

Supplemental table S1. Overview of study details of the EORTC 62043 and 62072 trials.

	EORTC 62043 trial	EORTC 62072 trial
Type of trial	Phase II	Phase III
Design	Single arm	Randomized (2:1), double blind, placebo-controlled
Drug	Pazopanib 800mg daily	Pazopanib 800mg daily or placebo
Inclusion criteria	Locally advanced/metastatic STS Ineligible to chemotherapy or failure to no more than two prior cytotoxic agents (sequentially as single agents or one combination regimen)	Metastatic non-adipocytic STS Failure to standard chemotherapy (including an anthracycline), with a maximum of 4 previous lines or two lines of combination regimens
Primary outcome	Progression-free survival at 12 weeks	Progression-free survival
Secondary outcome	Response rate Duration of response Safety Overall survival	Overall survival Response rate Safety Quality of life
ClinicalTrial.gov number	NCT00297258	NCT00753688
Reference	Sleijfer et al., JCO, 2009	van der Graaf et al., Lancet, 2012

Supplemental table S2. Complete results of the multivariate Cox regression models for PFS and OS of patients receiving pazopanib with and without cardiotoxicity grade 3-4 at landmark time point of 60 days.

Landmark Analysis at t=60 days		Multivariate Cox model of progression-free survival				Multivariate Cox model of overall survival			
Covariates		Patients (N=257)	Observed Events (O=246)	Hazard Ratio (95% CI)	Wald p-value	Patients (N=311)	Observed Events (O=244)	Hazard Ratio (95% CI)	Wald p-value
Cardiotoxic Adverse Event (Grade 3-4)	No	242 (94.2)	231 (93.9)	1.00	0.897	294 (94.5)	231 (94.7)	1.00	0.801
	Yes	15 (5.8)	15 (6.1)	0.97 (0.57, 1.64)		17 (5.5)	13 (5.3)	0.93 (0.52, 1.65)	
Performance status	0	145 (56.4)	139 (56.5)	1.00	0.403	165 (53.1)	123 (50.4)	1.00	<.001
	1	112 (43.6)	107 (43.5)	0.90 (0.69, 1.16)		146 (46.9)	121 (49.6)	1.58 (1.22, 2.04)	
Gender	Male	101 (39.3)	98 (39.8)	1.00	0.027	126 (40.5)	106 (43.4)	1.00	0.129
	Female	156 (60.7)	148 (60.2)	0.74 (0.56, 0.97)		185 (59.5)	138 (56.6)	0.81 (0.62, 1.06)	
Tumor grade	Low	24 (9.3)	19 (7.7)	1.00	0.002	28 (9.0)	16 (6.6)	1.00	0.013
	Intermediate	87 (33.9)	85 (34.6)	2.35 (1.43, 3.84)		105 (33.8)	85 (34.8)	2.04 (1.21, 3.43)	
	High	146 (56.8)	142 (57.7)	1.79 (1.08, 2.97)		178 (57.2)	143 (58.6)	1.59 (0.93, 2.73)	
Histology subtype	Leiomyosarcoma	106 (41.2)	104 (42.3)	1.00	0.182	129 (41.5)	97 (39.8)	1.00	0.009
	Synovial sarcoma	50 (19.5)	47 (19.1)	0.76 (0.57, 1.02)		60 (19.3)	50 (20.5)	1.36 (1.01, 1.84)	
	Other sarcoma	101 (39.3)	95 (38.6)	0.91 (0.63, 1.31)		122 (39.2)	97 (39.8)	1.81 (1.23, 2.66)	
Age at randomization	≤50 years	101 (39.3)	94 (38.2)	1.00	0.048	122 (39.2)	93 (38.1)	1.00	0.035
	>50 years	156 (60.7)	152 (61.8)	1.34 (1.00, 1.79)		189 (60.8)	151 (61.9)	1.37 (1.02, 1.83)	
Cardiac history	No	194 (75.5)	186 (75.6)	1.00	0.303	233 (74.9)	182 (74.6)	1.00	0.539
	Yes	63 (24.5)	60 (24.4)	0.85 (0.61, 1.16)		78 (25.1)	62 (25.4)	1.11 (0.80, 1.52)	

Supplemental table S3. Complete results of the multivariate Cox regression models for PFS and OS of patients receiving pazopanib with and without cardiotoxicity of any grade at landmark time point of 60 days.

Landmark Analysis at t=60 days		Multivariate Cox model of progression-free survival				Multivariate Cox model of overall survival			
Covariates		Patients (N=257)	Observed Events (O=246)	Hazard Ratio (95% CI)	Wald p-value	Patients (N=311)	Observed Events (O=244)	Hazard Ratio (95% CI)	Wald p-value
Cardiotoxic Adverse Event (Any grade)	No	151 (58.8)	144 (58.5)	1.00	0.380	190 (61.1)	155 (63.5)	1.00	0.120
	Yes	106 (41.2)	102 (41.5)	1.12 (0.87, 1.46)		121 (38.9)	89 (36.5)	0.81 (0.63, 1.06)	
Performance status	0	145 (56.4)	139 (56.5)	1.00	0.415	165 (53.1)	123 (50.4)	1.00	<0.001
	1	112 (43.6)	107 (43.5)	0.90 (0.69, 1.16)		146 (46.9)	121 (49.6)	1.57 (1.21, 2.03)	
Gender	Male	101 (39.3)	98 (39.8)	1.00	0.027	126 (40.5)	106 (43.4)	1.00	0.121
	Female	156 (60.7)	148 (60.2)	0.74 (0.56, 0.97)		185 (59.5)	138 (56.6)	0.81 (0.62, 1.06)	
Tumor grade	Low	24 (9.3)	19 (7.7)	1.00	0.001	28 (9.0)	16 (6.6)	1.00	0.023
	Intermediate	87 (33.9)	85 (34.6)	2.40 (1.46, 3.95)		105 (33.8)	85 (34.8)	1.93 (1.14, 3.26)	
	High	146 (56.8)	142 (57.7)	1.84 (1.10, 3.06)		178 (57.2)	143 (58.6)	1.51 (0.88, 2.60)	
Histology subtype	Leiomyosarcoma	106 (41.2)	104 (42.3)	1.00	0.222	129 (41.5)	97 (39.8)	1.00	0.013
	Synovial sarcoma	50 (19.5)	47 (19.1)	0.77 (0.58, 1.04)		60 (19.3)	50 (20.5)	1.33 (0.98, 1.80)	
	Other sarcoma	101 (39.3)	95 (38.6)	0.92 (0.63, 1.32)		122 (39.2)	97 (39.8)	1.76 (1.20, 2.58)	
Age at randomization	≤50 years	101 (39.3)	94 (38.2)	1.00	0.056	122 (39.2)	93 (38.1)	1.00	0.019
	>50 years	156 (60.7)	152 (61.8)	1.33 (0.99, 1.78)		189 (60.8)	151 (61.9)	1.42 (1.06, 1.91)	
Cardiac history	No	194 (75.5)	186 (75.6)	1.00	0.273	233 (74.9)	182 (74.6)	1.00	0.570
	Yes	63 (24.5)	60 (24.4)	0.84 (0.61, 1.15)		78 (25.1)	62 (25.4)	1.10 (0.80, 1.50)	

Supplemental table S4. Complete results of the multivariate Cox regression models for PFS and OS of patients receiving placebo with and without cardiotoxicity of any grade at landmark time point of 60 days.

Landmark Analysis at t=60 days		Multivariate Cox model of progression-free survival				Multivariate Cox model of overall survival			
Covariates		Patients (N=41)	Observed Events (O=41)	Hazard Ratio (95% CI)	Wald p-value	Patients (N=101)	Observed Events (O=75)	Hazard Ratio (95% CI)	Wald p-value
Cardiotoxic Adverse Event (Any grade)	No	36 (87.8)	36 (87.8)	1.00	0.301	93 (92.1)	68 (90.7)	1.00	0.988
	Yes	5 (12.2)	5 (12.2)	0.52 (0.15, 1.79)		8 (7.9)	7 (9.3)	1.01 (0.41, 2.46)	
Performance status	0	22 (53.7)	22 (53.7)	1.00	0.261	48 (47.5)	33 (44.0)	1.00	0.034
	1	19 (46.3)	19 (46.3)	1.54 (0.73, 3.25)		53 (52.5)	42 (56.0)	1.76 (1.04, 2.96)	
Gender	Male	15 (36.6)	15 (36.6)	1.00	0.012	41 (40.6)	31 (41.3)	1.00	0.801
	Female	26 (63.4)	26 (63.4)	0.29 (0.11, 0.76)		60 (59.4)	44 (58.7)	0.93 (0.55, 1.59)	
Tumor grade	Low	2 (4.9)	2 (4.9)	1.00	0.004	3 (3.0)	2 (2.7)	1.00	0.218
	Intermediate	13 (31.7)	13 (31.7)	10.01 (1.42, 70.42)		25 (24.8)	17 (22.7)	2.12 (0.49, 9.17)	
	High	26 (63.4)	26 (63.4)	34.89 (3.61, 337.59)		73 (72.3)	56 (74.7)	1.37 (0.29, 6.49)	
Histology subtype	Leiomyosarcoma	19 (46.3)	19 (46.3)	1.00	0.021	42 (41.6)	31 (41.3)	1.00	0.964
	Synovial sarcoma	3 (7.3)	3 (7.3)	7.92 (1.72, 36.51)		11 (10.9)	7 (9.3)	0.94 (0.38, 2.35)	
	Other sarcoma	19 (46.3)	19 (46.3)	1.02 (0.44, 2.34)		48 (47.5)	37 (49.3)	1.05 (0.62, 1.77)	
Age at randomization	≤50 years	19 (46.3)	19 (46.3)	1.00	0.703	50 (49.5)	34 (45.3)	1.00	0.114
	>50 years	22 (53.7)	22 (53.7)	1.17 (0.53, 2.60)		51 (50.5)	41 (54.7)	1.57 (0.90, 2.76)	
Cardiac history	No	27 (65.9)	27 (65.9)	1.00	0.203	68 (67.3)	51 (68.0)	1.00	0.234
	Yes	14 (34.1)	14 (34.1)	1.70 (0.75, 3.85)		33 (32.7)	24 (32.0)	0.70 (0.40, 1.25)	

Supplemental table S5. Complete results of the multivariate Cox regression models for PFS and OS of patients receiving pazopanib with and without proteinuria at landmark time point of 60 days.

Landmark Analysis at t=60 days		Multivariate Cox model of progression-free survival				Multivariate Cox model of overall survival			
Covariates		Patients (N=257)	Observed Events (O=246)	Hazard Ratio (95% CI)	Wald p-value	Patients (N=311)	Observed Events (O=244)	Hazard Ratio (95% CI)	Wald p-value
Proteinuria	No	194 (75.5)	186 (75.6)	1.00	0.953	237 (76.2)	182 (74.6)	1.00	0.196
	Yes	63 (24.5)	60 (24.4)	1.01 (0.75, 1.36)		74 (23.8)	62 (25.4)	1.22 (0.90, 1.64)	
Performance status	0	145 (56.4)	139 (56.5)	1.00	0.400	165 (53.1)	123 (50.4)	1.00	0.001
	1	112 (43.6)	107 (43.5)	0.89 (0.69, 1.16)		146 (46.9)	121 (49.6)	1.53 (1.18, 1.99)	
Gender	Male	101 (39.3)	98 (39.8)	1.00	0.028	126 (40.5)	106 (43.4)	1.00	0.114
	Female	156 (60.7)	148 (60.2)	0.74 (0.56, 0.97)		185 (59.5)	138 (56.6)	0.81 (0.62, 1.05)	
Tumor grade	Low	24 (9.3)	19 (7.7)	1.00	0.002	28 (9.0)	16 (6.6)	1.00	0.017
	Intermediate	87 (33.9)	85 (34.6)	2.34 (1.43, 3.82)		105 (33.8)	85 (34.8)	2.00 (1.18, 3.37)	
	High	146 (56.8)	142 (57.7)	1.79 (1.08, 2.98)		178 (57.2)	143 (58.6)	1.58 (0.92, 2.70)	
Histology subtype	Leiomyosarcoma	106 (41.2)	104 (42.3)	1.00	0.203	129 (41.5)	97 (39.8)	1.00	0.011
	Synovial sarcoma	50 (19.5)	47 (19.1)	0.77 (0.58, 1.03)		60 (19.3)	50 (20.5)	1.33 (0.98, 1.79)	
	Other sarcoma	101 (39.3)	95 (38.6)	0.93 (0.64, 1.34)		122 (39.2)	97 (39.8)	1.76 (1.21, 2.57)	
Age at randomization	≤50 years	101 (39.3)	94 (38.2)	1.00	0.089	122 (39.2)	93 (38.1)	1.00	0.028
	>50 years	156 (60.7)	152 (61.8)	1.27 (0.96, 1.67)		189 (60.8)	151 (61.9)	1.37 (1.03, 1.82)	

Supplemental table S6. Complete results of the multivariate Cox regression models for PFS and OS of patients receiving pazopanib with and without persistent proteinuria at landmark time point of 60 days.

<u>Landmark Analysis at t=60 days</u>		Multivariate Cox model of progression-free survival				Multivariate Cox model of overall survival			
Covariates		Patients (N=257)	Observed Events (O=246)	Hazard Ratio (95% CI)	Wald p-value	Patients (N=311)	Observed Events (O=244)	Hazard Ratio (95% CI)	Wald p-value
Persistent proteinuria	No	235 (91.4)	225 (91.5)	1.00	0.937	285 (91.6)	223 (91.4)	1.00	0.169
	Yes	22 (8.6)	21 (8.5)	0.98 (0.62, 1.55)		26 (8.4)	21 (8.6)	1.38 (0.87, 2.19)	
Performance status	0	145 (56.4)	139 (56.5)	1.00	0.408	165 (53.1)	123 (50.4)	1.00	<.001
	1	112 (43.6)	107 (43.5)	0.90 (0.69, 1.16)		146 (46.9)	121 (49.6)	1.55 (1.20, 2.01)	
Gender	Male	101 (39.3)	98 (39.8)	1.00	0.028	126 (40.5)	106 (43.4)	1.00	0.121
	Female	156 (60.7)	148 (60.2)	0.74 (0.56, 0.97)		185 (59.5)	138 (56.6)	0.81 (0.62, 1.06)	
Tumor grade	Low	24 (9.3)	19 (7.7)	1.00	0.002	28 (9.0)	16 (6.6)	1.00	0.015
	Intermediate	87 (33.9)	85 (34.6)	2.34 (1.43, 3.83)		105 (33.8)	85 (34.8)	2.01 (1.20, 3.40)	
	High	146 (56.8)	142 (57.7)	1.79 (1.08, 2.98)		178 (57.2)	143 (58.6)	1.58 (0.92, 2.71)	
Histology subtype	Leiomyosarcoma	106 (41.2)	104 (42.3)	1.00	0.203	129 (41.5)	97 (39.8)	1.00	0.010
	Synovial sarcoma	50 (19.5)	47 (19.1)	0.77 (0.58, 1.03)		60 (19.3)	50 (20.5)	1.78 (1.22, 2.59)	
	Other sarcoma	101 (39.3)	95 (38.6)	0.93 (0.64, 1.34)		122 (39.2)	97 (39.8)	1.34 (0.99, 1.80)	
Age at randomization	≤50 years	101 (39.3)	94 (38.2)	1.00	0.087	122 (39.2)	93 (38.1)	1.00	0.031
	>50 years	156 (60.7)	152 (61.8)	1.27 (0.97, 1.68)		189 (60.8)	151 (61.9)	1.37 (1.03, 1.82)	

Supplemental table S7. Complete results of the multivariate Cox regression models for PFS and OS of patients receiving placebo with and without proteinuria at landmark time point of 60 days.

<u>Landmark Analysis at t=60 days</u>		Multivariate Cox model of progression-free survival				Multivariate Cox model of overall survival			
Covariates		Patients (N=41)	Observed Events (O=41)	Hazard Ratio (95% CI)	Wald p-value	Patients (N=101)	Observed Events (O=75)	Hazard Ratio (95% CI)	Wald p-value
Proteinuria	No	32 (78.0)	32 (78.0)	1.00	0.244	82 (81.2)	62 (82.7)	1.00	0.324
	Yes	9 (22.0)	9 (22.0)	1.78 (0.67, 4.69)		19 (18.8)	13 (17.3)	0.73 (0.39, 1.37)	
Performance status	0	22 (53.7)	22 (53.7)	1.00	0.128	48 (47.5)	33 (44.0)	1.00	0.055
	1	19 (46.3)	19 (46.3)	1.77 (0.85, 3.70)		53 (52.5)	42 (56.0)	1.58 (0.99, 2.54)	
Gender	Male	15 (36.6)	15 (36.6)	1.00	0.050	41 (40.6)	31 (41.3)	1.00	0.564
	Female	26 (63.4)	26 (63.4)	0.44 (0.19, 1.00)		60 (59.4)	44 (58.7)	0.86 (0.53, 1.42)	
Tumor grade	Low	2 (4.9)	2 (4.9)	1.00	0.016	3 (3.0)	2 (2.7)	1.00	0.298
	Intermediate	13 (31.7)	13 (31.7)	6.59 (1.10, 39.46)		25 (24.8)	17 (22.7)	2.18 (0.51, 9.35)	
	High	26 (63.4)	26 (63.4)	16.82 (2.18, 129.84)		73 (72.3)	56 (74.7)	1.53 (0.32, 7.18)	
Histology subtype	Leiomyosarcoma	19 (46.3)	19 (46.3)	1.00	0.011	42 (41.6)	31 (41.3)	1.00	0.841
	Synovial sarcoma	3 (7.3)	3 (7.3)	0.73 (0.34, 1.60)		11 (10.9)	7 (9.3)	0.89 (0.36, 2.21)	
	Other sarcoma	19 (46.3)	19 (46.3)	7.20 (1.60, 32.28)		48 (47.5)	37 (49.3)	1.11 (0.66, 1.88)	
Age at randomization	≤50 years	19 (46.3)	19 (46.3)	1.00	0.921	50 (49.5)	34 (45.3)	1.00	0.123
	>50 years	22 (53.7)	22 (53.7)	0.96 (0.43, 2.14)		51 (50.5)	41 (54.7)	1.52 (0.89, 2.60)	

Supplemental table S8. Complete results of the multivariate Cox regression models for PFS and OS of patients receiving pazopanib with and without hypothyroidism at landmark time point of 60 days.

<u>Landmark Analysis at t=60 days</u>		Multivariate Cox model of progression-free survival				Multivariate Cox model of overall survival			
Covariates		Patients (N=257)	Observed Events (O=246)	Hazard Ratio (95% CI)	Wald p-value	Patients (N=311)	Observed Events (O=244)	Hazard Ratio (95% CI)	Wald p-value
Hypothyroidism	No	200 (77.8)	191 (77.6)	1.00	0.210	247 (79.4)	198 (81.1)	1.00	0.093
	Yes	57 (22.2)	55 (22.4)	0.82 (0.61, 1.12)		64 (20.6)	46 (18.9)	0.75 (0.54, 1.05)	
Performance status	0	145 (56.4)	139 (56.5)	1.00	0.457	165 (53.1)	123 (50.4)	1.00	<.001
	1	112 (43.6)	107 (43.5)	0.91 (0.70, 1.17)		146 (46.9)	121 (49.6)	1.62 (1.25, 2.10)	
Gender	Male	101 (39.3)	98 (39.8)	1.00	0.031	126 (40.5)	106 (43.4)	1.00	0.157
	Female	156 (60.7)	148 (60.2)	0.74 (0.57, 0.97)		185 (59.5)	138 (56.6)	0.82 (0.63, 1.08)	
Tumor grade	Low	24 (9.3)	19 (7.7)	1.00	0.002	28 (9.0)	16 (6.6)	1.00	0.016
	Intermediate	87 (33.9)	85 (34.6)	2.37 (1.45, 3.87)		105 (33.8)	85 (34.8)	2.01 (1.19, 3.39)	
	High	146 (56.8)	142 (57.7)	1.82 (1.10, 3.03)		178 (57.2)	143 (58.6)	1.59 (0.93, 2.72)	
Histology subtype	Leiomyosarcoma	106 (41.2)	104 (42.3)	1.00	0.186	129 (41.5)	97 (39.8)	1.00	0.017
	Synovial sarcoma	50 (19.5)	47 (19.1)	0.76 (0.57, 1.02)		60 (19.3)	50 (20.5)	1.34 (0.99, 1.80)	
	Other sarcoma	101 (39.3)	95 (38.6)	0.91 (0.63, 1.31)		122 (39.2)	97 (39.8)	1.70 (1.17, 2.48)	
Age at randomization	≤50 years	101 (39.3)	94 (38.2)	1.00	0.103	122 (39.2)	93 (38.1)	1.00	0.034
	>50 years	156 (60.7)	152 (61.8)	1.26 (0.95, 1.65)		189 (60.8)	151 (61.9)	1.36 (1.02, 1.80)	

Supplemental table S9. Complete results of the multivariate Cox regression models for PFS and OS of patients receiving placebo with and without hypothyroidism at landmark time point of 60 days.

<u>Landmark Analysis at t=60 days</u>		Multivariate Cox model of progression-free survival				Multivariate Cox model of overall survival			
Covariates		Patients (N=41)	Observed Events (O=41)	Hazard Ratio (95% CI)	Wald p-value	Patients (N=101)	Observed Events (O=75)	Hazard Ratio (95% CI)	Wald p-value
Hypothyroidism	No	31 (75.6)	31 (75.6)	1.00	0.557	85 (84.2)	64 (85.3)	1.00	0.765
	Yes	10 (24.4)	10 (24.4)	1.34 (0.51, 3.55)		16 (15.8)	11 (14.7)	0.90 (0.46, 1.78)	
Performance status	0	22 (53.7)	22 (53.7)	1.00	0.149	48 (47.5)	33 (44.0)	1.00	0.059
	1	19 (46.3)	19 (46.3)	1.75 (0.82, 3.76)		53 (52.5)	42 (56.0)	1.58 (0.98, 2.53)	
Gender	Male	15 (36.6)	15 (36.6)	1.00	0.057	41 (40.6)	31 (41.3)	1.00	0.656
	Female	26 (63.4)	26 (63.4)	0.38 (0.14, 1.03)		60 (59.4)	44 (58.7)	0.89 (0.53, 1.49)	
Tumor grade	Low	2 (4.9)	2 (4.9)	1.00	0.015	3 (3.0)	2 (2.7)	1.00	0.242
	Intermediate	13 (31.7)	13 (31.7)	5.51 (0.97, 31.47)		25 (24.8)	17 (22.7)	2.19 (0.51, 9.37)	
	High	26 (63.4)	26 (63.4)	16.82 (2.11, 134.07)		73 (72.3)	56 (74.7)	1.46 (0.31, 6.81)	
Histology subtype	Leiomyosarcoma	19 (46.3)	19 (46.3)	1.00	0.015	42 (41.6)	31 (41.3)	1.00	0.886
	Synovial sarcoma	3 (7.3)	3 (7.3)	0.81 (0.38, 1.73)		11 (10.9)	7 (9.3)	0.89 (0.36, 2.22)	
	Other sarcoma	19 (46.3)	19 (46.3)	7.01 (1.57, 31.23)		48 (47.5)	37 (49.3)	1.08 (0.64, 1.83)	
Age at randomization	≤50 years	19 (46.3)	19 (46.3)	1.00	0.640	50 (49.5)	34 (45.3)	1.00	0.187
	>50 years	22 (53.7)	22 (53.7)	1.19 (0.58, 2.44)		51 (50.5)	41 (54.7)	1.41 (0.85, 2.36)	