Systematic review of neurotrophic tropomyosin-related kinase inhibition as a tumor-agnostic management strategy

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Aim: To conduct a systematic review and meta-analysis feasibility of clinical, quality of life and economic evidence for neurotrophic tropomyosin-related receptor tyrosine kinases (*NTRK*) inhibitors in patients with *NTRK* gene fusion-positive tumors. **Materials & methods:** Databases were searched for studies on *NTRK* inhibitors in adult and pediatric patients. **Results:** 27 publications reported clinical data for seven interventions. Efficacy/safety data were available for two interventions only. Four trials each reported data for larotrectinib and entrectinib with pooled analyses reporting objective response rates of 75% (95% CI: 61–85) and 57.4% (43.2–70.8), respectively. No publications reported economic or quality of life evidence. **Conclusion:** Preliminary data demonstrate that *NTRK* inhibitors are well tolerated and show impressive clinical benefit; corroboration of existing studies and real-world data are required.

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Tumor-agnostic therapy, whereby treatment is tailored to match specific gene alterations regardless of tumor location is becoming increasingly common [1]. The introduction of biomarkers into drug development has led to multiple new challenges stretching from the implementation of biomarker screening approaches to the development of appropriate market access reimbursement strategies. One such set of biomarkers are gene fusions involving the neurotrophic tropomyosin-related kinases (*NTRK*).

Fusions in the *NTRK1*, *NTRK2* and *NTRK3* genes, which are thought to be present in up to 1% of all solid tumors, are found in a wide range of adult and pediatric tumor types [2,3]. The genes encode neurotrophic tyrosine kinase receptors (TRK, or tropomyosin-related receptor tyrosine kinases) TRKA, TRKB and TRKC, which in a normal state contribute to neuronal development, function, survival and proliferation during childhood and into adulthood. However, in a rearranged state, fusions may activate signal transduction leading to oncogenesis [4]. TRK fusions resulting from *NTRK1/2/3* genetic alterations drive oncogenic transformations in more than 20 different malignancies over diverse tissue/cell lineages, in both the pediatric and adult populations [5]. These *NTRK* fusions provide novel therapeutic anticancer targets and several Phase I and II trials of ‘tumor-agnostic’ tropomyosin-related receptor tyrosine kinase inhibitors (TKI) are ongoing to assess their potential clinical effectiveness in patients with tumors harboring *NTRK* gene fusions [6]. Several TKIs with varying degrees of activity against TRKA, TRKB and/or TRKC are available, which can broadly be grouped into multikinase inhibitors with activity against a range of targets including TRK or more selective TRK inhibitors [7]. The multikinase inhibitor group includes entrectinib, repotrectinib (formally known as ropotrectinib), cabozantinib, merestinib, MGCD516, PLX7486, DS-6051b and TSR-011 [2]. Larotrectinib and entrectinib both selective TRK inhibitors have recently been granted accelerated approval from the US FDA as tumor-agnostic therapies [8,9]. Due to the rarity of *NTRK* fusions in single tumor types, nonrandomized controlled trial (RCT) study designs such as basket trials, whereby the effect of one drug on

a single mutation in a variety of tumor types is considered, are more commonplace. This leads to challenges when seeking reimbursement where RCT study designs are favored by health technology assessment (HTA) bodies.

In order to identify patients who would benefit from TKI therapy, several methods of detecting TRK fusions in cancer are currently in use. Initially, most fusions were detected by fluorescence *in situ* hybridization probes, which is a rapid and relatively inexpensive method to identify TRK fusions and appears to be highly specific in tumor histologies with a high incidence of TRK fusion. More recently, clinical grade next-generation sequencing has been employed to detect TRK fusions [10].

The aim of the current systematic review is to provide a summary of published evidence for the currently available TRK-targeted agents. End points considered for inclusion were clinical, economic, quality of life (QoL) and cost/resource use outcomes. On completion of the clinical systematic review, the feasibility of conducting meta-analyses to allow a quantitative comparison of TRK-targeted agents for outcomes of interest was conducted.

Materials & methods

Systematic literature searches were performed in October 2018 (to identify clinical, economic evaluation and QoL publications) and in January 2019 (to identify cost/resource use publications) in adherence with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [11]. Subject headings and keywords were used to identify English language publications reporting on the use of TRK-targeted agents with no restriction on solid tumor type in the following electronic databases: Medline®, Medline® Epub Ahead of Print (In-Process & Other Non-Indexed Citations), Embase and EBM Reviews. Additional searches of congress proceedings from the past 3 years, reference lists of included publications, relevant HTA bodies and clinical trial registries were conducted to identify relevant evidence. Eligibility criteria included clinical studies of any design (with the exception of single-patient case reports), economic evaluations, QoL studies or cost/resource use studies conducted in patients (adults or pediatric patients) with *NTRK*-fusion-positive solid tumors. Interventions of interest (clinical and economic evaluation systematic reviews only) were restricted to the following TKIs currently studied in this indication: entrectinib, larotrectinib, ropotrectinib, cabozantinib, LOXO-195, ONO-7579, sitravatinib and merestinib. Records were reviewed based on title and abstract in the first instance, and those included were reviewed based on the full publication. Records were reviewed by an analyst and independently checked by a second analyst, with any discrepancies resolved by consensus. This procedure complies with HTA guidelines for conducting a robust systematic review [12]. Quality (risk of bias) assessment of primary studies published as a full article was conducted using a quality appraisal checklist, as recommended by the National Institute for Health and Care Excellence (NICE) for the assessment of quantitative intervention studies [13].

Full details of the eligibility criteria and the electronic database search strategies are provided as Supplementary data.

A meta-analysis feasibility assessment was conducted using data from the identified publications to ascertain whether it was possible to generate indirect estimates of relative treatment effects across the TRK-targeted agents in all-comers, stratified by tumor type. Outcomes of interest included overall survival (OS), progression-free survival (PFS) and objective response rate (ORR). The feasibility included an assessment of heterogeneity across the studies included in the outcome-specific networks in terms of differences in study design and enrolled patient characteristics.

Results

Study inclusion & characteristics

The electronic database search to identify clinical, economic evaluation and QoL publications (October 2018) identified a total of 3244 articles. After the removal of 599 duplicates, 2645 articles were screened by title and abstract. In total, 2565 articles were excluded, and 80 articles were deemed potentially relevant. After the review of the full publications, a further 39 articles were excluded and 19 single-patient case reports were tagged. Handsearching identified a further five relevant clinical studies and therefore a total of 27 relevant clinical studies were eligible for inclusion in the systematic review [14–40]. No relevant economic evaluations or QoL studies were identified (Figure 1). The electronic database search to identify cost and resource use publications (January 2019) retrieved a total of 183 articles for screening on the basis of title and abstract (following removal of a single duplicate). However, no relevant cost/resource use studies (in any territory) were identified (Figure 2).

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flow diagram for clinical, economic evaluation, quality of life systematic review.

QoL: Quality of life.

Clinical studies

The 27 publications reporting on clinical studies that met the inclusion criteria for the systematic review were associated with seven relevant interventions [14–40]. All clinical studies were of a single-arm trial design. The largest published evidence base was available for larotrectinib where 14 publications (reporting on four unique

Figure 2. Preferred reporting items for systematic reviews and meta-analyses flow diagram for cost/resource use systematic review.

studies) were identified [15,20,21,27–34,37,38,40], followed by entrectinib with seven publications (of four unique trials) [16–19,25,26,35]. There was a general paucity of data for other targeted agents with only two publications reporting on belizatinib and one each for LOXO-195 [22], cabozantinib [23], repotrectinib [24] and sitravatinib (MGCD516) [14]. Clinical efficacy/safety data were only available for three interventions: larotrectinib [15,20,21,27–34,37,38,40], entrectinib [16–19,25,26,35] and repotrectinib (Table 1 [24] & Supplementary information) with only early-stage pharmacokinetic and dose-finding data being reported for the other interventions [14,22,23,24].

Larotrectinib

Four trials reported data for larotrectinib in patients with *NTRK* mutations: NCT02122913 (Phase I) [15,21,29,30,32,34,40,41], SCOUT (NCT02637687; Phase I/II) [21,27,28,30–34,38,40], NAVIGATE (NCT02576431; Phase II) [20,21,30,32,34,40], NCT03025360 (expanded access program) [37]. At the time of the review, a fifth trial (MATCH, NCT03213704; Phase II) was recruiting pediatric patients and therefore no results were available. Of the five trials, two exclusively enrolled patients with *NTRK*-fusion-positive solid tumors (NAVIGATE and NCT03025360) and the other three recruited patients with a range of mutations (i.e., not limited to *NTRK*-

Table 1. Published pooled analyses of clinical trials investigating the efficacy and safety of TRK-targeted agents in patients with *NTRK* gene fusions.

Study, study design	Patient population	No. of participants (no. with <i>NTRK</i> fusion)	Outcome data reported for <i>NTRK</i> fusion population	Ref.
Larotrectinib				
Pooled analysis (NCT02122913, SCOUT and NAVIGATE)	<i>NTRK</i> fusion patients with RECIST measurable disease enrolled to the adult (NCT02122913, n = 8) and pediatric (SCOUT, NCT02637687, n = 12) Phase I trials and adult/adolescent Phase II trial (NAVIGATE, NCT02576431, n = 35)	55 (55)	<ul style="list-style-type: none"> • ORR, 75% (95% CI: 61–85)[†] • ORR, 80% (95% CI: 67–90)[‡] <p>After 1 year:</p> <ul style="list-style-type: none"> • 71% were still alive <p>Safety</p> <ul style="list-style-type: none"> • Most AEs were Grade 1/2 and reversible • Most common Grade 3, Grade 4, any treatment-related AEs: <ul style="list-style-type: none"> • Increased ALT or AST level, 5, 0, 38% • Dizziness, 2, 0, 25% • Nausea, 2, 0, 16% • Anemia, 2, 0, 9% • Decreased neutrophil count, 2, 0, 9% • Fatigue, 0, 0, 16% • Constipation, 0, 0, 16% • Weight gain, 0, 0, 11% • Treatment-related AEs leading to <ul style="list-style-type: none"> • Dose reduction, 15% • Discontinuation in patients with response to treatment, 0% • No Grade 4 or 5 treatment-related events occurred <p>Subgroup results from the analysis were also reported for the type of tumor (thyroid and salivary gland and GI tumors)</p> <p>An additional 19 children and 25 adults (age range, 0.1–78 years) with TRK fusion cancer were subsequently enrolled in the NCT02122913, SCOUT and NAVIGATE trials after the primary analysis set. In the 35 evaluable patients with a median follow-up of 5.5 months:</p> <ul style="list-style-type: none"> • Median DoR not been reached • 88% of responses were ongoing at 6 months, consistent with the primary analysis set (above) 	[21,32]
Entrectinib				
Pooled analysis of ALKA-371-001 and STARTRK-1	Cohort of patients with tumors harboring <i>NTRK1/2/3</i> , <i>ROS1</i> or <i>ALK</i> gene fusions, naive to prior TKI treatment targeting the specific gene, and who were treated at doses that achieved therapeutic exposures consistent with the recommended Phase II dose	119 (8)	It is reported that in three patients with <i>NTRK1/2/3</i> -rearranged advanced solid tumors with RECIST-measurable disease, the ORR was 100% (95% CI: 44–100).	[26]
Pooled analysis of ALKA-371-001, STARTRK-1 and STARTRK-2	Adult patients with advanced/metastatic <i>NTRK</i> -fusion-positive solid tumors (ten tumor types, >19 histopathology types), including patients with baseline CNS metastases	54 (54)	<p>After 15.5 months follow-up:</p> <ul style="list-style-type: none"> • BICR ORR, 57.4% (95% CI: 43.2–70.8) • CR, n = 4 (7.4%) • Median BICR DoR: 10.4 months (95% CI: 7.1–NR) • Median BICR PFS: 11.2 months (95% CI: 8.0–14.9) <ul style="list-style-type: none"> • 12.0 months (95% CI: 8.7–15.7; patients without CNS disease) • 7.7 months (95% CI: 4.7–NR; patients with CNS disease) • Median OS: 20.9 months (95% CI: 14.9–NE) <p>Safety population (n = 355)</p> <ul style="list-style-type: none"> • Most AEs were Grade 1/2 and reversible • Most common Grade 1/2: <ul style="list-style-type: none"> • Dysgeusia, 41.1% • Fatigue, 25.1% • Constipation, 23.4% • Diarrhoea, 23.4% • Dizziness, 24.8% • Peripheral edema, 13.8% • Most common Grade 3: <ul style="list-style-type: none"> • Weight gain, 5.1% • Anemia, 4.5% • Fatigue, 2.8% • Treatment-related AEs leading to <ul style="list-style-type: none"> • Dose reduction, 27.3% • Dose interruption, 25.4% • Discontinuation from treatment, 3.9% • No Grade 5 treatment-related events occurred 	[17]

†Independent review.

‡Investigator assessment.

AE: Adverse event; BICR: Blinded-independent central review; CR: Complete response; DoR: Duration of response; GI: Gastrointestinal; NE: Not evaluable; NR: Not reported; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; RECIST: Response evaluation criteria in solid tumors.

fusion-positive solid tumors) with patients with *NTRK*-fusion-positive solid tumors representing a proportion (ranging from 2 to 71%) of the total study populations. The results available across these individual studies for patients with *NTRK* fusion tumors are limited both in terms of end points reported and the number of patients included; a single patient (out of 41 patients in the trial; NCT02122913), six patients (NCT03025360) or 17 patients (out of 24 patients in the trial; SCOUT). However, a pooled analysis of patients with *NTRK*-fusion-positive tumors from the single-arm studies conducted in adult (NCT02122913), pediatric (SCOUT) and mixed adolescent and adult (NAVIGATE) populations has been reported across multiple publications [21,32] and includes subgroup data for patients with a gastrointestinal malignancy [34] and for patients with thyroid and salivary gland cancers [40] (data shown in [Supplementary information](#)). The pooled analysis of the NCT02122913, SCOUT and NAVIGATE studies ([Table 1](#)) represents the most comprehensive dataset available for larotrectinib-treated tumor patients ($n = 55$, including one patient with CNS metastases) and it reports an ORR of 75% (95% CI: 61–85) and 80% (95% CI: 67–90) as assessed by independent review and investigator assessment, respectively [21]. After 1 year, 71% of responses were on-going, 55% of patients remained progression free and 90% of patients were still alive. In a second phase of this pooled analysis, 44 patients were subsequently added after the primary analysis set and after 5.5 months although the median duration of response (DoR) has not been reached, 88% of responses were ongoing [32].

Larotrectinib was also well tolerated as adverse events (AEs) as clinically significant AEs were uncommon, with the majority (93%) of all the AEs being of Grade 1 or 2 [21]. Few AEs of Grade 3 or 4, regardless of attribution, were observed. The most common were anemia (in 11% of the patients), an increase in the ALT or AST level (in 7%), weight increase (in 7%) and a decrease in the neutrophil count (in 7%). No Grade 4 or 5 events were considered by the investigators to be related to treatment, and no treatment-related Grade 3 AEs occurred in more than 5% of the patients. Treatment-related AEs that lead to dose reduction occurred in 15% of patients and no patients who had a response discontinued larotrectinib because of an AE.

Entrectinib

Four trials were identified that reported the efficacy entrectinib in patients with *NTRK*-fusion-positive solid tumors: ALKA 372–001 (EudraCT 2012-000148-88; Phase I) [16,17,26], STARTRK-1 (NCT02097810; Phase I) [17,26,35], STARTRK-NG (NCT02650401; Phase I) [18,19] and STARTRK-2 (NCT02097810; Phase I) [17,25]. All entrectinib studies included patients with multiple fusion-driven solid tumors (i.e., not limited to *NTRK*-fusion-positive solid tumors) with patients with *NTRK*-fusion-positive solid tumors representing a small proportion of the total study populations (ranging from 1.9% in ALKA 372–001 [EudraCT 2012-000148-88] [16,17,26] to 25% in STARTRK-2 [NCT02097810] [17,25]; data shown in [Supplementary information](#)). The studies reported limited outcome data specifically for the subpopulation of patients with *NTRK*-fusion-positive solid tumors; however, a recently published abstract reported a pooled analysis of patients with *NTRK*-fusion-positive tumors from the single-arm studies conducted in adult populations identified as part of the systematic review (STARTRK-2, STARTRK-1 and ALKA-371-001) [17]. The pooled analysis provides outcome data for a total of 54 *NTRK*-fusion-positive tumor patients including 12 patients with CNS metastases receiving entrectinib who were followed-up for a duration of 15.5 months and this analysis represents the most comprehensive dataset available for entrectinib-treated tumor patients ([Table 1](#)) [17]. After 15.5 months of follow-up, an ORR of 57.4% (95% CI: 43.2–70.8) assessed by blinded independent central review (BICR) was reported and a complete response (CR) was observed in four patients (7.4%). The median DoR (by BICR) was 10.4 months (95% CI: 7.1–NR) and the median OS was 20.9 months (95% CI: 14.9–not reported). The overall median PFS (as assessed by BICR) was 11.2 months (95% CI: 8.0–14.9), which was longer than in patients with CNS disease (7.7 months [95% CI: 4.7–NR]), but slightly less than patients without CNS disease (12.0 months [95% CI: 8.7–15.7]).

In the pooled analyses of the entrectinib trials, the overall safety population consisted of 355 patients with the *NTRK*-fusion-positive safety population including 68 patients [17]. Most AEs were Grade 1/2 and reversible with the most common being dysgeusia (41.1% in the overall and 47.1% in the *NTRK*-fusion-positive population), followed by fatigue (25.1 and 27.9%), constipation (23.4 and 27.9%), diarrhea (23.4 and 27.9%), dizziness (24.8 and 23.5%) and peripheral edema (13.8 and 23.5%) in the overall and *NTRK*-fusion-positive population, respectively. The most common Grade 3 AEs were weight gain (5.1% in the overall and 10.3% in the *NTRK*-fusion-positive population), followed by anemia (4.5 and 11.8%) and fatigue (2.8 and 7.4%) in the overall and *NTRK*-fusion-positive population, respectively. In the overall safety population treatment-related AEs that lead to dose reduction occurred in 27.3%, dose interruption in 25.4% and discontinuation from treatment occurred in

3.9% of patients. No Grade 5 treatment-related events were observed. Treatment-related AEs in the *NTRK*-fusion-positive safety population were consistent with the overall safety population.

Repotrectinib

Clinical data relating to repotrectinib were reported in a single clinical study in patients with advanced solid tumors harboring *ALK*, *ROS1* or *NTRK1-3* rearrangements (NCT03093116; TRIDENT-1). The trial enrolled seven evaluable *NTRK*-fusion-positive patients, but outcome data were limited and generally related to single patients [24].

Current evidence for other treatments

Data on other treatments were limited. Two publications reported the baseline characteristics and study design of a Phase I/IIa open-label trial assessing the efficacy and safety of oral belizatinib in patients with advanced solid tumors and lymphomas (NCT02048488) [30,33]. Preliminary dose-finding results from these studies were published as an abstract in 2014 [36] and an update on the enrolled patients with an *ALK*⁺ mutation was published in 2015 [42]. One publication reported on the efficacy of LOXO-195 in two patients with TRK-fusion-positive cancers who developed acquired resistance mutations to larotrectinib. Treatment with LOXO-195 led to rapid tumor responses and extended the overall duration of disease control achieved with TRK inhibition in both patients [22]. A single publication reported results from a trial on the efficacy of cabozantinib (NCT01639508) with participants divided into three groups based on their gene fusion: tumors with a *RET* fusion; tumors with an *NTRK* fusion, or *MET* or *AXL* overexpression, amplification or mutation; and tumors with a *ROS1* fusion. Only data from patients whose tumors have a *RET* fusion have been published to date [19]. Preliminary data from a Phase Ia clinical trial assessing sitravatinib (MGCD516) in patients with non-small-cell lung cancer with genetic alterations in *MET*, *AXL*, *RET*, *TRK*, *DDR2*, *KDR*, *PDGFRA*, *KIT* or *CBL* (NCT02219711) indicate favorable pharmacokinetic characteristics, on-target pharmacodynamic effects and treatment was associated primarily with constitutional or GI-related AEs [14].

A number of ongoing early-phase trials using targeted agents for the treatment of *NTRK*-fusion-positive tumors were identified through searching of clinical trial websites, and although preclinical results are available, there are as yet no published reports of trial efficacy or safety. Merestinib (LY2801653) is being evaluated in patients with advanced non-small-cell lung cancer with a *MET* exon 14 mutation or patients with advanced cancer harboring an *NTRK1/2/3* rearrangement in a trial that is expected to complete by March 2024 (NCT02920996). Two clinical trials were identified that examined the safety and efficacy of DS-6051b in patients with advanced solid malignant tumors harboring either a *ROS1* or *NTRK* fusion gene (NCT02279433 and NCT02675491), which were estimated to complete by March 2019 and November 2019, respectively. The safety and pharmacokinetics of PLX7486 was assessed in a Phase I, open-label study in patients with solid tumors harboring *NTRK*-fusion mutations, who reported tumor progression following standard therapy, had treatment-refractory disease, or for whom there was no effective standard therapy (NCT01804530). This trial was expected to complete in early 2018, however, no results have been published to date.

Quantitative analysis of clinical data

On completion of the systematic review, a meta-analysis feasibility assessment was conducted to ascertain whether a robust comparison of relative treatment effects for TRK-targeted agents for outcomes of interest and restricted to specific tumor types was possible. The assessment of single-arm studies relies on naive indirect comparisons and it is generally recommended that such comparisons are avoided due to the susceptibility of bias [43]. In the current project, naive indirect comparisons were technically ‘feasible’ using data from the published pooled analyses for entrectinib and larotrectinib for the outcome of ORR only [17,21,32]. However, the data for entrectinib [17] were based on adult populations versus the data for larotrectinib [21,32], which were based on a mixed pediatric and adult population and there were substantial differences in follow-up period between the analyses (15.5 months vs 1 year, respectively). An unanchored matching adjusted indirect comparison analysis was not feasible for specific tumor types due to the small-sample size of the available entrectinib (54 patients across ten different tumor types, 12 patients with CNS metastases) and larotrectinib (55 patients across 12 different tumor types, one patient with CNS metastases) datasets (Table 2). After completion of the full feasibility assessment, it was concluded that a robust meta-analysis comparing entrectinib and larotrectinib was not feasible due to small-sample size and heterogeneity between the patient populations.

Table 2. Baseline characteristics of patients with *NTRK* gene fusions from pooled analyses for larotrectinib and entrectinib clinical trials.

Study	No. with <i>NTRK</i> fusion	Age, years, median (range)	Sex, male/female	ECOG performance status, n (%)	Prior systemic therapies, n (%)	No. with CNS metastases	Tumor type, n (%)	Ref.
Larotrectinib								
Pooled analysis (NCT02122913, SCOUT and NAVIGATE)	55	45 (0.3–76.0)	29/26	0, 24 (44%) 1, 27 (49%) 2, 4 (7%) Unknown, 0	0–1, 27 (49%) 2, 9 (16%) ≥3, 19 (35%)	1	Salivary gland, 12 (22%) Soft tissue sarcoma, 11 (20%) Infantile fibrosarcoma, 7 (13%) Thyroid, 5 (9%) Colon, 4 (7%) Lung, 4 (7%) Melanoma, 4 (7%) GIST, 3 (5%) Cholangiocarcinoma, 2 (4%) Appendix, 1 (2%) Breast, 1 (2%) Pancreas, 1 (2%)	[21,32]
Entrectinib								
Pooled analysis of ALKA-371-001, STARTRK-1 and STARTRK-2	54	57.5 (21–83)	22/32	NR	0, 20 (37%) 1, 11 (20.4%) ≥2, 23 (42.6%)	12	Soft tissue sarcoma, 13 (24%) Thyroid, 5 (9%) Colon, 4 (7%) Lung, 10 (19%) Cholangiocarcinoma, 1 (2%) Breast, 6 (11%) Pancreas, 3 (6%) Neuroendocrine, 3 (6%) Gynaecological, 2 (4%) MASC, 7 (13%)	[17]

ECOG: Eastern Cooperative Oncology Group; GIST: Gastrointestinal stromal tumor; MASC: Mammary analogue secretory carcinoma; NR: Not reported; NSCLC: Non-small-cell lung cancer; *NTRK*: Neurotrophic tyrosine kinase.

Economic evaluation, QoL & cost/resource use studies

No publications were identified that reported economic evaluations or QoL or cost/resource use data in patients with *NTRK*-fusion-positive solid tumors. Although a small number of conference abstracts were identified, which discussed the economics of genetic tests (e.g., next-generation sequencing or sequential single-gene testing) to detect genomic alterations in patients, such studies were not focused specifically on the detection of *NTRK* mutations, therefore, did not meet the criteria for inclusion in the systematic review [44,45].

Discussion

This systematic review identified a general paucity of data regarding TRK-targeted agents. Despite a total of 19 single-arm clinical studies examining ten unique interventions to treat patients with *NTRK*-fusion-positive tumors, clinical data were only available for three interventions: entrectinib, larotrectinib and repotrectinib [15–38] and no evidence was identified for economic evaluation, QoL and cost/resource use outcomes for these tumors. Clinical research in this indication is in its early stages and much of the data on clinical efficacy and safety have been reported in single-patient case reports [46–64]. However, despite a lack of data, the initial results for TRK-targeted agents have been encouraging with agents showing promising efficacy and favorable safety profiles in Phase I trials although these data require further corroboration from an expansion of the current published evidence base and the addition of ‘real world’ data as observed in routine clinical practice. The paucity of published economic evaluations, cost/resource use data or QoL specific to the *NTRK* indication is not surprising, primarily due to the low prevalence of the disease.

Quantitative synthesis remains a challenge in a tumor-agnostic setting. As *NTRK* fusions are only expressed in up to 1% of all solid tumors [2,3], there are inherent difficulties in assessing the efficacy of interventions in the rare tumor types, which exhibit this genomic alteration at a high frequency as was observed in the current review. Patient numbers enrolled in trials are low, the ongoing trials are single-arm, open-label studies and the study population is heterogenous with regard to baseline characteristics (e.g., age, ECOG status and tumor site, presence of CNS metastases). Therefore, a robust quantitative synthesis of results comparing the relative efficacy of the different *NTRK* mutation-specific agents versus the current standards of care is challenging.

Although the available clinical evidence to date suggests a pivotal role for TRK-targeted agents in selected patients with solid tumors, there are several issues associated with their use which need to be considered. There is evidence in some patients that *NTRK*-TKI treatment has resulted in an acquired resistance [65], as has been observed in EGFR mutant, *ALK*- or *ROS1*-fusion-positive lung cancer [66–68]. Two cases of entrectinib resistance [49,57] and nine cases of an acquired resistance to larotrectinib have been reported [21]. *In vitro* studies have reported that experimental drugs such as ponatinib and nintedanib effectively inhibited the survival of specific *NTRK* mutants, which showed resistance to entrectinib or larotrectinib [65] and in the clinic, two next-generation TRK inhibitors (LOXO-195 and repotrectinib) are being tested to overcome these recurrent resistance mutations [22,30,69–71]. A recent Phase I study investigating the effects of LOXO-195 on patients with larotrectinib-resistant *NTRK*-fusion-positive tumors showed that of the 29 patients who were evaluable for response, ten (34%) had a confirmed CR or partial response. When the response rates were analyzed by the mechanism of underlying resistance to the first-generation TRK inhibitors, it was reported that 9 of 20 patients (45%) whose tumors had become resistant by acquiring an *NTRK* gene mutation had a CR or partial response. None of the three patients whose tumors had become resistant by TRK-independent mechanisms responded to LOXO-195 [70].

The development of tumor-agnostic therapies brings new challenges when seeking payer reimbursement. In the current regulatory landscape, due to the lack of experience and precedent, neither regulators nor researchers or sponsors know precisely what is required for approval of new agents based solely on presence and response of a molecular target [72]. This may require further methodological development for regulatory acceptance [73]. Encouraging data from the clinical trial programs have recently culminated in the approval of the first ‘tumor-agnostic’ TKI agents (larotrectinib and entrectinib) by the FDA for patients with solid tumors that have an *NTRK* gene fusion despite there being no FDA-approved test for *NTRK* fusions [8,9,74]. However, there may be additional challenges when seeking approval from more traditional HTA agencies where current oncology appraisal pathways are structured based on treating tumors from a single origin site. Fitting the evidence to the HTA framework in these situations is difficult. Although in the UK the NICE has previously made recommendations based on single-arm trials [75], NICE and most other HTA agencies have a preference for evidence generated from RCTs, which are considered to be the ‘gold-standard’ design for assessing treatment effectiveness [76]. However, conducting adequately powered RCTs as part of the development of treatments for rare mutations such as *NTRK* is not feasible; consequently basket trials are more commonplace [77]. Challenges are also present when defining an active comparator. Most HTA agencies require that the new technology is assessed against the standard of care for that indication. In cases with tumor-agnostic therapies, multiple standards of care are available depending on the tumor location. In addition, traditional accepted end points in oncology such as OS and PFS (as are preferred by HTA bodies) may not be available for rarer diseases and a lack of certainty of how particular biomarker-based end points link to these outcomes may devalue the level of submitted evidence.

Screening procedures to identify gene fusions are costly to apply to all patients and it is uncertain whether HTA agencies should consider the cost of the diagnostic testing as part of the overall treatment cost for the drug as part of any reimbursement assessment. In July 2019, the European Society of Medical Oncology (ESMO) published recommendations on standard methodology to detect *NTRK* fusions in daily practice and clinical research [78]. It is recommended that fluorescence *in situ* hybridization or reverse transcription-PCR (RT-PCR) should be used in tumors where *NTRK* fusions are highly recurrent compared with assays allowing fusion gene detection in an agnostic manner where a limited proportion of cases are expected to harbor *NTRK* fusions. As more tumor-agnostic therapies become available in the future, it will be imperative that HTA bodies consider any additional diagnostic costs in light of improvements in clinical efficacy reported for these agents in the management of patients where there is currently a substantial unmet need.

Other challenges lie in the HTA assessment of the cost, economic valuation and quality of life evidence. In such cases, there is liable to be a lack of data and in a traditional oncology reimbursement the indication may be widened (i.e., the costs/QoL of treating a less specific cancer type in that site would be considered). However, this is not possible for tumor-agnostic tumors as locations vary between patients. Often, there are no standard protocols within the HTA submission processes to deal with these issues. In England, however, the Cancer Drugs Fund exists as an interim funding option for cancer medicines whose cost-effectiveness is subject to a higher than normal degree of uncertainty; during the interim funding period, data collection is usually mandated to help address this uncertainty. The Cancer Drugs Fund is, therefore, a potential option for tumor-agnostic therapies, since it provides a framework with which to address key areas of clinical and economic uncertainty [79]. In addition, NICE also has a

highly specialized technology pathway, with adjusted thresholds and evidence requirements, although the pathway is limited at the moment to single indications in very rare conditions, and it has yet to consider oncology drugs [75].

To our knowledge, this is the first systematic review that assessed the efficacy and safety of TKIs in patients with *NTRK* fusions. However, the study had some limitations. First, as previously mentioned due to the rare nature of the indication, low patient numbers, single-arm trials and heterogeneous populations made it difficult to make robust comparisons between interventions. Second, only two full primary publications containing efficacy data were included [27,31]. Apart from one full publication containing pooled evidence for several trials [21], the remaining data were extracted from conference abstracts and due to their brevity, it was not possible to assess the quality of the study or the reporting. There was also a lack of access to individual patient data and data on AEs were missing for several reports.

Conclusion

Overall, this review identified several tumor-agnostic treatments that target cancers with an *NTRK* gene fusion that are being studied in ongoing clinical studies. So far, the clinical response reported to date is impressive. Such treatments may provide a molecular basis for personalized therapy in tumor types that have traditionally been considered prognostically poor and therefore the further development of such TKI agents should be considered a priority in cancer research.

Future perspective

Although data demonstrate that TRK-targeted agents are clinically beneficial and are well tolerated in hard-to-treat *NTRK*-fusion-positive solid tumors, challenges remain in their integration into routine clinical practice. Further clinical data are required to enable quantitative comparison of the relative efficacy of agents for clinically meaningful outcomes. Due to the rarity of these mutations, it will take time to generate a substantial robust dataset, therefore data will likely come from a real-world evidence base. Research is also required to address the potential challenge of treatment resistance, although preliminary studies have shown encouraging results in overcoming resistance through the use of next-generation TRK inhibitors (LOXO-195 and repotrectinib). Following the recent FDA approvals of larotrectinib and entrectinib, progress is required in the validation and establishment of large-scale, readily accessible, cost-effective pretreatment testing algorithms to identify suitable patients. Current hurdles when seeking HTA reimbursement for tumor-agnostic therapies must also be overcome, including the acceptance of data from single-arm trials to demonstrate the efficacy and safety of potential tumor-agnostic therapies, and how to account for substantial testing costs in economic modeling without penalizing first movers. Incorporation of the TRK-targeted agents into routine clinical practice would permit a paradigm shift in the management of patients, identified through routine biomarker testing, based on the genetic makeup of their tumor and not by anatomical location.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2019-0534

Author contributions

All the authors, including the authors employed by the sponsor (M Hodgson, A Steenrod and P Chu), participated in the development of the research question. The literature searches and screening of retrieved articles were conducted by CR Mitchell and S Batson of Mtech Access Ltd. (Bicester, UK). All the authors were involved in the analysis and interpretation of the data and in the development of the manuscript. The authors did not receive any compensation for the writing of the manuscript. The decision to submit for publication was that of the authors alone, and all the authors were involved in this decision. All the authors have approved the final version of the article, including the authorship list.

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Ethical conduct of research

No ethical approval was required for this research, however the systematic review was conducted using the PRISMA guidelines (<http://www.prisma-statement.org/>).

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Summary points

Background

- Neurotrophic tropomyosin-related receptor tyrosine kinases (*NTRK*) mutations occur in up to 1% of all solid tumors and are observed in more than 20 different malignancies over diverse tissue/cell lineages. The clinical effectiveness of TRK inhibitors is being assessed in Phase I and II trials.
- A systematic review (SR) was conducted to provide a summary of published evidence for the currently available TRK-targeted agents and a meta-analysis feasibility was also conducted to assess whether quantitative comparisons could be made on their relative efficacy and safety.

Methods

- The electronic databases Medline®, Medline® Epub Ahead of Print (In-Process & Other Non-Indexed Citations), Embase and EBM Reviews were interrogated.
- Eligibility criteria included clinical studies, economic evaluations, utility studies or cost/resource use studies conducted in patients (adults or pediatric patients) with *NTRK*-fusion-positive solid tumors.

Results of the SR

- A total of 27 relevant clinical studies associated with seven TRK-targeted agents were eligible for inclusion in the SR.
- However, clinical efficacy/safety data were only available for two interventions: entrectinib and larotrectinib.
- Data from pooled analyses demonstrate that both larotrectinib and entrectinib are effective in treating tumors-harboring *NTRK*-fusion-positive mutations and are well tolerated across multiple tumor types.
- No relevant economic or quality of life studies were identified.

Meta-analysis feasibility

- A meta-analysis feasibility assessment to compare the relative efficacy of entrectinib and larotrectinib for outcomes of interest.
- However, a robust meta-analysis was not feasible due to the single-arm design of eligible studies, heterogeneity of outcome data and small sample sizes.

Conclusion

- Preliminary data clearly demonstrate the currently available TRK-targeted agents to be generally well tolerated and associated with an impressive clinical benefit (as assessed by objective response rate).
- Further corroboration from the expansion of existing studies and real-world data is required to further elucidate the optimum positioning of TRK-targeted agents in the treatment pathway.

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