



**CDDF 11TH SPRING
CONFERENCE 2020**

THE NETHERLANDS | 10-12 FEBRUARY 2020

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Case-Study: Tumor Agnostic Approval of VITRAKVI[®] (larotrectinib)

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Disclaimer

This presentation reflects my personal views and not necessarily those of Bayer

VITRAKVI® - FIRST TISSUE AGNOSTIC INDICATION APPROVED IN THE EU

Conditional approval granted in September 2019

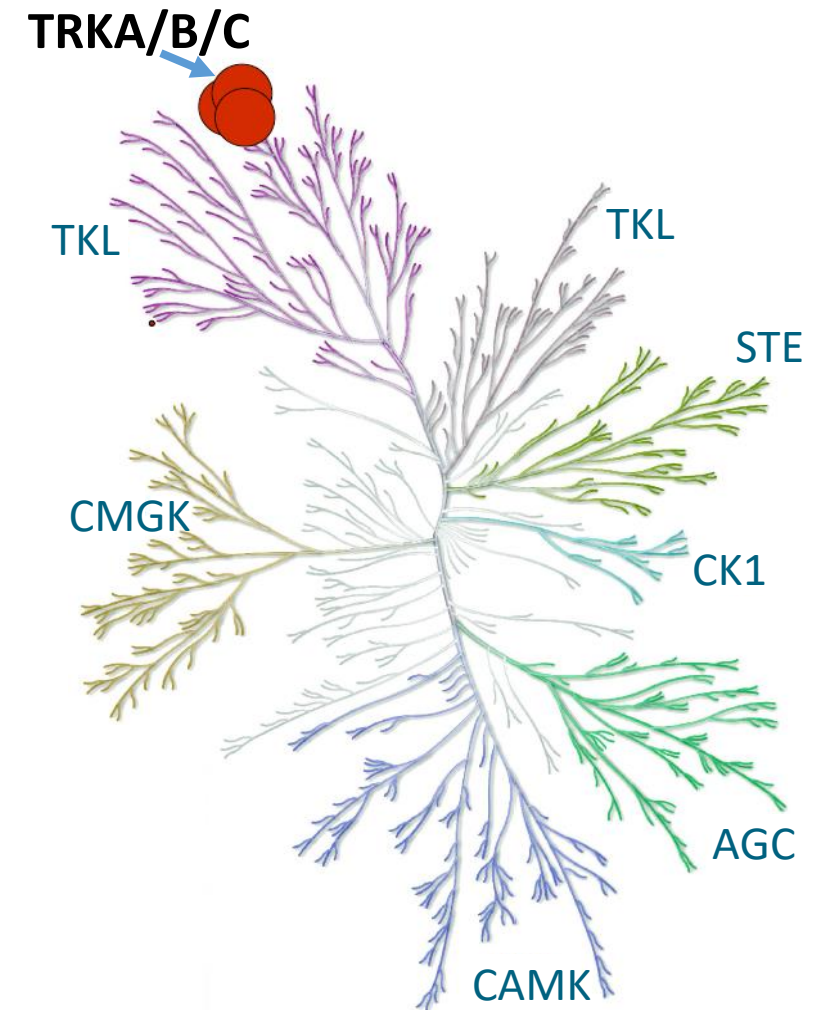
4.1 Therapeutic indications

VITRAKVI as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (*NTRK*) gene fusion,

- who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and
- who have no satisfactory treatment options (see sections 4.4 and 5.1).

Mechanism of Action: VITRAKVI[®] Exclusively Targets TRK Kinases

- Structure-activity relationship insights – avoidance of binding to structurally similar kinases: e.g. ALK, ROS1, JAK2, FGFR1
- 100 to 1,000-fold selectivity versus 226 non-TRK kinases
- No interaction with additional 82 receptors, enzymes, and nuclear targets at clinically- or toxicologically-relevant concentrations



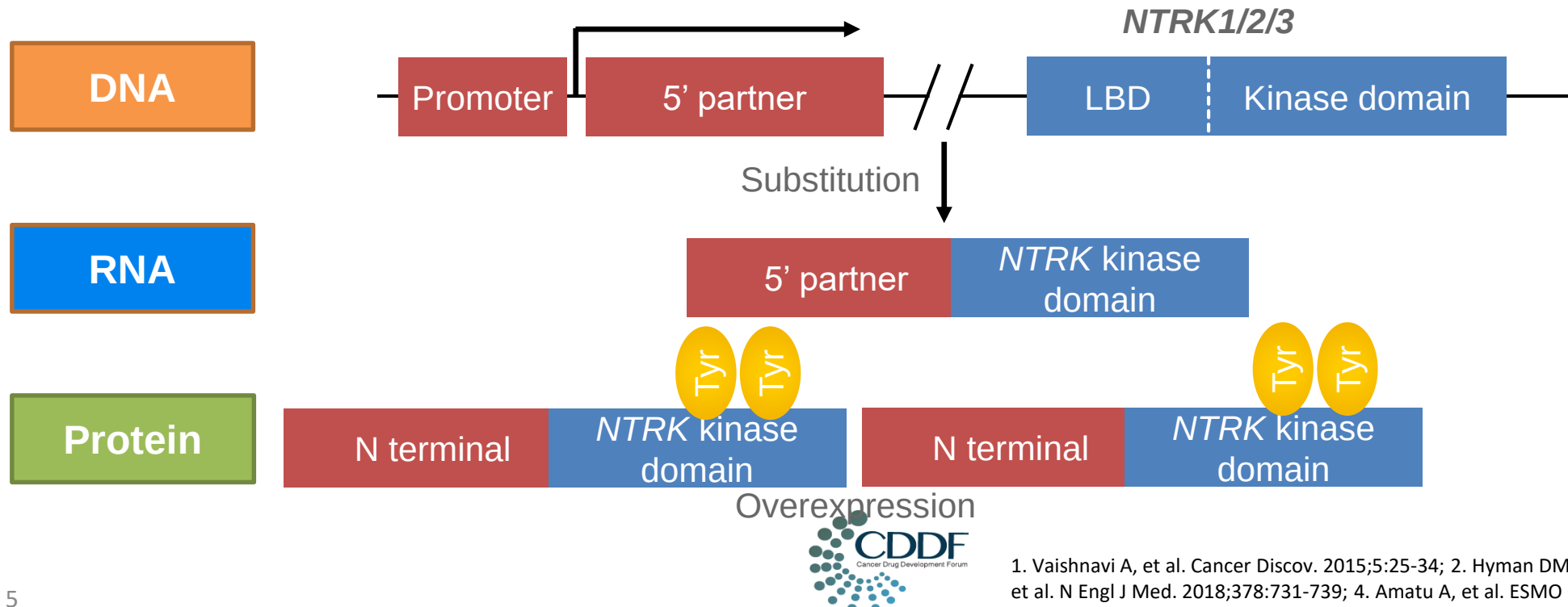
NTRK Gene Fusions Drive Oncogenic Signaling Through Canonical Downstream Pathways

Chromosomal rearrangements of *NTRK* genes are generally characterised by substitution of the ligand-binding domain by a different 5' fusion partner¹⁻⁴

// *NTRK* gene fusion represents a genomic alteration with known oncogenic and transforming potential

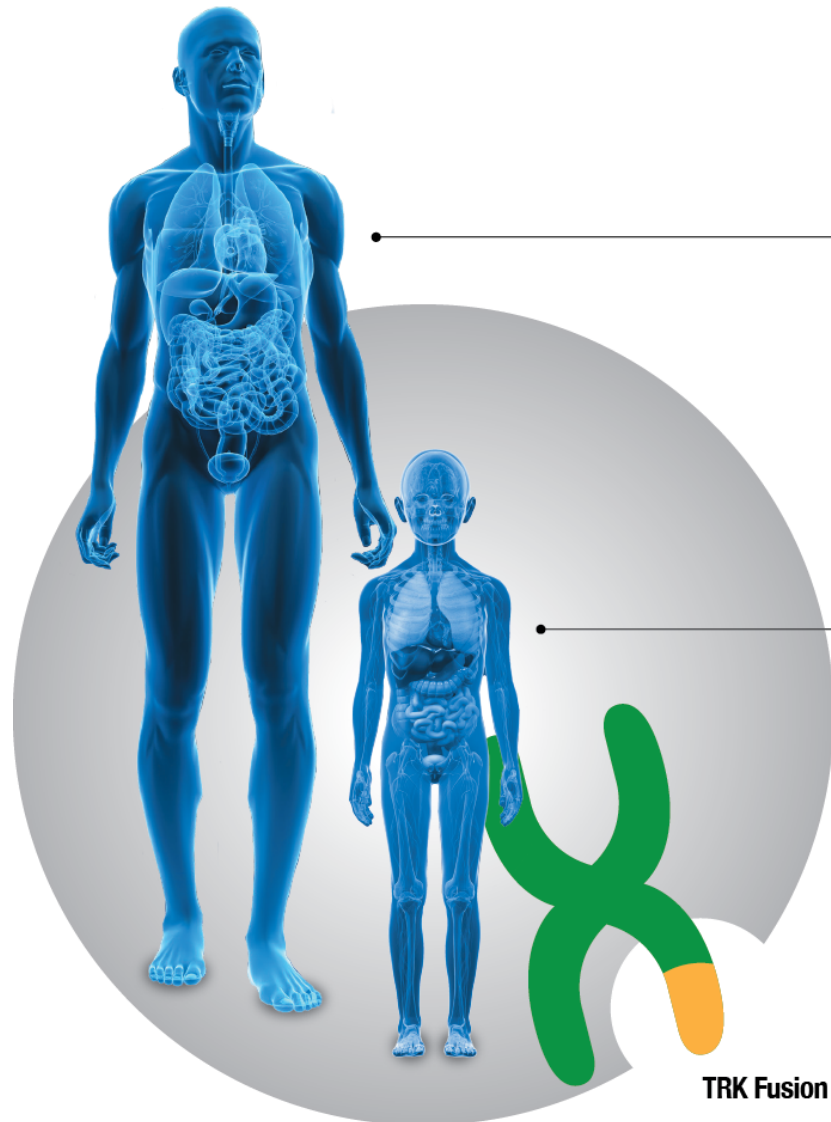
// A large number of 5' *NTRK* gene fusion partners have been described

NTRK gene fusions result in a constitutively active and aberrantly expressed TRK fusion protein¹⁻³



1. Vaishnavi A, et al. Cancer Discov. 2015;5:25-34; 2. Hyman DM, et al. J Clin Oncol. 2017;35:LBA2501; 3. Drilon A, et al. N Engl J Med. 2018;378:731-739; 4. Amatu A, et al. ESMO Open. 2016;1:e000023.

NTRK Fusions Are Found In Diverse Tumours



- Spitzoid melanoma
- Glioma
- Thyroid cancer
- Infantile fibrosarcoma
- Congenital mesoblastic nephroma
- Secretory breast cancer
- Various sarcomas

- Glioma
- Mammary analogue secretory carcinoma of the salivary gland
- Secretory breast cancer
- Pancreatic cancer
- Cholangiocarcinoma
- Appendiceal cancer
- Thyroid cancer
- Lung cancer
- GIST
- Colorectal cancer
- Melanoma
- Various sarcomas

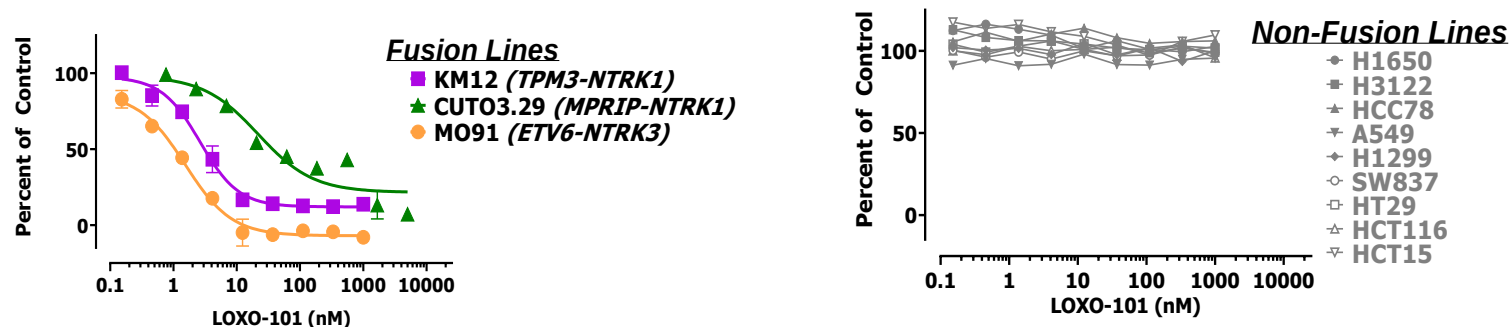
NTRK Fusions Occur Commonly in Certain Rare Tumours and Rarely in Common Tumours

≤5%	5%-25%	≥75%
CNS ✓ Astrocytoma¹ ✓ Low-grade glioma² ✓ Glioblastoma³ GI ✓ Colorectal cancer^{2,4} ✓ Cholangiocarcinoma⁵ ✓ Pancreatic cancer⁶ Head and Neck ✓ Squamous cell carcinoma²	Lung ✓ Adenocarcinoma^{2,7} ✓ Large cell neuroendocrine carcinoma⁸ Other ✓ Acute myeloid leukemia⁹ ✓ Breast-invasive carcinoma² ✓ Melanoma² ✓ Sarcoma²	✓ Congenital mesoblastic nephroma^{10,11} ✓ Recurrent papillary thyroid cancer¹² ✓ Pontine glioma¹³ ✓ Spitzoid melanoma¹⁴ ✓ Pediatric and young adult soft tissue sarcomas¹⁵ ✓ Pan-negative gastrointestinal stromal tumors (GIST)¹⁶ ✓ Mammary analogue secretory carcinoma (MASC) of the salivary gland¹⁷ ✓ Secretory breast carcinoma¹⁸ ✓ Infantile fibrosarcoma¹⁹

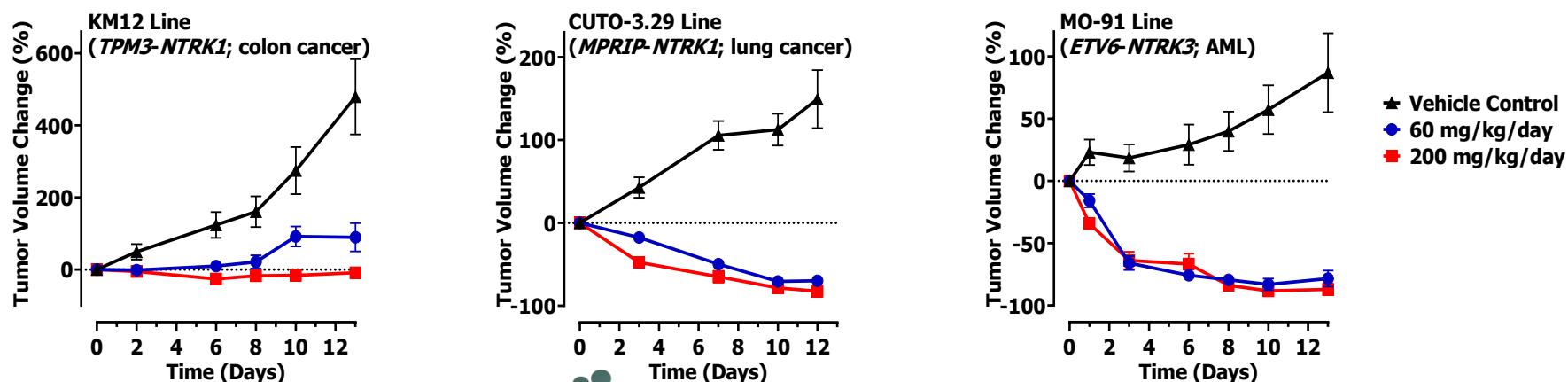
References: 1. Jones DT, et al. Nat Genet. 2013;45:927-934. 2. Stransky N, et al. Nat Commun. 2014;5:4846. 3. Kim J, et al. PLoS One. 2014;9:3. 4. DeBraud F, et al. ASCO. 2014 (abstr 2502). 5. Ross JS, et al. Oncologist. 2014;19: 235-242. 6. Bailey P, et al. Nature 2016;531:47-52. 7. Vaishnavi A, et 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. 200R0;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 in Vitro and in Vivo Activity

In Vitro: Potency in TRK Fusion Cell Models; Spares Unselected Cell Models^{1,2}



In Vivo: Tumor Regressions in TRK Fusion Xenografts^{1,2}





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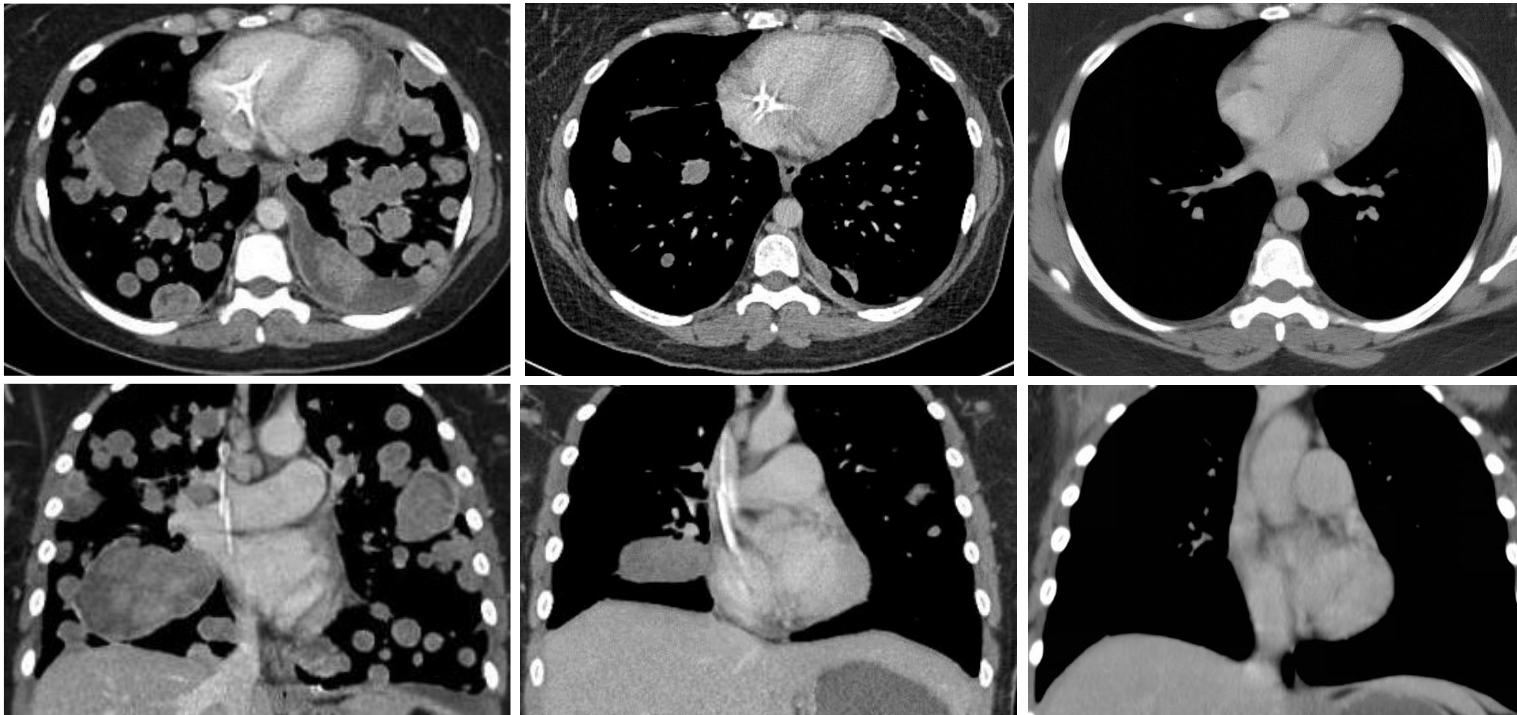
Early Development



First TRK Fusion Patient Treated With Larotrectinib

An Oncogenic *NTRK* Fusion in a Patient with Soft-Tissue Sarcoma with Response to the Tropomyosin-Related Kinase Inhibitor LOXO-101

Robert C. Doebele, Lara E. Davis, Aria Vaishnavi, Anh T. Le, Adriana Estrada-Bernal, Stephen Keyzar, Antonio Jimeno, Marileila Varella-Garcia, Dara L. Aisner, Yali Li, Philip J. Stephens, Deborah Morosini, Brian B. Tuch, Michele Fernandes, Nisha Nanda, and Jennifer A. Low.



Baseline

Cycle 3, day1

Cycle 13, day1

41 year old female with *LMNA-NTRK1* fusion undifferentiated sarcoma previously treated with epirubicin, ifosfamide, sorafenib and doxorubicin

Rapid resolution of dyspnea and hypoxemia with larotrectinib 100mg BID

Confirmed PR by cycle 3, DOR 40.7+ months at data cutoff of July 30, 2018

Safety And Efficacy Of Larotrectinib In Phase 1 Trial

Larotrectinib in adult patients with solid tumours: a multi-centre, open-label, phase I dose-escalation study

D. S. Hong¹*, T. M. Bauer², J. J. Lee³, A. Dowlati⁴, M. S. Brose⁵, A. F. Farago⁶, M. Taylor⁷, A. T. Shaw⁸, S. Montez⁹, F. Meric-Bernstam¹⁰, S. Smith¹¹, B. B. Tuch¹², K. Ebata¹³, S. Cruickshank¹⁴, M. C. Cox¹⁵, H. A. Burris III¹⁶ & R. C. Doebele¹⁷

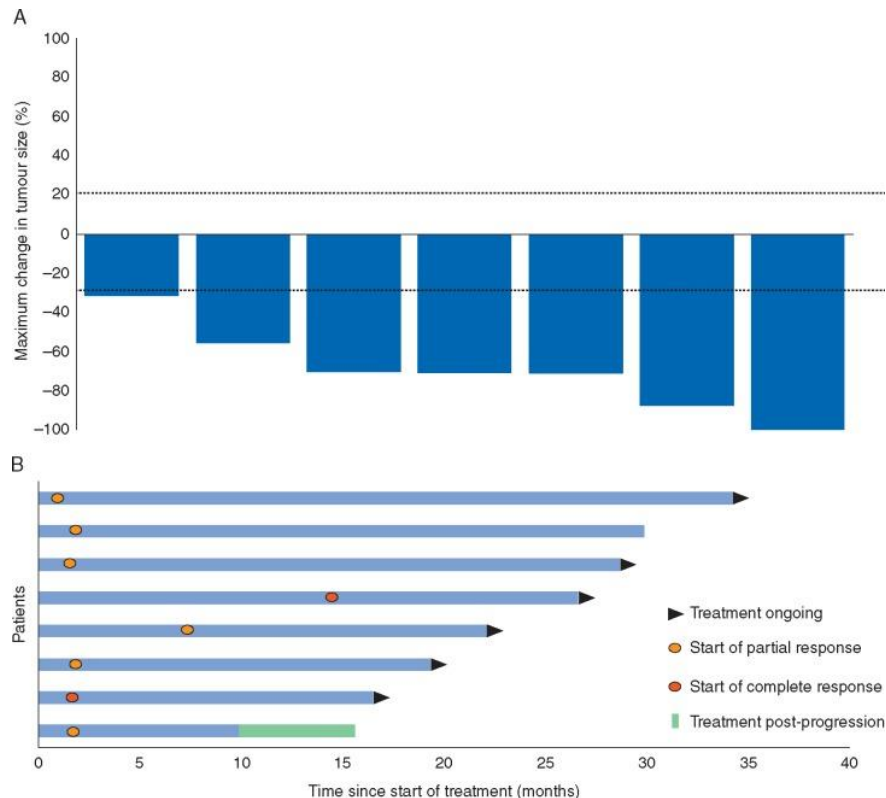


Table 2. Treatment-emergent adverse events

	All patients, n 570			
	Grade 1-2	Grade 3	Grade 4	Grade 5
Fatigue	28 (40)	5 (7)	0	0
Dizziness	22 (31)	1 (1)	0	0
Anaemia	12 (17)	10 (14)	0	0
Nausea	20 (29)	0	0	0
Constipation	17 (24)	1 (1)	0	0
Dyspnoea	15 (21)	3 (4)	0	0
Cough	16 (23)	0	0	0
Vomiting	14 (20)	1 (1)	0	0
Diarrhoea	13 (19)	1 (1)	0	0
Decreased appetite	10 (14)	3 (4)	0	0
Oedema peripheral	13 (19)	0	0	0
Myalgia	11 (16)	1 (1)	0	0
Arthralgia	10 (14)	1 (1)	0	0
Pyrexia	11 (16)	0	0	0
Aspartate aminotransferase increased	6 (9)	4 (6)	0	0
Muscular weakness	10 (14)	0	0	0
Abdominal pain	7 (10)	2 (3)	0	0
Dysgeusia	9 (13)	0	0	0
Back pain	8 (11)	0	0	0
Hypertension	6 (9)	2 (3)	0	0
Blood alkaline phosphatase increased	6 (9)	1 (1)	0	0
Gait disturbance	6 (9)	1 (1)	0	0
Hypoalbuminaemia	6 (9)	1 (1)	0	0
Insomnia	7 (10)	0	0	0
Memory impairment	7 (10)	0	0	0
Paraesthesia	7 (10)	0	0	0

Data are n (%). Table shows adverse events occurring in 2:10% of patients at any grade.



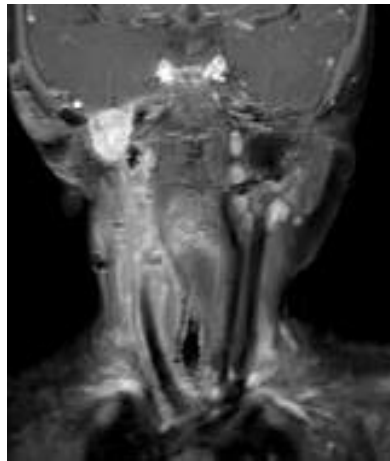
SCOUT (PEDIATRIC TRIAL): First Case Study Publication

Pediatr Blood Cancer 0000;00:000–000

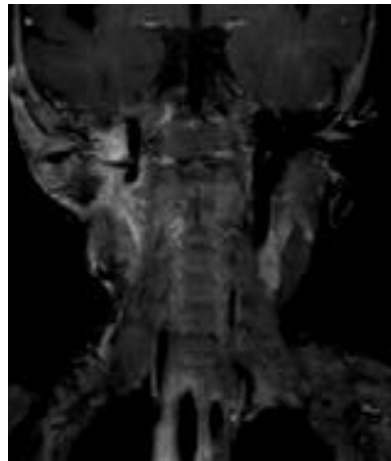
BRIEF REPORT

Infantile Fibrosarcoma With *NTRK3-ETV6* Fusion Successfully Treated With the Tropomyosin-Related Kinase Inhibitor LOXO-101

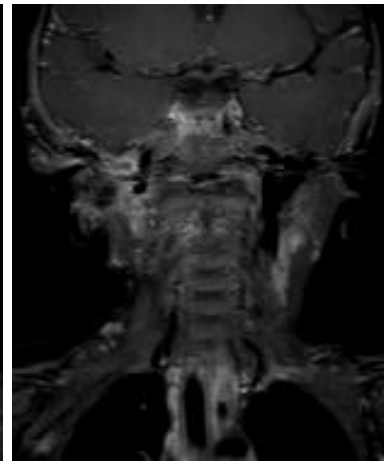
Ramamoorthy Nagasubramanian, MD,^{1*} Julie Wei, MD,¹ Paul Gordon, MD,¹ Jeff C. Rastatter, MD,² Michael C. Cox, Pharm.D., MHSc,³ and Alberto Pappo, MD⁴



Baseline



End of cycle 1



End of cycle 2

16 month old female with infantile fibrosarcoma who had failed all standard chemotherapy regimens and had undergone 3 surgical resections

Started on 100mg AED BID – liquid formulation of larotrectinib

> 90% reduction in tumor mass by end of cycle 1, duration of treatment of 7.4 months

References:

1. Nagasubramanian et al. *Pediatric Blood Cancer*. 2016. DOI 10.1002/pbc.
2. Laetsch et al, *Lancet Oncol*. 2018 May;19(5):705-714



Early clinical trial data demonstrated that VITRAKVI® can be effective in IFS patients who would otherwise need limb amputation

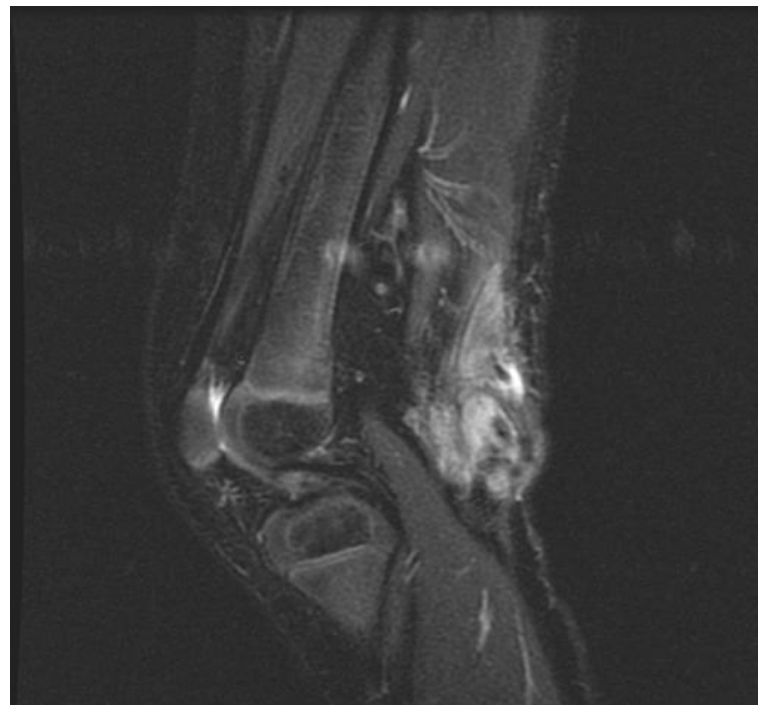
Original Article

The Use of Neoadjuvant Larotrectinib in the Management of Children With Locally Advanced TRK Fusion Sarcomas

Steven G. DuBois, MD¹; Theodore W. Laetsch, MD²; Noah Federman, MD³; Brian K. Turpin, DO⁴; Catherine M. Albert, MD⁵; Ramamoorthy Nagasubramanian, MD⁶; Megan E. Anderson, MD⁷; Jessica L. Davis, MD⁸; Hope E. Qamoos, MSN⁹; Mark E. Reynolds, PhD⁹; Scott Cruickshank, MA⁹; Michael C. Cox, PharmD⁹; Douglas S. Hawkins, MD⁵; Leo Mascarenhas, MD¹⁰; and Alberto S. Pappo, MD¹¹



Baseline



Start of Cycle 3

2 year old girl with progressive *ETV6-NTRK3* infantile fibrosarcoma previously treated with 2 cycles of vincristine/ actinomycin-D/ cyclophosphamide → progression → amputation was only alternative

4 cycles larotrectinib → PR → referred for surgery

Pathologic CR with clear margins (R0 resection);
>98% necrosis
No functional deficit post-surgery

Off larotrectinib for 19+ months and no evidence of disease

Data cut-off: July 30, 2018



References: 1. DuBois et al., *Cancer*. 2018 Nov 1;124(21):4241-4247
2. Kummar S and Lassen UN, *Targeted Onc*. 2018. Oct;13(5):545-556; Lassen et al. ESMO 2018



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Path to Registration



Background

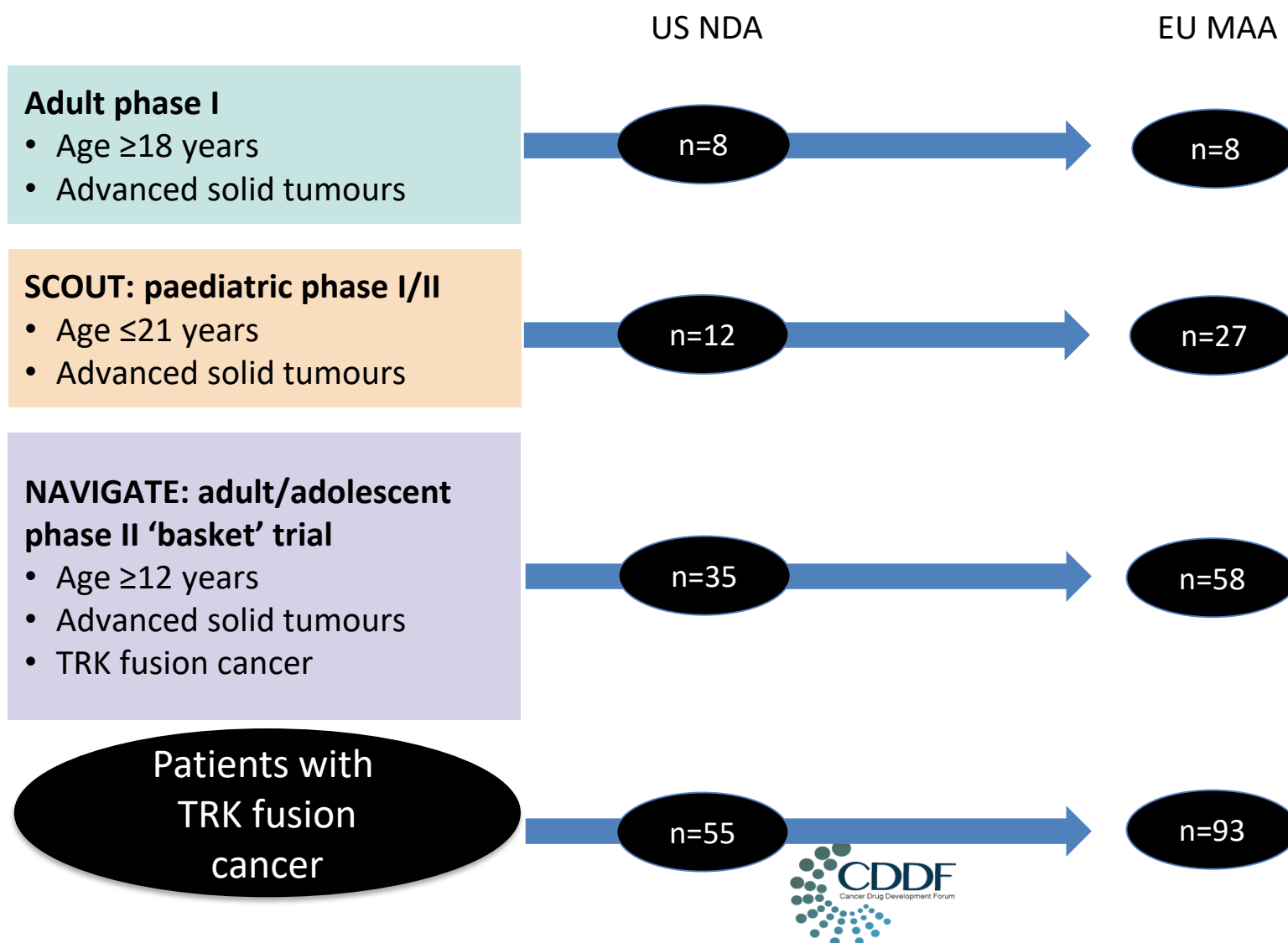
- At the time of MAA submission in the EU (August 2018), larotrectinib was not approved in any country
 - US NDA was under Priority Review with a tissue agnostic orphan drug designation
- Novel indication in the EU
- No tissue-agnostic or histology-independent orphan drug designation in the EU
- Clinical guidelines available in the US (NCCN) by March 2019 on the use of TRK inhibitors
- Scientific advice from EU agencies indicated willingness and flexibility to consider this novel paradigm provided key methodological and scientific questions can be addressed
 - MPA, MHRA, and ANSM in 2016
 - BfArM, MPA, and MHRA in 2017
 - Pre-submission Meetings with EMA in March 2018 and with Rapporteur, Co-Rapporteur and EMA PTL in June 2018
- EMA Workshop in December 2017 on “histology-independent indications” provided insight into multiple stakeholder considerations for this novel development paradigm

VITRAKVI® Pivotal Clinical Studies: Adult and Paediatric Patients

Study No.	Study Design Number of sites/Regions	Study Population
Study 14001	- Phase 1, open-label, 3 + 3 dose escalation study in adult patients - Safety, MTD/DLT, and efficacy	Locally advanced or metastatic solid tumour that had progressed or was nonresponsive to available therapies, unfit for standard chemotherapy or for which no standard or available curative therapy existed
Study 15002 (NAVIGATE)	- Phase 2, open-label “basket” study in patients ≥12 years of age - Efficacy and safety	Locally-advanced or metastatic malignancy with <i>NTRK</i> gene fusion. Patients must have received appropriate prior standard therapy, or be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy per investigator opinion
Study 15003 (SCOUT)	- Phase 1/2, open-label, dose escalation study in paediatric patients - Safety, MTD/DLT, and efficacy	Locally advanced or metastatic solid tumour or primary CNS tumour that had relapsed , progressed or was nonresponsive to available therapies and for which no standard or available systemic curative therapy, or: for locally advanced IFS would require, disfiguring surgery or limb amputation to achieve a complete surgical resection

Composition of Pivotal Pooled Efficacy Data Set

NTRK Fusion Positive Patients



Primary endpoint

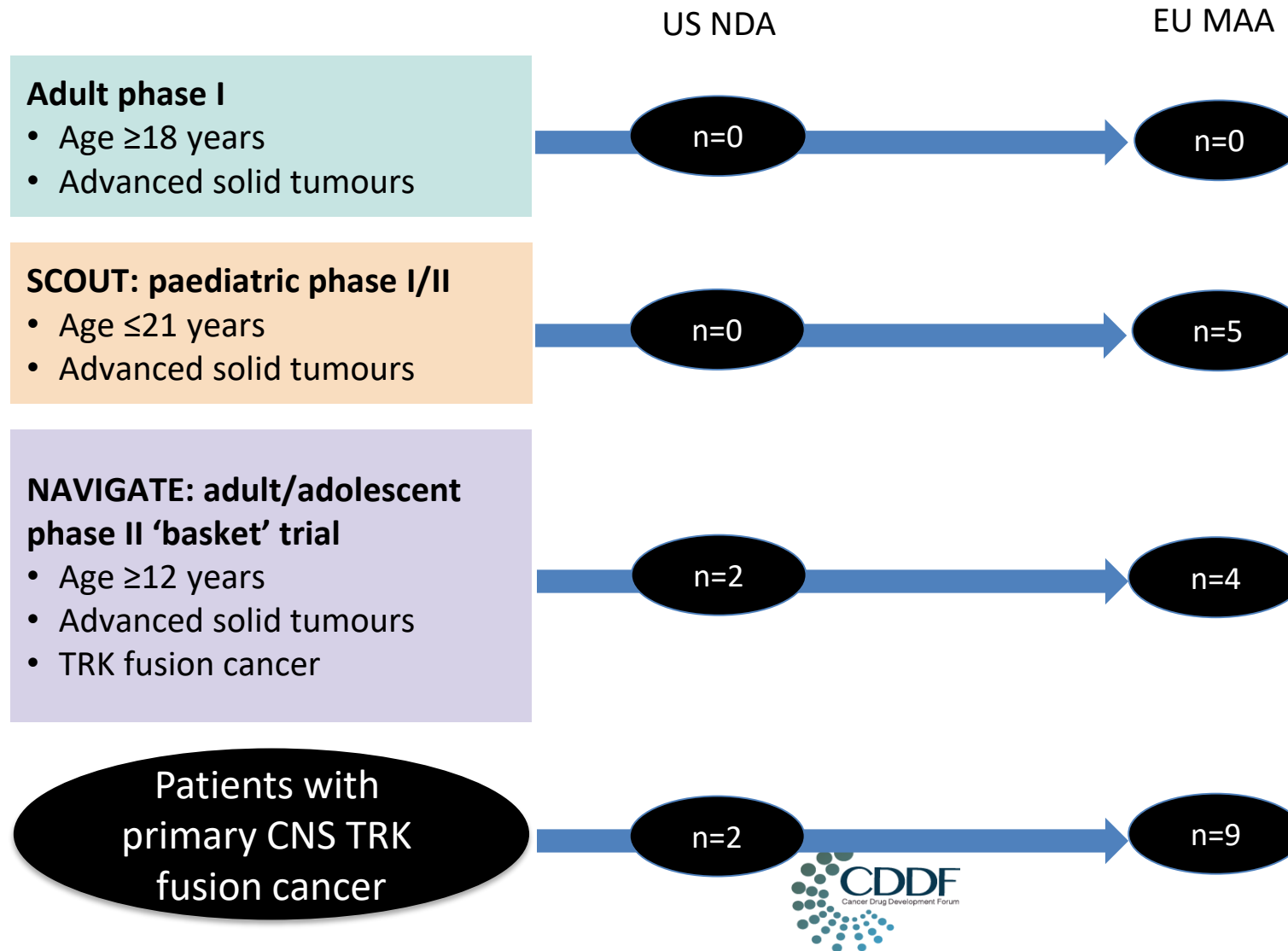
- Best objective response rate (RECIST 1.1)

Pooling

- Pooling was prospectively planned and patients were enrolled consecutively
- Patients who met all eligibility criteria of ISE SAP
- IRC assessment of the tumour responses is primary endpoint
- Pooling strategy for subsequent data cuts was identical to the pre-planned primary analysis in the SAP for the US NDA

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

Composition of Primary Central Nervous System (CNS) Tumour Dataset



- Patients with a primary CNS tumour were evaluated separately using either RANO or RECIST v1.1
- Data for patients with primary CNS tumours were assessed by the investigator
- TRK fusion status determined by local CLIA or similarly accredited laboratories

Clinically Meaningful Efficacy Observed Across Tumour Types (N=93; 30 July 2018 Data cut off)



Table 2: Adverse drug reactions reported in TRK fusion-positive cancer patients treated with VITRAKVI at recommended dose (n=125)

System organ class	Frequency	All grades	Grades 3 and 4
Blood and lymphatic system disorders	Very common	Anaemia Neutrophil count decreased (Neutropenia) Leukocyte count decreased (Leukopenia)	
	Common		Anaemia Neutrophil count decreased (Neutropenia) ^a Leukocyte count decreased (Leukopenia)
Nervous system disorders	Very common	Dizziness Paraesthesia	
	Common	Gait disturbance	Dizziness Paraesthesia
Gastrointestinal disorders	Very common	Nausea Constipation Vomiting	
	Common	Dysgeusia	Nausea
Musculoskeletal and connective tissue disorders	Very common	Myalgia Muscular weakness	
	Common		Myalgia
General disorders and administration site conditions	Very common	Fatigue	
	Common		Fatigue
Investigations	Very common	Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain)	
	Common	Blood alkaline phosphatase increased	Alanine aminotransferase (ALT) increased ^a Aspartate aminotransferase (AST) increased Weight increased (Abnormal weight gain)

^a Grade 4 reactions were reported

Table 2 from EU SmPC

- Majority Grade 1/2
- No related deaths
- No anaphylactic/anaphylactoid reactions



Supportive Data of Relevance to Histology-Independent Indication

Additional Data from Compassionate Use Program and NAVIGATE study

- 29 patients treated in single patient protocols in the US or under compassionate use outside the US
 - Examples of partial responses in patients with breast cancer (including one triple-negative) and recurrent glioblastoma multiforme, as well as complete responses in patients with IFS (surgical CRs) and STS were reported,.
- 2 patients with preliminary, investigator-assessed, outcomes: non-secretory breast cancer and first patient with prostate cancer, who entered the pooled study population after the data cut-off for the ePAS2. Both have larotrectinib treatment ongoing.
 - The patient with non-secretory breast cancer had metastatic disease in liver, adrenal gland, lymph nodes and brain; Investigator reported Partial Response at cycle 4 assessment, followed by unconfirmed Complete Response at cycle 8
 - The patient with prostate cancer had metastatic disease in bone and lymph nodes. The investigator reported stable disease at the first tumour assessment after cycle 2, and an unconfirmed partial response at cycle 4



Supportive Data of Relevance to Histology-Independent Indication

Updated investigator-assessed data on intracranial activity of larotrectinib, presented at ASCO 2019

- 6 patients with non-primary CNS tumours with brain metastases; Thyroid cancer (1 papillary, 1 follicular) and NSCLC
 - median age of 65 years (range 25-76).
 - 5/6 had prior systemic therapy and 2 patients had prior radiotherapy to the brain > 1 year before larotrectinib, and 1 of these also had CNS surgery > 1 year prior.
 - Among 5 evaluable patients 3 had PR (2 thyroid, 1 lung) and 2 had SD (lung); **overall ORR was 60% (95% CI: 15-95)**.
 - Partial responses occurred at cycle 2 (1 lung), and cycle 4 (2 thyroid).
- 18 patients with primary CNS tumours were identified in the 3 pivotal studies (n=109); histologies included 6 glioblastoma, 4 glioma, 3 glioneuronal, 3 not otherwise specified, and 2 astrocytoma.
 - Median age was 10 years (range 1-79); 14 patients were paediatric and 4 adults.
 - 15 (83%) had prior systemic therapy, 13 (72%) had prior local surgery or radiotherapy.
 - Among 14 evaluable patients, 2 CR, 3 PR, and 9 SD were noted per investigator-assessment.
 - **ORR was 36% (95% CI: 13-65)**
 - 4 of the responses occurred before/at cycle 2, the remaining 1 PR at the cycle 4 assessment.
 - All responses were seen in paediatric patients (11 evaluable)

Key Topics During MAA Review

Assessment of Clinical Efficacy

- The efficacy data were considered by the CHMP to be “*outstanding in this generally late stage disease setting*”.
- However, the CHMP deemed that the dataset is supportive of conditional marketing authorization rather than regular approval and recommended that additional data need to be generated as a post-approval measure in order to make the dataset more comprehensive and to address specific objectives:
 - In order to further confirm the histology-independent efficacy of larotrectinib and to investigate the primary and secondary resistance mechanisms, the MAH should submit a pooled analysis for the increased sample size including the final report of study LOXO-TRK-15002 (NAVIGATE).

Post-Approval Measure to Address Missing Efficacy Data

- In order to further confirm the histology-independent efficacy of larotrectinib and to investigate the primary and secondary resistance mechanisms, the MAH should submit a pooled analysis for the increased sample size including the final report of study LOXO-TRK-15002 (NAVIGATE)
 - Study 15002 (NAVIGATE): submit a prospective cohort of 75 patients, for which at least 1 year of follow-up is available, and perform an overall pooled analysis where the target population includes the ePAS2/SAS3 cohort (with the updated data) along with the prospective cohort, which would give increased precision of the estimates for the ORR and DoR.
 - Enroll at least 9 and up to 20 patients in total in each of the identified common tumour type subgroups (lung, melanoma, colorectal cancer, non-secretory breast), and pre-specify rules for conclusions of adequate/inadequate clinical activity using a Bayesian approach
 - Continue enrolment in the prospective cohort for 36 months post approval. The plan is to enroll 200 patients (75 already enrolled) including 80 in the common tumour types and 120 in the other tumour types and discuss with the Agency whether enrolment should continue.

Key Topics During MAA Review

Assessment of Clinical Safety

- CHMP assessment: *From an overall safety perspective (adult patients and paediatric patients), larotrectinib appears reasonably tolerable and the toxicity is considered to be manageable with appropriate risk minimization measures as evidenced by the low treatment discontinuation rate*
- CHMP acknowledged that the long-term safety profile of larotrectinib will be further characterized in the post-marketing setting through registry and a non-intervention post authorisation safety study proposed by Bayer
- Post-approval measure: In order to generate comprehensive data on the long-term toxicity and developmental effects of larotrectinib in paediatric patients, with particular focus on neurodevelopment including cognitive function, a specific post-approval to measure submit the final report of study 15003 (SCOUT) including 5 year follow up data was proposed by the CHMP

Key Topics During MAA Review

Assessment of Clinical Pharmacology

- Overall, clinical pharmacology data were generally acceptable and supportive of conditional marketing authorisation; CHMP noted uncertainty in exposure estimates for the youngest children
 - MAH agreement to provide an updated PK model including available data up to cut-off date June 2019
 - MAH commitment to continue collecting more paediatric PK data to refine dose if necessary
- Post-Approval Measure: In order to further confirm the appropriate dose recommended in paediatric patients, the MAH should submit an updated pop PK model based on additional PK sampling in patients aged 1 month to 6 years from study LOXO-TRK-15003 (SCOUT).

Key Success Factors

- Clear and consistent assessment/feedback on key topics from the Rapporteur (Dr. Filip Josephson, SE) , the Co-Rapporteur, (Dr. Alexandre Moreau, FR), the EMA PTL (Dr. Elias Pean, NL) and their teams at the pre-submission meetings and throughout the MAA review
- Robust scientific discussions combined with pragmatic assessment of feasibility of post approval commitments
- EMA Workshop on “Histology-Independent Indication” held in December 2017 which served as a key forum in the EU for multiple stakeholders to discuss a potential path forward for such a novel paradigm/indication
- Precedent setting positive opinion from the CHMP/EMA for a histology independent indication demonstrating flexibility and support for patient-focused scientific innovation

Future Considerations Regarding Tissue Agnostic Development

- Mechanism of action (Fit for purpose?)
- Rarity of disease
- Clinical efficacy and safety of drug
- Conditional Marketing Authorisation
- Post-approval commitments
- Orphan Drug Designation
- Early interactions with EMA/CHMP
- PRIME Designation and accelerated assessment (if applicable)

Acknowledgements

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- Dr. Isabelle Stoeckert, Bayer
- Dr. Jens Leopold, Bayer
- Members of the VITRAKVI Global Development Team
- Members of the Loxo Oncology Team

We thank the patients and their families, many of whom traveled long distances to participate in the clinical trials