Cancer Treatment and Research Communications 33 (2022) 100623

Contents lists available at ScienceDirect

Cancer Treatment and Research Communications

journal homepage: www.sciencedirect.com/journal/cancer-treatment-and-research-communications

Prognosis and oncogenomic profiling of patients with tropomyosin receptor kinase fusion cancer in the 100,000 genomes project

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ARTICLE INFO

Keywords:
NTRK
TRK
Gene fusion
Genomic profiling
Real world evidence

ABSTRACT

Introduction: Neurotrophic tyrosine receptor kinase (*NTRK)* gene fusions are oncogenic drivers in various tumor types. Limited data exist on the overall survival (OS) of patients with tumors with *NTRK* gene fusions and on the co-occurrence of *NTRK* fusions with other oncogenic drivers.

Materials and Methods: This retrospective study included patients enrolled in the Genomics England 100,000 Genomes Project who had linked clinical data from UK databases. Patients who had undergone tumor whole genome sequencing between March 2016 and July 2019 were included. Patients with and without *NTRK* fusions were matched. OS was analyzed along with oncogenic alterations in *ALK, BRAF, EGFR, ERBB2, KRAS*, and *ROS1*, and tumor mutation burden (TMB) and microsatellite instability (MSI).

Results: Of 15,223 patients analyzed, 38 (0.25%) had *NTRK* gene fusions in 11 tumor types, the most common were breast cancer, colorectal cancer (CRC), and sarcoma. Median OS was not reached in both the *NTRK* gene fusion-positive and -negative groups (hazard ratio 1.47, 95% CI 0.39–5.57, $P = 0.572$). A *KRAS* mutation was identified in two (5%) patients with *NTRK* gene fusions, and both had hepatobiliary cancer. High TMB and MSI were both more common in patients with *NTRK* gene fusions, due to the CRC subset. While there was a higher risk of death in patients with *NTRK* gene fusions compared to those without, the difference was not statistically significant.

Conclusion: This study supports the hypothesis that *NTRK* gene fusions are primary oncogenic drivers and the co-occurrence of *NTRK* gene fusions with other oncogenic alterations is rare.

1. Introduction

The neurotrophic tyrosine receptor kinase (*NTRK*) genes *NTRK1, 2*, and *3* encode tropomyosin receptor kinase (TRK) proteins A, B, and C, respectively, and are expressed during normal neuronal development [1]. TRK receptors play a key role in the regulation of pain and body temperature [2,3], appetite control [4–6], learning, proprioception, and memory [7].

Recurrent *NTRK* gene fusions have been reported as oncogenic drivers in a wide variety of adult and pediatric tumor types [1]. *NTRK* gene fusions occur when the 3′ region of the *NTRK* gene is joined with the 5′ end of a fusion partner gene through intra- or inter-chromosomal rearrangement. This *NTRK* gene fusion encodes a TRK fusion protein that contains the catalytic tyrosine kinase domain from the *NTRK* gene, as well as one or more dimerization domains from the partner gene. The result is a TRK fusion protein that is constitutively activated, leading to

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https://doi.org/10.1016/j.ctarc.2022.100623

Available online 23 August 2022

uninterrupted downstream signaling activity, and thus conferring oncogenic potential of the TRK fusion protein [1,8]. These genomic alterations have emerged as targets for cancer therapy [1].

The prevalence of *NTRK* gene fusions varies widely across tumor types and they are estimated to occur in up to 1% of all solid tumors [1, 9]. *NTRK* gene fusions occur more frequently (>80%) in certain rare tumors (e.g., secretory carcinoma of the salivary gland and infantile fibrosarcoma), and less frequently (<1%) in more common cancers (e.g., lung cancer and colorectal cancer (CRC)) [9–13].

TRK inhibitors have been demonstrated to be highly effective treatment options in several clinical trials in patients with tumors that harbor *NTRK* gene fusions [14,15]. In particular, larotrectinib is a first-in-class, central nervous system (CNS)-active, highly selective TRK inhibitor approved in more than 47 countries, including the US, for adult and pediatric patients with TRK fusion cancer [16,17]. Larotrectinib demonstrated a high objective response rate (ORR) in a pooled analysis of three phase I/II trials in adults and/or children (NCT02122913, NCT02637687, and NCT02576431) that included 153 evaluable patients with 17 different tumor types. Investigator-assessed ORR was 79% (95% confidence interval [CI] 72–85), regardless of tumor type and age. Median duration of response (DoR) was 35.2 months (95% CI 22.8–not estimable [NE]) and median progression-free survival (PFS) was 28.3 months (95% CI 22.1–NE). In the 12 evaluable patients with CNS metastases at baseline, the ORR was 75% (95% CI 43–95) [18]. The high ORR, median DoR and median PFS have been confirmed in expanded datasets that have had independent review committee assessments. In this centrally reviewed assessment, the ORR was 69% (95% CI 63–75), with a median DoR and PFS of 32.9 months (95% CI 27.3–41.7) and 29.4 months (95% CI 19.3–34.3), respectively [19].

Entrectinib is a multi-kinase inhibitor that targets *ALK, ROS1*, and *NTRK1/2/3* and is approved for adult and pediatric patients aged 12 years or older with locally advanced or metastatic TRK fusion cancer [20,21]. Entrectinib demonstrated an ORR of 57% (95% CI 43.2–70.8) in a pooled subgroup analysis of 54 *NTRK* fusion-positive patients. The median DoR was 10.4 months (95% CI 7.1–not estimable) and median PFS was 11.2 months (95% CI 8.0–14.9) [22].

Although there has been progress in treating patients with TRK fusion cancer, data on the frequency and distribution of *NTRK* gene fusions in various cancer types are still limited. There are minimal data regarding real-world characteristics of patients with TRK fusion cancer and understanding of the natural history of TRK fusion cancer in the absence of TRK inhibitors is limited [23,24].

The UK 100,000 Genomes Project was developed by Genomics England to sequence 100,000 whole genomes from National Health Service patients to understand the genomics of patients with rare diseases and cancer. It aimed to benefit patients by providing advanced diagnosis and enabling personalized treatments [25].

We conducted a retrospective study to evaluate the overall survival (OS) in patients with *NTRK* gene fusions and frequency of *NTRK* gene fusions across solid tumor types, as well as co-occurrence of other genomic biomarkers in patients with *NTRK* gene fusions versus patients without *NTRK* gene fusions enrolled in the UK 100,000 Genomes Project [25]. These patients had not received TRK inhibitors previously.

2. Materials and methods

This retrospective cohort study used whole genome sequencing (WGS) data from the 100,000 Genomes Project (Genomics England database). Where possible, Genomics England links their genomic data with clinical data from UK health care and cancer databases, including Hospital Episode Statistics [26], which lists each visit of a patient to the hospital, and the National Cancer Registration and Analysis Service (NCRAS) [27], which contains a set of curated datasets with detailed information on the tumor, as well as information on treatment received. In addition, mortality data are provided based on the Office of National Statistics (ONS) [28]. All analyses were conducted on the latest version available at the time of analysis (Data Release version 9 – 2020–04–02).

To be included in the Genomics England 100,000 Genomes Project, patients must have a diagnosis from a World Health Organization (WHO)/International Agency for Research on Cancer (IARC) cancer classification. All participants must receive the usual clinical care and tumor samples should be obtained as fresh or fresh-frozen. Access to appropriate high-quality DNA from both tumor and germline samples, enabling WGS, is required [29].

The study was conducted in two steps (Fig. 2A). In Step 1, cancer patients with *NTRK* gene fusions were identified and their frequency, demographic, and clinical characteristics at baseline were described. Cancer patients who had undergone WGS between March 2016 and July 2019 were included. All patients had tumor and germline material sequenced to an average coverage of 75x and 30x, respectively. Read alignment against human reference genome GRCh38-Decoy+EBV was performed with ISAAC (version iSAAC- 03.16.02.19). All coverage metrics were calculated by including non-overlapping bases with minimal base quality of 30, where the read had a minimum mapping quality of 10 after duplicates were removed. Structural variants (SVs) were then called using Manta (version 0.28.0) [30]. Four filters were applied to all Manta calls meaning that the following were excluded: SVs with a normal sample depth near one or both variant breakpoints three times higher than the chromosomal mean; SVs with somatic quality score <30; somatic deletions and duplications >10 kb in length; and Manta-called somatic small variants (<1 kb) where the fraction of reads with MAPQ0 around either breakpoint was >0.4.

Subsequently, the remaining SVs were filtered to retain only *NTRK* gene fusions, i.e., SVs were filtered to exclude out-of-frame fusions, fusions where the TRK kinase domain was fully or partially omitted, fusions where one of the breakpoints was within an intergenic region, fusions where the transcriptional direction of the fused genes did not match, and fusions with a low number of supporting reads (see Supplementary Fig. S1 for details) since such fusions are unlikely to be oncogenic.

In Step 2, a matched cohort of cancer patients without *NTRK* gene fusions was created. A comparative analysis of OS and co-occurrence of other biomarkers in patients with and without *NTRK* gene fusions was conducted. *NTRK* gene fusion-positive and negative patients who linked to NCRAS data at the tumor level were included to obtain detailed demographic information. Matching was then conducted using exact matching for the following baseline variables: primary tumor type (International Classification of Diseases, Tenth Revision), histology, stage at diagnosis, and sex; followed by the Mahalanobis distance matching [31] for other variables including age, year of diagnosis, and Charlson Comorbidity Index [32].

The primary OS and biomarker analyses included 18 patients who were *NTRK* gene fusion-positive and 72 matched patients who were *NTRK* gene fusion-negative (Fig. 1). A sensitivity analysis was performed on the OS objectives in order to maximize the number of patients included in the analysis. The sensitivity OS analysis used less stringent criteria for linkage to NCRAS and, therefore, included a total of 31 patients who were *NTRK* gene fusion-positive and had date of diagnosis information available and 124 matched *NTRK* gene fusion-negative cohort patients. The matched biomarker analysis also included 31 patients that were *NTRK* gene fusion-positive and 124 matched *NTRK* gene fusion-negative cohort patients. The sensitivity biomarker analysis included all 38 *NTRK* gene fusion-positive patients, 124 matched *NTRK* gene fusion-negative patients, and an additional 838 participants (totaling 962 patients in the *NTRK* gene fusion-negative group) randomly selected from the tumor types observed in the *NTRK* gene fusion-positive cohort. The sensitivity analysis was capped at 1000 patients due to data access limitations (Fig. 2B).

3. Eligibility criteria

Step 1 of the analysis included all cancer patients who had

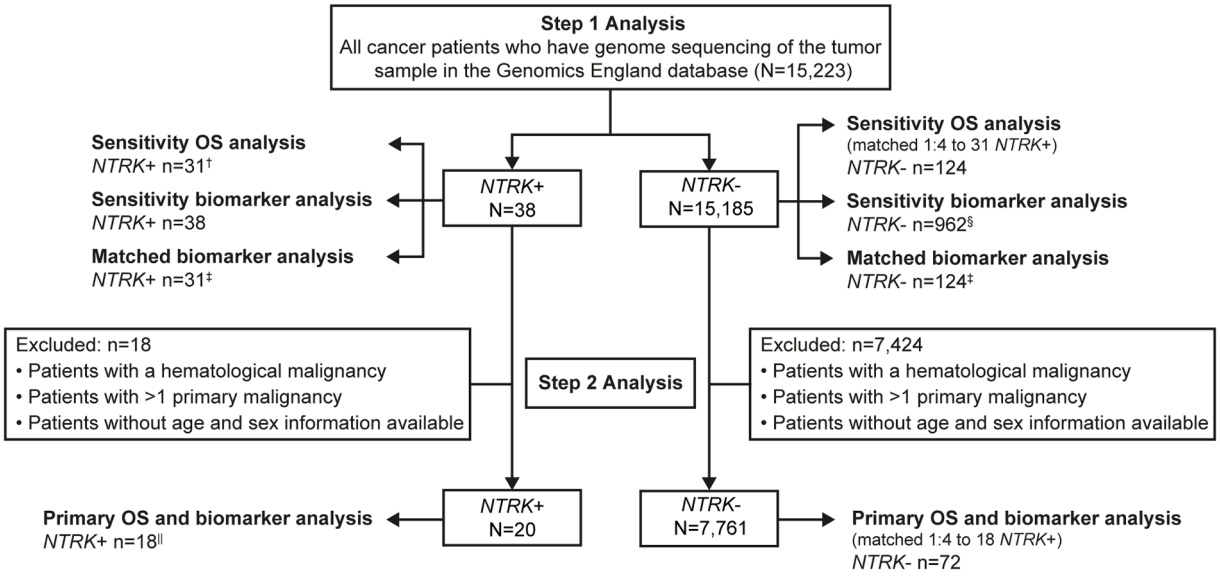

Fig. 1. CONSORT diagram. Shown is a CONSORT diagram describing the various cohorts in the analysis.
†A sensitivity analysis was performed on the OS objectives in order to maximize the number of patients included in the analysis. This utilized additional data on diagnosis date and tumor type from HES for patients who did not have CAS data available. Date of diagnosis (i.e., index date for OS analysis) was only available in 31 patients who were *NTRK*+, so the seven other patients were excluded. ‡This sensitivity analysis was conducted using the same patients that were included in the OS sensitivity cohort. §124 matched *NTRK*- patients and an additional 838 participants (totaling 962 patients in the *NTRK*- group) randomly selected from the tumor types observed in the *NTRK*+ cohort. The sensitivity analysis was capped at 1000 patients due to data access limitations. ‖Two patients in the *NTRK*+ group were excluded from the OS analysis as their tumor and histology type were not present in the *NTRK*- group. CAS, Cancer Analysis System; HES, Hospital Episodes Statistics; *NTRK*, neurotrophic tyrosine receptor kinase; *NTRK*+, *NTRK* gene fusion-positive; *NTRK-; NTRK* gene fusion-negative; OS, overall survival.

undergone tumor WGS in the Genomics England database between March 2016 and July 2019 (Data Release version 9 – 2020–04–02). A total of 38 *NTRK* gene fusion-positive patients were included in Step 1. Patients from the full cohort included in Step 1 (Fig. 2A) who had a diagnosis of a solid malignant tumor within the study period according to NCRAS dataset, and with linked age and sex data available from clinical databases, were eligible to be included in the sub-cohort of patients analyzed in Step 2. In the sub-cohort, patients with *NTRK* gene fusions were matched with patients without *NTRK* gene fusions. Patients who had more than one primary malignancy and those with a hematological malignancy were excluded from this sub-cohort. After applying the inclusion and exclusion criteria, a total of 20 *NTRK* gene fusion-positive patients remained available for matching in Step 2.

4. Statistical analysis

In Step 1, the frequency of *NTRK* gene fusions and patient characteristics were calculated based on the full cohort. In Step 2, patients in the sub-cohort with linked clinical data and *NTRK* gene fusions were matched with patients without *NTRK* gene fusions. We analyzed co-occurrence of the following biomarkers: small variant mutations in *BRAF, EGFR, ERBB2*, and *KRAS*; exon insertions and deletions in *EGFR*; exon insertions in *ERBB2*; fusions involving *ALK* or *ROS1*; tumor mutation burden (TMB); and microsatellite instability (MSI). These biomarkers were selected because in addition to being a part of the *NTRK* signaling pathway and its parallel pathways, they are biomarkers that are either clinically actionable (i.e., with an associated targeted therapy) or of emerging research interest. OS was analyzed between the matched patients.

Descriptive analysis of patient characteristics was conducted. Frequencies were provided for categorical variables, while means, standard deviations, and medians were provided for continuous variables. OS of patients with and without *NTRK* gene fusions was analyzed by the Kaplan–Meier method and Cox regression. Patients were followed up until death or until the ONS data cut-off (Nov 2019). The index date for OS was the date of initial diagnosis of cancer. Patients who were still alive at the ONS data cut-off date were censored at that time.

5. Results

5.1. Patient characteristics

A total of 15,223 cancer patients present in the Genomics England database (Data Release version 9 – 2020–04–02) were included in the analysis. Thirty-eight patients (0.25%) were identified with *NTRK* gene fusions, comprising 11 distinct tumor types per Genomics England database classification. Frequency of *NTRK* gene fusions within these tumor types ranged from 2.44% (brain and CNS childhood cancer) to 0.06% (lung cancer; Table 1A). The most common tumor types reported in patients with *NTRK* gene fusions were breast cancer ($n = 9$), colorectal cancer ($n = 9$), and sarcomas ($n = 7$; Fig. 3).

Among the 38 patients with *NTRK* gene fusions, 66% were female and 34% were male. The median age at diagnosis was 62 (interquartile range [IQR] 43–72) years (Table 1B). In the *NTRK* gene fusion-positive group, fusions occurred more frequently in *NTRK3,* reported in 24 patients (63%), followed by *NTRK2* in eight patients (21%), then *NTRK1* in six patients (16%; Fig. 3). A total of 29 different *NTRK* gene fusion partners were identified (Supplementary Table S1). *NTRK3, −2,* and *−1* were identified with 17, 8, and 4 different fusion partners, respectively. Of the 29 different fusion partners identified, 25 were novel fusions that have not been previously reported in the Quiver database, a curated database of known gene fusions involved in cancer [33].

Of the 15,185 *NTRK* gene fusion-negative patients, 56% were female and 44% were male, with a median age at diagnosis of 65 (IQR 55–73) years (Table 1B). The most common tumor types reported in *NTRK* gene fusion-negative patients were breast cancer (20%), CRC (18%), and lung cancer (10%). These three tumor types make up the largest cohorts in the Genomics England database.

5.2. Survival analysis

Based on the clinical database linkage and data availability, 20

A. Study design

Step 1: Identify and describe the frequency of patients with *NTRK* gene fusions, and their demographic and clinical characteristics at baseline

- Patients who had undergone WGS between March 2016 and July 2019 were included
- Likely functional *NTRK* gene fusions in the genomics database were identified using an algorithm

Inclusion Criteria

- All patients who had undergone tumor WGS in the Genomics England database

Step 2: Create a matched cohort of patients without *NTRK* gene fusions and conduct a comparative analysis of co-occurrence of other biomarkers and OS in patients with and without *NTRK* gene fusions

- Matching was conducted using exact matching for the following baseline variables: primary tumor type (ICD-10), histology, stage at diagnosis, and sex. The MDM method[31] was used for age, year of diagnosis, and CCI[32]
- A 1:4 ratio (*NTRK* gene fusion-positive:*NTRK* gene fusion-negative) was used

Inclusion Criteria

- Patients from Step 1 who had a diagnosis of solid malignant tumor within the study period, and with linked age and sex data available from clinical databases

Exclusion Criteria

- Patients who had more than one primary malignancy and those with a hematological malignancy

B. Patient population for OS analysis and biomarker analysis

Analysis	Patient Population
OS Analysis	
Primary OS Analysis	18 patients that were *NTRK* gene fusion-positive and 72 matched patients that were *NTRK* gene fusion-negative
Sensitivity OS Analysis	31 patients that were *NTRK* gene fusion-positive and 124 matched patients that were *NTRK* gene fusion-negative
Biomarker Analysis	
Primary biomarker analysis	18 patients that were *NTRK* gene fusion-positive and 72 matched patients that were *NTRK* gene fusion-negative
Matched biomarker analysis	31 patients that were *NTRK* gene fusion-positive and 124 matched patients that were *NTRK* gene fusion-negative
Sensitivity biomarker analysis	All 38 patients that were *NTRK* gene fusion-positive, 124 matched *NTRK* gene fusion-negative patients, and an additional 838 randomly selected patients from tumor types observed in the *NTRK* gene fusion-positive cohort

Fig. 2. Study design and patient population for OS analysis and biomarker analysis. Shown is the study design of the study including inclusion and exclusion criteria (A) and patient populations for the OS analysis and biomarker analysis (B). CCI, Charlson comorbidity index; ICD-10, International classification of diseases, tenth revision; MDM, Mahalanobis distance matching.

patients with *NTRK* gene fusions were available for matching in the OS analysis. Following covariate matching of demographic and clinical characteristics using both exact matching and the Mahalanobis distance method, the majority of variables were balanced, with a standardized mean difference for each covariate between −0.1 and 0.1 (Supplementary Fig. S2). A threshold of 0.1 or 0.25 for the Mahalanobis distance represent reasonable cut-offs for matching of baseline covariates [34]. In this study a threshold of 0.1 was used, as an absolute mean difference of <0.1 indicates a negligible difference between groups [35].

Two patients with *NTRK* gene fusions were excluded from the OS analysis as their tumor and histology type were not present in the *NTRK* gene fusion-negative group; therefore, 18 *NTRK* gene fusion-positive patients were matched with 72 *NTRK* gene fusion-negative patients (based on a 1:4 ratio). The median follow-up for OS was 2.01 years (IQR 1.40–2.97) in the *NTRK* gene fusion-positive group and 2.28 years (IQR 1.57–2.98) in the *NTRK* gene fusion-negative group. At the time of the analysis, median OS was not reached for either group (hazard ratio [HR] 1.47 [95% CI 0.39–5.57, $P = 0.572$]; Fig. 4; Table 2). The 12-month OS rate was 94% and 96% in the *NTRK* gene fusion-positive and *NTRK* gene fusion-negative groups, respectively. The difference between the two groups was not statistically significant.

5.3. Biomarkers

In the matched analysis, a *KRAS* mutation was identified in one patient (3.2%) with an *NTRK* gene fusion. In patients without *NTRK* gene fusions, the tested oncogenic drivers were detected in 33 patients (26.6%; Table 3). In the sensitivity analysis, a *KRAS* mutation was identified in two patients (5.3%) with an *NTRK* gene fusion; both patients had hepatopancreatobiliary cancer. In patients without *NTRK* gene fusions, the tested oncogenic drivers were identified in 184 patients (19%): *KRAS* ($n = 112$, 11.6%), *BRAF* ($n = 50$, 5.2%), *ERBB2* ($n = 14$, 1.5%), *EGFR* ($n = 6$, 0.6%), *ALK* ($n = 1$, 0.1%), and *ROS1* ($n = 1$, 0.1%; Table 3). High TMB and MSI were more common in the *NTRK* gene fusion-positive group than the *NTRK* gene fusion-negative group. This appeared to be driven by patients with CRC: of the nine patients with

Table 1
Baseline characteristics.

A.

Tumor type (Genomics England classification)	Total number of patients, *n*	*NTRK* gene fusion-positive patients ($n = 38$)	
		n	%
Childhood – brain and CNS	41	1	2.44
Childhood – other	127	3	2.36
Upper GI	267	2	0.75
Hepatopancreatobiliary	332	2	0.60
Sarcoma	1174	7	0.60
Adult glioma	597	2	0.34
Colorectal	2693	9	0.33
Breast	2983	9	0.30
Bladder	407	1	0.25
Renal	1390	1	0.07
Lung	1560	1	0.06

B.

Characteristics	*NTRK* gene fusion-negative ($n = 15,185$)	*NTRK* gene fusion-positive ($n = 38$)
Age, median (IQR), years	65 (55–73)	62 (43–72)
Sex, *n* (%)		
Male	6659 (44)	13 (34)
Female	8526 (56)	25 (66)
Stage at diagnosis, *n* (%)		
0	93 (1)	0
I	1293 (9)	4 (11)
II	2360 (16)	6 (16)
III	1864 (12)	4 (11)
IV	548 (4)	1 (3)
Missing	9027 (59)	23 (61)
ECOG performance status, *n* (%)		
0	769 (5)	1 (3)
1	423 (3)	1 (3)
≥2	42 (0.3)	1 (3)
Missing	13,951 (92)	35 (92)
Charlson Comorbidity Index		
Mean (SD)	1.3 (1.1)	1.1 (0.9)
Median (IQR)	1.0 (1.0–2.0)	1.0 (1.0–2.0)
Multiple primary malignancies, *n* (%)		
Yes	1494 (10)	6 (16)
No	8393 (55)	19 (50)
Missing	5298 (35)	13 (34)

Frequency of NTRK gene fusions by tumor type (A) and demographics and cancer history (B). GI, gastrointestinal; SD, standard deviation.

CRC, eight (89%) had high TMB and seven (78%) were MSI-high. Similar results can be found in the primary analysis (Supplementary Table S2).

6. Discussion

There is limited information on the natural history and genomic context of TRK fusion cancer. Identifying co-occurring oncogenic drivers in patients with an *NTRK* gene fusion is of particular importance as it may not only help understand the role of an *NTRK* gene fusion as an oncogenic driver in patients harboring these mutations, but also help develop testing strategies to identify patients with *NTRK* gene fusions. Understanding the prognostic effect of *NTRK* gene fusions is a critical component of contextualizing the efficacy of TRK inhibitors observed in single-arm studies in this disease area. This retrospective study investigated the characteristics and OS outcomes of patients with and without *NTRK* gene fusions.

While the median OS was not reached in this study, there was a numerically higher risk of death in patients with *NTRK* gene fusions compared to those without (HR 1.47 [95% CI 0.39–5.57]); however, the difference was not statistically significant. As this is a historic cohort, no patients had received TRK inhibitors, and therefore the findings reported reflect the natural history of tumors with *NTRK* gene fusions under current standard of care. The results from this study are consistent with a recent US study, in which a HR of 1.44 (95% CI 0.61–3.37) in OS was observed [23]. In the absence of TRK inhibitors, the two studies did not find statistically different survival between patients with or without *NTRK* gene fusions, suggesting *NTRK* gene fusion is not a prognostic indicator itself. A strength of this study is that the index date for this analysis was the date of initial diagnosis of cancer, which allowed for OS to be measured from a more uniform time point in the patient journey. Access to advanced molecular diagnostics in the US study may have varied more widely than in the UK Genomics England cohort, which had stricter inclusion criteria. Our sequencing data are more consistent due to the use of comprehensive WGS testing compared to the US study which used NGS with targeted panels that varied over time in *NTRK* gene coverage.

NTRK gene fusions are known to be rare, occurring at frequencies of <1% in common cancer types such as lung cancer, CRC, and breast cancer [9]. This study confirms the rarity of *NTRK* fusions in these tumor types: among patients with lung cancer, only one (0.1%) was reported to have an *NTRK* fusion, and among patients with CRC, *NTRK* gene fusions were reported in nine patients (0.3%). In patients with breast cancer, *NTRK* gene fusions were reported in nine patients (0.3%). Co-occurrence of oncogenic alterations in *ALK, BRAF, EGFR, ERBB2, KRAS,* and *ROS1* was infrequent in patients with *NTRK* gene fusions. This was consistent in both the matched analysis and sensitivity analysis, which was conducted with a larger sample size, thus supporting the hypothesis that *NTRK* gene fusions may be mutually exclusive to other oncogenic drivers [36,37]. The co-occurring biomarkers analyzed were selected for this study based partially on the *NTRK* signaling pathway and its parallel pathways (e.g., signaling into the RAS-RAF axis). It would be of interest to expand the scope of co-occurring mutation interrogation (e.g., CDKN2A/B loss) in future studies.

These results are consistent with other studies based on large populations that evaluated the co-occurrence of *NTRK* gene fusions with known oncogenic drivers [23,24,38]. High MSI and TMB were more frequent in patients with *NTRK* gene fusions and were observed in patients with CRC only. While MSI status and TMB are typically correlated in CRC, around 3% of microsatellite-stable cases were confirmed as high TMB in a recent cohort of patients with CRC, and a typical pattern of aberrations were identified [39]. In the patients with CRC in this analysis, MSI-high frequency among *NTRK* gene fusion-positive patients was 77.8% and among *NTRK* gene fusion-negative patients was 33.3%. This is consistent with current literature indicating that *NTRK* gene fusions are enriched in MSI-high CRC [40–42], a pattern that has been documented at the molecular level [43]. While we did not study the patients with breast cancer in detail, other studies have found a negative correlation of *NTRK* fusion occurrence with HER2 and estrogen receptor status, and also with high TMB/MSI [44].

The main limitation of this study was the small sample size of *NTRK* gene fusion-positive patients in the study cohort. Patient selection was limited to those with sufficient linkage between all data sources; therefore, it was not possible for all the *NTRK* gene fusion-positive patients identified in the database to be included in all aspects of the analysis. Furthermore, there were some limitations with the matching process due to the modest level of data that was available. For instance, Eastern Cooperative Oncology Group performance (ECOG) status was missing in the majority of patients, and *NTRK* gene fusion-positive patients with missing ECOG were matched with *NTRK* gene fusion-negative patients who also had missing ECOG, assuming missing at

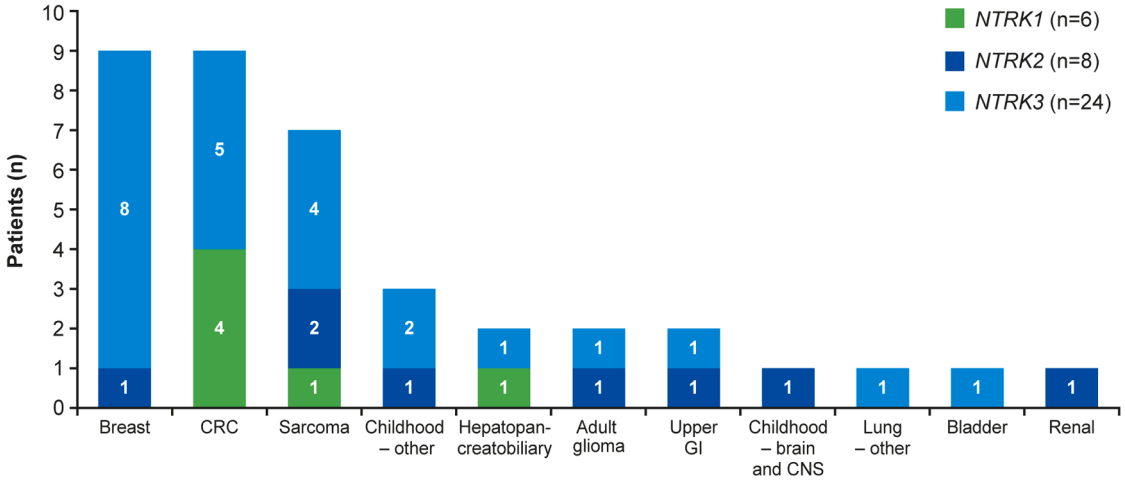

Fig. 3. Distribution of tumor types in the *NTRK* gene fusion-positive group. Shown are the tumor types in the *NTRK* gene fusion-positive group, divided into *NTRK1* (green), *NTRK2* (dark blue), and *NTRK3* (light blue) for each tumor type. GI, gastrointestinal.

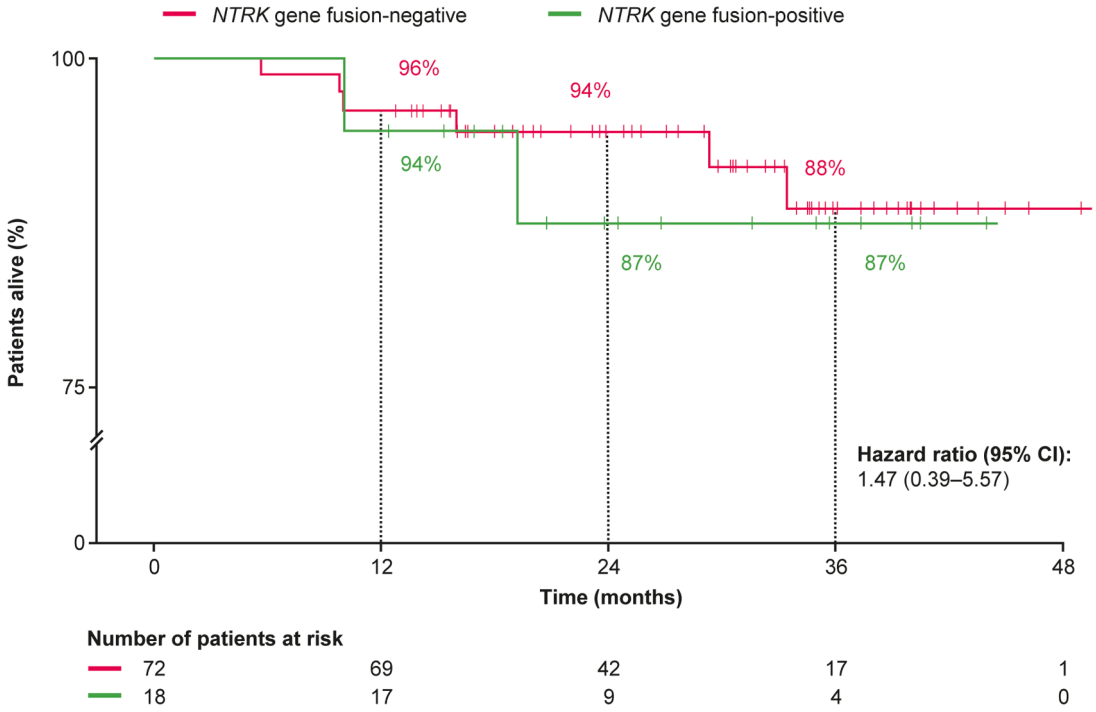

Fig. 4. Kaplan–Meier plot for OS analysis. Shown is the overall survival for both *NTRK* gene fusion-negative and *NTRK* gene fusion-positive patients at 12, 24 and 36 months.

random; this may be a potential source of bias for OS analysis if the assumption does not hold. Another limitation of this study was that while the sequencing algorithm ensured an intact open reading frame was present prior to the call of an *NTRK* gene fusion (see Supplementary Fig. S1 for details), RNA was not available to confirm that the fusions identified here are expressed and are in frame. Analysis of other biomarkers was limited to the six common, actionable biomarkers, and further comprehensive genome profiling analysis is needed. Further studies, with a larger sample size, should be conducted to determine whether there is a difference in survival between *NTRK* gene fusion-positive and *NTRK* gene fusion-negative patients as well as to improve our understanding of this disease.

In the present study, out of the 38 patients that were *NTRK* gene fusion-positive, 24 (63.2%) patients had *NTRK3* fusions, compared to eight (21.1%) with *NTRK2* fusions and six (15.8%) with *NTRK1* fusions. A total of 29 different *NTRK* gene fusion partners were identified, with 25 of those being novel gene partners. These gene partners have not previously been reported in the Quiver database and indicate potentially new mechanisms of action for the *NTRK* fusion events and their role in oncogenesis. Several of these novel genes were partnered with *NTRK3*, which combined with the fact that many DNA-based next-generation sequencing assays use *ETV6* as a surrogate for detecting *NTRK3* fusions, suggests that *NTRK3* fusion events may be under reported [45,46]. Due to the large size of *NTRK3* introns, various NGS platforms utilized *ETV6* as a surrogate for detecting *NTRK3* fusions and, therefore, would not have discovered novel partners because the testing methods were not agnostic to fusion partners, in contrast to the WGS approach used in our study. Other NGS approaches currently used to detect *NTRK* fusions, such as RNA-based technologies, are also agnostic to the fusion partner. Therefore, an increasing number of fusion partners are being discovered.

Table 2
Overall survival.

	Primary analysis		Sensitivity analysis	
	NTRK gene fusion-negative (n = 72[†])	*NTRK* gene fusion-positive (n = 18[†])	*NTRK* gene fusion-negative (n = 124[‡])	*NTRK* gene fusion-positive (n = 31[‡])
Median follow-up (IQR), years	2.28 (1.57–2.98)	2.01 (1.40–2.97)	1.96 (1–3)	1.86 (1–3)
Median OS (IQR), years	NE (NE–NE)	NE (NE–NE)	7.94 (7.52–NE)	7.92 (7.92–8.59)
Landmark OS,% (95% CI)				
1 year	96 (91–100)	94 (84–100)	92 (87–97)	90 (80–100)
2 years	94 (89–100)	87 (71–100)	88 (82–94)	80 (65–98)
3 years	88 (78–99)	87 (71–100)	79 (70–90)	80 (65–98)
HR (95% CI)	1.47 (0.39–5.57)		1.39 (0.59–3.3)	

[†] Only patients with linked clinical data and who were matched were included in the OS analysis. [‡]Sensitivity analysis was conducted to maximize the number of patients included in the analysis and patients were matched according to the source of their diagnostic information.

Table 3
Co-occurrence of biomarkers.

Biomarker, *n* (%)	Matched analysis		Sensitivity analysis	
	NTRK gene fusion-negative n = 124	*NTRK* gene fusion-positive n = 31	*NTRK* gene fusion-negative n = 962	*NTRK* gene fusion-positive n = 38
ALK	1 (0.8)	0	1 (0.1)	0
BRAF	15 (12.1)	0	50 (5.2)	0
EGFR	1 (0.8)	0	6 (0.6)	0
ERBB2/HER2	1 (0.8)	0	14 (1.5)	0
KRAS	15 (12.1)	1 (3.2)[†]	112 (11.6)	2 (5.3)[†]
ROS1	0	0	1 (0.1)	0
TMB high (≥20 mut/mB)	16 (12.9)	8 (25.8)[‡]	55 (5.7)	8 (21.1)[‡]
TMB medium (<20, ≥5 mut/mB)	9 (7.3)	0	109 (11.3)	0
MSI high (≥6)	14 (11.3)	7 (22.6)[‡]	53 (5.5)	7 (18.4)[‡]
MSI low/MSS (<6)	110 (88.7)	24 (77.4)	909 (94.5)	31 (81.6)

[†] Patients had hepatopancreatobiliary cancer.
[‡] All had colorectal cancer. MSS, microsatellite stable.

This is significant progress over older literature where *ETV6*-based screening technologies were used to identify cases and estimate prevalence of fusions [47,48]. We anticipate that in the future, advances in technology may allow all biologically possible partners to be identified. Other actionable fusions of this type (e.g., neuregulin 1 [*NRG1*] fusions) also have this characteristic [49].

Both entrectinib and larotrectinib are approved by the UK National Institute for Clinical Excellence (NICE) and, consequently, *NTRK* fusion has been placed into the national directory [50,51]. We hope this will help expand the existing database of *NTRK* fusion data.

In conclusion, the study did not find a statistically significant difference in survival between the *NTRK* gene fusion-positive and -negative groups, where none of the patients had received TRK inhibitors. The results from the present study suggest that in patients with tumors harboring an *NTRK* gene fusion, co-occurrence of other actionable biomarkers is generally uncommon, except for high-MSI and TMB, which were mainly driven by colorectal cancers [40,41], supporting the hypothesis that *NTRK* gene fusions are the primary oncogenic drivers in tumors that harbor them. This highlights the importance of *NTRK* gene fusions as actionable drug targets and emphasizes the need for widespread adoption of broad panel genomic testing in routine oncology clinical practice. This underscores the potential clinical benefits of TRK inhibitor therapy for patients with TRK fusion cancer.

Funding

This study was funded by Bayer Healthcare Pharmaceuticals, Inc.

Ethics

This research study was conducted retrospectively from data obtained for clinical purposes in accordance with the 1964 Helsinki Declaration and its amendments.

Data availability

The data underlying this publication were provided by Genomics England under contract to Bayer. Requests for access to the data should be sent to the corresponding author.

CRediT authorship contribution statement

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

J. Bridgewater discloses consultancy for Roche, Bayer, Celgene, BMS, Taiho, and Incyte, as well as speakers' fees for Merck Serono and grant/research support from Incyte. X. Jiao, J. Zong, K. Keating, A. Bruno, and M. Fellous are employees of Bayer HealthCare Pharmaceuticals, Inc. M. Parimi and C. Flach are employees of IQVIA. J. Stratford is an employee of RTI International. A. Kamburov and A.A. Schmitz are employees of and hold stock of Bayer AG. J.A. Reeves is an external employee of Bayer HealthCare Pharmaceuticals, Inc. M.B. Pereira is an employee of Genomics England. L. Bazhenova has served on advisory boards for Genentech, AstraZeneca, Boehringer Ingelheim, Takeda, and Blueprint.

Acknowledgements

The authors would like to thank the patients, their families, and all investigators involved in these studies. We would also like to thank Genomics England for their support. This research was made possible through access to the data and findings generated by the 100,000 Genomes Project (https://www.genomicsengland.co.uk/about-genomics-england/the-100000-genomes-project/). The 100,000 Genomes Project is managed by Genomics England Limited (a wholly owned company of the UK Department of Health and Social Care). The 100,000 Genomes Project is funded by the National Institute for Health Research and NHS England. The Wellcome Trust, Cancer Research UK and the Medical Research Council have also funded research infrastructure. The 100,000 Genomes Project uses data provided by patients and collected by the National Health Service as part of their care and support. All local and regional laws on data protection and privacy were adhered to. Medical writing support was provided by Anastasija Pesevska, Pharm D, and editorial and typesetting assistance was provided by George Chappell, MSc, both of Scion (London, UK), supported by Bayer Healthcare Pharmaceuticals, Inc., according to Good Publications Practice guidelines (Link). The Sponsor was involved in the study design, collection, analysis, and interpretation of data, as well as data checking of information provided in the manuscript. However, ultimate responsibility for opinions, conclusions, and data interpretation lies with the authors.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ctarc.2022.100623.

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