Phase I trial of concurrent sunitinib and radiation therapy as preoperative treatment for soft tissue sarcoma

Jens Jakob,¹ Geraldine Rauch,² Frederik Wenz,³ Peter Hohenberger¹

To cite: Jakob J, Rauch G, Wenz F, *et al.* Phase I trial of concurrent sunitinib and radiation therapy as preoperative treatment for soft tissue sarcoma. *BMJ Open* 2013;**3**:e003626. doi:10.1136/bmjopen-2013-003626

► Prepublication history for this paper is available online. To view these files please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2013-003626>).

Received 19 July 2013

Accepted 29 July 2013

¹Division of Surgical Oncology and Thoracic Surgery, Department of Surgery, University Medical Center Mannheim, University of Heidelberg, Mannheim, Germany

²Institute of Medical Biometry and Informatics, University of Heidelberg, ImNeuenheimer Feld 305, Heidelberg, Germany

³Department of Radiation Oncology, University Medical Center Mannheim, University of Heidelberg, Mannheim, Germany

Correspondence to

Dr Jens Jakob;
jens.jakob@umm.de

ABSTRACT

Introduction: Although the introduction of multimodal treatment of soft tissue sarcoma improved local tumour control, local failure still occurs in a good number of patients. Therefore, further improvement of current treatment strategies is necessary. The proposed study treatment will combine standard external beam radiation and the orally administered receptor tyrosine kinase inhibitor sunitinib.

Methods and analysis: Patients with soft tissue sarcoma will receive sunitinib and irradiation as neoadjuvant treatment. Radiotherapy will be administered as intensity modulated radiation therapy with a total dose of 50.4 Gy in 28 fractions (5 1/2 weeks). Patients will receive sunitinib daily for 2 weeks prior to and then concurrently with irradiation. Sunitinib will be given in two dose levels. The first dose level will be 25 mg sunitinib per os daily. The second dose level will be 37.5 mg. A dose modification schedule according to a 3+3 design will be applied. Restaging and tumour resection will be performed 6 weeks after completion of sunitinib and irradiation. Primary outcome measures will be the dose-limiting toxicity and maximal tolerated dose of sunitinib administered concurrently with irradiation. Toxicity of the study treatment will be documented according to Common Terminology Criteria of Adverse Events (CTCAE) 4.0. Secondary outcome measures will be the response to the study treatment and morbidity of the tumour resection. Imaging response will be determined according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria comparing MRI performed prior to and 6 weeks after completion of study treatment. Pathological response will be determined evaluating the fraction of non-viable tumour in the resection specimen. Resection morbidity will be evaluated according to CTCAE 4.0.

Ethics and dissemination: Approval was obtained from the ethics committee II of the University of Heidelberg, Germany (Reference number 2011-064F-MA). Furthermore, the study was approved by the German Federal Institute for Drugs and Medical Devices (Reference number 4037708).

Trial Registration EudraCT: 2007-002864-87
Clinicaltrials.gov: NCT01498835

INTRODUCTION

Soft tissue sarcomas (STS) arise from mesenchymal tissue and occur most frequently in the extremities and the retroperitoneum.¹ Their estimated incidence is approximately 5/100 000.² The prognosis of soft tissue sarcoma is determined by histological subtype, tumour size, localisation, grade and the presence of metastases.^{3–5} Despite great progress in surgery and multimodal therapy of non-metastatic tumours, local control and limb salvage remain major challenges in large, high-grade or recurrent tumours.^{6 7}

Multimodal treatment of soft tissue sarcomas with chemotherapy and irradiation has been introduced in the 1970s.⁸ The mainstay of therapy of non-metastasised soft tissue sarcomas is complete surgical resection combined with irradiation in large, high-grade tumours which are located deep to the superficial body fascia.^{9 10} Radiation may be administered preoperatively or postoperatively. Neoadjuvant irradiation may facilitate tumour resection by devitalisation and down-sizing of the tumour.¹¹ Furthermore, vital structures such as organs, nerves or vessels may be preserved from radiation toxicity since the radiation field is smaller in the preoperative setting.^{12 13} Chemotherapy, definitive radiotherapy or chemotherapy combined with irradiation may be applied in locally advanced or irresectable tumours.^{9 10 14–16} In case of locally advanced tumours, chemotherapy may be combined with heat.¹⁷ Doxorubicin and ifosfamide are the most commonly administered chemotherapeutic agents. Yet, in the past decades various other promising substances have been tested in phase II and III trials with promising results.¹⁸

Sunitinib is a small molecular inhibitor that acts on the transmembrane receptor tyrosine kinases PDGFR, VGFR, c-Kit, FLOT3

and CSF 1R that regulate vital cell functions such as proliferation, differentiation and cell death. Preclinical tumour models demonstrated antitumoral and antiangiogenic activity of sunitinib.^{19–20} Soft tissue sarcomas are highly vascularised and show an overexpression of vascular endothelial growth factor receptor (VEGFR) and other receptor tyrosine kinases.^{21–23} Therefore, soft tissue sarcomas seem to be suitable for the treatment with antiangiogenic substances. Accordingly, previous clinical studies demonstrated promising results of sunitinib and other receptor tyrosine kinase inhibitors in advanced soft tissue sarcoma.^{24–26}

The rationale behind a combination of irradiation and sunitinib is the possible additive or even synergistic effect of both treatment modalities. It is well known that tumour vascularisation is chaotic and exhibits poor function due to an imbalance of proangiogenic and antiangiogenic factors.²⁷ The administration of antiangiogenic agents such as sunitinib may 'normalise' the chaotic neovascularisation and thus decrease tumour hypoxia and increase the efficacy of radiation therapy.²⁸ Preclinical experiments demonstrated increased efficacy of irradiation if combined with antiangiogenic substances.^{20–29} Furthermore, they contradict the hypothesis that treatment with antiangiogenic substances may cause radiations resistance due to tumour hypoxia.

Kao *et al*³⁰ published the first feasibility study of sunitinib combined with percutaneous irradiation. Primary end point of the study was dose-limiting toxicity of sunitinib in oligometastasised patients of different primary tumours. The irradiated lesions were maximal 6 cm in size and were irradiated with 40–50 Gy. Sunitinib was administered in 4 weeks on and 2 weeks off regimen. Dose-limiting toxicity occurred only in patients with 50 mg sunitinib daily (grade 4 myelosuppression and grade 3 nausea and vomiting). Complete or partial remission according to RECIST was achieved in 59% of the patients. Although the results of the study are promising, the included patients cannot be compared with soft tissue sarcoma patients, in general. Soft tissue sarcoma are frequently large tumours at critical anatomic sites where irradiation inevitably involves vital organs or major vessels and nerves. The combination of radiotherapy and tyrosine kinase inhibitors may cause excessive toxicity in these cases. Therefore, further evaluation of the toxicity of combined regimens is indicated.³¹ We present the protocol of a phase I trial of concurrent sunitinib and irradiation in soft tissue sarcoma patients.

METHODS AND ANALYSIS

Design

This is an open-label, single-arm, national phase I trial performed at two study centres of sunitinib administered concurrently to preoperative irradiation in patients with soft tissue sarcoma (figure 1).

Figure 1 Study design.

Aims

1. To describe the toxic effects of sunitinib administered concurrently with preoperative radiotherapy to patients with soft tissue sarcoma.
2. To describe any preliminary evidence of antitumoral activity of the study treatment (imaging and pathological response).
3. To assess postoperative morbidity of tumour resection after preoperative treatment with sunitinib and irradiation.

Patient population

The aim was to include all patients with soft tissue sarcomas that require preoperative irradiation and subsequent resection. Therefore, patients not only with primary tumours but also with local recurrences will be eligible unless the primary tumour has been irradiated. Patients with metachronous singular metastases may be included if the singular metastatic lesion shall be treated by irradiation and surgery.

Inclusion and exclusion criteria are displayed in table 1.

Treatment

Patients will receive sunitinib and irradiation as neoadjuvant treatment before tumour resection (figure 1). The administration of sunitinib concurrently to radiation therapy will be the study intervention. Staging before study inclusion and restaging before tumour resection

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> ▶ Histological proven soft tissue sarcoma except the following entities: angiosarcoma, gastrointestinal stromal tumor (GIST), Ewing-sarcoma, dermatofibrosarcoma protuberans, embryonal rhabdomyosarcoma ▶ The tumour appears to be resectable or resectability is expected after prior treatment ▶ Age of 18 years or older ▶ Eastern cooperative oncology group (ECOG) performance status 0 or 1 ▶ Normal organ function (kidney, liver, bone marrow) ▶ Written informed consent ▶ Sufficient contraception (Pearl-Index <1) 	<ul style="list-style-type: none"> ▶ Intake of inductors or inhibitors of CYP3A4 ▶ Prior therapy with receptor tyrosine kinase inhibitors or conventional chemotherapy until 4 weeks before study inclusion ▶ History of myocardial infarction, cardiac insufficiency (NYHA grade III or IV), apoplex, thrombosis or embolism ▶ Major surgery 4 weeks before study inclusion ▶ Uncontrolled medical disease such as art. hypertension or diabetes mellitus ▶ Antihypertensive medication with more than 2 drugs ▶ Therapeutical anticoagulation with coumadin or similar medication (this does not include ASS and low-dose heparins medication) ▶ Known allergy or intolerance of study medication ▶ Known hereditary coagulopathy ▶ History or other malignancies during the last year before study inclusion ▶ Metastatic disease with the exception of a singular metachronous metastatic lesion ▶ Pregnancy ▶ Known allergy to sunitinib

will include MRI of the tumour site and a thoracic CT. These cross-sectional images shall be performed within 4 weeks before study inclusion and shortly before tumour resection which is scheduled 5–8 weeks after completion of preoperative treatment. Staging, radiation therapy and surgery will be performed according to standard procedures.

Radiation therapy

Intensity-modulated radiation therapy (IMRT) will be applied according to standard protocols of the University Medical Center Mannheim.³² The dose of IMRT will be 50.4 Gy (median planning target volume (PTV) dose) administered in 28 fractions within 5.5 weeks. All patients will be adequately immobilised depending on the body site during irradiation including ABC breathhold technique for locations with relevant breathing cycle-dependent movement. A CT simulation will be performed before administration of irradiation. According to calculated three-dimensional models derived from the planning CT the gross tumour volume (GTV) will be defined. In general, the clinical target volume (CTV) will be the GTV with a 2 cm margin axially. The margin placed around the GTV in the superior–inferior direction will be 5 cm. The planning target volume will be the CTV with a 5 mm margin. Larger PTV–CTV margins may apply in rare cases when no IGRT and/or breathhold are possible. The dose constraint for the small intestine will be 45 Gy at the maximum and the mean dose for kidneys shall not be greater than 10 Gy. Optimised dose

distributions will be obtained from an inverse planning algorithm (Monaco, Elekta, Stockholm). Treatment will be performed using step-and-shoot IMRT or volumetric modulated arc therapy (VMAT) with expected daily treatment times of less than 10 min. A strip of 2–3 cm will be spared in case of extremity STS.

Surgery

Surgery will be planned 5–8 weeks after completion of neoadjuvant treatment with sunitinib and irradiation. In extremity STS, en bloc resection with wide margins (1–2 cm of uninvolved tissue or intake adjacent fascial layer) will be performed whenever possible. When the tumour is abutting neurovascular bundles, the adventitia or epineurium will be taken as the margin of resection. When encasement or infiltration of the neurovascular bundle is present, they will be resected and reconstructed if appropriate. In case of infiltration of the bone, the periosteum will be taken en bloc with the tumour. Plastic reconstruction (eg, free or pediculated flaps) will be used whenever necessary. In retroperitoneal sarcoma the surgical standard procedure for the majority of the patients comprises multivisceral resection as principle, with colectomy, nephrectomy and resection of abdominal wall musculature or, respectively, the psoas muscle in order to achieve an R0 resection of the retroperitoneal compartment. Resection of the aorta, inferior vena cava, iliac vessels, femoral nerve, diaphragm, duodenum or pancreas will only be performed if macroscopic invasion is present.

Sunitinib

Sunitinib malate will be supplied by Pfizer as hard gelatine capsules of 25 and 12.5 mg. Sunitinib will be administered orally on a daily basis starting 14 days before radiation therapy and completed on the last day of irradiation therapy.

Dose escalation of sunitinib

According to a 3+3 phase I trial design sunitinib will be escalated in two dose levels. The starting dose of sunitinib will be 25 mg. The second dose level will be 37.5 mg. The dose escalation scheme is described in box 1. The first three patients will be included in dose level 1 (25 mg sunitinib). Before patients may be included in the second dose level, treatment of all patients in the first dose level including combined sunitinib and irradiation and tumour resection must be completed. Inpatient dose escalation is not permitted.

Anticipated toxicities

The most frequent risks from preoperative irradiation are skin and gastrointestinal toxicities. The most frequent adverse events experienced within studies of sunitinib were gastrointestinal toxicities, skin toxicities, hypertension peripheral oedema, altered taste, headache, back pain, arthralgia, extremity pain, cough, dyspnoea, anorexia, fatigue, fever and bleeding. Thromboembolic events, leucopenia and lymphopenia, left ventricular dysfunction, pancreatitis and liver failure were the most frequent severe adverse events (CTCAE grades 3–5). Additional administration of sunitinib may increase radiation toxicity (eg, increased gastrointestinal toxicity in retroperitoneal sarcoma or increased skin toxicity in extremity sarcoma) or may cause further adverse

reaction that is yet unknown but related to the combination of both.

Dose-limiting toxicities and dose adjustments

Any adverse event that occurs after intake of the first capsule of sunitinib until 4 weeks after last administration of sunitinib and that may be related to the drug will be documented and classified according to common toxicity criteria of adverse events (CTCAE 4.0). Dose-limiting toxicities will be defined as follows:

- ▶ Any toxicity that causes a discontinuation of concurrent radiation therapy for more than 6 days.
- ▶ Toxicity classified CTCAE 4.0 grade 4 or 5.
- ▶ Toxicity classified CTCAE 4.0 grade 3 with the following exceptions:
 - Arterial hypertension CTCAE 4.0 grade 3 will only be regarded as dose limiting if it persists longer than 14 days despite adequate medical treatment.
 - Haematological toxicity CTCAE 4.0 grade 3.
 - Elevated serum levels of liver and pancreas enzymes of any CTCAE 4.0 grade will only be regarded as dose-limiting toxicity (DLT) if they are related with clinical symptoms of pancreatitis, hepatitis or liver failure.

In case of dose-limiting toxicities the administration of sunitinib must be stopped. After recovery from toxicity to CTCAE grade 1 sunitinib will be reintroduced in a reduced dose (25 mg instead of 37.5 mg or 12.5 instead of 25 mg). In case of hematological toxicity CTCAE grade 3 sunitinib will be reduced (37.5–25 or 25–12.5 mg) until recovery to CTCAE grade 1. In case of prolonged toxicity of any CTCAE grade the dose of sunitinib may also be reduced temporarily (37.5–25 or 25–12.5 mg). After recovery from toxicity to CTCAE grade 1 sunitinib will be reintroduced in the original dose.

Box 1 Dose escalation of sunitinib

First dose level (25 mg)

- ▶ If 0/3 patients exhibit dose-limiting toxicity (DLT) at the first dose level dose escalation at the second dose level (37.5 mg) will begin in the second cohort.
- ▶ If 1/3 patients exhibit DLT at the first dose level the first dose level will be expanded to a total of 6 patients.
 - If no further DLT events will be seen dose escalation to the second dose level can begin.
 - If one or more further DLT events are seen the dose will not be escalated and no does will be recommended for phase II.
- ▶ If 2/3 patients suffer from DLT the dose will not be escalated.

Second dose level (37.5 mg)

- ▶ If 0/3 patients exhibit DLT at the second dose level, then the second dose level will be recommended for phase II.
- ▶ If 1/3 patient exhibits DLT events another 3 patients will be included in the second dose level.
 - If no further DLT events will be seen, the second dose level will be recommended for phase II.
 - If one or more further DLT events are seen the recommended dose for phase II will be the first dose level.

End points

Primary end points of the study are the determination of the dose-limiting toxicity and the recommended phase II dose of sunitinib administered concurrently to percutaneous irradiation as neoadjuvant treatment for soft tissue sarcoma.

The recommended dose of sunitinib will be dose level 2 (37.5 mg) if not more than 0/3 or 1/6 patients in dose level 1 AND dose level 2 develop DLT.

The recommended dose of sunitinib will be dose level 1 (25 mg) if not more than 0/3 or 1/6 patients develop DLT AND 2 or more patients develop DLT in dose level 2.

No recommended dose will be defined if two or more patients develop DLT in dose level 1.

Secondary end points are pathological and imaging response to the treatment and postoperative morbidity of tumour resection.

Pathological response will be defined as the fraction of non-viable tissue in the resection specimen.

Imaging response will be defined according to RECIST and Choi criteria.

Postoperative morbidity until the 30th postoperative day will be documented according to CTCAE grade 4.

Screening and assessment of end points

The study will be performed on an outpatient basis. Patients who presented with primary or recurrent tumours or singular metachronous metastasis will be screened. Eligibility criteria will be assessed by review of biopsy histology and imaging, clinical examination and further organ function tests. This will include interrogation for pre-existent diseases and medication, clinical examination, differential blood count and determination of serum levels of kidney, hepatic and pancreatic enzymes, ECG and cardiac ultrasound. The investigator will explain the nature of the trial, its purpose, procedures as well as the potential risks and benefits. If inclusion criteria are met, informed consent will be obtained and the patient will be informed that participation is voluntary and that withdrawal of informed consent is possible at any time.

To assess the primary end point toxicity, study visits including clinical examination, interrogation for adverse events, laboratory tests and ECG will be performed on a weekly basis until the fourth week after completion of radiation therapy. As described above toxicity will be classified according to CTCAE 4.0.

To assess the secondary end point tumour response restaging with thoracic computertomography and MRI of the tumour site will be performed before tumour resection which will be scheduled 5–8 weeks after completion of radiation therapy.

To assess the secondary end point postoperative morbidity there will be a study visit between the 30th and 40th day after the operation which includes review of the reports of the operation, the perioperative hospital stay and the histopathological examination.

Statistics

Sunitinib will be administered in two dose levels according to a classical 3×3 design. The total number of patients will thus lay between 2 at minimum and 12 at maximum. Only two patients will be treated if the first two patients in the first dose level both show a DLT. Twelve patients will be treated if a DLT occurs in one patient out of the first three in each dose level.

The power properties of the applied $3+3$ design are as follows: assuming an unacceptable high true DLT rate of 50% the probability to observe at least one DLT of three patients is given by 87.5%, the probability to observe at least two of six patients, which means no further dose escalation, is given by 89.1%. If the true DLT rate is 40%, then the probabilities are given by 78.4% and

76.7%, respectively. Consequently, the power properties of the 3×3 design are appropriate in the context of a phase I trial.

Primary and secondary end points will be analysed descriptively by the measures of the empirical distribution. For continuous data means and SDs, minimal and maximal values and median and quartiles will be calculated. For categorical data absolute and relative frequency will be given. All analyses will be performed using SAS V.9 or higher (SAS Institute Inc, USA).

Setting

Sponsor of the study is the University of Heidelberg, Germany. The trial is coordinated by the Division of Surgical Oncology of the Department of Surgery of the University Medical Center Mannheim, University of Heidelberg, Germany. Study centres are the University Medical Center Mannheim and the Sarcoma Center Berlin-Brandenburg in Germany. The study is funded by the German Research Foundation (Identifier JA 2030/1-1) and the Medical Faculty Mannheim of the University of Heidelberg. Funding from the DFG was obtained in a competitive selection process that included peer reviewing. The study medication is sponsored by Pfizer Oncology Germany. Pfizer Oncology had no influence on the design of the trial and will have no influence on conduction of the study and publication of the results. Monitoring will be performed by the Division of Surgical Oncology and Thoracic Surgery, Department of Surgery, University Medical Center Mannheim, University of Heidelberg. Issues of pharmacovigilance will be handled by the Coordination Centre for Clinical Trials Heidelberg. The Institute of Medical Biometry and Informatics of the University of Heidelberg is the data centre of the trial and will be responsible for statistical analysis.

Ethics and dissemination

If sunitinib and irradiation therapy do have synergistic effects patients treated within the trial may have potential benefits. They may experience less tumour recurrences and may have an improved disease-free and overall survival. However, additional administration of sunitinib to the standard treatment may cause additional adverse events, increase radiation toxicities or interfere with the planned tumour treatment. The most frequent risks from preoperative irradiation are skin and gastrointestinal toxicities. Both maybe increased by the additional administration of sunitinib. Among the most common other severe adverse toxicities of sunitinib were thromboembolic events, leucopenia and lymphopenia, pancreatitis and left ventricular failure. These events may not only severely harm the patients immediately but may also impede the continuation of irradiation and the subsequent tumour resection which may deteriorate disease-free and overall survival.

The study is performed in accordance with the declaration of Helsinki, the European directive for clinical

trials and the German drug law. Approval was obtained from the ethics committee II of the University of Heidelberg (Reference number 2011-064F-MA). Furthermore, the study was approved by the German Federal Institute for Drugs and Medical Devices (Reference number 4037708). The study was registered in the public clinical trial database Clinicaltrials.gov (Identifier NCT01498835) and the European Clinical Trials Database (EudraCT number 2007-002864-87).

The analysis of the primary and secondary end points will be performed immediately after completion of data collection which is expected for 2014. We aim to disseminate the results by publication in a peer-reviewed journal and to present the study at national and international sarcoma and oncology meetings.

DISCUSSION

We present here the study protocol of an innovative and promising neoadjuvant therapy for soft tissue sarcoma combining radiation therapy and the antiangiogenic multityrosine kinase inhibitor sunitinib. Although single agent toxicity of sunitinib is well known we chose toxicity as primary end point since excessive toxicity of the combination may impair completion of standard radiation therapy and surgery.³¹ For the same reason, postoperative morbidity was chosen as a secondary end point.

The classical 3 × 3 dose escalation was selected because of possibly effective dose levels known from previous single agent trials. Sunitinib is approved for a 4 weeks on/2 weeks off regimen at a dose of 50 mg. Alternatively, a continuous dosing of 37.5 mg may be applied.³³ The latter dosing is suitable for combination with preoperative radiation therapy and therefore was chosen as the final dose level.

If the combination of sunitinib and radiation therapy proves to be well tolerable in the neoadjuvant setting we plan to proceed to perform a multicenter phase II trial focusing on local tumour control. Regarding the promising results of other multityrosine kinase inhibitors for metastatic disease we may then consider to combine neoadjuvant sunitinib and irradiation with adjuvant sunitinib.^{24–26}

Trial status

The study has been initiated in February 2012. As of April 2013, six patients have been included in dose level 1.

Acknowledgements The study was designed at the EORTC/AACR workshop at Flims, Switzerland. The protocol was further developed at the academy for young investigators of the German Research Foundation (DFG).

Contributors JJ, PH and FW designed and planned the trial. JJ wrote the study protocol. GR was responsible for the statistical design and will perform the statistical analysis. PH is the principal investigator of the trial. JJ wrote the manuscript. All authors read and approved the final manuscript.

Funding German Research Foundation (DFG), grant number JA 2030/1-1.

Competing interests None.

Ethics approval Medical ethics committee II, Maybachstr. 14, 68169 Mannheim, Germany. Federal Institute for drugs and medical devices, Germany (BfArM).

Provenance and peer review Not commissioned; internally peer reviewed.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 3.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/3.0/>

REFERENCES

- Clark MA, Fisher C, Judson I, *et al.* Soft-tissue sarcomas in adults. *N Engl J Med* 2005;353:701–11.
- Stiller CA, Trama A, Serraino D, *et al.* Descriptive epidemiology of sarcomas in Europe: report from the RARECARE project. *Eur J Cancer* 2012;49:684–95.
- Kattan MW, Leung DH, Brennan MF. Postoperative nomogram for 12-year sarcoma-specific death. *J Clin Oncol* 2002;20:791–6.
- Anaya DA, Lahat G, Wang X, *et al.* Postoperative nomogram for survival of patients with retroperitoneal sarcoma treated with curative intent. *Ann Oncol* 2010;21:397–402.
- Mariani L, Miceli R, Kattan MW, *et al.* Validation and adaptation of a nomogram for predicting the survival of patients with extremity soft tissue sarcoma using a three-grade system. *Cancer* 2005;103:402–8.
- Biau DJ, Ferguson PC, Chung P, *et al.* Local recurrence of localized soft tissue sarcoma: a new look at old predictors. *Cancer* 2012;118:5867–77.
- Ferrone ML, Raut CP. Modern surgical therapy: limb salvage and the role of amputation for extremity soft-tissue sarcomas. *Surg Oncol Clin N Am* 2012;21:201–13.
- Rosenberg SA, Kent H, Costa J, *et al.* Prospective randomized evaluation of the role of limb-sparing surgery, radiation therapy, and adjuvant chemoimmunotherapy in the treatment of adult soft-tissue sarcomas. *Surgery* 1978;84:62–9.
- Demetri GD, Antonia S, Benjamin RS, *et al.* Soft tissue sarcoma. *J Natl Compr Canc Netw* 2010;8:630–74.
- ESMO: Soft tissue and visceral sarcomas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012;23(Suppl 7):vii92–9.
- Hohenberger P, Wysocki WM. Neoadjuvant treatment of locally advanced soft tissue sarcoma of the limbs: which treatment to choose? *Oncologist* 2008;13:175–86.
- Gronchi A, Lo Vullo S, Fiore M, *et al.* Aggressive surgical policies in a retrospectively reviewed single-institution case series of retroperitoneal soft tissue sarcoma patients. *J Clin Oncol* 2009;27:24–30.
- O'Sullivan B, Davis AM, Turcotte R, *et al.* Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. *Lancet* 2002;359:2235–41.
- Curtis KK, Ashman JB, Beauchamp CP, *et al.* Neoadjuvant chemoradiation compared to neoadjuvant radiation alone and surgery alone for Stage II and III soft tissue sarcoma of the extremities. *Radiat Oncol* 2011;6:91.
- Eckert F, Matuschek C, Mueller AC, *et al.* Definitive radiotherapy and single-agent radiosensitizing ifosfamide in patients with localized, irresectable soft tissue sarcoma: a retrospective analysis. *Radiat Oncol* 2010;5:55.
- Gronchi A, Frustaci S, Mercuri M, *et al.* Short, full-dose adjuvant chemotherapy in high-risk adult soft tissue sarcomas: a randomized clinical trial from the Italian Sarcoma Group and the Spanish Sarcoma Group. *J Clin Oncol* 2012;30:850–6.
- Issels RD, Lindner LH, Verweij J, *et al.* Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study. *Lancet Oncol* 2010;11:561–70.
- Penel N, Van Glabbeke M, Marreaud S. Testing new regimens in patients with advanced soft tissue sarcoma: analysis of publications from the last 10 years. *Ann Oncol* 2011;22:1266–72.
- Osusky KL, Hallahan DE, Fu A, *et al.* The receptor tyrosine kinase inhibitor SU11248 impedes endothelial cell migration, tubule formation, and blood vessel formation in vivo, but has little effect on existing tumor vessels. *Angiogenesis* 2004;7:225–33.
- Yoon SS, Stangenberg L, Lee YJ, *et al.* Efficacy of sunitinib and radiotherapy in genetically engineered mouse model of soft-tissue sarcoma. *Int J Radiat Oncol Biol Phys* 2009;74:1207–16.

21. DuBois S, Demetri G. Markers of angiogenesis and clinical features in patients with sarcoma. *Cancer* 2007;109:813–19.
22. Potti A, Ganti AK, Foster H, *et al.* Immunohistochemical detection of HER-2/neu, c-kit (CD117) and vascular endothelial growth factor (VEGF) overexpression in soft tissue sarcomas. *Anticancer Res* 2004;24:333–7.
23. Yudoh K, Kanamori M, Ohmori K, *et al.* Concentration of vascular endothelial growth factor in the tumour tissue as a prognostic factor of soft tissue sarcomas. *Br J Cancer* 2001;84:1610–15.
24. 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;27:3154–60.
25. Tariq Mahmood S, Agresta S, Vigil CE, *et al.* Phase II study of sunitinib malate, a multitargeted tyrosine kinase inhibitor in patients with relapsed or refractory soft tissue sarcomas. Focus on three prevalent histologies: leiomyosarcoma, liposarcoma and malignant fibrous histiocytoma. *Int J Cancer* 2011;129:1963–9.
26. Van der Graaf WT, Blay JY, Chawla SP, *et al.* Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2012;379:1879–86.
27. Folkman J. Tumor angiogenesis: therapeutic implications. *N Engl J Med* 1971;285:1182–6.
28. Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. *Science* 2005;307:58–62.
29. Nieder C, Wiedenmann N, Andratschke N, *et al.* Current status of angiogenesis inhibitors combined with radiation therapy. *Cancer Treat Rev* 2006;32:348–64.
30. Kao J, Packer S, Vu HL, *et al.* Phase 1 study of concurrent sunitinib and image-guided radiotherapy followed by maintenance sunitinib for patients with oligometastases: acute toxicity and preliminary response. *Cancer* 2009;115:3571–80.
31. Niyazi M, Maihoefer C, Krause M, *et al.* Radiotherapy and “new” drugs—new side effects? *Radiat Oncol* 2011;6:177.
32. Jakob J, Wenz F, Dinter DJ, *et al.* Preoperative intensity-modulated radiotherapy combined with temozolomide for locally advanced soft-tissue sarcoma. *Int J Radiat Oncol Biol Phys* 2009;75:810–16.
33. Escudier B, Roigas J, Gillessen S, *et al.* Phase II study of sunitinib administered in a continuous once-daily dosing regimen in patients with cytokine-refractory metastatic renal cell carcinoma. *J Clin Oncol* 2009;27:4068–75.