DESIGN AND FIRST RESULTS OF THE REALTRK REGISTRY

MOLECULAR TESTING, TREATMENT, AND OUTCOME OF PATIENTS WITH ADVANCED SOLID TUMORS HARBORING A *NTRK1*, *NTRK2*, OR *NTRK3* GENE FUSION

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INTRODUCTION

- *Neurotrophic tyrosine receptor kinase (NTRK)* gene fusions involving either *NTRK1*, *NTRK2*, or *NTRK3* (encoding the tropomyosin receptor kinases TRKA, TRKB, and TRKC, respectively) are oncogenic drivers.[1]
- The overall prevalence of *NTRK* fusion-positive tumors is ~0.30%,[2] though frequencies vary by tumor type, with >75% reported for rare tumor types such as secretory carcinoma of the breast and salivary glands.[3]
- In Europe, two TRK inhibitors (entrectinib and larotrectinib) received tumor-agnostic approval. A very good clinical activity and a favorable overall safety profile was shown for both, making this new targeted approach highly relevant for patients with *NTRK*-fused tumors.[4,5]

However, approvals were based on pooled data of international, non-comparative phase I/II clinical trials with moderate numbers of patients.

- Currently, no systematically collected real-world data are available on diagnostics, treatment, and outcome for patients with *NTRK* fusion harboring tumors.
- REALTRK is a multicenter registry to provide data on the treatment reality of adult patients with advanced solid tumors harboring *NTRK1*, *NTRK2*, or *NTRK3* gene fusions, including an in-depth description of molecular testing and patient-relevant aspects, including treatment effectiveness and patient-reported quality of life (QoL) (**Fig. 1**).

METHODS

Study design and participants

REALTRK is a retro- and prospective, observational, intersectoral, cohort study conducted in up to 100 sites (office-based oncologists and hospitals) in Germany (NCT04557813). In total, 120 patients with advanced (locally advanced or metastatic) solid tumors harboring a *NTRK* gene fusion diagnosed with a validated assay (according to ESMO recommendations[6], **Fig. 2**) will be included within three years, while the inclusion of deceased patients is also allowed.

Patients with detailed information on *NTRK* testing methods and results qualify for complete documentation. For NGS analyses, for example, details on test results include the *NTRK* and fusion partner gene names, the genomic positions of breakpoints, and the presence of an intact TRK kinase domain. Data on *NTRK* testing methods and results are documented and evaluated centrally by the sponsor.

The first patient was included on December 02, 2020. Due to an amendment of the observational plan, patient inclusion was paused from March to November 2021. The focus of the amendment was the tightening of the eligibility criteria to guarantee that the *NTRK* gene fusions are analyzed with validated assays. Furthermore, the availability of high-quality and informative molecular pathology reports with detailed information on *NTRK* testing methods and results was added as inclusion criterion.

Herein, we report the results of a first data snapshot. Descriptive statistics were used to analyze the data.

RESULTS

Patient and disease characteristics

Until February 02, 2022, eleven patients were included, seven patients before and four patients after the approval of the amendment. Four of the seven patients that have been included before the protocol amendment qualified for complete documentation, three are not eligible. Of the four patients included since the approval of the amendment, one patient was a screening failure, one patient qualified for complete documentation, and for two patients, data on molecular testing and results are currently under review. All five patients that qualified for complete documentation until now are described hereafter.

So far, one female patient with colorectal cancer and four male patients (three with colorectal cancer and one with lung cancer) qualified for analysis. At the time of *NTRK* fusion diagnosis, the median age was 78.2 (59.7-84.6) years and 1.1 (0.2-7.9) months after *NTRK* fusion diagnosis, a new treatment line was started (**Table 1**). All patients received a TRK inhibitor upon *NTRK* fusion diagnosis: two patients received entrectinib and three patients received larotrectinib.

Data on molecular testing of *NTRK* fusions

For all five patients, NGS was used as a diagnostic method to detect the *NTRK* gene fusion. While in the case of colorectal cancer three times RNA-based NGS and once DNA-based NGS was used, a hybrid DNA/RNA test panel was used for the analysis of the lung cancer sample (**Table 2**). *NTRK1* was identified four times as *NTRK* gene fused to *LMNA*, *TPM3*, *TP53*, or *KIF5B*, whereas *NTRK3* was identified in one case to be fused to *EML4* (**Table 3**).

Test and treatment decision making

To identify factors that affect physicians' decision to test for *NTRK* gene fusions as well as factors influencing treatment decision making after diagnosis of a *NTRK* fusion-positive tumor, physicians were asked to complete questionnaires to evaluate factors considered as relevant to their decision making. The evaluations of all five treating physicians are summarized in **Fig. 3**.

Figure 1

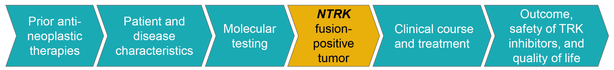

Figure 1: Concept and objectives of REALTRK.

Patients whose tumors harbor a *NTRK* gene fusion can be included in REALTRK (yellow tile). For these patients, aspects shown in blue tiles will be described as key objectives of REALTRK.

Figure 2

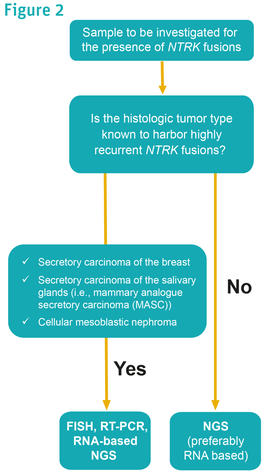

Figure 2: *NTRK* testing algorithm adapted based on ESMO recommendations[6].

Abbreviations: ESMO, European Society for Medical Oncology | FISH, Fluorescence In Situ Hybridization | NGS, Next-Generation Sequencing | RNA, Ribonucleic Acid | RT-PCR, Reverse Transcription Polymerase Chain Reaction.

CONCLUSION

REALTRK is the first registry to provide real-world data on the molecular characteristics of *NTRK* gene fusions and treatment of patients with *NTRK* fusion-positive tumors in Germany. Despite the low incidence of *NTRK* gene fusions, already eleven patients could be included in REALTRK within six months of active recruiting. Five of these patients qualified for complete documentation. This highlights that the implementation of a highly sophisticated real-world registry of patients harboring *NTRK* gene fusions is feasible.

Upcoming analyses will include additional endpoints regarding outcome, safety of TRK inhibitors, and QoL.

Table 1

	Total (n=5)
Sex	
Female	1 (20%)
Male	4 (80%)
Tumor type	
Colorectal cancer	4 (80%)
Lung cancer	1 (20%)
Ethnicity	
Caucasian	5 (100%)
Age at *NTRK* fusion diagnosis (years), median (min-max)	78.2 (59.7-84.6)
<75	2 (40%)
≥75	3 (60%)
Time from diagnosis of *NTRK* fusion to start of TRK inhibitor therapy (months), median (min-max)	1.1 (0.2-7.9)
Age at start of first therapy after *NTRK* fusion diagnosis (years), median (min-max)	78.5 (59.8-85.0)
CNS metastases present at start of first therapy after diagnosis	
No	5 (100%)
ECOG Performance Status at start of TRK inhibitor therapy	
1	3 (60%)
2	1 (20%)
Missing	1 (20%)

Table 1: Patient and disease characteristics

Table 2

	RNA-based NGS	DNA-based NGS	RNA- and DNA-based NGS
Test method – overall (n = 5)[a]	3 (60%)	1 (20%)	1 (20%)
Test method – by tumor type			
Colorectal cancer (n = 4)[a]	3 (75%)	1 (25%)	0 (0.0%)
Lung cancer (n= 1)[a]	0 (0.0%)	0 (0.0%)	1 (100%)

Table 2: Data on molecular testing

[a]Percentages refer to the total per row.

Table 3

Tumor type	5'- Fusion partner gene	*NTRK* gene -3'
Colorectal cancer	*LMNA*	*NTRK1*
Colorectal cancer	*TPM3*	
Colorectal cancer	*TP53*	
Lung cancer	*KIF5B*	
Colorectal cancer	*EML4*	*NTRK3*

Table 3: Data on *NTRK* gene fusions

Figure 3

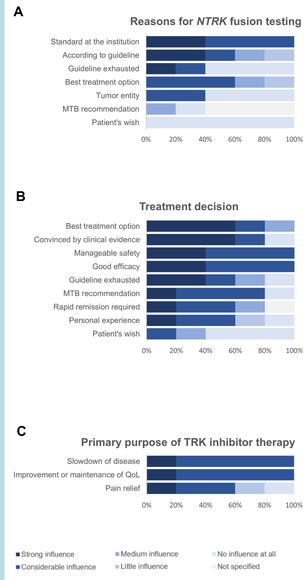

Figure 3: Test and treatment decision making

Factors affecting decision for *NTRK* fusion testing (A) as well as treatment decision after diagnosis of *NTRK* fusion-positive tumor (B) and therapy goals (C) based on physician's questionnaires.

Abbreviations: MTB: Molecular Tumor Board | QoL: Quality of Life.