16 December 2021
EMA/CHMP/2190/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Teysuno

International non-proprietary name: **tegafur / gimeracil / oteracil**

Procedure No. EMEA/H/C/001242/II/0045

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE(s)	Adverse event(s)
5-FU	5-fluorouracil
BID	Twice per day
CapeOX	Capecitabine plus oxaliplatin
CI	Confidence interval
CRC	Colorectal cancer
DPD	Dihydropyrimidine dehydrogenase
ECOG PS	Eastern cooperative oncology group performance status
ETS	Early tumour shrinkage
FOLFIRI	5-FU, leucovorin, irinotecan
FOLFOX	5-FU, leucovorin, oxaliplatin
GI	Gastrointestinal
HFS	Hand-foot syndrome
HR	Hazard ratio
IQR	Interquartile range
IRIS	S-1 plus irinotecan
ITT	Intent to treat
IV	Intravenously
MAH	Marketing authorisation holder
mCRC	Metastatic colorectal cancer
MTD	Maximum tolerated dose
NCI-CTC	National cancer institute common toxicity criteria
OS	Overall survival
PFS	Progression-free survival
QoL	Quality of life
RDI	Relative dose intensity
RECIST	Response evaluation criteria in solid tumours
RR	Response rate
S-1	Teysuno
SOX	S-1 plus oxaliplatin
TNM	Tumour, node, metastasis
TTF	Time to treatment failure
UFT	Oral tegafur and uracil (Uftoral)
WHO	World health organisation

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Nordic Group B.V. submitted to the European Medicines Agency on 13 October 2020 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of metastatic colorectal cancer in adult patients where it is not possible to initiate or continue treatment with another fluoropyrimidine. As a consequence, sections 4.1, 4.2, 4.3, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 10 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/0001/2015 on the granting of a class waiver for the class of pyrimidine- and pyrimidine analogue-containing medicinal products for treatment of (…) **intestinal malignant neoplasms** (…). As Teysuno falls into this category, the need for a PIP and subsequent paediatric studies is waived.

Information relating to orphan market exclusivity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Paula Boudewina van Hennik Co-Rapporteur: N/A

Timetable	**Actual dates**
Submission date	13 October 2020
Start of procedure:	31 October 2020

Timetable	Actual dates
CHMP Co-Rapporteur Assessment Report	22 December 2020
CHMP Rapporteur Assessment Report	22 December 2020
PRAC Rapporteur Assessment Report	4 January 2021
PRAC members comments	6 January 2021
PRAC Outcome	14 January 2021
CHMP members comments	18 January 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 January 2021
Request for supplementary information (RSI)	28 January 2021
CHMP Rapporteur Assessment Report	25 August 2021
CHMP members comments	6 September 2021
Updated CHMP Rapporteur Assessment Report	9 September 2021
Request for supplementary information (RSI)	16 September 2021
CHMP Rapporteur Assessment Report	19 November 2021
CHMP members comments	6 December 2021
Updated CHMP Rapporteur Assessment Report	9 December 2021
Opinion	16 December 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

This application is for patients with metastatic colorectal cancer (mCRC), a common and lethal disease.

Claimed therapeutic indication

Teysuno is indicated in adults as monotherapy or in combination with oxaliplatin or irinotecan, with or without bevacizumab, for the treatment of patients with metastatic colorectal cancer for whom it is not possible to continue treatment with another fluoropyrimidine due to hand-foot syndrome or cardiovascular toxicity that developed in the adjuvant or metastatic setting.

Epidemiology

Based on reports by Globocan colorectal cancer is responsible for 10.2% of all cancers worldwide and for 9.2% of the cancer deaths (Globocan 2018). In Europe, it is the second most frequent cancer causing 13.2% and 12.7% of all cancer cases in men and women, respectively, and a leading cause of death. In terms of absolute numbers, in 2012 there were 447,000 new cases of CRC in Europe with 215,000 deaths and worldwide 1.4 million new cases were reported with 694,000 deaths. Approximately 25% of patients

are diagnosed with metastatic disease (van Cutsem et al., *Annals of Oncology*, 2014; van Cutsem et al., *Annals of Oncology*, 2016; Yoshino et al., *Annals of Oncology*, 2018).

Clinical presentation, diagnosis and stage/prognosis

Colorectal cancer is usually diagnosed after the onset of symptoms, or through screening methods using fecal occult blood testing or colonoscopy. Patients can present themselves with symptoms of local growth of the tumour within the lumen or adjacent structures leading to changes in bowel habits, bleeding, abdominal or rectal pain, or iron deficiency anaemia. Patients can be diagnosed with more acute symptoms of intestinal obstruction, peritonitis, or acute bleeding. Symptomatic colorectal cancer is usually associated with a more advanced disease stage and patients can also experience symptoms from metastatic disease with the most common metastatic sites being regional lymph nodes, liver, lungs, and peritoneum (Macrae et al., Clinical presentation, diagnosis, and staging of colorectal cancer, *UpToDate*, 2020). When colorectal cancer is suspected, this is confirmed by radiological imaging and histology of the primary tumour or metastases. The tumour, node, metastasis (TNM) staging system of the combined American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) is used to stage colorectal cancer (van Cutsem et al., *Annals of Oncology*, 2014).

The median overall survival (OS) for patients with metastatic CRC (mCRC) is around 30 months with a 5-year survival rate of 60% (van Cutsem et al., *Annals of Oncology*, 2016). The reported median OS of 30 months is based on the results of clinical trials. Population-based studies suggest that the survival outside clinical trials is worse with a median OS of approximately 12 months in the total population and 15 months in patients who received systemic therapy (Hamers et al., *International Journal of Cancer*, 2020).

Management

Generally, in the metastatic setting the typical first-line chemotherapy for CRC contains a fluoropyrimidine (intravenous 5-FU or oral capecitabine) used in various combinations and schedules with irinotecan or oxaliplatin. Biologicals (e.g., anti-VEGF and anti-EGFR antibodies) are also indicated for the first-line treatment, unless contraindications exist. Second-line treatment depends on the type of prior therapy administered. Antiangiogenic treatment can be started in bevacizumab naïve patients. After first-line bevacizumab, aflibercept, ramucirumab or EGFR antibodies for patients with *RAS* wild-type (*BRAF* wild-type) tumours are options. According to ESMO guidelines, patients should receive all three available cytotoxic agents (fluoropyrimidine, oxaliplatin and irinotecan) and all targeted treatments (anti-VEGF and, if *RAS* wild-type, anti-EGFR) during the course of the treatment whenever possible, although the optimal sequence is not known. For third-line therapy, cetuximab or panitumumab monotherapy can be considered in *RAS* wild-type and *BRAF* wild-type patients not previously treated with EGFR antibodies. Alternative options are regorafenib and trifluridine/tipiracil (van Cutsem et al., *Annals of Oncology*, 2016).
For specific biomarker-defined subgroups the combination of encorafenib and cetuximab is approved in patients with BRAF V600E mutation who have received prior systemic therapy. The NTRK-inhibitors larotrectinib and entrectinib are approved for patients with NTRK gene fusion positive tumours who have no satisfactory treatment options.
Despite all the new developments, chemotherapy remains the backbone of first-line systemic treatment with fluoropyrimidine as basis. As an alternative to intravenous 5-fluorouracil, the oral fluoropyrimidine capecitabine has been developed. Capecitabine has been shown to be non-inferior compared to intravenous 5-fluorouracil regarding efficacy. The safety profile is different for oral capecitabine versus the intravenous alternatives, with for example higher frequencies of hand-foot syndrome with capecitabine. Hand-foot syndrome is also frequently reported for capecitabine, depending on the regimen

used, in 22-63% of the patients. Diarrhoea is also frequently reported (up to 50%). Cardiotoxicity is reported at lower frequency (1.2%-5.9%) (EPARs, SmPC Xeloda). There is therefore still a need for the development of alternatives of intravenous 5-fluorouracil or capecitabine.

2.1.2. About the product

Teysuno is an oral, fixed-dose combination product comprised of tegafur, a fluoropyrimidine prodrug of 5-fluorouracil (5-FU), and 2 modulators of 5-FU metabolism, gimeracil and oteracil, in a 1:0.4:1 molar ratio (tegafur:gimeracil:oteracil). Teysuno has been designed to provide oral delivery of 5-FU, a pyrimidine analogue antimetabolite antineoplastic agent, while reducing the rate of degradation of 5-FU and its conversion in the gastrointestinal (GI) tract to its toxic phosphorylated metabolite. As a 5-FU prodrug, Teysuno exerts its anti-tumour activity by inhibiting DNA and RNA synthesis after uptake by cancer cells.

Teysuno (25 mg/m2 twice per day [b.i.d.] d1-21 of a 28-day cycle), in combination with cisplatin, has been approved for use in the European Union (EU) for treatment of advanced gastric cancer since 2011.

Of note, oral tegafur has been in use for the treatment of colorectal and other types of cancer for over 30 years in the EU. Tegafur monotherapy is approved in Spain for the treatment of colorectal cancer, gastric cancer, and advanced or recurrent gastrointestinal tumours (including oesophagus and pancreas), metastatic carcinoma of the breast, and treatment of advanced head and neck tumours (stages III and IV). Tegafur is also approved in Hungary, Latvia, and Lithuania. The combination of oral tegafur and uracil (UFT) was approved in the EU in 2000 via the Mutual Recognition Procedure under the brand name Uftoral. Uftoral is indicated for first-line treatment of metastatic colorectal cancer in combination with calcium folinate. UFT is also approved in Bulgaria, Czech Republic, Hungary, Romania, and Slovakia.

Teysuno formulation

Teysuno capsules are immediate release solid oral hard gelatin capsules that contain standard pharmaceutical excipients. Teysuno capsules in 15-mg and 20-mg strengths are currently used for commercialisation in advanced gastric cancer in Europe (Teysuno SmPC). No changes from the marketed product have been made to the formulation described in this application. The different capsules all use a common blend; the strengths are achieved by adjusting the fill weight of the capsules.

The capsule dosage form used in clinical trials has remained unchanged throughout clinical development, and has been produced using the same manufacturing process and at the same scale as that proposed for commercialisation. The proposed commercial dosage form is the same as that used to generate the phase 3 clinical data.

Teysuno capsules (or granules/tablets approved in Japan based on bioequivalence to the capsules) manufactured by Taiho were used in most of the Japanese and Korean studies (Hong et al., 2012; Kim et al., 2014; Yamada et al., 2013; Baba et al., 2017; Yamada et al., 2018; Kim et al., 2015; Yasui et al., 2015; Muro et al., 2010). A generic form of Teysuno licensed in Japan in 2013 and also manufactured by Taiho (and bioequivalent) was used in three Phase 2 Japanese studies (Iwasa et al., 2015; Yamazaki et al., 2015; Kato et al., 2012). Three studies conducted in China were unavailable in PubMed or other online resources and thus, the formulation of Teysuno used in these studies is unknown (Tian et al., J Qihihar Univ Med 2011;32:2580-2; Ning et al., Anhui Med Pharm J

2017;21:1669-72; Zong et al., Medicine 2019;98:30 (e16667)). All of the European studies used the commercially available capsule formulation of Teysuno manufactured by Taiho (Kwakman et al., 2017c; Kwakman et al., 2019; Winther et al., 2019; Punt et al., 2021, in preparation; Kwakman et al., 2017b; Österlund et al., 2021, submitted; Kwakman et al., 2017d; Derksen et al., 2021, in preparation).

Proposed dose

The proposed dose for monotherapy in mCRC is 30 mg/m2 b.i.d. days 1-14 with a one-week pause (± bevacizumab 7.5 mg/kg on day 1) (Kwakman et al., 2017, Österlund et al., 2021 (submitted)). For combination therapy with oxaliplatin (130 mg/m2 day 1) or irinotecan (180 mg/m2 day 1), 25 mg/m2 b.i.d. d1-14 followed by one-week pause (± bevacizumab 7.5 mg/kg on day 1) is recommended (Chung et al., 2011, Österlund et al., 2021 (submitted), Punt et al., 2021 (in preparation), Winther et al., 2019). In frail, elderly patients (≥70 years of age), the recommended dose is 20 mg/m2 b.i.d. on days 1-14 followed by one-week pause, in combination with a reduced dose of oxaliplatin (100 mg/m2 on day 1 of a 3-week cycle) (Winther et al., 2019).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH did not seek scientific advice.

2.1.4. General comments on compliance with GCP

The current application for a new indication is based on literature review. According to the MAH, all studies conducted during the clinical development programme for Teysuno have been conducted in compliance with good clinical practice (GCP) principles. The Japanese studies (Yamada et al., 2013; Baba et al., 2017; Yamada et al., 2018; Muro et al., 2010; Yasui et al., 2015) were conducted in accordance with Japanese ethical guidelines for clinical studies and the ethical principles in the Declaration of Helsinki. The protocols for these studies were approved by the institutional review board or ethics committee in each participating institution. Written informed consent was obtained before patient enrolment.

It needs to be noted that the essential documents of the Japanese guidelines are different from those of the ICH-GCP.

The SOX vs. CapeOX study in Korean patients (Hong et al., 2012; Kim et al., 2014) was conducted in accordance with Korean GCP, in agreement with the Declaration of Helsinki and in keeping with local regulations.

The European studies were all conducted according to GCP guidelines, ethical approval for protocols was obtained and all patients submitted informed consent before admission to the trial as required (Kwakman et al., 2017c; Kwakman et al., 2019; Chung et al., 2011; Winther et al., 2019; Österlund et al., 2021, submitted).

2.2. Non-clinical aspects

Environmental Risk Assessment:

An updated environmental risk assessment has been submitted in this application.

Phase I:

Assessment for Persistence, Bioaccumulation and Toxicity:

According to the guideline, drug substances with a log Kow >4.5 should be screened for persistence, bioaccumulation and toxicity according to the EU Technical Guidance Document (TGD).

The log Kow values for tegafur, gimeracil and oteracil monopotassium salt are <4.5, as detailed in Tables 1.6-2, 1.6-4 and 1.6-6 above. Therefore, an assessment for Persistence, Bioaccumulation and Toxicity (PBT) is not necessary.

Calculations of the Predicted Environmental Concentrations (PEC) for Tegafur, Gimeracil and Oteracil Monopotassium Salt:

In Phase I, the PEC calculation is restricted to the aquatic compartment. The calculation of the PEC in surface water further assumes that the predicted amount used per year is evenly distributed over the year and throughout the geographic area, the sewage system is the main route of entry, there is no biodegradation or retention of the drug substance in the sewage treatment plant (STP) and metabolism in the patient is not taken into account. Thus, a PEC is only calculated for the active entity.

An Fpen default value of 0.01 (1%) is proposed in the guideline. However, if data (reasonably justified market penetration data, e.g. based on published epidemiological data) are available to estimate a more accurate Fpen, this may be used. As shown in this environmental risk assessment, data are available to estimate a more accurate refined Fpen for the use of S-1 15 and 20 mg capsules for the treatment of advanced gastric cancer when given in combination with cisplatin or for treatment of metastatic colorectal cancer in the EU. These published epidemiological data and treatment regimen information have been included below to support Phase I estimation of exposure.

Using values for tegafur, the refined Fpen is calculated as:

$$F_{PEN\text{-}REFINED} = \frac{P_{REGION} \times t_{TREATMENT} \times n_{TREATMENT}}{Nd}$$

$F_{PEN\text{-}REFINED}$ = Refined fraction of a population receiving the active substance during a given time
P_{REGION} = Prevalence for the region with the highest prevalence
$t_{TREATMENT}$ = Duration of one treatment period
$n_{TREATMENT}$ = Number of treatments per year
Nd = Number of days per year

Fpen is refined based on prevalence data for Europe of the separate indications stomach cancer and metastatic colorectal cancer:

Stomach cancer:

Indication	Source	Prevalence	Fpen
stomach cancer	**Ferlay** et al (2020)[1]	0.0108%	0.000108
stomach cancer stage III-IV	**Alberts** et al (2003)[2] (70%)	0.00756%	0.0000756

Fpen is further refined based on treatment regimen:

Stomach cancer stage III-IV refined by treatment regimen

21 consecutive days followed by 7 days rest (1 treatment cycle). This treatment cycle is repeated

every 4 weeks.

21 * 13 / 365 = 0.75

Fpen refined = 0.75 * 0.0000756 = 0.0000567

Colorectal cancer:

colorectal cancer TNM stage IV	**Brouwer** et al (2018)[3] (24%)	0.0122%	0.000122

Colorectal cancer TNM stage IV refined by treatment regimen

14 consecutive days followed by 7 days rest (1 treatment cycle). This treatment cycle is repeated every 3 weeks.

14 * 17.4 / 365 = 0.667

Fpen refined = 0.667 * 0.000122 = 0.0000814

Calculation of PEC

Estimation of PEC surface water in the Phase I assessment is calculated below using the refined Fpen of above for both indications.

$$\text{PEC surface water (mg/mL)} = \frac{\text{DOSEai} \times \text{Fpen}}{\text{WASTWinhab} \times \text{DILUTION}}$$

DOSEai = Maximum daily dose consumed per inhabitant

Fpen = Fraction of market penetration = 0.01 (default value but can be refined)

WASTWinhab = Amount of wastewater per inhabitant per day = 200 L (default value)

DILUTION = Dilution factor = 10 (default value)

The maximum total daily dose of tegafur administered in stomach cancer is 120 mg and in metastatic colorectal cancer is 140 mg.

Stomach cancer stage III-IV refined treatment regimen

Stomach cancer stage III-IV refined treatment regimen

$$PEC_1 \text{ surface water (mg/L)} = \frac{120\ mg * 0.0000567}{200\ L * 10} = 0.000003402 \text{ mg/L} = \underline{0.003402\ \mu g/L}$$

Colorectal cancer TNM stage IV refined treatment regimen

$$PEC_2 \text{ surface water (mg/L)} = \frac{140\ mg * 0.0000814}{200\ L * 10} = 0.000005698 \text{ mg/L} = \underline{0.005698\ \mu g/L}$$

$$PEC_{total} = PEC_1 + PEC_2 = \underline{0.003402} + \underline{0.005698} = \mathbf{0.0091\ \mu g/L}$$

The refined Fpen has been calculated only for tegafur and the PECSURFACEWATER value has been

obtained for tegafur, as shown above. Since S-1 is a Fixed- Combination, this means that PECSURFACEWATER values for gimeracil and oteracil as shown below can be calculated from the PECSURFACEWATER value for tegafur on the basis of the relative fixed amounts in the doses.

PECSURFACEWATER for gimeracil = 0.00264 µg/L

PECSURFACEWATER for oteracil monopotassium salt = 0.00892 µg/L

Action Limit

The PECSURFACEWATER values of 0.0091 µg/L, 0.00264 µg/L and 0.00892 µg/L, for tegafur, gimeracil and oteracil monopotassium salt are lower than the action limit of 0.01 µg/L, respectively.

Therefore, it is concluded that S-1 15 and 20 mg capsules will not represent a risk to the environment following its prescribed usage in patients treated for advanced gastric cancer or metastatic colorectal cancer when given in combination with cisplatin in the EU. A Phase II analysis is not applicable in view of the extremely low environmental exposures to tegafur, gimeracil and oteracil monopotassium salt.

2.2.1. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of tegafur, gimeracil and oteracil.

Considering the above data, tegafur, gimeracil and oteracil should be used according to the precautions stated in the SmPC in order to minimize any potential risks to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The current application for a new indication is based on literature review. Please refer to section 5.1.4 for more information regarding GCP.

- Tabular overview of clinical studies

The efficacy and safety studies supporting the proposed indication are published manuscripts and summarised in Table 1.

Table 1. Overview of clinical studies

First author	Study design	Study population	Investigational arm	Control arm	Supportive for
Derksen, 2021, *in preparation*	Meta-analysis	Phase 2/3 studies in mCRC in Asian or Western patients	S-1 monotherapy or in combination with oxaliplatin or irinotecan, ± bevacizumab	Capecitabine or 5-FU monotherapy or in combination with oxaliplatin or irinotecan, ± bevacizumab	Efficacy

Kwakman, 2017 Kwakman, 2019	Randomised phase 3	Western patients with previously untreated mCRC	S-1 (bevacizumab optional)	Capecitabine (bevacizumab optional)	Efficacy and Safety
Hong, 2012 Kim, 2014	Randomised phase 3	First-line mCRC South Korea	S-1 plus oxaliplatin	Capecitabine plus oxaliplatin	Efficacy and Safety
Yamada, 2013 Baba, 2017	Randomised phase 3	First-line mCRC Japan	S-1 plus oxaliplatin/bevacizumab	mFOLFOX6/bevacizumab	Efficacy and Safety
Yamada, 2018	Randomised phase 3	First-line mCRC Japan	S-1 plus irinotecan/bevacizumab	mFOLFOX6/bevacizumab or capecitabine plus oxaliplatin/bevacizumab	Efficacy and Safety
Muro, 2010 Yasui, 2015	Randomised phase 3	Second-line mCRC Japan	S-1 plus irinotecan/bevacizumab	FOLFIRI	Efficacy and Safety
Chung, 2011	Phase 1	Solid tumours European/Caucasian population	S-1 plus oxaliplatin/bevacizumab	Not applicable	Efficacy
Winther, 2019	Randomised phase 2	Older (>70 years of age), vulnerable patients with mCRC	S-1 monotherapy	Reduced dose S-1 plus oxaliplatin	Efficacy and Safety
Punt, 2021, *in preparation*	Retrospective	European patients with mCRC	S-1 monotherapy or in combination	Not applicable	Safety, switch after HFS or cardiotoxicity
Kwakman, 2017	Retrospective case series	Solid tumours European/Caucasian population	S-1 monotherapy or in combination	Not applicable	Safety, switch after cardiotoxicity
Osterlund, 2021,	Retrospective study	Solid tumours European/Caucasian population	S-1 monotherapy or in combination	Not applicable	Safety, switch after

submitted					cardiotoxicity
Kwakman, 2017	Retrospective study	Gastrointestinal tumours European/ Caucasian population	S-1 monotherapy or in combination	Not applicable	Safety, switch after HFS

2.3.2. Pharmacokinetics

Introduction

Teysuno is an oral combination of three active substances, tegafur (FT), gimeracil (CDHP), and oteracil (Oxo). After absorption, tegafur is converted by the liver into 5-fluorouracil (5-FU). Gimeracil and oteracil are included to reduce the metabolism of 5-FU thereby improving the bioavailability of 5-FU and reducing the toxic effects of its metabolites. Each hard capsule contains 15 mg tegafur, 4.35 mg gimeracil and 11.8 mg oteracil (as monopotassium).

Teysuno (25 mg/m^2) is currently approved for the treatment of advanced gastric cancer when given in combination with cisplatin (75 mg/m^2). This type II variation is to include the additional indication for Teysuno (30 mg/m2) given in combination with cisplatin (75 mg/m2) in patients with metastatic colorectal cancer.

The dosage for Teysuno in patients with advanced gastric cancer is as follows:

The recommended standard dose of Teysuno when administered in combination with cisplatin is 25 mg/m2 (expressed as tegafur content) twice daily, morning and evening, for 21 consecutive days followed by 7 days rest (1 treatment cycle). This treatment cycle is repeated every 4 weeks.

The dosage for Teysuno patients with metastatic colorectal cancer is proposed as follows:

The proposed dose in mCRC is 30 mg/m2 b.i.d. days 1-14 with a one-week pause (± bevacizumab 7.5 mg/kg on day 1). For combination therapy, 25 mg/m2 b.i.d. d1-14 followed by one-week pause is recommended.

To support this type II variation an overview of pharmacokinetic data in literature were provided of Teysuno.

Pharmacokinetics in patients

Pharmacokinetic results with the proposed dosage as presented in the overview provided by Zhang et al (2007):

Table 3 Pharmacokinetic parameters after a single oral dose of S-1

PK parameter	Zhu[a] $AUC_{(0-8)}$		Hoff[b] $AUC_{(0-\infty)}$		Ajani[c] $AUC_{(0-12)}$		Zhu[a] $AUC_{(0-8)}$		Hoff[b] $AUC_{(0-\infty)}$		Van Groeningen[d]		Hirata[e]	
	30 mg/m² $n = 13$		30 mg/m² $n = 7$		30 mg/m² $n = 6$		35 mg/m² $n = 3$		35 mg/m² $n = 4$		35 mg/m² $n = 5$		35.9 mg/m² Range (32–40 mg/m²) $n = 12$	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
5-FU														
C_{max} (ng/ml)	168	43	144	19.5	158	29	156	32	176	21.9	179.5[f]	32.5	128.5	41.5
AUC (ng h/ml)	875	211	782	135.9	872	137	894	151	1,004	56.7	1,133.0[f]	331.3	723.9	272.7
T_{max} (h)	2.5	1.0	2.6	0.98	–	–	2.7	1.2	2.5	1.0	2.85	1.1	3.5	1.7
FT														
C_{max} (ng/ml)	1,503	617	1,426	304.3	1,430	567	2,507	490	1,943	365.2	–	–	1,971	269
AUC (ng h/ml)	6,621	1,048	13,653	2,250.1	7,367	1,417	10,322	612	18,863	2,189.8	18,427.3[f]	7,577	28,216.9	7,771.4
T_{max} (h)	1.5	1.3	1.79	1.150	–	–	0.7	0.3	1.75	0.5	–	–	2.4	1.2
CDHP														
C_{max} (ng/ml)	309	133	298	79.1	328	145	539	66	398	196.3	–	–	284.6	116.6
AUC (ng h/ml)	1,163	376	1,583	459.7	1,168	183	1,898	206	1,784	590.6	1,562.5[f]	443	1,372.2	573.7
T_{max} (h)	1.9	1.1	1.57	0.535	–	–	1.3	0.6	2.25	1.258	–	–	2.1	1.2
Oxo														
C_{max} (ng/ml)	80	86	57.8	60.31	126	24	69	57	42.9	28.51	–	–	78.0	582
AUC (ng h/ml)	255	194	232	206.0	533	204	280	246	206	227.6	347.7[f]	219	365.7	248.6
T_{max} (h)	2.1	1.2	1.79	1.150	–	–	1.7	0.6	2.50	1.00	–	–	2.3	1.1
FBAL														
C_{max} (ng/ml)	82	21	–	–	–	–	65	19	–	–	–	–	–	
AUC (ng h/ml)	451	140	–	–	–	–	346	169	–	–	–	–	–	
T_{max} (h)	6.5	1.9	–	–	–	–	7.4	1.2	–	–	–	–	–	
Uracil														
C_{max} (ng/ml)	891	188	764	166	–	–	1,035	118	924	141	–	–	890	259
AUC (ng h/ml)	4,751	1,168	8,408	2,821	–	–	5,585	285	9,828	2,424	–	–	8,483	3,859
T_{max} (h)	5.4	1.3	6.3	2.1	–	–	6.7	1.2	6.0	2.3	–	–	5.3	1.8

[r] The last measurable plasma concentration

FT and CDHP: $AUC_{(0-48)}$; 5-FU: $AUC_{(0-14)}$; Oxo: $AUC_{(0-24)}$

[a] S-1 was administered 1 h before or at least 1 h after a meal. Data from the present study

[b] S-1 was administered within 1 h after a meal. Data from Hoff et al. [12]

[c] S-1 was administered 1 h before or after a meal. Data from Ajani et al. [1]

[d] S-1 was administered within 1 h after a meal. Data from Van Groeningen et al. [38]

[e] S-1 administered within 30 min following a meal. FT and CDHP: $AUC_{(0-48)}$; 5-FU: $AUC_{(0-14)}$; Oxo: $AUC_{(0-24)}$. Data from Hirata et al. [11]

[f] Units converted from original publication by Ajani et al. [1]

Renal function

In a Phase 1 study designed to determine the effect of renal function on the pharmacokinetics of Teysuno components and metabolites (Study S1111), patients with normal renal function (creatinine clearance [CrCl] >80 mL/min) and those with mild renal impairment (CrCl 51 to 80 mL/min) received Teysuno 30 mg/m2 b.i.d., while patients with moderate renal impairment (CrCl 30 to 50 mL/min) received a reduced

Teysuno dose of 20 mg/m2 b.i.d. The results showed an increase in mean 5-FU AUC0-inf in the mild renal impairment group compared to the normal group receiving the same dose, while there was no increase in mean 5-FU AUC0-inf in the moderate renal impairment group (receiving 20 mg/m2 BID) relative to that of the normal group (receiving 30 mg/m2 b.i.d.). These results suggest that a dose reduction to 20 mg/m2 is warranted in patients with moderate renal impairment in order to obtain 5-FU plasma concentrations similar to that obtained in patients with normal renal function receiving 30 mg/m2. For patients with mild renal impairment, the results suggest that a dose reduction to 25 mg/m2 Teysuno may be needed to achieve 5-FU plasma concentrations similar to those obtained in patients with normal renal function receiving 30 mg/m2.

Hepatic Function

No dose adjustment is recommended for patients with hepatic impairment. There were no significant differences in AUCs of 5-FU, tegafur, gimeracil, or oteracil after either single or multiple dose administration of Teysuno 30 mg/m2 b.i.d. in patients with mild, moderate, or severe impairment compared to those with normal hepatic function (Study S1112). After single dose administration, there was a statistically significant decrease in 5-FU and gimeracil Cmax values for the severe hepatic impairment group relative to that of the normal group, but this difference was not observed after multiple dose administration.

Ethnic differences in pharmacokinetics

Teysuno has mainly been administered to Asian patients, who have a markedly different tolerability of Teysuno compared with Western populations and in whom the standard dose used in trials in mCRC patients was 40 mg/m2 b.i.d. (Yamada et al., 2013; Baba et al., 2017; Hong et al., 2012; Kim et al., 2014; Yamada et al., 2018; Muro et al., 2010; Yasui et al., 2015). Differences in tolerability of fluoropyrimidines in different ethnic populations have previously been observed but the basis for these differences is unknown (Haller et al., 2008; Shirao et al., 2004). In Western patients, the maximum tolerated dose for Teysuno as monotherapy has been established in a Phase 1 study at 30 mg/m2 twice daily, dose-limiting toxicities occurred at dose levels of 35 mg/m2 twice a day (Zhu et al., 2007). On the basis of these findings, 30 mg/m2 twice daily is recommended as the starting dose for future studies in Western patients.

2.3.1. Pharmacodynamics

No pharmacodynamic data were provided.

2.3.2. PK/PD modelling

No PK/PD modelling was provided.

2.3.3. Discussion on clinical pharmacology

No new PK data was provided in support of this type II variation. Information on the 30 mg/m^2 dose was already available in the original dossier, and was confirmed by a published overview article by Zhang et al (2007). Presented data supported the original pharmacokinetic data with Teysuno in advanced gastric cancer. With regard to the intrinsic factors there is an increase in 5-FU steady state exposure in patients with renal impairment. The effects of other intrinsic factors, including age, were generally small with a minimal impact on 5-FU AUC. Pharmacokinetics were not found to be different between ethnic groups to a clinically relevant extent. It is agreed that the probably the reason for different recommended doses of TesyunoS-1 between Western and Japanese patients is the ethnic differences in 5-FU tolerability rather than the difference in pharmacokinetics. This trend is also observed for other fluoropyrimidine

chemotherapies. With regard to extrinsic factors, food has a small influence on the bioavailability of oteracil (32% decrease with food).

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

The results of a phase 1 study to determine the schedule of a combination of S-1 with oxaliplatin and bevacizumab in a Caucasian population with advanced or metastatic solid tumours for which no established standard therapy exists (Chung et al., 2011) are used by the MAH to support the indication. The results will be discussed in the section "Main studies".

2.4.2. Main studies

The MAH based the support for the indication in colorectal cancer on published articles which were summarised in the clinical overview. In the efficacy part below, the MAH's summary of each publication will be reported. In response to the D120 LoQ, the MAH included the more detailed results as published by the primary articles from the Rapporteur's comment boxes in the clinical overview. The comment boxes are, therefore, included in the text of the assessment report. A critical assessment of the provided literature will be discussed in the clinical efficacy discussion.

In response to the D120 LoQ, the MAH performed a new meta-analysis of efficacy in all phase 2 and 3 studies of Teysuno-based regimens compared to 5-FU- and capecitabine-based regimens in mCRC, which will be discussed first (Derksen et al., 2021, *in preparation*), followed by the separate articles. Lastly, exploratory efficacy results from two additional studies will be discussed that were performed in European patients who switched to S-1 based therapy due to toxicity on other fluoropyrimidine-based therapy.

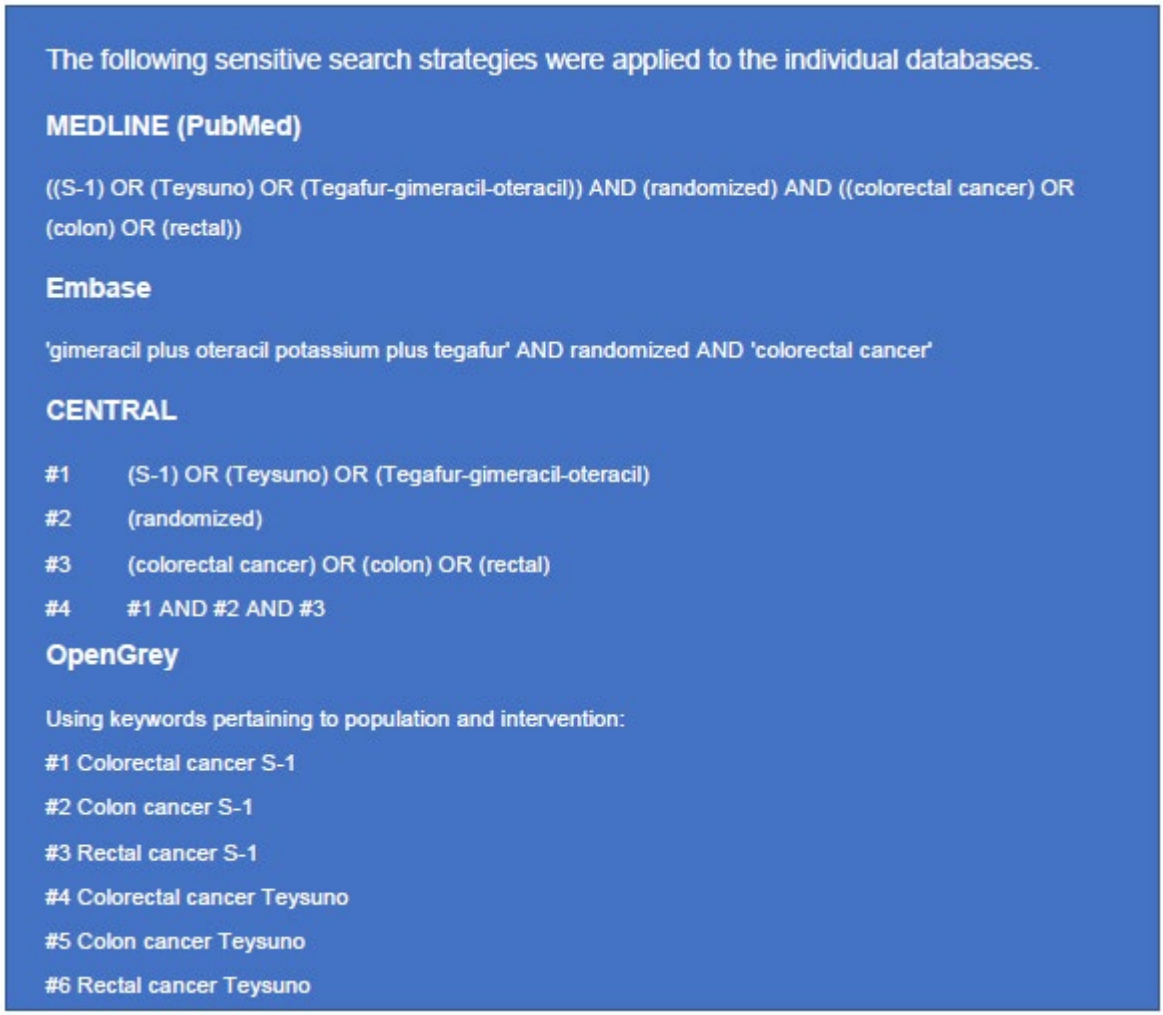
Systematic review and meta-analysis on the non-inferiority of S-1 containing regimens versus 5-FU/capecitabine-containing regimens in the treatment of patients with metastatic colorectal cancer

Methods

- **Literature search**

For the searching of the electronic scientific databases, i.e. MEDLINE (PubMed), Embase and Cochrane Central Register of Controlled Trials (CENTRAL), a sensitive search strategy without date restriction was applied using medical subject headings pertaining to the study design, population, and intervention relevant to this review. In addition, grey literature was searched for using OpenGrey; an online database containing bibliographical references of grey literature in Europe. Reference lists of review papers included in our search results were screened for potentially relevant publications. When publications could not be retrieved online, but contact information was provided, authors were contacted. The full search strategies for all utilized databased are provided in Figure 1. For this systematic review the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement was considered.

Figure 1. Full search strategy



- **Inclusion criteria**

Studies had to meet the following eligibility criteria: (1) patients with age >18 years; (2) histologically proved colorectal cancer with distant metastases (mCRC); (3) palliative S-1 based (mono or combination) therapy, compared with Fluorouracil (5-FU)- or Capecitabine-based (mono or combination) therapy (5FU/Cap); and (4) prospective phase II or phase III randomized clinical trials.

- **Statistical analysis**

The primary outcome was progression free survival (PFS), secondary outcomes were overall survival (OS) and objective response rate (ORR). For the time-to-event outcomes, PFS and OS, hazard ratios (HRs) with their 95% confidence intervals (CIs) and - to support our main meta-analysis results - median survival and time to progression with corresponding p-values were extracted from the individual studies. Analyses were based on the intention-to-treat population of the included studies with PFS and OS data. Pooled HRs are provided for the total population of mCRC patients, and per subgroup of treatment line, including 99% CIs. When treatment arms of individual studies compared 5FU or capecitabine with S-1, using the same combination therapy, a direct evaluation of 5FU/Cap-based therapy vs. S-1 based therapy in this meta-analysis is justified. Sensitivity analyses were performed by comparing the observed overall effect estimate to the estimate when studies with a divergent design were omitted. The aim of this meta-analysis is to show that the effect of S-1 based therapy is not inferior to the effect of 5FU/Cap-

based therapy by a specified amount, called the non-inferiority margin (ΔNI). Here, a pre-defined ΔNI of 1.25 for PFS was selected based on the trial with the most conservative ΔNI in this review, i.e. Yamada, 2018 [3]. Thus, non-inferiority of S-1 based therapy relative to 5FU/Cap-based therapy is established when the upper limit of the 99% CI of the pooled HR_{total} remains <1.25.

Data for our meta-analysis on the ORR were extracted from the primary publications of studies included in this review. From these publications we extracted the number of patients with a complete or partial response and divided this by the total number of patients with evaluable lesions for response analysis. Then, risk ratios (RRs) and 99% CIs were calculated.

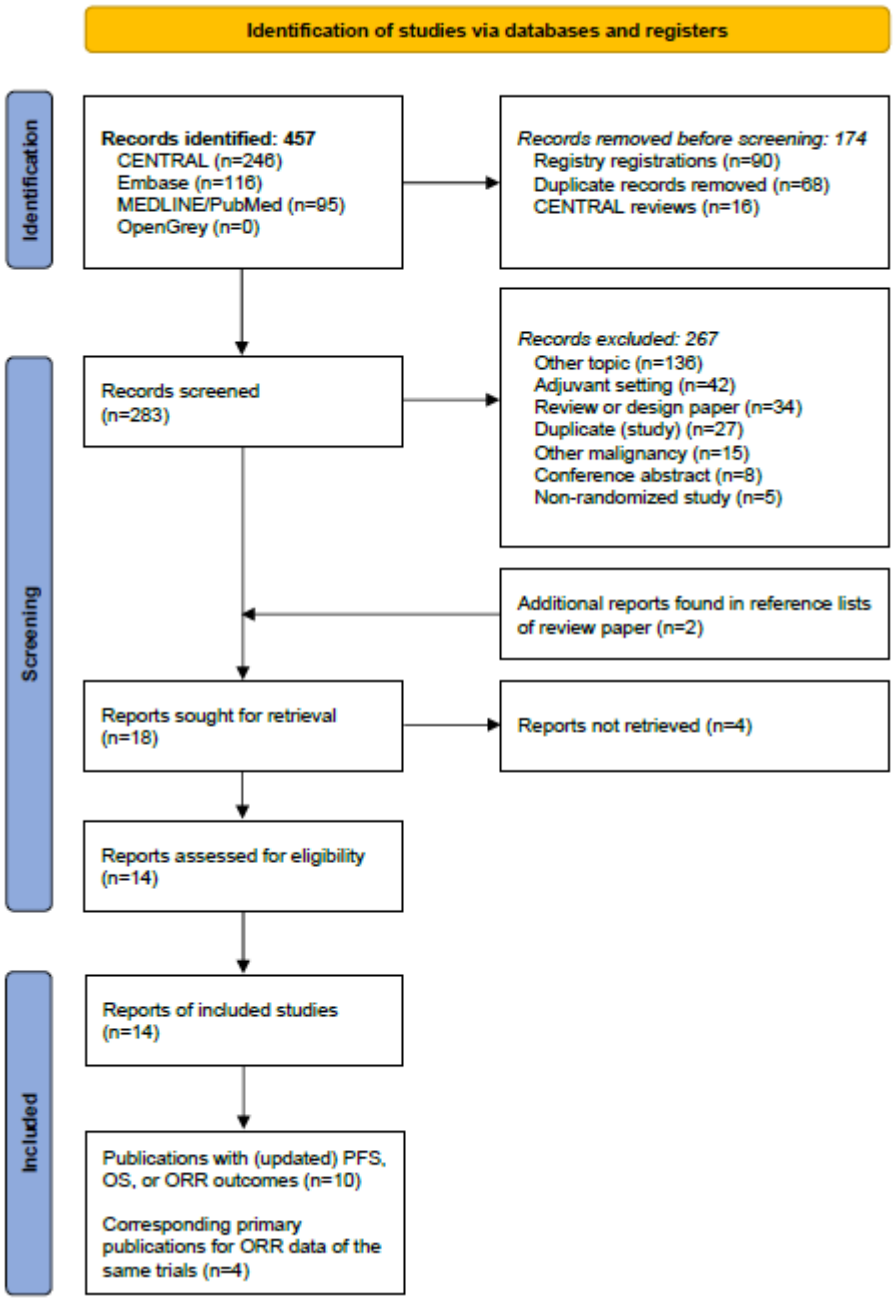
Meta-analyses of all outcomes mentioned above were conducted in Review Manager 5.4, using random-effect models with generic inverse-variance weighing to minimize the imprecision of the pooled effect estimate. All tests were two-sided, and heterogeneity was assessed by the Cochran Q-test and quantified by the I^2 index.

Results

- **Literature search**

The PRISMA flowchart with a complete overview of the systematic search can be found in Figure 2.

Figure 2. PRISMA flow chart



A total of four hundred and fifty-seven unique references were identified through our sensitive systematic search in MEDLINE, Embase, CENTRAL, and OpenGrey until May 21, 2021, of which 174 review, registry registration, or duplicate references were removed, leaving 283 references for title and abstract screening (for full list and decisions, please see Appendix Table A3 Derksen et al., 2021, Meta-analysis appendix file). Eligibility screening based on title and abstract led to the exclusion of 267 references. Two additional potentially relevant publications were found in one of the retrieved review articles. In total, 18 publications were sought for retrieval, of which four publications - after contacting two authors - could not be obtained (Table 2). The remaining 14 publications were assessed for eligibility. Ten publications with (updated) PFS, OS or ORR outcomes were included [1-10], and for the analysis on ORR, four corresponding primary publications of the same trials were included [11-14].

Table 2. Publications not obtained

Authors	Title	Year	Journal	Authors contacted
J. Ning *et al.*	Efficacy and safety of s-1 and oxaliplatin (sox) as first-line chemotherapy for metastatic colorectal cancer	2017	Anhui Med Pharm J	Yes
S. Tian *et al.*	Clinical assessment of efficacy and safety of irinotecan combined with s-1 as second line treatment in patients with metastatic colorectal cancer	2011	J Qiqihar Univ Med	Yes
D. Zhou *et al.*	Clinical Study on S-1 plus Irinotecan in the Treatment of FOLFOX-resistant Advanced Colorectal Cancer	2014	Medicine	No
M. Zong *et al.*	Comparison of clinical effectiveness of oxaliplatin plus capecitabine vs oxaliplatin plus S-1 in treatment of advanced colorectal cancer	2018	Tumor	No

There were no major differences in study and patient characteristics among the studies included (Table 3). Two studies with a noticeable difference in study design include the publication by Yamada et al. [3], and Kato et al. [8]. First, in the study by Yamada et al., a different combination therapy was used in the two arms, i.e. S-1 + irinotecan and bevacizumab in the intervention arm vs. 5FU + oxaliplatin and bevacizumab, or capecitabine + oxaliplatin and bevacizumab in the control arm. Based on the recent meta-analysis by Kawai et al. [15] that showed no significant difference in irinotecan- and oxaliplatin-based first-line therapies for mCRC, a direct comparison of S-1 based vs. 5FU/Cap-based therapy was justified. Second, in the study by Kato et al., patients were treated in both first-line and second-line [8]. Since the majority of patients in this study were treated in first-line setting (78%), and no significant bias between the two groups was observed according to the authors, this reference was considered a first-line study in the current meta-analysis.

Table 3. Study and baseline characteristics of included studies

Study	Phase	Line	Design	ΔNI	Primary endpoint	Region	Center	Enrolment period	Arm	N (ITT)	Men	Median age (range)	ECOG PS ≥2	≥2nd line	Median no. of cycles
Kim *et al.* 2014 [1]	III	First	NI	1.43	PFS	Korea	Multicenter	May 2008 Sept 2009	Cap + Ox	172	102 (59%)	126 (73%) ≤65 years	4 (2%)	NR	Cap: 6 (5-9) Ox: 6 (5-9)
Primary publication: Hong *et al.* 2012 [11]									S-1 + Ox	168	109 (65%)	121 (72%) ≤65 years	4 (2%)	NR	S-1: 9 (5-10.5) Ox: 8 (4.5-9)
Baba *et al.* 2017 [2]	III	First	NI	1.33	PFS	Japan	Multicenter	Feb 2009 Mar 2011	mFOLFOX6 + Beva	255	159 (62%)	63 (39–79)	0	203 (80.2%)	12 (range 1-97+)
Primary publication: Yamada *et al.* 2013 [12]									S-1 + Ox + Beva	256	170 (66%)	63 (33–79)	0	209 (81.6%)	8 (range 1-58)
Yamada *et al.* 2018 [3]	III	First	NI	1.25	PFS	Japan	Multicenter	June 2012 Sept 2014	mFOLFOX6 + Beva or Cap + Ox + Beva	243	143 (58.8%)	65 (29–85)	0	206 (87.7%)	NR
									S-1 + IRI + Beva	241	151 (62.7%)	64 (22–87)	0	198 (87.6%)	NR
Kwakman *et al.* 2019 [4]	III	First	SU	NR	HFS incidence	Netherlands	Multicenter	Jan 2014 July 2015	Cap (+/- Beva)	81	56 (69%)	73 (66–78)	8 (10%)*	40 (49%)	8 (IQR 4-12)
Primary publication: Kwakman *et al.* 2017 [13]									S-1 (+/- Beva)	80	45 (56%)	74 (68–79)	8 (10%)*	41 (51%)	9 (IQR 3-13)
Kim *et al.* 2015 [5]	II	First	Efficacy and safety	NR	Response Rate	South Korea	Multicenter	Apr 2008 Aug 2011	Cap + Ox	44	27 (61.4%)	66 (29-76)	1 (2.3%)	30 (68.2%)	5 (range 1-19)
									S-1 + Ox	42	28 (66.7%)	67 (46-83)	2 (4.8%)	28 (66.7%)	6 (range 1-39)
Yamazaki *et al.* 2015 [6]	II	First	Efficacy and safety	NR	PFS	Japan	Multicenter	July 2008 July 2009	mFOLFOX6	49	23 (46.9%)	61.0 (27-76)	0	45 (91.8%)	11 (range 1-69)
									S-1 + Ox + LV	56	33 (58.9%)	60.5 (27-77)	0	56 (100%)	12 (range 1-63)
Sadahiro *et al.* 2020 [7]	II	First	Efficacy and safety	NR	1-y PFS	Japan	Monocenter	Dec 2013 Jan 2018	FOLFIRI + Beva	59	28 (59.6%)	64 (38–83)	0	NR	15 (range 2-44)
									S-1 + IRI + Beva	61	33 (64.7%)	65 (23–79)	0	NR	17 (range 4-58)
Kato *et al.* 2012 [8]	II	First †	Efficacy and safety	NR	Safety (AE)	Japan	Multicenter	Nov 2007 Feb 2010	mFOLFIRI + Beva	30	18 (60%)	62.5 (46-77)	0	NA	NR
									S-1 + IRI + Beva	30	17 (57%)	62 (31-73)	0	NA	NR
Yasui *et al.* 2015 [9]	III	Second	NI	1.333	PFS	Japan	Multicenter	Jan 2006 Jan 2008	FOLFIRI	213	123 (57.7%)	63 (32–75)	0	168 (78.9%)	4 (range 1-27)
Primary publication: Muro *et al.* 2010 [14]									S-1 + IRI	213	120 (56.3%)	61 (29–75)	0	153 (71.8%)	4 (range 1-23)
Liu *et al.* 2015 [10]	II	Second	Efficacy and safety	NR	Response Rate	China	Monocenter	Oct 2009 Oct 2011	Cap + Ox	35	20 (57.1%)	60 (37-70)	0	NR	NR, at least 2
									S-1 + Ox	35	19 (54.3%)	60 (35-72)	0	NR	NR, at least 2

ITT, intention-to-treat; PS, performance status; ΔNI, non-inferiority margin; SU, superiority; PFS, progression-free survival; AE, adverse event; NR, not reported; NA, not applicable; IQR interquartile range. * WHO PS 2. † incl. n=13 (22%) patients treated as second-line.

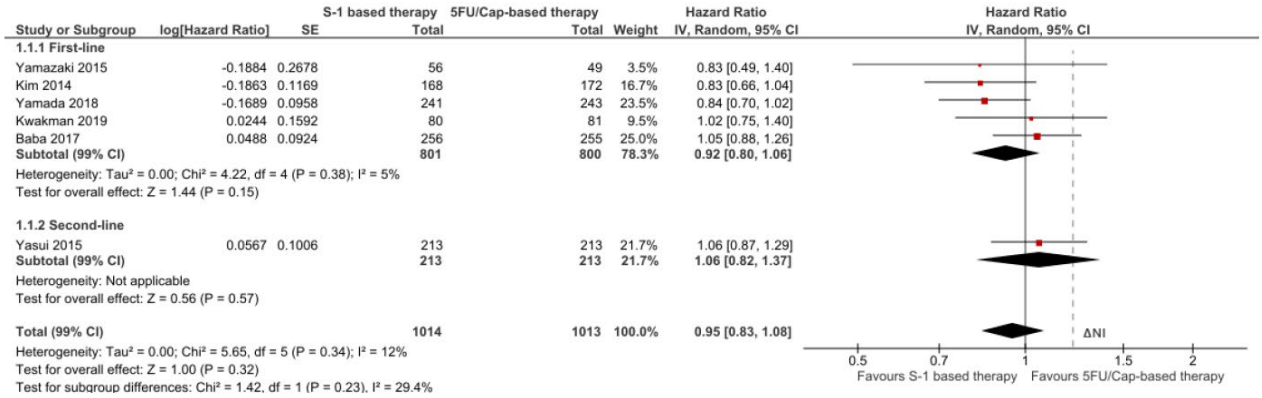
- **Efficacy of S-1 based therapy versus 5FU/Cap-based therapy**

Ten studies (n=2,117) were included in the meta-analysis; 1,062 patients received S-1 based therapy and 1,055 patients received 5FU/Cap-based therapy. Nine studies were conducted in Asia, and one study was conducted in Europe. We were able to extract HRs for PFS and OS from six studies [1-4,6,9], whereas ORR data were available from 10 studies [3,5-8,10-14].

Progression-free survival

As the upper limit of the 99%CI of the HR_{total} for PFS does not reach the predefined ΔNI of 1.25, it was shown that S-1 based therapy is non-inferior to 5FU/Cap-based therapy, in the treatment of mCRC (HR_{total} 0.95, 99%CI 0.83–1.08) (Figure 3). When stratified by treatment line, a pooled $HR_{subgroup}$ of 0.92 (99%CI 0.80–1.06) was observed for first-line treatment, and a $HR_{subgroup}$ of 1.06 (99%CI 0.82–1.37) for second-line treatment. No significant heterogeneity was detected for PFS (I^2 = 12%, P = 0.34).

Figure 3. Forest plot for the comparison S-1 based therapy vs. 5FU/Cap based therapy, outcome PFS



S-1, oral anticancer drug composed of tegafur (FT), 5-chloro-2, 4-dihydroxypyridine (gimestat [CDHP]) and oteracil potassium (Oxo); 5FU, 5-fluorouracil; Cap, capecitabine; SE, standard error; IV, inverse variance; CI, confidence interval; ΔNI, non-inferiority margin; PFS, progression-free survival.

Sensitivity analysis showed that the direction of the estimator of the HRs for PFS and non-inferiority were not influenced by omission of the study by Yamada et al. [3] that used a different combination therapy in the intervention and control arm.

In addition, median PFS (months) per arm was reported by four other studies; three first-line studies [5,7,8] and one second-line study [10]. An overview of studies and median PFS data are presented in Table 4. Except for the study by Kim et al. [5], which reported a median time to progression of 7.4 months for the control arm vs. 6.1 months for the S-1 based arm, the other three studies reported a numerically longer time to progression in the S-1 based arm, with an increase ranging from 0.2 to 0.7 months [7,8,10]. All four studies reported no statistically significant difference in PFS between 5FU/Cap based vs. S-1 based therapy (P > 0.05).

Table 4. Results of included studies only reporting median PFS and/or median OS

Study	Arm	Median PFS (months)	P value PFS	Median OS (months)	P value OS
Kim *et al.* 2015 [5]	Cap + Ox	7.4	P = 0. 599	20.1	P = 0.340
	S-1 + Ox	6.1		18.7	
Sadahiro *et al.* 2020 [7]	FOLFIRI + Beva	10.0	P = 0.375	28.8	P = 0.823
	S-1 + IRI + Beva	10.2		29.7	
Kato *et al.* 2012 [8] †	Cap + Ox	10.6	P = 0.71	NR	NR
	S-1 + Ox	11.3		NR	
Liu *et al.* 2015 [10]	mFOLFIRI + Beva	8.2	P > 0.05	19.2	P > 0.05
	S-1 + IRI + Beva	8.5		18.8	

PFS, progression-free survival; NR, not reported; † incl. n=13 (22%) patients treated as second-line.

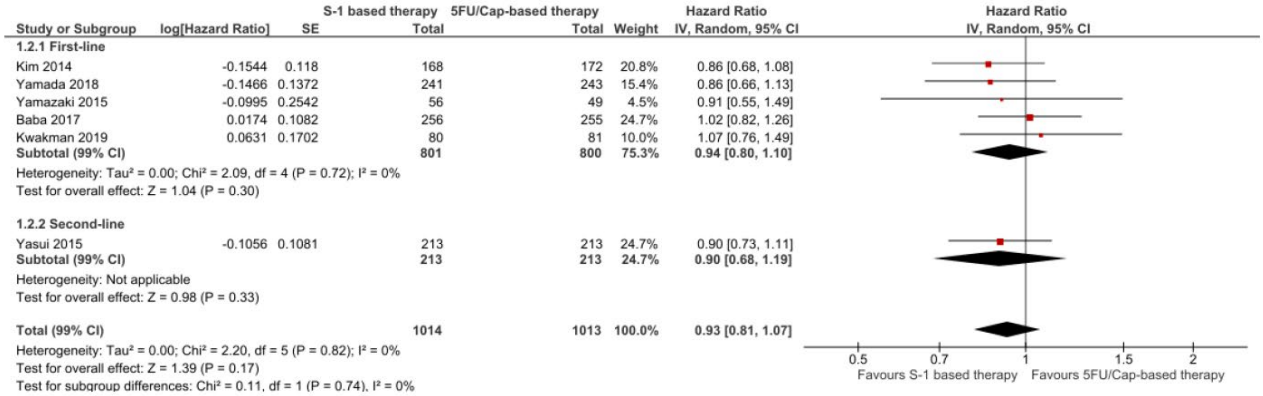
Note that, based on literature, we selected a slightly less stringent non-inferiority margin as compared to the previously used margin of 1.23 for the approval of capecitabine (Xeloda). However, to increase preciseness of our meta-analysis results the pooled HRs are presented with corresponding 99% CIs, and

the HRtotal for PFS - with an upper limit of 1.08 – also remains below the previously used margin of 1.23.

Overall survival

Although the endpoint OS was a secondary outcome in all of the included studies, the current results indicate that S-1 based therapy is at least as effective as 5FU/Cap-based therapy in terms of OS (HR_{total} 0.93, 99%CI 0.81–1.07) (Figure 4). When stratified by treatment line, a pooled $HR_{subgroup}$ of 0.94 (99%CI 0.80–1.10) was observed for first-line treatment, and a $HR_{subgroup}$ of 0.90 (99%CI 0.68–1.19) for second-line treatment. No significant heterogeneity was detected for OS (I^2 = 0%, P = 0.82).

Figure 4. Forest plot for the comparison S-1 based therapy vs. 5FU/Cap based therapy, outcome OS



S-1, oral anticancer drug composed of tegafur (FT), 5-chloro-2, 4-dihydroxypyridine (gimestat [CDHP]) and oteracil potassium (Oxo); 5FU, 5-fluorouracil; Cap, capecitabine; SE, standard error; IV, inverse variance; CI, confidence interval; OS, overall survival.

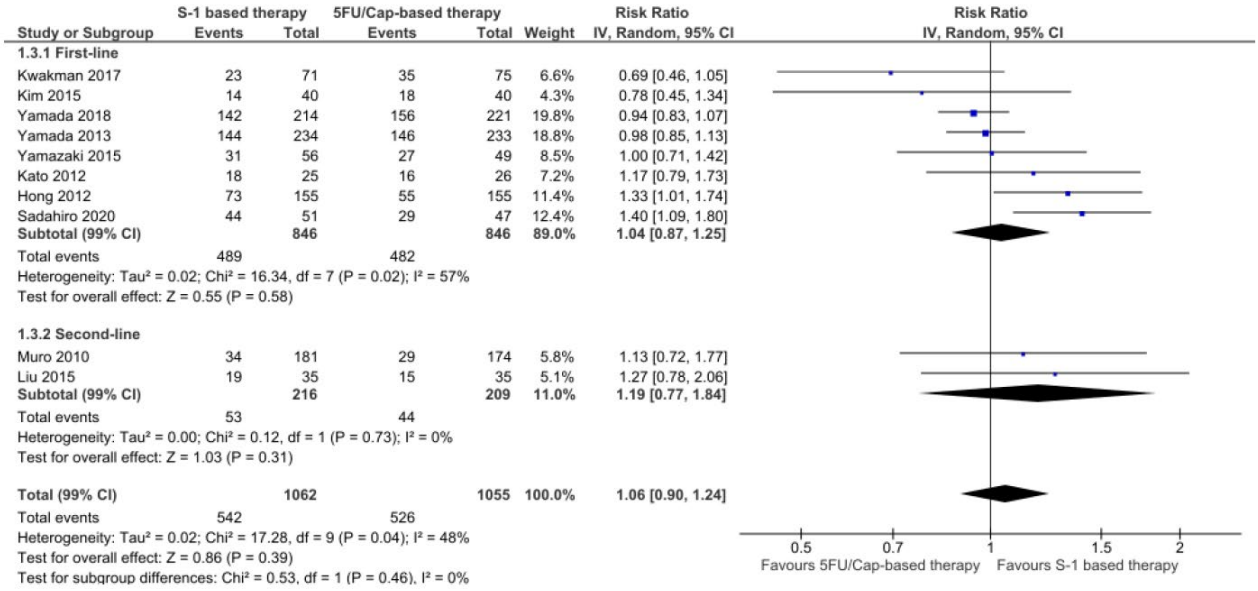
Sensitivity analysis showed that the direction of the estimator of the HRs for OS and its significance were both not influenced by omission of the study by Yamada et al. [3] that used a different combination therapy in the intervention and control arm.

In addition, median OS (months) per arm was reported by three other studies; two first-line studies [5,7] and one second-line study [10]. An overview of studies and median OS data are presented in Table 4. All three studies reported no statistically significant difference in OS between 5FU/Cap based therapy vs. S-1 based therapy (P > 0.05).

Objective response rate

Based on the pooled risk ratio for response, i.e. a complete or partial response to the received therapy, it was shown that S-1 based therapy is at least as effective as 5FU/Cap-based therapy in terms of ORR (RR_{total} 1.06, 99%CI 0.90–1.24) (Figure 5). When stratified by treatment line, a pooled $RR_{subgroup}$ of 1.04 (99%CI 0.87–1.25) was observed for first-line treatment, and a pooled $RR_{subgroup}$ of 1.19 (99%CI 0.77–1.84) for and second-line treatment. Moderate heterogeneity was detected for ORR (I^2 = 48%, P = 0.04).

Figure 5. Forest plot for the comparison S-1 based therapy vs. 5FU/Cap based therapy, outcome ORR



S-1, oral anticancer drug composed of tegafur (FT), 5-chloro-2, 4-dihydroxypyridine (gimestat [CDHP]), and oteracil potassium (Oxo); 5FU, 5-fluorouracil; Cap, capecitabine; IV, inverse variance; CI, confidence interval; ORR, objective response rate.

Sensitivity analyses showed that the direction of the estimator of the RRs for response and its significance were both not influenced by omission of the studies by Yamada et al. [3] and Kato et al. [8] that respectively used a different combination therapy in the intervention and control arm, and a heterogeneous patient population including both first and second-line treatment.

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Efficacy monotherapy in European mCRC patients

Kwakman et al., Annals of Oncology, 2017, Randomized phase III trial of S-1 versus capecitabine in the first-line treatment of metastatic colorectal Cancer: SALTO study by the Dutch Colorectal Cancer Group.

Kwakman et al., Clinical Colorectal cancer, 2019, Updated survival analysis of the randomized phase III trial of S-1 versus capecitabine in the first-line treatment of metastatic colorectal cancer by the Dutch Colorectal Cancer Group.

Methods

- **Study participants**

Patients with previously untreated mCRC in the Netherlands were included. The main eligibility criteria were age ≥18 years, histologically proven CRC with distant metastases, WHO performance status of 0–2, adequate bone marrow, liver and renal function, and planned first-line treatment with fluoropyrimidine monochemotherapy with or without bevacizumab. Patients were excluded if they had prior adjuvant treatment completed within 6 months prior to randomisation, planned radical resection of metastatic

disease after downsizing by systemic treatment, history of a second malignancy in the past 5 years, previous intolerance of capecitabine, known dihydropyrimidine dehydrogenase (DPD) deficiency, any significant cardiovascular disease within 1 year before randomisation, or concomitant administration of any other experimental or anti-cancer therapy.

Written informed consent was obtained from all patients before study entry.

- **Treatments**

Patients received oral capecitabine (1250 mg/m2 for <70 years; 1000 mg/m2 for ≥70 years) or oral Teysuno (30 mg/m2) twice daily on days 1-14 of a 21-day cycle with the option to add bevacizumab (7.5 mg/kg IV on day 1) at the discretion of the local investigator. Treatment in both arms was continued until disease progression, unacceptable toxicity or patient refusal.

Detailed dose modification and supportive measures were also described by Kwakman et al., 2017. In case of grade 2-3 HFS or other grade ≥2 non-haematological toxicities, capecitabine or S-1 was interrupted until recovery to grade ≤1, or in case of grade ≥2 diarrhoea until complete recovery. At the second occurrence of any grade 2 or first occurrence of any grade 3 non-haematological toxicity, the dose of capecitabine or S-1 was reduced to 75% and 80% of the original dose, respectively. The dose was reduced to 50% for capecitabine or 70% for S-1 at the third occurrence of any grade 2, second occurrence of any grade 3, or first occurrence of any grade 4 non-haematological toxicity. If despite these dose reductions a given non-haematological toxicity occurred for a fourth time at grade 2, a third time at grade 3, or a second time at grade 4, study treatment was discontinued. In case of grade 4 haematological toxicity and/or febrile neutropaenia, the dose of capecitabine or S-1 was reduced to 75% and 80%, respectively. Upon recurrence of a grade 4 haematological toxicity, doses were further reduced to 50% and 70%, respectively. If grade 4 haematological toxicity recurred, study treatment was discontinued. Treatment was delayed with a week for a maximum of two weeks if the white blood cell or platelet counts were below 3.0 and $75x10^9$/L, respectively, at the start of each treatment cycle. Bevacizumab was administered each cycle when blood pressure did not exceed 150/100 mmHg, a diastolic increase was lower than 20 mmHg compared to baseline, and 24-hour urine protein was lower than 2 grams (only collected in the presence of a 2+–4+ dipstick). In case of a thrombo-embolic event, nephrotic syndrome, or grade 3–4 haemorrhage, bevacizumab was permanently discontinued. Dose reductions for bevacizumab were not performed and dose reductions for capecitabine or S-1 were not re-escalated. Omitted doses were not made up for after resuming treatment. All patients were provided with a home prescription and instructions for prophylactic anti-emetics (metoclopramide or 5-HT3 antagonists). Supportive measures as specified in the study protocol included emollients in case of HFS, loperamide for diarrhoea and amlodipine for hypertension.

- **Objectives**

The primary objective was to show an improvement of the incidence of HFS of at least 20%—from 30% for capecitabine to 10% for S-1.

- **Outcomes/endpoints**

The primary endpoint was the incidence of hand-foot syndrome (HFS) and secondary endpoints included grade 3 HFS, other toxicity, relative dose intensity (RDI), progression-free survival (PFS), response rate (RR), and overall survival (OS).

The primary endpoint was the incidence of any grade HFS as assessed by the local investigators using the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 4.0. The results of this endpoint will be discussed in the safety section.

Secondary endpoints included the incidence of grade 3 HFS, any grade and grade 3 HFS as assessed by patients, other toxicities, PFS, response rate, OS and RDI. Patient-reported HFS-related symptoms were collected in a diary, which was designed specifically for this trial. The symptoms were graded centrally according to the NCI-CTC by an investigator who was unaware of treatment.

Patients in both study groups were evaluated every 3 weeks for toxicity by NCI CTC and every 9 weeks for disease status by CT-scan according to the Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 criteria. Patients were asked to score symptoms associated with HFS in a diary at the end of each cycle. Diaries were collected at the end of study treatment, and scores were unknown to local investigators. After discontinuation of treatment for reasons other than disease progression, patients were followed every 3 months until progression or death.

- **Sample size**

The primary objective was to show an improvement of the incidence of HFS of at least 20%—from 30% for capecitabine to 10% for S-1—based on a previous Asian study (Hong et al., Lancet Oncology, 2012). The study required 150 patients to detect this difference with 90% power (two-sided a=0.05). The intention-to-treat population was defined as all randomised patients and the safety population as all patients who received at least one dose of study medication.

- **Randomisation**

Patients were randomly assigned (1:1) to either capecitabine or S-1 with the use of TENALEA (an online, central randomisation service). Minimisation techniques were used with stratification for the planned use of bevacizumab (yes versus no), WHO performance status (0–1 versus 2), serum LDH (normal versus abnormal) and institution.

- **Blinding (masking)**

Not applicable, this was an open-label trial.

- **Statistical methods**

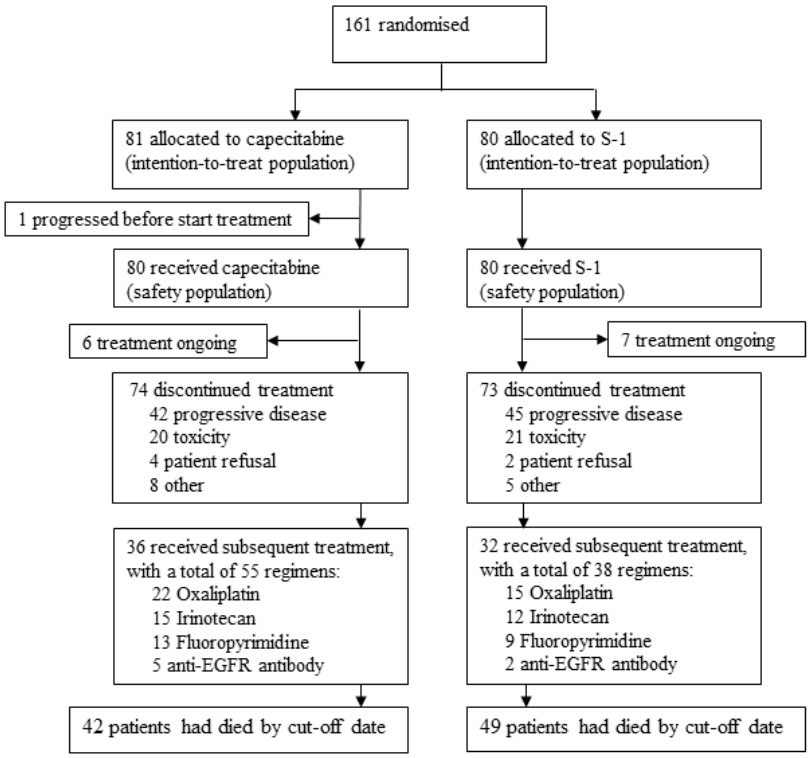
The frequency of HFS and other adverse events were compared with Fisher's exact test in the safety population. The cumulative incidence of grades 2 and 3 HFS was calculated by censoring patients without grades 2 and 3 HFS and treating death and progression as a competing risk. Logistic regression was used for pre-planned subgroup analyses of cotreatment with bevacizumab (yes versus no), WHO performance score (0–1 versus 2), serum LDH (normal versus abnormal), sex (male versus female) and age (<70 versus ≥70 years), and for exploratory analyses of prior adjuvant therapy (yes versus no), and localisation of metastasis (liver only versus extrahepatic). PFS and OS were calculated from randomisation in the intention-to-treat population and compared with Cox proportional hazard models and Kaplan–Meier curves. Patients alive or alive without progression at last follow-up were censored for OS and PFS, respectively.

RDI was calculated as the ratio of the total dose of study medication administered divided by the target dose for the total treatment duration (only for patients who completed treatment) and compared with Wilcoxon's rank sum test.

Results

- **Participant flow**

Figure 6. Flow diagram of the study population SALTO trial



- **Recruitment**

Between January 2014 and July 2015, 161 patients from 27 Dutch hospitals were randomly assigned in either the capecitabine group (n=81) or S-1 group (n=80). The trial was conducted and sponsored by the Dutch Colorectal Cancer Group in 27 hospitals in the Netherlands.

- **Conduct of the study**

The study was conducted in accordance to the standards of Good Clinical Practice, in agreement with the Declaration of Helsinki. The study was approved centrally by the Ethics Review Committee of the Academic Medical Center, Amsterdam, and by the local institutional review boards.

- **Baseline data**

Median age was 73 years (range 50-86) and co-treatment with bevacizumab was administered to 59% of patients (capecitabine, n=47; S-1, n=48). Disease characteristics between the treatment groups were similar in terms of the presence of synchronous disease (41% capecitabine, 43% S-1) and site of primary tumour (colon 54% capecitabine, 55% S-1; rectum 30% capecitabine, 29% S-1). A majority of patients in each group had undergone surgery (60% capecitabine, 64% S-1) of the primary tumour but most had not received adjuvant chemotherapy (83% capecitabine, 88% S-1). See Table 5 for more detailed information of the baseline characteristics.

Table 5. Baseline characteristics SALTO trial

	Capecitabine (*n* = 81)	S-1 (*n* = 80)
Sex		
Male	56 (69%)	45 (56%)
Female	25 (31%)	35 (44%)
Age		
Median, years (IQR)	73 (66–78)	74 (68–79)
WHO performance status		
0	36 (44%)	33 (41%)
1	37 (46%)	39 (49%)
2	8 (10%)	8 (10%)
Co-treatment with bevacizumab		
Yes	47 (58%)	48 (60%)
No	34 (42%)	32 (40%)
Serum lactate dehydrogenase		
Normal	53 (65%)	52 (65%)
Above normal	28 (35%)	28 (35%)
Stage of disease		
Synchronous	33 (41%)	34 (43%)
Metachronous	48 (59%)	46 (58%)
Site of primary tumour		
Colon	44 (54%)	44 (55%)
Rectum	24 (30%)	23 (29%)
Rectosigmoid	13 (16%)	13 (16%)
Resection of primary tumour		
Yes	49 (60%)	51 (64%)
No	32 (40%)	29 (36%)
Adjuvant chemotherapy		
Yes	14 (17%)	10 (13%)
No	67 (83%)	70 (88%)

Data are number of patients (%) unless otherwise specified.
IQR, interquartile range.

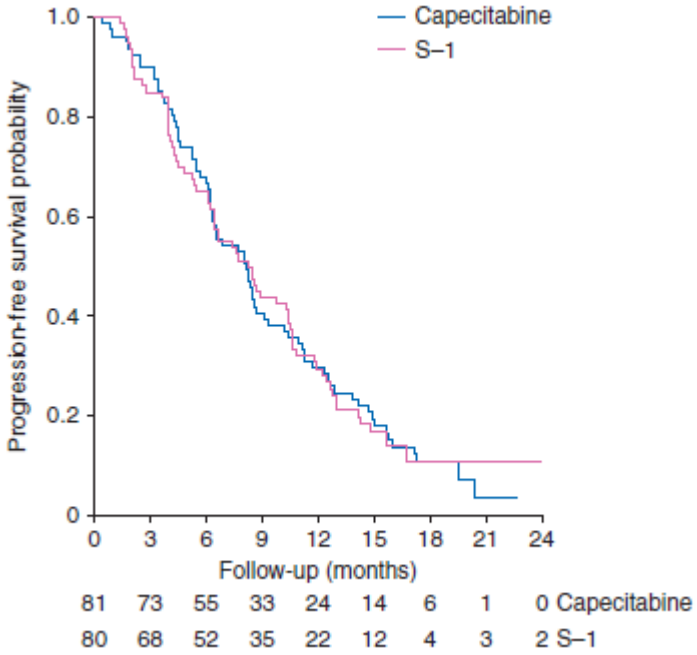
- **Numbers analysed**

As is shown in the flow diagram of the study population above, 80 patients in both groups were analysed (Figure 6).

- **Outcomes and estimation**

There were no significant differences in PFS, RR, or OS between the treatment groups. After a median follow-up duration of 20.2 months (IQR 17.0-23.5), 73 (90%) patients in the capecitabine group and 70 (88%) patients in the S-1 group had progressed or died. Median PFS was 8.2 months (95% CI 6.4-10.3) in the capecitabine group and 8.4 months (6.4-10.6) in the S-1 group (hazard ratio (HR) 0.99, 95% CI 0.71-1.37, p=0.93, Figure 7).

Figure 7. Kaplan-Meier curves of PFS



OS at 12 months and 18 months was 67% (95% CI 57-78) and 50% (40-63) in the capecitabine group, compared to 62% (53-74) and 41% (30-54) in the S-1 group (HR 1.23, 95% CI 0.82-1.86, p=0.32). Additional long-term OS results are shown below.

The overall objective response rate in 146 evaluable patients was 47% in the capecitabine group and 32% in the S-1 group (n=35 vs n=23, p=0.09). Disease control was observed in 95% of the patients in the capecitabine group and 89% in the S-1 group (n=71 vs n=63, p=0.24) (Table 6).

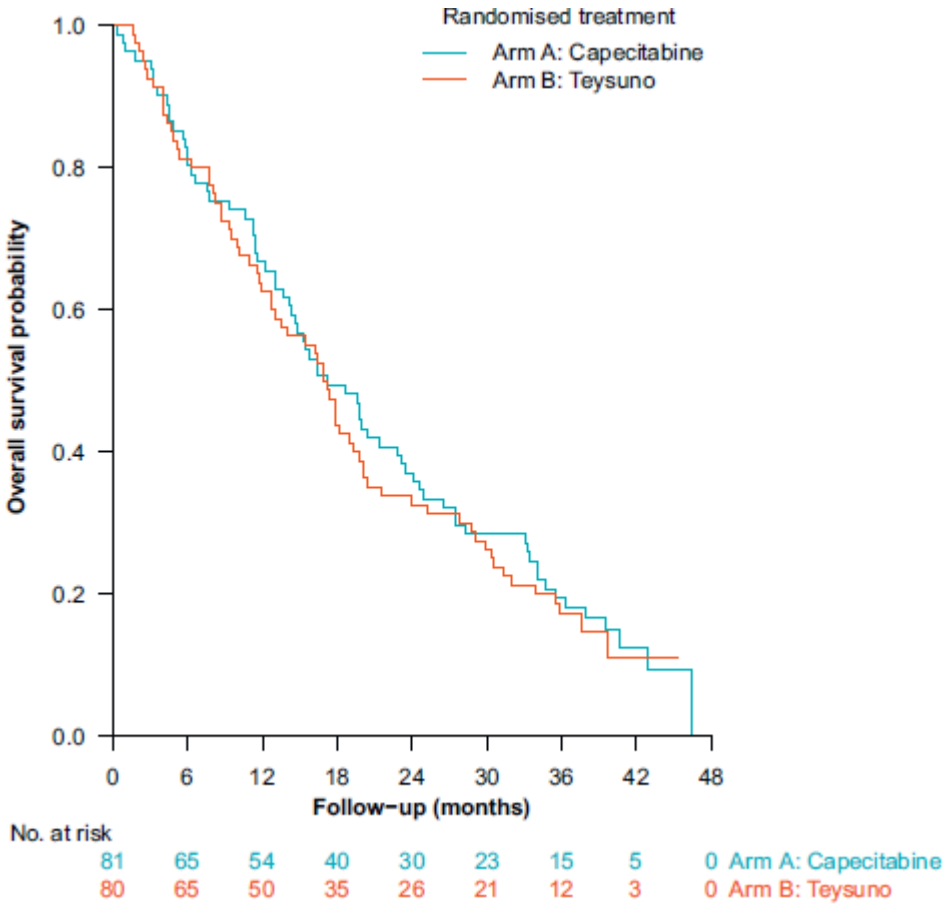
Table 6. Best response to treatment according to RECIST

	Capecitabine (*n*=81)	S-1 (*n*=80)
Complete response	3 (4%)	0
Partial response	32 (40%)	23 (29%)
Stable disease	36 (44%)	40 (50%)
Progressive disease	4 (5%)	8 (10%)
Missing data or not evaluable*	6 (7%)	9 (11%)

Data are number of patients (%). *Tumour assessment data were missing in 15 patients. These patients died or discontinued treatment prior to the planned assessment after nine weeks and no assessments were performed.

Long-term survival results for this study were reported after a median follow-up of 40.3 months and after 71 (88%) of patients in the capecitabine group and 68 (85%) of patients in the S-1 group had died (Kwakman et al., 2019). Median PFS was 8.2 months (95% CI 6.4-10.3) for patients treated with capecitabine compared to 8.4 months (95%CI 6.4-10.6) for S-1 (HR1.02, 95%CI 0.75-1.40, p=0.89). Long-term results also demonstrated that there were no statistically significant differences in OS between the two treatments. OS was 17.1 months (95%CI 14.3-23.5) for capecitabine and 17.0 months (95%CI 13.0-20.1) for S-1 (HR 1.07, 95%CI 0.76-1.49, p=0.70) (Figure 8).

Figure 8. Long-term follow-up Kaplan Meier curves of OS SALTO trial



The following additional results are described in the provided publication by Kwakman et al., 2017. The addition of bevacizumab to capecitabine/S-1 was associated with an improved PFS [8.7 months (7.8–10.8) with bevacizumab (n=95) versus 6.6 months (5.3–8.5) without bevacizumab (n=66), HR 0.74, 95% CI 0.53–1.03, p=0.08]. There was a statistically significant difference in median PFS between capecitabine (n=34) and capecitabine plus bevacizumab (n=47) [6.6 months (5.5–8.5) versus 9.2 months (6.6–13.8); HR 0.61, 95% CI 0.38–0.97; p=0.04]. Median PFS for S-1 alone (n=32) and S-1 plus bevacizumab (n=48) was 6.4 months (4.3–12.8) and 8.7months (6.7–10.6), respectively (HR 0.91, 95% CI 0.56–1.47; p=0.69).

Subsequent treatments are listed in the flow chart of Figure 6. Patients in the capecitabine group received more subsequent lines of treatment than patients in the S-1 group, although not statistically significant (p=0.30).

Kwakman et al., 2019 present updated results on survival with data cutoff on August 6, 2018. In addition to the data described above, this publication also reports that exploratory survival analysis of treatment with or without bevacizumab showed a median PFS of 8.7 versus 6.6 months, and median OS of 17.8 versus 15.1 months, respectively. Forty patients (49%) in the capecitabine group and 41 patients (51%) in the S-1 group received 1 or more subsequent treatments (p=0.88).

Efficacy combination therapies in mCRC patients

The proposed new indication will recommend the use of S-1 in the same regimens as other fluoropyrimidines in mCRC. Therefore, the MAH first discussed the data supporting the use of fluoropyrimidines regimens in combination therapies in mCRC. ESMO guidelines currently recommend

intravenous 5-FU or capecitabine as the backbone of cytotoxic therapy in combination with irinotecan and/or oxaliplatin, combined with a targeted agent such as bevacizumab or anti-epidermal growth factor receptor (EGFR) agents such as cetuximab or panitumumab, when appropriate, for first-line treatment (Van Cutsem et al., 2016).

Studies that form the basis for current approval of fluoropyrimidines (5-FU and capecitabine) in combination therapies in mCRC in the EU as provided by the MAH

FOLFOX (5-FU, leucovorin, oxaliplatin) and FOLFIRI (5-FU, leucovorin, irinotecan) were approved by EMA for the first-line treatment of advanced/metastatic colorectal cancer based on the phase 3 EFC2962 study (FOLFOX; de Gramont et al., 2000) and a phase 3 randomised trial from Douillard et al. (FOLFIRI; Douillard et al., 2000). Based on the results from these studies, the Gruppo Oncologico dell'Italia Meridionale (GOIM) conducted a randomized trial (GOIM protocol No. 9901) to compare FOLFIRI with FOLFOX for first-line treatment of colorectal cancer. This study concluded that "There was no difference in ORR, TTP, and OS for patients treated with the FOLFIRI or FOLFOX4 regimen, and both therapies seemed effective as first-line treatment in these patients." (Table 7) (Colucci et al., 2005).

Table 7. Summary of efficacy data from the GOIM 9901 study

	FOLFIRI	FOLFOX4	p-value
ORR	31% (95%CI: 24.6-38.3)	34% (95%CI: 27.2-41.5)	p=0.60
Median TTP	7 months	7 months	-
Median OS	14 months	15 months	p=0.28

ORR, overall response rate; TTP, time to progression; OS, overall survival; FOLFIRI, 5-fluorouracil, leucovorin, irinotecan; FOLFOX, 5-fluorouracil, leucovorin, oxaliplatin, CI, confidence interval.

Therefore, both FOLFOX and FOLFIRI were established as the standard of care for first-line treatment of advanced colorectal cancer with equivalent efficacy.

Additional studies have demonstrated the efficacy of switching between various FOLFOX and FOLFIRI regimens after disease progression, allowing patients to continue on fluoropyrimidine-based treatment in the second line (Tournigand et al., 2004; Bidard et al., 2009).

XELOX (capecitabine plus oxaliplatin; also referred to as CapeOX) is a standard care for first-line treatment of colorectal cancer that was approved in several countries based on the NO16966 study, a non-inferiority study of XELOX (+/- bevacizumab) vs. FOLFOX4 (5-FU, leucovorin, oxaliplatin) (+/- bevacizumab) for first-line treatment of colorectal cancer (Cassidy et al., 2008). The primary endpoint of NO16966 was PFS, which demonstrated non-inferiority with a margin of 1.23, corresponding to retention of at least 50% of the benefit that oxaliplatin plus 5-FU/LV had shown over 5-FU/LV alone (Cassidy et al., 2008). The non-inferiority margin was set based on the results of the EFC2962 study (de Gramont et al., 2000) by which FOLFOX4 was approved as first-line treatment of colorectal cancer by the EMEA after comparison to infusional 5-FU plus leucovorin alone (Oxaliplatin SmPC). Therefore, a non-inferiority margin of 1.23 has been shown to be acceptable as the non-inferiority measure for first-line treatment of colorectal cancer with oxaliplatin-based chemotherapy according to the MAH.

In addition, two large observational cohort studies were conducted for bevacizumab containing regimens including FOLFIRI, FOLFOX, and XELOX in Europe (BEAT study; Van Cutsem et al., 2009) and the US (BRiTE study; Kozloff et al., 2009) (Table 8).

Table 8. Summary of efficacy from the BEAT and BRiTE studies

	BEAT study			BRiTE study		
	N	mPFS (mos.) [95%CI]	mOS (mos.) [95%CI]	N	mPFS (mos.) [95%CI]	mOS (mos.) [95%CI]
FOLFIRI + Bev	503	11.6 [10.8-12.5]	23.7 [21.7-25.9]	279	10.8 [9.7-11.7]	22.9 [19.6-27.4]
FOLFOX + Bev	552	11.3 [10.3-12.4]	25.9 [22.4-28.1]	1093	9.8 [9.3-10.2]	24.4 [22.6-26.0]
XELOX + Bev	346	10.8 [10.3-12.0]	23.0 [20.6-26.1]	94	11.0 [8.4-12.4]	23.6 [19.6-28.4]

Bev, bevacizumab, FOLFIRI, 5-fluorouracil, leucovorin, irinotecan; FOLFOX, 5-fluorouracil, leucovorin, oxaliplatin; XELOX, capecitabine, oxaliplatin; PFS, progression-free survival; OS, overall survival.

According to the MAH, these studies have established FOLFOX, FOLFIRI, and XELOX, with or without bevacizumab, as equivalent standard treatment in mCRC (Van Cutsem et al., 2016). ESMO recommendations state that the combination of capecitabine plus irinotecan (XELIRI) is less often used due to early concerns about its toxicity in comparison to FOLFIRI regimen, but that these results are controversial (Van Cutsem et al., 2016).

Teysuno combination therapy in Asian mCRC patients

The MAH presents four supportive phase 3 non-inferiority studies of Teysuno in combination with oxaliplatin or irinotecan, with or without bevacizumab, in metastatic colorectal cancer in Asian patients:

1. SOX (Teysuno plus oxaliplatin) vs. CapeOX (Capecitabine plus oxaliplatin) study (Hong et al., 2012; Kim et al., 2014)
2. SOFT study (SOX/bevacizumab vs. mFOLFOX6 [modified 5-FU, leucovorin, oxaliplatin]/bevacizumab for first-line treatment of CRC) (Yamada et al., 2013; Baba et al., 2017)
3. TRICOLORE study (IRIS [irinotecan, Teysuno]/bevacizumab vs. mFOLFOX6/bevacizumab or CapeOX/bevacizumab for first-line treatment of CRC) (Yamada et al., 2018)
4. FIRIS study (IRIS vs. FOLFIRI [5-FU, leucovorin, irinotecan] for 2nd line treatment of CRC) (Muro et al., 2010; Yasui et al., 2015)

Oxaliplatin combination regimens

Hong et al., Lancet Oncology, 2012, S-1 plus oxaliplatin versus capecitabine plus oxaliplatin for first-line treatment of patients with metastatic colorectal cancer: a randomised, non-inferiority phase 3 trial.

Kim et al., BMC Cancer, 2014, S-1 plus oxaliplatin versus capecitabine plus oxaliplatin for the first-line treatment of patients with metastatic colorectal cancer: updated results from a phase 3 trial.

Methods

- **Study participants**

This was a non-inferiority study of SOX vs. CapeOX for first-line treatment of mCRC conducted in 340 patients in South Korea. The study was a randomised, open-label, multicenter phase 3 study. Patients were recruited from 11 institutions in South Korea. To be eligible, patients with metastatic colorectal cancer were required to have histologically confirmed adenocarcinoma, have measurable or assessable lesions, have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, be aged 18 years or older, have had no previous chemotherapy or immunotherapy in the metastatic setting, and have adequate haematological, hepatic, and renal functions. Adjuvant chemotherapy or radiotherapy

was allowed if it had been completed at least 6 months before enrolment. All patients provided written informed consent before study entry, and the study protocol was approved by the institutional review boards of all participating institutions. This study is registered with ClinicalTrials.gov, number NCT00677443.

- **Treatments**

All treatment cycles were administered every 3 weeks. Oral S-1 (40 mg/m²) was administered twice a day on days 1–14, oral capecitabine (1000 mg/m²) twice a day on days 1–14, and oxaliplatin (130 mg/m²) on day 1 as a 2-h intravenous infusion. Treatment was continued for as many as nine cycles of oxaliplatin-containing chemotherapy, except in instances of disease progression, unacceptable toxicity, or a patient's refusal. Maintenance chemotherapy with S-1 or capecitabine was allowed after discontinuation of oxaliplatin (Hong et al., 2012).

- **Objectives**

No details were provided.

- **Outcomes/endpoints**

The primary endpoint was PFS with a pre-defined non-inferiority margin of 1.43. Secondary endpoints were response rate, time to treatment failure (TTF), OS, toxicity, and QoL. Data collection was done by the Velos system of the National Cancer Centre, South Korea.

Treatment responses were assessed every three cycles (9 weeks) during study treatments or sooner if needed for documentation of disease progression. Objective tumour responses were independently reviewed according to RECIST; version 1.0. Clinical and laboratory toxicities were monitored according to the NCI-CTC for Adverse Events (version 3.0). QoL was assessed before treatment and at every point of response assessments with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ C30; Korean version).

- **Sample size**

PFS at 15 months in both groups was assumed to be 38%, and the lower non-inferiority limit was set as −13%, corresponding to a hazard ratio of 1.43. On the basis of these conditions, 192 events were needed for a one-sided type-I error of 5% and a power of 80%. Assuming a 10% loss, 344 patients were needed (172 per treatment group). The protocol was amended on Jan 28, 2009: initially, 165 events were targeted and accrual of 298 patients (149 per treatment group) of which the upper limit of non-inferiority margin was 1.31.

- **Randomisation**

Eligible patients were randomly assigned to either CapeOX or SOX in a 1:1 ratio. Randomisation was done centrally with a computer-generated sequence and a permutation block technique that ensured equal distribution of patients on the basis of primary tumour sites (colon vs rectum), history of previous adjuvant or neoadjuvant treatment, and the presence of measurable lesions. Investigators or research coordinators sent the randomisation form by fax to the Clinical Research Coordination Centre of the National Cancer Centre, South Korea. After checking the inclusion criteria, the study coordinator sent the allocated treatment back to the investigator by fax. A web-based clinical research management platform (Velos Inc, Fremont, CA, USA) for randomisation was used. Investigators who assessed the response to the treatment were not masked to group assignment.

- **Blinding (masking)**

Not applicable (open-label study design).

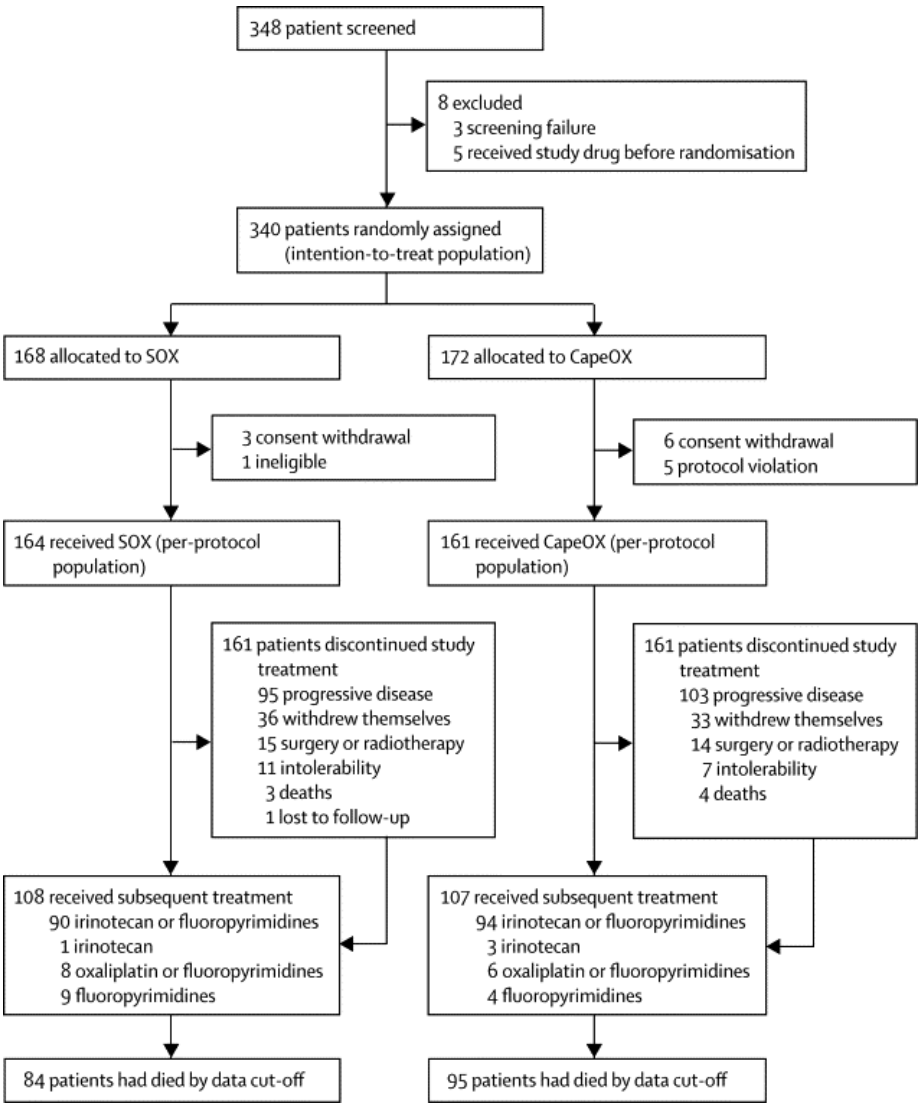
- **Statistical methods**

For the primary efficacy analysis, in which it was aimed to assess the non-inferiority of SOX to CapeOX in terms of PFS, all patients allocated to treatment were assessed (ITT), and also a per-protocol analysis was performed in those who received protocol treatments without major violations. For the safety analysis, data was assessed for all patients who received at least one dose of study treatment. OS (time to death), PFS (time to progression or death), and TTF (time to treatment discontinuation from any cause including disease progression, patients' refusal, lost to follow-up, chemotherapy-free interval after completion of planned nine cycles of study treatment even without evidence of disease progression, and intolerability from adverse events), along with 95% CI for median time to event, were assessed with the Kaplan-Meier method. Patients who entered into a chemotherapy-free interval after completion of planned treatment were censored for the PFS estimations. The HR and corresponding 95% CI were estimated using the Cox proportional hazard regression model. The dose intensity was calculated as the ratio of the total dose divided by the total treatment duration. EORTC QLQ C30 score changes from baseline were compared between treatment groups using the Wilcoxon rank sum test. SAS (version 9.1) and SPSS (version 20.0) was used for all statistical analyses.

Results

- **Participant flow**

Figure 9. Flow chart SOX vs CapeOX trial



- **Recruitment**

Between May 14, 2008, and Sept 23, 2009, 348 patients were enrolled from 11 institutions and 340 patients who met the eligibility criteria were randomly assigned to treatment: 168 to the SOX group and 172 to the CapeOX group (ITT).

- **Conduct of the study**

The Ethics Committee at Samsung Medical Center approved the study in accordance with the Declaration of Helsinki. The institutional review boards of all participating institutions approved the study protocol. Written, informed consent was required for participation.

- **Baseline data**

Table 9. Baseline characteristics SOX vs CapeOX trial (ITT)

	SOX (n=168)	CapeOX (n=172)
Primary site		
Colon	109 (65%)	108 (63%)
Rectum	59 (35%)	64 (37%)
Sex		
Male	109 (65%)	102 (59%)
Female	59 (35%)	70 (41%)
Age in years (median [IQR])	61 (53–66)	60 (52–66)
≤65 years	121 (72%)	126 (73%)
>65 years	47 (28%)	46 (27%)
ECOG performance status		
0–1	164 (98%)	168 (98%)
2	4 (2%)	4 (2%)
Previous (neo)adjuvant therapy		
Yes	37 (22%)	38 (22%)
No	131 (78%)	134 (78%)
Tumour differentiation		
Well-differentiated	35 (21%)	29 (17%)
Moderately differentiated	116 (69%)	120 (70%)
Poorly differentiated	13 (8%)	19 (11%)
Mucinous or signet ring cell	1 (1%)	3 (2%)
Undetermined	3 (2%)	1 (1%)
Site of metastasis		
Liver	105 (63%)	111 (65%)
Lymph node	81 (48%)	100 (58%)
Lung	66 (39%)	79 (46%)
Peritoneum	40 (24%)	33 (19%)
Bone	4 (2%)	9 (5%)
Number of metastatic organs		
One organ	65 (39%)	49 (29%)
Two organs	61 (36%)	70 (41%)
Three or more organs	42 (25%)	53 (31%)
Measurability		
Measurable lesions	155 (92%)	155 (90%)
Assessable lesions only	13 (8%)	17 (10%)

Data are n (%), unless stated otherwise. SOX=S-1 plus oxaliplatin. CapeOX=capecitabine plus oxaliplatin. ECOG=Eastern Cooperative Oncology Group.

- **Numbers analysed**

In the ITT 168 patients were analysed in the SOX group and 172 in the CapeOX group. In the per-protocol population these numbers were 164 vs 161.

- **Outcomes and estimation**

Median PFS was 8.5 months (95% CI 7.6-9.3) for patients who received SOX and 6.7 months (95% CI 6.2-7.1) for the CapeOX group (p noninferiority<0.0001).

The non-inferiority margin for this study was set at a less conservative value (1.43) than the 1.23 used in the NO16966 study (Cassidy et al., 2008). Therefore, a post-hoc analysis was performed showing that the hazard ratio [95% confidential interval] of SOX to CapeOX in PFS of 0.79 [0.60, 1.04] would meet the primary endpoint even if the analysis was carried out using a non-inferiority margin of 1.23.

For the secondary endpoint of OS, the hazard ratio [95%CI] of SOX to CapeOX was 0.86 [0.68, 1.08].

No statistical difference was recorded in the median number of oxaliplatin cycles between the two groups (p=0.16). 31 patients in the SOX group entered into maintenance chemotherapy (median duration of maintenance 3.7 months, IQR 1.4–6.9 [S-1 alone for eight cycles]) and 20 patients in the CapeOX group entered into maintenance chemotherapy (2.3 months, 0.5–4.8 [capecitabine alone for five cycles]).

At the cut-off date for data collection (Aug 31, 2011), study treatments had been discontinued in 161 patients in the SOX group and 161 patients in the CapeOX group; median follow-up was 20.6 months (IQR 12.0–29.4). In the SOX group, PFS at 15 months was 38.7% (95% CI 31.3–46.1) and the median PFS was 8.5 months (7.6–9.3); the corresponding values in the CapeOX group were 32.2% (25.2–39.2) and 6.7 months (6.2–7.1; intention-to-treat analysis; Table 10 and Figure 10). The HR comparing PFS between the two groups was 0.79 (95% CI 0.60–1.04, p non-inferiority<0.0001, p log-rank=0.09), and the upper limit of the CI was below the predefined margin of 1.43. Non inferiority was also shown in the per-protocol analysis (Table 10).

In both the intention-to-treat population and per-protocol population, median TTF was statistically significantly longer in the SOX group than it was in the CapeOX group, but no statistically significant difference between groups were recorded when comparing overall survival (Table 10 and Figure 10).

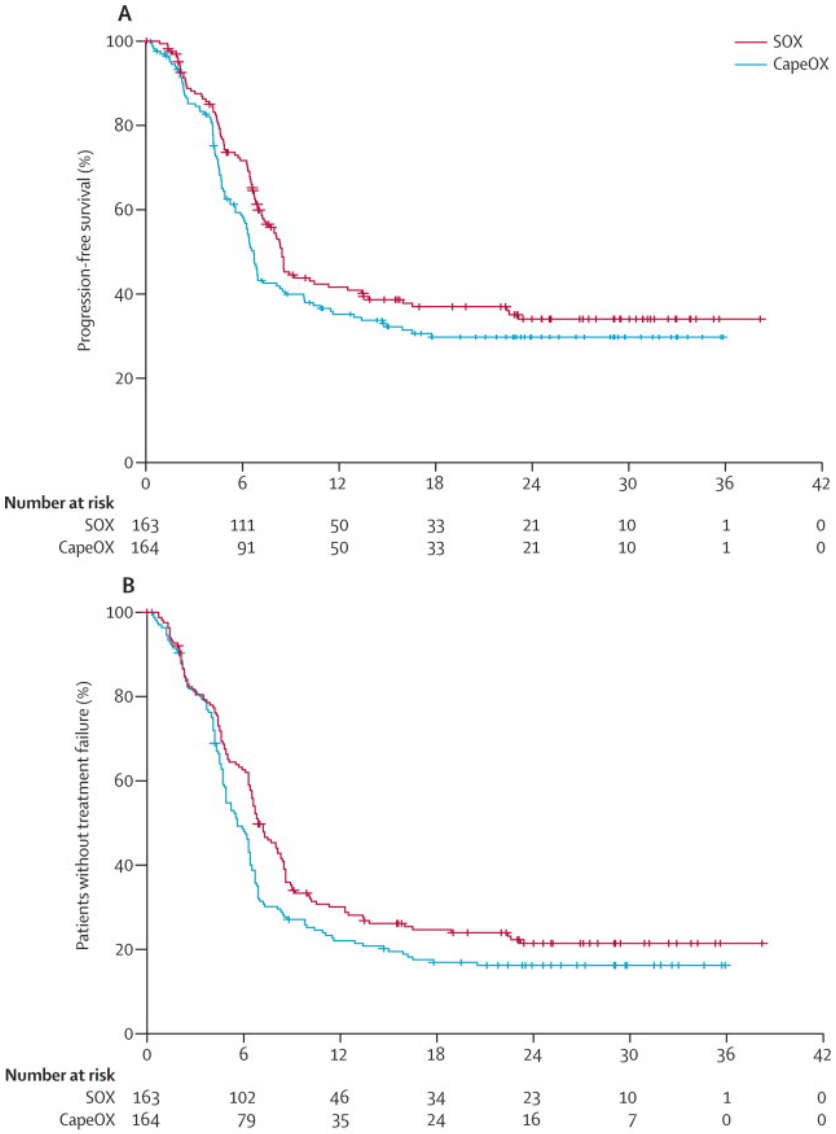
Of 340 randomized patients, 310 patients with measurable lesion(s) were included in the assessment of objective responses. Overall objective response in both the intention-to-treat and per-protocol population was greater in the SOX group than it was in the CapeOX group (Table 10). No statistically significant difference in disease control rate was recorded in either the ITT or per-protocol population (Table 10).

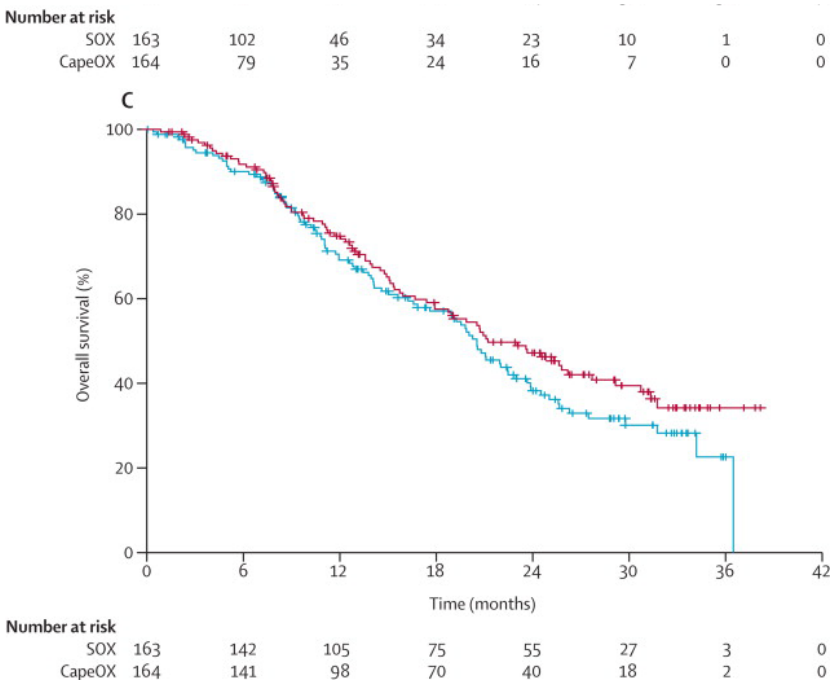
Table 10. Efficacy outcomes SOX vs CapeOX trial

	Intention-to-treat population			Per-protocol population		
	SOX	CapeOX	Effect size (95% CI); p value	SOX	CapeOX	Effect size (95% CI); p value
Number of patients	168	172		164	161	
Primary endpoint						
PFS at 15 months	38·7 (31·3–46·1)	32·2 (25·2–39·2)		38·7 (31·2–46·2)	31·9 (24·7–39·1)	
Median PFS (95% CI)*	8·5 (7·6–9·3)	6·7 (6·2–7·1)	0·79 (0·60–1·04); $p_{non\text{-}inferiority}$<0·0001	8·5 (7·6–9·3)	6·6 (6·0–7·0)	0·78 (0·60–1·03); $p_{non\text{-}inferiority}$<0·0001
Secondary endpoints						
Median TTF (95% CI)*	6·9 (6·1–7·8)	5·6 (4·7–6·4)	0·78 (0·62–0·99); $p_{log\text{-}rank}$=0·036	6·9 (6·1–7·8)	5·6 (4·7–6·4)	0·79 (0·63–0·99); $p_{log\text{-}rank}$=0·042
Median overall survival (95% CI)*	21·2 (16·2–26·2)	20·5 (18·2–22·9)	0·82 (0·61–1·10); $p_{log\text{-}rank}$=0·18	21·2 (16·2–26·2)	20·3 (18·6–21·9)	0·80 (0·60–1·08); $p_{log\text{-}rank}$=0·15
Number of patients with measurable disease	155	155		153	148	
Response rates						
Complete response	1 (1%)	1 (1%)		1 (1%)	1 (1%)	
Partial response	72 (47%)	54 (35%)		72 (47%)	54 (37%)	
Stable disease	53 (34%)	70 (45%)		53 (35%)	67 (45%)	
Progressive disease	18 (12%)	20 (13%)		18 (12%)	20 (14%)	
Not determinable	11 (7%)	10 (7%)		9 (6%)	6 (4%)	
Objective response†	73 (47%)	55 (36%)	1·68 (1·05–2·69); p=0·029	73 (48%)	55 (37%)	1·63 (1·02–2·60); p=0·042
Disease control†	126 (81%)	125 (81%)	1·12 (0·57–2·22); p=0·75	126 (82%)	122 (82%)	1·15 (0·58–2·27); p=0·69

Data are n (%), time in months (95% CI), or effect size (95% CI). SOX=S-1 plus oxaliplatin. CapeOX=capecitabine plus oxaliplatin. PFS=progression-free survival. TTF=time to treatment failure. HR=hazard ratio. OR=odds ratio. *Effect size given as hazard ratio. †Effect size given as odds ratio.

Figure 10. Kaplan Meier curves of progression-free survival (A), time to treatment failure (B), and overall survival (C) SOX vs CapeOX trial





Overall completion of the quality-of-life questionnaire for comparisons between baseline and final visits were >80% for both groups. No statistically significant differences were recorded between the two groups with respect to changes in global health status or functioning and symptom scales (see appendix Hong et al., 2012).

Of 325 patients, 215 (66%) received further treatment after SOX or CapeOX (Figure 9). No statistically significant differences were observed between the SOX group and the CapeOx group in terms of the proportion of patients who received all three cytotoxic agents (irinotecan, oxaliplatin, and S-1 or capecitabine) during the whole treatment period (98 [60%] of 164 patients vs 104 [65%] of 161 patients), or in terms of those subsequently given bevacizumab (10 [6%] of 164 patients vs eight [5%] of 161 patients) or cetuximab (27 [17%] of 164 patients vs 32 [20%] of 161 patients).

In the publication of Kim et al., 2014, updated data were provided. The updated data were collected at the cut-off date of December 24, 2013. Median follow-up was 17.91 months in the SOX group and 16.41 months in the CapeOX group. Updated efficacy outcomes are shown in the table and figures below (Table 11, Figure 11, and Figure 12).

Table 11. Updated efficacy outcomes SOX vs CapeOX trial

	Intention to treat population			Per-protocol population		
	SOX	CapeOX	Effect size (95% CI); *p* value	SOX	CapeOX	Effect size (95% CI), *p* value
Number of patients	168	172		164	161	
Median PFS	7.1 (6.4-8.1)	6.3 (4.9-6.7)	0.83 (0.66-1.04), *p* = .10	6.9 (6.4-7.9)	6.3 (5.2-6.7)	0.84 (0.67-1.06), *p* = .13
Median OS	19.0 (15.3-23.0)	18.5 (14.1-20.8)	0.86 (0.68-1.08), *p* = .19	19.1 (15.0-23.0)	17.6 (14.1-20.5)	0.85 (0.67-1.08), *p* = .17
Number of patients	150	151		147	145	
Median PPS	9.3 (6.7-11.6)	9.5 (7.4-12.1)	0.97 (0.76-1.23), *p* = .81	9.3 (6.9-11.6)	9.6 (7.4-12.1)	0.96 (0.75-1.23), *p* = .75

Data are represented as n (%), time in months (95% CI) or effect size (95% CI). SOX, S-1 plus oxaliplatin; CapeOX, Capecitabine plus oxaliplatin; PFS, progression-free survival; PPS, post-progression survival, OS = overall survival.

Figure 11. Updated Kaplan-Meier curves of PFS (A) and post-progression survival (PPS) (B) in SOX vs CapeOX trial

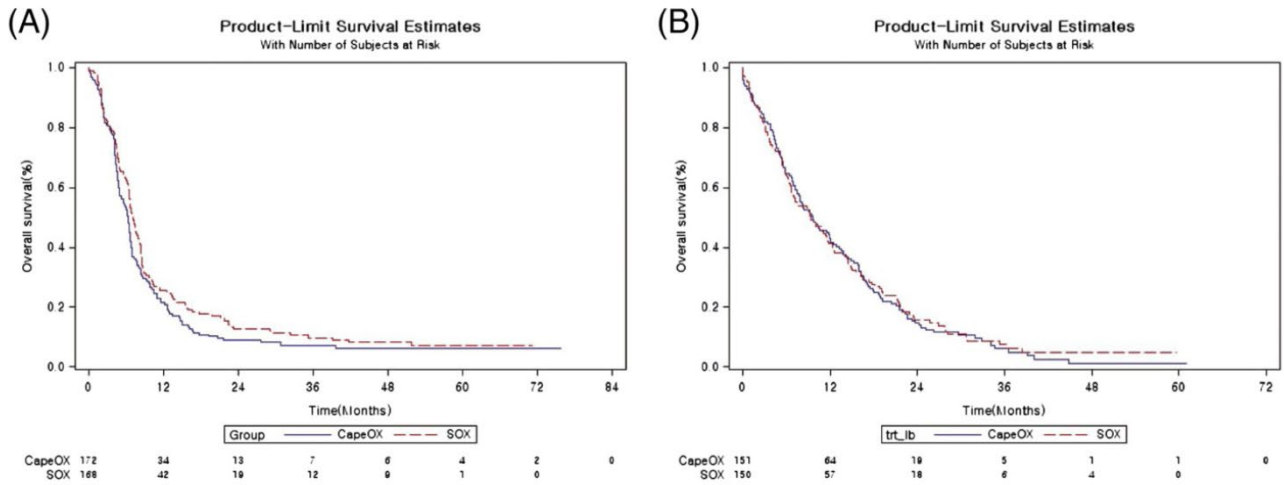
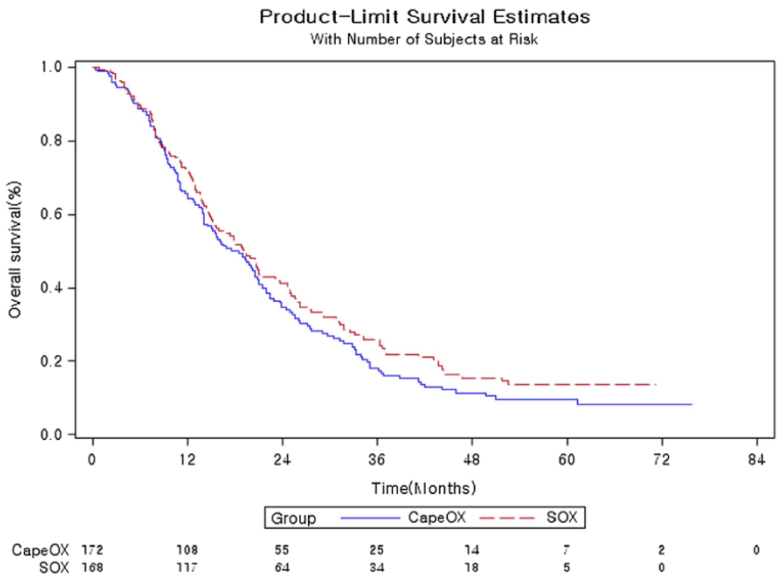
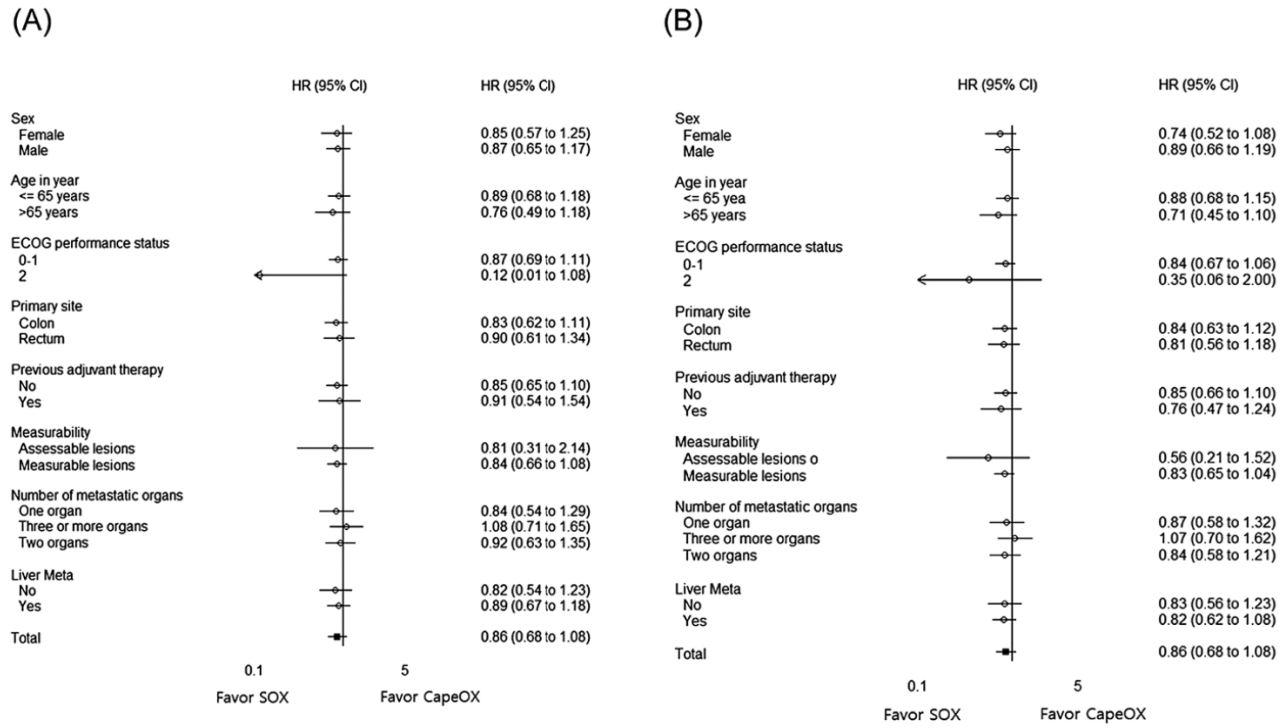


Figure 12. Updated Kaplan-Meier curves of OS in SOX vs CapeOX trial



OS and PFS in assigned patients were analysed according to sex, age, ECOG PS, primary tumour site, previous adjuvant therapy, measurability, number of metastatic organs, and liver metastasis. There was no interaction between the treatment and any of these factors (Figure 13).

Figure 13. Subgroup analysis of OS (A) and PFS (B) for ITT SOX vs CapeOX trial



Yamada et al., Lancet Oncology, 2013, Leucovorin, fluorouracil, and oxaliplatin plus bevacizumab versus S-1 and oxaliplatin plus bevacizumab in patients with metastatic colorectal cancer (SOFT): an open-label, non-inferiority, randomised phase 3 trial.

Baba et al., ESMO Open, 2017, S-1 and oxaliplatin (SOX) plus bevacizumab versus mFOLOX6 plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer: updated overall survival analysis of the open-label, non-inferiority, randomised phase III: SOFT study.

Methods

- **Study participants**

The SOFT study was an open-label, non-inferiority, randomised phase 2 trial of SOX/bevacizumab vs mFOLFOX6/bevacizumab for first-line treatment of metastatic colorectal cancer in 82 centers in Japan. Individuals who met eligibility criteria were enrolled: age 20–80 years; histologically proven colorectal adenocarcinoma; curatively unresectable, advanced, or recurrent colorectal cancer; ECOG performance status of 0 or 1; presence of assessable lesions as confirmed by CT or MRI; no previous chemotherapy or radiotherapy; could take drugs orally; leucocyte count of 3–12×10⁹ per L; neutrophil count at least 1.5×10⁹ per L; platelet count at least 100×10⁹ per L; haemoglobin concentration of at least 90 g/L; total serum bilirubin concentration of no more than 34.21 μmol/L; serum aspartate aminotransferase con centration of no more than 100 U/L, or no more than 200 U/L in patients with hepatic metastasis; serum creatinine concentration of no more than 106.08 μmol/L; creatinine clearance of at least 1 mL/s; urinary protein score of no more than 1+; and an international normalised ratio of no more than 1.5. Patients were excluded if they had active infection, serious concurrent disease, substantially impaired cardiac function, gastrointestinal ulcers or bleeding, sensory neuropathy, serious diarrhoea, a history of

gastrointestinal perforation in the 6 months before enrolment, a history of thromboembolism or interstitial pneumonia, or a history of haemoptysis. Patients were also excluded if they had previously or were presently receiving oxaliplatin-based regimens as adjuvant chemotherapy.

When 299 patients had been enrolled, enrolment was temporally discontinued because four patients receiving SOX plus bevacizumab had gastrointestinal perforation. In accordance with the recommendation of the independent data monitoring committee, other exclusion criteria were then added: the presence of a primary lesion associated with severe stricture, precluding passage of an endoscope; and substantial peritoneal metastasis as confirmed on imaging studies. Enrolment was then resumed.

The trial is registered with the Japan Pharmaceutical Information Center, number JapicCTI-090699.

- **Treatments**

On day 1 of each 2-week chemotherapy cycle, patients assigned to mFOLFOX6 plus bevacizumab received a 5 mg/kg intravenous infusion of bevacizumab (30–90 min) and a simultaneous intravenous infusion of 85 mg/m2 oxaliplatin (2 h), 200 mg/m2 *l*-leucovorin (2 h), 400 mg/m2 bolus fluorouracil, and 2400 mg/m2 infusional fluorouracil (46 h) delivered with an infusion pump. On day 1 of each 3-week cycle, patients assigned to receive SOX plus bevacizumab received a 7.5 mg/kg intravenous infusion of bevacizumab (30–90 min), followed by an intravenous infusion of 130 mg/m2 oxaliplatin (2 h). S-1 was taken orally twice daily from after dinner on day 1 to after breakfast on day 15, followed by a 7-day rest. The dose of S-1 was assigned according to body surface area: patients with a body surface area of less than 1.25 m2 received 80 mg/day; those with a body surface area of between 1.25 m2 and less than 1.5 m2 received 100 mg/day; and those with a body surface area of at least 1.5 m2 received 120 mg/day. Cycles were repeated for each patient until the criteria for withdrawal of the study treatment were met. In view of the neurological toxicity of oxaliplatin, treatment could be skipped when patients had received at least 600 mg/m2 overall, even when no grade 3 toxic effects were recorded. If patients had grade 2 or higher proteinurea or grade 2 or higher bleeding before the scheduled starting day of each cycle, they received only mFOLFOX6 or SOX; treatment with bevacizumab could be resumed in subsequent cycles if treatment criteria were satisfied. Additionally, investigators decided not to give bevacizumab to some patients to minimise the risk of bleeding immediately after port placement.

In both treatment groups, the dose of cytotoxic drugs (fluorouracil, oxaliplatin, and S-1) was reduced by one level if the neutrophil count was less than 0.5×10^9 per L at any time during a cycle, the neutrophil count was less than 1.5×10^9 per L on the first day of a cycle, grade 3 or higher febrile neutropenia developed, or the platelet count was less than 50×10^9 per L. In the event of grade 3 or higher diarrhoea, the dose of fluorouracil or S-1 was reduced by one level. If the platelet count was between 50×10^9 and 75×10^9 per L at any time during a cycle, or between 75×10^9 and 100×10^9 per L on the first day of a cycle, the oxaliplatin dose was reduced by one level. S-1 was withheld when the neutrophil count was less than 1×10^9 per L; the platelet count was less than 75×10^9 per L; the serum creatinine concentration was at least 132.6 µmol/L; suspected infection was diagnosed with a fever of at least 38°C; or diarrhoea, mucositis, or stomatitis of grade 2 or higher developed. S-1 was subsequently reinitiated when the neutrophil count was at least 1×10^9 per L; the platelet count was at least 75×10^9 per L; the serum creatinine concentration was less than 132.6 µmol/L; no fever of 38°C or higher suggesting infection was evident; and diarrhoea, mucositis, and stomatitis were no higher than grade 1.

- **Objectives**

Not provided.

- **Outcomes/endpoints**

The SOFT study was a non-inferiority study of SOX/bevacizumab vs mFOLFOX6/bevacizumab for first-line treatment of 512 patients with mCRC in Japan. The primary endpoint of the SOFT study was PFS with a pre-defined non-inferiority margin of 1.33. The primary endpoint PFS was defined as the interval from the date of enrolment to the date on which progressive disease was first confirmed or the date of death from any cause, whichever came first. Lesions were measured every 8 weeks with diagnostic imaging (e.g., CT or MRI). Progressive disease was assessed solely by the investigator in charge of the patient. Progressive disease, defined as a greater than 20% increase in the sum of the longest dimensions of target lesions from baseline, was included in assessment of disease progression for target lesions. Exacerbation of underlying disease and appearance of new lesions (a clinical diagnosis of distinct disease progression) was included in assessment of disease progression for new non-target lesions. In a sensitivity analysis, we also calculated PFS on the basis of progressive disease assessed according to RECIST; version 1.0.

Secondary endpoints were OS (interval from the date of enrolment to the date of death from any cause or last follow-up), TTF (interval from the date of enrolment to the date of a PFS event or withdrawal from the study for any reason), proportion of patients achieving a response, proportion of patients achieving disease control (a complete or partial response or stable disease), proportion of patients having a curative resection, and adverse events. Attending physicians assessed response according to RECIST (version 1.0). After initiation of study treatment, target and non-target lesions were assessed every 8 weeks in the same way as at baseline, with the same imaging conditions (e.g., contrast media and slice thickness). The best overall response was identified. Because the primary endpoint was PFS, response was not confirmed, in accordance with RECIST (version 1.0). Adverse events were graded according to CTCAE. Data for lactate dehydrogenase concentrations, whether disease was unresectable or recurrent at diagnosis, and disease stage at the time of surgery were not obtained.

- **Sample size**

On the basis of results of previous studies, the median PFS associated with mFOLFOX6 plus bevacizumab was estimated to be about 10 months. The study coordinating committee deemed that a median PFS with SOX plus bevacizumab that was 2.5 months shorter than that with mFOLFOX6 plus bevacizumab would be acceptable as the lower margin for inferiority, which corresponded to a non-inferiority HR of 1.33. The required number of progression events was estimated to be 388. With a two-sided α of 0.05 and a power of 80%, 250 patients would be needed in each group to achieve the required number of events by 1.5 years after enrolment of the last patient (3.5 years after initiation of the study).

- **Randomisation**

Participants were randomly assigned (1:1) to receive either mFOLFOX6 plus bevacizumab or SOX plus bevacizumab. Randomisation was done centrally with the minimisation method, with stratification by institution and whether postoperative adjuvant chemotherapy had been given. To ensure allocation concealment, a minimisation algorithm with an 80:20 random element was used. The randomisation sequence was generated by a team (EPS Corporation, Tokyo, Japan; independent from the trial sponsor and investigators) who used a validated computer system. Local investigators used a web-based system during enrolment, which then automatically assigned patients to treatment groups.

- **Blinding (masking)**

Not applicable.

- **Statistical methods**

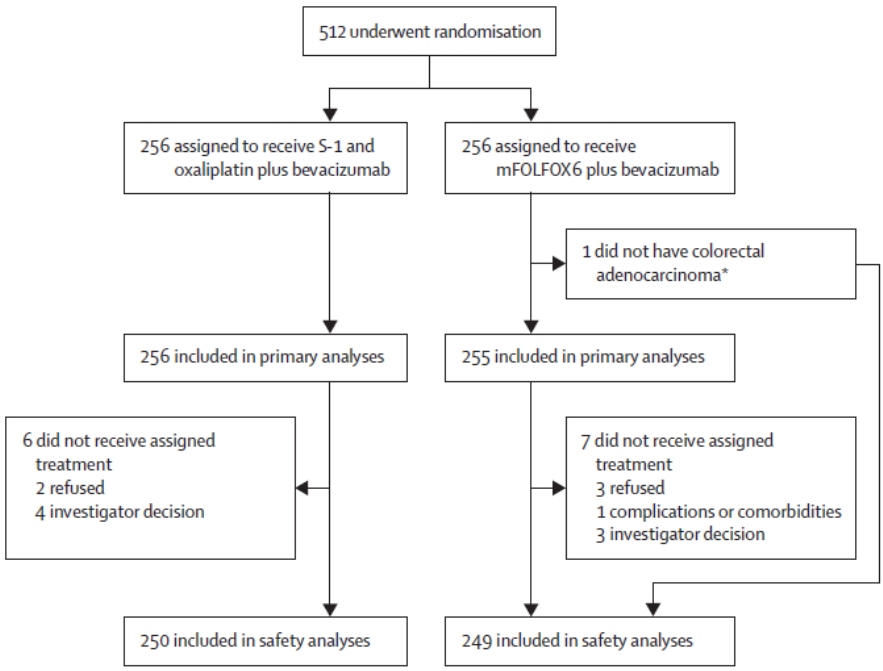
The primary analysis of the primary endpoint would occur at the end of the month in which the number of progression events reached 388. Primary analyses were performed by modified intention to treat: individuals who underwent randomisation but who were subsequently shown not to meet inclusion criteria were excluded. A per-protocol sensitivity analysis of PFS was also performed. Time-dependent events were estimated with the Kaplan-Meier method. HRs and their CIs were calculated with the Cox proportional-hazards model, adjusted for whether postoperative adjuvant chemotherapy had been given and the treatment groups as covariate. CIs for median PFS were calculated with Brookmeyer and Crowly's method. The follow-up periods for PFS and OS were calculated separately for censored patients only. Additionally, interaction tests were done to assess the treatment effects by baseline characteristics, such as history of adjuvant chemotherapy.

Patients who received at least one dose of the assigned study drugs were included in analyses of dose intensity and safety. For bevacizumab, body weight instead of body surface area was used as is recommended by the manufacturer. For the calculation of relative dose intensity and dose delays or modifications, up to 24 cycles of mFOLFOX6 plus bevacizumab and 16 cycles of SOX plus bevacizumab were included. All statistical analysis was done in SAS (version 9.2).

Results

- **Participant flow**

Figure 14. Participant flow SOFT trial



- **Recruitment**

Between Feb 1, 2009, and March 31, 2011, 512 patients were enrolled (see also Figure 14).

- **Conduct of the study**

The study was done in accordance with the ethical principles of the Declaration of Helsinki and in compliance with ethical guidance for clinical studies in Japan. An institutional clinical trial review board

or a corresponding committee at every participating hospital reviewed the ethical and scientific appropriateness of the study and granted approval. All participants provided written informed consent.

Please also refer to the Methods section (study participants) for a change in exclusion criteria due to the occurrence of gastrointestinal perforation in the SOX + bevacizumab arm.

- **Baseline data**

The demographic characteristics of patients included in the primary analyses are shown in Table 12. Six patients had sequentially received more than one adjuvant chemotherapy regimen in each group.

Table 12. Baseline characteristics SOFT trial

	Patients assigned to mFOLFOX6 plus bevacizumab (n=255)	Patients assigned to S-1 and oxaliplatin plus bevacizumab (n=256)
Men	159 (62%)	170 (66%)
Women	96 (38%)	86 (34%)
Age (years)	63 (39–79)	63 (33–79)
Primary lesion		
Colon	126 (49%)	131 (51%)
Rectosigmoid	41 (16%)	44 (17%)
Rectum	88 (35%)	78 (30%)
Other	0	3 (1%)
Differentiation assessed by histology		
Well or moderate	217 (85%)	220 (86%)
Poorly	10 (4%)	11 (4%)
Other	28 (11%)	25 (10%)
Adjuvant chemotherapy for colorectal cancer		
No	216 (85%)	217 (85%)
Yes	39 (15%)	39 (15%)
Fluorouracil plus leucovorin	2 (<1%)	5 (2%)
Uracil and tegafur plus leucovorin	22 (9%)	16 (6%)
Uracil and tegafur	3 (1%)	6 (2%)
S-1	9 (4%)	6 (2%)
Capecitabine	7 (3%)	7 (3%)
Other	2 (<1%)	5 (2%)
Target lesion		
No	22 (9%)	22 (9%)
Yes	233 (91%)	234 (91%)
Liver metastases		
No	91 (36%)	86 (34%)
Yes	164 (64%)	170 (66%)
Lung metastases		
No	137 (54%)	147 (57%)
Yes	118 (46%)	109 (43%)
Lymph node metastases		
No	187 (73%)	194 (76%)
Yes	68 (27%)	62 (24%)
Other metastases		
No	208 (82%)	194 (76%)
Yes	47 (18%)	62 (24%)
Metastatic organs		
1	126 (49%)	117 (46%)
≥2	129 (51%)	139 (54%)

Data are n (%) or median (range). mFOLFOX6=modified regimen of leucovorin, fluorouracil, and oxaliplatin.

- **Numbers analysed**

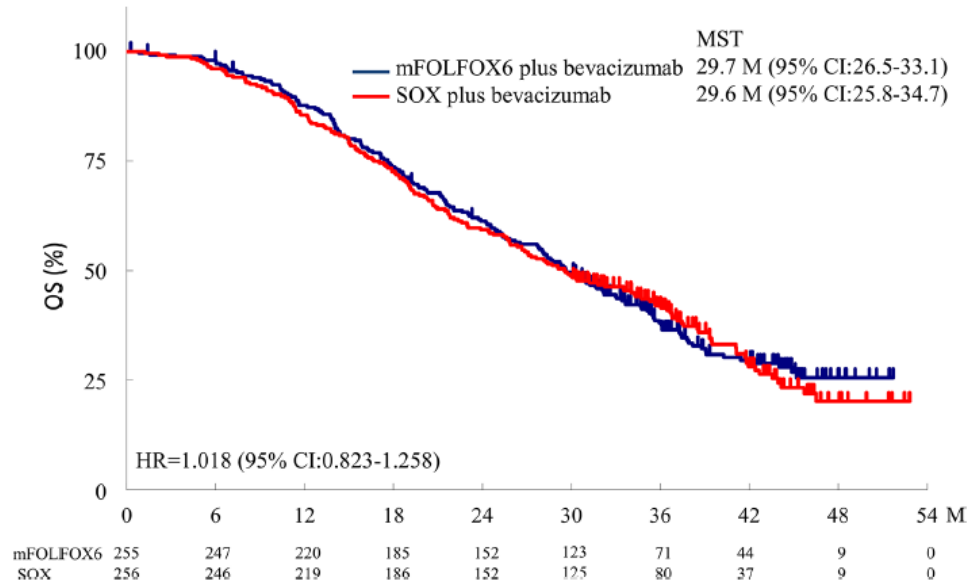
The cutoff date for primary analysis of the primary endpoint was June 30, 2012. One patient assigned to receive mFOLFOX6 plus bevacizumab was identified as not having a colorectal adenocarcinoma after randomisation and was for that reason excluded from primary analyses.

- **Outcomes and estimation**

Median PFS was 11.5 months (95% CI 10.7-13.2) for mFOLFOX6/bevacizumab and 11.7 months (95% CI 10.7-12.9) for SOX/bevacizumab (HR 1.04, 95% CI 0.86-1.27; less than the non-inferiority margin of 1.33; p noninferiority=0.014). These data also met a non-inferiority margin of 1.23 for PFS in post-hoc analysis.

In an updated analysis of the secondary endpoint of OS, HR [95%CI] of SOX/bevacizumab to mFOLFOX6/bevacizumab was 1.018 [0.823, 1.258] (median OS: 29.6 months vs. 29.7 months) at the final cut-off date. The survival curves are shown in Figure 15.

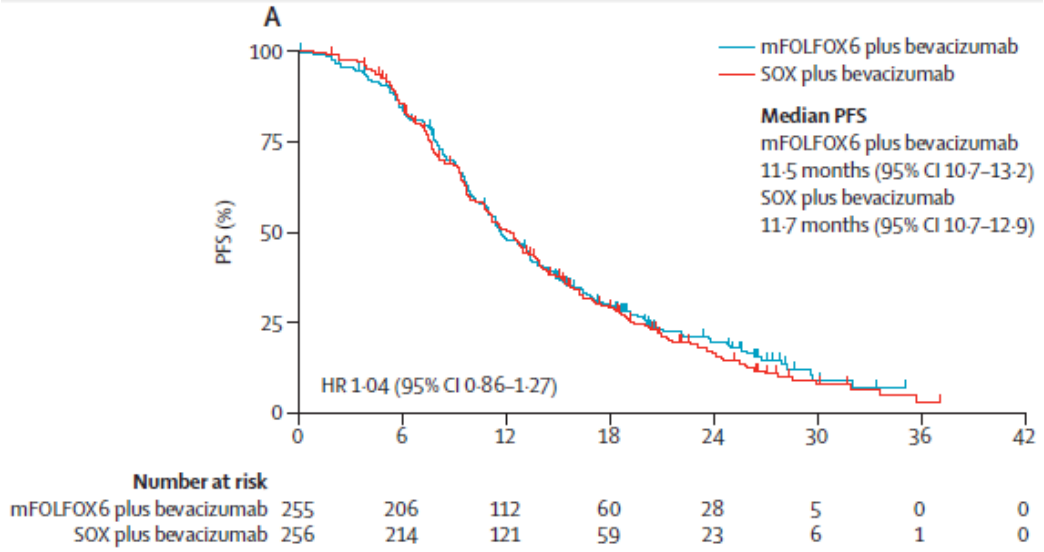
Figure 15. OS results SOFT trial (Baba et al., 2017)



Median follow-up for the PFS analysis was 18.4 months (IQR 13.1–24.9), and 413 events were confirmed during this period. In addition to the ITT PFS results reported above (see also Figure 16), results in the per-protocol analysis were described: PFS was 11.5 months (95% CI 10.4–13.2) in the group assigned to mFOLFOX6 plus bevacizumab and 11.5 months (10.6–12.7) in the group assigned to SOX plus bevacizumab (HR 1.04, 95% CI 0.86–1.27, p non-inferiority=0.015). Median PFS based on RECIST was shorter than that solely based on investigator discretion, but non-inferiority was confirmed (p non-inferiority=0.0057; Figure 16). In the subgroup analysis of PFS, no significant interactions were recorded between the assigned regimen and any factors (Figure 17).

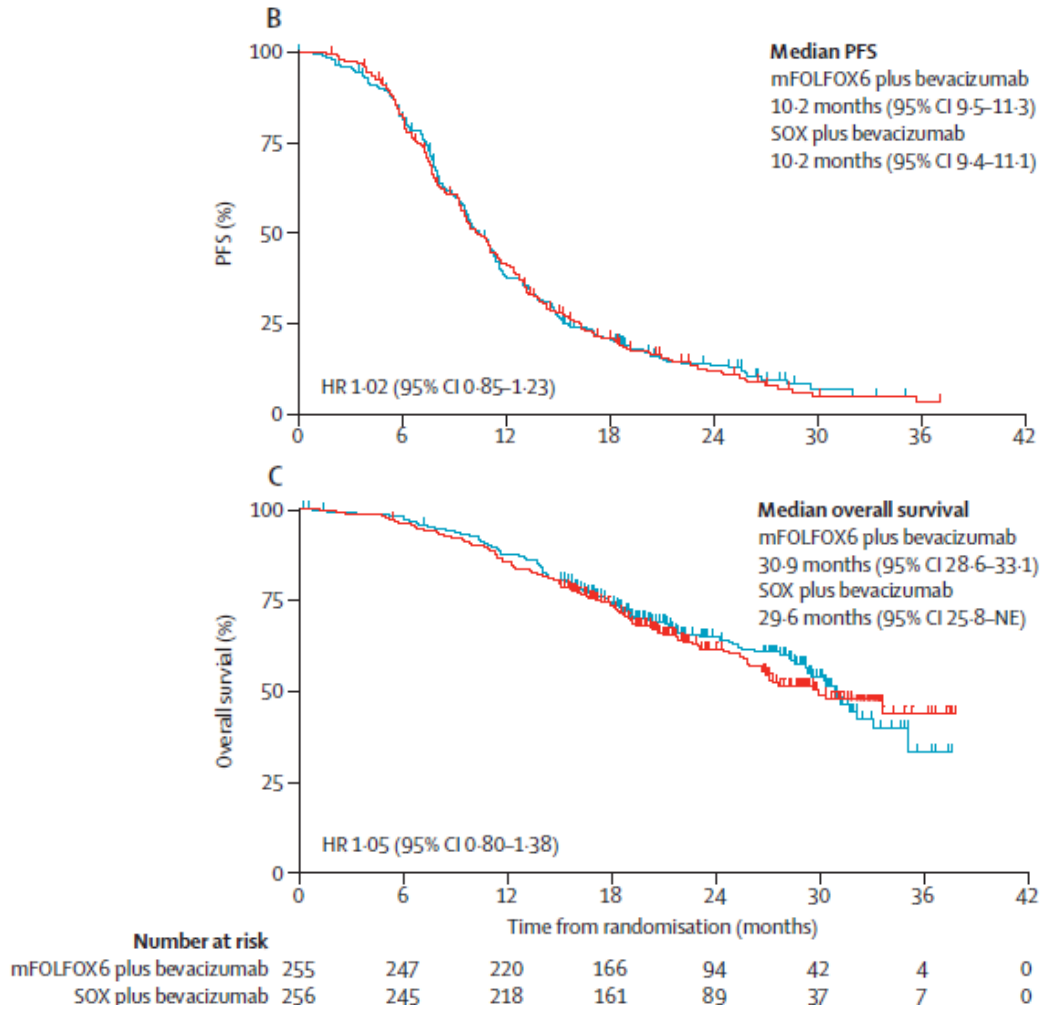
After a median follow-up of 23.4 months (IQR 19.5–29.6), 105 patients (41%) assigned to mFOLFOX6 plus bevacizumab had died (98 because of progressive disease, 2 because of other diseases, 3 because of other reasons, 2 for unknown reasons) as had 109 (43%) assigned to SOX plus bevacizumab (102 because of progressive disease, 4 because of other diseases, 1 because of other reasons, and 2 for unknown reasons). Median overall survival did not differ between groups (Figure 16).

Figure 16. Kaplan-Meier curves SOFT trial for PFS assessed by investigator (A), PFS assessed with RECIST (B), and OS (C)



Number at risk

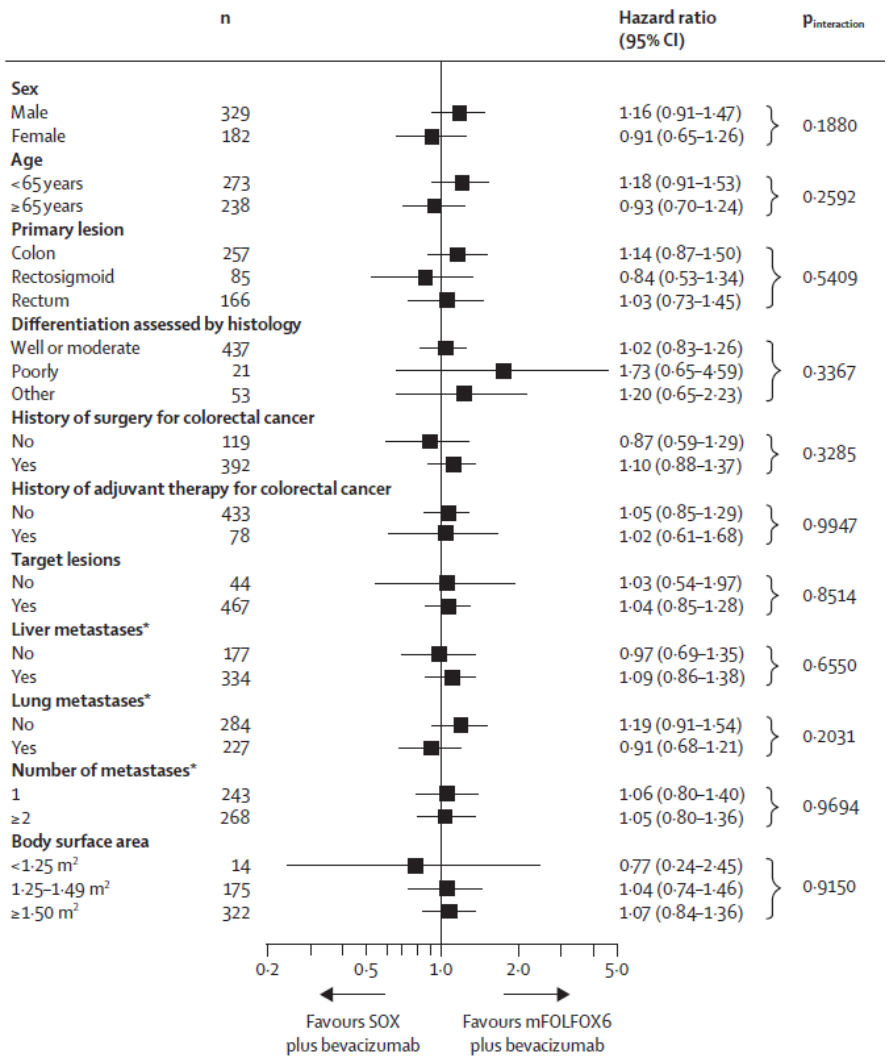
mFOLFOX6 plus bevacizumab	255	206	112	60	28	5	0	0
SOX plus bevacizumab	256	214	121	59	23	6	1	0



Number at risk

mFOLFOX6 plus bevacizumab	255	247	220	166	94	42	4	0
SOX plus bevacizumab	256	245	218	161	89	37	7	0

Figure 17. Subgroup analysis of PFS SOFT trial



In the group assigned to mFOLFOX6 plus bevacizumab, 146 patients (63%) had a complete or partial response and 208 (89%) achieved disease control (7 achieved complete response, 139 partial response, 62 stable disease). In the group assigned to SOX plus bevacizumab, 144 patients (62%) had a complete or partial response and 209 (89%) achieved disease control (4 achieved complete response, 140 partial response, 65 stable disease). 22 patients (9%) assigned to mFOLFOX6 plus bevacizumab and 24 (9%) assigned to SOX plus bevacizumab underwent curative resection after completion of first-line treatment (p=0.77). Four patients in the group assigned to SOX plus bevacizumab and nine in the group assigned to mFOLFOX6 plus bevacizumab had progressive disease. 16 patients in the group assigned to mFOLFOX6 plus bevacizumab and 21 in the group assigned to SOX plus bevacizumab were not assessed.

Median time to treatment failure was 6.7 months (95% CI 5.9–7.6) in patients assigned to mFOLFOX6 plus bevacizumab and 6.2 months (5.7–7.1) in those assigned to SOX plus bevacizumab.

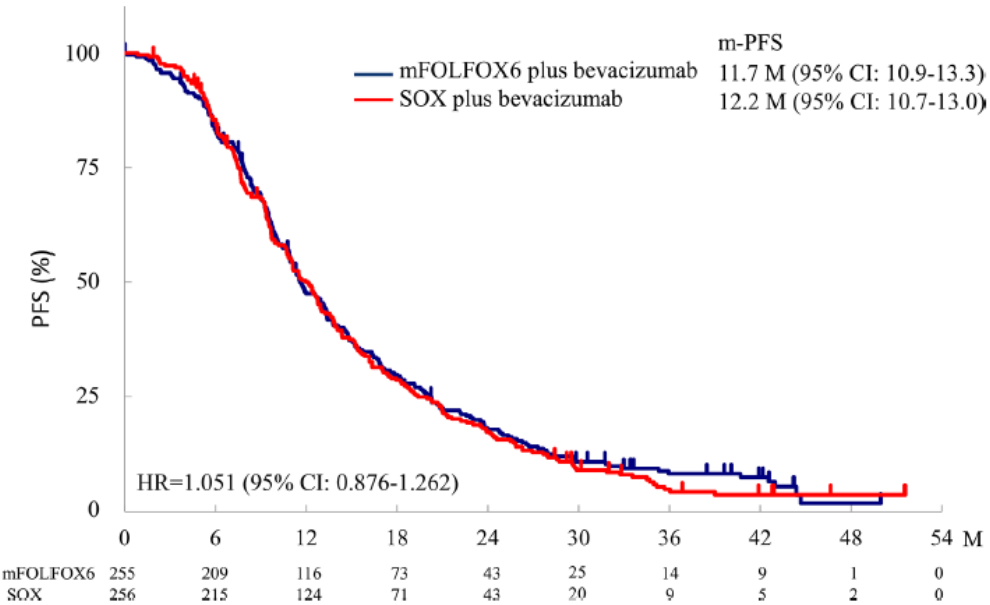
Treatment had been discontinued at data cutoff in 247 patients given mFOLFOX6 plus bevacizumab and 246 given SOX plus bevacizumab. A few reasons for discontinuation of treatment were recorded: progressive disease (95 [38%] of the 247 given mFOLFOX6 plus bevacizumab; 93 [38%] of the 246 given SOX plus bevacizumab); investigators judged surgery to be possible because of tumour shrinkage (25 [10%]; 28 [11%]); and requests from patients and adverse events (127 [51%]; 125 [51%]). 188 patients given mFOLFOX6 plus bevacizumab and 198 given SOX plus bevacizumab received second-line treatment. Irinotecan was used as second-line treatment in 122 (65%) of the 188 patients given

mFOLFOX6 plus bevacizumab, oxaliplatin in nine (5%), bevacizumab in 70 (37%), cetuximab in ten (5%), and panitumumab in nine (5%). Irinotecan was used in 116 (59%) of the 198 patients given SOX plus bevacizumab, oxaliplatin in 23 (12%), bevacizumab in 67 (34%), cetuximab in 15 (8%), and panitumumab in nine (5%).

Due to the immaturity of the data reported by Yamada et al., 2013, updated data were published by Baba et al., 2017. As of September 30, 2013, the final cut-off date for data collection, median follow-up for the OS analysis was 37.7 months (range, 0.3–52.8). In the mFOLFOX6 plus bevacizumab group, 169 patients (66.3%) had died. The causes of death were progressive disease in 161 patients, other diseases in 2 patients, other reasons in 3 patients and unknown in 3 patients. In the SOX plus bevacizumab group, 174 patients (68.0%) were confirmed to have died. The causes of death were progressive disease in 165 patients, other diseases in 5 patients, other reasons in 2 patients and unknown in 2 patients. In both groups combined, a total of 343 patients had died, representing an increase of 129 deaths as compared with the primary analysis.

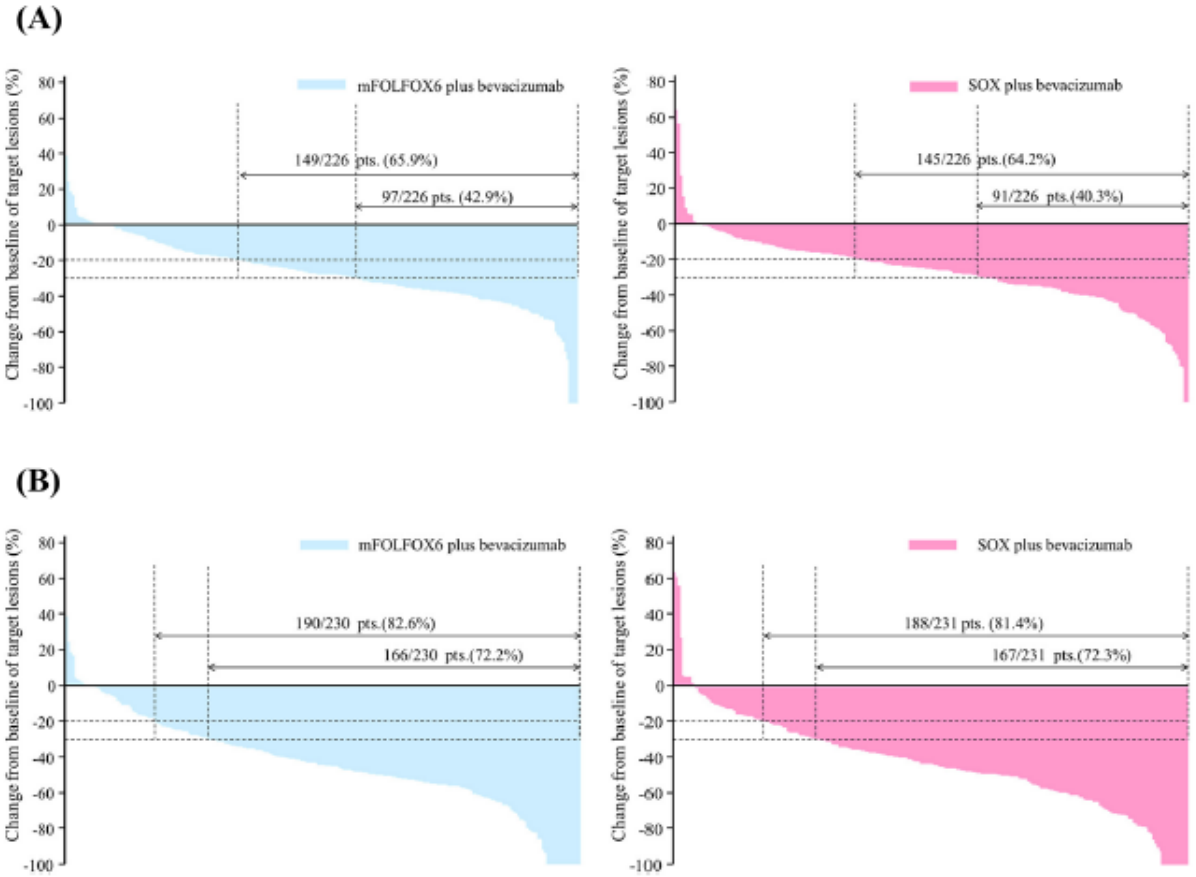
Median OS was 29.7 months (95% CI 26.5 to 33.1) in the mFOLFOX6 plus bevacizumab group and 29.6 months (25.8–34.7) in the SOX plus bevacizumab group (HR, 1.018; 95% CI 0.823 to 1.258; p non-inferiority=0.0133; Figure 15 as provided by MAH in clinical overview). Median OS did not differ between the groups. In the subgroup analysis of OS, a significant interaction was observed between assigned regimen and number of metastases (1 vs ≥2) (p=0.0247, HR in group with 1 metastasis 1.331 (95% CI 0.967-1.832) vs HR in ≥2 metastases 0.811 (95% CI 0.610-1.077). When data collection was finally cut-off, the median follow-up for PFS analysis was 31.2 months (range, 0.0–51.6), and 465 events were confirmed. Median PFS was 11.7 months (95% CI 10.9 to 13.3) in the mFOLFOX6 plus bevacizumab group and 12.2 months (10.7–13.0) in the SOX plus bevacizumab group (HR, 1.051; 95% CI 0.876 to 1.262; p non-inferiority=0.0115; Figure 18). The response rates (62.7% for mFOLFOX6 plus bevacizumab, 61.5% for SOX plus bevacizumab) were similar to those in the primary analysis.

Figure 18. Updated Kaplan-Meier curves PFS SOFT trial



The waterfall plots represent the individual responses of target lesions evaluated according to RECIST in each group (Figure 19). At the first evaluation at 8 weeks, the number of patients with early tumour shrinkage (ETS) was 149 (65.9%) of 226 in the mFOLFOX6 plus bevacizumab group and 145 (64.2%) of 226 in the SOX plus bevacizumab group (p=0.6932). The median depth of response was 44.4% in the mFOLFOX6 plus bevacizumab group (230 patients) and 43.5% in the SOX plus bevacizumab group (231 patients).

Figure 19. Waterfall plots SOFT trial first evaluation at 8 weeks (A) and maximum tumour response (B)



The median number of administered treatment cycles, including cycles in which protocol treatment continued but oxaliplatin (L-OHP) was omitted, was 12 (range, 1 to 97+) in the mFOLFOX6 plus bevacizumab group and 8 (range, 1–58) in the SOX plus bevacizumab group. Two patients continued to receive mFOLFOX6 plus bevacizumab at the time of data cut-off. Among patients who discontinued the study treatment, second-line treatment was given to 203 (80.2%) of the 253 patients in the mFOLFOX6 plus bevacizumab group and 209 (81.6%) of the 256 patients in the SOX plus bevacizumab group.

Irinotecan combination regimens

Yamada et al., Annals of Oncology, 2018, S-1 and irinotecan plus bevacizumab versus mFOLFOX6 or CapeOX plus bevacizumab as first-line treatment in patients with metastatic colorectal cancer (TRICOLORE); a randomized, open-label, phase III, noninferiority trial.

Methods

- **Study participants**

The TRICOLORE study was a randomised, phase 3, non-inferiority trial of IRIS/bevacizumab vs mFOLFOX6/bevacizumab or CapeOX/bevacizumab for first-line treatment of mCRC patients in Japan.

The main inclusion criteria were histologically confirmed colorectal adenocarcinoma; unresectable mCRC; age 20 years or older; ECOG performance status of 0 or 1; no previous chemotherapy or radiotherapy; adequate oral intake; and adequate organ function. The main exclusion criteria were sensory

neuropathy; serious diarrhea; gastrointestinal obstruction; symptomatic peritoneal metastasis; and a history of gastrointestinal perforation within the 6 months before enrollment. All patients provided written informed consent before enrollment.

- **Treatments**

The mFOLFOX6 plus bevacizumab regimen consisted of bevacizumab (5mg/kg) given as an intravenous infusion on day 1 of each 2-week cycle, followed by a simultaneous intravenous infusion of oxaliplatin (85mg/m2) plus l-leucovorin (200mg/m2), an intravenous bolus 5-FU (400mg/m2), and a continuous intravenous infusion of 5-FU (2400mg/m2). The CapeOX plus bevacizumab regimen consisted of bevacizumab (7.5mg/kg) given as an intravenous infusion on day 1 of each 3-week cycle, followed by an intravenous infusion of oxaliplatin (130mg/m2). Capecitabine (1000mg/m2) was taken orally twice daily, from after dinner on day 1 to after breakfast on day 15, followed by a 7-day rest. The 3-week S-1 and irinotecan plus bevacizumab regimen consisted of bevacizumab (7.5mg/kg) given as an intravenous infusion on day 1 of each 3-week cycle, followed by an intravenous infusion of irinotecan (150mg/m2). S-1 (40mg/m2) was taken orally twice daily, from after dinner on day 1 to after breakfast on day 15, followed by a 7-day rest. The 4-week S-1 and irinotecan plus bevacizumab regimen consisted of bevacizumab (5mg/kg) given as an intravenous infusion on day 1 and day 15 of each 4-week cycle, followed by an intravenous infusion of irinotecan (100mg/m2). S-1 (40mg/m2) was taken orally twice daily, from after dinner on day 1 to after breakfast on day 15, followed by a 14-day rest. Cycles were repeated for each patient until criteria for withdrawal of the study treatment were met. For the mFOLFOX6 plus bevacizumab and CapeOX plus bevacizumab regimens, oxaliplatin-induced sensory neuropathy was taken into consideration, and treatment could be skipped if patients had received at least 600mg/m2 of oxaliplatin overall.

- **Objectives**

Not provided.

- **Outcomes/endpoints**

The primary endpoint of the TRICOLORE study was PFS with a pre-defined non-inferiority margin of 1.25. The primary endpoint PFS was defined as the period from the date of enrollment to the date of disease progression or of death from any cause without progression, whichever came first. Secondary endpoints were OS, TTF, response rate, adverse events, QoL, quality-adjusted life years (QALYs), cost-effectiveness, and biomarker analysis.

Tumour assessment by means of diagnostic imaging was carried out every 8 weeks, and tumour responses were assessed according to RECIST version 1.1. Observed adverse events were evaluated according to CTCAE v4.0. QoL was assessed according to FACT-C TOI scale and FACT/GOG-Ntx scale before the start of treatment and at 16 and 24 weeks.

- **Sample size**

On the basis of the results of previous studies, the median PFS was estimated to be 11 months for the control group and 12 months for the experimental group [hazard ratio (HR), 0.917]. Given that the permissible limit for the HR was 1.25, with a statistical power of 85%, an alpha level of 0.025 (one-sided), an enrollment period of 36 months, and a follow-up period of 18 months for the primary end point of PFS, it was estimated that 434 patients would be required (required number of events, 374). To compensate for ineligible patients, the target number of patients was set at 450.

- **Randomisation**

Participants were randomly assigned (1:1) to receive either mFOLFOX6 or CapeOX plus bevacizumab (control group) or to receive either a 3-week or a 4-week regimen of S-1 and irinotecan plus bevacizumab (experimental group). Each participating institution could select either mFOLFOX6 plus bevacizumab or CapeOX plus bevacizumab and either a 3-week or 4-week regimen of S-1 and irinotecan plus bevacizumab. After reporting to the data center (AC Medical Inc., Tokyo, Japan), patient enrollment was initiated. Randomisation was performed centrally using the minimisation method with the following stratification factors: institution; adjuvant chemotherapy (none, including oxaliplatin, or not including oxaliplatin); and the number of metastatic organs (0 or 1 versus ≥2).

- **Blinding (masking)**

Not applicable.

- **Statistical methods**

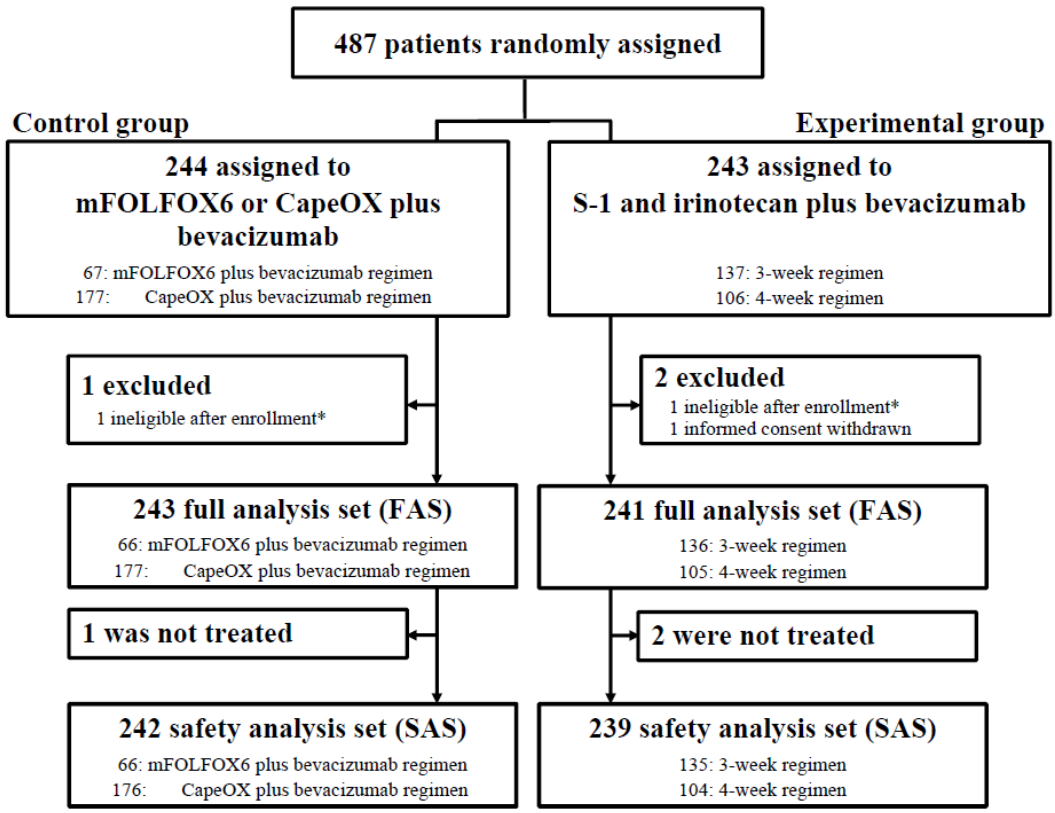
The non-inferiority margin for post-hoc analysis of TRICOLORE was set based on previous evidence that showed that FOLFIRI is clinically equivalent to FOLFOX or CapeOX in terms of efficacy (i.e. the efficacy of irinotecan is equivalent to oxaliplatin for the first-line treatment of colorectal cancer) (Colucci et al., 2005; Kozloff et al., 2009; Van Cutsem et al., 2009). Therefore, the post-hoc non-inferiority margin for the TRICOLORE study was set by the 50% effect retention method using the HR used in the EFC2962 trial that compared FOLFOX vs infusional 5-FU (non-inferiority margin = 1.23 for PFS) (de Gramont et al., 2000).

Noninferiority would be established if the upper limit of the 95% CI for the HR of the control group versus the experimental group was <1.25. If non-inferiority was demonstrated in the study, superiority would be tested. The primary analysis was conducted using the full analysis set on an ITT basis. Time-dependent events were estimated using the Kaplan–Meier method. HRs and their CIs were calculated with Cox proportional-hazards models and adjusted for stratification factors (excluding institutions) and treatment groups as covariates. Patients who received at least one dose of the assigned study drugs were included in the analyses of dose intensity and safety. QoL analysis was conducted using data from patients in the safety analysis population for whom the pretreatment QoL could be evaluated. All statistical analyses were carried out using SAS, version 9.4 (SAS Institute, Cary, NC). This trial is registered with UMIN-CTR (http://www.umin.ac.jp/ctr/) (000007834).

Results

- **Participant flow**

Figure 20. Participant flow TRICOLORE trial



*After randomization, it was verified that these patients did not have colorectal carcinoma.

- **Recruitment**

From 1 June 2012 through 16 September 2014, 487 patients from 53 institutions were randomly assigned, 244 patients to the control group and 243 patients to the experimental group (Figure 20). Two patients who were confirmed to have no colorectal adenocarcinoma after randomisation and one patient who withdrew consent were excluded from the primary analysis. The cut-off date for primary analysis of the primary end point was 30 April 2016.

- **Conduct of the study**

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and complied with the Japanese ethical guidelines for clinical studies. The study was approved by the institutional review board of each participating institution.

- **Baseline data**

Table 13. Baseline characteristics TRICOLORE trial

	mFOLFOX6 or CapeOX plus bevacizumab (*n* = 243)		S-1 and irinotecan plus bevacizumab (*n* = 241)	
	n	**(%)**	***n***	**(%)**
Sex				
Male	143	(58.8)	151	(62.7)
Female	100	(41.2)	90	(37.3)
PS (ECOG)				
0	205	(84.4)	204	(84.6)
1	38	(15.6)	37	(15.4)
Age				
Median [range]	65 [29–85]		64 [22–87]	
≥65	134	(55.1)	118	(49.0)
CCr at enrollment				
Median [range]	80.9 [60.0–153.1]		82.7 [60.0–182.8]	
≥70	181	(74.5)	185	(76.8)
Complications				
Yes	107	(44.0)	108	(44.8)
No	136	(56.0)	133	(52.2)
Adjuvant chemotherapy for colorectal cancer				
Yes	31	(12.8)	32	(13.3)
No	212	(87.2)	209	(86.7)
Differentiation assessed by histology				
Well or moderate	212	(87.2)	209	(86.7)
Poorly	14	(5.8)	14	(5.8)
Other	17	(7.0)	18	(7.5)
Primary lesion				
Colon	122	(50.2)	130	(53.9)
Rectosigmoid	39	(16.0)	32	(13.3)
Rectum	82	(33.7)	79	(32.8)
Primary lesion resection				
Yes	164	(67.5)	156	(64.7)
No	79	(32.5)	85	(35.3)
Metastatic organs				
0–1	124	(51.0)	127	(52.7)
≥2	119	(49.0)	114	(47.3)
Target lesion				
Yes	221	(90.9)	214	(88.8)
No	22	(9.1)	27	(11.2)
RAS status				
Wild type	99	(40.7)	105	(43.6)
Mutant type	65	(26.7)	58	(24.1)
Not definable	6	(2.5)	3	(1.2)
Missing data	73	(30.0)	75	(31.1)

CCr, creatinine clearance.

- **Numbers analysed**

Please see Figure 20 above.

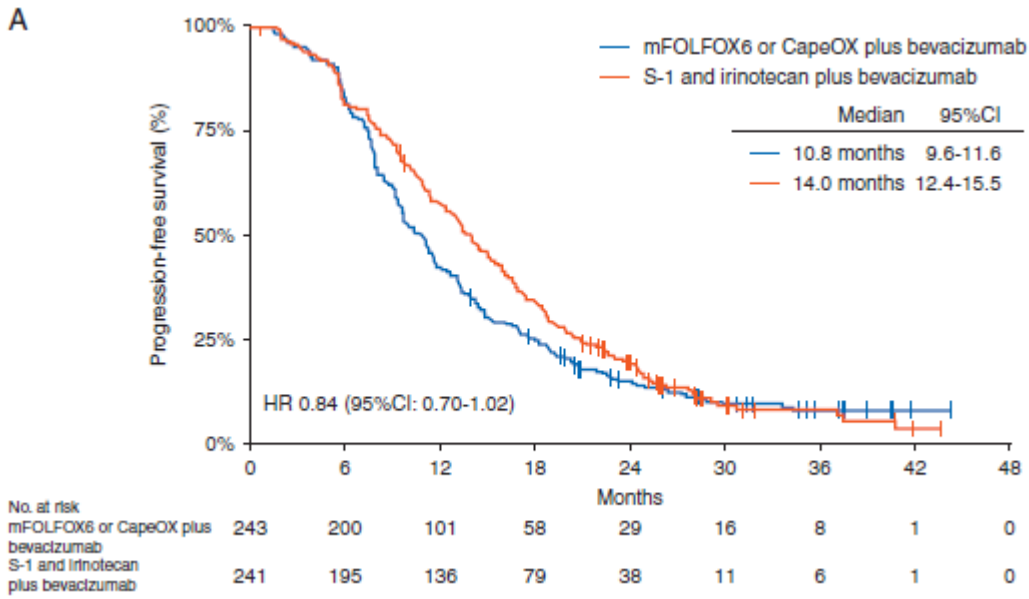
- **Outcomes and estimation**

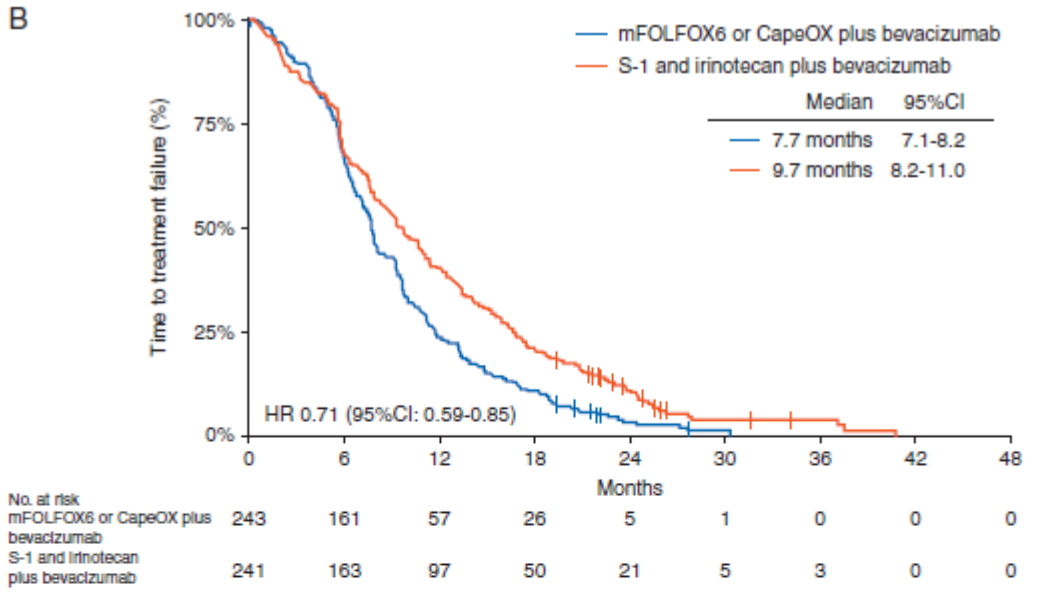
The hazard ratio [95% CI] of IRIS/bevacizumab compared to mFOLFOX6/bevacizumab or CapeOX/bevacizumab for PFS was 0.84 [0.70, 1.02] (median PFS: 14.0 months [95% CI 12.4-15.5] vs 10.8 months [95% CI 9.6-11.6]) which met the primary endpoint (p noninferiority<0.0001). The hazard ratio [95%CI] for IRIS/bevacizumab compared to mFOLFOX6/bevacizumab or CapeOX/bevacizumab for

the secondary endpoint of OS was 0.86 (0.66, 1.13) with median OS rates of 34.9 months and 33.6 months, respectively.

The median follow-up period was 32.4 months (range 1.5–46.6). During this period, PFS events occurred in 426 (88%) of 484 patients and PFS results are shown in Figure 21. The details of PFS for each chemotherapy regimen are given in Figure 22. In the subgroup analysis of PFS, significant interactions were observed between the allocated groups and age (Figure 23). Median TTF in the control group and the experimental group was 7.7 months (95% CI 7.1–8.2) and 9.6 months (95% CI 8.2–11.0), respectively (HR 0.71, 95% CI 0.59–0.85, p=0.0002; Figure 21). The response rate of target lesions was 70.6% in the control group and 66.4% in the experimental group (p=0.34; Table 14). The curative resection rate was 8.6% in the control group and 12.4% in the experimental group (p=0.17). OS analysis was conducted on the basis of 218 deaths (45%) among 484 patients and results are shown in Figure 21. The p-value for OS was 0.2841.

Figure 21. Kaplan-Meier curves TRICOLORE trial for PFS (A), time to treatment failure (B), and OS (C)




B
100%
75%
50%
25%
0%
Time to treatment failure (%)
mFOLFOX6 or CapeOX plus bevacizumab
S-1 and irinotecan plus bevacizumab
Median 95%CI
7.7 months 7.1-8.2
9.7 months 8.2-11.0
HR 0.71 (95%CI: 0.59-0.85)
0 6 12 18 24 30 36 42 48
Months
No. at risk
mFOLFOX6 or CapeOX plus bevacizumab 243 161 57 26 5 1 0 0 0
S-1 and irinotecan plus bevacizumab 241 163 97 50 21 5 3 0 0

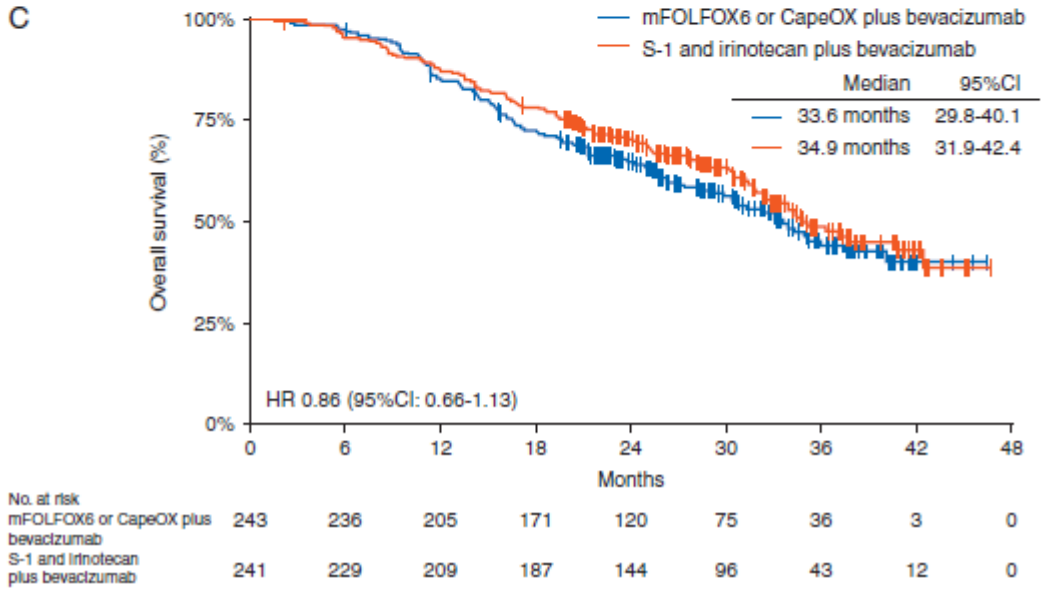

C
100%
75%
50%
25%
0%
Overall survival (%)
mFOLFOX6 or CapeOX plus bevacizumab
S-1 and irinotecan plus bevacizumab
Median 95%CI
33.6 months 29.8-40.1
34.9 months 31.9-42.4
HR 0.86 (95%CI: 0.66-1.13)
0 6 12 18 24 30 36 42 48
Months
No. at risk
mFOLFOX6 or CapeOX plus bevacizumab 243 236 205 171 120 75 36 3 0
S-1 and irinotecan plus bevacizumab 241 229 209 187 144 96 43 12 0

Figure 22. Kaplan-Meier curves TRICOLORE trial for PFS in each treatment regimen

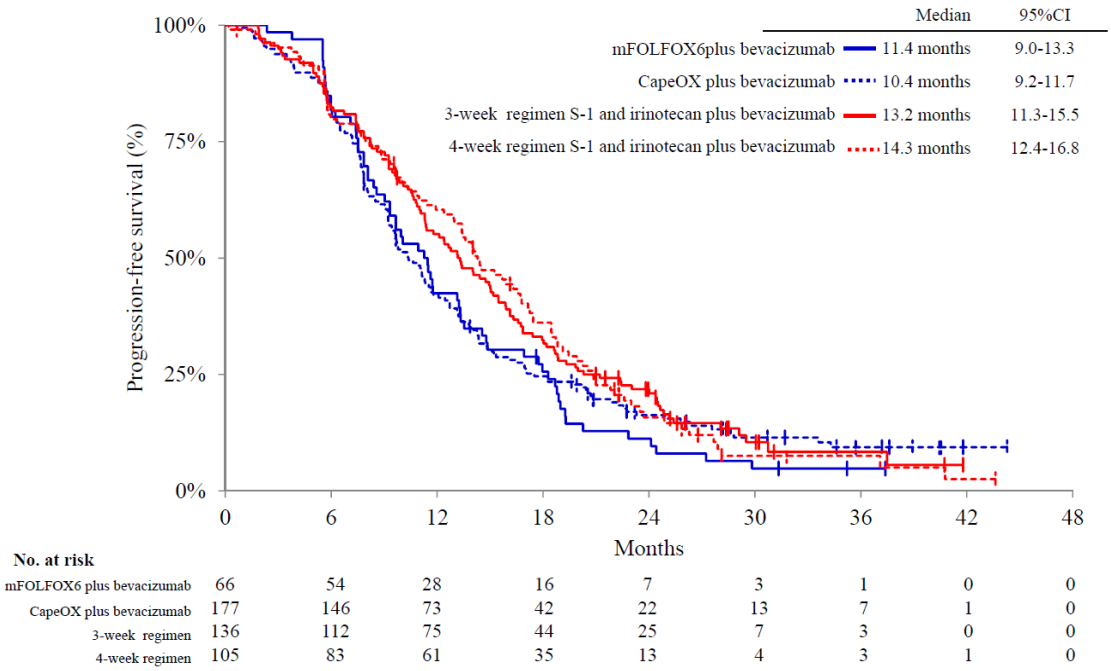


Figure 23. Subgroup analyses for PFS TRICOLORE trial

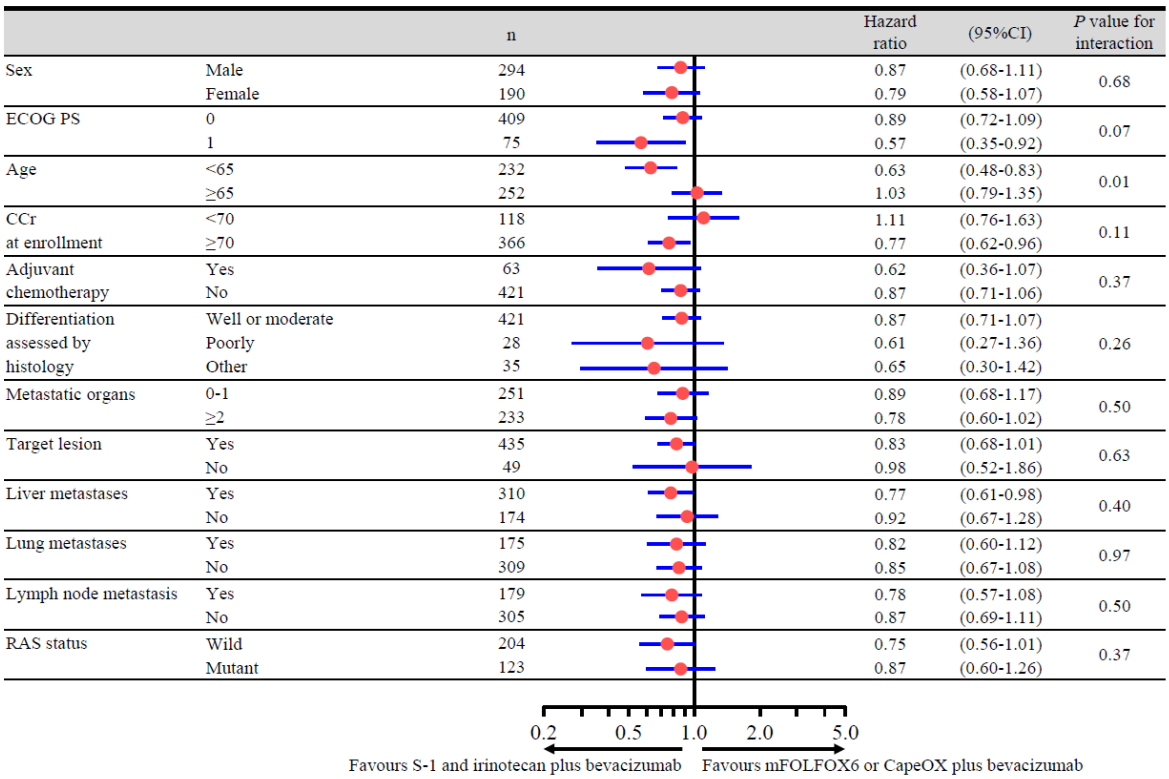


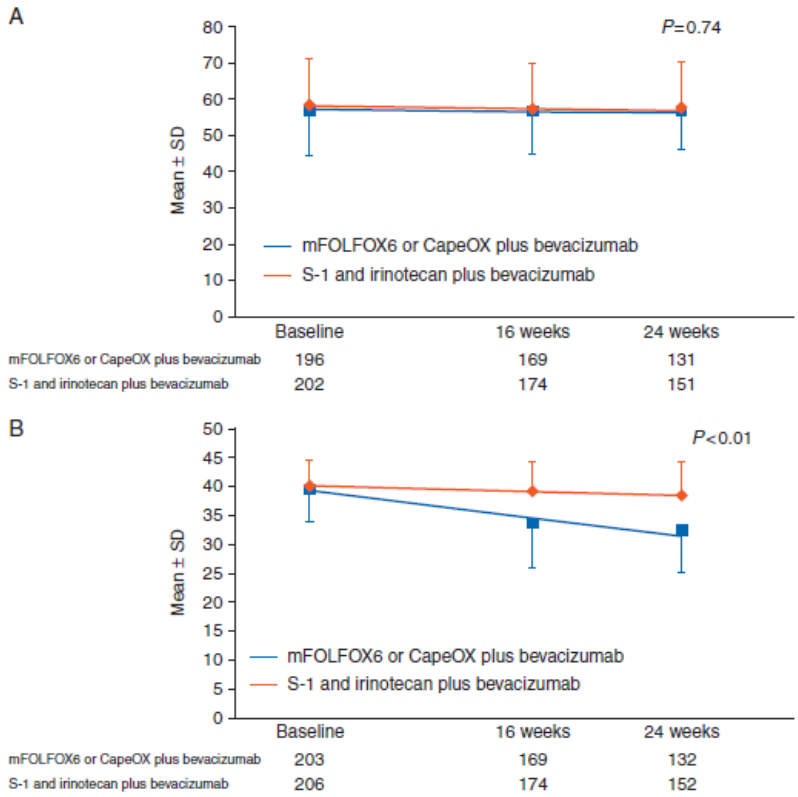
Table 14. Best overall response TRICOLORE trial

	mFOLFOX6 or CapeOX plus bevacizumab (*n*=221*)	S-1 and irinotecan plus bevacizumab (*n*=214*)
	n (%)	*n* (%)
complete response	15	12
partial response	141	130
stable disease	48	56
progressive disease	9	3
not evaluable	8	13
response rate	**156 (70.6)**	**142 (66.4)**

* Number of patients with measurable lesions according to RECIST version1.1.

Before treatment, 436 (90.6%) patients completed the QoL questionnaire. There was no statistically significant difference in the FACT-C TOI score trends over time between the control group and the experimental group (p=0.74; Figure 24). The FACT/GOG-Ntx scores showed a significantly more favorable trend over time in the experimental group (p<0.01; Figure 24).

Figure 24. Quality of life assessed by (A) FACT-C TOI and (B) FACT/GOG-Ntx. The line on the graph is a straight line drawn from average values using a mixed-effects model. FACT-C TOI, the Functional Assessment of Cancer Therapy-Colorectal Trial Outcome Index scale; FACT/GOGNtx, the neurotoxicity subscale of the FACT/Gynecology Oncology Group-Neurotoxicity.



The number of patients in whom the study treatment was discontinued by the data cut-off date was 235 in the control group and 226 in the experimental group. Among the patients whose study treatment was discontinued, second-line treatment was given to 206 patients (87.7%) in the control group and 198 patients (87.6%) in the experimental group. Oxaliplatin, irinotecan, bevacizumab, and EGFR antibodies were, respectively, administered to 12 (5.8%), 125 (60.7%), 111 (53.9%), and 26 (12.6%) patients in

the control group and 112 (56.6%), 22 (11.1%), 106 (53.5%), and 20 (10.1%) patients in the experimental group. In addition, 106 (53.5%) patients in the experimental group were given an oral fluoropyrimidine.

Muro et al., Lancet Oncology, 2010, Irinotecan plus S-1 (IRIS) versus fluorouracil and folinic acid plus irinotecan (FOLFIRI) as second-line chemotherapy for metastatic colorectal cancer: a randomised phase 2/3 non-inferiority study (FIRIS study).

Yasui et al., Journal of Cancer Research and Clinical Oncology, 2015, A phase 3 non-inferiority study of 5-FU/l-leucovorin/irinotecan (FOLFIRI) versus irinotecan/S-1 (IRIS) as second-line chemotherapy for metastatic colorectal cancer: updated results of the FIRIS study.

Methods

- **Study participants**

The FIRIS study was a phase 3 non-inferiority study of IRIS vs FOLFIRI for second-line treatment of metastatic colorectal cancer.

Inclusion criteria were histologically confirmed colorectal adenocarcinoma; unresectable metastatic disease; age 20–75 years; ECOG performance status of 0 or 1; withdrawal from first-line chemotherapy due to toxicity or progressive disease, or relapse within 24 weeks after the final dose of preoperative or postoperative chemotherapy; no previous treatment with irinotecan; sufficient oral intake; adequate organ function (white blood cell count 3000–12 000 cells per μL, platelet ≥100 000 per μL, aspartate aminotransferase [AST] ≤100 IU/L, alanine aminotransferase [ALT] ≤100 IU/L, total bilirubin ≤25.7 μmol/L [≤15 mg/L], and creatinine ≤106.1 μmol/L [≤12 mg/L]); and no abnormal electrocardiographic findings within 28 days before enrolment. Exclusion criteria were pregnancy or lactation; second non-colorectal cancer; complications such as ileus, uncontrolled diabetes mellitus, or hypertension; severe diarrhoea; clinically evident gastrointestinal haemorrhage; and ascites or pleural effusion needing treatment.

- **Treatments**

Patients in the FOLFIRI group received concurrent folinic acid (200 mg/m2) and irinotecan (150 mg/m2) and then a bolus injection of fluorouracil (400 mg/m2) on day 1 and subsequent continuous infusion of fluorouracil (2400 mg/m2) over 46 h, repeated every 2 weeks (4 weeks counted as one cycle). In the FOLFIRI group, the dose of irinotecan was 150 mg/m2, the approved dose in Japan. The IRIS group received irinotecan (125 mg/m2) on days 1 and 15 and S-1 (40 mg for patients with body surface area [BSA] <1.25 m2; 50 mg for patients with BSA 1.25<1.5 m2; 60 mg for patients with BSA ≥1.5 m2) twice daily for 2 weeks from days 1–14 and then a 2-week pause, on the basis of results of phase 2 studies. This regimen was selected from several documented regimens of irinotecan and S-1 to match the regimen of FOLFIRI in the control arm. Regimens in which irinotecan is given every 2 weeks and every 3 weeks are in clinical use in Japan.

In both FOLFIRI and IRIS groups, treatment was delayed until recovery if white blood cell count fell below than 3000 cells per μL, platelets fell below 100 000 per μL, AST or ALT were over 100 IU/L, total bilirubin was higher than 25.7 μmol/L, creatinine was higher than 106.1 μmol/L, the patient experienced diarrhoea of grade one or greater, or other non-haematological toxicities greater than grade two. If a patient experienced a grade four haematological or grade three or higher non-haematological toxicity, the dose was decreased by one level for the next course of treatment, and therapy was resumed.

Treatment was continued until progressive disease, unacceptable toxicity, or patient's refusal to continue treatment. Because molecularly targeted agents such as bevacizumab, cetuximab, and panitumumab were not approved in Japan at the start of the study, no restriction for such agents was specifically placed on treatment before or after the study.

- **Objectives**

The primary objective of our study was to show non-inferiority of IRIS to FOLFIRI for progression-free survival in the whole randomised population.

- **Outcomes/endpoints**

The primary endpoint of the FIRIS study was PFS with a pre-defined non-inferiority margin of 1.333. PFS was counted from the date of randomisation to the date when the progressive disease was first confirmed by the investigator's assessment. For patients without documented progressive disease, data was censored on the date of the last tumour assessment with non-progression status. OS was calculated from the date of randomisation to the date of death or confirmation of survival. Toxicity was evaluated on the basis of CTCAE version 3.0.

Physical examination, electrocardiography, performance status, and laboratory tests were done at baseline and repeated at least every 2 weeks during treatment. Tumours were assessed at baseline (within 1 month before enrolment), and at 2, 3, and 4 months after enrolment, and thereafter every 2 months until progression. Progression was defined as progressive disease on the basis of RECIST version 1.0, clinical progression judged by the investigator, or death from any cause without progression.

- **Sample size**

On the basis of data from previous reports in patients with metastatic colorectal cancer who received second-line chemotherapy, median PFS with both FOLFIRI and IRIS was assumed to be 4 months. The steering committee deemed that response assessment could not be repeated more frequently than once a month, so a difference in progression-free survival shorter than 1 month could not be detected precisely. Thus, PFS with IRIS that was 1 month shorter than with FOLFIRI would be acceptable as a lower margin for inferiority, given the expected HR of 1.0. The 95% CI upper limit of the HR, calculated using Cox regression analysis with stratification factors other than institution, was prespecified as less than 1.333, meaning the null hypothesis was that median progression-free survival with IRIS would be 1 month shorter than with FOLFIRI. Because 379 events were needed to show non-inferiority with a two-sided α of 0.05 and a power of 80%, a target sample size of 400 patients was required.

- **Randomisation**

Investigators provided the patient's details to the central registration centre through a web-based registration system. After an eligibility check, patients were randomly assigned to receive FOLFIRI or IRIS at the central registration centre by a computer program, by use of a minimisation method with stratification by institution, prior therapy (with or without oxaliplatin), and performance status (0 or 1). Assignment of patients was concealed from the investigator. Treatment assignment was not masked from the investigators or patients.

- **Blinding (masking)**

Not applicable.

- **Statistical methods**

The FIRIS study was a non-inferiority study of IRIS (Teysuno/Irinotecan) vs FOLFIRI for second-line treatment of mCRC. The primary efficacy analysis was done with all randomised patients. A per-protocol analysis in which patients in whom there was a major violation such as inclusion or exclusion criteria or protocol treatments were excluded was also performed. Safety was assessed in all patients who received at least one dose of the study drug.

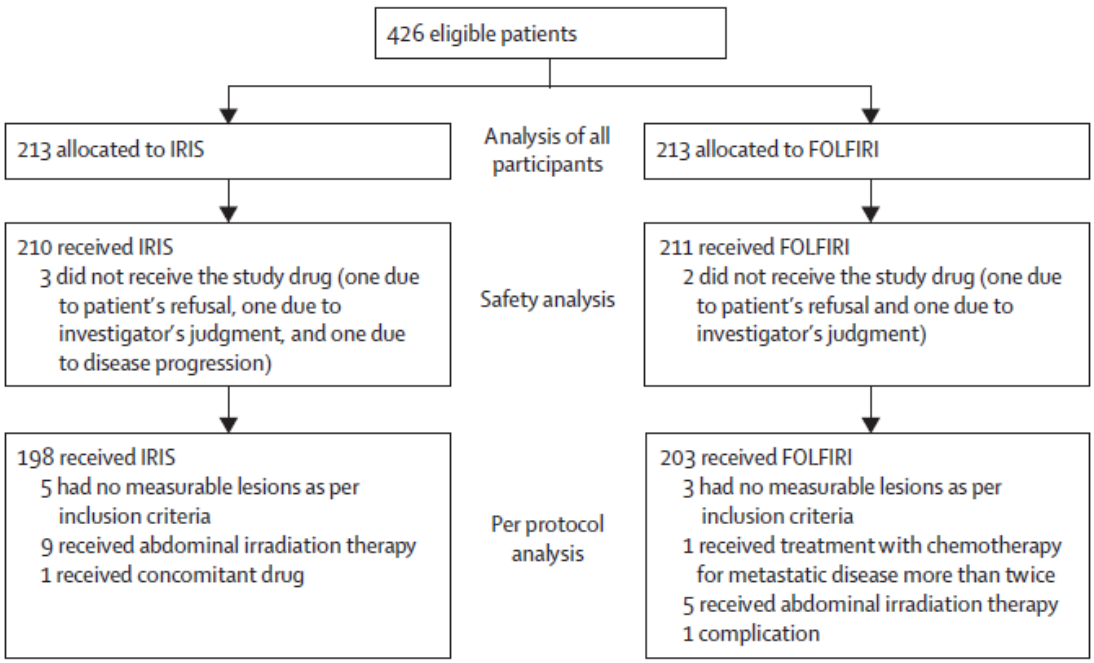
The primary endpoint was PFS. Secondary endpoints were OS, response rate, and toxicity. Subgroup analyses were done to establish whether therapeutic efficacy was affected by sex, age, histological type, performance status, and prior chemotherapy with or without oxaliplatin. PFS and OS were estimated using the Kaplan-Meier method. The 95% CI for median PFS and OS was calculated using the method of Brookmeyer and Crowley. All p values were two-sided. All statistical analyses were done with SAS version 8.2.

This study is registered with ClinicalTrials.gov, number NCT00284258.

Results

- **Participant flow**

Figure 25. Participant flow FIRIS trial



- **Recruitment**

Please refer to Figure 25.

- **Conduct of the study**

The protocol of this study was approved by the institutional review board or ethics committee of each institution. The study was conducted in compliance with the Declaration of Helsinki. Written informed consent was obtained from all patients participating in the study.

- **Baseline data**

Table 15. Baseline characteristics FIRIS trial

	FOLFIRI (n=213)	IRIS (n=213)
Sex		
Male	123 (57·7%)	120 (56·3%)
Female	90 (42·3%)	93 (43·7%)
Age (years)	63·0 (32–75)	61·0 (29–75)
ECOG performance status		
0	160 (75·1%)	158 (74·2%)
1	53 (24·9%)	55 (25·8%)
Histological type		
Well differentiated	62 (29·1%)	60 (28·2%)
Moderately differentiated	124 (58·2%)	133 (62·4%)
Poorly differentiated	13 (6·1%)	8 (3·8%)
Other	13 (6·1%)	11 (5·2%)
Undetermined	1 (0·5%)	1 (0·5%)
Previous chemotherapy with oxaliplatin		
Yes	128 (60·1%)	129 (60·6%)
No	85 (39·9%)	84 (39·4%)
Number of metastatic sites		
One	92 (43·2%)	88 (41·3%)
Two or more	120 (56·3%)	124 (58·2%)

Data are number (%) or median (range). FOLFIRI=folinic acid, fluorouracil, and irinotecan. IRIS=irinotecan and S-1. ECOG=Eastern Cooperative Oncology Group.

- **Numbers analysed**

426 patients from 40 institutions in Japan were enrolled in the study from Jan 30, 2006, to Jan 29, 2008, and randomised either to the FOLFIRI or IRIS group (213 patients in each; Figure 25). Of the per-protocol population, 203 patients were in the FOLFIRI group and 198 were in the IRIS group; reasons for exclusion are shown in Figure 25. All patients who received study treatment (211 patients in the FOLFIRI group and 210 patients in the IRIS group) were included in the safety evaluation.

- **Outcomes and estimation**

Median PFS for IRIS was 5.8 months compared to 5.1 months for FOLFIRI. The hazard ratio [95% CI] for IRIS compared to FOLFIRI for PFS was 1.077 [0.897, 1.319] which met the primary endpoint of noninferiority (Muro et al., 2010). The hazard ratio [95%CI] of IRIS to FOLFIRI for the secondary endpoint of OS as was 0.900 [0.728, 1.112].

The mean number of cycles of protocol treatment was 4.7 (range 1–20) for FOLFIRI and 4.9 (1–23) for IRIS. Treatments were discontinued because of disease progression in 68.5% (146 patients) in the FOLFIRI group and in 66.2% (141) in the IRIS group, adverse events in 10.8% (23) and in 16.9% (36), and patient's refusal 1.9% (four) and 6.1% (13). 179 patients in the FOLFIRI group and 184 patients in the IRIS group needed a dose delay or dose reduction. Treatment after the trial (i.e., treatment after failure of second-line regimen) was given to 159 (74.6%) patients in the FOLFIRI group and 147 (69.0%) in the IRIS group. As third-line treatment, an oxaliplatin-containing regimen was given to 58 (27.2%) patients in the FOLFIRI and 63 (29.6%) in the IRIS group. Molecularly targeted agents as treatments after the trial were used in 24 patients in the FOLFIRI group and 16 in the IRIS group.

As of Dec 31, 2008, collection of PFS and OS data was cut off, with 389 confirmed events (194 FOLFIRI and 195 IRIS). Median follow-up was 12.9 months (IQR 11.5–18.2). Median PFS was 5.1 months in the FOLFIRI group and 5.8 months in the IRIS group. In the entire randomised population, the HR of PFS in the IRIS group compared with the FOLFIRI group was 1.077 (95% CI 0.879–1.319, p=0.039). Similar results were seen in the per protocol population: median PFS was 5.1 months in the FOLFIRI group and 5.7 in the IRIS group (HR 1.050, 95% CI 0.851–1.294; Figure 26).

The data on OS were preliminary according to Muro et al., 2010, because of short follow-up. 117 of the 213 patients in the FOLFIRI group and 110 of the 213 patients in the IRIS group died due to any cause. Median OS in the entire randomised population was 18.2 months in the FOLFIRI group and 19.5 months in the IRIS group (HR 0.909, 95% CI 0.699–1.181; Figure 26). In the per protocol population, median OS was 18.1 months in the FOLFIRI group and 19.3 months in IRIS group (HR 0.896, 95% CI 0.685–1.172).

The overall response rate was 16.7% (one patient had a complete response, 28 patients had a partial response) of 174 patients with evaluable response data in the FOLFIRI group and 18.8% (one patient had a complete response, 33 patients had a partial response) of 181 in the IRIS group.

Figure 26. PFS and OS FIRIS trial

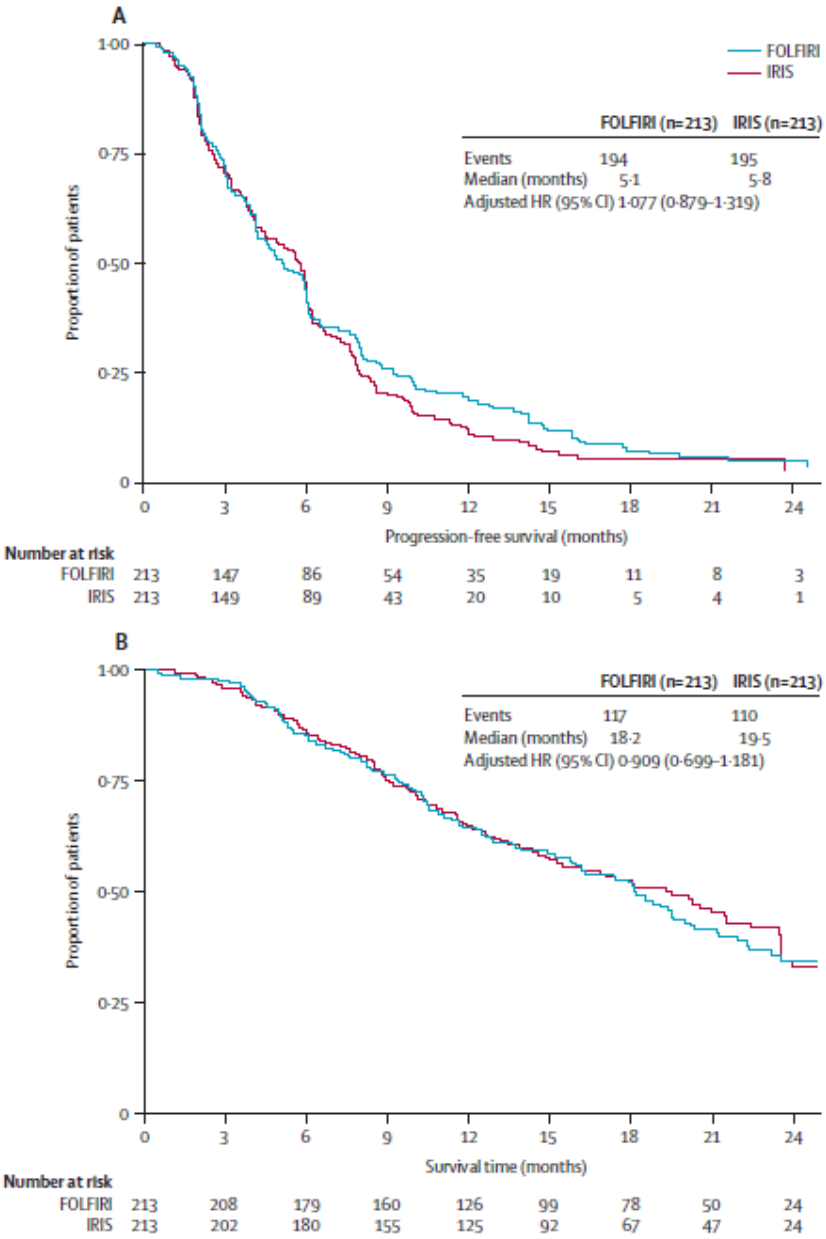


Figure 27 shows the results of subgroup analyses of PFS. Although no interaction was identified between sex, age, histological type, or performance status and therapeutic effects of IRIS compared with FOLFIRI, a statistically significant interaction was noted between prior chemotherapy (with or without oxaliplatin) and therapeutic effects (p=0.030). In the subgroup of patients receiving prior chemotherapy with oxaliplatin, median PFS was 5.7 months in the IRIS group and 3.9 months in the FOLFIRI group (adjusted HR 0.876, 95% CI 0.677–1.133), whereas in patients without prior oxaliplatin treatment it was 6.0 months and 7.8 months, respectively (HR 1.490, 95% CI 1.079–2.059). A similar tendency was noted in the OS (Figure 28).

Figure 27. Subgroup analysis PFS FIRIS trial

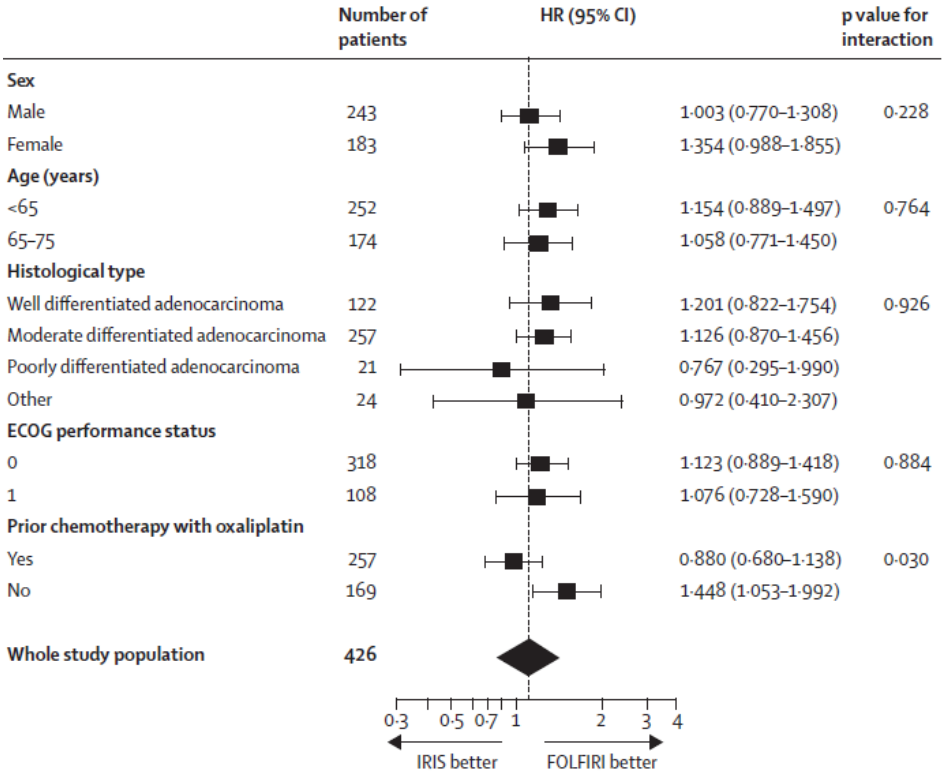
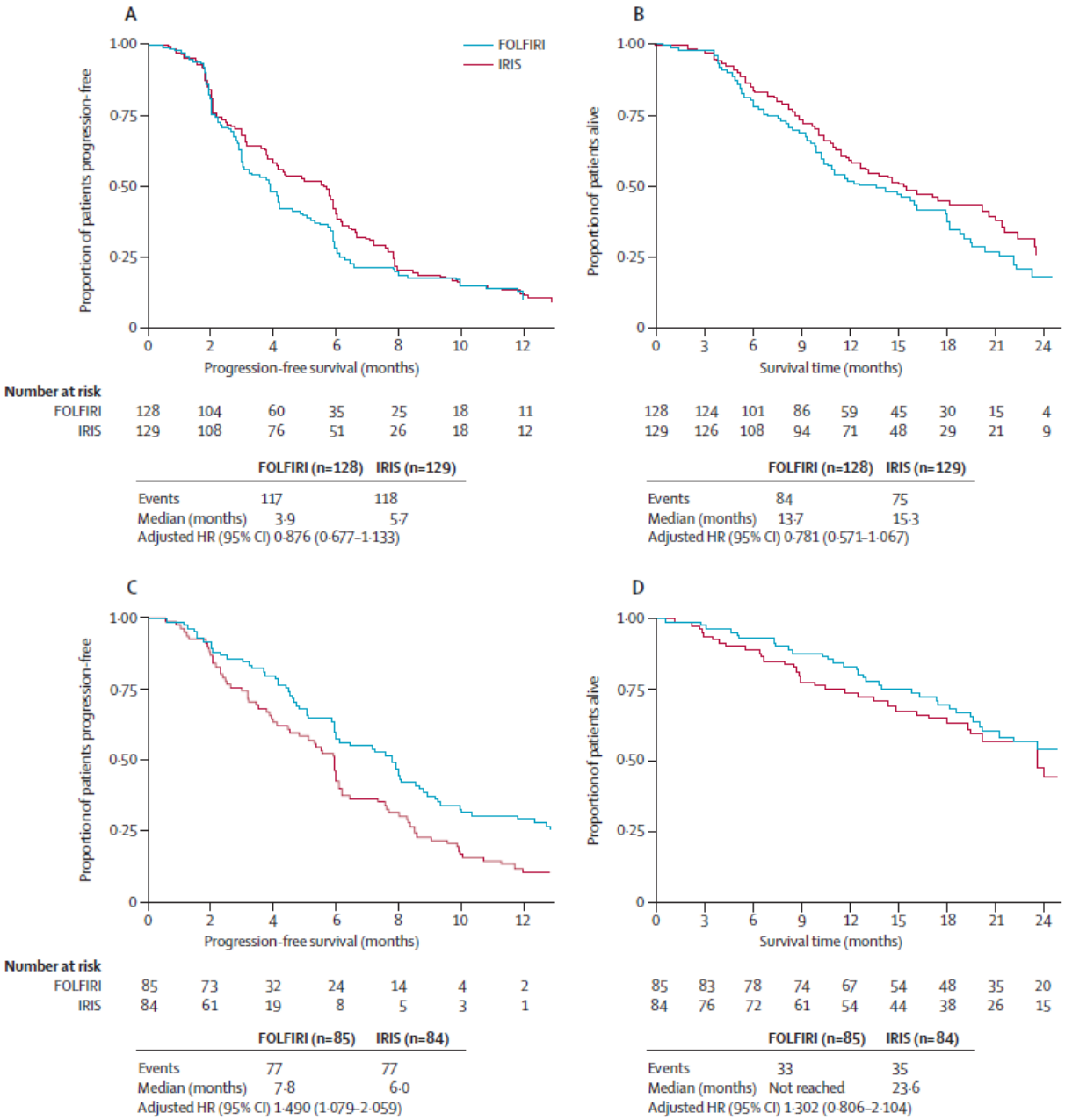


Figure 28. Survival according to prior chemotherapy FIRIS trial, PFS with prior oxaliplatin (A), OS with prior oxaliplatin (B), PFS without prior oxaliplatin (C), OS without prior oxaliplatin (D)

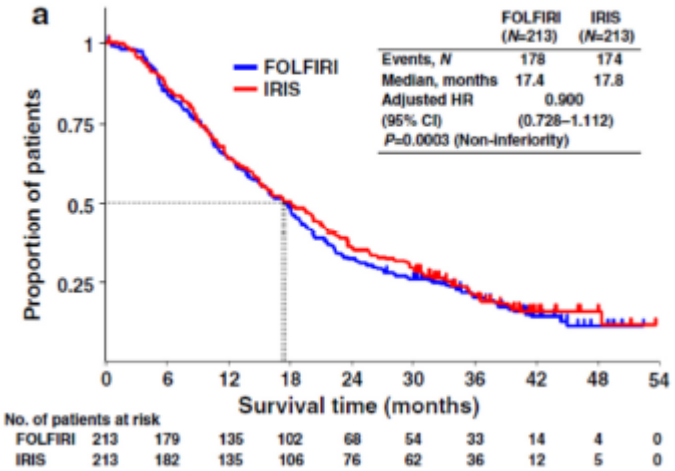


After the primary analysis, the follow-up survey was cut off on 29 July 2010, and the final OS data were analysed and reported by Yasui et al., 2015. At the final cutoff, 352 deaths (FOLFIRI, 178; IRIS, 174) were confirmed with a median follow-up of 39.2 months. A total of 125 censored cases resolved from the last cut-off reported. The median OS was 17.4 months in the FOLFIRI group and 17.8 months in the IRIS group (HR 0.900; 95% CI 0.728–1.112; p=0.003 for a non-inferiority margin of 1.333; Figure 29). In the PPS population, the median OS was 17.4 months in the FOLFIRI group and 17.4 months in the IRIS group (HR 0.905; 95 % CI 0.728–1.126). The Bayesian posterior probabilities that the HR of IRIS relative to FOLFIRI would be <1.333 and <1.15 were calculated to be >99.9 % and >98.7 %, respectively. For PFS, when the data collection was finally cut off, 412 events including an increase of 23 events from the primary analysis were confirmed. The median PFS was 5.1 months in the FOLFIRI group and 5.8 months in the IRIS group. In the ITT population, the HR for IRIS to FOLFIRI was 1.058

(95% CI 0.869–1.289; p=0.022) and consistent with the primary analysis. In the PPS population, the median PFS was 5.1 months in the FOLFIRI group and 5.7 months in the IRIS group (HR 1.035; 95 % CI 0.843–1.271), being consistent with the primary analysis. Regarding subgroup analyses for OS, except for the interaction of prior chemotherapy containing oxaliplatin (yes vs no) and therapeutic effect, no interaction was observed between sex (male vs female), age (<65 vs 65–75 years), histological type (adenocarcinoma, well differentiated vs moderately differentiated vs poorly differentiated), or PS (0 vs 1), and the therapeutic effect of IRIS was comparable to that of FOLFIRI. In the subgroups of patients treated with FOLFIRI (n=128) or IRIS (n=129) who had received prior chemotherapy containing oxaliplatin, the median OS was 15.3 months in the IRIS group and 12.7 months in the FOLFIRI group (adjusted HR 0.755; 95% CI 0.580–0.983), showing better survival in the IRIS group than in the FOLFIRI group. On the other hand, in the subgroups of patients treated with FOLFIRI (n=85) or IRIS (n=84) who had received prior chemotherapy without oxaliplatin, the median OS was more favourable in the FOLFIRI group than in the IRIS group (26.9 vs. 23.6 months; adjusted HR 1.229; 95 % CI 0.866–1.745).

Figure 29 shows the final analysis for OS from the FIRIS study that was predefined in the protocol.

Figure 29. OS IRIS vs FOLFIRI in the FIRIS trial (Yasui et al., 2015)



Personal communication EU experts

The MAH states that when EU oncology experts were asked whether the above discussed data in Asian patients provides a sufficient basis for prescribing Teysuno to their European patients, these clinical experts stated that the data are convincing and sufficient to provide confidence to treat their mCRC patients in EU countries. The personal communication refers to individual online meetings and interviews in the period of May-July 2020 with EU medical oncologist (Alphabetically: prof. Bodoky (Hungary), prof. Eberhard (Sweden), dr. Cremolini (Italy), prof. van Cutsem (Belgium), prof Heinemann (Germany), prof. Maughan (UK), prof McDermott (Ireland), prof. Österlund (Finland), prof. Pfeiffer (Denmark), prof Punt (the Netherlands)) and consensus shared in a summarizing online advisory board meeting on 27th of August 2020.

Teysuno combination therapy in European patients with mCRC

Chung et al., Oncology, 2011, Phase I study of two schedules of oral S-1 in combination with fixed doses of oxaliplatin and bevacizumab in patients with advanced solid tumors.

Methods

- **Study participants**

A phase 1 study was performed to determine the schedule of a combination with S-1 plus oxaliplatin (SOX) with bevacizumab in a European/Caucasian population. Patient eligibility criteria required histologically confirmed advanced or metastatic solid tumour(s) for which no established standard therapy existed at the time of the study. Patients had to be at least 18 years of age and able to take oral medications. Any number of prior therapies for metastatic disease was allowed, including prior fluoropyrimidine treatment; however, prior oxaliplatin was excluded. Only patients with ECOG performance status of 0 or 1 were included. Adequate organ function [AST and ALT ≤ 2.5xULN, or 5xULN if liver metastasis was required; total bilirubin ≤ 1.5xULN; calculated creatinine clearance 1 60 ml/min; absolute granulocyte count ≥ 1,500/mm^3 ; haemoglobin ≥ 9.0 g/dl; platelet count 6 100,000/mm^3]. The presence of measurable disease was not required. Patients not yet recovered from prior cancer therapies were ineligible. Any known hypersensitivity to 5-FU, bevacizumab or other platinum compounds was cause for exclusion.

- **Treatments**

S-1 was administered orally (20 mg/m2) b.i.d. (with cohort escalation of 5 mg/m2) for 14 days with fixed dose bevacizumab (7.5 mg/kg) and oxaliplatin (130 mg/m2) on day one of a 3-week cycle or at 25 mg/m2 b.i.d. for 7 days (cohort escalation by 5 mg/m2) with fixed-dose bevacizumab 5 mg/kg and oxaliplatin (85 mg/m2) on day 1 of each 2-week cycle.

Patients received either schedule A or B of S-1, oxaliplatin and bevacizumab in a non-randomized fashion.

Schedule A. S-1 was provided by Taiho Pharma, USA, Inc., Princeton, N.J., USA, in capsules containing 15 and 20 mg FT. S-1 was administered orally, twice daily for 14 consecutive days followed by a 7-day recovery period in a 21-day cycle. Patients were instructed to take S-1 1h before or at least 1h after a meal to avoid food effects. The actual S-1 doses for individual patients were calculated based on body surface area, and the number of capsules rounded as closely as possible to the calculated dose were dispensed. Oxaliplatin 130 mg/m 2 and bevacizumab 7.5 mg/kg were administered intravenously in fixed doses on day 1 of each 3-week cycle. Oxaliplatin was stopped after 4 cycles of treatment. A minimum of 3 patients were planned for enrollment in each dose level. The starting dose of S-1 in level 1 was 20 mg/m 2 with a cohort dose escalation by 5 mg/m 2 increments.

Schedule B. S-1 was administered orally, twice daily on day 1 for 7 consecutive days followed by a 7-day recovery period in a 14-day cycle. Oxaliplatin 85 mg/m 2 and bevacizumab 5 mg/kg were administered intravenously in fixed doses on day 1 of each 2-week cycle. Oxaliplatin was stopped after 6 cycles of treatment; a minimum of 3 patients were planned for enrollment in each dose level. The starting dose of S-1 was 25 mg/m 2 , with a cohort dose escalation by 5 mg/m 2 increments.

The MTD was the highest dose level at which <33% of patients experienced a DLT during the first 2 cycles for schedule A and the first 3 cycles for schedule B. Once the MTD was determined, an additional 6–12 patients were to be treated at the same level.

- **Objectives**

Not provided.

- **Outcomes/endpoints**

All AEs were collected according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. A DLT that occurred during the first 2 cycles for schedule A and the first 3 cycles for schedule B was defined as: grade >3 non-haematologic toxicity including nausea, vomiting and diarrhoea uncontrolled by aggressive treatment, febrile neutropaenia, grade 4 neutropaenia or thrombocytopaenia, or any failure of the patient to take >80% of the planned S-1 treatment. The S-1 doses as well as oxaliplatin were reduced or delayed if patients experienced unacceptable drug-related toxicity.

Radiological evaluations were obtained at baseline and every 6 weeks thereafter during the course of the trial; however, if a patient responded, response confirmation was to be obtained through tumour assessments/scans at least 4 weeks after the first documentation of response. Tumour measurements and responses were determined according to RECIST criteria.

- **Sample size**

Please refer to Treatments section above.

- **Randomisation**

Not applicable.

- **Blinding (masking)**

Not applicable.

- **Statistical methods**

All safety analyses were performed using the safety population, defined as all patients who received at least one dose of study medication. The efficacy population included all patients in the safety population who had a baseline plus at least one efficacy assessment after starting study treatment. Descriptive statistics (mean and standard deviation) were used to summarise plasma concentration data at each planned relative time point. PK parameters were summarised descriptively for schedule A only.

Results

- **Participant flow**

Not provided.

- **Recruitment**

In Schedule A, between June 2005 and March 2006, a total of 24 patients were enrolled and treated. Between February 2007 and June 2008, a total of 24 patients were enrolled and treated in Schedule B.

- **Conduct of the study**

The protocol and the informed consent document were approved by the Institutional Review Board of the Memorial Sloan-Kettering Cancer Center. All patients were required to provide written, informed consent before the start of study screening to participate in the trial.

- **Baseline data**

Schedule A. Most patients (67%) have been previously treated with at least 1 prior chemotherapy regimen. Three patients were treated at the S-1 20-mg/m 2 dose level in combination with fixed doses of oxaliplatin and bevacizumab. Fourteen and 7 patients were treated at the S-1 25- and 30-mg/m 2 dose levels, respectively, in combination with fixed doses of oxaliplatin and bevacizumab. A median of 8 cycles has been initiated (range 1–40) (Table 16).

Schedule B. Most patients (83%) have been previously treated with at least 1 chemotherapy regimen. Three patients were treated at the S-1 25- and 30- mg/m 2 dose levels. Twelve and 6 patients were treated at the S-1 35- and the 40-mg/m 2 dose levels, respectively. A median of 11 cycles were completed (range 1–45) (Table 16).

Table 16. Baseline characteristics phase 1 study

	Schedule A (n = 24)				Schedule B (n = 24)				
S-1 dosage:	20 mg/m^2 (n = 3)	25 mg/m^2 (n = 14)	30 mg/m^2 (n = 7)	total (n = 24)	25 mg/m^2 (n = 3)	30 mg/m^2 (n = 3)	35 mg/m^2 (n = 12)	40 mg/m^2 (n = 6)	total (n = 24)
Age, years									
Median	55.0	54.5	58.0	55.0	39.0	54.0	65.0	63.5	63.0
Range	47–60	37–70	22–76	22–76	37–72	53–67	27–72	52–64	27–72
Gender									
Male	1 (33)	11 (79)	5 (71)	17 (71)	2 (67)	2 (67)	9 (75)	3 (50)	16 (67)
Female	2 (67)	3 (21)	2 (29)	7 (29)	1 (33)	1 (33)	3 (25)	3 (50)	8 (33)
ECOG PS									
0	3 (100)	8 (57)	4 (57)	15 (63)	0 (0)	3 (100)	5 (42)	3 (50)	11 (46)
1	0 (0)	6 (43)	3 (43)	9 (38)	3 (100)	0 (0)	7 (58)	3 (50)	13 (54)
Race									
White	3 (100)	11 (79)	6 (86)	20 (83)	3 (100)	2 (67)	11 (92)	6 (100)	22 (92)
African American	0	0	1 (14)	1 (4)	0	0	0	0	0
Asian	0	3 (21)	0	3 (13)	0	1 (33)	1 (8)	0	2 (8)
Other	0	0	0	0	0	0	0	0	0
BSA, m^2									
Median	1.650	1.840	2.010	1.840	2.080	1.860	1.795	1.795	1.840
Range	1.62–2.24	1.49–2.11	1.68–2.04	1.49–2.24	1.74–2.08	1.73–1.87	1.37–2.75	1.47–2.36	1.37–2.75
Primary lesion at baseline									
Pancreas	0	4 (29)	1 (14)	5 (21)	0	0	4 (33)	2 (33)	6 (25)
Biliary tract	0	0	1 (14)	1 (4)	1 (33)	0	1 (8)	1 (17)	3 (13)
Esophagus	1 (33)	0	1 (14)	2 (8)	0	0	1 (8)	0	1 (4)
Head and neck	0	2 (14)	1 (14)	3 (13)	0	0	0	0	0
Liver	0	1 (7)	0	1 (4)	0	1 (33)	0	1 (17)	2 (8)
Non-small cell lung	0	1 (7)	0	1 (4)	0	0	0	0	0
Colorectal	0	0	1 (14)	1 (4)	0	0	0	0	0
Other	2 (67)	6 (43)	2 (29)	10 (42)	2 (67)	2 (67)	6 (50)	2 (33)	12 (50)
Prior chemotherapy									
Yes	2 (67)	8 (57)	6 (86)	16 (67)	3 (100)	3 (100)	10 (83)	4 (67)	20 (83)
No	1 (33)	6 (43)	1 (14)	8 (33)	0	0	2 (17)	2 (33)	4 (17)
Prior radiotherapy									
Yes	0	6 (43)	4 (57)	10 (42)	0	1 (33)	5 (42)	0	6 (25)
No	3 (100)	8 (57)	3 (43)	14 (58)	3 (100)	2 (67)	7 (58)	6 (100)	18 (75)

Figures in parentheses are percentages.
ECOG PS = Eastern Cooperative Oncology Group performance status; BSA = body surface area.

- **Numbers analysed**

Please refer to above.

- **Outcomes and estimation**

Of a total of 22 evaluable patients, a disease control rate of 83% was achieved with a median PFS of 7.2 months [3.8-18.9], and a median OS of 16.9 months [10.3-26.9].

DLTs and MTD

Schedule A. A total of 22 patients completed the first 2 cycles of study treatment and were assessed for DLT evaluation. Two patients were excluded from DLT evaluation due to inadequate supportive treatment of diarrhoea and non-compliance. Three patients in the 20 mg/m2 dose group and the first 3 patients in the 25 mg/m2 dose group experienced no DLTs. In the 30 mg/m2 dose group, 2 out of 6 patients treated experienced DLTs: 1 patient with metastatic pancreatic adenocarcinoma experienced grade 3 diarrhoea on day 15 of cycle 2 despite aggressive antidiarrhoeal treatment, and 1 patient with recurrent metastatic undifferentiated nasopharyngeal carcinoma developed grade 3 mucositis after the first cycle, tolerating the subsequent dose level of S-1 (25 mg/m2) without toxicity. The next 3 patients enrolled in the reduced 25 mg/m2 S-1 dose level tolerated therapy well without DLT. The 25 mg/m2 S-1 cohort was expanded with an additional 7 patients who tolerated therapy well without DLT. For Schedule A MTD was determined to be S-1 25 mg/m2 administered orally twice daily for 14 days followed by 7 days of rest in a 3-week cycle in combination with oxaliplatin and bevacizumab once every 3 weeks.

Schedule B. All 24 patients completed the first 3 cycles of study treatment and were assessed for DLT evaluation. Three patients in each of the 25, 30 and 35 mg/m2 dose groups experienced no DLTs. Two of 6 patients in the 40 mg/m2 dose group developed DLTs (1 patient with grade 3 diarrhoea, fatigue, dehydration, proteinuria, nausea and vomiting, and 1 patient with grade 4 neutropaenia, grade 3 diarrhoea, rectal bleeding and dehydration). An additional 9 patients were treated in the 35 mg/m2 expansion cohort. Only 2 patients developed DLTs. One patient experienced grade 3 abdominal pain and another patient experienced grade 3 diarrhoea. Hence, the MTD of schedule B was S-1 35 mg/m2 administered in combination with 85 mg/m 2 oxaliplatin and 5 mg/kg bevacizumab once every 2 weeks.

Anti-tumour activity (Table 17)

Schedule A. The median numbers of cycles received were 11, 7 and 8 in 20, 25 and 30 mg/m2 dose groups, respectively. A total of 22 patients with at least 1 postbaseline imaging study were included in the tumour response evaluation. Of the total of 22 evaluable patients, 2 patients (9%) achieved a partial response (PR), 17 patients (74%) had stable disease (SD) and 4 patients (17%) demonstrated progression of disease as the best response, corresponding to a disease control rate of 83%. Two patients with PR had metastatic gastroesophageal junction adenocarcinoma: 1 previously treated with 2 prior regimens and the other chemotherapy naïve. At the data cutoff, the calculated median PFS and OS in this group with all dose levels combined was 7.2 months (95%CI 3.8–18.9; n=23) and 16.7 months (95%CI 10.3–26.9; n=23), respectively.

Schedule B. The median numbers of cycles received were 32, 21, 9 and 7 in 25, 30, 35 and 40 mg/m2 dose groups, respectively. A total of 24 patients with at least 1 post-baseline imaging study were included in the tumour response evaluation. Of the 24 evaluable patients, 8 patients (35%) achieved a PR, 10 patients (44%) demonstrated SD, and 5 patients (22%) demonstrated progressive disease as best response, corresponding to a disease control rate of 78%. At the data cutoff, the calculated median PFS and OS for this schedule was 6.9 months (95% CI 2.8–15.0; n=23) and 11.1 months (95% CI 8.2–17.1; n=24), respectively.

Table 17. Response rates by investigator assessment phase 1 study

S-1 dosage:	Schedule A (n = 22)				Schedule B (n = 24)				
	20 mg/m² (n = 3)	25 mg/m² (n = 13)	30 mg/m² (n = 7)	total (n = 23)	25 mg/m² (n = 3)	30 mg/m² (n = 3)	35 mg/m² (n = 11)	40 mg/m² (n = 6)	total (n = 23)
Response									
Complete response	0	0	0	0	0	0	0	0	0
PR	0	2 (15)	0	2 (9)	1 (33)	2 (67)	3 (27)	2 (33)	8 (35)
SD	2 (67)	9 (69)	6 (86)	17 (74)	2 (67)	0	6 (55)	2 (33)	10 (44)
Progressive disease	1 (33)	2 (15)	1 (14)	4 (17)	0	1 (33)	2 (18)	2 (33)	5 (22)
Not available	0	0	0	0	0	0	0	0	0
Overall response rate	0	2 (15)	0	2 (9)	1 (33)	2 (67)	3 (27)	2 (33)	8 (35)
95% CI				1–28					16–57
Disease control rate	2 (67)	11 (85)	6 (86)	19 (83)	3 (100)	2 (67)	9 (82)	4 (67)	18 (78)
95% CI				61–95					56–93

Figures in parentheses are percentages.

Winther et al., Lancet Gastroenenterology & Hepatology, 2019, Reduced-dose combination chemotherapy (S-1 plus oxaliplatin) versus full-dose monotherapy (S-1) in older vulnerable patients with metastatic colorectal cancer (NORDIC9): a randomised, open-label phase 2 trial.

Methods

- **Study participants**

Patients older than 70 years of age who were not candidates for full-dose combination therapy were included. Eligible patients were aged 70 years or older and had histopathologically proven colorectal adenocarcinoma, non-resectable metastases, and a WHO performance status of 0–2. Participants had received no prior chemotherapy except adjuvant fluoropyrimidine therapy completed more than 180 days before randomisation and had a life expectancy of at least 3 months. Additionally, haematological, liver, and renal functions had to be within normal range; glomerular filtration rate (GFR) had to be greater than 30 mL/min, bilirubin no higher than 1.5xULN, neutrophil cell count at least $1.5x10^9$ cells per L, and platelet count of at least $100x10^9$ per L. Furthermore, patients could not be candidates for standard full-dose combination chemotherapy as assessed by the treating physician. Exclusion criteria were evidence of CNS metastasis; concurrent history of malignant neoplasm other than colorectal adenocarcinoma within the past 5 years; peripheral chronic neuropathy; current history of chronic diarrhoea, infection, or unresolved bowel obstruction; or contraindications to fluoropyrimidine—e.g., myocardial infarction within 6 months. All patients provided written informed consent before enrolment.

- **Treatments**

Patients were randomised to receive full-dose S-1 (30 mg/m2 b.i.d, orally, d1-14 every 3 weeks) followed by second-line irinotecan (250 mg/m2, IV, d1 every 3 weeks or 180 mg/m2 IV, d1 every 2 weeks) at progression or reduced-dose Teysuno (20 mg/m2 b.i.d. d1-14 every 3 weeks) plus oxaliplatin (100 mg/m2 d1 every 3 weeks) followed by second-line treatment at disease progression with reduced dose S-1 plus irinotecan (180 mg/m2 d1 every 3 weeks). Addition of bevacizumab was optional (7.5 mg/kg IV d1 every 3 weeks).

In either group, the S-1 dose was reduced by 5 mg/m² in patients with GFR of 30–49 mL/min. If dose reduction was needed during treatment due to toxicity, the S-1 dose was reduced by 5 mg/m² and oxaliplatin or irinotecan were reduced by 25%.

The protocol recommended treatment until progression, unacceptable toxicity, or patients' wish for a treatment break. In case of progressive disease during a treatment break, treatment could be re-introduced. Due to potential treatment breaks before the time of progressive disease, the decision was made to calculate dose intensity for S-1 and oxaliplatin after nine treatment cycles. Second-line treatment according to the protocol was offered after progression of disease on first-line treatment and continued until progression on second-line treatment.

- **Objectives**

The NORDIC9 trial was designed to evaluate whether dose-reduced combination therapy with S-1 and oxaliplatin improves efficacy and is as tolerable as full-dose monotherapy with S-1 in older (>70 years of age) and vulnerable patients with metastatic colorectal cancer. Furthermore, it was assessed if geriatric screening tools administered at baseline can predict efficacy and toxicity of the treatments.

- **Outcomes/endpoints**

The primary endpoint was PFS and secondary endpoints included OS, response, toxicity, QoL, and time to failure of strategy. The primary endpoint PFS was calculated from the date of randomisation to the first date of radiological or clinical progression on first-line treatment, time of death, or censored on the cutoff date. Secondary endpoints were OS, defined as deaths of all causes or censored at cutoff date; proportion of patients achieving investigator-evaluated response; toxicity; quality of life; and time to failure of strategy, calculated from the date of randomisation to the date of progression on planned first-line and second-line treatment. If treatment was re-introduced after progressive disease during a treatment break, the last date for progressive disease in first-line treatment was used to calculate time to failure of strategy for first-line treatment. Correlations between pretreatment characteristics or geriatric screening tool results and efficacy (PFS and OS) and toxicity (at least one grade 3–4 adverse event, hospitalisation, or receiving no more than one cycle or fewer than three cycles of treatment) were evaluated.

Toxicity was evaluated after each chemotherapy cycle and graded by NCI-CTCAE version 4.0. Nadir haematology was measured on days 10–14 after the first cycle and when indicated. CT scans and clinical evaluations were performed every three cycles until progression. Achievement of objective response and date of progression were determined by the local investigator according RECIST 1.1. Quality of life was assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30 (EORTC QLQ-C30) at baseline and after three and six treatment cycles.

- **Sample size**

In the power calculation, it was estimated that monotherapy without bevacizumab would result in PFS of 4 months whereas the addition of bevacizumab would increase this to 8 months. It was anticipated that 50% of the patients would be offered bevacizumab; thus it was estimated that median PFS in the full-dose monotherapy group would be 6 months. If median PFS for the reduced-dose combination group is 9 months, at least 71 individuals were needed to be treated in the experimental arm and 71 in the control arm to reject the null hypothesis that the experimental and control survival curves are equal with a power of 80% and a type I error probability of 0.2. There was no adjustment for expected loss to follow-up or dropouts.

- **Randomisation**

Patients were randomly assigned to sequential full-dose monotherapy (S-1 followed by irinotecan monotherapy at progression) or sequential dose-reduced combination chemotherapy (S-1 and oxaliplatin followed by S-1 and irinotecan at progression). Bevacizumab was optional in first-line therapy at the

discretion of the treating physician but the decision had to be made before randomisation. Patients were randomly assigned (1:1) with block sizes of ten, eight, or four using a web-based tool managed by a statistical third part provider (OPEN randomise). Randomisation was stratified by institution and planned treatment with bevacizumab. Only trained study nurses at the Data Centre (Odense University Hospital) had access to the electronic randomization system. They communicated the randomisation to the investigator of the institution who wished to include a patient, when inclusion and exclusion criteria were checked and registration papers approved.

- **Blinding (masking)**

Not applicable (open-label design).

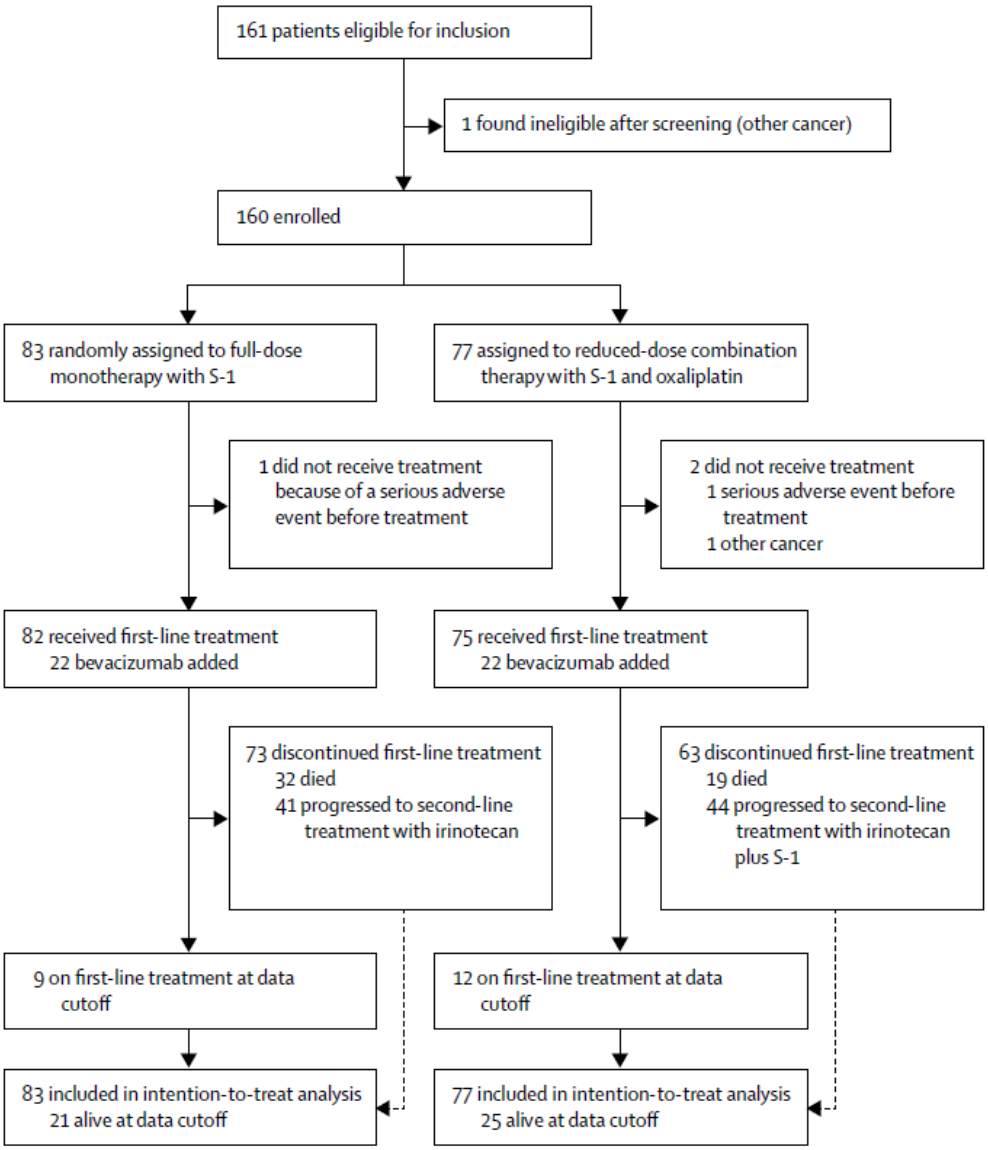
- **Statistical methods**

Categorical binary variables were compared with Fisher's exact test or χ^2 test (depending on the number of observations) and ordinal variables were compared using the Mann-Whitney test. OS and PFS curves were estimated by the Kaplan-Meier method, with comparisons between treatment arms done by the log-rank test in the intention-to-treat population (consisting of all randomised patients). Hazard ratios (HRs) and corresponding 95% CIs were estimated by Cox proportional hazard regression. HRs adjusted for treatment with bevacizumab but not for institutions were also calculated. Cox regression (for PFS and OS) and logistic regression (for grade 3–4 adverse events, number of cycles, and hospitalisations) were used for univariable analyses with respect to pretreatment characteristics and geriatric screening results. A multivariable model used clinically relevant covariates defined in advance (treatment arm, addition of bevacizumab, performance status, number of metastatic sites, and resection of primary tumour) and covariates with p-values of less than 0.10 in univariable analyses. The number of covariates took into consideration the number of observations. For Cox regression, the proportional hazards assumptions were tested based on Schoenfeld residuals, and for logistic regression the goodness-of-fit test was performed. Toxicity and treatment-related characteristics were assessed in all patients who received treatment. An interim safety analysis focusing on toxicity and dose intensity was performed when the first 50 patients had received three cycles. In all analyses, a two-tailed p value of less than 0.05 was deemed statistically significant. Statistical analyses were done in Stata version 15.1.

Results

- **Participant flow**

Figure 30. Participant flow NORDIC9 trial



- **Recruitment**

A total of 160 patients were randomised and 157 received treatment. Patient recruitment was done in 23 oncology clinics in four Nordic countries: Denmark, Finland, Norway, and Sweden. From March 9, 2015, to Oct 11, 2017, 160 patients were randomly assigned to full-dose monotherapy (n=83) or reduced-dose combination chemotherapy (n=77; Figure 30). Two patients did not start treatment because of adverse events, and one patient was excluded due to other cancer; therefore, toxicity and treatment-related characteristics were analysed for 157 patients.

- **Conduct of the study**

The study was approved by national ethical committees and conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol has been published. This trial is registered with EudraCT, number 2014-000394-39.

- **Baseline data**

Median age was 78 years (IQR 76-81), 51 (32%) were 80 or older, and 53 (33%) had a WHO performance status of 0. Bevacizumab was administered to 22 patients in each group (Table 18).

Table 18. Baseline characteristics NORDIC9 trial

	Full-dose monotherapy (n=83)	Reduced-dose combination therapy (n=77)
Age (years)		
70–74	16 (19%)	19 (25%)
75–79	38 (46%)	36 (47%)
≥80	29 (35%)	22 (29%)
Median (IQR)	78 (76–81)	78 (75–80)
Sex		
Female	40 (48%)	38 (49%)
Male	43 (52%)	39 (51%)
WHO performance status		
0	30 (36%)	23 (30%)
1	37 (45%)	38 (49%)
2	16 (19%)	16 (21%)
Location of primary tumour		
Left side	50 (60%)	47 (61%)
Right side	32 (39%)	30 (39%)
Unknown	1 (1%)	0
Surgery for primary tumour		
Yes	46 (55%)	45 (58%)
No	37 (45%)	32 (42%)
Prior adjuvant chemotherapy		
Yes	18 (22%)	11 (14%)
No	65 (78%)	66 (86%)
Number of metastatic sites		
1–2	66 (80%)	61 (79%)
≥3	17 (20%)	16 (21%)
Liver-only disease		
Yes	16 (19%)	15 (19%)
No	67 (81%)	62 (81%)
Site of metastatic disease		
Liver	58 (70%)	44 (57%)
Lung	34 (41%)	31 (40%)
Peritoneum	12 (14%)	28 (36%)
Other	12 (14%)	13 (17%)
Surgery metastases		
Yes	8 (10%)	8 (10%)
No	75 (90%)	69 (90%)
Presentation at diagnosis		
Synchronous	54 (65%)	42 (55%)
Metachronous	29 (35%)	35 (45%)

(Table 1 continues in next column)

	Full-dose monotherapy (n=83)	Reduced-dose combination therapy (n=77)
(Continued from previous column)		
RAS* mutation status		
Wild-type	31 (37%)	27 (35%)
Mutant	30 (36%)	29 (38%)
Unknown	22 (27%)	21 (27%)
***BRAF* mutation status**		
Wild-type	45 (54%)	37 (48%)
Mutant	11 (13%)	10 (13%)
Unknown	27 (33%)	30 (39%)
Weight loss >5% within 2 months		
Yes	24 (29%)	13 (17%)
No	59 (71%)	64 (83%)
White blood cells (10^9/L)		
<10	58 (70%)	56 (73%)
≥10	25 (30%)	21 (27%)
Platelets (10^9/L)		
<400	65 (78%)	57 (74%)
≥400	18 (22%)	20 (26%)
Lactate dehydrogenase (U/L)		
<255	46 (55%)	49 (64%)
≥255	29 (35%)	26 (34%)
Unknown	8 (10%)	2 (3%)
Alkaline phosphatase (U/L)		
≤105	50 (60%)	41 (53%)
>105	33 (40%)	34 (44%)
Unknown	0	2 (3%)
C-reactive protein (mg/L)		
<10	26 (31%)	37 (48%)
≥10	55 (66%)	34 (44%)
Unknown	2 (2%)	6 (8%)
Carcinoembryonic antigen (µg/L)		
<5	10 (12%)	15 (19%)
≥5	69 (83%)	60 (78%)
Unknown	4 (5%)	2 (3%)

(Table 1 continues on next page)

	Full-dose monotherapy (n=83)	Reduced-dose combination therapy (n=77)
(Continued from previous page)		
Calculated glomerular filtration rate (mL/min)		
>70	45 (54%)	43 (56%)
50–70	31 (37%)	21 (27%)
<50	7 (8%)	13 (17%)
Köhne prognostic index		
Low risk	23 (28%)	24 (31%)
Intermediate risk	26 (31%)	23 (30%)
High risk	34 (41%)	30 (39%)
G8 (possible range 0–17)		
>14	21 (25%)	23 (30%)
12–14	30 (36%)	26 (34%)
≤11	30 (36%)	24 (31%)
Unknown	2 (2%)	4 (5%)
VES-13 (possible range 0–10)		
<3	59 (71%)	54 (70%)
≥3	19 (23%)	17 (22%)
Unknown	5 (6%)	6 (8%)
TUG		
≤10 s	58 (70%)	43 (56%)
>10 s	18 (22%)	26 (34%)
Unknown	7 (8%)	8 (10%)
Handgrip strength		
Weak: <21 kg (female), <34 kg (male)	38 (46%)	31 (40%)
Strong: ≥21 kg (female), ≥34 kg (male)	40 (48%)	40 (52%)
Unknown	5 (6%)	6 (8%)
CCI		
0–1	65 (78%)	60 (78%)
≥2	18 (22%)	17 (22%)

Data are n (%) or median (IQR). G8=Geriatric 8. VES-13=Vulnerable Elders Survey 13. TUG=Timed Up and Go. CCI=Charlson Comorbidity Index. *RAS* mutations are *KRAS* or *NRAS* mutations in codons 12, 13, 59, 61, 117, and 146.

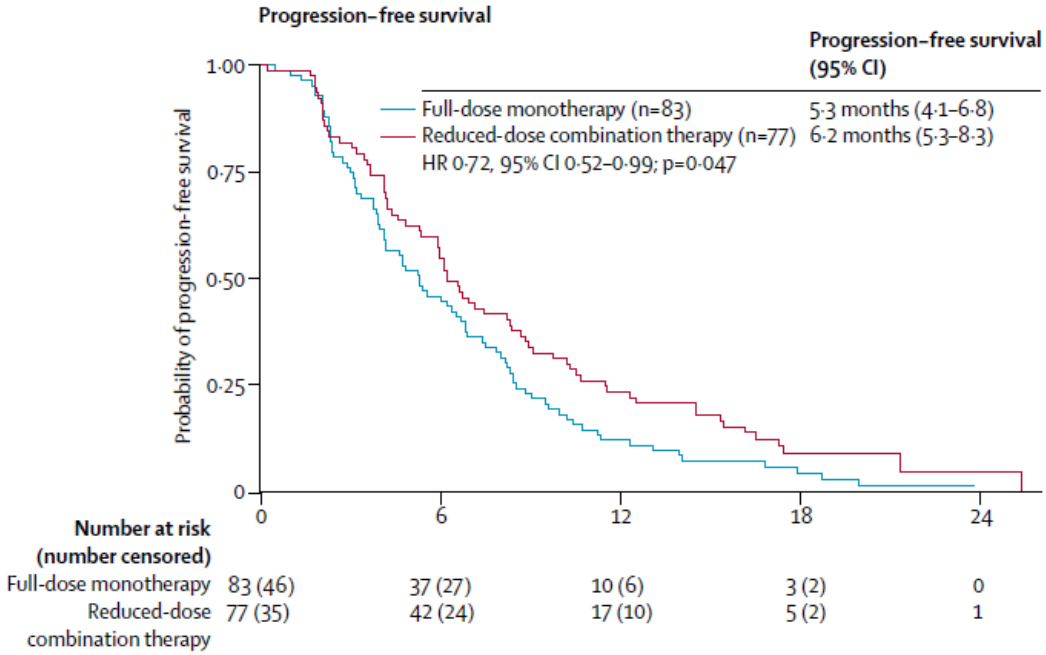
- **Numbers analysed**

Please refer to numbers described above.

- **Outcomes and estimation**

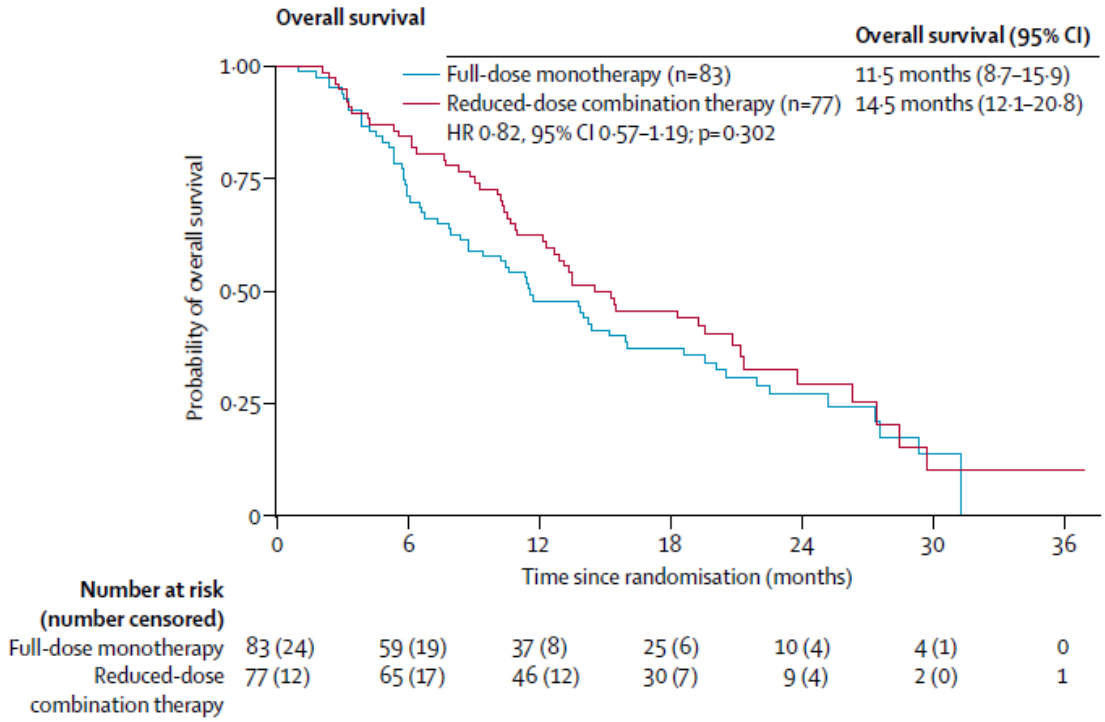
With a median follow-up of 23.8 months (IQR 18.8-30.9) PFS was 5.3 months (95% CI 4.1-6.8) in the full-dose group compared to 6.2 months (95% CI 5.3- 8.3) in the reduced-dose combination therapy group (HR 0.72, 95% CI 0.52-0.99, p=0.047) (Figure 31).

Figure 31. PFS NORDIC9 trial



Median time to failure of strategy was 6.7 months (95% CI 5.29-10.8) in the full-dose group and 10.5 months (95% CI 8.61-12.7) in the reduced dose combination therapy group (HR 0.74, 95% CI 0.52–1.04; p=0.085). Median OS was 11.5 months (95% CI 8.7-15.9) in the full-dose monotherapy group compared to 14.5 months (95% CI 12.1- 20.8 in the reduced-dose combination therapy group (HR 0.82, 95% CI 0.57-1.19, p=0.302) (Figure 32).

Figure 32. OS NORDIC9 trial

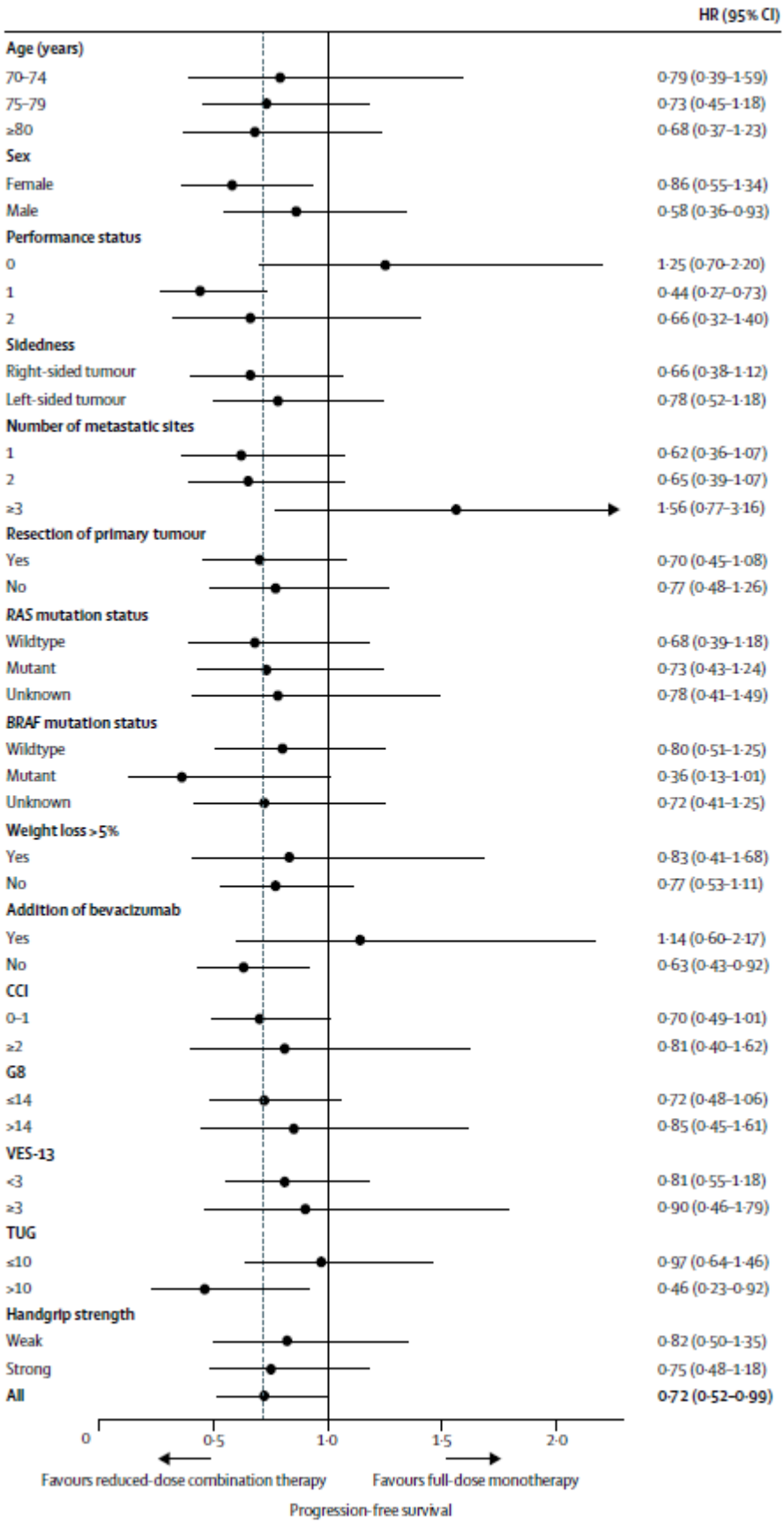


Most patients who had a treatment break of at least 2 months had first-line treatment reintroduced. 85 (63%) of 136 patients who discontinued first-line treatment started second-line treatment, of whom seven (8%) did not receive therapy according to the protocol. Among those who discontinued first-line treatment, a greater proportion of patients in the reduced-dose combination group started second-line

treatment than in the full-dose monotherapy group (44 [70%] of 63 patients vs 41 [56%] of 73 patients; p=0.100).

Median follow-up was 23.8 months (IQR 18.8–30.9). At data cutoff, 81 (98%) patients in the full-dose monotherapy group and 71 (92%) patients in the reduced-dose combination group had progressed or died. At the cutoff date 114 (71%) patients had died. PFS results are shown above. The difference in PFS was enhanced when adjusted for treatment with bevacizumab (0.69, 0.50–0.95; p=0.025). Exploratory subgroup analyses of progression-free survival are shown in Figure 33.

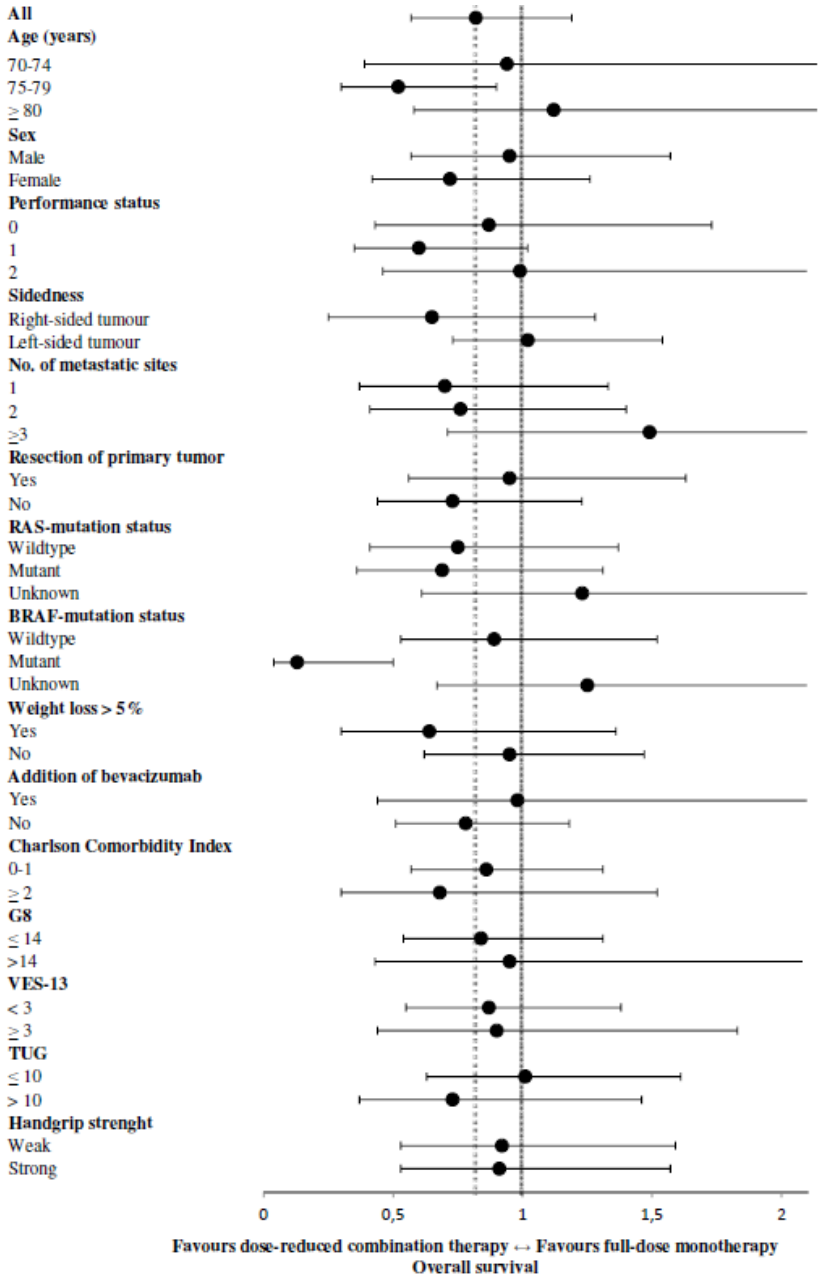
Figure 33. Forest plot for subgroups analyses of PFS NORDIC9 trial



Median time to failure of strategy is reported above. Owing to the use of treatment breaks, the median time to failure of first-line treatment was calculated, resulting in a median time to failure of 6.0 months (4.2–8.2) in the full-dose monotherapy group and 7.4 months (5.9–9.1) in the reduced-dose combination group (0.77, 0.56–1.06; p=0.110).

Median OS results are shown above. When adjusted for the use of bevacizumab, the HR was 0.82 (0.57–1.19; p=0.298). At data cutoff, 51 patients had died during or after first-line treatment and 63 patients during or after second-line treatment. Exploratory subgroup analyses of OS are shown in Figure 34.

Figure 34. Forest plot for subgroups analyses of OS NORDIC9 trial



The proportion of patients achieving objective response with first-line treatment was numerically but not significantly higher in the reduced-dose combination group (42% [95% CI 30–55; 30 patients] vs 33% [23–45; 27 patients] in the full-dose monotherapy group; p=0.257).

13 (8%) patients received only one chemotherapy cycle, of whom nine were treated with full-dose monotherapy. Eight of these nine patients had synchronous metastatic disease with their primary tumour

in situ. Of the nine patients, the reason for ending treatment prematurely was mainly toxicity (six patients), but also colonic perforation (one) and progressive disease (two), whereas reasons for ending treatment prematurely after one cycle were more diverse in the reduced-dose combination group (one patient each for toxicity, perforation of rectum, ileus, and progressive disease).

Österlund et al., submitted, 2021, Continuation of fluoropyrimidine treatment with S-1 after cardiotoxicity on capecitabine- or 5-fluorouracil-based therapy in patients with solid tumours: a multi-centre retrospective observational cohort study (manuscript draft).

Methods

- **Study participants**

All identified patients with solid tumours experiencing grade 1-4 cardiotoxicity during fluoropyrimidine treatment, who were switched to S-1-based therapy were included. Population-based data on S-1 treatment was available for Tampere and Helsinki university hospitals, and for colorectal cancers in Turku, and cases were included if switch due to cardiotoxicity was the indication. Further, patients with switch due to cardiotoxicity in the RAXO study (NCT01531621) were included. Additional cases were retrospectively identified and included from the other participating institutions. The total number of patients receiving fluoropyrimidines at all participating centres could not be extracted. Data collected at baseline included patient characteristics, cardiovascular comorbidities, current medications (with anatomical therapeutic chemical [ATC] code), cardiac evaluations, cardiac treatment, cardiotoxicity on first treatment and recurrence on S-1-based therapy, previous and concurrent cancer therapies. Clinically meaningful non-cardiac adverse events included haematologic toxicity grade 3-4, and non-haematologic toxicity grade 2-4.

- **Treatments**

Included patients were switched to S-1-based therapy after cardiotoxicity during fluoropyrimidine treatment.

- **Objectives**

The purpose of the study was to evaluate cardiotoxicity during re-challenge of a different modality of fluoropyrimidine (primary end-point S-1 and secondary any other fluoropyrimidine) after having perceived cardiotoxicity with a fluoropyrimidine based regimen previously. The patient population is being treated for solid tumours.

- **Outcomes/endpoints**

The primary endpoint was recurrence of cardiotoxicity after switch to S-1-based treatment from any other fluoropyrimidine due to cardiotoxicity. Secondary endpoints were cardiac symptoms and alteration in cardiac functional parameters during fluoropyrimidine therapy; diagnostic work-up for cardiotoxicity in real-world practice; timelines for cardiotoxicity and dose intensity.

- **Sample size**

No power calculation was performed. The data cut-off for inclusion was October 7, 2020, upon reaching the per protocol target of 200 patients.

- **Randomisation**

Not applicable.

- **Blinding (masking)**

Not applicable.

- **Statistical methods**

The primary endpoint was recurrent cardiotoxicity after switch to S-1-based treatment. The cumulative incidence with its 95% CI was calculated in a competing risks analysis, where first onset of recurrent cardiotoxicity was the event of interest and stopping of S-1 without recurrent cardiotoxicity a competing risk.

Worst grade of cardiotoxicity is presented if multiple events were present. Continuous characteristics are presented as median with range and interquartile range (IQR). Systematic missing information for Dutch patients (n=28) included ECOG PS, some comorbidities, and survival. Missing values were not imputed. Demographic variables were screened for associations with the crude percentage of recurrent cardiotoxicity with Chi-square tests with Bonferroni correction for multiple comparisons (data not shown), and, if statistically significant differences were noted, odds ratios (OR) and 95% CIs were calculated using logistic regression. OS from initiation of S-1-based therapy to death of any cause or to end of follow-up was estimated using the Kaplan-Meier method.

Results

- **Participant flow**

Not available.

- **Recruitment**

This was a retrospective, cohort study conducted at 13 centres in Finland, Sweden, Norway, Denmark, The Netherlands, and Ireland.

- **Conduct of the study**

The study was approved by each institution and/or the local ethics committee, if required. The study was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki, as applicable for register studies.

- **Baseline data**

S-1-based treatment started between November 1, 2011 and October 5, 2020. Data cut-off was May 10, 2021 when median follow-up was 33 months from S-1 initiation, and minimum 50 days. Per protocol 200 patients were included (median age 66 years [range 19-86] and 118 [59%] male). Patient characteristics are presented in Table 19. At baseline 101 (51%) patients had no cardiovascular comorbidities.

Table 19. Baseline patient characteristics for all patients having had cardiotoxicity during treatment with capecitabine or 5FU

		Total	
		n=200	100%
Age	Median (range)	66	(19-86)
	< 70 years	123	62%
	≥ 70 years	77	39%
Sex	Female	82	41%
	Male	118	59%
ECOG	PS 0	51	26%
	PS 1	105	53%
	PS 2	16	8%
	NA	28	14%
Cardiovascular comorbidity*	No	101	51%
	Yes	99	50%
Metabolic comorbidity*	NA	25	13%
	No	117	59%
	Yes	58	29%
Renal comorbidity*		28	14%
	No	165	83%
	Yes	7	4%
Chronic obstructive pulmonary disease*		26	13%
	No	168	84%
	Yes	6	3%
Other comorbidity*		28	14%
	No	102	51%
	Yes	70	35%
Primary tumour	Anal cancer	2	1%
	Biliary cancer	3	2%
	Breast cancer	3	2%
	Cancer of unknown primary	2	1%
	Colon cancer	103	52%
	Colon cancer MINEN	1	1%
	Oesophageal cancer	3	2%
	Gastric cancer	20	10%
	Pancreas cancer	5	3%
	Pancreas neuroendocrine	2	1%
	Rectal cancer	55	28%
	Small bowel cancer	1	1%
Localized disease	Stage I-III	114	57%
Metastatic disease	Stage IV	86	43%
Resection	Primary tumour	126	64%
	Metastases	14	7%
Radiotherapy	Chest wall or Breast	4	2%
	Abdomen or Pelvis	19	10%

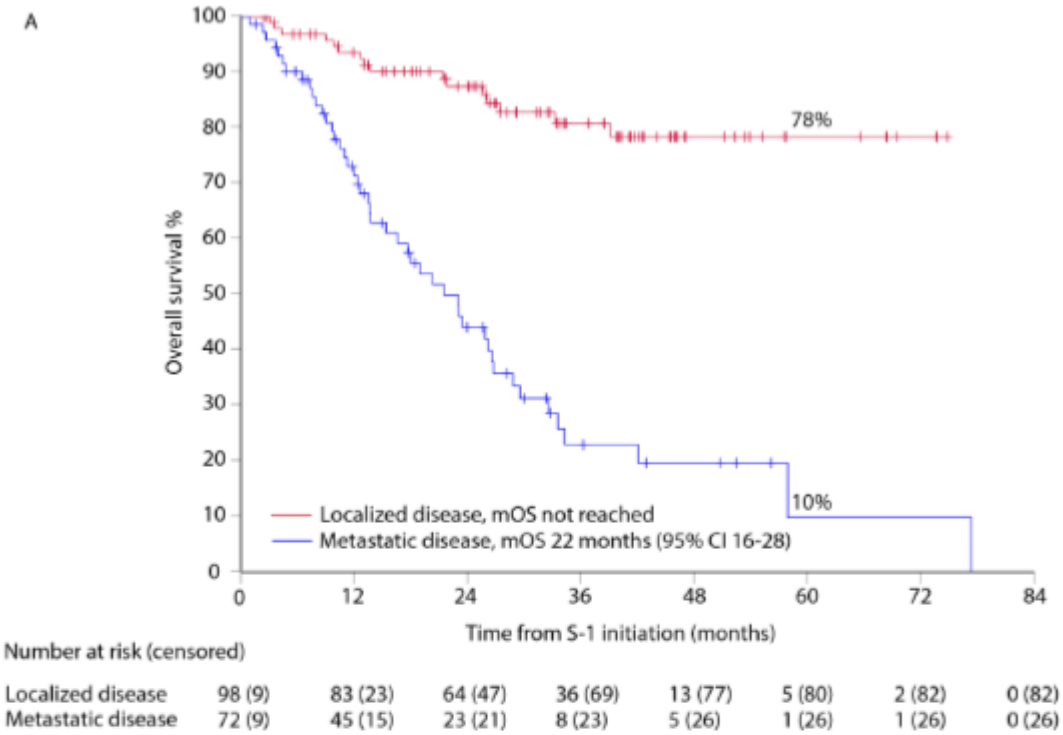
- **Numbers analysed**

Per protocol 200 patients were analysed.

- **Outcomes and estimation**

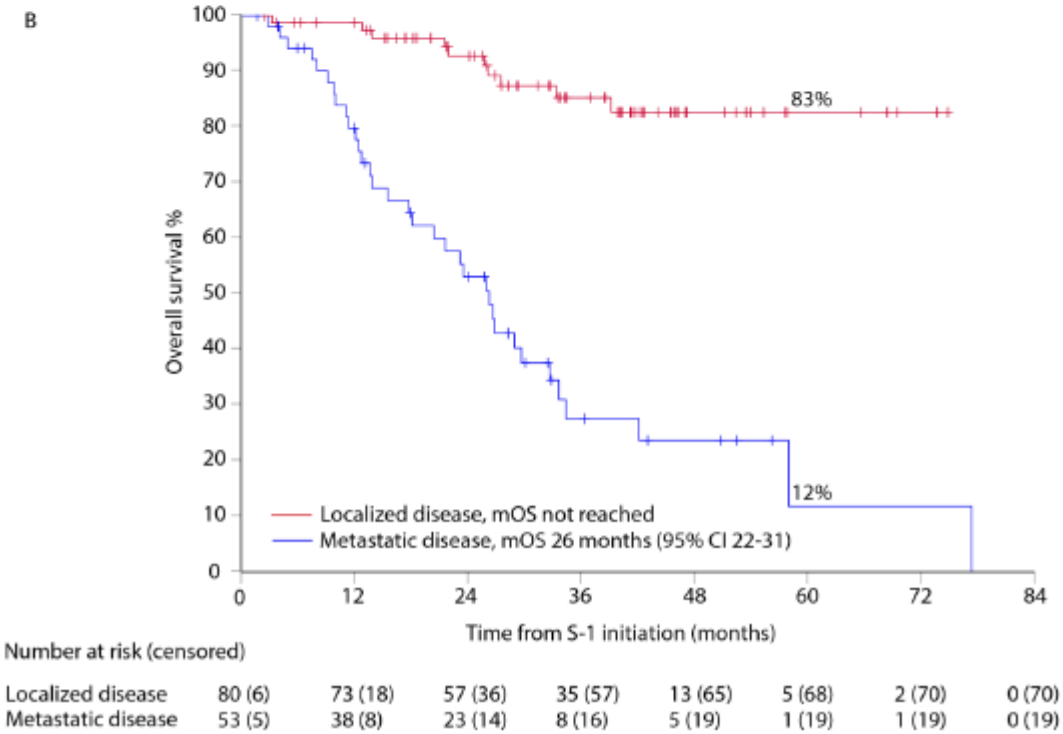
Please refer to the safety section for the safety outcomes. Regarding efficacy, median OS from S-1 initiation (n=170) of the patients with localised disease was not reached and was 22 months (95% CI 16-28 months) in patients with metastatic disease, with 5-year survival rates of 78% and 10%, respectively (Figure 35). The largest subgroup with colorectal primary (n=133) had a median OS of not reached in localised disease and 26 months (95% CI 22-31) in metastatic disease with 5-year survival rates of 83% and 12%, respectively (Figure 35).

Figure 35. OS from S-1 initiation for patients with localized or metastatic solid cancer (panel A), and colorectal cancer (panel B)



Number at risk (censored)

Localized disease	98 (9)	83 (23)	64 (47)	36 (69)	13 (77)	5 (80)	2 (82)	0 (82)
Metastatic disease	72 (9)	45 (15)	23 (21)	8 (23)	5 (26)	1 (26)	1 (26)	0 (26)



Number at risk (censored)

Localized disease	80 (6)	73 (18)	57 (36)	35 (57)	13 (65)	5 (68)	2 (70)	0 (70)
Metastatic disease	53 (5)	38 (8)	23 (14)	8 (16)	5 (19)	1 (19)	1 (19)	0 (19)

Punt et al., in preparation, 2021, Long-term safety data on S-1 (Teysuno) administered after previous intolerance to capecitabine-containing systemic treatment for metastatic colorectal cancer

Methods

- **Study participants**

Data were retrospectively collected from patients participating to the Dutch Prospective Colorectal Cancer Cohort (PLCRC) (Burbach et al., Acta Oncol, 2016). PLCRC has been initiated in 2015, and is since then being implemented in an increasing number of Dutch hospitals, with currently 59/80 Dutch hospitals participating and more than 10.000 patient being included (www.plcrc.nl). All CRC patients (stage I-IV) are eligible for inclusion in PLCRC, and patients give informed consent to register longitudinal clinical data and to use any further clinical data upon approval by the scientific board of PLCRC. Since more than 90% of patients who are informed on PLCRC give their informed consent, patients in PLCRC are considered to represent daily practice. PLCRC patients in whom S-1 was administered at any stage of disease were identified, and patients with mCRC in whom treatment was switched from capecitabine to S-1 were eligible. Patients were excluded in case they had been included two previous retrospective studies on a treatment switch from capecitabine to S-1 (Kwakman et al., Eur J Cancer, 2017; Kwakman et al., Acta Oncol, 2017).

- **Treatments**

The starting dose of capecitabine was either 1250 mg/m2 or 1000 mg/m2 when given as monochemotherapy, and 1000 mg/m2 when given in combination with oxaliplatin. The starting dose of S-1 was either 30 mg/m2 when given as monochemotherapy, and 25 mg/m2 when given in combination with oxaliplatin.

The standard procedure for dose reductions for capecitabine is a first dose reduction to 75% of the initial dose and a second dose reduction to 50% of initial dose. Dose reductions are commonly performed upon the occurrence of grade ≥ 3 toxicity or by recurrence of grade 2. However, given the potential impact of prolonged grade 2 HFS on quality of life and daily activities, especially in elderly patients, a switch from capecitabine to S-1 was often performed at the occurrence of grade 2 HFS.

- **Objectives**

To conduct a retrospective analysis of safety data from mCRC patients in the Dutch PLCRC cohort who were switched to Teysuno after development of HFS or cardiotoxicity while on capecitabine.

- **Outcomes/endpoints**

Data were collected from June 1st 2016, and the cut-off date was June 15th 2021. Patients were followed from the first administration of capecitabine until the end of S-1 treatment for any reason (i.e. progression of disease, toxicity, watch-and-wait strategy).

The electronic records of eligible patients were examined for the following items: patient characteristics (age, gender, height, weight, WHO performance status) at time of switch to S-1, treatment setting before switch to S-1, schedule of capecitabine-containing regimen, dates of first and last dose of capecitabine, starting dose of capecitabine, dose reduction of capecitabine, and if so, its underlying reason, reason to switch to S-1, date of first dose and total number of cycles of S-1, dose reductions of S-1, and if so, its underlying reason, reason to permanently discontinue S-1, date of first disease progression after S-1 administration, and any adverse event occurring during treatment of capecitabine and S-1 of which the maximal grade was recorded using CTC criteria (CTCAE version 5.0). Data were recorded from the start of treatment with capecitabine until the end of treatment with S-1.

- **Sample size**

Not reported.

- **Randomisation**

Not applicable.

- **Blinding (masking)**

Not applicable.

- **Statistical methods**

Not reported.

Results

- **Participant flow**

Not reported.

- **Recruitment**

Please refer to the section "Study participants".

- **Conduct of the study**

Patients gave informed consent to register longitudinal clinical data and to use any further clinical data upon approval by the scientific board of PLCRC. The study was approved by the scientific board of PLCRC.

- **Baseline data**

A total of 53 patients were identified who were exposed to treatment with S-1. Four patients were excluded since capecitabine was administered in the adjuvant setting, and two patients were excluded because their previous treatment did not contain capecitabine but continuous infusion of 5-fluorouracil. Therefore 47 patients were eligible for further analysis.

Patient characteristic are shown in Table 20. Patients were treated in 13 different Dutch hospitals. There were 25 males and 22 females, and at the time of switch to S-1 median age was 62 years (range 40-84), and median WHO PS was 1 (0-2).

Table 20. Patient characteristics PLCRC cohort

	n (%)	median (range)
n	47 (100%)	
Age (years)		62 (40-84)
Female	22 (47 %)	
Male	25 (53 %)	
Height (cm)		175 (162-195)
Weight (kg)		74 (55-100)
WHO PS 0	18 (38 %)	
WHO PS 1	27 (57%)	
WHO PS 2	2 (4%)	

- **Numbers analysed**

Please refer to Table 20.

- **Outcomes and estimation**

Please refer to the safety section for the safety results. As stated by the authors, due to the relatively small number of patients, the heterogeneity of treatment schedules and the varying timepoints of initiation of treatment with S-1, this cohort does not allow a valid assessment of clinical outcome in terms of progression-free survival. The median time from initiation of treatment with capecitabine to first documented progression of disease after initiation of treatment with S-1 was 414 days (95% confidence interval 332-568 days), which is in the upper range of outcomes as observed in clinical studies on first-line treatment with capecitabine-based regimens in patients with metastatic colorectal cancer. Although this analysis does not allow assessment of efficacy, a switch to S-1 does not appear to have any detrimental effect on progression-free survival, according to the authors.

When only the 36 patients who switched from capecitabine to S-1 for reason of HFS were considered, median duration of capecitabine treatment was 115 days (range 21-454), median time between end of capecitabine and start of S-1 treatment was 8 days (range 2-49), median number of S-1 cycles was 8 (range 1-36), and median PFS was 414 days (95%CI: 332-629).

Ancillary analyses

Gimeracil and oteracil single agents

No clinical data are available for gimeracil and oteracil as single agents as they have never been administered to humans, except when combined with tegafur in Teysuno. This was accepted previously for the MAA.

Extrapolation of Asian efficacy data to Western patients

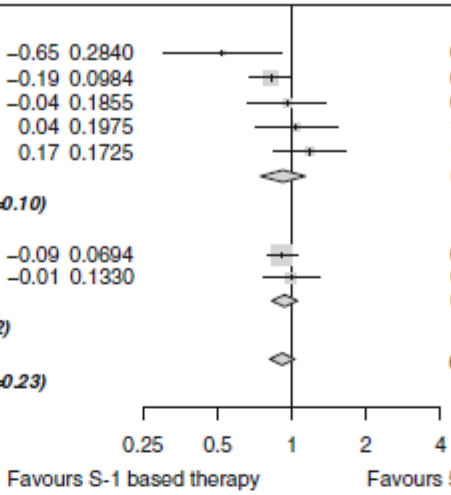
The MAH discussed two published meta-analyses that have been conducted that concluded that Teysuno-based regimens have similar efficacy with better tolerability than 5-FU- and capecitabine-based regimens in Western patients and in Asian patients with gastric cancer (Ter Veer et al., 2017; Ter Veer et al., 2016).

Subgroup analyses that compared Teysuno regimens to 5-FU regimens did not detect any differences in efficacy attributable to ethnicity (Figure 36) (Ter Veer et al., 2016).

Figure 36. S-1 based therapy compared with 5-FU based therapy for Asian and Western patient subgroups for a) OS, b) PFS, and c) ORR

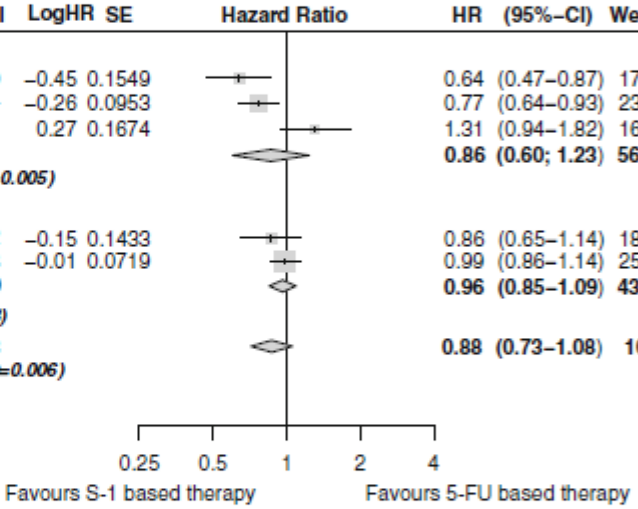
a

Study	Experimental Arm	Total	Comparator Arm	Total	LogHR	SE	HR (95%–CI)	Weight
Asia								
Jin 2008	S-1+Cis	74	5-FU+Cis	73	−0.65	0.2840	0.52 (0.30–0.91)	4.0%
Boku 2009	S-1	234	5-FU	234	−0.19	0.0984	0.82 (0.68–1.00)	22.4%
Nishikawa 2012	S-1+PTX	77	5-FU+PTX	80	−0.04	0.1855	0.96 (0.67–1.38)	8.7%
Xu 2013	S-1+Cis	120	5-FU+Cis	118	0.04	0.1975	1.05 (0.71–1.54)	7.8%
Sawaki 2009	S-1+Lv	88	5-FU+Lv	89	0.17	0.1725	1.19 (0.85–1.67)	9.8%
Subtotal		**593**		**594**			**0.91 (0.74–1.12)**	**52.8%**
E: Z=0.88 (p=0.38) H: ChF=7.67 (df=4), I²=48%, tau²=0.03 (p=0.10)								
West								
Ajani 2010	S-1+Cis	521	5-FU+Cis	508	−0.09	0.0694	0.92 (0.80–1.05)	32.4%
Ajani 2015	S-1+Cis	239	5-FU+Cis	122	−0.01	0.1330	0.99 (0.76–1.28)	14.8%
Subtotal		**760**		**630**			**0.93 (0.83–1.05)**	**47.2%**
E: Z=1.16 (p=0.25) H: Chi²=0.24 (df=1), I²=0%, tau²=0 (p=0.62)								
Total		**1353**		**1224**			**0.92 (0.82–1.03)**	**100%**
E: Z=1.39 (p=0.16) H: ChF=8.06 (df=6), I²=26%, tau²=0.01 (p=0.23)								
Subgroup differences: Chi²=0.04, df=1 (p=0.85), I²=0%								



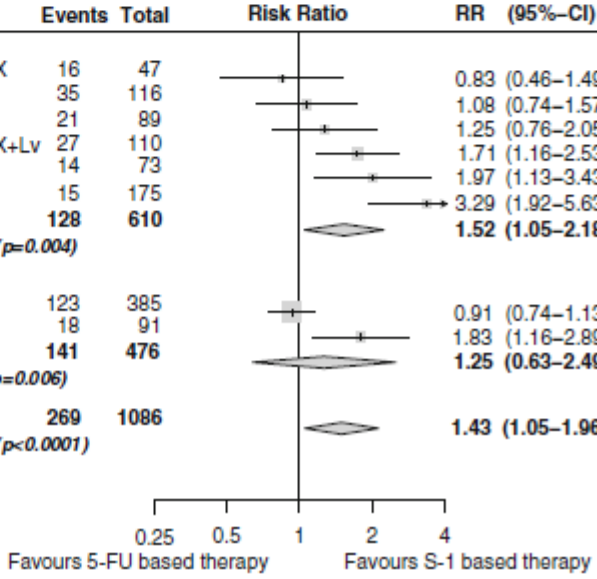
b

Study	Experimental Arm	Total	Comparator Arm	Total	LogHR	SE	HR (95%–CI)	Weight
Asia								
Huang 2012	S-1+PTX	119	5-FU+PTX+Lv	110	−0.45	0.1549	0.64 (0.47–0.87)	17.2%
Boku 2009	S-1	234	5-FU	234	−0.26	0.0953	0.77 (0.64–0.93)	23.1%
Sawaki 2009	S-1	88	5-FU+Lv	89	0.27	0.1674	1.31 (0.94–1.82)	16.1%
Subtotal		**441**		**433**			**0.86 (0.60; 1.23)**	**56.3%**
E: Z=0.85 (p=0.40) H: Chi²=10.77 (df=2), I²=81%, tau²=0.0 (p=0.005)								
West								
Ajani 2015	S-1+Cis	239	5-FU+Cis	122	−0.15	0.1433	0.86 (0.65–1.14)	18.3%
Ajani 2010	S-1+Cis	521	5-FU+Cis	508	−0.01	0.0719	0.99 (0.86–1.14)	25.4%
Subtotal		**760**		**630**			**0.96 (0.85–1.09)**	**43.7%**
E: Z=0.59 (p=0.55) H: ChF=0.76 (df=1), I²=0%, tau²=0 (p=0.38)								
Total		**1201**		**1063**			**0.88 (0.73–1.08)**	**100%**
E: Z=1.23 (p=0.22) H: Chi²=14.30 (df=4), I²=72%, tau²=0.03 (p=0.006)								
Subgroup differences: Chi²=0.36, df=1 (p=0.55), I²=0%								



c

Study	Experimental Arm	Events	Total	Comparator Arm	Events	Total	RR (95%–CI)	Weight
Asia								
Nishikawa 2012	S-1+Cis	15	53	5-FU+PTX	16	47	0.83 (0.46–1.49)	10.6%
Xu 2013	S-1+Cis	39	120	5-FU+Cis	35	116	1.08 (0.74–1.57)	13.6%
Sawaki 2009	S-1	26	88	5-FU+Lv	21	89	1.25 (0.76–2.05)	11.9%
Huang 2012	S-1+PTX	50	119	5-FU+PTX+Lv	27	110	1.71 (1.16–2.53)	13.4%
Jin 2008	S-1+Cis	28	74	5-FU+Cis	14	73	1.97 (1.13–3.43)	11.1%
Boku 2009	S-1	49	174	5-FU	15	175	3.29 (1.92–5.63)	11.3%
Subtotal		**207**	**628**		**128**	**610**	**1.52 (1.05–2.18)**	**71.8%**
E: Z=2.25 (p=0.02) H: Chi²=17.13 (df=5), I²=71%, tau²=0.14 (p=0.004)								
West								
Ajani 2010	S-1+Cis	117	402	5-FU+Cis	123	385	0.91 (0.74–1.13)	15.7%
Ajani 2015	S-1+Cis	70	193	5-FU+Cis	18	91	1.83 (1.16–2.89)	12.5%
Subtotal		**187**	**595**		**141**	**476**	**1.25 (0.63–2.49)**	**28.2%**
E: Z=0.65 (p=0.52) H: Chi²=7.58 (df=1), I²=87%, tau²=0.15 (p=0.006)								
Total		**394**	**1223**		**269**	**1086**	**1.43 (1.05–1.96)**	**100%**
E: Z=2.25 (p=0.02) H: Chi²=31.68 (df=7), I²=78%, tau²=0.15 (p<0.0001)								
Subgroup differences: Chi²=0.23, df=1 (p=0.63), I²=0								



Cap, capecitabine; CI, confidence interval; cis, cisplatin; df, degrees of freedom; E, effect; H, heterogeneity; HR, hazard ratio; Lv, leucovorin; PTX, paclitaxel; RR, risk ratio; SE, standard error (Ter Veer et al., 2016).

Similarly, a network meta-analysis that further compared Teysuno-based regimens to 5-FU and capecitabine regimens, as well as comparing 5-FU to capecitabine regimens, concluded that this method of indirectly comparing all of the Asian and Western Teysuno studies to available comparable fluoropyrimidine studies provides confidence that the Teysuno-, capecitabine-, and 5-FU-based regimens have equal efficacy in Asian and Western patients (Table 21) (Ter Veer, et al., 2017).

Table 21. Network meta-analysis stratified by Asian and Western studies in OS and PFS

	Overall survival		Progression free survival	
	Asian	Western	Asian	Western
Capecitabine vs 5-FU	0.84 (0.59–1.18)	0.92 (0.64–1.36)	0.82 (0.49–1.36)	1.06 (0.63–2.03)
S-1 vs 5-FU	0.90 (0.71–1.13)	0.94 (0.62–1.47)	0.84 (0.60–1.20)	0.94 (0.52–1.66)
S-1 vs capecitabine	1.08 (0.78–1.52)	1.02 (0.58–1.81)	1.03 (0.61–1.74)	1.00 (0.44–2.28)

Relative effects in combined hazard ratio and 95% Credible Intervals (CrI) derived from network meta-analysis for capecitabine-, 5-FU-, and Teysuno-based cytotoxic regimens stratified by Asian studies and Western studies for overall survival and progression-free survival. No significant differences were found among Asian and Western patients in efficacy between all fluoropyrimidines (Ter Veer et al., 2017)

Supportive evidence for rationale posology S-1 in combination with irinotecan

In addition to the study by Winther et al, 2019, 3 levels of supportive evidence for the posology of the S-1 and irinotecan combination: a study of older mCRC patients treated with S-1 (Winther et al., 2016), data from the CardioSwitch study (Österlund et al., submitted), and clinical experience in Nordic European countries.

Publication Winther et al., Acta Oncologica, 2016

In this study safety and efficacy of S-1 alone or in combination with oxaliplatin (SOx) or irinotecan (IRIS) in mCRC patients of 70 years or older was evaluated. A total of 18 patients received the combination IRIS, mainly administered as second- or later-line therapy for metastatic disease with a posology of S-1 25 mg/m2 orally twice daily on days 1–14 with irinotecan 200 mg/m2 iv on day 1 every three weeks. The dose of irinotecan was higher than the applied for 180 mg/m2.

In the IRIS subgroup, median age was 73 years and ten patients (56%) completed at least six cycles of therapy. Reasons for discontinuing chemotherapy included radiological PD (n=5) and toxicity/patient's wish (n=2). Fifteen patients (83%) started with full dose therapy and three patients started with reduced dose IRIS (reduced dose in previous line n=2, comorbidity n=1). The median relative dose intensities for irinotecan and S-1 were 97% and 87%, respectively.

In the IRIS group, PR was 28% based on investigator-assessed RECIST 1.1, median PFS was 7.8 months and the median OS 16.5 months.

The most common non-haematological adverse events were fatigue (89%), diarrhoea (56%), and nausea (44%). Adverse events were generally mild in nature with grade 3 diarrhoea being observed in 11% of patients. One patient developed grade 1 HFS. Haematological adverse events were mild and one

patient (6%) developed febrile neutropaenia.

Based on these data and knowledge gained from Asian studies with irinotecan, the authors recommend S-1 25 mg/m2 orally twice daily on days 1–14 with IRIS 200 mg/m2 iv on day 1 every three weeks in fit patients.

CardioSwitch study (Österlund et al., submitted 2021)

In the CardioSwitch trial 17 patients with solid tumours who were switched to Teysuno-based regimens after developing cardiotoxicity on another fluoropyrimidine-based regimen were treated with the IRIS combination: 12 patients with irinotecan 180-200 mg/m2 with S-1 50 mg/m2 and 5 patients with irinotecan 150-180mg/m2 and S-1 of 40 mg/m2 (of which 4 were frail or had renal impairment). The majority of patients received IRIS on this 21-day schedule, some were also treated with a 28-day schedule.

There were no concerns regarding the toxicity of the 21-day regimen of irinotecan 180 mg/m2 (on day 1) combined with S-1 50 mg/m2 (25 mg/m2 b.i.d.) on Days 1-14 for non-frail patients. No toxicity issues were observed for the reduced dose regimen used for Nordic9-like patients (Winther et al., 2019), that were frail or in conjunction with impaired renal function, irinotecan 150-180 mg/m2 (on day 1) combined with S-1 40 mg/m2 (20 mg/m2 B.I.D.) on days 1-14. The dose intensities were 100% for S-1 for the 15 full dose patients and, when corrected for age and renal function, were 100% for 16 of the 17 patients. This demonstrates that most patients tolerated and could continue their initially planned treatment schedule. The 17 mCRC patients on IRIS had a median treatment time of 168 days (range 42-588) and median overall survival of 25 months (range 2-35 months), which are very similar to the full CardioSwitch study population: 147 days on treatment (for both localised and metastatic disease, with or without recurrent cardiotoxicity) and an OS of 26 months (95% CI 22-31) in mCRC, respectively.

Clinical experience from Denmark, Sweden, and Finland

According to MAH there is experience with the combination of S-1 and irinotecan in Nordic countries, for example in clinical trials (described in Winther et al., 2016; Winther et al., 2019) or as off label use as an alternative for capecitabine.

The experience at the Odense University Hospital (Denmark) since 2014 of involving 140 patients with CRC treated with IRIS was provided per personal communication with a clinical expert. Patients received 25 mg/m2 S-1 b.i.d. and 200 mg/m2 irinotecan on day 1 in 3-week schedules, most often as second or later line of therapy. From the period between 2012-2014 18 patient were reported in the publication by Winther et al., 2016. The remaining patients seem to have been treated off label. The median number of treatment cycles was 5. The observed PFS was 4 months and was, according to the clinical expert, as could be expected considering the target population. The clinical value of this treatment combination is demonstrated by the fact that the combination has not been changed since that time and has been used as a standard treatment combination since 2015 at the Odense hospital, according to personal communication provide by a clinical expert.

In addition, treatment with IRIS is mentioned in a Swedish regimen database as a treatment option for colorectal cancer on a 3-week schedule with 25 mg/m2 S-1 (once per day d1, 15 and b.i.d. day 2-14) combined with 225 mg/m2 irinotecan on day 1 (http://www.regimbiblioteket.se/regim.html?id=1915&b=23). It is not reported by the MAH how often this combination is actually prescribed.

Lastly, on top of those reported in the CardioSwitch trial, 13 patients have been treated with IRIS combinations in Finland. Three of these patients were CardioSwitch patients who were added to the database after data cut-off in October 2020 and the remaining patients seems to have been treated off label. Six received irinotecan 150-180 mg/m2 with S-1 at 28-37 mg/m2, 4 received irinotecan with full

dose S-1 (25 mg/m2 b.i.d) and 3 received irinotecan with a reduced dose S-1 20 mg/m2 b.i.d., on a 28-day schedule.

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Clinical studies in special populations

Not applicable.

Supportive study(ies)

Not applicable.

2.4.3. Discussion on clinical efficacy

This application is based on published literature and supported by exploratory **pivotal evidence** in the target population and, mainly, **supportive evidence** of patients who are randomised at baseline to either S-1 based therapy or another fluoropyridimine-based therapy. As direct evidence in the target population, exploratory efficacy results are reported from studies in European patients after switching to S-1 based therapy due to toxicity on other fluoropyrimidine-based therapy. As part of the indirect evidence, the MAH performed a meta-analysis of efficacy in phase 2 and 3 studies of Teysuno-based regimens compared to 5-FU- and capecitabine-based regimens in metastatic colorectal cancer (mCRC), which will be discussed first (Derksen et al., 2021, in preparation). Moreover, the MAH discussed a selection of studies included in the meta-analysis comparing S-1 based therapies versus therapies based on another fluoropyrimidine in more detail. In the efficacy discussion, first the meta-analysis and individual studies will be discussed, followed by an overall discussion of the data supporting efficacy of S-1 as monotherapy or in combination with oxaliplatin or irinotecan, with or without bevacizumab, in adult patients with mCRC for whom it is not possible to continue treatment with another fluoropyrimidine due to hand-foot syndrome (HFS) or cardiovascular toxicity.

Discussion of individual studies

Pivotal evidence

Regarding available data in the EU target population of patients who switched to S-1 after toxicity on another fluoropyrimidine, the MAH provided additional data from a retrospective study (CardioSwitch) that included 53 mCRC European patients who were switched to S-1 based therapy after development of cardiotoxicity on another fluoropyrimidine). In addition, data is reported from a retrospective analysis of data from a prospectively collected Dutch database (PLCRC Switch Cohort Study) that evaluated long-term safety in 47 mCRC patients who were switched to S-1 regimens after development of either cardiotoxicity or HFS on capecitabine.

The study by **Österlund et al., submitted**, investigated retrospectively a cohort of patients with solid tumours experiencing grade 1-4 cardiotoxicity during fluoropyrimidine treatment, who were switched to S-1 based therapy. The main purpose was to evaluate cardiotoxicity during rechallenge, but exploratory efficacy data were also provided. For the patient group with mCRC specifically (n=53), median OS was 26 months (CI95% 22-31) with a 5-year survival rate of 12%. Median reported OS mCRC treated in clinical studies is around 30 months (van Cutsem et al., *Annals of Oncology*, 2016) and population-based median OS is approximately 12 months in the total population and 15 months in patients who received systemic therapy (Hamers et al., *International Journal of Cancer*, 2020). It is noted that the 5-year

survival rate of 12% in patients switched to S-1 due to toxicity described by Österlund et al. is lower than the reported 60% in clinical trials (van Cutsem et al., *Annals of Oncology*, 2016), but based on the KM curve in Figure 35 the 5-year survival rate is difficult to interpret due to the low number of patients and median OS is regarded as more relevant.

Furthermore, the MAH provided retrospective data from Dutch patients who switched to S-1 after previous intolerance to capecitabine-based treatment for mCRC (**Punt et al., in preparation**). The main objective was to conduct a retrospective analysis of the long-term safety, but also exploratory efficacy data were provided for 47 patients. Of these 47 patients, for 10 (21%) the reason to switch to S-1 was cardiac toxicity, for 36 (77%) the reason was HFS, and for 1 (2%) there was another reason. Patients received a median of 6 cycles of S-1 based therapy. The median time from initiation of treatment with capecitabine to first documented progression of disease after initiation of treatment with S-1 was 414 days (95% confidence interval 332-568 days). When only the 36 patients who switched from capecitabine to S-1 for reason of HFS were considered, median PFS was 414 days (95%CI: 332-629). As also acknowledged by the authors the interpretation of these data is limited by the small number of patients, heterogeneity of the treatment schedules and varying timing of the switch to S-1, next to that it's difficult to draw conclusions based on cross study comparisons without matching for baseline characteristics.

Supportive evidence

The majority of the data is indirect evidence in a population that was randomised at baseline between therapy based on S-1 or another fluoropyrimidine. The MAH performed a systematic literature search using the electronic databases MEDLINE, Embase, and Cochrane Register of Controlled Trials and a search for grey literature using OpenGrey to identify randomised trials comparing S-1 versus 5-FU or capecitabine.

Literature search- With the literature search 457 articles were identified. Articles were included based on age of the patients >18 years, histologically proven mCRC, palliative S-1 based therapy compared with 5-FU or capecitabine-based therapy, and prospective phase II or III randomised clinical trial. Using the inclusion criteria, 14 studies were included for the meta-analysis. For 4 studies the publication could not be retrieved, also not after contacting the authors and were excluded. Out of the 14 included studies, 4 studies had updated publications and the MAH used the updated publications for inclusion in the PFS and OS meta-analyses, which is agreed. Based on the characteristics of the study designs and included study populations, the MAH concluded that the 10 relevant studies that were identified by the literature search could be used for a meta-analysis. The studies investigated first (8) and second line (2) mCRC setting. The study by Kato et al., 2012, investigated both first and second line, but was regarded as first line study as the majority of patients were treated in first line according to the authors of the original publication. Most of the studies were multicenter and performed in Asia between 2008-2018. One study investigated S-1 monotherapy (+/- bevacizumab), the other studies investigated combinations with oxaliplatin or irinotecan (+/- bevacizumab). The study of Yamada et al., 2018, had a different combination in the control (combination with oxaliplatin and bevacizumab) versus the investigational arm (combination with irinotecan). The MAH states that based on the results of the meta-analysis of Kawai et al., 2021, it is justified to compare irinotecan- and oxaliplatin-based therapies in first line mCRC. Baseline characteristics of the included patients, i.e. gender, age, and ECOG performance scale, were comparable between the studies.

Overall, the provided search and selection strategy seems reasonable, even though the description leaves uncertainties precluding to assess whether it is on par with Cochrane systematic reviews. For instance, it is not clear whether synonyms (e.g., randomis/zation, randomis/zed) were included (applies to all databases). Also it is not clear whether only the substance name in EMBASE is sufficient (MeSH is not Emtree) and no details were given on the execution of the screening (e.g., if two independent

reviewers were used). However, the studies previously described in the overview to support the indication were included with additional studies that were also described in other published meta-analyses (Chionh et al., *Cochrane Database of Systematic Reviews*, 2017; Chen et al., *Medicine*, 2019; Wang et al., *International Journal of Colorectal Disease*, 2020). It is agreed that based on the included studies a meta-analyses reporting on PFS and OS is of additional value.

Methods for meta-analysis including non-inferiority margin- PFS was the primary outcome for the meta-analysis with OS and ORR as secondary outcomes, which is acceptable. A non-inferiority margin of 1.25 was defined for PFS which was selected based on the trial with the most conservative non-inferiority margin (i.e. Yamada et al., 2018). This corresponds approximately to a loss of at most 20% in the median. Non-inferiority for S-1 based therapy compared to 5-FU or capecitabine-based therapy was to be concluded when the upper limit of the 99% CI of the pooled HR was lower than 1.25, which is acceptable in view of the likely significant detriment when continuation 5-FU is not possible. The MAH used random-effect models with generic inverse-variance weighing to minimise the imprecision of the pooled effect estimate. All tests were two-sided, and heterogeneity was assessed by the Cochran Q-test and quantified by the I^2 index. Overall, the methods described are considered acceptable.

Results meta-analysis- In total 10 studies were included in the meta-analysis treating 2117 patients: 1062 with S-1 based therapy and 1055 with 5-FU or capecitabine-based therapy. HRs for PFS and OS could be extracted from six studies and ORR data were available from 10 studies. In addition, median PFS per arm was reported by 4 other studies and median OS per arm by 3 other studies.

For the primary endpoint PFS, pooled HR was 0.95 with the upper boundary of the 99% CI being 1.08, which is below the non-inferiority margin of 1.25. For first line studies pooled HR was 0.92 with an 99% CI upper bound of 1.06. In addition, the results are described for three other studies in first line that only reported median PFS. Except for the study by Kim et al., 2015, which reported a median time to progression of 7.4 months for the control arm vs 6.1 months for the S-1 based arm, the other studies reported a numerically longer time to progression in the S-1 based arm with a difference of 0.2 and 0.7 months. For second line studies pooled HR was 1.06 with an 99% CI upper bound of 1.37. Although the HR for PFS in the second line subgroup has an upper bound of the 99% CI above 1.25, it is noted that this is only based on one study (Yasui et al, 2015) and OS is in favour of S-1 in second line (see below). Another second line study that only reported on median PFS showed a median PFS of 8.5 months in the S-1+irinotecan+bevacizumab arm versus 8.2 months in the mFOLFIRI+bevacizumab arm (Liu et al., 2015). No suggestion of important heterogeneity was observed for PFS (I^2 = 12%, P = 0.34) and all studies' point estimates were well below the non-inferiority margin.

OS was a secondary outcome in the studies included in the meta-analysis and supported the PFS results. For all pooled studies HR was 0.93 with CI99% upper bound of 1.07. For both first and second line HR was also <1 with the upper bounds of the CI99% <1.25. No indication of important heterogeneity was observed for OS (I^2 = 0%, P = 0.82), most studies point estimates were below or close to one. Additional three studies only reporting medians for OS all showed non-relevant differences between S-1 versus 5-FU or capecitabine-based therapies.

Based on a pooled risk ratio for response RR was 1.06 with CI99% upper bound of 1.24. When looking at the subgroups of first and second line therapy separately, the upper bounds of the CI99% exceed 1.25 (1.25 for first line and 1.84 for second line). Moderate heterogeneity was detected for ORR (I^2 = 48%, P = 0.04) as was also evident from the larger spread of point estimates of the studies.

Next to the meta-analysis described above, the MAH presented the results of individual studies, which are discussed below.

For **S-1 monotherapy**, one supportive study is provided by the MAH. This concerns the randomised phase 3 trial comparing S-1 versus capecitabine in the first-line treatment of mCRC (**Kwakman et al., 2017**; **Kwakman et al., 2019**).

Design- Patients with previously untreated mCRC in the Netherlands were included, making this the only randomised controlled trial of S-1 versus another fluoropyrimidine provided in a Caucasian population. Bevacizumab could be added at the discretion of the local investigator. S-1 was administered at a dose of 30 mg/m2. The primary endpoint was the incidence of HFS, efficacy endpoints were amongst the secondary endpoints (PFS, RR, OS). Patients were evaluated via RECIST 1.1. Of note, data of this study was previously submitted in fulfilment of the commitment to increase the knowledge about the clinical safety and efficacy of S-1 in clinical practice in advanced gastric cancer (EMEA 001; EMEA/H/C/001242/II/0029).

Results- After randomisation, 81 patients were allocated to the capecitabine arm and 80 to the S-1 arm. In 59%, patients also received bevacizumab. Baseline characteristics were generally balanced, only more females were treated in the S-1 group (31% of capecitabine treated patients were female versus 44% in the S-1 arm). Based on the first analysis published by Kwakman et al., 2017, there were no significant differences in PFS, RR, and OS between the treatment groups after a median follow-up of 20.2 months, although responses were numerically higher in the capecitabine (47%) versus S-1 (32%) group (p=0.09). HR for PFS was 0.99 (95% CI 0.71-1.37, p=0.93) and for OS 1.23 (95% CI 0.82-1.86, p=0.32). Additional long-term results were published by Kwakman et al., 2019, after a median follow-up of 40.3 months. Median PFS was 8.2 months for patients treated with capecitabine compared to 8.4 months for S-1 (HR 1.02, 95% CI 0.75-1.40, p=0.89). Median OS was 17.1 months for capecitabine and 17.0 months for S-1 (HR 1.07, 95% CI 0.76-1.49, p=0.70). As also stated by the authors, the study was not powered for non-inferiority analysis for efficacy measures. The proposed posology of S-1 monotherapy of 30 mg/m2 in the SmPC is based on this study and acceptable.

In addition, the MAH presents the results of four phase 3 non-inferiority studies of **S-1 in combination with oxaliplatin or irinotecan with or without bevacizumab** in Asian mCRC patients.

The first study investigated the combination with oxaliplatin for first-line mCRC patients and results are published by **Hong et al. 2012** and **Kim et al., 2014**.

Design- This was a randomised, non-inferiority trial comparing S-1 plus oxaliplatin (SOX) with capecitabine plus oxaliplatin (CapeOX) for first-line mCRC patients in South Korea. The dosing of S-1 with 40 mg/m^2 is higher than as applied for in this MAA (i.e. 25 mg/m2 in combination therapy). This study did not include the use of bevacizumab, which is part of a standard first-line regimen and the representativeness for the applied for EU indication is therefore questioned. The primary endpoint was PFS with a predefined non-inferiority margin of 1.43. Secondary efficacy endpoints were RR, TTF, OS, and QoL. Tumour responses were reviewed according to RECIST 1.0.

Results- After randomisation, 168 patients were allocated to the SOX combination and 172 to CapeOX. The reported baseline characteristics were balanced between the groups. With a median age of ~60 years, the patients were overall young compared to for example the study by Kwakman et al., 2017 in a European population. Median PFS was 8.5 months in the SOX group and 6.7 months in the CapeOX group (p noninferiority <0.0001). HR of SOX versus CapeOX in PFS was 0.79 (95% CI 0.60-1.04). For the secondary endpoint of OS, HR was 0.86 (95% CI 0.68-1.08). The provided data by the MAH were based on the data cutoff as published by Hong et al., 2012 with a median follow-up of 20.6 months. This publication also reported that TTF was significantly longer in the SOX vs CapeOX group (6.9 vs 5.6 months) and the number of responses higher (47 vs 36%). Updated data are provided by Kim et al., 2014, providing a follow-up exploratory analysis of PFS and OS. Median follow-up was ~17 months, which is unexpected as it is shorter than reported in the first publication and might be a typing error.

Both PFS and OS were not significantly different for SOX versus CapeOX in the updated analyses. The upper limit of the 95% CI of HR for the primary endpoint PFS was <1.23, which was also the case for OS.

Another clinical study investigating the combination with oxaliplatin is published by **Yamada et al., 2013** and **Baba et al., 2017**.

Design- In this open-label, non-inferiority, randomised phase 3 trial, SOX plus bevacizumab was compared with mFOLFOX6 plus bevacizumab as first-line treatment of mCRC patients in Japan. The primary endpoint PFS was tested with a predefined non-inferiority margin of 1.33 according to RECIST 1.0. Secondary efficacy endpoints were amongst others OS, TT, RR.

Results- In both groups 256 patients were assigned. Baseline characteristics of this study population with a median age of 63 years were balanced between the arms. Median PFS was 11.5 months in the mFOLFOX6/bevacizumab arm and 11.7 months in the SOX/bevacizumab arm as published by Yamada et al., 2013 with a median follow-up of 18.4 months. With a HR of 1.04 and corresponding 95% CI of 0.86-1.27, this was below the non-inferiority margin of 1.33 (p=0.014). Due to the immaturity of the data, Baba et al., 2017, reported the final PFS and OS analysis. With this final data cutoff, median follow-up for PFS was 31.2 months. Median PFS was 11.7 months in the mFOLFOX6/bevacizumab group and 12.2 months in the SOX/bevacizumab group (HR 1.05; 95%CI 0.88-1.26; p non-inferiority=0.0115 based on the predefined non-inferiority margin). At the final data cutoff, median OS was 29.7 months in the mFOLFOX6/bevacizumab arm and 29.6 months in the SOX/bevacizumab arm (HR 1.02; 95% CI 0.82-1.26). The response rates were similar between the treatment groups (62.7% for mFOLFOX6/bevacizumab, 61.5% for SOX/bevacizumab).

The next study investigated the combination of S-1 with irinotecan plus bevacizumab versus mFOLFOX6 or CapeOX plus bevacizumab (**Yamada et al., 2018**).

Design- This was a randomised, open-label, phase 3, non-inferiority trial in first-line mCRC patients in Japan. Dosing of S-1 was again higher (40 mg/m^2) compared to the posology as proposed in the SmPC for this application. The primary endpoint was PFS with a predefined non-inferiority margin of 1.25 based on RECIST 1.1. Superiority would be tested if non-inferiority was demonstrated. Secondary efficacy endpoints were OS, TTF, RR, and QoL.

Results- In the mFOLFOX6/CapeOX plus bevacizumab arm 243 patients were analysed for efficacy (66 mFOLFOX6 and 177 CapeOX) and 241 in the S-1 plus irinotecan and bevacizumab arm (136 3-week regimen and 105 4-week regimen). Median PFS was 10.8 months in the mFOLFOX6/CapeOX plus bevacizumab group and 14.0 months in the S-1 plus irinotecan and bevacizumab group (HR 0.84; 95%CI 0.70–1.02; p<0.0001 for non-inferiority). The reported p-value for superiority was 0.0815 at a median follow-up of 32.4 months. Median TTF in the mFOLFOX6/CapeOX plus bevacizumab group and the S-1 plus irinotecan and bevacizumab arm group was 7.7 months and 9.6 months, respectively (p=0.0002). The response rate of target lesions was 70.6% in the mFOLFOX6/CapeOX plus bevacizumab group and 66.4% in the S-1 plus irinotecan and bevacizumab arm group (p=0.34). The p-value for OS was 0.2841 with a median OS in the mFOLFOX6/CapeOX plus bevacizumab group of 33.6 months and 34.9 months in the S-1 plus irinotecan and bevacizumab arm (HR 0.86; 95% CI 0.66-1.13).

The fourth study investigated the combination of S-1 plus irinotecan versus FOLFIRI as second-line treatment (**Muro et al., 2010; Yasui et al., 2015**).

Design- This was a randomised, open-label phase 2/3 study investigating the combination of S-1 plus irinotecan (IRIS) versus FOLFIRI as second-line treatment in mCRC patients in Japan. S-1 dosing was weight-dependent; 40 mg for patients with BSA <1.25 m2; 50 mg for patients with BSA 1.25<1.5 m2; 60 mg for patients with BSA ≥1.5 m2. The primary endpoint was PFS with a predefined non-inferiority

margin of 1.333. Patients were evaluated with RECIST 1.0. Secondary efficacy endpoints were OS and RR.

Results- After randomisation, 213 patients each were allocated to both treatment arms. Reported baseline characteristics were balanced between the groups and the median age was ~62 years. Again, the results of two database cutoffs were published. At the first database cutoff median PFS was 5.8 months for IRIS compared to 5.1 months for FOLFIRI (median follow-up 12.9 months). The HR for IRIS compared to FOLFIRI for PFS was 1.077 (95% CI 0.897-1.319) which met the primary endpoint of non-inferiority as defined by the study with a margin of 1.333. The HR for the secondary endpoint of OS as was 0.900 (95% CI 0.728-1.112) at the latest data cutoff with a median OS of 17.8 months in the IRIS arm and 17.4 months in the FOLFIRI arm (median follow-up 39.2 months). At the final data cutoff, median PFS was 5.1 months in the FOLFIRI group and 5.8 months in the IRIS group. In the ITT population, the HR for IRIS to FOLFIRI was 1.058 (95% CI 0.869–1.289; p=0.022). It should be noted that the study population was not representative for a second-line European mCRC population (see also commentary by Schmoll, *Lancet Oncology*, 2010). Only 60% of the study population received prior chemotherapy with oxaliplatin. As stated by Muro et al., 2010, FOLFOX was already the standard first-line treatment worldwide when the study started, but oxaliplatin had just been launched in Japan. In the subgroup of patients receiving prior chemotherapy with oxaliplatin, median PFS was 5.7 months in the IRIS group and 3.9 months in the FOLFIRI group (adjusted HR 0.876, 95% CI 0.677–1.133), whereas in patients without prior oxaliplatin treatment it was 6.0 months and 7.8 months, respectively (HR 1.490, 95% CI 1.079–2.059). A similar tendency was noted in OS results. The subgroup analysis in patients with or without prior oxaliplatin are limited by low numbers and it is difficult to draw conclusions based on these subgroups, but it seems that pretreatment with or without oxaliplatin influences the results of 2L treatment.

In addition, the MAH provided the efficacy results in the clinical overview of studies performed in a Caucasian population. The first study is a phase 1 trial to determine the schedule of a combination of S-1 with oxaliplatin and bevacizumab in a Caucasian population with advanced or metastatic solid tumours for which no established standard therapy existed (**Chung et al., 2011**). Two treatment schedules were tested: schedule A was a 21-day cycle with 14 consecutive dose of S-1 and in schedule B a 14-day cycle was used with 7 days S-1 treatment. S-1 was administered in increasing doses. For Schedule A MTD was determined to be S-1 25 mg/m2 administered orally twice daily for 14 days followed by 7 days of rest in a 3-week cycle in combination with oxaliplatin and bevacizumab once every 3 weeks. The MTD of schedule B was S-1 35 mg/m2 administered in combination with 85 mg/m 2 oxaliplatin and 5 mg/kg bevacizumab once every 2 weeks. Of the total of 22 evaluable patients in schedule A, 2 patients (9%) achieved PR, 17 patients (74%) had SD and 4 patients (17%) demonstrated PD as the best response based on RECIST. For schedule B, 24 patients were evaluable: 8 patients (35%) demonstrated PR, 10 patients (44%) SD, and 5 patients (22%) PD as best response. The MAH proposed a S-1 posology of 25 mg/m2 for combination chemotherapy, which can be supported for oxaliplatin based on the results by Chung et al., 2011.

The second study discussed in the clinical overview is a randomised study with both study arms receiving S-1 in an older, vulnerable mCRC population (**Winther at al., 2019**).

Design- First-line mCRC patients were included of 70 years and older who were not candidates for full-dose combination therapy. Patients were randomised to receive full-dose S-1 (30 mg/m2 b.i.d, orally, d1-14 every 3 weeks) followed by second-line irinotecan (250 mg/m2, IV, d1 every 3 weeks or 180 mg/m2 IV, d1 every 2 weeks) at progression or reduced-dose S-1 (20 mg/m2 b.i.d. d1-14 every 3 weeks) plus oxaliplatin (100 mg/m2 d1 every 3 weeks) followed by second-line treatment at disease progression with reduced dose S-1 plus irinotecan (180 mg/m2 d1 every 3 weeks). Addition of bevacizumab was optional (7.5 mg/kg IV d1 every 3 weeks). The primary endpoint was PFS and

secondary efficacy endpoints included OS, response, QoL, and time to failure of strategy. RECIST 1.1 was used by the local investigators to determine responses. Patients were recruited in Denmark, Finland, Norway, and Sweden.

Results- 83 patients were randomised to the full-dose monotherapy and 77 to the reduced-dose combination therapy. Median age was 78 years and ~20% had ECOG PS2. Bevacizumab was administered to 22 patients in each group. With a median follow-up of 23.8 months (IQR 18.8-30.9) PFS was 5.3 months (95% CI 4.1-6.8) in the full-dose group compared to 6.2 months (95% CI 5.3- 8.3) in the reduced-dose combination therapy group (HR 0.72, 95% CI 0.52-0.99, p=0.047). Median OS was 11.5 months (95% CI 8.7-15.9) in the full-dose monotherapy group compared to 14.5 months (95% CI 12.1- 20.8 in the reduced-dose combination therapy group (HR 0.82, 95% CI 0.57-1.19, p=0.302). The proportion of patients achieving objective response with first-line treatment was numerically but not significantly higher in the reduced-dose combination group (42%) than in the full-dose monotherapy group (33%, p=0.257). The MAH proposes in section 4.2 of the SmPC that the recommended dose of S-1 in combination with oxaliplatin in elderly, more vulnerable patients should be reduced to 20 mg/m2, which is acceptable.

Overall discussion

In this type II variation, the MAH applies for an extension of the indication for the treatment of mCRC patients where the current chemotherapy cannot be continued due to the fluoropyrimidine intolerability causing cardiotoxicity or HFS. It is agreed with the MAH that there is an **unmet medical need** in patients who cannot continue with other fluoropyrimidines due to HFS and cardiovascular safety issues. Without the option to continue an effective therapy with fluoropyrimidines due to toxicity, there is a potential loss of extended overall survival. S-1 is designed to reduce the rate of degradation of 5-FU and its conversion to its toxic phosphorylated metabolite and can, therefore, hypothetically act as an alternative to patients for whom continuation with another fluoropyrimidine is not an option.

In support of the indication, the MAH performed a **literature search and meta-analysis** of randomised phase II and III clinical trials. The meta-analysis showed that S-1 based therapy was non-inferior to 5-FU or capecitabine-based therapy regarding PFS using a non-inferiority margin of 1.25. This non-inferiority applies to patients starting first-line or second line therapy and is as such not direct evidence for the indication. Secondary outcomes of OS and ORR supported this finding. Although the HR for PFS in the second line subgroup has an upper bound of the 99% CI above 1.25, it is noted that this is only based on one study. Another study performed in second line that was not included in the meta-analysis as only median PFS was reported, showed a median PFS of 8.5 months in the S-1+irinotecan+bevacizumab arm versus 8.2 months in the mFOLFIRI+bevacizumab arm. Combined with the finding that the CI99% upper bound for OS was <1.25 in the second line subgroup, excluding the subgroup treated in second line is not considered necessary.

In addition to the meta-analysis that was performed mainly in Asian patients who were randomised at baseline, the MAH also provided direct but **exploratory efficacy data in European patients who switched to S-1 because of cardiotoxicity or HFS on another fluoropyrimidine**. Although the interpretation of these data are hampered by the retrospective and non-comparative nature, it seems that fluoropyrimidine activity is not lost after switching to S-1. It is also acknowledged that a randomised controlled trial in a population that cannot be treated with another fluoropyrimidines is not feasible due to lack of a proper control. With the newly performed meta-analysis using published results of clinical comparative studies in mainly Asian population supported by exploratory data in an European population that switched, the use of bibliographic evidence is considered sufficient for this application.

The indication only includes S-1 monotherapy or the combination with oxaliplatin or irinotecan with or without bevacizumab. With the restriction to patients who developed HFS or cardiovascular toxicity on

another fluoropyrimidine, it can be considered that the same unmet medical need as identified for metastatic patients also applies to patients who developed these specific toxicities upon fluoropyrimidine for colorectal cancer in the adjuvant setting. While only a few patients treated in the adjuvant setting were included in the studies that form the basis of this application, it is to be expected that HFS or cardiovascular toxicity will recur when patients will subsequently be treated with 5-FU or capecitabine in the metastatic setting. Furthermore, the posology of 5-FU/capecitabine and the combinations in which they are used in the adjuvant and metastatic setting are similar. Therefore, it is acceptable to include this population in the indication.

GCP- The clinical studies have been performed in accordance with GCP as claimed by the MAH, which is acceptable.

Formulation- The MAH stated that in the European and most of the Japanese and Korean studies the Teysuno formulation manufactured by Taiho was investigated. In three phase 2 Japanese studies a generic, bioequivalent form, also manufactured, by Taiho was used. For three studies conducted in China, the formulation was not known. However, as these studies were not included in the meta-analysis, this is not considered to be an issue.

Posology- The indication is restricted in this round to S-1 monotherapy (+/- bevacizumab) or the combination with oxaliplatin (+/- bevacizumab) or irinotecan (+/- bevacizumab). As described above, the dosing for S-1 monotherapy (+/- 7.5 mg/kg bevacizumab) is based on the publications by Kwakman et al., 2017 and acceptable. The combination of S-1 with oxaliplatin (+/- bevacizumab) is based on the publication by Chung et al., 2011 and also agreed. The combination with irinotecan was initially only supported by data in a Caucasian population that is frail with a reduced regimen, i.e. the publication of Winther et al., 2019. In the response, the MAH provided 3 additional levels of supportive evidence for the posology of the S-1 and irinotecan combination: a study in older mCRC patients treated with S-1 (Winther et al., 2016), data from the CardioSwitch study (Österlund et al., submitted), and clinical experience in Nordic European countries. Based on these data, the MAH concludes that the recommended dose of 180 mg/m2 irinotecan dose was chosen as this is the dose used in the CardioSwitch study, it is the standard dose in Finland and is the published dose in the observational Scandinavian chart study (by Winther et al., 2016). Experiences treating mCRC with this recommended dose of 25 mg/m2 S-1 b.i.d combined with 180 mg/m2 irinotecan in 3-week schedules are that it is effective and tolerable. It is agreed with the MAH that, albeit limited, most experience of the IRIS combination in European mCRC patients is with a 3-week schedule and S-1 dosing of 25 mg/m2 with no efficacy or safety concerns. Regarding the choice of 180 mg/m2 irinotecan, most studies and clinical practices use a higher dose of 200 mg/m2 though a range of 150-225 mg/m2 is reported, which is reflected in the SmPC. The recommendation on the dose reduction was updated in section 4.2 of the SmPC. No recommendation can be made and dose reduction will be dependent on the starting dose.

Extrapolation- The first extrapolation is *from Asian patients, the population in which most of the clinical studies were performed, to the European target population*. For this extrapolation, the MAH discusses PK, efficacy and safety data. Pharmacokinetics were not found to be clinically significantly different between ethnic groups. It is agreed that probably the reason for different recommended doses of S-1 between Western and Japanese patients is the ethnic differences in 5-FU tolerability rather than the difference in pharmacokinetics. This trend is also observed for other fluoropyrimidine chemotherapies. Regarding efficacy, the MAH describes meta-analyses results from studies in first-line advanced gastric cancer (ter Veer et al., *Gastric Cancer*, 2016; ter Veer et al., *Scientific Reports*, 2017).The meta-analysis published in 2016 investigated efficacy and safety of S-1 based therapy compared to 5-FU or capecitabine-based therapy in advanced gastric cancer. The authors concluded that there were no subgroup differences in efficacy among Asian and Western patients (ter Veer et al., *Gastric Cancer*, 2016). The network meta-analysis published in 2017 included overlapping studies and also concluded

that effects were similar in Asian and Western subgroups (ter Veer et al., *Scientific Reports*, 2017). However, regarding safety, extrapolation is hampered by the ethnic differences in S-1 pharmacodynamics and toxicity reported in the literature and underlined also by the differences in S-1 posologies as monotherapy and in combinations regimens applied in the studies performed in the different ethnic groups (refer to the safety section of this report).

For the second extrapolation from *patients who are randomised at baseline between S-1 or another fluoropyrimidine to patients who are not able to continue with another fluoropyrimidine*, the MAH refers to the newly conducted meta-analysis supporting non-inferiority of the efficacy of S-1 based regimens compared to 5-FU or capecitabine-based regimens as first or second line treatment in mCRC (Derksen et al., 2021, in preparation). In addition, the two previously described retrospective analyses of patients who switched to S-1 after toxicity on another fluoropyrimidine, support that S-1 will be an effective and better tolerated option in patients who develop HFS or cardiotoxicity on another fluoropyrimidine (Österlund et al., submitted; Punt et al., in preparation). Although this is formally no evidence of comparable efficacy when patients are randomised at baseline between S-1 or another fluoropyrimidine to patients who switch to S-1 after fluoropyrimidine-associated toxicity, it is not possible to gather this information as the treatment options for patients become limited when 5-FU cannot be used. In addition, based on the MoA it is not expected that efficacy of S-1 will be different in patients who switch compared to start with S-1. Therefore, S-1 can be regarded as a treatment option considering the perspective of not being able to use another fluoropyrimidine, and this extrapolation step is considered less relevant in the restricted population.

The third extrapolation part is *from the treatments studied to all established combinations of mCRC therapy in a line agnostic indication*. As the MAH narrowed the indication to S-1 monotherapy or specific combinations for which data are provided, i.e. the combination with oxaliplatin or irinotecan with or without bevacizumab, this extrapolation is not applicable anymore. The combination with EGFR inhibitors is not included in the adjusted wording of the indication.

2.4.4. Conclusions on the clinical efficacy

With the restricted indication, exploratory efficacy data in European patients who switched to S-1 after toxicity on another fluoropyrimidine and the additional supportive meta-analysis, efficacy for patients who show intolerable toxicity on current standard mCRC treatment with a 5-FU or capecitabine backbone is supported. When another fluoropyrimidine cannot be continued due to toxicity, treatment options become limited with the potential loss of extended overall survival. Based on the provided efficacy data S-1 demonstrated to be a valuable treatment option considering the perspective of not being able to continue fluoropyrimidine treatment.

With the restriction to patients who developed HFS or cardiovascular toxicity on another fluoropyrimidine, it can be considered that the same unmet medical need also applies to patients who developed these specific toxicities in the adjuvant setting for colorectal cancer and it is supported to include this population in the indication.

2.5. Clinical safety

Introduction

The safety profile of S-1 for the existing indication (i.e., in combination with cisplatin in advanced gastric cancer) has been established on the basis of the FLAG study, where S-1 in combination with cisplatin was compared with 5FU in combination with cisplatin. The most frequently reported adverse events

associated with S1 were fatigue, gastrointestinal toxicity (i.e., diarrhoea, vomiting, mucositis/stomatitis) and haematological toxicity. A lower frequency of HFS and cardiac toxicity was reported in comparison with 5FU. Inter-ethnic differences in S-1 pharmacodynamics and toxicity have been reported in the literature.

In support for the assessment of the risks related to the type II variation sought according to the revised indication (i.e., extension of indication to "*as monotherapy or in combination with oxaliplatin or irinotecan, with or without bevacizumab, is indicated for the treatment of patients with metastatic colorectal cancer for whom it is not possible to continue treatment with another fluoropyrimidine due to hand-foot syndrome or cardiovascular toxicity*") the MAH has submitted the following literature data:

1-European mCRC – S-1 as Monotherapy:

a) SALTO Study: Phase 3 randomized controlled trial in 161 **European** previously untreated mCRC patients randomized (1:1) to capecitabine vs S-1 (with or without bevacizumab) (Kwakman et al., 2017 and Clinical Study Report);

2-Asian mCRC – S-1 in combination therapy:

a) SOX vs CAPOX study: Phase 3 randomized study of SOX vs CAPOX in 340 patients in South Korea (Hong et al., 2012);

b) SOFT: Phase 3 randomized study of SOX-bevacizumab (SOX-B) vs mFOLFOX6-bevacizumab (mFOLFOX-B) in 512 patient in Japan (Yamada et al., 2013);

c) TRICOLORE: Phase 3 randomized study of IRIS-B vs mFOLFOX6-B or CAPOX-B in 487 patients in Japan (Yamada et al., 2018);

d) FIRIS: Phase 3 randomized study of FOLFIRI vs IRIS in 426 patients in Japan (Muro et al., 2010);

3-European mCRC – S-1 in combination therapy

a) NORDIC9: Phase 2 randomized study of full-dose S1 monotherapy vs reduced-dose SOX in 160 European older vulnerable mCRC patients (Winther et al., 2019);

4- Safety of S-1 in special populations: S-1 after adverse events (HFS or cardiac toxicity) with other fluoropyrimidines in European patients:

a) Case series of patients treated with S-1 after capecitabine-induced coronary artery vasospasm (Kwakman et al., 2017)

b) Tolerability of S1 after HFS – related discontinuation of capecitabine in western cancer patients (Kwakman et al., 2017).

c) Continuation of fluoropyrimidine treatment with S-1 after cardiotoxicity on capecitabine- or 5-fluorouracil-based therapy in patients with solid tumours: a multi-centre retrospective observational cohort study (Österlund et al., submitted, 2021, manuscript draft).

d) Dutch Prospective Colorectal cancer Cohort (PLCRC Switch Study)- Long-term safety data on S-1 (Teysuno) administered after previous intolerance to capecitabine-containing systemic treatment for metastatic colorectal cancer (Punt et al., in preparation, 2021).

Patient exposure

SALTO Study

A total of 161 previously untreated mCRC patients were randomized 1:1 to receive either capecitabine (1250 mg/m2 orally for patients <70 years; 1000 mg/m2 for patients ≥70 years, BID on days 1-14

Q3W) or S1 (30 mg/m2 orally BID on days 1-14 Q3W) in 27 centres in The Netherlands. Primary endpoint was incidence of any grade HFS as assessed by both physicians and patients (diaries). Secondary endpoints included incidence of grade 3 HFS, incidence of other toxicities, and efficacy (i.e., PFS, ORR and OS). Toxicity was recorded according to NCI CTCAE version 4.0. One patient did not start study treatment and therefore was not included in the safety database.

SOFT study

A total of 512 previously untreated mCRC patients were randomized 1:1 to receive either mFOLFOX6 plus bevacizumab (mFOLFOX6-B, 85 mg/m² oxaliplatin, 200 mg/m² l-leucovorin, 400 mg/m² bolus fluorouracil, and 2400 mg/m² infusional fluorouracil, and 5 mg/kg bevacizumab on day 1 Q2W) or SOX plus bevacizumab (SOX-B, 130 mg/m² oxaliplatin and bevacizumab 7.5 mg/kg Q3W, and assigned dose of S-1 BID day 1-15 Q3W) in 82 centres in Japan. Primary endpoint was PFS evaluated in a non-inferiority setting.

SOX vs CAPOX study

A total of 340 previously untreated mCRC patients were randomized 1:1 to receive either CAPOX (capecitabine 1000 mg/m² BID on days 1–14 and oxaliplatin 130 mg/m² on day 1, bevacizumab 7.5 mg/kg Q3W) or SOX (S-1 40 mg/m² BID on days 1–14 and oxaliplatin 130 mg/m² on day 1) every 3 weeks in 11 centres in South Korea. Primary endpoint was PFS evaluated in a non-inferiority setting.

TRICOLORE study

A total of 487 previously untreated mCRC patients were randomized 1:1 to receive either CAPOX (capecitabine 1000 mg/m² BID on days 1–14 and oxaliplatin 130 mg/m² on day 1) or mFOLFOX6-B (oxaliplatin 85 mg/m2, leucoverin 200 mg/m2 , 5FU 400 mg/m2 followed by 2400 mg/m2, bevacizumab 5 mg/kg Q2W) vs IRIS-B (3-weekly: irinotecan 150 mg/m2 and bevacizumab 7.5 mg/kg on day 1, oral S-1 80 mg/m2 BID for 2 weeks, followed by a 1-week rest; or 4-weekly: irinotecan 100 mg/m2 and bevacizumab 5 mg/kg on days 1 and 15, S-1 80 mg/m2 BID for 2 weeks, followed by a 2-week rest). Patients were enrolled in 53 centres in Japan. Primary endpoint was PFS evaluated in a non-inferiority setting.

FIRIS study

A total of 426 mCRC patients in need of second-line treatment were randomized 1:1 to receive either FOLFIRI (150 mg/m² irinotecan, 200 mg/m² l-leucovorin, 400 mg/m² bolus fluorouracil, and 2400 mg/m² infusional fluorouracil on day 1 Q2W) or IRIS (125 mg/m² irinotecan on day 1 and 15, S-1 (40-60 mg according to body surface area) BID day 1-15, Q4W) in 40 centres in Japan. Primary endpoint was PFS evaluated in a non-inferiority setting.

NORDIC9 study

A total of 157 previously untreated mCRC patients aged ≥ 70 years and not considered candidates for full-dose combination chemotherapy were randomized 1:1 to receive either full dose S1 (30 mg/m2 BID day 1-14 Q3W) followed by second line treatment at progression with irinotecan (250 mg/m2 Q3W or 180 mg/m2 Q2W) vs reduced-dose chemotherapy with S1 (20 mg/m2 BID day 1-14) and oxaliplatin (100 mg/m2 Q3W) followed by second line treatment at progression with S1 (20 mg/m2 BID day 1-14) and irinotecan (180 mg/m3 Q3W) in 23 Nordic European centres. The use of bevacizumab was allowed at discretion of investigator (7.5 mg/kg Q3W). Primary endpoint was PFS.

Adverse events

SALTO study

In the SALTO trial, the incidence of any grade HFS (primary study endpoint) as assessed by local investigators was 73% in the capecitabine group and 45% in the S1 group (n=58 vs 36; odds ratio [OR], 95% confidence interval [CI] 0.31 (0.16-0.60, p=0.0005)). The incidence of grade 3 HFS was 21% for capecitabine and 4% for S-1 (n=17 vs n=3, p=0.003) (Kwakman et al., 2017).

Table 22. Incidence of HFS as assessed by investigators

	Capecitabine (*n*=80)	S-1 (*n*=80)	*p*-value
Any grade	**58 (73%)**	**36 (45%)**	**0·0005**
Grade 1	17 (21%)	22 (28%)	0·37
Grade 2	24 (30%)	11 (14%)	0·02
Grade 3	17 (21%)	3 (4%)	0·003

Data are number of patients (%)

Any grade diarrhoea (p=0.01) and grade 3 anorexia (p=0.03) occurred more frequently in the S-1 group.

Table 23. Treatment-related adverse events in SALTO

	Capecitabine (*n* =80)			S-1 (*n* =80)			*P*-value
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4	
Diarrhoea	38 (48%)	9 (11%)	1 (1%)	55 (69%)	12 (15%)	1 (1%)	0.65
Anorexia	23 (29%)	2 (3%)	0	33 (41%)	10 (13%)	0	0.03
Stomatitis	19 (24%)	2 (3%)	0	21 (26%)	2 (3%)	0	1.00
Nausea	31 (39%)	4 (5%)	0	35 (44%)	3 (4%)	0	1.00
Vomiting	15 (19%)	2 (3%)	1 (1%)	24 (30%)	2 (3%)	0	1.00
Dehydration	4 (5%)	3 (4%)	0	5 (6%)	0	0	0.25
Fatigue	59 (74%)	6 (8%)	0	63 (79%)	8 (10%)	0	0.78
Hypertension	28 (35%)	15 (19%)	0	34 (43%)	18 (23%)	0	0.70
Peripheral artery thrombosis	0	0	2 (4%)	0	0	0	0.50
Proteinuria	7 (9%)	1 (1%)	0	16 (20%)	0	0	1.00
Neutropenia	0	0	0	0	0	0	NA
Thrombocytopenia	2 (3%)	1 (1%)	0	0	0	0	1.00

Data are number of patients (%). *P*-value showed for grade ≥3 adverse events.
NA, not applicable.

Patients who received S-1 had significantly higher rates of grade 3 anorexia (12.5% vs 2.5%, p=0.032), grade 2 anorexia and diarrhea compared to those who received capecitabine. Patients who received capecitabine had significantly higher rates of grade 3 HFS (21.3% vs 3.75%, p=0.0013) and grade 2 HFS compared with S-1 treated patients.

Adverse events (capecitabine vs S-1)

	Grade ≥ 1	p-value	Grade ≥ 2	p-value	Grade ≥ 3	p-value
Anorexia	23/80 vs. 33/80	0.14	8/80 vs. 19/80	0.033	2/80 vs. 10/80	0.032
Constipation	9/80 vs. 26/80	0.0019	4/80 vs. 5/80	1	0/80 vs. 1/80	1
Cough	13/80 vs. 14/80	1	1/80 vs. 4/80	0.37	0/80 vs. 0/80	1
Dehydration	4/80 vs. 5/80	1	3/80 vs. 4/80	1	3/80 vs. 0/80	0.25
Diarrhea	38/80 vs. 55/80	0.01	15/80 vs. 27/80	0.047	10/80 vs. 13/80	0.65
Dyspnea	16/80 vs. 16/80	1	4/80 vs. 6/80	0.75	1/80 vs. 2/80	1
Fatigue	59/80 vs. 63/80	0.58	26/80 vs. 33/80	0.33	6/80 vs. 8/80	0.78
Fever	12/80 vs. 19/80	0.23	5/80 vs. 6/80	1	0/80 vs. 1/80	1
Heartburn/dyspepsia	7/80 vs. 10/80	0.61	0/80 vs. 3/80	0.25	0/80 vs. 0/80	1
Hypertension	28/80 vs. 34/80	0.42	26/80 vs. 27/80	1	15/80 vs. 18/80	0.7
Ileus	3/80 vs. 5/80	0.72	3/80 vs. 4/80	1	3/80 vs. 3/80	1
Infection	21/80 vs. 29/80	0.23	17/80 vs. 23/80	0.36	6/80 vs. 9/80	0.59
Infusion site extravasation	0/80 vs. 2/80	0.5	0/80 vs. 0/80	1	0/80 vs. 0/80	1
Mucositis/stomatitis	19/80 vs. 21/80	0.86	7/80 vs. 3/80	0.33	2/80 vs. 2/80	1
Myocarcial infarction	0/80 vs. 1/80	1	0/80 vs. 0/80	1	0/80 vs. 0/80	1
Nausea	31/80 vs. 35/80	0.63	12/80 vs. 10/80	0.82	4/80 vs. 3/80	1
Other cardiac disorders	10/80 vs. 8/80	0.8	3/80 vs. 7/80	0.33	1/80 vs. 3/80	0.62
Other gastrointestinal disorders	29/80 vs. 32/80	0.74	9/80 vs. 13/80	0.49	1/80 vs. 5/80	0.21
Other metabolic disorders	9/80 vs. 6/80	0.59	4/80 vs. 3/80	1	1/80 vs. 3/80	0.62
Other neurologic disorders	22/80 vs. 32/80	0.13	7/80 vs. 12/80	0.33	3/80 vs. 3/80	1
Other pulmonary symptoms	17/80 vs. 16/80	1	5/80 vs. 5/80	1	1/80 vs. 1/80	1
Other renal/urinary disorder	10/80 vs. 10/80	1	2/80 vs. 6/80	0.28	1/80 vs. 1/80	1
Other skin disorders	29/80 vs. 39/80	0.15	7/80 vs. 5/80	0.77	0/80 vs. 1/80	1
Other vascular disorders	10/80 vs. 13/80	0.65	4/80 vs. 2/80	0.68	2/80 vs. 0/80	0.5
PPE syndrome(hand-foot syndr.)	58/80 vs. 36/80	0.0007	41/80 vs. 14/80	<0.0001	17/80 vs. 3/80	0.0013
Pain	44/80 vs. 51/80	0.33	20/80 vs. 23/80	0.72	4/80 vs. 4/80	1
Perforation	1/80 vs. 3/80	0.62	0/80 vs. 1/80	1	0/80 vs. 1/80	1
Peripheral sensory neuropathy	24/80 vs. 20/80	0.6	8/80 vs. 2/80	0.1	0/80 vs. 0/80	1
Proteinuria	7/80 vs. 16/80	0.07	2/80 vs. 3/80	1	1/80 vs. 0/80	1
Vomiting	15/80 vs. 24/80	0.14	6/80 vs. 12/80	0.21	3/80 vs. 2/80	1
Hematology						
platelets	2/80 vs. 0/80	0.5	1/80 vs. 0/80	1	1/80 vs. 0/80	1
Any	80/80 vs. 80/80	1	73/80 vs. 71/80	0.79	49/80 vs. 52/80	0.74

No relevant differences between the two study arms were observed regarding the percentage and kind of post-study treatment received by patients enrolled in the SALTO study.

SOFT study

In the SOFT study comparing SOX-B vs mFOLFOX6-B, SOX-B was associated with a significantly lower incidence of grade ≥3 neutropenia (9% vs 34%, respectively) and leucopenia (2% vs 8%, respectively) compared with mFOLFOX6-B. Nevertheless, frequency of grade ≥3 diarrhoea (9% vs 3%, respectively) and anorexia (5% vs 1%, respectively) was increased with SOX-B.

Table 24. Adverse events SOFT study

	Group given mFOLFOX6 plus bevacizumab (n=249)		Group given S-1 and oxaliplatin plus bevacizumab (n=250)		p value*
	Any	≥Grade 3	Any	≥Grade 3	
Haematological					
Leucopenia	175 (70%)	21 (8%)	145 (58%)	6 (2%)	0·0029
Neutropenia	180 (72%)	84 (34%)	148 (59%)	22 (9%)	<0·0001
Thrombocytopenia	135 (54%)	2 (1%)	175 (70%)	9 (4%)	0·063
Anaemia	99 (40%)	6 (2%)	98 (39%)	13 (5%)	0·16
Increased aspartate aminotransferase concentration	107 (43%)	8 (3%)	138 (55%)	11 (4%)	0·64
Increased alanine aminotransferase concentration	99 (40%)	8 (3%)	98 (39%)	12 (5%)	0·49
Increased creatinine concentration	37 (15%)	0	26 (10%)	0	..
Proteinurea	120 (48%)	0	115 (46%)	0	..
Non-haematological					
Mucositis or stomatitis	123 (49%)	0	103 (41%)	4 (2%)	0·12
Anorexia	160 (64%)	3 (1%)	160 (64%)	13 (5%)	0·019
Nausea	139 (56%)	3 (1%)	130 (52%)	5 (2%)	0·72
Vomiting	50 (20%)	1 (<1%)	51 (20%)	2 (1%)	1·00
Diarrhoea	96 (39%)	7 (3%)	133 (53%)	23 (9%)	0·0040
Rash or desquamation	58 (23%)	0	55 (22%)	0	..
Hyperpigmentation	96 (39%)	..	125 (50%)	..	..
Fatigue	134 (54%)	3 (1%)	140 (56%)	7 (3%)	0·34
Sensory neuropathy	224 (90%)	35 (14%)	228 (91%)	25 (10%)	0·17
Hypertension	76 (31%)	14 (6%)	65 (26%)	15 (6%)	1·00
Hyperbilirubinaemia	10 (4%)	1 (<1%)	33 (13%)	5 (2%)	0·22
Alopecia	61 (24%)	..	15 (6%)	..	..
Infusion reaction	1 (<1%)	0	11 (4%)	0	..
Hand-foot syndrome	44 (18%)	0	39 (16%)	1 (<1%)	1·00
Paralytic ileus, gastrointestinal obstruction, or gastrointestinal constriction	7 (3%)	7 (3%)	9 (4%)	7 (3%)	1·00
Gastrointestinal perforation	1 (<1%)	1 (<1%)	5 (2%)	5 (2%)	0·22
Fever	44 (18%)	0	38 (15%)	0	..
Infection (documented clinically or micro-biologically) with grade 3 or 4 neutrophils	1 (<1%)	1 (<1%)	0	0	0·50
Watery eye	4 (2%)	0	12 (5%)	0	..
Thrombosis, thrombus, or embolism	7 (3%)	4 (2%)	3 (1%)	2 (1%)	0·45

Data are n (%). mFOLFOX6=modified regimen of leucovorin, fluorouracil, and oxaliplatin. *Fisher's exact test; comparing frequency of adverse event of grade 3 or higher.

SOX vs CAPOX Study in South Korea

In the SOX vs CAPOX study, patients in the SOX group experienced significantly more grade 3-4 neutropenia, thrombocytopenia, and diarrhoea but less any grade hand-foot syndrome (HFS) than those in the CAPOX group (Hong et al., 2012).

Table 25. Adverse events SOX vs CAPOX study

	Any grade			Grade 3 or grade 4		
	SOX (N=169)	CapeOX (N=166)	p value	SOX (N=169)	CapeOX (N=166)	p value
Haematological						
Leucopenia	2 (1%)	4 (2%)	0·23	1 (1%)	1 (1%)	0·50
Neutropenia	82 (49%)	67 (40%)	0·08	49 (29%)	24 (15%)	0·001
Febrile neutropenia	2 (1%)	2 (1%)	0·38	2 (1%)	2 (1%)	0·38
Thrombocytopenia	84 (50%)	52 (31%)	0·001	37 (22%)	11 (7%)	<0·0001
Anaemia	27 (16%)	17 (10%)	0·08	6 (4%)	3 (2%)	0·26
Non-hematological						
Jaundice	23 (14%)	9 (5%)	0·008	3 (2%)	4 (2%)	0·27
ALP abnormality	3 (2%)	2 (1%)	0·51	0	1 (1%)	0·50
AST or ALT abnormality	21 (12%)	21 (13%)	0·13	3 (2%)	7 (4%)	0·11
Anorexia	120 (71%)	94 (57%)	0·004	11 (7%)	4 (2%)	0·06
Fatigue	77 (46%)	66 (40%)	0·17	10 (6%)	6 (4%)	0·23
Constipation	54 (32%)	50 (30%)	0·40	1 (1%)	0	0·50
Diarrhoea	75 (44%)	57 (34%)	0·038	16 (10%)	7 (4%)	0·045
Stomatitis	64 (38%)	38 (23%)	0·002	1 (1%)	0	0·50
Nausea	95 (56%)	92 (55%)	0·09	5 (3%)	4 (2%)	0·51
Vomiting	62 (37%)	59 (36%)	0·46	3 (2%)	6 (4%)	0·16
Bleeding	28 (17%)	27 (16%)	0·53	2 (1%)	0	0·25
Hand-foot syndrome	23 (14%)	51 (31%)	<0·0001	1 (1%)	3 (2%)	0·25
Sensory neuropathy	133 (79%)	129 (78%)	0·47	14 (8%)	9 (5%)	0·21
Hypersensitivity	10 (6%)	9 (5%)	0·52	2 (1%)	2 (1%)	0·38

Data are n (%). SOX=S-1 plus oxaliplatin. ALP=alkaline phosphatase. ALT=alanine aminotransferase. AST=aspartate aminotransferase. CapeOX=capecitabine plus oxaliplatin.

TRICOLORE study

In the TRICOLORE, comparing IRIS-B vs mFOLFOX-B or CAPOX-B, study patients who received IRIS-B had significantly higher rates of grade ≥3 leukopenia, neutropenia, febrile neutropenia, thromboembolism, and diarrhoea but lower rates of grade ≥3 sensory neuropathy, HFS, and paralytic ileus than those who received FOLFOX6-B or CAPOX-B (Yamada et al., 2018).

According to the article published by Yamada et al. (2018), the incidence of all grades anaemia (50.6% vs 38%), hyperbilirubinemia (43.5% vs 33.1%), mucositis/stomatitis (53.6% vs 43%), vomiting (24.7% vs 15.3%), diarrhoea (62.3% vs 45%), alopecia (59.8% vs 12.4%) was higher in the experimental vs the control arm. In contrast, a lower incidence of thrombocytopenia (31% vs 62.4%), AST increase (33.5% vs 49.2%), HFS (51.7% vs 24.7%), and peripheral sensory neuropathy (19.7% vs 92.1%) was observed in the experimental arm vs the control arm.

The incidence of grade ≥3 leukopenia (8.8% vs 2.5%, respectively), neutropenia (24.3% vs 13.6%), febrile neutropenia (3.3% vs 0%), thromboembolism (3.8% vs 0.8%), and diarrhoea (13.4% vs 6.6%)

was significantly higher in the experimental group than in the control group. The incidences of grade ≥3 sensory neuropathy (0% vs 21.9%), hand–foot syndrome (0.8% vs 6.2%), and paralytic ileus (0% vs 2.9%) were significantly lower in patients receiving the experimental treatment than in those receiving the control treatment.

Table 26. Adverse events TRICOLORE study

	mFOLFOX6 or CapeOX plus bevacizumab (*n* = 242)				S-1 and irinotecan plus bevacizumab (*n* = 239)				*P* value[a]
	Any		≥Grade 3		Any		≥Grade 3		
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	
Patients with at least 1 AE	242	(100.0)	157	(64.9)	236	(98.7)	140	(58.6)	0.16
Laboratory findings									
Leukopenia	154	(63.6)	6	(2.5)	157	(65.7)	21	(8.8)	<0.01
Neutropenia	139	(57.4)	33	(13.6)	150	(62.8)	58	(24.3)	<0.01
Thrombocytopenia	151	(62.4)	4	(1.7)	74	(31.0)	2	(0.8)	0.69
Anemia	92	(38.0)	5	(2.1)	121	(50.6)	12	(5.0)	0.09
Bilirubin	80	(33.1)	6	(2.5)	104	(43.5)	8	(3.3)	0.60
AST	119	(49.2)	8	(3.3)	80	(33.5)	5	(2.1)	0.58
ALT	82	(33.9)	6	(2.5)	84	(35.1)	5	(2.1)	1.00
Creatinine	30	(12.4)	2	(0.8)	30	(12.6)	2	(0.8)	1.00
Proteinuria	107	(44.2)	7	(2.9)	103	(43.1)	6	(2.5)	1.00
Clinical findings									
Mucositis/stomatitis	104	(43.0)	4	(1.7)	128	(53.6)	7	(2.9)	0.38
Anorexia	149	(61.6)	16	(6.6)	143	(59.8)	16	(6.7)	1.00
Nausea	119	(49.2)	9	(3.7)	136	(56.9)	8	(3.3)	1.00
Vomiting	37	(15.3)	4	(1.7)	59	(24.7)	5	(2.1)	0.75
Diarrhea	109	(45.0)	16	(6.6)	149	(62.3)	32	(13.4)	0.02
Rash/desquamation	39	(16.1)	1	(0.4)	50	(20.9)	0	(0.0)	1.00
Hyperpigmentation	99	(40.9)	–	–	100	(41.8)	–	–	–
Hand–foot syndrome	125	(51.7)	15	(6.2)	59	(24.7)	2	(0.8)	<0.01
Fatigue	149	(61.6)	12	(5.0)	142	(59.4)	9	(3.8)	0.66
Peripheral sensory neuropathy	223	(92.1)	53	(21.9)	47	(19.7)	0	(0.0)	<0.01
Alopecia	30	(12.4)	–	–	143	(59.8)	–	–	–
Watery eye	2	(0.8)	0	(0.0)	18	(7.5)	3	(1.3)	0.12
Hypertension	86	(35.5)	29	(12.0)	76	(31.8)	20	(8.4)	0.23
Paralytic ileus	8	(3.3)	7	(2.9)	2	(0.8)	0	(0.0)	0.02
Febrile neutropenia	0	(0.0)	0	(0.0)	8	(3.3)	8	(3.3)	<0.01
Thromboembolism	5	(2.1)	2	(0.8)	10	(4.2)	9	(3.8)	0.04
Hemorrhage, nose	28	(11.6)	0	(0.0)	40	(16.7)	0	(0.0)	–
Gastrointestinal perforation	3	(1.2)	3	(1.2)	0	(0.0)	0	(0.0)	0.25

[a]Comparison of the frequency of adverse events of grade 3 or higher in the two groups.
AE, adverse events; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

According to the information presented in the article no cardiac events were observed in the study.

FIRIS study

In the FIRIS study, comparing IRIS vs FOLFIRI, patients who received IRIS had higher rates of grade 3 diarrhoea and lower rates of grade ≥3 neutropenia than patients in the FOLFIRI group (Muro et al., 2010).

According to the article published by Muro et al., higher rates of grade ≥ 3 diarrhoea (20.5% vs 4.7%), fatigue (8.6% vs 3.3%), anorexia (11% vs 5.2%) and febrile neutropenia (4.8% vs 0.8%) were reported in the IRIS group compared to the FOLFIRI arm. In contrast, more patients in the FOLFIRI group experienced grade ≥3 neutropenia than did those in the IRIS group (52·1% vs 36·2%, respectively;

p=0·0012). According to the authors, grade 3 HFS was not observed in the study. Cardiac events were also not reported in the article.

Table 27. Adverse events FIRIS study

	FOLFIRI (n=211)			IRIS (n=210)			p value (grade 3–4)
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	
Neutropenia	179 (84·8%)	76 (36·0%)	34 (16·1%)	139 (66·2%)	54 (25·7%)	22 (10·5%)	0·0012
Leucopenia	170 (80·6%)	32 (15·2%)	1 (0·5%)	154 (73·3%)	32 (15·2%)	6 (2·9%)	0·5178
Anaemia	115 (54·5%)	13 (6·2%)	1 (0·5%)	156 (74·3%)	19 (9·0%)	2 (1·0%)	0·2221
Thrombocytopenia	63 (29·9%)	1 (0·5%)	1 (0·5%)	74 (35·2%)	0 (0·0%)	0 (0·0%)	0·4988
Diarrhoea	125 (59·2%)	10 (4·7%)	0 (0·0%)	167 (79·5%)	43 (20·5%)	0 (0·0%)	<0·0001
Fatigue	144 (68·2%)	7 (3·3%)	0 (0·0%)	153 (72·9%)	18 (8·6%)	0 (0·0%)	0·0242
Febrile neutropenia	3 (1·4%)	2 (0·9%)	0 (0·0%)	10 (4·8%)	10 (4·8%)	0 (0·0%)	0·0205
Mucositis or stomatitis	92 (43·6%)	1 (0·5%)	0 (0·0%)	102 (48·6%)	6 (2·9%)	0 (0·0%)	0·0677
Anorexia	129 (61·1%)	11 (5·2%)	0 (0·0%)	141 (67·1%)	23 (11·0%)	0 (0·0%)	0·0329
Nausea	111 (52·6%)	9 (4·3%)	0 (0·0%)	99 (47·1%)	4 (1·9%)	0 (0·0%)	0·2593

Data are number (%).

Of note, in the article the authors state that IRIS therapy might be less feasible in non-Asian patients and recommend that the optimal dose of S-1 should be explored in this population.

NORDIC9 study

In the NORDIC9 trial, exploring full-dose S1 monotherapy versus reduced-dose SOX therapy, 62% of patients in the full-dose group experienced at least one grade 3-4 adverse event compared to 43% of those on the reduced-dose combination therapy (p=0.014) (Winther et al., 2019). Grade 3-4 diarrhoea was more frequent in the full-dose monotherapy group compared to the reduced-dose combination therapy group (p=0.018). No grade 3-4 HFS was observed. Two patients in the reduced-dose combination therapy group experienced grade 3-4 cardiotoxicity that led to discontinuation and one patient in the reduced-dose group had febrile neutropenia. Hospitalization was more common in the full-dose monotherapy group than in the reduced-dose combination therapy group (61% vs 39%, p=0.0052).

Table 28. Adverse events NORDIC study

	Full-dose monotherapy (n=82)				Reduced-dose combination therapy (n=75)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Haematological toxicity*								
Neutrophils	11/76 (14%)	3/76 (4%)	0	0	14/71 (20%)	2/71 (3%)	0	0
Anaemia	54/76 (69%)	0	0	0	44/71 (62%)	2/71 (3%)	0	0
Platelets	13/78 (17%)	0	0	0	20/71 (28%)	0	1/71 (1%)	0
Non-haematological toxicity								
Nausea	34 (41%)	3 (4%)	0	0	40 (53%)	2 (3%)	0	0
Diarrhoea	31 (38%)	11 (13%)	1 (1%)	0	30 (40%)	2 (3%)	0	0
Vomiting	20 (24%)	4 (5%)	0	0	11 (15%)	2 (3%)	0	0
Hand-foot syndrome	13 (16%)	0	0	0	15 (20%)	0	0	0
Sensory neuropathy	18 (22%)	0	0	0	48 (64%)	7 (9%)	0	0
Mucositis	7 (9%)	2 (2%)	1 (1%)	0	8 (11%)	0	0	0
Fatigue	50 (61%)	10 (12%)	0	0	57 (76%)	3 (4%)	0	0
Dehydration	0	4 (5%)	1 (1%)	0	0	0	0	0
Obstipation	9 (11%)	1 (1%)	0	0	7 (9%)	2 (3%)	0	0
Ileus	0	3 (4%)	1 (1%)	0	0	0	2 (3%)	0
Thromboembolic event†	4 (5%)	3 (4%)	0	0	2 (3%)	1 (1%)	0	0
Pain	25 (30%)	7 (8·5%)	0	0	17 (23%)	8 (11%)	0	0
Infection	11 (13%)	12 (15%)	1 (1%)	2 (2%)	6 (8%)	8 (11%)	0	0
Hyponatraemia	1 (1%)	4 (5%)	0	0	1 (1%)	0	0	0

Data are n (%). Table shows any grade 1–2 adverse events occurring in at least 10% of patients in either treatment group and all grade 3, 4, or 5 adverse events occurring in at least 3% of patients in either treatment group. *Data not available for all patients receiving treatment. †Deep vein thrombosis and portal vein thrombosis are defined as grade 2.

According to the article published by Winther et al., dose modifications were reported in 44% of patients in the full-dose monotherapy arm vs 40% in the reduced-dose combination group. The main reason for reduction was impaired renal function (17% in the full-dose S1 arm vs 30% in the reduced dose SOX arm), followed by gastrointestinal (17% in both arms) and haematological (19% vs 13%, respectively) toxicity. A higher percentage of patients in the S-1 monotherapy arm discontinued study treatment due to toxicity (18% vs 12%, respectively) or patient's decision (4% vs 1%).

Compared with the SOX arm, patients enrolled in the S-1 monotherapy arm reported a higher incidence of all grade diarrhoea (52% vs 43%, respectively), vomiting (29% vs 18%), dehydration (6% vs 0%), infection (31% vs 19%). In contrast, more patients in the SOX arm experienced all grade thrombocytopenia (29% vs 17%), nausea (56% vs 45%), and sensory neuropathy (73% vs 22%). All grade HFS was slightly higher in the SOX arm (20% vs 16%).

Grade 3-4 AEs were observed in 53% of patients enrolled in the study, with higher incidence in the S1 monotherapy arm (62%) compared with the SOX arm (43%).

No grade 3-4 HFS events were observed. Two patients in the SOX arm experienced grade 3-4 cardiotoxicity leading to treatment discontinuation; both patients had a history of cardiac ischaemia and arrhythmia.

Serious adverse event/deaths/other significant events

SALTO study

One patient in the S-1 group died due to bevacizumab-related bowel perforation and one patient in the capecitabine group died due to sepsis which was possibly related to treatment. Three patients in the S-

1 group and two patients in the capecitabine group were hospitalized due to treatment related adverse events, essentially related to diarrhea.

SOFT study

Seven treated-related deaths were observed: 3 in the mFOLFOX-B arm and 4 in the SOX-B arm.

SOX vs CAPOX study

No information over SAEs and deaths related to study treatment can be retrieved by the published article (Hong et al., 2012) presented by the MAH.

TRICOLORE study

There was 1 treatment-related death among patients given the CAPOX-B regimen and 4 treatment-related deaths among patients given the SIRI-B regimen. No further information was provided in the article.

FIRIS study

No treatment-related deaths were reported in the IRIS arm, whereas a treatment-related death from hypotension due to shock was reported in the FOLFIRI group within 28 days after end of treatment.

NORDIC9 study

Hospitalization was reported in 61% of patients enrolled in the S-1 monotherapy arm vs 39% of patients enrolled in the SOX arm (p= 0.0052). A total of 6 treatment-related deaths were reported during the study: 2 patients with sepsis enrolled in the S-1 monotherapy arm and one rectum perforation in the SOX arm, all during first line therapy; and one patient with sepsis and one with perforation of the colon in the S-1 monotherapy arm and one with suspicion of a thromboembolic event in the SOX arm, in the second-line setting.

Laboratory findings

No information over laboratory findings can be retrieved in the literature data presented by the MAH.

Safety in special populations

S-1 after adverse events (HFS or cardiac toxicity) after other fluoropyrimidines in European patients:

a) Case series of patients treated with S-1 after capecitabine-induced coronary artery vasospasm (Kwakman et al., 2017)

In this case series of 7 patients (2 mCRC) who experienced capecitabine-induced coronary artery vasospasm, all patients were able to switch to full dose S-1 without additional cardiac toxicity.

In the article published by Kwakman et al. (2017), a case series of 7 cancer patients (of which 2 with mCRC) switching to S-1 after capecitabine-induced coronary vasospasm is discussed. Patients were derived from 4 centres in the Netherlands and according to the authors patients were treated with different combinations. Four patients had a history of cardiovascular comorbidities, of which two patients used calcium channels blockers. All patients experienced intermittent chest pain and in 6 patients symptoms occurred within a week of the start of treatment. Re-challenge of capecitabine in combination with a calcium channel blocker was tried in one patient with no success, and switch from capecitabine to intravenous 5-FU was tried in another patient without success. S-1 was administered at different dosing regimens/with different combinations and the time interval between capecitabine discontinuation and S-

1 start varied from 1 week to 2 years. According to the authors a median of 4 cycles (range 2-15) of S-1 was administered, with none of the patients experiencing any signs or symptoms related to cardiac toxicity.

Table 29. Patient and treatment characteristics of patients treated with S-1 after capecitabine-induced coronary artery vasospasm

No	Sex	Age	Diagnosis	Cardiovascular comorbidities	Capecitabine treatment	Symptoms	Time of onset	Related to exercise	ECG	Troponin	Cardiac stress test	Coronary imaging	Time interval start S-1	S-1 treatment	S-1 dose[a]	Number of cycles	Recurrence
1	M	63	Metastatic colorectal cancer	None	Capecitabine, oxaliplatin, bevacizumab	Intermitting chest pain	Day 2, cycle 1	No	Normal	Normal	Negative	n.a.	1 week	S-1, oxaliplatin, bevacizumab	25	3, ongoing	No
2	F	62	Stage III colon cancer	None	Capecitabine, oxaliplatin	Intermitting chest pain	Day 5, cycle 1	No	Normal	Normal	Negative	n.a.	1 week	S-1, oxaliplatin	25	6	No
3	F	50	ACUP	Hypertension, diabetes type 2	Capecitabine	Intermitting chest pain	Day 3, cycle 1	No	Normal	Normal	n.a.	n.a.	3 weeks	S-1, oxaliplatin	25	2	No
4	M	53	Stage III gastric cancer	Hypertension, cranial artery dissection	Capecitabine, epirubicine, oxaliplatin	Intermitting chest pain	Day 3, cycle 1	No	Ischaemia	Elevated	n.a.	Normal	4 months	S-1, cisplatin, radiotherapy	20[b]	5	No
5	F	50	Stage II signet ring cell appendix carcinoma	None	Capecitabine, oxaliplatin	Intermitting chest pain	Day 4, cycle 1	No	Ischaemia	Normal	n.a.	Normal	3 weeks	S-1, oxaliplatin	25	4, ongoing	No
6	F	66	Metastatic breast cancer	Hypertension	Capecitabine	Intermitting chest pain	Day 3, cycle 1	No	Ischaemia	Normal	n.a.	Normal	2 years	S-1	30	3	No
7	M	56	Metastatic colorectal cancer	Hypertension, cardiac failure, angina pectoris, sickle cell trait	Capecitabine, oxaliplatin, bevacizumab	Intermitting chest pain	Day 2, cycle 3	Yes	Normal	Unknown	Positive	n.a.	2 months	S-1, oxaliplatin, bevacizumab	25	15	No

ACUP, adenocarcinoma of unknown primary; n.a., not applicable.
[a] mg/m^2, twice daily, days 1−14 every 3 weeks.
[b] mg/m^2, twice daily, days 1−7 every week.

b) Tolerability of S-1 after HFS – related discontinuation of capecitabine in western cancer patients (Kwakman et al., 2017).

In this retrospective study of the tolerability of S-1 treatment after HFS-related discontinuation was evaluated in 52 Dutch and Danish cancer patients treated with capecitabine-based regimens, 29 (56%) of whom had mCRC, Kwakman et al. reported that 49 (94%) patients had a lower grade of HFS upon switching to S-1 treatment. A total of 29 (56%) of these patients had complete resolution of HFS symptoms. Three patients (12%) experienced ongoing grade 2 or 3 HFS that led to discontinuation.

c) Continuation of fluoropyrimidine treatment with S-1 after cardiotoxicity on capecitabine- or 5-fluorouracil-based therapy in patients with solid tumours: a multi-centre retrospective observational cohort study (Österlund et al., submitted, 2021, manuscript draft).

This was a retrospective, cohort study conducted at 13 centres in Finland, Sweden, Norway, Denmark, The Netherlands, and Ireland. All identified patients with solid tumours with cardiotoxicity grade 1-4, who were switched to S-1-based therapy were included. Population-based data on S-1 treatment was available for Tampere, Turku, and Helsinki university hospitals, and all cases were reviewed and included if switch due to cardiotoxicity was the indication for S-1-based treatment. Further, patients with switch due to cardiotoxicity in the RAXO study (NCT01531621) were included. Additional cases were retrospectively identified and included from the other participating institutions. The total number of patients receiving fluoropyrimidines could not be extracted. The data cut-off was October 29, 2020, when the per protocol target of 200 patients was reached. Data collected at baseline included: patient characteristics, cardiovascular comorbidities, current medications, cardiac evaluations, cardiac treatment, cardiotoxicity on first treatment and recurrence on S-1-based therapy, previous and concurrent cancer therapies. Clinically meaningful non-cardiac adverse events included presence of haematologic toxicity grade 3 or 4, and non-haematologic toxicity grade 2, 3, and 4. The study was approved by each institution and/or local ethics committee at each institution, if required.

Outcomes/endpoints.

The primary endpoint was recurrence of fluoropyrimidine-related cardiac toxicity after switch to S-1-based treatment from any other fluoropyrimidine due to cardiotoxicity. Secondary endpoints were:

cardiac symptoms during fluoropyrimidine therapy; diagnostic work-up for cardiotoxicity in real-world practice; timelines for cardiotoxicity; dose intensity; and alteration in cardiac functional parameters during fluoropyrimidine treatment-induced cardiotoxicity. Cardiotoxicity was defined according to NCI CTCAE 4.0 criteria. Cardiotoxicity was graded by two experienced oncologists who sought consensus on assessment of each patient. The causal relationship between cardiotoxicity and fluoropyrimidine-based treatment was retrospectively determined by the investigator at each institution.

Statistical analysis.

The primary endpoint was recurrent cardiotoxicity during switch to S-1-based treatment. The cumulative incidence with its 95% confidence interval (CI) was calculated in a competing risks analysis, where first onset of recurrent cardiotoxicity during S-1 treatment was considered as an event of interest and stopping of S-1 without recurrent cardiotoxicity as a competing risk. Worst grade of cardiotoxicity is presented if multiple events were present. Continuous characteristics are presented as median with range and interquartile range (IQR).

Systematic missing information for Dutch patients (n=28) included ECOG PS, some comorbidities, and survival information. Demographic variables were screened for associations with the crude percentage of recurrent cardiotoxicity with Chi-square tests with Bonferroni correction for multiple comparisons (data not shown), and, if statistically significant differences were noted, odds ratios (OR) and 95% CIs were calculated using logistic regression. OS was estimated using the Kaplan-Meier method.

Results

S-1-based treatment started between November 1, 2011 and October 29, 2020. Data cut-off was May 10, 2021 when median follow-up was 33 months from S-1 initiation, and minimum 50 days. A total of 200 patients were included. The median age was 66 years (range 19-86) and 118 (59%) were male. Included patients had oesophageal, gastric, small bowel, colon, rectal, anal, biliary, pancreatic, or breast cancer, or cancer of unknown primary, and 43% had metastatic disease. A total of 156 (78%) had colorectal cancer, 53 (27%) mCRC, and 101 (51%) patients had no cardiovascular comorbidities at baseline (Table 30).

Table 30. Baseline patient characteristics

		Total		No recurrent cardiotoxicity		Recurrent cardiotoxicity	
		n=200	100%	n=192		n=8	
Age	Median (range)	66	(19-86)	66	(19-86)	64	(51-72)
	< 70 years	123	62%	117	61%	6	75%
	≥ 70 years	77	39%	75	39%	2	25%
Sex	Female	82	41%	79	41%	3	38%
	Male	118	59%	113	59%	5	63%
ECOG	PS 0	51	26%	47	25%	4	50%
	PS 1	105	53%	101	53%	4	50%
	PS 2	16	8%	16	8%	0	0%
	NA	28	14%	28	15%	0	0%
Cardiovascular comorbidity*	No	101	51%	97	51%	4	50%
	Yes	99	50%	95	50%	4	50%
Metabolic comorbidity*	NA	25	13%	25	13%	0	0%
	No	117	59%	112	58%	5	63%
	Yes	58	29%	55	29%	3	38%
Renal comorbidity*		28	14%	28	15%	0	0%
	No	165	83%	157	82%	8	100%
	Yes	7	4%	7	4%	0	0%
Chronic obstructive pulmonary disease*		26	13%	26	14%	0	0%
	No	168	84%	160	83%	8	100%
	Yes	6	3%	6	3%	0	0%
Other comorbidity*		28	14%	28	15%	0	0%
	No	102	51%	99	52%	3	38%
	Yes	70	35%	65	34%	5	63%
Primary tumour	Anal cancer	2	1%	2	1%	0	0%
	Biliary cancer	3	2%	2	1%	1	13%
	Breast cancer	3	2%	3	2%	0	0%
	Cancer of unknown primary	2	1%	2	1%	0	0%
	Colon cancer	103	52%	99	52%	4	50%
	Colon cancer MINEN	1	1%	1	1%	0	0%
	Oesophageal cancer	3	2%	3	2%	0	0%
	Gastric cancer	20	10%	20	10%	0	0%
	Pancreas cancer	5	3%	5	3%	0	0%
	Pancreas neuroendocrine	2	1%	2	1%	0	0%
	Rectal cancer	55	28%	52	27%	3	38%
	Small bowel cancer	1	1%	1	1%	0	0%
Localized disease	Stage I-III	114	57%	110	57%	4	50%
Metastatic disease	Stage IV	86	43%	82	43%	4	50%
Resection	Primary tumour	126	64%	119	63%	7	88%
	Metastases	14	7%	14	8%	0	0%
Radiotherapy	Chest wall or Breast	4	2%	4	2%	0	0%
	Abdomen or Pelvis	19	10%	18	9%	1	13%

* Comorbidities and regular medications are specified in (Appendix p 10)
ECOG PS = performance status

Initial cardiotoxicity was associated with capecitabine in 170 (85%) patients, continuous infusion 5-FU (any de Gramont schedule) in 23 (12%), and bolus 5-FU in 7 (4%) patients. Initial therapy was single agent fluoropyrimidine in 67 (34%) patients and the remaining patients received combination therapy. Biologic therapy was administered to 17% (Table 31).

Table 31. Treatment regimens before and after cardiotoxicity

		Fluoropyrimidine causing cardiotoxicity						Switch to S-1					
		Total		No recurrent cardiotoxicity		Recurrent cardiotoxicity		Total		No recurrent cardiotoxicity		Recurrent cardiotoxicity	
		n=200	100%	n=192	96%	n=8	4%	n=200	100%	n=192	96%	n=8	4%
Fluoropyrimidine	Capecitabine	170	85%	163	85%	7	88%						
	Continuous / de Gramont	22	12%	21	12%	1	13%						
	Bolus	8	4%	8	4%	0	0%						
	S-1							200	100%	192	96%	8	4%
Chemotherapy	Single fluoropyrimidine	62	31%	131	32%	1	13%	58	29%	55	29%	3	38%
	Docetaxel	6	3%	6	3%	0	0%	1	1%	1	1%	0	0%
	Epirubicin	5	3%	5	3%	0	0%	2	1%	2	1%	0	0%
	Oxaliplatin	107	54%	100	52%	7	88%	99	50%	94	49%	5	63%
	Cisplatin	2	1%	2	1%	0	0%	1	1%	1	1%	0	0%
	Carboplatin	0	0%	0	0%	0	0%	1	1%	1	1%	0	0%
	Irinotecan	6	3%	6	3%	0	0%	16	8%	16	8%	0	0%
	Gemcitabine	2	1%	2	1%	0	0%	1	1%	1	1%	0	0%
	Mitomycin C	1	1%	1	1%	0	0%	1	1%	1	1%	0	0%
	Temozolamide	2	1%	2	1%	0	0%	3	2%	3	2%	0	0%
Biologic combined	No	166	83%	161	84%	5	63%	157	79%	150	78%	7	88%
	Trastuzumab	1	1%	1	1%	0	0%	1	1%	1	1%	0	0%
	Bevacizumab	29	15%	26	14%	3	38%	40	20%	39	20%	1	13%
	Cetuximab	2	1%	2	1%	0	0%	1	1%	1	1%	0	0%
	Panitumumab	0	0%	0	0%	0	0%	1	1%	1	1%	0	0%
	Octreotide	1	1%	1	1%	0	0%	1	1%	1	1%	0	0%
Radiotherapy combined	Pelvic	13	7%	13	7%	0	0%	14	7%	14	7%	0	0%
Treatment intent	Adjuvant	92	46%	88	46%	4	50%	91	46%	87	45%	4	50%
	Neo-adjuvant	53	27%	51	27%	2	25%	35	18%	33	17%	2	25%
	First line	46	23%	44	23%	2	25%	54	27%	53	28%	1	13%
	Second line	7	4%	7	4%	0	0%	12	6%	11	6%	1	13%
	Third or Later line	2	1%	2	1%	0	0%	8	4%	8	4%	0	0%
Dose Intensity single	median mg/m2/day (range)	¥1636	(400*-3000¤)	¥1636	(400*-3000¤)	¥2500	(¥2500-¥2500)	50	(33-61)	50	(33-61)	53	(42-60)
	Dose of scheduled regimen	69	(40-120)	68	(40-120)	100	(100-100)	83%	(50-102%)	83%	(50-102%)	88%	(82-100%)
Dose intensity combined	median mg/m2/day (range)	¥1786	(350*-2600¤)	¥1775	(400*-3000¤)	¥2500	(¥2500-¥2500)	50	(30-60)	50	(30-60)	46	(40-50)
	Dose of scheduled regimen	97	(38-101)	96	(38-101)%	99	(69-100)	100%	(60-120%)	100%	(60-120%)	92%	(80-100%)

¥ Capecitabine, * Nordic bolus regimen, ¤ Infused de Gramont

A single initial cardiac event was diagnosed in 176 (88%) patients, while 24 (12%) patients experienced 2-3 simultaneous events. Cardiotoxicity events (228 events/200 patients) were chest pain in 125 patients (63%), acute coronary syndrome including myocardial infarction in 69 (35%), atrial fibrillation in 8 (4%) and other arrythmias in 12 (6%), heart failure/cardiomyopathy in 7 (4%), cardiac arrest in 4 (2%), prolonged QT-time in 2 (1%) patients, and hypertension in 1 (0.5%) patient (Table 32).

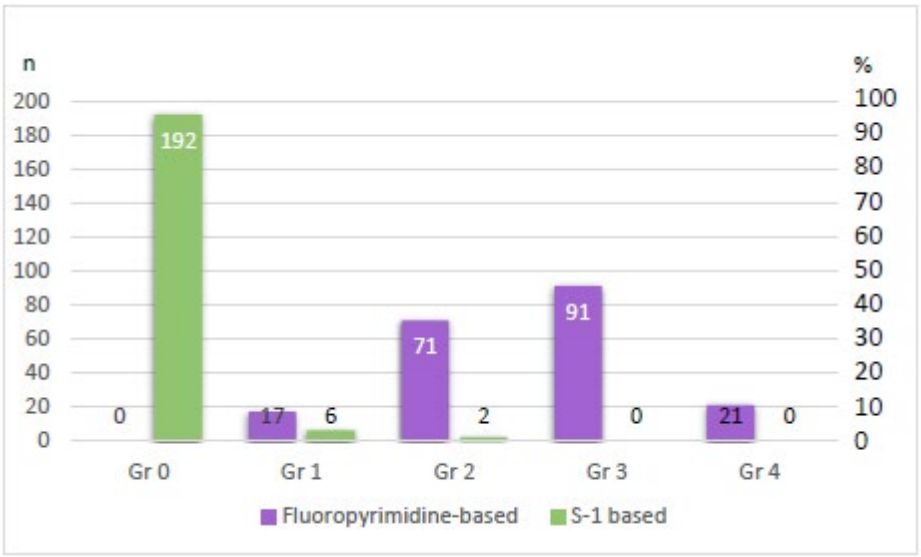
No difference in severity was noted for patients with ongoing cardiac medication including nitrates or calcium channel blockers, that were administered to 28 patients at baseline. Median time to onset of cardiotoxicity was 5 days (IQR 2-16) from initiation of fluoropyrimidine-containing regimen without any difference between fluoropyrimidines, and early in the treatment cycle (Figure 37).

Table 32. Cardiotoxicity during capecitabine or 5-fluorouracil or during switch to S-1 based therapy

		Fluoropyrimidine causing cardiotoxicity						Switch to S-1					
		Total		No recurrent cardiotoxicity		Recurrent cardiotoxicity		Total		No recurrent cardiotoxicity		Recurrent cardiotoxicity	
		n=200	100%	n=192	96%	n=8	4%	n=200	100%	n=192	96%	n=8	4%
Number of cycles to cardiotoxicity or total	1	153	77%	147	77%	6	75%	18	9%	15	8%	3	38%
	2	24	12%	23	12%	1	13%	16	8%	15	8%	1	13%
	3	8	4%	8	4%	0	0%	24	12%	23	12%	1	13%
	4+ *	15	8%	14	7%	1	13%	142	71%	139	72%	3	38%
Time to cardiotoxicity onset - regimen	Median (range) days	5	(0-466)	4.5	(0-209)	5.5	(1-466)	..	..	..	..	16	(6-195)
Time to cardiotoxicity onset - cycle	Median (range) days	3	(0-41)	3	(0-41)	4.5	(1-11)	..	..	..	..	7	(0-12)
Duration of therapy	Median (range) days	5	(0-466)	4.5	(0-209)	5.5	(1-466)	147	(6-966)	147	(21-966)	147	(6-357)
Number of cardiotoxicity events	1	176	88%	170	89%	6	75%	..	..	..	..	8	100%
	2	21	11%	20	10%	1	13%	..	..	..	..	0	0%
	3	3	2%	2	1%	1	13%	..	..	..	..	0	0%
Cardiotoxicity ǂ	Chest pain	125	63%	122	64%	3	38%	5	3%	..	..	5	63%
	Coronary artery syndrome / MI ¥	69	35%	65	34%	4	50%	..	..	..	..	..	..
	Atrial fibrillation	8	4%	8	4%	0	0%	..	..	..	..	..	..
	Cardiac arrest	4	2%	3	2%	1	13%	..	..	..	..	..	..
	Heart failure / Cardiomyopathy	7	4%	7	4%	0	0%	..	..	..	..	..	..
	Tachycardias	6	3%	3	2%	3	38%	3	2%	..	..	3	38%
	Arrythmia	4	2%	4	2%	0	0%	..	..	..	..	..	..
	Bradycardias	2	1%	2	1%	0	0%	..	..	..	..	..	..
	Prolonged QT	2	1%	2	1%	0	0%	..	..	..	..	..	..
	Hypertension	1	1%	1	1%	0	0%	..	..	..	..	..	..
Worst cardiotoxicity grade	1	17	9%	16	8%	1	13%	..	..	..	..	6	75%
	2	71	36%	68	35%	3	38%	..	..	..	..	2	25%
	3	91	46%	88	46%	3	38%	..	..	..	..	0	0%
	4	21	11%	20	10%	1	13%	..	..	..	..	0	0%
Action with chemotherapy	None	..	..	..	..	..	..	2	1%	..	..	2	25%
	Dose delayed	..	..	..	..	..	..	1	1%	..	..	1	13%
	Temporarily discontinued	8	4%	8	4%	0	0%	2	1%	..	..	2	25%
	Permanently discontinued	192	96%	184	96%	8	100%	3	2%	..	..	3	38%
Recovery from cardiac event	With sequelae	5	3%	4	2%	1	13%	..	..	..	..	0	0%
	Without sequelae	195	98%	188	98%	7	88%	..	..	..	..	8	100%
Time to recovery	Median (range) days	2	(0-274)	2	(0-274)	2	(0-8)	..	..	..	..	1	(0-6)
Time from cardiotoxicity to switch	Median (range) days	..	..	..	..	..	..	23	(1-3984)	22	(1-3984)	36	(15-870)
Causality	Not related	0	0%	0	0%	0	0%	..	..	..	..	3	38%
	Possibly related	33	17%	32	17%	1	13%	..	..	..	..	3	38%
	Probably related	117	59%	112	58%	5	63%	..	..	..	..	2	25%
	Related	50	25%	48	25%	2	25%	..	..	..	..	..	..

* 4-14 for cardiotoxicity and 4-46 in total
¥ ACS / MI = acute coronary syndrome / myocardial infarction
ǂ number of episodes of cardiotoxicity graded according to NCI CTC AE
† Arrythmia NAS was not further specified.

Figure 37. Severity of cardiotoxicity during 5-FU- or capecitabine-based initial treatment (purple) and during S-1- based treatment after cardiotoxicity on 5-FU or capecitabine-based treatment (green)



There were only slight differences in time to onset between the cardiac events, evaluated according to worst event present if the patient experienced multiple events. Cardiac arrest was the earliest event at a median of 2 days (95% CI not evaluable) from treatment initiation. Chest pain, both with or without ischemia, appeared on day 4 (95% CI 3-5), heart failure/cardiomyopathy on day 5 (0-31), atrial fibrillation on day 18 (4-32), and other arrythmias on day 41 (0-118) from treatment initiation. Cardiotoxicity appeared for the first time in cycle 1 in 153 (77%) patients, in cycle 2 in 24 (12%), and later (cycles 3-14) in 23 (12%). The causal relationship between cardiotoxicity and fluoropyrimidine treatment was determined by the investigator and categorized as related in 50 (25%), probably related in 117 (59%), and possibly related in 33 (17%). Median time to recovery from a cardiac event was 2 (IQR 0-4) days, with full recovery in 98% of cases.

Re-challenge with prophylactic medication (calcium-channel blocker and/or nitrates) was performed in 18 patients before the switch to S-1, and was successful in 0/4 (0%) with capecitabine, in 1/9 (11%) with infused 5-FU, and in 4/5 (80%) with bolus 5-FU. Capecitabine or 5-FU was permanently discontinued in 192 (96%) patients experiencing cardiotoxicity and temporarily discontinued in 8 (4%) patients, with re-challenge with prophylaxis in 3 patients before permanent discontinuation and reintroduction in subsequent lines in 5 patients.

Non-haematologic toxicity grade 2-4 was observed in 15% and haematologic toxicity grade 3-4 in 1% during initial fluoropyrimidine treatment, with a short median treatment duration of 5 days (IQR 2–16; range 0-466). DPD status was unknown in 162 patients and was not considered relevant to be tested in 38 patients with grade 2-4 non-cardiac toxicities.

Table 33. Adverse events during treatment with the fluoropyrimidine causing cardiotoxicity and during Teysuno-based therapy

		Fluoropyrimidine causing cardiotoxicity						Switch to Teysuno-based therapy					
		Total		No recurrent cardiotoxicity		Recurrent cardiotoxicity		Total		No recurrent cardiotoxicity		Recurrent cardiotoxicity	
		200	100%	192	96%	8	4%	200	100%	192	96%	8	4%
Non-haematological, grade 2–4													
	Peripheral neuropathy	10	5%	10	5%	0	0%	16	8%	15	8%	1	13%
	Nausea	5	3%	4	2%	1	13%	5	3%	4	2%	1	13%
	Diarrhoea	4	2%	4	2%	0	0%	6	3%	5	3%	1	13%
	Hand-foot syndrome	3	2%	3	2%	0	0%	1	1%	1	1%	0	0%
	Infection	2	1%	2	1%	0	0%	3	2%	3	2%	0	0%
	Stomatitis	1	1%	1	1%	0	0%	0	0%	0	0%	0	0%
	Laryngospasm	1	1%	1	1%	0	0%	0	0%	0	0%	0	0%
	Dyspnoea	1	1%	1	1%	0	0%	0	0%	0	0%	0	0%
	Hypertension	1	1%	1	1%	0	0%	0	0%	0	0%	0	0%
	Thromboembolism	1	1%	1	1%	0	0%	3	2%	3	2%	0	0%
	Epistaxis	1	1%	1	1%	0	0%	0	0%	0	0%	0	0%
	Blood bilirubin increased	0	0%	0	0%	0	0%	1	1%	1	1%	0	0%
	Acute kidney injury	0	0%	0	0%	0	0%	1	1%	1	1%	0	0%
	Abdominal pain	0	0%	0	0%	0	0%	1	1%	1	1%	0	0%
	Trigeminal nerve disorder	0	0%	0	0%	0	0%	1	1%	1	1%	0	0%
	Any	30	15%	29	15%	1	13%	43	22%	40	21%	3	38%
Haematological, grade 3–4													
	Neutropenia	1	1%	1	1%	0	0%	11	6%	10	5%	1	13%
	Leucopenia	0	0%	0	0%	0	0%	1	1%	1	1%	0	0%
	Any	1	1%	1	1%	0	0%	12	6%	11	6%	1	13%

Switch to S-1-based therapy. Of the 200 patients who were switched to S-1 therapy, 58 (29%) received S-1 as single agent therapy, all of whom initially had single-agent fluoropyrimidine. Combination chemotherapy was administered with the same cytotoxic drug as used initially in 121 (61%) patients

and/or with a biologic in 43 (22%), i.e. three more patients had combination chemotherapy and nine more patients had a biologic agent compared with the cardiotoxicity-causing regimen.

The median time from first signs of cardiotoxicity to the switch was 23 days. Of patients who were switched to S-1-based regimens after developing cardiotoxicity on another fluoropyrimidine, 50% (99/200) of patients also received oxaliplatin (5% of these had recurrent cardiotoxicity) and 8% (16/200) received irinotecan, none of whom had recurrent cardiotoxicity. In colorectal cancer patients (n=141, 53 mCRC) S-1 was administered at a dose of 25 mg/m2 (b.i.d. d1-14 with 7 days rest) in combination with oxaliplatin (130 mg/m2 d1) to 77 CRC patients with a dose intensity of 100% for S-1. Combination therapy with irinotecan was administered to 17 CRC patients, 12 of whom received S-1 at a dose of 25 mg/m2 (b.i.d. d1-14 with 7 days rest) with irinotecan (180 mg/m2 day 1) on a 3-week schedule and 5 of whom were frail and, concordant with Finnish practice, received a lower dose of irinotecan on day 1 and 15, plus 20 mg/m2 b.i.d. S-1 on a 4-week schedule.

One-hundred-ninety-two (96%) patients were able to switch to S-1-based treatment without recurrent toxicity. Recurrent cardiotoxicity was observed in 8 (4%) patients (with competing risk 95% CI 2·03–7·89) and included chest pain in 5 patients and tachycardia in 3 patients. Cardiotoxicity appeared after a median of 16 days (IQR 7-67) from therapy initiation. The tachycardia episodes appeared earlier than chest pain.

Of the 8 patients who experienced recurrent cardiotoxicity, 3 were on S-1 monotherapy, 5 on combination therapy with oxaliplatin, and one of these also received bevacizumab. Cardiac therapy including nitrates or calcium channel blockers had already been administered to 28 patients before and continued after the fluoropyrimidine switch. These drugs were given to an additional 47 patients during the cardiac event on the initial fluoropyrimidine, but their subsequent drug use after switch was not reliably recorded. Of this group of 75 patients known to have used either of these drugs and switched to S-1, 5 patients had recurrent cardiotoxicity whereas 70 did not (p= 0.136).

The patients with recurrent cardiotoxicity had a median age of 64 years (range 51-72), 5 were male, and 5 had cardiovascular comorbidities at baseline. There were no differences in terms of age, gender, ECOG status, baseline comorbidities, type of S-1-based therapy (including biologics), relative dose intensity, or severity of previous cardiotoxicity on the initial fluoropyrimidine between the 8 patients with recurrent cardiotoxicity compared to those without; only ischemic heart disease (OR 6·18; 95% CI 1·36–28·11) was more common in patients with recurrent cardiotoxicity. Recurrent cardiotoxicity was grade 1 in six patients and grade 2 in two patients.

Regarding the 8 patients with recurrent cardiotoxicity, 5 patients experienced chest pain (4 of these had previous cardiac comorbidities), and 3 had tachycardia, one of which was "cured" with appropriate treatment for panic attacks. All recovered without sequelae within a median of 1 (IQR 0-3) day. The causal relationship between S1-based treatment and cardiotoxicity was considered probably related in 2 patients, possibly related in 3, and not related in 3. Recurrent cardiotoxicity was grade 1 in 6 patients and grade 2 in 2 patients. All recovered without sequelae within a median of 1 day.

In patients with no recurrent cardiotoxicity (n=192, 96%), median duration of S-1-based treatment was 147 days, for both localised and metastatic disease, during which 139 (72%) patients received four or more cycles.

Median duration of S-1-based therapy was also 147 days in the patients with recurrent cardiotoxicity. S-1 was permanently discontinued due to cardiotoxicity in 3 patients, all receiving adjuvant therapy, 5 patients continued treatment with dose reduction in 1 patient, temporary interruption in 2 patients, and no action in 2 patients, for 147, 147+, 217+, 336+, and 357 days, respectively.

The successful completion rate with S-1-based treatment was 99% (197 patients). Treatment was discontinued due to completed adjuvant therapy in 88 patients, completed neoadjuvant therapy in 35 (including 14 with chemoradiation), or progressive disease in 74 with palliative therapy, and was stopped due to cardiotoxicity in only the 3 patients described above. Forty-one patients continued S-1-based treatment at progression by intensification of the regimen, mostly by adding irinotecan. Non-cardiac adverse events during S-1 treatment included grade 3-4 haematologic toxicity in 6%. Grade 2-4 non-haematologic adverse events occurred in 22%, including neuropathy, nausea, diarrhoea, infection, and hand-foot syndrome.

d) Dutch Prospective Colorectal Cancer Cohort (PLCRC)

The MAH has presented a retrospective analysis of safety data from mCRC patients in the Dutch Prospective Colorectal Cancer Cohort (PLCRC) who were switched to S-1 after development of intolerance (related to HFS or cardiotoxicity) while on capecitabine treatment (n=47) (Punt et al., 2021, in preparation). Data were retrospectively collected from patients participating to the Dutch Prospective Colorectal Cancer Cohort (PLCRC) (Burbach et al., 2016). PLCRC was initiated in 2015, with currently 59/80 Dutch hospitals participating and more than 10,000 patients being included (www.plcrc.nl) with all CRC stages (I-IV). Patients included in two previous retrospective studies on a treatment switch from capecitabine to S-1 (Kwakman et al., 2017b; Kwakman et al., 2017d) were excluded from the analysis. Data were recorded from the start of treatment with capecitabine until the end of treatment with S-1.

Adverse events occurring during treatment with capecitabine or S-1 were recorded according to the maximal grade using CTCAE (version 5) criteria.

A total of 53 patients were identified who were exposed to treatment with S-1. Four patients were excluded since capecitabine was administered in the adjuvant setting, and two patients were excluded because their previous treatment did not contain capecitabine but continuous infusion of 5-fluorouracil. Therefore 47 patients were eligible for further analysis. Patients were treated in 13 different Dutch hospitals. There were 25 males and 22 females, and at the time of switch to S-1 median age was 62 years (range 40-84), The starting dose of capecitabine was either 1250 mg/m2 or 1000 mg/m2 when given as monotherapy, and 1000 mg/m2 when given in combination with oxaliplatin. In 4 patients, a lower starting dose of capecitabine was applied due to partial DPD deficiency. Median duration of capecitabine treatment was 81 days (range 4-454). In 17 patients (41%) a dose reduction of capecitabine was applied prior to switch to S-1. Reasons for capecitabine dose reduction included HFS (12 pts), diarrhea (2 pts), HFS + diarrhea (1 pts), HFS + mucositis (1 pts) and HFS + nausea + diarrhea (1 pts). Reasons for switch to S-1 was HFS in 36 patients (77%), cardiac toxicity in 10 patients (21%) and a combination of dyspepsia, nausea, anorexia and dyspnea in one patient (2%). This latter patient

had experienced the same combination of symptoms during previous adjuvant treatment with capecitabine (Table 34).

Table 34. Treatment preceding switch to S-1

n	47 (100%)
Treatment line	
1st line	45 (96%)
2nd line	1 (2%)
3rd line	1 (2%)
capecitabine treatment initiated as	
capecitabine monotherapy	2 (4%)
capecitabine + bevacizumab	20 (43%)
capecitabine + oxaliplatin	2 (4%)
capecitabine + oxaliplatin + bevacizumab	23 (49%)
Starting dose of capecitabine	
<=850 mg/m^2 bid	4 (10%)
1000 mg/m^2 bid	33 (79%)
1250 mg/m^2 bid	5 (12%)
Dose reduction of capecitabine	
No	28 (60%)
Yes	19 (40%)
Reason to switch to S-1	
Cardiac toxicity	10 (21%)
Handfoot syndrome	36 (77%)
Other	1 (2%)

The starting dose of S-1 was either 30 mg/m2 when given as monotherapy, and 25 mg/m2 when given in combination with oxaliplatin. In 4 patients, a lower starting dose of S-1 was applied due to partial DPD

deficiency. In 6 patients, S-1 was started as monotherapy at 25 mg/m2 due to ongoing capecitabine-induced CTC grade 2 HFS. Median number of S-1 cycles was 6 (range 1-36). Median time between last dose of capecitabine and first dose of S-1 was 11 days (range 1-49). Reason for discontinuation of S-1 was progression of disease in 24 patients (51%), toxicity in 6 patients (13%), and other reasons in 11 patients (23%). Other reasons were a wait-and-see strategy in 9 patients, patient request in one patient (patient wished to continue with alternative medicine and was subsequently lost to follow-up), and head trauma upon which the clinical condition did not allow to resume treatment in one patient. In 6 patients (13%) S-1 treatment was still ongoing at the time of analysis. S-1 treatment discontinuation was due to mucositis grade 2, fever grade 2 and ongoing fatigue grade 1 (1 pt) terminal ileitis grade 2, proteinuria grade 3, hypertension grade 2 and deterioration of pre-existing renal insufficiency (1 pt), nausea grade 2 and abdominal cramps grade 1 (1 pt), nausea grade 2 and fatigue grade 2 (1 pt), diarrhea grade 2 and fatigue grade 2 (1 pt), and interstitial pneumonitis grade 2 (1 pt). Reported events of proteinuria, hypertension and renal impairment, which however were all considered related to bevacizumab by the local investigator, and interstitial pneumonitis which is discussed below in further detail. All toxicities were reversible.

Dose reductions of S-1 were applied in 7 patients (15%). Reasons for dose reductions were ongoing HFS grade 2 (1 pt), ongoing oxaliplatin-induced peripheral neurotoxicity (1 pt), thrombocytopenia grade 1 (1 pt), mucositis grade 2 (2 pts), mucositis grade 2 and fever grade 2 and ongoing fatigue grade 1 (1 pt), and diarrhea grade 1 and abdominal cramps grade 1 (1 pt).

Toxicities that occurred during treatment with S-1 which were not observed during prior treatment with capecitabine were documented in 26 patients (55%), and were fever grade 3 and ileus grade 2, considered related to progression of primary tumour (one patient), pulmonary embolism grade 3 with accompanying chest pain grade 2 (1 pt), pulmonary embolism grade 3 (1 pt), mucositis grade 2 (2 pt), mucositis grade 2 and fever grade 2 (1 pt), terminal ileitis grade 2, vomiting grade 1 and fatigue grade 1 in combination with bevacizumab-related proteinuria, hypertension and impaired renal function (see above) (1 pt), nausea grade 2 and fatigue grade 2 (1 pt), diarrhea grade 2 (1 pt), diarrhea grade 1, mucositis grade 2 and fatigue grade 1 (1 pt), diarrhea grade 2 and fatigue grade 2 (1 pt), thrombocytopenia grade 2 and mucositis grade 1 (1 pt), diarrhea grade 1, mucositis grade 1, fever grade 2, and terminal ileitis grade 1 (1 pt), mucositis grade 1 (1 pt), mucositis grade 1, anorexia grade 1 and HFS grade 1 (1 pt), thrombocytopenia grade 1 (1 pt), neutropenia grade 1 (1 pt), abdominal cramps grade 1 (1 pt), diarrhea grade 1 and abdominal cramps grade 1 (2 pt), diarrhea grade 1 (2 pt), pain grade 2 considered related to vertebral osteoporotic fracture (1), abdominal cramps grade 1 (1 pt), anorexia grade 1 (1 pt), and fever grade 1 (1 pt).

According to the results provided, in all patients experiencing *HFS* during treatment with capecitabine, the severity of this AE decreased or completely resolved during treatment with S-1. Several patients continued to experience the same grade of HFS during the first treatment cycle of S-1, possibly due to lack of delay between stop of capecitabine and start of S-1. One patient developed grade 1 HFS during treatment with S-1.

No case of recurrence of *cardiac toxicity* was reported in any of the 10 patients who switched to S-1 due to cardiac adverse events.

Two patients (4%) experienced terminal ileitis during S-1 treatment, considered probably related to S-1 in at least one of the two patients. One patient (2%) experienced interstitial pneumonitis that fully recovered after discontinuation of S-1. This patient had experienced the same symptoms and radiological abnormalities during a capecitabine-based treatment administered one year previously.

Two patients developed pulmonary embolism.

Extrapolation of Asian patient data to Western patients

There are known differences in the safety profile of fluoropyrimidines, particularly with respect to GI toxicity, in different regions of the world (Haller et al., 2008; Shirao et al., 2004). The reasons for regional differences in toxicity caused by fluoropyrimidines are not completely understood. In terms of safety, two published meta-analyses have been presented by the MAH in support of extrapolation of efficacy between Asian and Western patients. (Ter Veer et al., 2016; Ter Veer et al., 2017). Regarding safety, toxicity profiles capecitabine, 5FU and S-1 were different between Asian and Western patients. Western patients had lower rates of catheter-related complications, grade 3-4 mucositis and stomatitis, febrile neutropenia, and toxicity-related deaths and higher rates of grade 1-2 hand-foot syndrome with S-1 compared to 5-FU regimens while Asian patients had more grade 1-2 abdominal pain and grade 3-4 fatigue but less grade 1-2 nausea, neutropenia, and weight loss with S-1 compared to 5-FU regimens.

Safety related to drug-drug interactions and other interactions

No new information has been provided on this issue.

Discontinuation due to adverse events

SALTO study

Seven patients, all treated with capecitabine, discontinued treatment due to HFS (10% vs 0%, p=0.013).

SOFT study

Treatment was postponed, discontinued, or skipped, or the dose was reduced or escalated in 51% (1660 out of 3284) cycles in the mFOLFOX6-B arm (calculated up to 24 cycles) and in 56% (1215 out of 2183) cycles in the SOX-B arm. The fluorouracil dose was reduced at least once in 59% (146/249) of patients in the mFOLFOX6-B arm compared with 53% (133/250) in the S-1 arm. The rate of discontinuation due to AEs and/or patient refusal was similar in both arms (51%).

SOX vs CAPOX study

No information over rate of discontinuation due to AEs can be retrieved in the published article (Hong et al., 2012).

TRICOLORE study

No information over rate of discontinuation due to AEs can be retrieved in the published article (Yamada et al., 2018).

FIRIS study

No information over rate of discontinuation due to AEs can be retrieved in the published article (Muro et al., 2010).

Post marketing experience

No information over post-marketing experience has been submitted by the MAH.

2.5.1. Discussion on clinical safety

The safety database provided in support of the new indication sought by the MAH for S-1 consists essentially of a bibliographic review of articles and case reports. Information in several of the

articles/case reports/posters is limited, challenging any critical assessment of the S1 related toxicity in the intended setting.

A medical need is recognized for the population covered by the modified wording of indication proposed by the MAH, i.e. patients experiencing intolerable HFS and cardiac toxicity during treatment with another fluoropyrimidine. UFT has been approved in mCRC as an alternative fluoropyrimidine with reported lower incidence of HFS but it is not available in all EU Countries. Reiterating evidence is available in the literature indicating lower incidence of HFS and cardiac toxicity associated with S-1 in comparison with capecitabine/5FU in Asian and Caucasian patients. Differences in production of specific cardiotoxic and dermatotoxic metabolites have been advocated in the literature as basis of the observed diversity in toxicity profile of the various fluoropyrimidine compounds. The safety results of the SALTO study are considered relevant on this regard, as a prospective head to head comparison between S-1 and capecitabine was performed in an European mCRC patient population. Evaluation of HFS was the primary study endpoint. In the SALTO study treatment with S-1 was associated with a lower incidence of HFS (45% vs 73%, respectively; grade 3: 4% vs 21%, respectively), but higher incidence of diarrhoea (69% vs 48%; grade $\geqslant$3: 16% vs 12%), anorexia (41% vs 29%; grade $\geqslant$3: 13% vs 3%), vomiting (30% vs 19%), fatigue (79% vs 74%), hypertension (43% vs 35%) and proteinuria (20% vs 9%). The substantial S-1 treatment related toxicity in Western patients is further underscored by the safety results of the NORDIC9 study, in particular related to the full-dose S-1 monotherapy arm. The studies performed in Asian mCRC patients comparing combination therapies containing S-1 vs other fluoropyrimidines (i.e., capecitabine, 5FU) (i.e., CAPOX vs SOX, SOFT, TRICOLORE, FIRIS) support a lower incidence of HFS and sometimes of sensory neuropathy associated with S-1 treatment. However, they also frequently report higher incidence of diarrhoea, anorexia and haematological toxicity with S-1 compared with other fluoropyrimidines. Moreover, extrapolation of safety from Asian to Caucasian is hampered by the well-known differences identified in S-1 pharmacodynamics and toxicity between Asians and Caucasians. Reiterating warnings for caution on this issue are reported in the studies published in the literature and the safety results of the two published meta-analyses presented by the MAH further underscore this uncertainty. The uncertainty is reflected also by the different doses of S-1 as monotherapy or in combination regimens implemented in Phase 1-3 studies performed to date in Caucasians compared with Asian population. Therefore, from a safety point of view, extrapolation of results and S-1 dose recommendations from Asians to Caucasians merely on the basis of theoretical argumentations is not considered acceptable.

Regarding the proposed switch from another fluoropyrimidine to S-1 in case of development of intolerable HFS, the retrospective study published by Kwakman et al (Acta Oncologica 2017) including 141 western cancer patients supports this strategy. Indeed, according to the results presented in the article, switching from capecitabine to S-1 was able to reduce HFS severity in 94% of patients, with complete resolution of HFS-related symptoms in 56% of patients. Treatment with S-1 in these patients was reasonably well-tolerated, as indicated by the median number of cycles received by the patients (5, range 1-13) and the percentage of treatment discontinuations (7.6%), dose reductions (21%) and delays (15%) due to S-1 related AEs. The retrospective nature of the data remains of concern as well as the relatively low number of patients included in the study. Additional supportive evidence is represented by the analysis of a subgroup of patients enrolled in the Dutch Prospective Colorectal Cancer Cohort (PLCRC) presented by the MAH in the response document to the CHMP's RSI.

Regarding the proposed switch from another fluoropyrimidine to S-1 in case of development of cardiac toxicity, the results of the Cardioswitch study presented by the MAH support the feasibility and effectiveness of this strategy. Importantly, the study was performed in a Caucasian population and dose regimens of S-1 applied as monotherapy or in combination regimens appear in line with the ones suggested for the proposed posology. According to the presented results, after switch to S-1, 96% (n=192) of patients were able to continue treatment without recurrent cardiac events. Recurrent

cardiotoxicity was observed in 8 (4%) patients (competing risk 95 CI 0.02-7.89), with cardiac events at recurrence being limited to grade 1-2 severity, allowing continuation of S-1 based treatment in all but three patients. The success rate reported in this study is substantially higher than what is expected on the basis of alternative strategies applied in clinical practice reported in the literature, such as rechallenge with concomitant cardiac medication, dose reduction or switch to a different dosing regimen/formulation (e.g., from capecitabine or infusional 5-FU to bolus 5-FU). Treatment with S-1 appears to be reasonably tolerated, as also suggested by the number of treatment cycles received by patients and the high percentage of patients achieving the number of cycles planned at the beginning of treatment. However, it is emphasized that no accurate assessment can be made over the non-cardiac safety profile of S-1 in these patients, as according to the provided study protocol only cardiac adverse events were systematically collected. This represents a limitation of the submitted database, together with the retrospective nature of the analyses presented. Another relevant limitation is the heterogeneity of the population enrolled in the dataset in terms of primary tumour type, as all tumour types were allowed in the study, with CRC representing 78% of the enrolled population (n=156). Further support to the proposed strategy is provided by another case series (published by Kwakman) of 7 cancer patients (of which 2 with mCRC) switching to S-1 (administered at different dose regimens) after capecitabine-induced coronary vasospasm, with none of the patients experiencing any signs or symptoms related to recurrent cardiac toxicity (Kwakman et al., EJC 2017).

Overall, S-1 related toxicity reported in the studies presented by the MAH in support of the new indication appears in line with the known safety profile of the drug. Two events of terminal ileitis, one of which probably related to S1, have been reported, and the specific term is added as an ADR to the SmPC.

2.5.2. Conclusions on clinical safety

Despite the identified limitations of the database presented, the overall body of evidence regarding safety is considered sufficient to support the feasibility and effectiveness of the proposed switch from another fluoropyrimidine to S-1 in patients with mCRC developing intolerable HFS or cardiac toxicity.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 10.2 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 10.2 with the following content:

Safety concerns

Table 35 - Summary of safety concerns

Summary of safety concerns	
Important identified risks	None

Important potential risks	None
Important missing information	None

No new safety concerns related to the new proposed indication were identified.

Pharmacovigilance plan

Routine pharmacovigilance remains sufficient to monitor this medicinal product.

Risk minimisation measures

As there are no safety concerns identified for this medicinal product, no risk minimisation measures are proposed.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.3, 4.4, 4.8 and 5.1 of the SmPC have been updated. Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Teysuno is indicated in adults as monotherapy or in combination with oxaliplatin or irinotecan, with or without bevacizumab, for the treatment of patients with metastatic colorectal cancer for whom it is not possible to continue treatment with another fluoropyrimidine due to hand-foot syndrome or cardiovascular toxicity that developed in the adjuvant or metastatic setting.

3.1.2. Available therapies and unmet medical need

Generally, in the metastatic setting of CRC the typical first-line chemotherapy contains a fluoropyrimidine (intravenous fluorouracil (i.v. 5-FU) or oral capecitabine) used in various combinations and schedules with irinotecan or oxaliplatin. Biologicals (i.e., anti-VEGF and anti-EGFR) are also indicated for combination in the first-line treatment, unless use is contraindicated. Second-line treatment depends on the type of prior therapy administered. According to ESMO guidelines, patients should receive all three available cytotoxic agents (fluoropyrimidine, oxaliplatin and irinotecan) and all targeted treatments (anti-

VEGF and, if *RAS* wild-type, anti-EGFR) during the course of the treatment whenever possible, although the optimal sequence is not known. For third-line therapy, cetuximab or panitumumab monotherapy can be considered in *RAS* wild-type and *BRAF* wild-type patients not previously treated with anti-EGFR antibodies. Alternative options are regorafenib and trifluridine/tipiracil (van Cutsem et al., *Annals of Oncology*, 2016). For specific biomarker-defined subgroups the combination of encorafenib and cetuximab (tumours with BRAF V600E mutation) or NTRK-inhibitors (larotrectinib and entrectinib for NTRK gene fusion positive tumours) are approved. Checkpoint inhibitor pembrolizumab is approved to treat MSI-H tumours.
Despite all new developments, chemotherapy remains the backbone of first-line systemic treatment with fluoropyrimidine as basis. As an alternative to i.v. 5-FU, the oral fluoropyrimidine capecitabine has been developed. Capecitabine has been shown to be non-inferior compared to i.v. 5-FU regarding efficacy. The safety profile is different for oral capecitabine versus the i.v. alternatives, with for example higher frequencies of hand-foot syndrome (HFS) and cardiotoxicity with capecitabine. There is therefore still a need for the development of alternatives of intravenous 5-FU or capecitabine, especially in patients who have to discontinue treatment due to cardiotoxicity or HFS.

3.1.3. Main clinical studies

To support the indication, the MAH summarised study results described in literature and performed a meta-analysis (**Derksen et al., 2021, in preparation**).

As **pivotal** evidence for the target population, retrospective and exploratory data in the EU target population of patients who switched to S-1 after toxicity on another fluoropyrimidine were provided. The first results are from the retrospective CardioSwitch study that included 53 mCRC European patients who were switched to S-1-based therapy after development of cardiotoxicity on another fluoropyrimidine . In addition, data is reported from a retrospective analysis of data from a prospectively collected Dutch database (PLCRC Switch Cohort Study) that evaluated long-term safety in 47 mCRC patients who were switched to S-1 regimens after development of either cardiotoxicity or HFS on capecitabine .

As **supportive** evidence, data from patients who started first- or second-line treatment at baseline were described. Using a systemic literature search for prospective phase II or III randomised clinical trials comparing S-1 based versus 5-FU or capecitabine-based palliative therapy in adult patients with mCRC, 10 studies were identified to be used in the meta-analysis. The included studies investigated first or second line therapy of S-1 monotherapy or in combination with irinotecan or oxaliplatin (with or without bevacizumab). In total 1062 patients were treatment with S-1 based therapies and 1055 with 5-FU or capecitabine-based therapies. PFS was the primary outcome for the meta-analysis with OS and ORR as secondary outcomes. HR for PFS and OS were reported in 6 studies. Non-inferiority for S-1 based therapy compared to 5-FU or capecitabine-based therapy was concluded when the upper limit of the 99% CI of the pooled HR was lower than 1.25.

Next to the meta-analysis, supportive efficacy and safety results were provided by the following phase 3, randomised studies in mCRC patients investigating S-1 versus another fluoropyrimidine, which were also included in the meta-analysis:

- S-1 monotherapy
  - **Kwakman et al., 2017** (Annals of Oncology)**; Kwakman et al., 2019**: Randomised phase 3 study in Western patients with 1L mCRC comparing S-1 (combined with optional bevacizumab) vs capecitabine (combined with optional bevacizumab)
- S-1 combination therapy
  - **Hong et al., 2012; Kim et al., 2014**: Randomised phase 3, non-inferiority study in 1L mCRC patients in South Korea comparing S-1 plus oxaliplatin vs capecitabine plus oxaliplatin

- **Yamada et al., 2013; Baba et al., 2017**: Randomised phase 3, non-inferiority study in 1L mCRC patients in Japan comparing S-1 plus oxaliplatin/bevacizumab vs mFOLFOX6/bevacizumab
- **Yamada et al., 2018**: Randomised phase 3, non-inferiority study in 1L mCRC patients in Japan comparing S-1 plus irinotecan/bevacizumab vs mFOLFOX6/bevacizumab or capecitabine plus oxaliplatin/bevacizumab
- **Muro et al., 2010; Yasui et al., 2015**: Randomised phase 3, non-inferiority study in 2L mCRC patients in Japan comparing S-1 plus irinotecan/bevacizumab vs FOLFIRI

3.2. Favourable effects

Pivotal evidence

In support of the target population, exploratory and retrospective efficacy data of European mCRC patients who switched to S-1 based therapies after toxicity during treatment with another fluoropyrimidine is provided.. Median OS was 26 months (95% CI 22-31 months) in 53 mCRC patients who switched due to cardiotoxicity. In another cohort of 47 mCRC patients who switched after development of HFS or cardiotoxicity while on capecitabine, median time from initiation of treatment with capecitabine to first documented progression of disease after initiation of treatment with S-1 was 414 days (95% CI 332-568 days). When only the 36 patients who switched from capecitabine to S-1 for reason of HFS were considered, median PFS was 414 days (95%CI: 332-629).

Supportive evidence

Supportive evidence of patients who are randomised at baseline to either S-1 based therapy or another fluoropyridimine-based therapy is also provided. The meta-analysis by Derksen et al. reported a pooled HR for the primary endpoint PFS of 0.95 with the upper boundary of the 99% CI being 1.08. OS was a secondary outcome in the studies included in the meta-analysis and showed a pooled HR of 0.93 with an upper CI99% bound of 1.07. Based on a pooled risk ratio for response, RR was 1.06 with an upper CI99% bound of 1.24. No suggestion of important heterogeneity was observed for PFS and OS and a moderate heterogeneity for ORR.

To support efficacy of S-1 compared to another fluoropyrimidine, efficacy results were also provided from individual studies performed in patients who were randomised at baseline to a treatment arm containing S-1 or another fluoropyrimidine. The results of these studies were also included in the meta-analysis. No significant differences were found for PFS, RR, and OS between the treatment groups. Four randomised phase 3 studies investigated S-1 combination therapy with either oxaliplatin or irinotecan in Asian patients and supported that S-1 had non-inferior efficacy to combination therapy with 5-FU or capecitabine when patients are randomised at baseline.

3.3. Uncertainties and limitations about favourable effects

First of all, there are limitations inherent to the use of literature as basis for the support of favourable effects. These pertain to differences in posology and the need for extrapolation from the patients who were studied in the clinical trials to the intended target population.

Regarding available data in the EU target population of patients who switched to S-1 after toxicity on another fluoropyrimidine, only retrospective, non-comparative and exploratory efficacy data are provided. The interpretation of these data are, furthermore, limited by the small number of patients, heterogeneity of the treatment schedules and varying timing of the switch to S-1.

Lastly, on the choice for 180 mg/m^2 irinotecan as recommended posology, most studies and clinical practice use a higher dose of 200 mg/m^2 and a range of 150-225 mg/m^2 is reported. This is reflected in the SmPC.

3.4. Unfavourable effects

The S-1-related toxicity in mCRC as reported in the submitted application appears at a high level in line with the already known safety profile of the drug. The data support the presence of inter-ethnic differences in the tolerability of S-1.

In the SALTO study comparing capecitabine to S-1 (with or without bevacizumab) in a western previously untreated mCRC population, treatment with S-1 was associated with a lower incidence of HFS (45% vs 73%, respectively; grade 3: 4% vs 21%, respectively), and higher incidence of diarrhoea (69% vs 48%; grade ≥3: 16% vs 12%), anorexia (41% vs 29%; grade ≥3: 13% vs 3%), vomiting (30% vs 19%), fatigue (79% vs 74%), hypertension (43% vs 35%) and proteinuria (20% vs 9%).

Several studies (CAPOX vs SOX, SOFT, TRICOLORE, FIRIS) performed in Asian mCRC patients comparing combination therapies containing S-1 vs other fluoropyrimidines (i.e., capecitabine, 5FU) support a lower incidence of HFS and sometimes of sensory neuropathy associated with S-1 treatment and a higher incidence of diarrhoea, anorexia and haematological toxicity.

The retrospective study published by Kwakman et al (Acta Oncologica 2017) including 141 western cancer patients switching from capecitabine to S-1 due to HFS provides evidence in support of the feasibility of the switch from capecitabine to S-1 in patients experiencing significant HFS. According to the results presented in the article, the switching strategy from capecitabine to S-1 was able to reduce HFS severity in 94% of patients, with complete resolution of HFS-related symptoms in 56% of patients. Treatment with S-1 in these patients was reasonably well-tolerated, as indicated by the median number of cycles received by the patients (5, range 1-13) and the percentage of treatment discontinuations (7.6%), dose reductions (21%) and delays (15%) due to S-1 related AEs.

In a subgroup of 53 mCRC patients, within the Cardioswitch cohort study of 200 patients with different solid tumours, the majority of these mCRC patients (92%) who developed cardiotoxicity while on capecitabine- or 5-FU-based chemotherapy could safely switch to S-1 and continue treatment, with recurrent cardiotoxicity (grade 1) seen in 8%. Other adverse events during S-1 treatment in this subgroup included grade 3-4 haematologic toxicity in 8% and grade 2-4 non-haematologic adverse events in 36% (neuropathy 15%, infection 7%, thromboembolic event 6%, diarrhoea 4%, nausea 2%, hand-foot syndrome 2%).

In another case series of 7 cancer patients (of which 2 with mCRC) switching to S-1 (administered at different dose regimens) after capecitabine-induced coronary vasospasm a median of 4 cycles (range 2-15) of S-1 was administered, with none of the patients experiencing any signs or symptoms related to recurrent cardiac toxicity (Kwakman et al., EJC 2017).

In a retrospective cohort study of 47 metastatic colorectal cancer patients from the Dutch colorectal cancer registry (PLCRC Switch Cohort Study) switching to S-1 due to capecitabine-induced hand-foot syndrome (n=36) or cardiotoxicity (n=10) the severity of HFS decreased or completely resolved during treatment with S-1 and no case of recurrence of cardiac toxicity was reported in any of the 10 patients that switched to S-1 due to cardiac adverse events.

Two cases of terminal ileitis have been identified, one of which considered probably related to treatment with S1. Terminal ileitis is added to the SmPC as it represents a specific condition and the terms related to gastrointestinal toxicity currently present are not considered sufficient to cover this specific event.

3.5. Uncertainties and limitations about unfavourable effects

The safety database as provided consists essentially of a bibliographic review of articles and case reports published. Information in several of the articles/case reports/posters is very limited, challenging any critical assessment of the S-1 related toxicity in the intended setting. A section has been added to the SmPC with a description of the safety database in support of the new proposed indication in order to reflect the limitations of the data available.

Uncertainties are identified based on the retrospective and non-comparative nature of the data presented to support a switching strategy to S-1 in patients unable to continue treatment with another fluoropyrimidine due to HFS or cardiac toxicity as well as the limited number of (mCRC) patients included in the analyses.

In the Cardioswitch study, no accurate assessment can be made of the non-cardiac toxicity profile of S-1 in this specific target population, as according to the provided study protocol only cardiac adverse events were systematically collected.

Another limitation of the Cardioswitch study is the heterogeneity of the population enrolled in the dataset in terms of primary tumour type (as patients with CRC were 78% of the enrolled population (n=156)) and of the different dose regimens and posologies implemented.

The studies where S-1 combination treatments have been administered to mCRC (i.e., SOX vs CAPOX, SOFT, TRICOLORE, FIRIS) have all been performed in non-Caucasian patients. Safety extrapolation from Asians to Caucasians (including the applicable S-1 dose regimens in the different combinations) is hampered by the reported ethnic differences in S-1 pharmacodynamics and toxicity.

A section has been added in section 4.8 of the SmPC with description of the safety database in the population covered by this new indication,

3.6. Effects Table

Effects Table for S-1 in metastatic colorectal cancer patients where it is not possible to initiate or continue treatment with another fluoropyrimidine (latest data cut-off per study)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
OS	Overall survival	Months (95% CI)	26 (22-31)	NA	Target population, but retrospective, non-comparative, and exploratory	Österlund, 2021
TTP	Time from initiation capecitabine to progression after start with S-1	Days (95% CI)	414 (332-568)	NA	Target population, but retrospective, non-comparative, and exploratory	Punt, 2021
PFS OS	Progression-free survival Overall survival	HR pooled	NA	NA	Meta-analysis pooled studies in first and second line mCRC monotherapy and combination therapies, no significant heterogeneity detected for PFS and OS HR_{total} PFS 0.95 (99% CI 0.83-1.08)	Derksen, 2021

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
					HR_{total} OS 0.93 (99% CI 0.81-1.07) Support that efficacy of S-1 is non-inferior to other fluoropyrimidines in mCRC treatment	
Unfavourable Effects						
HFS	Hand-foot syndrome	%	45	73	1L S-1 vs capecitabine (+/- bevacizumab) in western mCRC. HFS grade >=3: 4% vs 21%.	Kwakman, 2017
Diarrhoea		%	69	48	Grade >=3: 16% vs 12%	Kwakman, 2017
Anorexia		%	41	29	Grade >=3: 13% vs 3%	Kwakman, 2017
Vomiting		%	30	19		Kwakman, 2017
ReCx	Recurrent cardiotoxicity	%	4	-	Retrospective design, heterogeneous population, lack of information on tolerability of S-1 after switch.	Osterlund, 2021
ReHFS	Recurrent HFS	%	-	3.4	Retrospective study, heterogeneous population (mCRC: 56%), no detailed information on S1 dose regimens applied.	Kwakman, 2017

Abbreviations: CI (confidence interval), HR (hazard ration), OS (overall survival), PFS (progression-free survival), ReCx recurrent cardiotoxicity after switching to S-1, ReHFS recurrent HFS after switch to S1, TTP time to progression.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In this type II variation, the MAH applies for an extension of the indication for the treatment of mCRC patients where the current chemotherapy cannot be continued due to fluoropyrimidine intolerability causing cardiotoxicity or HFS. Without the option to continue an effective therapy with fluoropyrimidines due to toxicity, there is a potential loss of extended overall survival and the unmet medical need is fully acknowledged. S-1 is designed to reduce the rate of degradation of 5-FU and its conversion to its toxic phosphorylated metabolite and can, therefore, hypothetically act as an alternative to patients where continuation with another fluoropyrimidine is not an option.

In support for the indication, the MAH provided retrospectively collected efficacy data in European patients who switched to S-1 because of cardiotoxicity or HFS on another fluoropyrimidine. Although the interpretation of these data is hampered by the retrospective and non-comparative nature, it provides evidence that fluoropyrimidine activity is not lost after switching to S-1. In addition, the MAH performed a literature search and meta-analysis of randomised phase II and III clinical trials. The meta-analysis showed that S-1 based therapy was non-inferior to 5-FU or capecitabine-based therapy regarding PFS in first and second line therapy using a non-inferiority margin of 1.25. Secondary outcomes of OS and ORR supported this finding. Although the HR for PFS in the second line subgroup has an upper bound of

the 99% CI above 1.25, this is only based on one study. Another study performed in second line that was not included in the meta-analysis as only median PFS was reported, showed a median PFS of 8.5 months in the S-1+irinotecan+bevacizumab arm versus 8.2 months in the mFOLFIRI+bevacizumab arm. Combined with the finding that the 99% CI upper bound for OS was <1.25 in the second line subgroup, excluding the subgroup treated in second line is not considered necessary.

Pharmacokinetics were not found to be clinically significantly different between ethnic groups. In addition, based on data from studies with S-1 in gastric cancer, there are no observed differences in efficacy between Asian and Western patients due to ethnic variations. However, extrapolation of safety remains hampered by the identified ethnic differences in S-1 tolerability. As a consequence, there is still an uncertainty regarding the posology for the S-1 combination with irinotecan, which is reflected in the SmPC section 4.2.

It is acknowledged that a randomised controlled trial in a population that cannot be treated with another fluoropyrimidines is not feasible due to the lack of a proper control. Although there is formally no evidence whether efficacy is comparable between patients started at baseline with S-1 or another fluoropyrimidine and patients who switch to S-1 after fluoropyrimidine-associated toxicity, it is not possible to gather this information as the treatment options for patients become limited when 5-FU cannot be used. In addition, based on the MoA it is not expected that efficacy of S-1 will be different in patients who switch compared to those initiating therapy with S-1. Therefore, S-1 can be regarded as a treatment option considering the perspective of not being able to use another fluoropyrimidine. The newly performed meta-analysis supports non-inferiority of the efficacy of S-1 based regimens compared to 5-FU or capecitabine-based regimens as first or second line treatment in mCRC. Taken together with exploratory data in an European population that switched from another fluoropyrimidine to S-1 due to toxicity, it is agreed that S-1 is a valuable treatment option in patients not able to continue fluoropyrimidine treatment.

Regarding safety, relevant limitations of the provided dataset have been identified, essentially related to the retrospective and uncontrolled nature of the data, the limited sample size and the heterogeneity in terms of cancer population included and regimens/posologies applied. The challenges associated with the known ethnic differences in S-1 pharmacodynamics and safety further complicate the safety assessment. On the other hand, the overall body of evidence supports an a priori reduced chance of developing HFS during treatment with S-1 compared with capecitabine/5FU (refer to SALTO study results) due to intrinsic differences of the safety profile of the drugs. Moreover, the several case series presented consistently support the feasibility and effectiveness of the switch from another fluoropyrimidine to S-1 in case of intolerable HFS and/or cardiac toxicity, where the need for alternative strategies in order to continue anticancer treatment is obvious.

While only a few patients treated in the adjuvant setting were included in the studies that form the basis of this application, it is to be expected that HFS or cardiovascular toxicity will recur when patients will subsequently be treated with 5-FU or capecitabine in the metastatic setting. Furthermore, the posology of 5-FU/capecitabine and the combinations in which they are used in the adjuvant and metastatic setting are similar. Therefore, it is supported to include this population in the indication.

3.7.2. Balance of benefits and risks

Efficacy and safety data in European patients who switched to S-1 after toxicity on another fluoropyrimidine is considered established based on the provided data. By providing patients who have to discontinue another fluoropyrimidine with an alternative option which has a similar mechanism of action, patients will be able to continue effective systemic treatment and the initiation of salvage regimens can be postponed. In this population the benefits outweigh the risks and the B/R is considered positive.

It is also considered that the same unmet medical need applies to patients who developed HFS or cardiovascular toxicity on another fluoropyrimidine in the adjuvant setting for colorectal cancer. As the B/R is also positive in this population, it is supported to include in the indication the patients who developed HFS or cardiovascular toxicity in the adjuvant setting in addition to metastatic patients.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The B/R is considered to be positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include as monotherapy or in combination with oxaliplatin or irinotecan, with or without bevacizumab, for the treatment of patients with metastatic colorectal cancer for whom it is not possible to continue treatment with another fluoropyrimidine due to hand-foot syndrome or cardiovascular toxicity that developed in the adjuvant or metastatic setting. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 10.2 of the RMP has also been submitted.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.