Medicinrådet

Bilag til Medicinrådets anbefaling vedr. trifluridin/tipiracil i kombination med bevacizumab til behandling af metastatisk tyk- og endetarmskræft

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. trifluridin/tipiracil i kombination med bevacizumab
2. Forhandlingsnotat fra Amgros vedr. trifluridin/tipiracil i kombination med bevacizumab
3. Ansøgers endelige ansøgning vedr. trifluridin/tipiracil i kombination med bevacizumab

November 21, 2024

Danish Medicine Council (DMC) report, reply from Servier.

In general, we are in line with Danish Medicine Council (DMC) and believe that the report conforms with our assessment document.

However, there are 2 assumptions from DMC we would like to challenge.

1. According to the survival data we are not in line with DMC evaluation that we believe is a bit vague in its description and has a more pessimistic approach regarding stage IV patients alive at 3 and 5 years after diagnosis. In the model DMC use the generalized gamma with an OS of 3,2% at 3 years and 0,2% at 5 years which doesn't match the literature. We have used a more realistic approach, still conservative, with 8% alive at 3 years and 2,9% year 5 which is lower with existing evidence and the consequences seen in the table and described below.

	ICER
Servier	489,568 DKK
Medicinrådet	703,454 DKK

2. The total additional cost being 97.000.000 DKK is not reflecting the reality, as many patients in Denmark are offered rechallenge, since no other options exist for patients in a good performance status.
   Clinical practice seen in the phase II from P. Pfeiffer et. al, illustrating that BSC normally is used in later line than 3rd as described below in patients receiving previous active lines of treatment before randomization: (1)
   - ≤2 lines 20 patients (42%) monotherapy.
   - 3 lines, 13 patients (28%) monotherapy.
   - 4 lines, 8 patients (17%) monotherapy.
   - ≥5 lines, 6 patients (13%) monotherapy.

Reference

1. Pfeiffer et al. Lancet Oncol 2020 Published Online January 27, 2020 https://doi.org/10.1016/S1470-2045(19)30827-7

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14.11.2024

CAF/MBA

Forhandlingsnotat

Dato for behandling i Medicinrådet	18.12.2024
Leverandør	Servier A/S
Lægemiddel	Lonsurf (trifluridin/tipiracil)
Ansøgt indikation	Lonsurf i komb. med bevacizumab til behandling af metastatisk kolorektal cancer (mCRC) hos voksne patienter, som har modtaget to tidligere behandlingsregimer, herunder fluorpyrimidin-, oxaliplatin- og irinotecan-baseret kemoterapi, anti-VEGF-midler og/eller anti-EGFRmidler
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har forhandlet følgende pris på Lonsurf som gælder fra 01-01.2025. Prisen er betinget af Medicinrådets anbefaling af Lonsurf til den ansøgte indikation.

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	SAIP pr. 1. januar 2025 (DKK)	Betinget forhandlet SAIP (DKK) pr. 1. januar 2025	Rabatprocent ift. AIP for betinget forhandlet SAIP
Lonsurf	15 mg + 6,14 mg	20 stk. tabletter	6.135,53	[redacted]	[redacted]	[redacted]
Lonsurf	15 mg + 6,14 mg	60 stk. tabletter	18.398,64	[redacted]	[redacted]	[redacted]

Lonsurf	20 mg + 8,19 mg	20 stk. tabletter	8.180,71	[redacted]	[redacted]	[redacted]
Lonsurf	20 mg + 8,19 mg	60 stk. tabletter	24.534,17	[redacted]	[redacted]	[redacted]

Det betyder, at hvis Medicinrådet ikke anbefaler Lonsurf, indkøbes lægemidlet til den angivne SAIP per 1. januar 2025.

Aftaleforhold

[redacted]

Konkurrencesituationen

Tabel 2 viser lægemiddeludgifterne for Lonsurf + bevacizumab. Nuværende standardbehandling i 3. linje er best supportive care (BSC) dvs. ingen onkologisk behandling for mCRC, men alene palliativ behandling.

Tabel 2: Lægemiddeludgifter pr. patient

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift for et behandlingsforløb (SAIP, DKK)***
Lonsurf	20 mg + 8,19 mg	60 stk.	35 mg/m^2 2 gange dagligt på dag 1-5 og dag 8-12 i en 28 dages serie	[redacted]	[redacted]
Bevacizumab	25mg/ml	1*16 ml	5 mg/kg hver 2. uge i 14-dages serie	[redacted]	[redacted]
Pris for kombinationsbehandling					[redacted]

*Patientens kropsoverflade areal (BSA) = 1,91 jf. Medicinrådets vurderingsrapport.
** Patientens vægt = 78.6 kg jf. Medicinrådets vurderingsrapport.
*** Den gennemsnitlige behandlingslængde vurderes at være 6,2 måneder jf. Medicinrådets vurderingsrapport.

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Anbefalet (kun monoterapi)	Link til anbefaling
Sverige	Anbefalet (kun monoterapi)	Link til anbefaling
England	Anbefalet	Link til anbefaling

Konklusion

[redacted]

Application for the assessment of Lonsurf (Trifluridine/tipiracil) in combination with bevacizumab for the treatment of adult patients with metastatic colorectal cancer who have received two prior anticancer treatment regimens, including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents

Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
	Confidential information

Contact information

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Tables and Figures

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Abbreviations

AEs	Adverse events
AFT	Acceleration Failure Time
AIC	Akaine information criterion
BIC	Bayesian information criterion
BSA	Body surface area
BSC	Best supportive care
CEAC	Cost-effectiveness acceptability curves
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CRC	Colorectal cancer
CrI	Credible intervals
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DMC	Danish Medicines Council
DRG	Diagnosis related groups
ECOG	Eastern Coorperative Oncology Group
EGFR	Epidermal growth factor receptor
Embase	Excerpta Medica dataBASE
EQ-5D-5L	EuroQoL-5-Dimension-5-Levels
FAS	Full analysis set
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
HSUV	Health State Utility Value
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
ITC	Indirect treatment comparison
KM	Kaplan-Meier
KRIS	Coordinating Council for the Use of Hospital Medicine
LCHP	Log-cumulative hazards plot
LY	Life years
mCRC	Metastatic colorectal cancer
MEDLINE	Medical Literature Analysis and Retrieval System Online
MoM	Methods of moments
mOS	Median OS
mPFS	Median PFS
N/A	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICE DSU	NICE Decision Support Unit
NMA	Network meta-analysis
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PD	Progressed Disease

PF	Progression-Free
PFS	Progression-Free Survival
PH	Proportional Hazard
PICOS	Population, intervention, comparator, outcome and study design
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSM	Partioned Survival Model
QALY	Quality-adjusted life year
Q-Q	Quantile-Quantile
QoL	Quality of Life
RCT	Randomized Control Trial
RDI	Relative dose intensity
SAE	Serious Adverse Events
SD	Standard Deviation
SE	Standard error
SLR	Systematic Literature Review
SmPC	Summary of product characteristics
SoC	Standard of Care
SS	Safety set
TEAE	Treatment emergent adverse events
ToT	Time on Treatment
TSD	Technical Support Document
VEGF	Vascular endothelial growth factor
WTP	Willingness-to-pay
2L	Second line
3L	Third line
4L	Fourth line

1. Regulatory information on the medicine

Overview of the medicine [1,2]	
Proprietary name	Lonsurf®
Generic name	Trifluridine/tipiracil or FTD/TPI or TAS-102
Therapeutic indication as defined by EMA	Lonsurf is indicated in combination with bevacizumab for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have received two prior anticancer treatment regimens including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-vascular endothelial growth factor (VEGF) agents, and/or anti-epidermal growth factor receptor (EGFR) agents
Marketing authorization holder in Denmark	Servier A/S
ATC code	L01BC59
Combination therapy and/or co-medication	Bevacizumab
(Expected) Date of EC approval	EC approved July 26th, 2023
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	Yes
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	Lonsurf is indicated as monotherapy for the treatment of adult patients with mCRC who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents. (first approved April 2016)

Overview of the medicine [1,2]	
	Lonsurf is indicated as monotherapy for the treatment of adult patients with metastatic gastric cancer including adenocarcinoma of the gastroesophageal junction, who have been previously treated with at least two prior systemic treatment regimens for advanced disease. (first approved July 2019)
Other indications that have been evaluated by the DMC (yes/no)	Yes. Lonsurf have been evaluated by the DMC for the following indication: 1. Lonsurf monotherapy for the treatment of adult patients with metastatic gastric cancer including adenocarcinoma of the gastroesophageal junction, who have been previously treated with at least two prior systemic treatment regimens for advanced disease. Evaluation can be found here: https://medicinraa-det.dk/anbefalinger-og-vejledninger/laegemidler-og-indikationsudvidelser/t/trifluridintipiracil-lonsurf-gastrisk-kraeft
Dispensing group	BEGR/NBS
Packaging – types, sizes/number of units and concentrations	Lonsurf is supplied in two dosage strengths: • 15 mg/6.14 mg film-coated tablet (15 mg trifluridine/6.14 mg tipiracil) • 20 mg/8.19 mg film-coated tablet (20 mg trifluridine/8.19 mg tipiracil) Lonsurf is available in aluminium blister packs of 20 or 60 film-coated tablets Bevacizumab: Each ml of concentrate contains 25 mg of bevacizumab. One 4 ml vial contains 100 mg of bevacizumab, and one 16 ml vial contains 400 mg of bevacizumab.

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Lonsurf is indicated in combination with bevacizumab for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have received two prior anticancer treatment regimens including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-vascular endothelial growth factor

Summary	
	(VEGF) agents, and/or anti-epidermal growth factor receptor (EGFR) agents
Dosage regiment and administration	35 mg/m^2/dose administered orally twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle (until disease progression or unacceptable toxicity) and bevacizumab 5 mg/kg body weight iv q 2 weeks (days 1 & 15)
Choice of comparator	1. Lonsurf monotherapy 2. Best supportive care (BSC)
Prognosis with current treatment (comparator)	Colorectal cancer (CRC) is the second highest cause of cancer death worldwide. Metastases are the primary cause of death and patients with mCRC face a poor prognosis: low 5-year survival rates of between 10%-16% (across geographies). Increasing lines of systemic therapy is associated with a worse prognosis. It is therefore important to continue to optimise treatment across all lines of therapy for patients with mCRC [3–6]. The introduction of Lonsurf monotherapy provided patients with significant improvement in overall survival (OS) and progression-free survival (PFS) alongside maintenance of quality of life (QoL) and a manageable safety profile compared with BSC. The RECOURSE study comparing Lonsurf monotherapy with BSC + placebo in patients with refractory mCRC demonstrated a median overall survival (mOS) of 5.2 months and 7.2 for BSC and Lonsurf, respectively [3].
Type of evidence for the clinical evaluation	1. **Lonsurf plus bevacizumab versus Lonsurf:** Head-to-head study named SUNLIGHT. The SUNLIGHT study was a global phase 3 trial comparing Lonsurf plus bevacizumab with Lonsurf monotherapy for patients with mCRC in third line (3L) [7]. 2. **Lonsurf plus bevacizumab versus BSC:** The comparison of Lonsurf plus bevacizumab and BSC is based on an indirect comparison, as no head-to-head study is available. The indirect comparison if using the head-to-head study RECOURSE. The study was a phase 3 trial comparing comparing Lonsurf monotherapy with BSC + placebo in patients with refractory mCRC [3].
Most important efficacy endpoints (Difference/gain compared to comparator)	**Lonsurf plus bevacizumab versus Lonsurf (SUNLIGHT)** [7]**:** 1. mOS (primary endpoint): 10.8 months vs 7.5 months in Lonsurf plus bevacizumab and Lonsurf, respectively

Summary	
	(hazard ratio (HR): 0.61 [95% confidence interval (CI): 0.49-0.77]; p= 0.001). 2. Median progression-free survival (mPFS) (secondary end-point): 5.6 months in the Lonsurf plus bevacizumab arm and 2.4 months in the Lonsurf arm (HR: 0.44 [95% CI: 0.36–0.54]; p= 0.001). **Lonsurf plus bevacizumab versus BSC (Indirect comparison based on RECOURSE)** [3]**:** 1. mOS (primary endpoint): 10.8 months vs 5.2 months in Lonsurf plus bevacizumab and BSC, respectively (Random-effects: HR: [redacted] [95% credible interval (CrI): [redacted]]). 2. mPFS (secondary endpoint): 5.6 months in the Lonsurf plus bevacizumab arm and 1.7 months in the BSC arm (Random-effects: HR: [redacted] [95% CrI: [redacted]]).
Most important serious adverse events for the intervention and comparator	Anemia, neutropenia, hypertension, and neutrophil count decreased.
Impact on health-related quality of life	[redacted] [redacted]
Type of economic analysis that is submitted	Type of analysis: cost-utility Type of model: partitioned survival model
Data sources used to model the clinical effects	The SUNLIGHT trial and an NMA based on the RECOURSE trial.
Data sources used to model the health-related quality of life	The SUNLIGHT trial
Life years gained	Lonsurf + bevacizumab: [redacted] years Lonsurf monotherapy: [redacted] years BSC: [redacted]
QALYs gained	Lonsurf + bevacizumab: [redacted] QALY Lonsurf monotherapy: [redacted] QALY BSC: [redacted] QALY
Incremental costs	Lonsurf + bevacizumab vs. Lonsurf monotherapy: [redacted] Lonsurf + bevacizumab vs. BSC: [redacted]

Summary	
ICER (DKK/QALY)	Lonsurf + bevacizumab vs. Lonsurf monotherapy: [redacted] Lonsurf + bevacizumab vs. BSC: [redacted]
Uncertainty associated with the ICER estimate	Relative dose intensity
Number of eligible patients in Denmark	Approximately 420-492 new patients per year.
Budget impact (in year 5)	[redacted]

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

3.1 The medical condition

Colorectal cancer (CRC) involves the large intestine and the rectum, the lowest part of the digestive system (Figure 1) [8]. Colon cancer accounts for 72% of CRCs, and rectal cancer for 28% of CRCs [9], although these tumours are generally considered as a single tumour entity rather than separate cancer types [10]. Colon cancer can be further divided by location: left-sided CRC arises from the descending colon, sigmoid colon, and rectum, while right-sided CRC originates from the caecum, ascending colon, and transverse colon [11].

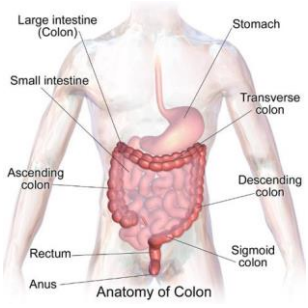

Figure 1 Diagram of the colon and rectum

The environmental and genetic factors that cause CRC do so by promoting the acquisition of hallmark behaviours of cancer in colon epithelial cells. One way these hallmark cancer traits are acquired is through the progressive accumulation of genetic and

epigenetic alterations that activate oncogenes and inactivate tumour suppressor genes. The loss of genomic and/or epigenomic stability has been observed in the majority of early neoplastic lesions in the colon (namely, aberrant crypt foci, adenomas, and serrated polyps) and is likely a central molecular and pathophysiological event in the initiation and formation of CRC. The loss of genomic and epigenomic stability accelerates the accumulation of mutations and epigenetic alterations in tumour suppressor genes and oncogenes, which drive the malignant transformation of colon cells through rounds of clonal expansion that select for those cells with the most aggressive and malignant behaviour [12].
A diagnosis of CRC either results from an assessment of a patient presenting with symptoms, or as a result of screening. The disease can be associated with spectrum of symptoms, including blood in stools, change in bowel habits, and abdominal pain. Other symptoms include fatigue, anaemia-related symptoms such as pale appearance and shortness of breath, and weight loss [12].

The site of the primary tumour influences prognosis [13]. Left-sided metastatic colorectal cancer (mCRC) has a better response to current available systemic therapies than right-sided mCRC [14]. The observed differences in treatment response may be attributed to the distinct tumour biology of right and left-sided tumours [14]:

- Right-sided tumours are more likely to be hypermutated and be associated with BRAF mutations.
- Left-sided tumours are characterised by a higher prevalence of microsatellite instability high (MSI-H) and a higher tumour mutational burden (TMB), and both of these factors predict better response to immunotherapy.

Therefore, patients with left-sided mCRC tend to have better overall survival (OS) than patients with right-sided mCRC [14].

Prognosis with third- and further-line treatment
Patients with mCRC generally receive first- and second-line treatment with fluorouracil-based chemotherapy (with oxaliplatin and irinotecan), vascular endothelial growth factor (VEGF)–based therapy (mainly bevacizumab), and epidermal growth factor receptor (EGFR)–targeted therapies (the last in patients with RAS wild-type tumors). Patients who have disease progression after receiving these therapies are considered to have refractory disease; however, many of these patients have a good performance status (PS) and may be considered for further therapy [15].
The proportion of patients who achieve an objective response to first-line systemic treatment of mCRC is approximately 50%, but only 10–20% of patients with mCRC will have tumour shrinkage during second-line treatment. Despite treatment with fluorouracil, irinotecan, and oxaliplatin, many patients with mCRC maintain an excellent PS, and effective therapy with a new drug is definitely indicated because progression-free survival (PFS) is less than 2 months without further therapy; hence, there is an unmet medical need for new treatment regimens. For patients with chemo refractory disease, the goal of therapy is to prevent tumour progression and prolong survival without compromising quality of life (QoL). Regorafenib and Lonsurf monotherapy have both shown prolonged PFS and OS compared with Best supportive care (BSC) in patients who had previously received all available standard therapies [16].

3.2 Patient population

The relevant patient population is adult patients with metastatic colorectal cancer (mCRC) who have received two prior anticancer treatment regimens including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents. Many patients progressing beyond second line (2L) treatment are still fit and well, and willing to receive further active treatment [17]; 86% of patients who progress to the third line (3L) treatment setting have an Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1 [18]. The ESMO guidelines recommend that at least 50%-60% of these "fit" patients should be offered systemic therapy as 3L treatment [19]. At this 3L stage, the aim of systemic treatment is to control disease progression, extend life, and to try and delay the continuum of treatment into fourth line (4L).
The incidence and prevalence of Danish patients with CRC can be found in Table 1 below [20,21].

Table 1 Incidence and prevalence in the past 5 years

Year	2019	2020	2021	2022	2023
Incidence of CRC in Denmark	4848	4537	4780	4534	NR
Prevalence of CRC in Denmark	26919	27533	NR	NR	NR

The estimation of annual eligible mCRC patients for treatment with e.g. Lonsurf plus bevacizumab in a 3L setting is provided in Table 2 below [22]. For more information refer to the budget impact sheet in the health economic model.

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	420	443	475	486	492

3.3 Current treatment options

Extract from Danish guidelines [23];

"*Ved progression under 1. linje behandling og med fortsat god almen tilstand bør patienten tilbydes yderligere medicinsk onkologisk behandling. Behandlingsvalget afhænger af tidligere behandlinger samt RAS/RAF mutationsstatus og inkluderer:*

- *Ved progression på irinotecan-baseret 1. linje kemoterapi skiftes til 2. linje oxaliplatin-baseret kemoterapi (A)*

- *Ved progression på oxaliplatin-baseret 1. linje kemoterapi skiftes til 2. linje irinotecan-baseret kemoterapi (A)*
- *Patienter med mKRC, der ikke tidligere har fået bevacizumab, bør behandles med tillæg af bevacizumab i senere behandlings linjer (A)*
- *Patienter med RAS-wildtype mKRC, der ikke tidligere er behandlet med anti-EGFR-antistoffer, bør behandles med anti-EGFR-antistof i kombination med irinotecan i senere behandlings linjer (A)*
- *Patienter med mKRC med BRAFV600E-mutation bør behandles med encorafenib og cetuximab (A)*
- *Re-introduktion med tidligere givet kemoterapi med eller uden biologisk behandling er et alternativ, såfremt sygdommen har et langt progressions-frit interval (B)*
- *For patienter med mKRC eksponeret og progredieret på al standard behandling bør mulighed for behandling med trifluridine/tiperacil i kombination med bevazicumab afsøges (ikke vurderet af Medicinrådet) (A)"*

3L treatment in mCRC primarily involves Lonsurf monotherapy, the only other 3L option for most patients is rechallenge with earlier effective therapies.
Lonsurf is recommended in all patients, irrespective of KRAS or BRAF mutation, who have been pre-treated with fluoropyrimidines, oxaliplatin, irinotecan, and biologics, if available, or in earlier lines of therapy following oxaliplatin and irinotecan regimen failure, depending on local approval [I, A; ESMO-MCBS score: 4] [24]. Additional treatment options are available for specific mutation subgroups, as shown in Figure 2.
Re-challenging with previously used systemic therapies, after an adequate time interval, may also be an option in later lines of treatment. When maintenance of QoL is the main goal, treatment selection for individual patients should consider differences in mechanisms of action and the safety profile of available 3L and further line options, including rechallenge treatments [25].

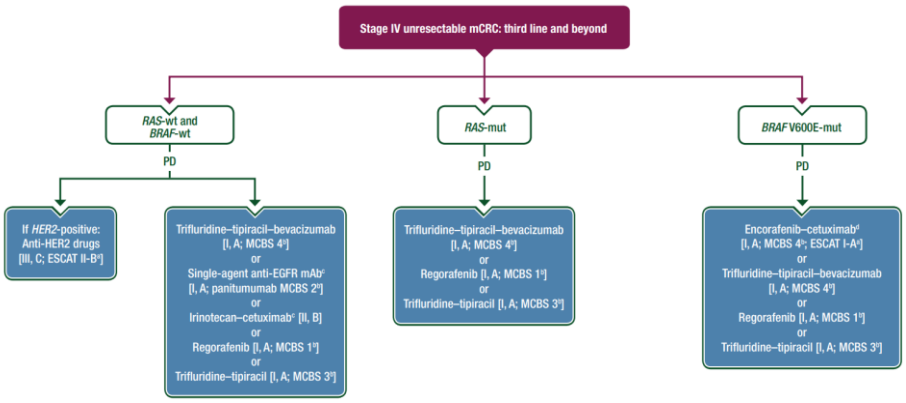

Figure 2 ESMO mCRC Living Guidelines recommended use of Lonsurf plus bevacizumab in 3L+ mCRC [24]

3.4 The intervention

The intervention in this submission is the combined treatment of Lonsurf plus bevacizumab. Lonsurf is an oral cytotoxic chemotherapy consisting of FTD and TPI, with the active metabolite of FTD inducing DNA dysfunction and cell death in tumour cells and the co-administration of TPI increasing the bioavailability of FTD. Bevacizumab is an anti-VEGF antibody that inhibits the activation of the VEGF signalling pathway, normalising the vasculature, facilitating the delivery of cytotoxic chemotherapy, and directly affecting tumour cells by inhibiting the formation of new vessels. Lonsurf in combination with bevacizumab showed enhanced activity on tumour volume compared with either drug alone in animal models of CRC, and Early data suggested the combination of Lonsurf with bevacizumab would significantly improve PFS and OS compared with Lonsurf monotherapy in patients with mCRC. An informative overview of the intervention is found in Table 3 below [1].

Table 3 Overview of intervention

Overview of intervention [1]	
Therapeutic indication relevant for the assessment	Lonsurf is indicated in combination with bevacizumab for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have received two prior anticancer treatment regimens including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents
Method of administration	Lonsurf: Per os (tablet) Bevacizumab: IV
Dosing	Lonsurf: 35 mg/m^2/dose administered orally twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle Bevacizumab: 5 mg/kg of body weight given once every 2 weeks
Dosing in the health economic model (including relative dose intensity (RDI))	Lonsurf: 35 mg/m^2/dose administered orally twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle (dose intensity; 85 %) Bevacizumab: 5 mg/kg every second week (dose intensity: 86.9 %)
Should the medicine be administered with other medicines?	No

Overview of intervention [1]	
Treatment duration / criteria for end of treatment	Lonsurf plus bevacizumab should be administered until disease progression or unacceptable toxicity
Necessary monitoring, both during administration and during the treatment period	Only during the treatment period
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No
Package size(s)	Lonsurf is supplied in two dosage strengths: • 15 mg/6.14 mg film-coated tablet (15 mg trifluridine/6.14 mg tipiracil) • 20 mg/8.19 mg film-coated tablet (20 mg trifluridine/8.19 mg tipiracil) Lonsurf is available in aluminium blister packs of 20 or 60 film-coated tablets Bevacizumab: Each ml of concentrate contains 25 mg of bevacizumab. One 4 ml vial contains 100 mg of bevacizumab, and one 16 ml vial contains 400 mg of bevacizumab.

3.4.1 The intervention in relation to Danish clinical practice

Lonsurf plus bevacizumab establishes a new standard of care (SoC) for mCRC patients who have progressed on two prior anticancer therapies and will replace BSC and Lonsurf monotherapy. Lonsurf plus bevacizumab is expected to replace BSC and Lonsurf monotherapy as the combination provides a statistically significant and clinically meaningful OS and PFS benefit when directly being compared with Lonsurf monotherapy or indirectly with other mCRC treatments, while maintaining health-related quality of life (HRQoL) and safety [5]. Even though the combination of Lonsurf plus bevacizumab is already used in some cases following Tværregionalt forum 2021 decision, there are currently no approved combination regimens specifically for 3L mCRC. There is therefore a need to improve efficacy and maintain QoL through therapeutic options used in new combinations in 3L mCRC.

3.5 Choice of comparator(s)

Prior to the introduction of Lonsurf monotherapy, patients reaching the 3L had very limited treatment options. The introduction of Lonsurf monotherapy created new possibilities within the continuum of care, extending OS and PFS in patients with

chemorefractory mCRC, as well as maintaining ECOG PS and QoL [3] (Table 4). As a result, Lonsurf monotherapy is currently one of the primary SoC treatment options in the 3L setting, however, not yet been reimbursed in Denmark. One comparator is, therefore, Lonsurf monotherapy. A second treatment option is BSC as suggested by the Danish Medicines Council (DMC). BSC in this context would be equal to the placebo-arm in the RECOUSE study (described in section 7), as guided by the DMC, and includes no antineoplastic chemotherapy, hormonal therapy, or immunotherapy.
Overviews of the comparators are found in Table 4 and Table 5, respectively.

Table 4 Overview of comparator (Lonsurf monotherapy)

Overview of comparator (Lonsurf monotherapy) [1]	
Generic name	FTD/TPI (Trifluridin/tipiracil)
ATC code	L01BC59
Mechanism of action	Lonsurf is an oral cytotoxic chemotherapy consisting of FTD/TPI, with the active metabolite of FTD inducing DNA dysfunction and cell death in tumour cells and the co-administration of tipiracil increasing the bioavailability of FTD
Method of administration	Per os (tablet)
Dosing	35 mg/m^2/dose administered orally twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle
Dosing in the health economic model (including RDI)	35 mg/m^2/dose administered orally twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle (dose intensity; 85%)
Should the medicine be administered with other medicines?	No
Treatment duration/ criteria for end of treatment	Only during the treatment period
Need for diagnostics or other tests (i.e. companion diagnostics)	No

Overview of comparator (Lonsurf monotherapy) [1]	
Package size(s)	Lonsurf is supplied in two dosage strengths: • 15 mg/6.14 mg film-coated tablet (15 mg trifluridine/6.14 mg tipiracil) • 20 mg/8.19 mg film-coated tablet (20 mg trifluridine/8.19 mg tipiracil) Lonsurf is available in aluminium blister packs of 20 or 60 film-coated tablets

Table 5 Overview of comparator (Best Supportive Care)

Overview of comparator (BSC)	
Generic name	BSC/placebo
ATC code	N/A
Mechanism of action	N/A
Method of administration	Per os (tablet)
Dosing	Placebo in a 28-day cycle (days 1-5 & 8-12)
Dosing in the health economic model (including RDI)	N/A
Should the medicine be administered with other medicines?	No active pharmaceutical, BSC
Treatment duration/ criteria for end of treatment	N/A
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	N/A

3.6 Cost-effectiveness of the comparator(s)

Reimbursement for Lonsurf is currently only provided on an individual basis in Denmark for patients with mCRC. In 2016, the Medicines Council's predecessor (the Coordinating Council for the Use of Hospital Medicine (KRIS)) declined the reimbursement of Lonsurf

monotherapy for the treatment of adult patients with metastatic colorectal cancer who have been previously treated with, or not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents. Subsequently, in September 2020, the Danish Medicines Council (DMC) disapproved the request for assessment based on exploratory data from RECOURSE study in patients with good prognostic characteristics. The reason for disapproving the request for assessment was due to a lack of internal resources in the DMC to conduct a health economic model. In 2021, DCCG requested to apply for the reimbursement of the combination of Lonsurf with bevacizumab based on the data from the Danish phase II study by Pfeiffer et al, however, DMC was not able to initiate a reassessment due to the limited resources.
A description of cost-effectiveness for BSC is not applicable (N/A).

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

The relevant efficacy outcomes included in this submission are OS, PFS and HRQoL. The efficacy outcomes are based on the SUNLIGHT trial and a network meta-analysis (NMA) based on the RECOURSE trial. See definitions for the respective outcome in Table 6 below [3,7,22].

Table 6 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
OS [SUNLIGHT]		Time elapsed between the date of randomisation and the date of death due to any cause	The HR is based on a Cox proportional hazards model with adjustment for the variables used for stratification for randomization, and study arm
OS [RECOURSE]		Time from randomization to death from any cause	The HR and two-sided 95% CIs based on a stratified Cox model and the associated Kaplan–Meier survival estimates. The median follow-up time for survival was calculated by means of the reverse Kaplan–Meier method.
PFS [SUNLIGHT]		Time elapsed between the randomisation and the date of radiologic tumour progression or death from any cause	A stratified log-rank test at a two-sided 5% significance level was used to compare the distributions of overall survival and progression-free survival between the two trial groups,

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
			and a stratified Cox proportional-hazards model was used to assess the magnitude of the treatment difference
PFS [RECOURSE]		Time from randomization to the first radiologic confirmation of disease progression or death from any cause	The HR and two-sided 95% CIs based on a stratified Cox model and the associated Kaplan–Meier survival estimates.
HRQoL [SUNLIGHT]		Utility	EQ-5D-5L

Validity of outcomes

A study by Pfeiffer et al. (2020) investigated treatment with Lonsurf monotherapy and Lonsurf plus bevacizumab in Danish mCRC patients, and the endpoints in the trial corresponded to the relevant efficacy outcomes in this submission; OS and PFS. Patients in a 3L setting are facing a poor prognosis, and the relevancy of focusing on OS, PFS and HRQoL is assessed to be highly relevant and clinically plausible [16].

4. Health economic analysis

4.1 Model structure

The economic analysis uses a cost-utility framework, presenting outcomes in terms of cost per quality-adjusted life year (QALY) and incremental cost-effectiveness ratio (ICER). The adaptable feature of the model permits customization to accommodate health technology assessments (HTAs) in multiple national settings.

The model underwent an adaption to the context of the DMC while maintaining its original structure as a partitioned survival model evaluating the progression of mCRC over time in both Lonsurf in combination with bevacizumab, Lonsurf monotherapy and BSC treatment arms. This structure adheres to previous submissions to the National Institute for Health and Care Excellence (NICE) [26,27] and follows a three-health-state framework: Progression Free (PF), Progressed Disease (PD), and Death, see Figure 3. The endpoints of the model were OS and time in PFS derived from the PHASE III open-labeled clinical trial, SUNLIGHT [28]. All patients initiate the model in the PF state and remain until progression is confirmed, after which they transition to the PD state. Eventually, all patients enter the absorbing state of Death, where they will remain. All health states are

mutually exclusive, reflecting the inability of patients to re-enter less severe states that are initially being in.

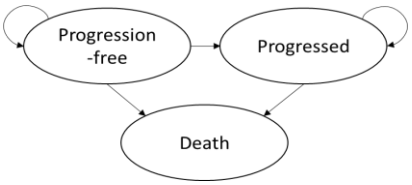

Figure 3 Partitioned survival model

4.2 Model features

The features of the model are aligned with the DMC's guidelines. See Table 7 for a summary of the model's features. The model's cycle length was determined to be 7 days, deemed sufficiently brief to capture diverse dosing regimens. Lonsurf was dosed twice daily on days 1-5 and 8-12 in a 28-day cycle until disease progression or unacceptable toxicity. Bevacizumab was dosed intravenously every two weeks alongside the oral dose of Lonsurf. Given the short cycle length, it is assumed that a half-cycle correction is unnecessary in this economic model. The model's time horizon of 10 years was chosen to reflect all relevant costs and health benefits in line with DMC guidelines. Based on data from the SUNLIGHT trial, the time horizon of 10 years was assumed to be sufficient to analyze the intervention Lonsurf plus bevacizumab and comparators (Lonsurf monotherapy and BSC) as <1% of patients are alive longer than this timeframe. All costs and potential health benefits were discounted at 3.5% in line with the DMC and Danish Ministry of Finance, and lastly, background mortality was applied to reflect the Danish population's general mortality.

All treatments are assumed to stop upon progression, and therefore a cap was applied to ensure time on treatment (ToT) remained equal to or below PFS. All assumptions are illustrated in Table 8.

Table 7 Features of the economic model

Model features	Description	Justification
Patient population	The total model population only includes adult patients with mCRC, who have previously received two anti-cancer treatment regimens including: fluoropyrimidine, oxaliplatin and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents.	The population of the model is in line with current Lonsurf approval, and the population investigated in the SUNLIGHT trial [28].
Perspective	Limited societal perspective	According to DMC guidelines

Model features	Description	Justification
Time horizon	Lifetime (10 years)	To capture health benefits and costs in line with DMC guideline Based on the median age from the SUNLIGHT trial, the starting age of the patient population is 62 Years of age. A time horizon of 10 years is thereby assumed to be sufficient to analyse the intervention and comparator as <1% of patients are alive longer than this timeframe [28].
Cycle length	One week	A cycle length of 7 days is used in the model as this is considered short enough to capture the various dosing regimens included.
Half-cycle correction	No	Given the short cycle length, a half cycle correction is deemed not relevant.
Discount rate	3.5%	According to the DMC guidance and in accordance with the Danish Ministry of Finance
Intervention	Lonsurf (Trifluridine/tipiracil) in combination with bevacizumab	Servier's product
Comparator(s)	Lonsurf monotherapy BSC	Danish clinical practice according to DMC
Outcomes	OS, PFS, ToT and EQ-5D-5L	

Table 8 Model feature assumptions

	Description
Assumptions	

1	Cycle length is assumed to have a length of 1 week. This cycle length is in accordance with the administration of multiple treatments included in the treatment regimen.
2	The time horizon is chosen to be 10 years to reflect the maximum lifetime of patients based on a starting age of 62 years of age and that less than 1% of patients are estimated to survive for longer than this period [28].
3	Treatment is assumed to stop upon progression, and therefore a cap was applied to ensure ToT remained equal or below PFS
4	Efficacy: individual models were fit to each treatment arm where patient-level data was available. Using the same network for the comparators was deemed more appropriate than employing results from different networks.
5	Health state utility values were derived from the clinical trial SUNLIGHT. Separate disutilities were applied to account for different treatment toxicities.
6	BSC costs are assumed to be captured in routine visits, for administrations costs associated with oral treatment those are assumed to be captured in routine monitoring.

5. Overview of literature

5.1 Literature used for the clinical assessment

The literature used for the clinical assessment of Lonsurf plus bevacizumab and Lonsurf monotherapy is based on a head-to-head study; the SUNLIGHT trial. Thus, a systematic literature review (SLR) was not conducted which is in correlation with the DMC guidelines.

The literature used for the clinical assessment of Lonsurf plus bevacizumab and BSC is based on an indirect comparison, an NMA, why a systematic literature review was conducted. Appendix H includes a detailed description of the SLR.

All studies included in the assessment of efficacy and safety of Lonsurf are listed in Table 9 below.

Table 9 Relevant literature included in the assessment of efficacy and safety

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
Full paper; Prager, G. W. et al. (2023b). Trifluridine-Tipiracil and Bevacizumab in Refractory Metastatic Colorectal Cancer. N Engl J Med 388(18): 1657-1667. [7]	SUNLIGHT	NCT04737187	Start: 25/11/2020 Completion: 18/02/2022 Data cut-off 05/07/2022 Future data cut-offs: Not reported	Lonsurf plus bevacizumab vs. Lonsurf monotherapy in adults with unresectable, refractory mCRC
Full paper; Mayer R.J et al. Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer. N Engl J Med 2015;372:1909-19. [3]	RECOURSE	NCT01607957	Start: June 17, 2012 Completion: October 8, 2013 Data cut-off: Not reported Future data cut-offs: 2016	Double- Blind, Phase 3 Study of TAS-102 plus BSC versus Placebo plus BSC in Patients with Metastatic Colorectal Cancer Refractory to Standard CT.
Lipsyc-Sharf M et al. Oncologist 2022;27:292-98. [29]	BOND-3	NCT02292758	Study start: Dec 2014 Study completion: Sep 2019	Lonsurf plus bevacizumab and BSC
Poulin-Costello et al. Target Oncol. 2013;(2):127-36. [29]	20020408	NCT00113763	Study start: Jan 2004 Study completion: Jun 2009	Lonsurf plus bevacizumab and BSC
Price et al. Lancet Oncol. 2014;6:569-79. [30]	ASPECCT	NCT01001377	Study start: Feb 2010 Study completion: Mar 2017	Lonsurf plus bevacizumab and BSC

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
Jonker et al. N Engl J Med 2007;357:2040-8. [31]	CO.17	NCT00079066	Study start: Aug 2003 Study completion: Feb 2009	Lonsurf plus bevacizumab and BSC
Li et al. Lancet Oncol. 2015;(6):619-29. [32]	CONCUR	NCT01584830	Study start: apr 2012 Study completion: Jan 2016	Lonsurf plus bevacizumab and BSC
Grothey et al. Lancet. 2013;381:303-12. [33]	CORRECT	NCT01103323	Study start: Apr 2010 Study completion: Jan 2014	Lonsurf plus bevacizumab and BSC
Li et al. JAMA. 2018;319:2486-96. [34]	FRESCO	NCT02314819	Study start: Dec 2014 Study completion: Jan 2017	Lonsurf plus bevacizumab and BSC
Dasari et al. Lancet. 2023;402:41-53. [35]	FRESCO-2	NCT04322539	Study start: Aug 2020 Study Completion: Jul 2022	Lonsurf plus bevacizumab and BSC
Segelov et al. J Clin Oncol. 2016;34:2258-64. [36]	ICECREAM	ACTRN12612000901808	Study start: Nov 2012 Study completion: Dec 2014	Lonsurf plus bevacizumab and BSC
Pfeiffer et al. Lancet Oncol. 2020;(3):412-20. [37]	Pfeiffer 2020	EudraCT 2016-005241-23	Study start: Aug 2017 Study completion: June 2019	Lonsurf plus bevacizumab and BSC

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
Xu et al. J Clin Oncol. 2018;36:350-58. [38]	TERRA	NCT01955837	Study start: Sep 2013 Study completion: Jun 2016	Lonsurf plus bevacizumab and BSC
Napolitano et al. Int J Cancer 2023;153:1520-28. [39]	VELO	NCT05468892	Study start: Oct 2019 Study completion: Jun 2022	Lonsurf plus bevacizumab and BSC
Xu et al. J Hematol Oncol. 2017;10:22. [40]	Xu 2017	NCT02196688	Study start: Apr 2014 Study completion: Nov 2015	Lonsurf plus bevacizumab and BSC
Yoshino et al. Lancet oncol 2012;(10):993-1001. [41]	Yoshino 2012	JapicCTI-090880	Study start: Aug 2009 Study completion: Apr 2010	Lonsurf plus bevacizumab and BSC

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

The assessment of HRQoL is based on the EuroQoL-5-Dimension-5-Levels (EQ-5D-5L) data from the SUNLIGHT trial (see Table 10). Thus, no SLR has been conducted.

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

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Prager, G. W. et al. (2023b). Trifluridine-Tipiracil and Bevacizumab in Refractory Metastatic Colorectal Cancer. N Engl J Med 388(18): 1657-1667. SUNLIGHT	Utilities for pre- and post-progression disease state	Section 11

5.3 Literature used for inputs for the health economic model

Literature used for the health economic model was sourced based on relevant trials for OS, PFS and ToT. adverse events (AEs), safety data and disutility's were sourced based on the Sunlight trial. See Table 11.

Table 11 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
Prager, G. W. et al. (2023b). Trifluridine-Tipiracil and Bevacizumab in Refractory Metastatic Colorectal Cancer. N Engl J Med 388(18): 1657-1667. SUNLIGHT	OS, PFS, ToT	Phase III trial	Section 9

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
NMA	HR for BSC	A NMA comparing multiple drug candidates for mCRC. Comparisons for Lonsurf plus bevacizumab, Lonsurf monotherapy and BSC.	Section 9.1
Full paper; Mayer R.J et al. Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer. N Engl J Med 2015;372:1909-19.	Input for NMA on HR for BSC Grade >3 AEs for BSC	Phase II trial	Section 9.1
Yoshino T, Mizunuma N, Yamazaki K, et al. TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial. *Lancet Oncol*. 2012;13(10):993-1001. doi:10.1016/S1470-2045(12)70345-5	Input for NMA on HR for BSC	Phase II trial	Section 9.1
Xu J, Kim TW, Shen L, et al. Results of a Randomized, Double-Blind, Placebo-Controlled, Phase III Trial of Trifluridine/Tipiracil (TAS-102) Monotherapy in Asian Patients With Previously Treated Metastatic Colorectal Cancer: The TERRA Study. *J Clin Oncol*. 2018;36(4):350-358. doi:10.1200/JCO.2017.74.3245	Input for NMA on HR for BSC	Phase III trial	Section 9.1
Sullivan PW, Ghushchyan V. Preference-Based EQ-5D index scores for chronic conditions in the United States. *Med Decis Making*. 2006;26(4):410-420. doi:10.1177/0272989X06290495	Disutility: Anaemia	Targeted literature review	Section 11.2.2
Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. *Health Qual Life Outcomes*. 2008;6:84. Published 2008 Oct 21. doi:10.1186/1477-7525-6-84	Disutility: Neutropenia	Targeted literature review	Section 11.2.2

6. Efficacy – Lonsurf plus bevacizumab vs Lonsurf monotherapy

This section describes the comparison of Lonsurf plus bevacizumab and Lonsurf monotherapy, which is one of the comparators in this submission. The comparison is solely based on the head-to-head study SUNLIGHT which provides key evidence for the clinical efficacy and safety of Lonsurf plus bevacizumab and Lonsurf monotherapy.

6.1 Efficacy of Lonsurf plus bevacizumab compared to Lonsurf monotherapy for patients with metastatic colorectal cancer

6.1.1 Relevant studies

The SUNLIGHT trial was an open-label, multi-national, randomised, controlled two-arm Phase 3 trial that investigated the efficacy and safety of Lonsurf plus bevacizumab vs. Lonsurf monotherapy in adults with unresectable, refractory mCRC who had received a maximum of two prior chemotherapy regimens containing fluoropyrimidines, irinotecan, oxaliplatin, and anti-VEGF, and/or (in patients with RAS WT tumours) an anti-EGFR antibody therapy. The SUNLIGHT trial is the first Phase 3 clinical study conducted in the 3L setting of mCRC to assess a treatment versus an active comparator. Patients were randomly assigned 1:1 to receive either Lonsurf plus bevacizumab or Lonsurf monotherapy, given as 28-day treatment cycles. Patients were screened for eligibility at 87 sites in 13 countries (Austria, Belgium, Brazil, Denmark, France, Germany, Hungary, Italy, Poland, Russia, Spain, Ukraine, and the US) [7].

An overview of the study design of SUNLIGHT is presented in Table 12 below. More information about the study is found in Appendix A.

Table 12 Overview of the study design for SUNLIGHT [7,42]

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
SUNLIGHT, Phase 3, NCT04737187 N Engl J Med 2023; 388(18): 1657-1667.	Randomized phase III / open-label / placebo-control/ active comparator-control	Randomization from November 25, 2020, to February 18, 2022, cut-off date of July 5, 2022.	mCRC refractory to standard therapies in the US, Europe, and rest of the world	Lonsurf plus bevacizumab	Lonsurf	Primary endpoint was OS, defined as the time from randomization to death from any cause (maximum duration: up to 20 months). Secondary end points included investigator-assessed PFS (up to 20 months); ORR and DCR according to Response Evaluation Criteria in Solid Tumours, version 1.1 (up to 20 months); QoL, assessed with EORTC QLQ–C30, version 3.0, and EQ-5D-5L; and safety, which included treatment-related emergent AEs and Serious Adverse Events (SAEs) assessed by Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (From Baseline up to 30 days after the last dose of study treatments, i.e. up to 19.5 months).

6.1.2 Comparability of studies (N/A)

In accordance with the DMC guidelines, this section is omitted since it is not relevant for comparisons based on head-to-head studies.

6.1.3 Comparability of patients across studies (N/A)

In accordance with the DMC guidelines, this section is omitted since it is not relevant for comparisons based on head-to-head studies.

Table 13 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety (N/A)

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

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

The combination of Lonsurf plus bevacizumab and Lonsurf monotherapy has been studied in an Investigator-initiated, open-label, randomized phase 2 clinical trial in Denmark (EudraCT, 2016-005241-23). The study enrolled 93 patients with mCRC who were refractory to standard therapies from four cancer centres in Denmark. From August 24, 2017, to October 31, 2018, participants were enrolled and randomly assigned (1:1) in block sizes of two, four, or six by a web-based tool to receive oral Lonsurf monotherapy (35 mg/m2 twice daily on days 1–5 and 8–12 every 28 days) alone or combined with intravenous bevacizumab (5 mg/kg on days 1 and 15) until progression, unacceptable toxicity, or patient decision to withdraw [16].The primary endpoint was investigator-evaluated PFS, calculated from the date of randomization to the first date of radiological or clinical progression, time of death, or censored on cutoff date. The secondary endpoint was OS, defined as death due to any cause or censored at the cutoff date [16]. The combination of Lonsurf plus bevacizumab was associated with significantly longer median PFS (mPFS) and median OS (mOS) than Lonsurf monotherapy (mPFS: 4.6 vs. 2.6 months, p=0.0015; mOS: 9.4 vs. 6.7 months, p=0.028). The combination of Lonsurf plus bevacizumab could be a new treatment option for patients with refractory mCRC and could be a practice-changing development [16]. The baseline characteristics of the patient population in the SUNLIGHT trial and the Danish patient population included in the study by Pfeiffer et al. 2020 are assessed to be in accordance with each other (See Table 88 in Appendix K). Therefore, it is believed that the SUNLIGHT trial is representative of Danish patients who suffer from mCRC. In Table 14, the characteristics used in this submission are stated. The SUNLIGHT trial will be the base case for model inputs as a greater patient population has been investigated [7,16].

Table 14 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population [16]	Value used in health economic model [7]
Age, calculated mean	66	63
Male sex (%), calculated mean	58	52
Weight, kg	NR	74

6.1.5 Efficacy – results per SUNLIGHT

The primary outcome from SUNLIGHT was OS, with PFS, Objective response rate (ORR), Disease control rate (DCR), Treatment-emergent adverse events (TEAEs), and QoL as secondary outcomes. TEAEs and QoL are documented in sections 10 and 11, respectively. An overview of the efficacy results is shown in Table 15 below, and a description of each efficacy result is also found in this section. All patients to whom treatment was randomly assigned were included in the full analysis set (FAS) for efficacy outcomes, with patients analysed in the arm they were assigned. All

patients who took at least one dose of Lonsurf were included in the safety set (SS), with patients analysed according to the treatment they received. Definitions and methods for measuring the efficacy outcome are stated in section 3.7 [7].

Table 15 Overview of the efficacy results per SUNLIGHT

Outcome measure	Lonsurf+bevacizumab (N=246)	Lonsurf (N=246)	Result
OS	Median: 10,8 months (95% CI: 9.36, 11.83)	Median: 7,5 months (95% CI: 6.34, 8.57)	Median: 3,3 months HR: 0.61 (95% CI: 0.49, 0.77); p=0.001)
PFS	Median: 5.6 months (95% CI, 4.5 to 5.9)	Median: 2.4 months (95% CI, 2.1 to 3.2)	Median: 3,2 months HR: 0.44; (95% CI, 0.36 to 0.54; p=0.001)
DCR	69,5%	41,9%	Difference of 27.6% (95% CI:19.21, 36.07; p < 0.001).
ORR	6,1%	1,2%	Difference of 4.9% (95% CI: 1.59, 8.17; p = 0.007).

Overall survival

The primary analysis of OS was performed at the survival cut-off of July 19, 2022. As of this survival cut-off, events (deaths) in the FAS were observed for 148 patients (60.2%) in the Lonsurf plus bevacizumab group and 183 patients (74.4%) in the Lonsurf group [22].

The median follow-up was 14.2 months (interquartile range: 12.6 to 16.4 months) in the Lonsurf plus bevacizumab group and 13.6 months (interquartile range: 12.7 to 15.9 months) in the Lonsurf monotherapy group (Prager 2023b). At the time of the analysis, 13.0% of the patients in the combination group and 1.6% of the patients in the Lonsurf monotherapy group were still receiving treatment [7].

The combination of Lonsurf plus bevacizumab resulted in a clinically meaningful and statistically significant survival benefit compared to Lonsurf monotherapy. Lonsurf plus bevacizumab improved OS by 3.3 months compared to Lonsurf monotherapy (mOS of 10.8 months [95% CI: 9.36, 11.83] with Lonsurf plus bevacizumab vs. 7.5 months [95% CI: 6.34, 8.57] with Lonsurf monotherapy) (Prager 2023b). The improvement in mOS with Lonsurf plus bevacizumab compared with Lonsurf monotherapy resulted in an HR of 0.61 (95% CI: 0.49, 0.77; p<0.001). A Kaplan-Meier (KM) curve for OS is depicted in Figure 4 [7].

The estimate of survival probability was consistently higher with Lonsurf plus bevacizumab than with Lonsurf monotherapy at 6 months, 12 months, and 18 months (Table 16) [7].

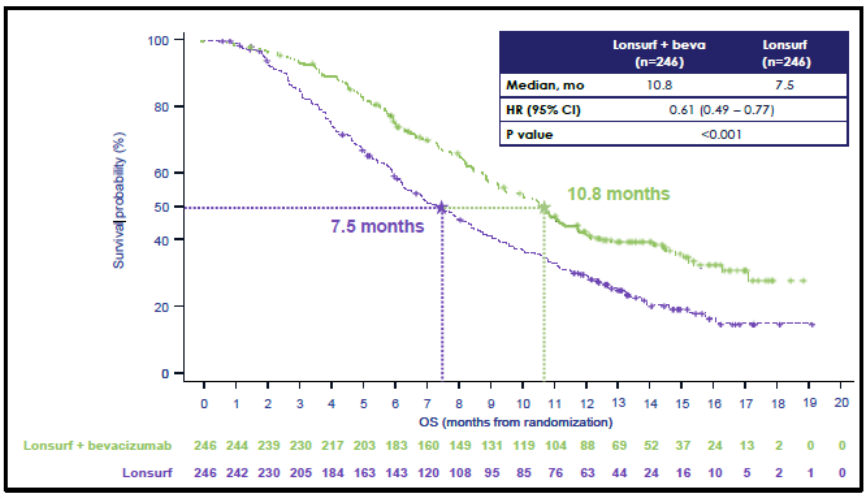

Figure 4 Kaplan-Meier curve for OS in patients with mCRC receiving Lonsurf plus bevacizumab or Lonsurf monotherapy as 3L treatment

Table 16 Median OS and survival probability for patients with mCRC receiving Lonsurf plus bevacizumab or Lonsurf monotherapy as 3L treatment

	Lonsurf plus bevacizumab (n=246)	Lonsurf Monotherapy (n=246)
OS, median months (95% CI)	10.78 (936, 11.83)	7.46 (6.34, 8.57)
HR (95% CI)	0.61 (0.49, 0.77)	
p-value	P<0.001	
Survival probability		
Survival probability at 6 months (95% CI)	77% (72%, 82%)	61% (55%, 67%)
Survival probability at 12 months (95% CI)	43% (36%, 49%)	30% (24%, 36%)
Survival probability at 18 months (95% CI)	28% (19%, 37%)	15% (9%, 22%)

Progression-free survival

Lonsurf plus bevacizumab resulted in a clinically and statistically significant improvement in PFS compared to Lonsurf monotherapy, with an estimated HR of 0.44 (95% CI: 0.36, 0.54; p<0.001), corresponding to a 56% reduction in relative risk of disease progression or death. Lonsurf plus bevacizumab resulted in an increase of 3.15 months mPFS, a greater than two-fold increase versus Lonsurf monotherapy (5.55 months [95% CI: 4.50, 5.88] vs. 2.40 months [95% CI: 2.07, 3.22]. The probability of being PF was consistently higher in patients receiving Lonsurf plus bevacizumab than in patients receiving Lonsurf monotherapy at 3 months, 6 months, 9 months, and 12

months. A KM curve for PFS and PFS probabilities at the mentioned times are found in Figure 5 and Table 17, respectively [7].

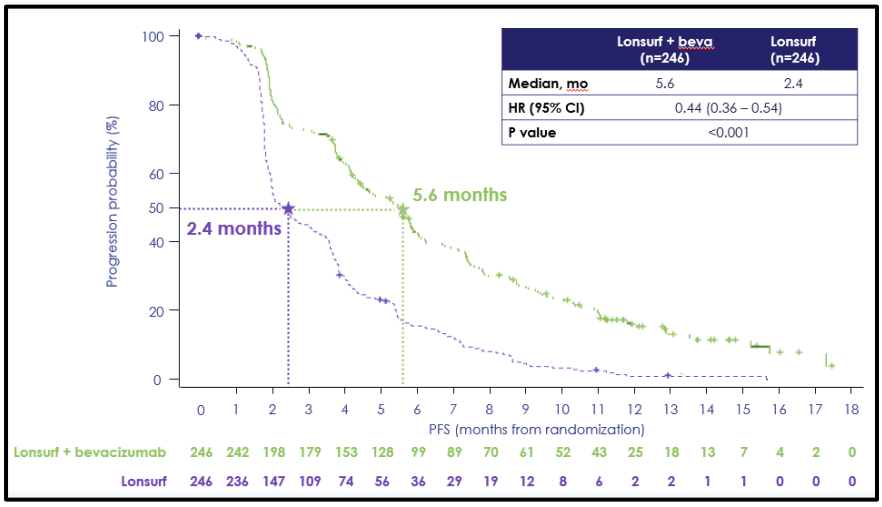

Figure 5 Kaplan-Meier curve for PFS for patients with mCRC receiving Lonsurf plus bevacizumab or Lonsurf monotherapy as 3L treatment

Table 17 PFS data for patients with mCRC receiving Lonsurf plus bevacizumab or Lonsurf monotherapy as 3L treatment

	Lonsurf plus bevacizumab (n=246)	Lonsurf Monotherapy (n=246)
PFS, median months (95% CI)	5.55 (4.50, 5.88)	2.40 (2.07, 3.22)
HR (95% CI)	0.44 (0.36, 0.54)	
p-value	P<0.001	
PSF probability		
Survival probability at 3 months (95% CI)	73% (67%, 78%)	45% (39%, 51%)
Survival probability at 6 months (95% CI)	43% (37%, 49%)	16% (11%, 21%)
Survival probability at 12 months (95% CI)	28% (22%, 34%)	5% (3%, 9%)
Survival probability at 18 months (95% CI)	16% (12%, 21%)	1% (0%, 3%)

ORR and DCR

ORR was significantly higher for patients receiving Lonsurf plus bevacizumab (6.1% [95% CI: 3.5%, 9.9%]) compared with Lonsurf monotherapy (1.2% [95% CI: 0.3%, 3.5%]). The between-group difference in ORR was 4.9%-points (95% CI: 1.59, 8.17; p=0.007), translating to a five-fold increase in ORR with the combination regimen [7].

DCR was also significantly higher in patients treated with Lonsurf plus bevacizumab compared with Lonsurf monotherapy: 69.5% of patients receiving Lonsurf plus bevacizumab had their disease controlled compared with 41.9% receiving Lonsurf. The between-group difference in DCR was 27.6% (95%CI: 19.21, 36.07; p<0.007) [7].

7. Efficacy – Lonsurf in combination with bevacizumab vs best supportive care

This section describes the comparison of Lonsurf plus bevacizumab and best supportive care. As the DMC expert committee for CRC requested a comparison of BSC and Lonsurf in combination with bevacizumab based on RECOURSE, a naïve comparison between the BSC-arm in RECOURSE and the Lonsurf + bevacizumab-arm in SUNLIGHT is presented. Additionally, an NMA including studies relevant for the comparison has been conducted. In this section, only RECOURSE is described in detail to simplify the submission dossier.

7.1 Efficacy of Lonsurf in combination with bevacizumab compared to placebo for patients with metastatic colorectal cancer

7.1.1 Relevant studies

The RECOURSE trial was a randomized, double-blinded phase 3 study that investigated the efficacy and safety of Lonsurf monotherapy vs. placebo in 800 patients with mCRC whose cancer had been refractory to antitumor therapy or who had had clinically significant AEs that precluded the re-administration of those therapies. Patients were randomly assigned to receive Lonsurf monotherapy or placebo in a 2:1 ratio, and were stratified based on tumour status, the time between first diagnosis of metastases and randomization, and geographic region. Treatment was administered twice daily, 5 days a week, with 2 days of rest, for 2 weeks, followed by a 14-day rest period which corresponds to completing one treatment cycle. This regimen was repeated every 4 weeks and a maximum of three reductions in dose in decrements of 5 mg per square meter was allowed as of [3]. More information about the study is found in Appendix A.

For the NMA, 16 studies (including RECOURSE and SUNLIGHT) were included in based a SLR, including studies with patients with unresectable adenocarcinoma of the colon or rectum who had received two prior chemotherapy regimens for the treatment of advanced or metastatic CRC and demonstrated progressive disease or intolerance to the last regimen (i.e., third-line or beyond).

An overview of the studies is presented in Table 18 below.

Table 18 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
RECOURSE, NCT01607957 Mayer RJ et al. N Engl J Med 2015;372:1909-19.	Randomized, Double-Blind, Phase 3 Study	Randomization between June 17, 2012, and October 8, 2013.	mCRC refractory to standard therapies.	Lonsurf monotherapy	Placebo (BSC)	The primary endpoint was OS (time frame was every 8 weeks, up to 12 months after the last participant was randomized or until the target number of events (deaths) was met, whichever was later). The secondary endpoint was PFS, response rate, DCR, and safety. The time frame for PFS was every 8 weeks, up to 12 months after the last participant was randomized or until the date of the investigator-assessed radiological disease progression or death due to any cause, whichever was later. The time frame for safety was from the time of signing the informed consent form until the period of participant follow up (30 days following the administration of last dose of study medication) or until initiation of new antitumor therapy, whichever was earlier.
BOND-3, NCT02292758 Lipsyc-Sharf M et al. Oncologist 2022;27:292-98	Randomized, Double-Blind, Phase 2 Study	Study start: Dec 2014 Study completion: Sep 2019	mCRC refractory to irinotecan.	Cetuximab + irinotecan + bevacizumab	Cetuximab + irinotecan + placebo	The primary endpoint was PFS and 6-month and 12-month PFS rates (From the date of randomization to the date of 1st documented disease progression or death dye to any cause, whichever occurs first, assessed up to 24 months). Secondary endpoints were number of participants who experienced at least one grade 3 or higher AEs, OS, DCR and DOR, and ORR. Follow-up was up to 2 years.

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
20020408, NCT00113763 Poulin-Costello et al. Target Oncol. 2013;(2):127-36	Randomized, open-label, phase 3 study	Study start: Jan 2004 Study completion: Jun 2009	mCRC refractory to fluoropyrimidines with prespecified exposure to oxaliplatin and irinotecan	Panitumumab + BSC	BSC	The primary endpoint was PFS (From randomization to the data cut-off date of 30 June 2005. The median follow-up time was 20.0 weeks in the panitumumab plus BSC group and 18.2 weeks in the BSC alone group). Secondary endpoints were OS, OTR, DOR, TTR, TDP, time to treatment failure and DSD. The follow-up time was up to 29.6 weeks in the panitumumab group plus BSC and 31.8 weeks in the BSC alone group.
ASPECCT, NCT01001377 Price et al. Lancet Oncol. 2014;6:569-79	Randomized, open-label, phase 3 study	Study start: Feb 2010 Study completion: Mar 2017	mCRC refractory to irinotecan and oxaliplatin	Panitumumab	Cetuximab	The primary endpoint was OS. Secondary endpoints were PFS, objective response per RECIST v1.1, DOR, TTR, time to treatment failure, change from baseline in EuroQOL 5, change from baseline NCCN FCSI Symptoms and Functional well-being scores, change from baseline in EuroQOL 5 Dimension (health state index and VAS) and number of participants wit AEs. Primary and secondary endpoints were measured from randomization until the data cut-off date of 5 February 2013. Time spent on study was up to 155 weeks
CO.17, NCT00079066 Jonker et al. N Engl J Med 2007;357:2040-8	Randomized, open-label, phase 3 study	Study start: Aug 2003 Study completion: Feb 2009	CRC patients previously treated with a fluoropyrimidine, irinotecan and oxaliplatin or had contraindications	Cetuximab + BSC	BSC	The primary endpoint was OS. Secondary endpoints were TTP, ORR, EORTC QLQ-C30, HU 13, economic value and safety profile.

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
			to treatment of the above.			
CONCUR, NCT01584830 Li et al. Lancet Oncol. 2015;(6):619-29	Randomized, triple-blind, phase 3 study	Study start: apr 2012 Study completion: Jan 2016	mCRC refractory to treatment	Regorafenib	Placebo	The primary endpoint was OS. The secondary endpoints were PFS, CR + PR, DCR and safety variables summarized using descriptive statistics based on adverse events collection. Measurements were taken from randomization of the first subject until 154 death events observed, up to 2 years.
CORRECT, NCT01103323 Grothey et al. Lancet. 2013;381:303-12	Randomized, double-blinded, phase 3 study	Study start: Apr 2010 Study completion: Jan 2014	mCRC refractory to all approved drugs for CRC	Regorafenib + BSC	Placebo + BSC	The primary endpoint was OS (from randomization of the first subject until the database cut-off approximately 14 months later). Secondary endpoints were PFS, OTR, DC and TR assessed in timeframe from randomization of the first subject until the database cut-off approximately 14 months later. Tumour assessed at 8-week intervals.
FRESCO, NCT02314819 Li et al. JAMA. 2018;319:2486-96	Randomized, quadruple-blinded, phase 3 study	Study start: Dec 2014 Study completion: Jan 2017	mCRC refractory to second line or standard chemotherapy	Fruquintinib	Placebo	The primary endpoint was OS (from randomization up to progressive disease or EOT due to anu cause, assessed up to 2 years). The secondary endpoints were PFS, ORR, DCR (assessed up to 1 year) or stable disease recorded within 30 days after the last dose.

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
FRESCO-2, NCT04322539 Dasari et al. Lancet. 2023;402:41-53	Randomized, double-blinded, phase 3 study	Study start: Aug 2020 Study Completion: Jul 2022	mCRC refractory to chemotherapy, anti-VEGF, anti-EGFR biologics and TAS-102 or regorafenib	Fruquintinib	Placebo	The primary endpoint was OS (from date of randomization to death from any cause (up to 22 months)). The secondary endpoints were PFS and DORassessed using RECIST v1.1 from randomization date until the first documentation of objective progression of death (up to 22 months), ORR and DCRper RECIST v1.1 from randomization until the first documentation of best overall response (up to 22 months), TEAEs from start of study drug administration up to 22 months, observed plasma concentrations of Fuquintiv and metabolite M11 over 28 cycle days, change from baseline ECG using Fridericia's Formula and Bazzett's Formula throughout 28 day cycle, Correlation between OS and AEs (up to 42 months), QOL and EORTC QLQ-C30, EQ-5D-5L (baseline, Cycle 2, 3 and 4 (each cycle = 28 days)) and healthcare resource utilization from start of drug administration up to 22 months.
ICECREAM, ACTRN12612000901808 Segelov et al. J Clin Oncol. 2016;34:2258-64	Randomized, open-label, phase 2 study	Study start: Nov 2012 Study completion: Dec 2014	mCRC patients with KRAS WT or KRAS G13D	Cetuximab	Cetuximab + irinotecan	The primary endpoint was to determine PFS benefit of cetuximab alone or in combination with irinotecan, from randomization to disease progression as defined by RECIST v1.1. The secondary endpoint was to determine response rate, OS and evaluate QoL using FACT-C, DLQI and FACT-EGFRI 18 questionnaires in patients with KRAS WT or KRAS G13D mutated mCRC treated with cetuximab alone or in combination with irinotecan. Evaluations of endpoints were assessed at the end of the study (25 months).

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
Pfeiffer 2020, EudraCT 2016-005241-23 Pfeiffer et al. Lancet Oncol. 2020;(3):412-20	Randomized, open-label, phase 2 study	Study start: Aug 2017 Study completion: June 2019	mCRC refractory to chemotherapy	FTD/TPI	FTD/TPI + bevacizumab	The primary endpoint was to determine PFS (timeframe was up to 24 months).
SUNLIGHT, NCT04737187 Prager et al. N Engl J Med 2023;388:1657-67	Randomized, open-label, phase 3 study	Study start: Nov 20 Study completion: Sep 2023	Refractory mCRC patients	FTD/TPI + bevacizumab	FTD/TPI	The primary endpoints were OS from date of randomization to the death due to any cause or cut-off date, whichever comes first (up to 20 months) and survival probability from randomization date at 6, 12 and 18 months. The secondary outcomes were probability of participants PFS at 3, 6, 9 and 12 months, PFS, ORR, percentage of participants with disease control (up to 20 months) and number of participants with TEAE and TESAEs up to 19.5 months.
TERRA, NCT01955837 Xu et al. J Clin Oncol. 2018;36:350-58	Randomized, double-blinded, phase 3 study	Study start: Sep 2013 Study completion: Jun 2016	mCRC patients	FTD/TPI	Placebo	The primary endpoint was OS which was assessed every 8 weeks. Survival status was collected up to 12 months after the last patient is randomized or until the target number of events (deaths) was met, whichever is later. The secondary outcomes were PFS determined by tumour assessments performed until radiologic progression develops or the start of new anticancer treatment, for up to 12 months after the last patient is randomized or until the target number of events (deaths) is met, TTF, ORR, DCR duration of response and safety and tolerability (AEs, and laboratory assessments) from randomization until the date of radiologic disease progression (assessed up to 30 months).

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
VELO, NCT05468892 Napolitano et al. Int J Cancer 2023;153:1520-28	Randomized, open-label, phase 2 study	Study start: Oct 2019 Study completion: Jun 2022	mCRC refractory to first line anti-EGFR agent panitumumab or cetuximab	FTD/TPI + panitumumab	FTD/TPI	The primary endpoint was PFS. The secondary outcomes were ORR pr RECIST v1.1, OS and safety and tolerability analysis (AEs graded according to NCI- CTCAE, v5.0). Measurements were obtained from screening for up to 30 months.
Xu 2017, NCT02196688 Xu et al. J Hematol Oncol. 2017;10:22	Randomized, double-blinded, phase 2 study	Study start: Apr 2014 Study completion: Nov 2015	mCRC patients with ≥2 prior therapies	Fruquintinib + BSC	Placebo + BSC	The primary endpoint was PFS which was evaluated using RECIST v1.1. PFS was obtained from randomization until the date of first documented progression or date of death from any cause, whichever came first. The secondary endpoints were ORR according to RECIST v1.1 (from randomization up to pro, DCR pr RECIST v1.1 and OS (from randomization until death due to any cause).
Yoshino 2012, JapicCTI-090880 Yoshino et al. Lancet oncol 2012;(10):993-1001	Randomized, double-blinded, phase 2 study	Study start: Aug 2009 Study completion: Apr 2010	CRC patients with ≥2 prior standard chemotherapies and refractory or intolerant to fluoropyrimidine, irinotecan and oxaliplatin	FTD/TPI	Placebo	The primary endpoint was overall survival. The median follow up was 11.3 months.

7.1.2 Comparability of studies

A feasibility assessment for the NMA has been conducted and a summary of the comparability of the included studies are described below.

Because most clinical trials of drugs for refractory metastatic CRC are not conducted exclusively in the third-line setting, the feasibility assessment draws from an evidence base of studies including a broader population of patients undergoing second-line or beyond therapy for metastatic disease. To investigate the impact of line of treatment on relative treatment effects for different studies included in the NMA, the HRs for different lines of treatment within the same trial were compared when available; in all, there was wide overlap in the CIs and no conclusive trend in the impact of different lines of treatment on the relative treatment effects for studies included in the feasibility assessment.

Additionally, a post-hoc analysis of data from RECOURSE was conducted to understand whether the number of prior treatment regimens modified the treatment effect for FTD/TPI vs. placebo. Three methods were used to investigate the treatment effect by the number of prior regimens: interaction term analysis in a univariate model, interaction term analysis in a multivariate model, and stratification analysis in a multivariate model. In the univariate model, the interaction term between treatment and number of prior regimens was not statistically significant. In the RECOURSE clinical study report, the only selected prognostic factors in the multivariate model were KRAS status, time since diagnosis of metastasis, region, primary tumor site, ECOG status at baseline, and number of metastatic sites. To investigate whether the number of prior regimens was an effect modifier, it was added into the multivariate model, and an interaction analysis was conducted. In this analysis, p-values for number of prior regimens were not statistically significant. In the multivariate analyses stratifying by two, three, or four prior regimens, the HRs were similar (all <1), implying that line of treatment is not an important effect modifier for FTD/TPI vs. placebo.

In all, there was not conclusive evidence that line of treatment modifies the relative treatment effects of studies included in the feasibility assessment and, therefore, it was feasible to include trials evaluating different proportions of patients undergoing third-line treatment in the same network.

Other differences between trials included patient race/ethnicity, with some trials enrolling multinational populations and others enrolling patients exclusively in East Asian countries, although available within-trial data suggests that race/ethnicity is not an important effect modifier.

Considering study designs, baseline patient characteristics, and outcome definitions, the feasibility assessment revealed no critical dissimilarities among connected trials that would prohibit their inclusion in the NMA [22].

Some studies in the NMA (BOND-3 and ICECREAM) are not relevant for the comparison between Lonsurf in combination with bevacizumab and BSC but could not be excluded from the analysis. As the studies include relatively few patients overall (89/6219), the effect on the results is negligible.

7.1.2.1 Comparability of patients across studies

The baseline characteristics of SUNLIGHT and RECOURSE are shown below in Table 19. Baseline characteristics for the rest of the studies included in the NMA is listed in appendix C.2.

As mentioned in the section above, there is a difference in the patient distribution of race/ethnicity and the number of prior treatment regimens, but none of these are evaluated as treatment effect modifiers [3,7].

Table 19 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	SUNLIGHT		RECOURSE	
	Intervention (N=246)	**Comparator (N=246)**	**Intervention (N=534)**	**Comparator (N=266)**
Age (median)	62	64	63	63
Male n, (%)	122 (49.59)	134 (54.47)	326 (61.04)	165 (62.03)
Region n, (%)			US, Europe, Aus-	US, Europe, Aus-
North America	8 (3.25)	8 (3.25)	tralia	tralia
Europe (incl DK)	158 (64.22)	157 (63.82)	356 (66.66)	178 (66.91)
Rest of world	80	81	178 (Japan)	88 (Japan)
Ethnicity n, (%)				
White	215 (87.39)	220 (89.43)	306 (57.30)	55 (20.67)
Black	4 (1.62)	3 (1.21)	4 (0.74)	5 (1.87)
Asian	0 (0)	1 (0.40)	184 (34.45)	94 (35.33)
Other/unknown	27 (10.97)	22 (8.94)	-	-
Primary diagnosis n, (%)	180 (73.17)	181 (73.57)	338 (63.29)	161 (60.52)
Colon	66 (26.82)	65 (26.42)	196 (36.70)	105 (39.47)
Rectum				
Location n, (%)				
Right	62 (25.20)	77 (31.30)	NR	NR
Left	184 (74.79)	169 (68.69)	NR	NR
Median duration of disease (Y)	2.0	2.1	NR	NR
Time from diagnosis of first metastasis to				

	SUNLIGHT		RECOURSE	
	Intervention (N=246)	Comparator (N=246)	Intervention (N=534)	Comparator (N=266)
randomization n, (%)				
<18 months	104 (42.27)	105 (42.68)	111 (20.78)	55 (20.67)
≥18 months	142 (57.72)	141 (57.31)	423 (79.21)	211 (79.32)
No. of sites of metastasis n, (%)				
1 or 2	152 (61.78)	141 (57.31)	NR	NR
≥3	94 (38.21)	105 (42.68)	NR	NR
RAS status n, (%)				
Mutated	171 (69.51)	170 (69.10)	262(49.06)	131 (49.24)
wild type	75 (30.48)	76 (30.89)	272 (50.93)	135 (50.75)
BRAF status n, (%)				
Mutated	8 (3.25)	11 (4.47)	NR	NR
Wild type	159 (64.63)	156 (63.41)	NR	NR
Unknown	79 (32.11)	79 (32.11)	NR	NR
MMR and MSI status n, (%)				
MMR deficient and high MSI.	13 (5.28)	8 (3.25)	NR	NR
MMR proficient and stable or low MSI.	139 (56.50)	145 (58.94)	NR	NR
Unknown or missing data.	94 (38.21)	93 (37.80)	NR	NR
No. of previous treatments for metastatic disease — n, (%) §				
1	11 (4,47)	15 (6,09)	NR	NR
2	229 (93.08)	224 (91.05)	95 (17.79)	45 (16.91)
≥3	6 (2.43)	7 (2.84)	439 (82.20)	221 (83.08)
Previous treatments received for metastatic				

	SUNLIGHT		RECOURSE	
	Intervention (N=246)	Comparator (N=246)	Intervention (N=534)	Comparator (N=266)
disease n, (%)				
Fluoropyrimidine	246 (100)	246 (100)	534 (100)	266 (100)
Irinotecan Oxali-	246 (100)	245 (99.59)	534 (100)	266(100)
platin	241 (97.96)	243 (98.78)	534 (100)	266 (100)
Anti-VEGF	178 (72.35)	176 (71.54)	534 (100)	265 (99.62)
Anti-EGFR	71 (28.86)	71 (28.86)	278 (52.05)	144 (54.13)
Other/regorafenib	-	-	91 (17.04)	53 (19.92)
ECOG PS score n, (%)				
0				
1	119 (48.37)	106 (43.08)	301 (56.36)	147 (55.26)
2	127 (51.62)	139 (56.50)	233 (43.63)	119 (44.73)
	0 (0)	1 (0.40)	0 (0)	0 (0)
Neutrophil–lym- phocyte ratio n, (%)	128 (52.03)	115 (46.74)	NR	NR
<3	117 (47.56)	131 (53.25)	NR	NR
≥3				

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

Based on section 6.1.4 describing a Danish study investigating treatment with Lonsurf monotherapy, it is believed that the RECOURSE study is also representative of the Danish population. The base case values used in the health economic model are based on data from the SUNLIGHT trial. See Table 20 below [7,16].

Table 20 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population [7,16]	Value used in health economic model [7,16]
Age	66	63
Gender	58	52
Patient weight	NR	74

7.1.4 Efficacy – results per RECOURSE

Only results for RECOURSE are described in detail in this section. HR for OS and PFS for the rest of the studies included in the NMA is listed in appendix C.2.

Overall Survival

Based on the original analysis at 19-month follow-up time, Lonsurf monotherapy was associated with significantly greater mOS compared with placebo (7.1 vs 5.3 months; hazard ratio (HR): 0.68 (0.58-0.81); p < 0.001). The 1-year OS rates were 27 % for Lonsurf monotherapy and 18 % for placebo. The benefit in OS was observed in all prespecified subgroups including those defined in accordance with the three stratification factors (KRAS status, time between first diagnosis of metastases and randomization, and geographic region). In the final analysis at 27-month follow-up, the OS results were consistent with the original analysis. See Table 21 and KM plots in Figure 6 [3].

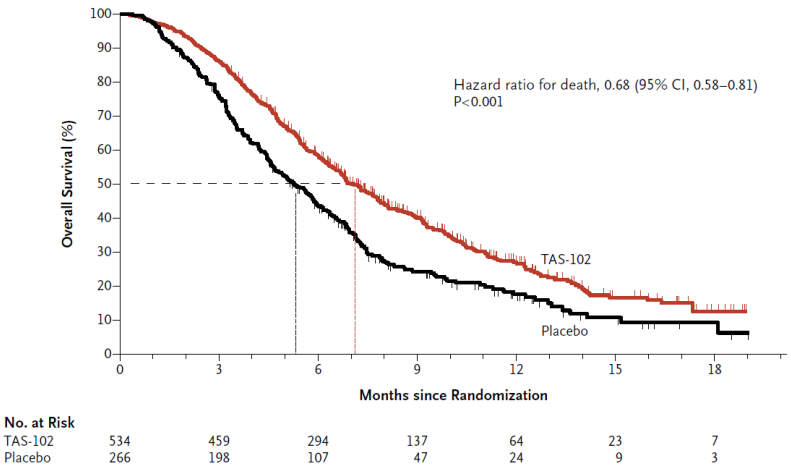

Figure 6 Overall survival from the RECOURSE study

Table 21 RECOURSE study

	RECOURSE (19 month F/U)	
	FTD/TPI (n = 534)	Placebo (n = 266)
mOS (months)	7.1	5.3
(95% CI)	(6.5-7.8)	(4.6-6.0)
HR	0.68	
(95% CI)	(0.58-0.81)	
P value (1-sided)	<0.001	
1-year survival, %	26.6	17.6

(95% CI)	(22.2-31.1)	(12.7-23.1)

Progression-free survival

Lonsurf monotherapy was associated with significantly better PFS (2.0 vs. 1.7 months; HR: 0.48 (0.41-0.57; p<0.001)) compared to placebo. See Figure 7 below [3].

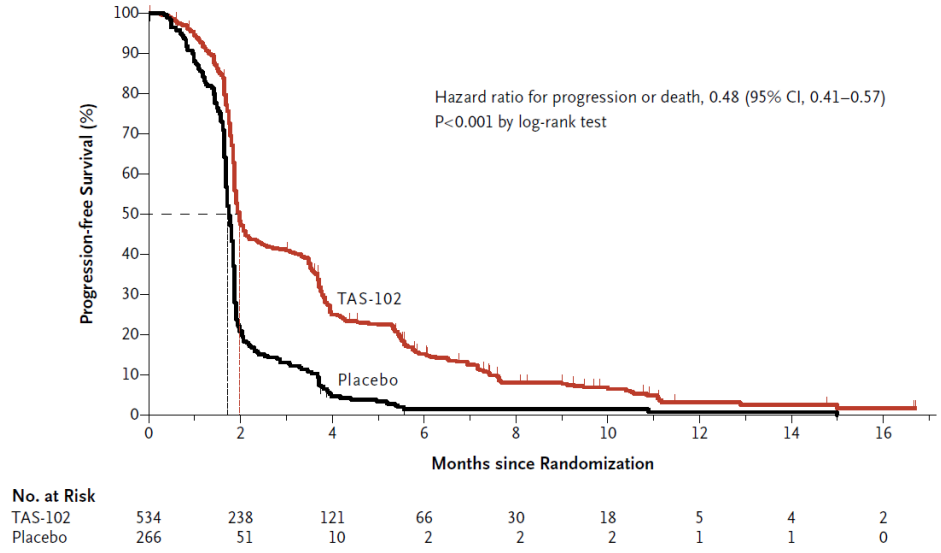

Figure 7 Progression-free survival based on the RECOURSE study

ORR and DCR

8 patients receiving Lonsurf monotherapy reported partial response, and 1 patient in the placebo group reported complete response, resulting in ORR of 1.6 % with Lonsurf monotherapy and 0.4 % with placebo (P=0.29).

Disease control was defined as a complete or partial response or stable disease, assessed at least 6 weeks after randomization and was achieved in 44 % and 16 % of patients receiving Lonsurf monotherapy or placebo (P<0.001). This corresponds to 221 and 42 patients, respectively [3].

Safety

Safety is reported in section 10 [3].

8. Comparative analysis of efficacy

The following section briefly describes the NMA that was conducted to identify and quantitatively synthesize evidence on the relative efficacy of Lonsurf plus bevacizumab compared with BSC.

The comparison of Lonsurf plus bevacizumab and Lonsurf monotherapy is based on a

head-to-head study (SUNLIGHT), and clinical efficacy is presented in the previous section (Section 6). For a more detailed description of the NMA, refer to Appendix C [22].

8.1.1 Differences in definitions of outcomes between studies

The clinical efficacy outcomes for Lonsurf plus bevacizumab and BSC presented in the NMA are OS and PFS and there are no differences in the definition of outcomes. OS is defined as "t*ime elapsed between the date of randomisation and the date of death due to any cause*" in the SUNLIGHT trial, and "*time from randomization to death from any cause*" in the RECOURSE trial. PFS is investigator-assessed on both trials and defined as "*time elapsed between the randomisation and the date of radiologic tumour progression or death from any cause*" in the SUNLIGHT trial, and "*time from randomization to the first radiologic confirmation of disease progression or death from any cause*" in the RECOURSE trial [22]. For the rest of the studies included in the NMA, the definitions of PFS and OS are available in appendix C.2.

8.1.2 Method of synthesis

The method for comparing the efficacy of Lonsurf plus bevacizumab and BSC is an NMA. The objective of the NMA was to estimate the relative treatment effects of Lonsurf plus bevacizumab versus BSC (among others) for patients undergoing third-line treatment for refractory metastatic CRC. A key assumption of this approach is that differences between the study designs and populations of trials in the NMA and the target population do not modify the relative treatment effects for the included interventions [22].

Relevant studies were identified through comprehensive searches of the Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica dataBASE (Embase), and Cochrane Central Register of Controlled Trials (CENTRAL) databases; relevant conference proceedings; and clinical trial registries using search terms for the population, interventions, and study designs of interest. To guide study selection, the titles/abstracts and full texts of identified studies were screened against pre-specified population, intervention, comparator, outcome, and study design (PICOS) criteria. The risk of bias in included studies was assessed using the Cochrane Risk of Bias tool, version 2 for randomized controlled trials (RCTs) and the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies for non-randomized trials and single-arm trials. The process of study selection, data extraction, and risk of bias assessment was conducted by two reviewers [22].

To gauge the appropriateness of proceeding with an NMA, the feasibility of performing an NMA of OS and PFS was assessed by:

1. determining whether the RCT evidence for the interventions of interest formed one network for each population and the outcome of interest
2. examining the distribution of trial, treatment, patient, and outcome characteristics that may affect treatment effects across comparisons within the networks [22]

Where RCTs identified in the SLR formed a connected network and were deemed to be

sufficiently similar for each population and outcome of interest, their results were synthesized using NMA. NMA of reported HRs in terms of OS and PFS assuming proportional hazards between treatments was performed using random-effects and fixed-effects models with a contrast-based normal likelihood for the log HR of each trial in the network. Normal non-informative prior distributions were used for all parameters. Relative treatment effects were expressed as HRs with 95% credible intervals (CrIs), reflecting a 95% probability that the estimate is within the specified range [22].

8.1.3 Results from the comparative analysis

To investigate the efficacy (OS and PFS) of Lonsurf plus bevacizumab a broader set of trials enrolling 2L and beyond (2L+) patients was evaluated in the NMA. BSC and placebo were treated as the same node in the network, as they were assumed to have equivalent efficacy. In the random-effects and fixed-effects NMA models, Lonsurf plus bevacizumab had statistically favourable effects on both OS and PFS relative to BSC.

The results from the comparative analysis are found in Table 22 below [22]. For the naïve comparison, OS and PFS results for Lonsurf in combination with bevacizumab from SUNLIGHT and placebo from RECOURSE are also listed in Table 22 below.

Table 22 Results from the comparative analysis of Lonsurf plus bevacizumab vs. BSC for 2L+ mCRC patients based on constant HRs

Outcome measure	Lonsurf plus bevacizumab in SUNLIGHT (N=246)	BSC plus placebo in RECOURSE (N=266)	Result from the NMA
OS	Median: 10.8 months (95 % CI: 9.4-11.8)	Median: 5.2 months (95 % CI: N/A)	[redacted]
PFS	Median: 5.6 (95 % CI: 4.5-5.9)	Median: 1.7 months (95 % CI: 1.7-1.8)	[redacted]

8.1.4 Efficacy – results per [outcome measure] (N/A)

This section is N/A as the available efficacy results for OS and PFS based on the NMA is presented in the section above.

9. Modelling of efficacy in the health economic analysis

Despite the relatively mature KM curves observed in the SUNLIGHT study data, extrapolation of OS and PFS was required due to incomplete occurrence of clinical events within the trial period.

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

Initially before extrapolation of survival data with standard parametric models, an assessment of the proportional hazards (PH) assumption and acceleration failure time (AFT) were made (Appendix D). The results of the PH and AFT illustrate that the log-cumulative hazards plot (LCHP), cloglog- and Q-Q plot from the SUNLIGHT trial show that the LCHP is approximately linear for both treatment arms, and the two lines are approximately parallel to each other. The Schoenfeld's non-proportionality test returned a p-value of [redacted] deeming that the null hypothesis cannot be rejected with a 95% confidence interval (CI) but can be rejected within a 90% CI. The Q-Q plot appears to show a straight line indicating that the AFT assumption may hold [Appendix D]. Despite the lack of evidence to contradict the PH and AFT assumptions, standard parametric models (exponential, Weibull, log-normal, log-logistic, Gompertz, generalized gamma and gamma) were fitted. However, given the results of the plots and evidence to indicate a fundamental difference in the shape or behaviour of the underlying hazards, it was concluded that the same distribution should be selected for both treatment arms to inform OS projections [7]. The fitting followed the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 Guidance [22,43].

The final choice of extrapolation was made considering the Akaine Information Criterion (AIC) and Bayesian Information Criterion (BIC) scores, which determine the relative fit of alternative partioned survival models (PSMs) to observed data. The AIC and BIC are both reported to assess the models' fit against observed data. A visual inspection vs. the KM estimates was also applied. The identification of the best-fitting parametric extrapolation was evaluated by the sum of ranks of both criterions, the overall ranking was thereby derived, where the lowest sum of ranks indicates the best-fitting extrapolation [Appendix D] [22].

9.1.1 Extrapolation of efficacy data

An evaluation of the PH was conducted and is presented in Appendix D. Based on the results from the log-cumulative hazard plot cloglog plot, Q-Q plot, and Schoenfeld's non-parametric test, the PH assumption could not be rejected within a 95% CI but was acceptable within a 90% CI level. However, leveraging the availability of individual patient data (IPD), the data were specifically fitted for the intervention arm [22].

Various standard parametric models (exponential, Weibull, log-normal, log-logistic, Gompertz, and Generalized gamma) were applied, following the guidance outlined in the NICE DSU TSD 14 [43]. Based on AIC and BIC criteria, [redacted] demonstrated the best fit for Lonsurf plus bevacizumab. However, most models provided reasonably similar fits to the data. Therefore, a visual inspection of the model fits was employed to select the most appropriate extrapolation method (see Appendix D) [22].

Subsequently, long-term outcomes were evaluated for their clinical plausibility. Goodness-of-fit statistics, including AIC and BIC, are provided in Appendix D. To determine the model with the best fit, AICs and BICs were initially ranked separately, followed by a synthesis of both ranks for each parametric model. The overall ranking was derived from the sum of ranks, where a lower sum indicated a better fit [22].

A full parametrization of the BSC could not be performed as there was no direct link between the intervention arm and the comparator. The HR for BSC was therefore derived from an NMA allowing to compare the results [22].

9.1.1.1 Extrapolation of OS

Assumptions associated with extrapolation of OS are found in Table 23.

Table 23 Summary of assumptions associated with extrapolation of OS

Method/approach	Description/assumption
Data input	SUNLIGHT: NCT04737187 RECOURSE: NCT01607957 (NMA)
Model	Full parametrization
Assumption of proportional hazards between intervention and comparator	Yes
Function with best AIC fit	Lonsurf plus bevacizumab: [redacted] Lonsurf monotherapy: [redacted] BSC: N/A
Function with best BIC fit	Lonsurf plus bevacizumab: [redacted] Lonsurf monotherapy: [redacted] BSC: N/A
Function with best visual fit	Lonsurf plus bevacizumab: [redacted] Lonsurf monotherapy: [redacted] BSC: N/A
Function with best fit according to evaluation of smoothed hazard assumptions	Not performed
Validation of selected extrapolated curves (external evidence)	OS data from the SUNLIGHT study was compared to OS outputs from the model. The majority of the model appears to be consistent with the observed data. The biggest discrepancies being towards the end of the model, where numbers are small (Appendix D).
Function with the best fit according to external evidence	N/A

Method/approach	Description/assumption
Selected parametric function in base case analysis	Lonsurf plus bevacizumab: [redacted] Lonsurf: [redacted] BSC: [redacted]
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	Not relevant
Assumptions of waning effect	Not relevant
Assumptions of cure point	Not relevant

The observed time-to-event on OS for Lonsurf plus Bevacizumab and Lonsurf monotherapy from the SUNLIGHT Trial are presented in in Figure 8. The base case comparator was chosen to be Lonsurf monotherapy and BSC in the Danish population, with the latter not being included in the SUNLIGHT trial [7].

Figure 8 Observed time to OS for Lonsurf plus Bevacizumab and Lonsurf monotherapy arms from the SUNLIGHT study

The OS KM curve from the SUNLIGHT trial and all investigated extrapolations for the base case analysis for Lonsurf plus bevacizumab and Lonsurf monotherapy are presented in Figure 9. The estimate for BSC used in the model and all reference cases for BSC from included studies in the indirect treatment comparison (ITC) are presented in Figure 10 [22].

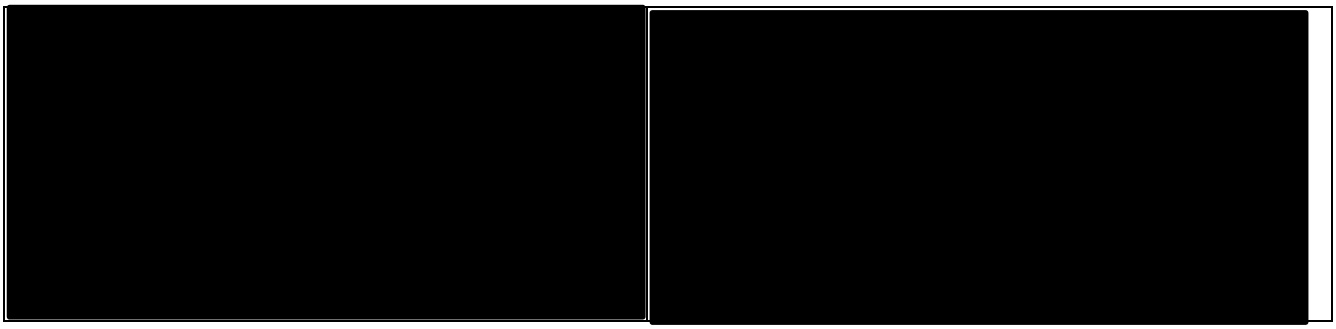

Figure 9 Overall survival KM curve for Lonsurf monotherapy, Lonsurf plus bevacizumab and all parametric extrapolations

Figure 10 Overall survival estimate for BSC and KM curves for BSC from the studies included in the ITC

9.1.1.2 Extrapolation of PFS

Assumptions associated with extrapolation of PFS is found in Table 24.

Table 24 Extrapolation of PFS

Method/approach	Description/assumption
Data input	Sunlight: NCT04737187 RECOURSE: NCT01607957 (NMA)
Model	Full parametrization
Assumption of proportional hazards between intervention and comparator	Yes
Function with best AIC fit	Lonsurf plus bevacizumab: [redacted] Lonsurf monotherapy: [redacted] BSC: N/A

Method/approach	Description/assumption
Function with best BIC fit	Lonsurf plus bevacizumab: [redacted] Lonsurf monotherapy: [redacted] BSC: N/A
Function with best visual fit	Lonsurf plus bevacizumab: [redacted] Lonsurf monotherapy: [redacted] BSC: N/A
Function with best fit according to evaluation of smoothed hazard assumptions	Not performed
Validation of selected extrapolated curves (external evidence)	PFS data from the SUNLIGHT study was compared to PFS outputs from the model. The majority of the model appears to be consistent with the observed data. The biggest discrepancies being towards the end of the model, where numbers are small (Appendix D).
Function with the best fit according to external evidence	N/A
Selected parametric function in base case analysis	Lonsurf plus bevacizumab: [redacted] Lonsurf monotherapy: [redacted] BSC: Apply HR from NMA
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	Not relevant
Assumptions of waning effect	Not relevant
Assumptions of cure point	Not relevant

The observed time-to-event on PFS for Lonsurf plus Bevacizumab and Lonsurf monotherapy from the SUNLIGHT Trial are presented in Figure 11. The base case comparators were chosen to be Lonsurf monotherapy and BSC for the Danish population. BSC was not investigated in the SUNLIGHT trial [7].

Figure 11 Observed time to PFS for Lonsurf plus bevacizumab and Lonsurf arms from the SUNLIGHT study

The PFS KM curve from SUNLIGHT and all the investigated extrapolations for the base case analysis for Lonsurf plus bevacizumab and Lonsurf monotherapy are presented in Figure 12 and Figure 13. The estimate for BSC used in the model and all the KM curves for BSC from the studies included in the ITC are presented in Figure 14 [7,22].

Figure 12 PFS KM curve for Lonsurf plus bevacizumab and all explored parametric estimates

Figure 13 PFS KM curve for Lonsurf monotherapy and all explored parametric estimates

Figure 14 PFS estimate for BSC and KM curves for BSC from the studies included in the ITC

9.1.1.3 Extrapolation of Time-on-Treatment

Patient-level ToT data from the SUNLIGHT study is used within the model to determine the drug and administration costs associated with Lonsurf plus Bevacizumab and Lonsurf Monotherapy. A summary of the ToT data from SUNLIGHT is presented below in Figure 15.

Figure 15 SUNLIGHT – Kaplan-Meier – ToT

To ensure that treatments are costed accurately and appropriately, Lonsurf plus bevacizumab arm has been separated and all curves have been modelled independently. In Table 25, it is described what and which assumptions that have been used for extrapolating ToT.

Table 25 Extrapolation of ToT

Method/approach	Description/assumption
Data input	Sunlight: NCT04737187
Model	Full parametrization

Method/approach	Description/assumption
Assumption of proportional hazards between intervention and comparator	Yes
Function with best AIC fit	Lonsurf plus bevacizumab: [redacted] Lonsurf monotherapy: [redacted] BSC: N/A
Function with best BIC fit	Lonsurf plus bevacizumab: [redacted] Lonsurf monotherapy: [redacted] BSC: N/A
Function with best visual fit	Lonsurf plus bevacizumab: [redacted] Lonsurf monotherapy: [redacted] BSC: N/A
Function with best fit according to evaluation of smoothed hazard assumptions	Not performed
Validation of selected extrapolated curves (external evidence)	ToT data from the SUNLIGHT study was compared to ToT outputs from the model. Given the maturity of the data, very little extrapolation was required therefore curves which closely match the observed data were considered (Appendix D).
Function with the best fit according to external evidence	N/A
Selected parametric function in base case analysis	Lonsurf plus bevacizumab: [redacted] Lonsurf monotherapy: [redacted] BSC: Apply HR from NMA
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	Not relevant
Assumptions of waning effect	Not relevant

Method/approach	Description/assumption
Assumptions of cure point	Not relevant

A visual presentation of the extrapolated ToT and KM are presented below in Figure 16, Figure 17, and Figure 18. For Lonsurf plus bevacizumab, [redacted] curves were all very close to the observed data. As [redacted] was also the best statistically fitting, this has been chosen for the base case. For Lonsurf monotherapy, all curves except [redacted] closely fitted the observed data. As [redacted] is statistically the best fitting according to AIC and BIC combined, this extrapolation was chosen for the base case. To have an overview of the statistical fit, it is presented in appendix D.3.

Figure 16: Parametric curve fits – FTD/TPI (FTD + bevacizumab) - ToT

Figure 17: Parametric curve fits – bevacizumab (FTD/TPI + bevacizumab) – ToT

Figure 18: Parametric curve fits – FTD/TPI – ToT

9.1.2 Calculation of transitions probabilities (N/A)

Not applicable

9.2 Presentation of efficacy data from [additional documentation] (N/A)

Not applicable

9.3 Modelling effects of subsequent treatments

No subsequent treatment has been modeled for this submission.

9.4 Other assumptions regarding efficacy in the model (N/A)

Not applicable

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

In Table 26, estimates of the modelled median and average are presented for OS and PFS by the chosen extrapolation model. The table includes the intervention and comparators [3,7].

Table 26 Estimates in the model

	Modelled average	Modelled median	Observed median from relevant study
Overall Survival			
Lonsurf + bevaci-zumab			

Lonsurf monotherapy	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]
	Modelled average	**Modelled median**	**Observed median from relevant study**
	Progression-Free Survival		
Lonsurf plus bevacizumab	[redacted]	[redacted]	[redacted]
Lonsurf monotherapy	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]

In Table 27 an overview of the modelled average treatment length and time in progression-free and progressed health states are provided for the intervention and comparators.

Table 27 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]	Progression-free [months]	Overall survival [months]
Lonsurf plus bevacizumab	[redacted]	[redacted]	[redacted]
Lonsurf monotherapy	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]

10. Safety

10.1 Safety data from the clinical documentation

The safety data from the clinical documentation is based on the SUNLIGHT and RECOURSE trials. Thus, this section is divided into two safety sub-sections [3,7].

10.1.1 Safety based on the SUNLIGHT trial

All patients who took at least one dose of Lonsurf were included in the SS, with patients analysed according to the treatment they received. Safety analyses were performed in the SS as of the cut-off date of July 5, 2022 (N=492). All randomised patients received study treatment, with all patients receiving their treatment as assigned at randomisation [7].

As of the clinical cut-off date, treatment duration (mean [Standard Deviation (SD)]; median) was longer for patients receiving Lonsurf plus bevacizumab than for patients receiving Lonsurf monotherapy (6.1 months [±4.3], 5.0 months vs. 3.4 months [±2.5], 2.1 months). Similarly, the number of initiated cycles was higher in the Lonsurf plus bevacizumab group than in the Lonsurf monotherapy group (6.0 [±4.1], 5.0 vs. 3.4 [±2.4], 2.0). In the Lonsurf plus bevacizumab group, 15.8% of patients initiated >10 cycles of treatment compared to 2.4% of patients in the Lonsurf monotherapy group [7,22].

At the data cut-off, 36 patients (7.3%) were still receiving treatment: 13.0% in the Lonsurf plus bevacizumab group and 1.6% in the Lonsurf monotherapy group. The main reason for study treatment discontinuation was clinical and/or radiological disease progression (77.6% vs. 88.6%). The rate of withdrawal due to patients having both radiological and clinical progressive disease was higher in the Lonsurf monotherapy group (21.1%) than in the Lonsurf plus bevacizumab group (10.6%). The other most frequent reason for treatment withdrawal was AEs (6.5% in each group) [7].

The overall safety events and serious AEs are provided in Table 28 and Table 29, respectively. AE of any cause occurred in 98.0% of the patients in each group. The most common AEs that occurred during the treatment period in both groups were neutropenia, nausea, and anaemia [7].

Table 28 Overview of safety events. November 25, 2020 to July 5, 2022.

	Intervention (N=246)	Comparator (N=246)	Difference, % (95 % CI)
Number of AEs, n	241	241	NR
Number and proportion of patients with ≥1 AEs, n (%)	241 (98)	241 (98)	NR
Number of SAEs*, n	61	77	NR
Number and proportion of patients with ≥ 1 SAEs*, n (%)	61 (24.8)	77 (31.3)	NR
Number of CTCAE grade ≥ 3 events, n	178	171	NR

	Intervention (N=246)	Comparator (N=246)	Difference, % (95 % CI)
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events[§], n (%)	178 (72.4)	171 (69.5)	NR
Number of adverse reactions, n	NR	NR	NR
Number and proportion of patients with ≥ 1 adverse reaction, n (%)	NR	NR	NR
Number and proportion of patients who had a dose reduction, n (%)	40 (16.3)	31 (12.2)	NR
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	31 (12.6)	31 (12.6)	NR
Number and proportion of patients who discontinue treatment due to AEs, n (%)	31 (12.6)	31 (12.6)	NR

* 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.

Table 29 Serious adverse events. November 25, 2020 to July 5, 2022.

Adverse events	Intervention (N=246)		Comparator (N=246)	
	Number of patients with AEs	Number of AEs	Number of patients with AEs	Number of AEs
Neutropenia, n (%)	106 (43.1)	NR	79 (32.1)	NR

Adverse events	Intervention (N=246)		Comparator (N=246)	
Neutrophil count, n (%)	22 (8.9)	NR	13 (5.3)	NR
Anaemia, n (%)	15 (6.1)	NR	27 (11.0)	NR
Hypertension, n (%)	14 (5.7)	NR	3 (1.2)	NR
Febrile neutropenia	1 (0.4%)	NR	6 (2.4%)	NR

* 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).

10.1.2 Safety based on the RECOURSE trial

The overall safety events and serious AEs reported in the RECOURSE trial are provided in Table 30 and Table 31, respectively.

Table 30 Overview of safety events. June 17, 2012 to October 8, 2013 [3]

	Lonsurf monotherapy (N=533)	Placebo (N=265)	Difference, % (95 % CI)
Number of AEs, n (%)	524 (98)	247 (93)	NR
Number and proportion of patients with ≥1 AEs, n (%)	NR	NR	NR
Number of SAEs*, n (%)	158 (30)	89 (34)	NR
Number and proportion of patients with ≥ 1 SAEs*, n (%)	NR	NR	NR
Number of CTCAE grade ≥ 3 events, n	69%	52%	NR
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	NR	NR	NR

	Lonsurf monotherapy (N=533)	Placebo (N=265)	Difference, % (95 % CI)
Number of adverse reactions, n	NR	NR	NR
Number and proportion of patients with ≥ 1 adverse reaction, n (%)	NR	NR	NR
Number and proportion of patients who had a dose reduction, n (%)	73 (14)	NR	NR
Number and proportion of patients who discontinue treatment regardless of reason	4%	2%	NR
Number and proportion of patients who discontinue treatment due to AEs, n (%)	NR	NR	NR

* 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.

Table 31 Serious adverse events. June 17, 2012 to October 8, 2013 [3]

Adverse events	Lonsurf monotherapyNR (N=533)		Placebo (N=265)NR	
	Number of patients with AEs	**Number of AEs**	**Number of patients with AEs**	**Number of AEs**
Neutropenia, n (%)	200 (38)	NR	0	NR
Leukopenia, n (%)	113 (21)	NR	0	NR
Anaemia, n (%)	96 (18)	NR	8 (3)	NR

Adverse events	Lonsurf monotherapyNR (N=533)		Placebo (N=265)NR	
Thrombocytopenia, n (%)	27 (5)	NR	1 (<1)	NR
Increase in aspartate aminotransferase level	23 (4)	NR	16 (6)	NR
Increase in total bilirubin, n (%)	45 (9)	NR	31 (12)	NR
Increase in alkaline phosphatase level, n (%)	42 (8)	NR	28 (11)	NR

* 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).

10.1.3 Safety used in the health economic model

The safety used in the health economic model is grade ≥3 AEs with an incidence of greater than 5% in either SUNLIGHT or RECOURSE (Table 32). Five percent was selected as this cut-off ensured that all the important AEs were costed whilst enabling the list of AEs to be consolidated to a reasonable amount which is also in accordance with the DMC guidelines [3,7,22].

Table 32 Adverse events used in the health economic model

Adverse events	Intervention	Comparator 1	Comparator 2		
	Lonsurf plus bevacizumab	**Lonsurf Monotherapy**	**BSC**	**Source**	**Justification**
Anaemia, n (%)	15 (6.1%)	27 (11%)	~8 (3%)	[3,7]	Above ≥5 %
Anorexia (decreased appetite) n (%)	2 (0.8%)	3 (1.2%)	13 (5.0%)	[3,7,22]	Above ≥5 %
Fatigue, n (%)	3 (1.2%)	9 (3.7%)	15 (6.0%)	[3,7,22]	Above ≥5 %

Adverse events	Intervention	Comparator 1	Comparator 2		
Hypertension, n (%)	14 (5.7%)	3 (1.2%)	4 (1.2%)	[3,7,22]	Above ≥5 %
Neutropenia, n (%)	106 (43.1%)	79 (32.1%)	0 (0%)	[3,7,22]	Above ≥5 %
Neutrophil count decreased, n (%)	22 (8.9%)	13 (5.3%)	0 (0%)	[3,7,22]	Above ≥5 %

10.2 Safety data from external literature applied in the health economic model (N/A)

Table 33 Adverse events that appear in more than X % of patients (N/A)

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with AEs	Number of AEs	Frequency used in economic model for intervention	Number of patients with AEs	Number of AEs	Frequency used in economic model for comparator	Number of patients with AEs	Number of AEs
AE, n								

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

In the SUNLIGHT trial, QoL was assessed by using the EQ-5D-5L and EORTC-QLQ-C30 questionnaires. Based on the guidelines from the DMC, HRQoL based on the EQ-5D-5L measurement (see Table 34) is presented in this submission [7].

Table 34 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	SUNLIGHT	Utilities for Lonsurf plus bevacizumab, Lonsurf monotherapy, and BSC.

11.1 Presentation of the health-related quality of life

11.1.1 Study design and measuring instrument

In the SUNLIGHT trial, the EQ-5D-5L questionnaire was administered to patients to measure HRQoL. The EQ-5D-5L questionnaire is an acknowledged measuring instrument for gathering HRQoL data in terms of utilities and has been used as it was initially validated [7,22].

11.1.2 Data collection

The EQ-5D-5L questionnaire was to be completed within 7 days of randomization, then on day 1 of cycles ≥ 2 prior to any study procedure (e.g. treatment, blood test or scans), and then at the withdrawal visit. Not all patients completed the questionnaire, 490/492 (99.6%) have at least one EQ-5D-5L. In total, 2,279 EQ-5D-5L observations were available from the 490 patients. Of these, 1,975 observations were recorded while PF with the remaining 304 recorded post-progression [7,22]. Among patients of the FAS with evaluable EQ-5D-5L assessment, questionnaire and VAS completion rates decreased with each visit post-baseline in the two treatment groups as treatment discontinuations reduced the sample size. Among patients expected to complete the EQ-5D-5L i.e. still on treatment, the compliance rate was ≥ 83% across the timepoints up to cycle 11 both for questionnaire and VAS (questionnaire/VAS completed for 34 patients in FTD/TPI + Bev group, 6 patients FTD/TPI group) and was similar in the two treatment groups, except at cycle 7 with lower compliance rate in the FTD/TPI + Bev group than in the FTD/TPI group (86.2% vs 100%, respectively, both for questionnaire and VAS). The reasons for non-completion of EQ-5D-5L were mostly questionnaire/VAS not available, institutional error or other reason [7,22]. Pattern of missing data and completion is found in Table 35 below.

Table 35 Pattern of missing data and completion [7,22]**.**

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)
Lonsurf + bevacizumab				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 6	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 7	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 8	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 9	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 10	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 11	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 12	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 13	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 14	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 15	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 16	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 17	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 18	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 19	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 20	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal	[redacted]	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Lonsurf				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 6	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 7	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 8	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 9	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 10	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 11	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 12	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 13	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 14	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 15	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 16	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 17	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 18	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 19	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 20	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal	[redacted]	[redacted]	[redacted]	[redacted]

11.1.3 HRQoL results

HRQoL outcomes analysis included change from baseline in VAS and health utility index for the EQ-5D-5L (Figure 19). Patients were able to maintain functioning across physical, cognitive, and social subdomains with both treatments, with no decline over time observed in either group as measured by the EQ-5D-5L.

HRQoL summary statistics based on EQ-5D-5L are shown in Table 36. Each time point corresponds to an analysis visit, i.e. what actually happened. Some visits could have been missed or happened outside the protocol-defined win-dow, and there were no values for cycle 18, 19 and 20. From cycle 13-17 there are reported NA value in the difference between intervention and comparator due to some of the visits having only one observation, meaning that a confidence interval cannot be calculated, or data were missing [7,22].

Figure 19 General QoL scores (EQ-5D-5L) from Baseline to Cycle

Table 36 HRQoL [EQ-5D-5L] summary statistics

	Lonsurf+bevacizumab (intervention)		Lonsurf monotherapy (comparator)		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI), p-value
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Lonsurf+bevacizumab (intervention)		Lonsurf monotherapy (comparator)		Intervention vs. comparator
		[redacted]		[redacted]	[redacted]
Cycle 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Last value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

11.2.1 HSUV calculation

For the model base case, utility values were derived from the SUNLIGHT study, where EQ-5D-5L were obtained. The EQ-5D-5L utilities have been adjusted to the DK value set [44]. The utility values were based on progression status and were derived using a mixed-effects regression model. The regression model accounted for both the progression status but also treatment, where two models are inserted into the global model.

1. Dependent model: Utility ~ progression
2. Independent model: Utility ~ progression + treatment.

The results of the regression analysis are illustrated in section 11.2.3 HSUV results. The model base case was adapted to the treatment-independent model. This was chosen so that any influence of treatment used in the trial on HRQoL is captured in the model [22].

Additionally, utility decrements were also included for each AE that occurred during the trial period. Literature from previous mCRC appraisals was used to value the decrements, whereas the SUNLIGHT study was used to estimate the duration of each AE [22,26,27]. If no duration was captured in the SUNLIGHT trial, an average of the available duration estimates was used instead. To facilitate an adaption to a Danish setting, Danish age-related utility decrements were included to account for the natural decline in QoL associated with age [22].

11.2.1.1 Mapping

A mixed-effect regression model was applied to calculate the utility values for the base case model. The two available models are presented in Table 37 [22].

Table 37 Mixed-effect regression table

Parameter	Coefficient	Variance - covariance		
		Intercept	Lonsurf plus bevacizumab	PF
Dependent model				
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free	[redacted]	[redacted]	[redacted]	[redacted]
Independent model				
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Lonsurf plus bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free	[redacted]	[redacted]	[redacted]	[redacted]

11.2.2 Disutility calculation

The impact of Grade ≥3 AEs on HRQoL was explored in the cost-effectiveness analysis. Utility decrements for each of the AEs included in the analysis were sourced from the literature or previous mCRC appraisals. AE utility decrements are applied in the model for the expected duration of each AE, the data for which were sourced from the SUNLIGHT study. When an AE duration could not be estimated from SUNLIGHT, the duration was assumed to be the average of the available duration estimates from SUNLIGHT or sourced from other mCRC appraisals. The disutility and expected duration are presented in Table 38 [22].

Table 38 Disutilities of adverse events

Adverse event	Disutility	Duration (days)	Source	
			Assumption	Reference
Anaemia	-0.0209	118.8	[45]	[7]
Hypertension	-0.025	21.1	[45]	[7]
Neutropenia	-0.08973	11.8	[46]	[7]
Neutrophil count decreased	-0.08973	14.6	Assumed equal to neutropenia	[7]

11.2.3 HSUV results

A summary of the values deduced from the mixed-effects regression model is presented in Table 39. The 95% CI's have been calculated using a PSA with 1,000 runsTable 39 [22]. The treatment specific utilities of the FTD/TPI arm are used as an estimate for the BSC arm because HRQoL data for BSC was not available in the SUNLIGHT trial. This is considered as a conservative approach, because HRQoL outcomes is expected to be worse for the BSC when compared to treatment with FTD/TPI.

Table 39 Overview of health state utility values [and disutilities]

	Results [95% CI]	No. of patients	No. of observations	Instrument	Tariff (value set) used	Comments
HSUVs - Lonsurf plus bevacizumab						
Progression-free	[redacted]	447	1.975	EQ-5D-5L	DK	[redacted]

	Results [95% CI]	No. of patients	No. of observations	Instrument	Tariff (value set) used	Comments
Progressed disease	[redacted]	270	304	EQ-5D-5L	DK	[redacted]
HSUVs - Lonsurf monotherapy						
Progres-sion-free	[redacted]	447	1.975	EQ-5D-5L	DK	[redacted]
Progressed disease	[redacted]	270	304	EQ-5D-5L	DK	[redacted]
HSUVs – BSC						
Progres-sion-free	[redacted]	447	1.975	EQ-5D-5L	DK	[redacted]
Progressed disease	[redacted]	270	304	EQ-5D-5L	DK	[redacted]
Total AE disutilities						
Lonsurf plus bevaci-zumab	[redacted]	N/A	N/A	EQ-5D	UK	[redacted]
Lonsurf monother-apy	[redacted]	N/A	N/A	EQ-5D	UK	[redacted]
BSC	[redacted]	N/A	N/A	EQ-5D	UK	[redacted]

11.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy (N/A)

Table 40 Overview of health state utility values [and disutilities] - (N/A)

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
HSUV A				
HSUV B				
…				
[Disutilities]				
…				

Table 41 Overview of literature-based health state utility values – (N/A)

	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				
…				
[Disutility A]				
…				

12. Resource use and associated costs

The model's costs were estimated based on a limited societal perspective following the DMC guidelines. This encompasses expenses related to drug acquisition and administration, disease management costs pre- and post-disease progression, adverse event-related costs, as well as patient time and transportation costs. All expenses in the model are subject to a 3.5% annual discount rate as per the Danish Ministry of Finance guidelines [47].

12.1 Medicine costs - intervention and comparator

Treatment regimens with the dosing schedules and dose intensity and the unit drug costs for each treatment included within the cost-effectiveness model are summarized in Table 42. The unit costs have been sourced from Medicinpriser.dk[48] on the 27th of May 2024 and are reported in the pharmacy purchase price in accordance with the DMC guideline. However, tender prices are available.

Table 42 Medicine costs used in the model

Treatment		Dose	Relative dose intensity	Frequency	Vial sharing
Lonsurf plus bevacizumab	**Lonsurf**	35mg/m^2	[redacted]	Twice daily on days 1-5, 8-12 Q4W	No
	Bevacizumab	5mg / kg	[redacted]	Q4W	No
Lonsurf monotherapy		35mg/m^2	[redacted]	Twice daily on days 1-5, 8-12 Q4W	No

Pharmaceutical	Strength	Package size	Pharmacy purchase price in DKK
Lonsurf	15 mg + 6.14 mg	20 tablets	[redacted]

	15 mg + 6.14 mg	60 tablets	[redacted]
	20 mg + 8.19 mg	20 tablets	[redacted]
	20 mg + 8.19 mg	60 tablets	[redacted]
Bevacizumab	25 mg/ml	1 x 4 ml	[redacted]
	25 mg/ml	1 x 16 ml	[redacted]
BSC	N/A	N/A	0

The dosing schedule for each treatment was taken from the treatment summary of product characteristics (SmPC). Lonsurf is dosed at 35mg/m2 twice daily on days 1 to 5 and 8 to 12 in a 28-day cycle until disease progression or unacceptable toxicity. The distribution of Body surface area (BSA) used in the model base case was derived from a [redacted] to the BSA distribution in the SUNLIGHT trial. The total number of packs required per 28 days was then calculated and multiplied by the BSA distribution to calculate the average cost per 28 days. The dose is calculated according to BSA and is shown in Table 43 [1,7].

Table 43 Dose calculation according to BSA

BSA (m^2)	Dose in mg (2x daily)	Tablet per dose		Total daily dose (mg)	BSA distribution
		15mg	20mg		
< 1.07	35	1	1	[redacted]	[redacted]
1.07 – 1.22	40	0	2	[redacted]	[redacted]
1.23 – 1.37	45	3	0	[redacted]	[redacted]
1.38 – 1.52	50	2	1	[redacted]	[redacted]
1.53 – 1.68	55	1	2	[redacted]	[redacted]
1.69 – 1.83	60	0	3	[redacted]	[redacted]

1.84 – 1.98	65	3	1	[redacted]	[redacted]
1.99 – 2.14	70	2	2	[redacted]	[redacted]
2.15 – 2.29	75	1	3	[redacted]	[redacted]
➢ 2.30	80	0	4	[redacted]	[redacted]

Bevacizumab is given intravenously at 5mg/kg every 2 weeks alongside the oral dose of Lonsurf. For bevacizumab and other treatments dependent on patients' BSA or weight, patient-level data from SUNLIGHT are used with the method of moments (MoM) technique to calculate the average number of vials that would be required to satisfy one administration of treatment [7,49]. The MoM first derives a log-normal distribution for the patient BSA or weight within the study based upon the mean and SD measured at baseline. It then uses the log-normal distribution to predict what proportion of patients require each number of vials to administer the required dose. This method assumes that patients only receive whole vials (no vial sharing), and thus accounts for drug wastage. The number of vials needed per administration per patient weight is calculated based on the possible vial combinations of multiple vial sizes. All the possible vial combinations (up to four vials) and their respective doses were calculated; where there was more than one of the same doses, only the cheapest option was carried forward.

BSC can consist of a variety of concomitant treatments, procedures, and other palliative care. In line with assumptions made in previous NICE appraisals[50,51], the costs of BSC are assumed to be captured by disease management usage (see Section 12.1.4) and therefore treatment costs are assumed to be 0 DKK.

In the SUNLIGHT study, dose reductions were allowed for patients with AEs (up to 3 dose reductions for Lonsurf). In those cases of dose reductions in SUNLIGHT, doses of Lonsurf were reduced to from 35 mg/m2 to 30 mg/m2 (level 1), then from 30 mg/m2 to 25 mg/m2 (level 2), then from 25 mg/m2 to 20 mg/m2 (level 3). For bevacizumab, dose reductions due to AEs were not recommended with treatment having to either be permanently discontinued or temporarily suspended. If bevacizumab was discontinued, patients could continue with Lonsurf as monotherapy. To account for dose reductions, missed doses and treatment interruptions, the RDI from SUNLIGHT has been incorporated in the base case [7].

12.2 Medicine costs – co-administration (N/A)

Not applicable.

12.3 Administration costs

As Lonsurf is administered as an oral agent, no administration cost is assigned. Bevacizumab is administered as an infusion agent on days 1 and 15 of the 28-day cycle. BSC as a comparator is assumed to be equal to palliative care that only includes disease

management costs, therefore no administration cost is assigned to this comparator. Table 44 provides an overview of the administration costs related to the treatments.

Table 44 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Lonsurf oral therapy	Day 1-5 and day 8-12 of a 28-day cycle	0	N/A	
Bevacizumab i.v infusion	Days 1 and 15 of a 28-day cycle	1,561.00	06MA98 [MDC06 1-dagsgruppe, pat. Mindst 7 år]	[52]
BSC			N/A	

12.4 Disease management costs

A third of patients are assumed to undergo a computerized tomography (CT) every 4 weeks. It is assumed that BSC patients do not attend any routine oncologist visits. The assumptions are based on resource use estimates used in prior NICE appraisals TA405 and TA886. Table 45 summarizes the frequencies and proportion of patients undergoing CT with unit costs presented in Table 46. The unit costs were sourced from Sundhedsdatastyrelsen: Takstsystem 2024 [52].

Table 45 Disease monitoring resource use and frequencies

Resource use	Progression-free						Progressed	
	IV		Oral		BSC			
	Freq	%	Freq	%	Freq	%	Freq	%
CT scan	0.25	33%	0.25	33%	-	-	-	-

Table 46 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code/Region	Cost	Reference
		During the Progression Free Stage			
CT scan	1/3 of the patients every 4th week	2585	30PR06 [CT-scanning, kompliceret]		[52]

12.5 Costs associated with management of adverse events

The analysis accounts for the AE costs attributed to those of grade ≥3 occurring in greater than 5% of patients in either treatment arm. Frequencies of AEs are from the clinical study reports of SUNLIGHT and RECOURSE, respectively [3,7]. Unit costs concerning AEs were derived from the Danish diagnosis-related group (DRG) tariffs. AE costs are proportionally allocated based on the incidence rate of the respective AEs within each treatment group and furthermore, the costs are treated as a lump-sum, upfront expenditure for each treatment arm in the model. Frequencies and costs related to grade ≥3 AEs are illustrated in Table 47 and Table 48 [51,52].

Table 47 Frequencies of adverse events for Lonsurf plus bevacizumab, Lonsurf and Best supportive care

Adverse event	Lonsurf plus bevacizumab	Lonsurf	BSC
Anaemia	6.1%	11%	3.0%
Anorexia (decreased appetite)	0.8%	1.2%	5.0%
Fatigue	1.2%	3.7%	6.0%
Hypertension	5.7%	1.2%	1.2%
Neutropenia	43.1%	32.1%	-
Neutrophil count decreased	8.9%	5.3%	-

Table 48 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff [DKK]
Anaemia	16PR02 [Transfusion af blod, øvrig]	4,218.00
Anorexia	06MA11 [Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidlag]	7,818.00
Fatigue	03MA02 [Svimmelhed]	8,171.00
Hypertension	05MA11 [Hypertension]	18,261.00
Neutropenia	16MA98 [MDC16 1-dagsgruppe, pat. mindst 7 år]	2,111.00

	DRG code	Unit cost/DRG tariff [DKK]
Neutrophil count decreased	16MA98 [MDC16 1-dagsgruppe, pat. mindst 7 år]	2,111.00

12.6 Subsequent treatment costs (N/A)

The treatment protocols involving Lonsurf plus bevacizumab or Lonsurf monotherapy are intended to be positioned as the 3L option in the Danish treatment regimen for mCRC. Hence, it is presumed that no further treatments are administered following the regimens involving Lonsurf plus bevacizumab or Lonsurf monotherapy.

Table 49 Medicine costs of subsequent treatments (N/A)

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]		

12.7 Patient costs

Patients costs are applied as monitoring costs in the model. The monitoring costs include transportation to and from the hospital, which in accordance with the DMC 'Værdisætning af enhedsomkostninger v.1.7' a cost of DKK 3.73 is included per kilometre driven. An average of 40km is determined to be the settled distance patients commonly must travel back and forth from the hospital. The time spent on traveling the distance is assumed to be approximately 40 minutes, which reflects that that the patient drives to and from the hospital. Furthermore, the time spent on hospital visits in relation to the intravenous infusion of Bevacizumab was assumed to be 1 hour, based on a previous DMC application of combination therapy with bevacizumab, as well as estimated infusion times from administration methods in SmPCs of bevacizumab preparations used in Denmark [53–57]. The hospital visit time and time for settling the distance to and from the hospital were both multiplied by the average Danish salary per minute of DKK 3.13 [58]. The patient costs used in the model are presented in Table 50.

Table 50 Patient costs used in the model

Activity	Units
Distance to hospital	40 km
Cost per km	DKK 3.73
Time spent on traveling	40 minutes
Average Danish salary per hour	DKK 188.00
Time spent on hospital visit	1 hour
Total cost per transportation	DKK 462.53

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

The analysis follows the DMC's guidelines for palliative/terminal care. It is assumed that end-of-life costs are applied for all patients during the model time horizon. The cost of end-of-life is though assumed to be roughly the same in both treatment arms and with almost all patients in both arms having died within the time horizon, the base case does not include terminal care costs into the model.

13. Results

13.1 Base case overview

An overview of the base case results are provided in Table 51 and Table 52.

Table 51 Base case overview of Lonsurf plus bevacizumab compared to Lonsurf monotherapy

Feature	Description
Comparator	Lonsurf monotherapy
Type of model	PSM
Time horizon	10 years (life time, <1% alive)
Treatment line	3rd line

Measurement and valuation of health effects	HRQoL measured with EQ-5D-5L in the SUNLIGHT study. Danish population weights were used to estimate health-state utility values.	
Costs included	Medicine costs Administration costs Disease management cost Costs of AEs	
Dosage of medicine	Based on BSA, mean: [redacted]	
Average ToT	Lonsurf plus bevacizumab: [redacted] Lonsurf monotherapy: [redacted]	
Parametric function for PFS	Lonsurf plus bevacizumab: [redacted] Lonsurf monotherapy: [redacted]	
Parametric function for OS	Lonsurf plus bevacizumab: [redacted] Lonsurf monotherapy: [redacted]	
Inclusion of waste	Yes	
Average time in model health state (months)	Lonsurf plus bevacizumab	Lonsurf monotherapy
PFS **PD (OS)** **Death**	[redacted] Absorbing state	[redacted] Absorbing state

Table 52 Base case overview of Lonsurf plus bevacizumab compared to BSC

Feature	Description
Comparator	BSC
Type of model	PSM
Time horizon	10 years (life time, <1% alive)
Treatment line	3rd line
Measurement and valuation of health effects	HRQoL measured with EQ-5D-5L in the SUNLIGHT study. Danish population weights were used to estimate health-state utility values.

Costs included	Medicine costs Administration costs Disease management cost Costs of AEs Transportation cost	
Dosage of medicine	Based on BSA, mean: [redacted]	
Average ToT	Lonsurf plus bevacizumab: [redacted] BSC: [redacted]	
Parametric function for PFS	Lonsurf plus bevacizumab: [redacted] BSC: N/A. Applied HR from NMA	
Parametric function for OS	Lonsurf plus bevacizumab: [redacted] BSC: N/A. Applied HR from NMA	
Inclusion of waste	Yes	
Average time in model health state (months)	Lonsurf plus bevacizumab	BSC
PFS	[redacted]	[redacted]
PD (OS)	[redacted]	[redacted]
Death	Absorbing state	Absorbing state

13.1.1 Base case results

Table 53 presents the results of the base case comparison between Lonsurf plus bevacizumab compared to BSC. Patients treated with Lonsurf plus bevacizumab overall had an improved OS compared to BSC, additionally having patients staying in the PFS state for a longer duration. The treatment with Lonsurf plus bevacizumab was thereby associated with the highest life years (LYs) and QALYs though also incurring a cost premium compared to BSC. Over the time horizon of 10 years, Lonsurf plus bevacizumab is estimated to be associated with an increase of 1.29 LYs and 1.04 QALY compared to BSC with an increase of 0.63 LYs and 0.48 QALY. The improvement in outcomes for patients with mCRC was predominantly owed to a larger proportion of patients living for an extended period compared to BSC. The base case ICER was [redacted]. Important to note regarding the base case ICER is the fact that a conservative cost approach [redacted] was applied.

Table 53 Base case results, discounted estimates (Lonsurf plus bevacizumab vs. BSC)

	Lonsurf plus bevacizumab	BSC	Difference
Medicine costs	[redacted]	[redacted]	[redacted]
Medicine costs – co-administration	N/A	N/A	N/A
Administration	DKK 18,415	DKK 0	DKK 18,415
Disease management costs*	DKK 7075	DKK 0	DKK 7075
Costs associated with management of AEs	DKK 2,558	DKK 1,227	DKK 1,331
Subsequent treatment costs	N/A	N/A	N/A
Palliative care costs	N/A	N/A	N/A
Patient time and transportation	DKK 7672	DKK 0	DKK 7672
Total costs	[redacted]	[redacted]	[redacted]
Life years gained (Pro-gression-free)	[redacted]	[redacted]	[redacted]
Life years gained (Post progression)	[redacted]	[redacted]	[redacted]
Total life years	[redacted]	[redacted]	[redacted]
QALYs (PF)	[redacted]	[redacted]	[redacted]
QALYs (Post progres-sion)	[redacted]	[redacted]	[redacted]
QALYs (adverse reac-tions)	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental costs per life year gained		[redacted]	

	Lonsurf plus bevacizumab	BSC	Difference
Incremental cost per QALY gained (ICER)	[redacted]		

*Resource use during progression free state, resource use during progressed disease state, and resource use of transportation.

Table 54 presents the results of the base case comparison between Lonsurf plus bevacizumab compared to Lonsurf monotherapy. As with the previous comparison, patients treated with Lonsurf plus bevacizumab overall had an improved OS compared to Lonsurf monotherapy, additionally having patients staying in the PFS state for a longer duration. The treatment with Lonsurf plus bevacizumab was thereby associated with the highest Lys and QALYs, though also incurring a cost premium compared to Lonsurf monotherapy. Over the time horizon of 10 years, Lonsurf plus bevacizumab is estimated to be associated with an increase of [redacted] LYs and [redacted] QALY compared to Lonsurf monotherapy with an increase of [redacted] LYs and [redacted] QALY. Subsequently, the improvement in outcomes for patients with mCRC was predominantly owed to a larger proportion of patients living for an extended period. The base case ICER was [redacted] per QALY.

Table 54 Base case results, discounted estimates (Lonsurf plus bevacizumab vs. Lonsurf monotherapy)

	Lonsurf plus bevacizumab	Lonsurf Monotherapy	Difference
Medicine costs	[redacted]	[redacted]	[redacted]
Medicine costs – co-administration	N/A	N/A	N/A
Administration	DKK 18,415	DKK 0	DKK 18,415
Disease management costs*	DKK 7075	DKK 3500	DKK 3575
Costs associated with management of AEs	DKK 2,558	DKK 1,869	DKK 689
Subsequent treatment costs	N/A	N/A	N/A
Palliative care costs	N/A	N/A	N/A
Patient time and transportation	DKK 7672	DKK 1898	DKK 5774
Total costs	[redacted]	[redacted]	[redacted]
Life years gained (Progression-Free)	[redacted]	[redacted]	[redacted]

	Lonsurf plus bevacizumab	Lonsurf Monotherapy	Difference
Life years gained (Post progression)	[redacted]	[redacted]	[redacted]
Total life years	[redacted]	[redacted]	[redacted]
QALYs (Progression-free)	[redacted]	[redacted]	[redacted]
QALYs (Post progression)	[redacted]	[redacted]	[redacted]
QALYs (adverse reactions)	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental costs per life year gained		[redacted]	
Incremental cost per QALY gained (ICER)		[redacted]	

*Resource use during progression free state, resource use during progressed disease state, and resource use of transportation.

13.2 Sensitivity analyses

13.2.1 Deterministic sensitivity analyses

One-way sensitivity analyses (OWSA) were conducted to test the impact of individual parameters when their values are set to the lower and upper limits of their associated CI while other parameters are maintained at the base case default. If the variance in any inputs was not available, a simplified assumption was made assuming the standard error of the mean was 10%. A total of 71 parameters out of 374 global parameters were included in the Danish base case. Parameters that were excluded were either fixed parameters or subsequent treatment regimens used in other healthcare systems.
Figure 20 and Figure 21 present the tornado plots showing the 10 parameters which had the largest impact on the ICER of Lonsurf plus bevacizumab versus each comparator, respectively Lonsurf monotherapy and BSC.

Figure 20 Tornado diagram showing OWSA results on the ICER – versus Lonsurf Monotherapy

Figure 21 Tornado diagram showing OWSA results on the ICER – versus BSC

In Table 55 an overview of the 10 most impactful parameters is illustrated based on the comparison of Lonsurf + bevacizumab vs. Lonsurf monotherapy.

Table 55 ICER (Lonsurf plus bevacizumab vs. Lonsurf monotherapy) at lower and upper value of parameters from univariate sensitivity analysis

#	Parameter	Lower bound (DKK)	Upper bound (DKK)
1			
2			
3			
4			
5			
6			
7			
8			

9	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]

In Table 56 an overview of the 10 most impactful parameters is illustrated based on the comparison of Lonsurf + bevacizumab vs. BSC.

Table 56 ICER (Lonsurf plus bevacizumab vs. BSC) at lower and upper value of parameters from univariate sensitivity analysis

#	Parameter	Lower bound (DKK)	Upper bound (DKK)
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]

The results from the one-way sensitivity analyses are found in Table 57 below.

Table 57 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case, vs. Lonsurf monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RDI - FTD/TPI (FTD/TPI + bevacizumab)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RDI - Bevacizumab (FTD/TPI + bevacizumab)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RDI - FTD/TPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Base case, vs. BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RDI - FTD/TPI (FTD/TPI + bevacizumab)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR – OS - BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RDI - Bevacizumab (FTD/TPI + bevacizumab)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

13.2.2 Probabilistic sensitivity analyses

Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA). Hence, suitable probability distributions were assigned to 58 model parameters to characterize uncertainty related to the mean values of the parameters. All parameters can be assessed in Appendix G, with parameter input, point estimate, lower-, upper bound and belonging distribution. A Monte Carlo simulation was performed to do the 10,000 iterative processes of modelling the estimates. In Table 58, a presentation of the pair-wise PSA results for Lonsurf plus bevacizumab compared to the comparators, Lonsurf monotherapy and BSC is illustrated. For available parameters, the mean value and the SE of each parameter were used to parametrize the relevant probability distribution, however, if not possible a simplified 10% SE of the mean was assumed.

Table 58 PSA pair-wise results

Treatment	Total		Incremental		ICER
	Costs DKK	QALYs	Costs DKK	QALYs	
Lonsurf plus bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lonsurf monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The results of the PSA were presented in a cost-effectiveness plane with all 10,000 PSA iterations for all treatments and are presented in [redacted]. The spread of uncertainty shown in the figure demonstrates that the non-trial comparators have more uncertainty due to NMA results compared to parametric curves used for the within-trial treatments, which have less uncertainty in the total QALY gain.

Figure 22 Scatter plot of 10.000 iterations of the cost-effectiveness plane of Lonsurf plus Bevacizumab versus Lonsurf mono therapy and BSC

Figure 23 and Figure 24 present the cost-effectiveness acceptability curves (CEAC) for Lonsurf plus bevacizumab, Lonsurf monotherapy and BSC, based on 10,000 PSA iterations. The CEAC curves show the probability of each treatment being cost-effective at different willingness-to-pay (WTP) thresholds. [redacted]

Figure 23 Cost-effectiveness acceptability curve for Lonsurf plus bevacizumab and BSC

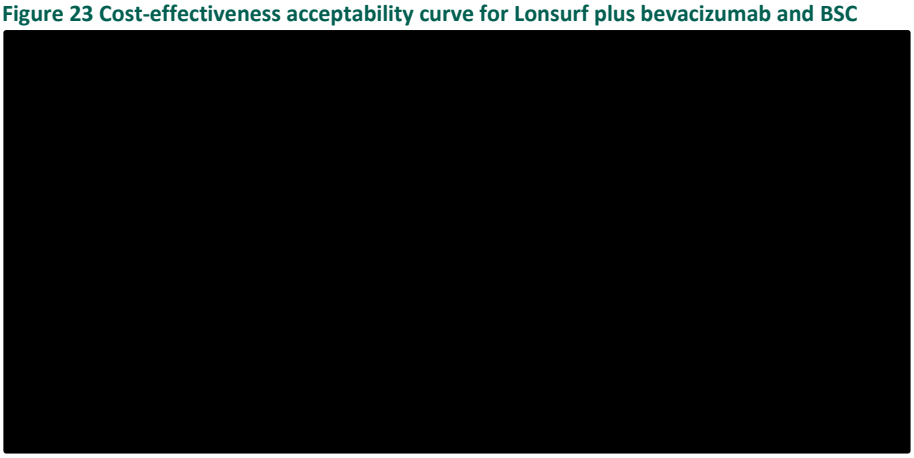

Figure 24 Cost-effectiveness acceptability curve for Lonsurf plus bevacizumab, Lonsurf Monotherapy and BSC

Figure 25 and Figure 26 illustrate the ICER convergence plots for Lonsurf plus bevacizumab compared to Lonsurf monotherapy and BSC. The plots illustrate all ICERs in a convergence formation, which is plotted by averaging the ICER iterations. Two lines are inserted to depict a +/- 2.5% change from the convergence ICER.

Figure 25 Convergence plot of the ICER (Lonsurf plus bevacizumab vs. Lonsurf Monotherapy)

Figure 26 Convergence plot of the ICER (Lonsurf plus bevacizumab vs. BSC)

13.2.3 Scenario analyses (N/A)

14. Budget impact analysis

This section outlines the budgetary implications of introducing Lonsurf in combination with bevacizumab or as a standalone treatment. It provides estimates of the incremental and cumulative budget impact for the patient population covered by the model. The yearly total predicted cost, including drug and administration expenses, along with current market shares, is calculated alongside the incremental budget impact. The expected budget impact of recommending the medicine for the indication is found in Table 61.

14.1 Eligible patients

The incidence is based on an internal, confidential forecast model. The incident numbers inserted in each year are adjusted to patients moving into several lines of therapy and mOS. The prevalent population is excluded from the calculations due to the poor prognosis of the mCRC 3L disease stage.

A rather quick market uptake is expected due to the unmet need for a 3L pharmaceutical that prolongs survival and QoL in Danish mCRC patients. The forecasted market share is presented in Table 59 below, and the corresponding expected candidates are presented in Table 60.

Table 59 Expected market share with and without recommendation

	Market share (%)				
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
The pharmaceutical under consideration	**15%**	**15%**	**15%**	**15%**	**15%**

is NOT recommended					
The pharmaceutical under consideration is recommended	**55%**	**75%**	**75%**	**75%**	**75%**

Table 60 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		
Lonsurf + bevacizumab	231	332	356	365	369
Lonsurf monotherapy	0	0	0	0	0
BSC	189	111	119	122	123
			Non-recommendation		
Lonsurf + bevacizumab	63	66	71	73	74
Lonsurf monotherapy	0	0	0	0	0
BSC	357	377	404	413	418

Table 61 Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The pharmaceutical under consideration is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
The pharmaceutical under consideration is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Year 1	Year 2	Year 3	Year 4	Year 5
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

15. List of experts

No clinical experts were consulted during the process of conducting this submission for the Danish Medicines Council.

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Appendix A. Main characteristics of studies included

Table 62 Main characteristics of SUNLIGHT [1,7,42]

Trial name: SUNLIGHT		**NCT number: 04737187**
Objective	Show the superiority of Lonsurf plus bevacizumab over Lonsurf monotherapy alone with respect to overall survival.	
Publications – title, author, journal, year	N Engl J Med 2023; 388(18): 1657-1667.	
Study type and design	Phase 3, international, prospective, randomized, active-controlled, trial involving patients with refractory metastatic colorectal. Enrolled patients were randomly assigned 1:1. Study is completed, however, QoL to be reported in a future publication.	
Sample size (n)	492 (246 in each arm)	
Main inclusion criteria	1. Age ≥18 years 2. Histologically confirmed unresectable mCRC 3. Prior treatment with ≤2 chemotherapy regimens for mCRC† and disease progression or intolerance to the last regimen 4. Prior regimens must have included a fluoropyrimidine, irinotecan, oxaliplatin and an anti-VEGF monoclonal antibody; and/or (in patients with RAS wild-type tumours) an anti-EGFR monoclonal antibody 5. Known RAS-mutation status 6. Ability to swallow oral tablets 7. Estimated life expectancy ≥12 weeks 8. ECOG PS ≤1 9. Adequate bone marrow, renal, hepatic and coagulation function‡ If applicable, negative pregnancy test and agreement to use highly effective contraception.	
Main exclusion criteria	1. More than 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer.	

Trial name: SUNLIGHT		NCT number: 04737187
	2. In the investigator's opinion, the patient was unlikely to be compliant with the oral medication regimen or the requirements of the study for scheduled evaluations. 3. Pregnant or lactating female patient or possibility of becoming pregnant during the study. 4. Participation in another interventional study within 4 weeks prior to the randomisation. Participation in study follow-up part without IMP administration, non-interventional registry or epidemiological study was allowed. 5. Patients receiving or having received anticancer therapies within 4 weeks prior to randomisation. Already randomised in this study.	
Intervention	Lonsurf in a 28 days cycle, 35 mg/m2 day 1-5 and 8-12 twice daily and bevacizumab 5 mg/kg day 1 and 15. 246 patients included in the intervention arm.	
Comparator(s)	Lonsurf in a 28 days cycle, 35 mg/m2 day 1-5 and 8-12 twice daily. 246 patients included in the comparator arm.	
Follow-up time	The median follow-up was 14.2 months (interquartile range, 12.6 to 16.4) in the combination group and 13.6 months (interquartile range, 12.7 to 15.9) in the Lonsurf monotherapy group.	
Is the study used in the health economic model?	Yes	
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** OS was the primary efficacy endpoint of this study. Secondary endpoints were progression free survival, confirmed objective response according to RECIST version 1.1, HRQoL as assessed by QLQ-C30 version 3.0, and EuroQol 5-Dimension 5-Level questionnaire, and safety assessed by CTCAE v5.0, including SAEs.	
Method of analysis	Efficacy was assessed in all the patients who had undergone randomization, in accordance with the intention-to-treat principle. Safety was assessed in all the patients who received one or more doses of a trial agent.	

Trial name: SUNLIGHT	NCT number: 04737187
Subgroup analyses	Planned stratification factors: • RAS-mutation status (mutant, wild type) • Time since first metastasis diagnosis (<18 months, ≥18 months) • Geographical location (North America, European Union, and Rest of the World) Pre-specified subgroup analyses: • Age (<65 years, ≥65 years) • Location of primary disease (right, left) • ECOG PS (0, ≥1) • Sex (female, male) • Prior surgical resection (yes, no) • Number of metastatic sites (1-2, ≥3) • Neutrophils to lymphocytes ratio (NLR <3, NLR ≥3) • Number of prior metastatic drug regimens (1, ≥2) • BRAF mutation status (mutant, wild type) • MSI status (MSI-H, MSS/MSI-L) • Prior bevacizumab (yes, no) • Subsequent regorafenib (yes, no)
Other relevant information	*N/A*

Table 63 Main characteristic of RECOURSE [1,3]

Trial name: RECOURSE	NCT number: 01607957
Objective	Assess the efficacy and safety of Lonsurf monotherapy in a global population with metastatic colorectal cancer whose cancer had been refractory to antitumor therapy or who had clinically significant AEs that precluded the re-administration of those therapies.
Publications – title, author, journal, year	N Engl J Med 2015;372:1909-19.
Study type and design	Double- Blind, Phase 3 Study of Lonsurf monotherapy plus BSC versus Placebo plus BSC in Patients with Metastatic Colorectal Cancer Refractory to Standard CT. Enrolled patients were randomly assigned in a 2:1 ratio.
Sample size (n)	*800 (534 in the intervention arm and 266 in the comparator arm)*

Trial name: RECOURSE	NCT number: 01607957
Main inclusion criteria	1. Has provided written informed consent prior to performance of any study procedure. 2. Is ≥18 years of age. 3. Has definitive histologically or cytologically confirmed adenocarcinoma of the colon or rectum. KRAS status must have been determined (mutant or wild). 4. Has received at least 2 prior regimens of standard chemotherapies for metastatic colorectal cancer and is refractory to or failing those chemotherapies. 5. Has Eastern Cooperative Group (ECOG) performance status of 0 or 1 in the Baseline period and on Cycle 1, Day 1. 6. Is able to take medications orally (ie, no feeding tube). 7. Has measurable or non-measurable metastatic lesion(s), as defined by RECIST version 1.1. 8. Has adequate organ function as defined by laboratory values obtained within 7 days prior to study drug administration on Day 1 of Cycle 1. 9. Women of childbearing potential must have a negative pregnancy test (urine or serum) within 7 days prior to randomization. Females must agree to adequate birth control if conception is possible during the study and up to 6 months after the discontinuation of study medication; and males must agree to adequate birth control during the study and up to 6 months after the discontinuation of study medication. 10. Is willing and able to comply with scheduled visits and study procedures.
Main exclusion criteria	1. Has a serious illness or medical condition(s) 2. Has had treatment within the specified time frame prior to study drug administration. 3. Has received TAS-102. 4. Has unresolved toxicity of greater than or equal to CTCAE Grade 2 attributed to any prior therapies (excluding anemia, alopecia, skin pigmentation, and platinum-induced neurotoxicity). 5. Is a pregnant or lactating female. 6. Is inappropriate for entry into this study in the judgment of the Investigator.

Trial name: RECOURSE	NCT number: 01607957
Intervention	Lonsurf monotherapy consisting of 35 mg per square meter was administered twice daily, after morning and evening meals, 5 days a week, with 2 days of rest, for 2 weeks, followed by a 14-day rest period. 534 patients received the intervention.
Comparator(s)	Placebo in the same schedule as for the intervention.
Follow-up time	Median follow-up of 11,8 months.
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** The primary endpoint was overall survival (OS) Secondary endpoints were progression-free survival (PFS) and safety. **Other endpoints:** Overall response rate (ORR), DCR, Safety.
Method of analysis	OS and PFS were analyzed in the intention-to-treat population.
Subgroup analyses	Planned stratification factors: • Tumor status: wildtype or mutant KRAS • Time between first diagnosis of metastases to randomization (<18 months, ≥18 months) • Geographical location (Japan, United States, Europe or Australia) Pre-specified subgroup analyses: • Sex (female, male) • Race (white, Asian, Black) • ECOG PS (0, 1) • Primary site of disease (colon, rectum) • Number of prior regimens (2,3,≥4) • Prior systemic anticancer agents • Refractory to fluropyrimidine
Other relevant information	*N/A*

Appendix B. Efficacy results per study

B.1 Results of SUNLIGHT and RECOURSE [3,7,22]

Table 64 Results of SUNLIGHT

Results of SUNLIGHT (NCT04737187)											
				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		
Median overall survival (time point, assessment every 8 weeks)	Lonsurf plus bevacizumab	246	10,8 (9.36-11.83) months	3.3 months	NA	NA	HR: 0.61	0.49-0.77	<0.001	The median survival is based on the Kaplan-Meier estimator and overall survival is defined as the time from randomization to death from any cause. The HR is based on a Cox proportional hazards model with adjustment for the variables used for stratification for randomization, and study arm.	Prager 2023
	Lonsurf	246	7.5 (6.34-8.57) months								
6 month survival	Lonsurf plus bevacizumab	246	77% (72%, 82%)	16%	NA	NA	NA	NA	NA	Using log-log transformation methodology of Kalbfleisch and Prentice; Stratified Cox proportional hazard model using IWRS stratification factors.	Prager 2023
	Lonsurf	246	61% (55%,								

Results of SUNLIGHT (NCT04737187)											
				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		
			67%)								
12 month survival	Lonsurf plus bevacizumab	246	43% (36%, 49%)	13%	NA	NA	NA	NA	NA	Using log-log transformation methodology of Kalbfleisch and Prentice; Stratified Cox proportional hazard model using IWRS stratification factors.	Prager 2023
	Lonsurf	246	30% (24%, 36%)								
18 month survival	Lonsurf plus bevacizumab	246	28% (19%, 37%)	13%	NA	NA	NA	NA	NA	Using log-log transformation methodology of Kalbfleisch and Prentice; Stratified Cox proportional hazard model using IWRS stratification factors.	Prager 2023
	Lonsurf	246	15% (9%, 22%)								
PFS (time point, assessment every 8 weeks)	Lonsurf plus bevacizumab	246	5,55 (4.50-5.88) months	3.15 months	NA	NA	HR:0.44	0,36-0.54	<0.001	Kaplan Meier curves and further characterized in terms of median and survival probabilities along with the corresponding 2-sided 95% CI for the estimates. The HR of PFS with its	Prager 2023
	Lonsurf	246	2.40 (2.07-3.22)								

Results of SUNLIGHT (NCT04737187)											
				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		
			months							95% CI was estimated with a stratified Cox proportional hazard model (stratification factors based on IWRS data).	
PFS 3 months	Lonsurf plus bevacizumab	246	73% (67%, 78%)	28%	NA	NA	NA	NA	NA	See description for PFS.	Prager 2023
	Lonsurf	246	45% (39%, 51%)								
PFS 6 months	Lonsurf plus bevacizumab	246	43% (37%, 49%)	27%	NA	NA	NA	NA	NA	See description for PFS	Prager 2023
	Lonsurf	246	16% (11%, 21%)								
PFS 9 months	Lonsurf plus bevacizumab	246	28% (22%, 34%)	23%	NA	NA	NA	NA	NA	See description for PFS	Prager 2023
	Lonsurf	246	5% (3%, 9%)								

Results of SUNLIGHT (NCT04737187)											
				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		
PFS 12 months	Lonsurf plus bevacizumab	246	16% (12%, 21%)	15%	NA	NA	NA	NA	NA	See description for PFS	Prager 2023
	Lonsurf	246	1% (0%, 3%)								
ORR	Lonsurf plus bevacizumab	15	6.1% (3.5-9.9)	4.9%	1.59-8.17	p=0.007	NA	NA	NA	Assessed in accordance with the Response Evaluation Criteria in Solid Tumors (version 1.1) and described using two-sided 95% Clopper-Pearson CI.	Prager 2023
	Lonsurf	3	1.2% (0.3-3.5)								
DCR	Lonsurf plus bevacizumab	171	69.5 %	27.6 %	19.21 - 36.07	P=0.007	NA	NA	NA	Assessed in accordance with the Response Evaluation Criteria in Solid Tumors (version 1.1) and described using two-sided 95% Clopper-Pearson CI.	Prager 2023
	Lonsurf	103	41.9 %								

Table 65 Results of RECOURSE

Results of RECOURSE (NCT01607957)											
				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		
Median overall survival (time point, assessment every 8 weeks)	Lonsurf	534	7.1 (6.5-7.8) months	1.8 months	NA	NA	HR: 0.68	0.58-0.81	<0.001	The median survival analyzed in the intention-to-treat population with the use of a two-sided, stratified log-rank test, with the HR and two-sided 95% CIs based on a stratified Cox model and the associated Kaplan–Meier survival estimates.	Mayer 2015
	Control	266	5.3 (4.6-6.0) months								
6 month survival	Lonsurf	534	58% (NA)	16%	NA	NA	NA	NA	NA	See method for overall survival	Mayer 2015
	Control	266	44% (NA)								
12 month survival	Lonsurf	534	27% (NA)	13%	NA	NA	NA	NA	NA	See method for overall survival	Mayer 2015
	Control	266	18% (NA)								
PFS (time	Lonsurf	534	2.0 (1.9-	0.3 months	NA	NA	HR:0.48	0.41-0.57	<0.001	Kaplan Meier curves and further	

Results of RECOURSE (NCT01607957)											
				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		
point, assessment every 8 weeks)			2.1) months							characterized in terms of median and survival probabilities along with the corresponding 2-sided 95% CI for the estimates. The HR of PFS with its 95% CI was estimated with a stratified Cox proportional hazard model (stratification factors based on IWRS data).	Mayer 2015
	Control	266	1.7 (1.7-1.8) months								
ORR	Lonsurf	534	1.6%	1.2%	NA	0.29	NA	NA	NA	Rates were compared using Fisher's exact test in the subgroup of the intention-to-treat population that had measurable disease at baseline.	Mayer 2015
	Control	266	0.4%								
DCR	Lonsurf	534	44%	28%	NA	0.001	NA	NA	NA	Rates were compared using Fisher's exact test in the subgroup of the intention-to-treat population that had measurable	Mayer 2015
	Control	266	16%								

Results of RECOURSE (NCT01607957)											
				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		
										disease at baseline.	

Appendix C. Comparative analysis of efficacy

A NMA has been conducted to allow for an indirect comparison between treatments where head-to-head evidence was not available. In this submission, the NMA is solely used to compare Lonsurf plus bevacizumab with BSC by using the RECOURSE trial. The description in this appendix includes more treatments [22].

C.1 Objective

The objectives of this study were to:

(1) identify and summarize clinical trial evidence regarding the efficacy and safety of treatments for patients with refractory mCRC by means of an SLR

(2) assess the feasibility of performing credible indirect comparisons of treatments relevant to HTA submissions

(3) estimate the relative treatment effects of Lonsurf plus bevacizumab versus other interventions for third-line treatment of mCRC by means of an NMA [22].

C.2 Methodology

Systematic literature review:
Relevant studies were identified through comprehensive searches of MEDLINE, Embase, and CENTRAL databases; relevant conference proceedings; and clinical trial registries using search terms for the population, interventions, and study designs of interest. To guide study selection, the titles/abstracts and full texts of identified studies were screened against pre-specified PICOS criteria. The risk of bias of included studies was assessed using the Cochrane Risk of Bias tool, version 2 for RCTs and the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies for non-randomized trials and single-arm trials. The process of study selection, data extraction, and risk of bias assessment was conducted by two reviewers.

Network meta-analysis:

To gauge the appropriateness of proceeding with an NMA, the feasibility of performing an NMA of OS and PFS was assessed by:

(1) determining whether the RCT evidence for the interventions of interest formed one network for each population and outcome of interest

(2) examining the distribution of trial, treatment, patient, and outcome characteristics that may affect treatment effects across comparisons within the networks.

Where RCTs identified in the SLR formed a connected network and were deemed to be sufficiently similar for each population and outcome of interest, their results were synthesized using NMA. NMA of reported HRs in terms of OS and PFS assuming proportional hazards between treatments was performed using random-effects and fixed-effects models with a contrast-based normal likelihood for the log HR of each trial in the network. Normal non-informative prior distributions were used for all parameters. Relative treatment effects were expressed as HRs with 95% CrIs, reflecting a 95% probability that the estimate is within the specified range.

Results:

Systematic literature review: The SLR identified 28 RCTs, 2 non-randomized trials, and 54 single-arm trials evaluating the efficacy or safety of treatments of interest in patients with refractory advanced or mCRC. Across the 28 RCTs, a total of 29 different active treatment regimens were evaluated, most commonly Lonsurf (n = 6 trials), cetuximab (n = 5 trials), cetuximab + irinotecan (n = 5 trials), panitumumab (n = 3 trials), and regorafenib (n = 3 trials). There was notable variation among RCTs in their eligibility criteria concerning both the number of prior lines of therapy and the treatment regimens received for advanced/metastatic disease.

Across RCTs, median OS ranged from 4.6 to 24.7 months, mPFS ranged from <1 to 11.3 months, ORR ranged from 0% to 50%, DCR ranged from 7% to 71%, and median duration of response ranged from 0 to 11.4 months. The proportion of patients who experienced any AE, grade ≥3 AEs, or SAEs ranged from 51.9% to 100%, 10.4% to 80.8%, and 5.8% to 49.6%, respectively. Fifteen trials had a low risk of bias, and 13 trials had some concerns of bias.

A list of study characteristics can be found in Table 66, Table 67, and Table 68.

Table 66 population characteristics in included trials

Trial ID	Age (y)	Disease classification	ECOG PS	Tumor histology	No. of prior treatment lines	Prior treatment regimens for advanced/metastatic disease
20020408	≥18	Metastatic	0-2	Adenocarcinoma	2-3	Fluoropyrimidine, irinotecan, and oxaliplatin; no prior anti-EGFR
ASPECCT	≥18	Metastatic	0-2	Adenocarcinoma	≥1	Thymidylate synthase inhibitor, irinotecan, and oxaliplatin; no prior anti-EGFR
BOND-3	≥18	Metastatic or locally advanced	0-1	Adenocarcinoma	≥1	Fluoropyrimidine, irinotecan, and bevacizumab; no prior

Trial ID	Age (y)	Disease classification	ECOG PS	Tumor histology	No. of prior treatment lines	Prior treatment regimens for advanced/metastatic disease
		(unresectable)				cetuximab or panitumumab
CO.17	≥18	Metastatic	0-2	--	--	Fluoropyrimidine, irinotecan, and oxaliplatin; no prior anti-EGFR
CONCUR	≥18	Metastatic	0-1	Adenocarcinoma	≥2	Fluoropyrimidine plus oxaliplatin or irinotecan
CORRECT	≥18	Metastatic	0-1	Adenocarcinoma	≥1	Fluoropyrimidine, pyrimidine, oxaliplatin, irinotecan, and/or bevacizumab; for KRAS WT tumors: cetuximab or panitumumab
FRESCO	18-75	Stage IV/ metastatic	0-1	--	≥2	Fluorouracil, oxaliplatin, irinotecan as second-line therapies
FRESCO-2	≥18	Metastatic	0-1	Adenocarcinoma	≥2	FTD/TPI or regorafenib; all standard treatments (fluoropyrimidine-, oxaliplatin-, or irinotecan-based chemotherapy, anti-VEGF therapy, and anti-EGFR therapy (if RAS WT)); ICI if dMMR/MSI-H; BRAF inhibitor if *BRAF V600E* mutation
ICECREAM	≥18	Metastatic	0-2	--	≥1	Fluoropyrimidine-, oxaliplatin-, and irinotecan-containing regimens; no prior anti-EGFR
Pfieffer 2020	≥18	Non-resectable metastatic	0-1[a]	Adenocarcinoma	≥1	Fluoropyrimidine, irinotecan, and oxaliplatin; for RAS WT tumors: cetuximab or panitumumab
RECOURSE	≥18	Metastatic	0-1	Adenocarcinoma	≥2	Standard chemotherapies
SUNLIGHT	≥18	Unresectable	0-1	Adenocarcinoma	1-2	Fluoropyrimidine, irinotecan, and oxaliplatin; for RAS WT tumors: anti-VEGF

Trial ID	Age (y)	Disease classification	ECOG PS	Tumor histology	No. of prior treatment lines	Prior treatment regimens for advanced/metastatic disease
						and/or anti-EGFR monoclonal antibody
TERRA	≥18	Metastatic	0-1	Adenocarcinoma	≥2	Fluoropyrimidine, irinotecan, and oxaliplatin
VELO	≥18	Metastatic	0-1	Adenocarcinoma	2	Chemotherapy and anti-EGFR monoclonal antibody
Xu 2017	18-75	Advanced	0-1	Adenocarcinoma	≥1	Fluorouracil, oxaliplatin, irinotecan
Yoshino 2012	≥20	Metastatic	0-2	Adenocarcinoma	≥2	Standard chemotherapies

Table 67 Baseline characteristics for the included studies

Trial ID	Arm	Median age, years (range)	Males, %	Race/ethnicity			ECOG performance status		
				White, %	Black, %	Asian, %	0, %	1, %	2, %
20020408	Panitumumab + BSC	62 (27-82)	63	99	<1	0	46	41	13
	BSC	63 (27-83)	64	98	0	<1	34	50	15
ASPECCT	Panitumumab	61 (19-86)	63.1	53.3	0.4	44.5	30.9	60.7	8.4
	Cetuximab	60.5 (20-89)	63.6	51.6	0.8	45.6	32.6	59.4	8
BOND-3	Cetuximab + irinotecan + bevacizumab	54 (50-68)[a]	58.8	88.2	0	5.9	70.6	29.4	0
	Cetuximab + irinotecan + placebo	58 (47-64)[a]	52.6	78.9	10.5	5.3	73.7	26.3	0
CO.17	Cetuximab + BSC	63 (28.6-88.1)	64.8	--	--	--	25.1	51.6	23.3
	BSC	63.6 (28.7-85.9)	63.9	--	--	--	22.5	54	23.5

Trial ID	Arm	Median age, years (range)	Males, %	Race/ethnicity			ECOG performance status		
				White, %	Black, %	Asian, %	0, %	1, %	2, %
CONCUR	Regoraf-enib	57.5 (50-66)[a]	62	0[b]	0[b]	100[b]	26	74	0
	Placebo	55.5 (48.5-62)[a]	49	0[b]	0[b]	100[b]	22	78	0
CORRECT	Regoraf-enib	61 (54-67)[a]	62	78	1	15	52	48	0
	Placebo	61 (54-68)[a]	60	79	3	14	57	43	0
FRESCO	Fruquin-tinib	55 (23-75)	56.8	--	--	--	27.7	72.3	0
	Placebo	57 (24-74)	70.3	--	--	--	26.8	73.2	0
FRESCO-2	Fruquin-tinib	64 (56-70)[a]	53	80	3	9	43	57	0
	Placebo	64 (56-69)[a]	61	83	3	8	44	56	0
ICECREAM	Cetuximab	61 (49-82)	76	--	--	--	40	56	4
	Cetuximab + iri-notecan	66 (48-85)	77	--	--	--	38	58	4
Pfieffer 2020	FTD/TPI	67 (58-72)[a]	64	--	--	--	32	68	0
	FTD/TPI + bevaci-zumab	64 (58-72)[a]	52	--	--	--	50	50	0
RECOURSE	FTD/TPI	63 (27-82)	61	57	<1	34	56	44	0
	Placebo	63 (27-82)	62	58	2	35	55	45	0
SUNLIGHT	FTD/TPI + bevaci-zumab	62 (20-84)	49.59	94.3	1.75	0	48.37	51.63	0
	FTD/TPI	64 (24-90)	54.47	96.07	1.31	0.44	43.09	56.5	0.41
TERRA	FTD/TPI	58 (26-81)	63	0	0	100	24	76	0
	Placebo	56 (24-80)	62	0	0	100	22	78	0
VELO	FTD/TPI + pani-tumumab	65 (39-81)	61.3	--	--	--	67.7	32.3	0
	FTD/TPI	66 (32-82)	54.8	--	--	--	71	29	0
Xu 2017	Fruquin-tinib + BSC	50 (25-69)	74.5	0	0	100	12.8	87.2	0

Trial ID	Arm	Median age, years (range)	Males, %	Race/ethnicity			ECOG performance status		
				White, %	Black, %	Asian, %	0, %	1, %	2, %
	Placebo + BSC	54 (38-70)	70.8	0	0	100	20.8	79.2	0
Yoshino 2012	FTD/TPI	63 (28-80)	57	--	--	--	64	33	3
	Placebo	62 (39-79)	49	--	--	--	61	37	2

[a]*Interquartile range;* [b]*Inferred based on eligibility criteria.* ***Abbreviations:*** *BSC, best supportive care; FTD/TPI, trifluridine/tipiracil.*

Table 68 OS and PFS definitions in the included studies

Trial ID	OS definition	PFS definition	PFS assessment method
20020408	Time from randomization to death	Time from randomization to either death or first observed disease progression, whichever occurred first	IRC
ASPECCT	Time from randomization to death	Time from the date of randomization to the date of disease progression or death	IA
BOND-3	Time from randomization to the date of death due to any cause	Time from the date of randomization to the date of 1st documented disease progression or death due to any cause, whichever occurs first	--
CO.17	Time from randomization until death from any cause	Time from randomization until the first objective observation of disease progression or death from any cause	--
CONCUR	Time from randomisation to death from any cause	Time from randomisation to first radiological or clinical finding of disease progression or death from any cause	IA
CORRECT	Time from randomisation to death from any cause	Time from randomisation to first radiological or clinical observation of disease progression or any-cause death	IA
FRESCO	Time from randomization to death caused by any reason	Time interval between the randomized date and the initial record of disease progression or date of death whichever comes first	--
FRESCO-2	Time from date of randomization to death from any cause	Time from randomization until the first radiographic documentation of objective progression or death from any cause, whichever comes first	IA
ICECREAM	From the date of random assignment to the date of death from any cause	--	--
Pfieffer 2020	Death due to any cause or censored at cutoff date	From the date of randomisation to the first date of radiological or clinical progression, time of death, or censored on cutoff date	IA

Trial ID	OS definition	PFS definition	PFS assessment method
RECOURSE	Time from randomization to death from any cause	Time from randomization to the first radiologic confirmation of disease progression or death from any cause	IA
SUNLIGHT	Time elapsed between the date of randomisation and the date of death due to any cause	Time elapsed between the randomisation and the date of radiologic tumour progression or death from any cause	IA
TERRA	Time from the date of randomization to the death date	Time from the date of randomization until the date of radiological disease progression or death due to any cause	IA
VELO	Time from randomization to death due to any cause	Time from randomization to the earliest documented disease progression or death due to any cause	IA
Xu 2017	Time interval between the randomization date and the date of death (any cause)	Time interval between the randomization date and the initial record of disease progression or date of death, whichever is earlier	IA
Yoshino 2012	Time between randomisation and death from any cause or the date of last follow-up	Time between randomisation and disease progression or death from any cause	IRC and IA

Network meta-analysis: Networks of evidence for OS and PFS were constructed for 16 connected RCTs evaluating Lonsurf plus bevacizumab or other interventions of interest. Although the target population was patients undergoing third-line treatment for mCRC, few studies evaluated treatments of interest in a pure third-line population. Therefore, after the results of feasibility assessment indicated that line of therapy was not an important treatment effect modifier, NMA was performed using a network of trials enrolling patients treated in a 2L+ setting. NMA of trials enrolling 2L+ patients showed that Lonsurf plus bevacizumab had statistical superiority over placebo/BSC (HR (95% credible interval): OS, random-effects: XXX, fixed-effect: XXX; PFS, random-effects: XXX, fixed-effects: XXX.

Conclusion:
Overall, the results of the NMA suggest that Lonsurf plus bevacizumab has superior outcomes in terms of prolonging OS and PFS compared with several other treatment regimens for patients with refractory mCRC, including placebo/BSC [22].

C.3 Results

The results from the NMA are presented in Table 69 below.

Table 69 Comparative analysis of studies comparing Lonsurf plus bevacizumab to BSC for patients with mCRC (2L+)

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
OS	The SUNLIGHT trial and the RECOURSE trial	NA	NA	NA	[redacted]	[redacted]	[redacted]	The HRs for the studies included were synthesized using random-effects meta-analysis	Yes
OS	The SUNLIGHT trial and the RECOURSE trial	NA	NA	NA	[redacted]	[redacted]	[redacted]	The HRs for the studies included were synthesized using fixed-effects meta-analysis	Yes
PFS	The SUNLIGHT trial and the RECOURSE trial	NA	NA	NA	[redacted]	[redacted]	[redacted]	The HRs for the studies included were synthesized using random-effects meta-analysis	Yes
PFS	The SUNLIGHT trial and the RECOURSE trial	NA	NA	NA	[redacted]	[redacted]	[redacted]	The HRs for the studies included were synthesized using fixed-effects meta-analysis	Yes

Appendix D. Extrapolation

D.1 Extrapolation of overall survival

D.1.1 Data input

Extrapolation of the OS was required as the data from the phase III trial SUNLIGHT did not include all observed clinical events within the trial period.

D.1.2 Model

Full parametrization.

A summary of the OS data from the SUNLIGHT study is provided in Figure 27. Lonsurf plus bevacizumab was associated with a statistically significant and clinically meaningful OS benefit compared to Lonsurf monotherapy with an estimated HR of 0.61 (95% CI: 0.49, 0.77; p<0.001). The median OS was 10.8 months (95% CI: 9.4, 11.8) for the Lonsurf plus bevacizumab arm versus 7.5 months (95% CI: 6.3, 8.6) for the Lonsurf monotherapy group. Although the KM curves are fairly mature, extrapolation of outcomes was required to inform cost-effectiveness estimates.

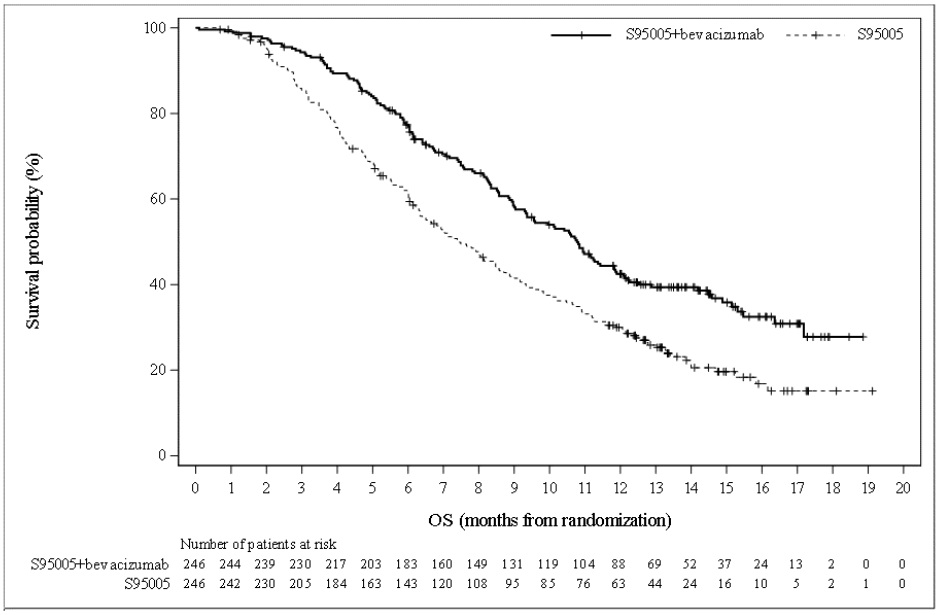

Figure 27 SUNLIGHT – Kaplan-Meier – OS

D.1.3 Proportional hazards

The Proportional hazards (PH) and AFT assumptions were visually assessed using a LCHP and a quantile-quantile (Q-Q) plot. The LCHP and Q-Q plot is presented in Figure 28 and Figure 29. The LCHP illustrates an almost linear line for both treatments arms, whereto

the lines are approximately parallel to each other indicating that the PH assumption is valid. Furthermore, the Q-Q plot presents itself as a diagonal straight line with the points being close to the line strengthen the assumption of PHs. Lastly the statistical test: Schoenfeld's non-proportionality test returned a p-value of [redacted] (Figure 31), thereby slightly indicating that the hazard rate may change over time, wherefore the null hypothesis cannot be rejected with 95% confidence but is still rejected with a 90% level of confidence.

Figure 28 Log-cumulative hazard plot – SUNLIGHT – OS

Figure 29 Q-Q plot – SUNLIGHT – OS

Figure 30 Cloglog plot – SUNLIGHT – OS

Figure 31 Schoenfeld's residual plot plot – SUNLIGHT – OS

Despite the lack of evidence to contradict the PH and AFT assumptions, independent models were fitted to the data given the availability of patient-level data for each treatment arm and data maturity. However, based on the results of the plots and any evidence to indicate a fundamental difference in the shape or behavior of the underlying hazards, it was concluded that the same distribution should be selected for both treatment arms to inform OS projections.

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

Based on the AIC and BIC scores, [redacted] provided the best fit for FTD/TPI + bevacizumab, however the majority of the parametric models provided a reasonably similar fit to the data and were therefore also visually compared in order to select the best match for the base-case extrapolation. In Table 70 an overview of the full parametrization is illustrated; it is clear that the majority of models, provided similar fit and so all were visually compared to select the base-case extrapolation.

Table 70 Statistical goodness-of-fit scores – OS

	FTD/TPI + bevacizumab			BSC		
Model	**AIC**	**BIC**	**Ranking**	**AIC**	**BIC**	**Ranking**
Exponential	[redacted]	[redacted]	[redacted]	N/A		
Generalized gamma	[redacted]	[redacted]	[redacted]			
Gompertz	[redacted]	[redacted]	[redacted]			
Log-logistic	[redacted]	[redacted]	[redacted]			
Log-normal	[redacted]	[redacted]	[redacted]			
Weibull	[redacted]	[redacted]	[redacted]			

Best supportive care comparator

In Denmark, it was deemed that BSC was the optimal comparison to FTD/TPI + Bevacizumab, but due to no comparison of BSC in the SUNLIGHT trial, a network-meta-analysis was derived to compare the HRs. For the base-case [redacted] was used and is visualized in Figure 32.

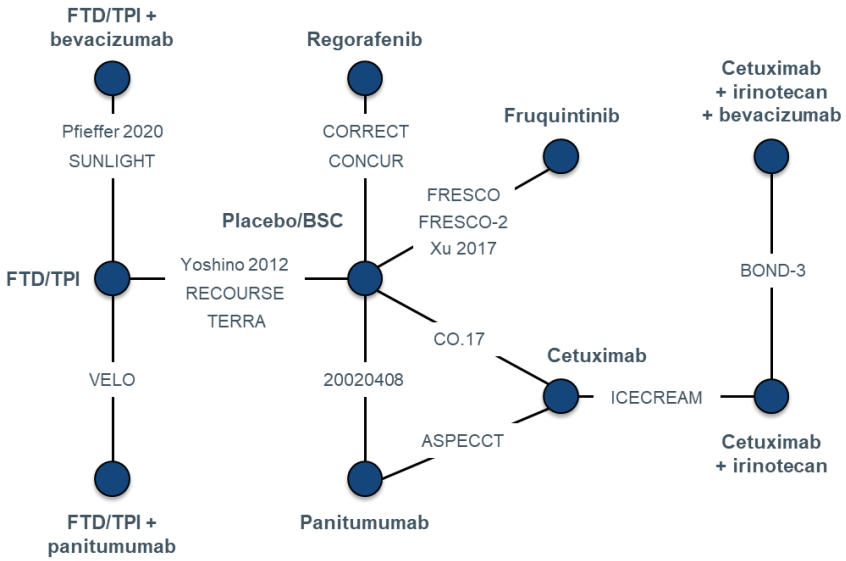

Figure 32 NMA scenario – 2L+ population

The NMAs were conducted as both random and fixed effects models. Random effects models are in general more appropriate to use, due to the underlying assumption of between study heterogeneity that fixed effects models do not include. For the base case, the random effects models are used with 2L+ network, as this is a more conservative approach than using the fixed effects results. However, all fixed effects are tested in scenario analyses. All HRs based on the NMA are presented in Table 71.

Table 71 HR based on the NMA

Comparator	HR (95% CrI)	Network used
Panitumumab	0.46 (0.28 – 0.72)	2L+
Cetuximab + irinotecan	0.44 (0.20 – 0.98)	2L+
BSC	XXX	**2L+**
Regorafenib	0.60 (0.39 – 0.94)	2L+
Cetuximab	0.47 (0.29 – 0.73)	2L+

A summary of the base case OS efficacy for all treatments is presented in Figure 33.

Figure 33 OS data for all treatments included in the NMA

D.1.5 Evaluation of visual fit

Except for the [redacted] the other models appear to visually fit the observed data reasonably well. Based on AIC, BIC and lastly the visual fit [redacted] was chosen to be the base-case, wherefore reimaging distributions will be explored in scenario analyses (see section 10.2). The parametric curve fits for OS is found in Figure 34.

Figure 34 Parametric curve fits – Lonsurf plus bevacizumab – OS

D.1.6 Evaluation of hazard functions

Hazards plots for Lonsurf plus bevacizumab and Lonsurf as monotherapy are provided. OS in

Figure 35 and

Figure 36. As the plots in general [redacted] was thought to be reasonable [redacted] do not provide the most plausible options as they [redacted] In combination with visual survivals plots and AIC and BIC statistics [redacted] deemed as the best fitting for OS data and [redacted] for PFS data.

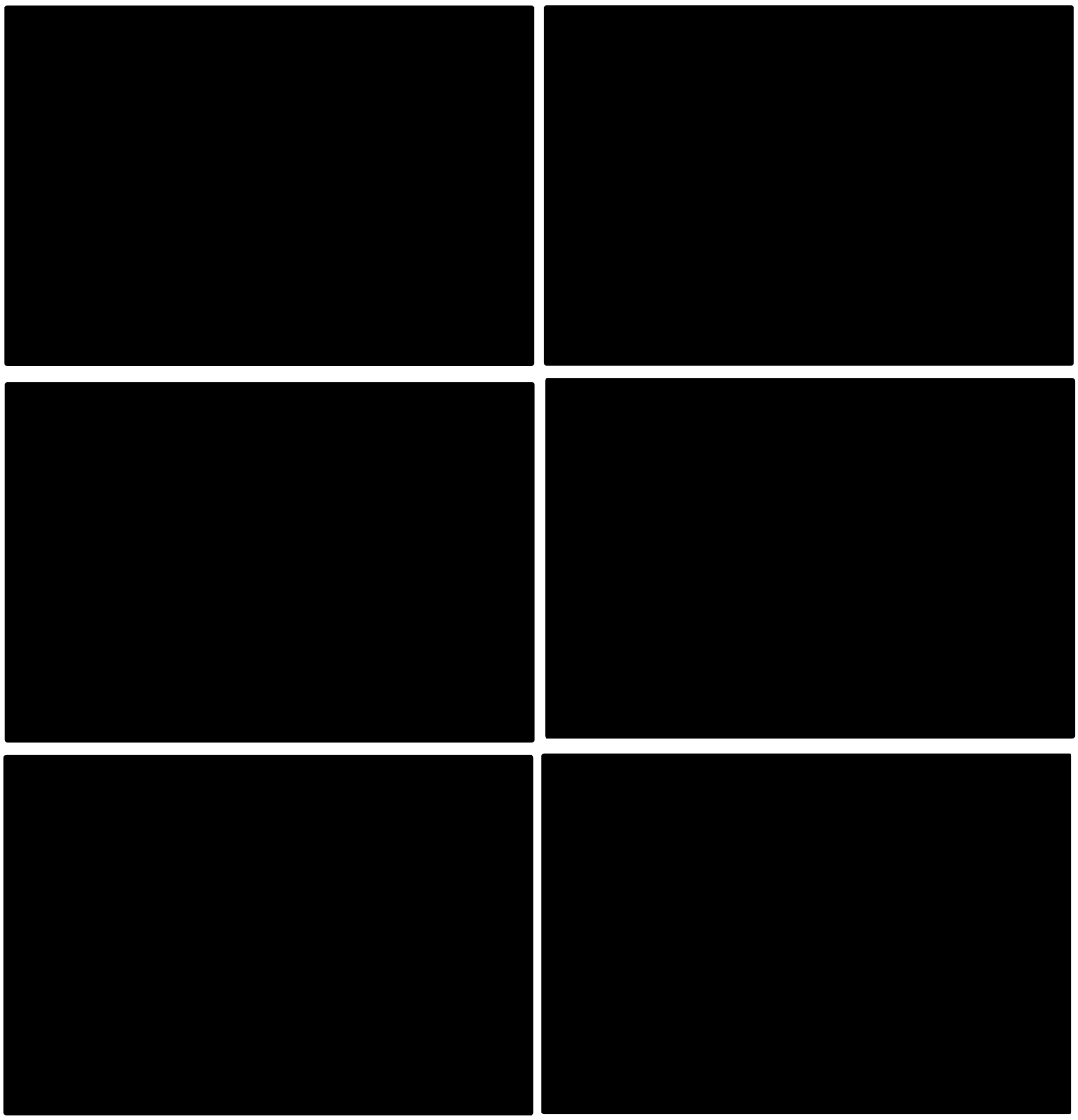

Figure 35 Lonsurf plus bevacizumab - OS graphs

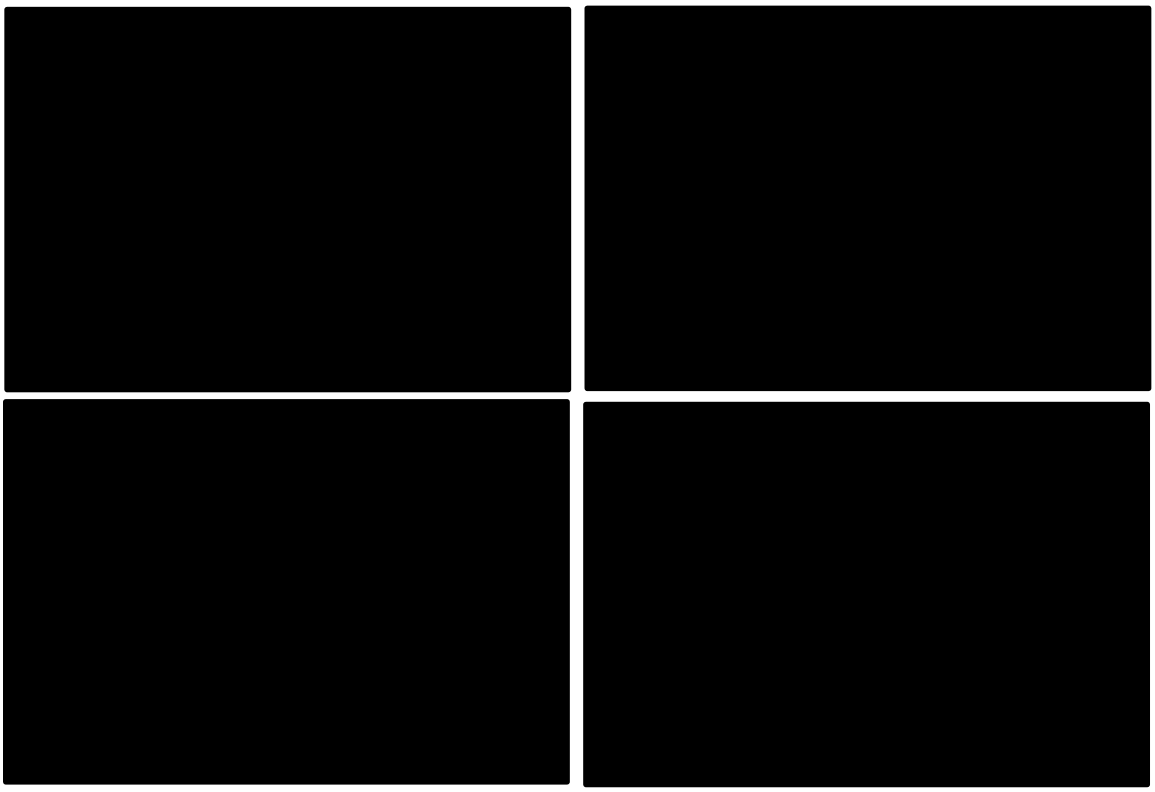

Figure 36 Lonsurf monotherapy – OS graphs

D.1.7 Validation and discussion of extrapolated curves

Lonsurf plus bevacizumab

PFS, OS and ToT KM data from the SUNLIGHT study were compared to PFS, OS and ToT outputs from the model for the intervention arm. The majority of the modelled outcomes appear to be consistent with the observed data for OS and PFS with the biggest

discrepancies being towards the end of the observed data where numbers at risk are small and are an artifact of censoring. Nevertheless, the discrepancy between KM and modelled % survival at 6 and 12 months remains small and likely due to the fit of the parametric models. See Table 72 and Figure 37.

Table 72 Summary of the model results compared to clinical data

Time	PFS		OS		ToT- Lonsurf		ToT - Bevacizumab	
	KM	Model	KM	Model	KM	Model	KM	Model
Lonsurf plus Bevacizumab								
Median (months)	[redacted]							
6 months %	[redacted]							
12 months %	[redacted]							
18 months %	[redacted]							

Key: KM, Kaplan-Meier; OS, Overall surival; PFS, Progression-free-survival; ToT, Time-on-treatment.

Figure 37 KM data vs. model data for PFS, OS and ToT

Best supportive care

Validation of the comparator arm(s) was conducted using published clinical studies available in the mCRC setting for each treatment which was considered feasible to include within the NMA.

As the DMC deemed BSC to be the appropriate comparator for Lonsurf plus bevacizumab as a potential third-line treatment, this analysis does not include additional comparator arms. The following sources were used to externally validate the modelled BSC outcomes:

- RECOURSE is a phase III randomized controlled trial compared FTD/TPI monotherapy with BSC versus placebo with BSC for patietns with adenocarcinoma of the colon or rectum who had received two or more previous treatments.
- TERRA is a phase III randomized controlled trial of Lonsurf montheraphy in Asian patients with previously treated mCRC versus placebo.
- Yoshino et al 2012 is a phase II placebo-controlled trial of Japan patients who had confirmed mCRC and a treatment history of two or more regimens.
- Trial 20020408 is a phase III open-label trial comparing panitumumab with BSC with BSC alone in previously treated mCRC patients.
- CO. 17 ® is a study comparing cetuximab to BSC in patients with advanced CRC expressing EGFR previously treated with fluoropyrimidine, oxaliplatin and irinotecan with no response.
- CONCUR is a placebo controlled randomized control Phase III trial of regorafenib with BSC versus placebo and BSC in Asian patients with previously treated mCRC.
- CORRECT is a Phase III randomized control trial of regorafenib versus placebo for previously treated mCRC patients.

For OS, the modelled BSC arm look more in line with the outcomes in TERRA, CONCUR and Yoshino than the other sources (Figure 38). However, all sources look consistent with the BSC projections of survival, with some slight under and over estimation from the naïve comparisons due to differences in study populations.

Figure 38 External validation – BSC – OS

D.1.8 Adjustment of background mortality

The background mortality rates were derived from Statistics Denmark to reflect the general mortality within the Danish population and to ensure that the survival models do not exceed those of the general population.

D.1.9 Adjustment for treatment switching/cross-over (N/A)

Not applicable since there was no treatment cross-over in the SUNLIGHT Study.

D.1.10 Waning effect (N/A)

Not applicable since there is no biological or clinical rationale for assuming a waning effect.

D.1.11 Cure-point

No cure-point is assumed since there is no medical rational to assume that 3rd line metastatic colorectal patients with current treatments can archive a cure.

D.2 Extrapolation of PFS

D.2.1 Data input

Extrapolation of the PFS was required as the data from the phase III trial SUNLIGHT did not include all observed clinical events within the trial period.

D.2.2 Model

Full parametrization

A summary of the PFS data from the SUNLIGHT study is provided in Figure 39. Lonsurf plus bevacizumab was associated with a statistically significant improvement in PFS compared to Lonsurf monotherapy with an estimated HR of 0.44 (95% CI: 0.36, 0.54; p<0.001). The mPFS was 5.6 months (95% CI: 4.5, 5.8) for the Lonsurf plus bevacizumab arm versus 2.4 months (95% CI: 2.1, 3.2) for the Lonsurf monotherapy group. Although the KM curves are quite mature (89.8% of patients had a PFS event), extrapolation of outcomes was required to extend the outcomes into the future to inform cost-effectiveness estimates.

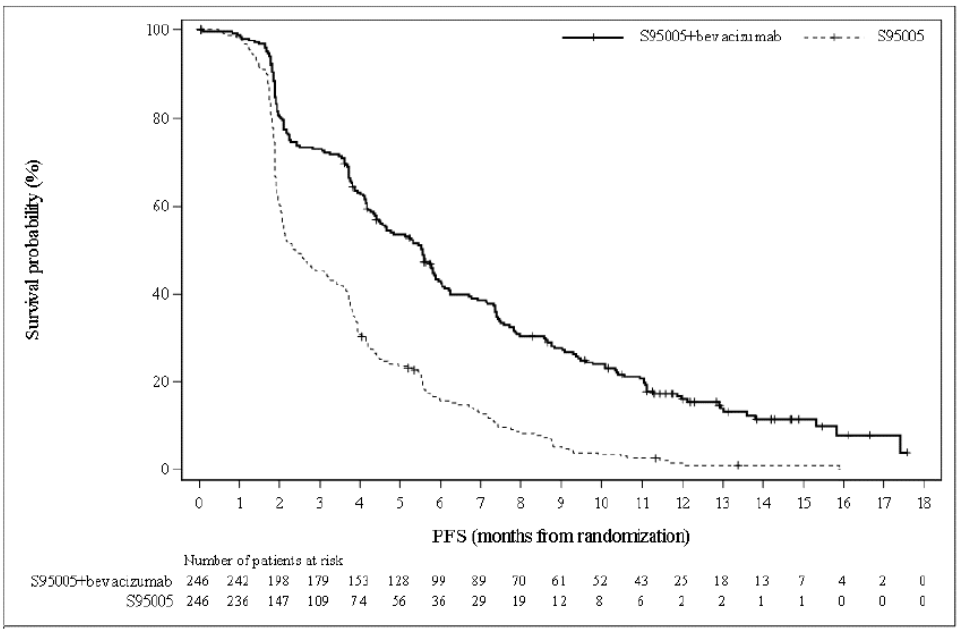

Figure 39 SUNLIGHT – Kaplan-Meier – PFS

D.2.3 Proportional hazards

The assumptions of PH and AFT were assessed visually through LCHP and Q-Q plots to determine if they were deemed to be sufficient. Figure 40 presents the LCHP and Q-Q plots of PFS from the SUNLIGHT study. These indicate that the PH and AFT assumptions [redacted]. The Schoenfeld residual test though had a p-value of [redacted] However, as with OS, [redacted] were fitted to the data due to the availability of patient-level data and maturity of data.

Figure 40 Log-cumulative hazard and Q-Q plot – SUNLIGHT – PFS

D.2.4 Evaluation of statistical fit (AIC and BIC)

The statistical goodness-of-fit of all fitted PSMs is provided in Table 73. Based on the AIC and BIC scores, [redacted] provided the best fit for the FTD/TPI + bevacizumab, however the majority of models provided a reasonably similar fit to the data and so were visually compared in order to select the base-case extrapolation (Figure 41).

Table 73 Statistical goodness-of-fit scores – PFS

	Lonsurf plus bevacizumab			BSC		
Model	AIC	BIC	Ranking	AIC	BIC	Ranking
Exponential	[redacted]	[redacted]	[redacted]	N/A		
Generalized gamma	[redacted]	[redacted]	[redacted]			
Gompertz	[redacted]	[redacted]	[redacted]			
Log-logistic	[redacted]	[redacted]	[redacted]			
Log-normal	[redacted]	[redacted]	[redacted]			
Weibull	[redacted]	[redacted]	[redacted]			

Figure 41 Parametric curve fits – FTD/TPI + bevacizumab – PFS

D.2.5 Evaluation of visual fit

All the extrapolated curves appear to fit the data reasonably well, only minor under- and over- estimating throughout due to 'steps' in the observed data that are likely caused by the protocol driven assessments of progression in the SUNLIGHT trial. Given that [redacted] was the best statistically fitting curve for Lonsurf plus bevacizumab and it also visually fits the data well, this has been chosen for the base case.

D.2.6 Evaluation of hazard functions

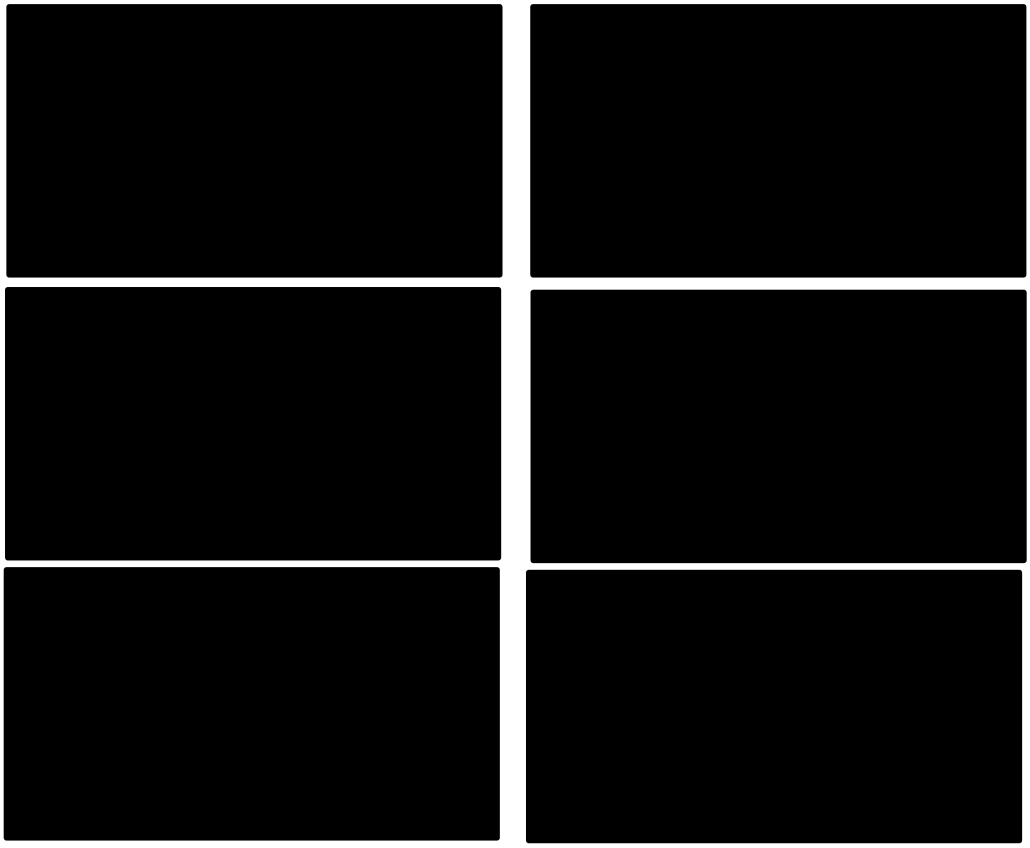

Figure 42 Lonsurf plus bevacizumab - PFS graphs

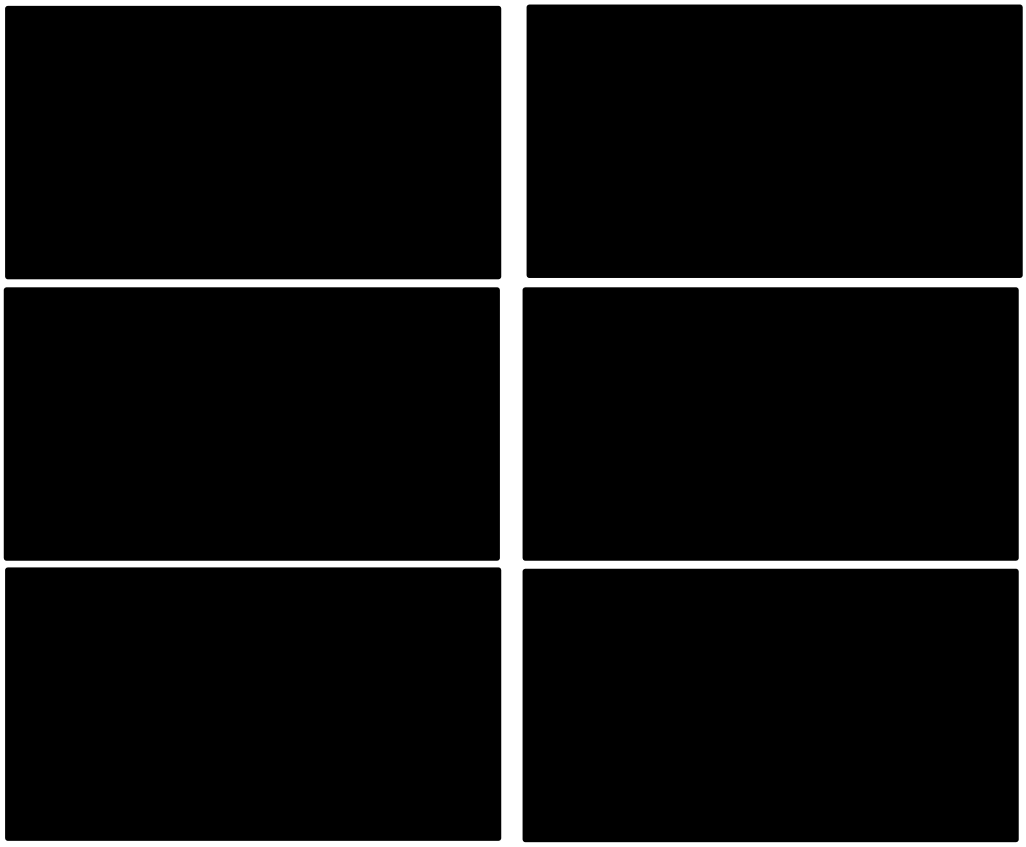

Figure 43 Lonsurf monotherapy – PFS graphs

D.2.7 Validation and discussion of extrapolated curves

Lonsurf plus Bevacizumab

PFS, OS and ToT KM data from the SUNLIGHT study were compared to PFS, OS and ToT outputs from the model for each treatment. The majority of the modelled outcomes appear [redacted] Nevertheless, the discrepancy between KM and modelled % survival at 6 and 12 months [redacted] See Table 74 below.

Table 74 Summary of the model results compared to clinical data

Time	PFS		OS		ToT- Lonsurf		ToT - Bevacizumab	
	KM	Model	KM	Model	KM	Model	KM	Model
Lonsurf plus Bevacizumab								
Median (months)	[redacted]							
6 months %	[redacted]							
12 months %	[redacted]							
18 months %	[redacted]							

Key: KM, Kaplan-Meier; OS, Overall surival; PFS, Progression-free-survival; ToT, Time-on-treatment.

In the previous section of the report (Section D.1.7) a presentation of the NMA plot and a list of studies was presented. For PFS the modelled BSC outcomes look consistent with the outcomes from the CO. 17 study, but is likely overestimated compared to other sources between 3 to 6 months (Figure 44). However, as with OS, [redacted]

Figure 44 External validation – BSC – PFS

D.2.8 Adjustment of background mortality

The background mortality rates were derived from Statistics Denmark to reflect the general mortality within the Danish population and to ensure that the survival models do not exceed those of the general population.

D.2.9 Adjustment for treatment switching/cross-over

N/A since there was no treatment cross-over in the SUNLIGHT trial.

D.2.10 Waning effect

N/A since there is no biological or clinical rational for assuming a waning effect

D.2.11 Cure-point

No cure-point is assumed since there is no medical rational to assume that 3rd line mCRC patients with current treatments can achieve a cure.

D.3 Extrapolation of ToT

Table 75: Statistical goodness-of-fit scores – ToT.

Parameterisation	Lonsurf (Lorsurf plus bevacizumab)		Bevacizumab (Lonsurf plus bevacizumab)		Lonsurf Monotherapy	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AIC, Alkaike information criterion; BIC, Bayesian information criterion; ToT, Time on treatment.

Appendix E. Serious adverse events (N/A)

Appendix F. Health-related quality of life (N/A)

Appendix G. Probabilistic sensitivity analyses

Table 76 Overview of parameters in the PSA

Input parameter	Point estimate	Lower Bound	Upper Bound	Probability distribution
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	Normal
Proportion female	[redacted]	[redacted]	[redacted]	Beta
Trial-based BSA	[redacted]	[redacted]	[redacted]	Normal
Trial-based Weight	[redacted]	[redacted]	[redacted]	Normal
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RDI - FTD/TPI (FTD/TPI + bevacizumab)	[redacted]	[redacted]	[redacted]	Normal
RDI - Bevacizumab (FTD/TPI + bevacizumab)	[redacted]	[redacted]	[redacted]	Normal
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use - progression free - IV - CT scan	[redacted]	[redacted]	[redacted]	Normal

Resource use % - progression free - IV - CT scan	[redacted]	[redacted]	[redacted]	Beta
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]				
[redacted]				
[redacted]				
HR - OS - BSC	[redacted]	[redacted]	[redacted]	Drawn from posterior
HR - PFS - BSC	[redacted]	[redacted]	[redacted]	Drawn from posterior
Utility - SUNLIGHT - pooled - Intercept				Multinorm inv
Utility - SUNLIGHT - pooled - Progression-free				Multinorm inv
Utility - SUNLIGHT - treatment independent - Intercept				Multinorm inv
Utility - SUNLIGHT - treatment independent - FTD/TPI + bev				Multinorm inv
Utility - SUNLIGHT - treatment independent - Progression-free				Multinorm inv
Gen pop utility - coefficient - Male				Multinorm inv
Gen pop utility - coefficient - Age				Multinorm inv
Gen pop utility - coefficient - Age^2				Multinorm inv
Gen pop utility - coefficient - Constant				Multinorm inv
OS curve parameters				Multinorm inv
PFS curve parameters				Multinorm inv
[redacted]				[redacted]

Appendix H. Literature searches for the clinical assessment

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

A literature search was conducted for the indirect comparison of efficacy and safety for Lonsurf plus bevacizumab and BSC. The objective of the SLR was to identify and summarize clinical trial evidence regarding the efficacy and safety of treatments for patients with refractory mCRC to provide information for the NMA. Sources and databases for the literature search are stated in Table 77 - Table 79 below.

Table 77 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Ovid	From 2010 to the present	12.10.2023
Medline	Ovid	From 2010 to the present	12.10.2023
CENTRAL	Ovid	From 2010 to the present	12.10.2023

Table 78 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
Clinical trial registries	The U.S. National Institutes of Health Clinical Trial Registry and European Clinical Trials Register	Manually searched to identify relevant completed or ongoing clinical trials with results available that were yet been published in full-text or conference proceeding formats	NR

Table 79 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
American Society of Clinical Oncology	NR	Handsearching conference websites or published proceedings	NR	2021-2023

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
(ASCO) Annual Meeting				
ASCO Gastrointestinal Cancers Symposium	NR	Handsearching conference websites or published proceedings	NR	2021-2023
European Society for Medical Oncology (ESMO) Congress	NR	Handsearching conference websites or published proceedings	NR	2021-2022
ESMO World Congress on Gastrointestinal Cancer	NR	Handsearching conference websites or published proceedings	NR	2021-2023

H.1.1 Search strategies

H.1.1.1 Study identification

Database searches

Relevant trials were identified by searching the following databases through the Ovid platform on October 12, 2023: Embase, MEDLINE, and CENTRAL. Publications were identified by the search strategies presented in Appendix A, which included a combination of subject headings and free-text terms for the population, interventions, study design, and/or outcomes of interest. MEDLINE and Embase search strategies employ SIGN's search filter for RCTs (https://www.sign.ac.uk/what-we-do/methodology/search-filters/), which was modified to include single-arm trials. As clinical trials of third-line treatments for mCRC patients did not appear until after 2010, all search results were limited to publications from 2010 to the present.

Grey literature searches

Relevant non-peer-reviewed materials reporting study results (i.e., grey literature) were identified by searching conference proceedings and clinical trial registries.

Conference proceedings. Proceedings from the most recent two iterations of the following conferences were searched using the Northern Light Life Science Conference Abstracts database through the Ovid platform or by handsearching conference websites or published proceedings:

- American Society of Clinical Oncology (ASCO) Annual Meeting (2021-2023)
- ASCO Gastrointestinal Cancers Symposium (2021-2023)
- European Society for Medical Oncology (ESMO) Congress (2021-2022)
- ESMO World Congress on Gastrointestinal Cancer (2021-2023)

Clinical trial registries. The U.S. National Institutes of Health Clinical Trial Registry and European Clinical Trials Register were manually searched to identify relevant completed or ongoing clinical trials with results available that were yet been published in full-text or conference proceeding formats.

See search strategies in Table 80 - Table 83 below.

Table 80 Embase search strategy.

No.	Criteria	Query	Results
#1	Population	exp colorectal cancer/ OR (colorectal cancer or colorectal neoplasm* OR colorectal carcinoma).mp.	428936
#2	Population	(advance$ OR metasta$ OR recurr$ OR unresect$ OR non-resect$ OR disseminated OR stage 3 OR stage III* OR stage 4 OR stage IV* OR spread$ OR migration$ OR progress$ OR invasive OR aggressive OR "not operable" OR untreatable OR "not treatable" OR secondary OR incurable OR "not curable").mp.	7407708
#3	Population	(prior or pretreat$ OR previous$ OR refractory OR recurrent OR fail$ OR subsequent OR salvage OR second line OR third line OR fourth line OR relapse OR compassionate).mp.	7760095
#4	Population	#1 AND #2 AND #3	69202
#5	Intervention	exp aflibercept/ OR (aflibercept OR ziv-aflibercept OR Eylea OR Zaltrap OR L01XX44 OR S01LA05).mp.	9509
#6	Intervention	exp palliative therapy/ OR (best supportive care OR supportive care OR palliative care OR palliative therapy).mp.	189660
#7	Intervention	exp bevacizumab/ OR (bevacizumab OR Avastin OR Alymsys OR Mvasi OR Zirabev OR rhuMab-VEGF OR ABP 215 OR BP102 OR HD204 OR MYL-1402O OR SCT501 OR SIBP04).mp.	77205
#8	Intervention	exp capecitabine/ OR (capecitabine OR CAPE OR Xeloda OR CAPEOX).mp.	57775
#9	Intervention	exp cetuximab/ OR (cetuximab OR Erbitux or C225).mp.	35618
#10	Intervention	exp encorafenib/ OR (encorafenib OR LGX818 OR braftovi).mp.	1639

#11	Intervention	exp fluorouracil/ OR (fluorouracil OR 5-fluorouracil OR 5-FU OR 5-fluracil OR fluouracil OR fluracil OR FOLFOX OR FOLFIRI OR mFOLFOX OR mFOLFIRI OR mFOLFOX-6 OR FOLFOX-6).mp.	171150
#12	Intervention	exp fruquintinib/ OR (fruquintinib OR HMPL-013 OR elunate).mp.	255
#13	Intervention	exp irinotecan/ OR (irinotecan OR camptothecin-11 OR Camptosar OR CPT-11 OR U-101440E).mp.	48841
#14	Intervention	exp oxaliplatin/ OR (oxaliplatin OR Eloxatin OR 1-OHP OR L-OHP OR JM-83 OR RP-54780 OR SR-96669).mp.	56885
#15	Intervention	exp panitumumab/ OR (panitumumab OR Vectibix OR ABX-EGF).mp.	10238
#16	Intervention	exp ramucirumab/ OR (ramucirumab OR Cyramza OR L01FG02).mp.	4965
#17	Intervention	exp regorafenib/ OR (regorafenib OR Stivarga OR BAY 73-4506 OR BAY73-4506).mp.	7245
#18	Intervention	exp tipiracil plus trifluridine/ OR ((tipiracil and trifluridine) OR FTD/TPI OR TAS102 OR TAS 102 OR Lonsurf).mp.	1711
#19	Intervention	OR/#5-#18	504169
#20	Study design	Clinical Trial/	1072019
#21	Study design	Randomized Controlled Trial/	787133
#22	Study design	controlled clinical trial/	471146
#23	Study design	multicenter study/	374874
#24	Study design	Phase 3 clinical trial/	69690

#25	Study design	Phase 4 clinical trial/	5456
#26	Study design	exp RANDOMIZATION/	98960
#27	Study design	Single Blind Procedure/	52043
#28	Study design	Double Blind Procedure/	211398
#29	Study design	Crossover Procedure/	75569
#30	Study design	PLACEBO/	403427
#31	Study design	randomi?ed controlled trial$.tw.	327805
#32	Study design	rct.tw.	54476
#33	Study design	(random$ adj2 allocat$).tw.	55196
#34	Study design	single blind$.tw.	31882
#35	Study design	double blind$.tw.	245540
#36	Study design	((treble OR triple) adj blind$).tw.	1946
#37	Study design	placebo$.tw.	368669
#38	Study design	Prospective Study/	884937

#39	Study design	single arm.tw.	28260
#40	Study design	(Phase II OR Phase 2).tw.	163389
#41	Study design	Phase 2 clinical trial/	107189
#42	Study design	OR/#20-#41	3046659
#43	Study design	Case Study/	97046
#44	Study design	case report.tw.	544316
#45	Study design	abstract report/ OR letter/	1302889
#46	Study design	Conference proceeding.pt.	0
#47	Study design	Conference abstract.pt.	4916104
#48	Study design	Editorial.pt.	782219
#49	Study design	Letter.pt.	1292002
#50	Study design	Note.pt.	960419
#51	Study design	OR/#43-#50	8505202
#52	Study design	#42 NOT #51	2170435

#53	Combination	#4 AND #19 AND #52	5697
#54	Time	limit #53 to yr=2010 - current	3039
#55	Language	limit #54 to english	2991

Table 81 MEDLINE search strategy.

No.	Criteria	Query	Results
#1	Population	exp colorectal cancer/ OR (colorectal cancer OR colorectal neoplasm* OR colorectal carcinoma).mp.	281028
#2	Population	(advance$ OR metasta$ OR recurr$ OR unresect$ OR non-resect$ OR disseminated OR stage 3 OR stage III* OR stage 4 OR stage IV* OR spread$ OR migration$ OR progress$ OR invasive OR aggressive OR "not operable" OR untreatable OR "not treatable" OR secondary OR incurable OR "not curable").mp.	5366184
#3	Population	(prior OR pretreat$ OR previous$ OR refractory OR recurrent OR fail$ OR subsequent OR salvage OR second line OR third line OR fourth line OR relapse OR compassionate).mp.	5327453
#4	Population	#1 AND #2 AND #3	32314
#5	Intervention	exp aflibercept/ OR (aflibercept OR ziv-aflibercept OR Eylea OR Zaltrap OR L01XX44 OR S01LA05).mp.	3460
#6	Intervention	exp palliative care/ OR (best supportive care OR supportive care OR palliative care OR palliative therapy).mp.	100090
#7	Intervention	exp bevacizumab/ OR (bevacizumab OR Avastin OR Alymsys OR Mvasi OR Zirabev OR rhuMab-VEGF OR ABP 215 OR BP102 OR HD204 OR MYL-1402O OR SCT501 OR SIBP04).mp.	23321
#8	Intervention	(exp capecitabine/ AND exp oxaliplatin/) OR (CAPEOX OR ((capecitabine OR CAPE OR Xeloda) AND (oxaliplatin OR Elox-atin OR 1-OHP OR L-OHP OR JM-83 OR RP-54780 OR SR-96669))).mp.	2720

#9	Intervention	exp cetuximab/ OR (cetuximab OR Erbitux OR C225).mp.	9149
#10	Intervention	exp encorafenib/ OR (encorafenib OR LGX818 OR braftovi).mp.	331
#11	Intervention	exp fluorouracil/ OR (fluorouracil OR 5-fluorouracil OR 5-FU OR 5-fluracil OR fluouracil OR fluracil OR FOLFOX OR FOLFIRI OR mFOLFOX OR mFOLFIRI OR mFOLFOX-6 OR FOLFOX-6).mp.	69369
#12	Intervention	exp fruquintinib/ OR (fruquintinib OR HMPL-013 OR elunate).mp.	95
#13	Intervention	exp irinotecan/ OR (irinotecan OR camptothecin-11 OR Camptosar OR CPT-11 OR U-101440E).mp.	13481
#14	Intervention	exp oxaliplatin/ OR (oxaliplatin OR Eloxatin OR 1-OHP OR L-OHP OR JM-83 OR RP-54780 OR SR-96669).mp.	15912
#15	Intervention	exp panitumumab/ OR (panitumumab OR Vectibix OR ABX-EGF).mp.	2184
#16	Intervention	exp ramucirumab/ OR (ramucirumab OR Cyramza OR L01FG02).mp.	1284
#17	Intervention	(regorafenib OR Stivarga OR BAY 73-4506 OR BAY73-4506).mp.	1944
#18	Intervention	((tipiracil and trifluridine) OR FTD/TPI OR TAS102 OR TAS 102 OR Lonsurf).mp.	554
#19	Intervention	OR/#5-#18	213431
#20	Study design	Randomized Controlled Trials as Topic/	164396
#21	Study design	randomized controlled trial/	600834
#22	Study design	Random Allocation/	107036
#23	Study design	Double Blind Method/	176265
#24	Study design	Single Blind Method/	32965
#25	Study design	clinical trial/	538835
#26	Study design	clinical trial, phase i.pt.	25261

#27	Study design	clinical trial, phase ii.pt.	40301
#28	Study design	clinical trial, phase iii.pt.	22055
#29	Study design	clinical trial, phase iv.pt.	2441
#30	Study design	controlled clinical trial.pt.	95416
#31	Study design	randomized controlled trial.pt.	600834
#32	Study design	multicenter study.pt.	338571
#33	Study design	clinical trial.pt.	538835
#34	Study design	exp Clinical Trials as topic/	385057
#35	Study design	OR/#20#-34	1578797
#36	Study design	(clinical adj trial$).tw.	488724
#37	Study design	((singl$ OR doubl$ OR treb$ OR tripl$) adj (blind$3 OR mask$3)).tw.	199863
#38	Study design	PLACEBOS/	35932
#39	Study design	placebo$.tw.	249896
#40	Study design	randomly allocated.tw.	37042
#41	Study design	(allocated adj2 random$).tw.	40859
#42	Study design	single arm.tw.	13582
#43	Study design	OR/#36-#42	806142
#44	Study design	#35 OR #43	1939382
#45	Study design	case report.tw.	405841
#46	Study design	letter/	1231643
#47	Study design	historical article/	369446

#48	Study design	OR/#45-#47	1987574
#49	Study design	#44 not #48	1896367
#50	Combination	#4 AND #19 AND #49	3603
#51	Time	limit #50 to yr=2010 - current	1932
#52	Language	limit #51 to english	1888

Table 82 CENTRAL search strategy

No.	Criteria	Query	Results
#1	Population	exp colorectal cancer/ OR (colorectal cancer OR colorectal neoplasm* OR colorectal carcinoma).mp.	20859
#2	Population	(advance$ OR metasta$ OR recurr$ OR unresect$ OR non-resect$ OR disseminated OR stage 3 OR stage III* OR stage 4 OR stage IV* OR spread$ OR migration$ OR progress$ OR invasive OR aggressive OR "not operable" OR untreatable OR "not treatable" OR secondary OR incurable OR "not curable").mp.	607594
#3	Population	(prior OR pretreat$ OR previous$ OR refractory OR recurrent OR fail$ OR subsequent OR salvage OR second line OR third line OR fourth line OR relapse OR compassionate).mp.	482054
#4	Population	#1 AND #2 AND #3	5740
#5	Intervention	exp aflibercept/ OR (aflibercept OR ziv-aflibercept OR Eylea OR Zaltrap OR L01XX44 OR S01LA05).mp.	1133
#6	Intervention	exp palliative care/ OR (best supportive care OR supportive care OR palliative care OR palliative therapy).mp.	10272
#7	Intervention	exp bevacizumab/ OR (bevacizumab OR Avastin OR Alymsys OR Mvasi OR Zirabev OR rhuMab-VEGF OR ABP 215 OR BP102 OR HD204 OR MYL-1402O OR SCT501 OR SIBP04).mp.	7515
#8	Intervention	(exp capecitabine/ AND exp oxaliplatin/) OR (CAPEOX OR ((capecitabine OR CAPE OR Xeloda) AND (oxaliplatin OR Eloxatin OR 1-OHP OR L-OHP OR JM-83 OR RP-54780 OR SR-96669))).mp.	1622

#9	Intervention	exp cetuximab/ OR (cetuximab OR Erbitux OR C225).mp.	2610
#10	Intervention	exp encorafenib/ OR (encorafenib OR LGX818 OR braftovi).mp.	144
#11	Intervention	exp fluorouracil/ OR (fluorouracil OR 5-fluorouracil OR 5-FU OR 5-fluracil OR fluouracil OR fluracil OR FOLFOX OR FOLFIRI OR mFOLFOX OR mFOLFIRI OR mFOLFOX-6 OR FOLFOX-6).mp.	15419
#12	Intervention	exp fruquintinib/ OR (fruquintinib OR HMPL-013 OR elunate).mp.	57
#13	Intervention	exp irinotecan/ OR (irinotecan OR camptothecin-11 OR Camptosar OR CPT-11 OR U-101440E).mp.	3925
#14	Intervention	exp oxaliplatin/ OR (oxaliplatin OR Eloxatin OR 1-OHP OR L-OHP OR JM-83 OR RP-54780 OR SR-96669).mp.	5544
#15	Intervention	exp panitumumab/ OR (panitumumab OR Vectibix OR ABX-EGF).mp.	793
#16	Intervention	exp ramucirumab/ OR (ramucirumab OR Cyramza OR L01FG02).mp.	654
#17	Intervention	(regorafenib OR Stivarga OR BAY 73-4506 OR BAY73-4506).mp.	650
#18	Intervention	((tipiracil and trifluridine) OR FTD/TPI OR TAS102 OR TAS 102 OR Lonsurf).mp.	337
#19	Intervention	OR/#5-#18	37523
#20	Combination	#4 AND #19	3543
#21	Time	limit #20 to yr=2010 - current	2612
#22	Language	limit #21 to english	2601

Table 83 Northern Light Life Sciences Conference Abstracts search strategy.

No.	Criteria	Query	Results
American Society of Clinical Oncology (ASCO) Annual Meeting, 2021-2023			

#1	Population	exp colorectal cancer/ OR (colorectal cancer OR colorectal neoplasm* OR colorectal carcinoma).mp.	64662
#2	Population	(advance$ OR metasta$ OR recurr$ OR unresect$ OR non-resect$ OR disseminated OR stage 3 OR stage III* OR stage 4 OR stage IV* OR spread$ OR migration$ OR progress$ OR invasive OR aggressive OR "not operable" OR untreatable OR "not treatable" OR secondary OR incurable OR "not curable").mp.	566498
#3	Population	(prior OR pretreat$ OR previous$ OR refractory OR recurrent OR fail$ OR subsequent OR salvage OR second line OR third line OR fourth line OR relapse OR compassionate).mp.	539266
#4	Population	#1 AND #2 AND #3	4381
#5	Intervention	exp aflibercept/ OR (aflibercept OR ziv-aflibercept OR Eylea OR Zaltrap OR L01XX44 OR S01LA05).mp.	1604
#6	Intervention	exp palliative care/ OR (best supportive care OR supportive care OR palliative care OR palliative therapy).mp.	16511
#7	Intervention	exp bevacizumab/ OR (bevacizumab OR Avastin OR Alymsys OR Mvasi OR Zirabev OR rhuMab-VEGF OR ABP 215 OR BP102 OR HD204 OR MYL-1402O OR SCT501 OR SIBP04).mp.	14261
#8	Intervention	(exp capecitabine/ AND exp oxaliplatin/) OR (CAPEOX OR ((capecitabine OR CAPE OR Xeloda) AND (oxaliplatin OR Elox-atin OR 1-OHP OR L-OHP OR JM-83 OR RP-54780 OR SR-96669))).mp.	1717
#9	Intervention	exp cetuximab/ OR (cetuximab OR Erbitux OR C225).mp.	5780
#10	Intervention	exp encorafenib/ OR (encorafenib OR LGX818 OR braftovi).mp.	139
#11	Intervention	exp fluorouracil/ OR (fluorouracil OR 5-fluorouracil OR 5-FU OR 5-fluracil OR fluouracil OR fluracil OR FOLFOX OR FOLFIRI OR mFOLFOX OR mFOLFIRI OR mFOLFOX-6 OR FOLFOX-6).mp.	14544
#12	Intervention	exp fruquintinib/ OR (fruquintinib OR HMPL-013 OR elu-nate).mp.	57
#13	Intervention	exp irinotecan/ OR (irinotecan OR camptothecin-11 OR Camp-tosar OR CPT-11 OR U-101440E).mp.	5779

#14	Intervention	exp oxaliplatin/ OR (oxaliplatin OR Eloxatin OR 1-OHP OR L-OHP OR JM-83 OR RP-54780 OR SR-96669).mp.	7752
#15	Intervention	exp panitumumab/ OR (panitumumab OR Vectibix OR ABX-EGF).mp.	1582
#16	Intervention	exp ramucirumab/ OR (ramucirumab OR Cyramza OR L01FG02).mp.	461
#17	Intervention	(regorafenib OR Stivarga OR BAY 73-4506 OR BAY73-4506).mp.	822
#18	Intervention	((tipiracil and trifluridine) OR FTD/TPI OR TAS102 OR TAS 102 OR Lonsurf).mp.	385
#19	Intervention	OR/#5-#18	55225
#20	Conference	American Society of Clinical Oncology.cf.	78034
#21	Combination	#4 AND #19 AND #20	447
#22	Time	limit #21 to yr = 2021	30
#23	Time	limit #21 to yr = 2022	27
#24	Time	OR/#22-#23	26
European Society for Medical Oncology (ESMO) Annual Meeting, 2021-2022			
#1	Population	exp colorectal cancer/ OR (colorectal cancer OR colorectal neoplasm* OR colorectal carcinoma).mp.	61460
#2	Population	(advance$ OR metasta$ OR recurr$ OR unresect$ OR non-resect$ OR disseminated OR stage 3 OR stage III* OR stage 4 OR stage IV* OR spread$ OR migration$ OR progress$ OR invasive OR aggressive OR "not operable" OR untreatable OR "not treatable" OR secondary OR incurable OR "not curable").mp.	538713
#3	Population	(prior OR pretreat$ OR previous$ OR refractory OR recurrent OR fail$ OR subsequent OR salvage OR second line OR third line OR fourth line OR relapse OR compassionate).mp.	515801
#4	Population	#1 AND #2 AND #3	4194

#5	Intervention	exp aflibercept/ OR (aflibercept OR ziv-aflibercept OR Eylea OR Zaltrap OR L01XX44 OR S01LA05).mp.	1457
#6	Intervention	exp palliative care/ OR (best supportive care OR supportive care OR palliative care OR palliative therapy).mp.	15593
#7	Intervention	exp bevacizumab/ OR (bevacizumab OR Avastin OR Alymsys OR Mvasi OR Zirabev OR rhuMab-VEGF OR ABP 215 OR BP102 OR HD204 OR MYL-1402O OR SCT501 OR SIBP04).mp.	13684
#8	Intervention	(exp capecitabine/ AND exp oxaliplatin/) OR (CAPEOX OR ((capecitabine OR CAPE OR Xeloda) AND (oxaliplatin OR Eloxatin OR 1-OHP OR L-OHP OR JM-83 OR RP-54780 OR SR-96669))).mp.	1671
#9	Intervention	exp cetuximab/ OR (cetuximab OR Erbitux OR C225).mp.	5641
#10	Intervention	exp encorafenib/ OR (encorafenib OR LGX818 OR braftovi).mp.	118
#11	Intervention	exp fluorouracil/ OR (fluorouracil OR 5-fluorouracil OR 5-FU OR 5-fluracil OR fluouracil OR fluracil OR FOLFOX OR FOLFIRI OR mFOLFOX OR mFOLFIRI OR mFOLFOX-6 or FOLFOX-6).mp.	14024
#12	Intervention	exp fruquintinib/ OR (fruquintinib OR HMPL-013 OR elunate).mp.	43
#13	Intervention	exp irinotecan/ OR (irinotecan OR camptothecin-11 OR Camptosar OR CPT-11 OR U-101440E).mp.	5584
#14	Intervention	exp oxaliplatin/ OR (oxaliplatin OR Eloxatin OR 1-OHP OR L-OHP OR JM-83 OR RP-54780 OR SR-96669).mp.	7440
#15	Intervention	exp panitumumab/ OR (panitumumab OR Vectibix OR ABX-EGF).mp.	1551
#16	Intervention	exp ramucirumab/ OR (ramucirumab OR Cyramza OR L01FG02).mp.	442
#17	Intervention	(regorafenib OR Stivarga OR BAY 73-4506 OR BAY73-4506).mp.	777
#18	Intervention	((tipiracil AND trifluridine) OR FTD/TPI OR TAS102 OR TAS 102 OR Lonsurf).mp.	352

#19	Intervention	OR/#5#-18	52732
#20	Conference	European Society for Medical Oncology.cf.	20811
#21	Combination	#4 AND #19 AND #20	270
#22	Time	limit #21 to yr = 2021	8
#23	Time	limit #21 to yr = 2022	11
#24	Time	or/#22-#23	0

H.1.2 Systematic selection of studies

The SLR was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and NICE guidance for systematic reviews. The target population was patients undergoing third-line treatment for mCRC, but it was anticipated most studies evaluating relevant comparators were conducted in a broader population; therefore, studies were included if they enrolled any proportion of third-line patients, and the plausibility of comparing studies with different proportions of third-line patients was evaluated in the feasibility assessment.

H.1.2.1 Study selection

Study selection occurred in two stages. First, titles and abstracts were screened against the PICOS criteria. Second, all studies identified for potential inclusion during title and abstract screening underwent full-text screening against the PICOS criteria. During both screening stages, each publication was assessed by two independent reviewers. Any disagreements were resolved by discussion between reviewers, including a third more senior reviewer if needed.

H.1.2.2 Data extraction

Data from publications included during the full-text screening stage were extracted into a standardized table template developed in Microsoft Excel specifically for this study. For RCTs, data were extracted by two independent reviewers. For non-randomized and single-arm trials, data were extracted by a single reviewer and independently validated by a second reviewer. Any discrepancies were resolved by discussion between reviewers, including a third more senior reviewer if needed.

Study characteristics. The following study characteristics were extracted: trial name, registry number(s), first author and year, type of publication (i.e., full-text article, conference proceeding, clinical trial registry), trial phase and blinding, target population, geographic location, eligibility criteria, trial start and completion dates, planned and actual follow-up duration, overall sample size, outcome definitions.

Intervention characteristics. The following intervention characteristics were extracted: treatment regimen, route of administration, dose, frequency of administration, duration of treatment, and concomitant/background therapies.

Baseline patient characteristics. The following baseline patient characteristics were extracted: sample size(s) at baseline, age, sex, race/ethnicity, disease stage and staging criteria, PS (e.g., Eastern Cooperative Oncology Group (ECOG), primary tumor location and sidedness, histological subtype, number of metastatic sites, prior treatment for advanced or metastatic disease, and biomarker status (i.e., Kirsten rat sarcoma 2 viral oncogene homolog (KRAS)/neuroblastoma rat sarcoma viral oncogene homolog (NRAS) mutation, B-Raf proto-oncogene (BRAF) mutation, mismatch repair-deficient (dMMR)/high microsatellite instability (MSI-H), and human epidermal growth factor receptor 2 (HER2) amplification).

Reported outcomes. The following efficacy and therapeutic outcomes were extracted: OS (N evaluated, median (95% CI), HR (95% CI), % of patients alive at x months); PFS (N evaluated, median (95% CI), HR (95% CI), duration of response (DOR; N evaluated, median (95% CI), HR (95% CI)); ORR, DCR, and numbers of patients with complete response, partial response, stable disease, or progressive disease; and time to deterioration in ECOG performance status (PS) ≥2.

The following therapeutic outcomes were extracted: actual ToT, subsequent therapies, and time to initiation of subsequent therapy.

The following safety outcomes were extracted: all and treatment-related AEs, all and treatment-related grade 3-5 AEs, all and treatment-related SAEs, availability of individual AE data, discontinuation due to AEs, and death due to AEs.

Table 84 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Adult (18+ years) patients with mCRC • Unresectable adenocarcinoma of the colon or rectum • Received two prior chemotherapy regimens for the treatment of advanced or metastatic CRC and demonstrated progressive disease or intolerance to the last regimen (i.e., third-line or beyond)	Studies consisting exclusively of with the following populations: • Early-stage CRC • Received fewer than two prior chemotherapy regimens (i.e., first- or second-line) • ECOG performance status scores of 2 or higher
Intervention	Any of the following treatments delivered alone or in combination with each other: • Aflibercept	• Surgical intervention without systemic treatment

	• Best supportive care • Bevacizumab • Capecitabine • Cetuximab • Encorafenib • Fluorouracil • Fruquintinib • Irinotecan • Oxaliplatin • Panitumumab • Ramucirumab • Regorafenib • FTD/TPI (TAS-102, LONSURF)	Radiation without chemo-therapy
Comparators	• Placebo • Any intervention listed above • Investigator's choice of therapy if options are among the interventions listed above	-
Outcomes	Efficacy outcomes: • Overall survival • Progression-free survival • Time to progression • Duration of response • Objective response rate • Time to deterioration in ECOG per-formance status ≥2 Safety outcomes: • Drug-related AEs • Grade 3-5 AEs (all, drug-related) • Serious AEs • Discontinuation due to AEs • Death due to AEs	-
Study design/publication type	• Randomized controlled trials • Non-randomized trials • Single-arm trials	• Observational studies • Animal or *in vitro* stud-ies • Case series/case reports • Editorials, commen-taries, letters, reviews
Language restrictions	English	-

Time	2010 - present

[a]Studies reporting at least one of the listed outcomes and meeting all other inclusion criteria were included in the SLR.

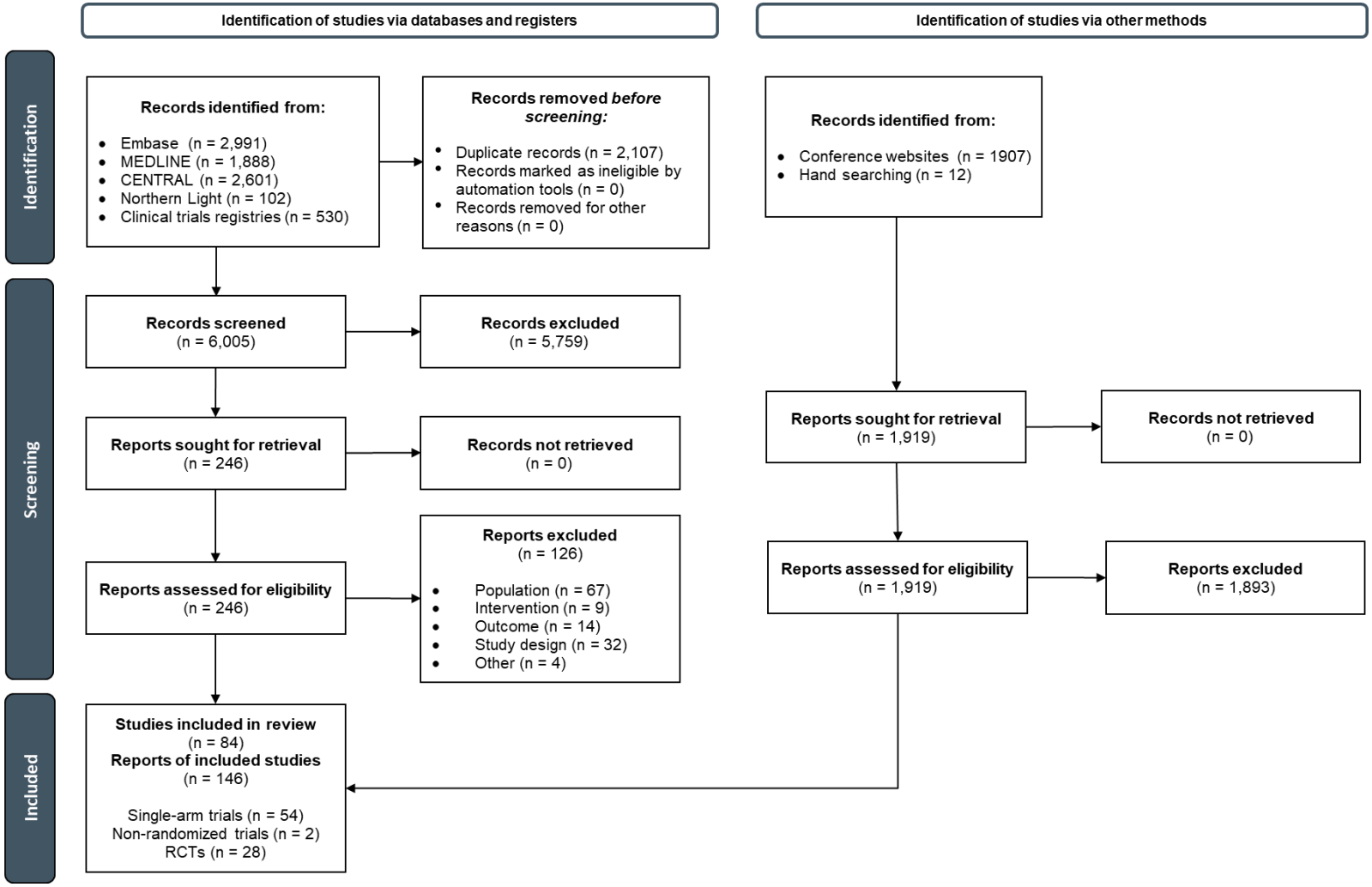

Figure 45 PRISMA flowchart for the SLR

Table 85 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	To assess efficacy and safety of TAS-102 in a global population of patients with mCRC.	Phase 3, randomized, double-blinded	Patients with metastatic colorectal cancer whose cancer had been refractory to antitumor therapy or who had had clinically significant adversed events that prevluded the readministration of those therapies	Lonsurf monotherapy (TAS-102) or placebo.	Overall survival.	Progression-free survival, response rate, rate of disease control, and safety

H.1.3 Quality assessment

This SLR followed the guidelines provided by the DMC, and were conducted in relevant and acknowledged databases. The systematic literature review process followed standard methods.

H.1.3.1 Study quality assessment

Risk of bias in included RCTs was assessed by two independent reviewers using the Cochrane Risk of Bias tool, version 2, which assesses risk of bias in five domains (bias arising from the randomization process, bias due to deviations for intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported results) as well as overall risk of bias (based on a tool algorithm that maps responses to signaling questions to an overall judgement). Quality assessment of non-randomized and single-arm trials was performed by a single reviewer and independently validated by a second reviewer using the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies

(https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp), which assesses study quality in three categories (selection, comparability, and outcome) as well as overall study quality. Any disagreements were resolved by discussion between reviewers, including a third more senior reviewer if needed.

H.1.4 Unpublished data

The NMA is unpublished data. There is not information on whether the NMA will be published later or not.

Appendix I. Literature searches for health-related quality of life (N/A)

Appendix J. Literature searches for input to the health economic model (N/A)

J.1 External literature for input to the health economic model (N/A)

[Describe and document how the literature for the model was identified and selected. This may be a combination of systematic database searches, targeted searches etc. Explain in separate sections (for each type of search) the sources used, the selection of the search criteria and terms used, and explain the process for inclusion and exclusion. Sufficient details should be provided so that the results may be reproduced where possible.]

J.1.1 Ex. Systematic search for […] (N/A)

[Objective of the literature search: What questions is the literature search expected to answer?]

Table 86 Sources included in the search (N/A)

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

Database	Platform/source	Relevant period for the search	Date of search completion
Medline			dd.mm. yyyy
CENTRAL	Wiley platform		dd.mm. yyyy

Abbreviations:

[Describe the selection process and criteria for inclusion or exclusion. For systematic searches, the requirements from the literature search for clinical evidence apply, see Appendix H].

J.1.2 Ex. Targeted literature search for [estimates] (N/A)

[Objective of the literature search: What questions is the literature search expected to answer?]

Table 87 Sources included in the targeted literature search (N/A)

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

Abbreviations:

[Describe the selection process and criteria for inclusion or exclusion.]

Appendix K. Additional information: Comparison of baseline characteristics to a Danish study by Pfeiffer et al. (2020)

Table 88 Baseline characteristics of the population from the SUNLIGHT trial and the study by Pfeiffer et al. (2020) [7,16]

	SUNLIGHT		DANISH study	
	Intervention (N=246)	**Comparator (N=246)**	**Intervention (N=46)**	**Comparator (N=47)**
Age (median)	62	64	64	67
Male	122	134	24	30
Region				
North America	8	8		
Europe (incl DK)	158	157	46 (Danish pts)	47 (Danish pts)
Rest of world	80	81		
Ethnicity			NR	NR
White	215	220		
Black	4	3		
Asian	0	1		
Other/unknown	27	22		
Primary diagnosis			NR	NR
Colon	180	181		
Rectum	66	65		
Location				
Right	62	77	11	11
Left	184	169	35	36
Median duration of disease (Y)	2.0	2.1	NR	NR
Time from diagnosis of first metastasis to				

	SUNLIGHT		DANISH study	
	Intervention (N=246)	Comparator (N=246)	Intervention (N=46)	Comparator (N=47)
randomization				
<18 months	104	105	<24 21	17
≥18 months	142	141	≥24 25	30
No. of sites of metastasis				
1 or 2	152	141	34	29
≥3	94	105	12	18
RAS status				
Mutated	171	170	27	29
wild type	75	76	19	18
BRAF status				
Mutated	8	11	2	0
Wild type	159	156	36	38
Unknown	79	79	8	9
MMR and MSI status				
MMR deficient and high MSI.	13	8	NR	NR
MMR proficient and stable or low MSI.	139	145	NR	NR
Unknown or missing data.	94	93	NR	NR
No. of previous treatments for metastatic disease — no. (%)§				
1 2 ≥3	11 229 6	15 224 7	≤2 21 ≥3 20 ≥5 5	20 21 6
Previous treatments received for metastatic disease				

	SUNLIGHT		DANISH study	
	Intervention (N=246)	Comparator (N=246)	Intervention (N=46)	Comparator (N=47)
Fluoropyrimidine	246	246	46	47
Irinotecan Oxali-	246	245	46	47
platin	241	243	45	47
Anti-VEGF	178	176	39	36
Anti-EGFR	71	71	19	18
Other	-	-	3	3
ECOG perfor- mance-status score				
0	119	106	23	15
1	127	139	23	32
2	0	1	0	0
Neutrophil–lym- phocyte ratio				
<3	128	115	NR	NR
≥3	117	131	NR	NR

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