Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende tegafur/gimeracil/oteracil til behandling af patienter med metastatisk tyk- og endetarmskræft, som har udviklet hånd-fod-syndrom eller kardiovaskulær toksicitet

Vers. 1.0

Bilagsoversigt

1. Forhandlingsnotat fra Amgros vedr. tegafur/gimeracil/oteracil
2. Ansøgers endelige ansøgning vedr. tegafur/gimeracil/oteracil

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

23.09.2024

DBS/MBA

Forhandlingsnotat

Dato for behandling i Medicinrådet	23.10.2024
Leverandør	Nordic Drugs
Lægemiddel	Teysuno (tegafur, gimeracil, oteracil)
Ansøgt indikation	Til patienter med metastatisk kolorektal cancer (mCRC) for hvem behandling med et andet fluoropyrimidin ikke kan fortsætte på grund af hånd-fod-syndrom eller kardiovaskulær toksicitet.
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har følgende aftalepris på Teysuno (tegafur, gimeracil, oteracil):

Tabel 1: Aftalepris

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP, (DKK)	SAIP (DKK) pr. 01.04.2025	Rabatprocent ift. AIP
Teysuno	15 mg tegafur + 4,35 mg gimeracil+ 11,8 mg oteracil	42 stk.	1.021,79	949,33	[redacted]	[redacted]
Teysuno	20 mg tegafur + 5,8 mg gimeracil + 5,8 mg oteracil	42 stk.	1.329,91	1.253,95	[redacted]	[redacted]

Aftaleforhold

Amgros har allerede en aftale på Teysuno, og der er indgået en ny aftale pr. 01.04.2025 -31.03.2026 uden mulighed for prisregulering og med offentlige priser.

Konkurrencesituationen

Teysuno har været godkendt til ventrikel cancer siden 2012, og har i dag en omsætning på 3,4 mio DKK (SAIP 2023). Der er ingen konkurrence på metastatisk kolorektal cancer (mCRC).

Tabel 2 viser lægemiddeludgiften for behandlingslængden på 9 måneder jævnfør Medicinrådets vurderingsrapport.

Tabel 1: Lægemiddeludgift pr. patient

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. 9 måneder (SAIP, DKK)
Teysuno	20 mg tegafur + 5,8 mg gimeracil + 15,8 mg oteracil	42 kapsler	30 mg/m2 tegafur givet 2 gange daglig i 14 dage efterfulgt af 7 dages pause*	[redacted]	[redacted]

*Patientens kropsoverflade areal (BSA) = 1,93 og den gennemsnitlige behandlingslængde vurderes at være 9 måneder jævnfør Medicinrådets vurderingsrapport.

Status fra andre lande

Tabel 2: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Under vurdering		Link til vurdering

Konklusion

Det er Amgros' vurdering, at leverandøren på nuværende tidspunkt ikke kan tilbyde en bedre pris.

Medicinrådet

Instructions for companies

This is the template for submitting evidence to the Danish Medicines Council (DMC) as part of the appraisal process for a new medicinal product or a new indication for an existing medicine. The template is not exhaustive.

Please note the following requirements:

- When preparing their application, companies must adhere to the current version of the DMC's methods guide, in addition to using the current version of this template.
- Headings, subheadings and appendices must not be removed. Tables must not be edited, unless it is explicitly stated in the text.
- Text in grey and [in brackets] is only for example purposes and must be deleted.
- All sections in the template must be filled in. If a section or an appendix is not applicable, state "not applicable" (N/A) and explain why.
- The main body of the application must not be longer than 100 pages, excluding appendices.
- The formatting is not to be altered and all cross-references must work.
- All applications must comply with the general data protection regulations, find more information on DMC's data policy here.
- Submissions in either Danish or English are accepted.

The assessment process cannot be initiated before all the requirements are met.

Documentation to be submitted

The following documentation must be sent to the DMC's email medicinraadet@medicinraadet.dk:

- Application in word format*
- Application in PDF format*
- Health economic model including budget impact model in one Excel file, with full access to the programming code. The model must include relevant sheets from the DMC Excel template 'Key figures including general mortality' available on the DMC's website.
- The European Public Assessment Report (EPAR) should be submitted as soon as possible (draft versions will be accepted).

* Later in the appraisal process, once the application has received Day 0, the application must be assembled and sent to the DMC in one blinded version and one highlighted version (both in word and pdf).

Confidential information

- In the preparation of the documentation, companies must ensure that all confidential information is highlighted in yellow and provide the expected date of publication, if applicable. If confidential appendices are provided, these must be watermarked as "confidential".

Medicinrådet

About macros in Excel

Due to IT security requirements, Excel files containing macros must be authorized and signed by the applicant before being submitted to the DMC. Find more information here.

Version log

Version log		
Version	**Date**	**Change**
2.2	3 November 2023	‘Pharmaceutical’ is exchanged with ‘medicine’. Tabel 26 is new.
2.1	1 September 2023	Section 4.2: Updated information about discount rate (The DMC applies a discount rate of 3.5 % for all years) Section 10.1.3: Clarification regarding EQ-5D-5L and Danish preference weights Section 11.1: Updated information about Excel sheet ‘Key Figures’
2.0	15 June 2023	New application template
1.3	6 December 2022	Clarification regarding new IT security requirements concerning macros in Excel files has been added, see page 1.
1.2	20 June 2022	Clarification of the introduction, including instructions on how to complete the form.
1.1	9 February 2022	Appendix K and onwards have been deleted (company-specific appendices) Color scheme for text highlighting table added after table of contents Section 6: Specific requirements for literature search Section 7: Stated it explicitly that statistical methods used need to be described Section 8.3.1: Listed the standard parametric models Section 8.4.1: Added the need for description of quality of life mapping Appendix A: Specified that the literature search needs to be specific for the Danish context and the application Appendices B and D: Stated it explicitly that statistical methods need to be described in the tables in the appendices
1.0	27 November 2020	Application form for assessment made available on the website of the Danish Medicines Council.

Application for the assessment of Teysuno for the treatment of metastatic colorectal cancer

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of color-code]

Contact information

Contact information	
Name	**Fredrik Ahlgren**
Title	Marketing Director, Nordic Drugs AB
Phone number	+46 765 25 16 86
E-mail	fredrik.ahlgren@nordicpharma.com
Name (External representation)	**Not applicable**
Title	Not applicable
Phone number	
E-mail	

[If a company wishes to use external representation in relation to the application for evaluation of a new medicine / extension of indications, the following power of attorney must be completed and sent to medicinraadet@medicinraadet.dk.]

Table of contents

Tables and Figures

Figures

Tables

Abbreviations

Abbreviation	Definition
5-FU	5-fluorouracil
APC	Adenomatous polyposis coli
BRAF	B-Raf proto-oncogene, serine/threonine kinase
BSA	Body surface area
CAPIRI (XELIRI)	Capecitabine and irinotecan
CAPOX (XELOX) (CapeOX)	Capecitabine and oxaliplatin
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMA	Cost minimization analysis
CpG	Region of DNA: cytosine nucleotide followed by a guanine nucleotide
CRC	Colorectal Cancer
CrCl	Creatinine clearance
DCCG	Danish Colorectal Cancer Group
DKK	Danish krone
DMA	Danish Medicines Agency
DMC	Danish Medicines Council
dMMR	DNA missmacth repair
DNI	Non-inferiority margin

DPD	Dihydropyrimidine dehydrogenase
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
ESC	European Society of Cardiology
ESMO	European Society for Medical Oncology
FAP	Familial Adenomatous Polyposis
FBAL	α-fluoro-β-alanine
FdUMP	5-fluoro-deoxyuridine-monophosphate
FLIRI	Fluorouracil, folinic acid, irinotecan
FLOX	Fluorouracil, folinic acid, oxaliplatin
FOLFIRI	Folinic acid, fluorouracil, irinotecan
FOLFOX	Leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin
FOLFOXIRI	Folinic acid, fluorouracil, oxaliplatin and irinotecan
FUTP	5-fluorouridine-triphosphate
GI	Gastro intestinal
HFS	Hand-foot syndrome
HR	Hazard Ratio
IRIS	Irinotecan and Teysuno
Lv/FA 5-FU/FA	Combination of 5-FU and leucovorin/folinic acid
mCRC	Metastatic colorectal cancer
mFOLFOX6	Modified regimen of leucovorin, fluorouracil, and oxaliplatin
MLH1	MutL protein homolog 1
MSH2	MutS homolog 2
MSH-I	Microsatellite instability
N/A	Not Applicable
OPRT	Orotate phosphoribosyltransferase
OPRT	Orotate phosphoribosyltransferase
ORR	Objective response rate
mOS	Mean overal survival
OS	Overall survival
PFS	Progression-free survival
PPP	Pharmacy Purchasing Price
PS	Performance status
QOL	Quality of life
RADS	Rådet for Anvendelse af Dyr Sygehusmedicin
RAF	Rapidly accelerated fibrosarcoma

RAS	Rat sarcoma
RR	Risk Ratio
S-1	Teysuno
SOX	Teysuno + oxaliplatin
TAS102	Trifluridine + tipiracil (Lonsurf)

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Teysuno
Generic name	tegafur / gimeracil / oteracil
Therapeutic indication as defined by EMA	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 (Type II variation) [1].
Marketing authorization holder in Denmark	Nordic Drugs
ATC code	L01BC53
Combination therapy and/or co-medication	For metastatic colorectal cancer: As monotherapy or in combination with oxaliplatin or irinotecan, with or without bevacizumab [1].
(Expected) Date of EC approval	Teysuno received CHMP positive opinion 16th of December 2010 (gastric cancer) and 16th of December 2021 (metastatic colorectal cancer, mCRC)
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	N/A, already approved
Orphan drug designation (include date)	Teysuno has not been granted orphan drug-status.
Other therapeutic indications approved by EMA	Teysuno is indicated, in adults, for the treatment of advanced gastric cancer when given in combination with cisplatin (type I indication) [2].
Other indications that have been evaluated by the DMC (yes/no)	No
Dispensing group	BEGR

Overview of the medicine	
Packaging – types, sizes/number of units and concentrations	PCTFE/PVC/Al opaque blisters containing 14 capsules each. Each pack contains either 42 capsules, 84 capsules or 126 capsules. Teysuno (PCTFE/PVC/Al) - 15 mg/4.35 mg/11.8 mg: 42, 126 capsules Teysuno (PCTFE/PVC/Al) - 20 mg/5.8 mg/15.8 mg: 42, 82 capsules

2. Summary table

Provide the summary in the table below, maximum 2 pages.

Summary	
Therapeutic indication relevant for the assessment	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 [1] No deviations from EMA indication.
Dosage regiment and administration	The proposed dose in mCRC for monotherapy is 30 mg/m^2 b.i.d. days 1-14 with a one-week pause (± bevacizumab 7.5 mg/kg on day 1). For combination therapy (with oxaliplatin or irinotecan), 25 mg/m^2 b.i.d. d1-14 followed by one-week pause is recommended [1, 3].
Choice of comparator	According to clinical expert (consulted) dose reduction and rechallenge or Lonsurf are the options in clinical practice, however, Lonsurf has not been assessed by the DMC therefore dose reduction and rechallenge is the comparator chosen for this analysis.
Prognosis with current treatment (comparator)	Median OS of approximately 12 months in the total population and 15 months in patients who receive systemic therapy. Around 1,800 people die from colorectal cancer in Denmark each year.
Type of evidence for the clinical evaluation	Meta-analysis [4]
Most important efficacy endpoints (Difference/gain compared to comparator)	PFS, OS, ORR – non-inferior

Summary	
Most important serious adverse events for the intervention and comparator	**Recurrence of cardiotoxcicity** Teysuno-based therapy: 8% [5] 5-FU/cap-based therapy: 75% [6] **Recurrence of hand-foot-syndrome** Teysuno-based therapy: 12% [6] 5-FU/cap-based therapy: 33% [6]
Impact on health-related quality of life	Clinical documentation: Not Applicable (not reported in literature) Health economic model: Not Applicable (no cost-effectiveness model)
Type of economic analysis that is submitted	Cost-minimization analysis
Data sources used to model the clinical effects	N/A, cost-minimization analysis
Data sources used to model the health-related quality of life	N/A, cost-minimization analysis
Life years gained	N/A, cost-minimization analysis
QALYs gained	N/A, cost-minimization analysis
Incremental costs	Range [DKK -522,642 to DKK 3,212]; Base case results: DKK -173,609 (negative values imply cost-savings with Teysuno, positive values an incremental cost with Teysuno).
ICER (DKK/QALY)	N/A, cost-minimization analysis
Uncertainty associated with the ICER estimate	N/A, cost-minimization analysis
Number of eligible patients in Denmark	Incidence CRC: 66.5 Prevalence CRC: 4,270 Number of eligible patients: 224
Budget impact (in year 5)	DKK -75,006,275 (cost-savings with Teysuno)

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition: colorectal cancer

Colorectal cancer (CRC) is the third most common malignancy and second most deadly cancer globally, with an estimated 1.9 million cases and 0.9 million deaths worldwide in 2020[7]. Approximately 20% of CRC patients have metastatic (m)CRC at the time of diagnosis, and a further 20% will develop mCRC within 5 years of diagnosis [8].

CRC commonly arises from adenomatous polyps that typically acquire dysplastic changes in a 10- to 15-year period before developing invasive carcinoma [9]. This transformation of the normal colonic epithelium requires an accumulation of genetic mutations, either somatic and/or germline, through one of the following pathways: chromosomal instability, mismatch repair, or hypermethylation:

- The chromosomal instability pathway is a gain of mutations that unbalance the equilibrium of oncogenes and tumor suppressors, as seen with mutations in the adenomatous polyposis coli (APC), a hallmark of Familial Adenomatous Polyposis (FAP).
- Cells with deficiency of DNA mismatch repair (dMMR), commonly MLH1 or MSH2, accumulate errors within the genome that further will be repeated, causing high levels of microsatellite instability (MSI-H), a hallmark of Lynch syndrome.
- CpG hypermethylation of DNA could either activate or silence the expression of certain genes (BRAF and MLH1, respectively) [9]. Metastatic CRC tumours should be tested through molecular profiling in order to identify tumour subtypes for which targeted therapy may be available [10].

The most common sites of mCRC include lymph nodes, liver, lung, and peritoneum[11]. Patients with CRC typically present with rectal bleeding, microcytic anemia, altered bowel habits, and chronic abdominal pain [12] as well as such unexplained general symptoms as weight loss and weakness [13]. Approximately half of CRCs arise in the right side (or proximal) colon; these tumours typically present with fatigue, anaemia, and abdominal pain or cramping. Left-sided tumours (i.e., those in the distal colon and rectum) typically present with altered bowel habits such as constipation, narrow caliber stool, or rectal bleeding [14, 15].

Due to the non-specific and late-appearing symptoms of CRC, patients typically seek care at a late stage of disease development, which results in approximately 20-30% of patients already having mCRC at time of diagnosis [16]. The five-year overall survival (OS)

for colon cancer is 63% for men and 65% for women; the corresponding figures for rectal cancer are 66% and 69%, respectively [17]. The reported median OS is based on the results of clinical trials; population-based studies suggest that the survival outside clinical trials is much worse, with a median OS of approximately 12 months in the total population and 15 months in patients who receive systemic therapy[18].

3.2 Patient population

Colorectal cancer is one of the most widespread types of cancer in the Danish population, although it is rarely seen before the age of 40 and most cases are not seen until after the age of 60 [19]. The median ages of patients with colon cancer and rectal cancer have been reported as 72 and 70 years, respectively[20].

In 2021, 4,270 patients were diagnosed with colorectal cancer (2,987 patients with colon cancer and 1,283 with rectal cancer) in Denmark [21].

Table 1 Incidence and prevalence in the past 5 years

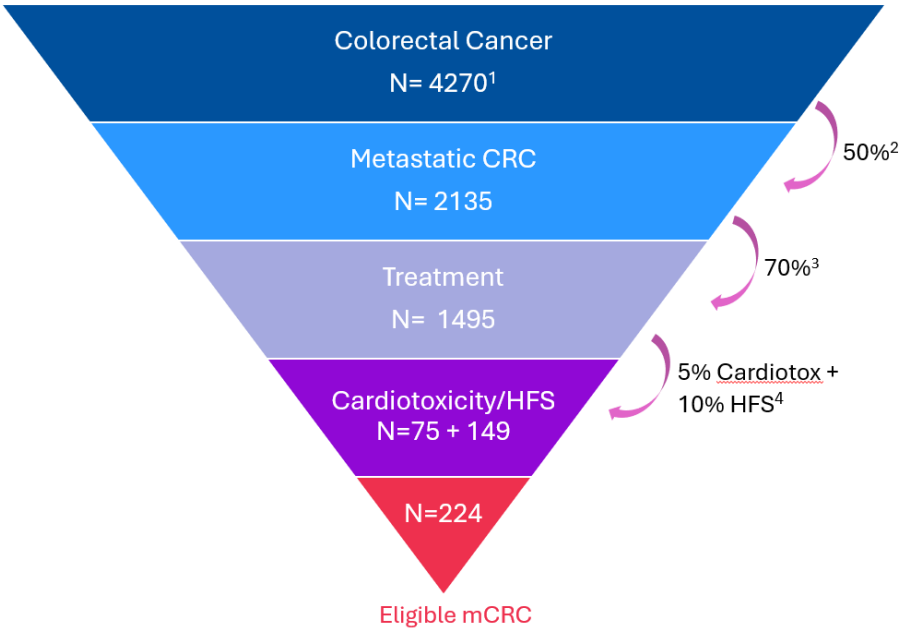
Year	[2019]	[2020]	[2021]	[2022]	[2023]
Incidence in Denmark (Age-Standardized Rate (Nordic) per 100 000) **[22]**	69.7	64.3	66.5	66.5	66.5
Prevalence in Denmark	4,296 [19]	4,032 [23]	4,270 [21]	4,270*	4,270*

*Based on predicted incidence reported by NORDCAN [22]

According to Rådet for Anvendelse af Dyr Sygehusmedicin (RADS), about half of the patients will develop metastatic disease [24, 25]. Approximately 70% of the mCRC patients will be offered medical treatment [24, 26]. Around 1,800 people die from colorectal cancer in Denmark each year [27].

Based on estimates from multiple sources [5, 28-33] it is projected that approximately 5% of patients undergoing first-line fluoropyrimidine treatment develop cardiotoxicity, and 10% experiencing severe hand-foot syndrome (HFS). This translates to approximately 224 patients per year eligible for treatment with Teysuno in Denmark as illustrated in Figure 1.

Figure 1. Patients eligible for treatment with Teysuno in Denmark



1. Danish Colorectal Cancer Group (DCCG), 2019 [19] 2. Rådet for Anvendelse af Dyr Sykehusmedicin (RADS), 2016, DCCG, 2023 [24, 25] 3. RADS, 2016 [24] 4. [5, 28-33]

Table 2 Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	224	224	224	224	224

3.3 Current treatment options

The treatment of mCRC in Denmark is described in clinical guidelines from the Danish Colorectal Cancer Group (DCCG) from 2023 [25]. Choice of treatment strategy depends on a number of factors, including spread of disease, resectability, symptomatology, comorbidity, general condition, tumor biological profile, location of primary tumor, whether primary tumor is *in situ*, and patient preference [34].

Where CRC is limited to a few metastatic foci (typically the liver or lung) it may be resectable i.e., amenable to complete surgical removal or other curative intended modalities[25]. However, resection of mCRC only achieves long-lasting results in fewer than 20% of mCRC patients[10].

In patients with widespread metastases, the intention of treatment is to prolong the patient's life and relieve any disease symptoms, with the fewest possible side-effects and preservation or improvement of quality of life (QoL) for as long as possible [25].

3.3.1 First line treatment in patients with mCRC and good general condition/ performance status

Patients should be offered systemic oncology therapy, where treatment choice depends on presence/absence of symptoms, primary tumour localization, tumour biology profile (with information on RAS and BRAF mutation status), MMR status, comorbidity, general condition, any prior adjuvant therapy, and patient preference [25].

According to the Danish Treatment Guidelines [25], 5-fluorouracil (5-FU) is the cornerstone of CRC treatment. The combination of 5-FU and leucovorin/folinic acid (Lv/FA) (5-FU/FA) causes tumor shrinkage in approximately 25% of patients, and mean overall survival (mOS) increases from 6 months (untreated) to 12 months [35, 36]. A number of different treatment regimens have been developed where 5-FU is given as a bolus and/or infusion over one or several days, in combination with different doses of FA [37-39].

Treatment options in the 1st line consist of the following chemotherapy regimens [25]:

- Combination chemotherapy in the form of FOLFIRI (5-FU/FA + irinotecan) or FOLFOX (5-FU/FA + oxaliplatin) or CAPOX (capecitabine, oxaliplatin)
- Three-drug chemotherapy in the form of FOLFOXIRI (5-FU/FA + oxaliplatin + irinotecan)
- Monotherapy with capecitabine
- Pembrolizumab (in patients with *microsatellite instability high* [MSI-H]/dMMR mCRC)

FOLFIRI, FOLFOX, FOLFOXIRI, CAPOX and capecitabine may be administered in combination with targeted therapy, which can be either an Epidermal growth factor receptor (EGFR) inhibitor (cetuximab or panitumab) or the angiogenesis inhibitor bevacizumab.

Table 3. First line treatment options for patients with mCRC and good general condition/performance status (PS)

mCRC type	Left-sided disease	Right-sided disease
RAS- wildtype, BRAF-wildtype, pMMR	FOLFIRI (+ anti-EGFR antibody) FOLFOX (+ anti-EGFR antibody)	FOLFOX or CAPOX FOLFIRI FOLFOXIRI (younger, good PS) FOLFIRI (+ anti-EGFR antibody) FOLFOX (+ anti-EGFR antibody)
RAS-mutated	FOLFIRI FOLFOX/CAPOX FOLFOXIRI (younger patients)	FOLFIRI FOLFOX/CAPOX FOLFOXIRI (younger patients)

BRAF-mutated	FOLFOX/CAPOX FOLFIRI	FOLFOX/CAPOX FOLFIRI
dMMR	Pembrolizumab	Pembrolizumab
Unresectable pMMR without the need for tumor shrinkage (regardless of location and RAS/RAF status)	Capecitabine/5-FU (+ bevazicumab)	Capecitabine/5-FU (+ bevazicumab)

3.3.2 Treatment after the first line

The treatment of patients with mCRC is perceived as a "continuum of care" and patients should be exposed to all available active substances in their treatment course [25]. In case of progression (either during or after completion of 1st line treatment), 2nd line chemotherapy depends on what the patient received as 1st line therapy: in case of progression on irinotecan-based chemotherapy, oxaliplatin-based chemotherapy will be offered in the 2nd line, and vice versa. In Danish clinical practice, treatment with angiogenesis inhibitors (e.g., bevacizumab) is usually used first during 2nd line treatment (unless they are used in combination with capecitabine in 1st line treatment) [25].

Re-introduction with a previously-used chemotherapy, with or without biological treatment, is an option if the disease has a long progression-free interval [25].

3.3.3 Treatment complications

Dihydropyrimidine dehydrogenase (DPD) is the most important enzyme in fluoropyrimidine metabolism, and a lack of DPD function (which occurs in 3-5% of patients) leads to increased fluoropyrimidine toxicity, which can be fatal [40]. It has been recommended by the European Medicines Agency (EMA) that DPD tests should be performed on all patients before first treatment with fluorouracil, capecitabine and tegafur, in order to identify lack of function. In case of reduced DPD activity, it is recommended to start with a reduced dose of fluoropyrimidine [41].

Cardiotoxicity is a common and potentially lethal complication of fluoropyrimidine treatment, with a reported incidence of between 0% and 35%, depending on assessment method, dose, and schedule [28, 32, 33]. The clinical manifestations of fluoropyrimidine-induced cardiotoxicity range from chest pain and hypotension, to myocardial infarction and death [42], with reports of mortality from fluoropyrimidine-related cardiotoxicity varying between 0 and 2.2% in prospective studies [43].

Fluoropyrimidine treatment can also lead to HFS, a skin reaction to systemic chemotherapy that can cause significant discomfort and impairment of function, thereby compromising quality of life, especially in elderly patients[44].

It is estimated that an average of 5% of patients develop cardiotoxicity and 10% develop severe HFS during 1st line fluoropyrimidine treatment [5, 28-33]. There is therefore a need for the development of alternatives to 5-FU and capecitabine treatment in case of toxicity.

3.4 The intervention

Teysuno is an oral fluoropyrimidine anti-cancer medicinal product comprised of tegafur, a fluoropyrimidine prodrug of 5-FU, and 2 modulators of 5-FU metabolism, gimeracil and oteracil. Teysuno is available as in two strengths: i) hard capsules of Teysuno that contain 15 mg tegafur, 4.35 mg gimeracil and 11.8 mg oteracil (as monopotassium) and ii) hard capsules of Teysuno that contain 20 mg of tegafur, 5.8 mg gimeracil and 15.8 mg oteracil [2, 3].

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.

Overview of intervention	
Therapeutic indication relevant for the assessment	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 [1].
Method of administration	The capsules should be taken by mouth with water at least 1 hour before or 1 hour after a meal. Teysuno should only be prescribed by a qualified physician experiences in treating cancer patients with anti-neoplastic medicinal products [3] .
Dosing	The proposed dose in mCRC for monotherapy is 30 mg/m^2 b.i.d. days 1-14 with a one-week pause (± bevacizumab 7.5 mg/kg on day 1). For combination therapy (with oxaliplatin or irinotecan), 25 mg/m^2 b.i.d. d 1-14 followed by one-week pause is recommended [3].
Dosing in the health economic model (including relative dose intensity)	120 mg per treatment day – based on body surf area (BSA) of 1.93m^2 (weighted average calculated from average Danish height and weight), RDI is not included.
Should the medicine be administered with other medicines?	As per the therapeutic indication, Teysuno may be administered in combination with oxaliplatin or irinotecan, with or without bevacizumab.

Overview of intervention	
	Patients should be provided with outpatient prescriptions for anti-emetic and anti-diarrheal medicinal products [3].
Treatment duration / criteria for end of treatment	Common regime: - 2 weeks of treatment followed by 1 week of rest (repeated every 3 weeks) - 4 weeks of treatment followed by 2 weeks of rest (repeated every 6 weeks) The number of cycles a patient undergoes can vary, with some patients receiving treatment for a fixed number of cycles, while others continue until disease progression or unacceptable toxicity occurs [3].
Necessary monitoring, both during administration and during the treatment period	Creatinine clearance (CrCl) must be determined for every cycle before the start of treatment on Day 1. Monitoring of haematologic toxicities (i.e., neutrophils, platelets, haemoglobin) during the treatment period [2, 3].
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	*Testing for DPD deficiency recommended* Phenotype and/or genotype testing prior to the initiation of treatment with Teysuno is recommended despite uncertainties regarding optimal pre-treatment testing methodologies. Consideration should be given to applicable clinical guidelines. When this was not done before, testing is recommended for patients for whom a switch to Teysuno from another fluoropyrimidine is considered due to hand-foot syndrome or cardiovascular toxicity in order to determine whether a DPD phenotype and/or genotype could have played a role in the development of toxicity on another fluoropyrimidine [1, 41]. Not included in the model as DPD testing is not directly related to treatment with Teysuno. It is expected that any patient that experiences HFS or cardiotoxicity would be tested for DPD deficiency if has not already been done before initiation of treatment with a fluoropyrimidine as according to Danish Treatment Guidelines of 2023 [25].
Package size(s)	PCTFE/PVC/Al opaque blisters containing 14 capsules each. Each pack contains either 42 capsules, 84 capsules or 126 capsules [2, 3].

3.4.1 Mechanism of action

Teysuno is a fixed-dose combination of three active substances:

- Tegafur, a prodrug of 5-FU, i.e., a drug that is converted into the anti-cancer substance 5-FU after absorption,
- Gimeracil, a DPD inhibitor to prevent degradation of 5-FU by the body,

- Oteracil, an orotate phosphoribosyltransferase (OPRT) inhibitor that decreases the activity of 5-FU in normal gastrointestinal mucosa.

The combination of tegafur, gimeracil, and oteracil was set at 1:0.4:1 molar ratio as optimum in order to maintain 5-FU exposure and thus sustain anti-tumour activity while reducing toxicity associated with 5-FU alone.

Tegafur is a prodrug of 5-FU with good oral bioavailability. Following oral administration, tegafur is gradually converted to 5-FU in vivo, mainly by CYP2A6 enzyme activity in the liver. 5-FU is metabolised by the liver enzyme DPD. 5-FU is activated within cells by phosphorylation to its active metabolite, 5-fluoro-deoxyuridine-monophosphate (FdUMP). FdUMP and reduced folate are bound to thymidylate synthase leading to formation of a ternary complex which inhibits DNA synthesis. In addition, 5-fluorouridine-triphosphate (FUTP) is incorporated into RNA causing disruption of RNA functions [1, 2].

Gimeracil inhibits the metabolism of 5-FU by reversibly and selectively inhibiting DPD, the primary metabolic enzyme for 5-FU, so that higher plasma concentrations of 5-FU are achieved with the administration of a lower dose of tegafur [1, 2].

3.4.2 The intervention in relation to Danish clinical practice

As described in Section 3.3, there is a need for the development of alternatives to 5-FU and capecitabine treatment in patients who are intolerant and experience cardiotoxicity and/or HFS.

In December 2021, a favorable scientific opinion was granted by the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP), recommending Teysuno type II variation: indicated as monotherapy or in combination with oxaliplatin or irinotecan, with or without bevacizumab, for the 1st line treatment of patients with mCRC who are unable to continue standard 1st line 5-FU-containing treatment due to cardiovascular toxicity or HFS that developed in the adjuvant or metastatic setting [1, 45]. It has been shown to be a safe and feasible option after switch from fluoropyrimidines following cardiotoxicity [5]. Teysuno provides a valuable option for patients to continue their recommended fluoropyrimidine-based treatment, thereby avoiding the difficult trade-off between the continued use of standard 1st line 5-FU-containing treatment and the associated risk of toxicity. This advantage allows for sustained therapeutic benefits without compromising patient safety.

It's important to emphasize that the use of Teysuno in this context is not intended to replace any 1st line therapies but rather serve as an option for clinicians to consider in the event of toxicity.

3.4.2.1 Management of patients who experience cardiotoxicity

As described in the 2022 European Society of Cardiology (ESC) guidelines[46]: where cardiotoxicity leads to coronary vasospasm (secondary to fluoropyrimidines and in the absence of an alternative therapy), a rechallenge – although controversial – can be considered in a monitored unit after exclusion of severe coronary artery disease and

initiation of prophylactic therapy with long-acting nitrates and calcium channel blockers [46]. Even with these prophylactic treatments, however, dose reduction and rechallenge still lead to recurrence of cardiotoxicity in 44%-90% of patients [5]. This illustrates the challenge of continuing (potentially beneficial) fluoropyrimidine treatment once cardiotoxicity has occurred and it is recommended that when the completion of the fluoropyrimidine-based regimen is limited, clinicians should consider other, less cardiotoxic alternatives and ways of management [47].

After the EMA approved Teysuno for treating metastatic CRC patients unable to continue treatment with another fluoropyrimidine due to HFS or cardiotoxicity, the revised 2022 European Society for Medical Oncology (ESMO) guidelines for CRC recommend Teysuno as an alternative fluoropyrimidine when intravenous 5-FU- or capecitabine-based chemotherapy cannot be used due to cardiotoxicity and/or HFS [1]. Subsequently, in a 2023 ESMO publication, recommendations for daily practice were provided stating that: "In patients who experience pain and/or functional impairment due to HFS during treatment with capecitabine or infusional 5-FU, a switch to S-1 is recommended without prior dose reduction of capecitabine/5-FU. S-1 should preferably be initiated at full dose when HFS has decreased to grade 1. In patients with cardiac complaints, in whom an association with capecitabine or infusional 5-FU treatment cannot be excluded, capecitabine/5-FU should be discontinued and a switch to S-1 is recommended."

According to the Danish Treatment Guidelines of 2023 [25], it is emphasized that prior to the initial administration of fluorouracil, capecitabine, or tegafur, all patients exhibiting intolerance to 5-FU should undergo evaluation for DPD activity. Furthermore, the guidelines specify that patients with mCRC encountering cardiotoxicity or hand-foot syndrome while on capecitabine or 5-FU therapy treatment with tegafur/gimeracil/oteracil (S-1) should be considered, as endorsed by the EMA but not evaluated by the Medicines Council [25].

Along with literature [5, 6] and as confirmed by consulted clinical expert, for patients who experience cardiotoxicity during therapy with fluoropyrimidines, the following options are available:

1. *Dose reduction and rechallenge in a cardiac monitoring unit.*
2. *Switch therapy to tegafur/gimeracil/oteracil (Teysuno).*
3. *Switch therapy to trifluridine/tipiracil (Lonsurf).*

Teysuno is a prodrug for 5-FU, comprising a combination of the fluoropyrimidine tegafur and two metabolic inhibitors designed to slow metabolism of 5-FU, gimeracil and oteracil. Lonsurf, on the other hand, is a combination of substances that contain DPD inhibitors. As a result, less of the metabolite FBAL (α-fluoro-β-alanine) is concentrated, and lower rates of cardiac complications may be observed [47].

3.4.2.2 Management of patients who experience severe skin-toxicity

According to consulted clinical expert, for patients experiencing severe skin-toxicity during therapy during fluoropyrimidines, the following options are available:

- Dose reduction and rechallenge.
- Switch to tegafur/gimeracil/oteracil (Teysuno).

3.5 Choice of comparator(s)

According to the literature and as confirmed by consulted clinical expert, the current treatment options for patients who have experienced cardiotoxicity or HFS include switching to Teysuno, switching to Lonsurf, or implementing dose reduction and rechallenge strategies (see **Section 3.3**).

During the dialogue meeting with DMC (28th of February, 2024), it was decided that since Lonsurf had not been assessed by DMC, dose reduction and rechallenge would serve as the relevant treatment comparator to Teysuno.

The relevant comparator is therefore not a specific product but rather a treatment regimen/strategy were dose reduction of an already used therapy is applied.

Overview of comparator	
Generic name	N/A
ATC code	N/A
Mechanism of action	N/A
Method of administration	N/A
Dosing	Dose reduction typically entails switch from continuous dose to bolus dosing. FOLFOX: reduction of Oxaliplatin and 5-FU by 25%; CAPOX: reduction Capecetabine by 25%; FOLFIRI: Dose reduction by 25% of 5-FU and Irinotecan – dosing is based on BSA of 1.93m^2 (weighted average calculated from average Danish height and weight), RDI is not included.
Dosing in the health economic model (including relative dose intensity)	
Should the medicine be administered with other medicines?	N/A
Treatment duration/ criteria for end of treatment	According to DCCG guidelines [25] on medical treatment of mCRC, a rational length for induction treatment length is 6 months. This is assumed for both intervention and comparator
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A
Package size(s)	N/A

3.6 Cost-effectiveness of the comparator(s)

Dose reduction and rechallenge regimens with 5-FU/capecitabine-based treatment has not been evaluated by DMC as such, and cost-effectiveness considerations of this regimen for mCRC patients with toxicity are not available and considered not applicable for the current submission.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Rational for the efficacy outcomes

Evidence from various publications suggests that S-1 could serve as a viable alternative to 5-FU/capecitabine-based therapies for patients with mCRC who experience intolerance due to HFS or cardiac toxicity. In 2022, Derksen et al.[4] conducted a systematic review encompassing randomized clinical phase II and III trials, along with a non-inferiority meta-analysis of S-1-based regimens in comparison to therapies based on 5-FU or capecitabine for mCRC patients. The primary outcome evaluated was Progression-Free Survival (PFS), with secondary outcomes including Overall Survival (OS), objective response rate, and adverse events. These analyses were conducted based on the intention-to-treat population of the studies included, utilizing data pertaining to PFS and OS. These outcomes are also considered relevant for the purpose of the current application.

Overall Survival (OS)

OS is often considered the gold standard efficacy endpoint in oncology clinical trials. It measures the time from randomization or treatment initiation until death from any cause. For metastatic colorectal cancer, where the disease is advanced and often fatal, improving overall survival is a critical goal of therapy.

Progression Free Survival (PFS)

PFS measures the time from randomization or treatment initiation until disease progression or death from any cause. In metastatic colorectal cancer, where disease progression significantly impacts quality of life and treatment decisions, delaying disease progression is an important therapeutic goal.

Objective Response Rate (ORR)

ORR measures the proportion of patients who experience a predefined degree of tumor shrinkage (partial response) or tumor disappearance (complete response) in response to treatment. In metastatic colorectal cancer, where tumor burden reduction can alleviate symptoms and improve quality of life, achieving objective responses is a key therapeutic objective.

Key safety outcomes

Key outcomes when evaluating Teysuno for treating patients with mCRC who can’t continue treatment with other fluoropyrimidines due to HFS or cardiovascular toxicity

include monitoring for cardiotoxicity recurrence and assessing HFS incidence. These outcomes provide specific insights into the safety and tolerability of Teysuno in a challenging patient population where alternative treatment options are limited due to specific toxicities.

Recurrence of Cardiotoxicity: Given the cardiovascular toxicity observed in patients with mCRC on 5-FU- or capecitabine-based therapy, it is essential to track the recurrence of any cardiotoxic events during treatment with Teysuno. This outcome helps evaluate the drug's impact on cardiac health and identifies potential risks or concerns associated with its use in this context.

Incidence of Hand-Foot Syndrome: HFS is a known side effect of fluoropyrimidines. Monitoring the incidence and severity of HFS in patients who cannot tolerate other fluoropyrimidines due to this toxicity is crucial.

Table 4. Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Progression free survival (PFS) Included in the meta-analysis by Derksen et al, (2022) [4]		Time between randomisation to the date of first documented tumour progression	For the time-to-event outcomes Hazard ratios (HRs) with their 95% confidence intervals (CIs) were extracted from the individual studies. Median survival and time to progression with corresponding p-values were extracted. 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.
Overall survival (OS) Included in the meta-analysis by Derksen et al, (2022) [4]		Time from randomization to death from any cause.	
Objective response rate (ORR) Included in the meta-analysis by Derksen et al, (2022) [4]		Not Reported	ORR were extracted from the primary publications of studies included in this review. For ORR, the number of patients with a complete or partial response were extracted and divided by the total number of patients with evaluable lesions for response analysis. Then, risk ratios (RRs) and 99% CIs were calculated.

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Cardiac toxicity Included in study: PLCRC, Punt et al. (2022) [48]	Data were recorded from the start of treatment with capecitabine until the end of treatment with S-1. Data were collected from June 1, 2016, and the cut-off date was June 15, 2021.	Not reported	Diagnosis of cardiac toxicity was based on the occurrence of chest pain suggestive for coronary spasms as assessed by physicians
Recurrence of cardiotoxicity Included in study: CardioSwitch, Osterlund et al. (2022) [5]	(Retrospective study)	Defined and graded using the Cardiac Disorders in National Institutes of Health Common Terminology Criteria for Adverse Events NCI CTCAE 4.0 criteria and causality to fluoropyrmidines was assessed according to World Health Organization Uppsala Monitoring Centre (WHO-UMC)	Based on clinical records (that included evaluations at the local cardiology unit in most patients), two experienced oncologists guided by a cardiologist (AT) [as needed] graded cardiac disorders and determined causality, with consensus reached for all patients
Incidence of Hand-Foot Syndrome Included in studies: SALTO, Kwakman et al, 2017), [30] and PLCRC, Punt et al, (2022) [48]	Patients were evaluated every 3 weeks	Evaluated according to toxicity by NCI CTC	Incidence of any grade HFS as assessed by the local investigators using the National Cancer Institute Common Toxicity Criteria (NCI CTC), version 4.0.

Validity of outcomes

Efficacy outcomes

PFS and ORR are well-established and widely used clinical endpoints in randomized controlled trials for cancer therapies. [49] OS is universally recognized as being unambiguous, unbiased, with a defined endpoint of paramount clinical relevance, and

positive results provide confirmatory evidence that a given treatment extends the life of a patient. [50]

Safety outcomes

The validity of these outcomes relies on their direct relevance to the targeted patient population. Patients who cannot tolerate other fluoropyrimidines due to HFS or cardiovascular toxicity represent a specific subgroup with unique treatment challenges. Assessing recurrence of cardiotoxicity and incidence of HFS directly addresses the clinical need within this population and directly relates to the safety profile of Teysuno in patients with mCRC.

4. Health economic analysis

4.1 Model structure

The current analysis is a cost-minimization analysis (CMA).

The rationale behind this decision is that the expected differences between Teysuno and dose reduction and rechallenge are not related to efficacy outcomes such as progression free survival, overall survival or objective response rate [4]. The distinction between the intervention and the comparator lies in the safety outcomes related to cardiotoxicity and hand-foot syndrome (HFS), as well as the associated costs.

In a prospective study by Kosmas et al., the cardiotoxicity of fluoropyrimidines with different schedules of administration was evaluated. The study demonstrated that reducing the dose by 50%-70% successfully managed cardiotoxicities of grade 1-2 in 20%-60% of patients receiving 5-FU or capecitabine. However, the authors recommend cautious cardiologic monitoring and a thorough risk-benefit assessment due to the limited number of patients studied [51]. In the model between comparator and intervention no differences in the typo of monitoring are made.

The most commonly used first-line combination regimens for metastatic colorectal cancer include FOLFOX, CAPOX and FOLFIRI. The choice of regimen is primarily determined by considering the adverse reaction profile, patient comorbidities and patient preference [25]. Accordingly, for the purpose of this CMA-model, following the literature, dose reduction is applied. For the different treatment regimens (FOLFOX: reduction of Oxaliplatin and 5-FU by 25%; CAPOX: reduction Capecetabine by 25%; FOLFIRI: Dose reduction by 25% of 5-FU and Irinotecan) the relevant dose reduction is applied, followed by calculation of their respective costs (see section 11).

4.2 Model features

Table 5 Features of the economic model

Model features	Description	Justification
Patient population	Adult patients with mCRC, who have experienced cardiotoxicity or HFS on first line treatments containing 5-FU or capecitabine.	In line with Teysuno's indication
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	1 cycle and 6 months	Treatment duration varies individually, in the studies of Teysuno, the median number of cycles varies from 4 to 12 with ranges of 1 up to 98.
Cycle length	N/A	N/A, as CMA is used
Half-cycle correction	N/A	N/A, as CMA is used
Discount rate	N/A	N/A, as time horizon is <1 year
Intervention	Teysuno, both as monotherapy and combination therapy	
Comparator(s)	Dose reduction and rechallenge	According to literature [44, 47]. Validated by Danish clinical expert. Requested as comparator by DMC.
Outcomes	N/A	N/A, as CMA is used

5. Overview of literature

5.1 Literature used for the clinical assessment

In December 2021, CHMP recommended the approval of Teysuno for use in metastatic colorectal cancer [45]. The decision was informed by a comprehensive analysis of indirect evidence derived from the meta-analysis by Derksen et al., (2022) encompassing efficacy data from all phase II and III trials of Teysuno-based regimens versus those based on 5-FU and capecitabine in mCRC [ref]. Additionally, exploratory efficacy results from two supplementary studies conducted on European patients transitioning to Teysuno-based therapy due to fluoropyrimidine-related toxicity provided direct evidence within the target population (Punt et al, 2022 [48] and Österlund et al, 2022 [5]).

In the EMA assessment report, it was concluded that: "*With the restricted indication, exploratory efficacy data in European patients who switched to S-1 (Teysuno) 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*" [45].

In the current application aiming to introduce Teysuno as an alternative treatment to 5-FU dose reduction regimens following cardiotoxicity, it is presumed reasonable that the efficacy and safety studies forming the basis for the positive CHMP opinion remain pertinent also in this context. It's important to emphasize that the use of Teysuno in this context is not intended to replace any 1st line therapies but rather serve as an option for clinicians to consider in the event of cardiotoxicity/HFS. As described in section 4 the expected differences between Teysuno and dose reduction and rechallenge are not related to efficacy outcomes such as progression free survival, overall survival or objective response rate [4], the distinction between the intervention and the comparator lies in the safety outcomes related to cardiotoxicity and HFS. It should also be 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.

Based on the above foundation, no systematic literature review on Teysuno compared to dose reduction regimens in patients experiencing cardiotoxicity has been undertaken.

Essential literature for this application is listed in the table below.

Table 6 Relevant literature included in the assessment of efficacy and safety [sample text in table for full paper, data on file and conference abstract]

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Derksen JWG et al. Systematic review and non-inferiority meta-analysis of randomised phase II/III trials on S-1-based therapy versus 5-fluorouracil- or capecitabine-based therapy in the treatment of patients with metastatic colorectal cancer. Eur J Cancer. 2022 May;166:73-86. doi: 10.1016/j.ejca.2022.02.004. Epub 2022 Mar 10. PMID: 35279472. [4]	N/A Meta-analysis	N/A	N/A	S-1 monotherapy or in combination with oxaliplatin or irinotecan, ± bevacizumab vs. Capecitabine or 5-FU monotherapy or in combination with oxaliplatin or irinotecan, ± bevacizumab
Kwakman, J.J.M., et al., 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. *Ann Oncol*, 2017. 28(6): p. 1288-1293. [31] Kwakman, J.J.M., et al., 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	SALTO	NCT01918852	Start: 12/2013 Completion: 03/2018	S-1: 30 mg/m^2 twice daily on days 1-14 vs. Capecitabine: 1250 mg/m^2 (patients >70 years) or 1000 mg/m^2 (patients ≥70 years), administered orally twice daily on days 1-14 for patients aged ≥18 years with previously untreated mCRC

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Cancer Group. *Clin Colorectal Cancer*, 2019. 18(2): p. e229-e230. [52]				
Winther, S. B. et al. 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. *Lancet Gastroenterol Hepatol* 4: 378-88 (2019)[30]	NORDIC9	EudraCT: 2014-000394-39	Start: 02/2015 Completion: 09/2018	Sequential full-dose monotherapy: S-1 30 mg/m^2 orally twice daily on days 1-14 every 3 weeks, followed by second-line treatment at progression with irinotecan (250 mg/m^2 intravenously on day 1 every 3 weeks or 180 mg/m^2 intravenously on day 1 every 2 weeks) vs. Sequential dose-reduced combination chemotherapy: S-1 20 mg/m^2 orally twice daily on days 1-14 and oxaliplatin 100 mg/m^2 intravenously on day 1 every 3 weeks followed by second-line treatment at progression with S-1 20 mg/m^2 orally twice daily on days 1-14 and irinotecan 180 mg/m^2 intravenously on day 1 every 3 weeks for patients with mCRC aged 70 years and older
Punt, C. J. A. et al, Long-Term Safety Data on S-1 Administered After Previous Intolerance to	PLCRC	NCT02070146	Start: 01/06/2016 Completion: 15/06/2021	S-1 at either 30 mg/m^2 bid or 25 mg/m^2 bid when given as monochemotherapy, or 25 mg/m^2

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Capecitabine-Containing Systemic Treatment for Metastatic Colorectal Cancer. *Clinical Colorectal Cancer* (2022)[48]				bid when given in combination with oxaliplatin vs. N/A for patients with metastatic CRC in whom treatment was switched from capecitabine to S-1
Osterlund, p. et al, Continuation of fluoropyrimidine treatment with S-1 after cardiotoxicity on capecitabine- or 5-fluorouracil-based therapy in patients with solid tumours: a multicentre retrospective observational cohort study. *ESMO Open 7(3): 100427* (2022)[5]	CardioSwitch	NCT04260269	Start: 01/06/2018 Completion: 12/2025	S-1-based treatment vs. N/A
Kwakman, J. J. M et al. Incidence of capecitabine-related cardiotoxicity in different treatment schedules of metastatic colorectal cancer: A retrospective analysis of the CAIRO studies of the Dutch Colorectal Cancer Group. *Euro. J. of Cancer* 76 (2017)[29]	CARIO, CARIO2, CARIO3	N/A	Retrospective analysis of CAIRO studies	N/A
Jurczyk M, et al,. Cardiotoxicity of Fluoropyrimidines: Epidemiology, Mechanisms, Diagnosis, and	N/A	N/A	N/A	N/A

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Management. J Clin Med. 2021 Sep 27;10(19):4426. doi: 10.3390/jcm10194426. PMID: 34640443; PMCID: PMC8509845. [47]				
Kwakman, J.J.M, et al. Case series of patients treated with the oral fluoropyrimidine S-1 after capecitabine-induced coronary artery vasospasm. *Euro. J. of Cancer* 81 (2017)[32] Kwakman, J.J.M, et al. Tolerability of the oral fluoropyrimidine S-1 after hand-foot syndrome-related discontinuation of capecitabine in western cancer patients. *Acta Oncologica* (2017)[22]	N/A (case series)	N/A	N/A	S-1 at a dose of 20 mg/m^2 bid, 25 mg/m^2 bid, or 30 mg/m^2 bid, with or without oxaliplatin and/or bevacizumab vs. N/A for patients in the Netherlands and Denmark with any type of cancer who switched from capecitabine to S-1

* If there are several publications connected to a trial, include all publications used.

5.2 Literature used for the assessment of health-related quality of life

Not applicable as the distinction between the intervention and the comparator solely lies in the safety outcomes related to cardiotoxicity and HFS.

Table 7 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Authors. Article title. Journal. Year; volume(issue): pp [reference number]	E.g. First line metastatic recurrence	

5.3 Literature used for inputs for the health economic model

Not applicable as the distinction between the intervention and the comparator lies in the safety outcomes related to cardiotoxicity and HFS. Moreover, given that the current health economic analysis is a CMA, there's no necessity for incorporating inputs from an extensive and systematic literature review to assess cost-effectiveness in the health economic model.

Table 8 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Authors. Article title. Journal. Year; volume (issue): pp [reference number]	Overall survival	Targeted literature review	Section 9.2. Table X

6. Efficacy

Not applicable - The expected differences between Teysuno and dose reduction and rechallenge are not related to efficacy outcomes such as progression free survival, overall survival or objective response rate [4]. The distinction between the intervention and the comparator lies in the safety outcomes related to cardiotoxicity and HFS, as well as the associated costs. Further, when considering dose reduction and rechallenge with FU-containing treatment as the selected comparator, the available literature on this specific approach is limited. The literature consists of mainly case reports and case series, with even fewer publications describing the efficacy and safety of dose reduction or rechallenge in the patient population relevant to this submission. Currently there is no head-to-head study comparing Teysuno to dose reduction and rechallenge with FU-containing treatment. It should also be 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. EMA approval was based on the meta-analysis by Derksen et al. and the result from this study is presented in section 7. Comparative analyses of efficacy.

6.1 Efficacy of [intervention] compared to [comparator] for [patient population]

6.1.1 Relevant studies

Table 9 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
Study 1	Randomized phase III / open-label / placebo-control/ active comparator-control			Treatment, administration, dosing	Treatment, administration, dosing	[All primary and secondary outcomes in the study must be listed with timepoints.]
Trial name, NCTxxxx (reference for publication(s))	Randomized, double blinded, placebo controlled, phase III study of drug X versus placebo.	12 weeks double blinded period follow by 40 weeks open label (52 weeks in total). Patients that were randomized to placebo switched to open label drug X after week 12.	Treatment naive patients with active disease and incomplete response to conventional treatment.	Drug X (subcutaneous administration), 90 mg week 0, 4, 8, 12 hereafter every 12 weeks.	Drug X matching placebo (s.c.) week 0, 4, 8, 12 hereafter every 12 weeks.	ACR20-response (week 24), ACR50-response (week 24), ACR70-response (week 24), PASI75-response (week 24), PASI90-response (week 24), PASI100 response (week 24), body surface area affected by psoriasis (week 24), HAQ-DI-score (week 24), SF-36 PCS-score (week 24), mTSS-score (week 24), Leeds Enthesistis Index (LEI)-score (week 24), Leeds Dactylitis Index-Basic (LDI_B)-score (week 24), Nail Psoriasis Severity Index (NAPSI) (week 24).

6.1.2 Comparability of studies

6.1.2.1 Comparability of patients across studies

Table 10 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	[Study name]		[Study name]		[Study name]	
	[int./ comp.]	[int./ comp.]	[int./ comp.]	[int./ comp.]	[int./ comp.]	[int./ comp.]
Age						
Gender						
[characteristic]						
[characteristic]						
[characteristic]						

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

Table 11 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)	Value used in health economic model (reference if relevant)
Age		
Gender		
Patient weight		
[characteristic]		
[characteristic]		

6.1.4 Efficacy – results per study

7. Comparative analyses of efficacy

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. Derksen et al., 2022. [4]

Background: S-1 is an oral fluoropyrimidine that is increasingly used in Western countries for the treatment of metastatic colorectal cancer (mCRC). The current study aimed to provide up-to-date and conclusive evidence on the non-inferiority of S-1-based regimens compared to 5-FU- or capecitabine-based therapy in the treatment of patients with mCRC by means of a systematic review of randomised clinical Phase II and phase III trials and a non-inferiority metanalysis.

Results: Ten studies (n=2117) were included, of which six studies reported PFS and OS data and 10 studies reported ORR data. S-1-based therapy was shown to be non-inferior to 5-FU/capecitabine-based therapy in terms of PFS (HR_{total} 0.95, 99% CI 0.83e1.08) with its CI upper limit well below the non-inferiority margin (DNI), and at least as efficacious in terms of OS (HR_{total} 0.93, 99% CI 0.81e1.07), and ORR (RR_{total} 1.06, 99% CI 0.90 -1.24).

7.1.1 Differences in definitions of outcomes between studies

No differences identified.

7.1.2 Method of synthesis

MEDLINE, Embase, the Cochrane Central Register of Controlled Trials and Opengrey were searched for randomised clinical trials until May 2021. Data were extracted for progression-free survival (PFS), overall survival (OS), objective response rate (ORR) and adverse events. Pooled effect estimates, stratified by treatment line, with corresponding 99% confidence intervals (CI) were presented. For the time-to-event outcomes, PFS and OS, hazard ratios (HRs) with their 95% confidence intervals (CIs) were extracted from the individual studies. For PFS, a pre-defined non-inferiority margin (ΔNI) of 1.25 was selected. In order to support the meta-analysis, median survival and time to progression with corresponding p-values were extracted.

7.1.3 Results from the comparative analysis

The meta-analysis included ten studies (n = 2117), on the efficacy of Teysuno therapy (=S-1 therapy) (fluoropyrimidine with low rates of cardiotoxicity) versus 5-fluorouracil (5-FU)- or capecitabine-based therapy in the treatment of patients with metastatic colorectal cancer (mCRC). Ten selected studies in the systematic review of randomized clinical phase II and III trials and a non-inferiority meta-analysis were not restricted based

on treatment line and met the following criteria: patients with age >18 years, histologically proved mCRC, and palliative S-1-based (mono or combination) therapy, compared with 5-FU- or capecitabine-based (mono or combination) therapy. There were no major differences in study and patient characteristics among the studies included.

Table 12. Doses of Teysuno/S-1 based therapy for the individual studies included in Dersken et al.

Individual study	Teysuno based therapy dose
Kwakman et al, 2019 [52]	S-1 twice daily on day 1 to 14 at a dose of 30 mg/m^2. Co-treatment with bevacizumab, 7.5 mg/kg intravenously on day 1, was left to the discretion of the local investigator, and was administered to 59% of patients in treatment and control arms. Cycles were repeated every 3 weeks.
Yamada et al, 2018 [53]	IRIS plus bevacizumab, on either a 3-week regimen of intravenous infusions of irinotecan 150 mg/m^2 and bevacizumab 7.5 mg/kg on day 1, oral S-1 80 mg/m^2 twice daily for 2 weeks, followed by a 1-week rest, or a 4-week regimen of irinotecan 100 mg/m^2 and bevacizumab 5 mg/kg on days 1 and 15, S-1 80 mg/m^2 twice daily for 2 weeks, followed by a 2-week rest.
Hong et al, 2012 [54]	SOX: S-1 40 mg/m2 twice daily on days 1-14 and oxaliplatin 130 mg/m^2 on day 1, treatment repeated every 3 weeks and continued for as many as 9 cycles of oxaliplatin-containing chemotherapy, except in instances of disease progression, unacceptable toxicity, or a patient's refusal.
Baba et al, 2017 [55]	SOX plus bevacizumab (7.5 mg/kg of bevacizumab, 130 mg/m^2 of oxaliplatin on day 1 and 40-60 mg of S-1 two times per day for 2 weeks, followed by a 1-week rest).
Kim et al, 2015 [56]	Oxaliplatin was administered intravenously to all patients at a dose of 130 mg/m^2 on day 1. Patients in the SOX arm received S-1 (40 mg/^{2}) twice a day for 2 weeks, followed by a 1-week rest.
Yamazaki et al, 2015 [57]	SOL: S-1 (40-60 mg bid) plus oral LV (25 mg bid) for 1 week and oxaliplatin (85 mg/m^2) on day 1, repeated every 2 weeks.
Sadhario et al, 2020 [58]	A 24-h infusion of irinotecan at a dose of 125 mg/m^2 on days 1 and 15, combined with oral S-1 80 mg/m^2 on days 1-14 (24h-SIRI/B). Bevacizumab was given at a dose of 5.0 mg/kg on days 1 and 15 in both groups. Treatment was repeated every 4 weeks.
Kato et al, 2012 [59]	IRIS + bevacizumab (7.5 mg/kg of bevacizumab and 150 mg/m^2 of irinitecan, and 80 mg/m^2/day of S-1 orally from day 3 until day 16 as a 3-week course).
Yasui et al, 2015 [60]	IRIS: irinotecan (125 mg/m^2) on days 1 and 15 and S-1 (40-60 mg according to body surface area) twice daily for 2 weeks, repeated every 4 weeks.

Individual study	Teysuno based therapy dose
Liu et al, 2015 [61]	SOX: 130 mg/m^2 oxaliplatin by intravenous infusion on day 1, every three weeks, S-1 30-40 mg/m^2 twice daily for 14 days.

Abbreviations: IRIS, irinotecan plus S-1; SOL, S-1, oxaliplatin and leucovorin; SOX, S-1 plus oxaliplatin.

Six out of ten studies reported PFS, and OS data and all ten studies reported ORR data. 1062 patients received S-1-based therapy and 1055 patients received 5-FU/capecitabine-based therapy. Nine studies were conducted in Asia, and one study in Europe. There were no major differences in study and patient characteristics among the studies included.

S-1-based therapy was shown to be non-inferior to 5-FU/capecitabine-based therapy in terms of PFS (HR_{total} 0.95, 99% CI 0.83-1.08) with its CI upper limit well below ΔNI, and at least as efficacious in terms of OS (HR_{total} l 0.93, 99% CI 0.81-1.07), and ORR (RR_{total} 1.06, 99% CI 0.90-1.24). In addition, median PFS (months) per arm was reported by four other studies and median OS per arm was reported by three studies. The studies reported no statistically significant difference in PFS or OS between 5FU/Cap based vs. S-1 based therapy. Results for the meta-analysis as well as the individual studies reporting median PFS and OS are presented in Table 13.

Table 13. Results from the comparative analysis of Teysuno based therapy vs. 5-FU/cap-based therapy for patients with mCRC

Outcome measure	Teysuno based therapy	5-FU/Cap-based therapy	Result
PFS – Meta-analysis	(N=1014)	(N=1013)	HR_{total} 0.95, 99%CI 0.83–1.08
PFS – individual studies:			
Kwakman et al, 2019 [52]	Median PFS (months) = 8.4	Median PFS (months) = 8.2	HR 1.02, 95%CI 0.75-1.40 P=0.89
Yamada et al, 2018 [62]	Median PFS (months) = 10.8	Median PFS (months) = 14.0	HR 0.84, 95%CI 0.70-1.02 P<0.0001 (for non-inferiority)
Hong et al, 2012 [54]	Median PFS (months) = 8.5	Median PFS (months) = 6.7	HR 0.79, 95%CI 0.60-10.4 P<0.0001 (for non-inferiority)
Kim et al 2014 [56]	Median PFS (months) = 7.1	Median PFS (months) = 6.3	HR 0.83, 95%CI 0.66-1.04

Outcome measure	Teysuno based therapy	5-FU/Cap-based therapy	Result
Baba et al, 2017 [62]	Median PFS (months) = 12.2	Median PFS (months) = 11.7	HR 1.051, 95%CI 0.876-1.262 P=0.0115 (for non-inferiority)
Kim et al, 2015 [56]	Median PFS (months) = 6.1	Median PFS (months) = 7.4	P=0.599
Yamazaki et al, 2015 [57]	Median PFS (months) = 9.6	Median PFS (months) = 6.9	HR 0.83, 95%CI 0.49-1.40
Sadahiro et al, 2020 [58]	Median PFS (months) = 10	Median PFS (months) = 10.2	P=0.375
Kato et al,2012 [59]	Median PFS (months) = 11.3	Median PFS (months) = 10.6	P=0.71
Liu et al, 2015 [61]	Median PFS (months) = 8.5	Median PFS (months) = 8.2	P>0.05
Yasui et al, 2015 [60]	Median PFS (months) = 5.8	Median PFS (months) = 5.1	HR 1.06, 95%CI 0.87-1.29 P=0.022 (for non-inferiority)
OS – Meta-analysis			HR_{total} 0.93, 99%CI 0.81–1.07
OS – individual studies:			
Kwakman et al, 2019 [52]	Median OS (months) = 17.0	Median 0S (months) = 17.1	HR 1.07, 95%CI 0.76-1.49 P=0.70
Baba et al, 2017 [62]	Median OS (months) = 29.6	Median OS (months) = 29.7	HR 1.018, 95%CI 0.823-1.258
Kim et al, 2015 [63]	Median OS (months) = 18.7	Median 0S (months) = 20.1	P=0.340
Yamazaki et al, 2015 [57]	Median OS (months) = 29.9	Median OS (months) = 25.9	HR 0.91, 95%CI 0.55-1.49
Sadahiro et al, 2020 [58]	Median OS (months) = 29.7	Median OS (months) = 28.8	P=0.823

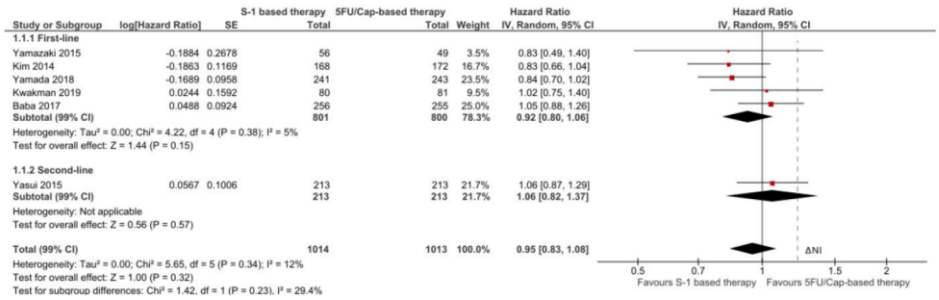
Outcome measure	Teysuno based therapy	5-FU/Cap-based therapy	Result
Yasui et al, 2015 [60]	Median OS (months) = 17.8	Median OS (months) = 17.4	HR 0.900, 95%CI 0.728-1.112
Liu et al, 2015 [61]	Median OS (months) = 18.8	Median OS (months) = 19.2	P>0.05
Hong et al, 2012 [54]	Median OS (months) = 21.2	Median OS (months) = 20.5	HR 0.82, 95%CI 0.61-1.10 P=0.18
Kim et al 2014 [56]	19.0	18.4	HR 0.86, 95%CI 0.68-1.08
Yamada et al, 2018 [62]	Median OS (months) = 34.9	Median OS (months) = 33.6	HR 0.86, 95%CI 0.66-1.13
ORR – meta-analysis	(N=1062)	(N=1055)	RR_{total} 1.06, 99%CI 0.90–1.24

Abbreviations: HR, hazard ratio; OS, overall survival; ORR, overall response rate; PFS, progression-free survival; RR, response rate.

7.1.4 Efficacy – results per 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 2). No significant heterogeneity was detected for PFS (I2 = 12%, P = 0.34).

Figure 2. Forest plot for the comparison S-1 based therapy vs. 5FU/Cap based therapy, outcome PFS

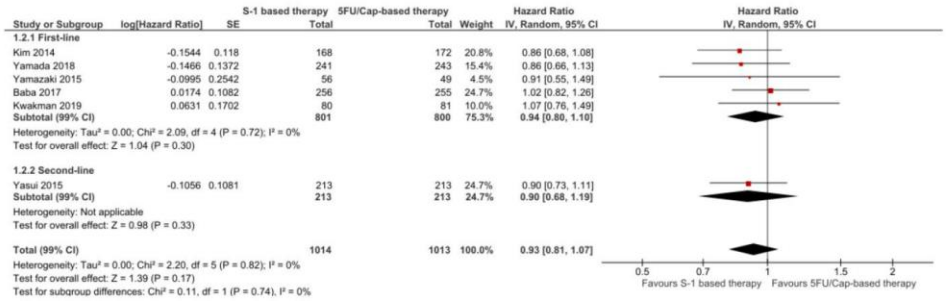


S-1, oral anticancer drug composed of tegafur (FT), 5-chloro-2, 4-dihydroxypyridine (gimestat [CDHP]) and oteracil potassium (Oxo); 5FU, 5-fluorouracil; Cap, capecitabine; SE, standard error; IV, inverse variance; CI, confidence interval; ΔNI, non-inferiority margin; PFS, progression-free survival.

7.1.5 Efficacy - results per 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 3). No significant heterogeneity was detected for OS (I2 = 0%, P = 0.82).

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

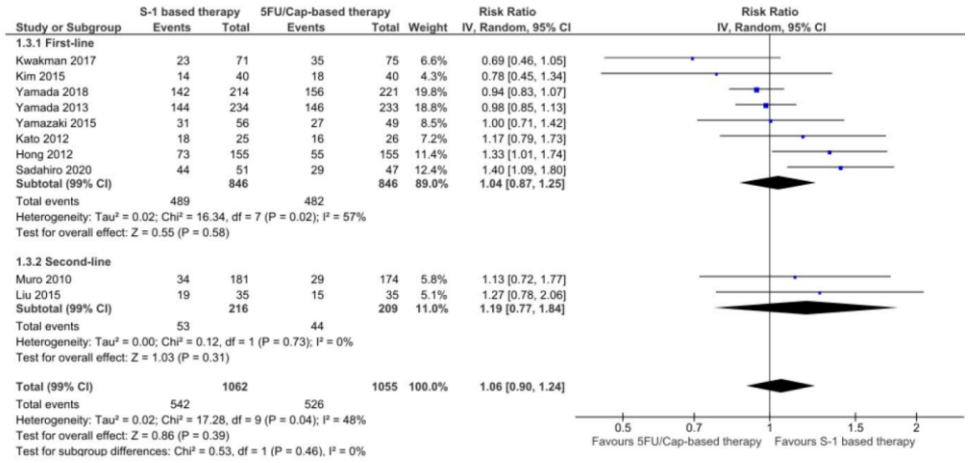


S-1, oral anticancer drug composed of tegafur (FT), 5-chloro-2, 4-dihydroxypyridine (gimestat [CDHP]) and oteracil potassium (Oxo); 5FU, 5-fluorouracil; Cap, capecitabine; SE, standard error; IV, inverse variance; CI, confidence interval; OS, overall survival.

7.1.6 Efficacy - results per 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 4). Moderate heterogeneity was detected for ORR (I2 = 48%, P = 0.04).

Figure 4. 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.

The conclusion of the meta-analysis was that S-1-based therapy is non-inferior to 5-FU/capecitabine-based therapy in the treatment of mCRC regarding PFS and at least as efficacious as 5-FU/capecitabine-based therapy [4].

8. Modelling of efficacy in the health economic analysis

Not applicable, CMA is conducted.

8.1 Presentation of efficacy data from the clinical documentation used in the model

8.1.1 Extrapolation of efficacy data

8.1.1.1 Extrapolation of [effect measure 1]

Table 14 Summary of assumptions associated with extrapolation of [effect measure]

Method/approach	Description/assumption
Data input	Not applicable
Model	Not applicable
Assumption of proportional hazards between intervention and comparator	Not applicable
Function with best AIC fit	Not applicable
Function with best BIC fit	Not applicable
Function with best visual fit	Not applicable
Function with best fit according to evaluation of smoothed hazard assumptions	Not applicable
Validation of selected extrapolated curves (external evidence)	Not applicable
Function with the best fit according to external evidence	Not applicable
Selected parametric function in base case analysis	Not applicable

Method/approach	Description/assumption
Adjustment of background mortality with data from Statistics Denmark	Not applicable
Adjustment for treatment switching/cross-over	Not applicable
Assumptions of waning effect	Not applicable
Assumptions of cure point	Not applicable

8.1.1.2 Extrapolation of [effect measure 2]

8.1.2 Calculation of transition probabilities

Table 15 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
Disease-free survival	Recurrence		
	Death		
Recurrence	Death		
Health state/Transition			

8.2 Presentation of efficacy data from [additional documentation]

8.3 Modelling effects of subsequent treatments

8.4 Other assumptions regarding efficacy in the model

8.5 Overview of modelled average treatment length and time in model health state

Table 16 Estimates in the model

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
[Name of intervention]	[X months/years]	[X months/years]	[X months/years]
[Name of comparator]	[X months/years]	[X months/years]	[X months/years]

Table 17 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model)

Treatment	Treatment length [months]	Health state 1 [months]	Health state 2 [months]
[Intervention]	[xx]	[xx]	[xx]
[Comparator]	[xx]	[xx]	[xx]

9. Safety

9.1 Safety data from the clinical documentation

The meta-analysis by Derksen et al., serves as the basis for the clinical documentation and the safety results from the study are presented below. However, please note that the reported safety results do not fully correspond to the information in example Table 18; therefore, this table has not been used to present the results.

Table 18 Overview of safety events. State the time period the table covers.

	Intervention (N=x) (source)	Comparator (N=x) (source)	Difference, % (95 % CI)
Number of adverse events, n			
Number and proportion of patients with ≥1 adverse events, n (%)			
Number of serious adverse events*, n			
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)			
Number of CTCAE grade ≥ 3 events, n			
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)			
Number of adverse reactions, n			
Number and proportion of patients with ≥ 1 adverse reactions, n (%)			
Number and proportion of patients who had a dose reduction, n (%)			
Number and proportion of patients who discontinue treatment regardless of reason, n (%)			
Number and proportion of patients who			

	Intervention (N=x) (source)	Comparator (N=x) (source)	Difference, % (95 % CI)
discontinue treatment due to adverse events, n (%)			

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).
§ CTCAE v. 5.0 must be used if available.

9.1.1 Summary of safety from the meta-analysis (Derksen et al, 2022)

In the meta-analysis by Derksen et al, treatment-related toxicity data from five studies that investigated oxaliplatin-containing S-1 combination therapy [54, 57, 61, 63, 64], and three studies that investigated irinotecan-containing S-1 combination therapy [58, 59, 65], were extracted.

Oxaliplatin-containing S-1 combination therapy
Significant differences in any grade toxicity between S-1 based therapy and 5-FU/ capecitabine-based therapy include **leukopenia** (RR 0.85, 95% CI 0.76, 0.94), **HFS** (RR 0.50, 95% CI 0.27, 0.91) and **diarrhoea** (RR 1.35, 95% CI 1.17, 1.55) (Table 19). Significant differences in toxicities ≥grade 3 include **anorexia** (RR 2.55, 95% CI 1.33, 4.89) **diarrhoea** (RR 2.41, 95% CI 1.45, 4.02) and **stomatitis/mucositis** (RR 5.30, 95% CI 1.16, 24.17) (Table 19) [4].

Irinotecan-containing S-1 combination therapy
Significant differences in any grade toxicity between S-1 based therapy and 5-FU/ capecitabine-based therapy include **neutropenia** (RR 0.80, 95% CI 0.68, 0.94) and **anaemia** (RR 1.26, 95% CI 1.03, 1.54). Toxicities ≥ grade 3 were only significant for **neutropenia** (RR 0.80, 95% CI 0.65, 0.98). Of note, HFS was not evaluated in any of these studies. Only one study compared mono-chemotherapy of capecitabine with S-1, which showed significantly less any grade and ≥grade 3 HFS but more ≥grade 3 anorexia and any grade diarrhoea in S-1 treated patients.

Table 19. Any grade and ≥grade 3 treatment-related toxicities of S-1 based versus 5-FU/capecitabine-based therapy (oxaliplatin-containing S-1 combination therapy)

Adverse events	S-1 based tharpy	5-FU/Capecitabin based therapy	RR (95 % CI,)
Any grade toxicity	**Events/Total**	**Events/Total**	
Leukopenia	223/552	265/543	0.85 (0.76- 0.94)
HFS	66/496	112/492	0.50 (0.27, 0.91)
Diarrhoea	271/552	199/543	1.25 (1.17-1.55)

Adverse events	S-1 based tharpy	5-FU/Capecitabin based therapy	RR (95 % CI,)
Toxicity ≥grade 3	**Events/Total**	**Events/Total**	
Anorexia	33/517	12/508	2.55 (1.33- 4.89)
Diarrhoea	50/552	20/543	2.41 (1.45-4.02)
Stomatitis/mucositis	10/552	0/543	5.30 (1.16- 24.17)

RRs below 1 favour S-1 based therapy, while RRs above 1 favour 5-FU/capecitabine-based therapy [4]

Table 20. Any grade and ≥grade 3 treatment-related toxicities of S-1 based versus 5-FU/capecitabine-based therapy (irinotecan-containing S-1 combination therapy)

Adverse events	S-1 based tharpy	5-FU/Capecitabin based therapy	RR (95 % CI,)
Any grade toxicity	**Events/Total**	**Events/Total**	
Neutropenia	184/290	265/543	0.80 (0.68- 0.94)
Anemia	66/496	112/492	1.26 (1.03- 1.54)
Toxicity ≥grade 3	**Events/Total**	**Events/Total**	
Neutropenia	102/290	125/286	0.80 (0.65- 0.98)

9.1.1.1 Safety results by individual studies included in the meta-analysis

The safety results per individual study for the studies included in the meta-analysis that informed the pooled analysis above are summarised below in further detail.

Yamada et al, 2018 [53]

The incidences of grade 3 or higher leukopenia, neutropenia, febrile neutropenia, thromboembolism, and diarrhea were significantly higher in the experimental group than in the control group. In post hoc analyses, the incidences of grade 3 or higher diarrhea in patients with a creatinine clearance (CCr) of 70 ml/min or higher and patients with a CCr of <70 ml/min at enrollment were, respectively, 6.7% and 6.5% in the control group as compared with 11.5% and 19.6% in the experimental group. The incidences of grade 3 or higher sensory neuropathy, hand–foot syndrome, and paralytic ileus were significantly higher in patients receiving the control treatment than in those receiving the experimental treatment. Further information on the types of adverse events occurring in each treatment regimen is given in supplementary Table S3, available at Annals of Oncology online. There was one treatment-related death among patients given the CapeOX regimen and four treatment-related deaths among patients given the S-1 and irinotecan plus bevacizumab regimen.

Table 21. Adverse events reported in Yamada et al, 2018

Table 2. Adverse events

	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.

Hong et al, 2012 [54]

There was a higher incidence of grade 3-4 neutropenia (49 [29%] vs 24 [15%]), thrombocytopenia (37 [22%] vs 11 [7%]), and diarrhoea (16 [10%] vs seven [4%]) in the SOX group than in the CapeOX group. The frequency of any grade of hand-foot syndrome was greater in the CapeOX group than it was in the SOX group (51 [31%] vs 23 [14%]).

Baba et al, 2017 [54]

The incidences of grade 3 or higher leucopenia and neutropenia were significantly higher in the mFOLFOX6 plus bevacizumab group (8.4% and 33.7%, respectively) than in the SOX plus bevacizumab group (2.4% and 8.8%, respectively). The incidences of grade 3 anorexia and diarrhoea were significantly higher in the SOX plus bevacizumab group (5.2% and 9.2%, respectively) than in the mFOLFOX6 plus bevacizumab group (1.2% and 2.8%, respectively). The incidence of alopecia was significantly higher in the mFOLFOX6 plus bevacizumab group (24.5%) than in the SOX plus bevacizumab group (6.0%). The incidences of sensory neuropathy and hand-foot syndrome (HFS) of any grade did not differ significantly between the mFOLFOX6 plus bevacizumab group (90.0% and 17.7%, respectively) and the SOX plus bevacizumab group (91.2% and 15.6%, respectively). In the updated results of the safety analyses, there were no cases of gastrointestinal perforation, which had occurred in one patient in the mFOLFOX6 plus bevacizumab

group and five patients in the SOX plus bevacizumab group at the time of the primary analysis.4.

Kim et al, 2015 [56]

The most common grade 3/4 hematologic toxicity was thrombocytopenia in both arms (19.0% in the OS arm and 28.6% in the XELOX arm, P = 0.306). Grade 3/4 neutropenia was observed more frequently in the XELOX arm than in the OS arm (2.4% in the OS arm vs. 16.7% in the XELOX arm, P = 0.026). Non-hematologic toxicities were usually mild (mostly grade 1/2), showing no significant differences between the two arms. As anticipated, hand foot syndrome (HFS) of any grade was observed frequently in the XELOX arm (4.8% in the OS arm vs. 23.8% in the XELOX arm, P = 0.013). Grade 3/4 HFS and peripheral neuropathy were observed only in the XELOX arm (4.8% and 7.1%, respectively). There were no treatment-related deaths in either arm.

Table 22. Adverse events reported in Kim et al, 2015

Table 4. Adverse events.

Toxicities	OS (n = 42)		XELOX (n = 42)		*P*-values	
	All grades No. (%)	Grade 3/4 No. (%)	All grades No.(%)	Grade 3/4 No. (%)	All grades	Grade 3/4
Hematologic						
Leukopenia	18 (42.9)	2 (4.8)	21 (50.0)	1 (2.4)	0.512	0.557
Neutropenia	18 (42.9)	1 (2.4)	27 (64.3)	7 (16.7)	0.049	0.026
Anemia	39 (92.9)	4 (9.5)	36 (85.7)	5 (11.9)	0.290	0.724
Thrombocytopenia	26 (54.2)	8 (19.0)	32 (76.2)	12 (28.6)	0.157	0.306
Non-hematologic						
Asthenia	17 (40.5)	3 (7.1)	12(28.6)	2 (4.8)	0.251	0.645
Anorexia	25 (59.5)	2 (4.8)	24 (57.1)	1 (2.4)	0.825	0.557
Nausea	18 (42.9)	3 (7.1)	19 (45.2)	4 (9.5))	0.826	0.457
Vomiting	16 (38.1)	2 (4.8)	17 (40.5)	4 (9.5)	0.823	0.397
Diarrhea	11 (26.2)	3 (7.1)	11 (26.2)	2 (4.8)	1.0	0.645
Constipation	8 (19.0)	0	4 (9.5)	0	0.212	1.0
Stomatitis	4 (9.5)	1 (2.4)	2 (4.8)	0	0.397	0.314
Hand-foot syndrome	2 (4.8)	0	10 (23.8)	2 (4.8)	0.013	0.152
Peripheral neuropathy	21 (50.0)	0	22 (52.4)	3 (7.1)	0.827	0.078
Hyperbilirubinemia	16 (38.1)	1 (2.4)	15 (35.7)	2 (4.8)	0.821	0.557
Elevated AST/ALT	17 (40.5)	0	24 (57.1)	1 (2.4)	0.127	0.314

Abbreviations: AST, aspartic acid transaminase; ALT, alanine transaminase

Yamazaki et al, 2015 [57]

Grade 3 or 4 adverse drug reactions were neutropenia (20 % with SOL vs 41 % with mFOLFOX6), sensory neuropathy (20 vs 2.0 %), anorexia (13 vs 7.8 %), fatigue (11 vs 5.9 %), and diarrhea (11 vs 3.9 %).

Sadahiro et al, 2020 [58]

The incidence rates of grade 3 or higher hematologic toxicities were similar. The incidence rates of grade 3 or higher gastrointestinal toxicities, such as diarrhea, anorexia, and nausea, were higher in the 24h-SIRI/B group.

Table 23. Adverse events reported in Sadahiro et al, 2020

	24 h-SIRI/B (n = 51)		FOLFIRI/B (n = 47)	
	all	grade ≥3	all	grade ≥3
Leukopenia	56.9	15.7	55.3	12.8
Neutropenia	54.9	29.4	53.2	23.4
Hemoglobin	72.5	3.9	66.0	2.1
Thrombocytopenia	5.9	0.0	4.3	0.0
Liver	19.6	0.0	23.4	0.0
Anorexia	72.5	9.8	72.3	2.1
Nausea	74.5	9.8	68.1	2.1
Vomiting	7.8	2.0	6.4	0.0
Diarrhea	60.8	11.8	55.3	6.4
Fatigue	60.8	2.0	63.8	2.1
Stomatitis	43.1	0.0	27.7	0.0
Alopecia	17.6	0.0	10.6	0.0
Hypertension	7.8	2.0	6.4	0.0

Liu et al, 2015 [61]

The toxicity, including myelosuppression, gastrointestinal effects, and neurotoxicity, of the two regimens was also compared. Observed thrombocytopenia in the treatment group was higher than in the control group. In particular, one patient in the treatment group developed grade 3 thrombocytopenia. However, there was no statistical difference in myelosuppression between the two groups (P > 0.05). While hand-foot syndrome was more common in the control group (9/35), no statistical difference was observed for any of the parameters between the two groups.

Table 24. Adverse events reported in Liu et al, 2015

Toxic reactions*	Treatment group					Control group				
	0	I	II	III	IV	0	I	II	III	IV
Myelosuppression										
Leucopenia	7	16	10	2	0	7	15	11	2	0
Thrombocytopenia	25	6	3	1	0	30	5	0	0	0
Gastrointestinal reactions										
Nausea and vomiting	9	15	9	2	0	10	16	8	1	0
Diarrhea	22	7	4	2	0	23	7	3	2	0
Dysfunction of liver	24	10	1	0	0	23	9	3	0	0
Mouth mucositis	30	5	0	0	0	31	4	0	0	0
Neurotoxicity										
Peripheral neuritis	25	7	3	0	0	26	7	2	0	0
Hand-foot syndrome	33	2	0	0	0	28	6	1	0	0

*The comparisons of side-effect items within table 3 were performed the x^2 test (the age was set for the analysis of variance), all the P values were >0.05

9.1.1.2 Safety results summarized from the EMA assessment report [45]

For this submission, safety results from European/Western patient populations are considered relevant and are presented below. Safety results from Asian patients, as included in the EMA assessment, are not detailed here (these are **SOFT- study,** (Yamada et al., 2013 [64])**; SOX vs CAPOX Study in South Korea,** (Hong et al., 2012 [54]); **TRICOLORE study,** (Yamada et al., 2018 [53]); **FIRIS study,** (Muro et al., 2010 [65])).

SALTO- study [31, 52]

A total of 161 previously untreated mCRC patients were randomized 1:1 to receive either capecitabine or S-1. Primary endpoint was incidence of any grade HFS and 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.

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. 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 (Table 25). 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.

Table 25. Incidence of HFS as assessed by investigators

	S1 (N=80) (source)	Capecitabin (N=80) (source)	OR (95 % CI, p)
HFS any grade n (%)	36 (45%)	58 (73%)	0,31 (0,16-0,60, p=0,005)
HFS grade 1, n (%)	22 (28%)	17 (21%)	NR, p=0,37
HFS grade 2, n (%)	11 (14%)	24 (30%)	NR, p=0,02
HFS grade 3, n (%)	3 (4%)	17 (21%)	NR, p=0,003

Table 26 Overview of safety events.

	S1 (N=80) (source)	Capecitabine (N=80) (source)	Difference, % (95 % CI)
Number of adverse events, n	674	570	NR
Number and proportion of patients with ≥1 adverse events, n (%)	80 (100%)	80 (100%)	
Number of serious adverse events*, n	NR	NR	NR
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	4 (5%)	3 (3,75%)	NR

	S1 (N=80) (source)	Capecitabine (N=80) (source)	Difference, % (95 % CI)
Number of CTCAE grade ≥ 3 events, n	52	49	NR, p=0,74

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

NORDIC9 study [66]

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.
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, [66]). 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 (Figure 5). 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).

Figure 5. 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.

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.
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.

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

Case series of patients treated with S-1 after capecitabine-induced coronary artery vasospasm (Kwakman et al., 2017, [67])

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. 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.

Tolerability of S-1 after HFS – related discontinuation of capecitabine in western cancer patients (Kwakman et al., 2017 [30]).

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.

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., 2022 [5])

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. The study included 200 patients with solid tumours that were treated between 2011 and 2020. Data cut-off was 10 May 2021 when median follow-up was 33 months from S-1 initiation, and minimum 50 days. The median age of the patients was 66 years (range 19-86); 118 (59%) were male. Treatment intent was curative in 145 (73%) patients and palliative in 55 (28%) patients. The primary endpoint was recurrence of cardiotoxicity after switch to S-1-based treatment due to 5-FU- or capecitabine-related cardiotoxicity: clinically meaningful if the upper boundary of the 95% confidence interval (CI; by competing risk) is not including 15%. Secondary endpoints included cardiac risk factors, diagnostic work-up, treatments, outcomes, and timelines of 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.

Cardiotoxicity was observed in eight (4%) patients with 95% CI 2.03-7.89, not including the prespecified upper boundary of 15% and thus, the primary endpoint was met. Cardiotoxicity included chest pain in five and tachycardia in three patients and occurred after a median of 16 days (IQR 7-67) from initiation of S-1. The tachycardia episodes were observed earlier than chest pain. Of the eight patients who experienced recurrent cardiotoxicity, three were on S-1 monotherapy, five on combination therapy with oxaliplatin, and one of these also received bevacizumab. 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%) 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 three patients, all receiving adjuvant therapy, and five patients continued treatment with dose reduction in one, temporary discontinuation in two, and no action in two, for 147, 147+,

217+, 336+, and 357 days, respectively. The successful completion rate with S-1-based treatment was 99% (197 patients).

The authors concluded that switching to S-1-based therapy is safe and feasible after development of cardiotoxicity on 5-FU- or capecitabine-based therapy and allows patients to continue their pivotal fluoropyrimidine-based treatment [5].

Figure 6. Adverse events during treatment with the fluoropimidine 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%

Dutch Prospective Colorectal Cancer Cohort (PLCRC) (Punte et al., 2022 [48])

Long-term safety data on S-1 administered after previous intolerance upon treatment with capecitabine, either due to hand-foot syndrome or cardiac toxicity, was studied by Punt and co-workers in patients with mCRC. The data for the long-term safety study were collected from patients (n = 47) who switched from cabecitabine to S-1, participating in the Dutch Prospective Colorectal Cancer Cohort (treated in 13 different Dutch hospitals) from June 1, 2016, and the cut-off date was June 15th, 2021. Prospective Colorectal Cancer Cohort 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 who had been included in 2 previous retrospective studies on a treatment switch from capecitabine to S-1 were excluded. This study was limited to patients developing hand-foot syndrome (HFS), and patients were only followed until the maximum decrease of HFS symptoms without data on long-term follow-up. Median age of the patients was 62 years (range 40-84), 25 (53%) were male.

The median duration of capecitabine treatment was 81 days (range 4-454). In 19 patients (40%) a dose reduction was applied prior to switch to S-1. Reasons for discontinuation of capecitabine were HFS in 36 (77%) patients, coronary artery vasospasms in 10 (21%) patients, and gastrointestinal toxicities in 1 patient (2%). The median number of S-1 cycles was 6 (range 1-36). After switch to S-1, all patients with prior HFS developed a lower grade or complete resolution of symptoms, and in all other patients, symptoms did not recur. Other S-1-related adverse events were limited to grade 1-2. Six patients (13%) discontinued S-1 due to either known fluoropyrimidine-related or bevacizumab-related toxicities. In all patients experiencing HFS during treatment with capecitabine, its severity decreased or completely resolved during treatment with S-1. Since S-1 was usually initiated without delay, some patients continued to experience the same grade of HFS during the first treatment cycle of 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. This study demonstrated that capecitabine can be safely replaced by S-1 upon the occurrence of HFS or cardiac toxicity in patients with mCRC (Punt et al. 2022). Toxicities that were the reason for discontinuation of capecitabine either decreased in severity or completely resolved during treatment with S-1. Most toxicities that occurred during treatment with S-1 concerned gastro-intestinal side effects and were limited to grade 1-2 [48].

9.1.1.2.2 Conclusion on clinical safety in the EMA assessment report

"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." [45]

See section 9.2 for adverse events applied in the model.

Table 27 Adverse events used in the health economic model

Adverse events	Intervention	Comparator		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
Adverse event, n (%)				
[Add a new row for each adverse event included in the model]				

9.2 Safety data from external literature applied in the health economic model

Key safety outcomes for the purpose of evaluating Teysuno for treating patients with mCRC who can't continue treatment with other fluoropyrimidines due to HFS or cardiovascular toxicity include recurrence of cardiotoxicity and HFS. However, the efficacy and safety of dose reduction and rechallenge in the patient population relevant to this submission is not well studied. The literature consists of mainly case reports and case series. Data regarding the incidence of cardiotoxicity and HFS, along with the frequency of cardiotoxicity events in dose reduction and rechallenge 5-FU/cap-based regimens and Teysuno-based regimens, were gathered from the following sources to inform the model:

Kwakman, J.J.M., et al., *Tolerability of the oral fluoropyrimidine S-1 after hand-foot syndrome-related discontinuation of capecitabine in western cancer patients.* Acta Oncol, 2017. **56**(7): p. 1023-1026. [30]
Jurczyk M, et al,. *Cardiotoxicity of Fluoropyrimidines: Epidemiology, Mechanisms, Diagnosis, and Management*. J Clin Med. 2021 Sep 27;10(19):4426. doi: 10.3390/jcm10194426. PMID: 34640443; PMCID: PMC8509845. [47]
Punt CJA, et al,. *Fluoropyrimidine-induced hand-foot syndrome and cardiotoxicity: recommendations for the use of the oral fluoropyrimidine S-1 in metastatic colorectal cancer*. ESMO Open. 2023 Apr;8(2):101199. doi: 10.1016/j.esmoop.2023.101199. Epub 2023 Apr 3. PMID: 37018874; PMCID: PMC10163153. [6]
Osterlund, P., et al., *Continuation of fluoropyrimidine treatment with S-1 after cardiotoxicity on capecitabine- or 5-fluorouracil-based therapy in patients with solid tumours: a multicentre retrospective observational cohort study.* ESMO Open, 2022. **7**(3): p. 100427.[5]

In the assessment of Teysuno by EMA, Osterlund et al. and Kwakman et al. were among the publications included to support the safety evidence of Teysuno [45].

Table 28, Table 29, and Table 30 below, presents the data used in the model.

Table 28. Incidence of recurrent cardiotoxixity and HFS

	Teysuno-based therapy	5-FU/cap-based therapy
Cardiotoxicity		
Jurczyk et al,. (2021) [47]; Punt et al,. (2023) [6]	8%	82-100%
HFS		
Punt et al,. (2023), [6] Kwakman et al,. (2017) [30]	12%	33%

Table 29. Cardiotoxicity events in 5-FU/Capecitabine-based therapy used in the model

5-FU/Capecitabine-based therapy		
Event	**Frequency**	**Source**
Chest pain	63%	Österlund et al (2022) [5]
acute coronary syndrome/myocardial infarction	34%	
Atrial fibrillation	4%	
Cardiac arrest	2%	
Heart failure/cardiomyopathy	4%	
Tachycardias	3%	
Arrhythmia	2%	
Bradycardias	1%	
Prolonged QT	1%	
Hypertension	1%	

Table 30. Cardiotoxicity events in Teysuno-based therapy used in the model

Teysuno-based therapy		
Event	**Frequency**	**Source**
Chest pain	3%	Österlund et al (2022) [5]
Tachicardia	2%	

10. Documentation of health-related quality of life (HRQoL)

Not Applicable as there is no available documentation regarding the HRQoL specifically for the current indication being studied and the model being used for analysis, which is a CMA, does not incorporate HRQoL measurements.

Table 31 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
Instrument 1 (e.g. EQ-5D-5L)	Trial x	Describe purpose of HRQoL instrument (clinical effectiveness, utilities, disutilities etc.)
Instrument 2		
…		

10.1 Presentation of the health-related quality of life [make a subsection for each of the applied HRQoL instruments]

10.1.1 Study design and measuring instrument

10.1.2 Data collection

Table 32 Pattern of missing data and completion

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	E.g. 100	10 (10%)	99	90 (91%)
Time point 1	100	12 (12%)	85	80 (94%)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Time point 2	100	20 (20%)	80	…
Etc.	…	…	…	…

10.1.3 HRQoL results

Example of figure displaying the mean change from baseline through the different data collection time points for both the intervention and comparator:

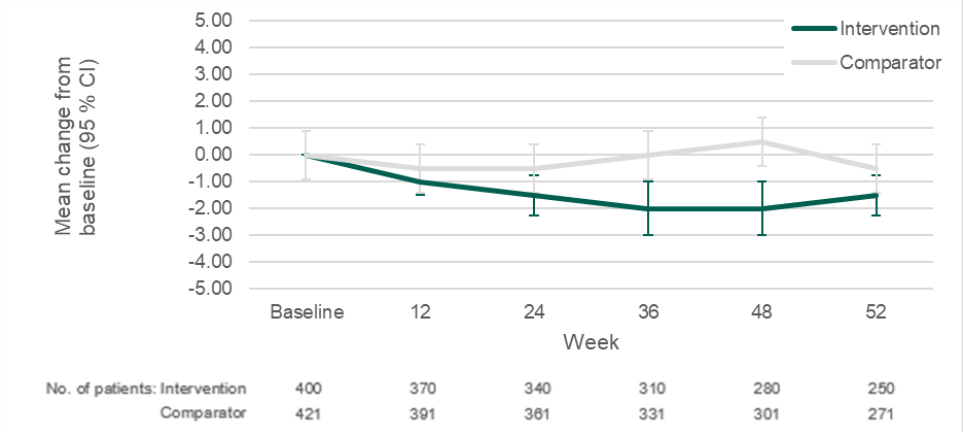


Table 33 HRQoL [instrument 1] summary statistics

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline					
Time point 1					
Time point 2					
…					
Follow-up					

10.2 Health state utility values (HSUVs) used in the health economic model

10.2.1 HSUV calculation

10.2.1.1 Mapping

10.2.2 Disutility calculation

10.2.3 HSUV results

Table 34 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
HSUV A	0.761 [0.700-0.810]	EQ-5D-5L	DK	For example: Estimate is based on mean of both trial arms.
HSUV B	0.761 [0.700-0.810]	EQ-5D-5L	DK	For example: Estimate is based on mean of both trial arms.
…				
[Disutilities]				
…				

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

10.3.1 Study design

10.3.2 Data collection

10.3.3 HRQoL Results

10.3.4 HSUV and disutility results

Table 35 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
HSUV A	0.761 [0.700-0.810]	EQ-5D-5L	DK	Estimate is based on mean of both trial arms.
HSUV B	0.761 [0.700-0.810]	EQ-5D-5L	DK	Estimate is based on mean of both trial arms.
…				
[Disutilities]				
…				

Table 36 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUV A				
Study 1	0.761 [0.700-0.810]	EQ-5D-5L	DK	EQ-5D-5L data was collected in X trial. Estimate is based on mean of both trial arms.
Study 2				
Study 3				
HSUV B				
…				

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
[Disutility A]				
…				

11. Resource use and associated costs

The CMA presented with this application uses drug costs in form as Pharmacy Purchasing Prices (PPPs) from the Danish Medicine Agencies (DMA) database medicinpriser.dk. Furthermore, costs for the management of cardiotoxicities and or HFS, i.e., costs associated with management of adverse events are collected. Costs were estimated using DRG tariffs based on the treatment of cardiotoxicities (Diagnoses related to Chapter IX: diseases of the circulatory system)" and hand-foot syndrome (dermatological treatments) from the tariff list 2024 ("Takstsystem 2024") by the Danish Health Data Authority [68]. The DRG codes that are assumed to be most relevant were assigned to each of the individual adverse events and costs calculated by weighting with their frequency. As discussed in Section 4.1, cautious cardiologic monitoring is recommended for patients who experience adverse events with prior 5-FU therapy and will now be treated with dose reduction and re-challenge (the comparator). Therefore, besides drug costs and costs for management of adverse events, in the comparator arm one additional monitoring visit is assumed to be required.

11.1 Medicine costs - intervention and comparator

Medicine costs in the model are calculated from the PPP for drugs. The treatment, Teysuno is possible to be used in mono- as well as combination therapy. The same applies to the comparator (dose-reduction and rechallenge) where in the model three possible combination therapies (FOLFOX, CAPOX and FOLFIRI) are included in a reduced dose scheme. Drug costs are calculated using PPP prices of the individual drugs from medicinpriser.dk.. Wastage is not included in the calculation of costs and follows a previous evaluation of chemotherapy from 2022 by DMC according to which hospital pharmacies strive to share vials between patients as far as possible [69]. Therefore drug costs are derived using price mg/ml multiplied by dose.

Dose is calculated based on Body Surface Area (BSA) using the Du Bois Formula based on height in cm and weight in kg and recommendations on mg/m^2 dosing of the respective drug according to the Swedish database on cancer treatments [70]. BSA is calculated for an individual of average height and weight using information in population size in 2024 from Statistics Denmark [71]. Height and weight are sourced from the 2021 report on the Danish population's health by the Danish Health authority [72]. Difference in average weight and height by gender are considered by weighing the averages with the share of each gender in the total population. Teysuno doses are based on the information in the SmPC [2]. To take dose-reduction into account the above recommended doses were reduced by 25% (see calculations in the provided CMA and BIA file)

Additional to the below table in this template, the prices of all individual drugs (comparator and intervention) are tabulated in this application document as well as provided according to the Excel file 'Key figures including general mortality' from DMC's website (Added corresponding sheets to the provided CMA and BIA file).

Table 37 Medicine costs used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Teysuno (Gimeracil / oteracil / tegafur)	20.0 mg / 5.8 mg / 15.8 mg x 6 tablets [2] **Cost per cycle: DKK 2,659.82 (monotherapy) DKK 2,679.78 (combination Therapy)**	100% (Not modelled)	21d cycle – 14 days with 120mg Teysuno in monotherapy; 100mg if Teysuno in combination therapy with Oxaliplatin and Irinotecan	
Dose reduction and rechallenge (FOLFOX) (5-FU / Calcium folinate	300mg x1 + 1800mg infusion over 48h /	100% (Not modelled)	14d cycle with 2d 5-FU/1d Calcium folinate / 1d Oxaliplatin per cyle	Yes

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
/ Oxaliplatin)	400mg x1/ 64mg x1 [73] **Cost per cycle: DKK 820**			
Dose reduction and rechallenge (CAPOX) (Capecetabine / Capecetabine / Oxaliplatin)	750mg x1 / 750mg x1/ 130mg x1 [74] **Cost per cycle: DKK 465**	100% (Not modelled)	21d cycle with 2d Capecitabine/ 13d Capecitabine / 1d Oxaliplatin per cyle	Yes
Dose reduction and rechallenge (FOLFIRI) (5-FU / Calcium folinate /Irinotecan)	300mg x1 + 1800mg infusion over 48h/ 400mg x1 /135mg x1 [75] **Cost per cycle: DKK 1,163**	100% (Not modelled)	14d cycle with 2d 5-FU/ 2d Calcium folinate / 1d Irinotecan	Yes

Non-propietary name	Product	Vnr	Strength	Pack size	Mg per pack	Company	PPP
Gimeracil + oteracil + tegafur	Teysuno	482719	15.0 mg / 4.35 mg / 11.8 mg	42	630	Nordic Drugs	**DKK 1,022**
	Teysuno	134175	15.0 mg / 4.35 mg / 11.8 mg	126	1,890	Nordic Drugs	**DKK 3,198**
	Teysuno	185610	20.0 mg / 5.8 mg / 15.8 mg	42	840	Nordic Drugs	**DKK 1,330**
	Teysuno	582618	20.0 mg / 5.8 mg / 15.8 mg	84	1,680	Nordic Drugs	**DKK 2,814**
Oxaliplatin	Oxaliplatin "Accord"	099957	5.0 mg/ml	10 ml	50	Accord Healthcare B.V.	**DKK 145**
	Oxaliplatin "Fresenius Kabi"	073354	5.0 mg/ml	10 ml	50	Fresenius Kabi	**DKK 41**
	Oxaliplatin "Accord"	483681	5.0 mg/ml	20 ml	100	Accord Healthcare B.V.	**DKK 240**
	Oxaliplatin "Fresenius Kabi"	073365	5.0 mg/ml	20 ml	100	Fresenius Kabi	**DKK 69**
	Oxaliplatin "Accord"	559404	5.0 mg/ml	40 ml	200	Accord Healthcare B.V.	**DKK 480**
	Oxaliplatin "Fresenius Kabi"	434128	5.0 mg/ml	40 ml	200	Fresenius Kabi	**DKK 128**
Irinotecan	Irinotecan "Accord"	380487	20.0 mg/ml	5 ml	100	Accord Healthcare B.V.	**DKK 125**
	Irinotecan "Accord"	178347	20.0 mg/ml	15 ml	300	Accord Healthcare B.V.	**DKK 3,050**
	Irinotecan "Accord"	445169	20.0 mg/ml	25 ml	500	Accord Healthcare B.V.	**DKK 350**
	Irinotecan "Fresenius Kabi"	046070	20.0 mg/ml	5 ml	100	Fresenius Kabi	**DKK 125**
	Irinotecan "Fresenius Kabi"	414571	20.0 mg/ml	25 ml	500	Fresenius Kabi	**DKK 350**
	Irinotecan "Sun"	542186	1.5 mg/ml	180 ml	270	SUN Europe	**DKK 426**
	Irinotecan "Sun"	548055	1.5 mg/ml	200 ml	300	SUN Europe	**DKK 459**
	Irinotecan "Sun"	192068	1.5 mg/ml	220 ml	330	SUN Europe	**DKK 385**
	Irinotecan "Sun"	688241	1.5 mg/ml	240 ml	360	SUN Europe	**DKK 344**

Bevacizumab	Abevmy	404176	25.0 mg/ml	4 ml	100	Biocon Biologics Finland OY	**DKK 2,091**
	Avastin	019445	25.0 mg/ml	4 ml	100	Roche Pharmaceuticals A/S	**DKK 1,895**
	Aybintio	161173	25.0 mg/ml	4 ml	100	Samsung	**DKK 2,091**
	Oyavas	441441	25.0 mg/ml	4 ml	100	Stada Nordic	**DKK 2,038**
	Abevmi	430347	25.0 mg/ml	16 ml	400	Biocon Biologics Finland OY	**DKK 7,708**
	Avastin	019781	25.0 mg/ml	16 ml	400	Roche Pharmaceuticals A/S	**DKK 6,987**
	Aybintio	567984	25.0 mg/ml	16 ml	400	Samsung	**DKK 7,708**
	Oyavas	441579	25.0 mg/ml	16 ml	400	Stada Nordic	**DKK 7,515**
Calcium folinate	Calciumfolinat Fresenius Kabi	494327	10.0 mg/ml	100 ml	1,000	Fresenius Kabi	**DKK 600**
	Calciumfolinat Fresenius Kabi	457070	10.0 mg/ml	350 ml	3,500	Fresenius Kabi	**DKK 1,160**
	Calciumfolinat Fresenius Kabi	540548	10.0 mg/ml	1,000 ml	10,000	Fresenius Kabi	**DKK 3,300**
	Calciumfolinate "Sandoz"	489899	10.0 mg/ml	10 ml	100	Sandoz	**DKK 111**
	Calciumfolinate "Sandoz"	563008	10.0 mg/ml	35 ml	350	Sandoz	**DKK 220**
	Calciumfolinate "Sandoz"	183562	10.0 mg/ml	100 ml	1,000	Sandoz	**DKK 340**
5-FU	Fluorouracil "Accord"	068671	50.0 mg/ml	10 ml	500	Accord Healthcare B.V.	**DKK 70**
	Fluorouracil "Accord"	382001	50.0 mg/ml	50 ml	2,500	Accord Healthcare B.V.	**DKK 200**
	Fluorouracil "Accord"	565141	50.0 mg/ml	100 ml	5,000	Accord Healthcare B.V.	**DKK 400**
	Fluorouracil "Pfizer"	546414	50.0 mg/ml	50 ml	2,500	Pfizer	**DKK 160**

	Fluorouracil "Pfizer"	453726	50.0 mg/ml	100 ml	5,000	Pfizer	**DKK 300**
Capecitabine	Capecitabin "Stada"	155487	150 mg	60	9,000	PharmaCoDane	**DKK 650**
	Capecitabin "Stada"	377357	500 mg	120	60,000	PharmaCoDane	**DKK 566**
	Capecitabin "Zentiva"	524775	150 mg	60	9,000	Zentiva	**DKK 679**
	Capecitabin "Zentiva"	596439	500 mg	120	60,000	Zentiva	**DKK 600**
	Capecitabine Accord	161150	150 mg	60	9,000	Accord	**DKK 635**
	Capecitabine Accord	556687	300 mg	60	18,000	Accord	**DKK 567**
	Capecitabine Accord	581539	500 mg	120 ml	60,000	Accord	**DKK 566**

11.2 Medicine costs – co-administration

Not applicable - No co-administration of drugs is included in the model; only the main drug costs were included. While some literature discusses the use of cardioprophylaxis treatment co-administered alongside flouropyrimidine-based treatment, other sources indicate that there are no recommendations for cardioprophylaxis and that the risk of cardiotoxicity is not reduced by prophylaxis. Treatment with Teysuno is not expected to require prophylaxis, as its purpose is to offer a better safety profile in terms of cardiotoxicity. Regarding the implications for the provided health economic model, the inclusion of prophylaxis would only have been relevant for the comparator. Excluding the costs for prophylactic treatment in the model can be considered a conservative assumption, which ultimately favors the comparator.

11.3 Administration costs

In the case of formulations of the drugs intended either intravenous injection or infusion, administration costs according to DRG code 06MA98 (MDC06 1-dagsgruppe, pat. mindst 7 år) (as requested by DMC) [76] were selected. The costs are added for every day intravenous drug infusion is required within a treatment cycle the comparator as well as intervention whenever applicable. The cost is only applied once even when multiple drugs are scheduled for infusion on the same day. The selection of DRG code follows a request by DMC to use this code for administration [77].

Table 38 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
IV infusion	Each time drugs are administered within cycle	DKK 1,561	06MA98 (MDC06 1-dagsgruppe, pat. mindst 7 år)	DRG 2024

11.4 Disease management costs

Not applicable - not included. As described above, the expected differences between Teysuno and dose reduction and rechallenge are not related to efficacy outcomes such as PFS, OS or ORR [4]. The distinction between the intervention and the comparator lies in the safety outcomes related to cardiotoxicity and HFS, as well as the associated costs. It is therefore assumed that disease management costs are equal between intervention and comparator and are thus disregarded in this CMA.

Table 39 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
[Activity]	[E.g. every 3rd week]			DRG 202[X]

11.5 Costs associated with management of adverse events

The expected differences between Teysuno and dose reduction and rechallenge are not related to efficacy outcomes such as PFS, OS or ORR [4]. The distinction between the intervention and the comparator lies in the safety outcomes related to cardiotoxicity and HFS, as well as the associated costs. The CMA therefore includes the costs of treatment of adverse events that occur for both intervention and comparator weighted with their frequency of appearance as described in Section 9.2 (see also Table 41 below). Adverse event treatment has been modelled as a one-time cost. Adverse events are modeled for Teysuno based therapy and 5-FU based therapy. For the latter no difference between FOLFOX, CAPOX or FOLFIRI is made. Costs for adverse events were retrieved using DRG tariff. As discussed in Section 4.2, cautious cardiologic monitoring is recommended for patients who experience adverse events with prior 5-FU therapy and will now be treated with dose reduction and re-challenge (the comparator). Besides costs for management of adverse events, in the comparator arm one additional monitoring visit is assumed to be required.

Table 40 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
Kardiologisk undersøgelse, udvidet	05PR04	2,026.00 DKK
Akut myokardieinfarkt med ST-segment elevation	05MA01	22,387.00 DKK
Andre hjertesygdomme	05MA08	2,167.00 DKK
Hjertesvigt og shock	05MA04	39,083.00 DKK
Hjertearytmi og synkope	05MA07	19,623.00 DKK
Kardiologisk undersøgelse, kompliceret	05PR03	3,543.00 DKK
Hypertension	05MA11	18,261.00 DKK
Dermatologisk procedure	09PR08	7,212.00 DKK
Kardiologisk undersøgelse, udvidet	05PR04	2,026.00 DKK

Average adverse events are grouped into cardiotoxicity-related or HFS management costs and shown in Table 41 below.

Table 41: Treatment cost of recurrent cardiotoxicity and HFS

	Teysuno-based therapy	5-FU/Capecitabine-based therapy
Cardiotoxocity	104.12 DKK	12,016.80 DKK
HFS	865.44 DKK	2,379.96 DKK
Sum	**969.56 DKK**	**14,396.76 DKK**

11.6 Subsequent treatment costs

Not applicable – subsequent treatments are not included. The CMA exclusively focuses on costs related to the treatment of metastatic colorectal cancer.

Table 42 Medicine costs of subsequent treatments

Medicine	Strength	Package size	Pharmacy purchase price [DKK]	Relative dose intensity	Average duration of treatment
[Name of subsequent treatment]	[X]	[X]	[X]		
	[X]	[X]	[X]		
[Name of subsequent treatment]	[X]	[X]	[X]		
	[X]	[X]	[X]		

11.7 Patient costs

Patient costs in form of transportation costs to and from the hospital are applied in the case of intravenous drug administration. The fixed rate of DKK 140 transport cost to and from treatment in hospital as specified by DMC in section 5.2 5. Patient and relative related costs of the recommendations for valuation of unit costs are applied [78].

Table 43 Patient costs used in the model

Activity	Time spent [minutes, hours, days]
Transportation to and from hospital	Lump sum of DKK 140 applied according to Recommendations concerning unit costs by DMC [78]

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Not applicable – palliative care costs between intervention and comparator are thought to roughly the same and are thus excluded from the model.

12. Results

12.1 Base case overview

Table 44 Base case overview

Feature	Description
Comparator	Dose-reduction and rechallenge (weighted average of costs for FOLFOX, CAPOX FOLFIRI))
Type of model	CMA
Time horizon	6 months (adjustable in model)
Treatment line	1st line (only after HFS and/or cardiotoxicity has been experienced with initial treatment).
Measurement and valuation of health effects	N/A – CMA presented
Costs included	Medicine costs Administration costs Monitoring costs Costs of adverse events Patient time and transport costs
Dosage of medicine	Based on weight
Average time on treatment	Intervention: 6 months Comparator: 6 months
Parametric function for PFS	N/A
Parametric function for OS	N/A
Inclusion of waste	N/A
Average time in model health state Health state 1	N/A - CMA

Feature	Description
Health state 2	
Health state 3	
Death	

12.1.1 Base case results

The base case consists of a weighted average of 50% of patients receiving Teysuno as monotherapy and the remaining 50% receiving Teysuno as combination therapy together with oxaliplatin and irinotecan. The comparator is a weighted average of FOLFOX, CAPOX and FOLFIRI therapy in reduced dose were each is weighted with one third. Results comparing Teysuno mono- and combination therapy with each of the comparator regimes are presented as deterministic sensitivity analysis below in Section 12.2.1. As can be seen in Table 45, Teysuno is associated with cost savings both due to lower drug costs and lower costs for the treatment of adverse events.

Table 45 Base case results, discounted estimates

Time horizon: 6 months	Teysuno therapy (50% mono – 50% combination)	Dose reduction and rechallenge (combined)	Difference
Medicine costs	DKK 24,154	DKK 8,863	DKK 15,291
Medicine costs – co-administration	-	-	-
Administration	DKK 16,072	DKK 31,675	DKK -21,494 (Teysuno cost saving)
Disease management costs	-	-	-
Costs associated with management of adverse events (incl. Monitoring)	DKK 11,578	DKK 33,993	DKK -17,921 (Teysuno cost saving)
Subsequent treatment costs	-	-	-
Patient costs	DKK 913	DKK 3,044	DKK -2,131 (Teysuno cost saving)
Palliative care costs	-	-	-
Total costs	**DKK 51,320**	**DKK 77,575**	**DKK -26,255 (Teysuno cost saving)**

Time horizon: 6 months	Teysuno therapy (50% mono – 50% combination)	Dose reduction and rechallenge (combined)	Difference
Life years gained (health state A)	-	-	-
Life years gained (health state B)	-	-	-
Total life years	**-**	**-**	**-**
QALYs (state A)	-	-	-
QALYs (state B)	-	-	-
QALYs (adverse reactions)	-	-	-
Total QALYs	**-**	**-**	**-**
Incremental costs per life year gained		**-**	
Incremental cost per QALY gained (ICER)		**-**	

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

Uncertainty in the model is present in terms of share of patients on Teysuno mono- or combination therapy on the intervention side. Uncertain is also what share of patients are on either FOLFOX, CAPOX or FOLFIRI as reduced dose and rechallenge regime on the comparator side. To address this uncertainty, Teysuno monotherapy and combination therapy are also individually compared with FOLFOX, CAPOX or FOLFIRI. See Table 46.

Table 46 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	-	Base case	DKK -26,255	-	-
Difference, TEYSUNO monotherapy – combined comparator	Comparison Teysuno monotherapy vs combined FOLFOX, CAPOX and FOLFIRI	Uncertainty concerning share of patients with Teysuno mono- or	DKK -38,373	-	-

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Difference, TEYSUNO monotherapy - FOLFOX	Comparison Teysuno monotherapy vs FOLFOX	Teysuno combination therapy and share of patients with either FOLFOX, CAPOX or FOLFIRI	DKK -49,867	-	-
Difference, TEYSUNO monotherapy - CAPOX	Comparison Teysuno monotherapy vs CAPOX		DKK -14,236	-	-
Difference, TEYSUNO monotherapy - FOLFIRI	Comparison Teysuno monotherapy vs FOLFIRI		DKK -51,014	-	-
Difference, TEYSUNO combination therapy – Combined comparator	Comparison Teysuno as combination therapy vs combined FOLFOX, CAPOX and FOLFIRI		DKK -14,137	-	-
Difference, TEYSUNO combination therapy - FOLFOX	Comparison Teysuno combination therapy vs FOLFOX		DKK -25,632	-	-
Difference, TEYSUNO combination therapy - CAPOX	Comparison Teysuno combination therapy vs CAPOX		DKK 10,000	-	-
Difference, TEYSUNO combination therapy - FOLFIRI	Comparison Teysuno combination therapy vs FOLFIRI		DKK -26,779	-	-

12.2.2 Probabilistic sensitivity analyses

Not applicable – a probabilistic Sensitivity analysis is not provided as the health economic model is a CMA.

13. Budget impact analysis

The Budget Impact Analysis estimates the impact on regional hospital budgets.

The Analysis is based on:

- Inclusion of both costs of pharmaceuticals and other treatment-related costs
- The cost of the new pharmaceutical are calculated at PPP (Danish: AIP) (pharmacy purchase price) level (see sheet "CMA-BIA Unit Costs" in the CMA-BIM excel file)
- Costs are estimated without discounting.
- Estimates for prevalence and incidence as discussed defined and referenced in the Section 3.2 “Patient Population"

Estimation of costs is done for the situation where:

i) The Danish Medicines Council does recommend the pharmaceutical as a possible standard treatment

ii) The Danish Medicines Council does not recommend the pharmaceutical as a possible standard treatment

When calculating yearly treatment over five-year period the analysis in the results makes use of a baseline scenario assuming all patients receiving TEYSUNO as combination therapy.

The primary results are derived comparing Teysuno combination therapy treatment with the combined dose-reduction and rechallenge therapy where FOLFOX, CAPOX and FOLFIRI are each contributing by 1/3.

13.1 Number of patients

The number of patients for the Budget Impact Analysis (BIA) is derived from the calculation in Section 3.2. As shown in Table 2, in the next five years 224 patients are expected to be eligible for treatment yearly. Of those, respectively 75 and 149 are expected to switch to Teysuno-based therapy due to cardiotoxicity or HFS (75 and 149 patients correspond to respectively 5% and 10% of treated patients with mCRC as discussed in Section 3.2 and is shown in Figure 1).

Table 47 summarizes the number of patients in Denmark who are expected to receive Teysuno treatment in the next five years. The numbers are based on an assumption of a gradual market uptake as shown in Table 48.

Table 47: Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Teysuno- based therapy	22	112	179	202	213
5-FU/cap-based therapy	202	112	45	22	11
			Non-recommendation		
Teysuno- based therapy	0	0	0	0	0
5-FU/cap-based therapy	224	224	224	224	224

Table 48: Market share (%) for Teysuno in the coming 5 years in patients with mCRC who cannot continue treatment with 5-FU due to toxicity

	Year 1	Year2	Year 3	Year 4	Year 5	Source:
Teysuno	10%	50%	80%	90%	95%	Estimation By Nordic Drugs
Dose-reduction and rechallenge 5-FU	90%	50%	20%	10%	5%	

13.2 Expenditure per patient

Average 6-month drug costs are shown in Table 45. For the BIA, the costs were derived by converting the 6-monthly costs to annual costs (i.e. doubling these costs). To account for treatment of either HFS or cardiotoxicity the relevant one-time costs for each toxicity (Table 41) is multiplied with the number of patients expected experiencing each complication. The number of complications for each year and therapy type is shown below in Table 49.

Table 49: Number of Patients affected by HFS or cardiotoxicity for intervention and comparator

		Year 1	Year 2	Year 3	Year 4	Year 5
Teysuno- based therapy	Cardiotoxicity	7	37	60	67	71
	HFS	15	75	120	135	142

Total Teysuno based		**22**	**112**	**179**	**202**	**213**
5-FU/cap-based therapy	Cardiotoxicity	67	37	15	7	4
	HFS	135	75	30	15	7
Total 5FU 5-FU/cap-based therapy		**202**	**112**	**45**	**22**	**11**
Total		**224**	**224**	**224**	**224**	**224**

13.3 Budget impact

The resulting estimated budget impact over the next five years if Teysuno is recommended for the current indication is presented in Table 50, showing that the added annual savings five years forward would total to **DKK 41,885,466**. Taking only drug costs into account (including administration and patient time), yearly savings for year 1 to year 5 are respectively **DKK 1,177,132, DKK 5,885,658, DKK 9,417,052, DKK 10,594,184, DKK 11,182,750** and sum up to **DKK 38,256,776** (not shown in table)**.** Management of adverse events over year 1 to year 5 is **DKK 111,652, DKK 558,260, DKK 893,216, DKK 1,004,868, DKK 1,060,694** respectively and accumulates to a saving of **DKK 3,628,690** (not shown in table). 91% of the total savings come from drug costs, which are calculated based on annual treatment expenses. In contrast, the costs associated with treating adverse events are accounted for as a one-time lump sum. The aggregated results (drug costs, administration, monitoring, Management of AEs) are summarized in Table 50.

Budget impact

Table 50 Expected budget impact of recommending the medicine for the indication, DKK

	Year 2
	29,590,508
The medicine under consideration is recommended	

	Year 2
	36,034,426
The medicine under consideration is NOT recommended	
	-6,443,918

Budget impact of the recommendation

13.4 Conclusion

In summary, switching to a Teysuno-based therapy is both safe and feasible for patients who develop toxicity from 5-FU- or capecitabine-based treatments. This switch allows patients to continue their recommended fluoropyrimidine-based therapy without interruption. Moreover, the budget impact analysis demonstrates that the introduction of Teysuno leads to cost savings. This financial benefit, combined with the safety and feasibility of Teysuno makes it a valuable option for maintaining effective cancer treatment regimens for mCRC patients who develop toxicity from 5-FU- or capecitabine-based treatments.

14. List of experts

[redacted]

15. References

1. European Medicines Agency, *Assessment report Teysuno (type II variation). Available at: https://www.ema.europa.eu/en/documents/variation-report/teysuno-h-c-001242-ii-0045-epar-assessment-report-variation_en.pdf*. 2021.
2. European Medicines Agency, *Teysuno: EPAR - Product Information*. 2011.
3. European Medicines Agency, *Produktresume Teysuno. Available at: https://www.ema.europa.eu/da/documents/product-information/teysuno-epar-product-information_da.pdf*. 2021.
4. Derksen, J.W.G., et al., *Systematic review and non-inferiority meta-analysis of randomised phase II/III trials on S-1-based therapy versus 5-fluorouracil- or capecitabine-based therapy in the treatment of patients with metastatic colorectal cancer.* Eur J Cancer, 2022. **166**: p. 73-86.
5. Osterlund, P., et al., *Continuation of fluoropyrimidine treatment with S-1 after cardiotoxicity on capecitabine- or 5-fluorouracil-based therapy in patients with solid tumours: a multicentre retrospective observational cohort study.* ESMO Open, 2022. **7**(3): p. 100427.
6. Punt, C.J.A., et al., *Fluoropyrimidine-induced hand-foot syndrome and cardiotoxicity: recommendations for the use of the oral fluoropyrimidine S-1 in metastatic colorectal cancer.* ESMO Open, 2023. **8**(2): p. 101199.
7. Xi, Y. and P. Xu, *Global colorectal cancer burden in 2020 and projections to 2040.* Translational Oncology, 2021. **14**(10): p. 101174.
8. Elferink, M.A., et al., *Metachronous metastases from colorectal cancer: a population-based study in North-East Netherlands.* Int J Colorectal Dis, 2015. **30**(2): p. 205-12.
9. Lotfollahzadeh S., Recio-Boiles A., and Cagir B., *Colon Cancer*, Treasure Island, Editor. 2023, StatPearls Publishing,: FL.
10. Biller, L.H. and D. Schrag, *Diagnosis and Treatment of Metastatic Colorectal Cancer: A Review.* Jama, 2021. **325**(7): p. 669-685.
11. Riihimäki, M., et al., *Patterns of metastasis in colon and rectal cancer.* Sci Rep, 2016. **6**: p. 29765.
12. National Cancer Institute: Surveillance, E., and End Results Program. *Cancer Stat Facts: Colorectal Cancer*. [cited 2023 11 October]; Available from: https://seer.cancer.gov/statfacts/html/colorect.html.
13. Medicinrådet, *Protokol for Medicinrådets grundlag for klinisk ligestilling vedrørende tillægsbehandling med EGFR-hæmmer ved behandling af metastaserende tyk- og endetarmskræft* 2023.
14. Moreno, C.C., et al., *Colorectal Cancer Initial Diagnosis: Screening Colonoscopy, Diagnostic Colonoscopy, or Emergent Surgery, and Tumor Stage and Size at Initial Presentation.* Clin Colorectal Cancer, 2016. **15**(1): p. 67-73.
15. Ulanja, M.B., et al., *Colon Cancer Sidedness, Presentation, and Survival at Different Stages.* J Oncol, 2019. **2019**: p. 4315032.
16. Christensen, T.D., et al., *Associations between primary tumor RAS, BRAF and PIK3CA mutation status and metastatic site in patients with chemo-resistant metastatic colorectal cancer.* Acta Oncol, 2018. **57**(8): p. 1057-1062.
17. S. B. Tausen and G. Engholm. *Kræftens Bekæmpelse: Statistik om endetarmskræft og analkræft*. 28 June 2022 [cited 2023 11 October]; Available from: https://www.cancer.dk/endetarmskraeft-rektumcancer/statistik-endetarmskraeft/.
18. Hamers, P.A.H., et al., *Informing metastatic colorectal cancer patients by quantifying multiple scenarios for survival time based on real-life data.* Int J Cancer, 2021. **148**(2): p. 296-306.

19. Danish Colorectal Cancer Group, *Landsdækkende database for kræft i tyk- og endetarm, National årsrapport 2019*. 2019.
20. Brændegaard Winther, S., et al., *Trends in colorectal cancer in the elderly in Denmark, 1980-2012.* Acta Oncol, 2016. **55 Suppl 1**: p. 29-39.
21. Group, D.C.C., ***Landsdækkende database for kræft i tyk- og endetarm, National årsrapport 2021***. 2021.
22. NORDCAN, *Available at: https://nordcan.iarc.fr/en/dataviz/trends?cancers=520&sexes=0&populations=208; [Accessed May 2024].*
23. Danish Colorectal Cancer Group, *Landsdækkende database for kræft i tyk- og endetarm, National Årsrapport 2020 (DCCG.dk)* 2020.
24. Rådet for Anvendelse af Dyr Sygehusmedicin (RADS), *Baggrundsnotat for medicinsk 1. og 2. linjebehandling af patienter med metastaserende kolorektalkræft.* 2016.
25. (DCCG), D.C.C.G., *Medicinsk onkologisk behandling af metastaserende kolorektal cancer*. 2023.
26. Sorbye, H., et al., *Clinical trial enrollment, patient characteristics, and survival differences in prospectively registered metastatic colorectal cancer patients.* Cancer, 2009. **115**(20): p. 4679-87.
27. S. B. Tausen and G. Engholm. *Kræftens Bekæmpelse: Statistik om kræft i tyktarmen*. 1 July 2022 [cited 2023 11 October]; Available from: https://www.cancer.dk/tyktarmskraeft-coloncancer/statistik-tyktarmskraeft/.
28. Dyhl-Polk, A., et al., *Incidence and risk markers of 5-fluorouracil and capecitabine cardiotoxicity in patients with colorectal cancer.* Acta Oncol, 2020. **59**(4): p. 475-483.
29. Kwakman, J.J., et al., *Incidence of capecitabine-related cardiotoxicity in different treatment schedules of metastatic colorectal cancer: A retrospective analysis of the CAIRO studies of the Dutch Colorectal Cancer Group.* Eur J Cancer, 2017. **76**: p. 93-99.
30. Kwakman, J.J.M., et al., *Tolerability of the oral fluoropyrimidine S-1 after hand-foot syndrome-related discontinuation of capecitabine in western cancer patients.* Acta Oncol, 2017. **56**(7): p. 1023-1026.
31. Kwakman, J.J.M., et al., *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.* Ann Oncol, 2017. **28**(6): p. 1288-1293.
32. Polk, A., et al., *Cardiotoxicity in cancer patients treated with 5-fluorouracil or capecitabine: a systematic review of incidence, manifestations and predisposing factors.* Cancer Treat Rev, 2013. **39**(8): p. 974-84.
33. Polk, A., et al., *A systematic review of the pathophysiology of 5-fluorouracil-induced cardiotoxicity.* BMC Pharmacol Toxicol, 2014. **15**: p. 47.
34. Cervantes, A., et al., *Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up.* Ann Oncol, 2023. **34**(1): p. 10-32.
35. Scheithauer, W., et al., *Randomised comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer.* Bmj, 1993. **306**(6880): p. 752-5.
36. Best, L., et al., *Palliative chemotherapy for advanced or metastatic colorectal cancer. Colorectal Meta-analysis Collaboration.* Cochrane Database Syst Rev, 2000. **2000**(2): p. Cd001545.
37. de Gramont, A., et al., *Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French intergroup study.* J Clin Oncol, 1997. **15**(2): p. 808-15.

38. Köhne, C.H., et al., *Randomized phase III study of high-dose fluorouracil given as a weekly 24-hour infusion with or without leucovorin versus bolus fluorouracil plus leucovorin in advanced colorectal cancer: European organization of Research and Treatment of Cancer Gastrointestinal Group Study 40952.* J Clin Oncol, 2003. **21**(20): p. 3721-8.
39. Meyerhardt, J.A. and R.J. Mayer, *Systemic therapy for colorectal cancer.* N Engl J Med, 2005. **352**(5): p. 476-87.
40. Henricks, L.M., et al., *DPYD genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis.* Lancet Oncol, 2018. **19**(11): p. 1459-1467.
41. European Medicines Agency, *EMA recommendations on DPD testing prior to treatment with fluorouracil, capecitabine, tegafur and flucytosine. [reference 26 May 2023]. Available at: http://www.ema.europa.eu/en/news/ema-recommendations-dpd-testing-prior-treatment-fluorouracil-capecitabine-tegafur-flucytosine.* 2020.
42. Sara, J.D., et al., *5-fluorouracil and cardiotoxicity: a review.* Ther Adv Med Oncol, 2018. **10**: p. 1758835918780140.
43. Lu, Y., et al., *Treatment-Related Coronary Disorders of Fluoropyrimidine Administration: A Systematic Review and Meta-Analysis.* Front Pharmacol, 2022. **13**: p. 885699.
44. Kwakman, J.J.M., et al., *Management of cytotoxic chemotherapy-induced hand-foot syndrome.* Oncol Rev, 2020. **14**(1): p. 442.
45. European Medicines Agency, *CHMP post-authorization summary of positive opinion for Teysuno (type II variation). Available at: https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-teysuno-ii-45_en.pdf* 2021.
46. Lyon, A.R., et al., *2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS).* Eur Heart J, 2022. **43**(41): p. 4229-4361.
47. Jurczyk, M., et al., *Cardiotoxicity of Fluoropyrimidines: Epidemiology, Mechanisms, Diagnosis, and Management.* J Clin Med, 2021. **10**(19).
48. Punt, C.J.A., J.J.M. Kwakman, and L. Mol, *Long-Term Safety Data on S-1 Administered After Previous Intolerance to Capecitabine-Containing Systemic Treatment for Metastatic Colorectal Cancer.* Clin Colorectal Cancer, 2022. **21**(3): p. 229-235.
49. Dancey, J.E., et al., *Recommendations for the assessment of progression in randomised cancer treatment trials.* Eur J Cancer, 2009. **45**(2): p. 281-9.
50. Driscoll, J.J. and O. Rixe, *Overall survival: still the gold standard: why overall survival remains the definitive end point in cancer clinical trials.* Cancer J, 2009. **15**(5): p. 401-5.
51. Kosmas, C., et al., *Cardiotoxicity of fluoropyrimidines in different schedules of administration: a prospective study.* J Cancer Res Clin Oncol, 2008. **134**(1): p. 75-82.
52. Kwakman, J.J.M., et al., *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.* Clin Colorectal Cancer, 2019. **18**(2): p. e229-e230.
53. Yamada, Y., et al., *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.* Ann Oncol, 2018. **29**(3): p. 624-631.

54. Hong, Y.S., et al., *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.* Lancet Oncol, 2012. **13**(11): p. 1125-32.
55. Baba, H., et al., *S-1 and oxaliplatin (SOX) plus bevacizumab versus mFOLFOX6 plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer: updated overall survival analyses of the open-label, non-inferiority, randomised phase III: SOFT study.* ESMO Open, 2017. **2**(1).
56. Kim, S.T., et al., *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.* BMC Cancer, 2014. **14**: p. 883.
57. Yamazaki, K., et al., *A randomized phase II study of combination therapy with S-1, oral leucovorin, and oxaliplatin (SOL) and mFOLFOX6 in patients with previously untreated metastatic colorectal cancer.* Cancer Chemother Pharmacol, 2015. **75**(3): p. 569-77.
58. Sadahiro, S., et al., *Oral S-1 with 24-h Infusion of Irinotecan plus Bevacizumab versus FOLFIRI plus Bevacizumab as First-Line Chemotherapy for Metastatic Colorectal Cancer: An Open-Label Randomized Phase II Trial.* Oncology, 2020. **98**(9): p. 637-642.
59. Kato, S., et al., *Safety Verification Trials of mFOLFIRI and Sequential IRIS + Bevacizumab as First- or Second-Line Therapies for Metastatic Colorectal Cancer in Japanese Patients.* Oncology, 2012. **83**(2): p. 101-107.
60. Yasui, H., et al., *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.* J Cancer Res Clin Oncol, 2015. **141**(1): p. 153-60.
61. Liu, H., et al., *Clinical study of tegafur-gimeracil-oteracil potassium capsule (s-1) and oxaliplatin combination chemotherapy in advanced colorectal cancer.* J Cancer Res Ther, 2015. **11**(2): p. 331-5.
62. Baba, H., et al., *S-1 and oxaliplatin (SOX) plus bevacizumab versus mFOLFOX6 plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer: updated overall survival analyses of the open-label, non-inferiority, randomised phase III: SOFT study.* ESMO Open, 2017. **2**(1): p. e000135.
63. Kim, J.H., et al., *A Muti-center, Randomized Phase II Study of Oxaliplatin and S-1 versus Capecitabine and Oxaliplatin in Patients with Metastatic Colorectal Cancer.* J Cancer, 2015. **6**(10): p. 1041-8.
64. Yamada, Y., et al., *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.* Lancet Oncol, 2013. **14**(13): p. 1278-86.
65. Muro, K., et al., *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).* Lancet Oncol, 2010. **11**(9): p. 853-60.
66. Winther, S.B., et al., *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.* Lancet Gastroenterol Hepatol, 2019. **4**(5): p. 376-388.
67. Kwakman, J.J.M., et al., *Case series of patients treated with the oral fluoropyrimidine S-1 after capecitabine-induced coronary artery vasospasm.* Eur J Cancer, 2017. **81**: p. 130-134.
68. Danish Health Data Authority / Sundhetsdatastyrelsen, *Takstsystem 2024. Available at: https://sundhedsdatastyrelsen.dk/-/media/sds/filer/finansiering-og-afregning/takster/2024/takstvejledning_2024.pdf*. 2024.

69. Medicinrådet, *Medicinrådets anbefaling vedrørende nivolumab i kombination med kemoterapi til 1. linjebehandling af fremskredent HER2-negativ adenokarcinom i mavesæk, mavemund eller spiserør og PD-L1 CPS ≥ 5.* 2022.
70. Cancentrum, R. *Kunskapsbanken*. 09.07.2024]; Available from: https://kunskapsbanken.cancercentrum.se/.
71. Denmark, S. *BEFOLK2: Population 1. January by sex and age*. 2024 09.07.2024]; Available from: https://www.statbank.dk/statbank5a/default.asp?w=1920.
72. Sundhetsstyrelsen. *Danskernes sundhed – Den Nationale Sundhedsprofl 2021*. 2022 09.07.2024]; Available from: https://www.sst.dk/-/media/Udgivelser/2022/Sundhedsprofil/Sundhedsprofilen.ashx?sc_lang=da&hash=5C9A9A81483F6C987D5651976B72ECB2.
73. Cancercentrum, R. *Kunskapsbanken - FOLFOX*. 2024 09.07.2024]; Available from: https://kunskapsbanken.cancercentrum.se/lakemedelsregimer/tjock--och-andtarmscancer/folfox/.
74. Cancercentrum, R. *Kunskapsbanken - CAPOX*. 2024 09.07.2024]; Available from: https://kunskapsbanken.cancercentrum.se/lakemedelsregimer/tjock--och-andtarmscancer/capox/.
75. Cancercentrum, R. *Kunskapsbanken - FOLFIRI*. 2024 09.07.2024]; Available from: https://kunskapsbanken.cancercentrum.se/lakemedelsregimer/tjock--och-andtarmscancer/folfiri/.
76. Sundhedsdatastyrelsen, *Takstsystem 2024. available at: https://sundhedsdatastyrelsen.dk/-/media/sds/filer/finansiering-og-afregning/takster/2024/takstvejledning_2024.pdf*. 2024.
77. Medicinrådet, *Email communication - Vurdering af ansøgning vedr. Teysuno til mCRC received July 3, 2024 10:33:11 AM* N. Drugs, Editor. 2024.
78. Medicinrådet, *Værdisætning af enhedsomkostninger.* 2023.

Appendix A. Main characteristics of studies included

Table 51. Main characteristic of SALTO

Trial name: SALTO	**NCT number: NCT01918852**
Objective	This study is designed to compare S-1 and capecitabine monotherapy in terms of safety, with particular interest in hand-foot syndrome (HFS), in European/Caucasian metastatic colorectal cancer patients
Publications – title, author, journal, year	*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*. J. J. M. Kwakman, L. H. J. Simkens, J. M. van Rooijen, A. J. van de Wouw, A. J. ten Tije, G. J. M. Creemers, M. P. Hendriks, M. Los, R. J. van Alphen, M. B. Pole´e, E. W. Muller, A. M. T. van der Velden, T. van Voorthuizen, M. Koopman, L. Mol, E. van Werkhoven & C. J. A. Punt. Annals of Oncology 28: 1288-1293 (2017)[31] *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.* J. J. M. Kwakman, E. van Werkhoven, L. H. J. Simkens, J. M. van Rooijen, Y. A. J. van de Wouw, A. J. ten Tije, G. J. M. Creemers, M. P. Hendriks, M. Los, R. J. van Alphen, M. B. Polée, E. W. Muller, A. M. T. van der Velden, T. van Voorthuizen, M. Koopman, L. Mol, C. J. A. Punt. *Clinical Colorectal Cancer* 18 (2): e229-30 (2019)[52]
Study type and design	Interventional, randomized, parallel assignment, open label Phase III study
Sample size (n)	161
Main inclusion criteria	Patients aged ≥18 years with previously untreated mCRC and planned treatment with fluoropyrimidine monochemotherapy. Inclusion criteria: • Histological proof of colorectal cancer. • Distant metastases (patients with only local recurrence are not eligible). • Unidimensionally measurable disease (≥1 cm on spiral CT scan or ≥2 cm on chest X-ray; liver ultrasound is not allowed). Serum CEA may not be used as a parameter for disease evaluation. • In case of previous radiotherapy, at least one measurable lesion should be located outside the irradiated field.

Trial name: SALTO		NCT number: NCT01918852
	• Age ≥ 18 years • Planned treatment with fluoropyrimidine monotherapy with or without bevacizumab. • WHO performance status 0-2 (Karnofsky PS ≥70%) • Adequate bone marrow function (Hb ≥ 6.0 mmol/L, absolute neutrophil count ≥1.5 x 109/L, platelets ≥ 100 x 109/L), renal function (serum creatinine ≤ 1.5x ULN and creatinine clearance, Cockroft formula, ≥30 ml/min), liver function (serum bilirubin ≤ 2 x ULN, serum transaminases ≤ 3 x ULN without presence of liver metastases or ≤ 5x ULN with presence of liver metastases). • Life expectancy > 12 weeks. • Negative pregnancy test in women with childbearing potential. • Expected adequacy of follow-up. • Institutional Review Board approval. • Written informed consent.	
Main exclusion criteria	• Prior adjuvant treatment for stage II/III colorectal cancer completed within 6 months prior to randomisation. • Any prior adjuvant treatment after resection of distant metastases. • Any previous systemic treatment for metastatic disease. • History or clinical signs/symptoms of CNS metastases. • History of a second malignancy <5 years with the exception of adequately treated carcinoma of cervix or basal/squamous cell carcinoma of skin. • Previous intolerance of capecitabine. • Known dihydropyrimidine dehydrogenase (DPD) deficiency or treatment within 4 weeks with DPD inhibitors, including sorivudine or its chemically related analogues such as brivudine. • Planned radical resection of metastases after downsizing by systemic treatment. • Significant cardiovascular disease < 1 yr before randomisation (symptomatic congestive heart failure, myocardial ischemia or infarction, unstable angina pectoris, serious uncontrolled cardiac arrhythmia, arterial thrombosis, cerebrovascular event, pulmonary embolism). • Any significant cardiovascular events during previous fluoropyrimidine therapy.	
Intervention	Capecitabine: 1250 mg/m^2 (patients >70 years) or 1000 mg/m^2 (patients ≥70 years), administered orally twice daily on days 1-14 (n=80)	
Comparator(s)	S-1: 30 mg/m^2 twice daily on days 1-14 (n=80)	

Trial name: SALTO		NCT number: NCT01918852
Follow-up time	2013-12 to 2018-03 (Final data collection for primary outcome measure: 2015-12)	
Is the study used in the health economic model?	No	

Primary, secondary and exploratory endpoints	**Primary**
	• Incidence of HFS in first line treatment [Time Frame: HFS will be assessed every 3 weeks up to 6 months average.]
	  ○ To determine the incidence of HFS in first line treatment with S-1 compared to capecitabine in patients with metastatic colorectal cancer.
	Secondary
	• Grade 3 HFS [Time Frame: HFS will be assessed every 3 weeks, up to 6 months average]
	  ○ Incidence of grade 3 hand-foot syndrome, according to CTC 4.0.
	• Progression-free survival [Time Frame: Every 9 weeks, for 6 months (average)]
	  ○ Time from randomisation until progression or death whichever comes first
	• Overall toxicity [Time Frame: Every 3 weeks, for 6 months (average)]
	  ○ Adverse events graded accoording to the NCI CTCAE version 4
	• Overall survival [Time Frame: 2 years]
	  ○ From date of randomisation to death or last known to be alive
	• Response rate [Time Frame: Response will be assessed every 9 weeks, up to 6 months average.]
	  ○ Response acccording to RECIST 1.1	

Method of analysis		
Subgroup analyses	None	
Other relevant information		

Table 52. Main characteristic of NORDIC9

Study name/NCT number	NORDIC9 (EudraCT: 2014-000394-39)
Study objective	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 and vulnerable patients with metastatic colorectal cancer. Furthermore, the study aimed to assess if geriatric screening tools administered at baseline could predict efficacy and toxicity of the treatments.
Publications	*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*. S. B. Winther, G. Liposits, H. Skuladottir, E. Hofsli, C. H. Shah, L. Ø. Poulsen, J.Ryg, P. Osterlund, Å. Berglund, C. Qvortrup, B. Glimelius, H. Sorbye, P. Pfeiffer. *Lancet Gastroenterol Hepatol* 4: 378-88 (2019) [66]
Study type and design	Interventional, randomised, open-label Phase II trial
Duration of study	2015-02 to 2018-09
Intervention	Sequential full-dose monotherapy: S-1 30 mg/m^2 orally twice daily on days 1-14 every 3 weeks, followed by second-line treatment at progression with irinotecan (250 mg/m^2 intravenously on day 1 every 3 weeks or 180 mg/m^2 intravenously on day 1 every 2 weeks) (n=83)
Comparator	Sequential dose-reduced combination chemotherapy: S-1 20 mg/m^2 orally twice daily on days 1-14 and oxaliplatin 100 mg/m^2 intravenously on day 1 every 3 weeks followed by second-line treatment at progression with S-1 20 mg/m^2 orally twice daily on days 1-14 and irinotecan 180 mg/m^2 intravenously on day 1 every 3 weeks (n=77)
Patient population	Inclusion criteria: • Aged 70 years or older • Histopathologically proven colorectal adenocarcinoma, non-resectable metastases, and a WHO performance status of 0-2 • Patients had received no prior chemotherapy except adjuvant fluoropyrimidine therapy completed more than 180 days before randomisation • Life expectancy of at least 3 months • Haematological, renal and liver functions within normal range (glomerular filtration rate <30 mL/min, bilirubin ≤1.5x upper normal limit, neutrophil cell count ≥1.5x10^9 cells/L, platelet count ≥100x10^9/L) • Patients could not be candidates for standard full-dose combination chemotherapy as assessed by the treating physician • Written consent Exclusion criteria: • Evidence of central nervous system 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 • Contraindications to fluoropyrimidine e.g., myocardial infarction within 6 months
Sample size	160
Primary objectives	Progression-free survival [Time frame: calculated from date of randomization to the first date of radiological or clinical progression on first-line treatment, time of death, or censored on the cut-off date (36 months)]

Secondary objectives	• Overall survival [Time frame: cur-off date (36 months)]
	  ○ Defined as deaths of all causes or censored at cut-off date
	• Proportion of patients achieving investigator-evaluated response
	• Toxicity
	  ○ Graded by NCI-CTCAE
	• Quality of life [Time frame: measured at baseline and after 3 and 6 treatment cycles]
	  ○ Assessed using the EORTC QLQ-C30
	• Time to failure of strategy [Time frame: calculated from the date of randomisation to the date of progression on planned first-line and second-line treatment]

Exploratory endpoints	• Evaluation: cut-off of G8 of 11 or less • Exploration: the predictive value of Köhne prognostic index in regard to survival and toxicity • Evaluation: efficacy and safety in a sub-population of patients who received additional bevacizumab
Subgroup analyses (if any)	

Table 53. Main characteristic of PLRCRC

Study name/NCT number	The Dutch Prospective Colorectal Cancer Cohort (PLCRC) (NCT02070146) [ongoing]
Study objective	To assess the long-term tolerability of S-1 in patients who discontinued capecitabine for reasons of HFS or cardiac toxicity.
Publications	*Long-Term Safety Data on S-1 Administered After Previous Intolerance to Capecitabine-Containing Systemic Treatment for Metastatic Colorectal Cancer*. C. J. A. Punt, J. J. M. Kwakma, L. Mol, on behalf of the PLCRC working group. *Clinical Colorectal Cancer* (2022)[48]
Study type and design	Retrospective
Duration of study	Data collected from June 1, 2016 to June 15, 2021
Intervention	S-1 at either 30 mg/m^2 bid or 25 mg/m^2 bid when given as monochemotherapy, or 25 mg/m^2 bid when given in combination with oxaliplatin

Comparator	N/A
Patient population	Inclusion criteria: • Patients with metastatic CRC in whom treatment was switched from capecitabine to S-1 Exclusion criteria: • Patients who were included in 2 previous retrospective studies on a treatment switch from capecitabine to S-1
Sample size	47
Primary objectives	Examine the electronic records of eligible patients 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 • Starting dose of capecitabine • Dose reduction of capecitabine, and if so, the underlying reason • Reason for switch to S-1 • Time interval between last dose of capecitabine and first dose of S-1 • Total number of cycles of S-1 • Dose reductions of S-1, and if so, the underlying reason • Reason for permanent discontinuation of S-1 • Date of first disease progression after S-1 administration • Any adverse events occurring during treatment with capecitabine and S-1 of which the maximal grade was recorded using CTC criteria (CTCAE version 5.0)
Secondary objectives	N/A
Exploratory endpoints	N/A
Subgroup analyses (if any)	Separate analysis of patients who switched for reason of HFS showed no significant differences in any outcome parameter

Table 54. Main characteristic of Case series

Study name/NCT number	N/A
Study objective	To present case studies of patients treated with oral fluoropyrimidine S-1 after HFS related discontinuation of capecitabine
Publications	*Case series of patients treated with the oral fluoropyrimidine S-1 after capecitabine-induced coronary artery vasospasm*. J. J. M. Kwakman, A. Baars, A. A. van Zweeden, P. de Mol, M. Koopman, W. E. M. Kok, C. J. A. Punt. *Euro. J. of Cancer* 81 (2017)[67] *Tolerability of the oral fluoropyrimidine S-1 after hand-foot syndrome-related discontinuation of capecitabine in western cancer patients*. J. J. M. Kwakman, A. Baars, H. Boot, J. F. M. Pruijt, S. B. Winther, P. Pfeiffer, C. J. A. Punt. *Acta Oncologica* (2017)[30]

Study type and design	Retrospective
Duration of study	N/A
Intervention	S-1 at a dose of 20 mg/m^2 bid, 25 mg/m^2 bid, or 30 mg/m^2 bid, with or without oxaliplatin and/or bevacizumab
Comparator	N/A
Patient population	Patients in the Netherlands and Denmark with any type of cancer who switched from capecitabine to S-1
Sample size	52 + 7
Primary objectives	To investigate the tolerability of S-1 after HFS-related discontinuation of capecitabine Endpoints included: • Incidence of any grade HFS upon treatment switch to S-1
Secondary objectives	• The incidence of grade 3 HFS • Other S-1-related adverse events • S-1 dose reductions
Exploratory endpoints	N/A
Subgroup analyses (if any)	N/A

Table 55. Main characteristic of CardioSwitch

Study name/NCT number	Feasibility of Switching Fluoropyrimidine Due to Cardiotoxicity Study (CardioSwitch) (NCT04260269)
Study objective	To compare different 5-fluorouracil-based dosing modalities and S-1, and compare cardiotoxicity during these treatments
Publications	*Continuation of fluoropyrimidine treatment with S-1 after cardiotoxicity on capecitabine- or 5-fluorouracil-based therapy in patients with solid tumours: a multicentre retrospective observational cohort study.* P. Osterlund, S. Kinos, P. Pfeiffer, T. Salminen, J. J. M. Kwakman, J.-E. Frödin, C. H. Shah, H. Sorbye, R. Ristamäki, P. Halonen, L. M. Soveri, E. Heervä, A. Ålgars, M. Bärlund, H. Hagman, R. McDermott, M. O'Reilly, R. Röckert, G. Liposits, R. Kallio, P. Flygare, A. J. Teske, E. van Werkhoven, C. J. A. Punt & B. Glimelius. *ESMO Open 7(3): 100427* (2022)[5]
Study type and design	Retrospective cohort study
Duration of study	2018-06-01 to 2020-12 (estimated study completion: 2025-12)
Intervention	S-1-based treatment
Comparator	N/A
Patient population	All consecutive patients who fulfil the following inclusion criteria will be included in the database until the target number of patients has been included: • Solid tumor

	• Cardiotoxicity grade 1-4 during fluoropyrimidine-based treatment • Re-challenge with a different fluoropyrimidine-based treatment. Primary endpoint is switch to S-1 and secondary any fluoropyrimidine population.
Sample size	200
Primary objectives	• Recurrence of fluoropyrimidine related cardiac toxicity after switch to S-1 based treatment [Time Frame: After switch to and during one line of S-1 based chemotherapy (average 6 months)] ○ Cardiac tolerability according to NCI-CTCAE following cardiotoxicity initiated switch of fluoropyrimidine to S-1
Secondary objectives	• Recurrence of fluoropyrimidine related cardiac toxicity after switch to any fluoropyrimidine [Time Frame: After switch to and during one line of another fluoropyrimidine regimen (average 6 months)] • Cardiac symptoms during fluoropyrimidine chemotherapy [Time Frame: During one line of fluoropyrimidine based chemotherapy (average 6 months)] • Diagnostic work-up [Time Frame: During one line of fluoropyrimidine based chemotherapy (average 6 months)] • Time-lines for cardiotoxicity [Time Frame: During one line of fluoropyrimidine based chemotherapy (average 6 months)] • Dose-intensity [Time Frame: During one cycle (average 3 weeks) of fluoropyrimidine-based chemotherapy causing cardiac toxicity] • Alteration in cardiac functional parameters during fluoropyrimidine treatment induced cardiotoxicity [Time Frame: During one cycle (average 3 weeks) of fluoropyrimidine-based chemotherapy causing cardiac toxicity]
Exploratory endpoints	N/A
Subgroup analyses (if any)	N/A

Appendix B. Efficacy results per study

Results per study

Not applicable, for rational see section 6. Efficacy.

Table 56 Results per study

Results of [trial name (NCT number)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Example: median overall survival (time point)	XXX	247	22.3 (20.3–24.3) months	4.9	1.79–8.01	0.002	HR: 0.70	0.55–0.90	0.005	The median survival is based on the Kaplan-Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for the variables used for stratification for randomization, and study arm.	
	ZZZ	248	17.4 (15.0–19.8) months								
Example: 1-year survival	XXX	247	74.5% (68.9–80.2)	10.7	2.39–19.01	0.01	HR: 0.70	0.55–0.90	0.005	The survival rates are based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm.	
	ZZZ	248	63.8% (57.6–70.0)								

Results of [trial name (NCT number)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Example: HRQoL (time point)	XXX	211	−1.5 (-3.1 to 0.1)	4.5	−8.97 to −0.03	0.04	NA	NA	NA	The absolute difference in effect is estimated using a two-sided t-test.	
	ZZZ	209	−6.0 (−10.2 to −1.8)								
Insert outcome 4	Intervention										
	Comparator										

Appendix C. Comparative analysis of efficacy

The study by Derksen et al (2022) [4], aimed to provide up-to-date and conclusive evidence on the non-inferiority of S-1-based regimens compared to 5-FU- or capecitabine-based therapy in the treatment of patients with mCRC by means of a systematic review of randomised clinical Phase II and phase III trials and a non-inferiority metanalysis.

C.1 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. Two reviewers (JWGD and KCS) reviewed the literature independently, and discrepancies were resolved by discussion until consensus was reached. This systematic review was registered at the International prospective register of systematic reviews (PROSPERO) with identification number CRD42021264921 and performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.

The following sensitive search strategies were applied to the individual databases.
MEDLINE (PubMed):
((S-1) OR (Teysuno) OR (Tegafur-gimeracil-oteracil)) AND (randomized) AND ((colorectal cancer) OR (colon) OR (rectal))

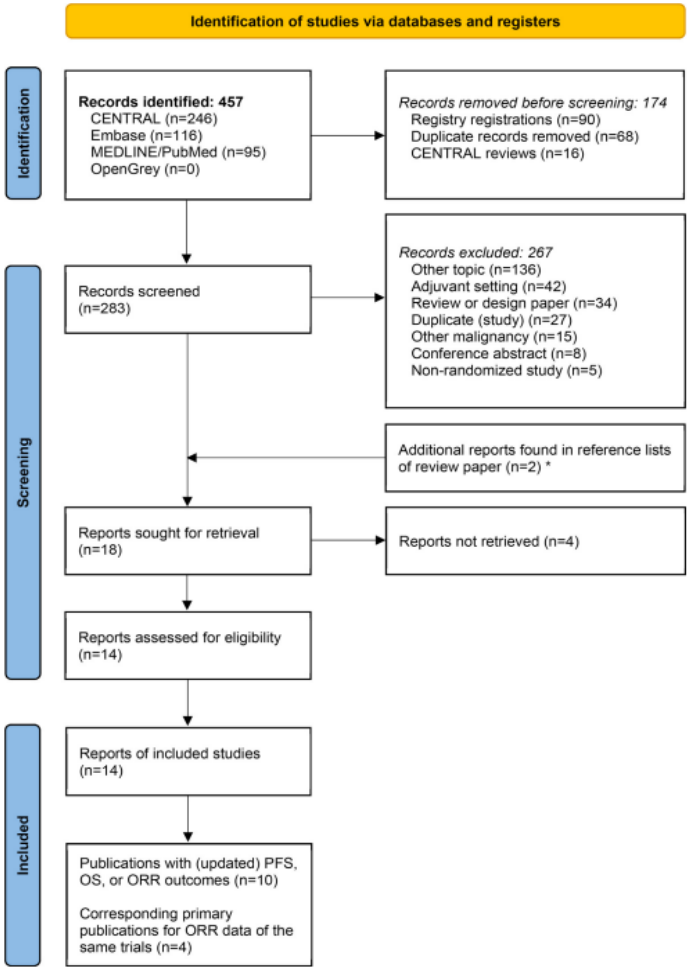
Embase
'gimeracil plus oteracil potassium plus tegafur' AND randomized AND 'colorectal cancer'

CENTRAL
#1 (S-1) OR (Teysuno) OR (Tegafur-gimeracil-oteracil)
#2 (randomized)
#3 (colorectal cancer) OR (colon) OR (rectal)
#4 #1 AND #2 AND #3

OpenGrey
Using keywords pertaining to population and intervention: #1 Colorectal cancer S-1 #2 Colon cancer S-1 #3 Rectal cancer S-1 #4 Colorectal cancer Teysuno #5 Colon cancer Teysuno #6 Rectal cancer Teysun

The PRISMA flowchart with a complete overview of the systematic search is presented in Figure 7.

Figure 7. PRISMA flow diagram



C.2 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. A pre-defined non-inferiority margin (DNI) of 1.25 was selected based on the trial with the most conservative ΔNI in this review. 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 HRtotal remains <1.25.

C.3 Results

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. 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. The remaining 14 publications were assessed for eligibility and met the following criteria: patients with age >18 years, histologically proved mCRC, and palliative S-1-based (mono or combination) therapy, compared with 5-FU- or capecitabine-based (mono or combination) therapy. Ten publications with (updated) PFS, OS or ORR outcomes were included [52, 53, 55-61, 63], and for the analysis on ORR, four corresponding primary publications of the same trials were included [31, 54, 64, 65], Table 57. Nine studies were conducted in Asia, and one study was conducted in Europe. The meta-analysis included 1,062 patients that received S-1 based therapy and 1,055 patients that received 5FU/Cap-based therapy. The primary outcome was progression-free survival (PFS, months), and the secondary outcomes were overall survival (OS, months), objective response rate (ORR) and adverse events. There were no major differences in study and patient characteristics among the studies included. HRs for PFS and OS were available from six studies[52, 53, 55, 60], whereas ORR data were available from 10 studies [31, 53, 54, 57-59, 61, 63-65]. For the time-to-event outcomes, PFS and OS, hazard ratios (HRs) with their 95% confidence intervals (CIs) were extracted from the individual studies. For PFS, a pre-defined non-inferiority margin (ΔNI) of 1.25 was selected. In order to support the meta-analysis, median survival and time to progression with corresponding p-values were extracted. The selection of toxicities for meta-analysis was based on two criteria: incidence ≥ 5% and reported by the majority of the publications.

S-1-based therapy was shown to be non-inferior to 5-FU/capecitabine-based therapy in terms of PFS (HR_{total} 0.95, 99% CI 0.83-1.08) with its CI upper limit well below ΔNI, and at least as efficacious in terms of OS (HR_{total} 0.93, 99% CI 0.81-1.07), and ORR (RR_{total} 1.06, 99% CI 0.90-1.24), Table 58. According to this meta-analysis, S-1-based therapy is non-inferior to 5-FU/capecitabine-based therapy in the treatment of mCRC regarding PFS and at least as efficacious as 5-FU/capecitabine-based therapy. The conclusion of this meta-analysis was that S-1-based therapy is non-inferior to 5-FU/capecitabine-based therapy in the treatment of mCRC regarding PFS and at least as efficacious as 5-FU/capecitabine-based therapy [4].

Table 57. List of studies included in the meta-analysis

1.
• **Kim ST**, Hong YS, Lim HY, Lee J, Kim TW, Kim KP, Kim SY, Baek JY, Kim JH, Lee KW, Chung IJ, Cho SH, Lee KH, Shin SJ, Kang HJ, Shin DB, Lee JW, Jo SJ, Park YS. 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. BMC Cancer. 2014 Nov 26;14:883. doi: 10.1186/1471-2407-14-883. PMID: 25424120; PMCID: PMC4289339.
- *Primary publication:* **Hong YS**, Park YS, Lim HY, Lee J, Kim TW, Kim KP, Kim SY, Baek JY, Kim JH, Lee KW, Chung IJ, Cho SH, Lee KH, Shin SJ, Kang HJ, Shin DB, Jo SJ, Lee JW. 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. Lancet Oncol. 2012 Nov;13(11):1125-32. doi: 10.1016/S1470-2045(12)70363-7. Epub 2012 Oct 10. PMID: 23062232.
2.
• **Baba H,** Yamada Y, Takahari D, Matsumoto H, Yoshida K, Nakamura M, Yoshida M, Iwamoto S, Shimada K, Komatsu Y, Sasaki Y, Satoh T, Takahashi K, Mishima H, Muro K, Watanabe M, Sakata Y, Morita S, Shimada Y, Sugihara K. S-1 and oxaliplatin (SOX) plus bevacizumab versus mFOLFOX6 plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer: updated overall survival analyses of the open-label, non-inferiority, randomised phase III: SOFT study. ESMO Open. 2017 Mar 9;2(1):e000135. doi: 10.1136/esmoopen-2016-000135. PMID: 28761727; PMCID: PMC5519807.
- *Primary publication:* **Yamada Y**, Takahari D, Matsumoto H, Baba H, Nakamura M, Yoshida K, Yoshida M, Iwamoto S, Shimada K, Komatsu Y, Sasaki Y, Satoh T, Takahashi K, Mishima H, Muro K, Watanabe M, Sakata Y, Morita S, Shimada Y, Sugihara K. 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. Lancet Oncol. 2013 Dec;14(13):1278-86. doi: 10.1016/S1470-2045(13)70490-X. Epub 2013 Nov 11. Erratum in: Lancet Oncol. 2014 Jan;15(1):e4. PMID: 24225157.
3.
• **Yamada Y**, Denda T, Gamoh M, Iwanaga I, Yuki S, Shimodaira H, Nakamura M, Yamaguchi T, Ohori H, Kobayashi K, Tsuda M, Kobayashi Y, Miyamoto Y, Kotake M, Shimada K, Sato A, Morita S, Takahashi S, Komatsu Y, Ishioka C. 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. Ann Oncol. 2018 Mar 1;29(3):624-631. doi: 10.1093/annonc/mdx816. PMID: 29293874; PMCID: PMC5889030.
4.
• **Kwakman JJM**, van Werkhoven E, Simkens LHJ, van Rooijen JM, van de Wouw YAJ, Tije AJT, Creemers GM, Hendriks MP, Los M, van Alphen RJ, Polée MB, Muller EW, van der Velden AMT, van Voorthuizen T, Koopman M, Mol L, Punt CJA. 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. Clin Colorectal Cancer. 2019 Jun;18(2):e229-e230. doi: 10.1016/j.clcc.2019.01.002. Epub 2019 Jan 29. PMID: 30782413.
- *Primary publication:* **Kwakman JJM**, Simkens LHJ, van Rooijen JM, van de Wouw AJ, Ten Tije AJ, Creemers GJM, Hendriks MP, Los M, van Alphen RJ, Polée MB, Muller EW, van der Velden AMT, van Voorthuizen T, Koopman M, Mol L, van Werkhoven E, Punt CJA. 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. Ann Oncol. 2017 Jun 1;28(6):1288-1293. doi: 10.1093/annonc/mdx122. PMID: 28383633.
5.
• **Kim JH**, Zang DY, Chung IJ, Cho SH, Park KU, Oh HS, Lee KH, Lee BH, Kim MJ, Park CK, Han B, Kim HS, Choi DR, Song HH, Jung JY. A Multi-center, Randomized Phase II Study of Oxaliplatin and S-1 versus Capecitabine and Oxaliplatin in Patients with Metastatic Colorectal Cancer. J Cancer. 2015 Aug 29;6(10):1041-8. doi: 10.7150/jca.12819. PMID: 26366218; PMCID: PMC4565854.
6.
• **Yamazaki K**, Kuwano H, Ojima H, Otsuji T, Kato T, Shimada K, Hyodo I, Nishina T, Shirao K, Esaki T, Ohishi T, Denda T, Takeuchi M, Boku N. A randomized phase II study of combination therapy with S-1, oral leucovorin, and oxaliplatin (SOL) and mFOLFOX6 in patients with previously untreated metastatic colorectal cancer. Cancer Chemother Pharmacol. 2015 Mar;75(3):569-77. doi: 10.1007/s00280-015-2676-0. Epub 2015 Jan 10. PMID: 25575764.
7.

• **Sadahiro S**, Suzuki T, Okada K, Saito G, Miyakita H, Ogimi T, Chan LF, Kamei Y. Oral S-1 with 24-h Infusion of Irinotecan plus Bevacizumab versus FOLFIRI plus Bevacizumab as First-Line Chemotherapy for Metastatic Colorectal Cancer: An Open-Label Randomized Phase II Trial. Oncology. 2020;98(9):637-642. doi: 10.1159/000507293. Epub 2020 May 29. PMID: 32474564; PMCID: PMC7592907.
8.
• **Kato S**, Andoh H, Gamoh M, Yamaguchi T, Murakawa Y, Shimodaira H, Takahashi S, Mori T, Ohori H, Maeda S, Suzuki T, Kato S, Akiyama S, Sasaki Y, Yoshioka T, Ishioka C; Tohoku Clinical Oncology Research and Education. Safety verification trials of mFOLFIRI and sequential IRIS + bevacizumab as first- or second-line therapies for metastatic colorectal cancer in Japanese patients. Oncology. 2012;83(2):101-7. doi: 10.1159/000339541. Epub 2012 Jul 9. PMID: 22777333.
9.
• **Yasui H**, Muro K, Shimada Y, Tsuji A, Sameshima S, Baba H, Satoh T, Denda T, Ina K, Nishina T, Yamaguchi K, Esaki T, Tokunaga S, Kuwano H, Boku N, Komatsu Y, Watanabe M, Hyodo I, Morita S, Sugihara K. 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. J Cancer Res Clin Oncol. 2015 Jan;141(1):153-60. doi: 10.1007/s00432-014-1783-3. Epub 2014 Aug 9. PMID: 25106731.
- *Primary publication:* **Muro K**, Boku N, Shimada Y, Tsuji A, Sameshima S, Baba H, Satoh T, Denda T, Ina K, Nishina T, Yamaguchi K, Takiuchi H, Esaki T, Tokunaga S, Kuwano H, Komatsu Y, Watanabe M, Hyodo I, Morita S, Sugihara K. 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). Lancet Oncol. 2010 Sep;11(9):853-60. doi: 10.1016/S1470-2045(10)70181-9. Epub 2010 Aug 12. PMID: 20708966
10.
• **Liu H**, Wang Y, Li G, Song W, Wang R. Clinical study of tegafur-gimeracil-oteracil potassium capsule (s-1) and oxaliplatin combination chemotherapy in advanced colorectal cancer. J Cancer Res Ther. 2015 Apr;Jun;11(2):331-5. doi: 10.4103/0973-1482.157339. PMID: 26148595.

Table 58 Comparative analysis of studies comparing Teysuno to 5-FU/cap for patients with metastatic CRC

Outcome	Studies included in the analysis	Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference	CI	P value		
Progression-free survival	Kim et al 2014 [56]; Baba et al, 2017 [55]; Yamada et al 2018 [53] Kwakman et al, 2019 [52]; Yamazaki et al 2015 [57]; Yasui et al, 2015 [60]	HR_{total} 0.95	99%CI 0.83–1.08		Meta-analyses were conducted in Review Manager 5.4 using 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	No
Overall survival		HR_{total} 0.93	99%CI 0.81–1.07			
Objective Response Rate	Yamada et al 2018 [53]; Kim et al, 2015 [63]; Yamazaki et al 2015 [57]; Sadahiro et al 2020 [58]; Kato et al 2012 [59]; Yasui et al, 2015 [60]; Hong et al 2012 [54]; Yamada et al 2013 [64]; Kwakman et al 2017 [31]; Muro et al 2010 [65]	RR_{total} 1.06	99%CI 0.90–1.24			

Appendix D. Extrapolation

Not applicable. No extrapolation performed.

D.1 Extrapolation of [effect measure 1]

D.1.1 Data input

D.1.2 Model

D.1.3 Proportional hazards

[If the extrapolation model relies on proportional hazards, provide a plot with Schoenfeld residuals and a log-cumulative hazard plot.]

D.1.4 Evaluation of statistical fit (AIC and BIC)

[Provide a table with the AIC and BIC and discuss the statistical fit.]

D.1.5 Evaluation of visual fit

D.1.6 Evaluation of hazard functions

[Provide a plot of the hazard function of the effect measure. The plots must be presented in separate figures for the intervention and comparator, respectively, and must include the estimated hazard for the observed data (if applicable). The plot must be discussed in the context of chosen the distribution for extrapolating the data of the effect measure.]

D.1.7 Validation and discussion of extrapolated curves

D.1.8 Adjustment of background mortality

D.1.9 Adjustment for treatment switching/cross-over

D.1.10 Waning effect

D.1.11 Cure-point

D.2 Extrapolation of [effect measure 2]

[For each effect measure please, fill in this section using the same template as stated in section D.1]

Appendix E. Serious adverse 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- Assessment report EMA/2190/2022 Page 115/116 1 group and two patients in the capecitabine group were hospitalized due to treatment related adverse events, essentially related to diarrhea. Seven patients discontinued the study, all treated with capecitabine, discontinued treatment due to HFS (10% vs 0%, p=0.013).

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.

Appendix F. Health-related quality of life

Not applicable, for rational see Section 10.

Appendix G. Probabilistic sensitivity analyses

Not applicable, CMA is conducted.

Table 59. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Probabilities				
Efficacy Outcome A	0.72			Beta
HSUV				
State A	0.79			Beta
Costs				
Hospitalization	20000			Gamma

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

Not applicable. No SLR is performed.

Table 60 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	e.g. Embase.com	E.g. 1970 until today	dd.mm.yyyy
Medline			dd.mm.yyyy
CENTRAL	Wiley platform		dd.mm.yyyy

Abbreviations:

Table 61 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk		dd.mm.yyyy
e.g. EMA website			dd.mm.yyyy

Abbreviations:

Table 62 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	e.g. conference website	Manual search	List individual terms used to search in the conference material:	dd.mm.yyyy
	Journal supplement [insert reference]	Skimming through abstract collection		dd.mm.yyyy

H.1.1 Search strategies

Table 63 of search strategy table for [name of database]

No.	Query	Results
#1		88244
#2		85778
#3		115048
#4		7011
#5		10053
#6		12332
#7		206348
#8		211070
#9	#7 OR #8	272517
#10	#3 AND #6 AND #9	37

H.1.2 Systematic selection of studies

Table 64 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population		
Intervention		
Comparators		
Outcomes		
Study design/publication type		
Language restrictions		

Table 65 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Study 1						
Study 2						

H.1.3 Quality assessment

H.1.4 Unpublished data

No unpublished data.

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

Not applicable, no data on HRQoL is applied in the dossier.

Table 66 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Embase.com		dd.mm.yyyy
Medline	Ovid		dd.mm.yyyy
Specific health economics databases[1]			dd.mm.yyyy

Abbreviations:

Table 67 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk		dd.mm.yyyy
ScHARRHUD	www.scharrhud.org		dd.mm.yyyy

Table 68 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	e.g. conference website	Electronic search	List individual terms used to search in the congress material:	dd.mm.yyyy

[1] Papaioannou D, Brazier J, Paisley S. Systematic searching and selection of health state utility values from the literature. Value Health. 2013;16(4):686-95.

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
	Journal supplement [insert reference]	Skimming through abstract collection		dd.mm.yyyy

I.1.1 Search strategies

[Describe the development of the search strategy and search string. Enter the inclusion and exclusion criteria for the search and justify (e.g. patient population, outcomes, study design, language, time frame, etc.).

The search must be documented for each database or resource incl. terms and syntax used, number of results retrieved in the table below.

Describe which criteria have been used to reject irrelevant studies (for example of a table to record exclusions, see Table 5 in NICE DSU Technical Support Document 9) and how the final selection has been made. Use PRISMA charts if appropriate (see example here) or use the editable table at the end of this document].

Table 69 Search strategy for [name of database]

No.	Query	Results
#1		88244
#2		85778
#3		115048
#4		7011
#5		10053
#6		12332
#7		206348
#8		211070
#9	#7 OR #8	272517
#10	#3 AND #6 AND #9	37

Literature search results included in the model/analysis:

[Insert results in a table]

I.1.2 Quality assessment and generalizability of estimates

[Provide a complete quality assessment for each relevant study identified. When non-Danish estimates are used, generalizability must be addressed.]

I.1.3 Unpublished data

[The quality of any unpublished data must be specifically addressed and a publication plan for unpublished data must be submitted.]

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

Not applicable, no systematic literature search was conducted for the purpose of this submission.

J.1.1 Ex. Systematic search for […]

Table 70 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	e.g. Embase.com	e.g. 1970 until today	dd.mm.yyyy
Medline			dd.mm. yyyy
CENTRAL	Wiley platform		dd.mm. yyyy

Abbreviations:

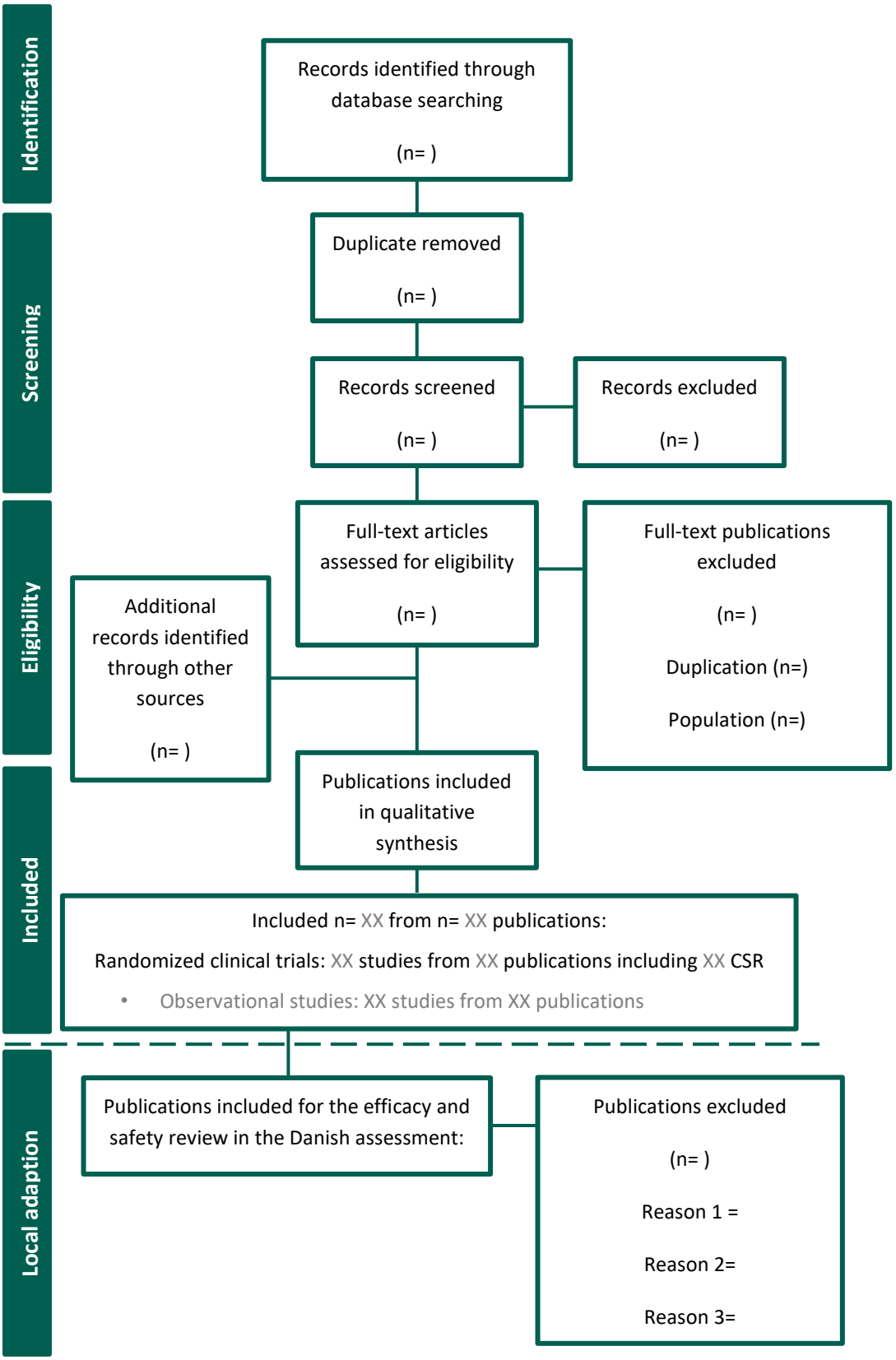
J.1.2 Ex. Targeted literature search for [estimates]

Table 71 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk		dd.mm.yyyy
			dd.mm.yyyy

Abbreviations:

Example of PRISMA diagram. The diagram is editable and may be used for recording the records flow for the literature searches and for the adaptation of existing SLRs.



Medicinrådet

Danish Medicines Council
Secretariat
Dampfærgevej 21-23, 3rd floor
DK-2100 Copenhagen Ø

+ 45 70 10 36 00
medicinraadet@medicinraadet.dk

www.medicinraadet.dk