Phase 2 study of sorafenib in malignant mesothelioma previously treated with platinum-containing chemotherapy.

Sophie Papa MRCP, PhD[1,5], Sanjay Popat FRCP PhD[2,3], Riyaz Shah FRCP PhD[4], A. Toby Prevost PhD[5], Rohit Lal MRCP PhD[1], Blair McLennan BAppSc[1], Paul Cane FRCPath[1], Loic Lang-Lazdunski MD[1,5], Zaid Viney MRCP FRCR[1], Joel T Dunn PhD[5], Sally Barrington FRCP FRCR[1,5], David Landau MRCP [1,5] & James Spicer FRCP PhD*[1,5]

[1]Guy's and St Thomas' NHS Foundation Trust, London, UK; [2]Royal Marsden Hospital, London, UK; [3]National Heart and Lung Hospital, Imperial College London, UK; [4]Kent Cancer Centre, Maidstone, Kent, UK; [5]King's College London, UK

Abstract

Introduction: The incidence of mesothelioma is rising. Cisplatin and pemetrexed first line confers a survival benefit, with a median progression-free survival (PFS) of 5.7 months. Sorafenib inhibits tyrosine kinases, including receptors for vascular endothelial growth factor (VEGF), which are implicated in mesothelioma pathogenesis by pre-clinical and clinical data.

Materials and Methods: Sorafenib at 400mg BD was assessed in a single arm multi-centre phase 2 study. A Simon 2-stage design was used. Eligible patients had received prior platinum combination chemotherapy. The primary endpoint was PFS at 6 months, with secondary endpoints including response rate and metabolic response assessed using FDG-PET. Published reference values for PFS in mesothelioma provide a benchmark for the null hypothesis of 28% progression-free at 6 months, and for moderate or significant clinical activity, respectively, of 35% or 43% progression-free at 6 months.

Results: 53 patients were treated. Most had epithelioid histology (72%). 93% of patients were performance status 0 or 1. Treatment was well tolerated with few grade 3/4 toxicities. Median PFS was 5.1 months, with 36% of patients progression-free at 6 months. 9% of patients remained on study beyond one year. Changes in FDG-PET parameters did not predict clinical outcome.

Conclusions: Sorafenib is well tolerated in patients with mesothelioma after completion of platinum containing chemotherapy. PFS compares favourably to that reported for other targeted agents, and suggests moderate activity in this disease.

Introduction

Malignant mesothelioma is a disease of the mesothelial surfaces of pleural and peritoneal cavities. In excess of 80% of cases are pleural, and there is an overwhelming relationship with exposure to asbestos [1]. The incidence of the disease is predicted to continue to rise in the current decade [2]. Combination platinum chemotherapy with the anti-folate pemetrexed has become the standard of care as first line treatment. Median overall survival is 11.4 and 12.1 months in phase 3 trials combining third generation antifolates with cisplatin [3, 4]. In the second line setting no standard has yet been established.

A significant role for angiogenesis in the evolution of mesothelioma has been suggested both by pre-clinical *in vivo* and cell line studies, and by translational data from patient samples. Elevated or over-expressed vascular endothelial growth factor (VEGF), VEGF-C, fibroblast growth factor-1 and 2 (FGF-1 and FGF-2), tumour necrosis factor beta (TNF-β), VEGFR-1/FLT-1, kinase domain insert receptor/VEGFR-2 (KDR) and VEGFR-3/FLT-4 have been associated with mesothelioma [5-8]. Local production of VEGF leads to receptor phosphorylation in an autocrine loop, which can be arrested *in vitro* with neutralising antibodies to both VEGF and its receptors [8]. Antisense oligonucleotides that inhibit VEGF and VEGF-C, antibodies to VEGFR-2 and VEGFR-3, and directly conjugated VEGF-diphtheria toxin have all be shown to inhibit mesothelioma cell growth *in vitro* [9]. Furthermore there is an inverse correlation between circulating VEGF and FGF-2 and survival [6, 8, 10], with higher levels of pre-treatment VEGF possibly acting as a predictive marker for anti-angiogenesis in mesothelioma [11]. Taken together this evidence provides a rationale for a therapeutic disruption of angiogenesis pathways in mesothelioma.

Sorafenib was originally developed as a Raf-1 kinase inhibitor [12]. It was subsequently found to be a potent inhibitor of both wild type B-Raf and oncogenic B-Raf V600E serine/threonine kinases, and of the pro-angiogenic receptor tyrosine kinases (RTKs) VEGFR1/2/3, platelet-derived growth factor receptor-β (PDGFR-β), FGFR-1, c-Kit, FLT-3 and RET [13]. In xenograft models of human colon cancer, and murine and human renal cell carcinoma,

sorafenib significantly reduced tumour microvascular density [13, 14]. Combinations of antiangiogenic effects, inhibition of signalling through the MAPK pathway, and MAPK independent induction of apoptosis have all been shown to contribute to *in vivo* sorafenib activity in multiple tumour xenograft models [15-18]. Sorafenib has undergone extensive investigation in a range of solid tumours [19-24], and is approved for the treatment of clear cell renal and hepatocellular carcinoma [25, 26]. We conducted a phase 2 study of sorafenib in patients with mesothelioma previously treated with first line pemetrexed plus platinum chemotherapy.

Materials and methods

Eligibility criteria

Eligible patients had malignant pleural mesothelioma not suitable for surgery. Relapse after surgery was allowed. All patients had received first line chemotherapy with pemetrexed and platinum. Patients had an ECOG performance status of 0-2 and measurable disease according to the RECIST criteria modified for mesothelioma [27]. Adequate bone marrow, renal, liver and coagulation function as defined by protocol mandated laboratory tests within seven days of starting first dose were required, and patients were excluded in the presence of significant congestive cardiac failure or arrhythmias requiring anti-arrhythmic therapy, or other major co-morbidity such as uncontrolled hypertension, impaired immunity, active infection, coagulopathy, anticoagulation, thrombosis or haemorrhage. Prior palliative radiotherapy was permitted. The study was approved by the UK national research ethics service, and all patients signed written informed consent prior to commencement of study procedures.

Study treatment and evaluation

This was a single arm phase 2 study of continuous dosing with sorafenib 400mg twice-daily, with a cycle defined as 28 days. Dose interruptions were permitted for toxicity, as were dose reductions (to 400mg once daily, then to 400mg alternate days if required) for any grade 3 or 4 toxicity (excluding hypertension, diarrhoea or rash not adequately treated with supportive medication), or for recurrent grade 2 toxicity after dose interruption. Patients were reviewed in clinic day 1 and 15 of the first cycle, and on day 1 of each subsequent cycle. Safety blood tests, including thyroid function, and blood pressure observations were performed regularly. Treatment was continued until disease progression, withdrawal of consent or unacceptable toxicity.

Baseline disease was imaged by computed tomography (CT) with subsequent scans performed at 8-weekly intervals using modified RECIST [27]. A sub-group of sequentially-recruited patients underwent a baseline fluorodeoxyglucose positron emission tomography scan with low dose CT (FDG-PET-CT) at baseline and at 8 weeks after commencing sorafenib.

Statistical Methods

The primary end-point of the study was progression-free survival (PFS) at 6 months. Secondary end-points were partial response rate assessed by CT scan, disease control rate (partial response rate plus stable disease rate), and overall survival (OS). Change in FDG-PET-CT avidity was included as an exploratory endpoint. For FDG-PET, changes in maximum standardised uptake value (SUVmax), metabolic tumour volume (MTV), and total lesion glycolysis (TLG) were assessed before and after 8 weeks of treatment.

Using published reference data for PFS at 6 months, a null hypothesis of 28% and an alternative hypothesis of 43% were assumed [28]. Accrual of 55 patients was required for a significance level of 0.10 with an 80% power to detect that the true 6 month PFS would be $\geq$43%. A two-stage optimum design was used [29], with an initial 19 patients enrolled and evaluated for 6 month PFS, such that the trial would be continued only if 6 or more of these 19 patients were progression-free at 6 months. OS and PFS were estimated using the Kaplan-Meier method. Data was collected via an electronic database (MedSciNet AB), and statistical analysis was carried out using SSPS. The relationship between the changes in FDG avidity and outcome (PFS and OS) was assessed using Pearson's correlation coefficient using SPSS version 20 with a significance level of $p = 0.05$.

Results

Patients Characteristics

Fifty-six patients were recruited at three centres between November 2008 and April 2011. Three patients were excluded due to ineligibility. Baseline characteristics are shown in Table 1. Overall 77% were male, with 72% having epithelioid histology. Performance status was 1 or better in the great majority (93%) of patients. In total 225 cycles of sorafenib were administered with a median number of 4 cycles.

Toxicity

All patients were evaluable for toxicity assessment, shown in Table 2. The most common grade 3/4 adverse events were fatigue (15%), palmar-plantar

erythrodysesthesia (PPE) (13%), and rash (9%). Other toxicities of any grade occurring in more than 10% of patients were typical for sorafenib, namely diarrhoea, mucositis, anorexia, alopecia, dysphonia, nausea, vomiting, constipation, dry skin and pruritis. Only 1 grade 4 event was recorded, myocardial infarction in a patient previously treated for coronary artery disease. There were no deaths clearly related to study drug. At least 1 dose reduction was required in 39% of patients, with a dose interruption in 32%. 21% of patients required dose reduction in the first cycle. 11 patients (21%) discontinued treatment because of toxicity, but most (66%) were withdrawn because of disease progression (data not shown).

Efficacy

19 patients completed treatment in the first stage of the trial, with 6 patients progression-free after 6 months. Therefore recruitment of a total of 53 patients continued in the second stage. Median PFS was 5.1 months (95% CI: 3.5 to 6.7 months), with 36% (95% CI: 22% to 49%) of patients progression-free at 6 months, and 9% of patients still receiving study drug at 1 year (Figure 1A). Median OS was 9.0 months ((95% CI: 6.7 to 11.3 months; Figure 1B).

Three patients had a partial response (6%), with stable disease in 30 (56%) at 8 weeks for a disease control rate (DCR; partial response plus stable disease) of 62%. Eight patients progressed (15%) and 12 were not evaluable due to discontinuation of study drug before the first disease assessment (Figure 2).

Functional imaging

14 patients underwent paired FDG-PET-CT scans at baseline and 8 weeks after commencing sorafenib. There was no significant correlation between any of the FDG quantitative measures and PFS or OS (data not shown).

Discussion

In the evaluation of targeted agents, for which disease stabilisation may be as important as response, meaningful endpoints need to be defined to ensure that only potentially active agents progress to further study. The use of PFS in single arm trials is rational in the phase 2 study of antiangiogenic drugs in less common diseases [30]. The EORTC studied nine phase 2 trials and one phase 3 trial involving 523 evaluable chemotherapy-naïve mesothelioma patients. This group was pooled to determine PFS at 3, 4, 5, and 6 months as comparators for endpoints in subsequent studies [28]. These trials were conducted in the first line setting but in an era before current standard of care with platinum doublet chemotherapy was established. PFS was derived for three groups of study drug, designated as having significant, moderate or insufficient clinical activity. 6 month PFS was determined to be 43% for an agent with significant clinical activity, and 35% for moderate activity [28].

The primary endpoint of progression-free survival at 6 months of 36% in this trial is indicative of moderate clinical activity for sorafenib in this disease [28]. The comparator PFS values used set a high hurdle for this second line study because they were observed in chemotherapy-naïve patients. Like other single agent vascular targeting agents in mesothelioma, the response rate was low [11, 31-34] in keeping with a predominantly cytostatic role for such agents. RECIST assessment of response in this disease is less straightforward than for some other solid tumours [27] and we explored in a subset of patients the utility of FDG-PET parameters as alternative predictors of outcome. None of the PET parameters (change in SUVmax, MTV or TLG) correlated with PFS or OS. However, with a sample size of 14, the power to detect a correlation coefficient of r=0.5 is only 46%.

Median PFS in this study was 5.1 months. A number of phase 2 trials has studied other single agent VEGFR-targeting agents in mesothelioma. Cediranib and sunitinib showed median PFS results of 2.6 and 2.7 months respectively in patients pre-treated with platinum [32, 35]. In chemotherapy-naïve patients median PFS with vatalanib and sunitinib was 4.1 and 6.7 months respectively [33, 35]. One other trial studied sorafenib in a heterogeneous group of 50 evaluable patients, 60% of whom had been exposed to prior

pemetrexed-based combination chemotherapy. The response rate was 6% with a median PFS of only 3.6 months [31]. The higher PFS seen in our trial compared with other VEGFR inhibitors may indicate superior activity for sorafenib than for other drugs in this class tested in mesothelioma, but comparison with this last study [31] suggests that patient selection is likely to play a significant role. All patients treated in our trial were originally fit enough to receive platinum-based chemotherapy, all had received only one prior line of treatment, and the great majority had PS $\leq$1 on enrolment. Nevertheless, 28% had non-epithelioid histology, which is associated with poor prognosis. This is a relatively high proportion compared with large published trials in this disease [3,4].

The anti-VEGF antibody bevacizumab has been investigated in combination with gemcitabine/cisplatin chemotherapy in a placebo-controlled randomised phase 2 study. The primary endpoint was not met, but the results suggest a negative prognostic role for circulating VEGF [11]. The modest activity of antiangiogenic drugs in this disease, despite promising pre-clinical rationale, may reflect the absence of any biomarker selection strategy for clinical use of these agents.

Sorafenib was well tolerated in this trial with adequate supportive medication. The toxicity profile observed was similar to that previously reported for sorafenib. Fatigue, rash and PPE were common, resulting in relatively high rates of dose interruption and reduction. However with these interventions, and supportive medication for common toxicities, discontinuation due to intolerable toxicity occurred in only 21% of patients.

The main limitation of this study was absence of randomisation [36]. This in part reflects the difficulty in defining a standard of care in this setting, although the relative rarity of the disease justifies carefully designed single arm studies to explore activity for new treatment approaches in mesothelioma [34]. Many patients with mesothelioma remain fit even following completion of first line chemotherapy, so that placebo-controlled trials face the challenge of low patient acceptability, which can compromise recruitment [37]. However, strategies do exist to minimise placebo exposure in future trials [38].

In conclusion sorafenib is well tolerated in mesothelioma. It has moderate clinical activity when benchmarked against pooled historical data [28]. A median PFS of 5.1 months compares favourably with other VEGFR inhibitors in patients previously treated with first line platinum combination chemotherapy.

References

1. Wagner JC, Sleggs CA, Marchand P. Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province. *Br J Ind Med* 1960;17:260-271.
2. Hodgson JT, McElvenny DM, Darnton AJ, et al. The expected burden of mesothelioma mortality in Great Britain from 2002 to 2050. *Br J Cancer* 2005;92:587-593.
3. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol* 2003;21:2636-2644.
4. van Meerbeeck JP, Gaafar R, Manegold C, et al. Randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: an intergroup study of the European Organisation for Research and Treatment of Cancer Lung Cancer Group and the National Cancer Institute of Canada. *J Clin Oncol* 2005;23:6881-6889.
5. Konig J, Tolnay E, Wiethege T, et al. Co-expression of vascular endothelial growth factor and its receptor flt-1 in malignant pleural mesothelioma. *Respiration* 2000;67:36-40.
6. Kumar-Singh S, Weyler J, Martin MJ, et al. Angiogenic cytokines in mesothelioma: a study of VEGF, FGF-1 and -2, and TGF beta expression. *J Pathol* 1999;189:72-78.
7. Ohta Y, Shridhar V, Bright RK, et al. VEGF and VEGF type C play an important role in angiogenesis and lymphangiogenesis in human malignant mesothelioma tumours. *Br J Cancer* 1999;81:54-61.
8. Strizzi L, Catalano A, Vianale G, et al. Vascular endothelial growth factor is an autocrine growth factor in human malignant mesothelioma. *J Pathol* 2001;193:468-475.
9. Masood R, Kundra A, Zhu S, et al. Malignant mesothelioma growth inhibition by agents that target the VEGF and VEGF-C autocrine loops. *Int J Cancer* 2003;104:603-610.
10. Demirag F, Unsal E, Yilmaz A, et al. Prognostic significance of vascular endothelial growth factor, tumor necrosis, and mitotic activity index in malignant pleural mesothelioma. *Chest* 2005;128:3382-3387.
11. Kindler HL, Karrison TG, Gandara DR, et al. Multicenter, double-blind, placebo-controlled, randomized phase II trial of gemcitabine/cisplatin plus bevacizumab or placebo in patients with malignant mesothelioma. *J Clin Oncol* 2012;30:2509-2515.
12. Lowinger TB, Riedl B, Dumas J, et al. Design and discovery of small molecules targeting raf-1 kinase. *Curr Pharm Des* 2002;8:2269-2278.
13. Wilhelm SM, Carter C, Tang L, et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Res* 2004;64:7099-7109.
14. Chang YS, Adnane J, Trail PA, et al. Sorafenib (BAY 43-9006) inhibits tumor growth and vascularization and induces tumor apoptosis and hypoxia in RCC xenograft models. *Cancer Chemother Pharmacol* 2007;59:561-574.
15. Liu L, Cao Y, Chen C, et al. Sorafenib blocks the RAF/MEK/ERK pathway, inhibits tumor angiogenesis, and induces tumor cell apoptosis in hepatocellular carcinoma model PLC/PRF/5. *Cancer Res* 2006;66:11851-11858.

16. Panka DJ, Wang W, Atkins MB, et al. The Raf inhibitor BAY 43-9006 (Sorafenib) induces caspase-independent apoptosis in melanoma cells. *Cancer Res* 2006;66:1611-1619.
17. Rahmani M, Davis EM, Bauer C, et al. Apoptosis induced by the kinase inhibitor BAY 43-9006 in human leukemia cells involves down-regulation of Mcl-1 through inhibition of translation. *J Biol Chem* 2005;280:35217-35227.
18. Yu C, Bruzek LM, Meng XW, et al. The role of Mcl-1 downregulation in the proapoptotic activity of the multikinase inhibitor BAY 43-9006. *Oncogene* 2005;24:6861-6869.
19. Sun W, Powell M, O'Dwyer PJ, et al. Phase II study of sorafenib in combination with docetaxel and cisplatin in the treatment of metastatic or advanced gastric and gastroesophageal junction adenocarcinoma: ECOG 5203. *J Clin Oncol* 2010;28:2947-2951.
20. Gupta-Abramson V, Troxel AB, Nellore A, et al. Phase II trial of sorafenib in advanced thyroid cancer. *J Clin Oncol* 2008;26:4714-4719.
21. Dahut WL, Scripture C, Posadas E, et al. A phase II clinical trial of sorafenib in androgen-independent prostate cancer. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2008;14:209-214.
22. Moreno-Aspitia A, Morton RF, Hillman DW, et al. Phase II trial of sorafenib in patients with metastatic breast cancer previously exposed to anthracyclines or taxanes: North Central Cancer Treatment Group and Mayo Clinic Trial N0336. *J Clin Oncol* 2009;27:11-15.
23. Kelly RJ, Rajan A, Force J, et al. Evaluation of KRAS mutations, angiogenic biomarkers, and DCE-MRI in patients with advanced non-small-cell lung cancer receiving sorafenib. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2011;17:1190-1199.
24. Blumenschein GR, Jr., Gatzemeier U, Fossella F, et al. Phase II, multicenter, uncontrolled trial of single-agent sorafenib in patients with relapsed or refractory, advanced non-small-cell lung cancer. *J Clin Oncol* 2009;27:4274-4280.
25. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *The New England journal of medicine* 2007;356:125-134.
26. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *The New England journal of medicine* 2008;359:378-390.
27. Byrne MJ, Nowak AK. Modified RECIST criteria for assessment of response in malignant pleural mesothelioma. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* 2004;15:257-260.
28. Francart J, Legrand C, Sylvester R, et al. Progression-free survival rate as primary end point for phase II cancer clinical trials: application to mesothelioma--The EORTC Lung Cancer Group. *J Clin Oncol* 2006;24:3007-3012.
29. Simon R. Optimal two-stage designs for phase II clinical trials. *Controlled clinical trials* 1989;10:1-10.
30. Sleijfer S, Wagner AJ. The challenge of choosing appropriate end points in single-arm phase II studies of rare diseases. *J Clin Oncol* 2012;30:896-898.
31. Dubey S, Janne PA, Krug L, et al. A phase II study of sorafenib in malignant mesothelioma: results of Cancer and Leukemia Group B 30307. *J Thorac Oncol* 2010;5:1655-1661.
32. Garland LL, Chansky K, Wozniak AJ, et al. Phase II study of cediranib in patients with malignant pleural mesothelioma: SWOG S0509. *J Thorac Oncol* 2011;6:1938-1945.

33. Jahan T, Gu L, Kratzke R, et al. Vatalanib in malignant mesothelioma: a phase II trial by the Cancer and Leukemia Group B (CALGB 30107). *Lung Cancer* 2012;76:393-396.
34. Nowak AK, Millward MJ, Creaney J, et al. A phase II study of intermittent sunitinib malate as second-line therapy in progressive malignant pleural mesothelioma. *J Thorac Oncol* 2012;7:1449-1456.
35. Laurie SA, Gupta A, Chu Q, et al. Brief report: a phase II study of sunitinib in malignant pleural mesothelioma. the NCIC Clinical Trials Group. *J Thorac Oncol* 2011;6:1950-1954.
36. Ratain MJ. Bar the windows but open the door to randomization. *J Clin Oncol* 2010;28:3104-3106.
37. Muers MF, Stephens RJ, Fisher P, et al. Active symptom control with or without chemotherapy in the treatment of patients with malignant pleural mesothelioma (MS01): a multicentre randomised trial. *Lancet* 2008;371:1685-1694.
38. Freidlin B, Simon R. Evaluation of randomized discontinuation design. *J Clin Oncol* 2005;23:5094-5098.

Tables and Figure Legends

Table 1: Baseline patient characteristics.

Table 2: Toxicity. All related or possibly related grade 3 or grade 4 adverse events are shown, together with of any grade adverse events occurring at a frequency of ≥10% for the 53 evaluable patients. Events were graded according to CTCAE version 3.
[a] palmar-plantar erythrodysesthesia; [b] myocardial infarction.

Figure 1: Kaplan-Meier plots for A) progression-free survival, B) overall survival. 53 of the patients provided data for both analyses. Median PFS was 5.1 months (95% CI: 3.5 to 6.7 months), with 36% (95% CI: 22% to 49%) of patients progression-free at 6 months. Median OS was 9.0 months (95% CI: 6.7 to 11.3 months).

Figure 2: Best response by RECIST criteria modified for mesothelioma. Each bar represents an individual patient. Two patients were not evaluable due to non-target lesion progression at 8 weeks, and 12 patients did not complete the first response assessment at 8 weeks (white = partial response; black = stable disease; hatched = progressive disease).

Table 1

Patient Characteristics		
Age (range)		66 (49-82)
Gender (%)	Male Female	41 (72) 12 (23)
Histology (%)	Epithelioid Sarcomatoid Mixed Not recorded	38 (72) 2 (4) 8 (15) 5 (9)
Performance Status	0 1 2	4 (7) 45 (85) 4 (7)

Table 2

	Grade 1/2 (%)	Grade 3/4 (%)	Grade 1-4 %
Fatigue	27 (51)	8 (15)	66
Rash	23 (43)	5 (9)	53
PPE[a]	16 (30)	7 (13)	43
Diarrhoea	17 (32)	1 (2)	34
Mucositis	16 (30)	2 (4)	34
Anorexia	14 (26)	4 (8)	34
Alopecia	12 (23)	0	23
Dysphonia	9 (17)	0	17
Nausea	7 (13)	2 (4)	17
Constipation	7 (13)	0	13
Dry Skin	7 (13)	0	13
Puritis	6 (11)	0	11
Vomiting	6 (11)	0	11
Hypertension	4 (8)	1 (2)	9
Weight loss	4 (8)	1 (2)	9
Low mood	4 (8)	1 (2)	9
Chest pain	2 (4)	1 (2)	6
Thrombocytopenia	1 (2)	1 (2)	4
Back pain		1 (2)	2
MI[b]		1 (2)	2
Knee swelling		1 (2)	2
Allergic reaction		1 (2)	2

Figure 1

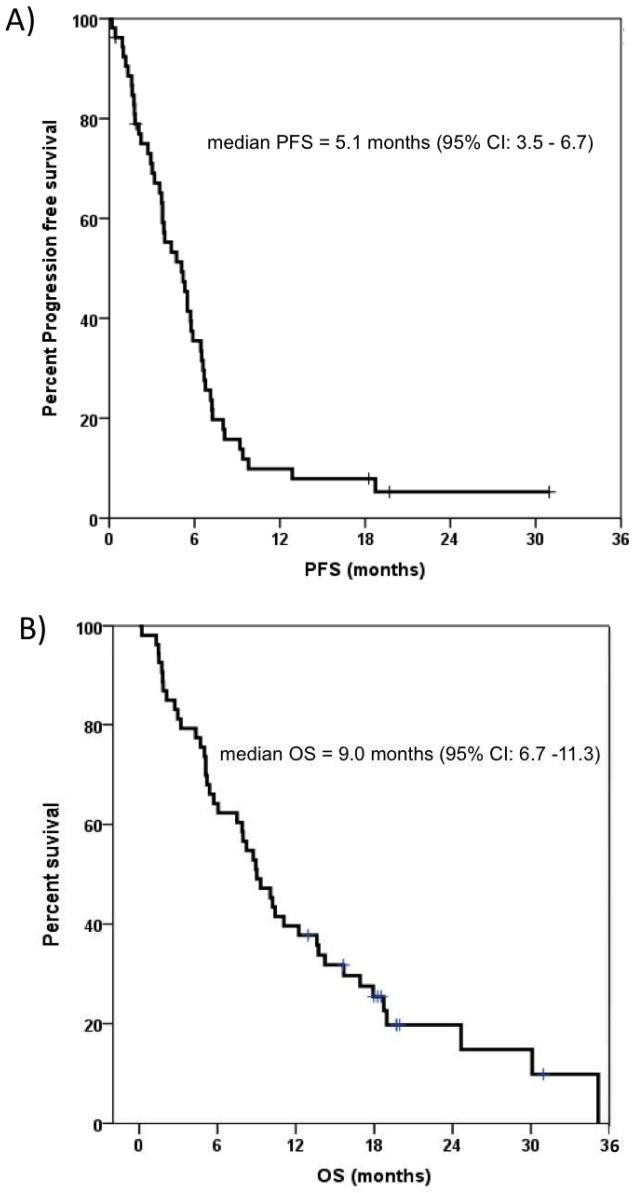
A)
Percent Progression free survival
median PFS = 5.1 months (95% CI: 3.5 - 6.7)
PFS (months)
B)
Percent suvival
median OS = 9.0 months (95% CI: 6.7 -11.3)
OS (months)

Figure 2