Tropomyosin receptor kinase inhibitors in the management of sarcomas

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Purpose of review
Genetic aberrations resulting in tropomyosin receptor kinase (TRK) fusion proteins can drive oncogenesis and are postulated to occur in up to 1% of solid tumours. However, TRK fusions in adult sarcomas are rare and there is a significant challenge in identifying patients with sarcomas harbouring TRK fusions in the clinical setting. Despite a recent European Society of Medical Oncology consensus article regarding screening of tumours for TRK fusions, economical and practical limitations present a barrier to widespread screening of sarcomas.

Recent findings
Larotrectinib and entrectinib are pan-TRK inhibitors which have both received FDA approval for the management of solid tumours harbouring NTRK fusions. Initial results of a number of clinical trials have demonstrated promising efficacy and safety data, including dramatic and durable responses in patients with sarcomas. As such, TRK inhibitors represent a promising treatment option in a small cohort of adult sarcoma patients, where currently treatment options are limited. The emergence of acquired resistance is a concern associated with TRK inhibitor therapy and a number of second-generation agents targeting TRK kinase mutations driving acquired resistance have entered early-phase clinical trials.

Summary
With the growing appreciation of the implications of TRK fusions, this review will summarize the emerging clinical trial data of TRK inhibitors in sarcomas. Although in their infancy, clinical trial results are encouraging, and as further results and analyses are released, we will have a greater understanding of their impact on clinical practice and the management of patients with sarcomas.

Keywords
neurotrophic tyrosine receptor kinase, sarcomas, tropomyosin receptor kinase, tyrosine kinase inhibitor

INTRODUCTION
Sarcomas are a rare and heterogeneous group of cancers, comprising over 150 histological subtypes with vastly differing molecular characteristic and clinical behaviour [1,2]. This degree of heterogeneity makes sarcomas inherently difficult to manage medically. In the advanced setting, following failure of first-line cytotoxic chemotherapy, there are limited treatment options, leading to dismal outcomes for these patients [3,4]. However, targeted therapies, such as tyrosine kinase inhibitors (TKIs), have been approved for specific sarcoma subtypes, for example pazopanib in nonadipocytic soft tissue sarcomas (STS) and pexidartinib in tenosynovial giant cell tumours [5,6]. Indeed, the management of gastrointestinal stromal tumours (GIST) has been revolutionized by the approval of a number of TKIs including imatinib, sunitinib, regorafenib, ripretinib and avapritinib [7–11]. Additionally, molecularly driven basket trials have shown encouraging results through the enrolment of multiple cancer subtypes harbouring common genetic

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occurring in up to 1% of all solid tumours [17]. These fusions are the most commonly described, and genes can drive oncogenesis, with chromosomal translocations for neurotrophins [16]. Mutations in these NTRK1, NTRK2, and NTRK3 genes, and function as high-affinity receptors for neurotrophins [16]. Owing to difficulties associated with pan-TRK immunohistochemistry of tissue with neuronal or smooth muscle differentiation, screening for sarcomas for TRK fusions should involve NGS methods early in the screening paradigm.

- Larotrectinib has demonstrated encouraging safety and efficacy data in the pan-cancer setting and also in the recently reported sarcoma-specific data set. Further data are expected as the trial matures and this will improve our understanding of the clinical implications of this novel agent.
- Entrectinib has also demonstrated encouraging response rates in TRK fusion-positive solid tumours, including those with CNS metastases; however, formal reports of the complete phase I/II trial data are awaited, including sarcoma-specific cohort data.
- Novel agents targeting TRK kinase domain mutations driving acquired resistance following TRK inhibitor therapy have shown promising efficacy in case reports and have entered early-stage clinical trials, with early phase I data regarding LOXO-195 showing encouraging efficacy in the second-line setting.

DETECTION OF TROPOMYOSIN RECEPTOR KINASE FUSIONS IN THE CLINICAL SETTING

Aside from infantile fibrosarcoma, we have little knowledge as to which sarcoma subtypes are most likely to harbour TRK fusions. Therefore, one critical clinical challenge is identifying which patients should be offered TRK fusion screening and identifying the most effective screening method.

Pan-TRK immunohistochemistry (IHC) represents a quick and cost-effective method for detecting overexpression of TRK fusion proteins, and initial work on smaller pan-cancer cohorts suggested reasonable reliability, with a reported sensitivity and specificity of 95.2 and 100%, respectively [27]. However, further studies have demonstrated that false-positive expression is frequently observed in tumours of neuronal and smooth-muscle differentiation as wild-type TRK protein is physiologically expressed. Indeed, a recent study demonstrated that pan-TRK IHC was poor at identifying TRK expression in sarcoma samples, with a sensitivity and specificity of 80 and 74.4%, respectively, worse than all the other cancer subtypes studied [25,28]. As such, the evidence remains unclear as to whether IHC should be adopted as the preliminary screening method for diagnosing TRK fusions in sarcomas.

Fluorescence in-situ hybridization (FISH) may be used as an alternative approach to detecting TRK fusions in sarcomas. However, the need for individual probes for NTRK1, NTRK2, and NTRK3, and the fact that FISH is unable to identify the S’ partner of the fusion, limits its clinical applicability. Furthermore, complex rearrangement patterns, or
when the deleted genomic region is small enough to leave sufficient complementary regions for hybridization of both FISH probes, can result in false negatives, with one study reporting this to be over 30% in paediatric mesenchymal tumours [29].

With the technological advances in next-generation sequencing (NGS), a number of RNA and DNA-based assays have been developed to detect TRK fusions. Anchored multiplex polymerase chain reaction (PCR) utilizing RNA as input material can target-known fusion exons and is commercially available through ArcherDx [30,31]. One advantage of this system is that only one fusion partner needs to be targeted, allowing characterization of novel or variable fusion sequences. However, all RNA-based assays are reliant on reasonable quality input material, a potentially limiting factor with FFPE samples [32]. Targeted DNA-based sequencing assays have also been developed, with the deep-coverage hybridization Memorial Sloan Kettering Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) assay recently approved by the FDA as a diagnostic test [33]. The panel includes coverage of introns 3 and 7–12 of NTRK1, intron 15 of NTRK2 and introns 4 and 5 of ETV6, the most common fusion partner of NTRK3 [25]. NTRK3 itself is not included as introns 13, 14 and 15 where the majority of breakpoints occur span 193 kb and include repetitive nucleotide sequences making sequencing unfeasible [25]. Furthermore, studies have demonstrated that actionable drivers may be undetected by targeted DNAsseq but subsequently identifiable through targeted RNAsseq assays, particularly in tumours with low mutational burden [34]. Given the cost and low frequency of TRK fusions, the practicality of diagnosing TRK fusions through Whole Genome Sequencing (WGS) assays remains unclear, but a sequential screen initially utilizing DNAsseq assays followed by targeted RNAsseq may be advisable. This highlights the importance of expert sarcoma disease input and the advantages of centralizing diagnosis and treatment [35].

Owing to the lack of clarity dictating which screening methods would be most appropriate, the European Society of Medical Oncology (ESMO) released a working group consensus article detailing a recommended approach for the detection of TRK fusions [36]. In sarcomas known to harbour highly recurrent TRK fusions, any validated confirmatory analysis would suffice, with FISH utilizing targeted probes or nested reverse transcription PCR the most cost-effective methods. To screen for TRK fusions in an unselected histology-agnostic approach, RNAsseq techniques are the gold standard [32]. The most exhaustive approach, however, would entail a targeted DNAsseq assay. If negative a further targeted RNAsseq assay, and a final IHC step to confirm expression of the pharmacologically targetable protein kinase [37]. However, economic and practical considerations limit the feasibility of such in-depth screening, and further characterization of cohorts of TRK fusion-positive cancers is needed to guide clinicians on which sarcomas should routinely undergo screening.

**LAROTRECTINIB**

Larotrectinib (Vitraki/LOXO-101/ARRY-470) is a first-in-class orally available, potent and highly selective pan-TRK inhibitor which received FDA accelerated approval for adult and paediatric patients with solid tumours harbouring a TRK fusion [38]. The efficacy of larotrectinib has been assessed in three separate phase I/II tumour-agnostic clinical trials. The adult-only open-label, multicentre phase I dose-escalation study recruited 70 patients over the age of 18 years, with locally advanced or metastatic solid tumours refractory to standard therapy (NCT02122913) [39]. Confirmed presence of a TRK fusion was not a prerequisite for inclusion into the study. A standard 3 and 3-dose escalation scheme was adopted, starting at a safe starting dose of 50 mg once daily, with six dosing schedule cohorts adopted.

Results of the dose-escalation phase I study carried out as part of the multicentre, open-label phase I/II trial of larotrectinib in the paediatric/teenage and young adult population have also been reported (SCOUT, NCT02637687) [40]. Patients aged from 1 month to 21 years, with a locally advanced or metastatic solid tumour for which no standard systemic or curative therapy existed were enrolled. As with the adult-only phase I trial, TRK fusion status was not a prerequisite for enrolment; however, TRK fusion testing was undertaken prior to enrolment, resulting in enrichment of the trial cohort with tumours harbouring TRK fusions. A total of 24 patients were enrolled onto the phase I arm of the study, with a median age of 4.5 years. Of the cohort of 24, 17 patients had a tumour harbouring a TRK fusion, eight (47%) had infantile fibrosarcoma, seven (41%) had other sarcoma subtypes and the remaining two (12%) had papillary thyroid cancer. The subsequent phase II trial remains actively recruiting with results currently awaited.

The combined safety and efficacy results of the aforementioned phase I study involving adults, phase I study involving children, and the phase II basket clinical trial (NAVIGATE) involving adults were published by Drilon et al. (NCT02576431) [17]. The decision to pool the efficacy data from the three trials was driven by the rarity of TRK fusions and the inherent heterogeneity of cancer
types recruited. Across the three studies, 55 patients were included for analyses made up of eight patients from the adult phase I study, 12 from the paediatric phase I study and 35 from the adult phase II study. Inclusion criteria for analysis included patients who had a locally advanced or metastatic, TRK fusion-positive solid tumour, adequate organ function, an Eastern Cooperative Oncology Group performance status of 0–3, and who had received standard therapy previously. For the purposes of the phase II trial in adults, patients exposed to prior treatment with a TKI with anti-TRK activity were excluded. The cohort of 55 patients was made up of 17 unique cancer diagnoses, and from a sarcoma perspective included seven (13%) with infantile fibrosarcoma, three (5%) with GIST, three (5%) with spindle-cell tumours, two (4%) with malignant peripheral nerve sheath tumours, two (4%) with myxopercytoma, two (4%) with sarcoma not otherwise specified and a single case (2%) of infantile myofibromatosis. Across the whole cohort, independent radiology review per response evaluation criteria in solid tumours (RECIST) identified an overall response rate of 75% (41 of 55 patients), made up of seven (13%) complete responses and 34 (62%) partial responses. These responses were seen independent of age, tumour subtype or type of TRK fusion. At one year, 71% of observed responses were maintained, and at a median follow-up of 9.9 months, the median progression-free survival was not reached. In keeping with the results from the phase I trials, larotrectinib was well tolerated with clinically significant adverse events uncommon. No grade 4 or 5 drug-related adverse events were documented, and the commonest grade 3 event was anaemia which was identified in five (11%) of the 55 patients.

More recently, Demetri et al. [41] presented the sarcoma specific efficacy and safety data from the three aforementioned trials at the 2019 Connective Tissue Oncology Society (CTOS) meeting. As of February 2019, a total of 69 patients with TRK fusion-positive sarcomas had been treated, made up of 29 (42%) with infantile fibrosarcoma, four (6%) with GIST, and the remaining 36 (52%) with a range of other sarcoma subtypes. The median age in this sarcoma-specific cohort was 5.2 years, with 48 (70%) coming from the paediatric and young adult phase I/II trial. The cohort was heavily pretreated, 42 (61%) patients had received prior surgery, 50 (72%) prior systemic therapy, and 13 (19%) prior radiotherapy. Treatment response was evaluable in 68 of the 69 patients with an overall response rate per RECIST of 88% (60 of 68 patients), consisting of 16 (24%) complete responses and 44 (65%) partial responses. The median duration of treatment response had not been reached, and at data cut-off treatment was ongoing in 47 (68%) patients. As with previous reports, larotrectinib was well tolerated with adverse events mostly grade 1–2.

Furthermore, five children with sarcomas enrolled onto the phase I study went on to undergo surgical resection following a partial response to larotrectinib [42]. Surgical resections were R0 in 3 (60%) of the 5 cases, with a pathological complete response in 2 patients (100% treatment effect) and near pathological complete response in 1 patient (>98% treatment effect). None of the five patients suffered any postoperative or wound healing complications, demonstrating the potential utility of larotrectinib as a presurgical treatment option in patients with TRK fusion-positive sarcomas.

Based upon the results of these trials, and the recently presented sarcoma-specific data, larotrectinib has rapid, potent and durable efficacy in patients with tumours harbouring TRK fusions. The activity observed in a diverse population of cancer subtypes confirms the validity TRK fusions as a therapeutic target and the tumour-agnostic efficacy of larotrectinib, whereas the sarcoma-specific data support the importance of identifying TRK fusions in patients with sarcomas.

ENTRECTINIB

Entrectinib (Rozlytrek/RXDX-101/NMS-E628) is another pan-TRK inhibitor which was granted accelerated FDA approval for the treatment of adults and children over the age of 12 years, with solid tumour-harbouring TRK fusions [43]. Based upon promising preclinical work, entrectinib was taken forward for evaluation in phase I/II studies [44–46]. The combined efficacy and safety results of the ALKA-372-001 phase I basket trial, the STARTRK-1 phase I basket trial and the ongoing STARTRK-2 trial were recently reported by Doebele et al. [47**] (NCT02097810, EudraCT 2012-000148-88 and NCT02568267). A total of 54 patients with tumours harbouring a TRK fusion were included for analysis, 51 patients from the phase II STARTRK2, two from the phase I STARTRK1 and one from the phase I ALKA-372-001. The median age was 58 years, and the cohort was heavily pretreated with 46 (85%) having received prior chemotherapy, 13 (24%) previous targeted therapy and seven (13%) previous immunotherapy. A total of 12 (22%) patients had central nervous system (CNS) metastases at the start of entrectinib. Of the 54 patients, 13 (24%) had a sarcoma making it the largest cohort; however, specific sarcoma subtypes were each represented only by a single case, aside from sarcoma not otherwise specified, seven (13%) cases. Of the 54 patients evaluable for treatment efficacy per RECIST, 31 (57%) achieved an objective response
made up of four (7%) complete responses and 27 (50%) partial responses. Stable disease was observed in nine (17%) cases. As with larotrectinib, objective responses were observed independent of tumour subtype and type of TRK fusion. Entrectinib therapy resulted in a median progression-free survival of 11.2 months, and a median duration of response of 10.4 months. Of the 12 patients with CNS metastases at baseline, a partial response was observed in six (50%) and stable disease in four (33%), with the remaining two (17%) having incomplete data thus preventing response analysis. For the cohort of sarcoma patients, 12 had sufficient data for inclusion in outcome analysis, of which six (50%) had a partial response to entrectinib and the remaining six (50%) had stable disease.

For the safety assessment of entrectinib, all patients enrolled across the three aforementioned trials, and patients from the paediatric phase I/II STARTRK-NG study were included, a total of 355 patients (NCT02650401). Across this larger cohort, most treatment-related adverse events were grade 1 or 2. However, serious treatment-related adverse events were recorded in 30 (9%) of the 355 patients, the most frequent of which was nervous system disorder in 10 (3%). Dose interruption due to a treatment-related adverse event was required in 90 (25%), a dose reduction in 97 (27%), and entrectinib was discontinued in 14 (4%). No treatment-related deaths were recorded.

The integrated analysis of entrectinib efficacy shows that it is well tolerated, able to induce robust responses and has durable antitumour activity. Importantly, this combined analysis also confirms the ability of entrectinib to cross the blood–brain barrier, and patients with CNS metastases at baseline had similar response rates. The objective response rate observed for entrectinib is lower than that reported in the combined analysis of larotrectinib (57 versus 75%); however, differences in study population make direct comparison challenging. For example, in the entrectinib cohort 22% of patients had CNS metastases at baseline, associated with a poorer prognosis, compared with only 2% in the larotrectinib analysis. Furthermore, the larotrectinib combined cohort presented by Drilon et al. included patients enrolled in the paediatric and young adult phase I/II trial and was heavily enriched for cases of the TRK inhibitor responsive infantile fibrosarcoma; however, no such cases were available for inclusion in the entrectinib analysis.

Figure 1 illustrates a response to NTRK inhibitor in a patient with histiocytic sarcoma.

**Figure 1.** Radiological response in a patient with a high grade sarcoma with histiocytic differentiation (ETV6:NTRK3 exon 14) treated with entrectinib (clinical trial).

**TARGETING ON-TARGET TROPOMYOSIN RECEPTOR KINASE MUTATIONS DRIVING ACQUIRED RESISTANCE**

Despite the promising efficacy data, as with all TKIs acquired resistance invariably develops and as such
CONCLUSION
From the results of the basket trials of entrectinib and larotrectinib, it is apparent that TRK inhibitors are able to induce dramatic and durable responses in patients with sarcomas harbouring a TRK fusion. As such, they offer a valuable and effective treatment option in a small cohort of adult sarcoma patients, who otherwise have limited treatment options. However, sarcomas are a heterogeneous group of cancers and TRK fusions are rare in adult sarcomas. With the economic and practical limitations of utilizing NGS assays to screen a large population of patients with sarcoma to identify a small subset harbouring TRK fusions, one of the key clinical challenges is identifying which patients should undergo screening. Further retrospective and prospective studies are required to help guide clinical practice in defining which sarcoma subtypes should be considered for TRK fusion screening. Complete trial data, and further sarcoma-specific results are awaited, and are likely to yield further insight into the role of TRK inhibitors in the management of sarcomas. It should be noted that disease review by a specialist sarcoma histopathologist was not required in previous trials, and should be included in future study designs. Furthermore, although showing promise in a small cohort of children in the phase I trial of larotrectinib, TRK inhibitors may play an important role as a preoperative therapy or in the combination setting, and this should be examined in future preclinical and clinical studies.

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