Do all patients with advanced HER2 positive breast cancer need upfront-chemo when receiving trastuzumab? Randomized Phase III trial SAKK 22/99

Pagani, O; Klingbiel, D; Ruhstaller, T; Nolè, F; Eppenberger, S; Oehlschlegel, C; Bernhard, J; Brauchli, P; Hess, D; Mamot, C; Munzone, E; Pestalozzi, B; Rabaglio, M; Aebi, S; Ribi, K; Rochlitz, C; Rothgiesser, K; Thürlimann, B; Moos, R von; Zaman, K; Goldhirsch, A; Swiss Group for Clinical Cancer Research (SAKK)

Abstract: Background: HER2-targeted therapy plus chemotherapy is standard treatment in advanced HER2+ breast cancer. Trastuzumab alone followed by addition of chemotherapy at disease progression versus upfront combination therapy has not been elucidated.Patients and methodsOne-hundred-seventy-five patients with measurable/evaluable HER2+ advanced disease without previous HER2-directed therapy were randomized to trastuzumab alone followed, at disease progression, by the combination with chemotherapy (Arm A) or upfront trastuzumab plus chemotherapy (Arm B). Chemotherapy could be stopped after 6 cycles in responding patients, trastuzumab was continued until progression. The primary endpoint of this superiority trial was time to progression (TTP) on combined trastuzumabchemotherapy (Combination-TTP) in both arms. Secondary endpoints included response rate, TTP, overall survival, quality of life and toxicity.ResultsCombination-TTP was longer than expected in both arms, 12.2 months in Arm A and 10.3 months in Arm B and not significantly different (hazard ratio [HR] 0.7; 95% CI 0.5-1.1; P =0.1). Overall survival was also not significantly different (HR 0.9; 95% CI 0.6-1.5; P=0.55). In Arm A, the median TTP before introduction of chemotherapy was 3.7 months (95% CI 2.3-5.4), yet at two years 6% of patients were still on trastuzumab alone. Patients without visceral disease had a Combination-TTP of 21.8 months in arm A, compared with 10.1 months in arm B (unplanned analysis HR 2.1, 95% CI 1.1-4.2, p=0.03). Patients with visceral disease showed no difference. Toxicity was chemotherapy-related.ConclusionThe outcome of patients receiving sequential trastuzumab-chemotherapy or upfront combination was similar. We failed to demonstrate superiority of the sequential approach. These results nevertheless suggest chemotherapy and its toxicity can be deferred, especially in patients with indolent, non-visceral disease. Despite a larger non-inferiority confirmatory study would be needed, these findings represent an additional proof of concept that de-escalation strategies can be discussed in individual patients.

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Original article

Do all patients with advanced HER2 positive breast cancer need upfront-chemo when receiving trastuzumab? Randomized Phase III trial SAKK 22/99

Running head
Minimising HER2-directed therapy: more is not always better.

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The preliminary results of the study were presented at the 2014 San Antonio Breast Cancer Symposium (abstract P4-15-11)

Key message
Sequential administration of trastuzumab and chemotherapy compared to upfront combination therapy, delays chemotherapy and seems not to affect patients' outcomes, in particular in indolent, non-visceral disease. The SAKK 22-99 results reinforce the accumulating evidence of treatment

de-escalation. The approach is being evaluated with dual HER2-directed therapy (SAKK 22/10 PERNETTA trial).

Abstract

Background

HER2-targeted therapy plus chemotherapy is standard treatment in advanced HER2+ breast cancer. Trastuzumab alone followed by addition of chemotherapy at disease progression versus upfront combination therapy has not been elucidated.

Patients and methods

One-hundred-seventy-five patients with measurable/evaluable HER2+ advanced disease without previous HER2-directed therapy were randomized to trastuzumab alone followed, at disease progression, by the combination with chemotherapy (Arm A) or upfront trastuzumab plus chemotherapy (Arm B). Chemotherapy could be stopped after ≥6 cycles in responding patients, trastuzumab was continued until progression. The primary endpoint of this superiority trial was time to progression (TTP) on combined trastuzumab-chemotherapy (Combination-TTP) in both arms. Secondary endpoints included response rate, TTP, overall survival, quality of life and toxicity.

Results

Combination-TTP was longer than expected in both arms, 12.2 months in Arm A and 10.3 months in Arm B and not significantly different (hazard ratio [HR] 0.7; 95% CI 0.5–1.1; *P* =0.1). Overall survival was also not significantly different (HR 0.9; 95% CI 0.6–1.5; *P*=0.55). In Arm A, the median TTP before introduction of chemotherapy was 3.7 months (95% CI 2.3–5.4), yet at two years 6% of patients were still on trastuzumab alone. Patients without visceral disease had a Combination-TTP of 21.8 months in arm A, compared with 10.1 months in arm B (unplanned analysis HR 2.1, 95% CI 1.1–4.2, p=0.03). Patients with visceral disease showed no difference. Toxicity was chemotherapy-related.

Conclusion

The outcome of patients receiving sequential trastuzumab-chemotherapy or upfront combination was similar. We failed to demonstrate superiority of the sequential approach. These results nevertheless suggest chemotherapy and its toxicity can be deferred, especially in patients with indolent, non-visceral disease. Despite a larger non-inferiority confirmatory study would be needed, these findings represent an additional proof of concept that de-escalation strategies can be discussed in individual patients.

Words: 297/300

Key words

HER2+ breast cancer, advanced breast cancer, trastuzumab, chemotherapy, sequential therapy, combination therapy

Introduction

Fifteen-twenty-percent of breast cancers (BC) overexpress HER2. In advanced BC (ABC), HER2-targeted therapies significantly improved disease outcomes (1,2). Trastuzumab (T) plus pertuzumab and chemotherapy is recommended as 1st-line treatment, T-DM1 as the preferred 2nd/3rd-line therapy (3) as both improved overall survival (OS) (4,5).
The impact of HER2-targeted therapy alone followed by the addition of chemotherapy at disease progression (PD) versus upfront combination therapy is not yet elucidated.

In 1999, the Swiss Group for Clinical Cancer Research (SAKK) and the European Institute of Oncology in Milan launched a randomized phase III trial of sequential versus combination therapy in patients with HER2-positive ABC. The trial aimed to test the superiority of a sequential approach, to postpone the toxicity of chemotherapy.

Patients and methods

Patient selection

Eligibility criteria: women aged 18–70 with histologically proven HER2-positive ABC. The original design included 1st-line, chemotherapy-naïve patients. In July 2000, based on T activity in chemotherapy-pretreated patients (6), amended criteria allowed 2nd/3rd-line chemotherapy, without previous HER2-directed therapy for ABC. First-line patients could have received neo/adjuvant chemotherapy completed ≥6 months before enrolment. In case of previous anthracyclines the cumulative dose had to be ≤240 mg/m^2 doxorubicin or ≤360 mg/m^2 epirubicin. No previous taxanes were allowed. Adjuvant/palliative endocrine therapy (ET) was allowed. Patients must had: Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤1, life expectancy ≥12 weeks, adequate hematological, renal and liver function (total bilirubin <upper normal limits, ASAT and/or ALAT ≤3x upper normal limit if liver metastases), left ventricular ejection fraction (LVEF) at rest by

echocardiography within local normal limits, clinically/radiologic measurable/evaluable disease (bi- or uni-dimensionally). Exclusion criteria: known brain/meningeal involvement, contraindications to corticosteroids, other concomitant anticancer drugs, any other serious disease. Bisphosphonates, started >3 months prior to enrolment, were allowed provided bone metastases were not the only disease indicator.

Patients provided written informed consent and the protocol was approved by local ethics committees. The trial (NCT00004935) was conducted according to Good Clinical Practice, the Declaration of Helsinki and applicable regulatory requirements.

Study design

This was a multicenter, prospective, non-blinded, randomized phase III trial: patients were randomly assigned (1:1) to T alone followed, at PD, by the combination with chemotherapy (Arm A) versus the upfront combination of T and chemotherapy (Arm B) (Supplementary Figure 1). Randomization was stratified by degree of HER2 overexpression (3+/2+), estrogen receptor (ER) status, 1^{st}- versus $2^{nd}/3^{rd}$-line therapy, previous anthracyclines and institution.

The T loading dose of 4 mg/kg/iv was followed by 2 mg/kg/iv weekly. In the 1^{st}-line population (n=84) chemotherapy was weekly paclitaxel (90 mg/m^2/iv-3/4 weeks). After the amendment chemotherapy was at investigator's choice (taxanes, vinorelbine, cisplatin) according to label indications/schedules and could be stopped after ≥24 weeks (6–8 cycles) in responding patients or after unacceptable toxicity. Reintroduction of the same chemotherapy under maintenance T was allowed if clinically indicated. In case of chemotherapy-related adverse events, chemotherapy could be changed. T was continued until progression. Treatment after PD under combined therapy was at investigators' decision.

Assessments

HER2 expression was measured by immunohistochemistry (DAKO HercepTest™), overexpression defined according to the manufacturer's manual. Local HER2 assessment was accepted for randomization with central confirmatory review.

Patients underwent blood testing, medical history, physical examination, cardiac (ECG and echocardiography) and tumor (chest X-ray, bone scan, liver ultrasound) assessments ≤4 weeks before randomization. During study treatment, blood tests were repeated on day1 of every cycle and until recovery after the last cycle. Tumor assessment was planned after cycles 2-4-6 and then every 3 cycles, at PD and after the last cycle. Cardiac evaluation was repeated every 3 cycles during study treatment and every 3 months until recovery in case of LVEF decrease.

Adverse events were graded using the NCIC-CTG Expanded Common Toxicity criteria V2. Specific dose reductions, delay and discontinuation algorithms were foreseen for T and chemotherapy. Eligible patients receiving at least one dose of T ± Chemotherapy were considered evaluable.

Quality of life (QoL) evaluation was completed prior to randomization, at day1 of each cycle for the first six months and every second cycle from months 7-12. The assessment included global indicators for physical well-being, mood, functional performance, treatment burden and coping effort (7,8) and specific indicators for tiredness, appetite, nausea/vomiting, taste changes, peripheral numbness/paresthesia, pain, hair loss, and weight gain, based on QLQ-8 (9). Physical well-being, mood and coping effort were primary endpoints, based on previous data (10). All indicators were in the linear analogue self-assessment (LASA) format.

Statistical analysis

The primary endpoint was TTP on combined treatment (Combination-TTP), defined as interval from randomization to PD under T plus Chemotherapy. Based on the available evidence of a 3-month improvement in disease progression with the combination of T and chemotherapy (11), 153–205 events or 166–252 patients were required to detect a clinically meaningful 3 months increase from the 5–6 months expected median Combination-TTP in Arm B to 8–9 months by a log-rank test at a power of 80% and significance level of 5%, with a group-sequential design allowing for two interim analyses. Secondary endpoints were response rate, time to 1st TTP and to treatment failure (Combination-TTP plus toxicity events and refusal; TTF), OS, toxicity, and QoL. Analyses were done according to the intention-to-treat principle. Survival curves were determined using Kaplan-Meier methods and compared using the log-rank test. Frequencies were compared using Fisher's exact tests. HRs with 95% CI were computed with uni/multivariable proportional hazard models. QoL scores were plotted over time and by treatment. Testing was restricted to values from baseline and cycle 1 in a mixed effects model. In both Cox and mixed models interactions were assessed by Wald-type tests. P-values are two-sided, not adjusted for multiple testing, and considered significant if <0.05. Analyses were carried out using SAS v9.2 or the R software package (www.r-project.org) version 3.2 or later.

Results

Patient characteristics

From September 1999–January 2013, 175 patients were randomized in 9 centers to sequential (Arm A n=86) or combination (Arm B n=87) treatment: 2 patients were not eligible (1 HER2-negative centrally, 1 treatment refusal; CONSORT diagram). The interim analyses in October 2004-July 2011 did not cross the predefined boundaries for either futility or efficacy.

Baseline characteristics were well balanced (Table 1). Median age was 55 years (33–79), 99% of patients had an ECOG PS of 0-1. One-hundred-twenty-five patients (72%) received study treatment as 1st-line, 48 patients (28%), without previous T, as 2nd/3rd-line (112 taxanes, 49 vinorelbine, 2 both, 10 in arm A never started chemotherapy); 77 patients (45%) had neo/adjuvant chemotherapy (40% anthracycline-based), 102 patients (59%) radiation therapy (24% for ABC). Sixty-three-percent of patients (109) had ER+ and/or progesterone-receptor-positive (PR+) tumors: 67% (73) had received ET as adjuvant (48, 68%) or palliative (23, 32%) treatment (2 unknown indications). One-hundred-fourteen patients (66%) had visceral disease, 39% of them (44) both visceral and bone disease, 17% (19) had bone disease only, 72% of the patients (124) had ≥3 disease sites. One third of patients had ABC at diagnosis.

Treatment

At cutoff date (November 2014) 3 patients were still under T alone, 1 under maintenance T after chemotherapy interruption. The median TTF was 11.5 months (95% CI 8.9–18.1) in Arm A and 6.4 months (95% CI 5.6–7.0) in Arm B. Fifty-two patients (30%) were censored (45 off-protocol treatment before PD, 7 maintenance metronomic chemotherapy/ET before PD). Seven patients were lost to follow-up, 4 experiencing an event and 2 starting a new treatment. The overall exposure to chemotherapy in months was similar in both arms.

Efficacy

At 77.7 months median follow-up, 53 and 68 events occurred in Arm A and B, respectively. The median Combination-TTP was 12.2 months in Arm A (95% CI 9.2-15.3) and 10.3 months in Arm B (95% CI 9.2–12.6) (HR 0.7, 95% CI 0.5–1.1; p=0.1) (Figure 1A). In Arm A the median TTP before introduction of chemotherapy was 3.7 months (HR 2.1; p<0.001) (Figure 1B): early PD (<2 months) occurred in 24 patients in Arm A (28%) and 4 patients in

Arm B (4%). Twelve-percent of patients in Arm A received T alone for one year, 6% for two years.

Death occurred in 65 patients in Arm A and 68 patients in Arm B. The median OS was 35.6 months in Arm A (95% CI 30.9–41.4) and 36.3 months in Arm B (95% CI 30.6-40.5), (HR 0.9; p=0.55) (Figure 1C).

In an unplanned subgroup analysis, Combination-TTP in Arm A was 21.8 months (95% CI 11.3–NA) in patients without visceral disease and 10.4 months (95% CI 8.3–12.2) in patients with visceral disease. In Arm B, Combination-TTP was similar (10.1 months, 95% CI 8.5–17.3 and 10.3 months, 95% CI 8.7–12.3) in patients with or without visceral disease ($p_{interaction}$=0.055; Figure 2A). For TTP, the interaction between arm and visceral disease was significant ($P_{interaction}$=0.03; Figure 2B). For OS, no evidence for an interaction between treatment and visceral disease status was found ($P_{interaction}$=1; Figure 2C).

Combination-TTP was significantly shorter in ER+/PR+ patients who received previous palliative ET (10.0 months, 95% CI 8.8–12.7) than in ET-naïve patients (18.1 months, 95% CI 11.0–21.8) (logrank p=0.03). Of note, only 2 of these patients had a disease response under palliative ET. Small numbers prevented a stratified efficacy analysis of HER2 2+/3+patients. Brain metastases were reported in 6% (7/115) of progressing patients (1 in Arm A, 6 in Arm B).

No interaction was evident between Combination-TTP and age (Supplementary Figure 2). The chemotherapy backbone (vinorelbine versus taxanes) did not impact TTP (HR 1.0, 95% CI 0.5–1.9, p=0.89).

Quality of life and safety

After 3-4 weeks' therapy (first on-treatment visit) patients in both arms reported better mood and less coping effort (all p <0.001) compared to baseline. Patients receiving

combined treatment upfront reported substantially more hair loss ($p_{interaction}$<0.0001) and weight gain (p<0.01). A descriptive investigation (Supplementary Figure 3) indicates these differences persist over the first six cycles, as associated with more treatment burden. The remaining global QoL indicators showed no substantial differences between arms.

Toxicity was chemotherapy- and regimen-related and not substantially different in the 2 arms: grade 3-4 toxicity was very rare (Table 2). Cardiac toxicity was mild (no grade 4, 1 G3 cardiac failure in arm A). No treatment-related death was reported.

Discussion

The sequential administration of trastuzumab followed at PD by the addition of chemotherapy delays chemotherapy and its toxicity.

Our trial, designed as a superiority trial, failed to show a benefit in Combination-TTP in the sequential arm but we observed a longer than projected Combination-TTP, not significantly different in the 2 arms. Survival was also not significantly different between arms, despite a higher early progression rate in the sequential arm. When looking at patients without visceral disease, in an unplanned subgroup analysis, trastuzumab alone allowed a remarkably long disease control (up to 1-2 years) resulting in a significantly longer Combination-TTP compared to upfront combination therapy. These hypothesis generating results seem to suggest chemotherapy can be safely postponed in the subgroup of patients without visceral disease.

Two trials addressed timing of chemotherapy in presence of trastuzumab. In the Japanese JO17360 1st-line phase III trial, 112 patients were randomized to T followed at PD by T plus docetaxel (D) or combination T+D (12). Accrual was prematurely stopped because progression-free survival (PFS) was significantly worse in the sequential arm (3.7 versus 14.6 months, p<.01). OS was also significantly longer in the T+D arm (HR 2.72; p=0.04),

although it was not possible to calculate the median OS because the number of deaths was very low in both arms.

In the Dutch Breast Cancer Trialists' Group 1st-line phase II HERTAX Trial, 101 patients were randomized between upfront T+D and sequential T followed at PD by D alone (13). The primary endpoint was PFS after completed sequential/combination therapy. Sequential and combination treatments resulted in similar PFS (9.9 versus 9.4 months). The trial was not powered for OS analysis but the overall response rate (ORR) was significantly lower in the sequential arm (79% versus 53%, p=0.016).

Several aspects distinguish the three trials. Although the Japanese study had the same design as ours, in the sequential arm PFS was calculated at PD with single agent T and not after the addition of chemotherapy: our trial evaluated TTP under combination therapy in both arms as we did want to study timing of chemotherapy, not if we can omit it. The Dutch trial explored sequential T followed at PD by single-agent chemotherapy. Our trial was the only to evaluate the impact of combination therapy in both arms while maintaining T at PD.

In our trial, patients under sequential treatment reported more side effects but no substantial difference in physical well-being, mood or coping effort: however, the sample size was too small for a conclusive QoL evaluation.

Our trial has several limitations. The planned accrual in 5 years (40–50 patients/year) was not achieved and >13 years were required to enroll 175 patients. Different reasons explain this delay: the availability of T with chemotherapy other than paclitaxel outside the trial and the need to continue chemotherapy until PD, both removed by the amendment; emerging new anti-HER2 therapies over time. A substantial number of patients were censored due to off-protocol treatments, mainly maintenance ET/metronomic chemotherapy added to

trastuzumab. However, even when considering them as events the results did not change substantially. Failure to enroll an appropriate number of participants and to stick to protocol therapy resulted in reduction of the number of events and statistical power, prolonging study duration and decreasing the possibility to show a significant difference between the two tested strategies.

Despite these limitations, we found no significant differences in TTP and OS when postponing chemotherapy in patients under HER2-directed therapy. This result, not foreseen in the trial design in 1999, is hypothesis-generating and of clinical interest especially in patients without visceral disease, recognizing the barriers to conduct a new trial in this setting and despite derived from an unplanned subgroup analysis. QoL, safety and cost considerations should also be part of the individual decision-making algorithm.

Our results represent an additional proof of concept of the expanding de-escalating strategy in HER2-positive BC, shown to be promising in early disease (14) and in the neoadjuvant setting (15). In ABC sequential single-agent chemotherapy is already the standard of care, with combination chemotherapy reserved for rapidly progressive or highly symptomatic disease (3).

HER2-targeted therapies and strategies are under continuous development: despite major improvements over the last 15 years, optimisation of sequencing, combination and alternating strategies is still needed to further impact outcomes. The SAKK 22/10 trial (PERNETTA trial NCT01835236), evaluating in 1st-line patients the sequential dual anti-HER2 targeting (Trastuzumab/Pertuzumab) strategy, finished accrual and will hopefully add evidence to better plan treatment individualization.

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Disclosure

The authors have declared no conflicts of interest.

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Table & Figure Legends:

Table 1. Patients' characteristics

Table 2. Treatment-related selected adverse events occurring in ≥10% of patients

Figure 1: TTP-TChemo (A), TTP (B), OS (C) according to treatment arm.
TTP: time to progression. TTP-TChemo: TTP on combined trastuzumab-chemotherapy. OS: overall survival.

Figure 2: TTP-TChemo (A), TTP (B), OS (C) according to treatment arm and presence of visceral disease (VD)

Supplementary Figure 1: Study design

Supplementary Figure 2: TTP-TChemo according to age and treatment arm

Supplementary Figure 3: Quality of Life

Table 1. Patients' characteristics

	arm A (n=86)	arm B (n=87)
Age (years)		
Median (range)	53 (33-79)	57 (33-79)
ECOG PS (%)		
0-1	85 (99%)	87 (100%)
N° CT regimens (%)		
1st line	63 (73%)	62 (71%)
2nd-3rd line	23 (27%)	25 (29%)
ER status (%)		
Positive	51 (59%)	52 (60%)
Negative	35 (41%)	35 (40%)
Adjuvant Anthracyclines (%)		
HER2 2+	11 (13%)	13 (15%)
No	52 (60%)	53 (61%)
Yes	34 (40%)	34 (39%)
Endocrine therapy (%)		
No	16 (33%)	17 (32%)
Adjuvant	22 (45%)	25 (47%)
Palliative	11 (22%)	11 (21%)
Disease sites (%)		
Bone only	7 (8%)	12 (14%)
Visceral only	32 (37%)	38 (44%)
Visceral + bone	26 (30%)	18 (21%)
Advanced disease at diagnosis (%)	25 (29%)	29 (33%)

Table 2. Treatment-related selected adverse events occurring in ≥10% of patients

	All grades		Grade 3-4	
	arm A (T→TChemo) (n=86)	arm B (TChemo) (n=88)	arm A (T→TChemo) (n=86)	arm B (TChemo) (n=88)
Neutropenia	46 (53%)	63 (71%)	13 (15%)	24 (27%)
Sensory neuropathy	43 (50%)	48 (54%)	6 (6%)	6 (7%)
Arthralgia/Myalgia	49 (57%)	41 (46%)	1 (1%)	1 (1%)
Lethargy	38 (44%)	41 (46%)	1 (1%)	1 (1%)
Alopecia	34 (39%)	44 (50%)	9 (10%)	9 (10%)
Nausea	30 (35%)	26 (29%)	1 (1%)	0
Diarrhoea	26 (30%)	22 (25%)	1 (1%)	2 (2%)
Infection without neutropenia	23 (27%)	19 (21%)	4 (4%)	4 (4%)
Constipation	16 (19%)	23 (26%)	1 (1%)	0
Fever without infection	23 (27%)	11 (13%)	0	0
Loss of appetite	18 (21%)	10 (11%)	1 (1%)	0
Vomiting	16 (19%)	8 (9%)	0	0
Peripheral oedema	11 (13%)	13 (14%)	0	0

Figure Legends

CONSORT 2010 Flow Diagram

Figure 1: TTP-TChemo (A), TTP (B), OS (C) according to treatment arm.

TTP: time to progression. TTP-TChemo: TTP on combined trastuzumab-chemotherapy. OS: overall survival.

Figure 2: TTP-TChemo (A), TTP (B), OS (C) according to treatment arm and presence of visceral disease (VD)

CONSORT 2010 Flow Diagram

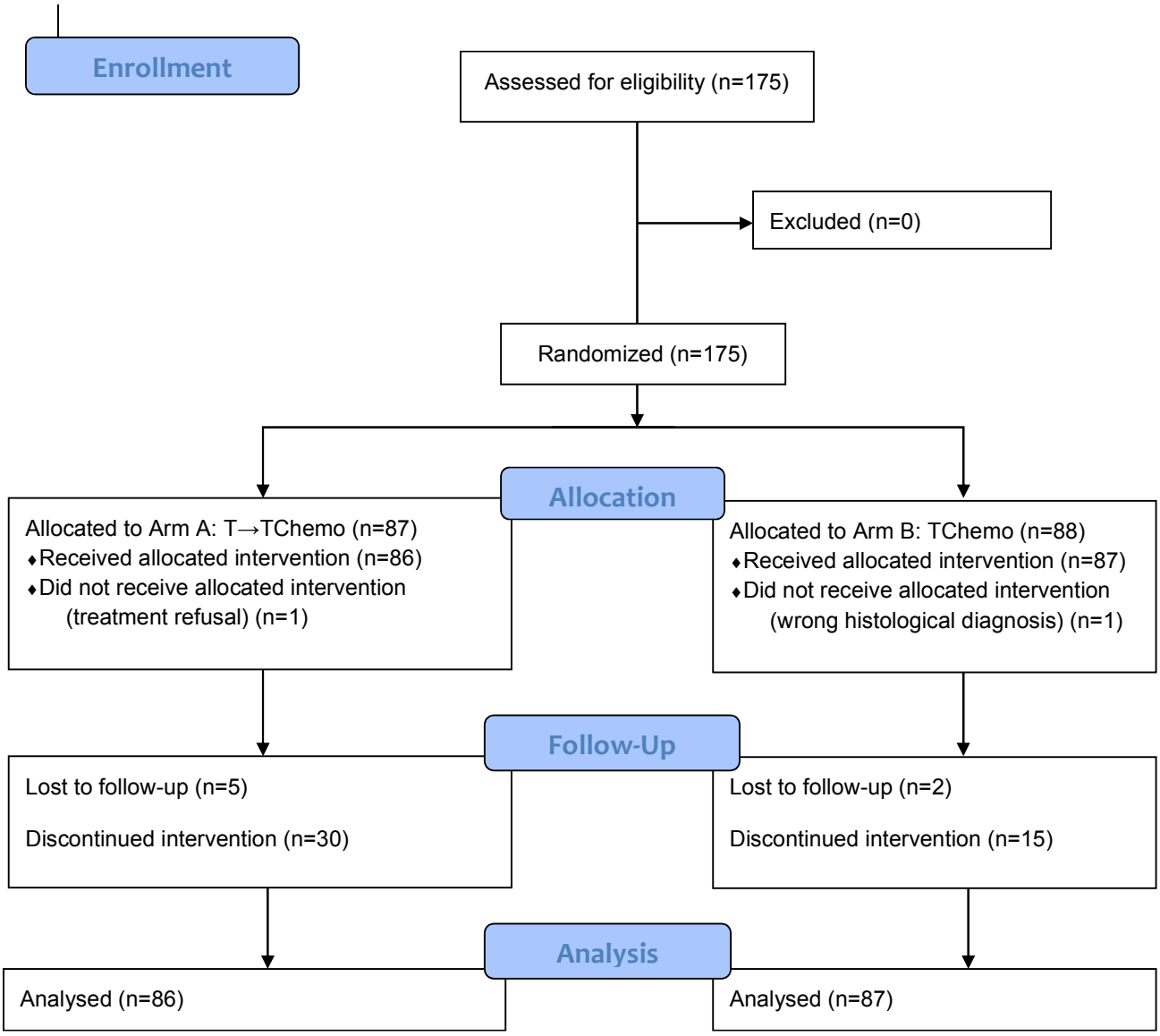
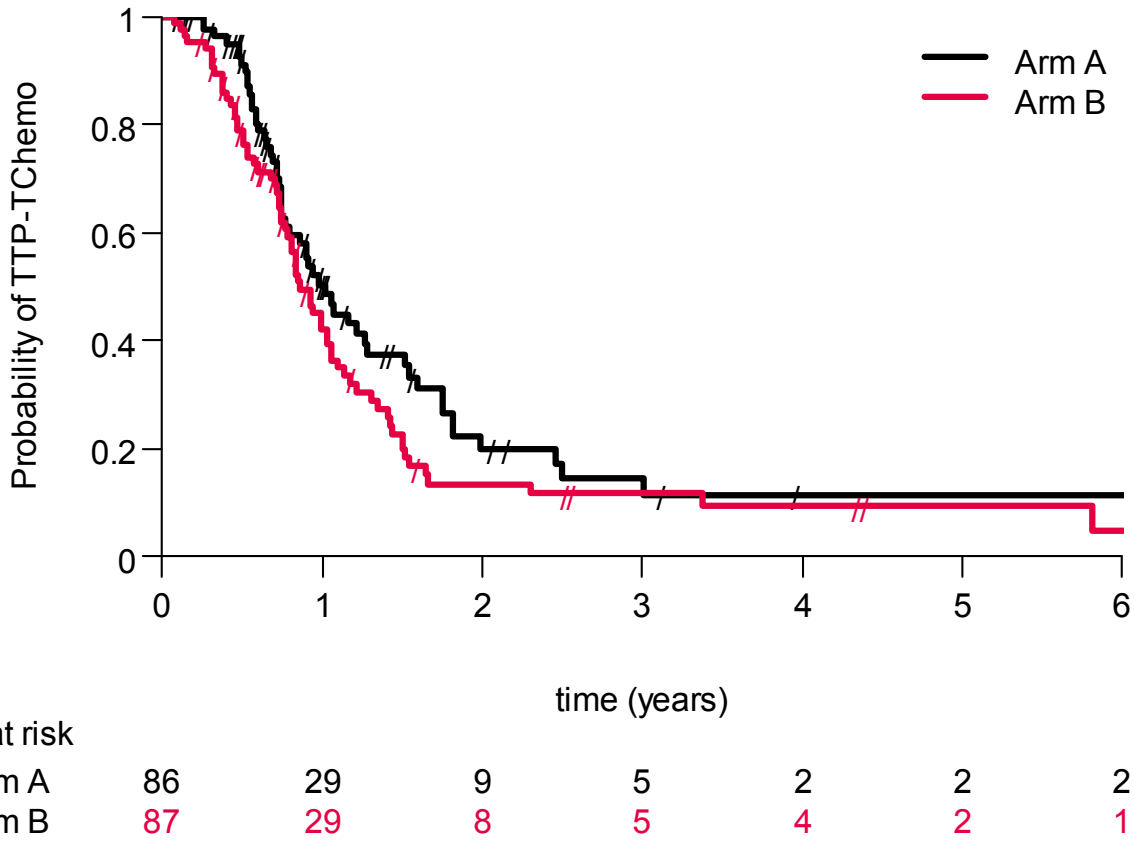
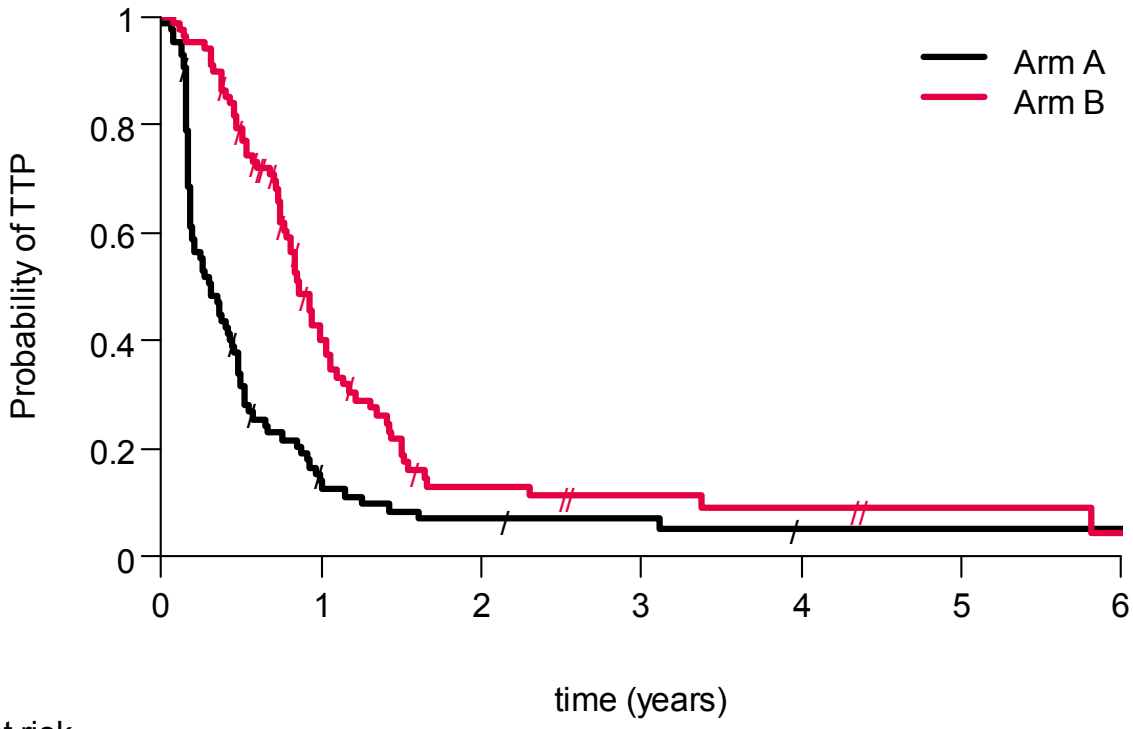


Figure 1A. TTP-TChemo according to treatment arm



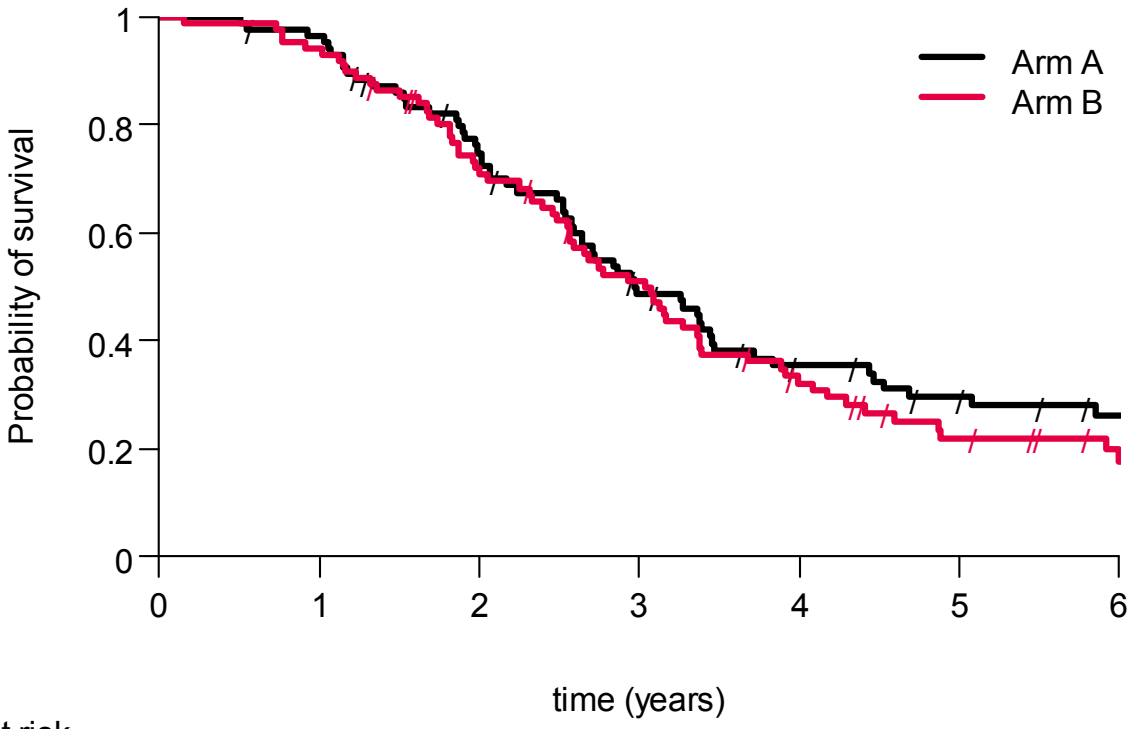
# at risk							
Arm A	86	29	9	5	2	2	2
Arm B	87	29	8	5	4	2	1

Figure 1B. TTP according to treatment arm



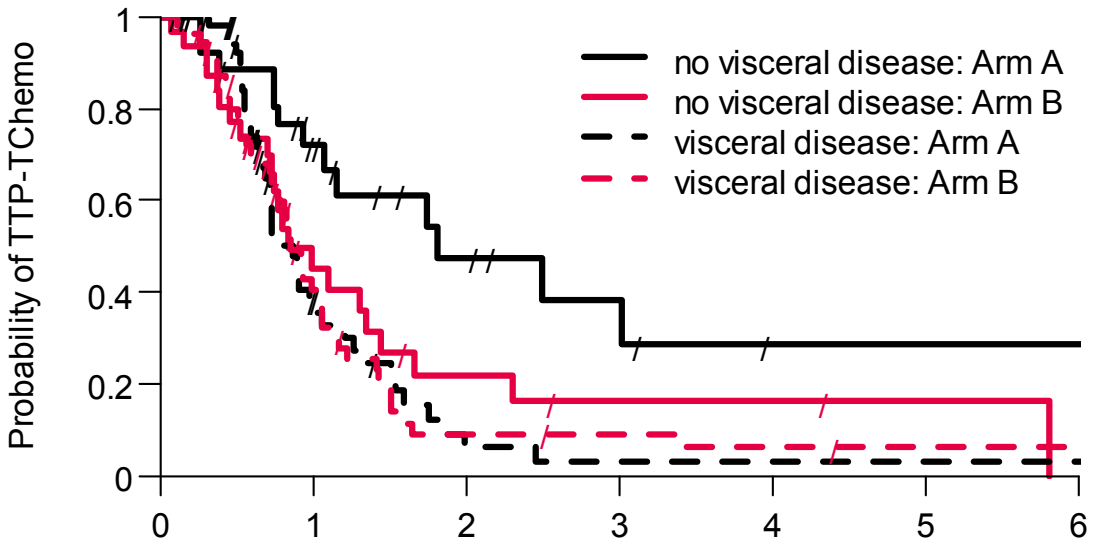
# at risk							
Arm A	85	10	5	4	2	2	2
Arm B	87	29	8	5	4	2	1

Figure 1C. OS according to treatment arm



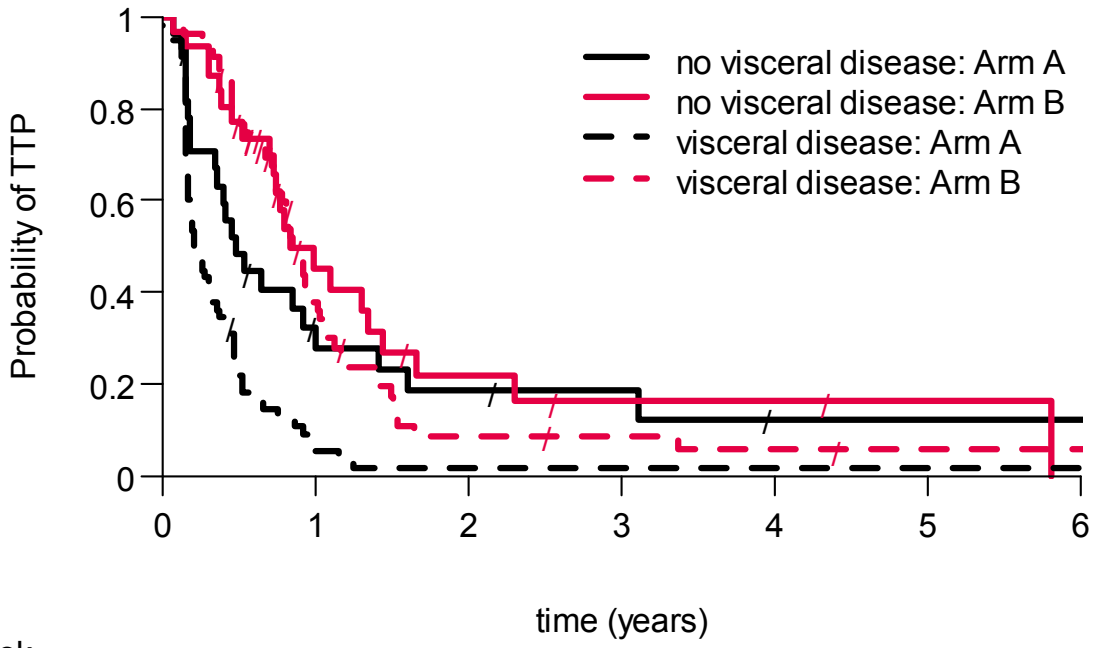
# at risk							
Arm A	86	82	61	38	25	18	14
Arm B	87	82	59	41	24	14	8

Figure 2A. TTP-TChemo according to treatment arm and visceral disease status



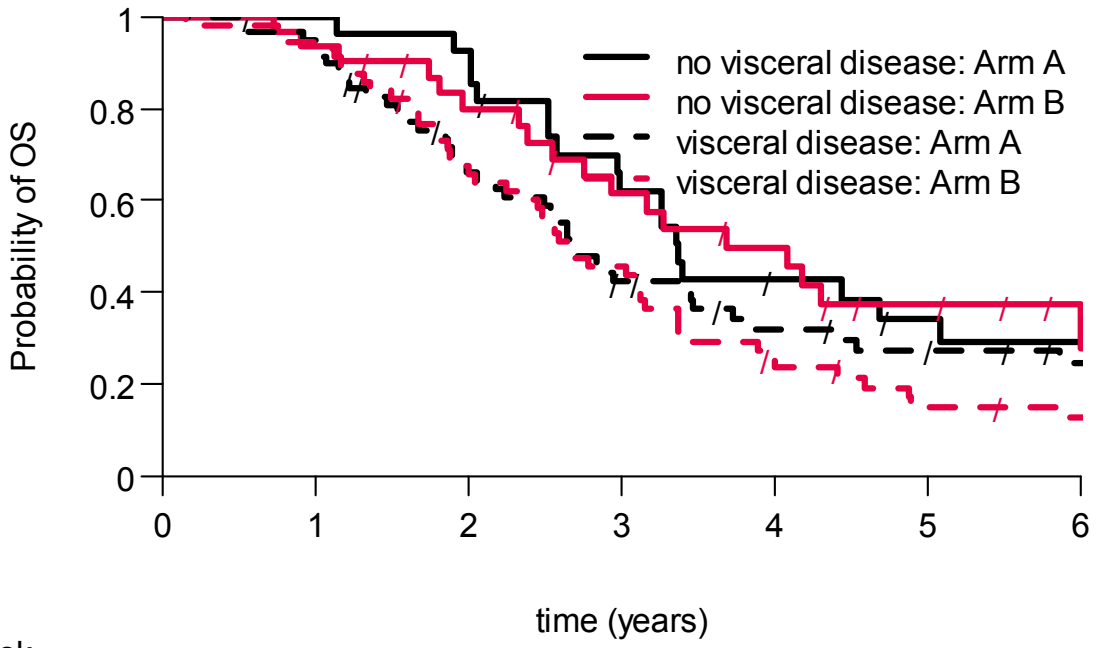
# at risk							
no VD: A	28	15	7	4	1	1	1
no VD: B	31	10	4	2	2	1	0
VD: A	58	14	2	1	1	1	1
VD: B	56	19	4	3	2	1	1

Figure 2B. TTP according to treatment arm and visceral disease status



# at risk							
no VD: A	28	7	4	3	1	1	1
no VD: B	31	10	4	2	2	1	0
VD: A	57	3	1	1	1	1	1
VD: B	56	19	4	3	2	1	1

Figure 2C. OS according to treatment arm and visceral disease status



# at risk							
no VD: A	28	27	25	16	10	7	6
no VD: B	31	29	23	16	12	7	3
VD: A	58	55	36	22	15	11	8
VD: B	56	53	36	25	12	7	5

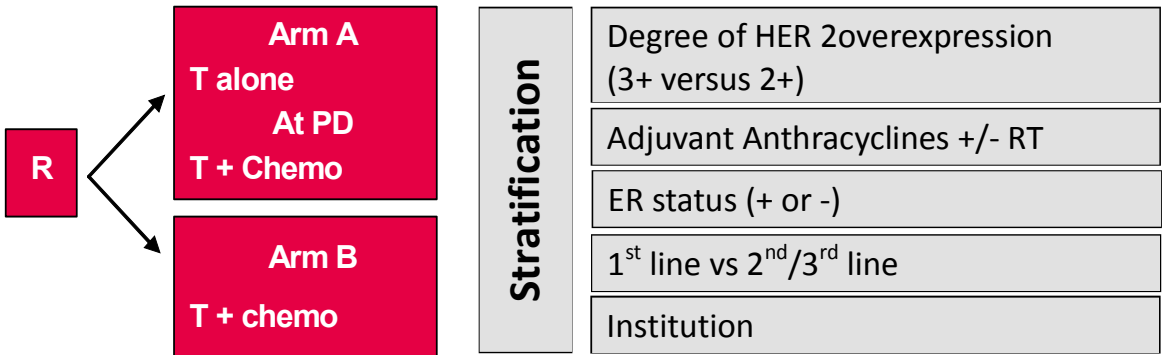
Figure Legends

Supplementary Figure 1: Study design

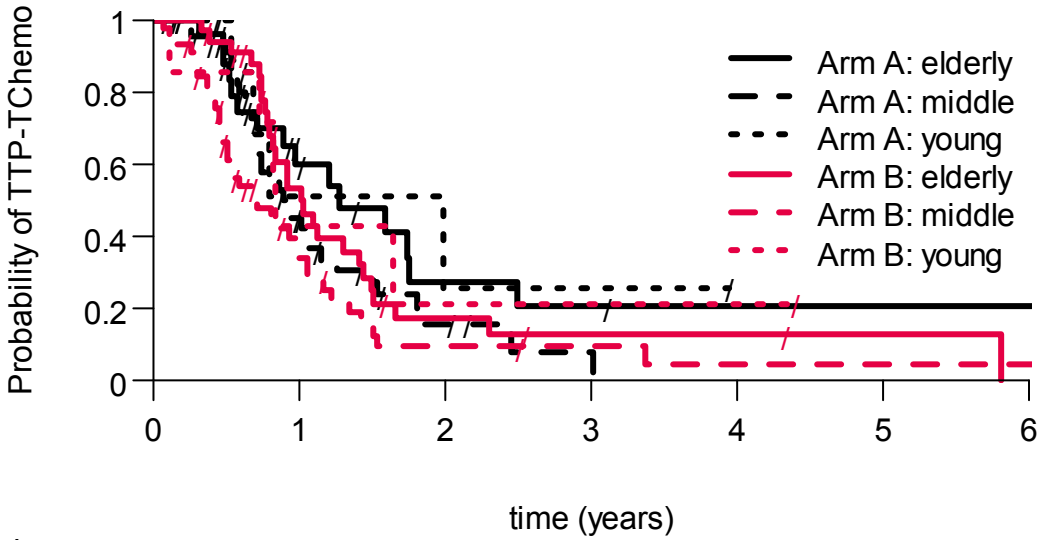
Supplementary Figure 2: TTP-TChemo according to age and treatment arm

Supplementary Figure 3: Quality of Life

Supplementary Figure 1. Study design



Supplementary Figure 2: TTP-TChemo according to age and treatment arm



# at risk							
A: >60y	27	11	4	3	2	2	2
A: 40–60y	50	16	4	1	0	0	0
A: <40y	9	2	1	1	0	0	0
B: >60y	34	15	4	2	2	1	0
B: 40–60y	46	12	3	2	1	1	1
B: <40y	7	2	1	1	1	0	0

Supplementary Figure 3. Quality of Life