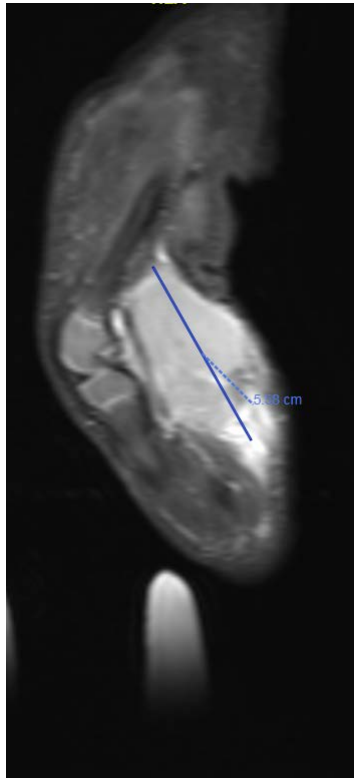
Infant with calf/popliteal *ETV6-NTRK3* Infantile fibrosarcoma



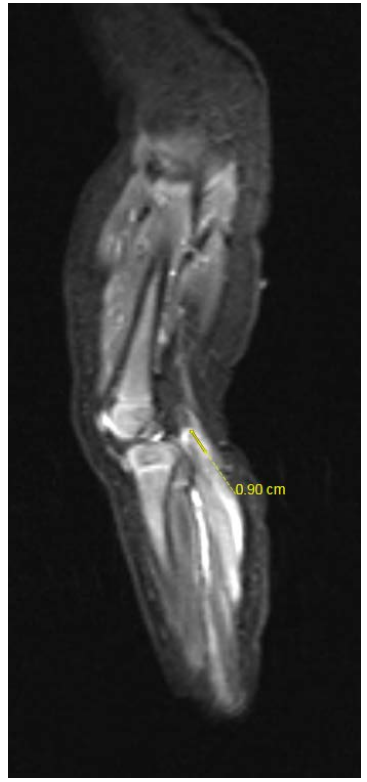
Baseline MRI



Cycle 3 Day 1 MRI



Baseline MRI



Cycle 3 Day 1 MRI

- 1 month-old infant boy with *ETV6-NTRK3* Infantile fibrosarcoma
- Unresectable without potential major morbidity
- Started larotrectinib 100mg/m^2 PO BID
- Rapid response after 2 cycles
- R0 Resection of residual 0.5cm mass after Cycle 6. No residual tumor in specimen
- Remains on therapy after 9 cycles

Conclusions

- Oncogenic *NTRK* gene fusions can be detected in sarcomas
  - Frequency of *NTRK* gene fusions vary with type of sarcoma
- Larotrectinib demonstrates robust antitumor activity across the spectrum of TRK fusion sarcomas, including complete responses, in adult and pediatric patients
  - ORR of 93% (n=46) in the integrated dataset, per investigator assessment
- Responses to larotrectinib therapy were generally durable in TRK fusion sarcomas
  - The median duration of response has not yet been reached with a median follow-up of 17.5 months in the primary dataset
- Prolonged larotrectinib therapy was well tolerated
- Genomic profiling with assays capable of identifying *NTRK* gene fusions should be strongly considered in patients with sarcomas when determining systemic treatment options, especially in the setting of recurrence

Acknowledgments

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SCOUT

NAVIGATE