Activity of Larotrectinib in Patients with Advanced TRK Fusion Thyroid Cancer

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LEARNING OBJECTIVES

- To understand the nature of *NTRK* gene fusions and TRK fusion cancer
- To describe the efficacy of larotrectinib in both adult and pediatric patients with diverse malignancies in Phase 1/2 clinical trials
- To describe the involvement of TRK fusion proteins in thyroid cancer
- To describe the clinical benefit of larotrectinib in treating TRK fusion thyroid cancer patients

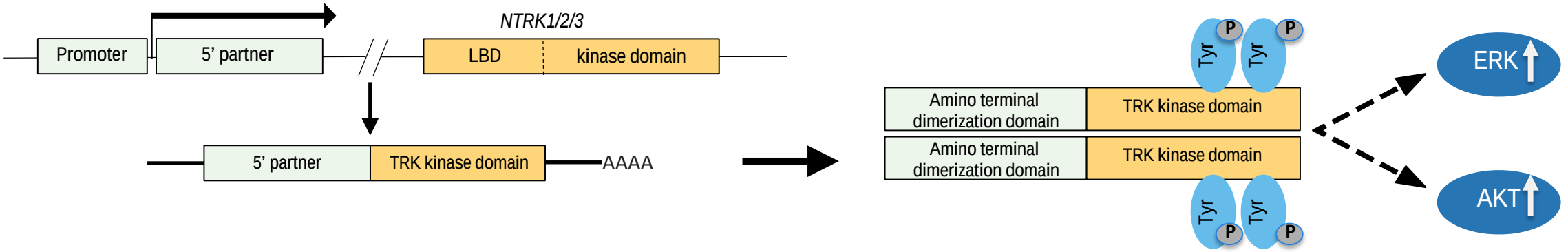
TRK fusions are oncogenic drivers

- 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]

  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]

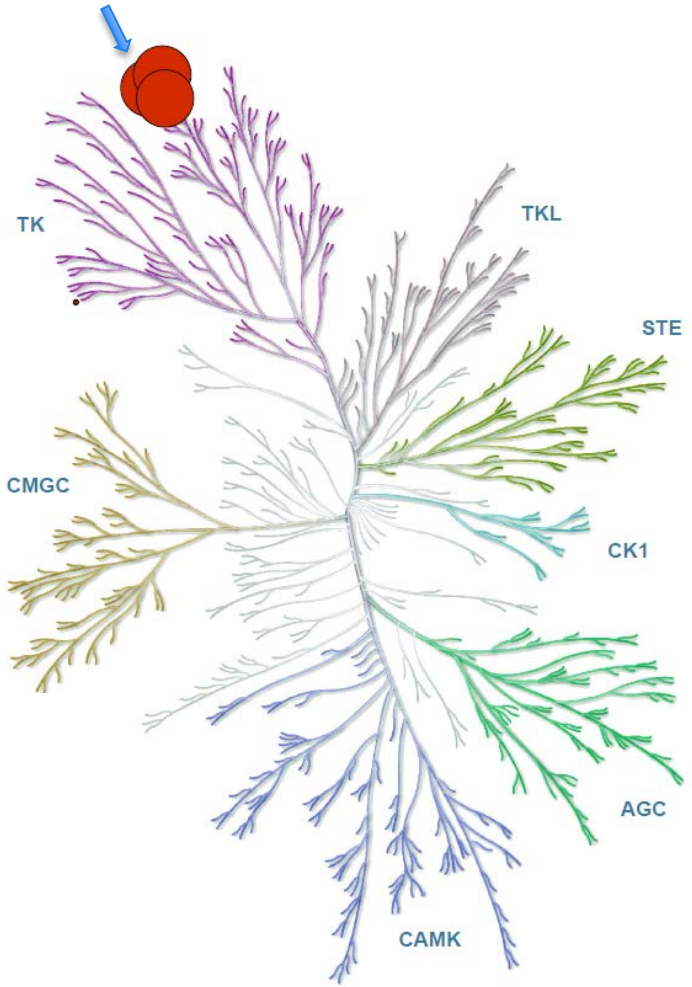
≥75%
- ✓ Mammary analogue secretory carcinoma (MASC) of the salivary gland[17]
- ✓ Secretory breast carcinoma[18]
- ✓ Infantile fibrosarcoma[19]

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 TRK inhibitor

- Larotrectinib is a highly potent TRK inhibitor against TRKA, TRKB, TRKC (5–11 nM IC_{50} in cellular assays) [1]
- Highly selective, with little or no interaction with other kinase and non-kinase targets
  - limited inhibition of other kinases and >1,000x selective over other off targets[1]
- Larotrectinib is highly active against TRK fusion cancer with durable responses in both children and adults

TRKA/B/C



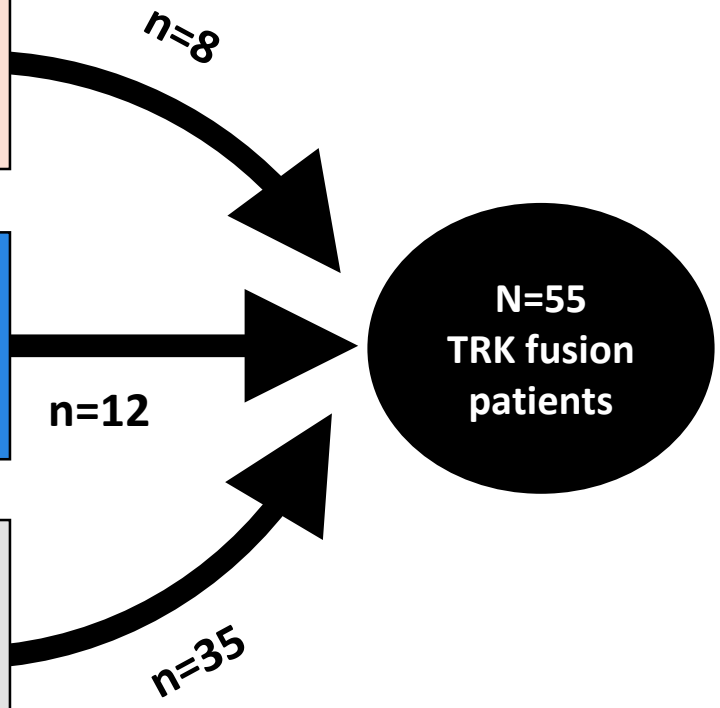
References: 1. Doebele et al. *Cancer Discov*. 2015 Oct;5(10):1049-57. 2. Chartier et al. 2013 Kinome Render: a stand-alone and web-accessible tool to annotate the human protein kinome tree. *PeerJ* 1:e126.

Integrated clinical development of larotrectinib simultaneously across adult and pediatric cancers

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
- *NTRK* gene fusion positive

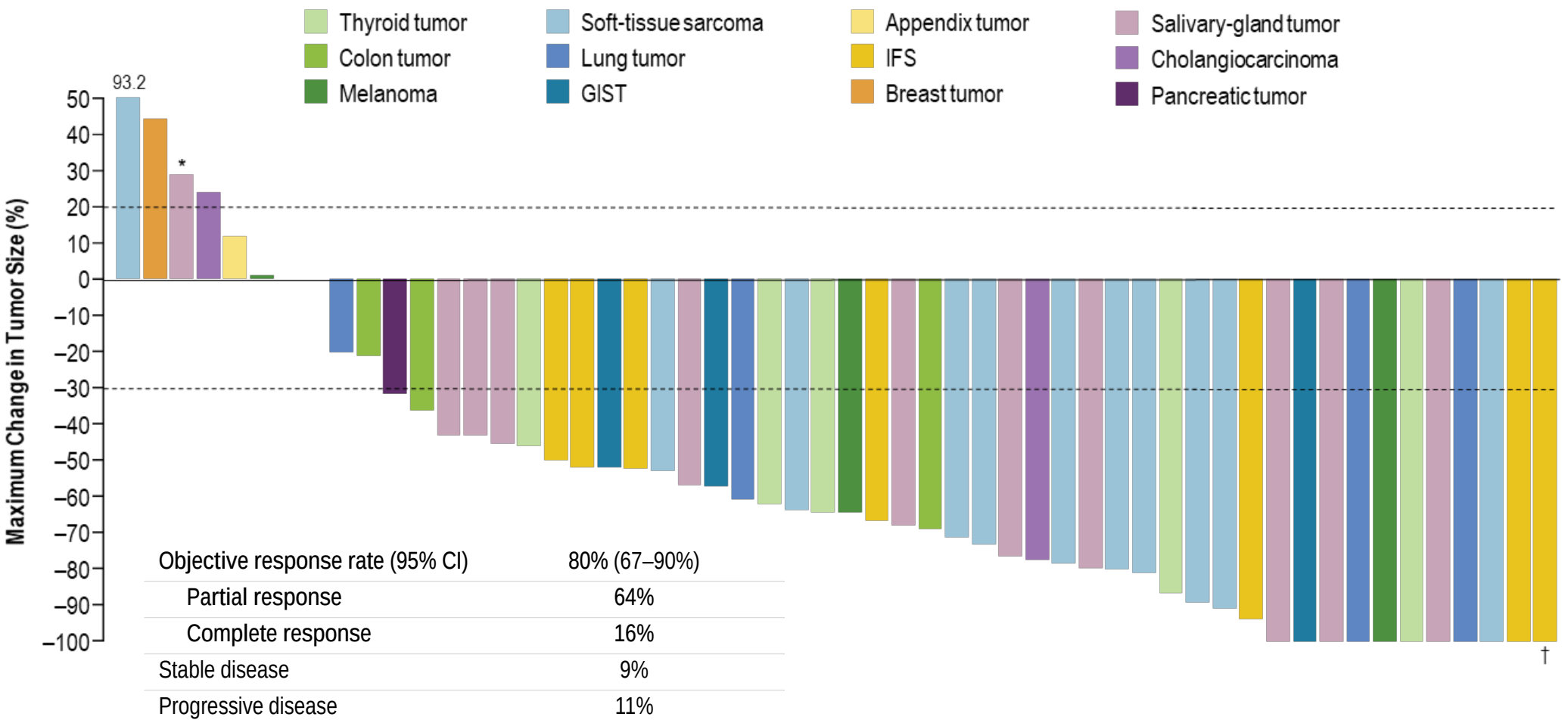


Data cut-off: July 17, 2017

- **TRK fusion status** determined by local clinically approved laboratory assay (or similarly accredited) laboratories
- **Primary endpoint**
  - Best objective response rate (ORR) per RECIST v1.1
- **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 cancer



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 TRK fusion thyroid subset

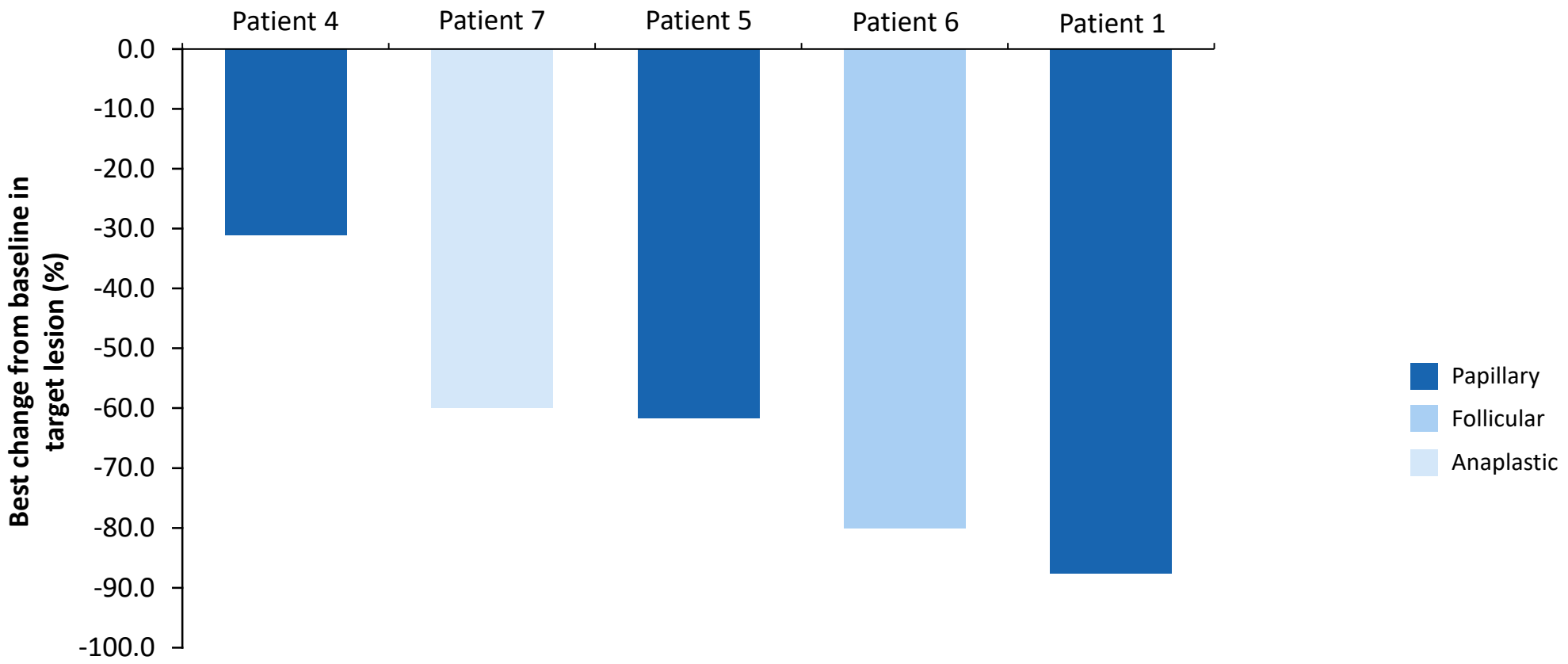
Characteristic	Total N=7
Median age (range) years	57 (15-75)
Gender female: male, n	3:4
Histology type, n	
Papillary	5
Follicular	1
Anaplastic	1
Fusions, n	
TPM3-NTRK1	1
PPL-NTRK1	1
IRF2BP2-NTRK1	1
ETV6-NTRK3	4
Prior therapies	
Thyroidectomy	7
Systemic treatment	5
I-131	3

Efficacy of larotrectinib in patients with TRK fusion thyroid cancer

	Age	Gene fusion	Histology	Measurable disease	Best response	DOT (months)	DOR (months)	Ongoing treatment
Patient 1	33	*ETV6-NTRK3*	Papillary	Yes	PR	>28.7	>27.0	Yes
Patient 2	15	*TPM3-NTRK1*	Papillary	No	-	>16.6	-	Yes
Patient 3	18	*ETV6-NTRK3*	Papillary	No	-	>15.7	-	Yes
Patient 4	75	*ETV6-NTRK3*	Papillary	Yes	PR	>14.7	>8.3	Yes
Patient 5	65	*PPL-NTRK1*	Papillary	Yes	CR	>13.8	>12.0	Yes
Patient 6	63	*ETV6-NTRK3*	Follicular	Yes	PR	>12.9	>9.3	Yes
Patient 7	57	*IRF2BP2-NTRK1*	Anaplastic	Yes	PR	7.7	3.7	No

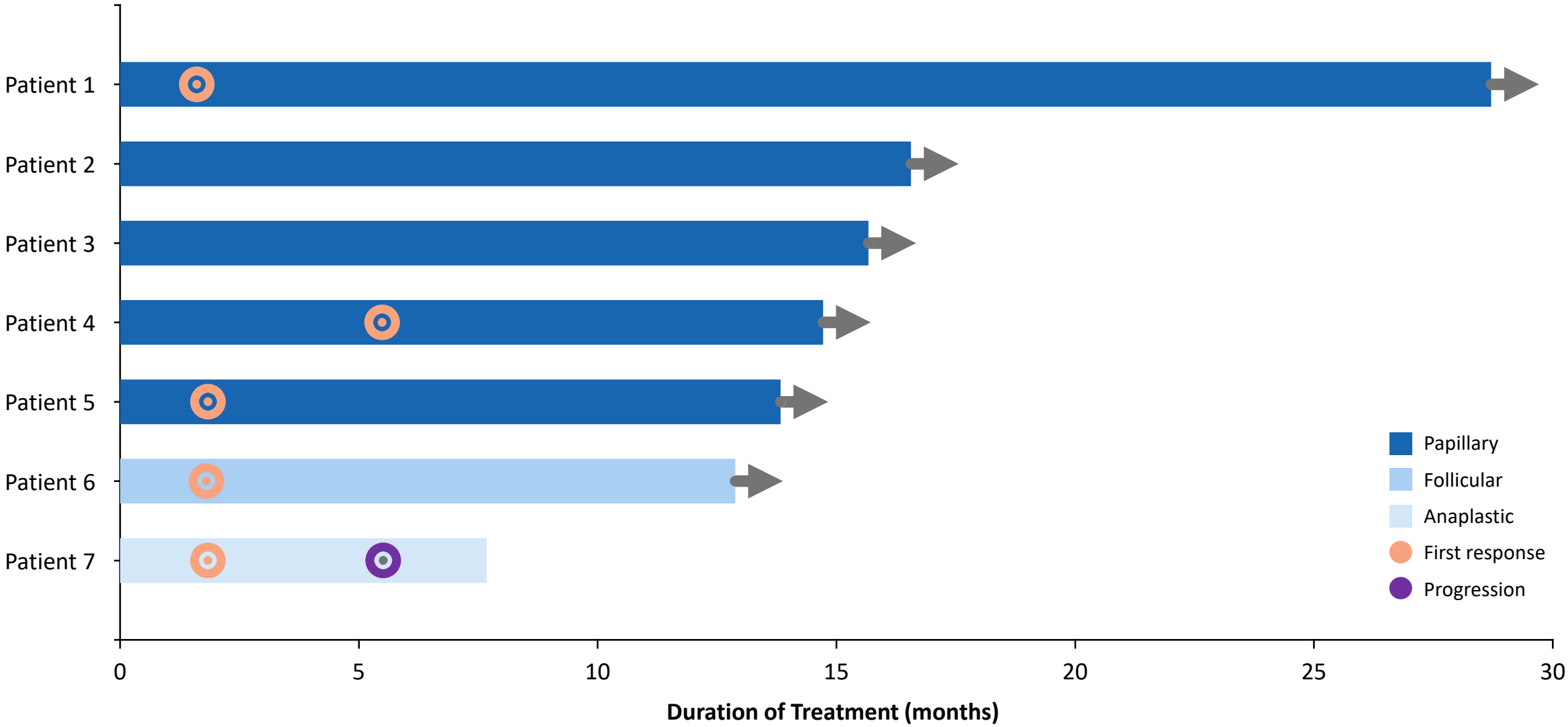
Based on IRC assessment of February 19, 2018

Efficacy of larotrectinib in TRK fusion thyroid cancer patients*



* Does not include 2 patients with non-measureable disease

Duration of treatment



Data cutoff : February 19 2018

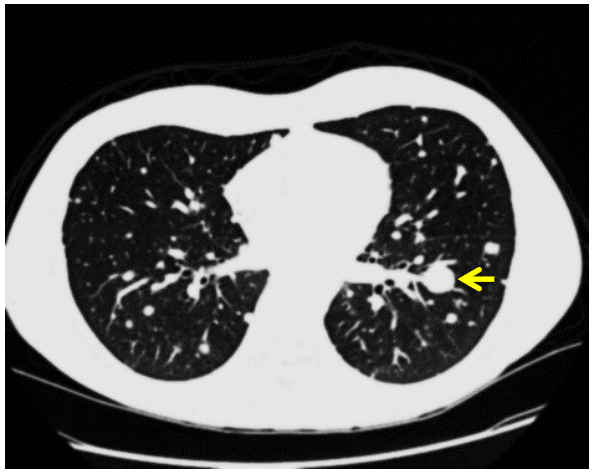
Treatment-emergent adverse events (n=55)

	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
Adverse event	*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

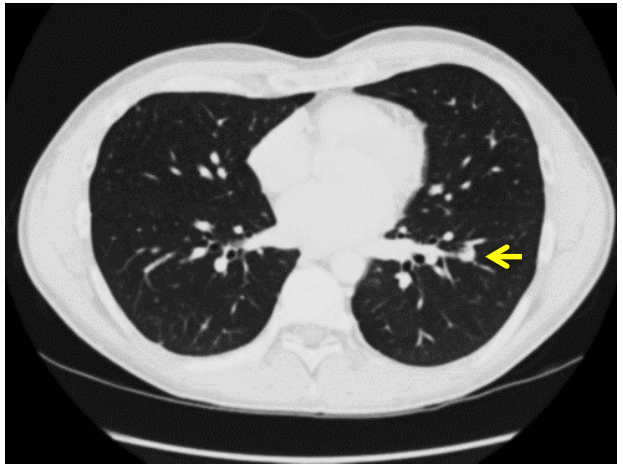
- The adverse events listed here are those that occurred in at least 15% of the patients, regardless of attribution. The relatedness of the treatment to adverse events was determined by the investigators.

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

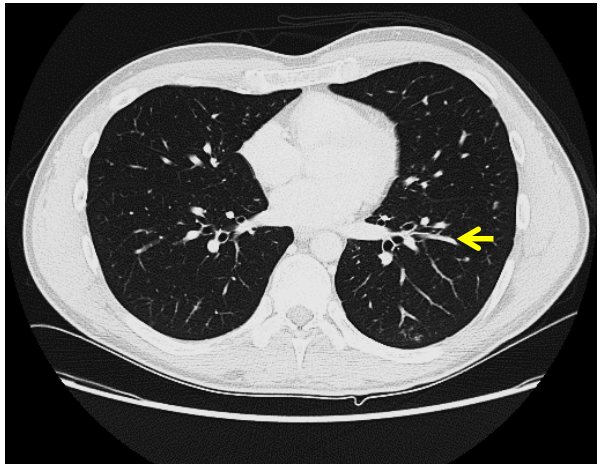
Durable response in *ETV6-NTRK3* fusion papillary TC



Study baseline



Study cycle 3 day 1



Study cycle 7 day 1

33 year old male
progressed
through RAI, pazopanib,
trametinib

Confirmed partial response
with larotrectinib 100mg
BID;

Rapid improvement in
cervical lymphadenopathy

Duration of treatment

>28 months and ongoing
at Feb 19, 2018 data cutoff

Conclusions

- *NTRK* gene fusions are detected in thyroid cancer
- Larotrectinib treatment yielded high response rates, including complete responses, in adolescents and adults with recurrent TRK fusion thyroid cancer
- Responses with larotrectinib therapy were generally durable
- Prolonged larotrectinib therapy was associated with minimal toxicity and no drug discontinuation due to adverse events
- Genomic profiling with assays capable of identifying *NTRK* gene fusions should be strongly considered in patients with differentiated or anaplastic thyroid carcinoma when determining systemic treatment options

Acknowledgments

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