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Randomised study of tegafur–uracil plus leucovorin versus capecitabine as first-line therapy in elderly patients with advanced colorectal cancer — TLC study

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ABSTRACT

Background: Prospective data on chemotherapy for (frail) elderly patients with advanced colorectal cancer (aCRC) are scant. UFT/leucovorin might be as effective as and less toxic than capecitabine. We firstly randomized both agents in patients ≥65 years with aCRC not amenable to receive combination chemotherapy.

Patients and Methods: Patients were randomised between first-line oral UFT/leucovorin and capecitabine in a Dutch multicentre trial. Primarily, efficacy and toxicity were determined. Secondary, quality of life (QoL) and abbreviated common geriatric assessment (aCGA) were analysed.

Results: Sixty-seven patients were randomised with a median age of 77 years and 96% being frail. After interim analysis it was decided to stop recruitment because of low accrual. At a median follow up of 34 months, the median progression-free survival (PFS) and overall survival (OS) were similar for both therapies, being 21 weeks ($p = 0.17$) and 12 months ($p = 0.83$), respectively. The overall response rates were 24% and 21%, respectively. Two patients died of possible treatment related complications in the UFT/leucovorin arm and 3 patients in the capecitabine arm. For UFT/leucovorin significantly less grade 3 or 4 hand/foot syndrome (0 vs 5) was observed. Overall, PFS was related to Charlson-comorbidity index ($p = 0.049$), LDH ($p = 0.0011$) and albumin ($p = 0.009$). OS was related to LDH ($p = 0.0003$),

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albumin (p = 0.0001), QoLC30/CR38 (p = 0.041), QoL visual analogue scale (VAS; p = 0.016), and GFI (p = 0.028).

Conclusion: UFT/leucovorin and capecitabine had similar efficacy and different toxicity profiles in frail elderly patients with aCRC. Baseline serum levels of albumin and LDH, Charlson-comorbidity index, GFI and QoL were prognostic for clinical outcome.

1. Introduction

About 70% of patients with colon cancer are >65 years of age and the number of elderly patients is increasing, both due to an increase in life expectancy and the increasing population.[1] Despite this growing colorectal cancer burden in elderly patients the majority of studies exploring the optimal strategy in patients with advanced colorectal cancer (aCRC) is based on studies in patients that are considerably younger. Elderly patients more often have co-morbidity and for them combination chemotherapy can be associated with greater toxicity and less overall benefit.[2] Currently, the most common first line chemotherapy for treatment of patients with aCRC unsuitable to receive combination chemotherapy or mono-chemotherapy with bevacizumab, is monotherapy with a fluoropyrimidine. Both 5-fluorouracil prodrugs UFT, tegafur plus uracil that inhibits dihydropyrimidine dehydrogenase the rate-limiting enzyme in 5-fluorouracil catabolism, and capecitabine have already shown good tolerability and efficacy in the elderly.[3,4] However, these agents have never been compared in a randomised study. We hypothesised that the different patterns of toxicity may result in a preferable drug for this population. In addition, this study would add to the limited prospective data on elderly patients with aCRC s treated with first line systemic palliative chemotherapy. We therefore initiated this randomised trial comparing UFT and capecitabine in elderly patients with aCRC not suitable for or not willing to receive combination chemotherapy. In order to better monitor the study population we measured, in addition to efficacy and toxicity of the two oral treatments, serum levels of albumin and LDH, quality of life (QoL) and an abbreviated comprehensive geriatric assessment (aCGA).

1.1. Study Population

Patients were eligible for inclusion if they were at least 65 years of age, had histologically proven aCRC, measurable disease, not amenable to treatment with curative intent and not amenable or willing to receive combination chemotherapy or mono-chemotherapy with bevacizumab. Patients also had to have a WHO performance score 0–2, a life expectancy of >3 months, and adequate bone marrow, liver and renal function. Frailty was defined as having two or more comorbidities according to the Charlson co-morbidity index and/or a Gronigen frailty indicator (GFI) score $\geq$4. Patients were excluded from the study if they had received prior chemotherapy for aCRC (prior adjuvant chemotherapy was allowed provided that the last administration was given > 6 months prior to randomisation), known or suspected central nervous system metastasis, another malignancy in the previous 5 years (with exception of a history of previous basal cell carcinoma of the skin or pre-invasive carcinoma of the cervix), chronic diarrhoea or inflammatory bowel disease, known as dihydropyrimidine dehydrogenase (DPD) deficiency, clinically relevant coronary artery disease, a high risk of uncontrolled arrhythmia, or history of myocardial infarction in the last 12 months or a medical or psychological condition which, in the opinion of the investigator, would not permit the patient to complete the study or sign meaningful informed consent. The study was approved by the Ethics Committees of the Leiden University Medical Center and all local participating institutions. Written informed consent was obtained from all patients.

1.2. Treatment and Evaluation

After randomisation patients received UFT/leucovorin (UFT 150 mg/m^2 orally, b.i.d, plus leucovorin 30 mg, b.i.d., days 1–28, Q5 weeks) or capecitabine (1250 mg/m^2, b.i.d, days 1–14, Q3 weeks) until disease progression or unacceptable toxicity in the TLC study (NTR1268, Dutch trial register, www.trialregister.nl).

Toxicity was graded according to the common toxicity criteria for adverse events (CTCAE), version 3.0. Patients were assessed clinically at least every 5 weeks and response evaluation was carried out every 9 weeks during therapy and at the end of study treatment, using RECIST criteria version 1.0. Questionnaires on QoL, using the EORTC QoL Questionnaire C-30, CR38 and visual analogue scale (VAS), and an aCGA were completed at study entry. The surveys were planned to be administered prior to randomization, and thereafter every 9 weeks with a final survey at the end of treatment. The aCGA examined the co-morbidity (Charlson co-morbidity index, cut-off score $\geq$2),[5] instrumental activities of daily life (IADL; cut-offs for partial dependence 14–27, full functional dependence $\leq$13),[6] geriatric depression scale (GDS; cut-off for severe depressive symptoms $\geq$10, moderate depressive symptoms 5–9),[7] and Groningen Frailty Index (GFI; cut-off of 4 or more for frailty).[8] Subgroup analyses of PFS and OS were performed for baseline patients characteristics (WHO performance score and age), baseline serum levels of LDH <400 vs $\geq$400 and albumin <35 vs $\geq$35, QOL and aCGA.

1.3. Statistical Methods

The primary end point of the study was progression free survival (PFS), defined as the duration from the time of randomisation until first observation of radiologically confirmed progressive disease or death due to any cause, whichever occurred first. Secondary endpoints included overall survival (OS) defined as the duration from the time of randomisation until death from any cause, objective response rate, toxicity and the evaluation of QoL and aCGA.

Assuming that the treatments have a similar hazard of progression, it was considered that only differences in the median PFS of ≥6 weeks (HR = 1.4 UFT/capecitabine) were medically relevant. With 277 events, the upper limit of the confidence interval of the hazard ratio would not exceed 1.4 with 80% power and a sample size of 300 patients.

Randomisation was stratified by WHO performance status (0–1 vs. 2), age (65–69, 70–79, and ≥80 years) and prior adjuvant therapy (with fluoropyrimidine vs. without a fluoropyrimidine vs. any prior adjuvant therapy). If the difference in PFS was not medically relevant, the choice of treatment would be based on other considerations: better QoL or less toxicity.

All end points were analysed according to the intention-to-treat principle, except toxicity which included only patients who received at least one therapy dose. The analyses of PFS and OS by treatment were based on the stratified log-rank test. The Kaplan–Meier method was used to estimate PFS and OS curves and hazard ratios were calculated using Cox proportional hazards models. Two sided *p*-values are presented.

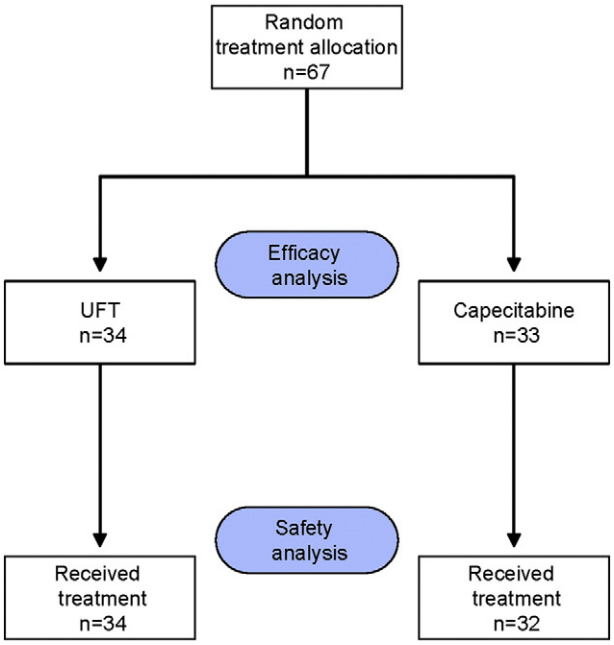

Fig. 1 – CONSORT diagram of the study.

2. Results

2.1. Conduct of the Trial

Between January 8, 2008 and July 30, 2012, 15 participating Dutch hospitals enrolled a total of 67 patients. An interim analysis on grade 3/4 adverse events was done in December 2011 after inclusion of 46 patients. This test, with 1-sided significance level 0.05 and 90% power for the hypothesis of 40% grade 3/4 adverse events in the capecitabine and 20% in the UFT arm, showed that the futility boundary was not crossed. The study was closed prematurely in July 2012 due to slow accrual, partly because of the introduction of bevacizumab for treatment of first line aCRC. This limited the sample size to 67. The cut-off date for analysis was January 29, 2014, resulting in a median follow up of 34 months. All patients were eligible for efficacy analysis and 66 for toxicity analysis.

2.2. Patient Characteristics

Fig. 1 depicts the CONSORT diagram of the study. Patient characteristics are shown in Table 1. The median age was 77 years. Most patients (94%) were ≥70 years. The median Charlson co-morbidity index was 1 with a range from 0–10. The majority of patients (96%) were frail, defined as having two or more comorbidities, with 22% and 33% of the patients in the UFT and capecitabine arm, respectively and/or a GFI 4–9 score in 94% of patients.

2.3. Survival and Response Rate

Sixty-five of the 67 patients had a PFS event, 33 in the UFT/leucovorin group and 32 in the capecitabine group. The median PFS was 20 weeks (95% confidence interval (CI) 19.5–27.6) in the UFT/leucovorin group and 23 weeks (95% CI 13.4–40.4) in the capecitabine group, hazard ratio (HR) 0.66 (95% CI 0.37–1.19, $p = 0.17$, Fig. 2a).

No significant difference in overall survival (OS) was observed between the chemotherapy regimens (Fig. 3). Median OS was 12 months (95% CI 8–16 months) for UFT/leucovorin and 13 months (95% CI 5–17 months) for capecitabine (HR 0.94;95% CI 0.52–1.70; $p = 0.83$).

The best overall response rate percentages were 24% (all partial responses) for UFT/leucovorin and for capecitabine 21% (2 complete responses and 5 partial responses, Table 2).

2.4. Baseline Quality of Life and Comprehensive Geriatric Assessment

Baseline QLQ-C30 and -CR38 questionnaires were available from 60/67 and 52/67 patients respectively. Baseline co-morbidity was known from 55/67 patients. Baseline IADL, GDS, GFI and VAS was known from 54, 54, 51 and 39 out of 67 patients, respectively. All missing questionnaires were well-balanced between the arms.

Subgroup analyses for PFS were performed for all patients combined as well as compared between the 2 chemotherapy regimens. For all patients combined, PFS was significantly higher for those without co-morbidity as compared to those with a Charlson comorbidity index ≥2 (Fig. 2b; log rank test $p = 0.049$). PFS was almost statistically significantly different for Charlson comorbidity index with optional age extension ($p = 0.07$) and for age ($p = 0.10$), and not different for QoL ($p = 0.57$), IADL ($p = 0.45$), GDS ($p = 0.14$), VAS ($p = 0.64$) and GFI ($p = 0.82$).PFS was significantly related to serum LDH (p=0.0011) and albumin (p=0.009) (Fig.4).

OS was significantly related to baseline WHO performance score ($p = 0.042$), serum LDH ($p = 0.0011$) and albumin ($p = 0.009$), QoL ($p = 0.041$), VAS ($p = 0.016$) and GFI ($p = 0.028$).

The subgroup analyses for all these variables in terms of PFS and OS showed no difference between the 2 chemotherapy regimens.

Table 1 – Patient characteristics.

Patients	UFT/ leucovorin	Capecitabine	Total
	34	33	67
Age			
Median (range)	77 (66–88)	76 (66–88)	77 (66–88)
65–69	2 (6%)	2 (6%)	4 (6%)
70–79	19 (56%)	19 (58%)	38 (57%)
80–88	13 (38%)	12 (36%)	25 (37%)
Gender			
Male	19 (56%)	17 (52%)	36 (54%)
Female	15 (44%)	16 (48%)	31 (46%)
WHO performance status			
0	10 (30%)	6 (20%)	16 (25%)
1	20 (61%)	19 (63%)	39 (62%)
2	3 (9%)	5 (17%)	8 (13%)
NA	1	3	4
Charlson co-morbidity index			
Median (range)	1 (0–10)	1 (0–7)	1 (0–10)
Frailty (Charlson and/or GFI)			
CCI ≥ 2 or GFI ≥ 4	24 (92%)	27 (100%)	51 (96%)
CCI 0–1 and GFI ≤ 3	2 (8%)	0 (0%)	2 (4%)
NA	8	6	14
Disease stage			
IIIA	0 (0%)	0 (0%)	0 (0%)
IIIB	1 (3%)	2 (7%)	3 (5%)
IIIC	0 (0%)	1 (3%)	1 (2%)
IV	30 (97%)	27 (90%)	57 (93%)
NA	3	3	6
Site of primary tumour			
Colon	19 (56%)	19 (59%)	37 (57%)
Rectum	13 (39%)	12 (38%)	25 (38%)
Both	1 (3%)	0 (0%)	1 (2%)
Prior adjuvant therapy			
With a fluoropyrimidine	3 (9%)	3 (9%)	6 (9%)
Without a fluoropyrimidine	1 (3%)	0 (0%)	1 (1%)
No prior adjuvant therapy	30 (88%)	30 (91%)	60 (90%)

CCI = Charlson comorbidity index; GFI = Groningen frailty indicator; NA = not available.

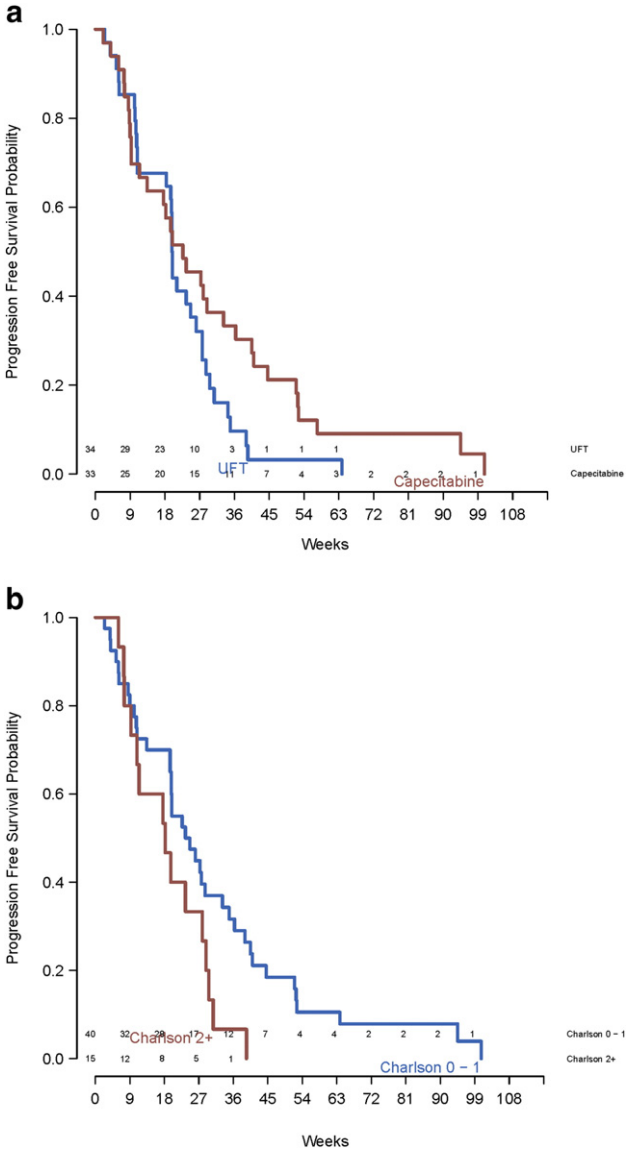

Fig. 2 – a: Progression free survival UFT/lV vs capecitabine (stratified logrank test $p = 0.17$). b: Progression free survival by Charlson index (logrank test $p = 0.049$).

2.5. *Toxicity*

The safety population consisted of 66 patients in the randomised population who received any dose of study drug (one patient in the capecitabine arm, who did not start therapy, was excluded). Adverse events of CTC grade 3 or higher were considered. During treatment, there were 56 ≥ grade 3 adverse events, 28 events in both arms (Table 3). Two patients died of possibly treatment related complications in the UFT/leucovorin arm (pulmonary embolus and unknown reason) and 3 in the capecitabine arm (1 dyspnoea and 2 ischemic CVA). Only 2 patients developed grade ≥3 hematologic toxicity. Five patients, all in the UFT/leucovorin group received erythropoietin and only one patient in the capecitabine arm had a grade 3 anaemia. For UFT/leucovorin there seemed to be more grade 3/4 diarrhoea (9 vs 4 patients, although not statistically significant $p = 0.22$), but there was significantly less grade 3/4 hand/foot syndrome (0 vs 5 patients, $p = 0.023$).

Adverse events ≥grade 3 were not related to baseline co-morbidity, quality of life or one of the other aCGAs.

2.6. *Treatment Duration*

A median of 4 cycles of chemotherapy were administered for both UFT/leucovorin and capecitabine with a range of 1–8 and 0–21, respectively. A dose reduction was applied for UFT/leucovorin in 15/34 (44%) patients after a median of 43 days and for capecitabine in 15/33 (47%) after a median of 44 days. Reasons for permanent treatment cessation for UFT/leucovorin and capecitabine were toxicity (15 vs 33%), progressive disease (65 vs 39%), patient refusal (both 9%), death (both 6%) and other reasons (6%: investigator decision that included the patients

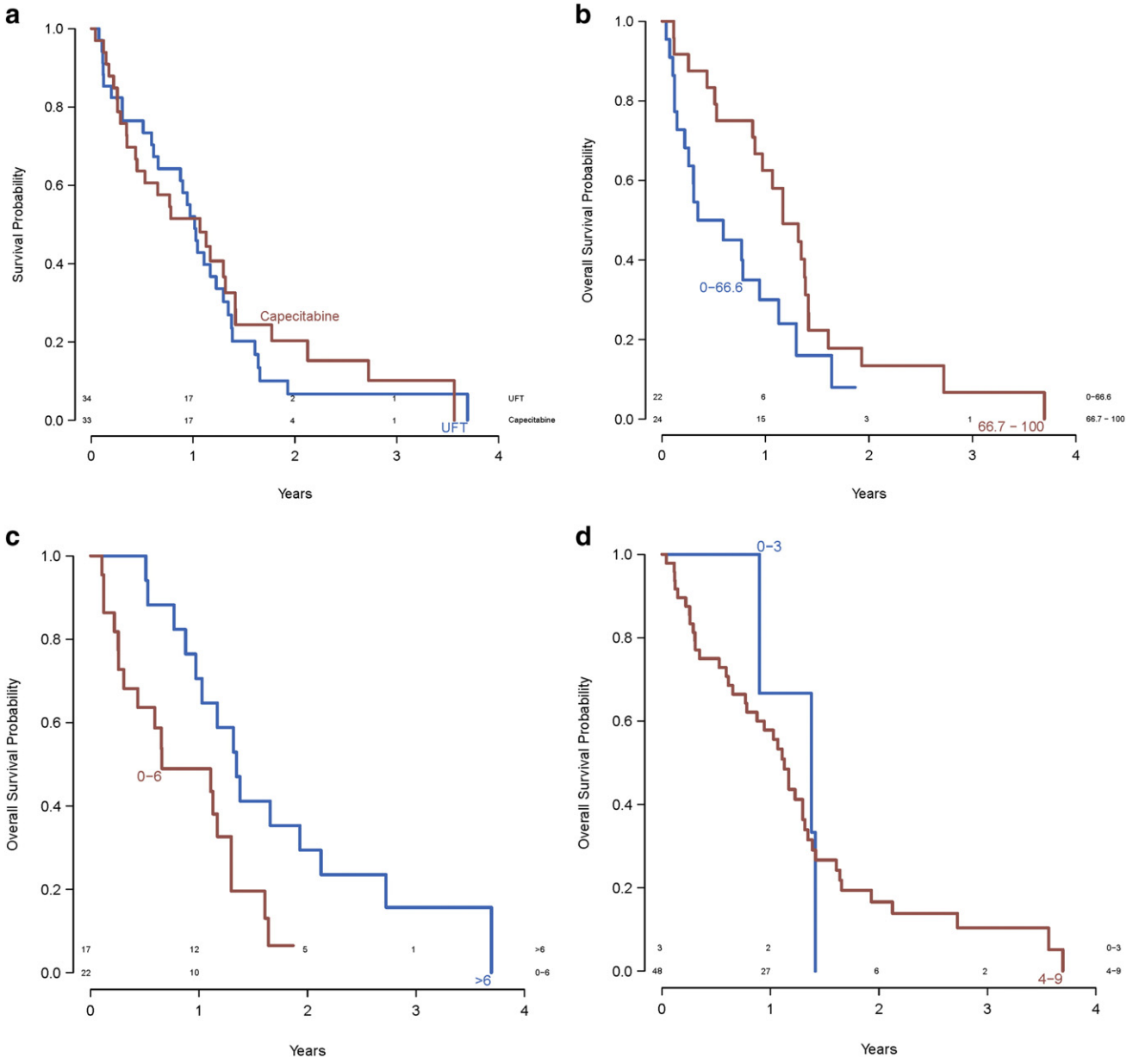

Fig. 3 – a: Overall survival UFT/LV vs capecitabine (stratified logrank test $p = 0.83$). b: Overall survival by QoL (logrank test $p = 0.041$). c: Overall survival by VAS (logrank test $p = 0.016$). d: Overall survival by GFI (logrank test $p = 0.028$).

condition and radiofrequency ablation, vs 12%: not eligible according to exclusion criteria, investigator decision because of the patients condition, CVA, liver surgery, delayed restart of chemotherapy).

3. Discussion

In this multicenter randomised phase III study in elderly patients with aCRC, for the first time, two oral 5-fluorouracil analogues were compared; tegafur–uracil/leucovorin and capecitabine. Efficacy defined by response rate, PFS and OS was similar for both agents. However, as this study was closed prematurely owing to poor accrual it may have failed to meet its primary end point of showing a difference in PFS between the two arms. Therefore, data in these elderly patients on toxicity, QoL, and geriatric indexes and on toxicities between the regimens was of more importance.

Sequential treatment, starting with first-line fluoropyrimidine monotherapy, is a valid alternative, for advanced colorectal cancer, to combination chemotherapy in the majority of patients with metastatic colorectal cancer.[9] In elderly patients the toxicity profile of mono-chemotherapy with both UFT/leucovorin or capecitabine seems to be favourable as compared to combination chemotherapy and 5-fluorouracil monotherapy.[10] In a recent phase III trial comparing first line capecitabine plus bevacizumab with capecitabine alone in elderly patients with aCRC, PFS was significantly longer with bevacizumab plus

Table 2 – The best overall response and reasons for non-evaluability.

	Randomized treatment		
	UFT	Capecitabine	Total
Patients	34	33	67
Best overall response			
Complete response	0 (0%)	2 (6%)	2 (3%)
Partial response	8 (24%)	5 (15%)	13 (19%)
Stable disease	11 (32%)	11 (33%)	22 (33%)
Progressive disease	6 (18%)	7 (21%)	13 (19%)
Not evaluable	9 (26%)	8 (24%)	17 (25%)
Reasons for non-evaluability			
Not finished enough cycles to evaluate response (<3 cycles)	9	6	14
Never started therapy	0	1	1
Clinical PD (not measured)	0	1	1

capecitabine than with capecitabine alone with a median 9·1 months vs 5·1 months (hazard ratio 0·53, $p < 0·0001$) while OS was not significantly different.[11] Treatment-related adverse events of grade 3 or worse occurred twice as much in the combination group; with hand–foot syndrome being most common (16% vs 7%). In our trial chemotherapy was feasible, even in the frail patients. In the UFT/leucovorin arm numerically more grade 3/4 diarrhoea was observed, while there was significantly more grade 3/4 hand–foot syndrome in the capecitabine arm. For both UFT/leucovorin and capecitabine a lower incidence of leucopenia, stomatitis/mucositis and less fever and infection have been reported compared to 5FU/leucovorin.[12–15] However, as compared to 5FU/leucovorin, capecitabine displayed a higher incidence of hand–foot syndrome. Especially in frail elderly patients the trade-off between benefits and side effects, even possible mortality, should be discussed and shared decision making implemented.[16] The evidence obtained in this trial might help in this discussion.

Uniquely, this trial recruited a high proportion of frail patients, not amenable to combination chemotherapy or mono-chemotherapy with bevacizumab. There are various outcome measurements to measure frailty.[17] Using the Charlson co-morbidity index and the Groningen frailty index 96% of our patients were characterized as being frail. Frailty is one of the greatest challenges for healthcare professionals. Frail older adults are at high risk for major adverse health outcomes, including disability, toxicity, falls, institutionalization, hospitalization, and mortality.

Although the majority of patients in the trial was frail elderly, efficacy results with a median OS of 12 months are comparable to earlier trials with less frail patients. In Phase III trials that compared both agents separately with 5-fluorouracil/leucovorin, an OS of 12 months for UFT/leucovorin[12,13] and 13 months for capecitabine[14,18] were reported; phase II trials that made the same comparison in 26 and 51 elderly (70+) patients with aCRC showed an OS of 9.8 months and 11 months, respectively.[3,4]

CGA is helpful in identifying vulnerability in elderly patients with cancer so that treatment can be adjusted accordingly[19,20] and predicts morbidity and mortality in older patients with cancer.[21] However, this process is time-consuming and the exact roles of the aCGA or a frailty screening tool in decision-making regarding treatment remain to be clarified.[22] The optimal balance between feasibility and predictive value remains to be determined.

Interestingly, in this study both baseline serum albumin and LDH were related to PFS and OS. PFS was significantly higher for patients with one comorbidity or less as compared to those with more than one comorbidity, while Qol scores and GFI scores were predictive for OS. The data on serum albumin are in accordance with our earlier data that malnutrition was strongly associated with an increased mortality risk in patients with aCRC who underwent palliative chemotherapy.[23] Instead of a mini-nutritional assessment we only measured baseline serum albumin in this study as a surrogate parameter for nutritional status. Serum LDH level has previously been defined as the main prognostic factor in predicting survival in patients treated with first-line chemotherapy for aCRC.[24] Also, QOL, co-morbidity and GFI have been previously associated with clinical outcome in elderly patients.[21,25] To the best of our knowledge, the use of VAS for QoL has not been related to outcome in the elderly before. Importantly baseline LDH, albumin and VAS are relatively easy to obtain. With the growing incidence of cancer in elderly patients, understanding of chemotherapy sensitivity and toxicity with an emphasis on patient selection by a reliable and efficient aCGA is becoming essential.

Since February 2013 the trade licence for UFT expired in Europe. In Japan, Taiwan, South Korea, Singapore and Malaysia, UFT is still commercially available. The oral fluoropyrimidine, S-1, might become the successor of UFT. S-1 consists of tegafur combined with two biochemical fluorouracil modulators. It has shown good efficacy combined with oxaliplatin, has a similarly favourable toxicity profile to UFT and is currently being tested in phase III trials.[27]

Our trial has some limitations. Firstly the study was closed prematurely due to slow accrual, partly because of the registration of bevacizumab for treatment of first line aCRC, which resulted in the inclusion of mostly frail patients not suitable for or not willing to receive combination chemotherapy or mono-chemotherapy with bevacizumab. Frail patients are less amenable to receive chemotherapy and frail patients often start with chemotherapy at a lower dose. However, now we have data on the usage of chemotherapy in a unique population of frail patients. During treatment, a dose reduction was necessary in almost half of the patients.

Secondly, the patients in our study underwent an aCGA after the medical oncologist decided that they were eligible to receive chemotherapy, which may have introduced some selection bias. Furthermore, we did not screen parameters like nutritional status and mini-mental state examination (MMSE). However, we could therefore minimise the burden of testing which resulted in good compliance (>80%).

In conclusion, this is one of the few randomised studies in frail elderly patients with aCRC. It shows that UFT/leucovorin and capecitabine had similar efficacy and dissimilar toxicity profiles in favour of UFT. In this frail population we identified QoL using VAS as a new prognosticator for clinical outcome and were able to confirm that baseline serum levels of LDH and albumin, Charlson co-morbidity index, Qol and GFI were predictors for clinical outcome.

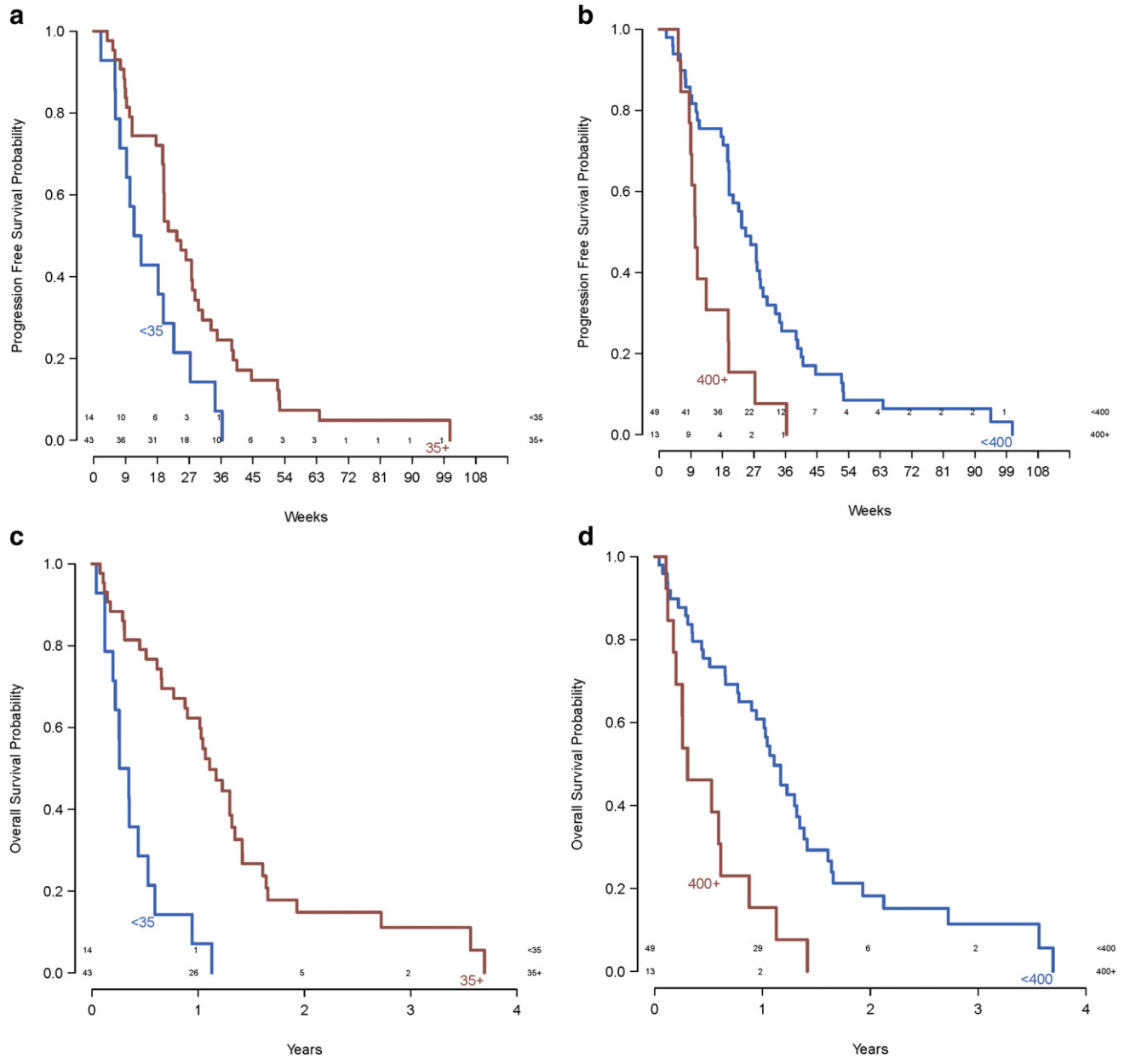

Fig. 4 – a: Progression free survival by albumin (logrank test $p = 0.009$). b: Progression free survival by LDH (logrank test $p = 0.0011$). c: Overall survival by albumin (logrank test $p = 0.0001$). d: Overall survival by LDH (logrank test $p = 0.0003$).

Disclosures and Conflict of Interest Statements

This study was financially assisted with funds from Merck KGaA and Janssen-Cilag BV. All remaining authors have declared no conflicts of interest.

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Table 3 – Grade 3–5 adverse events (CTCAE v 3.0).

	Randomised treatment						
	UFT			Capecitabine			
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5	Total
Anorexia	4			1			5
Acute coronary syndrome	1						1
Constipation				1			1
CVA, ischaemic						2	2
Diarrhoea	7	2		4			13
Dyspnoea						1	1
Haematology				1	1		2
Hand–foot-skin reaction				5			5
Hyperbilirubinemia	2			1			3
Hypertension				2			2
Infection	1			1			2
Nausea	1			1			2
Pain	3	1		3			7
Pulmonary embolus			1				1
Skin/rash				1			1
Stomatitis/mucositis	1			1			2
Thrombosis/embolism	1			1	1		3
Unknown			1				1
Vomiting	2						2
Any adverse event	*23*	*3*	*2*	*23*	*2*	*3*	56

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