The landscape of tyrosine kinase inhibitors in sarcomas: looking beyond pazopanib

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ABSTRACT

1. Introduction

Soft tissue sarcomas (STS) are a group of rare cancers that account for approximately 1% of all adult malignancies [1,2]. STS are highly heterogeneous with over 50 different histological subtypes that can occur in different anatomical locations and display vastly differing pathologies, genetic aberrations, and clinical behavior [3,4]. This heterogeneity makes STS an inherently challenging group of diseases to treat effectively.

Tyrosine kinase inhibitors (TKIs) represent the largest class of targeted therapies approved by the Food & Drug Administration (FDA) with multiple inhibitors having been licensed for the treatment of a range of different cancer types including STS [5]. For instance, imatinib is the primary treatment of patients with inoperable and advanced gastrointestinal stromal tumors (GIST) [6]. GIST is the most common subtype of STS and is characterized (in 85–90% of patients) by activating mutations in the receptor tyrosine kinases (RTKs) KIT and platelet-derived growth factor receptor (PDGFR) [7,8]. Following disease progression on imatinib, second- and third-line standard treatment in GIST utilizes the TKIs sunitinib and regorafenib, respectively [8]. Furthermore, a number of newer TKIs are at various stages of development. For instance, ripretinib, a switch control type II inhibitor of KIT, and avapritinib, a potent type I KIT/PDGFRα inhibitor, are both currently undergoing phase III trials in the third/fourth line-setting and may further improve the outcomes of patients with advanced GIST (NCT03353753, NCT03465722) [9,10]. Conversely, vandetanib, a TKI targeting vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR)-dependant signaling, recently completed a phase II study in GIST patients deficient in the expression of succinate dehydrogenase (SDH), however, with no partial or complete responses observed in nine patients, the authors concluded vandetanib lacked activity in these patients [11]. Recently published preclinical work in a patient-derived xenograft model showed that SDH-deficient GIST respond to fibroblast growth factor receptor (FGFR) inhibitor monotherapy, which is further sensitized by the addition of a KIT inhibitor in combination [12]. The current gold-standard treatment paradigm for GIST, and the ongoing drive for newer agents, has been guided by the well understood underlying mechanisms of response and resistance that have been extensively described elsewhere and interested readers are directed to other reviews on this topic [6–8].

In contrast, the mechanisms of TKI response and resistance in non-GIST STS subtypes are not well understood and currently approved targeted therapies for this broad range of diseases is limited to the multi-target TKI pazopanib (Votrient®/GW786034) [5]. The approval of pazopanib in STS was based on data from the double-blind, placebo-controlled, randomized, PALETTE phase III trial (NCT00753688) that found a significant improvement in progression-free survival (PFS) in patients with non-adipocytic STS treated with pazopanib.
Soft tissue sarcomas (STS) are a highly heterogeneous group of cancers comprising over 50 different histological subtypes that display contrasting responses to systemic therapy.

Tyrosine kinase inhibitors (TKIs) have the potential to become an increasingly important component in the arsenal of targeted therapies to treat STS for which they have shown promising preclinical activity.

Pazopanib is currently the only TKI approved for use in advanced STS, with associated issues concerning clinical efficacy, overall survival benefit, and drug resistance, thereby highlighting the unmet need for novel therapeutic strategies in improving STS therapy.

The phase III trial of sorafenib in desmoid tumors provides evidence of TKI activity in this soft tissue tumor, with durable benefit seen in a substantial proportion of patients.

The CASPS international, phase III trial of cediranib in alveolar soft part sarcoma presents high-quality evidence of efficacy of a TKI in this rare disease, with a significant decrease in tumor size in the cediranib treatment arm versus placebo.

In solitary fibrous tumors, axitinib represents a promising potential compound for further exploration, demonstrating activity in progressive or malignant cases including those patients pre-treated with pazopanib, but showing inactivity in high grade/differentiated cases.

The basket-type trials of larotrectinib show the promise of biomarker-driven trials and represent an exciting opportunity to embed patients with sarcomas within trials of focused targeted therapies.

Phase III clinical trials in sarcoma are rare and a large proportion of treated patients in this trial [13]. Furthermore, clinical experience shows that a subset of patients either do not respond to pazopanib (known as intrinsic resistance) or rapidly develop acquired drug resistance upon treatment. These challenges highlight the importance of developing validated predictive biomarkers which can identify STS patients most likely to benefit from pazopanib [13,14]. Additionally, pazopanib is currently not licensed for use in liposarcomas (LPS), one of the more prevalent subtypes of STS, for which there are limited treatment options in the advanced disease setting [14,15]. In light of these challenges, there has been an ongoing effort to assess other inhibitors in the TKI class for improved efficacy in STS. The development and current clinical status of pazopanib in STS has recently been reviewed elsewhere and for the purposes of this article, we will focus on reviewing the preclinical and clinical development of other TKIs in non-GIST STS [14,15].

2. Preclinical characterization of TKIs

The majority of TKIs that have shown promising preclinical and clinical efficacy in STS are multi-target TKIs that primarily target the angiogenic and growth-promoting RTKs. These RTKs include VEGFRs, PDGFRs, FGFRs, and KIT (Figure 1; Table 1) [16–26]. These TKIs are thought to exert their antitumor effects through inhibition of angiogenesis, with additional blockade of tumor growth-promoting RTKs. Examples include sunitinib, sorafenib, regorafenib, axitinib, cediranib, nintedanib, anlotinib, and sitravatinib. The preclinical characterization of these antiangiogenic TKIs have mostly followed a common drug discovery pathway starting with the identification of candidate compounds through biochemical screens of VEGFR2 kinase inhibition [20–25]. The exceptions to this are sorafenib, which was identified utilizing RAF1 kinase inhibition screens, and sitravatinib, for which preclinical characterization data are not publicly available [26]. These antiangiogenic TKIs have been found to potently inhibit VEGF-induced VEGFR2 autophosphorylation in human umbilical vein endothelial cells (HUVECs), with associated decreases in endothelial cell proliferation, migration, and endothelial tube formation [18,20,23–30].

The antiangiogenic properties of these multi-target TKIs have been further corroborated in in vivo murine xenograft models of varying cancer types, where drug treatment resulted in a significant reduction in microvessel area and qualitative tumor vascularity [20,23,25–34]. Furthermore, treatment of xenograft models with these TKIs commonly led to a decrease in tumor perfusion, extravasation, vascular permeability, and/or formation of metastases, thereby highlighting their antimetastatic properties [25,27,30,32,34–37]. In addition to their antiangiogenic and antimetastatic properties, these TKIs also elicited direct antitumor effects through inhibition of growth-promoting RTKs, such as PDGFRs and KIT, resulting in reductions in proliferation and migration in various tumor cell line models and bulk tumor growth in a range of xenograft models [17–37].

Other multi-target TKIs that were not developed to target the VEGF signaling pathway have also been evaluated for the treatment of STS. These include imatinib, crizotinib, and dasatinib (Figure 1). Imatinib, crizotinib, and dasatinib were discovered through biochemical kinase screens to assess for potent inhibition of the ABL kinases, MET RTK, and Src-family kinases respectively [38–40]. These three TKIs have been shown to exert antiproliferative and antimetastatic properties in an extensive array of in vitro and in vivo preclinical models of hematological and solid malignancies [38–49]. Additionally, in HUVEC and human lung microvascular endothelial cells, crizotinib inhibited hepatocyte growth factor (HGF)-induced MET phosphorylation and vascular tube formation [40]. Crizotinib also displayed antiangiogenic properties in vivo with reductions in microvessel area observed in MET-dependent murine xenografts of glioblastoma, gastric, and lung cancers [40].

More recently, highly selective TKI that target the neurotrophic receptor kinases (NTRK) have shown promising results in selected STS subtypes [50–53]. One of the most clinically advanced NTRK inhibitors is larotrectinib which inhibits all NTRK receptors at low nanomolar drug concentrations [51–53]. This inhibitor has been shown to inhibit cell proliferation and growth in in vitro and in vivo preclinical models harboring fusion NTRK oncoproteins with concurrent blockade of AKT, signal transducer and activator of transcription 3 (STAT3), and/or extracellular signal-regulated kinases (ERK) downstream signaling pathways [51–53].

Building on these preclinical data, the following sections will focus on the preclinical and clinical development of these TKIs in the context of STS, as well as other clinical considerations in TKI therapy.
3. Histological changes associated with TKI therapy

Given the lack of “window of opportunity” studies in TKIs in sarcomas, there are only a small number of published reports of histopathological changes associated with TKI therapy. For instance, in patients with dermatofibrosarcoma protuberans (DFSP) who have undergone imatinib treatment, there is a replacement of tumor with copious amounts of hyalinized collagen, minimal necrosis, and a marked decrease in cellularity with absent mitotic figures [54]. A similar post-treatment histology is observed in GIST following imatinib therapy, characterized by extensive cystic change and hyalinization of the tumor mass [55]. Conversely, it has been reported that the use of pazopanib in infantile fibrosarcoma results in a histological response characterized by significant tumor necrosis and tumor cell death [56]. Further published descriptions of the histological effects following TKI therapy are limited to other cancer types. For example, sunitinib in the treatment of renal cell carcinoma (RCC) results in a histological response similar to that of pazopanib in infantile fibrosarcoma, characterized by extensive tumor necrosis, an associated foreign body giant-cell reaction, and absence of viable tumor [57,58]. Similarly, a complete histological response following sorafenib treatment in hepatocellular carcinoma is characterized microscopically by areas of amorphous necrosis with a surrounding fibrous capsule and complete absence of viable tumor [59]. Furthermore, as well as the histological

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**Figure 1. Kinase selectivity maps.** Kinome-wide profiling measuring the dissociation constant ($K_d$), inhibitory constant ($IC_{50}$), or percent of control (POC) of the TKIs discussed within the review. The $K_d$ for imatinib, sunitinib, sorafenib, axitinib, cediranib, nintedanib, crizotinib, and dasatinib were obtained from PMID: 22037378 [16]. The $K_d$ for regorafenib was obtained from PMID: 27734608 [17]. The $IC_{50}$ for anlotinib and sitravatinib were obtained from PMID: 29446853 and PMID: 26675259, respectively [19,20]. The POC for larotrectinib was obtained from PMID: 24162815 [51]. Abbreviations: CK1; Casein kinase 1, TK; Tyrosine kinase, STE; Sterile kinase, RGC; Receptor guanylate cyclase, CMGC; Cyclin-dependent kinase, mitogen-activated protein kinase, glycogen synthase kinase, and cyclin-dependent-kinase-like kinases, PI3K; Phosphoinositide 3-kinase, TKL; Tyrosine kinase-like, AGC; Protein kinases A, G, and C, CAMK; Ca$^{2+}$/calmodulin-dependent protein kinase.
Table 1. Table of tyrosine kinase selectivity of tyrosine kinase inhibitors discussed within this review.

| Tyrosine kinase inhibitors | Commonly targeted tyrosine kinases in order of selectivity | References |
|---------------------------|-----------------------------------------------------------|------------|
| Imatinib                  | ABL1, PDGFRB, PDGFRα, PDGFRβ (K_i)                      | [16]       |
| Sunitinib                 | PDGFRB, PDGFRα, VEGFR2, VEGFR1, RET, SRC, ALK, ABL1, FGFR3, FGFR1/2, NTRK1, NTRK2 | [16] |
| Sorafenib                 | RET, SRC, VEGFR1, PDGFRB, VEGFR2, NTRK1, NTRK2, FGFR2, FGFR1, FGFR3 | [16] |
| Regorafenib               | RET, PDGFRB, PDGFRα, VEGFR1, ABL1, VEGFR3, VEGFR2, NTRK1, NTRK2, ALK, SRC, ALK | [17] |
| Axitinib                  | PDGFRβ, PDGFRα, VEGFR2, RET, SRC, MET, ABL1, ALK, FGFR3, FGFR1, FGFR2, NTRK1 | [16] |
| Cediranib                 | PDGFRβ, PDGFRα, VEGFR1, VEGFR2, VEGFR3, RET, SRC, ABL1, EGFR | [16] |
| Nintedanib               | VEGFR2, NTRK1, RET, PDGFRB, ALK, SRC, VEGFR1, RAS, ABL1, FGFR3, FGFR3 | [16] |
| Anlotinib                 | VEGFR2, RET, PDGFRα, SRC, PDGFRβ, VEGFR1 | [20] |
| Sitravatinib             | VEGFR3, VEGFR2, NTRK1, VEGFR1, RET, SRC, ABL1, ALK, FGFR3 | [19] |
| Crizotinib               | MET, ALK, NTRK2, ABL1, NTRK3, SRC, RET, VEGFR1, EGFR, FGFR3 | [16] |
| Dasatinib                | ABL1, SRC, PDGFRα, PDGFRβ, KIT, EGFR, RET, FGFR2, VEGFR2, FGFR1, FGFR3, VEGFR1, KIT | [16] |
| Larotrectinib            | NTRK1, NTRK2, MET, EGFR, RET, VEGFR1, VEGFR3, ABL1, FGFR3, RET, ALK, SRC, DC, SRC, ABL1, PDGFR | [51] |

Key: K_i or IC_{50} (µM) of: x ≤ 1 nM, x < 10 nM, 10 ≤ x < 50 nM, 50 ≤ x < 100 nM, x ≥ 100 nM. For larotrectinib, values expressed as a percent of control (POC); ≤ 10%.

Abbreviations: EGFR, Epidermal growth factor receptor; FGFR, Fibroblast growth factor receptor; IC_{50}, Inhibitory constant; K_i, Dissociation constant; NTRK, Neurotrophic receptor kinase; PDGFR, Platelet-derived growth factor receptor; VEGFR, Vascular endothelial growth factor receptor.

4. Imatinib

Imatinib (Glivec®/CGP057148B/ST-1571) was the first TKI approved for the treatment of advanced and metastatic GIST in 2002 and has been evaluated in non-GIST STS [5]. Imatinib has shown promising preclinical activity in models of malignant peripheral nerve sheath tumor (MPNST), malignant rhabdoid tumor (MRT), leiomyosarcoma (LMS), and DFSP. In MPNST cell lines, imatinib suppressed ligand-induced PDGFRβ phosphorylation and associated cellular proliferation/invasion, with a consistent phenotype also seen in vivo [60,61]. Imatinib has also shown antitumor effect in preclinical models of DFSP and giant-cell fibroblastoma, which are rare, recurrent, and infiltrative tumors of the dermis classically characterized by a COL1A1/PDGFB translocation [62,63]. Imatinib reduced DFSP and giant-cell fibroblastoma cellular proliferation and PDGFRβ autophosphorylation in a dose-dependent manner, with concomitant induction of apoptosis, in both in vitro and in vivo models [62,63]. Finally, imatinib has been shown to reduce in vitro proliferation of MRT cells, an aggressive pediatric malignancy characterized by loss of the tumor suppressor SMARC81, which display constitutive ABL1 expression, as well as the SK-UT-1B LMS cell line model [64-66].

Chugh et al. reported results of their single-arm, open-label, phase II trial of imatinib in 10 histological subtypes of sarcoma (NCT00031915) (Table 2) [67]. They recruited 190 patients, of which 185 were assessable for response, and included patients older than 10 years with metastatic or locally advanced disease with a diagnosis of LMS, LPS, synovial sarcoma (SS), MPNST, fibrosarcoma, osteosarcoma, malignant fibrous histiocytoma, rhabdomyosarcoma (RMS), angiosarcoma, and Ewing's sarcoma. There was no limit placed on number of prior therapies, with 141 (74.6%) patients having received prior doxorubicin. Patients received oral imatinib at a dose of 100mg-300mg twice a day. The primary end-point was clinical benefit rate (CBR), defined as a complete response, partial response, or stable disease, assessed on cross-sectional imaging, with an observed CBR rate of greater than 30% deemed clinically meaningful for each subtype. Across each of the subtypes assessed, a CBR of greater than 30% was not achieved in this trial, leading the authors to conclude that imatinib lacked activity in these subtypes [67]. It is interesting to note that subsequently, Chugh et al. embedded an unplanned desmoids tumor (DT) cohort in this trial and demonstrated a stable disease rate of 84% and, at 3 years follow-up, 58% of patients in this cohort were progression free [68]. DTs are a rare and locally invasive soft tissue tumor characterized by catenin beta-1 (CTNNB1) or adenomatous polyposis coli (APC) mutations. In light of these findings, subsequent phase II trials have focused their recruitment on patients with progressive DT [69,70]. Penel et al. recruited 40 patients over the age of 18 years, with proven progressive DT on cross-sectional imaging, to receive 400mg imatinib daily in a single-arm trial (NCT00287846) [69]. The primary end-point was progression arrest rate (PAR) at 3 months and the authors reported this to be 91%, with a PFS rate at 1 year of 67% and a median progression-free survival (mPFS) of 25 months. Premature drug cessation was required in 4 of the 40 patients (10%) due to the effects of drug toxicity. Kasper et al. also enrolled 38 patients with progressive DTs into a single-arm phase II study (NCT01137916) [70]. The primary end-point was progression arrest after 6 months of imatinib at a dose of 800mg daily, with the authors reporting PAR at 6 months of 65%, a rate of PFS at 1 year of 59%, and an mPFS of 21 months.

The pooled results of two separate phase II trials of imatinib in DFSP have also been reported [71]. Conducted by the Southwest Oncology Group (SWOG) (SWOG-0245, NCT00084630) and European Organization for Research and Treatment of Cancer (EORTC) (EORTC-62,027, NCT00085475), the two trials were single-arm, single-agent, open-label, phase II trials aiming to recruit...
Table 2. Table summarizing the published results of each tyrosine kinase inhibitor discussed within this review.

| Study                        | Study Type               | Patient Number | Chemotherapy Regimen | Subtypes (n)                               | Best Response              | Survival               |
|------------------------------|--------------------------|----------------|----------------------|--------------------------------------------|----------------------------|------------------------|
| Imatinib                     | Single arm phase II trial | 190            | Imatinib 300mg BD    | Angiosarcoma (16)                          | Observed CBR 13.3%         | mPFS – 2.76 months     |
| Chugh et al. [67]            |                          |                |                      | Ewing's sarcoma (13)                       | Observed CBR 0%            | mPFS – 1.92 months     |
|                              |                          |                |                      | Fibrosarcoma (12)                          | Observed CBR 8.3%          | mPFS – 2.76 months     |
|                              |                          |                |                      | LMS (29)                                   | Observed CBR 21.4%         | mPFS – 2.76 months     |
|                              |                          |                |                      | LPS (31)                                   | Observed CBR 24.1%         | mPFS – 3.72 months     |
|                              |                          |                |                      | MFH (30)                                   | Observed CBR 10.3%         | mPFS – 1.92 months     |
|                              |                          |                |                      | Osteosarcoma (27)                          | Observed CBR 19.2%         | mPFS – 1.92 months     |
|                              |                          |                |                      | MPNST (7)                                  | Observed CBR 20%           | mPFS – 1.92 months     |
|                              |                          |                |                      | SS (22)                                    | Observed CBR 15%           | mPFS – 2.52 months     |
|                              |                          |                |                      | RMS (2)                                    | Observed CBR 0%            | mPFS – 25 months       |
|                              |                          | 51             | Imatinib 300mg BD    | DT (51)                                    | Stable Disease 84%         | PFS at 3 years – 58%   |
| Penel et al. [69]            | Single arm phase II trial| 35             | Imatinib 400mg OD    | Progressive DT (35)                        | Complete Response 3%       | PFS at 25 months       |
| Kasper et al. [70]           | Single arm phase II trial| 38             | Imatinib 800mg OD    | Progressive DT (38)                        | Partial Response 52.3%     | PFS at 1 year – 59%    |
| Rutkowski et al. [71]        | EORTC single arm phase II trial | 16         | Imatinib 400mg BD    | Advanced or metastatic DFSP not amenable to curative surgery (24) | Partial Response 19%       | PFS at 1 year – 59.7%  |
|                              | SWOG single arm phase II trial | 8          | Imatinib 400mg OD    | DT (19)                                    | Stable Disease 80%         | mPFS – 20.4 months     |
|                              |                          |                |                      | Stable Disease 28.6%                       |                            |                        |
|                              |                          |                |                      | Disease Progression 19%                    |                            |                        |
| Sunitinib                    | Single arm phase II trial | 53             | Sunitinib 37.5mg OD  | Cohort A (18) – LMS (11), SFT (3), others (4) | n/a                        | Stable disease at 12 weeks – 11% |
|                              |                          |                |                      | Cohort B (21) – Sarcoma NOS (5), SS (4), LPS (2), Others (10) | Partial Response 4%       | Stable disease at 12 weeks – 19% |
|                              |                          |                |                      | Cohort C (9) – Chordoma (9)                 | n/a                        | Stable disease at 12 weeks – 44% |
|                              |                          |                |                      |                                            |                            | Median duration of response – 8.2 months |
|                              |                          |                |                      |                                            |                            | mOS – 19 months        |
|                              |                          |                |                      |                                            |                            | mPFS – 17 months       |
|                              |                          |                |                      |                                            |                            | mOS – 56 months        |
|                              |                          |                |                      |                                            |                            | mPFS – 19 months       |
|                              |                          |                |                      |                                            |                            | mPFS – 6 months        |
|                              |                          |                |                      |                                            |                            |                        |
| Sunitinib                    | Single arm phase II trial | 19             | Sunitinib 37.5mg OD  | DT (19)                                    | Partial Response 26.3%     | Stable disease at 12 weeks – 44% |
|                              |                          |                |                      |                                            |                            | Median duration of response – 8.2 months |
|                              |                          |                |                      |                                            |                            | mOS – 19 months        |
|                              |                          |                |                      |                                            |                            | mPFS – 17 months       |
|                              |                          |                |                      |                                            |                            | mOS – 56 months        |
|                              |                          |                |                      |                                            |                            | mPFS – 19 months       |
|                              |                          |                |                      |                                            |                            | mPFS – 6 months        |
| Stacchiotti et al. [76]      | Retrospective case series| 9              | Sunitinib 37.5mg OD  | Progressive or metastatic ASPS (9)          | Partial Response 55%       | mPFS not reached at median follow-up – 8.5 months |
| Stacchiotti et al. [77]      | Retrospective case series| 15             | Sunitinib 37.5mg OD  | Metastatic ASPS (15)                        | Partial Response 40%       | mPFS not reached at median follow-up – 8.5 months |
| Jagodzinska-Mucha et al. [77]| Retrospective case series| 31             | Sunitinib 37.5mg OD  | Progressive SFT (31)                        | Partial Response 6.5%      | mPFS not reached at median follow-up – 8.5 months |
| Stacchiotti et al. [78]      | Retrospective case series| 10             | Sunitinib 37.5mg OD  | Metastatic extraskeletal myxoid chondrosarcoma (10) | Partial Response 60%       | mPFS not reached at median follow-up – 8.5 months |
|                              |                          |                |                      |                                            | Stable Disease 20%         |                        |
|                              |                          |                |                      |                                            | Progressive Disease 20%    |                        |
|                              |                          |                |                      |                                            | Complete Response 5%       |                        |
|                              |                          |                |                      |                                            | Partial Response 5%        |                        |
|                              |                          |                |                      |                                            | Stable Disease 20%         |                        |
|                              |                          |                |                      |                                            | Partial Response 15.4%     |                        |
|                              |                          |                |                      |                                            | Stable Disease 30.8%       |                        |
|                              |                          |                |                      |                                            | Median time to response – 10 months |
|                              |                          |                |                      |                                            | mPFS not reached with median follow-up – 6 months |
|                              |                          |                |                      |                                            |                        |
| Sorafenib                    | Single arm phase II trial| 41             | Sorafenib 400mg BD   | Superficial angiosarcoma (26)               | Complete Response 5%       | mPFS – 1.8 months      |
|                              |                          |                |                      | Visceral angiosarcoma (15)                  | Partial Response 5%        |                        |
|                              |                          |                |                      |                                            | Stable Disease 20%         |                        |
|                              |                          |                |                      |                                            | Partial Response 15.4%     | mPFS – 3.8 months      |
|                              |                          |                |                      |                                            | Stable Disease 30.8%       |                        |
|                              |                          |                |                      |                                            | Median time to response – 10 months |
|                              |                          |                |                      |                                            | mPFS not reached with median follow-up – 6 months |
|                              |                          |                |                      |                                            |                        |
| Gounder et al. [96]          | Retrospective case series| 26             | Sorafenib 400mg OD   | Aggressive DT (26)                          | 25% Partial Response       | PFS at 1 year – 89%    |
|                              |                          |                |                      |                                            | 70% Stable Disease        |                        |
| Gounder et al. [97]          | Phase III trial           | 87             | 2:1 randomization to placebo or sorafenib 400mg OD | Aggressive DT (87)         | Complete Response 2%      | Hazard ratio for progression or death vs placebo – 0.13 (p < 0.0001) |
| Study           | Study Type          | Patient Number | Chemotherapy Regimen | Subtypes (n) | Best Response | Survival         |
|-----------------|---------------------|----------------|----------------------|--------------|---------------|------------------|
| Regorafenib     | Placebo-controlled phase II trial | 182 | 1:1 Randomization to placebo or regorafenib 160mg OD | LPS (43) | Stable Disease 45% | mPFS = 1.0 months vs 1.7 months in placebo (p = 0.70) |
|                 |                     |               |                      | LMS (56)    | Progressive Disease 55% | mPFS = 3.7 months vs 1.8 months in placebo (p = 0.0045) |
|                 |                     |               |                      | SS (27)     | Stable Disease 86% | mPFS = 5.6 months vs 1.0 months in placebo (p < 0.0001) |
|                 |                     |               |                      | Other sarcomas (56) | Progressive Disease 11% | mPFS = 2.9 months vs 1.0 months in placebo (p < 0.0061) |
|                 |                     |               |                      |             | Partial Response 8% | ||
|                 |                     |               |                      |             | Stable Disease 77% | ||
|                 |                     |               |                      |             | Progressive Disease 15% | ||
|                 |                     |               |                      |             | Partial Response 11% | ||
|                 |                     |               |                      |             | Stable Disease 67% | ||
|                 |                     |               |                      |             | Progressive Disease 22% | ||
| Axitinib        | Single arm phase II trial | 17 | Axitinib 5mg BD | Advanced and progressive SFT (17) | Partial Response 41.2% | mPFS = 5.1 months |
|                 |                     |               |                      |             | Stable Disease 35.3% | Disease control at 6 months – 84% |
| Cediranib       | Single arm phase II trial | 46 | Cediranib 30mg OD | Metastatic, unresectable ASPS (46) | Partial Response 35% | |
|                 |                     |               |                      |             | Stable Disease 60% | |
|                 |                     |               |                      |             | Partial Response 19.4% | |
|                 |                     |               |                      |             | Stable Disease 39.3% | |
| Judson et al.   | Placebo-controlled phase II trial | 48 | 2:1 randomization to placebo or cediranib 30mg OD | Metastatic, progressive ASPS (48) | Partial Response 19.4% | |
|                 |                     |               |                      |             | Stable Disease 39.3% | Best median % change in sum of diameters of target lesion –15.7% vs + 1.2% in placebo (p < 0.0001) |
| Anlotinib       | Single arm phase II trial | 166 | Anlotinib 12mg OD | LPS (13) | Partial Response 7.7% | mPFS at 12 months – 38.7% |
|                 |                     |               |                      | LMS (26)    | Partial Response 7.7% | mPFS = 5.6 months |
|                 |                     |               |                      | SS (47)     | Partial Response 17% | mPFS = 11 months |
|                 |                     |               |                      | Fibrosarcoma (18) | Partial Response 11.1% | mPFS = 5.6 months |
|                 |                     |               |                      | UPS (19)    | Partial Response 5.5% | mPFS = 4.1 months |
|                 |                     |               |                      | ASPS (13)   | Partial Response 46.2% | mPFS = 21 months |
|                 |                     |               |                      | CCS (7)     | Partial Response 14.3% | mPFS = 11 months |
|                 |                     |               |                      | Others (23) | Partial Response 0% | mPFS = 2.8 months |
|                 |                     |               |                      |             | Partial Response 4.4% | mPFS = 8.1 months |
| Crizotinib      | Single arm phase II trial | 45 | Crizotinib 250mg BD | Advanced or metastatic ASPS (45) | Objective Response 50% | |
|                 |                     |               |                      |             | Stable Disease 86.7% | |
|                 |                     |               |                      |             | Partial Response 0% | |
|                 |                     |               |                      |             | Partial Response 4.4% | |
|                 |                     |               |                      |             | Objective Response 14% | |
|                 |                     |               |                      |             | PFS at 1 year – 73.3% | |
|                 |                     |               |                      |             | PFS at 1 year – 53.6% | |
| Schöffski et al. | Single arm phase II trial | 19 | Crizotinib 250mg BD | Advanced or metastatic ALK-positive IMT (12) | Objective Response 50% | |
|                |                     |               |                      |             | Stable Disease 86.7% | |
|                |                     |               |                      |             | Partial Response 0% | |
|                |                     |               |                      |             | Partial Response 4.4% | |
|                |                     |               |                      |             | Objective Response 14% | |
|                |                     |               |                      |             | PFS at 1 year – 73.3% | |
|                |                     |               |                      |             | PFS at 1 year – 53.6% | |
| Schöffski et al. | Single arm phase II trial | 26 | Crizotinib 250mg BD | Advanced or metastatic CCS with MET activation (26) | Partial Response 3.8% | mPFS = 4.4 months |
|                |                     |               |                      |             | Stable Disease 65.4% | |
|                |                     |               |                      |             | Choi ORR 8% | |
|                |                     |               |                      |             | Choi ORR 15% | |
|                |                     |               |                      |             | Choi ORR 19% | |
|                |                     |               |                      |             | Choi ORR 29% | |
|                |                     |               |                      |             | Choi ORR 20% | |
| Dasatinib       | Single arm phase II trial | 109 | Dasatinib 100mg BD | Advanced or metastatic SFT with MET activation (26) | Partial Response 3.8% | mPFS = 11 months |
| Abbreviations: ASPS; Alveolar soft part sarcoma, BD; Bis die (twice daily), CBR; Clinical benefit rate, CCS; Clear cell sarcoma, DT; Desmoid tumor, ES; Epithelioid sarcoma, IMT; Inflammatory myofibroblastic tumor, LMS; Leiomyosarcoma, LPS; Liposarcoma, MFH; Malignant fibrous histiocytoma, mOS; Median overall survival, mPFS; Median progression-free survival, MPNST; Malignant peripheral nerve sheath tumor, NOS; Not otherwise specified, OD; Omne die (once daily), ORR; Overall response rate, PFS; Progression-free survival, RMS; Rhabdomyosarcoma, SFT; Solitary fibrous tumor, SS; Synovial sarcoma, UPS; Undifferentiated pleomorphic sarcoma. |
approximately 40 patients. Due to slow accrual, and following regulatory body approval of imatinib in DFSP, the trials were closed before the target recruitment was met and, as a result, the data were pooled to provide greater numbers for outcome analysis. Patients aged over 18 years with advanced or metastatic DFSP not amenable to surgery with curative intent were included, with the SWOG trial additionally including those patients in whom R0 resection was not feasible with acceptable functional or cosmetic outcomes. PDGFB rearrangement was confirmed in the upstream signaling node AKT 75977 and downstream signaling node AKT 75977. Table 3 was found to phenocopy the antiproliferative effects of sunitinib.

Sunitinib has been evaluated in a number of clinical trials in non-GIST STS (Table 2). George et al. reported a multicenter, single-arm, phase II study of sunitinib in metastatic or locally advanced non-GIST STS (NCT00474994) [74]. They enrolled 53 patients over the age of 18 years, of which 48 were eligible for response assessment, into three cohorts; cohort A consisting of patients with sarcoma subtypes previously shown to demonstrate response to kinase-targeted agents, cohort B consisting of subtypes with previously demonstrated inactivity to kinase-targeted agents, and cohort C consisting of patients with chordomas. A maximum of three prior lines of cytotoxic therapy was permitted, although exposure to prior sunitinib or other investigational agents was a criterion for study exclusion. When evaluated using RECIST, mPFS was 1.8 months, with 11 of 48 patients (22%) having stable disease at 12 weeks and 7 patients (14%) maintaining stable disease after 24 weeks of treatment. Given the similarities in the survival and response data of this phase II study with the PALETTE trial, in which the placebo arm had a similar mPFS of 1.6 months and stable disease as best response in 38% of the patients, it remains to be established if sunitinib is an active agent in non-GIST STS [13].

A further small, non-randomized, open-label, prospective, phase II trial of sunitinib has been undertaken by Jo et al. in which 19 patients with advanced DTs not amenable to surgery with curative intent were recruited (Table 3) [75]. Patients who had received prior arms of therapy were included in the study; four of the 19 patients (21.1%) had received prior systemic therapy, 5 of 19 (26.3%) had received prior surgery, and 4 of 19 (21.1%) had received both prior systemic therapy and surgical management. Following treatment with 37.5mg sunitinib once daily, 5 patients (26.3%) were observed to have a partial response, including response in one patient that was significant enough to enable complete resection, and a further 8 patients (42.1%) had stable disease. It should be noted that in this trial, potentially due to the prevalence of mesenteric DTs (12 out of 19), there was a high rate of serious adverse effects likely related to tumor necrosis in close proximity to the small and large bowel and the mesenteric vasculature. Of the 19 patients, one experienced an ileal perforation, one experienced a fistulous tract forming between the tumor and bowel, and there was a further episode of mesenteric bleeding.

Further published evidence of sunitinib is limited to smaller, often retrospective case series in subtype-specific patient groups. Stacchiotti et al. have reported the role of sunitinib in alveolar soft part sarcoma (ASPS) and SFT, separately, with varying evidence of antitumor effect (Table 3). In 9 patients with progressive/advanced ASPS treated with sunitinib, 5 (55%) patients had a partial response based on RECIST, and a further 3 (33%) had stable disease [76]. Jagodzińska-Mucha et al. demonstrated a similar degree of efficacy, enrolling 15 patients with metastatic ASPS, with 6 patients (40%) observed to have a partial response to treatment and 8 (53%) with stable disease [77]. However, in 31 patients with progressive advanced SFT treated with sunitinib, of which 25 patients were pre-treated with conventional chemotherapeutic regimens, disease control was only achieved in 18 of 31 patients (58%) with a mPFS of 6 months [78]. These results are inferior.
to a previously published retrospective case series by Khalifa et al. of advanced SFT response to trabectedin. All of these patients received trabectedin following failure of first-line chemotherapy and the authors reported a mPFS of 11.6 months and a CBR of 81.8% [79]. Stacchiotti et al. have also reported their experience in cases of extraskeletal myxoid chondrosarcoma, which is another malignancy with an indolent natural history but with frequent metastases and known to be poorly responsive to cytotoxic chemotherapy. In their retrospective case series of 10 patients treated with sunitinib, 6 out of 10 patients (60%) had a partial response per RECIST, 2 patients had stable disease (20%), and 2 patients had disease progression on sunitinib (20%) [80].

The single-arm, non-randomized design of these studies limit any definitive conclusions regarding the efficacy of sunitinib in STS. However, the activity in specific subtypes such as SFT, extraskeletal myxoid chondrosarcoma, and ASPS are very promising despite the often indolent nature of these tumors [81–83]. Of note, there have been promising responses observed in these sarcoma subtypes traditionally resistant to chemotherapy, thereby offering salvage options in these hard to treat cases [76,77,80].

6. Sorafenib

Sorafenib (Nexavar®/BAY 43–9006) is another multi-target TKI, with additional activity against the RAF family kinases, currently undergoing evaluation for use in STS. Preclinically, in primary cell models of DT, sorafenib diminished cell proliferation, migration, and invasion [84,85]. These phenotypes were accompanied by a reduction in ERK, AKT, and MEK signaling with a concurrent reduction in total MEK expression [85]. Similar effects were observed in MPNST and RMS cell line models, with suppression of cell growth and associated decreases in ERK, AKT, and MEK phosphorylation [86–88]. Additionally, in the MPNST cell lines, sorafenib treatment induced G1 cell cycle arrest through reduction in both cyclin D1 expression and retinoblastoma protein phosphorylation [88]. Furthermore, in xenograft models of alveolar rhabdomyosarcoma (aRMS), sorafenib significantly decreased tumor growth, cell proliferation, and vascularity, accompanied by an increase in tumor necrosis [86,87]. Finally, sorafenib also displayed potent antiproliferative effects in cell line models of SFT, MRT, and LMS, with the deactivation of PDGFR signaling observed in the SFT model [64,73].

The clinical efficacy of sorafenib in STS has been evaluated in a study undertaken by the French Sarcoma Group in various vascular sarcoma subtypes (Table 2). In a single-arm, phase II study of sorafenib in angiosarcoma (NCT00874874), patients were stratified based upon the location of the tumor being either superficial (26 patients) or visceral (15 patients), with 37 (73%) patients pre-treated with conventional chemotherapy. The results were somewhat disappointing, with PFS of only 1.8 months in the superficial angiosarcoma cohort and 3.8 months in the visceral group [89]. These results are comparable to a previously published retrospective case series of a variety of second-line therapies following the failure of first-line cytotoxic regimens in metastatic angiosarcoma, which reported a median time to progression of 3.7 months [90].

In the same French Sarcoma Group trial, 5 patients with progressive SFT were included and 2 of the 5 patients (40%) achieved disease control for a period of 9 months despite having tumor progression in the month prior to commencing sorafenib [91]. Although this study showed some promising antitumor activity in SFT, the small cohort size in this study remains a limitation and larger patient cohorts are required to objectively evaluate the efficacy of sorafenib in advanced SFTs.

A further cohort of 15 patients with metastatic or locally advanced epithelioid hemangioendothelioma (EHE) not amenable to curative resection were enrolled onto this trial [92]. PFS at 9 months was chosen as the primary end-point given the indolent nature of EHE [93]. Seven of the 15 patients (46%) had undergone previous surgery and 5 patients (33%) had received prior systemic anticancer therapy. mPFS was 6 months, with a non-progression rate at 9 months of 30.7% (4 of 13 assessable patients). Best response rate on cross-sectional imaging per RECIST following sorafenib was a partial response in 2 of 13 assessable patients (13.3%) and stable disease in 9 of 13 (69.2%). In the French Sarcoma Group study, a sorafenib dose reduction was required in 3 of 15 patients (20%), whilst 5 patients (33.3%) required a transient drug discontinuation due to toxicity.

As part of these studies, circulating biomarkers for sorafenib response in the EHE and the angiosarcoma cohorts were analyzed [94,95]. Serum samples were collected at baseline and at Day 7 following commencement of treatment, with samples available for analysis from 32 patients in the angiosarcoma cohort and 13 patients from the EHE cohort. The authors reported a significant increase in the level of VEGF-A following treatment with sorafenib, with low levels of VEGF-A at baseline associated with best objective response (p = 0.04) and non-progression at 180 days (p = 0.03).

Gounder et al. performed a retrospective analysis of a case series of 26 patients with aggressive DTs treated with sorafenib. The authors reported 6 of 24 evaluable patients (25%) had a partial response to treatment and a further 17 patients (70%) had stable disease as best response (Table 3) [96]. This retrospective case series formed the basis for the subsequent double-blind phase III ALLIANCE A091105 trial of sorafenib vs. placebo in patients with DTs not amenable to surgical intervention (NCT02066181) [97]. Eighty-seven patients deemed inoperable and with proven radiographic progression were recruited and randomized to sorafenib at a starting dose of 400mg once daily or placebo at a 2:1 ratio. Aside from the absence of previous sorafenib exposure, there was no restriction on previous lines of treatment and of the 50 patients in the sorafenib cohort, 23 (46%) had previously undergone surgical resection and 18 (36%) had previously received other systemic therapy. Of the 87 patients enrolled, 84 patients were included in the analysis of response rates and primary/secondary end-points. The primary end-point of the trial was PFS and the authors reported a PFS rate after two years in the sorafenib group of 81%, compared to 36% in the placebo group (hazard ratio for progression or death 0.13, p < 0.001). An objective response per RECIST was observed in 33% of the sorafenib group (1 complete response and 15 partial responses in the 49 patients) and in 20% of the placebo group (7 partial responses in the cohort of 35). Of note, the median time to response to sorafenib was 9.6 months, which is relatively long.
Table 3. Table summarizing the clinical trials of tyrosine kinase inhibitors presented by specific soft tissue sarcoma subtype.

| TKI          | Study                          | Patient Number | Study Type                  | Patient Number | Chemotherapy Regimen | Best Response | Survival          |
|--------------|--------------------------------|----------------|-----------------------------|----------------|----------------------|---------------|-------------------|
| **DESMOID TUMORS** |                                |                |                             |                |                      |               |                   |
| Imatinib     | Chugh et al. [68]              | 51             | Single arm phase II trial   | 71             | Imatinib 300mg BD    | 10% Progressive Disease | PFS at 1 year – 66% |
|             | Penel et al. [69]              | 35             | Single arm phase II trial   | 35             | Imatinib 400mg OD    | 8.5% Progressive Disease | Median follow-up – 34 months |
| Sunitinib    | Kasper et al. [70]             | 38             | Single arm phase II trial   | 19             | Sunitinib 37.5mg OD  | 15.8% Progressive Disease | PFS at 1 year – 59% |
|             | Jo et al. [75]                 | 38             | Single arm phase II trial   | 19             | Sunitinib 800mg OD   | 42.1% Stable Disease | Median duration of response – 8.2 months |

| **SOLITARY FIBROUS TUMORS** |                                |                |                             |                |                      |               |                   |
| Sunitinib     | Stacchiotti et al. [78]        | 37             | Retrospective case series   | 31             | Placebo              | 20% Partial Response | PFS at 1 year – 36% |
| Axitinib      | Stacchiotti et al. [101]       | 17             | Single arm phase II trial   | 17             | Axitinib 5mg BD      | Partial Response 41.2% | mPFS – 5.1 months |
| Dasatinib     | Stacchiotti et al. [76]        | 25             | Single arm phase II trial   | 25             | Dasatinib 100mg BD   | Choi ORR 20%       | mPFS per Choi – 2 months |
| Sunitinib     | Stacchiotti et al. [76]        | 9              | Retrospective case series   | 9              | Sunitinib 37.5mg OD  | Partial Response 55% | mOS – 19 months |
| Jagodzinska-Mucha et al. [77] | Retrospective case series     | 15             | Retrospective case series   | 15             | Sunitinib 37.5mg OD  | Stable Disease 33% | mPFS – 17 months |
| Cediranib     | Kummar et al. [106]            | 46             | Single arm phase II trial   | 46             | Cediranib 30mg OD    | Partial Response 35% | mOS – 56 months |
| Judson et al. [114] | Placebo-controlled phase II trial | 48             | Placebo-controlled phase II trial | 48 | 2:1 cediranib 30mg OD to placebo | Partial Response 19.4% | Best median % change in sum of diameters of target lesion –15.7% vs +1.2% in placebo (p < 0.0001) |
| Anlotinib     | Chi et al. [122]               | 13             | Single arm phase II trial   | 13             | Anlotinib 12mg OD    | Partial Response 46.2% | mPFS – 21 months |
| Crizotinib    | Schöffski et al. [130]         | 45             | Single arm phase II trial   | 45             | Crizotinib 250mg BD  | Partial Response 4.4% | mPFS – 8.1 months |
| Dasatinib     | Schuetze et al. [142]          | 12             | Single arm phase II trial   | 12             | Dasatinib 100mg BD   | Choi ORR 8%         | mPFS per Choi – 11 months |

**Abbreviations:** BD; Bis die (twice daily), mOS; Median overall survival, mPFS; Median progression-free survival, OD; Omne die (once daily), ORR; Objective response rate, PFS; Progression-free survival, TKI; Tyrosine kinase inhibitor.
for a TKI. OS data for this trial has not been reported. Grade 3 adverse events occurred in 14 of the 49 patients (29%) in the sorafenib arm. Dose interruptions were necessary in 65% of patients in the sorafenib arm and, as a result of adverse events, 20% of patients in the sorafenib group discontinued the trial protocol compared to none in the placebo arm.

This study is the only phase III trial of a systemic treatment that has been conducted in DTs to date and was able to demonstrate the efficacy of sorafenib to achieve durable clinical responses in this sarcoma subtype. The response rates observed in the placebo group support the role of active surveillance as the initial management for the majority of patients with DT. However, in patients with aggressively expanding or symptomatic DTs not amenable to surgical resection, the trial by Grounder et al. is potentially practice changing and has identified sorafenib as a valuable systemic treatment option in this clinical setting.

7. Regorafenib

Regorafenib (Stivarga®/BAY 73–5406) is a near-identical analogue of sorafenib with similar kinase selectivity and differs by the addition of one fluorine atom on the central aromatic ring [17,18,26]. As with sorafenib, regorafenib has shown promising results in preclinical STS models of MRT, LMS, and SFT [31,64,98]. In MRT, regorafenib significantly reduces cell viability in the A204 MRT cell line [31,64]. Teicher et al. reported a similar phenotype in the SK-UT-1B MRS cell line upon treatment with regorafenib [64]. When assessed in a number of SFT xenograft models, regorafenib was found to be the greatest antitumor effect in a panel of antiangiogenic TKIs and bevacizumab – a humanized therapeutic antibody that binds circulating VEGF and blocks the ligand from binding to VEGFR [73,98]. Immunoblotting analysis of these xenograft tumors 4 weeks post-treatment found that regorafenib led to decreases in PDGFRβ and VEGFR2 phosphorylation, whereas the rest of the TKI panel inhibited only either one or none of these targets, thereby explaining the greater effect of regorafenib in SFT [73].

Regorafenib was evaluated in STS in the REGOSARC trial (NCT01900743) [99]. This randomized, placebo-controlled, double-blind, phase II clinical trial was undertaken by a French-Austrian collaborative and enrolled patients aged over 18 years with advanced STS pre-treated with doxorubicin or any other anthracycline-based therapy. Patients were randomized 1:1 into either the placebo or the regorafenib arm and stratified based on sarcoma histological subtype into one of the four cohorts: LPS, LMS, SS, or other sarcomas. When compared with placebo, regorafenib induced significantly prolonged mPFS in the LMS subgroup (3.7 months vs 1.8 months, p = 0.0045), the SS subgroup (5.6 months vs 1.0 months, p < 0.0001), and in the other sarcomas subgroup (2.9 months vs 1.0 months, p = 0.0061). However, regorafenib failed to demonstrate efficacy in the LPS cohort with a worse mPFS compared to placebo (1.0 months vs 1.7 months, p = 0.70). These data represent the most compelling evidence thus far for the use of regorafenib in the treatment of non-adipocytic STS. Unfortunately, as was the case in the PALETTE trial, this improvement in mPFS was not translated into a significant improvement in OS in any of the four subtype cohorts (Table 2) [13]. Based on these results, regorafenib warrants further evaluation in STS and investigation of potential molecular biomarkers that may stratify patients and identify those most likely to gain OS benefit from this drug. Identification of such predictive biomarkers for benefit from regorafenib would facilitate rational patient selection in future clinical trials.

8. Axitinib

Preclinical studies of axitinib (Inlyta*/AG013736) in STS have reported efficacy in models of myxoid LPS; an STS subtype for which there are currently no approved TKIs [100]. In a screen of 43 drugs, axitinib was found to strongly inhibit the growth of patient-derived myxoid LPS cell lines and xenografts, with an observed reduction in the phosphorylation of KIT, VEGFR3, PDGFRβ, and downstream signaling proteins AKT and ERK [100]. Furthermore, axitinib was also found to repress VEGFR1 and VEGFR3 as well as VEGFA and VEGFB gene expression [100]. Consistent with this antiangiogenic activity, addition of conditioned media from myxoid LPS cells treated with axitinib to HUVECs reduced endothelial tube formation compared to conditioned media from vehicle-treated cells [100]. In these myxoid LPS models, axitinib treatment led to $G_1$ phase cell cycle arrest and induced cell death [100]. In addition to activity against myxoid LPS, axitinib has also shown potent antiproliferative effects in MRT, LMS, and SS cell lines [64].

Axitinib has been evaluated in a phase II clinical trial in progressive and advanced SFT (NCT02261207) [101]. In this study, 17 patients with advanced SFT, with evidence of progression per Choi criteria in the 6 months prior to commencing axitinib therapy, were enrolled to receive 5mg axitinib twice daily until progression or toxicity (Table 3). Of the 17 patients, 4 (23.5%) had a histopathological diagnosis of high-grade/dedifferentiated SFT with the remaining 13 (76.5%) classified as metastatic SFT. Eight of the 17 (47%) patients had received previous lines of therapy, including pazopanib (7 of 17) and sunitinib (2 of 17). The primary endpoint of the study was objective response rate based on Choi criteria and the authors reported that 7 of 17 patients (41%) had a partial response as their best observed response, 6 (35%) had stable disease, and 4 had progressive disease (23%). Interestingly, 4 of the 7 (57.1%) patients pre-treated with pazopanib had a partial response to axitinib. Of note, none of the 4 patients with high grade/dedifferentiated SFT responded to axitinib.

This trial showed good antitumor activity of axitinib in metastatic SFT. Notably, over half of the patients who were pre-treated with pazopanib obtained a partial response upon subsequent treatment with axitinib. This highlights the potential for axitinib to play a role in the multi-line treatment of metastatic SFT following pazopanib failure. The apparent lack of activity in high-grade/dedifferentiated SFT suggests that the biology regulating axitinib response in SFT varies with grade. A better understanding of the biological factors driving axitinib response will not only shed light on the mechanisms of drug resistance in high-
grade/dedifferentiated SFTs but also highlight candidate biomarkers of drug response.

9. Cediranib

Cediranib (Recentin®/AZD2171) has been evaluated in a number of preclinical models of pediatric sarcomas including MRT and RMS [64,102,103]. In these studies, cediranib displayed negligible efficacy in in vitro sarcoma cell line models that were tested but was observed to induce moderate reductions in in vivo tumor growth, with notable tumor regression observed in the rhabdoid tumor xenograft model KT-16 [102,103]. Later studies have shown cediranib to possess antiproliferative effects in cell line models of MRT, SS, and LMS [64].

Cediranib has been evaluated in several clinical trials in ASPS following the reports of activity in a small series of ASPS patients treated within a larger phase II trial conducted primarily in GIST (Table 3) [104,105]. Kummar et al. conducted an open-label, single-arm, phase II trial of cediranib in patients with metastatic ASPS not amenable to surgery, with no restrictions on prior lines of treatment (NCT00942877) [106]. Forty-six patients with histologically confirmed ASPS were enrolled onto the study, with 28 of the 46 (61%) having received prior systemic therapy, including 12 (26%) who received previous antiangiogenic therapy. Treatment efficacy was assessed by cross-sectional imaging and effect on tumor size determined by RECIST, with 43 patients evaluable for response. Of the 43 patients, 15 (35%) demonstrated a partial response to cediranib and a further 26 (60%) had a stable disease as best response. The context of these results is important, as the CBR of 95% is superior to historical reports of various cytotoxic chemotherapy schedules in metastatic ASPS demonstrating a CBR of between 31% and 80.9% [107–109]. From the trial performed by Kummar et al., pre- and post-treatment biopsies were also available for gene expression analysis by microarray, with the angiopoietin-2 (ANGPT2), VEGFR1 (FLT1), glutamate carboxypeptidase II (FOLH1), and atypical chemokine receptor 3 (ACKR3) genes all downregulated following treatment with cediranib. Validation by RT-PCR confirmed the downregulation of ANGPT2, FLT1, and FOLH1, as well as endothelial cell-specific molecule 1 (ESM1) and lysine demethylases (KDM), in response to cediranib. ANGPT2, FLT1, and ESM1 are pro-angiogenic genes, with ANGPT2 and FLT1 playing a role in enhancing sprouting angiogenesis, and ESM1 being upregulated in hyper-vascularised cancers [110,111]. Uprogulation of FOLH1 is associated with increased cellular proliferation in cancer models and is found in the vasculature of many tumors, whilst KDM are modulators of histone methylation and important epigenetic regulators [112,113]. Downregulation of these genes following cediranib provides evidence of the on-target effect of this drug through the blockade of pro-angiogenic and pro-proliferative signaling pathways which provides mechanistic insights into the molecular basis for cediranib activity.

Following on from this single-arm, phase II study, an international, multi-center, double-blinded, placebo-controlled, randomized, phase II trial of cediranib in the treatment of patients with ASPS (CASPS) was undertaken by Judson et al. (NCT01337401) [114]. Patients over the age of 16 years were enrolled and were required to have measurable metastatic disease with evidence of progression based upon RECIST in the preceding six months. Participants were randomized 2:1 to either 30mg cediranib orally daily or matched placebo. The primary end-point of this trial was the median percentage change in sum of target lesion diameters from baseline to week 24, or progression if sooner, and the results showed a significant decrease in tumor size in patients on cediranib compared to the placebo group (−8.3% vs +13.4%, p = 0.0010). Six of 31 patients (19%) in the cediranib arm had a partial response as their best response, compared to none in the placebo group (p = 0.072), with a median response duration of 16 months. PFS analysis revealed no significant difference between the two cohorts (12-month PFS 38.7% in cediranib group vs 34.4% in placebo, p = 0.28) although this was likely confounded by crossover of patients from the placebo arm to cediranib after week 24. Median OS in the cediranib arm was 27.8 months and in the placebo arm, the median has not yet been reached. Of note, when published, the median OS of the placebo arm will also likely be confounded by treatment group crossover, thereby limiting comparability between the two study arms.

Along with the study by Kummar et al., Judson et al. have confirmed the activity of cediranib in advanced, metastatic ASPS. The CASPS trial represents an important step in improving outcomes in patients with ASPS, as well as demonstrating the ability to undertake randomized, multi-center, collaborative trials in rare sarcoma subtypes. There is a need to further understand the biology of ASPS response to cediranib to shed light on the mechanisms driving both primary and acquired resistance observed in the CASPS trial. This understanding will offer further insights into strategies to overcome resistance either through the use of combination or salvage therapies with further lines of alternative TKIs. Of interest, the subset of patients who enrolled in the CASPS trial with prior exposure to TKI therapy, aside from those pre-treated with crizotinib, appeared to have equal outcomes to those without prior TKI exposure.

Looking to the future, the role of the immune system and immunomodulating therapies in the treatment of ASPS is exciting. Preclinical studies in a mouse model of ASPS have demonstrated the upregulation of monocarboxylate transporter 1 (SLC16A1) and basigin (BSG), both associated with the importation of lactate into the cells, and the downregulation of monocarboxylate transporter 4 (SLC16A3), a gene associated with lactate export [115]. As well as stimulating cell proliferation and angiogenesis, the excess intracellular lactate is converted to pyruvate that leads to the upregulation of hypoxia-inducible factor (HIF). Not only does HIF activate VEGF transcription, but upregulation of HIF results in the accumulation of regulatory T-cells in the tumor microenvironment, leading to T-cell suppression and heightened immune system evasion [116]. As such, the question remains whether part of the response seen with cediranib and other antiangiogenic therapies is associated with improved immune activity through the downregulation of suppressive regulatory T-cells by VEGFR targeting. The recent trial of axitinib with the anti-programmed-death-1 checkpoint inhibitor pembrolizumab lends support to the combination of antiangiogenic therapy with immune checkpoint inhibition, with promising activity...
demonstrated particularly in ASPS (NCT02636725) [117]. Moving forward, through a deeper understanding of the tumor immune microenvironment and its association with antiangiogenic therapy in ASPS, we may be able to develop rational combinational therapies which leverage on this interaction to provide patients with better treatments.

10. Nintedanib

Nintedanib (Ofev®/Vargatef®/BIBF 1120) has shown preclinical activity in a range of STS subtypes including MRT, SS, and MPNST, most of which harbor overexpression of kinases targeted by nintedanib [64,118,119]. For instance, nintedanib was found to decrease cellular proliferation of MPNST and SS cell lines, both of which express relatively high levels of PDGFR and FGFR RTKs [64,118]. This reduction in growth was associated with inhibition of PDGFR and FGFR phosphorylation and downstream AKT and/or ERK signaling, which was not observed in nintedanib-resistant Ewing’s sarcoma cell lines [118]. These properties of nintedanib were also observed in vivo in a SS xenograft model, with an associated decrease in tumor microvessel area [118]. Combination therapy utilizing AKT and MEK inhibitors was able to phenocopy the effects of nintedanib, thereby confirming the importance of dual blockade of the AKT and ERK signaling as a means of inhibiting growth of SS and MPNST cells [118]. This study also found that nintedanib confers its antiproliferative and downstream inhibitory effects through dual inhibition of PDGFR and FGFR, as monotherapy using an FGFR inhibitor was not able to fully recapitulate the phenotype observed with nintedanib [118]. Utilizing RNA interference (RNAi), the authors showed that only the combined knockdown of FGFR1, FGFR2, and PDGFRα was able to phenocopy nintedanib treatment [118].

Similarly, nintedanib was found to display significant potency toward MRT and RMS cell lines A204 and SJCRH30, respectively, both of which overexpress PDGFR [64,119].

The EORTC Soft Tissue and Bone Sarcoma Group (STBSG) is conducting a multicenter, open-label, phase II trial randomizing advanced STS patients to receive ifosfamide or nintedanib as second-line therapy (NCT02808247, EORTC1506) [120]. Although unselective in its recruitment of STS subtypes, this trial may offer insights into the efficacy of nintedanib in STS and provide evidence for its use in the clinical setting.

11. Anlotinib

Anlotinib (AL3818) is a multi-target TKI that has only recently been developed and, as a result, published preclinical studies of anlotinib in STS are limited. In addition to its ability to block the activation of angiogenic and tumorigenic RTKs, it has been shown that anlotinib reduces SS cellular proliferation and xenograft tumor growth through targeting of GINS1, a DNA replication complex subunit found to be highly expressed in SS and associated with poor prognosis [121]. RNAi-mediated knockdown of GINS1 was able to phenocopy the antiproliferative effects of anlotinib in SS cell lines, thereby confirming that the targeting of GINS1 by anlotinib was essential in achieving its antitumor effect [121]. Further preclinical studies into anlotinib may be useful in identifying additional STS subtypes that may benefit clinically from treatment with this TKI.

A phase II clinical trial of anlotinib has been completed (see Table 2) and this TKI is currently undergoing phase III evaluation in advanced STS [122,123]. Chi et al. reported data from their multi-center, single-arm, phase II study of anlotinib in antiangiogenic therapy-naïve patients with metastatic STS that had progressed on first-line anthracycline therapy (NCT02449343) [122]. They enrolled 166 patients with a broad range of STS subtypes, including LMS, LPS, SS, undifferentiated pleomorphic sarcoma, ASPS, clear cell sarcoma (CCS), and a further subgroup of other sarcomas. In this trial, anlotinib demonstrated broad-spectrum antitumor activity in chemotherapy-refractory STS, with disease control achieved in 74% of patients (107 of 166); mPFS was 5.6 months and median OS of 12 months. The context of these data are promising, particularly given the historical survival data of chemotherapy-refractory STS, such as the placebo arm of the PALETTE trial which reported an mPFS of 1.6 months and median OS of 10.7 months [13]. Such comparisons are of course limited given the heterogeneity of clinical behavior in STS; however, this does suggest that anlotinib is a promising agent in advanced STS. Interestingly, in the ASPS subgroup, a sarcoma subtype particularly resistant to cytotoxic chemotherapy, 6 of the 13 patients (46%) had a partial response to anlotinib per RECIST, with a cohort mPFS of 21 months.

The promising data from this phase II trial has led to an ongoing phase III, anlotinib in metastatic or advanced ASPS, LMS, and SS (APROMISS, NCT03016819) trial which aims to recruit 95 patients with SS and 68 with LMS who will be randomized 2:1 to anlotinib or dacarbazine, with a further 56 patients with ASPS to receive open-label anlotinib [123]. APROMISS is currently the only phase III trial currently evaluating the efficacy of a TKI across a number of different STS subtypes. Should the promising efficacy signals detected in the phase II trial translate into definitive data in the APROMISS trial, the sarcoma community may well have another TKI option for use as part of the therapeutic arsenal in advanced STS.

12. Sitravatinib

The published preclinical evaluation of sitravatinib (MGCD516) in STS is limited to a single publication [19]. This study reports potent inhibition of proliferation in dedifferentiated-LPS and MPNST cell lines upon sitravatinib treatment, with associated blockade of PDGFRβ, MET, and insulin-like growth factor 1 receptor (IGF1R) phosphorylation, as well as downstream AKT signaling [19]. This significant reduction in LPS growth in vitro is important as there are currently no TKIs approved for use in this STS subtype. In the LPS and MPNST cell lines assessed, sitravatinib displayed greater antiproliferative effects compared to pazopanib, crizotinib, and imatinib, with an associated increased reduction in RTK and AKT phosphorylation both in vitro and in vivo [19]. To determine if the antiproliferative effects observed in cells were due to the inhibition of RTKs by sitravatinib, the authors utilized siRNA-mediated knockdown of PDGFRβ, MET, IGF1R, and KIT to phenocopy sitravatinib’s effects [19]. The antiproliferative effect induced by silencing multiple RTKs simultaneously was comparable to
those observed with sitravatinib, thereby confirming the correlation between inhibition of these RTKs and the significant reduction in tumor cell proliferation [19].

The efficacy of sitravatinib in LPS in the preclinical setting has been translated into an ongoing phase II clinical trial in well-differentiated/dedifferentiated-LPS, as well as other advanced sarcomas (NCT02978859) [124,125]. This prospective, open-label, single-arm, phase II study is currently enrolling a target of 29 patients under a Simon II stage design and the study is expected to complete in January 2021 [124,125]. The first stage of the study will recruit 13 patients with a diagnosis of progressive well-differentiated or dedifferentiated-LPS to receive 150mg of oral sitravatinib daily, with PFS at 12 weeks as the primary endpoint. Interim analysis will determine efficacy and, if satisfactory, the second stage of the trial will involve enrollment of a further 16 patients with well-differentiated or dedifferentiated-LPS. If the Simon II stage design fails, the next 16 patients enrolled will be made up of cohorts of 4 patients each, with a diagnosis of MPNST, SS, aRMS, and ASPS. Due to the lack of demonstrated efficacy in LPS in a number of previous clinical trials involving TKIs, this trial represents an important opportunity toward identifying an effective treatment for these patients.

### 13. Crizotinib

Crizotinib (Xalkori/PF-02341066) is a multi-target TKI that inhibits the anaplastic lymphoma kinase (ALK) and MET signaling pathways. It has shown antitumor effects in models of small round cell tumors, SS, and aRMS. Utilizing a 119 anticancer inhibitor screen, crizotinib was found to be the only TKI that resulted in significant suppression of cellular growth in patient-derived CIC-DUX4 fusion-positive small round cell tumor primary cells [126]. In another study, a panel of SS cell lines were subjected to phosphoproteomic profiling and ALK was shown to be an oncogenic driver in a subset of cell lines [127,128]. SS cell lines were therefore subjected to escalating doses of crizotinib treatment and only those lines found to highly express either ALK or MET displayed significant sensitivity to the drug [64,127]. The observed decrease in cell proliferation was coupled with a reduction in downstream ERK, AKT, and STAT3 phosphorylation, as well as induction of G1 cell cycle arrest and apoptosis [127]. Xenograft models of ALK- and MET-dependent SS cells also displayed sensitivity to crizotinib which resulted in durable tumor regression alongside a significant reduction in microvessel area [127]. In another study, it was demonstrated that ALK and MET-expressing aRMS cell lines were sensitive to crizotinib and that this drug inhibited cell migration and invasiveness [129].

The EORTC STBSG-sponsored CREATE trial was an international, biomarker-driven, single-arm, non-randomized, open-label, phase II trial with the aim of assessing the efficacy and safety of crizotinib in ASPS, inflammatory myofibroblastic tumors (IMT), CCS, and aRMS (NCT01524926, EORTC90101) (Table 3) [130–132]. These sarcoma subtypes were chosen as they are known to harbor specific alterations that result in ALK and/or MET activation. All the patients enrolled received 250mg crizotinib orally twice daily without masking or randomization. The primary end-point across all cohorts was objective response rate as determined by RECIST on cross-sectional imaging (Table 2).

The rationale for including a cohort of ASPS in the trial was driven by the characteristic chromosomal translocation seen in this subtype which comprises of a fusion of the transcription factor E3 (TFE3) gene to the ASPCR1 gene. The resulting chimeric transcription factor leads to overexpression of MET [133]. The ASPS cohort in CREATE consisted of 48 patients with metastatic or advanced ASPS not amenable to routine curative management, of which 45 were available for assessment of crizotinib activity [130]. Twenty-five of the 48 (52.1%) patients had no previous systemic anticancer therapy. The best observed responses were 2 (4.4%) partial responses, 39 (86.7%) with stable disease, and 4 (8.9%) with progressive disease. Six of the 48 patients (12.5%) suffered grade 3/4 toxicities.

Approximately 50% of IMTs are known to harbor ALK gene rearrangements, predominantly translocations with variable fusion partners, resulting in the overexpression of chimeric ALK protein. The IMT cohort in CREATE consisted of 20 patients with advanced IMT deemed incurable through routine management options and 19 of those enrolled were available for assessment of efficacy [131]. The presence of ALK gene rearrangement was determined centrally using immunohistochemistry and FISH techniques and deemed positive if greater than 15% of cells demonstrated confirmed gene rearrangements on FISH analysis or positive staining for ALK on immunohistochemistry. In the cases which harbored the ALK fusion, 6 of 12 (50%) patients achieved an objective response to crizotinib, compared to only 1 of 7 (14.3%) patients with unaltered ALK. In terms of toxicity, 8 serious adverse events related to crizotinib were observed in 5 patients (25%). With an objective response observed in half of IMT patients with a proven rearrangement of ALK, the CREATE trial supports the use of crizotinib in this clinical setting [131].

CCS is a sarcoma affecting tendons and aponeuroses and is characterized by a chromosomal translocation resulting in the generation of a EWSR1-ATF1 fusion gene and subsequent aberrant overexpression of MET [134]. For the CCS cohort in CREATE, 34 patients with a centrally confirmed diagnosis of CCS were enrolled onto the study, of which 28 were assessable for response [132]. Presence of the EWSR1-ATF1 fusion gene was confirmed through FISH analysis, with a minimum of 15% of cells required to demonstrate the EWSR1-ATF1 fusion gene for the case to be deemed positive for MET amplification. Twenty-five of the 34 (73.5%) patients had not received prior systemic therapy. Partial response was observed in 1 of 26 (3.8%) patients, with stable disease observed in 17 (65.4%) and progressive disease in the remaining 8 (30.8%) patients. The mPFS observed in this cohort of 4.4 months is favorable compared to previously published data reporting a mPFS of 2.6 months in patients with CCS treated with first-line cytotoxic chemotherapy [135].

The CREATE trial is an example of a biomarker-driven basket trial, leveraging on the demonstrated biological activity of crizotinib in preclinical work and applying that to sarcoma subtypes with known genetic alterations resulting in the upregulation of ALK and/or MET. This trial has simultaneously identified a novel targeted therapy with clinical efficacy in multiple STS subtypes and is a good model for biomarker or genotype-driven trial designs for the future evaluation of TKIs in non-GIST STS.
14. Dasatinib

Promising preclinical results in a variety of STS subtypes has revealed a potential emerging role of dasatinib (Spryce®/BMS-354,825) in the evolving landscape of contemporary STS treatment. For instance, dasatinib significantly inhibited the growth of CRKL-dependent embryonal RMS and aRMS cell line and xenograft models through inhibition of the Src-family kinases, which are associated regulators of CRKL activity [136]. Dasatinib has also been shown to block tumor cell growth by directly repressing Ephrin B4 receptor and PDGFRβ phosphorylation in primary cell and allograft models of aRMS [137]. Similar anti-proliferative effects have been observed in SS, ASPS, LPS, aRMS, and MRT preclinical models, with direct inhibition of Src and/or PDGFRα [64,65,138–140]. Within these models, dasatinib was also found to induce apoptosis and cell cycle arrest, with concomitant inhibition of cellular migration and invasiveness [137–141]. Additionally, dasatinib sensitivity has also been reported in cell line models of fibrosarcoma, MPNST, RMS, spindle cell sarcoma, epithelioid sarcoma, and LMS [64]. Furthermore, a recent preclinical study has reported the activity of dasatinib in a panel of patient-derived sarcoma cells that harbor a broad range of translocations [141].

Despite the promising potency of dasatinib in a broad range of preclinical models, the efficacy of this drug in the clinical setting has largely been disappointing. Dasatinib has been evaluated in an open-label, single-arm, phase II trial in ASPS, chondrosarcoma, chordoma, epithelioid sarcoma, and SFT (NCT00464620, SARC009) (Table 2) [142]. These subtypes were selected due to their indolent nature and the lack of effective therapies in cases with unresectable or metastatic lesions. Eligibility criteria included patients over the age of 13 years, a diagnosis of ASPS or grade 1/2 for the other subtypes, a measurable lesion on cross-sectional imaging, and tumors incurable using conventional therapies. Each patient was treated with dasatinib at a dose of 100mg twice daily. One hundred and nine patients were recruited to the study, composed of 12 patients with ASPS (11%), 33 (30%) with chondrosarcoma, 32 (29%) with chordoma, 7 (6%) with epithelioid sarcoma, and 25 (23%) with SFT. The overall rate of 6 month PFS by Choi criteria was 48%, falling short of the trial’s stated primary end-point of achieving disease control at 6 months in at least 50% of the recruited patients. There was considerable between-subtype variation, with the rate of PFS at 6 months of 62% in the ASPS cohort, 57% in epithelioid sarcoma, 54% in chordoma, 47% in chondrosarcoma, and lowest in the SFT cohort at 30% (Table 3). Of note, 18% of patients with chondrosarcoma or chordoma, both known to be chemoresistant, were seen to have an objective response to dasatinib on cross-sectional imaging as per Choi criteria. Across the whole cohort, a median of 4 cycles of dasatinib were administered with treatment interruption necessary due to toxicity in 62 of the 109 patients (57%) and a dose reduction in 36 (33%) patients.

Based on this study, dasatinib failed to demonstrate clinically meaningful antitumor effect in a number of the subgroups enrolled, most notably SFT. The lack of placebo control limits our ability to draw substantial conclusions from the results, however, based on the encouraging antitumor activity observed in ASPS, epithelioid sarcoma, and chordoma there may be a basis for further investigation of this drug in these subtypes.

15. NTRK inhibitors

The NTRK family consists of the neurotrophic factor receptors TRKA, TRKB, and TRKC, which play pivotal roles in physiological neuronal development and differentiation, but have also been established as oncogenic drivers in a range of human malignancies [50]. The most common mechanism of NTRK oncogenesis occurs through intra- and inter-chromosomal rearrangements resulting in constitutively active NTRK fusion proteins, some of which have been identified in STS [50]. For instance, the gene fusion, ET6-NTRK3, is considered pathognomonic in infantile fibrosarcomas, with >90% incidence within this subtype [50,52].

The NTRK inhibitor larotrectinib (Vitrakvi®/LOXO-101/ARRY-470) has recently been approved by the FDA for advanced or metastatic solid tumors harboring NTRK gene fusions [143]. The approval was based on the findings of a clinical development program which included patients of any age and any tumor type and encompassed three clinical study protocols (NCT02122913, NCT02637687, and NCT02576431) [144]. The three clinical studies were; a safety and dose-escalation phase I study involving adults, a phase I-II study involving children with advanced solid or primary central nervous system tumors, and a single-arm, non-randomized, phase II study of adolescents and adults with NTRK-fusion positive tumors. A maximally tolerated dose of larotrectinib was not defined during the phase I study and the recommended dose of 100mg twice daily of larotrectinib was utilized for the phase II study. The primary end-point of the study was overall response rate, assessed by independent radiology review, and determined by RECIST. The combined program cohort of 55 patients was made up of 17 unique cancer diagnoses, including 7 cases of infantile fibrosarcoma and 11 STS of unspecified histological subtypes. The reported overall response rate was 80% (44 out of 55 patients) and was independent of tumor type, age, or type of NTRK fusion. mPFS had not been reached at a median follow-up of 9.9 months, nor had a median duration of response been met at a median follow-up of 8.3 months. Larotrectinib was well tolerated with a dose reduction only required in 8 of the 55 patients (15%) and no treatment-related grade 4 or 5 adverse events noted.

The significant antitumor effect observed in these trials demonstrates the rationale for undertaking biomarker focused trials against known molecular targets. The impressive overall response rate supports the use of larotrectinib in patients with sarcomas harboring NTRK alterations. In addition, across the three clinical trials described above, the authors were able to obtain post-treatment tumor tissue in 10 patients with disease progression following a minimum 6 months of stable disease or an objective response, with the goal of determining the mechanisms driving acquired resistance. A variety of kinase domain mutations in the NTRK gene were identified from these specimens. Moving forward, LOXO-195, a next-generation NTRK inhibitor specifically designed to inhibit
these kinase domain mutations associated with acquired drug resistance may emerge as an important option for patients who progress on larotrectinib. LOXO-195 is currently undergoing phase I/II trials in adults and children with progressive disease following NTRK-targeted therapy (NCT03215511) [145].

16. Biomarkers for TKI response in STS

At present, there is an unmet clinical need for validated biomarkers predictive of response to TKIs in STS. In the grouped post-hoc analysis of the cohorts of patients treated with pazopanib in the PALETTE trial and the preceding phase II clinical trial, only performance status and tumor grade were identified as predictive of response to pazopanib [13,146]. However, these are well established prognostic factors in STS and no new biomarkers for response were identified [147]. Other clinical trials of TKIs in STS have included sample collection with the goal of biomarker identification. In patients with GIST treated with sunitinib, Deprimo et al. identified that a decreased level from baseline of soluble KIT in plasma was associated with increased time to progression, whilst Norden-Zfoni et al. showed that increased circulating endothelial cells upon treatment initiation was associated with improved outcomes [148,149]. Raut et al. identified that following initiation of sorafenib in advanced unselected soft tissue sarcomas, decreased levels of VEGFR2 following 28 days of therapy correlated with disease progression [150].

Advances in imaging technology have also paved the way for imaging modalities that are potentially able to define TKI responses more accurately and at earlier stages of treatment. The most widely utilized modality at present is positron emission tomography (PET) which enables visualization of cell processes in vivo through radioactive probes, most commonly 18F-fluorodeoxyglucose (FDG). FDG-PET has shown value as a candidate imaging biomarker in the treatment of GIST with the TKI imatinib, with Goerres et al. reporting that after one cycle of treatment, tumors without pathological FDG accumulation went on to have a longer mean overall survival when compared to tumors displaying ongoing FDG-avid areas [151]. Furthermore, Vlenterie et al. performed FDG-PET scans at baseline and 2 weeks after treatment initiation in 20 patients with unselected STS treated with pazopanib. They reported that visual response analysis of FDG-PET scans after 2 weeks of pazopanib therapy was able to classify 42% of patients as non-responders who subsequently went on to cease pazopanib at 8 weeks due to disease progression as determined by computerized tomography scan [152]. This ability to identify non-responders earlier in their treatment results in less exposure of patients to costly and potentially toxic therapies.

The progress being made in biomarker discovery is encouraging, however, the markers discussed above are yet to be validated and can only be assessed after initiation of therapy. Looking to the future, more research is necessary to discover better predictive and validated biomarkers to allow the prospective selection of patients most likely to respond to specific TKIs.

17. Inter-patient pharmacological variability associated with TKI therapy

Many pharmacological studies in a variety of cancer types have shown that patients treated with TKIs display high inter-patient pharmacokinetic variability [153–166]. This metabolic variation will therefore result in certain patients being under- or overdosed, when using a standard dosing regimen, leading to a lack of clinical efficacy or increased toxicity and adverse effects, respectively. In addition, many of the independent, individual covariables within a studied population (such as age, gender, body weight, and race), often show a significant inter-covariable difference in pharmacokinetics. However, these are currently not applicable to the clinical adjustment of dose for the entire population [155,158,162,163,167]. Pharmacokinetic variability has also been shown to occur over time with decreased TKI exposure being observed upon long-term treatment [157,168,169].

The observed inter-patient variability is due to numerous pharmacokinetic parameters such as cytochrome P450 (CYP) activity, drug–drug interactions (DDI), drug-transporter activity such as P-glycoprotein (PGP), and plasma protein binding. The main phase I metabolic pathway of most TKIs is through the CYP pathway, with the CYP3A4 isoenzyme accounting for the main route of metabolism for all of the TKIs discussed except for nintedanib [170–172]. Although marginally metabolized by CYP3A4, nintedanib is primarily metabolized by esterases and UDP-glucuronosyltransferases [170]. Therefore, patients with increased or decreased levels of CYP activity or those harboring CYP polymorphisms will result in substantial differences in TKI plasma concentrations [173]. In addition, TKI plasma levels can also be greatly altered due to DDI mediated by CYP activity where concomitant treatment of TKIs with CYP inhibitors or inducers can result in the decrease or increase of TKI metabolism [170,173]. Similar considerations in terms of activation levels and genetic polymorphisms must be taken into account for cellular drug efflux pumps such as PGP, for which the majority of TKIs discussed are substrates [160,164,170]. Furthermore, many of the TKIs discussed are incidental CYP and/or PGP inhibitors themselves, further exacerbating potential DDIs [170]. Finally, all of these TKIs display very high plasma protein binding (90–99%), except for larotrectinib (70%) [170,174,175]. Therefore, the vast majority of administered TKI become bound to proteins within the plasma and are unable to fulfill their biological intracellular activity. Consequently, a greater dosage of TKI needs to be administered to ensure adequate drug levels to have the desired therapeutic effect.

Therefore, there is a need for a broader discussion about the implementation of therapeutic drug monitoring (TDM) techniques for personalized TKI therapy. Several studies have highlighted how maintaining the patient plasma concentration of a TKI above a trough plasma concentration ($C_{\text{min}}$) threshold through inter-patient and time-point specific dosage variation, whilst also maintaining a concentration below one that would result in toxicity/adverse effects, has resulted in increased molecular responses and PFS in GIST, RCC, and chronic myeloid leukemia patients [153,154,156,168,169,176,177]. For instance, in RCC, a $C_{\text{min}}$...
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threshold of ≥20mg/L pazopanib has been clinically validated to provide a significant increase in PFS and tumor shrinkage when compared to patients displaying < 20mg/L Cmin [177]. In STS, Verheijen et al. have described similar trends with an increased PFS and tumor shrinkage in patients with an average Cmin of pazopanib at ≥20mg/L [178,179]. The 2016 Verheijen study also showed that this relationship between Cmin and treatment response occurred in the overall population of analyzed patients with solid tumors, rather than just in the STS subset [178]. These studies both concluded that individualized pazopanib dose escalation through TDM could optimize treatment in underexposed STS patients who displayed a Cmin of <20mg/L, thereby elevating individual Cmin levels above this threshold to result in a greater therapeutic response [178,179].

TDM could therefore limit the possibility of sub- and supra-exposure in TKI therapy through variation of dosages on a patient-and time-specific basis to increase therapeutic activity, reducing toxicity/adverse effects, and to limit the intrinsic inter-patient response variability universally observed in TKI therapy [153,154,169,178,179]. Inter-patient pharmacokinetic variability is therefore an important consideration for clinicians in the treatment of STS patients with TKIs.

18. Expert opinion

The introduction of TKIs into the clinic has revolutionized the way many cancers are treated. One of the biggest challenges related to the current management of non-GIST sarcomas with TKIs is the lack of any validated predictive biomarkers. As a field, more translational research needs to be undertaken over the next five years to discover robust biomarkers to identify patients who are most likely to achieve durable benefit from TKIs. Should such biomarkers be identified, the emphasis in clinical trial design in sarcomas should move away from the ‘one size fits all’ paradigm in which heterogeneous cohorts of multiple histological subtypes in small numbers are treated with the same drug or schedule [180]. In contrast, where possible, biomarker-guided basket trials such as the CREATE trial, which evaluate multiple disease types with a common oncogenic driver matched to a specific targeted therapy, should be considered. We anticipate that moving toward biomarker-guided clinical studies in sarcoma will transform the current ‘one size fits all’ approach into a personalized medicine paradigm where the right patient is treated with the right drug at the right time. Not only will this benefit patients, through rational administration of the most effective anticancer therapies, it will also improve cost-effectiveness and quality of life measures in the management of sarcomas. Due to the rarity of sarcomas, the step from phase II to phase III trials is expensive, time consuming, and resource intensive, often requiring international collaboration over a long period to recruit sufficient numbers for an adequately powered trial. We anticipate that biomarker-guided trials will also help address the problem faced in sarcoma where a large number of phase II trials of TKIs have been conducted but relatively few placebo-controlled phase III trials.

The underlying biology driving TKI response and resistance in STS is also poorly understood and this remains an important knowledge gap to address in this field. Through the use of patient-derived preclinical models and molecular profiling of tissue specimens, it is anticipated that we will gain a better understanding of the biological factors that govern TKI response. At present, there is a paucity of clinical evidence related to the role of TKIs in the multi-line setting in non-GIST STS. In order to optimize patient management and drug selection, the role of regorafenib and other TKIs described in this review in the multi-line setting should be explored. As we develop a better understanding of the biology and mechanisms of TKI activity and acquired resistance in non-GIST STS, this knowledge will shed light on the role of sequential drug treatment and direct the development of clinical trials to evaluate multi-line TKI strategies as a means of achieving durable tumor responses in patients. The clinical experience in RCC may act as a template in this regard where the use of multiple lines of multi-target TKIs is the standard of care [181]. Indeed, evidence from the CASPS trial where patients with prior exposure to other TKIs had the same cediranib outcomes to those without prior TKI exposure suggests that selected STS subtypes may similarly benefit from such a multi-line strategy [114]. Another important area to consider is that a standard dosing regimen of TKI may not be a therapeutically beneficial strategy for many patients due to the high inter-patient variability that exists in TKI pharmacokinetics and pharmacodynamics. There is therefore an increasing movement towards utilizing TDM where patient-specific TKI doses are administered over time, resulting in optimal TKI exposure. TKIs represent an exciting shift in the paradigm in the treatment of multiple cancer types. However, there is much progress to be made in STS before similar benefits can be achieved in this group of rare cancers. Over the next five years, we envisage that the number of TKIs licensed for use in STS is likely to increase, which will offer new hope for patients with these cancers with poor outcomes in the advanced disease setting. However, we also anticipate that such TKIs will face similar issues as those encountered with pazopanib, namely drug resistance and heterogeneity in patient response. As our understanding of the biology driving TKI therapeutic response improves, the sarcoma community will need to identify predictive biomarkers that will enable TKI regimens to be matched to individual patients. This deeper biological understanding will also define the role of sequential TKI therapies in the management of STS, providing clinicians with salvage options following failure of first-line TKI therapy. The next five years offers the sarcoma research community an exciting opportunity to take great strides forward in defining the role TKIs in the management of STS and improving long-term survival in patients.

19. Conclusion

The role of TKIs in the treatment of sarcomas continues to expand with recent positive trials such as crizotinib in IMT (CREATE), cediranib in ASPS (CASPS), and soroferanib in desmoid tumors (ALLIANCE A091105). Ongoing phase III trials such as APROMISS highlight the potential that additional TKI options are on the horizon for non-GIST STS. As our knowledge of the biology underlying response and resistance in TKIs increases, our ability to develop patient-specific therapies and multi-line treatment strategies will improve. To drive this promising area of research forward, the research and medical communities must continue to come together to collaborate on large-scale trials of
the most promising agents in this rare group of cancers to ensure they make the transition from bench to bedside.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Soft tissue sarcoma statistics, Cancer Research UK. 2010 [cited 2019 Jun 2]. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/soft-tissue-sarcoma

2. Bone and Soft Tissue Sarcoma UK incidence and survival: 1996 to 2010 version 2.0. National Cancer Intelligence Network, 2013 [cited 2019 Jun 2]. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3901765/

3. Linch M, Miah AB, Thway K, et al. Systemic treatment of soft-tissue sarcoma – gold standard and novel therapies. Nat Rev Clin Oncol. 2014;11:187–202.

4. Schafer IM, Cote GM, Hornick JL. Contemporary sarcoma diagnosis, genetics, and genomics. J Clin Oncol. 2018;36:101–110.

5. Wu P, Nielsen TE, Clausen MH. FDA-approved small-molecule kinase inhibitors. Trends Pharmacol Sci. 2015;36:422–439.

6. Wozniak A, Gebreyohannes YK, Debiec-Rychter M, et al. New targets and therapies for gastrointestinal stromal tumours. Expert Rev Anticancer Ther. 2017;17:1117–1129.

7. Corless CL, Barnett CM, Heinrich MC. Gastrointestinal stromal tumours: origin and molecular oncology. Nat Rev Cancer. 2011;11:865–878.

8. Judson I, Bulusu R, Seddon B, et al. UK clinical practice guidelines for the management of gastrointestinal stromal tumours (GIST). Clin Sarcoma Res. 2017;7:6.

9. Phase 3 study of DCC-2618 vs placebo in advanced GIST patients who have been treated with prior anti-cancer therapies, deciphera pharmacueticals LLC. 2019 [cited 2019 Oct 15]. Available from: https://clinicaltrials.gov/ct2/show/NCT03535753

10. (VOYAGER) Study of avapritinib vs regorafenib in patients with locally advanced unresectable or metastatic GIST, blueprint medicines corporation. 2019 [cited 2019 Oct 15]. Available from: https://clinicaltrials.gov/ct2/show/NCT03465722

11. Gloc J, Arnaldez F, Wiener L, et al. A phase II trial of vandetanib in children and adults with succinate dehydrogenase-deficient gastrointestinal stromal tumour. Clin Cancer Res. 2019;25:6302–6308.

12. Flavahan WA, Drier Y, Johnstone SE, et al. Altered chromosomal topology drives oncogenic programs in SDH-deficient GIST. Nature. 2019 Oct. doi: 10.1038/s41586-019-1668-3. [Epub ahead of print].

13. Van Der Graaf WTA, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALAETE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2012;379:1879–1886.

•• A randomised, double-blind, placebo-controlled, phase III trial of pazopanib in a range of STS subtypes which provided the basis for the groundbreaking approval of a TKI in a broad range of non-adipocytic STS. When compared to placebo, pazopanib treatment resulted in significantly improved PFS, however no significant OS benefit was observed.

14. Lee ATJ, Jones RL, Huang PH. Pazopanib in advanced soft tissue sarcomas. Signal Transduct Target Ther. 2019;4:16.

15. Chamberlain FE, Widing C, Jones RL, et al. Pazopanib in patients with advanced intermediate-grade or high-grade liposarcoma. Expert Opin Investig Drugs. 2019;28:505–511.

16. Davis MI, Hunt JP, Herrgard S, et al. Comprehensive analysis of kinase inhibitor selectivity. Nat Biotechnol. 2011;29:1046–1051.

• In-depth interrogation of >80% of the human catalytic kinome to determine the protein interactions of 72 kinase inhibitors. Provides an invaluable source of inhibitor-kinase specificity in terms of dissociation constants to help elucidate kinase inhibitor biology, mechanisms, and toxicity.

17. Zopf D, Fichtner I, Bhargava A, et al. Pharmacokinetic activity and pharmacokinetics of regorafenib in preclinical models. Cancer Med. 2016;5:3176–3185.

18. Wilhelm SM, Dumas J, Adnane L, et al. Regorafenib (BAY 73-4506): a new oral multi-kinase inhibitor of angiogenic, stromal and onco- genetic receptor tyrosine kinases with potent preclinical anticancer activity. Int J Cancer. 2011;129:245–255.

19. Patwardhan PP, Ivy KS, Musi E, et al. Significant blockade of multiple receptor tyrosine kinases by MGCD16 (siravatinib), a novel small molecule inhibitor, shows potent tumor-activity in preclinical models of sarcoma. Oncotarget. 2016;7:4093–4109.

20. Xie C, Wan X, Quan H, et al. Preclinical characterization of anlotinib, a highly potent and selective vascular endothelial growth factor receptor-2 inhibitor. Cancer Sci. 2018;109:1207–1219.

21. Dumas J, Boyer S, Riedl B, et al. Fluoro substituted omega-carboxyaryl diphenyl urea for the treatment and prevention of diseases and conditions. 2005:WO2005009961A2.

22. Sun L, Liang C, Shirazian S, et al. Discovery of 5-[5-fluoro-2-oxo-1,2-dihydroindolin-3(2H)-yldenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide, a novel tyrosine kinase inhibitor targeting vascular endothelial and platelet-derived growth factor receptor tyrosine kinase. J Med Chem. 2003;46:1116–1119.

23. Wedge SR, Kendrew J, Hennequin LF, et al. AZD2171: a highly potent, orally bioavailable, vascular endothelial growth factor receptor-2 tyrosine kinase inhibitor for the treatment of cancer. Cancer Res. 2005;65:4389–4400.

24. Roth GJ, Heckel A, Colbatzky F, et al. Design, synthesis, and evaluation of indolinones as triple angiokinase inhibitors and the discovery of a highly specific 6-methoxy carbonyl substituted indolinone (IBIF 1120). J Med Chem. 2009;52:4466–4480.

25. Hu-Lowe DD, Zou HY, Grazzini ML, et al. Nonclinical antiangiogenesis and antitumor activities of axitinib (AG-013736), an oral, potent, and selective inhibitor of vascular endothelial growth factor receptor tyrosine kinases 1, 2, 3. Clin Cancer Res. 2008;14:7272–7283.

26. Wilhelm SM, Carter C, Tang L, et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res. 2004;64:7099–7109.
27. Schmieder R, Hoffmann J, Becker M, et al. Regorafenib (BAY 73-4506): antitumor and antimetastatic activities in preclinical models of colorectal cancer. Int J Cancer. 2014;135:1487–1496.

28. Mendel DB, Laird AD, Xin X, et al. In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. Clin Cancer Res. 2003;9:327–337.

29. Gomez-Rivera F, Santillan-Gomez AA, Younes MN, et al. The tyrosine kinase inhibitor, AZD2171, inhibits vascular endothelial growth factor receptor signalling and growth of anaplastic thyroid cancer in an orthotopic nude mouse model. Clin Cancer Res. 2007;13:4519–4527.

30. Hilberg F, Roth GJ, Krssek M, et al. BIBF 1120: triple angio kinase inhibitor with sustained receptor blockade and good antitumor efficacy. Cancer Res. 2008;68:4774–4782.

31. Daudigeos-Dubus E, Le Dret L, Lanvers-Kaminsky C, et al. Regorafenib: antitumor activity upon mono and combination therapy in preclinical pediatric malignancy models. PLoS One. 2010;5:e104261.

32. Rössler J, Monnet Y, Farace F, et al. The selective VEGFR1-3 inhibitor axitinib (AG-013736) shows antitumor activity in human neuroblastoma xenografts. Int J Cancer. 2011;128:2748–2758.

33. Liu L, Cao Y, Chen C, et al. Sorafenib blocks the RAF/MEK/ERK pathway, inhibits tumor angiogenesis, and induces tumor cell apoptosis in hepatocellular carcinoma model PLC/PRF/5. Cancer Res. 2006;66:11851–11858.

34. Zhang L, Smith KM, Chong AL, et al. In vivo antitumor and anti metastatic activity of sunitinib in preclinical neuroblastoma mouse model. Neoplasia. 2009;11:426–435.

35. Murray LJ, Abrams TJ, Long KR, et al. SU11248 inhibits tumor growth and CSF-1R-dependent osteolysis in an experimental breast cancer bone metastasis model. Clin Exp Metastasis. 2003;20:757–766.

36. Yin JJ, Zhang L, Munasinghe J, et al. Cediiranib/AZD2171 inhibits bone and brain metastasis in a preclinical model of advanced prostate cancer. Cancer Res. 2010;70:8662–8673.

37. Najy AJ, Jung YS, Won JJ, et al. Cediiranib inhibits both the intrasosseous growth of PDGF D-positive prostate cancer cells and the associated bone reaction. Prostate. 2012;72:1328–1338.

38. Lombardo LJ, Lee FY, Chen P, et al. Discovery of N-(2-chloro-6-methyl-phenyl)-2-(6-(4-hydroxyethyl)-piperazin-1-yl)-2-methyl-pyrimidin-4-ylamino)thiazole-5-carboxamide (BMS-354825), a dual Src/Abl kinase inhibitor with potent antitumor activity in preclinical assays. J Med Chem. 2004;47:6588–6661.

39. Buchdunger E, Zimmermann J, Mett H, et al. Inhibition of the Abl protein-tyrosine kinase in vitro and in vivo of a 2-phenylaminopyrimidine derivative. Cancer Res. 1996;56:100–104.

40. Zou HY, Li Q, Lee JH, et al. Dasatinib (BMS-354825) inhibits vascular endothelial growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. BMC Cancer. 2006;6:492.

41. Deininger MW, Goldman JM, Lydon N, et al. The tyrosine kinase inhibitor CGP57148B selectively inhibits the growth of BCR-ABL-positive cells. Blood. 1997;90:3691–3698.

42. Heinrich MC, Griffith DJ, Druker BJ, et al. Inhibition of c-kit receptor tyrosine kinase activity by STI 571, a selective tyrosine kinase inhibitor. Blood. 2000;96:925–932.

43. Deininger MW, Goldman JM, Lydon N, et al. The tyrosine kinase inhibitor CGP57148B selectively inhibits the growth of BCR-ABL-positive cells. Blood. 1997;90:3691–3698.

44. Heinrich MC, Griffith DJ, Druker BJ, et al. Inhibition of c-kit receptor tyrosine kinase activity by STI 571, a selective tyrosine kinase inhibitor. Blood. 2000;96:925–932.

45. Tuveson DA, Willis NA, Jacks T, et al. STI571 inactivation of the gastrointestinal stromal tumor c-KIT oncoprotein: biological and clinical implications. Oncogene. 2001;20:5054–5058.

46. Carroll M, Ohno-Jones S, Tamura S, et al. CGP 57148, a tyrosine kinase inhibitor, inhibits the growth of cells expressing BCR-ABL, TEL-ABL, and TEL-PDGFR fusion proteins. Blood. 1997;90:4947–4952.

47. Araki J, Logothetis C, Dasatinib: a potent SRC inhibitor in clinical development for the treatment of solid tumors. Cancer Treat Rev. 2010;36:492–500.

48. O’Hare T, Walters DK, Stoffregen EP, et al. In vitro activity of Bcr-Abl inhibitors AMN107 and BMS-354825 against clinically relevant imatinib-resistant Abl kinase domain mutants. Cancer Res. 2005;65:4500–4505.

49. Shah NP, Lee FY, Luo R, et al. Dasatinib (BMS-354825) inhibits KITD816V, an imatinib-resistant activating mutation that triggers neoplastic growth in most patients with systemic mastocytosis. Blood. 2006;108:286–291.

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

51. Vaishnavi A, Capelletti M, Le AT, et al. Oncogenic and drug-sensitive NTRK1 rearrangements in lung cancer. Nat Med. 2013;19:1469–1472.

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

53. Doebele RC, Davis LE, Vaishnavi A, et al. An oncogenic NTRK fusion in a patient with soft-tissue sarcoma with response to the tropomyosin-related kinase inhibitor LOXO-101. Cancer Discov. 2015;5:1049–1057.

54. Thomison J, McCarter M, McClain D, et al. Hyalinized collage in a dermatofibrosarcoma protuberans after treatment with imatinib mesylate. J Cutan Pathol. 2008;35:1003–1006.

55. Vassos N, Agaimy A, Schlabakovski A, et al. An unusual and potentially misleading phenotypic change in a primary gastrointestinal stromal tumour (GIST) under imatinib mesylate therapy. Virchows Arch. 2011;458:363–369.

56. Yanagisawa R, Noguchi M, Fujita K, et al. Preoperative treatment with pazopanib in a case of chemotherapy-resistant infantile fibrosarcoma. Pediatr Blood Cancer. 2016;63:348–351.

57. Robert G, Gabbay G, Bram R, et al. Case study of the month. Complete histologic remission after sunitinib neoadjuvant therapy in T3b renal cell carcinoma. Eur Urol. 2009;55:1477–1480.

58. Shuch B, Riggs SB, LaRochelle JC, et al. Neoadjuvant targeted therapy and advanced kidney cancer: observations and implications for a new treatment paradigm. BJU Int. 2008;102:692–696.

59. Kermiche-Rahali S, Di Fiore A, Drieux F, et al. Complete pathological regression of hepatocellular carcinoma with portal vein thrombosis treated with sorafenib. World J Surg Oncol. 2013;11:171.

60. Ohishi J, Aoki M, Nabeshima K, et al. Imatinib mesylate inhibits cell growth of malignant peripheral nerve sheath tumors in vitro and in vivo through suppression of PDGF-R β. BMC Cancer. 2013;13:224.

61. Aoki M, Nabeshima K, Koga K, et al. Imatinib mesylate inhibits cell invasion of malignant peripheral nerve sheath tumor induced by platelet-derived growth factor-BB. Lab Invest. 2007;87:767–779.

62. Greco A, Roccato E, Miranda C, et al. Growth-inhibitory effect of STI571 on cells transformed by the COL1A1/PDGFB rearrangement. Int J Cancer. 2001;92:354–360.

63. Sjöblom T, Shimizu A, O'Brien KP, et al. Growth inhibition of dermofibrosarcoma protuberans tumors by the platelet-derived growth factor receptor antagonist STI571 through induction of apoptosis. Cancer Res. 2001;61:5778–5783.

64. Teicher BA, Polley E, Kunkel M, et al. Sarcoma cell line screen of oncology drugs and investigational agents identifies patterns associated with gene and microRNA expression. Mol Cancer Ther. 2015;14:2452–2462.

65. Wong JP, Todd JR, Finetti MA, et al. Dual targeting of PDGFRα and FGFR1 displays synergistic efficacy in malignant rhabdoid tumors. Cell Rep. 2016;17:1265–1275.

66. Koos B, Jeibmann A, Lünenburger H, et al. The tyrosine kinase c-Abl promotes proliferation and is expressed in atypically teratoid and malignant rhabdoid tumors. Cancer. 2010;116:5075–5081.
67. Chugh R, Watthen JK, Maki RG, et al. Phase II multicenter trial of imatinib in 10 histologic subtypes of sarcoma using a bayesian hierarchical statistical model. J Clin Oncol. 2009;27:3148–3153.

68. Chugh R, Watthen JK, Patel SR, et al. Efficacy of imatinib in aggressive fibromatosis: results of a phase II multicentre sarcoma alliance for research through collaborations (SARC) trial. Clin Cancer Res. 2010;16:4884–4891.

69. Penel N, Le Cesne A, Bui BN, et al. Imatinib for progressive and recurrent aggressive fibromatosis (desmoid tumors): an FNCLCC/ French Sarcoma Group phase II trial with a long-term follow-up. Ann Oncol. 2011;22:452–457.

70. Kasper B, Gruenwald V, Reichardt P, et al. Imatinib induces sustained progression arrest in RECIST progressive desmoid tumours: final results of a phase II study of the German Interdisciplinary Sarcoma Group (IGISG). Eur J Cancer. 2017;76:60–67.

71. Rutkowski P, Van Glabbeke M, Rankin CJ, et al. Imatinib mesylate in advanced dermatofibrosarcoma protubersans: pooled analysis of two phase II clinical trials. J Clin Oncol. 2010;28:1772–1779.

72. Fields RC, Hameed M, Qin LX, et al. Dermatofibrosarcoma protubersans (DFSP): predictors of recurrence and the use of systemic therapy. Ann Surg Oncol. 2018;18:328–336.

73. Stacchiotti S, Tortoreto M, Baldi GG, et al. Preclinical and clinical evidence of activity of pazopanib in soft fibrous tumors. Eur J Cancer. 2014;50:3021–3028.

74. George S, Merriam P, Maki RG, et al. Multicenter phase II trial of sunitinib in the treatment of nongastrointestinal stromal tumor sarcomas. J Clin Oncol. 2009;27:3154–3160.

75. Jo JC, Hong YS, Kim KP, et al. A prospective multicentre phase II study of sunitinib in patients with advanced aggressive fibromatosis. Invest New Drugs. 2014;32:369–376.

76. Stacchiotti S, Negri T, Zaffaroni N, et al. Sunitinib in advanced alveolar soft part sarcoma: evidence of a direct antitumor effect. Ann Oncol. 2011;22:1682–1690.

77. Jagodzińska-Mucha P, Swiat T, Kozak K, et al. Long-term results of therapy with sunitinib in metastatic alveolar soft part sarcoma. Tumori. 2017;103:231–235.

78. Stacchiotti S, Negri T, Libertini M, et al. Sunitinib malate in solitary fibrous tumor (SFT). Ann Oncol. 2012;23:3171–3179.

79. Khalifa J, Ouali M, Chaltiel L, et al. Efficacy of trabectedin in malignant solitary fibrous tumors: a retrospective analysis from the French Sarcoma Group. BMC Cancer. 2015;15:700.

80. Stacchiotti S, Pantaleo MA, Astolfi A, et al. Activity of sunitinib inextraskeletal myxoid chondrosarcoma. Eur J Cancer. 2014;50:1657–1664.

81. Lieberman PH, Brennan MF, Kimmel M, et al. Alveolar soft-part sarcoma a clinico-pathologic study of half a century. Cancer. 1989;63:1–13.

82. Drilon AD, Popat S, Bhuchar G, et al. Extraskeletal myxoid chondrosarcoma. Cancer. 2008;113:3364–3371.

83. Cranshaw IM, Gikas PD, Fisher C, et al. Clinical outcomes of extra-thoracic solitary fibrous tumours. Eur J Surg Oncol. 2009;35:994–998.

84. Braggio D, Koller D, Jin F, et al. Autophagy inhibition overcomes sorafenib resistance in S45F-mutated desmoid tumors. Cancer. 2019;125:2693–2703.

85. Rosenberg L, Yoon CH, Sharma G, et al. Sorafenib inhibits proliferation and invasion in desmoid-derived cells by targeting Ras/MEK/ERK and PI3K/Akt/mTOR pathways. Carcinogenesis. 2018;39:681–688.

86. Abraham J, Chua YX, Glover JM, et al. An adaptive Src-PDGFR-RAF axis in rhabdomyosarcoma. Biochem Biophys Res Commun. 2012;426:363–368.

87. Maruwa W, D’Arcy P, Folin A, et al. Sorafenib inhibits tumor growth and vascularization of rhabdomyosarcoma cells by blocking IGF-1R-mediated signalling. Oncogenesis. 2008;1:67–78.

88. Ambrosini G, Cheema HS, Seelman S, et al. Sorafenib inhibits growth and mitogen-activated protein kinase signalling in malignant peripheral nerve sheath cells. Mol Cancer Ther. 2008;7:890–896.

89. Ray-Coquard I, Italiano A, Bompas E, et al. Sorafenib for patients with advanced angiosarcoma: a phase II Trial from the French Sarcoma Group (GSP/GETO). Oncologist. 2012;17:260–266.

90. D’Angelo SP, Munhoz RR, Kuk D, et al. Outcomes of systemic therapy for patients with metastatic angiosarcoma. Oncology. 2015;89:205–214.

91. Valentin T, Fournier C, Penel N, et al. Sorafenib in patients with progressive malignant solitary fibrous tumors: a subgroup analysis from a phase II study of the French Sarcoma Group (GS/GETO). Invest New Drugs. 2013;31:1626–1627.

92. Chevreau C, Le Cesne A, Ray-Coquard I, et al. Sorafenib in patients with progressive epithelioid hemangioendothelioma: a phase 2 study by the French Sarcoma Group. Cancer. 2013;19:2639–2644.

93. Kitachi M, Nagai S, Nishimura K, et al. Pulmonary epithelioid haemangioendothelioma in 21 patients, including three with partial spontaneous regression. Eur Respir J. 1998;12:89–96.

94. Yusaf N, Maruzzo M, Judson I, et al. Systemic treatment options for epithelioid haemangioendothelioma: the royal marsden hospital experience. Anticancer Res. 2015;35:473–480.

95. Penel N, Ray-Coquard I, Bal-Mahieu C, et al. Low level of baseline circulating VEGF-A is associated with better outcome in patients with vascular sarcomas receiving sorafenib: an ancillary study from a phase II trial. Target Oncol. 2014;9:273–277.

96. Gounder MM, Lefkowitz RA, Keohan ML, et al. Activity of sorafenib against desmoid tumor/deep fibromatosis. Clin Cancer Res. 2011;17:4082–4090.

97. Gounder MM, Mahoney MR, Van Tine BA, et al. Sorafenib for advanced and refractory desmoid tumors. N Engl J Med. 2018;379:2417–2428.

98. Gold JS, Antonescu CR, Hajdu C, et al. Clinicopathologic correlates of solitary fibrous tumors. Cancer. 2002;94:1057–1068.

99. Mir O, Brodowicz T, Italiano A, et al. Safety and efficacy of regorafenib against desmoid tumor/deep fibromatosis. J Clin Oncol. 2011;29:205–210.

100. Kier LM, Donoghue JF, Wilding AL, et al. Axitinib has antiangiogenic and antimitogenic activity in myxoid liposarcoma. Sarcoma. 2016;3484673. doi: 10.1155/2016/3484673 [Epub]

101. Stacchiotti S, Simeone N, Lo Vullo S, et al. Activity of axitinib in progressive advanced solitary fibrous tumor: results from an exploratory, investigator-driven phase 2 clinical study. Eur J Cancer. 2019;106:225–233.

102. Maris JM, Courtright J, Houghton PJ, et al. Initial testing of the VEGFR inhibitor AZD2171 by the pediatric preclinical testing program. Pediatr Blood Cancer. 2008;50:581–587.

103. Morton CL, Maris JM, Keir ST, et al. Combination testing of cediranib (AZD2171) against childhood cancer models by the pediatric preclinical testing program. Pediatr Blood Cancer. 2012;58:566–571.

104. Judson I, Scurr M, Gardner K, et al. Phase II study of cediranib in patients with advanced gastrointestinal stromal tumors or Soft-Tissue Sarcoma. Clin Cancer Res. 2014;20:3603–3612.

105. Dreys J, Siegent P, Medinger M, et al. Phase I clinical study of AZD2171, an oral vascular endothelial growth factor signalling inhibitor, in patients with advanced solid tumors. J Clin Oncol. 2007;25:3045–3054.

106. Kumm R, Allen D, Monks A, et al. Cediranib for metastatic alveolar soft part sarcoma. J Clin Oncol. 2013;31:2296–2302.

107. Zhao J, Yang Y. Treatment and prognosis of stage IV alveolar soft part sarcoma. Zhonghua Zhong Liu Za Zhi. 2012;34:932–936.
108. Ogose A, Yazawa Y, Ueda T, et al. Alveolar Soft Part Sarcoma in Japan: multi-institutional study of 57 patients from the Japanese Musculoskeletal Oncology Group. Oncology. 2003;65:7–13.

109. Portera CA Jr, Ho V, Patel SR, et al. Alveolar soft part sarcoma. Cancer. 2001;91:585–591.

110. Jin-Sung Park A, Kim I-K, Han S, et al. Normalization of tumor vessels by tie2 activation and ang2 inhibition enhances drug delivery and produces a favorable tumor microenvironment. Cancer Cell. 2017;31:157–158.

111. Nesmith JE, Chappell JC, Clucerus JG, et al. Blood vessel anastomosis is spatially regulated by Flt1 during angiogenesis. Development. 2017;144:889–896.

112. Noss KR, Wolfe SA, Grimes SR. Upregulation of prostate specific membrane antigen/folate hydrolase translocation by an enhancer. Gene. 2002;285:247–256.

113. Filipp FV. Crosstalk between epigenetics and metabolism—yin and Yang of histone demethylases and methyltransferases in cancer. Brief Funct Genomics. 2017;16:320–325.

114. Judson I, Morden JP, Kibbourn L, et al. Cederinab in patients with alveolar soft part sarcoma (CASPS): a double-blind, placebo-controlled, randomised, phase 2 trial. Lancet Oncol. 2019; S1470-2045(19)30215-0;30213.

- A groundbreaking and practice changing international, double-blind, placebo-controlled, randomised, phase II trial of cederinab in patients with progressive ASPS. Relative to placebo, cederinab treatment led to a significant decrease in tumor size measured on cross-sectional imaging.

115. Goodwin ML, Jin H, Staessens K, et al. Modeling alveolar soft part sarcomagenesis in the mouse: A Role for Lactate in the Tumor Microenvironment. Cancer Cell. 2014;26:851–862.

116. Kumar V, Gabrilovich DI. Hypoxia-inducible factors in regulation of immune responses in tumour microenvironment. Immunology. 2014;143:512–519.

117. Wilky BA, Trucco MM, Subhawong TK, et al. Axitinib plus pembrolizumab in patients with advanced sarcomas including alveolar soft-part sarcoma: a single-centre, single-arm, phase 2 trial. Lancet Oncol. 2019;20(6):837–848.

118. Patwardhan PP, Musi E, Schwartz GK. Preclinical evaluation of nintedanib, a triple angiokinase inhibitor, in soft-tissue sarcoma: potential therapeutic implication for synovial sarcoma. Mol Cancer Ther. 2018;17:2329–2340.

119. Hilberg F, Tontsch-Grunt U, Baum A, et al. Triple angiokinase inhibitor nintedanib directly inhibits tumor cell growth and induces tumor shrinkage via blocking oncogenic receptor tyrosine kinases. J Pharmacol Exp Ther. 2018;364:494–503.

120. Ph II nintedanib vs ifosfamide in soft tissue sarcoma (ANITA), EORTC. 2018 [cited 2019 Jun 5]; NCT02808247, Available from: https://clinicaltrials.gov/ct2/show/NCT02808247

121. Tang L, Yu W, Wang Y, et al. Anlotinib inhibits synovial sarcoma by targeting GINS1: a novel downstream target oncogene in progressive synovial sarcoma. Clin Transl Oncol. 2019. doi: 10.1007/s12094-019-02090-2 [Epub ahead of print].

122. Chi Y, Fang Z, Hong X, et al. Safety and efficacy of anlotinib, a multikinase angiogenesis inhibitor, in patients with refractory metastatic soft-tissue sarcoma. Clin Cancer Res. 2018;24:5233–5238.

123. A phase III trial of anlotinib in metastatic or advanced alveolar soft part sarcoma, leiomyosarcoma and synovial sarcoma (APROMISS), Advencehon Laboratories LLC. 2019 [cited 2019 Jun 5]; NCT03010819, Available from: https://clinicaltrials.gov/ct2/show/NCT03010819

124. Ingham M, Lee SM, Patwardhan P, et al. Phase 2 trial of the novel multi-receptor tyrosine kinase inhibitor sitratavatinib in well-differentiated/dedifferentiated liposarcoma. J Clin Oncol. 2017;35:TPS11082.

125. Sitratavatinib in advanced liposarcoma and other soft tissue sarcomas, Mirati Therapeutics Inc. 2019 [cited 2019 Jun 5]; NCT02978859, Available from: https://clinicaltrials.gov/ct2/show/NCT02978859

126. Oyama R, Takahashi M, Yoshida A, et al. Generation of novel patient-derived CIC-DUX4 sarcoma xenografts and cell lines. Sci Rep. 2017;7:4712.

127. Fleuren ED, Vlietmeier M, Van Der Graaf WTA, et al. Phosphoproteomic profiling reveals ALK and MET as novel actionable targets across synovial sarcoma subtypes. Cancer Res. 2017;77:4279–4292.

128. Noujaim J, Payne LS, Judson I, et al. Phosphoproteomics in translational research: a sarcoma perspective. Ann Oncol. 2016;27:787–794.

129. Megiorni F, McDowell HP, Camero S, et al. Crizotinib-induced anti-tumor activity in human alveolar rhabdomyosarcoma cells is not solely dependent on ALK and MET inhibition. J Exp Clin Cancer Res. 2015;34:112.

130. Schoffski P, Wozniak A, Kasper B, et al. Activity and safety of crizotinib in patients with alveolar soft part sarcoma with rearrangement of TFE3: European Organization for Research and Treatment of Cancer (EORTC) phase II trial 9010 ‘CREATE’. Ann Oncol. 2018;29:758–765.

131. Schoffski 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, non-randomised phase 2 trial. Lancet Respir Med. 2018;6:431–441.

132. Schoffski 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.

133. Tsuda M, Davis UJ, Argani P, et al. TFE3 Fusions Activate MET Signaling by Transcriptional Up-regulation, Defining Another Class of Tumors as Candidates for Therapeutic MET Inhibition. Cancer Res. 2017;77:919–929.

134. Davis U, McFadden AW, Zhang Y, et al. Identification of the receptor tyrosine kinase c-Met and its ligand, hepatocyte growth factor, as therapeutic targets in clear cell sarcoma. Cancer Res. 2010;70:639–645.

135. Jones RL, Constantindou A, Thway K, et al. Chemotherapy in clear cell sarcoma. Med Oncol. 2011;28:859–863.

136. Yeung CL, Ngo VN, Grohar PJ, et al. Loss-of-function screen in rhabdomyosarcoma identifies CRKL-YES as a critical signal for tumor growth. Oncogene. 2013;32:5429–5438.

137. Aslam MI, Abraham J, Mansoor A. PDGFRβ reverses EphB4 signalling in alveolar rhabdomyosarcoma. Proc Natl Acad Sci U S A. 2014;111:6383–6388.

138. Michels S, Trautmann M, Sievers E, et al. SRC signalling is crucial in the growth of synovial sarcoma cells. Cancer Res. 2013;73:2518–2528.

139. Sievers E, Trautmann M, Kindler D, et al. SRC inhibition represents a potential therapeutic strategy in liposarcoma. Int J Cancer. 2015;137:2578–2588.

140. Mukaihara K, Tanabe Y, Kubota D, et al. Cabozantinib and dasatinib exert anti-tumor activity in alveolar soft part sarcoma. PloS One. 2017;12:e0185321.

141. Brodin BA, Wennbergk K, Lidbrink E, et al. Drug sensitivity testing on patient-derived sarcoma cells predicts patient response to treatment and identifies c-Sarc inhibitors as active drugs for translocation sarcomas. Br J Cancer. 2019;120:435–443.

142. Schuetze SM, Bolejack V, Choy E, et al. Phase 2 study of dasatinib in patients with alveolar soft part sarcoma and leiomyosarcoma identifies c-Sarc inhibitors as active drugs for translocation sarcomas. Br J Cancer. 2013;108:2518–2528.

143. Schuetze SM, Bolejack V, Choy E, et al. Phase 2 study of dasatinib in patients with alveolar soft part sarcoma, chondrosarcoma, chondroma, epithelioid sarcoma, or solitary fibrous tumor. Cancer. 2017;123:90–97.

144. FDA approves larotrectinib for solid tumors with NTRK gene fusions. 2018 [cited 2019 Jul 3]; Food and Drug Administration, Available from: https://www.fda.gov/drugs/fda-approves-larotrectinib-solid-tumors-ntrk-gene-fusions-0

145. Drilon A, Laetsch TW, Kummer S, et al. Efficacy of Larotrectinib in TRK Fusion–positive Cancers in Adults and Children. N Engl J Med. 2018;378:731–739.
**A biomarker-driven, basket-type study of larotrectinib in NTRK fusion-positive cancers.** Due to the nature of the study, a number of unspecified sarcoma subtypes were enrolled in the study, which reported an overall response rate of 80%. These biomarker driven studies offer great potential for the future of clinical trials in soft tissue sarcomas.

145. Phase 1/2 Study of LOXO-195 in patients with previously treated NTRK Fusion Cancers, Loxo Oncology, Inc. [cited 2019 Jun 21]; NCT03215511, ClinicalTrials.gov. Available from: https://clinicaltrials.gov/ct2/show/NCT03215511

146. Kasper B, Sleijfer S, Litière S, et al. Long-term responders and survivors on pazopanib for advanced soft tissue sarcomas: subanalysis of two European Organisation for Research and Treatment of Cancer (EORTC) clinical trials 62043 and 62072. Ann Oncol. 2014;25:719–724.

147. Sleijfer S, Ouali M, van Giabbeke M, et al. Prognostic and predictive factors for outcome to first-line ifosfamide-containing chemotherapy for adult patients with advanced soft tissue sarcomas: an exploratory, retrospective analysis on large series from the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STRSG). Eur J Cancer. 2010;46:72–83.

148. Degprimo SE, Huang X, Blackstein ME, et al. Circulating levels of soluble KIT serve as a biomarker for clinical outcome in gastrointestinal stromal tumor patients receiving sunitinib following imatinib failure. Clin Cancer Res. 2009;15:5869–5877.

149. Norden-Zfoni A, Desai J, Manola J, et al. Blood-based biomarkers of SU11248 activity and clinical outcome in patients with metastatic imatinib-resistant gastrointestinal stromal tumor. Clin Cancer Res. 2007;13:2643–2650.

150. Raut CP, Boucher Y, Duda DG, et al. Effects of sorafenib on intra-tumoral interstitial fluid pressure and circulating biomarkers in patients with refractory sarcomas (NCI protocol 6948). PLoS One. 2012;7:e26331.

151. Goerres GW, Stupp R, Barghouth G, et al. The value of PET, CT and in-line PET/CT in patients with gastrointestinal stromal tumours: long-term outcome of treatment with imatinib mesylate. Eur J Nucl Med Mol Imaging. 2005;32:153–162.

152. Vlenterie M, Oyen WJ, Steeghs N, et al. Early metabolic response as a predictor of treatment outcome in patients with metastatic soft tissue sarcomas. Anticaner Res. 2019;39:1309–1316.

153. Bouchet S, Titier K, Moore N, et al. Therapeutic drug monitoring of imatinib in chronic myeloid leukemia: experience from 1216 patients at a centralized laboratory. Fundam Clin Pharmacol. 2013;27:690–697.

154. Bouchet S, Poulette S, Titier K, et al. Relationship between imatinib trough concentration and outcomes in the treatment of advanced gastrointestinal stromal tumours in a real-life setting. Eur J Cancer. 2016;57:31–38.

155. Houk BE, Bello CL, Kang D, et al. A population pharmacokinetic meta-analysis of sunitinib malate (SU11248) and its primary metabolite (SU12662) in healthy volunteers and oncology patients. Clin Cancer Res. 2009;15:2497–2506.

156. Homecker M, Blanchet B, Billemont B, et al. Saturable absorption of sorafenib in patients with solid tumors: a population model. Invest New Drugs. 2012;30:1991–2000.

157. Strumberg D, Clark JW, Awada A, et al. Safety, pharmacokinetics, and preliminary antitumour activity of sorafenib: a review of four phase I trials in patients with advanced refractory solid tumors. Oncologist. 2007;12:426–437.

158. Trnkova ZJ, Grothey A, Sobrero A, et al. Population pharmacokinetics analysis of regorafenib and its active metabolites from the phase III CORRECT study of metastatic colorectal cancer. Ann Oncol. 2013;24:v37.

159. Strumberg D, Scheulen ME, Schultheis B, et al. Regorafenib (BAY 73-4506) in advanced colorectal cancer: a phase I study. Br J Cancer. 2012;106:1722–1727.

160. Garrett M, Poland B, Brennan M, et al. Population pharmacokinetic analysis of axitinib in healthy volunteers. Br J Clin Pharmacol. 2014;77:480–492.

161. Fox E, Aplicon R, Baggett R, et al. A phase 1 trial and pharmacokinetic study of cediranib, an orally bioavailable pan-vascular endothelial growth factor receptor inhibitor, in children and adolescents with refractory solid tumors. J Clin Oncol. 2010;28:15174–15181.

162. Schmid U, Liesenfeld KH, Fleury A, et al. Population pharmacokinetics of nintedanib, an inhibitor of tyrosine kinases, in patients with non-small cell lung cancer or idiopathic pulmonary fibrosis. Cancer Chemother Pharmacol. 2018;81:89–101.

163. Wang E, Nickens DJ, Bello A, et al. Clinical implications of the pharmacokinetics of crizotinib in populations of patients with non-small cell lung cancer. Clin Cancer Res. 2016;22:5722–5728.

164. van Erp NP, Gelderblom H, Guechelhaar J. Clinical pharmacokinetics of tyrosine kinase inhibitors. Cancer Treat Rev. 2009;35:692–706.

165. 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.

166. Verheijen RB, Beijnen JH, Schellens JHM, et al. Clinical pharmacokinetics and pharmacodynamics of pazopanib: towards optimized dosing. Clin Pharmacokinet. 2017;56:987–997.

167. Wind S, Schmid U, Freiwald M, et al. Clinical pharmacokinetics and pharmacodynamics of nintedanib. Clin Pharmacokinet. 2019;58:1131–1147.

168. Eechoute K, Fransson MN, Reynolds AK, et al. A long-term prospective population pharmacokinetic study on imatinib plasma concentrations in GIST patients. Clin Cancer Res. 2012;18:5780–5787.

169. Boudou-Rouquette P, Ropert S, Mir O, et al. Variability of sorafenib toxicity and exposure over time: a pharmacokinetic/pharmacodynamic analysis. Oncologist. 2012;17:1204–1212.

170. FDA Approved Drug Products, FDA. [cited 2019 Oct 16]. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/

171. Lassen U, Miller WH, Hotte S. Phase I evaluation of the effects of ketoconazole and rifampicin on cediranib pharmacokinetics in patients with solid tumours. Cancer Chemother Pharmacol. 2013;71:543–549.

172. Sun Y, Niu W, Du F, et al. Safety, pharmacokinetics, and antitumor properties of anlotinib, an oral multi-target tyrosine kinase inhibitor, in patients with advanced refractory solid tumors. J Hematol Oncol. 2016;9:105.

173. Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacol Ther. 2013;138:103–141.

174. Tang W, McCormick A, Li J, et al. Clinical pharmacokinetics and pharmacodynamics of cediranib. Clin Pharmacokinet. 2017;56:689–702.

175. Zhong CC, Chen F, Yang JL, et al. Pharmacokinetics and disposition of anlotinib, an oral tyrosine kinase inhibitor, in experimental animal species. Acta Pharmacol Sin. 2018;39:1048–1063.

176. Houk BE, Bello CL, Poland B, et al. Relationship between exposure to sunitinib and efficacy and tolerability endpoints in patients with cancer: results of a pharmacokinetic/pharmacodynamic meta-analysis. Cancer Chemother Pharmacol. 2010;66:357–371.

177. Suttle AB, Ball HA, Molimard M, et al. Relationships between pazopanib exposure and clinical safety and efficacy in patients with advanced renal cell carcinoma. Br J Cancer. 2014;111:1909–1916.

178. Verheijen RB, Bins S, Mathijssen RH, et al. Individualized pazopanib dosing: a prospective feasibility study in cancer patients. Clin Cancer Res. 2016;22:5738–5746.

179. Verheijen RB, Swart LE, Beijnen JH, et al. Exposure-survival analyses of pazopanib in renal cell carcinoma and soft tissue sarcoma patients: opportunities for dose optimization. Cancer Chemother Pharmacol. 2017;80:1171–1178.

180. Lee ATJ, Pollack SM, Huang P, et al. Phase III Soft Tissue Sarcoma Trials: success or failure? Curr Treat Options Oncol. 2017;18:19.

181. Calvo E, Schmidinger M, Heng DYC, et al. Improvement in survival end points of patients with metastatic renal cell carcinoma through sequential targeted therapy. Cancer Treat Rev. 2016;50:109–117.