CURRENT OPINION

Tropomyosin receptor kinase inhibitors in the management of sarcomas

Christopher P. Wilding[a], *Herbert H. Loong*[b,c], *Paul H. Huang*[a,*], *and Robin L. Jones*[d,e,*]

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

[a]Division of Molecular Pathology, The Institute of Cancer Research, London, UK, [b]Department of Clinical Oncology, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, NT, [c]State Key Laboratory in Translational Oncology, Hong Kong Cancer Institute, The Chinese University of Hong Kong, Hong Kong SAR, China, [d]Department of Medical Oncology, Sarcoma Unit, The Royal Marsden Hospital and [e]Division of Clinical Studies, Institute of Cancer Research, London, UK

Correspondence to Robin L. Jones, Division of Medical Oncology, Sarcoma Unit, Royal Marsden Hospital, London SW3 6JJ, UK. E-mail: robin.jones@rmh.nhs.uk

*Joint senior authors.

Curr Opin Oncol 2020, 32:307–313

DOI:10.1097/CCO.0000000000000650

KEY POINTS

- Owing to difficulties associated with pan-TRK immunohistochemistry of tissue with neuronal or smooth muscle differentiation, screening of 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.

aberrations, for example the CREATE trial which demonstrated the efficacy of the TKI crizotinib [12–14]. The role of TKIs in soft tissue sarcomas (STS) is beyond the scope of this article and interested readers are directed to a recent in-depth review on this topic [15]. Herein, we review TKIs targeting fusions in the tropomyosin receptor kinases A, B and C (TRKA, TRKB and TRKC; collectively referred to as TRK hereafter), focusing on the biological significance of these fusions, the challenges in identifying sarcomas harbouring TRK fusions, as well as clinical trials.

TROPOMYOSIN RECEPTOR KINASE ACTIVITY AND MUTATIONS

TRKs are single-pass transmembrane receptor tyrosine kinases encoded by the neurotrophic tyrosine receptor kinase 1, 2 and 3 (*NTRK1*, *NTRK2* and *NTRK3*) genes, and function as high-affinity receptors for neurotrophins [16]. Mutations in these genes can drive oncogenesis, with chromosomal fusions being the most commonly described, and occurring in up to 1% of all solid tumours [17▪▪]. The first established TRK fusion implicated in sarcomagenesis was demonstrated in a landmark article by Kenzevich *et al.* [18], which confirmed the *ETV6–NTRK3* fusion was recurrently rearranged in congenital infantile fibrosarcoma. Since then, sporadic TRK fusions have been described in a number of sarcomas subtypes; *ETV6–NTRK3* fusions in a subset of patients with ALK-negative inflammatory myofibroblastic tumours, in *KIT* and *PDFGRA*-negative GIST and further established as drivers of infantile fibrosarcoma [19–21]. *LMNA–NTRK1* fusions have been shown in haemangiopericytoma, infiltrative spindle cell sarcomas, and the recently described lipofibromatosis-like neural tumours, which have also been shown to harbour *TPM3–NTRK1* fusions [22–25]. Furthermore, *NTRK1* and *NTRK3* fusions with variable partners have been described in a subset of patients with uterine leiomyosarcoma [26]. These translocations lead to oncogenesis when the catalytic tyrosine kinase domain containing the 3′ region of the *NTRK* gene fuses to the 5′ region of the variable fusion partner, promoting gene expression and facilitating protein dimerization. The subsequent chimeric oncogene is both aberrantly expressed and leads to ligand-independent constitutive activation of the tyrosine kinase domain.

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 5′ 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 DNAseq but subsequently identifiable through targeted RNAseq 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 DNAseq assays followed by targeted RNAseq 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, RNAseq techniques are the gold standard [32]. The most exhaustive approach, however, would entail a targeted DNAseq assay. If negative a further targeted RNAseq 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 myopericytoma, 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.

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

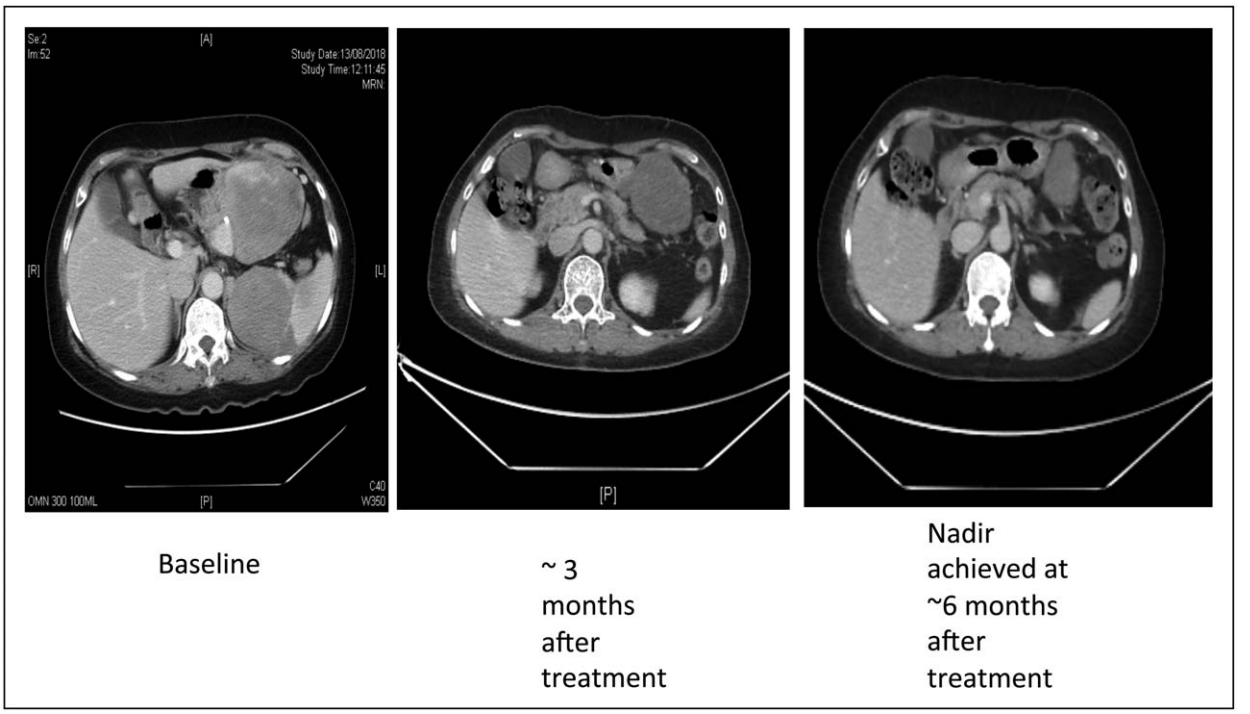

FIGURE 1. Radiological response in a patient with a high grade sarcoma with histiocytic differentiation (ETV6:NTRK3 exon 14) treated with entrectinib (clinical trial).

identifying mechanisms of treatment failure and methods to overcome them is of immediate clinical relevance. To date, the best-described mutations leading to secondary resistance following TRK inhibition are on-target mutations involving the *NTRK* kinase domain [48,49].

Second-generation TRK inhibitors have been developed and are entering early phase clinical trials. Following promising efficacy in the compassionate use and preclinical setting, a phase I/II clinical trial of LOXO-195 in adults and children previously treated with TRK inhibitors has been initiated (NCT03215511). Preliminary results reported that of 20 patients with acquired resistance secondary to an *NTRK* gene mutation, nine (45%) had a complete or partial response to therapy, although sarcoma-specific data are awaited [50▪▪]. Repotrectinib (TPX-0005) is another next-generation pan-TRK, ROS1 and ALK TKI which has shown promise in preclinical studies leading to a phase I/II study of repotrectinib in six cohorts, including a cohort of TRK inhibitor pretreated TRK fusion positive solid tumours. The results of this trial are yet to be released (TRIDENT-1, NCT03093116) [51].

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 sarcomas 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.

Acknowledgements

None.

Financial support and sponsorship

The authors acknowledge grant funding from the Wellcome Trust, Cancer Research UK and the Royal Marsden/Institute of Cancer Research National Institute for Health Research Biomedical Research Centre.

Conflicts of interest

C.P.W. and P.H.H. declare no competing financial interests. R.L.J. has received financial research support from Merck and GlaxoSmithKline and has undertaken consultancy for Adaptimmune, Athenex, Blueprint, Clinigen, Eisai, Epizyme, Daiichi Sankyo, Deciphera, Immunedesign, Lilly, Merck and Pharmamar. H.H.L. has received financial research support from Athenex, Merck, Mundipharma and Novartis and has undertaken consultancy for AbbVie, Bayer, Boehringer-Ingelheim, Celgene, Eli-Lilly, Guardant Health, Merck Sereno, and Pfizer.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ▪ of special interest
- ▪▪ of outstanding interest

1. Taylor BS, Barretina J, Maki RG, *et al.* Advances in sarcoma genomics and new therapeutic targets. Nat Rev Cancer 2011; 11:541–557.
2. Lucchesi C, Khalifa E, Laizet Y, *et al.* Targetable alterations in adult patients with soft-tissue sarcomas: insights for personalized therapy. JAMA Oncol 2018; 4:1398–1404.
3. Savina M, Le Cesne A, Blay JY, *et al.* Patterns of care and outcomes of patients with METAstatic soft tissue SARComa in a real-life setting: the METASARC observational study. BMC Med 2017; 15:78.
4. Wagner MJ, Amodu LI, Duh MS, *et al.* A retrospective chart review of drug treatment patterns and clinical outcomes among patients with metastatic or recurrent soft tissue sarcoma refractory to one or more prior chemotherapy treatments. BMC Cancer 2015; 15:175.
5. van der Graaf WT, Blay JY, Chawla SP, *et al.* Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2012; 379:1879–1886.
6. Tap WD, Gelderblom H, Palmerini E, *et al.* Pexidartinib versus placebo for advanced tenosynovial giant cell tumour (ENLIVEN): a randomised phase 3 trial. Lancet 2019; 394:478–487.
7. Demetri GD, von Mehren M, Blanke CD, *et al.* Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002; 347:472–480.
8. Demetri GD, van Oosterom AT, Garrett CR, *et al.* Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 2006; 368: 1329–1338.
9. Demetri GD, Reichardt P, Kang YK, *et al.* Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet (London, England) 2013; 381:295–302.
10. Heinrich MC, Jones RL, von Mehren M, et al. Avapritinib in advanced PDGFRA D842V-mutant gastrointestinal stromal tumor (NAVIGATOR): a multicenter, open-label, phase 1 trial. Lancet Oncol 2020. [accepted]
11. Call JW, Wang Y, Montoya D, *et al.* Survival in advanced GIST has improved over time and correlates with increased access to postimatinib tyrosine kinase inhibitors: results from Life Raft Group Registry. Clin Sarcoma Res 2019; 9:4.

12. Schöffski P, Sufliarsky J, Gelderblom H, *et al.* Crizotinib in patients with advanced, inoperable inflammatory myofibroblastic tumours with and without anaplastic lymphoma kinase gene alterations (European Organisation for Research and Treatment of Cancer 90101 CREATE): a multicentre, single-drug, prospective, nonrandomised phase 2 trial. Lancet Respir Med 2018; 6:431–441.

13. Schöffski P, Wozniak A, Stacchiotti S, *et al.* Activity and safety of crizotinib in patients with advanced clear-cell sarcoma with MET alterations: European Organization for Research and Treatment of Cancer phase II trial 90101 'CREATE'. Ann Oncol 2017; 28:3000–3008.

14. Schöffski P, Wozniak A, Escudier B, *et al.* Crizotinib achieves long-lasting disease control in advanced papillary renal-cell carcinoma type 1 patients with MET mutations or amplification: EORTC 90101 CREATE trial. Eur J Cancer 2017; 87:147–163.

15. Wilding CP, Elms ML, Judson I, *et al.* The landscape of tyrosine kinase inhibitors in sarcomas: looking beyond pazopanib. Expert Rev Anticancer Ther 2019; 19:1–21.

16. Barbacid M. The Trk family of neurotrophin receptors. J Neurobiol 1994; 25:1386–1403.

17. ■■ Drilon A, Laetsch TW, Kummar S, *et al.* Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med 2018; 378:731–739.
Combined efficacy and safety analysis of larotrectinib across three distinct phase I/II clinical trials. The first example, and best evidence thus far, of larotrectinib's potential importance as treatment of *NTRK* fusion-positive solid tumours.

18. Knezevich SR, McFadden DE, Tao W, *et al.* A novel ETV6-NTRK3 gene fusion in congenital fibrosarcoma. Nat Genet 1998; 18:184–187.

19. Sheng WQ, Hisaoka M, Okamoto S, *et al.* Congenital-infantile fibrosarcoma: a clinicopathologic study of 10 cases and molecular detection of the ETV6-NTRK3 fusion transcripts using paraffin-embedded tissues. Am J Clin Pathol 2001; 115:348–355.

20. Shi E, Chmielecki J, Tang CM, *et al.* FGFR1 and NTRK3 actionable alterations in 'wild-Type' gastrointestinal stromal tumors. J Transl Med 2016; 14:339.

21. Alassiri AH, Ali RH, Shen Y, *et al.* ETV6-NTRK3 is expressed in a subset of ALK-negative inflammatory myofibroblastic tumors. Am J Surg Pathol 2016; 40:1051–1061.

22. Haller F, Knopf J, Ackermann A, *et al.* Paediatric and adult soft tissue sarcomas with NTRK1 gene fusions: a subset of spindle cell sarcomas unified by a prominent myopericytic/haemangiopericytic pattern. J Pathol 2016; 238:700–710.

23. Kohsaka S, Saito T, Akaike K, *et al.* Pediatric soft tissue tumor of the upper arm with LMNA-NTRK1 fusion. Hum Pathol 2018; 72:167–173.

24. Agaram NP, Zhang L, Sung YS, *et al.* Recurrent NTRK1 gene fusions define a novel subset of locally aggressive lipofibromatosis-like neural tumors. Am J Surg Pathol 2016; 40:1407–1416.

25. Solomon JP, Linkov I, Rosado A, *et al.* NTRK fusion detection across multiple assays and 33,997 cases: diagnostic implications and pitfalls. Mod Pathol 2019; 33:38–46.

26. Chiang S, Cotzia P, Hyman DM, *et al.* NTRK fusions define a novel uterine sarcoma subtype with features of fibrosarcoma. Am J Surg Pathol 2018; 42:791–798.

27. Hechtman JF, Benayed R, Hyman DM, *et al.* Pan-Trk immunohistochemistry is an efficient and reliable screen for the detection of NTRK fusions. Am J Surg Pathol 2017; 41:1547–1551.

28. Gatalica Z, Xiu J, Swensen J, Vranic S. Molecular characterization of cancers with NTRK gene fusions. Mod Pathol 2019; 32:147–153.

29. Davis JL, Lockwood CM, Stohr B, *et al.* Expanding the spectrum of pediatric NTRK-rearranged mesenchymal tumors. Am J Surg Pathol 2019; 43:435–445.

30. Reeser JW, Martin D, Miya J, *et al.* Validation of a targeted RNA sequencing assay for kinase fusion detection in solid tumors. J Mol Diagn 2017; 19:682–696.

31. Beadling C, Wald AI, Warrick A, *et al.* A multiplexed amplicon approach for detecting gene fusions by next-generation sequencing. J Mol Diagn 2016; 18:165–175.

32. Sheng Q, Vickers K, Zhao S, *et al.* Multiperspective quality control of Illumina RNA sequencing data analysis. Brief Funct Genomics 2016; 16:elw035.

33. FDA. FDA unveils a streamlined path for the authorization of tumor profiling tests alongside its latest product action. FDA [Internet]. Available from: https://www.fda.gov/news-events/press-announcements/fda-unveils-streamlined-path-authorization-tumor-profiling-tests-alongside-its-latest-product-action [cited February 10, 2020].

34. Benayed R, Offin M, Mullaney K, *et al.* High yield of RNA sequencing for targetable kinase fusions in lung adenocarcinomas with no mitogenic driver alteration detected by DNA sequencing and low tumor mutation burden. Clin Cancer Res 2019; 25:4712–4722.

35. Loong HH, Blay JY, Munhoz RR. International collaborations and regional challenges in providing specialist multidisciplinary sarcoma care. Am Soc Clin Oncol Educ Book 2019; 39:616–623.

36. Marchiò C, Scaltriti M, Ladanyi M, *et al.* ESMO recommendations on the standard methods to detect NTRK fusions in daily practice and clinical research. Ann Oncol 2019; 30:1417–1427.

37. ■■ Marchiò C, Scaltriti M, Ladanyi M, *et al.* ESMO recommendations on the standard methods to detect NTRK fusions in daily practice and clinical research. Ann Oncol 2019; 30:1417–1427.
ESMO working group consensus article discussing the recommended screening paradigm for detecting *NTRK* fusions.

38. FDA. FDA approves larotrectinib for solid tumors with NTRK gene fusions. FDA [Internet]. Available from: https://www.fda.gov/drugs/fda-approves-larotrectinib-solid-tumors-ntrk-gene-fusions-0 [cited February 5, 2020].

39. ■ Hong DS, Bauer TM, Lee JJ, *et al.* Larotrectinib in adult patients with solid tumours: a multicentre, open-label, phase i dose-escalation study. Ann Oncol 2019; 30:325–331.
Article describing the methodology and results of the adult-only phase I study of larotrectinib in solid tumours.

40. ■ Laetsch TW, DuBois SG, Mascarenhas L, *et al.* Larotrectinib for paediatric solid tumours harbouring NTRK gene fusions: phase 1 results from a multicentre, open-label, phase 1/2 study. Lancet Oncol 2018; 19:705–714.
Article describing the methodology and results of the phase I arm of the study of children and young adults with solid tumours treated with larotrectinib.

41. ■■ Demetri GD, Albert CM, Tan DS, *et al.* Larotrectinib efficacy and safety in patients with trk fusion sarcomas. Connect Tissue Oncol Soc Meet 2019.
Sarcoma-specific combined efficacy and safety data from the adult-only phase I trial, paediatric phase I trial, and adult-only phase II trial of larotrectinib in solid tumours. This confirmed the activity and safety of larotrectinib in sarcomas with a proven *NTRK* fusions.

42. DuBois SG, Laetsch TW, Federman N, *et al.* The use of neoadjuvant larotrectinib in the management of children with locally advanced TRK fusion sarcomas. Cancer 2018; 124:4241–4247.

43. FDA. FDA approves entrectinib for NTRK solid tumors and ROS-1 NSCLC. FDA [Internet]. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-entrectinib-ntrk-solid-tumors-and-ros-1-nsclc [cited February 5, 2020].

44. Farago AF, Le LP, Zheng Z, *et al.* Durable clinical response to entrectinib in NTRK1-rearranged non-small cell lung cancer. J Thorac Oncol 2015; 10:1670–1674.

45. Ambati SR, Slotkin EK, Chow-Maneval E, Basu EM. Entrectinib in two pediatric patients with inflammatory myofibroblastic tumors harboring ROS1 or ALK gene fusions. JCO Precis Oncol 2018; 2018:.

46. Sartore-Bianchi A, Ardini E, Bosotti R, *et al.* Sensitivity to entrectinib associated with a novel LMNA-NTRK1 gene fusion in metastatic colorectal cancer. JNCI J Natl Cancer Inst 2016; 108:.

47. ■■ Doebele RC, Drilon A, Paz-Ares L, *et al.* Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020; 21:271–282.
This is the first article reporting safety and efficacy data of entrectinib in patients with *NTRK* fusion positive solid tumours. The article reports the combined data from three clinical trials – two phase I adult-only clinical trials, and one phase II adult-only global basket trial, and confirmed the activity of entrectinib to induce response in *NTRK*-fusion positive solid tumours, including in those with CNS metastases.

48. Cocco E, Scaltriti M, Drilon A. NTRK fusion-positive cancers and TRK inhibitor therapy. Nat Rev Clin Oncol 2018; 15:731–747.

49. Russo M, Misale S, Wei G, *et al.* Acquired resistance to the TRK inhibitor entrectinib in colorectal cancer. Cancer Discov 2016; 6:36–44.

50. ■■ Hyman D, Kummar S, Farago A, *et al.* Phase I and expanded access experience of LOXO-195 (BAY 2731954), a selective next-generation TRK inhibitor (TRKi). In: Proceedings of the 110th annual meeting of the American Association for Cancer Research. Philadelphia, PA: AACR; 2019:; 2019 March 29–April 3, Atlanta, GA.
The first published evidence of LOXO-195 overcoming acquired resistance following previous TRK inhibitor therapy. This phase I study confirmed efficacy of LOXO-195 to overcome acquired resistance secondary to TRK kinase mutations, but lacked efficacy in patients with TRK-independent resistance mechanisms.

51. A study of repotrectinib (TPX-0005) in patients with advanced solid tumors harboring ALK, ROS1, or NTRK1-3 rearrangements – full text view – ClinicalTrials.gov [Internet]. Available from: https://clinicaltrials.gov/ct2/show/NCT03093116 [cited December 5, 2019].

