# Activity of larotrectinib in patients with TRK fusion GI malignancies

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# Disclosures for Presenting Author, Michael Nathenson MD

Travel, Accommodations, Expenses-Bayer

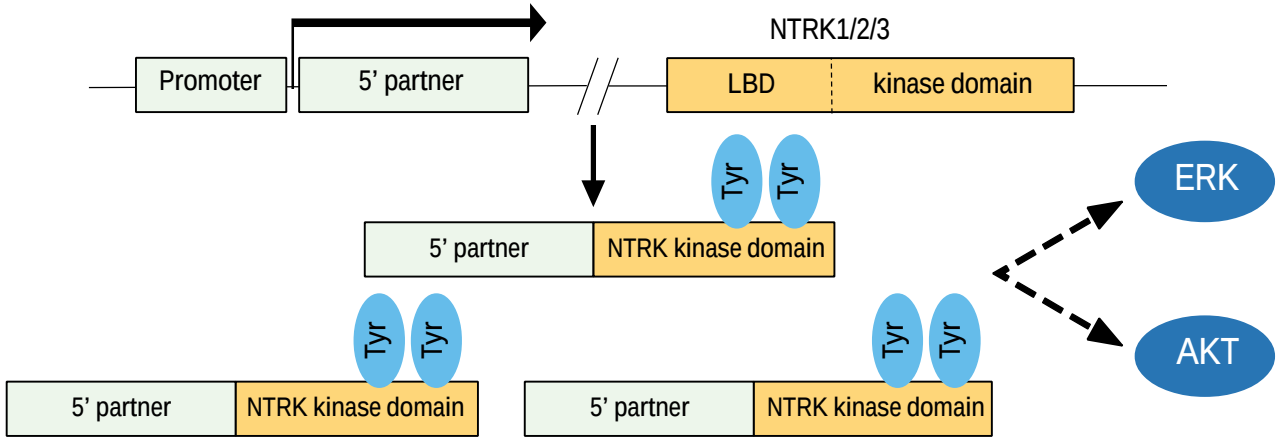
# TRK fusions are rare but recurrent oncogenic drivers

- After embryonal development, tropomyosin receptor kinases (TRK) are primarily limited to the nervous system[1]
- 3 structurally related neurotrophin receptors encoded by 3 distinct genes that regulate specific normal functions[2-6]

  ***GENE*** **PROTEIN**

  - *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]




References:1. Vaishnavi et al. *Cancer Discovery*. 2014;5(1):1-10. 2. Crowley et al. *Cell.* 1994;76(6):1001-1011. 3. Smeyne et al. *Nature.* 1994;368(6468):246-249. 4.Skaper. *CNS Neurol Disord Drug Targets.* 2008;7(1):46-62. 5. Ammendrup-Johnsen I et al. *J Neurosci.* 2015;35(36):12425-12431. 6. Huang et al. *Annu Rev Neurosci.* 2001;24:677-736. 7. Chen et al. *Anticancer Res.* 2014;34(4):1595-1600. 8. Fujimoto J et al. *Proc Natl Acad Sci U S A.* 1996;93(9):4181-4186. 9. Dupain C et al. *Mol Ther Nucleic Acids.* 2017;6:315-326. 10. Wang D et al. *Comput Math Methods Med.* 2015;2015:912742. 11. Tognon C et al. *Cancer Res.* 2001;61(24):8909-8916. 12. Roccato E et al. *Br J Cancer.* 2002;87(6):645-653. 13. Ardini E, et al. *Mol Oncol.* 2014;8(8):1495-1507.

# 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]

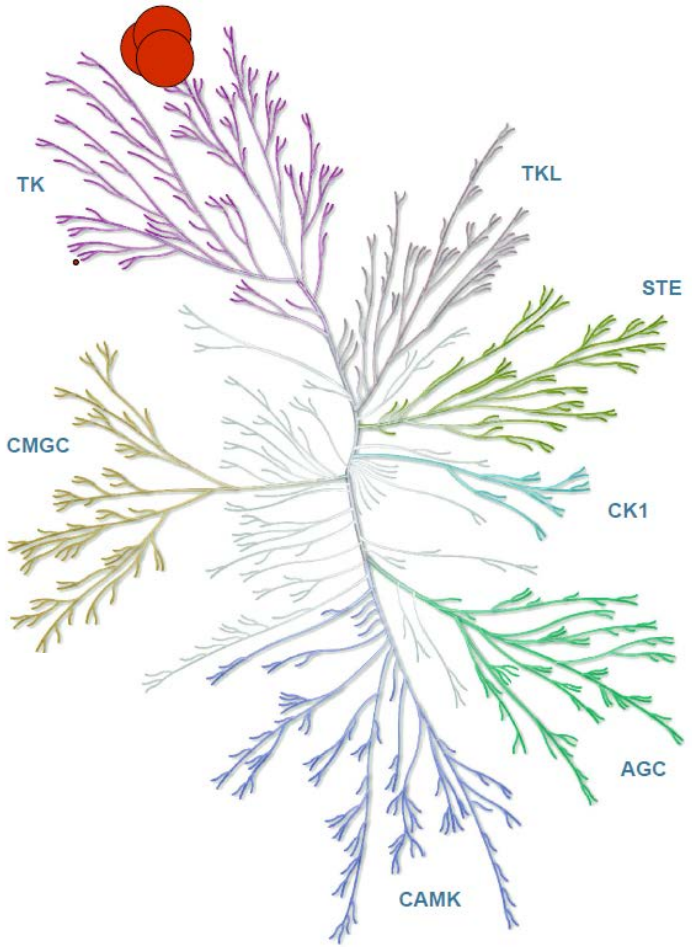
## ≥75%
- ✓ Mammary analogue secretory carcinoma (MASC) of the salivary gland[17]
- ✓ Secretory breast carcinoma[18]
- ✓ Infantile fibrosarcoma[19]

References: 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

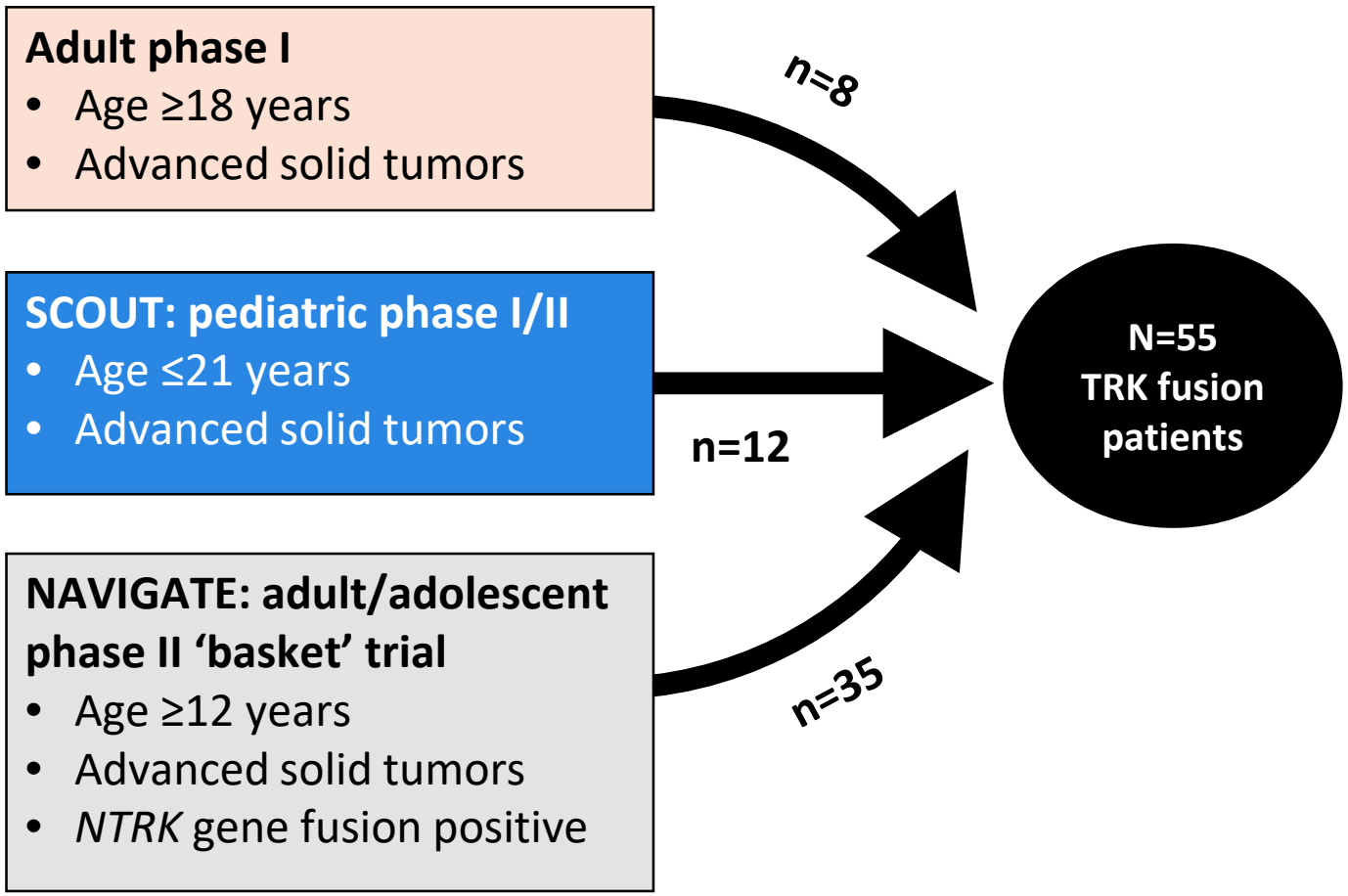
- Larotrectinib is the first and only highly selective TRK inhibitor in clinical development
- Highly potent against TRKA, TRKB, TRKC (5–11 nM $IC_{50}$ in cellular assays) [1]
- Highly selective
  - limited inhibition of other kinases and >1,000x selective over other off targets[1]

**TRKA/B/C** [2]




References: 1. Doebele et al. *Cancer Discov*. 2015 Oct;5(10):1049-57. 2. Chartier et al. 2013 Kinome Render: a stand-alone and web-accessible tool to annotate the human protein kinome tree. *PeerJ* 1:e126.

# Integrated clinical development of larotrectinib simultaneously across adult and pediatric cancers

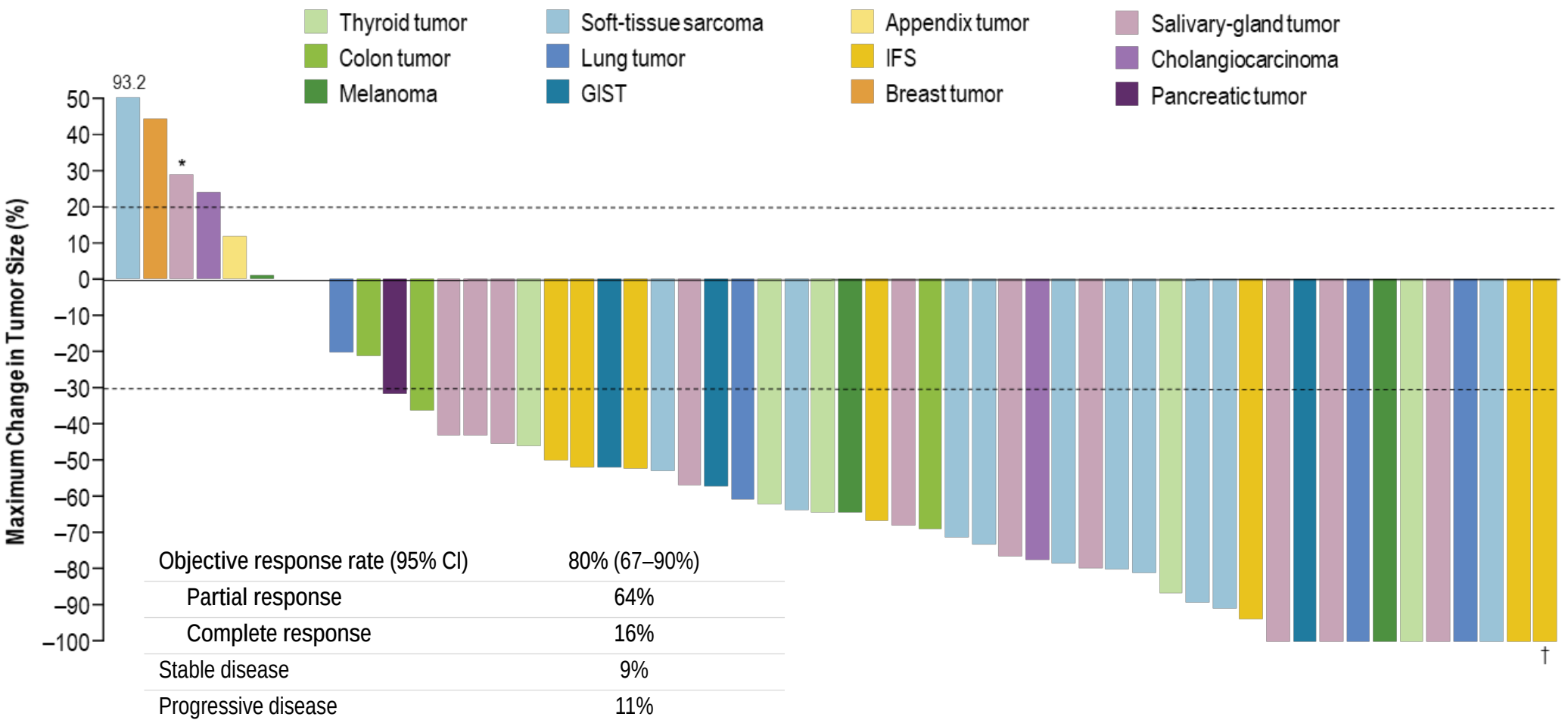



**Data cut-off:** July 17, 2017

- **TRK fusion status** determined by local clinically approved laboratory assay (or similarly accredited) laboratories
- **Primary endpoint**
  - Best objective response rate (ORR)
  - RECIST v1.1 per investigator assessment
- **Secondary endpoints**
  - Duration of response (DOR)
  - Progression-free survival (PFS)
  - Safety
- **Dosing**
  - Single-agent larotrectinib, administered predominantly at 100 mg BID continuously; 28-day cycle
  - Treatment beyond progression permitted if patient continuing to benefit

Reference: Drilon et al. *N Engl J Med*.2018;378:731-9

# Clinical Efficacy of larotrectinib in TRK fusion cancers




| | |
|---|---|
| Objective response rate (95% CI) | 80% (67–90%) |
| Partial response | 64% |
| Complete response | 16% |
| Stable disease | 9% |
| Progressive disease | 11% |

*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.

Reference: Drilon et al. *N Engl J Med*.2018;378:731-9

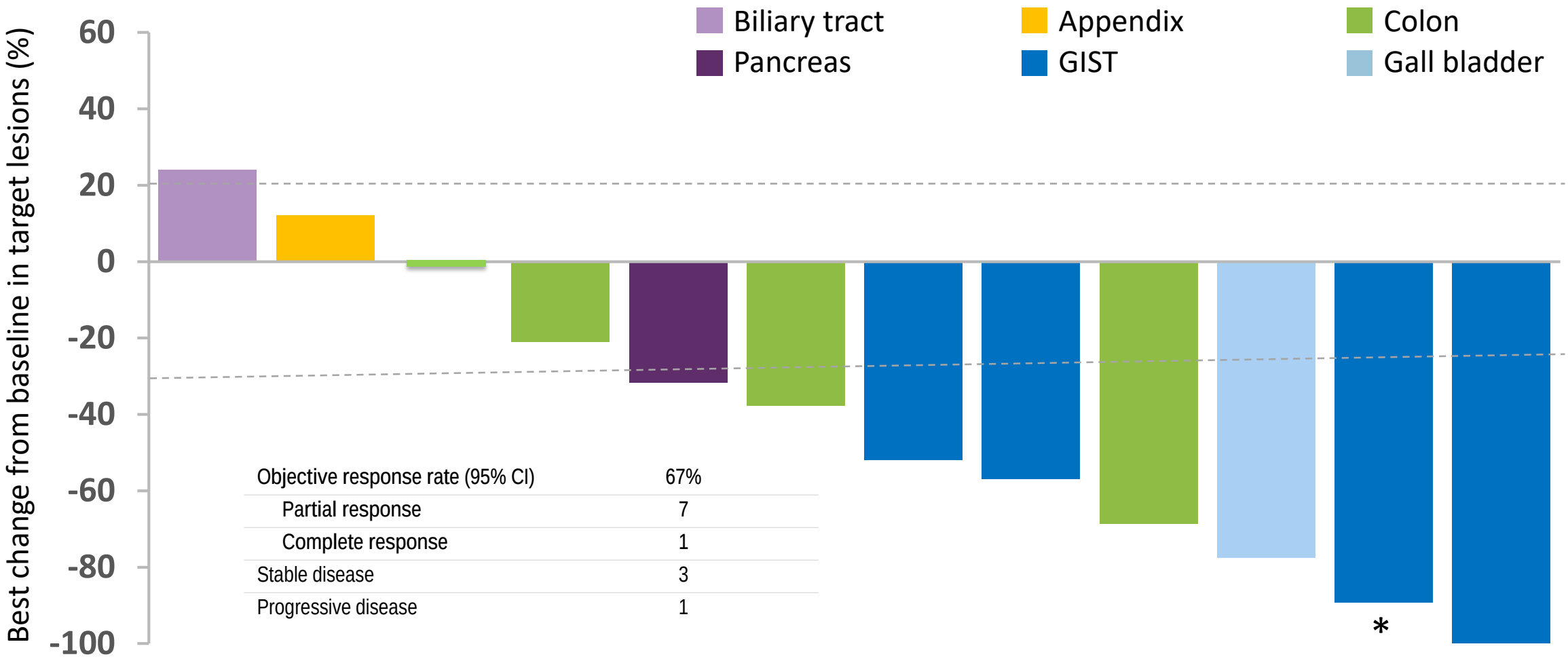
Note: Investigator assessment

# Patient and disease characteristics of Gastrointestinal subset

| Characteristic | Total N=12 |
|---|---|
| Median age (range) years | 56 (32–74) |
| Gender female: male, n | 7:5 |
| Tumor type, n | |
| Colon | 4 |
| GIST* | 4 |
| Gall bladder | 1 |
| Biliary tract | 1 |
| Appendix | 1 |
| Pancreas | 1 |
| Fusion partners | |
| *TPM3-NTRK1* | 4 |
| *LMNA-NTRK1* | 3 |
| *CTRC-NTRK1* | 1 |
| *PLEKHA6-NTRK1* | 1 |
| *ETV6-NTRK3* | 3 |
| Prior therapies | |
| All therapies, median (range) | 3 (2-14) |
| Systemic therapies, median (range) | 2 (0-9) |

*One patient initially diagnosed as GIST was determined to have peri-rectal undifferentiated soft tissue sarcoma

# Efficacy of larotrectinib in TRK fusion Gastrointestinal cancers

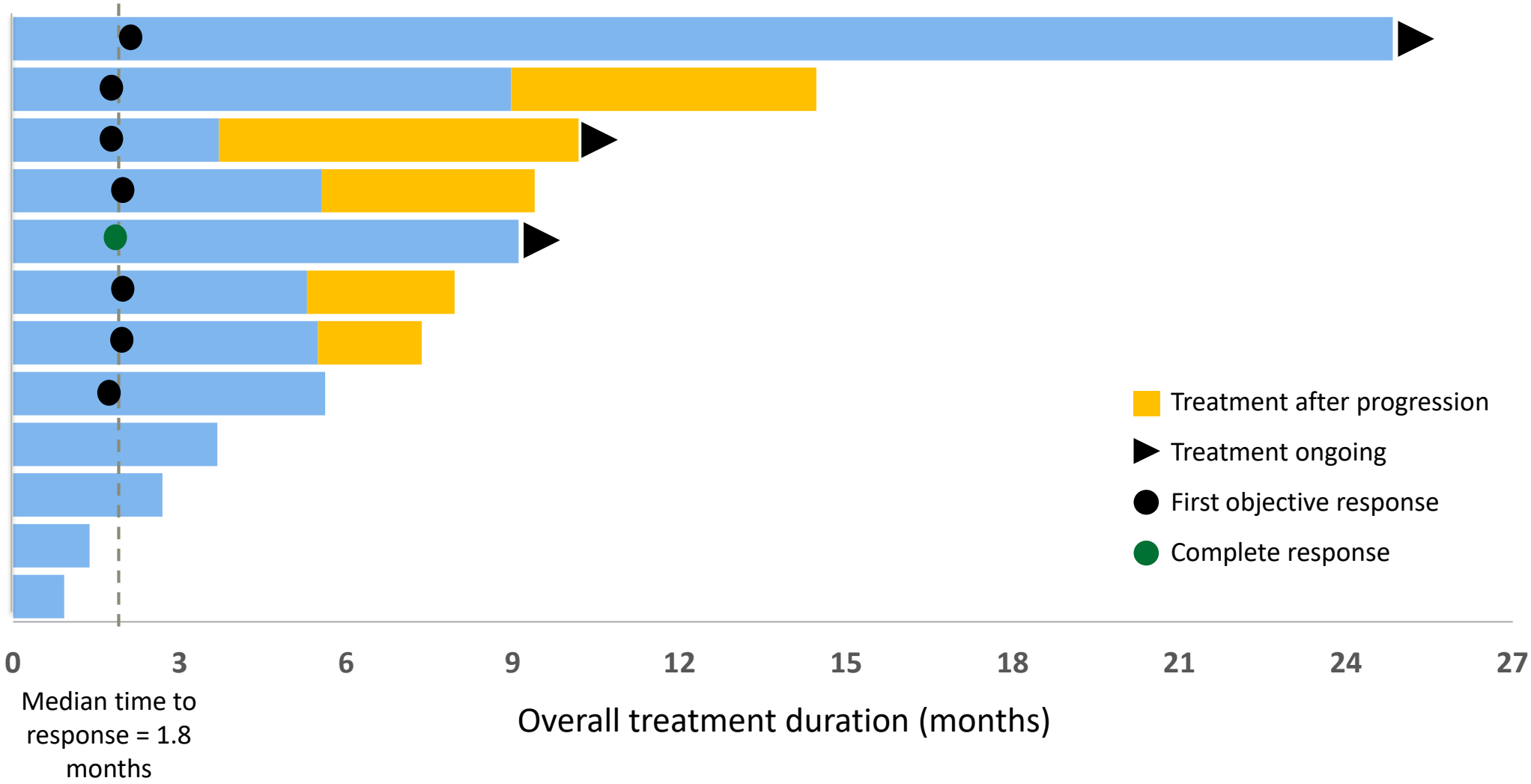



| | |
|---|---|
| Objective response rate (95% CI) | 67% |
| Partial response | 7 |
| Complete response | 1 |
| Stable disease | 3 |
| Progressive disease | 1 |

*One patient initially diagnosed as GIST was determined to have peri-rectal undifferentiated soft tissue sarcoma

Note: Investigator assessment

# Duration of response in TRK fusion Gastrointestinal cancers




Note: Investigator assessment

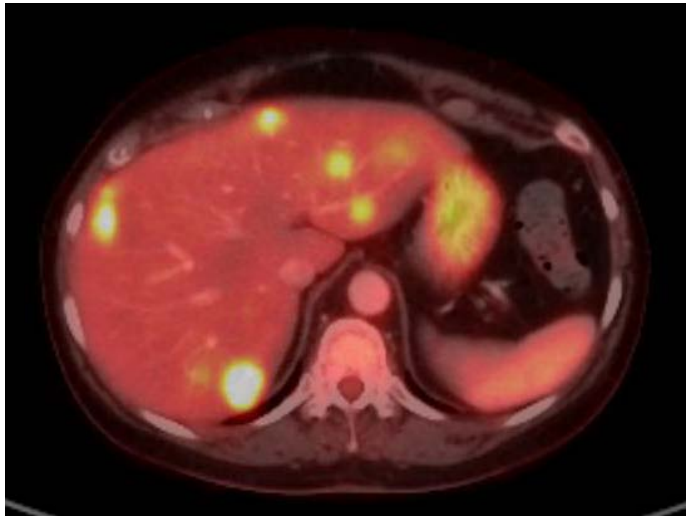
# Adverse events (n=55)

| Adverse event | Adverse events, regardless of attribution | | | | | Treatment-related adverse events | | |
|---|---|---|---|---|---|---|---|---|
| | Grade 1 | Grade 2 | Grade 3 | Grade 4 | All grades | Grade 3 | Grade 4 | All grades |
| | *Percent of patients with event* | | | | | | | |
| Increased ALT/AST | 31 | 4 | 7 | 0 | 42 | 5 | 0 | 38 |
| Fatigue | 20 | 15 | 2 | 0 | 36 | 0 | 0 | 16 |
| Vomiting | 24 | 9 | 0 | 0 | 33 | 0 | 0 | 11 |
| Dizziness | 25 | 4 | 2 | 0 | 31 | 2 | 0 | 25 |
| Nausea | 22 | 7 | 2 | 0 | 31 | 2 | 0 | 16 |
| Anemia | 9 | 9 | 11 | 0 | 29 | 2 | 0 | 9 |
| Diarrhea | 15 | 13 | 2 | 0 | 29 | 0 | 0 | 5 |
| Constipation | 24 | 4 | 0 | 0 | 27 | 0 | 0 | 16 |
| Cough | 22 | 4 | 0 | 0 | 25 | 0 | 0 | 2 |
| Weight increased | 11 | 5 | 7 | 0 | 24 | 0 | 0 | 11 |
| Dyspnea | 9 | 9 | 0 | 0 | 18 | 0 | 0 | 2 |
| Headache | 13 | 4 | 0 | 0 | 16 | 0 | 0 | 2 |
| Pyrexia | 11 | 2 | 2 | 2 | 16 | 0 | 0 | 0 |
| Arthralgia | 15 | 0 | 0 | 0 | 15 | 0 | 0 | 2 |
| Back pain | 5 | 9 | 0 | 0 | 15 | 0 | 0 | 0 |
| Decreased neutrophil count | 0 | 7 | 7 | 0 | 15 | 2 | 0 | 9 |

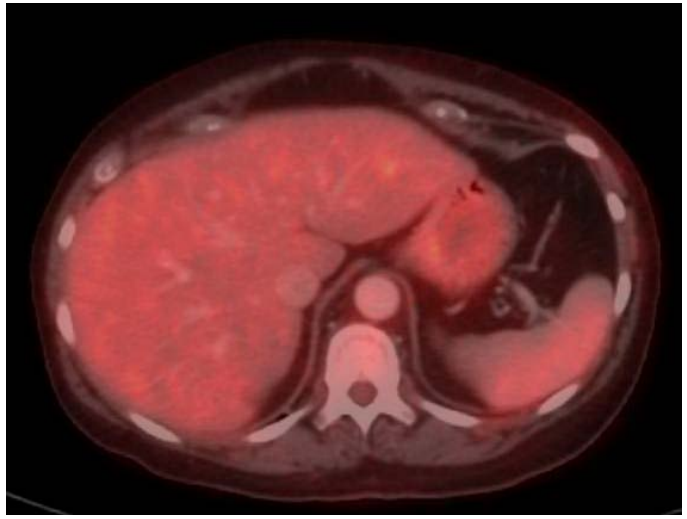
* The adverse events listed here are those that occurred in at least 15% of the patients, regardless of attribution. The relatedness of the treatment to adverse events was determined by the investigators.

Reference: Drilon et al. *N Engl J Med*.2018;378:731-9

# Larotrectinib response in patient with TRK fusion colon cancer



**Baseline**



**Cycle 3**

54 year old female with
TRK fusion (*LMNA-NTRK1)* colon cancer
diagnosed in 2013

Treated with primary resection and
3 prior systemic therapies including
FOLFOX, FOLFIRI, bevacizumab,
5-fluorouracil, leucovorin and
denosumab

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Marked improvement of abdominal
symptoms within the first cycle of
larotrectinib

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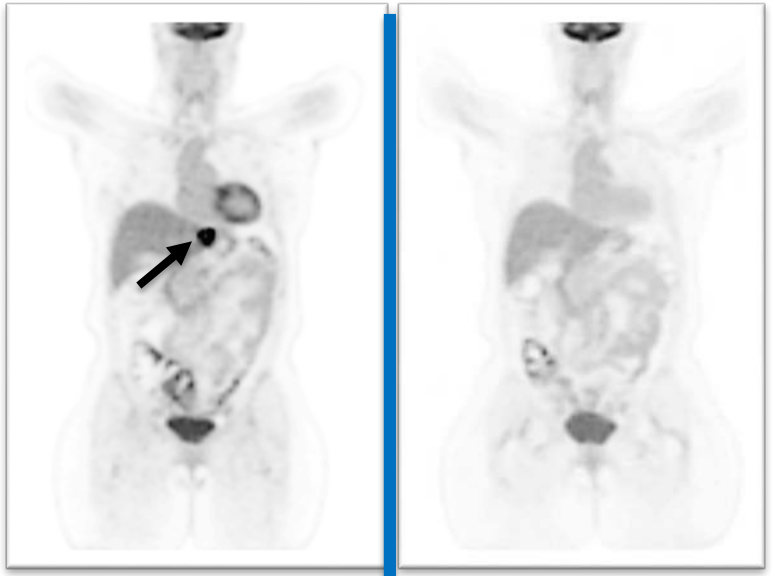
**PR by cycle 3**

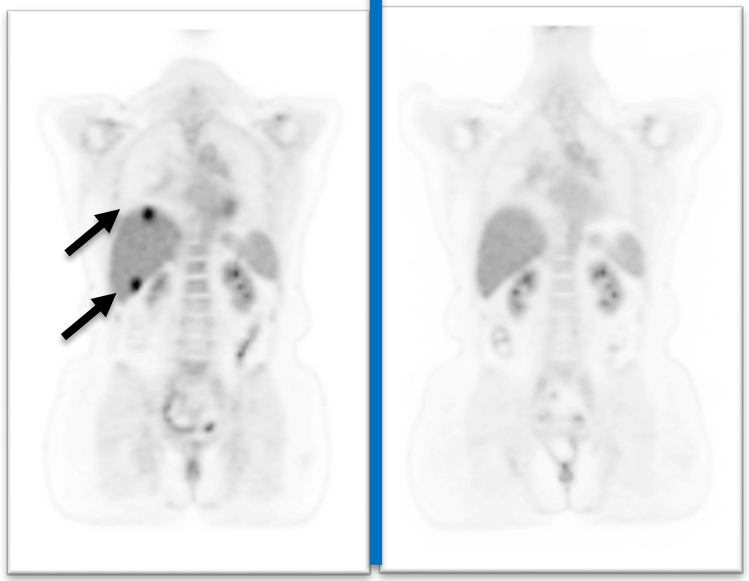
# Larotrectinib response in patient with TRK fusion pancreatic cancer



**Baseline**



**End of cycle 2**



63 year old female with
TRK fusion (*CTRC-NTRK1*)
pancreatic adenocarcinoma
diagnosed in 2014

3 prior lines of systemic therapy
including gemcitabine, nab-paclitaxel,
ADI-PEG 20, FOLFIRINOX and FOLFIRI

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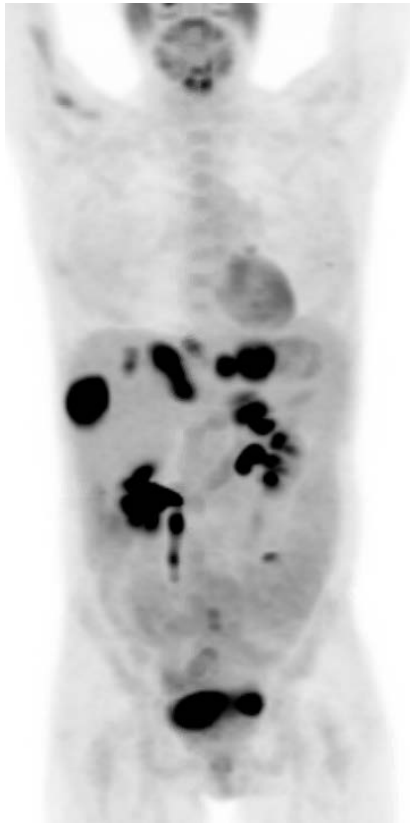
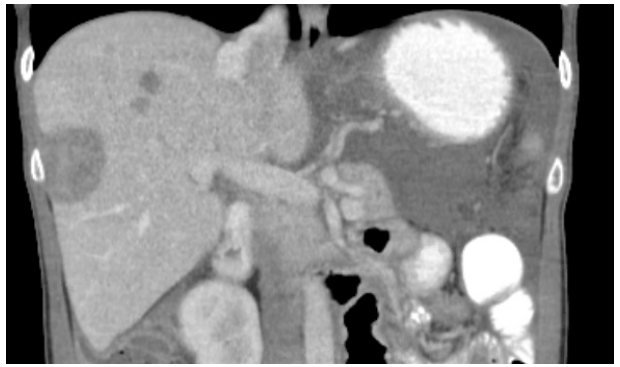
**PR after 2 cycles**

# Larotrectinib response in patient with TRK fusion rectal sarcoma

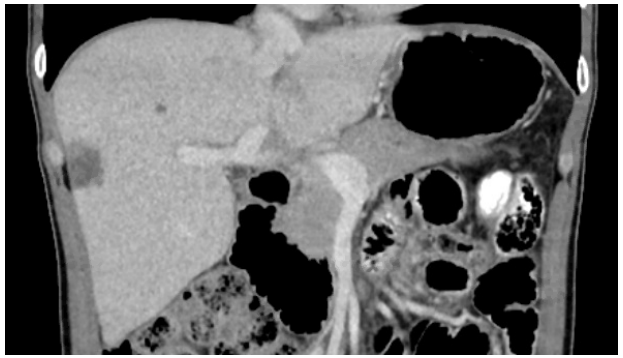


Baseline

Cycle 1



Baseline



Cycle 1

46 year old female with TPM3-*NTRK1* fusion rectal sarcoma diagnosed in March 2016

Treated with surgical resection in April 2016 and developed local and metastatic disease to lung and liver on 1st restaging scan

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**PR after 1 cycle**

# Conclusions

- TRK fusions can occur with any of the *NTRK* genes in a wide variety of gastrointestinal cancers
- TRK inhibition with larotrectinib yields high response rates in TRK fusion cancer, including those that are heavily pre-treated
- Responses with larotrectinib therapy are generally durable and clinically meaningful
- Prolonged larotrectinib therapy is associated with minimal toxicity
- Molecular tumor profiling with assays capable of identifying TRK fusions, ideally to identify *NTRK* gene fusions at DNA or RNA level should be strongly considered when determining systemic treatment options, especially in the setting of metastatic disease

# Acknowledgments


- We thank the patients and their families, many of whom traveled long distances to participate in these studies