Larotrectinib efficacy and safety in TRK fusion cancer: an expanded clinical dataset showing consistency in an age and tumor agnostic approach

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Disclosures

Advisory roles: Bayer, Pfizer

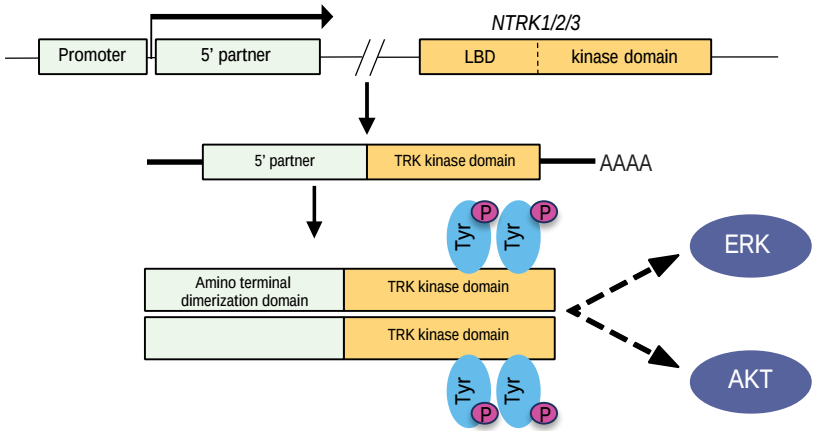
Grants: none

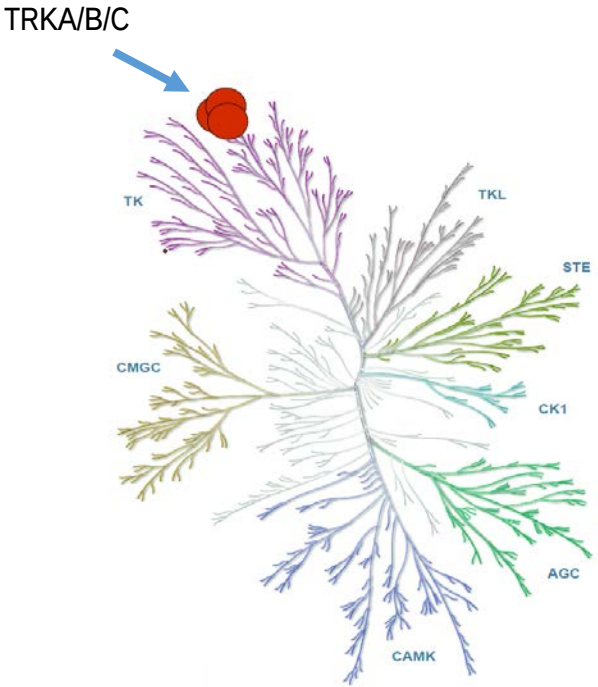
Stocks: none

Others: none

Larotrectinib is a selective, CNS-active TRK inhibitor

NTRK gene fusions are rare but recurrent oncogenic drivers





- Larotrectinib is a highly potent small-molecule inhibitor of TRKA, TRKB, and TRKC (5–11 nM IC_{50} in cellular assays)
- Demonstrated activity in CNS disease[1]
- Liquid formulation allows dosing of children as young as at birth and delivers equivalent pharmacokinetics to capsules

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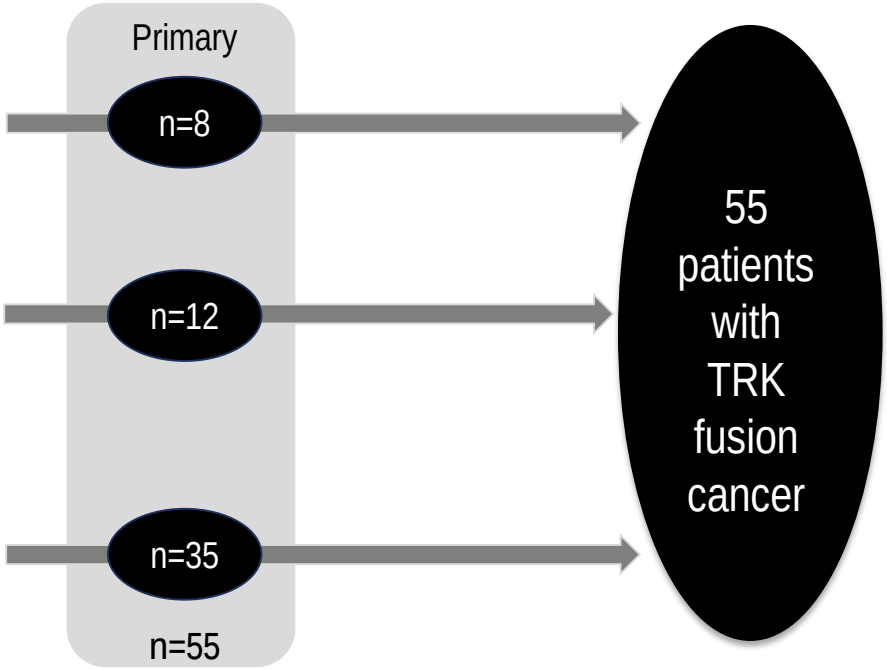
1. Ziegler et al. *British Journal of Cancer*. 2018; 119:693–696

Patients with TRK fusion cancer: Primary 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 cutoff: 30 July 2018

BID, twice-daily; CLIA, clinical laboratory improvement amendments; RECIST, Response Evaluation Criteria In Solid Tumors

Patients with TRK fusion cancer: Supplementary dataset

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

SCOUT: pediatric phase I/II
- Age ≤21 years
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NAVIGATE: adult/adolescent phase II 'basket' trial
- Age ≥12 years
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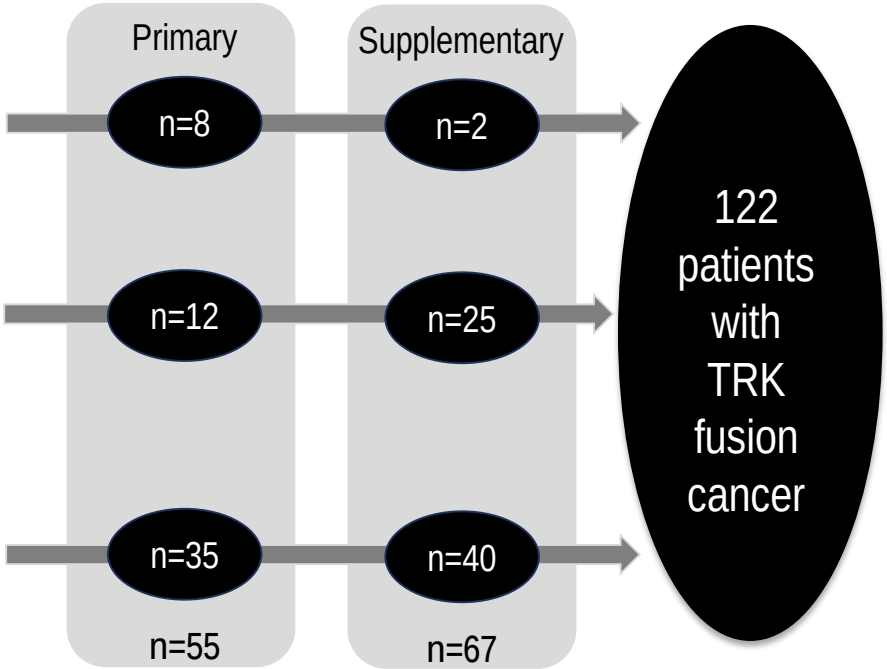
- TRK fusion cancer



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BID, twice-daily; CLIA, clinical laboratory improvement amendments; RECIST, Response Evaluation Criteria In Solid Tumors

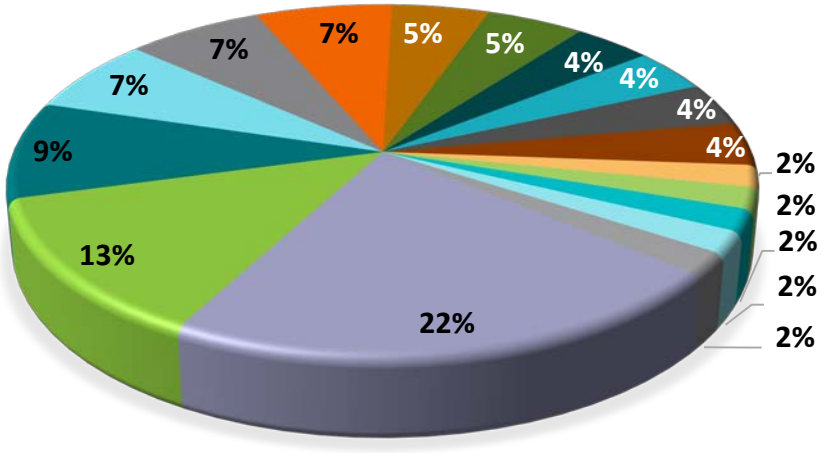
Patient demographics

Characteristic	Primary (n=55)	Supplementary (n=67)	Integrated (n=122)
Gender, n (%)			
Male	29 (53)	31 (46)	60 (49)
Female	26 (47)	36 (54)	62 (51)
Median age (range), years	45.0 (0.3–76.0)	35.0 (0.1–80.0)	41.0 (0.1–80.0)
Age group, n (%)			
<2 years	6 (11)	12 (18)	18 (15)
2–<6 years	5 (9)	2 (3)	7 (6)
6–<15 years	1 (2)	13 (19)	14 (11)
15–39 years	12 (22)	9 (13)	21 (17)
≥40 years	31 (56)	31 (46)	62 (51)
ECOG PS, n (%)			
0	24 (44)	33 (49)	57 (47)
1	27 (49)	26 (39)	53 (43)
2	4 (7)	8 (12)	12 (10)
No. of prior systemic regimens, n (%)			
0–1	27 (49)	39 (58)	66 (54)
2	9 (16)	16 (24)	25 (20)
≥3	19 (35)	12 (18)	31 (25)

ECOG PS, Eastern Cooperative Oncology Group performance status

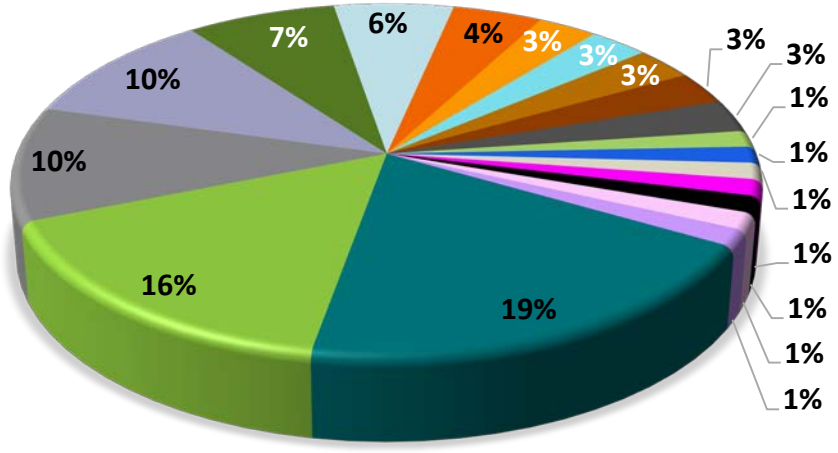
Diversity of cancers treated

Primary dataset (n=55)



- Appendix
- Bone sarcoma
- Breast
- Cholangiocarcinoma
- Colon
- Congenital mesoblastic nephroma
- Gastrointestinal stromal tumor
- Infantile fibrosarcoma
- Lung
- Melanoma
- Pancreas
- Salivary gland
- Thyroid
- Unknown primary

Supplementary dataset (n=67)



Subtypes of soft tissue sarcoma

- Infantile myofibromatosis
- Inflammatory myofibroblastic kidney tumor
- Inflammatory myofibroblastic tumor
- Lipofibromatosis
- Myopericytoma
- Peripheral nerve sheath
- Sarcoma NOS
- Small round cell sarcoma
- Spindle cell sarcoma
- Stromal sarcoma
- Not determined

NOS, not otherwise specified

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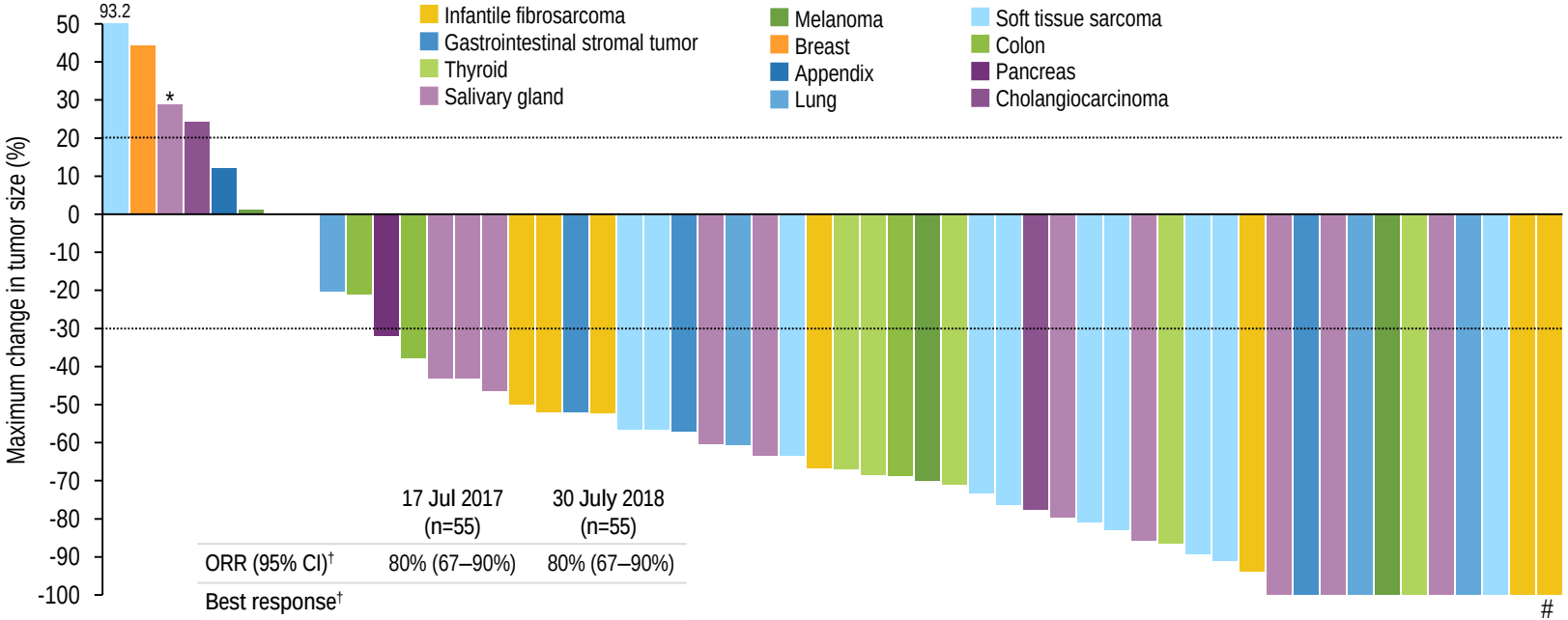
Primary dataset: Larotrectinib has proven efficacy in TRK fusion cancer



	17 Jul 2017 (n=55)	30 July 2018 (n=55)
ORR (95% CI)†	80% (67–90%)	80% (67–90%)
Best response†		
PR	64%	62%
CR	16%	18%

*Patient had TRKC solvent front resistance mutation (G623R) at baseline due to prior therapy; #Surgical CR; †RECIST 1.1
Note: One patient not shown here. The patient discontinued treatment prior to any post-baseline tumor measurements.
CR, complete response; ORR, objective response rate; PR, partial response

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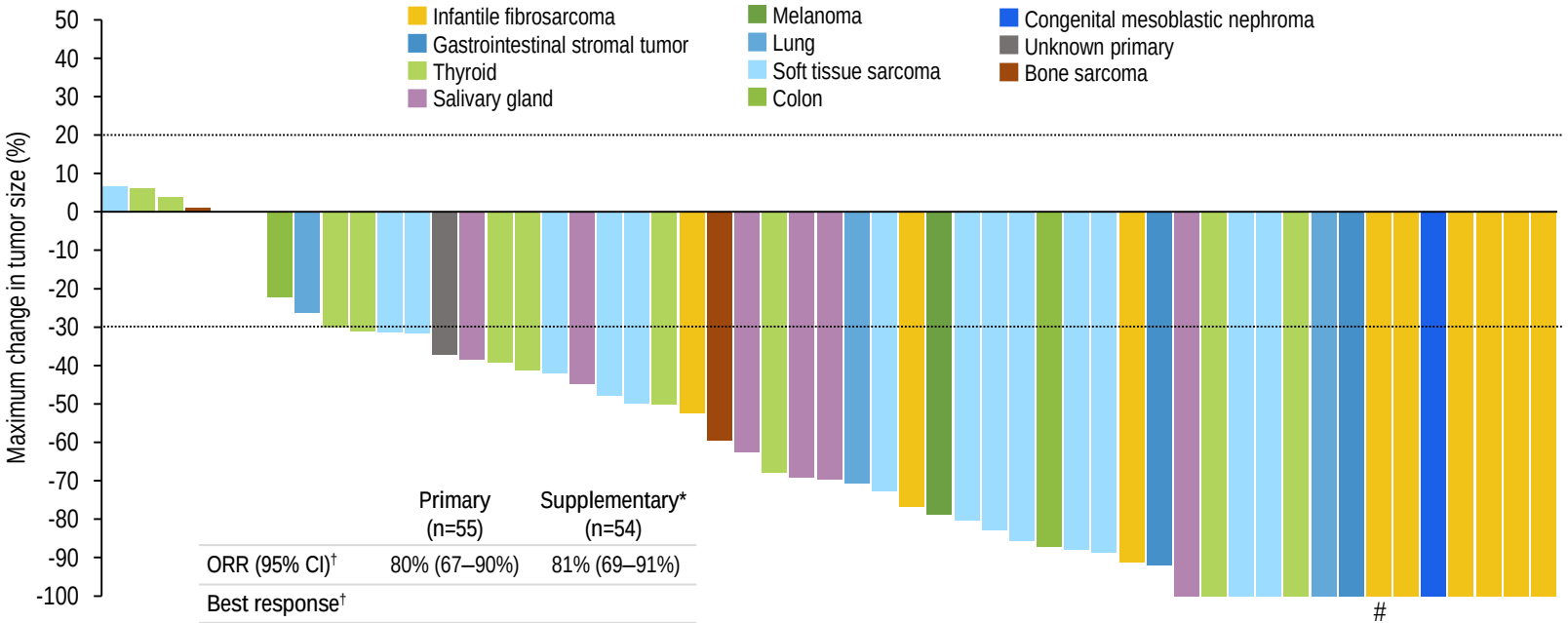
Investigator response assessments, as of 30 July 2018

Supplementary dataset: Larotrectinib efficacy consistent with primary dataset



	Primary (n=55)	Supplementary* (n=54)
ORR (95% CI)†	80% (67–90%)	81% (69–91%)
Best response†		
PR	62%	65%
CR	18%	17%

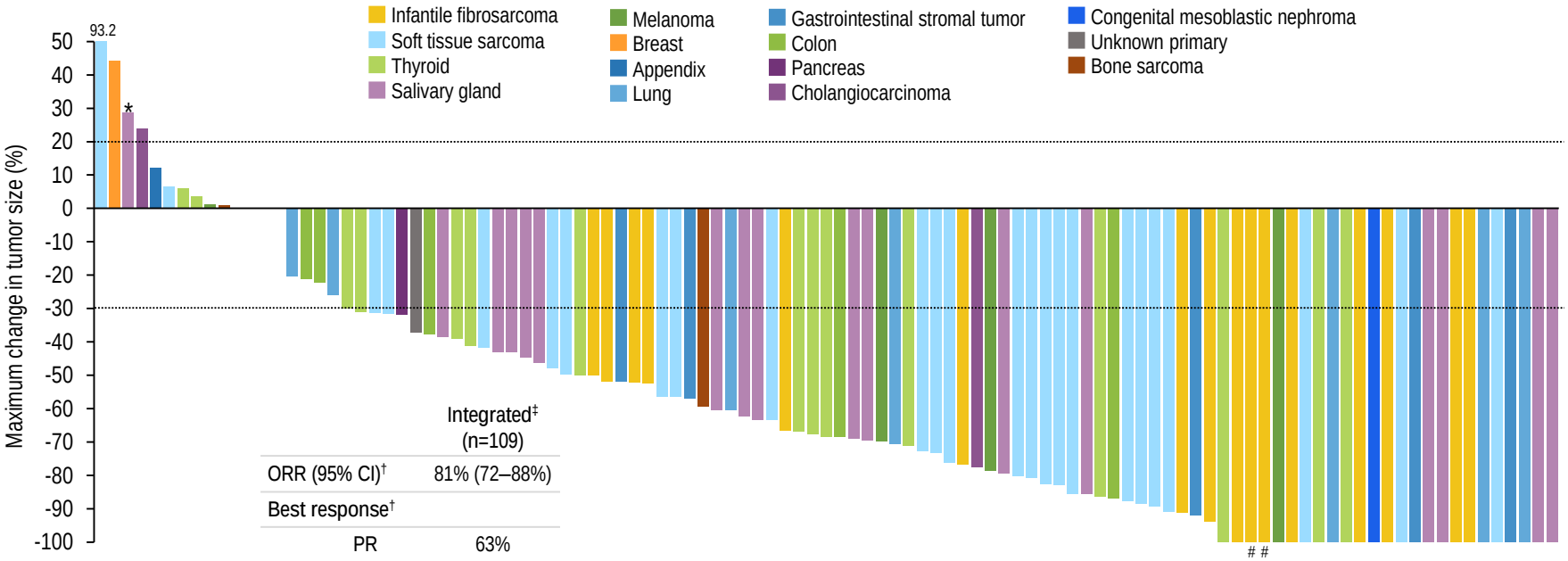
*Evaluable patients; includes 9 unconfirmed PRs pending confirmation; does not include 13 patients continuing on study and awaiting initial response assessment; #Surgical CR; †RECIST 1.1

Note: One patient not shown here. The patient discontinued treatment prior to any post-baseline tumor measurements.

CR, complete response; ORR, objective response rate; PR, partial response

Investigator response assessments, as of 30 July 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

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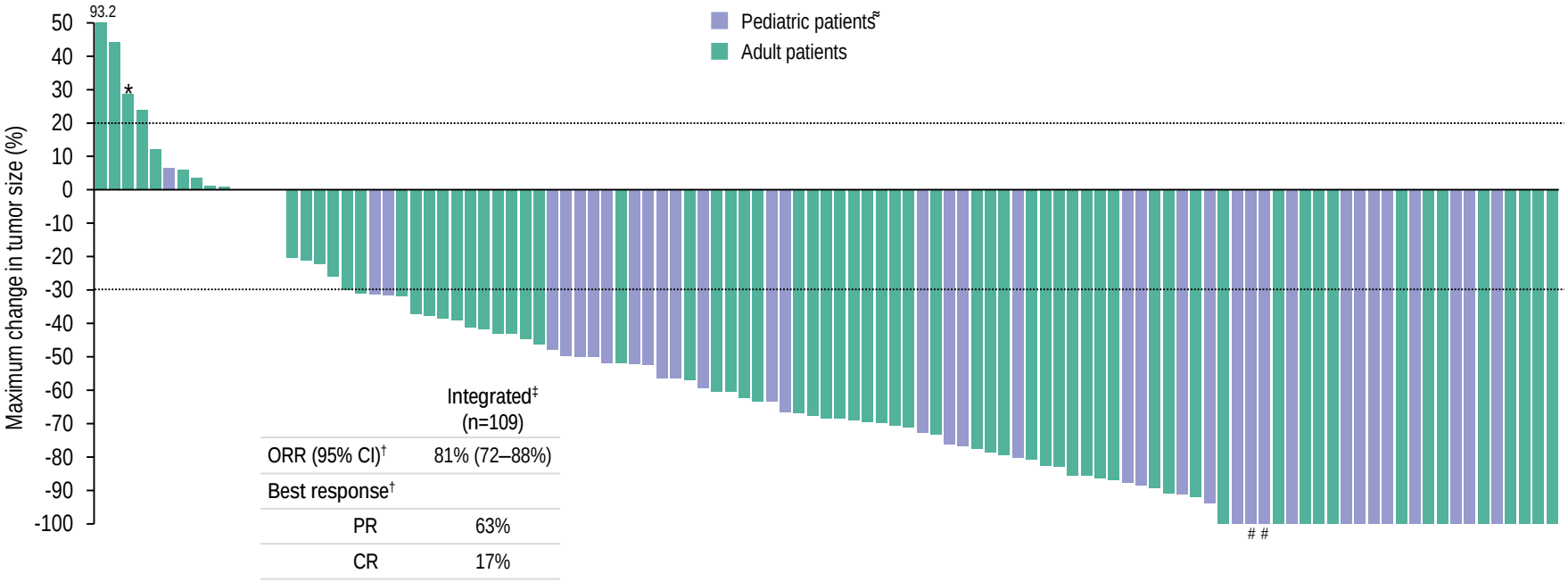
Investigator response assessments, as of 30 July 2018

Integrated dataset: Larotrectinib is efficacious regardless of age



	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
≃Age <21 years *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

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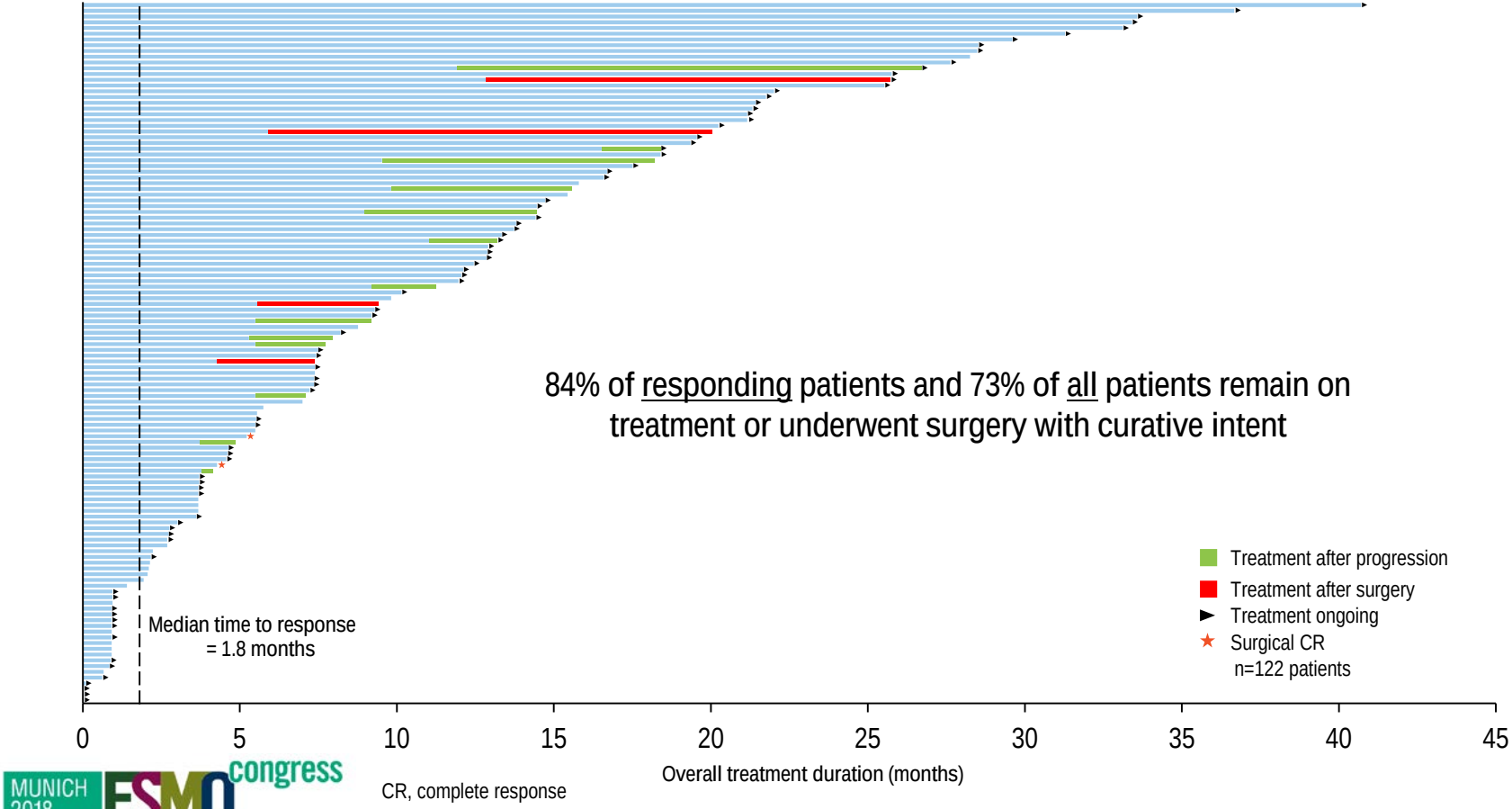
Investigator response assessments, as of 30 July 2018

Integrated dataset (n=122): Duration of larotrectinib treatment



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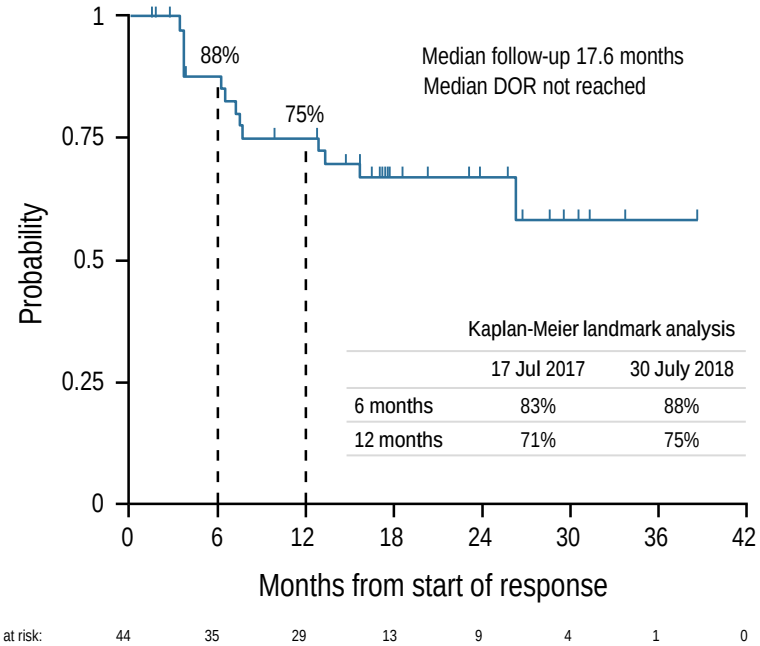
CR, complete response

Investigator response assessments, as of 30 July 2018

Sustained responses with larotrectinib (DOR)

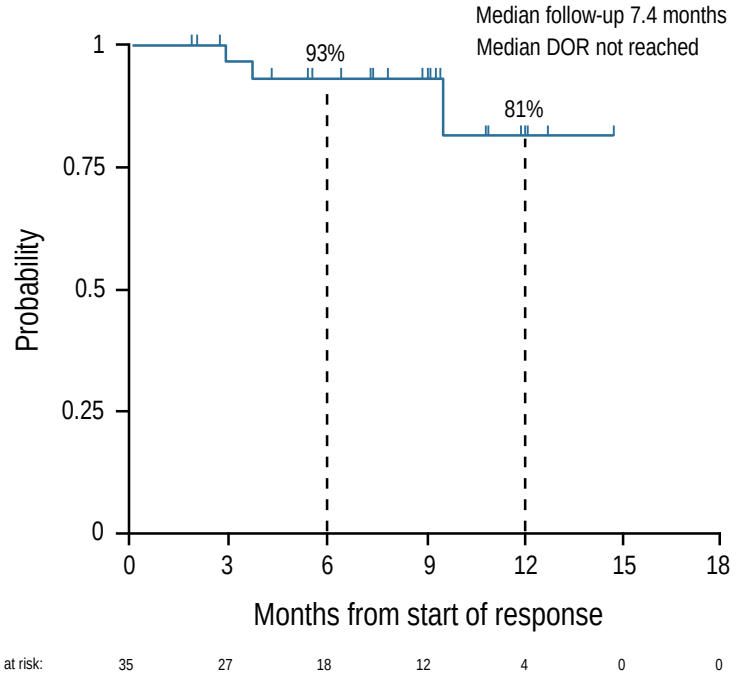
Primary dataset*



Kaplan-Meier landmark analysis

	17 Jul 2017	30 July 2018
6 months	83%	88%
12 months	71%	75%

Supplementary dataset*



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*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 oedema	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

As of 30 July 2018

Patient with *EPS15-NTRK1* lung cancer and CNS metastases

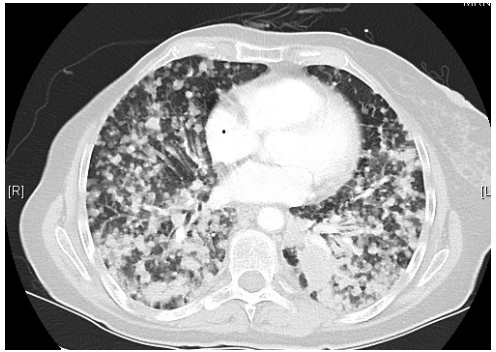
77-year-old female with *EPS15-NTRK1* NSCLC diagnosed with stage IV disease with distant metastases to liver and brain

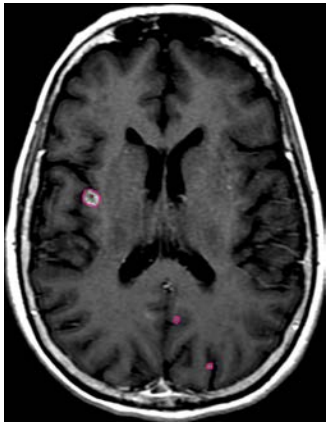
- Prior history of breast cancer
- Pre-existing symptoms of anorexia, fatigue, cough, hyperlipidemia
- ECOG 1
- No prior surgery, radiation or chemotherapy

Started on larotrectinib 100 mg BID and treatment ongoing

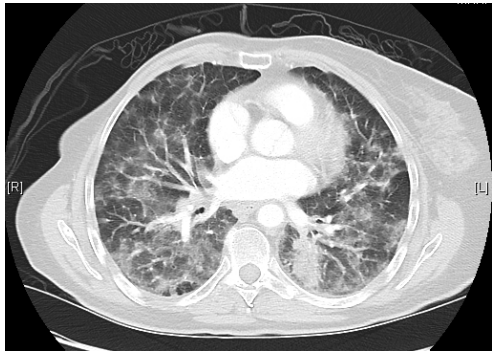
- Start of cycle 3:
  - PR in lung target lesions
  - CNS non-target lesion shows aggregate volume decrease of 95%

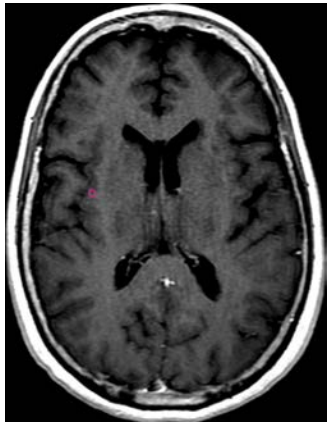
Baseline, June 2018





Cycle 3, Aug 2018





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BID, twice-daily; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; PR, partial response

Images courtesy of Rob Young and Ezra Rosen, Memorial Sloan Kettering Cancer Center

Patient with *ETV6-NTRK3* infantile fibrosarcoma

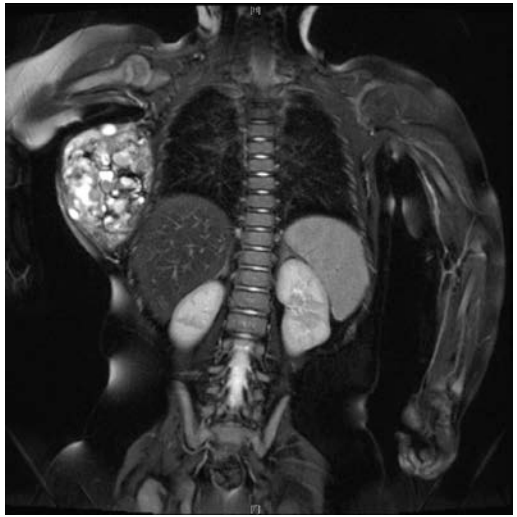
8-month-old infant boy with congenital *ETV6-NTRK3* infantile fibrosarcoma

- Refractory to 2 prior lines of chemotherapy
  - Vincristine & actinomycin
  - Doxorubicin & ifosfamide

Started on larotrectinib 100 mg BID and treatment ongoing

- PR at cycle 3, day 1

Baseline, July 2018



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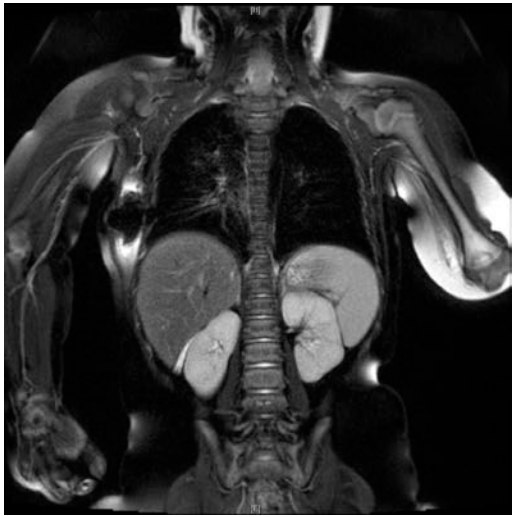

BID, twice-daily; PR, partial response

Images courtesy of Cornelis van Tilburg, Hopp Children's Cancer Center at the NCT Heidelberg, Heidelberg University Hospital and German Cancer Research Center

Conclusions

- Larotrectinib continues to demonstrate robust tumor-agnostic and age-agnostic antitumor activity against TRK fusion cancer, regardless of *NTRK* gene or fusion partner involved
  - ORR of 80% (n=55) and 81% (n=54) in primary and supplementary datasets, respectively, per investigator assessment
  - Demonstrated activity in CNS disease
- Duration of response has improved with additional follow-up
  - At a median follow-up of 17.6 months in the primary dataset, median DOR not reached
  - 12-month landmark DOR of 75% and 81% for the primary and supplementary datasets, respectively
- NDA on file with FDA (PDUFA date November 26, 2018) and MAA submitted to EMA in August 2018
- Genomic profiling with assays capable of identifying *NTRK* gene fusions should be strongly considered in patients with solid tumors of all histologies when determining systemic treatment options

DOR, duration of response; MAA, marketing authorization application; NDA, New Drug Application; ORR, objective response rate; PDUFA, Prescription Drug User Fee Act

Acknowledgments

- We thank the patients and their families, many of whom traveled long distances to participate in these studies
- These studies are funded by Loxo Oncology, Inc and Bayer AG

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SCOUT

NAVIGATE