Pharmacogenetics and cost-effectiveness of systemic treatment in soft tissue sarcoma

Verboom, M.C.

1

General introduction

This thesis on systemic treatment options in soft tissue sarcoma (STS) focusses on two topics. In the first part single nucleotide polymorphisms (SNPs) are explored that potentially influence drug effects in the treatment of gastrointestinal stromal tumors (GIST). In the second part the introduction of trabectedin chemotherapy for the treatment of STS is examined with a cost-effectiveness analysis (CEA) and description of venous access related adverse events.

Part I: Pharmacogenetics of systemic GIST-treatment

Gastrointestinal stromal tumors

Gastrointestinal stromal tumor (GIST) is a tumor arising from mesenchymal cells of the gastro-intestinal tract and has a unique biology and clinical course. Most GISTs are the result of a gain-of-function mutation in the *KIT* gene, encoding for the KIT/CD117 transmembranous receptor.[1,2] This receptor can be blocked by intracellular active tyrosine kinase inhibitors (TKIs), such as imatinib.[3] Imatinib is an oral drug that was first used in the treatment of chronic myeloid leukemia due to its binding to the oncogenic BCR-ABL protein.[4] This potent drug can be employed in the neo-adjuvant, adjuvant and palliative stages of GIST therapy.[5] In case the GIST is resectable, surgery can cure patients. In case the tumor has metastasized, TKIs are used to suppress tumor activity for as long as possible.

Imatinib is firmly positioned as the first-line option for advanced GIST.[6] Its position has been challenged by nilotinib, a drug that has even higher affinity for the wild-type BCR-ABL kinase, while retaining its activity against KIT and PDGFR.[7] A head-to-head phase III trial in advanced GIST patients showed, however, that imatinib treatment resulted in longer progression free survival and overall survival compared to nilotinib.[8] A recent trial investigated the activity of dasatinib, another TKI, as first-line agent for GIST, but the progression free survival was far shorter than obtained in previous imatinib trials.[9] The fact that this study failed to meet the envisioned enrollment of 52 patients over a period of almost four years is a clear sign of imatinib's paramount position. Masitinib might have been a useful alternative, as the results phase II trial with GIST patients during first line therapy who received this drug are comparable to imatinib, but the future of masitinib is uncertain.[10]

Sunitinib is the second-line treatment option following imatinib resistance or intolerability.[6] The majority of trials with sunitinib in GIST patients were performed in a setting following imatinib treatment. Long term safety and efficacy have been shown in large international patient cohorts.[11,12] Thus far only one randomized clinical trial directly compared two TKIs in a setting of advanced GIST after imatinib failure, the TKIs being

sunitinib and masitinib.[13] Masitinib yielded somewhat better progression free survival, but in patients receiving sunitinib survival was far shorter than what has been reported in previous studies with sunitinib.

Regorafenib is the third-line option for GIST patients following imatinib and sunitinib resistance or intolerance.[6] It was one of many agents tested in this setting and its activity has been demonstrated in clinical trials.[14,15] As patients receive more lines of therapy, each line offers less survival gains than the previous line of therapy, as a result of ongoing development of TKI-resistance in the heterogeneous GIST metastases.[16]

Currently, there is no established fourth-line treatment option. Many targeted agents have been explored in patients with advanced GIST. Several clinical trials are currently investigating the activity of new drugs compared to imatinib, sunitinib and regorafenib in first, second and third line setting. Among these are the new TKIs DCC-2618 and BLU-285. DCC-2618 has anti-tumor potential against GISTs with *KIT* mutations exon 13, 14, 17 or 18. In a dose escalation trial partial responses have been observed. Clinical trials with DCC-2618 in the second line versus sunitinib (NCT03673501) and in the fourth line versus placebo (NCT03353753) have subsequently been initiated. Due to the clinical success of the phase I study with DCC-2618 (NCT02571036), this study was expanded to include patients in the second and third line of therapy. Of the 46 patients treated with 150mg once daily in the second or third line 10 had a response and the median progression free survival was 36 weeks with 61% of patients censored.[17] BLU-285, now called avapritinib, has activity against GISTs with specific mutation that other TKIs do not inhibit. It is being investigated in clinical trials as third line therapy versus regorafenib (NCT03465722) and in a fourth line phase II setting (NCT02508532).

Pharmacogenetics

Whereas treatment for illnesses such as malignancies are based on evidence derived from clinical trials involving large numbers of patients, the response of individual patients to a certain drug is dependent on patient specific characteristics.[18] These characteristics include age, sex, body size, kidney function, co-medication, as well as a patient's specific germline genetic traits.[19] The most prevalent genetic variations are single nucleotide polymorphisms and the focus of the research in this part of the thesis.

SNPs may or may not affect gene function and patient phenotype. Some SNPs will not alter which amino acid is built into the protein, termed synonymous SNPs. Non-synonymous SNPs, on the other hand, do have an effect. These SNPs will either change an amino acid at particular location, being a missense SNPs, or in case of a nonsense SNPs will result in the premature insertion of a stop codon and ending further amino acids being added to the protein. SNPs do also occur in non-coding regions and these

can affect the splicing, binding and alteration of the pre-mRNA molecule. SNPs studied in this thesis were all selected to have a functional effect, as found in the National Institute of Environmental Health Sciences SNP database.[20]

SNPs in genes related to the pharmacokinetics or pharmacodynamics of drugs may influence the response to these drugs. In case of GIST, imatinib or sunitinib efficacy may be enhanced or reduced in terms of longer or shorter survival. Equally, the adverse effects of these drugs may vary according to a patient's genetic profile. One such example that has found its way into clinical practice is the determination of *DPYD* polymorphisms in patients receiving 5-fluorouracil.[21]

Pharmacogenetic research has shown associations of SNPs in genes related to TKI pharmacokinetics and pharmacodynamics with clinical outcome in TKI treated malignancies. Imatinib is primarily metabolized by CYP3A4 and CYP3A5, while other CYP-enzymes have a limited role.[19] The drug is a substrate for the influx transporters hOCT1 (*SLC22A1*), OCTN1 (*SLC22A4*), OCTN2 (*SLC22A5*) and OATP1B3 (*SLCO1B3*).[22-24] Active efflux transporters are the ATP-binding cassette (*ABCB1*) and the breast cancer resistance protein (*ABCG2)*.[19] Time to progression in advanced GIST patients who were treated with imatinib has been associated to SNPs in *SLC22A4* (rs1050152) and *SLC22A5* (rs2631367, rs2631372).[25] Response to imatinib in the treatment of chronic myeloid leukemia has been associated to SNPs in *ABCB1* (rs868755, rs1045642, rs28656907), *ABCG2* (rs2231137), *CYP3A5* (rs776746), *SLC22A1* (rs683369) and in *SLCO1B3* (rs4149117).[26-28] Imatinib trough levels have been associated in multiple studies to SNPs in *ABCB1*, *ABCG2* and *CYP3A4*.[24,29,30]

Even more pharmacogenetic studies have been performed with sunitinib, many of them in patients with metastatic renal cell carcinoma.[31] Sunitinib is metabolized into the SU12662 metabolite by CYP3A4 and both are active compounds.[19] CYP3A4 expression or activity is in turn influenced by *NR1I2*, *NR1I3* and *POR* effects.[32,33] CYP3A5 and CYP1A1 may also metabolize sunitinib, as these CYPs are active in other TKIs.[19] Sunitinib is a substrate for the drug efflux transporters ATP-binding cassette (*ABCB1*) and breast cancer resistance protein (*ABCG2)*.[19] Survival during sunitinib treatment in metastatic renal cell carcinoma has been associated with SNPs in *ABCB1* (rs1045642, rs1128503, rs2032582) and *CYP3A5* (rs776746) and these associations have been confirmed in a separate patient cohort.[34,35] Individual sunitinib adverse events were associated with several SNPs in *ABCB1*, *ABCG2* , *CYP1A1*, *NR1I3*, *IL8* and *IL13*.[36,37] Sunitinib clearance has been associated with a SNP in *CYP3A4* (rs35599367).[38] In sunitinib treated GIST, associations have been found with SNPs in *VEGFR3* (rs6877011, rs7709359) and time to progression, and with a SNP in *VEGFA* (rs7709359) and toxicity.[39] Until the work described in this thesis was started, pharmacogenetic studies with a large cohort of advanced GIST patients had not yet been performed.

Part II: Use of trabectedin in STS

Soft tissue sarcoma

STS comprise 50 to 60 distinct types of histology and constitute one percent of all solid malignancies. Due to its rarity STS have long been grouped together in treatment and research.[40] As knowledge on the tumor biology of histologic subtypes expands, it has become evident that specific subtypes should be treated as specific as possible. Due to its unique pathophysiology, treatment and clinical course, GIST already has its separate guideline.[6]

Systemic agents tested in STS trials may have anti-tumor activity in only some STS subtypes. The first line therapy in advanced STS is doxorubicin for almost all subtypes.[40] For second line options, the specific STS histology is to be taken into account when selecting treatments. Most patients will be offered the oral TKI pazopanib, but patients with adipocytic tumors will not respond. Adipocytic tumors such as liposarcomas, as well as the otherwise unrelated leiomyosarcomas have shown favorable response to trabectedin.[41] Trabectedin is a marine derived compound with a unique mechanism of action involving DNA binding, influencing transcription factors and modulating the tumor micro-environment.[42]

In the past decade, the number of available systemic agents and combinations thereof in advanced STS has increased. First line doxorubicin can be augmented by adding ifosfamide to increase the chance of a response.[43] Alternately, adding the PDGFR-inhibitor olaratumab to doxorubicin might prolong survival. This was seen in a phase II trial, but not in the subsequent phase III trial.[44] Apart from trabectedin and pazopanib, some patient may benefit from ifosfamide monotherapy, or from eribulin in case of a liposarcoma.[45,46] In patients with undifferentiated pleomorphic sarcoma, gemcitabine-docetaxel cycles may be considered. Angiosarcomas can respond to taxanes.[47] In all, while the number of treatment options has grown and survival may be prolonged, advanced STS still is disease with very slim chances of survival and almost all affected patients will die due to it.

Cost-effectiveness analysis

Cost-effectiveness analysis requires data on the efficacy and toxicity of a certain drug in a certain clinical setting and a comparator that can be seen as a valid option for that disease. Together with data on health care usage and costs, an analysis can be performed. In the analysis an incremental cost effectiveness ratio is calculated, denoting the costs per QALY of the new treatment compared to the other treatment. In the Netherlands, health care authorities have published a report entitled 'Sensible and sustainable care'

in which an ICER of a maximum of €80,000 is considered acceptable.[48] This number is now frequently used as the acceptable cost per QALY in the Netherlands.

As the number of systemic anti-cancer drugs grows, choices have to be made concerning treatment allocation on a single patient basis, as well as on a group level. Apart from data on efficacy and toxicity, the societal costs of drug will need to be taken in consideration.[48] Treatment with new drugs, with their patent still active, will usually have substantial costs and health care regulators are keen to learn whether a new drug is worth its price tag. When trabectedin was introduced into the Dutch market, Dutch health care regulators also wished to see its cost-effectiveness investigated in STS.

Outline of this thesis

The subject of **Part I** of this thesis is further introduced in an updated review article (**chapter 2**) on the systemic treatment in GIST. The development of imatinib, sunitinib and regorafenib are described, the results of the most relevant trials, as well as mechanisms of drug resistance. Additionally, other drugs tested in phase II or phase III trials are summarized. In the subsequent chapters, SNPs involved in the pharmacokinetics and pharmacodynamics of imatinib are investigated for an association with treatment effect in GIST. The efficacy of imatinib is studied in advanced GIST patients (**chapter 3**), seeking SNPs that are predictive for survival duration during first-line imatinib treatment. A similar study was performed with sunitinib (**chapter 4**), exploring associations with sunitinib efficacy during second-line of therapy. These two studies aim to identify SNPs that may serve to predict the duration of survival and the associated risk of progressive disease. SNPs are selected using a pharmacologically informed pathway approach. In case SNPs are associated with reduced survival, patients with these SNPs may benefit from intensified follow-up. In case SNPs are associated with prolonged survival, these SNPs could potentially influence future treatment decisions in favor of the specific drug if more active agents become available. In regard to GIST, the specific mutation causing the disease also is an important factor influencing therapy. Therefore, in these two chapters with pharmacogenetic studies with imatinib and sunitinib, the associations of SNPs with survival is corrected for the mutation found in the primary tumor.

The relation of imatinib adverse events was studied next (**chapter 5**), aiming to find SNPs that will predict the clinical impact of severe toxicity requiring therapy restriction. Although imatinib has a relatively mild toxicity profile, clinical trials have shown a need for dose reduction in around 15% of patients.[49-51] If patients in need of a dose reduction can be identified through their genetic polymorphisms before therapy is initiated, adverse events necessitating the dose reduction may be prevented. Averting toxicity in this way, pharmacogenetics may contribute to improving patients' safety and quality

of life. The last study in this section (**chapter 6**) aims to associate SNPs in *CYP2C8* with imatinib steady-state trough levels after prolonged period of use. CYP3A4 and CYP3A5 are the primary metabolizers of imatinib, but chronic use of imatinib leads to auto-inhibition of these CYP enzymes and then CYP2C8 becomes an important metabolizer.[52] CYP2C8 activity in regard to imatinib has been shown *in vitro* to vary according to polymorphism is present, but an *in vivo* study has not yet been performed.[53]

The subject of **Part II** of this thesis is further introduced in a review article (**chapter 7**) on the development of trabectedin and the first clinical studies with this drug in STS. The cost-effectiveness of trabectedin was tested in patients with advanced STS after treatment with first line doxorubicin. This study (**chapter 8**) originally was meant to compare trabectedin with best supportive care in this regard, but as is explained in further detail later, the study eventually went to compare the cost-effectiveness of trabectedin versus ifosfamide chemotherapy in a second line setting. Data from EORTC trials with ifosfamide in STS patients was used. This study was started on the request of Dutch health care authorities as part of the registration process of trabectedin. The adverse events relating to the venous access devices for trabectedin (**chapter 9**) are reported as last study in this thesis. In some patients sterile inflammation along the catheter trajectory of the Port-a-Cath developed and this had not yet been reported as a possible adverse event when administering trabectedin. Placing the catheter deeper in the skin resolved this issue.

This thesis is concluded with a general discussion (**chapter 10**) on the studies performed. It highlights the key results and delivers comments on how to interpret these results and the studies in general.

Reference list

1. Miettinen M, Lasota J: Gastrointestinal stromal tumors--definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. Virchows Arch 438:1-12, 2001
2. Hirota S, Isozaki K, Moriyama Y, et al: Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 279:577-580, 1998
3. Joensuu H, Roberts PJ, Sarlomo-Rikala M, et al: Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. N. Engl. J. Med 344:1052-1056, 2001
4. Druker BJ, Tamura S, Buchdunger E, et al: Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. Nat. Med 2:561-566, 1996
5. Dagher R, Cohen M, Williams G, et al: Approval summary: imatinib mesylate in the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors. Clin. Cancer Res 8:3034-3038, 2002
6. Casali PG, Abecassis N, Bauer S, et al: Gastrointestinal stromal tumours: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol, 2018
7. Blay JY, von Mehren M: Nilotinib: a novel, selective tyrosine kinase inhibitor. Semin Oncol 38 Suppl 1:S3-9, 2011
8. Blay JY, Shen L, Kang YK, et al: Nilotinib versus imatinib as first-line therapy for patients with unresectable or metastatic gastrointestinal stromal tumours (ENESTg1): a randomised phase 3 trial. Lancet Oncol 16:550-60, 2015
9. Montemurro M, Cioffi A, Domont J, et al: Long-term outcome of dasatinib first-line treatment in gastrointestinal stromal tumor: A multicenter, 2-stage phase 2 trial (Swiss Group for Clinical Cancer Research 56/07). Cancer 124:1449-1454, 2018
10. Le Cesne A, Blay JY, Bui BN, et al: Phase II study of oral masitinib mesilate in imatinib-naive patients with locally advanced or metastatic gastro-intestinal stromal tumour (GIST). Eur. J. Cancer 46:1344-1351, 2010
11. Reichardt P, Kang YK, Rutkowski P, et al: Clinical outcomes of patients with advanced gastrointestinal stromal tumors: safety and efficacy in a worldwide treatment-use trial of sunitinib. Cancer 121:1405-13, 2015
12. Demetri GD, van Oosterom AT, Garrett CR, et al: Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 368:1329-1338, 2006
13. Adenis A, Blay JY, Bui-Nguyen B, et al: Masitinib in advanced gastrointestinal stromal tumor (GIST) after failure of imatinib: A randomized controlled open-label trial. Ann. Oncol 25:1762-1769, 2014
14. George S, Wang Q, Heinrich MC, et al: Efficacy and safety of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of imatinib and sunitinib: a multicenter phase II trial. J. Clin. Oncol 30:2401-2407, 2012

15. Demetri GD, Reichardt P, Kang YK, et al: Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 381:295-302, 2013

16. Liegl B, Kepten I, A. LC, et al: Heterogeneity of kinase inhibitor resistance mechanisms in GIST. J. Pathol 216:64-74, 2008

17. George S, Heinrich M, Chi P, et al: Initial Results of Phase 1 Study of DCC-2618, a Broad-spectrum KIT and PDGFRa Inhibitor, in Patients (pts) with Gastrointestinal Stromal Tumor (GIST), ESMO 2018 Congress, Annals of Oncology (2018) 29 (suppl_8): viii576-viii595., 2018

18. Van Glabbeke M, Verweij J, Casali PG, et al: Predicting toxicities for patients with advanced gastrointestinal stromal tumours treated with imatinib: a study of the European Organisation for Research and Treatment of Cancer, the Italian Sarcoma Group, and the Australasian Gastro-Intestinal Trials Group (EORTC-ISG-AGITG). Eur J Cancer 42:2277-85, 2006

19. Van Erp NP, Gelderblom H, Guchelaar HJ: Clinical pharmacokinetics of tyrosine kinase inhibitors. Cancer Treat. Rev 35:692-706, 2009

20. Xu Z, Taylor JA: SNPinfo: integrating GWAS and candidate gene information into functional SNP selection for genetic association studies. Nucleic Acids Res 37:W600-5, 2009

21. Henricks LM, Lunenburg C, de Man FM, et al: DPYD genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis. Lancet Oncol, 2018

22. Roth M, Obaidat A, Hagenbuch B: OATPs, OATs and OCTs: the organic anion and cation transporters of the SLCO and SLC22A gene superfamilies. Br J Pharmacol 165:1260-87, 2012

23. Thomas J, Wang L, Clark RE, et al: Active transport of imatinib into and out of cells: implications for drug resistance. Blood 104:3739-45, 2004

24. Takahashi N, Miura M, Scott SA, et al: Influence of CYP3A5 and drug transporter polymorphisms on imatinib trough concentration and clinical response among patients with chronic phase chronic myeloid leukemia. J. Hum. Genet 55:731-737, 2010

25. Angelini S, Pantaleo MA, Ravegnini G, et al: Polymorphisms in OCTN1 and OCTN2 transporters genes are associated with prolonged time to progression in unresectable gastrointestinal stromal tumours treated with imatinib therapy. Pharmacol. Res 68:1-6, 2013

26. Kim DH, Sriharsha L, Xu W, et al: Clinical relevance of a pharmacogenetic approach using multiple candidate genes to predict response and resistance to imatinib therapy in chronic myeloid leukemia. Clin. Cancer Res 15:4750-4758, 2009

27. Nambu T, Hamada A, Nakashima R, et al: Association of SLCO1B3 polymorphism with intracellular accumulation of imatinib in leukocytes in patients with chronic myeloid leukemia. Biol. Pharm. Bull 34:114-119, 2011

28. Dulucq S, Bouchet S, Turcq B, et al: Multidrug resistance gene (MDR1) polymorphisms are associated with major molecular responses to standard-dose imatinib in chronic myeloid leukemia. Blood 112:2024-2027, 2008

29. Harivenkatesh N, Kumar L, Bakhshi S, et al: Influence of MDR1 and CYP3A5 genetic polymorphisms on trough levels and therapeutic response of imatinib in newly diagnosed patients with chronic myeloid leukemia. Pharmacol Res 120:138-145, 2017

30. Ni LN, Li JY, Miao KR, et al: Multidrug resistance gene (MDR1) polymorphisms correlate with imatinib response in chronic myeloid leukemia. Med. Oncol 28:265-269, 2011

31. Diekstra MH, Swen JJ, Gelderblom H, et al: A decade of pharmacogenomics research on tyrosine kinase inhibitors in metastatic renal cell cancer: a systematic review. Expert Rev Mol Diagn 16:605-18, 2016

32. Elens L, Nieuweboer AJ, Clarke SJ, et al: Impact of POR*28 on the clinical pharmacokinetics of CYP3A phenotyping probes midazolam and erythromycin. Pharmacogenet Genomics 23:148-55, 2013

33. Lamba J, Lamba V, Strom S, et al: Novel single nucleotide polymorphisms in the promoter and intron 1 of human pregnane X receptor/NR1I2 and their association with CYP3A4 expression. Drug Metab Dispos 36:169-81, 2008

34. Van der Veldt AA, Eechoute K, Gelderblom H, et al: Genetic polymorphisms associated with a prolonged progression-free survival in patients with metastatic renal cell cancer treated with sunitinib. Clin. Cancer Res 17:620-629, 2011

35. Diekstra MH, Swen JJ, Boven E, et al: CYP3A5 and ABCB1 polymorphisms as predictors for sunitinib outcome in metastatic renal cell carcinoma. Eur Urol 68:621-9, 2015

36. Van Erp NP, Eechoute K, van der Veldt AA, et al: Pharmacogenetic pathway analysis for determination of sunitinib-induced toxicity. J. Clin. Oncol 27:4406-4412, 2009

37. Diekstra MH, Liu X, Swen JJ, et al: Association of single nucleotide polymorphisms in IL8 and IL13 with sunitinib-induced toxicity in patients with metastatic renal cell carcinoma. Eur J Clin Pharmacol 71:1477-84, 2015

38. Diekstra MH, Klumpen HJ, Lolkema MP, et al: Association analysis of genetic polymorphisms in genes related to sunitinib pharmacokinetics, specifically clearance of sunitinib and SU12662. Clin Pharmacol Ther 96:81-9, 2014

39. Ravegnini G, Nannini M, Zenesini C, et al: An exploratory association of polymorphisms in angiogenesis-related genes with susceptibility, clinical response and toxicity in gastrointestinal stromal tumors receiving sunitinib after imatinib failure. Angiogenesis 20:139-148, 2017

40. Casali PG, Abecassis N, Bauer S, et al: Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol, 2018

41. Demetri GD, Chawla SP, Von Mehren M, et al: Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior anthracyclines and ifosfamide: results of a randomized phase II study of two different schedules. J. Clin. Oncol 27:4188-4196, 2009

42. Larsen AK, Galmarini CM, D'Incalci M: Unique features of trabectedin mechanism of action. Cancer Chemother. Pharmacol 77:663-671, 2016

43. Judson I, Verweij J, Gelderblom H, et al: Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. Lancet Oncol 15:415-23, 2014

44. Tap WD, Jones RL, Van Tine BA, et al: Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial. Lancet 388:488-97, 2016

45. Lorigan P, Verweij J, Papai Z, et al: Phase III trial of two investigational schedules of ifosfamide compared with standard-dose doxorubicin in advanced or metastatic soft tissue sarcoma: a European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study. J Clin Oncol 25:3144-50, 2007

46. Schoffski P, Chawla S, Maki RG, et al: Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. Lancet 387:1629-37, 2016

47. Penel N, Bui BN, Bay JO, et al: Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX Study. J Clin Oncol 26:5269-74, 2008

48. Council for Public Health and Health Care of the Dutch Ministry of Health Welfare and Sport: report 'Sensible and sustainable care' summary available at https://www.raadrvs.nl/uploads/docs/Sensible_and_sustainable_care.pdf, 2006, 2006

49. Verweij J, Casali PG, Zalcberg J, et al: Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. Lancet 364:1127-1134, 2004

50. Blanke CD, Rankin C, Demetri GD, et al: Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. J. Clin. Oncol 26:626-632, 2008

51. DeMatteo RP, Ballman KV, Antonescu CR, et al: Long-term results of adjuvant imatinib mesylate in localized, high-risk, primary gastrointestinal stromal tumor: ACOSOG Z9000 (Alliance) intergroup phase 2 trial. Ann Surg 258:422-9, 2013

52. Filppula AM, Neuvonen M, Laitila J, et al: Autoinhibition of CYP3A4 leads to important role of CYP2C8 in imatinib metabolism: variability in CYP2C8 activity may alter plasma concentrations and response. Drug Metab Dispos 41:50-59, 2013

53. Khan MS, Barratt DT, Somogyi AA: Impact of CYP2C8*3 polymorphism on in vitro metabolism of imatinib to N-desmethyl imatinib. Xenobiotica 46:278-287, 2016