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Characteristics and outcomes of patients with *NTRK* fusion-positive (*NTRK*+) metastatic / locally advanced solid tumours receiving non-TRK inhibitor standard of care, and prognostic value of *NTRK* fusions in clinical practice

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BACKGROUND

- *NTRK* gene fusions are oncogenic drivers and therapeutic targets across a large range of tumour types.[1]
- The efficacy and safety of TRK inhibitors (TRKis; e.g. larotrectinib and entrectinib) have been reported, with objective response rates >65% and durable responses.[2–5]
- However, **the clinical characteristics, treatment patterns and outcomes in patients with *NTRK*+ solid tumours under standard-of-care (SoC) therapies are not well known**
  - The rarity of these fusions means that patient populations are small and difficult to enrol in clinical trials.
- **Real-world data** from electronic health record databases can be used to overcome the challenges surrounding limited patient recruitment from single-arm, tumour-agnostic clinical trials.
- We used real-world data to characterise the **profile and overall survival** (OS) of patients with *NTRK*+ versus those with *NTRK*– solid tumours.

METHODS

- Data were extracted from the Flatiron Health / Foundation Medicine clinicogenomic database (FH-CGDB; Flatiron Health, Inc.), a US-wide longitudinal database of routine healthcare practice data, curated through technology-enabled abstraction.

NTRK+ cohort

- De-identified demographic and clinical data were selected from the database for adult patients (≥18 years of age) who had:
  - ≥1 test by next-generation sequencing (NGS on tumour tissue; Foundation Medicine, Inc.) and ≥1 *NTRK*+ test result
  - Locally advanced / metastatic solid tumour diagnosed between 1 Jan 2011 and 31 Dec 2019
  - No prior treatment with entrectinib or larotrectinib in any therapy line
  - No visit gap of >90 days after diagnosis of locally advanced/metastatic disease
  - No prior unlabelled study drug as part of a clinical trial.
- *NTRK* positivity was defined by the presence of a fusion or rearrangement involving *NTRK1/2/3* with predicted known/likely functional status.

Matched *NTRK*– cohort

- *NTRK*– patients from the database were matched 10:1 to *NTRK*+ patients based on tumour type and nearest neighbour propensity score matching model
  - The propensity score was developed by logistic regression with preselected prognostic variables: age; smoking status; practice type; number of lines of therapy since diagnosis; stage at diagnosis; reported time between diagnosis and NGS test; co-alterations.

Objectives and outcomes

- Patient demographics and clinical characteristics were analysed descriptively.
- OS was derived for the *NTRK*+ and matched *NTRK*– cohorts and also estimated for the overall (non-matched) *NTRK*– cohort.
- OS was calculated from two index dates corrected by time from diagnosis of locally advanced (not amenable to radical therapy)/metastatic disease to NGS test reporting, to account for left truncation due to differences in the timing of cohort eligibility:
  - i) locally advanced / metastatic / recurrent disease diagnosis;
  - ii) start of last available treatment line before NGS report.
- The prognostic value of the *NTRK* fusion biomarker was evaluated via univariate Cox proportional hazard model.

Co-alterations

- Selected co-alterations assessed included: *ALK* fusions, *ROS1* fusions, *RET* fusions, *EGFR* L858R mutation, *EGFR* acquired T790M mutation, *EGFR* exon19 deletion, *BRAF* V600E mutation, *BRAF* V600K mutation, *MET* exon14 mutation, *KRAS* G12 mutation, and *KRAS* G13 mutation.
- Tumour mutational burden (TMB) and microsatellite instability (MSI) were also assessed
  - High TMB (TMB-H) was defined as ≥20 mutations per Mb and low TMB as <6 mutations per Mb.

Sensitivity analyses

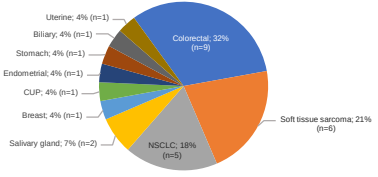
- The robustness of the main analysis on the prognosis of the *NTRK*+ cohort was tested using different matching ratios and evaluating differences between the results.
- Selected co-alterations prior to propensity score matching were restricted in the *NTRK*+ and the *NTRK*– cohorts; a matching model allowing for co-alterations in both cohorts was also derived.

RESULTS

Characteristics of patients in the *NTRK*+ cohort

- 58,001 patients with solid tumours from the database were eligible. Of these, 28 had *NTRK*+ locally advanced/metastatic solid tumours that matched the eligibility criteria.
- **10 different *NTRK*+ tumour types** were identified; the most common were colorectal cancer (32%), sarcoma (21%), and non-small cell lung cancer (NSCLC; 18%) (Fig. 1).
- 82% of patients had a fusion involving *NTRK1*; the most common *NTRK1* fusion partners were ***TPM3* (26%)** and ***LMNA* (22%)**.
- The mean (SD) time from diagnosis of locally advanced/metastatic disease to reported NGS test result was **151.21 (245.20) days**.

Figure 1: Tumour types identified in the *NTRK*+ cohort (N=28)



CUP, cancer of unknown primary; NSCLC, non-small cell lung cancer

- Co-alterations were rare in the *NTRK*+ cohort: two patients presented a co-mutation (*EGFR* L858R and *KRAS* G12); 5/18 MSI-evaluable patients were categorised as MSI-high; 6/16 TMB-evaluable patients were classified as TMB-high.

Patient characteristics in the *NTRK*+ versus *NTRK*– cohorts

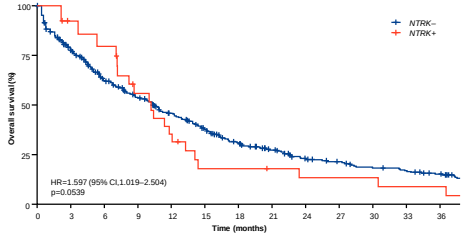
- The overall unselected *NTRK*– population comprised 24,903 patients, and the matched *NTRK*– cohort consisted of 280 patients.
- **Table 1** presents patient characteristics for the three populations.
- Although the differences were not significant, compared with the unselected *NTRK*– cohort, patients in the *NTRK*+ cohort:
  - tended to be **younger**;
  - were more commonly **non-smokers**;
  - were **less frequently** diagnosed with **stage III–IV** disease;
  - had a **shorter time from diagnosis** of locally advanced/metastatic disease to a reported NGS test;
  - had a lower frequency of ***KRAS*** mutations, but **a higher frequency of high TMB and high MSI** (although the testing frequency differed between the two cohorts).
- Variables were generally **balanced** between the *NTRK*+ and the matched *NTRK*– cohorts.

Table 1: Patient characteristics for the unselected and matched *NTRK*– cohorts and the *NTRK*+ cohort

Characteristic	Unselected *NTRK*– patients (N=24,903)	Matched *NTRK*– patients (N=280)	*NTRK*+ patients (N=28)
Age ≥65 years, %	49.6	43.9	39.3
No history of smoking, %	40.5	54.6	57.1
ECOG performance status, %			
0–1 / 2–4 / Unknown	49.7 / 12.1 / 38.1	45.0 / 11.4 / 43.6	50.0 / 7.1 / 42.9
Practice type, %			
Academic / Community	11.4 / 88.6	18.9 / 81.1	14.3 / 85.7
Lines of therapy from diagnosis to NGS report, %			
0–2 / ≥3 / Unknown	68.0 / 19.4 / 12.6	70.0 / 10.4 / 19.6	71.4 / 10.7 / 17.9
Stage at initial diagnosis, %			
0–II / III–IV / Unknown	17.8 / 72.0 / 10.2	16.8 / 66.8 / 16.4	17.9 / 64.3 / 17.9
Brain metastases, %			
Yes / No or Unknown	10.6 / 89.4	4.6 / 95.4	17.9 / 82.1
Metastatic / advanced diagnosis to NGS report, %			
Mean (SD), days	272.10 (446.92)	158.95 (371.16)	151.21 (245.20)

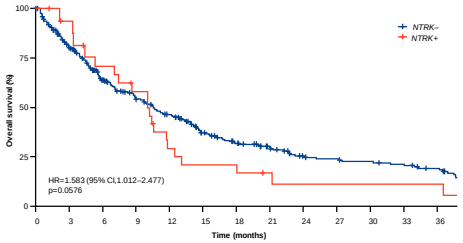
NGS, next-generation sequencing; *NTRK*+, *NTRK* fusion-positive; *NTRK*–, *NTRK* fusion-negative; SD, standard deviation.

Figure 2: OS from time of metastatic/locally advanced diagnosis index date, for the *NTRK*+ vs. the matched *NTRK*– cohorts



Risk set adjusted for left truncation. Due to immortal time bias, not all patients entered the risk set at t0.
HR, hazard ratio; *NTRK*+, *NTRK* fusion-positive; *NTRK*–, *NTRK* fusion-negative

Figure 3: OS from last line of therapy before NGS test report index date, for the *NTRK*+ vs. the matched *NTRK*– cohorts



Risk set adjusted for left truncation. Due to immortal time bias, not all patients entered the risk set at t0.
HR, hazard ratio; *NTRK*+, *NTRK* fusion-positive; *NTRK*–, *NTRK* fusion-negative

Survival outcomes

- When diagnosis was used as the index date (Fig. 2):
  - Median OS was rather poor (**10.2 months**; 95% CI, 7.2–14.1) in ***NTRK*+** patients and similar (**10.4 months** [95% CI, 6.7–14.3]) in the matched ***NTRK*–** cohort
  - HR: 1.6 (95% CI, 1.0–2.5)
  - This difference was not significant.
- Similar results were seen when using last line of therapy before NGS test report as the index date (Fig. 3):
  - Median OS was **10.1 months** (95% CI, 7.1–13.1) in ***NTRK*+** patients and **10.5 months** (95% CI, 8.6–13.9) in matched ***NTRK*–** patients
  - HR: 1.6 (95% CI, 1.0–2.5)
  - This difference was not significant.

Sensitivity analyses

- Reanalysis of the prognosis for patients in the *NTRK*+ cohort using matching ratios from 1:1 to 1:10, showed model stabilisation starting after a minimum ratio of 1:6, which appeared to fully stabilise at a ratio of 1:10.
- When patient matching was done regardless of the co-alteration profile, OS for the *NTRK*– cohort was numerically shorter than in the main analysis (9.3 months; 95% CI 5.8–12.4) but the HR point estimate was not substantially changed (HR 1.5; 95% CI, 1.0–2.4)
  - When using a more restrictive matching (i.e. not allowing for any selected alterations in the initial *NTRK*– cohort), OS was slightly improved at 9.9 months (95% CI, 6.3–13.8)
  - The HR point estimate for this sensitivity analysis remained unchanged (HR 1.5; 95% CI, 1.0–2.5).

CONCLUSIONS

- In these TRKi-naïve patients with solid tumours treated with non-TRKi SoC, *NTRK* fusions were associated with a **poor OS** that was similar to that of matched patients who do not harbour these fusions.
- This suggests that **SoC therapies provide equally unsatisfactory OS outcomes** in *NTRK*+ and *NTRK*–patients.
- Together with clinical efficacy and tolerability results from TRKi trials in NTRK+ solid tumours, these data suggest that **currently approved TRKis**, such as entrectinib, **are likely to achieve improved outcomes over SoC** in this population.

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