



Genomic-guided precision therapy for soft tissue sarcoma

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ABSTRACT

Soft tissue sarcoma (STS), although heterogeneous in histopathology presentation, has mostly been treated with chemotherapy agents as one entity. Our understanding of crucial genomic alterations in different STS histologies and the advent of molecular-targeted agents have reshaped the treatment paradigm for advanced STS. Small-molecule inhibitors of c-KIT, plate-derived growth factor receptor alpha, c-MET, BRAF, anaplastic lymphoma kinase, ROS1 and colony-stimulating factor-1 receptor have been successfully validated in clinical studies to yield practice-changing results. Inhibitors of other novel genomic targets including mouse double minute 2 homolog, cyclin-dependent kinase 4/6, mitogen-activated protein kinase and epigenetic regulators are expected to be developed in the near future. Furthermore, with the advancement and accessibility of molecular diagnosis and next-generation sequencing, a genomic-based therapeutic approach should be widely applicable to advanced STS patients. This review will focus on the progress of genomic-guided therapy tailored to each molecular alteration of different STS histologies.

INTRODUCTION

Soft tissue sarcoma (STS) is a rare malignancy arising from mesenchymal connective tissue, accounting for approximately 1%–2% of all cancers. In the USA, 12 750 cases are newly diagnosed annually, and STS results in 5270 deaths.¹ In Europe, the crude incidence of STS was 4.71 per 100 000 people, with estimated 25 851 new cases in the 28 member states in the European Union.² On the basis of the 2013 WHO classification of soft tissue tumours, the diagnosis integrates conventional histology and molecular genetics.³ Some sarcomas show characteristic histologic patterns such as spindle cells, epithelioid or epithelial-like cells, myxoid tumour, round cells and pleomorphic morphology. However, diagnosing mesenchymal tumours solely based on morphology and immunohistochemical staining is often challenging.⁴ Moreover, conventional histologic diagnosis often does not provide a specific direction for anticancer therapy.⁵ To further elucidate biomarkers for diagnosis and treatment selection, cytogenetic and molecular genetic analyses, including karyotyping, fluorescence in situ hybridisation, reverse-transcription

PCR, and targeted sequencing, are now widely applied in the diagnostic work-up of sarcomas.

Few most advanced, unresectable or metastatic STS, excluding gastrointestinal stromal tumours (GISTs), doxorubicin remains the standard first-line treatment. However, when applying doxorubicin as first-line treatment, the median overall survival (OS) is 12–20 months; scope for improvement exists. A randomised phase III trial comparing the combination of doxorubicin and ifosfamide versus doxorubicin alone showed a significant increase in progression-free survival (PFS) in the combination arm, but no significant increase for OS, and an increased toxicity rate was found for the combination arm.⁶ Docetaxel in combination with gemcitabine was compared with doxorubicin alone in the first-line setting, but the combination regimen did not show superiority in advanced STS.⁷ Olaratumab, a platelet-derived growth factor receptor alpha (PDGFRα) monoclonal antibody, plus doxorubicin showed promising results in the phase Ib/II trial,⁸ but a follow-up confirmatory phase III randomised control trial failed to show any benefit in terms of PFS or OS for the combination arm.⁹

In the second/later-line settings, several chemotherapy or multi-targeted agents were tested but with modest improvements. Pazopanib, a multi-targeted antiangiogenic molecular agent, improved PFS in nonadipocytic STS compared with placebo (4.6 vs 1.6 months; HR=0.31, 95% CI=0.24 to 0.40; $p<0.0001$) but with no significant differences in OS.¹⁰ In the two most common STS histologies, leiomyosarcoma and liposarcoma (also called L-sarcomas), trabectedin improved PFS compared with dacarbazine (median PFS: 4.2 vs 1.5 months; HR=0.55; $p<0.001$) in the second/later-line setting. However, no significant improvement was observed in OS.¹¹ In a similar setting for L-type STS, eribulin significantly improved OS compared with dacarbazine (median 13.5 vs 11.5 months; HR=0.77; $p=0.0169$).¹² However, in subgroup analysis, the benefit of eribulin was mainly observed in

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liposarcoma (liposarcoma: HR=0.51, 95% CI 0.35 to 0.75; leiomyosarcoma: HR=0.93, 95% CI 0.71 to 1.20); therefore, The U.S. Food and Drug Administration approved eribulin only for patients with advanced liposarcoma.

Our understanding of the molecular mechanisms underlying tumorigenesis for different tumour types has dramatically changed our selection of treatment for patients with advanced cancer. In renal cell carcinoma, where chemotherapy is generally refractory, the understanding of pathognomonic Hypoxia-inducible factor (HIF)-1 α and correlation with antiangiogenesis upregulation have led to the wide application of antiangiogenic agents as front-line treatments for renal cell carcinoma.¹³ Furthermore, the discovery of epidermal growth factor receptor (*EGFR*) mutations and the outstanding response from *EGFR* tyrosine kinase inhibitors in non-small-cell lung cancer have transformed the treatment paradigm for some patients with lung cancer, steering away from the use of cytotoxic chemotherapy as front-line treatment.¹⁴ Moreover, in the past decade, driver mutations were found in certain types of STS (table 1), and this has reshaped a part of the paradigm of sarcoma treatment. In this article, we review targetable genomic alterations in STS and discuss other new genomic-guided therapy for STS in the future (table 2). We have also included a concise video abstract summarising this review (online supplementary video).

PART 1. DEVELOPED GENOMIC-GUIDED PRECISION THERAPY FOR STS

Gastrointestinal stromal tumour (*KIT*/*PDGFRA* mutant)

GIST is the most common mesenchymal tumour in the gastrointestinal (GI) tract. No effective systemic treatment existed for GISTs until 1998, when *KIT* and *PDGFRA* mutations of the interstitial cells of Cajal were found to drive GIST development.^{15 16} Imatinib, a tyrosine kinase inhibitor for BCR-ABL, c-KIT and *PDGFRA*, is effective either as adjuvant therapy or treatment for unresectable or metastatic disease. For unresectable or metastatic disease, single-agent imatinib produced a response rate of 45%–69%, with PFS of 18–26 months.^{17–21} For *PDGFRA* mutant GISTs, patients with the *PDGFRA* exon 18 D842V mutation were resistant to imatinib therapy, whereas patients with exon 4, exon 12 and non-D842V exon 18 mutations may still respond to imatinib, with the overall response rate of 38% and PFS of 28.5 months in a retrospective study.²²

Despite the promising efficiency, imatinib resistance can occur within a median of 2–3 years due to secondary mutations in *KIT*. In contrast to primary *KIT* mutations that are predominately in the juxtamembrane regions encoded by exons 9 and 11, secondary mutations mainly occur in two regions of imatinib binding sites. One is the ATP-binding pocket coded by exons 13 and 14, which can directly interfere with imatinib binding; the second is the activation loop encoded by exons 17 and 18, which

stabilise c-KIT in the active conformation despite imatinib interference.²³

For unselected patients who show disease progression after first-line imatinib, the standard second-line treatment is sunitinib, an oral, small-molecule, multi-targeted receptor tyrosine kinase inhibitor, with targets including *PDGFRs*, vascular endothelial growth factor receptors (*VEGFRs*), c-KIT and RET (Rearranged during Transfection). The objective response rate (ORR) is 7%, and PFS can extend from 6.4 weeks in the placebo group to 27.3 weeks in the sunitinib group.²⁴ For metastatic or unresectable GIST patients with treatment failure for previous imatinib and sunitinib, regorafenib, another multi-targeted tyrosine kinase inhibitor extended OS from 0.9 months with placebo to 4.8 months with regorafenib treatment. The ORR was 4.7% with regorafenib as the third-line treatment.²⁵

KIT exon 17 mutations account for 30%–40% of *KIT* secondary mutations and are responsible for resistance to imatinib or sunitinib.²⁶ Compared with imatinib or sunitinib, regorafenib exhibited stronger activity towards the exon 17-associated kinase activation loop mutation. A prospective phase II trial tested the efficacy of regorafenib in GIST patients with exon 17 mutations and showed an ORR of 30% (6/15) and the median PFS of 22.1 months.²⁶ Avapritinib (formerly known as BLU-285) had broad activity against primary or secondary *KIT* and *PDGFRA* mutations, including *PDGFRA* D842V.²⁷ In a phase I study of avapritinib in patients with advanced GIST (the NAVIGATOR trial), patients who had received at least three prior therapies, including *PDGFRA* exon 18 mutations patients, were treated at the maximal tolerated dose (400 mg) or recommended phase II dose (RP2D) 300 mg per day. In patients who underwent at least three lines of systemic therapy, avapritinib as the fourth/late-line of systemic therapy had an ORR of 22%, and the disease stabilised at 16 weeks in 47% of the patients. The median duration of the response was 10.2 months. Remarkably, in patients with *PDGFRA* exon 18 mutation, the response rate was 86%, and the disease control rate was 95%. The mean duration of the response was not reached. Most adverse effects were grade 1–2, including GI symptoms, fatigue, oedema and memory impairment.²⁸

Another next-generation TKI (DCC-2618, also known as ripretinib) is a ‘switch-control’ kinase inhibitor that forces the activation loop (or activation ‘switch’) into an inactive conformation. It broadly inhibits activation loop mutations in *KIT* and *PDGFRA*.²⁹ In a phase I trial, 114 GIST patients were treated with RP2D (150 mg daily), and the ORR was 14%. The 3-month disease control rate was 70%, and the median PFS was 24 weeks. For patients receiving ripretinib as the second/third-line treatment, the ORR was 22%, with a 3-month disease control rate of 81% and the median PFS of 36 weeks.³⁰ The result of the INVICTUS phase III trial, which compared ripretinib with placebo in patients of GISTs as the fourth/late-line treatment, was recently released. Ripretinib provided significant improvement in PFS compared with placebo

Table 1 Genomic-guided treatments in soft tissue sarcoma

Subtype	Target genomic alteration	Drug	ORR	PFS	Reference
GIST	KIT expression	Imatinib (first line)	69% (400 mg four times a day) 68% (600 mg four times a day)	TTP 20 months TTP 26 months (p=0.371)	B2222 ^{17 18}
	KIT expression	Imatinib (first line)	45% (400 mg four times a day) 45% (400 mg two times a day)	18 months 20 months (p=0.31)	S0033 ¹⁹
	KIT expression	Imatinib (first line)	51% (400 mg four times a day) 57% (400 mg two times a day)	1.7 years 2.0 years (0.91; 95% CI, 0.79 to 1.04; p=0.18)	EORTC 62005 ^{20 21}
	PDGFRA	Imatinib	0% (Exon 18 D842V) 38% (others)	2.8 months 28.5 months (p=0.0001)	Retrospective ²²
	KIT exon 17 secondary mutation	Regorafenib	30%	22.1 months	²⁶
	KIT and PDGFRA	Avapritinib (BLU 285)	22% (>=4 line) 86% (PDGFRA Exon 18)	DOR 10.2 months (>=4 line) DOR not reached (95% CI: 11.3-NE) (PDGFRA Exon 18)	NAVIGATOR ²⁸
	KIT and PDGFRA	Ripretinib (DCC 2618)	9.4%	6.3 months	INVICTUS ³¹
	MET	Cabozatinib	14%	6 months	EORTC 1317 'CaboGIST' ³³
	BRAF	Dabrafenib	Case report	Case report	³⁹
	mTOR	Sirolimus (80%) Everolimus (12.5%) Temozolimus (7.5%)	41%	9 months	Retrospective ⁴⁶
	mTOR	ABI-009 (nab-sirolimus)	42%	8.9 months	⁵²
IMT	ALK, ROS-1	Crizotinib	50% (ALK positive) 14% (ALK negative)	1 year PFS 73%, 2 year PFS 49%(ALK positive) 1 year PFS 54%, 2 year PFS 36%(ALK negative)	EORTC 90101 ⁵⁷
DFSP	PDGFB	Imatinib	46%	Median TTP: 1.7 years	Pooled analysis of EORTC 62027 and SWOG S0345 ⁶⁶
TGCT	CSF-1R	Imatinib	19% (additional 74% SD)	20.9 months	Retrospective ⁷¹
	CSF-1R	Nilotinib	6% (additional 90% SD)	Not reached (PFS at 1 year was 77.1%)	⁷²
	CSF-1R	Pexidartinib	52% (DCR 83%)	Not reached	⁷³
	CSF-1R	Pexidartinib	39%	Not reached (mean 22 months of follow-up)	ENLIVEN ⁷⁴

Continued

Table 1 Continued

Subtype	Target genomic alteration	Drug	ORR	PFS	Reference
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ALK, anaplastic lymphoma kinase; CSF-1R, colony-stimulating factor-1 receptor; DCR, disease control rate; DFSP, dermatofibrosarcoma protuberans; DOR, duration of response; EORTC, European Organisation for Research and Treatment of cancer; GIST, gastrointestinal stromal tumour; IMT, inflammatory myofibroblastic tumour; mTOR, mechanistic target of rapamycin; ORR, objective response rate; PDGFB, platelet-derived growth factor beta; PDGFRA, platelet-derived growth factor receptor alpha; PEComa, perivascular epithelioid cell neoplasm; PFS, progression-free survival; SD, stable disease; SWOG, Southwest Oncology Group; TGCT, tenosynovial giant cell tumours; TTP, time to progression; VEGFR, vascular growth factor receptor.

(median PFS: 6.3 vs 1.0 month, HR=0.15, $p<0.0001$). The ORR in the treatment group was 9.4% compared with 0% in the placebo group.³¹

Furthermore, other counter mechanisms for imatinib resistance in GIST treatment are worth exploring. In a cell-line study, Cohen *et al* determined that a subset of imatinib-resistant human GIST specimens had compensatory upregulation of the MET oncogene. MET activation also occurred after imatinib therapy in a mouse model of GIST.³² In a single-arm phase II study (EORTC 1317 'CaboGIST'), patients with resistance to imatinib and sunitinib treated with carbozantinib, a c-MET inhibitor, had a 12 week PFS rate of 58% (24/41), reaching the prespecified efficiency endpoint. The ORR was 14%, and the median PFS was 6.0 months.³³

Gastrointestinal stromal tumour (KIT/PDGFRα wild-type)

Approximately 10%–15% of GIST patients do not harbour *KIT* and *PDGFRα* mutations, and these GISTs are called wild-type GISTs. Although they have wild-type GIST, these patients can be classified into three molecular subtypes based on molecular or mutation signatures: succinate dehydrogenase (SDH)-competent and two types of SDH-deficient GIST (SDHX mutations and SDHC promoter hypermethylation). SDH-deficient GISTs account for the

majority (>80%) of wild-type GISTs.³⁴ Epigenetic inactivation of O6-methylguanine-DNA methyltransferase (MGMT) through promoter methylation promotes the response of alkylating agents in several cancer types including gliomas, colorectal cancer and diffuse large B cell lymphoma. MGMT methylation is preferentially observed in SDH-deficient cases. Alkylating agents have theoretical effectiveness in SDH-deficient GISTs, but this has not been well investigated.^{35 36} In SDH-deficient GISTs, upregulation of hypoxia-inducible factor 1α results in increased growth signalling through IGF1R and VEGFR. Vandetanib, an oral small-molecule inhibitor of VEGFR2, EGFR and RET, was tested in patients with SDH-deficient GIST. In a phase II trial with Simon two-stage design, no objective response was observed in the first nine patients, and vandetanib was thus considered inactive.³⁷ In wild-type GIST patients with competent SDH, 4%–13% carried the BRAF V600E mutation.³⁸ One case report described a response to the BRAF inhibitor in a patient with BRAF V600E-mutated GIST.³⁹

The introduction of imatinib has single-handedly transformed the treatment paradigm of GIST but in the past few years we have a much better understanding of other non-KIT genetic alterations in GIST such as PDGFR,

Table 2 Selected targeted therapies trials for soft tissue sarcomas

Target	Drug	Soft tissue sarcoma subtype	Reference
MDM2	RG7112 (RO5045337)	MDM2-amplified, well-differentiated or dedifferentiated liposarcoma	78
		Advanced soft tissue sarcoma.	79
	RG7112 +doxorubicin	Relapsed/refractory solid tumours and sarcomas	80
	DS-3032b	Well/de-differentiated liposarcoma, solid tumours and lymphomas	81
CDK 4/6	Palbociclib	CDK4-amplified well-differentiated or dedifferentiated liposarcoma	83
		Well-differentiated or dedifferentiated liposarcoma	84
	Abemaciclib	Dedifferentiated liposarcoma	86
CDK4/6+MDM2	HDM201 +LEE011	Locally advanced or metastatic liposarcoma	87
MAPK kinase (MEK)	Selumetinib	NF1 related plexiform neurofibroma	93
EZH2	Tazemetostat	Epithelioid sarcoma	97

CDK, cyclin-dependent kinase; EZH2, enhancer of zeste homolog 2; MDM2, mouse double minute homolog 2; NF1, neurofibromatosis type 1.

BRAF, SDH and neurofibromatosis type 1 (NF1).^{40,41} It is recommended that every GIST patient should be tested for at least KIT and PDGFRA mutations as these are both prognostic and guidance for treatment selection.⁴² For GIST patients who are KIT and PDGFRA mutation negative, BRAF, SDH and NF1 status should be investigated. The recently approved PDGFRA D842V-targeted avapritinib by the US FDA is a manifest that molecular-targeted therapy in GIST is still under evolution and the optimal treatment for every subtype of GIST is fully anticipated.

PEComa

Perivascular epithelioid cell tumour (PEComa), which was first described in 1992,⁴³ is a rare mesenchymal neoplasm composed of histologically and immunohistochemically distinctive perivascular epithelioid cells expressing myomelanocytic markers. The 'PEComa family' now includes angiomyolipoma, clear-cell 'sugar' tumour of the lung and extrapulmonary sites, lymphangioleiomyomatosis, clear-cell myomelanocytic tumour of the falciform ligament/ligamentum teres and rare clear-cell tumours of other anatomical sites.⁴⁴ A behaviour spectrum exists among PEComas, which can be classified as 'benign', 'uncertain malignant potential' and 'malignant' according to features that predict the aggressiveness of the tumour, including tumour size >5 cm, infiltrative growth pattern, high nuclear grade, necrosis and mitotic activity >1/50 HPF (High power field).⁴⁵ Traditionally, the mainstay treatment for PEComas is surgery. For unresectable or metastatic disease that is not amenable to operation, cytotoxic chemotherapy, including gemcitabine/anthracycline-based regimens, could be considered, although the treatment potential and efficacy are unclear.⁴⁶

Tuberous sclerosis complex (TSC), characterised by mental disability, seizures and cellular proliferations, is an autosomal dominant disease caused by the loss of TSC1 (9q34) or TSC2 (16p13.3) genes.⁴⁷ The TSC protein complex acts as an inhibitor of the mechanistic target of rapamycin (mTOR) signalling pathway, which regulates cell growth, proliferation, autophagy, and protein and lipid syntheses. A significant number of PEComas are associated with TSC gene alteration, either as sporadic cases or in patients with TSC.⁴⁷

Case series reports have demonstrated the efficacy of mTOR inhibitors in PEComas.^{48,49} In one retrospective study including patients treated during 2000 and 2008 in Europe, 40 patients treated with mTOR inhibitors including sirolimus (n=32), everolimus (n=5) and temsirolimus (n=3) were evaluated. The reported ORR was 41%, and the median PFS was 9 months; the median PFS of responding patients was 15.4 months. Notably, PFS was worse in patients with uterine PEComa compared with patients with extra-uterine PEComa, although it was not statistically significant (median PFS: 6.4 vs 10.4 months, HR=1.51; 95% CI=0.94 to 2.43; p=0.09).⁴⁶ This may be related to the higher prevalence of TFE3 translocation in gynecologic PEComas,⁵⁰ and PEComas harbouring TFE3

gene rearrangements lack the TSC2 alteration characteristics of conventional PEComas and possibly show insensitivity to mTOR inhibition.⁵¹ ABI-009 (nab-sirolimus), an injectable nanoparticle form of human albumin-bound sirolimus, showed increased uptake in the tumour tissue in preclinical models. In the prospective phase II AMPACT trial of ABI-009 in malignant PEComa, the 31 evaluable patients showed the ORR of 42% with the median PFS of 8.9 months. However, most of the responders in the study showed either TSC1/TSC2 mutations or strong expression of pS6, a downstream signal of mTOR activation, whereas patients without either TSC1 or TSC2 mutations are less likely to derive benefits from ABI-009.⁵² This outcome further supported that even with a rare cancer such as PEComa, different underlying genomic alterations will have different effects on the outcome of molecular-guided treatments.⁴⁶

Overall, mTOR inhibitors are considered the most active agent in PEComa. Gemcitabine/doxorubicin-based chemotherapy may be helpful to a small proportion of advanced PEComa patients. Subclassification based on genomic non-TSC alterations such as TFE3 or other secondary mutations may further delineate a more precise and selective treatment for PEComa patients in the future.

Inflammatory myofibroblastic tumour

"Inflammatory pseudotumor" is a term used to describe a wide range of non-neoplastic (reactive) and neoplastic lesions, which exhibit common histopathological features such as spindle myofibroblastic cell proliferation accompanied by a chronic inflammatory lymphoplasmacytic infiltrate. The 'inflammatory pseudotumor' family includes inflammatory myofibroblastic tumour (IMT), pseudosarcomatous myofibroblastic proliferations of the genitourinary tract, infectious and reparative processes and inflammatory pseudotumours of the lymph node, spleen and orbit.^{53,54} IMT describes a specific and distinct entity diagnosed pathologically based on the WHO criteria³; based on these criteria, it is classified as an intermediate neoplastic lesion (aggressive with occasional metastases). IMT can occur in any part of the body but is more commonly found in the lung, retroperitoneum and GI tract.⁵⁴ Approximately 50% of the IMTs are positive for gene arrangement involving the *anaplastic lymphoma kinase (ALK)* gene on chromosome 2p23.⁵⁵ Several different fusion partners, including *TPM3*, *TPM4*, *CLTC*, *CARS*, *RANBP2*, *ATIC*, *SEC31L1* and *PPFIBP1*, have been reported. The presence of the *ALK* fusion gene can be detected either through fluorescence in situ hybridisation of the split *ALK* signal or through immunohistochemistry (IHC) for identifying the overexpressed ALK protein. A highly sensitive IHC, the intercalated antibody-enhanced polymer method, may detect a low level of ALK expression, which may be negative when the conventional method is used.⁵⁶

Unlike localised diseases, the treatment choices for unresectable or metastatic IMTs are limited. Crizotinib,

an ALK tyrosine kinase inhibitor, has shown activity in IMT. In a phase I trial, a patient with *ALK*-rearranged IMT showed a sustained partial response to crizotinib.⁵⁵ In another phase II single-arm trial of crizotinib, 6 of 12 ALK-positive IMT patients (50%, 95% CI=21.1 to 78.9) and only 1 of 7 ALK-negative patients (14%, 95% CI=0.0 to 57.9) achieved objective responses.⁵⁷ However, approximately half of the IMTs do not harbour *ALK* rearrangement, which may be an unfavourable prognostic indicator.⁵⁸ In *ALK*-negative IMTs, gene rearrangements of *ROS1*, *ETV6* and *NTRK3* have been identified and considered the oncogenic driver for drug targets.^{59–60} A case report presented *ROS1*-rearranged IMT that responded to crizotinib,⁶¹ and *NTRK* (Neurotrophic tyrosine receptor kinase) inhibitors have been shown to be efficacious in a *NTRK*-fusion positive IMTs.⁶²

In summary, IMT is a more indolent STS but occasionally occurs in critical anatomical sites or metastasise that are not amenable to surgery. Genetic alterations of ALK, ROS-1 and *NTRK* should be examined either sequentially or simultaneously to determine the optimal genomic-guided treatment. The role of chemotherapy is less certain and may be reserved for patients who are refractory to molecular-targeted agents.

Dermatofibrosarcoma protuberans

Dermatofibrosarcoma protuberans (DFSP) is a soft tissue tumour with slow-growing but locally aggressive behaviour, and it has a high rate of recurrence after surgical resection but a low rate of metastasis.⁶³ The incidence peaks in the second to fourth decades of life but can occur at any age. It can occur in any part of the body, with the trunk (40%–50%), proximal extremities (30%–40%) and head and neck (10%–15%) being the most common sites. Histologically, DFSP is characterised by storiform islands of bland spindle cells⁶⁴ and has numerous variants, including pigmented, myxoid, giant cell, atrophic and fibrosarcomatous. Fibrosarcomatous areas occasionally arise in DFSP, which is associated with increased metastasis risk, gains of p53 mutations and increased proliferative activity.⁶⁵ The mainstay management of localised disease is surgical resection. The prognosis is generally good if a margin-negative resection can be achieved. Adjuvant radiotherapy may be considered for patients with a positive surgical margin not amenable to re-excision or with unresectable disease. The role of cytotoxic chemotherapy in DFSP remains unclear.⁶³

DFSP is characterised by the reciprocal translocation t(17;22)(q22;q13), resulting in the fusion of the genes collagen type 1 alpha 1 (*COL1A1*) on chromosome 17q21-22 and platelet-derived growth factor beta (*PDGFB*) on 22q13. The *COL1A1*-*PDGFB* chimeric protein leads to the constitutive activation of the *PDGFB* receptor and results in tumour development.⁶⁴ Two independently conducted phase II clinical trials, one in the USA by the Southwest Oncology Group (SWOG-S0345) and one in Europe by the European organisation for Research and Treatment of Cancer (EORTC 62027), were designed to

test imatinib (400–800 mg daily) in patients with locally advanced or metastatic DFSP with *PDGFB* rearrangement (EORTC trial) or t(17;22) (SWOG study). Both trials targeted enrolling 40 patients, but both trials were discontinued prematurely due to regulatory approval of imatinib in DFSP treatment. The combined analysis of the two trials revealed a partial response rate of 46% and median time to progression of 1.7 years.⁶⁶ A recent meta-analysis including 152 DFSP patients treated with imatinib demonstrated a complete response rate of 5.2% (8 of 152) and a partial response rate of 55.2% (84 of 152). The dose of imatinib (400 vs 800 mg) did not have a significant differential treatment effect.⁶⁷ Furthermore, the presence of a fibrosarcomatous component in DFSP was correlated with worse imatinib activity in terms of PFS and OS.⁶⁸

In general, surgery is curative for most DFSP patients. For locally advanced or metastatic DFSP patients imatinib is the choice of treatment. Fibrosarcomatous DFSP has a tendency of shorter treatment on imatinib, and future research should focus on mechanisms of resistance to imatinib in DFSP to improve the outcome of these patients.

Tenosynovial giant cell tumours

The tenosynovial giant cell tumour (TGCT) is a locally aggressive tumour of synovial cells, which form the lining of joints. It often causes joint swelling, pain and stiffness. It usually involves the digits and wrist (85% of cases), but any joint may be affected.⁶⁹ Based on clinical presentation and biological behaviour, TGCT can be classified into localised type (single nodule in a joint or along a tendon sheath) and diffuse type (forming multiple nodules along the synovial layer). The latter was previously called villonodular synovitis and is aggressive.⁶⁹

TGCT is composed of a minor proportion of neoplastic stromal cells with a majority of macrophages. West *et al* showed that the neoplastic stromal cells of TGCT harbour a pathognomonic fusion gene involving colony-stimulating factor-1 (*CSF1*) gene (chromosome 1p13) and *COL6A3* (chromosome 2q35), causing the over-expression of the *CSF1* cytokine, and attract abundant colony-stimulating factor-1 receptor (*CSF-1R*)-positive macrophages to the tumour site (the landscape effect).⁷⁰

In a retrospective analysis, imatinib, which antagonises *CSF-1R* activation, produced an ORR of 19%, stable disease of 70% and median PFS of 20.9 months.⁷¹ In a phase II trial of nilotinib, another *CSF-1R* tyrosine kinase inhibitor, the ORR was 6%, but 49 of 51 (96%) evaluable patients were progression free at 12 weeks, and 1 year PFS was 77.1%.⁷² Pexidartinib (formerly known as PLX3397) is a potent, selective *CSF-1R* inhibitor that traps the kinase in the autoinhibited conformation. In the phase II cohort of a phase I/II trial of pexidartinib, the ORR was 52% and the DCR was 83%. The median PFS time was not reached.⁷³ A randomised phase III trial of pexidartinib versus placebo for advanced TGCT (ENLIVEN) was recently reported. The primary endpoint—the proportion of patients who

achieved objective responses—was significantly higher for pexidartinib than for placebo at week 25 with RECIST (24 (39%) of 61 vs none of 59; absolute difference: 39% (95% CI 27 to 53); $p < 0.0001$).⁷⁴ Although few patients developed severe liver toxicity with pexidartinib (possibly a class effect of CSF-1R inhibitors), the recent approval by the FDA for pexidartinib for unresectable TCGT still is a sign of success in the genomic-targeted treatment for TCGT patients.

In conclusion, a multidisciplinary approach should be taken in the management of TCGT. Medical treatments such as pexidartinib or imatinib could be an alternative for TCGT patients whose surgical treatment would result in severe morbidity or functional loss.

PART 2. GENOMIC-GUIDED PRECISION THERAPY UNDER ACTIVE INVESTIGATION

Mouse double minute 2 homolog

Mouse double minute 2 homolog (MDM2) is a crucial negative regulator of the p53 tumour suppressor protein, which induces apoptosis and cell cycle arrest in response to various types of cellular stress. The MDM2 level is tightly regulated in normal cells and forms an autoregulatory feedback loop with p53 protein. By contrast, the MDM2 level is upregulated in several types of malignancies.⁷⁵ The elevated MDM2 protein downregulates the function of p53 through either blocking the transcriptional activation domain or inducing proteasome degradation of p53 protein by ubiquitination.⁷⁶

Liposarcoma is one of the most common histological types of STS, accounting for approximately 15%–20% of all STS. It is further classified into four subtypes: well-differentiated liposarcoma (WDLPS), dedifferentiated liposarcoma (DDLPS), myxoid round cell liposarcoma and pleomorphic liposarcoma. While WDLPS and DDLPS are histologically different, they are considered at the two ends of the spectrum of the same disease. DDLPS is mostly observed in the areas of WDLPS where an abrupt change in the histological feature occurs from well-differentiated fat cells with occasional atypical nucleus to an area where spindle malignant cell rise. Further evidence supporting that WDLPS and DDLPS are similar concatenate are that both WDLPS and DDLPS have high-level amplifications in the chromosomal 12q14-15 region, which includes the MDM2 and cyclin-dependent kinase 4 (CDK4) oncogenes. MDM2 is amplified in nearly 100% of patients. WDLPS/DDLPS, and CDK4 is co-amplified in 90% of the patients.⁷⁷ Because of this pathognomonic feature, drugs that target the MDM2 and CDK4 proteins have gained much attention in the past few years.

Small-molecule inhibitors of MDM2 function through the inhibition of p52-MDM2 binding and lead to p53 protein stabilisation, activating the downstream signal, thus inhibiting cancer cell growth. The first study of the MDM2 inhibitor RG7112 was a proof-of-mechanism study performed in the neoadjuvant setting. Twenty patients with WDLPS or DDLPS were treated with RG7112 for 3

months before surgical resection or a tumour biopsy if unresectable. After 3 months of treatment, one patient had a confirmed partial response, and 14 had stable disease. Biomarker studies confirmed that the post-treatment p53 protein concentration increased by a median of 4.86 times (IQR 4.38 to 7.97; $p = 0.0001$) and revealed a mean decrease in tumour Ki67 of -5.05% , confirming the mechanism of action of the MDM2 inhibitor. The most common side effects of grade ≥ 3 are neutropenia (30%), thrombocytopenia (15%) and vomiting (10%).⁷⁸ Similarly, other phase I trials of MDM2 inhibitors provided evidence of p53 activation.^{79 80}

In a phase Ib trial of RG7112 in combination with doxorubicin in advanced STS, the best response was stable disease in 8 of 16 patients, and this combination resulted in a higher rate of grade 3/4 neutropenia (60%) and thrombocytopenia (45%). However, this combination also resulted in increased p53 activation, as indicated by increased MIC-1 levels (an indicator of p53 activation), which was greater than that achieved with the additive effect of single agents.⁸⁰ In another phase I trial of another MDM2 inhibitor DS-3032b in patients with WDLPS/DDLPS, solid tumours and lymphomas, partial responses were found in DDLPS and synovial sarcoma. The most common adverse effect was GI and haematologic side effects, but the safety profile is acceptable.⁸¹ Several other MDM2 inhibitors are under development.⁸²

CDK4

CDK4 is amplified in $>90\%$ of patients with WDLPS/DDLPS.⁷⁷ The CDK4/6 inhibitor palbociclib was investigated in a phase II trial at the dose of 200 mg orally once per day for 14 consecutive days in 21 day cycles in patients with WDLPS/DDLPS. PFS at 12 weeks was 66% (90% CI 51% to 100%), meeting the predefined primary endpoint (12-week PFS 40%) for efficacy. Grade 3–4 events included anaemia (17%), thrombocytopenia (30%) and neutropenia (50%).⁸³ To eliminate side effects, the same research group tested palbociclib at the dose of 125 mg daily for 21 days in a 28-day cycle. PFS at 12 weeks was 57.2% (two-sided 95% CI 42.4% to 68.8%), and the median PFS was 17.9 weeks (two-sided 95% CI 11.9 to 24.0 weeks). The side effects were reduced and were primarily haematologic, including neutropenia (grade 3=33%; grade 4=3%), but no neutropenic fever was detected.⁸⁴

Abemaciclib, which is structurally different from palbociclib, is more potent against CDK4 than against CDK6 in in vitro studies. The IC50 of palbociclib for CDK4 and CDK6 is 11 nM and 15 nM, respectively, and it is 2 nM and 9.9 nM, respectively, for abemaciclib.⁸⁵ The toxicity profile is different. Neutropenia ($>60\%$) is frequent in patients taking palbociclib, but the main side effect of abemaciclib is diarrhoea.⁸⁵ Moreover, abemaciclib has been tested in DDLPS. PFS at 12 weeks was 76% (95% CI 57% to 90%), and it met the predefined criteria for positive result (12-week PFS $\geq 60\%$). The median PFS was 30.4 weeks (95% CI 28.9 to not evaluable). The ORR was 3% (1 of 29 evaluable patients), with another 10.3% of

patients showing >10% decrease in tumour size.⁸⁶ Further development of CDK4/6 inhibitors in WDLPS/DDLPS is highly anticipated.

Combination of MDM2 and CDK4/6 inhibition

Because *MDM2* gene amplification is often associated with *CDK4* amplifications, clinical trials have investigated the efficacy and safety of the combination of MDM2 and CDK4/6 inhibitors. In a dose-finding phase Ib study of HDM201 (an MDM2 inhibitor) in combination with ribociclib (a CDK4/6 inhibitor) in patients with WDLPS/DDLPS, partial responses were observed in 4% of the patients, and stable disease was achieved by 49% of patients. Again, the most common side effect is haematologic including neutropenia, thrombocytopenia and anaemia.⁸⁷

Future development of MDM2 and CDK4/6 inhibitors in STS

The preliminary efficacy of MDM2 inhibitors and CDK4/6 inhibitors has provided much enthusiasm in MDM2/CDK4 amplified STS such as WDLPS/DD LPS and intimal sarcoma. However, the optimal doses of these agents, especially MDM2 inhibitors because of the strong bone marrow suppression activity, have been the limiting step for the full-scale exploration of these agents. Biomarkers in addition to the targeted genomic alterations are necessary to facilitate the drug development process in STS of these agents.

Mitogen-activated protein kinase

NF1, an autosomal dominant disorder caused by germ line alterations in the *NF1* tumour suppressor gene, is characterised by pigmentary skin lesions (café-au-lait macules) and dermal neurofibromas. In some cases, the disease is associated with skeletal abnormalities, brain tumours (optic pathway gliomas and glioblastoma), peripheral nerve tumours (plexiform neurofibromas and malignant peripheral nerve sheath tumours (MPNSTs)) and neurocognitive problems.⁸⁸ The *NF1* gene codes for the protein neurofibromin, which is a GTPase-activating protein (GAP). GAP accelerates the conversion of the active GTP-bound RAS to its inactive GDP-bound form, thus reducing RAS-mediated growth signalling. In *NF1* mutated patients, RAS transmits its pro-tumoural signal through the AKT–mTOR and MEK–extracellular signal-regulated kinase effector pathways. Plexiform neurofibroma develops in 20%–50% of the NF1 patients and may cause complications including pain, functional impairment and disfigurement and are subject to transformation into MPNST. The current mainstay treatment of plexiform neurofibromas is surgical resection, but complete resection is often difficult because they tend to be large and spread across tissue compartment boundaries.

Previously, clinical trials of mTOR inhibitor have shown preliminary evidence of activity in the control of plexiform neurofibroma growth.⁸⁹ Selumetinib, an oral selective inhibitor of MEK 1 and 2, has shown activity in *KRAS*-mutant advanced non-small-cell lung cancer⁹⁰ and

BRAF-mutant metastatic melanoma.⁹¹ In a phase I trial of selumetinib in children with NF1 and inoperable plexiform neurofibromas, partial responses (tumour volume decreases from baseline of $\geq 20\%$) was observed in 17 of the 24 children (71%). The most common adverse effects included acneiform rash, GI effects and asymptomatic creatine kinase elevation.⁹² The success in the control of plexiform neurofibroma paved the road for targeted therapy for MPNST. However, MPNST treatment with mTOR inhibitor everolimus plus bevacizumab showed only modest activity, with a clinical benefit rate of 12% (3/25).⁹³ Clinical trials evaluating selumetinib in combination with mTOR inhibitor sirolimus in MPNSTs are ongoing (NCT03433183).

To apply our understanding of MEK dysregulation to MPNST treatment, it is pertinent to understand the crucial process from the transformation of plexiform neurofibroma to MPNST to find a driver event that could be targeted as treatment.

Enhancer of zeste homolog 2 inhibitor

Previously, epigenetic modifying agents such as histone deacetylase inhibitors showed limited efficiency in STS.⁹⁴ Recently, a novel class of drug targeting chromatin modifying activity, the enhancer of zeste homolog 2 (EZH2) inhibitor, has shown promising activity in a specific type of STS. Polycomb repressive complex 2 (PRC2) is a molecular complex that methylates lysine 27 on histone 3 (H3K27) to regulate the transcription or silencing of specific genes, and EZH2 is a major catalytic unit in PRC2. In normal physiology, another chromatin-modifying complex, the SWI/SNF complex, antagonises the EZH2 function. Gain-of-function alterations of EZH2 or loss of function of the SWI/SNF components, such as SMARCB1 (SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1, also known as INI-1) or SMARCA4, is linked to many cancer types.⁹⁵

INI-1 is commonly lost in many types of STS, including epithelioid sarcoma (high frequency, >90%), epithelioid MPNSTs, myoepithelial tumour and extraskelatal myxoid chondrosarcomas.⁹⁶ The loss of INI-1 enhances unopposed EZH2 function and portend susceptibility to EZH2 inhibition. In a phase II multicentre, open-label study of tazemetostat in patients with epithelioid sarcoma harbouring INI-1 loss, the ORR was 13% (4 out of 31 patients), and an additional two patients had stable disease for >32 weeks.⁹⁷ Only minor adverse events such as grade 1/2 fatigue (39%), nausea (26%) and vomiting (19%) were reported. The activity of tazemetostat in epithelioid sarcoma, which is generally chemo/radio-resistant, also recently received accelerated approval from the US FDA.

The success of tazemetostat in epithelioid sarcoma suggested that targeting epigenetic regulators is another mechanism for other STS harbouring epigenetic dysregulation molecules.

ROLE OF MOLECULAR PROFILING FOR STS IN THE MODERN ERA

The advent of next-generation sequencing (NGS) has expanded our understanding of biology and has optimised treatment for various cancer types. NGS can test for hundreds of genomic alterations in a single session. In STS, approximately 80% of patients have at least one genomic variant detectable through NGS. The commonly detected genomic mutations include TP53, ATRX, RB, MDM2, CDK4 and CDKN2A.^{98 99} In a retrospective study of 5749 sarcoma patients, Gaucher *et al* reported that by using an in-house bioinformatics pipeline OncoKB for NGS, 16% and 7% of patients were found to have received treatment with FDA-approved or actionable study drugs, respectively. Among these patients were a patient with S100 +sarcoma having the *BRAF* V600E mutation responding to vemurafenib, a patient with initial sarcoma having *MDM2* amplification responding to a MDM2 inhibitor and a patient with angiosarcoma having the *KDR* mutation responding to an antiangiogenic inhibitor.^{100 101} Similarly, Sen *et al* reported that patients with sarcoma enrolled into phase I studies based on NGS results had significantly better PFS and OS than those who were enrolled into non-genomic-guided phase I clinical trials.¹⁰²

However, despite the wide applications of NGS, it remains unaffordable for many patients in various countries without reimbursement. Furthermore, although many of these 'actionable' targets play significant roles in tumourigenesis and progression, drugs that specifically target these commonly found mutations, namely *TP53*, *ATRX* and *RBI*, in STS are still undiscovered. Finally, the majority of the hospitals treating patients with STS may not have phase I or investigational agents for genomic-guided treatment other than approved medications. Thus, whether NGS testing should be applied for every advanced STS should depend on the accessibility of clinical trials and investigational agents of each institution, and the treatment strategy should be discussed individually with patients.

Certain levels of genomic testing should be used to meet the standard for advanced STS treatment. For instance, the National Comprehensive Cancer Network Guideline recommended mutation testing for all GIST patients scheduled for imatinib treatment. To test the mutations, although NGS is helpful, a valid but less expensive diagnostic procedure such as PCR for *KIT* and *PDGFRA* mutations is readily available. Moreover, other diagnostic tests such as ALK and INI-1 IHC for IMT and epithelioid sarcoma, respectively, can be considered instead of NGS when choosing the optimal treatment for the patients. Importantly, to integrate these tests into the daily practice of sarcoma pathology diagnostics, oncologists need to work closely with pathologists and determine the importance of these biomarkers in treatment selection for different patients. A multidisciplinary team approach is one of the best methods to share and collaborate between

different subspecialties for determining the optimal treatment for sarcoma patients.¹⁰³

CONCLUSION

As the response rate and response duration of traditional cytotoxic chemotherapy remain poor, novel genomic-guided therapy offers an opportunity of long-term disease control. Genomic-based precision therapy may be considered after resistance to cytotoxic chemotherapy, but it should also be considered in the earlier treatment phase in chemotherapy-refractory sarcoma subtypes. Tyrosine kinase inhibitors that block the driver mutation may result in a median PFS of more than 1 year in certain STS, and durable disease control is not uncommon. Several novel drugs are under development and undergoing clinical trials, and in the meantime, the cost of genetic testing, including NGS, is decreasing. Collaboration with sarcoma pathologists is crucial to identify specific genomic mutations within a confirmed pathological diagnosis for the selection of an optimal treatment. With the advancement of both sarcoma diagnosis and the introduction of new treatments, the paradigm has changed and is continuously evolving, and it is hoped that patients with unresectable or metastatic STS will have better outcomes and quality in the near future.

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