Final Statistical Report

A randomized phase II study to explore the efficacy and feasibility of upfront bi-monthly rotations between Everolimus and Pazopanib with sequential treatment of first line Pazopanib and second line Everolimus until progression in patients with advanced or metastatic clear cell renal cancer.

Rotating Pazopanib & Everolimus to avoid resistance. (the ROPETAR trial)

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1 Database

All data entered in the database until 2018-06-22 was included in the analysis. The data is not complete, as several subjects are still on treatment at this date. (See section 5.) The report is written using the Knitr protocol to compute all numbers, dates, figures and tables directly from the data. Hence, in the future we can easily produce an updated version when new data has been entered into the database through the ECRF system.

Randomization data form the ALEA system was obtained at 2015-06-01. This information will not change as the last patient was randomized over a year ago. (See section 3.)

2 Protocol Summary

Study design

From the protocol:

This is an open-label, randomized phase II study to determine the feasibility of alternating cycles of treatment with Pazopanib and Everolimus followed thereafter by Pazopanib or Everolimus mono-therapy compared to sequential treatment of Pazopanib followed by Everolimus. The purpose of the study is to determine the progression free survival, feasibility and tolerability of the experimental arm (Arm A) compared to standard of care. In the experimental arm (Arm A) alternating treatment will consist of repeating periods of 16 weeks of treatment consisting of 8 weeks of Pazopanib 800 mg qd followed by 8 weeks of Everolimus 10 mg qd until progression followed thereafter by Pazopanib (if progressive disease after 8 weeks Everolimus) or Everolimus (if progressive disease after 8 weeks of Pazopanib) mono-therapy in patients with advanced or metastatic clear cell renal cancer. The comparative arm (Arm B) will be the standard regimen of Pazopanib (800 mg qd continuously) until progression, followed thereafter by Everolimus (10 mg qd continuously) until progression.

Trial Objectives

Primary: Progression free survival (PFS1), defined as time from randomization to first as progressive disease per RECIST 1.1 or death, whichever comes first.

Secondary:

- PFS2, defined as time from randomization to second progression or death, whichever comes first.
- Toxicity
- Quality of life (QOL)
- Overall survival (OS)
- To determine the feasibility and tolerability of alternating Pazopanib and Everolimus compared to sequential treatment of Pazopanib and Everolimus.
- To develop biomarkers that may predict responsiveness to either of the agents used.

Statistical considerations

From the protocol:

The primary objective of this study is to assess whether the experimental arm (alternating Pazopanib and Everolimus) yields anti-tumor activity deemed worthwhile to be further explored in a randomized phase III study. The primary endpoint will be the progression-free survival after treatment start (PFS).

Stratification: for randomization and efficacy analyses, patients will be stratified according to the Memorial Sloan Kettering Cancer Center (MSKCC) risk criteria (Appendix 2) (favorable vs. intermediate vs. poor risk groups, based on Karnofsky performance status, hemoglobin and corrected serum calcium, LDH and time from initial diagnosis < 1 year).

The primary endpoint is PFS. PFS curves will be constructed by means of the Kaplan-Meier technique, and analysed using a log-rank test according to the intention-to-treat principle (i. e. according to randomization). A total of 100 patients will be randomized in this study, 50 in each arm. The expected accrual period is two years. From a previous series it is estimated that the 1 year PFS in the standard arm will be 50%. If patients are followed until a total of 60 events (progression or death) are observed roughly one year after the last randomization assuming exponentially), the study will have 90% power to detect an increase in 1 year PFS of 30% (i. e. 50% vs. 80%), and a 80% power to detect an increase of 22% (i. e. 50% to 72%) (alpha = 0.05, 2 tailed test).

3 Accrual

The accrual is depicted in Table 1. The first patient was randomized in Sep 2012 and the last patient was randomized in Apr 2014.

Table 1: Accrual

	Arm		
	Arm A: experimental arm	Arm B: comparative arm	All
	52	49	101
Sep 2012 - Dec 2012	9 (17%)	8 (16%)	17 (17%)
Jan 2013 - Jun 2013	16 (31%)	14 (29%)	30 (30%)
Jul 2013 - Dec 2013	16 (31%)	13 (27%)	29 (29%)
Jan 2014 - Apr 2014	11 (21%)	14 (29%)	25 (25%)

Table 2 lists the distribution of the stratification factor: the Memorial Sloan Kettering Cancer Center risk criteria) over the arms as well as the distribution of the factors influencing this score: Karnofsky performance status, hemoglobin, corrected serum calcium, LDH and whether or not time from initial diagnosis is less than 1 year. The values reported here are those measured at baseline and reported in the ECRF. For 16 patients the MSKC risk assessment on the ECRF differs from that entered into the Alea randomization system, which might explain possible imbalances in the table.

Institute is not a stratification factor but is included in the table as well.

Table 2: Stratification

	Arm			
	Arm A: experimental arm	Arm B: comparative arm	All	p-Value
	52	49	101	
MSKCC prognostic criteria. Result				0.77
Favourable	14 (27%)	12 (24%)	26 (26%)	
Intermediate-risk	31 (60%)	27 (55%)	58 (57%)	
High-risk	7 (13%)	9 (18%)	16 (16%)	
NA	0 (0%)	1 (2%)	1 (1%)	
KARNOFSKY				0.005
No	52 (100%)	42 (86%)	94 (93%)	
Yes	0 (0%)	7 (14%)	7 (7%)	
CALCIUM				0.6
No	42 (81%)	41 (84%)	83 (82%)	
Yes	10 (19%)	7 (14%)	17 (17%)	
NA	0 (0%)	1 (2%)	1 (1%)	
HEMOGLOBIN				1
No	29 (56%)	28 (57%)	57 (56%)	
Yes	23 (44%)	21 (43%)	44 (44%)	
LDH				0.2
No	51 (98%)	45 (92%)	96 (95%)	
Yes	1 (2%)	4 (8%)	5 (5%)	
Within one year of diagnosis				0.69
No	20 (38%)	21 (43%)	41 (41%)	
Yes	32 (62%)	28 (57%)	60 (59%)	
Institute				0.66
antoni van leeuwenhoek ziekenhuis	2 (4%)	4 (8%)	6 (6%)	
academisch medisch centrum	0 (0%)	1 (2%)	1 (1%)	
academisch ziekenhuis maastricht	2 (4%)	4 (8%)	6 (6%)	
umcu	3 (6%)	1 (2%)	4 (4%)	
st. antonius ziekenhuis, locatie nieuwegein	4 (8%)	4 (8%)	8 (8%)	
hagaziekenhuis, lokatie leyenburg	1 (2%)	1 (2%)	2 (2%)	
maxima medisch centrum, lok eindhoven	7 (13%)	4 (8%)	11 (11%)	
sint franciscus gasthuis	12 (23%)	5 (10%)	17 (17%)	
sint elisabeth ziekenhuis	4 (8%)	1 (2%)	5 (5%)	
medisch centrum leeuwarden (locatie zuid)	2 (4%)	4 (8%)	6 (6%)	
isala klinieken	1 (2%)	3 (6%)	4 (4%)	
orbis medisch centrum	0 (0%)	1 (2%)	1 (1%)	
erasmus mc centrumlocatie	6 (12%)	6 (12%)	12 (12%)	
atrium medisch centrum	3 (6%)	3 (6%)	6 (6%)	
amphia ziekenhuis	5 (10%)	7 (14%)	12 (12%)	

4 Baseline characteristics

Tables 3, 4 describe patient characteristics and medical history at baseline.

Table 3: Patient characteristics at baseline. Ex-smokers have stopped smoking more than one month before start study.

	Arm			
	Arm A: exp	Arm B: comp	All	p-Value
	52	49	101	
Gender				0.39
male	38 (73%)	31 (63%)	69 (68%)	
female	14 (27%)	18 (37%)	32 (32%)	
Ethnic origin				0.87
Caucasian (European, Mediterranean Middle Eastern)	50 (96%)	48 (98%)	98 (97%)	
East/Southeast Asian (Burmese, Chinese, Japanese, Korean, Mongolian	0 (0%)	1 (2%)	1 (1%)	
Hispanic (Mexican-American, Mexico, Central and South America)	1 (2%)	0 (0%)	1 (1%)	
Other (Mixed-racial parentage, American Indian, Eskimo)	1 (2%)	0 (0%)	1 (1%)	
Performance status (WHO 0-4, 9=ND)				0.85
WHO 0	31 (60%)	26 (53%)	57 (56%)	
WHO 1	19 (37%)	20 (41%)	39 (39%)	
WHO 2	2 (4%)	2 (4%)	4 (4%)	
ND	0 (0%)	1 (2%)	1 (1%)	
Does the patient have any signs and / or symptoms? (use name and grading according to CTC 4.0)				0.01
No	19 (41%)	7 (16%)	26 (29%)	
Yes	27 (59%)	38 (84%)	65 (71%)	
Neurological examination. Result				0.23
Normal	26 (51%)	19 (40%)	45 (45%)	
Abnormal	1 (2%)	4 (8%)	5 (5%)	
Not done	24 (47%)	25 (52%)	49 (49%)	
WHAT IS THE SMOKING STATUS OF THE PATIENT?				0.72
Non-smoker, lifetime exposure of fewer than 100 cigarettes or equiva	19 (40%)	21 (46%)	40 (43%)	
Former smoker	23 (48%)	18 (39%)	41 (44%)	
Current smoker?	6 (12%)	7 (15%)	13 (14%)	
What is the average weekly consumption of alcohol for this patient				0.94
Subject has not consumed alcohol in the past year	17 (35%)	12 (26%)	29 (31%)	
< 1 unit per week	7 (15%)	6 (13%)	13 (14%)	
1 5 units of alcohol per week	5 (10%)	4 (9%)	9 (9%)	
6 10 units of alcohol per week	7 (15%)	9 (19%)	16 (17%)	

11 15 units of alcohol per week	3 (6%)	3 (6%)	6 (6%)	
16 20 units of alcohol per week	0 (0%)	1 (2%)	1 (1%)	
> 21 units of alcohol per week	2 (4%)	2 (4%)	4 (4%)	
Other	7 (15%)	10 (21%)	17 (18%)	
Metas stomach				0.11
Yes	0 (0%)	3 (6%)	3 (3%)	
No	52 (100%)	46 (94%)	98 (97%)	
Metas gastro oesophageal junction				1
Yes	2 (4%)	1 (2%)	3 (3%)	
No	50 (96%)	48 (98%)	98 (97%)	
Metas lung				0.83
Yes	35 (67%)	34 (69%)	69 (68%)	
No	17 (33%)	15 (31%)	32 (32%)	
Metas pleural fluid				0.43
Yes	2 (4%)	4 (8%)	6 (6%)	
No	50 (96%)	45 (92%)	95 (94%)	
Metas liver				1
Yes	6 (12%)	5 (10%)	11 (11%)	
No	46 (88%)	44 (90%)	90 (89%)	
Metas peritoneum				0.31
Yes	3 (6%)	6 (12%)	9 (9%)	
No	49 (94%)	43 (88%)	92 (91%)	
Metas lymph nodes				0.84
Yes	21 (40%)	18 (37%)	39 (39%)	
No	31 (60%)	31 (63%)	62 (61%)	
Metas ascites				1
Yes	1 (2%)	0 (0%)	1 (1%)	
No	51 (98%)	49 (100%)	100 (99%)	
Metas bone				0.41
Yes	16 (31%)	19 (39%)	35 (35%)	
No	36 (69%)	30 (61%)	66 (65%)	
Metas cns				1
Yes	1 (2%)	0 (0%)	1 (1%)	
No	51 (98%)	49 (100%)	100 (99%)	
Metas other organs				0.31
Yes	36 (69%)	29 (59%)	65 (64%)	
No	16 (31%)	20 (41%)	36 (36%)	
Age				0.73
Median	65	67	66	
0% 25% 75% 100% quantile	44 59 71 87	38 58 72 82	38 58 72 87	
Mean	65	65	65	
Standard Deviation	10	10	10	
Height				0.1
Median	176	173	176	
0% 25% 75% 100% quantile	153 170 185 197	74 164 182 192	74 168 182 197	
Mean	176	169	173	
Standard Deviation	9.9	21.1	17	
Weight				0.38
Median	79	77	78	

0% 25% 75% 100% quantile	56 68 93 145	47 64 93 122	47 66 94 145	
Mean	81	78	79	
Standard Deviation	17	18	17	
Estimated weight loss in previous 6 months				0.73
Median	0	0	0	
0% 25% 75% 100% quantile	0 0 5 28	0 0 3 29	0 0 5 29	
Mean	3.3	3.2	3.3	
Standard Deviation	5.5	6.0	5.7	

Every patient had the same tumor type: Progressive metastatic clear cell Renal Cell Cancer, no patient had any immunotherapy, hormonal therapy or chemotherapy.

Table 4: Medical history

	Arm			
	Arm A: exp	Arm B: comp	All	p-Value
	52	49	101	
Was the patient ever diagnosed with cancer other than RCC?				0.26
No	50 (96%)	44 (90%)	94 (93%)	
Yes	2 (4%)	5 (10%)	7 (7%)	
If yes, type of cancer				0.33
resected non-melanoma skin cancer	0 (0%)	2 (40%)	2 (29%)	
Succesfully treated in situ carcinoma	1 (50%)	0 (0%)	1 (14%)	
other	1 (50%)	3 (60%)	4 (57%)	
				0.15
no surgery	22 (42%)	14 (29%)	36 (36%)	
nephractomy	17 (33%)	25 (51%)	42 (42%)	
other surgery	2 (4%)	4 (8%)	6 (6%)	
both nephractomy and other	11 (21%)	6 (12%)	17 (17%)	
Has the patient had any radiotherapy?				1
No	37 (73%)	36 (73%)	73 (73%)	
Yes	14 (27%)	13 (27%)	27 (27%)	
Has the patient had any biologic/investigational therapy?				1
No	51 (98%)	49 (100%)	100 (99%)	
Yes	1 (2%)	0 (0%)	1 (1%)	
Is the patient suffering from, or has he / she ever suffered from significant medical or surgical conditions (other than protocol cancer or conditions related to protocol cancer)?				0.43
No	7 (13%)	10 (20%)	17 (17%)	
Yes	45 (87%)	39 (80%)	84 (83%)	

We note that although the tables in this section as well as table 2 contain p-values, these do not signify anything *clinically* important. They just test if our randomization does its job as expected.

The adverse events at baseline are listed in Table 30 in the appendix, which also contains more detailed accounts of some of the baseline characteristics discussed here.

5 Treatment

Flow chart data

Although it is technically possible to draw a flow chart here, I just put the information in a series of written statements and tables because that is much easier to program. We can draw a flow chart in PowerPoint (say) when we are confident these numbers will no longer change. We follow the structure of the flow chart of the SWITCH study.

- As has been noted before 101 patients were randomized, 52 to the experimental arm and 49 to the comparative arm.
- Not all patients started treatment. Patient 39 (Arm A: experimental arm) died before receiving any treatment. This means that 51 patients in the experimental arm and 49 in the comparative arm did get at least part of one cycle of Pazopanib.
- At the analysis cut-off: 2018-06-22, 12 patients, 9 in arm A and 3 in arm B, were still on first line treatment.

  Of 0 others, 0 in arm A and 0 in arm B, the treatment status at analysis is unknown.
- 88 of the 100 patients that started first line treatment have already ended it. They are listed in table 5 according to their reason for ending treatment. Details on some of the reasons (notably 'adverse event') are given in table 6.

  Please notice an important difference with the SWITCH trial. A patient whose first line treatment is ended because of an adverse event can later either resume first line treatment or stop treatment according to the ROPETAR study all together. Switching to second line treatment because of an AE on first treatment is not an option.

  As a consequence of this (and of the nature of the other reasons for stopping first line treatment) only people listed in table 5 as ending first line treatment because of 'First disease progression' are eligible for second line treatment.
- Of these patients 41 started second line treatment. For the patients that progressed on first line treatment and did *not* start second line treatment the reasons (in as far as they are known) are listed in table 7.
- As said before, 41 patients started second line treatment. 16 patients in arm A received Pazopanib in second line, 4 patient in arm A received Everolimus in second line and 18 patients in arm B received Everolimus in second line. Besides, 3 patients in arm B received Pazopanib after first progression, they are 36, 70, 99. For patient 36, disease progression was measured at the end of Pazopanib cycle six, but for some reason this did not influence treatment. Patient continued using Pazopanib up to a total of 13 cycles.
- Of the patients that started second line treatment 4 patients, 1 in arm A and 3 in arm B, were still on treatment at the analysis cut-off date.
- For the remaining patients the reasons for end of treatment and their distributions over the arms are described in tables 8 and 9.

Table 5: Reason end of first line treatment

	Arm		
	Arm A: experimental arm	Arm B: comparative arm	All
	52	49	101
Reason end of treatment			
On treatment	9 (17%)	3 (6%)	12 (12%)
First disease progression	31 (60%)	37 (76%)	68 (67%)
Adverse event	5 (10%)	4 (8%)	9 (9%)
Withdrawal of consent/patient refusal	1 (2%)	0 (0%)	1 (1%)
Death	2 (4%)	3 (6%)	5 (5%)
Patient never started	1 (2%)	0 (0%)	1 (1%)
Withdrawn by investigator	3 (6%)	0 (0%)	3 (3%)
Other	0 (0%)	2 (4%)	2 (2%)

Table 6: Reasons end of first line treatment other than progression. Patients with reason death and specification "other" are further described in table 22

Arm	Patnr	Reason
Arm A: experimental arm	12	Death: 8=Other
Arm A: experimental arm	17	Death: 8=Other
Arm A: experimental arm	20	Adverse event: liver toxicity
Arm A: experimental arm	24	Withdrawn by investigator: NA
Arm A: experimental arm	32	Adverse event: diarrhea, nausea, vomiting
Arm A: experimental arm	39	Patient never started
Arm A: experimental arm	43	Withdrawn by investigator: patient will be operated (planned on 29-11-2013 nephrectomy)
Arm A: experimental arm	58	Adverse event: abdominal pain. patient don't want to restart the medication withdrawal
Arm A: experimental arm	60	Withdrawn by investigator: withdrawn because patient tolerate pazopanib better than evorolimus and there is a better response on pazopanib. so everolimus will be stopped.
Arm A: experimental arm	82	Adverse event: pneumocystis jiroveci pneumonia
Arm A: experimental arm	89	Withdrawal of consent/patient refusal
Arm A: experimental arm	91	Adverse event: hepatotoxicity grade D; recoverd to grade 1
Arm B: comparative arm	1	Adverse event: proteinuria
Arm B: comparative arm	4	Other: near complete remission
Arm B: comparative arm	8	Adverse event: trombocytopenia, grade 3
Arm B: comparative arm	16	Adverse event: humerus fraction
Arm B: comparative arm	18	Death: 3=Toxicity
Arm B: comparative arm	47	Death: 1=Progresive disease
Arm B: comparative arm	62	Adverse event: liver failure
Arm B: comparative arm	72	Other: intolerance pazopanib stop date 16-12-2013
Arm B: comparative arm	84	Death: 3=Toxicity

Following the SWITCH trial, we compare the fractions (0.48 vs 0.46) of people having started and ended first line treatment that also started second line treatment between arms. Fisher's exact test yields a p-value of 1

Table 7: Reasons for not starting second line treatment after progression on first line treatment. Patients with reason death and specification "other" are further described in table 22

Arm	Patnr	Reason
Arm A: experimental arm	10	Adverse event: anorexia grade 3
Arm A: experimental arm	14	Other: disease progression and performance score
Arm A: experimental arm	19	Adverse event: hepatitis
Arm A: experimental arm	25	Adverse event: liver failure ->intolerance pazopanib and everolimus (pneumonitis)
Arm A: experimental arm	31	Adverse event: Patient suffered extreme form pain bonemetastasis, almost impossible to relief. Switching to pazopanib was not opportune at that moment
Arm A: experimental arm	44	First disease progression
Arm A: experimental arm	57	Adverse event: diarrhea, heartburn, fatigue, nausea, leucositis combination of all toxicitiespatient refused to continue everolimus with dose reduction
Arm A: experimental arm	66	Adverse event: no specific adverse event. several adverse events. patient will receive radiotherapy on thorax, 13 times.
Arm A: experimental arm	76	First disease progression
Arm A: experimental arm	85	Adverse event: pain
Arm B: comparative arm	22	First disease progression
Arm B: comparative arm	26	Adverse event: malaise, patient feels to weak
Arm B: comparative arm	40	Death: 1=Progresive disease
Arm B: comparative arm	41	First disease progression
Arm B: comparative arm	48	Withdrawal of consent/patient refusal
Arm B: comparative arm	51	First disease progression
Arm B: comparative arm	54	Adverse event: NA
Arm B: comparative arm	74	Other: intolerance study medication / pazopanib 15-01-2014
Arm B: comparative arm	75	Adverse event: pt has low tolerance: fatigue, diarrhea, malaise
Arm B: comparative arm	77	Adverse event: NA
Arm B: comparative arm	87	Adverse event: elevated liverenzymes
Arm B: comparative arm	90	Death: 1=Progresive disease
Arm B: comparative arm	93	Adverse event: stomatitis
Arm B: comparative arm	94	Death: 8=Other
Arm B: comparative arm	97	Adverse event: CVA
Arm B: comparative arm	100	Death: 8=Other

Table 8: Reason end of second line treatment

	Arm		
	Arm A: experimental arm	Arm B: comparative arm	All
	19	18	37
Reason end of treatment			
First disease progression	0 (0%)	1 (6%)	1 (3%)
Second disease progression	15 (79%)	11 (61%)	26 (70%)
Adverse event	2 (11%)	4 (22%)	6 (16%)
Death	2 (11%)	0 (0%)	2 (5%)
Withdrawn by investigator	0 (0%)	1 (6%)	1 (3%)
Other	0 (0%)	1 (6%)	1 (3%)

Table 9: Reasons end of second line treatment other than progression. Patients with reason death and specification "other" are further described in table 22

Arm	Patnr	Reason
Arm A: experimental arm	34	Death: 1=Progresive disease
Arm A: experimental arm	50	Adverse event: Treatment was stopped on 09-12-2014 due to AE pneumonitis grade 2
Arm A: experimental arm	59	Adverse event: pain back
Arm A: experimental arm	80	Death: 1=Progresive disease
Arm B: comparative arm	13	Adverse event: mood alteration
Arm B: comparative arm	53	Other: dyspnea and very poor condition. Patient went to hospice on 19-01-2015.
Arm B: comparative arm	68	Adverse event: acute kidney injury
Arm B: comparative arm	81	Adverse event: everolimus induced pneumonitis
Arm B: comparative arm	92	Adverse event: Decompensatio cordis
Arm B: comparative arm	95	Withdrawn by investigator: NA
Arm B: comparative arm	99	First disease progression

Number of cycles, modifications, interruptions

Table 10 records the number of cycles of treatment in each arm, before and after first progression.

Table 11 gives the number of patients that had a dose modification, escalation or reduction while treated with Everolimus, or had their treatment prematurely stopped, before the patient had the first progression. The lines labeled '[Event]s per cycle' give the fraction of cycles of Everolimus, at which the given event happened. For example, treatment interruptions occurred in 21% of cycles of Everolimus before PD1, while dose reductions only occurred in 6% of cycles. Table 12 lists the same information for Everolimus treatment after the first progression.

Tables 13 and 14 give the same information as tables 11, 12 but now for Pazopanib.

Table 10: Number of cycles

	Arm		
	Arm A: experimental arm	Arm B: comparative arm	All
	52	49	101
Started first line treatment			
yes	51 (98%)	49 (100%)	100 (99%)
no	1 (2%)	0 (0%)	1 (1%)
Total number of cycles before first PD			
Sample size	52	49	101
Median	3	4	3
0% 25% 75% 100% quantile	0 2 9 27	1 1 6 27	0 1 8 27
Cycles of Pazopanib before first progression			
Sample size	52	49	101
Median	2	4	2
0% 25% 75% 100% quantile	0 1 5 19	1 1 6 27	0 1 5 27
Cycles of Everolimus before first progression			
Sample size	52	49	101
Median	1	0	0
0% 25% 75% 100% quantile	0 1 4 13	0 0 0 0	0 0 1 13
Started second line treatment			
yes	20 (38%)	21 (43%)	41 (41%)
no	32 (62%)	28 (57%)	60 (59%)
Total number of cycles after first PD			
Sample size	20	21	41
Median	3	2	2
0% 25% 75% 100% quantile	1.0 1.8 4.2 14.0	1 1 4 11	1 1 4 14
Pazopanib after first progression			
yes	16 (80%)	3 (14%)	19 (46%)
no	4 (20%)	18 (86%)	22 (54%)
Cycles of Pazopanib after first progression			
Sample size	16	3	19
Median	3	7	3
0% 100% quantile	1 14	2 9	1 14
Everolimus after first progression			
yes	4 (20%)	18 (86%)	22 (54%)
no	16 (80%)	3 (14%)	19 (46%)
Cycles of Everolimus after first progression			
Sample size	4	18	22
Median	1.5	2.0	2
0% 25% 75% 100% quantile	1.0 1.0 2.8 5.0	1.0 1.0 2.8 11.0	1.0 1.0 2.8 11.0

Table 11: Data on Everolimus before first progression: experimental arm only

Dose reduction before PD1	
no	43
yes	8
Total	51
Dose reductions per cycle before PD1	
Mean	0.059
Dose escalation before PD1	
no	49
yes	2
Total	51
Dose escalations per cycle before PD1	
Mean	0.0073
Dose interr. in one or more cycles before PD1	
no	31
yes	20
Total	51
Dose interruptions per cycle before PD1	
Mean	0.28
Treatment delay before PD1	
no	50
yes	1
Total	51
Treatment delays per cycle before PD1	
Mean	0.0022

Table 12: Data on Everolimus after first progression: both arms

	Arm		
	Arm A: experimental arm	Arm B: comparative arm	All
	4	18	22
Dose reduction after PD1			
no	4 (100%)	14 (78%)	18 (82%)
yes	0 (0%)	4 (22%)	4 (18%)
Dose reductions per cycle after PD1			
Sample size	4	18	22
Mean	0.00	0.14	0.12
Dose escalation after PD1			
no	4 (100%)	18 (100%)	22 (100%)
yes	0 (0%)	0 (0%)	0 (0%)
Dose escalations per cycle after PD1			
Sample size	4	18	22
Mean	0	0	0
Dose interr. in one or more cycles after PD1			
no	2 (50%)	7 (39%)	9 (41%)
yes	2 (50%)	11 (61%)	13 (59%)
Av. no. of interruptions per cycle after PD1			
Sample size	4	18	22
Mean	0.50	0.44	0.45
Treatment delay after PD1			
no	3 (75%)	13 (72%)	16 (73%)
yes	1 (25%)	5 (28%)	6 (27%)
Treatment delays per cycle after PD1			
Sample size	4	18	22
Mean	0.05	0.20	0.17

Table 13: Data on Pazopanib before first progression

	Arm		
	Arm A: experimental arm	Arm B: comparative arm	All
	52	49	101
Dose reduction before PD1			
no	31 (61%)	30 (61%)	61 (61%)
yes	20 (39%)	19 (39%)	39 (39%)
Dose reductions per cycle before PD1			
Sample size	51	49	100
Mean	0.18	0.17	0.18
Dose escalation before PD1			
no	50 (98%)	48 (98%)	98 (98%)
yes	1 (2%)	1 (2%)	2 (2%)
Dose escalations per cycle before PD1			
Sample size	51	49	100
Mean	0.0033	0.0051	0.0042
Dose interr. in one or more cycles before PD1			
no	21 (41%)	14 (29%)	35 (35%)
yes	30 (59%)	35 (71%)	65 (65%)
Dose interruptions per cycle before PD1			
Sample size	51	49	100
Mean	0.37	0.41	0.39
Treatment delay before PD1			
no	49 (96%)	44 (90%)	93 (93%)
yes	2 (4%)	5 (10%)	7 (7%)
Treatment delays per cycle before PD1			
Sample size	51	49	100
Mean	0.029	0.018	0.024

Table 14: Data on Pazopanib after first progression

	Arm		
	Arm A: experimental arm	Arm B: comparative arm	All
	16	3	19
Dose reduction after PD1			
no	12 (75%)	2 (67%)	14 (74%)
yes	4 (25%)	1 (33%)	5 (26%)
Dose reductions per cycle after PD1			
Sample size	16	3	19
Mean	0.078	0.074	0.078
Dose escalation after PD1			
no	15 (94%)	1 (33%)	16 (84%)
yes	1 (6%)	2 (67%)	3 (16%)
Dose escalations per cycle after PD1			
Sample size	16	3	19
Mean	0.062	0.085	0.066
Dose interr. in one or more cycles after PD1			
no	7 (44%)	0 (0%)	7 (37%)
yes	9 (56%)	3 (100%)	12 (63%)
Dose interruptions per cycle after PD1			
Sample size	16	3	19
Mean	0.25	0.25	0.25
Treatment delay after PD1			
no	12 (75%)	3 (100%)	15 (79%)
yes	4 (25%)	0 (0%)	4 (21%)
Treatment delays per cycle after PD1			
Sample size	16	3	19
Mean	0.07	0.00	0.059

6 Response

None of the patients had a complete response. Table 15 gives the best response on treatment for each patient; some of the patients whose best response is partial response (PR) or stable disease (SD) also had progressive disease at a different moment in time – see table 23.

Table 15: Best response to treatment

	Arm		
	Arm A: experimental arm	Arm B: comparative arm	All
	52	49	101
Best response to study treatment			
Complete Response	0 (0%)	1 (2%)	1 (1%)
Partial Response	14 (27%)	17 (35%)	31 (31%)
Stable Disease	30 (58%)	19 (39%)	49 (49%)
Progressive Disease	6 (12%)	9 (18%)	15 (15%)
Non-Evaluable	2 (4%)	3 (6%)	5 (5%)

The percentages in the table are according to the Intend to Treat principle, so including non-evaluable patients. Analyzing Per Protocol, so excluding these patients we find response rates of 28% for the rotating arm and 39% for the comparative arm. ($p = 0.28$.)

7 Adverse Events

We present tables with adverse events, both of all grades and of grade at least 3. There are four tables: table 16 lists all adverse events (and all adverse events of grade at least 3) since start treatment and before first progression. Table 17 lists *toxicities*: adverse events marked as possible, probable or definitely related to treatment and tables 18, 19 list adverse events marked as (possible, probable or definitely) related to Pazopanib or Everolimus respectively. The numbers in the tables are the number of patients experiencing at least one event of the given type rather than the number of events. The p-values are produced by Fisher's exact test comparing these numbers relative to the number of patients in the arms that were 'at risk' for experiencing the given adverse event (as listed in the header of the table), that is: patient that started first line treatment. (Hence the numbers in the heading of the table should match the number of patient starting first line treatment reported in section 5.)

Events are grouped in categories by Geert Cirkel, the original descriptions of the adverse events in table 16 are given in table 31 in the appendix.

Adverse events at baseline are also described in the appendix, in table 30.

In table 20 we list the serious adverse events since start of treatment and in table 21 we list all adverse events of the patients that did have a grade 5 adverse event.

Table 16: All AEs during first line treatment

	All grades				Grades 3, 4, 5			
	Arm A	Arm B	All	p	Arm A	Arm B	All	p
	51	49	100		51	49	100	
"burned" eyes (unclear)	1	0	1	1	0	0	0	1
Abdominal infection	0	1	1	0.49	0	1	1	0.49
Abdominal pain	9	7	16	0.79	0	1	1	0.49
Abdominal wall herniation	1	0	1	1	0	0	0	1
Acute kidney injury	0	1	1	0.49	0	0	0	1
Alanine aminotransferase increased	17	16	33	1	8	11	19	0.45
Alkaline phosphatase increased	10	7	17	0.6	1	2	3	0.61
Allergic reaction	0	1	1	0.49	0	0	0	1
Allergic rhinitis	1	0	1	1	0	0	0	1
Alopecia	4	6	10	0.52	0	1	1	0.49
Amnesia	1	1	2	1	0	0	0	1
Anal pain	1	0	1	1	0	0	0	1
Anemia	6	4	10	0.74	1	0	1	1
Angina pectoris	0	1	1	0.49	0	0	0	1
Anorexia	23	12	35	0.04	3	1	4	0.62
Anxiety	0	1	1	0.49	0	0	0	1
Arthralgia	3	1	4	0.62	0	0	0	1
Asparate aminotransferase increased	15	16	31	0.83	7	9	16	0.59
Bloating	1	0	1	1	0	0	0	1
Blood bilirubin increased	5	4	9	1	1	0	1	1
Blood lactic dehydrogenase increased	2	1	3	1	0	0	0	1
Blurred vision	0	1	1	0.49	0	0	0	1
Bradycardia	0	1	1	0.49	0	0	0	1
Bullous dermatitis	1	1	2	1	0	0	0	1

Table 16: *(continued)*

	All grades				Grades 3, 4, 5			
	Arm A	Arm B	All	p	Arm A	Arm B	All	p
	51	49	100		51	49	100	
Candida infection	1	1	2	1	0	0	0	1
Carpal tunnel syndrome	1	0	1	1	0	0	0	1
Cerebral hemorrhage	1	0	1	1	1	0	1	1
Chills	2	1	3	1	0	0	0	1
Cholesterol high	1	0	1	1	0	0	0	1
Chondrodermatitis nodularis helicis	1	0	1	1	0	0	0	1
Chronic obstructive pulmonary disease	1	0	1	1	1	0	1	1
Coagulopathy unspecified	1	0	1	1	0	0	0	1
Cognitive disturbance	0	1	1	0.49	0	0	0	1
cold hand/feet (unclear)	0	1	1	0.49	0	0	0	1
Colonic perforation	0	1	1	0.49	0	1	1	0.49
Concentration impairment	0	1	1	0.49	0	0	0	1
Conjunctivitis infective	0	1	1	0.49	0	0	0	1
Constipation	10	9	19	1	0	2	2	0.24
corn (dermatology) (unclear)	1	0	1	1	0	0	0	1
Cough	13	11	24	0.82	0	0	0	1
Cramps	0	1	1	0.49	0	0	0	1
Creatinine increased	5	3	8	0.72	0	0	0	1
Dehydration	2	2	4	1	2	2	4	1
Delirium	0	2	2	0.24	0	0	0	1
Dermatitis unspecified	1	0	1	1	0	0	0	1
Diarrhea	22	29	51	0.12	5	3	8	0.72
Disseminated intravascular coagulation	0	1	1	0.49	0	0	0	1
Disturbed vision	3	3	6	1	0	0	0	1
Dizziness	8	3	11	0.2	1	0	1	1
Dry eye	2	0	2	0.5	0	0	0	1
Dry mouth	2	2	4	1	0	0	0	1
Dry skin	9	2	11	0.05	0	0	0	1
Dysarthria	0	1	1	0.49	0	0	0	1
Dysgeusia	11	12	23	0.81	1	0	1	1
Dyspepsia	4	7	11	0.35	0	0	0	1
Dysphagia	4	2	6	0.68	1	1	2	1
Dyspnea	20	12	32	0.14	3	1	4	0.62
Eczema	2	0	2	0.5	0	0	0	1
Edema	11	5	16	0.17	0	0	0	1
Ejalulation disorder	1	0	1	1	0	0	0	1
Elevated liver enzymes	1	0	1	1	0	0	0	1
Empyema	1	0	1	1	1	0	1	1
Enterocolitis infectious	0	1	1	0.49	0	1	1	0.49
Epistaxis	7	6	13	1	0	0	0	1
Erectile dysfunction	0	1	1	0.49	0	0	0	1

Table 16: *(continued)*

	All grades				Grades 3, 4, 5			
	Arm A	Arm B	All	p	Arm A	Arm B	All	p
	51	49	100		51	49	100	
Erythema	0	1	1	0.49	0	0	0	1
Erythema multifore	0	1	1	0.49	0	0	0	1
Erythema multiforme	1	1	2	1	0	0	0	1
Extrapyramidal disorder	1	0	1	1	0	0	0	1
Eye infection	1	0	1	1	0	0	0	1
Fall	1	0	1	1	0	0	0	1
Fatique	30	25	55	0.55	2	3	5	0.67
Fecal incontinence	0	1	1	0.49	0	0	0	1
Fever	4	4	8	1	0	1	1	0.49
Flu like symptoms	7	3	10	0.32	0	0	0	1
Fracture	0	1	1	0.49	0	0	0	1
Gammaglutamyltransferase increased	14	10	24	0.49	9	5	14	0.39
Gastroenteritis	1	1	2	1	0	0	0	1
Gastroesophageal reflux disease	1	0	1	1	0	0	0	1
Generalized muscle weakness	3	0	3	0.24	2	0	2	0.5
Hair discoloration	7	8	15	0.78	0	0	0	1
Hallucinations	0	1	1	0.49	0	0	0	1
Headache	14	11	25	0.65	0	0	0	1
Hearing impaired	1	0	1	1	0	0	0	1
Heart failure	0	1	1	0.49	0	1	1	0.49
Heartburn	3	0	3	0.24	0	0	0	1
Hemangioma	0	1	1	0.49	0	0	0	1
Hematoma	1	3	4	0.36	0	0	0	1
Hematuria	1	1	2	1	0	0	0	1
Hemoptysis	0	2	2	0.24	0	0	0	1
hemorrhoids	0	1	1	0.49	0	0	0	1
Hepatic disorder	0	1	1	0.49	0	1	1	0.49
Hepatic failure	2	0	2	0.5	1	0	1	1
Hepatotoxicity	3	1	4	0.62	1	0	1	1
Hernia inguinalis	1	0	1	1	0	0	0	1
Hiccups	1	1	2	1	0	0	0	1
Hoarseness	6	10	16	0.28	0	0	0	1
Hot flashes	2	2	4	1	0	0	0	1
Hypercalcemia	1	0	1	1	1	0	1	1
Hyperglycemia	3	2	5	1	1	0	1	1
Hyperhidrosis	1	0	1	1	0	0	0	1
Hyperkalemia	0	1	1	0.49	0	0	0	1
Hypersomnia	1	0	1	1	0	0	0	1
Hypertension	22	14	36	0.15	14	10	24	0.49
Hypertriglyceridemia	3	3	6	1	1	0	1	1
Hypocalcemia	0	1	1	0.49	0	0	0	1
Hypokalemia	1	2	3	0.61	0	0	0	1
Hypomagnesemia	0	1	1	0.49	0	0	0	1

Table 16: *(continued)*

	All grades				Grades 3, 4, 5			
	Arm A	Arm B	All	p	Arm A	Arm B	All	p
	51	49	100		51	49	100	
Hyponatremia	1	1	2	1	1	0	1	1
Hypotension	0	5	5	0.03	0	1	1	0.49
Hypothyroidism	1	3	4	0.36	0	0	0	1
Ileus	1	0	1	1	1	0	1	1
Impaired wound healing	1	0	1	1	0	0	0	1
Infection airway	1	1	2	1	0	0	0	1
Infection herpes	1	0	1	1	0	0	0	1
Infection unspecified	0	1	1	0.49	0	0	0	1
Inflammation left leg (unclear)	0	1	1	0.49	0	0	0	1
Insomnia	4	3	7	1	0	1	1	0.49
iriitability (unclear)	0	1	1	0.49	0	0	0	1
Ischemia cerebrovascular	1	0	1	1	0	0	0	1
Lipase increased	1	1	2	1	1	1	2	1
Malaise	7	6	13	1	0	1	1	0.49
Mucositis	19	4	23	0	4	0	4	0.12
Muskuloskeletal pain	13	16	29	0.51	1	1	2	1
Myalgia	6	1	7	0.11	0	0	0	1
Nail loss	1	0	1	1	0	0	0	1
Nail ridging	4	0	4	0.12	0	0	0	1
Nausea	24	17	41	0.23	1	2	3	0.61
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other specify: squamouscell carcinoma	1	0	1	1	0	0	0	1
neuropathy	1	0	1	1	0	0	0	1
Neuropathy	6	8	14	0.57	0	2	2	0.24
Night sweats	1	0	1	1	0	0	0	1
Osteoporosis	1	0	1	1	0	0	0	1
Pain abdomen	0	1	1	0.49	0	0	0	1
Pain unspecified	1	0	1	1	1	0	1	1
Pain unspecified (pain)	1	3	4	0.36	0	2	2	0.24
Pain unspecified (Pain)	0	1	1	0.49	0	0	0	1
Palmar-plantar erythrodysesthesia syndrome	5	6	11	0.76	0	0	0	1
Palpitations	5	2	7	0.44	1	0	1	1
Pancreatitis	1	1	2	1	0	1	1	0.49
Paronychia	1	0	1	1	0	0	0	1
Periodontal disease	3	3	6	1	0	0	0	1
pespine (unclear)	1	0	1	1	0	0	0	1
Platelet count decreased	4	4	8	1	0	1	1	0.49
Pleural effusion	2	1	3	1	1	0	1	1
Pneumonia	2	2	4	1	1	1	2	1
Pneumonitis	4	0	4	0.12	0	0	0	1
PNP (unclear)	0	1	1	0.49	0	0	0	1

Table 16: *(continued)*

	All grades				Grades 3, 4, 5			
	Arm A	Arm B	All	p	Arm A	Arm B	All	p
	51	49	100		51	49	100	
Pollakiuria	1	0	1	1	0	0	0	1
Prostate infection	0	1	1	0.49	0	0	0	1
Proteinuria	4	3	7	1	0	3	3	0.11
Pruritis	0	1	1	0.49	0	0	0	1
Pruritus	7	2	9	0.16	0	0	0	1
Rash acneiform	4	1	5	0.36	0	0	0	1
Rash maculo-papular	4	1	5	0.36	0	0	0	1
Rash unspecified	12	7	19	0.31	0	0	0	1
Raynaud phenomenon	1	0	1	1	0	0	0	1
Rectal hemorrhage	2	1	3	1	0	0	0	1
Retinal detachment	1	0	1	1	0	0	0	1
scaly skinperianal (unclear)	1	0	1	1	0	0	0	1
Seizure	0	1	1	0.49	0	0	0	1
Skin hyperpigmentation	1	1	2	1	0	0	0	1
Skin hypopigmentation	0	1	1	0.49	0	0	0	1
Skin infection	3	1	4	0.62	0	0	0	1
Skin toxicity head (unclear)	1	0	1	1	0	0	0	1
Skin unspecified	3	2	5	1	0	0	0	1
small coaguluar nose (unclear)	1	0	1	1	0	0	0	1
Soft tissue infection	1	0	1	1	0	0	0	1
Sore throat	2	0	2	0.5	0	0	0	1
stiffness hands (unclear)	1	0	1	1	0	0	0	1
Stomach pain	2	3	5	0.67	0	1	1	0.49
Stomatitis	8	9	17	0.79	0	1	1	0.49
Stroke	0	1	1	0.49	0	0	0	1
Syncope	4	0	4	0.12	4	0	4	0.12
Thoracic pain	9	2	11	0.05	2	0	2	0.5
Thromboembolic event	1	0	1	1	1	0	1	1
Tinnitus	3	2	5	1	0	0	0	1
Toothache	0	1	1	0.49	0	0	0	1
Tremor	2	0	2	0.5	0	0	0	1
Unguis incarnatus hallux	1	0	1	1	1	0	1	1
Urinary frequency	1	0	1	1	0	0	0	1
Urinary incontinence	1	1	2	1	0	0	0	1
Urinary tract infection	2	5	7	0.26	1	0	1	1
Urinary tract obstruction	0	1	1	0.49	0	1	1	0.49
Urine output decreased	0	1	1	0.49	0	0	0	1
Vertigo	1	1	2	1	0	0	0	1
Vomiting	14	9	23	0.34	1	0	1	1
Watering eyes	2	1	3	1	0	0	0	1
Weight loss	8	8	16	1	0	0	0	1
White blood cell decreased	4	0	4	0.12	3	0	3	0.24
Wound	0	1	1	0.49	0	0	0	1

Table 17: Toxicities during first line treatment

	All grades				Grades 3, 4, 5			
	Arm A	Arm B	All	p	Arm A	Arm B	All	p
	51	49	100		51	49	100	
Abdominal pain	6	4	10	0.74	0	0	0	1
Alanine aminotransferase increased	16	16	32	1	7	11	18	0.3
Alkaline phosphatase increased	8	7	15	1	1	2	3	0.61
Allergic reaction	0	1	1	0.49	0	0	0	1
Alopecia	3	3	6	1	0	0	0	1
Amnesia	1	0	1	1	0	0	0	1
Anal pain	1	0	1	1	0	0	0	1
Anemia	6	1	7	0.11	1	0	1	1
Anorexia	21	11	32	0.06	1	1	2	1
Arthralgia	0	1	1	0.49	0	0	0	1
Asparate aminotransferase increased	14	15	29	0.83	7	9	16	0.59
Bloating	1	0	1	1	0	0	0	1
Blood bilirubin increased	5	4	9	1	1	0	1	1
Blood lactic dehydrogenase increased	1	1	2	1	0	0	0	1
Blurred vision	0	1	1	0.49	0	0	0	1
Bullous dermatitis	1	1	2	1	0	0	0	1
Candida infection	0	1	1	0.49	0	0	0	1
Chills	1	1	2	1	0	0	0	1
Cholesterol high	1	0	1	1	0	0	0	1
Coagulopathy unspecified	1	0	1	1	0	0	0	1
Colonic perforation	0	1	1	0.49	0	1	1	0.49
Conjunctivitis infective	0	1	1	0.49	0	0	0	1
Constipation	7	5	12	0.76	0	0	0	1
Cough	5	6	11	0.76	0	0	0	1
Cramps	0	1	1	0.49	0	0	0	1
Creatinine increased	4	2	6	0.68	0	0	0	1
Dehydration	2	2	4	1	2	2	4	1
Dermatitis unspecified	1	0	1	1	0	0	0	1
Diarrhea	19	25	44	0.23	4	3	7	1
Disseminated intravascular coagulation	0	1	1	0.49	0	0	0	1
Disturbed vision	2	2	4	1	0	0	0	1
Dizziness	8	1	9	0.03	1	0	1	1
Dry eye	2	0	2	0.5	0	0	0	1
Dry mouth	1	2	3	0.61	0	0	0	1
Dry skin	8	2	10	0.09	0	0	0	1
Dysgeusia	10	11	21	0.81	1	0	1	1
Dyspepsia	4	5	9	0.74	0	0	0	1
Dysphagia	3	1	4	0.62	1	0	1	1
Dyspnea	12	7	19	0.31	1	1	2	1
Eczema	2	0	2	0.5	0	0	0	1

Table 17: *(continued)*

	All grades				Grades 3, 4, 5			
	Arm A	Arm B	All	p	Arm A	Arm B	All	p
	51	49	100		51	49	100	
Edema	8	1	9	0.03	0	0	0	1
Elevated liver enzymes	1	0	1	1	0	0	0	1
Enterocolitis infectious	0	1	1	0.49	0	1	1	0.49
Epistaxis	6	4	10	0.74	0	0	0	1
Erectile dysfunction	0	1	1	0.49	0	0	0	1
Erythema multifore	0	1	1	0.49	0	0	0	1
Erythema multiforme	1	1	2	1	0	0	0	1
Extrapyramidal disorder	1	0	1	1	0	0	0	1
Fatique	28	24	52	0.69	2	2	4	1
Fever	3	2	5	1	0	1	1	0.49
Flu like symptoms	3	3	6	1	0	0	0	1
Gammaglutamyltransferase increased	12	10	22	0.81	7	5	12	0.76
Gastroenteritis	1	1	2	1	0	0	0	1
Gastroesophageal reflux disease	1	0	1	1	0	0	0	1
Generalized muscle weakness	1	0	1	1	1	0	1	1
Hair discoloration	6	8	14	0.57	0	0	0	1
Hallucinations	0	1	1	0.49	0	0	0	1
Headache	14	10	24	0.49	0	0	0	1
Hearing impaired	1	0	1	1	0	0	0	1
Heartburn	2	0	2	0.5	0	0	0	1
Hematoma	1	2	3	0.61	0	0	0	1
Hemoptysis	0	2	2	0.24	0	0	0	1
hemorrhoids	0	1	1	0.49	0	0	0	1
Hepatic disorder	0	1	1	0.49	0	1	1	0.49
Hepatic failure	2	0	2	0.5	1	0	1	1
Hepatotoxicity	2	1	3	1	0	0	0	1
Hiccups	1	0	1	1	0	0	0	1
Hoarseness	5	10	15	0.17	0	0	0	1
Hot flashes	1	0	1	1	0	0	0	1
Hyperglycemia	1	0	1	1	0	0	0	1
Hyperhidrosis	1	0	1	1	0	0	0	1
Hypertension	19	13	32	0.29	11	10	21	1
Hypertriglyceridemia	3	2	5	1	1	0	1	1
Hypocalcemia	0	1	1	0.49	0	0	0	1
Hypokalemia	0	1	1	0.49	0	0	0	1
Hyponatremia	0	1	1	0.49	0	0	0	1
Hypotension	0	4	4	0.05	0	1	1	0.49
Hypothyroidism	1	3	4	0.36	0	0	0	1
Ileus	1	0	1	1	1	0	1	1
Impaired wound healing	1	0	1	1	0	0	0	1
Infection airway	1	1	2	1	0	0	0	1
Infection herpes	1	0	1	1	0	0	0	1
Insomnia	0	1	1	0.49	0	0	0	1

Table 17: *(continued)*

	All grades				Grades 3, 4, 5			
	Arm A	Arm B	All	p	Arm A	Arm B	All	p
	51	49	100		51	49	100	
Lipase increased	1	1	2	1	1	1	2	1
Malaise	6	6	12	1	0	1	1	0.49
Mucositis	19	4	23	0	4	0	4	0.12
Muskuloskeletal pain	3	2	5	1	0	0	0	1
Myalgia	4	1	5	0.36	0	0	0	1
Nail loss	1	0	1	1	0	0	0	1
Nail ridging	4	0	4	0.12	0	0	0	1
Nausea	22	15	37	0.22	1	2	3	0.61
neuropathy	1	0	1	1	0	0	0	1
Neuropathy	4	3	7	1	0	1	1	0.49
Night sweats	1	0	1	1	0	0	0	1
Pain abdomen	0	1	1	0.49	0	0	0	1
Pain unspecified (pain)	0	1	1	0.49	0	0	0	1
Pain unspecified (Pain)	0	1	1	0.49	0	0	0	1
Palmar-plantar erythrodysesthesia syndrome	4	6	10	0.52	0	0	0	1
Palpitations	1	1	2	1	0	0	0	1
Pancreatitis	0	1	1	0.49	0	1	1	0.49
Paronychia	1	0	1	1	0	0	0	1
Periodontal disease	0	1	1	0.49	0	0	0	1
pespine (unclear)	1	0	1	1	0	0	0	1
Platelet count decreased	3	3	6	1	0	1	1	0.49
Pleural effusion	1	0	1	1	0	0	0	1
Pneumonia	0	1	1	0.49	0	1	1	0.49
Pneumonitis	4	0	4	0.12	0	0	0	1
Proteinuria	4	3	7	1	0	3	3	0.11
Pruritis	0	1	1	0.49	0	0	0	1
Pruritus	7	2	9	0.16	0	0	0	1
Rash acneiform	4	1	5	0.36	0	0	0	1
Rash maculo-papular	3	1	4	0.62	0	0	0	1
Rash unspecified	10	5	15	0.26	0	0	0	1
Rectal hemorrhage	2	1	3	1	0	0	0	1
Skin hyperpigmentation	1	1	2	1	0	0	0	1
Skin hypopigmentation	0	1	1	0.49	0	0	0	1
Skin infection	1	0	1	1	0	0	0	1
Skin toxicity head (unclear)	1	0	1	1	0	0	0	1
Skin unspecified	3	1	4	0.62	0	0	0	1
small coaguluar nose (unclear)	1	0	1	1	0	0	0	1
Stomach pain	1	2	3	0.61	0	0	0	1
Stomatitis	8	9	17	0.79	0	1	1	0.49
Syncope	1	0	1	1	1	0	1	1
Thoracic pain	4	1	5	0.36	1	0	1	1
Thromboembolic event	1	0	1	1	1	0	1	1
Tinnitus	2	1	3	1	0	0	0	1

Table 17: *(continued)*

	All grades				Grades 3, 4, 5			
	Arm A	Arm B	All	p	Arm A	Arm B	All	p
	51	49	100		51	49	100	
Urinary tract infection	2	0	2	0.5	1	0	1	1
Urinary tract obstruction	0	1	1	0.49	0	1	1	0.49
Vertigo	0	1	1	0.49	0	0	0	1
Vomiting	13	7	20	0.21	1	0	1	1
Watering eyes	1	1	2	1	0	0	0	1
Weight loss	5	6	11	0.76	0	0	0	1
White blood cell decreased	4	0	4	0.12	3	0	3	0.24

Table 18: Toxicities during first line treatment related to Pazopanib

	All grades				Grades 3, 4, 5			
	Arm A	Arm B	All	p	Arm A	Arm B	All	p
	51	49	100		51	49	100	
Abdominal pain	5	4	9	1	0	0	0	1
Alanine aminotransferase increased	15	16	31	0.83	7	11	18	0.3
Alkaline phosphatase increased	7	7	14	1	1	2	3	0.61
Allergic reaction	0	1	1	0.49	0	0	0	1
Alopecia	2	3	5	0.67	0	0	0	1
Anal pain	1	0	1	1	0	0	0	1
Anemia	2	1	3	1	0	0	0	1
Anorexia	18	11	29	0.19	1	1	2	1
Arthralgia	0	1	1	0.49	0	0	0	1
Asparate aminotransferase increased	13	15	28	0.66	7	9	16	0.59
Blood bilirubin increased	5	4	9	1	1	0	1	1
Blood lactic dehydrogenase increased	1	1	2	1	0	0	0	1
Blurred vision	0	1	1	0.49	0	0	0	1
Bullous dermatitis	0	1	1	0.49	0	0	0	1
Candida infection	0	1	1	0.49	0	0	0	1
Chills	1	1	2	1	0	0	0	1
Coagulopathy unspecified	1	0	1	1	0	0	0	1
Colonic perforation	0	1	1	0.49	0	1	1	0.49
Conjunctivitis infective	0	1	1	0.49	0	0	0	1
Constipation	7	5	12	0.76	0	0	0	1
Cough	3	6	9	0.31	0	0	0	1
Cramps	0	1	1	0.49	0	0	0	1
Creatinine increased	3	2	5	1	0	0	0	1
Dehydration	1	2	3	0.61	1	2	3	0.61
Diarrhea	16	25	41	0.07	3	3	6	1
Disseminated intravascular coagulation	0	1	1	0.49	0	0	0	1
Disturbed vision	1	2	3	0.61	0	0	0	1
Dizziness	8	1	9	0.03	1	0	1	1
Dry mouth	1	2	3	0.61	0	0	0	1
Dry skin	5	2	7	0.44	0	0	0	1
Dysgeusia	10	11	21	0.81	1	0	1	1
Dyspepsia	4	5	9	0.74	0	0	0	1
Dysphagia	1	1	2	1	0	0	0	1
Dyspnea	7	7	14	1	1	1	2	1
Eczema	1	0	1	1	0	0	0	1
Edema	0	1	1	0.49	0	0	0	1
Elevated liver enzymes	1	0	1	1	0	0	0	1
Enterocolitis infectious	0	1	1	0.49	0	1	1	0.49
Epistaxis	3	4	7	0.71	0	0	0	1
Erectile dysfunction	0	1	1	0.49	0	0	0	1

Table 18: *(continued)*

	All grades				Grades 3, 4, 5			
	Arm A	Arm B	All	p	Arm A	Arm B	All	p
	51	49	100		51	49	100	
Erythema multifore	0	1	1	0.49	0	0	0	1
Erythema multiforme	1	1	2	1	0	0	0	1
Extrapyramidal disorder	1	0	1	1	0	0	0	1
Fatique	26	24	50	1	1	2	3	0.61
Fever	3	2	5	1	0	1	1	0.49
Flu like symptoms	3	3	6	1	0	0	0	1
Gammaglutamyltransferase increased	10	10	20	1	6	5	11	1
Gastroenteritis	1	1	2	1	0	0	0	1
Gastroesophageal reflux disease	1	0	1	1	0	0	0	1
Generalized muscle weakness	1	0	1	1	1	0	1	1
Hair discoloration	4	8	12	0.23	0	0	0	1
Hallucinations	0	1	1	0.49	0	0	0	1
Headache	9	10	19	0.8	0	0	0	1
Hearing impaired	1	0	1	1	0	0	0	1
Heartburn	1	0	1	1	0	0	0	1
Hematoma	0	2	2	0.24	0	0	0	1
Hemoptysis	0	2	2	0.24	0	0	0	1
hemorrhoids	0	1	1	0.49	0	0	0	1
Hepatic disorder	0	1	1	0.49	0	1	1	0.49
Hepatic failure	2	0	2	0.5	1	0	1	1
Hepatotoxicity	2	1	3	1	0	0	0	1
Hiccups	1	0	1	1	0	0	0	1
Hoarseness	5	10	15	0.17	0	0	0	1
Hyperhidrosis	1	0	1	1	0	0	0	1
Hypertension	19	13	32	0.29	11	10	21	1
Hypertriglyceridemia	1	2	3	0.61	0	0	0	1
Hypocalcemia	0	1	1	0.49	0	0	0	1
Hypokalemia	0	1	1	0.49	0	0	0	1
Hyponatremia	0	1	1	0.49	0	0	0	1
Hypotension	0	4	4	0.05	0	1	1	0.49
Hypothyroidism	1	3	4	0.36	0	0	0	1
Ileus	1	0	1	1	1	0	1	1
Impaired wound healing	1	0	1	1	0	0	0	1
Infection airway	0	1	1	0.49	0	0	0	1
Infection herpes	1	0	1	1	0	0	0	1
Insomnia	0	1	1	0.49	0	0	0	1
Lipase increased	1	1	2	1	1	1	2	1
Malaise	5	6	11	0.76	0	1	1	0.49
Mucositis	7	4	11	0.53	2	0	2	0.5
Muskuloskeletal pain	3	2	5	1	0	0	0	1
Myalgia	3	1	4	0.62	0	0	0	1
Nail ridging	2	0	2	0.5	0	0	0	1
Nausea	18	15	33	0.67	0	2	2	0.24

Table 18: *(continued)*

	All grades				Grades 3, 4, 5			
	Arm A	Arm B	All	p	Arm A	Arm B	All	p
	51	49	100		51	49	100	
neuropathy	1	0	1	1	0	0	0	1
Neuropathy	4	3	7	1	0	1	1	0.49
Night sweats	1	0	1	1	0	0	0	1
Pain abdomen	0	1	1	0.49	0	0	0	1
Pain unspecified (pain)	0	1	1	0.49	0	0	0	1
Pain unspecified (Pain)	0	1	1	0.49	0	0	0	1
Palmar-plantar erythrodysesthesia syndrome	4	6	10	0.52	0	0	0	1
Palpitations	1	1	2	1	0	0	0	1
Pancreatitis	0	1	1	0.49	0	1	1	0.49
Periodontal disease	0	1	1	0.49	0	0	0	1
Platelet count decreased	3	3	6	1	0	1	1	0.49
Pleural effusion	1	0	1	1	0	0	0	1
Pneumonia	0	1	1	0.49	0	1	1	0.49
Proteinuria	4	3	7	1	0	3	3	0.11
Pruritis	0	1	1	0.49	0	0	0	1
Pruritus	2	2	4	1	0	0	0	1
Rash acneiform	1	1	2	1	0	0	0	1
Rash maculo-papular	2	1	3	1	0	0	0	1
Rash unspecified	4	5	9	0.74	0	0	0	1
Rectal hemorrhage	1	1	2	1	0	0	0	1
Skin hyperpigmentation	1	1	2	1	0	0	0	1
Skin hypopigmentation	0	1	1	0.49	0	0	0	1
Skin infection	1	0	1	1	0	0	0	1
Skin toxicity head (unclear)	1	0	1	1	0	0	0	1
Skin unspecified	1	1	2	1	0	0	0	1
Stomach pain	0	2	2	0.24	0	0	0	1
Stomatitis	4	9	13	0.14	0	1	1	0.49
Syncope	1	0	1	1	1	0	1	1
Thoracic pain	3	1	4	0.62	1	0	1	1
Thromboembolic event	1	0	1	1	1	0	1	1
Tinnitus	2	1	3	1	0	0	0	1
Urinary tract infection	2	0	2	0.5	1	0	1	1
Urinary tract obstruction	0	1	1	0.49	0	1	1	0.49
Vertigo	0	1	1	0.49	0	0	0	1
Vomiting	12	7	19	0.31	0	0	0	1
Watering eyes	1	1	2	1	0	0	0	1
Weight loss	5	6	11	0.76	0	0	0	1
White blood cell decreased	4	0	4	0.12	3	0	3	0.24

Table 19: Toxicities during first line treatment related to Everolimus

	All grades				Grades 3, 4, 5			
	Arm A	Arm B	All	p	Arm A	Arm B	All	p
	51	49	100		51	49	100	
Abdominal pain	2	0	2	0.5	0	0	0	1
Alanine aminotransferase increased	6	1	7	0.11	0	0	0	1
Alkaline phosphatase increased	3	0	3	0.24	1	0	1	1
Alopecia	3	0	3	0.24	0	0	0	1
Amnesia	1	0	1	1	0	0	0	1
Anemia	6	0	6	0.03	1	0	1	1
Anorexia	9	0	9	0	0	0	0	1
Asparate aminotransferase increased	5	1	6	0.2	0	0	0	1
Bloating	1	0	1	1	0	0	0	1
Blood lactic dehydrogenase increased	1	0	1	1	0	0	0	1
Bullous dermatitis	1	0	1	1	0	0	0	1
Cholesterol high	1	0	1	1	0	0	0	1
Constipation	1	0	1	1	0	0	0	1
Cough	3	0	3	0.24	0	0	0	1
Creatinine increased	2	0	2	0.5	0	0	0	1
Dehydration	1	0	1	1	1	0	1	1
Dermatitis unspecified	1	0	1	1	0	0	0	1
Diarrhea	6	0	6	0.03	2	0	2	0.5
Disturbed vision	1	0	1	1	0	0	0	1
Dizziness	1	0	1	1	0	0	0	1
Dry eye	2	0	2	0.5	0	0	0	1
Dry skin	5	0	5	0.06	0	0	0	1
Dysgeusia	2	0	2	0.5	0	0	0	1
Dysphagia	3	0	3	0.24	1	0	1	1
Dyspnea	6	0	6	0.03	0	0	0	1
Eczema	1	0	1	1	0	0	0	1
Edema	8	0	8	0.01	0	0	0	1
Epistaxis	3	0	3	0.24	0	0	0	1
Fatique	12	1	13	0	1	1	2	1
Fever	1	0	1	1	0	0	0	1
Flu like symptoms	2	0	2	0.5	0	0	0	1
Gammaglutamyltransferase increased	6	0	6	0.03	4	0	4	0.12
Hair discoloration	2	0	2	0.5	0	0	0	1
Hallucinations	0	1	1	0.49	0	0	0	1
Headache	6	1	7	0.11	0	0	0	1
Heartburn	1	0	1	1	0	0	0	1
Hematoma	1	0	1	1	0	0	0	1
Hot flashes	1	0	1	1	0	0	0	1
Hyperglycemia	1	0	1	1	0	0	0	1
Hypertension	2	0	2	0.5	1	0	1	1

Table 19: *(continued)*

	All grades				Grades 3, 4, 5			
	Arm A	Arm B	All	p	Arm A	Arm B	All	p
	51	49	100		51	49	100	
Hypertriglyceridemia	2	0	2	0.5	1	0	1	1
Infection airway	1	0	1	1	0	0	0	1
Malaise	1	0	1	1	0	0	0	1
Mucositis	16	0	16	0	3	0	3	0.24
Myalgia	2	0	2	0.5	0	0	0	1
Nail loss	1	0	1	1	0	0	0	1
Nail ridging	4	0	4	0.12	0	0	0	1
Nausea	6	1	7	0.11	1	0	1	1
Neuropathy	1	0	1	1	0	0	0	1
Night sweats	1	0	1	1	0	0	0	1
Paronychia	1	0	1	1	0	0	0	1
pespine (unclear)	1	0	1	1	0	0	0	1
Platelet count decreased	1	0	1	1	0	0	0	1
Pneumonitis	4	0	4	0.12	0	0	0	1
Proteinuria	1	0	1	1	0	0	0	1
Pruritus	5	0	5	0.06	0	0	0	1
Rash acneiform	3	0	3	0.24	0	0	0	1
Rash maculo-papular	3	0	3	0.24	0	0	0	1
Rash unspecified	8	0	8	0.01	0	0	0	1
Rectal hemorrhage	1	0	1	1	0	0	0	1
Skin toxicity head (unclear)	1	0	1	1	0	0	0	1
Skin unspecified	2	0	2	0.5	0	0	0	1
small coaguluar nose (unclear)	1	0	1	1	0	0	0	1
Stomach pain	1	0	1	1	0	0	0	1
Stomatitis	6	0	6	0.03	0	0	0	1
Thoracic pain	2	0	2	0.5	0	0	0	1
Vomiting	2	0	2	0.5	1	0	1	1
White blood cell decreased	1	0	1	1	0	0	0	1

Table 20: All Serious Adverse Events

Arm	Patnr	Event	Grade	Rel. to Ev.	Rel. to Paz.	Time
Arm A: exp. arm	3	Hepatotoxicity	2		3=possible	Treatment 1
Arm A: exp. arm	3	Pleural effusion	2		3=possible	After EOT
Arm A: exp. arm	7	Nausea	3	4=Probable	1=not related	Treatment 1
Arm A: exp. arm	7	Headache	2	2=Unlikely	1=not related	Treatment 2
Arm A: exp. arm	12	Dyspnea	5		2=unlikely	Treatment 1
Arm A: exp. arm	12	Pneumonia	3	2=Unlikely		Treatment 1
Arm A: exp. arm	12	Chronic obstructive pulmonary disease	3	2=Unlikely		Treatment 1
Arm A: exp. arm	14	Generalized muscle weakness	3		1=not related	Treatment 1
Arm A: exp. arm	14	Syncope	3		1=not related	Treatment 1
Arm A: exp. arm	17	Fracture	1	1=Unrelated	1=not related	Baseline
Arm A: exp. arm	17	Muskuloskeletal pain	2	2=Unlikely	1=not related	Treatment 1
Arm A: exp. arm	17	Cerebral hemorrhage	5	1=Unrelated	1=not related	Treatment 1
Arm A: exp. arm	19	Alanine aminotransferase increased	3		3=possible	After EOT
Arm A: exp. arm	19	Asparate aminotransferase increased	3		3=possible	After EOT
Arm A: exp. arm	19	Alkaline phosphatase increased	3		3=possible	After EOT
Arm A: exp. arm	19	Gammaglutamyltransferase increased	3		3=possible	After EOT
Arm A: exp. arm	19	Hepatic failure	3		4=probable	After EOT
Arm A: exp. arm	20	Hepatotoxicity	3	1=Unrelated		Treatment 1
Arm A: exp. arm	24	Vomiting	2	1=Unrelated	3=possible	Treatment 1
Arm A: exp. arm	24	Hypertension	3	1=Unrelated	4=probable	Treatment 1
Arm A: exp. arm	32	Gastroenteritis	2	1=Unrelated	3=possible	Treatment 1
Arm A: exp. arm	33	Pneumonia	1	1=Unrelated	2=unlikely	Treatment 1
Arm A: exp. arm	33	Transient ischemic attacks	1	1=Unrelated	4=probable	Treatment 2
Arm A: exp. arm	33	Dyspnea	2	2=Unlikely	2=unlikely	Treatment 2
Arm A: exp. arm	33	Cough	1	2=Unlikely	2=unlikely	Treatment 2
Arm A: exp. arm	33	Fever	1	2=Unlikely	2=unlikely	Treatment 2
Arm A: exp. arm	33	Otitis	2	2=Unlikely	2=unlikely	Treatment 2
Arm A: exp. arm	34	Dyspnea	3	1=Unrelated		Treatment 1
Arm A: exp. arm	38	Ileus	3	1=Unrelated	4=probable	Treatment 1
Arm A: exp. arm	38	Nausea	2	1=Unrelated	4=probable	Treatment 1
Arm A: exp. arm	38	Vomiting	2	1=Unrelated	4=probable	Treatment 1
Arm A: exp. arm	38	Abdominal pain	2	1=Unrelated	4=probable	Treatment 1
Arm A: exp. arm	38	Abdominal wall herniation	2	1=Unrelated	2=unlikely	Treatment 1
Arm A: exp. arm	39	Abdominal pain	3	1=Unrelated	1=not related	After EOT
Arm A: exp. arm	39	Muskuloskeletal pain	3	1=Unrelated	1=not related	After EOT
Arm A: exp. arm	39	Fever	1	1=Unrelated	1=not related	After EOT
Arm A: exp. arm	39		3	1=Unrelated	1=not related	After EOT
Arm A: exp. arm	44	Thoracic pain	2		2=unlikely	Treatment 1
Arm A: exp. arm	44	Dehydration	3		4=probable	Treatment 1
Arm A: exp. arm	44	Nausea	3		3=possible	After EOT

Table 20: *(continued)*

Arm	Patnr	Event	Grade	Rel. to Ev.	Rel. to Paz.	Time
Arm A: exp. arm	56	Thromboembolic event	4	1=Unrelated	3=possible	Treatment 1
Arm A: exp. arm	56	Syncope	3	2=Unlikely	1=not related	Treatment 1
Arm A: exp. arm	56	Dehydration	3	3=Possible	1=not related	Treatment 1
Arm A: exp. arm	56	Creatinine increased	2	3=Possible	1=not related	Treatment 1
Arm A: exp. arm	58	Constipation	2	1=Unrelated	3=possible	Treatment 1
Arm A: exp. arm	59	Hypercalcemia	2	1=Unrelated	1=not related	After EOT
Arm A: exp. arm	59	Hypercalcemia	2	1=Unrelated	1=not related	After EOT
Arm A: exp. arm	59	Pain unspecified (pain whole body)	2	1=Unrelated	1=not related	After EOT
Arm A: exp. arm	60	Alanine aminotransferase increased	3		4=probable	Treatment 1
Arm A: exp. arm	60	Asparate aminotransferase increased	3		4=probable	Treatment 1
Arm A: exp. arm	71	Asparate aminotransferase increased	3	1=Unrelated	4=probable	Treatment 1
Arm A: exp. arm	71	Alanine aminotransferase increased	3	1=Unrelated	4=probable	Treatment 1
Arm A: exp. arm	73	Fever	1	1=Unrelated	1=not related	Treatment 1
Arm A: exp. arm	73	Fever	1	1=Unrelated	1=not related	Treatment 1
Arm A: exp. arm	76	Alanine aminotransferase increased	3		4=probable	Treatment 1
Arm A: exp. arm	76	Asparate aminotransferase increased	2		4=probable	Treatment 1
Arm A: exp. arm	76	Neuropathy	3		2=unlikely	After EOT
Arm A: exp. arm	78	Malaise	2	1=Unrelated	4=probable	Treatment 1
Arm A: exp. arm	78	Hepatic failure	3	1=Unrelated	4=probable	Treatment 1
Arm A: exp. arm	78	Generalized muscle weakness	3	1=Unrelated	4=probable	Treatment 1
Arm A: exp. arm	78	Confusion	2	2=Unlikely	2=unlikely	After EOT
Arm A: exp. arm	78	Generalized muscle weakness	2	2=Unlikely	2=unlikely	After EOT
Arm A: exp. arm	78	Night sweats	1	2=Unlikely	2=unlikely	After EOT
Arm A: exp. arm	78	Infection unspecified	2	2=Unlikely	2=unlikely	After EOT
Arm A: exp. arm	80	Pleural effusion	3	1=Unrelated	1=not related	Treatment 1
Arm A: exp. arm	80	Dyspnea	3	1=Unrelated	1=not related	Treatment 2
Arm A: exp. arm	82	Pain unspecified	3	1=Unrelated	1=not related	Treatment 1
Arm A: exp. arm	82	Lung infection	2	4=Probable	1=not related	After EOT
Arm A: exp. arm	85	Muskuloskeletal pain	2	1=Unrelated	1=not related	After EOT
Arm A: exp. arm	85	Aphasia	3	1=Unrelated	1=not related	After EOT
Arm A: exp. arm	86	Vertigo	1	2=Unlikely	2=unlikely	Treatment 1
Arm A: exp. arm	86	Mucositis	3	3=Possible	3=possible	Treatment 1
Arm A: exp. arm	88	Alanine aminotransferase increased	3	1=Unrelated	4=probable	Treatment 1
Arm A: exp. arm	88	Blood bilirubin increased	2	1=Unrelated	4=probable	Treatment 1
Arm A: exp. arm	88	Asparate aminotransferase increased	3	1=Unrelated	4=probable	Treatment 1

Table 20: *(continued)*

Arm	Patnr	Event	Grade	Rel. to Ev.	Rel. to Paz.	Time
Arm A: exp. arm	88	Muskuloskeletal pain	3	1=Unrelated	1=not related	Treatment 1
Arm A: exp. arm	88	Urinary frequency	1	1=Unrelated	1=not related	Treatment 1
Arm A: exp. arm	88	Muskuloskeletal pain	3	1=Unrelated	1=not related	Treatment 1
Arm A: exp. arm	88	Urinary frequency	1	1=Unrelated	1=not related	Treatment 1
Arm A: exp. arm	91	Hepatotoxicity	3	1=Unrelated	4=probable	After EOT
Arm A: exp. arm	98	Asparate aminotransferase increased	3		3=possible	Treatment 1
Arm A: exp. arm	98	Alanine aminotransferase increased	3		3=possible	Treatment 1
Arm A: exp. arm	98	Pancreatitis	2			Treatment 1
Arm B: comp. arm	2	Alanine aminotransferase increased	3	1=Unrelated	4=probable	Treatment 1
Arm B: comp. arm	2	Acute coronary syndrome	3	2=Unlikely	1=not related	Treatment 2
Arm B: comp. arm	4	Fever	3	1=Unrelated	3=possible	Treatment 1
Arm B: comp. arm	6	Pain unspecified (progressive pain)	3	5=Certain		Treatment 2
Arm B: comp. arm	6		2			Treatment 2
Arm B: comp. arm	8	Fever	1		1=not related	After EOT
Arm B: comp. arm	8	Hemoptysis	1		3=possible	After EOT
Arm B: comp. arm	9	Fatique	2	3=Possible	1=not related	Treatment 2
Arm B: comp. arm	9	Hypercalcemia	3	3=Possible	3=possible	Treatment 2
Arm B: comp. arm	9	Hypophosphatemia	3	3=Possible	1=not related	Treatment 2
Arm B: comp. arm	13	Dyspnea	3	1=Unrelated		Treatment 2
Arm B: comp. arm	13	Muskuloskeletal pain	2	2=Unlikely		Treatment 2
Arm B: comp. arm	13	Diarrhea	3	3=Possible		Treatment 2
Arm B: comp. arm	13	Dyspnea	2	1=Unrelated		Treatment 2
Arm B: comp. arm	16	Dehydration	3		4=probable	Treatment 1
Arm B: comp. arm	16	Hypotension	3		4=probable	Treatment 1
Arm B: comp. arm	16	Dehydration	3		4=probable	Treatment 1
Arm B: comp. arm	16	Hypotension	3		4=probable	Treatment 1
Arm B: comp. arm	16	Urinary tract obstruction	3		3=possible	Treatment 1
Arm B: comp. arm	18	Neuropathy	3		2=unlikely	Treatment 1
Arm B: comp. arm	18	Constipation	3		1=not related	Treatment 1
Arm B: comp. arm	18	Colonic perforation	5		3=possible	Treatment 1
Arm B: comp. arm	21	Hemoptysis	2	1=Unrelated	3=possible	Treatment 1
Arm B: comp. arm	23	Dyspnea	1	2=Unlikely	2=unlikely	Treatment 1
Arm B: comp. arm	23	Anemia	3	3=Possible		Treatment 2
Arm B: comp. arm	23	Anemia	2	3=Possible		Treatment 2
Arm B: comp. arm	26	Hepatitis	3	1=Unrelated	5=definite	After EOT
Arm B: comp. arm	29	Alanine aminotransferase increased	3	1=Unrelated	4=probable	Treatment 1
Arm B: comp. arm	29	Asparate aminotransferase increased	3	1=Unrelated	4=probable	Treatment 1
Arm B: comp. arm	29	Dyspnea	2	3=Possible		Treatment 2
Arm B: comp. arm	29	Abdominal pain	2	2=Unlikely		After EOT
Arm B: comp. arm	30	Muskuloskeletal pain	3	1=Unrelated		Treatment 2

Table 20: *(continued)*

Arm	Patnr	Event	Grade	Rel. to Ev.	Rel. to Paz.	Time
Arm B: comp. arm	30		3	4=Probable		Treatment 2
Arm B: comp. arm	30	Acute kidney injury	3	4=Probable		Treatment 2
Arm B: comp. arm	35	Hypertension	3	1=Unrelated	5=definite	Treatment 1
Arm B: comp. arm	35	Pain unspecified (pain (tumor related))	3	1=Unrelated	1=not related	After EOT
Arm B: comp. arm	40			1=Unrelated		Treatment 1
Arm B: comp. arm	40		3	1=Unrelated	3=possible	Treatment 1
Arm B: comp. arm	47	Dysphagia	3	1=Unrelated	2=unlikely	Treatment 1
Arm B: comp. arm	47	Dysphagia	5	1=Unrelated	2=unlikely	After EOT
Arm B: comp. arm	48	Urinary tract infection	3		1=not related	After EOT
Arm B: comp. arm	48	Progressive disease	3		1=not related	After EOT
Arm B: comp. arm	51	Abdominal pain	3	1=Unrelated	4=probable	Baseline
Arm B: comp. arm	51	Vomiting	2	1=Unrelated	4=probable	Baseline
Arm B: comp. arm	51	Diarrhea	1	1=Unrelated	4=probable	Baseline
Arm B: comp. arm	51	Seizure	2	1=Unrelated	1=not related	Treatment 1
Arm B: comp. arm	51	Pancreatitis	3	1=Unrelated	4=probable	Treatment 1
Arm B: comp. arm	51	Pain abdomen	2	1=Unrelated	4=probable	Treatment 1
Arm B: comp. arm	51	Pancreatitis	2	1=Unrelated	4=probable	Treatment 1
Arm B: comp. arm	53	Dyspnea	2	1=Unrelated	1=not related	Treatment 1
Arm B: comp. arm	53	Dyspnea	2		1=not related	Treatment 1
Arm B: comp. arm	53	Dyspnea	3	4=Probable	1=not related	Treatment 2
Arm B: comp. arm	53	Pneumonia	2	4=Probable	1=not related	After EOT
Arm B: comp. arm	54	Alanine aminotransferase increased	3	1=Unrelated	3=possible	Treatment 1
Arm B: comp. arm	54	Malaise	4		3=possible	Treatment 1
Arm B: comp. arm	62	Hepatic disorder	3		4=probable	Treatment 1
Arm B: comp. arm	62	Hepatic disorder	3		4=probable	Treatment 1
Arm B: comp. arm	63	Creatinine increased	1			Baseline
Arm B: comp. arm	63	Dehydration	3		1=not related	Baseline
Arm B: comp. arm	63	Dehydration	3		1=not related	Baseline
Arm B: comp. arm	63	Asparate aminotransferase increased	3		5=definite	Treatment 1
Arm B: comp. arm	63	Alanine aminotransferase increased	3		5=definite	Treatment 1
Arm B: comp. arm	63	Gammaglutamyltransferase increased	3		4=probable	Treatment 1
Arm B: comp. arm	63	central venous a (unclear)	2	2=Unlikely	1=not related	Treatment 2
Arm B: comp. arm	68	Asparate aminotransferase increased	3	1=Unrelated	4=probable	Treatment 1
Arm B: comp. arm	68	Alanine aminotransferase increased	3	1=Unrelated	4=probable	Treatment 1
Arm B: comp. arm	68		3	1=Unrelated	1=not related	Treatment 2
Arm B: comp. arm	68		3	4=Probable	1=not related	After EOT
Arm B: comp. arm	74	Dehydration	3	1=Unrelated	4=probable	Treatment 1
Arm B: comp. arm	77	Alanine aminotransferase increased	3		3=possible	Treatment 1

Table 20: *(continued)*

Arm	Patnr	Event	Grade	Rel. to Ev.	Rel. to Paz.	Time
Arm B: comp. arm	77	Asparate aminotransferase increased	3		3=possible	Treatment 1
Arm B: comp. arm	77	Gammaglutamyltransferase increased	1		3=possible	Treatment 1
Arm B: comp. arm	77	Blood lactic dehydrogenase increased	1		3=possible	Treatment 1
Arm B: comp. arm	84	Diarrhea	3	1=Unrelated	2=unlikely	After EOT
Arm B: comp. arm	84	Thromboembolic event	5	1=Unrelated	2=unlikely	After EOT
Arm B: comp. arm	87	Amnesia	2	1=Unrelated	2=unlikely	Treatment 1
Arm B: comp. arm	87	Alanine aminotransferase increased	3	1=Unrelated	5=definite	Treatment 1
Arm B: comp. arm	87	Asparate aminotransferase increased	3	1=Unrelated	5=definite	Treatment 1
Arm B: comp. arm	87	Gammaglutamyltransferase increased	3	1=Unrelated	5=definite	Treatment 1
Arm B: comp. arm	90	Asparate aminotransferase increased	3	1=Unrelated	5=definite	Treatment 1
Arm B: comp. arm	90	Alanine aminotransferase increased	3	1=Unrelated	5=definite	Treatment 1
Arm B: comp. arm	90	Blood bilirubin increased	2	1=Unrelated	5=definite	Treatment 1
Arm B: comp. arm	90	Urine output decrease	3	1=Unrelated	1=not related	After EOT
Arm B: comp. arm	90	Fever	1	1=Unrelated	3=possible	After EOT
Arm B: comp. arm	90	Urinary tract infection	3	1=Unrelated	1=not related	After EOT
Arm B: comp. arm	90	Delirium	2	1=Unrelated	1=not related	After EOT
Arm B: comp. arm	92	Arterial injury	1	1=Unrelated	1=not related	Baseline
Arm B: comp. arm	92	Heart failure	2	2=Unlikely	1=not related	Treatment 2
Arm B: comp. arm	94	Abdominal pain	3		1=not related	Treatment 1
Arm B: comp. arm	94	Stomach pain	3		1=not related	Treatment 1
Arm B: comp. arm	94	Muskuloskeletal pain	3		1=not related	Treatment 1
Arm B: comp. arm	97	Vertigo	2	1=Unrelated	3=possible	Treatment 1
Arm B: comp. arm	97	Disturbed vision	2	1=Unrelated	3=possible	Treatment 1
Arm B: comp. arm	99	Pneumonia	3		3=possible	Treatment 1
Arm B: comp. arm	100	Pain unspecified (pain)	3		1=not related	Treatment 1
Arm B: comp. arm	100	Fever	2		1=not related	Treatment 1

Table 21: All adverse events of patients experiencing a grade 5 adverse event

Arm	Patnr	Event	Grade	Rel. to Ev.	Rel. to Paz.	Time
Arm A: exp. arm	12	Dyspnea	5		2=unlikely	Treatment 1
Arm A: exp. arm	12	Thoracic pain	3		2=unlikely	Treatment 1
Arm A: exp. arm	12	Empyema	4		2=unlikely	Treatment 1
Arm A: exp. arm	12	Anorexia	3		1=not related	Treatment 1
Arm A: exp. arm	12	Disturbed vision	2		1=not related	Treatment 1
Arm A: exp. arm	12	Pneumonia	3	2=Unlikely		Treatment 1
Arm A: exp. arm	12	Chronic obstructive pulmonary disease	3	2=Unlikely		Treatment 1

Table 21: *(continued)*

Arm	Patnr	Event	Grade	Rel. to Ev.	Rel. to Paz.	Time
Arm A: exp. arm	17	Fatique	2	1=Unrelated	4=probable	Treatment 1
Arm A: exp. arm	17	Vomiting	1	1=Unrelated	2=unlikely	Treatment 1
Arm A: exp. arm	17	Constipation	1	1=Unrelated	1=not related	Treatment 1
Arm A: exp. arm	17	Muskuloskeletal pain	2	2=Unlikely	1=not related	Treatment 1
Arm A: exp. arm	17	Nausea	2	1=Unrelated	1=not related	Treatment 1
Arm A: exp. arm	17	Anorexia	3	1=Unrelated	1=not related	Treatment 1
Arm A: exp. arm	17	Diarrhea	2	3=Possible	1=not related	Treatment 1
Arm A: exp. arm	17	Gammaglutamyltransferase increased	3	1=Unrelated	1=not related	Treatment 1
Arm A: exp. arm	17	Cerebral hemorrhage	5	1=Unrelated	1=not related	Treatment 1
Arm B: comp. arm	18	Neuropathy	3		2=unlikely	Treatment 1
Arm B: comp. arm	18	Pain unspecified (pain)	3		1=not related	Treatment 1
Arm B: comp. arm	18	Constipation	3		1=not related	Treatment 1
Arm B: comp. arm	18	Stomatitis	2		3=possible	Treatment 1
Arm B: comp. arm	18	Rash unspecified	1		3=possible	Treatment 1
Arm B: comp. arm	18	Colonic perforation	5		3=possible	Treatment 1
Arm B: comp. arm	18	Abdominal infection	4		1=not related	Treatment 1
Arm B: comp. arm	18	Gammaglutamyltransferase increased	2		4=probable	After EOT
Arm B: comp. arm	47	Vomiting	1	1=Unrelated	2=unlikely	Treatment 1
Arm B: comp. arm	47	Fatique	2	1=Unrelated	3=possible	Treatment 1
Arm B: comp. arm	47	Weight loss	1	1=Unrelated	3=possible	Treatment 1
Arm B: comp. arm	47	Dysphagia	5	1=Unrelated	2=unlikely	After EOT
Arm B: comp. arm	84	Nausea	2	1=Unrelated	3=possible	Treatment 1
Arm B: comp. arm	84	Diarrhea	3	1=Unrelated	2=unlikely	After EOT
Arm B: comp. arm	84	Hypokalemia	3	1=Unrelated	2=unlikely	After EOT
Arm B: comp. arm	84	Thromboembolic event	5	1=Unrelated	2=unlikely	After EOT

8 Quality of Life

We present plots of the three main outcome measures: FKSI-DRS symptom scale, Physical Functioning according to QLQ-C30 and Quality of Life according to QLQ-C30. Development over time of these scales for each individual patient, as well as summary plots for the other QOL-measures are plotted in the appendix. Here we present summary measures for development over time as well as Kaplan-Meier plots of time to definitive deterioration.

FKSI

Figure 1 depicts the development of the FKSI-DRS symptom scale over time during the first line of treatment. Scores range form 0 to 36 and are the sum of the scores on the 9 individual symptom outcome scales.

The picture is constructed as follows. First, for each patient a curve following the development of the FKSI score over time is constructed as in the appendix (section 14) by linearly interpolating the measured FKSI-scores. (When the first FKSI-measurement of a patient takes place during the first treatment cycle, the FKSI-score from the start of treatment until the first measurement is imputed as being constant on the first measured value.)

Next for each patient and each treatment cycle the average FKSI score of that patient during that cycle is computed by taking the area under the curve between the start date and end date of the cycle and dividing that number by the duration of the cycle (typically 8 weeks).

It are these averages per cycle per patient that are plotted in figure 1: for each cycle number the distributions of the scores of the patients in each arm are plotted in the box-and-whisker plot, while the means of these scores are connected by the solid lines.

Only patients that had treatment cycle n during their *first line* of treatment contribute to the boxplots and averages above treatment n in the plot. The number of these patients in each arm are given at the bottom of the plot. A similar plot taking in account all QOL-data, irrespective of the study period they were measured (i.e. during first line of treatment, during second line or after end of treatment) is given in the appendix (figure 43.)

Figures 2 and 3 present Kaplan-Meier curves for the time since randomization to first deterioration or definitive deterioration of quality of life as measured by the FKSI-DRS scale. Here deterioration means a FKSI-score that is more than 20% below the FKSI score measured at (or closest in time to) baseline for the same patient. A deterioration is considered *definitive* if there are no later QOL-measurement for the patient at which the FKSI-scale is back up at baseline level or above.

Of course not all patients will experience a deterioration, which is why we use the Kaplan-Meier technique to estimate the time to deteriorations: patient who do not experience a (definitive) deterioration are censored at the time of their last QOL-measurement.

By contrast, patients that reported a FKSI-DRS score of 0 at baseline and hence have no way to deteriorate any further are excluded from the curves.

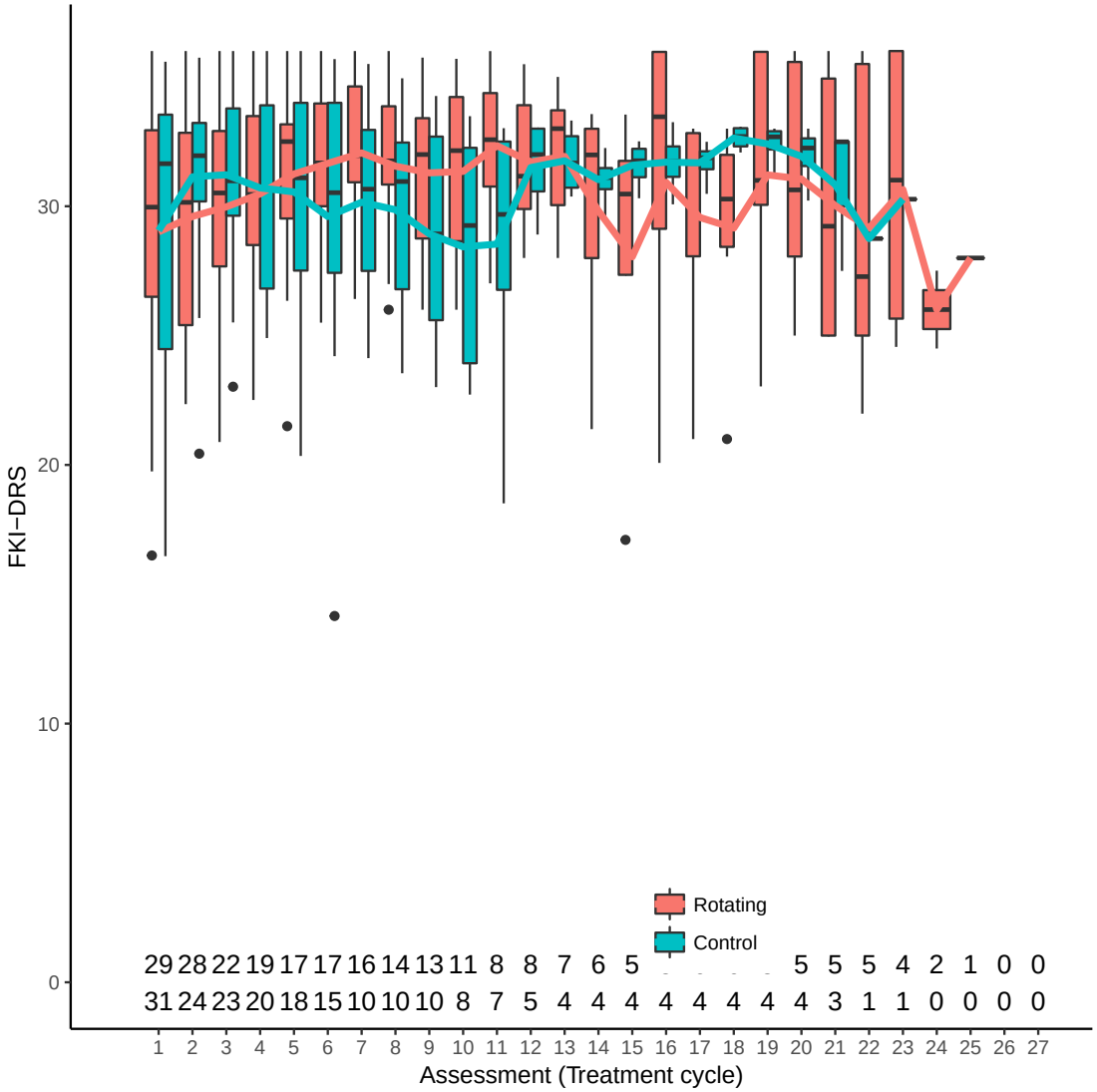


Figure 1: Development of the FKSI-DRS symptom scale over the treatment cycles during first line treatment. Scores range form 0 to 36 and are the sum of the scores on the 9 individual symptom outcome. At cycle boxplots describing the distribution of the scores of the patients in each arm as well as the means (line) of these scores is plotted. The bold black line in the middle of the boxplot indicates the median. Higher score corresponds to better quality of life.

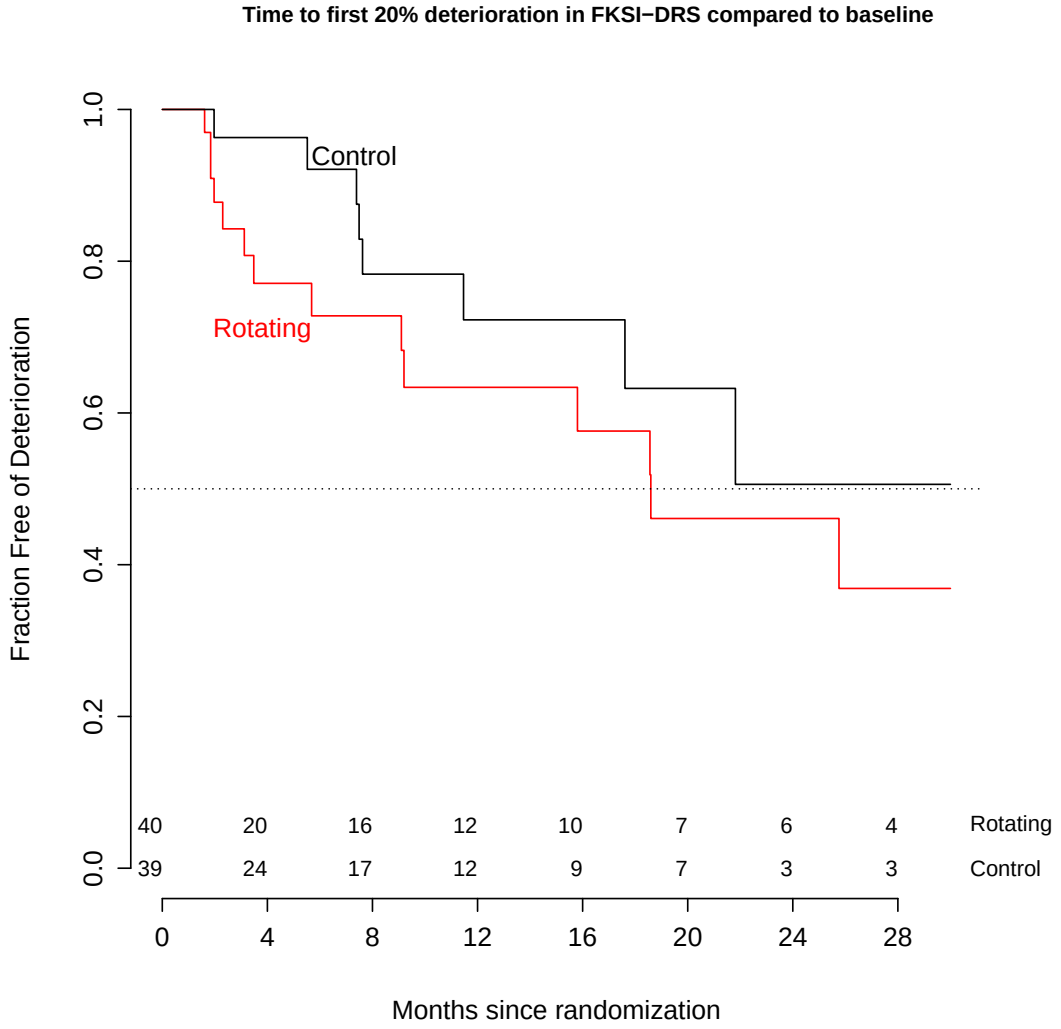


Figure 2: Time to first 20% deterioration in FKSI by arm

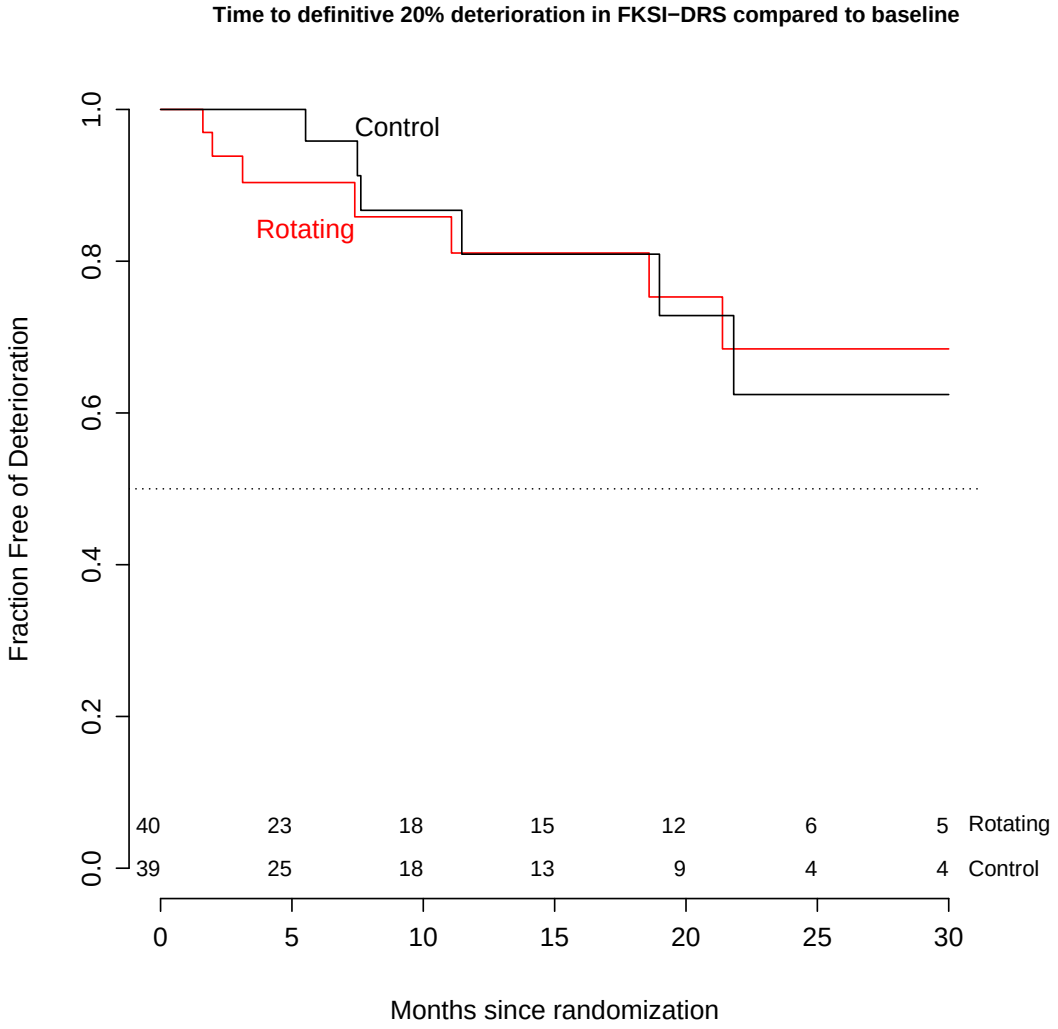


Figure 3: Time to definitive 20% deterioration in FKSI by arm

Physical Functioning

The plots in this section are constructed in the same way as those in the previous section, but using the Physical Functioning (PF) scale of the QLQ-C30 questionnaire rather than the FKSI.

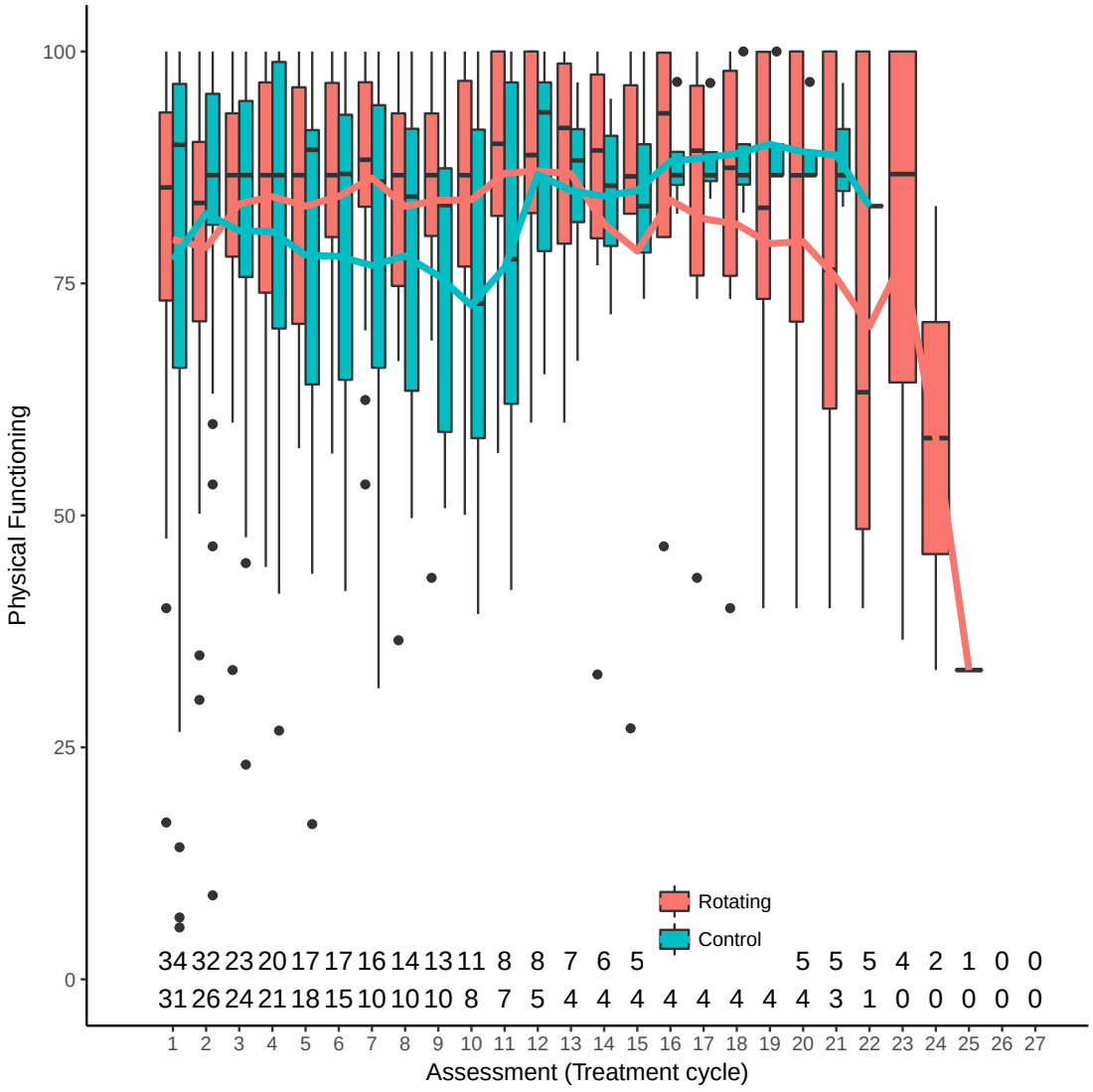


Figure 4: Development of the QLQ-C30 PF scale over time. Scores range form 0 to 100 and are based on the scores on 5 individual questions. At each cycle box and whisker plots describing the distribution of the scores of the patients in each arm as well as the means (line) of these scores is plotted. Higher score corresponds to better quality of life.

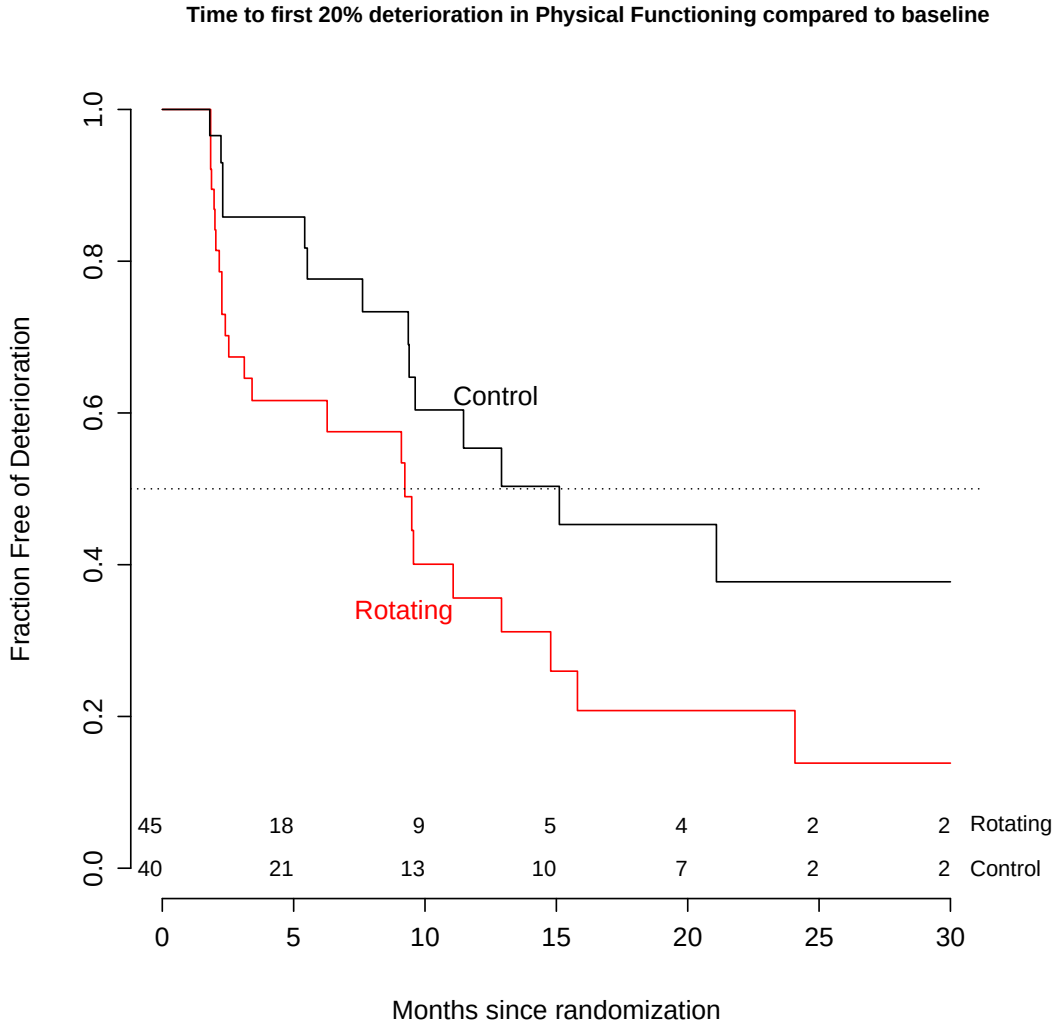


Figure 5: Time to first 20% deterioration in Physical Functioning according to the QLQ-C30 by arm

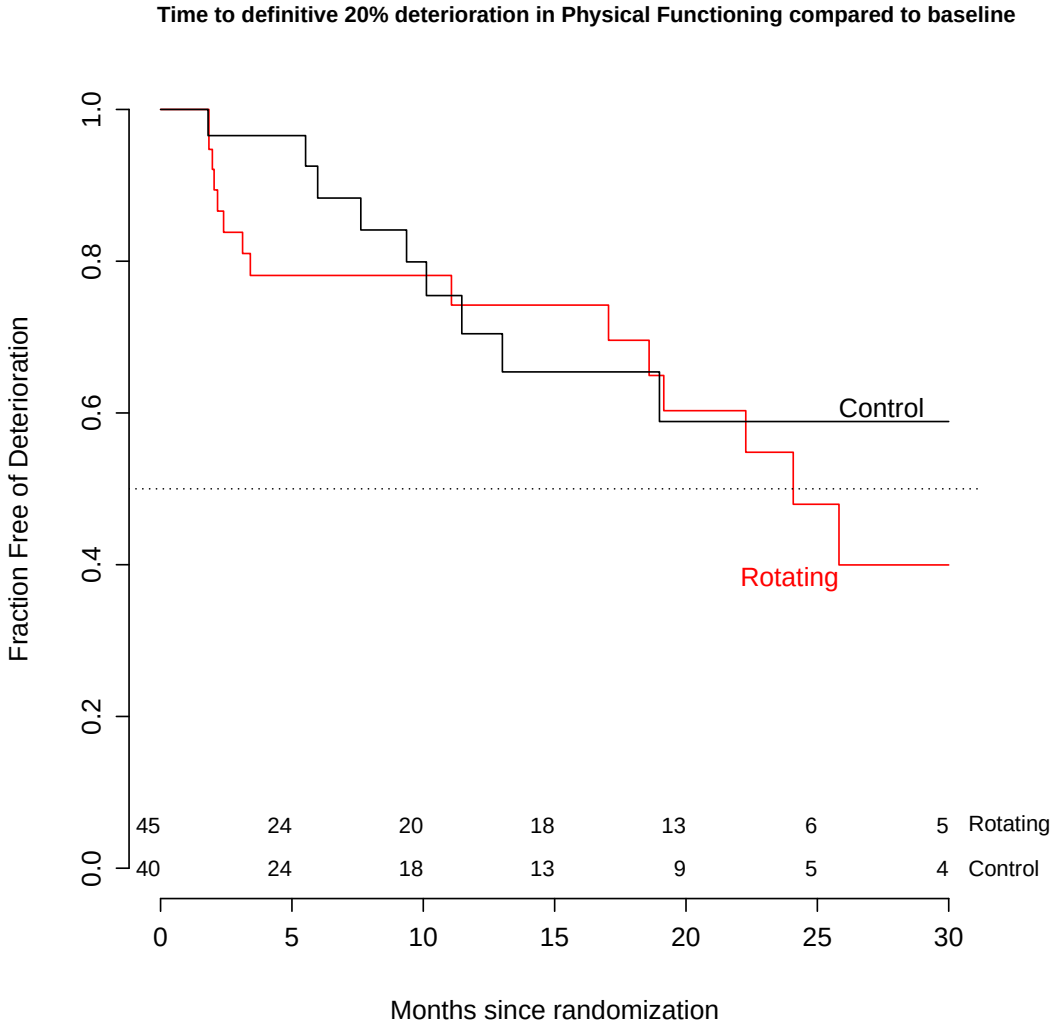


Figure 6: Time to definitive 20% deterioration in Physical Functioning according to the QLQ-C30 by arm

Overall QOL

At each QLQ-C30 questionnaire there are two question asking the patients directly to rate their overall health and overall quality of life on a 7 point scale. Combined and re-scaled to a 0-100 scale in compliance with the QLQ-C30 scoring manual we obtain the so called QL scale of the QLQ-C30, which is plotted in the figures of this section in the same way we plotted the FKSI and PF scores before.

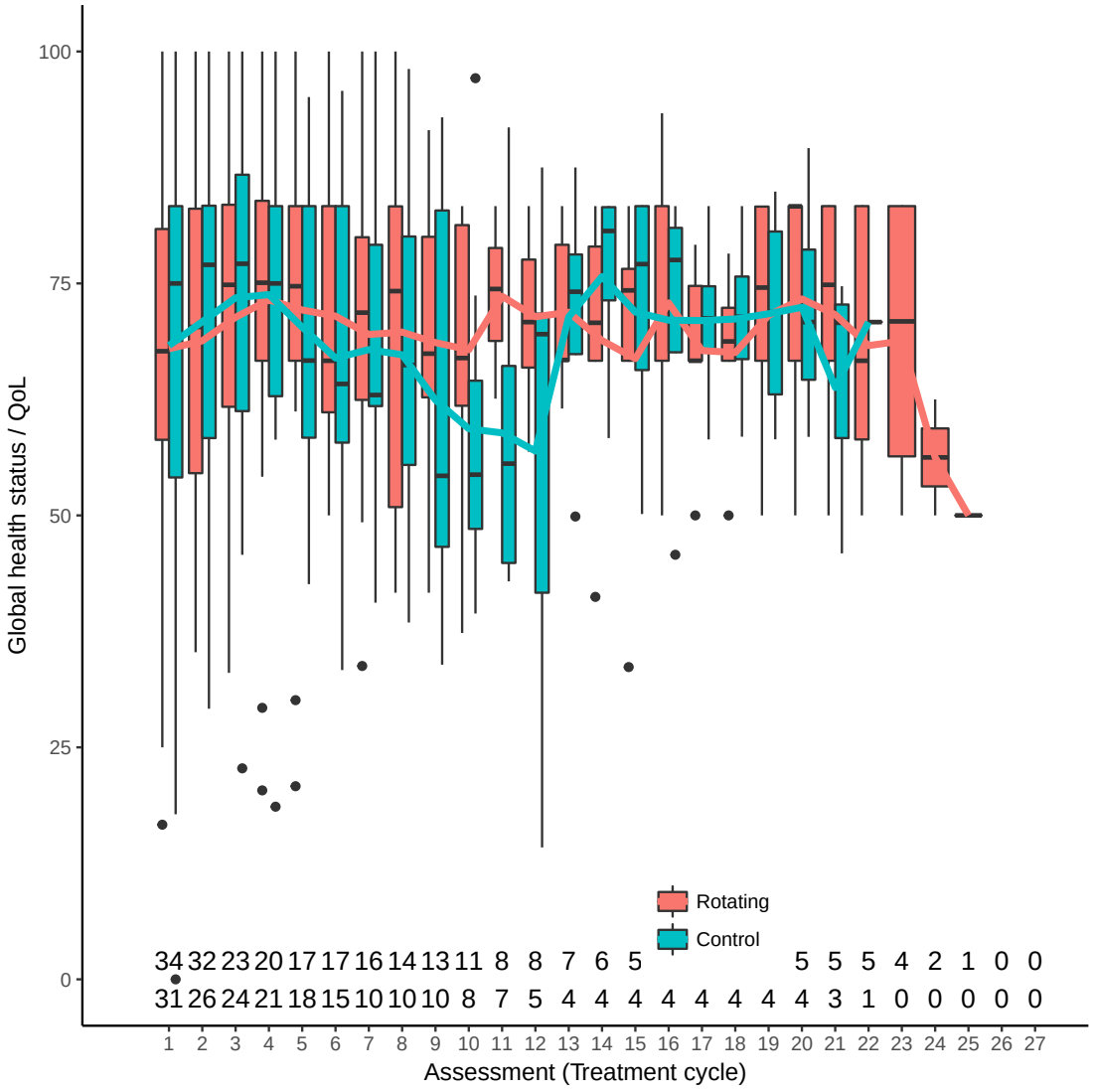


Figure 7: Development of the QLQ-C30 QL scale over time. Scores range form 0 to 100 and are based on the scores on 2 questions. At each month since randomization box and whisker plots describing the distribution of the scores of the patients in each arm as well as the means (line) of these scores is plotted. Higher score corresponds to better quality of life.

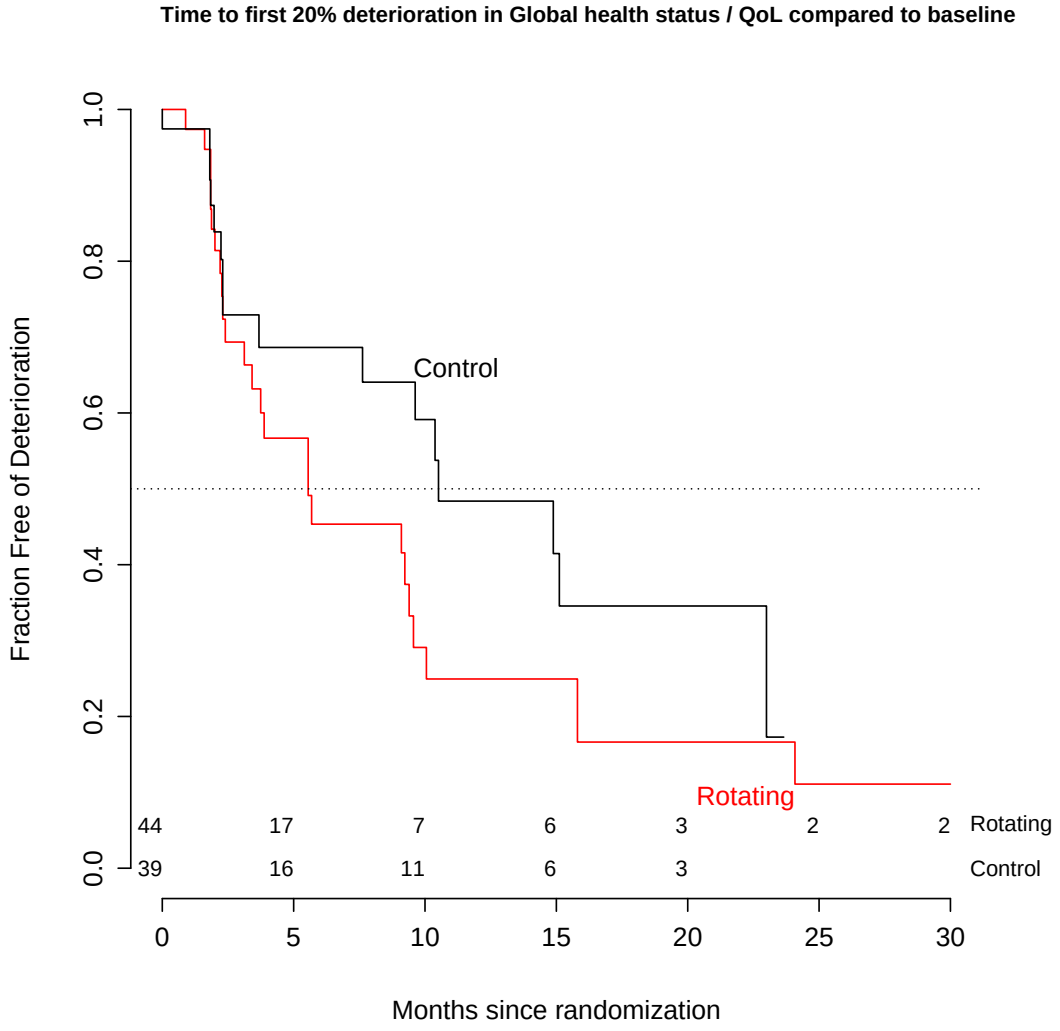


Figure 8: Time to first 20% deterioration in QLQ-C30 QL score by arm

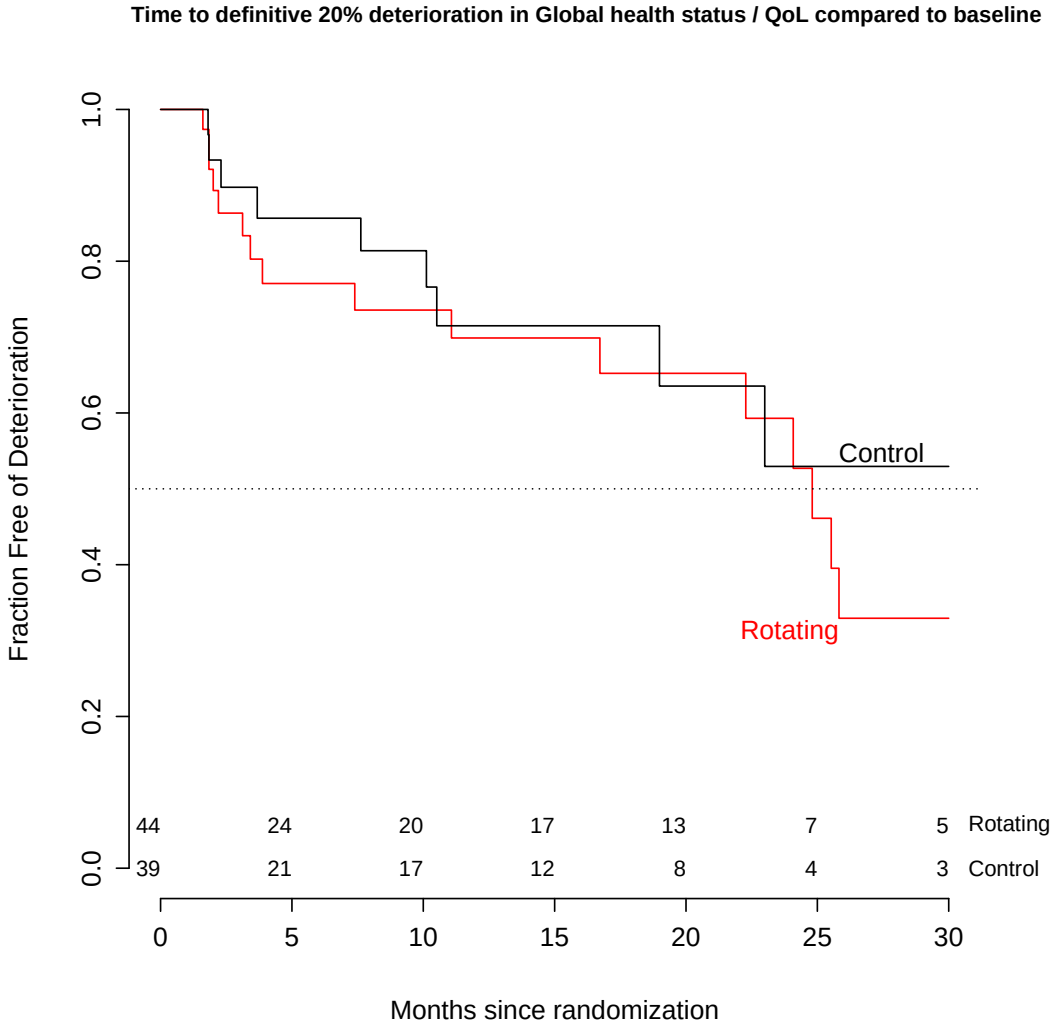


Figure 9: Time to definitive 20% deterioration in QLQ-C30 QL score by arm

9 Survival

Causes of death

Table 22: Causes of death

Arm	Patnr	Cause of death	Specification
3	Arm A: experimental arm		
5	Arm A: experimental arm		
7	Arm A: experimental arm	1=Progressive disease	
10	Arm A: experimental arm	1=Progressive disease	
11	Arm A: experimental arm	8=Other	euthanasia
12	Arm A: experimental arm	8=Other	Dyspnoe, COPD, lung problems
14	Arm A: experimental arm	1=Progressive disease	
15	Arm A: experimental arm		
17	Arm A: experimental arm	8=Other	intra cerebral bleedingintra cerebral bleeding
19	Arm A: experimental arm	1=Progressive disease	
20	Arm A: experimental arm	1=Progressive disease	
24	Arm A: experimental arm		
25	Arm A: experimental arm	1=Progressive disease	
27	Arm A: experimental arm		
31	Arm A: experimental arm	1=Progressive disease	
32	Arm A: experimental arm	1=Progressive disease	
33	Arm A: experimental arm	1=Progressive disease	
34	Arm A: experimental arm	1=Progressive disease	
37	Arm A: experimental arm		
38	Arm A: experimental arm		
39	Arm A: experimental arm	1=Progressive disease	
42	Arm A: experimental arm	8=Other	unknown, probably PD
43	Arm A: experimental arm		
44	Arm A: experimental arm	1=Progressive disease	
46	Arm A: experimental arm	1=Progressive disease	
49	Arm A: experimental arm		
50	Arm A: experimental arm		
55	Arm A: experimental arm	8=Other	aspiration pneumonia after bleeding cva
56	Arm A: experimental arm	1=Progressive disease	
57	Arm A: experimental arm		
58	Arm A: experimental arm	1=Progressive disease	
59	Arm A: experimental arm	1=Progressive disease	
60	Arm A: experimental arm		
61	Arm A: experimental arm		
64	Arm A: experimental arm		
66	Arm A: experimental arm		
67	Arm A: experimental arm		
69	Arm A: experimental arm		
71	Arm A: experimental arm	1=Progressive disease	
73	Arm A: experimental arm		
76	Arm A: experimental arm	1=Progressive disease	

Table 22: *(continued)*

Arm	Patnr	Cause of death	Specification
78	Arm A: experimental arm	1=Progressive disease	
80	Arm A: experimental arm	1=Progressive disease	
82	Arm A: experimental arm	1=Progressive disease	
83	Arm A: experimental arm	1=Progressive disease	
85	Arm A: experimental arm	1=Progressive disease	
86	Arm A: experimental arm	1=Progressive disease	
88	Arm A: experimental arm		
89	Arm A: experimental arm	1=Progressive disease	
91	Arm A: experimental arm		
98	Arm A: experimental arm		
101	Arm A: experimental arm		
1	Arm B: comparative arm	1=Progressive disease	
2	Arm B: comparative arm	1=Progressive disease	
4	Arm B: comparative arm		
6	Arm B: comparative arm	1=Progressive disease	
8	Arm B: comparative arm		
9	Arm B: comparative arm	1=Progressive disease	
13	Arm B: comparative arm	3=Toxicity	
16	Arm B: comparative arm		
18	Arm B: comparative arm	3=Toxicity	Perforation colon
21	Arm B: comparative arm	4=Infection	pneumonia, secundair after mediastinal lymphadenopathy
22	Arm B: comparative arm	1=Progressive disease	
23	Arm B: comparative arm	1=Progressive disease	
26	Arm B: comparative arm	1=Progressive disease	
28	Arm B: comparative arm		
29	Arm B: comparative arm	1=Progressive disease	
30	Arm B: comparative arm		
35	Arm B: comparative arm	1=Progressive disease	
36	Arm B: comparative arm		
40	Arm B: comparative arm	1=Progressive disease	
41	Arm B: comparative arm	1=Progressive disease	
45	Arm B: comparative arm	1=Progressive disease	
47	Arm B: comparative arm	1=Progressive disease	
48	Arm B: comparative arm	1=Progressive disease	
51	Arm B: comparative arm		
52	Arm B: comparative arm		
53	Arm B: comparative arm	8=Other	unknown
54	Arm B: comparative arm		
62	Arm B: comparative arm		
63	Arm B: comparative arm	8=Other	epileptic insult
65	Arm B: comparative arm		
68	Arm B: comparative arm	1=Progressive disease	
70	Arm B: comparative arm		
72	Arm B: comparative arm	1=Progressive disease	
74	Arm B: comparative arm	1=Progressive disease	

Table 22: *(continued)*

Arm	Patnr	Cause of death	Specification
75	Arm B: comparative arm		
77	Arm B: comparative arm	1=Progressive disease	
79	Arm B: comparative arm		
81	Arm B: comparative arm		
84	Arm B: comparative arm	3=Toxicity	basilar artery treombosis
87	Arm B: comparative arm	1=Progressive disease	
90	Arm B: comparative arm	1=Progressive disease	
92	Arm B: comparative arm		
93	Arm B: comparative arm	1=Progressive disease	
94	Arm B: comparative arm	1=Progressive disease	unknown
95	Arm B: comparative arm	1=Progressive disease	
96	Arm B: comparative arm	1=Progressive disease	
97	Arm B: comparative arm		
99	Arm B: comparative arm		
100	Arm B: comparative arm	8=Other	respiratory insufficiency with decompensatio cordis and probable progressive pulmonary metastatic disease. Probable heart failure.

Progression free survival

Table 23 lists the number of PFS-events and deaths in each arm. Figure 10 presents the KM-curves for PFS1: time from randomization to first progression or death, whatever comes first. Figure 12 presents the KM-curves for PFS2: time from randomization to second progression or death, whichever comes first. Figure 13 presents the KM-curves for OS and figure 14 describes the time to first progression, where death does not count as an event.

Finally figure 15 depicts PFS2 in a different way: not counting from randomization but from first progression and (hence) for only the patients that had a first progression.

The p-values of stratified and unstratified log-rank tests comparing the arm as well as the Hazard ratio from a Cox proportional hazard model are given in the figures. In all cases the stratified statistics are stratified by MSKCC risk criteria. Patients that did not have the event of interest are censored at the time of last followup.

Table 23: PFS events

	Arm		
	Arm A: experimental arm	Arm B: comparative arm	All
	52	49	101
PFS1 event			
no	16 (31%)	9 (18%)	25 (25%)
yes	36 (69%)	40 (82%)	76 (75%)
PFS2 event			
no	24 (46%)	18 (37%)	42 (42%)
yes	28 (54%)	31 (63%)	59 (58%)
OS event			
no	21 (40%)	17 (35%)	38 (38%)
yes	31 (60%)	32 (65%)	63 (62%)

The KM-estimates of the PFS1 at one year since randomization are $32\%(95\%\text{C.I.}21-49)$ for the control arm and $42\%(95\%\text{C.I.}30-59)$ for the Rotating arm.

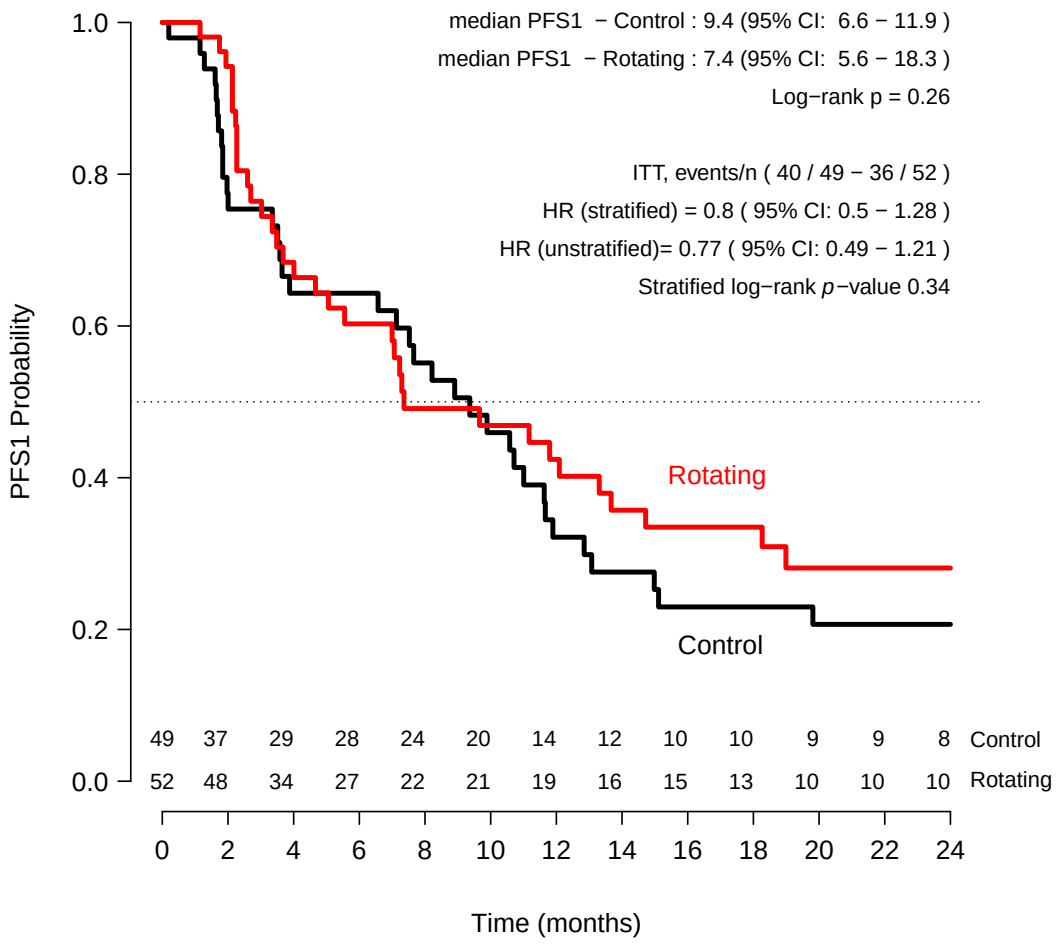


Figure 10: Progression free survival by arm

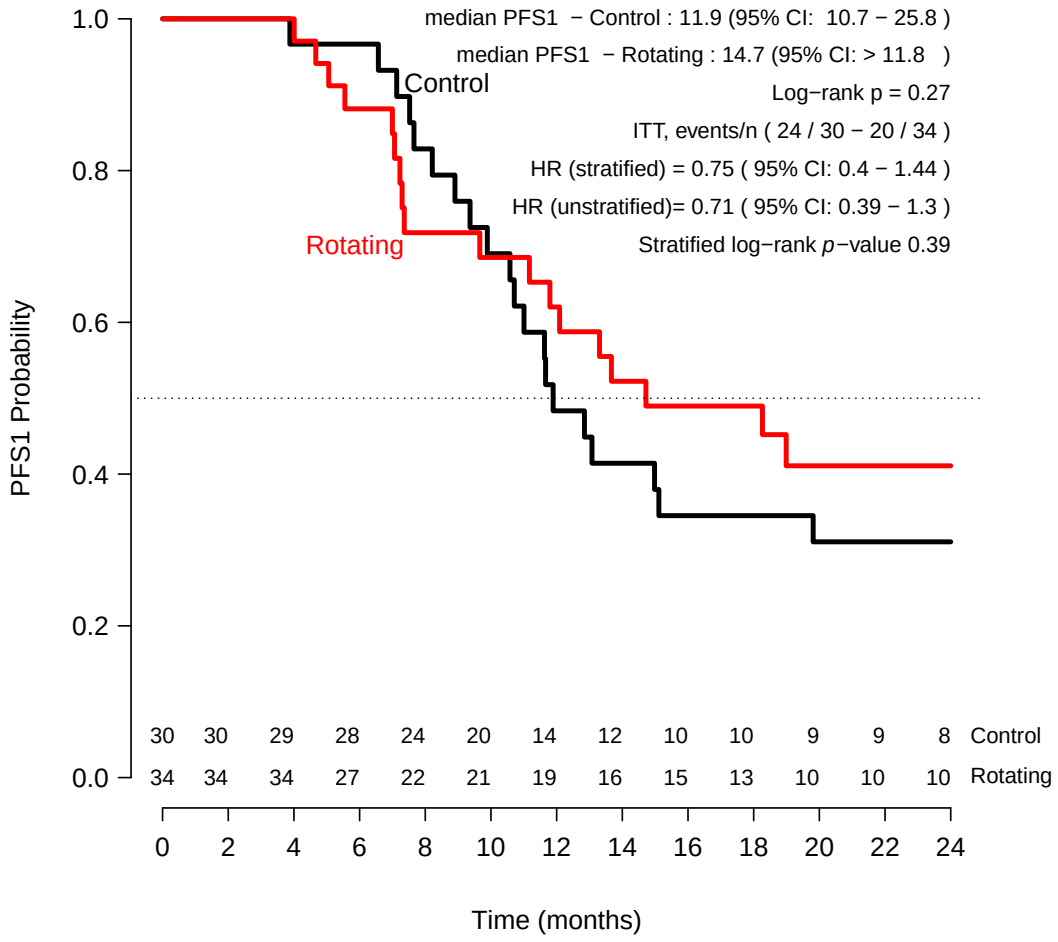


Figure 11: Progression free survival by arm: only patients with at least 16 weeks followup and no event in the first 16 weeks

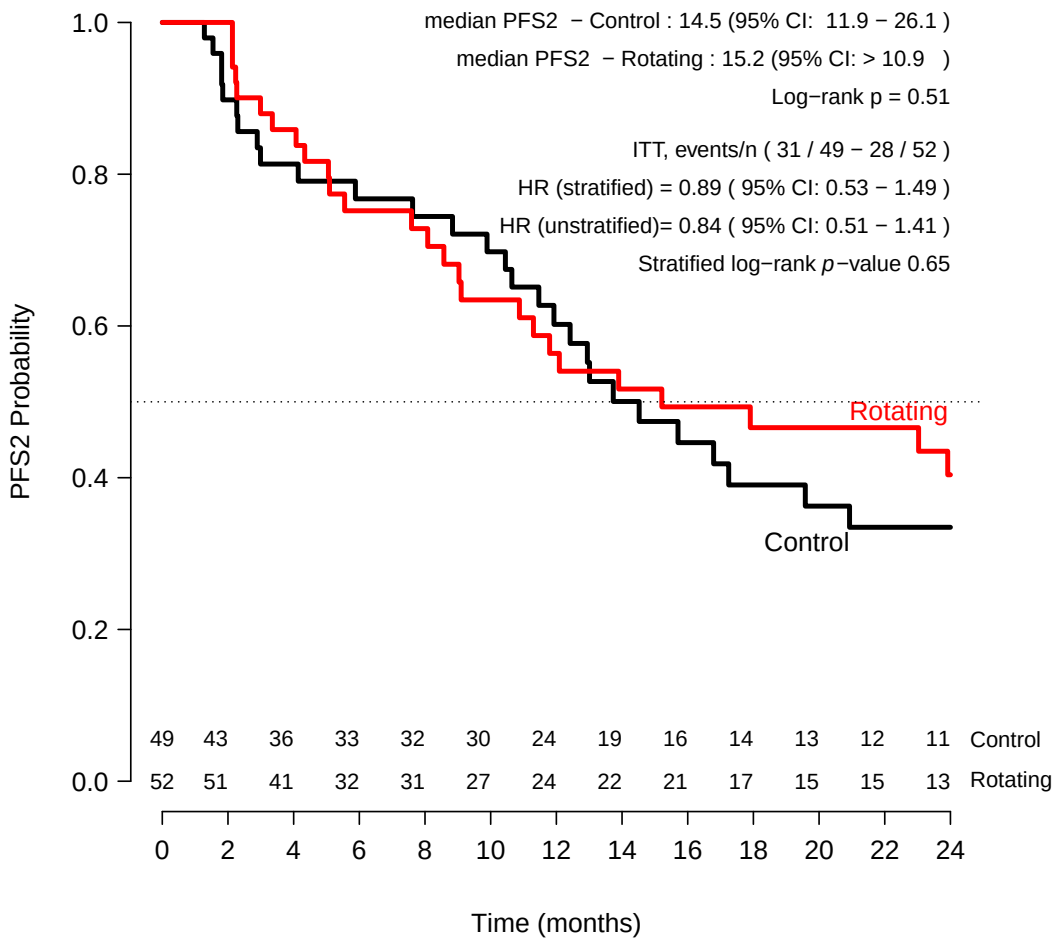
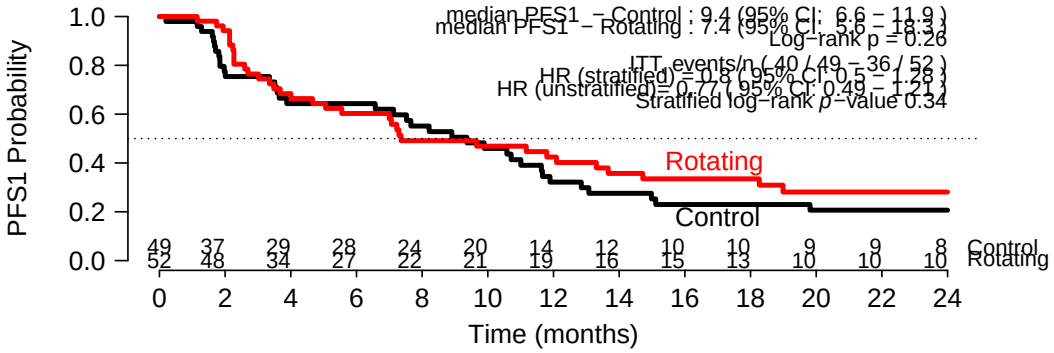
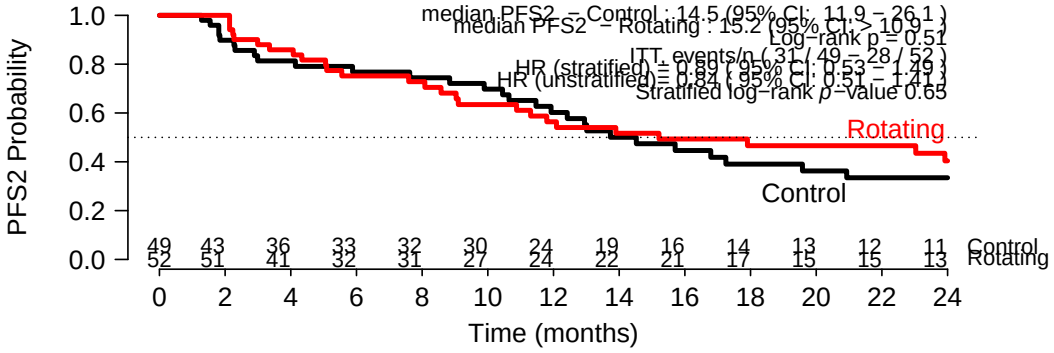


Figure 12: PFS2: time from randomization to second progression or death, by arm


median PFS1 – Control : 9.4 (95% CI: 6.6 – 11.9)
median PFS1 – Rotating : 7.4 (95% CI: 5.6 – 18.3)
Log–rank p = 0.26
ITT events/n (40 / 49 – 36 / 52)
HR (stratified) = 0.8 (95% CI: 0.5 – 1.28)
HR (unstratified) = 0.77 (95% CI: 0.49 – 1.21)
Stratified log–rank p–value 0.34
PFS1 Probability
1.0
0.8
0.6
0.4
0.2
0.0
Rotating
Control
49 37 29 28 24 20 14 12 10 10 9 9 8 Control
52 48 34 27 22 21 19 16 15 13 10 10 10 Rotating
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (months)


median PFS2 – Control : 14.5 (95% CI: 11.9 – 26.1)
median PFS2 – Rotating : 15.2 (95% CI: > 10.9)
Log–rank p = 0.51
ITT events/n (31 / 49 – 28 / 52)
HR (stratified) = 0.89 (95% CI: 0.53 – 1.49)
HR (unstratified) = 0.84 (95% CI: 0.51 – 1.41)
Stratified log–rank p–value 0.65
PFS2 Probability
1.0
0.8
0.6
0.4
0.2
0.0
Rotating
Control
49 43 36 33 32 30 24 19 16 14 13 12 11 Control
52 51 41 32 31 27 24 22 21 17 15 15 13 Rotating
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (months)

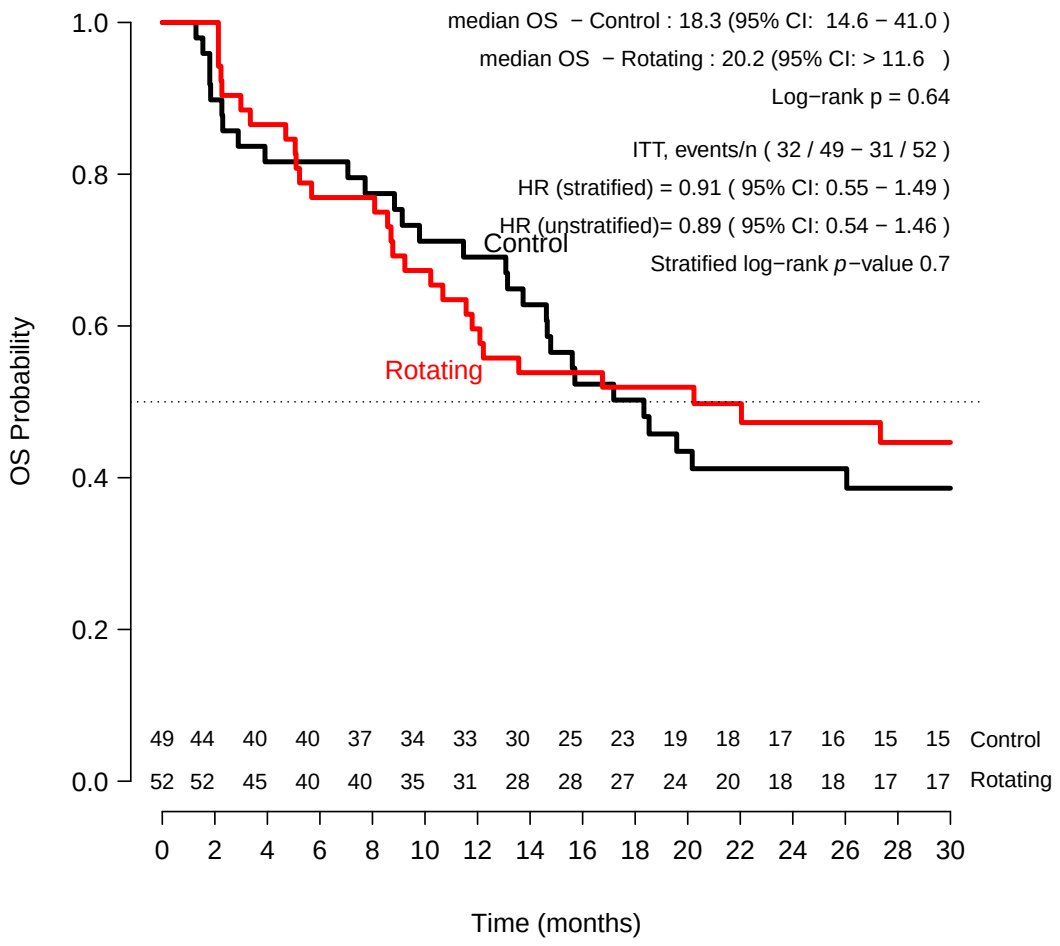


Figure 13: Overall survival by arm

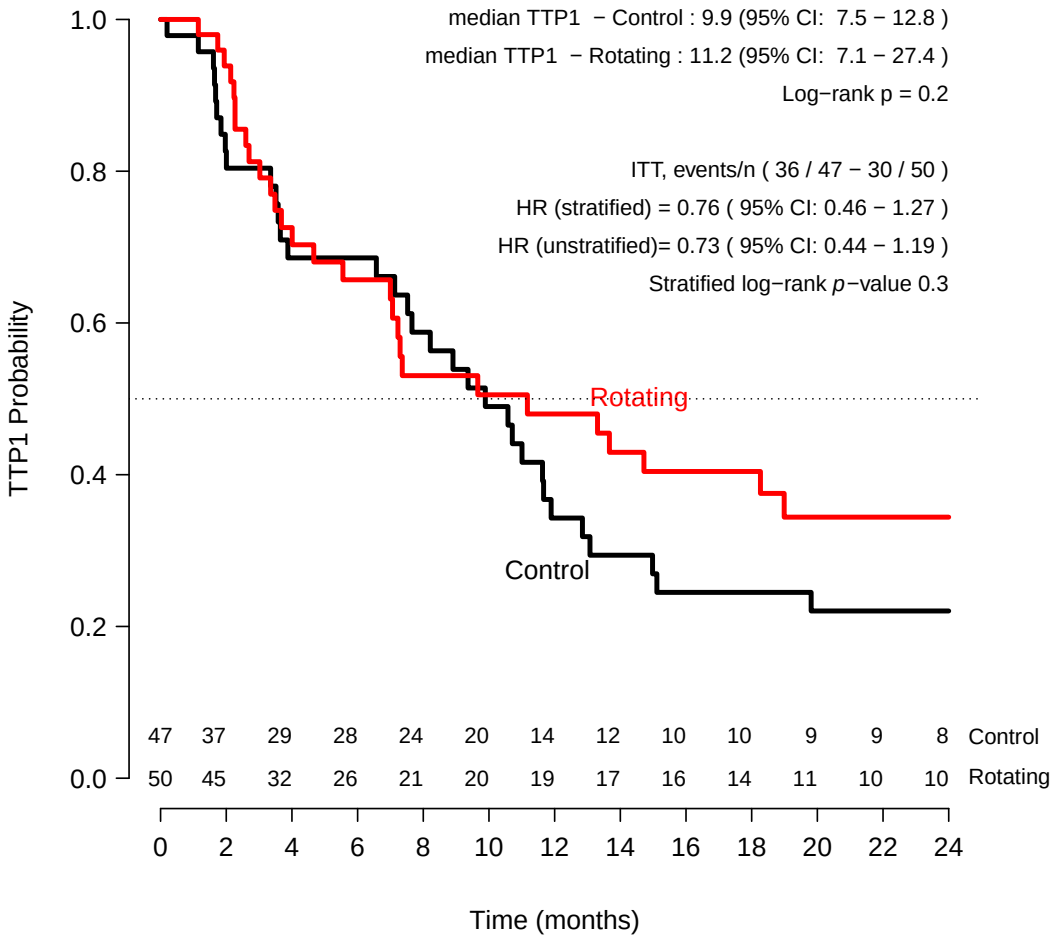


Figure 14: Time to first progression by arm

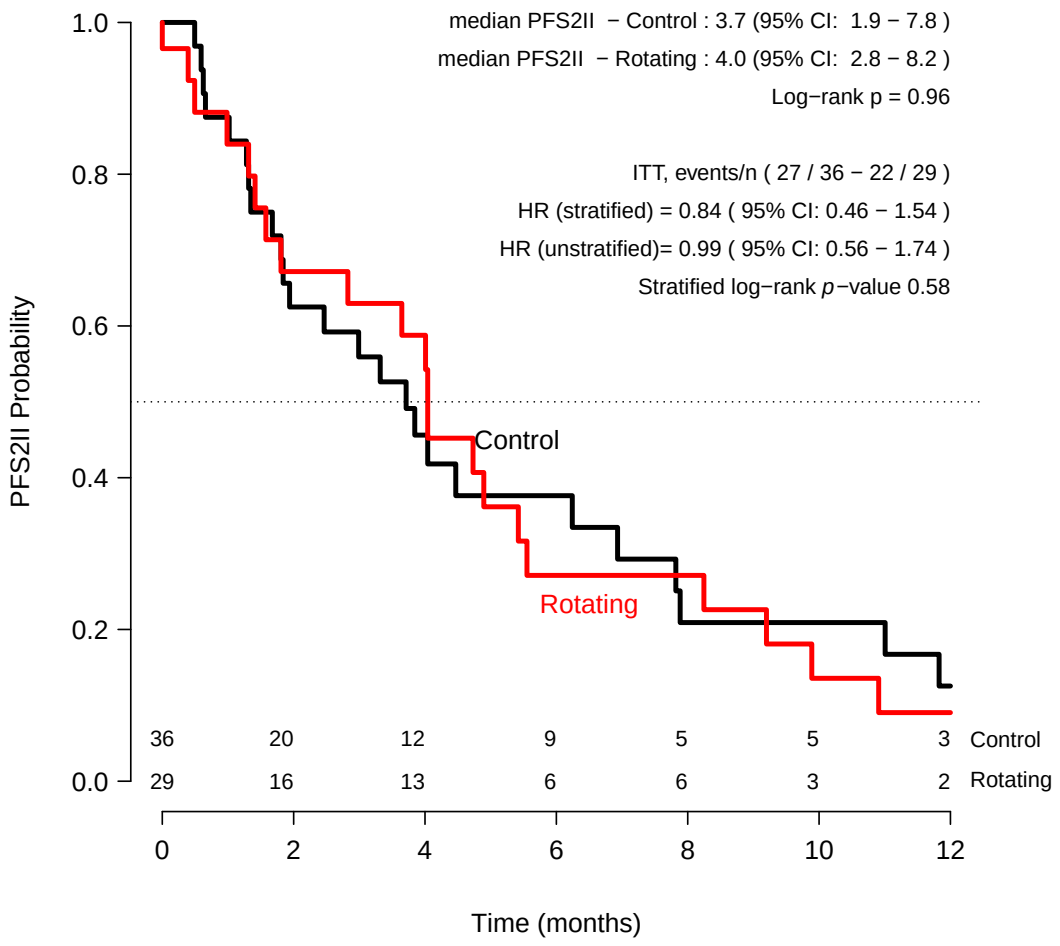


Figure 15: PFS2B (by lack of a better name): time from first progression to second progression or death, by arm

Subgroup analyses

The following forest-plots consider the influence on progression free and overall survival of the stratification factor (Memorial Sloan Kettering Cancer Center risk criteria) as well of other factor expected to be of interest.

In the forest-plots, for each category within the factors, the number of events per arm and the totals per arm are shown. When there is information missing it is indicated between brackets. Next to the numbers, the hazard ratio (HR) is given together with a 99% confidence interval. The area of the square is proportional to the weight given to the category (number of events). The diamond at the bottom corresponds to the overall effect and includes the 95% confidence interval.

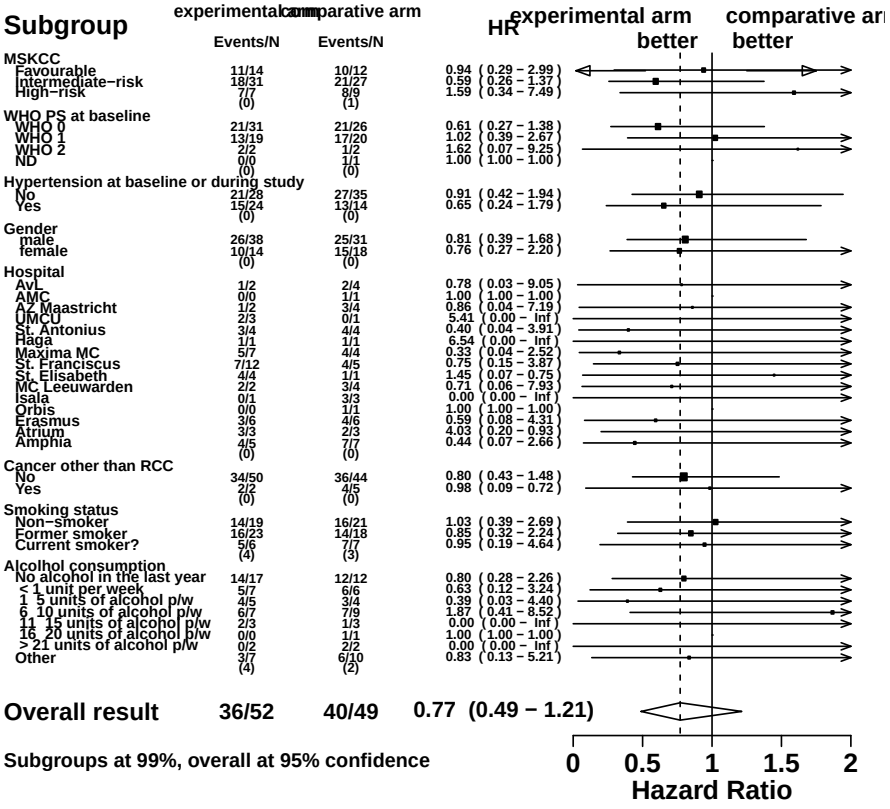


Figure 16: Subgroup analysis for PFS1

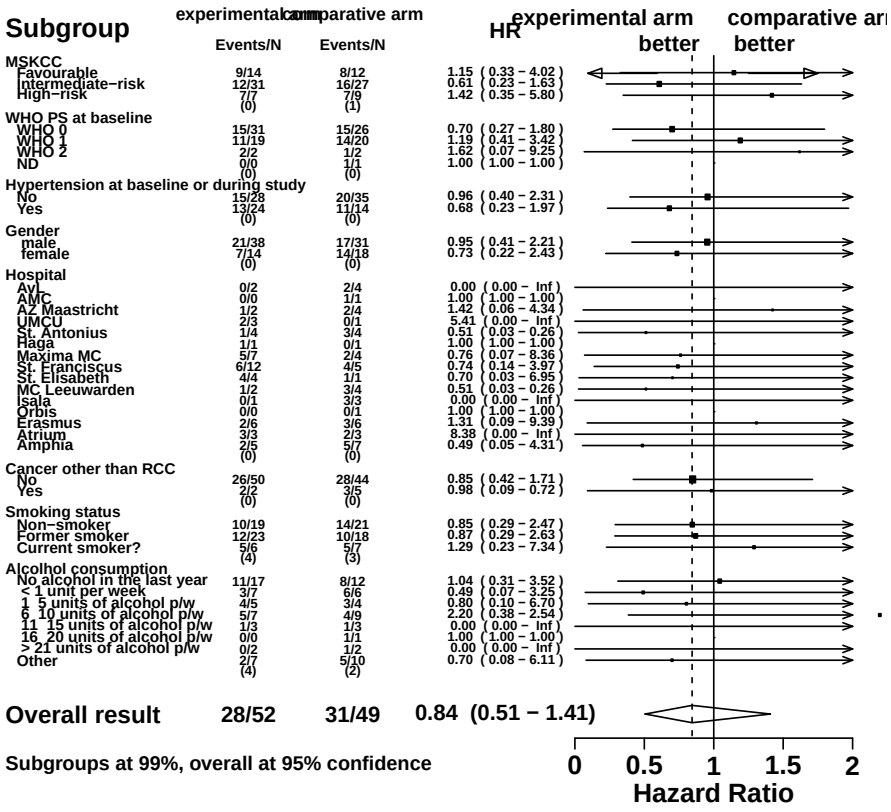


Figure 17: Subgroup analysis for pfs2

10 Appendix A: additional baseline characteristics

Table 24: Significant medical history

Arm	Patnr	Diagnosis	Year	Condition
Arm A: experimental arm	3	total hipprottesis left	2009	1=Past
Arm A: experimental arm	3	appendectomy	1900	1=Past
Arm A: experimental arm	3	hypertension	1900	3=Current/Active
Arm A: experimental arm	5	hernia Nuclei Pulposi (HNP)	1999	1=Past
Arm A: experimental arm	7	hypertension	2007	3=Current/Active
Arm A: experimental arm	7	cholecystectomy		1=Past
Arm A: experimental arm	7	fybromyalgia		3=Current/Active
Arm A: experimental arm	10	angina pectoris	2004	2=Present/Dormant
Arm A: experimental arm	10	hypertension		2=Present/Dormant
Arm A: experimental arm	10	appendectomy		1=Past
Arm A: experimental arm	10	prostatitis	2010	1=Past
Arm A: experimental arm	10	hearing impaired		3=Current/Active
Arm A: experimental arm	11	acute coronary syndrome	2000	1=Past
Arm A: experimental arm	11	acule coronary syndrome	2010	1=Past
Arm A: experimental arm	11	hypertension		3=Current/Active
Arm A: experimental arm	11	arthrosis knee	2012	3=Current/Active
Arm A: experimental arm	12	osteopenia	2000	3=Current/Active
Arm A: experimental arm	12	copd gold II	2005	3=Current/Active
Arm A: experimental arm	12	recurrent resperatory infections since	2002	2=Present/Dormant
Arm A: experimental arm	12	hyperglycaemia without cause	2004	2=Present/Dormant
Arm A: experimental arm	12	empyeem ri lower lob 3x since	2011	2=Present/Dormant
Arm A: experimental arm	15	gout		2=Present/Dormant
Arm A: experimental arm	15	hypertension		3=Current/Active
Arm A: experimental arm	15	arthrosis		2=Present/Dormant
Arm A: experimental arm	15	atrial fibrillation	2012	1=Past
Arm A: experimental arm	17	uterus extripation (benign)	1989	1=Past
Arm A: experimental arm	17	hypertension		3=Current/Active
Arm A: experimental arm	17	osteoporose	2001	2=Present/Dormant
Arm A: experimental arm	19	Abdominal uterus extirpartion	1997	1=Past
Arm A: experimental arm	19	Candida oris	2007	1=Past
Arm A: experimental arm	20	ovariectomie right	2007	1=Past
Arm A: experimental arm	24	hypertension	2008	2=Present/Dormant
Arm A: experimental arm	24	atrial fibrillation	2008	2=Present/Dormant
Arm A: experimental arm	25	sinusitis, surgery	1960	1=Past
Arm A: experimental arm	25	nasal polyp resection	1960	1=Past
Arm A: experimental arm	25	osteoporosis		2=Present/Dormant
Arm A: experimental arm	25	hypertension		2=Present/Dormant
Arm A: experimental arm	25	aortic valve sterosis	2012	2=Present/Dormant
Arm A: experimental arm	27	appendectomy	1969	1=Past
Arm A: experimental arm	27	nefrectomy right	2000	1=Past
Arm A: experimental arm	27	lobectomy	2004	1=Past
Arm A: experimental arm	27	pancreas+spleen metastase	2010	2=Present/Dormant
Arm A: experimental arm	31	partial anterior circulation infarct	2007	1=Past

Table 24: *(continued)*

Arm	Patnr	Diagnosis	Year	Condition
Arm A: experimental arm	31	(paci)		
Arm A: experimental arm	32	pulmonary embolism	2012	1=Past
Arm A: experimental arm	33	glaucoma	2010	2=Present/Dormant
Arm A: experimental arm	33	aberrante RCX	2011	2=Present/Dormant
Arm A: experimental arm	33	lungembolism	2011	1=Past
Arm A: experimental arm	33	gout/monoarthritis	2010	2=Present/Dormant
Arm A: experimental arm	34	COPD	1900	3=Current/Active
Arm A: experimental arm	37	keloid thorax		3=Current/Active
Arm A: experimental arm	42	colitis ulcerosa	2006	1=Past
Arm A: experimental arm	42	acute coronary syndrome	2009	1=Past
Arm A: experimental arm	42	dyspnea	2013	3=Current/Active
Arm A: experimental arm	42	gastoesophageal reflux disease	1996	2=Present/Dormant
Arm A: experimental arm	43	hip dysplasia	1989	
Arm A: experimental arm	44	hypertension	1987	3=Current/Active
Arm A: experimental arm	44	DM II	2001	3=Current/Active
Arm A: experimental arm	44	hemochromatose	2007	3=Current/Active
Arm A: experimental arm	44	hypothyreoidie	2007	3=Current/Active
Arm A: experimental arm	46	diabetes mellitus	2003	2=Present/Dormant
Arm A: experimental arm	46	gastric perforation	2006	1=Past
Arm A: experimental arm	46	gastritis HLO+	2006	1=Past
Arm A: experimental arm	46	abdominal wall hernia surgery	2008	1=Past
Arm A: experimental arm	46	hypertension	2013	2=Present/Dormant
Arm A: experimental arm	46	hypercholesterolemie	2013	2=Present/Dormant
Arm A: experimental arm	46	inguinal hernia surgery	2013	1=Past
Arm A: experimental arm	55	aneurysma thoracal	2009	1=Past
Arm A: experimental arm	55	venous thrombosis	2009	1=Past
Arm A: experimental arm	55	cholesterol high	1900	1=Past
Arm A: experimental arm	55	hypertension	1900	2=Present/Dormant
Arm A: experimental arm	56	hypertension	1900	2=Present/Dormant
Arm A: experimental arm	56	diabetes mellitus	1900	2=Present/Dormant
Arm A: experimental arm	56	hyper cholesterolemia	1900	2=Present/Dormant
Arm A: experimental arm	57	hypertension	1997	2=Present/Dormant
Arm A: experimental arm	57	PTCA	1997	1=Past
Arm A: experimental arm	57	Prostate hyperthrophy	1900	1=Past
Arm A: experimental arm	58	atypical thoracal pain	2010	1=Past
Arm A: experimental arm	59	hypertension		
Arm A: experimental arm	60	hernia abdominal wall	2013	2=Present/Dormant
Arm A: experimental arm	61	mucopurulent secretion nose	1992	1=Past
Arm A: experimental arm	64	Diabetes mellitus type 2	2013	3=Current/Active
Arm A: experimental arm	64	acute appendicitis		1=Past
Arm A: experimental arm	66	PTCA and stent	2009	1=Past
Arm A: experimental arm	66	myocard infarct	2003	1=Past
Arm A: experimental arm	66	appendectomy	1973	1=Past
Arm A: experimental arm	66	hypertension	1900	3=Current/Active
Arm A: experimental arm	67	hernia	1995	1=Past
Arm A: experimental arm	69	COPD		2=Present/Dormant

Table 24: *(continued)*

Arm	Patnr	Diagnosis	Year	Condition
Arm A: experimental arm	69	pneumothorax	1994	1=Past
Arm A: experimental arm	69	fracture (collum)	2013	1=Past
Arm A: experimental arm	69	pneumothorax	2000	1=Past
Arm A: experimental arm	71	ablation mamma DCIS	2005	1=Past
Arm A: experimental arm	71	diabetes mellitus	2013	2=Present/Dormant
Arm A: experimental arm	73	kidney stone	1990	1=Past
Arm A: experimental arm	73	urethra stone	2013	1=Past
Arm A: experimental arm	76	urinary tract infection	2013	1=Past
Arm A: experimental arm	78	polyp colon	2012	1=Past
Arm A: experimental arm	78	diabetis type 2	2010	3=Current/Active
Arm A: experimental arm	78	hypertension	2010	3=Current/Active
Arm A: experimental arm	78	anorexia	2013	3=Current/Active
Arm A: experimental arm	78	bronchitis	2011	1=Past
Arm A: experimental arm	78	fatigue	2013	3=Current/Active
Arm A: experimental arm	78	weight loss	2013	3=Current/Active
Arm A: experimental arm	82	hypertension	2008	2=Present/Dormant
Arm A: experimental arm	85	polipectomy colon	1999	1=Past
Arm A: experimental arm	85	hypertension	2001	2=Present/Dormant
Arm A: experimental arm	85	diabetes mellitus	2009	2=Present/Dormant
Arm A: experimental arm	85	acute coronary syndrome	2013	2=Present/Dormant
Arm A: experimental arm	85	colitis ulcerosa	2013	2=Present/Dormant
Arm A: experimental arm	86	myocardial infarction	2003	1=Past
Arm A: experimental arm	86	cough	2013	3=Current/Active
Arm A: experimental arm	86	hypercholesterolemia	1900	2=Present/Dormant
Arm A: experimental arm	86	arthritis	2012	1=Past
Arm A: experimental arm	86	hypercalcemia	2014	1=Past
Arm A: experimental arm	86	hyperglycemia	2014	3=Current/Active
Arm A: experimental arm	88	back pain	2008	2=Present/Dormant
Arm A: experimental arm	89	partial strumectomy	1960	1=Past
Arm A: experimental arm	89	hyperthyroid M. graves	1996	3=Current/Active
Arm A: experimental arm	91	hypertension	2007	2=Present/Dormant
Arm A: experimental arm	91	DM 2	2005	2=Present/Dormant
Arm A: experimental arm	91	vit b12 deficiency	1975	2=Present/Dormant
Arm A: experimental arm	98	hypertension	2011	2=Present/Dormant
Arm A: experimental arm	98	dyslipidemia	2011	2=Present/Dormant
Arm A: experimental arm	98	CABG	2012	1=Past
Arm A: experimental arm	98	bone metastasis	2013	2=Present/Dormant
Arm A: experimental arm	101	hyperchholesterolemy	1994	2=Present/Dormant
Arm A: experimental arm	101	osteoporosis	1997	2=Present/Dormant
Arm A: experimental arm	101	hypertension	2007	2=Present/Dormant
Arm A: experimental arm	101	polymyalgia reumatica	2009	2=Present/Dormant
Arm A: experimental arm	101	rectum polyp	2002	1=Past
Arm A: experimental arm	101	palpitations	2014	2=Present/Dormant
Arm B: comparative arm	1	morbus hodgkin	1985	1=Past
Arm B: comparative arm	1	hypercholesterlomy	1995	1=Past
Arm B: comparative arm	1	renal insufficiency	1995	2=Present/Dormant

Table 24: *(continued)*

Arm	Patnr	Diagnosis	Year	Condition
Arm B: comparative arm	1	hypertension	1995	2=Present/Dormant
Arm B: comparative arm	1	hypothyroidism	1990	2=Present/Dormant
Arm B: comparative arm	1	pericarditis	2007	1=Past
Arm B: comparative arm	2	nephorectomy left for renal cyst	1990	1=Past
Arm B: comparative arm	2	angina pectoris	1992	1=Past
Arm B: comparative arm	2	lacunar stroke	2010	1=Past
Arm B: comparative arm	2	basalcellcarcinoma	2009	1=Past
Arm B: comparative arm	2	diabetes mellitus		2=Present/Dormant
Arm B: comparative arm	2	hypercholesterolomia		2=Present/Dormant
Arm B: comparative arm	2	hypertension	2008	2=Present/Dormant
Arm B: comparative arm	4	hypertension	2000	2=Present/Dormant
Arm B: comparative arm	8	hypertension	1970	3=Current/Active
Arm B: comparative arm	8	besnier boeck (sarcoidosis)	1971	1=Past
Arm B: comparative arm	8	nephrolithiasis	1993	1=Past
Arm B: comparative arm	8	Positional vertigo (benigne paroxysmal)	2002	3=Current/Active
Arm B: comparative arm	8	collaps (e causa ignota)	2003	1=Past
Arm B: comparative arm	8	palpitations	2003	2=Present/Dormant
Arm B: comparative arm	8	TIA (transient ischaemic attack)	2010	1=Past
Arm B: comparative arm	8	Diastolic dysfunction	2010	1=Past
Arm B: comparative arm	8	tinnitis	1900	1=Past
Arm B: comparative arm	8	adipositas	1900	3=Current/Active
Arm B: comparative arm	8	fatigue, grade 1	2012	3=Current/Active
Arm B: comparative arm	8	anxiety, grade 1	1900	2=Present/Dormant
Arm B: comparative arm	8	skin rash (perineum inguinal) grade 1	1900	2=Present/Dormant
Arm B: comparative arm	9	turp	2009	1=Past
Arm B: comparative arm	9	hip prothesis both sides	2006	1=Past
Arm B: comparative arm	9	pain hip	2012	3=Current/Active
Arm B: comparative arm	9	cts	2010	2=Present/Dormant
Arm B: comparative arm	9	anorexia	2012	3=Current/Active
Arm B: comparative arm	13	hypertension	2012	3=Current/Active
Arm B: comparative arm	13	cholesterol		3=Current/Active
Arm B: comparative arm	18	diabetes type 2	2012	2=Present/Dormant
Arm B: comparative arm	18	suspicion of m. crohn	1993	1=Past
Arm B: comparative arm	22	hypertension	1994	2=Present/Dormant
Arm B: comparative arm	22	ulcus ventriculi	2000	2=Present/Dormant
Arm B: comparative arm	22	fibromyalgia	1900	2=Present/Dormant
Arm B: comparative arm	22	hematuri	2012	2=Present/Dormant
Arm B: comparative arm	22	pain back	2012	3=Current/Active
Arm B: comparative arm	26	hypertension	1995	2=Present/Dormant
Arm B: comparative arm	26	low back pain	2012	3=Current/Active
Arm B: comparative arm	26	headache	2012	3=Current/Active
Arm B: comparative arm	26	eczema	2008	1=Past
Arm B: comparative arm	26	quinques edema tongue	2006	1=Past
Arm B: comparative arm	26	appendectomy	1974	1=Past

Table 24: *(continued)*

Arm	Patnr	Diagnosis	Year	Condition
Arm B: comparative arm	26	hysterectomy	1973	1=Past
Arm B: comparative arm	28	knee surgery both sides	1900	1=Past
Arm B: comparative arm	28	myocard infarction	1990	1=Past
Arm B: comparative arm	28	aneurysma surgery a iliara both sides	2011	1=Past
Arm B: comparative arm	28	arthrelin both hands	2013	3=Current/Active
Arm B: comparative arm	28	renal cell nefrectomy carin left	2011	2=Present/Dormant
Arm B: comparative arm	28	surgery: hennianuclei pulposi	1993	1=Past
Arm B: comparative arm	28	cerino brachalogy left	2012	3=Current/Active
Arm B: comparative arm	29	Uterus extirpartion+ovarectomy (1 ovary)	1988	1=Past
Arm B: comparative arm	36	depression		2=Present/Dormant
Arm B: comparative arm	36	hypertension	2013	3=Current/Active
Arm B: comparative arm	40	joint range of motion decreased lumbar spine (HNP)	2013	2=Present/Dormant
Arm B: comparative arm	41	barett esophagus	2007	2=Present/Dormant
Arm B: comparative arm	41	duodenitis	2009	2=Present/Dormant
Arm B: comparative arm	41	hernia diaphragmatica	2007	2=Present/Dormant
Arm B: comparative arm	41	Colitis (ischemic)	2009	1=Past
Arm B: comparative arm	41	hypertension	2001	3=Current/Active
Arm B: comparative arm	41	collapses eci	2001	1=Past
Arm B: comparative arm	41	Chest pain	2006	1=Past
Arm B: comparative arm	41	hemorrhoids with rubber band	2012	2=Present/Dormant
Arm B: comparative arm	41	cataract r. eye	2011	3=Current/Active
Arm B: comparative arm	45	hypertension	1900	2=Present/Dormant
Arm B: comparative arm	45	fatigue	2013	1=Past
Arm B: comparative arm	45	diabetes melitus	1900	2=Present/Dormant
Arm B: comparative arm	45	cardiac dysrhythmia	2011	2=Present/Dormant
Arm B: comparative arm	47	pneumonia	2013	2=Present/Dormant
Arm B: comparative arm	47	back pain	2013	3=Current/Active
Arm B: comparative arm	48	hypothyreodism	2013	3=Current/Active
Arm B: comparative arm	48	hypertension	2006	3=Current/Active
Arm B: comparative arm	48	prolaps uteri	2010	2=Present/Dormant
Arm B: comparative arm	51	astmatic bronchitis	1900	2=Present/Dormant
Arm B: comparative arm	51	hypertension	1970	3=Current/Active
Arm B: comparative arm	51	diabetes mellitus type 2	2004	2=Present/Dormant
Arm B: comparative arm	51	eye problems	1993	2=Present/Dormant
Arm B: comparative arm	51	eye problems	2007	2=Present/Dormant
Arm B: comparative arm	51	eye problems	2008	2=Present/Dormant
Arm B: comparative arm	51	atrroscopy	2007	1=Past
Arm B: comparative arm	51	vascular bypass	2004	1=Past
Arm B: comparative arm	52	small myocardinfarction	2005	1=Past
Arm B: comparative arm	52	arrhythmia (cardial)	2005	1=Past
Arm B: comparative arm	52	angina pectoris	2011	1=Past
Arm B: comparative arm	52	angioplastic intervention	2006	1=Past
Arm B: comparative arm	53	allergic asthma	2008	2=Present/Dormant

Table 24: *(continued)*

Arm	Patnr	Diagnosis	Year	Condition
Arm B: comparative arm	53	renal failure	2009	1=Past
Arm B: comparative arm	53	fat metabolism disorder	2008	2=Present/Dormant
Arm B: comparative arm	53	vasovagal reaction	2013	1=Past
Arm B: comparative arm	53	hay fever	2013	2=Present/Dormant
Arm B: comparative arm	54	esophageal stenosis	1995	2=Present/Dormant
Arm B: comparative arm	62	colon polyp	2001	1=Past
Arm B: comparative arm	62	anterior myocard infarction	2003	2=Present/Dormant
Arm B: comparative arm	62	hip complaints	2005	1=Past
Arm B: comparative arm	62	ventricular ejection fract	2007	1=Past
Arm B: comparative arm	62	hernia inguinal R+L	2007	1=Past
Arm B: comparative arm	62	TIA left hemisfere	2011	1=Past
Arm B: comparative arm	63	hernia NP	1990	1=Past
Arm B: comparative arm	63	meniscus surgery left	1991	1=Past
Arm B: comparative arm	63	diabetes mellitus	2006	2=Present/Dormant
Arm B: comparative arm	63	hypercholesteremya	2006	
Arm B: comparative arm	63	posterior infarction	1900	1=Past
Arm B: comparative arm	65	fracture right hip	2013	1=Past
Arm B: comparative arm	65	partial paraplegie	2013	3=Current/Active
Arm B: comparative arm	65	hypertension gr 1	2013	3=Current/Active
Arm B: comparative arm	68	hypertension	2012	2=Present/Dormant
Arm B: comparative arm	70	psoriasis	1986	3=Current/Active
Arm B: comparative arm	70	COPD	2000	3=Current/Active
Arm B: comparative arm	70	hypertension	2011	3=Current/Active
Arm B: comparative arm	70	transient ischemic attack	2006	2=Present/Dormant
Arm B: comparative arm	74	claudicatio intermittens		2=Present/Dormant
Arm B: comparative arm	74	hyperthyreoidism	1997	1=Past
Arm B: comparative arm	74	pacemaker (artificial cardiac)	2004	2=Present/Dormant
Arm B: comparative arm	75	diabetes mellitus	1976	3=Current/Active
Arm B: comparative arm	75	HNP- operation	1982	1=Past
Arm B: comparative arm	75	Hypertension	2008	3=Current/Active
Arm B: comparative arm	77	hypertension		2=Present/Dormant
Arm B: comparative arm	77	hypercholesterolemia		2=Present/Dormant
Arm B: comparative arm	79	nose correction	1900	1=Past
Arm B: comparative arm	79	uterus extirpartion	2009	1=Past
Arm B: comparative arm	81	hypothyreoidie	2006	3=Current/Active
Arm B: comparative arm	81	lung embolism	2013	3=Current/Active
Arm B: comparative arm	84	morbus paget introductal mamma left	1982	1=Past
Arm B: comparative arm	84	hypertension	1990	3=Current/Active
Arm B: comparative arm	84	hypercholesterolemia	1990	2=Present/Dormant
Arm B: comparative arm	84	artrosis ankles and feet	2000	2=Present/Dormant
Arm B: comparative arm	84	pneumonia	2005	1=Past
Arm B: comparative arm	84	high urid acid	2010	2=Present/Dormant
Arm B: comparative arm	84	proteinuria	2009	2=Present/Dormant
Arm B: comparative arm	84	atherosclerosis	2009	2=Present/Dormant
Arm B: comparative arm	87	rheumatic fever	1982	1=Past

Table 24: *(continued)*

Arm	Patnr	Diagnosis	Year	Condition
Arm B: comparative arm	87	overactive bladder	2013	3=Current/Active
Arm B: comparative arm	90	prostate hyperthropy	2011	2=Present/Dormant
Arm B: comparative arm	90	DM	2007	2=Present/Dormant
Arm B: comparative arm	90	hypercholesterol	1900	2=Present/Dormant
Arm B: comparative arm	90	hypertension	1900	2=Present/Dormant
Arm B: comparative arm	92	claudication intermittens	2007	2=Present/Dormant
Arm B: comparative arm	92	angina pectoris	2007	1=Past
Arm B: comparative arm	92	coronary artery disease	2005	1=Past
Arm B: comparative arm	92	hypertension	1900	2=Present/Dormant
Arm B: comparative arm	92	alcohol abuses	1900	3=Current/Active
Arm B: comparative arm	92	hypercholesterolemia	1900	2=Present/Dormant
Arm B: comparative arm	95	uterusextirpartion	1900	1=Past
Arm B: comparative arm	96	hypertension	1900	2=Present/Dormant
Arm B: comparative arm	99	diabetes mellitus 2		3=Current/Active
Arm B: comparative arm	99	hypertension		3=Current/Active
Arm B: comparative arm	99	dislipidemia		2=Present/Dormant
Arm B: comparative arm	99	atrial tachycardia		1=Past
Arm B: comparative arm	100	COPD		1=Past
Arm B: comparative arm	100	chronical veneus insufficiency		2=Present/Dormant
Arm B: comparative arm	100	wolff parkinson white syndrome with atrial fibrillation	1979	1=Past
Arm B: comparative arm	100	hyperthyreoidism	1983	1=Past

Table 25: Surgery as described on the ECRF with my reclassification (for checking purposes) and year

Arm	Patnr	Type of surgery	Type in baseline table	Year
Arm A: experimental arm	5	nefrectomy left	nephractomy	2010
Arm A: experimental arm	7	radical nephnectomy	nephractomy	2011
Arm A: experimental arm	11	nefrectomy	nephractomy	2009
Arm A: experimental arm	12	nefrectomy left	nephractomy	2005
Arm A: experimental arm	14	nefrectomy	nephractomy	2012
Arm A: experimental arm	20	nephrectomy	nephractomy	2012
Arm A: experimental arm	25	nephrectomy, adrenalectomy, retroperitoneal left-para-aortal LN dissection	nephractomy	2012
Arm A: experimental arm	27	nefrectomy right (gtj 2 olizmeter 9cm)	nephractomy	2000
Arm A: experimental arm	31	nephrectomy	nephractomy	2012
Arm A: experimental arm	32	open nephrectomy left	nephractomy	2012
Arm A: experimental arm	33	Partial nefrectomy	nephractomy	2010
Arm A: experimental arm	38	laparascopic nephrectomy	nephractomy	2013
Arm A: experimental arm	42	nefrectomy laparascopy	nephractomy	2007
Arm A: experimental arm	44	nefrectomy right	nephractomy	2008
Arm A: experimental arm	49	nefrectomy left side (partial)	nephractomy	2012
Arm A: experimental arm	49	partial nefrectomy left side (recurrence)	nephractomy	2013

Table 25: *(continued)*

Arm	Patnr	Type of surgery	Type in baseline table	Year
Arm A: experimental arm	50	abdominal nefrectomy right	nephractomy	2013
Arm A: experimental arm	55	nefrectomy right	nephractomy	2009
Arm A: experimental arm	56	nephrectomy left	nephractomy	2007
Arm A: experimental arm	60	abdominal radical nefrectomy	nephractomy	2011
Arm A: experimental arm	61	nephrectomy	nephractomy	2007
Arm A: experimental arm	66	nefrectomy	nephractomy	2008
Arm A: experimental arm	67	laparoscopic nefrectomy left	nephractomy	2008
Arm A: experimental arm	73	nefrectomy	nephractomy	1993
Arm A: experimental arm	76	laparoscopic nefrectomy	nephractomy	2010
Arm A: experimental arm	78	nefrectomy left	nephractomy	2007
Arm A: experimental arm	82	nephrectomy right	nephractomy	2008
Arm A: experimental arm	88	nefrectomie	nephractomy	2013
Arm A: experimental arm	89	Nefrectomy right	nephractomy	2009
Arm A: experimental arm	7	resection rib metastasis	other surgery	2011
Arm A: experimental arm	11	pancreatic tail resection (meta)	other surgery	2011
Arm A: experimental arm	12	pancreztectomy for meta renal cel ca.	other surgery	2011
Arm A: experimental arm	12	lobectomy for meta renal cel ca.	other surgery	2011
Arm A: experimental arm	17	embolisation and laminectomy L5 + tumor	other surgery	2012
Arm A: experimental arm	27	lobectomy for meta renal celca (up-perlob left)	other surgery	2004
Arm A: experimental arm	32	pen placement for humerusfracture	other surgery	2013
Arm A: experimental arm	42	excision recurrence adrenal	other surgery	2008
Arm A: experimental arm	42	excision lung meta lobectomy	other surgery	2009
Arm A: experimental arm	42	excision lung meta	other surgery	2011
Arm A: experimental arm	55	cavotomie	other surgery	2009
Arm A: experimental arm	60	minithoractomy LOK	other surgery	2013
Arm A: experimental arm	67	excision subcutane lesion	other surgery	2013
Arm A: experimental arm	76	VATS-re and wigexcision (middle lobe)	other surgery	2011
Arm A: experimental arm	82	middle lobe resection lung right (metastases ccrc)	other surgery	2008
Arm A: experimental arm	82	resection metastasis right upper arm (metastasis ccrc)	other surgery	2010
Arm A: experimental arm	83	macrosic resection metastasis L 1 (lamissectomy and spondylodesis)	other surgery	2013
Arm B: comparative arm	4	Nehprectomy	nephractomy	2008
Arm B: comparative arm	6	nefrectomy abdominal	nephractomy	2009
Arm B: comparative arm	8	Partial nephrectomy right	nephractomy	2011
Arm B: comparative arm	9	nefrectomy	nephractomy	2012
Arm B: comparative arm	13	nefrectomy rightq	nephractomy	2012
Arm B: comparative arm	18	laparoscopic nefrectomy	nephractomy	2012
Arm B: comparative arm	21	Tumor nefrectomy left and splenec-tomy	nephractomy	2002
Arm B: comparative arm	23	nefrectomy left	nephractomy	2012

Table 25: *(continued)*

Arm	Patnr	Type of surgery	Type in baseline table	Year
Arm B: comparative arm	26	tumor nefrectomy laparoscopic right	nephractomy	2012
Arm B: comparative arm	28	nefrectomy left	nephractomy	2011
Arm B: comparative arm	29	nephrectomy	nephractomy	2011
Arm B: comparative arm	30	Nefrectomy laparascopy	nephractomy	2012
Arm B: comparative arm	35	Nephrectomy	nephractomy	2013
Arm B: comparative arm	41	radical abdominal nephrectomy right	nephractomy	2007
Arm B: comparative arm	45	nefrectomy right	nephractomy	
Arm B: comparative arm	51	tumornefrectomy ri+cavatomy	nephractomy	2010
Arm B: comparative arm	52	nefrectomomia and adrenalectomia	nephractomy	2005
Arm B: comparative arm	53	nephrectomy	nephractomy	2007
Arm B: comparative arm	54	nephrectomy	nephractomy	2004
Arm B: comparative arm	63	nefrectomy left	nephractomy	2009
Arm B: comparative arm	68	laparoscopic nephrectomy right	nephractomy	2012
Arm B: comparative arm	72	laparoscopic tumornephrectomy (clear cell renal carcinoma)	nephractomy	2012
Arm B: comparative arm	75	nefrectomy left	nephractomy	2008
Arm B: comparative arm	77	nefrectomie	nephractomy	2013
Arm B: comparative arm	79	nefrectomy right	nephractomy	2012
Arm B: comparative arm	81	nefrectomy	nephractomy	2013
Arm B: comparative arm	90	nefrectomy	nephractomy	1993
Arm B: comparative arm	96	nefrectomy left	nephractomy	2013
Arm B: comparative arm	97	abdominal nephrectomy right	nephractomy	2006
Arm B: comparative arm	99	nefrectomy	nephractomy	2012
Arm B: comparative arm	100	nefrectomy, left	nephractomy	2010
Arm B: comparative arm	4	Adrenalectomy	other surgery	2009
Arm B: comparative arm	9	excision bcc	other surgery	2010
Arm B: comparative arm	9	excision bcc	other surgery	2012
Arm B: comparative arm	23	splenectomy	other surgery	2012
Arm B: comparative arm	30	Morbus paget vulvectomy	other surgery	2008
Arm B: comparative arm	36	parotidectomy	other surgery	2013
Arm B: comparative arm	65	resection right mouth corner	other surgery	2013
Arm B: comparative arm	65	THP collum fracture (metastases)	other surgery	2013
Arm B: comparative arm	75	retroperitoneale endoscopiche adrenalectomy re	other surgery	2013
Arm B: comparative arm	75	laparoscopic low anterior resection	other surgery	2008
Arm B: comparative arm	90	lymphadectomy	other surgery	1993
Arm B: comparative arm	90	extirpartion adrenal	other surgery	1993
Arm B: comparative arm	94	fixation L5, (L4-S1)	other surgery	2014
Arm B: comparative arm	95	gamnaanail operation for femur fracture	other surgery	2014

11 Appendix B: reasons for dose reduction and modifications

Table 26: Pazopanib prematurely stopped

Arm	Patnr	Cycle	Reason for stopping
Arm A: experimental arm	3	1	hepatotoxicity
Arm A: experimental arm	3	1	hepatotoxicity
Arm A: experimental arm	5	11	
Arm A: experimental arm	5	11	
Arm A: experimental arm	5	11	
Arm A: experimental arm	5	11	
Arm A: experimental arm	5	11	
Arm A: experimental arm	10	1	anorexia grade 3
Arm A: experimental arm	12	1	dyspnoe
Arm A: experimental arm	14	1	muscle weakness due to cerebral metastases
Arm A: experimental arm	14	1	muscle weakness due to cerebral metastases
Arm A: experimental arm	15	6	radiotherapy
Arm A: experimental arm	17	3	patient died
Arm A: experimental arm	19	1	SAE, hepatitis
Arm A: experimental arm	20	1	liver tox
Arm A: experimental arm	25	1	increased AE no5, switch to everolimus
Arm A: experimental arm	25	3	liver failure
Arm A: experimental arm	32	1	gastroenteritis
Arm A: experimental arm	32	3	diarrhea, nausea
Arm A: experimental arm	32	3	diarrhea, nausea
Arm A: experimental arm	34	5	pat. stopped, very bad condition
Arm A: experimental arm	38	5	
Arm A: experimental arm	38	5	
Arm A: experimental arm	39	1	pain abdominal and renal
Arm A: experimental arm	44	1	
Arm A: experimental arm	46	5	progressive disease
Arm A: experimental arm	46	5	progressive disease
Arm A: experimental arm	55	1	
Arm A: experimental arm	58	3	
Arm A: experimental arm	60	1	increased liver function disturbances
Arm A: experimental arm	69	1	hip herniarthroplasty
Arm A: experimental arm	73	3	logistic reason due to vacation of the doctor
Arm A: experimental arm	76	1	ALT >8 x ULN
Arm A: experimental arm	78	3	
Arm A: experimental arm	80	1	progression
Arm A: experimental arm	85	1	progressive pain due to metastasis arm
Arm A: experimental arm	86	10	RT for cerebral meta's
Arm A: experimental arm	89	1	

Table 26: *(continued)*

Arm	Patnr	Cycle	Reason for stopping
Arm A: experimental arm	91	1	hepatotoxicity
Arm B: comparative arm	1	2	proteinuria
Arm B: comparative arm	2	9	progression
Arm B: comparative arm	8	1	dose delay>21 days, due to AE trombocytopenia grade 3
Arm B: comparative arm	13	4	
Arm B: comparative arm	16	4	
Arm B: comparative arm	16	4	
Arm B: comparative arm	16	23	numerus fracture
Arm B: comparative arm	18	1	hospitalization for perforation colon
Arm B: comparative arm	21	2	progression
Arm B: comparative arm	22	1	proteinuria
Arm B: comparative arm	23	1	PD
Arm B: comparative arm	26	1	toxicity liver function, nausea and malaise
Arm B: comparative arm	26	2	malaise, patients wish
Arm B: comparative arm	36	13	AE's
Arm B: comparative arm	40	21	
Arm B: comparative arm	41	11	PD (clinical and radiological)
Arm B: comparative arm	47	1	esophageal obstruction
Arm B: comparative arm	48	1	patient refusal
Arm B: comparative arm	53	9	PD
Arm B: comparative arm	54	1	SAE: ALAT increased
Arm B: comparative arm	54	4	
Arm B: comparative arm	62	1	hepatic impairment (ALAT)
Arm B: comparative arm	62	1	hepatic impairment (ALAT)
Arm B: comparative arm	63	6	progressive disease
Arm B: comparative arm	72	1	intolerance pazopanib stop 18-11-2013 and restarted 23-11-2013 with reduction.
Arm B: comparative arm	72	1	intolerance pazopanib stop 18-11-2013 and restarted 23-11-2013 with reduction.
Arm B: comparative arm	72	1	intolerance pazopanib stop 18-11-2013 and restarted 23-11-2013 with reduction.
Arm B: comparative arm	74	1	
Arm B: comparative arm	74	1	
Arm B: comparative arm	77	1	liver toxicity
Arm B: comparative arm	84	1	diarrhea
Arm B: comparative arm	87	2	elevated liver enzymes CPF, GGT, Asat and Alat
Arm B: comparative arm	93	1	stomatitis
Arm B: comparative arm	94	1	8: pt died
Arm B: comparative arm	94	1	8: pt died

Table 26: *(continued)*

Arm	Patnr	Cycle	Reason for stopping
Arm B: comparative arm	97	4	pat got a CVA
Arm B: comparative arm	100	1	
Arm B: comparative arm	100	1	

Table 27: Everolimus prematurely stopped

Arm	Patnr	Cycle	Reason for stopping
Arm A: experimental arm	7	4	progression
Arm A: experimental arm	7	4	progression
Arm A: experimental arm	12	2	dyspnoe
Arm A: experimental arm	17	2	
Arm A: experimental arm	25	2	fatigue
Arm A: experimental arm	31	2	progresive disease
Arm A: experimental arm	34	4	progressive disease
Arm A: experimental arm	49	16	one day before switch ti pazopanib, reason unknown
Arm A: experimental arm	57	2	unacceptable toxicity
Arm A: experimental arm	80	2	progression
Arm A: experimental arm	86	6	PD
Arm A: experimental arm	88	18	skin toxicity
Arm A: experimental arm	98	10	progressive disease
Arm B: comparative arm	9	2	clinical disease progression
Arm B: comparative arm	9	2	clinical disease progression
Arm B: comparative arm	29	6	progressive dyspnea ->lungmetastases
Arm B: comparative arm	30	6	progressive disease
Arm B: comparative arm	45	4	
Arm B: comparative arm	45	4	
Arm B: comparative arm	51	21	
Arm B: comparative arm	53	10	dyspnea
Arm B: comparative arm	63	8	CVA
Arm B: comparative arm	68	17	acute kidney injury
Arm B: comparative arm	79	8	AE anemia

Table 28: Pazopanib modified

Arm	Patnr	Cycle	Modification	Reason
Arm A: experimental arm	3	1	dose interrupted	tooth extraction
Arm A: experimental arm	3	1	dose interrupted	hepatotoxicity
Arm A: experimental arm	3	3	dose reuction	liver function disturbances
Arm A: experimental arm	3	10	delay	delay because of dental surgery
Arm A: experimental arm	5	1	delay	day 55 not taken because of diarrea/nausea
Arm A: experimental arm	5	10	dose interrupted	forgotten (dose)
Arm A: experimental arm	5	11	dose interrupted	vomiting

Table 28: *(continued)*

Arm	Patnr	Cycle	Modification	Reason
Arm A: experimental arm	5	11	dose interrupted	diarrhea+vomiting
Arm A: experimental arm	5	12	dose interrupted	logistics
Arm A: experimental arm	5	12	dose interrupted	dizziness, headache, abdominal pain
Arm A: experimental arm	5	13	dose interrupted	logistics
Arm A: experimental arm	5	13	dose interrupted	nausea/abdominal pain + melena
Arm A: experimental arm	5	13	dose interrupted	nausea/vomiting/headache/dizziness
Arm A: experimental arm	5	14	dose interrupted	abdominal pain, headache, neck-pain, vomiting
Arm A: experimental arm	5	14	dose interrupted	vomiting, nausea, abdominal pain, headache
Arm A: experimental arm	5	14	dose reuction	dysphagia
Arm A: experimental arm	5	14	dose interrupted	abdominal pain, nausea, headache, dysphagia
Arm A: experimental arm	5	14	dose reuction	dysphagia
Arm A: experimental arm	5	14	dose reuction	dysphagia
Arm A: experimental arm	5	14	dose reuction	dysphagia
Arm A: experimental arm	5	15	dose reuction	dysphagia
Arm A: experimental arm	5	15	dose interrupted	narcose (gastroscopy)
Arm A: experimental arm	5	15	dose reuction	dysphagia
Arm A: experimental arm	5	15	Other	0
Arm A: experimental arm	5	15	dose reuction	dysphagia
Arm A: experimental arm	5	15	dose reuction	dysphagia
Arm A: experimental arm	5	15	dose reuction	dysphagia
Arm A: experimental arm	5	15	dose reuction	dysphagia
Arm A: experimental arm	5	15	dose interrupted	dysphagia
Arm A: experimental arm	5	15	dose reuction	dysphagia
Arm A: experimental arm	5	15	dose reuction	dysphagia
Arm A: experimental arm	5	15	dose interrupted	dysphagia
Arm A: experimental arm	5	15	dose reuction	dysphagia / flu
Arm A: experimental arm	7	1	dose interrupted	hypertension
Arm A: experimental arm	7	1	dose reuction	hypertension
Arm A: experimental arm	7	3	dose interrupted	hypertension
Arm A: experimental arm	7	3	dose interrupted	hypertension
Arm A: experimental arm	7	3	dose interrupted	hypertension
Arm A: experimental arm	11	5	dose reuction	polyneuropathy sensory and PPE
Arm A: experimental arm	11	8	dose interrupted	PPE
Arm A: experimental arm	11	8	dose reuction	PPE
Arm A: experimental arm	11	9	dose reuction	PPE
Arm A: experimental arm	12	1	dose interrupted	
Arm A: experimental arm	14	1	dose interrupted	muscle weakness due to cerebral metastases
Arm A: experimental arm	15	6	dose interrupted	radiotherapy
Arm A: experimental arm	15	7	delay	radiotherapy
Arm A: experimental arm	17	1	dose interrupted	nausea
Arm A: experimental arm	17	1	dose interrupted	logistic reason: stop on day 55

Table 28: *(continued)*

Arm	Patnr	Cycle	Modification	Reason
Arm A: experimental arm	17	3	Other	(reduction + delay) toxicity cycle 1(fatigue) reason delay: patients condition
Arm A: experimental arm	19	1	dose interrupted	dizziness
Arm A: experimental arm	20	1	dose interrupted	AE liver toxicity
Arm A: experimental arm	24	1	dose interrupted	interrupted for 3 days due to new recept
Arm A: experimental arm	24	7	dose interrupted	toxicity
Arm A: experimental arm	24	7	dose reuction	toxicity
Arm A: experimental arm	24	9	dose reuction	toxicity
Arm A: experimental arm	24	11	dose reuction	toxicity
Arm A: experimental arm	25	1	dose interrupted	improved AE no5
Arm A: experimental arm	25	3	dose reuction	liver failure
Arm A: experimental arm	32	1	dose interrupted	
Arm A: experimental arm	32	3	dose reuction	due to toxicities during 1e cycle started with reduced dose
Arm A: experimental arm	32	3	dose reuction	diarhhea, nausea
Arm A: experimental arm	34	5	omitted	progressive disease
Arm A: experimental arm	38	3	dose interrupted	1 day interruption due to nausea/abdominal cramps
Arm A: experimental arm	38	5	dose interrupted	ileus
Arm A: experimental arm	38	5	dose reuction	nausea; vomiting
Arm A: experimental arm	38	11	dose interrupted	interrupted due to hernia wall operation(planned)
Arm A: experimental arm	42	3	dose reuction	PPE
Arm A: experimental arm	42	5	dose interrupted	malaise
Arm A: experimental arm	42	7	dose reuction	earlier malaise, anorexia
Arm A: experimental arm	42	9	dose reuction	earlier reduction
Arm A: experimental arm	42	9	dose reuction	toxicity; fatigue, diarrhoea
Arm A: experimental arm	44	1	dose interrupted	nausea
Arm A: experimental arm	46	1	delay	vomiting
Arm A: experimental arm	46	1	dose reuction	hypertension
Arm A: experimental arm	46	5	delay	xray right femur
Arm A: experimental arm	46	5	omitted	progressive disease
Arm A: experimental arm	49	15	dose interrupted	
Arm A: experimental arm	49	17	dose escalation	
Arm A: experimental arm	49	19	dose reuction	adevrse event
Arm A: experimental arm	49	19	dose escalation	
Arm A: experimental arm	50	3	dose reuction	AE: dizziness
Arm A: experimental arm	50	5	dose reuction	ae
Arm A: experimental arm	50	7	dose reuction	
Arm A: experimental arm	55	1	dose interrupted	liver function
Arm A: experimental arm	55	3	dose reuction	liver toxicity cycle 1
Arm A: experimental arm	56	1	Other	reduced due to fatigue, interrupted due to nausea
Arm A: experimental arm	56	5	dose reuction	nausea

Table 28: *(continued)*

Arm	Patnr	Cycle	Modification	Reason
Arm A: experimental arm	58	1	dose reuction	hypertension
Arm A: experimental arm	58	3	dose reuction	hypertension during first cycle
Arm A: experimental arm	60	1	dose interrupted	increased liver functions
Arm A: experimental arm	60	3	dose reuction	toxicity liver
Arm A: experimental arm	66	1	dose interrupted	fatigue and pain
Arm A: experimental arm	66	1	dose reuction	fatigue+pain. 400 choice of patient
Arm A: experimental arm	66	5	dose reuction	AE's previous cycle 1
Arm A: experimental arm	66	7	dose reuction	AE's cycle 1
Arm A: experimental arm	66	9	dose reuction	AE's cycle 1
Arm A: experimental arm	67	8	dose interrupted	progression
Arm A: experimental arm	69	1	dose interrupted	hip herniarthroplasty
Arm A: experimental arm	71	1	dose interrupted	toxicity
Arm A: experimental arm	71	5	dose reuction	toxicity
Arm A: experimental arm	71	7	dose reuction	toxicity
Arm A: experimental arm	73	19	dose interrupted	vacation
Arm A: experimental arm	73	19	dose reuction	general malaise
Arm A: experimental arm	76	1	dose interrupted	liver toxicity
Arm A: experimental arm	78	1	dose interrupted	malaise, anorexia and hepatotoxicity
Arm A: experimental arm	78	1	dose reuction	toxicity with 800 mg
Arm A: experimental arm	78	3	dose escalation	due to earlier malaise not the whole dose given
Arm A: experimental arm	86	7	delay	mucositis oral->SAE
Arm A: experimental arm	86	10	dose interrupted	cerebral metastasis ->RT
Arm A: experimental arm	88	1	dose interrupted	liver toxicity
Arm A: experimental arm	88	1	dose reuction	liver toxicity
Arm A: experimental arm	88	3	dose reuction	due to earlier liver toxicity
Arm A: experimental arm	88	5	dose reuction	due to earlier liver toxicity
Arm A: experimental arm	89	1	omitted	Refusal patient. Pat. want only palliative policy by the family doctor!
Arm A: experimental arm	91	1	dose interrupted	hepatotoxicity
Arm A: experimental arm	98	1	dose interrupted	liver toxicity
Arm A: experimental arm	98	3	dose reuction	toxicity
Arm A: experimental arm	101	7	dose reuction	fatigue
Arm A: experimental arm	101	15	dose interrupted	24/07/2016: no pazopanib (abdominal pain)
Arm B: comparative arm	1	1	dose interrupted	
Arm B: comparative arm	1	1	dose reuction	
Arm B: comparative arm	1	2	dose reuction	
Arm B: comparative arm	2	1	Other	by mistake patient and increased liver enzymes
Arm B: comparative arm	2	2	dose reuction	increased liver enzymes (by mistake patient started on 01/12/2012)
Arm B: comparative arm	2	3	dose reuction	increased liver enzymes
Arm B: comparative arm	2	4	dose reuction	increased liver enzymes
Arm B: comparative arm	4	1	dose interrupted	SAE Fever, Mucositis

Table 28: *(continued)*

Arm	Patnr	Cycle	Modification	Reason
Arm B: comparative arm	6	5	delay	because of diarrhea gr2
Arm B: comparative arm	6	5	dose reuction	because of diarrhea gr2
Arm B: comparative arm	6	6	dose reuction	because of diarrhea
Arm B: comparative arm	8	1	Other	AE: trombocytopenia gr 3, discontinuation
Arm B: comparative arm	16	4	dose interrupted	SAE
Arm B: comparative arm	16	12	dose interrupted	toxicity
Arm B: comparative arm	16	13	dose interrupted	lithotripsy + removal nsc
Arm B: comparative arm	16	23	omitted	
Arm B: comparative arm	18	1	dose interrupted	hospitalization for perforation colon
Arm B: comparative arm	21	2	dose interrupted	progression
Arm B: comparative arm	22	1	dose interrupted	proteinuria
Arm B: comparative arm	26	1	dose interrupted	
Arm B: comparative arm	26	2	dose reuction	toxicity liver function
Arm B: comparative arm	28	4	Other	cycle=70 days due to holidays
Arm B: comparative arm	28	25	Other	start too early due to holidays
Arm B: comparative arm	29	1	dose interrupted	ALAT>10xULN
Arm B: comparative arm	29	1	dose reuction	hepatotoxicity
Arm B: comparative arm	29	3	dose reuction	hepatoxicity cycle 1
Arm B: comparative arm	29	4	dose reuction	hepatoxicity cycle 1
Arm B: comparative arm	35	1	dose interrupted	hypertension
Arm B: comparative arm	35	1	dose reuction	hypertension
Arm B: comparative arm	35	1	dose interrupted	hypertension
Arm B: comparative arm	35	2	Other	dose reduced and delay: hypertension
Arm B: comparative arm	36	4	dose reuction	Nausea grade 2, diarrhea grade 2
Arm B: comparative arm	36	5	dose reuction	Nausea grade 2, diarrhea grade 2
Arm B: comparative arm	36	7	omitted	Error Patient
Arm B: comparative arm	36	7	omitted	Error Patient
Arm B: comparative arm	36	7	omitted	Error Patient
Arm B: comparative arm	36	11	dose escalation	pt. took 2 tablets by mistake
Arm B: comparative arm	36	11	omitted	AE epistaxis
Arm B: comparative arm	40	5	dose reuction	
Arm B: comparative arm	40	20	dose interrupted	lung infection
Arm B: comparative arm	40	20	dose reuction	lung infection (interaction voriconazol and pazopanib)
Arm B: comparative arm	40	21	Other	lung infection
Arm B: comparative arm	41	2	delay	
Arm B: comparative arm	41	2	dose reuction	
Arm B: comparative arm	41	5	dose interrupted	
Arm B: comparative arm	41	7	dose interrupted	
Arm B: comparative arm	41	11	Other	
Arm B: comparative arm	47	1	dose interrupted	esophageal obstruction
Arm B: comparative arm	51	1	dose interrupted	hypertension
Arm B: comparative arm	51	1	dose reuction	hypertension

Table 28: *(continued)*

Arm	Patnr	Cycle	Modification	Reason
Arm B: comparative arm	51	5	Other	cycle to long
Arm B: comparative arm	51	7	dose interrupted	epileptic convultion
Arm B: comparative arm	51	9	dose interrupted	fatigue
Arm B: comparative arm	51	11	omitted	SAE: pancreatitis (abdominal pain)
Arm B: comparative arm	51	12	dose reuction	reduction and delay; pancreatitis
Arm B: comparative arm	51	13	dose reuction	pancreatitis + fatigue
Arm B: comparative arm	51	14	dose reuction	previous pancreatitis, 2nd pr after interruption and dose reduction
Arm B: comparative arm	51	19	Other	longer cycle due to holidays
Arm B: comparative arm	51	20	Other	later visit due to holidays
Arm B: comparative arm	51	25	Other	stopped early due to pd
Arm B: comparative arm	52	3	Other	due to holidays: visits to hospital are slightly out of window
Arm B: comparative arm	52	23	dose interrupted	deviation on ct (wall thickens colon) Possible effect of pazopanib.
Arm B: comparative arm	52	23	dose reuction	start-up dose
Arm B: comparative arm	52	23	Other	new daily dose = 600mg
Arm B: comparative arm	53	9	dose interrupted	PD
Arm B: comparative arm	54	3	dose reuction	too much ae
Arm B: comparative arm	54	4	dose reuction	AE and QOL
Arm B: comparative arm	62	1	dose interrupted	hepatic impairment
Arm B: comparative arm	62	1	dose reuction	hepatic impairment
Arm B: comparative arm	63	1	delay	creatinine increase
Arm B: comparative arm	63	2	dose reuction	toxicity (increased liver functions)
Arm B: comparative arm	63	6	delay	
Arm B: comparative arm	65	5	dose interrupted	patient mistake
Arm B: comparative arm	65	5	dose reuction	patient mistake(reason uk)
Arm B: comparative arm	65	5	dose reuction	patient mistake(reason uk)
Arm B: comparative arm	65	5	dose reuction	patient mistake(reason uk)
Arm B: comparative arm	65	5	dose reuction	patient mistake(reason uk)
Arm B: comparative arm	65	5	dose reuction	patient mistake(reason uk)
Arm B: comparative arm	68	1	dose interrupted	toxicity
Arm B: comparative arm	68	6	dose interrupted	toxicity
Arm B: comparative arm	70	1	delay	more screening abducenparesis needed
Arm B: comparative arm	70	19	dose interrupted	gamma knife (cerebral meta's)
Arm B: comparative arm	72	1	dose reuction	fatigue
Arm B: comparative arm	72	1	dose interrupted	worsening fatigue
Arm B: comparative arm	75	2	dose interrupted	toxicity
Arm B: comparative arm	75	2	dose reuction	toxicity
Arm B: comparative arm	87	2	dose reuction	high alat/asat and af
Arm B: comparative arm	90	2	delay	due to liver toxicity and fatigue
Arm B: comparative arm	90	3	dose escalation	going up to 75% next day
Arm B: comparative arm	93	1	dose interrupted	stomatitis
Arm B: comparative arm	94	1	dose interrupted	SAE, pt admitted 21/03/14 stop 26/03/14

Table 28: *(continued)*

Arm	Patnr	Cycle	Modification	Reason
Arm B: comparative arm	94	1	dose interrupted	hypertension 190/90 RR
Arm B: comparative arm	99	1	dose interrupted	malaise
Arm B: comparative arm	99	1	dose interrupted	malaise
Arm B: comparative arm	99	1	dose reuction	malaise
Arm B: comparative arm	99	2	dose reuction	malaise(cycle 1)
Arm B: comparative arm	99	3	dose reuction	malaise (cycle 1)
Arm B: comparative arm	99	4	dose reuction	malaise cycle 1
Arm B: comparative arm	99	5	Other	reduction: malaise cycle 1. delay: pain lowerback
Arm B: comparative arm	99	6	Other	reduction. already reported
Arm B: comparative arm	99	7	Other	malaise after cycle 1
Arm B: comparative arm	99	7	dose escalation	complaint-free on 400 mg so trying forward to 600mg
Arm B: comparative arm	99	10	dose interrupted	toxicity: epistaxis, cough, fatigue, diarrhea, hoarseness
Arm B: comparative arm	100	1	dose interrupted	hospitalization(pack)
Arm B: comparative arm	100	1	Other	condition patient lower, respiratory insufficience

Table 29: Everolimus modified

Arm	Patnr	Cycle	Modification	Reason
Arm A: experimental arm	3	2	none	
Arm A: experimental arm	3	4	none	
Arm A: experimental arm	3	6	dose interrupted	biopt taken at 17-09-2013
Arm A: experimental arm	5	4	none	
Arm A: experimental arm	7	2	dose interrupted	nausea, fatigue
Arm A: experimental arm	7	4	dose interrupted	headache
Arm A: experimental arm	7	4	other	stopped due to progressive disease
Arm A: experimental arm	11	2	dose interrupted	mucositis mouth
Arm A: experimental arm	11	2	dose reduction	mucositis mouth
Arm A: experimental arm	11	4	none	
Arm A: experimental arm	11	6	none	
Arm A: experimental arm	12	2	omitted	
Arm A: experimental arm	15	2	none	
Arm A: experimental arm	15	4	none	
Arm A: experimental arm	17	2	dose interrupted	diarrhea
Arm A: experimental arm	24	2	none	
Arm A: experimental arm	24	4	dose reduction	
Arm A: experimental arm	24	6	none	
Arm A: experimental arm	24	8	none	
Arm A: experimental arm	24	10	none	
Arm A: experimental arm	24	12	dose interrupted	one day not taken, patient forgot.
Arm A: experimental arm	24	14	none	
Arm A: experimental arm	24	16	none	
Arm A: experimental arm	24	18	none	

Table 29: *(continued)*

Arm	Patnr	Cycle	Modification	Reason
Arm A: experimental arm	24	20	none	
Arm A: experimental arm	24	22	none	
Arm A: experimental arm	24	24	none	
Arm A: experimental arm	24	26	none	
Arm A: experimental arm	25	2	omitted	fatigue gr 2
Arm A: experimental arm	27	2	none	
Arm A: experimental arm	27	4	none	
Arm A: experimental arm	27	6	none	
Arm A: experimental arm	27	8	none	
Arm A: experimental arm	27	10	none	
Arm A: experimental arm	27	14	none	carnaval
Arm A: experimental arm	27	16	none	
Arm A: experimental arm	31	2	dose interrupted	asat/alat increase
Arm A: experimental arm	32	2	none	
Arm A: experimental arm	33	2	dose interrupted	skintoxicity, oral muc.
Arm A: experimental arm	33	2	dose reduction	toxicity (see above): skintoxicity, oral muc.
Arm A: experimental arm	33	4	dose reduction	toxicity previous cycle
Arm A: experimental arm	34	2	dose interrupted	pneumonitis gr 2
Arm A: experimental arm	34	4	none	progressive disease
Arm A: experimental arm	37	2	none	
Arm A: experimental arm	37	4	none	
Arm A: experimental arm	37	6	none	
Arm A: experimental arm	37	8	none	
Arm A: experimental arm	37	10	none	
Arm A: experimental arm	37	12	none	
Arm A: experimental arm	37	14	none	
Arm A: experimental arm	37	16	none	
Arm A: experimental arm	37	18	none	
Arm A: experimental arm	37	20	none	
Arm A: experimental arm	37	22	none	
Arm A: experimental arm	37	24	none	
Arm A: experimental arm	38	2	none	
Arm A: experimental arm	38	4	none	
Arm A: experimental arm	38	6	delay	operation for abdominal wall herniation
Arm A: experimental arm	38	8	none	
Arm A: experimental arm	38	10	none	
Arm A: experimental arm	38	12	none	
Arm A: experimental arm	38	14	none	
Arm A: experimental arm	38	16	none	
Arm A: experimental arm	38	18	none	
Arm A: experimental arm	38	20	none	
Arm A: experimental arm	38	22	none	
Arm A: experimental arm	42	2	none	
Arm A: experimental arm	42	4	none	

Table 29: *(continued)*

Arm	Patnr	Cycle	Modification	Reason
Arm A: experimental arm	42	4	dose reduction	mucositis
Arm A: experimental arm	42	4	none	
Arm A: experimental arm	42	4	dose escalation	mucositis
Arm A: experimental arm	42	6	other	mucositis ->50% 2 months because of holiday
Arm A: experimental arm	42	8	none	earlier reduction
Arm A: experimental arm	42	10	none	earlier reduction
Arm A: experimental arm	43	2	none	
Arm A: experimental arm	46	2	omitted	progressive disease
Arm A: experimental arm	49	2	none	
Arm A: experimental arm	49	4	none	
Arm A: experimental arm	49	6	none	
Arm A: experimental arm	49	8	none	
Arm A: experimental arm	49	10	none	
Arm A: experimental arm	49	12	none	
Arm A: experimental arm	49	14	none	
Arm A: experimental arm	49	18	none	
Arm A: experimental arm	49	20	none	
Arm A: experimental arm	49	22	dose reduction	
Arm A: experimental arm	50	2	none	
Arm A: experimental arm	50	4	none	
Arm A: experimental arm	50	6	none	
Arm A: experimental arm	50	8	none	
Arm A: experimental arm	50	9	none	
Arm A: experimental arm	55	2	none	
Arm A: experimental arm	55	4	none	
Arm A: experimental arm	55	6	other	patient forgot intake on 26-07-2014
Arm A: experimental arm	55	6	none	
Arm A: experimental arm	55	8	none	
Arm A: experimental arm	55	9	none	
Arm A: experimental arm	55	10	delay	dicussion over progressive disease and second opinion
Arm A: experimental arm	55	11	none	
Arm A: experimental arm	55	12	none	
Arm A: experimental arm	56	2	none	
Arm A: experimental arm	56	2	dose interrupted	1 day interruption due to admission for collaps
Arm A: experimental arm	57	2	dose interrupted	unacceptable toxicity
Arm A: experimental arm	58	2	none	
Arm A: experimental arm	59	2	none	
Arm A: experimental arm	60	4	none	
Arm A: experimental arm	60	6	none	
Arm A: experimental arm	60	8	none	
Arm A: experimental arm	60	10	none	
Arm A: experimental arm	60	12	none	
Arm A: experimental arm	60	14	none	

Table 29: *(continued)*

Arm	Patnr	Cycle	Modification	Reason
Arm A: experimental arm	60	20	none	
Arm A: experimental arm	60	22	none	
Arm A: experimental arm	61	2	none	
Arm A: experimental arm	61	4	none	
Arm A: experimental arm	61	6	none	
Arm A: experimental arm	61	8	none	
Arm A: experimental arm	64	2	dose interrupted	stomatitis gr 2
Arm A: experimental arm	64	2	none	
Arm A: experimental arm	64	4	omitted	tablet forgotten on 30/04/2014
Arm A: experimental arm	64	4	none	
Arm A: experimental arm	64	6	none	
Arm A: experimental arm	64	8	none	
Arm A: experimental arm	66	2	none	
Arm A: experimental arm	66	4	none	
Arm A: experimental arm	66	6	none	
Arm A: experimental arm	66	8	none	
Arm A: experimental arm	67	2	none	
Arm A: experimental arm	69	2	dose interrupted	SAE
Arm A: experimental arm	69	2	none	
Arm A: experimental arm	69	4	none	
Arm A: experimental arm	69	6	none	
Arm A: experimental arm	69	8	none	
Arm A: experimental arm	69	10	none	
Arm A: experimental arm	71	2	none	
Arm A: experimental arm	71	6	none	
Arm A: experimental arm	71	8	none	
Arm A: experimental arm	71	10	dose reduction	toxicity
Arm A: experimental arm	73	2	dose interrupted	fatigue gr 3
Arm A: experimental arm	73	2	dose reduction	
Arm A: experimental arm	73	4	dose reduction	earlier fatigue and mucositis
Arm A: experimental arm	73	6	dose reduction	earlier reduction
Arm A: experimental arm	73	8	none	(earlier reduction)
Arm A: experimental arm	73	10	none	earlier reduction
Arm A: experimental arm	73	12	dose escalation	good toleration, worth a try
Arm A: experimental arm	73	16	none	
Arm A: experimental arm	73	18	none	
Arm A: experimental arm	73	20	none	
Arm A: experimental arm	78	2	none	
Arm A: experimental arm	80	2	none	
Arm A: experimental arm	82	2	dose interrupted	radiotherapy Th1 + Th12
Arm A: experimental arm	82	2	none	
Arm A: experimental arm	86	2	none	
Arm A: experimental arm	86	4	none	
Arm A: experimental arm	86	6	dose interrupted	brain meta, PD
Arm A: experimental arm	88	2	dose reduction	
Arm A: experimental arm	88	4	none	

Table 29: *(continued)*

Arm	Patnr	Cycle	Modification	Reason
Arm A: experimental arm	88	6	none	
Arm A: experimental arm	88	8	none	
Arm A: experimental arm	88	10	none	
Arm A: experimental arm	88	12	dose reduction	
Arm A: experimental arm	88	14	none	
Arm A: experimental arm	88	16	none	
Arm A: experimental arm	88	16	dose interrupted	diarrhea
Arm A: experimental arm	88	18	none	
Arm A: experimental arm	88	20	dose interrupted	
Arm A: experimental arm	88	20	none	
Arm A: experimental arm	98	2	none	
Arm A: experimental arm	98	4	none	
Arm A: experimental arm	98	6	none	
Arm A: experimental arm	98	8	none	
Arm A: experimental arm	98	10	none	
Arm A: experimental arm	101	2	none	
Arm A: experimental arm	101	4	none	
Arm B: comparative arm	2	10	dose interrupted	toxicity
Arm B: comparative arm	2	10	dose interrupted	toxicity
Arm B: comparative arm	2	10	dose interrupted	unknown
Arm B: comparative arm	6	7	delay	because of radiation
Arm B: comparative arm	6	7	delay	because of hospitalization
Arm B: comparative arm	9	2	dose interrupted	malaise and hypercalsemia
Arm B: comparative arm	9	2	dose reduction	disease progression
Arm B: comparative arm	13	8	dose interrupted	chostridium infection
Arm B: comparative arm	21	3	none	
Arm B: comparative arm	21	4	none	
Arm B: comparative arm	23	2	none	
Arm B: comparative arm	23	3	none	
Arm B: comparative arm	23	4	none	
Arm B: comparative arm	23	5	none	
Arm B: comparative arm	23	6	none	
Arm B: comparative arm	23	7	none	
Arm B: comparative arm	29	5	dose interrupted	toxicity
Arm B: comparative arm	29	5	dose reduction	
Arm B: comparative arm	29	6	omitted	progressive dyspnea
Arm B: comparative arm	30	3	delay	mucositis gr 3
Arm B: comparative arm	30	3	dose reduction	Mucositis
Arm B: comparative arm	30	4	dose reduction	mucositis
Arm B: comparative arm	30	4	delay	because of radiation
Arm B: comparative arm	30	4	dose interrupted	because of radiation
Arm B: comparative arm	30	5	dose reduction	mucositis
Arm B: comparative arm	30	6	dose reduction	see before
Arm B: comparative arm	35	5	none	
Arm B: comparative arm	35	6	none	
Arm B: comparative arm	45	3	none	

Table 29: *(continued)*

Arm	Patnr	Cycle	Modification	Reason
Arm B: comparative arm	45	4	dose interrupted	pneumonitis
Arm B: comparative arm	45	4	omitted	ejection fraction decreased
Arm B: comparative arm	53	10	dose interrupted	dyspnea
Arm B: comparative arm	63	8	omitted	central venous accident
Arm B: comparative arm	68	7	none	
Arm B: comparative arm	68	8	none	
Arm B: comparative arm	68	9	none	
Arm B: comparative arm	68	10	none	
Arm B: comparative arm	68	11	none	
Arm B: comparative arm	68	12	none	
Arm B: comparative arm	68	13	none	
Arm B: comparative arm	68	14	dose reduction	
Arm B: comparative arm	68	15	delay	delayed due to planned metastectomy
Arm B: comparative arm	68	16	none	
Arm B: comparative arm	68	17	dose interrupted	toxicity
Arm B: comparative arm	79	6	none	
Arm B: comparative arm	79	7	none	
Arm B: comparative arm	79	8	none	
Arm B: comparative arm	81	7	none	
Arm B: comparative arm	81	8	none	
Arm B: comparative arm	81	9	none	
Arm B: comparative arm	81	10	none	
Arm B: comparative arm	92	6	delay	first radio therapy than start everolimus
Arm B: comparative arm	95	6	none	
Arm B: comparative arm	95	6	dose interrupted	toxicity
Arm B: comparative arm	96	2	delay	pt received RT

12 Appendix C: adverse events at baseline and after end of study treatment

Table 30: Adverse events of grade at least 3 at baseline per event type per patient by highest grade

	Arm		
	Arm A: experimental arm	Arm B: comparative arm	All
	5	3	8
Event			
Abdominal pain, grade 3	0 (0%)	1 (33%)	1 (12%)
Anorexia, grade 3	0 (0%)	1 (33%)	1 (12%)
Dehydration, grade 3	0 (0%)	1 (33%)	1 (12%)
Fatique, grade 3	1 (20%)	0 (0%)	1 (12%)
Gammaglutamyltransferase increased, grade 3	2 (40%)	0 (0%)	2 (25%)
Hypertension, grade 3	1 (20%)	0 (0%)	1 (12%)
Pain unspecified (pain), grade 4	1 (20%)	0 (0%)	1 (12%)

13 Appendix D: adverse events as denoted on the ECRF

Table 31: Adverse events since start treatment of grade at least 3 as written on the CRF per event type per patient by highest grade

	Arm		
	Arm A: exp. arm	Arm B: comparative arm	All
	111	120	231
Event			
abdominal pain, grade 3	1 (1%)	0 (0%)	1 (0%)
abdominal sepsis, grade 4	0 (0%)	1 (1%)	1 (0%)
acute coronary syndrome, grade 3	0 (0%)	1 (1%)	1 (0%)
acute kidney injury, grade 3	0 (0%)	1 (1%)	1 (0%)
alanine aminotransferase increased, grade 3	0 (0%)	1 (1%)	1 (0%)
ALAT > 10xUIN, grade 3	0 (0%)	1 (1%)	1 (0%)
ALAT high, grade 3	1 (1%)	0 (0%)	1 (0%)
alat increase, grade 3	1 (1%)	0 (0%)	1 (0%)
alat increased, grade 3	2 (2%)	0 (0%)	2 (1%)
ALAT increased, grade 3	4 (4%)	4 (3%)	8 (3%)
ALAT intermittent grades, grade 3	0 (0%)	1 (1%)	1 (0%)
alat, grade 3	1 (1%)	1 (1%)	2 (1%)
ALAT, grade 3	0 (0%)	1 (1%)	1 (0%)
alk. phosph. increased, grade 3	1 (1%)	0 (0%)	1 (0%)
Alk. Phosphatase iincraesed, grade 3	0 (0%)	1 (1%)	1 (0%)
alkaline phosphatase increased, grade 3	0 (0%)	1 (1%)	1 (0%)
alkaline phosphate, grade 3	0 (0%)	1 (1%)	1 (0%)
allc. phosph high, grade 3	1 (1%)	0 (0%)	1 (0%)
Alopecia, grade 3	0 (0%)	1 (1%)	1 (0%)
amylase increase, grade 4	0 (0%)	1 (1%)	1 (0%)
anemia, grade 3	1 (1%)	3 (2%)	4 (2%)
anorexia +SV (04/05/2013), grade 3	1 (1%)	0 (0%)	1 (0%)
anorexia, grade 3	2 (2%)	2 (2%)	4 (2%)
anuria, grade 3	0 (0%)	1 (1%)	1 (0%)
aphasia, grade 3	1 (1%)	0 (0%)	1 (0%)
asal, grade 3	0 (0%)	1 (1%)	1 (0%)
ASAT > 5x UIN, grade 3	0 (0%)	1 (1%)	1 (0%)
ASAT high, grade 3	1 (1%)	0 (0%)	1 (0%)
asat increase, grade 3	1 (1%)	0 (0%)	1 (0%)
asat increased, grade 3	2 (2%)	0 (0%)	2 (1%)
ASAT increased, grade 3	4 (4%)	3 (2%)	7 (3%)
ASAT intermittent grades, grade 3	0 (0%)	1 (1%)	1 (0%)
ASAT, grade 3	0 (0%)	1 (1%)	1 (0%)
asthenia muscle weakness, grade 3	1 (1%)	0 (0%)	1 (0%)
back pain, grade 3	1 (1%)	0 (0%)	1 (0%)
backpain, grade 3	1 (1%)	0 (0%)	1 (0%)
biliruben, grade 4	0 (0%)	1 (1%)	1 (0%)
bilirubin increased, grade 3	1 (1%)	0 (0%)	1 (0%)
constipation, grade 3	0 (0%)	2 (2%)	2 (1%)

copd GIII, grade 3	1 (1%)	0 (0%)	1 (0%)
dehydration, grade 3	2 (2%)	2 (2%)	4 (2%)
diarrhea, grade 3	5 (5%)	4 (3%)	9 (4%)
diarrhea/due to clostridium, grade 3	0 (0%)	1 (1%)	1 (0%)
dizziness, grade 3	1 (1%)	0 (0%)	1 (0%)
dysphagia, grade 3	1 (1%)	0 (0%)	1 (0%)
dyspnea, grade 3	1 (1%)	3 (2%)	4 (2%)
dyspneu, grade 3	1 (1%)	0 (0%)	1 (0%)
dyspnoe, grade 3	0 (0%)	1 (1%)	1 (0%)
dyspnoe, grade 5	1 (1%)	0 (0%)	1 (0%)
Dyspnoea, grade 3	1 (1%)	0 (0%)	1 (0%)
Elevated Alat, grade 3	0 (0%)	1 (1%)	1 (0%)
elevated Asat, grade 3	0 (0%)	1 (1%)	1 (0%)
Elevated GGT, grade 3	0 (0%)	1 (1%)	1 (0%)
Empyeem, grade 4	1 (1%)	0 (0%)	1 (0%)
enterocolitis infectious, grade 3	0 (0%)	1 (1%)	1 (0%)
esophageal obstruction, grade 5	0 (0%)	1 (1%)	1 (0%)
fatigue, grade 3	2 (2%)	4 (3%)	6 (3%)
Fatigue, grade 3	0 (0%)	2 (2%)	2 (1%)
fever, grade 3	0 (0%)	1 (1%)	1 (0%)
Gamma-GT increased, grade 3	1 (1%)	0 (0%)	1 (0%)
gamma GT increased, grade 3	1 (1%)	0 (0%)	1 (0%)
gamma gt, grade 3	1 (1%)	0 (0%)	1 (0%)
GGT high, grade 3	1 (1%)	0 (0%)	1 (0%)
ggt increased, grade 3	1 (1%)	1 (1%)	2 (1%)
Ggt increased, grade 3	1 (1%)	0 (0%)	1 (0%)
GGt increased, grade 3	1 (1%)	0 (0%)	1 (0%)
GGT increased, grade 3	1 (1%)	2 (2%)	3 (1%)
ggt, grade 3	1 (1%)	0 (0%)	1 (0%)
ggt, grade 4	0 (0%)	1 (1%)	1 (0%)
hepatic disorder0, grade 3	0 (0%)	1 (1%)	1 (0%)
hepatic failure, grade 3	2 (2%)	0 (0%)	2 (1%)
hepatitis, grade 3	0 (0%)	1 (1%)	1 (0%)
hepatotoxicity, grade 3	1 (1%)	0 (0%)	1 (0%)
hypercalcemia, grade 3	0 (0%)	1 (1%)	1 (0%)
hypercalcemia, grade 4	1 (1%)	0 (0%)	1 (0%)
hyperglycemia, grade 3	1 (1%)	2 (2%)	3 (1%)
hypertension intermittent, grade 3	1 (1%)	0 (0%)	1 (0%)
hypertension, grade 3	13 (12%)	10 (8%)	23 (10%)
hypertriglyceridemia, grade 3	1 (1%)	0 (0%)	1 (0%)
hypokalemia, grade 3	0 (0%)	1 (1%)	1 (0%)
hyponatremia, grade 3	1 (1%)	0 (0%)	1 (0%)
Hyponatremia, grade 3	1 (1%)	0 (0%)	1 (0%)
hypophosphatemia, grade 3	0 (0%)	1 (1%)	1 (0%)
hypotension, grade 3	0 (0%)	1 (1%)	1 (0%)
ileus, grade 3	1 (1%)	0 (0%)	1 (0%)
increased ALT, grade 3	0 (0%)	1 (1%)	1 (0%)
increased AST, grade 3	0 (0%)	1 (1%)	1 (0%)
increased Ggt, grade 3	1 (1%)	0 (0%)	1 (0%)

insomnia, grade 3	0 (0%)	1 (1%)	1 (0%)
insult (syncope), grade 3	1 (1%)	0 (0%)	1 (0%)
intracerebral bleeding, grade 5	1 (1%)	0 (0%)	1 (0%)
irregular menstruation, grade 3	0 (0%)	1 (1%)	1 (0%)
left ventricular systolic dysp (extrasystole), grade 3	1 (1%)	0 (0%)	1 (0%)
lipase increase, grade 3	1 (1%)	0 (0%)	1 (0%)
lipase increased, grade 3	0 (0%)	1 (1%)	1 (0%)
liver toxicity, grade 3	1 (1%)	0 (0%)	1 (0%)
loss of taste, grade 3	1 (1%)	0 (0%)	1 (0%)
lung infection, grade 3	0 (0%)	1 (1%)	1 (0%)
malaise, grade 4	0 (0%)	1 (1%)	1 (0%)
mood alteration, grade 3	0 (0%)	1 (1%)	1 (0%)
mucositis mouth, grade 3	1 (1%)	0 (0%)	1 (0%)
mucositis oral, grade 3	1 (1%)	0 (0%)	1 (0%)
mucositis, grade 3	2 (2%)	0 (0%)	2 (1%)
mucositis, oral, grade 3	1 (1%)	1 (1%)	2 (1%)
muscle weakness, grade 3	1 (1%)	0 (0%)	1 (0%)
nausea, grade 3	2 (2%)	2 (2%)	4 (2%)
neuropathy motor (power lost right foot), grade 3	0 (0%)	1 (1%)	1 (0%)
neuropathy, grade 3	0 (0%)	1 (1%)	1 (0%)
neutropenia, grade 3	2 (2%)	0 (0%)	2 (1%)
pain (after rth), grade 3	1 (1%)	0 (0%)	1 (0%)
pain (tumor related), grade 3	0 (0%)	1 (1%)	1 (0%)
pain back hip, grade 3	1 (1%)	0 (0%)	1 (0%)
pain due to bone, grade 3	0 (0%)	1 (1%)	1 (0%)
pain left flank, grade 3	0 (0%)	1 (1%)	1 (0%)
pain legs, grade 3	0 (0%)	1 (1%)	1 (0%)
pain thoracal, grade 3	1 (1%)	0 (0%)	1 (0%)
pain, grade 3	0 (0%)	2 (2%)	2 (1%)
pancreratitis, grade 3	0 (0%)	1 (1%)	1 (0%)
perforation colon, grade 5	0 (0%)	1 (1%)	1 (0%)
pleural effusion, grade 3	1 (1%)	1 (1%)	2 (1%)
pneumonia, grade 3	1 (1%)	1 (1%)	2 (1%)
progressive disease, grade 3	0 (0%)	2 (2%)	2 (1%)
progressive pain, grade 3	0 (0%)	1 (1%)	1 (0%)
proteinuria, grade 3	0 (0%)	3 (2%)	3 (1%)
pulmonary embolism, grade 4	1 (1%)	0 (0%)	1 (0%)
renal insufficiency, grade 3	0 (0%)	1 (1%)	1 (0%)
respiratory failure(with decompensatio cordis), grade 4	0 (0%)	1 (1%)	1 (0%)
sensory neuropathy, grade 3	1 (1%)	0 (0%)	1 (0%)
sepsis, grade 3	0 (0%)	1 (1%)	1 (0%)
skin lesions head (squamouscellcarcinoma), grade 3	1 (1%)	0 (0%)	1 (0%)
stomach pain, grade 3	0 (0%)	1 (1%)	1 (0%)
stomatitis, grade 3	0 (0%)	2 (2%)	2 (1%)
syncope, grade 3	3 (3%)	0 (0%)	3 (1%)
Thoracal pain, grade 3	1 (1%)	0 (0%)	1 (0%)
tooth flesh infection, grade 3	0 (0%)	1 (1%)	1 (0%)
Trombocytopenia, grade 4	0 (0%)	1 (1%)	1 (0%)
trombosis artery basilaris, grade 5	0 (0%)	1 (1%)	1 (0%)

unguis incarnatus hallux, grade 3	1 (1%)	0 (0%)	1 (0%)
urinairy tract obstruction, grade 3	0 (0%)	1 (1%)	1 (0%)
urinary tract infection, grade 3	0 (0%)	1 (1%)	1 (0%)
Urinary tract infection, grade 3	1 (1%)	0 (0%)	1 (0%)
urosepsis, grade 3	0 (0%)	1 (1%)	1 (0%)
vomiting, grade 3	1 (1%)	0 (0%)	1 (0%)
White blood cells decreased, grade 3	1 (1%)	0 (0%)	1 (0%)
yGT, grade 3	0 (0%)	1 (1%)	1 (0%)

14 Appendix E: graphical representation of patient reported outcomes over time for each patient

Arm A: experimental arm

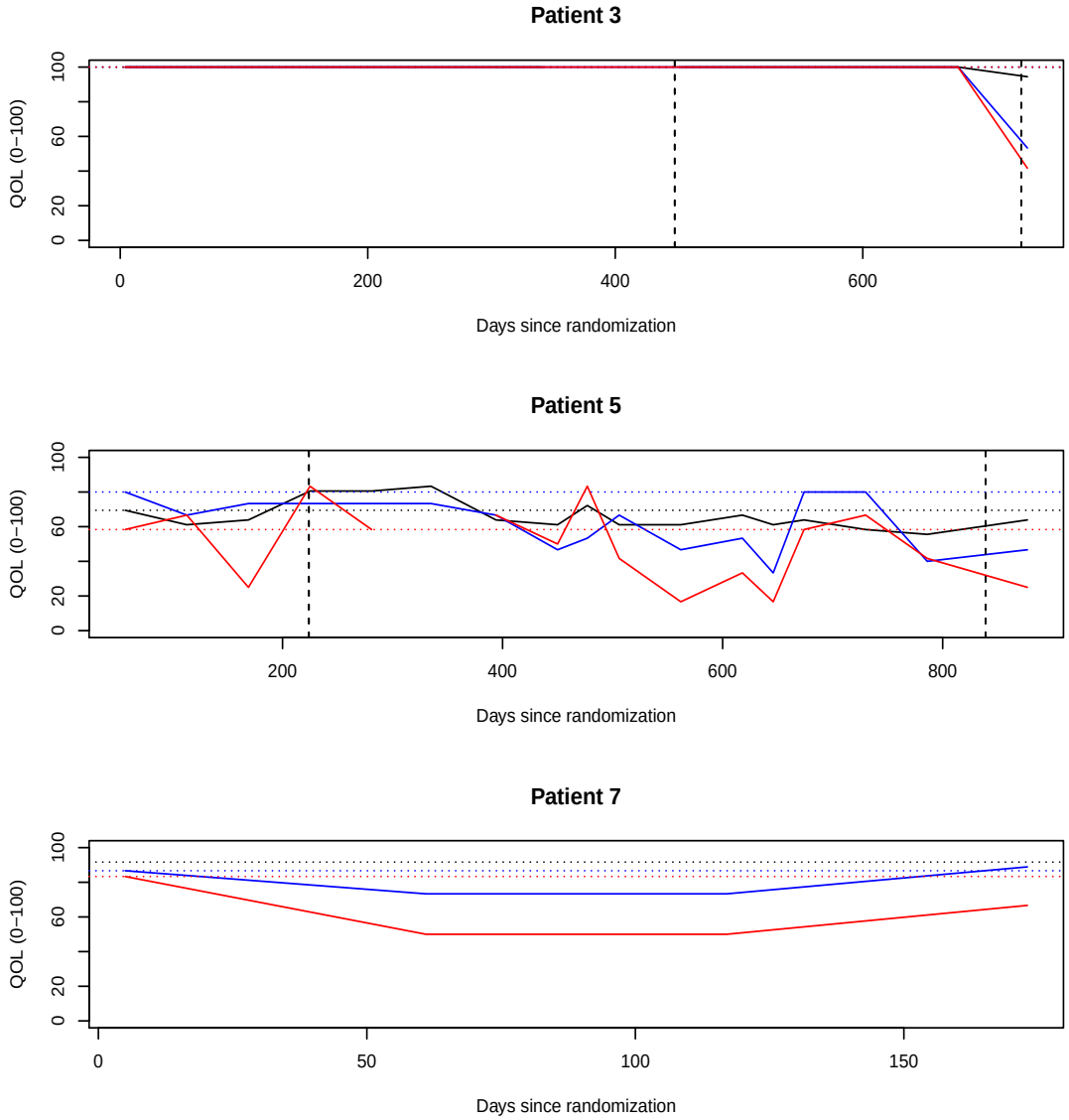


Figure 18: Patient reported quality of life over time for patients randomized in the experimental arm. Displayed are the scores on the FKSI-DRS symptom scale (black) renormalized to 0-100 to fit the picture, the Physical Functioning (PF) scale of the QLQ-C30 (blue) and the Overall Quality of Life (QL) scale of the QLQ-C30 (red). Time is measured in days, time is set to 0 at the day of randomization. Scores measured closest to randomization are also depicted by the horizontal dotted lines for comparison. First and second progression (if they occur durring the period for which QOL-information is available) are indicated by dotted vertical lines and death by a solid vertical line

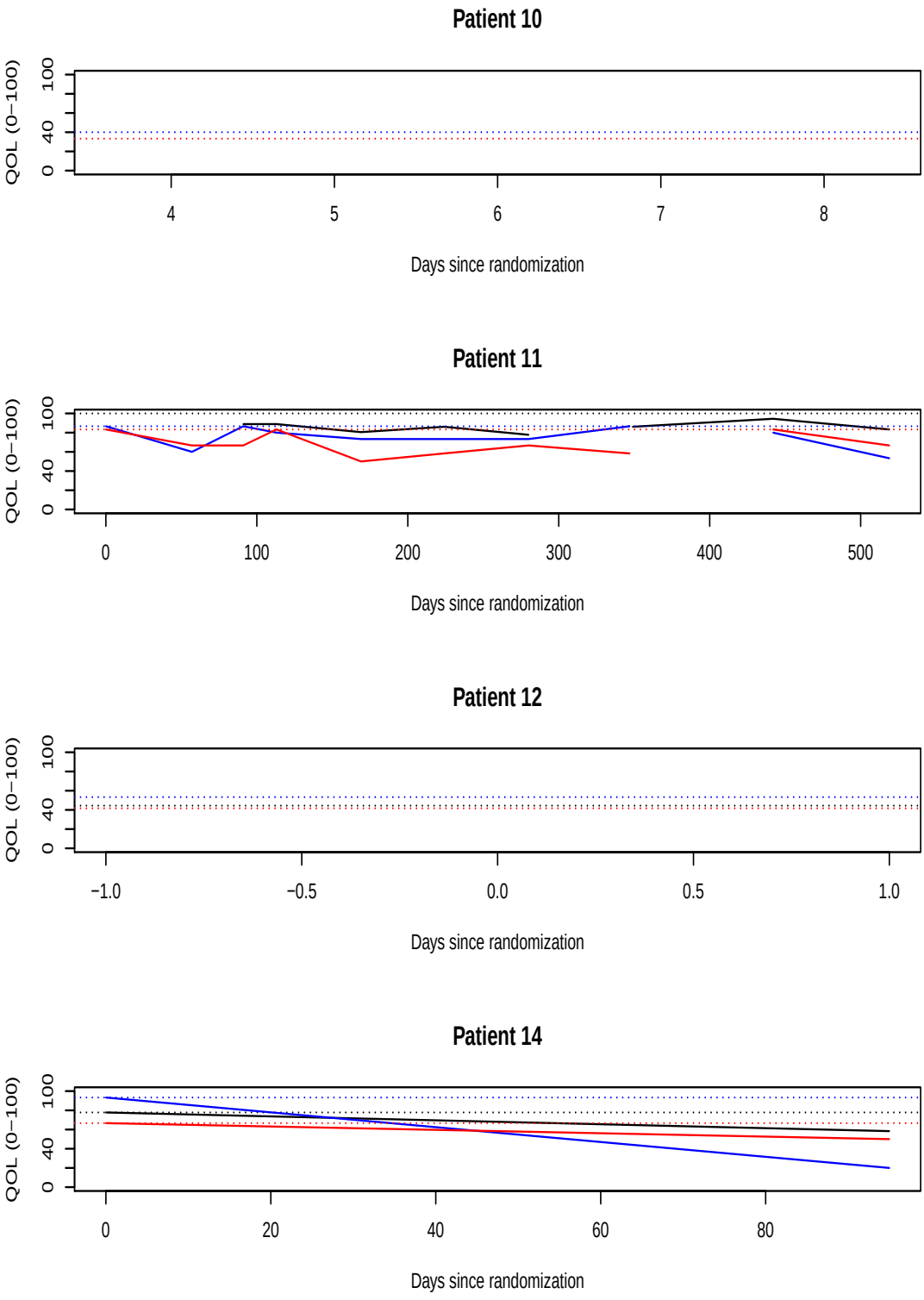


Figure 19: Patient reported FKSI-DRS (black), PF (blue) and QL (red) for patients in the experimental arm, ctd

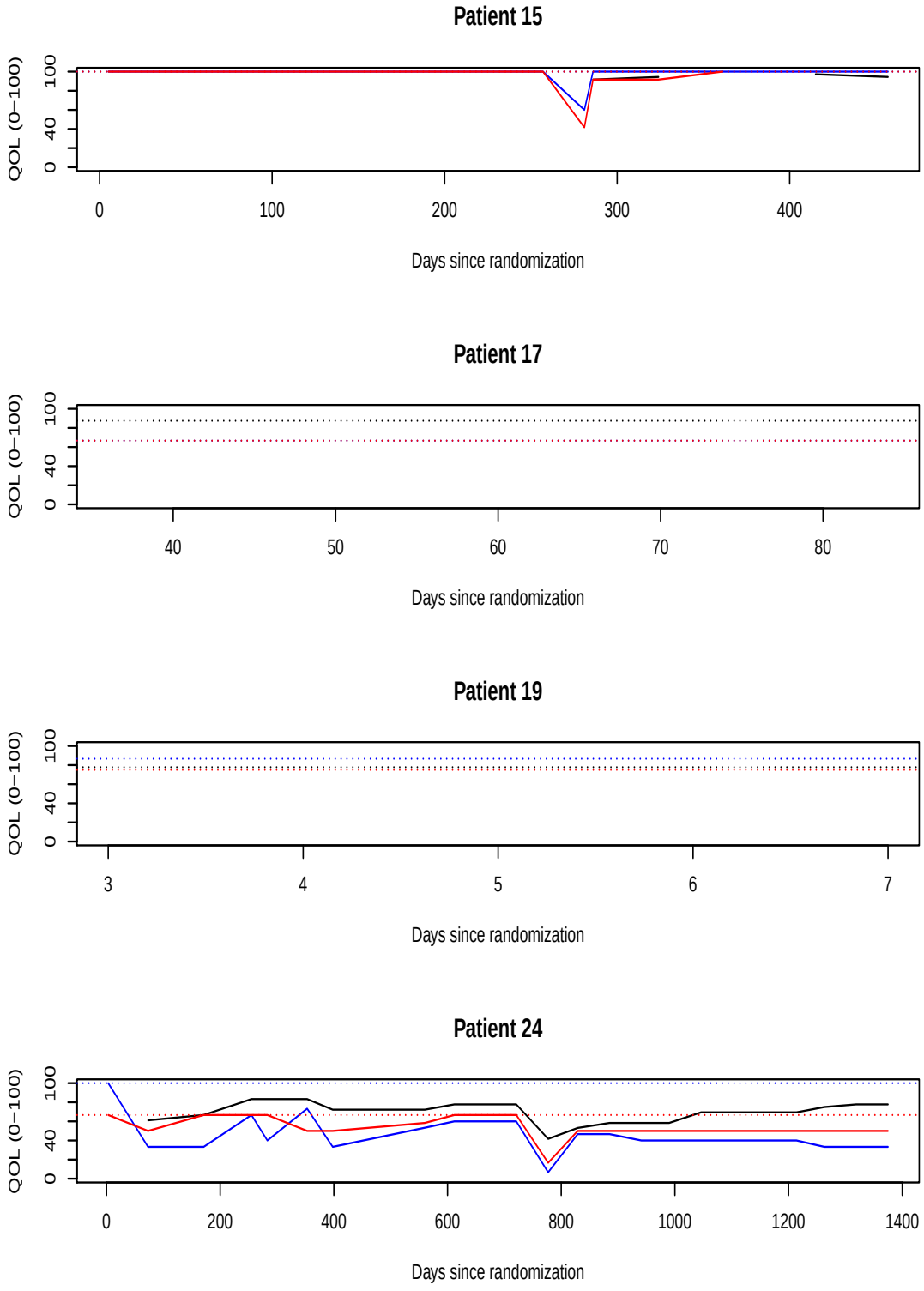
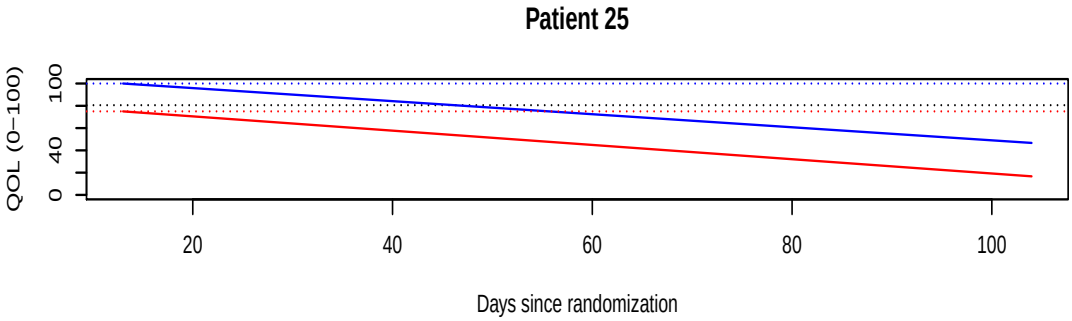
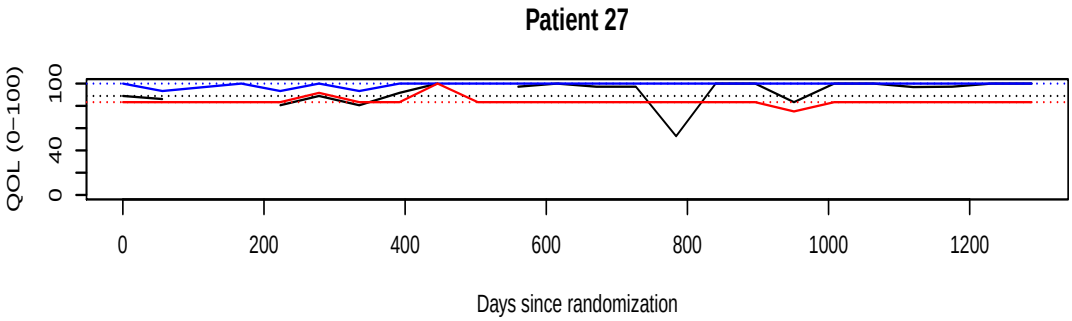
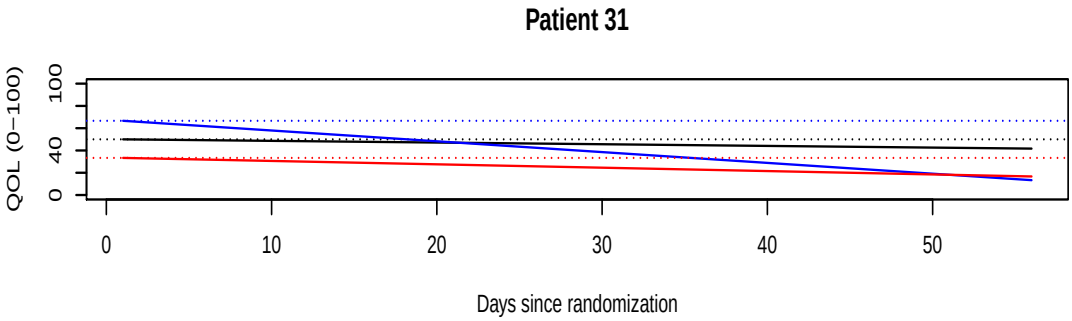


Figure 20: Patient reported FKSI-DRS (black), PF (blue) and QL (red) for patients in the experimental arm, ctd







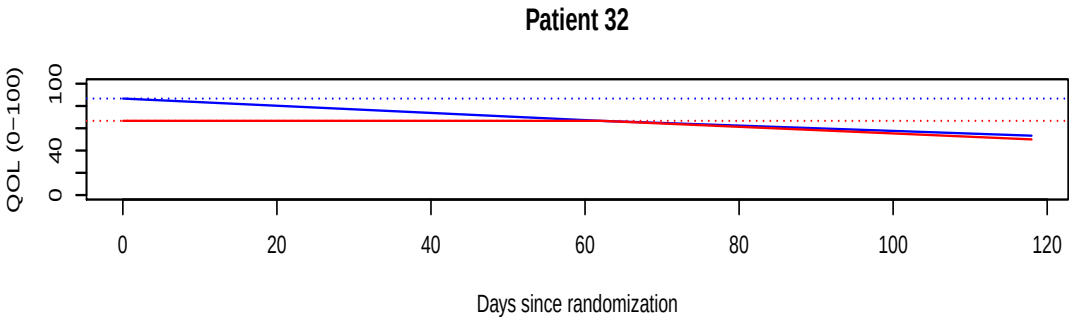


Figure 21: Patient reported FKSI-DRS (black), PF (blue) and QL (red) for patients in the experimental arm, ctd

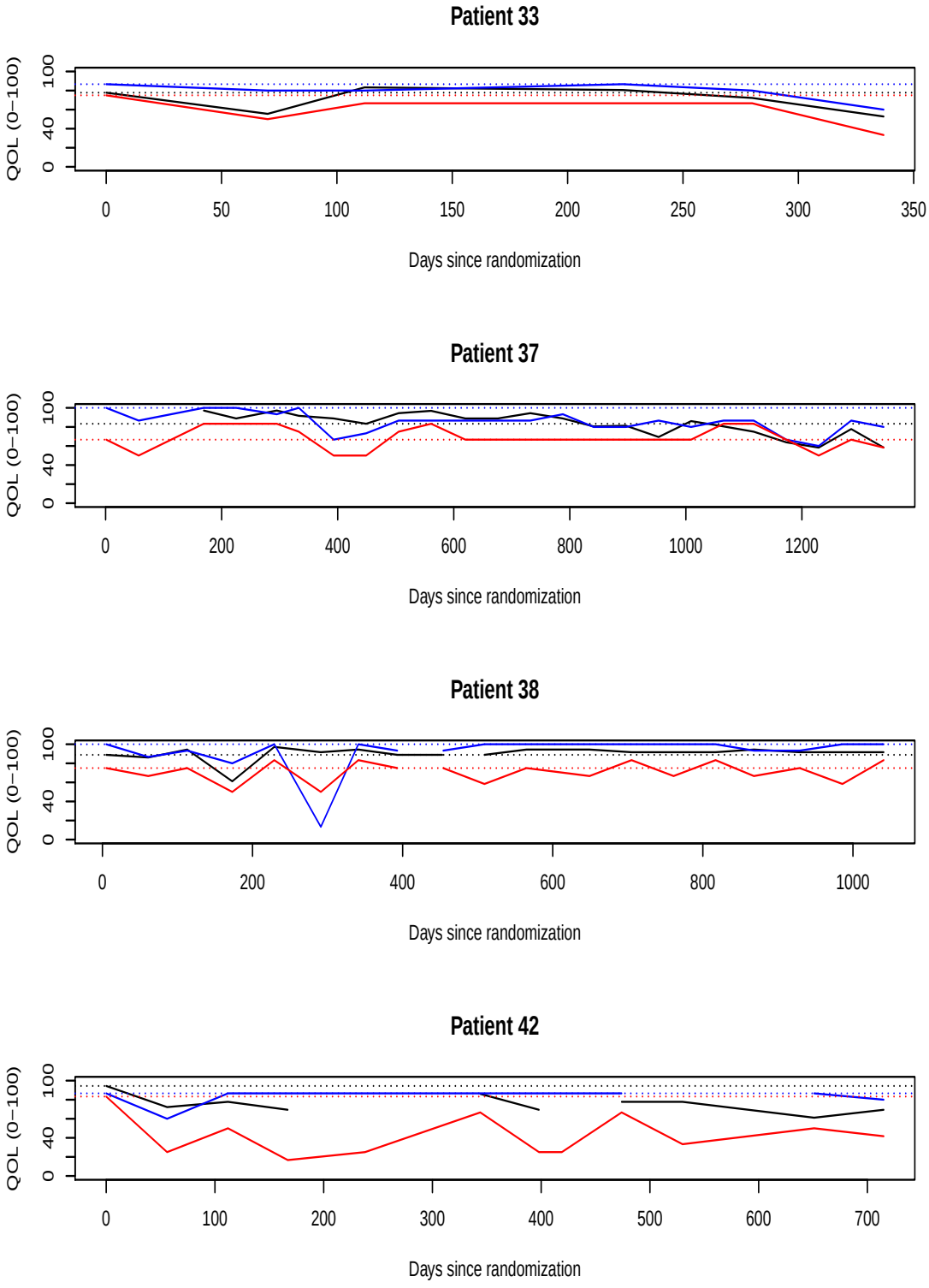
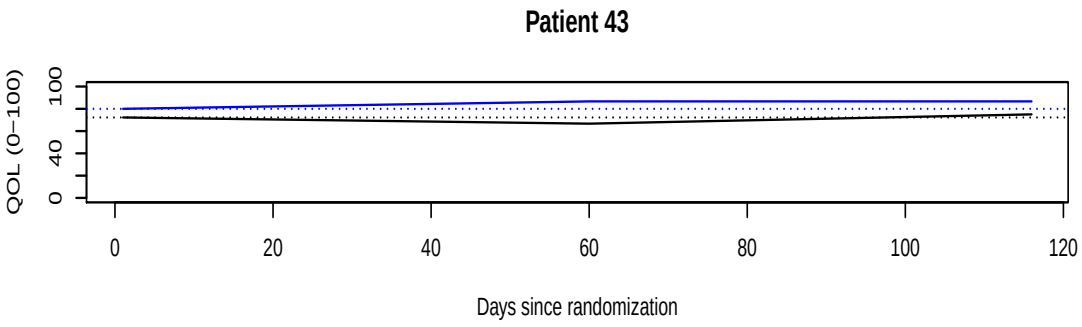
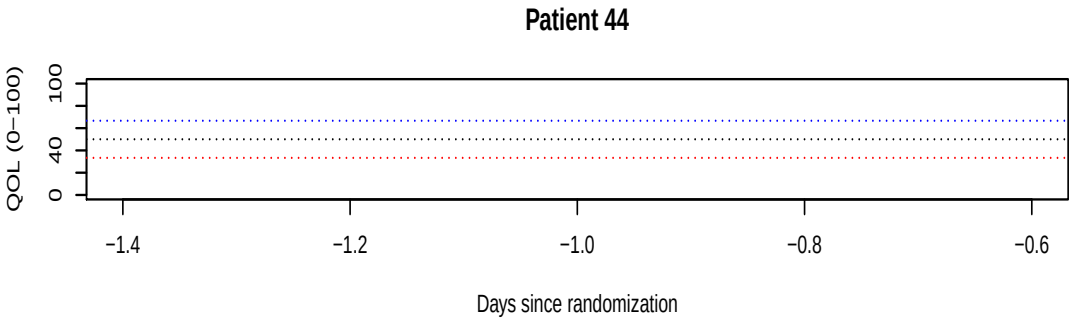
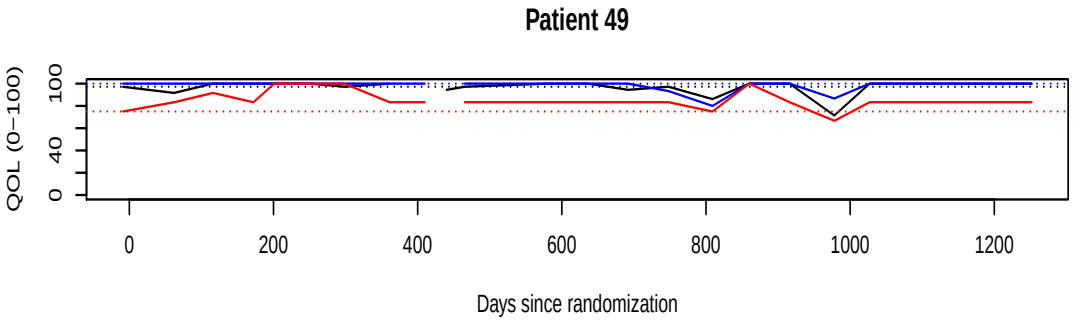


Figure 22: Patient reported FKSI-DRS (black), PF (blue) and QL (red) for patients in the experimental arm, ctd







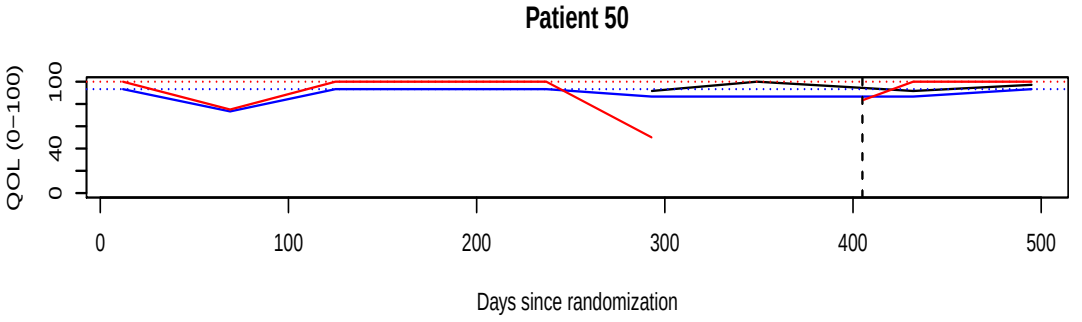
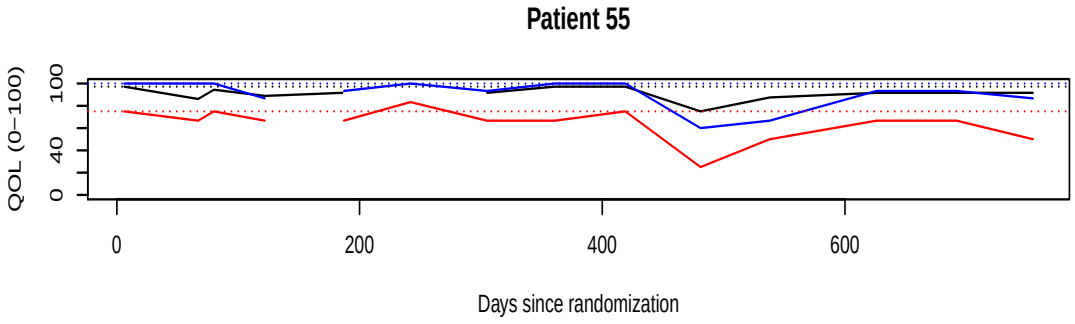
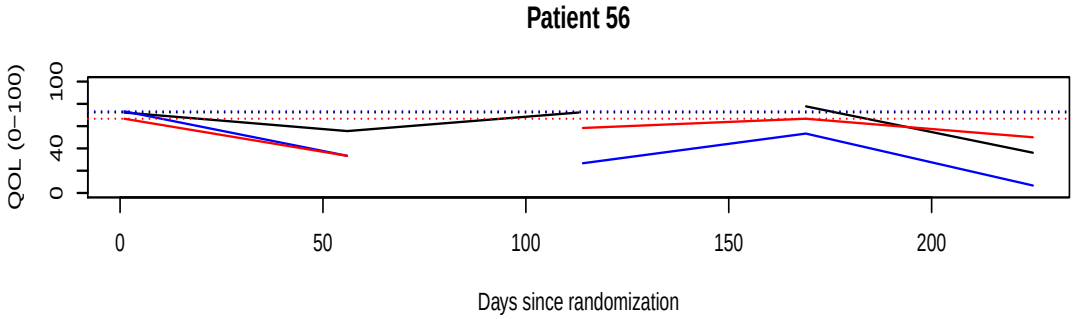
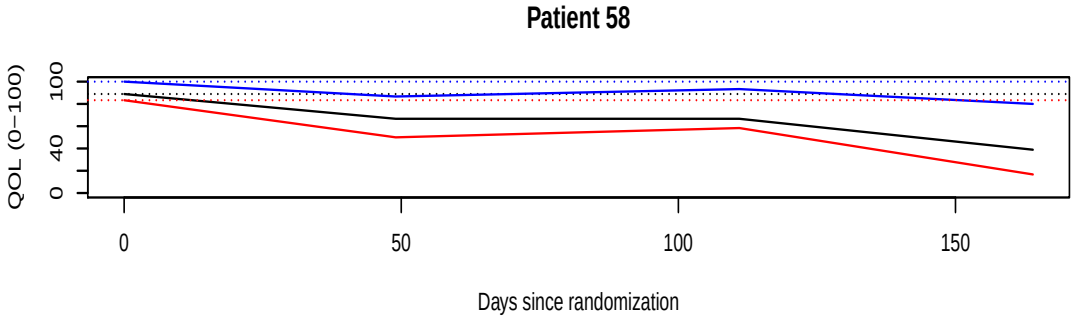


Figure 23: Patient reported FKSI-DRS (black), PF (blue) and QL (red) for patients in the experimental arm, ctd







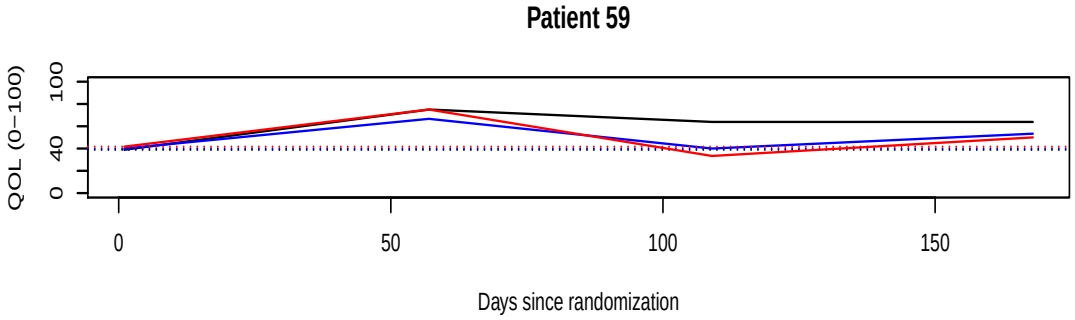
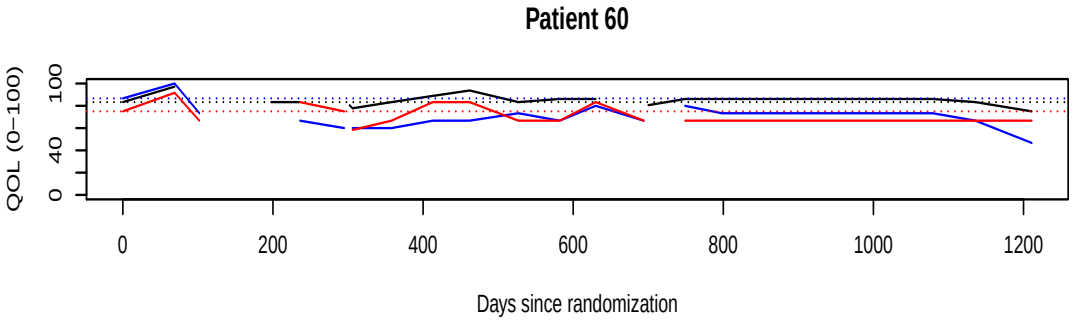
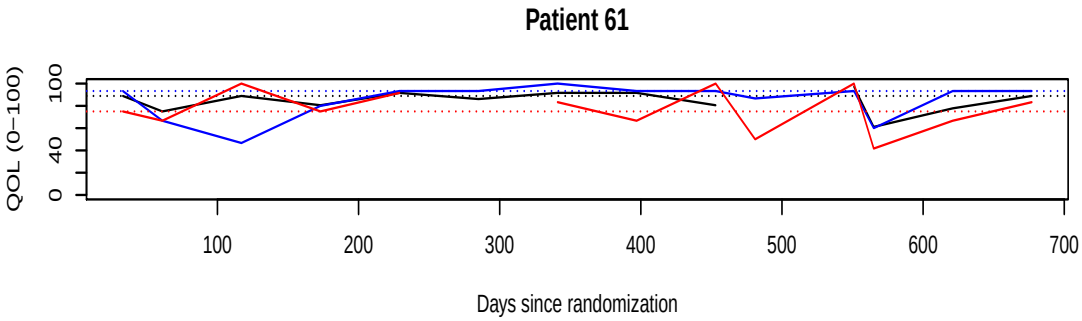
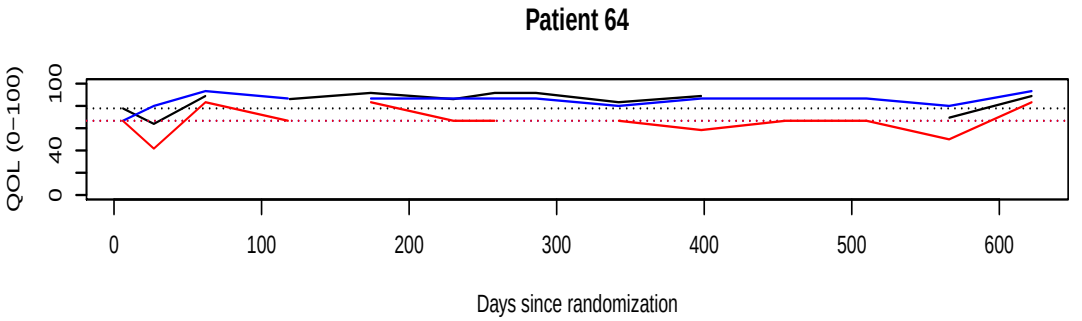


Figure 24: Patient reported FKSI-DRS (black), PF (blue) and QL (red) for patients in the experimental arm, ctd







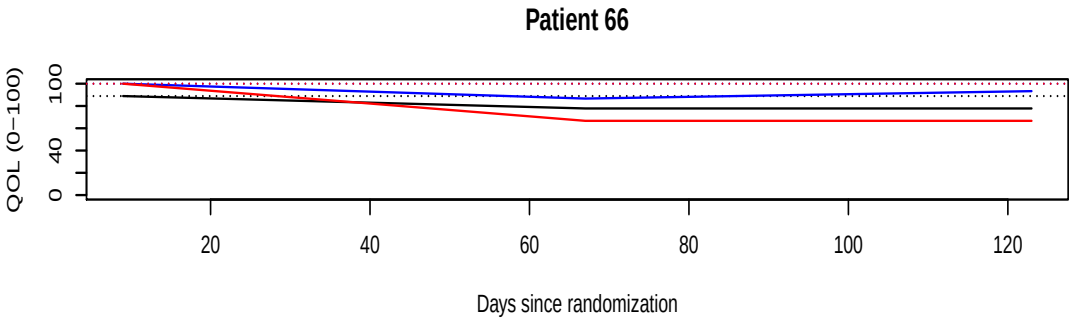


Figure 25: Patient reported FKSI-DRS (black), PF (blue) and QL (red) for patients in the experimental arm, ctd

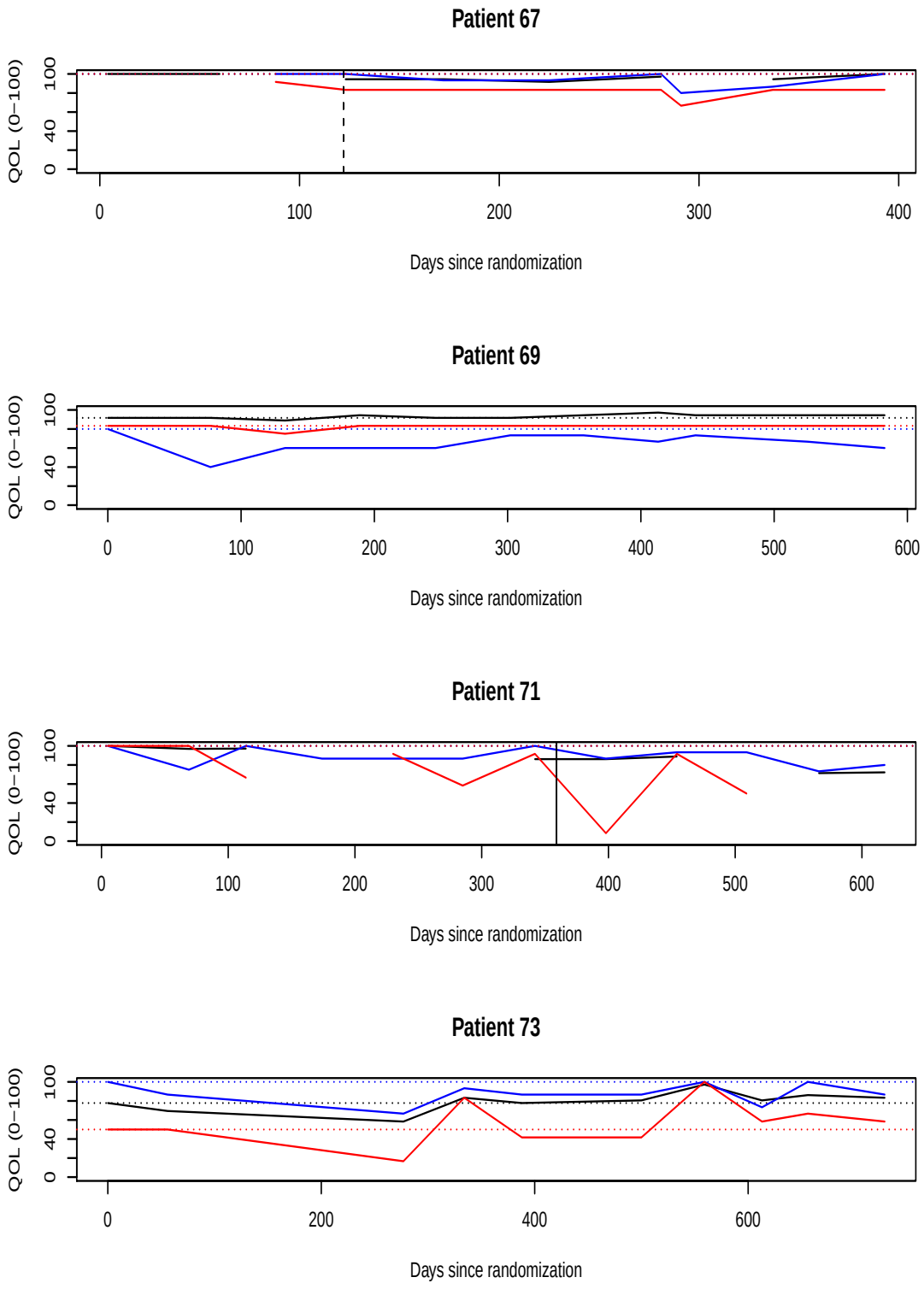
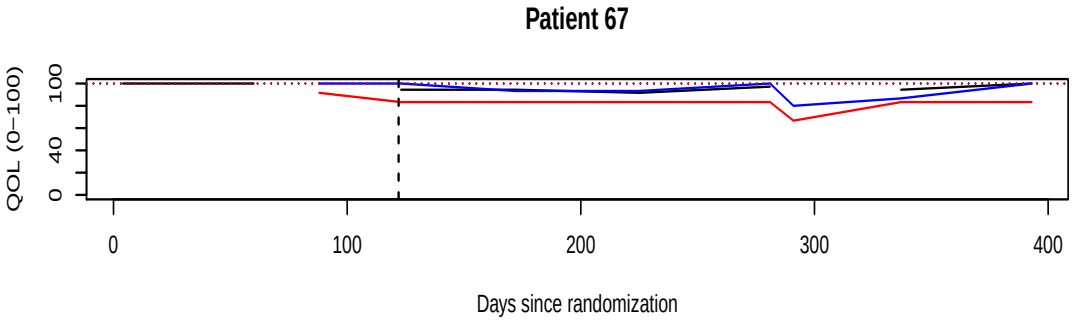
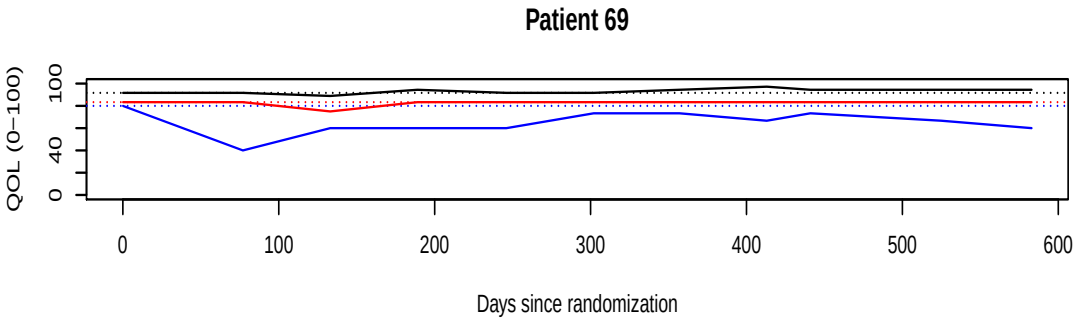
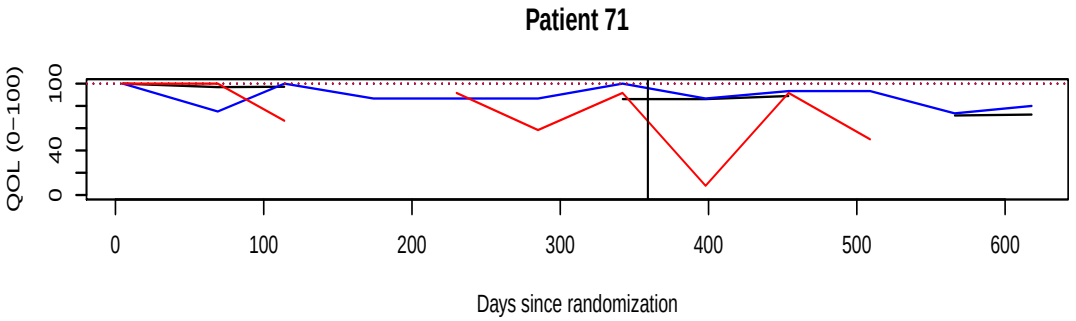


Figure 26: Patient reported FKSI-DRS (black), PF (blue) and QL (red) for patients in the experimental arm, ctd







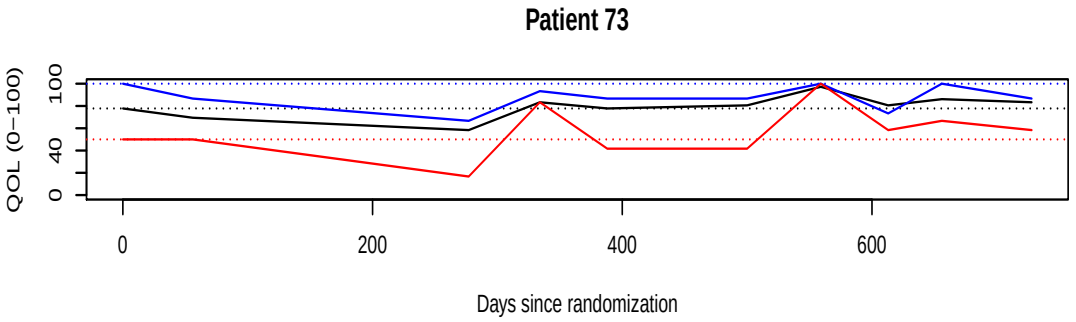


Figure 27: Patient reported FKSI-DRS (black), PF (blue) and QL (red) for patients in the experimental arm, ctd

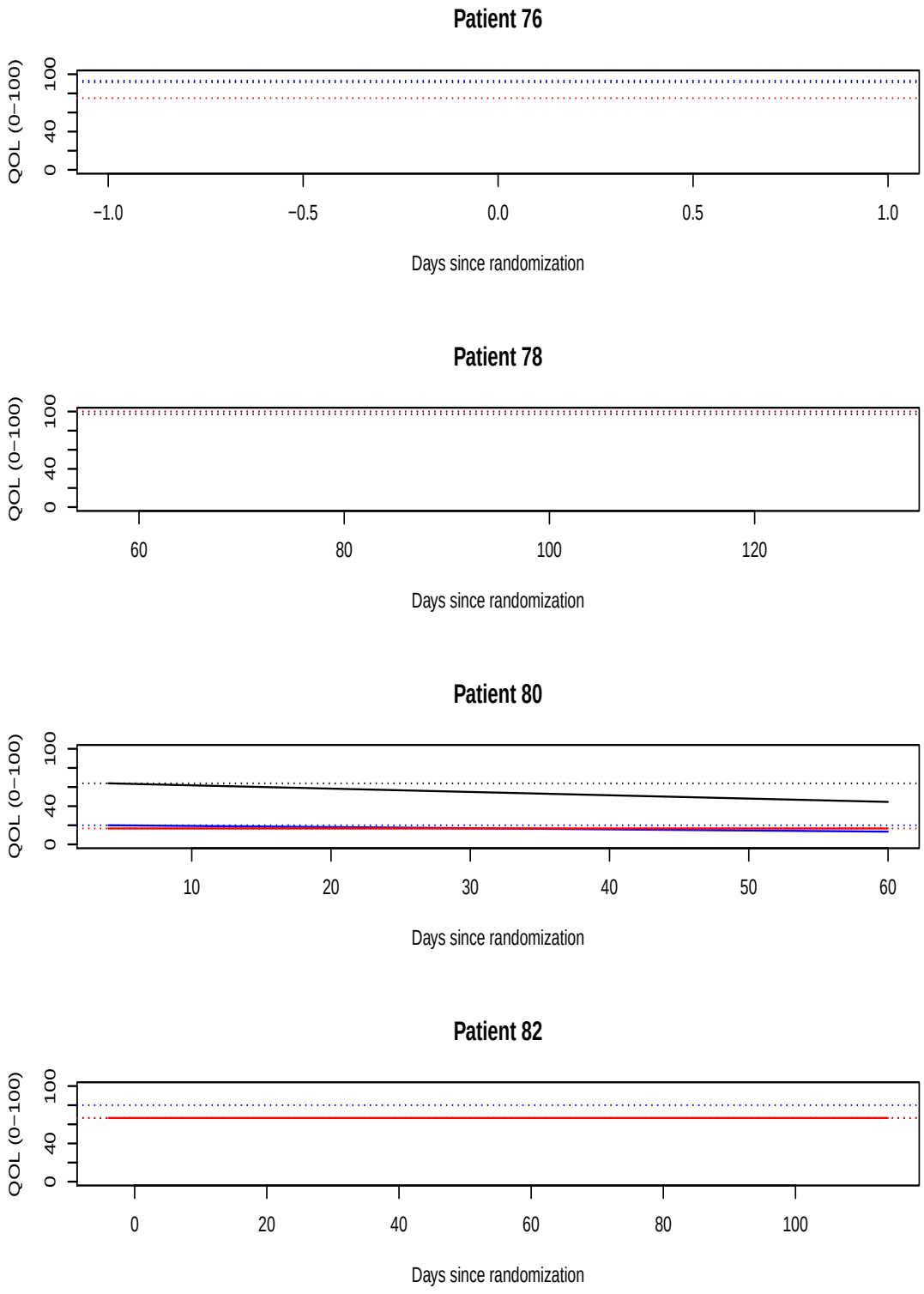


Figure 28: Patient reported FKSI-DRS (black), PF (blue) and QL (red) for patients in the experimental arm, ctd

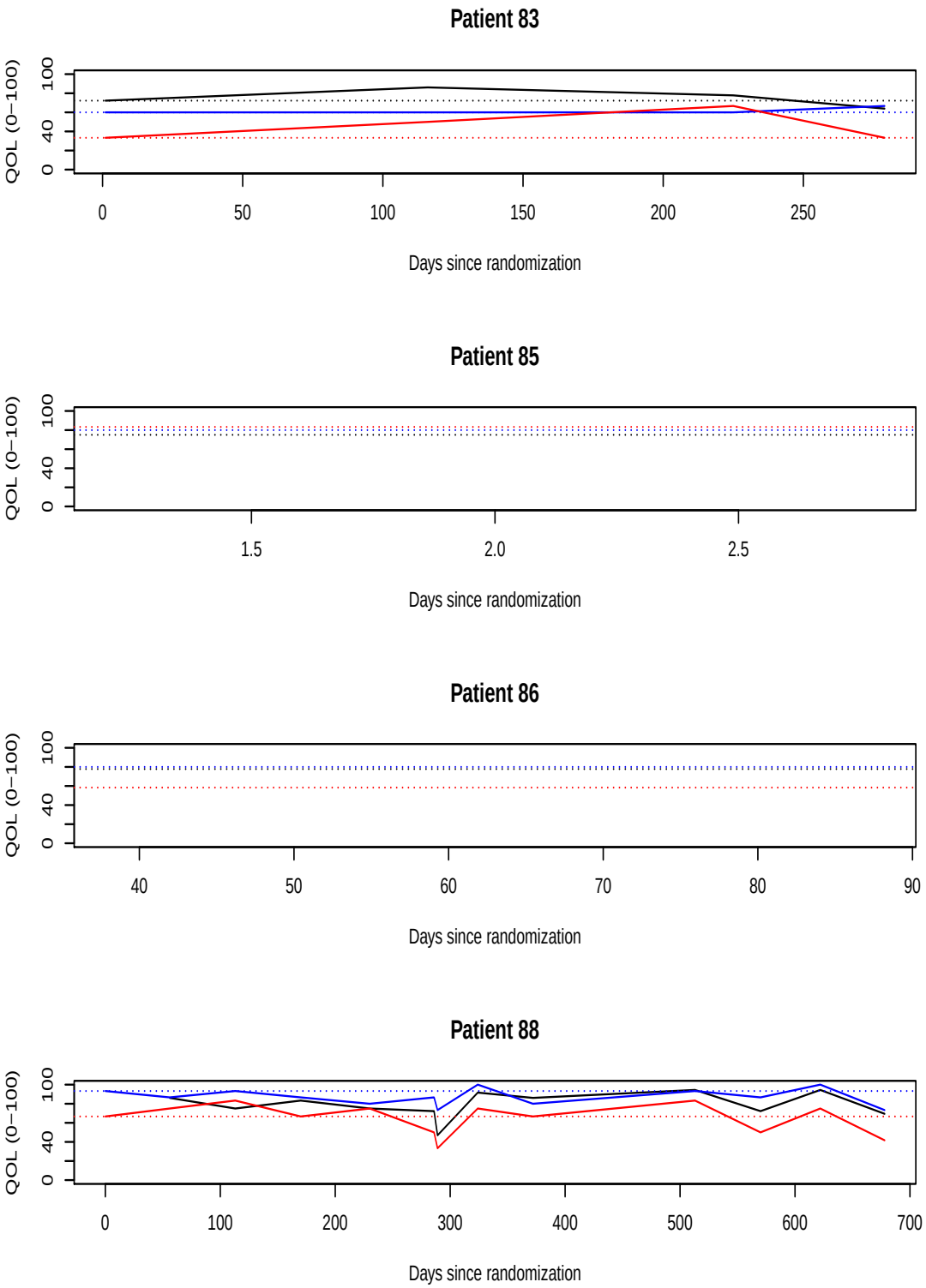
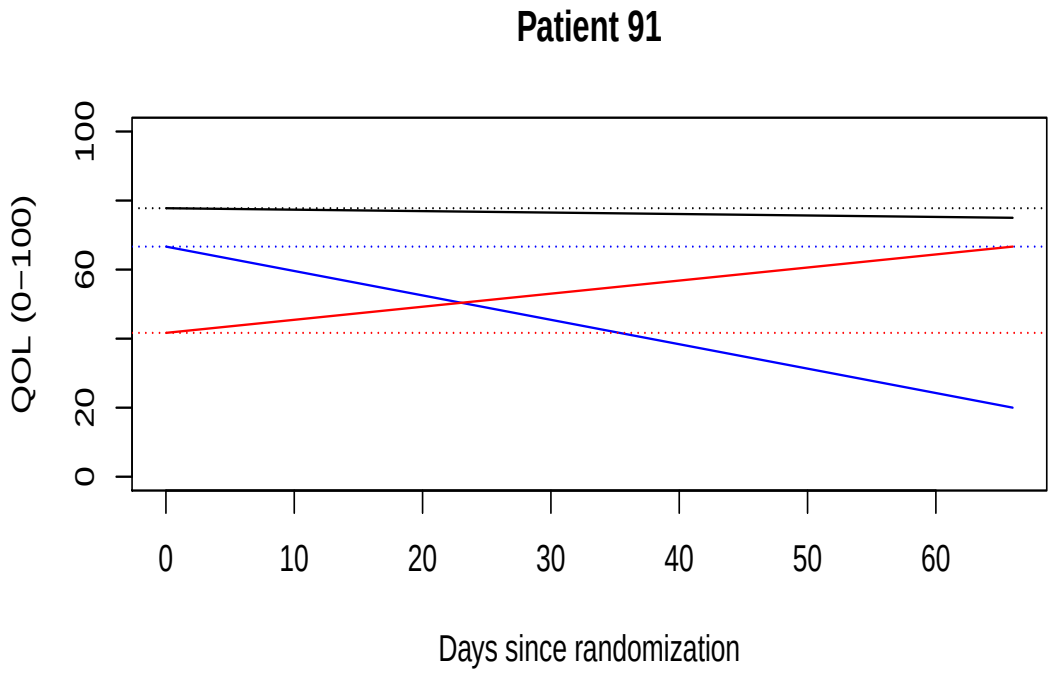


Figure 29: Patient reported FKSI-DRS (black), PF (blue) and QL (red) for patients in the experimental arm, ctd



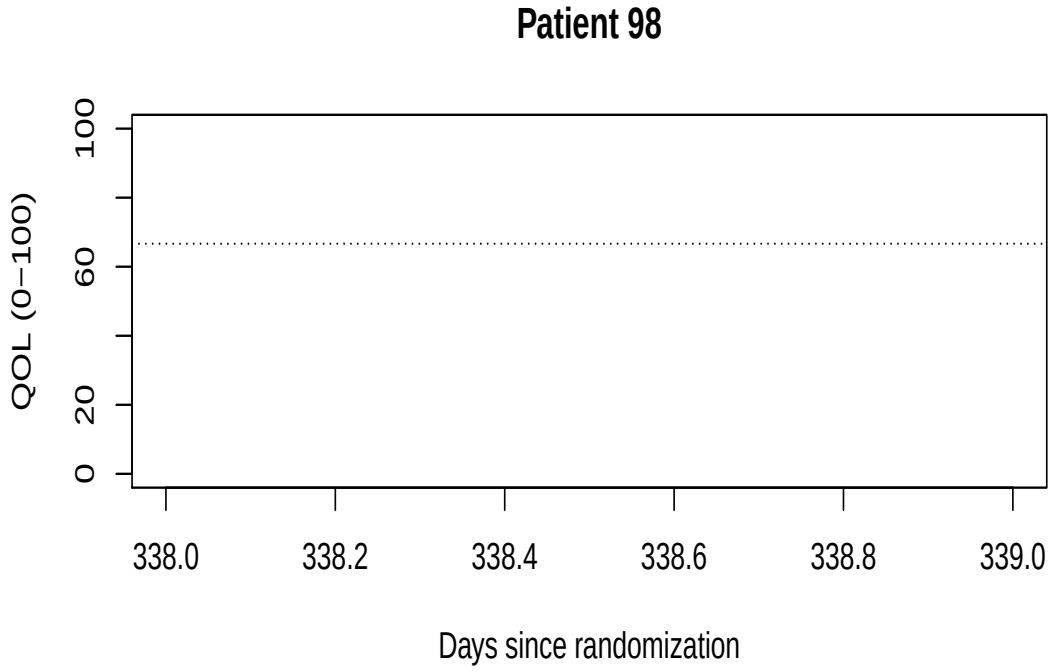


Figure 30: Patient reported FKSI-DRS (black), PF (blue) and QL (red) for patients in the experimental arm, ctd

Arm B: comparative arm

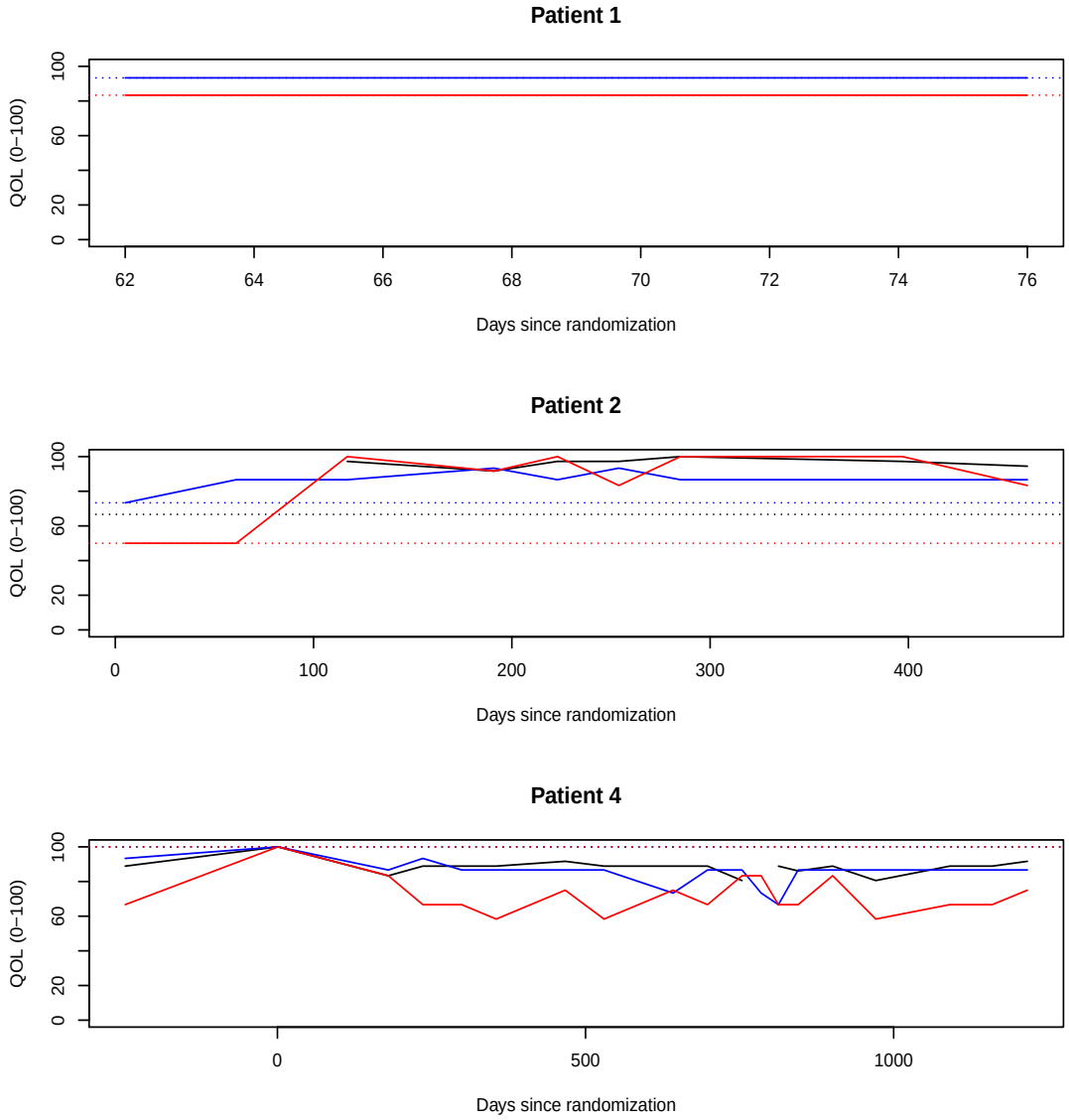


Figure 31: Patient reported quality of life over time for patients randomized in the comparitive arm. Displayed are the scores on the FKSI-DRS symptom scale (black) renormalized to 0-100 to fit the picture, the Physical Functioning (PF) scale of the QLQ-C30 (blue) and the Overall Quality of Life (QL) scale of the QLQ-C30 (red). Time is measured in days, time is set to 0 at the day of randomization. Scores measured closest to randomization are also depicted by the horizontal dotted lines for comparison.

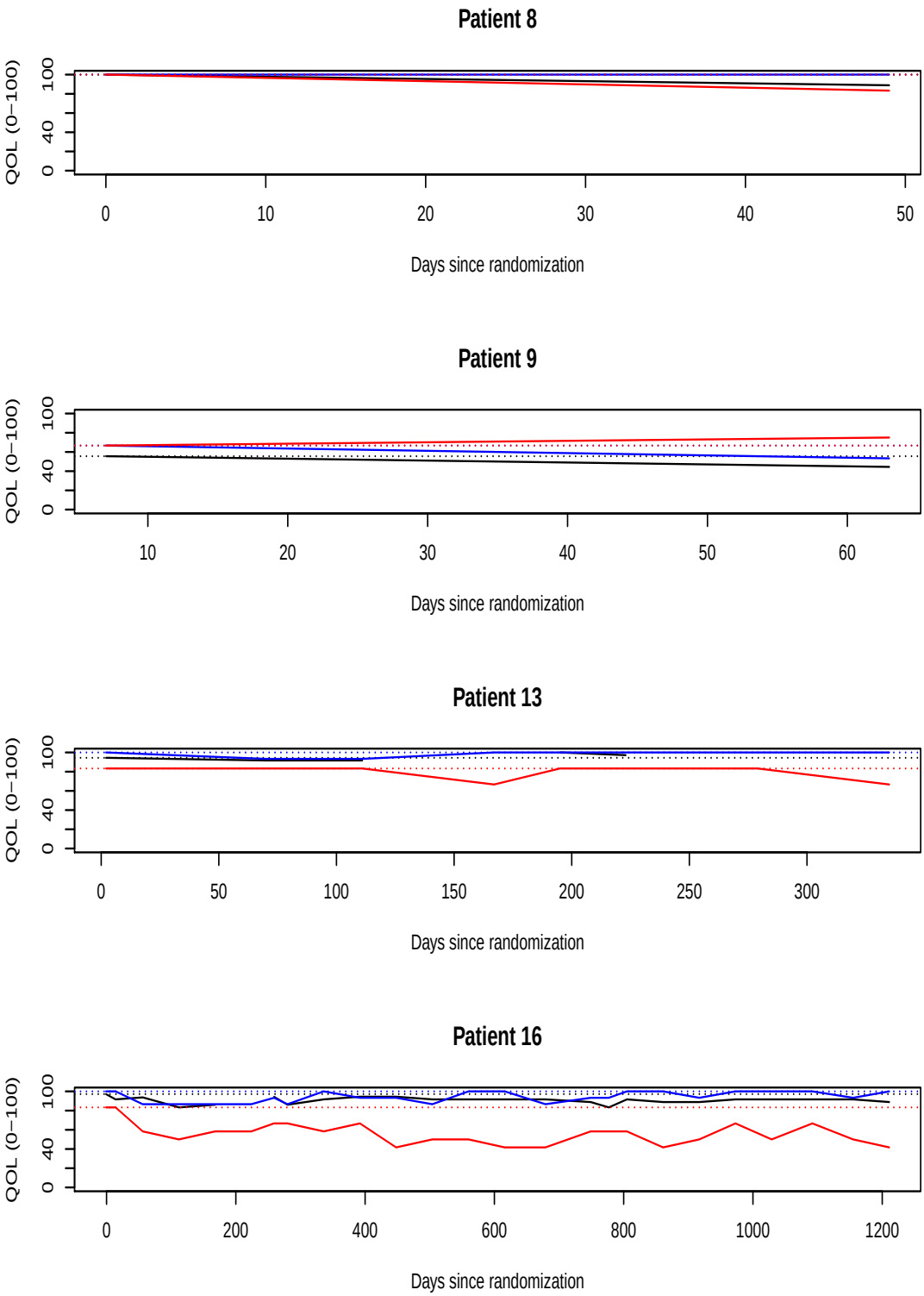


Figure 32: Patient reported FKSI-DRS (black), PF (blue) and QL (red) for patients in the comparitive arm, ctd

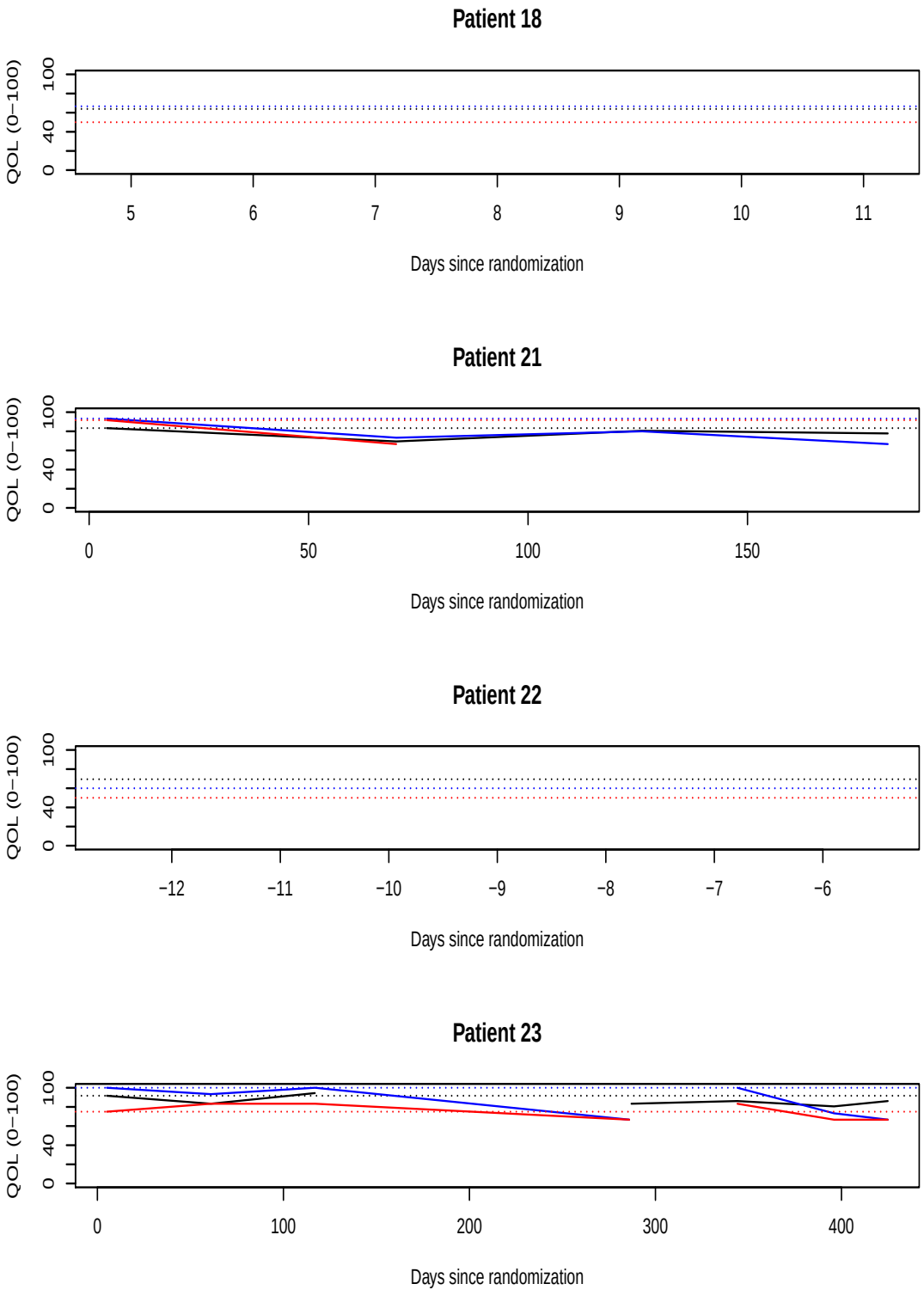


Figure 33: Patient reported FKSI-DRS (black), PF (blue) and QL (red) for patients in the comparitive arm, ctd

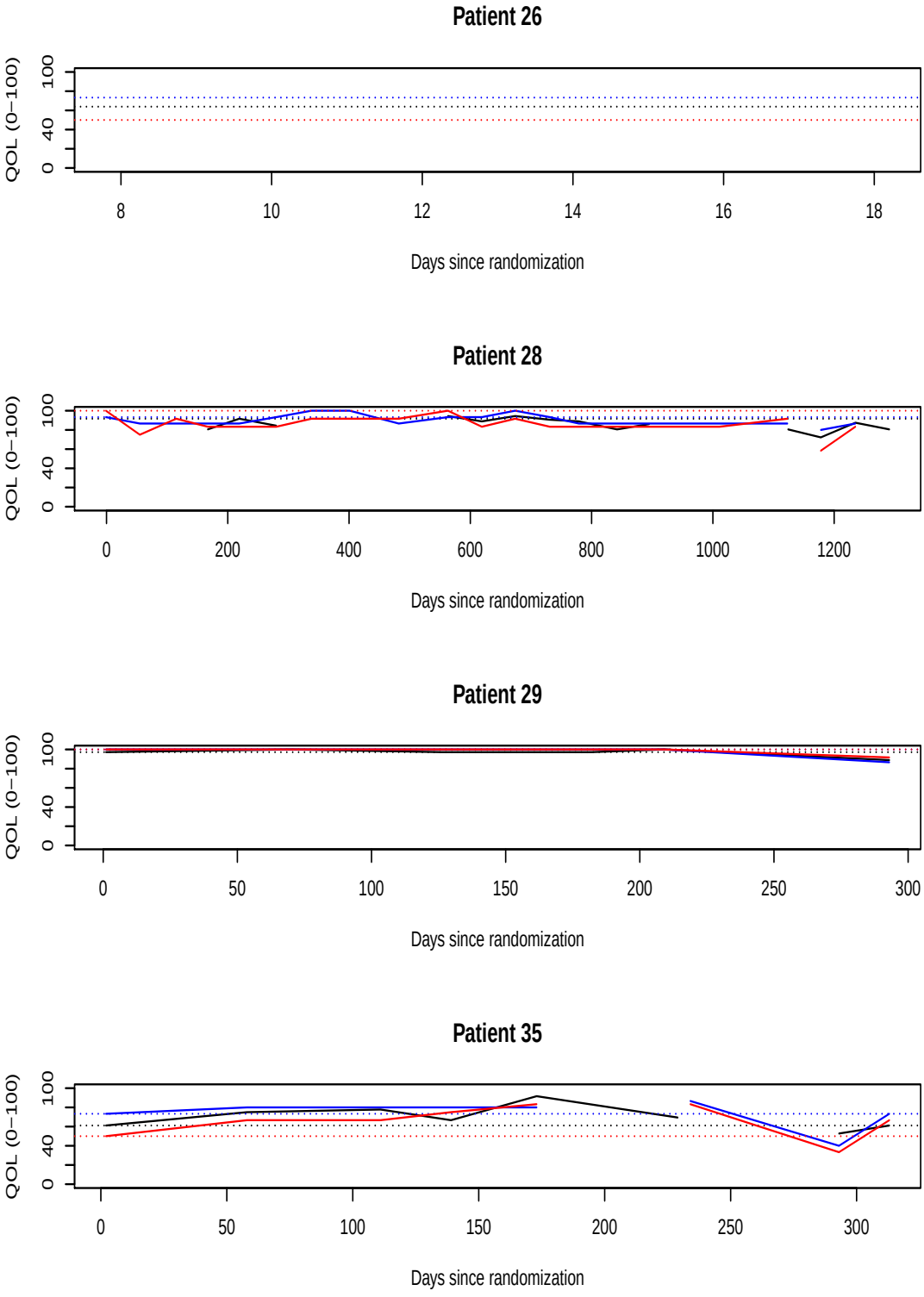


Figure 34: Patient reported FKSI-DRS (black), PF (blue) and QL (red) for patients in the comparitive arm, ctd

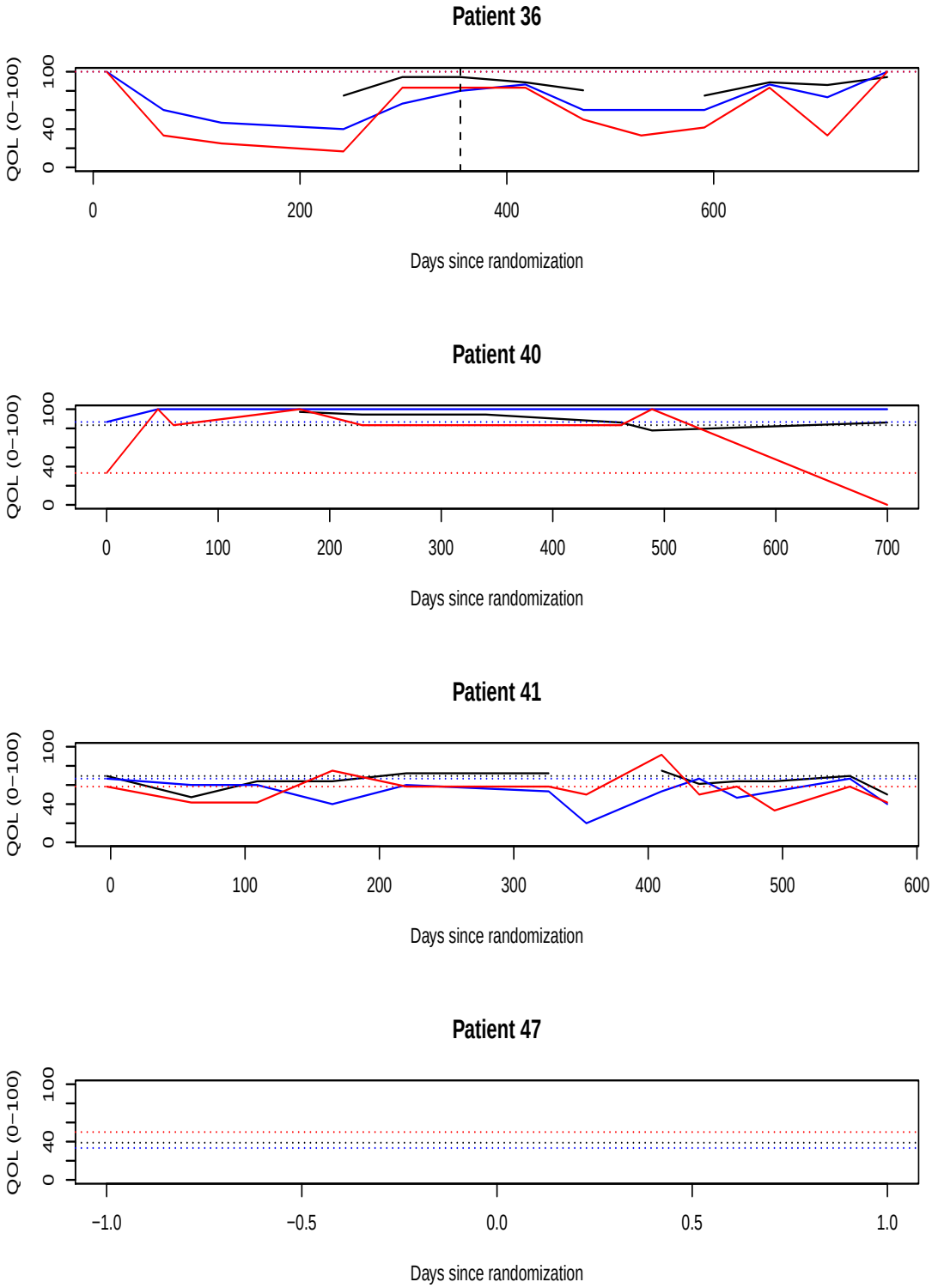


Figure 35: Patient reported FKSI-DRS (black), PF (blue) and QL (red) for patients in the comparitive arm, ctd

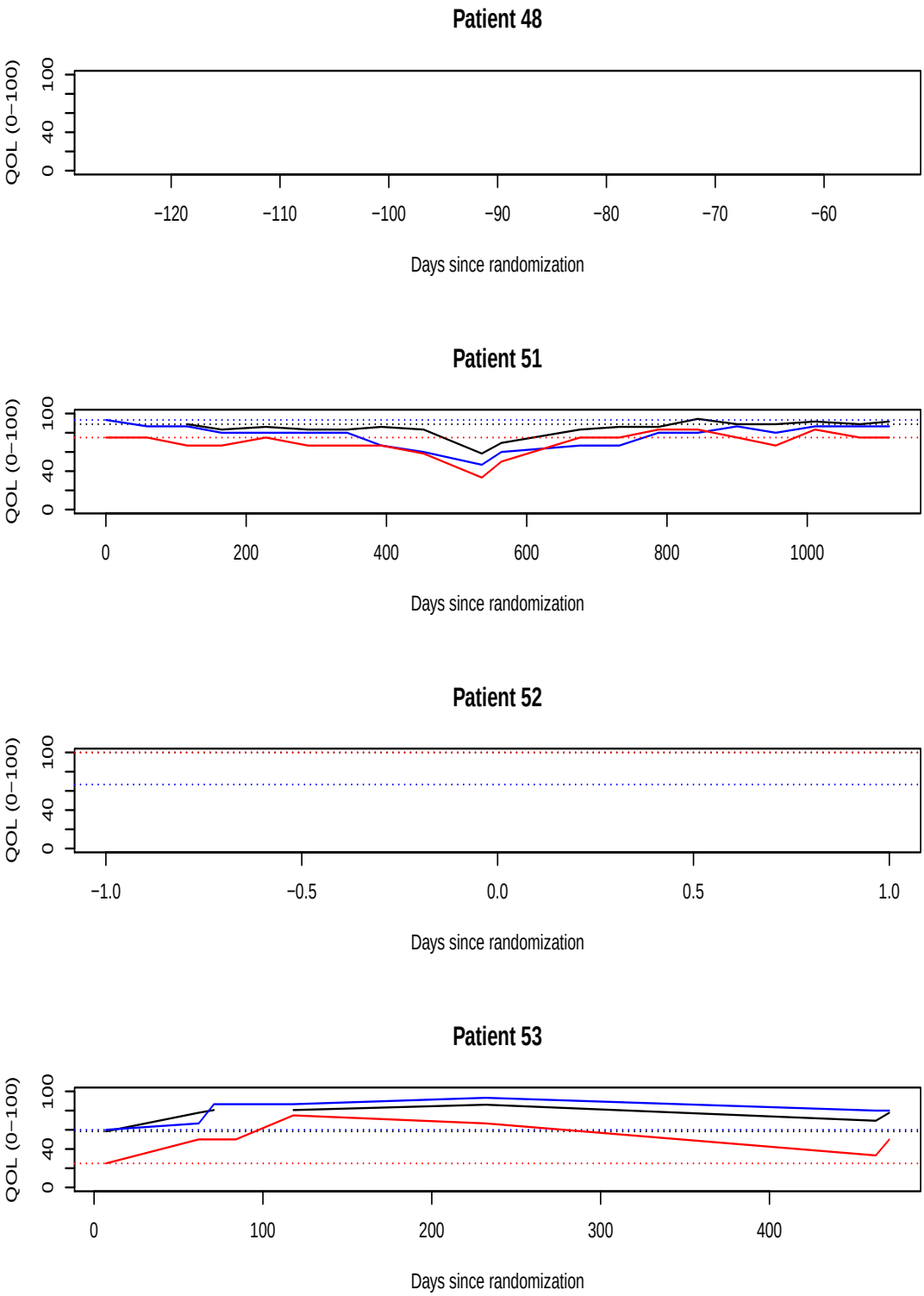


Figure 36: Patient reported FKSI-DRS (black), PF (blue) and QL (red) for patients in the comparitive arm, ctd

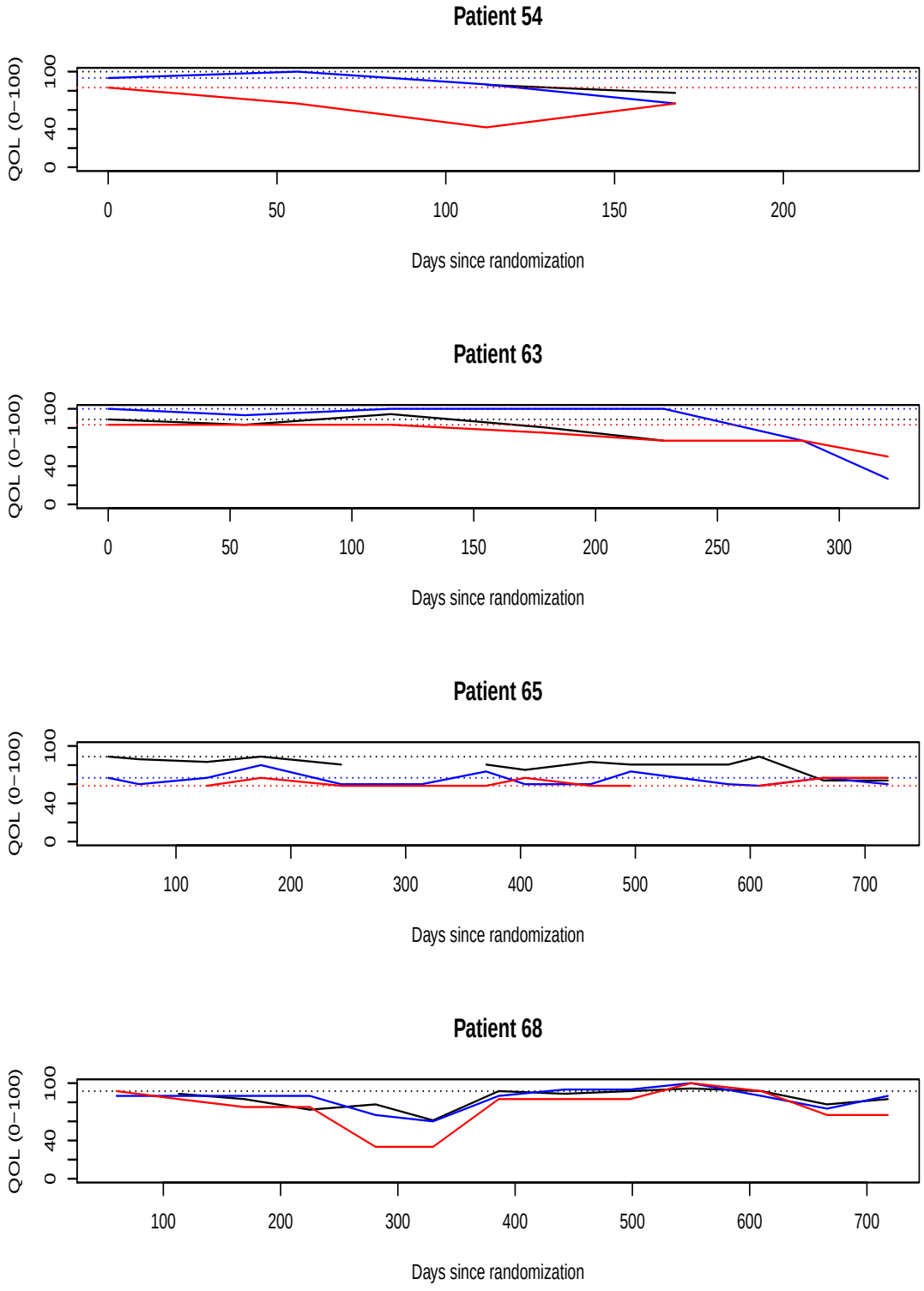


Figure 37: Patient reported FKSI-DRS (black), PF (blue) and QL (red) for patients in the comparitive arm, ctd

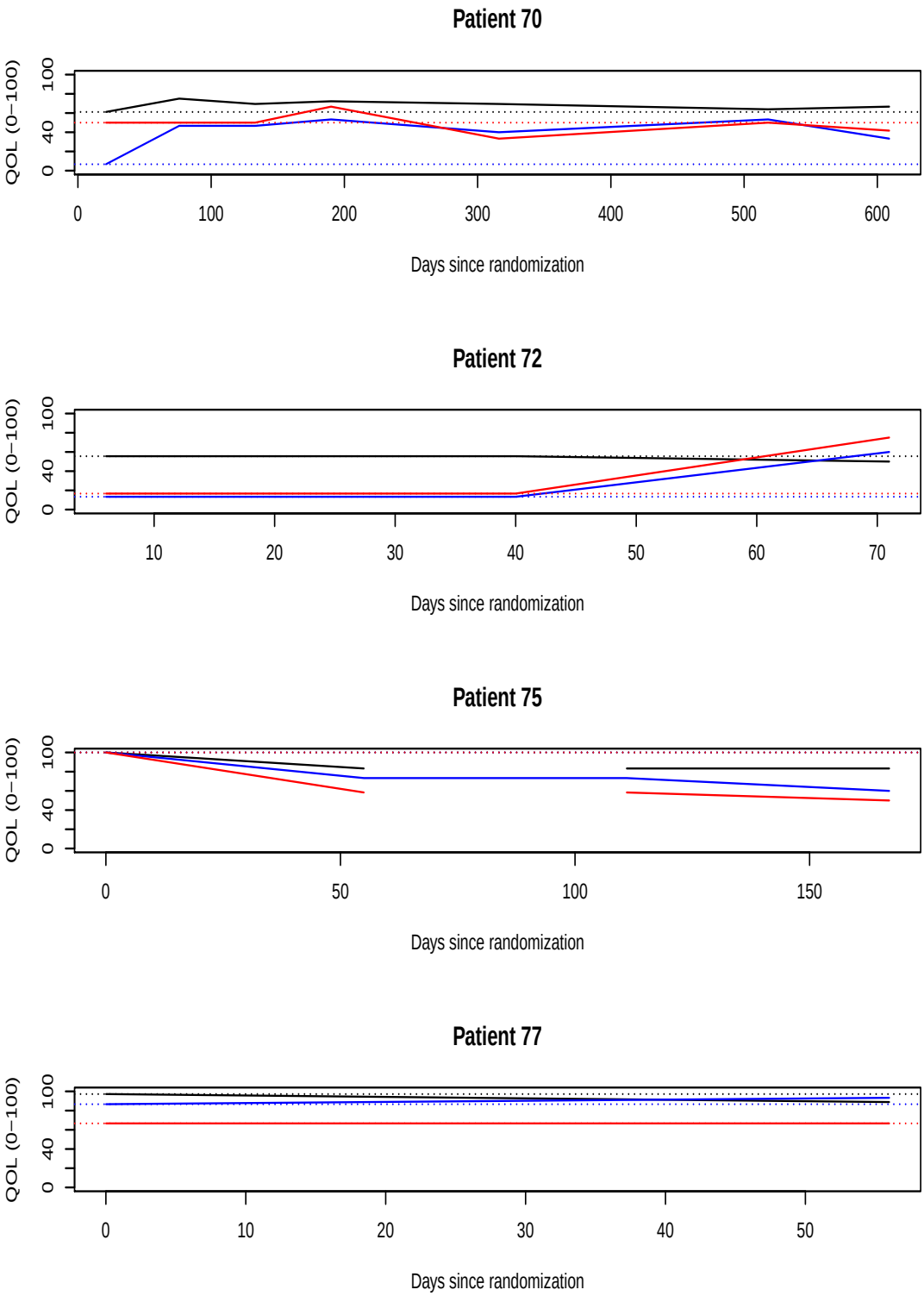


Figure 38: Patient reported FKSI-DRS (black), PF (blue) and QL (red) for patients in the comparitive arm, ctd

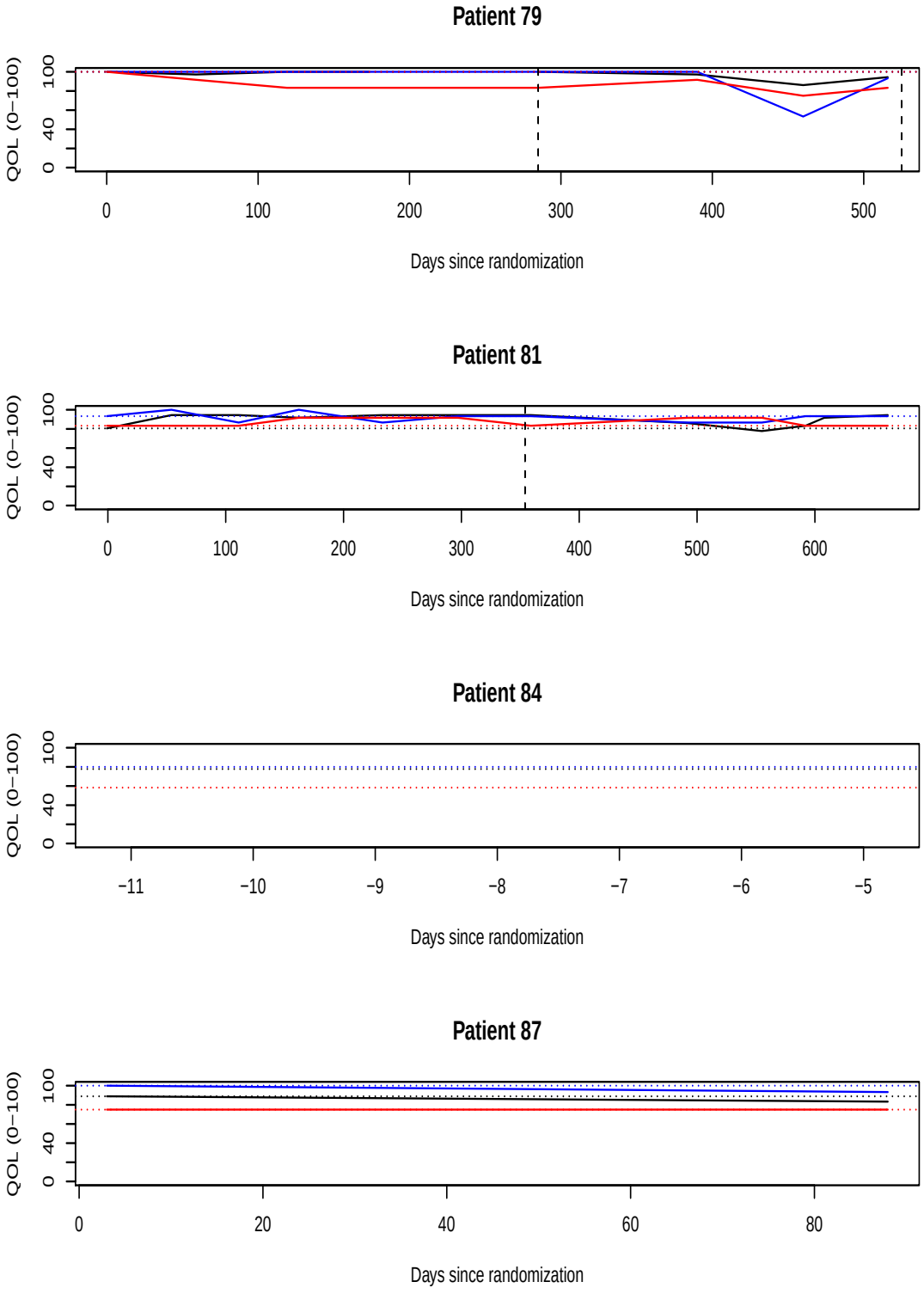


Figure 39: Patient reported FKSI-DRS (black), PF (blue) and QL (red) for patients in the comparitive arm, ctd

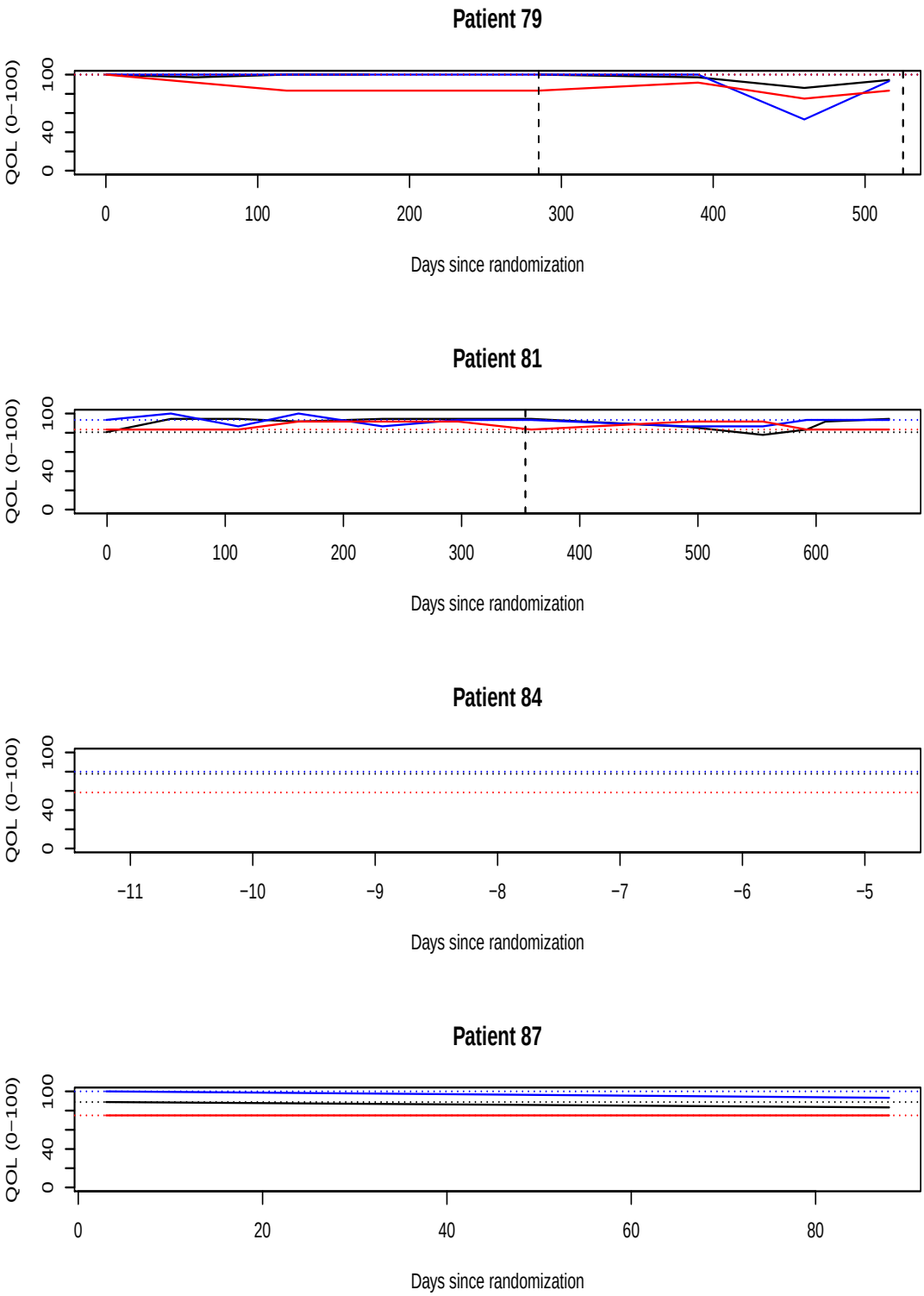
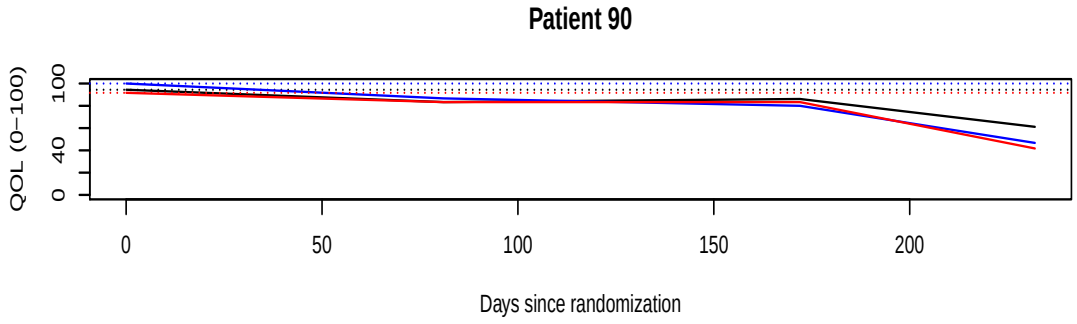
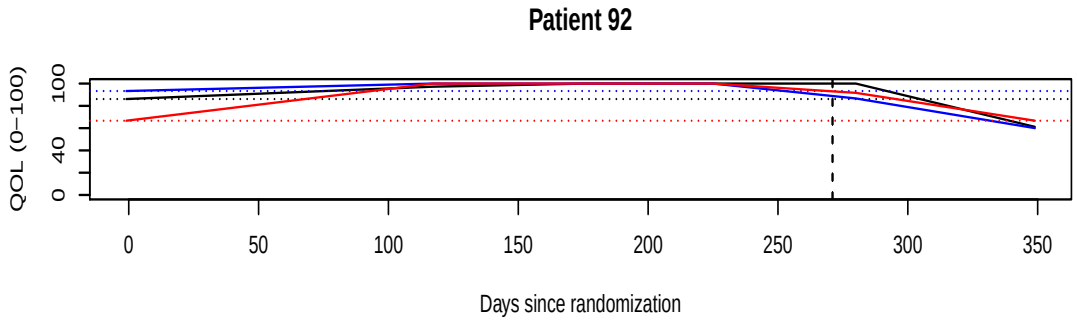
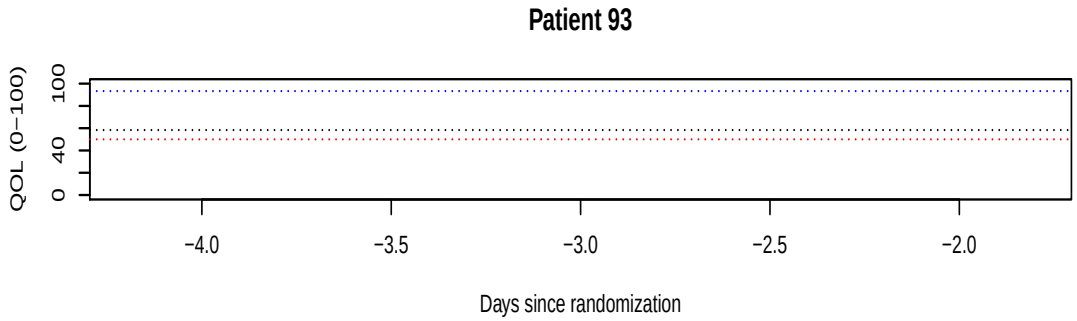


Figure 40: Patient reported FKSI-DRS (black), PF (blue) and QL (red) for patients in the comparitive arm, ctd







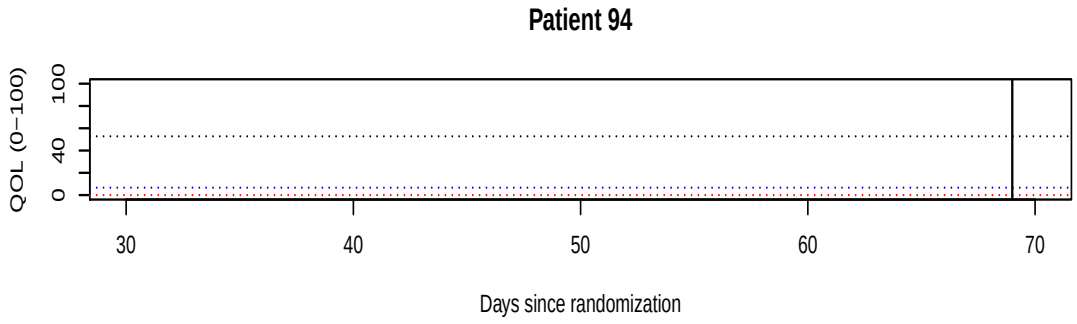
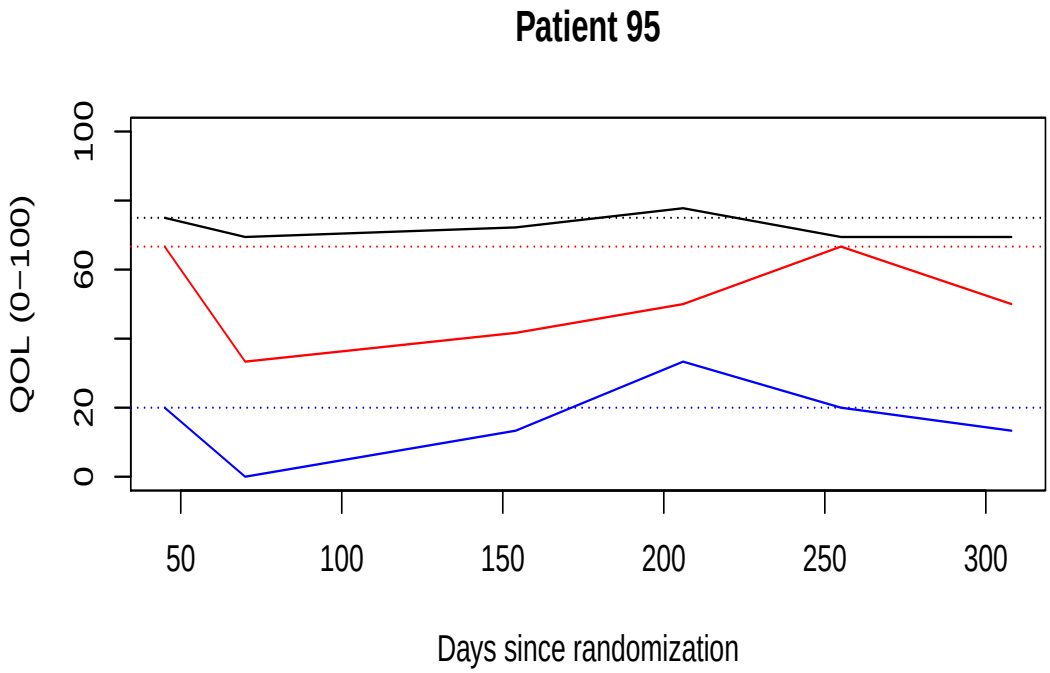


Figure 41: Patient reported FKSI-DRS (black), PF (blue) and QL (red) for patients in the comparitive arm, ctd



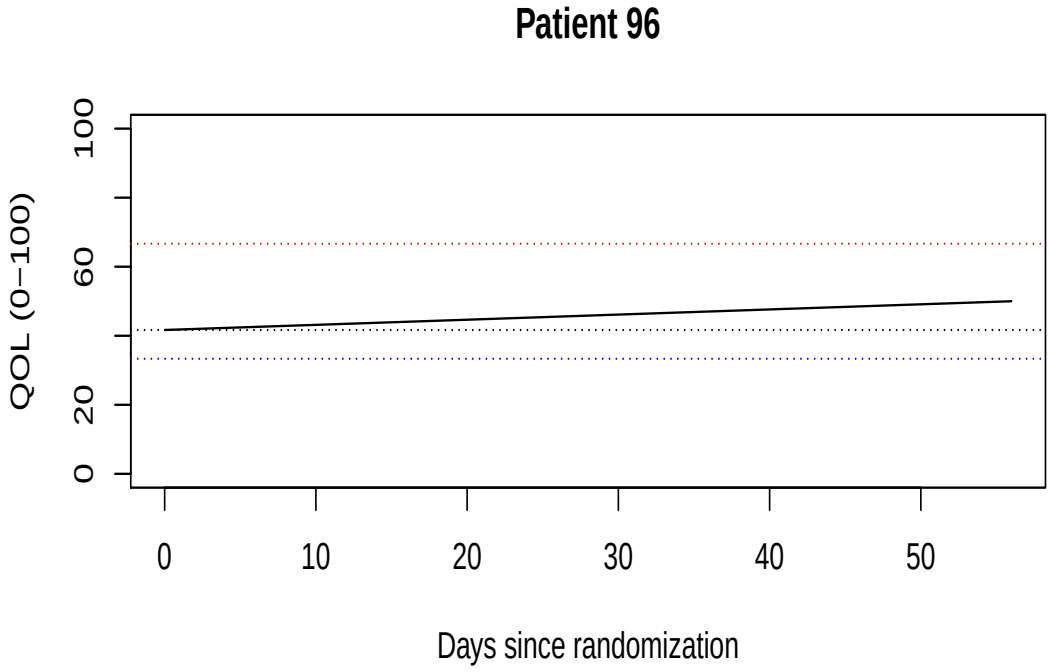


Figure 42: Patient reported FKSI-DRS (black), PF (blue) and QL (red) for patients in the comparitive arm, ctd

15 Appendix F: graphical representation of patient reported outcomes over time, summary measures, independent of line of study treatment

The plots give the development of the FKSI, PF and QL scales in the same fashion as the plots in section 8 but with two differences. First, patients are not censored at their first progression. Second: outcomes are not grouped by treatment cycle but by the time since randomization at which they were measured, rounded to the nearest integer multiple of 8 weeks.

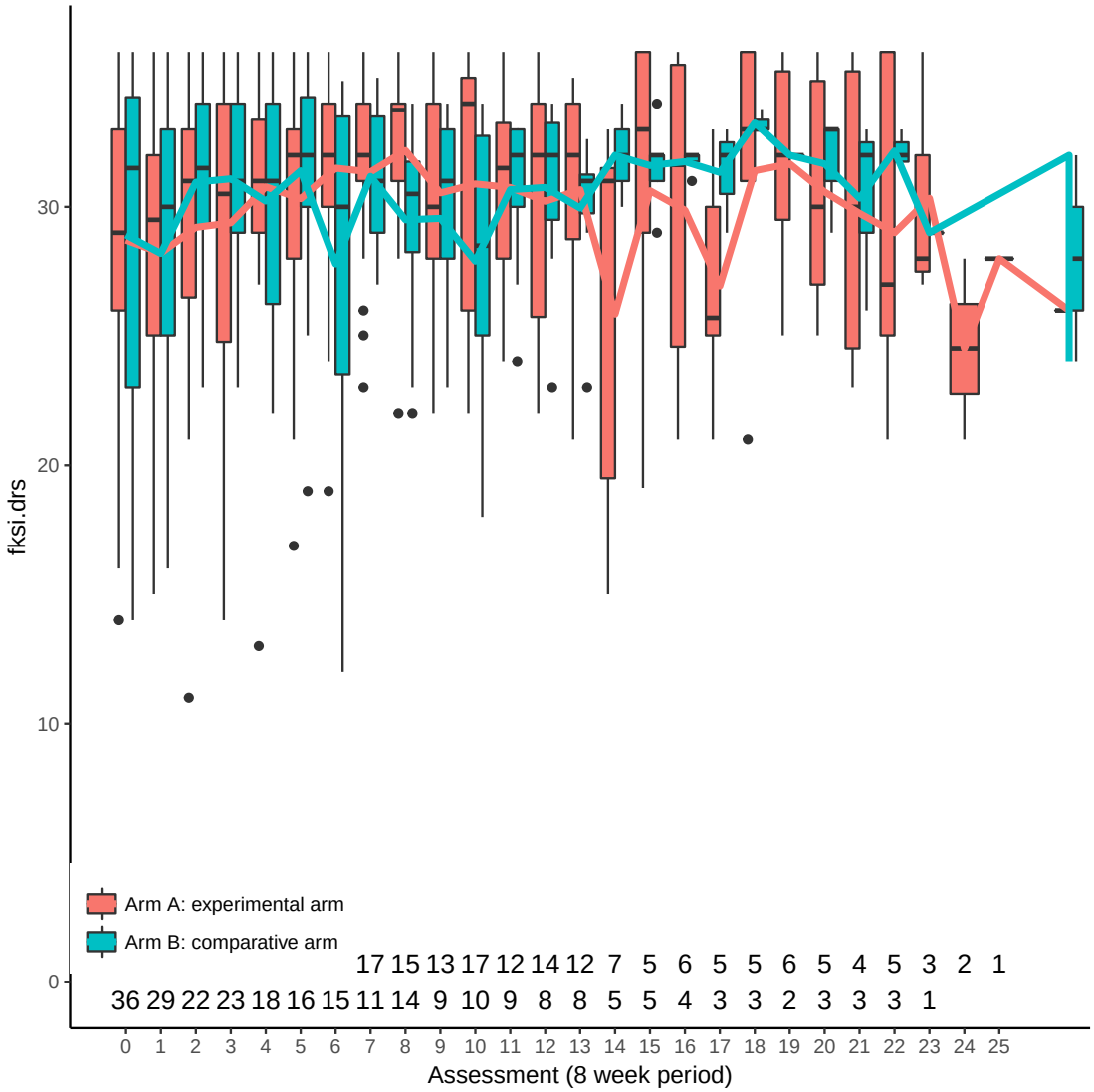


Figure 43: Development of the FKSI-DRS symptom scale over time. Scores range form 0 to 36 and are the sum of the scores on the 9 individual symptom outcome. At each month since randomization boxplots describing the distribution of the scores of the patients in each arm as well as the means (line) of these scores is plotted. The bold black line in the middle of the boxplot indicates the median. Higher score corresponds to better quality of life.

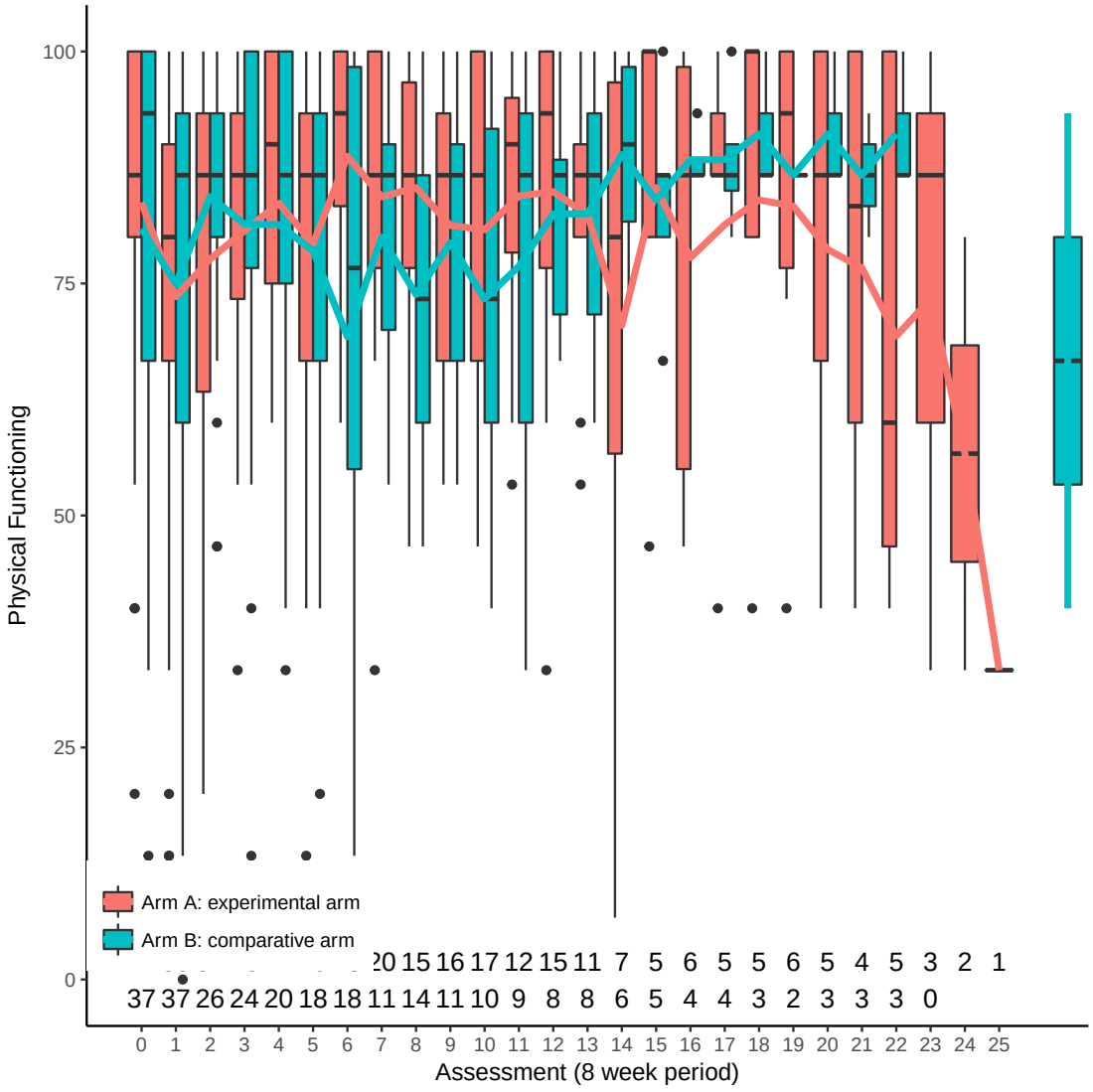


Figure 44: Development of the QLQ-C30 PF scale over time. Scores range form 0 to 100 and are based on the scores on 5 individual questions. At each month since randomization boxplots describing the distribution of the scores of the patients in each arm as well as the means (line) of these scores is plotted. Higher score corresponds to better quality of life.

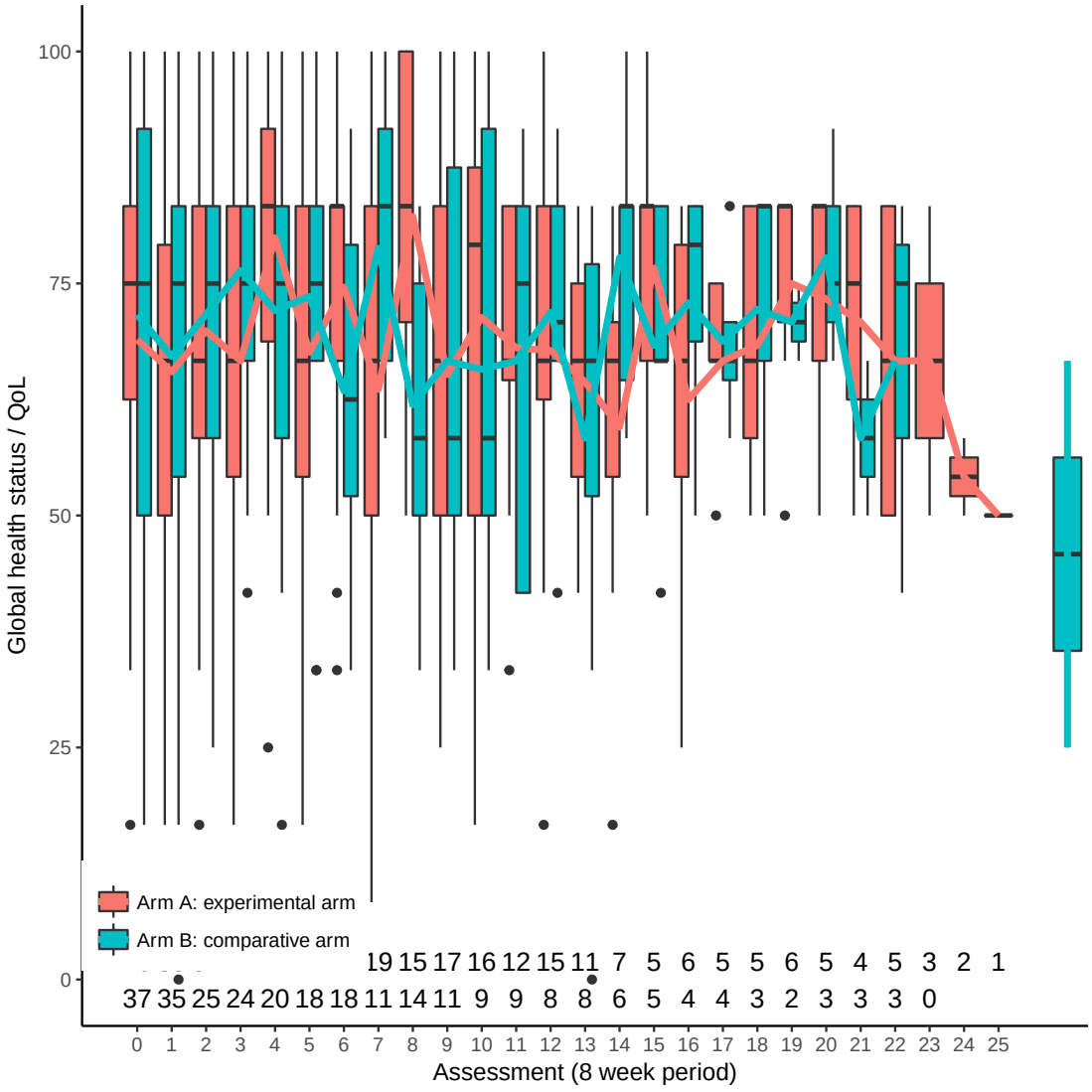


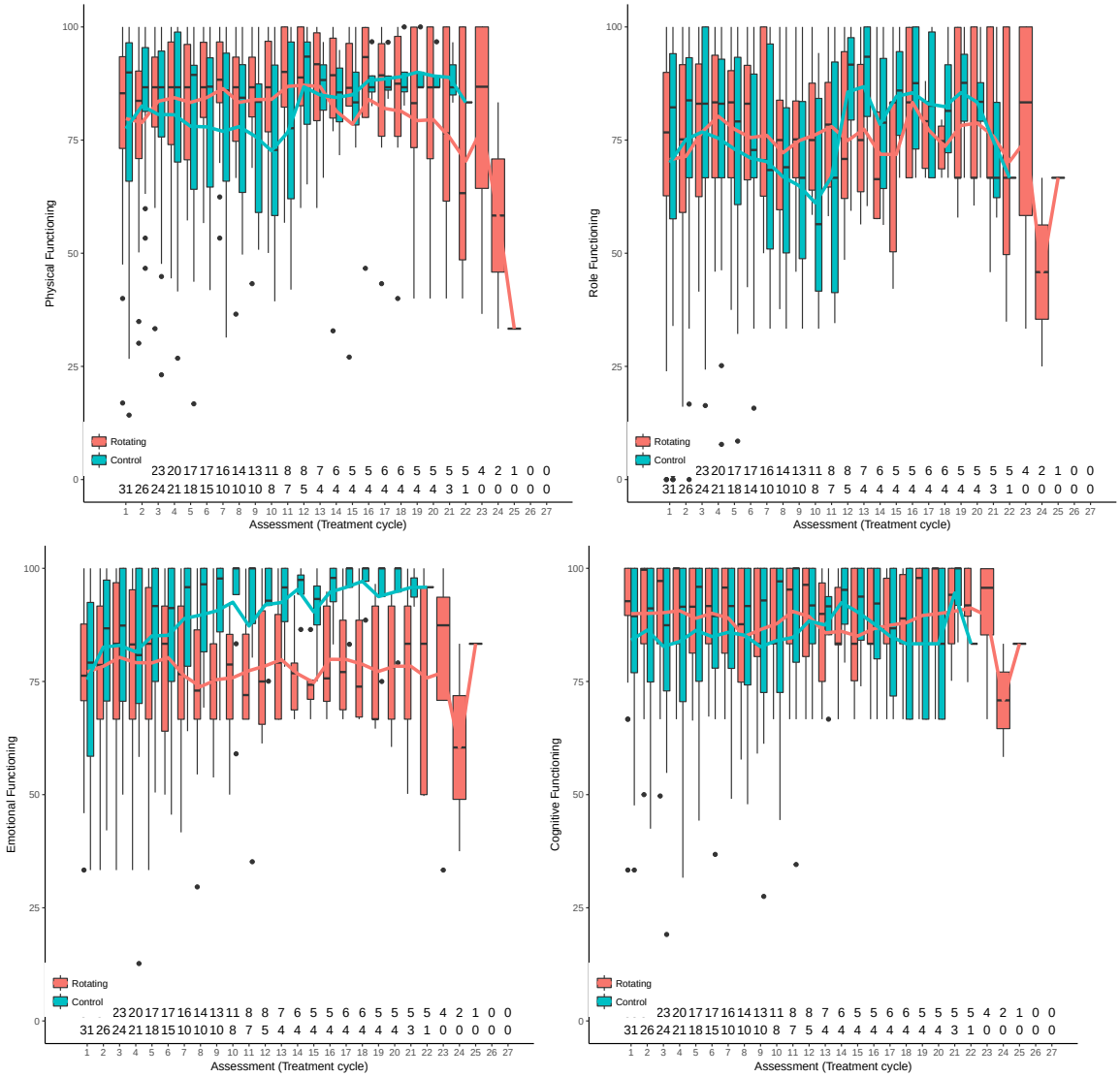
Figure 45: Development of the QLQ-C30 QL scale over time. Scores range form 0 to 100 and are based on the scores on 2 questions. At each month since randomization boxplots describing the distribution of the scores of the patients in each arm as well as the means (line) of these scores is plotted. Higher score corresponds to better quality of life.

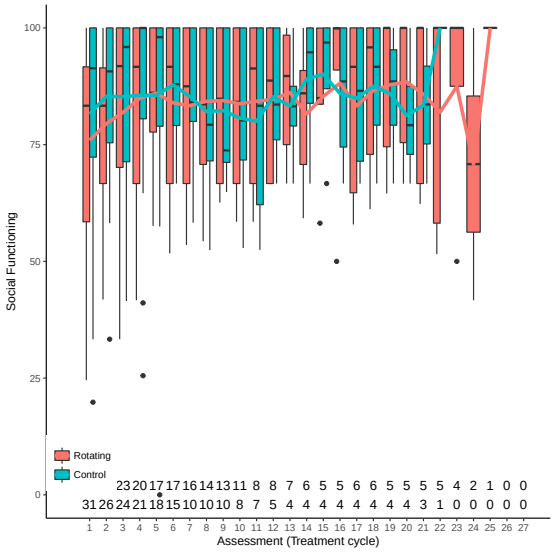
16 Appendix G: graphical representation of patient reported outcomes over time: individual performance and symptom scales during first line treatment

We make plots analogous to (and according to the same procedure as) figure 1 for the various functioning and symptom scales measured by the QOL questionnaires.

QLQ-C30 functional scales

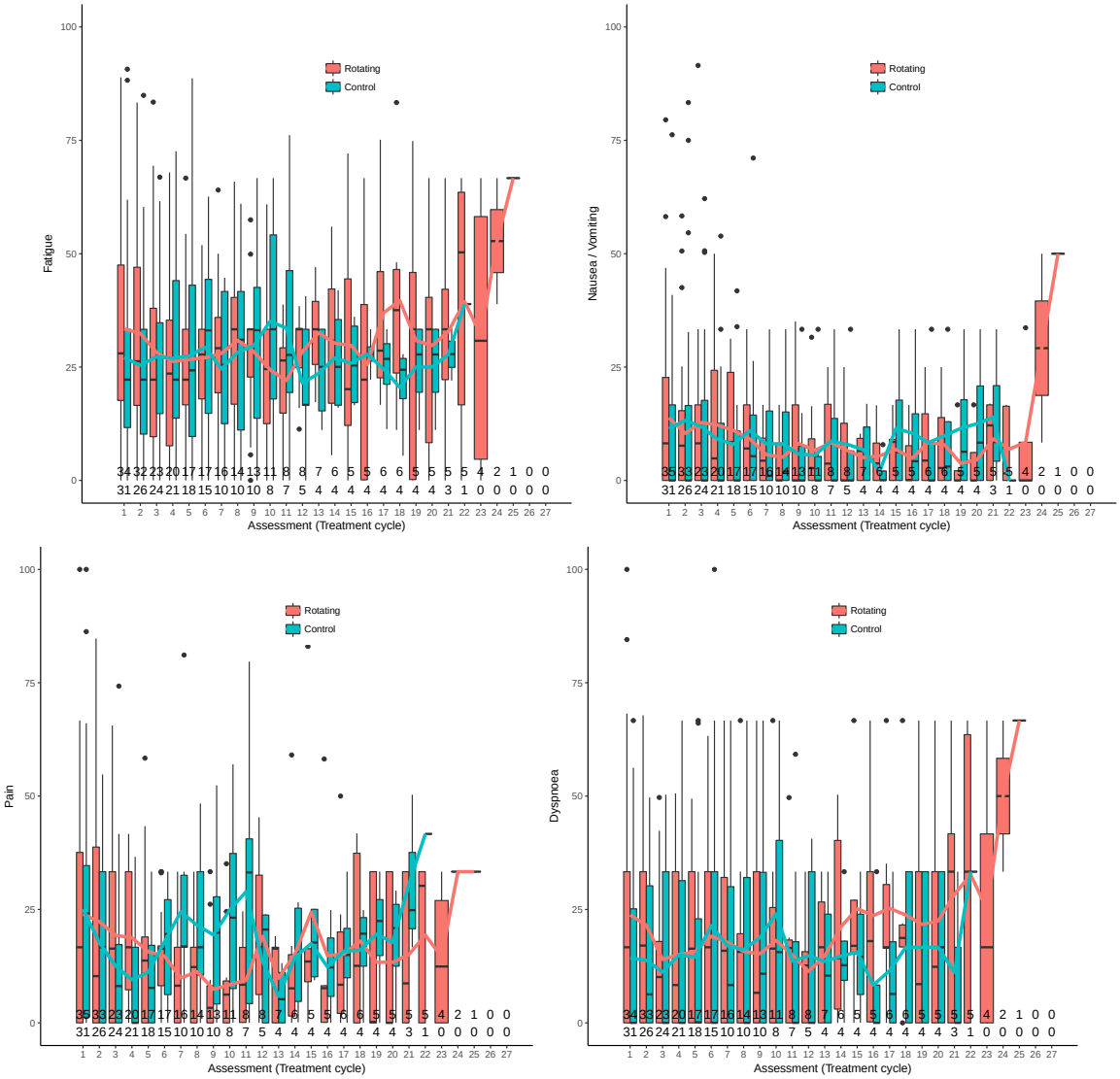
There are five functioning scales: Physical functioning, Role functioning, Emotional functioning, Cognitive functioning and Social functioning. Each runs from 0 to 100 and is computed from the answers to 2 (RF, CF, SF), 4 (EF) or 5 (PF) questions on the QLQ-CR30. For functioning scales, a higher outcome corresponds to better functioning and hence better quality of life.

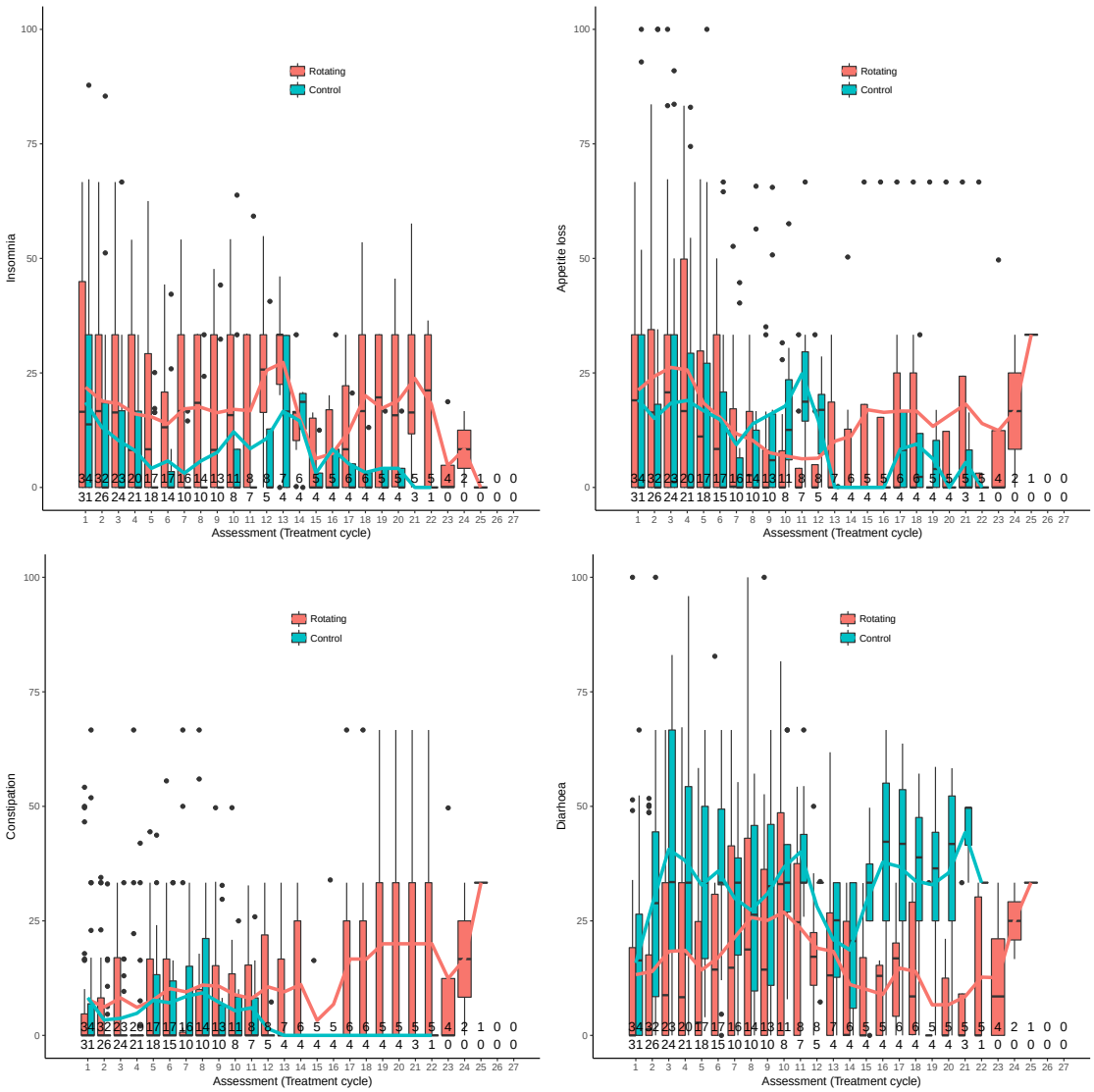


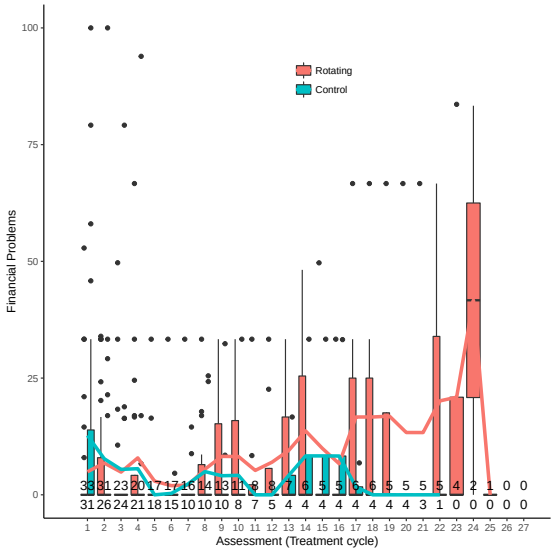

Social Functioning
100
75
50
25
0
Rotating
Control
23 20 17 17 16 14 13 11 8 8 7 6 5 5 6 6 5 5 5 5 4 2 1 0 0
31 26 24 21 18 15 10 10 10 8 7 5 4 4 4 4 4 4 4 3 1 0 0 0 0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27
Assessment (Treatment cycle)

QLQ-C30 symptom scales

There are nine symptoms which are investigated on the QLQ-C30: Fatigue (3 questions), Nausea and vomiting (2 questions), Pain (2 questions), Dyspnea, Insomnia, Appetite loss, Constipation, Diarrhea and Financial difficulties (one question each). Each symptom scale runs from 0 to 100. However it is important to notice that for QLQ symptom scales, *a higher outcome corresponds higher level of symptomatology* and hence *worse* quality of life.

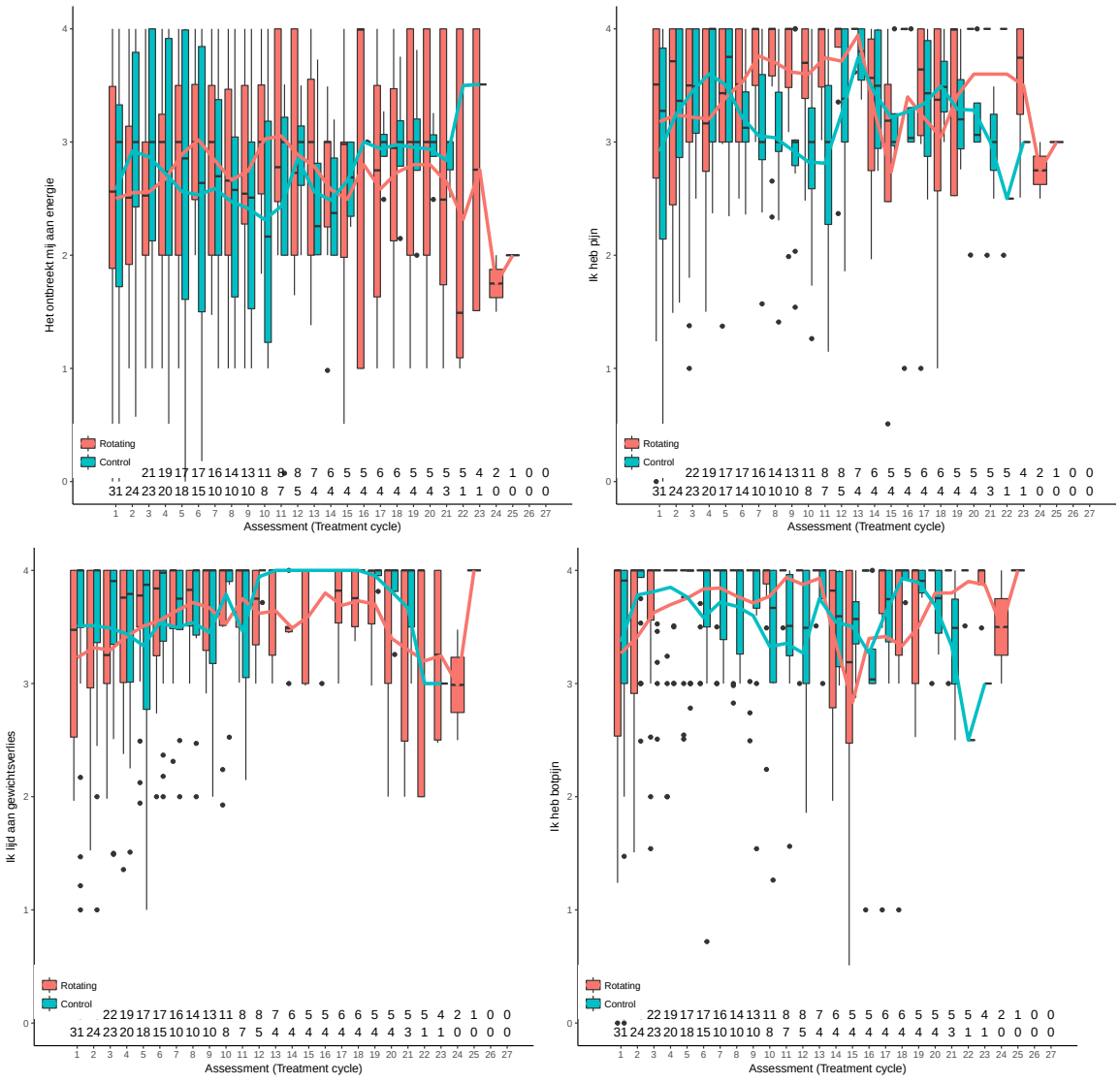


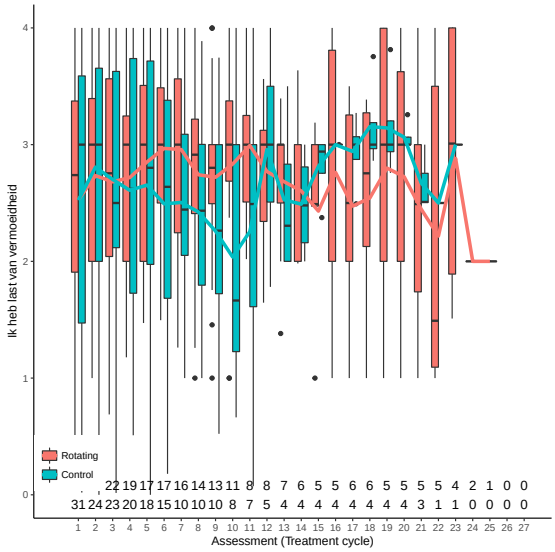

Insomnia
Appetite loss
Constipation
Diarhoea
Rotating
Control
Assessment (Treatment cycle)

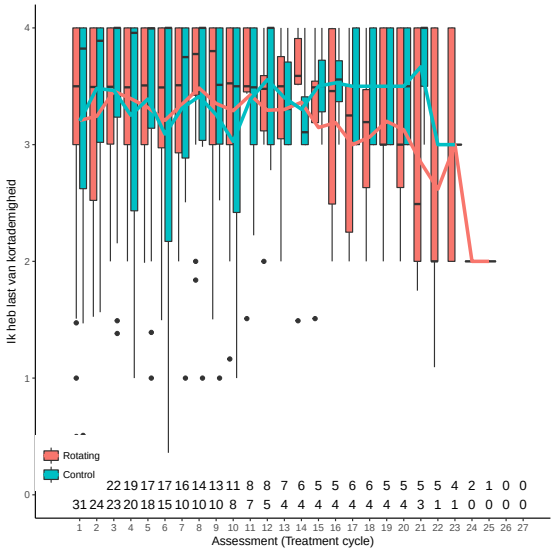

Rotating
Control
Financial Problems
100
75
50
25
0
Assessment (Treatment cycle)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27
33 31 23 20 17 17 16 14 13 11 8 8 7 6 5 5 6 6 5 5 5 5 4 2 1 0 0
31 26 24 21 18 15 10 10 8 7 5 4 4 4 4 4 4 4 3 1 0 0 0 0 0

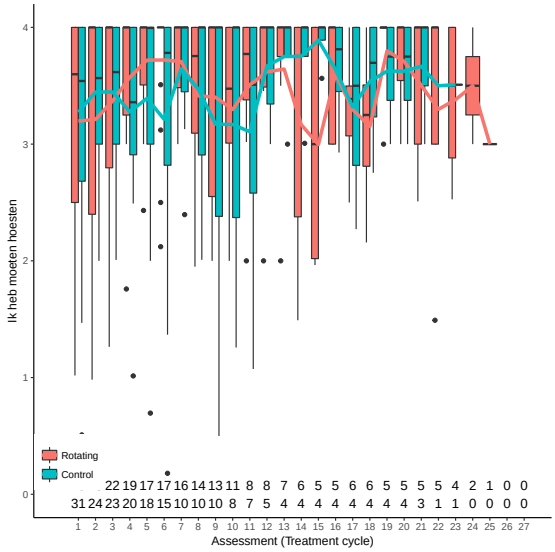
FKSI-DRS symptom scales

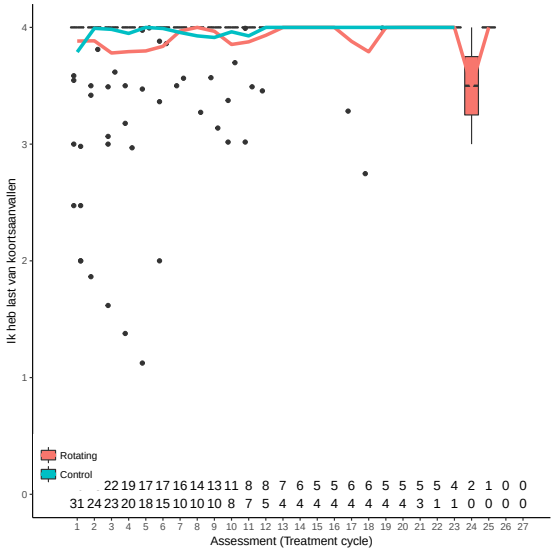
There are seven symptoms which are investigated on the FKSI-DRS questionnaire: lack of energy, pain, weight loss, bone pain, fatigue, shortness of breath, coughing, fever, and blood in urine (one question each). Each symptom scale runs from 0 to 4 and together the symptom scales make up the overall FKSI score depicted in figure 1. Contrary to the situation for QLQ symptom scales, on FKSI symptom scales a higher outcome corresponds to a *lower* level of symptomatology and hence *better* quality of life. (Much like the functioning and overall health/QoL scales of the QLQ-C30.)

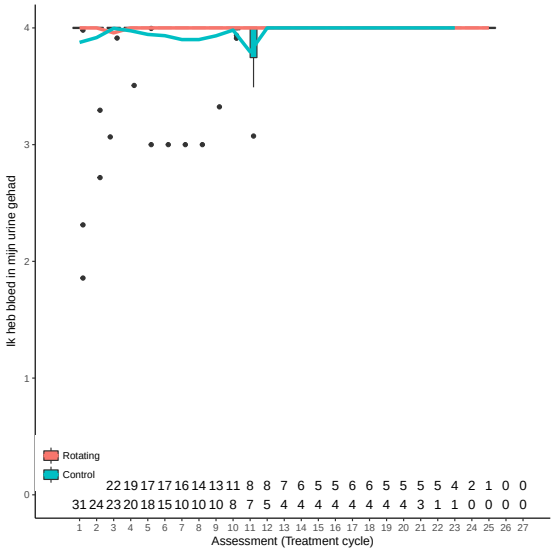



Ik heb last van vermoeidheid
Rotating
Control
Assessment (Treatment cycle)


Ik heb last van kortademigheid
Rotating
Control
Assessment (Treatment cycle)


Ik heb moeten hoesten
Rotating
Control
Assessment (Treatment cycle)


Ik heb last van koortsaanvallen
Rotating
Control
Assessment (Treatment cycle)


Ik heb bloed in mijn urine gehad
Rotating
Control
22 19 17 17 16 14 13 11 8 8 7 6 5 5 6 6 5 5 5 4 2 1 0 0
31 24 23 20 18 15 10 10 8 7 5 4 4 4 4 4 4 4 3 1 1 0 0 0 0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27
Assessment (Treatment cycle)