

DOSAGE study: A multicenter randomized phase III trial of DOSe-reduced Chemotherapy for Advanced Colorectal Cancer in Older patients

CLINICAL TRIAL TITLE

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Sponsor (in Dutch: verrichter/opdrachtgever)	**Leiden University Medical Center, department of Medical Oncology** **P.O. box 9600** **2300 RC Leiden**
Legal representative(s) of the sponsor:	**H. Onstein, Managing director Division 2** **Leiden University Medical Center**
Principal investigators (in Dutch: hoofdonderzoeker/uitvoerder) ***<Multicenter research: per site>***	**Prof. dr. J.E.A. Portielje, J.E.A.Portielje @lumc.nl** **Department of Medical Oncology, Leiden University Medical Center, the Netherlands** **Reinier de Graaf Gasthuis, Delft, the Netherlands** **Groene Hart Ziekenhuis, Gouda, the Netherlands** **Elkerliek Ziekenhuis, Helmond, the Netherlands** **Maasstad Ziekenhuis, Rotterdam, the Netherlands** **Jeroen Bosch Ziekenhuis, 's-Hertogenbosch, the Netherlands** **Streekziekenhuis Koningin Beatrix, Winterswijk, the Netherlands** **Laurentius Ziekenhuis, Roermond, the Netherlands** **ZorgSaam Ziekenhuis, Terneuzen, the Netherlands** **Ikazia Ziekenhuis, Rotterdam, the Netherlands** **Wilhelmina Ziekenhuis Assen, the Netherlands** **VieCuri Medisch Centrum, Venlo, the Netherlands** **Ziekenhuis Gelderse Vallei, Ede, the Netherlands** **Slingeland Ziekenhuis Doetinchem, the Netherlands** **Rodekruis Ziekenhuis Beverwijk, the Netherlands** **Catharina Ziekenhuis, Eindhoven, the Netherlands** **Diakonessenhuis, Utrecht, the Netherlands** **Ziekenhuis St Jansdal, Harderwijk, the Netherlands** **Admiraal de Ruijter Ziekenhuis, Goes, the Netherlands** **Medisch Centrum Leeuwarden, the Netherlands** **Noordwest Ziekenhuisgroep, Alkmaar, the Netherlands** **Amsterdam UMC, Amsterdam, the Netherlands** **Spaarne Gasthuis, Hoofddorp, the Netherlands** **Tergooi MC, Hilversum, the Netherlands**

	Haaglanden Medisch Centrum, The Hague, the Netherlands **Rivas Beatrixziekenhuis, Gorinchem, the Netherlands** **Ommelander Ziekenhuis Groningen, Scheemda, the Netherlands** **Ziekenhuis Amstelland, Amstelveen, the Netherlands** **St. Antonius Ziekenhuis, Nieuwegein, the Netherlands** **Treant, Emmen, the Netherlands** **Bernhoven, Uden, the Netherlands** **Alrijne Ziekenhuis, Leiderdorp, the Netherlands** **Rijnstate Ziekenhuis, Arnhem, the Netherlands** **Hagaziekenhuis, The Hague, the Netherlands** **Bravis Ziekenhuis Roosendaal, the Netherlands** **Ziekenhuisgroep Twente, Hengelo, the Netherlands** **Cansius-Wilhemlina Ziekenhuis, Nijmegen, the Netherlands** **Medisch Spectrum Twente, Enschede, the Netherlands** **Isala, Zwolle, the Netherlands** **Deventer Ziekenhuis, Deventer, the Netherlands** **IJsselland Ziekenhuis, Capelle aan den IJssel, the Netherlands** **Maxima Medisch Centrum, Eindhoven, the Netherlands** **Meander Medisch Centrum, Amersfoort, the Netherlands** **Zaans Medisch Centrum, Zaandam, the Netherlands** **Franciscus, Schiedam, the Netherlands**
Sub Investigators	**Dr. N.A. de Glas, Department of Medical Oncology, Leiden University Medical Center** **Dr. F. van de Bos, Department of Gerontology & Geriatrics, Leiden University Medical Center** **dr. M. Slingerland, Department of Medical Oncology, Leiden University Medical Center** **dr. F. Speetjens, Department of Medical Oncology, Leiden University Medical Center** **dr. W. van den Hout, Department of Biomedical Data Sciences, Leiden University Medical Center** **prof. dr. M. Fiocco, Department of Biomedical Data Sciences, Leiden University Medical Center** **dr. G.J. Liefers, Department of Surgery, Leiden University Medical Center**
Coordinating investigator/project leader	**drs. T.R.R. Binda, t.r.r.binda@lumc.nl** **Department of Medical Oncology, Leiden University Medical Center**
Clinical Research Center	**A.G.H. Roodvoets, MSc** **Leiden University Medical Center** **Clinical Research Center** **Department of Surgery, J-10-S**

	P.O. Box 9600, 2300 RC LEIDEN, the Netherlands **Phone: +31-71-526 3500** **ClinicalResearchCenter@lumc.nl**
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PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Sponsor or Legal representative: **Head of Department:** Prof. dr. A.J. Gelderblom Head of department of Medical Oncology Leiden University Medical Center		
Coordinating Investigator: Drs. T.R.R. Binda, PhD student Department of Medical Oncology Leiden University Medical Center		
Principal Investigator: Prof. dr. J.E.A. Portielje, Professor Medical Oncology, Department of Medical Oncology Leiden University Medical Center		
Local Principal Investigator: *<please include name of site, name and function>*		

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CONFIDENTIALITY STATEMENT

This document contains confidential information that must not be disclosed to anyone other than the sponsor, the investigative team, regulatory authorities, and members of the Research Ethics Committee.

TABLE OF CONTENTS

ABBREVIATIONS 10
1. SYNOPSIS 11
2. INTRODUCTION AND RATIONALE 13
2.1 Therapeutic condition and current treatment status 13
2.2 Clinical trial rationale 17
2.3 Mechanism of action, Drug class 18
2.4 Rationale for Dose Regimen/Dose Justification 19
3. STRUCTURED RISK ANALYSIS 20
3.1 Potential issues of concern 20
3.2 Overall synthesis of the direct risks for the research subjects 20
4. OBJECTIVES AND ENDPOINTS 21
5. STUDY PLAN AND DESIGN 22
5.1 Trial design 22
5.2 Number of Patients 22
5.3 Overall study duration and follow-up 22
5.4 Patient participation 23
6. STUDY POPULATION 24
6.1 Population 24
6.2 Inclusion criteria 24
6.3 Exclusion criteria 24
6.4 Vulnerable populations and clinical trials in emergency situations 25
7. STUDY TREATMENTS 26
7.1 Investigational Medicinal Product(s) (IMP(s)) 26
7.1.1 Name and description of the IMP 26
7.1.2 Status of development of the IMP 26
7.1.3 Description and justification of dosage and route of administration 26
7.1.4. Description of adverse events 29
7.2 Comparator IMP(s) 31
7.3 Placebo 31
7.4 Observational cohort for patients who do not want to undergo randomization 31
7.5 Auxiliary Medicinal Product(s) (AxMP(s)) 31
7.5.1 Name and description of the AxMP 32
7.5.2 Statement on authorisation and justification unauthorised AxMP (if applicable) 32
7.5.3 Description and justification of dosage and route of administration 33
7.6 Additional considerations for trials involving a medical device 33
7.7 Additional considerations for trials involving an in-vitro diagnostic or companion diagnostic 33
7.8 Preparation and labelling of the study treatment(s) 33
8. OTHER TREATMENTS AND RESTRICTIONS 33
8.1 Concomitant therapy 33
8.1.1 Permitted medication(s) 33
8.1.2 Prohibited medication(s) 34
8.2 Lifestyle restrictions 34
8.2.1 Contraception measures 34
8.2.2 Other requirements 34

9. TRACEABLILITY, STORAGE, ACCOUNTABLILITY AND COMPLIANCE 35
9.1 Traceability and storage of the study treatment(s)? 35
9.2 Accountability of the study treatment(s) and compliance 35
10. STUDY ASSESSMENTS AND PROCEDURES 36
10.1 Screening procedure 36
10.2 Randomisation, blinding and treatment allocation 36
10.3 Study procedures and assessments 37
10.3.1 Study procedures 37
10.3.2 Study measurement 38
10.3.2.1. QoL and physical functioning at baseline 39
10.3.2.1. Baseline geriatric assessment 39
10.3.2.2. Follow-up of treatment 40
10.3.2.3. Follow-up QoL and physical functioning 41
10.4. Efficacy assessments 41
10.4.2. Safety assessments 42
11. STUDY DISCONTINUATION AND COMPLETION 43
11.1 Definition End of Trial 43
11.2 Criteria for temporary halt and early termination of the clinical trial 43
11.3. Discontinuation/withdrawal of individual subjects 43
11.4. Arrangements for subjects after their participation in the clinical trial ended 43
12. SAFETY REPORTING 44
12.1 Definitions 44
12.1.1. Adverse events (AEs) 44
12.1.2. Serious adverse events (SAEs) 44
12.1.3. Suspected unexpected serious adverse reactions (SUSARs) 44
12.2. Recording of AEs/SAEs/SUSARS by the local principal investigator to the sponsor 44
12.3. Reporting of AEs and SAEs 44
12.3.2. Reporting of AEs/SAEs/SUSARS by the investigator to the METc 44
12.3.3. List of SAEs which do not require immediate reporting and procedure for reporting . 45
12.4. Follow-up of adverse events 45
12.5. Reporting of SUSARs by the sponsor to EudraVigilance 45
12.6. Annual safety report 45
12.7. Unblinding procedures for safety reporting 45
12.8. Temporary halt for reasons of subject safety 45
12.9. Urgent safety measures and other relevant safety reporting 46
12.10. Data Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC) 46
13. STATISTICAL ANALYSIS 47
13.1 Analysis sets 47
13.2 Participant demographics and other baseline characteristics 47
13.1. Randomisation and blinding 47
13.2. Sample size, trail power and level of significance used 47
13.3. Planned analysis 48
13.3.2. Analysis primary endpoint 48
13.3.3. Analysis secondary endpoints 48
13.3.4. Cost-effectiveness 49
13.4. (Statistical) criteria for termination of the trial 49
13.5. Procedure for accounting for missing, unused and spurious data 49

13.6. Procedure for reporting any deviation(s) from the original statistical plan 49
14. ETHICAL CONSIDERATIONS 50
14.1 Declaration of Helsinki 50
14.2 Recruitment and informed consent procedures 50
14.1. Benefits and risks assessment, group relatedness 50
14.2. Compensation for injury 50
14.3. Compensation for subjects 51
14.4. Compensation for investigators 51
14.5. Other ethical considerations 51
15. ADMINISTRATIVE ASPECTS, MONITORING AND CONFIDENTIALITY 52
15.1 Approval initial application and substantial modifications 52
15.2 Monitoring 52
15.1. Recording, handling and storage of information 52
15.3.1 Handling of data and data protection 52
15.3.2 Data collection 52
15.4 Data management 53
15.4.1. Source documents and case report forms (CRF) 53
15.4.2. Clinical trial master file and data archiving 53
15.4.3. Collection and storage of biological samples 54
15.5. Audits and inspections and direct access to source data/documents 54
15.6. Notification of the start and the end of the recruitment 54
15.7. Temporary halt/(early) termination 54
15.7.1. Temporary halt/early termination for reasons not affecting the benefit-risk balance 54
15.7.2. Temporary halt/early termination for reasons of subject safety 55
15.8. Summary of the results 55
15.9. Public disclosure and publication policy 55
16. REFERENCES 56
Appendix 1: List of principal investigators of each site 59
Appendix 2: G8-score 62

ABBREVIATIONS

AE	Adverse Event
AxMP	Auxiliary Medicinal Product
CA	Competent Authority
CCMO	Centrale Commissie Mensgebonden Onderzoek (Central Committee on Research Involving Human Subjects)
CRF	Case Report Form
CRO	Contract Research Organisation
CRC	Colorectal cancer
CT	Clinical Trial
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Event
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
e-CRF	Electronic Case Report Form
EU	European Union
EMA	European Medicines Agency
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
G8	Geriatric-8
IB	Investigator's Brochure
IC	Informed Consent
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
OS	Overall survival
PI	Principal Investigator
PFS	Progression-free survival
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
QOL	Quality of life
5-FU	5-fluorouracil

1. SYNOPSIS

EU trial number: 2023-506115-17
Full trial title: DOSAGE study: A multicenter randomized phase III trial of DOSe-reduced Chemotherapy for Advanced Colorectal Cancer in Older patients

Rationale

Colorectal cancer is one of the most frequently occurring cancers in older adults. Each year, approximately 7,000 older adults (≥70 years) are diagnosed with colorectal cancer in the Netherlands[1]. Half of these patients will eventually develop distant metastases or have metastasized disease at time of diagnosis and will be treated with chemotherapy. Yet, pivotal chemotherapy trials included very few older patients, and if included, patients were generally very fit. This strongly limits the evidence base for the treatment of the majority of older adults with an average vitality and cancer. Due to this lack of evidence, there are no Dutch guidelines on how to tailor treatment for older adults with metastasized colorectal cancer, leading to high toxicity rates, unplanned hospitalizations and reduced quality of life (QoL). This makes chemotherapy both less effective (due to early treatment discontinuation) and expensive for society. In addition, data from the Dutch cancer registry show a lack of survival improvement for older patients with metastasized CRC in the past 10 years[1]. Since society faces an ageing population as well as concerns of increasing health care costs, specific trials targeting this growing population are thus an unmet societal and medical need.
In metastasized colorectal cancer, older adults are frequently treated with either fluoropyrimidine-based monotherapy or doublet treatment (a fluoropyrimidine with oxaliplatin). High toxicity rates are seen in both regimens, but this effect is more pronounced in frail patients. Toxicity rates are also generally higher in doublet chemotherapy[2]. Dutch colorectal cancer guidelines do not give specific advice on the selection of older patients for either doublet chemotherapy or monotherapy in relation to risk of frailty or vitality, resulting in undesirable interhospital variations in treatment regimens. The Geriatric-8 (G8) questionnaire can be used to detect health deficits and risk of frailty in older patients. Previous research showed that older adults who scored low on the G8, were more likely to experience severe chemotherapy-related toxicity compared to those with a normal G8 score, but the association between G8 and toxicity has not always been consistent[3-5]. In daily practice, the G8 is already frequently used in Dutch hospitals. However, it does not yet play a role in the choice between polychemotherapy or monotherapy for individual patients. Tailor-made treatment decisions between mono- or doublet chemotherapy based on toxicity risk can improve individualized treatment.
Prior research showed that upfront dose reduction of chemotherapy in older adults with metastasized colorectal cancer strongly reduced toxicity rates of up to 20-30%, while efficacy is maintained[6,7]. This can lead to improved QoL and physical functioning and reduced healthcare costs. However, in daily practice, upfront dose reduction is not yet in general use and so far has not been studied in a phase III study nor in chemotherapy schemes used in this setting.

Objective

To show that upfront dose-reduced chemotherapy in patients with metastasized colorectal cancer is non-inferior to full-dose treatment with regard to progression-free survival (PFS), will lead to lower toxicity rates, better QoL and physical functioning, lower hospital admissions and health care costs, with a stratification for single agent versus polychemotherapy depending on individual risk of toxicity.

Main trial endpoints

The primary outcome of the study is PFS, defined as time from randomization until either progression or death due to any cause, whichever occurs first. Secondary endpoints include QoL (as measured by the EQ-5D and EORTC Core QLQ-C30), physical functioning (as measured with the Katz and Lawton (instrumental) activities of daily living scales) and home and informal care after 1, 3, 6, 9 and 12 months, grade ≥3 toxicity according to the CTCAE, number of treatment cycles, dose reductions or delays (all measured during study duration), hospital admissions during the first year, overall survival, cumulative received dosage and cost-effectiveness during the first year.

Trial design

Phase III open-label non-inferiority randomized controlled clinical trial, with a maximum participation duration of one year.

Trial population

Patients with metastatic colorectal cancer aged 70 years and older who are eligible for palliative chemotherapy as judged by their treating oncologist.

Interventions

All participating patients will undergo geriatric screening by the G8 questionnaire. When patients have a G8-score of 15 or higher, their treating oncologist will be notified that the G8 results do not imply an increased risk of toxicity. When patients have a G8-score of 14 or lower, their treating oncologist will be notified that the G8 results may indicate a relatively high risk of toxicity. With this information the treating oncologists may decide together with the individual patient between treatment with monotherapy or polychemotherapy.

Patients treated with polychemotherapy will be randomized between combination treatment of a fluoropyrimidine (physicians' choice 5-FU or capecitabin) and oxaliplatin in either full-dose (CAPOX: capecitabine 1000 mg/2, oxaliplatin 130 mg/m2; FOLFOX6: 5-FU 400 mg/m2 bolus followed by 2400 mg/m2 in 46 hours, leucovorin 400 mg/m2 and oxaliplatin 85 mg/m2), or with an upfront dose-reduction of 25% (CAPOX: capecitabine 750 mg/2, oxaliplatin 98 mg/m2; FOLFOX6: 5-FU 300 mg/m2 bolus followed by 1800 mg/m2 in 46 hours, leucovorin 300 mg/m2 and oxaliplatin 64 mg/m2). Patients may receive additional bevacizumab or EGFR inhibition up to physician's choice. After 18 weeks of doublet chemotherapy, maintenance therapy with capecitabine or 5-FU (with or without bevacizumab) can be started at the discretion of the treating oncologist.

Patients treated with monotherapy will be randomized between capecitabin in either full-dose (1000 mg/m2) or with upfront dose-reduction of 25% (750 mg/m2), again with or without bevacizumab or EGFR inhibition. If patients in the dose-reduced arm tolerate the first two cycles well, dose escalation is allowed (but not mandatory).

If patients develop progression or discontinue first-line treatment due to other reasons (such as toxicity), the study will end, and any further treatment lines are allowed by the discretion of the oncologist.

Ethical considerations relating to the clinical trial including the expected benefit to the individual subject or group of patients represented by the trial subjects as well as the nature and extent of burden and risks

The benefit of study participation to the individual patients is that those who have randomized for the reduced-dose arm may experience less toxicity and a better QoL. Since previous studies have demonstrated that survival of patients treated with reduced-dose chemotherapy is comparable to full-dose chemotherapy, we expect that individuals in the dose-reduced arm therefore do not have an inferior survival. The GO2 trial has shown that older patients receiving dose-reduced chemotherapy completed more cycles without reduction or stoppage compared to patients receiving the full dose and experienced less toxicity. In the NORDIC9 trial, older patients in the dose-reduced arm had a longer time to failure of first-line treatment than patients treated in the full-dose arm (10,5 months versus 6,7 months, respectively) with better quality of life and physical functioning. Furthermore, since dose-escalation is allowed if patients tolerate treatment well, we believe that there is no risk of undertreating these patients. The MRFOCUS2 trial showed that, in patients treated with upfront dose-reduced chemotherapy, dose escalation was possible in only 20-30%, of the patients, and 14% could sustain a dose escalation to 12 weeks, while 50% needed a further dose reduction or stopped.

If patients progress on first-line treatment, any follow-up treatment in second-line is allowed. Thus, if patients would be “undertreated” based on an impaired G8 score (meaning that they receive mono-chemotherapy in first-line), they can still be treated with doublet chemotherapy of a fluoropyrimidine and oxaliplatin in second-line, which is common practice in current standards as well. The Dutch CAIRO showed that this approach (sequential use of chemotherapy instead of combination chemotherapy) does not jeopardize overall survival, making this a safe treatment option[8].

Apart from the G8 questionnaire, that is used to advice the treating oncologist about the possible increased risk of toxicity patients will also undergo geriatric assessment consisting of validated questionnaires at baseline. This will take approximately 30 minutes. During follow-up they will undergo short follow-up questionnaires after 1, 3, 6, 9 and 12 months on QoL and physical functioning, which will take 10-15 minutes. These follow-up questionnaires will be performed by telephone calls or email depending on preference of the participant. There will be no additional biopsies or blood withdrawals besides standard care and no additional hospital visits or physical examinations. Hence, the burden and risks for patients are minimal.

2. INTRODUCTION AND RATIONALE

2.1 Therapeutic condition and current treatment status

Colorectal cancer is one of the most frequently occurring cancers in older adults. Each year, approximately 7.000 older adults (≥70 years) are diagnosed with colorectal cancer in the Netherlands. Half of these patients will eventually develop distant metastases or have metastasized disease at time of diagnosis and may be candidates for systemic therapies. Studies from the Dutch cancer registry clearly show that survival for patients with colorectal cancer has improved for younger patients, but above age 65 survival did not improve in the past years[9]. Recent data in synchronously metastasized older patients even showed decreasing survival in the past 15 years in

adults over the age of 70 years, together with a reduced use of chemotherapy and increased use of best supportive care[10]. These real-world data suggest that only a subset of older patients currently benefit from the availability of novel treatment options.

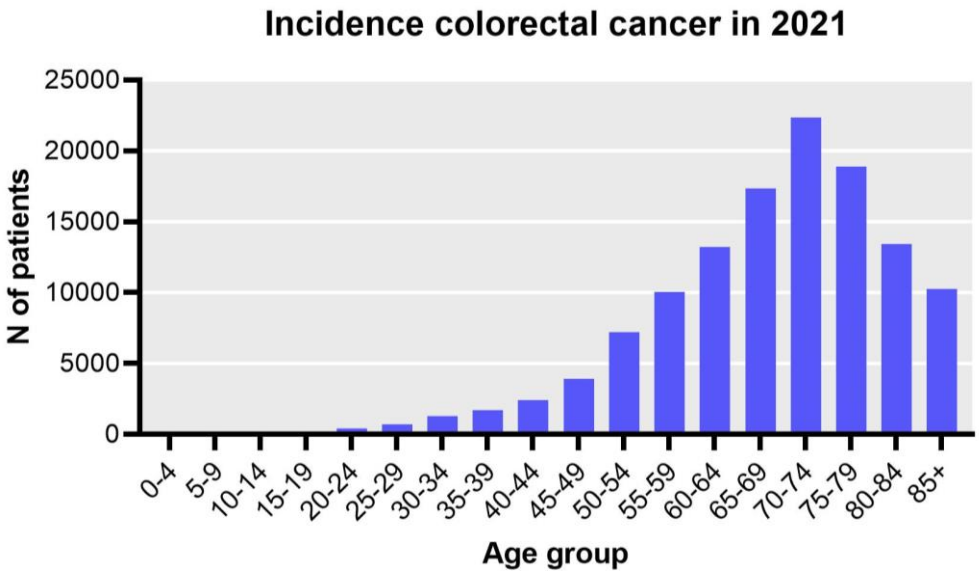


Figure 1: Incidence of colorectal cancer in the Netherlands in 2021, stratified for age group. 52% of the Dutch patients diagnosed with colorectal cancer is 70 years or older. Source: Netherlands Cancer Registry (NCR). [1]

One reason for this unimproved survival for older adults might be that previous chemotherapy trials for patients with metastasized colorectal cancer included relatively few older patients, and if included, patients were generally healthy[11]. This strongly limits the evidence base for the treatment of older adults with colorectal cancer. This limited evidence base for the treatment of older adults precludes specific guidelines on the treatment of older adults with metastasized colorectal cancer.

The main challenge in individualizing treatment of older adults with metastasized colorectal cancer, is the large heterogeneity between patients. While some patients are physically fit and have few other concomitant diseases, others may have age-associated problems such as multimorbidity or physical or cognitive impairments, which makes them frail. It is well-known that these factors strongly influence the ability to endure chemotherapy[12].

In daily practice, medical oncologists and older patients deliberate and weigh what the best treatment option should be. Several real-world cohort studies reveal that older adults treated with chemotherapy have high toxicity rates, resulting in a reduced QoL and physical functioning and frequently discontinue treatment early [13-15]. High toxicity rates are seen both in fit and frail older patients, but the toxicity risk is even more pronounced in frail patients[15]. These high rates of toxicity and toxicity-related hospital admissions negatively impact current treatment of older patients with metastasized colorectal cancer. Preliminary results on patient-related outcomes (PROs) of Dutch older patients with metastasized colorectal cancer from the Prospective Dutch CRC Cohort (PLCRC)[16] show that approximately 65-75% of the older patients treated for metastasized colorectal cancer with palliative chemotherapy either experience a decline in QoL/physical functioning or die over time (Figure 3). These data illustrate that, in current oncology practice, the treatment goal of maintaining QoL is not met in the majority of this population. This makes treatment of metastasized colorectal cancer in older patients both less effective (due to early treatment discontinuation) and expensive for society (due to hospitalizations, treatment of toxicity and increased need for long-term care), while treatment goals are only reached in a subset of the population. Since society faces an ageing population as well as concerns of increasing health care costs and a predicted shortage of healthcare workers worldwide, specific trials targeting this growing population are thus an unmet societal and medical need.

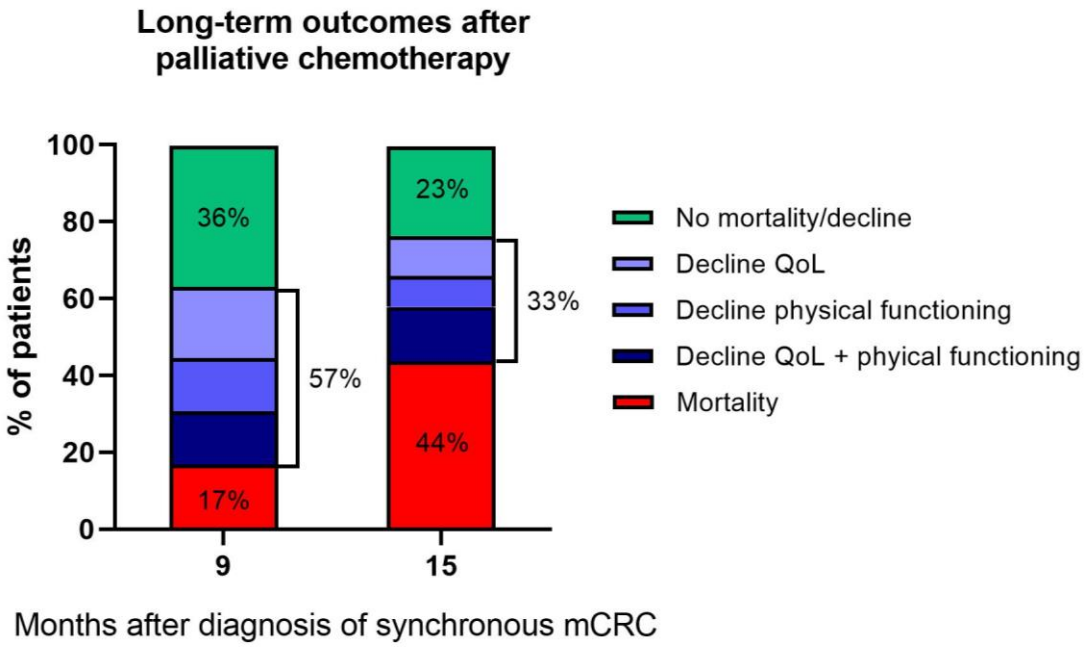


Figure 3: Preliminary results showing long-term outcomes of Dutch older (≥70 years) patients with synchronous metastasized colorectal cancer treated with palliative chemotherapy from the PLCRC cohort. At 9 months after diagnosis, 17% of the patients died, 57% experienced a decline in QoL or/and physical functioning and 36% did not experience a decline. At 15 months, 44% died, 33% experienced a decline and 23% did not die or experience a decline.

To identify which older patients are at higher risk of chemotherapy-related toxicities, the U.S.-based Cancer and Aging Research Group (CARG) has developed a prediction tool, using various treatment characteristics and geriatric variables[14,17]. Unfortunately we previously showed that the tool has a poor performance in Dutch older patients treated with chemotherapy, most likely due to other

chemotherapy schedules and a different patient selection for treatments in the Netherlands[18]. Other geriatric predictors for severe toxicity should therefore be identified to aid which individuals are at risk of poor treatment tolerability.
The G8 tool is a commonly used, 8-item questionnaire that evaluates calendar age, self-rated health, polypharmacy, weight loss, food intake, BMI and physical and psychological health and was developed to separate fit older cancer patients from less fit patients with frailties that may benefit from more tailored treatment[19]. The tool is easy to use and has been well-validated in daily oncology practice. Multiple studies have shown that older adults with a low G8 score were more likely to experience severe chemotherapy-related toxicity compared to those with a normal G8 score[3,5,20,21]. However, several other studies did not find an association between the G8 and toxicity.[4] The G8 is already frequently used in the Dutch hospitals, which is underscored by a recent study showing that 97% of the Dutch hospitals offering colorectal cancer surgery use the G8 as frailty screening[22]. This will facilitate implementation. As the G8 serves as a simple risk stratification tool for toxicity, it can be used to apply tailored treatment in older adults eligible for chemotherapy.

For patients with colorectal cancer and distant metastases without local treatment options, systemic therapy can prolong life and improve QoL. Selected, very fit older adults, especially with right sided tumours, or KRAS- or NRAS-mutated tumors may be candidate for combination therapy with FOLFOXIRI plus bevacizumab. However, the majority of older patients with metastasized colorectal cancer are treated with either fluoropyrimidine-based monotherapy or a combination treatment of a fluoropyrimidine with oxaliplatin (both regimens optionally in combination with added bevacizumab or EGFR inhibition). Although fit older patients derive similar benefits from systemic polychemotherapies compared to younger patients, several studies report an increased toxicity [2,23]. Therefore, for less fit older patients with relevant comorbidities or age-related functional deficits but not considered too frail for treatment, fluoropyrimidine-based monotherapy might be the preferred option, as monotherapy has less toxic effects[6,14]. Several trials have demonstrated a non-inferior efficacy of fluoropyrimidine monotherapy compared to doublet chemotherapy. In addition, patients who tolerate monotherapy well can receive doublet chemotherapy in the second-line, and the CAIRO study showed that this approach (sequential use of chemotherapy instead of combination chemotherapy) does not jeopardize overall survival[8]. These data confirm that first-line treatment with a fluoropyrimidine as a single agent is a reasonable option, particularly in frail patients[24].
In daily clinical practice, there is a large treatment variation between hospitals and oncologists in choice between either monotherapy or polychemotherapy, but also in terms of upfront dose reduction of full-dose treatment. This shows the daily struggle of treating oncologists to find the optimal treatment for the right patient and justifies a study in which these different regimens are compared in subgroups based on expected toxicity risk.

In summary, treatment outcomes in older patients are highly dependent on frailty status and treatment regimen, but the current guideline does not include assessing the risk of frailty nor gives any advice on specific treatment regimens in older patients, resulting in undesirable interhospital variations in treatment regimens[25]. For these reasons, treatment of older adults with metastasized colorectal cancer remains a therapeutic challenge and tailored clinical trials including older adults are urgently needed to address this evidence gap[26].

2.2 Clinical trial rationale

To improve treatment outcomes of older patients with metastatic colorectal cancer, the choice between doublet chemotherapy or mono-chemotherapy for first-line treatment of metastatic disease (with or without targeted therapy) will be tailored to individual risk of toxicity as judged by the treating oncologist advised by the results of the G8 questionnaire. Adaptation of the individual treatment plan, choosing for mono-chemotherapy or polychemotherapy based on the risk of toxicity, is one way to optimize treatment and reduce toxicity for older adults with metastatic colorectal cancer.

A second possible solution to avoid unnecessary toxicity is to perform upfront dose-reduction of palliative chemotherapy[26]. Previous studies showed that dose-reduced chemotherapy in older adults with metastatic gastro-intestinal cancer strongly reduces toxicity rates up to 20-30%, while maintaining efficacy[6,7,27]. For example, the phase II NORDIC9 trial compared full-dose S1 monotherapy with upfront dose-reduced S1 with oxaliplatin in 160 older adults with metastatic colorectal cancer who were deemed to be “unfit” for full-dose treatment as judged by their oncologist. The study showed that doublet chemotherapy with upfront dose reduction resulted in a better PFS (6,2 months for reduced-dosed versus 5,3 months for full-dose). Furthermore, toxicity rates fell markedly in the reduce-dosed arm compared to the full-dose arm (43% versus 62%, respectively).

The recent GO2-trial compared different levels of dose-reduced CAPOX in 559 advanced gastroesophageal cancer patients deemed unfit for full-dose chemotherapy and showed that upfront dose reduced chemotherapy was non-inferior to full-dose treatment with respect to survival, and resulted in an improved toxicity profile, even in less frail patients[27]. Additionally, several international studies, for example the GAP70+ study, have shown that geriatric assessment and interventions aids in selecting those patients who benefit from primary treatment adaption with up-front dose reduction and resultant reduction of toxicity, improved QOL and preserved survival[26,28,29].

Additionally, the FOCUS2 2x2 factorial trial investigated upfront dose reduction of various chemotherapy regimens in vulnerable patients with advanced colorectal cancer and showed that only 37% could receive dose escalation after 6 weeks of treatment, and only 14% could sustain the higher dose to 12 weeks, supporting the idea that high dose is less well-tolerated in older adults. Their data also showed that PFS of patients with frailties treated with dose-reduced capecitabine was similar to PFS of those treated with dose-reduced oxaliplatin and capecitabin combination therapy, demonstrating that the use of dose-reduced monotherapy is no undertreatment in this population.

Hence, upfront dose-reduced chemotherapy guided by geriatric factors can decrease the risk of treatment toxicity, while maintaining efficacy with regard to progression and survival. Eventually, these outcomes translate to improved QoL and physical functioning, and a reduction of health care costs. However, in Dutch daily practice, upfront dose reduction is not yet standard of care and so far dose reduced chemotherapy has not been studied in a phase III study nor for the chemotherapy schemes used for metastasized colorectal cancer in the Netherlands. In addition, tailor-made treatment decisions between monotherapy or doublet chemotherapy based on toxicity risk can improve individualized treatment decisions. Therefore, this randomized phase III non-inferiority trial will compare upfront dose-reduced with full dose chemotherapy in older adults with metastatic

colorectal cancer, with adaption of the treatment plan (monotherapy or doublet chemotherapy) based on expected risk of treatment toxicity for the individual patient. We expect that this strategy will not compromise PFS and will lead to improved QoL and physical functioning, reduced chemotherapy-related toxicity, hospitalizations and treatment withdrawal, increased received cumulative dosage and decreased healthcare costs.

This is a low-intervention trial, as all investigational medicinal products are authorized and are used in accordance with the terms of the marketing authorization and the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned. All four treatment options are currently used in daily clinical practice (currently at the discretion of the treating oncologist).

2.3 Mechanism of action, Drug class

- *Capecitabine*

Capecitabine is an oral fluoropyrimidine, a non-cytotoxic fluoropyrimidine carbamate, which functions as an orally administered precursor of the cytotoxic moiety 5-fluorouracil (5-FU). There is evidence that the metabolism of 5-FU in the anabolic pathway blocks the methylation reaction of deoxyuridylic acid to thymidylic acid, thereby interfering with the synthesis of deoxyribonucleic acid (DNA). The incorporation of 5-FU also leads to inhibition of RNA and protein synthesis.
Capecitabine is indicated and approved for use in many gastro-intestinal tumors, including metastatic colorectal cancer. It is used within the authorized indications.
See also the SmPC: https://www.geneesmiddeleninformatiebank.nl/smpc/h109393_smpc.pdf

- *5-FU*

5-fluorouracil (5-FU) is an i.v. fluoropyrimidine, a pyrimidine analogue which competitively inhibits the enzyme thymidylate synthase (TS), thereby creating a thymine deficiency and resulting in inhibition of deoxyribonucleic acid (DNA) synthesis and cytotoxicity. It also inhibits, to a lesser extent, the formation of ribonucleic acid (RNA). These effects are most marked in rapidly growing cells and may lead to cell death. 5-FU is a component of the standard therapy for a variety of malignancies, including colorectal, pancreatic, gastric, breast and head and neck cancers. Parenteral 5-fluorouracil (intravenous use) can be administered as bolus, infusion or continuous infusion for up to several days. It is used within the authorized indications.
See also the SmPC: https://www.geneesmiddeleninformatiebank.nl/smpc/h100701_smpc.pdf

- *Oxaliplatin*

Oxaliplatin is an antineoplastic active substance belonging to a new class of platinum-based compounds in which the platinum atom is complexed with 1,2-diaminocyclohexane (“DACH”) and an oxalate group. Aqua-derivatives resulting from the biotransformation of oxaliplatin interact with DNA to form both inter and intra-strand cross-links, resulting in the disruption of DNA synthesis leading to cytotoxic and anti-tumour effects. Oxaliplatin in combination with a fluoropyrimidine is indicated for treatment of metastatic colorectal cancer. It is used within the authorized indications.
See also the SmPC: https://www.geneesmiddeleninformatiebank.nl/smpc/h103779_smpc.pdf

- *Calcium folinate*

Calcium folinate (leucovorin) is a reduced form of folic acid. Leucovorin enhances the activity of 5-fluorouracil by binding to the enzyme thymidylate synthetase and decreasing intracellular levels of

thymidylate. Leucovorin is indicated for use in combination with 5-fluorouracil to prolong survival in the palliative treatment of patients with metastatic colorectal cancer. It is used within the authorized indications.
See also the SmPC: https://www.geneesmiddeleninformatiebank.nl/smpc/h15828_smpc.pdf

2.4 Rationale for Dose Regimen/Dose Justification

See 2.2

3. STRUCTURED RISK ANALYSIS

3.1 Potential issues of concern

Since this trial solely investigates registered products used within the indication and not in combination with other products, the risk for participating patients is generally considered as low and chapter 3.1 can be skipped.

3.2 Overall synthesis of the direct risks for the research subjects

Based on previous trials, we expect a similar efficacy of dose-reduced chemotherapy compared to full-dose chemotherapy. Since we hypothesize that patients in the dose-reduced arm will be able to complete more chemotherapy cycles, we consider the risk of undertreatment in the dose-reduced arm as very low. The GO2 trial showed that older patients receiving dose-reduced chemotherapy completed more cycles without reduction or stoppage compared to patients receiving the full dose. In the NORDIC9 trial, older patients in the dose-reduced arm had a longer time to failure of first-line treatment than patients treated in the full-dose arm (10,5 months versus 6,7 months, respectively) with a better quality of life and physical functioning

To further lower the risk of undertreatment of patients treated with a dose reduction (in either one of the stratification arms), we allow dose-escalation if the treatment is well tolerated, at the discretion of the treating oncologist. However, the MRFOCUS2 trial showed that, in patients treated with upfront dose-reduced chemotherapy, dose escalation was possible in only 20-30%, of the patients, and 14% could sustain a dose escalation to 12 weeks, while 50% needed a further dose reduction or stopped.[6] These data confirm that risk of undertreatment in the dose-reduced arm can be considered low.
One of the possible risks is that the G8 screening might wrongly identify a small subset of older fit patients as having high risk of toxicity, resulting in an advice for treatment in the monotherapy arm. One might argue that this could lead to undertreatment. However, these patients can still be considered for second-line doublet chemotherapy in case of progression if they remained robust during monotherapy treatment. Since these patients already progressed on first-line treatment and thus met the primary endpoint (PFS), this will not bias study outcomes. In addition, it has been shown in previous studies such as the Dutch CAIRO study, that this approach (sequential use of chemotherapy instead of combination chemotherapy) does not jeopardize overall survival so it is safe to do this.[8]. On the other hand, there is a possibility that a patient might be classified as “low risk of toxicity” based on the G8, but is frail in reality and at risk of increased toxicity when treated with doublet chemotherapy. Therefore, the treating oncologists can classify patients as “high risk of toxicity” or “low risk of toxicity” based on their own judgement or the baseline geriatric questionnaires, irrespective of the G8 score. However, as the G8 is one of the most sensitive screening tools for frailty[30], we believe that this will not be a frequently occurring issue.

An important benefit for subjects who have randomized for the reduced-dose arm may experience less toxicity and a better quality of life and physical functioning.

4. OBJECTIVES AND ENDPOINTS

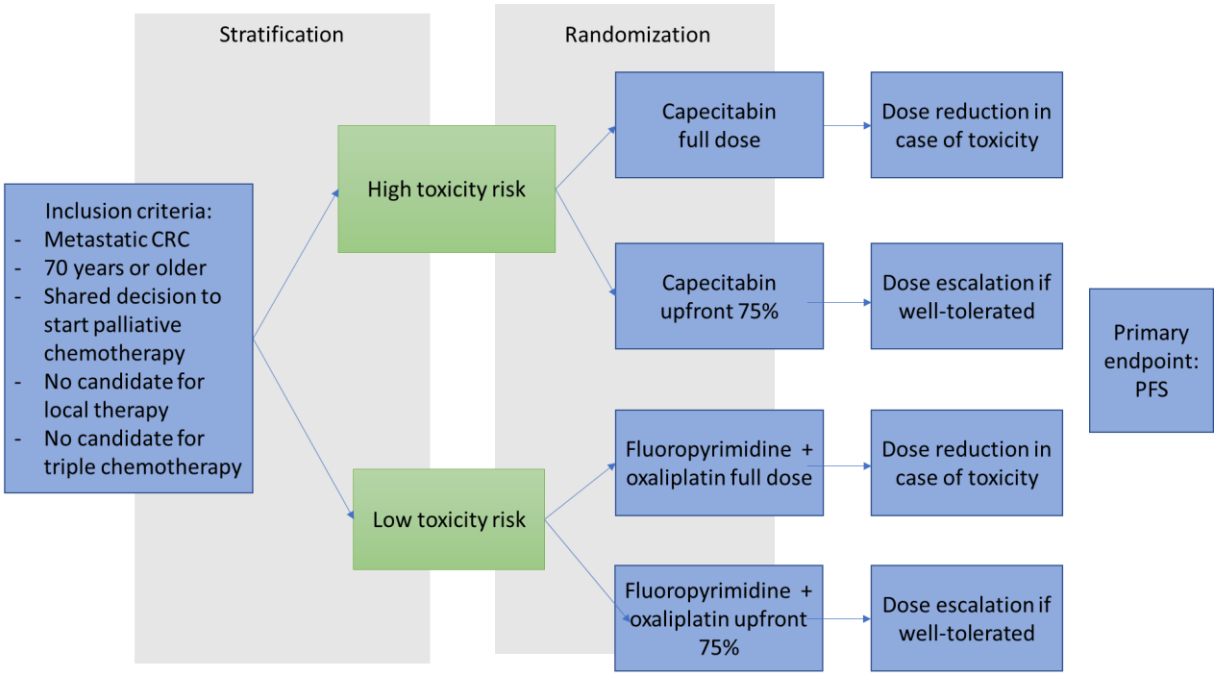
Objective(s)	**Endpoint(s)**
Primary objective	**Endpoint for the primary objective**
• To demonstrate that upfront dose-reduced chemotherapy is non-inferior to full-dose treatment with regard to progression-free survival in patients with metastasized colorectal cancer, with a stratification for mono-chemotherapy versus doublet chemotherapy depending on individual risk of toxicity.	• PFS, defined as time from randomization until either radiological or clinical progression or death, whichever occurs first. PFS will be assessed up to at least one year.
Secondary objective(s),	**Endpoint(s) for secondary objective(s)**
• To determine whether upfront dose reduction of chemotherapy improves QoL and physical functioning	• QoL, using the EQ-5D questionnaire and EORTC Core QLQ-C30 questionnaire at 1, 3, 6, 9 and 12 months after randomization • Physical functioning, using the Lawton-IADl and Katz-ADL and assessing home and informal care at 1, 3, 6, 9 and 12 months after randomization
• To determine whether upfront dose reduction of chemotherapy reduces grade 3-5 toxicity	• Grade 3-5 chemotherapy-related toxicity according to the CTCAE V5 through study duration
• To determine whether upfront dose reduction leads to more treatment completion, less dose reductions and lower hospital admission rates	• Number of completed treatment cycles during study treatment • Dose reductions during study treatment (defined as ≥25% reduction of the initial dosage) • Dose delay during study treatment • Unplanned hospitalizations in the first year after treatment initiation
• To study whether upfront dose reduction is non-inferior to full-dose treatment with regard to overall survival	• OS, computed as time between randomization until death.
• To study whether upfront dose reduction lead to an increase in received cumulative dosage, and to estimate whether this is associated with PFS	• Cumulative received dosage adjusted for BSA during study treatment • Association between cumulative received dosage and PFS as defined above
• To identify predictive geriatric markers of poor outcomes using a geriatric assessment (GA)	• Association between geriatric predictors with PFS, OS, grade 3-5 toxicity
• To study whether upfront dose reduction is cost-effective	• Cost-effectiveness in the first year

5. STUDY PLAN AND DESIGN

5.1 Trial design

The study is designed as an open-label, phase III non-inferiority randomized controlled clinical trial. We believe that this study design is the most optimal design to prove that upfront dose reduction will not compromise PFS and will improve QoL and reduce toxicity rates and early treatment withdrawal.

When patients fulfill the inclusion criteria, are considered eligible for first-line chemotherapy and have provided informed consent to participate in the study, a G8 questionnaire will be performed (*see Appendix 1)*. Based on the toxicity risk as judged by the treating oncologist in combination with the results of the G8 screening tool, patients will be treated either with polychemotherapy or single agent chemotherapy. Afterwards, randomization between full-dose or reduced-dose chemotherapy (75%) will be performed according to the schedule below.



5.2 Number of Patients

We will include 293 patients per stratification arm meaning 587 patients in total. This is based on the power calculation that is presented in Chapter 12.7.

5.3 Overall study duration and follow-up

Time schedule:

Month 1-6: Initiation of trial in participating hospitals.
Month 7-42: Inclusion of patients
Month 7-54: Follow-up of patients
Month 55-60: Primary and secondary analyses and publication of results

The study will be performed in five years. In the first six months, the study will be launched nationally. The planned duration of enrolment of patients (i.e. first patient randomized to last patient

randomized) will be three years, in which 587 patients are to be randomized in the study, followed by one year of follow-up and six months of analyses and reporting of the study.

5.4 Patient participation

Stichting Darmkanker is a co-initiator of this study. The foundation has actively participated in the first two phases of the study (defining the research question and writing a study proposal)and has given extensive feedback on the current protocol and design. The foundation emphasizes the importance of a study that “focuses on the older patient with metastasized colorectal cancer”, and is particularly positive about the fact that we distinguish between different older people on basis of fitness and risk of side effects. Since dose adaption during treatment is allowed, the feasibility of the study was positively assessed. Another positive aspect of the trial was the national collaboration. The foundation will remain actively involved in the last two study phases as well (data collection and analyses/dissemination). They will give advice regarding the human subject information and questionnaires, monitoring of patient inclusion and patient burden and giving context on the data and patient-reported outcomes. Moreover, they will supervise on communicating the study results to non-medically trained people involved. A member of the foundation is an active member in our research group and money has been budgeted for their participation.

6. STUDY POPULATION

6.1 Population

The study will recruit patients in peripheral and academic hospitals in the Netherlands. Patients will all have metastasised colorectal cancer (mCRC) and are aged 70 years or older and a decision has been made to start with palliative chemotherapy.

6.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Patients aged 70 years or older with colorectal cancer and distant metastases without localized treatment options.
- Patients who are candidates for first-line palliative chemotherapy as judged by their treating oncologist
- Being able to understand the Dutch language
- Written informed consent
- Adequate bone marrow and organ function as defined by following laboratory values: Absolute neutrophil count (ANC) > 1.5 x 10^9 mmol/L, Hemoglobin (Hb) > 6.0 mmol/L, Platelets >100 x 109 / L, Serum bilirubin ≤ 2 x upper limit of normal (ULN), serum transaminases ≤ 3 x ULN without presence of liver metastases or ≤ 5x ULN with presence of liver metastases.
- Because of the risks of drug treatment to the developing foetus, male patients with child bearing potential should avoid impregnating a female partner. Male patients, even if surgically sterilized, (i.e. post-vasectomy) must agree to one of the following: practice effective barrier contraception during the entire study treatment period and through four months after the last dose of study drug, or completely abstain from sexual intercourse.

6.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Patients who received prior palliative chemotherapy
- Patients in whom local treatment of metastases with curative intent is scheduled (i.e. liver surgery or stereotactic radiotherapy)
- Patients who are candidates for triplet chemotherapy (i.e. FOLFOXIRI)
- Patients who received prior adjuvant chemotherapy in the one year before inclusion in the study (chemotherapy before that time is allowed)
- Patients with complete or incomplete dihydropyrimidine dehydrogenase (DPD) deficiency
- Patients with Microsatellite instable (MSI)-high colorectal cancer
- Patients with known HIV or active hepatitis infection
- Patients with severe kidney failure (defined as GFR ≤30ml/min)
- Patients with severe cognitive deficits making informed consent not possible
- Patients with grade ≥2 peripheral polyneuropathy

6.4 Vulnerable populations and clinical trials in emergency situations

We will not include any vulnerable populations. Patients need to be able to provide written informed consent themselves. Patients who are unable to do this (for example due to cognitive deficits related to ageing) cannot participate in this study.

7. STUDY TREATMENTS

7.1 Investigational Medicinal Product(s) (IMP(s))

7.1.1 Name and description of the IMP

Fluoropyrimidines
- Capecitabine, film-coated tablets
- 5- Fluorouracil (5-FU), infusion

Platinum derivative
- Oxaliplatin, infusion

Folinic acid
- Calcium Folinate (Leucovorin), infusion

7.1.2 Status of development of the IMP

An overview of the IMPs used are described in Chapter 2.3

Above-mentioned drugs have been approved for use in metastatic colorectal cancer based on findings from prospective randomized clinical studies, and are considered as standard drugs in the treatment of this disease according to (inter)national guidelines[24]. All drugs have been approved by the committee BOM (Beoordeling Oncologische Middelen) of the Dutch Society of Medical Oncologists (NVMO). There is sufficient experience with these treatments, both with full-dose and with reduced dose, and treatment as described in this study is not considered experimental treatment. All drugs have extensively been investigated in trials with older patients with metastatic colorectal cancer, both in standard dosage as in reduced-dosage (for example in the AVEX, NORDIC9 and MRFOCUS2 trials).

Clinical trials have explored different combinations based on fluoropyrimidines, both i.v. 5-FU or oral capecitabine; these are considered equivalent with regard to efficacy and toxicity profile[31]. Since the choice of fluoropyrimidine varies between participating centers, both therapies are allowed according to the current guidelines.

7.1.3 Description and justification of dosage and route of administration

Dose schedules and rationale

In the intervention-arm, patients will receive chemotherapy with an upfront dose-reduction of 75% of full-dose. For patients classified as “fit”, this will be a fluoropyrimidine (either 5-FU or capecitabin) combined with oxaliplatin. Additional targeted therapy is allowed in all arms and will be prescribed in standard dose. Dosing schemes are included below and can be used according to local standardized practice.

Low risk patients

<u>Control arm (full-dose)</u>

CAPOX:
- Capecitabine 1000 mg / m2 oral at day 1-14 (every 3 weeks)
- Oxaliplatin 130 mg/m2 at day 1 (every 3 weeks)

OR
FOLFOX6:
- 5-FU 400 mg/m2 IV bolus at day 1 followed by 2400 mg/m2 in 46 hours (every 2 weeks)
- Leucovorin 400 mg/m2 day 1 (every 2 weeks)
- Oxaliplatin 85 mg/m2 day 1 (every 2 weeks)

Intervention arm (reduced dose)
In the intervention-arm, 75% of all the above-mentioned schedules are prescribed:
CAPOX:
- Capecitabine 750 mg/m2 oral at day 1-14 (every 3 weeks)
- Oxaliplatin 98 mg/m2 at day 1 (every 3 weeks)
OR
FOLFOX6:
- 5-FU 300 mg/m2 IV bolus at day 1 followed by 1800 mg/m2 in 46 hours (every 2 weeks)
- Leucovorin 300 mg/m2 day 1 (every 2 weeks)
- Oxaliplatin 64 mg/m2 day 1 (every 2 weeks

High risk patients
Control-arm (full-dose)
- Capecitabine 1000mg/m2 oral at day 1-14 (every 3 weeks)

Intervention arm (reduced dose):
In the intervention-arm, 75% of the above-mentioned dosage (is prescribed:
- Capecitabine 750g/m2 oral at day 1-14 (every 3 weeks)

In comparison with some previous studies, we selected 1000mg/m2 as full-dose of capecitabine instead of 1250mg/m2. The rationale behind this choice is that we believe frail older adults should not be exposed to a dose of 1250mg/m2, and 1000mg/m2 is the most commonly used dosage in the Netherlands according to the PI's of the seven regional hospitals. Although some studies with capecitabine were performed with the dosage of 1250mg/m2 as full-dose, the AVEX trial, randomizing older patients between capecitabine plus bevacizumab or capecitabine alone[32], and the CAIRO7 trial, designed for older and frail patients with unresectable liver metastases of colorectal cancer, also used 1000mg/m2 as full-dose. In addition, the SALTO trial, comparing S-1 and capecitabine as first-line treatment for metastatic colorectal cancer also used 1000mg/m2 as full-dose for older adults[33]. The DCCG agreed to the definition of 1000mg/m2 as standard dose, further supporting this decision.

Patients with a moderate renal impairment (GFR 30- 50 mL/min), in line with international recommendations, will be treated with 25% reduced starting dose of capecitabine when randomized for full dose treatment and treated with 40% reduced starting dose when randomized for upfront dose reduction.

Dose modifications
After each treatment cycle, treatment tolerability will be assessed. Patients in the upfront dose-reduced arm who have tolerated the first two cycles of their treatment well, can (but do not have to) receive dose-escalation to 100%, at the discretion of the treating oncologist. At least the first two courses have to be fully completed and considered safe, before dose increases are allowed.

The below-mentioned advices for discontinuation and dose modifications are advised. Treating physicians can deviate from these guidelines if there is good reason to do this. This should be documented in the medical charts.
In both arms, in case of grade 3-4 non-hematologic toxicity, further dose-reductions should be performed as follows (table 1-2): dose-reduction of 25% per cycle, with a minimum of 50% of the starting dose. If a dosage of 50% of the starting dose is not tolerated, treatment should be discontinued. For neuropathy, in case of grade 2 toxicity, oxaliplatin dose is reduced with 25%. In case of grade 3 neuropathy, oxaliplatin is definitively stopped. Dose reduction is allowed at any time. In addition, we will register unplanned dose interruptions (for example due to toxicity or hospitalization).

In case of hematologic toxicity, dose adaptations are suggested according to the advice in table 3. WBC and platelet counts should have been recovered to ≥ 3.0 and ≥ 75 x 109/L, respectively, before the start of the next treatment cycle. If these conditions are not met dosing should be delayed for a maximum of 2 weeks. If hematological toxicity has not recovered to the above mentioned values after 2 weeks delay patients will discontinue treatment with chemotherapy.

Table 1: dose modifications of non-hematologic toxicity of capecitabine / 5FU/LV

	Grade 2	**Grade 3**	**Grade 4**
1st occurrence	Interrupt treatment • Until symptom recovery to grade 0-1 • Continue with 100% of the starting dose	Interrupt treatment • Until symptom recovery to grade 0-1 • Continue with 75% of the starting dose	Interrupt treatment • Until symptom recovery to grade 0-1 • Continue with 50% of the starting dose
2nd occurrence	Interrupt treatment • Until symptom recovery to grade 0-1 • Continue with 75% of the starting dose	Interrupt treatment • Until symptom recovery to grade 0-1 • Continue with 50% of the starting dose	• Discontinue treatment
3rd occurrence	Interrupt treatment • Until symptom recovery to grade 0-1 • Continue with 50% of the starting dose	• Discontinue treatment	
4th occurrence	• Discontinue treatment		

Table 2: dose modifications for oxaliplatin sensory neuropathy

Sensory neuropathy	**Oxaliplatin dose**
Non-painful paresthesia ≥ 14 days or temporary (7-14 days) painful paresthesia/functional impairment	25% reduction of starting dose
Persistent (pain≥ 14 days) painful paresthesia/functional impairment	Omit until recovery, then restart at 50%

Recurrent neurotoxicity after 50% dose reduction	Permanently discontinued

Table 3: dose modifications for hematologic toxicity (both of capecitabine/5-FU or oxaliplatin)

Neutrophils (10^9/l)	WBC (10^9/l)	Platelets (10^9/l)	Next dose oxaliplatin	Next dose Capecitabine/5-FU
< 0.5 (grade 4) or febrile neutropenia	< 1.0 (grade 4)	< 25 (grade 4)	-25%	No adjustment

Treatment duration

After 6 cycles of CAPOX or 8 cycles of FOLFOX6, oxaliplatin administration should be interrupted in all patients and treatment can be continued with monotherapy with capecitabine or 5-FU in line with current guidelines. When bevacizumab was part of the initial treatment, this can be continued too. Chemotherapy treatment will be continued until progression, unacceptable toxicity or a patient's or clinicians' decision to stop. When progression occurs, next treatment line will be at the discretion of the physician (outside the scope of this study).

7.1.4. Description of adverse events

7.1.4.1 Non-hematological toxicity

The most frequently occurring non-hematologic toxicities of capecitabine are: diarrhoea, nausea/vomiting (not requiring anti-emetic prophylaxis), abdominal pain, stomatitis, asymptomatic hyperbilirubinaemia, hand-foot syndrome and anorexia.

The most frequently occurring non-haematologic toxicities of 5-FU/leucovorin are: diarrhoea, nausea/vomiting (not requiring anti-emetic prophylaxis), abdominal pain, stomatitis, and anorexia.

The most frequent adverse events of oxaliplatin in combination with a fluoropyrimidine are gastrointestinal (diarrhoea, nausea, vomiting and mucositis), and neurological (acute and dose cumulative peripheral sensory neuropathy). Overall, these adverse events occur more frequent and severe with oxaliplatin and 5-FU/FA doublet chemotherapy than with 5-FU/FA alone[2].

Hand-foot syndrome

If painful swelling or erythema of hands or feet occur, emollients are beneficial. In case of grade 2-3 hand-foot syndrome, capecitabine dosing should be interrupted until recovery until ≤ grade 1. The omitted doses should not be administered after resuming of treatment, i.e. the total length of each capecitabine treatment period should not exceed 14 days. The dose should be reduced 25% relative to the starting dose. In case of grade 3 or persisting grade 2 handfoot-syndrome, capecitabine may be replaced by S-1 (TeysunoR) at a dose of 30 mg/m2/dose, twice daily on days 1-14 of each treatment cycle.

Diarrhoea

No prophylaxis must be given, especially no loperamide should be administered prophylactically. In case of diarrhoea grade 2-4, capecitabine intake should be interrupted immediately. Patients experiencing severe diarrhoea should be followed cautiously. In case of risk of dehydration, fluids and electrolytes should be administered. Standard treatment for diarrhoea should be prescribed (i.e. loperamide). Treatment can only be restarted when diarrhoea is resolved. In case of interruption of capecitabine therapy, the omitted doses should not be administered after resuming of treatment, i.e. the total length of each capecitabine treatment period should not exceed 14 days. If diarrhoea persists for more than 48 hours despite the recommended loperamide treatment, the patient should

be hospitalised for parenteral support. Loperamide may be replaced by other anti-diarrhoeal treatment (e.g. octreotide etc.).
Patients who experience concomitant vomiting or fever or have a performance status > 2 should be hospitalised immediately for i.v. rehydration.

Cardiac toxicity
Patients rarely may experience chest pain during treatment with capecitabine, which is considered due to coronary spasms. In case no alternative diagnosis is considered, capecitabine should be replaced by S-1 (TeysunoR).

Cold induced sensory neuropathy
For cold induced sensory neuropathy persistent (≥14 days) a 25% dose reduction of oxaliplatin should be made. In case of functional impairment, oxaliplatin should be omitted until recovery and may be restarted at 50% of the dose. If despite a 50% dose reduction, cold induced neurotoxicity does recur, oxaliplatin will be discontinued permanently and patients will continue treatment with all other drugs. In case oxaliplatin infusion is not possible according to this schedule on day 1 of the next cycle, this cycle should not be delayed, and oxaliplatin should be withheld until the following cycle. Acute neurosensory effects (acute laryngeopharyngeal dysesthesia with subjective feelings of dyspnea and dysphagia without signs of bronchospasms or pulmonary abnormalities) have been observed.

Extravasation of oxaliplatin or 5-FU
As a general recommendation in the event of extravasation, the following measures are advised (like for any other cytotoxic drug):
1. Stop the infusion immediately.
2. Do not remove the needle or cannula.
3. Aspirate with the same needle as much infiltrated drug as possible from the subcutaneous site.
4. Watch the area closely during the following days in order to determine whether any further treatment is necessary.

Extravasation of oxaliplatin may cause necrosis. Specific measures to be taken in the case of extravasation of oxaliplatin are:
1. Infiltrate the area with subcutaneous injections of 2-5ml sodium-thiosulfate 10%
2. Cover area with warm compresses

Allergic/ideosyncratic reactions to oxaliplatin
These reactions have been described occurring shortly after oxaliplatin infusion, and a massive cytokine release has been suggested as its cause [49, 50].

7.1.4.2 Hematological toxicity

Hematological toxicity may be induced by oxaliplatin, and less frequently by capecitabine or 5-FU. The most frequent types of hematological toxicity for capecitabine, 5-FU and oxaliplatin are neutropenia and thrombocytopenia.
In case of grade 3-4 thrombocytopenia and/or grade 4 neutropenia and/or febrile neutropenia, the dose of chemotherapy should be reduced to 75% in the next cycle. Upon recurrence of haematological toxicity, the dose should be further reduced to 50%. No further dose reductions should be performed, so if toxicity recurs upon 50% dose reduction, treatment should be discontinued. WBC and platelet counts should have been recovered to ≥ 3.0 and ≥75 x 109/L, respectively, before the start of the next treatment cycle. If these conditions are not met, the administration should be delayed for 1 week with a maximum of 2 weeks. If haematological toxicity

has not recovered to the above mentioned values after 2 weeks delay patients will discontinue treatment. Prophylactic use of growth factors is not permitted.

7.1.5 Salvage treatment

Any treatment given upon progression of disease during experimental or standard treatment is to the discretion of the local investigator, according to guideline recommendations. Salvage treatments will be recorded in the medical file, and will be collected by the datamanager.

7.2 Comparator IMP(s)

In the control arm, the same drugs are used as in 7.1., but in full-dose:

Low risk patients
Control arm (full-dose)
- Capecitabine 1000mg / m2 oral at day 1-14 (every 3 weeks)
- Oxaliplatin 130mg/m2 at day 1 (every 3 weeks)
OR
- 5-FU 400mg/m2 IV bolus at day 1 followed by 2400mg/m2 in 46 hours (every 2 weeks)
- Leucovorin 400mg/m2 day 1 (every 2 weeks)
- Oxaliplatin 85mg/m2 day 1 (every 2 weeks)

High risk patients
Control-arm (full-dose):
- Capecitabine 1000mg/m2 oral at day 1-14 (every 3 weeks)

7.3 Placebo

Not applicable

7.4 Observational cohort for patients who do not want to undergo randomization

It has been shown in many previous studies that inclusion of older adults with cancer can be challenging. One of the reasons for this fact is that individual patients or their physicians may have a strong preference for a certain treatment strategy and therefore do not want to participate in randomized studies. In order to still register all eligible patients, we will additionally register these patients in an observational study arm. These patients are not counted for the required sample size of 587 patients. The goal of the observational arm is to describe patient characteristics, disease progression and survival of a group of patients who declined to undergo randomization and received standard of care. Data for the observational arm could provide insight on unforeseen consequences, the inclusion of very frail older patients and on representativeness of the study population.

If the patient or clinician decide that the patient will not undergo randomization, patients can instead enter the observational cohort. Patients need to fill in a written consent as well but will not be randomized. If patients will give written consent for the observational cohort, they will be invited to undergo a few questionnaires at baseline (the G8, Katz-ADL, Lawton-IADL and EQ-5D and questions about living status, dementia, previous falls and delirium in the past) and they will receive one follow-up request at 3 months for the EQ-5D. Outcomes from the medical chart will be registered (including progression, and survival).

7.5 Auxiliary Medicinal Product(s) (AxMP(s))

7.5.1 Name and description of the AxMP

For patients with metastasized colorectal cancer, chemotherapy in first line is often supplemented with anti-VEGF therapy (bevacizumab) or an eGFR antibody (panitumumab or cetuximab). This will a be a stratification factor in the randomization in order to ensure that treatments are equally distributed among randomization arms. With all patients, addition of targeted therapy (bevacizumab or EGFR inhibition) to chemotherapy in first line will be discussed conform (Dutch) guidelines. This can be added at the discretion of the treating oncologist. Hence, targeted therapy is allowed within the study but not mandatory. Targeted therapy will be prescribed in standard dose in all treatment arms.

Anti-VEGF therapy

- Bevacizumab (Avastin)
    - Bevacizumab in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of adult patients with metastatic carcinoma of the colon or rectum. It binds to vascular endothelial growth factor (VEGF), the key driver of vasculogenesis and angiogenesis, and thereby inhibits the binding of VEGF to its receptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells. Neutralising the biological activity of VEGF regresses the vascularisation of tumours, normalises remaining tumour vasculature, and inhibits the formation of new tumour vasculature, thereby inhibiting tumour growth. See also the SmPC: https://www.ema.europa.eu/en/documents/product-information/avastin-epar-product-information_en.pdf

eGFR antibody

- Cetuximab (Erbitux)
    - Erbitux is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic left-sided colon or rectal cancer in first-line in combination with FOLFOX. Cetuximab is a chimeric monoclonal IgG1 antibody that is specifically directed against the EGFR. EGFR signalling pathways are involved in the control of cell survival, cell cycle progression, angiogenesis, cell migration and cellular invasion/metastasis. See also the SmPC: https://www.ema.europa.eu/en/documents/product-information/erbitux-epar-product-information_en.pdf

- Panitumumab (Vectibix)
    - Panitumumab is indicated for the treatment of adult patients with wild-type RAS metastatic colorectal cancer (mCRC) in first-line in combination with FOLFOX or FOLFIRI, or in second-line in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan). It is a recombinant, fully human IgG2 monoclonal antibody that binds with high affinity and specificity to the human EGFR. Binding of panitumumab to EGFR results in internalisation of the receptor, inhibition of cell growth, induction of apoptosis, and decreased interleukin 8 and vascular endothelial growth factor production. See also the SmPC: https://www.ema.europa.eu/en/documents/product-information/vectibix-epar-product-information_en.pdf

7.5.2 Statement on authorisation and justification unauthorised AxMP (if applicable)

All AxMPs will be used in the trial in accordance with the terms of its marketing authorisation.

7.5.3 Description and justification of dosage and route of administration

- Bevacizumab can be administered intravenously at a dose of 5 mg/kg every 2 weeks or 7,5 mg/kg every 3 weeks
- Cetuximab can be administered intravenously at a dose of 500mg/m2 every 2 weeks
- Panitumumab can be administered intravenously at a dose of 6 mg/kg every 2 weeks or 9 mg/kg every 3 weeks

7.6 Additional considerations for trials involving a medical device

Not applicable

7.7 Additional considerations for trials involving an in-vitro diagnostic or companion diagnostic

Not applicable

7.8 Preparation and labelling of the study treatment(s)

Drugs will be prepared according to standard practice and are all authorized medicinal products. There are no specific circumstances needed to ensure subject safety and the reliability and robustness of data generated clinical trials. Therefore, no additional labelling is required.

8. OTHER TREATMENTS AND RESTRICTIONS

8.1 Concomitant therapy

As standard of care, chemotherapy regimens are supported by anti-emetics in order to prevent nausea. The schemes of used anti-emetics can be different per participating center and deviation from these schemes is allowed. All patients should receive instructions on how to use this medication in case nausea/vomiting occurs at home.

8.1.1 Permitted medication(s)

Anti-emetics

- Dexamethason (one time 8 mg) and if necessary in days after chemotherapy (1 – 4mg at discretion of oncologist)
- Granisetron (2 times 1 mg daily) or ondansetron (3 times 4 mg daily)
- Metoclopramide (maximum 3 times 10 mg daily on demand).
- Aprepitant (80mg / 125mg) or akynzeo (300mg/0,5mg) once before chemotherapy,

Trombo-embolic prophylaxis

Trombo-embolic prophylaxis can be used according to local protocols during pre-operative treatment, peri-operatively and during adjuvant treatment.

Prophylactic treatment for diarrhea:
No prophylaxis must be given, especially no loperamide should be administered prophylactically. Patients experiencing severe diarrhoea should be followed cautiously. In case of risk of dehydration, fluids and electrolytes should be administered. Standard treatment for diarrhoea should be prescribed (i.e. loperamide).

If diarrhoea persists for more than 48 hours despite the recommended loperamide treatment, the patient can be hospitalised for parenteral support at the discretion of the treating physician. Loperamide may be replaced by other anti-diarrhoeal treatment (e.g. octreotide etc.).

8.1.2 Prohibited medication(s)

The following medications may interact with trial medications. These medications are not contraindicated but should be avoided unless there is no reasonable alternative:

- Vitamin K Antagonists: no interaction with oxaliplatin or fluoropyrimidines, but INR control may be affected by capecitabine. Consider increased frequency of INR monitoring.
- Phenytoin: blood phenytoin levels may increase with capecitabine. Consider checking therapeutic levels after 3-6 weeks of chemotherapy therapy.
- Folic acid or interferon α: multivitamin supplements containing folic acid or interferon α should be avoided as this may increase capecitabine toxicity.
- Allopurinol: may potentially reduce the effectiveness of capecitabine.
- Vaccination with live or live attenuated vaccines should be avoided in patients receiving oxaliplatin or fluoropyrimidines.
- Metronidazole may enhance the toxicity of capecitabine or 5-FU.
- Use caution when combining with drugs that may cause electrolyte disturbances and/or prolong the QT interval

8.2 Lifestyle restrictions

8.2.1 Contraception measures

Patients will be advised to use contraception measures during participation in the trial, as described in 6.2

8.2.2 Other requirements

Not applicable

9. TRACEABLILITY, STORAGE, ACCOUNTABLILITY AND COMPLIANCE

9.1 Traceability and storage of the study treatment(s)?

Since this is a low-interventional clinical trial following normal prescribing practice and documentation and documentation of prescribed amounts and doses taken is available in the medical records, routinely maintained pharmacy documentation on receipt, storage and handling is sufficient.

9.2 Accountability of the study treatment(s) and compliance

Accountability for the supply and administration of medicinal products to subjects: not applicable

10. STUDY ASSESSMENTS AND PROCEDURES

10.1 Screening procedure

The study will include patients in whom the decision to treat with chemotherapy has already been made between the oncologist and the patient before study participation is discussed. Next, a verbal explanation about the trial and a written information sheet is given to patients. We will obtain written consent after the explanation. Patients must be given as long as they need to consider whether they want to participate. They should be encouraged to discuss their decision with their family, caregivers and healthcare professionals during this time.

After obtaining informed consent to participate, the treating oncologist (or local research nurse) will enter the patient in the central Castor database and complete the inclusion and exclusion criteria. Next, the G8 questionnaire will be performed by the local research nurse or survey coordinator. When patients have a G8-score of 15 or higher, their treating oncologist will be notified that the G8 results do not imply an increased risk of toxicity. When patients have a G8-score of 14 or lower, their treating oncologist will be notified that the G8 results may indicate a relatively high risk of toxicity. With this information the treating oncologists may decide together with the individual patient between treatment with monotherapy or polychemotherapy.

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Within 3 days, the patient will be called by the survey coordinator (a research nurse from the LUMC independent of the study team) to perform other baseline geriatric questionnaires.
After stratification for either mono-chemotherapy or poly-chemotherapy, randomization will take place by the central or local datacenter. Treating physicians will be informed of the outcome of randomization and will communicate this with the patient, after which the treatment can be started.

10.2 Randomisation, blinding and treatment allocation

Participating patients will be randomly assigned to full-dose or dose-reduced chemotherapy. Randomization is performed to avoid bias by investigators and minimize bias in the assessment of the disease. After final eligibility check and when written informed consent is obtained, patients will be included in the study and randomized online via the Castor electronic data capture (EDC) system (https://data.castoredc.com) under the study “DOSAGE” at the LUMC Clinical Research Center. Randomization will be performed in a 1:1 ratio. After randomization, a sequential identification number will be applied. This key to the patient code is a combination of country, institute code, study code and sequential patient number and is safeguarded by the participating center itself in the screening log. The number has to be recorded on the randomization form, along with the randomization date. Treatment allocation will not be masked from study investigators or patients as this is considered as not feasible, since dose reduction will influence the number of pills that patients will have to take, and it will influence clinical decisions when toxicity occurs.

We will include three randomization stratification factors that may influence prognosis, and are therefore important to be balanced between the randomization arms.

Randomization stratification factors:
- Additional treatment with bevacizumab or EGFR inhibition (yes versus no)
- Institution
- Tumor side (right-sided or left-sided)

10.3 Study procedures and assessments

Systemic therapy can be administered at each participating hospital. Until the primary endpoint (PFS) has been reached, systemic treatment should be administered according to protocol, and no other experimental systemic treatment should be administered.

10.3.1 Study procedures

3.1.2 Randomization of patients with a low toxicity risk

Patients classified as “low risk of toxicity” will be randomized between combination treatment of a fluoropyrimidine and oxaliplatin in either full-dose, or with an upfront 25% reduction. Physicians can choose between capecitabine or 5-Fluoruracil (5-FU) as fluoropyrimidine treatment. Optional bevacizumab or EGFR inhibition can be prescribed at the discretion of the oncologist. In the full-dose arm, the following dosing schemes are allowed:
- CAPOX: Capecitabine 1000mg / m2 at day 1-14 (every 3 weeks) and oxaliplatin 130mg/m2 at day 1 (every 3 weeks)
- FOLFOX6: 5-FU 400mg/m2 IV bolus at day 1 followed by 2400mg/m2 in 46 hours (every 2 weeks), leucovorin 400mg/m2 day 1 (every 2 weeks) and oxaliplatin 85mg/m2 day 1 (every 2 weeks)

In the intervention arm, 75% of all compounds in the above-mentioned schedules are prescribed.

3.1.2 Randomization of patients with a high toxicity risk

Patients classified as “high risk of toxicity” will be randomized between monotherapy with a fluoropyrimidine (this is in clinical practice always capecitabine) in either full-dose or with an upfront 25% reduction. Optional bevacizumab or EGFR inhibition can be prescribed at the discretion of the oncologist. The following dosing scheme is allowed in the full-dose arm:

- Capecitabine 1000mg/m2 at day 1-14 (every 3 weeks)

In the intervention arm, 75% of the above-mentioned schedule (750 mg/m2) is prescribed.

Patients with a moderate renal impairment (GFR 30- 50 mL/min), in line with international recommendations, will be treated with 25% reduced starting dose of capecitabine when randomized for full dose treatment and treated with 40% reduced starting dose when randomized for upfront dose reduction.

10.3.2 Study measurement

DOSAGE trial	Screening (T<0)	Pre-randomisation	Randomisation (T=0)	Before every new cycle and after last cycle, until progression	Each 8-12 weeks	After 1 month	After 3 months	After 6 months	After 9 months	After 12 months	End of study
Informed consent		E									
Geriatric-8		E									
In-/exclusion	X										
Patient/tumor characteristics	X										
Laboratory analyses^	X			X							
Toxicity				X							
Radiologic evaluation⁺	X				X						
N of cycles				X							
Dose reductions				X							
Hospitalizations				X							
Survival					X						X
EQ-5D-5L*		E				E	E	E	E	E	
EORTC QLQ-C30*		E				E	E	E	E	E	
Home and informal care*		E				E	E	E	E	E	
MNA		E									
Lawton-IADL*		E				E	E	E	E	E	
Katz-ADL*		E				E	E	E	E	E	
TICS-M		E									
PHQ-2		E									

Window for questionnaires: +/- 4 weeks. *Follow-up questionnaires will be performed until disease progression or until 12 months after randomization in case of no disease progression. ^Recommended laboratory analyses include: total blood count (Hb, WBC, differential, platelets), kidney and liver function. ⁺Radiologic evaluation: performed according to local standard practice (CT-scan, PET-scan and/or MRI-scan). Baseline evaluation should be performed within 6 weeks prior to starting protocol treatment. X = procedures are standard of care. E = extra procedure in study context.

Green = registered / assessed by central research center (LUMC)

Blue = registered by local data manager in participating hospital

Baseline clinical measurements should be performed within 6 weeks prior to starting protocol treatment and will include the following tumor- and patient characteristics:

- Sex, age, current medication, adjuvant treatments in the past
- Comorbidities using the Charlson Comorbidity Index, excluding the current malignancy
- Polypharmacy
- Tumor side (right sided: coecum, ascending colon, hepatic flexure, transverse colon, left sided: splenic flexure, descending colon, sigmoid, rectum)
- Number of metastatic sites, location of metastatic sites, mutational status (KRAS, NRAS, BRAF)
- Baseline routine blood counts according to local practice, with at least full blood count (Hb, WBC, differential, platelets), renal and liver function tests and CEA
- Baseline radiologic evaluation (CT scan Thorax and abdomen or PET-CT scan)
- Geriatric questionnaires, including the European Organisation for Research and Treatment of Cancer (EORTC) Core Questionnaire QLQ-C30 v3.0 for QoL, the EQ-5D-5L for QoL, Mini Nutritional Assessment (MNA) for malnutrition, Patient Health Questionnaire-2 (PHQ-2) for mood, Lawton-IADL for physical functioning, Katz-ADL for physical functioning, TICS-M for cognition.

In case of undue delay between the baseline evaluation and start of study treatment (>6 weeks) repeating the diagnostic procedures is recommended.

10.3.2.1. QoL and physical functioning at baseline

As QoL is an important outcome of our study, we will use multiple questionnaires to measure this endpoint at baseline and during follow-up. First, the EQ-5D-5L will be used, as the EQ-5D-5L is needed to measure QALYs in the cost-effectiveness analyses[34]. Second, we will use the EORTC core questionnaire (QLQ-C30), a well-validated questionnaire developed to assess the health-related QoL of cancer patients in clinical trials[35,36]. The EORTC QLQ-C30 incorporates five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status/QoL scale, and a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea) and perceived financial impact of the disease. We chose not to use the EORTC Colorectal questionnaire (QLQ-CR29), as this questionnaire predominantly addresses stoma, ano-rectal and sexual function and is therefore less suitable for our study population. Physical functioning will be measured by using the Lawton-IADL[37] and Katz-ADL, two well-validated questionnaires for older patients.
In order to ensure feasibility in all participating centers, we will perform the questionnaires via telephone or we will send the questionnaires online via mail from the coordinating center (LUMC). Patients can choose whether the questionnaires will be either sent by email or will be performed by telephone to maximize follow-up response rates. Patient email addresses will be written on the randomization form. We have a longstanding experience in performing questionnaires by telephone, and this has proven to be feasible and has been validated in previous studies[38,39].

10.3.2.1. Baseline geriatric assessment

Apart from G8 that is performed to advice in the stratification of patients between “high risk of toxicity” and ”low risk of toxicity”, participants will also undergo a geriatric assessment (GA) before randomization. A GA is an evidence-based way of describing different health domains that are associated with ageing in the older population and focuses on older adults’ functional, psychosocial

and medical capacities. The results from the GA will be used to characterize the study population and find predictors of poor outcomes.
In order to increase feasibility of the trial, the questionnaires will be performed by a survey coordinator from the organizing center via telephone calls. Performing a telephone-based GA has proven to be feasible in previous studies with older adults[39-41]. The GA is estimated to take 30 minutes and will be performed at the same moment as the G8 screening.
As our study population consists of patients who are in a vulnerable phase of life, we want to keep the study burden as low as possible. Because the EORTC QLQ C-30, EQ-5D and (I)ADL questionnaires that are administered at baseline already cover most domains from the GA (including ADL function and QoL), we will only perform the following additional questionnaires:

- Mini Nutritional Assessment (MNA)[42]
- Telephone Interview of Cognitive Status (TICS-M)[43]
- Home and informal care, living status (alone, with other, institutionalized), walking aid
- PHQ-2 (mood) [44]

Obtained from the medical charts:

- Comorbidity (from medical charts) according to Charlson comorbidity index
- Polypharmacy (from medical charts) defined as 5 or more types of medication.

Thus, the GA covers the somatic (polypharmacy, comorbidity, malnutrition), physical (ADL and IADL, institutionalization), mental (cognition, mood) and social (living situation, home and informal care) domains.

When the outcomes of (one of) these questionnaires demonstrate deficits, this will be communicated with the treating oncologist. Interventions based on outcomes of the geriatric assessment are at the discretion of the treating oncologists, as intervention options differ in participating hospitals and most oncologic care pathways already incorporate interventions like physiotherapy and dietary advice. Moreover, data on the benefits of referral to a geriatrician on treatment outcomes of Dutch patients with metastasized colorectal cancer are not yet robust enough to make firm recommendations. In contrary to medical oncologist from other countries, Dutch medical oncologists are trained in Internal Medicine, including basic geriatric medicine and are usually capable of initiating geriatric interventions or indicating specialist geriatric consultations.

We chose to use the G8 to advice in stratifying patients between mono- or doublet therapy instead of the GA because a GA is much more time-consuming and more difficult to implement. Additionally, of the randomized controlled trials investigating the effectiveness of a GA, trials that administered the GA before treatment initiation, which could lead to de-escalation of treatment such as dose reduction, found a positive effect of the GA on toxicity[29], whereas trials that administered the GA after the oncological treatment decision found no positive effect[45,46]. Thus, less effects can be expected from non-oncological interventions targeting geriatric deficits.

10.3.2.2. Follow-up of treatment

Before every next treatment cycle, patients will visit the outpatient clinic as part of standard of care to evaluate treatment tolerability. The average visit time is estimated to take 15 minutes.
It is recommended to do a physical examination before every treatment cycles, consisting of at least evaluation of adverse events (CTCAE criteria) and blood pressure (in bevacizumab-treated patients).

It is recommended to perform at least the following laboratory tests before every treatment cycle: full blood count (Hb, WBC, differential, platelets) and renal and liver function tests.

Physicians are allowed to continue with capecitabine monotherapy after 6 CAPOX treatment cycles (optionally with bevacizumab), and number of treatment cycles, toxicity, dose reductions and laboratory counts will be monitored in these patients as well. Follow-up of treatment will be performed according to protocol until progression of disease, except in case of withdrawal of informed consent. In case of progression, type of second-line therapy will be registered. Survival will be recorded for all patients at the end of the study.

10.3.2.3. Follow-up QoL and physical functioning

After 1 month and 3, 6, 9 and 12 months, all alive patients will be invited to complete short questions regarding QoL and physical functioning. Participating hospitals are requested to report death of a patient directly, in order to avoid telephone calls to patients who have died.
Again, we try to make the burden for patients as low as possible and only use questionnaires we need to achieve the proposed aims, taking into account the outcomes that are important for patients (like QoL and independency). The follow-up questions will include the questionnaires on QoL (EORTC QLQ-C30 and EQ-5D) and physical functioning (Lawton-IADL and Katz-ADL) plus questions about home and informal care. Similar to the baseline questionnaires, these questionnaires can be answered by telephone, which is estimated to take 15 minutes per timepoint, or can be filled in and sent by email (whatever the patient prefers). Questionnaires performed via telephone is preferred to avoid selective loss to follow-up in patients with deficits in functional status or a QoL deterioration, as has frequently been observed in previous studies. The survey coordinator will be responsible for this part of the project. Questionnaires within +/-4 weeks of the specified time points will be included in the analyses.
Follow-up will be performed according to protocol until end of study (progression on study treatment), except in case of withdrawal of informed consent (or death).

10.4. Efficacy assessments

In line with the ESMO guidelines[24], radiological evaluation should be carried out every 8-12 weeks. Imaging should be performed as close as possible to every 8-12 weeks (no earlier than 7 or later than 13 weeks). Imaging technique and assessment will be as per local standard practice.

Progression can be defined based on one of the three criteria below:
1) If the Response Evaluation Criteria in Solid Tumours (RECIST) principles are utilized for response assessment, radiological progression should preferably be defined according to RECIST criteria.

2) In cases where RECIST criteria are not applicable, radiological progression can be determined based on the results of radiological evaluations.

3) If there is clinical evidence of cancer progression without radiological evaluation, progression can be defined based on clinical evidence such as clinical deterioration due to cancer combined with abnormal laboratory values or tumor markers, such as CEA. The date of the clinical assessment at which clinical progression is encountered, will be used for follow-up time measurement.
Local investigators are responsible for explaining the basis of progression. In case of doubt regarding cancer progression, the date of the clinical assessment at which the study treatment is discontinued early due to progression, will be used for follow-up time measurement.

10.4.2. Safety assessments

During follow-up, treatment toxicity will be registered after every treatment cycle (or earlier if severe toxicity occurs). Toxicity will be monitored in terms of physical examination and laboratory assessment conform clinical practice. Data on grade 3-5 toxicity will be obtained from the medical charts and laboratory results at every treatment cycle.

As described in Chapter in 7.1.3. dose reduction or treatment discontinuation should be performed in case of severe toxicity. Adverse events occurring upon treatment with targeted therapy should be handled according to standard practice.

11. STUDY DISCONTINUATION AND COMPLETION

11.1 Definition End of Trial

The trial will be ended after the last visit of the last subject.

11.2 Criteria for temporary halt and early termination of the clinical trial

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

The study will be ended prematurely if the standard treatment schedules change during the study (in that case an amendment of the study will be considered).

11.3. Discontinuation/withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.
Patients who withdraw from the study treatment before the primary endpoint is reached could still undergo follow-up assessments on QoL and physical functioning if they are willing to do so. The PI or delegate should make every effort to ensure that the specific wishes of any participant who wishes to withdraw consent for further involvement in the trial are defined and documented in order that the correct processes are followed by the sponsor and sites following the withdrawal of consent. If subjects withdraw from the trial including follow-up, information from the medical file will no longer be received. We suggest that the participant is also made aware that if significant new information becomes available about the treatment they have received in the trial it may be necessary to contact them in the future.
If treatment is withdrawn due to disease progression or toxicity then this is not classed as a patient withdrawal.

If treatment is discontinued due to any reason (such as toxicity or progressive disease), patients will not be treated within the study, but their endpoints will still be registered from medical charts.
A dropout of 10% is accounted for in the sample size calculations, so no individual replacement of subjects will be performed.

11.4. Arrangements for subjects after their participation in the clinical trial ended

Not applicable.

12. SAFETY REPORTING

12.1 Definitions

12.1.1. Adverse events (AEs)

Adverse events are defined as any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.
All adverse events classified as grade 3, 4 or 5 from protocol chemotherapy will be reported and scored for severity using the CTCAE version 5.

12.1.2. Serious adverse events (SAEs)

Serious adverse event is any untoward medical occurrence in a patient or trial subject that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect

12.1.3. Suspected unexpected serious adverse reactions (SUSARs)

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. The event must be serious;
2. There must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. The adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in the reference safety information (RSI).

12.2. Recording of AEs/SAEs/SUSARS by the local principal investigator to the sponsor

AEs, SAEs and SUSARS will be recorded using Castor by (an authorized delegate of) the local principal investigator. The local principal investigator and/or the authorized persons will be responsible for SAE assessment and reporting in Castor. SAEs that result in unexpected admissions, death, or are life threatening should be reported expedited. The expedited reporting will occur no later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

12.3. Reporting of AEs and SAEs

12.3.2. Reporting of AEs/SAEs/SUSARS by the investigator to the METc

All SAEs will be reported annually through line-listing by the Clinical Research Center to the METc that approved the protocol. The in Castor reported AEs, SAEs and SUSARS will be reported to the METC by the Clinical Research Center in accordance with all requirements of the Dutch law.

12.3.3. List of SAEs which do not require reporting and procedure for reporting

In this study, the following SAEs will not require reporting and procedure for reporting:

1. Admission for diagnosis or treatment of progression.
2. Death due to progression of disease
3. Planned admissions.

12.4. Follow-up of adverse events

Conform local standard practise, AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

12.5. Reporting of SUSARs by the sponsor to EudraVigilance

The sponsor will keep detailed records of all AEs which are reported to him/her by the investigator or investigators (CTR: Article 41(3)).

The sponsor will report electronically and without delay to EudraVigilance all relevant information about any SUSAR (CTR: Article 42).

The period for the reporting of SUSARs by the sponsor to EudraVigilance will take account of the seriousness of the reaction and will be as follows:

- In the case of fatal or life-threatening SUSARs, as soon as possible and in any event not later than **7 days** after the sponsor became aware of the reaction (CTR: Article 42(2(a)));
- In the case of non-fatal or non-life-threatening SUSARs, not later than **15 days** after the sponsor became aware of the reaction (CTR: Article 42(2(b)));
- In the case of a SUSARs which was initially considered to be non-fatal or nonlife threatening but which turns out to be fatal or life-threatening, as soon as possible and in any event not later than **7 days** after the sponsor became aware of the reaction being fatal or life-threatening (CTR: Article 42(2(c))).

Where necessary to ensure timely reporting, the sponsor may, in accordance with section 2.4 of Annex III, submit an initial incomplete report followed up by a complete report (CTR: Article 42(2)).

12.6. Annual safety report

Regarding investigational medicinal products other than placebo, the sponsor shall submit annually through CTIS to all Member States concerned a report on the safety of each investigational medicinal product used in a clinical trial (CTR: Article 43).

12.7. Unblinding procedures for safety reporting

Not applicable (no blinding)

12.8. Temporary halt for reasons of subject safety

The sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will submit the notification through CTIS without undue delay of a temporary halt but not later than in 15 days of the date of the temporary halt. It

shall include the reasons for such action and specify follow-up measures. The study will be suspended pending a further positive decision by the concerned member state (CTR: Article 38). The investigator will take care that all subjects are kept informed.

12.9. Urgent safety measures and other relevant safety reporting

Where an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor and the investigator will take appropriate urgent safety measures to protect the subjects. In addition the sponsor will notify the Member States concerned, through CTIS, of the event and the measures taken. That notification will be made without undue delay but no later than **7 days** from the date the measures have been taken (CTR: Article 54).

12.10. Data Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC)

Since the study compares two frequently used and well-characterized chemotherapy regimens (and not a “new” treatment) conform clinical practice and the safety profiles of all regimens are well-known, the study is classified as low risk, and a DSMB to monitor the safety of participants is not needed.

13. STATISTICAL ANALYSIS

13.1 Analysis sets

We will perform both a per-protocol and an intention-to-treat analysis. Patients will be grouped according to the treatment they were randomized to receive.

13.2 Participant demographics and other baseline characteristics

Descriptive characteristics of patients will be reported using frequencies and proportions for categorical data and means and standard deviations for continuous data. To present the differences between the stratification arms (high versus low toxicity risk), where no randomization occurs, the T-test will be used for continuous variables and chi-square for discrete ones. In case of violation of normality the non-parametric test will be employed.

13.1. Randomisation and blinding

Randomization will be performed in a 1:1 ratio. Block randomization will be used. As mentioned earlier, patients will be stratified for:

- Additional treatment with bevacizumab or EGFR inhibition (yes versus no)
- Institution
- Tumor side (right-sided or left-sided)

Blinding of the subjects/caregivers and physicians is not considered feasible. However, the sponsor statistician will be blinded and not have knowledge of the subject's assignment until the database is locked and the study is officially unblinded.

The primary endpoint is an objective endpoint instead of a subjective endpoint about how a patient feels or functions, making it less prone to bias. Moreover, the subjects in the different treatment arms will be treated identically except for the received treatment: visit schedules and procedures are the same, as well as adverse event data collection, inclusion criteria and the timing of the primary endpoint measurements, to minimize bias.

13.2. Sample size, trail power and level of significance used

The study is powered on the primary endpoint, which is PFS, defined as time from randomization until either radiological or clinical progression or death, whichever occurs first. The study assumes non-inferiority of the intervention arm with a median PFS of 8 months based on previous studies in metastasized colorectal cancer in older adults, including the MRFOCUS2, AVEX, NORDIC9 and SALTO trials (Table 2), with an excepted margin of 8 weeks. This is considered as an acceptable upper margin for non-inferiority. We determined the non-inferiority margin for the dose-reduced treatment arms based on previous trials[7,27] and extensive consultation with the seven primary investigators from different participating hospitals and Stichting Darmkanker, who all agreed on this margin.

Table 2: Median PFS estimates in previous trials with older adults

Trial	Patient population	Median PFS
MRFOCUS2[6]	"Non-fit" older or frail mCRC patients receiving upfront dose reduction	Median PFS was 3.5, 5.8, 5.2 and 5.8 months in the FU, OxFU, Cap and OxCap groups respectively; a reasonable estimate for all patients is 5 months
AVEX[32]	Older mCRC patients, no candidate for oxaliplatin /irinotecan	Median PFS 9.1 months for Cap/Beva, 5.1 months for Cap monotherapy.

NORDIC9[7]	"Non-fit" older mCRC patients	Median PFS 5.1 months for full-dose S-1, 6.2 months for reduced-dose Ox/S-1. 25% received bevacizumab.
SALTO[33]	mCRC patients with median age 73 years (not specifically older patients)	Median PFS 8.2 months for Cap monotherapy, 8.4 for S-1 monotherapy.

Power analysis was performed in PASS, version 15.0.13. A non-inferiority logrank test with an overall sample size of 528 subjects (264 in the reference group and 264 in the treatment group) achieves 80.0% power at a one-sided 5% significance level to detect an equivalence hazard ratio of 1.25. The study will last for 48 time periods of which subject accrual (entry) occurs in the first 36 time periods. The accrual pattern across time periods is uniform. The proportion switching from the reference group to another group with a hazard rate equal to the treatment group is 0. The proportion switching from the treatment group to another group with a hazard rate equal to the reference group is 0. To account for an expected drop-out rate of 10%, 293 patients per stratification arm meaning 587 patients in total are required. The NORDIC-9 trial assumed a 5% drop-out and eventually only 3/160 patients did not start the assigned treatment. The GO2 trial assumed a drop-out of 12% and eventually 22/514 did not start the assigned treatment. Therefore, we believe that a dropout rate of 10% is reasonable in this target population.

13.3. Planned analysis

13.3.2. Analysis primary endpoint

PFS will be estimated from randomization by using Kaplan Meier's methodology and Cox regression modelling. Non-inferiority of the dose-reduced arm can be claimed if the upper limit of the confidence interval of the hazard ratio is below 1.25. To investigate the effect of possible risk factors age, comorbidity, geriatric domains, cumulative received dose and tumour characteristics on survival outcome, univariate and multivariable Cox proportional hazard regression models will be estimated. An interaction term between risk group and treatment arms will be added to the model together with additional targeted therapy and center. As an exploratory planned subgroup analysis, PFS will be stratified based on molecular pathologic feature (BRAF/RAS mutations).

13.3.3. Analysis secondary endpoints

A logistic regression model will be estimated to study the effect of groups on toxicity with the same confounders as discussed before.

Patient-reported outcomes, including QoL and physical functioning, will be measured at several timepoints and will be analyzed by using linear mixed models to assess the difference between the intervention and the treatment. The difference in time-trends between the two arms will be explored by adding an interaction term in the model. Both univariate and multivariate analyses will be performed by using the same confounders discussed in the section "Primary outcome". The cumulative dose received by patients in each treatment arm (divided by BSA) will be reported, and descriptive statistics including t-test and chi-square will be used to test between these differences.

Finally, we will assess which geriatric assessment domains are predictive of favorable outcomes with regard to PFS, OS, grade 3+ toxicity, QoL and physical functioning. These will be analyzed depending on the outcome, Cox Regression models for PFS and OS, logistic regression models for toxicity, and

linear mixed models for the patient-reported outcomes. First, we estimate a univariate model. Clinically relevant and significant predictors will be included in a multivariate analysis.

13.3.4. Cost-effectiveness

For cost-effectiveness, a cost-utility analysis will be performed ('costs per QALY') from a societal perspective and with a life-long time horizon, in accordance with the Dutch guidelines for economic evaluations in healthcare. Costs will include the chemotherapy and other hospital costs (assessed from study registrations) and home and informal care (assessed using patient questionnaires at 1, 3, 6, 9 and 12 months). Quality-adjusted life years (QALYs) will be calculated using the Dutch tariff for the five-level EQ-5D questionnaires filled-out by patients (at 1, 3, 6, 9 and 12 months). In the analysis, incremental costs and QALYs will be compared using net-benefit analysis, according to intention to treat.

12.5.5. Interim analysis

Since the study compares two frequently used chemotherapy regimens (and not a "new" treatment), and it will not last for a very long time period, no interim analyses will be performed.

13.4. (Statistical) criteria for termination of the trial

Not applicable.

13.5. Procedure for accounting for missing, unused and spurious data

Some missing values might be present, as it is possible that patients in whom QoL or physical functioning deteriorates, are less likely to complete the questionnaires. To overcome this, part of the assessments will be performed via telephone as mentioned elsewhere. The percentage of missing will be reported. Imputation methods which account for informative missing may be used.

13.6. Procedure for reporting any deviation(s) from the original statistical plan

Not applicable. No deviation from the statistical plan are expected here; the classical statistical methodology will be applied.

14. ETHICAL CONSIDERATIONS

14.1 Declaration of Helsinki

The study will be conducted according to the principles of the Declaration of Helsinki (version 3, 2015) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

14.2 Recruitment and informed consent procedures

Informed consent will be obtained prior to any study related procedures being undertaken at screening. Potential participants will be identified and approached by treating oncologists at the outpatient clinic or during multidisciplinary consultations. This contact will be the first act of recruitment. Informed consent will be written, dated and signed by the person performing the interview, and by the subject. The format of resources that will be used is the printed Subject Information Sheet, presented to the patient by the treating oncologist in the clinic. There will be no other resources used.The investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. In the interview it will be verified that the subject has understood the information. The subject will be provided with a copy of the document (or the record) by which informed consent has been given. The informed consent will be documented. Adequate time will be given for the subject to consider his or her decision to participate in the clinical trial (CTR: Article 29). They will be encouraged to discuss their decision with their family, caregivers and healthcare professionals during this time.

14.1. Benefits and risks assessment, group relatedness

Older adults with cancer have rarely been included in previous clinical trials in which the benefits of chemotherapy were studied. They comprise a possibly vulnerable group as the risk toxicity in increased. Therefore, we developed this elderly-specific trial to avoid risks while still improving outcome. As extensively described previously, previous studies have suggested that upfront dose-reduced chemotherapy can reduce the risk of treatment toxicity, thereby improving QoL. These previous studies suggest that dose-reduction does not have a negative impact on the efficacy of chemotherapy, which justifies the current study design. In order to further minimize the risk of "undertreating" patients in the intervention arm, dose-escalations are allowed if patients tolerate the treatment well. Furthermore, if patients progress on first-line treatment, any follow-up treatment in second line is allowed. This means that if patients would be "undertreated" (meaning that they receive monotherapy in this study), they can still be treated with doublet chemotherapy of a fluoropyrimidine and oxaliplatin in second line, which is common practice in current standards as well.

On the other hand, the risk of "overtreatment" of patients in the control arm of full-dose chemotherapy are also limited, as the risk of toxicity is estimated beforehand, and patients at high risk are treated with a single agent which also limits the chance of severe toxicity.

Hence, the risks for patients are minimal.

14.2. Compensation for injury

The sponsor has an insurance that is in accordance with the legal requirements in the Netherlands (Article 7 WMO, under 1). This insurance provides cover for damage to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

The sponsor/investigator has a liability insurance that is in accordance with article 7, under 9, of the WMO.

14.3. Compensation for subjects

Not applicable. No extra hospital visits will be required for the study, so there will be no compensation for travel expenses.

14.4. Compensation for investigators

All participating hospitals will receive reimbursement for trial coordination, inclusion of patients and local data entry. Central data management, geriatric assessment and follow-up questionnaires are coordinated from the LUMC Clinical Research Center, which means that the burden for participating hospitals is low.

14.5. Other ethical considerations

Not applicable

15. ADMINISTRATIVE ASPECTS, MONITORING AND CONFIDENTIALITY

The study will be conducted in compliance with the protocol, with Clinical Trials Regulation No 536/2014 and with the principles of good clinical practice (CTR: Annex I D17a).

15.1 Approval initial application and substantial modifications

The trial protocol, informed consent form, subject information leaflet, investigational medicinal product dossier, investigators brochure and any other documents required by the Regulation will be submitted for the regulatory approval before the clinical trial is started via CTIS.

The sponsor will also submit and obtain approval for substantial modifications to the original approved documents via CTIS.

A 'substantial modification' is defined in the CTR as any change to any aspect of the clinical trial which is made after notification of a decision referred to in Articles 8, 14, 19, 20 or 23 and which is likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial.

15.2 Monitoring

On site monitoring will be organized according to table 2 of the Netherlands Federation of University (NFU) Medical Centers guideline 'Kwaliteitsborging mensgebonden onderzoek 2.0' chapter 6 by dedicated monitors from the LUMC. Site monitoring will be performed by an independent LUMC monitor to whom the monitoring tasks have been delegated. During monitoring visits, Investigator Site File and eCRFs will be reviewed for eligibility, adherence to completion and verified against source documents by the monitor.
Amongst others, the following will be reviewed:

- Compliance with the protocol, Good Clinical Practice and all applicable regulatory requirements
- Informed Consent, including date of consent and signatures
- Study progress
- Source Data Verification
- Investigator Site File
- (Serious) Adverse Events

15.1. Recording, handling and storage of information

15.3.1 Handling of data and data protection

The handling of personal data will comply with the EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation. (in Dutch: Uitvoeringswet AVG, UAVG).

15.3.2 Data collection

Clinical data will be collected in all participating hospitals and will be managed by the treating physician or a local datamanager. Clinical data will be extracted from the electronic health records of participating patients. We will code patient data using a unique patient number. The code will not be based on the patient initials and birthdate. A subject identification code list will be used to link data to an individual subject. Only the local study team has the key to the subject identification list with

uncoded data. Only competent authorities, monitoring and the treating physician will have access to the list via local study team. Data will be collected on the electronic case report forms (eCRFs), specially designed for this study. Clinical data and the questionnaires will be stored using direct entry. At the informed consent procedure patients can choose between a version of the questionnaires asked via telephone or a link by e-mail. The link relates to a Survey Package in Castor. Both ways, data will be collected using direct entry. The participants' telephone number and email address will be recorded encrypted in the database Castor EDC by the local principal investigator (or their delegates) and can only be decrypted by the local study team or survey coordinator. These data will be recorded separately in a locked dedicated database exclusively for the purpose of sending out these questionnaires.

15.4 Data management

Castor EDC, an electronic data capture system, will be used for data entry and storage. The database specifically designed for this study will be developed by the LUMC Clinical Research Center. Multiple users can be created with access limitations to data entry, data export, surveys, medical coding, database designing, or quality check. This ensures that each user can access only the respective functionalities selected for that user and cannot make other changes in the database. The software will record changes that are made, the user that made the change and the time and date of change, for audit purposes. The handling of personal data will comply with the EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation. Trial management will be organized by the Clinical Research Center. They will ensure that data is complete, consistent, and up to date. All Clinical Research Center personnel is qualified at the Netherlands Association of Oncology Data Managers. Moreover, the assigned PhD student will assist with trial management. There will be no trial management agencies involved.

In all cases, it remains the responsibility of the principal investigator and coordinating investigators/project leaders to check that case report forms are completely and correctly filled out. If an investigator or the coordinating investigator/project leader needs to modify a case report form after the original copy has been filed already, he/she should write a signed notification and append a copy of the notification to his/her own copy of the case report forms.

15.4.1. Source documents and case report forms (CRF)

Source documents for this study will include hospital records and procedure reports and data collection forms. These documents will be used to enter data on the CRFs. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained. All documents will be stored safely in confidential conditions. On all study-specific documents other than the signed consent, the subject will be referred to by the study subject identification code.

15.4.2. Clinical trial master file and data archiving

The sponsor and the investigator shall keep a clinical trial master file. The clinical trial master file shall at all times contain the essential documents relating to the clinical trial which allow verification of the conduct of a clinical trial and the quality of the data generated (CTR: Article 57).

The sponsor and the investigator shall archive the content of the clinical trial master file for at least 25 years after the end of the clinical trial, unless other EU law requires archiving for a longer period. The medical files of subjects shall be archived in accordance with national law (CTR: Article 58).

The content of the clinical trial master file shall be archived in a way that ensures that it is readily available and accessible, upon request (CTR: Article 57).

All essential documents (including patient files, the Investigator Study File, CRF's and electronic study data), data management and statistical files will be kept for 25 years and archived externally.

15.4.3. Collection and storage of biological samples

There will be no new sampling of human biological samples of the subjects.

15.5. Audits and inspections and direct access to source data/documents

This trial may be subject to internal or external monitoring, auditing or inspections procedure to ensure adherence to GCP. Access to all trial-related documents including direct access to source data will be given at that time.

Reporting of serious breaches

The sponsor will notify the Member States concerned about a serious breach of the Regulation or of the version of the protocol applicable at the time of the breach through CTIS without undue delay but not later than **seven days** of becoming aware of that breach (CTR: Article 52).

15.6. Notification of the start and the end of the recruitment

The sponsor will notify within 15 days each Member State concerned of the start of a clinical trial in relation to that Member State through CTIS (CTR: Article 36(1)).

The sponsor will notify within 15 days each Member State concerned of the first visit of the first subject in relation to that Member State through CTIS (CTR: Article 36(2)).

The sponsor will notify within 15 days each Member State concerned of the end of the recruitment of subjects for a clinical trial in that Member State through the EU (CTR: Article 36(3)).

15.7. Temporary halt/(early) termination

The sponsor will notify within 15 days each Member State concerned of the end of a clinical trial in relation to that Member State through CTIS (CTR: Article 37(1)).

The sponsor will notify within 15 days each Member State concerned of the end of a clinical trial in all Member States concerned and in all third countries in which the clinical trial has been conducted through CTIS (CTR: Article 37(3)).

15.7.1. Temporary halt/early termination for reasons not affecting the benefit-risk balance

The sponsor will notify with 15 days each Member State concerned of a temporary halt of a clinical trial in all Member States concerned for reasons not affecting the benefit-risk balance through CTIS (CTR: Article 37(5)).

When a temporarily halted clinical trial for reasons not affecting the benefit-risk balance is resumed the sponsor will notify each Member State concerned through CTIS (CTR: Article 37(6)).

The sponsor will notify to the EU portal CTIS of early termination of the clinical trial for reasons not affecting the benefit-risk balance through CTIS. The reasons for such action and, when appropriate, follow-up measures for the subjects will be provided as well (CTR: Article 37(7)).

15.7.2. Temporary halt/early termination for reasons of subject safety

In accordance to article 38 of the CTR, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The temporary halt or early termination of a clinical trial for reasons of a change of the benefit-risk balance will be notified to the Member States concerned through the EU portal CTIS without undue delay but not later than in 15 days of the date of the temporary halt or early termination. It shall include the reasons for such action and specify follow-up measures. The restart of the clinical trial following a temporary halt as referred to in paragraph 1 shall be deemed to be a substantial modification subject to the authorisation procedure laid down in Chapter III of the CTR (CTR: Article 38).

15.8. Summary of the results

Within one year from the end of the clinical trial, the sponsor will submit to the EU database CTIS a summary of the results of the clinical trial. The content of the summary of the results is set out in CTR Annex IV. It shall be accompanied by a summary written in a manner that is understandable to laypersons. The content of the summary is set out in CTR Annex V (CTR: Article 37(4)).

15.9. Public disclosure and publication policy

Prior to initiation, the study will be submitted to the clinical trial register, available on https://clinicaltrials.gov. All the results will officially be published, as according to CCMO guidelines. After completion of the trial, all trial results and analyses as described in the analyses sections will be published in peer-reviewed journals.

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Appendix 1: List of principal investigators of each site

1. Leiden University Medical Center, Leiden, the Netherlands
Prof. dr. J.E.A. Portielje, J.E.A.Portielje @lumc.nl

2. Groene Hart Ziekenhuis, Gouda, the Netherlands
Drs. M. Cloos-van Baalen, Marissa.Cloos@ghz.nl

3. Reinier de Graaf Gasthuis, Delft, the Netherlands
Dr. A. Verschoor, A.Verschoor@rdgg.nl

4. Elkerliek Ziekenhuis, Helmond, the Netherlands
Dr. M.M. Teeuwen – van Genderen, mm.vangenderen@elkerliek.nl

5. Maasstad Ziekenhuis, Rotterdam, the Netherlands
Dr. B.C.M. Haberkorn, HaberkornB@maasstadziekenhuis.nl

6. Jeroen Bosch Ziekenhuis, 's-Hertogenbosch, the Netherlands
Dr. H. Pruijt, H.Pruijt@jbz.nl

7. Streekziekenhuis Koningin Beatrix, Winterswijk, the Netherlands
M. Duizer, m.duizer@skbwinterswijk.nl

8. Laurentius Ziekenhuis, Roermond, the Netherlands
Drs. L. Verhoeven, loes.verhoeven@lzr.nl

9. ZorgSaam Ziekenhuis, Terneuzen, the Netherlands
Dr. M.A. van Dijk, m.vandijk@zzv.nl

10. Ikazia Ziekenhuis, Rotterdam, the Netherlands
Dr. F.E. de Jongh, fe.de.jongh@ikazia.nl

11. Wilhelmina Ziekenhuis Assen, the Netherlands
Dr. T. Lamberts, titia.lamberts@wza.nl

12. VieCuri Medisch Centrum, Venlo, the Netherlands
Dr. Vestjens, hvestjens@viecuri.nl

13. Ziekenhuis Gelderse Vallei, Ede, the Netherlands
Dr. A. Baars, BaarsA@zgv.nl

14. Slingeland Ziekenhuis Doetinchem, the Netherlands
Dr. C. van Arkel, c.van.arkel@slingeland.nl

15. Rodekruis Ziekenhuis Beverwijk, the Netherlands
Dr. A. Goosens, agoosens@rkz.nl

16. Catharina Ziekenhuis, Eindhoven, the Netherlands
Dr. I.E.G. van Hellemond, irene.v.hellemond@catharinaziekenhuis.nl

17. Diakonessenhuis, Utrecht, the Netherlands
Dr. T. Oostergo, researchoncologie@diakhuis.nl

18. Ziekenhuis St Jansdal, Harderwijk, the Netherlands
Dr. J.A. Ropela, ja.ropela@stjansdal.nl

19. Admiraal de Ruijter Ziekenhuis, Goes, the Netherlands
Dr. H. van Halteren, hk.vanhalteren@adrz.nl

20. Medisch Centrum Leeuwarden, the Netherlands
J.A.J. Douma, joeri.douma@mcl.nl

21. Noordwest Ziekenhuisgroep, Alkmaar, the Netherlands
Dr. I.Hermsen, igc.hermsen@nwz.nl

22. Amsterdam UMC, Amsterdam, the Netherlands
Dr. K. Versteeg, k.versteeg@amsterdamumc.nl

23. Spaarne Gasthuis, Hoofddorp, the Netherlands
Dr. J.G. Schrama, JSchrama@spaarnegasthuis.nl

24. Tergooi MC, Hilversum, the Netherlands
A.M.T. van der Velden, avandervelden@tergooi.nl

25. Haaglanden Medisch Centrum, The Hague, the Netherlands
Dr. A. Jochems, a.jochems@haaglandenmc.nl

26. Rivas Beatrixziekenhuis, Gorinchem, the Netherlands
Dr. M.A. Davidis, m.davidis@rivas.nl

27. Ommelander Ziekenhuis Groningen, Scheemda, the Netherlands
Dr. T. Osinga-Fickweller, t.osinga@ozg.nl

28. Ziekenhuis Amstelland, Amstelveen, the Netherlands
Dr. A. van Zweeden, a.vanzweeden@zha.nl

29. St. Antonius Ziekenhuis, Nieuwegein, the Netherlands
Dr. M. Los, m.los@antoniusziekenhuis.nl

30. Treant, Emmen, the Netherlands
Dr. M. Tent, m.tent@treant.nl

31. Bernhoven, Uden, the Netherlands
Dr. M. Janssen, mar.janssen@bernhoven.nl

32. Alrijne Ziekenhuis, Leiderdorp, the Netherlands
Dr. L. Spierings, leaspierings@alrijne.nl

33. Rijnstate Ziekenhuis, Arnhem, the Netherlands
Dr. I. Werter, iwerter@rijnstate.nl

34. Hagaziekenhuis, The Hague, the Netherlands
Dr. D. Houtsma, d.houtsma@hagaziekenhuis.nl

35. Bravis Ziekenhuis Roosendaal, the Netherlands
Dr. F. Terheggen, f.terheggen@bravis.nl

36. Ziekenhuisgroep Twente, Hengelo, the Netherlands
Dr. R. de Jong – Wever, raziawever@gmail.com

37. Cansius-Wilhemlina Ziekenhuis, Nijmegen, the Netherlands
Dr. J.J.B. Janssen, Johan.janssen@cwz.nl

38. Medisch Spectrum Twente, Enschede, the Netherlands
Dr. A. Wymenga, a.wymenga@mst.nl

39. Isala, Zwolle, the Netherlands
Dr. R. Lugtenberg, r.t.lugtenberg@isala.nl

40. Deventer Ziekenhuis, Deventer, the Netherlands
Dr. L. Kessels, L.Kessels@dz.nl

41. IJsselland Ziekenhuis, Capelle aan den IJssel, the Netherlands
Dr. L. Poppe, lpoppe@ysl.nl

42. Maxima Medisch Centrum, Eindhoven, the Netherlands
Dr. L. Simkens, l.simkens@mmc.nl

43. Meander Medisch Centrum, Amersfoort, the Netherlands
Dr. J. Otten, JMMB.Otten@meandermc.nl

44. Zaans Medisch Centrum, Zaandam, the Netherlands
Dr. A. Conijn, Conijn.A@zaansmc.nl

45. Franciscus, Schiedam, the Netherlands
Dr. D. Mathijssen, d.mathijssen-vanstein@franciscus.nl

Appendix 2: G8-score

	Items	Possible answers (score)
A.	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?	0: severe decrease in food intake 1: moderate decrease in food intake 2: no decrease in food intake
B.	Weight loss during the last 3 months	0: weight loss > 3 kg 1: does not know 2: weight loss between 1 and 3 kgs 3: no weight loss
C.	Mobility	0: bed or chair bound 1: able to get out of bed/chair but does not go out 2: goes out
E.	Neuropsychological problems	0: severe dementia or depression 1: mild dementia or depression 2: no psychological problems
F.	Body Mass Index (BMI)	0: BMI < 19 1: BMI = 19 to BMI < 21 2: BMI = 21 to BMI < 23 3: BMI = 23 and > 23
H.	Takes more than 3 medications per day	0: yes 1: no
I.	In comparison with other people of the same age, how does the patient consider his/her health status?	0: not as good 0.5: does not know 1: as good 2: better
J.	Age	0: >85 1: 80-85 2: <80
	TOTAL SCORE	**0-17**