The Oncologist®

Precision Medicine Clinic: Molecular Tumor Board

Antitumor Activity of Larotrectinib in Esophageal Carcinoma with *NTRK* Gene Amplification

Dirk Hempel,[a] Thomas Wieland,[b] Beate Solfrank,[b] Vera Grossmann,[b] Johanna Steinhard,[b] Andrea Frick,[b] Louisa Hempel,[c] Thomas Eberl,[d] Andreas Gaumann[e]

[a]Oncology Center, Donauwörth, Germany; [b]FMI Germany GmbH, Penzberg, Germany; [c]Sigmund Freud University, Vienna, Austria; [d]Department of Gastroenterology, Klinikum Donauwörth, Donauwörth, Germany; [e]Pathology, Kaufbeuren, Germany

Disclosures of potential conflicts of interest may be found at the end of this article.

Abstract

Background. Increasing knowledge about the genomic changes underpinning cancer development and growth has led to a rapidly expanding number of individualized therapies that specifically target these changes in a patient's tumor. Here we present a case report of a patient with metastatic esophageal carcinoma whose tumor harbored *NTRK1* gene amplification and who received targeted systemic therapy with larotrectinib. At initial diagnosis, the patient presented with tumor obstruction of the middle esophagus, simultaneous liver and lung metastases, UICC IV and WHO performance status 3.

Materials and Methods. The solid tumor genomic profiling test FoundationOne CDx (F1CDx) was used to detect clinically relevant genomic alterations that, in turn, might identify a targeted therapeutic approach if suggested by the findings. The patient was then treated with larotrectinib and had subsequent follow-up biopsies.

Results. Simultaneous biopsies of the primary tumor and liver lesions identified a metastatic squamous cell esophageal carcinoma. Comprehensive genomic profiling obtained from liver metastases identified numerous genomic alterations including amplification of *NTRK1*. Owing to the reduced performance status of the patient, chemotherapy could not be applied and was denied. Although larotrectinib is only approved for the treatment of cancers with *NTRK* gene fusions, treatment was started and led to a shrinkage of the primary tumor as well as the liver and lung metastases within 6 weeks according to RECIST criteria accompanied by tumor marker decrease. The *NTRK1* gene amplification was below the limit of detection in a subsequent liver biopsy.

Conclusion. The use of comprehensive genomic profiling, specifically F1CDx, enabled the selection of a targeted therapy that led to a rapid reduction of the tumor and its metastases according to RECIST criteria. This case suggests that larotrectinib is not only effective in *NTRK* fusions but may be efficacious in cases with gene amplification. ***The Oncologist*** 2020;25:e881–e886

Key Points

- Advances in precision medicine have revolutionized the treatment of cancer and have allowed oncologists to perform more individualized therapy.
- This case shows that larotrectinib could also be effective in cases of *NTRK* amplification of cancer.
- Today, there is only limited knowledge about *NTRK* alterations in squamous epithelial carcinoma of the esophagus. Longitudinal tumor sequencing during the course of the disease may allow for the detection of a molecular genetic cause once the tumor progresses. Additional actionable gene alterations may then be identified, which may provide the rationale for a therapy switch.

Introduction

Cancer has long been categorized and treated based on its anatomic origin and localization. However, with the development of clinically available and robust comprehensive genomic sequencing assays, genomic driver alterations that are involved in the tumor development and progression could be detected and allow personalized therapies of actionable gene alterations.

NTRK gene fusions represent one of the most important molecular changes with known oncogenic and transforming

Correspondence: Dirk Hempel, M.D., Oncology Center, Steinbeis Hochschule Berlin, Neudegger Allee 10, 86609 Donauwörth, Germany. Telephone: 49-906-2999-390; e-mail: dirk.hempel@gmail.com Received August 18, 2019; accepted for publication March 5, 2020; published Online First on April 23, 2020. http://dx.doi.org/10.1634/theoncologist.2019-0641

potential [1]. Gene fusions lead to transcription of chimeric TRK oncoproteins that are constitutively active and serve as oncogenic drivers in a wide variety of cancers. Therefore, *NTRK* gene fusions are currently being investigated in several tumor types as targets for cancer therapy [2].

Regarding a treatment of *NTRK* gene fusions, several TRK inhibitors have been developed, including larotrectinib. Larotrectinib is an orally available selective inhibitor of the TRK receptor family that has shown significant clinical benefit in pediatric and adult patients with *NTRK* gene fusion in recent years and is now approved in the European Union (EU) and the U.S. [3, 4]. *NTRK* gene amplification has shown to result in TRK overexpression as well [5]. However, knowledge on the efficacy of targeted therapy for *NTRK* gene amplification is yet rare. To our knowledge, there has been only one patient described so far who harbored an *NTRK1* gene amplification and who had a partial response after treatment with larotrectinib [6]. This patient was described in a multicenter, open-label, phase I dose-escalation study, which investigated larotrectinib in adult patients with solid tumors [6].

Esophageal cancer remains a major cause of cancer-related mortality worldwide and is associated with a poor prognosis in both the locally advanced and metastatic setting [7, 8]. The majority of patients with esophageal cancer suffer from the metastatic disease at the time of diagnosis or relapse after surgery or chemotherapy [9]. Esophageal cancer includes two main subtypes: oesophageal squamous cell carcinoma and oesophageal adenocarcinoma [10]. The standard therapy for patients with advanced/metastatic squamous cell carcinoma of the esophagus is palliative chemotherapy, usually consisting of cisplatin and a fluropyrimidine. The aim of this therapy is solely to improve the quality of life [11, 12]. Although this therapy has a life-prolonging effect in adenocarcinoma, the effect of treatment in squamous cell carcinoma is not assured [12]. The efficacy of targeted therapies has so far only been shown for adenocarcinoma of the esophagus [12].

In this case report, we present the case of a patient with metastatic squamous cell esophageal carcinoma with *NTRK1* gene amplification who received targeted therapy with larotrectinib. In a search of 879 cases with squamous cell carcinoma of the esophagus identified in the Foundation Medicine database, *NTRK1* fusions were detected in none and gene amplification in two cases (0.2%). Therefore, this case report is of outstanding relevance. Furthermore, to our knowledge, this is merely the second published case of a patient with *NTRK* gene amplification who received larotrectinib.

Clinical Presentation

The patient was a 71-year-old male who presented in December 2018 at the Oncology Center with dysphagia, dyspnea, cough, swallowing disorders, and weight loss of 20 kg within 3 months. The patient was in a poor general condition with Eastern Cooperative Oncology Group (ECOG) performance status of 3 and had no other pre-existing conditions. He did not consume alcohol or nicotine and had no previous tumors. Esophagogastroduodenoscopy showed a stenosing esophageal carcinoma in the middle third of the esophagus with an extension of 10–21 cm from the upper row of teeth. Computed tomography (CT) showed bilateral lung metastases, and contrast-enhanced abdominal ultrasound sonography and CT showed multiple liver metastases. A tumor biopsy from the esophagus and a sonographically controlled liver biopsy were performed to confirm the diagnosis. The results confirmed the diagnosis of both a squamous cell carcinoma of the esophagus and liver metastases consistent with esophageal origin (Fig. 1). Because of swallowing disorders and stenosis, an esophageal stent was implanted on February 10, 2019 (Fig. 2).

Genotyping Results and Interpretation of the Molecular Results

FoundationOne CDx Test

Approval for this test, including a waiver of informed consent and a Health Insurance Portability and Accountability Act waiver of authorization, was obtained from the Western Institutional Review Board (Protocol 20152817). Informed consent of the patient was obtained to perform genomic profiling. The DNA was isolated from the histological tumor enrichment and its quality and quantity were further investigated. Subsequently, relevant areas of the genome were further enriched by hybrid capture (Agilent SureSelect custom kit) and examined after ligation of adaptors by next-generation sequencing (NGS; FoundationOne CDx). FoundationOne CDx is a solid tumor genomic profiling test that detects clinically relevant mutations in cancer-associated genes and provides a comprehensive molecular tumor profile [13–16].

Sequencing Results

The conventional histology examination from February 2019 identified a metastatic squamous cell esophageal carcinoma (Fig. 1). Genomic alterations of *CCND1*, *EGFR*, *MET*, *PIK3CA*, *CCND2*, *CDK6*, *HGF*, *SOX2*, *CCND3*, *CDKN2A/B*, *EPHB4*, *FGF19*, *FGF3*, *FGF4 MCL1*, *NTRK1*, *PIM1*, *TP53*, and *VEGFA* were detectable in the examined tumor tissue (primary tumor and liver) and are summarized below (Table 1). Among the strongly amplified genes, several showed much higher initial amplification levels than *NTRK1* (*EGFR*, *PIK3CA*, *CCND1*, *FGF19*, *FGF3*, and *FGF4*). The microsatellite status was stable and the tumor mutational burden was classified as intermediate with 10 Muts/Mb. Furthermore, genomic variants of unknown significance were detected but did not have a clinical impact.

A fluorescence in situ hybridization (FISH) assay for *NTRK1*, *2*, and *3* fusions was also performed. FISH confirmed the results of NGS. Specifically, there was an absence of *NTRK* fusions but a presence of an *NTRK1* amplification with a copy number of 8 (Table 1).

After the failure of larotrectinib in May 2019, a subsequent liver biopsy continued to display strong amplification events in the abovementioned genes. However, the total number of amplicons decreased by half, consistently within the analyzed genes (Table 1).

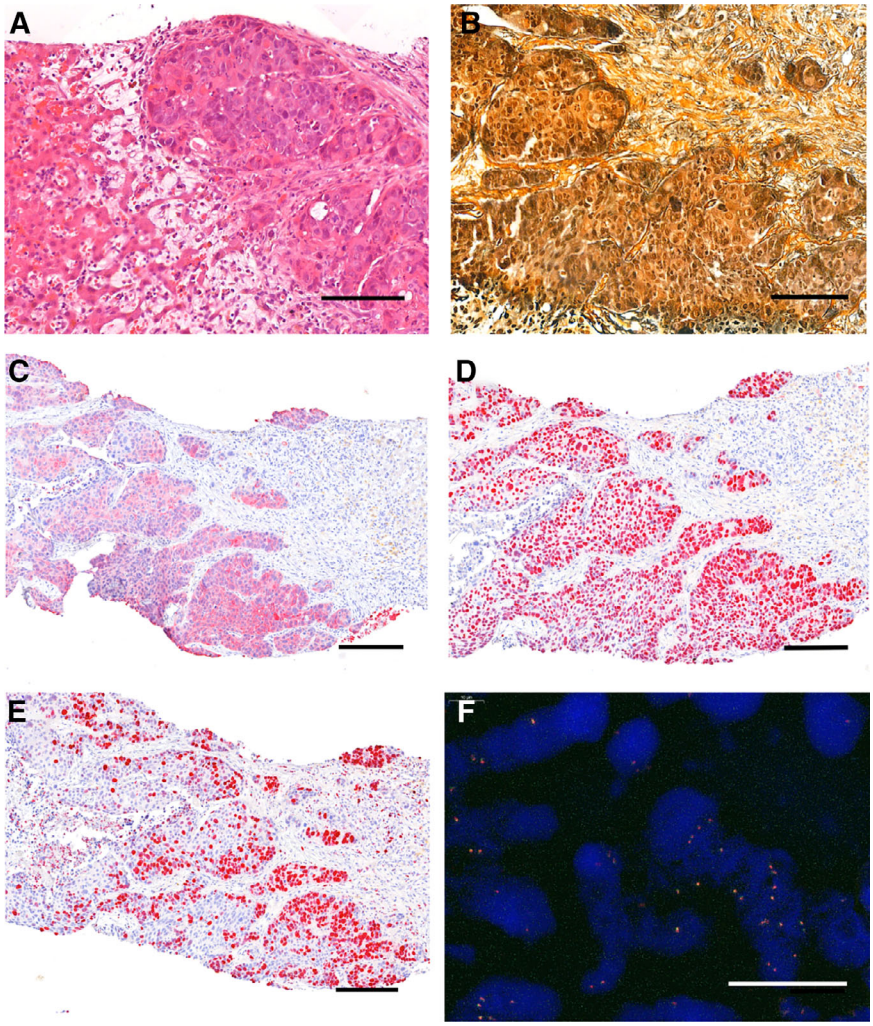

Figure 1. Tumor histology. Hematoxylin and eosin staining showed a solid nodular tumor mass in the liver (**A**; — 100 µm) with a brown-colored desmoplastic collagen reaction (**B**; — 100 µm) using the Gomori staining. Immunohistochemistry showed a strong positivity for CK5 and p63 (**C** and **D**; — 200 µm) to sustain a squamous differentiation of the metastasis. There was a prominent proliferation marked by Ki-67 (**E**; — 200 µm) in tumor formation. Fluorescence in situ hybridization analysis for NTRK 3 showed no translocation (**F**; — 50 µm)

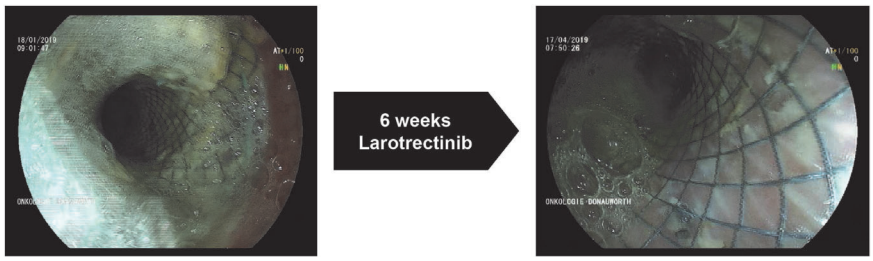

Figure 2. Esophageal stent before therapy with larotrectinib (left) and 6 weeks after treatment (right).

Patient Update

On February 4, 2019, therapy with larotrectinib was initiated. The patient received a standard dose of 2 × 100 mg larotrectinib orally. Side effects did not occur during treatment. Larotrectinib was not yet approved in the EU when the patient was treated but was imported from the U.S. A spiral CT scan done on January 4, 2019, before the treatment initiation showed multiple lung and liver metastases. Two metastases in the left lung segment I/II and in segment VI and two metastases in liver segment VII were considered target lesions for tumor assessment according to RECIST 1.1. With respect to tumor response, the sum of the longest diameters of target lesions was 67.5 mm at baseline. Several pathologically enlarged pre- and paracaval lymph nodes were still present. ECOG performance status improved to 1 and the patient recorded a weight gain of 9 kg. He was able to leave the clinic and continue via self-care. The pathological follow-up examination performed on April 17, 2019, by esophagogastroduodenoscopy confirmed the decline of the tumor, as the esophageal re-biopsy was tumor-free (Fig. 2).

Table 1. Sequencing results

Gene variation	**Initial liver biopsy 02/19**		**Second liver biopsy 05/19**		
Microsatellite status	MSS		MSS		
Tumor mutational burden	**Intermediate (10 mut/1MB)**		**Intermediate (6 mut/1MB)**		
Estimated tumor content	35.5%		40.8%		
Short variant					
Gene	**Substitution**	**MAF**	**Gene**	**Substitution**	**MAF**
TP53	P278T	0.42	TP53	P278T	0.37
CNV					
Gene	**Alteration**	**Copy number**	**Gene**	**Alteration**	**Copy number**
CCND1	Amplification	40	CCND1	Amplification	21
EGFR	Amplification	126	EGFR	Amplification	65
MET	Amplification	13	MET	Amplification[a]	7
PIK3CA	Amplification	45	PIK3CA	Amplification	20
CCND2	Amplification	8			
CDK6	Amplification	10	CDK6	Amplification[a]	6
HGF	Amplification	13	HGF	Amplification[a]	7
SOX2	Amplification	14	SOX2	Amplification	8
CCND3	Amplification	12	CCND3	Amplification[a]	7
CDKN2A/B	Loss	0	CDKN2A/B	Loss	0
EPHB4	Amplification	8			
FGF19	Amplification	39	FGF19	Amplification	20
FGF3	Amplification	39	FGF3	Amplification	20
FGF4	Amplification	41	FGF4	Amplification	20
MCL1	Amplification	8			
NTRK1	**Amplification**	**8**			
PIM1	Amplification	14	PIM1	Amplification	8
VEGFA	Amplification	12	VEGFA	Amplification[a]	7

[a]Equivocal.
Abbreviations: CNV, copy number variation; MAF, Mutant Allel Frequency; MSS, microsatellite stable.

The duodenal mucosa, the antral mucosa, and the corpus mucosa presented without morphologically detectable pathological findings.

On March 22, 2019, a response assessment was undertaken with a CT of the thorax and abdomen. Compared with the examination carried out on February 4, 2019, there was now improvement of the findings, with regression in size of the multiple pulmonary metastases accompanied by tumor marker (squamous cell carcinoma [SCC]) decrease (Figs. 3, 4). The sum of the longest diameters of the target lesions decreased to 33 mm, which constitutes a partial response according to RECIST criteria. The pleural effusions had receded.

On May 11, 2019, another CT scan and a liver biopsy with contrast medium–guided ultrasound (SonoVue) were performed as a result of a rise of the tumor marker SCC antigene (Fig. 4). A progressive disease of liver and lung metastases was observed. Results of the rebiopsy of the liver revealed that the *NTRK1* amplification was now below the limit of detection, which could explain the disease progression. The patient refused conventional chemotherapy. He received crizotinib after approval by his health insurance because of the presence of a *MET* amplification. The treatment resulted in stable disease for another 3 months.

Functional and Clinical Significance of *NTRK* Gene Alterations in Esophageal Cancer

NTRK 1, *NTRK 2*, and *NTRK 3* encode for the transmembrane proteins TRK A, B, and C, respectively. These tropomyosin receptor kinase proteins are expressed in human neuronal tissue and play an important role in the physiology of the development and function of the nervous system [2].

In numerous malignancies, mutations in *NTRK* gene family have been confirmed, although only fusions, in-frame deletions, and splice variations have been identified as oncogenic [1]. Very little has been reported about *NTRK* gene alterations in esophageal carcinoma. Considering our findings, *NTRK1* alterations in squamous cell carcinoma occur at an extremely low frequency of 0.2%, as identified in the Foundation Medicine database. In two separate studies describing the frequency of *NTRK* fusions in esophageal carcinoma, there was only one case of *NTRK3* fusion defined within 100 biopsies and, respectively, no *NTRK* fusions among 185 biopsies [17, 19]. However, despite the low *NTRK* fusion and amplification findings, TRK A was observed to be overexpressed in 9/20 cases of esophagus cancer [18]. Therefore, TRK-specific protein kinase inhibitors might be considered an appropriate therapy.

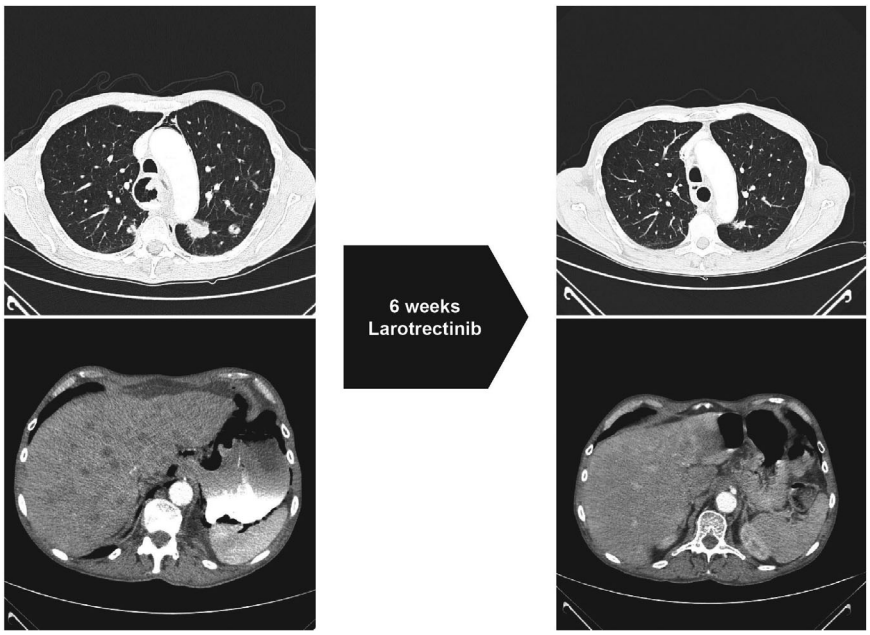

Figure 3. Computed tomography of lung (upper panel) and liver (lower panel) before treatment with larotrectinib and 6 weeks later, showing partial remission of liver and lung metastases.

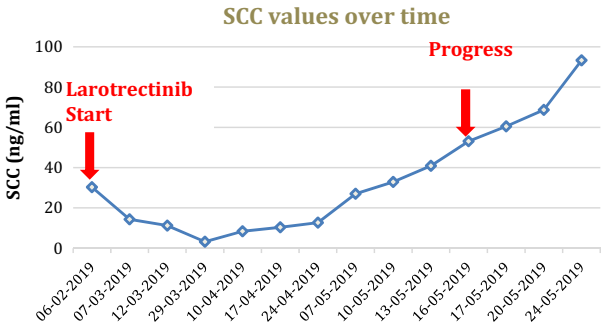

Figure 4. Tumor marker value SCC over time.
Abbreviation: SCC, squamous cell carcinoma.

Discussion

With larotrectinib, entrectinib, and selitrectinib (formerly known as LOXO-195), three TRK inhibitors are either already available or still in clinical development. *NTRK1, 2, and 3* genes fuse with unrelated genes, which results in ligand-independent activation of the protein kinase domain of the TRK receptor. Whereas the activity of larotrectinib and entrectinib in *NTRK* gene fusions is established, their role on *NTRK* amplification is unclear [3, 20, 21]. Nonfusion NTRK alterations, for example, mutation or amplification, have been associated with a lack of response with some *NTRK* inhibitors [2], but recently, in a multicenter, open-label, phase I dose-escalation study investigating larotrectinib in adult patients with solid tumors, one patient harbored an *NTRK1* gene amplification and had a partial response with larotrectinib, which was the rationale for treatment decision. The described patient had a single, small target lesion (11 mm) that shrank by 5 mm (45.5%) and the duration of response was 3.7 months [5], which is similar to the response outcome observed in our patient. We also found a high amplification of *EGFR* in our sample, and this patient could have been treated with anti-*EGFR* therapy as well. According to the abovementioned publication, the molecular tumor board decided on a treatment with larotrectinib in this particular case, and we saw a short but significant tumor shrinkage according to RECIST criteria classified as partial remission.

Similar to *ERBB2* gene amplification, which is a well-established class of driver gene alteration in breast and gastric cancer, protein overexpression of *NTRK* amplified tumors is inconsistent. Recently, *NTRK* amplification (copy number ≥4) was reported to result in a protein overexpression in 14.8% of patients [22]. To our knowledge, this is the second report that describes a short but significant tumor response of larotrectinib in *NTRK* amplified tumors. Whereas larotrectinib is very specific for inhibition of TRK A, B, and C kinase domain, entrectinib is also active in *ROS1* and *ALK* fusion [21]. The high specificity of larotrectinib for TRK A, B, C protein kinase could explain the fact that the substance seemed to be active in *NTRK* amplified cancers, whereas for entrectinib, the aforesaid efficacy was not assessed [23].

Conclusion

Results of the liver rebiopsy after larotrectinib failure revealed that there was a loss of the *NTRK1* amplification, hand in hand with a significant decrease of copy number of other observed genes as well. Because of the fact that the initial amplification copy number of certain genes (*EGFR* in particular, followed by *PIK3CA*, *CCND1*, *FGF19*, *FGF3*, and *FGF4*) was much higher than that of *NTRK1* (5- to 15-fold), it could be speculated that some of these genes were later driving the clonal expansion of the tumor cells, influencing its possible mechanism of acquired resistance. Additionally, the mechanisms of resistance and progression in this patient may include the presence or emergence of *NTRK*-associated coalterations, which were commonly discerned in genes that are involved in PI3K signaling, tyrosine kinase families, cell-cycle

machinery, and MAPK pathways. Additional investigation is needed to elucidate whether these genes mediate resistance to *NTRK* inhibition and if cotargeting them augments anti-NTRK antitumor activity. This way, we could explain only the short-lived patient's response to larotrectinib. In spite of finding an appropriate driver alteration, further mRNA-based clinical studies should be conducted.

Glossary of Genomic Terms and Nomenclature

NTRK1: neurotrophic receptor tyrosine kinase 1RK
CCND1: cyclin D1
CCND2: cyclin D2
CCND3: cyclin D3
EGFR: epidermal growth factor receptor
PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
CDK6: cyclin dependent kinase 6
HGF: hepatocyte growth factor
SOX2: SRY-box transcription factor 2
CDKN2A/B: cyclin dependent kinase inhibitor 2A/B
EPHB4: ePH receptor B4
FGF19: fibroblast growth factor 19
FGF3: fibroblast growth factor 3
FGF4: fibroblast growth factor 4
MCL1: MCL1 apoptosis regulator
PIM1: Pim-1 proto-oncogene, serine/threonine Kinase
TP53: tumor protein P53
VEGFA: vascular endothelial growth factor A

Acknowledgments

Medical writing services were provided by co.medical (Juliane Schreier) and were funded by Bayer Vital GmbH.

Author Contributions

Conception/design: Dirk Hempel, Thomas Wieland, Beate Solfrank, Vera Grossmann, Johanna Steinhard, Andrea Frick, Louisa Hempel, Thomas Eberl, Andreas Gaumann
Provision of study material or patients: Dirk Hempel, Thomas Wieland, Beate Solfrank, Vera Grossmann, Johanna Steinhard, Andrea Frick, Louisa Hempel, Thomas Eberl, Andreas Gaumann
Manuscript writing: Dirk Hempel, Thomas Wieland, Beate Solfrank, Vera Grossmann, Johanna Steinhard, Andrea Frick, Louisa Hempel, Thomas Eberl, Andreas Gaumann
Final approval of manuscript: Dirk Hempel, Thomas Wieland, Beate Solfrank, Vera Grossmann, Johanna Steinhard, Andrea Frick, Louisa Hempel, Thomas Eberl, Andreas Gaumann

Disclosures

Vera Grossmann: Foundation Medicine Germany GmbH (E). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

References

1. Vaishnavi A, Le AT, Doebele RC. TRKing down an old oncogene in a new era of targeted therapy. Cancer Discov 2015;5:25–34.

2. Amatu A, Sartore-Bianchi A, Siena S. NTRK gene fusions as novel targets of cancer therapy across multiple tumour types. ESMO Open 2016; 1:e000023.

3. Berger S, Martens UM, Bochum S. Larotrectinib (LOXO-101). Recent Results Cancer Res 2018;211:141–151.

4. EMA/CHMP/413258/2019, Committee for Medicinal Products for Human Use (CHMP) 2019. Available at https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-vitrakvi_en.pdf

5. Lee SJ, Kim NKD, Lee S-H et al. NTRK gene amplification in patients with metastatic cancer. Precis Future Med 2017;1:129–137.

6. Hong DS, Bauer TM, Lee JJ et al. Larotrectinib in adult patients with solid tumours: A multi-centre, open-label, phase I dose-escalation study. Ann Oncol 2019;30:325–331.

7. Bray F, Ferlay J, Soerjomataram I et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68: 394–424.

8. Wong MCS, Hamilton W, Whiteman DC et al. Global Incidence and mortality of oesophageal cancer and their correlation with socioeconomic indicators temporal patterns and trends in 41 countries. Sci Rep 2018;8:4522.

9. Krug S, Michl P. Esophageal cancer: New insights into a heterogenous disease. Digestion 2017;95:253–261.

10. Lordick F, Mariette C, Haustermans K et al. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27:50–57.

11. Tanaka Y, Yoshida K, Suetsugu T et al. Recent advancements in esophageal cancer treatment in Japan. Ann Gastroenterol Surg 2018;2:253–265.

12. Deutsche Krebsgesellschaft: Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): S3-Leitlinie Diagnostik und Therapie der Plattenepithelkarzinome und Adenokarzinome des Ösophagus, Langversion 2.01 (Konsultationsfassung), 2018, AWMF Registernummer: 021/023OL. Available at https://www.leitlinienprogramm-onkologie.de/leitlinien/oesophaguskarzinom/. Accessed May 24, 2019.

13. Drilon A, Wang L, Arcila ME et al. Broad, hybrid capture-based next-generation sequencing identifies actionable genomic alterations in lung adenocarcinomas otherwise negative for such alterations by other genomic testing approaches. Clin Cancer Res 2015;21: 3631–3639.

14. Rozenblum AB, Ilouze M, Dudnik E et al. Clinical impact of hybrid capture-based next-generation sequencing on changes in treatment decisions in lung cancer. J Thorac Oncol 2017;12: 258–268.

15. FoundationOne CDx: Technical Information. Available at https://www.foundationmedicine.com/genomic-testing/foundation-one-cdx

16. U.S. Food & Drug Administration: FoundationOne CDx FDA Approval, 2017. Available at https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019a.pdf. Accessed May 7, 2019.

17. Ling Q, Li B, Wu X et al. The landscape of NTRK fusions in Chinese patients with solid tumor. Ann Oncol 2018;29:14–57.

18. Narayanan R, Yepuru M, Coss CC et al. Discovery and preclinical characterization of novel small molecule TRK and ROS1 tyrosine kinase inhibitors for the treatment of cancer and inflammation. PLoS One 2013;8e83380:1–14.

19. Okamura R, Boichard A, Kato S et al. Analysis of NTRK alterations in pan-cancer adult and pediatric malignancies: Implications for NTRK-targeted therapeutics. JCO Precis Oncol 2018;2:1–20.

20. Kummar S, Lassen UN. TRK inhibition: A new tumor-agnostic treatment strategy. Target Oncol 2018;13:545–556.

21. Farago AF, Le LP, Zheng Z et al. Durable clinical response to entrectinib in NTRK1-rearranged non-small cell lung cancer. J Thorac Oncol 2015; 10:1670–1674.

22. Lee SJ, Kim NKD, Lee SH et al. NTRK gene amplification in patients with metastatic cancer. Precis Future Med 2017;1:129–137.

23. Demetri GD, Paz-Ares L, Farago AF et al. Efficacy and safety of entrectinib in patients with NTRK fusion-positive (NTRK-fp) tumors: Pooled analysis of STARTRK-2, STARTRK-1 and ALKA-372-001. Paper presented at: ESMO 2018 Congress; November 23, 2018; Munich, Germany.