# Adherence Management

# for Cancer Patients on Capecitabine

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LINDA KROLOP

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1. Gutachter: Prof. Dr. Ulrich Jaehde

2. Gutachter: Prof. Dr. Yon-Dschun Ko

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# Abbreviations

| | |
|---|---|
| ABDA | Federal Union of German Associations of Pharmacists (Bundesvereinigung Deutscher Apothekerverbände) |
| ADL | Activities of Daily Living |
| AMG | German drug law (Arzneimittelgesetz) |
| ALT | Alanine transaminase |
| AP | Appetite loss, symptom scale of the EORTC QLQ-C30 questionnaire |
| AST | Aspartate transaminase |
| BfArM | Federal Institute of Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte) |
| CF | Cognitive functioning, functional scale of the EORTC QLQ-C30 questionnaire |
| CI | Confidence interval |
| $CL_{CR}$ | Creatinine clearance |
| CO | Constipation, symptom scale of the EORTC QLQ-C30 questionnaire |
| CT | Satisfaction with information on cancer therapy, scale of the PSCaTE questionnaire |
| CUP | Cancer of unknown primary |
| DI | Diarrhoea, symptom scale of the EORTC QLQ-C30 questionnaire |
| DY | Dyspnoe, symptom scale of the EORTC QLQ-C30 questionnaire |
| e.g. | For example (Latin ”exempli gratia”) |
| EF | Emotional functioning, functional scale of the EORTC QLQ-C30 questionnaire |
| EMA | European Medicines Agency |
| EORTC | European Organisation for Research and Treatment of Cancer |
| EQ-5D | Quality of life questionnaire of the EuroQol Group |

| | |
|---|---|
| FA | Fatigue, symptom scale of the EORTC QLQ-C30 questionnaire |
| FI | Financial difficulties, symptom scale of the EORTC QLQ-C30 questionnaire |
| FIP | Fédération internationale pharmaceutique (International Pharmaceutical Federation) |
| HDPE | High-density polyethylene |
| HFS | Abbreviation for hand-foot syndrome and symptom scale of the EORTC QLQ-C30 questionnaire (see PPE) |
| i.e. | That is (Latin ”id est”) |
| IQR | Interquartile range |
| KBV | Associations of Statutory Health Insurance Physicians (Kassenärztliche Bundesvereinigung) |
| MEMS® | Medication Event Monitoring System |
| n | Number of patients |
| n.a. | Not applicable |
| NCI | National Cancer Institute |
| NV | Nausea and vomiting, symptom scale of the EORTC QLQ-C30 questionnaire |
| OV | Overall satisfaction, scale of the PSCaTE questionnaire |
| PA | Pain, symptom scale of the EORTC QLQ-C30 questionnaire |
| PEI | Paul-Ehrlich-Institut |
| PF2 | Physical functioning, functional scale of the EORTC QLQ-C30 questionnaire |
| PPE | Palmar plantar erythrodysaesthesia (see HFS) |
| QL2 | Global health status/QoL, scale of the EORTC QLQ-C30 questionnaire |
| QLQ-C30 | Quality of life questionnaire core 30 of the EORTC QLQ-C30 questionnaire |
| QoL | Quality of life |
| RF2 | Role functioning, functional scale of the EORTC QLQ-C30 questionnaire |
| RS | Satisfaction with information sources, scale of the PSCaTE questionnaire |

| | |
|---|---|
| SD | Standard deviation |
| SE | Satisfaction with information on adverse effects, scale of the PSCaTE questionnaire |
| SF | Social functioning, functional scale of the EORTC QLQ-C30 questionnaire |
| SL | Insomnia, symptom scale of the EORTC QLQ-C30 questionnaire |
| SPC | Summary of product characteristics (Fachinformation) |
| SPSS® | Statistical package for the social sciences |
| ULN | Upper limit of normal |
| VC | Satisfaction with information on vitamins, herbal medicines and complementary treatment options, scale of the PSCaTE questionnaire |
| WHO | World Health Organization |

# Preliminary note

For the sake of clarity and to improve readability the use of the female gender was largely avoided in the present study (e.g. the patient is mostly referred to as “he”). The respective wording “he” is meant to include the female gender.

Furthermore, the author of this work was anxious to consider the copyright of all used texts, figures and data.

# 1 Introduction

## 1.1 Oral cancer treatment

Cancer therapy has traditionally been dominated by intravenously administered agents [1]. A few oral anticancer drugs have been used for a long time such as chlorambucil, methotrexate, cyclophosphamide and 6-mercaptopurine [2]. However, during the previous decade many orally administered anticancer drugs have been developed. The mechanisms of action of these agents are heterogenous including oral cytotoxic drugs as well as targeted therapies which have a high specificity for a cancer-specific molecular target structure, e.g. cell surface receptors or other proteins [2, 3]. The National Comprehensive Cancer Network predicts that the percentage of anti-cancer treatment given as oral agents will rise up to 20 to 25% over the next years. Although oral anti-cancer drugs are unlikely to substantially substitute intravenous treatment, they will become more important in the combination with intravenous therapy [2]. Approximately one-quarter of all anti-cancer drugs under development are orally administered medicinal products [1].

The acceptance of oral treatments by cancer patients is widespread. Convenience is the most important advantage of oral anti-cancer therapy among patients. Medicines can be taken at home without the need for time-consuming appointments at treatment sites [2, 4]. Further benefits are the avoidance of venipuncture and paravasates as well as a greater patient autonomy. Patients appreciate the decrease of daily presence of the psychologically very distressing disease by use of oral administered anti-cancer therapy (better coping) [5]. Additionally, the reduction of institutionally triggered adverse drug reactions like e.g. psychogenic nausea or vomiting and the avoidance of confrontations with other patients which might cause high emotional involvement are benefits of an oral treatment. However, patient preference for an orally administered treatment might decrease if the alternative intravenous therapy is superior in efficacy or toxicity [2, 5, 6]. Even with such advantages and if similar efficacy and tolerability profiles are assumed, the use of oral anti-cancer agents does involve many challenges which have to be addressed to achieve best possible outcome for the patient. Due to less intense contact between patient and health care providers, responsibilities in terms of managing the course of treatment are transferred to the patient such as monitoring of doses and toxicity [2, 7]. In contrast to intravenously administered anti-cancer treatments, health care providers cannot always assume that the patients are adherent to their treatment which is, however, the key prerequisite for treatment success (see 1.3). Multidisciplinary patient care and

specific patient education regarding all aspects of the treatment regimen are crucial to maintain adherence [5, 7–10].

### 1.1.1 Capecitabine

Patients of the present study were treated with the chemotherapeutic agent capecitabine, an orally administered prodrug of cytotoxic fluorouracil (5-FU). Capecitabine belongs to the pharmacological group of antimetabolites and is a non-cytotoxic fluoropyrimidine carbamate. The development was driven by the idea of increased drug concentrations inside the tumour cells through tumour-specific conversion to the active drug [11]. Capecitabine is activated via several enzymatic steps. The enzymes involved in the catalytic activation of capecitabine usually exhibit higher activity in tumour tissue than in normal tissue. Thus, sequential enzymatic biotransformation of capecitabine to 5-FU leads to higher concentrations within tumour tissue. The registered product Xeloda® received approval in the United States of America in April 1998 [2]. In Germany it was approved in February 2001 [12]. Xeloda® is available as 150 mg or 500 mg film-coated tablets. Capecitabine is indicated for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer, for the treatment of metastatic colorectal cancer and for first-line treatment of advanced gastric cancer in combination with a platinum-based regimen. In combination with docetaxel, capecitabine is indicated for the treatment of patients suffering from locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. An anthracycline should have been part of a previous therapy. Capecitabine is also indicated as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated [12, 13].

In the present investigation, capecitabine was most frequently used as single agent treatment. Table 1-1 gives an overview of all applied treatment regimens.

Capecitabine tablets should be taken in the morning and in the evening with a glass of water up to 30 minutes after a meal. In case of disease progression or intolerable adverse drug reactions the treatment should be discontinued. Prescribed as single agent treatment, the recommended starting dose for capecitabine in the treatment of metastatic colorectal cancer, adjuvant treatment of colon cancer or of locally advanced or metastatic breast cancer is 1250 mg/m$^2$ administered twice per day for two weeks separated by twelve hours, followed by a one-week medication-free interval. Usually capecitabine is given in three-week cycles. Dose calculations are provided in Table 1-2. In case of toxicity, dose reduction to 75% or 50% according to toxicity grade is recommended [12, 13].

*Table 1-1: Treatment regimens used in the present study*

| **Cancer entity** | **Treatment regimen** |
|---|---|
| Breast cancer | Capecitabine [12, 13] |
| | Capecitabine/bevacizumab [12, 14, 15] |
| | Capecitabine/lapatinib [12, 14, 15] |
| | Capecitabine/vinorelbin [16] |
| | Capecitabine/trastuzumab [16] |
| | Capecitabine/fulvestrant |
| | Capecitabine/vinorelbin/letrozole |
| Colorectal cancer | Capecitabine [12, 13] |
| | Capecitabine/bevacizumab [12, 14] |
| | Capecitabine/bevacizumab/oxaliplatin [17] |
| | Capecitabine/oxaliplatin [12, 14] |
| | Capecitabine/mitomycin C [18] |
| Gastric cancer | Capecitabine [19] |
| Pancreatic cancer | Capecitabine [11] |
| Endometrial cancer | Capecitabine |
| Cancer of unknown primary (CUP) | Capecitabine |
| Oesophageal cancer | Capecitabine/oxaliplatin [20] |
| | Capecitabine/oxaliplatin/trastuzumab [20] |
| Ovarian cancer | Capecitabine [11] |
| | Capecitabine/bevacizumab |

*Table 1-2: Standard and reduced capecitabine dosing according to body surface area for a starting dose of 1250 mg/m$^2$ twice daily [12, 13]*

| | Full dose (100%) 1250 mg/m$^2$ | Reduced dose (75%) 950 mg/m$^2$ | Reduced dose (50%) 625 mg/m$^2$ |
|---|---|---|---|
| Body Surface Area [m$^2$] | Dose per administration [mg] | Dose per administration [mg] | Dose per administration [mg] |
| ≤1.26 | 1500 | 1150 | 800 |
| 1.27 - 1.38 | 1650 | 1300 | 800 |
| 1.39 - 1.52 | 1800 | 1450 | 950 |
| 1.53 - 1.66 | 2000 | 1500 | 1000 |
| 1.67 - 1.78 | 2150 | 1650 | 1000 |
| 1.79 - 1.92 | 2300 | 1800 | 1150 |
| 1.93 - 2.06 | 2500 | 1950 | 1300 |
| 2.07 - 2.18 | 2650 | 2000 | 1300 |
| ≥2.19 | 2800 | 2150 | 1450 |

Safety and efficacy data in patients with hepatic impairment are unavailable. Close monitoring in patients with mild to moderate liver impairment is mandatory. Capecitabine therapy should be interrupted in case of treatment-related elevations in bilirubin of >3.0 x the upper limit of

normal (ULN) or treatment-related elevations in hepatic aminotransferases (alanine transaminase (ALT), aspartate transaminase (AST)) of >2.5 x ULN. Capecitabine monotherapy may be restarted as soon as bilirubin decreases to ≤3.0 x ULN or hepatic aminotransferases decrease to ≤2.5 x ULN. Severe renal impairment at baseline (Creatinine Clearance ($CL_{CR}$) <30 ml/min, Cockroft and Gault) is a contraindication for capecitabine. The recommended starting dose for patients with moderate renal impairment at baseline ($CL_{CR}$ 30-50 ml/min) is 75% of a starting dose of 1250 mg/m². No modification is recommended in patients with mild renal impairment ($CL_{CR}$ 51-80 ml/min at baseline) [12, 13].

**Adverse drug reactions**

The development of capecitabine as a prodrug of 5-FU was aimed to increase efficacy and tolerability by selectively targeting the active drug to tumour cells with the convenient secondary effect of sparing healthy cells. Oral capecitabine proved to achieve superior response rates, equivalent time to disease progression and equivalent survival compared with intravenously administered 5-FU. A secondary aim during development was a superior safety profile when compared to 5-FU. This has been achieved with capecitabine. The incidence of alopecia, nausea, stomatitis, diarrhea, and neutropenia requiring medical intervention was found to be significantly lower in patients treated with capecitabine. Capecitabine does, however, cause a higher incidence of hand-foot syndrome (HFS, 53.5%). Most frequently occurring adverse effects apart from HFS are diarrhea (47.7%), nausea (37.9%), stomatitis (24.3%), vomiting (23.3%) and fatigue (21.1%). Thus, in patients treated with capecitabine HFS and diarrhea are the most common adverse events leading to treatment interruptions or dose reductions [11, 21, 22].

Capecitabine toxicity can be managed with symptomatic therapy, treatment interruption or decrease of the dose. Table 1-3 provides recommended dose adjustments for toxicity according to the toxicity grade [12, 13]. The Cancer Therapy Evaluation Program (CTEP) within the National Cancer Institute (NCI) developed the “Common Terminology Criteria for Adverse Events” (CTCAE, current version: 4.03). The CTCAE are standards for the description of toxicity grades and help to find the extent of the required dose reduction. The descriptive terminology provides standards for the description and exchange of safety information in oncology research. It is used for adverse event reporting and a grading (severity) scale is provided for each term. The grading scale implies the adverse event severity descriptions “mild” (grade 1), “moderate” (grade 2), “severe” (grade 3), “life-threatening” (grade 4) and “death” (grade 5) [23]. Once the dose of capecitabine has been reduced, it should not be increased again. Omitted doses due to adverse effects should not be replaced by a further dose [12, 13].

*Table 1-3: Scheme for reducing capecitabine dose in case of adverse drug reactions [12, 13]*

| Toxicity grades | Dose changes during a treatment cycle | Dose adjustment for next cycle/dose (% of starting dose) |
|---|---|---|
| **Grade 1** | Maintain dose level | Maintain dose level |
| **Grade 2** | | |
| 1st appearance | Interrupt until resolved to grade 0-1 | 100% |
| 2nd appearance | Interrupt until resolved to grade 0-1 | 75% |
| 3rd appearance | Interrupt until resolved to grade 0-1 | 50% |
| 4th appearance | Discontinue treatment permanently | Not applicable |
| **Grade 3** | | |
| 1st appearance | Interrupt until resolved to grade 0-1 | 75% |
| 2nd appearance | Interrupt until resolved to grade 0-1 | 50% |
| 3rd appearance | Discontinue treatment permanently | Not applicable |
| **Grade 4** 1st appearance | Discontinue permanently OR If physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1 | 50% |

Patients treated with capecitabine who require a treatment interruption or a dose reduction, frequently fear a decrease or loss of efficacy of their anti-cancer therapy. However, it has been shown that toxicity-associated interruptions or dose modifications are not accompanied by reduced efficacy. No increase in risk of disease progression or mortality has been observed [11, 22, 24]. Therefore, dosing flexibility allows an effective management of adverse drug reactions leading to improved tolerability and fewer treatment interruptions [24]. Thus, it should be explained to patients that there is no need to tolerate toxicity in order to achieve optimal efficacy [25]. They should promptly report occurring adverse drug reactions to their physician. The physician may then conduct a dose adjustment which might ensure long-lasting capecitabine treatment.

**Hand-foot syndrome (HFS)**

As mentioned above, HFS is the most common adverse effect in patients treated with capecitabine chemotherapy. This toxicity might be dose- and treatment limiting. HFS was first reported in 1974 by Zuehlke in patients treated with intravenously administered mitotane. Patients developed a syndrome of “erythematous eruption on the palms and soles” [26]. HFS is a cutaneous skin reaction and also referred to as palmar-plantar erythrodysesthesia (PPE) or chemotherapy-induced acral erythema. The median time to first occurrence is 79 days with a range of 11 to 360 days [11]. It is defined as “a disorder characterised by redness, marked discomfort, swelling, and tingling in the palms of the hands or the soles of the feet” [23]. The first HFS symptoms usually are dysesthesia and tingling in the palms, fingers and soles of feet

connected with erythema. Over several days the HFS may progress to burning pain with rash, dryness, cracking, ulceration, oedema and desquamation [27, 28]. Other symptoms can be pruritus, paresthesia or sensory impairment [29]. HFS can significantly affect a patient's quality of life (QoL) [30]. The severity grades of HFS can be classified according to CTCAE (see Table 1-4) [23]. Hospitalisation and death due to HFS is rare [31, 32]. Other anti-cancer drugs causing HFS are docetaxel, doxorubicin and the tyrosine kinase inhibitors sorafenib and sunitinib [27].

*Table 1-4: Severity grades of hand-foot syndrome according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 [23] (the severity grades "life-threatening" (grade 4) and "death" (grade 5) are not applicable in the context of HFS)*

| Grade 1 | Grade 2 | Grade 3 |
|---|---|---|
| Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain | Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL* | Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self-care ADL* |

** ADL=Activities of Daily Living (Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.)*

**Pathomechanisms of the hand-foot syndrome**

The pathogenesis of HFS and the causes for increased incidence with capecitabine are unknown but various theories exist [29, 30, 33]. HFS occurs under the treatment of miscellaneous anti-cancer drugs with diverse mechanisms of action. The explaining theory of HFS pathomechanisms could hence be broad [27]. A direct toxic effect caused by the chemotherapeutic agent on the skin is considered to be one explanation. However, this assumption does not provide an explanation for the occurrence of HFS especially at the hands and feet [28]. Another explanation for the toxicity indicates an involvement of eccrine sweat glands in the pathogenesis. Anti-cancer agents causing HFS are thought to accumulate in eccrine sweat ducts and thus cause local damage. Since the palm of the hands and the sole of the feet exhibit more sweat ducts, this theory would explain the typical anatomical distribution of this adverse event [30, 33]. Further reports consider HFS to be a type of inflammation due to an overexpression of cyclooxygenase 2 in the skin as a result of chemotherapy [30, 34]. Hands and feet are usually exposed to a high degree of mechanical pressure during everyday life. Capillary damage and leakage of chemotherapeutic agents from the blood vessels into the acral tissue may occur [27]. A further pathomechanism postulated implies the involvement of thymidine phosphorylase. Thymidine phosphorylase is one of the capecitabine-metabolising enzymes and shows an elevated expression in the palms. This increased expression may result in higher

concentrations of cytotoxic metabolites in this area and in skin damage. Additionally, an elevated proliferation rate has been observed in the epidermal basal cells of the palm area which might sensitise this skin area to the elevated amount of locally produced cytotoxic metabolites [30, 35].

**Management of hand-foot syndrome**

No evidence-based effective possibility to prevent or to treat this toxicity exists. The current mainstays of HFS management are temporary treatment interruption and dose reductions [12, 13, 34]. Table 1-3 shows the recommended schedule for capecitabine treatment interruptions and dose reductions in case of HFS (grade 4 "life-threatening" is not applicable in terms of HFS). As mentioned before, interruptions and dose reductions of capecitabine treatment do not diminish efficacy and will most likely lead to a relief of adverse effects [25]. Thus, health care professionals should use this evidence to educate their patients and to tell them that a toleration of HFS is not necessary. However, it should be avoided that this information leads to an underestimation of capecitabine therapy by the patient and accordingly to an increased non-adherence.

All attempts of prophylaxis and treatment of HFS besides dose reduction and therapy interruption are basically limited to a relief of the patient's clinical symptoms. As long as the pathomachnisms of HFS are not fully understood, a causal prevention and therapy of this toxicity is not possible. However, various interventions are available, both pharmacological and non-pharmacological [30].

As denoted already, patient education and effective patient management strategies play a key role in HFS management to ensure correctly executed treatment interruptions and dose reductions. This is especially important since capecitabine is administered in the outpatient setting. Patients should be educated on how to use the drug properly. The importance of taking the correct dose and duration of treatment should be stressed. In terms of toxicity it should be highlighted that it is essential to adhere to the seven day rest period and not continue treatment. Moreover, patients need to know how to identify HFS as a toxicity of their cancer treatment. For this purpose they need to know nature and severity grades of HFS and when to contact their health care team for advice. Written information material and continuous care might complete patient education [24, 25].

Empirical interventions that are recommended for prophylaxis and treatment of HFS are the avoidance of hot water, excessive rubbing, pressure and constrictive footwear. Moreover, the patients might wear cotton gloves or socks and air their skin regularly to avoid severe sweating. Full-body skin examination, pedicure or evaluation by an orthotist (e.g. in terms of providing padded shoes) are further non-pharmacological interventions. To relieve HFS symptoms, hands

and feet can be immersed in cool water or cooled with cold compresses. Moisturising emollients and creams should be applied to the skin regularly both to prevent and to relieve HFS symptoms (e.g. containing 20-40% urea or petroleum-lanolin based ointment with antiseptic hydroxyquinoline sulphate). Sore areas should be padded with appropriate cushions and, in case of blisters or ulcers, topical wound care as well as consultation with a dermatologist should be considered [30, 32, 36].

The use of topically applied creams in HFS is not evidence-based. Corticosteriods have been described to be useful for prevention and treatment of HFS, e.g. clobetasol 0.05% ointment. The anti-inflammatory properties of corticosteroids might explain their beneficial effect in HFS. However, long-term use can be connected with thinning of the skin and this is likely to worsen HFS symptoms [30, 32, 36]. Moreover, uridine hand-foot ointment might be an option for the treatment of patients suffering from HFS. Nevertheless, a broader application or a controlled trial has to show the real value of this intervention [37]. The application of urea cream was found to be valuable in the prevention of HFS by Hoesly et al. [30]. This conflicts with the findings of a randomized, double-blind phase III trial evaluating 137 patients receiving capecitabine. Patients were treated with an urea/lactic acid–based cream or placebo. The results did not strengthen evidence of a beneficial effect of the cream for prophylaxis of HFS. There was no significant difference in HFS symptoms between the treatment and control group [38]. Topical anaesthetics can be applied for symptom relief [32]. Since October 2011, an ointment containing several antioxidants (Mapisal®) is available on the German market. It is advertised to prevent and to treat HFS effectively [39]. Further phase III studies are in progress to provide evidence for its efficacy [40].

Systemic medications for prevention and treatment of HFS include celecoxib [34], pyridoxine (vitamin $B_6$) [41] and vitamin E [31] and can be tried in combination with topical interventions or alone. Zhang et al. conducted a single-centre, prospective randomised clinical trial to evaluate if HFS can be prevented by additional intake of celecoxib, a selective cyclooxygenase-2-inhibitor. They found a reduced occurrence of HFS in the capecitabine/celecoxib group compared to the capecitabine group and concluded that celecoxib can be applied for the prevention of capecitabine-related HFS [34]. Studies investigating the use of pyridoxine for prevention of HFS caused by capecitabine do not show a beneficial effect on incidence or severity [41, 42]. However, pyridoxine might be beneficial in the treatment of HFS and can provide symptom relief once HFS develops [41]. Patients treated with a combination of capecitabine and cisplatin should not take pyridoxine for symptomatic or secondary prophylactic treatment of HFS. There have been reports that pyridoxine can impair the efficacy of cisplatin [12, 13].

HFS is not life-threatening, but without an appropriate management this adverse drug reaction can be extremely painful and debilitating for the patient [36]. Moreover, non-adherence might be enhanced. Further randomised-controlled trials are needed to establish an evidence base for the prevention and treatment of HFS.

The occurrence of HFS in patients treated with capecitabine might be associated with a better clinical outcome [43]. Upon request of the European Medicines Agency (EMA), Roche performed a meta-analysis of 14 clinical trials with data from over 4,700 patients suffering from multiple cancer entities treated with capecitabine monotherapy or combination chemotherapy. The development of HFS was connected with a longer overall survival [12, 13]. Thus, HFS might possibly be a valuable marker for the evaluation and monitoring of the efficacy of capecitabine treatment [43].

## 1.2 Pharmaceutical care

The term pharmaceutical care has been used in pharmacy in one context or another for many years [44]. Pharmaceutical care was first formally defined in 1990 by Hepler and Strand as "the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life" [45]. Since the definition of 1990 seemed incomplete in terms of the practitioner's responsibility, Strand stated in 1997 that "pharmaceutical care is a practice in which the practitioner takes responsibility for a patient's drug-related needs and holds him or herself accountable for meeting these needs" [44]. In 1998, the Fédération Internationale Pharmaceutique (FIP) published an extended definition of pharmaceutical care which stresses the collaborative approach and the continuous care process. They defined pharmaceutical care as "the responsible provision of pharmaco-therapy for the purpose of achieving definite outcomes that improve or maintain a patient's quality of life. It is a collaborative process that aims to prevent or identify and solve medicinal product and health-related problems. This is a continuous quality improvement process for the use of medicinal products" [46]. Since the pharmacist is not especially mentioned in the definitions of pharmaceutical care, this health care service might basically be delivered by every health care provider like e.g. the physician, pharmacist or a nurse. However, the pharmacist has a comprehensive qualification and a broad knowledge regarding drugs, adverse effects, drug administration and so on. These prerequisites make him predestined for the provision of pharmaceutical care. According to this, it was proposed for pharmacists to provide pharmaceutical care just like nurses provide nursing care and physicians provide medical care [45]. Through the systematic process of pharmaceutical care for an individual patient, the pharmacist develops, implements and monitors a therapeutic plan in collaboration with the

respective patient and other health care professionals. This plan helps to achieve predefined health outcomes. Three main competencies of the pharmacists are demanded: identifying potential and actual drug-related problems, resolving actual drug-related problems and preventing drug-related problems. By performing pharmaceutical care the pharmacist is a provider of quality of care and directly responsible for the benefit of the patient [45, 47–49].

### 1.2.1 Pharmaceutical care for cancer patients

Cancer diagnosis is connected with psychological stress and a high disease burden for the patient concerned. Additionally, the patient is strained by complex treatment regimens. Surgery, radiation and antineoplastic pharmacotherapy form the three pillars of cancer treatment. Besides the use of classical cytotoxic chemotherapies, the availability of so called targeted therapies has recently increased. The development of modern, highly effective, and individually tailored treatment options has led to the circumstance that cancer has largely become a chronic condition [50]. The patient's treatment regimen is complicated by supportive therapies to limit treatment-associated toxicity, complementary therapy options, additional medication against other underlying conditions, and self-medication [51, 52]. The consequence of complex treatment regimens is an increased risk of drug-related problems such as adverse drug reactions, drug-drug interactions, non-adherence, and medication errors. Consequences of drug-related problems in the treatment of cancer can be severe since they emerge from a high toxicity and narrow therapeutic range of anticancer agents [53]. Through the establishment of central services for compounding of anti-cancer drugs or the offering of therapeutic drug monitoring for critical agents, the pharmacist began to play a more important role in oncology [51]. Moreover, it has been shown that a pharmacist integrated in the health-care team can improve drug use on an oncology ward. The pharmacist can contribute to risk minimisation with a systematic focus on the patient from a drug perspective [54]. The pharmacist is the only health care provider who might have a complete overview of the drugs a patient is taking. In addition to drugs prescribed by general practitioners, patients receive prescriptions from consultants or purchase over-the-counter medicines themselves in community pharmacies. The pharmacist can use his specific drug-related knowledge to optimise individual drug therapy [51, 53]. Therefore, the detection and solution of drug-related problems can be facilitated by the integration of a pharmacist into the health care team. Multidisciplinary provision of care is highly appreciated by patients and the pharmacist is valued as an information source. In addition, physicians and nurses acknowledge the pharmacist's contribution to improved drug use [54, 55].

Published studies conducted at the department of clinical pharmacy, University of Bonn verified the positive influence of pharmaceutical care on outcome parameters. Complete response to antiemetic prophylaxis was significantly improved amongst breast and ovarian cancer patients

receiving pharmaceutical care consisting of detailed patient counselling on the management of treatment-associated toxicity and optimisation of supportive medication compared to patients receiving usual care [56]. The provision of intensified pharmaceutical care to colorectal and breast cancer patients achieved a significant increase in mean daily adherence (proportion of days with correct drug intake), prolonged treatment with capecitabine, and reduced deviations of drug intake intervals. Detailed patient education before and during anti-cancer treatment combined with patient counselling regarding drug therapy, adverse drug reactions, and complementary treatment options were part of this intervention [51, 57]. Furthermore, a multiprofessional cancer medication management model was developed allocating tasks to physicians, pharmacists and nurses which was appreciated nationwide by the professions. The pharmacist was integrated with responsibilities in patient education and counselling as well as the prevention of drug-related problems. Such a model can improve effectiveness and efficiency of the provision of health-related services [58]. These results underline the potential of pharmaceutical care to contribute significantly to a safe and effective anti-cancer treatment. Further projects conducted at the department of clinical pharmacy, University of Bonn and parts of the projects mentioned above respectively could show significant beneficial effects of pharmaceutical care for cancer patients on important outcome and process parameters like cost-effectiveness, detection and solution of drug-related problems, patient satisfaction with information on cancer treatment, and quality of life [55, 59–62].

## 1.3 Adherence

Referring to the literature, one can find diverse terms for the description of medication taking behaviour of patients (see Table 1-5). The term ‘adherence’ is increasingly used due to the fact that it implies the best relationship between patient and health care provider, while using the abilities of each party [63]. Therefore, the term ‘adherence’ will be used in this thesis. The World Health Organization (WHO) defines adherence as “the extent to which a person’s behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider” [63]. The term ‘persistence’ describes the duration from treatment initiation to discontinuation [64]. There is no overarching term that combines the two concepts [65]. Since to date there is no uniform terminology to describe insufficient medication taking behaviour, Vrijens et al. recently proposed a taxonomy which is supposed to be focused on promoting consistency and quantification in terminology and methods to aid in the conduct, analysis and interpretation of scientific studies of medication. Adherence to medication, management of adherence and adherence-related sciences are the three elements this taxonomy is consisting of [66].

*Table 1-5: Definition of different terms describing patient medication taking behaviour*

| Term | Definition |
|---|---|
| **Compliance** | Extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider [63, 67, 68]. |
| **Adherence** | Same definition and synonymic use like compliance [65], however disconnection of the patient being a passive, acquiescent recipient of expert advice and of a hierarchical relationship between the patient and the health care provider [69, 70]. |
| **Concordance** | Equal, cooperative relationship between patient and health care provider, respect for the patient's views, open exchange of information, mutual confidence, cooperative decisions concerning treatment [69, 70]. |
| **Persistence** | Time elapsed between first dose taken and time of treatment discontinuation, no information about correctness of intake [64, 65]. |

A patient who does not adhere to his treatment regimen is referred to as non-adherent. Non-adherence may be divided into two different types, intentional and unintentional non-adherence.

**Intentional** non-adherence is associated with the patient's motivation and views in terms of his disease and pharmacotherapy. If a patient does not accept his diagnosis or treatment, the patient may not begin or correctly administer therapy. This lack of patient desire to continue the medication may also lead to discontinuation of therapy. Furthermore, personal preferences of the patient which have not been taken into account regarding drug treatment can lead to intentional non-adherence.

**Unintentional** non-adherence is not planned by the patient and in most cases practical barriers are the problem. The patient omits dosages throughout the whole duration of his treatment without any obvious pattern [71, 72].

Moreover, particular patterns of non-adherence may be understood as cross forms of intentional and unintentional non-adherence, e.g. in a phenomenon known as 'white-coat adherence', i.e. an improvement of patient adherence shortly before and after an appointment with the health care provider [73].

### 1.3.1 Causes and identification of non-adherence

The literature knows about 200 factors which may influence patient adherence. According to the WHO "adherence is a multidimensional phenomenon determined by the interplay of five sets of factors" or dimensions [63].

**Social and economic factors**

Examples for social and economic factors known to significantly influence adherence are a low level of education, unemployment, high cost of medication, culture and lay beliefs about illness and treatment, illiteracy and family dysfunction.

**Health care team and system-related factors**

These factors e.g. imply lack of knowledge and training for health care providers on managing chronic diseases, overworked health care providers, short consultations, lack of incentives and feedback on performance, weak capacity of the system to educate patients and provide follow-up and lack of knowledge on adherence and of effective interventions for improving it.

**Therapy-related factors**

Therapy-related factors that most notably affect adherence are those related to the complexity of the medication treatment, such as duration of treatment, previous treatment failures, frequent changes in treatment and adverse drug reactions. The adherence to a once-daily intake is significantly higher than to a three or four times daily intake [73, 74].

**Patient-related factors**

Examples for patient-related factors are forgetfulness, anxieties about possible adverse effects, low motivation, inadequate knowledge and skills in managing the disease symptoms and treatment, lack of self-perceived need for treatment, lack of perceived effect of treatment, lack of acceptance of monitoring and low attendance at follow-up.

**Condition-related factors**

Condition-related factors that strongly determine adherence include severity of symptoms, level of disability of any kind, rate of progression, severity of the disease and availability of effective treatments. Consequences depend on these factors' influence on patients' risk perception, the importance of following treatment, and the priority placed on adherence. Co-morbidity (e.g. depression in HIV/AIDS or diabetes) and drug as well as alcohol abuse are central modifiers of medication taking behaviour.

### 1.3.2 Adherence measurement

The detection of extent, pattern, and cause of low adherence is very important for the selection of an appropriate adherence-enhancing strategy. Thus, detailed information on the exact nature of patient medication behaviour is required.

Adherence-measuring methods can be divided into direct and indirect methods, for detailed information see Table 1-6 [73, 75].

Concerning all methods for measuring adherence that actively include the patient, it should be taken into account that the patient's knowledge of the adherence measurement may influence his behaviour [75]. Thus, methods that imply a questioning of the patient tend to overestimate patient adherence. Rates of refilling prescriptions are an objective measure of overall adherence. This chronological medication history considers a defined period of time and shows all prescribed drugs of the patient. However, a complete and central documentation either by the physician or the pharmacist of all refilled prescriptions is a mandatory requirement. Electronic medication monitors like the Medication Event Monitoring System (MEMS®) are medication bottles with a screw cap containing a microprocessor. These bottles can be filled with orally administered dosage forms and are capable of recording and displaying date and time of bottle openings [76]. Thus, special behavioural patterns can be tracked, e.g. if a patient mostly forgets his evening dosage or does not take his medication mostly on the weekends, see also 3.7.2. A disadvantage of these devices is the non-documentation of the actual ingestion of the drug. The patient might have opened the bottle without taking his drug, taking his medication from another source (other medication container, medication package) or taking multiple doses at the same time. Furthermore, costs for electronic medication monitors are not covered by the health insurance and the execution of this method is relatively complex. Patients need to visit their therapy site more often than normally required and the healthcare provider needs to read data from medication vials using special software. Thus, electronic monitoring of adherence is not used in daily routine so far. But despite existing disadvantages, this measure provides the most accurate and valuable data on patient medication intake behaviour [73, 75].

*Table 1-6: Direct and indirect methods for measuring patient adherence including advantages and disadvantages [73, 75]*

| | Advantages | Disadvantages |
|---|---|---|
| **Direct methods** | | |
| Direct supervision of the intake | + Most precise | – Impractical for routine use<br>– Prone to Hawthorne effect [75], see 1.3.3<br>– Patients can hide tablets in the mouth and discard them |
| Measurement of the level of drugs or metabolites in plasma | + Objective | – Variations in metabolism and white-coat adherence can give a false impression of adherence<br>– Expensive<br>– Blood samples required |

*Table 1-6: continued*

| | Advantages | Disadvantages |
|---|---|---|
| **Indirect methods** | | |
| Patient questionnaires, patient self-reports | + Generally easy to perform<br>+ Inexpensive<br>+ Most useful method in the clinical setting | – Susceptible to errors with increases in time between visits<br>– Easily altered by the patient |
| Patient diaries | + Help to correct for poor recall | – Easily altered by the patient |
| Pill counts | + Objective<br>+ Quantifiable<br>+ Easy to perform | – Easily altered by the patient (e.g., pill dumping) |
| Rates of prescription refills | + Objective<br>+ Easy to obtain data | – A prescription refill is not equivalent to ingestion of medication<br>– Requires a closed pharmacy system |
| Electronic medication monitors | + Precise<br>+ Quantifiable<br>+ Tracks patterns of taking medication | – Expensive<br>– Requires return visits and reading data from medication vials<br>– No proof of actual intake |
| Assessment of the patient's clinical or pharmacodynamic response (e.g., blood pressure in hypertensive patients) | + Simple<br>+ Generally easy to perform | – Factors other than medication adherence can affect clinical response<br>– Marker may be absent for other reasons (e.g., increased metabolism, poor absorption)<br>– Often no appropriate marker available |

### 1.3.3 Adherence enhancement

In short-term drug treatments, patient counselling and written patient information helps to improve adherence [77]. In chronic disease patients, adequate medication use is harder to achieve. Interventions are complex and require a combination of different measures [77]. They have been divided into four categories [73, 77]:

**Educational interventions**

Patient education, counselling and written information material contribute to a better understanding of the disease and therapy. These interventions are appropriate for the improvement of intentional non-adherence. Patients who better understand their disease and their pharmacotherapy are more apt to follow their treatment plan. Decker et al. identified that the misunderstanding of the intended duration of treatment was the main reason for premature discontinuation of clopidogrel treatment in myocardial infarction patients [78]. Such information appears trivial and thus, may not be passed on to the patient by the prescribing physician or the delivering pharmacist. Dosing instructions need to be communicated in a

precise, definite and unambiguous manner. Abbreviations which may not be clear to the patient should be avoided. Simple advice should always be given, e.g. regarding nasal sprays or the shaking of aqueous suspensions before use [69].

**Behavioural interventions**

Such interventions are treatment diaries, medication dosette boxes, reminder cards pinned at a distinctive spot, alarm clocks, and/or the inclusion of family members into the process of care. Behavioural interventions aim to improve unintentional non-adherence and remind forgetful patients of their medication intake. "Cue-dosing" is also a behavioural intervention. It is the linking of drug intake with a certain activity in daily life such as dental hygiene or watching a certain TV programme.

**Monitoring interventions**

The regular monitoring of patients' blood pressure or other health outcomes increases the patients' motivation to take their medication as prescribed. Furthermore, measurement of adherence itself may have a potential effect on the medication taking behaviour and improve adherence. This beneficial effect of the observation itself on the outcome is termed the "Hawthorne effect" [75].

**Pharmacotherapeutic interventions**

This group of interventions comprises the simplification of treatment regimens such as the prescription of extended release or combination formulations. Information regarding the divisibility of tablets is lacking frequently. Thus, half or quartered tablets should be prescribed as rarely as possible. Additionally, faith in treatment and adherence can decrease in patients who are instructed to split their tablets [71, 79].

### 1.3.4 Adherence of cancer patients

Long-term adherence in patients with chronic, non-oncologic conditions is estimated at 50% [63, 80]. Since cancer is a distressing and life-threatening disease, cancer patients' medication taking behaviour is presumed to be particularly precise and adherent [73, 81–84]. For oral anti-cancer agents, adherence rates from 16 to 100 % have been reported. The variability can be explained by the different anti-cancer agents, the definition of adherence and the method of measurement [82, 85]. The adherence to oral capecitabine treatment has been explored by several recent studies.

Partridge et al. used MEMS® for adherence assessment in 161 older women (aged from 65 to 89 years) with early-stage breast cancer. Adherence was defined as the number of doses taken

divided by doses expected. Patients were considered adherent if ≥80% of the expected doses were recorded by MEMS®. 124 patients (83%) persisted with capecitabine up to the completion of the planned protocol (six cycles). 75% of participants performed more than 80% of expected openings and were regarded as adherent. Average adherence was 78% across all cycles, and adherence did not vary by cycle. This study was part of a clinical trial and might not reflect usual care [86, 87].

Winterhalder et al. used participant self-reports in 143 gastrointestinal and 34 breast cancer patients to assess adherence to capecitabine. Patients recorded their capecitabine intake each day in patient diaries. Ninety-one percent (161/177) of the participants were found to be fully adherent, whereas only 9% (16/177) participants reported some kind of adherence error which was defined as any violation of the recommended regimen. Reasons for non-adherence included forgetfulness (n=9), adverse drug reactions (n=4) and misunderstanding of instructions (n=3) [81].

Mayer et al. explored adherence amongst metastatic breast cancer patients by means of MEMS® vials (n=13) as well as self-reports using a daily drug diary completed by each patient (n=12). Adherence was defined as observed divided by expected doses. An adherence of >80% was used to define acceptable adherence. Adherence measured by MEMS® ranged from 75% to 100% and both median and mean adherence accounted for 96%. Self-reported adherence ranged from 89% to 100% and median adherence was 97% (mean adherence: 99%) [88].

The authors of another study recruited breast and colorectal cancer patients treated with capecitabine in a UK teaching hospital and assessed self-reported patient non-adherence using the Medication Adherence Report Scale (MARS). Respondents were asked to report whether any divergence to treatment originates from dose alteration, omission, intentional termination, or forgetting. Non-adherence was stated by 10 of the 43 patients (23%). Four patients reported several types of deviation. Forgetting to take a capecitabine dose was the most commonly stated reason for a deviation [89].

Adherence to capecitabine was also assessed using a qualitative approach in 42 patients. Adherence was defined as being against not taking their treatment. The results of group and individual interviews did not suggest deliberate non-adherence but poor observance of the dosing schedule. Most frequently, patients deviated from the instruction to take capecitabine after a meal [90].

A Canadian study from 2007 surveyed 25 patients treated with capecitabine. Adherence was measured using pill counts and patient self-reports and defined as any indication of not having 100% adherence. Patients were randomly assigned to either receive capecitabine provided in convention pill bottles or pre-filled per patient's prescription into daily pill boxes. After the

completion of one cycle the patients switched over to the alternate packaging method. It could not be demonstrated that daily pill boxes improved adherence to capecitabine. Adherence rates were similar when using daily (81%, 17/21) and conventional pill bottles (86%, 18/21) [91].

### 1.3.5 Adherence and pharmaceutical care

Continuous pharmaceutical care has been shown to be particularly suitable to enhance medication adherence. Several studies proved that the integration of a pharmacist in patient care has a beneficial effect on adherence.

A community pharmacist-led intervention in heart failure patients improved their adherence to loop diuretics. The effect of monthly consultations in the community pharmacy led to a significant better outcome in MEMS® recordings compared to usual care without community pharmacist consultations. Non-adherence was expressed as the number of days without any loop diuretic although at least once daily was prescribed. Over the six-month study period, patients in the intervention group (n=74) exhibited 140/7656 days without use of loop diuretics compared with 337/6196 days in the usual care group (n=78) [92].

A Belgian study investigated the effect of a pharmaceutical care programme provided by community pharmacies on the adherence of once-daily atorvastatin treatment in patients with elevated cholesterol levels. Electronically measured adherence was defined as the proportion of days with correct administration. The intervention resulted in a 6.5% increase in post-baseline adherence ($p<0.001$). Furthermore, only 25/194 (13%) subjects in the intervention group discontinued medication, in contrast to 51/198 (26%) subjects in the control group [93].

The efficacy of a comprehensive pharmaceutical care programme to improve medication adherence and its associated effects on blood pressure and low-density lipoprotein cholesterol was evaluated in a randomised controlled trial conducted in a US military medical center. After a run-in phase, patients entered an intervention phase. Following the six-month intervention phase, patients were randomized to continued pharmaceutical care versus usual care for additional six months. Adherence was calculated as the proportion of drugs taken for all chronic medications and measured by pill counts. Mean baseline medication adherence was 61.2%. After six months of intervention, medication adherence increased to 96.9% ($p=0.001$) and was associated with significant improvements in systolic blood pressure and low-density lipoprotein cholesterol. Six months after randomisation, adherence decreased to 69.1% among usual care patients, whereas it was sustained at 95.5% under pharmaceutical care ($p=0.001$). This was associated with significant reductions in systolic blood pressure in the pharmaceutical care group versus the usual care group, but did not result in significant differences in low-density lipoprotein cholesterol levels [94].

Adler et al. conducted a randomised controlled trial and studied 533 depressed patients in primary care. Intervention patients received consultations in person and by telephone performed by a clinical pharmacist. Adherence was measured using self-reported six-month antidepressant use rates. Intervention patients exceeded controls (57.5% vs. 46.2%, p=0.03). The pharmacist intervention also improved antidepressant use rates for patients not taking antidepressants at enrollment (32.3% versus 10.9%, p=0.001) [95].

Klein et al. examined the influence of a pharmaceutical care programme on liver transplant patients' adherence to immunosuppressive therapy. Adherence was defined as the percentage of days with the correct number of bottle openings and was measured using MEMS®. The intervention group (n=26) receiving pharmaceutical care in addition to traditional patient care showed a mean adherence of 90% compared with 81% in the control group (n=24; p=0.015) [96].

A British study reports the adherence-enhancing potential of a telephone-based pharmacy advisory service which was provided to patients of the intervention group by community pharmacists. Self-reported non-adherence to newly prescribed medicines for chronic conditions was significantly lower in the intervention group (10/87, 11%) when compared to the control group (23/118, 19%; p<0.05) [97].

A randomised, controlled trial from Hongkong showed an association between adherence of patients receiving polypharmacy and mortality. Patients receiving five or more drugs for chronic disease and showing an adherence of less than 80% were included. Throughout the study period of two years, patients allocated to the intervention group received a telephone call from a pharmacist at the midpoint between clinic visits (six to eight conversations lasting 10 to 15 minutes). Telephone counselling improved adherence and reduced mortality by 41% which was mainly attributed to the decrease of cardiovascular events in the intervention group. The number needed to treat to prevent one death during two years accounted for 16 [98].

In Switzerland, several adherence-enhancing interventions are even anchored in the health care system. After prescription by a physician, weekly dosing systems, polymedication checks or intake controls provided by the pharmacist are reimbursed by the health insurances [99].

A first step in Germany was the publication of a future concept to optimise patient care by the Federal Union of German Associations of Pharmacists (ABDA) and the Associations of Statutory Health Insurance Physicians (KBV) in April 2011. Through continuous care of multimorbid patients provided by both a physician and a pharmacist (medication management) it is aimed to enhance adherence and reduce costs. A shared reimbursement is intended. In practice, a general practitioner could send his patient to the collaborating pharmacy where the pharmacist compiles an individual medication plan and conducts an interaction check [100].

The legislative basis for a practical implementation of this concept is provided since January 2012 [101] and a definite start of the model in two German test regions is intended for the second half of 2013 [102].

To the author's knowledge, only one study investigated the influence of pharmaceutical care on the adherence of cancer patients treated with any kind of oral anti-cancer agent. The effect of an intensified multidisciplinary pharmaceutical care programme on the adherence of cancer patients treated with capecitabine was investigated by Simons et al. Adherence was measured using MEMS® and was defined as the percentage of days with correct medication taking behaviour. Patients who received pharmaceutical care showed a higher mean daily adherence compared to the control group who received standard care (96.8% vs 87.2%, p=0.029) [57].

Thus, adherence rates of patients treated with capecitabine are relatively high compared to non-oncologic oral drugs but can still be increased by specific measures [57]. Conversely, this implies that only some patients treated with capecitabine are in need of an adherence-enhancing intervention and the limited resources could be used more efficiently. Certain patients manage their oral treatment regimen independently and do not benefit from a specialised patient care. Since lack of time is a restricting factor in daily practice, it is important to know which patients especially take advantage of such an intervention and which patients do not benefit. In this study, we screened cancer patients for their adherence during their first cycle of capecitabine to detect potential non-adherers. Initially adherent as well as non-adherent patients received basic pharmaceutical care and adverse event management. Specific adherence support, however, was only provided to initially non-adherent patients.

# 2 Aim

The aim of the present study was to assess medication adherence over time of initially adherent as well as initially non-adherent cancer patients treated with the chemotherapeutic agent capecitabine and receiving a modular medication management.

In the present project a strategy to identify non-adherent patients at an early stage of their anti-cancer treatment (adherence screening) was developed as well as a special adherence-enhancing intervention for these patients (adherence support).

It was hypothesised that adherence of initially adherent patients would remain high over time without a special adherence supporting intervention and that initially non-adherent patients would benefit from such an intervention.

# 3 Patients and Methods

The present study was conducted to evaluate medication adherence and further patient-relevant outcomes in initially adherent as well as initially non-adherent cancer patients treated with the oral chemotherapeutic agent capecitabine under the provision of modular medication management.

## 3.1 Legal status of the study

The legal classification of this study resulted under consideration of § 4, 40 and 67 of the German drug law (Arzneimittelgesetz, AMG) and the recommendations of the Federal Institute of Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM) and the Paul-Ehrlich-Institut (PEI) from 07 July 2010. The patients' treatment including diagnosis and monitoring was not based on a pre-determined study protocol. The participating physicians' decision on diagnosis, prescribing capecitabine, and monitoring was not influenced. All patients included in the study were treated according to clinical routine. Therefore, this study was classified as 'non-interventional trial' [103].

On 06 May 2009 the ethics committee of the Faculty of Medicine of the University of Bonn, Germany voted positively for this study (consecutive number 042/09). In September 2009 an amendment to the study protocol to include patients treated with capecitabine suffering from further tumour entities besides breast cancer was approved by the ethics committee. A further amendment to include three additional study centres was approved in November 2010.

## 3.2 Participating study centres and cooperation partners

The study was conducted in two oncology outpatient wards and two oncology practices in the area of Bonn and Cologne (Table 3-1).

*Table 3-1: Participating study centres*

| Treatment setting | Study centres |
|---|---|
| Oncology outpatient ward | Johanniter Hospital Bonn, Department of Internal Medicine |
| | St. Elisabeth Hospital Cologne-Hohenlind, Specialist Breast Unit/Senology |
| Oncology practice | Dr. Peter F. Schwindt, Bonn |
| | Dr. Helmut Forstbauer, Troisdorf |

The provided patient care (modular medication management) was delivered by a multidisciplinary team consisting of physicians, nurses and pharmacists. Physicians and nurses employed at the respective study centre carried out usual patient care (standard care). Two pharmacists of the Department of Clinical Pharmacy, Institute of Pharmacy of the University of Bonn accomplished the pharmaceutical services, including the author of this thesis and an additional research pharmacist (in the following referred to as 'study pharmacists'). Data collection was carried out by the study pharmacists in the respective study centre. The analysis of the collected data was accomplished at the Department of Clinical Pharmacy, University of Bonn (in the following to be called 'central study office').

In addition, the following cooperation partners supported the project:

- Dr. Rolf Fimmers, Institute of Medical Biometrics, Computer Sciences and Epidemiology, University of Bonn (advice on statistical methodology)
- Prof. Dr. Steve A. Hudson, Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, Scotland (advice on cancer care)
- Klaus Ruberg, Pharmacy Kronen-Apotheke Marxen, Wesseling (advice on palliative care)
- Roche Pharma AG, Basel (breast cancer patients were recruited and studied in association with the non-interventional study ML 21725, see 3.3)

## 3.3 Study design

The study was designed as a prospective, multi-centred, two-arm observational cohort study. One study arm consisted of patients classified as initially adherent (baseline daily adherence ≥90%), the other arm of initially non-adherent patients (baseline daily adherence <90%), see Figure 3-1. This classification was based on an 'adherence screening' during the first capecitabine cycle. Since no standard for the definition of sufficient adherence exists [73], the threshold of 90% was defined empirically based on the results of an earlier research project [57]. Modular medication management consisted of three modules: module 1 (basic pharmaceutical care), module 2 (adverse event management) and module 3 (adherence support). Every recruited patient received module 1 and 2 which were initiated after inclusion and provided by physicians, nurses and the study pharmacists. If a patient was found to be initially non-adherent, module 3 (adherence support) was provided additionally by the study pharmacists. Adherence screening plus adherence support is referred to as 'adherence management'. Details regarding the course of the study and the three patient care modules are given in 3.6.

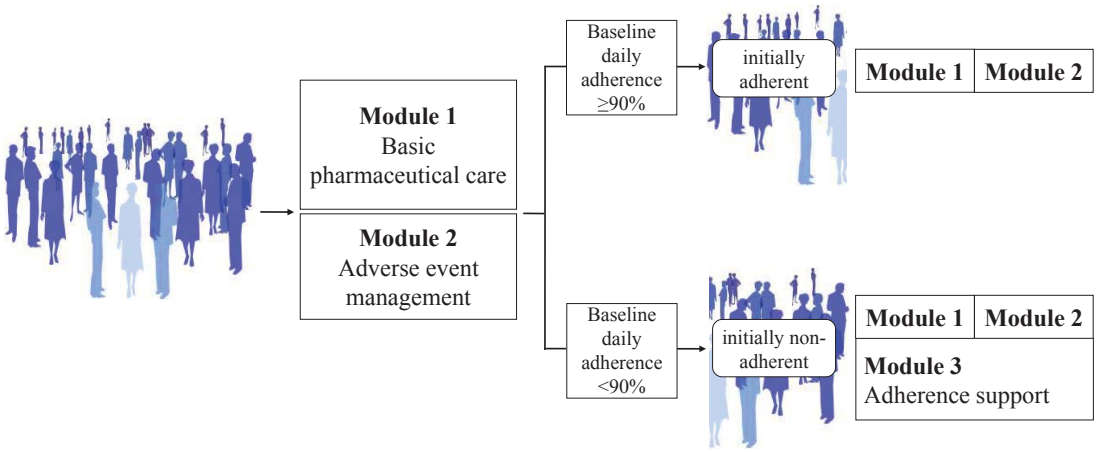



*Figure 3-1: Study design*

In terms of breast cancer patients, the present study was conducted in association with the non-interventional study with capecitabine (Xeloda®) ML 21725 executed by Roche Pharma AG, Basel [104, 105]. Patients suffering from breast cancer were included in both studies. The assessment of the following outcome parameters overlapped:

- Patient satisfaction with information at the time of inclusion ($t_0$) assessed by the Patient Satisfaction with Cancer Treatment Education (PSCaTE) questionnaire
- Cancer-specific quality of life at the time of inclusion ($t_0$), after the third capecitabine cycle ($t_3$) and after the sixth capecitabine cycle ($t_6$) assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) questionnaire
- Self-assessed adherence after each conducted capecitabine cycle ($t_1$, $t_2$, $t_3$, $t_4$, $t_5$, $t_6$) assessed by the adherence questionnaire I
- Self-assessed adherence after the last conducted capecitabine cycle ($t_6$) assessed by the adherence questionnaire II

For detailed information regarding outcome assessment see section 3.7.

## 3.4 Patient selection

To obtain a sufficient number of patients during the study period the following inclusion and exclusion criteria were defined.

**Inclusion criteria:**

- Patient suffered from a cancer entity which required an oral chemotherapy with capecitabine.
- Patient received chemotherapy with capecitabine as single agent or combination therapy for treatment of cancer.
- Patient was therapy-naïve concerning capecitabine.
- Patient was at least 18 years old.
- Patient gave written informed consent.
- Patient was able to speak, read and write German.

**Exclusion criteria:**

- Patient suffered from a disease or mental state compromising full understanding of purpose and course of the study (e.g. Alzheimer's disease).
- Patient had the intention to change his site of treatment.
- Patient showed a contraindication to capecitabine.

## 3.5 Patient recruitment

Data were collected between July 2009 and March 2012.

After the identification of eligibility by the collaborating oncologists, patients were briefly informed about the study. In case of patients' agreement on a further briefing conversation, the physician informed the patient that his name and his contact details would be referred to the study pharmacists. The physician passed on the contact details to the study pharmacists via fax (see Appendix A), e-mail or telephone. If a study pharmacist was present at the study centre at this particular time, the physician transmitted the information on the eligible patient personally and the further briefing conversation between the patient and the study pharmacist took place immediately. Otherwise a study pharmacist contacted the patient as soon as possible to arrange a meeting for further conversation. The first personal meeting usually took place at the oncology outpatient ward/oncology practice. If this was not suitable (e.g. long time until next visit of the patient in the study centre) the meeting took place at the patient's home. During the first conversation with the study pharmacist the patient was explicitly informed on the aim, content and course of the study. The patient received a written patient information brochure (see Appendix A) and had the opportunity to ask questions regarding the trial. After an appropriate amount of time the patient was asked to decide on his participation in the study. In case of acceptance, each participant signed a written informed consent (see Appendix A).

## 3.6 Course of the study

The study protocol defined a maximum observation period of six capecitabine cycles for every participant. Since each capecitabine cycle consists of 21 days (14 days with twice daily capecitabine intake and seven days without capecitabine intake) the observation period covered a maximum of 126 days or 18 weeks respectively. The observation period could exceed 126 days, if e.g. the physician prescribed a temporary treatment discontinuation for a certain patient.

The outcome assessment was orientated at the course of the patients' anti-cancer treatment with capecitabine. During the full study period patients' adherence was assessed by electronic monitoring (see 3.7.2). After written informed consent the study pharmacist handed over the MEMS® container to the patient and explained its features in detail. The study pharmacists executed the first refill of the MEMS® container together with the patient. If this was not possible (e.g. the patient was not in possession of his capecitabine chemotherapy yet) the study pharmacist explained exactly how to fill and refill the container. The patient was advised to store his capecitabine chemotherapy in the container only and to only withdraw his twice daily dose out of the container. The correct usage of MEMS® was illustrated by the written MEMS® patient information (compare Appendix C, see also 3.7.2). The MEMS® monitor of every patient was read out after the completion of the first capecitabine intake period plus first day of treatment break. According to the result, the patients were defined as initially adherent (baseline daily adherence ≥90%) or initially non-adherent (baseline daily adherence <90%). This particular period was chosen for evaluation of participants' baseline daily adherence as a longer observation period (21 days) was not feasible. If adherence screening resulted in a participant being defined as initially non-adherent, the adherence supporting module had to be initiated before the start of the second intake period. It was not feasible to schedule an appointment with every participant exactly on day 21 of the first capecitabine cycle in order to guarantee a timely initiation of the adherence support.

Concerning initially adherent patients, further readout of the MEMS® monitor was performed after the sixth cycle of capecitabine treatment ($t_6$). Regarding initially non-adherent patients, the MEMS® monitor was read out after each chemotherapy cycle (at $t_1$, $t_2$, $t_3$, $t_4$, $t_5$, and $t_6$). These regular readouts were the central requirement for the accomplishment of module 3 'adherence support' (for details see 3.6.3).

Before the first ($t_0$), after the third ($t_3$) and after the sixth ($t_6$) capecitabine cycle, patients completed two questionnaires on quality of life (EQ-5D and EORTC QLQ-C30, see 3.7.3) and the questionnaire on patient satisfaction with information (for more details see 3.7.4). After each cycle ($t_{1-6}$) the patients filled in the questionnaire on hand-foot syndrome (compare 3.7.5) and the one on adherence regarding the preceding chemotherapy cycle (see 3.7.2). At $t_6$ additionally

the adherence questionnaire regarding the capecitabine cycles 1 to 6 (compare 3.7.2) and the patient evaluation questionnaire (see 3.7.7) was completed. General and disease-related patient data were collected by means of a special questionnaire (compare 3.7.1) and on the basis of the patient file. The study pharmacists had access to the patient files during the full study period on a regular basis.

After each capecitabine cycle a personal interview between patient and study pharmacist took place (for details see 3.6.1, 3.6.2 and 3.6.3). During these visits the respective questionnaires were delivered to the patient personally by the study pharmacist. The patient had the opportunity to fill in the questionnaires without being observed. After completion the study pharmacist collected the questionnaires.

All questionnaires are shown in Appendix B. Figure 3-2 shows the course of the study schematically and the outcome measurement during the observation period.

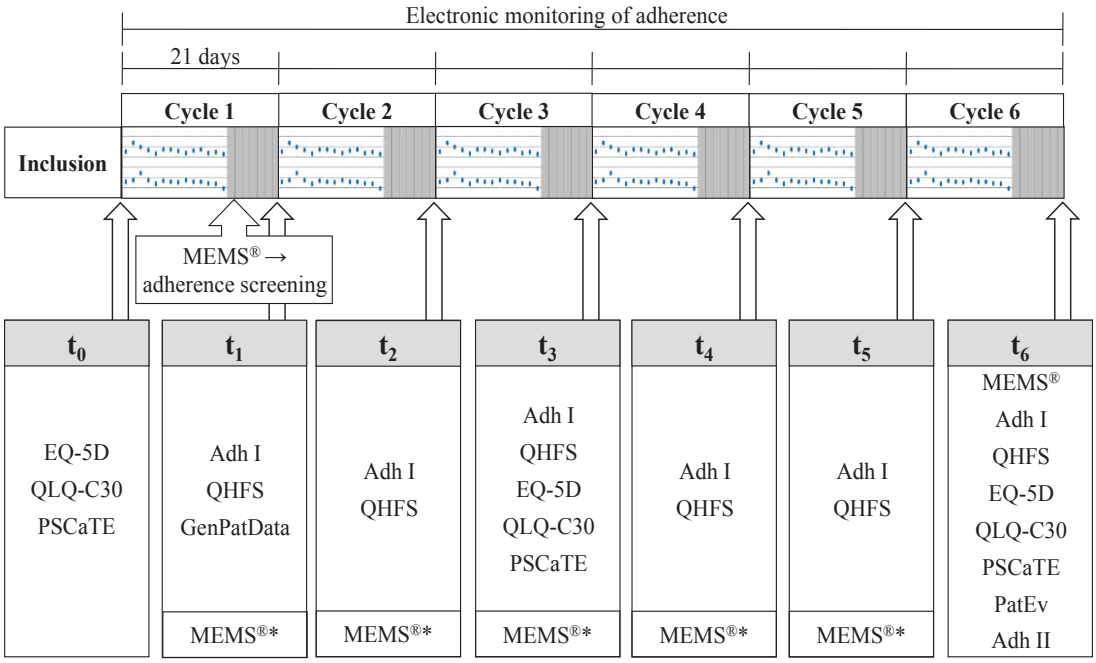



*Figure 3-2: Course of the study and outcome measurement*

*t=time point; EQ-5D=generic questionnaire on quality of life; QLQ-C30=cancer-specific questionnaire on quality of life; PSCaTE=questionnaire on patient satisfaction with information; GenPatData=questionnaire on general patient data; MEMS®=reading of MEMS® (Medication Event Monitoring System); Adh I=adherence questionnaire regarding preceding chemotherapy cycle; Adh II=adherence questionnaire regarding all chemotherapy cycles; QHFS=questionnaire on hand-foot syndrome; PatEv=questionnaire on therapeutic success and adverse drug reactions.*

** At this time point MEMS® was read out in initially non-adherent patients only.*

### 3.6.1 Module 1 – Basic pharmaceutical care

Every patient received module 1 (basic pharmaceutical care) which was provided by physicians, nurses, and the study pharmacists. Module 1 started after signing the informed consent during the first personal meeting of the study pharmacist and the patient ($t_0$). During the initial visit the study pharmacist discussed the following issues with the patient:

- Medication history including all prescribed and over-the-counter (OTC) drugs.
- Education concerning cytotoxic capecitabine (e.g. pro-drug and tumour selectivity, administration, drug-drug interactions).
- Education concerning further anti-cancer therapy (e.g. administration, mechanism of action).
- Education concerning supportive therapy (e.g. administration, mechanism of action).

Additional issues depending on the individual patient were discussed and questions brought up by the patient were answered. To complete the counselling session the patient received written information material as follows:

- Appropriate information brochures ("Blaue Ratgeber") published by the German Cancer Aid (Deutsche Krebshilfe).
- A patient brochure on frequently asked questions regarding the chemotherapy with capecitabine („Meine Therapie mit Xeloda® - Fragen und Antworten zu Ihrer Krebsbehandlung") developed by Roche Pharma AG.

Since it was part of the attending physician's usual patient care, the patients of one study centre received a treatment diary („Persönliches Therapietagebuch - Begleitheft für Xeloda Patienten während der Therapie").

All issues of the initial visit were documented in the first consultation documentation form (Appendix C). Following this counselling session, the study pharmacist checked the patient's current medication in terms of contraindications, dosages and interactions. The computer-based interaction check was conducted using the data bases DrugDex® and DIMDI SmartSearch® which were also used for information search regarding contraindications and dosages. The summary of product characteristics (SPC, Fachinformation) of the respective drugs served as an additional source of information. In case of drug-drug interactions or further identified drug-related problems (e.g. contraindication), necessary changes of the medication were made in collaboration with the responsible physician. Every patient received an individual information letter from the study pharmacist repeating important issues, answering remaining questions and, if necessary, additional written information brochures. Furthermore, the letter contained the result of the interaction check and an individual medication plan for the patient (Appendix C).

At the end of each capecitabine intake period (every three weeks, at $t_1$, $t_2$, $t_3$, $t_4$, $t_5$ and $t_6$) a further scheduled counselling session took place. During these follow-up visits the patient was

asked if changes regarding his medication had been performed during the last cycle or if he have had any problems regarding his medication. The patient had the possibility to ask questions or discuss individual issues. If necessary, advice was given, written information material was handed out and the attending physician was contacted. If the patient was prescribed a new drug or took additional OTC products, the interaction check was repeated. The results were documented and passed on to the patient. If necessary, the physician was contacted. In addition the patient's medication plan was updated. Contents of the follow-up discussions with the study pharmacist, the patient and, if applicable, the attending physician were documented using the further consultation documentation form (Appendix C). In case of urgent questions the patient had the possibility to call the study pharmacist in the central study office or on a special study mobile phone.

Figure 3-3 shows schematically the general course of module 1 (basic pharmaceutical care).

### 3.6.2 Module 2 – Adverse event management

In addition to module 1, every study patient received module 2 (adverse event management). Module 2 was carried out by physicians, nurses and the study pharmacists. The start of module 2 was in parallel to module 1 after the patient had signed the informed consent sheet. Module 2 was conducted during the initial visit of the study pharmacist ($t_0$) and the further scheduled counselling sessions ($t_1$, $t_2$, $t_3$, $t_4$, $t_5$ and $t_6$).

In module 2, the patient received written information material as follows:

- A general information sheet on prophylaxis and treatment of important adverse effects of anti-cancer drugs (Appendix C). This leaflet was developed at the Department of Clinical Pharmacy at the University of Bonn in cooperation with participating physicians.
- A patient brochure on advice in terms of prophylaxis and management of typical adverse effects of capecitabine („Richtiges Verhalten bei Nebenwirkungen – Eine Information für Xeloda® Patienten“) developed by Roche Pharma AG.

During the initial visit of module 2, patients were educated regarding common adverse effects (e.g. HFS and diarrhoea). Prophylaxis, detection and treatment were discussed in detail. If patients took other drugs or were prescribed a concomitant anti-cancer treatment, they were counselled regarding the adverse effects of these drugs as well. During the follow-up scheduled counselling sessions, the patient was questioned about adverse drug reactions he had experienced during the last cycle of capecitabine. He was given advice in terms of treatment and had the opportunity to ask questions or discuss problems. Generally, in case of issues that needed further clarification the treating physician was contacted. The first consultation documentation form and the follow-up consultation documentation form were used for the

documentation of all issues discussed during the initial visit or further sessions (see Appendix C).

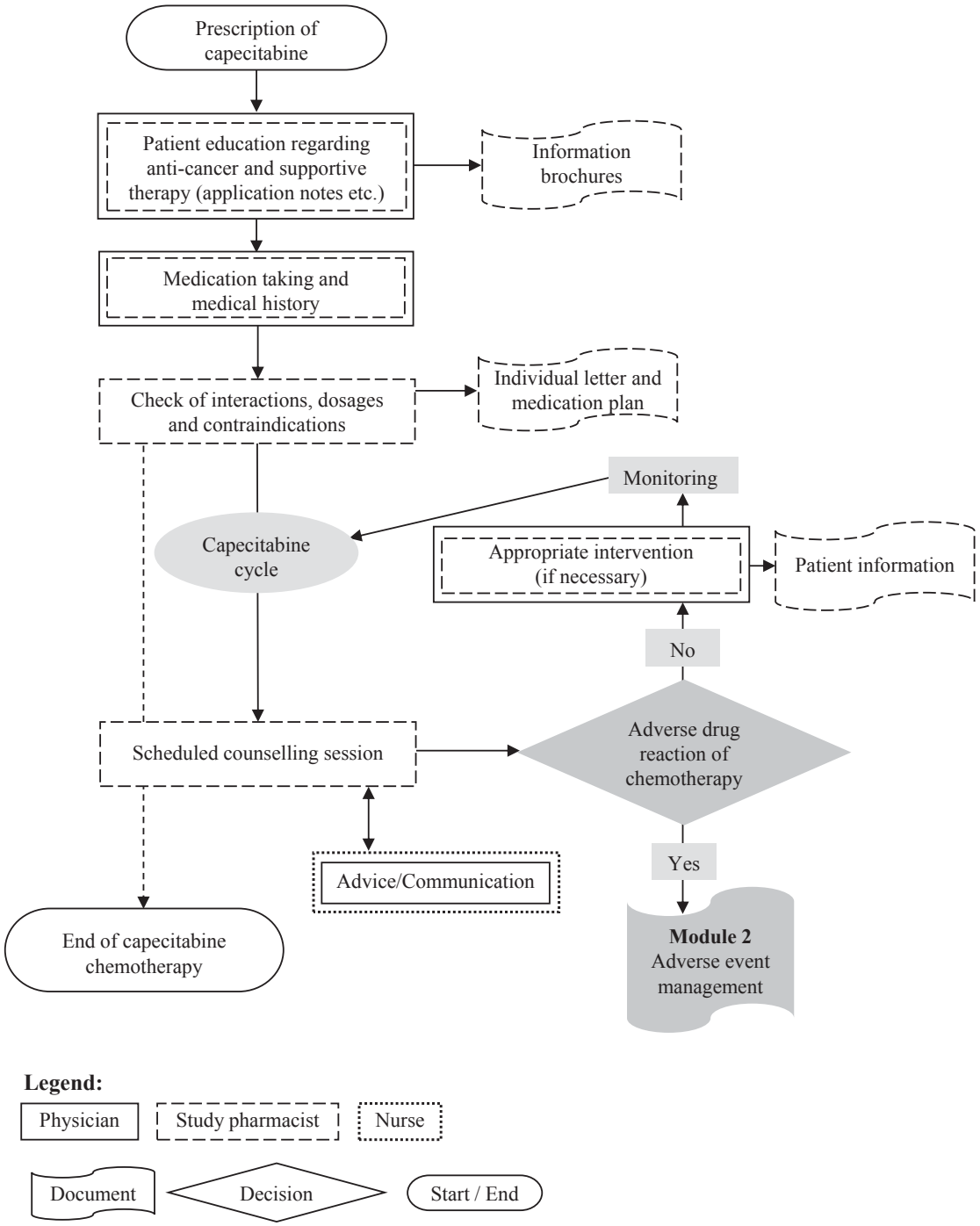



*Figure 3-3: Flow diagram of module 1 (basic pharmaceutical care)*

### 3.6.3 Module 3 – Adherence support

As the two other modules, module 3 (adherence support) was developed on the basis of currently available evidence. Module 3 was only applied to those patients who were found to be

initially non-adherent (for details regarding adherence screening compare 3.3). Module 3 was started after cycle 1 and personal follow-up visits took place at least once during every capecitabine cycle. Module 3 contained detailed discussion of the patient's individual adherence results on the basis of cycle 1 adherence data. Adherence support focussed on the identification of reasons for non-adherence in order to define a feasible adherence-enhancing strategy. Since various types of non-adherence exist, strategies to overcome individual barriers to adherence were designed individually. Strategies to improve unintentional non-adherence (e.g. due to forgetfulness) included treatment diaries or linking drug intake with a certain act of daily routine (cue dosing). In contrast, intentional non-adherence had to be approached in a completely different manner. If an adverse drug reaction was the reason for not taking capecitabine, management and prevention of further adverse drug reactions were addressed in accordance with module 2. Patients' expectations and experiences were included in all considerations. Moreover, an increase of the patient's awareness of the importance of adherence to capecitabine treatment was aimed. Routinely, beginning and end of the current and next capecitabine cycle were explicitly discussed and noted down. After each cycle further detailed discussions of the patient's adherence results on the basis of the preceding cycle MEMS® data were undertaken. The content and course of the adherence-supporting sessions was adapted according to the patient's medication taking behaviour. If the patient's adherence accounted for ≥90%, a shortened conversation was performed. Due to the pleasant adherence result, compliment and support of the behaviour during the preceding cycle was given by the study pharmacist. Moreover, the proper functioning of the adherence-enhancing strategies was discussed and the patient was asked for problems that needed further clarification. If necessary, the patient was given appropriate advice. If the patient showed a daily adherence value of <90%, the content of the first counselling session of module 3 was repeated and adherence-enhancing strategies were reassessed, discussed and adapted.

Between scheduled appointments every participant had the possibility to reach individual advice in person, by telephone or by email. All contents of module 3 discussions were documented using the adherence support documentation forms (either the one for use after cycle 1 or the one for use after cycle 2 to 6, see Appendix C). If necessary, the attending physician was contacted in order to report relevant issues or discuss problems.

## 3.7 Outcome measurement

The primary endpoint in the present study was daily total adherence to capecitabine chemotherapy determined by electronic monitoring. Additional endpoints were self-assessed adherence, overall adherence, persistence, dosing intervals, health-related quality of life, patient

satisfaction with information, the occurrence of the adverse effect hand-foot syndrome, pharmacist's working time for pharmaceutical care and patients' evaluation of capecitabine treatment.

### 3.7.1 General patient data

A questionnaire on general patient data (see Appendix B) was handed out to the study subjects to record their marital status, current living situation, education, responsibility for pharmacotherapy, education, current employment situation, activity in self-help groups and time required to reach treatment site.

### 3.7.2 Adherence

Patient adherence to capecitabine was assessed by means of electronic monitoring using the Medication Event Monitoring System (MEMS® by Aardex® Group Ltd., Zug, Switzerland). MEMS® consists of a medication container made from high-density polyethylene (HDPE) and a screw cap containing a microprocessor (MEMS® monitor). Every participant was provided with a MEMS® container and asked to use it for storage of capecitabine medication during study participation. Patients were instructed to open the containers only when taking their capecitabine dose and for no other reason. In case of required refills, patients were requested to schedule refill and regular capecitabine intake at the same time in order to avoid additional openings. If this was not possible or in case of further extraordinary openings, patients were asked to document the respective information on a special documentation sheet every participant was provided with. The MEMS® technology is illustrated in Figure 3-4.

Each MEMS® monitor was delivered in the so called 'sleeping mode'. Before use, the monitor was activated by a special software called MEMS® WakeUp (Aardex® Group Ltd., Zug, Switzerland). After activation the monitor was usable for 36 months.

The microprocessor contained in the caps recorded date and time of each opening of the container. Using the hardware component MEMS® reader, data could be transferred from the monitor to the web-based application medAmigo® which was used to read out, visualise and store patients' dosing history data. If no internet access was available, data could alternatively be transferred from the monitor to a personal computer using the MEMS® reader and the software PowerView®. PowerView® was able to visualise drug dosing histories as well. A subsequent transfer of all data from PowerView® to medAmigo® was performed. Table 3-2 shows details of the MEMS® components used.

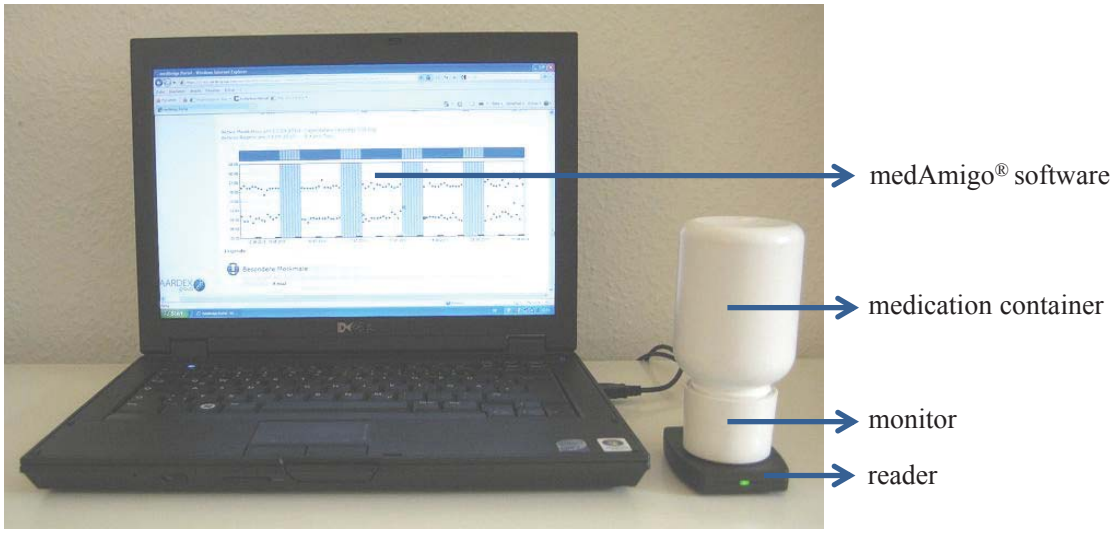



*Figure 3-4 Medication Event Monitoring System (MEMS®)*

*Table 3-2: Components of the MEMS® technology used*

| Element | Version |
|---|---|
| Monitor | MEMS® 6 TrackCap, screw cap 45 mm |
| Container | 250 cc HDPE container |
| Software | medAmigo® (online display of MEMS® data)<br>MEMS® 6 WakeUp Version 2.3.1 (initialising of MEMS® monitors)<br>PowerView® Version 3.5.1 (offline display of MEMS® data) |
| Hardware | MEMS® 6 reader USB |

Both medAmigo® and PowerView® were able to create patients' medication taking profiles. Figure 3-5 shows the drug dosing history of one initially adherent patient displayed by medAmigo®. The medication taking profile of the same patient displayed by PowerView® is shown in Figure 3-6. In each case the profile describes one capecitabine cycle of the patient which consisted of 21 days (14 days with twice daily capecitabine intake followed by seven days of break). MedAmigo® and PowerView® allowed the setting of a twice daily drug intake. Thus, the software expected two MEMS® openings per day for the removal of the capecitabine tablets. A blue dot represents an opening of the screw cap in dependence of clock time on the y-axis and date on the x-axis. MedAmigo® represents omitted doses by a grey bar. PowerView® represents two omitted openings of the screw cap as a red bar which covers the whole day. One omitted dose is shown as a red triangle. Subsequent corrections of the medication taking profiles were possible in both softwares. Since uncensored MEMS® data might overestimate non-adherence [106], adherence data were censored according to information derived from patients notes (e.g. documented in MEMS® patient information or treatment diary) and interviews. Reasons for exclusions of openings or time periods were e.g. extra openings due to MEMS®

container refills or self-reported non-monitoring intervals (e.g. due to hospital stays). Insertions were undertaken e.g. because of doses taken from another source than MEMS®. Reported divergences of opening and drug intake (e.g. earlier opening than intake due to an invitation, opening without intake) were corrected. In medAmigo® as well as in PowerView®, a blue cross depicts an excluded opening (event). In medAmigo®, a square represents a subsequently added opening. An added event is shown as a blue star in PowerView®.

After the readout of all MEMS® data to medAmigo®, the raw data were converted and transferred to Excel® 2007 and SPSS® Version 20 for further data analysis.

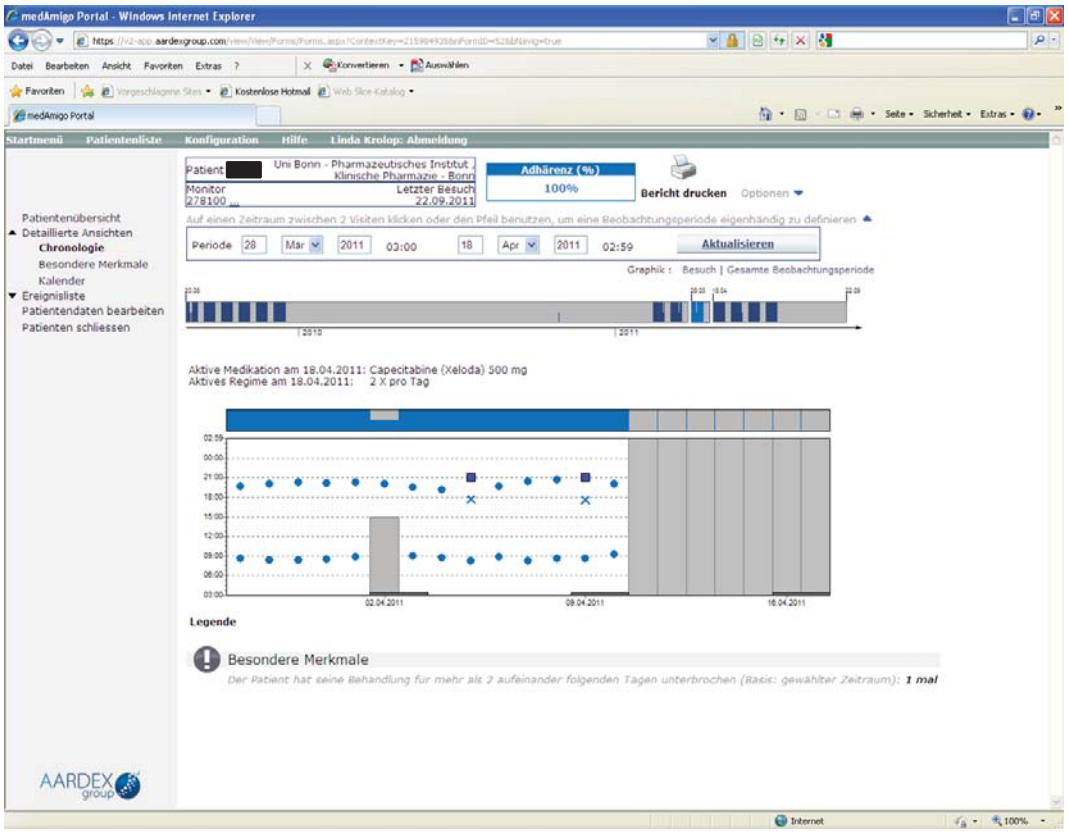



*Figure 3-5: Graphical view of adherence data in medAmigo®*

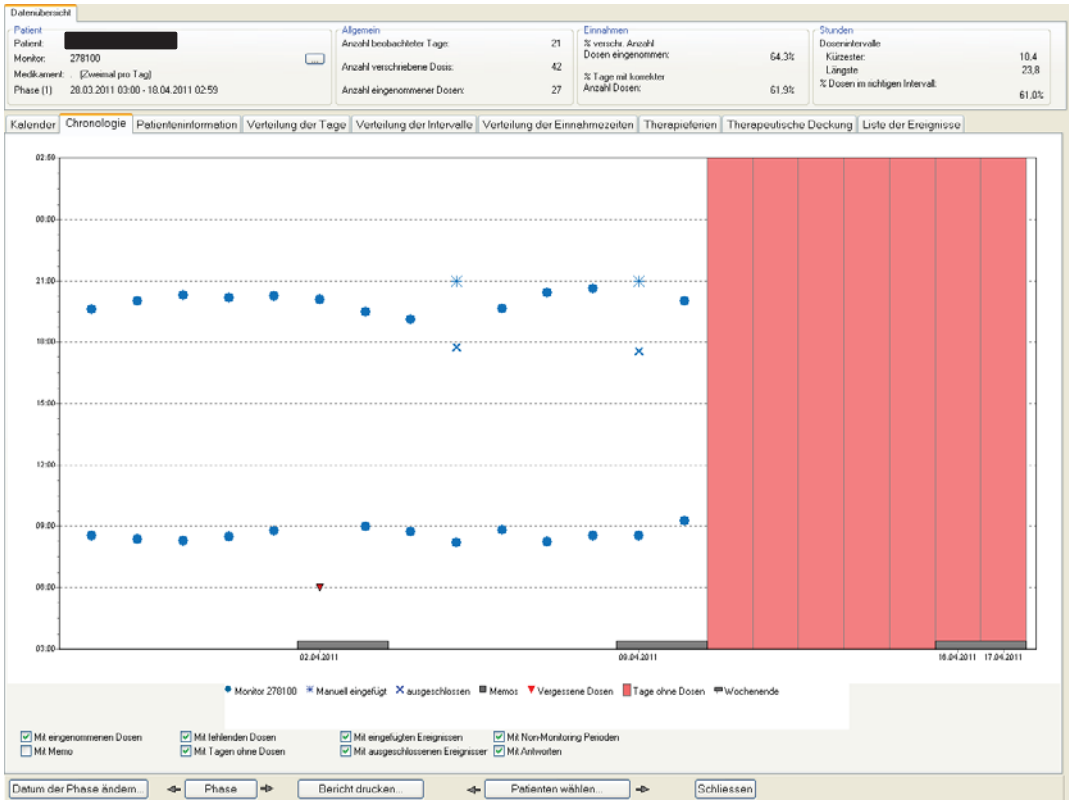



*Figure 3-6: Graphical view of adherence data in PowerView®*

**Observation period**

The observation period comprised days with drug intake as well as days without medication intake and started at the first day of patient's capecitabine intake or the morning after the day the study pharmacist delivered the MEMS® vial to the patient, respectively.

If the first capecitabine intake took place in the evening and thus the last drug intake took place in the morning, these two days were excluded from the observation period.

Observation period ended at the end of the last day of the intake period of the patient's sixth or last cycle (if the patient was prescribed less than six cycles). If days of the patient's sixth or last drug intake break were observed by MEMS®, they were added to the observation period. A further possibility for the observation period to end was the final discontinuation of treatment on doctor's order. The number of observed days had to be a whole number.

The day of an either temporary or final discontinuation of treatment on doctor's order was counted as a whole observation day. Since most frequently discontinuations were initiated sometime during the day (after breakfast and before dinner), the morning of this day counted as half a day with drug intake and the evening of this day counted as half a day without capecitabine intake.

**Daily adherence**

Daily adherence (DA) was selected as primary endpoint in this study. It was defined as the percentage of days with correctly administered capecitabine doses and was calculated according to Equation 3-1:

$$DA\,[\%] = \left( \frac{number\ of\ days\ with\ correct\ drug\ intake}{number\ of\ observed\ days} \right) \times 100 \qquad \textit{Equation 3-1}$$

Adherence and non-adherence was assessed regarding the correct administration of capecitabine on days with drug intake as well as days during the rest period. Generally a day was considered as adherent, if the patient exactly followed the instructions for his prescribed chemotherapy. A day was considered as adherent only, if two openings of the MEMS® monitor were recorded on a day during the drug intake period (dosing interval greater or equal six hours) or if no openings were recorded during the rest period. In case of ambiguity, adherence assessment was discussed and decided by a group of experts of the Department of Clinical Pharmacy, Institute of Pharmacy of the University of Bonn.

Different daily adherence parameters were calculated:

- **Daily total adherence** was calculated for each individual cycle referring to days with and days without capecitabine intake.
- **Daily intake adherence** was calculated for each individual cycle on the basis of the drug intake interval only (excluding capecitabine-free days).
- **Daily break adherence** was calculated for each individual cycle on the basis of treatment-free days only (excluding days with drug intake). Daily intake and break adherence were calculated to investigate the influence of the rest period on the adherence.
- **Baseline daily adherence** was calculated for cycle 1 referring to the intake period of the first cycle plus the first day of the first therapy-free interval. This parameter was used for the classification of a participant as initially adherent or non-adherent.
- Daily adherence was calculated for the **whole** observation period of every patient including each intake and break period.

Moreover, daily total adherence of patient subgroups which were built according to gender, tumour entity, therapy regimen and treatment intention was calculated.

**Self-assessed adherence**

Furthermore, adherence was assessed from the patients themselves by means of two adherence questionnaires (adherence questionnaire I and II, see Appendix B).

The adherence questionnaire I was handed out to the patients after every conducted capecitabine cycle ($t_1$, $t_2$, $t_3$, $t_4$, $t_5$, and $t_6$). It asked for the number of days (during the last 14 days) on which the patient took his capecitabine tablets both in the morning and in the evening. If the patient stated that he did not take his capecitabine tablets in the morning and in the evening on one or more days, he was asked for the reason. The adherence parameter was referred to as **self-assessed daily intake adherence**. To compare MEMS®- and patient self-assessed adherence (results of the adherence questionnaire I), the questionnaire was converted from the parameter 'patient-stated number of days with full adherence' to daily adherence expressed as percentage. Table 3-3 illustrates this conversion.

*Table 3-3: Conversion of patient self-assessed adherence measured by adherence questionnaire I to daily adherence expressed as percentage*

| Response options question 1 of the adherence questionnaire I | Conversion to daily adherence range [%] |
|---|---|
| 0/14 days | 0.0 |
| 1/14 to 7/14 days | >0.0-50.0 |
| 8/14 to 10/14 days | >50.0-71.4 |
| 11/14 to 12/14 days | >71.4-85.7 |
| 13/14 to 14/14 days | >85.7-100.0 |

Patients were asked to fill in the second adherence questionnaire after the last cycle of their capecitabine treatment (normally after the sixth cycle at $t_6$). They were supposed to assess their adherence to capecitabine during the whole intake period on a scale from 0% (never) to 100% (always). This adherence parameter was referred to as **self-assessed total adherence**.

**Overall adherence**

Overall adherence (OA) was determined for each cycle and throughout the whole observation period (including days without drug intake). It was defined as the percentage of correctly conducted openings of the MEMS® container and calculated according to Equation 3-2:

$$OA\,[\%] = \left( \frac{number\ of\ actual\ openings}{number\ of\ expected\ openings} \right) \times 100 \qquad \textit{Equation 3-2}$$

**Persistence**

Additionally, adherence data were analysed in terms of persistence and non-persistence. Duration of physician's capecitabine prescription was compared with the duration of the actual treatment performance by the patient.

**Dosing intervals**

Dosing intervals (time in between two capecitabine intake events) were examined as all registered time intervals between two openings of the MEMS® vial were downloaded and analysed. Dosing intervals >24 hours were excluded from analysis.

### 3.7.3 Quality of life

**EORTC QLQ-C30 questionnaire**

A modified version of the cancer-specific EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30) questionnaire, version 3.0 (German language) was completed by the patients at $t_0$, $t_3$ and $t_6$ (for version 3.0 and modified version 3.0 see Appendix B). Changes have been reported to the EORTC and comprised the insertion of a question regarding hand-foot syndrome (question 16, "Have you had symptoms of hand-foot syndrome?"). Consequently, the modified version 3.0 consisted of 31 questions instead of 30 questions and the numbering from question 16 onwards was changed, accordingly. Furthermore, patient's initials were not asked and design as well as layout of the questionnaire was changed. The modified version 3.0 comprised three pages instead of two.

The modified version 3.0 of the questionnaire consisted of five functional scales, ten symptom scales (originally nine symptom scales, hand-foot syndrome was added) and the global health status [107], see Table 3-4.

To answer each item, patients could score on a four-point Likert-scale from "not at all" (1) to "very much" (4). At first the raw scores were calculated for all scales and for the global health status as the mean of the component items (see Equation 3-3). Subsequently, a linear transformation was used to standardise the raw score. Thus, the scores ranged from 0 to 100. A higher numerical value of the score represented a higher (better) level of functioning, a higher (worse) level of symptoms and a higher (better) global health status, compare Equation 3-4, 3-5 and 3-6. The range represents the difference between the possible maximum and the minimum response to individual items. Most items take values from 1 to 4, resulting in a range of 3 [108].

Raw score

$$Raw\ score\ (RS) = \frac{I_1 + I_2 + \ldots + I_n}{n} \qquad \textit{Equation 3-3}$$

Functional scales

$$Score = \left\{1 - \frac{(RS - 1)}{range}\right\} \cdot 100 \qquad \textit{Equation 3-4}$$

Symptom scales/items $$Score = \left\{\frac{(\mathrm{RS}-1)}{\mathrm{range}}\right\} \cdot 100$$ *Equation 3-5*

Global health status/QoL $$Score = \left\{\frac{(\mathrm{RS}-1)}{\mathrm{range}}\right\} \cdot 100$$ *Equation 3-6*

*Table 3-4: Functional scales, symptom scales and global health status of the EORTC QLQ-C30 questionnaire modified version 3.0*

| | Scale | Number of items | Item numbers version 3.0 | Item numbers modified version 3.0 |
|---|---|---|---|---|
| **Functional scales** | | | | |
| Physical function | PF2 | 5 | 1 to 5 | 1 to 5 |
| Role function | RF2 | 2 | 6, 7 | 6, 7 |
| Emotional function | EF | 4 | 21 to 24 | 22 to 25 |
| Cognitive function | CF | 2 | 20, 25 | 21, 26 |
| Social function | SF | 2 | 26, 27 | 27, 28 |
| **Symptom scales/items** | | | | |
| Fatigue | FA | 3 | 10, 12, 18 | 10, 12, 19 |
| Nausea and vomiting | NV | 2 | 14, 15 | 14, 15 |
| Pain | PA | 2 | 9, 19 | 9, 20 |
| Dyspnoe | DY | 1 | 8 | 8 |
| Insomnia | SL | 1 | 11 | 11 |
| Appetite loss | AP | 1 | 13 | 13 |
| Constipation | CO | 1 | 16 | 17 |
| Diarrhea | DI | 1 | 17 | 18 |
| Financial difficulties | FI | 1 | 28 | 29 |
| Hand-foot syndrome | HFS | 1 | - | 16 |
| **Global health status/QoL** | | | | |
| Global health status/QoL | QL2 | 2 | 29, 30 | 30, 31 |

**EQ-5D-3L questionnaire**

Additionally patient's quality of life was measured at $t_0$, $t_3$ and $t_6$ using the EQ-5D-3L (EuroQol – five dimensions – three levels) questionnaire, a standardised generic measure of health status which is applicable to a wide range of health conditions and treatments (see Appendix B). The first part of the questionnaire comprises a descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each dimension can take one of three responses on a three-point Likert-scale representing three levels of severity. These levels are no problems (level 1), some or moderate problems (level 2) or extreme problems (level 3). The second part of the EQ-5D questionnaire consists of a vertical, visual analogue scale (VAS) on the patient's self-rated

health state. The scale's endpoints are labeled "best imaginable health state" (100) and "worst imaginable health state" (0) [109].

### 3.7.4 Patient satisfaction with information

The Canadian Patient Satisfaction with Cancer Treatment Education (PSCaTE) questionnaire was translated into German in the year 2002 and version 1.0 was used in patients with various cancer entities [59, 60, 110, 111]. In collaboration with the Department for Psychology of the University of Mannheim version 1.1 of the PSCaTE questionnaire was developed (compare Appendix B). The aim of the revision was an enhancement of the questionnaire's comprehensibility for the patients [61]. In the present study patient satisfaction with information among initially adherent and initially non-adherent patients was measured before the first capecitabine cycle ($t_0$), after the third cycle ($t_3$) and after the sixth cycle ($t_6$) using a modified version of the PSCaTE questionnaire version 1.1 (03/2006, see Appendix B). The first two pages of the PSCaTE questionnaire version 1.1 were used only (questions 1 to 16), design and layout were modified, date and date of birth were asked and the questionnaire's introduction was worded differently.

The 16 items of the PSCaTE questionnaire can be combined in four different scales (see Table 3-5). In addition to the individual items and the different scales, overall satisfaction (OV) can be calculated. As a response scale a five-point Likert-scale was utilised. Patients had the possibility to score each item either strongly disagree (1), disagree (2), uncertain (3), agree (4) or strongly agree (5).

*Table 3-5: Scales of the PSCaTE questionnaire version 1.1*

| PSCaTE | Scale | Number of items | Item number version 1.1 |
|---|---|---|---|
| Satisfaction with information... | | | |
| …on cancer therapy | CT | 5 | 1, 5, 6, 8, 14 |
| …on adverse effects | SE | 4 | 2, 3, 9, 15 |
| …on vitamins, herbal medicines and complementary treatment options | VC | 3 | 4, 10, 16 |
| …sources | RS | 4 | 7, 11, 12, 13 |

According to Equation 3-7, individual patient's answers (item values) were utilised to calculate each individual scale of the PSCaTE questionnaire. To calculate the overall satisfaction of a patient at a certain time point, the mean scale values were used (Equation 3-8). If at least half of the items from a scale were answered, the respective scale was calculated. Regarding the calculation of the overall satisfaction, if at least half of the scale values were available, the overall satisfaction was calculated. As a basic principle, for ordinal data like answers to a

Likert-scale the calculation of the mean is not an adequate method as the distances between the scale values are not even. However, if one and the same person answered the items of the respective questionnaire the distances between the individual scale values of the different items are supposed to be equal for this individual.

$$\bar{\chi} = \frac{\sum \chi_i}{n}$$

$\bar{\chi} =$ PSCaTE Scale

$\chi_i =$ Item value

$n =$ Number of items

*Equation 3-7*

$$\bar{\chi} = \frac{\sum \chi_i}{n}$$

$\bar{\chi} =$ Overall satisfaction

$\chi_i =$ Scale value

$n =$ Number of scales

*Equation 3-8*

### 3.7.5 Hand-foot syndrome (HFS)

After each conducted capecitabine cycle (at $t_1$, $t_2$, $t_3$, $t_4$, $t_5$, and $t_6$) patients were requested to fill in the questionnaire on HFS (see Appendix B). By ticking the respective box, patients documented if they experienced HFS and, if yes, how severe it was. The questionnaire on HFS was developed by the Department of Clinical Pharmacy of the University of Bonn in cooperation with oncologists. The description of the HFS severity grades was based on the Common Terminology Criteria for Adverse Events of Cancer Therapy Evaluation Program from the National Cancer Institute and reached from mild skin reactions at the hands and feet (grade 1) to major skin reactions with bleeding, ulceration and severe pain (grade 3) [23].

### 3.7.6 Pharmacist's working time

The study pharmacists documented the duration of patient interviews and counselling sessions (see Appendix C). Also, the time needed for extra work was recorded. Extra work included e.g. literature search, time needed to provide written patient information, e.g. medication plan, and discussions with other health care professionals. The duration of the initial counselling session was documented separately from the time needed for follow-up visits. The time required for module 3 was added to the duration of follow-up visits.

### 3.7.7 Patient evaluation

Upon completion of the patients' last capecitabine cycle, they were requested to evaluate their capecitabine therapy by means of a specific questionnaire (see Appendix B). The questionnaire consisted of three questions asking for the patients' assessment of the therapy outcome compared with their expectations. This included experienced adverse drug reactions and overall experience with capecitabine therapy.

### 3.7.8 Further analyses in the entire patient cohort

The whole patient cohort was analysed concerning two different aspects. An existing relationship between overall adherence and hand-foot syndrome was explored. Moreover, potential predictors of adherence were evaluated. Therefore, the relationship and correlation, respectively, between daily total adherence during the first cycle of capecitabine treatment and diverse socio-demographic and disease-related characteristics were tested. For detailed information regarding applied statistical analyses see 3.9.

## 3.8 Working hypotheses and sample size determination

The following working hypotheses were investigated in the present study:

- Patients who show a baseline adherence of ≥90% do not require a special adherence supporting intervention.
- Patients who show a baseline adherence of <90% require a special adherence supporting intervention.
- Patient adherence to capecitabine chemotherapy is increased by a special adherence supporting intervention.
- Quality of life and patient satisfaction with information can be maintained during therapy with capecitabine by means of a multiprofessional, modular medication management.

Regarding the primary outcome measure daily adherence two hypotheses were phrased:

**Hypothesis 1**

Null hypothesis $H_0$: ≤75% of initially adherent patients remain being adherent without adherence supporting intervention.

Alternative hypothesis $H_1$: >75% of initially adherent patients remain being adherent without adherence supporting intervention.

**Hypothesis 2**

Null hypothesis $H_0$: ≤80% of initially non-adherent patients are adherent after the adherence supporting intervention.

Alternative hypothesis $H_1$: >80% of initially non-adherent patients are adherent after the adherence supporting intervention.

**Sample size determination**

Sample size determination was conducted for the primary endpoint 'daily adherence' and was based on available adherence data of 44 cancer patients collected in a prospective, multi-centred observational cohort study between 05/2006 and 04/2008 [57]. These patients had a diagnosis of breast or colorectal cancer and were treated with capecitabine. Patients' adherence was monitored by MEMS® over a time period of six months. These data were analysed with regard to daily adherence of the patient's first capecitabine cycle (compare 3.7.1): 59.1% were adherent (≥90%) during their first cycle and 40.9% were non-adherent (<90%).

Regarding initially adherent participants a sample size of 45 patients was required to show with a power (1-β) of 80% that >75% of these patients remain being adherent (error of first kind (α) = 5%). The true population value of patients who persist being adherent was assumed to account for >90%.

Regarding initially non-adherent patients, a sample size of 30 patients was required to show with a power (1-β) of 80% that >80% of these patients become adherent after receiving adherence support (error of first kind (α) = 5%). The true population value of patients who became adherent was assumed to account for >95%.

Finally a dropout rate of 20% was estimated resulting in a total sample size of 90 patients (54 initially adherent patients and 36 initially non-adherent patients).

## 3.9 Statistical analysis

Data entry and statistical data analysis of the results were carried out using the software Excel® 2007 (Microsoft, Redmond, USA) as well as SPSS® Version 20 (SPSS® Inc., Chicago, USA, Statistical Package for the Social Sciences).

Data were mostly binary, nominal, ordinal, or failed to follow a normal distribution, thus, non-parametric testing was utilised consistently. A p value of <0.05 was considered as statistically significant in all cases. Statistical evaluations were conducted separately for the groups of initially adherent and initially non-adherent patients. Only the analysis of the relationship

between overall adherence and hand-foot syndrome and the evaluation of potential predictors of adherence were conducted including the entire patient cohort.

**Descriptive statistics**

Appropriate descriptive statistics calculating mean, standard deviation (SD), median, interquartile range (IQR), range, absolute and relative frequency distribution was used to characterise the patient population and summarise the study results. Moreover, appropriate graphical presentation was carried out in terms of boxplots, bar charts, pie charts, scatter plots, line charts and histograms. Kaplan-Meier plots were used for graphical presentation of data regarding time until a particular event occurred (e.g. time to dose reduction of capecitabine, time to first occurrence of HFS) [112].

**Inductive statistics**

Furthermore, inductive statistics was employed. The Mann-Whitney-U test for independent samples was employed to analyse existing differences between two samples regarding continuous (not normally distributed) data (e.g. daily adherence in initially adherent and initially non-adherent patients).

The Kruskal-Wallis-H test for independent samples was used to test for differences between more than two independent samples in terms of continuous data (e.g. daily adherence in patients with breast cancer, colorectal cancer and other cancer entities).

The Wilcoxon test was applied to look for differences regarding continuous data between two dependent samples (e.g. MEMS®- versus self-assessed adherence in initially adherent patients).

To test whether two categorical variables were associated or independent the Chi-square test was employed (e.g. relationship of dichotomised adherence with adherence group membership). However, the Chi-square test is not appropriate when more than 20% of the cells of a cross tabulation exhibit an expected frequency less than five. Thus, when the expected frequencies were too low, the Fisher's exact test for nominal data was used, a method for computing the exact probability of the Chi-square statistics that is accurate when sample sizes are small [113]. In this study differences regarding socio-demographic and disease-related characteristics between initially adherent and non-adherent patients were tested using the Fisher's exact test.

Cox regression models are used to investigate the influence of several variables on the time until a particular event occurred (predictive models for time-to-event data) [112]. In this study the effect of two overall adherence variables and the cancer entity on the time to first occurrence of HFS grade 1 to 3 and grade 2 to 3, respectively, was explored.

To explore the strength of relationship between adherence and potential predictors of adherence, Spearman's rank correlation coefficient was utilised for comparing two ordinal or continuous (not normally distributed) data sets [113].

The log-rank test was used to compare time-to-event rates of independent samples, i.e. to test for statistically significant differences between Kaplan-Meier curves [112].

**Missing data and study drop-outs**

If adherence data were missing, the corresponding days were not included in analysis. The number of observed days was reduced accordingly. In the event of missing data regarding further endpoints, available data of the respective patient were analysed. Study drop-outs due to withdrawal of informed consent, non-use of the MEMS® container or death before the containers could be read out were not analysed. Patient data collected until drop-out were not included in further analyses (per-protocol analysis). However, study drop-outs due to other reasons were included in analyses, e.g. because of premature treatment discontinuation as a result of an adverse drug reaction, if they completed at least one entire cycle.

# 4 Results

## 4.1 Patient recruitment

Patient recruitment took place on two oncology outpatient wards (one Department of Internal Medicine and one Specialist Breast Unit/Senology) and two oncology practices. Between July 2009 and November 2011, participating oncologists assessed 97 patients for eligibility, 78 of these were enrolled in the study (80.4%). Figure 4-1 provides a detailed overview of patient recruitment. Nineteen patients were excluded from participation, because they did not fulfil inclusion criteria or declined participation. The main reason (seven out of eight refusals) for non-participation was perceived stress by the study in addition to their mentally and/or physically impaired condition. Other reasons for non-participation were capecitabine non-naivity (five patients), participation in another trial (four patients), and insufficient knowledge of German language (two patients). Five patients who dropped out of the present study were not analysed. One patient withdrew his informed consent because he refused to fill in questionnaires and did not want to receive patient care provided by the study pharmacists. Two patients did not use their MEMS® container during the course of the study. Two patients died before it was possible for the study pharmacists to read out the MEMS® monitor. Study drop-outs due to other reasons than the reasons mentioned above were included in analyses. Finally, 73 patients were analysed.

## 4.2 Patient characteristics

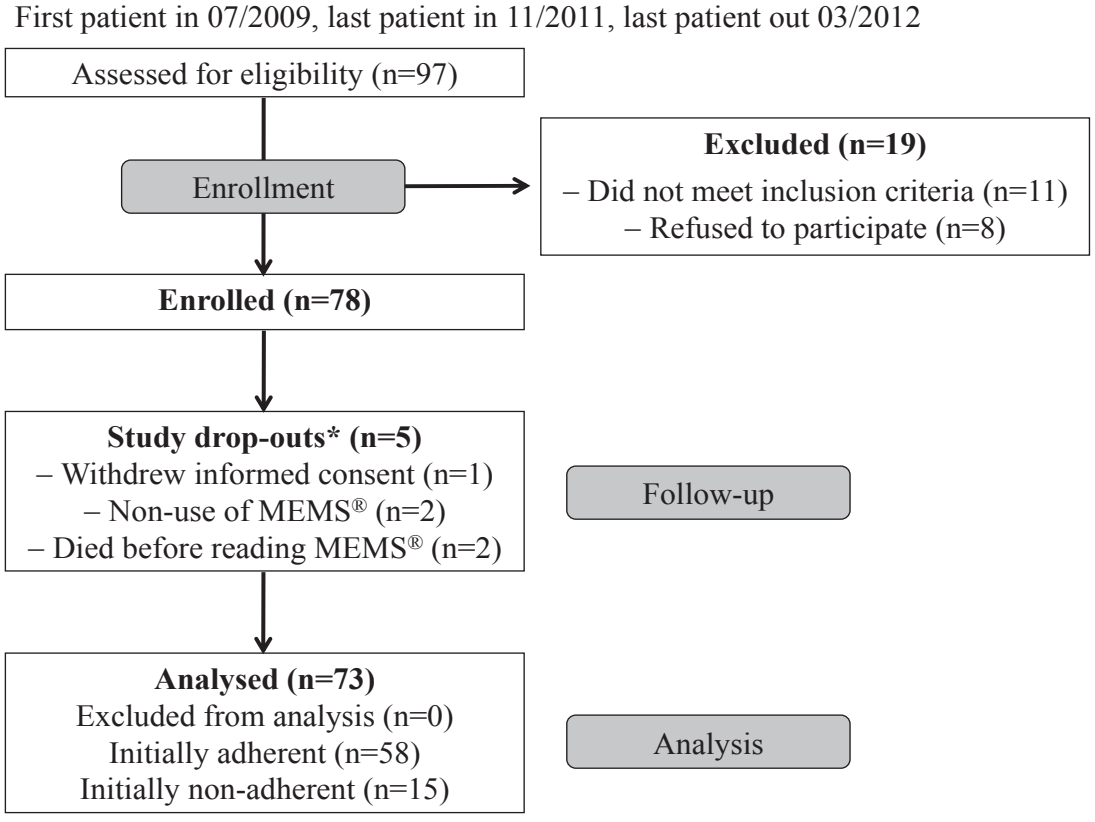
Seventy-three patients were analysed for baseline daily adherence. Fifty-eight of them (79.5%) were found to be initially adherent and 15 initially non-adherent (20.5%). Table 4-1 and Table 4-2 show that there was no statistically significant difference between initially adherent and non-adherent patients regarding socio-demographic and disease-related characteristics. A higher number of patients from oncology outpatient wards than patients from oncology practices were initially adherent (p=0.021, Fisher's exact test).

In initially adherent patients the mean age at $t_0$ was 62.5 years (median 62.0, SD 12.6, range 36-87, IQR 55.5-73.0). The mean age at $t_0$ of the initially non-adherent patients was 66.6 years (median 65.0, SD 11.5, range 52.0-90.0, IQR 55.0-76.0). Therefore initially adherent patients were on average 4.1 years younger than initially non-adherent patients. This difference was not statistically significant (p=0.335, Mann-Whitney-U test).

The mean time for initially adherent patients to reach their treatment site was 23.1 minutes (median 20.0, SD 14.4, range 5.0-90.0, IQR 15.0-30.0). In initially non-adherent patients the mean time to treatment site accounted for 25.1 minutes (median 27.5, SD 7.7, range 10.0-36.0, IQR 20.0-30.0). No statistically significant difference between the two patient groups was observed (p=0.187, Mann-Whitney-U test).

Concerning the number of additional drugs (regularly, orally administered) at time of inclusion ($t_0$) the two patient groups did not differ either (p=0.062, Mann-Whitney-U test). In initially adherent patients, the mean number of additional drugs accounted for 3.5 (median 3.0, SD 3.2, range 0.0-13.0, IQR 1.0-5.0). Initially non-adherent patients took on average 5.1 additional drugs at $t_0$ (median 5.0, SD 3.3, range 1.0-12.0, IQR 2.0-6.0).

Mean time since diagnosis [months] at $t_0$ in the group of initially adherent patients was found to be 30.2 months (median 12.5, SD 45.6, range 1.0-216.0, IQR 5.0-32.8). Initially non-adherent patients' diagnosis was on average 74.9 months ago (median 16.0, SD 112.7, range 0.0-393.0, IQR 5.0-120.0). However, this difference between the two patient groups was not statistically significant (p=0.342, Mann-Whitney-U test).




* Excluding study drop-outs due to other reasons than the reasons mentioned above

*Figure 4-1: Patient recruitment flow diagram*

*Table 4-1: Socio-demographic patient characteristics*

| Socio-demographic characteristics | | initially adherent | | initially non-adherent | | p value* |
|---|---|---|---|---|---|---|
| | | n | % | n | % | |
| Classified age [years] | ≤50 | 11 | 19.0 | 0 | 0.0 | 0.203 |
| | 51-60 | 15 | 25.9 | 6 | 40.0 | |
| | 61-70 | 17 | 29.3 | 3 | 20.0 | |
| | 71-80 | 10 | 17.2 | 5 | 33.3 | |
| | >80 | 5 | 8.6 | 1 | 6.7 | |
| Sex | Female | 44 | 75.9 | 10 | 66.7 | 0.516 |
| | Male | 14 | 24.1 | 5 | 33.3 | |
| Marital status | Married/partner | 33 | 56.9 | 8 | 53.3 | 0.639 |
| | Single | 6 | 10.3 | 3 | 20.0 | |
| | Divorced | 4 | 6.9 | 0 | 0.0 | |
| | Widow | 8 | 13.8 | 3 | 20.0 | |
| | No answer | 7 | 12.1 | 1 | 6.7 | |
| Current living situation | Living alone | 8 | 13.8 | 3 | 20.0 | 0.759 |
| | With family/partner | 42 | 72.4 | 11 | 73.3 | |
| | Living in institution | 1 | 1.7 | 0 | 0.0 | |
| | No answer | 7 | 12.1 | 1 | 6.7 | |
| Education | Elementary school | 8 | 13.8 | 1 | 6.7 | 0.650 |
| | Secondary school | 4 | 6.9 | 2 | 13.3 | |
| | O-levels | 15 | 25.9 | 3 | 20.0 | |
| | Journeyman | 4 | 6.9 | 1 | 6.7 | |
| | A-levels | 6 | 10.3 | 2 | 13.3 | |
| | Master of a trade | 2 | 3.4 | 2 | 13.3 | |
| | Bachelor | 2 | 3.4 | 1 | 6.7 | |
| | University/College | 8 | 13.8 | 1 | 6.7 | |
| | Higher university degree | 1 | 1.7 | 1 | 6.7 | |
| | No answer | 8 | 13.8 | 1 | 6.7 | |
| Current employment situation | Housewife/-man | 5 | 8.6 | 1 | 6.7 | 0.643 |
| | Public servant | 2 | 3.4 | 0 | 0.0 | |
| | Pensioner | 27 | 46.6 | 7 | 46.7 | |
| | Employee | 12 | 20.7 | 3 | 20.0 | |
| | Self-employed | 3 | 5.2 | 3 | 20.0 | |
| | Worker | 1 | 1.7 | 0 | 0.0 | |
| | No answer | 8 | 13.8 | 1 | 6.7 | |
| Number of additional drugs | ≤5 | 45 | 77.6 | 10 | 66.7 | 0.514 |
| | 6-10 | 9 | 15.5 | 3 | 20.0 | |
| | >10 | 3 | 5.2 | 2 | 13.3 | |
| | No answer | 1 | 1.7 | 0 | 0.0 | |

** Fisher´s exact test*

*Table 4-2:* Disease-related patient characteristics

| Disease-related characteristics | | initially adherent | | initially non-adherent | | p value* |
|---|---|---|---|---|---|---|
| | | n | % | n | % | |
| Tumour entity | Breast cancer | 21 | 36.2 | 7 | 46.7 | 0.818 |
| | Colorectal cancer | 25 | 43.1 | 7 | 46.7 | |
| | Gastric cancer | 3 | 5.2 | 0 | 0.0 | |
| | Oesophageal cancer | 1 | 1.7 | 1 | 6.7 | |
| | Ovarian cancer | 3 | 5.2 | 0 | 0.0 | |
| | Cancer of unknown primary (CUP) | 1 | 1.7 | 0 | 0.0 | |
| | Pancreatic cancer | 3 | 5.2 | 0 | 0.0 | |
| | Endometrial cancer | 1 | 1.7 | 0 | 0.0 | |
| Therapy regimen at inclusion[1,2] | Cap | 35 | 60.3 | 7 | 46.7 | 0.313 |
| | Cap Beva | 11 | 19.0 | 4 | 26.7 | |
| | Cap Beva Ox | 1 | 1.7 | 0 | 0.0 | |
| | Cap Lap | 1 | 1.7 | 0 | 0.0 | |
| | Cap Ox | 3 | 5.2 | 1 | 6.7 | |
| | Cap Vin | 1 | 1.7 | 1 | 6.7 | |
| | Cap Mito | 0 | 0.0 | 1 | 6.7 | |
| | Cap Trastu Ox | 0 | 0.0 | 1 | 6.7 | |
| | Cap Fulve | 2 | 3.4 | 0 | 0.0 | |
| | Cap Vin Letro | 1 | 1.7 | 0 | 0.0 | |
| | Cap Trastu | 3 | 5.2 | 0 | 0.0 | |
| Treatment intention | curative | 8 | 13.8 | 3 | 20.0 | 0.686 |
| | palliative | 50 | 86.2 | 12 | 80.0 | |
| Classified time since diagnosis | <½ year | 15 | 25.9 | 4 | 26.7 | 0.712 |
| | ½ to 2 years | 22 | 37.9 | 4 | 26.7 | |
| | >2 years | 21 | 36.2 | 7 | 46.7 | |
| Treatment setting | Oncology outpatient ward | 51 | 87.9 | 9 | 60.0 | 0.021 |
| | Oncology practice | 7 | 12.1 | 6 | 40.0 | |
| Responsibility for pharmacotherapy | Independently | 46 | 79.3 | 13 | 86.7 | 1.000 |
| | Partner/family | 3 | 5.2 | 1 | 6.7 | |
| | Nursing service | 1 | 1.7 | 0 | 0.0 | |
| | Nursing service or partner/family | 1 | 1.7 | 0 | 0.0 | |
| | No answer | 7 | 12.1 | 1 | 6.7 | |
| Activity in self-help group | Yes | 5 | 8.6 | 1 | 6.7 | 1.000 |
| | No | 44 | 75.9 | 13 | 86.7 | |
| | No answer | 9 | 15.5 | 1 | 6.7 | |
| Classified distance to treatment site [minutes] | <15 | 9 | 15.5 | 1 | 6.7 | 0.448 |
| | 15-29 | 25 | 43.1 | 6 | 40.0 | |
| | 30-44 | 14 | 24.1 | 7 | 46.7 | |
| | ≥45 | 2 | 3.4 | 0 | 0.0 | |
| | No answer | 8 | 13.8 | 1 | 6.7 | |

** Fisher´s exact test*

[1]*Therapy regimens:* ***Cap****=capecitabine monotherapy;* ***Cap Beva****=capecitabine+bevacizumab;* ***Cap Bev Ox****=capecitabine+bevacizumab+oxaliplatin;* ***Cap Lap****=capecitabine+lapatinib:* ***Cap Ox****=capecitabine +oxaliplatin;* ***Cap Vin****=capecitabine+vinorelbine;* ***Cap Mito****=capecitabine+mitomycin;* ***Cap Trastu Ox*** *=capecitabine+trastuzumab+oxaliplatin;* ***Cap Fulve****=capecitabine+fulvestrant;* ***Cap Vin Letro****=capecitabine+vinorelbine+letrozole;* ***Cap Trastu****=capecitabine+trastuzumab*

[2]*Bisphosphonate and radiation therapies are not considered*

## 4.3 Initially adherent patients

Initially adherent participants were observed for a median time of 119.0 days (mean 100.5 days; SD 37.1; range 21.0-152.0; IQR=69.8-126.0).

### 4.3.1 Daily adherence

As described in 3.7.2, baseline daily adherence was calculated based on the first capecitabine intake period plus first day of treatment break for reasons of feasibility. According to this adherence parameter, patients were screened and classified as either initially adherent or non-adherent. Moreover, daily total adherence was calculated based on the intake period plus the treatment-free interval. Values of baseline daily adherence and daily total adherence during cycle 1 might differ. Figure 4-2 compares median baseline daily adherence and median daily total adherence during cycle 1 of initially adherent patients and visualises that baseline daily adherence was marginally lower.

Further adherence parameters calculated were daily intake and daily break adherence.

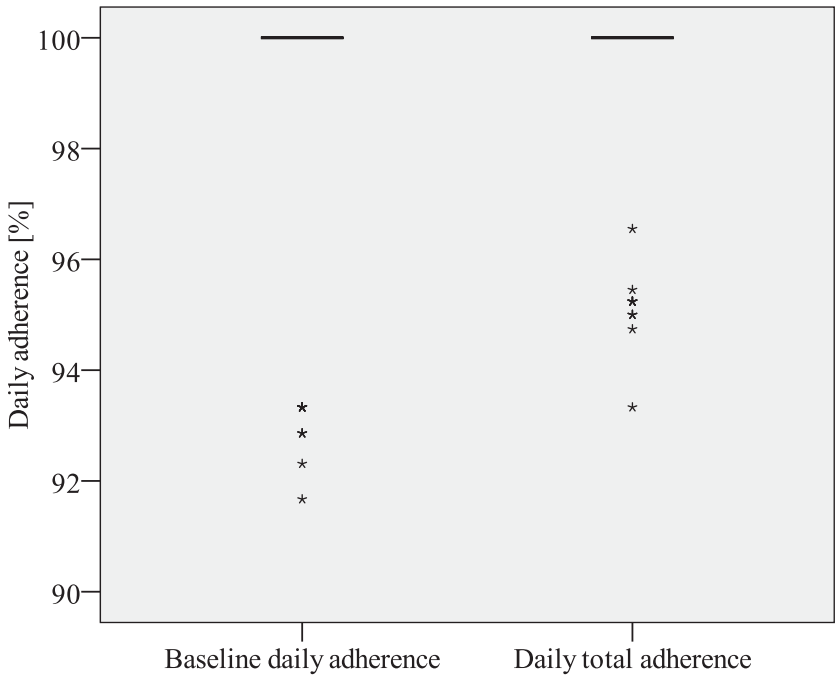



*Figure 4-2: Baseline daily adherence versus daily total adherence during cycle 1 of initially adherent patients (n=58)*

Figure 4-3 shows the individual daily total adherence profiles of each patient over the observation period. Although these participants did not receive specific adherence support, the modular medication management led to a consistently high daily total adherence in a majority

of these patients. Only in exceptional cases daily total adherence was observed to be lower than 90%. One patient did not adhere to the minimum intake interval of six hours between two capecitabine doses on several days. A further patient took capecitabine for three weeks instead of two weeks. Hand-foot syndrome, epistaxis, gum bleeding, and mental disorders represented additional barriers to sufficient adherence in the presented patient group. In one patient, only three days were observed via MEMS® in cycle two and therefore minor deviations from the prescribed regimen caused low adherence parameters.

One patient refused the receipt of modular medication management provided by the study pharmacist. The reason for this was extreme psychological stress of the patient caused by his life-threatening condition. Conversations, interviews, and questionnaires concerning cancer disease were perceived as additional stress. However, daily total adherence of this patient accounted for 100.0% during all observed capecitabine cycles.

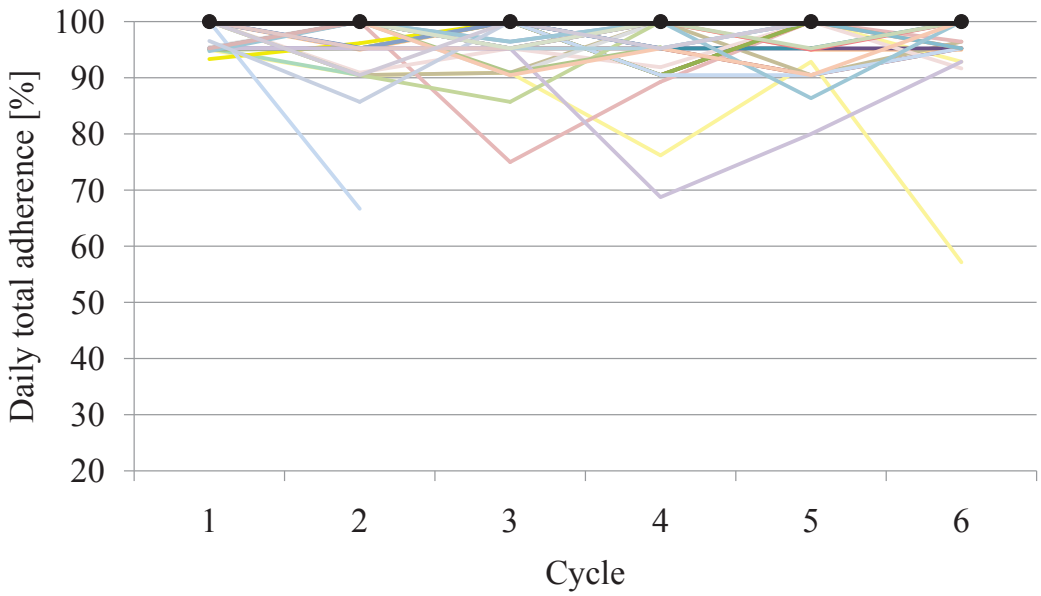



*Figure 4-3: Individual daily total adherence of initially adherent patients during the course of the study; cycle 1: n=58, cycle 2: n=56, cycle 3: n=48, cycle 4: n=45, cycle 5: n=40, cycle 6: n=37, the black line represents median daily total adherence*

Average daily total adherence decreased by 1.6% points from cycle 1 to 6. Median daily total adherence was found to be 100% in each cycle. Table 4-3 shows the respective details.

*Table 4-3: Daily total adherence of initially adherent patients (calculation based on intake and rest period)*

| | n | Mean [%] | Median [%] | SD [%] | Range [%] | IQR [%] |
|---|---|---|---|---|---|---|
| Cycle 1 | 58 | 98.9 | 100.0 | 2.1 | 93.3-100.0 | 100.0-100.0 |
| Cycle 2 | 56 | 97.3 | 100.0 | 5.5 | 66.7-100.0 | 95.2-100.0 |
| Cycle 3 | 48 | 97.2 | 100.0 | 4.9 | 75.0-100.0 | 95.2-100.0 |
| Cycle 4 | 45 | 96.7 | 100.0 | 6.3 | 68.8-100.0 | 95.2-100.0 |
| Cycle 5 | 40 | 97.4 | 100.0 | 4.7 | 80.0-100.0 | 95.2-100.0 |
| Cycle 6 | 37 | 97.3 | 100.0 | 7.3 | 57.1-100.0 | 95.2-100.0 |

Figure 4-4 demonstrates that variability with regard to daily total adherence increased marginally in further cycles compared to cycle 1. Outliers and extreme values during the different capecitabine cycles did not belong to the same patients (compare explanation given to Figure 4-3). One patient exhibited extreme values during three cycles for reasons of mental disorder and two patients during two cycles due to forgetfulness, hand-foot syndrome, epistaxis, and gum bleeding.

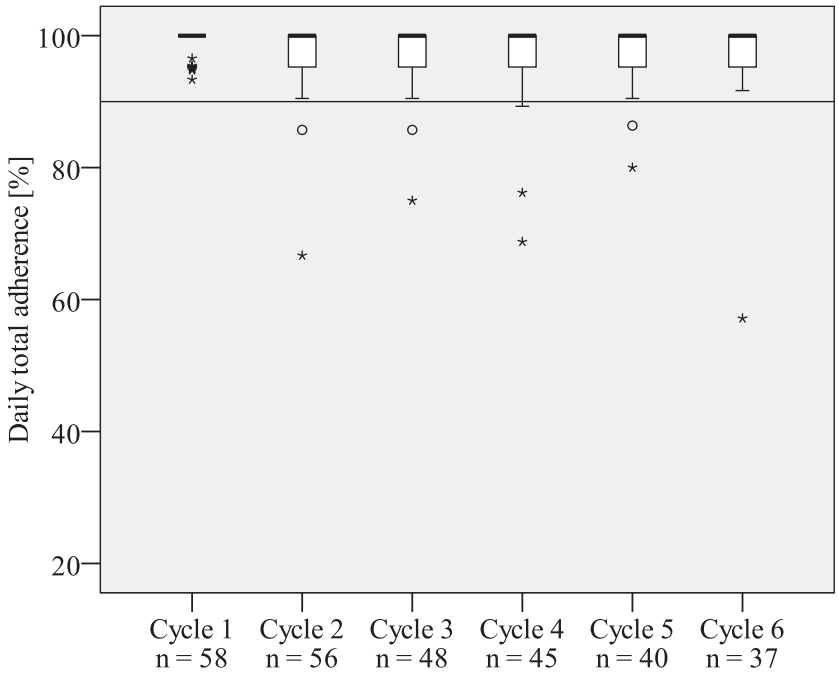



*Figure 4-4: Daily total adherence of initially adherent patients during cycle 1 to 6*

Compared to daily total adherence of initially adherent patients, values of daily intake adherence showed a higher variability, and more outliers and extreme values were observed (Figure 4-5). More detailed information on daily intake adherence of initially adherent patients during cycle 1 to 6 is presented in Appendix D, Table D-1.

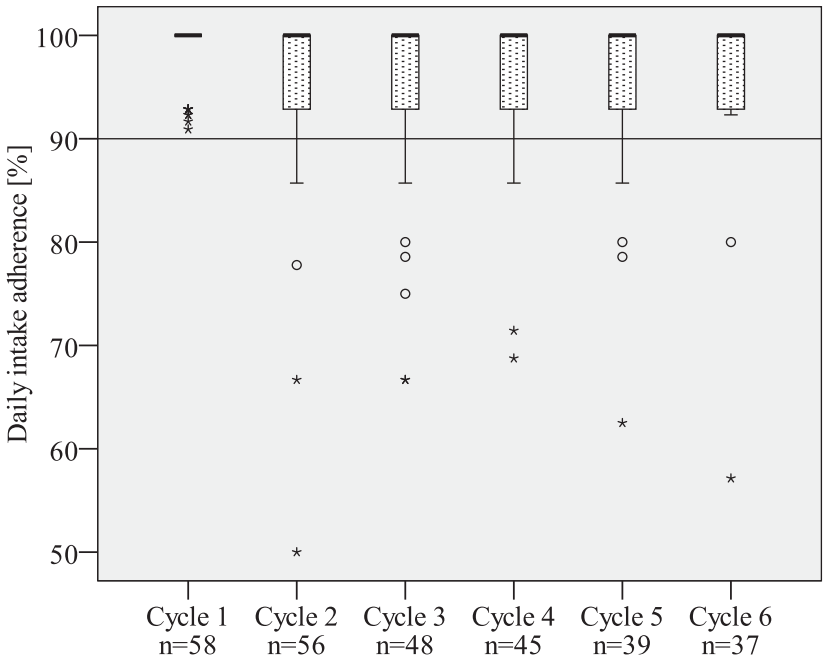



*Figure 4-5: Daily intake adherence [%] of initially adherent patients during cycle 1 to 6*

Daily adherence of initially adherent patients during capecitabine treatment-free intervals was found to be better than these patients' daily total adherence and daily intake adherence, see Figure 4-6. More detailed information on daily break adherence is tabulated in Appendix D, Table D-2.

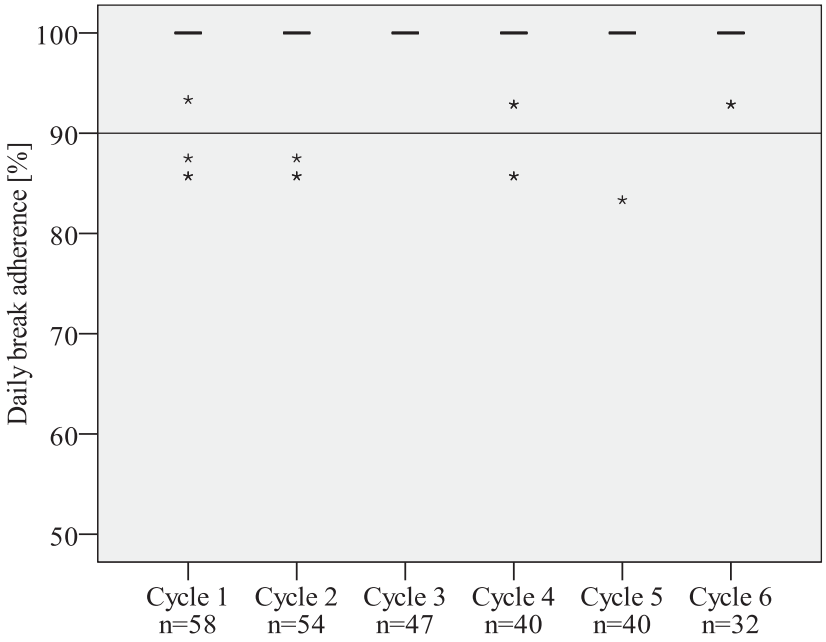



*Figure 4-6: Daily break adherence [%] of initially adherent patients during cycle 1 to 6*

During all observed cycles, a high percentage of initially adherent participants showed a daily total adherence equal 100% and equal or greater 90% and 80%, respectively. After the sixth cycle, 36 of 37 (97.3%, confidence interval (CI) 88.8%-99.4%) initially adherent patients showed a daily total adherence of ≥90%. Since the CI does not include 75% it is shown with an error of the first kind of 5% that more than 75% of the initially adherent patients remained adherent without specific adherence support. Figure 4-7 illustrates the data as a bar chart and Appendix D, Table D-3 comprises more detailed information in tabular form.

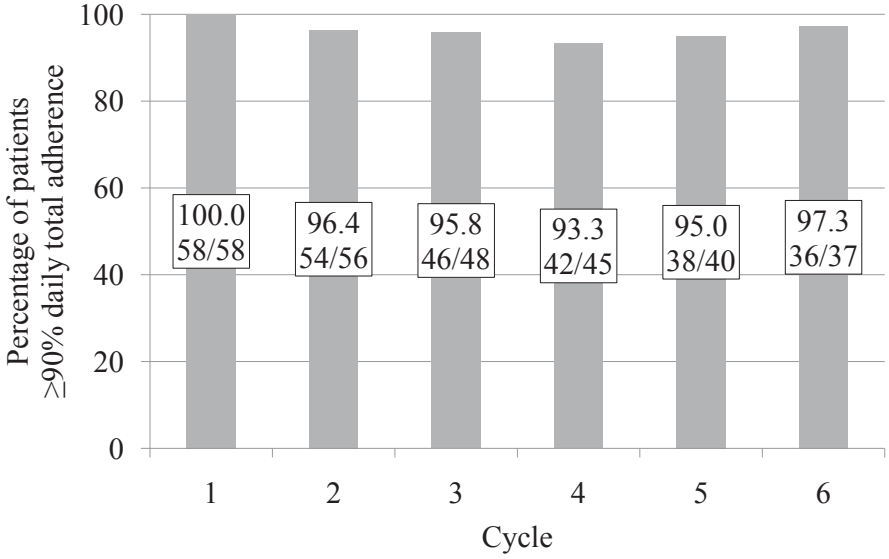



*Figure 4-7: Percentage of initially adherent patients exhibiting a daily total adherence ≥90% during intake and rest periods of cycle 1 to 6; the numbers inside the boxes show the exact percentage (first row) and absolute patient numbers (second row)*

Figure 4-8 shows the percentage of initially adherent patients exhibiting a daily intake adherence (excluding therapy-free interval) ≥90%. The proportion of patients who showed a daily intake adherence ≥90% was lower compared to the proportion of patients who showed a daily total adherence ≥90%. This suggests that adherence is lower during intake than rest periods.

Figure 4-9 shows intra-individual differences of daily total adherence between the end of study and baseline. Thus, initially adherent patients' daily total adherence at the end of study was mostly found to be as high as at baseline. Adherence variation of more than ±10% was observed in 3.4% (2/58) of initially adherent patients only, and variation of more than ±5% was observed in 10.3% (6/58) of patients. Two patients' adherence diminished by 37.9% and 33.3%. Reasons for this decrease were epistaxis and gum bleeding in one patient. Regarding the second patient,

only three days were observed in the second cycle. Two of three days were adherent, resulting in a daily total adherence of 66.7%.

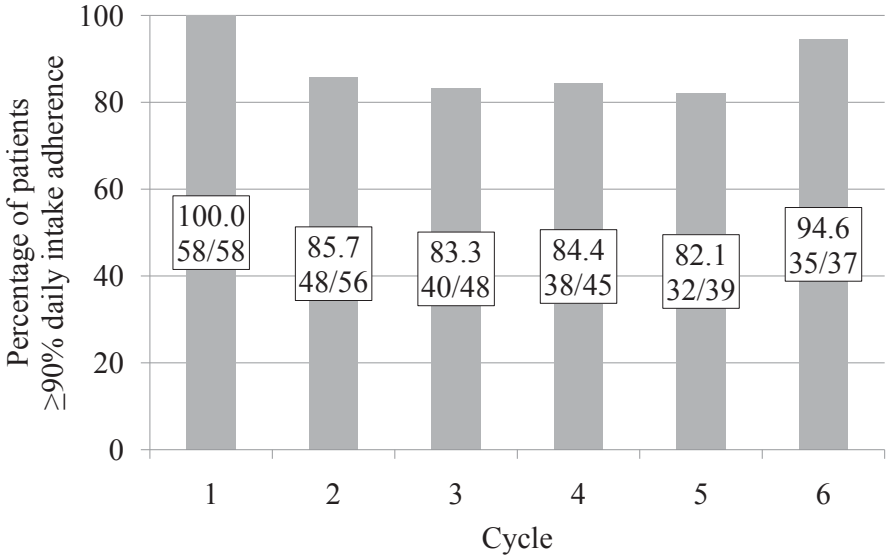



*Figure 4-8: Percentage of initially adherent patients exhibiting a daily intake adherence ≥90% during the intake periods of cycle 1 to 6; the numbers inside the boxes show the exact percentage (first row) and absolute patient numbers (second row)*

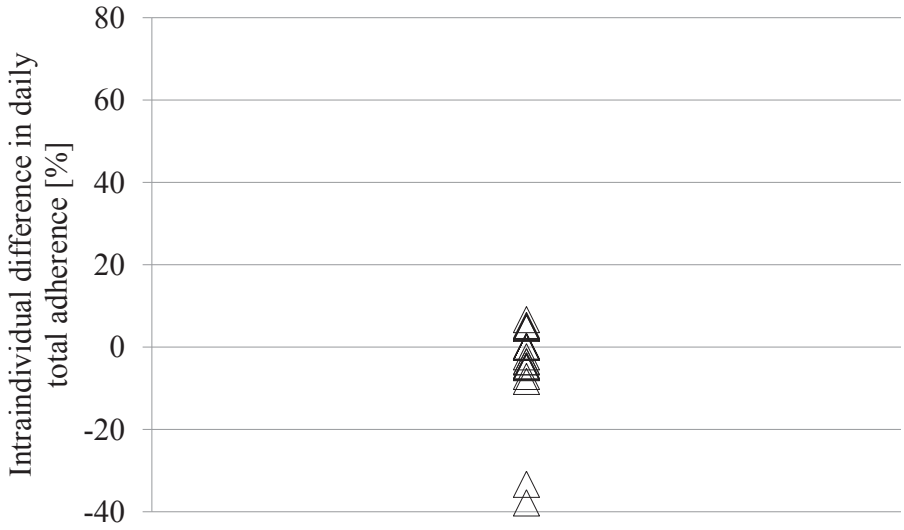



*Figure 4-9: Intra-individual difference in daily total adherence [%] between the last and first capecitabine cycle of initially adherent patients (n=58); every triangle represents one patient*

After classification as either adherent (≥90%) or non-adherent (<90%), adherence patterns by cycle revealed that 12.1% (7/58) of initially adherent patients were at least one cycle non-adherent, see Figure 4-10. Four of fifty-eight (6.9%) patients were non-adherent for one cycle and 3/58 (5.2%) patients for two cycles (either two subsequent cycles or two non-adherent cycles with one adherent cycle in between). Approximately half of all initially adherent patients were prescribed less than six capecitabine cycles (see 4.3.3).

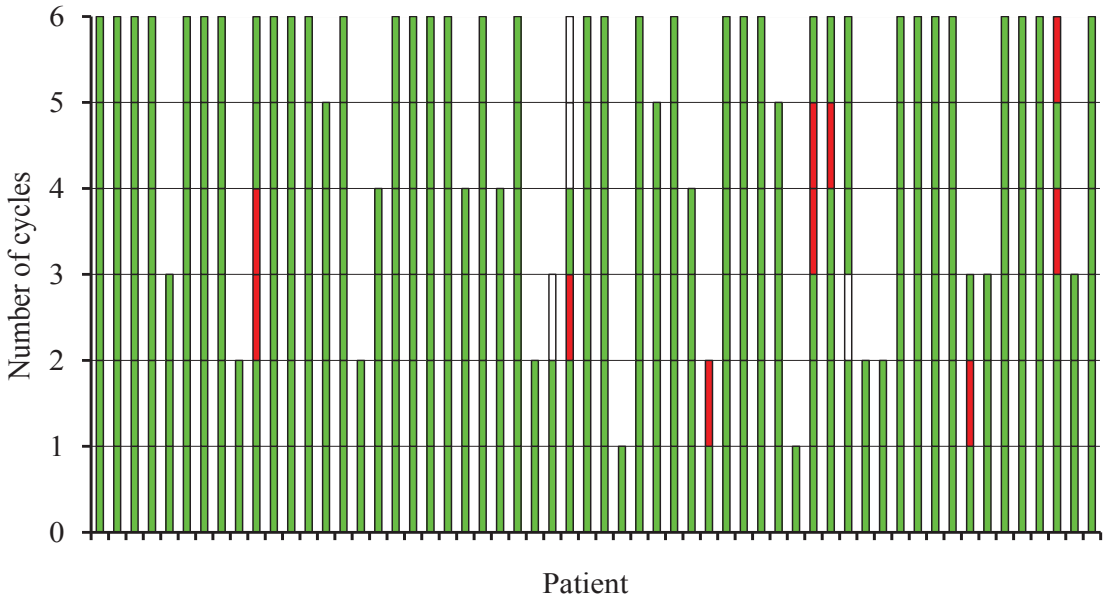



*Figure 4-10: Individual daily total adherence of initially adherent patients (n=58); green bars indicate adherent cycles (daily total adherence ≥90%), red bars non-adherent cycles (daily total adherence <90%) and white bars non-use of MEMS® by the patient during the respective cycle; non-complete bars imply treatment duration of less than six cycles, for information on reasons for shortened prescription of capecitabine see 4.3.3*

**Influence of gender**

Daily total adherence was analysed separately in terms of female and male initially adherent participants. No statistical significant difference was observed between genders. Table 4-4 summarises the respective results. Median daily total adherence of female and male patients was 100.0% throughout all cycles. Mean daily total adherence of female patients ranged from 96.2% to 98.8% and of male patients from 95.0% to 99.3%. In both genders the highest value was observed during the first completed capecitabine cycle.

**Influence of tumour entity**

There were no statistically significant differences concerning daily total adherence at $t_1$, $t_2$, $t_3$, $t_4$, $t_5$, and $t_6$ between breast cancer, colorectal cancer, and other cancer subgroups. Median daily total adherence of the three mentioned subgroups at all six time points was 100.0% (Table 4-5).

**Influence of therapy regimen**

Between the two patient subgroups who were treated with capecitabine as single agent or with a combination of capecitabine and one or more further anti-cancer agents no statistically significant difference was found concerning daily total adherence at the first five time points. During cycle 6, mean daily total adherence of patients treated with capecitabine as monotherapy was 99.2% and the median accounted for 100.0%. Mean daily total adherence of patients who received combination anti-cancer treatment was 95.2% and the median was 98.2%. The results differed statistically significant between the two subgroups (p value=0.023, Mann-Whitney-U test). Table 4-6 summarises the findings.

**Influence of treatment intention**

Daily total adherence was analysed in terms of differences between patients who were treated with curative or palliative intention. Between these two subgroups no statistically significant differences were observed. Mean and median daily total adherence was high during the whole course of the study. For details see Table 4-7.

*Table 4-4: Daily total adherence [%] of initially adherent female and male patients during the course of the study*

| | | Female | Male | p value* |
|---|---|---|---|---|
| $t_1$ | n | 44 | 14 | 0.411 |
| | Mean | 98.8 | 99.3 | |
| | Median | 100.0 | 100.0 | |
| | SD | 2.1 | 1.9 | |
| | IQR | 97.7-100.0 | 100.0-100.0 | |
| | Range | 94.7-100.0 | 93.3-100.0 | |
| $t_2$ | n | 42 | 14 | 0.244 |
| | Mean | 98.1 | 95.0 | |
| | Median | 100.0 | 100.0 | |
| | SD | 3.3 | 9.2 | |
| | IQR | 95.2-100.0 | 95.0-100.0 | |
| | Range | 90.5-100.0 | 66.7-100.0 | |
| $t_3$ | n | 35 | 13 | 0.611 |
| | Mean | 96.9 | 97.9 | |
| | Median | 100.0 | 100.0 | |
| | SD | 5.3 | 3.6 | |
| | IQR | 95.2-100.0 | 95.2-100.0 | |
| | Range | 75.0-100.0 | 90.9-100.0 | |
| $t_4$ | n | 34 | 11 | 0.378 |
| | Mean | 96.2 | 98.3 | |
| | Median | 100.0 | 100.0 | |
| | SD | 7.0 | 3.2 | |
| | IQR | 95.2-100.0 | 95.5-100.0 | |
| | Range | 68.8-100.0 | 90.5-100.0 | |
| $t_5$ | n | 31 | 9 | 0.298 |
| | Mean | 97.6 | 96.8 | |
| | Median | 100.0 | 100.0 | |
| | SD | 4.9 | 4.2 | |
| | IQR | 95.2-100.0 | 95.0-100.0 | |
| | Range | 80.0-100.0 | 90.5-100.0 | |
| $t_6$ | n | 29 | 8 | 0.912 |
| | Mean | 97.0 | 98.3 | |
| | Median | 100.0 | 100.0 | |
| | SD | 8.1 | 2.3 | |
| | IQR | 95.2-100.0 | 95.8-100.0 | |
| | Range | 57.1-100.0 | 95.0-100.0 | |

** Mann-Whitney-U test*

*Table 4-5: Daily total adherence [%] of initially adherent patients with breast cancer, colorectal cancer and other cancer entities[1] during the course of the study (n=58)*

| | | Breast cancer | Colorectal cancer | Other[1] | p value* |
|---|---|---|---|---|---|
| $t_1$ | n | 21 | 25 | 12 | 0.242 |
| | Mean | 98.4 | 99.1 | 99.4 | |
| | Median | 100.0 | 100.0 | 100.0 | |
| | SD | 2.4 | 1.9 | 1.9 | |
| | IQR | 95.2-100.0 | 100.0-100.0 | 100.0-100.0 | |
| | Range | 94.7-100.0 | 95.0-100.0 | 93.3-100.0 | |
| $t_2$ | n | 21 | 25 | 10 | 0.304 |
| | Mean | 98.6 | 96.2 | 97.3 | |
| | Median | 100.0 | 100.0 | 100.0 | |
| | SD | 3.1 | 7.3 | 4.0 | |
| | IQR | 100.0-100.0 | 95.2-100.0 | 95.4-100.0 | |
| | Range | 90.5-100.0 | 66.7-100.0 | 90.5-100.0 | |
| $t_3$ | n | 19 | 23 | 6 | 0.617 |
| | Mean | 97.8 | 96.5 | 97.6 | |
| | Median | 100.0 | 100.0 | 100.0 | |
| | SD | 3.2 | 5.8 | 5.8 | |
| | IQR | 95.2-100.0 | 95.2-100.0 | 100.0-100.0 | |
| | Range | 90.5-100.0 | 75.0-100.0 | 85.7-100.0 | |
| $t_4$ | n | 18 | 22 | 5 | 0.513 |
| | Mean | 95.1 | 97.4 | 99.1 | |
| | Median | 100.0 | 100.0 | 100.0 | |
| | SD | 8.8 | 4.1 | 2.1 | |
| | IQR | 95.2-100.0 | 95.2-100.0 | 100.0-100.0 | |
| | Range | 68.8-100.0 | 89.3-100.0 | 95.2-100.0 | |
| $t_5$ | n | 17 | 20 | 3 | 0.327 |
| | Mean | 96.2 | 98.1 | 100.0 | |
| | Median | 100.0 | 100.0 | 100.0 | |
| | SD | 5.9 | 3.6 | 0.0 | |
| | IQR | 95.2-100.0 | 97.5-100.0 | 100.0-100.0 | |
| | Range | 80.0-100.0 | 90.5-100.0 | 100.0-100.0 | |
| $t_6$ | n | 16 | 19 | 2 | 0.514 |
| | Mean | 95.5 | 98.4 | 100.0 | |
| | Median | 100.0 | 100.0 | 100.0 | |
| | SD | 10.6 | 2.6 | 0.0 | |
| | IQR | 95.2-100.0 | 96.4-100.0 | 100.0-100.0 | |
| | Range | 57.1-100.0 | 91.7-100.0 | 100.0-100.0 | |

** Kruskal-Wallis-H test*

*[1]Other cancer entities: gastric, oesophageal, ovarian, pancreatic, endometrial cancer and cancer of unknown primary*

*Table 4-6: Daily total adherence [%] of initially adherent patients who received capecitabine as single agent or in combination during the course of the study (n=58)*

| | | Single agent | Combination | p value* |
|---|---|---|---|---|
| $t_1$ | n | 35 | 23 | 0.257 |
| | Mean | 99.1 | 98.6 | |
| | Median | 100.0 | 100.0 | |
| | SD | 2.0 | 2.2 | |
| | IQR | 100.0-100.0 | 95.2-100.0 | |
| | Range | 93.3-100.0 | 95.0-100.0 | |
| $t_2$ | n | 33 | 23 | 0.520 |
| | Mean | 96.9 | 97.9 | |
| | Median | 100.0 | 100.0 | |
| | SD | 6.4 | 4.0 | |
| | IQR | 95.2-100.0 | 95.2-100.0 | |
| | Range | 66.7-100.0 | 85.7-100.0 | |
| $t_3$ | n | 27 | 21 | 0.755 |
| | Mean | 97.3 | 97.0 | |
| | Median | 100.0 | 100.0 | |
| | SD | 3.9 | 5.9 | |
| | IQR | 95.2-100.0 | 95.2-100.0 | |
| | Range | 85.7-100.0 | 75.0-100.0 | |
| $t_4$ | n | 25 | 20 | 0.384 |
| | Mean | 97.9 | 95.1 | |
| | Median | 100.0 | 100.0 | |
| | SD | 3.4 | 8.6 | |
| | IQR | 95.2-100.0 | 93.6-100.0 | |
| | Range | 90.5-100.0 | 68.8-100.0 | |
| $t_5$ | n | 21 | 19 | 0.375 |
| | Mean | 98.0 | 96.8 | |
| | Median | 100.0 | 100.0 | |
| | SD | 4.1 | 5.3 | |
| | IQR | 100.0-100.0 | 95.0-100.0 | |
| | Range | 86.4-100.0 | 80.0-100.0 | |
| $t_6$ | n | 19 | 18 | 0.023 |
| | Mean | 99.2 | 95.2 | |
| | Median | 100.0 | 98.2 | |
| | SD | 2.0 | 9.9 | |
| | IQR | 100.0-100.0 | 95.2-100.0 | |
| | Range | 92.9-100.0 | 57.1-100.0 | |

** Mann-Whitney-U test*

*Table 4-7: Daily total adherence [%] of initially adherent patients who received capecitabine with a curative or palliative treatment intention during the course of the study (n=58)*

| | | Curative intention | Palliative intention | p value* |
|---|---|---|---|---|
| $t_1$ | n | 8 | 50 | 0.988 |
| | Mean | 98.8 | 98.9 | |
| | Median | 100.0 | 100.0 | |
| | SD | 2.2 | 2.1 | |
| | IQR | 97.7-100.0 | 100.0-100.0 | |
| | Range | 95.2-100.0 | 93.3-100.0 | |
| $t_2$ | n | 8 | 48 | 0.336 |
| | Mean | 97.0 | 97.3 | |
| | Median | 97.6 | 100.0 | |
| | SD | 3.5 | 5.8 | |
| | IQR | 95.2-100.0 | 95.3-100.0 | |
| | Range | 90.5-100.0 | 66.7-100.0 | |
| $t_3$ | n | 8 | 40 | 0.472 |
| | Mean | 97.0 | 97.2 | |
| | Median | 97.6 | 100.0 | |
| | SD | 3.5 | 5.1 | |
| | IQR | 95.2-100.0 | 95.2-100.0 | |
| | Range | 90.5-100.0 | 75.0-100.0 | |
| $t_4$ | n | 7 | 38 | 0.673 |
| | Mean | 98.0 | 96.4 | |
| | Median | 100.0 | 100.0 | |
| | SD | 3.7 | 6.7 | |
| | IQR | 95.2-100.0 | 95.2-100.0 | |
| | Range | 90.5-100.0 | 68.8-100.0 | |
| $t_5$ | n | 6 | 34 | 0.092 |
| | Mean | 100.0 | 97.0 | |
| | Median | 100.0 | 100.0 | |
| | SD | 0.0 | 4.9 | |
| | IQR | 100.0-100.0 | 95.0-100.0 | |
| | Range | 100.0-100.0 | 80.0-100.0 | |
| $t_6$ | n | 5 | 32 | 0.108 |
| | Mean | 100.0 | 96.8 | |
| | Median | 100.0 | 100.0 | |
| | SD | 0.0 | 7.7 | |
| | IQR | 100.0-100.0 | 95.2-100.0 | |
| | Range | 100.0-100.0 | 57.1-100.0 | |

** Mann-Whitney-U test*

**MEMS®- versus self-assessed adherence**

Patient self-assessment in terms of adherence was compared with MEMS®-assessed daily intake adherence. Figure 4-11 illustrates a high daily intake adherence of initially adherent patients throughout the whole study period, more than 80.0% of the patients showed adherence values of >85.7% in each cycle. However, adherence self-assessment was found to be even higher, see Figure 4-12. Almost 100.0% of the studied patients stated that their daily intake adherence accounted for >85.7% during all observed capecitabine cycles.

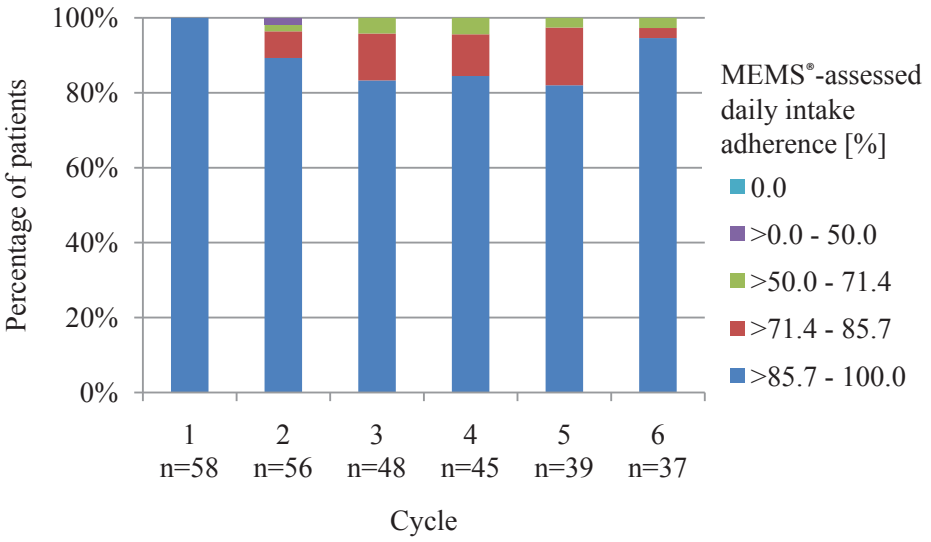



*Figure 4-11: Percentage of initially adherent patients within MEMS®-assessed daily intake adherence ranges during the course of the study*

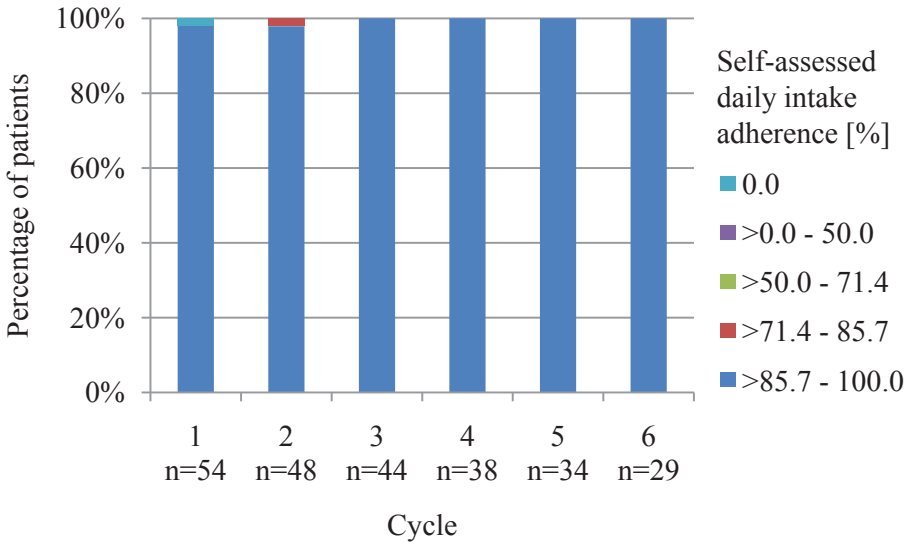



*Figure 4-12: Percentage of initially adherent patients within self-assessed daily intake adherence ranges during the course of the study*

Table 4-8 shows the comparison of MEMS®- versus self-assessed adherence concerning the whole capecitabine treatment period assessed after the sixth cycle (or after an earlier cycle in case of premature discontinuation of treatment). In the cohort of initially adherent patients, mean self-assessed total adherence was 97.9% and median was 100.0%. Mean MEMS®-assessed daily adherence during the whole observation period accounted for 97.7% and the median was 98.4%. Thus, self-assessment came relatively close to a more objective method of measurement. No statistically significant difference was observed (p value=0.353, Wilcoxon test).

*Table 4-8: MEMS®-assessed [%] versus self-assessed adherence [%] during the **whole** study period (cycle 1 to 6) assessed at $t_6$ in initially adherent patients*

| | **MEMS®-assessed daily adherence [%]** | **Self-assessed total adherence [%]** | **p value*** |
|---|---|---|---|
| n | 58 | 38 | 0.353 |
| Mean | 97.7 | 97.9 | |
| Median | 98.4 | 100.0 | |
| SD | 2.8 | 5.4 | |
| IQR | 96.5-100.0 | 100.0-100.0 | |
| Range | 85.7-100.0 | 75.0-100.0 | |

** Wilcoxon test*

### 4.3.2 Overall adherence

Overall adherence of initially adherent patients under modular medication management was high throughout the complete observation period (see Figure 4-13). Variability of overall adherence was found to be minor. Median overall adherence was 100.0% in each cycle, mean overall adherence ranged from 98.2% to 100.5%. The extreme value in cycle 3 accounted for 153.6%. This patient took capecitabine for three weeks (seven-day treatment break followed) instead of two weeks. More detailed information regarding mean, median, standard deviation, range, and interquartile range of overall adherence during individual cycles is summarised in Appendix D, Table D-4.

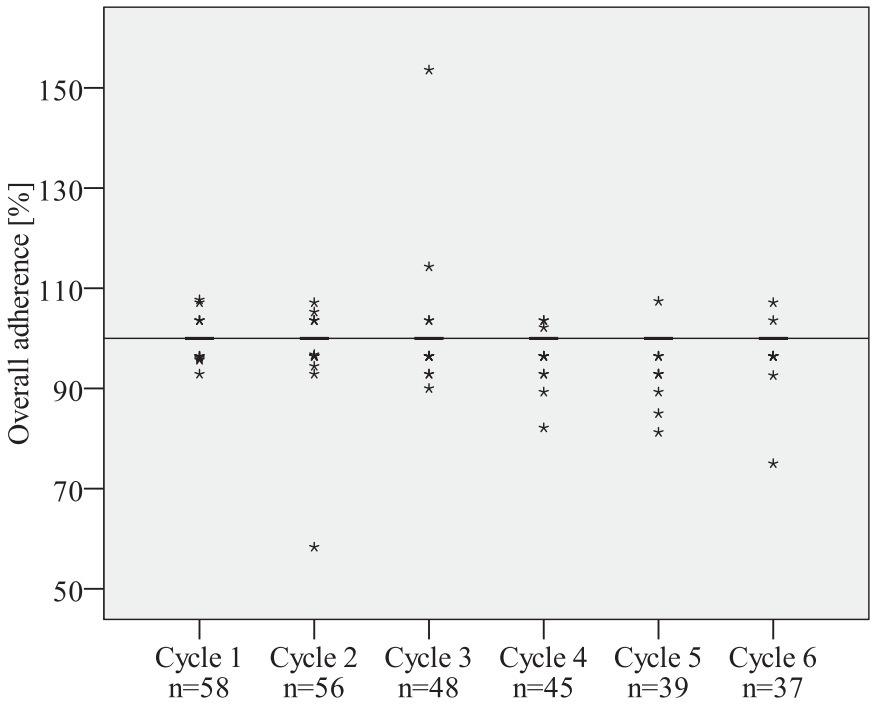



*Figure 4-13: Overall adherence [%] of initially adherent patients during cycle 1 to 6*

### 4.3.3 Persistence

All initially adherent patients were persistent during the whole period of capecitabine prescription. No patient performed an unauthorised discontinuation of his capecitabine treatment.

However, in 17 of 58 initially adherent patients capecitabine therapy was discontinued prematurely by their physicians. In 12 patients this decision was taken due to tumour progression (one patient had to stop treatment on day three of the sixth cycle due to progression, so data for the sixth cycle were available for analysis). Five patients discontinued therapy because of adverse drug reactions (hand-foot syndrome and haemolytic anaemia), hospital admission, the toxicity of a co-administered drug, and the patient's wish to stop treatment. The chronological sequence of treatment discontinuations is illustrated in Figure 4-14. Short vertical lines indicate censored patient data (patients who were not advised to discontinue treatment prematurely by their physician). Thirty-six patients completed six cycles as planned, two patients completed less than six capecitabine cycles as planned, one patient died after the completion of the third cycle, and two patients quit their study participation during the second cycle.

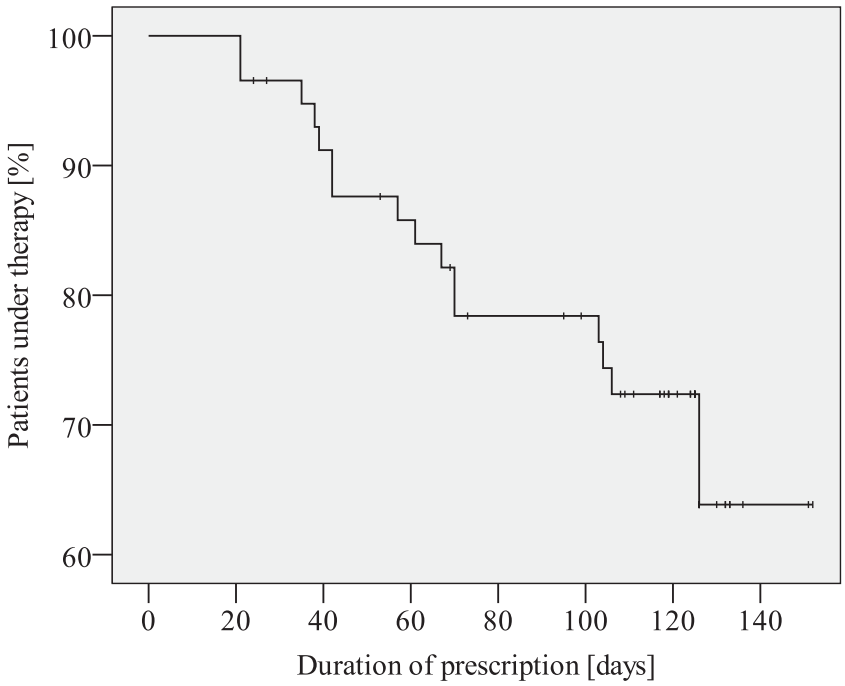



*Figure 4-14: Duration of capecitabine prescription [days] for initially adherent patient, n=58; short vertical lines indicate censored patient data*

### 4.3.4 Dosing intervals

Capecitabine tablets should be taken in the morning and in the evening with a dosing interval of twelve hours. In the cohort of initially adherent patients, 7064 dosing intervals were recorded by the MEMS® monitors during the observation period and the median dosing interval was 11:59 hours. A detailed overview of the results of the interval analysis is shown in Table 4-9. For the analysis of dosing intervals, intervals ≥24 hours were not considered.

*Table 4-9: Dosing intervals [hours] <24 hours recorded by MEMS® in initially adherent patients (n=58)*

| | **Dosing intervals [hours]** |
|---|---|
| n | 7064 |
| Mean | 11:59 |
| Median | 11:59 |
| SD | 2:13 |
| IQR | 10:51-13:04 |
| Range | 0:15-23:57 |

Table 4-10 shows classified dosing intervals. For this consideration, a threshold of 12±2 hours was defined within which a dosing interval was regarded as adherent. The majority of the

registered dosing intervals was within this range (71.5%). Proportions of the dosing intervals <10 hours and >14 hours were lower and approximately equivalent (14.7% and 13.9%).

*Table 4-10: Classified dosing intervals <24 hours recorded by MEMS® in initially adherent patients (n=58)*

| | **Number of dosing intervals** | **Proportion [%]** |
|---|---|---|
| <10 hours | 1037 | 14.7 |
| 10-14 hours | 5048 | 71.5 |
| >14 hours | 979 | 13.9 |
| Total | 7064 | 100.0 |

Dosing intervals in initially adherent patients are shown as a histogram in Figure 4-15. The main peak of the twice daily capecitabine regimen was located at twelve hours representing 17.3% (1,219/7064) of all registered dosing intervals in initially adherent patients.

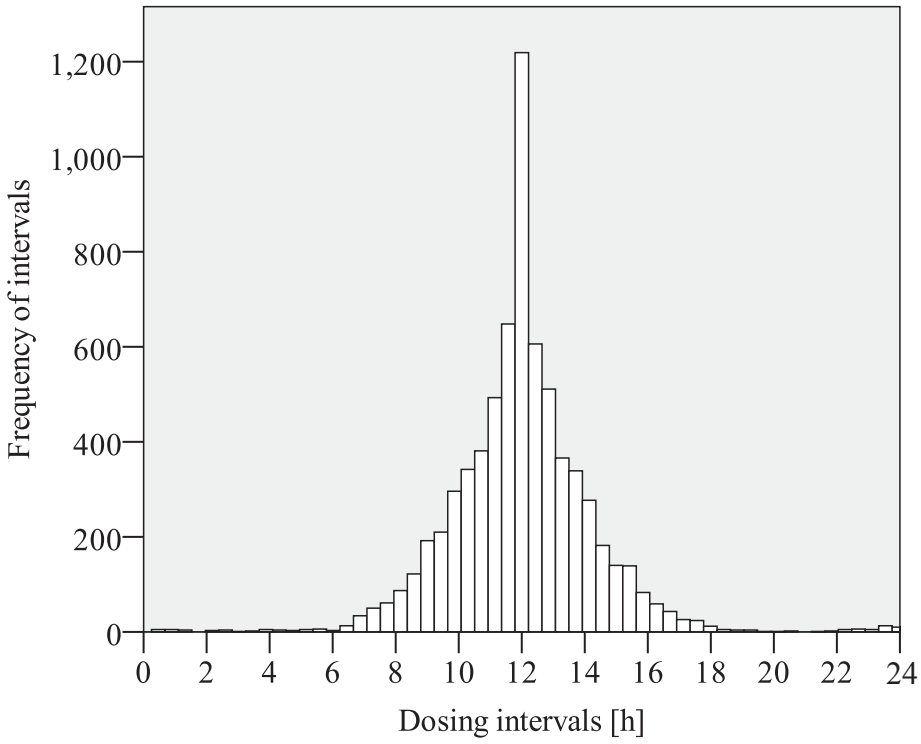



*Figure 4-15: Frequency of dosing intervals in initially adherent patients*

### 4.3.5 Quality of life

**EORTC QLQ-C30 questionnaire**

High scores in functional scales of the EORTC QLQ-C30 questionnaire represent a better functioning in that category. In this study, no noticeable differences were observed in terms of physical, role, emotional, cognitive and social functioning during the course of the study. Compared to the reference values of the QLQ-C30 scoring manual [114], no distinctive divergence was found either. For details see Table 4-11. Reference values can be accessed in Appendix D, Table D-5.

Table 4-11: *EORTC QLQ-C30 (modified version 3.0) functional scales at $t_0$, $t_3$ and $t_6$ in initially adherent patients (n=58)*

| QLQ-C30 dimension | | n | Mean | SD | Median | IQR |
|---|---|---|---|---|---|---|
| Physical functioning (PF2) | $t_0$ | 50 | 65.9 | 25.5 | 73.3 | 53.3-86.7 |
| | $t_3$ | 41 | 69.1 | 19.7 | 73.3 | 53.3-86.7 |
| | $t_6$ | 33 | 72.5 | 23.6 | 73.3 | 53.3-93.3 |
| Role functioning (RF2) | $t_0$ | 49 | 55.4 | 36.1 | 66.7 | 16.7-83.3 |
| | $t_3$ | 41 | 58.1 | 33.8 | 66.7 | 33.3-100.0 |
| | $t_6$ | 33 | 56.1 | 34.8 | 66.7 | 33.3-83.3 |
| Emotional functioning (EF) | $t_0$ | 50 | 64.4 | 23.9 | 66.7 | 41.7-83.3 |
| | $t_3$ | 41 | 77.2 | 22.3 | 83.3 | 66.7-100.0 |
| | $t_6$ | 32 | 71.6 | 24.3 | 75.0 | 54.2-91.7 |
| Cognitive functioning (CF) | $t_0$ | 50 | 82.7 | 27.1 | 100.0 | 66.7-100.0 |
| | $t_3$ | 41 | 80.9 | 22.8 | 83.3 | 66.7-100.0 |
| | $t_6$ | 32 | 77.1 | 28.9 | 83.3 | 66.7-100.0 |
| Social functioning (SF) | $t_0$ | 50 | 63.7 | 35.1 | 66.7 | 33.3-100.0 |
| | $t_3$ | 41 | 71.1 | 29.8 | 83.3 | 66.7-100.0 |
| | $t_6$ | 32 | 75.0 | 28.7 | 83.3 | 66.7-100.0 |

High scores in a symptom scale of the EORTC QLQ-C30 questionnaire stand for stronger symptoms of the patient in that category. Initially adherent patients had the same median values of symptom scales at $t_0$ as the reference values of the QLQ-C30 scoring manual [114], apart from slightly worse fatigue and dyspnoea (Table 4-12). Median values of symptom scales did not vary during the course of the study, apart from worse pain at $t_6$, worse hand-foot syndrome at $t_3$ and $t_6$, and improved dyspnoea at $t_6$. High scores in global health status represent better quality of life. The global health status was slightly worse than the reference at $t_0$ and $t_3$ and increased to the level of reference at $t_6$ (Table 4-12). Details on the reference values see Appendix D, Table D-5.

*Table 4-12: EORTC QLQ-C30 (modified version 3.0) symptom scales and global health status at $t_0$, $t_3$ and $t_6$ in initially adherent patients (n=58)*

| QLQ-C30 dimension/QoL | | n | Mean | SD | Median | IQR |
|---|---|---|---|---|---|---|
| Fatigue (FA) | $t_0$ | 50 | 48.9 | 27.7 | 44.4 | 33.3-66.7 |
| | $t_3$ | 41 | 48.0 | 28.5 | 44.4 | 22.2-66.7 |
| | $t_6$ | 33 | 47.5 | 30.3 | 44.4 | 22.2-66.7 |
| Nausea and Vomiting (NV) | $t_0$ | 50 | 7.7 | 14.0 | 0.0 | 0.0-16.7 |
| | $t_3$ | 41 | 11.8 | 21.2 | 0.0 | 0.0-16.7 |
| | $t_6$ | 32 | 5.7 | 11.7 | 0.0 | 0.0-0.0 |
| Pain (PA) | $t_0$ | 50 | 27.3 | 33.1 | 16.7 | 0.0-33.3 |
| | $t_3$ | 41 | 26.4 | 29.1 | 16.7 | 0.0-50.0 |
| | $t_6$ | 33 | 29.3 | 26.4 | 33.3 | 0.0-50.0 |
| Dyspnoea (DY) | $t_0$ | 50 | 35.3 | 35.3 | 33.3 | 0.0-66.7 |
| | $t_3$ | 41 | 30.9 | 32.0 | 33.3 | 0.0-33.3 |
| | $t_6$ | 33 | 26.3 | 32.0 | 0.0 | 0.0-33.3 |
| Insomnia (SL) | $t_0$ | 50 | 33.3 | 33.0 | 33.3 | 0.0-66.7 |
| | $t_3$ | 41 | 33.3 | 33.3 | 33.3 | 0.0-66.7 |
| | $t_6$ | 33 | 31.3 | 28.8 | 33.3 | 0.0-66.7 |
| Appetite loss (AP) | $t_0$ | 50 | 21.3 | 34.8 | 0.0 | 0.0-33.3 |
| | $t_3$ | 41 | 19.5 | 30.7 | 0.0 | 0.0-33.3 |
| | $t_6$ | 33 | 16.2 | 25.2 | 0.0 | 0.0-33.3 |
| Constipation (CO) | $t_0$ | 50 | 11.3 | 20.9 | 0.0 | 0.0-33.3 |
| | $t_3$ | 41 | 9.8 | 18.6 | 0.0 | 0.0-0.0 |
| | $t_6$ | 32 | 10.4 | 21.5 | 0.0 | 0.0-0.0 |
| Diarrhoea (DI) | $t_0$ | 49 | 19.0 | 31.2 | 0.0 | 0.0-33.3 |
| | $t_3$ | 40 | 18.3 | 33.7 | 0.0 | 0.0-33.3 |
| | $t_6$ | 32 | 15.6 | 26.8 | 0.0 | 0.0-33.3 |
| Financial difficulties (FI) | $t_0$ | 50 | 19.3 | 30.9 | 0.0 | 0.0-33.3 |
| | $t_3$ | 41 | 22.0 | 36.2 | 0.0 | 0.0-33.3 |
| | $t_6$ | 32 | 17.7 | 30.5 | 0.0 | 0.0-33.3 |
| Hand-foot syndrome (HFS) | $t_0$ | 50 | 21.3 | 34.8 | 0.0 | 0.0-66.7 |
| | $t_3$ | 41 | 53.7 | 37.9 | 66.7 | 33.3-100.0 |
| | $t_6$ | 32 | 58.3 | 34.9 | 66.7 | 33.3-100.0 |
| Global health status/ QoL (QL2) | $t_0$ | 50 | 53.5 | 22.8 | 50.0 | 41.7-66.7 |
| | $t_3$ | 40 | 59.2 | 21.1 | 58.3 | 45.8-79.2 |
| | $t_6$ | 33 | 64.1 | 19.8 | 66.7 | 50.0-75.0 |

**EQ-5D questionnaire**

Each of the five EQ-5D dimensions comprises three levels of perceived problems. Level 1 indicates **no problems**, level 2 is a sign of **some problems** and level 3 indicates **extreme problems**. The results of the descriptive system of the EQ-5D-3L questionnaire are shown in Table 4-13. Generally, the EQ-5D dimensions ‘mobility’ and ‘self-care’ were least impaired in

the cohort of initially adherent patients. Most patients reported problems regarding ‘usual activities’ and ‘pain/discomfort’. Regarding the dimensions ‘mobility’, ‘usual activities’, and ‘pain/discomfort’ the proportion of patients reporting no problems decreased during the course of the study, whereas it increased for the dimensions ‘self-care’ and ‘anxiety/depression’. Figure 4-16 visualises this by means of a bar chart and shows the proportion of patients reporting problems (level 2 plus level 3) concerning the five EQ-5D dimensions at the three different time points.

*Table 4-13: Proportion of patients [%] reporting level 1, 2 or 3 of the EQ-5D-3L descriptive system at $t_0$, $t_3$ and $t_6$ concerning the five EQ-5D dimensions*

| EQ-5D dimension | | n | Level 1 | Level 2 | Level 3 |
|---|---|---|---|---|---|
| Mobility | $t_0$ | 51 | 70.6 | 27.5 | 2.0 |
| | $t_3$ | 46 | 69.6 | 30.4 | 0.0 |
| | $t_6$ | 36 | 66.7 | 33.3 | 0.0 |
| Self-care | $t_0$ | 51 | 88.2 | 11.8 | 0.0 |
| | $t_3$ | 46 | 87.0 | 13.0 | 0.0 |
| | $t_6$ | 37 | 91.9 | 5.4 | 2.7 |
| Usual activities | $t_0$ | 51 | 54.9 | 37.3 | 7.8 |
| | $t_3$ | 46 | 58.7 | 34.8 | 6.5 |
| | $t_6$ | 37 | 43.2 | 56.8 | 0.0 |
| Pain/discomfort | $t_0$ | 51 | 45.1 | 49.0 | 5.9 |
| | $t_3$ | 46 | 45.7 | 54.3 | 0.0 |
| | $t_6$ | 37 | 35.1 | 64.9 | 0.0 |
| Anxiety/depression | $t_0$ | 51 | 54.9 | 43.1 | 2.0 |
| | $t_3$ | 46 | 67.4 | 32.6 | 0.0 |
| | $t_6$ | 37 | 75.7 | 24.3 | 0.0 |

The median of most EQ-5D dimensions was found to account for level 1. Regarding the dimensions ‘usual activities’ at $t_6$ and ‘pain/discomfort’ at all three time points, the median was on level 2. Mean, standard deviation, median and interquartile range of the EQ-5D dimensions at $t_0$, $t_3$ and $t_6$ for initially adherent patients are tabulated in Appendix D, Table D-6.

Interestingly, the mean EQ-5D visual analogue scale (VAS) value of initially adherent patients increased from 59.1 at $t_0$, to 62.8 at $t_3$ and to 67.5 at $t_6$ (see Table 4-14).

*Table 4-14: EQ-5D-3L VAS values at $t_0$, $t_3$, and $t_6$ (n=58)*

| | n | Mean | SD | Median | IQR |
|---|---|---|---|---|---|
| $t_0$ | 50 | 59.1 | 18.8 | 60.0 | 49.0-75.0 |
| $t_3$ | 46 | 62.8 | 17.8 | 60.0 | 50.0-80.0 |
| $t_6$ | 37 | 67.5 | 15.5 | 69.0 | 55.0-80.0 |

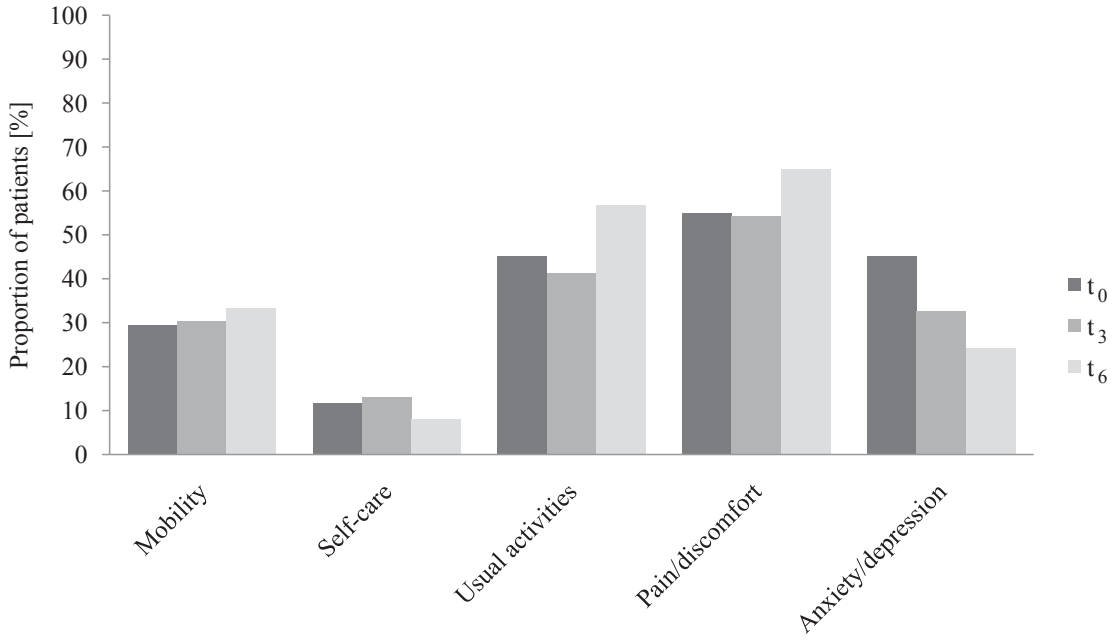



*Figure 4-16: Proportion of patients [%] reporting problems concerning the five EQ-5D dimensions (sum of proportion of patients reporting level 2 and 3)*

### 4.3.6 Patient satisfaction with information

Patient satisfaction with information of initially adherent patients was found to be high at $t_0$ and even increased during the course of the study for all PSCaTE dimensions. Patients could score strongly disagree (1), disagree (2), uncertain (3), agree (4), or strongly agree (5). The results are summarised in Table 4-15. Data shown in Table 4-15 are presented in Appendix D, Figures D-1, D-2 and D-3 additionally as boxplots.

*Table 4-15: Patient satisfaction with information of initially adherent patients at $t_0$, $t_3$ and $t_6$*

| PSCaTE dimension | | n | Mean | SD | Median | IQR |
|---|---|---|---|---|---|---|
| Satisfaction with information on cancer therapy (CT) | $t_0$ | 48 | 4.4 | 0.6 | 4.4 | 4.0-5.0 |
| | $t_3$ | 46 | 4.4 | 0.7 | 4.6 | 3.8-5.0 |
| | $t_6$ | 37 | 4.6 | 0.5 | 4.8 | 4.4-5.0 |
| Satisfaction with information on adverse effects (SE) | $t_0$ | 49 | 4.4 | 0.7 | 4.5 | 4.0-5.0 |
| | $t_3$ | 46 | 4.5 | 0.7 | 4.8 | 4.0-5.0 |
| | $t_6$ | 37 | 4.6 | 0.7 | 5.0 | 4.5-5.0 |
| Satisfaction with information on vitamins, herbal medicines and complementary treatment options (VC) | $t_0$ | 47 | 3.6 | 1.2 | 3.7 | 2.7-4.7 |
| | $t_3$ | 45 | 3.7 | 1.3 | 4.0 | 2.7-5.0 |
| | $t_6$ | 37 | 4.0 | 1.1 | 4.0 | 3.7-5.0 |
| Satisfaction with information sources (RS) | $t_0$ | 47 | 4.6 | 0.5 | 4.8 | 4.3-5.0 |
| | $t_3$ | 46 | 4.6 | 0.6 | 5.0 | 4.3-5.0 |
| | $t_6$ | 37 | 4.7 | 0.4 | 5.0 | 4.5-5.0 |
| Overall satisfaction (OV) | $t_0$ | 49 | 4.2 | 0.7 | 4.3 | 3.8-4.9 |
| | $t_3$ | 46 | 4.3 | 0.7 | 4.7 | 3.7-4.9 |
| | $t_6$ | 37 | 4.5 | 0.5 | 4.5 | 4.3-5.0 |

### 4.3.7 Hand-foot syndrome (HFS)

In the group of initially adherent patients the median severity grade of the adverse drug reaction HFS was zero at $t_1$ and $t_2$ and increased to 1 at $t_3$, $t_4$, $t_5$, and $t_6$. Figure 4-17 shows the results of the questionnaire on HFS as a boxplot.

Capecitabine treatment was temporarily discontinued in 39.7% (23/58) of initially adherent patients. The most common reasons for temporary capecitabine discontinuation were HFS (10/23, 43.5%) and hospital stays (5/23, 21.7%). Other reasons (8/23, 34.8%) were e.g. femur fracture, abdominal influenza or selective internal radiation therapy.

Figure 4-18 illustrates the cumulative proportion of initially adherent patients who had to reduce their capecitabine dose (22/58, 37.9%). The period between the first day of capecitabine treatment and the day of the physicians' decision to reduce the dose was assessed. Performed dose reductions were mostly due to HFS (19/22, 86.4%), the common adverse drug reaction of capecitabine. Three exceptions were observed; in one patient the dose was reduced due to diarrhea, in another patient due to gastric phlegmon, and in the third patient due to bone pain.

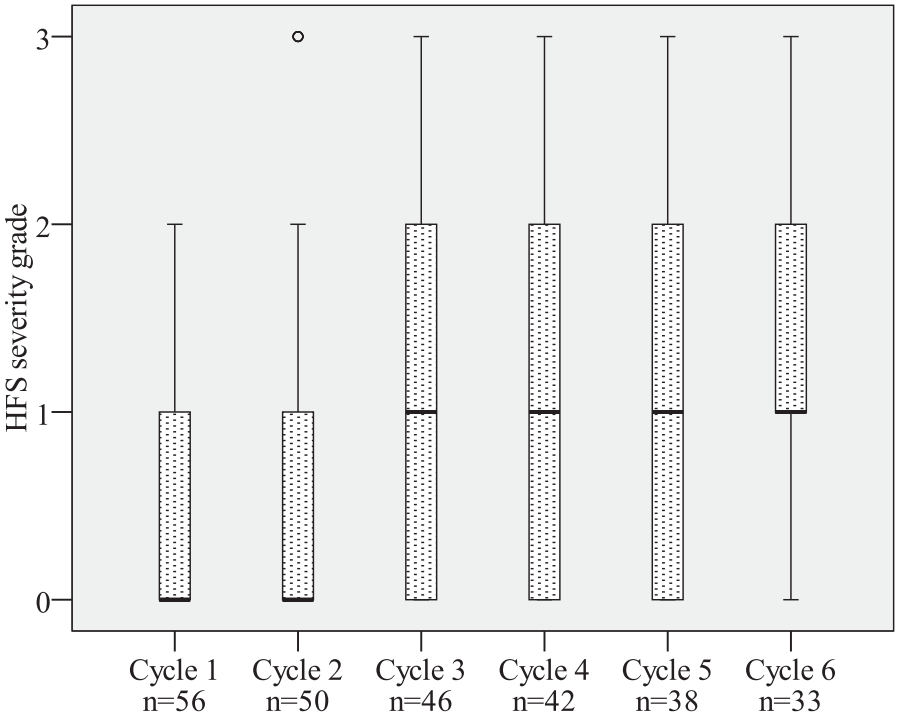



*Figure 4-17: HFS severity grades of initially adherent patients under treatment with capecitabine at $t_1$, $t_2$, $t_3$, $t_4$, $t_5$ and $t_6$*

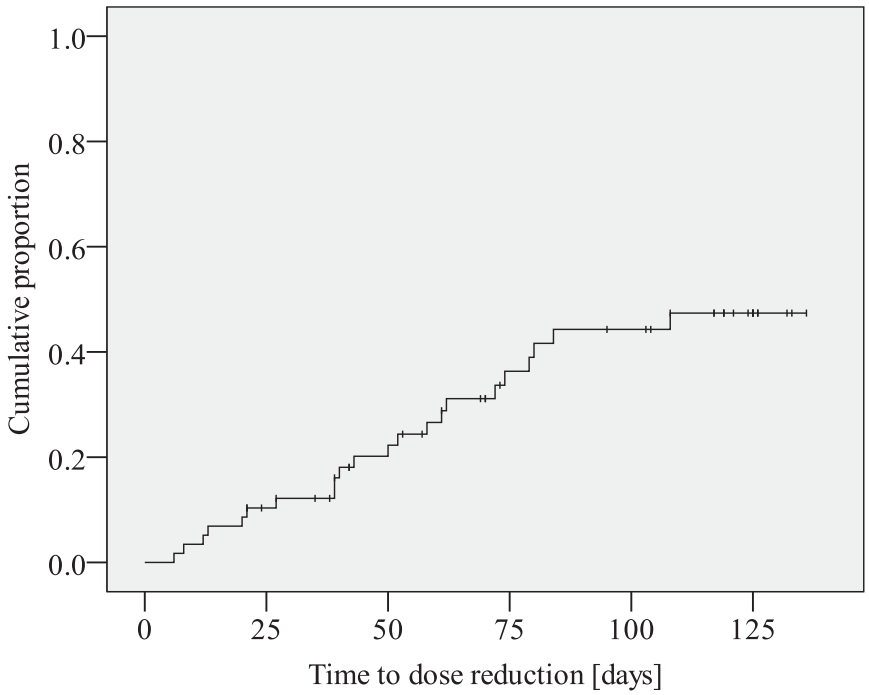



*Figure 4-18: Time to dose reduction [days] of capecitabine in initially adherent patients; vertical lines represent censored data*

### 4.3.8 Pharmacist's working time

Pharmacist's working time needed for the provision of modular medication management was documented regarding the duration of interviews and rework (see Table 4-16). The initial patient conversation differed from the follow-up patient interviews. This was because contents such as the course of the study, aims, outcome assessment, and time schedule were explained in detail. Basically, the first counselling session took place before the start of the patient's capecitabine therapy ($t_0$). If required, more than one interview was conducted. Nine patients had more than one conversation with the study pharmacist at that time point (seven patients had two, one patient had three and one patient had four conversations).

*Table 4-16: Duration and rework of the initial counselling conversation with initially adherent patients (n=58, 70 conversations)*

| | **Duration [min]** | **Rework [min]** |
|---|---|---|
| Mean | 29 | 8 |
| Median | 25 | 6 |
| SD | 16 | 9 |
| Range | 8-90 | 0-60 |
| IQR | 16-35 | 2-11 |

Conversations per patient ranged from 1.1 in cycle 3 to 1.6 in cycle 6, compare Table 4-17. Table 4-18 shows information on the duration and rework of patient interviews during the course of the modular medication management. Median duration of patient interviews ranged from 2 minutes during cycle 5 to 8 minutes during cycle 1 and 2.

*Table 4-17: Number of patient interviews during the course of the study*

| | **Cycle 1** | **Cycle 2** | **Cycle 3** | **Cycle 4** | **Cycle 5** | **Cycle 6** |
|---|---|---|---|---|---|---|
| n | 58 | 56 | 50 | 45 | 41 | 38 |
| Conversations | 88 | 75 | 56 | 61 | 44 | 62 |
| Conversations/patient | 1.5 | 1.3 | 1.1 | 1.4 | 1.1 | 1.6 |

*Table 4-18: Duration and rework of follow-up counselling conversations with initially adherent patients*

| | | Duration [min] | Rework [min] | | | Duration [min] | Rework [min] |
|---|---|---|---|---|---|---|---|
| $t_1$ | n | 58 | 58 | $t_4$ | n | 45 | 45 |
| | Mean | 12 | 4 | | Mean | 8 | 3 |
| | Median | 8 | 0 | | Median | 6 | 0 |
| | SD | 13 | 12 | | SD | 8 | 16 |
| | Range | 0-52 | 0-62 | | Range | 0-29 | 0-120 |
| | IQR | 3-17 | 0-1 | | IQR | 0-12 | 0-1 |
| $t_2$ | n | 56 | 56 | $t_5$ | n | 41 | 41 |
| | Mean | 12 | 3 | | Mean | 7 | 3 |
| | Median | 8 | 0 | | Median | 2 | 0 |
| | SD | 17 | 7 | | SD | 11 | 11 |
| | Range | 0-105 | 0-34 | | Range | 0-58 | 0-60 |
| | IQR | 4-13 | 0-2 | | IQR | 0-11 | 0-1 |
| $t_3$ | n | 50 | 50 | $t_6$ | n | 38 | 38 |
| | Mean | 7 | 1 | | Mean | 9 | 2 |
| | Median | 5 | 0 | | Median | 6 | 0 |
| | SD | 9 | 3 | | SD | 13 | 8 |
| | Range | 0-43 | 0-15 | | Range | 0-68 | 0-60 |
| | IQR | 0-7 | 0-1 | | IQR | 0-13 | 0-0 |

### 4.3.9 Patient evaluation

The questionnaire on patient evaluation asked patients for their assessment of the therapy outcome compared with their expectations, assessment of adverse drug reactions compared with their expectations, and their overall assessment regarding treatment. More than half of initially adherent patients evaluated the outcome of their capecitabine therapy as much better (10/39, 25.6%) and slightly better (10/39, 25.6%) than expected. Only 2/39 (5.1%) patients assessed therapy outcome as much worse than expected. The adverse drug reactions of capecitabine were evaluated even better. 13/39 (33.3%) patients stated that they perceived adverse drug reactions as much better than expected and 10/30 (25.6%) as slightly better. 2/39 (5.1%) found toxicity much worse than expected. Figure 4-19 visualises these results.

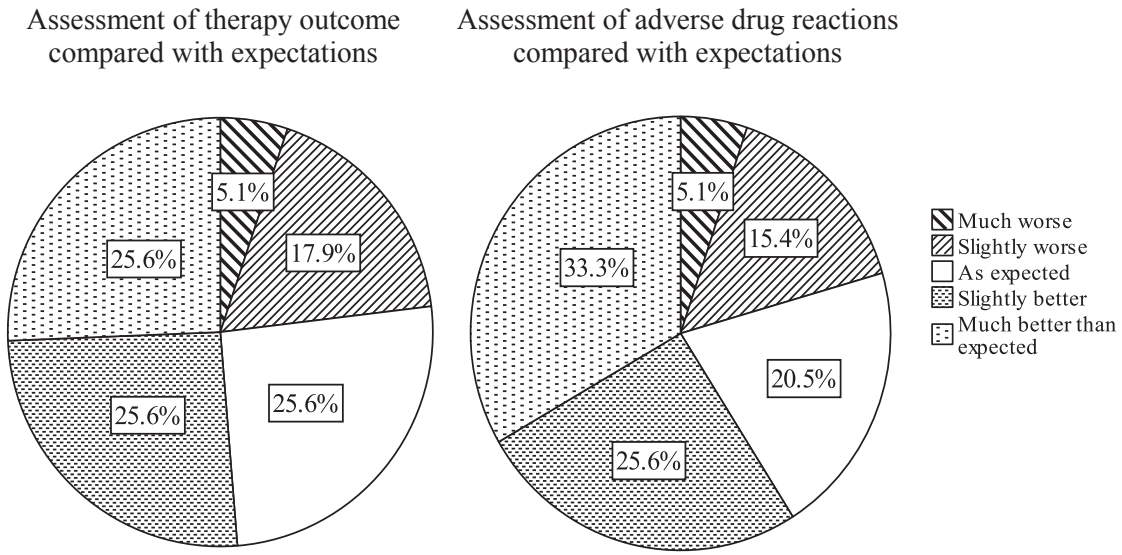



*Figure 4-19: Initially adherent patients' evaluation of two different aspects of the capecitabine treatment; assessed at $t_6$; n=39*

Overall, capecitabine treatment was rated as very good and excellent by 16 of 39 patients (41.0%), see Figure 4-20.

Tabulated results of the questionnaire on patient evaluation are presented in Appendix D, Table D-7.

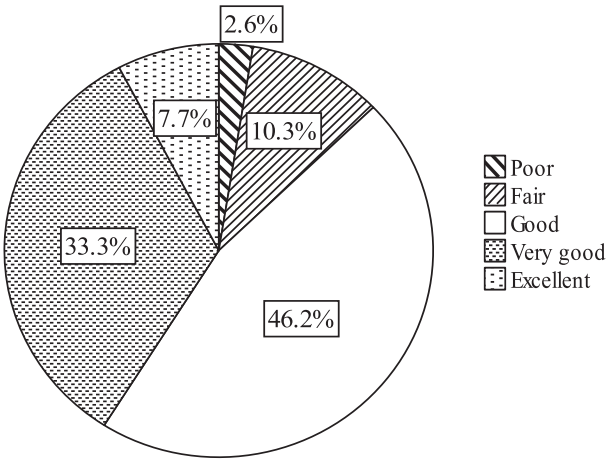



*Figure 4-20: Initially adherent patients' overall assessment of capecitabine treatment assessed at $t_6$; n=39*

## 4.4 Initially non-adherent patients

Initially non-adherent participants were observed for a median time of 118.0 days (mean 103.5 days; SD 32.1; range 35.0-140.0; IQR=96.0-126.0).

### 4.4.1 Adherence support

Various adherence-enhancing strategies were utilised by the application of module 3 (adherence support). Table 4-19 lists the different measures and the number of patients receiving these strategies. Treatment diaries (n=11) and patient education regarding treatment efficacy (n=7) were used most frequently.

*Table 4-19: Adherence-enhancing strategies applied in module 3 (n=15; more than one strategy could be applied to one patient)*

| Strategy | n |
|---|---|
| Entry in treatment diary | 11 |
| Patient education regarding importance of adherence | 7 |
| Reminder card | 4 |
| Link to daily activity | 2 |
| Information on process of drug supply | 1 |
| Reminder by mobile phone | 0 |

Figure 4-21 illustrates the number of adherence-enhancing strategies per patient. 1.7 strategies per patient were applied on average.

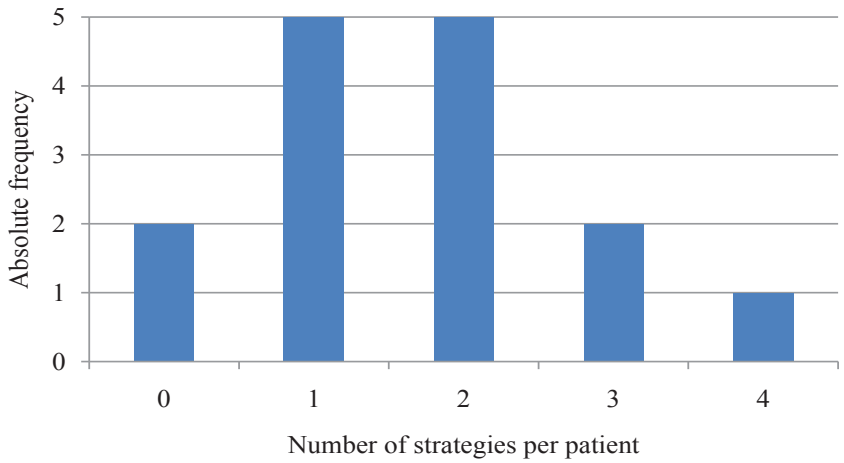



*Figure 4-21: Absolute frequency of the number of adherence-enhancing strategies applied to initially non-adherent patients*

Figure 4-22 shows the percentage of days with intentional, unintentional, or unknown non-adherence. In total, 155 non-adherent days were found in 15 initially non-adherent patients receiving adherence support. The study pharmacists assessed the type of non-adherence according to patients' statements during counselling sessions or patient documentation (e.g. in the treatment diary). However, it was not always possible to find a reason for non-adherence. Thus, not every non-adherent day could be classified as either intentionally or unintentionally non-adherent.

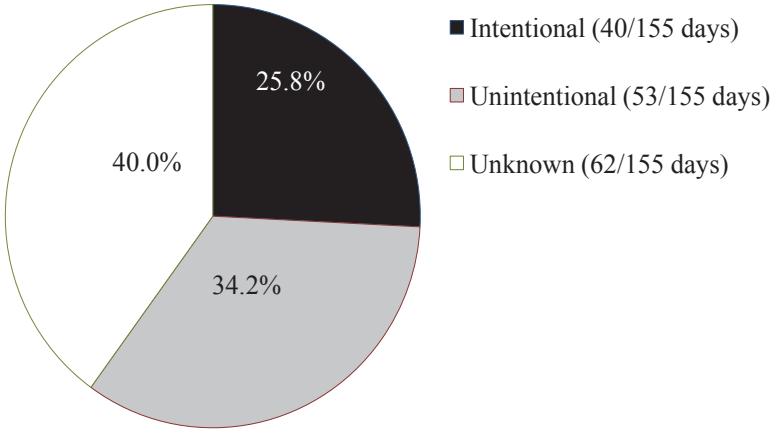



*Figure 4-22: Percentage of days with intentional, unintentional and unknown non-adherence in 15 patients*

Most common reasons for intentional non-adherence were nausea and emesis and averseness to medication. Further details are shown in Table 4-20. Most of unintentionally non-adherent days were due to miscellaneous errors. Non-performance of the seven-day treatment break, belated begins of the capecitabine intake period, and over-adherence are examples for non-adherence falling in this category. Further unintentional barriers to sufficient medication taking behaviour were forgetfulness and too short intake intervals. External circumstances were the reason for two unintentionally non-adherent days: one patient had a collapse that made it impossible for him to take capecitabine and another patient ordered capecitabine belatedly and the community pharmacy did not have it on stock.

*Table 4-20: Reasons for intentional and unintentional non-adherence observed in initially non-adherent patients (n=15)*

| | No. of days | No. of patients |
|---|---|---|
| **Reasons for intentional non-adherence** | | |
| Nausea and emesis | 17 | 1 |
| Averseness to medication | 17 | 2 |
| „Compensation“ for non-adherence in treatment break | 3 | 1 |
| Hand-foot syndrome | 1 | 1 |
| Constipation | 1 | 1 |
| Bad general condition | 1 | 1 |
| **Reasons for unintentional non-adherence** | | |
| Miscellaneous errors | 22 | 7 |
| Forgetfulness | 15 | 6 |
| Too short intake interval | 14 | 6 |
| External circumstances | 2 | 2 |

### 4.4.2 Daily adherence

Figure 4-23 compares median baseline daily adherence and median daily total adherence during cycle 1 of initially non-adherent patients. As discussed more explicitly later in this chapter, baseline daily adherence was found to be slightly lower than daily total adherence during cycle 1.

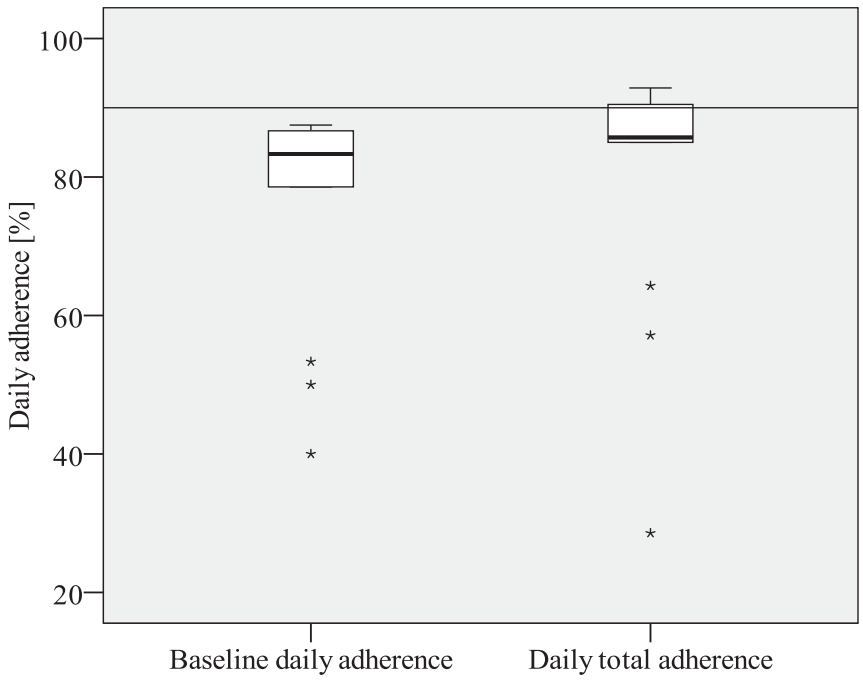



*Figure 4-23: Baseline daily adherence versus daily total adherence during cycle 1 of initially non-adherent patients (n=15)*

Figure 4-24 shows individual daily total adherence profiles of initially non-adherent patients during the course of the study calculated for intake plus rest period. Adherence varied widely between patients but also from cycle to cycle in the same patients. Reasons for non-adherence are discussed in chapter 4.4.1.

Three patients refused to receive modular medication management provided by the study pharmacists. Two patients expressed that they would not need any support and would get along with the situation themselves. These patients' daily total adherence accounted for >90% throughout all observed capecitabine cycles. A further patient stated that the comprehensive care of his daughter was sufficient and no further support was required. Daily total adherence was >90% during the observation period except in cycle 5 (85.7%).

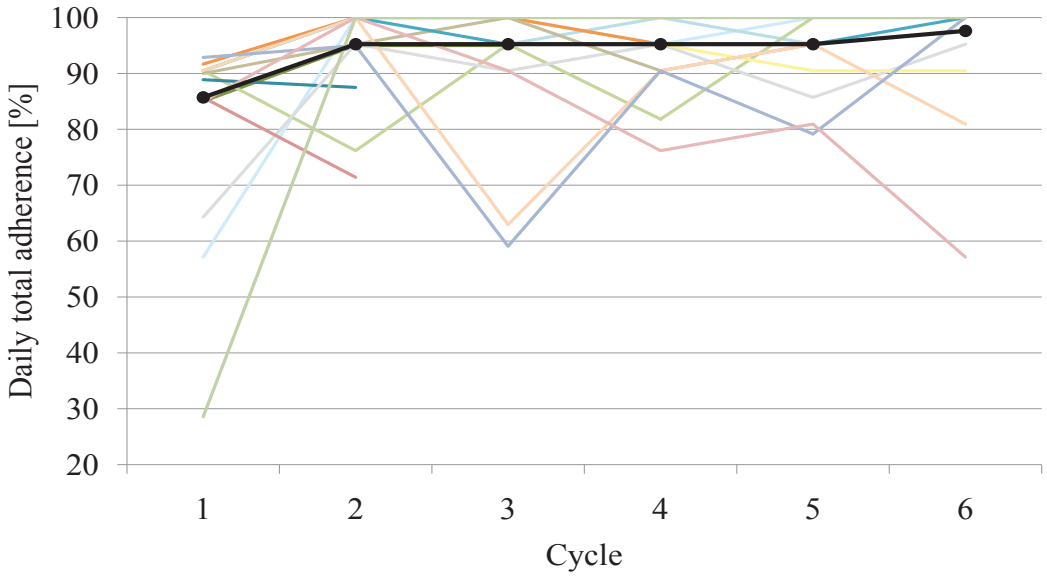



*Figure 4-24: Individual daily total adherence of initially non-adherent patients during the course of the study; cycle 1: n=15, cycle 2: n=15, cycle 3: n=13, cycle 4: n=12, cycle :5 n=12, cycle 6: n=8; the black line represents the median daily total adherence*

Average daily total adherence accounted for 80.8% during the first cycle and was found to be greater than 90% during the application of the adherence support module. Table 4-21 presents the according results.

*Table 4-21: Daily total adherence of initially non-adherent patients (calculation based on intake and rest period)*

| | n | Mean [%] | Median [%] | SD [%] | Range [%] | IQR [%] |
|---|---|---|---|---|---|---|
| Cycle 1 | 15 | 80.8 | 85.7 | 17.6 | 28.6-92.9 | 85.0-90.5 |
| Cycle 2 | 15 | 93.7 | 95.2 | 8.8 | 71.4-100.0 | 95.0-100.0 |
| Cycle 3 | 13 | 90.7 | 95.2 | 13.6 | 59.1-100.0 | 90.5-100.0 |
| Cycle 4 | 12 | 92.1 | 95.2 | 7.0 | 76.2-100.0 | 90.5-95.2 |
| Cycle 5 | 12 | 92.7 | 95.2 | 7.2 | 79.2-100.0 | 88.1-97.6 |
| Cycle 6 | 8 | 90.5 | 97.6 | 15.1 | 57.1-100.0 | 85.7-100.0 |

Median daily total adherence increased from 85.7% in cycle 1 to 97.6% in cycle 6, see Figure 4-25. Some patients exhibited outliers and extreme values during the different cycles. Reasons for non-adherence are discussed in chapter 4.4.1.

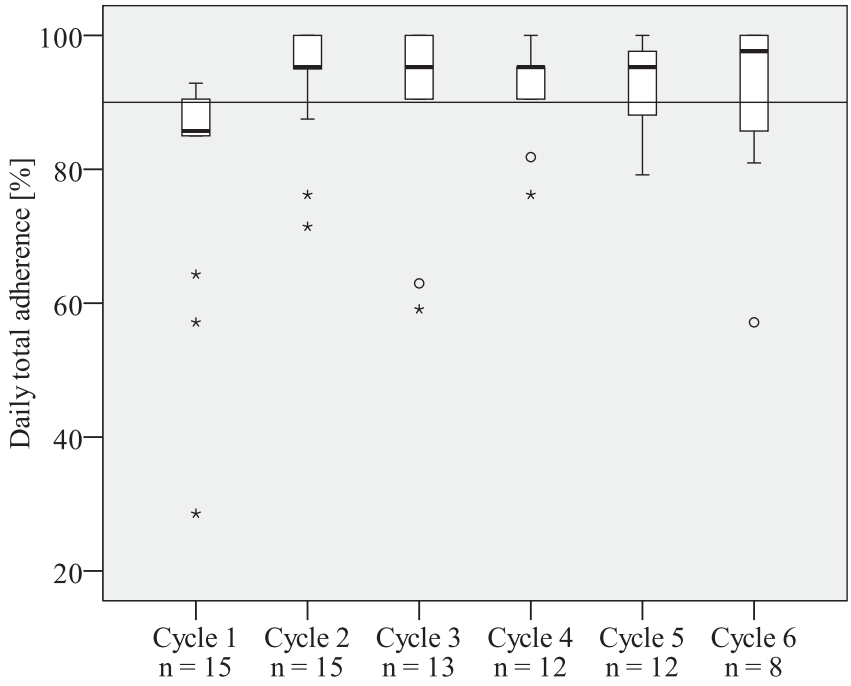



*Figure 4-25: Daily total adherence of initially non-adherent patients during cycle 1 to 6*

Considering daily intake adherence, variability is higher compared to daily total adherence, see Figure 4-26. However, the median of both adherence measures accounted for <90% during the first cycle and clearly increased over time. Only few outliers and extreme values can be observed. More detailed information on daily intake adherence can be found in Appendix E, Table E-1.

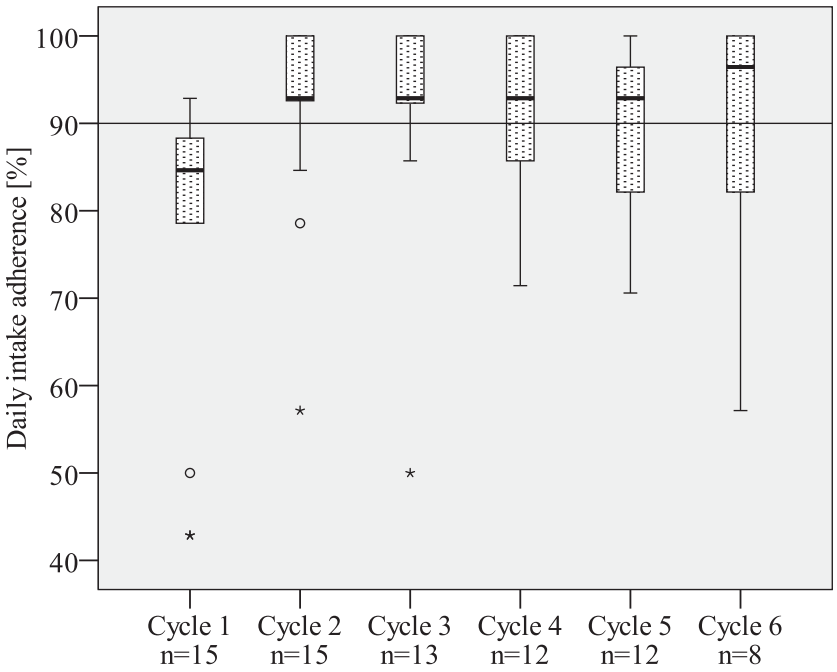



*Figure 4-26: Daily intake adherence [%] of initially non-adherent patients during cycle 1 to 6*

Median daily break adherence of initially non-adherent patients was higher than the median of all other adherence parameters, compare Figure 4-27. However, the interquartile range during cycle 1 and 4 was relatively large, 85.7% to 100.0% in both cycles. More detailed information on daily break adherence is tabulated in Appendix E, Table E-2.

Figure 4-28 illustrates the percentage of patients who showed a daily total adherence equal or greater than 90% during the different cycles. The results indicate a clear effect of adherence support. In cycle 2 the number of adherent patients was twice as high as in cycle 1 and remained more or less constant in the later cycles. After completion of the sixth cycle, daily total adherence of six out of eight (75.0%, CI 46.0%-91.3%) initially non-adherent patients accounted for ≥90%. Since the CI includes 80% which was the cut-off value used for sample size determination of initially non-adherent patients, it could not be confirmed in this study that >80% of initially non-adherent patients were adherent after the intervention. In Appendix E, Table E-3 the percentage of participants who showed a daily total adherence =100%, ≥90% and 80%, respectively, during the different cycles is illustrated.

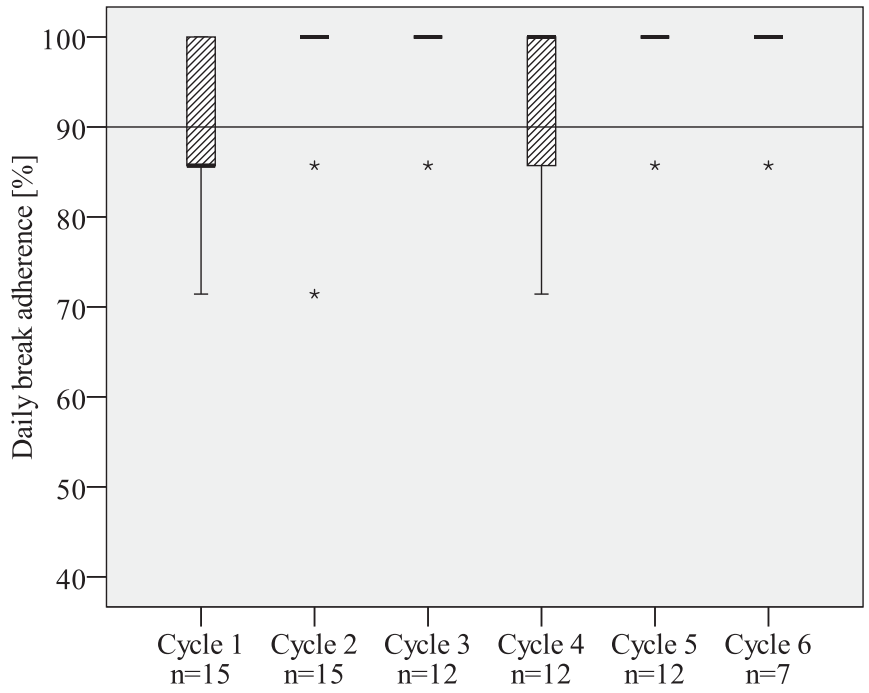



*Figure 4-27: Daily break adherence [%] of initially non-adherent patients during cycle 1 to 6*

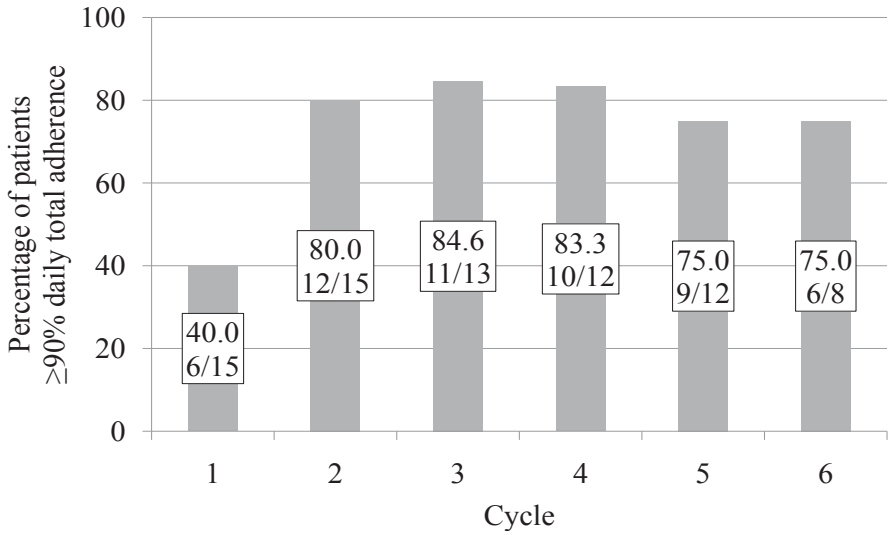



*Figure 4-28: Percentage of initially non-adherent patients exhibiting a daily total adherence ≥90% during intake and rest periods of cycle 1 to 6; the numbers inside the boxes show the exact percentage (first row) and absolute patient numbers (second row)*

Figure 4-29 shows the percentage of initially non-adherent patients with a daily intake adherence ≥90% over the cycles. In contrast to the initially adherent patients, the fractions of patients exhibiting a daily total adherence ≥90% and a daily intake adherence ≥90% did not exhibit major differences.

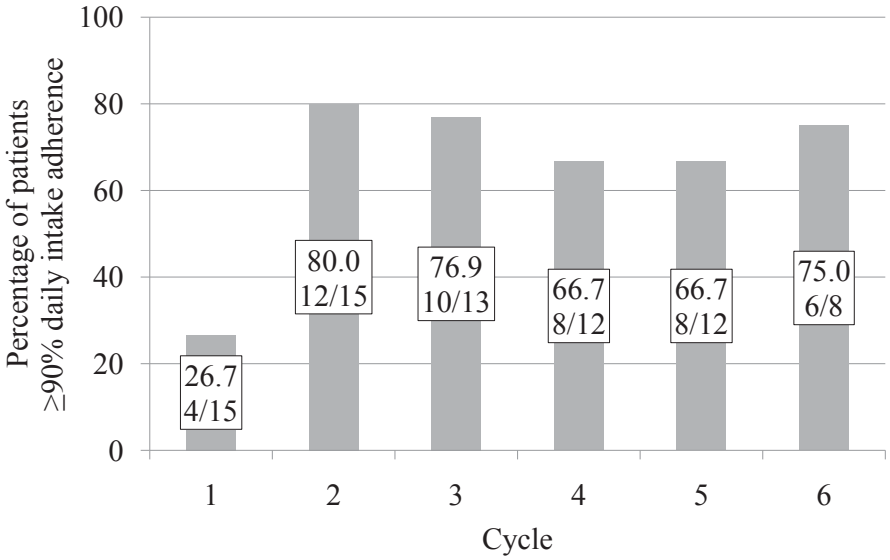



*Figure 4-29: Percentage of initially non-adherent patients exhibiting a daily intake adherence ≥90% during the intake periods of cycle 1 to 6; the numbers inside the boxes show the exact percentage (first row) and absolute patient numbers (second row)*

Considering intra-individual differences of daily total adherence between the end of study and baseline, it becomes obvious that most initially non-adherent patients' adherence improved. The adherence of 11 patients improved, maximum increases were 31.0%, 42.9%, and 71.4%. Four patients' adherence diminished by 1.4%, 9.5%, 14.3%, and 27.9%. Figure 4-30 illustrates these findings.

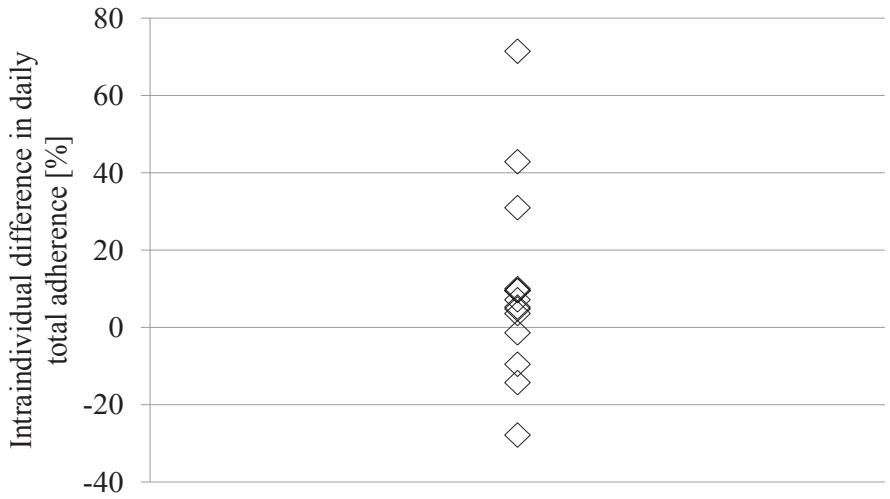



*Figure 4-30: Intra-individual difference in daily total adherence [%] between the last and first capecitabine cycle of initially non-adherent patients (n=15); every rhombus represents one patient*

Each capecitabine cycle completed by an initially non-adherent patient was defined as either adherent (≥90%) or non-adherent (<90%) and plotted in Figure 4-31. The fact that six initially non-adherent patients showed a daily total adherence of ≥90% during cycle 1 is explained in chapter 3.6 and 3.7.2. 46.7% of the patients (7/15) were non-adherent at least during one cycle (except cycle 1). Three of 15 patients (20.0%) were non-adherent during one cycle and two cycles, respectively. Maximum number of non-adherent cycles per patient was three (1/15 patients, 6.7%). From cycle 2 onwards, 53.3% (8/15) did adhere during all completed cycles. Seven of 15 of all initially non-adherent patients (46.7%) were prescribed less than six capecitabine cycles (see 4.4.4).

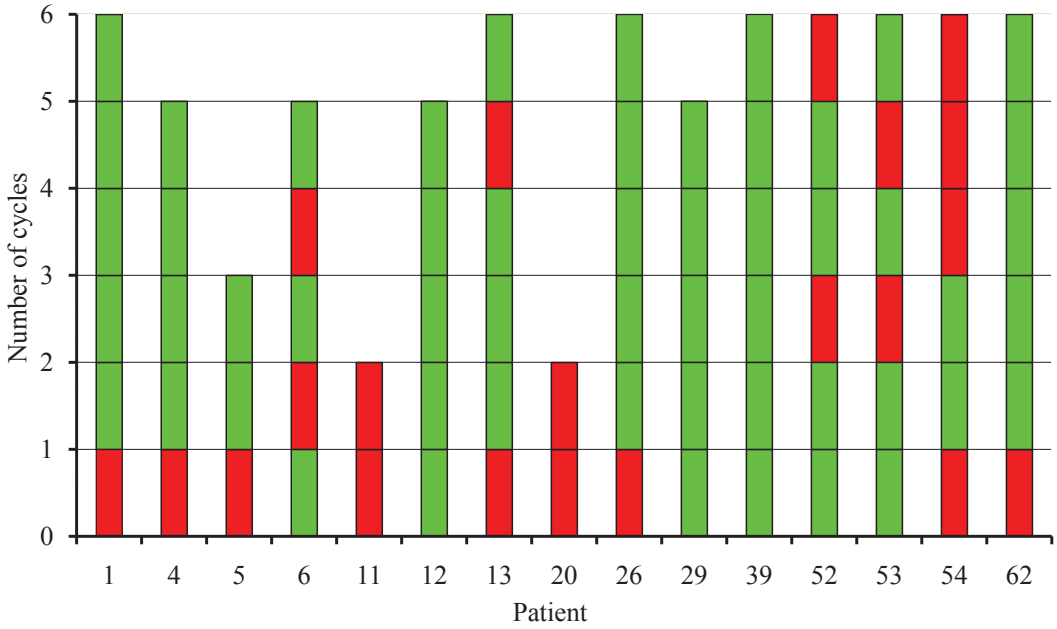



*Figure 4-31: Individual daily total adherence of initially non-adherent patients; green bars indicate adherent cycles (daily total adherence ≥90%), and red bars non-adherent cycles (daily total adherence <90%); non-complete bars imply treatment duration of less than six cycles, for information on reasons for shortened prescription of capecitabine see 4.4.4*

**Influence of gender**

No statistically significant difference in terms of daily total adherence was observed between initially non-adherent women and men, compare Table 4-22. In both gender groups, the minimum values were observed during the first capecitabine cycle, both mean and median daily total adherence accounted for <90%. From the second cycle on, median daily total adherence was found to be ≥90%. However, mean daily total adherence of male patients was <90% in cycle 3, 5, and 6. Thus, a marginal trend to a better adherence in female patients was seen.

**Influence of tumour entity**

At no time point a statistically significant difference regarding daily total adherence between patients with breast, colorectal or other cancer was observed, apart from $t_1$ (p value=0.046, Mann-Whitney-U test). At $t_1$ median daily total adherence of breast cancer patients accounted for 90.5%, whereas colorectal cancer patients' exhibited a median value of 85.0%. Table 4-23 shows the results in detail.

**Influence of therapy regimen**

At $t_1$, $t_2$, $t_3$, $t_5$, and $t_6$ no statistically significant difference could be seen between patients who received capecitabine as a single agent therapy and patients who were prescribed capecitabine in combination with one or more further anti-cancer agents. However, the difference between these two patient subgroups was statistically significant at $t_4$ (p value=0.044, Mann-Whitney-U test). Mean daily total adherence of patients treated with capecitabine as monotherapy was 96.0%, the median accounted for 95.2%. Patients who were treated with more than one anti-cancer agent showed a mean daily total adherence of 88.2% and the median was 90.5%. Details are listed in Table 4-24.

**Influence of treatment intention**

Differences concerning daily total adherence between patients who were treated with a curative or palliative intention were not found to be statistically significant (see Table 4-25).

*Table 4-22: Daily total adherence [%] of initially non-adherent female and male patients during the course of the study*

| | | Female | Male | p value* |
|---|---|---|---|---|
| $t_1$ | n | 10 | 5 | 0.758 |
| | Mean | 83.0 | 76.4 | |
| | Median | 87.3 | 85.7 | |
| | SD | 12.1 | 27.0 | |
| | IQR | 85.0-90.5 | 85.0-90.0 | |
| | Range | 57.1-91.7 | 28.6-92.9 | |
| $t_2$ | n | 10 | 5 | 0.565 |
| | Mean | 92.1 | 97.1 | |
| | Median | 95.2 | 95.2 | |
| | SD | 10.4 | 2.6 | |
| | IQR | 87.5-100.0 | 95.2-100.0 | |
| | Range | 71.4-100.0 | 95.0-100.0 | |
| $t_3$ | n | 8 | 5 | 1.000 |
| | Mean | 91.8 | 89.0 | |
| | Median | 95.2 | 95.2 | |
| | SD | 12.0 | 17.2 | |
| | IQR | 92.7-97.6 | 90.5-100.0 | |
| | Range | 63.0-100.0 | 59.1-100.0 | |
| $t_4$ | n | 7 | 5 | 0.497 |
| | Mean | 93.3 | 90.5 | |
| | Median | 95.2 | 90.5 | |
| | SD | 5.8 | 8.9 | |
| | IQR | 90.5-95.2 | 90.5-95.2 | |
| | Range | 81.8-100.0 | 76.2-100.0 | |
| $t_5$ | n | 7 | 5 | 0.203 |
| | Mean | 95.2 | 89.2 | |
| | Median | 95.2 | 90.5 | |
| | SD | 4.7 | 9.0 | |
| | IQR | 95.2-100.0 | 81.0-95.2 | |
| | Range | 85.7-100.0 | 79.2-100.0 | |
| $t_6$ | n | 4 | 4 | 0.758 |
| | Mean | 94.1 | 86.9 | |
| | Median | 97.6 | 95.2 | |
| | SD | 9.0 | 20.3 | |
| | IQR | 88.1-100.0 | 73.8-100.0 | |
| | Range | 81.0-100.0 | 57.1-100.0 | |

** Mann-Whitney-U test*

*Table 4-23: Daily total adherence [%] of initially non-adherent patients with breast cancer, colorectal cancer and other cancer entities[1] during the course of the study*

| | | Breast cancer | Colorectal cancer | Other[1] | p value* |
|---|---|---|---|---|---|
| $t_1$ | n | 7 | 7 | 1 | 0.046 |
| | Mean | 85.0 | 74.9 | 92.9 | |
| | Median | 90.5 | 85.0 | 92.9 | |
| | SD | 12.4 | 22.1 | n.a. | |
| | IQR | 85.7-90.5 | 64.3-85.7 | n.a. | |
| | Range | 57.1-91.7 | 28.6-90.0 | n.a. | |
| $t_2$ | n | 7 | 7 | 1 | 0.683 |
| | Mean | 90.7 | 96.6 | 95.0 | |
| | Median | 100.0 | 95.2 | 95.0 | |
| | SD | 12.5 | 2.4 | n.a. | |
| | IQR | 76.2-100.0 | 95.2-100.0 | n.a. | |
| | Range | 71.4-100.0 | 95.0-100.0 | n.a. | |
| $t_3$ | n | 5 | 7 | 1 | 0.237 |
| | Mean | 90.7 | 95.2 | 59.1 | |
| | Median | 95.2 | 95.2 | 59.1 | |
| | SD | 15.7 | 3.9 | n.a. | |
| | IQR | 95.2-100.0 | 90.5-100.0 | n.a. | |
| | Range | 63.0-100.0 | 90.5-100.0 | n.a. | |
| $t_4$ | n | 5 | 6 | 1 | 0.612 |
| | Mean | 91.6 | 92.9 | 90.5 | |
| | Median | 95.2 | 95.2 | 90.5 | |
| | SD | 5.8 | 8.9 | n.a. | |
| | IQR | 90.5-95.2 | 90.5-100.0 | n.a. | |
| | Range | 81.8-95.2 | 76.2-100.0 | n.a. | |
| $t_5$ | n | 5 | 6 | 1 | 0.093 |
| | Mean | 97.1 | 91.3 | 79.2 | |
| | Median | 95.2 | 92.9 | 79.2 | |
| | SD | 2.6 | 7.0 | n.a. | |
| | IQR | 95.2-100.0 | 85.7-95.2 | n.a. | |
| | Range | 95.2-100.0 | 81.0-100.0 | n.a. | |
| $t_6$ | n | 3 | 4 | 1 | 0.478 |
| | Mean | 93.7 | 85.7 | 100.0 | |
| | Median | 100.0 | 92.9 | 100.0 | |
| | SD | 11.0 | 19.4 | n.a. | |
| | IQR | 81.0-100.0 | 73.8-97.6 | n.a. | |
| | Range | 81.0-100.0 | 57.1-100.0 | n.a. | |

** Kruskal-Wallis-H test*
*[1]Other cancer entity: oesophageal cancer*

*Table 4-24: Daily total adherence [%] of initially non-adherent patients who received capecitabine as single agent or in combination during the course of the study (n=15)*

| | | Single agent | Combination | p value* |
|---|---|---|---|---|
| $t_1$ | n | 7 | 8 | 0.351 |
| | Mean | 74.8 | 86.0 | |
| | Median | 85.7 | 89.5 | |
| | SD | 23.4 | 9.2 | |
| | IQR | 57.1-90.5 | 85.0-91.1 | |
| | Range | 28.6-90.5 | 64.3-92.9 | |
| $t_2$ | n | 7 | 8 | 0.227 |
| | Mean | 94.6 | 93.0 | |
| | Median | 100.0 | 95.1 | |
| | SD | 10.4 | 7.8 | |
| | IQR | 95.2-100.0 | 91.3-97.6 | |
| | Range | 71.4-100.0 | 76.2-100.0 | |
| $t_3$ | n | 6 | 7 | 0.418 |
| | Mean | 91.5 | 90.0 | |
| | Median | 95.2 | 95.0 | |
| | SD | 14.2 | 14.2 | |
| | IQR | 95.2-100.0 | 90.5-100.0 | |
| | Range | 63.0-100.0 | 59.1-100.0 | |
| $t_4$ | n | 6 | 6 | 0.044 |
| | Mean | 96.0 | 88.2 | |
| | Median | 95.2 | 90.5 | |
| | SD | 3.6 | 7.7 | |
| | IQR | 95.2-100.0 | 81.8-95.2 | |
| | Range | 90.5-100.0 | 76.2-95.2 | |
| $t_5$ | n | 6 | 6 | 0.181 |
| | Mean | 96.0 | 89.4 | |
| | Median | 95.2 | 90.5 | |
| | SD | 3.6 | 8.6 | |
| | IQR | 95.2-100.0 | 81.0-95.2 | |
| | Range | 90.5-100.0 | 79.2-100.0 | |
| $t_6$ | n | 5 | 3 | 0.525 |
| | Mean | 94.3 | 84.1 | |
| | Median | 100.0 | 95.2 | |
| | SD | 8.5 | 23.5 | |
| | IQR | 90.5-100.0 | 57.1-100.0 | |
| | Range | 81.0-100.0 | 57.1-100.0 | |

** Mann-Whitney-U test*

*Table 4-25: Daily total adherence [%] of initially non-adherent patients who received capecitabine with a curative or palliative treatment intention during the course of the study (n=15)*

| | | Curative intention | Palliative intention | p value* |
|---|---|---|---|---|
| $t_1$ | n | 3 | 12 | 0.424 |
| | Mean | 85.5 | 79.6 | |
| | Median | 85.7 | 89.4 | |
| | SD | 0.4 | 19.7 | |
| | IQR | 85.0-85.7 | 74.6-90.5 | |
| | Range | 85.0-85.7 | 28.6-92.9 | |
| $t_2$ | n | 3 | 12 | 0.598 |
| | Mean | 96.8 | 93.0 | |
| | Median | 95.2 | 95.2 | |
| | SD | 2.7 | 9.7 | |
| | IQR | 95.2-100.0 | 91.3-100.0 | |
| | Range | 95.2-100.0 | 71.4-100.0 | |
| $t_3$ | n | 3 | 10 | 0.663 |
| | Mean | 93.7 | 89.8 | |
| | Median | 95.2 | 95.2 | |
| | SD | 2.7 | 15.5 | |
| | IQR | 90.5-95.2 | 90.5-100.0 | |
| | Range | 90.5-95.2 | 59.1-100.0 | |
| $t_4$ | n | 3 | 9 | 0.847 |
| | Mean | 90.5 | 92.7 | |
| | Median | 95.2 | 95.2 | |
| | SD | 12.6 | 5.2 | |
| | IQR | 76.2-100.0 | 90.5-95.2 | |
| | Range | 76.2-100.0 | 81.8-100.0 | |
| $t_5$ | n | 3 | 9 | 0.209 |
| | Mean | 88.9 | 94.0 | |
| | Median | 90.5 | 95.2 | |
| | SD | 7.3 | 7.1 | |
| | IQR | 81.0-95.2 | 95.2-100.0 | |
| | Range | 81.0-95.2 | 79.2-100.0 | |
| $t_6$ | n | 2 | 6 | 0.076 |
| | Mean | 73.8 | 96.0 | |
| | Median | 73.8 | 100.0 | |
| | SD | 23.6 | 7.6 | |
| | IQR | 57.1-90.5 | 95.2-100.0 | |
| | Range | 57.1-90.5 | 81.0-100.0 | |

** Mann-Whitney-U test*

**MEMS®- versus self-assessed adherence**

The percentage of initially non-adherent patients whose MEMS®-assessed daily total adherence accounted for >85.7% was relatively low and varied from 26.7% in cycle 1 to 80.0% in cycle 2. Values during cycles 3 to 6 were 76.9%, 66.7%, 33.3%, and 75.0%, compare Figure 4-32. Despite the impaired MEMS®-assessed adherence, interestingly adherence self-assessment was found to be high, see Figure 4-33. Almost 100.0% of the patients stated that their adherence accounted for >85.7% during all observed capecitabine cycles.

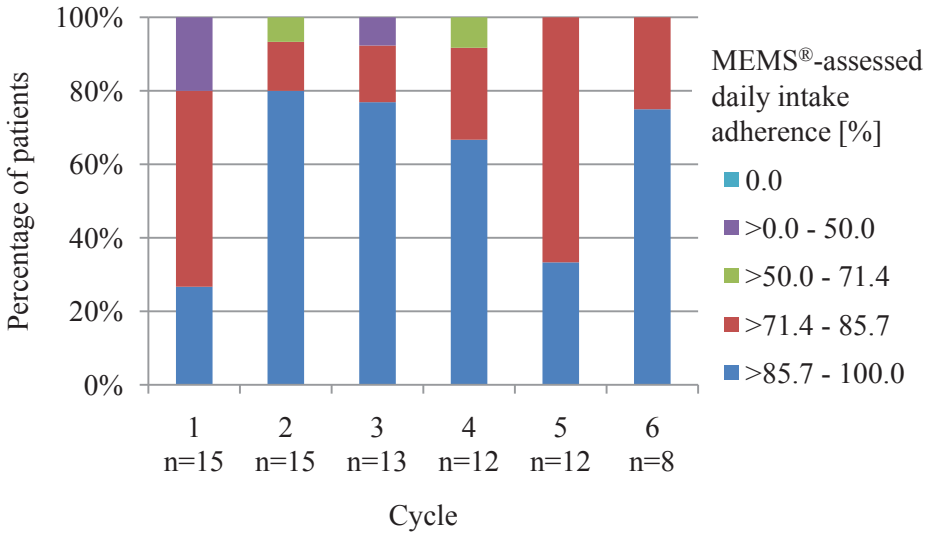



*Figure 4-32: Percentage of initially non-adherent patients within MEMS®-assessed daily intake adherence ranges during the course of the study*

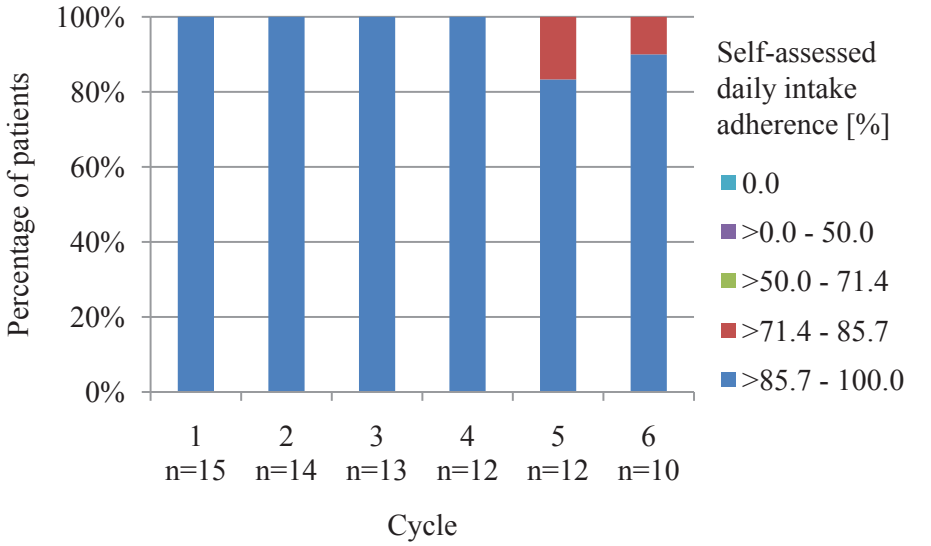



*Figure 4-33: Percentage of initially non-adherent patients within self-assessed daily intake adherence ranges during the course of the study*

However, the difference between MEMS®- and self-assessed total adherence during the total study period was not significant (p value=0.050, Wilcoxon test). Mean self-assessed total adherence was 95.9% and the median was 100.0%. Mean MEMS®-assessed daily adherence during the whole observation period was 89.7% and the median was 89.1%. Table 4-26 depicts the respective details. Altogether, adherence self-assessment of initially non-adherent patients does not seem to be objective.

*Table 4-26: MEMS®-assessed [%] versus self-assessed total adherence [%] during the **whole** study period (cycle 1 to 6) assessed at $t_6$ in initially non-adherent patients*

| | **MEMS®-assessed daily adherence [%]** | **Self-assessed total adherence [%]** | **p value*** |
|---|---|---|---|
| n | 15 | 11 | 0.050 |
| Mean | 89.7 | 95.9 | |
| Median | 89.1 | 100.0 | |
| SD | 5.0 | 9.2 | |
| IQR | 86.4-94.2 | 95.0-100.0 | |
| Range | 78.6-96.9 | 70.0-100.0 | |

** Wilcoxon test*

### 4.4.3 Overall adherence

Overall adherence of initially non-adherent patients under basic pharmaceutical care, adverse event management and adherence management was high. Mean overall adherence ranged from 93.8% in cycle 1 to 102.7% in cycle 3, median overall adherence from 96.2% in cycle 1 to 100.0% in cycle 2, 3, and 4. Logically, lowest values were observed during the first completed capecitabine cycle. More detailed information on data shown in Figure 4-34 are tabulated in Appendix E, Table E-4. Regarding overall adherence, it has to be kept in mind that over-adherence (too many container openings at one point) might compensate under-adherence (missing openings at another time).

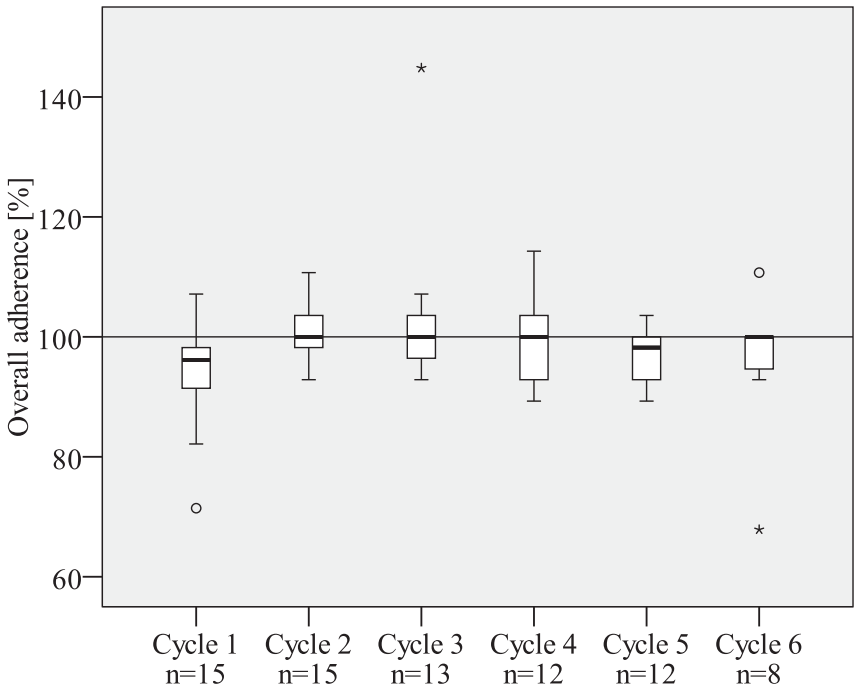



*Figure 4-34: Overall adherence [%] of initially non-adherent patients during cycle 1 to 6*

### 4.4.4 Persistence

All initially non-adherent patients persisted with their oral anti-cancer treatment during the whole period they were prescribed capecitabine. No patient performed an unauthorised discontinuation of his capecitabine treatment.

In five of 15 initially non-adherent patients capecitabine was discontinued prematurely due to tumour progression. The chronological sequence of treatment discontinuations is illustrated in Figure 4-35. Since treatment in ten patients was not discontinued prematurely by the physicians, their data were censored (eight patients completed six capecitabine cycles as planned, one patient completed five cycles as planned, and one patient died during the second cycle).

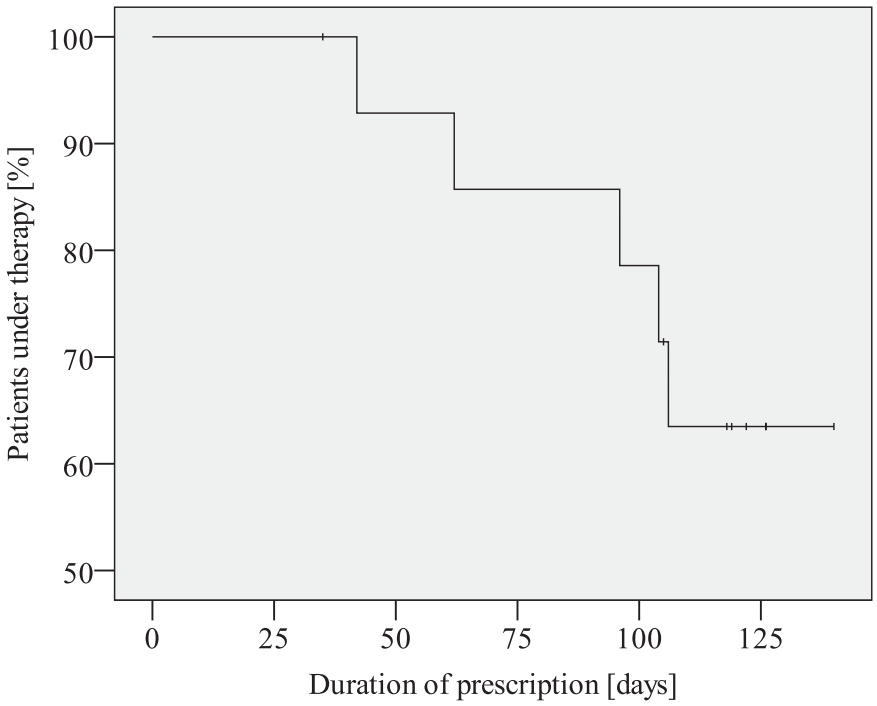



*Figure 4-35: Duration of capecitabine prescription [days] for initially non-adherent patient, n=15; short vertical lines indicate censored patient data*

### 4.4.5 Dosing intervals

The administration of capecitabine is supposed to take place twice per day separated by twelve hours. During the study period 1906 dosing intervals were recorded in initially non-adherent patients and the median dosing interval accounted for 12:00 hours. Dosing intervals ≥24 hours were not considered in this analysis. More detailed information on the registered dosing intervals is shown in Table 4-27.

*Table 4-27: Dosing intervals [hours] <24 hours recorded by MEMS® in initially non-adherent patients (n=15)*

| | **Dosing intervals [hours]** |
|---|---|
| n | 1906 |
| Mean | 11:58 |
| Median | 12:00 |
| SD | 2:46 |
| IQR | 10:15-13:38 |
| Range | 0:16-23:42 |

Furthermore, classified dosing intervals were analysed (see Table 4-28). For this consideration, a range of 10 to 14 hours was defined. More than half of all registered dosing intervals (58.3%)

in initially non-adherent patients was within this range and was, therefore, regarded as adherent. Percentages of the dosing intervals <10 hours and >14 hours were lower and roughly equal (21.8% and 19.9%).

*Table 4-28: Classified dosing intervals <24 hours recorded by MEMS® in initially non-adherent patients (n=15)*

| | **Number of dosing intervals** | **Proportion [%]** |
|---|---|---|
| <10 hours | 415 | 21.8 |
| 10-14 hours | 1111 | 58.3 |
| >14 hours | 380 | 19.9 |
| Total | 1906 | 100.0 |

Figure 4-36 shows the results of the analysis of dosing intervals as a histogram. The main peak of the dosing intervals was situated at approximately twelve hours. However, the dosing intervals are relatively broad distributed within the range of approximately 8 and 16 hours.

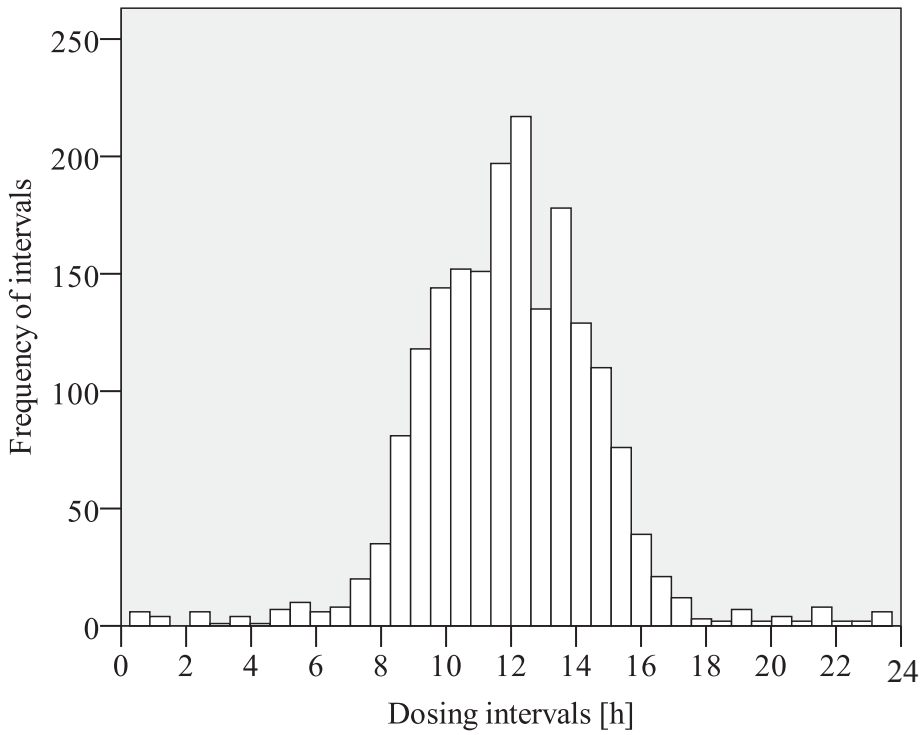



*Figure 4-36: Frequency of dosing intervals in initially non-adherent patients*

### 4.4.6 Quality of life

**EORTC QLQ-C30 questionnaire**

Initially non-adherent patients had lower median values of functional scales at $t_0$ compared to the reference values of the QLQ-C30 scoring manual [114]. However, during the course of the study the median score of the dimensions physical functioning, role functioning, emotional functioning, and social functioning increased. Cognitive functioning remained constant at $t_0$, $t_3$, and $t_6$. Nevertheless, the level of the reference values was not reached. For details see Table 4-29. Reference values can be accessed in Appendix D, Table D-5.

*Table 4-29: EORTC QLQ-C30 (modified version 3.0) functional scales at $t_0$, $t_3$ and $t_6$ in initially non-adherent patients (n=15)*

| QLQ-C30 dimension | | n | Mean | SD | Median | IQR |
|---|---|---|---|---|---|---|
| Physical functioning (PF2) | $t_0$ | 13 | 60.0 | 21.8 | 53.3 | 46.7-73.3 |
| | $t_3$ | 11 | 65.5 | 23.1 | 73.3 | 40.0-86.7 |
| | $t_6$ | 12 | 62.8 | 26.1 | 60.0 | 40.0-86.7 |
| Role functioning (RF2) | $t_0$ | 13 | 39.7 | 33.0 | 33.3 | 16.7-66.7 |
| | $t_3$ | 11 | 48.5 | 34.5 | 33.3 | 33.3-66.7 |
| | $t_6$ | 12 | 54.2 | 39.6 | 50.0 | 25.0-100.0 |
| Emotional functioning (EF) | $t_0$ | 13 | 46.8 | 28.6 | 41.7 | 33.3-58.3 |
| | $t_3$ | 11 | 55.3 | 23.1 | 50.0 | 41.7-66.67 |
| | $t_6$ | 11 | 51.5 | 35.5 | 50.0 | 16.7-100.0 |
| Cognitive functioning (CF) | $t_0$ | 13 | 70.5 | 27.3 | 66.7 | 50.0-100.0 |
| | $t_3$ | 11 | 62.1 | 29.9 | 66.7 | 50.0-83.3 |
| | $t_6$ | 11 | 65.2 | 20.4 | 66.7 | 50.0-83.3 |
| Social functioning (SF) | $t_0$ | 13 | 42.3 | 24.2 | 33.3 | 33.3-50.0 |
| | $t_3$ | 11 | 47.0 | 31.5 | 33.3 | 16.7-66.7 |
| | $t_6$ | 11 | 57.6 | 31.9 | 66.7 | 33.3-83.3 |

The median values of the symptom scales nausea and vomiting, pain, constipation, diarrhoea, and financial difficulties at $t_0$ of initially non-adherent patients were in the same range as the reference values of the QLQ-C30 scoring manual [114]. Since the symptom scale 'HFS' was added to the questionnaire in the present study, no reference values are available. Worse fatigue, dyspnoea, insomnia, and appetite loss compared to the reference were observed. The global health status was lower compared to the reference values of the QLQ-C30 scoring manual [114]. However, it remained constant at $t_0$, $t_3$, and $t_6$. Detailed information on the symptom scales and the global health status at the three different measuring points is tabulated in Table 4-30. For details on the reference values see Appendix D, Table D-5.

*Table 4-30: EORTC QLQ-C30 (modified version 3.0) symptom scales and global health status at $t_0$, $t_3$ and $t_6$ in initially non-adherent patients (n=15)*

| QLQ-C30 dimension/QoL | | n | Mean | SD | Median | IQR |
|---|---|---|---|---|---|---|
| Fatigue (FA) | $t_0$ | 13 | 67.5 | 23.3 | 66.7 | 44.4-88.9 |
| | $t_3$ | 11 | 59.6 | 33.4 | 66.7 | 33.3-100.0 |
| | $t_6$ | 12 | 60.2 | 28.6 | 61.1 | 33.3-83.3 |
| Nausea and Vomiting (NV) | $t_0$ | 13 | 5.1 | 8.0 | 0.0 | 0.0-16.7 |
| | $t_3$ | 11 | 13.6 | 23.4 | 0.0 | 0.0-50.0 |
| | $t_6$ | 11 | 13.6 | 20.8 | 0.0 | 0.0-16.7 |
| Pain (PA) | $t_0$ | 13 | 34.6 | 39.9 | 16.7 | 0.0-66.7 |
| | $t_3$ | 11 | 40.9 | 36.8 | 33.3 | 0.0-66.7 |
| | $t_6$ | 12 | 47.2 | 38.8 | 41.7 | 8.3-83.3 |
| Dyspnoea (DY) | $t_0$ | 12 | 38.9 | 42.2 | 33.3 | 0.0-83.3 |
| | $t_3$ | 11 | 36.4 | 40.7 | 33.3 | 0.0-66.7 |
| | $t_6$ | 12 | 38.9 | 31.2 | 33.3 | 16.7-66.7 |
| Insomnia (SL) | $t_0$ | 13 | 53.8 | 39.8 | 66.7 | 33.3-100.0 |
| | $t_3$ | 11 | 39.4 | 36.0 | 33.3 | 0.0-66.7 |
| | $t_6$ | 12 | 50.0 | 38.9 | 50.0 | 16.7-83.3 |
| Appetite loss (AP) | $t_0$ | 13 | 38.5 | 40.5 | 33.3 | 0.0-66.7 |
| | $t_3$ | 11 | 33.3 | 29.8 | 33.3 | 0.0-66.7 |
| | $t_6$ | 12 | 44.4 | 38.5 | 50.0 | 0.0-66.7 |
| Constipation (CO) | $t_0$ | 13 | 20.5 | 34.8 | 0.0 | 0.0-33.3 |
| | $t_3$ | 11 | 18.2 | 34.5 | 0.0 | 0.0-33.3 |
| | $t_6$ | 11 | 36.4 | 40.7 | 33.3 | 0.0-66.7 |
| Diarrhoea (DI) | $t_0$ | 13 | 10.3 | 28.5 | 0.0 | 0.0-0.0 |
| | $t_3$ | 11 | 6.1 | 20.1 | 0.0 | 0.0-0.0 |
| | $t_6$ | 11 | 12.1 | 27.0 | 0.0 | 0.0-0.0 |
| Financial difficulties (FI) | $t_0$ | 13 | 28.2 | 42.7 | 0.0 | 0.0-33.3 |
| | $t_3$ | 11 | 36.4 | 37.9 | 33.3 | 0.0-66.7 |
| | $t_6$ | 11 | 27.3 | 36.0 | 0.0 | 0.0-66.7 |
| Hand-foot syndrome (HFS) | $t_0$ | 12 | 25.0 | 32.2 | 0.0 | 0.0-66.7 |
| | $t_3$ | 11 | 42.4 | 44.9 | 33.3 | 0.0-100.0 |
| | $t_6$ | 11 | 39.4 | 38.9 | 33.3 | 0.0-66.7 |
| Global health status/ QoL (QL2) | $t_0$ | 13 | 42.3 | 20.8 | 50.0 | 25.0-50.0 |
| | $t_3$ | 11 | 53.0 | 23.4 | 50.0 | 33.3-75.0 |
| | $t_6$ | 11 | 50.0 | 31.8 | 50.0 | 16.7-83.3 |

**EQ-5D questionnaire**

The results of the descriptive system of the EQ-5D-3L questionnaire for the initially non-adherent patients are shown in Table 4-31. Most patients reported to have no problems with 'self-care'; the proportion was high throughout the study period. However, it slightly decreased from 100.0% at $t_0$ to 91.7 at $t_3$ and $t_6$. The percentage of patients reporting level 1 for the

dimension ‘mobility’ increased from 57.1% at $t_0$ to 66.7% at $t_3$ and decreased to 58.3% at $t_6$. The proportion of patients reporting level 2 or 3 (some or extreme problems) for the dimensions ‘usual activities’ and ‘pain/discomfort’ increased over time. The percentage of patients reporting no problems concerning the dimension ‘anxiety/depression’ slightly increased from 35.7% at $t_0$ to 41.7% at $t_3$ and $t_6$.

*Table 4-31: Proportion of patients [%] reporting level 1, 2 or 3 of the EQ-5D-3L descriptive system at $t_0$, $t_3$ and $t_6$ concerning the five EQ-5D dimensions*

| EQ-5D dimension | | n | Level 1 | Level 2 | Level 3 |
|---|---|---|---|---|---|
| Mobility | $t_0$ | 14 | 57.1 | 42.9 | 0.0 |
| | $t_3$ | 12 | 66.7 | 33.3 | 0.0 |
| | $t_6$ | 12 | 58.3 | 41.7 | 0.0 |
| Self-care | $t_0$ | 14 | 100.0 | 0.0 | 0.0 |
| | $t_3$ | 12 | 91.7 | 8.3 | 0.0 |
| | $t_6$ | 12 | 91.7 | 8.3 | 0.0 |
| Usual activities | $t_0$ | 14 | 42.9 | 57.1 | 0.0 |
| | $t_3$ | 12 | 41.7 | 58.3 | 0.0 |
| | $t_6$ | 12 | 33.3 | 66.7 | 0.0 |
| Pain/discomfort | $t_0$ | 14 | 57.1 | 42.9 | 0.0 |
| | $t_3$ | 12 | 41.7 | 41.7 | 16.7 |
| | $t_6$ | 12 | 41.7 | 50.0 | 8.3 |
| Anxiety/depression | $t_0$ | 14 | 35.7 | 64.3 | 0.0 |
| | $t_3$ | 12 | 41.7 | 58.3 | 0.0 |
| | $t_6$ | 12 | 41.7 | 58.3 | 0.0 |

Figure 4-37 visualises the proportion of patients reporting problems (level 2 plus level 3) concerning the five EQ-5D dimensions at the three different time points by means of a bar chart.

Mean, standard deviation, median and interquartile range of the EQ-5D descriptive system at $t_0$, $t_3$ and $t_6$ for initially non-adherent patients are tabulated in Appendix E, Table E-5. The median of the EQ-5D dimensions ‘usual activities’ and ‘anxiety/depression’ was found to account for level 2 at all time points. Regarding the dimensions ‘mobility’ and ‘self-care’, the median was on level 1 at all three time points. ‘Pain/discomfort’ increased from level 1 to level 2 at $t_3$ and $t_6$.

The mean EQ-5D VAS value of initially non-adherent patients increased from 58.1 at $t_0$, to 63.3 at $t_3$ and decreased to 57.7 at $t_6$, see Table 4-32.

*Table 4-32: EQ-5D-3L VAS values at $t_0$, $t_3$ and $t_6$ (n=15)*

| | n | Mean | SD | Median | IQR |
|---|---|---|---|---|---|
| $t_0$ | 14 | 58.1 | 17.4 | 50.0 | 50.0-70.0 |
| $t_3$ | 12 | 63.3 | 26.3 | 65.0 | 45.0-80.0 |
| $t_6$ | 12 | 57.7 | 23.4 | 50.0 | 44.5-74.5 |

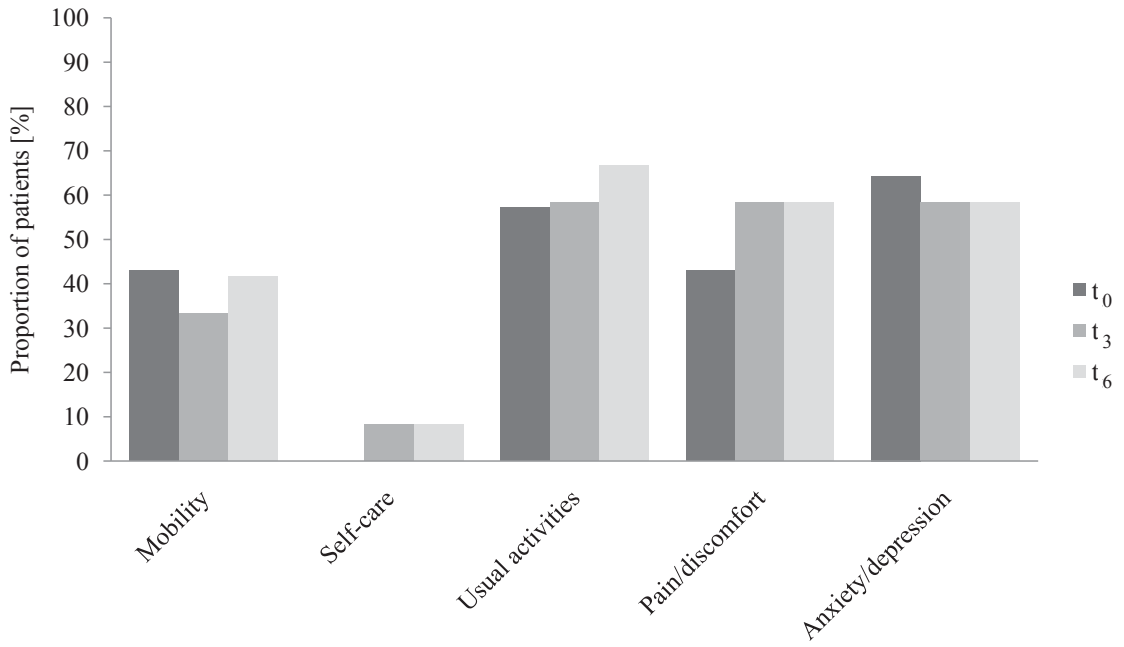



*Figure 4-37: Proportion of patients [%] reporting problems concerning the five EQ-5D dimensions (sum of proportion of patients reporting level 2 and 3)*

### 4.4.7 Patient satisfaction with information

The Likert-scale of the PSCaTE questionnaire ranged from strongly disagree (1) to strongly agree (5). Median scoring of patient satisfaction with information on cancer therapy, adverse effects, information sources and overall satisfaction of initially non-adherent patients was high at $t_0$ (in the median 4.0 to 4.3). Merely patient satisfaction with information on complementary treatment options was found to be lower (median 2.3). Patient satisfaction increased for all five dimensions during the course of the modular medication management and even median satisfaction with information on complementary treatment options accounted for 4.0 at $t_6$. The respective details are shown in Table 4-33 and presented additionally as boxplots in Appendix E, Figures E-1, E-2 and E-3.

*Table 4-33: Patient satisfaction with information of initially non-adherent patients (n=15) at $t_0$, $t_3$ and $t_6$*

| PSCaTE dimension | | n | Mean | SD | Median | IQR |
|---|---|---|---|---|---|---|
| Satisfaction with information on cancer therapy (CT) | $t_0$ | 13 | 4.2 | 0.7 | 4.2 | 4.0-4.6 |
| | $t_3$ | 11 | 4.4 | 0.8 | 4.6 | 4.0-5.0 |
| | $t_6$ | 12 | 4.7 | 0.5 | 4.9 | 4.5-5.0 |
| Satisfaction with information on adverse effects (SE) | $t_0$ | 13 | 4.3 | 0.8 | 4.3 | 4.0-5.0 |
| | $t_3$ | 11 | 4.5 | 0.6 | 4.5 | 4.3-5.0 |
| | $t_6$ | 12 | 4.6 | 0.5 | 4.7 | 4.3-5.0 |
| Satisfaction with information on vitamins, herbal medicines and complementary treatment options (VC) | $t_0$ | 13 | 2.8 | 1.5 | 2.3 | 1.7-4.0 |
| | $t_3$ | 11 | 3.3 | 1.4 | 3.3 | 2.3-4.7 |
| | $t_6$ | 12 | 3.9 | 1.0 | 4.0 | 3.7-4.7 |
| Satisfaction with information sources (RS) | $t_0$ | 13 | 4.4 | 0.5 | 4.3 | 4.0-5.0 |
| | $t_3$ | 11 | 4.5 | 0.5 | 4.8 | 4.3-5.0 |
| | $t_6$ | 12 | 4.7 | 0.3 | 4.8 | 4.5-5.0 |
| Overall satisfaction (OV) | $t_0$ | 13 | 3.9 | 0.7 | 4.0 | 3.4-4.5 |
| | $t_3$ | 11 | 4.2 | 0.7 | 4.3 | 3.8-4.9 |
| | $t_6$ | 12 | 4.5 | 0.5 | 4.5 | 4.2-4.9 |

### 4.4.8 Hand-foot syndrome (HFS)

Patient information regarding severity grades of the hand-foot syndrome during the different capecitabine cycles are shown as boxplots in Figure 4-38. Median HFS severity grade increased from 0 at $t_1$ to 1 at all other time points.

Three of 15 (20.0%) initially non-adherent patients had to discontinue their capecitabine treatment temporarily. Reasons for these treatment breaks were HFS, hospital stay, and worsening of general condition.

Figure 4-39 shows the cumulative proportion of initially non-adherent patients whose capecitabine dose had to be reduced (5/15, 33.3%). All dose reductions were due to HFS.

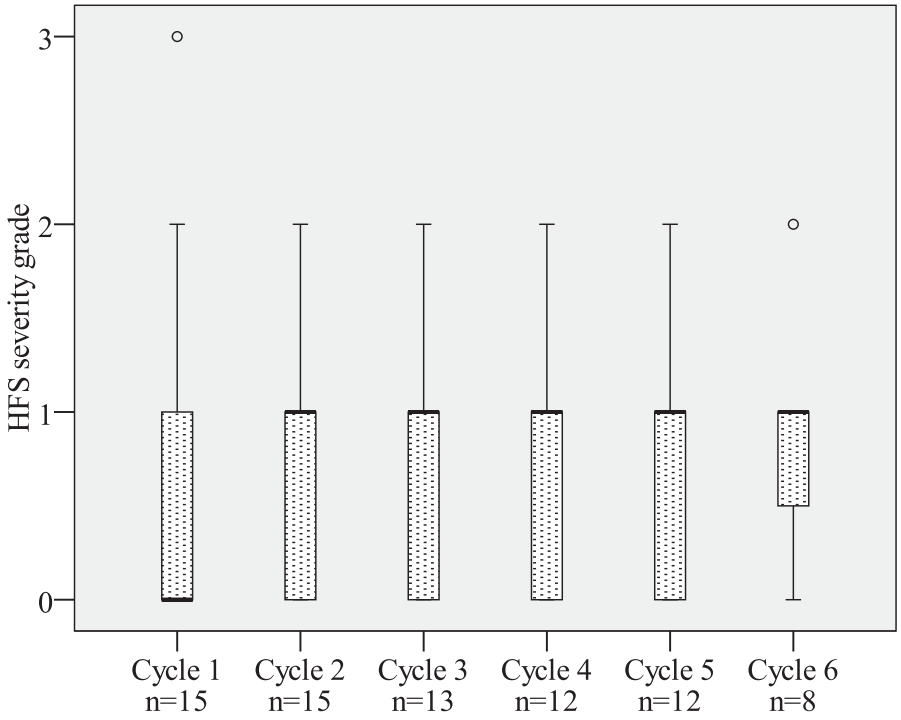



*Figure 4-38: HFS severity grades of initially non-adherent patients under treatment with capecitabine at $t_1$, $t_2$, $t_3$, $t_4$, $t_5$ and $t_6$*

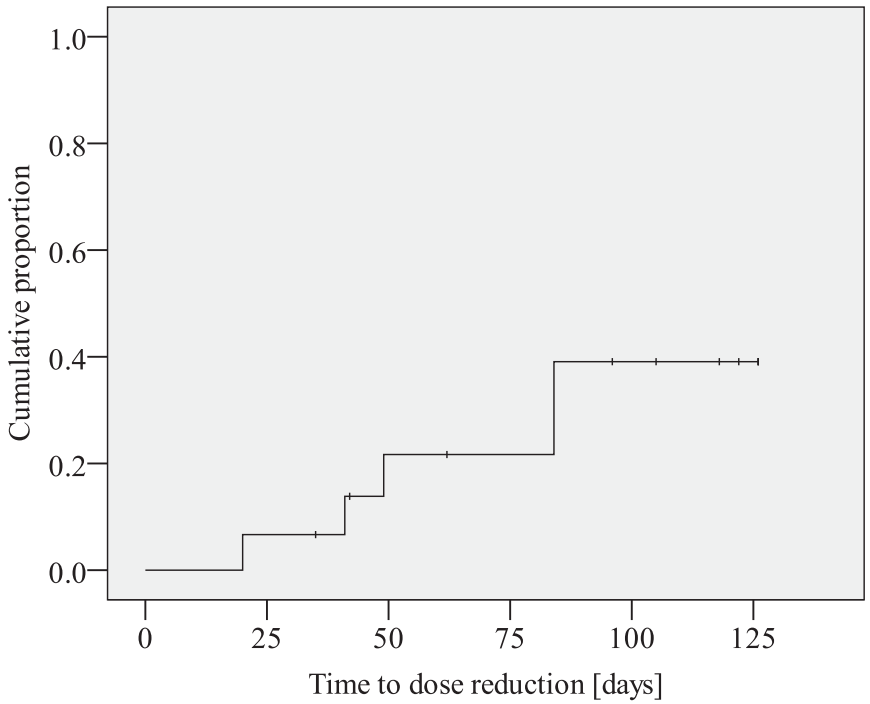



*Figure 4-39: Time to dose reduction [days] of capecitabine in initially non-adherent patients; vertical lines represent censored data*

### 4.4.9 Pharmacist's working time

Pharmacist's working time needed for modular medication management was documented regarding the duration of interviews and rework. In terms of initially non-adherent patients, it has to be considered that the time needed for patient interviews and rework in the context of module 3 (adherence support) is included in the data shown in Table 4-34 and Table 4-36. The median duration of the initial patient interview accounted for 30 minutes (Table 4-34). One initially non-adherent patient had four discussions with the study pharmacist before the start of his capecitabine treatment.

*Table 4-34: Duration and rework of the initial counselling conversation with initially non-adherent patients (n=15, 18 conversations)*

| | **Duration [min]** | **Rework [min]** |
|---|---|---|
| Mean | 36 | 12 |
| Median | 30 | 7 |
| SD | 27 | 16 |
| Range | 10-107 | 0-60 |
| IQR | 17-40 | 2-14 |

The number of conversations per patient ranged from one in cycle 4 up to two conversations in cycle 5 and 6 (compare Table 4-35). Information on the duration and rework of follow-up patient interviews conducted during the course of the modular medication management at $t_1$, $t_2$, $t_3$, $t_4$, $t_5$, and $t_6$ are shown in Table 4-36. Median duration of follow-up patient interviews ranged from four minutes in cycle 4 to eight minutes in cycle 1 and 2.

*Table 4-35: Number of patient conversations during the course of the study*

| | **Cycle 1** | **Cycle 2** | **Cycle 3** | **Cycle 4** | **Cycle 5** | **Cycle 6** |
|---|---|---|---|---|---|---|
| n | 15 | 15 | 13 | 12 | 12 | 8 |
| Conversations | 24 | 21 | 18 | 8 | 22 | 14 |
| Conversations/patient | 1.6 | 1.4 | 1.4 | 0.7 | 1.8 | 1.8 |

*Table 4-36: Duration and rework of follow-up counselling conversations with initially non-adherent patients*

| | | Duration [min] | Rework [min] | | | Duration [min] | Rework [min] |
|---|---|---|---|---|---|---|---|
| $t_1$ | n | 15 | 15 | $t_4$ | n | 12 | 12 |
| | Mean | 14 | 2 | | Mean | 7 | 1 |
| | Median | 11 | 0 | | Median | 4 | 0 |
| | SD | 16 | 5 | | SD | 8 | 1 |
| | Range | 0-60 | 0-20 | | Range | 0-23 | 0-5 |
| | IQR | 4-22 | 0-1 | | IQR | 0-14 | 0-0 |
| $t_2$ | n | 15 | 15 | $t_5$ | n | 12 | 12 |
| | Mean | 13 | 1 | | Mean | 13 | 1 |
| | Median | 9 | 0 | | Median | 12 | 0 |
| | SD | 18 | 2 | | SD | 13 | 1 |
| | Range | 0-67 | 0-8 | | Range | 0-40 | 0-3 |
| | IQR | 0-16 | 0-1 | | IQR | 0-20 | 0-2 |
| $t_3$ | n | 13 | 13 | $t_6$ | n | 8 | 8 |
| | Mean | 15 | 2 | | Mean | 8 | 2 |
| | Median | 6 | 0 | | Median | 8 | 0 |
| | SD | 18 | 5 | | SD | 11 | 4 |
| | Range | 0-50 | 0-20 | | Range | 0-40 | 0-15 |
| | IQR | 0-36 | 0-2 | | IQR | 0-11 | 0-1 |

### 4.4.10 Patient evaluation

Twelve initially non-adherent patients filled in the questionnaire on patient evaluation. 66.7% (8/12) assessed the therapy outcome of their oral chemotherapy as expected. Two of 12 patients (16.7%) evaluated the outcome as slightly worse and 1/12 patients (8.3%) as much worse than expected. Assessment of adverse drug reactions of capecitabine compared with the patients' expectations was distributed all over the Likert scale. Thirty-three percent (4/12) evaluated experienced adverse drug reactions as they expected them before, 2/12 (16.7%) stated 'slightly better' and the same number of patients stated 'slightly worse'. For details see Figure 4-40.

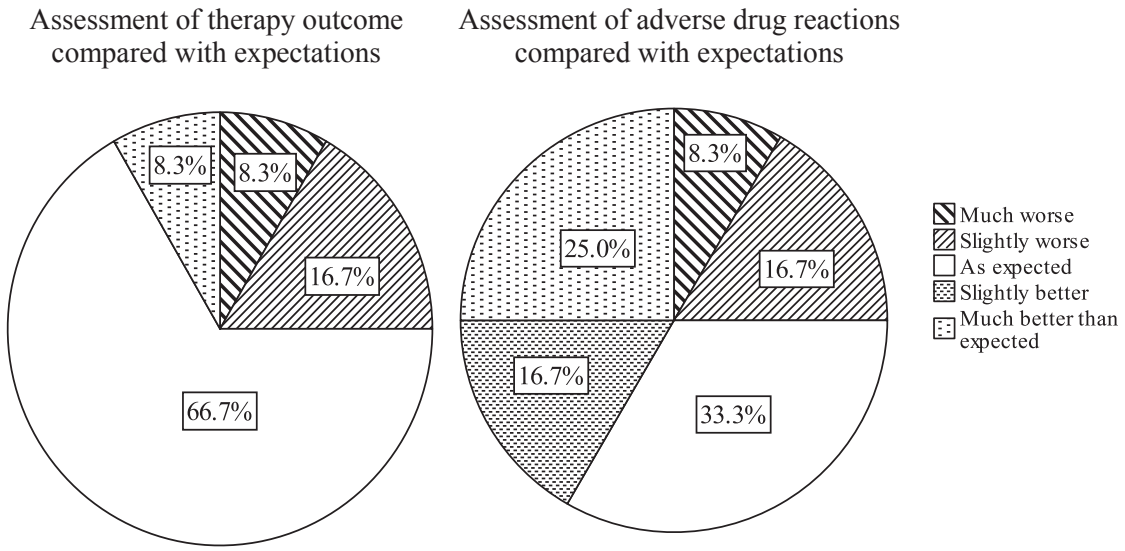



*Figure 4-40: Initially non-adherent patients' evaluation of two different aspects of the capecitabine treatment assessed at $t_6$; n=12*

Overall assessment of treatment was mostly fair (4/12, 33.3%) and good (4/12, 33.3%), see Figure 4-41.

Details on the results of the questionnaire on patient evaluation are accessible in Appendix E, Table E-6.

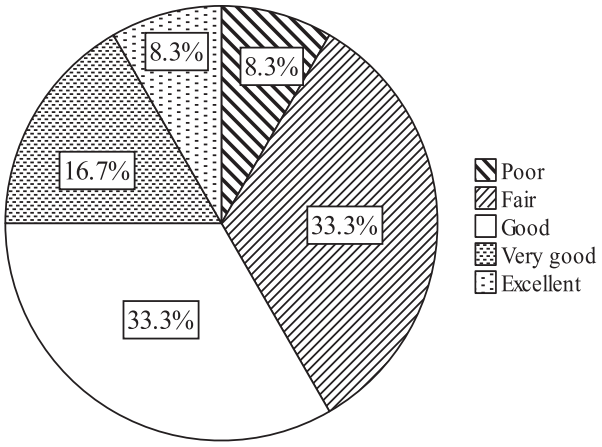



*Figure 4-41: Initially non-adherent patients' overall assessment of capecitabine treatment assessed at $t_6$; n=12*

## 4.5 Further analyses in the entire patient cohort

### 4.5.1 Relationship between overall adherence and hand-foot syndrome

Since the occurrence of hand-foot syndrome (HFS) is not likely to be confounded by cancer entity, the entire patient cohort was analysed in terms of an existing relationship between HFS and overall adherence. Since a possible drug over-consumption also is reflected by the calculation of overall adherence, this adherence parameter was chosen for the analysis of the relationship between adherence and HFS. In order to revise the assumption that the cancer type is not likely to influence HFS, cancer entity as influencing factor on the occurrence of HFS was investigated additionally.

Overall adherence (referring to the whole observation period) as continuous variable and dichotomised by median was not found to be connected to the occurrence of HFS in a statistically significant manner. HFS was classified into individual HFS grades (HFS grade 1 to 3, or HFS grade 2 to 3). Table 4-37 shows the respective results.

*Table 4-37: Tests on significant relationship between overall adherence [%] and HFS*

| Dependent variable | Independent variable | n | p value |
|---|---|---|---|
| Overall adherence [%] | No HFS | 16 | 0.273* |
| | HFS max. grade 1 | 16 | |
| | HFS max. grade 2 | 25 | |
| | HFS max. grade 3 | 14 | |
| | Missing | 2 | |
| Overall adherence [%] | No HFS grade 1-3 | 16 | 0.301** |
| | HFS grade1-3 | 55 | |
| | Missing | 2 | |
| Overall adherence [%] | No HFS grade 2-3 | 32 | 0.583** |
| | HFS grade2-3 | 39 | |
| | Missing | 2 | |
| Overall adherence dichotomised by median [<100% / ≥100%] | No HFS grade 1-3 | 16 | 0.165*** |
| | HFS grade 1-3 | 55 | |
| | Missing | 2 | |
| Overall adherence dichotomised by median [<100% / ≥100%] | No HFS grade 2-3 | 32 | 0.309*** |
| | HFS grade 2-3 | 39 | |
| | Missing | 2 | |

** Kruskal-Wallis-H test*
*** Mann-Whitney-U test*
**** Chi-square test*

No difference in time to first occurrence of HFS grade 1 to 3 between patients whose overall adherence accounted for greater or equal the median (black line) and patients with an overall adherence of less than the median (dotted line) could be observed (p value=0.458, log-rank test). Figure 4-42 illustrates this finding by means of a Kaplan-Meier plot. Triangles and rhombi mean censored data (either patients who did not experience HFS at all until the end of the sixth cycle or patients who completed less than six cycles). Regarding time to first occurrence of HFS grade 2 to 3, no statistically significant difference between the two described overall adherence groups was found either (p value=0.202, log-rank test), see Figure 4-43.

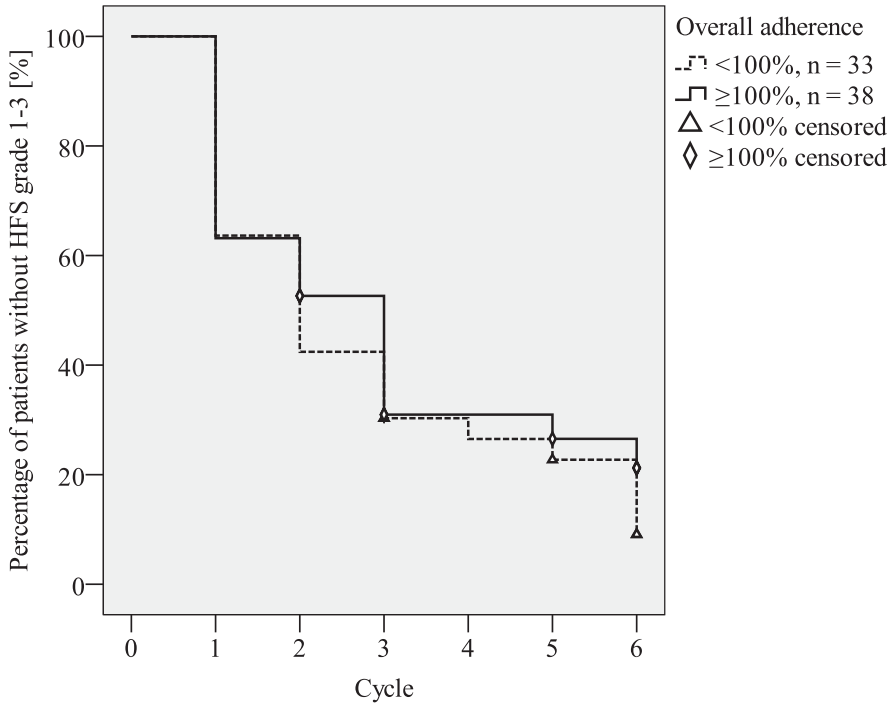



*Figure 4-42: Time to first occurrence of HFS grade 1-3 during the study period of patients showing an overall adherence ≥ median and < median, respectively (median=100%); p value=0.458, log-rank test; numbers in the legend represent the number of studied patients*

No statistically significant effect of overall adherence parameters on time to HFS was observed by means of Cox regression models. Table 4-38 and Table 4-39 summarise three models each for time to first occurrence of HFS grade 1 to 3 and grade 2 to 3, respectively. The effect of tumour entity on time to HFS was investigated in order to verify the assumption that occurrence of HFS is not likely to be confounded by cancer entity (see 3.9). A statistically not significant result in time to occurrence of HFS grade 1 to 3 and grade 2 to 3 indicate the correctness of the assumption.

Therefore, the conducted analyses suggest that a significant association between overall adherence and the occurrence of HFS is unlikely.

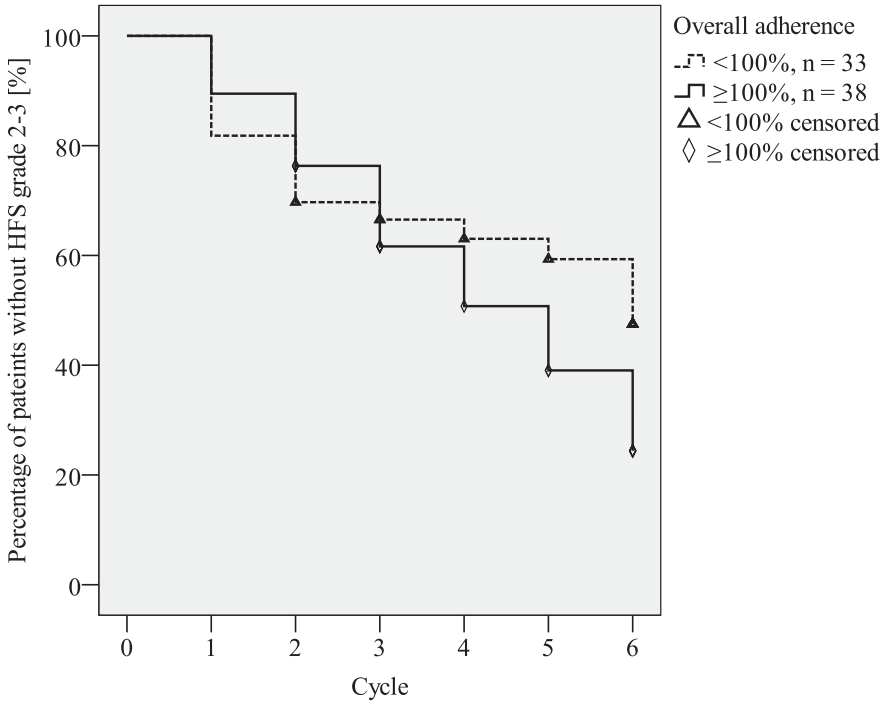



*Figure 4-43: Time to first occurrence of HFS grade 2-3 during the study period of patients showing an overall adherence ≥ median and < median, respectively (median=100%); p value=0.202, log-rank test; numbers in the legend represent the number of studied patients*

*Table 4-38: Cox regression models for time to first occurrence of hand-foot syndrome grade 1-3 (enter method)*

| **Covariates** | **n** | **HR** | **95%-CI** | **b** | **p** |
|---|---|---|---|---|---|
| Overall adherence [%] | 71 | 0.992 | 0.905-1.088 | -0.008 | 0.870 |
| Overall adherence dichotomised | | | | | |
| ≥100.0% | 38 | 0.847 | 0.499-1.437 | -0.166 | 0.538 |
| <100.0%* | 33 | | | | |
| Tumour entity | | | | | |
| Breast cancer | 28 | 1.053 | 0.445-2.495 | 0.052 | 0.906 |
| Colorectal cancer | 31 | 1.390 | 0.606-3.185 | 0.329 | 0.437 |
| Other cancers* | 12 | | | | 0.557 |

*n: number of patients; HR: hazard ratio; 95%-CI: 95%-confidence interval for hazard ratio; p: p value of the 'likelihood ratio'-test; b: coefficient estimated by Cox regression; * reference group in case of categorical variables*

*Table 4-39: Cox regression models for time to first occurrence of hand-foot syndrome grade 2-3 (enter method)*

| Covariates | n | HR | 95%-CI | b | p |
|---|---|---|---|---|---|
| Overall adherence [%] | 71 | 1.030 | 0.918-1.156 | 0.030 | 0.612 |
| Overall adherence dichotomised | | | | | |
| ≥100.0% | 38 | 1.476 | 0.774-2.814 | 0.389 | 0.237 |
| <100.0%* | 33 | | | | |
| Tumour entity | | | | | |
| Breast cancer | 28 | 2.130 | 0.616-7.363 | 0.756 | 0.232 |
| Colorectal cancer | 31 | 2.579 | 0.769-8.648 | 0.947 | 0.125 |
| Other cancers* | 12 | | | | 0.301 |

*n: number of patients; HR: hazard ratio; 95%-CI: 95%-confidence interval for hazard ratio; p: p value of the 'likelihood ratio'-test; b: coefficient estimated by Cox regression; * reference group in case of categorical variables*

### 4.5.2 Potential predictors of adherence

There was no indication for a relationship between patients' daily total adherence during the first cycle and their age (Spearman's r=0.009, p=0.941). The age of the entire patient cohort ranged from 36 to 90 years. It was observed that those three participants who showed the lowest adherence results during cycle 1 (28.6%, 57.1%, and 64.3%) were of a relatively high age (90, 75, and 79 years), see Figure 4-44.

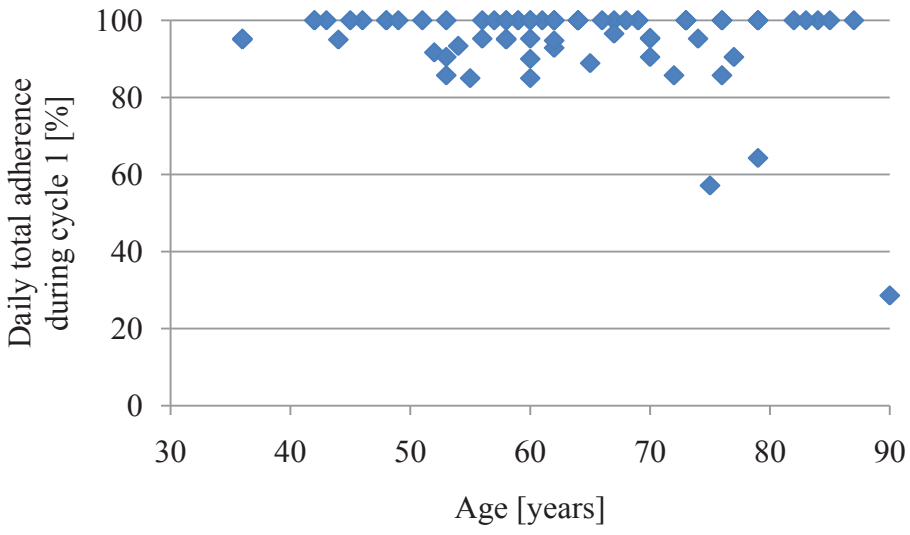



*Figure 4-44: Relationship of daily total adherence during cycle 1 [%] and age [years]; n=73*

A relationship between daily total adherence during cycle 1 and participants' gender was not found either (p=0.891, Mann-Whitney-U test). In addition, there was not any significant association between daily total adherence and any of the further socio-demographic and disease-related characteristics. Appendix F, Tables F-1, F-2 and F-3 contain detailed information on the

relationship and correlation, respectively, between daily total adherence during cycle 1 and all potential influencing factors and covariates, respectively, tested.

Spearman correlation of daily total adherence during cycle 1 and the covariate EORTC QLQ-C30 scale 'social functioning' revealed a statistically significant association (Spearman's r=0.285, p=0.023). However, on close examination it became obvious that outliers biased the result and no actual relationship between these two variables exists, see Figure 4-45.

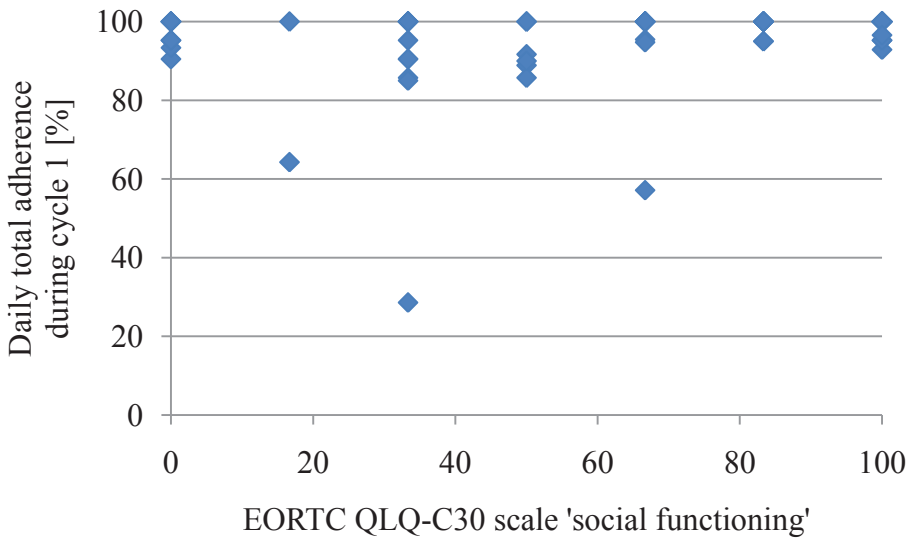



*Figure 4-45: Relationship of daily total adherence during cycle 1 [%] and the EORTC QLQ-C30 scale 'social functioning'; n=63*

Correlation of daily total adherence during cycle 1 and the covariate PSCaTE dimension VC (satisfaction with information on vitamins, herbal medicines and complementary treatment options) revealed a result that was close to statistically significant (Spearman's r=0.239, p=0.066). The same applied to the correlation of the mentioned adherence parameter with distance to patients' treatment site (Spearman's r=-0.225, p=0.075). However, the same phenomenon was observed and outlier values biased the finding as described above. Corresponding scatter diagrams clarified this circumstance and can be accessed in Appendix F, Figures F-1 and F-2.

# 5 Discussion

The future of pharmacy is based on presenting the beneficial effects of pharmaceutical care services on patient outcomes [115]. In this study, we applied a systematic screening for non-adherent patients at an early stage of their capecitabine chemotherapy in order to provide a patient-tailored modular medication management. The results indicate that specific adherence support might improve adherence of initially non-adherent patients to capecitabine and that initially adherent patients' medication taking behaviour persists over time under basic pharmaceutical care and adverse event management.

## 5.1 Study set-up

### Study design

The present study utilised a prospective, multi-centred, two-arm observational cohort study design. All patients received modular medication management consisting of basic pharmaceutical care and adverse event management. Adherence screening gave information about patient adherence during the first capecitabine cycle. Only initially non-adherent patients received special adherence support accompanying their anti-cancer treatment.

Previous studies conducted at the Department of Clinical Pharmacy, University of Bonn, also utilised a prospective, multi-centred observational cohort design. However, a preceding control group was used instead of two study arms. The impact of pharmaceutical care provided by study pharmacists on various outcome parameters was evaluated. In each of the earlier studies the control group received standard care provided by health care professionals of the respective study centre and intervention group patients additionally received pharmaceutical care provided by study pharmacists. Beneficial effects of pharmaceutical care on nausea and emesis, adherence, cost-effectiveness, quality of life, and patient satisfaction with information were shown [55–62]. These findings built the basis for the present study. As benefits of pharmaceutical care on patient adherence have been shown previously [55–62], this study focused on resource-saving adherence management (early adherence screening and specific adherence support). Since patients were purposely separated according to their baseline daily adherence, randomisation of study participants in terms of receipt of the adherence support intervention was not applicable in the present study.

The pharmaceutical care intervention applied was complex because it implied changes in the traditional interactions between pharmacist, physician, nurse, and patient, and contained an

altered organisation and process of patient care. [116]. The definition of clear outcomes is particularly important in the design of such a study which has the aim to evaluate the benefit of pharmaceutical care services [117]. In studies evaluating complex interventions, the combination of one single primary outcome with some secondary outcomes is the most straightforward way for statistical analysis. Moreover, appropriate subgroup analyses should be incorporated [116]. Any analysis of quality should consider all three quality measures, structure, process, and outcomes. No isolated measure is able to describe the quality of care provided. Important structural inputs are e.g. patient profiles. Medication history taking, monitoring, and patient counselling on the correct way to use treatment are examples for crucial process activities. Outcomes are both intended endpoints of care and unintended consequences (e.g., adverse drug reactions) [115]. In Germany, the additional evaluation of subjective endpoints (e.g., quality of life, patient expectations) is increasingly demanded [118]. The combination of outcome parameters which has been chosen to be assessed in the present study meet the demands mentioned above, and therefore the outcomes are valid for the evaluation of benefits of pharmaceutical care service.

**Study realisation**

Patients who are treated at the same treatment site – be it an oncology outpatient ward or practice – usually initiate conversations with each other and exchange their experiences regarding received treatments and patient care. Initially adherent patients did not receive module 3 (adherence support) during the course of the present trial. Since patient counselling sessions of the modules ‘basic pharmaceutical care’ and ‘adverse event management’ were scheduled after every conducted capecitabine cycle as well as adherence support visits, a perceived disadvantage was avoided. Consequently, initially adherent patients did not get the impression to receive less intense patient care provided by the study pharmacists and less information concerning their cancer treatment.

Modular medication management was mainly provided by one study pharmacist (the author of this thesis). However, a second study pharmacist was involved in patient care for four patients. To diminish the influence of the individual competences and skills of the study pharmacists, the process of medication management was standardised where possible. All patient conversations were held and documented in a structured way using predefined documentation forms (pharmaceutical care plan, consultation documentation forms etc. which can be found in Appendix C). It was defined beforehand which exact situations required a contact with the responsible physician. Furthermore, every patient received the same standard components of care like an interaction check and a medication plan. The kind of written information material handed out to every patient at the beginning of study participation was exactly determined in advance.

During the accomplishment of the present study the study pharmacists provided broad pharmaceutical information to patients and health care professionals. To improve patient care and guarantee high quality pharmaceutical care services, relevant evidence was searched according to the concept of evidence-based medicine. The five-step approach to effectively practice evidence-based medicine was taken into account (formulation of clinical question, search of evidence, critical appraise of evidence, integration of critical appraisal with physician's expertise and individual patient, evaluation and improvement of personal approach) [119]. Basically, information given during the course of pharmaceutical care was provided orally or in written form depending on the particular situation taking into account that provision of written information in addition to oral information is essential for the content's sustainability [120].

In the present study, the two clinical pharmacists provided pharmaceutical care and performed all activities concerning data collection and analysis of the results. Thus, they were both practitioners and researchers. This set-up might possibly imply conflicting interests. A more appropriate approach would have been a strict separation of the delivery of modular medication management and research and evaluation of this service. Moreover, it would have been reasonable if the person who analysed the results would not have been aware of patients' baseline adherence and group assignment. Due to personnel and budget constraints it was not possible to realise these demands. However, every effort was taken to minimise possible bias caused by the study pharmacists. Standard procedures for the analysis of MEMS® profiles were defined beforehand and analysis of questionnaires was carried out in the exact same manner consistently. In the event of controversial results, a group of experts of the Department of Clinical Pharmacy, University of Bonn, was consulted. The group discussed the debatable result in detail and a majority decision was made. Furthermore, patients filled in the questionnaires unobserved and independently, only in very rare cases the study pharmacists provided minor help in terms of completion of the questionnaire (e.g., if a patient had problems to understand individual questions or to read the questionnaire). Even though the mentioned limitations exist, standardised procedures were utilised in terms of methods of data collection and analysis of the results in order to ensure a robust and reliable evaluation of study endpoints.

Feasibility of modular medication management applied in this study was not distinctively investigated and proven by scientific approaches. However, experience gained by the study pharmacists shall not be missing at this point. The conduction of modular medication management implied a close collaboration between the pharmacists and other health care providers like mainly physicians and nurses. During the accomplishment, it became apparent that it takes time to implement such a complex pharmaceutical care intervention and to establish a successful multidisciplinary collaboration based on mutual trust. Doucette et al. described that

trustworthiness is crucial in the development of collaborative relationships and also, to facilitate open communication between health care professionals. As time passes and the pharmacist is able to demonstrate his expertise by the quality of recommendations he gives, the physicians increasingly trust the pharmacist's competence. This is especially the case when useful recommendations are made consistently over time. Moreover, the relationship is more likely to become collaborative when pharmacists and physicians jointly determine specific roles. In addition, the extent of professional interactions between physician and pharmacist has been described to be significantly associated with collaborative patient care. At marginal levels of cooperation, most multidisciplinary communications were initiated by the pharmacist. As the pharmacist's role increased, the physician began to address the pharmacist for opinions, updates, and other information [121]. During the conduction of the present trial, especially trustworthiness and professional interaction have been experienced to foster collaboration between pharmacists and other health care providers. Possibly, routine face-to-face interactions contributed to a trust-based relationship [122].

Time or the lack of it is another limiting factor in the feasibility of pharmaceutical care services [123–126]. Analysis of pharmacist's working time gave information about additional expenditure of time caused by an implementation of pharmaceutical care concepts. In the present study, pharmacist's working time was assessed in terms of duration of patient interviews and rework. Rework included activities like preparation of the counselling sessions, post processing, literature search, interaction checks, generation of medication plans, and discussions with other health care professionals. Initially, a raised expenditure of time has to be taken into account. However, the median duration of follow-up interviews ranged from 2 to 12 minutes. These results are in line with previous findings and show that additional expenditure of time for the conduction of pharmaceutical care is kept within reasonable dimensions [57, 61, 95].

**Patient recruitment**

A major limitation of our study is the relatively small number of initially non-adherent patients. Instead of the required sample size of 30 initially non-adherent patients, only 15 patients could be enrolled during the study period. Previous data suggested a distribution of 60% initially adherent and 40% initially non-adherent patients [57]. The actual distribution in our patient population, however, was 80% to 20%. This has to be considered before interpreting data of the initially non-adherent patients. However, a clear trend towards an improved adherence over time was observed. Further multicenter studies are needed to be able to generalise the findings.

Apart from the proportion of initially non-adherent patients which has been different than expected, patient recruitment was connected with several difficulties. Especially in the early stages of the project it was difficult to sustain a fluent recruitment process. This might be

explained by lack of time in daily routine of the study centers [127]. Patient recruitment improved during the course of the study. Possibly, it took some time for collaborating health care professionals to bear the announcement of eligible patients to the study pharmacists in mind and to get familiar with changed processes of patient care. Nevertheless, it seems possible that collaborating physicians might not have announced every eligible patient to the study pharmacists. Possibly, a certain pre-selection of study participants by the collaborating physicians happened (knowingly or unknowingly). Data on the total number of cancer patients treated in the respective study centres during the study period are not available. Especially information on the number of eligible patients who were not announced to the study pharmacists would be of particular interest for further analysis. One oncology outpatient ward requires further explanation. This centre recruited the vast majority of study participants (54 of 73). Therefore, one of the two study pharmacists spent a lot of time at that site becoming a constantly integrated member of the respective health care team. Accordingly, it is likely that most eligible patients of this centre were included in the study. This can be explained by the constant awareness of the physicians about the study due to the presence of the study pharmacist. Due to personnel constraints it was not possible to integrate a pharmacist in the cancer care team of each study centre. However, this seems to be an effective measure to improve patient recruitment.

It is known that one possible reason for participant recruitment problems is a smaller percentage of patients agreeing to participate than expected [127]. In this study, eight patients refused to participate. The most common reason was perceived additional stress during the study period in addition to their mentally and/or physically impaired condition. Moreover, 11 patients did not meet the inclusion criteria. Five patients were not capecitabine-naïve, four patients participated in another trial and two patients were not able to understand and speak German. Concerning the present study, participation in another trial precluded the use of the MEMS® containers. Since the other study's protocol demanded a return of the empty and whole capecitabine blister packs, it was not possible to handle the blister packs as usual in this study (reduce them to small pieces and store them in the MEMS® container). Language difficulties as well as competing research are known recruitment problems [127].

**Patient population**

Although randomisation of patients was not applicable in the present study and patients were separated intentionally according to their baseline adherence, comparable patient groups were created in terms of general participant characteristics. No statistically significant differences concerning socio-demographic and disease-related variables were found. The observed median age of patients treated with capecitabine (initially adherent: 62 years, initially non-adherent: 65 years) is consistent with data from previous studies which reported a median age of 61 to 71

years [19, 22, 61, 128, 129]. Hence, initially non-adherent patients were in the median four years older than initially adherent patients. Moreover, initially non-adherent patients took a median number of two additional orally administered drugs more (5 versus 3). All initially non-adherent patients (15/15) took at least one additional drug, whereas the relative frequency distribution of initially adherent patients under additional oral treatment was 88% (50/57). Since an older age and a cancer diagnosis are usually connected with a higher medication usage, this finding is reasonable and in line with the results of a study from 2010 [130], in which 112 patients older than 65 years and newly diagnosed with breast, colorectal or lung cancer, lymphoma or multiple myeloma were surveyed. At baseline, the majority of these patients (92%, 103/112) were taking medications and the median number of medications per patient was five. Although no statistically significant difference between the adherence groups studied in the present study in terms of age and additional drugs was discovered, this result indicates a slight trend towards lower adherence in patients with increasing age and number of additional drugs.

**Study drop-outs and missing data**

The EMA recommends the usage of an intention-to-treat analysis (analysis of all patients based on initial treatment group allocation) in order to minimise bias due to inconsistencies between treatment groups. Intention-to-treat analysis is especially recommended in terms of analysing the results of a randomised controlled trial in order to ensure group consistency and, thus, to achieve best possible internal validity [131]. The present study, however, is a non-randomised cohort study and in this case intention-to-treat analysis is not as essential as in randomised controlled trials. Five study drop-outs were recorded who were not analysed, one patient withdrew informed consent, two patients did not use the MEMS® container and two patients died before the containers could be read out. Thus, a classification as either initially adherent or non-adherent of the latter four patients was impossible which, however, represented the prerequisite for their assignment to one of the two study arms. Patients who dropped out of the present study because of other reasons than the reasons mentioned above were included in analysis. Other reasons for a shortened observation period included premature discontinuations of capecitabine treatment by the physician (due to tumour progression, adverse drug reaction, hospital admission, toxicity of a co-administered drug, or patient's wish to stop treatment), a planned treatment period of less than six cycles, the death of a patient, or the patient's wish to quit the study participation. Nevertheless, the number of study drop-outs who were not analysed was relatively low, so that it did not represent a difficulty in the present study. Therefore, per-protocol-analysis was used.

In the present study, missing data could not be avoided completely. As recommended by the EMA [131], every effort was undertaken to fulfill all the requirements of the protocol concerning data collection and management. A close contact between study pharmacists and

participating patients on a regular basis ensured the minimisation of missing data. Furthermore, the integration of one study pharmacist in the health care team of the study centre which recruited most participants contributed to the completion of collected data. In reality, however, missing data will almost always occur to some extent [131]. In the event of missing patient data in the present study (e.g., missing questionnaires, periods of MEMS® container non-usage), available data of the respective participant were analysed. Since the amount was not substantial, missing data did not represent a problem.

## 5.2 Adherence measurement

### Adherence screening

For the classification of patients as initially non-adherent or adherent, daily adherence of the first drug intake period plus the first day of the therapy-free interval assessed by MEMS® was used. Consideration of the whole capecitabine cycle would have provided a more complete picture of the participant's adherence during the first cycle. However, this was not feasible. In order to initiate adherence support before the start of cycle 2, an exact appointment on day 21 of the first cycle for group allocation would have been necessary. A belated start of the adherence-supporting module would have biased the results of initially non-adherent patients.

Although the presented approach was suitable to discriminate between adhering and non-adhering patients it would be easier to identify non-adhering patients by means of possible predictors. With knowledge of adherence predictors a screening method without electronic monitoring could be developed, e.g. by a specific questionnaire. In general, numerous factors associated with non-adherence to oral anti-cancer drugs have been identified like e.g. side effects, forgetfulness, or disliking aspects of treatment [85, 132]. On the basis of our data, it was not possible to predict adherence from socio-demographic or disease-related characteristics, e.g. age. Indeed, we observed that the three patients exhibiting the lowest baseline adherence during cycle 1 (28.6%, 57.1%, and 64.3%) were of a relatively old age (90, 75, and 79 years). Moreover, initially non-adherent patients were in the median older than initially adherent patients (65 versus 62 years). Although it has been described previously that older age was associated with poor adherence to oral anti-cancer treatment [85, 132–134], however, it cannot be concluded that adherence decreases with increasing age as there were also elderly patients exhibiting high adherence. These findings are in line with the findings of Partridge et al. who did not find an association of adherence and age [86]. Furthermore, Bhattacharya et al. did not identify significant associations between self-reported adherence to capecitabine and experience of side effects, beliefs about capecitabine, or satisfaction with information. However, the generalisability of this study was limited by a relatively small sample size as well [89].

Therefore, larger multi-centre studies are necessary to identify predictors of non-adherence to capecitabine.

The current study suggests an association between the adherence status at the beginning of the oral anti-cancer treatment and the treatment setting. Sixty patients (51 initially adherent/nine initially non-adherent) were recruited on two oncology outpatient wards and 13 patients (seven initially adherent/six initially non-adherent) in two oncology practices (p value=0.021, Fisher's exact test). One oncology practice recruited six initially adherent and six initially non-adherent participants and the other practice recruited one initially adherent patient. Thus, relatively more initially non-adherent patients were recruited in private oncology practices than in oncology outpatient wards (46% versus 15%). According to the study design, adherence status was not known at time of recruitment. It seems reasonable that the larger oncology outpatient wards basically recruited more patients during the study period than the collaborating oncology practices. However, it is remarkable that the distribution of initially adherent and non-adherent patients recruited from the different settings is that diverse. It has been described previously that the private community-based treatment sector (versus an academic setting) is a factor which is significantly associated with poor patient adherence to physician's prescription directives regarding chemotherapy [85, 135]. On the other hand, no statistically significant relationship between daily total adherence during cycle 1 and the patients' treatment setting could be observed. It has to be taken into account that this differing distribution might have occurred randomly due to the small sample size of 15 initially non-adherent patients. However, the result might indicate an interesting trend.

Other potential factors with a negative influence on adherence also include a prolonged travelling time for patients to their treatment site [63], complex treatment regimens and multiple co-medication [63, 136], low level of education [63], longer time since cancer diagnosis, and living alone [132]. Focusing on the studied patient cohort, initially non-adherent patients travelled a longer median time to reach their treatment site than initially adherent patients (28 versus 20 minutes), and took a higher median number of additional regularly and orally administered drugs (5 versus 3). A lower percentage of initially non-adherent patients than initially adherent patients was treated with capecitabine as a single-agent treatment (47% versus 60%) and had a university/college degree (7% versus 14%). Median time since diagnosis was longer in initially non-adherent patients (16 versus 13 months) and a higher proportion of initially non-adherent patients lived on their own (20% versus 14%). Although the differences between the two adherence groups regarding the mentioned socio-demographic or disease-related characteristics were not statistically significant and no significant relationships between daily total adherence during cycle 1 and the mentioned variables were found, these results may be considered as trends. Nevertheless, the small sample size of the studied patients limits the

validity of the observed results. Therefore, larger multi-centre studies are necessary to identify precise and specific predictors of non-adherence to capecitabine. If predictors were identified a more user-friendly adherence screening method than the measurement with MEMS® (e.g., specific questionnaires like MARS) could be developed and MEMS® measurement could be replaced. However, as long as the respective evidence is not available, assessment of adherence by means of MEMS® would be necessary.

Subgroup analyses of daily total adherence results were conducted in terms of gender, tumour entity, treatment regimen, and treatment intention groups. Regarding initially adherent patients, no statistically significant differences of daily total adherence between particular subgroups were observed, apart from the difference between patients who were treated with single agent versus combination therapy in cycle 6. Patients who received single agent capecitabine exhibited a higher adherence. Accordingly, a statistically significant difference between these two regimen groups was shown in initially non-adherent patients at $t_4$. Additionally, a trend towards better adherence of patients treated with capecitabine monotherapy could be observed during most other cycles. These findings are consistent with previous research showing that complex treatment regimens negatively affect adherence [63, 136]. However, this result was only observed in individual cycles and it would be interesting to see if this finding would be confirmed by the assessment of a larger patient population. A marginal trend towards higher adherence in female initially non-adherent patients could be observed. However, the studied patient cohort was small and the difference was not statistically significant. Concerning this matter, previous research presented conflicting results. On the one hand, adherence of HIV-seropositive patients with antiretroviral therapy was lower among women than among men [137]. On the other hand, a patient-related determinant associated with higher non-adherence to imatinib therapy was found to be male sex [132].

**Effect of modular medication management**

Mean daily total adherence of initially adherent participants under modular medication management (without receiving adherence support) was high throughout all six observed cycles; it ranged from 96.7% to 98.9%.

All but one patient showed an adherence of ≥90% after the sixth cycle (36/37, CI 88.8%-99.4%). Thus, the current study proved that >75% of initially adherent patients were adherent after the modular medication management. The present data demonstrate that one of the postulated working hypotheses (patients with a baseline adherence of >90% do not require adherence support) is correct. Initially non-adherent patients' mean daily total adherence during cycle 1 accounted for 80.8%. During the course of cycle 2 to 6 this adherence parameter ranged from 90.5% to 93.7%. These patients received adherence support in addition to basic

pharmaceutical care and adverse event management. Seventy-five percent (6/8, CI 46.0%-91.3%) of initially non-adherent patients exhibited an adherence of ≥90% after the sixth cycle. Consequently, the hypothesis that >80% of these patients were adherent after the modular medication management (including the adherence support module) was not confirmed. Despite the small sample size of 15 initially non-adherent patients, a trend towards an improved adherence under medication management including adherence support over time was, however, observed. Nevertheless, large multi-centre studies are needed to provide more generalisable findings concerning the development of initially adherent and non-adherent patients' adherence under medication management.

Correct interpretation of adherence results is dependent on the exact way of calculating the respective adherence parameter, e.g. daily adherence, overall adherence, variability of dosing intervals (compare 3.7.2) [138]. Moreover, adherence results are dependent on the method used for measuring. Self-reports tend to overestimate adherence and have been criticised as too subjective [67, 73, 75]. The present results confirm that both initially adherent and non-adherent patients overestimate their adherence compared to the electronic adherence measurement. The observed discrepancy of the two measures was more pronounced in the group of initially non-adherent patients exhibiting a MEMS®-assessed daily total adherence between 33% and 80% during cycles 2 to 6. Patient self-report revealed higher results, 83% to 100% of the patients stated that their adherence was high (correct intake on 13 of 14 days). Concerning initially adherent patients, MEMS®-assessed daily intake adherence was high throughout the whole treatment period, self-assessed daily intake adherence, however, was even higher. When evaluating the treatment period as a whole, the difference between initially non-adherent patients' statement (mean 95.9%) and electronic monitoring (mean 89.7%) was not statistically significant (p value=0.050, Wilcoxon test). In initially adherent patients the difference was marginal (97.9% versus 97.7%). Therefore, electronic monitors like MEMS® provide a more objective impression even though expensive and complex to handle [67, 73, 75]. Consequently, comparison of adherence results from different studies that used different parameters and measuring methods might remain vague and methodologically flawed. This applies to the present study, as further studies that used the same approach are missing. Most studies which investigated adherence to capecitabine assessed medication taking behaviour by means of patient self-reports (one study in combination with MEMS®, another study combined with pill counts). These studies did not imply the concept of pharmaceutical care and adherence parameters were defined diversely. Generally, patient adherence was found to be relatively high even without the provision of pharmaceutical care services [81, 88–91]. However, individual patients who possibly showed poor adherence were not identified and analysed separately as it was the case in the present study. Since the number of non-adherers to capecitabine seems to be generally low, final adherence results are not influenced to a great extent. Results of the second

interim analysis of a German non-interventional study with capecitabine reported that the adherence rate of capecitabine intake was between 84.5% (cycle 1) and 73.2% (cycle 12) [104]. This seems lower compared to self-reported adherence results of the present study, but may be explained by the fact that the patients did not receive pharmaceutical care.

The study conducted by Simons et al. measured adherence using MEMS® and calculated daily adherence as it was done in the present study. The results demonstrated a high mean daily adherence of patients under pharmaceutical care (96.8%) [57]. Daily adherence was not calculated for each capecitabine cycle but for the whole observation period. These findings are consistent with the present results showing a high mean daily adherence during the whole observation period (97.7%) and a high mean daily total adherence during cycle 1 (98.9%) in initially adherent participants under medication management.

The adherence rates in this study are higher than those reported by Partridge et al. who found an average overall adherence measured by MEMS® (defined as the number of doses taken divided by the number of doses prescribed) between 70% to 80% [86]. Analysing our data the same way, overall adherence values ranged between 98.2% and 100.5% in initially adherent patients and between 93.8% and 102.7% in initially non-adherent patients. This might be explained by the fact that every participant of the present study received two medication management modules during all six cycles. In case of initially non-adherent patients, the provided adherence support might have increased adherence additionally. This finding is consistent with previous results from studies conducted at the Department of Clinical Pharmacy, University of Bonn. Under the provision of intensified pharmaceutical care to 48 breast and colorectal cancer patients, the intervention group showed an increased mean overall adherence in comparison to the control group [57]. In line with previous results [57, 86], non-persistence was not a problem in the studied group of patients.

In terms of overall adherence, some values exceeded 100%. The phenomenon of over-adherence in the actual sense has been described as an intentional intake of more doses than prescribed [139, 140]. However, when analysing the MEMS® profiles of our studied patient cohorts it became apparent that an intentional intake of more capecitabine than prescribed could be precluded. These medication taking behaviours might rather be characterised as unintentional over-adherence. Two values were particularly conspicuous. One initially adherent patient exhibited an overall adherence of 154% in cycle 3 and one initially non-adherent patient's overall adherence in cycle 3 accounted for 145%. The first patient mentioned took by mistake capecitabine for a period of three weeks instead of only for two with a subsequent week of treatment break. The latter patient took capecitabine during his intended treatment break as well. Further reasons for overall adherence values >100% were capecitabine intake events during the intended treatment break. Occasionally, patients forgot to stop capecitabine intake after 14

treatment days and took capecitabine on the first day of treatment break. Furthermore, it happened that patients started with their next cycle one day too early. Since over-adherence occurred to a certain extent in this study, patients should be educated carefully in terms of the complex treatment regimen of capecitabine.

Seventy-two percent (5048/7064) of the registered dosing intervals performed by the group of initially adherent patients were within the range of 10 to 14 hours. This result is reasonable and in line with previous results regarding adherence to capecitabine. Simons et al. found that 82.0% (2187/2667) of the dosing intervals of patients who received pharmaceutical care were within the mentioned range compared to 64.4% (1221/1897) in patients who did not receive pharmaceutical care [57]. Initially non-adherent patients exhibited only 1111/1906 (58.3%) dosing intervals between 10 to 14 hours. Consequently, it may be concluded that it is particularly essential to counsel patients treated with capecitabine regarding the importance of adherence to the correct dosing interval. Regnier Denios et al. reported satisfactory adherence of patients under capecitabine but poor observance of the dosing schedule [90]. Accordingly, adherence of our studied patient cohorts was high and dosing intervals were found to be improvable.

A factor which might have led to overestimation of adherence in our study is the so-called ‘Hawthorne effect’. If patients are aware of being monitored for adherence, it is possible that they manipulate the MEMS® monitor in order to show a higher level of adherence than actually true. Moreover, patients might have been more adherent than they would have been without adherence monitoring. However, since all patients were subject to the Hawthorne effect inter-individual comparisons should be valid.

The fact that patients were defined as initially adherent or non-adherent on the basis of an empirical threshold value (90%) represents a limitation of the study. It is unknown which adherence rates are necessary to achieve therapeutic success. A definition of required adherence rates gained e.g. from clinical studies would be helpful to assess the clinical relevance of enhanced patient adherence. Despite extensive literature search, no information could be found on the question how much adherence is needed in order to maximise efficacy of capecitabine treatment. To date, few adherence-improving interventions were demonstrated to have an impact on clinical outcomes [141]. Wu et al. demonstrated that poor adherence was associated with an increased mortality in patients receiving polypharmacy. Regular telephone counselling provided by a pharmacist enhanced adherence and, therefore, reduced mortality [98]. It is known that pharmaceutical care is able to enhance patient adherence [57]. Future research should examine the effect of adherence to capecitabine on the course of disease, clinical outcomes, and mortality and, thus, examine clinical relevance of adherence-enhancing interventions.

**Adherence management**

Even though daily total adherence could be improved in initially non-adherent patients, it has to be pointed out that this patient population did not reach the same adherence level as initially adherent patients. Moreover, inter-individual variability of adherence was higher. This finding suggests that a subgroup of patients with low adherence benefits from the adherence-enhancing intervention as suggested by Simons et al. [57]. However, a certain number of patients cannot be reached and shows a resistant medication taking behaviour. Reasons for intentional non-adherence in those patients were difficulties in swallowing tablets due to nausea and emesis caused by capecitabine (despite the provision of antiemetic prophylaxis and treatment), averseness to medication, or 'compensating' intake for previous non-adherence during treatment break. Unintentional non-adherence was mainly based on forgetfulness. Further research should include a systematic approach to develop strategies for adherence management in those 'resistant' patients.

An intentional background was detected in 26% (40/155) of non-adherent days compared to 34% (53/155) with unintentional non-adherence. However, reasons for the highest proportion of non-adherent days remained unknown (62/155, 40%) mainly because patients were not able to remember what had happened on that special day or period when they were asked by the study pharmacist (recall bias). Moreover, reasons for non-adherence were defined as unknown if the patients' explanations did not match with the adherence profiles recorded by MEMS® (e.g. the patient reported that medication taking went without variations, but the profile displayed non-adherent behaviour). This demonstrates that it is challenging to fully investigate every detail of the process of patients' adherence.

Per initially non-adherent patient 1.7 adherence-enhancing strategies were used during the accomplishment of the adherence-supporting module. Most frequently, treatment diaries and patient education regarding capecitabine efficacy were used. It has been described before that patient diaries and education as parts of a complex intervention to enhance adherence represent effective possibilities [77, 141].

**Daily total adherence versus daily intake adherence**

Daily adherence during the intake periods of each cycle was generally lower compared to daily total adherence calculated on the basis of drug intake plus rest period. This implies that adherence to the regimen was better in the rest period when the drug should not be taken, i.e. not many patients took the drug by mistake. However, difficulties concerning the change of capecitabine intake to capecitabine-free period became apparent. Eight of 15 patients took capecitabine one day too long, too short or even completely ignored the break. From this finding we conclude that special attention has to be paid to the change of drug intake to drug-free days

during the first capecitabine cycle. Patients have to be educated in detail regarding this particularity of the capecitabine treatment regimen.

## 5.3 Other endpoints

**Quality of life**

Health-related quality of life has been considered as an important outcome measure in clinical cancer research [142]. Chemotherapy, its related side effects and psychological distress diminish cancer patients' quality of life [143, 144]. In the assessment of an oral anti-cancer treatment such as capecitabine, quality of life is an important endpoint. The current study used the generic questionnaire EQ-5D and the cancer-specific questionnaire EORTC QLQ-C30 at three time points to investigate quality of life under modular medication management.

In initially adherent patients, it became apparent that no problems were mentioned in terms of 'mobility', 'self-care', 'anxiety/depression'. Slight deterioration was observed in the dimension 'usual activities'. In the dimension 'pain/discomfort' initially adherent patients had some problems throughout the observation period. Initially non-adherent patients remarked no problems in terms of 'mobility' and 'self-care'. Concerning 'usual activities' and 'anxiety/depression' they expressed to have had some problems during the course of therapy. 'Pain/discomfort' was not perceived as a problem at $t_0$, however at $t_3$ and $t_6$ patients had some problems. Thus, these results indicate a high and stable health state during the observation period although patients were treated with capecitabine. Data acquired by means of the EQ-5D visual analogue scale (VAS) also revealed high and stable quality of life values both among initially adherent and non-adherent patients. Remarkably, quality of life increased under modular medication management, an improvement in VAS values after the sixth cycle could be observed among initially adherent patients. Initially non-adherent patients' median VAS value increased from $t_0$ to $t_3$ and decreased to the baseline value after the sixth cycle. As hypothesised, these findings suggest that the provision of modular medication management might stabilise health-related quality of life over time. This is in line with results gained from the study conducted by Döhler who found that pharmaceutical care for breast cancer patients contributed to the stabilization of the patient's quality of life during cancer therapy [55].

Compared to the EORTC-QLQC30 reference values initially adherent patients had equal median symptom scale values, despite slightly worse symptoms in terms of fatigue, dyspnoea, and pain [114]. Median values did not vary remarkably during the course of the study, only slight variations were observed (pain got worse, dyspnoea better). An increase of HFS symptoms was observed in initially adherent patients. The symptom scale HFS was added to the

questionnaire for the present study, thus, no reference values were available. Since HFS is one of the most common side effects of capecitabine, this result is not surprising [11, 21, 22]. Nevertheless, median symptom scale values did not exceed a moderate level. On the whole, initially non-adherent patients showed median symptom scale values which tended be worse than the reference values [114]. Since it is known that side effects negatively affect adherence [145–147], it is possible that initially non-adherent patients' medication taking behaviour has been influenced hereby. However, no statistically significant relationship between patients' daily total adherence in cycle 1 and EQ-5D dimensions or EORTC QLQ-C30 scores were observed. Since the small sample size of this study might limit the validity of observed results, larger studies are needed to address this question.

In general, functional scale values of initially adherent patients were comparable to the reference values of the QLQ-C30 scoring manual [114]. Physical and role functioning were slightly worse than the reference values but stable over the cycles. Emotional and social functioning as well as global health status increased to the level of the reference values at $t_6$ compared to the time-point of recruitment. Cognitive functioning decreased slightly but not below the reference value. In the median, initially non-adherent patients had worse functional scale values than the reference values. However, during the course of treatment physical, role, emotional, and social functioning increased. Global health status and cognitive functioning were stable at each point of measurement. Interestingly, median values concerning emotional functioning increased during the course of medication management both in the initially adherent and in the initially non-adherent patient group. This is in contrast to the work of Westfeld and Simons. In their studies the impact of pharmaceutical care on quality of life of breast and ovarian cancer patients under intravenous chemotherapy and of breast and colorectal cancer patients treated with capecitabine was assessed. A remarkable deterioration of emotional functioning was observed during the course of the study in the control and the intervention group [60, 61]. In accordance with median EQ-5D VAS results, median global health status of initially adherent patients increased to the level of the reference values [114] during the course of treatment. An increase is remarkable taking into account that patients were treated with a cytotoxic agent. Initially non-adherent patients' global health was stable during the provision of medication management, as it was found by Simons [61].

A German non-interventional study which was conducted in association with the present study (see 3.2) found stable quality of life in metastatic breast cancer patients treated with capecitabine. The second interim analysis included QLQ-C30 data for 556 patients for up to 12 cycles. Roughly, observed mean values of functional scales and global health status were about 10 to 30 lower than the reference values, approximately 10 to 20 lower than the values of initially adherent patients and about 10 higher than initially non-adherent patients' values. The

authors did not report symptom scales [104]. The majority of these patients did not receive medication management, apart from 25 patients who were analysed in both studies. It has to be taken into account that these moderate differences might have occurred randomly due to the relatively small sample size of the present study. However, future studies could focus on further investigation of the differing quality of life values in the described patient groups.

In conclusion, quality of life of initially adherent patients treated with capecitabine was high and stable under the provision of modular medication management. Initially non-adherent patients' quality of life was stable as well but lower. It has been shown previously that the global health status, nausea/vomiting and appetite loss of the EORTC QLQ-C30 questionnaire are beneficially influenced by pharmaceutical care [56]. But so far no significant impact of pharmaceutical care services on quality of life of patients under capecitabine treatment was shown, neither measured with the EQ-5D nor with the EORTC QLQ-C30 questionnaire [61, 62]. Overall, previously observed quality of life of patients treated with capecitabine was high and stable as well [62].

In general, comparability of observed results with the reference values might be limited. Higher observed symptom scale values and lower observed functional scale values might be explained by the fact that EORTC QLQ-C30 reference values are based on baseline quality of life data only. These data were assessed before any kind of treatment had been initiated and included symptoms originating from the cancer only. Data from patients presently receiving therapy or who finished/paused treatment were excluded [114]. However, most patients surveyed in the present study (85%) were treated with a palliative intention. Thus, most likely many of them had received treatments before the initiation of capecitabine therapy (surgery, radiation, oral or intravenous anti-cancer drugs). Additionally, the reference patient cohort included only 12% breast and 8% colorectal cancer patients and only 14% were from Germany [114]. Most patients in our study suffered from breast or colorectal cancer and were German.

The sample size of this study was small and heterogenous (different entities, treatment regimens etc.). These facts might limit the validity of the observed results. Therefore, larger studies of homogenous patient cohorts are required to confirm the beneficial effect of modular medication management on quality of life. Since quality of life is influenced by numerous factors such as adverse drug reactions, anxiety/depression, age, marital status, physical activity level, or race/ethnicity [143, 144, 148, 149], it is crucial that evaluations control for placebo effects and determinants of quality of life not related to cancer or its therapy [150].

**Patient satisfaction with information**

Patients have specific information needs and information satisfaction has been shown to be an important predictor of overall quality of life in individuals with cancer. Thus, adequate

information provision is essential in cancer care [151]. Initially adherent and non-adherent patients showed a high median baseline satisfaction with information (≥4, apart from 3.7 and 2.3, in both patient groups, respectively, regarding satisfaction with complementary treatments). Apart from initially adherent patients' satisfaction with information sources (median $t_0$: 4.3, $t_3$: 4.7, $t_6$: 4.5), patient satisfaction improved in each dimension during the course of the study. Initially non-adherent patients basically showed marginally lower satisfaction with information throughout the study. The second interim analysis of the non-interventional study with capecitabine (ML 21725) which was associated to the present study in terms of breast cancer patients showed high patient satisfaction regarding information on cancer therapy and adverse effects (mean value ≥4) as well [104]. At first view this result is remarkable since these patients did not receive additional pharmaceutical care (despite those patients who were included in both studies). However, the final evaluation has not been published yet and since patient satisfaction with information on complementary treatment options, with information sources and overall satisfaction is not described, a comprehensive discussion is not possible at this point. Previous studies showed that the provision of pharmaceutical care to a cohort of breast and ovarian cancer patients and to a cohort of breast and colorectal cancer patients, respectively, had a significant beneficial effect on patient satisfaction with information. Patients of the respective control groups who received standard care by physicians and nurses were less satisfied with the information they received [56, 60, 61]. A study by Döhler investigated whether the continuous integration of a pharmacist in the cancer care team is capable to further increase patient satisfaction with information. This was, however, not the case [55]. Patient satisfaction with information measured in the present study was higher than in the three mentioned studies. Thus, modular medication management seems to be a suitable instrument for the stabilisation (and a slight increase) of patient satisfaction with information.

**Hand-foot syndrome (HFS)**

After each conducted capecitabine cycle occurrence and severity grade of HFS was measured using the questionnaire on HFS. Regarding initially adherent and initially non-adherent patients, the percentage of patients who experienced HFS grade 3 was reasonable (13/56, 23.2%; 1/15, 6.7%). Only one initially adherent patient had to finally stop treatment because of HFS. However, every third patient had to reduce the capecitabine dose due to HFS (initially adherent patients: 32.8% (19/58), initially non-adherent patients: 33.3% (5/15)). Most frequently, temporary treatment discontinuation in initially adherent patients was due to HFS. This is consistent with Steffens et al. who reported that patients stated interruption of capecitabine therapy most frequently as a result of HFS [104]. Neither among initially adherent nor among initially non-adherent patients, median HFS grade exceeded 1. Since HFS grade 1 is well tolerable for patients, this is a pleasant result and might be explained by the provision of adverse

event management to every patient. In the context of this module, patients were educated regarding HFS in detail. Prophylaxis, detection and treatment of this cutaneous toxicity were explicitly discussed. Although available recommendations for prophylactic and therapeutic interventions are empirical only, intensive education and monitoring of patients in terms of HFS seems to have a positive impact on the severity of HFS. Additionally, close contact and good communication between study pharmacist and attending physician might have accelerated an immediate HFS management. If recommended by the SPC (Fachinformation), a dose reduction or treatment interruption was prescribed and initiated immediately [12, 13]. Regarding initially adherent and initially non-adherent patients, 76.8% (43/56) and 80.0% (12/15) reported to have experienced any grade of HFS during the course of the study. The mentioned proportions are higher than in a previous study where a proportion of 53.5% patients under capecitabine treatment were found to suffer from HFS. In that study toxicity was assessed by clinicians [22]. Since occurrence and severity of HFS in the present study were assessed by patients themselves and not by their attending physician or nurse, results might be biased (in the direction of higher values than actually true). It is likely that patients did not strictly ignore adverse drug reactions of other co-administered anti-cancer drugs, e.g. peripheral neuropathy by oxaliplatin and skin alterations by cetuximab. Therefore, in the assessment of HFS, patients might have mixed up symptoms caused by different anti-cancer drugs. Moreover, previous work has demonstrated that patients more frequently report worse symptom severity than clinicians. Furthermore, patients tend to report adverse symptoms earlier in the course of treatment than their clinicians [152]. Despite this possible bias, occurrence and severity grades of HFS under adverse event management were found to be satisfying.

**Patient evaluation**

Oral anti-cancer treatment with capecitabine was evaluated by the patients after six cycles in terms of treatment success, adverse drug reactions and overall impression. More than half of initially adherent patients assessed their therapy outcome as better than they had expected it before starting their treatment (either slightly or much better). The same applies to the assessment of adverse drug reactions, 59% assessed experienced toxicity as better than expected. A good overall assessment (good, very good and excellent) was stated by 87%. The group of initially non-adherent patients had a worse impression of capecitabine therapy. Treatment outcome was assessed as better than expected by only 8%. Adverse drug reactions were perceived as better than expected by 42% and 58% stated good overall assessment. This finding might indicate that a higher degree of dislike of capecitabine therapy was present among initially non-adherent patients than among initially adherent patients. Atkins et al. studied non-adherence to medication amongst 131 breast cancer patients and found out that those patients who disliked aspects of their actual medication (e.g. adverse drug reactions, difficulties

swallowing tablets, inconvenience) were significantly less likely to adhere [153]. Although adherence of initially non-adherent patients improved during later cycles in comparison to the first cycle, they did not reach the level of adherence found in initially adherent patients. Disliking aspects of the treatment might have contributed to a lower adherence among initially non-adherent patients. However, since patients' perceptions to aspects of their capecitabine treatment was not assessed in a structured way in the present study, further research is needed to gain insight into patients' attitudes towards capecitabine in association with their adherence.

**Relationship between overall adherence and hand-foot syndrome**

Previous research showed that the development of HFS under capecitabine treatment is associated with a better clinical outcome, more precisely with a longer overall survival [12, 13, 43]. Hence, HFS might be regarded as a surrogate endpoint for the evaluation and monitoring of capecitabine efficacy [43]. We investigated the question whether the occurrence of HFS increases with increasing overall adherence. However, conducted analyses suggest that an association between overall adherence and the occurrence of HFS is unlikely. Moreover, no statistically significant difference in time to first occurrence of HFS grade 1 to 3 could be observed between patients exhibiting an overall adherence ≥100% (median) and <100%. The same applies to time to first occurrence of HFS grade 2 to 3. Overall adherence of 38 patients accounted for ≥100% and 31 patients were found to be in the range of 90.5% to 99.4%. Only two patients' adherence was <90% (88.0% and 89.8%). Possibly, the range of adherence values was too small to observe an influence of overall adherence on the development of HFS. Additionally, the sample size might have been too small. Nevertheless, a trend towards an earlier occurrence of HFS grade 2 to 3 with increasing overall adherence was observed. According to this, final clarification has to be revealed by the conduction of further studies investigating a larger number of patients.

## 5.4 Conclusion and perspectives

In this study, a systematic screening for non-adherent patients at an early stage of their capecitabine chemotherapy was applied in order to provide a patient-tailored modular medication management. In summary, the results of this study demonstrate the potential of an early adherence screening for non-adherence and an individually applied modular medication management to use limited resources most efficiently. The provided adherence support improved the medication taking behaviour of initially non-adherent patients to oral chemotherapy. Moreover, the provision of basic pharmaceutical care as well as adverse event management was sufficient to maintain adherence in initially adherent patients for at least six

cycles. The identification of potential predictors of adherence would facilitate the utilisation and broad application of the proposed adherence screening and modular medication management.

Multiprofessional, modular medication management seems to have a stabilising effect on quality of life and patient satisfaction with information. Additional expenditure of time for the provision of modular medication management by pharmacists was found to be reasonable.

Initially adherent patients were satisfied with therapy outcome and side effects of capecitabine treatment and had a good overall impression. Initially non-adherent patients expressed lower satisfaction with their treatment. For future research, it would be interesting to investigate initially non-adherent patients' reasons for this assessment and if there is a relationship of patients' perceptions on capecitabine therapy and adherence.

Incidence of HFS was found to be high among patients treated with capecitabine. Thus, further research concerning effective options for prophylaxis and treatment of this cutaneous toxicity is needed. This is especially required since this side effect can impair mobility and activities of daily living. Nevertheless, a general limitation of symptoms to a tolerable level under modular medication management was achieved.

Since the small sample size of 15 initially non-adherent patients might limit the validity of the present findings, further studies with a larger sample size are required to verify the observed results. Moreover, reliable subgroup analyses could be conducted.

No evidence-based information is available on the question how much adherence to capecitabine is needed to maximise efficacy. Thus, further research should urgently address this question. A well-founded knowledge regarding particular consequences of poor adherence would be very helpful for clinical practice and the development of patient-tailored care.

For future research projects, a sustainable approach should be used. Upon completion of the present project it was not possible to continue modular medication management in the collaborating study centres seamlessly and implemented patient care was ceased without substitution. It should be aimed to integrate a clinical pharmacist in every cancer care team on a permanent basis. This would guarantee continuity of pharmaceutical care and enable advancement of services. Moreover, in this way the roles of the clinical pharmacist and the scientist could be separated which would be beneficial for the quality of acquired data.

Despite the discussed limitations of the present study, the innovative approach used and the data obtained might build a useful base for further investigations of adherence-enhancing interventions.

# 6 Summary

Capecitabine, an orally administered prodrug of fluorouracil, is given twice daily for 14 days followed by a seven day rest period. An adequate patient adherence is essential for treatment success. The early identification of potential non-adherers followed by adherence-enhancing measures may contribute to the effectiveness of oral anticancer drug therapy.

The present study aimed at distinguishing initially adherent from non-adherent cancer patients treated with capecitabine and to enhance adherence of the latter patient group by providing specific adherence support. Moreover, it was aimed to investigate further patient-related endpoints under the provision of modular medication management.

The study was conducted as a prospective, multi-centred observational cohort study. All participating patients received two pharmaceutical care modules consisting of oral and written information (basic pharmaceutical care and adverse event management). Daily adherence was assessed as primary endpoint using electronic monitoring (MEMS®) over a maximum period of six cycles. According to their daily adherence during the first treatment cycle, patients treated with capecitabine were identified as either initially non-adherent (<90% adherence) or initially adherent (≥90% adherence). Initially non-adherent patients received an additional adherence supporting module. Further adherence parameters were assessed. Secondary endpoints included quality of life, patient satisfaction with information, occurrence of hand-foot syndrome, pharmacist's working time, and patients' evaluation of capecitabine treatment.

Seventy-three patients with various tumour entities were enrolled, 58 were initially adherent and 15 non-adherent according to the above-mentioned definition. Median daily total adherence of initially non-adherent patients significantly increased from 85.7% to 97.6% during the observation period of six cycles. Throughout all cycles, median daily total adherence of initially adherent patients was 100.0%. Daily adherence was not associated with socio-demographic and disease-related factors. No patient was non-persistent. Median overall adherence of initially adherent patients accounted for 100% in all cycles. In initially non-adherent patients, this parameter was 96.2% in cycle 1 and increased in cycles 2 to 6. Initially adherent patients generated 7064 dosing intervals (median 11:59 hours) of which 72% were between 10 to 14 hours. A quantity of 1906 dosing intervals was recorded in initially non-adherent patients (median 12:00 hours) of which 58% were in the range between 10 and 14 hours. Self-assessment revealed a higher adherence than electronically measured, especially among initially non-adherent patients. Quality of life of initially adherent patients under modular medication management was high and stable, initially non-adherent patients' values were lower but also stable over the cycles. Patient satisfaction with information was high and increased in all

dimensions during the observation period. Median HFS severity grade did not exceed a well tolerable level. Pharmacist's working time for provision of medication management was kept within reasonable limits. Evaluation of treatment success, adverse drug reactions and overall impression of capecitabine by initially adherent patients was good, whereas initially non-adherent patients expressed a worse impression.

An early adherence screening effectively distinguishes between patients adhering and non-adhering to capecitabine. The provision of specific adherence support can enhance adherence of initially non-adherent patients, whereas initially adherent patients remain adherent for at least six cycles without specific support. Our needs-based approach helps to use available resources for adherence management efficiently. Our results are in line with previous studies showing a beneficial impact of pharmaceutical care on patient-related endpoints like quality of life, patient satisfaction with information, and the severity grade of hand-foot syndrome. Since the small sample size of initially non-adherent patients limits the validity of the observed results, larger studies are required to verify these findings.

# 7 Disclosure

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# 9 Appendix

**Appendix A: Patient recruitment**

Patient recruitment fax

Information brochure

Consent form

**Appendix B: Outcome measurement**

Adherence questionnaires I and II

EORTC QLQ-C30 questionnaire modified version 3.0 and version 3.0

EQ-5D-3L questionnaire

PSCaTE questionnaires modified version 1.1 and version 1.1 (03/2006)

Questionnaire on hand-foot syndrome

Questionnaire on patient evaluation

Questionnaire on general patient data

**Appendix C: Material for patient care**

Pharmaceutical care plan

Patient brochure on adverse drug reactions

Patient letter containing medication plan

Consultation documentation forms

MEMS® patient information

Adherence support documentation form

Reminding card

**Appendix D: Results of initially adherent patients**

Adherence

Quality of life

Patient satisfaction with information

Patient evaluation

**Appendix E: Results of initially non-adherent patients**

Adherence

Quality of life

Patient satisfaction with information

Patient evaluation

**Appendix F: Results of the entire cohort**

## Appendix A: Patient recruitment

Patient recruitment fax (example Johanniter Hospital Bonn)

Absender:
Dr. Geisen/Prof. Dr. Ko/Dr. Schwandt
Johanniterstraße 3-5
53113 Bonn

universitätbonn

An:
Linda Krolop
Klinische Pharmazie
An der Immenburg 4
53121 Bonn

**Fax: 0228 – 739757**

**Interdisziplinäres, modulares Medikationsmanagement als Beitrag zur Arzneimitteltherapiesicherheit bei onkologischen Patienten**

Patientenname: _____

Anschrift: _____

_____

Telefon: _____

Stärke: ☐ 150 mg ☐ 500 mg (bitte ankreuzen)

Dosierungsschema: _____
(z.B. 2 – 0 – 2)

**Bitte ankreuzen:**

☐ Mamma-Ca ☐ Kolorektal-Ca ☐ andere: _____

Therapienaivität Xeloda®: ☐ ja ☐ nein

Information brochure (example Johanniter Hospital Bonn, page 1)

**Interdisziplinäres, modulares Medikationsmanagement**

**als Beitrag zur Arzneimitteltherapiesicherheit**

**bei onkologischen Patienten**

-Eine Anwendungsbeobachtung-

Version vom 01.09.2010

**Patienteninformation**

**Verantwortlicher Leiter:**

Prof. Dr. Y. Ko, Arzt, Johanniter-Krankenhaus Bonn

**Projektgruppe:**

Prof. Dr. U. Jaehde, Apotheker, Klinische Pharmazie, Universität Bonn

Dipl.-Pharm. L. Krolop, Apothekerin, Klinische Pharmazie, Universität Bonn

F. Schröder, Apothekerin, Klinische Pharmazie, Universität Bonn

Dr. P. F. Schwindt, Arzt, Fachübergreifende Gemeinschaftspraxis, Bonn

Dr. C. Schumacher, Ärztin, St. Elisabeth-Krankenhaus Köln-Hohenlind

Dr. H. Forstbauer, Arzt, Praxisnetzwerk Hämatologie und internistische Onkologie, Troisdorf

Priv.-Doz. Dr. C. M. Kurbacher, Arzt, Medizinisches Zentrum, Bonn

K. Ruberg, Apotheker, Kronen-Apotheke Marxen, Wesseling

**Kooperationspartner:**

Dr. R. Fimmers, Mathematiker, Medizinische Biometrie, Informatik und Epidemiologie, Universität Bonn

Prof. S. Hudson, Apotheker, Professor of Pharmaceutical Care, University of Strathclyde in Glasgow, Schottland

universitätbonn

Information brochure (example Johanniter Hospital Bonn, page 2)



**Kontaktadresse**

Linda Krolop
Friederike Schröder

Pharmazeutisches Institut
Klinische Pharmazie
An der Immenburg 4
53121 Bonn
Tel: 0228-73-5229
Fax: 0228-73-9757
Email: l.krolop@uni-bonn.de
friederike.schroeder@uni-bonn.de

Sehr geehrte Patientin, sehr geehrter Patient,

Sie erhalten momentan eine Chemotherapie gegen Ihre Krebserkrankung. Über den gesamten Verlauf Ihrer Therapie kümmert sich ein Team aus Ärzten, Apothekern, Pflegenden und weiteren Mitgliedern eines fachübergreifenden Teams um Sie, um Ihre Behandlung möglichst gut und belastungsarm zu gestalten.

Wir möchten in diesem Projekt herausfinden, welchen Einfluss ein strukturiertes, fachübergreifendes Management Ihrer Arzneimittel auf die Sicherheit und Verträglichkeit Ihrer Arzneimitteltherapie hat.

Dabei sind wir auf Ihre Hilfe angewiesen.

In dem Ihnen vorliegenden Informationsmaterial wird Ihnen das geplante Projekt genau vorgestellt. Es wird beschrieben, welche Überlegungen zur Planung des Projekts geführt haben, wie das Projekt ablaufen soll und was eine Teilnahme für Sie als Patient/-in ganz praktisch bedeuten würde.

Nehmen Sie sich für das Lesen ruhig viel Zeit. Legen Sie die Unterlagen zwischendurch beiseite, um darüber nachzudenken. Machen Sie sich überall in dieser Information Notizen zu den Dingen, die Sie gerne noch mit uns klären würden.

Sollte Ihnen während des Lesens irgendetwas unklar erscheinen oder Fragen aufwerfen, so scheuen Sie sich nicht, Ihren behandelnden Arzt, oder die verantwortliche Apothekerin Linda Krolop bzw. Friederike Schröder anzusprechen.

**Vielen Dank für Ihr Interesse und Ihre Mühe und viel Erfolg bei Ihrer Behandlung!**

Prof. Dr. Y. Ko/Dr. G. Geisen
Dr. P.F. Schwindt
Dr. H. Forstbauer
PD Dr. C.M. Kurbacher
Dr. C. Schumacher
(Studien-Ärzte)

Dipl.-Pharm. Linda Krolop
Friederike Schröder
(Studien-Apothekerinnen)

Information brochure (example Johanniter Hospital Bonn, page 3)



**INHALT** **Seite**



Information brochure (example Johanniter Hospital Bonn, page 4)



## 1. Hintergründe und Ziele

Im Rahmen dieses Projektes wird der Nutzen eines fachübergreifenden, strukturierten Medikationsmanagements für die Sicherheit Ihrer Arzneimitteltherapie untersucht. Das Projekt wird von der Arbeitsgruppe „Klinische Pharmazie" der Universität Bonn in Zusammenarbeit mit verschiedenen Kliniken und Arztpraxen durchgeführt (Johanniter Krankenhaus Bonn, Gemeinschaftspraxis Hauke/Schäfer/Schwindt/Weiss Bonn-Bad Godesberg, Praxisnetzwerk Hämatologie und internistische Onkologie Rheinsieg, Medizinisches Zentrum Bonn, St. Elisabeth-Krankenhaus Köln-Hohenlind).

In den vergangenen Jahren hat sich aus der traditionell eher krankheitsorientierten immer weiter eine patientenorientierte Arzneimitteltherapie entwickelt. Als ein Resultat dieser Entwicklung werden nun auch in Deutschland schrittweise Konzepte eines Medikationsmanagements eingeführt, um individuelle Arzneimitteltherapien und deren Sicherheit zu verbessern. Das Bundesministerium für Gesundheit hat Ende des Jahres 2007 einen Aktionsplan zur Verbesserung der Arzneimitteltherapiesicherheit in Deutschland veröffentlicht, mit dem das Ziel verfolgt wird, die Sicherheit der Arzneimitteltherapie zu erhöhen und verbesserte therapeutische Ergebnisse zu erreichen. Dies ist besonders notwendig, wenn man sich vor Augen hält, dass in Deutschland heute ca. 45.000 zugelassene Arzneimittel am Markt erhältlich sind. Mit der wachsenden Zahl an Medikamenten gehen verschiedene Probleme einher. Zum einen wird es immer schwieriger, das Angebot zu überblicken und alle Neuerungen kritisch zu bewerten, zum anderen steigt die Gefahr, Medikamente zu kombinieren, die sich in ihrer Wirkung gegenseitig beeinflussen, was möglicherweise zu unerwünschten Wirkungen führen kann.

Diese Entwicklung macht es notwendig, dass alle an einer Therapie Beteiligten, also sowohl Sie als Patient/-in, wie auch die Ärzte und Apotheker, möglichst gut zusammenarbeiten, um eine optimale Therapie zu erreichen. Ein wichtiger Punkt dabei ist die Information und Beratung rund um die Arzneimitteltherapie. Gerade in einer Dauertherapie ist es wichtig, dass der Patient durch ein klinisches Team begleitet wird und möglicherweise aufkommende Fragen zu den Medikamenten erörtert bzw. Probleme beseitigt werden können. Für die besonders betreuungsbedürftige Gruppe der Krebspatienten hat es am Johanniter Krankenhaus bereits Untersuchungen dazu gegeben. Aufbauend darauf soll nun in diesem Projekt ein strukturiertes Medikationsmanagement unter Einbeziehung einer Apothekerin untersucht werden.

### Was bedeutet das konkret für Sie als Krebspatient/-in?

In Ihrem Fall ist eine Chemotherapie · nach heutigem Stand der Wissenschaft · Teil einer optimalen Therapie Ihrer Erkrankung. Die für Sie vorgeschlagene

Information brochure (example Johanniter Hospital Bonn, page 5)



Therapie sieht die Gabe des Wirkstoffs Capecitabin in Form von Filmtabletten (Xeloda®) vor. Diese Therapie zeichnet sich, wie die Erfahrungen gezeigt haben, durch eine gute Wirksamkeit aus.

Es ist schwierig, die Wirkung der Krebsbehandlung auf die Krebszellen allein zu beschränken. Das hat zur Folge, dass auch gesunde Zellen geschädigt werden, was zu unangenehmen Nebenwirkungen führen kann.

Ziel dieser Untersuchung ist es:

- die Qualität und Sicherheit der Arzneimitteltherapie zu erhöhen
- das Ausmaß der Nebenwirkungen bei jedem einzelnen Patienten zu senken, ohne die Wirksamkeit der Behandlung zu beeinträchtigen
- die Lebensqualität und Patientenzufriedenheit der Patientin/des Patienten zu steigern bzw. zu erhalten

Wenn im Zusammenhang mit diesem Projekt von Therapieverbesserung gesprochen wird, so ist damit vor allem die so genannte „Supportivtherapie" gemeint. „Supportiv" bedeutet im eigentlichen Sinne „unterstützend". Auf die Therapie einer Krebserkrankung bezogen sind damit alle Behandlungsmaßnahmen gemeint, die zur Vorbeugung und/oder Therapie von unerwünschten Wirkungen (z.B. Durchfall) eingesetzt werden, die mit der eigentlichen Therapie der Krebserkrankung einhergehen können. Auf diese unterstützenden Therapien soll besonderes Augenmerk gelegt werden.

Es soll an dieser Stelle ausdrücklich darauf hingewiesen werden, dass es sich bei dem geplanten Projekt **nicht** um eine klinische Prüfung von Arzneimitteln handelt. Es werden also keine neuen, noch nicht erprobten Arzneimittel zum Einsatz kommen.

Des Weiteren möchten wir Sie darauf aufmerksam machen, dass sich die betreuende Apothekerin zwar mit Ihrer Arzneimitteltherapie befasst, es aber keine Rolle spielt, woher Sie Ihre Arzneimittel beziehen. Sie können also auch während der Teilnahme an diesem Projekt, so wie Sie es gewohnt sind, weiter bei den von Ihnen bevorzugten Apotheken die Arzneimittel beziehen.

## 2. Konzeption

Dieses Kapitel beschreibt, welche Untersuchungsmethode dem Projekt zugrunde liegt und auf welche Weise die Ergebnisse zustande kommen sollen.
Im Rahmen dieses Projekts werden Sie und alle anderen teilnehmenden Patienten/-innen von einem fachübergreifenden klinischen Team betreut. Sie werden von diesem Team ein strukturiertes Medikationsmanagement erhalten. Im Rahmen des Managements Ihrer Arzneimitteltherapie spielt eine Apothekerin, die besondere Erfahrungen in der Patientenbetreuung hat, eine wichtige Rolle. Sie wird während des Projektes Ihre Ansprechpartnerin sein. Der Kontakt zur Apothekerin wird über den behandelnden Arzt hergestellt, der Sie auch über die Möglichkeit informiert hat, an diesem Projekt teilzunehmen. Apothekerin und Arzt stehen in ständigem, engem Kontakt zueinander (siehe 1.).

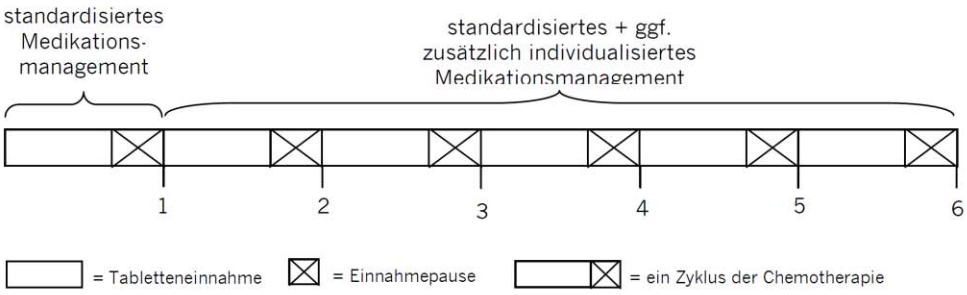
Information brochure (example Johanniter Hospital Bonn, page 6)



Ein Bestandteil des Medikationsmanagements (Modul 1) umfasst u.a. Informationsgespräche, die Aushändigung von schriftlichem Informationsmaterial, die Überprüfung der Arzneimittel hinsichtlich Wechselwirkungen, Dosierungen und Gegenanzeigen. Außerdem wird ein persönlicher Einnahmeplan mit genauen Hinweisen zur Einnahme der Arzneimittel erstellt. Eine genauere Beschreibung des Betreuungsablaufes finden Sie unter Punkt 3 dieser Information.

Ein weiterer Teil (Modul 2) des Medikationsmanagements beinhaltet vorbeugende Maßnahmen gegen Nebenwirkungen, die ggf. aufgrund der Chemotherapie bei Ihnen auftreten könnten. Außerdem findet eine Behandlung der tatsächlich auftretenden Nebenwirkungen Ihrer Arzneimitteltherapie statt. Sowohl vorbeugende Maßnahmen als auch Therapien von Nebenwirkungen werden dokumentiert.

Diese beiden Module bilden zusammen das standardisierte Medikationsmanagement.




Nach einer ersten einleitenden Phase, in der Sie das standardisierte Medikationsmanagement erhalten, wird ggf. eine Erweiterung des Medikationsmanagements Ihren ganz individuellen Bedürfnissen entsprechend vorgenommen (Modul 3). Den Ablauf können Sie der obigen Abbildung entnehmen.

Während der Studie werden Sie gebeten, bestimmte Fragebögen zu festgelegten Zeitpunkten auszufüllen (siehe 3 b.). Abschließend werden die Ergebnisse der Fragebögen und Aufzeichnungen ausgewertet. Diese Analyse wird zeigen, welchen Nutzen das strukturierte Medikationsmanagement für Krebspatienten/-innen hat.

### 3. Ablauf des Projekts

#### 3 a. Gespräche

Während der Teilnahme an diesem Projekt werden Sie verschiedene Gespräche mit der Apothekerin führen, die alle während Ihrer regulären Aufenthalte in der

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Klinik bzw. in der Praxis (z.B. auf Grund von intravenös zu verabreichenden Arzneimitteln, Blutwertkontrollen, diagnostischen Verfahren etc.) stattfinden werden. Im Folgenden werden die Gespräche näher erläutert.

**Informationsgespräche**

Im **Aufklärungsgespräch** (ca. 5 Minuten) werden Sie von der betreuenden Apothekerin über die Ziele und Hintergründe des geplanten Projekts informiert.

- In diesem Gespräch wird Ihnen vermittelt, was Sie von dem Projekt erwarten können und was als Patient/-in auf Sie zukommt.
- Sie erhalten Informationsmaterial zum Projekt, welches Sie zu Hause in Ruhe lesen können, bevor Sie eine Entscheidung über Ihre Teilnahme treffen.

Im Verlauf dieses Gespräches haben Sie die Gelegenheit, Fragen zu stellen und sich Dinge erläutern zu lassen, die Ihnen unklar erscheinen.

Im **folgenden Gespräch**, das ebenfalls etwa 5 Minuten dauern wird, können Sie Ihre Entscheidung mitteilen, ob Sie bereit sind, an dem Projekt teilzunehmen oder lieber davon absehen möchten. Zuvor besteht die Möglichkeit, weitere Fragen zu klären. Falls Sie bereit sind, am Projekt teilzunehmen:

- werden Sie gebeten, Ihre Einwilligung zur Teilnahme an dem Projekt und zur Speicherung Ihrer persönlichen Daten schriftlich zu bestätigen.
- werden Ihnen zu jedem Zyklus die in diesem Projekt auszufüllenden Fragebögen sowie das in dieser für die Aufbewahrung Ihrer Tabletten zu verwendende Arzneimittelbehältnis ausgehändigt und vollständig erläutert sowie Ihre Fragen diesbezüglich beantwortet.

**Betreuungsgespräche**

Wenn Sie zur Teilnahme an diesem Projekt bereit sind, sollte das **erste Betreuungsgespräch** vor dem ersten Therapiezyklus stattfinden. Wenn dies nicht möglich sein sollte, wird ein anderer passender Termin gesucht. Dieses erste Gespräch wird etwa 20 Minuten dauern.

Während des Gesprächs ist geplant:

- Ihre persönlichen Daten, die für die Betreuung wichtig sind (z.B. Alter u.ä.), aufzunehmen.
- Eine Übersicht über die Arzneimittel, die Sie regelmäßig einnehmen, zu erstellen.
- Fragen zur Arzneimitteltherapie zu klären.
- Ihre persönlichen Ziele und Hoffnungen verbunden mit der Arzneimitteltherapie zu erörtern und daraus gemeinsam einen Plan zu erstellen.

Die **folgenden Betreuungsgespräche** sollten möglichst einmal pro Therapiezyklus stattfinden und werden ca. 5 Minuten in Anspruch nehmen. Während dieser Gespräche werden:

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- in der Zwischenzeit aufgekommene Fragen zur Arzneimitteltherapie geklärt.
- Probleme und Wünsche im Zusammenhang mit der Arzneimitteltherapie gemeinsam erörtert.
- Ziele gesteckt, um Ihren Bedürfnissen bestmöglich gerecht zu werden.
- Sie über Nebenwirkungen, die möglicherweise eintreten können, informiert.

Die Apothekerin steht für alle aufkommenden arzneimittelbezogenen Fragen zur Verfügung. Eine fortlaufende Dokumentation der aktuellen Medikation ist erforderlich, um einen Überblick zu bekommen, wie die Arzneimittel vertragen werden. Die Daten werden ständig verarbeitet und ausgewertet, sodass eine bestmögliche Therapiebegleitung erfolgen kann.

Ihre Teilnahme an dem Projekt endet nach dem letzten oder spätestens nach dem sechsten Zyklus der verordneten Chemotherapie oder selbstverständlich jederzeit, wenn Sie dies wünschen.

### 3 b. Ergebnisqualitätsmessungen

Im Folgenden werden Ihnen die Messinstrumente vorgestellt, mit denen ermittelt werden soll, ob das intensivierte Medikationsmanagement in den angestrebten Punkten eine Verbesserung der Arzneimitteltherapiesicherheit herbeiführen kann. Hierzu soll die Qualität der durchgeführten Betreuung mit verschiedenen Fragebögen zu Ihrer Lebensqualität und Patientenzufriedenheit überprüft werden, die alle jeweils innerhalb von ein paar Minuten in der Klinik/Praxis ausgefüllt werden können. Unter Anwendung eines speziellen Arzneimittelbehältnisses werden Ihre zeitlichen Einnahmegewohnheiten beobachtet.

### Medikationsliste

In unserem Projekt spielen die Arzneimittel, die Sie im Rahmen Ihrer Krebstherapie erhalten, eine wichtige Rolle. Auch Vitaminpräparate, Spurenelemente (z.B. Selen, Zink), Mineralstoffe (z.B. Calcium, Magnesium) und andere ergänzende Therapien (z.B. Mistelpräparate), die Sie anwenden, sind wichtig. Auch die Arzneimittel, die Sie eventuell aufgrund anderer Erkrankungen einnehmen, werden erfasst. Daher bitten wir Sie, die **zu jedem Zyklus** von Ihrem Arzt verordneten bzw. von Ihnen selbst erworbenen Arzneimittel zu notieren und auch die Stärke, Packungsgröße und Dosierung zu vermerken.

### Erfassung von Nebenwirkungen

Da es sich bei dem Ihnen verordneten Arzneimittel Xeloda® um einen Stoff handelt, der eine Reihe von Nebenwirkungen hervorrufen kann, ist es für uns von großer Bedeutung, die bei Ihnen tatsächlich aufgetretenen Nebenwirkungen zu erfassen, den Schweregrad der Nebenwirkung einzustufen und diese Informationen zu dokumentieren.

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**Fragebogen zur Messung der Lebensqualität**

Immer wieder wurde festgestellt, dass die Lebensqualität der Patienten für den Therapieverlauf von entscheidender Bedeutung ist. Um einen Eindruck zu bekommen, inwieweit die Therapie Einfluss auf die Lebensqualität hat, sollen zu dieser Fragestellung zwei Fragebögen ausgefüllt werden. Einer dieser Fragebögen wurde speziell für Krebspatienten entwickelt. Während der Projektphase werden Sie gebeten, die Fragebögen zu drei Zeitpunkten auszufüllen: vor Beginn, in der Mitte, und am Ende Ihrer Teilnahme am Projekt. Die Fragebögen umfassen 2 bzw. 3 Seiten und das Ausfüllen beider Fragebögen dauert bei jedem der drei vorgesehenen Zeitpunkte in etwa 6-7 Minuten.

**Fragebogen zur Messung der Patientenzufriedenheit**

Nicht zuletzt ist auch die Zufriedenheit ein Ziel des Projekts. Um die Qualität der Betreuung festzuhalten, soll Ihre Zufriedenheit als Patient/-in ermittelt werden. Hierbei wird ein besonderes Augenmerk auf die Information gelegt, die Sie zu Ihrer Behandlung erhalten. Anhand der ermittelten Ergebnisse können Strategien entwickelt werden, wie Patienten gemäß ihren individuellen Bedürfnissen informiert werden sollten. Sie werden gebeten, auch diesen 2-seitigen Fragebogen, dessen Beantwortung ungefähr 4 Minuten dauert, dreimal auszufüllen: zu Beginn, in der Mitte und am Ende Ihrer Teilnahme an dem Projekt.

Am Ende des Projektes werden Sie darum gebeten, Ihre Therapie in einem weiteren Fragebogen mit Rückblick auf Ihre Erwartungen und Erfahrungen zu beurteilen. Der Fragebogen umfasst eine Seite und das Ausfüllen erfordert ca. 2 Minuten.

**Beobachtung der zeitlichen Einnahmegewohnheiten**

Um mehr über Ihre zeitlichen Einnahmegewohnheiten der Ihnen verordneten Chemotherapie mit Xeloda® zu erfahren, wird in diesem Projekt ein speziell entwickeltes Arzneimittelbehältnis (siehe Abbildung rechts) verwendet. Im Deckel dieses Behältnisses befindet sich ein kleiner elektronischer Prozessor, der Datum und Uhrzeit jeder Öffnung und Schließung des Behältnisses registriert. Dieses System wird als MEMS® - Medication Event Monitoring System bezeichnet. Sie werden gebeten, während Ihrer Studienteilnahme ausschließlich dieses Behältnis zur Aufbewahrung und Entnahme Ihrer Xeloda®-Tabletten zu verwenden. Das Verfahren mit diesem Arzneimittelbehältnis ist notwendig, um Vergleichswerte zu erhalten, die es später ermöglichen, Veränderungen im Einnahmeverhalten, die durch die Betreuungsmaßnahme eingetreten sein könnten, zu messen.

Das Behältnis wird hierzu den gesetzlichen Vorgaben entsprechend beschriftet sein und Sie erhalten zusätzlich die Original-Packungsbeilage des Ihnen verordneten Arzneimittels Xeloda®.

Information brochure (example Johanniter Hospital Bonn, page 10)



Die Tabletten werden zur Umfüllung in dieses Behältnis in ihren einzelnen Folienverpackungen verbleiben, sodass kein Risiko einer Beschädigung der Tabletten beim Umfüllvorgang besteht.

**Bitte beachten Sie die Hinweise zur Verwendung des Studien-Arzneimittelbehältnisses, die Ihnen gesondert ausgehändigt werden.**

Zusätzlich zur Beobachtung mit dem MEMS®-Behältnis, werden Ihre zeitlichen Einnahmegewohnheiten ebenfalls mit Fragebögen untersucht. Sie werden gebeten, einmal pro Zyklus einen diesbezüglichen Fragebogen auszufüllen sowie einen Fragebogen am Ende. Beide Fragebögen umfassen jeweils eine Seite und die Beantwortung nimmt jeweils 2-3 Minuten in Anspruch.

## 4. Datenschutz und Patienteneinwilligung

Die Information, die Sie bisher über dieses Projekt erhalten haben, lässt schon vermuten, dass im Zusammenhang mit diesem Projekt eine Vielzahl von Daten über Ihre Person erfasst werden sollen. Dies geschieht allerdings erst dann, wenn Ihre schriftliche Einwilligung dazu vorliegt.

Zum einen sollen bestimmte, für die Betreuung notwendige Daten aus Ihrer vom Arzt geführten Patientenakte übertragen werden (z.B. Laborwerte u.ä.). Weiterhin sollen hilfreiche Informationen, die gemeinsam mit Ihnen im Gespräch erörtert werden, gespeichert werden (z.B. Unsicherheiten oder Schwierigkeiten mit der Arzneimitteltherapie). Ebenso sollen Daten gespeichert werden, die neben Ihrer Betreuung speziell zur Auswertung des Projekts benötigt werden. Das sind zum Beispiel die Ergebnisse der Fragebögen.

Alle Informationen, die zu Ihrer Person erfasst werden sollen, werden in einer computergestützten Datenbank gespeichert. Diese Datenbank unterstützt die Apothekerin bei ihrer Aufgabe, Sie umfassend zu betreuen. Die Ergebnisse des Projekts sollen mit einem Statistikprogramm (SPSS®) ausgewertet werden. Dadurch soll auch in Zahlen dargestellt werden können, ob das strukturierte Medikationsmanagement einen Nutzen gezeigt hat.

Die im Zusammenhang mit diesem Projekt erhobenen Daten unterliegen den Bestimmungen des Datenschutzes und werden ausschließlich zum Zweck der Durchführung des Projekts erhoben und ausgewertet. Das bedeutet, dass Sie der Verwendung Ihrer Daten für Projektzwecke zustimmen müssen, bevor mit der Dokumentation begonnen wird. Außerdem ist gewährleistet, dass aus Veröffentlichungen der in dem Projekt erhobenen Daten Ihr Name nicht hervorgeht. Die Ergebnisse des Projekts werden anonymisiert veröffentlicht und stehen Ihnen dann selbstverständlich auf Anfrage zur Verfügung.

Die Teilnahme an diesem Projekt birgt für Sie keine zusätzlichen Risiken.

**Sie haben selbstverständlich das Recht, jederzeit und ohne Angabe von Gründen von der Teilnahme an dem Projekt zurückzutreten. Es entstehen Ihnen dadurch keine Nachteile in Ihrer Behandlung!**

Information brochure (example Johanniter Hospital Bonn, page 11)



Wenn Sie dieses Informationsmaterial eingehend gelesen haben und Ihre Fragen beantwortet wurden, können Sie frei über die Teilnahme am Projekt entscheiden. Ihre Teilnahme und Ihr Einverständnis mit den erläuterten Bestimmungen zum Datenschutz bestätigen Sie schriftlich mit einer so genannten **Einwilligungserklärung**, die Sie gesondert erhalten.

Information brochure (example Johanniter Hospital Bonn, page 12)

**Projektzentrale**

Universität Bonn
Pharmazeutisches Institut
Klinische Pharmazie
Prof. Dr. Ulrich Jaehde
An der Immenburg 4
53121 Bonn

Ansprechpartner:
Apothekerinnen **Linda Krolop** und **Friederike Schröder**
Tel.: 0228 – 73-5229
Fax: 0228 – 73-9757
Email: l.krolop@uni-bonn.de
friederike.schroeder@uni-bonn.de

Consent form



universitätbonn

Rheinische Friedrich-Wilhelms-Universität Bonn
Pharmazeutisches Institut
Prof. Dr. U. Jaehde
Klinische Pharmazie
Ansprechpartnerinnen:
Linda Krolop
Friederike Schröder
Tel.: 0228-73-5229
l.krolop@uni-bonn.de
friederike.schroeder@uni-bonn.de

## Einwilligungserklärung

Name: _____

Geburtsdatum: _____

Das Original dieser Einwilligungserklärung verbleibt bei den Unterlagen. Eine Kopie der Einwilligungserklärung wird dem Patienten ausgehändigt.

Ich erkläre, dass ich die Patienteninformation zur wissenschaftlichen Untersuchung

**Interdisziplinäres, modulares Medikationsmanagement als Beitrag zur Arzneimitteltherapiesicherheit bei onkologischen Patienten**

und diese Einwilligungserklärung erhalten habe.

☐ Ich wurde ausreichend mündlich und schriftlich über die wissenschaftliche Untersuchung informiert.

☐ Ich weiß, dass ich jederzeit meine Einwilligung, ohne Angaben von Gründen, widerrufen kann, ohne dass dies für mich nachteilige Folgen hat.

☐ **Ich bin damit einverstanden, dass die im Rahmen der wissenschaftlichen Untersuchung über mich erhobenen Krankheitsdaten sowie meine sonstigen mit dieser Untersuchung zusammenhängenden personenbezogenen Daten aufgezeichnet werden. Es wird gewährleistet, dass meine personenbezogenen Daten nicht an Dritte weitergegeben werden. Bei der Veröffentlichung in einer wissenschaftlichen Zeitschrift wird aus den Daten nicht hervorgehen, wer an dieser Untersuchung teilgenommen hat. Meine persönlichen Daten unterliegen dem Datenschutzgesetz.**

☐ Ich bin bereit, die in dieser Studie eingesetzten Arzneimittelbehältnisse zu verwenden, die an mich ausgegebenen Fragebögen ordnungsgemäß auszufüllen und die Beratungstermine mit dem/der betreuenden Apotheker/-in wahrzunehmen.

☐ Mit der vorstehend geschilderten Vorgehensweise bin ich einverstanden und bestätige dies mit meiner Unterschrift.

_____ , den _____
Ort Datum

_____
Unterschrift

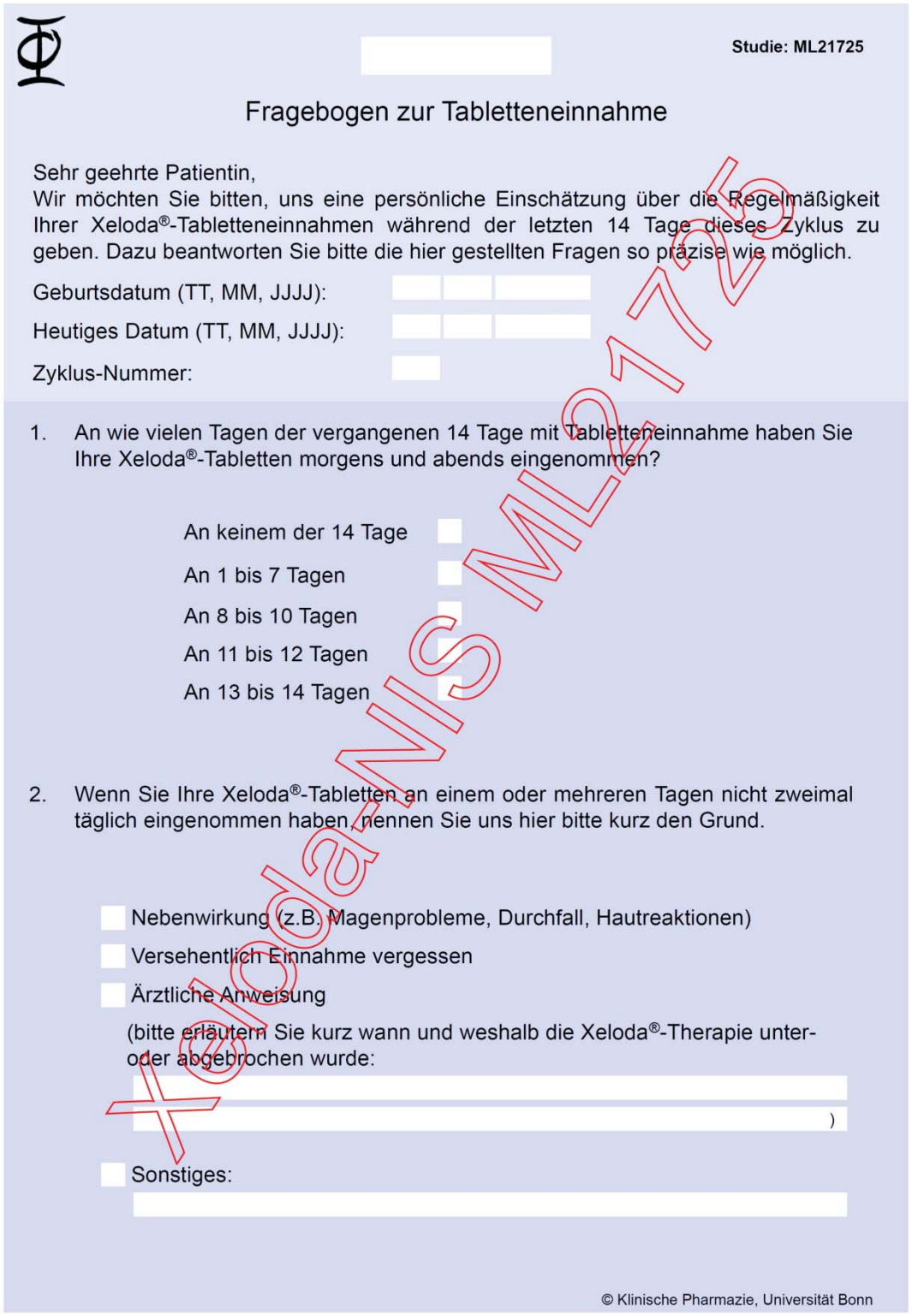
_____
Name in Druckbuchstaben

_____
Unterschrift des/der Arztes/Ärztin

_____
Unterschrift des/der Apothekers/Apothekerin

## Appendix B: Outcome measurement

Adherence questionnaire I



Studie: ML21725

Fragebogen zur Tabletteneinnahme

Sehr geehrte Patientin,
Wir möchten Sie bitten, uns eine persönliche Einschätzung über die Regelmäßigkeit Ihrer Xeloda®-Tabletteneinnahmen während der letzten 14 Tage dieses Zyklus zu geben. Dazu beantworten Sie bitte die hier gestellten Fragen so präzise wie möglich.

Geburtsdatum (TT, MM, JJJJ):

Heutiges Datum (TT, MM, JJJJ):

Zyklus-Nummer:

1. An wie vielen Tagen der vergangenen 14 Tage mit Tabletteneinnahme haben Sie Ihre Xeloda®-Tabletten morgens und abends eingenommen?

- An keinem der 14 Tage
- An 1 bis 7 Tagen
- An 8 bis 10 Tagen
- An 11 bis 12 Tagen
- An 13 bis 14 Tagen

2. Wenn Sie Ihre Xeloda®-Tabletten an einem oder mehreren Tagen nicht zweimal täglich eingenommen haben, nennen Sie uns hier bitte kurz den Grund.

- Nebenwirkung (z.B. Magenprobleme, Durchfall, Hautreaktionen)
- Versehentlich Einnahme vergessen
- Ärztliche Anweisung

(bitte erläutern Sie kurz wann und weshalb die Xeloda®-Therapie unter- oder abgebrochen wurde:

)

- Sonstiges:

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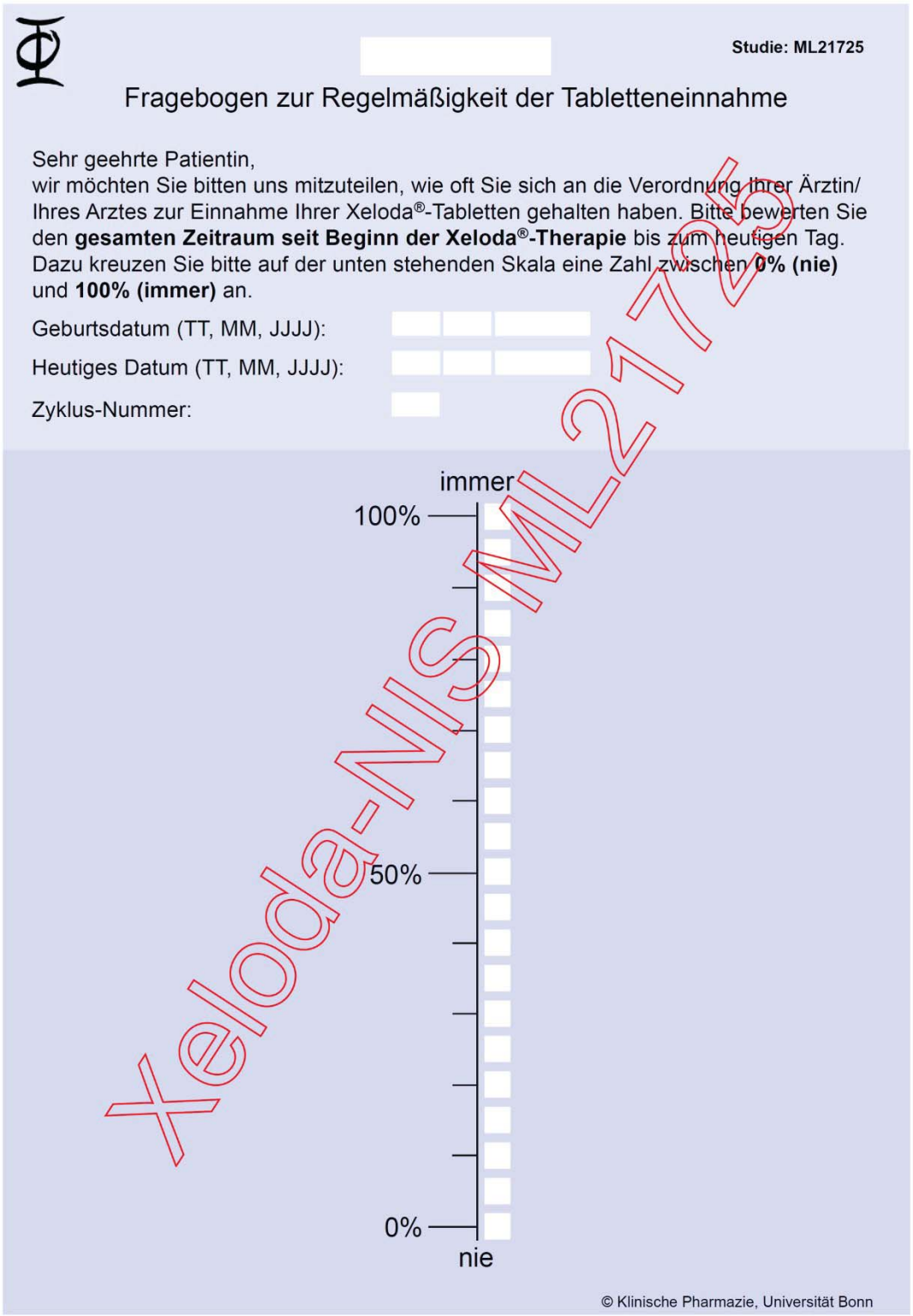
Adherence questionnaire II



Studie: ML21725

Fragebogen zur Regelmäßigkeit der Tabletteneinnahme

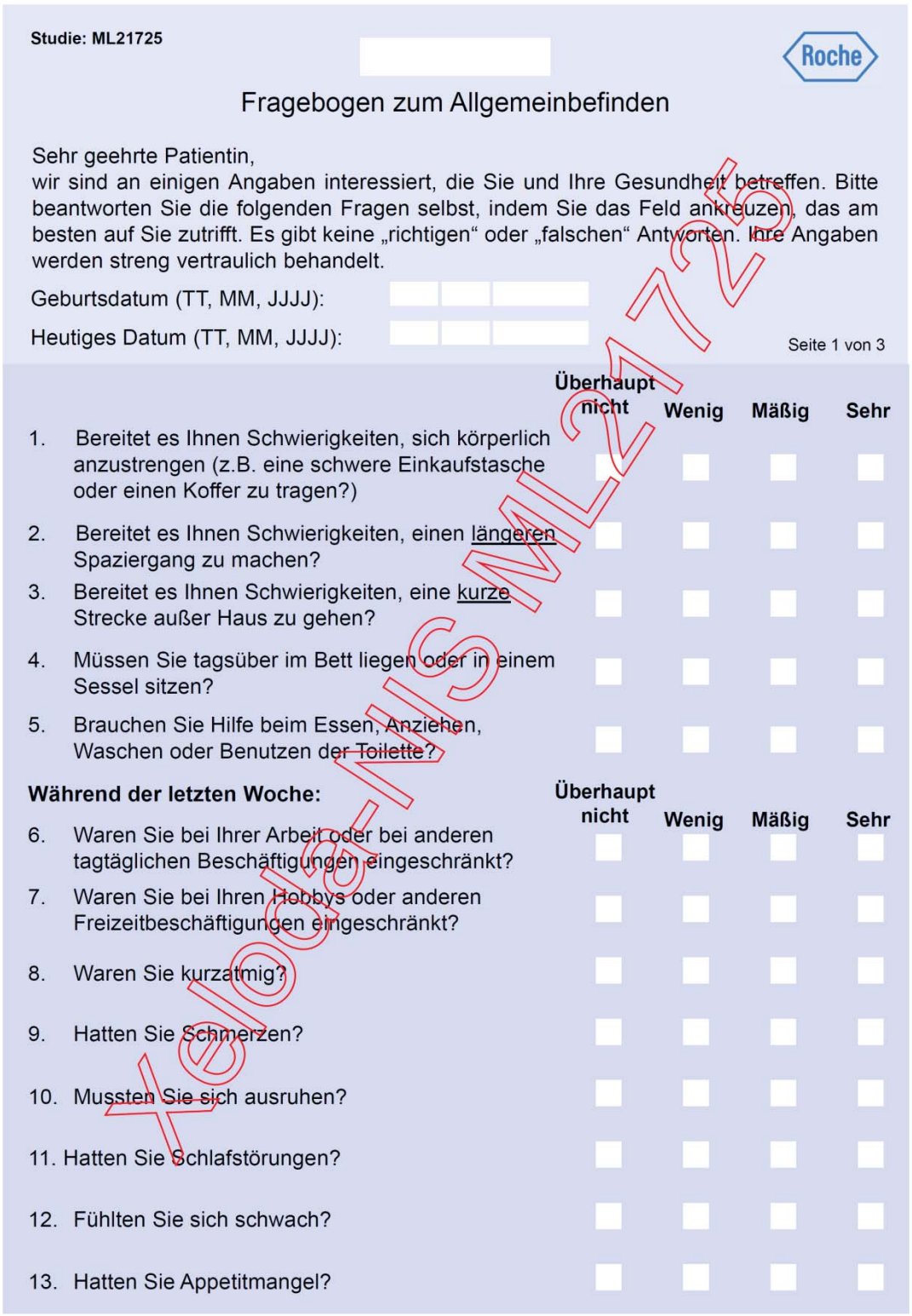
Sehr geehrte Patientin,
wir möchten Sie bitten uns mitzuteilen, wie oft Sie sich an die Verordnung Ihrer Ärztin/ Ihres Arztes zur Einnahme Ihrer Xeloda®-Tabletten gehalten haben. Bitte bewerten Sie den **gesamten Zeitraum seit Beginn der Xeloda®-Therapie** bis zum heutigen Tag. Dazu kreuzen Sie bitte auf der unten stehenden Skala eine Zahl zwischen **0% (nie)** und **100% (immer)** an.

Geburtsdatum (TT, MM, JJJJ):

Heutiges Datum (TT, MM, JJJJ):

Zyklus-Nummer:

EORTC QLQ-C30 questionnaire modified version 3.0 (page 1)



**Studie: ML21725**

Roche

## Fragebogen zum Allgemeinbefinden

Sehr geehrte Patientin,
wir sind an einigen Angaben interessiert, die Sie und Ihre Gesundheit betreffen. Bitte beantworten Sie die folgenden Fragen selbst, indem Sie das Feld ankreuzen, das am besten auf Sie zutrifft. Es gibt keine „richtigen“ oder „falschen“ Antworten. Ihre Angaben werden streng vertraulich behandelt.

Geburtsdatum (TT, MM, JJJJ):

Heutiges Datum (TT, MM, JJJJ):

Seite 1 von 3

| | Überhaupt nicht | Wenig | Mäßig | Sehr |
|---|---|---|---|---|
| 1. Bereitet es Ihnen Schwierigkeiten, sich körperlich anzustrengen (z.B. eine schwere Einkaufstasche oder einen Koffer zu tragen?) | | | | |
| 2. Bereitet es Ihnen Schwierigkeiten, einen längeren Spaziergang zu machen? | | | | |
| 3. Bereitet es Ihnen Schwierigkeiten, eine kurze Strecke außer Haus zu gehen? | | | | |
| 4. Müssen Sie tagsüber im Bett liegen oder in einem Sessel sitzen? | | | | |
| 5. Brauchen Sie Hilfe beim Essen, Anziehen, Waschen oder Benutzen der Toilette? | | | | |

**Während der letzten Woche:**

| | Überhaupt nicht | Wenig | Mäßig | Sehr |
|---|---|---|---|---|
| 6. Waren Sie bei Ihrer Arbeit oder bei anderen tagtäglichen Beschäftigungen eingeschränkt? | | | | |
| 7. Waren Sie bei Ihren Hobbys oder anderen Freizeitbeschäftigungen eingeschränkt? | | | | |
| 8. Waren Sie kurzatmig? | | | | |
| 9. Hatten Sie Schmerzen? | | | | |
| 10. Mussten Sie sich ausruhen? | | | | |
| 11. Hatten Sie Schlafstörungen? | | | | |
| 12. Fühlten Sie sich schwach? | | | | |
| 13. Hatten Sie Appetitmangel? | | | | |

EORTC QLQ-C30 questionnaire modified version 3.0 (page 2)

**Studie: ML21725**

Roche

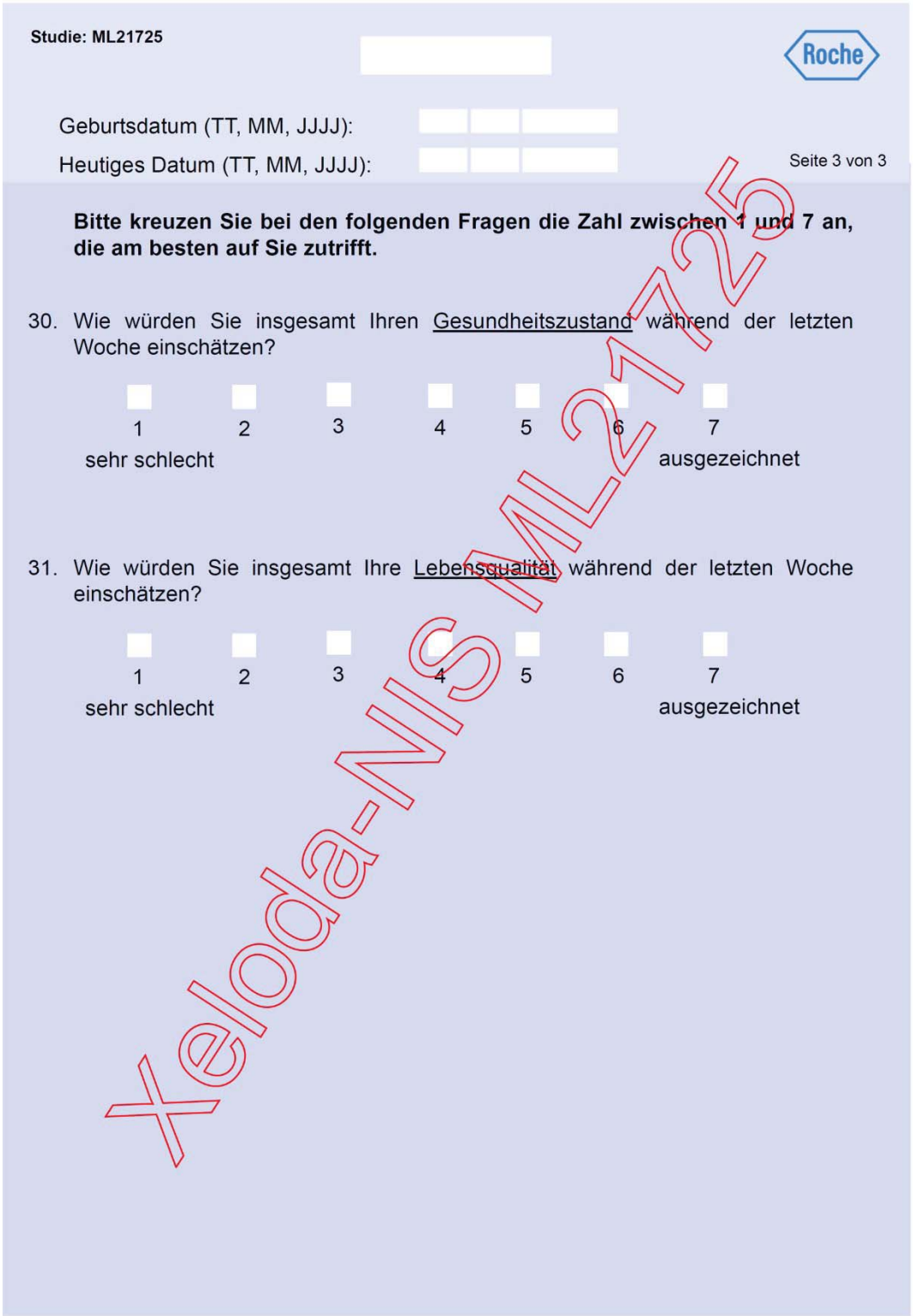
Geburtsdatum (TT, MM, JJJJ):

Heutiges Datum (TT, MM, JJJJ):



| **Während der letzten Woche:** | **Überhaupt nicht** | **Wenig** | **Mäßig** | **Sehr** |
|---|---|---|---|---|
| 14. War Ihnen übel? | | | | |
| 15. Haben Sie erbrochen? | | | | |
| 16. Hatten Sie Symptome eines Hand-Fuß-Syndroms? | | | | |
| 17. Hatten Sie Verstopfung? | | | | |
| 18. Hatten Sie Durchfall? | | | | |
| 19. Waren Sie müde? | | | | |
| 20. Fühlten Sie sich durch Schmerzen in Ihrem alltäglichen Leben beeinträchtigt? | | | | |
| 21. Hatten Sie Schwierigkeiten, sich auf etwas zu konzentrieren, z.B. auf das Zeitunglesen oder das Fernsehen? | | | | |
| 22. Fühlten Sie sich angespannt? | | | | |
| 23. Haben Sie sich Sorgen gemacht? | | | | |
| 24. Waren Sie reizbar? | | | | |
| 25. Fühlten Sie sich niedergeschlagen? | | | | |
| 26. Hatten Sie Schwierigkeiten, sich an Dinge zu erinnern? | | | | |
| 27. Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung Ihr Familienleben beeinträchtigt? | | | | |
| 28. Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung Ihr Zusammensein oder Ihre gemeinsamen Unternehmungen mit anderen Menschen beeinträchtigt? | | | | |
| 29. Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung für Sie finanzielle Schwierigkeiten mit sich gebracht? | | | | |

EORTC QLQ-C30 questionnaire modified version 3.0 (page 3)



Studie: ML21725

Roche

Geburtsdatum (TT, MM, JJJJ):

Heutiges Datum (TT, MM, JJJJ):

Seite 3 von 3

**Bitte kreuzen Sie bei den folgenden Fragen die Zahl zwischen 1 und 7 an, die am besten auf Sie zutrifft.**

30. Wie würden Sie insgesamt Ihren Gesundheitszustand während der letzten Woche einschätzen?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| sehr schlecht | | | | | | ausgezeichnet |

31. Wie würden Sie insgesamt Ihre Lebensqualität während der letzten Woche einschätzen?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| sehr schlecht | | | | | | ausgezeichnet |

EORTC QLQ-C30 questionnaire version 3.0 (page 1)

GERMAN

## EORTC QLQ-C30 (version 3.0)

Wir sind an einigen Angaben interessiert, die Sie und Ihre Gesundheit betreffen. Bitte beantworten Sie die folgenden Fragen selbst, indem Sie die Zahl ankreuzen, die am besten auf Sie zutrifft. Es gibt keine "richtigen" oder "falschen" Antworten. Ihre Angaben werden streng vertraulich behandelt.

Bitte tragen Sie Ihre Initialen ein: ⌊ ⌋⌊ ⌋⌊ ⌋

Ihr Geburtstag (Tag, Monat, Jahr): ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Das heutige Datum (Tag, Monat, Jahr): 31⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

| | | Überhaupt nicht | Wenig | Mäßig | Sehr |
|---|---|---|---|---|---|
| 1. | Bereitet es Ihnen Schwierigkeiten sich körperlich anzustrengen (z.B. eine schwere Einkaufstasche oder einen Koffer zu tragen?) | 1 | 2 | 3 | 4 |
| 2. | Bereitet es Ihnen Schwierigkeiten, einen längeren Spaziergang zu machen? | 1 | 2 | 3 | 4 |
| 3. | Bereitet es Ihnen Schwierigkeiten, eine kurze Strecke außer Haus zu gehen? | 1 | 2 | 3 | 4 |
| 4. | Müssen Sie tagsüber im Bett liegen oder in einem Sessel sitzen? | 1 | 2 | 3 | 4 |
| 5. | Brauchen Sie Hilfe beim Essen, Anziehen, Waschen oder Benutzen der Toilette? | 1 | 2 | 3 | 4 |

### Während der letzten Woche:

| | | Überhaupt nicht | Wenig | Mäßig | Sehr |
|---|---|---|---|---|---|
| 6. | Waren Sie bei Ihrer Arbeit oder bei anderen tagtäglichen Beschäftigungen eingeschränkt? | 1 | 2 | 3 | 4 |
| 7. | Waren Sie bei Ihren Hobbys oder anderen Freizeitbeschäftigungen eingeschränkt? | 1 | 2 | 3 | 4 |
| 8. | Waren Sie kurzatmig? | 1 | 2 | 3 | 4 |
| 9. | Hatten Sie Schmerzen? | 1 | 2 | 3 | 4 |
| 10. | Mussten Sie sich ausruhen? | 1 | 2 | 3 | 4 |
| 11. | Hatten Sie Schlafstörungen? | 1 | 2 | 3 | 4 |
| 12. | Fühlten Sie sich schwach? | 1 | 2 | 3 | 4 |
| 13. | Hatten Sie Appetitmangel? | 1 | 2 | 3 | 4 |
| 14. | War Ihnen übel? | 1 | 2 | 3 | 4 |
| 15. | Haben Sie erbrochen? | 1 | 2 | 3 | 4 |

Bitte wenden

EORTC QLQ-C30 questionnaire version 3.0 (page 2)

GERMAN

| **Während der letzten Woche:** | **Überhaupt nicht** | **Wenig** | **Mäßig** | **Sehr** |
|---|---|---|---|---|
| 16. Hatten Sie Verstopfung? | 1 | 2 | 3 | 4 |
| 17. Hatten Sie Durchfall? | 1 | 2 | 3 | 4 |
| 18. Waren Sie müde? | 1 | 2 | 3 | 4 |
| 19. Fühlten Sie sich durch Schmerzen in Ihrem alltäglichen Leben beeinträchtigt? | 1 | 2 | 3 | 4 |
| 20. Hatten Sie Schwierigkeiten sich auf etwas zu konzentrieren, z.B. auf das Zeitunglesen oder das Fernsehen? | 1 | 2 | 3 | 4 |
| 21. Fühlten Sie sich angespannt? | 1 | 2 | 3 | 4 |
| 22. Haben Sie sich Sorgen gemacht? | 1 | 2 | 3 | 4 |
| 23. Waren Sie reizbar? | 1 | 2 | 3 | 4 |
| 24. Fühlten Sie sich niedergeschlagen? | 1 | 2 | 3 | 4 |
| 25. Hatten Sie Schwierigkeiten, sich an Dinge zu erinnern? | 1 | 2 | 3 | 4 |
| 26. Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung Ihr Familienleben beeinträchtigt? | 1 | 2 | 3 | 4 |
| 27. Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung Ihr Zusammensein oder Ihre gemeinsamen Unternehmungen mit anderen Menschen beeinträchtigt? | 1 | 2 | 3 | 4 |
| 28. Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung für Sie finanzielle Schwierigkeiten mit sich gebracht? | 1 | 2 | 3 | 4 |

**Bitte kreuzen Sie bei den folgenden Fragen die Zahl zwischen 1 und 7 an, die am besten auf Sie zutrifft**

29. Wie würden Sie insgesamt Ihren Gesundheitszustand während der letzten Woche einschätzen?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| sehr schlecht | | | | | | ausgezeichnet |

30. Wie würden Sie insgesamt Ihre Lebensqualität während der letzten Woche einschätzen?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| sehr schlecht | | | | | | ausgezeichnet |

EQ-5D-3L questionnaire (page 1)


**Gesundheitsfragebogen**

**(Deutsche Version)**

***(German version)***

EQ-5D-3L questionnaire (page 2)

Bitte geben Sie an, welche Aussagen Ihren heutigen Gesundheitszustand am besten beschreiben, indem Sie ein Kreuz in ein Kästchen jeder Gruppe machen.

**Beweglichkeit/Mobilität**

Ich habe keine Probleme herumzugehen ❑
Ich habe einige Probleme herumzugehen ❑
Ich bin ans Bett gebunden ❑

**Für sich selbst sorgen**

Ich habe keine Probleme, für mich selbst zu sorgen ❑
Ich habe einige Probleme, mich selbst zu waschen oder mich anzuziehen ❑
Ich bin nicht in der Lage, mich selbst zu waschen oder anzuziehen ❑

**Alltägliche Tätigkeiten** *(z.B. Arbeit, Studium, Hausarbeit, Familien- oder Freizeitaktivitäten)*

Ich habe keine Probleme, meinen alltäglichen Tätigkeiten nachzugehen ❑
Ich habe einige Probleme, meinen alltäglichen Tätigkeiten nachzugehen ❑
Ich bin nicht in der Lage, meinen alltäglichen Tätigkeiten nachzugehen ❑

**Schmerzen/Körperliche Beschwerden**

Ich habe keine Schmerzen oder Beschwerden ❑
Ich habe mäßige Schmerzen oder Beschwerden ❑
Ich habe extreme Schmerzen oder Beschwerden ❑

**Angst/Niedergeschlagenheit**

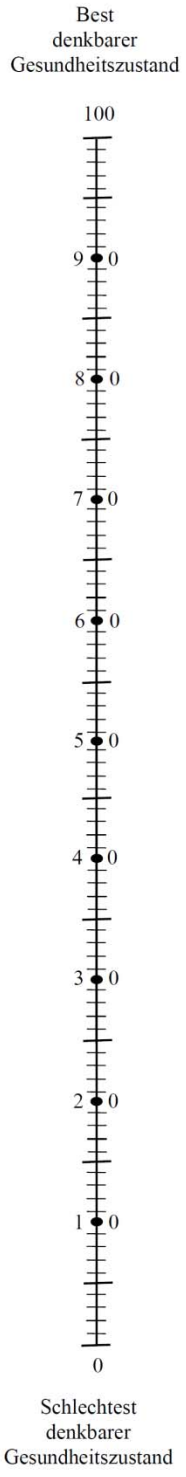
Ich bin nicht ängstlich oder deprimiert ❑
Ich bin mäßig ängstlich oder deprimiert ❑
Ich bin extrem ängstlich oder deprimiert ❑

EQ-5D-3L questionnaire (page 3)

Um Sie bei der Einschätzung, wie gut oder wie schlecht Ihr Gesundheitszustand ist, zu unterstützen, haben wir eine Skala gezeichnet, ähnlich einem Thermometer. Der best denkbare Gesundheitszustand ist mit einer "100" gekennzeichnet, der schlechteste mit "0".

Wir möchten Sie nun bitten, auf dieser Skala zu kennzeichnen, wie gut oder schlecht Ihrer Ansicht nach Ihr persönlicher Gesundheitszustand heute ist. Bitte verbinden Sie dazu den untenstehenden Kasten mit dem Punkt auf der Skala, der Ihren heutigen Gesundheitszustand am besten wiedergibt.

**Ihr heutiger Gesundheitszustand**



PSCaTE questionnaire modified version 1.1 (page 1)

Studie: ML21725

## Fragebogen zur Patientenzufriedenheit mit der Information zur Krebsbehandlung

Sehr geehrte Patientin,
wir möchten Sie bitten, uns einige Fragen zu Ihrer Zufriedenheit, was die Übermittlung von Informationen über Ihre Krebstherapie angeht, zu beantworten. Bitte kreuzen Sie bei jeder der folgenden Aussagen ein Kästchen an. Dadurch können Sie angeben, wie stark Sie mit der jeweiligen Aussage übereinstimmen oder nicht übereinstimmen. Bitte teilen Sie uns Ihre Meinung über sämtliche Informationen mit, die Sie bis zum heutigen Tage erhalten haben.

Geburtsdatum (TT, MM, JJJJ):

Heutiges Datum (TT, MM, JJJJ):



| | trifft auf keinen Fall zu | trifft eher nicht zu | unsicher | trifft eher zu | trifft voll zu |
|---|---|---|---|---|---|
| 1. Mit der Information , die ich zu meiner Krebsbehandlung insgesamt erhalten habe, bin ich zufrieden. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. Mit der Information zu den möglichen Nebenwirkungen meiner Behandlung bin ich zufrieden. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. Mit der Information darüber, was ich im Falle eintretender Nebenwirkungen machen soll, bin ich zufrieden. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. Man hat mich zufrieden stellend über ergänzende Therapien informiert. ( Ergänzende Therapien schließen Vitamine, pflanzliche Präparate, Akupunktur, Antioxidantien, Homöopathie, Naturheilkunde und anthroposophische Heilmethoden mit ein.) | ☐ | ☐ | ☐ | ☐ | ☐ |
| 5. Über mögliche Wechselwirkungen zwischen meiner Krebsbehandlung und anderen Medikamenten wurde ich zufriedenstellend aufgeklärt. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 6. Die mir vermittelten Informationen zu meiner Krebsbehandlung sind klar und einfach zu verstehen. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 7. Man hat mich freundlich und respektvoll informiert. | ☐ | ☐ | ☐ | ☐ | ☐ |

PSCaTE questionnaire modified version 1.1 (page 2)

Studie: ML21725

Geburtsdatum (TT, MM, JJJJ):

Heutiges Datum (TT, MM, JJJJ):



| | trifft auf keinen Fall zu | trifft eher nicht zu | unsicher | trifft eher zu | trifft voll zu |
|---|---|---|---|---|---|
| 8. Ich hatte ausreichend Gelegenheit, Fragen zu meiner Krebsbehandlung zu stellen. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 9. Ich hatte ausreichend Gelegenheit, Fragen darüber zu stellen, wie ich mich im Falle auftretender Nebenwirkungen verhalten soll. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 10. Ich hatte ausreichend Gelegenheit, Fragen zu ergänzenden Therapien zu stellen. (Ergänzende Therapien schließen Vitamine, pflanzliche Präparate, Akupunktur, Antioxidantien, Homöopathie, Naturheilkunde und anthroposophische Heilmethoden mit ein.) | ☐ | ☐ | ☐ | ☐ | ☐ |
| 11. Mir stehen ausreichend viele Informationsquellen zur Verfügung. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 12. Mit der Qualität der Informationsquellen, die mir zur Verfügung stehen, bin ich zufrieden. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 13. Man hat mich unvoreingenommen informiert. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 14. Ich fühle mich ausreichend informiert, um Entscheidungen über meine Krebsbehandlung mittreffen zu können. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 15. Ich fühle mich ausreichend informiert, um Entscheidungen zur Behandlung möglicher Nebenwirkungen mittreffen zu können. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 16. Ich fühle mich ausreichend informiert, um Entscheidungen zum Einsatz ergänzender Therapien mittreffen zu können. (Ergänzende Therapien schließen Vitamine, pflanzliche Präparate, Akupunktur, Antioxidantien, Homöopathie, Naturheilkunde und anthroposophische Heilmethoden mit ein.) | ☐ | ☐ | ☐ | ☐ | ☐ |

PSCaTE questionnaire version 1.1, 03/2006 (page 1)

universitätbonn

**Fragebogen zur Patientenzufriedenheit**
**mit der Information zur Krebsbehandlung**
**(Ver. 1.1 - 03/2006)**

Information zur Zufriedenheit

Bitte kreuzen Sie bei jeder der folgenden Aussagen eine Zahl an. Sie drückt aus, wie stark Sie mit der jeweiligen Aussage übereinstimmen oder nicht übereinstimmen.
Bitte teilen Sie uns Ihre Meinung über **sämtliche** Informationen mit, die Sie bis zum **heutigen Tage** erhalten haben.

Datum:

| | trifft auf keinen Fall zu | trifft eher nicht zu | unsicher | trifft eher zu | trifft voll zu |
|---|---|---|---|---|---|
| **1) Mit der Information, die ich zu meiner Krebsbehandlung insgesamt erhalten habe, bin ich zufrieden.** | 1 | 2 | 3 | 4 | 5 |
| **2) Mit der Information zu den möglichen Nebenwirkungen meiner Behandlung bin ich zufrieden.** | 1 | 2 | 3 | 4 | 5 |
| **3) Mit der Information darüber, was ich im Falle eintretender Nebenwirkungen machen soll, bin ich zufrieden.** | 1 | 2 | 3 | 4 | 5 |
| **4) Man hat mich zufrieden stellend über ergänzende Therapien informiert. (Ergänzende Therapien schließen Vitamine, pflanzliche Präparate, Akupunktur, Antioxidantien, Homöopathie, Naturheilkunde und anthroposophische Heilmethoden mit ein.)** | 1 | 2 | 3 | 4 | 5 |
| **5) Über mögliche Wechselwirkungen zwischen meiner Krebsbehandlung und anderen Medikamenten wurde ich zufrieden stellend aufgeklärt.** | 1 | 2 | 3 | 4 | 5 |
| **6) Die mir vermittelten Informationen zu meiner Krebsbehandlung sind klar und einfach zu verstehen.** | 1 | 2 | 3 | 4 | 5 |

PSCaTE questionnaire version 1.1, 03/2006 (page 2)

| | trifft auf keinen Fall zu | trifft eher nicht zu | unsicher | trifft eher zu | trifft voll zu |
|---|---|---|---|---|---|
| **7) Man hat mich freundlich und respektvoll informiert.** | 1 | 2 | 3 | 4 | 5 |
| **8) Ich hatte ausreichend Gelegenheit, Fragen zu meiner Krebsbehandlung zu stellen.** | 1 | 2 | 3 | 4 | 5 |
| **9) Ich hatte ausreichend Gelegenheit, Fragen darüber zu stellen, wie ich mich im Falle auftretender Nebenwirkungen verhalten soll.** | 1 | 2 | 3 | 4 | 5 |
| **10) Ich hatte ausreichend Gelegenheit, Fragen zu ergänzenden Therapien zu stellen. (Ergänzende Therapien schließen Vitamine, pflanzliche Präparate, Akupunktur, Antioxidantien, Homöopathie, Naturheilkunde und anthroposophische Heilmethoden mit ein.)** | 1 | 2 | 3 | 4 | 5 |
| **11) Mir stehen ausreichend viele Informations-Quellen zur Verfügung.** | 1 | 2 | 3 | 4 | 5 |
| **12) Mit der Qualität der Informationsquellen, die mir zur Verfügung stehen, bin ich zufrieden.** | 1 | 2 | 3 | 4 | 5 |
| **13) Man hat mich unvoreingenommen informiert.** | 1 | 2 | 3 | 4 | 5 |
| **14) Ich fühle mich ausreichend informiert, um Entscheidungen über meine Krebsbehandlung mittreffen zu können.** | 1 | 2 | 3 | 4 | 5 |
| **15) Ich fühle mich ausreichend informiert, um Entscheidungen zur Behandlung möglicher Nebenwirkungen mittreffen zu können.** | 1 | 2 | 3 | 4 | 5 |
| **16) Ich fühle mich ausreichend informiert, um Entscheidungen zum Einsatz ergänzender Therapien mittreffen zu können. (Ergänzende Therapien schließen Vitamine, pflanzliche Präparate, Akupunktur, Antioxidantien, Homöopathie, Naturheilkunde und anthroposophische Heilmethoden mit ein.)** | 1 | 2 | 3 | 4 | 5 |

PSCaTE questionnaire version 1.1, 03/2006 (page 3)

**Bitte beantworten Sie hier kurz ein paar Fragen zu Ihrem persönlichen Informationsbedarf und den von Ihnen verwendeten Informationsquellen.**

**1) Woher haben Sie bisher Informationen zu Krebsbehandlungen erhalten?**
(bitte markieren Sie **alle** Möglichkeiten, die auf Sie zutreffen!)

- ❑ Hausarzt/-ärztin
- ❑ Familienmitglied
- ❑ Freund/-in
- ❑ Internet
- ❑ Bücher
- ❑ Heilpraktiker/-in
- ❑ Sozialarbeiter/-in
- ❑ Selbsthilfegruppe
- ❑ krankenhausinterne Patientenbibliothek
- ❑ Reformhaus
- ❑ Tageszeitung
- ❑ Fernsehen
- ❑ Krankenschwester
- ❑ Ernährungsberater/-in
- ❑ Onkologe/-in
- ❑ Apotheker/-in
- ❑ Studien-Apotheker/-in
- ❑ Radiologe/-in
- ❑ Chirurg/-in
- ❑ Ich habe keine Information erhalten

**2) Was oder wer war bisher Ihre wichtigste Quelle für Informationen zu Ihrer Krebsbehandlung?** (bitte hier nur **eine** Antwort ankreuzen!)

- ❑ Hausarzt/-ärztin
- ❑ Familienmitglied
- ❑ Freund/-in
- ❑ Internet
- ❑ Bücher
- ❑ Heilpraktiker/-in
- ❑ Sozialarbeiter/-in
- ❑ Selbsthilfegruppe
- ❑ krankenhausinterne Patientenbibliothek
- ❑ Reformhaus
- ❑ Tageszeitung
- ❑ Fernsehen
- ❑ Krankenschwester
- ❑ Ernährungsberater/-in
- ❑ Onkologe/-in
- ❑ Apotheker/-in
- ❑ Studien-Apotheker/in
- ❑ Radiologe/-in
- ❑ Chirurg/-in
- ❑ Ich habe keine Information erhalten

PSCaTE questionnaire version 1.1, 03/2006 (page 4)

**3) Ich hatte Fragen bezüglich meiner Krebsbehandlung.**

❑ ja ❑ nein

**4) Ich hatte Fragen bezüglich ergänzender Therapien. (Ergänzende Therapien schließen Vitamine, pflanzliche Präparate, Akupunktur, Antioxidantien, Homöopathie, Naturheilkunde und anthroposophische Heilmethoden mit ein.)**

❑ ja ❑ nein

**5) Ich möchte an den Entscheidungen im Rahmen meiner Krebsbehandlung beteiligt sein.**

❑ trifft auf keinen Fall zu ❑ trifft eher nicht zu

❑ unsicher ❑ trifft eher zu

❑ trifft voll zu

PSCaTE questionnaire version 1.1, 03/2006 (page 5)

**Dieser Teil des Fragebogens beschäftigt sich mit allgemeinen Daten.**

**1) Lebensalter** in Jahren : _____

**2) Geschlecht** (Zutreffendes bitte ankreuzen):

- ❑ weiblich
- ❑ männlich

**3) Familienstand** (Zutreffendes bitte ankreuzen):

- ❑ verheiratet/ Lebensgemeinschaft
- ❑ ledig
- ❑ geschieden
- ❑ verwitwet

**4) Aktuelle Wohnsituation** (Zutreffendes bitte ankreuzen):

- ❑ allein lebend
- ❑ mit Familie/ Lebenspartner lebend
- ❑ in Institution lebend (z.B.: Altenheim/ Pflegeheim...)

**5) Höchster Ausbildungsabschluss** (Zutreffendes bitte ankreuzen):

- ❑ Volksschulabschluss
- ❑ Hauptschulabschluss
- ❑ Mittlerer Reife (Fachhochschulreife)
- ❑ Gesellenprüfung
- ❑ Abitur (Hochschulreife)
- ❑ Meisterschule
- ❑ Fachhochschulabsolvent/·in
- ❑ Hochschulabsolvent/·in
- ❑ Höherer universitärer Abschluss (Doktor, Priv.Doz., Prof. etc.)

**6) Aktueller Beruf** (Zutreffendes bitte ankreuzen):

- ❑ Hausfrau/·mann
- ❑ Schüler/·in / Student/·in
- ❑ Beamte/·r
- ❑ Rentner/·in
- ❑ Angestellte/·r
- ❑ Selbständige/·r
- ❑ Arbeiter/·in
- ❑ Handwerker/·in

PSCaTE questionnaire version 1.1, 03/2006 (page 6)

**7)** Man hat bei mir **folgende Krebsart** festgestellt: _____

**8)** Ich weiß seit _____ von meiner Erkrankung.

**9) Ich befinde mich wegen meiner Krankheit** (Zutreffendes bitte ankreuzen)

- ❑ in stationärer Behandlung
- ❑ in ambulanter Behandlung bei einem niedergelassenen Onkologen
- ❑ in ambulanter Behandlung eines im Krankenhaus tätigen Onkologen

**10) Ich bin in einer Selbsthilfegruppe aktiv** (Zutreffendes bitte ankreuzen)

❑ ja ❑ nein

**Wir sind jederzeit dankbar für weitere Kommentare und Vorschläge:**

**Vielen Dank für die Zeit, die Sie sich zum Ausfüllen genommen haben.**

**Sie helfen damit auch anderen Patientinnen und Patienten!**

Prof. Dr. U. Jaehde
Universität Bonn
Pharmazeutisches Institut
Klinische Pharmazie

Questionnaire on hand-foot syndrome

universitätbonn

**Fragebogen zu Hautreaktionen**

Sehr geehrte Patientin, sehr geehrter Patient,

bitte geben Sie auf diesem Bogen kurz an, ob Sie während des letzten Zyklus Ihrer Chemotherapie mit Xeloda® Probleme mit Hautreaktionen an Ihren **Händen und Füßen** hatten.

Kreuzen Sie hierzu bitte das Feld unter der für Sie zutreffenden Beschreibung an:

| Keine Probleme | Minimale Hautveränderungen (z.B. Rötungen), **KEINE Schmerzen** | Hautreaktionen (z.B. Risse, Blasen, Schwellungen) **und/oder Schmerzen, NICHT beeinträchtigend** | Sehr starke Reaktionen (z.B. Hautablösungen, Blasen, Bluten) **und/oder starke Schmerzen, BEEINTRÄCHTIGEND** |
|---|---|---|---|
| | | | |

Platz für zusätzliche Kommentare:

Questionnaire on patient evaluation

Studie: ML21725

Roche

## Fragebogen zum Erfolg der Therapie und Nebenwirkungen

Sehr geehrter Patient,
wir möchten Sie bitten Ihre Therapie mit Rückblick auf Ihre Erwartungen und Erfahrungen zu beurteilen. Bitte beantworten Sie die folgenden Fragen selbst, indem Sie die Zahl ankreuzen, die nach Ihrem eigenen Empfinden am Besten auf Sie zutrifft. Es gibt keine „richtigen" oder „falschen" Antworten. Ihre Angaben werden streng vertraulich behandelt.

Geburtsdatum (TT, MM, JJJJ):

Heutiges Datum (TT, MM, JJJJ):

**Bitte kreuzen Sie bei den folgenden Fragen die Zahl zwischen 0 und 4 an, die am besten auf Sie zutrifft.**

1. Wie würden Sie das bisherige Ergebnis der Therapie beurteilen im Vergleich zu dem, was Sie vorher erwartet haben?

| 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| sehr viel schlechter | etwas schlechter | wie erwartet | etwas besser | sehr viel besser als erwartet |

2. Wie würden Sie die Nebenwirkungen der Therapie insgesamt beurteilen, wenn Sie es mit dem vergleichen, was Sie vor der Therapie erwartet haben?

| 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| sehr viel schlechter | etwas schlechter | wie erwartet | etwas besser | sehr viel besser als erwartet |

3. Wie würden Sie die Therapie nach Ihren bisherigen Erfahrungen insgesamt beurteilen?

| 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| schlecht | mäßig | gut | sehr gut | ausgezeichnet |

Questionnaire on general patient data

Klinische Pharmazie

universitätbonn

## Allgemeine Angaben

**1) Familienstand:**

- ❑ verheiratet/Lebensgemeinschaft
- ❑ ledig
- ❑ geschieden
- ❑ verwitwet

**2) Aktuelle Wohnsituation:**

- ❑ allein lebend
- ❑ mit Familie/Lebenspartner lebend
- ❑ in Institution lebend (z.B.: Altenheim/ Pflegeheim...)

**3) Verantwortlichkeit für die Tabletteneinnahme:**

- ❑ selbständig
- ❑ Lebenspartner/Familienangehöriger
- ❑ Pflegedienst o.ä.
- ❑ _____

**4) Höchster Ausbildungsabschluss:**

- ❑ Volksschulabschluss
- ❑ Hauptschulabschluss
- ❑ Mittlerer Reife (Fachhochschulreife)
- ❑ Gesellenprüfung
- ❑ Abitur (Hochschulreife)
- ❑ Meisterschule
- ❑ Fachhochschulabsolvent/·in
- ❑ Hochschulabsolvent/·in
- ❑ Höherer universitärer Abschluss (Doktor, Priv.Doz., Prof. etc.)

**5) Aktueller Beruf:**

- ❑ Hausfrau/·mann
- ❑ Schüler/·in / Student/·in
- ❑ Beamte/·r
- ❑ Rentner/·in
- ❑ Angestellte/·r
- ❑ Selbständige/·r
- ❑ Arbeiter/·in
- ❑ Handwerker/·in

**6) Aktivität in einer Selbsthilfegruppe:** ❑ ja ❑ nein

**7) Entfernung zum Behandlungsort:** _____ Minuten

## Appendix C: Material for patient care

Pharmaceutical care plan (page 1)

**PHARMAZEUTISCHER BETREUUNGSPLAN: XELODA (Vers. 01-06) - SEITE 1/2**

| | | | |
|---|---|---|---|
| | Geschlecht: | Patientencode: | **Alter:** |
| Akt. Krebstherapie: | | Diagnose: | Metastasen: ja ☐ nein ☐ |
| | | | Erstdiagnose: |
| Arzt: | Krankenkasse: | Start MEMS: | Monitor-Nr.: |

| **RELEVANTE KRANKHEITSGESCHICHTE** | | | | | |
|---|---|---|---|---|---|
| | Datum | Problembeschreibung | | Datum | Problembeschreibung |
| 1 | | | 3 | | |
| 2 | | | 4 | | |
| **Bekannte Arzneimittel-Allergien:** | | | | | |

| **BISHERIGE UND AKTUELLE KREBSTHERAPIE** | | | |
|---|---|---|---|
| **Chemotherapie (+ RT?)**<br>**1.**<br>**2.**<br>**3.**<br>**4.** | **Datum** | **Zyklen** | **Besonderheiten** |
| **Hormontherapie**<br>**1.** | **Datum** | **Dosierung** | **Besonderheiten** |
| **2.** | | | |
| **3.** | | | |
| **4.** | | | |
| **OP**<br>**1.**<br>**2.** | **Datum** | **Besonderheiten** | |

| **XELODA-Therapie** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Zyklusnr. / Startdatum | | | | | | | |
| Stärke | | | | | | | |
| Dosierung | | | | | | | |

| **AKTUELLE MEDIKATION (zu Beginn jedes Zyklus zu aktualisieren)** | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Start | Stop | | | Start | Stop |
| 1 | | | | 8 | | | |
| 2 | | | | 9 | | | |
| 3 | | | | 10 | | | |
| 4 | | | | 11 | | | |
| 5 | | | | 12 | | | |
| 6 | | | | 13 | | | |
| 7 | | | | 14 | | | |

Pharmaceutical care plan (page 2)

**PHARMAZEUTISCHER BETREUUNGSPLAN: XELODA (Vers. 01-06) - SEITE 1/2**

| | | | |
|---|---|---|---|
| | Geschlecht: | Patientencode: | **Alter:** |
| Akt. Krebstherapie: | | Diagnose: | Metastasen: ja ☐ nein ☐ |
| | | | Erstdiagnose: |
| Arzt: | Krankenkasse: | Start MEMS: | Monitor-Nr.: |

| **RELEVANTE KRANKHEITSGESCHICHTE** | | | | | |
|---|---|---|---|---|---|
| | Datum | Problembeschreibung | | Datum | Problembeschreibung |
| 1 | | | 3 | | |
| 2 | | | 4 | | |
| **Bekannte Arzneimittel-Allergien:** | | | | | |

| **BISHERIGE UND AKTUELLE KREBSTHERAPIE** | | | |
|---|---|---|---|
| **Chemotherapie (+ RT?)**<br>**1.**<br>**2.**<br>**3.**<br>**4.** | **Datum** | **Zyklen** | **Besonderheiten** |
| **Hormontherapie**<br>**1.**<br>**2.**<br>**3.**<br>**4.** | **Datum** | **Dosierung** | **Besonderheiten** |
| | | | |
| | | | |
| | | | |
| **OP**<br>**1.**<br>**2.** | **Datum** | **Besonderheiten** | |

| **XELODA-Therapie** | | | | | | | |
|---|---|---|---|---|---|---|---|
| Zyklusnr. / Startdatum | | | | | | | |
| Stärke | | | | | | | |
| Dosierung | | | | | | | |

| **AKTUELLE MEDIKATION (zu Beginn jedes Zyklus zu aktualisieren)** | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Start | Stop | | | Start | Stop |
| 1 | | | | 8 | | | |
| 2 | | | | 9 | | | |
| 3 | | | | 10 | | | |
| 4 | | | | 11 | | | |
| 5 | | | | 12 | | | |
| 6 | | | | 13 | | | |
| 7 | | | | 14 | | | |

| Mögliche Nebenwirkung | Vorbeugende Maßnahmen | Im Falle des Falles |
|---|---|---|
| Verstopfung (Obstipation) | ○ Ausreichend trinken! (Pflaumensaft, Tee, Wasser)<br>○ Bewegung (z.B. Spazieren gehen)<br>○ Jedem Reiz, zur Toilette zu gehen, nachgeben<br>○ Ballaststoffreiche Ernährung (Vollkornbrot, Gemüse, Weizenkleie) | ○ Ursache mit dem Arzt klären, evtl. Abführmittel einnehmen<br>○ Viel trinken! |
| Geschmacksveränderungen | ○ Mundschleimhaut feucht halten durch häufiges Trinken (z.B. Salbeitee) | ○ Bonbons lutschen<br>○ Zur Geschmacksverstärkung trockene Nahrung in Flüssigkeiten einweichen (z. B. Saucen, Brot in Kaffee tunken) |
| Fieber / Infektionen | ○ Ausreichende Ruhephasen<br>○ Ungekochtes Obst/Gemüse vermeiden<br>○ Gründliche Körperhygiene<br>○ Kontakt meiden zu:<br>- Menschen mit ansteckenden Erkrankungen<br>- Frisch geimpften Menschen | ○ Bei Fieber > 38°C sofort den Arzt verständigen!<br>○ Erkältungsanzeichen genau beobachten<br>○ Bei längerer Heilungsdauer üblicher Erkrankungen den Arzt aufsuchen<br>○ Vom Arzt verordnete Antibiotika regelmäßig und gemäß der Verordnung einnehmen |
| Müdigkeit und Erschöpfung (Fatigue) | ○ Entspannungsübungen<br>○ Ruhephasen einplanen<br>○ Angemessene körperliche Bewegung (Spaziergänge im Freien)<br>○ Koffein und Alkohol vor dem Einschlafen vermeiden<br>○ Alltagspflichten auf andere übertragen (z.B. Familienmitglieder) | ○ Bei länger anhaltender Erschöpfung und Müdigkeit, die auch durch ausreichende Ruhepausen nicht deutlich verringert wird, den Arzt informieren<br>○ Vorbeugende Maßnahmen weiter verfolgen |
| Haarausfall (Alopezie) | Haarausfall ist leider nicht durch vorbeugende Maßnahmen zu vermeiden oder zu lindern. Sorgen Sie vorsorglich für geeigneten Haarersatz oder Kopfbedeckung anderer Art, die Ihnen gefällt. Die Haare werden nach Beendigung der Therapie wieder zu wachsen beginnen. | ○ Kopfhaut vor Kälte, Hitze und direkter Sonneneinstrahlung schützen<br>○ Bei Verlust der Wimpern, das Auge vor intensivem Licht und Staub bewahren |

Dipl.-Pharm. Linda Krolop und Friederike Schröder
Apothekerinnen
Klinische Pharmazie
Pharmazeutisches Institut
An der Immenburg 4
53121 Bonn

Telefon 0228 – 735229
Fax 0228 – 739757
Email l.krolop@uni-bonn.de
friederike.schroeder@uni-bonn.de

# Chemotherapie und die Nebenwirkungen

Was Sie darüber wissen sollten,
wie Sie Nebenwirkungen vorbeugen können,
und was Sie im Falle des Falles tun können!

**Klinische Pharmazie** universitätbonn

Sehr geehrte Patientin, sehr geehrter Patient,

im Rahmen Ihrer Behandlung bekommen Sie eine Chemotherapie in Tablettenform. Sie erhalten das Arzneimittel Xeloda® (Wirkstoff: Capecitabin) und dazu möglicherweise noch weitere Kombinationspartner, die individuell auf Ihre Erkrankung abgestimmt wurden.

Anders als die Operation und die Strahlentherapie wirken die in der Chemotherapie eingesetzten Wirkstoffe im ganzen Körper (systemisch), da sie über das Blut verteilt werden. Die Wirkstoffe sind gegen möglicherweise im Körper verteilte Krebszellen gerichtet. Die Wirkstoffe können jedoch nicht zwischen kranken und gesunden Zellen unterscheiden, so dass auch gesunde Zellen betroffen sein können. Das führt zu unerwünschten Nebenwirkungen. Hiervon sind hauptsächlich die Zellen in Ihrem Körper betroffen, die sich häufig teilen und dadurch erneuern. Dazu gehören zum Beispiel Haarzellen, Schleimhautzellen des Mundes und des Magen-Darmtraktes, Hautzellen und auch Zellen des Knochenmarks, welches Ihr Blut bildet.

Wichtig für Sie zu wissen ist, dass nicht alle der beschriebenen Nebenwirkungen auch tatsächlich auftreten. Falls es jedoch dazu kommen sollte, ist es gut, wenn Sie bereits davon gehört haben und wissen, was Sie dagegen tun können.

**Im Zweifel sprechen Sie Ihren betreuenden Arzt an und unterrichten ihn genau über die Nebenwirkung und die Maßnahmen, die Sie dagegen eingeleitet haben.**

Die Wirkstoffe, die Sie in Ihrer Chemotherapie erhalten, heißen:

| **Mögliche Nebenwirkung** | **Vorbeugende Maßnahmen** | **Im Falle des Falles** |
|---|---|---|
| Hand-Fuß-Syndrom | ○ Hautpflege mit milder, parfümfreier Feuchtigkeitslotion<br>○ Milde Seifen und Spülmittel verwenden<br>○ Druck vermeiden (offene, lockere Schuhe tragen, schwere Hand und/oder Gartenarbeit vermeiden)<br>○ Lauwarm duschen bzw. baden | ○ Hautpflege mit milder, parfümfreier Feuchtigkeitslotion<br>○ Bei starker Verschlechterung und/oder Beeinträchtigung den behandelnden Arzt informieren! |
| Übelkeit und Erbrechen (Nausea und Emesis) | ○ Vorbeugende Medikation wie verordnet einnehmen (nicht nur im Bedarfsfall!)<br>○ Generell gilt: Essen Sie, worauf Sie Appetit haben!!<br>○ Große Mahlzeiten vermeiden; 5-6 kleinere Mahlzeiten pro Tag essen<br>○ Kalte Speisen und Getränke werden häufig besser toleriert als warme<br>○ Appetit durch säuerliche Bonbons, Speisen oder Getränke anregen<br>○ Schlaf, entspannende Musik oder Spaziergänge im Freien<br>○ Süße, fette, stark riechende und gebratene Speisen vermeiden | ○ Viel frische Luft zuführen<br>○ Ausruhen<br>○ Bedarfsmedikation einnehmen<br>○ Ausreichend trinken |
| Entzündungen im Mundraum (Mukositis) | ○ Zahnsanierung beim Zahnarzt<br>○ Gründliche, schonende Mundhygiene<br>○ Weiche Zahnbürsten verwenden<br>○ Alkoholfreie Mundwässer verwenden<br>○ Spülung mit lauwarmem Salbeitee<br>○ Zahnreinigende Kaugummis zur Speichelanregung kauen<br>○ Ausreichend trinken<br>○ Nikotin und Alkohol vermeiden<br>○ Scharfe, heiße und sehr saure Speisen vermeiden | ○ Bei Anzeichen einer Mundschleimhautentzündung rechtzeitig den Arzt informieren und verordnete Medikamente einsetzen<br>○ Mundhygiene entsprechend der Vorbeugung fortsetzen<br>○ Weiche Speisen bevorzugen<br>○ Ananassaft-Eiswürfel lutschen<br>○ Zusätzliche Verletzungen vermeiden |
| Durchfall (Diarrhoe) | ○ Bei Durchfallneigung Ernährung umstellen (auf z.B. Weißbrot, Kartoffeln, Bananen, Äpfel, Mais usw.)<br>○ Vermeiden: Süßstoffe, Vollkornbrot, Kaffee, stark gewürzte Speisen, Fruchtsäfte, Obst (mit Ausnahmen s. o.), rohe Milch<br>○ Mineralwässer mit geringem Sulfatgehalt ($SO_4^{2-}$) trinken | ○ Ausreichend trinken<br>○ Ursache mit dem Arzt klären, evtl. Medikamente (Loperamid) einnehmen<br>○ Weiches Toilettenpapier und feuchte Tücher verwenden |

Patient letter containing medication plan (page 1)

universitätbonn

Rheinische
Friedrich-Wilhelms-
Universität Bonn Pharmazeutisches Institut

universität bonn · Klinische Pharmazie · An der Immenburg 4 · 53121 Bonn

Prof. Dr. U. Jaehde Klinische Pharmazie

Frau
Johanna Musterpatientin
Teststr. 13
54321 Bonn

Ansprechpartner:
Dipl.-Pharm. Linda Krolop
An der Immenburg 4
53121 Bonn
Tel.: 0228/73-5229
Fax: 0228/73-9757
l.krolop@uni-bonn.de
www.klinische-pharmazie.info

**Ihre Arzneimitteleinnahme**

Bonn, 12.08.2009

Sehr geehrte Frau Musterpatientin,

wie bei unserem Gespräch am letzten Freitag in der onkologischen Ambulanz des Johanniter-Krankenhauses besprochen, habe ich alle Medikamente, die Sie derzeit einnehmen, auf Wechselwirkungen überprüft und kann Ihnen erfreulicherweise bestätigen, dass keines der Arzneimittel einen Einfluss auf die Wirksamkeit und Sicherheit eines anderen nimmt, wenn man sich an die empfohlenen Einnahmezeitpunkte hält.

Als Anlage zu diesem Schreiben sende ich Ihnen einen Vorschlag für einen Einnahmezeitplan, der sich an Ihren Mahlzeiten im Laufe des Tages orientiert. Dieser Plan wurde von mir nach bestem Wissen und Gewissen zusammengestellt und ist hinsichtlich der unterschiedlichen Wirkweisen der Medikamente optimiert.

Die Einnahme der Opium-Tropfen kann bei Durchfall **unabhängig von den Mahlzeiten** erfolgen. Es ist nicht bekannt, dass die Wirkung durch Nahrung positiv oder negativ beeinflusst wird.

Wenn Sie sich einer Zahnoperation unterziehen, sollte die Behandlung mit **Avastin®** ca. 4-6 Wochen vor der Operation abgesetzt werden und frühestens 4 Wochen nach dem operativen Eingriff oder erst nach völliger Abheilung der Operationswunde fortgeführt werden. Auf jeden Fall sollten Sie diesbezüglich mit Frau Dr. Geisen Rücksprache halten.

Wie besprochen finden Sie außerdem in diesem Umschlag Informationsmaterial zu den komplementär-onkologischen Therapieoptionen Curcuma, Shiitake und Equizym® (dieses Präparat enthält Selen, Enzyme und Lektin aus der Linse).

Bei Fragen oder Problemen stehe ich Ihnen selbstverständlich jederzeit gerne zur Verfügung.

Alles Gute und beste Grüße

Linda Krolop

Patient letter containing medication plan (page 2)

universitätbonn Klinische Pharmazie

**Einnahmeplan für Frau Johanna Musterpatientin, aktualisiert am 25.11.2010**

| FRÜHSTÜCK | | | MITTAG-ESSEN | ABENDESSEN | |
|---|---|---|---|---|---|
| ½-1 h VOR dem Essen/ nüchtern | ZUM Essen | NACH dem Essen | | ZUM Essen | NACH dem Essen |
| Euthyrox® 100 µg 1 Tablette<br><br>Pantoprazol 40 mg 1 Tablette | Lisihexal® 5 mg* 1 Tablette | Xeloda® 500mg 3 Tabletten<br><br>Metohexal® 100mg ½ Tablette | - | Zyprexa® 7,5mg* 1 Tablette | Xeloda® 500mg 3 Tabletten |

**Weitere Arzneimittel:**

- **Fraxiparin® 0,6**
  Wie bisher einmal abends eine Spritze in die seitliche Bauchwand oder den Oberschenkel
- **Novalgin® Tropfen**
  Wie bisher bei Bedarf (bis zu 3-mal täglich 40 Tropfen)
- **Opium Tropfen**
  Bei Durchfall wie bisher (Einnahme ist unabhängig von den Mahlzeiten)
- **Avastin®**: Verabreichung als Infusion

**Wechselwirkung Xeloda® mit Folsäure**
Falls Sie ein Vitaminpräparat einnehmen möchten, sollten Sie darauf achten, dass es ein Präparat ist, welches **keine Folsäure** enthält. Durch die gemeinsame Einnahme von Xeloda® und Folsäure kann die Verträglichkeit von Xeloda® herabgesetzt sein.

* Die Einnahme kann vor, zu oder nach einer Mahlzeit geschehen, sollte jedoch jeden Tag etwa um die gleiche Uhrzeit erfolgen.

First consultation documentation form (page 1)

**Dokumentationsbogen Anamnesegespräch**

Apothekerin: _____ Datum: _____

Patientencode: _____

Alter: _____ Größe: _____ m

Gewicht: _____ kg KOF: _____ m²

Gespräch: von _____ bis _____ Uhr Dauer: _____ Min. Nachbereitung: ____ Min.

Diagnose: ❑ MammaCa T___ N ___ M ___ G ___ R _____ HER2 _____ ❑ _____

Menopausalstatus: ❑ prä ❑ peri ❑ post

Therapie: _____ Zyklus: _____

Radiotherapie: _____ OP: _____

Begleit-erkrankungen: _____ familiäre Erkrankungen: _____

Allergien: _____

Material:

| | | | | |
|---|---|---|---|---|
| blaue Ratgeber | ❑ Brustkrebs | ❑ | _____ | ❑ nein |
| „Richtiges Verhalten“ | ❑ ja | ❑ nein | | |
| „Fragen & Antworten“ | ❑ ja | ❑ nein | | |
| Chemotherapie & Nebenwirkungen | ❑ ja | ❑ nein | | |
| Video Xeloda® | ❑ ja | ❑ nein | | |

Erklärung → Wirkweise Capecitabin ❑ ja ❑ nein

→ Einnahme Capecitabin ❑ ja ❑ nein

→ HFS ❑ ja ❑ nein

→ Kombinationspartner ❑ ja ❑ nein

Fragen des Patienten: ❑ ja ❑ nein

Wenn ja, welche:

Ergänzungen:

First consultation documentation form (page 2)

| | **Arzneimittel** (Stärke, Dosis, Indikation etc.) | **Problem** z.B. UAW (potentiell, tatsächlich, subjektiv, objektiv) | **Intervention** |
|---|---|---|---|
| **Chemo** | | | |
| | | | |
| | | | |
| | | | |
| **Supportiv** | | | |
| | | | |
| | | | |
| | | | |
| **Weitere** z.B. Selbstmedikation | | | |
| | | | |
| | | | |
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| | | | |
| | | | |

Follow-up consultation documentation form (page 1)

**Dokumentationsbogen Folgegespräch**

Apothekerin: _____ Datum: _____

Patientencode: _____

Alter: _____ Größe: _____ m

Gewicht: _____ kg KOF: _____ m²

Ende aktueller Zyklus: _____ Beginn neuer Zyklus: _____

Gespräch: von _____ bis _____ Uhr Dauer: _____ Min. Nachbereitung: ____ Min.

Therapie: _____ nach Zyklus: _____

Fragen/Probleme: ❑ ja ❑ nein

Wenn ja, welche:

Probleme mit MEMS®: ❑ ja ❑ nein

Wenn ja, welche:

Ergänzungen:

Follow-up consultation documentation form (page 2)

| | **Arzneimittel** (Stärke, Dosis, Indikation etc.) | **Problem** z.B. UAW (potentiell, tatsächlich, subjektiv, objektiv) | **Intervention** |
|---|---|---|---|
| **Chemo** | | | |
| | | | |
| | | | |
| | | | |
| **Supportiv** | | | |
| | | | |
| | | | |
| | | | |
| **Weitere** z.B. Selbstmedikation | | | |
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| | | | |

MEMS® patient information (page 1)

**Das MEMS® (Medication Event Monitoring System) – Arzneimittelbehältnis**
**Hinweise zur Anwendung**

1. Es wurde Ihnen das Arzneimittel Xeloda® verordnet.
   Ihr Arzt _____ hat Ihnen folgendes Einnahmeschema verordnet: _____.
   Bitte halten Sie sich exakt an diese Verordnung!

2. Entnehmen Sie Ihre Xeloda®-Tabletten bitte nur aus dem MEMS®-Arnzeimittelbehältnis.

3. Öffnen Sie das Behältnis bitte nur, um tatsächlich Tabletten zu Ihrer Einnahme zu entnehmen. Sollte das Behältnis versehentlich doch einmal außerplanmäßig geöffnet worden sein, notieren Sie bitte Datum und Uhrzeit und teilen Sie diese der Studien-Apothekerin beim nächsten Treffen mit.

4. Schließen Sie das Behältnis anschließend umgehend, indem Sie den Deckel wieder ganz zuschrauben.

5. Lassen Sie das Behältnis niemals länger geöffnet, als dies zur Entnahme der Tabletten notwendig ist.

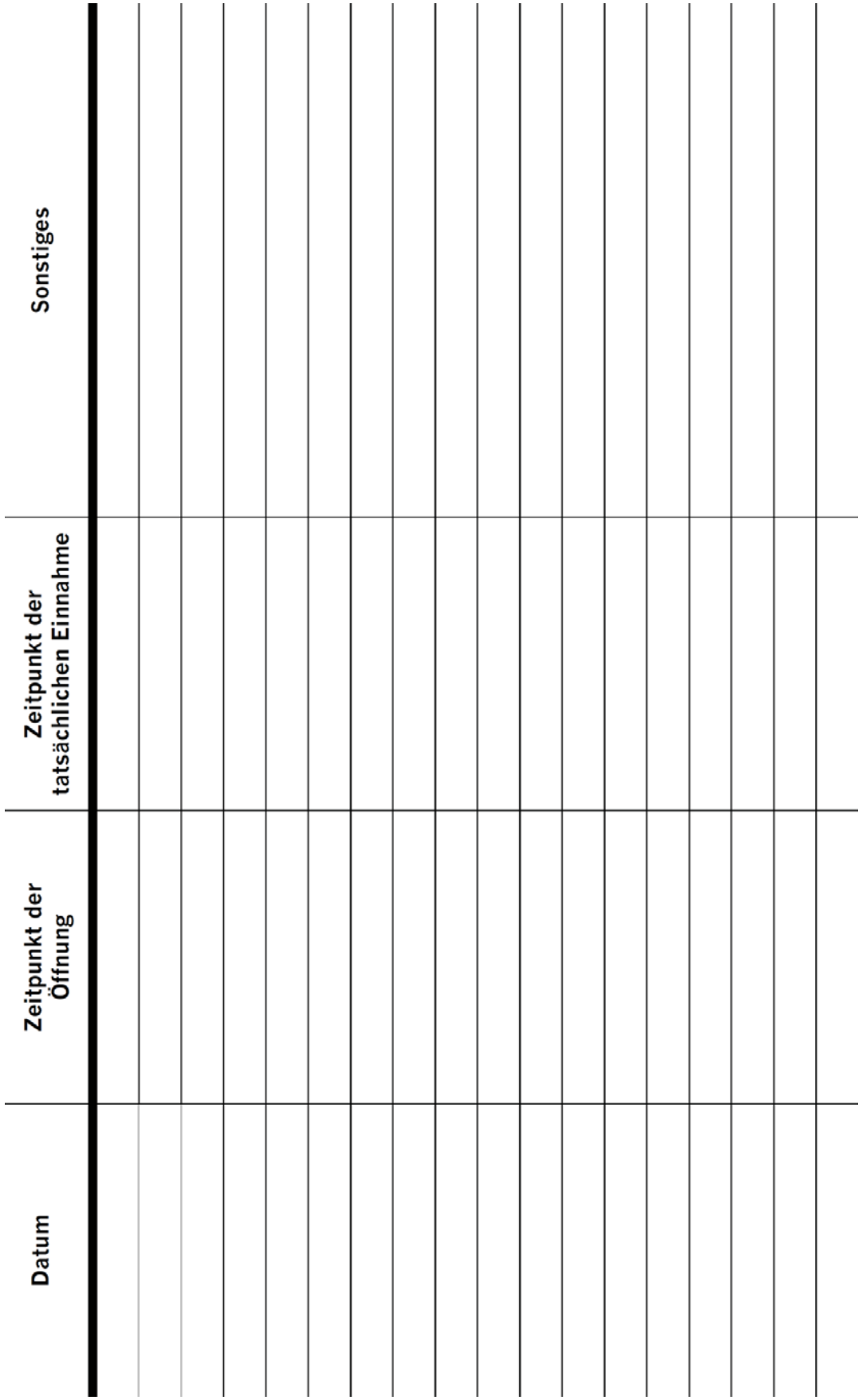
6. Lagern Sie das Behältnis an einem trockenen Ort und schützen Sie es vor Feuchtigkeit. Verwenden Sie bitte zur Reinigung kein Spülmittel oder Alkohol!

7. Bei Defekten am Behältnis oder Fragen zur Anwendung, wenden Sie sich bitte umgehend an die die Studie betreuende Apothekerin Linda Krolop bzw. Friederike Schröder.

**Ansprechpartner:**

Apothekerinnen Linda Krolop und Friederike Schröder
Telefon: 0228-73-5229
Fax: 0228-73-9757
Email: l.krolop@uni-bonn.de
friederike.schroeder@uni-bonn.de

MEMS® patient information (page 2)



Adherence support documentation form (cycle 1)

| Modul 3 - Checkliste zum Gesprächsablauf nach Zyklus 1 | | | | |
|---|---|---|---|---|
| Patient | | | Code | |
| Datum | | | Compliance Zyklus 1 | % |
| Gespräch von bis Uhr | | Dauer Min. | Nachbereitung | Min. |
| **Checkpoint** | | **Abgefragt ?** | | **Erläuterungen** |
| | | **Ja** | **Nein** | |
| 1 | Erwartungen hinsichtlich der Compliance | ❑ | ❑ | |
| 2 | Detaillierte Besprechung der Compliance-Ergebnisse anhand der MEMS-Daten | | | |
| 3 | Erfahrungen mit der Einnahme | ❑ | ❑ | |
| 4 | Gründe für Non-Compliance (Barrieren, Probleme etc.) | ❑ | ❑ | |
| 5* | Compliance-Strategie möglich, um Einnahmebarrieren zu überwinden? | | | |
| a | Verknüpfung mit Routinehandlung (Zähne-putzen, Tagesschau etc.) | ❑ | ❑ | |
| b | Selbstüberwachung der Tabletteneinnahme mit Tagebuch | ❑ | ❑ | |
| c | Einspeicherung einer Erinnerung in das Mobiltelefon | ❑ | ❑ | |
| d | Erinnerungskarte an einem markanten Ort | ❑ | ❑ | |
| e | Weitere Strategien | ❑ | ❑ | |
| 6* | Wichtigkeit der Compliance aufgezeigt durch Verdeutlichung der/des | | | |
| a | Wirkungsminderung/-verlustes | ❑ | ❑ | |
| b | häufigeren Arztbesuche | ❑ | ❑ | |
| c | längeren Behandlungszeiten | ❑ | ❑ | |
| d | häufigeren Krankenhausaufenthalte | ❑ | ❑ | |

* nicht alle Unterpunkte müssen abgefragt werden

Adherence support documentation form (cycle 2-6)

| **Modul 3 - Checkliste zum Gesprächsablauf nach Zyklus 2 3 4 5 6** (bitte markieren) | | | | |
|---|---|---|---|---|
| Patient | | | | Code |
| Datum | | | | Compl. Zyklus ____ % |
| Gespräch von | bis | Uhr | Dauer Min. | Nachbereitung Min. |

| **Checkpoint** | | **Abgefragt ?** | | **Erläuterungen** |
|---|---|---|---|---|
| | | **Ja** | **Nein** | |
| 1 | Erfüllung der Erwartungen hinsichtlich der Compliance | ❑ | ❑ | |
| 2 | Detaillierte Besprechung der Compliance-Ergebnisse anhand der MEMS-Daten | | | |
| 3 | Compliance ≥ 90% | ❑ | ❑ | |
| 4 | wenn ja | | | |
| a | Funktionieren der Compliance-Strategien | ❑ | ❑ | |
| b | Probleme | ❑ | ❑ | |
| c | Lob/Bekräftigung des Verhaltens | ❑ | ❑ | |
| 5 | wenn nein | | | |
| a | Erfahrungen mit der Einnahme | ❑ | ❑ | |
| b | Gründe für Non-Compliance (Barrieren, Probleme etc.) | ❑ | ❑ | |
| c* | Compliance-Strategie möglich, um Einnahmebarrieren zu überwinden? | | | |
| c1 | Verknüpfung mit Routinehandlung (Zähne-putzen, Tagesschau etc.) | ❑ | ❑ | |
| c2 | Selbstüberwachung der Tabletteneinnahme mit Tagebuch | ❑ | ❑ | |
| c3 | Einspeicherung einer Erinnerung in das Mobiltelefon | ❑ | ❑ | |
| c4 | Erinnerungskarte an einem markanten Ort | ❑ | ❑ | |
| c5 | Weitere Strategien | ❑ | ❑ | |
| d* | Wichtigkeit der Compliance aufgezeigt durch Verdeutlichung der/des | | | |
| d1 | Wirkungsminderung/-verlustes | ❑ | ❑ | |
| d2 | häufigeren Arztbesuche | ❑ | ❑ | |
| d3 | längeren Behandlungszeiten | ❑ | ❑ | |
| d4 | häufigeren Krankenhausaufenthalte | ❑ | ❑ | |

* nicht alle Unterpunkte müssen abgefragt werden

Reminding card

## Zu Ihrer Erinnerung

Bitte nehmen Sie Ihre Xeloda®-Tabletten jeweils 30 Min. **nach** dem Essen wie folgt ein:

morgens ___ Tabletten Xeloda® 500 mg

abends ___ Tabletten Xeloda® 500 mg

Klinische Pharmazie
Universität Bonn

## Appendix D: Results of initially adherent patients

### Adherence

*Table D-1: Daily intake adherence [%] of initially adherent patients during cycle 1 to 6*

| | n | Mean [%] | Median [%] | SD [%] | Range [%] | IQR [%] |
|---|---|---|---|---|---|---|
| $t_1$ | 58 | 98.8 | 100.0 | 2.8 | 90.9-100.0 | 100.0-100.0 |
| $t_2$ | 56 | 95.8 | 100.0 | 9.0 | 50.0-100.0 | 92.9-100.0 |
| $t_3$ | 48 | 94.9 | 100.0 | 8.7 | 66.7-100.0 | 92.9-100.0 |
| $t_4$ | 45 | 95.8 | 100.0 | 7.4 | 68.8-100.0 | 92.9-100.0 |
| $t_5$ | 39 | 95.8 | 100.0 | 8.3 | 62.5-100.0 | 92.9-100.0 |
| $t_6$ | 37 | 96.7 | 100.0 | 7.9 | 57.1-100.0 | 92.9-100.0 |

*Table D-2: Daily break adherence [%] of initially adherent patients during cycle 1 to 6*

| | n | Mean [%] | Median [%] | SD [%] | Range [%] | IQR [%] |
|---|---|---|---|---|---|---|
| $t_1$ | 58 | 99.2 | 100.0 | 3.2 | 85.7-100.0 | 100.0-100.0 |
| $t_2$ | 54 | 99.2 | 100.0 | 3.2 | 85.7-100.0 | 100.0-100.0 |
| $t_3$ | 47 | 100.0 | 100.0 | 0.0 | 100.0-100.0 | 100.0-100.0 |
| $t_4$ | 40 | 98.9 | 100.0 | 3.5 | 85.7-100.0 | 100.0-100.0 |
| $t_5$ | 40 | 99.6 | 100.0 | 2.6 | 83.3-100.0 | 100.0-100.0 |
| $t_6$ | 32 | 99.6 | 100.0 | 1.8 | 92.9-100.0 | 100.0-100.0 |

*Table D-3: Number of initially adherent patients exhibiting a daily total adherence below 100%, 90% and 80%, respectively, at $t_1$, $t_2$, $t_3$, $t_4$, $t_5$ and $t_6$*

| | Daily total adherence [%] | n | % | | Daily total adherence [%] | n | % |
|---|---|---|---|---|---|---|---|
| $t_1$ | =100% | 45 | 77.6 | $t_4$ | =100% | 29 | 64.4 |
| | <100% | 13 | 22.4 | | <100% | 16 | 35.6 |
| | ≥90 | 58 | 100.0 | | ≥90 | 42 | 72.4 |
| | <90 | 0 | 0.0 | | <90 | 3 | 5.2 |
| | ≥80 | 58 | 100.0 | | ≥80 | 43 | 74.1 |
| | <80 | 0 | 0.0 | | <80 | 2 | 3.4 |
| | Missing | 0 | 0.0 | | Missing | 13 | 22.4 |
| $t_2$ | =100% | 38 | 67.9 | $t_5$ | =100% | 28 | 70.0 |
| | <100% | 18 | 32.1 | | <100% | 12 | 30.0 |
| | ≥90 | 54 | 93.1 | | ≥90 | 38 | 65.5 |
| | <90 | 2 | 3.4 | | <90 | 2 | 3.4 |
| | ≥80 | 55 | 94.8 | | ≥80 | 40 | 69.0 |
| | <80 | 1 | 1.7 | | <80 | 0 | 0.0 |
| | Missing | 2 | 3.4 | | Missing | 18 | 31.0 |
| $t_3$ | =100% | 30 | 62.5 | $t_6$ | =100% | 25 | 67.6 |
| | <100% | 18 | 37.5 | | <100% | 12 | 32.4 |
| | ≥90 | 46 | 79.3 | | ≥90 | 36 | 62.1 |
| | <90 | 2 | 3.4 | | <90 | 1 | 1.7 |
| | ≥80 | 47 | 81.0 | | ≥80 | 36 | 62.1 |
| | <80 | 1 | 1.7 | | <80 | 1 | 1.7 |
| | Missing | 10 | 17.2 | | Missing | 21 | 36.2 |

*Table D-4: Overall adherence [%] of initially adherent patients during the course of the study*

| Overall adherence | n | Mean [%] | Median [%] | SD [%] | Range [%] | IQR [%] |
|---|---|---|---|---|---|---|
| $t_1$ | 58 | 99.9 | 100.0 | 2.3 | 92.9-107.7 | 100.0-100.0 |
| $t_2$ | 56 | 99.1 | 100.0 | 6.0 | 58.3-107.1 | 100.0-100.0 |
| $t_3$ | 48 | 100.5 | 100.0 | 8.5 | 90.0-153.6 | 100.0-100.0 |
| $t_4$ | 45 | 98.9 | 100.0 | 3.6 | 82.1-103.6 | 100.0-100.0 |
| $t_5$ | 39 | 98.2 | 100.0 | 4.6 | 81.3-107.4 | 100.0-100.0 |
| $t_6$ | 37 | 98.8 | 100.0 | 4.6 | 75.0-107.1 | 100.0-100.0 |

**Quality of life**

*Table D-5: EORTC QLQ-C30 reference values for 'all cancer patients: all stages'*

| | n | Mean | SD | Median | IQR |
|---|---|---|---|---|---|
| **Functional scales** | | | | | |
| Physical functioning (PF) | 10,158 | 76.7 | 23.2 | 80.0 | 66.7-93.3 |
| Role functioning (RF) | 19,155 | 70.5 | 32.8 | 83.3 | 50.0-100.0 |
| Emotional functioning (EF) | 23,024 | 71.4 | 24.2 | 75.0 | 58.3-91.7 |
| Cognitive functioning (CF) | 23,094 | 82.6 | 21.9 | 83.3 | 66.7-100 |
| Social functioning (SF) | 23,064 | 75.0 | 29.1 | 83.3 | 66.7-100 |
| **Symptom scales/items** | | | | | |
| Fatigue (FA) | 22,945 | 34.6 | 27.8 | 33.3 | 11.1-55.6 |
| Nausea and vomiting (NV) | 22,992 | 9.1 | 19 | 0.0 | 0.0-16.7 |
| Pain (PA) | 22,989 | 27.0 | 29.9 | 16.7 | 0.0-50.0 |
| Dyspnoea (DY) | 23,230 | 21.0 | 28.4 | 0.0 | 0.0-33.3 |
| Insomnia (SL) | 23,241 | 28.9 | 31.9 | 33.3 | 0.0-33.3 |
| Appetite loss (AP) | 23,241 | 21.1 | 31.3 | 0.0 | 0.0-33.3 |
| Constipation (CO) | 23,241 | 17.5 | 28.4 | 0.0 | 0.0-33.3 |
| Diarrhoea (DI) | 23,173 | 9.0 | 20.3 | 0.0 | 0.0-0.0 |
| Financial difficulties (FI) | 23,124 | 16.3 | 28.1 | 0.0 | 0.0-33.3 |
| **Global health status/QoL** | | | | | |
| Global health status/QoL (QL) | 19,237 | 61.3 | 24.2 | 66.7 | 50.0-83.3 |

*Table D-6: Mean, standard deviation, median and interquartile range of the EQ-5D descriptive system at $t_0$, $t_3$ and $t_6$ in initially adherent patients (n=58)*

| EQ-5D dimension | n | Mean | SD | Median | IQR |
|---|---|---|---|---|---|
| Mobility $t_0$ | 51 | 1.3 | 0.5 | 1.0 | 1.0-2.0 |
| Mobility $t_3$ | 46 | 1.3 | 0.5 | 1.0 | 1.0-2.0 |
| Mobility $t_6$ | 36 | 1.3 | 0.5 | 1.0 | 1.0-2.0 |
| Self-care $t_0$ | 51 | 1.1 | 0.3 | 1.0 | 1.0-1.0 |
| Self-care $t_3$ | 46 | 1.1 | 0.3 | 1.0 | 1.0-1.0 |
| Self-care $t_6$ | 37 | 1.1 | 0.4 | 1.0 | 1.0-1.0 |
| Usual activities $t_0$ | 51 | 1.5 | 0.6 | 1.0 | 1.0-2.0 |
| Usual activities $t_3$ | 46 | 1.5 | 0.6 | 1.0 | 1.0-2.0 |
| Usual activities $t_6$ | 37 | 1.6 | 0.5 | 2.0 | 1.0-2.0 |
| Pain/discomfort $t_0$ | 51 | 1.6 | 0.6 | 2.0 | 1.0-2.0 |
| Pain/discomfort $t_3$ | 46 | 1.5 | 0.5 | 2.0 | 1.0-2.0 |
| Pain/discomfort $t_6$ | 37 | 1.6 | 0.5 | 2.0 | 1.0-2.0 |
| Anxiety/depression $t_0$ | 51 | 1.5 | 0.5 | 1.0 | 1.0-2.0 |
| Anxiety/depression $t_3$ | 46 | 1.3 | 0.5 | 1.0 | 1.0-2.0 |
| Anxiety/depression $t_6$ | 37 | 1.2 | 0.4 | 1.0 | 1.0-1.0 |

**Patient satisfaction with information**

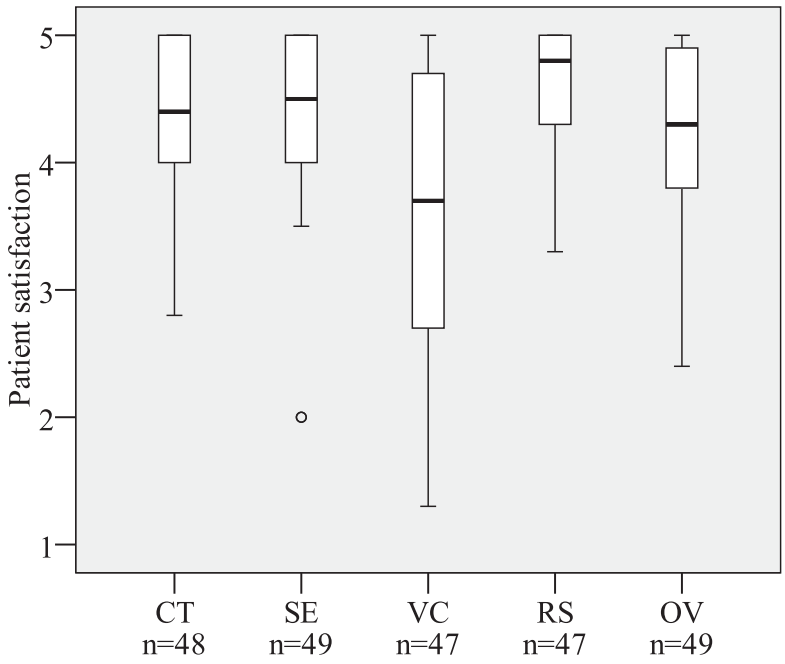



*Figure D-46: Five dimensions of patient satisfaction with information of initially adherent patients assessed by means of the PSCaTE questionnaire at $t_0$*

*CT = Satisfaction with information on cancer therapy; SE = Satisfaction with information on adverse effects; VC = Satisfaction with information on vitamins, herbal medicines and complementary treatment options; RS = Satisfaction with information sources; OV = Overall satisfaction*

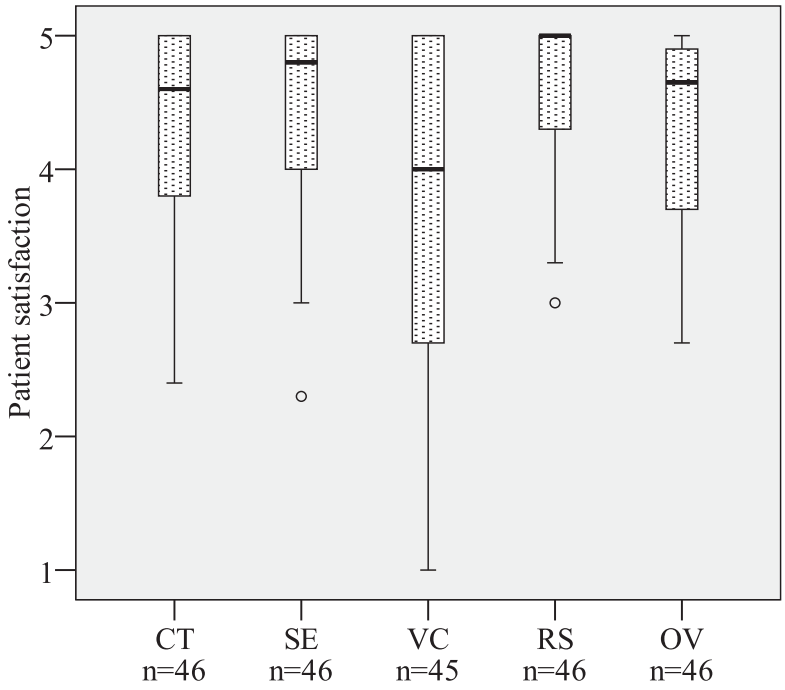



*Figure D-47: Five dimensions of patient satisfaction with information of initially adherent patients assessed by means of the PSCaTE questionnaire at $t_3$ (abbreviations see below)*

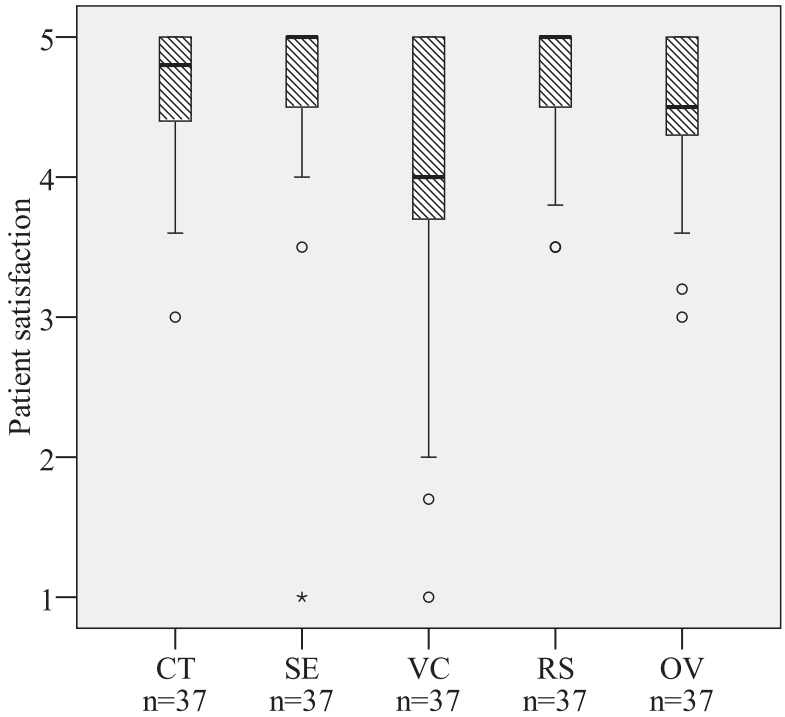



*Figure D-48: Five dimensions of patient satisfaction with information of initially adherent patients assessed by means of the PSCaTE questionnaire at $t_6$*

*CT = Satisfaction with information on cancer therapy; SE = Satisfaction with information on adverse effects; VC = Satisfaction with information on vitamins, herbal medicines and complementary treatment options; RS = Satisfaction with information sources; OV = Overall satisfaction*

**Patient evaluation**

*Table D-7: Patient evaluation of the capecitabine treatment at $t_6$ (n=58)*

| | | n | % |
|---|---|---|---|
| Assessment of therapy outcome compared with expectations | Much worse | 2 | 5.1 |
| | Slightly worse | 7 | 17.9 |
| | As expected | 10 | 25.6 |
| | Slightly better | 10 | 25.6 |
| | Much better than expected | 10 | 25.6 |
| Assessment of adverse drug reactions compared with expectations | Much worse | 2 | 5.1 |
| | Slightly worse | 6 | 15.4 |
| | As expected | 8 | 20.5 |
| | Slightly better | 10 | 25.6 |
| | Much better than expected | 13 | 33.3 |
| Overall assessment of treatment | Poor | 1 | 2.6 |
| | Fair | 4 | 10.3 |
| | Good | 18 | 46.2 |
| | Very good | 13 | 33.3 |
| | Excellent | 3 | 7.7 |

## Appendix E: Results of initially non-adherent patients

### Adherence

*Table E-1: Daily intake adherence [%] of initially non-adherent patients during cycle 1 to 6*

| | n | Mean [%] | Median [%] | SD [%] | Range [%] | IQR [%] |
|---|---|---|---|---|---|---|
| $t_1$ | 15 | 77.8 | 84.6 | 17.6 | 42.9-92.9 | 78.6-90.9 |
| $t_2$ | 15 | 92.3 | 92.9 | 11.6 | 57.1-100.0 | 92.3-100.0 |
| $t_3$ | 13 | 90.6 | 92.9 | 13.2 | 50.0-100.0 | 92.3-100.0 |
| $t_4$ | 12 | 91.7 | 92.9 | 8.5 | 71.4-100.0 | 85.7-100.0 |
| $t_5$ | 12 | 89.8 | 92.9 | 9.5 | 70.6-100.0 | 82.1-96.4 |
| $t_6$ | 8 | 89.3 | 96.4 | 16.2 | 57.1-100.0 | 82.1-100.0 |

*Table E-2: Daily break adherence [%] of initially non-adherent patients during cycle 1 to 6*

| | n | Mean [%] | Median [%] | SD [%] | Range [%] | IQR [%] |
|---|---|---|---|---|---|---|
| $t_1$ | 15 | 85.7 | 85.7 | 25.3 | 0.0-100.0 | 85.7-100.0 |
| $t_2$ | 15 | 97.1 | 100.0 | 8.0 | 71.4-100.0 | 100.0-100.0 |
| $t_3$ | 12 | 98.8 | 100.0 | 4.1 | 85.7-100.0 | 100.0-100.0 |
| $t_4$ | 12 | 93.2 | 100.0 | 10.8 | 71.4-100.0 | 85.7-100.0 |
| $t_5$ | 12 | 98.8 | 100.0 | 4.1 | 85.7-100.0 | 100.0-100.0 |
| $t_6$ | 7 | 98.0 | 100.0 | 5.4 | 85.7-100.0 | 100.0-100.0 |

*Table E-3: Number of initially non-adherent patients exhibiting a daily total adherence below 100%, 90% and 80%, respectively, at $t_1$, $t_2$, $t_3$, $t_4$, $t_5$ and $t_6$*

| | Daily total adherence [%] | n | % | | Daily total adherence [%] | n | % |
|---|---|---|---|---|---|---|---|
| $t_1$ | =100 | 0 | 0.0 | $t_4$ | =100 | 2 | 16.7 |
| | <100 | 15 | 100.0 | | <100 | 10 | 83.3 |
| | ≥90 | 6 | 40.0 | | ≥90 | 10 | 66.7 |
| | <90 | 9 | 60.0 | | <90 | 2 | 13.3 |
| | ≥80 | 12 | 80.0 | | ≥80 | 11 | 73.3 |
| | <80 | 3 | 20.0 | | <80 | 1 | 6.7 |
| | Missing | 0 | 0.0 | | Missing | 3 | 20.0 |
| $t_2$ | =100 | 6 | 40.0 | $t_5$ | =100 | 3 | 25.0 |
| | <100 | 9 | 60.0 | | <100 | 9 | 75.0 |
| | ≥90 | 12 | 80.0 | | ≥90 | 9 | 60.0 |
| | <90 | 3 | 20.0 | | <90 | 3 | 20.0 |
| | ≥80 | 13 | 86.7 | | ≥80 | 11 | 73.3 |
| | <80 | 2 | 13.3 | | <80 | 1 | 6.7 |
| | Missing | 0 | 0.0 | | Missing | 3 | 20.0 |
| $t_3$ | =100 | 4 | 30.8 | $t_6$ | =100 | 4 | 50.0 |
| | <100 | 9 | 69.2 | | <100 | 4 | 50.0 |
| | ≥90 | 11 | 73.3 | | ≥90 | 6 | 40.0 |
| | <90 | 2 | 13.3 | | <90 | 2 | 13.3 |
| | ≥80 | 11 | 73.3 | | ≥80 | 7 | 46.7 |
| | <80 | 2 | 13.3 | | <80 | 1 | 6.7 |
| | Missing | 2 | 13.3 | | Missing | 7 | 46.7 |

*Table E-4: Overall adherence [%] of initially non-adherent patients during the course of the study*

| Overall adherence | n | Mean [%] | Median [%] | SD [%] | Range [%] | IQR [%] |
|---|---|---|---|---|---|---|
| $t_1$ | 15 | 93.8 | 96.2 | 8.4 | 71.4-107.1 | 90.0-100.0 |
| $t_2$ | 15 | 100.6 | 100.0 | 4.4 | 92.9-110.7 | 96.4-103.6 |
| $t_3$ | 13 | 102.7 | 100.0 | 13.4 | 92.9-144.8 | 96.4-103.6 |
| $t_4$ | 12 | 99.4 | 100.0 | 7.3 | 89.3-114.3 | 92.9-103.6 |
| $t_5$ | 12 | 97.0 | 98.2 | 4.3 | 89.3-103.6 | 92.9-100.0 |
| $t_6$ | 8 | 96.0 | 100.0 | 12.4 | 67.9-110.7 | 94.7-100.0 |

**Quality of life**

*Table E-5: Mean, standard deviation, median and interquartile range of the EQ-5D descriptive system at $t_0$, $t_3$ and $t_6$ in initially non-adherent patients (n=15)*

| EQ-5D dimension | n | Mean | SD | Median | IQR |
|---|---|---|---|---|---|
| Mobility $t_0$ | 14 | 1.4 | 0.5 | 1.0 | 1.0-2.0 |
| Mobility $t_3$ | 12 | 1.3 | 0.5 | 1.0 | 1.0-2.0 |
| Mobility $t_6$ | 12 | 1.4 | 0.5 | 1.0 | 1.0-2.0 |
| Self-care $t_0$ | 14 | 1.0 | 0.0 | 1.0 | 1.0-1.0 |
| Self-care $t_3$ | 12 | 1.1 | 0.3 | 1.0 | 1.0-1.0 |
| Self-care $t_6$ | 12 | 1.1 | 0.3 | 1.0 | 1.0-1.0 |
| Usual activities $t_0$ | 14 | 1.6 | 0.5 | 2.0 | 1.0-2.0 |
| Usual activities $t_3$ | 12 | 1.6 | 0.5 | 2.0 | 1.0-2.0 |
| Usual activities $t_6$ | 12 | 1.7 | 0.5 | 2.0 | 1.0-2.0 |
| Pain/discomfort $t_0$ | 14 | 1.4 | 0.5 | 1.0 | 1.0-2.0 |
| Pain/discomfort $t_3$ | 12 | 1.8 | 0.8 | 2.0 | 1.0-2.0 |
| Pain/discomfort $t_6$ | 12 | 1.7 | 0.7 | 2.0 | 1.0-2.0 |
| Anxiety/depression $t_0$ | 14 | 1.6 | 0.5 | 2.0 | 1.0-2.0 |
| Anxiety/depression $t_3$ | 12 | 1.6 | 0.5 | 2.0 | 1.0-2.0 |
| Anxiety/depression $t_6$ | 12 | 1.6 | 0.5 | 2.0 | 1.0-2.0 |

**Patient satisfaction with information**

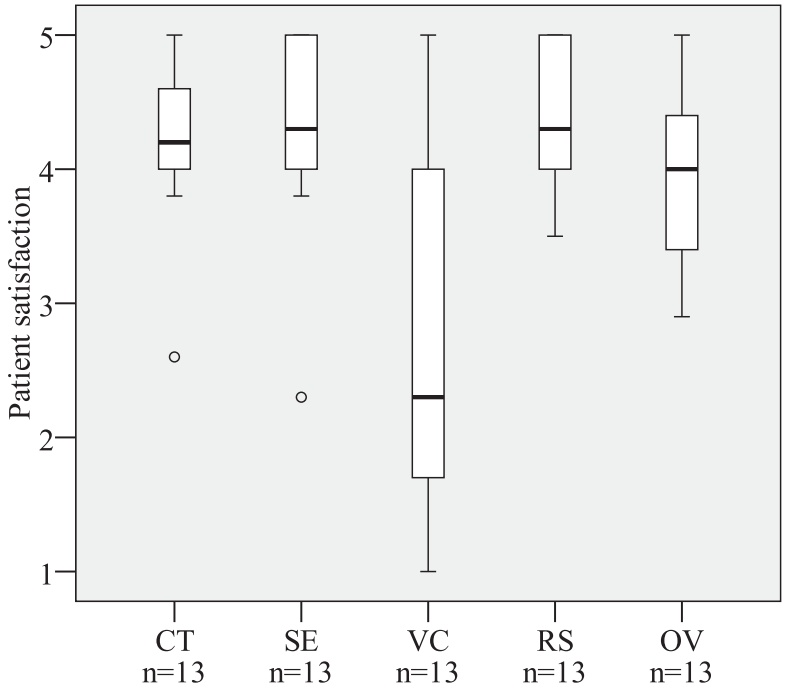



*Figure E-1: Five dimensions of patient satisfaction with information of initially non-adherent patients assessed by means of the PSCaTE questionnaire at $t_0$ (abbreviations see below)*

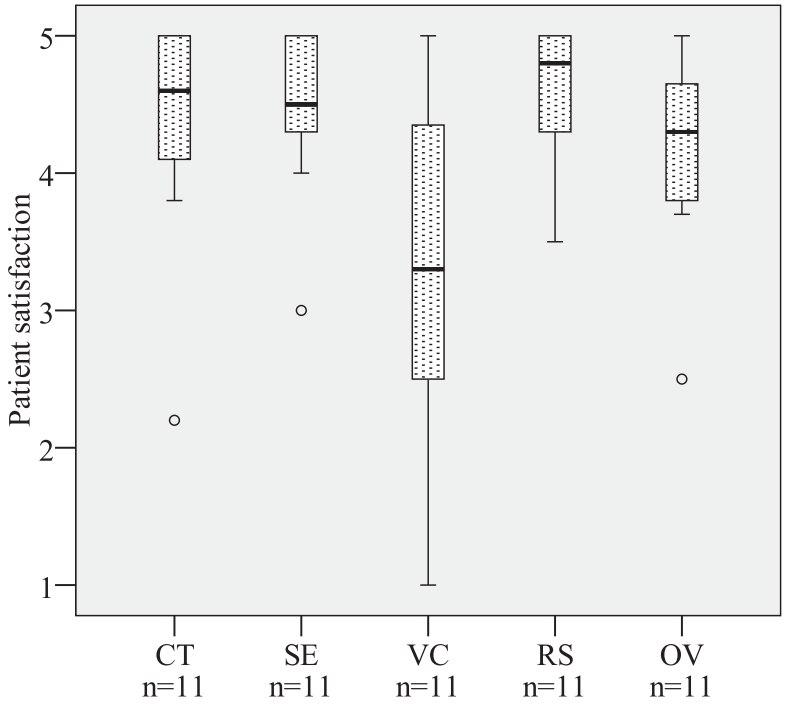



*Figure E-2: Five dimensions of patient satisfaction with information of initially non-adherent patients assessed by means of the PSCaTE questionnaire at $t_3$*

*CT = Satisfaction with information on cancer therapy; SE = Satisfaction with information on adverse effects; VC = Satisfaction with information on vitamins, herbal medicines and complementary treatment options; RS = Satisfaction with information sources; OV = Overall satisfaction*

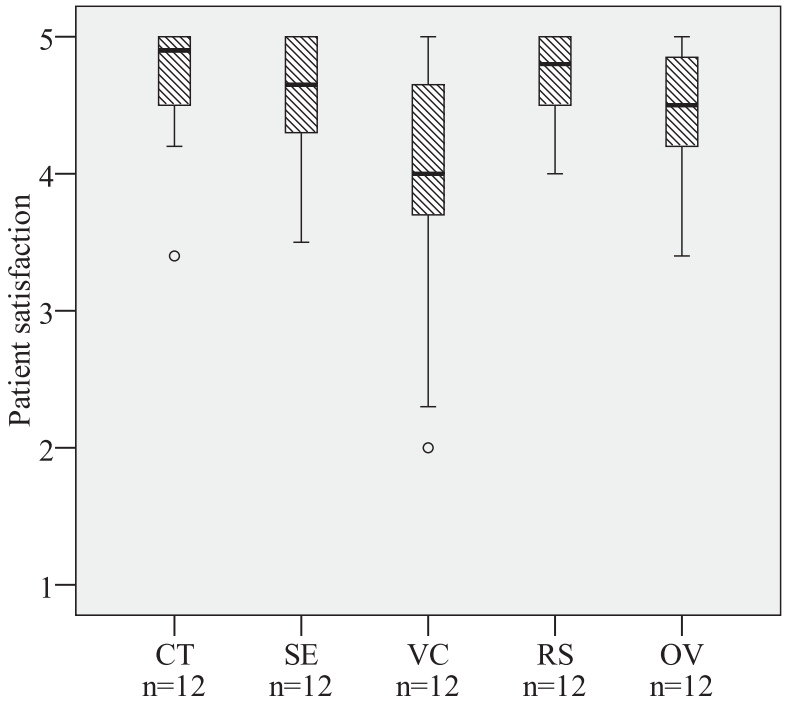



*Figure E-3: Five dimensions of patient satisfaction with information of initially non-adherent patients assessed by means of the PSCaTE questionnaire at $t_6$*

*CT = Satisfaction with information on cancer therapy; SE = Satisfaction with information on adverse effects; VC = Satisfaction with information on vitamins, herbal medicines and complementary treatment options; RS = Satisfaction with information sources; OV = Overall satisfaction*

**Patient evaluation**

*Table E-6: Patient evaluation of the capecitabine treatment at $t_6$*

| | | n | % |
|---|---|---|---|
| Assessment of therapy outcome compared with expectations | Much worse | 1 | 8.3 |
| | Slightly worse | 2 | 16.7 |
| | As expected | 8 | 66.7 |
| | Slightly better | 0 | 0.0 |
| | Much better than expected | 1 | 8.3 |
| Assessment of adverse drug reactions compared with expectations | Much worse | 1 | 8.3 |
| | Slightly worse | 2 | 16.7 |
| | As expected | 4 | 33.3 |
| | Slightly better | 2 | 16.7 |
| | Much better than expected | 3 | 25.0 |
| Overall assessment of treatment | Poor | 1 | 8.3 |
| | Fair | 4 | 33.3 |
| | Good | 4 | 33.3 |
| | Very good | 2 | 16.7 |
| | Excellent | 1 | 8.3 |

## Appendix F: Results of the entire cohort

*Table F-1: Relationship between daily total adherence during cycle 1 [%] and various binary or nominal influencing factors at $t_0$*

| **Influencing factor (binary or nominal) at $t_0$** | | **n** | **p value** |
|---|---|---|---|
| Age dichotomised by median | >62 years | 35 | 0.677* |
| | 62 years | 38 | |
| Sex | female | 54 | 0.891* |
| | male | 19 | |
| Marital status | Married/partner | 41 | 0.895** |
| | Single | 9 | |
| | Divorced | 4 | |
| | Widow | 11 | |
| | Missing | 8 | |
| Current living situation | Living alone | 11 | 0.469** |
| | With family/partner | 53 | |
| | Living in institution | 1 | |
| | Missing | 8 | |
| Education | Elementary school | 9 | 0.529** |
| | Secondary school | 6 | |
| | O-levels | 18 | |
| | Journeyman | 5 | |
| | A-levels | 8 | |
| | Master of a trade | 4 | |
| | Bachelor | 3 | |
| | University/College | 9 | |
| | Higher university degree | 2 | |
| | Missing | 9 | |
| Current employment situation | Housewife/-man | 6 | 0.333** |
| | Public servant | 2 | |
| | Pensioner | 34 | |
| | Employee | 15 | |
| | Self-employed | 6 | |
| | Worker | 1 | |
| | Missing | 9 | |
| Therapy at time of inclusion | single agent | 42 | 0.187* |
| | combination | 31 | |
| Treatment setting | Oncology outpatient ward | 60 | 0.171* |
| | Oncology practice | 13 | |
| Tumour entity | Breast cancer | 28 | 0.142** |
| | Colorectal cancer | 32 | |
| | Other | 13 | |
| Treatment intention | curative | 12 | 0.272* |
| | palliative | 61 | |
| Responsibility for pharmacotherapy | Independently | 59 | 0.785** |
| | Partner/family | 4 | |
| | Nursing service | 1 | |
| | Other | 1 | |
| | Missing | 8 | |
| Activity in support group | Yes | 6 | 0.874* |
| | No | 57 | |
| | Missing | 10 | |

** Mann-Whitney-U test ** Kruskal-Wallis-H test*

*Table F-2: Relationship between daily total adherence during cycle 1 [%] and various ordinal influencing factors at $t_0$*

| Influencing factor (ordinal) at $t_0$ | | n | p value (Kruskal-Wallis-H) | Spearman correlation | |
|---|---|---|---|---|---|
| | | | | Correlation coefficient | p value |
| Classified number of additional drugs | ≤5 | 55 | 0.969 | 0.018 | 0.877 |
| | 6-10 | 12 | | | |
| | >10 | 5 | | | |
| | Missing | 1 | | | |
| Classified distance to therapy site [minutes] | <15 | 10 | 0.111 | -0.216 | 0.087 |
| | 15-29 | 31 | | | |
| | 30-44 | 21 | | | |
| | ≥45 | 2 | | | |
| | Missing | 9 | | | |
| Classified time since diagnosis | <½ year | 18 | 0.838 | 0.014 | 0.906 |
| | ½ to 2 years | 26 | | | |
| | >2 years | 28 | | | |
| | Missing | 1 | | | |
| **EQ-5D dimension** | | | | | |
| Mobility | No problems | 44 | 0.476 | -0.145 | 0.249 |
| | Some problems | 20 | | | |
| | Extreme problems | 1 | | | |
| | Missing | 8 | | | |
| Self-care | No problems | 59 | 0.556 | 0.074 | 0.560 |
| | Some problems | 6 | | | |
| | Extreme problems | 0 | | | |
| | Missing | 8 | | | |
| Usual activities | No problems | 34 | 0.689 | 0.053 | 0.675 |
| | Some problems | 27 | | | |
| | Extreme problems | 4 | | | |
| | Missing | 8 | | | |
| Pain/ discomfort | No problems | 31 | 0.247 | 0.179 | 0.154 |
| | Some problems | 31 | | | |
| | Extreme problems | 3 | | | |
| | Missing | 8 | | | |
| Anxiety/ depression | No problems | 33 | 0.130 | -0.202 | 0.107 |
| | Some problems | 31 | | | |
| | Extreme problems | 1 | | | |
| | Missing | 8 | | | |

*Table F-3: Spearman correlation of daily total adherence during cycle 1 [%] and various covariates at $t_0$*

| Covariate at $t_0$ | n | Correlation coefficient | p value |
|---|---|---|---|
| Age [years] | 73 | 0.009 | 0.941 |
| Distance to therapy site [minutes] | 64 | -0.225 | 0.075 |
| Number of additional drugs | 72 | -0.088 | 0.463 |
| Time since diagnosis [months] | 73 | -0.082 | 0.488 |
| EQ-5D-3L VAS score | 64 | 0.027 | 0.832 |
| **PSCaTE scale** | | | |
| Satisfaction with information on cancer therapy (CT) | 61 | 0.125 | 0.336 |
| Satisfaction with information on adverse effects (SE) | 62 | 0.117 | 0.364 |
| Satisfaction with information on vitamins, herbal medicines and complementary treatment options (VC) | 60 | 0.239 | 0.066 |
| Satisfaction with information sources (RS) | 60 | 0.109 | 0.406 |
| Overall satisfaction (OV) | 62 | 0.206 | 0.109 |
| **EORTC QLQ-C30 score** | | | |
| Global health status/QoL (QL2) | 63 | 0.120 | 0.349 |
| Physical function (PF2) | 63 | 0.095 | 0.459 |
| Role function (RF2) | 62 | 0.112 | 0.387 |
| Emotional function (EF) | 63 | 0.218 | 0.085 |
| Cognitive function (CF) | 63 | 0.123 | 0.339 |
| Social function (SF) | 63 | 0.285 | **0.023** |
| Fatigue (FA) | 63 | -0.165 | 0.197 |
| Nausea and vomiting (NV) | 63 | 0.034 | 0.794 |
| Pain (PA) | 63 | -0.026 | 0.839 |
| Dyspnoe (DY) | 62 | -0.024 | 0.852 |
| Insomnia (SL) | 63 | -0.198 | 0.121 |
| Appetite loss (AP) | 63 | -0.207 | 0.103 |
| Constipation (CO) | 63 | -0.016 | 0.902 |
| Diarrhea (DI) | 62 | 0.077 | 0.552 |
| Financial difficulties (FI) | 63 | -0.073 | 0.571 |
| Hand-foot syndrome (HFS) | 62 | -0.069 | 0.596 |

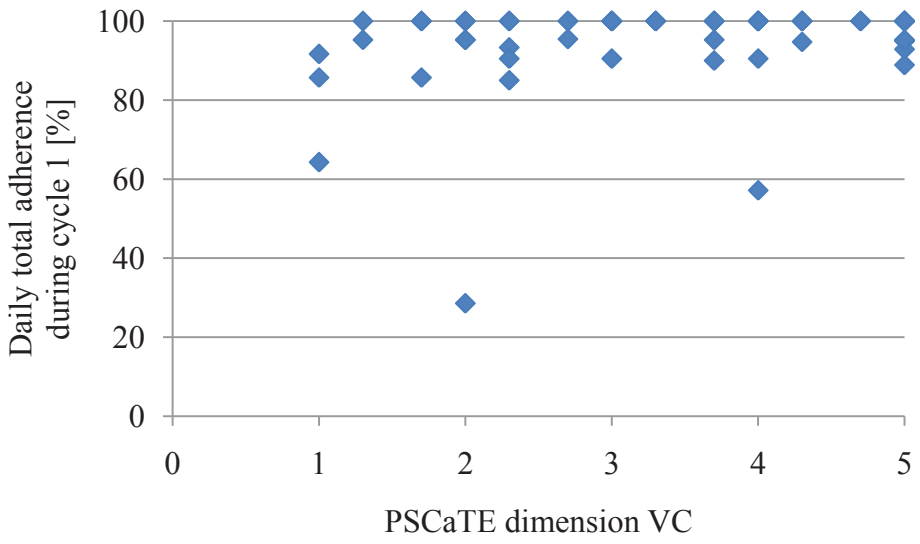



*Figure F-1: Relationship of daily total adherence during cycle 1 [%] and the PSCaTE dimension VC (Satisfaction with information on vitamins, herbal medicines and complementary treatment options); n=60*

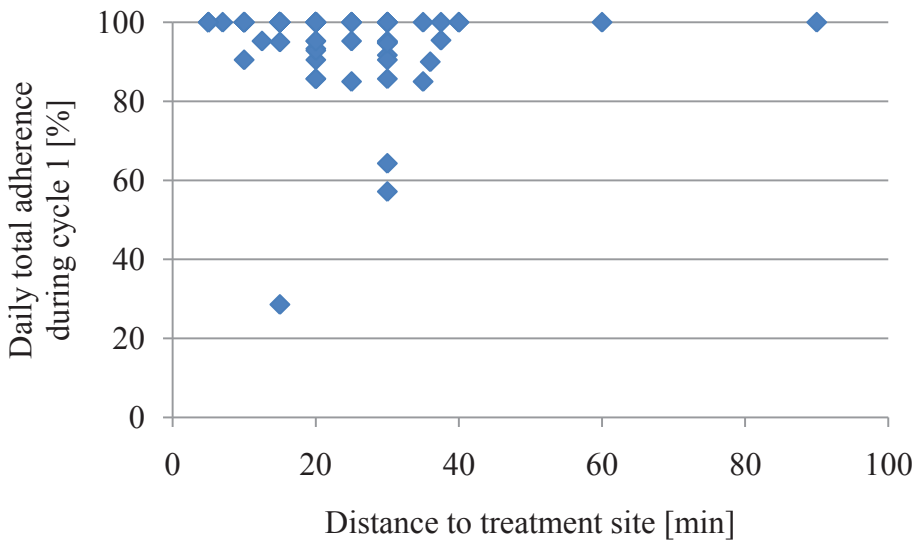



*Figure F-2: Relationship of daily total adherence during cycle 1 [%] and distance to treatment site [min]; n=64*