Title page:

Outcome of uterine sarcoma patients treated with pazopanib: a retrospective analysis based on two European Organisation for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group (STBSG) clinical trials 62043 and 62072.

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Abstract:

Background:

Uterine sarcomas are a group of mesenchymal tumours comprising several histologies. They have a high recurrence rate following surgery, modest outcome to systemic therapy, and poor overall survival. Pazopanib is a multi-targeted tyrosine kinase inhibitor approved for non-adipocytic advanced soft tissue sarcomas (STS). Here we investigated whether response to pazopanib in patients with uterine sarcomas differs from that of patients with non-uterine sarcomas.

Patients and methods: Uterine sarcoma patients were retrieved from all soft tissue sarcoma patients treated with pazopanib in EORTC Phase II (n=10) and Phase III (PALETTE) (n=34) studies. Patient and tumour characteristics, response, progression free and overall survival data were compared.

Results: Forty-four patients with uterine sarcoma were treated with pazopanib. The majority of patients had uterine leiomyosarcoma (LMS) (n = 39, 88.6%) with high grade tumours (n= 37, 84.1%) compared to 54.8% (n=164) in the non-uterine population. The median age was 55 years (range 33-79) and median follow up was 2.3 years. Uterine patients were heavily pre-treated, 61.3% having ≥ 2 lines of chemotherapy prior to pazopanib compared to 40.8% in the non-uterine population. Five patients (11%), all LMS, had a partial response (95% CI 3.8-24.6). Median progression free survival (PFS) 3.0 months (95% CI 2.5.-4.7) in uterine versus 4.5 (95% CI 3.7-5.1) in non-uterine STS. Median overall survival (OS) was 17.5 months (95% CI 11.1-19.6), longer than the non-uterine population, 11.1 months (95% CI 10.2-12.0) (p=0.352).

Conclusions: Despite heavy pre-treatment, pazopanib shows signs of activity in patients with uterine sarcoma with the similar outcomes to patients with non-uterine STS.

Full manuscript body text

Introduction

Uterine sarcomas are a rare and heterogeneous group of mesenchymal tumours that account for up to 5% of all uterine body malignancies. (1) Leiomyosarcoma (LMS) is the most common histological subtype comprising 63% in one series followed by endometrial stromal sarcoma (ESS) (21%), undifferentiated endometrial sarcoma (6%), with adenosarcoma and other rare subtypes making up the remainder. (2). Surgery is the mainstay of treatment in early stage disease whatever the histological subtype (3). However, recurrence rates are high. For example, in completely resected FIGO stage 1b uterine LMS 55% of patients relapse (4). In patients with advanced or locally recurrent disease, palliative systemic treatment can be considered. As holds true for all soft tissue sarcomas, outcomes to systemic treatment greatly differ across the different subtypes. Of all the uterine sarcomas uterine LMS is the most chemo-sensitive (5). In advanced disease, active agents in uterine LMS include doxorubicin, gemcitabine combined with docetaxel or gemcitabine alone, trabectedin and dacarbazine (6) However, response rates are typically modest, ranging from 10-36% and are of relatively short duration, with a median PFS of around 4 months (5). Patients with low grade ESS exhibit a more indolent disease pattern and are sensitive to hormonal manipulation with aromatase inhibitors (7) (8). In contrast, those patients with high grade undifferentiated uterine sarcoma have a particularly poor prognosis with a paucity of active agents in this disease type (9)(10). Given the median overall survival for all patients advanced uterine soft tissue

sarcoma (STS) remains in the order of 10 months there is a pressing need for new therapies. (5)

Anti-angiogenic approaches have been explored in patients with uterine LMS. A clinical trial of sunitinib revealed responses in 2 out of 23 patients with uterine LMS, failing to meet pre-defined criteria to warrant further examination (11)(12). The addition of bevacizumab to gemcitabine and docetaxel chemotherapy was also initially investigated in STS including those with uterine LMS where the toxicity of this regimen was relatively high. (13) Furthermore, a subsequent randomized, placebo controlled Phase III trial of gemcitabine, docetaxel +/- bevacizumab in patients with metastatic uterine LMS was stopped early due to futility with no improvement in PFS, OS or response rate (RR)(14). Pazopanib is another compound thought to exert its anti-tumour activity partially through inhibition of angiogenesis. This drug is a multi-targeted tyrosine kinase inhibitor which targets not only vascular endothelial growth factor (VEGFR)-1,-2, and -3 but also platelet- derived growth factor receptor (PDGFR) –α,-ß and KIT. Clinically relevant responses in patients with sarcoma were seen in the initial Phase 1 trial.(15) Subsequently a large stratified EORTC STBSG Phase II trial (62043) of 142 patients was performed which confirmed activity by progression free rate at 12 weeks in three out of four STS groups including the LMS cohort (16). The Phase III randomised double blind placebo controlled 62072 (PALETTE) study followed, assigning 369 patients with advanced or metastatic non-adipocytic STS progressing on previous chemotherapy to either pazopanib or placebo and a significant increase in PFS of 4.6 months versus 1.6 months was seen.

(17) On the basis of the trial, pazopanib was approved for non-adipocytic STS patients failing prior treatment with doxorubicin- and/or ifosfamide-based chemotherapy. These results were promising for physicians treating uterine sarcoma patients potentially highlighting a novel treatment pathway. This paper investigates in detail the outcome of patients with uterine sarcoma treated with pazopanib in both the Phase II and III EORTC/GSK jointly sponsored studies.

Patients and methods

(i) Patients included:

Patients eligible for this retrospective analysis were those with uterine sarcoma, included and treated with pazopanib in the Phase II study (n= 10) or randomized to the pazopanib arm of the Phase III trial (n= 34). Central pathological review was performed as per trial protocols.

(Figure 1 Consort diagram)

(ii) Definition of endpoints:

PFS was defined from the date of registration/randomization to the first documentation of progression or death, whichever occurred first. The radiological assessment of the principal investigator was used for the definition of progression; clinical progression in the absence of documented objective progression was also taken into account. Patients were censored at the date of last patient visit (before the clinical cut-off date). OS was defined as from the date of registration/randomization to the date of death. Patients

alive at the time of the clinical cut-off were censored at the date of last follow-up. Tumour response was measured by RECIST version 1.1 (18)

(iii) Statistical analysis:

The characteristics of uterine sarcoma patients were compared to those of the remaining STS patients receiving treatment in the pazopanib studies using descriptive tables (patient characteristics, disease characteristics, treatment exposure, toxicity and post protocol treatment). PFS and OS were estimated by the Kaplan-Meier method. Statistical significance for OS is based on a logrank test of the survival of the two subgroups, stratified by study.

Due to the limited number of patients available for this analysis, only univariate models (logistic regression for best overall response and Cox regression models for PFS and OS) were used to assess the value of selected prognostic factors to predict outcome of uterine sarcoma patients treated with pazopanib.

Results

(i) Characteristics

Out of the 343 eligible patients for this analysis,(ie the total number of patients receiving pazopanib in the Phase II and Phase III trials,) 44 presented with a uterine sarcoma. The median age was 55 years (range 33-79) in the uterine population, similar to that of the non-uterine sarcoma patients; the majority (59.1%) was performance status 1, compared to 48.8% of the non

uterine soft tissue sarcoma patients. Patient demographics are summarized in *Table 1.*

Five patients were treated with pazopanib in the first line metastatic setting having received anthracycline-based neo-adjuvant chemotherapy previously, twelve received treatment in the second line, thirteen in the third line, ten in the fourth and four patients in the fifth line. Compared to the other patients included, those with uterine sarcoma were more heavily pre-treated with 61.3% having ≥ 2 lines of chemotherapy prior to pazopanib compared to 40.8% of non-uterine patients.

Central pathological review was performed for all patients in the Phase III study and for all but 23 patients in the Phase II trial, 9 of whom had uterine sarcoma. Most patients (88.6%) had a diagnosis of uterine LMS and the majority had high grade tumors (84.1%), compared to 54.8% in non-uterine STS. The remaining pathological subtypes in the uterine sarcoma group included one patient with PEComa and one had undifferentiated sarcoma, three could not be classified further due to insufficient material on central histological review. No patients with ESS were treated in these studies.

The clinical cut-off dates for this pooled analysis resulted in an overall median follow-up of 2.3 years (IQR 1.9-2.9).

(ii) Treatment and response

The median time on treatment for all uterine sarcoma patients was 14.3 weeks (range 03-135.2 weeks) compared to 17.1 weeks (0.1-191.7 weeks) for non-uterine STS patients. Two patients with metastatic uterine sarcoma, both

with LMS, one intermediate and one high grade, were still on pazopanib at the cut off dates.

Five patients (11.4%) with uterine sarcoma achieved a partial response (PR) while on treatment with pazopanib with a median duration of 3.9 months (range 1.8-9.4 months); twenty-five patients (56.8%) had stable disease as best response with a median duration of 4.7 months (95% CI 3.0 – 8.8). These response data are comparable to those of the non-uterine sarcoma patients on pazopanib where 10.7 % of non-uterine patients achieved a PR and 57.2% stable disease with a median duration of response of 7.5 months .
Of the five patients with PR, four of them received pazopanib in the second line setting following anthracyline based chemotherapy, one in the third following anthracycline and gemcitabine/docetaxel. Four of these patients had high grade uterine LMS and one patient had intermediate grade. The age of these patients ranged from 33-74y.

(iii) Toxicity

Treatment related toxicity was similar in the group of uterine patients to that of the non-uterine patients. Grade 3-4 adverse events while on treatment included tumour pain (11.4%), fatigue (9.1%) and lymphopenia (11.4%). See *Table 2* for grade 3/4 toxicities. Six patients (14.3%) stopped treatment due to toxicity related to the study drug. The median time to stopping treatment for these patients was 41 days (range 2-141 days). The majority of patients (n=35, 83.3%) stopped treatment due to progressive disease.

(iv) Survival and prognostic factor analysis

Survival analysis revealed that median PFS in the uterine patients was 3 months (95% CI 2.5-4.7) compared to 4.5 months (3.7-5.1) in the non-uterine STS population. Median OS was 17.5 months (95% CI 11.1 – 19.6) compared to 11 months (10.2-12.9), p=0.352 and was not statistically significant. The corresponding hazard ratio and confidence interval based on the Cox proportional hazards model is 0.84 (0.59, 1.21) for uterine versus other. Survival curves are shown in *Figure 2 (a) and (b)*

Survival analysis was also performed for uterine versus non-uterine sarcoma in women, and uterine LMS versus LMS of other origin and there was no statistically significant difference in median PFS duration and OS duration for either group. Survival analysis for all males versus all females treated with pazopanib showed significantly longer PFS in women (4.60 months (95% CI 3.65-5.29) versus 3.94 months in men (2.76-4.67) p=0.032) and also OS (14.13 months ((95% CI 10.97, 17.15) versus 10.38 in men (8.02-11.66)p=0.018)

In addition a comparison was made between the uterine sarcoma patients on the PALETTE study treated with pazopanib compared to those randomised to placebo. Median PFS duration in the pazopanib arm was 2.99 months (95% CI 2.53, 4.67) versus 0.82 months in placebo arm (0.72, 1.02) p=0.000. Median OS duration in the pazopanib arm was 17.45 months (95% CI, 11.14, 19.61) versus 7.92 months (1.12, 14.82) p=0.038. The response rate of patients with uterine sarcoma to pazopanib in PALETTE was 11.4% versus 0.0% to placebo.

Prognostic factor analysis was performed. Due to the small overall number of patients with uterine sarcoma it was not possible to perform a multivariate analysis. Univariate prognostic factor analysis was performed for best overall response, PFS and OS, looking at the role of age, performance status, tumour grade and the presence or absence of lung, liver and bone metastases. None of these prognostic factors were found to be significant.

(v) Post protocol treatments

The majority of patients (n=41, 91%) received further lines of treatment as summarized in *Table 3.* Follow-up chemotherapy was the most frequently offered treatment provided to uterine sarcoma patients on disease progression (65.9%) radiotherapy was the second most frequent treatment (26.8%).

Discussion

This pooled analysis involving data from two large EORTC/GSK jointly sponsored studies has shown that patients with uterine sarcoma (the vast majority of whom had uterine LMS) have comparable outcomes to pazopanib to those of the non-uterine STS population, with similar toxicity profiles. It is notable that many of the uterine patients (61%) who took part in the PALETTE study received treatment in the ≥ 2nd line setting, a reflection of the number of treatment options available for this group. Also more patients in the uterine group were of performance status 1, than 0 compared to the non-uterine sarcoma population treated with pazopanib and more had higher grade

tumours. The response rate to pazopanib was 11.4% with a median PFS of 3 months, which is similar to other drugs active in uterine LMS such as doxorubicin (1st line RR 14%, PFS 4.6 months, all STS, Judson et al (19)), gemcitabine and docetaxel (1st line LMS, RR 25%, PFS 7.1 months Seddon et al (20)), gemcitabine and docetaxel (pre treated LMS, RR 53%, median time to progression 5.6 months, Hensley et al (21)) , single agent gemcitabine (metastatic STS, RR 8%, PFS 3.0 months Maki et al (22), trabectedin (RR 10% uterine LMS median PFS 5.8 months Monk et al (23)) and dacarbazine (previously treated STS overall RR 4%, PFS 2 months Garcia del Muro et al (24)).with the caveat that these studies cannot be meaningfully compared due to selection bias and differing patient populations.

The additional analyses performed have shown interesting insights. The fact that those patients with uterine LMS in the PALETTE study did significantly better than those with uterine LMS treated with placebo is unsurprising. There was no significant in difference in response to pazopanib between female patients with uterine sarcomas and females with non uterine sarcomas, nor was there a difference between those with uterine LMS and non uterine LMS. However overall female patients that were treated with pazopanib fared better than their male counterparts.

Pazopanib is the first tyrosine kinase inhibitor that has been approved both in Europe and the US for treatment of advanced non-adipocytic STS. It is a multi-targeted drug acting through VEGFR 1-3, PDGFR and KIT. The main mode of action of pazopanib in STS, both uterine and non-uterine STS is still not fully elucidated and further work is needed in order to identify those patients most likely to benefit. Apart from its suggested role as an

angiogenesis inhibitor, targeting VEGF receptors, PDGFR receptors are likely to be an important target in STS. The role of PDGFR-α in uterine sarcomas has been explored previously. Expression of PDGFR-α has been demonstrated in 60% of uterine LMS samples by immunohistochemistry (IHC) (25). A second study showed strong staining by IHC for PDGFR-α in 70% of uterine LMS samples (26). A recent analysis of 349 patient samples of uterine LMS showed significant overexpression of PDGFR- α ($p<0.0001$) and-ß ($p<0.0127$) compared to non-neoplastic controls. Furthermore VEGF was over-expressed in metastatic tumours when compared to primary tumours strengthening the rationale for drugs targeting these pathways. (27)

It is interesting to speculate whether response rates might have been higher if pazopanib had been used in an earlier treatment line and in a greater percentage of patients with a performance status of 0. Furthermore, the relationship between pazopanib and tumour grade is intriguing. Many more uterine sarcoma patients included were classified as high grade (84.1%) compared to the non-uterine population (54.8%). Both the PALETTE study and a separately published analysis of long term responders to pazopanib has revealed it was those with low or intermediate grade tumours and in addition those with performance status 0 that had the longest duration of pazopanib treatment (28). A possible future option would be to investigate the response of those patients with low grade uterine LMS or ESS to pazopanib. The non-significant trend towards improved OS for uterine sarcoma patients in this analysis compared to the advanced non-uterine STS population could possibly be explained by the widespread use of post protocol treatments including chemotherapy, radiotherapy and surgery and is indicative of the

greater number of treatment options for uterine LMS. However there is insufficient information on subsequent treatments available to investigate whether this correlates with overall survival.

Thus far systemic treatment of advanced high grade uterine sarcoma has relied on a range of cytotoxic treatments; whilst hormonal strategies play a role in the management of low grade hormone receptor positive LMS and ESS. Currently single agent doxorubicin remains the standard of care in the first line metastatic setting for those patients with uterine LMS . Data presented at ASCO 2015 of the randomised UK GEDDiS trial has shown that doxorubicin has superior outcomes compared to gemcitabine docetaxel in the first line and is better tolerated with less toxicity. Beyond first line gemcitabine in single agent or in combination with docetaxel, and also trabectedin are active and pazopanib can now be considered as an additional option. Modest response rates and survival outcomes to systemic treatment highlight the poor prognosis of the uterine sarcoma population and clearly underline the urgent requirement for innovative new strategies involving novel compounds in this patient group. These two large trials with pazopanib in STS and their subsequent pooled analyses represent the considerable recruitment ability of the EORTC and the centres involved and underline the importance of ongoing international collaboration in order to make meaningful progress in such rare tumour types.

Disclosures/Conflict of interest statement

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These studies were sponsored by GlaxoSmithKline; pazopanib is property of Novartis Pharma AG as of March 1, 2015

345 **Table/Figure legends**

346 Table 1 patient characteristics

347 This table describes demographic details of the patients included in the

348 analysis.

		Site of primary		
		Other (N = 299)	Uterine (N = 44)	Total (N = 343)
		N (%)	N (%)	N (%)
Age at trial entry (years)	Median	54	55	54
	Range	18–83	33–79	18–83
	Q1–Q3	38–63	51–67	40–64
Age at trial entry	≤40	84 (28.1)	2 (4.5)	86 (25.1)
	40–50	46 (15.4)	9 (20.5)	55 (16.0)
	50–70	139 (46.5)	26 (59.1)	165 (48.1)
	>70	30 (10.0)	7 (15.9)	37 (10.8)
Sex	Male	147 (49.2)	0 (0.0)	147 (42.9)
	Female	152 (50.8)	44 (100.0)	196 (57.1)
Performance status	0	153 (51.2)	18 (40.9)	171 (49.9)
	1	146 (48.8)	26 (59.1)	172 (50.1)
Histology (central review)	Leiomyosarcoma	95 (31.8)	39 (88.6)	134 (39.1)
	Synovial sarcoma	62 (20.7)	0 (0.0)	62 (18.1)
	Other	142 (47.5)	5 (11.4)	147 (42.8)
Tumour grade (central review)	Low	27 (9.0)	1 (2.3)	28 (8.2)
	Intermediate	106 (35.5)	6 (13.6)	112 (32.7)
	High	164 (54.8)	37 (84.1)	201 (58.6)
	Unknown	2 (0.7)	0 (0.0)	2 (0.6)
Extent of disease at entry (non-cumulative)	Primary (uterus)	85 (28.4)	6 (13.6)	91 (26.5)
	Lymph node	60 (20.1)	6 (13.6)	66 (19.2)
	Lung	238 (79.6)	32 (72.7)	270 (78.7)
	Liver	82 (27.4)	11 (25.0)	93 (27.1)
	Bone	40 (13.4)	12 (27.3)	52 (15.2)
Prior lines of systemic therapy for advanced disease	0	39 (13.0)	5 (11.4)	44 (12.8)
	1	138 (46.2)	12 (27.3)	150 (43.7)
	≥2	122 (40.8)	27 (61.3)	105 (43.5)

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Table 2: Grade 3 and 4 toxicities

The table below compares the occurrence of Common Toxicity Criteria Grade 3-4 events across the patient groups. The overview is limited to those toxicities reported as grade 3-4 in at least 5% of the overall patient population, but also summarizes the number of any grade 3-4 event across the patient groups.

Hematological and biochemistry events	Site of primary		
	Other (N = 299)	Uterine (N = 44)	Total (N = 343)
	N (%)	N (%)	N (%)
Lymphopenia	36 (12.0)	5 (11.4)	41 (12.0)
Anemia	19 (6.4)	2 (4.5)	21 (6.1)
ASAT	18 (6.0)	3 (6.8)	21 (6.1)
ALAT	24 (8.0)	2 (4.5)	26 (7.6)
Hypertension	20 (6.7)	2 (4.5)	22 (6.4)
Fatigue	43 (14.4)	4 (9.1)	47 (13.7)
Diarrhea	19 (6.4)	1 (2.3)	20 (5.8)
Infection without neutropenia	23 (7.7)	0 (0.0)	23 (6.7)
Tumour pain	27 (9.0)	5 (11.4)	32 (9.3)
Other pain	27 (9.0)	5 (11.4)	32 (9.3)
Dyspnea	19 (6.4)	2 (4.5)	21 (6.1)
Any Grade 3–4 event	202 (67.6)	28 (63.6)	230 (67.1)

Table 3 post protocol therapy

This table details treatments received by patients following treatment with pazopanib.

[1] Immunotherapy, Embolization (5), TACE, Sterile Compound C31510 as part of the CR0510 protocol (NCT01251562), Zometa, Sunitinib

[2] Sunitinib (1) , Sorafenib (1), Everolimus(1)

[3] Zometa and a phosphoinoside 3-kinase GSK inhibitor as part of a phase I dose escalation study,

Number of post protocol therapies — patients off protocol treatment	Site of primary		
	Other (N = 269)	Uterine (N = 41)	Total (N = 310)
	N (%)	N (%)	N (%)
Chemotherapy	139 (51.7)	27 (65.9)	166 (53.5)
Targeted therapy	21 (7.8)	3(7.3)[2]	25 (8.1)
Radiotherapy	51 (19.0)	11 (26.8)	62 (20.0)
Surgery	19 (7.1)	9 (22.0)	28 (9.0)
Other therapy	10 (3.7)[1]	2 (4.9)[3]	12 (3.9)

368 Figure 1 Consort diagram

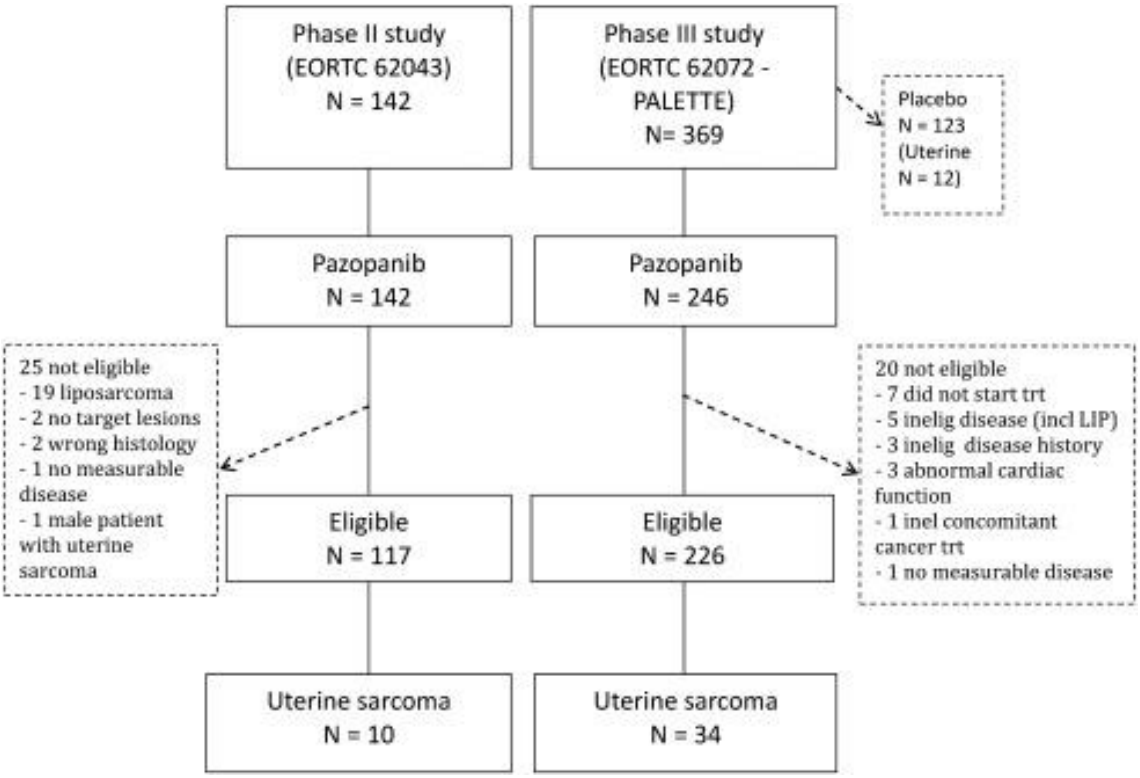

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Figure 2 (a) PFS by site of origin

Kaplan Meier survival curve showing progression free survival by site of origin

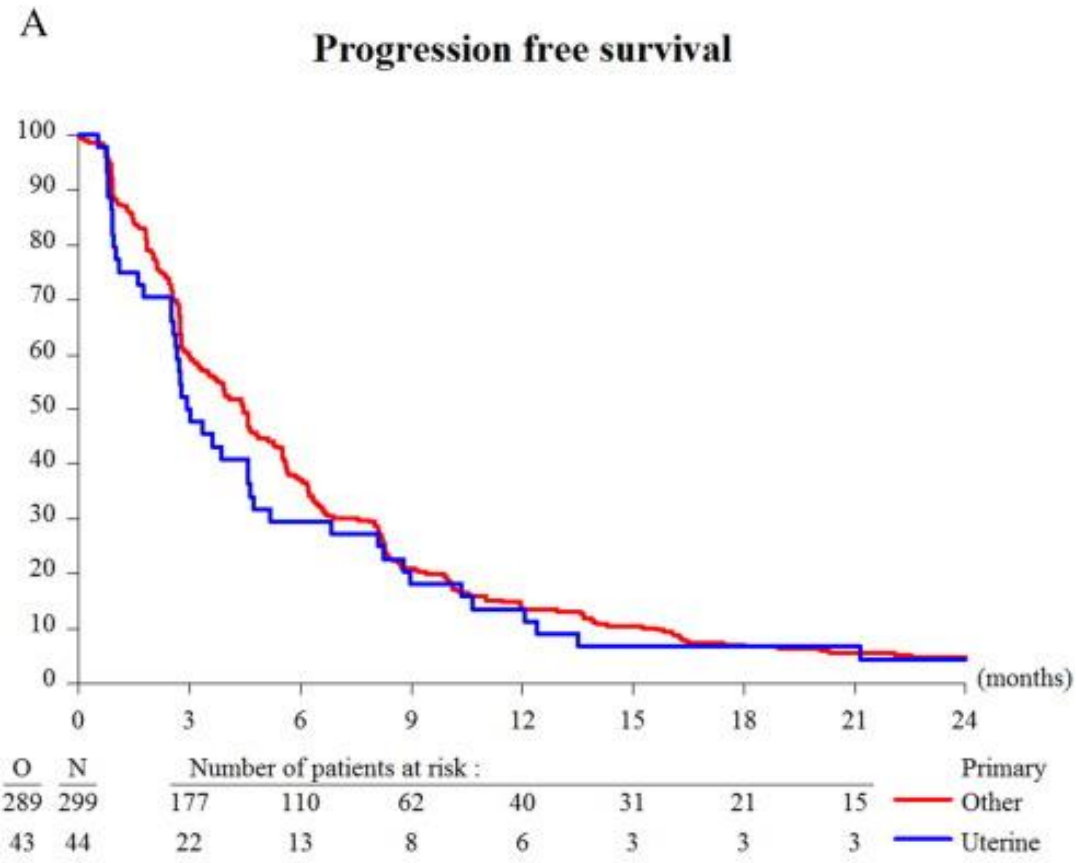
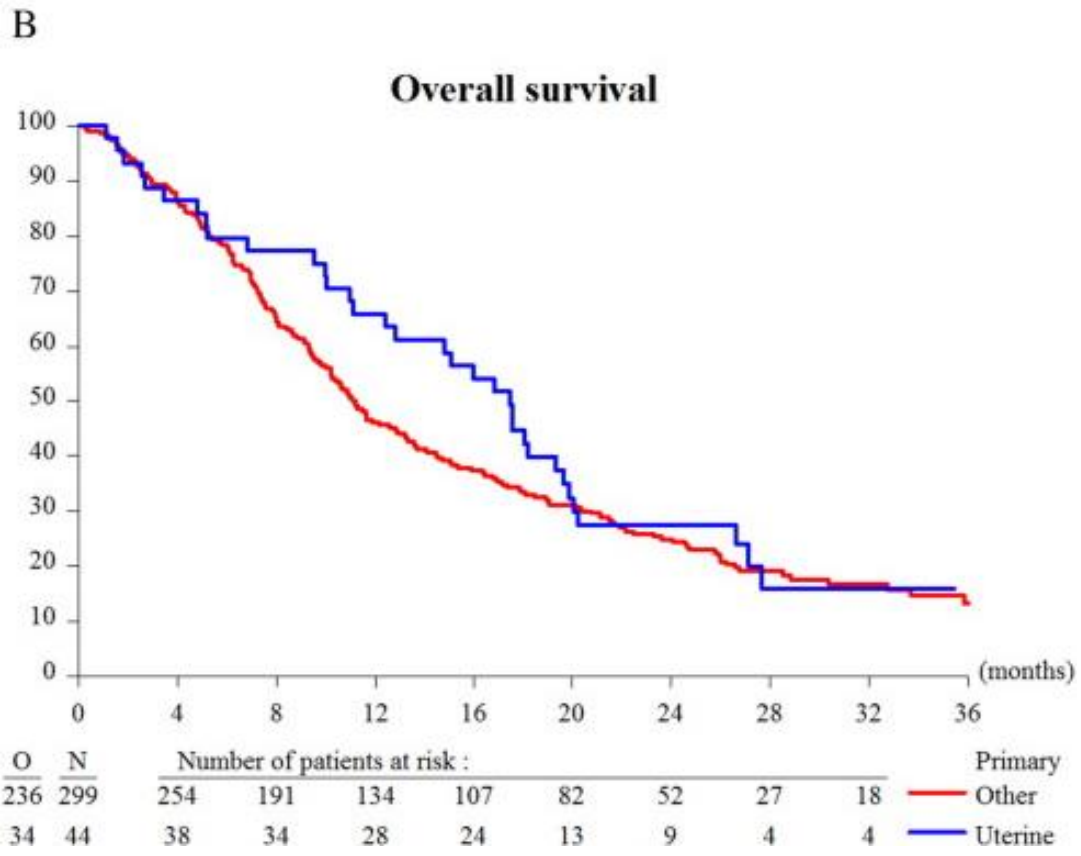


Figure 2 (b) OS by site of origin

Kaplan Meier survival curve showing overall survival by site of origin



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